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dissertation entitled

STILLE COUPLINGS CATALYTIC IN TIN AND RELATED REACTIONS

presented by

William P. Gallagher

has been accepted towards fulfillment
of the requirements for the

Ph.D degree in Chemistry

Robert E Maleczka Jr

Major Professor's Signature

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Date

STILLE COUPLINGS CATALYTIC IN TIN AND RELATED REACTIONS

Volume I

By

William P. Gallagher

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ABSTRACT

STILLE COUPLINGS CATALYTIC IN TIN AND RELATED REACTIONS

By

William P. Gallagher

The Stille coupling is a powerful C-C- bond forming reaction. It has been utilized extensively in synthetic chemistry. Although widely used, there are many drawbacks to it. These drawbacks have encouraged others to improve upon or replace the Stille coupling with alternative cross couplings. Our solution is to develop a one-pot hydrostannation/Stille coupling that can be rendered catalytic in tin. The initial "Sn-O" route proved very effective, but there were still disadvantages. After more experimentation, a "Sn-F" approach was realized, in which the organotin fluoride intermediate lessened the hazards of the trimethylstannanes while at the same time producing high yields of cross coupled products. Although the toxicity of the trimethylstannanes has been lessened by the use of the "Sn-F" route, the use of the tributylstannanes would be more attractive. Every attempt to amend the protocol to the use of the tributylstannanes failed. These attempts led to an efficient version of the Sonogashira coupling. These studies are discussed in full in the following account.

To John M. Gallagher and James J. Gallagher.

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Ac

Acac

AIBN

$AgNO_3$

aq

CH_2Cl_2

CI

CSA

Cy

DCC

DBU

DIAD

DIBAL

DMAP

DME

DMF

DMSO

EI

eq

FAB

h

HMPA

LIST OF ABBREVIATIONS

Ac	acetyl
Acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
$AgNO_3$	silver nitrate
aq	aqueous
CH_2Cl_2	dichloromethane
CI	chemical ionization
CSA	camphorsulfonic acid
Cy	cyclohexyl
DCC	dicyclohexylcarbodiimide
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
EI	electric ionization
eq	equation
FAB	fast atom bombardment
h	hour
HMPA	hexamethyl phosphoramide

HRMS

HWE

IMES-H_2

KHMDS

LiHMDS

m-CPBA

Mes

mL

mmol

NaHMDS

NBS

NMP

NOE

Ph

PMB

RCM

r.t.

TBAF

TBS

THF

TMS

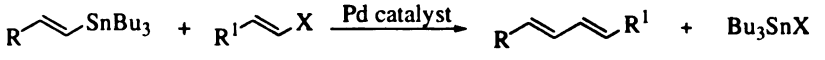
PTSA

HRMS	high resolution mass spectrometry
HWE	Horners-Wadsworth-Emmons reaction
IMES-H_2	4,5-dihydro-1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
KHMDS	potassium bis(trimethylsilyl)amide
LiHMDS	lithium bis(trimethylsilyl)amide
m-CPBA	*m*-chloroperbenzoic acid
Mes	mesityl
mL	milliliter
mmol	millimole
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	N-bromosuccinimide
NMP	N-methyl-2-pyrrolidinone
NOE	nuclear Overhauser effect
Ph	phenyl
PMB	p-methoxybenzyl
RCM	ring closing metathesis
r.t.	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
PTSA	*p*-toluenesulfonic acid

Chapter 1. An Introduction.

Beginning in the late 1970's and continuing throughout most of the 1980's, studies by the late J. K. Stille helped to establish the palladium-catalyzed cross coupling of organotin reactants with a variety of organic electrophiles as a highly useful method for carbon-carbon σ-bond construction.[1,2] Today, Stille reactions (Figure 1) commonly represent a key step in the preparation of natural products,[3] new raw materials,[4] medicinal agents,[5] etc.

Figure 1. The Stille Coupling



R and R^1 = many possiblities

X = halogen, Tf, Nf, OAc

Although the Stille reaction can be viewed as a routine synthetic tool, its study continues.[1d] Recent advances include adaptation of the method to aqueous,[6] combinatorial,[7] solid phase,[8] fluorous phase,[9] and super critical environments.[10] Recent work has also provided a greater mechanistic understanding of the reaction,[11] expanded its scope,[12] and improved existing Stille protocols.[13]

Many of the newly reported improvements to the Stille reaction offer greater ease in the separation of the cross-coupled product from the organotin byproducts. Difficulties in purification, along with cost and toxicity issues associated with using stoichiometric amounts of organostannanes,[14] have long been considered problematic features of these reactions. Solutions to the "tin problem" have largely focused on either derivatizing the organotin[5b,6b,8f,i,9,13b-d] or inventing reaction workups[1d,15] aimed at aiding removal of the tin byproducts.[16]

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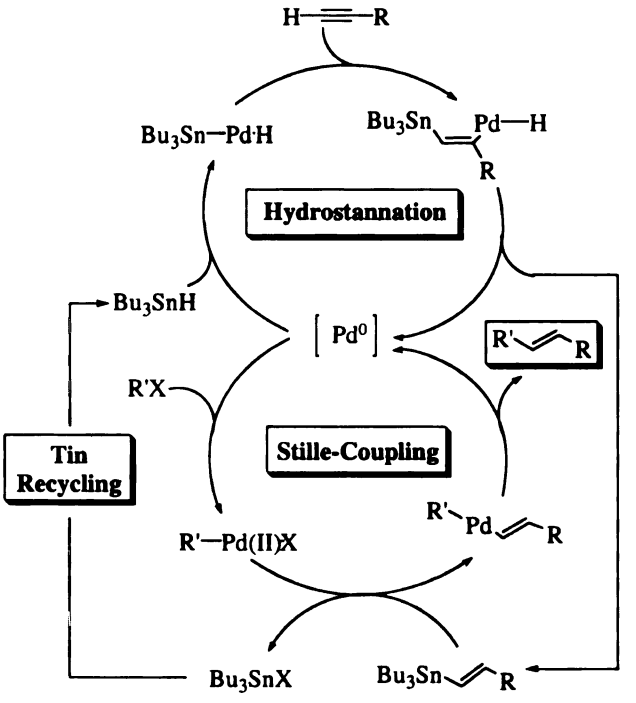
A complementary approach to this problem would be to develop a Stille cross-coupling protocol catalytic in tin. The development of such a method would involve the design of a catalytic process where the organotin species is the reactant,[17] meaning the tin moiety is fixed to the organic substrate via a stable, covalent bond,[18] as opposed to a reagent (a species that is not incorporated in the final product).

Chapter 2. Stille Couplings Catalytic in Tin: The "Sn-O" approach.

2.1 Introduction

Although the Stille coupling is a highly utilized reaction, a major drawback is the necessity for preparation and purification of the vinylstannane. Vinylstannanes are typically prepared via transition metal catalyzed hydrostannation of alkynes is the primary way of synthesizing vinylstannanes,[57b,19] most commonly with palladium.[20] The Stille coupling is also catalyzed by palladium. Thus, it was envisioned that a Stille reaction catalytic in tin could be achieved if an organotin hydride could undergo an in situ, chemoselective sequence of Pd(0)-catalyzed vinylstannane formation followed by cross-coupling, and then be regenerated from the organotin halide byproduct (Figure 2).

Figure 2. The Catalytic Cycles



Realization of a such a catalytic cycle would require addressing several issues, including: (1) regioselectivity during the Pd(0)-catalyzed hydrostannation, (2) identification of catalyst and solvent conditions which allow both hydrostannation and

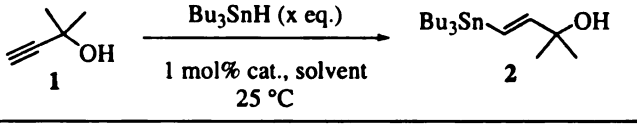
cross coupling to occur, while at the same time minimizing any unwanted side reactions, and (3) discovery of suitable methods for recycling the R_3SnX back to R_3SnH.

2.2. Initial Work

To avoid regiochemical complications, all alkynes initially studied were trisubstituted at the propargylic position. Such sterically hindered alkynes are known to heavily favor formation of the *E* (distal) isomer over the internal (proximal) isomer. [21]

Although the regiochemical outcome of the hydrostannation was assured, the feasibility of carrying out Pd-catalyzed hydrostannations in the presence of a Stille electrophile was not. A balance needed to be struck between the catalyst requirements for high yielding hydrostannations (strong σ-donor ligands like PPh_3) and efficient cross couplings (weaker σ-donor ligands). Equally important was the need to minimize side reactions, especially Pd-mediated Bu_3SnH dimerization[22] and/or reduction of the organohalides.[23] To address the dimerization issue, postdoc Ina Terstiege examined the palladium-catalyzed hydrostannation under a variety of "Stille-like" catalysts and solvent conditions. The results are listed in Scheme 1.

Scheme 1. Selection of Pd Catalyst and Solvent for Hydrostannation

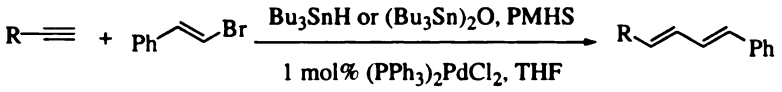


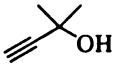
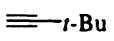
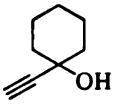
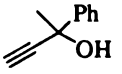
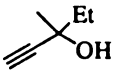
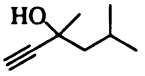
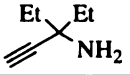
Entry	Catalyst	eq. of SnH	Solvent	Result
1	$Pd(PPh_3)_4$	1.1	THF or Et_2O	**2**: 85%
2	$Pd(PPh_3)_4$	2.1	DMF	**2**: 60%
3	$Pd(PPh_3)_4$	2.1	NMP	No product gas evolution
4	$Cl_2Pd(CH_3CN)_2$	1.1	THF or Et_2O NMP or DMF	incomplete reaction
5	Pd_2dba_3/TFP	1.7	THF or Et_2O	**2**: 85%
6	Pd_2dba_3/TFP	2.5	DMF or NMP	incomplete reaction

As can be seen from Scheme 1, the use of Pd_2dba_3/TFP in ethereal solvents proved to be the most useful system. Other systems promoted hexabutylditin formation to such an extent that the rate of the hydrostannation reactions could no longer compete.

With a suitable catalyst/solvent combination in hand, the next step was to combine the hydrostannation and Stille coupling into a single pot reaction. The first example of a stepwise one-pot palladium catalyzed hydrostannation/Stille coupling has been described.[24] Pattenden[24] and Guibe[20a] showed that, through the employment of 1-bromoalkynes instead of terminal alkynes, the regioselectivity of the palladium-catalyzed hydrostannation could be greatly improved in favor of the *E*-vinylstannanes. Using stoichiometric amounts of tin, Pattenden performed a one-pot hydrostannation/Stille coupling in a stepwise fashion. Initially, the reaction was operated with stoichiometric amounts of tin. Even though stoichiometric in tin, a one pot hydrostannation/Stille coupling which does not require isolation of the vinylstannane can be advantageous when dealing with unstable stannanes.[25] Here, Bu_3SnH was added to a solution of alkyne, (*E*)-β-bromostyrene, and Pd catalyst in THF. Although the reaction times where long, the one pot sequence gave cross-coupled products in yields comparable to those for the stepwise protocol (Table 1).

Table 1. One Pot Hydrostannation/Stille with Stoichiometric Tin



entry	alkyne		Product Yields Bu_3SnH	Stepwise	$(Bu_3Sn)_2O$/ PMHS
1		**1**	**3:** 87%	49%	66%
2		**4**	**5:** 89%	19%	52%
3		**6**	**7:** 51%	42%	52%
4		**8**	**9:** 75%	56%	69%
5		**10**	**11:** 86%	56%	60%
6		**12**	**13:** 76%	35%	58%
7		**14**	**15:** 47%	36%	-

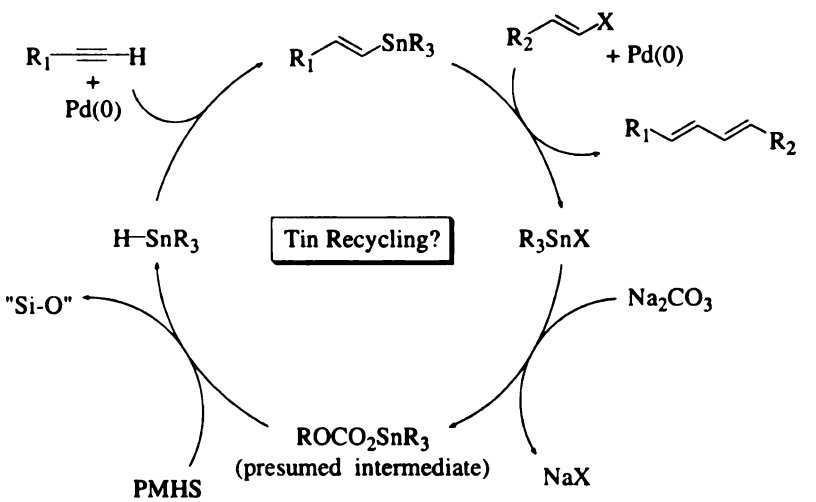
GC analysis of the reaction mixture showed that no Pd-catalyzed reduction of (*E*)-β-bromostyrene did occur; although it was possible that styrene was not stable under the reaction conditions and therefore could not be detected. However, as (*E*)-β-bromostyrene was used in only very small excess (with respect to the alkyne) and the Stille products were often isolated in high yields (86-89%), it was concluded that reduction occurs in only a very small amount.

As a check on our hydrostannation experiments, the one pot sequence was carried out in the better Stille solvent DMF.[1] In these experiments, a larger excess of Bu_3SnH (2.5 eq.) was required to consume the alkyne, affording the Stille product (~35%), recovered vinylstannane (~38%), and a large amount (~17%) of styrene dimer.

Now that the one pot sequence stoichiometric in tin could be carried out successfully,[26] methods for recycling the Bu_3SnX byproduct back to Bu_3SnH were considered. Strong hydride donors like $LiAlH_4$ or $NaBH_4$[27,28] are known to reduce Pd(II)

intermediates[29] and would severely curtail the broad functional group tolerance normally associated with the Stille coupling. Hayashi et al.[30] showed that Bu_3SnH can be generated via reduction of $(Bu_3Sn)_2O$ by the cheap, nontoxic, and relatively mild hydride donor polymethylhydrosiloxane (PMHS).[31] Furthermore, the $(Bu_3Sn)_2O$/PMHS mixture had been shown to work well as an in situ source of Bu_3SnH in free radical hydrostannations of 1-alkynes,[32] while the elegant work of Fu and coworkers demonstrated that PMHS and other silanes can serve as the stoichiometric reducing agent in reactions catalytic in tin.[33] Although PMHS does not reduce organotin halides, numerous methods exist for converting the Sn-X bond into a Sn-O bond.[27] Thus, a "Sn-O" approach to the development of a Stille reaction catalytic in tin was pursued (Figure 3).

Figure 3. The Catalytic Cycle of the "Sn-O" Route

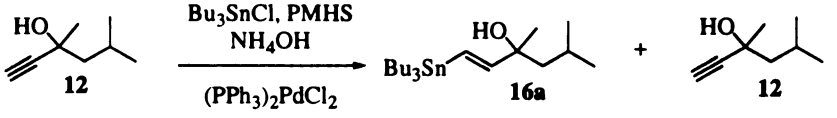


The $(Bu_3Sn)_2O$/PMHS method for Bu_3SnH formation was successfully applied to the one pot hydrostannation/Stille sequence (Table 1). Importantly, palladium catalyzed hydrosilylation of the alkyne or alkene was not observed.[34] Even though the combination of $(Bu_3Sn)_2O$/PMHS was capable of working, a 2-fold excess of $(Bu_3Sn)_2O$ was required

because generation of 2 eq. of Bu_3SnH from 1 eq. of $(Bu_3Sn)_2O$ occurs only at elevated temperatures (80-100 °C).[30]

With these results in place, a method of converting the tin halide into an Sn-O species that would be amendable to the sequence of reactions and reagents was sought. Various methods of effecting such a transformation were explored. Since treatment of Bu_3SnCl with NH_4OH had been previously reported[35] to afford $(Bu_3Sn)_2O$, $Bu_3SnCl/NH_4OH/PMHS$ as a potential in situ source of Bu_3SnH was studied (Scheme 2). However, when NH_4OH was added to an ethereal solution of Bu_3SnCl, **12**, Pd(0), and PMHS, formation of a white precipitate was observed (presumably NH_4Cl), and after 2.5 h, only a 1:1 ratio of product (**16a**) to starting material was obtained. Heating the reaction mixture in toluene/EtOH for 6.5 h increased the ration to 1.7:1; however, it was not possible to drive this reaction to completion. Thus, direct conversion of Bu_3SnX into bis(tributyltin) oxide appeared impractical under these conditions.

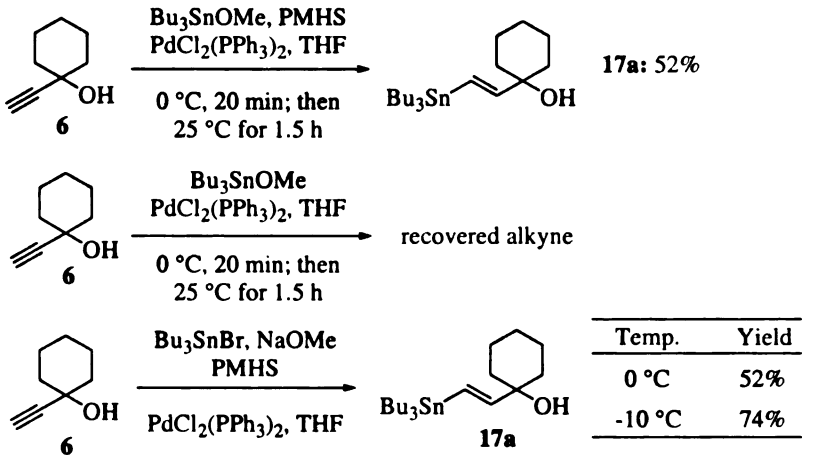
Scheme 2. Attempted Use of $Bu_3SnCl/NH_4OH/PMHS$



Entry	Time (h)	Solvent	Temp. (°C)	**16a**: **12**
1	2.5	Et_2O	25	1 : 1
2	6.5	$PhCH_3/EtOH$	100	1.7 : 1

Since organotin halides can be converted to organotin alkoxides,[36] attention turned to Bu_3SnOMe as a tributyltin hydride source. Hydrostannation of alkyne **6** using Bu_3SnOMe and PMHS as the in situ source of tin hydride produced only a small amount of product after 20 min at 0 °C; however, upon stirring at 25 °C for an additional 1.5 h, the vinylstannane **17a** could be isolated in 52 % yield (Scheme 3).

Scheme 3. Use of Bu_3SnOMe as the Source of Tin



Temp.	Yield
0 °C	52%
-10 °C	74%

In theory, Bu_3SnH could be generated from Bu_3SnOMe without PMHS via β-hydride elimination of a Bu_3Sn-Pd(II)-OMe species.[37] However, hydrostannation experiments performed in the absence of PMHS did not produce any product, thus arguing against such a mechanism (Scheme 3, reaction 2). Furthermore, a Bu_3SnX to Bu_3SnOMe to Bu_3SnH sequence also worked in the hydrostannation reaction. Reaction of Bu_3SnBr with NaOMe at 0 °C, followed by addition of **6**, PMHS, and Pd(0) was complete after 15 min, again affording vinylstannane **17a** in 52% yield (Scheme 3, reaction 3). The shorter reaction time when starting with Bu_3SnBr was interesting as this approach includes one more transformation. It did not seem likely that Bu_3SnBr was reduced directly by PMHS, as treatment of Bu_3SnBr and Bu_3SnCl/NaI with PMHS in the absence of NaOMe did not produce any product. That said, the possibility that NaOMe activated the PMHS via a pentacoordinate silane intermediate,[38] making it more reactive than the nonactivated PMHS toward either Bu_3SnBr or Bu_3SnOMe, could not be ruled out. The reaction sequence could also be carried out by mixing all the reagents at once, and if run below 0 °C, the yield could be improved to 74% (Scheme 3).

Unfortunately, attempts at carrying out the same sequence with catalytic quantities of tin failed. Stirring NaOMe, PMHS, alkyne 12, (*E*)-β-bromostyrene,

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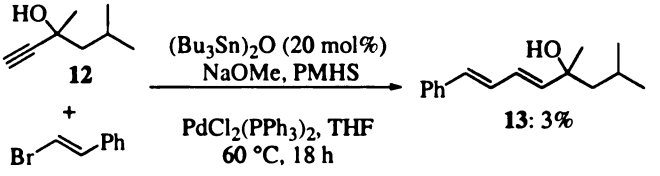
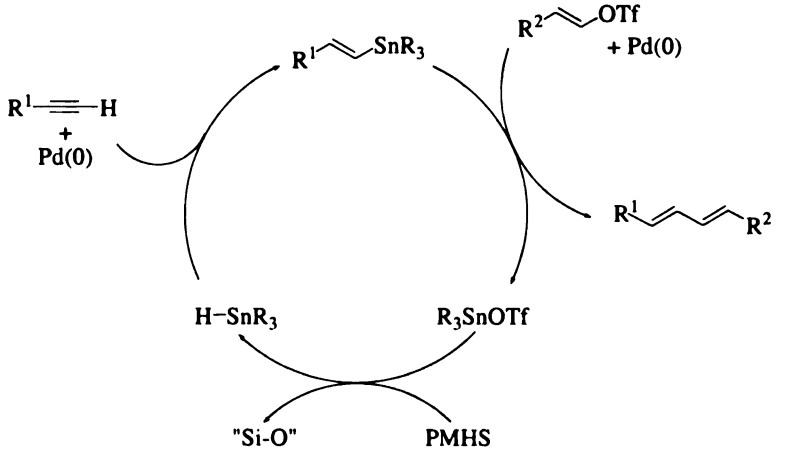
catalytic Pd(0), and 20 mol% $(Bu_3Sn)2O$[39] in THF at 60 °C for 18 h afforded only 3% of the cross-coupled product **13** (Scheme 4). Under low concentrations, the NaOMe reacts with PMHS rather than the organotin species, resulting in gas evolution (preseumable H_2) and formation of an insoluble gel.[40]

Scheme 4. Use of NaOMe in a Catalytic Tin Reaction



In theory, the problematic halide to oxide step could be circumvented through the employment of vinyl or aryl triflates as Stille electrophiles (Figure 4). However, attempts to generate vinylstannanes with Bu_3SnH derived from PMHS reduction of Bu_3SnOTf resulted in no observable reaction until prolonged stirring/heating decomposed all reactants. Based on these results, this approach was abandoned in favor of finding a PMHS compatible oxo-nucleophile for converting the organotin halide into an organotin alkoxides.

Figure 4. Catalytic Cycle Using Triflates



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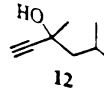
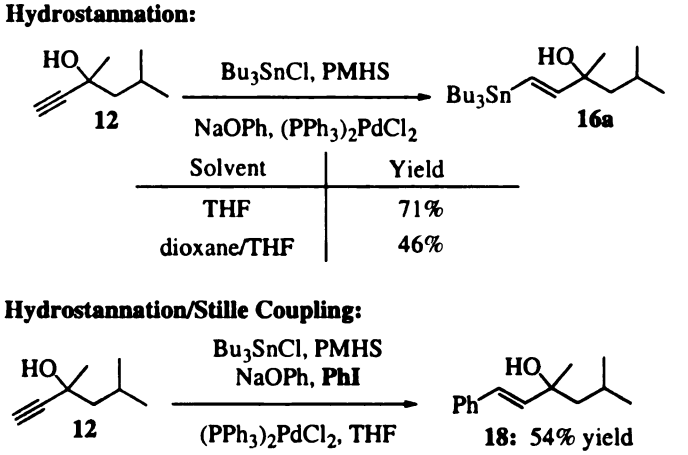


12

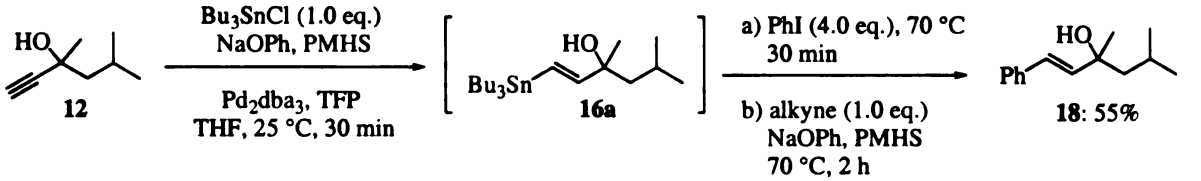
In this regard, alkoxides, which are less basic/nucleophillic than NaOMe, were examined. Although a solution of NaOPh and PMHS in Et_2O/THF polymerized within 15 min, qualitatively the reaction was slow as compared with NaOMe. Given the reactivity difference, NaOPh was tested in a Bu_3SnX to Bu_3SnOPh to Bu_3SnH to vinyltin sequence.

Scheme 5. Use of NaOPh/PMHS



As shown in Scheme 5, treatment of Bu_3SnX with NaOPh in THF, followed by alkyne **12**, $(PPh_3)_2PdCl_2$, and finally PMHS resulted in complete disappearance of the alkyne within 15 min at 25 °C, and ultimately allowed isolation of the vinylstannane **16a** in 71% yield. Adding iodobenzene to the reaction provided **18** in 54% yield. Running the reaction in THF/dioxane afforded the vinylstannanes in 46% yield along with homocoupled stannane, whereas with DMF/THF as solvent and $(MeCN)_2PdCl_2$ as catalyst only gave hexabutylditin.

Scheme 6. Catalytic Stille Sequence with NaOPh

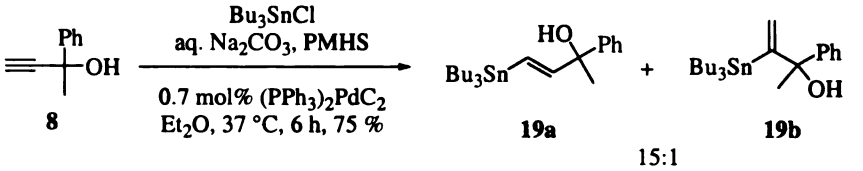


During attempts at carrying out the sequence with catalytic quantities of tin, the only suggestion of tin turnover came when the reactions were carried out in a repetitive stepwise fashion. In these experiments, 1 eq. of Bu_3SnCl in the presence of 1 eq of **12** was first reacted with NaOPh and then PMHS. Upon complete consumption of the alkyne (~30 min), the temperature was raised, 4 eq. of iodobenzene was added, and the cross coupling proceeded. Consumption of the vinylstannane then constituted completion of the catalytic cycle, at which time another equivalent of **12** and NaOPh followed by addition of more PMHS. This allowed the formation of the Stille product to occur in near quantitative yield based on tin (55% based on alkyne) (Scheme 6).

Organotin formates and acetates[41] were explored as potential reaction intermediates. Prolonged heating of the reaction mixtures containing Bu_3SnX, PMHS, Pd(0) catalyst, alkyne **8**, and either NaOAc or HCO_2NH_4 did indeed effect hydrostannation of the alkyne. However, crude ^1H NMR and TLC showed the reactions also contained significant amounts of starting material and/or protiodestannylated material. The protiodestannylated material might have arisen from Pd(0)/HCO_2NH_4-mediated hydrogenolysis of the alkyne.[42]

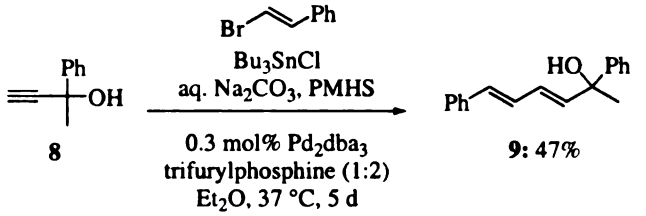
Following the failure of the carboxylates to react, carbonates were the next logical choice. When THF solutions of alkyne **8** and Bu_3SnCl were treated with PMHS, Pd(0) catalyst, and a 3-fold excess of the partially organic soluble Cs_2CO_3, only small amounts of vinylstannane were detected along with a large amount of decomposition products. On the other hand, with a mixture of Na_2CO_3 in refluxing Et_2O,[43] vinylstannanes **19a/19b** were afforded as a 15:1 ratio respectively (Scheme 7).

Scheme 7. Na_2CO_3/PMHS Mediated Hydrostannation



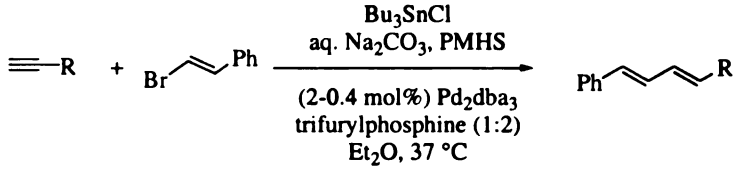
All attempts to optimize this reaction via the use of $K_2CO_{3(aq.)}$ in MeOH proved unproductive. The hydrostannation probably proceeds through a tin carbonate; however, the exact structure of organotin carbonates remains a subject of debate.[44] In fact, the possibility that Bu_3SnCl is being hydrolyzing in aqueous media,[45] with the resultant hydroxide (or oxide) being reduced by the PMHS, has not been ruled out. However, reactions run in carbonate-free water showed only trace amounts of vinylstannane **19a** by TLC. Experiments aimed at incorporating the cross coupling step into the sequence identified Pd_2dba_3 and P(2-furyl)$_3$ (TFP) as a better palladium ligand combination. Furthermore, experimentation was used to address the order and time over which reactants were added. Thus, a mixture of alkyne **8**, (*E*)-β-bromostyrene, and PMHS added via syringe pump to a solution of Bu_3SnCl, aqueous Na_2CO_3, and Pd(0) produced the Stille product **9** in 47% yield (after 5 days) or an average of 84% for each of the four reaction steps involved (tin carbonate formation, tin hydride formation, hydrostannation, and Stille coupling) (Scheme 8). In comparison, preparation and isolation of the vinylstannane via Bu_3SnH and Pd_2dba_3/TFP and then subjection of that material to the Stille coupling (via Pd_2dba_3/TFP) afford the cross-coupled product in 63% yield (56% yield with $(PPh_3)_2PdCl_2$), whereas a one pot hydrostannation/Stille with Bu_3SnH and $(PPh_3)_2PdCl_2$ afforded the diene in 75% yield (Table 1, entry 4). With this result in hand, reactions were attempted with catalytic amounts of tin.

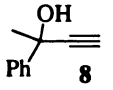
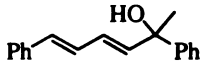
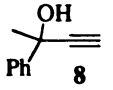
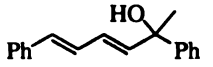
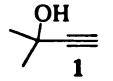
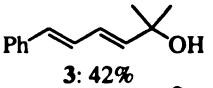
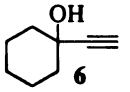
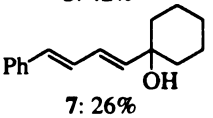
Scheme 8. Stoichiometric One Pot Hydrostannation/Stille with aq. Na_2CO_3/PMHS



Again experimenting with the rate and order of addition, several alkynes were mixed with (*E*)-β-bromostyrene, catalytic Pd_2dba_3/TFP, aqueous Na_2CO_3, and substoichiometric amounts of Bu_3SnCl. As illustrated in Table 2, such a blend of reactants afforded the first clear examples of Stille reactions catalytic in tin. With tin loads ranging from 20 to 4.0 mol%, the dienes were produced in yields representing 2-5 tin turnovers. The same reaction sequence without tin produced no Stille coupling products, ruling out the Pd-catalyzed coupling of a transient vinylsilane with the halide.[46]

Table 2. First Examples of a One-Pot Hydrostannation/Stille with Catalytic Tin



Entry	Alkyne	Bu_3SnCl (mol%)	Sn-turnovers	Yield
1	 **8**	20	2	 **9**: 40%
2	 **8**	4	5	 **9**: 22%
3	 **1**	10	2	 **3**: 42%
4	 **6**	10	2.5	 **7**: 26%

While the results of Table 2 established proof-of-principle, the modest to poor yields were less than practical. In part, the long reaction times (up to 72 h) offered ample time for the tin to react down nonproductive pathways. Attempts to accelerate the

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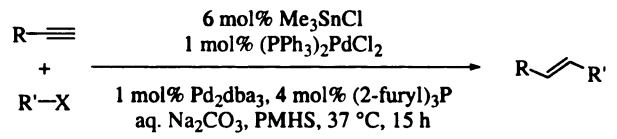
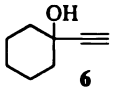
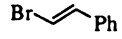
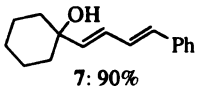
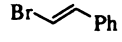
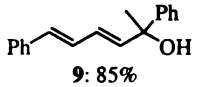
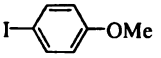
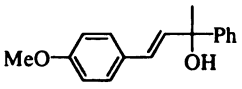
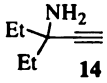
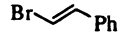
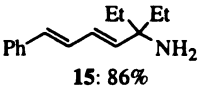
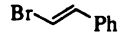
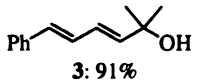
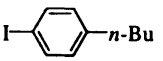
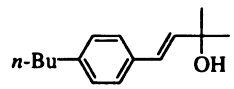
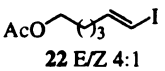
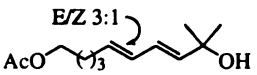
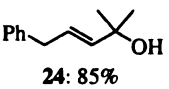
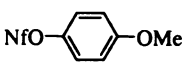
reaction through the use of polar solvents (DMF or NMP) or more active catalysts (such as $(MeCN)_2PdCl_2$) resulted in overall diminished yields because Pd-catalyzed conversion of Bu_3SnH into hexabutylditin predominated the reaction.[22] Furthermore, the addition of copper salts provided little or no improvement in the catalytic process.[47,13a,g] Since it is generally believed that transmetalation is the rate determining step of the Stille reaction, it was rationalized that switching from the tributylstannanes to the less sterically demanding trimethylstannanes should facilitate the overall reaction sequence. Stille has shown that vinyl trimethylstannanes couple faster than the corresponding tributylderivatives.[48] In accord with Stille's observations, switching from Bu_3SnCl to the less sterically demanding Me_3SnCl accelerated and significantly improved the efficiency of the catalytic cycle.[49]

Table 3. One-Pot Hydrostannation/Stille Coupling Using 6 mol% Me_3SnCl



Entry	Alkyne	R'—X	Product
1	 **6**		 **7**: 90%
2	 **8**		 **9**: 85%
3	 **8**		 **20**: 80%
4	 **14**		 **15**: 86%
5	 **1**		 **3**: 91%
6	1		 **21**: 75%
7	1	 **22** E/Z 4:1	 **23**: 80%
8	1		 **24**: 85%
9	1		No Stille Product
10	1	Me—I	No Stille Product
11	1	 **25**	No Stille Product

As shown in Table 3 (entries 1-8), syringe pump addition of 1.1 eq. of vinyl, aryl, or benzyl bromides or iodides to a 37 °C ethereal mixture of various α-trisubstituted alkynes, aq. Na_2CO_3, PMHS, Pd_2dba_3, tri-2-furylphosphine (TFP), $(PPh_3)_2PdCl_2$, and 6 mol% Me_3SnCl over a period of 15 h afforded the corresponding cross-coupled products

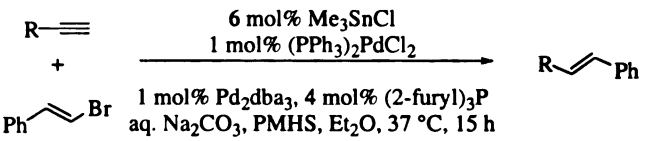
in 75-91% yield representing an average of ~15 tin turnovers. Allyl bromide and methyl iodide failed under these conditions, and somewhat consistent with earlier experience with triflates, nonaflate **25** gave no Stille product (Table 3, entries 9-11).

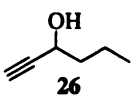
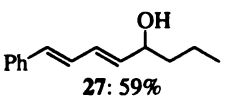
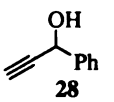
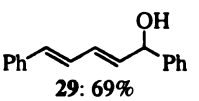
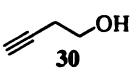
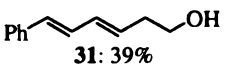
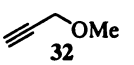
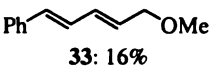
The use of Pd_2dba_3, tri-2-furylphosphine (TFP) and $(PPh_3)_2PdCl_2$ gave the best results. In situ reduction of $(PPh_3)_2PdCl_2$ forms coordinatively unsaturated Pd(0)-$(PPh_3)_2$. This species, along with the 1:1 mixture of Pd_2dba_3 and TFP affords Pd(0), which is capable of complexing with a PPh_3 and/or TFP. It was thought that this combination of ligands provides a good compromise between activity toward cross coupling and Bu_3SnH dimerization. However, simple addition of the appropriate quantities of PPh_3 or TFP to a solution of either Pd_2dba_3 or $(PPh_3)_2PdCl_2$ did not prove equally effective. Thus, the reason for the optimal performance of the mixed palladium system remains unclear. The experiment aimed at determining the necessity of Na_2CO_3 was repeated, since Me_3SnCl is more prone to hydrolysis than Bu_3SnCl. As noted before, reacting **8** with water, Me_3SnCl, Pd(0) catalyst, and PMHS in refluxing Et_2O failed to provide measurable amounts of the vinylstannane.

To more fully address regiochemical issues, sterically less demanding alkynes were applied to the protocol. Two α,α-disubstituted alkynes afforded the anticipated dienes (Table 4, entry 1-2), but in lower yields, presumably due to diminished regiocontrol during the hydrostannation sequence. α-Monosubstituted alkynes performed poorly (Table 4, entries 3-4). For example, reaction of **32** resulted in the formation of **33** (16% yield) and the cross-coupled product derived from the proximal vinylstannane (3% yield). These results were not entirely surprising, as unhindered alkynes are known to undergo non-regioselective palladium catalyzed hydrostannation.[20] For example,

hydrostannation of **30** afforded a 2.3:1 mixture of *E*/internal vinylstannanes and hydrostannation of **32** favors the internal stannane (*E*/internal 1:2.5). Furthermore, Stille coupling of internal (proximal) isomers is very sluggish, thus prohibiting efficient tin turnover. Surprisingly, the overwhelming balance of the reaction was not unreacted alkyne, but rather multiple multi-component cross-coupling products.

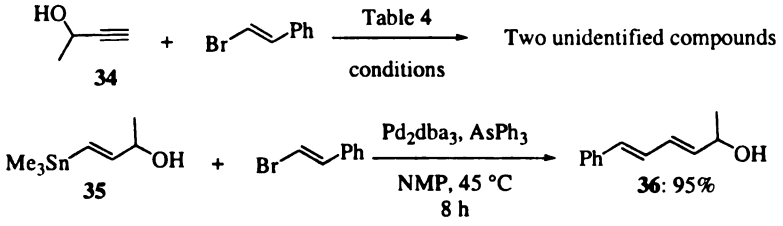
Table 4. Use of α,α-Di- and α-Monosubstituted Alkynes



Entry	Alkyne	Product
1	 **26**	 **27**: 59%
2	 **28**	 **29**: 69%
3	 **30**	 **31**: 39%
4	 **32**	 **33**: 16%

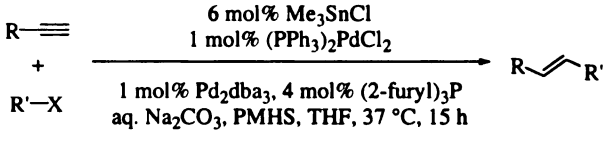
When 3-butyn-2-ol (**34**) was used, an interesting observation was made. Unlike alkynes **26** and **28**, **34** did not afford any of the desired diene. Rather, two unidentified, more polar compounds were formed. The analogous compounds were not detected when alkynes **26** and **28** were employed. As a control, the Stille coupling between vinylstannane **35** (formed via Pd-catalyzed hydrostannation of **34**) and (*E*)-β-bromostyrene afforded **36** in 95% yield (Scheme 9). This result indicated that a more complicated process is operative.

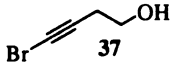
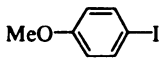
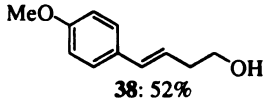
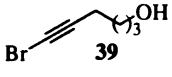
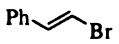
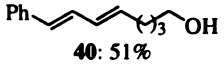
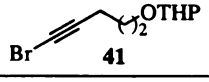
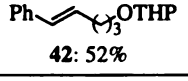
Scheme 9. Use of 3-Butyn-2-ol **34**: an Unusual Result



To circumvent problems associated with unhindered alkynes, the use of 1-bromoalkynes was investigated. As will be discussed in Chapter 3, palladium catalyzed hydrostannation of 1-bromoalkynes proceeds with a high bias toward the distal (*E*) vinylstannane.[24] Since these reactions produce R_3SnBr as a byproduct, we rationalized that 1-bromoalkynes should be amendable to a one-pot hydrostannation/Stille coupling catalytic in tin. Several 1-bromoalkynes were made (vide infra). Despite addition of a fifth tin reaction to the sequence, these substrates cleanly afforded dienes in ~50% yield (Table 5). Reactions with 1-bromoalkynes proved more efficient if THF was used instead of Et_2O, and if both the Stille electrophile and the 1-bromoalkyne were added as a solution via a syringe pump. Addition of the 1-bromoalkyne alone gave a complex mixture of products.

Table 5. Use of 1-Bromoalkynes in the Catalytic Stille Reaction



Entry	Alkyne	R'—X	Product
1	 **37**		 **38**: 52%
2	 **39**		 **40**: 51%
3	 **41**	Ph—I	 **42**: 52%

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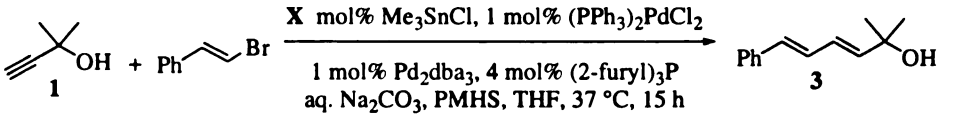
The effect of tin loading was also studied. While higher loads of Me_3SnCl saw little improvement, loadings below 6 mol% of tin resulted in fairly significant reductions in yield (Scheme 10). For example, at 1 mol% Me_3SnCl, the 1,3-diene was formed in only 18% yield. Looking more closely at the results, the number of tin turnovers remained almost constant, suggesting that a maximum number of turnovers had been reached.

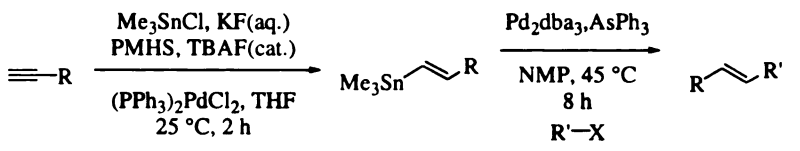
Scheme 10. The Effect of Tin Loading

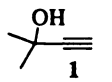
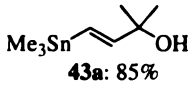
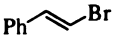
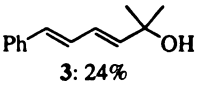
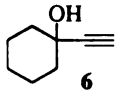
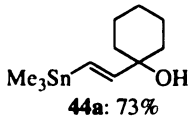
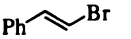
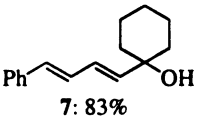
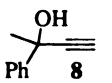
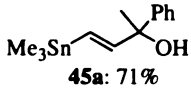
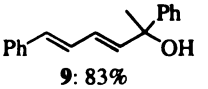
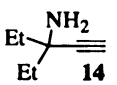
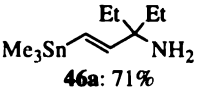
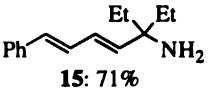
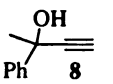
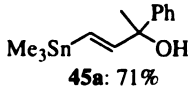
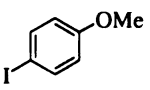
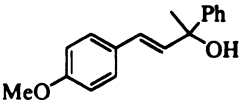
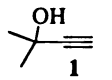
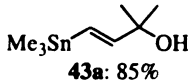
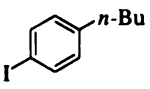
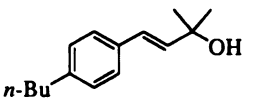
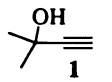
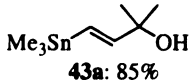
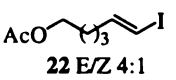
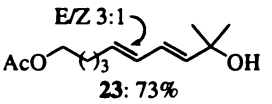
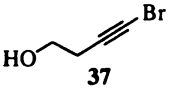
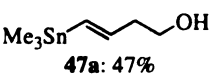
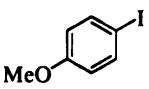
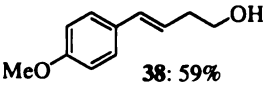
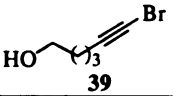
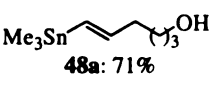
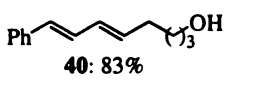


Entry	Me_3SnCl	Sn-turnovers	Yield
1	6 mol%	15	**3**: 91%
2	4 mol%	17	**3**: 67%
3	1 mol%	18	**3**: 18%

As a control, vinylstannanes were prepared, isolated, and then subjected to a traditional Stille coupling (Table 6). The one-pot results were comparable or better than the stepwise approach when using trimethylvinylstannanes.

Table 6. Traditional Stille Results



Entry	Alkyne	Stannane	R'—X	Product	Overall yield from alkyne
1	 **1**	 **43a**: 85%		 **3**: 24%	77%
2	 **6**	 **44a**: 73%		 **7**: 83%	61%
3	 **8**	 **45a**: 71%		 **9**: 83%	59%
4	 **14**	 **46a**: 71%		 **15**: 71%	50%
5	 **8**	 **45a**: 71%		 **20**: 83%	59%
6	 **1**	 **43a**: 85%		 **21**: 92%	78%
7	 **1**	 **43a**: 85%	 **22** E/Z 4:1	 **23**: 73%	62%
8	 **37**	 **47a**: 47%		 **38**: 59%	28%
9	 **39**	 **48a**: 71%		 **40**: 83%	59%

2.3. Conclusions

The limitations and problems associated with the stoichiometric tin requirement of traditional Stille reactions have been addressed. Studies have demonstrated the feasibility of a one pot tandem Pd-catalyzed hydrostannation/Stille coupling with either Bu_3SnH or $(Bu_3Sn)_2O$ and PMHS serving as the tin hydride source. Furthermore, by in

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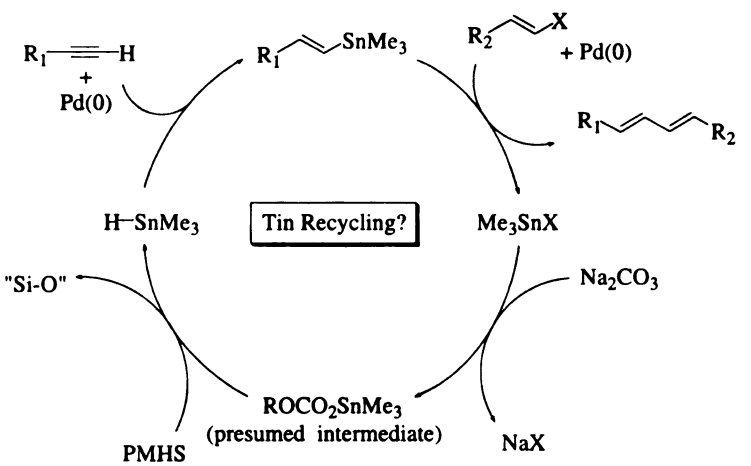
situ conversion of the organotin halide Stille byproduct into an intermediate organotin carbonate, and then back to organotin hydride, it was possible to conduct a hydrostannation/cross-coupling sequence with catalytic amounts of tin. Such a sequence is most effective with Me_3SnCl serving as the tin source. While trimethylstannanes carry the burden of increased toxicity, their use can allow for a 94% reduction of the tin requirement while maintaining good yields (up to 90%) for a variety of Stille products. Furthermore, since one cycle requires the tin to undergo at least four transformations (Scheme 11), each molecule of organostannane is experiencing a minimum of 60 reactions over the course of the hydrostannation/Stille sequence.

Scheme 11. The Catalytic Cycle Employing Me_3SnCl



For optimal efficiency, the hydrostannation/Stille sequence is best run with α-trisubstituted alkynes to avoid regiochemical mixtures during the hydrostannation sequence and beyond. This limitation can be mitigated by the employment of 1-bromoalkynes, which provide a good level of regiocontrol in the hydrostannation step and thereby enable the formation of the Stille product, albeit in more modest yields (50-55%).

Chapter 3. A One-Pot Hydrostannation/Stille Cascade Using the "Sn-F" Approach

3.1. Introduction

Initially, the approach to the Stille "tin" problem was to develop a Pd(0)-catalyzed hydrostannation/Stille coupling catalytic in tin. As described in Chapter 2, this was accomplished via a tin carbonate intermediate. Although the tin requirement was reduced by 94%, the use of Me_3SnCl was still a problem since organotin toxicity and volatility increase as the size of the alkyl group on tin decreases.[14] Trimethyltin halides and the presumed trimethyltin carbonate intermediate are also water soluble,[50] thereby complicating disposal of aqueous phases produced during workup. Furthermore, the reactivity and structure of $(Me_3SnO)CO$ is not well defined,[44] bringing into question its competence within the catalytic cycle.

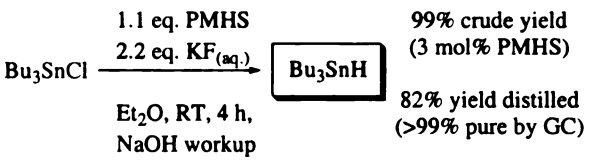
Thus, the next goal was to develop a new but equally efficient way to recycle Me_3SnH that did not involve tin carbonates and/or minimized the hazards and problems associate with trimethylstannanes. Several research groups have investigated reaction methodologies that allow for the in situ formation of tin hydride from cheaper starting materials or the employment of catalytic amounts of tin. An early method developed for the in situ generation of tin hydride involved the reduction of Bu_3SnX by $NaBH_4$.[51] In fact, Corey et al.[52] use sodium borane to successfully recycle the tin halide byproduct of a dehalogenation reaction. More recently, Fu[53] developed several elegant methodologies to perform "classical" reactions of tin hydride with only catalytic amounts of tin by using silanes such as polymethylhydrosiloxane (PMHS) to regenerate the tin. However, both of these methods have drawbacks. For example, the use of $NaBH_4$ is not compatible with functional groups susceptible to borohydride or borane reductions. Additionally, silanes

do not reduce tin halides, and therefore, their utilization has been limited to the recycling of tin alkoxides. Given these limitations, it was believed that a mild method that would allow the recycling of tin halides back to tin hydrides would be highly desirable.

3.2. Use of the Combination of PMHS/KF

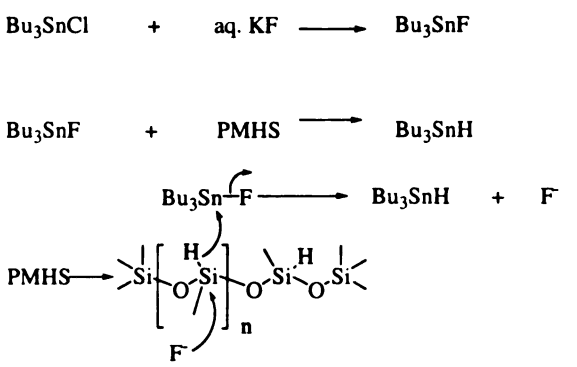
As fluoride had already been shown to heighten the reducing properties of PMHS,[54] it was postulated that PMHS made hypercoordinate by the action of KF[55] could be effective in converting tin halides to tin hydrides. In 1999, Maleczka and Terstiege found that simply stirring an ethereal solution of Bu_3SnCl with 1.1 eq. of PMHS and 2.2 eq. of $KF_{(aq.)}$ for 4 h, followed by NaOH workup, extraction, and removal of ether provided Bu_3SnH in nearly quantitative yield, albeit with approximately 3 mol% of residual PMHS (Scheme 12).[56] Distillation of this "crude" material afforded analytically pure Bu_3SnH in 82% yield.

Scheme 12. Reduction of Bu_3SnCl by PMHS/ KF



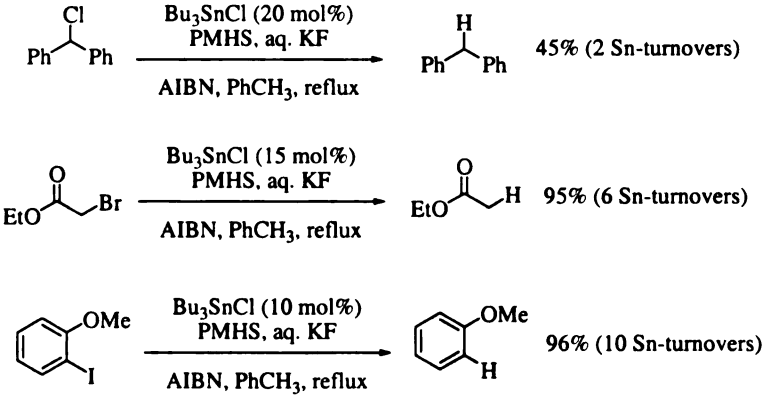
Initially, Bu_3SnCl reacts with $KF_{(aq.)}$ to form Bu_3SnF. With excess F^-, the PMHS silicon can be made hypercoordinate, which allows the hydride to be delivered to the tin. This process can also be complished with Bu_3SnF directly when catalytic amounts of TBAF (initial F^- source) are used (Figure 5).

Figure 5. Mechansim of Bu_3SnH Formation with $PMHS/KF_{(aq.)}$



The combination of Bu_3SnCl, KF(aq.), and PMHS performed well in "classical" tin hydride mediated free-radical dehalogenations (Scheme 13). These experiments demonstrated the feasibility of using catalytic quantities of tin.

Scheme 13. Free-Radical Dehalogenations Catalyzed by Tin



Importantly, organic halides were not reduced by the reagent combination $PMHS/KF_{(aq.)}$, since the coupling partner in a Stille coupling is an organic halide. Apparently, the hyper-coordinate silane alone requires either more polar solvents or anhydrous conditions to serve as an effective reducing agent. Having shown that Bu_3SnH could be generated and used in the same pot, application to palladium-catalyzed hydrostannations was explored.

3.3. Transition Metal Catalyzed Hydrostannations Utilizing $Bu_3SnCl/PMHS/KF_{(aq.)}$

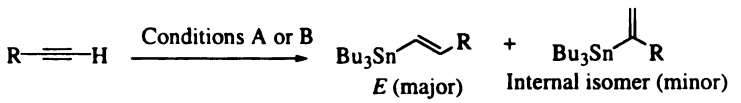
3.3.1. Initial Attempt at a One-Pot Hydrostannation/Stille

Based on the ability to carry out multiple transformations in one pot with in situ generated Bu_3SnH, and having established the feasibility of a catalytic one-pot hydrostannation/Stille coupling protocol (described in Chapter 2), it was decide to apply this combination of reagents to a catalytic, one-pot hydrostannation/Stille sequence. However, given the transient nature of the vinylstannanes, the overall efficiency of employing $Bu_3SnCl/KF_{(aq.)}/PMHS$ as an in situ source of Bu_3SnH in preparative[57] hydrostannation reactions was in question.

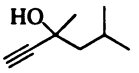
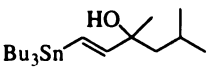
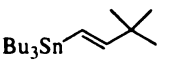
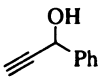
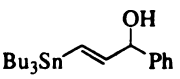
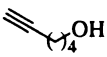
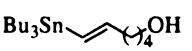
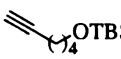
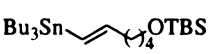
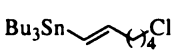
3.3.2. Palladium Catalyzed Hydrostannations Using $R_3SnCl/PMHS/KF_{(aq.)}$

Attention was turned to gaining a further understanding of the application of siloxane reductions of tin halides to the in situ hydrostannation of alkynes, in particular palladium-catalyzed hydrostannations. Initially when several alkynes were treated with Bu_3SnCl, $KF_{(aq.)}$, and PMHS in THF with a palladium catalyst, the results were inconsistent. The desired vinylstannanes were formed but in low yield and purity. After some experimentation, it was found that by using Et_2O as the solvent and including a catalytic amount of tetrabutylammonium fluoride or iodide (TBAF or TBAI)[58] in the reaction, the desired vinylstannanes were formed in good yields and with standard regiochemical outcomes (Scheme 14).[59]

Scheme 14. Pd Catalyzed Hydrostannations Using $Bu_3SnCl/KF_{(aq.)}/PMHS$



Conditions A	Conditions B
Bu_3SnCl, PMHS, $KF_{(aq.)}$ TBAF or TBAI (cat.) cat. $Pd_2Cl_2(PPh_3)_2$, Et_2O	Bu_3SnF, PMHS TBAF (cat.) cat. $Pd_2Cl_2(PPh_3)_2$, Et_2O

Entry	Alkyne		Product	Yields Conditions A	Yields Conditions B
1		**12**		66% *E*/int. (24:1) **16a/16b**	67% *E*/int. (21:1) **16a16b**
2		**4**		59% *E*/int. (>99:1) **49a/49b**	67% *E*/int. (>99:1) **49a/49b**
3		**28**		81% *E*/int. (9:1) **50a50b**	
4		**51**		72% *E*/int. (1.4:1) **52a/52b**	77% *E*/int. (1.4:1) **52a/52b**
5		**53**		51% *E*/int. (1:1) **54a/54b**	53% *E*/int. (1.3:1) **54a/54b**
6		**55**		84% *E*/int. (1.4:1) **56a/56b**	78% *E*/int. (1.4:1) **56a/56b**

As can be seen from Scheme 14, potentially reactive groups such as silyl ethers and alkyl halides remained intact throughout the reaction sequence. No evidence of palladium-catalyzed hydrosilylation by PMHS was observed.[60] Although the results of hydrostannations with Conditions A or B proved similar to those carried out with Bu_3SnH directly, there were a few differences. For example, palladium-catalyzed hydrostannations using Bu_3SnH directly were often complicated by the palladium promoted conversion of Bu_3SnH into Bu_3Sn-$SnBu_3$.[61] Under Conditions A, the vinylstannanes were accompanied by little if any tin dimer. Presumably, the rates of tin hydride formation and hydrostannation were such that the relative concentration of tin hydride was always low, thus minimizing dimer formation. These phenomena could be of particular practical advantage when vinylstannanes are desired in quantities that

dissu

chro

inclu

wate

anhy

hydr

vinyl

surpr

leadi

form

that

avail

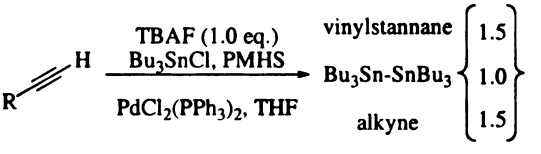
Bu_3S

allow

dissuade their distillation and when they are nonpolar enough to make the chromatographic separation from the dimer difficult.

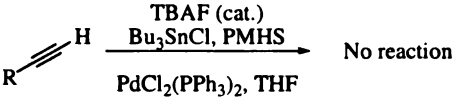
An obvious difference between this method and traditional hydrostannations is the inclusion of water. Although though there are advantages to running organic reactions in water,[62] the need for anhydrous conditions still exists. The use of CsF or KF in anhydrous ether both proved unsuccessful.

Scheme 15. Use of 1.0 eq. of TBAF



The use of 1 eq. of TBAF resulted in the formation of Bu_3SnH, but the subsequent hydrostannation did not go to completion, as the reaction afforded a 1:1 ratio of vinylstannane and alkyne alone with $Bu_3Sn\text{-}SnBu_3$ (Scheme 15). This result was not surprising since tetrabutylammonium salts are known to greatly activate the Sn-H bond, leading to the evolution of H_2 and $Bu_3Sn\text{-}SnBu_3$.[63] Since tin dimer and product were both formed, TBAF must serve to activate PMHS and generate Bu_3SnH; however, it was clear that the TBAF concentration would have to be minimized in order for Bu_3SnH to be available for the hydrostannation. When an alkyne was treated with catalytic TBAF, Bu_3SnCl and PMHS, in the absence of KF, afforded none of the desired vinylstannane.

Scheme 16. Use of a Catalytic Amount of TBAF



It was reasoned that TBAF was reacting with the Sn-Cl to form Sn-F, thus not allowing activation of the PMHS.[64] If this were the case, then the use of premade

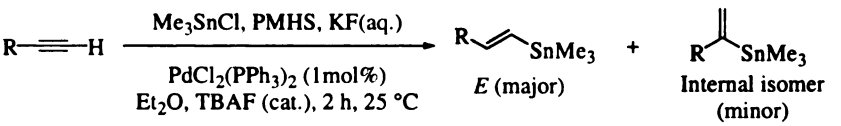
Bu_3SnF as the tin source, in combination with PMHS and catalytic TBAF, the necessary fluoride anion would be regenerated upon the PMHS conversion of Bu_3SnF into Bu_3SnH. As shown in Scheme 14, Conditions B gave the desired vinylstannanes in excellent yields and with little or no tin dimer formation.[65]

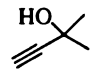
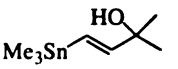
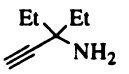
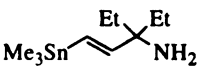
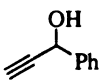
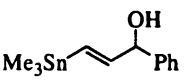
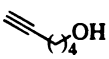
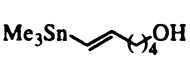
As mentioned earlier, the use of a NaOH workup was helpful in aiding purification. This workup can be problematic when base sensitive functional groups are present (i.e. OAc). However, without a NaOH workup, a "plastic-like" substance forms upon concentration of the reaction.[66] On small scale (1 mmol) to large scale (500 mmol), the use of chromatography is usually sufficient to remove this substance. The reaction should not be concentrated to dryness, since the plastic-like substance can be difficult to redissolve. Typically, the reaction was concentrated to about 1/10 the original volume, then the substance was loaded onto a SiO_2 column as usual. First, the column was eluted with hexanes, and then with the desired solvent system to obtain the pure product. Although ~1.2 times more silica gel may be required than normal, the products obtained are analytically pure.[67] Another approach is to concentrate the reaction to 1/10 its original volume and then dissolve in benzene. The benzene solution is then placed in a freezer overnight (~8 h). The PMHS by-product can be simply filtered off when allowed to warm to 25 °C.

Application of this methodology to other trialkyltin hydrides, namely trimethyltin hydride, was also explored. Trimethyltin hydride is extremely toxic and volatile (59 °C at 760 mmHg), making it quite dangerous to handle.[68] It is preferred to generate this reagent in situ. Me_3SnH has been traditionally synthesized via the reaction of $LiAlH_4$ and Me_3SnCl.[68a] The use of $(Me_3Sn)_2O$ with PMHS has been limited since

bis(trimethyltin) oxide is not commercially available. Since the substrate tolerance of this method is broad, use of Me_3SnCl in combination with PMHS/$KF_{(aq.)}$ would be an ideal way to utilize Me_3SnH.[69] As shown in Scheme 17, the corresponding trimethylstannanes were formed via palladium catalyzed hydrostannations with Me_3SnH generated in situ from the reaction of Me_3SnCl, $KF_{(aq.)}$, and PMHS.

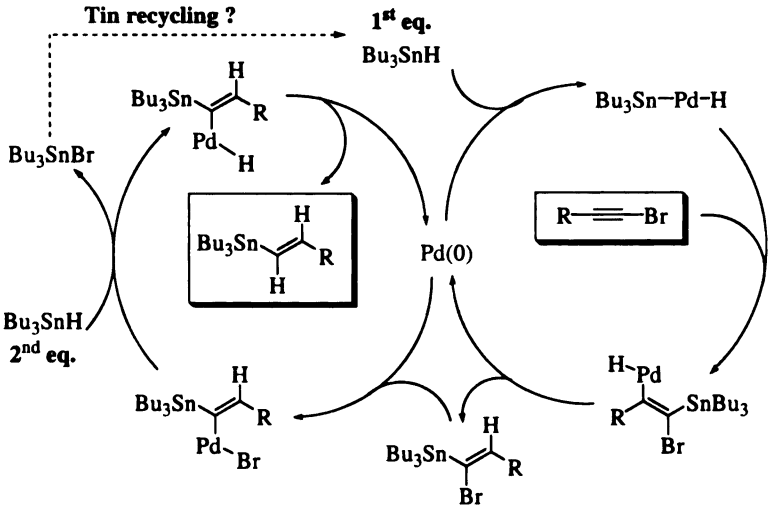
Scheme 17. Generation and Utilization of Me_3SnH



Entry	Alkyne		Product	Yields
1		**1**		85% *E*/int. (33:1) **43a/43b**
2		**14**		75% *E*/int. (40:1) **46a/46b**
3		**28**		81% *E*/int. (9:1) **57a/57b**
4		**51**		57% *E*/int. (1.2:1) **48a/48b**

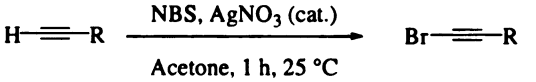
As can be seen from Scheme 14 and Scheme 17, the regiochemical outcome for α-monosubstituted alkynes is poor.[70] In order to better utilize these alkynes, the regioselectivity needed to be better, as the isomers can, at times, be difficult to separate. As mentioned earlier, Guibé[20a] and Pattenden[71] have shown that, through the employment of 1-bromoalkynes instead of terminal alkynes, the regioselectivity of the palladium-catalyzed hydrostannation could be greatly improved in favor of the *E*-vinylstannanes. This transformation typically required the use of at least 2 eq. of tin hydride; one for incorporation into the product and the second to effect the reduction of the intermediate vinyl bromide, forming 1 eq. of trialkyltin bromide in the process (Figure 6).

Figure 6. Mechanism of the Pd-Catalyzed Hydrostannation of 1-Bromoalkynes



Investigation into the feasibility of recycling the organotin bromide with the use of the KF/PMHS protocol, thus requiring only 1 eq. of tin for the reaction to go to completion, was undertaken.

Scheme 18. Preparation of 1-Bromoalkynes

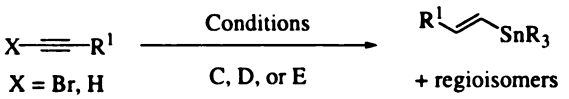


Entry	Alkyne	Product	Yield
1	≡–$(CH_2)_4OH$ **51**	Br–≡–$(CH_2)_4OH$	**39**: 95%
2	≡–$(CH_2)_4CH_3$ **58**	Br–≡–$(CH_2)_4CH_3$	**59**: 95%
3	≡–$(CH_2)_4OTHP$ **60**	Br–≡–$(CH_2)_4OTHP$	**41**: 97%

Several 1-bromoalkynes were prepared via Pattenden's procedure (Scheme 18).[71] These compounds were then subjected to the palladium catalyzed hydrostannation protocol, but with only 1.2 eq. of Bu_3SnCl or Me_3SnCl. Indeed, this method proved successful and the vinylstannanes were formed with substoichiometric amounts of tin hydride (Conditions D, Scheme 19). As is shown in Scheme 19, the yields and isomeric ratios using the KF/PMHS protocol proved even higher than those obtained in control experiments (Conditions C, Scheme 19)[72] using 2.2 eq. of Bu_3SnH. Further

simplification of this transformation was accomplished by forming and hydrostannating the 1-bromoalkyne without isolation (Conditions E, Scheme 19). This one pot protocol proceeded with little loss of regiocontrol, but with a modest reduction in yields as compared with the stepwise approach.

Scheme 19. Hydrostannation of 1-Bromoalkynes



Conditions C	Conditions D	Conditions E
X = Br 2.2 eq. Bu_3SnH $PdCl_2(PPh_3)_2$ THF	X = Br 1.2 eq. R_3SnCl PMHS, $KF_{(aq.)}$ $PdCl_2(PPh_3)_2$ Et_2O	X = H NBS, $AgNO_3$, acetone; then conditions D in pentane

Entry	Product	Conditions C	Conditions D	Conditions E
1	Bu_3Sn⟋⟍$(CH_2)_4OH$	54% *E*/int./*Z* (11:1:1) **52a/52b/52c**	51% *E*/int./*Z* (18:1:1) **52a/52b/52c**	42% *E*/int./*Z* (33:0:1) **52a/52b/52c**
2	Bu_3Sn⟋⟍$(CH_2)_4CH_3$	50% *E*/int./*Z* (8:1:1) **61a/61b/61c**	74% *E*/int./*Z* (18:1:1) **61a/61b/61c**	48% *E*/int./*Z* (20:0:1) **61a/61b/61c**
3	Bu_3Sn⟋⟍$(CH_2)_4OTHP$	69% *E*/int./*Z* (8:1:1) **62a/62b/62c**	63% *E*/int./*Z* (17:2:1) **62a/62b/62c**	45% *E*/int./*Z* (17:0:1) **62a/62b/62c**

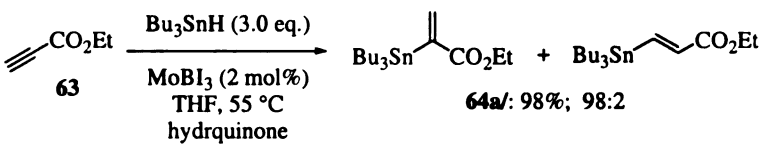
3.4. Use of Other Transition Metal Catalysts

3.4.1. Use of Molybdenum as a Hydrostannation Catalyst

As mentioned above, the use of palladium results in the formation of *E* (distal) and internal (proximal) isomers. The *Z* isomer is usually obtained via a free radical pathway.[73] The regioselectivity is dependent on the α-substitution pattern of the alkyne. When α-trisubstituted alkynes are used, the hydrostannation gives only the distal tin along with trace amounts of the proximal isomer. In general, once the steric bulk about the propargylic center begins to diminish, so does the regioselectivity. In 1990 Guibé[20a] reported on the palladium and molybdenum catalyzed hydrostannation reactions. In that

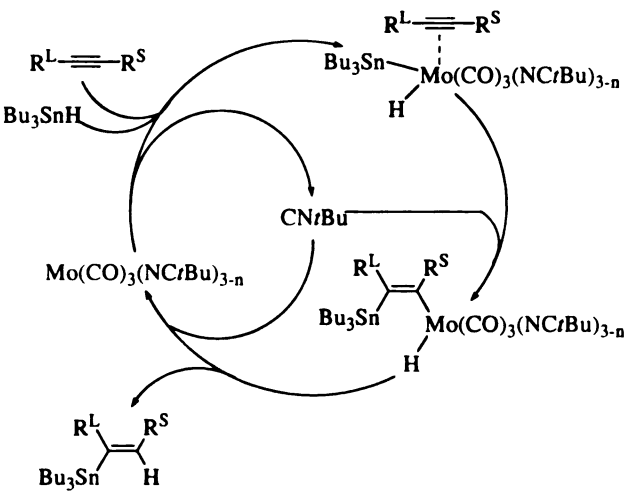
report, the authors found that $MoBr(allyl)(CO)_2(CH_3CN)_2$ was suitable for hydrostannation of propargylic alcohol derivatives, but the regioselectivity was poor. In order for Mo catalyzed hydrostannations to find application in synthesis, a more selective catalyst was needed. Kazmaier[74] has recently reported on a highly regioselective Mo catalyst, $Mo(CO)_3(CNtBu)_3$ ($MoBI_3$).

Scheme 20. Kazmaier's Use of $MoBI_3$



This catalyst showed preference for the proximal isomer (>95:5 proximal/distal) when applied to propargyl alcohol derivatives. In all the examples used, oxygen functionality (ester or ether) was present. The authors showed no examples of non-oxygenated alkynes. They reason the regioselectivity was due to addition of the sterically more demanding molybdenum fragment to the less hindered side of the alkyne. The proposed mechanism is shown in Figure 7. Due to interest in metal catalyzed hydrostannations, the examination of using $MoBI_3$ under our PMHS/KF conditions was examined.

Figure 7. Mechanism of $MoBI_3$ Catalyzed Hydrostannations

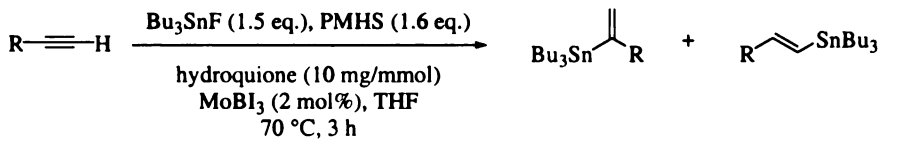


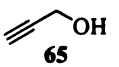
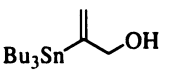
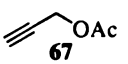
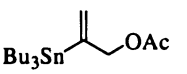
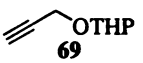
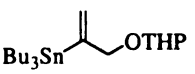
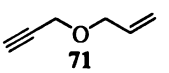
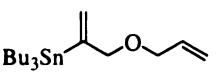
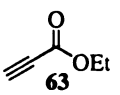
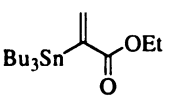
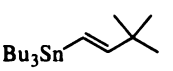
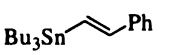
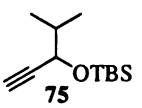
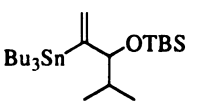
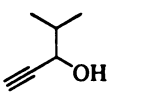
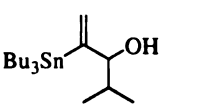
Initially, the combination of Bu_3SnCl/KF(aq.)/PMHS was used with $MoBI_3$ as the catalyst. With this system, results were inconsistent. It was thought that the presence of water could be decomposing the active catalyst. Thus, anhydrous conditions, Bu_3SnF/PMHS, were explored. Experimentally, when an alkyne was treated with 1.5 eq. of Bu_3SnF, 1.6 eq. of PMHS, hydroquinone (cat.), TBAF (1 drop) and 2 mol% $MoBI_3$ in THF at 70 °C, the corresponding vinylstannane was obtained (Scheme 21). As Kazmaier observed, the use of propargyl alcohol or propiolate derivatives provided the proximal isomer as the major product. One potential advantage of this protocol is that only 1.5 eq. of Bu_3SnF are used whereas Kazmaier was using 3 eq. Bu_3SnH. The use of catalytic quantities of hydroquinone was added to suppress any free-radical processes. All of our reactions proceeded faster (<3 h) than reported by Kazmaier (12 h). The regioselectivities were the same as reported by Kazmaier.

Kazmaier aruged that sterics dictated the regioselectivity, but bulky, non-oxo propargylic substituted alkynes were not attempted. When *tert*-butylacetylene (**4**) (entry 6, Scheme 21) and phenyl acetylene (**73**) (entry 7, Scheme 21) were subjected to the Bu_3SnF protocol, the distal (*E*) was obtained as the major isomer. When a α,α-

disubstituted alkyne (entry 8, Scheme 21) was subjected to the protocol, only a 3:1 (Int:*E*) ratio was obtained. Obviously, more experiments are needed to clarify the regiochemical outcome of this process.

Scheme 21. $MoBI_3$ Catalyzed Hydrostannations with Bu_3SnF/PMHS



Entry	Alkyne	Product	Yields
1	 **65**		90% Int/*E* (5:1) **66b/66a**
2	 **67**		73% Int/*E* (99:1) **68b/68a**
3	 **69**		85% Int/*E* (95:5) **70b/70a**
4	 **71**		75% Int/*E* (95:5) **72b/72a**
5	 **63**		92% Int/*E* (95:5) **64b/64a**
6	 **4**		75% Int/*E* (1:99) **49b/49a**
7	 **73**		77% Int/*E* (1:5) **74b/74a**
8	 **75**		62% Int/*E* (3:1) **76b/76a**
9	 **77**		92% Int/*E* (2:1) **78b/78a**

3.4.2. Use of Other Transition Metals

In 1988, Kikukawa[75] and co-workers showed that regioselective hydrostannations of terminal acetylenes could be performed with transition metals other than Pd or Mo. Kikukawa found that Rh complexes catalyzed the hydrostannation of acetylenes to give the internal isomer regioselectively. A variety of metals (Ru, Ni, Co, Pt) surveyed by

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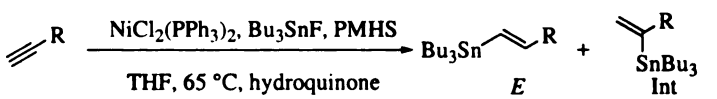
Kikukawa were also active, but with less selectivity than Rh. We sought to establish if the combination of $Bu_3SnCl/KF_{(aq.)}$/PMHS for the in situ generation of Bu_3SnH would be useful with these other transition metals.

$NiCl_2(PPh_3)_2$ was studied. This catalyst produced the corresponding vinylstannanes in good to excellent yields (Scheme 22).

Scheme 22. Use of $NiCl_2(PPh_3)_2$

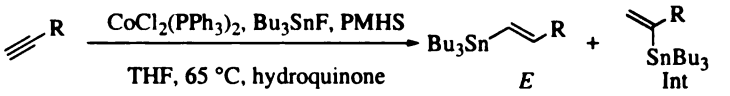


Entry	Alkyne	Product	
1	$\equiv$—CH_2OH **65**	Bu_3Sn OH	**66**: 73% *E*:Int:*Z* = 2.35:0:1
2	$\equiv$—CH_2OTHP **69**	OTHP, $SnBu_3$	**70**: 55% *E*:Int = 1:3
3	$\equiv$—C(Me)(Ph)OH **8**	OH, Ph, Bu_3Sn	**19**: 86% *E*:Int:*Z* = 2/1/0
4	$\equiv$—C(Ph)OH **28**	Ph, Bu_3Sn, OH	**50**: 92% *E*:Int:*Z* = 1:3.5:0
5	$\equiv$—$C(CH_3)_3$ **4**	Bu_3Sn	**49**: 83% *E*:Int:*Z* = 22:1:0

The selectivity for a propargylic derivative favored the internal isomer, as was the case under palladium catalysis. When the oxygen functionality was removed, the selectivity switched to favor the *E*-isomer (entry 5, Scheme 22).

The use of $CoCl_2(PPh_3)_2$ met with varying success. When **69** was used, the reaction did not occur. Using alkyne **76** produced vinylstannane **80** in 38% yield with a 2.6:0:2 ratio (*E*:Int:*Z*) (Scheme 23). Use of *tert*-butylacetylene allowed for the formation of the *E*-isomer exclusively in reasonable yield.

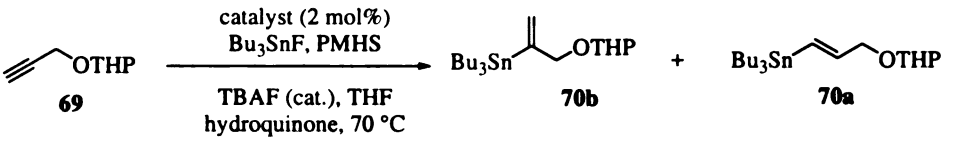
Scheme 23. Use of $CoCl_2(PPh_3)_2$ as a Catalyst



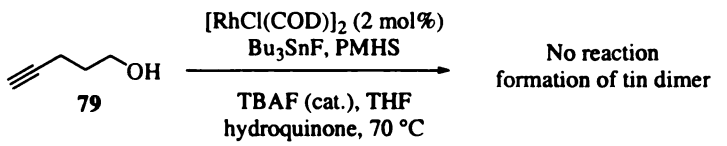
Entry	Alkyne	Product	
1	≡—CH_2OTHP **69**	No reaction	
2	≡—$(CH_2)_3OH$ **79**	Bu_3Sn OH 3	**80**: 38% *E*:Int:*Z* = 1.3:0:1
5	≡—$C(CH_3)_3$ **4**	Bu_3Sn	**49**: 71% *E*:Int:*Z* = 99:1:0

As noted above, Kikukawa states that the Rh complexes gave high regioselectivities. Using alkyne **69** and $[RhCl(COD)]_2$ afforded a 92% yield of **70**, which was comprised of a 1:2:0 *E*:Int:*Z* mixture. The use of hydroquinone was also used by Kikukawa. Other catalyst like $RhCl(CO)(PPh_3)_2$ and $PtCl_2(PPh_3)_2$ produced low yields and were not very selective (Scheme 24). Work to show the effectiveness of our method of Bu_3SnH generation with these and other catalysts are ongoing.

Scheme 24. Use of other transition metals



Entry	Catalyst	*E*:int:*Z*	Yield
1	$[ClRh(COD)]_2$	1:2:0	92%
2	$RhCl(CO)(PPh_3)_2$	1:1.4:0.17	18%
3	$RuCl_2(PPh_3)_4$	1.7:1.0:0.7	24%

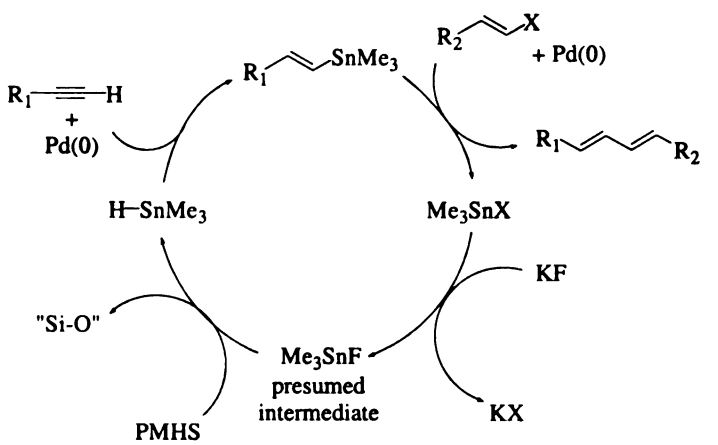


3.5. The "Sn-F" Route

3.5.1. Introduction

Organotin fluorides are nonvolatile aggregated solids, which are not easily absorbed through the skin and are sparingly soluble in most solvents.[76] As such, the risks posed by organotin fluorides are less than those of other organostannanes. Indeed, tin mediated reactions are often subjected to a fluoride workup to convert the organostannane waste into relatively benign and easily filterable organotin fluorides.[77] In 1986, Scott and Stille showed that the presence of CsF during the efficient cross coupling of organostannanes with vinyl triflates allowed for 80% of the tin waste to be removed by filtration. As described above, a Pd-catalyzed hydrostannation via R_3SnH generated in situ by reduction of R_3SnF or R_3SnCl with hyper-coordinate polymethylhydrosiloxane (PMHS + KF) has been successfully developed. Based on these precedents, it was considered that a "Sn-F" approach to Stille reactions catalytic in tin, such as that illustrated in (Figure 8), would be possible.

Figure 8. The "Sn-F" Catalytic Cycle



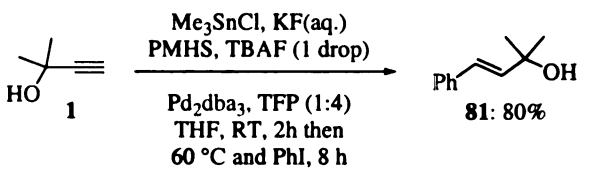
A R_3SnF catalyzed sequence would lessen the aforementioned problems associated with use of trimethylstannanes in the "Sn-O" approach. Furthermore, fluoride

activation of vinylstannanes could facilitate their coupling,[12,13b] therefore; exploration as to whether fluoride would positively impact reaction effectiveness was sought.

3.5.2. Initial Work

As noted earlier, the feasibility of carrying out a one-pot hydrostannation/Stille coupling has been proven effective by our group and Pattenden. At this time, a one-pot hydrostannation/Stille coupling was attempted to test the compatability of the combination of PMHS/KF with the sequential one pot reaction. To prove that both reactions could work in one pot, the hydrostannation was performed, and when complete by TLC, the desired electrophile was added. As shown in Scheme 25, this one pot protocol proved effective, affording the Stille product in 80% yield.

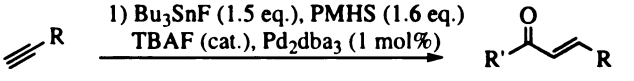
Scheme 25. One-Pot Hydrostannation/Stille Stoichiometric in Tin

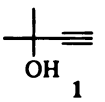
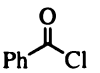
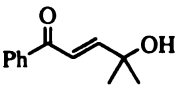
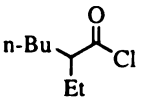
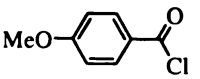
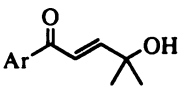
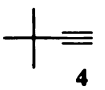
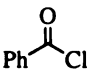
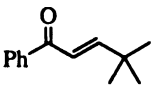
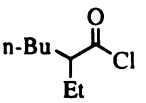
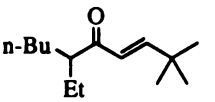
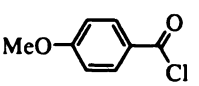
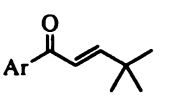
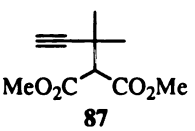
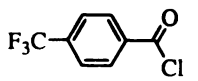
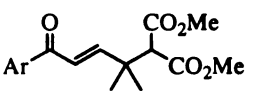
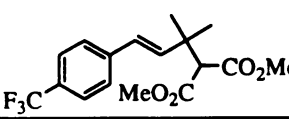


An advantage to a stoichiometric one-pot hydrostannation/Stille is the elimination of vinylstannane isolation. At times, some substrates can prove to be difficult to isolate (decomposition, volatility, etc.) The ability to form and then react that substrate in one-pot would be of great benefit. This one-pot protocol was further extended to acid chlorides,[2c,78] since their participation with the reaction mixture was in question. The reagents themselves or a combination thereof could prove detrimental to the survival of the acid chloride. Since acid chlorides are readily hydrolyzed in the presence of water, $Bu_3SnF/PMHS/TBAF_{(cat.)}$ (Conditions B) were chosen. As shown in Scheme 26, appropriate conditions were found that provided high yields of the desired enones. The presence of a tertiary alcohol did not affect the outcome of the reaction when aryl acid

chlorides were used. A malonate derivative also participated in the reaction without incident. The appearance of decarbonylated material was seen in one example (Scheme 26, entry 7). It has been shown that this can occur in Stille couplings with acid chlorides, as the acyl-palladium catalytic intermediate, at times, can decarbonylated.[78] Stille has shown that the reaction can be outfitted with a balloon of CO (1 atm) to suppress the decarbonylation.

Scheme 26. One-Pot Stoichiometric Hydrostannation/Stille Using Acid Chlorides

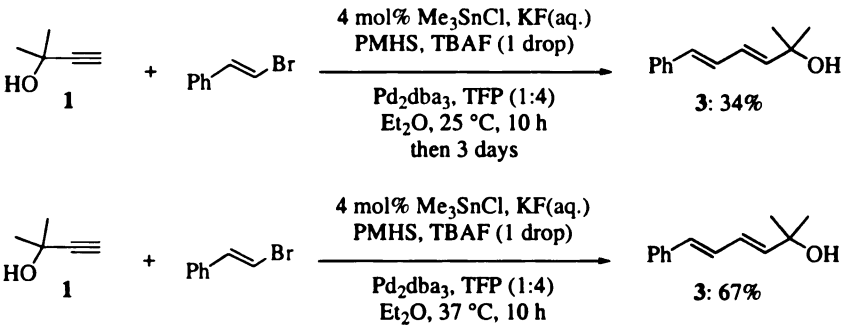


Entry	Alkyne	Acid Chloride	Time	Product	
1	 **1**		6 h		**82**: 77%
2	**1**		24 h	recovered vinylstannane	
3	**1**		5 h		**83**: 93%
4	 **4**		6 h		**84**: 96%
5	**4**		7 h		**85**: 95%
6	**4**		6 h		**86**: 91%
7	 **87**		2 h	 + 	**88**: 74% **89**: 16%

3.5.3. First Attempts at a Catalytic Variant

Having accomplished a stoichiometric one-pot hydrostannation/Stille with an aryl halide, a catalytic in tin variant was attempted. PMHS and **1** were added as a solution in Et_2O via a syringe pump over 15 h to a solution of all other reagents. When the addition was complete, the reaction was allowed to stir at 25 °C for three days with TLC monitoring. After workup, chromatographic purification afforded **3** in 34% yield. Performing the same reaction at 37 °C for 10 h afforded the desired cross couple product in 67% yield (Scheme 27).

Scheme 27. Catalytic Stille with the Sn-F Route

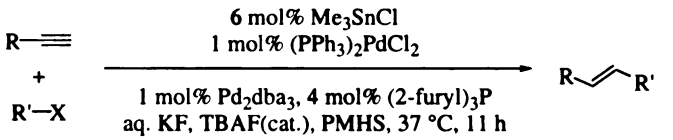


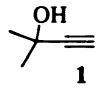
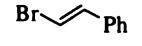
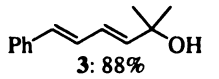
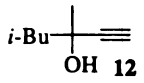
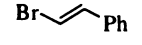
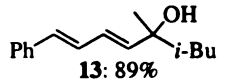
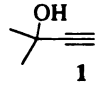
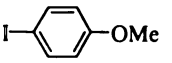
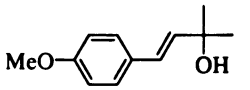
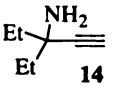
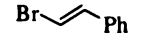
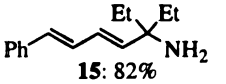
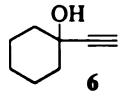
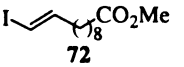
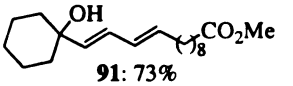
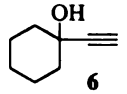
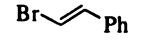
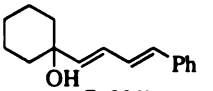
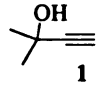
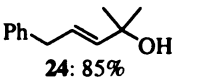
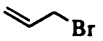
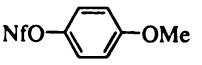
3.5.4. The Catalytic Sn-F Protocol

After experimentation in conjunction with the "Sn-O" route, the following catalyst system was found to be the most efficient: 1 mol% $(PPh_3)_2PdCl_2$, 1 mol% Pd_2dba_3, and 4 mol% TFP. Beyond the key substitution of fluoride for Na_2CO_3, this new approach required only minor alterations to our original protocol. The optimal method for the "Sn-F" route is as follows: addition of all necessary reagents in Et_2O and then addition of a solution of alkyne and PMHS in Et_2O over ~10 h (Scheme 27). Adding only the electrophile drop-wise resulted in diminished yields, presumably due to its reduction by PMHS/KF. Control experiments have shown that organic halides can be readily reduced by the combination of PMHS/KF and a Pd(0) catalyst.[79] The optimal

amount of tin required was determined to be 6 mol%. It was pleasing to find that, compared to the "Sn-O" method, the "Sn-F" approach afforded the Stille products in similar yields but in approximately 25% less time (10 vs. 15 h) (Table 7).

Table 7. The "Sn-F" Approach Using 6 mol% Me_3SnCl

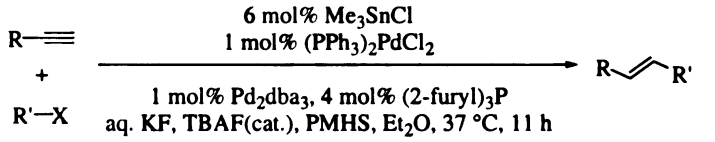


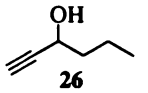
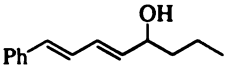
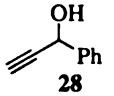
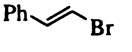
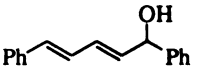
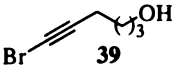
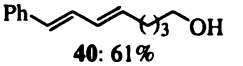
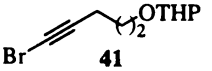
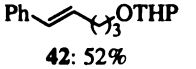
Entry	Alkyne	R'—X	Product
1	 **1**		 **3**: 88%
2	 **12**		 **13**: 89%
3	 **1**		 **90**: 78%
4	 **14**		 **15**: 82%
5	 **6**	 **72**	 **91**: 73%
6	 **6**		 **7**: 90%
7	 **1**		 **24**: 85%
8	**1**		No Stille Product
9	**1**	Me—I	No Stille Product
10	**1**	 **25**	No Stille Product

The "Sn-F" and "Sn-O" approaches showed similar substrate tolerance. Reaction efficiency was highly influenced by the regioselectivity of the Pd(0) catalyzed hydrostannation sequence. Alkynes that were trisubstituted at the propargylic position

worked better than those that were disubstituted (Table 8), while unhindered alkynes required the regiochemical assistance of a 1-bromo group (Table 8), as discussed above. As for electrophiles, vinyl, aryl, and benzyl halides were amendable to the new conditions, while allyl bromide, methyl iodide and an aryl nonaflate were not.

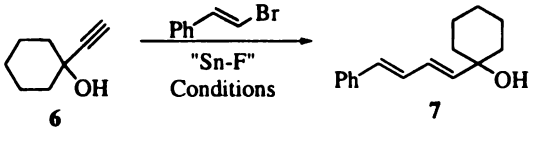
Table 8. Use of α,α-Disubstituted and 1-Bromoalkynes



Entry	Alkyne	R'—X	Product
1	 **26**		 **27**: 60%
2	 **28**		 **29**: 68%
3	 **39**		 **40**: 61%
4	 **41**	Ph—I	 **42**: 52%

Results of tin loading experiments were similar to those obtained during the study of the "Sn-O" method (Scheme 10). Dropping below 6 mol% of Me_3SnCl resulted in substantial yield reduction, while higher loads of tin (up to 20 mol%) offered little advantage (Scheme 28).

Scheme 28. Tin Loading in the "Sn-F" Approach



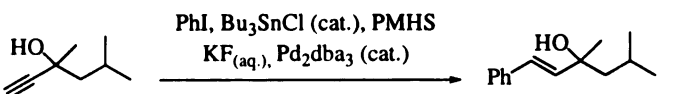
6 **7**

Entry	Me_3SnCl (mol%)	Sn turnovers	Yield
1	6	15	88%
2	4	16	63%
3	2	19	39%
4	1	19	19%

When 3,5-dimethyl-1-hexyn-3-ol was reacted with $KF_{(aq.)}$, PMHS, and catalytic amounts of Bu_3SnCl in the presence of catalytic Pd_2dba_3/TFP, and iodobenzene, a

palladium catalyzed hydrostannation took place, followed by a subsequent Stille coupling of the in situ formed vinylstannane.[56,80] Again, the use of Bu_3SnCl failed to produce any efficient results.

Scheme 29. Use of Bu_3SnCl with the Sn-F Protocol



12 18

Entry	Bu_3SnCl (mol%)	Pd (mol%)	Sn-turnovers	Yield
1	10	1.0	2.0	19
2	6	0.2	2.5	15
3	6	0.4	3.0	21

As a control, the corresponding trimethylvinylstannanes were prepared and isolated and then subjected to a traditional Stille coupling ($Pd_2dba_3/AsPh_3$). As compared to the traditional approach, the catalytic process performed as well or better (Table 6).

3.5.5. Mechanistic Insight

Experiments were also carried out to further explore the proposed mechanism. The reaction sequence was equally effective starting with 6 mol% Me_3SnF, the corresponding vinylstannane **43a**, or Me_3SnH. Furthermore, stoichiometric experiments followed by ^1H NMR indicated that the reduction of Me_3SnCl (δ 0.60 ppm in CD_3OD) to Me_3SnH (δ 0.14 ppm) proceeds through Me_3SnF (δ 0.45 ppm). Thus, while the presence of multiple aggregates of Me_3SnF, $[Me_3SnF(Cl)]K$, or related "ate" intermediates has not been completely ruled out, it was thought that the spectroscopic and chemical data suggest the sequence to be proceeding via a cycle like that illustrated in Figure 8.

Since organotin fluorides are known to be sparingly soluble in any media, the next logical step would be to determine where the tin residue resides at the end of the reaction. At the end of the reaction, the organic and aqueous phases were separated and analyzed

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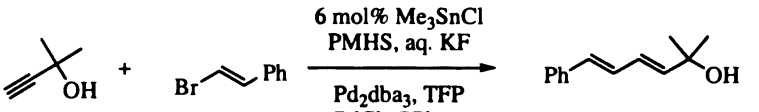
by ICP to determine the tin content. It was found that most of tin resided in the aqueous phase. The organic phase showed very small amounts of tin residue. When the solutions were filtered, ~20% of Me_3SnF could be recovered (Figure 9). The product, after column chromatography, was analyzed by ICP and showed no tin present.

Figure 9. ICP Results

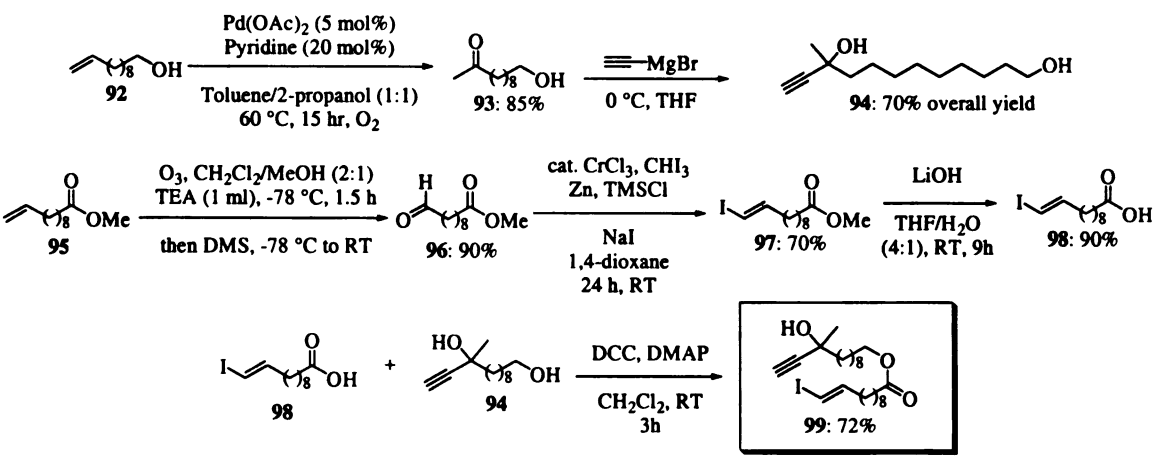


ICP Analysis	Aqueous Phase	Organic Phase	Solid	Total recovered	Initial Amount
Filtered	18 mg	0.12 mg	5 mg	23 mg	24 mg
Not filtered	22 mg	1.0 mg		23 mg	24 mg

3.6. Intramolecular One-Pot Hydrostannation/Stille Coupling with Catalytic Tin

Over the past decade, the intramolecular Stille reaction has emerged as a mild and useful way to form various sized rings.[81] It was pondered if either of our Stille protocols could be modified to perform a one-pot hydrostannation/*intramolecular* Stille coupling. Initially, an alkyne-vinyl iodide was chosen as the target, since vinylstannanes and vinyl iodides can couple effectively. The synthesis of **99** is shown in Scheme 30.

Scheme 30. Synthesis of Alkyne-Vinyl Iodide **99**

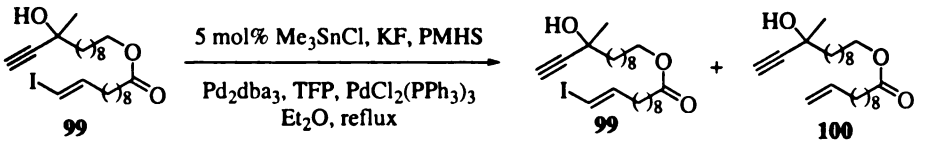


The synthesis began with a Pd(II)-catalyzed oxidation[82] of **92** using molecular oxygen to afford keto-alcohol **93** in 85% yield. A 1M keto-alcohol **93** solution in THF was then added dropwise to ethynylmagnesium bromide (2.5 eq.) in THF at 0 °C to afford alkynol **94** in 85% yield (70% from **93**). Ozonolysis of **95** followed by workup with DMS produced the desired aldehyde **96** in 90% yield. Aldehyde **96** was then subjected to a Takai iodoolefination using *catalytic* $CrCl_3$[83] to afford (*E*)-vinyl iodide **97** in 70% yield. Normally this transformation requires the use of excess $CrCl_2$, which is extremely air sensitive and expensive. This protocol allows the Cr(III) to be reduced to Cr(II) by Zn metal. At first, this reaction proved troublesome. Following the published procedure for the same substrate at an identical scale, inconsistent results were obtained. Instead of a reaction time of 12 h, 25 h and a large excess of Zn were required to get reproducible results. The ester was then saponified with LiOH to give acid **98** in 90% yield. The final step was a DCC-mediated coupling of acid **98** and alkynol **94** to produce alkyne-vinyl iodide **99** in 72% yield.

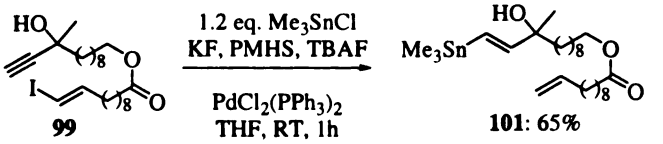
With **99** in hand, an intramolecular one-pot hydrostannation/Stille coupling with the catalytic "Sn-F" route was attempted (Scheme 31). Initially, only starting material and reduced vinyl iodide **100** were obtained. Subjecting **99** to the PMHS/KF hydrostannation protocol produced the vinylstannane **101**, but the iodide was reduced. Since the hydrostannation reduced the electrophile, a change in substrates was necessary.

Scheme 31. Attempted Intramolecular One-Pot with **99**

Attempted One-pot hydrostannation/*intramolecular* Stille using catalytic Me_3SnCl

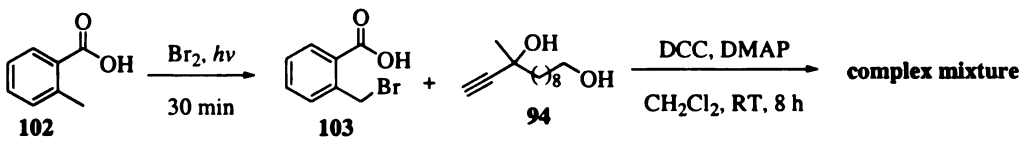


Hydrostannation of 102 using the PMHS/KF protocol



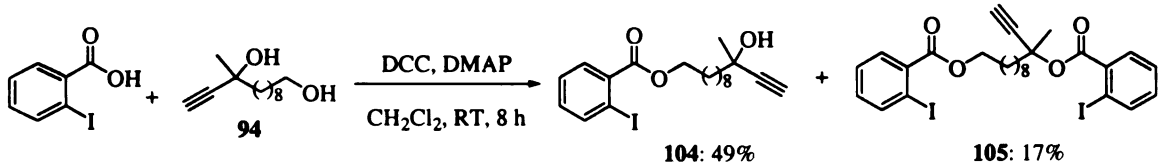
An electrophile was needed that would not undergo reduction during the hydrostannation portion of the sequence. The benzyl halides performed well in the one-pot protocols, thus, a benzyl halide/alkyne was sought. The synthesis is outlined in Scheme 32. Unfortunately, the DCC coupling of **103** and alkyne **94** produced a complex mixture of unidentifiable products.

Scheme 32. Attempted Synthesis of a Benzyl Bromide/Alkyne



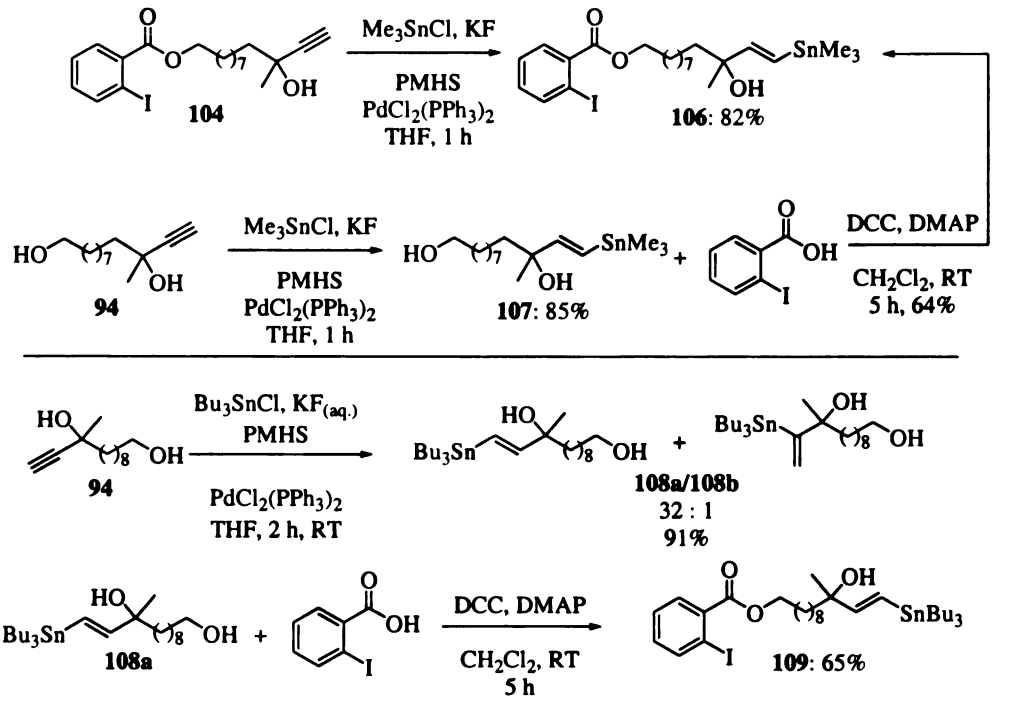
It was then decided to synthesize alkyne-aryl iodide **104** since Grigg[84] has shown that a hydrostannation of an alkyne can be performed in the presence of an aryl iodide. Alkyne-aryl iodide **104** was obtained via a DCC coupling between *o*-iodobenzoic acid and alkyne **94** in 42% yield along with diester **105** in 17% yield (Scheme 33). When performing the reaction, 1.3 eq. of *o*-iodobenzoic acid was used. Presumably, the yield would increase when using 1 eq. of acid.

Scheme 33. Synthesis of Alkyne/Aryl Iodide **104**



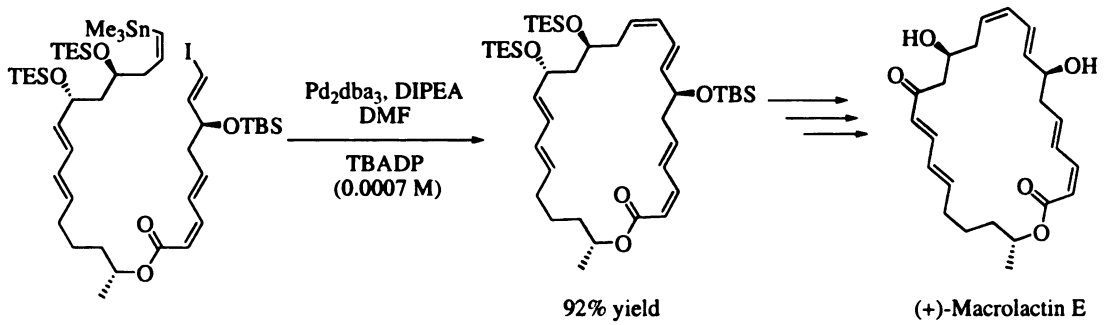
When **104** was subjected to the "Sn-F" protocol, a complex mixture of products was obtained. Taking a step back, **104** was subjected to our PMHS/KF Pd-catalyzed hydrostannation protocol. Indeed, as per Grigg, the desired (*E*)-vinylstannane **106** was obtained in 82% yield. To confirm the structure of **106**, alkynol **94** was hydrostannated and then subjected to a DCC-mediated coupling to afford **106** in 64% yield (Scheme 34). Since it was determined that the electrophilic portion of **104** could survive the hydrostannation, the Stille sequence could now be investigated.

Scheme 34. Hydrostannation in the Presence of an Aryl Iodide



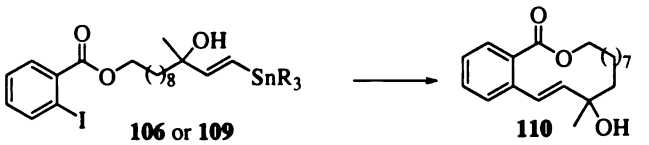
With the stannanes in hand, the intramolecular Stille was attempted with various catalysts at 0.005 M in different solvents. As shown in Scheme 35, the tributylstannanes took considerably longer to couple than the corresponding trimethylstannanes, a trend that has been seen in our lab and others. The use of NMP as the solvent increased the yield slightly. Triphenylarsine ($AsPh_3$) performed as well as tri-2-furylphosphine (TFP), regardless of solvent and stannane derivative.

Figure 10. Smith's Macrolactin Synthesis.



Smith's synthesis of the macrolactins[85] used an array of Stille reactions, in particular the intramolecular Stille (Figure 10). His best conditions were the ligandless palladium conditions (Pd_2dba_3) in NMP or DMF, with tetrabutylammonium diphenylphosphinate (TBADP) as an additive, at a concentration of 0.0007 M. Here he was able to couple a trimethylvinylstannane and a vinyl iodide at room temperature in 30 min. After the workup, he obtained the desired macrocycle in 91% yield. This represents the highest yielding intramolecular Stille to date. Given Smith's success, we decided to try these conditions. When a solution of Pd_2dba_3 in DMF was treated with DIPEA (suppresses protiodestannylation) and TBADP[86] (forms a tin-oxo species) with the desired substrate, after 1.5 h at RT macrocycle **110** was obtained in 91% yield. This last example has several benefits that will be discussed later.

Scheme 35. Intramolecular Stille: Survey of Conditions

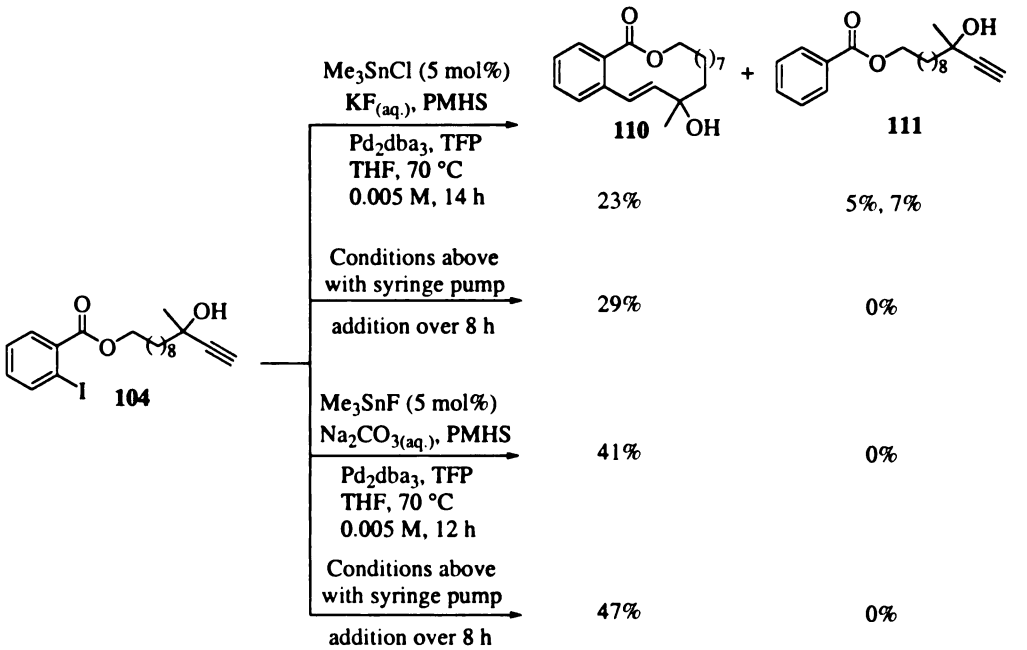


106 or **109** → **110**

Entry	R	Catalyst	Solvent	Temp/time	Isolated Yield
1	Bu	$Pd_2dba_3/AsPh_3$ (1:4)	NMP (0.005 M)	60 °C/22 h	60%
2	Bu	$Pd_2dba_3/AsPh_3$ (1:4)	THF (0.005 M)	70 °C/28 h	52%
3	Bu	Pd_2dba_3/TFP (1:4)	NMP (0.005 M)	60 °C/24 h	61%
4	Bu	Pd_2dba_3/TFP (1:4)	THF (0.005 M)	70 °C/27 h	63%
5	Me	$Pd_2dba_3/AsPh_3$ (1:4)	NMP (0.005 M)	60 °C/14 h	72%
6	Me	$Pd_2dba_3/AsPh_3$ (1:4)	THF (0.005 M)	70 °C/15 h	63%
7	Me	Pd_2dba_3/TFP (1:4)	NMP (0.005 M)	60 °C/10h	74%
8	Me	Pd_2dba_3/TFP (1:4)	THF (0.005 M)	70 °C/12 h	73%
9	**Me**	**Pd_2dba_3/TBADP DIPEA**	**DMF (0.0007 M)**	**RT/1.5 h**	**91%**

Based on the results shown above, the Pd_2dba_3/TFP in THF was chosen for the one-pot hydrostannation/intramolecular Stille using catalytic quantities of tin. Initially, the reaction was run with the KF conditions at 0.005 M at 70 °C for 14 h, where all the reagents were added at once. After workup, the macrocycle **110** and dehalogenated **111** were isolated in ~23% and ~6% yield respectively. Next, **104** was added via a syringe pump over 8 h with the same reagents as the first reaction. This produced macrocycle **110** in ~29% yield, but with no dehalogenated starting material (**111**). With less than ideal yields, it was decided to try catalytic Me_3SnF in conjunction with our Na_2CO_3 protocol. When everything was added at once at 0.005 M, a ~41% yield of **110** was obtained after 12 h at 70 °C. Use of the syringe pump method increased the yield slightly to ~47%. It should be noted that the conditions with the Na_2CO_3 route did not produce any dehalogenated starting material (Scheme 36).

Scheme 36. One-Pot Hydrostannation/*Intramolecular* Stille



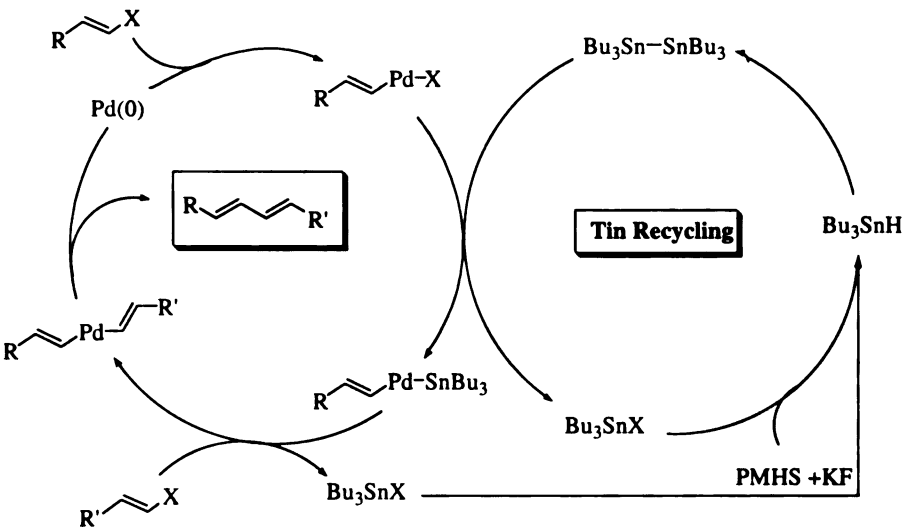
When the reactions in Scheme 36 were run in the absence of tin, macrocycle **110** was not detected, thus ruling out that any Heck type couplings are occurring. It now has been shown that a one-pot hydrostannation/intramolecular Stille can be carried out with only 5 mol% Sn, albeit with a modest yield.

3.7. Use of Hexaalkylditin.

As discussed earlier, the formation of tin dimer can be a problem at times. Hydrostannation of alkynes is just one way to form vinylstannanes. Another is from tin dimer and a vinyl/aryl halide. When a vinyl/aryl halide/triflate is treated with catalytic amounts of palladium in the presence of tin dimer, the corresponding vinylstannane is formed with retention of the geometry of the halide/triflate.[87] This process works well with both vinyl and aryl systems. At the end of the day, the byproduct is an organotin halide. Studies were then aimed at developing a way to accelerate tin dimer formation from an organotin halide and then use of the tin dimer to facilitate a one-pot palladium and tin catalyzed stannation/Stille coupling. With this type of system, potentially a more

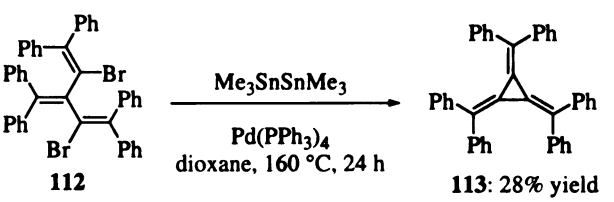
active system could be realized since active Stille catalyst and solvents expedite the formation of tin dimer. The proposed mechanism is shown in Figure 11.

Figure 11. Mechanism of the Tin Dimer Route



The literature contains reports of a one-pot stannation/Stille using stoichiometric amounts of ditin. For example, Iyoda[88] treated dibromide **112** with hexamethylditin to effect a stannation followed by a Stille coupling to provide cyclopropane **113** (Figure 12).

Figure 12. Iyoda's Stannation/Stille

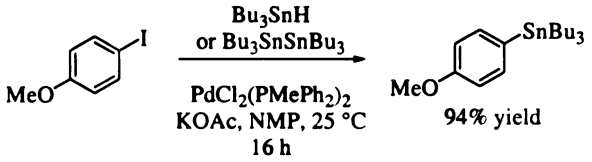


112

113: 28% yield

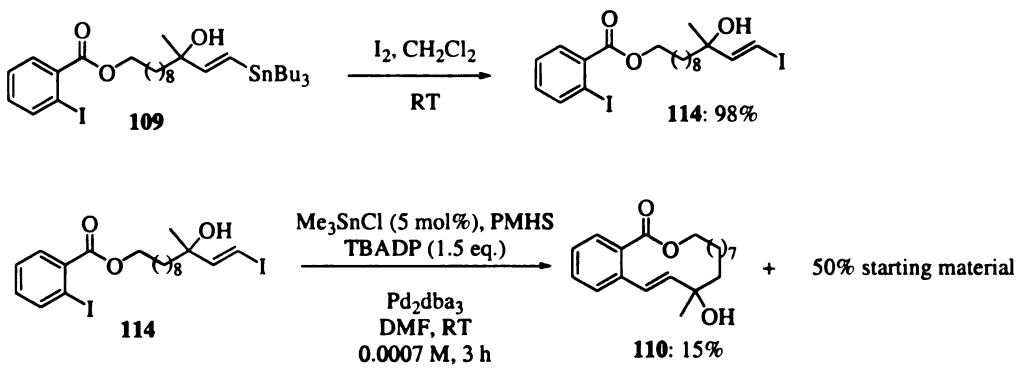
Although the yields were low, this indicated that with the correct choice of ligand and catalyst a more efficient system could be realized. Masuda[89] showed that an aryl stannanes could be formed via a cross coupling with tin hydride (Figure 13). According to the proposed mechanism, the system was actually going through a hexabutylditin intermediate. With this system, the authors could selectively stannylate an aryl iodide in the presence of an aryl bromide.

Figure 13. Masuda's System



An intramolecular approach was initially chosen since the starting substrate was already in hand. Aryl iodide-vinyl iodide **114** was synthesized via a tin halogen exchange with I_2 and vinystannane **109**. When subjecting **114** to catalytic amounts of Me_3SnCl, PMHS, TBADP[86] and DMF (0.0007 M) at room temperature for 3 h, the desired macrocycle **110** was obtained in 15% along with 50% of the starting material (Scheme 37).

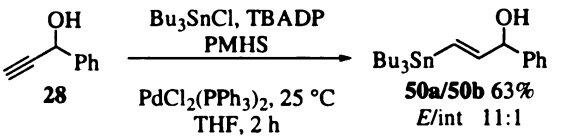
Scheme 37. First Attempt with Dimer Method



The idea here was to use the TBADP to generate tin dimer in situ. It has been shown that TBADP forms a Sn-O species. PMHS was added in hopes to generate the Sn-H, which would then form the tin dimer. There are several things that needed to be addressed: 1) the maximum concentration for an effective Stille to occur, 2) the minimum concentration for the vinylstannane formation, and 3) the efficiency with which TBADP/PMHS can furnish tin dimer. First, TBADP/PMHS were used in combination with a Pd-catalyzed hydrostannation to see whether the combination could efficiently

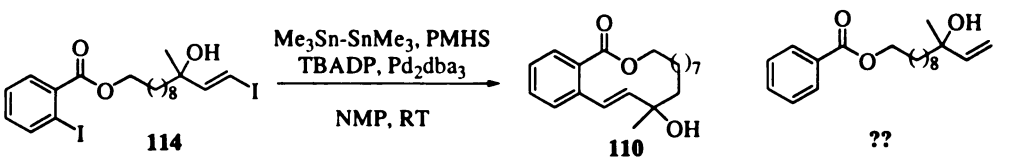
generate an organotin hydride. As seen in Scheme 38, these conditions did facilitate a hydrostannation producing vinylstannane **50** in 63% yield.

Scheme 38. Use of TBADP/PMHS For In Situ Tin Hydride



The next experiment conducted was to use stoichiometric amounts of tin. The aryl/vinyl diiodide were reacted with 0.5 eq. Me_3Sn-$SnMe_3$, 1.5 eq. TBADP and 0.05 eq. of Pd_2dba_3. After 4 h, the desired macrocycle **110** in 53% yield along with 8 mg of an unidentified product. The second trial used 0.1 eq. of Me_3Sn-$SnMe_3$, 1.5 eq. TBADP, 1.5 eq. PMHS and 0.05 eq. of Pd_2dba_3. Here, only 10 mg of the dehalogenated starting material and 12 mg of the unknown product were recovered.

Scheme 39. Initial Attempts to Use Catalytic Tin Dimer



Trial	Starting material	Me_3Sn-$SnMe_3$	TBADP	PMHS	Pd_2dba_3	Prodcuts Obtained
1	1.0 eq.	0.5 eq.	1.5 eq.		0.05 eq.	**110** (53%) + unknown (8 mg)
2	1.0 eq.	0.1 eq.	1.5 eq.	1.5 eq.	0.05 eq.	**110** (10%) + unknown (12 mg)

Diiodide **114** was attempted several times with no success. The concentration was changed (1 M, 0.01 M, 0.001 M), heat was used and the PMHS was added dropwise.

3.8. Conclusions

In summary, a modified protocol was developed for carrying out Stille couplings catalytic in tin. In comparison to the original "Sn-O" approach, the "Sn-F" route offers several advantages. Reactions can be completed in 25% less time with no loss in yield. Although this method still requires the trimethylstannanes, the reaction proceeds via the

less hazardous Me_3SnF, which can be filtered off at the end of the reaction. In contrast, trimethyltin residue from the "Sn-O" protocol resides in both the organic and aqueous phases, requiring additional manipulation and/or creating undesirable exposure or disposal problems. The methodology has also been extended to an intramolecular example, although yields were low. The use of the formation of hexamethylditin to appears to be advantageous. Initial experiments showed that this route could be possible with more experimentation.

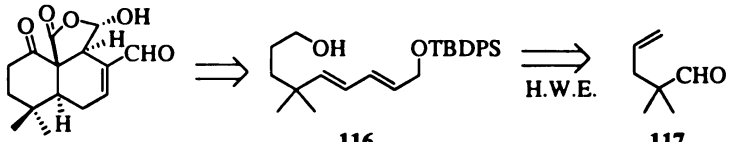
Chapter 4. Synthetic Applications of the "Sn-F" route

4.1. Formal Synthesis of (-)-Kuehneromycin A

4.1.1. Introduction

To further test the synthetic utility of the "Sn-F" approach, diene **116** was chosen as a synthetic target. Diene **116** was a key intermediate from Jauch's[90] recently reported synthesis of the reverse transcriptase inhibitor kuehneromycin A.[91] While Jauch formed **116** via a Horner-Wadsworth-Emmons olefination of aldehyde **117** (Scheme 40), this synthetic route would begin with 4,4-dimethyl-5-hexyn-1-ol **119**.

Scheme 40. Jauch's Retrosynthesis of (-)-kuehneromycin A

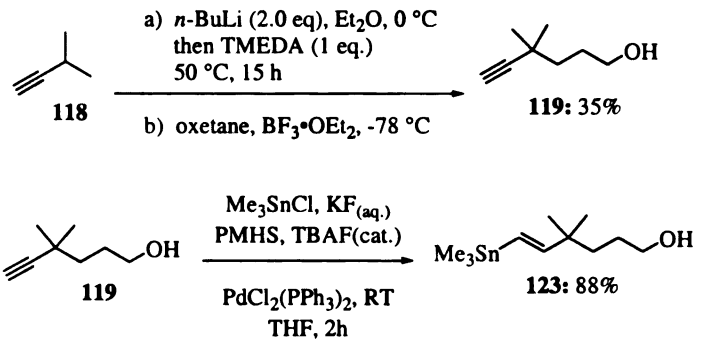


(-)-kuehneromycin A **116** **117**

4.1.2. Synthesis of the Alkyne 119 and Subsequent Hydrostannation

The reported synthesis[92] of **119** proved tedious. Therefore, a dianion alkylation based construction was investigated. After some experimentation, it was found that by exposing isopropylacetylene **118** to 2 eq. of *n*-BuLi and 1 eq. of TMEDA in Et_2O at 50 °C resulted in the formation of a red dianion solution (Scheme 41). This solution was treated with oxetane[93] followed by slow addition of $BF_3 \cdot Et_2O$ at –78 °C. This allowed the oxetane to be ring opened and alkyne **119** was formed in 35% yield. The addition of $BF_3 \cdot Et_2O$ in one portion resulted in a 20% yield and the reverse addition (adding the dianion slowly) produced **119** in 18% yield. Alkyne **119** underwent Pd-catalyzed hydrostannation to afford the (*E*)-vinylstannane **123** in 88% yield. Interestingly, the crude ^1H NMR showed the presence of only the *E* isomer, no internal isomer could be detected

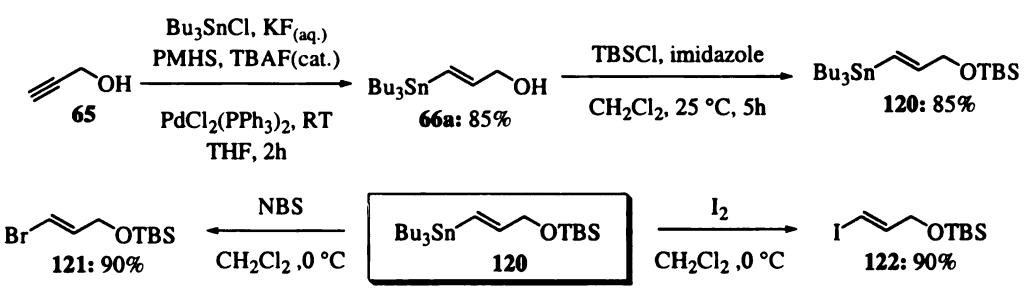
Scheme 41. Synthesis of Alkyne **119**



4.1.3. Synthesis of the Electrophile (TBS Derivative)

To help choose the appropriate electrophile, both the vinyl bromide **121** and vinyl iodide **122** were synthesized from **65** via the $Bu_3SnCl/KF/PMHS$ Pd-catalyzed hydrostannation protocol. After the hydrostannation, the (*E*)-vinylstannane was protected as its TBS ether and then subjected to a tin-halogen exchange with either NBS or I_2. (Scheme 42).

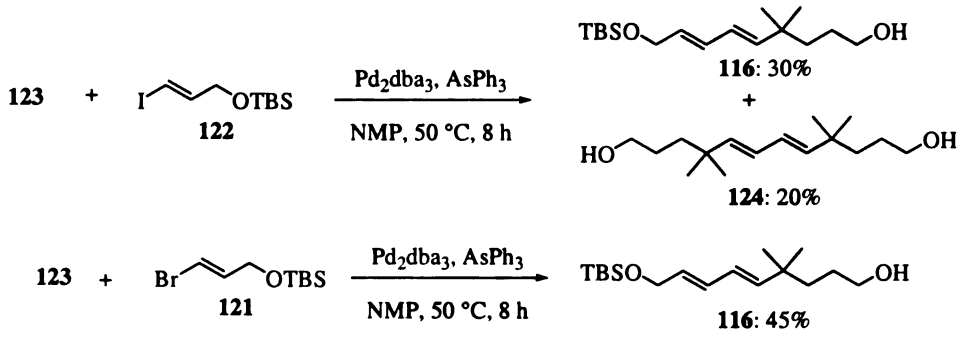
Scheme 42. Synthesis of Electrophiles and Vinylstannane **123**



4.1.4. Application of the Sn-F Catalytic Stille

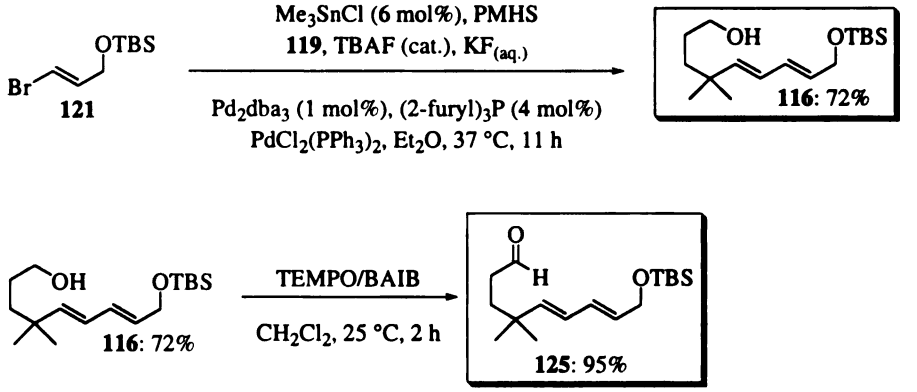
Both the vinyl bromide **121** and vinyl iodide **122** were subjected to a traditional Stille to determine which participated better in the Stille coupling. Vinyl bromide **121** produced only the Stille product in 45% yield, while vinyl iodide **122** produced a mixture of **116** and homocoupled stannane **124**. With this observation in hand, vinyl bromide **121** was chosen as the electrophile (Scheme 43).

Scheme 43. Traditional Stille with **121** and **122**



Alkyne **119** and vinyl bromide **121** were then subjected to the "Sn-F" catalytic Stille protocol using 6 mol% Me_3SnCl, affording the desired diene **116** in 72% yield. The primary alcohol was subjected to a TEMPO/bisacetoxyiodobenzene (BAIB) oxidation to afford aldehyde **125** in 95% yield (Scheme 44).

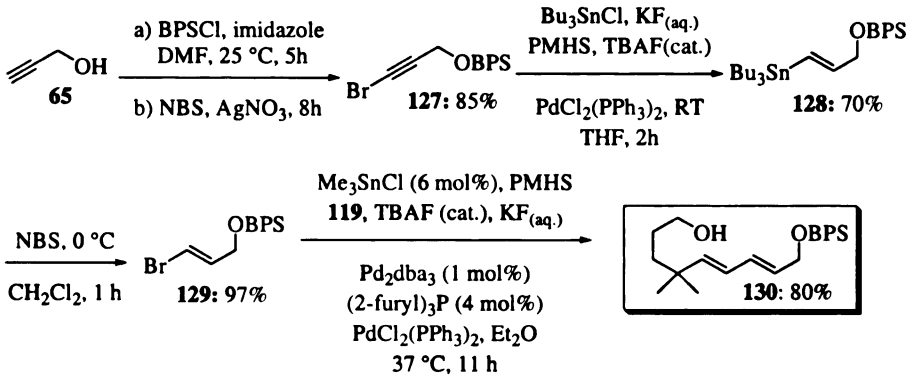
Scheme 44. Synthesis of Jauch Intermediate **125** via TBS ether



4.1.5. Use of the BPS derivative

The initial work for this synthesis was worked out using the TBS derivative since this material was readily available. Once the synthesis was worked out, the BPS derivative was synthesized (Scheme 45).

Scheme 45. Synthesis of Jauch Intermediate **130** via BPS ether



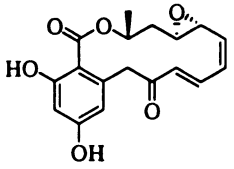
Synthesis of the electrophilic partner **129** began with the protection of propargyl alcohol **65** as its *tert*-butyldiphenylsilyl (BPS) ether (Scheme 45). Conversion to 1-bromoalkyne **127** was carried out to enhance the selectivity during the subsequent Pd(0) catalyzed hydrostannation. In practice, hydrostannation of **127** using $Bu_3SnCl/KF/PMHS$ as an in situ source of Bu_3SnH provided a separable 11:1 mixture of (*E*)-vinylstannane **128a** and its proximal isomer **128b**. Tin halogen exchange with NBS ultimately afforded (3-bromoallyloxy)-*tert*-butyldiphenylsilane **129** in 58% combined yield from propargyl alcohol **65**. Vinyl bromide **129** and alkyne **119** were reacted via the Me_3SnF-catalyzed hydrostannation/Stille protocol to afford diene **130** in 80% yield. Spectral data for **130** was not reported; however, its structure was in accord with IR, 500 MHz ^1H NMR and 125 MHz ^{13}C NMR, as well as appropriate ion identification by high-resolution mass spectrometry (See the Experimental Section). This example highlights the method's tolerance toward silyl protective groups.

4.2. Total Synthesis of Monocillin I

4.2.1. Introduction

To further demonstrate our protocol's utility in the theater of total synthesis, a venture aimed at the total synthesis of monocillin I was undertaken (Figure 14).

Figure 14. The Structure of Monocillin I



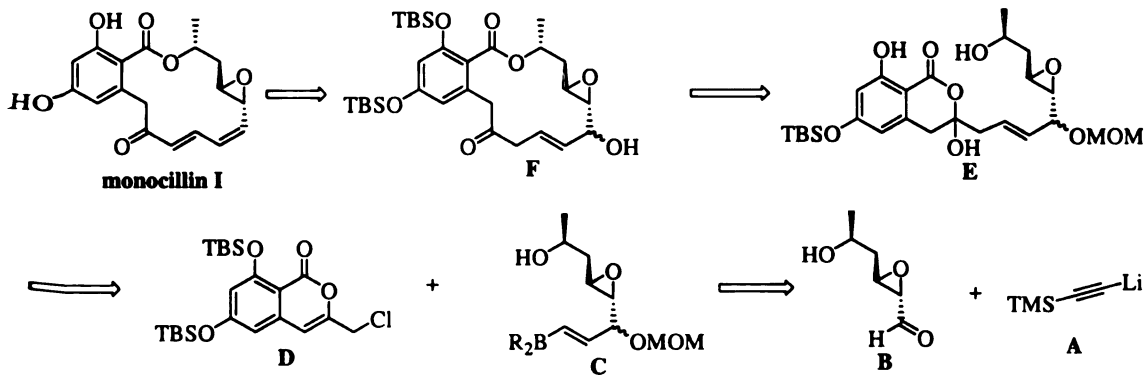
Monocillin I

Monocillin I is a resorcylic macrolide isolated from *Monocillium nordinii.*[94] The structure of monocillin I was confirmed by its direct conversion into radicicol.[95] Affirmation of these structures was achieved through their total syntheses by Lett[96] and Danishefsky.[97] Monocillin I exhibits a variety of antifungal and antibiotic properties not shared by other members of this class of natural products.

4.2.2. Previous Work

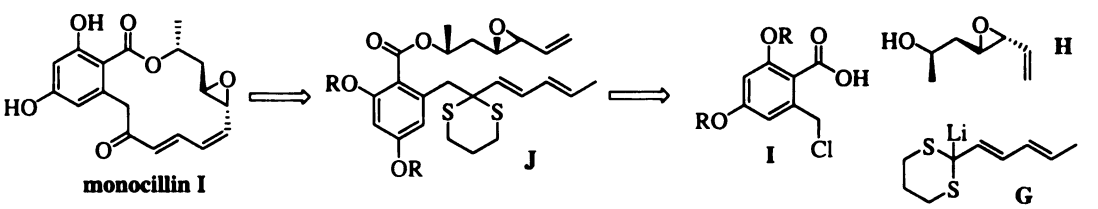
Lett's[96] retrosynthesis is shown in Scheme 46 and begins with a condensation between the lithiated alkyne **A** and aldehyde **B**, followed by the addition of R_2BH to afford vinylborane **C**. Isocoumarin **E** was obtained via a Suzuki-Miyaura coupling with allyl chloride **D**. Macrolide **F** was synthesized via an intramolecular Mitsunobu reaction. The conjugated *E,Z*-diene was installed by elimination of the in situ generated mesylate with Et_3N. Following deprotection, monocillin I was obtained in 15% overall yield from aldehyde **B** and TMS acetylene.

Scheme 46. Lett's Retrosynthesis



Danishefsky's synthesis is outlined in Scheme 47. Danishefsky planned a convergent coupling sequence for three key intermediates (**G-I**). The first coupling was an esterification of benzoic acid **I** with the optically active secondary alcohol **H**, which contained all three stereogenic centers of monocillin I. The second coupling requires a chemo- and regioselective addition of a masked acyl anion equivalent **G** to the benzyl chloride carbon in the presence of a vinyl epoxide. A stereospecific ring-closing metathesis of **J** affords the desired monocillin I to complete the synthesis..

Scheme 47. Danishefsky's Route

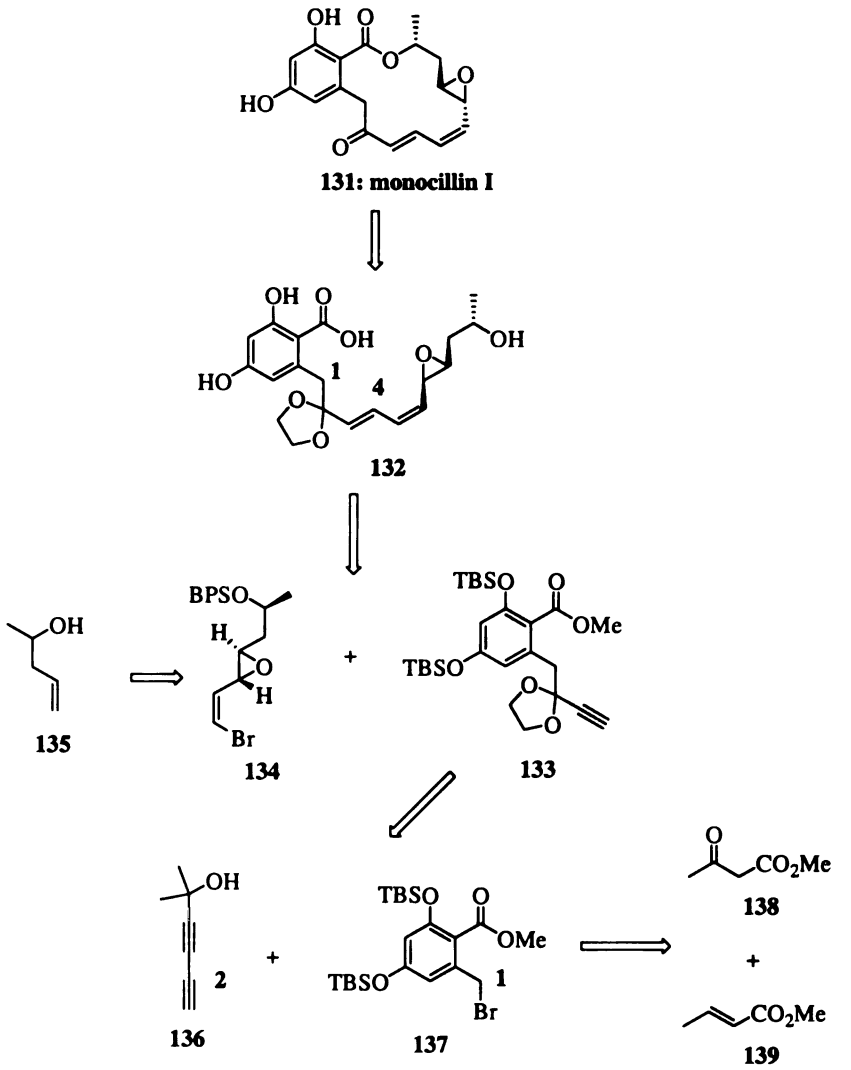


4.2.3. Retrosynthesis

Upon examining monocillin, it was envisioned that the newly developed Stille chemistry could be applied to the formation of C1–C2 and C4–C5. Retrosynthetic disassembly of monocillin I, in the manner illustrated in Scheme 48, provided intermediate **132** as a precursor that could undergo an intramolecular Mitsunobu reaction. The diene moiety in **132** would be installed via a one-pot hydrostannation/Stille sequence using catalytic quantities of tin involving alkyne **133** and *Z*-vinyl bromide **134**. The *Z*-vinyl bromide **134** could be obtained via routine synthetic operations starting from the commercially available (+/-)-4-penten-2-ol (**135**). During the initial catalytic Stille study, it was observed that coupling could occur with an interal stannane and benzyl bromide. The catalytic Stille protocol could then be used with benzyl bromide **137** and diyne **136**. This internal Stille product would be exclusively formed since the hydrostannation of

conjugated, terminal diynes occurs at the terminal postion with complete chemoselectivity and regioselectivity.[20] Benzyl bromide **137** could be synthesized via the commercially available methyl acetoacetate **138** and methyl crotonate **139**.

Scheme 48. Retrosynthesis



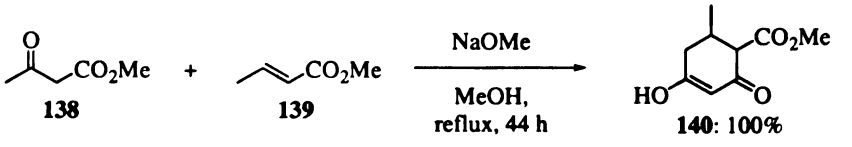
4.2.4. Synthesis of Benzyl Bromide 137

The key precursor to benzyl bromide **137** was methyl orsellinate **141**. Hirsenkorn[98] showed that this compound could be obtained by the treatment of methyl acetoacetate **138** and diketene with CaO in refluxing THF for 12 h. Following the protocol exactly as written provided a complex mixture of products. This could be due to

the problematic nature of diketene, which decomposes upon sitting. Sargent[99] has shown that methyl orsellinate **141** could be obtained via a three-step process: condensation of **138** and **139**, treatment with Br_2 in AcOH followed by Raney nickel dehalogenation. This sequence was attempted, but the Raney nickel dehalogenation was unsuccessful. Perhaps one reason for the lack of reproducibility was that the exact type of Raney nickel used was not specified.

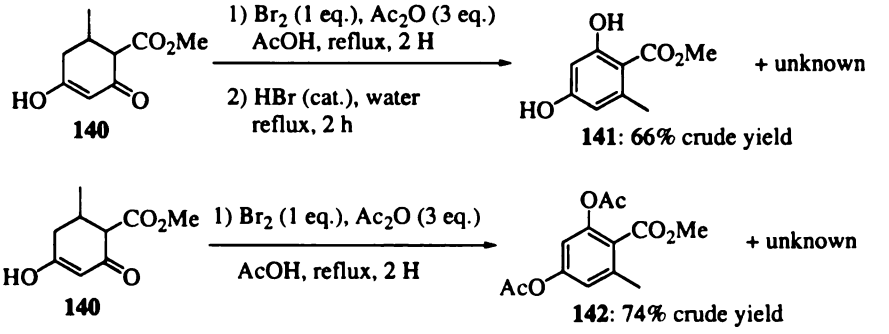
Despite these difficulties, methyl acetoacetate **138** and methyl crotonate **139** are both inexpensive, commercially available materials, and make for attractive starting materials. When these two compounds were refluxed in the presence of NaOMe, methyl dihydroorsellinate **140** was obtained in quantitative yield as shown in Scheme 49.

Scheme 49. Condensation Between **138** and **139**



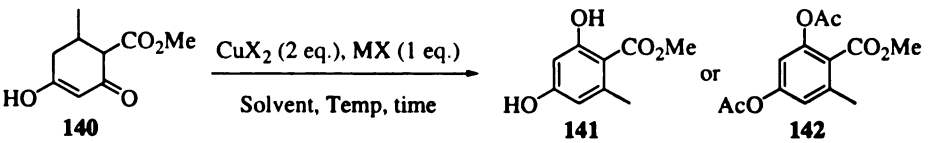
Elix[100] has shown that methyl orsellinate **141** could be formed in one step from methyl dihydroorsellinate **140**. When Elix's conditions were attempted, the desired product was obtained in moderate yield accompanied with some unidentifiable products (Scheme 50). When the second step was omitted, diacetate **142** was obtained in 74% yield along with an unidentified contaminate.

Scheme 50. Elix's Conditions



Pucci[101] and Babin[102] have shown that the combination of CuX_2 and LiX could affect the aromatization of orsellinate derivatives. As shown in Scheme 51, several attempts were made at using these conditions. So showed that the addition of Ac_2O to reaction increased yields, but this proved ineffective with **140** (Scheme 51, entry 6). Due to the inability of the reaction to produce high yields, another route was investigated.

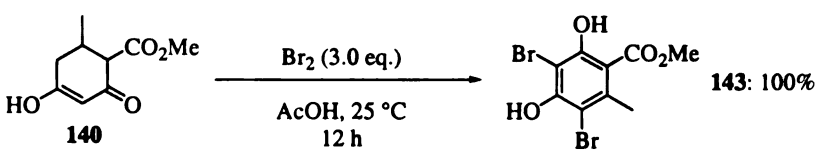
Scheme 51. Use of CuX_2 and MX



Entry	CuX_2	MX	Solvent	Temp	Time (h)	Yield
1	Br	LiBr	CH_3CN	65 °C	2	**141**: 33%
2	Br	LiBr	DMF	100 °C	2	**141**: 44%
3	Cl	LiCl	CH_3CN	65 °C	5	**141**: 33%
4	Cl	LiCl	DMF	100 °C	5	**141**: 47%
5	Cl	$MgCl_2$	CH_3CN	65 °C	12	**141**: 47%
6	Br	LiBr + Ac_2O (4 eq.)	DMF	100 °C	12	**142**: 56%

A Pd-catalyzed, PMHS/KF assisted dehalogenation procedure has been recently reported by Maleczka and Rahaim.[79] A variety of aryl and vinyl halides could be reduced at room temperature. The dibromide **143** was easily obtained in quantitative yield by treatment of **140** with 3.0 eq. of Br_2 in AcOH.

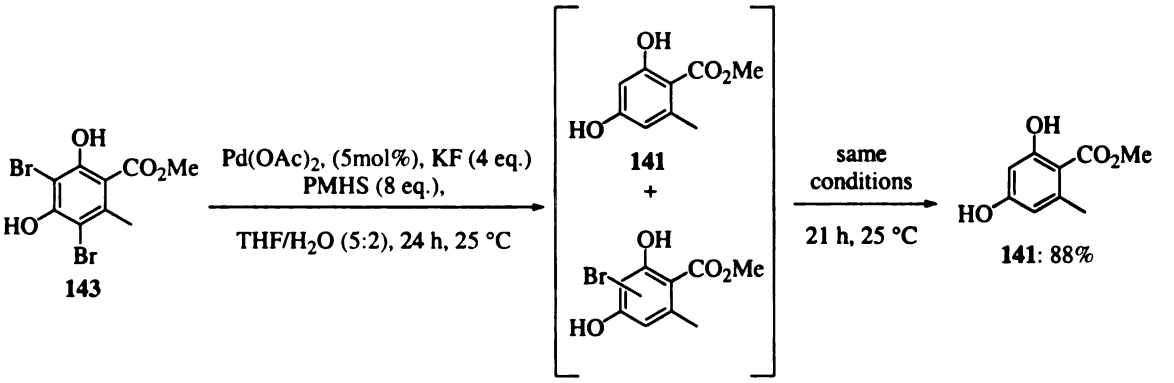
Scheme 52. Synthesis of Dibromide **143**



Treatment of **143** with $Pd(OAc)_2$, PMHS, KF and degassed water/THF (2:5) after 41 h at 25 °C afforded an inseparable 2:1 mixture of monobromide and **141**. More catalyst was added, but this had no effect and the ratio remained 2:1. After some

experimentation, it was found that **141** could be obtained in high yield via iterative application of this protocol. When **143** was treated with 5 mol% $Pd(OAc)_2$, KF (4 eq.) and PMHS (8 eq.) in THF/H_2O (5:2) at 25 °C for 24 h, crude ^1H NMR analysis indicated a 1.7:1.0 mixture of monobromide to **141**. The reaction was extracted with ether and the water was removed. The organics were then filtered to remove all of the palladium. The filtrate was then concentrated and resubjected to the same conditions. After workup and column chromatography, methyl orsellinate **141** was obtained in 88% yield.

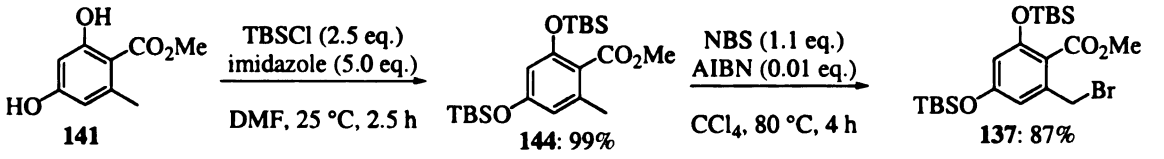
Scheme 53. PMHS/KF Dehydrohalogenation Catalyzed by $Pd(OAc)_2$



The phenol now needed to be protected. Initially, **141** was treated with Ac_2O/pyridine[103] to afford diacetate **142** in 96% yield. The diacetate proved problematic in the benzylic bromination step producing a mixture of products. With these unfavorable results, it was decided that a different blocking agent would be needed.

Following a literature procedure, treatment of **141** with TBSCl (2.0 eq.) and imidazole (5.0 eq.) in DMF at 25 °C for 2.5 h afforded the bisTBS ether **144** in 99% yield.[104] The desired benzyl bromide **137** was synthesized by treatment of **144** with NBS and catalytic AIBN in CCl_4 at 80 °C for 4 h. Unlike when diacetate **142** was used, no other products were formed. With the benzyl bromide **137** in hand, the synthesis of the diyne moiety was explored.[105]

Scheme 54. TBS protection and Benzylic Bromination



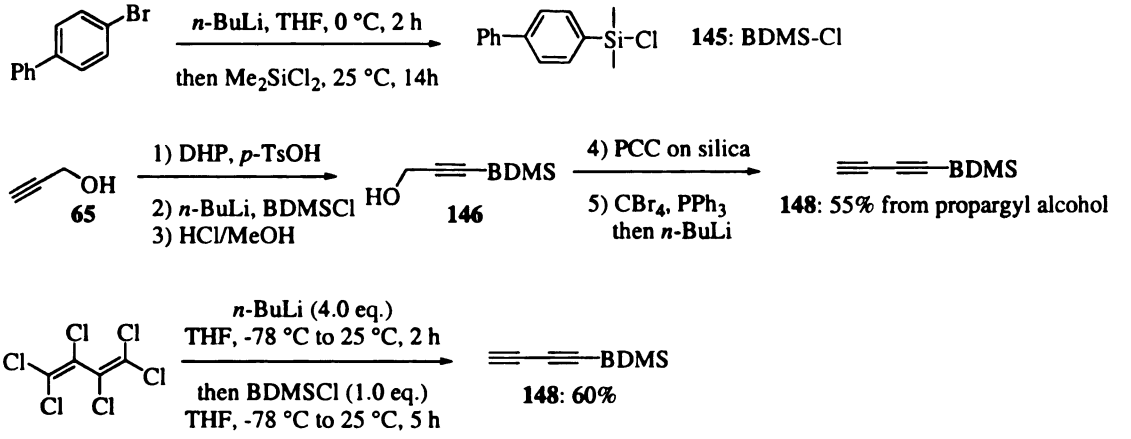
4.2.5. Synthesis of the Diyne Moiety

4.2.5.1 Synthesis of Silylalkyne 148

The diyne portion will be the precursor to the dienone portion of monocillin **131**. Initially, diyne **148** was chosen. 1,3-Butadiyne[106] can be generated from 1,4-dichloro-2-butyne and subsequently could be monolithiated, but due to its unstable and explosive nature, an alternative starting material was sought. The unique silyl-protecting group, biphenyldimethylchlorosilane (**145**), was chosen to simplify the purification, since most derivatives of this silyl group are solids.[107] Initially propargyl alcohol was protected as its THP ether, silylated with BDMS-Cl and finally treated with HCl/MeOH to furnish silyl alkyne **146**. Oxidation to aldehyde **147** was accomplished by treatment with PCC on silica.[108] The crude aldehyde **147** was then subjected to the Cory-Fuchs protocol to furnish diyne **148** in 55% overall yield from propargyl alcohol.[109] Though the approach to **148** was successful, a more direct route was considered. Literature shows that dilithiobutadiyne has been synthesized from hexachlorobutadiene and then allowed to react with various dichlorosilanes to form polymers.[110] It was postulated that if 1.0 eq. of BDMS-Cl in THF was added dropwise to the dilithiobutadiyne, the desired monosilylated alkyne could be obtained. When others have attempted this with other electrophiles, they were unsuccessful as they only obtained the bis-adduct. When hexachlorobutadiene was treated with 4.0 eq. of *n*-BuLi at –78 °C and then allowed to warm to 25 °C, the in situ

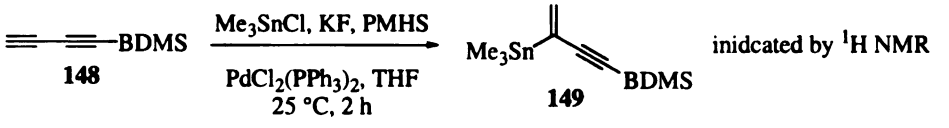
generated dilithiobutadiyne was cooled back to -78 °C and after treatment with 1.0 eq of BDMS-Cl in THF, the desired diyne **148** was formed in 60% yield.

Scheme 55. Synthesis of Diyne **148**



With **148** in hand, its hydrostannation was investigated. Guibé showed that terminal 1,3-butadiyne derivatives react specifically at the terminal alkyne to chemo- and regioselectively give the internal stannylenyne exclusively.[20] When **148** was subjected to the palladium catalyzed hydrostannation using the KF/PMHS conditions, only the internal stannylenyne **149** was obtained, as was determined by crude ^{1}H NMR. All attempts to isolate this compound failed (Scheme 56).

Scheme 56. Hydrostannation of Diyne **148**



Since the vinylstannane **149** could not be isolated, the one-pot methodology should be superior to the stepwise protocol. When diyne **148** was subjected to the "Sn-F" route, the desired diene was obtain in a crude 32% yield along with some unidentified contaminate. The low yield is likely attributable to the loss of the BDMS group during the reaction. Once this is cleaved, 1,3-butyadiyne is formed, which is a volatile gas. The

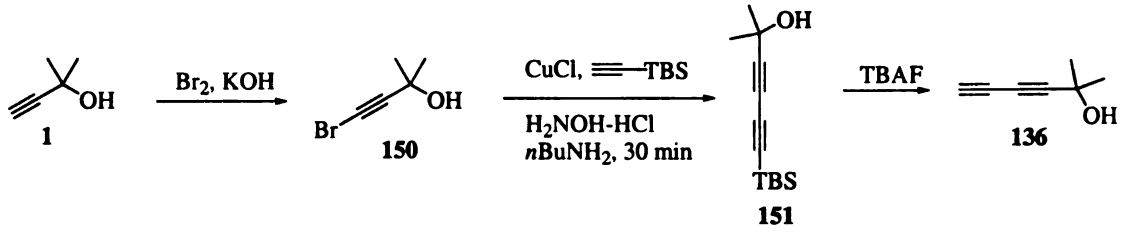
"Sn-O" protocol was attempted, but this proved equally ineffective affording **148** in a crude 12% yield. With the undesired outcome using diyne **148**, another diyne would obviously be needed.

4.2.5.2. Synthesis of Diyne 136

Since the C-Si bond was presumably cleaved under the reaction conditions, another protecting group would be needed. 2-Methy-3-butyn-2-ol **1** has long been known as a cheap and easily handled source of acetylene. There are many examples in the literature of coupling this compound followed by elimination of acetone to afford the desired terminal alkyne.[111]

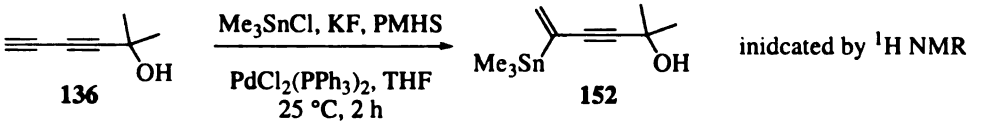
Diyne **136** was synthesized via a two-step protocol. First, 2-methyl-3-butyn-2-ol was converted into bromoalkyne **150**. Using conditions developed by Marino,[112] bromoalkyne **150** was coupled with TBS-acetylene to afford silyl diyne **151** in 65% yield. Subsequent treatment with TBAF removed the silyl group to afford diyne **136** in 90% yield (Scheme 57). The isolation of this compound was tedious due to its volatility.

Scheme 57. Synthesis of Diyne **136**



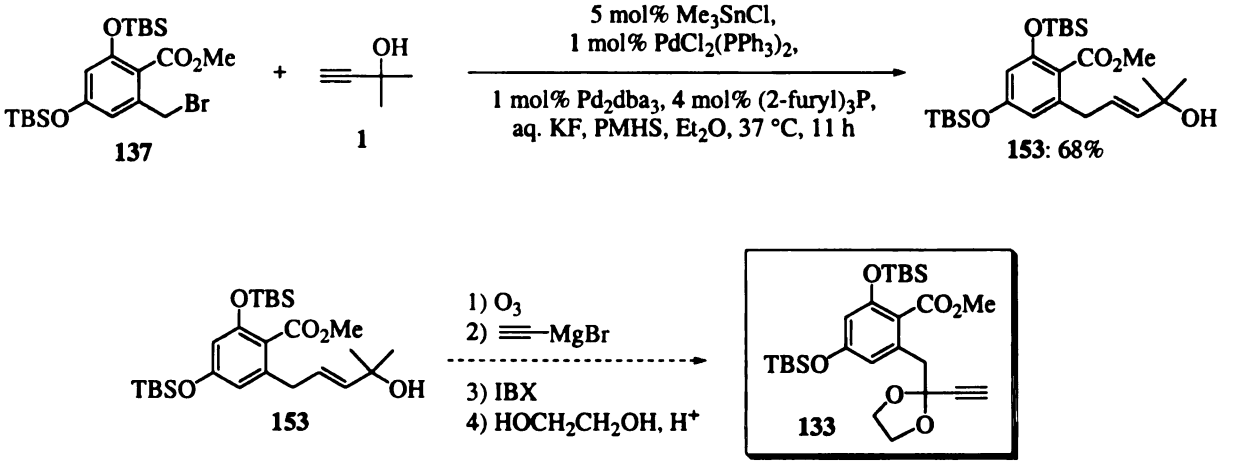
Diyne **136** was then subjected to a palladium-catalyzed hydrostannation using the KF/PMHS protocol. After two hours, the desired internal stannylenyne **152** was obtained, but again, isolation was not successful (Scheme 58). Nonetheless, knowing that the hydrostannation is chemo- and regioselective suggested that diyne **136** could be viable in the one pot hydrostannation/Stille protocol.

Scheme 58. Hydrostannation of Diyne **136**



However, all attempts to use **136** in a one-pot hydrostannation/Stille coupling failed. As mentioned earlier, 2-methyl-3-butyn-2-ol is a convenient and inexpensive acetylene alternative. Previously, this alkyne had used successfully in our catalytic Stille chemistry. Subjecting this alkyne to a catalytic Stille coupling using benzyl bromide **137** successfully formed the desired coupled product in 68% yield. Work is now in progress to take alkene **153** and transform it into the desired alkyne **133**. This could be achieved via an ozonolysis, addition of ethynylmagnesium bromide, IBX oxidation and finally protection of the ketone as a ketal (Scheme 59).

Scheme 59. Alternate Route

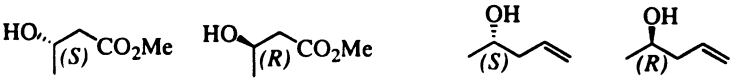


4.2.6. Synthesis of Vinyl Bromide 134

4.2.6.1 The Lipase Approach

One possible source of the stereochemistry at the ester linkage of monocillin I could be from commercially available, optically active materials. The one drawback to this is the cost of the desired compounds (>$72/gram) (Figure 15).

Figure 15. Commercially Available Chiral Compounds

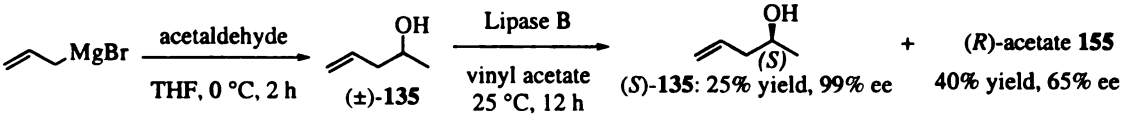


$70/g (aldrich) $72/g (Aldrich)

The necessary compounds could also be made asymmetrically in the laboratory, using for example Brown's asymmetric allylation chemistry. Alternatively, resolution of the cheaper racemic materials could also be an efficient way to access these compounds.

Racemic **135** is commercially available, but due to the cost ($16/gram), it was obtained via a Grignard reaction between allylmagnesium bromide and acetaldehyde.[113] Banwell[114] had successfully resolved (±)-**135** using *Canadida antarctica* Lipase B (CALB, Novo Nordisk).[115] Initially, Banwell's exact conditions did not work. After some experimentation, it was found that the reaction time needed to be increased to 12 h to afford <99 %ee's. This time discrepancy could be attributed to the differences between the batches of lipase used. Experimentally, (±)-**135** was dissolved into vinyl acetate and then the Lipase B was added in one portion. The reaction was allowed to stir at 25 °C for 12 h. After column chromatography, (*S*)-**135** was obtained in 25% yield with a 99% ee (Scheme 60). The ease and cost of the protocol, as well as the high enantiomeric purity, justified adopting this protocol for our synthesis.

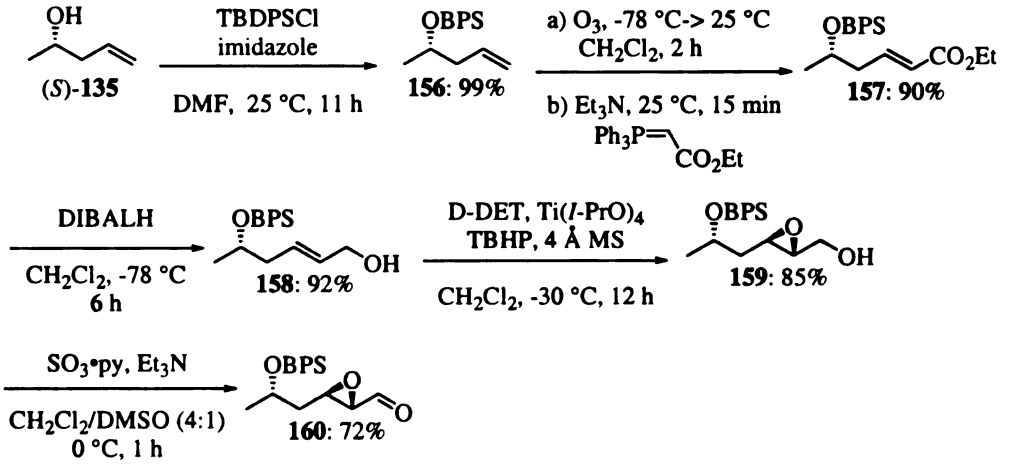
Scheme 60. Lipase Resolution of (±)-**135**



The homoallylic alcohol (*S*)-**135** was then protected as the corresponding *tert*-butyldiphenylsilyl ether **156**. The alkene moiety was then subjected to a one-pot ozonolysis-Wittig to afford ester **157** in 87% yield. Hon had previously demonstrated the usefulness of this one-pot procedure.[116] Here the ozonolysis was performed as usual and

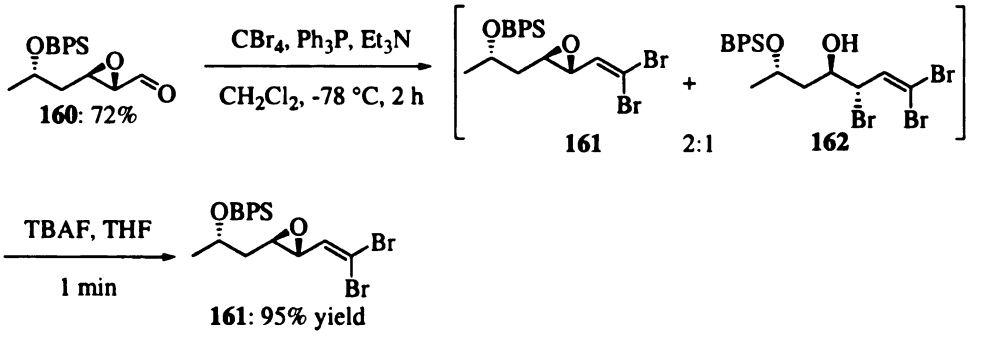
then the ozonide was treated with the Wittig reagent and 1.5 eq. of Et_3N at 25 °C. After 12 min, the desired ester was formed. In the absence of Et_3N, the reaction took 12 h to proceed to completion. DIBALH reduction of **157** gave the corresponding allylic alcohol **158** in 92% yield. Sharpless asymmetric epoxidation (D-DET)[117] afforded the corresponding epoxy alcohol **159** in 85% yield. The alcohol was then oxidized[118] with SO_3•py and Et_3N to afford epoxy aldehyde **160** in 72% yield (Scheme 61).

Scheme 61. Synthesis of Aldehyde **160**



Subjection of the epoxy aldehyde **160** to a modified Corey-Fuchs protocol was necessary so the epoxide moiety would remain inact.[119] The use of Et_3N had been shown to be essential for the success of the reaction. When the reaction was carried out, a mixture of gem-dibromide **161** and bromohydrin **162** was obtained. Diaz[120] demonstrated that the epoxy dibromide could be obtained exclusively by treating the mixture with TBAF (1.0 eq.) at 25 °C for 1 min. Follow Diaz's protocol produced **161** in 95% yield.

Scheme 62. Formation of Epoxy Gem-Dibromide **161**

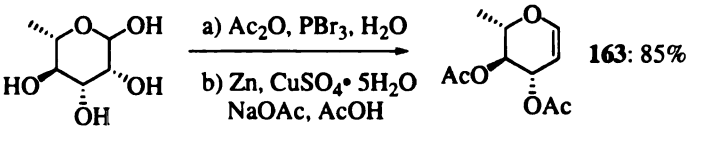


Treatment of **161** with 1.0 eq. of Bu_3SnH in the presence of $(PPh_3)_4Pd$ should afford the desired *Z*-vinyl bromide **134**.[121]

4.2.6.2 The Sugar Approach

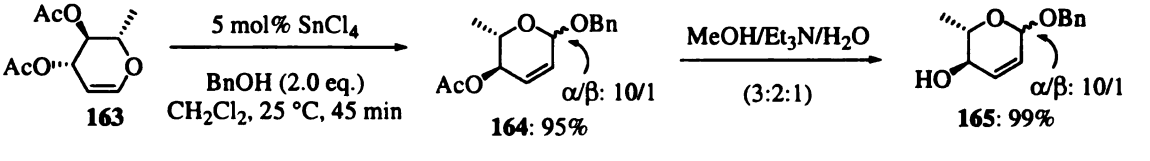
A second route to allylic alcohol **158** was also studied. Rhamnose contained the necessary (*S*) stereochemistry for the secondary alcohol. Thus, L-rhamnose was conveniently transformed into L-di-*O*-acetylrhamnal **163** using a 4-step one-pot procedure.[122] L-rhamnose was first peracetylated and transformed into acetobromo-rhamnose using PBr_3-H_2O as the brominating agent and then reduced by a zinc-copper alloy giving the expensive L-di-*O*-acetylrhamnal **163** in 85% yield.

Scheme 63. Synthesis of L-di-*O*-acetylrhamnal **163**



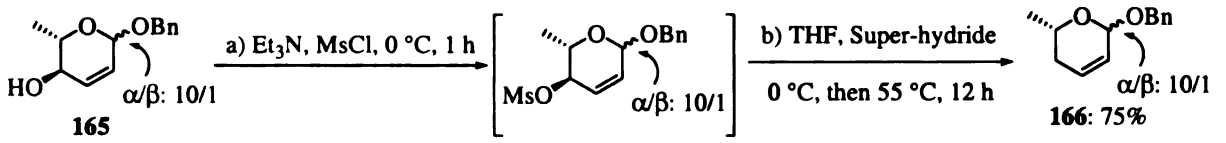
Treatment of L-di-*O*-acetylrhamnal **163** with 5 mol% $SnCl_4$ in the presence of benzyl alcohol allowed a Ferrier reaction to proceed[123] and subsequent deacetylation using a 3:2:1 mixture[124] of $MeOH/Et_3N/H_2O$ afforded the 2,3-unsaturated glycoside **165** in 95% yield (Scheme 64).

Scheme 64. Synthesis Glycoside **165**



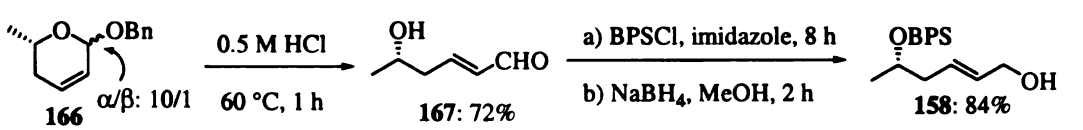
Glycoside **165** was then treated with MsCl and Et_3N to afford the corresponding mesylate. The crude mesylate was immediately treated with 2.2 eq. of Super-hydride® ($LiEt_3BH$)[125] at 55 °C for 12 h to effect the deoxygenation affording **166** in 75% yield over 2 steps.[126] The intermediate mesylate decomposed rather quickly when left under N_2 at 25 °C for 2 h affording a black sludge (Scheme 65).

Scheme 65. Deoxygenation of **166**



Lichtenthaler[127] and others[126b] have observed that when derivatives of **166** were treated with aqueous HCl, the desired acetal was not obtained, but instead the *trans*-aldehyde was obtained in high yield. Initially, the desired acetal was formed, but after every purification attempt (distillation or chromatography), the (*E*)-aldehyde **167** was obtained. It was later decided that a readily inducible, thermal *cis* → *trans* rearrangement was occurring during the purification, i.e. distillation. This rearrangement would also occur upon standing over a period of 2-3 days at 25 °C. In order to expedite this process, it was found that treatment of **166** with 0.5M HCl at 60 °C for 1 h afforded the desired (*E*)-aldehyde **167** in 72% yield.[128] The aldehyde **167** was then protected as the corresponding BPS ether and subsequently reduced with $NaBH_4$ to give allylic alcohol **158** in 84% yield. The spectral data and optical rotation matched the material made in Scheme 61 via the lipase procedure.

Scheme 66. Alternate Synthesis of Allylic Alcohol **158**



4.2.7. Conclusions

With the aromatic portion almost complete and the necessary vinyl bromide **171** one-step away, the synthesis of monocillin I using the one-pot hydrostannation/Stille coupling with catalytic quantities is now in the hands of Mr. Kyoungsoo Lee. It is hoped that this will lead the way to others utilizing our newly developed chemistry in total synthesis.

Chapter 5.0 Microwave Promoted Hydrostannation/Stille Couplings

5.1. Introduction

As mentioned previously, the classic Stille coupling typically required temperatures in the range of 45-100 °C and reaction times from hours to days. Recently Larhed, Hallberg and others[129] showed that the cross-coupling time for fluorous and organic phase Stille couplings could be reduced to minutes by using microwave flash heating.[130]

Of course, the overall speed in which a Stille product could be accessed was also dependent on the time required to (a) prepare the starting materials and (b) isolate the product. Thus, it was viewed that applying microwave assistance to a one-pot hydrostannation/Stille coupling sequence as an advance for both methodologies. The protocol was sought to be carried out in solvents that could be easily removable (THF as opposed to DMF or NMP) to facilitate product isolation and thereby further condense the time line to prepare 1,3-dienes from 1-alkynes.

5.2. Initial Work

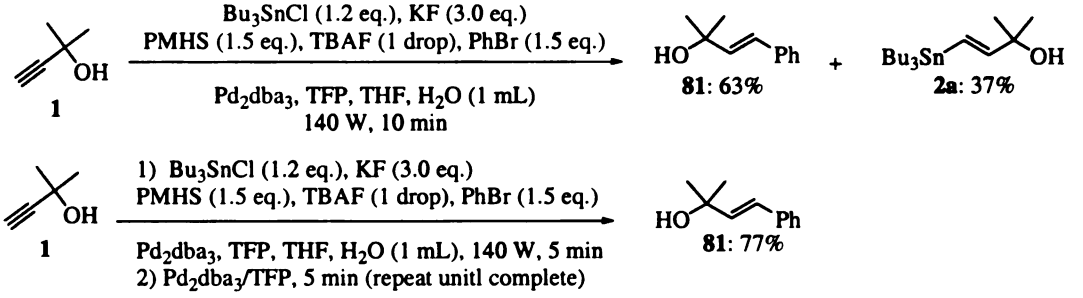
To achieve efficient one-pot palladium catalyzed hydrostannation/Stille couplings, it was crucial that Pd(0)-catalyzed conversion of Bu_3SnH into $Bu_3SnSnBu_3$ be minimized. Employing the previously discussed combination of Bu_3SnCl, KF, and PMHS as the source of Bu_3SnH allows a controlled production of Bu_3SnH, thereby decreasing the opportunity for Pd(0)-catalyzed tin dimerization.

Initial experiments were conducted in a domestic microwave oven. The first catalyst system used was Pd_2dba_3/TFP. This combination works well for both the hydrostannation and Stille coupling. After experimenting with various reaction vessels,

an Ace pressure vessel with a screw cap and Teflon o-ring was chosen. The black o-rings supplied with the Ace tube were prone to deterioration under the reaction conditions. This would then result in catastrophic failure of the tube.

Initial experiments involved irradiating an Ace pressure tube that contained Pd_2dba_3/TFP, Bu_3SnCl, KF (in 1 ml H_2O), PMHS, TBAF and bromobenzene. This produced **81** in 63% yield along with 37% of vinylstannane **2a**. At the end of the reaction, a black precipitate (decomposed catalyst) could be seen. In the second attempt, everything was added and then heated for only 5 min, cooled to 25 °C and then more catalyst was added and the reaction was heated for another 5 min. This produced **81** in 77% yield without any detectable amounts of vinylstannane present (Scheme 67).

Scheme 67. Initial Microwave Results



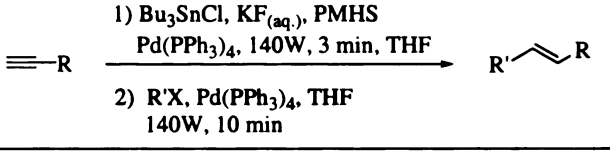
One problem that needed to be addressed was the reduction[131] of the electrophile that often accompanied cross coupling. Since the catalyst needed to be added in portions, a catalyst that did not require preactivation was sought. It was then decided to use $Pd(PPh_3)_4$ as the catalyst, even though it must be handled under N_2. Although the catalyst could be unpredictable, its use has been well documented in Stille cross couplings and hydrostannations. Second, could the hydrostannation be done first, followed by addition of the electrophile and additional catalyst to effect the Stille coupling?

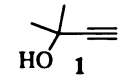
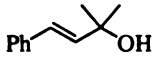
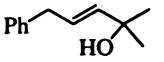
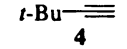
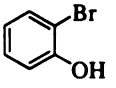
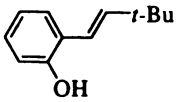
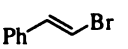
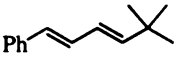
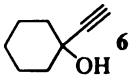
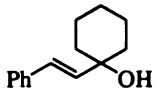
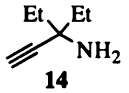
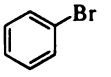
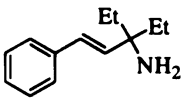
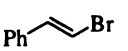
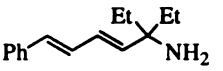
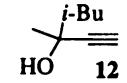
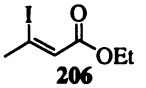
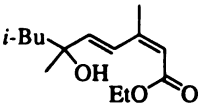
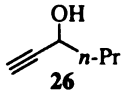
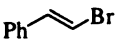
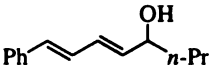
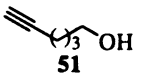
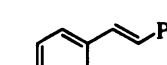
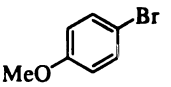
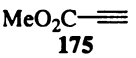
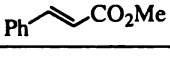
5.3. The Microwave Protocol

5.3.1. Palladium Catalyzed Hydrostannation/Stille Sequence

Experimentally, the hydrostannation was done with 1 mol% $Pd(PPh_3)_4$ in the absence of the electrophile. After 3 min of microwave irradiation at 140 W, the reaction vessel was either air cooled or cooled by placement in tepid water, after which another 1 mol% of $Pd(PPh_3)_4$ was added along with the electrophile. After reheating in the microwave for an additional 5 min, the reaction progress was checked. If not complete, a third portion of catalyst was added and the reaction was irradiated for an additional 5 min.

Scheme 68. One-Pot Hydrostannation/Stille Results



Entry	Alkyne	Electrophile	Product	Yield
1		PhBr		**81**: 94%
2	**1**			**24**: 90%
3	 **4**			**168**: 86%
4	**4**			**5**: 91%
5	 **6**	PhBr		**169**: 57%
6	 **14**			**170**: 90%
7	**14**			**15**: 81%
8	 **12**	 **206**		**172**: 70%
9	 **26**			**27**: 55%
10	 **51**	PhBr		**173**: 57%
11	 **73**			**174**: 86%
12	 **175**	PhBr		**176**: 80%

Via this protocol, a variety of alkynes underwent microwave-accelerated hydrostannation/Stille couplings with aryl, benzyl, and vinyl electrophiles. The expected dienes or styrenes were provided in good yields after totals of 8-13 min of microwave irradiation (Scheme 68).

Most of the alkynes employed in Scheme 68 (entries 1-8) were trisubstituted at the propargylic position. Such highly substituted alkynes are strongly biased toward

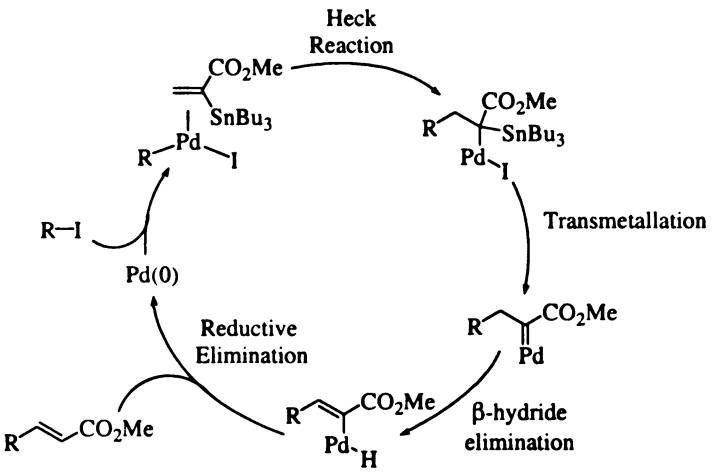
formation of the *E*-distal stannane upon palladium-catalyzed addition of Bu_3SnH, and thus subsequent cross-couplings were not complicated by a nonregioselective hydrostannation. In contrast, palladium catalyzed hydrostannations of unhindered alkynes typically afford mixtures of both distal and proximal stannanes. As such, it is not surprising that less substituted alkynes (entries 9 and 10) gave cross-coupled products in somewhat lower yields or as isomeric mixtures. Cinnamyl chloride and *p*-chloroaniline were also examined as potential coupling partners. However, under the standard conditions, no Stille reactions were observed with these electrophiles.[132] The observation of the *Z*-isomer in entry 10 was unexpected. $Pd(PPh_3)_4$ catalyzed hydrostannation or 5-hexyn-1-ol **51** unassisted by microwave irradiation affords a 2.7:1 ratio of *E*- to internal stannane without any observable formation of the *Z*-isomer. As postproduction isomerization seemed unlikely (vide infra), this result suggested that under high microwave temperatures, free radical hydrostannation may be competing with the Pd-catalyzed reaction.

Phenyl acetylene **73** and methyl propiolate **175** (entries 11 and 12) gave cross-coupled products corresponding to those expected from the *distal* vinylstannanes. Yet, product analysis after the hydrostannation portion of sequence indicated a 2.5/1 to 10:1 (entries 11 and 12, respectively) preference for the *proximal* vs. distal vinylstannanes. When the isolated vinylstannanes were used in a classical Stille, the same cross-coupled products were obtained. This effect had been documented in the literature. Busacca[133] proposed that these substrates might be reacting via a different mechanism.

Busacca's proposed mechanism is shown in Figure 16. The hydrostannation proceeded as normal to produce the proximal vinylstannane. The vinylstannane then

participated in a Heck reaction to give a stannyl-palladium intermediate. Intramolecular transmetalation would provide a Pd carbene intermediate. Following β-hydride elimination and subsequent reductive elimination, the *E*-cross-coupled product was formed.

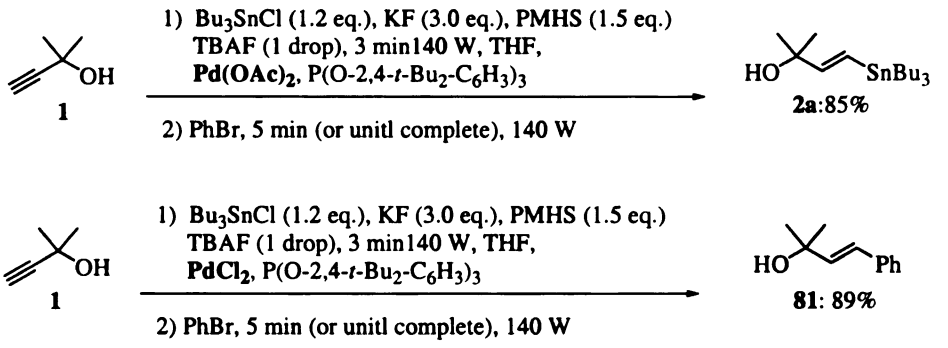
Figure 16. Busacca's Mechanism



The reaction also produced a black precipitate, suggesting thermal decomposition of the catalyst.[134] This was overcome by the addition of several portions of catalyst. Bedford[134b] and others[134a] have shown that mixtures of $Pd(OAc)_2$ or $PdCl_2$ and phosphites as ligands provide a more thermally robust catalyst. They have demonstrated their effectiveness in Suzuki and Stille couplings. As ligands, phosphites are advantageous compared with phosphines for several reasons. They are significantly cheaper and more easily accessible. Thus, a quick fine-tuning of catalyst properties is possible. In addition, phosphites are more stable toward oxygen. Hence, they could be handled and stored in air without problems. As shown in Scheme 69, the combination of $Pd(OAc)_2$ and P(O-2,4-*t*-Bu_2-$C_6H_3)_3$ proved incompatible with the sequence of reactions, as the uncoupled vinylstannane was isolated in high yield. When $PdCl_2$ was used as the source of Pd, the reaction proceeded to completion with only the initial catalyst added. Several iterations

with this catalyst system all gave different outcomes. With more experimentation, a catalyst combination with the phosphites might prove beneficial.

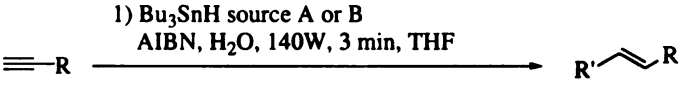
Scheme 69. Use of Phosphites

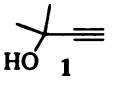
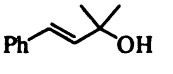
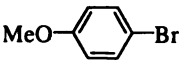
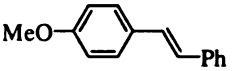
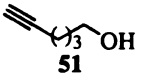
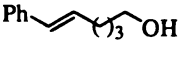
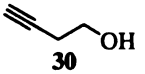
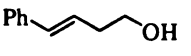
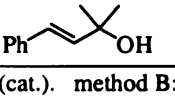


5.3.2. Free-Radical Hydrostannation/Pd Catalyzed Stille Protocol

As entry 10 of Scheme 68 suggested the possible occurrence of free radical processes, the next logical experiment was to carry out the hydrostannation portion of the sequence under free radical conditions. As indicated in Scheme 70, substituting AIBN for $Pd(PPh_3)_4$ during the first stage of the reaction gave similar results with 2-methyl-3-butyn-2-ol **1** and phenyl acetylene **73** (entries 1 and 2).[135]

Scheme 70. Free-Radical Hydrostannation/Pd Catalyzed Stille Coupling



Entry	Alkyne	Electrophile	Method	Product	Yield
1	 **1**	PhBr	A		**81**: 86% *E/Z*/int = 20:1:1
2	 **73**		A		**174**: 85%
3	 **51**	PhBr	B		**173**: 48% *E/Z*/int = 31:7:1
4	 **30**	PhBr	B		**177**: 46% *E/Z*/int = 27:4:1
5	**1**	PhBr	B		**81**: 79% *E/Z*/int = 23:1:0

Bu_3SnH source: method A: Bu_3SnCl, KF, PMHS, TBAF (cat.). method B: Bu_3SnH.

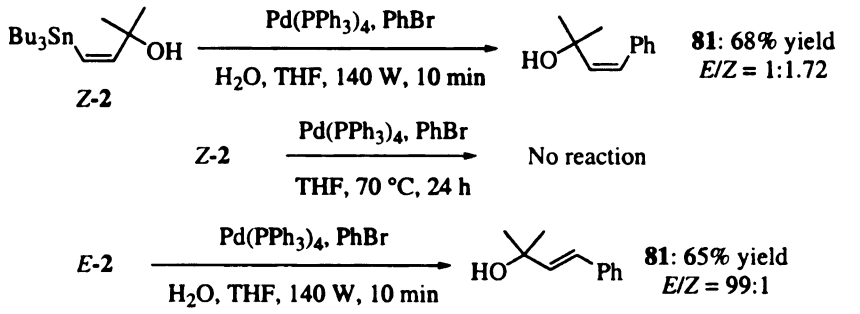
It was also necessary to establish that the protocol did not require the Bu_3SnH to be derived from our Bu_3SnCl/KF/PMHS combination. Several reactions were run using commercial Bu_3SnH (Scheme 70, entries 3-5). In these cases, it proved critical that water be included in the reaction mixture, as the reaction did not proceed in the anhydrous environment. Apparently, the water served as a microwave heat sink.

In principle, formation of the vinylstannanes under free radical conditions also allows for an added element of regiocontrol. In contrast to palladium-catalyzed hydrostannations, free radical hydrostannations strongly favor distal vinylstannane formation even when the alkynes are unhindered. As indicated by Scheme 70, unsubstituted alkynes (entries 3 and 4) gave the cross coupled products in relatively good yields with only minor contamination by other geometric or regioisomers.

In fact, *E*/*Z* product ratios were greater than those obtained during the hydrostannation step alone. AIBN-initiated hydrostannation of **1** reached a 20:8:1 (*E*/*Z*/internal) ratio of vinylstannanes after 3 min of microwave irradiation, where as the cross-coupled product displayed an *E*/*Z*/internal ratio of 20:1:1 (Scheme 70, entry 1).

To investigate this in more detail, isomerically pure vinylstannanes were irradiated for 10 min in the presence of PhBr and Pd(0). As illustrated in Scheme 71, microwave assisted cross-coupling of pure *Z*-vinylstannane and PhBr afforded a 1:1.7 mixture of *E*- and *Z*-cross coupled product in 68% yield, whereas attempted Stille coupling of these partners gave no reaction after 24 h in refluxing THF.

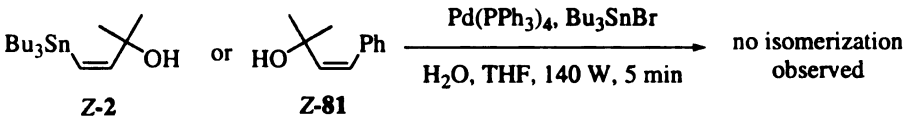
Scheme 71. Some Observations

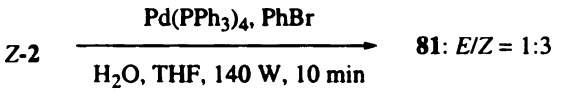


A possible explanation of these results would be that in the high temperatures of the microwave, reaction byproducts (Bu_3SnBr, $Bu_3SnSnBu_3$, etc.) or other components were facilitating geometric isomerization of the vinylstannane by a free radical (or other) processes. Thus, preferential cross coupling of the *E*-vinylstannane would lead to a kinetic resolution and stereoselective formation of the *E*-product. Alternatively, the product itself could be undergoing an isomerization leading to the observed *E*/*Z* ratio.

To explore these possibilities, *Z*-enriched vinylstannanes and cross-coupled products were both subjected to microwave irradiation in the presence of the experimental reagents and/or Bu_3SnBr (Scheme 72). Under such conditions, no isomerization was observed. However, addition of radical scavenger butylhydroxytoulene (BHT) to the Stille reaction of PhBr and **Z-2** did lessen the extent to which isomerization was observed in the product (*E*/*Z* = 1:3) (Scheme 72). This indicated that some adventitious free radical source might be contributing to the observed isomerizations. However, these results also suggest that the reaction conditions brought about by microwave irradiation may be leading to a non-radical isomerization process occurring during the course of the Stille coupling.

Scheme 72. Control Experiments

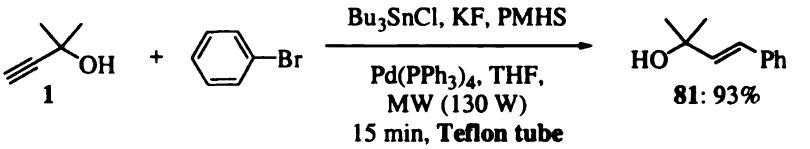




5.4. Modifications

In the past a thick walled, screw cap Pyrex tube was always used as the reaction vessel. The problem with these tubes was that if there was a slight scratch or imperfection in the glass, the tubes tended to explode. A suitable replacement was sought. Teflon is known to be transparent to microwaves. When the one-pot hydrostannation/Stille coupling was attempted in a Teflon tube with a screw cap, the reaction went to completion in the same amount of time needed for the glass tube. It was found that one could only heat the Teflon tube for a maximum of only 2-3 min at a time. If heated for 4 or more min, the tube softens and ballooned, but does not explode. The "Teflon-tube" protocol for the microwave one pot was to heat for 2 min, cool, add the desired electrophile and irradiate the reaction in 2 min increments, with cooling in between, until the stannane was consumed.

Scheme 73. Use of a Teflon Tube



5.5. Conclusions

In conclusion, an efficient microwave-assisted one-pot hydrostannation/Stille coupling protocol was developed. The hydrostannation portion of the sequence could be carried out under Pd-catalyzed or free radical conditions. Under the latter conditions, the bias for trans products was greater then the inherent selectivity of the hydrostannation.

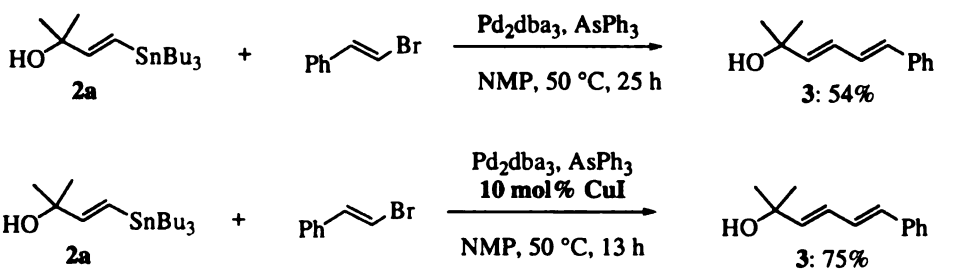
Irrespective of the hydrostannation method employed, this protocol allowed commercially available 1-alkynes to be transformed into purified 1,3-dienes or styrenes with a bottle to bottle time of approximately 2.5 h.

Chapter 6. Use of PMHS/CsF as an Additive in Sonogashira Reactions

6.1. Attempts at the Use of Co-Catalytic Copper

Although the traditional tin requirement in Stille reactions has been reduced by 94%, the current protocol needs Me_3SnCl, which is not the ideal reagent. Whenever the less toxic Bu_3SnCl was used, the reaction was low yielding (~30%). Reaction with Bu_3SnCl presumably fails due to the steric bulk of the butyl groups. Farina[47] showed that the use of Cu(I) salts facilitates the Stille reaction in a positive fashion. In 1996, Liebeskind[13g] developed a Cu(I) carboxylate that could perform a copper-mediated cross coupling between a vinylstannane and various vinyl iodides at or below 25 °C. The presence of co-catalytic Cu(I) allows for a transmetalation with the organostannane to occur to form an organocopper intermediate, which could transmetalate with Pd and following reductive elimination, affording the desired cross-coupled product and regenerating the Cu(I) salt. Since the coupling of tributylstannanes were sluggish, the use of co-catalytic Cu(I) proved to be beneficial. Initially, the traditional Stille couplings were performed (Scheme 74). Without the CuI, the Stille coupling took 25 h and produced the cross-coupled product in 54%. When 10 mol% CuI was used, the reaction time decreased to 13 h and the yield increased to 75% yield.

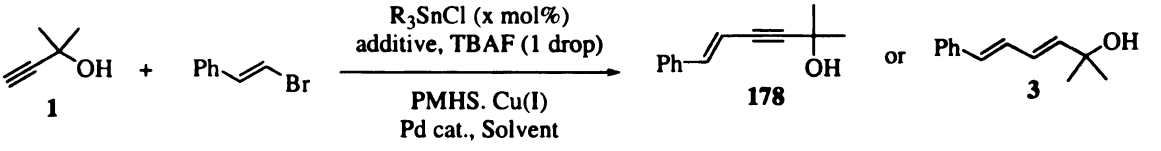
Scheme 74. Use of Co-Catalytic CuI in a Traditional Stille Coupling



With this result, the catalytic "Sn-F" conditions were used along with 10 mol% CuI. However, rather than affording the expected Stille product, the corresponding enyne

178 was isolated in 99% yield. The use of CuCl also produced enyne **178** in 96% yield. With CuTC, a tin carboxylate resulting from transmetalation with CuTC could be potentially generated, which in turn could be reduced to tin hydride in the presence of PMHS. Again, only enyne **178** was isolated in 99% yield. When Me_3SnCl was used with co-catalytic Cu(I), enyne **178** was still produced in near quantitative yield (Scheme 75)

Scheme 75. Attempts to Use Co-Catalytic Cu(I) Salts

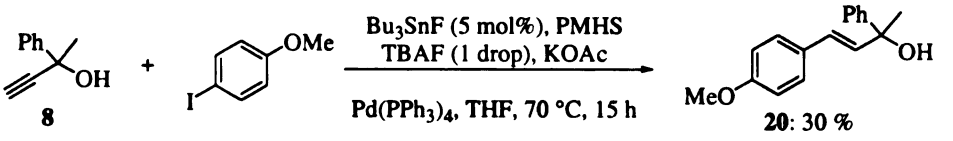


Entry	R_3SnCl (mol%)	Pd (mol%)	Cu(I) (mol%)	Additive	Solvent	Temp	Time	Result
1	Bu_3SnCl (5)	$(PPh_3)_2PdCl_2$ (1)		KF	THF	70 °C	15 h	**3**: 16%
2	Bu_3SnCl (5)	$(PPh_3)_2PdCl_2$ (1)	CuI (10)	Na_2CO_3	THF	70 °C	3 h	**178**: 99%
3	Bu_3SnCl (5)	$(PPh_3)_2PdCl_2$ (1)	CuCl (200)	CsF	THF	70 °C	3 h	**178**: 99%
4	Bu_3SnCl (5)	$(PPh_3)_2PdCl_2$ (1)	CuTC (200)	CsF	THF	70 °C	45 min	**178**: 99%
5	Me_3SnCl (5)	$(PPh_3)_2PdCl_2$ (1)	CuTC (200)	CsF	THF/NMP (1:1)	25 °C	45 min	**178**: 99%

In another attempt at the use of Cu(I), a modification of Murata's method[89] was employed. As earlier, Murata developed a method for the formation of aryl stannanes via a cross coupling with tin hydride. Potassium acetate was used to generate a "Sn-O" species. The idea here would be to use catalytic amounts of Bu_3SnF to generate the initial Bu_3SnH needed, and then the KOAc would facilitate the formation of Bu_3SnOAc which could then be reduced directly by PMHS to regenerate Bu_3SnH, thus completing the catalytic cycle. This was a combination of the "Sn-F" and "Sn-O" protocols. Experimentally, **8**, Bu_3SnF (5 mol%), PMHS, TBAF (1drop), KOAc and $Pd(PPh_3)_4$ were placed in THF and the reaction was refluxed for 15 hours. $Pd(PPh_3)_4$ was used in an attempt to simply the procedure. After chromatography, **20** was obtained in a modest

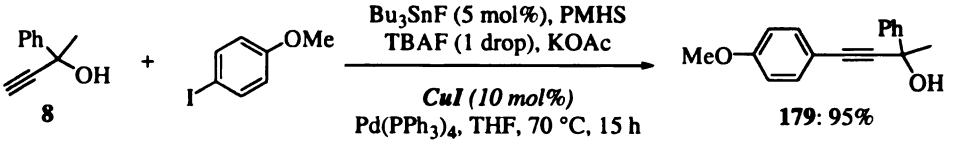
30% yield (Scheme 76). This result was similar to the results that were obtained using Bu_3SnCl in our initial study.

Scheme 76. Use of Bu_3SnF and KOAc



It was pleasing to see that the catalytic cycle was proceeding, albeit, rather slow (~6 turnovers). As noted above, the use of Cu(I) can enhance the Stille coupling. When 10 mol% CuI was added to the reaction, aqgain the corresponding enyne **179** was obtained in 95% yield (Scheme 77).

Scheme 77. Use of Bu_3SnF and KOAc with CuI



The use of Me_3SnF in conjunction with CuI produced a 5:1 mixture of **179**:**20**. When the tin was left out, enyne **179** was obtained in 72% yield. Since the yields of the enynes were near quantitative, further study of this methodology was warranted.

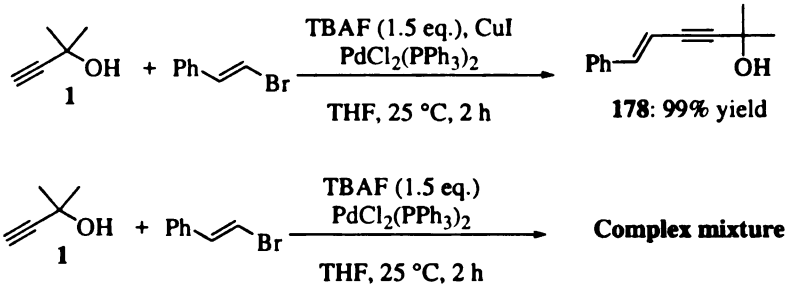
6.2. Use of PMHS as an Additive in Sonogashira Couplings

6.2.1. Use of TBAF as an Additive

After some experimentation, it was found that the tin was not required for the enyne formation. When performing these reactions, excessive gas evolution was observed upon addition of CsF in the presence of PMHS. The reaction failed in the absence of Pd, Cu, CsF or PMHS. However, when alkyne **1** and (*E*)-β-bromostyrene were treated with TBAF (1.5 eq.), catalytic $(PPh_3)_2PdCl_2$, 10 mol% CuI and after 2 h at 25 °C enyne **178** was obtained in 94% yield. Mori[136] has shown that one can form

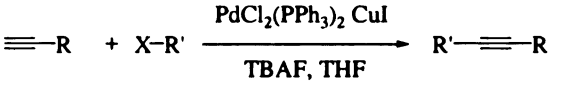
enynes by reaction of an alkyne with an aryl halide in the presence of TBAF or AgO and catalytic palladium in yields ranging from 60-99%. When the CuI was left out, a complex mixture of products was obtained in contrast to what Mori reported (Scheme 78).

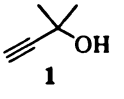
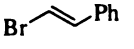
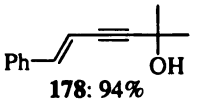
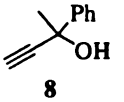
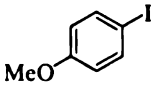
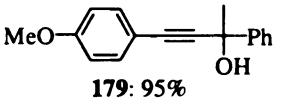
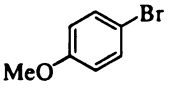
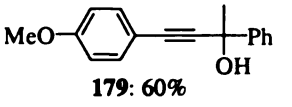
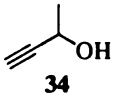
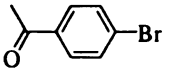
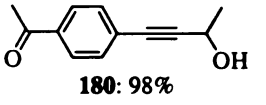
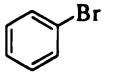
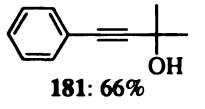
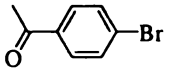
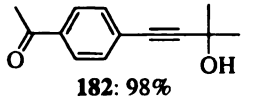
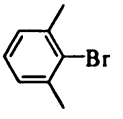
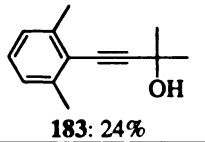
Scheme 78. Use of TBAF and Catalytic CuI



With these conditions, a few alkynes and electrophiles were tested. As shown in (Table 9), vinyl bromides reacted at 25 °C to produce the enyne in high yield. The use of aryl halides required heat at 65 °C to obtain high yields. A hindered aryl bromide produced the corresponding enyne in a low 24% yield.

Table 9. Use of TBAF/Cu Promoted Sonogashira Coupling



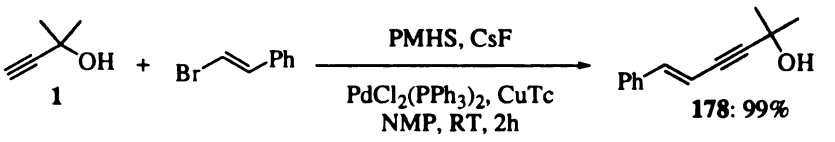
Entry	Alkyne	X-R'	°C/Time	Product (Yield)
1	 **1**		25 °C / 2 h	 **178**: 94%
2	 **8**		65 °C / 2 h	 **179**: 95%
3	**8**		65 °C / 2 h	 **179**: 60%
4	 **34**		65 °C / 6 h	 **180**: 98%
5	**1**		65 °C / 4 h	 **181**: 66%
6	**1**		65 °C / 3 h	 **182**: 98%
7	**1**		65 °C / 3 h	 **183**: 24%

Shortly after finishing the above examples, Mori[137] published a method that was identical to the one in Table 9; $(PPh_3)_2PdCl_2$, TBAF, alkyne and electrophile.

6.2.2. Use of CsF in Conjunction with PMHS

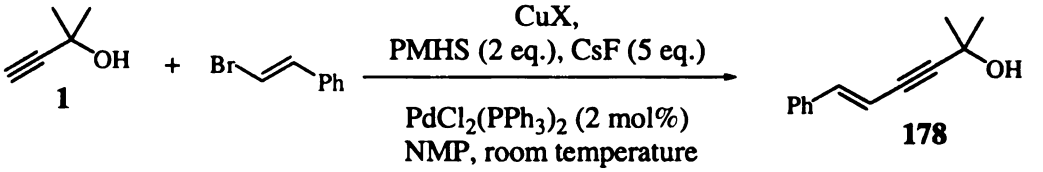
The conditions in Scheme 75 were then reexamined. If TBAF and tin were left out, the reactions still proceed in 99% yield. When these conditions were employed, a vigorous reaction took place when CsF, PMHS, and alkyne were present; foam briefly appeared along with gas evolution. After further experimentation, it was found that 1.5 eq. PMHS, 5.0 eq. CsF, alkyne, $(PPh_3)_2PdCl_2$, CuTC (2 eq.) in NMP/THF (1:1) and electrophile facilitated a Sonogashira coupling in an efficient manner at room temperature.

Scheme 79. CsF/PMHS Mediated Sonogashira: Initial Conditions



When this reaction was carried out in the absence of PMHS, CsF, Pd or Cu the reaction failed as noted above. Initially 2 eq. of CuTC were used, since Stille couplings require at least 1.5 eq. to produce high yields.

Table 10. Use of Varying Amounts and Sources of Cu(I)



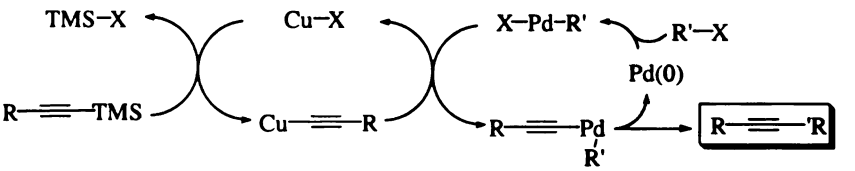
entry	CuX	(equivalents)	Time (hours)	Yield
1	CuTC	(2.0)	2	99%
2	CuTC	(0.02)	24	2%
3	CuCl	(1.5)	2	95%
4	CuCl	(0.02)	24	2%
5	CuI	(0.02–1.5)	24	<1%
6	CuBr	(0.02–1.5)	24	<1%
7	CuCN	(0.02–1.5)	24	<1%

Using less than 2 eq. of CuTC resulted in a dramatic decrease in yield. CuCl performed well when used in excess but CuI, CuBr and CuCN all performed poorly; either catalytically or stoichiometrically. Heating the reactions did not help the reaction at all.

In 1997, Hosomi[138] observed that alkynylsilanes could undergo a direct transfer from Si to Cu in 1,3-dimethyl-2-imidazolidinone (DMI) in the absence of fluoride. Recently, Mori showed that in the presence of Pd and Cu catalysts, a silyl alkyne and an electrophile could couple successfully.[141] The authors pointed out that the use of CuCl or a "Cu-O" species was needed for a successful reaction as noted by Hosomi. They

proposed that the silyl alkyne could undergo transmetalation with Cu to form an alkynyl Cu intermediate that would then undergo another transmetalation with Pd. Following reductive elimination, the cross-coupled product would be formed (Figure 17). There is a possibility of this mechanism being operative in this case since the Cu catalysis displays a similar profile as Mori[141] noted.

Figure 17. Mori's Catalytic Cycle

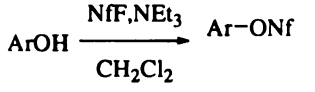


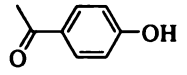
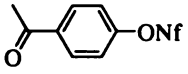
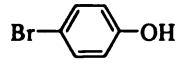
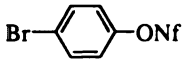
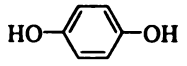
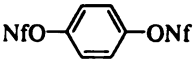
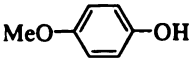
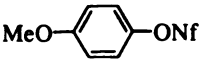
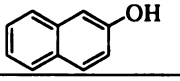
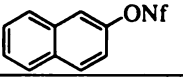
The use of alkynylsilanes in Sonogashira reactions is not without precedent. Alkynes are often protected as a silyl derivative during the syntheses of complex molecules. In order to perform the necessary Sonogashira coupling, the alkynylsilanes need to be deprotected, adding another step and purification. Hiyama[139] reported that alkynylsilanes could undergo a palladium catalyzed cross coupling directly with a vinyl iodide (3 examples) and a vinyl triflate (1 example) in the presence of TASF, a fluoride activator. Pale[140] and workers have devised a method to couple alkynylsilanes using K_2CO_3/MeOH with a Pd/Ag catalyst. Recently, Mori[141] has shown that one can simply cross-couple alkynylsilanes with a Pd/Cu catalyst system in DMF at 80 °C. Others have used various additives[137,142] to cross couple the alkynylsilanes directly. In particular, Nolan[143] had recently demonstrated that the use of alkynylsilanes could be advantageous in that the formation of unwanted side products (homocoupling) could be eliminated when using alkynylsilanes in a variant of the Sonogashira coupling. One common thread among the coupling methods is that the alkynylsilane must be formed in a separate

reaction. If one could form and react the alkynylsilane in one pot, the reaction could become more efficient.

If an alkynylsilane were being formed in this system, the use of aryl nonaflates would prove useful. The use of aryl nonaflates would allow the formation of the required "Cu-O" species; via alkynyl copper transmetalation with the NfO-Pd-R intermediate. Aryl nonaflates[144] were readily prepared from their corresponding phenols by treatment with NfF and NEt_3 in CH_2Cl_2. As shown in Scheme 80, all nonaflates were formed in reasonable isolated yields.

Scheme 80. Synthesis of Aryl Nonaflates

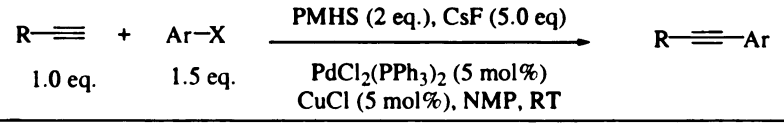


Entry	Phenol	Time	Nonaflate	Yield (%)
1		10 h		**184**: 94%
2		12 h		**185**: 51%
3		18 h		**186**: 95%
4		8 h		**25**: 85 %
5		21 h		**187**: 98 %

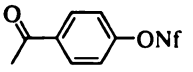
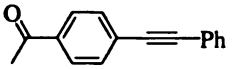
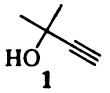
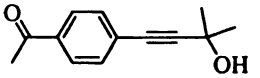
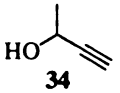
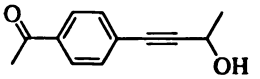
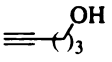
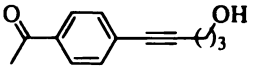
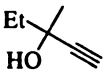
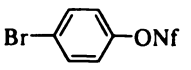
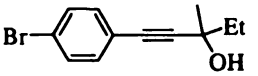
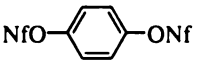
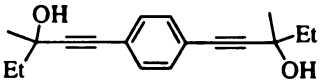
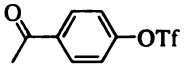
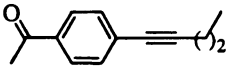
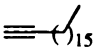
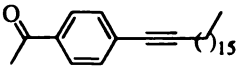
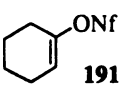
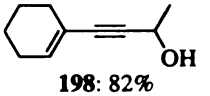
The nonaflates were then subjected to the CsF/PMHS protocol. As shown in Table 11, treatment of an alkyne with PMHS (2 eq.) and CsF (5 eq.) in NMP followed by the addition of CuCl (5 mol%), the desired electrophile (1.5 eq.) and $(PPh_3)_2PdCl_2$ (5 mol%) afforded the cross-coupled product in 71-97% yield at 25 °C. Upon the addition of CsF, the reactions appeared to have a foamy consistency followed by heavy gas evolution. Once the CuCl was added, a yellow-orange color appeared immediately, and

upon addition of all other reagents, the reaction turned to a reddish-brown to dark brown color.

Table 11. Use of Various Aryl and Vinyl Nonaflates



1.0 eq. 1.5 eq.

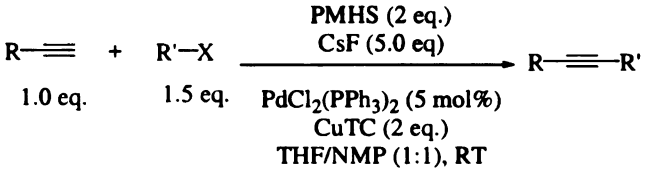
Entry	Alkyne	ArX	Time	Product (yield%)
1	Ph—≡ **73**	 **184**	4 h	 **192**: 96%
2	 **1**	**184**	5 h	 **182**: 96%
3	 **34**	**184**	5 h	 **180**: 82%
4	 **79**	**184**	6 h	 **193**: 86%
5	 **10**	 **185**	6 h	 **194**: 73%
6	**10**	 **186**	6 h	 **195**: 76%
7	**1**	 **190**	5 h	**182**: 86%
8	 **188**	**184**	8 h	 **196**: 73%
9	 **189**	**184**	8 h	 **197**: 73%
10	**34**	 **191**	5 h	 **198**: 82%

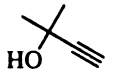
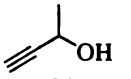
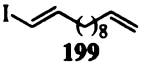
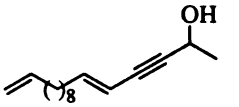
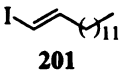
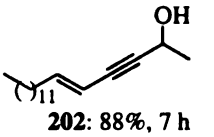
Using this protocol α-mono-, di- and trisubstituted alkynes all couple with ease to produce the desired product in excellent yield. The presence of hydroxyl groups was not

necessary for the success of the reaction (entry 8-9, Table 11). An aryl nonaflate can be selectively coupled in the presence of an aryl bromide (entry 5, Table 11). A bisnonaflate coupled at both positions in good yield (entry 6, Table 11). The use of the corresponding aryl triflate proved successful (entry 7, Table 11). It was also found that the protocol was not limited to aryl nonaflates, as a vinyl nonaflate coupled in excellent yield (entry 10, Table 11). CuTC could be used in place of CuCl with no loss of efficiency. An aryl chloride, *p*-chloroacteophenone, was attempted without success. Under the appropriate conditions, aryl chlorides should be able to participate in this protocol using only catalytic quantities of CuCl or CuTC. The use of TMS acetylene or other derivatives and propiolates proved ineffective under these conditions.

Due to the aforementioned inability of CuBr or CuI to efficiently undergo transmetalation with the alkynyl silane, the use of aryl or vinyl halides would require the use of 2.0 eq. CuCl or CuTC. Indeed vinyl or aryl bromides and iodides were amendable to the protocol with slight modifications (Table 12). Here it was found that 2 eq. of CuTC[145] and THF/NMP (1:1) were the most efficient conditions tested. The reaction proceeds with the use of CuCl, but the use of CuTC produced slightly higher yield. The addition of other additives was attempted without any success. For example, the use of LiCl is believed to transform the intermediate R-Pd-OTf to a R-Pd-Cl when using triflates in the Stille coupling. Addition of 3 eq. of LiCl did not allow *p*-iodoacetophenone to couple with catalytic amounts of CuCl or CuTC.

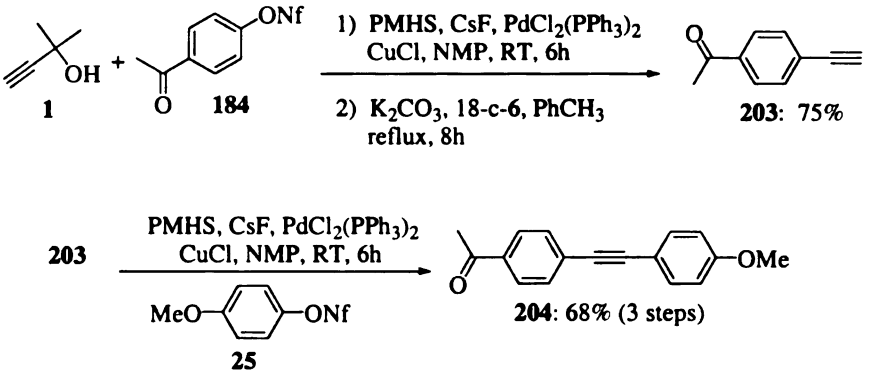
Table 12. Use of Vinyl/Aryl Halides



Entry	Alkyne	R'—X	Product (yield%, time)
1	 **1**		**178**: 99%, 2h
2	 **34**	 **199**	 **200**: 93%, 5 h
3	**1**	p-iodoacetophenone	**182**: 87%, 5 h
4	**1**	p-bromoacetophenone	**182**: 80%, 5 h
5	**34**	 **201**	 **202**: 88%, 7 h

The use of acetylene gas has been known to participate in Sonogashira reactions to produce symmetrical internal alkynes.[146] When acetylene gas was subjected to the conditions, the reaction failed to produce cross-coupled product. After chromatography, only the corresponding phenol, resulting from denonaflation, was obtained in 90% yield. Throughout the study, 2-methyl-3-butyn-2-ol (**1**), a convenient and cheap source of acetylene was used.[147] Since this alkyne couples smoothly under our conditions, could iterative application of the CsF/PMHS protocol be used to synthesize internal alkynes? As shown below (Scheme 81), the alkyne coupled with an aryl nonaflate and elimination of acetone furnished the corresponding aryl alkyne. Subjecting the newly formed aryl alkyne to the protocol with aryl nonaflate **25** afforded internal aryl alkyne **153** in 68% yield from 2-methyl-3-butyn-2-ol **1**.

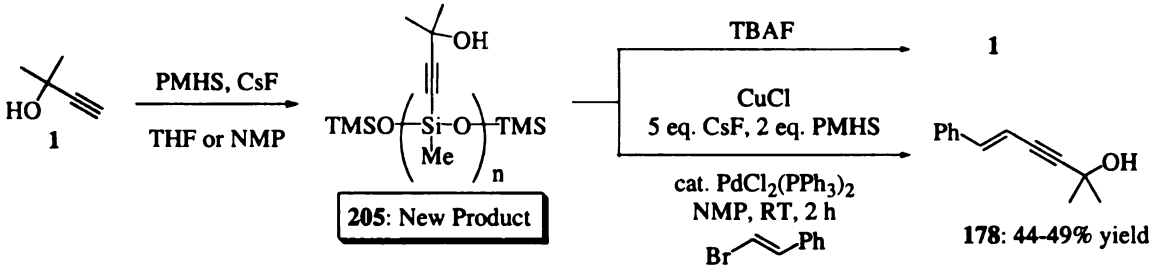
Scheme 81. Use of **1** as Cheap Acetylene Source



6.2.3. Mechanistic Insight

Since lack of coupling was observed in the absence of PMHS and a similar copper requirement that Mori saw, further proof was sought for the alkynyl silane intermediate. When CuI, CuBr, or CuCN was used, only trace amounts of cross-coupled product were obtained. This observation was in accord with the literature observation:[141] only CuCl or "CuO" species transmetalate with Si. No reaction was observed in the absence of PMHS or CsF. Simply reacting the alkyne, PMHS and CsF together produced a solid product whose ^{1}H NMR shows loss of the alkyne proton (~2.42 ppm) and the Si-H from PMHS (~4.85 ppm) (Scheme 82).

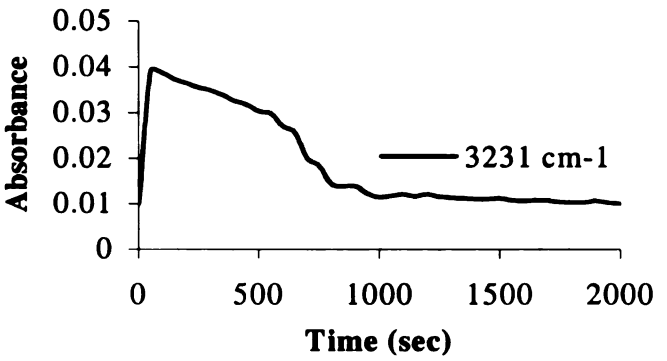
Scheme 82. Formation of Silyl Alkyne **205**



Since it was thought that a silyl alkyne was being generated, ReactIR™ could be used to follow the loss of the C-H stretch. The first experiment was run with 2-methy-3-butyn-2-ol **1**. Simply treating the alkyne with CsF and PMHS in NMP (0.75M) formed a new silyl alkyne **205**. Initially, everything was added together, but when doing so the

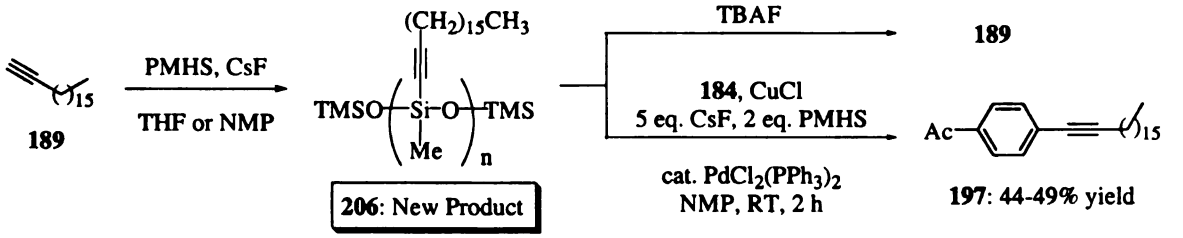
reaction took off rather quickly and overflowed. It was then decide to first add the alkyne and CsF and take an initial scan. After the first scan was complete, the dropwise addition of PMHS was started. The way the ReactIR™ was setup, there was a 20-30 sec delay between acquisitions. Care was taken to ensure that the addition of PMHS was within these 20-30 sec windows. The ReactIR™ clearly showed the disappearance of the C-H stretch and the O-H stretch remains intact through out, thus ruling out any O-silylation (Figure 18).

Figure 18. ReactIR™ Experiment



At the end of the reaction, a white solid was obtained that displayed a ^{1}H NMR spectrum consistent with the corresponding silylated alkyne. A second experiment was to use an alkyne that did not possess a free OH, to see if the OH was needed for the reaction to proceed. Starting with 1-octadecyne **189** produced the same results; the C-H stretch disappeared with the addition of PMHS (Scheme 83).

Scheme 83. Formation of Silyl Alkyne **206**



CsF could potentially be deprotonating the alkyne, but ReactIR, in the absence of PMHS, showed that the alkyne proton remained intact. Based on the experimental and spectroscopic evidence, the reaction appears to be going through an alkynylsilane.

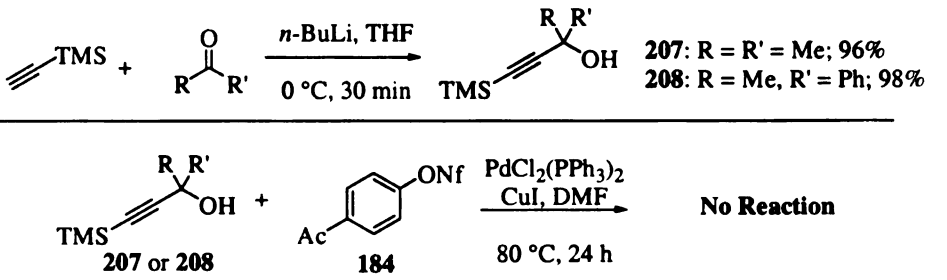
A nice procedural advantage to this method is the ease of the reaction work up. The reaction was diluted with Et_2O, washed with saturated aqueous NH_4Cl and the layers separated. The combined organics were washed with brine, dried ($MgSO_4$), filtered and concentrated. The products were then purified by flash chromatography on silica.

There are a few limitations to the CsF/PMHS protocol. The CsF/PMHS protocol was able to couple *p*-bromoacetophenone in excellent yield (Table 12, entry 4). Disappointingly, bromobenzene and *p*-bromoanisole did not participate in the reaction. Although the reaction proceeds at room temperature, 5 eq. of CsF are needed for high yields. The use of KF with 18-crown-6 was attempted without success. Corey[148] reported on a CsF/CsOH (2:1) fused salt, which worked equally well (1.5 eq.). When making the fused salt, great care was needed to get the salt. If not careful, the hygroscopic nature of the salt would take over. This salt should be handled in a glove bag under Ar.

In order to compare this method to Mori's, his conditions needed to be attempted on a substrate similar to the ones in this study. As shown in Scheme 84, trimethylsilyl acetylenes were prepared by standard literature procedure. When these compounds were subjected to Mori's conditions, the coupling did not take place after 24 h at 80 °C, just starting nonaflate was obtained. This result was not too surprising since when Mori was initially doing his research, they showed that the Cu acetylide derived from *tert*-butylacetylene could not be formed. They reasoned that the sterics of the *tert*-butyl group

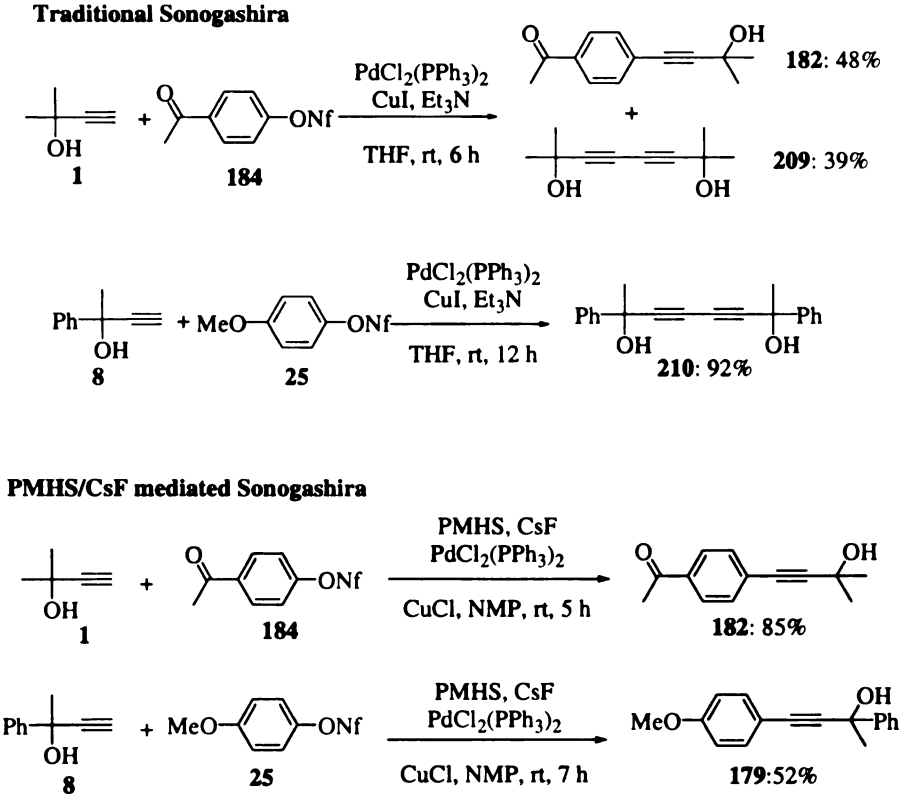
prohibited the transfer from Si to Cu. Our results clearly show this to be so, since no coupling or homocoupling of the acetylenes was observed.

Scheme 84. Comparison to Mori's Method



PMHS in combination with CsF facilitates room temperature Sonogashira couplings of alkynes with various electrophiles. These reactions could be run amine free, which among other things eases reaction workup. The involvement of an in situ generated alkynyl siloxane intermediate appears likely. Thus, some of the advantages of using silylalkynes in Sonogashira couplings could be realized without having to preform such a species in a separate step (usually by deprotonation with an alkyl lithium followed by trapping with TMSCl). Additionally, the use of silylalkynes could limit unwanted homocoupling of the parent alkyne, a common trait of a traditional Sonogashira. At first, the traditional route was performed open to the air. This allowed the homocoupling to predominate. When Ar degassing of the solvent and purging of the reaction was performed, the cross-coupled was then formed and isolated. The PMHS/CsF route obviated the need for this tedious routine. As shown in Scheme 85, the traditional route gave a significant amount of homocoupled alkyne **209** when using 2-methyl-3-butyn-2-ol **1**. When 2-phenyl-3-butyn-2-ol **8** was employed, the traditional route produced the homocoupled alkyne **210** exclusively, yet the CsF/PMHS protocol produced only the cross coupled product **179**in a modest 52% yield.

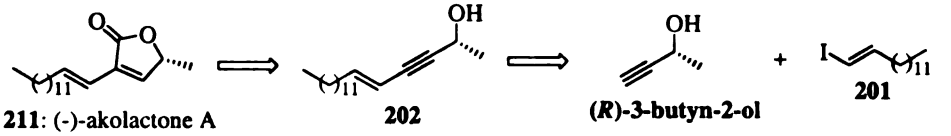
Scheme 85. Traditional vs. PMHS/CsF



6.2.3. Synthetic Utility: Synthesis of (-)-Akolactone A

To show the synthetic utility of this method, (-)-Akolactone A, a cytotoxic butanolide from *Litsea Akoensis*,[149] was chosen as a synthetic target. The synthesis of this molecule could be envisioned via a Pd-catalyzed cyclocarbonylation of enyne **202**, which would be synthesized via CsF/PMHS protocol with (*R*)-3-butyn-2-ol and vinyl iodide **201** (Figure 19).

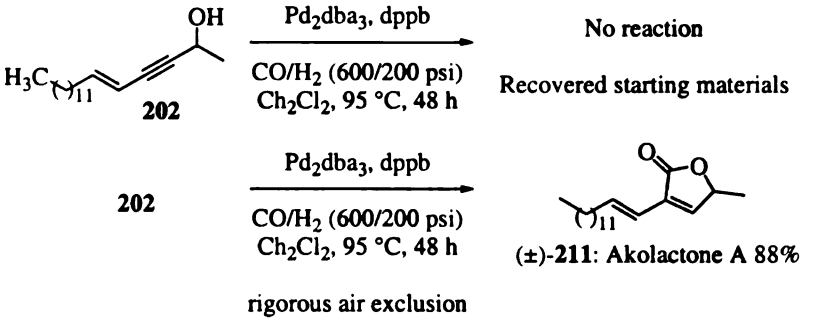
Figure 19. Retrosynthesis of (-)-Akolactone A



With (±)-**202** already in hand, the Pd-catalyzed cyclocarbonylation was examined. Alper[1] showed that terminal and internal alkynols could be subjected to a Pd catalyzed carbonylation that cyclizes them to the corresponding butanolide. As shown in Scheme

86, enyne (±)-**202** was subjected to Alper's protocol. At first, no attempt was made to exclude any air from the reaction, all the reagents were added, and the reaction vessel purged 3x with CO and then heated for 48 h at 95 °C. This method failed to produce any usable yields. After further experimentation, it was found that the reactions worked more efficiently if the whole reaction apparatus was put together in an Ar atmosphere and then was purged 7x with CO. Following this protocol, the reactions proceeded in excellent yield (Scheme 86).

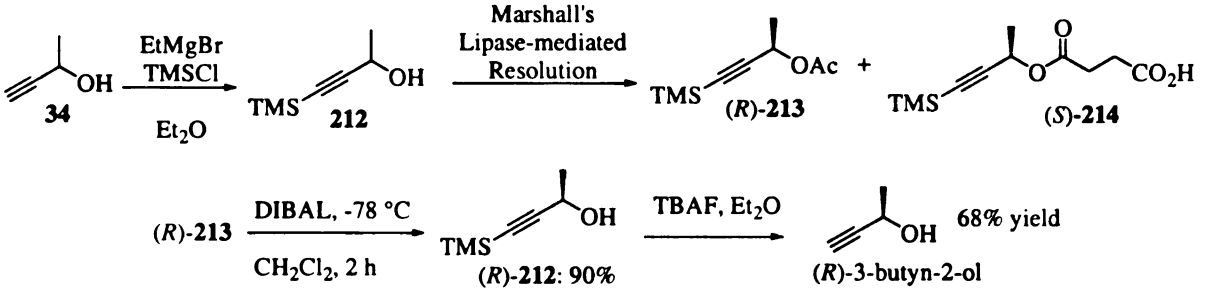
Scheme 86. Application of Alper's Method



The stereochemistry of the molecule was derived from (*R*)-3-butyn-2-ol. This material was available commercially from Aldrich, but it is expensive ($101.30/g). Another means to obtain (*R*)-3-butyn-2-ol was sought. As shown in Scheme 88, (*R*)-3-butyn-2-ol could be obtained via Marshall's lipase mediated resolution.[150] First, 4-TMS-3-butyn-2-ol **212** was prepared from 3-butyn-2-ol **34**.[151] The TMS derivative was then subjected to Marshall's protocol. First, **212**, Lipase Amano AK, vinyl acetate and 4 Å MS in pentane were reacted together for 72 hours. Then succinic anhydride, Et_3N and DMAP were all added in THF. After refluxing for 8 h, the corresponding *R*-acetate **213** and *S*-succinate **214** could be easily separated without chromatography. The *S*-succinate **214** was kept for future use. Treatment of the *R*-acetate **213** with DIBAL furnished (*R*)-**212**. The TMS group was removed by treatment with TBAF in Et_20/THF. Attempts to

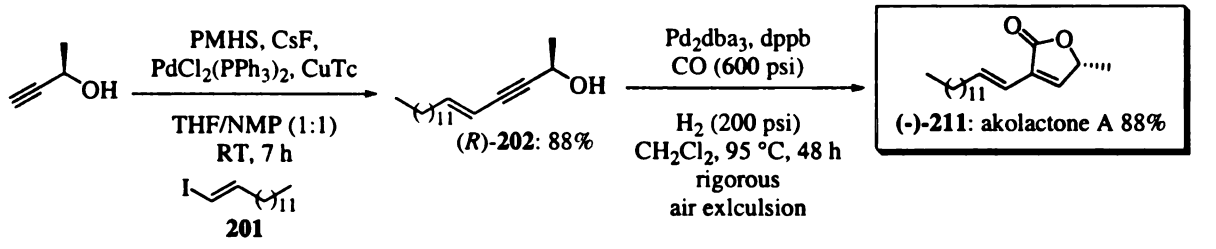
isolate this material in pure form were not successful. To get pure material, the Et_2O was distilled, followed by the THF to provide (*R*)-3-butyn-2-ol as a 0.49 M solution in THF (determined by ^1H NMR).

Scheme 87. Synthesis of (*R*)-3-Butyn-2-ol



Subsequent use of this solution in the CsF/PMHS protocol coupled with vinyl iodide **201** to afford enyne **202** in 88% yield. Enyne **202** was then subject to Alper's protocol as noted above (Scheme 88). This represents the first synthesis of this small molecule. The ^1H, ^{13}C NMR, optical rotation, IR and high-resolution mass spectra all matched to these data reported in the literature. An attempt was made to get a sample or NMR spectra of the natural material, but the lead author never responded to several emails and faxes over the course of a year.

Scheme 88. Synthesis of (-)-Akolactone A

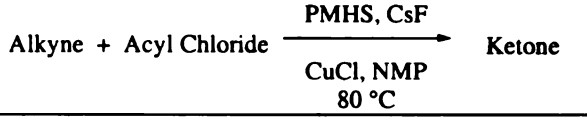


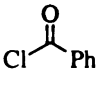
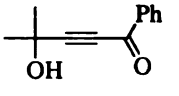
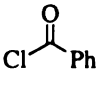
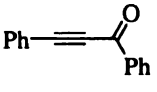
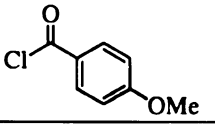
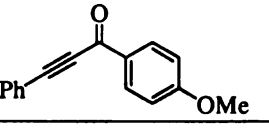
6.2.4. Coupling with Acid Chlorides

As the spectroscopic data and the experimental observations supported the involvement of an in situ generated polymethyl(alkynyl)siloxane in the reaction, the possibility of applying the protocol to other couplings was considered . For example,

acid chlorides were known to couple with alkynylsilanes.[138] Subjecting benzoyl chloride to the conditions proved successful. Treating 2-methyl-3-butyn-2-ol **1** with CsF, PMHS, CuCl in NMP at 80 °C for 5 h produced the desired alkynyl ketone **215** in 47% yield. This particular reaction was unusual, as the free alcohol was not esterified. When browsing the literature, this result had been seen before by Kundu.[152] Two more acyl chlorides were reacted with phenyl acetylene to afford the desired alkynyl ketones in 68 to 74% yield (Scheme 89).

Scheme 89. Use of Acid Chlorides

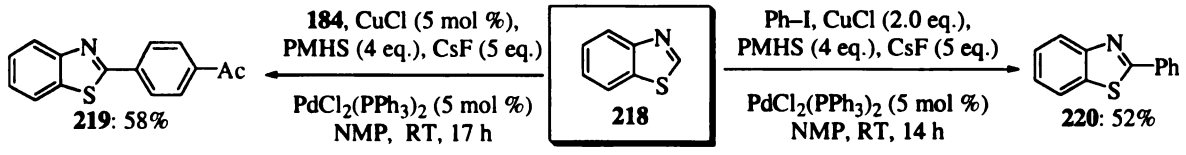


Entry	Alkyne	Acyl Chloride	Time (h)	Product	Yield
1	**1**		5		**215**: 47%
2	**73**		5		**216**: 68%
3	**73**		7		**217**: 73%

6.2.5. Coupling with Benzothiazole

Since the pKa of an alkyne is similar to that of benzothiazole, it was not unreasonable to envision that this class of compounds could possibly participate in PMS/CsF protocol. 2-trimethylsilylthiazole had been shown by Hosomi[153] to couple with iodobenzene in the presence of CuI, suggesting a similar coupling profile of thiazoles and alkynes. Indeed, iodobenzene or aryl nonaflate **131** could be coupled with benzothiazole **218** in modest yield at room temperature (Scheme 90). As with the alkynes studied, reaction in the absence of CsF or PMHS did not take place. Presumably, this reaction could proceed through a silylated benzothiazole intermediate.

Scheme 90. Coupling of Benzothiazole



6.3. Conclusions

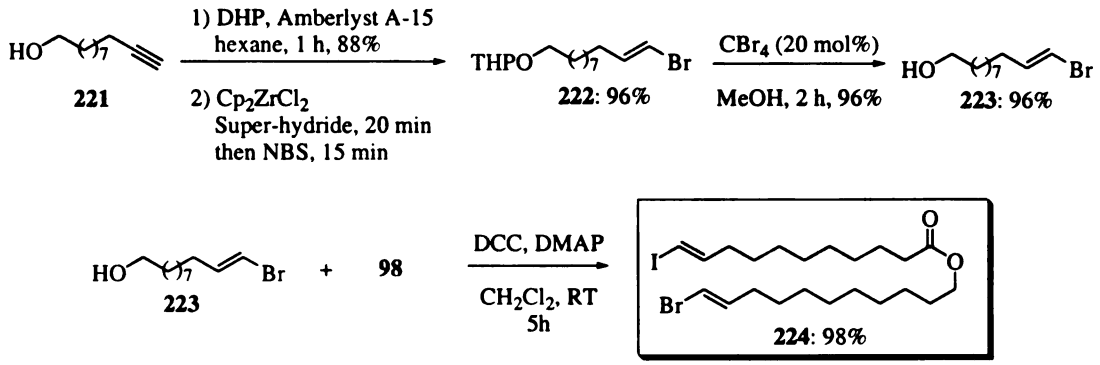
The use of PMHS/CsF in Sonogashira reactions is just one of many ways to facilitate this cross coupling. This protocol allowed the reaction to be performed without the need for an inert atmosphere or anhydrous conditions. The exclusion of amine bases eases the reaction workup. The involvement of an in situ generated alkynyl siloxane intermediate appears likely. Thus, some of the advantages, as well as the disadvantages of using silylalkynes in Sonogashira couplings could be realized without having to prepare such a species in a separate step (usually by deprotonation with an alkyl lithium followed by trapping with TMSCl).

Chapter 7. Future Work.

At this point, a few experiments were done that could not be included in the above chapters. This section will discuss these experiments in more detail.

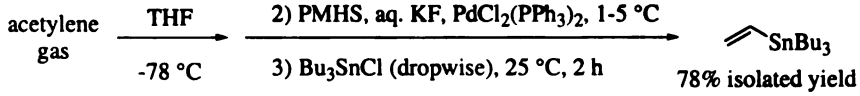
As noted in Chapeter 3, another intramolecular system was needed for the tin dimer chemistry. Here a vinyl bromide/vinyl iodide **224** was made. This vinyl bromide portion started from 10-undecyn-ol **221**, which was treated with dihydropyran and acid to form the corresponding THP ether **221p** in 88% yield. Subjection of **221p** to a hydrozirconation/halogen exchange, followed by removal of the THP provided vinyl bromide **223** in 96% yield. Acid **98** (Scheme 30) and vinyl bromide **223** were then subjected to a DCC-mediated coupling to afford vinyl Br/I **224** in 96% yield. With this substrate in hand, it is hoped that this methodology will work in some fashion.

Scheme 91. Synthesis of Vinyl Bromide/Iodide **224**



Using acetylene gas with our catalytic Stille chemistry would be interesting. First, the hydrostannation sequence would have to be evaluated before continuing. In the past vinyltributylstannane has been prepared by the addition of stannylcuprates to acetylene or a transmetalation between vinyl magnesium bromide and Bu_3SnCl. After some experimentation, a combination of acetylen gas, Bu_3SnCl, PMHS, aq. KF, and $PdCl_2(PPh_3)_2$ were found to effectively form vinyltributylstannae in high yield (See experimental for details). The key step was the slow addition of Bu_3SnCl once everything else was added at 5 °C. The crude ^1H NMR was extremely clean; very little tin dimer was present. After distillation, the desired vinyltributylstannae was isolated in 79% yield. The next step will be to perform a one-pot hydrostannation/Stille coupling using stoichiometric amounts of tin. Further experimentation could lead to a catalytic version.

Scheme 92. Pd-catalyzed Hydrostannation of Acetylene



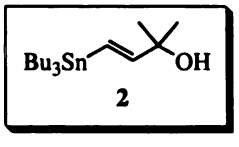
Chapter 8. Experimental Details

8.1. Materials and Methods

All air or moisture sensitive reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere unless otherwise noted. All commercial reagents were used without purification. All solvents were reagent grade. Diethyl ether and THF were freshly distilled from sodium/benzophenone under nitrogen. Benzene, toluene, DMSO, diisopropylethylamine and cyclohexane were freshly distilled from calcium hydride under nitrogen. Except as otherwise noted, all reactions were magnetically stirred and monitored by thin-layer chromatography with 0.25-mm precoated silica gel plates or capillary GC with a fused silica column. Flash chromatography was performed with silica gel 60 Å (particle size 230-400 mesh ASTM). High performance liquid chromatography (HPLC) was performed with Ranin component analytical/ semiprep system. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points were determined on a Thomas-Hoover Apparatus, uncorrected. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. Proton and carbon NMR spectra were recorded on a Varian Gemini-300, VXR 500 or INOVA 600 spectrometer. Chemical shifts for ^{1}H NMR and ^{13}C NMR are reported in parts per million (ppm) relative to $CDCl_3$ (δ = 7.24 ppm for ^{1}H NMR or δ = 77.0 ppm for ^{13}C NMR). Optical rotations were measured with a Perkin-Elmer Model 341 polarimeter. High resolution mass spectra (HRMS) data were obtained at either the Michigan State University Mass Spectrometry Service Center or at the Mass Spectrometry Laboratory of the University of South Carolina, Department of Chemistry & Biochemistry. GC/MS were performed with a fused silica column (30 m by 0.25 mm i.d.). ICP analysis was

performed on a Micromass Platform Inductively Coupled Plasma-Mass Spectrometer at the ICP-Hex-MS Laboratory at the department of Geological Sciences at Michigan State University.

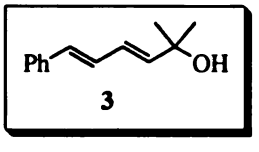
Procedure for the preparation of tri-2-furylphosphine (TFP). $CeCl_3 \cdot 7H_2O$ (60 g, 161 mmol) was placed into a 3 neck 1-L flask containing a stir bar. The flask was placed into a 150 °C oil bath and was then placed under vacuum (~1 mmHg) until a fine powder was obtained. The flask was then cooled to 25 °C under N_2 and THF (200 mL) was added. In a separate flask, a solution of furan (20 g, 294 mmol) in THF (100 mL) was cooled to 0 °C. To this solution was added *n*-BuLi (100 mL of a 1.6 M solution in hexanes, 160 mmol) dropwise. After the addition was complete, the mixture was stirred at 25 °C for 1 h. The flask containing the dried $CeCl_3$ in THF was cooled to –78 °C and then the α-furyllithium solution was added via cannula. Once the addition was complete, the solution was allowed to stir at –78 °C for 1 h, and then PCl_3 (3.50 mL, 40.1 mmol) was added and the cold bath was removed. The mixture was then allowed to warm to 25 °C overnight with stirring. The mixture was then poured into sat. aq. NH_4Cl (300 mL). The layers were separated and the aqueous layer was extracted with Et_2O. The combined organics were dried ($MgSO_4$), filtered, and concentrated (not to dryness). The residue was purified by column chromatography [silica; 90:10 hexane/EtOAc] to afford tri-2-furylphosphine (5.36 g, 58%) as a white crystalline solid (mp = 65 °C; lit.[154] mp = 63-65°C). The product could also be recrystallized from hexanes (3x). All spectral data match that reported in the literature.[154]



2

Representative procedure for the screening of Pd catalysts for the hydrostannation sequence. Use of $Pd(PPh_3)_4$ (Scheme 1). 2-

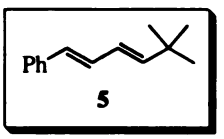
methyl-3-butyn-2-ol (0.10 mL, 1 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) were added to THF or ether (5 mL). The system was purged with nitrogen and Bu_3SnH (0.53 mL, 2 mmol) was added dropwise over 30 min. This mixture was then allowed to stir at room temperature for 2 h. The reaction was then washed with sat. aq. NH_4OH and the layers separated. The organics were dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography [silica; 90:10 hexane/EtOAc, 1% TEA] to afford (*E*)-4-(tributylstannyl)-2-methylbut-3-en-2-ol (**2**) (319 mg, 85%) as an oil. IR (neat) 3562 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.72-1.01 (m, 15 H), 1.16-1.35 (m, 12 H), 1.40-1.56 (m, 6 H), 5.96-6.26 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 13.7, 27.3, 29.0, 29.5, 72.5, 122.3, 155.5; HRMS (EI) *m/z* 318.1086 [(M^+-Bu); calcd. for $C_{13}H_{27}OSn$ 318.1084].



3

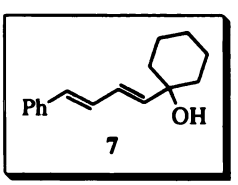
Representative Procedure for a stepwise hydrostannation/Stille cross coupling (Table 1, entry 1). Preparation of 5-methyl-1-phenyl-1,3-hexadien-5-ol (3). $(Ph_3P)_2PdCl_2$ (28 mg, 0.04 mmol) and 2-methyl-3-butyn-2-ol (**1**) (0.40 mL, 4 mmol) were added to 20 mL of THF. The solution was cooled to 0 °C with an ice bath, and then Bu_3SnH (1.18 mL, 4.4 mmol) was added dropwise. The reaction was stirred for 1 h and then concentrated. The resulting residue was then purified by column chromatography [silica gel; 90:10 pentane/EtOAc, 1% Et_3N) to afford 1-(tributylstannyl)-3-methyl-2-(*E*)-buten-3-ol (1.12 g, 75%) as a clear oil. A solution of (*E*)-4-(tributylstannyl)-2-methylbut-3-en-2-ol (**2**) (1.13 g, 3 mmol), (*E*)-β-bromostyrene (0.42 mL, 3.3 mmol), and $(Ph_3P)_2PdCl_2$ (7 mg, 0.01 mmol) in dry THF (5 mL) was heated for 6 days to 50 °C. A saturated aqueous KF solution (5 mL) was added to the reaction mixture, which was stirred for 3 h. The phases were separated, the aqueous layer

was extracted with Et_2O, and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent afforded the crude product, which was purified by radial chromatography [silica gel; 90:10 petroleum ether/EtOAc] to afford 5-methyl-1-phenyl-1,3-hexadien-5-ol (**3**) (363 mg, 65%; 49% from alkyne). IR ($CHCl_3$) 3598, 3451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3 H), 5.86 (d, J = 15.4 Hz, 1 H), 6.38 (ddd, J = 15.4, 10.4, 0.6 Hz, 1 H), 6.53 (d, J = 15.7 Hz, 1 H), 6.76 (ddd, J = 15.7, 10.4, 0.6 Hz, 1 H), 7.16-7.39 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3, 27.4, 35.2, 77.0, 126.2, 127.3, 127.8, 128.5, 128.6, 131.9, 137.2, 140.8; HRMS (EI) *m/z* 188.1204 [$(M)^+$; calcd for $C_{13}H_{16}O$ 188.1201].



5

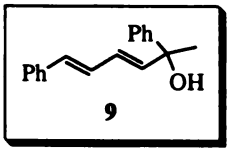
Preparation of (5,5-dimethylhexa-1,3-dienyl)benzene (5) (Table 1, entry 2). Applying the hydrostannation procedure above to 3,3-dimethyl-1-butyne (**4**) (0.492 g, 6 mmol) afforded after column chromatography [silica gel; pentane, 1% Et_3N] tributyl(3,3-dimethyl-but-1-enyl)stannane (970 mg, 44%) as a clear oil. Applying the Stille conditions above to tributyl(3,3-dimethyl-but-1-enyl)stannane (980 mg, 2.6 mmol) and (*E*)-β-bromostyrene (530 mg, 2.9 mmol) afforded after a 5 day reaction time and column chromatography [silica gel; 95:5 petroleum ether/EtOAc] (5,5-dimethylhexa-1,3-dienyl)benzene (**5**) (199 mg, 43%; 19% from alkyne). See above for spectroscopic data.



7

Preparation of 1-(4-phenylbuta-1,3-dienyl)cyclohexanol) (7) (Table 1, entry 3). Applying the hydrostannation procedure above to 1-ethynylcyclohexanol (**6**) (124 mg, 1 mmol) afforded after column chromatography [silica gel; 95:5 pentane/EtOAc 1% Et_3N] 1-(2-tributylstannylvinyl)cyclohexanol (290 mg, 70%) as a clear oil. Applying the Stille

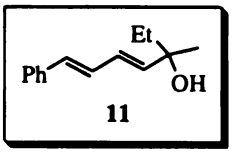
conditions above to 1-(tributylstannyl)-2-(cyclohexanol)-1-ethene (252 mg, 0.6 mmol) and (*E*)-β-bromostyrene (0.15 mL, 1.2 mmol) afforded after a 30 h reaction time and column chromatography [silica gel; 95:5 petroleum ether/EtOAc, 1% Et_3N] 1-(4'-phenyl-1',3'-butadienyl)cyclohexan-1-ol (**7**) (83 mg, 60%; 42% from alkyne). IR ($CHCl_3$) 3594, 2938, 2859, 2402, 1703, 1597, 1491, 1451, 1350, 1125, 992, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21-1.77 (m, 10 H), 5.92 (d, *J* = 15.4 Hz, 1 H), 6.42 (dd, *J* = 15.4, 10.4 Hz, 1 H), 6.53 (d, *J* = 15.4 Hz, 1 H), 6.75 (dd, *J* = 15.4, 10.4 Hz, 1 H), 7.19-7.38 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 25.4, 37.8, 71.6, 126.2, 127.4, 127.6, 128.5, 128.8, 132.0, 137.3, 141.7; HRMS (EI) *m/z* 228.1519 [$(M)^+$; calcd. for $C_{16}H_{20}O$ 228.1514].



9

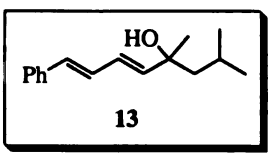
Preparation of 1,5-diphenylhexa-1,3-dien-5-ol (9) (Table 1, entry 4). Applying the hydrostannation procedure above to 2-phenylbut-3-yn-2-ol (**8**) (292.0 mg, 2 mmol) afforded after column chromatography [silica gel; 95:5 pentane/EtOAc, 1% Et_3N] of 2-phenyl-4-tributylstannylbut-3-en-2-ol (752 mg, 86%) as a clear oil. Applying the Stille conditions above to 1-(tributylstannyl)-3-phenyl-1-(*E*)-buten-3-ol (480 mg, 1.1 mmol) and (*E*)-β-bromostyrene (0.14 mL, 1.1 mmol) afforded after a 5 day reaction time and column chromatography [silica gel; 95:5 petroleum ether/EtOAc] 1,5-diphenyl-1,3-hexadien-5-ol (**9**) (180 mg, 65%; 56% from alkyne). IR ($CHCl_3$) 3592, 3088, 2930, 2861, 2400, 1725, 1684, 1599, 1449, 1360, 1111, 1073, 992, 981 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (s, 3 H), 2.07 (br, 1 H), 6.11 (d, *J* = 15.4 Hz, 1 H), 6.43 (dd, *J* = 15.3, 10.3 Hz, 1 H), 6.56 (d, *J* = 15.7 Hz, 1 H), 6.79 (dd, *J* = 15.6 Hz, 10.3 Hz, 1 H), 7.22-7.52 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 74.5, 125.2,

126.3, 127.0, 127.5, 128.3, 128.6, 132.8, 137.1, 140.5, 146.6; HRMS (EI) *m/z* 232.1254 $[(M - OH)]^+$; calcd. for $C_{18}H_{17}$ 232.1252].



11

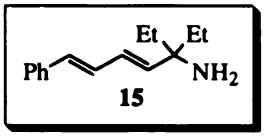
Preparation of 3-methyl-7-phenylhepta-4,6-dien-3-ol (11) (Table 1, entry 5). Applying the hydrostannation procedure above to 3-methylpent-1-yn-3-ol (**10**) (0.23 mL, 2 mmol) afforded after column chromatography [silica gel; 95:5 pentane/EtOAc, 1% Et_3N] of 3-methyl-1-tributylstannylpent-1-en-3-ol (624 mg, 80%) as a clear oil. Applying the Stille conditions above to 1-(tributylstannyl)-3-methyl-1-(*E*)-penten-3-ol (540 mg, 1.4 mmol) and (*E*)-β-bromostyrene (0.23 mL, 1.8 mmol) afforded after a 5 day reaction time and column chromatography [silica gel; 90:10 petroleum ether/EtOAc] 5-methyl-1-phenyl-1,3-hetadien-5-ol (**11**) (199 mg, 70%; 56% from alkyne). IR ($CHCl_3$) 3598, 3451, 3085, 2988, 2928, 2874, 1684, 1597, 1493, 1458, 1377, 1308, 1125, 992, 901 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.4 Hz, 3 H), 1.31 (s, 3 H), 1.60 (q, *J* = 7.4 Hz, 2 H), 5.86 (d, *J* = 15.4 Hz, 1 H), 6.38 (ddd, *J* = 15.4, 10.4, 0.6 Hz, 1 H), 6.53 (d, *J* = 15.7 Hz, 1 H), 6.76 (ddd, *J* = 15.7, 10.4, 0.6 Hz, 1 H), 7.16-7.39 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3, 27.4, 35.2, 77.0, 126.2, 127.3, 127.8, 128.5, 128.6, 131.9, 137.2, 140.8; HRMS (EI) *m/z* 202.1363 $[(M)^+$; calcd. for $C_{14}H_{18}O$ 202.1358].



13

Preparation of 2,4-dimethyl-8-phenylocta-5,7-dien-4-ol (13) (Table 1, entry 6). Applying the hydrostannation procedure above to 3,5-dimethyl-1-hexyn-1-ol (**12**) (757 mg, 6 mmol) afforded after column chromatography [silica gel; 90:10 pentane/EtOAc, 1% Et_3N] 3,5-dimethyl-1-tributylstannylhex-1-en-3-ol (1.94 g, 77%) as a clear oil. Applying the Stille conditions above to 3,5-dimethyl-1-tributylstannylhex-1-en-3-ol (1.30 g, 3.0 mmol) and (*E*)-β-

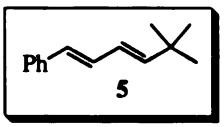
bromostyrene (620 mg, 3.3 mmol) in dry THF (5 mL) afforded after a 5 day reaction time and column chromatography [silica gel; 95:5 petroleum ether/EtOAc] 2,4-dimethyl-8-phenylocta-5,7-dien-4-ol (**13**) (306 mg, 45%; 35% from alkyne). IR ($CHCl_3$) 3594, 2955, 2928, 2870, 1690, 1597, 1464, 1368, 1310, 1111, 993 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, *J* = 4.7 Hz, 3 H), 0.94 (d, *J* = 4.4 Hz, 3 H), 1.33 (s, 3 H), 1.50 (d, *J* = 6.0 Hz, 2 H), 1.76 (m, 1 H), 5.88 (d, *J* = 15.4 Hz, 1 H), 6.39 (dd, *J* = 15.4, 10.4 Hz, 1 H), 6.53 (d, *J* = 15.7 Hz, 1 H), 6.76 (dd, *J* = 15.7, 10.4 Hz, 1 H), 7.22-7.39 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 24.6, 29.1, 51.4, 73.6, 126.2, 127.2, 127.3, 128.5, 128.6, 131.8, 137.3, 141.6; GC-MS (EI) *m/z* 212 (23) $[M - H_2O]^+$, 197 (11), 169 (55), 155 (15), 154 (11), 141 (17), 129 (12), 128 (15), 121 (18), 115 (25), 108 (13), 105 (20), 91 (100), 77 (19), 65 (8), 55 (8), 41 (16); HRMS (EI) *m/z* 212.1570 $[(M - H_2O)^+$; calcd. for $C_{16}H_{20}$ 212.1565.



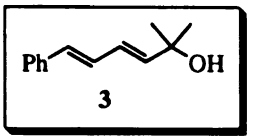
15

Preparation of 1,1-diethyl-5-phenylpenta-2,4-dienylamine (15) (Table 1, entry 7). Applying the hydrostannation procedure above to 1,1-diethylpropargylamine (**14**) (667 mg, 6 mmol) afforded after column chromatography [silica gel; 80:20 pentane/EtOAc, 1% Et_3N] 1,1-diethyl-3-tributylstannylallylamine (1.90 g, 80%) as a clear oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (m, 6 H), 0.87 (m. 15 H), 1.21-1.36 (m, 9 H), 1.38-1.57 (m, 9 H), 5.84 (d, *J* = 19.5 Hz, 1 H), 5.96 (d, *J* = 19.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.9, 9.5, 13.9, 27.3, 29.1, 33.7, 58.4, 123.0, 155.0. Applying the Stille conditions above to 1,1-diethyl-3-tributylstannylallylamine (1.30 g, 3.0 mmol) and (*E*)-β-bromostyrene (0.60 g, 3.3 mmol) in dry THF (5 mL) afforded after a 5 day reaction time and column chromatography [silica gel; 95:5 petroleum ether/EtOAc] 1,1-diethyl-5-phenylpenta-2,4-dienylamine (**15**)

(305 mg, 47%; 36% from alkyne). IR ($CHCl_3$) 3180, 2934, 2855, 1597, 1460, 1379, 992, 889 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.4 Hz, 6 H), 1.33 (br, 2 H), 1.48 (q, *J* = 7.4 Hz, 4 H), 5.74 (d, *J* = 15.4 Hz, 1 H), 6.28 (dd, *J* = 15.4, 10.4 Hz, 1 H), 6.49 (d, *J* = 15.7 Hz, 1 H), 6.78 (dd, *J* = 15.6, 10.3 Hz, 1 H), 7.15-7.38 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.1, 34.0, 56.3, 126.1, 127.1, 128.1, 128.6, 129.1, 130.9, 137.5, 142.4; GC-MS (EI) *m/z* 198 (44) $[M - NH_3]^+$, 183 (19), 169 (76), 155 (28), 154 (19), 153 (14), 152 (10), 141 (18), 129 (12), 128 (19), 115 (25), 107 (16), 105 (18), 92 (11), 91 (100), 79 (11), 77 (20), 64 (12); HRMS (EI) *m/z* 198.1411 $(M - NH_3)^+$; calcd. for $C_{15}H_{18}$ 198.1409.

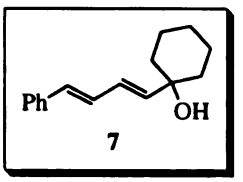


Representative Procedure for a Tandem One-Pot Hydrostannation/Stille Coupling with Bu_3SnH (Table 1). Preparation of (5,5-Dimethylhexa-1,3-dienyl)benzene (5) (Table 1, entry 2). Bu_3SnH (0.89 mL, 3.3 mmol) was added dropwise at 0 °C to a solution of 3,3-dimethylbut-1-yne (**4**) (0.37 mL, 3 mmol), (*E*)-β-bromostyrene (0.43 mL, 3.3 mmol), and $(PPh_3)_2PdCl_2$ (7 mg, 0.01 mmol) in THF (2 mL). The solution was allowed to warm to room temperature overnight and stirred at this temperature for an additional 2 days. The reaction mixture was then treated with a 10% aqueous NH_4OH solution (3 mL) and stirred for 4 h. The phases were separated, the aqueous layer was extracted with Et_2O, and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent afforded the crude product, which was purified by column chromatography [silica gel; petroleum ether] to yield (5,5-dimethylhexa-1,3-dienyl)benzene (**5**) (496 mg, 89%). For spectroscopic data see page 107-108.



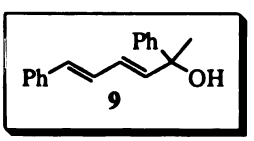
3

Preparation of 5-methyl-1-phenyl-1,3-hexadien-5-ol (3) with Bu_3SnH (Table 1, entry 1). Applying the conditions from above to 2-methylbut-3-yn-2-ol (**1**) (0.29 mL, 3 mmol) and (*E*)-β-bromostyrene (0.43 mL, 3.3 mmol) afforded after column chromatography [silica gel; 95:5 petroleum ether/EtOAc] 5-methyl-1-phenyl-1,3-hexadien-5-ol (**3**) (490 mg, 87%). For spectroscopic data see page 108-109.



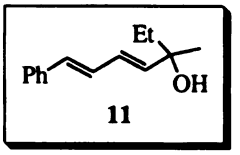
7

Preparation of 1-(4-phenylbuta-1,3-dienyl)cyclohexanol (7) with Bu_3SnH (Table 1, entry 3). The conditions from above were applied to 1-ethynylcyclohexanol (**6**) with the following modifications: After the addition of Bu_3SnH (0.89 mL, 3.3 mmol), the solution was allowed to warm to room temperature overnight and then heated for an additional 2 days to 45 °C. The reaction mixture was then treated with a 10% aqueous NH_4OH solution (3 mL) and stirred for 4 h. The phases were separated, the aqueous layer was extracted with Et_2O, and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent afforded the crude product, which was purified by column chromatography [silica gel; 95:5 petroleum ether/EtOAc] to afford 1-(4'-phenyl-1',3'-butadienyl)cyclohexan-1-ol (**7**) (349 mg, 51%). For spectroscopic data see page 110.



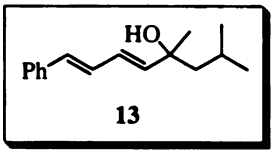
9

Preparation of 1,5-diphenyl-1,3-hexadien-5-ol (9) with Bu_3SnH (Table 1, entry 4). Applying the conditions from above to 2-phenylbut-3-yn-2-ol (**8**) (146 mg, 1 mmol) and (*E*)-β-bromostyrene (0.13 mL, 1 mmol) afforded after column chromatography [silica gel; 90:10 petroleum ether/EtOAc] 1,5-diphenyl-1,3-hexadien-5-ol (**9**) (188 mg, 75%). For spectroscopic data see page 110-111.



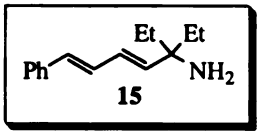
11

Preparation of 3-methyl-7-phenylhepta-4,6-dien-3-ol (11) with Bu_3SnH (Table 1, entry 5). Applying the conditions from above to 3-methylpent-1-yn-3-ol (**10**) (0.34 mL, 3 mmol) and (*E*)-β-bromostyrene (0.43 mL, 3.3 mmol) afforded after column chromatography [silica gel; 95:5 petroleum ether/EtOAc] 3-methyl-7-phenylhepta-4,6-dien-3-ol (**11**) (520 mg, 86%). For spectroscopic data see page 111.



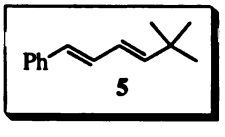
13

Preparation of 2,4-dimethyl-8-phenylocta-5,7-dien-4-ol (13) with Bu_3SnH (Table 1, entry 6). Applying the conditions from above using 3,5-dimethylhex-1-yn-3-ol (**12**) (0.44 mL, 3 mmol) and (*E*)-β-bromostyrene (0.43 mL, 3.3 mmol) afforded after column chromatography [silica gel; 95:5 petroleum ether/EtOAc] 2,4-dimethyl-8-phenylocta-5,7-dien-4-ol (**13**) (523 mg, 76%). For spectroscopic data see page 112.



15

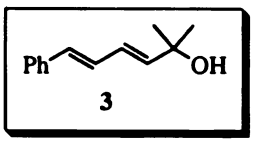
Preparation of 1,1-diethyl-5-phenylpenta-2,4-dienylamine (15) with Bu_3SnH (Table 1, entry 7). Applying the conditions from above to 1,1-diethylprop-2-ynylamine (**14**) (0.40 mL, 3 mmol) and (*E*)-β-bromostyrene (0.43 mL, 3.3 mmol) afforded after column chromatography [silica gel; 80:20 petroleum ether/EtOAc] 1,1-diethyl-5-phenylpenta-2,4-dienylamine (**15**) (190 mg, 29%) and recovered stannane (450 mg, 37%). For spectroscopic data see page 112-113.



5

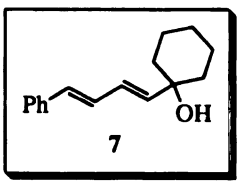
Representative procedure for one-pot hydrostannation/Stille coupling with in situ generated tin hydride (bistributyltin oxide and polymethylhydrosiloxane). Preparation of (5,5-dimethylhexa-1,3-dienyl)benzene (5) (Table 1, entry 2). A solution of 3,3-dimethylbut-1-yne (**4**) (0.37 mL, 3 mmol), $(Bu_3Sn)_2O$ (1.86 mL, 3.6 mmol), PMHS (0.42 mL, 7.2 mmol), (*E*)-β-bromostyrene (0.43

mL, 3.3 mmol), and $(PPh_3)_2$ $PdCl_2$ (7 mg, 0.01 mmol) in dry THF (2 mL) was stirred at room temperature for 5 days and then heated to reflux for 5 more days. Then a concentrated aqueous KF solution was added to the reaction mixture, which was stirred for 3 h. The phases were separated, the aqueous layer was extracted with Et_2O, and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent afforded the crude product, which was purified by radial chromatography [silica gel; petroleum ether] to yield (5,5-dimethylhexa-1,3-dienyl)benzene (**5**) (288 mg, 52%). For spectroscopic data see page 109-110.



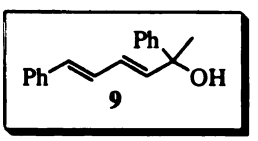
3

Preparation of 5-methyl-1-phenyl-1,3-hexadien-5-ol (3) with $(Bu_3Sn)_2O$/PMHS (Table 1, entry 1). Applying the conditions from to 2-methylbut-3-yn-2-ol (**1**) (0.29 mL, 3 mmol) and (*E*)-β-bromostyrene (0.43 mL, 3.3 mmol) afforded after radial chromatography [silica gel; 95:5 petroleum ether/EtOAc] 5-methyl-1-phenyl-1,3-hexadien-5-ol (**3**) (370 mg, 66%). For spectroscopic data see page 108-109.



7

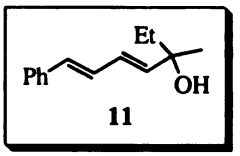
Preparation of 1-(4-phenylbuta-1,3-dienyl)cyclohexanol (7) with $(Bu_3Sn)_2O$/PMHS (Table 1, entry 3). Applying the conditions from above to 1-ethynylcyclohexanol (**6**) (375 mg, 3 mmol) and (*E*)-β-bromostyrene (0.4 mL, 3.1 mmol) afforded after column chromatography [silica gel; 95:5 petroleum ether/EtOAc] 1-(4-phenylbuta-1,3-dienyl)-cyclohexanol (**7**) (354 mg, 52%). For spectroscopic data see page 110.



9

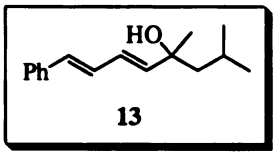
Preparation of 1,5-diphenyl-1,3-hexadien-5-ol (9) with $(Bu_3Sn)_2O$/PMHS (Table 1, entry 4). Applying the conditions from above to 2-phenylbut-3-yn-2-ol (**8**) (438 mg, 3 mmol) and (*E*)-β-bromostyrene (0.43 mL,

3.3 mmol) afforded after radial chromatography [silica gel; 95:5 petroleum ether/EtOAc] 1,5-diphenyl-1,3-hexadien-5-ol (**9**) (518 mg, 69%). For spectroscopic data see page 110-111.



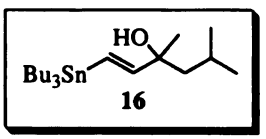
11

Preparation of 3-methyl-7-phenylhepta-4,6-dien-3-ol (111) with $(Bu_3Sn)_2O$/PMHS (Table 1, entry 5). Applying the conditions from above to 3-methylpent-1-yn-3-ol (**10**) (0.35 mL, 3 mmol) and (*E*)-β-bromostyrene (0.4 mL, 3.1 mmol) afforded after radial chromatography [silica gel; 95:5 petroleum ether/EtOAc] 3-methyl-7-phenylhepta-4,6-dien-3-ol (**11**) (364 mg, 60%). For spectroscopic data see page 111.



13

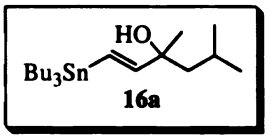
Preparation of 2,4-dimethyl-8-phenylocta-5,7-dien-4-ol (13) with $(Bu_3Sn)_2O$/PMHS (Table 1, entry 6). Applying the conditions from to 3,5-dimethylhex-1-yn-3-ol (**12**) (0.44 mL, 3 mmol) and (*E*)-β-bromostyrene (0.4 mL, 3.1 mmol) afforded after column chromatography [silica gel; 95:5 petroleum ether/EtOAc] 2,4-dimethyl-8-phenylocta-5,7-dien-4-ol (**13**) (400 mg, 58%). For spectroscopic data see page 112.



16

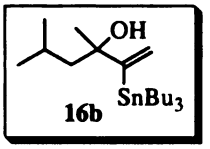
Pd(0)-mediated hydrostannation with Bu_3SnCl/NH_4OH/PMHS gnerated Bu_3SnH. Preparation of 3,5-dimethyl-1-tributylstannylhex-1-en-3-ol (16) (Scheme 2, entry 1). To a mixture of Bu_3SnCl (2 mmol, 0.46 mL) and aqueous NH_4OH (2 mL) in Et_2O were added 3,5-dimethylhex-1-yn-3-ol (**12**) (2 mmol, 0.29 mL), PMHS dimer (2 mmol, 0.66 mL), and $(PPh_3)_2PdCl_2$ (14 mg, 0.02 mmol). The solution was stirred at room temperature for 1.5 h and then heated overnight. TLC showed a greater than 1:1 ratio for alkyne/stannane; however, upon

column chromatography [silica gel; 95:5 pentane/EtOAc] only 3,5-dimethyl-1-tributylstannylhex-1-en-3-ol (**16**) (117 mg, 14%) was isolated.



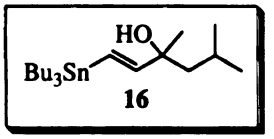
16a

For **16a**: IR ($CHCl_3$) 3594, 3463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86-0.95 (m, 21 H), 1.22-1.37 (m, 9 H), 1.42-1.55 (m, 8 H), 1.60-1.72 (m, 1 H), 6.01 (d, J = 19.3 Hz, 1 H), 6.08 (d, J = 19.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 122.5, 75.1, 50.8, 29.1, 28.9, 27.3, 24.6, 25.5, 24.4, 13.7, 9.4; HRMS (EI) *m/z* 361.1576 [(M^+ - Bu); calcd. for $C_{16}H_{33}OSn$ 361.1556].



16b

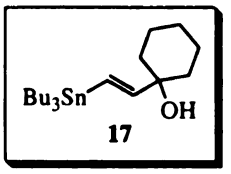
For **16b**: IR ($CHCl_3$) 3594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84-0.99 (m, 21 H), 1.20-1.37 (m, 9 H), 1.42-1.55 (m, 8 H), 1.62-1.70 (m, 1 H), 5.16 (d, J = 1.4 Hz, 1 H), 5.66 (d, J = 1.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 121.1. 78.4, 51.0, 29.8, 29.1, 27.5, 24.8, 24.7, 24.3, 13.7, 10.7; HRMS (EI) *m/z* 361.1562 [(M^+ - Bu); calcd. for $C_{16}H_{33}OSn$ 361.1556].



16

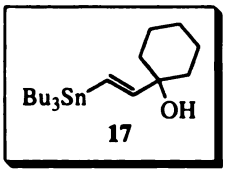
Pd(0)-mediated hydrostannation with Bu_3SnCl/NH_4OH/PMHS generated Bu_3SnH. Preparation of 3,5-dimethyl-1-tributylstannylhex-1-en-3-ol (16) (Scheme 2, entry 2). Aqueous NH_4OH (5 mL) was added to a solution of 3,5-dimethylhex-1-yn-3-ol (**12**) (0.29 mL, 2 mmol), Bu_3SnCl (0.46 mL, 2 mmol), PMHS dimer (0.33 mL, 1 mmol), $(PPh_3)_2PdCl_2$ (3.5 mg, 0.005 mmol) in EtOH (1 mL), and toluene (2 mL). The reaction mixture was heated to 55 °C for 30 min; TLC showed only formation of tin dimer and stannane and a small amount of unreacted alkyne. The solution was heated for an additional 6 h, but the composition did not change any further. The mixture was then washed with water, and the organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solvent yielded the crude product. ^1H NMR showed a 1.7:1 ratio of stannane/alkyne and a 21:1 ratio of (*E*)/int-stannane.

Column chromatography [silica gel; 96:4 hexane/EtOAc, 1% TEA] afforded 3,5-dimethyl-1-tributylstannylhex-1-en-3-ol (**16**) (177 mg, 21%). For spectroscopic data see page 119.



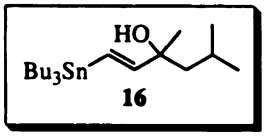
17

Pd(0)-Mediated Hydrostannation with Bu_3SnOMe/PMHS Generated Bu_3SnH. Preparation of 1-(2-tributylstannylvinyl) cyclohexanol (17) (Scheme 3, reaction 1). PMHS (0.06 mL, 1.1 mmol) was added dropwise at 0 °C under N_2 to a solution of 1-ethynylcyclohexanol (**5**) (124 mg, 1 mmol), Bu_3SnOCH_3 (0.29 mL, 1 mmol), and $(PPh_3)_2PdCl_2$ (3.5 mg, 0.005 mmol) in THF (2 mL). The solution was stirred for 1.5 h until GC showed a 13:1 ratio of stannane/Bu_3SnOCH_3. The solvent was evaporated, and column chromatography [silica gel; 95:5 petroleum ether/EtOAc, 1% TEA] afforded 1-(2-tributylstannylvinyl)cyclohexanol (**16**) (220 mg, 52%) as an oil.[155]



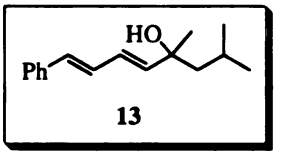
17

Pd(0)-Mediated Hydrostannation with Bu_3SnBr/NaOMe/PMHS Generated Bu_3SnH. Preparation of 1-(2-tributylstannylvinyl)cyclohexanol (17) Using Bu_3SnBr (Scheme 3, reaction 3). To a solution of 1-ethynylcyclohexanol (**6**) (124 mg, 1 mmol), Bu_3SnBr (90%, 0.31 mL, 1 mmol), and $(PPh_3)_2PdCl_2$ (3.5 mg, 0.005 mmol) in dry THF (1 mL) were added $NaOCH_3$ (162 mg, 3 mmol) and PMHS (0.06 mL, 1.1 mmol) at 0 °C under N_2. GC analysis after 15 min showed complete conversion of Bu_3SnBr. The mixture was washed with water; the organic phase was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography [silica gel; 95:5 petroleum ether/EtOAc, 1% TEA] to yield 1-(2-tributylstannyl vinyl)cyclohexanol (**17**) (220 mg, 52%) as an oil.[155]



16

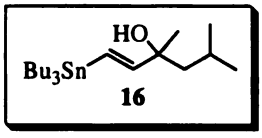
Pd(0)-mediated hydrostannation with Bu_3SnCl/NH_4OH/PMHS generated Bu_3SnH. Preparation of 3,5-dimethyl-1-tributylstannylhex-1-en-3-ol (16) (Scheme 3, reaction 3). $NaOCH_3$ (54 mg, 1 mmol) was added at -10 °C to a solution of 3,5-dimethylhex-1-yn-3-ol (**12**) (0.145 mL, 1 mmol), PMHS (0.06 mL, 1.1 mmol), Bu_3SnCl (0.27 mL, 1 mmol), and $(PPh_3)_2PdCl_2$ (3.5 mg, 0.005 mmol) in THF (1 mL). After stirring for 1.5 h at 0 °C, the reaction mixture was cooled to -7 °C again, treated with PMHS (0.06 mL, 1.1 mmol) and $NaOCH_3$ (110 mg, 2 mmol), and allowed to warm to 0 °C within 1 h. The solvent was then evaporated and the crude product purified by column chromatography [silica gel; 95:5 petroleum ether/EtOAc, 1% TEA] to yield 3,5-dimethyl-1-tributylstannylhex-1-en-3-ol (**16**) (306 mg, 74%) as an oil. For spectroscopic data see page 119.



13

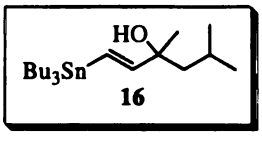
Attempted tandem one-pot hydrostannation/Stille cross coupling using substoichiometric amounts of tin (20 mol % of $(Bu_3Sn)_2O$ and $NaOCH_3$ and PMHS]. Preparation of 2,4-dimethyl-8-phenylocta-5,7-dien-4-ol (13) (Scheme 4). A solution of 3,5-dimethylhex-1-yn-3-ol (**12**) (0.15 mL, 1 mmol), (*E*)-β-bromostyrene (0.13 mL, 1 mmol), $(Bu_3Sn)_2O$ (0.1 mL, 0.2 mmol), PMHS (0.07 mL, 1.2 mmol), and $(PPh_3)_2PdCl_2$ (7 mg, 0.01 mmol) in THF was treated with $NaOCH_3$ (65 mg, 1.2 mmol). Gas evolution occurred, and the reaction mixture was heated to 60 °C. After 5 h additional PMHS (0.07 mL, 1.2 mmol) and $NaOCH_3$ (65 mg, 1.2 mmol) were added. The solution was heated overnight, additional PMHS (0.07 mL, 1.2 mmol) was added, and after an additional 3 h at 60 °C, a 10% aqueous NH_4OH solution was added. The aqueous phase was extracted with Et_2O, and the combined organic phases were washed with brine and dried over $MgSO_4$. After

evaporation of the solvent, the crude product was purified by column chromatography [silica gel; 95:5 petroleum ether/EtOAc] to yield 2,4-dimethyl-8-phenylocta-5,7-dien-4-ol (**13**) (8 mg, 3%) as an oil. S For spectroscopic data see page 112.



16

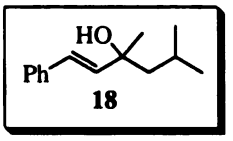
Pd(0)-mediated hydrostannation with Bu_3SnCl/NaOPh/PMHS generated Bu_3SnH using THF as the solvent. Preparation of 3,5-dimethyl-1-tributylstannylhex-1-en-3-ol (16) (Scheme 5, hydrostannation). Phenol (188 mg, 2 mmol) and Na (46 mg, 2 mmol) were stirred in dry THF until the sodium was dissolved. This solution was added to a mixture of 3,5-dimethylhex-1-yn-3-ol (**12**) (0.145 mL, 1 mmol), Bu_3SnCl (0.27 mL, 1 mmol), $(PPh_3)_2PdCl_2$ (3.5 mg, 0.005 mmol), and THF. A very fine precipitation of NaCl formed, and TLC indicated complete conversion of Bu_3SnCl into the phenoxide. PMHS (0.09 mL, 1.5 mmol) was added at room temperature, and after 15 min TLC showed complete conversion of the alkyne. The solvent was evaporated, and ^1H NMR of the crude product showed a 14:1 ratio for (*E*)/int-stannane. Column chromatography [silica gel; 95:5 pentane/EtOAc] afforded 3,5-dimethyl-1-tributylstannylhex-1-en-3-ol (**16**) (250 mg, 71%). For spectroscopic data see page 119.



16

Pd(0)-mediated hydrostannation with Bu_3SnCl/NaOPh/PMHS generated Bu_3SnH using dioxane/THF (1:1) as the solvent. Preparation of 3,5-dimethyl-1-tributylstannylhex-1-en-3-ol (16) (Scheme 5, hydrostannation). Phenol (188 mg, 2 mmol) and Na (46 mg, 2 mmol) were stirred in dry THF until the sodium was dissolved. This solution was added to a mixture of 3,5-dimethylhex-1-yn-3-ol (**12**) (0.145 mL, 1 mmol), Bu_3SnCl (0.27 mL, 1 mmol), $(PPh_3)_2PdCl_2$ (3.5 mg, 0.005 mmol), and THF/Dioxane (1:1). A very fine precipitation of

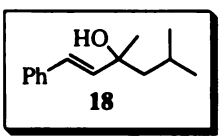
NaCl formed, and TLC indicated complete conversion of Bu_3SnCl into the phenoxide. PMHS (0.09 mL, 1.5 mmol) was added at room temperature, and after 15 min TLC showed complete conversion of the alkyne. The solvent was evaporated, and ^1H NMR of the crude product showed a 12:1 ratio for (*E*)/int-stannane. Column chromatography [silica gel; 95:5 pentane/EtOAc] afforded 3,5-dimethyl-1-tributylstannylhex-1-en-3-ol (**16**) (162 mg, 46%). For spectroscopic data see page 119.



18

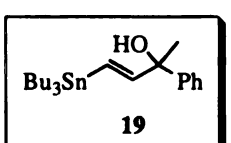
Bu_3SnCl/NaOPh/PMHS mediated tandem one-pot hydrostannation/Stille coupling. Preparation of 3,5-dimethyl-1-phenylhex-1-en-3-ol (18) (Scheme 5, one-pot). To a solution of Pd_2dba_3 (9.2 mg, 0.01 mmol), TFP (9.3 mg, 0.04 mmol), Bu_3SnCl (0.27 mL, 1 mmol), and NaOPh (0.5 mL of 4 M solution in THF, 2 mmol) in THF (2 mL) were added 3,5-dimethylhex-1-yn-3-ol (**12**) (0.145 mL, 1 mmol) and PMHS (0.09 mL, 1.5 mmol). The reaction mixture was stirred until TLC showed complete consumption of the alkyne. Iodobenzene (0.33 mL, 3 mmol) was added, and the solution was heated to reflux for 5 h. During this time additional iodobenzene (0.05 mL, 0.45 mmol) was added. A saturated aqueous KF solution was added, and the reaction mixture was stirred for additional 3 h. The organic phase was washed with water and brine and dried over $MgSO_4$. After evaporation of the solvent, column chromatography [silica gel; 95:5 pentane/EtOAc] of the crude product yielded of 3,5-dimethyl-1-phenylhex-1-en-3-ol (**18**) (110 mg, 54%). See above for spectroscopic data. IR ($CHCl_3$) 3594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91-0.99 (m, 6 H), 1.34 (s, 3 H), 1.35-1.81 (m, 3 H), 6.27 (d, J = 16.2 Hz, 1 H), 6.57 (d, J = 16.2 Hz, 1 H), 7.20-7.39 (m, 5 H), (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 24.6, 29.22, 51.5, 73.7,

126.3, 126.42, 127.2, 128.5, 137.1, 137.2; HRMS (EI) *m/z* 204.1465 [$(M)^+$; calcd for $C_{14}H_{20}O$ 204.1412].



18

Attempted tandem one-pot hydrostannation/Stille coupling with substoichiometric amounts of Bu_3SnCl/NaOPh/PMHS generated Bu_3SnH. Preparation of 3,5-dimethyl-1-phenylhex-1-en-3-ol (18) (Scheme 6). A NaOPh solution in THF (prepared from PhOH (94 mg, 1 mmol) and Na (23 mg, 1 mmol) was added to a solution of Bu_3SnCl (0.14 mL, 0.5 mmol), 3,5-dimethylhex-1-yn-3-ol (**12**) (0.07 mL, 0.5 mmol), Pd_2dba_3 (13 mg, 0.014 mmol), and TFP (13 mg, 0.06 mmol) in dry THF (2 mL). After stirring at room temperature for 15 min, PMHS (0.03 mL, 0.5 mmol) and iodobenzene (0.1 mL, 1 mmol) were added and the mixture was heated to 60 °C. After 30 min, an additional 2 equiv of iodobenzene was added and the solution was heated for an additional 2 h. 3,5-Dimethylhex-1-yn-3-ol (0.07 mL, 0.5 mmol) and a NaOPh solution in THF (0.25 mL, 4 M) were added. After stirring at room temperature for 15 min, PMHS (0.03 mL, 0.05 mmol) was added and the reaction mixture was heated until TLC showed complete consumption of stannane. The reaction mixture was extracted with water, and the organic phase was dried over $MgSO_4$, concentrated, and purified by column chromatography [silica gel; 97:3 pentane/EtOAc] to yield 3,5-dimethyl-1-phenylhex-1-en-3-ol (**18**) (112 mg, 55%). See For spectroscopic data see page 123-124.



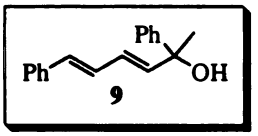
19

Pd(0)-mediated hydrostannation with Bu_3SnCl/Na_2CO_3/PMHS generated Bu_3SnH. Preparation of 2-phenyl-4-tributylstannyl-but-3-en-2-ol (19) (Scheme 3) (Scheme 7). A mixture of 2-phenylbut-3-yn-2-ol (**8**) (125 mg, 0.85 mmol), Bu_3SnCl (0.27 mL, 1 mmol), PMHS (0.12 mL, 2

mmol), $(PPh_3)_2PdCl_2$ (4.6 mg, 0.006 mmol), and Na_2CO_3 (318 mg, 3 mmol) in H_2O (0.5 mL) and Et_2O (5 mL) was heated to reflux for 30 min before additional PMHS (0.12 mL, 2 mmol) and Na_2CO_3 (159 mg, 1.5 mmol) were added. After heating the solution for an additional 5.5 h, water was added and the phases were separated. The organic phase was washed with brine and dried over $MgSO_4$. After evaporation of the solvent the crude product was purified by column chromatography [silica gel; 95:5 petroleum ether/EtOAc, 1% TEA] to yield a 15:1 separable mixture of 2-phenyl-4-tributylstannylbut-3-en-2-ol (**19a**) and 2-phenyl-3-tributylstannylbut-3-en-2-ol (**19b**) (278 mg, 75%).

For (*E*)-product (**19a**): IR (neat) 3592 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83-0.91 (m, 15 H), 1.22-1.34 (m, 6 H), 1.42-1.53 (m, 6 H), 1.62 (s, 3 H), 6.19 (d, J = 19.2 Hz, 1 H), 6.28 (d, J = 19.2 Hz, 1 H), 7.20- 7.46 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.5, 13.7, 27.2, 29.1, 29.2, 76.1, 124.5, 125.3, 126.8, 128.1, 146.7, 153.8; HRMS (EI) *m/z* 379.1225 [(M^+-Bu); calcd. for $C_{18}H_{29}O^{118}Sn$ 379.1238.

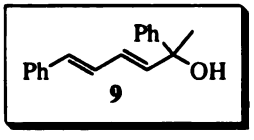
For the Int product (**19b**): IR (neat) 3596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.70-0.95 (m, 15 H), 1.18-1.34 (m, 6 H), 1.35-1.58 (m, 6 H), 1.65 (s, 3 H), 5.28 (d, J = 1.4 Hz, 1 H), 5.77 (d, J = 1.4 Hz, 1 H), 7.20- 7.44 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 13.7, 27.4, 29.0, 30.0, 79.1, 122.5, 125.5, 126.7, 128.0, 147.0, 163.4; HRMS (EI) *m/z* 363.1135 [(M^+-Bu-H_2O); calcd. for $C_{18}H_{27}OSn$ 363.1138].



9

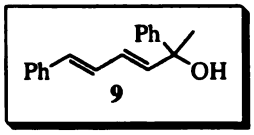
One-pot hydrostannation/Stille cross coupling with Bu_3SnCl and Na_2CO_3/PMHS generated Bu_3SnH. Preparation of 2,6-diphenylhexa-3,5-dien-2-ol (9) (Scheme 8). A mixture of Pd_2dba_3 (9.2 mg, 0.01 mmol) and TFP (9.3 mg, 0.04 mmol) in Et_2O (5 mL) was stirred at room temperature for 15 min before Bu_3SnCl (0.84 mL, 3 mmol), Na_2CO_3 (638 mg, 6 mmol), and H_2O (2 mL) were

added. Over a period of 18 h a solution of 2-phenylbut-3-yn-2-ol (**8**) (438 mg, 3 mmol), (*E*)-β-bromostyrene (0.67 mL, 5 mmol), and PMHS (0.3 mL, 5 mmol) in Et_2O (5 mL) was added with a syringe pump to the refluxing solution. The solution was stirred for an additional 4 days; then a saturated aqueous KF solution was added and the reaction mixture was stirred for an additional 3 h. The organic phase was washed with water and brine and dried over $MgSO_4$. After evaporation of the solvent, radial chromatography [silica gel; 95:5 pentane/EtOAc] of the crude product yielded 2,6-diphenylhexa-3,5-dien-2-ol (**9**) (354 mg, 47%). See For spectroscopic data see page 110-111.



9

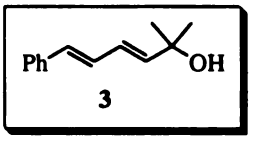
Tandem hydrostannation/Stille cross coupling using substoichiometric amounts of tin (20 mol % of Bu_3SnCl and PMHS). Preparation of 2,6-diphenylhexa-3,5-dien-2-ol (9) (Table 2, entry 1). A mixture of Pd_2dba_3 (9.2 mg, 0.01 mmol) and TFP (9.3 mg, 0.04 mmol) in Et_2O (5 mL) was stirred for 15 min at room temperature. 2-Phenylbut-3-yn-2-ol (**8**) (146 mg, 1 mmol), Bu_3SnCl (0.05 mL, 0.2 mmol), (*E*)-β-bromostyrene (0.13 mL, 1 mmol), Na_2CO_3 (560 mg, 5 mmol), PMHS (0.15 mL, 2.5 mmol), and H_2O (1 mL) were added, and the mixture was heated to reflux. After 1 h additional Na_2CO_3 (560 mg, 5 mmol) and after 2 h and 3.5 h additional PMHS (2×, 0.15 mL, 2.5 mmol) were added. The reaction mixture was refluxed for a total of 7.5 h and filtered, and the filtrate was washed with ether. After evaporation of the solvent, the residue was purified by column chromatography [silica gel; 90:10 petroleum ether/EtOAc] to yield 2,6-diphenylhexa-3,5-dien-2-ol (**9**) (100 mg, 40%). See For spectroscopic data see page 110-111.



9

Tandem hydrostannation/Stille cross coupling using substoichiometric amounts of tin (4 mol % of Bu_3SnCl and

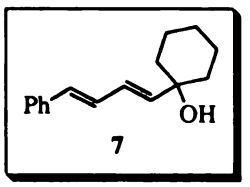
PMHS). Preparation of 2,6-diphenylhexa-3,5-dien-2-ol (9) (Table 2, entry 2). A solution of Pd_2dba_3 (9.2 mg, 0.01 mmol) and TFP (9.3 mg, 0.04 mmol) in ether (5 mL) was stirred for 15 min before (*E*)-β-bromostyrene (0.67 mL, 5 mmol), Bu_3SnCl (0.05 mL, 0.185 mmol), $(PPh_3)_2PdCl_2$ (7 mg, 0.01 mmol), Na_2CO_3 (425 mg, 4 mmol), and H_2O (1 mL) were added. While the solution was stirred at room temperature, a solution of 2-phenylbut-3-yn-2-ol (**8**) (730 mg, 5 mmol) and PMHS (0.45 mL, 7.5 mmol) in Et_2O (3 mL) was added with a syringe pump. After 5.5 h additional Na_2CO_3 (425 mg, 4 mmol) in H_2O (1 mL) were added. After 3 days at room temperature, an aqueous NH_4OH solution (10%, 2 mL) was added to the reaction mixture, which was then stirred for 30 min and extracted with ether. The organic phase was washed with water and brine and dried over $MgSO_4$. After evaporation of the solvent, column chromatography [silica gel; 100:0 to 90:10 petroleum ether/EtOAc] of the residue afforded 2,6-diphenylhexa-3,5-dien-2-ol (**9**) (250 mg, 22%). S See For spectroscopic data see page 110-111.



3

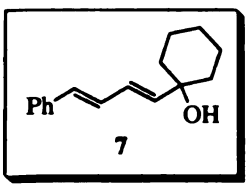
Tandem hydrostannation/Stille cross coupling using substoichiometric amounts of tin (10 mol % of Bu_3SnCl and PMHS). Preparation of 5-methyl-1-phenyl-1,3-hexadien-5-ol (3) (Table 2, entry 3). A mixture of Pd_2dba_3 (18.4 mg, 0.02 mmol) and TFP (18.6 mg, 0.08 mmol) in Et_2O (5 mL) was stirred for 15 min at room temperature. 2-Methylbut-3-yn-2-ol (**1**) (0.1 mL, 1 mmol), Bu_3SnCl (0.056 mL, 0.2 mmol), Na_2CO_3 (212 mg, 2 mmol), PMHS (0.12 mL, 2 mmol), (*E*)-β-bromostyrene (0.15 mL, 1.15 mmol), and H_2O (1 mL) were added, and the reaction mixture was heated to reflux for 1 h before additional alkyne (0.1 mL, 1 mmol) was added. After refluxing for 23 h, a saturated aqueous KF solution was added and the mixture was stirred for 3 h. The phases were separated; the organic phase was washed

with brine and dried over $MgSO_4$. Evaporation of the solvent and radial chromatography [silica gel; 97:3 pentane/EtOAc] yielded 5-methyl-1-phenyl-1,3-hexadien-5-ol (**3**) (90 mg, 42% ((*E*)-β-bromostyrene as limiting reagent), 2.4 cycles). See For spectroscopic data see page 108-109.



7

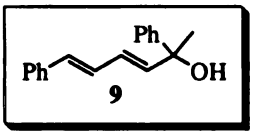
Tandem hydrostannation/Stille cross coupling using substoichiometric amounts of tin (10 mol % of Bu_3SnCl and PMHS). Preparation of 1-(4-phenylbuta-1,3-dienyl)cyclohexanol (7) (Table 2, entry 4). A mixture of Pd_2dba_3 (18.4 mg, 0.02 mmol) and TFP (18.6 mg, 0.08 mmol) in Et_2O (5 mL) was stirred for 15 min at room temperature. 1-ethynylcyclohexanol (**6**) (124 mg, 1 mmol), Bu_3SnCl (0.056 mL, 0.2 mmol), Na_2CO_3 (212 mg, 2 mmol), PMHS (0.12 mL, 2 mmol), (*E*)-β-bromostyrene (0.15 mL, 1.15 mmol), and H_2O (1 mL) were added, and the reaction mixture was heated to reflux for 1 h before additional alkyne (0.1 mL, 1 mmol) was added. After refluxing for 12 h, additional (*E*)-β-bromostyrene (0.15 mL, 1.15 mmol) was added together with PMHS (0.12 mL, 2 mmol). The solution was heated for an additional 24 h; then saturated aqueous KF solution was added and the mixture was stirred for 3 h. The phases were separated, and the organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solvent and radial chromatography [silica gel; 97:3 pentane/EtOAc] yielded 1-(4-phenylbuta-1,3-dienyl)cyclohexanol (**7**) (117 mg, 26%). See For spectroscopic data see page 110.



7

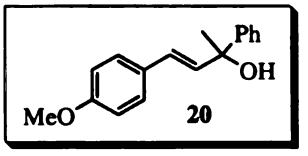
Representative procedure for the tandem one-pot hydrostannation/Stille cross coupling with catalytic amounts of tin using Me_3SnCl. Preparation of 1-(4'-phenyl-1'-3'-

butadienyl)cyclohexan-1-ol (7) (Table 3, entry 1). Tri-2-furylphosphine (9.3 mg, 0.04 mmol) was added to a solution of Pd_2dba_3 (9.2 mg, 0.01 mmol) in dry diethyl ether (5 mL). After 15 min of stirring the solution at room temperature, 1-ethynyl-1-cyclohexanol (**6**) (124 mg, 1.0 mmol), PMHS (0.1 mL, 1.5 mmol), Me_3SnCl (0.06 mL of a 1 M solution in THF, 0.06 mmol), Na_2CO_3 (85 mg, 0.8 mmol), H_2O (0.5 mL), and $(PPh_3)_2PdCl_2$ (7 mg, 0.01 mmol) were added. The reaction was heated to reflux, and a solution of (*E*)-β-bromostyrene (275 mg, 1.5 mmol) in diethyl ether (4 mL) was added dropwise via a syringe pump (0.24 mL/h). When the addition was complete, an aqueous NH_4OH solution (10%, 2 mL) was added and the reaction mixture stirred for 30 min. The reaction was then filtered and separated, and the aqueous phase was extracted with diethyl ether. The organics were combined, washed with water and then brine, dried over $MgSO_4$, and filtered. The solvent was evaporated, and the residue was purified by column chromatography [silica gel; 90:10 pentane/EtOAc, 1% Et_3N] to afford 1-(4'-phenyl-1'-3'-butadienyl)cyclohexan-1-ol (**7**) (205 mg, 90%) as an oil. See For spectroscopic data see page 110.



9

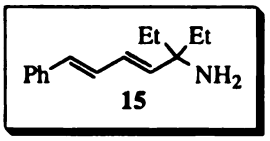
Preparation of 1,5-diphenyl-1,3-hexadien-5-ol (9) (Table 3, entry 2). Applying the conditions above to 2-phenyl-3-butyn-2-ol (**8**) (146 mg, 1.0 mmol) and (*E*)-β-bromostyrene (275 mg, 1.5 mmol) afforded after column chromatography [silica gel; 80:20 pentane/EtOAc, 1% Et_3N] 1,5-diphenyl-1,3-hexadien-5-ol (**9**) (211 mg, 85%) as an oil. See For spectroscopic data see page 110-111.



20

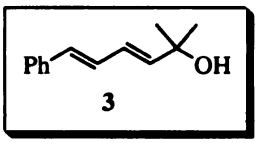
Preparation of 2-phenyl-4-(*p*-methoxyphenyl)-3-buten-2-ol (20) (Table 3, entry 3). Applying the conditions above to 2-phenyl-3-butyn-2-ol (**8**) (292 mg, 2.0 mmol) and *p*-iodoanisole

(702 mg, 3.0 mmol) afforded after column chromatography [silica gel; 90:10 pentane/EtOAc, 1% Et_3N] 2-phenyl-4-(*p*-methoxyphenyl)-3-buten-2-ol (**20**) (204 mg, 80%) as an oil.[202]



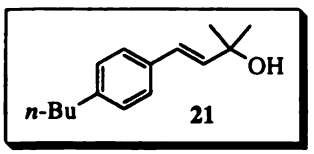
15

Preparation of 5-amino-5-ethyl-1-phenyl-1,3-heptadiene (15) (Table 3, entry 4). Applying the conditions above to 1,1-diethylpropargylamine (**14**) (111 mg, 0.14 mL, 1.0 mmol) and (*E*)-β-bromostyrene (275 mg, 1.5 mmol) afforded after column chromatography [silica gel; 50:50 pentane/EtOAc, 1% Et_3N] 5-amino-5-ethyl-1-phenyl-1,3-heptadiene (**15**) (170 mg, 86%) as an oil. See For spectroscopic data see page 112-113.



3

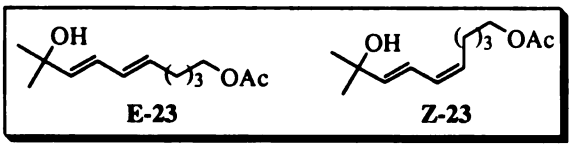
Preparation of 5-methyl-1-phenyl-1,3-hexadien-5-ol (3) (Table 3, entry 5). Applying the conditions above to 2-methyl-3-butyn-2-ol (**1**) (84 mg, 0.10 mL, 1.0 mmol) and (*E*)-β-bromostyrene (275 mg, 1.5 mmol) afforded after column chromatography [silica gel; 90:10 pentane/EtOAc, 1% Et_3N] 5-methyl-1-phenyl-1,3-hexadien-5-ol (**3**) (173 mg, 91%) as an oil which gave spectroscopic data consistent with that previously reported. See For spectroscopic data see page 108-109.



21

Preparation of 2-methyl-4-(*p*-*n*-butylphenyl)-3-buten-2-ol (21) (Table 3, entry 6). Applying the conditions above to 2-methyl-3-butyn-2-ol (**1**) (168 mg, 0.20 mL, 2.0 mmol) and *p*-*n*-butyliodobenzene (780 mg, 3 mmol) afforded after column chromatography [silica gel; 90:10 pentane/EtOAc, 1% Et_3N] 2-methyl-4-(*p*-*n*-butylphenyl)-3-buten-2-ol (**21**) (328 mg, 75%) as an oil. IR (neat) 3327 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (m, 3 H), 1.2-1.45 (m, 8 H), 1.58 (m, 2 H), 2.58 (t, J = 7.7 Hz, 2 H), 6.32 (d, J = 16.2 Hz 1 H), 6.56 (d, J = 15.9 Hz, 1 H), 7.12 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 7.9 Hz, 2 H); ^{13}C NMR (75

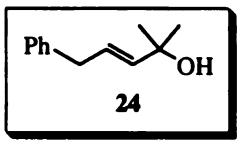
MHz, $CDCl_3$) δ 13.9, 22.3, 29.8, 33.6, 35.3, 71.1, 126.2, 126.3, 128.6, 134.2, 136.5, 142.3; HRMS (EI) *m/z* 218.1673 [(M^+); calcd. for $C_{15}H_{22}O$ 218.1671].



Preparation of 2-methyl-4-(6-aceto-1-(*E*)-hexene)-3-buten-2-ol (E-23) and 2-methyl-4-(6-aceto-1-(*Z*)-hexene)-3-buten-2-ol (Z-23) (Table 3, entry 7). Applying the conditions above to 2-methyl-3-butyn-2-ol (**1**) (84 mg, 0.10 mL, 1.0 mmol) and a 4:1 mixture of 6-aceto-1-iodo-1-(*E*)-hexene (**E-23**) and 6-aceto-1-iodo-1(*Z*)-hexene (**Z-23**) (402 mg, 1.5 mmol; experimental preparation provided below) afforded after column chromatography [silica gel; 80:20 pentane/EtOAc, 1% Et_3N] an oily inseparable 3:1 mixture of 2-methyl-4-(6-aceto-1-(*E*)-hexene)-3-buten-2-ol (**E-23**) and 2-methyl-4-(6-aceto-1-(*Z*)-hexene)-3-buten-2-ol (**Z-23**) (180 mg, 80%).

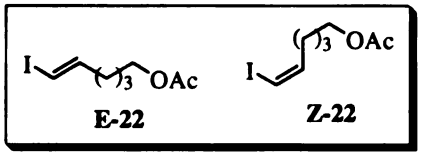
Data for **E-23**: IR (neat) 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 6 H), 1.38-1.52 (m, 2 H), 1.56-1.71 (m, 2 H), 2.04 (m, 3 H), 2.11 (m, 2 H), 4.05 (t, *J* = 6.5 Hz, 2 H), 5.66 (dt, *J* = 6.6, 15.3 Hz, 1 H), 5.72 (d, *J* = 15.7 Hz, 1 H), 5.93-6.07 (m, 1 H), 6.18 (dd, *J* = 10.2, 15.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 25.5, 25.8, 27.2, 28.0, 29.9, 29.8, 32.1, 64.3, 70.7, 126.7, 130.1, 133.9, 139.1, 171.2; HRMS (EI) *m/z* 226.1570 [(M^+), calcd. for $C_{13}H_{22}O_3$ 226.1569].

Data for **Z-23**: IR (neat) 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 6 H), 1.38-1.52 (m, 2 H), 1.56-1.71 (m, 2 H), 2.04 (m, 3 H), 2.21 (m, 2 H), 4.07 (t, *J* = 6.6 Hz, 2 H), 5.40 (dt, *J* = 8.2, 10.7 Hz, 1 H), 5.60-5.72 (m, 1 H), 5.80 (d, *J* = 15.2 Hz, 1 H), 6.49 (dd, *J* = 11.6, 16.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 25.5, 25.8, 27.2, 28.0, 29.9, 29.8, 32.1, 64.3, 70.7, 126.7, 130.1, 133.9, 139.1, 171.2; HRMS (EI) *m/z* 226.1570 [(M^+), calcd. for $C_{13}H_{22}O_3$ 226.1569].



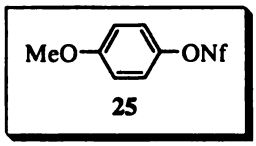
24

Preparation of 2-methyl-5-phenylpent-3-en-2-ol (24) (Table 3, entry 8). Applying the conditions above to 2-methyl-3-butyn-2-ol (1) (0.10 mL, 1.0 mmol) and benzyl bromide (0.18 mL, 1.5 mmol) afforded after flash chromatography [silica gel; 90:10 pentane/EtOAc, 1% Et_3N] 2-methyl-5-phenylpent-3-en-2-ol (**24**) (151 mg, 85%) as a thick yellow oil.[200]



E-22 Z-22

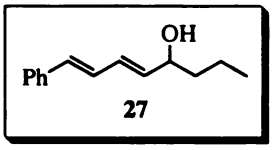
Preparation of 6-aceto-1-iodo-1(*E*)-hexene (E-22) and 6-aceto-1-iodo-1(Z)-hexene (Z-22). To a round bottom flask was added 6-aceto-1-(tributylstannyl)-1(*E* + Z)hexene (2.3 mmol, 1.01g) (prepared conditions A as noted above) in CH_2Cl_2 (20 ml). A solution of I_2 (2.6 mmol, 0.65 g) in CH_2Cl_2 (25 ml) was slowly added at 0 °C until a slight pink color persisted. When complete, the organics were washed with saturated $Na_2S_2O_3$ aq. (20 ml), dried over $MgSO_4$ and the solvent evaporated. The resulting residue was the purified by column chromatography [silica; 95:5 Pentane/EtOAc, 1% Et_3N] to afford a (4:1) mixture of 6-aceto-1-iodo-1-(*E*) hexane (**E-22**) and 6-aceto-1-iodo-1(*Z*) hexane (**Z-22**) (610 mg, 98%) as an oil. IR (neat) 3854, 3752, 3746, 2941, 2862, 1734, 1701, 1684, 1653, 1558, 1541, 1456, 1437, 1387, 1363, 1240, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40-1.725 (m, 8H), 2.00-2.23 (m, 10H), 4.00-4.10 (m, 4H), 6.02 (d, J = 14.3, 1H, (*E*)), 611-6.25 (m, 2H, (*Z*)), 6.42- 6.56 (m, 1H (*E*)); ^{13}C NMR (75 MHz, $CDCl_3$) 20.9, 24.3, 24.7, 27.8, 27.9, 34.2, 35.5, 64.1, 64.2, 75.0, 82.9, 140.6, 145.9, 171.1; HRMS (EI) *m/z* 268.9958 (M^+). Calcd. For $C_8H_{14}IO_2$ 268.9960.



25

Preparation of 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonic acid 4-methoxyphenyl ester (25). Following the general procedure of Corey, to a solution of *p*-methoxyphenol (1.24 g, 10 mmol) and Et_3N

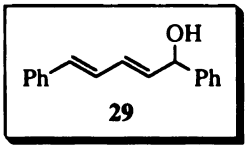
(1.70 mL, 12 mmol) in CH_2Cl_2 (80 mL) at room temperature was added perfluoro-1-butanesulfonyl fluoride (2.16 mL, 12 mmol) dropwise. The resulting solution was stirred for 2 h. The reaction mixture was then washed with 5% NaOH (2 × 100 mL), H_2O (2 × 100 mL), and brine (2 × 100 mL) and then dried over $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography [silica gel; 95:5 pentane/EtOAc, 1% Et_3N) to afford 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonic acid 4-methoxyphenyl ester (**25**) (3.28 g, 81%) as a clear oil.[156]



27

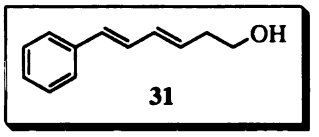
Representative procedure for the tandem one-pot hydrostannation/Stille cross-coupling with sub-stoichiometric amounts of tin using less sterically hindered alkynes (Scheme 18, Preparation of 8-Phenyl-octa-5,7-dien-4-ol (27) (Table 4, entry 1). Tri-2-furylphosphine (0.04 mmol, 9.3 mg) was added to a solution of Pd_2dba_3 (0.01 mmol, 9.2 mg) in dry diethyl ether (5 mL). After 15 min of stirring the solution at room temperature, 1-hexyn-3-ol (**26**) (.12 ml, 1.0 mmol), PMHS (1.5 mmol, 0.09 ml), Me_3SnCl (0.06 mmol, 0.06 mL of a 1 M solution in THF), Na_2CO_3 (0.8 mmol, 85.2 mg), and H_2O (0.5 mL), and $PdCl_2(PPh_3)_2$ (0.01 mmol, 7 mg) were added respectively. The reaction was heated to reflux and a solution of (*E*)-β-bromostyrene (1.5 mmol, 274.5 mg) in diethyl ether (4 mL) was added dropwise via a syringe pump (0.24 mL/hr). When the addition was complete, aqueous NH_4OH-solution (10%, 2 mL) was added and the reaction mixture stirred for 30 min. The reaction was then filtered, separated, and the aqueous phase was extracted with diethyl ether. The organics were combined, washed with water and then brine, dried over $MgSO_4$ and filtered. The solvent was evaporated and the residue was purified by column chromatography [silica gel; 90:10 pentane/EtOAc, 1% Et_3N] to afford 8-phenyl-octa-5,7-

dien-4-ol (**27**) (120 mg, 59%) as a yellow oil. IR (neat) 3352 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.34-1.72 (m, 4 H), 1.81 (br s, 1 H), 4.24 (q, *J* = 6.5 Hz, 1 H), 5.85 (dd, *J* = 6.9, 15.6 Hz, 1 H), 6.41 (dd, *J* = 10.4, 15.3 Hz, 1 H), 6.57 (d, *J* = 15.7 Hz, 1 H), 6.80 (dd, *J* = 10.4, 15.6 Hz, 1 H), 7.21-7.49 (m, 5 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 18.5, 39.5, 72.5, 126.3, 127.5, 128.3, 128.6, 130.5, 132.5, 136.8, 137.1; HRMS (EI) m/z 202.1349 [(M^+) calcd. for $C_{14}H_{18}O$ 202.1358].



29

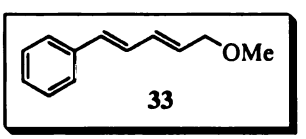
Preparation of 1,5-diphenyl-penta-2,4-dien-1-ol (29) (Table 4, entry 2). Applying the conditions above using 1-phenyl-2-propyn-1-ol (**28**) (0.25 ml, 2.0 mmol) and (*E*)-β-bromostyrene (0.5491 g, 3.0 mmol) afforded a residue which was purified by flash chromatography [siliac gel; 90/10 pentane/EtOAc; 1% TEA] to afford of 1,5-diphenyl-penta-2,4-dien-1-ol (**29**) (320 mg, 68%)as an oil: ; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (d, *J* = 7.1 Hz, 1 H), 6.03 (dd, *J* = 7.1, 15.1Hz, 1 H), 6.50 (dd, *J* = 10.4, 15.1 Hz, 1 H), 6.60 (d, *J* = 15.9 Hz, 1 H), 6.81 (dd, *J* = 10.4, 15.5 Hz, 1 H), 7.11-7.47 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.9, 126.3, 126.4, 127.6, 127.7, 128.2, 128.6, 130.9, 133.2, 135.5, 137.0; whose spectroscopic data was consistent with those reported earlier.[157]



31

Preparation of 6-phenyl-hexa-3,5-dien-1-ol (31) (Table 4, entry 3): Tri-2- furylphosphine (0.04 mmol, 9.3 mg) was added to a solution of Pd_2dba_3 (0.01 mmol, 9.2 mg) in dry diethyl ether (5 mL). After 15 min of stirring the solution at room temperature, 3-butyn-1-ol (**30**) (0.08 ml, 1.0 mmol), PMHS (1.5 mmol, 0.09 ml), Me_3SnCl (0.06 mmol, 0.06 mL of a 1 M solution in THF), Na_2CO_3 (0.8 mmol, 85.2 mg), and H_2O (0.5 mL), and $PdCl_2$ $(PPh_3)_2$ (0.01 mmol, 7 mg) were added respectively. The reaction was heated to reflux and a solution of (*E*)-β-

bromostyrene (1.5 mmol, 274.5 mg) in diethyl ether (4 mL) was added dropwise via a syringe pump (0.24 mL/hr). When the addition was complete, aqueous NH_4OH-solution (10%, 2 mL) was added and the reaction mixture stirred for 30 min. The reaction was then filtered, separated, and the aqueous phase was extracted with diethyl ether. The organics were combined, washed with water and then brine, dried over $MgSO_4$ and filtered. The solvent was evaporated and the residue was purified by column chromatography [silica gel; 80:20 pentane/EtOAc, 1% Et_3N] to afford 6-phenyl-hexa-3,5-dien-1-ol (**31**) (62 mg, 36%) as a white solid (mp = 63-64 °C). IR ($CHCl_3$) 3435 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.45 (q, *J* = 7.2 Hz, 2H) 3.75 (t, *J* = 6.6 Hz, 2H), 5.82 (dt, *J* = 7.2, 15.4 Hz, 1H), 6.35 (dd, *J* = 10.4, 15.4 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.79 (dd, *J* = 10.4, 15.9 Hz, 1H), 7.17-7.53 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 133.4, 131.2, 130.7, 128.7, 128.5, 127.3, 126.2, 65.8, 36.2; HRMS (EI) *m/z* 174.1039 [(M^+). calcd. for $C_{12}H_{14}O$ 174.1045].

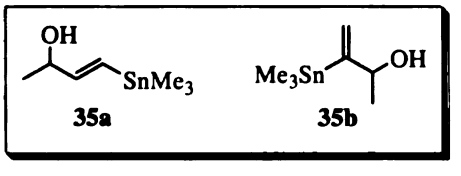


33

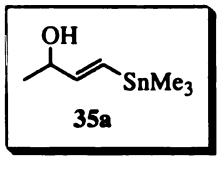
Preparation of (5-methoxy-penta-1,3-dienyl)-benzene (33) (Table 4, entry 4). Tri-2-furylphosphine (0.04 mmol, 9.3 mg) was added to a solution of Pd_2dba_3 (0.01 mmol, 9.2 mg) in dry diethyl ether (5 mL). After 15 min of stirring the solution at room temperature, Methyl propargyl ether (**32**) (0.08 ml, 1.0 mmol), PMHS (1.5 mmol, 0.09 ml), Me_3SnCl (0.06 mmol, 0.06 mL of a 1 M solution in THF), Na_2CO_3 (0.8 mmol, 85.2 mg), and H_2O (0.5 mL), and $PdCl_2(PPh_3)_2$ (0.01 mmol, 7 mg) were added respectively. The reaction was heated to reflux and a solution of (*E*)-β-bromostyrene (1.5 mmol, 274.5 mg) in diethyl ether (4 mL) was added dropwise via a syringe pump (0.24 mL/hr). When the addition was complete, aqueous NH_4OH-solution (10%, 2 mL) was added and the reaction mixture stirred for 30 min.

The reaction was then filtered, separated, and the aqueous phase was extracted with diethyl ether. The organics were combined, washed with water and then brine, dried over $MgSO_4$ and filtered. The resulting residue was purified by column chromatography [silica gel; 95:5 Pentane/EtOAc, 1% TEA] to afford (5-methoxy-penta-1,3-dienyl)-benzene (**33**) (54 mg, 16%) whose spectroscopic data was consistent with those reported earlier.[158]

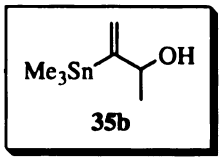
Use of (+/-)-3-butyn-2-ol. Procedure for the one pot hydrostannation/Stille with catalytic tin (Scheme 9). Following the general procedure from Table 3 using (+/-)-3-butyn-2-ol (**34**) (0.16 mL, 2.0 mmol) and (*E*)-β-bromostyrene (549 mg, 3.0 mmol) after column chromatography [silica; 80:20 Hexane/EtOAc] afforded two unidentified products (A, 20 mg) and (B, 170 mg).



Preparation of (*E*)-4-(trimethylstannyl)but-3-en-2-ol (Scheme 9). Using conditions A (Scheme 14) noted above with (+/-)-3-butyn-2-ol (**34**) (0.16 mL, 2.0 mmol) after column chromatography [silica; 95:5 Pentane/EtOAc, 1 %TEA] afforded (*E*)-4-(trimethylstannyl)but-3-en-2-ol (**35a**) (275 mg, 59%) as an oil and 3-(trimethylstannyl)but-3-en-2-ol (**35b**) (34 mg, 7.2 %) as an oil. Crude ^1H NMR indicated a *E*:int of 9:1.

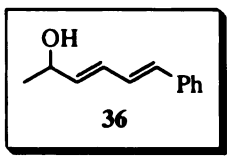


Data for (*E*)-4-(trimethylstannyl)but-3-en-2-ol (**35a**): IR (neat) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 9 H), 1.24 (d, J = 6.5 Hz, 3 H), 2.25 (br s, 1 H), 4.23 (m, 1 H), 6.03 (dd, J = 4.8, 19.0 Hz, 1 H), 6.17 (d, J = 19.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -9.8, 22.9, 70.8, 127.1, 151.5; HRMS (EI) *m/z* 236.0223 [(M^+), calcd for $C_7H_{16}OSn$ 236.0223].



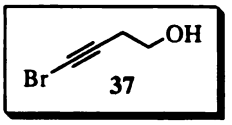
35b

Data for 3-(trimethylstannyl)but-3-en-2-ol (**35b**): IR (neat) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 9 H), 1.26 (d, *J* = 6.4 Hz, 3 H), 1.59 (br s, 1 H), 4.46 (q, *J* = 6.5 Hz, 1 H), 5.20 (m, 1 H), 5.76 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -8.6, 24.3, 75.0, 122.6, 160.7 ; HRMS (EI) *m/z* 236.0223 [(M^+), calcd for $C_7H_{16}OSn$ 236.0223].

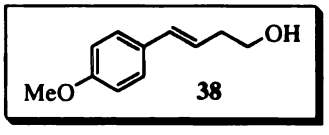


36

Procedure for a classic Stille coupling to check substrate. Preparation of (3*E*,5*E*)-6-phenylhexa-3,5-dien-2-ol (Scheme 9). Pd_2dba_3 (18.3 mg, 0.02 mmol) and $AsPh_3$ (24.5 mg, 0.08 mmol) were added to a flask that contained NMP (5 mL). This solution was allowed to stir at room temperature for ~10 min. At this point (*E*)-β-bromostyrene (183 mg, 1.1 mmol) was added and the flask was placed into a preheated oil bath (~45 °C). Now (*E*)-4-(trimethylstannyl)but-3-en-2-ol (229 mg, 0.98 mmol) was added immediately and this mixture was allowed to stir overnight (~8 h). The reaction was then cooled to room temperature and then diluted with water. The mixture was extracted with Et_2O (4x). The combined organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] afforded (3*E*,5*E*)-6-phenylhexa-3,5-dien-2-ol (**36**) (160 mg, 95%) as an oil. The spectroscopic data matched that to the material above. Data for (3*E*,5*E*)-6-phenylhexa-3,5-dien-2-ol (**36**): IR (neat) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, *J* = 6.4 Hz, 3 H), 1.67 (br s, 1 H), 4.44 (m, 1 H), 5.89 (dd, *J* = 5.9, 14.8 Hz, 1 H), 6.40 (dd, *J* = 9.9, 14.7 Hz, 1 H), 6.58 (d, *J* = 15.7 Hz, 1 H), 6.79 (dd, *J* = 10.4, 15.6 Hz, 1 H), 7.21-7.27 (m, 1 H), 7.30-7.38 (m, 2 H), 7.39-7.46 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 68.6, 126.3, 127.5, 128.2, 128.6, 129.8, 132.7, 137.1, 137.6; HRMS (EI) *m/z* 174.1051 [(M^+), calcd for $C_{12}H_{14}O$ 174.1045].

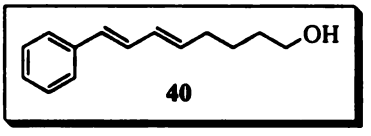


Preparation of 4-bromo-but-3-yn-1-ol (37). N-bromosuccimide (55 mmol, 9.78 g) and $AgNO_3$ (4.4 mmol, 0.750 g) were added to a solution of 3-butyn-1-ol (**30**) (50 mmol, 3.78 ml) in dry acetone (150 ml). The reaction was stirred at room temperature until complete by TLC (1hr.). The reaction was quenched by the addition of 200 mL of pentane and then washed with H_2O. The layers were separated and the aqueous layer was back-extracted with Et_2O:pentane (1:1), organics were combined, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was then purified by flash chromatography [silica gel; 90:10 Pentane/EtOAc, 1% TEA] to afford 4-bromo-but-3-yn-1-ol (**37**) (7.45 g, 94%) whose spectroscopic data was consistent with those previously reported.[159] For the preparation of 6-bromo-hex-5-yn-1-ol (**39**) and 2-(5-bromo-pent-4-ynyloxy)-tetrahydro-pyran (**41**) see .



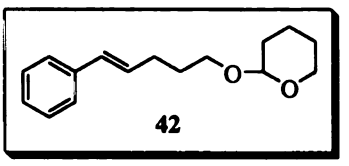
Representative procedure for the tandem one-pot hydrostannation/Stille cross-coupling with catalytic amounts of Me_3SnCl using 1-bromoalkynes. Preparation of 4-(4-methoxy-phenyl)-but-3-en-1-ol (38) (Table 5, entry 1). To 10 ml of THF was added Pd_2dba_3 (.0092g, 0.01 mmol) and tri-2-furylphosphine (.0093g, 0.04 mmol) and the mixture was allowed to stir for 15 min. Then, Me_3SnCl (0.06 mmol, 0.06 mL of a 1 M solution in THF), Na_2CO_3 (0.0852g, 0.80 mmol), 1 mL H_2O, PMHS (0.09 ml, 1.5 mmol) and $PdCl_2(PPh_3)_2$ (0.007g, 0.01 mmol) were all added respectively. The mixture was then heated to reflux and a solution of 4-bromo-but-3-yn-1-ol (**37**) (149 mg, 1.0 mmol) and iodoanisole (351 mg, 1.5 mmol) in 4 mL of Et_2O was added via a syringe pump (0.024 ml/hr). When addition was complete, 2 mL of 10% NH_4OH (aq.) was added and the mixture was stirred for an additional 30 minuets. The reaction was then filtered, separated and the aqueous layer

was extracted with ether. All organics were combined, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was then purified by flash chromatography [silica gel; 80:20 pentane/EtOAc, 1% TEA) to give of 4-(4-methoxy-phenyl)-but-3-en-1-ol (**38**) (91 mg, 51%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (q, J = 7.7 Hz, 2 H), 3.75 (t, J = 6.1 Hz 2 H), 3.82 (s, 3 H), 6.07 (dt, J = 7.1, 15.9 Hz, 1 H), 6.46 (d, *J* = 15.9 Hz, 1 H); 6.86 (d, *J* = 8.8 Hz, 2 H), 7.31 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 132.4, 130.3, 127.1, 123.9, 113.9, 61.9, 55.2, 36.4. Spectroscopic data was consistent those reported earlier.[160]



40

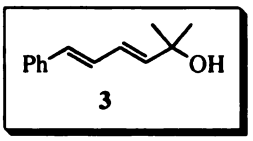
Preparation of 8-phenyl-octa-5,7-dien-1-ol (40) (Table 5, entry 2). Applying the conditions from above using 6-bromo-hex-5-yn-1-ol (**39**) (177 mg, 1.0 mmol) and (*E*)-β-bromostyrene (275 mg, 1,5 mmol) afforded a residue which was purified by flash chromatography [silica; 80:20 Pentane/EtOAc; 1% TEA] to give 8-phenyl-octa-5,7-dien-1-ol (**40**) (98 mg, 49%) as a white solid (mp = 38.6 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (m, 2H), 1.61 (m, 2H), 1.73 (br s, 1H), 2.19 (q, *J* = 7.9 Hz, 2H), 3.65 (t, *J* = 6.6 Hz, 2H), 5.83 (dt, *J* = 7.5, 15.5 Hz, 1H), 6.23 (dd, *J* = 10.4, 15.9 Hz 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.76 (dd, *J* = 10.2, 15.7 Hz 1H), 7.14-7.46 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 135.2, 130.9, 130.2, 129.3, 128.5, 127.1, 126.1, 62.7, 32.5, 32.2, 25.3. Spectroscopic data was consistent with those reported earlier.[161]



42

Preparation of 2-(5-phenyl-pent-4-enyloxy)-tetrahydro-pyran (42) (Table 5, entry 3). Applying the conditions above using 2-(5-bromo-pent-4-ynyloxy)tetrahydropyran (**41**) (143 mg, 0.58 mmol) and iodobenzene (0.17 ml, 1.5 mmol) afforded a residue which was

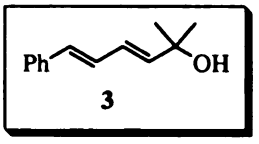
purified by flash chromatography [silica; 95:5 Pentane/EtOAc; 1% TEA] to give of 2-(5-phenylpent-4-enyloxy)tetrahydropyran (**42**) (75 mg, 52%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49-1.89 (m, 8H), 2.31 (dt, J = 7.1 Hz, 7.1 Hz, 2H), 3.41 (dt, J = 9.6 Hz, 6.5 Hz, 1H), 3.5 (m, 1H), 3.74 (dt, J = 6.8, 9.6 Hz, 1H), 3.85 (m, 1H), 4.60 (t, J = 3.5 Hz, 1H), 6.24 (dt, J = 6.6 15.8 Hz, 1H), 6.41 (d, J = 15.8 Hz, 1H), 7.15-7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 25.4, 29.3, 29.4, 30.7, 62.3, 66.9, 98.8, 125.9, 126.8, 128.4, 130.1, 137.7. Spectroscopic data was consistent with those reported earlier.[162]



3

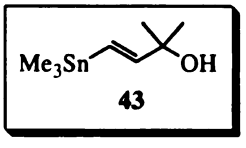
Representative procedure for the tandem one-pot hydrostannation/Stille cross coupling with 4 mol% Me_3SnCl. Preparation of (3*E*,5*E*)-2-methyl-6-phenylhexa-3,5-dien-2-ol (3) (Scheme 10, entry 2). Tri-2-furylphosphine (9.3 mg, 0.04 mmol) was added to a solution of Pd_2dba_3 (9.2 mg, 0.01 mmol) in dry diethyl ether (5 mL). After 15 min of stirring the solution at room temperature, 2-methyl-3-butyn-2-ol (**1**) (124 mg, 1.0 mmol), PMHS (0.1 mL, 1.5 mmol), Me_3SnCl (0.04 mL of a 1 M solution in THF, 0.04 mmol), Na_2CO_3 (85 mg, 0.8 mmol), H_2O (0.5 mL), and $(PPh_3)_2PdCl_2$ (7 mg, 0.01 mmol) were added. The reaction was heated to reflux, and a solution of (*E*)-β-bromostyrene (275 mg, 1.5 mmol) in diethyl ether (4 mL) was added dropwise via a syringe pump (0.24 mL/h). When the addition was complete, an aqueous NH_4OH solution (10%, 2 mL) was added and the reaction mixture stirred for 30 min. The reaction was then filtered and separated, and the aqueous phase was extracted with diethyl ether. The organics were combined, washed with water and then brine, dried over $MgSO_4$, and filtered. The solvent was evaporated, and the residue was purified by column chromatography [silica gel; 90:10 pentane/EtOAc, 1% Et_3N] to

afford (3*E*,5*E*)-2-methyl-6-phenylhexa-3,5-dien-2-ol (**3**) (126 mg, 67%) as an oil. See For spectroscopic data see page 108-109.



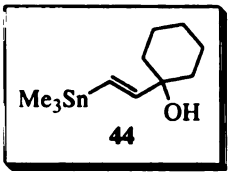
3

Use of 1 mol% Me_3SnCl (Scheme 10, entry 3). Applied the above conditions using Me_3SnCl (0.01 mL of a 1 M solution in THF, 0.01 mmol) afforded after the reaction was complete and column chromatography [silica gel; 90:10 pentane/EtOAc, 1% Et_3N] (3*E*,5*E*)-2-methyl-6-phenylhexa-3,5-dien-2-ol (**3**) (34 mg, 18%) as an oil. See For spectroscopic data see page 108-109.



43

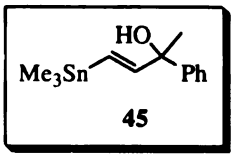
Representative procedure for the preparation of the trimethylvinylstannanes for the classic Stille coupling. Preparation of (*E*)-2-methyl-4-(trimethylstannyl)but-3-en-2-ol (43) (Table 6, entry 1). Applying conditions A (Scheme 14) with Me_3SnCl (18 mL, 18 mmol; 1M solution in THF) and 2-methyl-3-butyn-2-ol (**1**) (2.43 mL, 15 mmol) after 2 h and column chromatography [silica; 70:30 Hexane/Ether, 1% TEA] afforded (*E*)-2-methyl-4-(trimethylstannyl)-3-buten-2-ol (**43**) (3.17 g, 85%) as a yellow oil. IR (neat): 3362 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 9H), 1.27 (s, 6H), 1.64 (br s, 1H), 6.1 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 123.4, 72.2, 30.0, -9.3; HRMS (EI) *m/z* 235.1037 [(M^+-CH_3); calcd for $C_7H_{15}O^{116}Sn$ 235.1046].



44

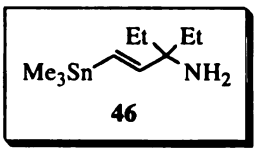
Preparation of 1-((*E*)-2-(trimethylstannyl)vinyl)cyclohexanol (44) (Table 6, entry 2). Applying conditions A (Scheme 14) with Me_3SnCl (9.6 mL, 9.6 mmol; 1M solution in THF) and 1-ethynylcyclohexanol (**6**) (994 mg, 8.0 mmol) after 2 h and column chromatography [silica; 70:30 hexane/Ether, 1% TEA] afforded 1-((*E*)-2-(trimethylstannyl)vinyl)cyclohexanol (**44**) (2.03g, 88%) as an off-white solid (mp = 72 °C). IR (neat) 3374, 2985, 2932, 2854,

1603, 1447, 1387, 1262, 1184, 1136, 986, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 9H), 1.32 (br, 1H), 1.52 (m, 10H), 6.07 (d, *J* = 19.2 Hz, 1H), 6.20 (d, *J* = 19.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 124.4, 72.9, 37.6, 25.6, 22.1, -9.7; HRMS (EI) *m/z* 271.0453 [(M^+-CH_3); calcd for $C_{10}H_{19}O^{116}Sn$ 271.0454].



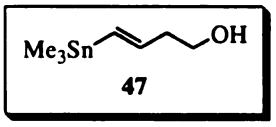
45

Preparation of (*E*)-4-(trimethylstannyl)-2-phenylbut-3-en-2-ol (45) (Table 6, entry 3). Applying conditions A (Scheme 14) with Me_3SnCl (8.4 mL, 8.4 mmol; 1M solution in THF) and 2-phenyl-3-butyn-2-ol (**8**) (1.02 mg, 7.0 mmol) after 2 h and column chromatography [silica; 90:10 pentane/EtOAc, 1% TEA] afforded (*E*)-4-(trimethylstannyl)-2-phenylbut-3-en-2-ol (**45**) (1.50 g, 71%%) as an oil. IR(neat): 3397, 3059, 3026, 2980, 2914, 1597, 1493, 1446, 1369, 1309 1190, 1095, 1064, 1028, 991, 939 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 9H), 1.65 (s, 3H), 2.05 (br s, 1H) 6.32 (m, 2H), 7.50-7.22 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 146.8, 128.1, 126.8, 125.4, 125.2, 75.9, 29.7, -9.7; HRMS (EI) *m/z* 293.0295 [(M^+-CH_3); calcd for $C_{12}H_{17}O^{116}Sn$ 293.0297].



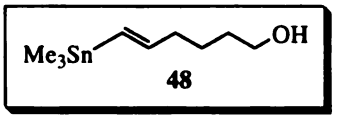
46

Preparation of (*E*)-3-ethyl-1-(trimethylstannyl)pent-1-en-3-amine (Table 6, entry 4). Applying conditions A (Scheme 14) with 3-ethylpent-1-yn-3-amine (**14**) (0.67 mL, 5 mmol) and Me_3SnCl (6 mL of a 1 M soution in THF, 6 mmol), after 2 h and column chromatography [silica; 50:50 pentane/EtOAc, 1% TEA] afford (*E*)-3-ethyl-1-(trimethylstannyl)pent-1-en-3-amine (**46**) (1.04 g, 75%) as a yellow oil. IR (neat): 3370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9H), 0.70 (t, *J* = 7.5 Hz, 6H), 1.02 (br s, 2H), 1.34 (q, *J* = 7.48 Hz, 4H), 5.78(d, *J* = 19.3, 1H), 5.95(d, *J* = 19.3, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 124.2, 57.7, 33.4, 7.7, -9.8; HRMS (EI) *m/z* 258.0619 [(M^+-CH_3); calcd for $C_9H_{20}N^{116}Sn$ 258.0613].



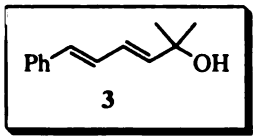
47

Preparation of (*E*)-4-(trimethylstannyl)but-3-en-1-ol (47) (Table 6, entry 8). Applying conditions A (Scheme 14) with Me_3SnCl (2.4 mL, 2.4 mmol; 1M solution in THF) and 4-bromo-3-butyn-1-ol (**37**)(298 mg, 2.0 mmol) after 2 h and column chromatography [silica; 90:10 pentane/EtOAc, 1% TEA] afford (*E*)-4-(trimethylstannyl) but-3-en-1-ol (**47**) (220 mg, 47%) as a yellow oil. IR (neat): 3397 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 9H), 2.13 (br s, 1H), 2.40 (m, 2 H), 3.66 (t, *J* = 6.4 Hz, 2 H), 5.95 (dt, *J* = 6.0, 18.8 Hz, 1 H), 6.10 (d, *J* = 18.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -9.78, 41.1, 61.1, 132.3, 144.5; HRMS (EI) *m/z* 220.9986 [(M^+-CH_3); calcd for $C_6H_{13}O^{116}Sn$ 220.9988].



48

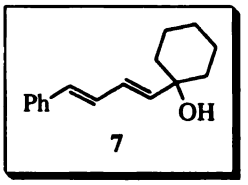
Preparation of 1-(trimethylstannyl)-1(*E*)-hexen-6-ol (48) (Table 6, entry 9). Applying conditions A to 6-bromo-5-hexyn-1-ol (**39**) (266 mg, 1.5 mmol) and Me_3SnCl (1.8 mL of a 1M solution in THF, 1.8 mmol) afforded after 2 h reaction time and column chromatography [silica; 90:10 hexane/EtOAc, 1% TEA] 1-(trimethylstannyl)-1(*E*)-hexen-6-ol (**48**) (263 mg, 71%) as a clear oil. IR (neat): 3423 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 9H), 1.41-1.49 (m, 2 H), 1.51-1.59 (m, 2 H), 1.95 (br s, 1 H), 2.14 (m, 2 H), 3.60 (t, *J* = 6.5 Hz, 2 H), 5.94 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -9.6, 25.2, 32.5, 37.3, 62.8, 128.7, 148.9; HRMS (EI) *m/z* 249.0302 [(M^+-CH_3); calcd for $C_6H_{13}O^{116}Sn$ 249.0301].



3

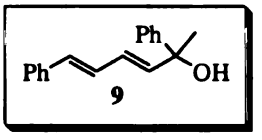
Representative procedure for the classic Stille coupling controls. Preparation of (3*E*,5*E*)-2-methyl-6-phenylhexa-3,5-dien-2-ol (3) (Table 6, entry 1). Pd_2dba_3 (18.3 mg, 0.02 mmol) and $AsPh_3$ (24.5 mg, 0.08 mmol) were added to a flask containing NMP (~5 mL). This mixture was stirred at 25 °C for 15 min. At this time (*E*)-β-bromostyrene (201 mg, 1.1 mmol) and (*E*)-2-methyl-4-

(trimethylstannyl)-3-buten-2-ol (**43**) (248 mg, 1.0 mmol) were added and the flask was placed into a preheated oil bath (~50 °C) and then was allowed to stir overnight (~10 h). The reaction was then cooled to room temperature and water was added. This mixture was extracted with Et_2O (3x). The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 90:10 hexane/EtOAc] to afford (3*E*,5*E*)-2-methyl-6-phenylhexa-3,5-dien-2-ol (**3**) (171 mg, 91%) as an oil. For spectroscopic data see page 108-109.



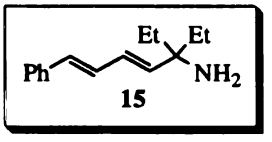
7

Preparation of 1-((1*E*,3*E*)-4-phenylbuta-1,3-dienyl)cyclohexanol (7) (Table 6, entry 2). Applying the above conditions to 1-((*E*)-2-(trimethylstannyl)vinyl)cyclohexanol (**44**) (289 mg, 1.0 mmol) and (*E*)-β-bromostyrene (201 mg, 1.1 mmol) afforded after 10 h and column chromatography [silica; 95:5 to 90:10 pentane/EtOAc] 1-((1*E*,3*E*)-4-phenylbuta-1,3-dienyl)cyclohexanol (**7**) (190 mg, 83%) as an oil. For spectroscopic data see page 110.



9

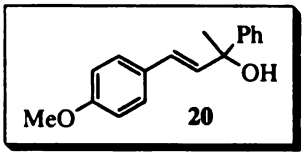
Preparation of (3*E*,5*E*)-2,6-diphenylhexa-3,5-dien-2-ol (9) (Table 6, entry 3). Applying the above conditions to (*E*)-4-(trimethylstannyl)-2-phenylbut-3-en-2-ol (**45**) (269 mg, 0.86 mmol) and (*E*)-β-bromostyrene (201 mg, 1.1 mmol) afforded after 10 h and column chromatography [silica; 90:10 Pentane/EtOAc] (3*E*,5*E*)-2,6-diphenylhexa-3,5-dien-2-ol (**9**) (180 mg, 83%) as an oil. For spectroscopic data see page 110-111.



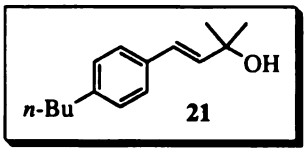
15

Preparation of (4*E*,6*E*)-3-ethyl-7-phenylhepta-4,6-dien-3-amine (15) (Table 6, entry 4). Applying the above conditions to (*E*)-3-ethyl-1-(trimethylstannyl)pent-1-en-3-amine (**46**) (259 mg, 0.94 mmol) and (*E*)-β-bromostyrene (257 mg, 1.4 mmol) afforded after 10 h and column chromatography

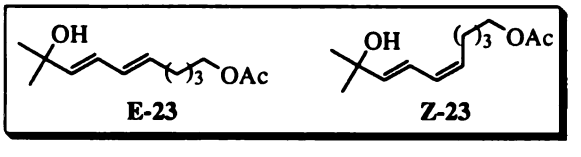
[silica; 50:50 Pentane/EtOAc] (4*E*,6*E*)-3-ethyl-7-phenylhepta-4,6-dien-3-amine (**15**) (132 mg, 71%) as an oil. For spectroscopic data see page 112.



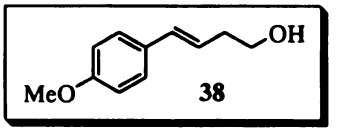
Preparation of (*E*)-4-(4-methoxyphenyl)-2-phenylbut-3-en-2-ol (20) (Table 6, entry 5). Applying the above conditions to (*E*)-4-(trimethylstannyl)-2-phenylbut-3-en-2-ol (**45**) (285 mg, 0.92 mmol) and *p*-iodoanisole (257 mg, 1.1 mmol) afforded after 10 h and column chromatography [silica; 80:20 pentane/EtOAc] (*E*)-4-(4-methoxyphenyl)-2-phenylbut-3-en-2-ol (**20**) (191 mg, 83%) as an oil. Se For spectroscopic data see page 129-130.



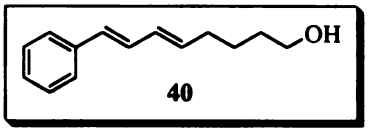
Preparation of (*E*)-4-(4-butylphenyl)-2-methylbut-3-en-2-ol (21) (Table 6, entry 6). Applying the above conditions to (*E*)-2-methyl-4-(trimethylstannyl)-3-buten-2-ol (**43**) (248 mg, 1.0 mmol) and 1-butyl-4-iodobenzene (286 mg, 1.1 mmol) afforded after 10 h and column chromatography [silica; 80:20 pentane/EtOAc] (*E*)-4-(4-butylphenyl)-2-methylbut-3-en-2-ol (**21**) (200 mg, 92%) as an oil. For spectroscopic data see page 130.



Preparation of (5*E*,7*E*)-9-hydroxy-9-methyldeca-5,7-dienyl acetate (E-23) and (5*Z*,7*E*)-9-hydroxy-9-methyldeca-5,7-dienyl acetate (Z-23) (Table 6, entry 7). Applying the above conditions to (*E*)-2-methyl-4-(trimethylstannyl)-3-buten-2-ol (**43**) (30 mg, 0.121 mmol) and 6-iodohex-5-enyl acetate (36 mg, 0.133 mmol; a 4:1 E:Z mixture) afforded after 10 h and column chromatography [silica; 80:20 Pentane/EtOAc] a (3:1, E:Z) mixture of (5*E*,7*E*)-9-hydroxy-9-methyldeca-5,7-dienyl acetate (**E-23**) and (5*Z*,7*E*)-9-hydroxy-9-methyldeca-5,7-dienyl acetate (**Z-23**) (20 mg, 73%) as an oil. For spectroscopic data see page 131.

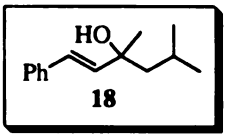


Preparation of (*E*)-4-(4-methoxyphenyl)but-3-en-1-ol (38) (Table 6, entry 8). Applying the above conditions to (*E*)-4-(trimethylstannyl) but-3-en-1-ol (**47**) (170 mg, 0.72 mmol) and *p*-iodoanisole (186 mg, 0.80 mmol) afforded after 10 h and column chromatography [silica; 80:20 pentane/EtOAc] (*E*)-4-(4-methoxyphenyl)but-3-en-1-ol (**38**) (75 mg, 59%) as an oil. For spectroscopic data see page 138-139.



Preparation of (5*E*,7*E*)-8-phenylocta-5,7-dien-1-ol (40) (Table 6, entry 9). Applying the above conditions to 1-(trimethylstannyl)-1(*E*)-hexen-6-ol (**48**) (330 mg, 1.25 mmol) and (*E*)-β-bromostyrene (253 mg, 1.38 mmol) afforded after 10 h and column chromatography [silica; 80:20 pentane/EtOAc] (5*E*,7*E*)-8-phenylocta-5,7-dien-1-ol (**40**) (210 mg, 83%) of a solid (mp 39 °C). For spectroscopic data see page 139.

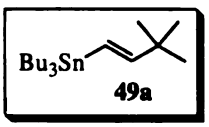
Procedure for the preparation of Bu_3SnH from Bu_3SnCl using PMHS/KF combination (Scheme 12). A solution of Bu_3SnCl (10 mL, 36.87 mmol), KF (4.71 g, 81.11 mmol), H_2O (5-10 mL) and PMHS (2.43 mL, 40.56 mmol) were added to a flask containing THF (50 mL). This mixture was then allowed to stir at room temperature until the initially formed Bu_3SnF precipitate disappeared. After 4-5 hours, 20 mL of 3M NaOH was added and this mixture was allowed to stir for 3-5 h (overnight can be used, but it is discouraged, as the yield suffers). The phases were separated and the aqueous phase was extracted with Et_2O. The combined organics were dried ($MgSO_4$), filtered and concentrated to 12 g of a residue. This residue was purified by vacuum distillation [80 °C @ 0.4 mmHg] to afford Bu_3SnH (8.21g, 79%) as a clear liquid. DO NOT GREASE THE JOINTS DURING THE DISTILLATION.



Representative Procedure for the initial one pot hydrostannation/Stille coupling using catalytic quantities of tin. Preparation of 3,5-dimethyl-1-phenyl-1-hexen-3-ol (18) (Error! Reference source not found., **entry 1).** Tri-2-furylphosphine (9.3 mg, 0.04 mmol) was added to a solution of Pd_2dba_3 (9.2 mg, 0.01 mmol) in Et_2O (5 mL). After stirring the solution at room temperature for 15 min., 3,5-dimethyl-1-hexyn-3-ol (**12**) (0.36 mL, 2.5 mmol), iodobenzene (0.42 mL, 3.75 mmol), Bu_3SnCl (0.05 mL, 0.185 mmol), PMHS (1.15 mL, 1.88 mmol) were added to the solution. The solution was then heated to 55 °C and aq. KF solution (435 mg, 7.5 mmol; 2 mL H_2O) was added dropwise via syringe pump over 2 days (after 12 h additional alkyne (0.36 mL, 2.5 mmol), PMHS (1.15 mL, 1.88 mmol) and iodobenzene (0.42 mL, 3.75 mmol) were added). The organic phase was separated, washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography [silica; 95:5 pet. ether/EtOAc] to afford 3,5-dimethyl-1-phenyl-1-hexen-3-ol (**18**) (107 mg, 21%) as a clear oil. For spectroscopic data see page 123-124.

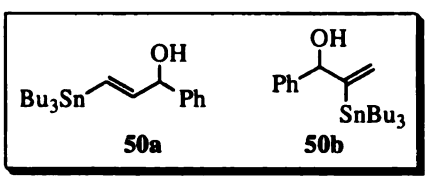
Representative procedure for palladium-mediated hydrostannations via Bu_3SnCl, aqueous KF, catalytic TBAF (or TBAI), and polymethylhydrosiloxane (PMHS). Preparation of 3,5-dimethyl-1-(tributylstannyl)-1(*E*)-buten-3-ol (16a) and 3,5-dimethyl-2-(tributylstannyl)-1-buten-3-ol (16b) (Scheme 14, Conditions A, entry 1). PMHS (0.09 mL, 1.5 mmol) was added to a solution of 3,5-dimethyl-1-hexyn-3-ol (126 mg, 1.0 mmol) (**12**), Bu_3SnCl (0.27 mL, 1.0 mmol), aqueous KF (174 mg, 3.0 mmol; 3 mL H_2O), $(PPh_3)_2PdCl_2$ (7 mg, 0.01 mmol), and TBAF (1drop of a 1M solution in THF; Aldrich) in diethyl ether or THF (5 mL). The biphasic reaction mixture was stirred at rt

until TLC showed complete consumption of the alkyne (~2 h), at which time 0.5 M NaOH (1 mL) was added and the reaction was allowed to stir an additional 2 h (NOT NECESSARY, unless large scale is used (<100 mmol)). The two phases were then separated, and the aqueous phase was extracted with diethyl ether (3×). The combined organics were washed with brine and dried over $MgSO_4$. After filtration, the solvent was evaporated, and the residue was purified by column chromatography [silica; 95:5 petroleum ether/EtOAc, 1% TEA] to afford 263 mg (63%) of 3,5-dimethyl-1-(tributylstannyl)-1(*E*)-buten-3-ol (**16a**) and 11 mg (3%) of 3,5-dimethyl-2-(tributylstannyl)-1-buten-3-ol (**16b**) as clear oils. For spectroscopic data see page 119.



49a

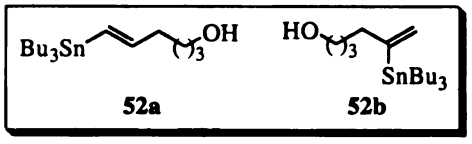
3,3-Dimethyl-1-(tributylstannyl)-1(*E*)-butene (49a) (Scheme 14, Conditions A, entry 2). Applying conditions A, 3,3-dimethyl-1-butyne (**4**) (82.2 mg, 1 mmol) afforded after 2 h reaction time and column chromatography [silica; hexanes, 1% TEA] 3,3-dimethyl-1-(tributylstannyl)-1(*E*)-butene (**49a**) (220 mg, 59%) as a clear oil. IR ($CHCl_3$) 3185, 2921, 2853, 1593, 1464, 1362, 995 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (m, 15 H), 0.98 (s, 9 H), 1.26-1.35 (m, 6 H), 1.43-1.53 (m, 6 H), 5.76 (d, J = 19.3 Hz, 1 H), 5.96 (d, J = 19.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 13.7, 27.2, 29.1, 29.2, 35.9, 119.7, 160.0; HRMS (EI) *m/z* 315.1292 [(M^+-Bu); calcd. for $C_{14}H_{29}{}^{118}Sn$ 315.1288.



50a **50b**

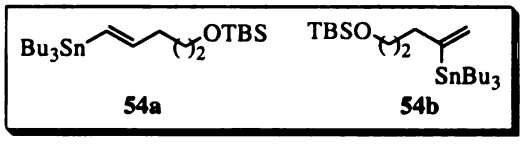
(*E*)-3-(Tributylstannyl)-1-phenylprop-2-en-1-ol (50a) and 2-(tributylstannyl)-1-phenylprop-2-en-1-ol (50b) (Scheme 14, Conditions A, entry 3). Applying conditions A to 1-phenylprop-2-yn-1-ol (**28**) (0.20 mL, 1.63 mmol) afforded after 2 h and column chromatography [silica; 90:10 Hexane/ EtOAc, 1% TEA] (*E*)-3-(tributylstannyl)-

1-phenylprop-2-en-1-ol (**50a**) (559 mg, 73%) and 2-(tributylstannyl)-1-phenylprop-2-en-1-ol (**50b**) (56 mg, 8%) as clear oils. **DATA**



52a **52b**

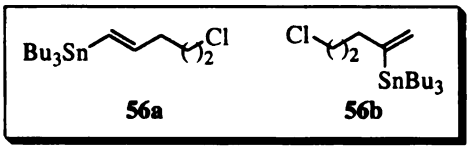
1-(Tributylstannyl)-1(*E*)-hexen-6-ol (52a) and 2-(tributylstannyl)-1-hexen-6-ol (52b) (Scheme 14, Conditions A, entry 4). Applying conditions A to 5-hexyn-1-ol (**51**) (98 mg, 0.11 mL, 1.0 mmol) afforded after 24 h reaction time and column chromatography [silica; 90:10 hexane/EtOAc, 1% Et_3N] a (1.4:1) mixture of 1-(tributylstannyl)-1(*E*)-hexen-6-ol (**52a**) and 2-(tributylstannyl)-1-hexen-6-ol (**52b**) (280 mg, 72%) as a clear oil. The spectroscopic data for **52a**[163] and **52b**[164] were consistent with those previously reported in the literature.



54a **54b**

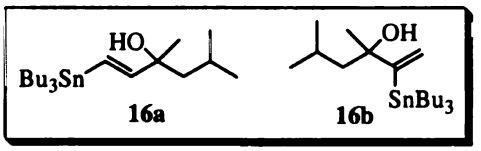
5-(*tert*-Butyldimethylsilyloxy)-1-(tributyl stannyl)-1(*E*)-pentene (54a) and 5-(*tert*-Butyldimethylsilyloxy)-2-(tributylstannyl)-1-pentene (54b) (Scheme 14, Conditions A, entry 5). Applying conditions A to 5-(*tert*-butyldimethylsilyloxy)-1-pentyne (**53**)[165] (200 mg, 1.01 mmol) afforded after 4 h reaction time and column chromatography [silica; pentane, 1% TEA] a (1:1) mixture of 5-(*tert*-butyldimethylsilyloxy)-1-(tributylstannyl)-1(*E*)-pentene (**54a**) and 5-(*tert*-butyldimethylsilyloxy)-2-(tributylstannyl)-1-pentene (**54b**) (260 mg, 51%) as a clear oil. IR ($CHCl_3$) 2957, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) for **54a** δ 0.03 (s, 6 H), 0.85 (m, 18 H), 1.20-1.40 (m, 6 H), 1.40-1.60 (m, 14 H), 2.15 (m, 2 H), 3.58 (t, *J* = 6.7 Hz, 2 H), 5.80-6.00 (m, 2 H), for **54b** δ 0.03 (s, 6 H), 0.85 (m, 18 H), 1.20-1.40 (m, 6 H), 1.40-1.60 (m, 14 H), 2.26 (t, *J* = 7.7 Hz, 2 H), 3.59 (t, *J* = 6.7 Hz, 2 H), 5.08 (dt, *J* = 2.8, 1.1 Hz, 1 H), 5.66 (dt, *J* = 2.8, 1.4 Hz, 1 H) ^{13}C NMR (75 MHz, $CDCl_3$) for **54a** δ -5.3, 9.4,

13.7, 18.3, 26.0, 27.3, 29.1 (2C), 31.9, 34.0, 62.8, 127.5, 149.5; for **54b** δ -5.3, 9.5, 13.7, 18.3, 26.0, 27.4, 29.1 (2C), 32.7, 37.5, 62.6, 124.7, 155.1; ; HRMS (CI) *m/z* 490.2653 [(M^+); calcd. for $C_{23}H_{50}OSiSn$ 490.2653].



56a **56b**

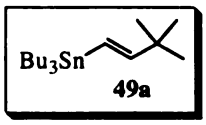
5-Chloro-1-(tributylstannyl)-1(*E*)-pentene (56a) and 5-Chloro-2-(tributylstannyl)-1-pentene (56b) (Scheme 14, Conditions A, entry 6). Applying conditions A to 5-chloro-1-pentyne (**55**) (1.16 mL, 1.0 mmol) afforded after 1 h reaction time and column chromatography [silica; hexanes, 1% TEA] a (1.4:1) mixture of 5-chloro-1-(tributylstannyl)-1(*E*)-pentene (**56a**) and 5-chloro-2-(tributylstannyl)-1-pentene (**56b**) (330 mg, 84%) as a clear oil. IR (neat) 2957, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) for **56a** δ 0.82-0.91 (m, 15 H), 1.25-1.33 (m, 6 H), 1.42-1.50 (m, 6 H), 1.83 (m, 2 H), 2.23-2.39 (m, 2 H), 3.49 (t, *J* = 6.6 Hz, 2 H), 5.92 (m, 2 H), for **56b** δ 0.82-0.91 (m, 15 H), 1.25-1.33 (m, 6 H), 1.42-1.50 (m, 6 H), 1.83 (m, 2 H), 2.23-2.39 (m, 2 H), 3.51 (t, *J* = 6.6 Hz, 2 H), 5.14 (m, 1 H), 5.69 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 9.5, 13.66, 13.69, 27.3, 27.4, 29.2, 31.7,32.2, 34.8, 38.1, 44.4, 126.0, 129.3, 147.1, 153.5; HRMS (CI) *m/z* 337.0749 [(M^+-Bu); calcd. for $C_{13}H_{26}ClSiSn$ 337.0740].



16a **16b**

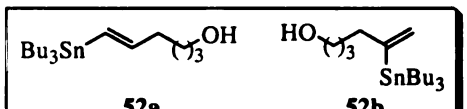
Representative Procedure for the Palladium-Mediated Hydrostannations via Bu_3SnF, catalytic TBAF, and PMHS. Preparation of 3,5-Dimethyl-1-(tributylstannyl)-1(*E*)-buten-3-ol (16a) and 3,5-Dimethyl-2-(tributylstannyl)-1-buten-3-ol (16b) (Scheme 14, Conditions B, entry 1). A solution of 3,5-dimethyl-1-hexyn-3-ol (**12**) (0.28 mL, 2.0 mmol), Bu_3SnF (0.65 g, 2.1 mmol), PMHS (0.13 mL, 2.1 mmol), TBAF crystals (catalytic), and $(PPh_3)_2PdCl_2$ (14 mg, 0.02 mmol) in diethyl ether (20 mL) was stirred at

rt for 2.5 h, at which time 0.5 M NaOH (2 mL) was added and the reaction was allowed to stir an additional 2 h. The reaction mixture was then filtered, and the filtrate was washed with brine. The aqueous layer was back extracted with ether (2×), and the combined organics were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography [silica; 95:5 hexane/EtOAc, 1% TEA] to afford 3,5-dimethyl-1-(tributylstannyl)-1(*E*)-buten-3-ol (**16a**) (536 mg, 64%) and 3,5-dimethyl-2-(tributylstannyl)-1-buten-3-ol (**16b**) (24 mg, 3%) as clear oils. For spectroscopic data see page 119.



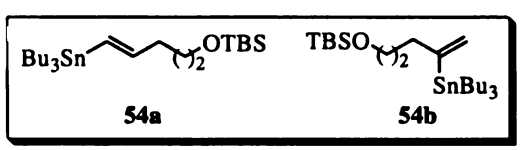
49a

3,3-Dimethyl-1-(tributylstannyl)-1(*E*)-butene (49a) (Scheme 14, Conditions B, entry 2). Applying conditions B to 3,3-dimethyl-1-butyne (**4**) (411 mg, 5.0 mmol) afforded after 2 h and column chromatography [silica; petroleum ether, 1% TEA] of 3,3-dimethyl-1-(tributylstannyl)-1(*E*)-butene (**49a**) (1.25 g, 67%) as a clear oil. For spectroscopic data see page 148.



52a **52b**

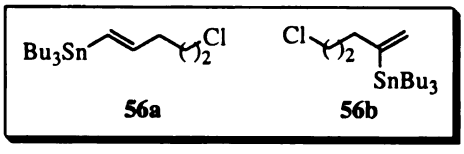
1-(Tributylstannyl)-1(*E*)-hexen-6-ol (52a) and 2-(tributylstannyl)-1-hexen-6-ol (52b) (Scheme 14, Conditions B, entry 4). Applying conditions B to 5-hexyn-1-ol (**51**) (98 mg, 0.11 mL, 1.0 mmol) afforded after 2 h reaction time and column chromatography [silica; 90:10 hexane/EtOAc, 1% TEA] 1-(tributylstannyl)-1(*E*)-hexen-6-ol (**52a**) (160 mg, 41%), a (1:1.3) mixture of **52a** and **52b** (111 mg, 28%), and 2-(tributylstannyl)-1-hexen-6-ol (**52b**) (30 mg, 8%) as clear oils. For spectroscopic data see page 149.



54a **54b**

5-(*tert*-Butyldimethylsilyloxy)-1-(tributyl stannyl)-1(*E*)-pentene (54a) and 5-(*tert*-Butyldimethylsilyloxy)-2-(tributylstannyl)-1-

pentene (54b) (Scheme 14, Conditions B, entry 5). Applying conditions A to 5-(*tert*-butyldimethylsilyloxy)-1-pentyne (**53**)[166] (200 mg, 1.01 mmol) afforded after 4 h reaction time and column chromatography [silica; pentane, 1% TEA] a (1:1) mixture of 5-(*tert*-butyldimethylsilyloxy)-1-(tributylstannyl)-1(*E*)-pentene (**54a**) and 5-(*tert*-butyldimethylsilyloxy)-2-(tributylstannyl)-1-pentene (**54b**) (265 mg, 53%) as a clear oil. For spectroscopic data see page 149-150.



56a **56b**

5-Chloro-1-(tributylstannyl)-1(*E*)-pentene (56a) and 5-chloro-2-(tributyl stannyl)-1-pentene (56b) (Scheme 14, Conditions B, entry 6). Applying conditions B to 5-chloro-1-pentyne (**55**) (1.07 mL, 1.0 mmol) afforded after 0.5 h reaction time and column chromatography [silica; hexanes, 1% TEA] a (1.4:1) mixture of 5-chloro-1-(tributylstannyl)-1(*E*)-pentene (**56a**) and 5-chloro-2-(tributylstannyl)-1-pentene (**56b**) (310 mg, 78%) as a clear oil. For spectroscopic data see page 150.

STILLE COUPLINGS CATALYTIC IN TIN AND RELATED REACTIONS

Volume II

By

William P. Gallagher

A DISSERTATION

Submitted to
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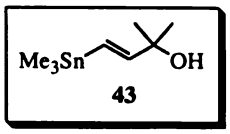
for the degree of

DOCTOR OF PHILOSOPHY

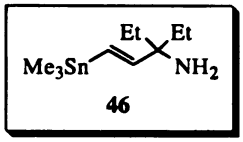
Department of Chemistry

2003



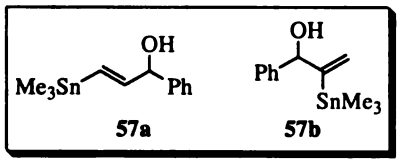
43

Generation and utilization of Me_3SnH. Representative procedure for the formation of trimethylstannanes. Preparation of (*E*)-2-methyl-4-(trimethylstannyl)but-3-en-2-ol (43) (Scheme 17, entry 1). Applying conditions A with Me_3SnCl (18 mL, 18 mmol; 1M solution in THF) and 2-methyl-3-butyn-2-ol (**1**) (2.43 mL, 15 mmol) after 2 h and column chromatography [silica; 70:30 hexane/Ether, 1% TEA] afforded (*E*)-2-methyl-4-(trimethylstannyl)-3-buten-2-ol (**43a**) (3.17 g, 85%) as a yellow oil. For spectroscopic data see page 141.



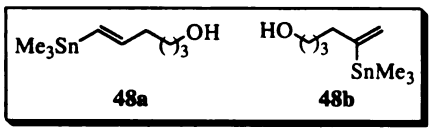
46

Preparation of (*E*)-3-ethyl-1-(trimethylstannyl)pent-1-en-3-amine (46) (Scheme 17, entry 2). Applying the above conditions with 3-ethylpent-1-yn-3-amine (**14**) (0.67 mL, 5 mmol) after 2 h and column chromatography [silica; 50:50 pentane/EtOAc, 1% TEA] afford (*E*)-3-ethyl-1-(trimethylstannyl)pent-1-en-3-amine (**46**) (1.04 g, 75%) as a yellow oil. For spectroscopic data see page 142-143.



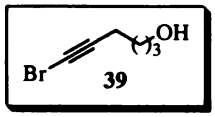
57a 57b

Preparation of 1-phenyl-3-trimethylstannanyl-prop-2-en-1-ol (57) (Scheme 17, entry 3). Applying the above conditions using 1-phenyl-2-propyn-1-ol (**28**) (0.5 mL, 4 mmol) gave a 9:1 *E*/int mixture that was purified by column chromatography [silica gel; 95/5 pentane/EtOAc, 1% TEA] to afford (*E*)-1-phenyl-3-trimethylstannanyl-prop-2-en-1-ol (**57a**) (722 mg, 73%) and 2-(trimethylstannyl)-1-phenylprop-2-en-1-ol (**57b**) (81 mg, 8%) as clear oils. IR (neat) 3343 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 9 H), 2.55 (br s, 1 H), 5.14 (m, 1 H), 5.95-6.58 (m, 2 H), 7.20-7.50 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –9.7, 76.4, 126.1, 127.3, 128.2, 128.9, 142.5, 148.8; HRMS (EI) *m/z* 298.0382 [(M^+); calcd. For $C_{12}H_{18}OSn$ 298.0380].



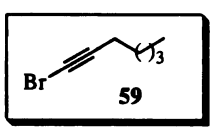
48a 48b

Preparation of 1-(trimethylstannyl)-1(*E*)-hexen-6-ol (48a) and 2-(Trimethylstannyl)-1-hexen-6-ol (48b) (Scheme 17, entry 4). Applying conditions A to 5-hexyn-1-ol (**51**) (98 mg, 0.12 mL, 1.0 mmol) and Me_3SnCl (0.20 g, 1.0 mmol) afforded after 3 h reaction time and column chromatography [silica; 90:10 hexane/EtOAc, 1% TEA] a (1.2:1) mixture of 1-(trimethylstannyl)-1(*E*)-hexen-6-ol (**48a**) and 2-(trimethylstannyl)-1-hexen-6-ol (**48b**) (150 mg, 57%) as a clear oil. For spectroscopic data see page 143.



39

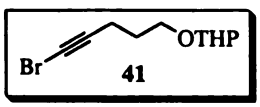
Representative preparation of 1-bromoalkynes. Preparation of 1-bromo-1-hexyn-6-ol (39) (Scheme 18, entry 1). *N*-Bromosuccinimide (NBS) (1.96 g, 11 mmol) and catalytic $AgNO_3$ (150 mg, 0.88 mmol) were added to a solution of 5-hexyn-1-ol (0.98 g, 10 mmol) (**51**) in dry acetone (40 mL). The reaction was stirred at rt until complete by GC (~1 h). At that time, the mixture was diluted with pentane (200 mL) and washed with water (2 × 50 mL). The separated aqueous layer was back extracted with diethyl ether/pentane (1:1, 100 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated to afford 1.68 g (95%)1-bromo-1-hexyn-6-ol (**39**),[167] which was used without further purification in the hydrostannation step (see below). IR (neat) 2363 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ1.59 (m, 4 H), 2.01 (bs, 1 H), 2.21 (t, J = 6.9 Hz, 2 H), 3.61 (t, J = 6.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.9, 62.2, 38.0, 31.6, 24.5, 19.4; HRMS (EI) *m/z* 175.9837 [(M^+); calcd for C_6H_9BrO 175.9837].



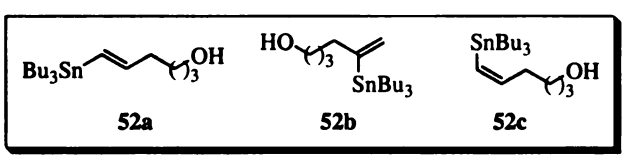
59

1-Bromo-1-heptyne (59) (Scheme 18, entry 2). Following the procedure for the preparation of **X**, 1-heptyne (1.3 mL, 10 mmol) (**58**) was converted into 1.66 g (95%) 1-bromo-1-heptyne (**59**),[168] which was used without

further purification in the hydrostannation step (see below). IR (neat) 2959 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 3 H), 1.30 (m, 4 H), 1.49 (m, 2 H), 2.17 (t, J = 7.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 19.6, 22.2, 28.0, 30.9, 37.4, 80.5; HRMS (EI) *m/z* 172.9960 [$(M-H)^+$; calc. for $C_7H_{10}Br$ 172.9966].



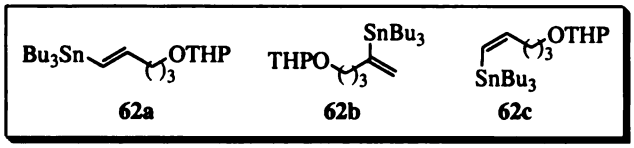
1-Bromo-5-(tetrahydropyranyloxy)-1-pentyne (41) (Scheme 18, entry 3). Following the established procedures,[169] 1-pentyn-4-ol (0.93 mL, 10 mmol) was converted to 1.59 g of 5-(tetrahydropyranyloxy)-1-pentyne (**60**) (95% yield following column chromatography [silica; 95:5 pentane/EtOAc]. Then, following the procedure for the preparation of **39**, compound **60** (1.5 g, 8.9 mmol) was converted into 1-bromo-5-(tetrahydropyranyloxy)-1-pentyne (**41**) (2.13 g, 97%),[24] which was used without further purification in the hydrostannation step (see below). IR (neat) 2944 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46-1.81 (m, 8 H), 2.30 (t, J = 7.1 Hz, 2 H), 3.44 (m, 2 H), 3.79 (m, 2 H), 4.56 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 19.4, 25.4, 28.4, 30.6, 37.9, 62.1, 65.7, 79.7, 98.7; HRMS (EI) *m/z* 245.0170 [$(M-H)^+$; calc. for $C_{10}H_{14}BrO_2$ 245.0177].



Hydrostannations of 1-bromoalkynes (Scheme 6). Representative procedure for hydrostannations with commercial Bu_3SnH. Preparation of 1-(tributylstannyl)-1(*E*)-hexen-6-ol (52a), 2-(tributylstannyl)-1-hexen-6-ol (52b), and 1-(tributylstannyl)-1(*Z*)-hexen-6-ol (52c) (Scheme 19, Conditions C, entry 1). Bu_3SnH (0.32 mL, 1.2 mmol) was added dropwise over 30 min to a 0 °C solution of 1-bromo-1-hexyn-6-ol (161 mg, 0.91 mmol) (**39**) and $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) in THF (5 mL). After 2 h, the reaction mixture was concentrated, and

diethyl ether (5 mL) and a saturated KF solution (7 mL) were added. This mixture was allowed to stir for 4 h before being filtered. The filtrate layers were separated, and the aqueous layer was extracted with ether. The combined organic phases were then washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography [silica; 95:5 to 90:10 pentane/EtOAc, 1% TEA] to afford a (11:1:1) mixture of 1-(tributylstannyl)-1(*E*)-hexen-6-ol (**52a**), 2-(tributylstannyl)-1-hexen-6-ol (**52b**), and 1-(tributylstannyl)-1(*Z*)-hexen-6-ol (**52c**) (193 mg, 54%) as a pale yellow oil. For spectroscopic data see page 149.

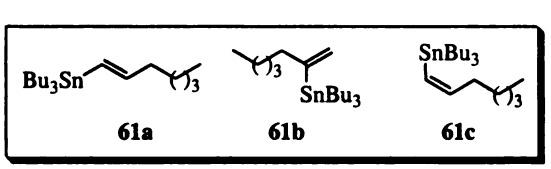
1-(Tributylstannyl)-1(*E*)-heptene (61a), 2-(tributylstannyl)-1-heptene (61b), and 1-(tributylstannyl)-1(*Z*)-heptene (61c) (Scheme 19, Conditions C, entry 2). Applying conditions C to 1-bromo-1-heptyne (**59**) (175 mg, 1.0 mmol) afforded after column chromatography [silica; pentane, 1%] a (8:1:1) mixture of 1-(tributylstannyl)-1(*E*)-heptene (**61a**), 2-(tributylstannyl)-1-heptene (**61b**), and 1-(tributylstannyl)-1(*Z*)-heptene (**61c**) (194 mg, 50%) as a clear yellow oil. The spectroscopic data was consistent with the literature.[170]



5-(Tetrahydropyranyloxy)-1(*E*)-(tributylstannyl)-1-pentene (62a), 5-(tetrahydropyranyloxy)-2-(tributylstannyl)-1-pentene (62b), and 5-(tetrahydropyranyloxy)-1(*Z*)-(tributylstannyl)-1-pentene (62c) (Scheme 19, Conditions C, entry 3). Applying conditions C to 1-bromo-5-(tetrahydropyranyloxy)-1-pentyne (247 mg, 1 mmol) (**41**) afforded after column chromatography [silica; 95:5 pentane/EtOAc, 1% TEA] a (8:1:1) mixture of 5-(tetrahydropyranyloxy)-1(*E*)-(tributylstannyl)-1-pentene (**62a**), 5-(tetrahydropyranyloxy)-2-(tributylstannyl)-1-pentene

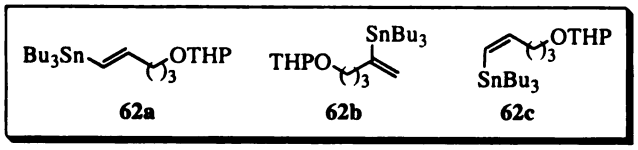
(**62b**), and 5-(tetrahydropyranyloxy)-1(*Z*)-(tributylstannyl)-1-pentene (**62c**) (316 mg, 69%) as a cloudy colorless oil. The spectroscopic data for **62a**[169] and **62b**[164] were consistent with those previously reported in the literature.

Representative Procedure for Hydrostannations with Catalytic Bu_3SnH Generated in Situ from KF/PMHS. Preparation of 1-(tributylstannyl)-1(*E*)-hexen-6-ol (52a), 2-(tributylstannyl)-1-hexen-6-ol (52b), and 1-(tributylstannyl)-1(*Z*)-hexen-6-ol (52c) (Scheme 19, Conditions D, entry 1). PMHS (0.18 mL, 3.0 mmol) was added to a solution of KF (176 mg, 3.0 mmol; 1 mL H_2O), $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol), Bu_3SnCl (0.32 mL, 1.2 mmol), and TBAI (cat.) and 1-bromo-1-hexyn-6-ol (**39**) (177 mg, 1 mmol) in diethyl ether (5 mL). The biphasic mixture was stirred at 25 °C for 4.5 h, at which time 3 M NaOH (1 mL) was added, and the reaction was allowed to stir an additional 3 h. The reaction mixture was separated, and the aqueous phase was extracted with diethyl ether. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography [silica; 95:5 to 90:10 pentane/EtOAc, 1% TEA] to afford a (18:1:1) mixture of 1-(tributylstannyl)-1(*E*)-hexen-6-ol (**52a**), 2-(tributylstannyl)-1-hexen-6-ol (**52b**), and 1-(tributylstannyl)-1(*Z*)-hexen-6-ol (**52c**) (200 mg, 51%) as a clear colorless oil. For spectroscopic data see page 149.



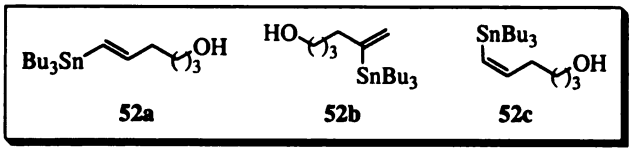
1-(Tributylstannyl)-1(*E*)-heptene (61a), 2-(Tributylstannyl)-1-heptene (61b), and 1-(Tributylstannyl)-1(*Z*)-heptene (61c) (Scheme 19, Conditions D, entry 2). Conditions D were applied to 1-bromo-1-heptyne

(**59**) (175 mg, 1.0 mmol) to afford after column chromatography [silica; pentane, 1% TEA] a (18:1:1) mixture of 1-(tributylstannyl)-1(*E*)-heptene (**61a**), 2-(tributylstannyl)-1-heptene (**61b**), and 1-(tributylstannyl)-1(*Z*)-heptene (**61c**) (285 mg, 74%) as a clear pale yellow oil. For spectroscopic data see page 156.



62a **62b** **62c**

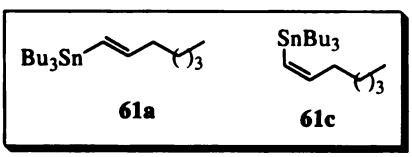
5-(Tetrahydropyranyloxy)-1(*E*)-(tributylstannyl)-1-pentene (62a), 5-(tetrahydropyranyloxy)-2-(tributylstannyl)-1-pentene (62b), and 5-(tetrahydropyrany loxy)-1(*Z*)-(tributylstannyl)-1-pentene (62c) (Scheme 19, Conditions D, entry 3). Conditions D were applied to 1-bromo-5-(tetrahydropyranyloxy)-1-pentyne (**41**) (247 mg, 1 mmol) to afford after column chromatography [silica; 95:5 pentane/EtOAc, 1% TEA] a (17:2:1) mixture of 5-(tetrahydropyranyloxy)-1(*E*)-(tributylstannyl)-1-pentene (**262a**), 5-(tetrahydropyrany loxy)-2-(tributylstannyl)-1-pentene (**62b**), and 5-(tetrahydropyrany-loxy)-1(*Z*)-(tributyl stannyl)-1-pentene (**62c**) (289 mg, 63%) as a clear oil. For spectroscopic data see page 156-157.



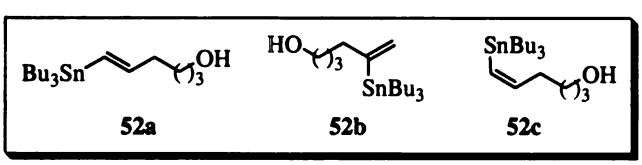
52a **52b** **52c**

Representative procedure for the one-pot bromination/hydrostann ation protocol. Preparation of 1-(tributylstannyl)-1(*E*)-hexen-6-ol (52a) and 1-(tributylstannyl)-1(*Z*)-hexen-6-ol (152c) (Scheme 19, Conditions E, entry 1). *N*-Bromosuccinimide (NBS) (0.20 g, 1.1 mmol) and catalytic $AgNO_3$ (5 mg, 0.03 mmol) were added to a solution of 5-hexyn-1-ol (0.11 mL, 0.98 mmol) (**51**) in acetone (4 mL). The reaction was stirred at 25 °C until complete by GC (~1 h). At this time, Bu_3SnCl (0.32 mL, 1.2 mmol), KF (232 mg, 4.0 mmol), TBAI (cat.), $PdCl_2(PPh_3)_2$ (7 mg, 0.01

mmol), PMHS (0.09 mL, 1.5 mmol), pentane (4 mL), and H_2O (1 mL) were added successively. This mixture was allowed to stir for 4.5 h. Then, 3 M NaOH (3 mL) was added, and the mixture was allowed to stir an additional 3 h before being filtered. The filtrate phases were separated, and the aqueous phase was extracted with pentane. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography [silica; 95:5 to 90:10 pentane/EtOAc, 1% TEA] to afford a (33:1) mixture of 1-(tributylstannyl)-1(*E*)-hexen-6-ol (**52a**) and 1-(tributylstannyl)-1(*Z*)-hexen-6-ol (**52c**) (163 mg, 42%) as a clear pale yellow oil. For spectroscopic data see page 149.



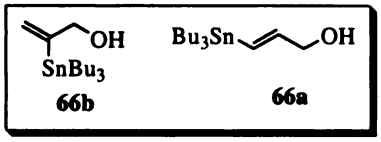
1-(Tributylstannyl)-1(*E*)-heptene (61a) and 1-(tributylstannyl)-1(*Z*)-heptene (61c) (Scheme 19, Conditions E, entry 2). Conditions E were applied to 1-heptyne (0.13 mL, 1.0 mmol) (**58**) to afford after column chromatography [silica; Pentane, 1% TEA] a (20:1) mixture of 1-(tributylstannyl)-1(*E*)-heptene (**61a**) and 1-(tributylstannyl)-1(*Z*)-heptene (**61c**) (184 mg, 48%) as a clear pale yellow oil. For spectroscopic data see page 156.



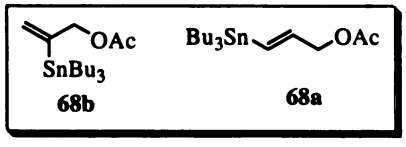
5-(Tetrahydropyranyloxy)-1(*E*)-(tributylstannyl)-1-pentene (62a) and 5-(tetrahydropyranyloxy)-1(*Z*)-(tributylstannyl)-1-pentene (62c) (Scheme 19, Conditions E, entry 3). Conditions E were applied to 5-(tetrahydropyranyloxy)-1-pentyne (**60**) (168 mg, 1 mmol) [169] to afford after column chromatography [silica; 95:5 pentane/EtOAc, 1% TEA] a (17:1) mixture of 5-(tetrahydropyranyloxy)-1(*E*)-(tributylstannyl)-1-pentene (**62a**) and 5-(tetrahydropyranyloxy)-1(Z)-(tributylstannyl)-1-

pentene (**62c**) (206 mg, 45%) as a cloudy colorless oil. For spectroscopic data see page 156-157.

Representative procedure for the preparation of $Mo(CO)_3(t\text{-}BuNC)_3$ ($MoBI_3$). PdO (49 mg, 0.40 mmol), $Mo(CO)_6$ (1.32 g, 5.0 mmol) and toluene (100 mL) were all placed in a 250 mL RB flask. The mixture was heated to reflux and then t-BuNC (1.75 mL, 15.40 mmol) was added via syringe (added slowly as CO gas is evolved quickly!). After 5 minutes the reaction was allowed to cool to room temperature. It was then filtered thru fluted filter paper to remove the palladium. The solvent was then concentrated and the resulting residue was purified by column chromatography [silica gel; 50/50 hexne/Et_2O] to afford $MoBI_3$ (1.53 g, 72%) as a pale yellow solid.[171]

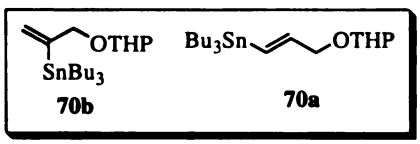


Representative procedure for the $MoBI_3$ catalyzed hydrostannation using the combination of Bu_3SnF and PMHS. Preparation of 2-tributylstannayl-2-propen-1-ol (66b) and 3-tributylstannyl-2(*E*)-propen-1-ol (66a) (Scheme 21, entry 1). Propargyl alcohol (**65**) (0.059 mL, 1.0 mmol) and $MoBI_3$ (8.6 mg, 0.02 mmol) were dissolved in THF (1 mL). Bu_3SnF (464 mg, 1.5 mmol) hydroquinone (10 mg/mmol) and PMHS (0.09 mL, 1.5 mmol) were added and the reaction was refluxed for 3.5 h. The reaction was then allowed to cool to room temperature and was then subjected to column chromatography [silica gel; 90/10 hexane/EtOAc, 1% TEA] to afford a separable (9/1) mixture of 2-tributylstannanyl-prop-2-en-1-ol (**66b**) and 3-tributylstannanyl-prop-2(*E*)-en-1-ol (**66a**) (305 mg, 88%) as clear oils. Spectroscopic data was consistent with the literature.[172]

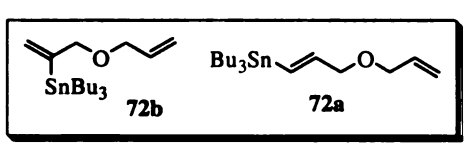


Preparation of 2-(tributylstannyl)allyl acetate (68b) (Scheme 21, entry 2). Applying the above conditions

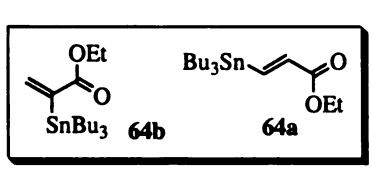
with propargyl acetate (**64**) (98 mg, 1 mmol) afforded after 4 h and column chromatography [silica; 98:2 hexane/EtOAc, 1% TEA] 2-(tributylstannyl)allyl acetate (**68b**) (284 mg, 73%) as a clear oil. Spectroscopic data was consistent with the literature.[172]



Preparation of tributyl(1-(tetrahydro-2H-pyran-2-yloxy)prop-2-en-2-yl) stannane (70b) and tributyl((*E*)-3-(tetrahydro-2H-pyran-2-yloxy)prop-1-enyl) stannane (70a) (Scheme 21, entry 3). Applying the above conditions with tetrahydro-2-(prop-2-ynyloxy)-2H-pyran (**69**) (140 mg, 1 mmol) afforded after 4 h and column chromatography [silica; 98:2 hexane/EtOAc, 1% TEA] a separable (95:5) mixture of tributyl(1-(tetrahydro-2H-pyran-2-yloxy)prop-2-en-2-yl)stannane (**70b**) and tributyl((*E*)-3-(tetrahydro-2H-pyran-2-yloxy)prop-1-enyl)stannane (**70a**) (366 mg, 85%) as a clear oil. Spectroscopic data was consistent with the literature.[172]

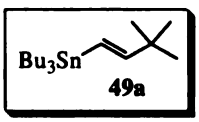


Preparation of (1-(allyloxy)prop-2-en-2-yl)tributylstannane (72b) and ((*E*)-3-(allyloxy)prop-1-enyl)tributylstannane (72a) (Scheme 21, entry 4). Applying the above conditions with 3-(prop-2-ynyloxy)prop-1-ene (**71**) (96 mg, 1 mmol) afforded after 4 h and column chromatography [silica; hexane, 1% TEA] a (95:5) mixture of (1-(allyloxy)prop-2-en-2-yl)tributylstannane (**72b**) and ((*E*)-3-(allyloxy)prop-1-enyl)tributylstannane (**72a**) (291 mg, 75%) as a clear oil. Spectroscopic data was consistent with the literature.[172]



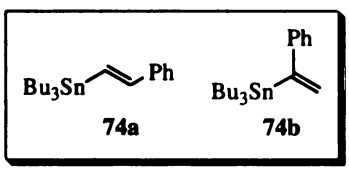
Preparation of ethyl 2-(tributylstannyl)acrylate (64b) and (*E*)-ethyl 3-(tributylstannyl)acrylate (64a) (Scheme

21, entry 5). Applying the above conditions with ethyl propiolate (**63**) (98 mg, 1 mmol) afforded after 5 h and column chromatography [silica; 95:5 hexane/EtOAc, 1% TEA] a (95:5) mixture of 2-(tributylstannyl)acrylate (**64b**) and (*E*)-ethyl 3-(tributylstannyl)acrylate (**64a**) (359 mg, 92%) as a clear oil. Spectroscopic data was consistent with the literature.[172]



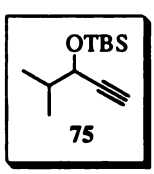
49a

Preparation of tributyl((*E*)-3,3-dimethylbut-1-enyl)stannane (49a) (Scheme 21, entry 6). Applying the above conditions with *tert*-butylacetlyene (**4**) (98 mg, 1 mmol) afforded after 5 h and column chromatography [silica; Hexane, 1% TEA] (*E*)-ethyl 3-(tributylstannyl)acrylate (**49a**) (281 mg, 75%) as a clear oil. For spectroscopic data see page 148.



74a **74b**

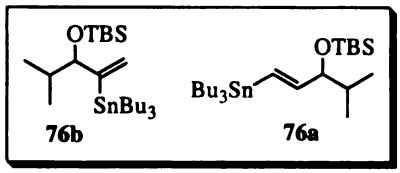
Preparation of (*E*)-tributyl(styryl)stannane (74a) and tributyl(1-phenylvinyl) stannane (74b) (Scheme 21, entry 7). Applying the above conditions with phenyl acetylene (**73**) (102 mg, 1 mmol) afforded after 5 h and column chromatography [silica; hexane, 1% TEA] a (5:1) mixture of (*E*)-tributyl(styryl)stannane (**74a**) and tributyl(1-phenylvinyl)stannane (**74b**) (304 mg, 77%) as a clear oil.[173]



75

Preparation of (4-methylpent-1-yn-3-yloxy)(*tert*-butyl)dimethylsilane (75). 4-Methyl-1-pentyn-3-ol (**77**) (982 mg, 10.0 mmol) was added to dry CH_2Cl_2 (50 mL) and this solution was cooled with an ice bath. At this time 2,6-lutidine (1.4 mL, 12 mmol) was added followed by the dropwise addition of TBSOTf (2.76 mL, 12 mmol). The reaction was complete after 40 min as shown by TLC analysis. The reaction was quenched by the addition of 1M $KHCO_3$. The mixture was then extracted with Et_2O and the combined organics were dried ($MgSO_4$), filtered, and

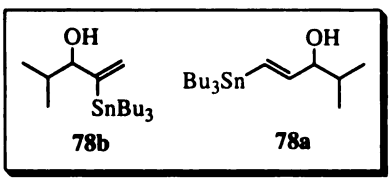
concentrated. The resulting residue was purified by column chromatography [silica; hexanes] to afford (4-methylpent-1-yn-3-yloxy)(*tert*-butyl)dimethylsilane (**75**) (2.10 g, 99%) as a liquid with an orange tint. IR (neat) 2978 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.16 (s, 3 H), 0.93 (s, 9 H), 0.98 (d, J = 6.6 Hz, 3 H), 1.00 (d, J = 6.6 Hz, 3 H), 1.85 (m, 1 H), 2.37 (m, 1 H), 4.13 (dd, J = 2.1, 5.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, -4.6, 17.7, 17.9, 18.2, 25.8, 35.2, 68.1, 72.5, 84.5; HRMS (EI) *m/z* 155.0895 [(M^+-Bu); calcd. for $C_8H_{15}OSi$ 155.0892.



Preparation of (2-(tributylstannyl)-4-methylpent-1-en-3-yloxy) (*tert*-butyl)dimethylsilane (76b) and ((*E*)-1-(tributylstannyl)-4-methylpent-1-en-3-yloxy)(*tert*-butyl)dimethylsilane (76a) (Scheme 21, entry 8). Applying the above conditions with (4-methylpent-1-yn-3-yloxy)(*tert*-butyl)dimethylsilane (**75**) (212 mg, 1 mmol) afforded after 5 h and column chromatography [silica; Hexane, 1% TEA] a (3:1) mixture of (2-(tributylstannyl)-4-methylpent-1-en-3-yloxy) (*tert*-butyl)dimethylsilane (**76b**) and ((*E*)-1-(tributylstannyl)-4-methylpent-1-en-3-yloxy)(*tert*-butyl)dimethylsilane (**76a**) (313 mg, 62%) as a clear oil.

Data for (2-(tributylstannyl)-4-methylpent-1-en-3-yloxy) (*tert*-butyl)dimethylsilane) (**76b**): IR (neat) 2964 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 6 H), 0.81-0.93 (m, 30 H), 1.22-1.37 (m, 6 H), 1.39-1.55 (m, 7 H), 3.73 (d, J = 6.9 Hz, 1 H), 5.16 (m, 1 H), 5.69 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.7, -3.8, 10.3, 13.7, 18.3, 19.8, 26.1, 27.5, 29.1, 33.9, 85.8, 124.8, 158.4; HRMS (EI) *m/z* 447.2109 [(M^+-Bu); calcd. for $C_{20}H_{43}OSiSn$ 447.2105.

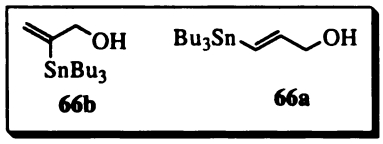
Data for ((*E*)-1-(tributylstannyl)-4-methylpent-1-en-3-yloxy)(*tert*-butyl)dimethylsilane (**76a**): IR (neat) 2939 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 6 H), 0.79-0.92 (m, 30 H), 1.22-1.36 (m, 6 H), 1.41-1.56 (m, 6 H), 1.57-1.70 (m, 1 H), 3.73 (t, *J* = 5.4 Hz, 1 H), 5.87 (dd, *J* = 5.7, 19.1 Hz, 1 H), 5.99 (d, *J* = 19.1, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.8, -4.2, 9.5, 13.7, 18.0, 18.5, 25.9, 27.3, 29.2, 34.4, 81.9, 127.7, 150.5; HRMS (EI) *m/z* 447.2099 [(M^+-Bu); calcd. for $C_{20}H_{43}OSiSn$ 447.2105.



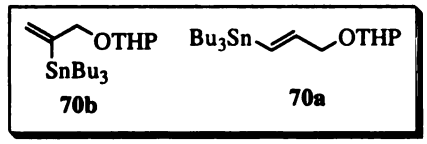
Preparation of 2-(tributylstannyl)-4-methylpent-1-en-3-ol (78b) and (*E*)-1-(tributylstannyl)-4-methylpent-1-en-3-ol (78a) (Scheme 21, entry 9). Applying the above conditions with 4-methyl-1-pentyn-3-ol (**77**) (1.08 mL, 10.2 mmol) afforded after 5 h and column chromatography [silica; 95:5 Hexane/EtOAc, 1% TEA] a (2:1) mixture of 2-(tributylstannyl)-4-methylpent-1-en-3-ol (**78b**) and (*E*)-1-(tributylstannyl)-4-methylpent-1-en-3-ol (**78a**) (3.60 g, 90%) as clear oils.

Data for 2-(tributylstannyl)-4-methylpent-1-en-3-ol (**78b**): IR (neat) 3483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (m, 21 H), 1.20-1.37 (m, 6 H), 1.39-1.64 (m, 7 H), 3.77-3.84 (m, 1 H), 5.23 (m, 1 H), 5.74 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.1, 13.7, 17.5, 19.6, 27.4, 29.1, 33.2, 85.1, 124.9, 158.4; HRMS (EI) *m/z* 333.1237 [(M^+-Bu); calcd. for $C_{14}H_{29}OSn$ 333.1240.

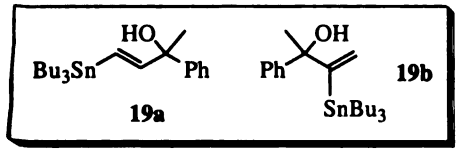
Data for (*E*)-1-(tributylstannyl)-4-methylpent-1-en-3-ol (**78a**): IR (neat) 3356 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78-0.93 (m, 21 H), 1.19-1.35 (m, 6 H), 1.40-1.54 (m, 6 H), 1.62-1.80 (m, 2 H), 3.79 (m, 1 H), 5.95 (dd, *J* = 5.5, 19.2 Hz, 1 H), 6.10 (d, *J* = 19.3, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.1, 13.7, 17.5, 19.8, 27.4, 29.1, 33.2, 85.1, 124.9, 158.4; HRMS (EI) *m/z* 333.1245 [(M^+-Bu); calcd. for $C_{14}H_{29}OSn$ 333.1240].



Representative procedure for the $NiCl_2(PPh_3)_2$ catalyzed hydrostannation using Bu_3SnF and PMHS. Preparation of 2-tributylstannayl-2-propen-1-ol (66b) and 3-tributylstannyl-2(*E*)-propen-1-ol (66a) (Scheme 22, entry 1). Propargyl alcohol (**65**) (0.059 mL, 1.0 mmol) and $NiCl_2(PPh_3)_2$ (8.6 mg, 0.02 mmol) were dissolved in THF (1 mL). Bu_3SnF (464 mg, 1.5 mmol) hydroquinone (10 mg) and PMHS (0.09 mL, 1.5 mmol) were added and the reaction was refluxed for 3.5 h. The reaction was then allowed to cool to room temperature and was then subjected to column chromatography [silica gel; 90:10 hexane/EtOAc, 1% TEA] to afford a (2.35:1) mixture of 3-tributylstannanyl-prop-2(*E*)-en-1-ol (**66a**) and 3-tributylstannanyl-prop-2(*Z*)-en-1-ol (**66b**) (253 mg, 73%) as clear oils. For spectroscopic data see page 160.

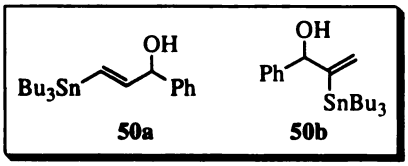


Preparation of tributyl((*E*)-3-(tetrahydro-2H-pyran-2-yloxy)prop-1-enyl) stannane (70a) and tributyl(1-(tetrahydro-2H-pyran-2-yloxy)prop-2-en-2-yl) stannane (70c) (Scheme 22, entry 2). Applying the above conditions with tetrahydro-2-(prop-2-ynyloxy)-2H-pyran (**69**) (140 mg, 1 mmol) afforded after 4 h and column chromatography [silica; 98:2 hexane/EtOAc, 1% TEA] a separable (3:1) mixture of tributyl(1-(tetrahydro-2H-pyran-2-yloxy)prop-2-en-2-yl)stannane (**70b**) and tributyl((*E*)-3-(tetrahydro-2H-pyran-2-yloxy)prop-1-enyl)stannane (**70a**) (237 mg, 85%) as a clear oil. For spectroscopic data see page 161.



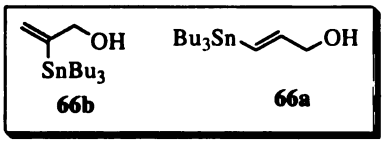
Preparation of (*E*)-4-(tributylstannyl)-2-phenylbut-3-en-2-ol (19a) and 3-(tributylstannyl)-2-phenylbut-3-en-2-ol (19b) (Scheme 22, entry 3).

Applying the above conditions with 2-phenyl-3-butyn-1-ol (**8**) (146 mg, 1 mmol) afforded after 4 h and column chromatography [silica; 95:5 Hexane/EtOAc, 1% TEA] a separable (2:1) mixture of (*E*)-4-(tributylstannyl)-2-phenylbut-3-en-2-ol (**19a**) and 3-(tributylstannyl)-2-phenylbut-3-en-2-ol (**19b**) (377 mg, 86%) as a clear oil. For spectroscopic data see page 125.



50a **50b**

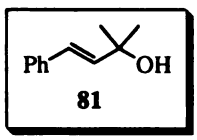
Preparation of (*E*)-3-(tributylstannyl)-1-phenylprop-2-en-1-ol (50a) and 2-(tributylstannyl)-1-phenylprop-2-en-1-ol (50b) (Scheme 22, entry 4). Applying the above conditions with 1-phenylprop-2-yn-1-ol (**28**) (132 mg, 1 mmol) afforded after 4 h and column chromatography [silica; 95:5 hexane/EtOAc, 1% TEA] a separable (1:3.5) mixture of (*E*)-4-(tributylstannyl)-2-phenylbut-3-en-2-ol (**50b**) and 3-(tributylstannyl)-2-phenylbut-3-en-2-ol (**50b**) (389 mg, 92%) as a clear oil. For spectroscopic data see page 148-149.



66b **66a**

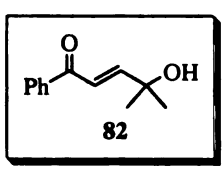
Representative procedure for the $CoCl_2(PPh_3)_2$ catalyzed hydrostannation using Bu_3SnF and PMHS. Preparation of 2-tributylstannayl-2-propen-1-ol (66b) and 3-tributylstannyl-2(*E*)-propen-1-ol (66a) (Scheme 23, entry 1). Propargyl alcohol (**65**) (0.059 mL, 1.0 mmol) and $CoCl_2(PPh_3)_2$ (13 mg, 0.02 mmol) were dissolved in THF (1 mL). Bu_3SnF (464 mg, 1.5 mmol) hydroquinone (10 mg) and PMHS (0.09 mL, 1.5 mmol) were added and the reaction was refluxed for 24 h. The reaction was then allowed to cool to room temperature and was then subjected to column chromatography [silica gel; 90:10 hexane/EtOAc, 1% TEA] to afford a (2.6/1) mixture of 3-tributylstannanyl-prop-2(*E*)-en-

1-ol (**66a**) and 3-tributylstannanyl-prop-2(*Z*)-en-1-ol (**66b**) (253 mg, 73%) as clear oils. For spectroscopic data see page 160.



81

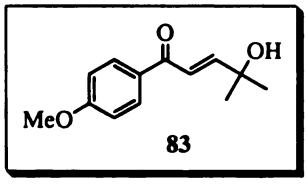
Representative Procedure for a tandem one-pot hydrostannation/Stille coupling with stoichiometric amounts of tin using the KF methodology. Preparation of 2-methyl-4-phenyl-3-buten-2-ol (81) (Scheme 25). Tri-2-furylphosphine (0.08 mmol, 18.6 mg) was added to a solution of Pd_2dba_3 (0.02 mmol, 18.2 mg) in dry THF (5 ml). After stirring for 15 min, 2-methyl-3-butyn-2-ol (**1**) (2 mmol, 0.2 ml), Me_3SnCl (2.4 mmol, 2.4 ml), PMHS (3 mmol, 0.18 ml), aq. KF (6 mmol, .3486g), H_2O (1 ml) and TBAF (catalytic) were added. Reaction progress was followed by TLC [90:10 pentane/EtOAc]. When complete (1 hr.), iodobenzene (3 mmol, 0.34 ml) was added and reaction was placed in a 60°C oil bath. After 8 hours, the reaction mixture is filtered and the aqueous layer is separated. The aqueous layer was then extract with pentane (2x, 10ml). Organics were combined and washed H_2O (2x, 10ml) and brine (2x, 10ml) and then dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography [silica gel; 90:10 pentane/EtOAc] to afford 2-methyl-4-phenyl-3-buten-2-ol (**81**) (260 mg, yield 80%) as an oil.[198]



82

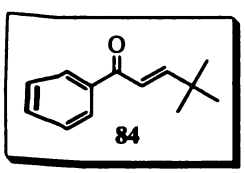
General procedure for the one-pot hydrostannation/Stille coupling of acid chlorides using Bu_3SnF/PMHS/TBAF(cat.) conditions. Preparation of (*E*)-4-hydroxy-4-methyl-1-phenylpent-2-en-1-one (82) (Scheme 26, entry 1). Pd_2dba_3 (27.1, mg, 0.03 mmol) and TFP (28 mg, 0.12 mmol) were added to ~10 mL of THF and this mixture was allowed to stir at room temperature for ~15 min. At this time 2-methyl-3-butyn-2-ol (**1**) (0.30 mL, 3.0 mmol), Bu_3SnF (1.40

g, 4.5 mmol), PMHS (0.29 mL, 4.8 mmol) and TBAF (1 drop of 1M solution in THF) were added successively. The reaction was then allowed to stir at room temperature for 2 h. Once complete (~2 h), benzoyl chloride (0.70 mL, 6 mmol) was added and the mixture was allowed to reflux until complete by TLC analysis. Once complete (3.5 h), the reaction was diluted with sat. aq. KF and stirred for 1 h. The reaction mixture was separated and the aqueous phase was extracted with Et_2O (3x). The combined organics were dried ($MgSO_4$) filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford (*E*)-4-hydroxy-4-methyl-1-phenylpent-2-en-1-one (**82**) (445 mg, 78%) as an oil. All spectroscopic data was consistent with that of the literature.[174]



83

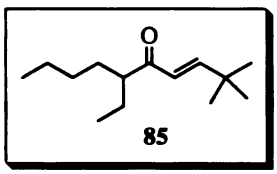
Preparation of (*E*)-4-hydroxy-1-(4-methoxyphenyl)-4-methylpent-2-en-1-one (83) (Scheme 26, entry 3). Following the general procedure above using 2-methyl-3-butyn-2-ol (**1**) (0.20 mL, 2.0 mmol) and *p*-anisoyl chloride (0.41 mL, 3.0 mmol) after column chromatography [silica; 70:30 hexane/EtOAc] afforded (*E*)-4-hydroxy-1-(4-methoxyphenyl)-4-methylpent-2-en-1-one (**83**) (410 mg, 93%) as purple solid [mp = 59 °C; lit. mp = 59 °C].[175] IR (neat) 3431 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 6 H), 3.80 (s, 3 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 7.04 (d, *J* = 15.5 Hz, 1 H), 7.11 (d, *J* = 15.2 Hz, 1 H), 7.91 (d, *J* = 9.1 Hz, 2 H); ^{13}C (125 MHz, $CDCl_3$) δ 29.3, 55.3, 71.1, 113.7, 121.2, 130.8, 132.0, 154.1, 163.4, 189.3; HRMS (EI) *m/z* 220.1094 [(M^+), calcd. for $C_{13}H_{16}O_3$ 220.1099].



84

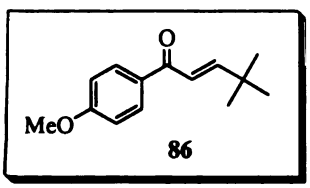
Preparation of (*E*)-4,4-dimethyl-1-phenylpent-2-en-1-one (84) (Scheme 26, entry 4). Following the general procedure above using

tert-butylacetylene (**4**) (0.25 mL, 2.0 mmol) and benzoyl chloride (0.31 mL, 2.6 mmol) after column chromatography [silica; 95:5 hexane/EtOAc] afforded (*E*)-4,4-dimethyl-1-phenylpent-2-en-1-one (**84**) (370 mg, 98%) as a yellow oil. All data matched with the literature.[176]



85

Preparation of (*E*)-6-ethyl-2,2-dimethyldec-3-en-5-one (85) (Scheme 26, entry 5). Following the general procedure above using *tert*-butylacetylene (**4**) (0.25 mL, 2.0 mmol) and 2-ethylhexanoyl chloride (0.45 mL, 2.6 mmol) after column chromatography [silica; 95:5 Hexane/EtOAc] afforded (*E*)-6-ethyl-2,2-dimethyldec-3-en-5-one (**85**) (400 mg, 95%) as a yellow oil. IR (neat) 2963, 1695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.82 (m, 6 H), 1.06 (s, 9 H), 1.10-1.30 (m, 4 H), 1.32-1.48 (m, 2 H), 1.52-1.66 (m, 2 H), 2.57 (m, 1 H), 6.05 (d, *J* = 15.9 Hz, 1 H), 6.81 (d, *J* = 16.1 Hz, 1 H); ^{13}C (125 MHz, $CDCl_3$) δ 11.8, 13.8, 22.8, 24.9, 28.7, 29.6, 31.2, 33.6, 51.3, 124.7, 156.7, 204.5; HRMS (EI) *m/z* 210.1980 [(M^+), calcd. for $C_{14}H_{26}O$ 210.1984].

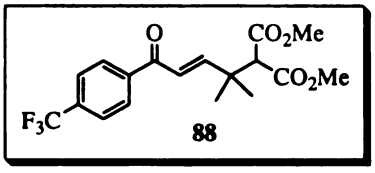


86

Preparation of (*E*)-1-(4-methoxyphenyl)-4,4-dimethylpent-2-en-1-one (86) (Scheme 26, entry 6). Following the general procedure above using *tert*-butylacetylene (**4**) (0.25 mL, 2.0 mmol) and *p*-anisoyl chloride (0.36 mL, 2.6 mmol) after column chromatography [silica; 95:5 hexane/EtOAc] afforded (*E*)-1-(4-methoxyphenyl)-4,4-dimethylpent-2-en-1-one (**86**) (400 mg, 91%) as a yellow oil. IR (neat) 1670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 9 H), 3.85 (s, 3 H), 6.77 (d, *J* = 15.6 Hz, 1 H), 6.92 (d, *J* = 8.9 Hz, 2 H), 7.02 (d, *J* = 15.4 Hz, 1 H), 7.92 (d, *J* = 8.4 Hz, 2 H); ^{13}C (125 MHz, $CDCl_3$) δ 28.7, 33.9, 55.4,

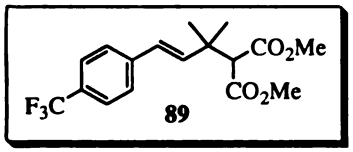
113.6, 120.5, 130.7, 131.0, 158.4, 163.2, 189.6; HRMS (EI) *m/z* 218.1312 [(M^+), calcd. for $C_{14}H_{18}O_2$ 218.1307].

Preparation of dimethyl 2-((*E*)-5-(4-(trifluoromethyl)phenyl)-2-methyl-5-oxopent-3-en-2-yl)malonate (88) and dimethyl 2-((*E*)-4-(4-(trifluoromethyl)phenyl)-2-methylbut-3-en-2-yl)malonate (89) (Scheme 26, entry 7). Following the general procedure above using dimethyl 2-(2-methylbut-3-yn-2-yl)malonate (**87**) (424 mg, 2.0 mmol) and *p*-(trifluoromethyl)benzoyl chloride (0.39 mL, 2.6 mmol) after column chromatography [silica; 95:5 hexane/EtOAc] afforded dimethyl 2-((*E*)-5-(4-(trifluoromethyl)phenyl)-2-methyl-5-oxopent-3-en-2-yl)malonate (**88**) (550 mg, 74%) as a yellow oil and dimethyl 2-((*E*)-4-(4-(trifluoromethyl)phenyl)-2-methylbut-3-en-2-yl)malonate (**89**) (110 mg, 16%) as an oil.



88

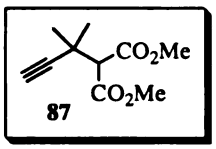
Data for 2-((*E*)-5-(4-(trifluoromethyl)phenyl)-2-methyl-5-oxopent-3-en-2-yl)malonate (**88**): IR (neat) 1738, 1676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 6 H), 3.45 (s, 1 H), 3.64 (s, 6 H), 6.66 (d, *J* = 15.9 Hz, 1 H), 7.15 (d, *J* = 15.9 Hz, 1 H), 7.66 (d, *J* = 8.2 Hz, 2 H), 7.96 (d, *J* = 8.0 Hz, 2 H); ^{13}C (75 MHz, $CDCl_3$) δ 24.9, 39.0, 52.2, 60.2, 123.8, 125.3, 128.9, 130.3, 133.5, 140.6, 155.6, 167.7, 190.9; HRMS (EI) *m/z* 372.1180 [(M^+), calcd. for $C_{18}H_{19}F_3O_5$ 372.1185].



89

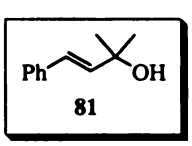
Data for dimethyl 2-((*E*)-4-(4-(trifluoromethyl)phenyl)-2-methylbut-3-en-2-yl)malonate (**89**): IR (neat) 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 6 H), 3.43 (s, 1 H), 3.67 (s, 6 H), 6.37 (d, *J* = 16.3 Hz, 1 H), 6.57 (d, *J* = 16.2 Hz, 1 H), 7.42 (d, *J* = 8.2 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H); ^{13}C (75 MHz, $CDCl_3$) δ 25.5, 38.8, 52.2, 60.8, 125.4, 126.4,

129.2, 130.4, 139.2, 140.9, 168.1; HRMS (EI) *m/z* 344.1242 [(M^+), calcd. for $C_{17}H_{19}F_3O_4$ 344.1235].



87

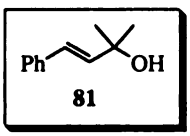
Preparation of dimethyl 2-(2-methylbut-3-yn-2-yl)malonate (87). Na (2.25 g, 98 mmol) was added to dry MeOH (50 mL) and once the initial reaction had subsided, dimethyl malonate was added dropwise. After 30 min, 3-chloro-3-methylbut-1-yne (10 mL, 89 mmol) was added dropwise to this solution and then the mixture was heated at ~60 °C for 1 h, then refluxed for 4 h and finally at 60 °C for 14 h. The precipitated NaCl was filtered off and the mixture was concentrated. The resulting oil was then dissolved into Et_2O and was washed with 1 M HCl (cold). The organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 90:10 Hexane/EtOAc] to afford dimethyl 2-(2-methylbut-3-yn-2-yl)malonate (**87**) (6.45 g, 34%) as a yellow oil. All spectroscopic data was consistent with the literature.[177]



81

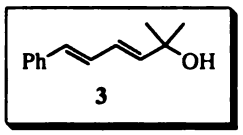
Representative Procedure for the initial attempt at a tandem one-pot hydrostannation/Stille coupling with catalytic amounts of tin (4-mol%) at room temperature using the KF methodology. Preparation of 2-methyl-4-phenyl-3-buten-2-ol (81) (Scheme 27, reaction 1). Tri-2-furylphosphine (27.9 mg, 0.12 mmol,) was added to a solution of Pd_2dba_3 (27.5 mg, 0.03 mmol) in dry Et_2O (5 ml). After stirring for 15 min, iodobenzene (0.34 mL, 3 mmol), Me_3SnCl (0.12 mL, 0.12 mmol), aq. KF (140 mg, 2.4 mmol), TBAF (cat.) and H_2O (1 ml) were added along with $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol). While the solution is stirred at room temperature, a solution of 2-methyl-3-butyn-2-ol (**1**) (0.30 mL, 3 mmol), PMHS (0.27 mL, 4.5 mmol) and Et_2O (4 mL) is added with a syringe pump (0.26 ml/hr).

After addition was complete, aqueous NH_4OH-soultion (10%, 2 ml) was added to the reaction mixture that was stirred for 30 minutes and then extracted with Et_2O. Organics were combined and washed H_2O (2x, 10ml) and Brine (2x, 10ml) and then dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography [silica gel; 90:10 pentane/EtOAc] to afford 2-methyl-4-phenyl-but-3-en-2-ol (**81**) (165 mg, 34%) as an oil. For spectroscopic data see page 167.



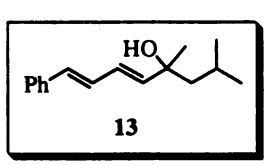
81

Representative Procedure for the initial attempt at a tandem one-pot hydrostannation/Stille coupling with catalytic amounts of tin (4-mol%) at 37 °C using the KF methodology. Preparation of 2-methyl-4-phenyl-3-buten-2-ol (81) (Scheme 27, reaction 2). Tri-2-furylphosphine (27.9 mg, 0.12 mmol,) was added to a solution of Pd_2dba_3 (27.5 mg, 0.03 mmol) in dry Et_2O (5 ml). After stirring for 15 min, iodobenzene (0.34 mL, 3 mmol), Me_3SnCl (0.12 mL, 0.12 mmol), aq. KF (140 mg, 2.4 mmol), TBAF (cat.) and H_2O (1 ml) were added along with $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol). While the solution is stirred at 37 °C, a solution of 2-methyl-3-butyn-2-ol (**1**) (0.30 mL, 3 mmol), PMHS (0.27 mL, 4.5 mmol) and Et_2O (4 ml) is added with a syringe pump (0.26 ml/hr). After addition was complete, aqueous NH_4OH-soultion (10%, 2 ml) was added to the reaction mixture that was stirred for 30 minutes and then extracted with Et_2O. Organics were combined and washed H_2O (2x, 10ml) and brine (2x, 10ml) and then dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography [silica gel; 90:10 Pentane/EtOAc] to afford 2-methyl-4-phenyl-but-3-en-2-ol (**81**) (485 mg, 67%) as an oil. For spectroscopic data see page 167.



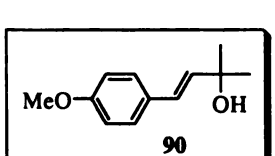
3

Representative procedure for the tandem one pot hydrostannation/Stille coupling with 6 mol% Me_3SnCl using the "Sn-F" route. Preparation of 2-methyl-6-phenyl-hexa-3,5-dien-2-ol (3) (Table 7, entry 1). Tri-2-furylphosphine (9.3 mg, 0.04 mmol) was added to a solution of Pd_2bda_3 (9.2 mg, 0.01 mmol) in Et_2O (5 mL). After stirring at room temperature for 15 min, (*E*)-β-bromostyrene (274.5 mg, 1.5 mmol), Me_3SnCl (0.06 mL, 0.06 mmol; 1M solution in THF), aq. KF (0.1743 g, 3 mmol; 1 mL H_2O), TBAF (1 drop of a 1M solution in THF) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were all added to the solution. The solution was heated to reflux and then a solution of 2-methyl-but-3-yn-2-ol (**1**) (0.10 mL, 1 mmol) and PMHS (0.09 mL, 1.5 mmol) in Et_2O (4mL) was added via a syringe pump over 11 hrs. The phases were separated and the organics washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by column chromatography [silica gel, 90:10 hexane/EtOAc] to afford 2-methyl-6-phenyl-hexa-3,5-dien-2-ol (**3**) (165 mg, 88%) as an oil. For spectroscopic data see page 108-109.



13

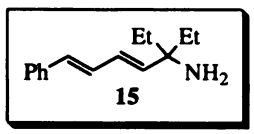
Preparation of 2,4-dimethyl-8-phenyl-octa-5,7-dien-4-ol (13) (Table 7, entry 2). Applying the above conditions to 3,5-dimethyl-hex-1-yn-3-ol (**12**) (0.15 mL, 1.0 mmol) and (*E*)-β-bromostyrene (274.5 mg, 1.5 mmol), afforded after column chromatography [silica gel; 90:10 hexane/EtOAc] 2,4-dimethyl-8-phenyl-octa-5,7-dien-4-ol (**13**) (205 mg, 89%) as an oil. For spectroscopic data see page 112.



90

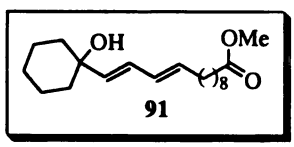
Preparation of 4-(4-methoxy-phenyl)-2-methyl-but-3-en-2-ol (90) (Table 7, entry 3). Applying the above conditions to 2-methyl-but-3-yn-2-ol (**1**) (0.10 mL, 1.0 mmol) and *p*-iodoanisole

(351.1 mg, 1.5 mmol), afforded after column chromatography [silica gel; 90:10 hexane/EtOAc] 4-(4-methoxy-phenyl)-2-methyl-but-3-en-2-ol (**90**) (198mg, 78%) as an oil.[178]



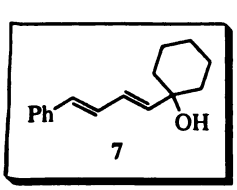
15

Preparation of 1,1-diethyl-5-phenyl-penta-2,4-dienylamine (15) (Table 7, entry 4). Applying the above conditions to 1,1-diethyl-prop-2-ynylamine (**14**) (0.10 mL, 1.0 mmol) and (*E*)-β-bromostyrene (274.5 mg, 1.5 mmol), afforded after column chromatography [silica gel; 60:40 hexane/EtOAc] 1,1-diethyl-5-phenyl-penta-2,4-dienylamine (**15**) (163 mg, 82%) as an oil. For spectroscopic data see page 112-113.



91

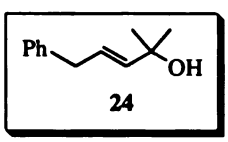
Preparation of 13-(1-hydroxy-cyclohexyl)-trideca-10,12-dienoic acid methyl ester (91) (Table 7, entry 5). Applying the above conditions to 1-ethynyl-cyclohexanol (**6**) (124.2 mg, 1.0 mmol) and (*E*)-11-iodo-undec-10-enoic acid methyl ester (**97**, see below for preparation) (486.3 mg, 1.5 mmol) afforded after column chromatography [silica gel; 90:10 hexane/EtOAc] 13-(1-hydroxy-cyclohexyl)-trideca-10,12-dienoic acid methyl ester (**91**) (235 mg, 73%) as an oil. IR 3356, 1774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21-1.38 (m, 11 H), 1.42-1.68 (m, 12 H), 2.03 (q, *J* = 7.51 Hz, 2 H), 2.26 (t, *J* = 7.29 Hz, 2 H), 3.70 (s, 3 H), 5.65 (m, 2 H), 5.99 (dd, *J* = 10.38, 15.02 Hz, 1 H); 6.19 (dd, *J* = 10.38, 15.46 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 22.14, 24.88, 25.50, 29.07, 29.13, 29.15, 29.19, 29.22, 32.50, 34.05, 37.94, 51.41, 71.30, 127.59, 129.84, 134.82, 138.58, 174.26; HRMS (EI) *m/z* 322.2511[(M^+), calcd. for $C_{20}H_{34}O_3$ 322.2508].



7

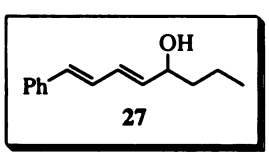
Preparation of 1-(4-phenyl-buta-1,3-dienyl)-cyclohexanol (7) (Table 7, entry 6). Applying the above conditions to 1-ethynyl-

cyclohexanol (**6**) (124.2 mg, 1.0 mmol) and (*E*)-β-bromostyrene (274.5 mg, 1.5 mmol) afforded after column chromatography [silica gel; 90:10 hexane/EtOAc] 1-(4-phenyl-buta-1,3-dienyl)-cyclohexanol (**7**) (205 mg, 90%) as an oil. For spectroscopic data see page 110.



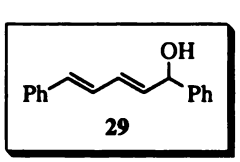
24

Preparation of 2-methyl-5-phenyl-pent-3-en-2-ol (24) (Table 7, entry 7). Applying the above conditions to 2-methyl-but-3-yn-2-ol (**1**) (0.10 mL, 1.0 mmol) and benzyl bromide (0.18 mL, 1.5 mmol) afforded after column chromatography [silica gel; 90:10 hexane/EtOAc] 2-methyl-5-phenyl-pent-3-en-2-ol (**24**) (149 mg, 85%) as an oil. For spectroscopic data see page 132.



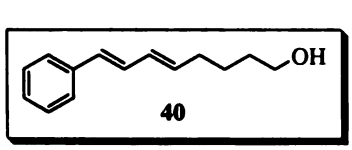
27

Preparation of 8-phenyl-octa-5,7-dien-4-ol (27) (Table 8, entry 1). Applying the above conditions to hex-1-yn-3-ol (**26**) (0.12 mL, 1.0 mmol) and (*E*)-β-bromostyrene (274.5 mg, 1.5 mmol) afforded after column chromatography [silica gel; 90:10 hexane/EtOAc] 8-phenyl-octa-5,7-dien-4-ol (**27**) (117 mg, 60%) as an oil. See above for spectroscopic data. For spectroscopic data see page 133-134.



29

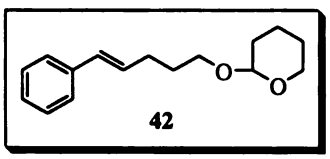
Preparation of 1,5-diphenyl-penta-2,4-dien-1-ol (29) (Table 8, entry 2). Applying the above conditions to 1-phenyl-prop-2-yn-1-ol (**28**) (0.13 mL, 1.0 mmol) and (*E*)-β-bromostyrene (274.5 mg, 1.5 mmol) afforded after column chromatography [silica gel; 90:10 hexane/EtOAc] 1,5-diphenyl-penta-2,4-dien-1-ol (**29**) (137 mg, 68%) as an oil. For spectroscopic data see page 134.



40

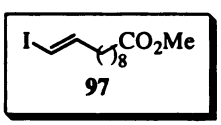
Preparation of 8-phenyl-octa-5,7-dien-1-ol (40) (Table 8, entry 3). Applying the above conditions to 6-bromo-hex-5-

yn-1-ol (**51**) (0.13 mL, 1.0 mmol) and (*E*)-β-bromostyrene (274.5 mg, 1.5 mmol) afforded after column chromatography [silica gel; 80:20 hexane/EtOAc] 8-phenyl-octa-5,7-dien-1-ol (**40**) (123 mg, 61%) as an oil. For spectroscopic data see page 139.



42

Preparation of 2-((*E*)-5-phenylpent-4-enyloxy)-tetrahydro-2H-pyran (42) (Table 8, entry 4). Applying the above conditions to 2-(5-bromopent-4-ynyloxy)-tetrahydro-2H-pyran (**41**) (246 mg, 1.0 mmol) and iodobenzene (0.15 mL, 1.5 mmol) afforded after column chromatography [silica gel; 80:20 hexane/EtOAc] 2-((*E*)-5-phenylpent-4-enyloxy)-tetrahydro-2H-pyran (**42**) (128 mg, 52%) as an oil. For spectroscopic data see page 139-140.

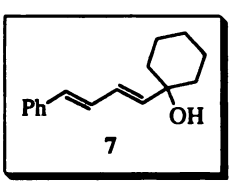


97

Preparation of (*E*)-11-iodo-undec-10-enoic acid methyl ester (97). Methyl 10-undecenoate (**95**) (10.0 g, 50.42 mmol) was dissolved in a 2:1 CH_2Cl_2/MeOH solution (200 mL) with 1 mL of NEt_3 added. The solution was purged with N_2 for 15 min. and then cooled to –78 °C. O_3 was then bubbled through the solution until a blue color persisted (~1.5 h). At this time N_2 was bubbled through the solution until the blue color disappeared. Dimethyl sulfide (15 mL, 202 mmol) was added dropwise and the solution was allowed to warm to room temperature overnight (~8 h). The solvent was then concentrated and the resulting residue was purified by column chromatography [silica gel; 80:20 hexanes/EtOAc] to afford 10-oxo-decanoic acid methyl ester (**96**) (8.96 g, 90%) as a clear liquid.[180]

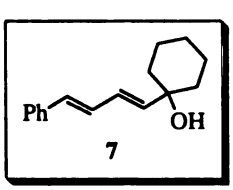
Under an Ar atmosphere, TMSCl (15.3 mL, 120 mmol) was added to a suspension of $CrCl_3$ (0.6334 g, 4 mmol), Zn (7.84 g, 120 mmol), and NaI (3.0 g, 20 mmol) in dioxane (100 mL) at 25 °C. After the reaction was stirred for 40 min, a

solution of 10-oxo-decanoic acid methyl ester (**96**) (4.01 g, 20 mmol) and CHI_3 (15.75 g, 40 mmol) in dioxane (50 mL) was added at 25 °C via a syringe pump over 24 hours. After the addition the mixture became very thick. The reaction was quenched by the addition of water. The reaction was then extracted with hexanes (5X). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 100:0 to 95:5 hexanes/EtOAc] to afford (*E*)-11-iodo-undec-10-enoic acid methyl ester (**97**) (12.14 g, 63%) as a peach colored liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14-1.40 (m, 10 H), 1.45-1.62 (m, 2 H), 1.98 (q, *J* = 6.94 Hz, 2 H), 2.24 (t, J = 7.42 Hz, 2 H), 3.60 (s, 3 H), 5.92 (dt, *J* = 1.40, 14.34 Hz, 1 H), 6.44 (dt, *J* = 7.14, 14.34 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 24.85, 28.25, 28.80, 29.00, 29.04, 29.09, 34.21, 35.92, 51.27, 74.43, 146.58, 174.36.[182]



7

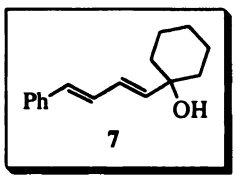
Representative procedure for the tin loading experiments. Preparation of 1-((1*E*,3*E*)-4-phenylbuta-1,3-dienyl)cyclohexanol (7), use of 4 mol % Me_3SnCl (Scheme 28, entry 2). Following the general procedure for Table 7 using Me_3SnCl (0.04 mL of a 1 M solution in THF, 0.04 mmol), 1-ethynyl-cyclohexanol (**6**) (124 mg, 1 mmol) and *E*-β-bromostyrene (275 mg, 1.5 mmol) after column chromatography [silica gel; 90:10 hexane/EtOAc] 1-(4-phenyl-buta-1,3-dienyl)-cyclohexanol (**7**) (144 mg, 63%) as an oil. For spectroscopic data see page 110.



7

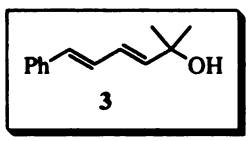
Preparation of 1-((1*E*,3*E*)-4-phenylbuta-1,3-dienyl)cyclohexanol (7), use of 2 mol % Me_3SnCl (Scheme 28, entry 3). Following the general procedure for Table 7 using Me_3SnCl (0.02 mL of a 1 M solution in THF, 0.02 mmol), 1-ethynyl-cyclohexanol (**6**) (124 mg, 1 mmol) and *E*-β-

bromostyrene (275 mg, 1.5 mmol) after column chromatography [silica gel; 90:10 hexane/EtOAc] 1-(4-phenyl-buta-1,3-dienyl)-cyclohexanol (**7**) (89 mg, 39%) as an oil. For spectroscopic data see page 110.



7

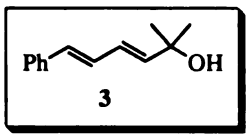
Preparation of 1-((1*E*,3*E*)-4-phenylbuta-1,3-dienyl)cyclohexanol (7), use of 1 mol % Me_3SnCl (Scheme 28, entry 4). Following the general procedure for Table 7 using Me_3SnCl (0.01 mL of a 1 M solution in THF, 0.01 mmol), 1-ethynyl-cyclohexanol (**6**) (124 mg, 1 mmol) and *E*-β-bromostyrene (275 mg, 1.5 mmol) after column chromatography [silica gel; 90:10 hexane/EtOAc] 1-(4-phenyl-buta-1,3-dienyl)-cyclohexanol (**7**) (43 mg, 19%) as an oil. For spectroscopic data see page 110.



3

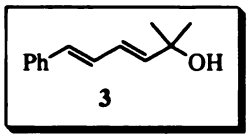
Representative procedure for the use of Me_3SnF as the tin source. Preparation of 2-methyl-6-phenyl-hexa-3,5-dien-2-ol (3). Tri-2-furylphosphine (9.3 mg, 0.04 mmol) was added to a solution of Pd_2bda_3 (9.2 mg, 0.01 mmol) in Et_2O (5 mL). After stirring at room temperature for 15 min, (*E*)-β-bromostyrene (274.5 mg, 1.5 mmol), Me_3SnF (11 mg, 0.06 mmol), aq. KF (0.1743 g, 3 mmol; 1 mL H_2O), TBAF (1 drop of a 1M solution in THF) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were all added to the solution. The solution was heated to reflux and then a solution of 2-methyl-but-3-yn-2-ol (**1**) (0.10 mL, 1 mmol) and PMHS (0.09 mL, 1.5 mmol) in Et_2O (4mL) was added via a syringe pump over 11 hrs. The phases were separated and the organics washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel, 90:10 hexane/EtOAc] to afford 2-methyl-6-phenyl-hexa-3,5-dien-2-ol (**3**) (152 mg, 81%) as an oil. For spectroscopic data see page 108-109.

Preparation of Me_3SnH. This was prepared as describe for Bu_3SnH (Scheme 12). Once the reaction was complete, the layers were separated and Me_3SnH was distilled as a 2.74 M solution in THF.



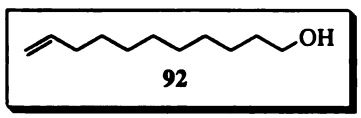
3

Representative procedure for the use of 6 mol% Me_3SnH as the tin source. Preparation of 2-methyl-6-phenyl-hexa-3,5-dien-2-ol (3). Following the above procedure outlined for Table 6, Me_3SnH (0.11 mL of a 2.74 M solution in THF, 0.30 mmol), (*E*)-β-bromostyrene (1.37 g, 7.5 mmol) and 2-methyl-but-3-yn-2-ol (**1**) (0.50 mL, 5 mmol) after column chromatography [silica gel, 90:10 hexane/EtOAc] 2-methyl-6-phenyl-hexa-3,5-dien-2-ol (**3**) (846 mg, 90%) was afforded as an oil. For spectroscopic data see page 108-109.



3

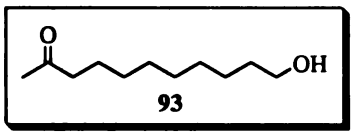
Representative procedure for the use of 6 mol% (*E*)-2-methyl-4-(trimethylstannyl)but-3-en-2-ol as the tin source. Preparation of 2-methyl-6-phenyl-hexa-3,5-dien-2-ol (3). Following the above procedure outlined for Table 6, (*E*)-2-methyl-4-(trimethylstannyl)but-3-en-2-ol (**43**) (15.0 mg, 0.06 mmol), (*E*)-β-bromostyrene (275 mg, 1.5 mmol) and 2-methyl-but-3-yn-2-ol (0.094 mL, 0.94 mmol) after column chromatography [silica gel, 90:10 hexane/EtOAc] 2-methyl-6-phenyl-hexa-3,5-dien-2-ol (**3**) (181 mg, 96%) was afforded as an oil. For spectroscopic data see page 108-109.



92

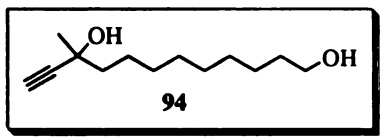
Procedure for the reduction of Ethyl undecylenate. Preparation of undec-10-en-1-ol (92) (Scheme 30). Ethyl undecylenate (**95**) (25 mmol, 5.31 g) was dissolved in CH_2Cl_2 (150 ml) and cooled to –78 °C and flushed with N_2. DIBAL (62.5 mmol, 62.5 mL of a 1M in THF) was added dropwise via an addition funnel and the mixture was then stirred for 3 hrs at –78 °C. The

reaction was quenched by the addition of Rochelle's Salt (300 mL, sat aq.) and then allowed to warm to room temperature for ~3 hrs. The phases are then separated and the aqueous phase was then extracted with CH_2Cl_2 (3X). Organics were then combined, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was the purified by column chromatography [silica gel; 80:20 hexane/EtOAc] to afford 4.30 g (96%) of undec-10-en-1-ol (**92**) (compared with commercial material).



93

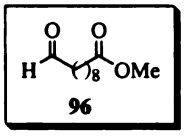
Procedure for the oxidation of undec-10-en-1-ol. Preparation of 11-hydroxy-undecan-2-one (93) (Scheme 30). Using Uemura's method, pyridine (3.53 mmol, 0.29 mL) was added to a mixture of $Pd(OAc)_2$ (0.89 mmol, 0.1978 g) and toluene (88 mL) in a 3 neck flask equipped with an O_2 balloon. O_2 was introduced into the flask and 2-propanol (17.62 mL) was added and the mixture heated to 60 °C with an oil bath. After the reaction had been left for 5 min at 60 °C, undec-10-en-1-ol (**92**) (17.62 mmol, 3.00 g) in 2-propanol (71 mL, 4 mL/1mmol) and the reaction was stirred for 25 hours at 60 °C under O_2. When complete the reaction was concentrated and the resulting residue was purified by column chromatography [silica gel; 75:25 Hexane/EtOAc] to afford 11-hydroxyundecan-2-one (**93**) (3.05 g, 85%) as a white solid.[179]



94

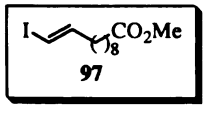
Procedure for the formation of 10-methyl-dodec-11-yne-1,10-diol (94) (Scheme 30). To a 0 °C solution of ethynylmagnesium bromide (37.66 mmol, 76 mL of a 1M THF solution) was added 11-hydroxyundecan-2-one (**93**) (16.37 mmol, 3.05 g) in 150 mL of THF. This mixture was stirred for 1 hour after the addition and then was quenched by the addition of 100 ml of sat. aq. NH_4Cl. The phases were separated and the aqueous phase was extracted with

Et_2O. The organics were combined, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 50:50 hexane/EtOAc] to afford 10-methyl-dodec-11-yne-1,10-diol (**94**) (2.94 g, 85%) as a thick yellow oil. IR (neat) 3304 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20-1.68 (m, 19 H), 2.41 (s, 1 H), 2.54 (br s, 2 H), 3.60 (t, J = 6.7 Hz, 2 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.8. 71.0, 67.9, 62.7, 43.4, 32.6, 29.6, 29.4, 29.3, 29.2, 25.6, 24.4 HRMS (EI) *m/z* 212.1771 [(M^+) calcd. for $C_{13}H_{24}O_2$ 212.1776].



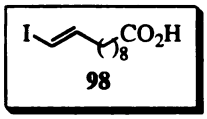
96

Preparation of 10-oxo-decanoic acid methyl ester (96) (Scheme 30). Methyl 10-undecenoate (**95**) (10.0 g, 50.42 mmol) was dissolved in a 2:1 CH_2Cl_2/MeOH solution (200 mL) with 1 mL of NEt_3 added. The solution was purged with N_2 for 15 minuets and then cooled to –78 °C. O_3 was then bubbled through the solution until a blue color persisted (~1.5 hrs.). At this time N_2 was bubbled through the solution until the blue color disappeared. Dimethyl sulfide (15 mL, 202 mmol) was added dropwise and the solution was allowed to warm to room temperature overnight (~8 hrs.). The solvent was then concentrated and the resulting residue was purified by column chromatography [silica gel; 80:20 hexanes/EtOAc] to afford 10-oxo-decanoic acid methyl ester[180] (**96**) (8.96 g, 90%) as a clear liquid.



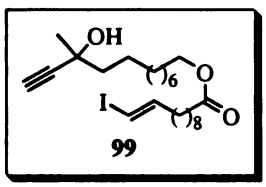
97

Procedure[181] for the preparation of (*E*)-11-iodo-undec-10-enoic acid methyl ester (97) (Scheme 30). Prepared as described on page 177. The resulting residue was purified by column chromatography [silica gel; hexanes to 95:5 hexanes/EtOAc] to afford (*E*)-11-iodo-undec-10-enoic acid methyl ester[182] (**97**) (12.14 g, 63%) as a peach liquid.



98

Preparation of (*E*)-11-iodo-undec-10-enoic acid (98) (Scheme 30). (*E*)-11-iodo-undec-10-enoic acid methyl ester (**97**) (3.47 g, 10.69 mmol) was added to a solution of LiOH (1.30 g, 53.44 mmol) in THF/H_2O (4:1) and the mixture was stirred until complete by TLC analysis. When complete (9 h), the reaction was diluted with H_2O and extracted with Et_2O. The aqueous layer was then acidified to ~pH 1.0 with 6N HCl. The acidified aqueous layer was then extracted with Et_2O (6x) and the combined extracts were dried over $MgSO_4$, filtered and concentrated to afford (*E*)-11-iodo-undec-10-enoic acid (**98**) (3.30 g, 99%) as a white solid (mp = 64 °C).[183]

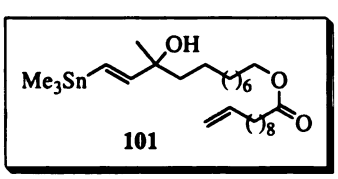


99

Preparation of 11-Iodo-undec-10-enoic acid 10-hydroxy-10-methyl-dodec-11-ynyl ester (99) (Scheme 30). To 100 ml of CH_2Cl_2 was added (*E*)-11-iodo-undec-10-enoic acid (**98**) (3.30 g, 10.62 mmol), 10-methyl-dodec-11-yne-1,10-diol (**94**) (2.71 g, 12.75 mmol), DCC (12.75 mL, 12.75 mmol; 1M solution in CH_2Cl_2) and DMAP (0.2595 g, 2.12 mmol). The reaction was stirred at room temperature until complete by TLC (4 h). The reaction was then filtered (paper) and the filtrate was concentrated. The resulting residue was purified by column chromatography [silica gel; 90:10 to 80:20 hexane/EtOAc] to afford 11-Iodo-undec-10-enoic acid 10-hydroxy-10-methyl-dodec-11-ynyl ester (**99**) (4.47 g, 85%) of a clear liquid with a yellowish tint. IR (neat) 3398 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20-1.40 (m, 22 H), 1.46 (s, 3 H), 1.53-1.66 (m, 6 H), 2.01 (qd, J = 1.5, 7.3 Hz, 1 H), 2.19 (br s, 1 H), 2.26 (t, J = 6.6 Hz, 2 H), 2.40 (s, 1 H), 4.02 (t, J = 6.6 Hz, 2 H), 5.94 (d, J = 14.4 Hz, 1 H), 6.47 (dt, J = 7.1, 14.4 Hz, 1 H); ^{13}C (125 MHz, $CDCl_3$) δ 24.4, 24.9, 25.8, 28.2, 28.5, 28.7, 28.9, 29.0, 29.05, 29.10, 29.31, 29.53, 29.64, 34.22, 35.93, 43.99,

64.27, 67.90, 71.02, 71.03, 74.17, 87.79, 146.59, 173.84; HRMS (EI) *m/z* 522.2450 [(M+NH_4), calcd. for $C_{24}H_{45}INO_3$ 522.2444].

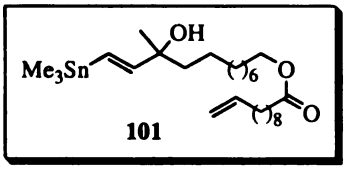
Initial attempt of a one-pot hydrostannation /intramolecular Stille coupling using 6 mol% Me_3SnCl (Scheme 31). To a solution of Pd_2dba_3 (9.2 mg, 0.01 mmol) in Et_2O was added tri-2-furylphosphine (9.3 mg, 0.04 mmol). This mixture was stirred for 15 minutes. Me_3SnCl (0.06 mL, 0.06 mmol), KF (0.1743 g, 3.0 mmol), H_2O (1 mL), PMHS (0.09 mL, 1.5 mmol) and $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) were all added. The solution was brought to reflux and a solution of 11-iodo-undec-10-enoic acid 10-hydroxy-10-methyl-dodec-11-ynyl ester (**99**) (0.5045 g, 1.0 mmol) in Et_2O (4 mL) was added dropwise via a syringe pump (0.24 mL/hr). When the addition was complete TLC show only starting material. The reaction was then separated and the organics were dried over $MgSO_4$, filtered, and concentrated. The starting material was recovered by column chromatography [silica gel; 90:10 to 80:20 hexane/EtOAc] along with a trace amount of reduced vinyl iodide (**100**) (^{1}H NMR analysis).



101

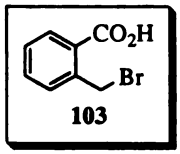
Hydrostannation attempt of 11-Iodo-undec-10-enoic acid 10-hydroxy-10-methyl-dodec-11-ynyl ester (99) using our KF/PMHS protocol with Me_3SnCl (Scheme 31). To 10 ml of THF was added 11-iodo-undec-10-enoic acid 10-hydroxy-10-methyl-dodec-11-ynyl ester (**99**) (261 mg, 0.50 mmol) Me_3SnCl (0.60 mL, 0.60 mmol), KF (0.0872 g, 1.5 mmol), H_2O (1 mL), PMHS (0.06 mL, 1.0 mmol) and $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol) and TBAF (1 drop of a 1M solution in THF). This mixture was stirred until complete by TLC analysis (40 min). The reaction was worked up in the usual manner and the resulting residue was purified by column chromatography [silica gel; 90:10

hexane/EtOAc, 1% NEt_3] to afford undec-10-enoic acid 10-hydroxy-10-methyl-12-trimethylstannanyl-dodec-11-enyl ester (**101**) (160 mg, 65%) as an oil. IR (neat) 3458, 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 9 H), 1.16-1.36 (m, 22 H), 1.40-1.64 (m, 9 H), 1.99 (q, *J* = 8.1 Hz, 2 H), 2.24 (t, *J* = 7.4 Hz, 2 H), 4.01 (t, *J* = 6.7 Hz, 2 H), 4.85-5.00 (m, 2 H), 5.68-5.84 (m, 1 H), 5.98 (d, *J* = 19.2 Hz, 1 H), 6.11 (d, *J* = 19.2, Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –9.7, 23.8, 24.9, 25.9, 27.5, 28.6, 28.8, 28.9, 29.0, 29.1, 29.2, 29.3, 29.4, 29.5, 30.0, 33.7, 34.3, 42.1, 64.3, 74.4, 114.1, 124.0, 139.1, 154.3, 173.9; HRMS *m/z* 529.2706, $[(M-Me)^+$, calcd. for $C_{26}H_{49}O_3Sn$ 529.2704].



101

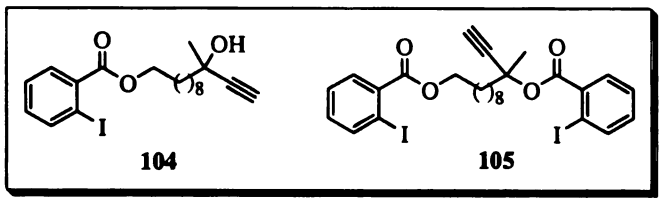
Procedure for the synthesis of undec-10-enoic acid 10-hydroxy-10-methyl-12-trimethylstannanyl-dodec-11-enyl ester (101) for structure confirmation. 10-Methyl-12-trimethylstannanyl-dodec-11-ene-1,10-diol (**107**) (1.03 g, 2.73 mmol; for preparation see below) and undecylenic acid (0.51 mL, 2.5 mmol) were placed in a flask containing CH_2Cl_2 (30 mL). DCC (2.73 mL of a 1M solution in CH_2Cl_2, 2.73 mmol) was added followed by DMAP (61 mg, 0.50 mmol). The reaction was then allowed to stir at 25 °C until complete by TLC analysis. Once complete (8 h), the reaction was filtered through Celite and the filtrate was concentrated. The resulting residue was purified by column chromatography [silica gel; 90:10 hexane/EtOAc, 1% NEt_3] to afford undec-10-enoic acid 10-hydroxy-10-methyl-12-trimethylstannanyl-dodec-11-enyl ester (**101**) (870 mg, 64%). For spectroscopic data see page 183-184.



103

Preparation of 2-bromomethyl-benzoic acid (103) (Scheme 32). *o*-Toluic acid (**102**) (13.62 g, 100 mmol) was added to 80 mL of CCl_4 in a 500 ml RB flask equipped with a condenser and dropping funnel. A lamp

was placed about 2 cm in front and the solution was gently refluxed while Br_2 (5.12 mL, 100 mmol) in 80 mL of CCl_4 was added at such a rate that a red color persisted at all times. The reaction was complete when all the Br_2 was added and the red color disappeared (~30 min). The mixture was allowed to cool to room temperature. The precipitate was collected by filtration and was washed with petroleum ether. The filtrate was then diluted with petroleum ether until turbid. This turbid solution was placed in the freezer over night. Drying the precipitate under vacuum afford 2-bromomethyl-benzoic acid (**103**) (18.12 g, 84%) as a white solid (mp = 149-150 °C).[184]

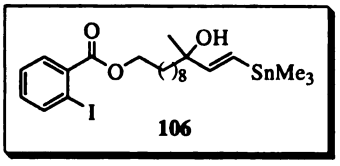


Procedure for the DCC coupling. Preparation of 2-iodo-benzoic acid 10-hydroxy-10-methyl-dodec-11-ynyl ester (104) (Scheme 33). To 285 mL of CH_2Cl_2 was added 2-iodobenzoic acid (7.44 g, 30 mmol), 10-methyl-dodec-11-yne-1,10-diol (**94**) (5.31 g, 25 mmol), DCC (30 mL of 1M solution in CH_2Cl_2, 30 mmol) and then DMAP (0.61 g, 5 mmol). This mixture was stirred for 8 h at room temperature. The reaction was then filtered through a bed a celite and then the celite cake was washed with CH_2Cl_2 (3X). The filtrate was concentrated and purified by column chromatography [silica gel; 85:15 hexane/EtOAc] to afford 2-iodo-benzoic acid 10-hydroxy-10-methyl-dodec-11-ynyl ester (**104**) (5.37 g, 49%) as an oil and diester adduct (**105**) (2.84 g, 17%) as an oil.

Date for the mono ester (**104**): IR (neat) 3443, 3302, 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15-1.56 (m, 15 H), 1.60-1.72 (m, 2 H), 1.73-1.86 (m, 2 H), 2.08 (br s, 1 H), 2.44 (s, 1 H), 4.34 (t, J = 6.5 Hz, 2 H), 7.15 (td, J = 1.7, 8.0 Hz, 1 H), 7.41 (td, J = 1.3, 8.5 Hz, 1 H), 7.79 (dd, J = 1.2, 7.4 Hz, 1 H), 7.99 (d, J = 8.0 Hz, 1 H); ^{13}C (75 MHz,

$CDCl_3$) δ 24.5, 25.9, 28.5, 29.1, 29.3, 29.4, 29.6, 29.7, 43.4, 65.8, 67.9, 71.2, 87.7, 93.9, 127.8, 130.8, 132.4, 135.4, 141.1, 166.6; HRMS (EI) *m/z* 442.1010 [(M^+), calcd. for $C_{20}H_{27}IO_3$ 442.1005].

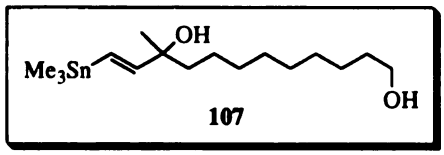
Data for diester (**105**): IR (neat) 3300, 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18-1.66 (m, 12 H), 1.70-1.89 (m, 5 H), 1.90-2.20 (m, 2 H), 2.65 (s, 1 H), 4.34 (t, J = 6.5 Hz, 2 H), 7.08-7.20 (m, 2 H), 7.35–7.45 (m, 2 H), 7.72-7.83 (m, 2 H), 7.94-8.03 (m, 2 H); ^{13}C (75 MHz, $CDCl_3$) δ 24.1, 26.0, 26.4, 28.5, 29.1, 29.3, 29.4, 41.3, 65.8, 73.9, 76.7, 83.5, 93.7, 93.9, 127.8, 127.8, 130.7, 130.8, 132.3, 132.4, 135.4, 135.8, 141.1, 141.2, 164.8, 166.6; HRMS (EI) *m/z* 672.0224 [(M^+), calcd. for $C_{27}H_{30}I_2O_4$ 672.0234].



106

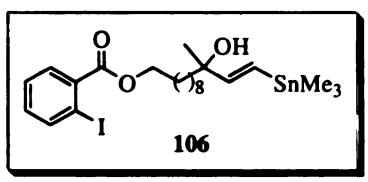
Procedure for the KF/PMHS hydrostannation of an alkyne in the presence of an aryl iodide. Preparation of 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-trimethyl stannanyl-dodec-11-enyl ester (106) (Scheme 34). To 10 mL of THF were added Me_3SnCl (1.2 mL of a 1M THF solution, 1.2 mmol), KF (175 mg, 3.0 mmol), 1 mL of water, PMHS (0.08 mL, 1.2 mmol), $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) and 2-iodo-benzoic acid 10-hydroxy-10-methyl-dodec-11-ynyl ester (**104**) (442 mg, 1.0 mmol). This mixture was stirred at room temperature for 2 h. The mixture was then washed with water and separated. The combined organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 90:10 hexane/EtOAc, 1% TEA] to afford 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-trimethylstannanyl-dodec-11-enyl ester (**106**) (500 mg, 82%) as an oil. IR (neat) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.14 (m, 9 H), 1.20-1.60 (m, 18 H), 1.79 (m, 2 H), 4.34 (t, J = 6.7 Hz, 2 H), 6.03 (d, J = 19.3 Hz, 1 H), 6.17 (d, J = 19.0 Hz, 1 H), 7.15 (tt, J = 1.7, 7.9, 1

H), 7.41 (tt, J = 1.2, 7.6, 1 H), 7.79 (dt, J = 1.4, 7.8, 1 H), 7.99 (dt, J = 1.2, 7.9, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -9.6, 23.8, 25.9, 27.6, 28.5, 29.2, 29.4, 29.4, 29.9, 42.2, 65.8, 74.4, 93.9, 124.1, 127.8, 130.8, 132.4, 135.5, 141.2, 154.2, 166.6; HRMS (EI) *m/z* 593.0563[(M^+-CH_3), calcd. for $C_{23}H_{37}IO_3Sn$] 593.0579.



107

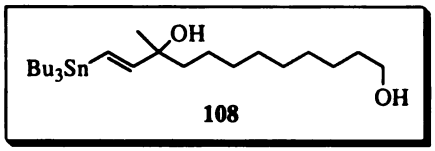
Procedure for the KF/PMHS hydrostannation of an alkyne. Preparation of 10-methyl-12-trimethylstannanyl-dodec-11-ene-1,10-diol (107) (Scheme 34). Apply the above conditions to 10-methyl-dodec-11-yne-1,10-diol (**94**) (2.06 g, 9.7 mmol) afforded after column chromatography [silica gel; 50:50 hexane/EtOAc, 1% TEA] 10-methyl-12-trimethylstannanyl-dodec-11-ene-1,10-diol (**107**) (3.13 g, 86%) as a thick waxy oil. IR (neat) 3304 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 9 H), 1.20-1.40 (m, 17 H), 1.43-1.61 (m, 2 H), 1.64 (br s, 2 H), 3.63 (t, J = 6.5 Hz, 2 H), 6.02 (d, J = 19.3 Hz, 1 H), 6.15 (d, J = 19.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -9.5, 23.8, 25.7, 27.5, 29.3, 29.4, 29.5, 30.0, 32.7, 42.2, 63.0, 74.4, 124.1, 154.2 HRMS (EI) *m/z* 363.1344 [$(M\text{-}Me)^+$, calcd. for $C_{15}H_{31}O_2Sn$ 363.1346].



106

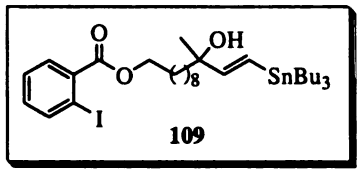
Procedure for a DCC mediated coupling. Preparation of 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-trimethylstannanyl-dodec-11-enyl ester (106) (Scheme 34). 2-Iodobenzoic acid (1.56 g, 6.31 mmol), 10-methyl-12-trimethylstannanyl-dodec-11-ene-1,10-diol (**107**) (2.50 g, 6.63 mmol), DCC (6.63 mL of a 1 M solution in CH_2Cl_2, 6.63 mmol), 4-methylaminiopyridine (154 mg, 1.26 mmol) were added to dry CH_2Cl_2 (65 mL) at room temperature. The mixture was allowed to stir until complete by TLC (5 h). Once complete the reaction was filtered through a plug of celite and the filtrate was

concentrated. The resulting residue was purified by column chromatography [silica gel; 90:10 hexane/EtOAc] to afford 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-trimethylstannanyl-dodec-11-enyl ester (**106**) (2.46 g, 64%) as an oil. For spectroscopic data see page 186-187.



108

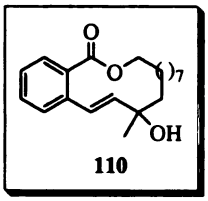
Procedure for the preparation of 10-methyl-12-tributylstannanyl-dodec-11-ene-1,10-diol (108) (Scheme 34). $PdCl_2(PPh_3)_2$ (174 mg, 0.19 mmol) was added to a flask containing THF (150 mL). 10-methyl-dodec-11-yne-1,10-diol (**94**) (4.0 g, 18.84 mmol), Bu_3SnCl (6.10 mL, 22.61 mmol), KF (3.28 g, 56.52 mmol), H_2O (10 mL) and PMHS (2.54 mL, 28.26 mmol) were added successively. This mixture was stirred at room temperature for 2 h. The reaction was then diluted with Ether and washed with brine. The aqueous phase was extracted with Ether. The combined organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 75:25 hexane/EtOAc, 1% TEA] to afford 10-methyl-12-tributylstannanyl-dodec-11(*E*)-ene-1,10-diol (**108**) (8.64 g, 91%) as an oil. IR (neat) 3447 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.80-0.95 (m, 15 H), 1.20 –1.40 (m, 23 H), 1.43-1.60 (m, 10 H), 3.62 (q, J = 6.7 Hz, 2 H), 6.00 (d, J = 19.2 Hz, 1 H), 6.06 (d, J = 19.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.5, 13.7, 23.9, 25.7, 27.2, 27.8, 29.1, 29.4, 29.5, 30.0, 32.8, 42.3, 63.0, 74.6, 123.0, 154.8; HRMS (EI) *m/z* 504.2991 [(M^+), calcd. for $C_{25}H_{52}O_2Sn$ 504.2989].



109

Procedure for the preparation of 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-tributylstannanyl-dodec-11-enyl ester (109) (Scheme 34). 2-Iodobenzoic acid (714 mg, 2.88 mmol), 10-methyl-12-tributylstannanyl-dodec-11(*E*)-ene-1,10-diol (**108**) (1.52 g, 3.02

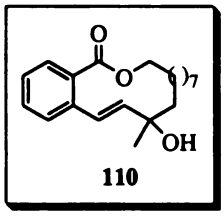
mmol), DCC (3.02 mL of a 1M THF solution, 3.02 mmol) and DMAP (73 mg, 0.60 mmol) were dissolved in CH_2Cl_2 (33 mL). This mixture was stirred at 25 °C for 5 h. Once the reaction was complete it was filtered through a plug of celite and the plug washed with CH_2Cl_2. The filtrate was concentrated and the resulting residue was purified by column chromatography [silica gel; 95:5 hexane/EtOAc, 1% TEA] to afford 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-tributylstannanyl-dodec-11-enyl ester (**109**) (1.32 g, 65%) as a clear oil. IR (neat) 3447 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 9 H), 1.20–1.62 (m, 36 H), 1.77 (m, 2 H), 4.33 (t, J = 6.7 Hz, 2 H), 6.05 (m, 2 H), 7.13 (td, J = 1.8, 7.8 Hz, 1 H), 7.39 (td, J = 1.1, 7.6 Hz, 1 H), 7.78 (dd, J = 1.6, 7.7 Hz, 1 H), 7.98 (dd, J = 1.1, 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 13.7, 23.9, 25.9, 27.2, 27.8, 28.5, 29.0, 29.2, 29.4, 29.5, 29.9, 42.2, 65.7, 74.6, 93.9, 122.9, 127.8, 130.7, 132.4, 135.4, 141.1, 154.7, 166.5; HRMS (EI) *m/z* 677.1502 [(M^+), calcd. for $C_{32}H_{55}IO_3Sn$ 677.1519].



110

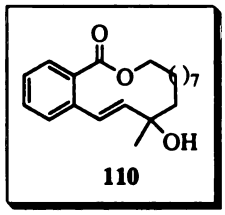
General procedure for the intramolecular Stille coupling control. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (110) (Scheme 35, entry 1). To 100 mL of degassed (Ar) NMP (0.005 M) was added Pd_2dba_3 (14 mg, 0.015 mmol) and $AsPh_3$ (19 mg, 0.06 mmol). This mixture was stirred for 10 min while Ar was bubbled through the solution. 2-Iodo-benzoic acid 10-hydroxy-10-methyl-12-tributylstannanyl-dodec-11-enyl ester (**109**) (354 mg, 0.5 mmol) was added in one portion. The mixture was then heated at ~60 °C for 22 h. The reaction was then cooled to room temperature and diluted with Et_2O. After washing with water and separation, the aqueous phase was extracted with Et_2O (3x). The combined organics were dried

($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 80:20 hexane/EtOAc] to afford 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (90 mg, 60 %) as an oil. IR (neat) 3487 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21-1.51 (m, 15 H), 1.65-1.91 (m, 5 H), 4.47 (t, J = 4.9 Hz, 2 H), 6.12 (d, J = 16.2 Hz, 1 H), 7.23-7.37 (m, 2 H), 7.45 (t, J = 8.8 Hz, 1 H), 7.56 (d, J = 7.7 Hz, 1 H), 7.78 (d, J = 8.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 24.3, 26.4, 26.8, 26.9, 27.7, 28.4, 29.1, 41.6, 63.8, 73.7, 126.1, 126.9, 129.8, 129.9, 131.5, 137.9, 139.4, 168.2; HRMS (EI) *m/z* 316.2038 [(M+), calcd. for $C_{20}H_{28}O_3$ 316.2038].



110

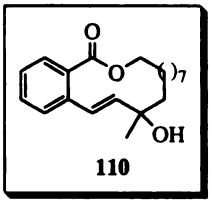
Intramolecular Stille coupling control. Use of tributylstannane with $AsPh_3$ and THF. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (110) (Scheme 35, entry 2). Applying the above conditions using 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-tributylstannanyl-dodec-11-enyl ester (**109**) (354 mg, 0.5 mmol) and $AsPh_3$ (19 mg, .06 mmol) in THF (0.005 M) at 70 °C for 28 h after column chromatography [silica gel; 80:20 hexane/EtOAc] to afford 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (79 mg, 52 %) as an oil. For spectroscopic data see page 189-190.



110

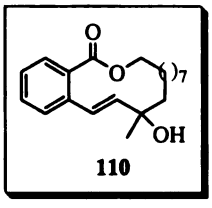
Intramolecular Stille coupling control. Use of tributylstannane with TFP and NMP. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (110) (Scheme 35, entry 3). Applying the above conditions using 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-tributylstannanyl-dodec-11-enyl

ester (**109**) (354 mg, 0.48 mmol) and TFP (14 mg, 0.06 mmol) in NMP (0.005 M) at 60 °C for 24 h after column chromatography [silica gel; 80:20 hexane/EtOAc] to afford 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (92 mg, 61 %) as an oil. For spectroscopic data see page 189-190.



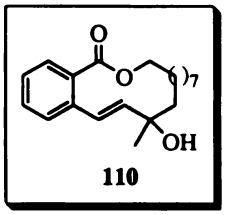
110

Intramolecular Stille coupling control. Use of tributylstannane with TFP and THF. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (110) (Scheme 35, entry 4). Applying the above conditions using 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-tributylstannanyl-dodec-11-enyl ester (**109**) (367 mg, 0.5 mmol) and TFP (14 mg, 0.06 mmol) in THF (0.005 M) at 70 °C for 27 h after column chromatography [silica gel; 80:20 Hexane/EtOAc] to afford 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (99 mg, 63 %) as an oil. For spectroscopic data see page 189-190.



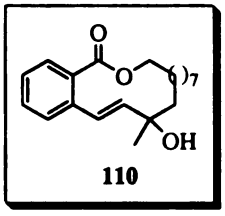
110

Intramolecular Stille coupling control. Use of trimethylstannane with $AsPh_3$ and NMP. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (110) (Scheme 35, entry 5). Applying the above conditions using 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-trimethylstannanyl-dodec-11-enyl ester (**106**) (304 mg, 0.5 mmol) and $AsPh_3$ (19 mg, 0.06 mmol) in NMP (0.005 M) at 60 °C for 14 h after column chromatography [silica gel; 80:20 hexane/EtOAc] to afford 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (114 mg, 72 %) as an oil. For spectroscopic data see page 189-190.



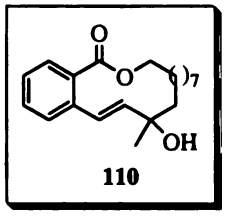
110

Intramolecular Stille coupling control. Use of trimethylstannane with $AsPh_3$ and THF. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (110) (Scheme 35, entry 6). Applying the above conditions using 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-trimethylstannanyl-dodec-11-enyl ester (**106**) (304 mg, 0.5 mmol) and $AsPh_3$ (19 mg, 0.06 mmol) in THF (0.005 M) at 70 °C for 15 h after column chromatography [silica gel; 80:20 hexane/EtOAc] to afford 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (100 mg, 63 %) as an oil. For spectroscopic data see page 189-190.



110

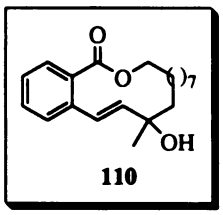
Intramolecular Stille coupling control. Use of trimethylstannane with TFP and NMP. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (110) (Scheme 35, entry 7). Applying the above conditions using 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-trimethylstannanyl-dodec-11-enyl ester (**106**) (304 mg, 0.5 mmol) and TFP (14 mg, 0.06 mmol) in NMP (0.005 M) at 60 °C for 10 h after column chromatography [silica gel; 80:20 hexane/EtOAc] to afford 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (117 mg, 74 %) as an oil. For spectroscopic data see page 189-190.



110

Intramolecular Stille coupling control. Use of trimethylstannane with TFP and THF. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (110) (Scheme 35, entry 8). Applying the above conditions using 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-trimethylstannanyl-dodec-11-enyl ester (**106**) (304 mg,

0.5 mmol) and TFP (14 mg, 0.06 mmol) in THF (0.005 M) at 70 °C for 12 h after column chromatography [silica gel; 80:20 hexane/EtOAc] to afford 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (115 mg, 73 %) as an oil. For spectroscopic data see page 189-190.

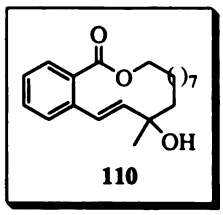


110

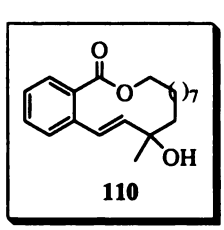
Intramolecular Stille coupling control. Use of trimethylstannane with Pd_2dba_3/TBADP and DMF. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (110) (Scheme 35, entry 9). A solution of 2-iodo-benzoic acid 10-hydroxy-10-methyl-12-tributylstannanyl-dodec-11-enyl ester (**109**) (30.4 mg, 0.05 mmol) DIPEA (0.09 mL, .50 mmol) and TBADP (34.5 mg, 0.075 mmol) in dry DMF (70 mL) was degassed with Ar for ~10 min. Pd_2dba_3 (4.6 mg, 0.005 mmol) was added and the mixture was degassed 10 min further. The flask was wrapped in foil and stirred at 25 °C until complete by TLC; 1.5 h. Once complete the reaction was diluted with Et_2O, washed with water, brine, dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 80:20 hexane/ EtOAc] to afford 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (14.4 mg, 91 %) as an oil. For spectroscopic data see page 189-190.

Procedure for the preparation of tetrabutylammonium diphenylphosphinate (TBADP). A 100 mL round bottom flask was charged with MeOH (22 mL) and diphenylphosphinic acid (4.36 g, 20 mmol) was added. Bu_4NOH (20 mL of 1 M solution in MeOH, 20 mmol) was added and the mixture was shaken for 5 min. The resulting cloudy solution was filtered through celite and the filtrate was concentrated under vacuum leaving a yellow oil. This oil was then placed under high vacuum overnight and

the resulting solid was purified by recrystallization from Et_2O/Hexane to afford TBADP (8.0 g, 86%) of a white solid. This solid must be kept under Ar due to its hygroscopic nature.[86]

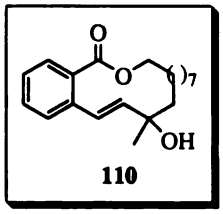

110

Representative procedure for a one-pot hydrostannation/intramolecular Stille. Use of the "Sn-F" route with everything added at once under high dilution. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclo-hexadecen-5-one (110) (Scheme 36, reaction 1). Pd_2dba_3 (27 mg, 0.03 mmol) and TFP (28 mg, .12 mmol) were added to degassed THF (200 mL). At this time Me_3SnCl (0.05 mL of a 1 M solution in THF, 0.05 mmol), KF (87 mg, 1.5 mmol), water (1 mL), PMHS (0.09 mL, 1.5 mmol) and 2-iodo-benzoic acid 10-hydroxy-10-methyl-dodec-11-ynyl ester (**104**) (431 mg, 1.0 mmol) were all added. This mixture was stirred for 14 h at 70 °C. The reaction was then diluted with Et_2O and washed with water. After separation of the phases, the aqueous phase was extracted with Et_2O. The combined organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 80:20 hexane/EtOAc] to afford 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (70 mg, 22%) as an oil. For spectroscopic data see page 189-190.


110

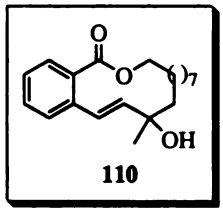
Representative procedure for a one-pot hydrostannation/intramolecular Stille. Use of syringe pump addition. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (110) (Scheme 36, reaction 2). Applying the conditions noted above except that 2-iodo-benzoic acid 10-hydroxy-10-methyl-dodec-11-ynyl ester (**104**) (431 mg, 1.0 mmol) was added via syringe pump over 8 h at 70 °C. After column chromatography [silica gel; 80:20 hexane/EtOAc] 16-hydroxy-16-methyl-

7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (93 mg, 29%) was obtained as an oil. For spectroscopic data see page 189-190.



110

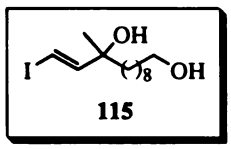
Representative procedure for a one-pot hydrostannation/intramolecular Stille. Use of the "Sn-F" route in conjunction with the "Sn-O" route with everything added at once under high dilution. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (110) (Scheme 36, reaction 3). Pd_2dba_3 (27 mg, 0.03 mmol) and TFP (28 mg, .12 mmol) were added to degassed THF (200 mL). At this time Me_3SnF (9.1 mg, 0.05 mmol), Na_2CO_3 (159 mg, 1.5 mmol), water (1 mL), PMHS (0.09 mL, 1.5 mmol) and 2-iodo-benzoic acid 10-hydroxy-10-methyl-dodec-11-ynyl ester (**104**) (431 mg, 1.0 mmol) were all added. This mixture was stirred for 12 h at 70 °C. The reaction was then diluted with Et_2O and washed with water. After separation of the phases, the aqueous phase was extracted with Et_2O. The combined organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 80:20 Hexane/EtOAc] to afford 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (130 mg, 41%) as an oil. For spectroscopic data see page 189-190.



110

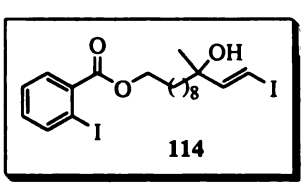
Representative procedure for a one-pot hydrostannation/intramolecular Stille. Use of the "Sn-F" route in conjunction with the "Sn-O" route with syringe pump addition. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexa decen-5-one (110) (Scheme 36, reaction 4). Applying the conditions noted above except that 2-iodo-benzoic acid 10-hydroxy-10-methyl-dodec-11-ynyl ester (**104**) (431

mg, 1.0 mmol) was added via syringe pump over 8 h at 70 °C. After column chromatography [silica gel; 80:20 hexane/EtOAc] 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (150 mg, 47%) was obtained as an oil. For spectroscopic data see page 189-190.



115

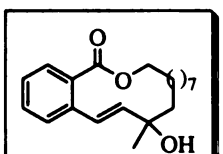
Procedure for the tin-iodine exchange. Preparation of 12-Iodo-10-methyl-dodec-11-ene-1,10-diol (115). 10-Methyl-12-tributylstannanyl-dodec-11-ene-1,10-diol (**108**) (4.15 g, 8.24 mmol) was dissolved in CH_2Cl_2 (50 mL). I_2 (2.20 g, 8.65 mmol) was dissolved in CH_2Cl_2 (25 mL). This solution was added until a pink color persisted. The reaction was then washed with $Na_2S_2O_3$. The organics were dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 70:30 hexane/EtOAc] to afford 12-iodo-10-methyl-dodec-11-ene-1,10-diol (**115**) (2.78 g, 98%) as an oil. IR (neat) 3354 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 –1.37 (m, 13 H), 1.41-1.63 (m, 6 H), 1.81 (br s, 2 H), 3.61 (t, J = 6.7 Hz, 2 H), 6.27 (d, J = 14.4 Hz, 1 H), 6.57 (d, J = 14.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 25.6, 27.5, 29.3, 29.4, 29.4, 29.8, 32.7, 42.2, 62.9, 74.7, 76.1, 152.4; HRMS (EI) *m/z* 340.0891 [(M^+), calcd. for $C_{13}H_{25}I0_2$ 340.0899].



114

Procedure for the DCC coupling. Preparation of 2-iodo-benzoic acid 10-hydroxy-12-iodo-10-methyl-dodec-11-enyl ester (114) (Scheme 37, reaction 1). 2-Iodobenzoic acid (1.56 g, 6.30 mmol), 12-iodo-10-methyl-dodec-11-ene-1,10-diol (**115**) (2.25 g, 6.61 mmol), DCC (6.61 mL of a 1M THF solution, 6.61 mmol) and DMAP (154 mg, 1.26 mmol) were dissolved in CH_2Cl_2 (75 mL). This mixture was stirred at 25 °C for 5 h. Once the reaction was complete it was filtered through a plug of celite and the plug washed with

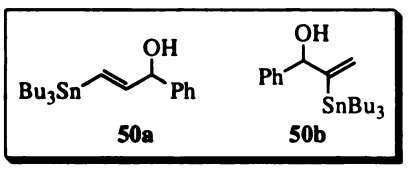
CH_2Cl_2. The filtrate was concentrated and the resulting residue was purified by column chromatography [silica gel; 80:20 hexane/EtOAc] to afford 2-iodo-benzoic acid 10-hydroxy-12-iodo-10-methyl-dodec-11-enyl ester (**114**) (3.08 g, 86%) as a clear oil. IR (neat) 3547 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 –1.58 (m, 17 H), 1.66-1.89 (m, 3 H), 4.33 (t, *J* = 6.7 Hz, 2 H), 6.30 (d, *J* = 14.4 Hz, 1 H), 6.59 (d, *J* = 14.4 Hz, 1 H), 7.15 (td, *J* = 1.8, 7.7 Hz, 1 H), 7.40 (td, *J* = 1.1, 7.6 Hz, 1 H), 7.78 (dd, *J* = 1.6, 7.8 Hz, 1 H), 7.99 (dd, *J* = 1.1, 7.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 25.9, 27.5, 28.5, 29.1, 29.3, 29.4, 29.8, 32.1, 65.8, 74.8, 76.1, 93.9, 127.8, 130.7, 132.4, 135.4, 141.1, 152.3, 166.6; HRMS (EI) *m/z* 570.0128 [(M^+), calcd. for $C_{20}H_{28}I_2O_3$ 570.0114].



110

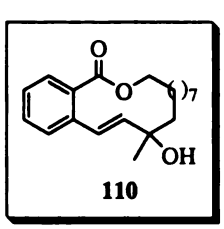
Intramolecular stannation/Stille coupling. Use of Pd_2dba_3/TBADP and DMF. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclo-hexadecen-5-one (110) (Scheme 37, reaction 2). A solution of 2-iodo-benzoic acid 10-hydroxy-12-iodo-10-methyl-dodec-11-enyl ester (**114**) (570 mg, 1.0 mmol) Me_3SnCl (0.05 mL of a 1M solution in THF, 0.05 mmol) PMHS (0.09 mL, 1.5 mmol) and TBADP (70 mg, 1.5 mmol) in dry DMF (70 mL; 0.0007 M with respect to Me_3SnCl) was degassed with Ar for ~10 min. Pd_2dba_3 (92 mg, 0.10 mmol) was added and the mixture was degassed 10 min further. The flask was wrapped in foil and stirred at 25 °C until complete by TLC; 3.0 h. Once complete the reaction was diluted with Et_2O, washed with water, brine, dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 80:20 hexane/EtOAc] to afford 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (47 mg,

15 %) as an oil along with starting material (50%). For spectroscopic data see page 189-190



50a 50b

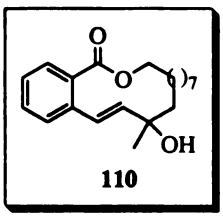
Procedure for the hydrostannation using TBADP/PMHS/Bu_3SnCl combination. Preparation of 1-phenyl-3-tributylstannanyl-prop-2(*E*)-en-1-ol (50a) and 1-Phenyl-2-tributylstannanyl-prop-2-en-1-ol (50b) (Scheme 38). TBADP (900.8 mg, 1.96 mmol) and Bu_3SnCl (0.53 mL, 1.96 mmol) were added to THF (10mL). After 5 min. at room temperature, PMHS (0.15 mL, 2.5 mmol), 1-phenyl-prop-2-yn-1-ol (**28**) (0.20 mL, 1.63 mmol) amd $PdCl_2(PPh_3)_2$ (11.4 mg, 0.0163 mmol) were all added sequentially. The reaction was complete by TLC (90:10 hexane/EtOAc) after stirring for 2 h at room temperature. The reaction was then concentrated and directly subjected to column chromatography [silica; 90:10 hexane/EtOAc, 1% TEA] to afford a 10:1 *E*:int mixture of 1-phenyl-3-tributylstannanyl-prop-2(*E*)-en-1-ol (**50a**) and 1-Phenyl-2-tributylstannanyl-prop-2-en-1-ol (**50b**) (430 mg, 63%) as an oil. For spectroscopic data see page 148-149.



110

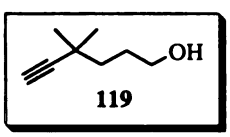
Procedure for the intramolecular tin dimer cyclization with stoichiometric amounts of Me_3Sn-$SnMe_3$. Preparation of 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (110) (Scheme 39, entry 1). A solution of 2-iodo-benzoic acid 10-hydroxy-12-iodo-10-methyl-dodec-11-enyl ester (**114**) (0.2851 g, 0.5 mmol) in NMP (50 mL) was degassed with Ar for ~30 min. The solution was then treated with Pd_2dba_3 (23 mg, 0.025 mmol) and degassed another 5 min. with Ar. Tetratbutylammonium diphenylphosphinate (TBADP) (0.3447 g, 0.75 mmol) was added

followed by the addition of hexamethylditin (0.065 mL, 0.30 mmol). This mixture was allowed to stir at 25 °C until complete (~4h). The reaction was then diluted with water and extracted with ether (3x). The organics were then dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford 16-hydroxy-16-methyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxa-benzocyclohexadecen-5-one (**110**) (85 mg, 54%) and 5 mg of an unknown. For spectroscopic data see page 189-190.



110

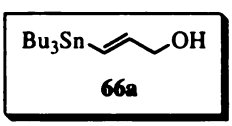
Procedure for the catalytic version of above (Scheme 39, entry 2). The procedure as stated above was followed except for the following: hexamethylditin (0.10 eq) and PMHS (1.5 eq.). After column chromatography [silica; 80:20 hexane/EtOAc], benzoic acid 10-hydroxy-10-methyl-dodec-11-enyl ester (**110**) (10 mg, 9%) and 12 mg of the unknown product from above were obtained. For spectroscopic data see page 189-190.



119

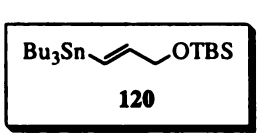
Representative Procedure for the preparation of 4,4-dimethyl-hex-5-yn-1-ol (119) (Scheme 41). Isopropyl acetylene (**118**) (7.51 mL, 73.4 mmol) was added to 50 mL of dry Et_2O in a flame dried 500 mL round bottom flask under N_2 and the solution was cooled to 0 °C. *n*-BuLi (92 mL of 1.6 M solution in hexanes, 147 mmol) was then added dropwise via an addition funnel. When the addition was complete the solution had a clear yellow appearance. Upon addition of N,N,N',N'-tetramethylethylenediamine (11.65 mL, 77.1 mmol) in one portion, the solution turned to a thick white slurry within minutes. This solution was then placed in a 60 °C oil bath and gently refluxed for 15 hours to produce a deep red solution (the dianion). The dianion solution was then allowed to cool to room temperature and then cooled to –78°C.

Oxetane (4.75 mL, 73.4 mmol) was then added followed by addition of $BF_3 \cdot OEt_2$ (9.31 mL, 73.4 mmol) via a syringe pump over 6 hours. The solution was then warmed to room temperature and diluted with 1 M HCl and stirred for 30 minutes. The mixture was then diluted with Et_2O and the phases separated. The aqueous phase was extracted with Et_2O (3x) and the combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by column chromatography [silica gel; 90:10 to 80:20 hexane/EtOAc] to afford 4,4-dimethyl-hex-5-yn-1-ol[185] (**119**) (2.58 g, 35%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 6H), 1.43-1.53 (m, 2H), 1.69-1.83 (m, 3H), 2.11 (s, 1H), 3.70 (t, J = 6.46 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 28.67, 29.10, 30.75, 39.27, 63.16, 67.94, 91.62.



66a

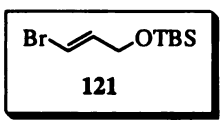
Procedure for the preparation of 3-tributylstannanyl-prop-2-en-1-ol (Scheme 42). To 50 mL of THF was added $PdCl_2(PPh_3)_2$ (0.0702 g, 10 mmol), propargyl alcohol (**65**) (0.582 mL, 10 mmol), Bu_3SnCl (3.25 mL, 12 mmol), KF (1.743 g, 30 mmol; 33 mL H_2O), PMHS (0.9 mL, 15 mmol), and TBAF (2 drops of a 1M solution in THF). This mixture was then stirred for 1 hour. The reaction was then separated and the aqueous phase extracted with Et_2O (2x). The combined organics were then washed with Brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 90:10 hexane/EtOAc, 1% NEt_3] to afford (*E*)-3-tributylstannanyl-prop-2-en-1-ol (**66a**) and 2-tributylstannanyl-prop-2-en-1-ol (**66b**) (3.26 g, 94%) as a light yellow oil. For spectroscopic data see page 160.



120

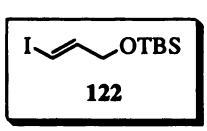
Procedure for the preparation of (*E*)-*tert*-butyl-dimethyl-(3-tributyl stannanyl-allyloxy)-silane (120) (Scheme 42). TBSCl

(1.86 g, 12.32 mmol) was added to a cooled (0 °C) solution of afford (*E*)-3-tributylstannanyl-prop-2-en-1-ol (**66a**) (4.50 g, 13 mmol), imidazole (1.10 g, 15.6 mmol), DMAP (0.16 g, 1.3 mmol) in CH_2Cl_2 (25 mL). The mixture was stirred until complete by TLC (~40 min). When complete the reaction was washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by column chromatography [silica gel; hexane, 1% NEt_3] to afford (*E*)-*tert*-butyl-dimethyl-(3-tributylstannanyl-allyloxy)-silane (**120**) (5.70 g, 95%) as clear liquid.[186]



121

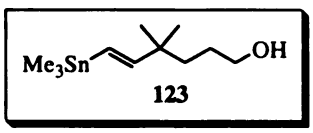
Procedure for the preparation of (3-bromo-allyloxy)-*tert*-butyl-dimethyl-silane (121) (Scheme 42). N-bromosuccinimide (1.83 g, 10.24 mmol) was added to a cold solution of (*E*)-*tert*-butyl-dimethyl-(3-tributylstannanyl-allyloxy)-silane (**120**) (4.50 g, 9.75 mmol) in dry CH_2Cl_2 (50 mL). When the reaction was complete (TLC, 1 hr), the reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ (25 mL). CH_2Cl_2 was added and the aqueous phase extracted with CH_2Cl_2 (3X). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; hexanes] to afford (*E*)-(3-bromo-allyloxy)-*tert*-butyl-dimethyl-silane (**121**) (2.43 g, 99%) as a clear liquid. IR 2957, 2858 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6 H), 0.92 (s, 9 H), 4.14 (m, 2 H), 6.30 (m, 2 H); ^{13}C (75 MHz, $CDCl_3$) δ -5.38, 18.30, 25.81, 63.25, 106.03, 136.70; HRMS (EI) m/z 250.0387 [(M^+), calcd. for $C_9H_{19}BrOSi$ 250.0389].



122

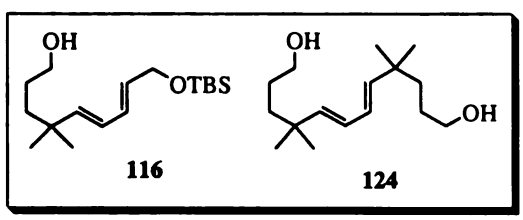
Procedure for the preparation of (3-iodo-allyloxy)-*tert*-butyl-dimethyl-silane (122) (Scheme 42). I_2 (3.45 g, 13.6 mmol) was added to a cold solution of (*E*)-*tert*-butyl-dimethyl-(3-tributylstannanyl-allyloxy)-silane (**120**) (5.7 g, 12.4 mmol) in dry CH_2Cl_2 (20 mL). When the reaction was complete (TLC, 1 hr),

the reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ (25 mL). CH_2Cl_2 was added and the aqueous phase extracted with CH_2Cl_2 (3X). The combined organics were washed with Brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography [silica gel; hexanes] to afford (*E*)-(3-iodo-allyloxy)-*tert*-butyl-dimethyl-silane (**122**) (3.32 g, 90%) as a clear liquid.[187]



123

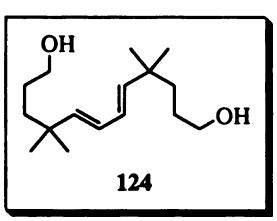
Procedure for the palladium catalyzed hydrostannation of 4,4-dimethyl-hex-5-yn-1-ol. Preparation of 4,4-dimethyl-6-trimethylstannanyl-hex-5-en-1-ol (123) (Scheme 42). To 50 mL of THF was added $PdCl_2(PPh_3)_2$ (0.029 g, 0.041 mmol), 4,4-dimethyl-hex-5-yn-1-ol (**119**) (0.5213 g, 4.13 mmol), Me_3SnCl (5 mL of a 1M solution in THF, 4.96 mmol), KF (.7199 g, 12.4 mmol; 3 mL H_2O), PMHS (0.37 mL, 6.2 mmol) and TBAF (1 drop of a 1M solution in THF). This mixture was then stirred for 1 hour. The reaction was then separated and the aqueous phase extracted with Et_2O (2x). The combined organics were then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 90:10 hexane/EtOAc, 1% NEt_3] to afford 4,4-dimethyl-6-trimethylstannanyl-hex-5-en-1-ol (**123**) (1.05 g, 88%) as a light yellow oil. IR (neat) 3327 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.11 (m, 9 H), 0.99 (s, 6 H), 1.28-1.36 (m, 2 H), 1.42-1.56 (m, 3 H), 3.61 (m, 2 H), 5.87 (m, 2 H); ^{13}C (75 MHz, $CDCl_3$) δ -9.65, 26.64, 28.04, 38.32, 38.45, 63.66, 122.90, 157.74; HRMS (EI) m/z 277.0613 [(M^+-CH_3), calcd. For $C_{10}H_{21}OSn$ 277.0616].



116 **124**

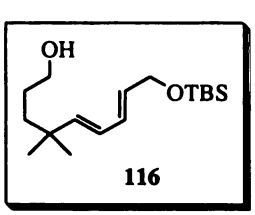
Representative procedure for the traditional Stille coupling with (*E*)-(3-iodo-allyloxy)-*tert*-butyldimethylsilane. Preparation of 9-(*tert*-

butyldimethylsilanyloxy)-4,4-dimethyl-nona-5,7-dien-1-ol (116) (Scheme 43, reaction 1). Pd_2dba_3 (18.3 mg, 0.02 mmol), and $AsPh_3$ (25 mg, 0.08 mmol) were added to 10 mL of NMP. This solution was stirred at room temperature for 15 minutes. At this point (*E*)-(3-iodo-allyloxy)-*tert*-butyldimethylsilane (**122**) (0.3132 g, 1.05 mmol) was added followed by 4,4-dimethyl-6-trimethylstannanyl-hex-5-en-1-ol (**123**) (0.2910 g, 1.0 mmol). This mixture was placed in a 50 °C oil bath for 8 h. When complete the reaction was diluted with Et_2O (25 mL) and then washed with H_2O (3x). The aqueous phase was then extracted with Et_2O and the combined organics were dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by column chromatography [silica gel; 80:20 Hex/EtOAc, 1% Et_3N] to afford of 9-(*tert*-butyldimethylsilanyloxy)-4,4-dimethyl-nona-5,7-dien-1-ol (**116**) (89 mg, 30%) as a clear oil and 4,4,9,9-tetramethyl-dodeca-5,7-diene-1,12-diol (**124**) (51 mg, 20%) and recovered stannane (**123**) (116 mg, 40%).



124

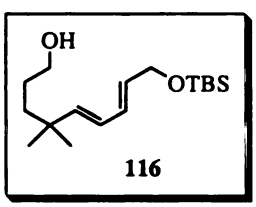
Data for 4,4,9,9-tetramethyl-dodeca-5,7-diene-1,12-diol (**124**): IR (neat) 3432 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (s, 12 H), 1.26-1.54 (m, 10 H), 3.59 (t, J = 6.3 Hz, 4 H), 5.91 (d, J = 14.7 Hz, 2 H), 6.46 (d, J = 14.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 27.9, 38.3, 40.6, 63.3, 72.7, 155.4; HRMS (EI) *m/z* 253.2251 [(M^+), calcd. for $C_{16}H_{30}O_2$ 254.2246].



116

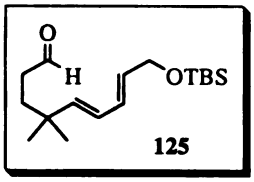
Representative procedure for the traditional Stille coupling with (*E*)-(3-bromo-allyloxy)-*tert*-butyl-dimethyl-silane. Preparation of 9-(*tert*-butyl-dimethylsilanyloxy)-4,4-dimethyl-nona-5,7-dien-1-ol (116) (Scheme 43, reaction 2). Pd_2dba_3 (18.3 mg, 0.02 mmol), and $AsPh_3$ (25 mg, 0.08 mmol) were added to 10 mL of NMP. This solution was stirred at room temperature for 15 minutes. At this point (*E*)-(3-bromo-allyloxy)-*tert*-butyldimethylsilane (**121**)

(0.2628 g, 1.05 mmol) was added followed by 4,4-dimethyl-6-trimethylstannanyl-hex-5-en-1-ol (**123**) (0.2910 g, 1.0 mmol). This mixture was placed in a 50 °C oil bath for 8 h. When complete the reaction was diluted with Et_2O (25 mL) and then washed with H_2O (3x). The aqueous phase was then extracted with Et_2O and the combined organics were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 80:20 hexane/EtOAc] to afford of 9-(*tert*-butyl-dimethylsilanyloxy)-4,4-dimethyl-nona-5,7-dien-1-ol (**116**) (134 mg, 45%) as a clear oil. IR (neat) 3348 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.00 (s, 6 H), 1.30-1.35 (m, 2H), 1.43-1.52 (m, 2 H), 1.55 (br s, 1 H), 3.57 (t, *J* = 6.52 Hz, 2 H), 4.18 (dd, *J* = 1.44, 5.30 Hz, 2 H), 5.59 (d, *J* = 15.02 Hz, 1 H), 5.65 (dt, *J* = 5.30, 15.24 Hz, 1 H), 5.94 (dd, *J* = 10.38, 15.57 Hz, 1 H), 6.17 (dd, *J* = 10.38, 15.24, 1 H); ^{13}C (125 MHz, $CDCl_3$) δ -5.23, 18.38, 25.93, 27.15, 28.07, 35.74, 38.94, 63.52, 63.63, 125.92, 130.32, 130.53, 143.79; HRMS (EI) m/z 298.2331 [(M^+), calcd. for $C_{17}H_{34}O_2Si$ 298.2328].

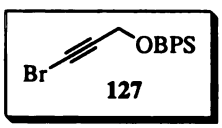


116

Representative procedure for the one pot hydrostannation/Stille coupling with catalytic amounts of tin using Me_3SnCl. Preparation of 9-(*tert*-butyl-dimethyl-silanyloxy)-4,4-dimethyl-nona-5,7-dien-1-ol (116) (Scheme 44). Applying the one KF/PMHS catalytic tin conditions to 4,4-dimethyl-hex-5-yn-1-ol (**119**) (0.1262 g, 1 mmol) and (*E*)-(3-bromo-allyloxy)-*tert*-butyl-dimethyl-silane (**121**) (0.3754 g, 1.5 mmol) afforded after column chromatography [silica gel; 80:20 hexane/EtOAc] afforded 9-(*tert*-butyl-dimethyl-silanyloxy)-4,4-dimethyl-nona-5,7-dien-1-ol (**116**) (105 mg, 72%) as an oil. For spectroscopic data see page 204-205.

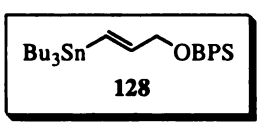


Representative procedure for the preparation of 9-(*tert*-butyl-dimethyl-silanyloxy)-4,4-dimethyl-nona-5,7-dienal (125) (Scheme 44). Bis(diacetoxy)iodobenzene (0.6231 g, 1.936 mmol) was added to a solution of 9-(*tert*-butyl-dimethyl-silanyloxy)-4,4-dimethyl-nona-5,7-dien-1-ol (**116**) (525 mg, 1.76 mmol) and TEMPO (0.0275 g, 0.10 mmol) in CH_2Cl_2 (1.76 mL). The reaction was stirred until the starting material was no longer detectable by TLC (2 hrs). The reaction was then diluted with CH_2Cl_2 (10 mL) and the solution was washed with sat. aq. $Na_2S_2O_3$ (5 mL) and then extracted with CH_2Cl_2. The combined organics were washed with $NaHCO_3$, brine, dried with Na_2SO_4, and concentrated. The resulting residue was purified by column chromatography [silica gel, 95:5 to 90:10 hexane/EtOAc] to afford 9-(*tert*-butyl-dimethyl-silanyloxy)-4,4-dimethyl-nona-5,7-dienal (**125**) (495 mg, 95%) as clear liquid. IR (neat) 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.91 (s, 9 H), 1.02 (s, 6 H), 1.63 (dd, J = 6.32, 8.10 Hz, 2 H), 2.35 (td, J = 1.65, 8.24 Hz, 2 H), 4.19 (dd, J = 1.37, 5.22 Hz, 2 H), 5.53 (d, J = 15.38 Hz, 1 H), 5.69 (dt, J = 5.22, 15.11 Hz, 1 H), 5.96 (dd, J = 10.31, 15.38 Hz, 1 H), 6.18 (dd, J = 10.3, 15.11 Hz, 1 H), 9.75 (t, J = 1.65 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ -5.30, 18.34, 25.87, 26.93, 34.30, 35.51, 39.86, 63.31, 126.80, 129.97, 130.94, 142.26, 202.48; HRMS (EI) m/z 296.2169 [(M^+), calcd. for $C_{17}H_{32}O_2Si$ 296.2172].



Preparation of (3-bromo-prop-2-ynyloxy)-*t*-butyldiphenylsilane (127) (Scheme 45). To a solution of propargyl alcohol (**65**) (1.40 g, 25 mmol) and imidazole (3.74 g, 55 mmol) in DMF (25 mL) was added BPSCl (7.15 mL, 27.5 mmol) dropwise at room temperature and stirred for 5 h. The reaction was then partitioned between sat. aq. NH_4Cl (100 mL) and hexane (100 mL) and the aqueous

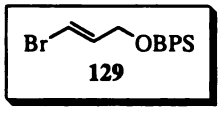
phase extracted with hexane (2x). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 95:5 hexane/EtOAc] to afford *t*-butyl-diphenyl-prop-2-ynyloxy-silane (**126**) (7.36 g, 100%). The silylated propargyl alcohol (**126**) was then dissolved in 75 mL of dry acetone. *N*-Bromosuccinimide (4.90 g, 27.5 mmol) and $AgNO_3$ (375 mg, 2.2 mmol) were added and the reaction was allowed to stir for 8 hours. The reaction was then diluted with ether and washed with H_2O. The aqueous phase was extracted with ether. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was then purified by column chromatography [silica, 95:5 hexane/EtOAc] to afford (3-bromo-prop-2-ynyloxy)-*t*-butyldiphenylsilane (**127**) (7.93 g, 85%) as a yellow oil. IR (neat) 3071, 2221 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 9 H), 4.38 (s, 2 H), 7.40-7.50 (m, 6 H), 7.70-7.80 (m, 4 H); ^{13}C (75 MHz, $CDCl_3$) δ 19.1, 26.7, 44.7, 53.5, 78.3, 127.7, 129.8, 132.8, 135.6; HRMS (EI) m/z 314.9851 [$(M-t\text{-Bu})^+$ calcd for $C_{15}H_{12}BrOSi$ 314.9841].



128

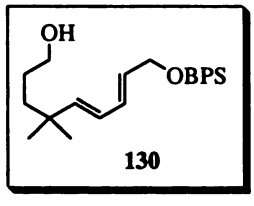
Preparation of *t*-butyl-diphenyl-(3-tributylstannanyl-allyloxy)-silane (128) (Scheme 45). To 100 mL of THF was added (3-bromo-prop-2-ynyloxy)-*t*-butyl-diphenyl-silane (**127**) (7.55 g, 20.2 mmol), Bu_3SnCl (6.60 ml, 24.3 mmol), KF (3.55 g, 61 mmol), H_2O (6 mL), PMHS (1.82 mL, 30.3 mmol), TBAF (1 drop of a 1M solution in THF), and $PdCl_2(PPh_3)_2$. The reaction was stirred at room temperature until complete by TLC (2 hours). Once complete, the reaction was diluted with ether. The phases were separated and the aqueous phase extracted with ether. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel,

hexane, 1% NEt_3] to afford (*E*)-*t*-butyl-diphenyl-(3-tributylstannanyl-allyloxy)-silane (**128**) (8.27 g, 70%) as a clear oil. IR (neat) 2956, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (m, 15 H), 1.12 (s, 9 H), 1.37 (m, 6 H), 1.56 (m, 6 H), 4.30 (dd, *J* = 1.8, 4.2 Hz, 2 H), 6.02-6.43 (m, 2 H), 7.38-7.48 (m, 6 H), 7.71-7.77 (m, 4 H); ^{13}C (125 MHz, $CDCl_3$) δ 9.44, 13.73, 19.30, 26.89, 27.23, 29.09, 67.15, 126.85, 127.54, 129.54, 133.95, 135.56, 146.71; HRMS (EI) m/z 529.1950 [$(M-Bu)^+$, calcd. for $C_{27}H_{41}OSiSn$ 529.1953].



129

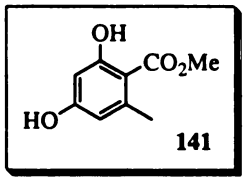
Preparation of (3-bromo-allyloxy)-*t*-butyl-diphenyl-silane (129) (Scheme 45). N-Bromosuccinimide (3.07 g, 17.23 mmol) was added to a cold solution of (*E*)-t-butyl-diphenyl-(3-tributylstannanyl-allyloxy)-silane (**128**) (9.61 g, 16.41 mmol) in dry CH_2Cl_2 (100 mL). Upon completion (TLC, 1 hr), the reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ (25 mL). CH_2Cl_2 was added and the aqueous phase extracted with CH_2Cl_2 (3X). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; hexanes] to afford (*E*)-(3-bromo-allyloxy)-*t*-butyl-diphenyl-silane (**129**) (6.01 g, 97%) as a clear liquid. IR 2959, 2857, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 9 H), 4.17 (m, 2 H), 6.30 (m, 1 H), 6.38 (m, 1 H), 7.44 (m, 6 H), 7.70 (m, 4 H); ^{13}C (75 MHz, $CDCl_3$) δ 19.20, 26.80, 64.03, 105.93, 127.76, 129.82, 133.13, 135.45, 136.29; HRMS (EI) m/z 316.9998 [$(M-Bu)^+$, calcd. for $C_{15}H_{14}BrOSi$ 316.9997].



130

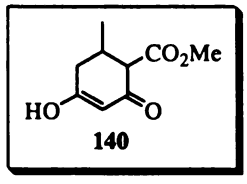
Preparation of 9-(*t*-butyldiphenylsilanyloxy)-4,4-dimethyl-nona-5,7-dien-1-ol (130) (Scheme 45). Applying the above "Sn-F" one catalytic Stille conditions (Table 7) to 4,4-dimethyl-hex-5-yn-1-ol (**119**) (126.2 mg, 1 mmol) and (*E*)-(3-bromo-allyloxy)-t-butyl-diphenyl-silane (**129**)

(563.1 mg, 1.5 mmol) afforded after column chromatography [silica gel; 80:20 hexane/EtOAc] 9-(t-butyl-diphenyl-silanyloxy)-4,4-dimethyl-nona-5,7-dien-1-ol (**130**) (336 mg, 80%) as an oil. IR (neat) 3352, 3071 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 6 H), 1.08 (s, 9 H), 1.37 (m, 3 H), 1.51 (m, 2 H), 3.61 (t, *J* = 6.4 Hz, 2 H), 4.25 (dd, *J* = 1.1, 5.1 Hz, 2 H), 5.61 (d, *J* = 15.5 Hz, 1 H), 5.70 (dt, *J* = 5.1, 15.2 Hz, 1 H), 5.98 (dd, *J* = 10.4, 15.5 Hz, 1 H), 6.24 (dd, *J* = 10.4, 15.2, 1 H), 7.36-7.45 (m, 6 H), 7.68-7.72 (m, 4 H); ^{13}C (125 MHz, $CDCl_3$) δ 19.17, 26.80, 27.13, 28.04, 35.71, 38.95, 63.47, 64.22, 125.99, 127.57, 129.52, 129.91, 130.47, 133.65, 135.48, 143.73; HRMS (EI) m/z 365.1923 [$(M–t\text{-}Bu)^+$, calcd. for $C_{23}H_{29}O_2Si$ 365.1937].



141

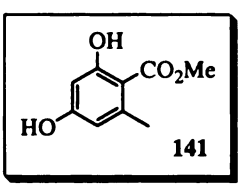
Procedure for the diketene route. Preparation of methyl 2,4-dihydroxy-6-methylbenzoate (141). Methyl acetoacetate (**138**) (5.2 mL, 48 mmol) and CaO (2.73 g, 48.7 mmol) were dissolved in THF (35 mL) under nitrogen and then were heated to 50 °C for 1 h. Diketene (stabilized with $CuSO_4$) (3.70 mL, 4.04 mmol) was added dropwise while the mixture was being cooled with a water bath to keep the temperature between 30-40 °C. Once the addition was complete, the reaction was refluxed for 8 h and then cooled to room temperature. The THF was removed (rotovap) and ether (50 mL) was added followed by enough 2 M HCl to dissolve the residual CaO in the mixture. After extracting with ether (3x), water was added and the aqueous phase was adjusted to pH 6.0 with 10% NaOH and then the mixture was extracted with ether (3x). The solvent was removed to provide a complex mixture of products that were not identifiable.



140

Procedure for the condensation reaction.[190] Preparation of methyl dihydroorsellinate (140) (Scheme 49). Na (18.4 g, 800

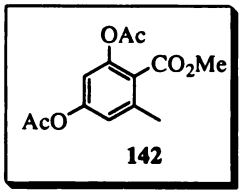
mmol) was added with stirring in small pieces to dry MeOH (275 mL). After the reaction had subsided, methyl acetoacetate (**138**) (86 mL, 800 mmol) was added dropwise followed by the dropwise addition of methyl crotonate (**139**) (85 mL, 800 mmol). After the addition was complete, the reaction was refluxed for 44h. At this time the MeOH was carefully removed in the original flask with the rotovap. The resulting residue was then cooled to 0 °C and ether (400 mL) was added with stirring. The solid formed was then removed by filtration and the filter cake was then washed with ether (100 mL). The solid was hen dissolved into water (275 mL), cooled to 0 °C, and then concentrated HCl was added until the aqueous phase turned the pH paper red (pH 3). This solution was then allowed to sit in the ice bath for ~1 h. The white solid was then filtered and washed with ice water (300 mL). This solid was then dried under vacuum for ~1 day to afford methyl dihydroorsellinate (**140**) (120 g, 82%) as a white solid (mp = 125-127 °C, lit mp = 127 °C).[188]



141

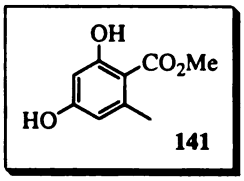
Procedure using Br_2/Ac_2O/AcOH and cat. HBr. Preparation of methyl 2,4-dihydroxy-6-methylbenzoate (141) (Scheme 50, reaction 1). Methyl dihydroorsellinate (**140**) (18.42 g, 100 mmol) was dissolved in a mixture of AcOH (60 mL) and Ac_2O (30 mL) by warming and once dissolved cooled to 0 °C (ice bath). A solution of Br_2 (5.12 mL, 100 mmol) in AcOH (10 mL) was added dropwise at 0 °C. A stream of N_2 was allowed to bubble through the solution as the temperature was brought to reflux (~125 °C). This mixture was then allowed to reflux for 2h. The authors suggest bubbling N_2 through the mixture during reflux, but this has to be watched carefully! The solution was then cooled to 25 °C and water (60 mL) was added followed by the addition of 48% HBr (1 mL). This solution

was then refluxed for 2 h. After cooling, the mixture was poured into water and extracted with ether (7x). The organics were washed with water, sat. aq. $NaHCO_3$, water, dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-dihydroxy-6-methylbenzoate (**141**) (12.05 g, 66%) as a white solid contaminated with a trace of an unknown product.

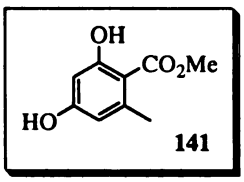


142

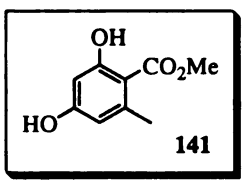
Procedure using $Br_2/Ac_2O/AcOH$. Preparation of methyl 2,4-diacetoxy-6-methylbenzoate (142) (Scheme 50, reaction 1). Methyl dihydroorsellinate (**140**) (18.42 g, 100 mmol) was dissolved in a mixture of AcOH (60 mL) and Ac_2O (30 mL) by warming and once dissolved cooled to 0 °C (ice bath). A solution of Br_2 (5.12 mL, 100 mmol) in AcOH (10 mL) was added dropwise at 0 °C. A stream of N_2 was allowed to bubble through the solution as the temperature was brought to reflux (~125 °C). This mixture was then allowed to reflux for 2h. The authors suggest bubbling N_2 through the mixture during reflux, but this has to be watched carefully! After cooling, the mixture was poured into water and extracted with ether (7x). The organics were washed with water, sat. aq. $NaHCO_3$, water, dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-diacetoxy-6-methylbenzoate (**142**) (19.54 g, 74%) as a white solid (mp 56 °C) contaminated with an unknown product. ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3 H), 2.26 (s, 3 H), 2.38 (s, 3 H), 3.85 (s, 3 H), 6.78 (s, 1 H), 6.86 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 20.7, 21.0, 52.2, 114.2, 121.3, 123.5, 139.7, 149.3, 151.7, 166.2, 168.6, 168.8.[100]



Procedure for the use of $CuBr_2$ and LiBr[189]. Preparation of methyl 2,4-dihydroxy-6-methylbenzoate (141) (Scheme 51, entry 1). Methyl dihydroorsellinate (**140**) (1.84 g, 10 mmol), $CuBr_2$ (4.46 g, 20 mmol) and LiBr (0.86 g, 10 mmol) were dissolved into CH_3CN (20 mL). This mixture was then refluxed for 2 h. After cooling to 25 °C, the reaction was poured into a solution of 10% HCl (50 mL) and ether (100 mL). The layers were separated and the aqueous phase was extracted with ether (2x). The combined organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-dihydroxy-6-methylbenzoate (**141**) (600 mg, 33%) as a white solid.

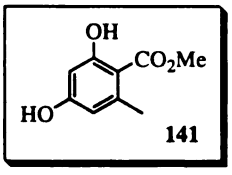


Procedure for the use of $CuBr_2$ and LiBr using DMF as solvent[189]. Preparation of methyl 2,4-dihydroxy-6-methylbenzoate (141) (Scheme 51, entry 2). Applying the above conditions except this entry used DMF (20 mL) as solvent at 100 °C. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-dihydroxy-6-methylbenzoate (**141**) (800 mg, 44%) as a white solid.



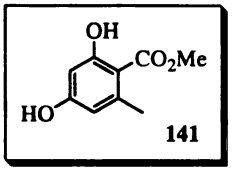
Procedure for the use of $CuCl_2$ and LiCl[189] in CH_3CN. Preparation of methyl 2,4-dihydroxy-6-methylbenzoate (141) (Scheme 51, entry 3). Methyl dihydroorsellinate (**140**) (10.0 g, 54.3 mmol), $CuCl_2$ (29.20 g, 217 mmol) and LiCl (4.60 g, 109 mmol) were dissolved into CH_3CN (200 mL). This mixture was then refluxed for 5 h. After cooling to 25 °C, the reaction was poured into a solution of 10% HCl (50 mL) and ether (100 mL). The layers were separated and the aqueous phase was extracted with ether (2x). The combined

organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-dihydroxy-6-methylbenzoate (**141**) (3.30 g, 33%) as a white solid.



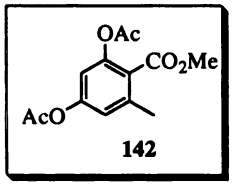
141

Procedure for the use of $CuCl_2$ and LiCl[189] in DMF. Preparation of methyl 2,4-dihydroxy-6-methylbenzoate (141) (Scheme 51, entry 4). Applying the above conditions using DMF as the solvent at 100 °C f6r 5 h after column chromatography [silica; 80:20 hexane/EtOAc] afforded methyl 2,4-dihydroxy-6-methylbenzoate (**141**) (4.47 g, 47%) as a white solid.



141

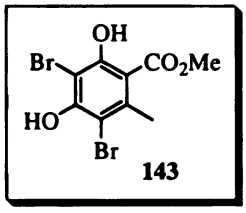
Procedure for the use of $CuCl_2$ and $MgCl_2$[189]. Preparation of methyl 2,4-dihydroxy-6-methylbenzoate (141) (Scheme 51, entry 5). Methyl dihydroorsellinate (**140**) (5.0 g, 27.15 mmol), $CuCl_2 \cdot 2H_2O$(9.26 g, 54.30 mmol) and $MgCl_2 \cdot 6H_2O$(2.76 g, 13.60 mmol) were dissolved into CH_3CN (30 mL). This mixture was then refluxed for 12 h. After cooling to 25 °C, the reaction was poured into a solution of 10% HCl (50 mL) and ether (100 mL). The layers were separated and the aqueous phase was extracted with ether (2x). The combined organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-dihydroxy-6-methylbenzoate (**141**) (3.0 g, 60%) contaminated with a trace of an unknown product.



142

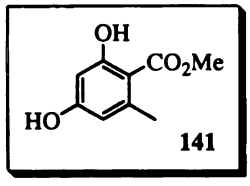
Procedure for the use of $CuBr_2$ and LiBr[189] with Ac_2O in DMF. Preparation of methyl 2,4-diacetoxy-6-methylbenzoate (142) (Scheme 51, entry 6). Methyl dihydroorsellinate (**140**) (1.84 g, 10 mmol), $CuBr_2$ (4.46 g, 20 mmol) Ac_2O (3.77 mL, 40 mmol) and LiBr (0.86 g, 10 mmol)

were dissolved into DMF (20 mL). This mixture was then heated to 100 °C for 12 h. After cooling to 25 °C, the reaction was poured into a solution of 10% HCl (50 mL) and ether (100 mL). The layers were separated and the aqueous phase was extracted with ether (2x). The combined organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-diacetoxy-6-methylbenzoate (**142**) (1.02 g, 56%) as a white solid (mp = 56 °C). For spectroscopic data see page 211.



143

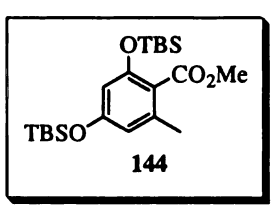
Procedure of the use of Br_2 in excess. Preparation of methyl 3,5-dibromo-2,4-dihydroxy-6-methyl-benzoate (143) (Scheme 52). Br_2 (56 mL, 1090 mmol) was added to a solution of methyl dihydroorsellinate (**140**) (66.35 g, 360 mmol) in AcOH (212 mL) at such a rate to keep the temperature between 40-45 °C. This mixture was allowed to stir for ~1h and then allowed to stand for ~10 h. Water was then added to this mixture and the solid was collected by filtration (course glass frit) and was washed with copious amounts of water. The white solid obtained was dried to afford methyl 3,5-dibromo-2,4-dihydroxy-6-methyl-benzoate (**143**) (142 g, 93%) as a white solid[190] (mp = 106 °C).



141

Procedure for PMHS/KF dehydrohalogenation catalyzed by $Pd(OAc)_2$. Preparation of methyl 2,4-dihydroxy-6-methylbenzoate (141) (Scheme 53). Methyl 3,5-dibromo-2,4-dihydroxy-6-methyl-benzoate (**143**) (117 g, 345 mmol) was dissolved into THF (1725 mL) and was purged with N_2. $Pd(OAc)_2$ (3.87 g, 17.25 mmol), KF (80.18 g, 1380 mmol) and H_2O (~690 mL) were all added under N_2. PMHS (166 mL, 2760 mmol) was then slowly added (*add the PMHS via an additional funnel and allow the PMHS to flow as a*

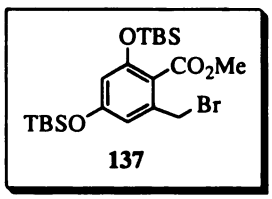
thin stream while using a mechanical stirrer. Also use a reflux condenser as the reaction is exothermic) and once the addition was complete, the reaction was allowed to stir at 25 °C for 24 h. Crude ^{1}H NMR analysis indicated a 1.7:1.0 ratio of product to monobromide. This reaction was then diluted with Et_2O and the layers were separated. The aqueous portion was extracted with Et_2O (3x). The combined organics were then concentrated to about ½ volumne. This solution was then filtered through a pad of silica gel with celite on top. The filter cake was rinsed with Et_2O until TLC analysis (80:20 Hexane/EtOAc) showed no product. The filtrate was then concentrated to dryness. This residue was then dissolved into THF (1725 mL) and was purged with N_2. $Pd(OAc)_2$ (3.87 g, 17.25 mmol), KF (80.18 g, 1380 mmol) and H_2O (~690 mL) were all added under N_2. PMHS (166 mL, 2760 mmol) was then slowly added and this mixture was allowed to stir at 25 °C for 21 h. Crude ^{1}H NMR analysis indicated that the reaction was complete. After diluting with Et_2O, the reaction was allowed to stand overnight (~10 h). The layers were separated and the aqueous portion was extracted with Et_2O. The combined organics were dried ($MgSO_4$), filtered through celite, and then concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-dihydroxy-6-methylbenzoate (**141**) (55.3 g, 88%) of a white solid.



144

Procedure for the protection of the bis-phenol as a bis-TBS ether. Preparation of methyl 2,4-di-(*t*-butyldimethylsiloxy)-6-methylbenzoate (144) (Scheme 54, reaction 1). Methyl 2,4-dihydroxy-6-methylbenzoate (**141**) (15.73 g, 86.35 mmol) was dissolved into DMF (130 mL). Imidazole (29.40 g, 432 mmol) was added followed by TBSCl (32.54 g, 216

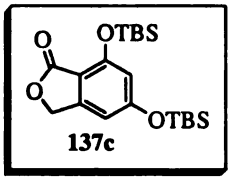
mmol). The reaction was then allowed to stir at 25 °C from 2.5 h. The reaction was then poured into water and extracted with EtOAc. The combined organics were washed with sat. aq. $NaHCO_3$, sat. aq. NH_4Cl, brine, dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 98:2 hexane/EtOAc] to afford methyl 2,4-di-(*t*-butyldimethylsiloxy)-6-methylbenzoate (**144**) (35.01 g, 99%) as a clear oil. IR (neat) 2957 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.18 (s, 6 H), 0.20 (s, 6 H), 0.96 (s, 9 H), 0.97 (s, 9 H), 2.22 (s, 3 H), 3.82 (s, 3 H), 6.16 (s, 1 H), 6.29 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.4, 18.0, 18.2, 19.7, 25.5, 25.6, 51.7, 108.5, 114.9, 119.8, 137.9, 153.8, 156.9, 168.8; HRMS (EI) 410.2305 *m/z* 410.2305 [(M^+), calcd. for $C_{21}H_{38}O_4Si$ 410.2309].



137

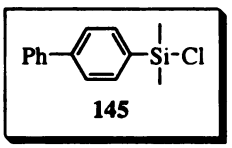
Procedure for the benzylic bromination using NBS/AIBN. Preparation of methyl 2-(bromomethyl)-4,6-di-(*t*-butyldimethylsiloxy)-benzoate (137) (Scheme 54, reaction 2). Methyl 2,4-di-(*t*-butyldimethyl siloxy)-6-methylbenzoate (**144**) (1.0 g, 2.44 mmol), NBS (477 mg, 2.68 mmol) and AIBN (4 mg, 0.024 mmol) were added to freshly distilled CCl4 (20 mL). This mixture was gently refluxed for 3.5 h. The reaction was then filtered, while still warm, through a pad of celite and the filtrate was concentrated. The resulting residue was purified by column chromatography [silica; 95:5 Hexane/EtOAc] to afford methyl 2-(bromomethyl)-4,6-di-(*t*-butyldimethylsiloxy)-benzoate (**137**) (1.03 g, 87%) as an oil. IR (neat) 2957 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.18 (s, 6 H), 0.20 (s, 6 H), 0.96 (s, 9 H), 0.97 (s, 9 H), 2.22 (s, 3 H), 3.82 (s, 3 H), 6.16 (s, 1 H), 6.29 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.4, 18.0, 18.2, 19.7, 25.5, 25.6, 30.5, 51.7, 111.2, 115.1, 138.0, 154.5, 156.9, 167.7; HRMS (EI) *m/z* 488.1410 [(M^+), calcd. for $C_{21}H_{37}BrO_4Si$

488.1414. **Note: If this compound is left to stand for a long period of time, another product forms. The product has been identified as 5,7-bis(*tert*-butyldimethylsiloxy)-isobenzofuran-1(3H)-one.



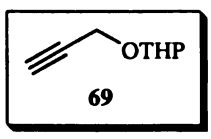
137c

Data for 5,7-bis(*tert*-butyldimethylsiloxy)-isobenzofuran-1(3H)-one (**137c**): IR (KBr) 1732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.23 (s, 6 H), 0.26 (s, 6 H), 0.98 (s, 9 H), 1.04 (s, 9 H), 5.09 (s, 2 H), 6.29 (s, 1 H), 6.45 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –4.4, 18.2, 25.6, 68.1, 106.4, 109.7, 112.5, 150.5, 156.2, 162.5, 168.4; HRMS (EI) *m/z* 394.1190 [(M^+), calcd. for $C_{20}H_{34}O_4Si_2$ 394.1996].



145

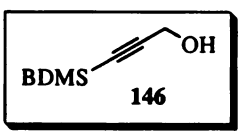
Procedure for the preparation of biphenyldimethylsilyl chloride (BDMSCl) (145) (Scheme 55). To a solution of 4-bromobiphenyl (50 g, 215 mmol) in dry Et_2O (200 mL) at 0 °C was added *n*-BuLi (135 mL of a 1.6 M solution in hexanes, 215 mmol). After stirring at 0 °C for 20 min., the mixture was warmed to room temperature and stirred for another 30 min. The resulting 4-lithiobiphenyl was then added via cannula to a precooled (0 °C) solution of Me_2SiCl_2 (25.83 mL, 215 mmol) in dry Et_2O (300 mL). This mixture was then left stirring for ~14 h at 25 °C. The solution was then filtered and the filtrate was concentrated to afford biphenyldimethylsilyl chloride (**145**) (46.30 g, 87%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 0.74 (s, 6 H), 7.34-7.42 (m, 1 H), 7.42-7.50 (m, 2 H), 7.57-7.69 (m, 4 H), 7.70-7.75 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 2.1, 126.8, 127.2, 127.7, 128.8, 133.6, 134.8, 140.6, 143.1.



69

Procedure for the THP protection. Preparation of tetrahydro-2-(prop-2-ynyloxy)-2H-pyran (69) (Scheme 55). Propargyl alcohol (**65**)

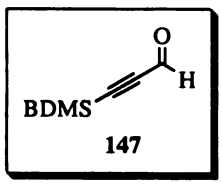
(35 mL, 600 mmol) was dissolved into CH_2Cl_2 (500 mL). DHP (46 mL, 500 mmol) and TsOH (9.51 g, 50 mmol) were then added. After stirring for 20 h at 25 °C, the reaction was poured into sat. aq. $NaHCO_3$ and then was extracted with CH_2Cl_2. The combined organics were washed with brine, dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by distillation [65 °C @ 10 mmHg] to afford tetrahydro-2-(prop-2-ynyloxy)-2H-pyran (**69**) (54.01 g, 77%) as a clear liquid. Spectral data was consistent with a commercial sample.



146

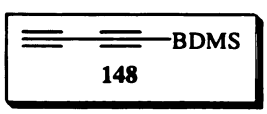
Procedure for the protection using BDMSCl. Preparation of 3-(dimethyl(4-biphenyl)silyl)prop-2-yn-1-ol (146) (Scheme 55). Tetrahydro-2-(prop-2-ynyloxy)-2H-pyran (**69**) (21.03 g, 150 mmol) was dissolved into dry THF (113 mL) and was cooled with an ice bath. At this time, *n*-BuLi (94 mL of a 1.6 M solution in hexanes, 150 mmol) was added dropwise. After 20 min, BDMSCl (**145**) (37.02 g, 150 mmol) was added and the reaction was allowed to warm to room temperature. After 4 h, the reaction was quenched by the addition of sat. aq. NH_4Cl. The phases were then separated and the aqueous phase was extracted with Et_2O. The organics were dried ($MgSO_4$), filtered, and concentrated. The residue was then dissolved in MeOH (150 mL) and concentrated HCl (23 mL) was added. After stirring at 25 °C for 12 h, TLC analysis indicated the complete removal the THP ether. The mixture was then diluted with Et_2O and was washed with water. The organics were dried ($MgSO_4$), filtered, and concentrated to afford a solid. The solid was then recrystallized from hexanes to afford 3-(dimethyl(4-biphenyl)silyl)prop-2-yn-1-ol (**146**) (31.65 g, 80%) as a white solid. Mp 85 °C (lit mp 84 °C).[107] IR (neat) 3406 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.47 (s, 6 H), 4.33 (m, 2 H), 7.33-7.39 (m, 1 H), 7.41-7.48 (m, 2 H), 7.57-7.65

(m, 4 H), 7.68-7.73 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -1.0, 51.8, 88.8, 105.6, 126.7, 127.2, 127.5, 128.8, 134.1, 135.2, 140.9, 142.4; HRMS (EI) *m/z* 266.1120 [(M^+), calcd. for $C_{17}H_{18}OSi$ 266.1127].



147

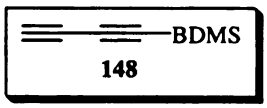
Procedure for the PCC oxidation. Preparation of 3-(dimethyl(4-biphenyl)silyl)propiolaldehyde (147) (Scheme 55). PCC on silica (283 g, 236 mmol; 1.2 g SiO_2/mmol) was placed into a flask containing CH_2Cl_2 (354 mL). 3-(dimethyl(4-biphenyl)silyl)prop-2-yn-1-ol (**146**) (31.37 g, 118 mmol) was then added in portions. Once all the material was added, the reaction was allowed to stir until complete by TLC analysis. Once complete then reaction was filtered through a pad of celite and silica gel. The filtrate was concentrated to afford a solid. Recrystallization of the solid from Hexanes afforded 3-(dimethyl(4-biphenyl)silyl)propiolaldehyde (**147**) (26.47 g, 86%) as an off white solid (mp 42 °C; lit mp 42 °C).[107] IR (neat) 1718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.61 (s, 6 H), 7.38-7.45 (m, 1 H), 7.46-7.54 (m, 2 H), 7.60-7.77 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -1.8, 100.7, 103.2, 110.5, 126.5, 126.9, 127.1, 128.8, 132.8, 134.2, 134.6, 140.6, 142.9, 176.4; HRMS (EI) *m/z* 264.0965 [(M^+), calcd. for $C_{17}H_{16}OSi$ 264.0970]



148

Procedure for the Cory-Fuchs protocol. Preparation of (buta-1,3-diynyl)dimethyl(4-biphenyl)silane (148) (Scheme 55). To a cold solution (0 °C) of PPh_3 (105 g, 401 mmol) in dry CH_2Cl_2 (1200 mL) was added CBr_4 (66.41 g, 332 mmol). This mixture turned orange. After 20 min, 3-(dimethyl(4-biphenyl)silyl)propiolaldehyde (**147**) (26.47 g, 100 mmol) was added in one portion and the mixture was allowed to stir for overnight. The reaction was then concentrated to half volume and then filtered through a pad of silica gel using 90:10 hexane/EtOAc as the

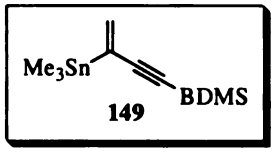
rinse agent. The filtrate was concentrated to afford (4,4-dibromobut-3-en-1-ynyl)dimethyl(4-biphenyl)silane (29.14 g, 69%) as a crude solid. This solid was then dissolved into dry THF (210 mL) and was then cooled to –78 °C. At this time, *n*-BuLi (90 mL of a 1.6 M solution in Hexanes, 144 mmol) was added dropwise. Once the addition was complete, the reaction was allowed to stir at –78 °C for 1 h followed by warming to 25 °C over a few hours. At this time 1M HCl was added followed by dilution with Et_2O. The phases were separated and the aqueous layer was extracted with Et_2O (3x). The combined organics were washed with brine, dried ($MgSO_4$), filtered and concentrated to afford a solid. Recrystallization from hexanes afforded (buta-1,3-diynyl)dimethyl(4-biphenyl)silane (**148**) (17.86 g, 98%) as solid. (mp = 77 °C; lit mp 76 °C).[107] IR (neat) 3323 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.50 (s, 6 H), 2.16 (s, 1 H), 7.32-7.40 (m, 1 H), 7.42-7.50 (m, 2 H), 7.55-7.65 (m, 4 H), 7.66-7.72 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -1.3, 67.2, 68.3, 82.6, 88.9, 126.8, 127.2, 127.5, 128.8, 134.2, 140.9, 142.6; HRMS (EI) *m/z* 260.1029 [(M^+), calcd. for $C_{18}H_{16}Si$ 260.1021].



148

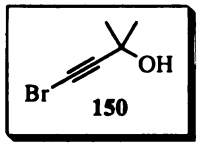
Procedure for the alternative diyne syntheis. Preparation of (buta-1,3-diynyl)dimethyl(4-biphenyl)silane (148) (Scheme 55). Hexachlorobutadiene (1.9 mL, 12.16 mmol) was added dropwise to a solution of *n*-BuLi (30.5 mL of a 1.6 M solution in hexanes, 49 mmol) at –78 °C in THF (15 mL). After the addition was complete, the mixture was allowed to warm to room temperature and then was stirred for 2 h. The solution was then recooled to –78 °C and BDMSCl (**145**) (3.0 g, 12.16 mmol) was added dropwise as a solution in THF (5 mL). After the addition, the reaction was allowed to warm to room temperature and the mixture was stirred for 5 h. The reaction was then washed with 1M HCl and extracted with Et_2O. The combined

organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford a dark oil. The resulting residue was purified by column chromatography [silica; pentane] to afford (buta-1,3-diynyl)dimethyl(4-biphenyl)silane (**148**) (1.84 g, 60%) as a white solid. For spectroscopic data see page 219-220.



149

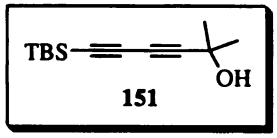
Procedure for the hydrostannation of the silyldiyne. Preparation of trimethylstannylenyne (149) (Scheme 56). (buta-1,3-diynyl)dimethyl(4-biphenyl)silane (**148**) (1.84 g, 7.07 mmol) was dissolved into THF (30 mL). Me_3SnCl (8.5 mL of a 1M solution in THF, 8.5 mmol), KF (1.23 g, 21.21 mmol), water (5-10 mL), PMHS (0.64 mL, 10.61 mmol) and $PdCl_2(PPh_3)_2$ (50 mg, 0.07 mmol) were all added. After 2 h of stirring at room temperature, the phases were separated and the organics were dried ($MgSO_4$), filtered and concentrated. Crude ^1H NMR analysis indicated only the formation of internal terminal vinylstannane (**149**). All attempts to isolate this compound failed.



150

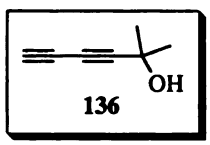
Procedure for the bromination of terminal alkynes. Preparation of 4-bromo-2-methyl-3-butyn-2-ol (150) (Scheme 57, reaction 1). A 1 L 3-neck flask was charged with KOH (89.2 g, 1600 mmol) and water (350 mL). This mixture was cooled with an ice bath followed by the addition of Br_2 (110 mL, 200 mmol) dropwise. Once the dark red color discharged, the reaction was allowed to stir for 15 min. To this solution was added 2-methyl-3-butyn-2-ol (**1**) (26.75 mL, 276 mmol) in hexanes (40 mL) via an addition funnel. Once the addition was complete, the reaction was allowed to stir for 15 min. A white solid could be seen floating on the surface of the colorless solution. The reaction was diluted with Et_2O, and washed with water. The organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was

purified by distillation [bp 68 °C @ 12 mmHg] to afford 4-bromo-2-methyl-3-butyn-2-ol (**150**) (32.60 g, 100%) as a clear liquid.[191]



151

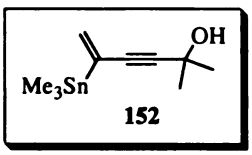
Procedure for the Marino's modified coupling. Preparation of 6-(*tert*-butyldimethylsilyl)-2-methylhexa-3,5-diyn-2-ol (151) (Scheme 57, reaction 2). CuCl (120 mg, 1.2 mmol) was added to a 30% aq. *n*-$BuNH_2$ solution (50 mL) which turned blue. A few crystals of $NH_2OH•HCl$ were added to discharge the color. TBS-acetylene (13.37 mL, 71.3 mmol) was added to the solution in one portion. The now yellow mixture was cooled with an ice bath. At this point, 4-bromo-2-methyl-3-butyn-2-ol (**150**) (9.68 g, 60 mmol) was added in one portion with vigorous stirring. If at any time during this addition the solution turned blue or green, a few crystals of $NH_2OH•HCl$ were added immediately. The reaction turned from red to a rusty color that denotes the reaction was complete. The mixture was extracted with Et_2O (3x), dried ($MgSO_4$), filtered, and concentrated to afford 6-(*tert*-butyldimethylsilyl)-2-methylhexa-3,5-diyn-2-ol (**151**) (6.67 g, 50%) of a white solid, mp = 75-76 °C; IR (KBr) 3395 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 6 H), 0.94 (s, 9 H), 1.52 (s, 6 H), 2.08 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.9, 16.7, 25.9, 31.0, 65.5, 67.5, 81.4, 86.4, 87.8; HRMS (EI) *m/z* 222.1436, [(M^+), calcd. for $C_{13}H_{22}OSi$ 222.1440].



136

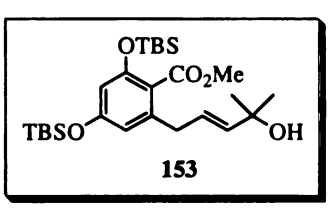
Procedure for the removal of the TBS group. Preparation of 2-methylhexa-3,5-diyn-2-ol (136) (Scheme 57, reaction 3). 6-(*tert*-butyldimethylsilyl)-2-methylhexa-3,5-diyn-2-ol (**151**) (6.67 g, 30 mmol) was dissolved into THF (50 mL) and this solution was cooled with an ice bath. TBAF (45 mL of a 1M solution in THF, 45 mmol) was added dropwise. After 5 h, the reaction was concentrated

and the residue was purified by column chromatography [silica; 90:10 pentane/Et_2O] to afford 2-methylhexa-3,5-diyn-2-ol (**136**) (3.24 g, 100%) as a clear liquid.[192]



152

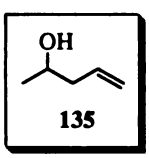
Procedure for the hydrostannation of the diyne. Preparation of trimethylstannylenyne (152) (Scheme 58). 2-methylhexa-3,5-diyn-2-ol (**136**) (765 mg, 7.07 mmol) was dissolved into THF (30 mL). Me_3SnCl (8.5 mL of a 1M solution in THF, 8.5 mmol), KF (1.23 g, 21.21 mmol), water (5-10 mL), PMHS (0.64 mL, 10.61 mmol) and $PdCl_2(PPh_3)_2$ (50 mg, 0.07 mmol) were all added. After 2 h of stirring at room temperature, the phases were separated and the organics were dried ($MgSO_4$), filtered, and concentrated. Crude ^1H NMR analysis indicated only the formation of internal terminal vinylstannane (**136**). All attempts to isolate this compound failed.



153

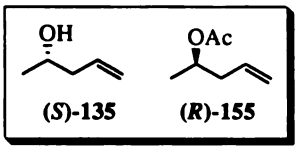
Procedure for the one-pot hydrostannation/Stille coupling using catalytic amounts of tin. Application to the synthesis of Monocillin I. Preparation of methyl 2-((*E*)-4-hydroxy-4-methylpent-2-enyl)-4,6-di-(*tert*-butyldiphenylsiloxy)benzoate (153) (Scheme 59). Tri-2-furylphosphine (9.3 mg, 0.04 mmol) was added to a solution of Pd_2bda_3 (9.2 mg, 0.01 mmol) in Et_2O (5 mL). After stirring at room temperature for 15 min, methyl 2-(bromomethyl)-4,6-di-(*tert*-butyldimethylsiloxy)-benzoate (**137**) (734 mg, 1.5 mmol), Me_3SnCl (0.06 mL, 0.06 mmol; 1M solution in THF), aq. KF (0.1743 g, 3 mmol; 1 mL H_2O), TBAF (1 drop of a 1M solution in THF) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were all added to the solution. The solution was heated to reflux and then a solution of 2-methyl-but-3-yn-2-ol (0.10 mL, 1 mmol) and PMHS (0.09 mL, 1.5 mmol) in Et_2O (4mL) was added via a syringe pump over 11 hrs. The phases were separated and the organics

washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel, 90:10 to 80:20 hexane/EtOAc] to afford methyl 2-((*E*)-4-hydroxy-4-methylpent-2-enyl)-4,6-di-(*tert*-butyldiphenylsiloxy) benzoate (**153**) (396 mg, 80%) as a yellow oil. IR (neat) 3492 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.18 (s, 6 H), 0.20 (s, 6 H), 0.96 (m, 18 H), 1.29 (s, 6 H), 1.42 (br s, 1 H), 3.27 (d, J = 6.0 Hz, 2 H), 3.81 (s, 3 H), 5.58-5.70 (m, 2 H), 6.19 (d, J = 2.2 Hz, 1 H), 6.29 (d, J = 2.0 Hz, 1 H); ^{13}C (125 MHz, $CDCl_3$) δ -4.4, -4.3, 18.0, 18.2, 25.5, 25.6, 29.6, 29.9, 36.6, 51.8, 70.6, 109.1, 110.6, 114.3, 125.0, 126.4, 127.4, 128.5, 139.6, 140.4, 153.9, 157.2, 168.7; HRMS (EI) *m/z* 494.2890 [(M^+), calcd. for $C_{26}H_{46}O_5Si_2$ 494.2884].

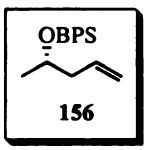


135

Procedure for the grignard reaction with allylmagnesium bromide. Preparation of (+/-)-4-penten-2-ol (135) (Scheme 60). A flask was charged with Mg turnings (110 g, 4.5 mol) and dry Et_2O (187 mL). While this mixture was stirring, a solution of allyl bromide (173 mL, 2.0 mol) in Et_2O (1.0 L) was added slowly so as to keep the reaction temperature ~30 °C. Once the addition was complete, the solution was allowed to stir for 1 h. The solution of allylmagnesium bromide was cooled with an ice bath and a solution of acetaldehyde (100 mL, 1.8 mol) in Et_2O (100 mL) was added via an addition funnel. Once the addition was complete, the reaction was refluxed for 3 h. The reaction was then poured into ice water was quenched by the addition of dilute H_2SO_4. The mixture was then extracted with Et_2O. The organics were dried ($MgSO_4$), filtered and concentrated (NO HEAT on rotovap). The resulting residue was purified by distillation [bp = 112-116 °C @ 760 mmHg] to afford (+/-)-4-penten-2-ol (**135**) (170 g, 98%) as a clear liquid. Spectra matched that of commercial material.

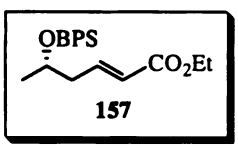


Procedure for the Lipase resolution. Preparation of (*S*)-4-penten-2-ol (135) and (*R*)-4-penten-2-yl acetate (155) (Scheme 60). (+/-)-4-penten-2-ol (**135**) (77.86 g, 904 mmol) was dissolved into freshly distilled vinyl acetate (83.3 mL, 904 mmol) and Novozyme 435 (8.22 g) was added. This slurry was stirred at room temperature for ~12 h. The reaction was then filtered and the filtrate was loaded onto a column of silica and was eluted with 90:10 pentane/Et_2O and once the acetate was off, 70:30 pentane/Et_2O was used to obtain the (*S*)-alcohol. The relevant fractions were rotovaped (NO HEAT!!!!) to afford (*S*)-4-penten-2-ol (**135**) (19.49 g, 25 %; 99% ee) and (*R*)-4-penten-2-yl acetate (**155**) (46 g, 40 %; 65 % ee).



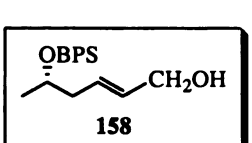
Procedure for the silyl protection. Preparation of (*S*)-*tert*-butyl(pent-4-en-2-yloxy)diphenylsilane (156) (Scheme 61). (*S*)-4-penten-2-ol (**135**) (11.97 g, 139 mmol) was dissolved into DMF (140 mL) and imidazole (20.82 g, 306 mmol) was added followed by BPSCl (35.8 mL, 138 mmol). After stirring at 28 °Cfor 10 h, the reaction was poured into sat. aq. NH_4Cl and then was extracted with Et_2O. The combined organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; hexanes] to afford (*S*)-*tert*-butyl(pent-4-en-2-yloxy)diphenylsilane (**156**) (44.95 g, 99%) as a clear oil. $[\alpha]^D_{25}$ –17.4 (c = 1.3 $CHCl_3$); IR (neat) 3072 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (m, 12 H), 2.24 (m, 2 H), 3.95 (m, 1 H), 4.96-5.03 (m, 2 H), 5.74-5.86 (m, 1 H), 7.35-7.48 (m, 6 H), 7.69-7.75 (m, 4 H); ^{13}C (125 MHz, $CDCl_3$) δ 19.3, 22.8, 27.0, 43.9, 69.2, 116.7, 127.4, 127.5, 129.4, 129.5, 134.5, 134.8, 135.1, 135.3, 135.8, 135.9; HRMS (EI) *m/z* 324.1913 [(M^+), calcd. for $C_{21}H_{28}OSi$ 324.1909].

Preparation of $Ph_3P{=}CHCO_2Et$ (Scheme 61). Ethyl-2-bromoacetate (111 mL, 1 mol), was added dropwise during 30 min to a stirred solution of PPh_3 (262 g, 1 mol) in benzene at 25 °C. This mixture was stirred for 5 h and then was allowed to stand overnight. The precipitate was filtered off and was successively washed with benzene and hexanes and then dried in vacuo to yield the corresponding bromide. This solid was then dissolved into cold water and 2 N NaOH was added dropwise until the mixture was alkaline to phenolphthalein. The precipitate was filtered off and air-dried to give the phosphorane as a white solid (312 g, 90%).[193]



157

Procedure for the one pot ozonolysis/Wittig. Preparation of (*S*)-(*E*)-ethyl 5-(*tert*-butyldiphenylsiloxy)-2-hexenoate (157) (Scheme 61). (*S*)-*tert*-butyl(pent-4-en-2-yloxy)diphenyl silane (**156**) (1.0 g, 3.08 mmol) was dissolved into CH_2Cl_2 (15 mL). This solution was then purged with N_2 and then cooled to –78 °C. O_3 was bubbled through the solution at –78 °C until a blue color persisted. The excess O_3 was removed by purging the solution with N_2. The reaction was then allowed to warm to room temperature and a condenser was added. Once at room temperature, a solution of Et_3N (0.47 mL, 3.4 mmol) and $Ph_3P{=}CHCO_2Et$ (1.18 g, 3.4 mmol) in CH_2Cl_2 (15 mL) was added to the solution. Once the addition was complete, the mixture was stirred for 20 min. The reaction was then concentrated and purified by column chromatography [silica; 95:5 hexane/EtOAc] to afford (*S*)-(*E*)-ethyl 5-(*tert*-butyldiphenylsiloxy)-2-hexenoate (**157**) (1.10 g, 90%) of a light yellow oil. All data matched that of the literature.[97]



158

Procedure for the DIBALH reduction. Preparation of (*S*)-(*E*)-5-(*tert*-butyldiphenylsiloxy)-hex-2-en-1-ol (158) (Scheme 61). (*S*)-

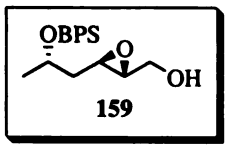
(*E*)-ethyl 5-(*tert*-butyldiphenylsiloxy)-2-hexenoate (**157**) (44.57 g, 113 mmol) was dissolved into CH_2Cl_2 (560 mL) and the solution was cooled to –78 °C. DIBALH (236 mL of a 1M solution in hexanes, 236 mmol) was added dropwise via an addition funnel. Once the addition was complete, the reaction was allowed to stir for 6 h at –78 °C. The reaction was quenched by the addition of water and Rochelle's salt. The reaction was then allowed to warm to room temperature for several hours (overnight if needed). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4x). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford (*S*)-(*E*)-5-(*tert*-butyldiphenylsiloxy)-hex-2-en-1-ol (**158**) (36.64 g, 92%) as a colorless oil. All data matched that of the literature.[97]

Procedure for the preparation of anyhydrous tert-butylhydrogen peroxide (TBHP) in toluene. To 1 L sep. funnel was added 360 mL of TBHP (30% aqueous solution) and 440 mL of toluene. The solution was swirled, not shaken. The aqueous phase was separated and the organic phase was transferred to a 1 L flask equipped with a Dean-Stark trap and reflux condenser. Boiling chips were added and the solution was refluxed for 4 h; during which ~120 mL of distillate was removed. The head temperature was ~80 °C. After cooling, the remaining TBHP/toluene solution was transferred to a brown glass bottle and stored at 25 °C over activated 4Å MS. The molarity was determined by the following equation:

$$\text{Molarity} = \frac{x}{0.1(x) + 0.32(y)}$$

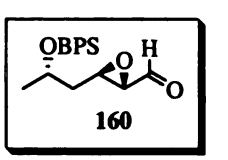
x = integration of tert-butyl resonance (~1.2 ppm)
y = integration of methyl resonance (~2.4 ppm)

$$\text{Molarity} = \frac{22.07}{0.1(22.07) + 0.32(10.95)} = 3.86 \text{ M}$$



159

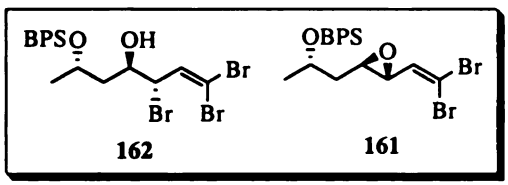
Procedure for the Sharpless asymmetric epoxidation. Preparation of (*S*, *R*, *R*)-(3-(2-(*tert*-butyldiphenylsiloxy)-propyl)oxiran-2-yl)methanol (159) (Scheme 61). To a suspension of 4Å MS (4 g) in CH_2Cl_2 (125 mL) at –30 °C was added in sequential fashion: D-DET (0.73 mL, 4.22 mmol), Ti(*i*-PrO)$_4$ (1.03 mL, 3.52 mmol) and dropwise addition of TBHP (14 mL of a 3.86 M solution in toluene, 54 mmol). After stirring at –30 °C for 30 min, a solution of (*S*)-(*E*)-5-(*tert*-butyldiphenylsiloxy)-hex-2-en-1-ol (**158**) (12.47 g, 35.2 mmol) in CH_2Cl_2 (18 mL) was added via a syringe so as to keep the reaction temperature at –30 °C. Once the addition was complete, stirring was stopped and the mixture was left at –30 °C for 12 h. The reaction was then warmed to –20 °C and quenched by the addition of 10% NaOH/brine (25 mL). Upon further warming to –10 °C, the reaction was diluted with Et_2O and $MgSO_4$ (15 g) and celite (4.0 g) were added and this mixture was stirred for 20 min. The reaction was then allowed to settle for ~1 h before filtering through celite. The filter cake was rinsed with Et_2O and the filtrate was concentrated. The residue was purified by column chromatography [silica; 80:20 to 70:30 hexane/EtOAc] to afford (*S*, *R*, *R*)-(3-(2-(*tert*-butyldiphenylsiloxy)-propyl)oxiran-2-yl)methanol (**159**) (11.12 g, 85%) as a clear oil. All data matched that of the literature.[97]



160

Procedure for the SO_3•py oxidation. Preparation of 3-(2-(*tert*-butyldiphenylsiloxy)-propyl)oxirane-2-carbaldehyde (160) (Scheme 61). A solution of (*S*, *R*, *R*)-(3-(2-(*tert*-butyldiphenylsiloxy)-propyl)oxiran-2-yl)methanol (**159**) (10.66 g, 28.77 mmol) and Et_3N (20 mL, 141 mmol) in 4:1 mixture of CH_2Cl_2/DMSO (300 mL) at 0 °C was treated with SO_3•py (16.08 g, 101 mmol) and this mixture was stirred at room temperature for 1 h. The reaction was then diluted with

EtOAc, washed with water, sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica; 95:5 hexane/EtOAc] to afford 3-(2-(*tert*-butyldiphenylsiloxy)-propyl)oxirane-2-carbaldehyde (**160**) (7.68 g, 72%) as a yellow oil. All data matched that of the literature.[97]

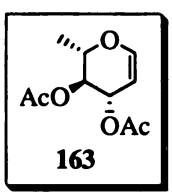


Procedure for modified Cory-Fuchs protocol. Preparation of 2-(2,2-dibromovinyl)-3-(2-(*tert*-butyldiphenylsiloxy)propyl)oxirane (161) (Scheme 62). To a mixture of CBr_4 (14.51 g, 43.76 mmol) in CH_2Cl_2 (120 mL) at 0 °C under Ar was added a solution of PPh_3 (22.96 g, 87.53 mmol) in CH_2Cl_2 (40 mL). After 20 min at 0 °C, the solution was cooled to –78 °C and Et_3N (3.2 mL, 22.92 mmol) was added. A solution of 3-(2-(*tert*-butyldiphenylsiloxy)-propyl)oxirane-2-carbaldehyde (**160**) (7.68 g, 20.84 mmol) in CH_2Cl_2 (70 mL) was added dropwise over 10 min. After 2 h, hexanes (120 mL) were added and the mixture was allowed to stir for 1 h. Filtering and concentration afforded a 2:1 mixture of bromohydrin (**162**) to epoxy dibromide (**161**). This mixture was then dissolved into THF (100 mL) and treated with TBAF (22 mL of a 1M solution in THF, 22 mmol) and stirred for 1 min at room temperature. The mixture was then washed with water, brine, dried ($MgSO_4$), filtered, and concentrated to afford 2-(2,2-dibromovinyl)-3-(2-(*tert*-butyldiphenylsiloxy)propyl)oxirane (**161**) (9.25 g, 85%) as a yellow oil.

Data for bromohydrin (**162**): $[\alpha]^{25}_D$= -77.8 (c = 1.12, $CHCl_3$); IR (neat) 3458 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (m, 9 H), 1.18 (d, *J* = 6.2 Hz, 3 H), 1.62 (m, 2 H), 3.13 (m, 1 H), 4.18 (m, 1 H), 4.62 (m, 1 H), 6.80 (d, *J* = 10.2 Hz, 1 H), 7.34-7.52 (m, 6 H), 7.64-7.79 (m, 4 H); ^{13}C (125 MHz, $CDCl_3$) δ 19.1, 23.0, 27.0, 41.8, 56.2, 67.7, 71.1, 95.1,

127.6, 127.8, 129.8, 129.9, 133.3, 133.7, 134.6, 135.8, 135.9; HRMS (EI) *m/z* 601.9492 [(M^+), calcd. for $C_{23}H_{29}Br_3O_2Si$ 601.9487].

Data for epoxy dibromide (**161**): $[\alpha]^{25}_D$= -7.6 (c = 1.08, $CHCl_3$); IR (neat) 3071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.6 (m, 9 H), 1.11 (d, *J* = 6.2 Hz, 3 H), 1.58-1.80 (m, 2 H), 3.00 (td, *J* = 2.1, 6.2 Hz, 1 H), 3.27 (dd, *J* = 2.1, 7.8 Hz, 1 H), 4.07 (m, 1 H), 6.06 (d, *J* = 10.2 Hz, 1 H), 7.33-7.47 (m, 6 H), 7.64-7.74 (m, 4 H); ^{13}C (75 MHz, $CDCl_3$) δ 19.2, 23.8, 25.9, 26.5, 26.9, 41.6, 56.7, 57.8, 67.4, 93.4, 127.5, 127.6, 127.7, 129.5, 129.6, 129.7, 133.8, 134.3, 134.7, 135.7, 135.8; HRMS (EI) *m/z* 522.0222 [(M^+), calcd. for $C_{23}H_{28}Br_2O_2Si$ 522.0225].

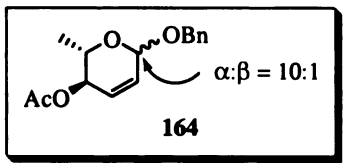


163

Procedure for the preparation of L-di-*O*-acetylrhamnal (163) (Scheme 63). Rhamnose (100 g, 550 mmol) was added to a mixture of Ac_2O (341 mL, 3601 mmol) and 70% perchloric acid (2 mL) in a 1 L flask in such a way to maintain an internal temperature between 30-40 °C. After stirring for 2 h, PBr_3 (70 mL, 737 mmol) was added dropwise at 0 °C. After the addition was complete, water (33 mL) was added and this mixture was allowed to stir for 2 h at 25 °C.

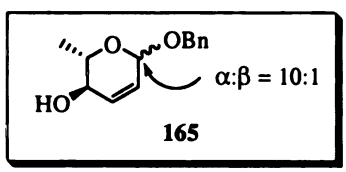
In a separate flask (5L) equipped with a mechanical stirrer was added NaOAc (227 g, 2761 mmol), water (700 mL) and AcOH (295 mL). This mixture was cooled with an ice bath. Zn powder (200 g, 3064 mmol) was added followed by addition of a solution of $CuSO_4$ (16.5 g, 66 mmol) in water (65 mL). Once the blue color disappeared and the evolution of gas ceased, the crude bromoaceto-rhamnose solution from above was added dropwise to this mixture and the temperature was maintained at 0 °C for 6 h. At this time 1 L of ice was added and the mixture was stirred for 10 min. The Zn and Cu were filtered off and the filtrate was extracted with CH_2Cl_2 (6x). The combined organics

were then washed with ice water, sat. aq. $NaHCO_3$, brine, dried (Na_2SO_4), filtered, and concentrated. The residue was distilled [bp 78-79 °C at 0.10 mmHg] to afford L-di-*O*-acetylrhamnal (**163**) (99.02 g, 84%) as a liquid. All spectroscopic data matched that of the literature.[194]



164

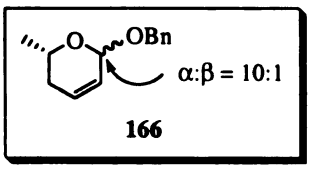
Procedure for the Ferrier rearrangement with BnOH. Preparation of (2S,3R)-6-(benzyloxy)-3,6-dihydro-2-methyl-2H-pyran-3-yl acetate (164) (Scheme 64). L-Di-*O*-acetylrhamnal (**163**) (99.02 g, 462 mmol) and benzyl alcohol (113 mL, 1090 mmol) were dissolved into CH_2Cl_2 (2.02 L) and freshly distilled $SnCl_4$ (2.71 mL, 23.11 mmol) was added. After stirring at 25 °C for 45 min, the reaction was quenched by the addition of 10% $NaHCO_3$ and then was extracted with CH_2Cl_2. The organics were then dried (Na_2SO_4), filtered and concentrated. Purifiaction by column chromatography [silica; 90:10 hexane/EtOAc] afforded a 10:1 mixture of α:β (2S,3R)-6-(benzyloxy)-3,6-dihydro-2-methyl-2H-pyran-3-yl acetate (**164**) (104 g, 86%) of a clear oil. All spectroscopic data matched that of the literature.[195]



165

Procedure for the deacetylation. Preparation of (2S,3R)-6-(benzyloxy)-3,6-dihydro-2-methyl-2H-pyran-3-ol (165) (Scheme 64). (2S,3R)-6-(benzyloxy)-3,6-dihydro-2-methyl-2H-pyran-3-yl acetate (**164**) (104.2 g, 397 mmol) was dissolved into a (3:2:1) mixture of MeOH (794 mL) / H_2O (516 mL) / Et_3N (258 mL) and this mixture was allowed to stir at 25 °C for 6 h. Once complete, the reaction was diluted with water and then extracted with CH_2Cl_2. The organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford a 10:1

mixture of α:β (2S,3R)-6-(benzyloxy)-3,6-dihydro-2-methyl-2H-pyran-3-ol (**165**) (85.62 g, 98%) of an oil. All spectroscopic data matched that of the literature.[195]

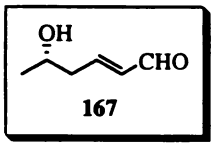


166

Procedure for the deoxygenation via the mesylate. Preparation of (2S)-6-(benzyloxy)-3,6-dihydro-2-methyl-2H-pyran (166) (Scheme 65). (2S,3R)-6-(Benzyloxy)-3,6-dihydro-2-methyl-2H-pyran-3-ol (**165**) (50 g, 227 mmol) was dissolved into dry CH_2Cl_2 (1135 mL). Et_3N (48 mL, 341 mmol) and DMAP (277 mg, 22.7 mmol) were added and this mixture was cooled with an ice bath. At this time MsCl (26.40 mL, 341 mmol) was slowly added in one portion. After stirring at 0 °C for 1 h, the reaction was washed with water and 5% $NaHCO_3$. The organics were then dried (Na_2SO_4), filtered and concentrated (carefully to avoid decomposition of the mesylate) to afford the crude mesylate (67.74 g, 100%). If the product was not used immediately, it would decompose upon standing after ~8 h.

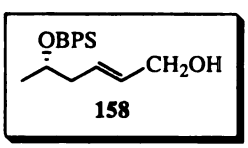
The crude mesylate (67.74 g, 227 mmol) was dissolved into THF (850 mL). After cooling to 0 °C, Superhydride® (454 mL of a 1M solution in THF, 454 mmol) was added slowly. Once the addition was complete, the ice bath was removed and the mixture was allowed to warm to 25 °C for 30 min. and then was heated to ~40 °C for 13 h. Once complete, the reaction was quenched by the slow addition of water (25 mL), then 3M NaOH (50 mL) followed by 30% H_2O_2 (50 mL). After stirring for 20 min, the layers were separated and the aqueous portion was extracted with Et_2O (3x). The combined organics were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica; 90:10 to 80:20 hexane/EtOAc] to afford

(2S)-6-(benzyloxy)-3,6-dihydro-2-methyl-2H-pyran (**166**) (32.58 g, 70%) as a clear oil. All spectroscopic data matched that of the literature.[196]



167

Procedure for the removal of the benzyl ether and thermal rearrangement. Preparation of (S,*E*)-5-hydroxyhex-2-enal (167) (Scheme 66). (2S)-6-(Benzyloxy)-3,6-dihydro-2-methyl-2H-pyran (**166**) (32.58 g, 160 mmol) was dissolved into THF (400 mL) and 0.5 M HCl (450 mL) was added and this solution was heated to 60 °C for 1 h. Once complete, the reaction was extracted with Et_2O. The organics were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica; 50:50 hexane/EtOAc] to afford (S,*E*)-5-hydroxyhex-2-enal (**167**) (13.14 g, 72%) as a yellow oil. All spectroscopic data matched that of the literature.[197]

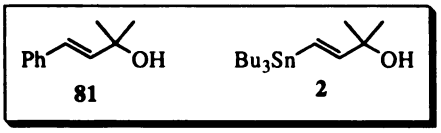


158

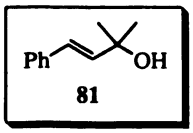
Procedure for the one pot silylation-reduction. Preparation of (*S*)-(*E*)-5-(*tert*-butyldiphenylsiloxy)-hex-2-en-1-ol (158) (Scheme 66). (S,*E*)-5-Hydroxyhex-2-enal (**167**) (2.10 g, 18.40 mmol) was dissolved into CH_2Cl_2 (40 mL) and was then cooled with an ice bath. Imidazole (2.51 g, 36.80 mmol) was added followed by BPSCl (4.77 mL, 5.04 mmol). This mixture was allowed to stir for 18 h. The reaction was then concentrated and used directly in the next step.

The crude silyl ether (6.48 g, 18.40 mmol) was dissolved into MeOH/THF (1:1; 77mL) and $NaBH_4$ (1.04 g, 27.6 mmol) was added in several portions. The reaction was stirred at 25 °C for 2 h. The reaction was then diluted with water and extracted with Et_2O. The organics were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica; 90:10 to 80:20 hexane/EtOAc] to afford (*S*)-

(*E*)-5-(*tert*-butyldiphenylsiloxy)-hex-2-en-1-ol (**158**) (5.48 g, 84%) as an oil. See above for spectroscopic data.

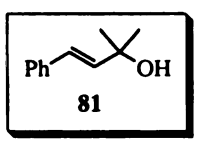


Procedure for a microwave assisted one pot hydrostannation/Stille coupling; first method (Scheme 9, reaction 1). Preparation of (*E*)-2-methyl-4-phenyl-but-3-en-2-ol (81) (Scheme 67, reaction 1). To a thick walled Pyrex tube containing to 5 mL THF were added Pd_2dba_3 (0.01 mmol, 9.2 mg) and tri-2-furylphosphine (0.04 mmol, 9.3 mg) and this mixture was stirred for until yellow or 10 min. 2-methyl-3-butyn-2-ol (**1**) (1 mmol, 0.10 mL), Bu_3SnCl (1.2 mmol, 0.33 mL), PMHS (1.5 mmol, 90 mg), KF (3.0 mmol, 0.1743 g), 1 mL H2O, bromobenzene (1.5 mmol, 0.16 mL) and catalytic TBAF (1 drop of a 1M THF solution) were all added. The reaction was closed, placed in a 250 mL beaker set in the center of a domestic microwave (glass turntable removed) and heated for 10 minutes at 140W (20% power setting on a 700W microwave oven). After cooling, TLC showed the reaction not to be complete even after heating for 5 min more. A saturated aqueous solution of KF (2 mL) was added and the mixture stirred for 30 min. The phases were separated and the organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography [silica gel; 90:10 pentane/EtOAc, 1% TEA] to afford (*E*)-2-methyl-4-phenyl-but-3-en-2-ol[198] (**81**) (100 mg, 63%) and 2-methyl-4-tributylstannanyl-but-3-en-2-ol[199] (**2**) (150 mg, 38%) as an oil. For spectroscopic data see pages 167 and 107-108 respectively.



Procedure for a microwave assisted one pot hydrostannation/Stille coupling; first method. Preparation of (*E*)-2-methyl-4-phenyl-but-3-

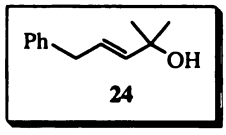
en-2-ol (81) (Scheme 67, reaction 2). To a thick walled Pyrex tube containing to 5 mL THF were added Pd_2dba_3 (0.01 mmol, 9.2 mg) and tri-2-furylphosphine (0.04 mmol, 9.3 mg) and this mixture was stirred for until yellow or 10 min. 2-Methyl-3-butyn-2-ol (**1**) (1 mmol, 0.10 mL), Bu_3SnCl (1.2 mmol, 0.33 mL), PMHS (1.5 mmol, 90 mg), KF (3.0 mmol, 0.1743 g), 1 mL H_2O, bromobenzene (1.5 mmol, 0.16 mL) and catalytic TBAF (1 drop of a 1M THF solution) were all added. The reaction was closed, placed in a 250 mL beaker set in the center of a domestic microwave (glass turntable removed) and heated for 5 minutes at 140W (20% power setting on a 700W microwave oven). Reaction was cooled and checked by TLC and stannane remained. Another equivalent of Pd_2dba_3 and TFP were added and the reaction was sealed and heated for another 5 min. After cooling, TLC showed the reaction not to be complete even after heating for 5 min more. A saturated aqueous solution of KF (2 mL) was added and the mixture stirred for 30 min. The phases were separated and the organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash chromatography (silica gel; 90:10 pentane/EtOAc with 1% TEA) to afford (*E*)-2-methyl-4-phenyl-but-3-en-2-ol[198] (**81**) (125 mg, 77%) as an oil. For spectroscopic data see pages 167.



81

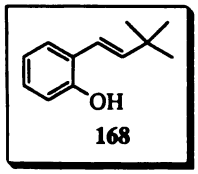
General procedure for the microwave-assisted palladium catalyzed one-pot hydrostannation/Stille coupling. Preparation of (*E*)-2-methyl-4-phenyl-but-3-en-2-ol (81) (Scheme 68, entry 1). To a thick walled Pyrex tube containing 5 mL THF were added $Pd(PPh_3)_4$ (12 mg, 0.01 mmol), 2-methyl-3-butyn-2-ol (**1**) (0.10 mL, 1 mmol), Bu_3SnCl (0.33 mL, 1.2 mmol), PMHS (90 mg, 1.5 mmol), KF (0.1743 g, 3.0 mmol), 1 mL H_2O, and catalytic TBAF (1 drop of a 1M THF solution).

The reaction was closed, placed in a 250 mL beaker set in the center of a domestic microwave (glass turntable removed) and heated for 3 minutes at 140 W (20% power setting on a 700 W microwave oven). After being allowed to air cool for 10 min, $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) and bromobenzene (0.16 mL, 1.5 mmol) were added and the sealed tube was irradiated at 140 W for 5 minutes. Upon cooling, the reaction was checked by TLC before a third portion of $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) was added and the sealed tube was again irradiated at 140 W for another 5 minutes. After cooling, TLC showed the reaction to be complete. A saturated aqueous solution of KF (2 mL) was added and the mixture stirred for 30 min. The phases were separated and the organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash chromatography [silica gel; 90:10 pentane/EtOAc, 1% TEA] to afford (*E*)-2-methyl-4-phenyl-but-3-en-2-ol (**81**) (153 mg, 94%) that gave spectroscopic data consistent with that shown on page 167.



24

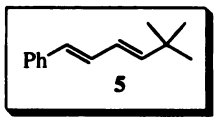
Preparation of (*E*)-2-methyl-5-phenyl-pent-3-en-2-ol (24) (Scheme 68, entry 2). Applying the conditions above to 2-methyl-3-butyn-2-ol (**1**) (0.10 mL, 1.0 mmol) and benzyl bromide (0.18 mL, 1.5 mmol) gave a residue, which was purified by flash chromatography [silica; 90:10 pentane/EtOAc, 1% TEA) to afford (*E*)-2-methyl-5-phenyl-pent-3-en-2-ol (**24**) (180 mg, 90%) as a thick yellow oil. Spectroscopic data were consistent with those reported earlier.[200] See page 132 aslo.



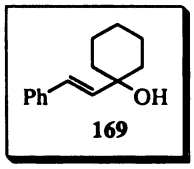
168

Preparation of (*E*)-2-(3,3-dimethyl-but-1-enyl)-phenol (168) (Scheme 68, entry 3). Applying the conditions above to 3,3-dimethyl-butyne (**4**) (0.12 mL, 1 mmol) and 2-bromophenol (0.39 mL, 1.5 mmol) gave a

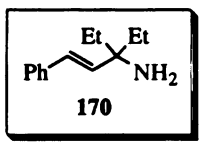
residue that was purified by flash chromatography [silica; pentane] to afford (*E*)-2-(3,3-dimethyl-but-1-enyl)-phenol (**168**) (120 mg, 86%) as an oil. Spectroscopic data were consistent with those reported earlier.[201]



Preparation of (*E*,*E*)-(5,5-dimethyl-hexa-1,3-dienyl)-benzene (5) (Scheme 68, entry 4). Applying the conditions above to 3,3-dimethyl-butyne (**4**) (0.12 mL, 1 mmol) and *E*-bromostyrene (0.19 mL, 1.5 mmol) gave a residue which was purified by flash chromatography [silica; pentane] to afford (*E*,*E*)-(5,5-dimethyl-hexa-1,3-dienyl)-benzene (**5**) (169 mg, 91%) as an oil. For spectroscopic data see page 109-110.

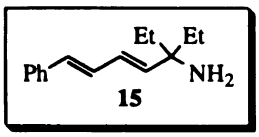


Preparation of (*E*)-1-styryl-cyclohexanol (169) (Scheme 68, entry 5). Applying the conditions above to 1-ethynyl-1-cyclohexanol (**6**) 0.124 g, 1 mmol) and bromobenzene (0.16 mL, 1.5 mmol) gave a residue, which was purified by flash chromatography [silica; 90:10 pentane/EtOAc] to afford of (*E*)-1-styryl-cyclohexanol (**169**) (115 mg, 57%) as an oil. Spectroscopic data were consistent with those reported earlier.[202]



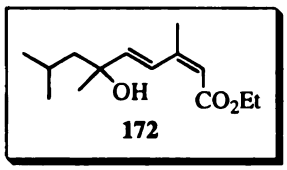
Preparation of (*E*)-1,1-diethyl-3-phenyl-allylamine (170) (Scheme 68, entry 6). Applying the conditions above to 1,1-diethylpropargylamine (**14**) (0.11 g, 1 mmol) and bromobenzene (0.16 mL, 1.5 mmol) gave a residue which was purified by flash chromatography [silica; 50:50 pentane/EtOAc] to afford (*E*)-1,1-diethyl-3-phenyl-allylamine (**170**) (170 mg, 90%) as an oil. IR (neat) 3368 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 7.4 Hz, 3 H), 0.91 (d, J = 7.4 Hz, 3 H), 1.33 (br s, 2 H), 1.56 (qd, J = 2.5, 7.4 Hz, 4 H), 6.16 (d, J = 16.2 Hz, 1 H), 6.47 (d, J = 16.2 Hz, 1 H), 7.17-7.42 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.0,

34.1, 56.3, 126.1, 127.0, 127.3, 128.5, 137.4, 137.7; HRMS (EI) *m/z* 189.1517 [(M+); calcd. for $C_{13}H_{19}N$ 189.1519].



15

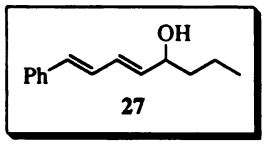
Preparation of (2*E*,4*E*)-1,1-diethyl-5-phenyl-penta-2,4-dienylamine (15) (Scheme 68, entry 7). Applying the conditions above to 1,1-diethylpropargylamine (**14**) (0.11 g, 1 mmol) and (*E*)-β-bromostyrene (0.19 mL, 1.5 mmol), but only irradiating in the presence of the electrophile for 5 minute, gave a residue which was purified by flash chromatography [silica; 50:50 pentane/EtOAc] to afford (2*E*,4*E*)-1,1-diethyl-5-phenyl-penta-2,4-dienylamine (**15**) (175 mg, 81%) as an oil. For spectroscopic data see page 112-113.



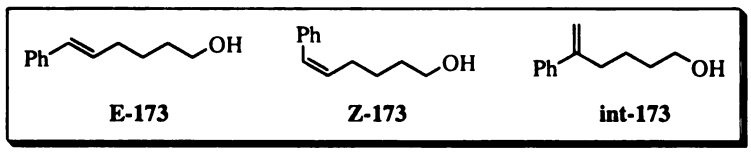
172

Preparation of (2*Z*,4*E*)-6-hydroxy-3,6,8-trimethyl-nona-2,4-dienoic acid ethyl ester (172) (Scheme 68, entry 8). Applying the conditions above to 3,5-dimethyl-but-1-yn-3-ol (**12**) (0.15 mL, 1 mmol) and *Z*-ethyl-3-iodo-2-butenoate (**171**) (0.36 g, 1.5 mmol; prepared according to Chalcat, J. *C. C. R. Acad. Sc. Paris (Serie C)* **1971**, 763-765), but only irradiating in the presence of the electrophile for 5 minutes, gave a residue which was purified by flash chromatography [silica; 90:10 pentane/EtOAc] to afford (2*Z*,4*E*)-6-hydroxy-3,6,8-trimethyl-nona-2,4-dienoic acid ethyl ester (**172**) (169 mg, 81%) as an oil. IR (neat) 3472, 1697, 1638, 1603, 1234, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 6.8 Hz, 3 H,), 0.91 (d, *J* = 6.8 Hz, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.32 (s, 3 H), 1.50 (dd, *J* = 5.8, 2.2 Hz, 2 H), 1.72 (t, *J* = 6.6 Hz, 1 H), 1.88 (br s, 1 H), 1.97 (d, *J* = 1.2 Hz, 3 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 5.65 (s, 1 H), 6.15 (d, *J* = 16.2 Hz, 1 H), 7.66 (d, *J* = 16.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 21.0, 24.3, 24.4, 24.5, 28.6, 51.1, 59.7, 73.7, 117.3,

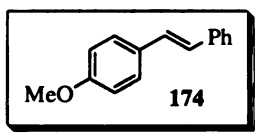
124.0, 144.6, 150.4, 166.2; LRMS (EI) m/z 223.4 (M^+–OH), 197.3, 183.2, 139.2, 137.2, 109.1 (100), 95.1.



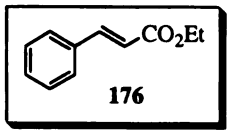
Preparation of (*E*,*E*)-8-phenyl-octa-5,7-dien-4-ol (27) (Scheme 68, entry 9). Applying the conditions above to 1-hexyn-3-ol (**26**) (0.12 mL, 1 mmol) and (*E*)-β-bromostyrene (0.19 mL, 1.5 mmol) gave a residue which was purified by flash chromatography [silica; 90:10 pentane/EtOAc] to afford 8-phenyl-octa-5*E*,7*E*-dien-4-ol (**27**) (112 mg, 55%) as an oil. For spectroscopic data see page 133-134.



Preparation of (*E*+*Z*) 6-phenyl-hex-5-en-1-ol (173) (Scheme 68, entry 10). Applying the conditions above to 5-hexyn-1-ol (**51**) (0.11 mL, 1 mmol) and bromobenzene (0.16 mL, 1.5 mmol) gave a residue that was purified by flash chromatography [silica; 90:10 pentane/EtOAc) to afford a 14:1.6:1 mixture of (*E*)-6-phenyl-hex-5-en-1-ol (**E-173**),[203] (*Z*)-6-phenyl-hex-5-en-1-ol (**Z-173**),[203] and 5-phenyl-hex-5-en-1-ol (**int-173**)[204] (90 mg, 57%). Spectroscopic data were consistent with those reported in the literature.

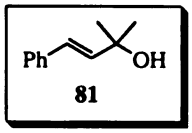


Preparation of (*E*)-(4-methoxyphenyl)-2-phenylethylene (174) (Scheme 68, entry 11). Applying the conditions above to phenyl acetylene (**73**) (0.1 mL, 1 mmol) and *p*-bromoanisole (0.19 mL, 1.5 mmol) gave a residue which was purified by flash chromatography [silica; pentane] to afford of (*E*)-(4-methoxyphenyl)-2-phenylethylene[205] (**174**) (180 mg, 86%) as a white solid. Spectroscopic data were consistent with those reported earlier.



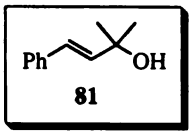
176

Preparation of (*E*)-3-phenyl-acrylic acid methyl ester (176) (Scheme 68, entry 12). Applying the conditions above to methyl propiolate (**175**) (0.08 mL, 1 mmol) and bromobenzene (0.16 mL, 1.5 mmol) gave a residue, which was purified by flash chromatography [silica; 99:1 pentane/EtOAc] to afford of (*E*)-3-phenyl-acrylic acid methyl ester (**176**) (130 mg, 80%) as an oil. The product was identical to an authentic sample (Aldrich).



81

Procedure for a one pot hydrostannlyation/Stille coupling using $Pd(OAc)_2$ and phosphites. Preparation of (*E*)-2-methyl-4-phenyl-but-3-en-2-ol (81) (Scheme 69, reaction 1). To a thick walled Pyrex tube containing to 5 mL THF were added $Pd(OAc)_2$ (0.01 mmol, 2.2 mg), P(O-2,4-*t*-Bu-$C_6H_3)_3$ (0.10 mmol, 65 mg), 2-methyl-3-butyn-2-ol (**1**) (1 mmol, 0.10 mL), Bu_3SnCl (1.2 mmol, 0.33 mL), PMHS (1.5 mmol, 90 mg), KF (3.0 mmol, 0.1743 g), 1 mL H_2O, and catalytic TBAF (1 drop of a 1M THF solution). The reaction was closed, placed in a 250 mL beaker set in the center of a domestic microwave (glass turntable removed) and heated for 3 minutes at 140W (20% power setting on a 700W microwave oven). After cooling, TLC showed the hydrostannation reaction to be complete. Bromobenzene (1.5 mmol, 0.16 mL) was then added and reaction heated for another 5 min. After repeated heating, the reaction did not proceed further. A saturated aqueous solution of KF (2 mL) was added and the mixture stirred for 30 min. The phases were separated and the organics were combined, washed with brine, dried over $MgSO_4$, filtered and, concentrated. The resulting residue was purified by flash chromatography [silica gel; 90:10 pentane/EtOAc, 1% TEA] to afford of (*E*)-2-methyl-4-tributylstannanyl-but-3-en-2-ol (**81**) (353 mg, 94%) as an oil. For spectroscopic data see page 167.

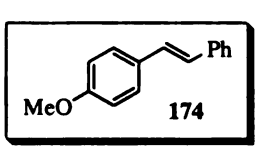


81

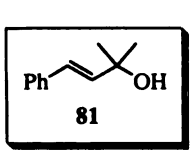
Procedure for a one-pot hydrostannation/Stille coupling using $PdCl_2$/phosphites. Preparation of *E*-2-methyl-4-phenyl-but-3-en-2-ol (81) (Scheme 69, reaction 2). To a thick walled pyrex tube containing to 5 mL THF were added $PdCl_2$ (0.01 mmol, 1.8 mg), P(O-2,4-*t*-Bu-$C_6H_3)_3$ (0.10 mmol, 65 mg), 2-methyl-3-butyn-2-ol (**1**) (1 mmol, 0.10 mL), Bu_3SnCl (1.2 mmol, 0.33 mL), PMHS (1.5 mmol, 90 mg), KF (3.0 mmol, 0.1743 g), 1 mL H_2O, and catalytic TBAF (1 drop of a 1M THF solution). The reaction was closed, placed in a 250 mL beaker set in the center of a domestic microwave (glass turntable removed) and heated for 3 minutes at 140W (20% power setting on a 700W microwave oven). After cooling, TLC showed the hydrostannation reaction to be complete. Bromobenzene (1.5 mmol, 0.16 mL) was then added and reaction heated for another 5 min. After 10 min, reaction was complete. A saturated aqueous solution of KF (2 mL) was added and the mixture stirred for 30 min. The phases were separated and the organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash chromatography [silica gel; 90:10 pentane/EtOAc, 1% TEA] to afford of (*E*)-2-methyl-4-phenyl-but-3-en-2-ol[206] (**81**) (145 mg, 89%) as an oil. For spectroscopic data see page 167.

General procedure for the one-pot free radical hydrostannation/palladium catalyzed Stille coupling (Method A). Preparation of (*E*)-2-methyl-4-phenyl-but-3-en-2-ol (81) (Scheme 70, entry 1). To a thick walled Pyrex tube containing 5 mL THF were added AIBN (2 mg), 2-methyl-3-butyn-2-ol (**1**) (0.10 mL, 1 mmol), Bu_3SnCl (0.33 mL, 1.2 mmol), PMHS (90 mg, 1.5 mmol), KF (0.1743 g, 3.0 mmol), 1 mL H_2O, and catalytic TBAF (1 drop of a 1M THF solution). The reaction was closed, placed in a 250 mL

beaker set in the center of a domestic microwave (glass turntable removed) and heated for 3 minutes at 140 W (20% power setting on a 700 W microwave oven). After being allowed to air cool for 10 min, $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) and bromobenzene (0.16 mL, 1.5 mmol) were added and the sealed tube was irradiated at 140 W for 5 minutes. After cooling the reaction, TLC showed the reaction to be incomplete. A third portion of $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) was added and the sealed tube was again irradiated at 140 W for another 5 minutes. After cooling, TLC showed the reaction to be complete. The reaction was poured into 10% ammonium hydroxide (25 mL), ether was added (25 mL) and the mixture stirred for 30 min. The phases were separated and the organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash chromatography [silica gel; 90:10 pentane/EtOAc, 1% TEA] to afford a 20:1:1 mixture of (*E*)-2-methyl-4-phenyl-but-3-en-2-ol (**E-81**),[206] (*Z*)-2-methyl-4-phenyl-but-3-en-2-ol (**Z-81**),[206] and 2-methyl-3-phenyl-but-3-en-2-ol (**81int**)[207] (140 mg, 86%), which gave spectroscopic data consistent with those reported earlier.

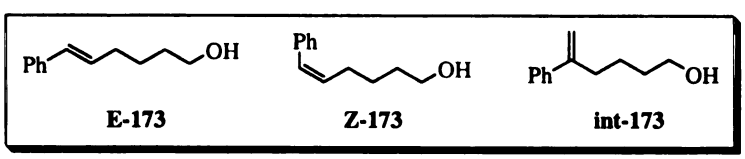


Preparation of (*E*)-(4-methoxyphenyl)-2-phenylethylene (174) (Scheme 70, entry 2). Applying the conditions above to phenyl acetylene (**73**) (0.1 mL, 1 mmol) and *p*-bromoanisole (0.19 mL, 1.5 mmol) gave a residue, which was purified by flash chromatography [silica; pentane] to afford (*E*)-(4-methoxyphenyl)-2-phenylethylene (**174**) (178 mg, 85%) as a white solid. Spectroscopic data were consistent with those reported earlier.[205]



General procedure for the one-pot free radical hydrostannation/palladium catalyzed Stille coupling (Method B).

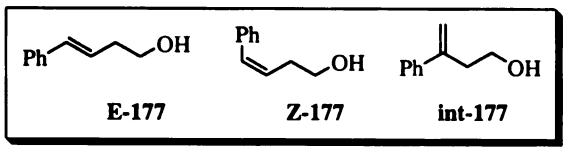
Preparation of (*E*)-2-methyl-4-phenyl-but-3-en-2-ol (81) (Scheme 70, entry 5). To a thick walled Pyrex tube containing 5 mL THF were added AIBN (2 mg), 2-methyl-3-butyn-2-ol (**1**) (0.10 mL, 1 mmol), Bu_3SnH (0.32 mL, 1.2 mmol), 1 mL H_2O, and catalytic TBAF (1 drop of a 1M THF solution). The reaction was closed, placed in a 250 mL beaker placed in the center of a domestic microwave (glass turntable removed) and heated for 3 minutes at 140 W (20% power setting on a 700 W microwave oven). After being allowed to air cool for 10 min, $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) and bromobenzene (0.16 mL, 1.5 mmol) were added and the sealed tube was irradiated at 140 W for 5 minutes. After cooling, the reaction was checked by TLC before a third portion of $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) was added and the reaction was again irradiated at 140 W for another 5 minutes. After cooling, TLC showed the reaction to be complete. The reaction was then poured into 10% ammonium hydroxide (25 mL), ether was added (25 mL and the mixture stirred for 30 min. The phases were separated and the organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash chromatography [silica gel; 90:10 pentane/EtOAc, 1% TEA] to afford a 23:1 (*E*/*Z*) mixture of 3-methyl-1-phenyl-but-1-en-3-ol (**81**) (128 mg, 79%). For spectroscopic data see page 167.



E-173 **Z-173** **int-173**

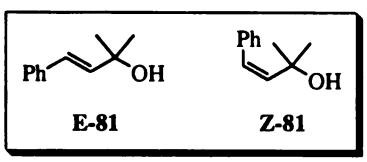
Preparation of (*E*)-6-phenyl-hex-5-en-1-ol (173) (Scheme 70, entry 3). Applying the conditions above to 5-hexyn-1-ol (**51**) (0.11 mL, 1 mmol) and bromobenzene (0.16 mL, 1.5 mmol) gave a residue that was purified by flash chromatography [silica; 90:10 pentane/EtOAc] to afford a 31:7:1 mixture of (*E*)-6-

phenyl-hex-5-en-1-ol (**E-173**), (*Z*)-6-phenyl-hex-5-en-1-ol (**Z-173**), and 5-phenyl-hex-5-en-1-ol (**int-173**) (84 mg, 48%). For spectroscopic data see page 239.



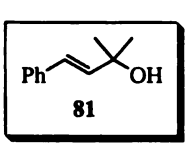
E-177 Z-177 int-177

Preparation of (*E*)-4-phenyl-but-3-en-1-ol (177) (Scheme 70, entry 4). Applying the conditions above to 3-butyn-1-ol (**30**) (0.07 mL, 1 mmol) and bromobenzene (0.16 mL, 1.5 mmol) gave a residue that was purified by flash chromatography [silica; 90:10 pentane/EtOAc] to afford a 27:4:1 *E*/*Z*/Int mixture of (*E*)-1-phenyl-but-1-en-4-ol (**E-177**),[208] (*Z*)-1-phenyl-but-1-en-4-ol (**Z-177**),[208] and 2-phenyl-but-1-en-4-ol (**int-177**)[209] (65 mg, 46%). Spectroscopic data obtained were consistent with those reported earlier.



E-81 Z-81

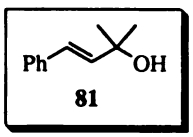
Procedure for the microwave assisted cross coupling of pure *Z*-vinylstannane with bromobenzene. Preparation of (*E*) and (*Z*)-2-methyl-4-phenylbut-3-en-2-ol (81) (Scheme 71, reaction 1). $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) was placed in a pyrex pressure tube containing THF (5 mL) and water (1 mL). Bromobenzene (0.16 mL, 1.5 mmol) and (*Z*)-4-(tributylstannyl)-2-methylbut-3-en-2-ol (**2c**) (375 mg, 1 mmol) were added and the tube was sealed. The sealed tube was then irradiated in a microwave for 10 min at 140 W. The reaction was then extracted with ether and the phases were separated. The organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 90:10 hexane/EtOAc] to afford a 1:1.72 (*E*/*Z*) mixture of 2-methyl-4-phenylbut-3-en-2-ol (**81**) (110 mg, 68%) as an oil. See above for spectroscopic data.



81

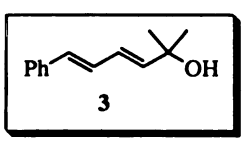
Procedure for the microwave assisted cross coupling of pure (*E*)-vinylstannane with bromobenzene. Preparation of (*E*)-2-methyl-4-

phenylbut-3-en-2-ol (81) (Scheme 71, reaction 3). Applying the above conditions using (*E*)-4-(tributylstannyl)-2-methylbut-3-en-2-ol (**2a**) (375 mg, 1 mmol) after column chromatography [silica; 90:10 hexane/EtOAc] afforded a (*E*)-2-methyl-4-phenylbut-3-en-2-ol (**81**) (106 mg, 65%) as an oil.



81

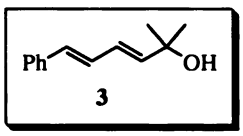
Revised procedure to a microwave assisted one-pot hydrostannation/Stille coupling. Preparation of 2-methyl-4-phenyl-but-3-yn-2-ol (81) (Scheme 73). A Teflon tube was charged with THF (5 mL) followed by $Pd(PPh_3)_4$ (12 mg, 0.01 mmol), 2-methyl-3-butyn-2-ol (**1**) (0.10 mL, 1.0 mmol), Bu_3SnCl (0.33 mL, 1.2 mmol), KF (175 mg, 3.0 mmol), H_2O (1.0 mL) and PMHS (0.09 mL, 1.5 mmol). The Teflon tube was sealed and placed in the microwave (Panasonic with inverter tech) and was heated for 2 min at 130 W, 10%). After cooling, bromobenzene (0.16 mL, 1.5 mmol) was added and the tube was sealed and heat for 2 min increments until complete by TLC analysis (7-8 increments, 15 min total time). Once complete the reaction was diluted with Et_2O and washed with brine. The organics were then dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel, 90:10 hexanes/EtOAc] to afford 2-methyl-4-phenyl-but-3-yn-2-ol (**81**) (152 mg, 94%) as an oil. For spectroscopic data page 167.



3

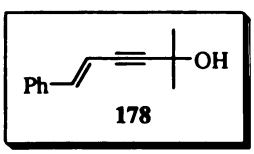
Representative procedure for the classic Stille coupling. Preparation of (3*E*,5*E*)-2-methyl-6-phenylhexa-3,5-dien-2-ol (3) (Scheme 74, reaction 1). Pd_2dba_3 (18.3 mg, 0.02 mmol) and $AsPh_3$ (24.5 mg, 0.08 mmol) were added to a flask containing NMP (~5 mL). This mixture was stirred at 25 °C for 15 min. At this time (*E*)-β-bromostyrene (201 mg, 1.1 mmol) and (*E*)-2-methyl-4-(tributylstannyl)-3-buten-2-ol (**2a**) (375 mg, 1.0 mmol) were added and the flask was

placed into a preheated oil bath (~50 °C) and then was allowed to stir overnight (~25 h). The reaction was then cooled to room temperature and water was added. This mixture was extracted with Et_2O (3x). The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 90:10 hexane/EtOAc] to afford (3*E*,5*E*)-2-methyl-6-phenylhexa-3,5-dien-2-ol (**3**) (101 mg, 54%) as an oil. For spectroscopic data see page 108-109.



3

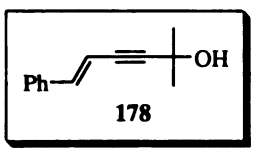
Representative procedure for the classic Stille coupling using co-catalytic CuI. Preparation of (3*E*,5*E*)-2-methyl-6-phenylhexa-3,5-dien-2-ol (3) (Scheme 74, reaction 2). Pd_2dba_3 (18.3 mg, 0.02 mmol) and $AsPh_3$ (24.5 mg, 0.08 mmol) were added to a flask containing NMP (~5 mL). This mixture was stirred at 25 °C for 15 min. At this time (*E*)-β-bromostyrene (201 mg, 1.1 mmol) and (*E*)-2-methyl-4-(tributylstannyl)-3-buten-2-ol (**2a**) (375 mg, 1.0 mmol) were added followed by CuI (19 mg, 0.10 mmol) and the flask was placed into a preheated oil bath (~50 °C) and then was allowed to stir overnight (~13 h). The reaction was then cooled to room temperature and water was added. This mixture was extracted with Et_2O (3x). The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 90:10 hexane/EtOAc] to afford (3*E*,5*E*)-2-methyl-6-phenylhexa-3,5-dien-2-ol (**3**) (140 mg, 75%) as an oil. For spectroscopic data see page 108-109.



178

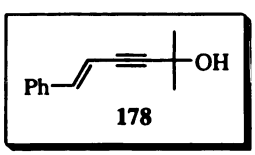
Procedure for the preparation of 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol; use of Cu(I) cocatalyst (178) (Scheme 75, entry 2). THF (30 mL) was added to a flask followed by 2-methyl-3-butyn-2-ol (**3**) (2 mmol, 0.20 mL), Bu_3SnCl (33 mg, 0.10 mmol), PMHS (3.0 mmol, 0.24 mL), CsF (10 mmol, 1.52 g),

$PdCl_2(PPh_3)_2$ (0.04 mmol, 28 mg), TBAF (1 drop), *E*-β-bromostyrene (3.0 mmol, 0.5491 g) and CuI (4.0 mmol, 762 mg). The reaction was allowed to stir at room temperature until complete by TLC (3 h). 3M NaOH was then added and the mixture was stirred for 20 min. The mixture was then filtered thru Celite (with a coarse filter) and diluted with H_2O and Et_2O. The phases were separated and the aqueous phase was extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; pentane/ EtOAc 90/10 1% TEA] to afford 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**178**) (370 mg, 99%) as an oil.[210] IR (neat) 3354 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 6 H), 2.71 (br s, 1 H), 6.18 (d, J = 16.5 Hz, 1 H), 6.95 (d, J = 16.5 Hz, 1 H), 7.25-7.42 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 136.0, 128.6, 128.5, 126.1, 107.6, 96.1, 81.1, 65.4, 31.3 HRMS (EI) *m/z* 186.1043 [(M^+). calcd. for $C_{13}H_{14}O$ 186.1045].



178

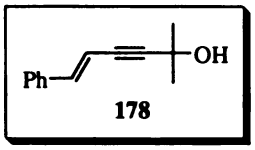
Procedure for the use of co-catalytic CuCl. Preparation of 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (178) (Scheme 75, entry 3). Applying the above conditions using CuCl (396 mg, 4 mmol) after 3 h and column chromatography [silica gel; 90:10 pentane/EtOAc, 1% TEA] afforded 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**178**) (369 mg, 99%) as an oil. For spectroscopic data see page 247.



178

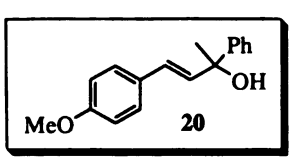
Procedure for the use of co-catalytic CuTC. Preparation of 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (178) (Scheme 75, entry 4). Applying the above conditions using CuTC (760 mg, 4 mmol) after

45 min. and column chromatography [silica gel; 90:10 pentane/EtOAc, 1% TEA] afforded 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**178**) (371 mg, 99%) as an oil. For spectroscopic data see page 247.



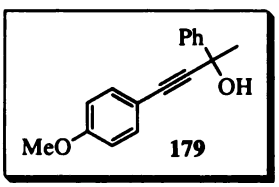
Procedure for the use of co-catalytic CuTC in THF/NMP (1:1) at 25 °C. Preparation of 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (178) (Scheme 75, entry 5). Applying the above conditions using CuTC (760 mg, 4 mmol) and Me_3SnCl (0.10 mL of a 1M solution in THF, 0.10 mmol) after 45 min. and column chromatography [silica; 90:10 pentane/EtOAc, 1% TEA] afforded 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**178**) (371 mg, 99%) as an oil. For spectroscopic data see page 247.

Preparation of Copper (I) thiophene-2-carboxylate (CuTC).[211] 2-Thiophene carboxylic acid (100 g, 780 mmol), Cu_2O (28 g, 196 mmol) and toluene (300 mL) were added to a 500 mL three-neck round bottom flask. The flask was outfitted with a Dean-Stark trap and condenser. The mixture was then allowed to reflux for 3 days with azeotropic removal of water. The yellow-brown suspension was then cooled to ~60 °C and the product were collected on a glass-sintered funnel (D-frit). Under a stream of nitrogen, the filter cake was washed with MeOH (300 mL), then with Et_2O until the filtrate was colorless and then with hexanes (75 mL). The product was dried under a flow of N_2 and then was transferred to a flask and dried under vacuum. The procedure afforded CuTC (70 g, 94%) as a light brown powder. CuTC can now be purchased from Frontier Scientific (Catalog #: C8422).



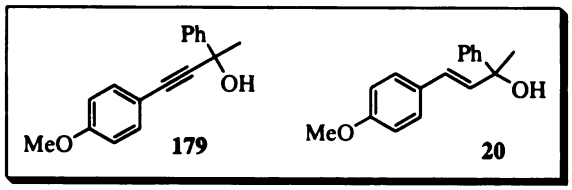
An attempt to use Bu_3SnF and KOAc. Procedure for the preparation of 4-(4-methoxy-phenyl)-2-phenyl-but-3-en-2-ol

(20) (Scheme 76). $Pd(PPh_3)_4$ (0.04 mmol, 0.0462 g), 2-phenyl-3-butyn-2-ol (**8**) (2.0 mmol, 0.2924 g), Bu_3SnF (0.10 mmol, 31 mg), PMHS (3.0 mmol, 0.18 mL), TBAF (2 drops), iodoanisole (3.0 mmol, 0.7021 g) and KOAc (6.0 mmol, 0.60 g) were added to 10 mL of THF. This mixture was heated to reflux and stirred for 15 hours. The reaction was then diluted with 5 mL of 10% NH_4OH and stirred for 20 minutes. The phases were separated and the aqueous phase was extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 80:20 hexanes/EtOAc, 1% TEA] to afford of 4-(4-methoxy-phenyl)-2-phenyl-but-3-en-2-ol (**20**) (135 mg, 29%) as an oil. For spectroscopic data see page 129-130.

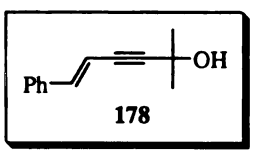


Procedure for the preparation of 6-(4-methoxy-phenyl)-2-phenyl-hex-5-en-3-yn-2-ol (179) (Scheme 77). $Pd(PPh_3)_4$ (0.04 mmol, 0.0462 g), 2-phenyl-3-butyn-2-ol (**8**) (2.0 mmol, 0.2924 g), Bu_3SnF (0.10 mmol, 31 mg), PMHS (3.0 mmol, 0.18 mL), TBAF (2 drops), iodoanisole (3.0 mmol, 0.7021 g), CuI (0.10 mmol, 19 mg), and KOAc (6.0 mmol, 0.60 g) were added to 10 mL of THF. This mixture was heated to reflux and stirred for 15 hours. The reaction was then diluted with 5 mL of 10% NH_4OH and stirred for 20 minuets. The phases were separated and the aqueous phase was extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 80:20 hexanes/EtOAc, 1% TEA] to afford 6-(4-methoxy-phenyl)-2-phenyl-hex-5-en-3-yn-2-ol (**179**) (475 mg, 92%) as an oil. IR (neat) 3372 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 6 H), 2.96 (br s, 1 H), 3.82 (s, 3 H), 6.87 (d, J = 8.9 Hz, 2 H), 7.27-7.50 (m, 5 H), 6.87 (d, J = 7.3 Hz, 2 H); ^{13}C (75 MHz, $CDCl_3$) δ 33.3,

55.2, 70.3, 84.7, 91.1, 113.8, 114.6, 124.9, 127.6, 128.2, 133.1, 145.8, 159.6; HRMS (EI) *m/z* 252.1153 [(M^+), calcd. for $C_{17}H_{16}O_2$ 252.1150].

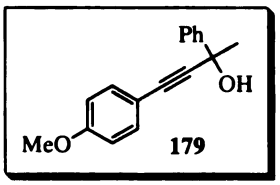


Procedure for the preparation of 6-(4-methoxy-phenyl)-2-phenyl-hex-5-en-3-yn-2-ol (179) (below Scheme 77). $Pd(PPh_3)_4$ (0.04 mmol, 0.0462 g), 2-phenyl-3-butyn-2-ol (**8**) (2.0 mmol, 0.2924 g), Me_3SnF (0.02 mmol, 3.9 mg), PMHS (3.0 mmol, 0.18 mL), TBAF (2 drops), iodoanisole (3.0 mmol, 0.7021 g), CuI (0.10 mmol, 19 mg), and KOAc (6.0 mmol, 0.60 g) were added to 10 mL of THF. This mixture was heated to reflux and stirred for 15 hours. The reaction was then diluted with 5 mL of 10% NH_4OH and stirred for 20 minuets. The phases were separated and the aqueous phase was extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 80:20 Hexanes/ EtOAc, 1% TEA] to afford a 5:1 inseparable mixture of 6-(4-methoxy-phenyl)-2-phenyl-hex-5-en-3-yn-2-ol (**179**) and 4-(4-methoxy-phenyl)-2-phenyl-but-3-en-2-ol (**20**), respectively (444 mg, 88%) as an oil. For spectroscopic data see page 249-250 and 129-130.

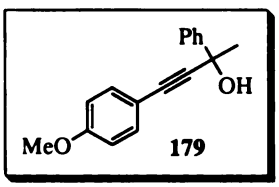


Representative procedure for the TBAF/CuI mediated Sonogashira reaction. Preparation of 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (178) (Table 9, entry 1). To 10 mL of THF in an ACE pressure tube with a Teflon o-ring was added $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (4 mg, .02 mmol), 2-methyl-3-butyn-2-ol (**1**) (0.10 mL, 1.0 mmol), *E*-β-bromostyrene (0.2745 g, 1.5 mmol) and TBAF (1.5 mL, 1.5 mmol). The reaction was stirred at room temperature until complete by TLC (2 h). At that time the reaction was washed with brine, dried over

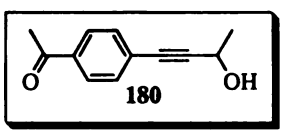
MgSO4, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 80/20 hexane/EtOAc] to afford 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**178**) (175 mg, 94%) as an oil. For spectroscopic data see page 249-250.



Preparation of 4-(4-methoxy-phenyl)-2-phenyl-but-3-yn-2-ol (179) (Table 9, entry 2). Applying the above conditions at 65 °C for 2 h to 2-phenyl-3-butyn-2-ol (**8**) (0.1754g, 1.2 mmol) and *p*-iodoanisole (0.2341 g, 1.0 mmol) after column chromatography [silica gel; 80:20 hexane/EtOAc] afforded 4-(4-methoxy-phenyl)-2-phenyl-but-3-yn-2-ol (**179**) (240 mg, 95%) as an oil. For spectroscopic data see page 249-250.

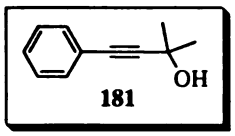


Preparation of 4-(4-methoxy-phenyl)-2-phenyl-but-3-yn-2-ol (179) (Table 9, entry 3). Applying the above conditions at 65 °C for 2 h to 2-phenyl-3-butyn-2-ol (**8**) (0.1754 g, 1.2 mmol) and *p*-bromoanisole (0.1870 g, 1.0 mmol) after column chromatography [silica gel; 80:20 hexane/EtOAc] afforded 4-(4-methoxy-phenyl)-2-phenyl-but-3-yn-2-ol (**179**) (152 mg, 60%) as an oil. For spectroscopic data see page 249-250.



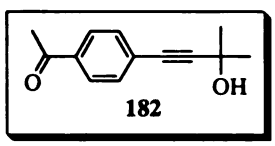
Preparation of 1-(4-(3-hydroxybut-1-ynyl)phenyl)ethanone (180) (Table 9, entry 4). Applying the above conditions at 65 °C for 3 h to 3-butyn-2-ol (**34**) (84 mg, 1.2 mmol) and *p*-bromoacetophenone (199 mg, 1.0 mmol) after column chromatography [silica gel; 75:25 hexane/EtOAc] afforded 1-[4-(3-hydroxybut-1-ynyl)-phenyl]-ethanone (**180**) (184 mg, 98%) a yellow solid (mp = 56-57 °C). IR (KBr) 3356 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (d, J = 6.6 Hz, 3 H), 2.55 (s, 3 H), 3.24 (br s, 1 H), 4.77 (q, J = 5.97, 6.39 Hz, 1 H), 7.40-7.47 (m, 2 H), 7.80-7.87

(m, 2 H); ^{13}C (75 MHz, $CDCl_3$) δ 24.04, 26.46, 58.44, 82.77, 94.53, 127.52, 128.03, 131.56, 136.00, 197.60; HRMS (EI) *m/z* 188.0837 [(M^+), calcd. for $C_{12}H_{12}O_2$ 188.0834].



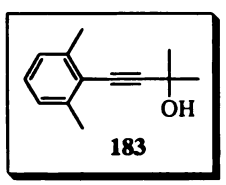
181

Preparation of 2-methyl-4-phenyl-but-3-yn-2-ol (181) (Table 9, entry 5). Applying the above conditions at 65 °C for 4 h to 2-methyl-3-butyn-2-ol (**8**) (0.12 mL, 1.2 mmol) and bromobenzene (0.11 mL, 1.0 mmol) after column chromatography [silica gel; 90:10 hexane/EtOAc] afforded 2-methyl-4-phenyl-but-3-yn-2-ol (**181**) (106 mg, 66%) as an oil.[212]



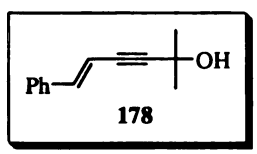
182

Preparation of 1-[4-(3-hydroxy-3-phenyl-but-1-ynyl)-phenyl]-ethanone (182) (Table 9, entry 6). Applying the above conditions at 65 °C for 3 h to 2-methyl-3-butyn-2-ol (**1**) (0.12 mL, 1.2 mmol) and *p*-bromoacetophenone (199 mg, 1.0 mmol) after column chromatography [silica gel; 75:25 hexane/EtOAc] afforded 1-[4-(3-hydroxy-3-phenyl-but-1-ynyl)-phenyl]-ethanone (**182**) (198 mg, 98%) as an oil.[213]



183

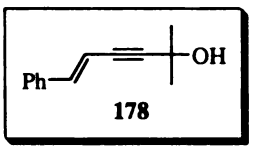
Preparation of 4-(2,6-dimethyl-phenyl)-2-methyl-but-3-yn-2-ol (183) (Table 9, entry 7). Applying the above conditions at 65 °C for 14 h to 2-methyl-3-butyn-2-ol (**1**) (0.12 mL, 1.2 mmol) and 2-bromo-1,3-dimethyl-benzene (0.14 mL, 1.0 mmol) after column chromatography [silica gel; 80:20 hexane/EtOAc] afforded 4-(2,6-dimethyl-phenyl)-2-methyl-but-3-yn-2-ol (**183**) (45 mg, 24%) as an oil.[214]



178

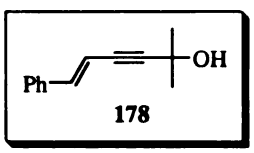
Representative procedure for a Tin-free PMHS/CsF mediated Sonogashira reaction. Preparation of 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (178) (Scheme 79). To 30 mL of NMP was added 2-methyl-3-butyn-2-ol (**1**) (0.10 mL, 1.0 mmol), PMHS (0.12 mL, 2.0 mmol), CsF (0.7595 g, 5.0 mmol),

$PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), TBAF (1 drop of a 1M solution in THF), *E*-β-bromostyrene (0.2745 g, 1.5 mmol), and CuTC (0.38 g, 2.0 mmol) respectively. The reaction was allowed to stir at room temperature for 2 h. When complete the reaction was diluted with Et_2O and washed with H_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 90:10 to 80:20 hexane/EtOAc] to afford 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**178**) (184 mg, 98%) as an oil. For spectroscopic data see page 247.



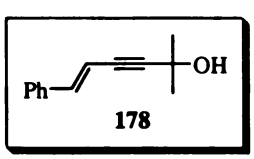
178

Use of only 2 mol% CuTC. Preparation of 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (178) (Table 10, entry 2). Applying the above conditions with CuTC (3.8 mg, 0.02 mmol) after 24 h at 25 °C and column chromatography [silica gel; 90:10 to 80:20 hexane/EtOAc] afforded 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**178**) (4 mg, 2%) as an oil. For spectroscopic data see page 247.



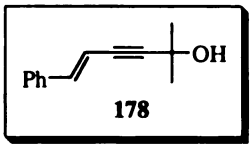
178

Use of only 1.5 eq. of CuCl. Preparation of 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (178) (Table 10, entry 3). Applying the above conditions with CuCl (198 mg, 2.0 mmol) after 2 h at 25 °C and column chromatography [silica gel; 90:10 to 80:20 hexane/EtOAc] afforded 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**178**) (179 mg, 95%) as an oil. For spectroscopic data see page 247.



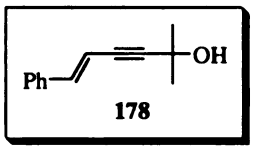
178

Use of only 2 mol% of CuCl. Preparation of 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (Table 10, entry 4). Applying the above conditions with CuCl (2.0 mg, 0.02 mmol) after 24 h at 25 °C and column chromatography [silica gel; 90:10 to 80:20 hexane/EtOAc] afforded 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (4.0 mg, 2%) as an oil. For spectroscopic data see page 247.



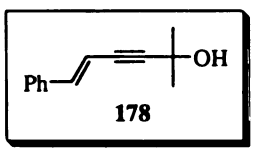
178

Use of only 2 mol% of CuI or 1.5 eq. of CuI. Preparation of 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (178) (Table 10, entry 5). Applying the above conditions with CuI (3.8 mg, 0.02 mmol) after 24 h at 25 °C and column chromatography [silica gel; 90:10 to 80:20 hexane/EtOAc] afforded 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**178**) (2.0 mg, 1%) as an oil For spectroscopic data see page 247.



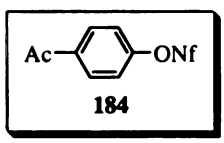
178

Use of only 2 mol% of CuBr or 1.5 eq. of CuBr. Preparation of 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (178) (Table 10, entry 6). Applying the above conditions with CuBr (2.9 mg, 0.02 mmol) after 24 h at 25 °C and column chromatography [silica gel; 90:10 to 80:20 hexane/EtOAc] afforded 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**178**) (1.9 mg, 1%) as an oil. For spectroscopic data see page 247.



178

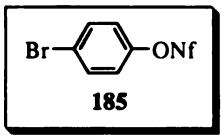
Use of only 2 mol% of CuCN or 1.5 eq. of CuCN. Preparation of 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (178) (Table 10, entry 7). Applying the above conditions with CuCN (3.8 mg, 0.02 mmol) after 24 h at 25 °C and column chromatography [silica gel; 90:10 to 80:20 hexane/EtOAc] afforded 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**178**) (1.2 mg, <1%) as an oil. For spectroscopic data see page 247.



184

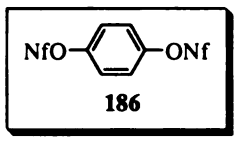
Representative procedure for the formation of aryl nonaflates. Preparation of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (184) (Scheme 80, entry 1). To a solution of *p*-hydroxyacetophenone (6.81 g, 50 mmol) and Et_3N (8.36 mL, 60 mmol) in CH_2Cl_2 (300 mL) at room temperature was added 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonyl

fluoride (10.8 mL, 60 mmol) in a dropwise fashion. The resulting solution was stirred at room temperature for 10 h. Once complete the reaction was washed with H_2O (2X), brine (2X), dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 80:20 hexane/EtOAc] to afford 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**184**) (19.62 g, 94%) as a white solid (mp = 42 °C, lit. mp = 41-42 °C).[215]



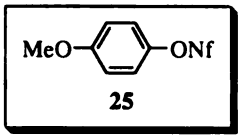
185

Preparation of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-bromo-phenyl ester (185) (Scheme 80, entry 2). Applying the above conditions for 12 h using *p*-bromophenol (3.46 g, 20 mmol) afforded after column chromatography [silica gel; 90:10 hexane/EtOAc] 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-bromo-phenyl ester (**185**) (4.61 g, 51%) as a clear oil. IR (neat) 1176 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15-7.19 (m, 2 H), 7.55-7.60 (m, 2 H); ^{13}C (125 MHz, $CDCl_3$) δ 109.88, 114.90, 115.94, 118.24, 122.00, 123.12, 133.44, 148.78; HRMS (EI) *m/z* 453.8921 [(M^+), calcd. for $C_{10}H_4BrF_9O_3S$ 453.8927].



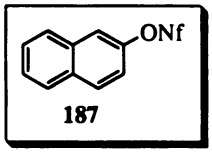
186

Preparation of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-(nonafluorobutane-1-sulfonyloxy)-phenyl ester (186) (Scheme 80, entry 3). Applying the above conditions for 18 h using hydroquinone (1.10 g, 10 mmol) afforded after column chromatography [silica gel; 90:10 hexane/EtOAc] 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-(nonafluorobutane-1-sulfonyloxy)-phenyl ester (**186**) (6.41 g, 95%) as a purple solid. Mp = 66-67 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 4 H); ^{13}C (75 MHz, $CDCl_3$) δ 123.4, 148.6; HRMS (EI) *m/z* 673.9162 [(M^+), calcd. for $C_{14}H_4F_{18}O_6S_2$ 673.9167].



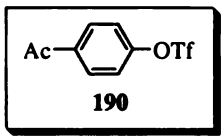
25

Preparation of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-methoxy-phenyl ester (25) (Scheme 80, entry 4). Applying the above conditions for 2 h to *p*-methoxyphenol (1.24 g, 10 mmol) afforded after column chromatography [silica gel; 95:5 pentane/EtOAc] of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-methoxy-phenyl ester (**25**) (3.28 g, 81%) as a clear oil.[216]



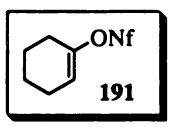
187

Preparation of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid naphthalen-2-yl ester (187) (Scheme 80, entry 5). Applying the above conditions to 2-naphthol (2.88 g, 20 mmol) afforded after column chromatography [silica gel; 95:5 pentane/EtOAc] 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid naphthalen-2-yl ester (**187**) (8.35 g, 98%) as an oil.[217]



190

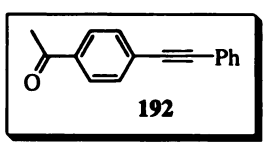
Preparation of trifluoromethanesulfonic acid 4-acetyl-phenyl ester (190). Tf_2O (5.61 mL, 33.3 mmol) was slowly added to a solution of 4-hydroxyacetophenone (4.08 g, 30 mmol) in 15 mL of pyridine at 0 °C. This mixture was then allowed to warm to 25 °C and stirred for 1 day. The resulting mixture was poured into water and extracted with Et_2O. The organics were washed with water, 10% HCl, water, and brine, dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 95:5 hexane/EtOAc] to afford trifluoromethanesulfonic acid 4-acetyl-phenyl ester (**190**)[218] (5.60 g , 70 %) as a colorless liquid.



191

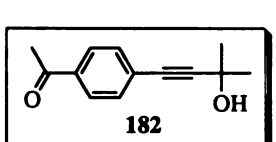
Preparation of 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid cyclohex-1-enyl ester (191). A solution of *n*-BuLi (13.13 mL of a 1.6 M solution in hexanes, 21 mmol) was added at –78 °C to a solution of *i*-Pr_2NH (2.94 mL, 21 mmol) in THF (300 mL). After 1h at –78 °C, cyclohexanone (2.07 mL, 20 mmol) was

added and stirring continued for 1 h –78 °C. Neat NfF (7.2 mL, 40 mmol) was added dropwise at –78 °C and after the addition; the reaction was allowed to warm to room temperature over 8 h. The reaction was then poured into a sat. aq. solution of NH_4Cl. The aqueous phase was extracted with EtOAc and the combined organics were dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by distillation (120 °C at 18 mmHg) to afford 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid cyclohex-1-enyl ester (**191**) (6.49 g, 86%) as a clear liquid.[219]



192

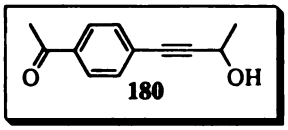
Representative procedure for PMHS-Sonogashira coupling of aryl/ and vinyl nonaflates/triflates. Preparation of 1-(4-phenylethynyl-phenyl)-ethanone (192) (Table 11, entry 1). To 30 mL of NMP was added phenylacetylene (**73**) (0.11 mL, 1.0 mmol), PMHS (0.12 mL, 2 mmol), CsF (0.7595 g, 5.0 mmol), CuCl (.0050 g, 0.05 mmol), 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**184**) (0.6273 g, 1.5 mmol), and $PdCl_2(PPh_3)_2$ (0.0350 g, 0.05 mmol). This mixture was stirred at room temperature until complete by TLC analysis (90/10 Hex/EtOAc). Once complete (4 h), the reaction was diluted with Et_2O and then washed with sat. aq. NH_4Cl. The phases were then separated and the combined organics were washed with H_2O (2X), brine (2X), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 90:10 hexane/EtOAc] to afford 1-(4-phenylethynyl-phenyl)-ethanone (**192**) (210 mg, 96%) as a light yellow solid (mp = 95 °C, lit mp 94-96 °C).[220]



182

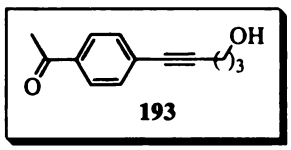
Preparation of 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (182) (Table 11, entry 2). Applying the above conditions at room temperature for 5 h to 2-methyl-3-butyn-2-ol (**1**) (0.10 mL, 1.0 mmol)

and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**184**) (0.6273 g, 1.5 mmol) after column chromatography [silica gel; 75:25 hexanes/EtOAc] afforded 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone[221] (**182**) (170 mg, 96%) as an oil. For spectroscopic data see page 252.



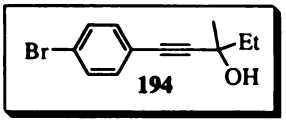
180

Preparation of 1-[4-(3-hydroxy-but-1-ynyl)-phenyl]-ethanone (180) (Table 11, entry 3). Applying the above conditions at room temperature for 5 h to 3-butyn-2-ol (**34**) (0.08 mL, 1.0 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**184**) (0.6273 g, 1.5 mmol) after column chromatography [silica gel; 70:30 hexanes/EtOAc] afforded 1-[4-(3-hydroxy-but-1-ynyl)-phenyl]-ethanone (**180**) (158 mg, 84%) as a yellow solid (mp = 56-57 °C). For spectroscopic data see page 251-252.



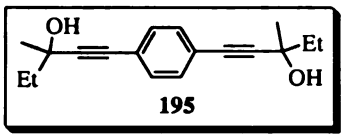
193

Preparation of 1-[4-(5-hydroxy-pent-1-ynyl)-phenyl]-ethanone (193) (Table 11, entry 4). Applying the above conditions to 4-pentyn-2-ol (**79**) (0.10 mL, 1.0 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**184**) (0.6273 g, 1.5 mmol) afforded after column chromatography [silica gel; 70:30 hexane/EtOAc] 1-[4-(3-hydroxy-but-1-ynyl)-phenyl]-ethanone (**193**) (175 mg, 86%) as an orange oil. IR (neat) 3426, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (quin., J = 6.6 Hz, 2 H), 2.40 br s, 1 H), 2.57 (m, 5 H), 3.80 (t, J = 6.18 Hz, 2 H), 7.43 (d, J = 8.24 Hz, 2 H), 7.85 (d, J = 8.17 Hz, 2 H); ^{13}C (75 MHz, $CDCl_3$) δ 15.94, 26.47, 31.13, 61.31, 80.34, 93.34, 128.07, 128.76, 131.52, 135.54, 197.54; HRMS (EI) *m/z* 202.0994 [(M^+), calcd. for $C_{13}H_{14}O_2$ 202.0987].



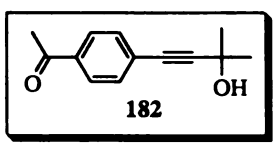
194

Preparation of 1-(4-bromo-phenyl)-3-methyl-pent-1-yn-3-ol (194) (Table 11, entry 5). Applying the above conditions to 3-methyl-pent-1-yn-3-ol (**10**) (0.23 mL, 2.0 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-bromo-phenyl ester (**185**) (1.09 g, 3.0 mmol) afforded after column chromatography [silica gel; 80:20 hexane/EtOAc] 1-(4-bromo-phenyl)-3-methyl-pent-1-yn-3-ol (**194**) (379 mg, 75%) as an oil. IR (neat) 3372 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (t, J = 7.4 Hz, 3 H), 1.55 (s, 3 H), 1.77 (m, 2 H), 2.09 (br s, 1 H), 7.24-7.28 (m, 2 H), 7.40-7.44 (m, 2 H); ^{13}C (125 MHz, $CDCl_3$) δ 9.02, 29.19, 36.56, 69.14, 82.34, 93.83, 121.76, 122.42, 131.48, 133.08; HRMS (EI) *m/z* 252.0150 [(M^+), calcd. for $C_{12}H_{13}BrO$ 252.0154].



195

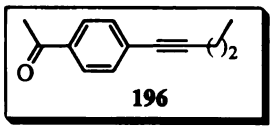
Preparation of 1-[4-(3-hydroxy-3-methyl-pent-1-ynyl)-phenyl]-3-methyl-pent-1-yn-3-ol (195) (Table 11, entry 6). Applying the above conditions to 3-methyl-pent-1-yn-3-ol (**10**) (0.24 mL, 2.1 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-(nonafluorobutane-1-sulfonyloxy)-phenyl ester (**186**) (0.6743 g, 1.0 mmol) afforded after column chromatography [silica gel; 80:20 hexane/EtOAc] 1-[4-(3-hydroxy-3-methyl-pent-1-ynyl)-phenyl]-3-methyl-pent-1-yn-3-ol (**195**) (202 mg, 75%) as a yellow solid. mp=100 °C; IR (KBr) 3367 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (t, J = 7.4 Hz, 3 H), 1.55 (s, 3 H), 1.77 (m, 2 H), 2.15 (br s, 1 H), 7.33 (s, 4 H); ^{13}C (125 MHz, $CDCl_3$) δ 8.94, 29.21, 36.59, 69.14, 82.95, 94.40, 122.64, 131.47; HRMS (EI) *m/z* 270.1620 [(M^+), calcd. for $C_{18}H_{22}O_2$ 270.1615].



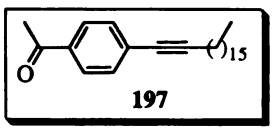
182

Preparation of 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (182) (Table 11, entry 7). Applying the above conditions at room temperature for 5 h to 2-methyl-3-butyn-2-ol (**1**) (0.10 mL, 1.0 mmol)

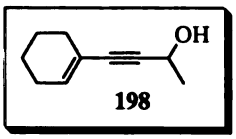
and trifluoromethanesulfonic acid 4-acetyl-phenyl ester (**184**) (0.8046 g, 1.5 mmol) after column chromatography [silica gel; 75:25 hexanes/EtOAc] afforded 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (**182**) (340 mg, 84%) as an oil. For spectroscopic data see page 252.


196

Preparation of 1-(4-pent-1-ynyl-phenyl)-ethanone (196) (Table 11, entry 8). Applying the above conditions at room temperature for 8 h to 1-pentyne (**188**) (0.10 mL, 1.0 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**184**) (0.6273 g, 1.5 mmol) after column chromatography [silica gel; 90:10 hexane/EtOAc] afforded of 1-(4-pent-1-ynyl-phenyl)-ethanone[222] (**196**) (145 mg, 73%) as a light yellow oil.

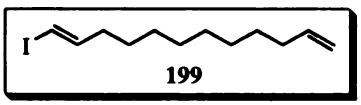

197

Preparation of 1-(4-octadec-1-ynyl-phenyl)-ethanone (194) (Table 11, entry 9). Applying the above conditions at room temperature for 8 h to 1-octadecyne (**189**) (0.2505 g, 1.0 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**184**) (0.6273 g, 1.5 mmol) after column chromatography [silica gel; 90:10 hexanes/EtOAc] afforded 1-(4-octadec-1-ynyl-phenyl)-ethanone (**197**) (349 mg, 95%) as an oil. IR (neat) 1691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.51-1.79 (m, 33 H), 2.63 (s, 3 H), 7.40 (m, 2 H), 8.07 (m, 2 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.11, 22.69, 28.35, 28.93, 29.36, 29.55, 29.64, 29.66, 29.69, 29.71, 31.92, 36.05, 74.23, 146.73; HRMS (EI) *m/z* 368.3079 [(M^+), calcd. for $C_{26}H_{40}O$ 368.3073].


198

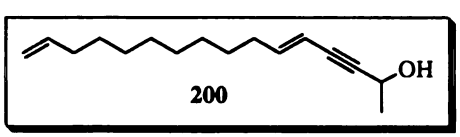
Preparation of 4-cyclohex-1-enyl-but-3-yn-2-ol (198) (Table 11, entry 10). Applying the above conditions at room temperature for 5 h with THF/NMP (1:1; 30 mL) to 3-butyn-2-ol (**34**) (0.24 mL, 2.0 mmol), CuTC (38 mg,

.20 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid cyclohex-1-enyl ester (**191**) (1.14 g, 3.0 mmol) after column chromatography [silica gel; 90:10 hexane/EtOAc] afforded 4-cyclohex-1-enyl-but-3-yn-2-ol (**198**) (360 mg, 85%) as an oil.[223]



199

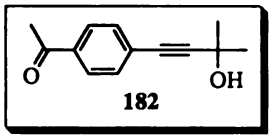
Procedure for the Takai iodoolefination using catalytic quantities of $CrCl_3$. Preparation of 1-iodo-dodeca-1,11-diene (199). Under an Ar atmosphere, TMSCl (15.3 mL, 120 mmol) was added to a suspension of $CrCl_3$ (0.6334 g, 4 mmol), Zn (7.84 g, 120 mmol), and NaI (3.0 g, 20 mmol) in dioxane (100 mL) at 25 °C. After the reaction was stirred for 40 min, a solution of 10-undecenal (4.16 mL, 20 mmol) and CHI_3 (15.75 g, 40 mmol) in dioxane (50 mL) was added at 25 °C via a syringe pump over 24 hours. After the addition the mixture became very thick. The reaction was quenched by the addition of water. The reaction was then extracted with hexanes (5X). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; hexanes] to afford (*E*)-1-iodo-1,11-dodecadiene[224] (**199**) (4.35 g, 75%, *E*/*Z* 98/2) as an oil and *E*-1-chloro-1,11-dodecadiene (trace by GC/MS).



200

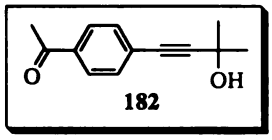
Procedure for the PMHS mediated Sonogashira coupling of vinyl and aryl halides using CuTC and (1:1) THF/NMP as solvent. Preparation of hexadeca-5(*E*),15-dien-3 -yn-2-ol (200) (Table 12, entry 2). To 30 mL of THF/NMP (1:1) was added 3-butyn-2-ol (**34**) (0.16 mL, 2.0 mmol), PMHS (0.24 mL, 4 mmol), CsF (1.52 g, 10.0 mmol), CuTC (297 mg, 3.0 mmol), *E*-1-iodo-1,11-dodecadiene (**199**) (0.8766 g, 3.0 mmol), and $PdCl_2(PPh_3)_2$ (70 mg, 0.10 mmol). This mixture was stirred at room temperature until

complete by TLC analysis (90:10 Hex/EtOAc). Once complete (5 h), the reaction was diluted with Et_2O and then washed with sat. aq. NH_4OH. The phases were then separated and the combined organics were washed with H_2O (2X), brine (2X), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 80:20 hexane/EtOAc] to afford hexadeca-5(*E*),15-dien-3-yn-2-ol[225] (**200**) (380 mg, 82%) as a yellow oil.



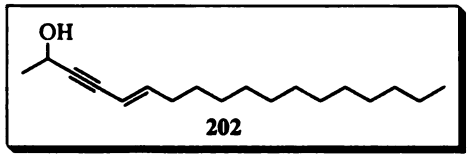
182

Preparation of 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone; use of *p*-iodoacetophenone (182) (Table 12, entry 3). Applying the above conditions at room temperature for 5 h to 2-methyl-3-butyn-2-ol (**1**) (0.10 mL, 1.0 mmol) and *p*-iodoacetophenone (0.3691 g, 1.5 mmol) after column chromatography [silica gel; 75:25 Hexanes/EtOAc] afforded 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone[226] (**182**) (170 mg, 87%) as an oil. For spectroscopic data see page 252.



182

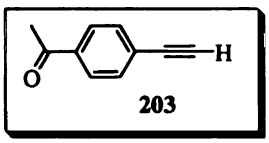
Preparation of 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (182); (Table 12, entry 4). Applying the above conditions at room temperature for 5 h to 2-methyl-3-butyn-2-ol (**1**) (0.10 mL, 1.0 mmol) and *p*-bromoacetophenone (0.2986 g, 1.5 mmol) after column chromatography [silica gel; 75:25 hexanes/EtOAc] afforded 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone[227] (**182**) (162 mg, 80%) as an oil. For spectroscopic data see page 252.



202

Preparation of (+/-)-octadec-5-en-3-yn-2-ol (202) (Table 12, Entry 5). To a solution of THF/NMP (180 mL; 1:1) was added CsF (9.11 g, 60 mmol), (+/-)-3-butyn-2-ol (**34**) (22.67 g of 3.71% solution in THF, 12.0 mmol), PMHS (1.44 mL,

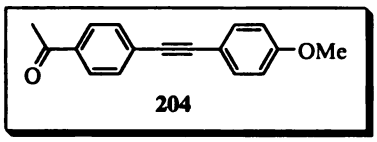
24 mmol), CuTc (4.56 g, 24 mmol), 1(*E*)-iodo-tetradec-1-ene (**201**) (5.80 g, 18 mmol), and $PdCl_2(PPh_3)_2$ (421.1 mg, 0.6 mmol). This mixture was stirred at room temperature until complete by TLC analysis (hexanes/EtOAc 90/10). Once complete (7 h), the reaction was diluted with Et_2O and then washed with sat. aq. NH_4OH. The phases were then separated and the combined organics were washed with H_2O (2X), brine (2X), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 90:10 hexane/EtOAc] to afford (+/-)-octadec-5-en-3-yn-2-ol (**202**) (2.80 g, 88%) as a solid. (mp. 32-34 °C). IR (neat) 3200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.11 Hz 3 H), 1.05-1.41 (m, 20 H), 1.45 (d, *J* = 6.52 Hz, 3 H), 2.08 (q, *J* = 6.80 Hz, 2 H), 2.50 (br s, 1 H), 4.62 (q, *J* = 5.56 Hz, 1 H), 5.47 (d, *J* = 15.86 Hz, 1 H), 6.13 (dt, *J* = 7.07, 14.50 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.03, 22.61, 24.27, 28.61, 29.03, 29.29, 29.37, 29.51, 29.58, 29.60, 31.85, 32.98, 58.59, 82.65, 89.39, 108.72, 145.27; HRMS (EI) *m/z* 264.2453 [(M^+), calcd. for $C_{18}H_{32}O$ 264.2456].



203

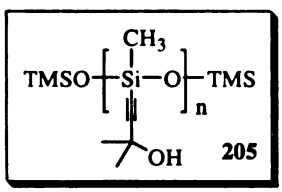
Preparation of 1-(4-ethynyl-phenyl)-ethanone (203) (Scheme 81). A 25 mL flask was charged with ground potassium carbonate (0.1380 g, 1.0 mmol) and 18-crown-6 (0.0530 g, 0.20 mmol) and then purged with nitrogen. To the flask was added the 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (**182**) (See Table 2, entry 2 for preparation) (0.1700 g, 0.95 mmol) in toluene (8 mL + 2 mL wash) and the suspension was heated to 120 °C. The mixture was vigorously stirred under a stream of nitrogen until completion. Water (20 mL) was added and the mixture poured into a separatory funnel containing ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting residue

was purified by column chromatography [silica gel; 90:10 hexanes/EtOAc] to afford 1-(4-ethynyl-phenyl)-ethanone[228] (**203**) (141, 98%) as an oil.



204

Preparation of 1-[4-(4-methoxy-phenylethynyl)-phenyl]-ethanone (204) (Scheme 81). Applying the above conditions at room temperature for 6 h to 1-(4-ethynyl-phenyl)-ethanone (**203**) (0.1440 g, 1.0 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-methoxy-phenyl ester (18) (0.4875 g, 1.5 mmol) after column chromatography [silica gel; 80:20 hexanes/EtOAc] afforded 1-[4-(4-methoxy-phenylethynyl)-phenyl]-ethanone[229] (**204**) (205mg, 82%) as an oil.

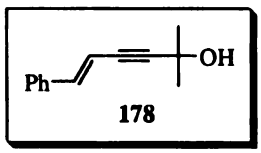


205

Procedure for the preparation and isolation of the new solid material (205) (Scheme 82). CsF (304 mg, 2.0 mmol) was dissolved in THF/NMP (10 mL; 1:1). 2-methyl-3-butyn-2-ol (**1**) (0.10 mL, 1 mmol) and PMHS (0.09 mL, 1.5 mmol) and were added successively. Once the initial reaction had subsided (foaming and gas evolution), the mixture was washed with water (3x) and extracted with ether (4x). The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford (**205**) (143 mg, 99%) as a white solid (mp 175-181 °C decomp.). ^1H NMR (300 MHz, $CDCl_3$) δ 0.01-0.24 (m), 1.43 (s), 2.7 (br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.8, 1.5, 31.3, 64.9, 85.7, 110.8.

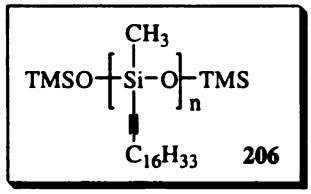
Treatment of silylated alkyne (205) with TBAF (Scheme 82). The silyl alkyne (**205**) (143 mg) was dissolved into THF (5 mL). TBAF (5 mL of a 1M solution in THF) was added and the reacted was stirred at 25 °C for 12 h. ^1H NMR analysis of the crude mixture indicated complete removal of the silyl group. After workup as noted above and

filtering through a plug of silica, 2-methyl-3-butyn-2-ol (**1**) (83 mg, 99%) was obtained as clear liquid.



178

Subjection of the silyl alkyne (205) to the coupling procedure (Scheme 82). Applying the above conditions from the Table 3 protocol at room temperature for 8 h to the silyl alkyne (**205**) (301 mg) and (*E*)-β-bromostyrene (0.2745 g, 1.5 mmol) after column chromatography [silica gel; 90:10 hexanes/EtOAc] afforded 2-methyl-6-phenyl-hex-5-en-3-yn-2-ol (**178**) (85 mg, 46%) as an oil. For spectroscopic data see page 247.

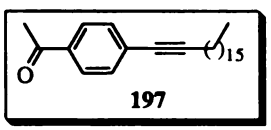


206

Procedure for the preparation and isolation of the new solid material (206) (Scheme 83). CsF (304 mg, 2.0 mmol) was dissolved in THF/NMP (10 mL; 1:1). 1-Octadecyne (**189**) (251 mg, 1 mmol) and PMHS (0.09 mL, 1.5 mmol) and were added successively. Once the initial reaction had subsided (foaming and gas evolution), the mixture was washed with water (3x) and extracted with ether (4x). The organic layer was dried ($MgSO_4$), filtered and concentrated to afford (**206**) (305 mg, 97%) as a white solid (mp 295 °C decomp.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00-0.30 (m), 0.90 (t, J = 5.6 Hz), 1.20-1.60 (m), 2.20 (td, J = 2.5, 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.86, 1.61, 14.12, 19.85, 22.71, 28.65, 28.82, 29.11, 29.40, 29.53, 29.63, 29.69, 29.73, 31.95, 84.15, 107.70.

Treatment of silylated alkyne (206) with TBAF (Scheme 83). The silyl alkyne (**206**) (305 mg) was dissolved into THF (5 mL). TBAF (5 mL of a 1M solution in THF) was added and the reacted was stirred at 25 °C for 12 h. ^{1}H NMR analysis of the crude mixture indicated complete removal of the silyl group. After workup as noted above and

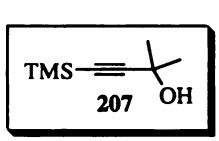
filtering through a plug of silica, 1-octadecyne (**189**) (247 mg, 97%) was obtained as an oil



197

Subjection of the silyl alkyne (206) to the coupling procedure (Scheme 83). Applying the above conditions from the Table 3 protocol at room temperature for 8 h to the silyl alkyne (**206**) (301 mg) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**184**) (0.6273 g, 1.5 mmol) after column chromatography [silica gel; 90:10 hexanes/EtOAc] afforded 1-(4-octadec-1-ynyl-phenyl)-ethanone (**197**) (158 mg, 43%) as an oil. For spectroscopic data see page 260.

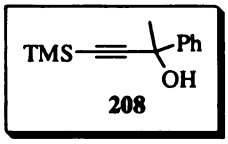
Procedure for the ReactIR™ studies (Figure 18). A three-neck flask was used. CsF (38.0 g, 250 mmol) was added to a solution of the alkyne (50 mmol) in NMP (50 ml) in a three neck flask and the mixture was stirred vigorously. The ReactIR™ probe was inserted through the middle port of the flask. An initial reading was taken as a reference point. PMHS (6 mL, 100 mmol) was added dropwise at a rate that would allow the reaction contents to remain in the flask. If the PMHS was added in one portion, the reaction took off rather quickly making a mess. The data collection was started right after the first drop of PMHS was added. Data acquisition was continued until all the PMHS was added.



207

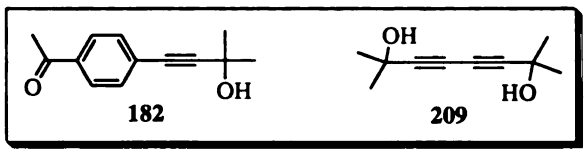
Representative procedure for the preparation of TMS acetylenes. Preparation of 4-trimethylsilanyl-2-methyl-3-butyn-2-ol (207) (Scheme 84). A solution of *n*-BuLi (6.25 mL of a 1.6M THF solution, 10 mmol) was added dropwise to a solution of 1-trimethylacetylene (1.41 mL, 10 mmol) in THF (15 mL) at 0 °C. After 30 min., the solution was cooled to –78 °C and acetone (0.74 mL, 10

mmol) was added dropwise. After 15 min., the solution was warmed to 25 °C and stirred from 30 min. The reaction was then diluted with water and extracted with ether (2x). The combined organics were then dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by column chromatography [silica; 90:10 hexane/EtOAc] to afford 4-trimethylsilanyl-2-methyl-3-butyn-2-ol[230] (**207**) (1.50 g, 96%) as a white solid (mp = 41 °C).



208

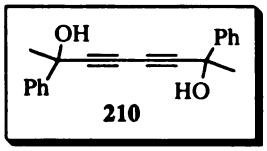
Preparation of 2-phenyl-4-trimethylsilanyl-3-butyn-2-ol (208) (Scheme 84). Apply the above conditions to 1-trimethylacetylene (1.41 mL, 10 mmol) and benzophenone (1.17 mL, 10 mmol) after column chromatography [silica: 90:10 hexane/EtOAc] afforded 2-phenyl-4-trimethylsilanyl-3-butyn-2-ol[231] (**208**) (2.1 g, 96%) as a colorless oil.



182 **209**

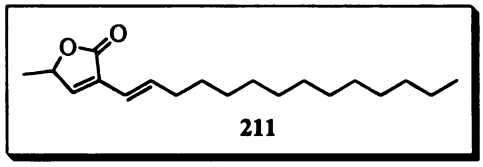
Representative procedure for a classic Sonogashira coupling (Ar degassing). Preparation of 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (182) (Scheme 85). 2-methyl-3-butyn-2-ol (**1**) (0.10 mL, 1.0 mmol), CuI (0.010 g, 0.05 mmol), $PdCl_2(PPh_3)_2$ (0.0350 g, 0.05 mmol), Et_3N (0.28 mL, 2 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**184**) (0.6273 g, 1.5 mmol) were all added to 10 mL of THF (degassed by 3 freeze-thaw cycles under vacuum) and stirred until complete by TLC analysis. Once complete (6 h), the reaction was concentrated and purified by column chromatography [silica gel; 70:30 hexanes/EtOAc] to afford 1-[4-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-ethanone (**182**) (97 mg, 48%) as an oil and 2,7-dimethyl-octa-3,5-

diyne-2,7-diol (**209**) (64 mg, 39%) as a solid (mp 130 °C; lit mp 129-132 °C).[232] For spectroscopic data for **182** see page 252.



210

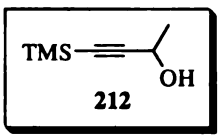
Preparation of 2,7-diphenyl-octa-3,5-diyne-2,7-diol (210) (Scheme 85). Applying the above degassing conditions (degassed by 3 freeze-thaw cycles under vacuum) to 2-phenyl-3-butyn-2-ol (**8**) (0.1462 g, 1.0 mmol) and 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-methoxy-phenyl ester (**25**) (0.4875 g, 1.5 mmol) for 11 h afforded after column chromatography [silica gel; 80:20 hexanes/EtOAc] 4-(4-methoxy-phenyl)-2-phenyl-but-3-yn-2-ol (**179**) (0 mg, 0%) and 2,7-diphenyl-octa-3,5-diyne-2,7-diol (**210**) (134 mg, 92%) as a solid (mp 133 °C; lit mp 132-134 °C).[232]



211

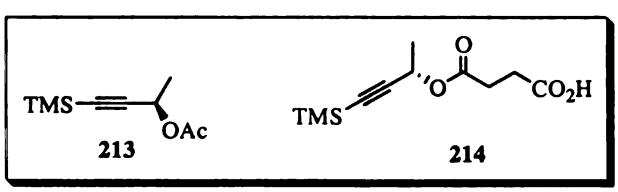
Representative procedure for the Pd catalyzed Cyclocarbonylation via Alper's protocol. Preparation of 5-methyl-3-tetradec-1-enyl-5H-furan-2-one (211, (+/-)-Akolactone A) (Scheme 86). Under an Ar atmosphere, octadec-5-en-3-yn-2-ol (**202**) (1.06 g, 4 mmol), Pd_2dba_3 (146.4 mg, 0.16 mmol), and dppb (136.4 mg, 0.32 mmol) were added to an oven dried stainless steel autoclave. Degassed (~2 h with N_2) CH_2Cl_2 (40 mL) was added and the autoclave was sealed in under an Ar atmosphere. The vessel was purged 6X with CO (200 psi each time). It was then charged with CO (600 psi) and then H_2 (200 psi). The vessel was placed in oil bath and the internal temperature was maintained at 95 °C for 48 h. The reaction vessel was cooled to room temperature before opening. Once opened, the reaction was concentrated and the resulting residue was purified by column chromatography [silica gel; 92:8 hexane/EtOAc] to afford 5-methyl-3-tetradec-1-enyl-5H-furan-2-one[233] (**211**) (1.02 g,

88%) as a clear oil. IR (neat) 1767, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.1 Hz, 3 H), 1.16-1.36 (br s, 18 H), 1.42 (m, 5 H), 2.16 (q, *J* = 6.9 Hz, 2 H), 5.02 (qd, *J* = 1.7, 7.4 Hz, 1 H), 6.09 (d, *J* = 17.23 Hz, 1 H), 6.79 (dt, *J* = 7.1, 15.8 Hz, 1 H), 7.03 (d, *J* = 1.80 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.0, 19.1, 22.6, 28.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 33.4, 76.9, 118.2, 129.3, 138.7, 146.8, 171.9; HRMS (EI) *m/z* 292.2402 [(M^+), calcd. for $C_{19}H_{32}O_2$ 292.2402].



212

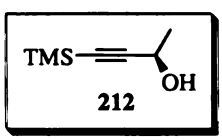
Preparation of 4-TMS-3-butyn-2-ol (212) (Scheme 87). Mg (9.72 g, 400 mmol) was covered with dry ether (85 mL). Grignard formation was initiated by the addition of neat EtBr (0.5 mL, 6.7 mmol). The reaction was maintained at a steady reflux by slow addition of EtBr (29.4 mL, 393.3 mmol) in ether (245 mL). To the solution was added 3-butyn-2-ol (**34**) (19.60 mL, 250 mmol) as a solution in ether (140 mL). To this mixture was added TMSCl (25.5 mL, 200 mmol). A second portion of TMSCl (25.5 mL, 200 mmol) was added and the reaction was allowed to stir at room temperature for 8 h. Pouring the reaction into ice water quenched the reaction. The organics were separated and the aqueous phase was extracted with ether. The combined organics were washed with 2N H_2SO_4, sat. aq. $NaHCO_3$, water, and brine. After drying ($MgSO_4$) the solution was filtered and concentrated. The resulting residue was purified by vacuum distillation (80-85 °C at 20 mmHg) to afford 4-TMS-3-butyn-2-ol (**212**) (20.4 g, 58%) as a clear liquid.[234]



213 214

Procedure for the Lipase mediated resolution.[5] Preparation of (*R*)-acetate (213) and the (*S*)-succinate (214) (Scheme 87). To a solution of 4-TMS-3-butyn-2-ol (**212**) (20.0 g, 140 mmol) in freshly

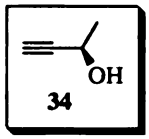
distilled pentane (500 mL) were added Lipase Amano AK (4.0 g), vinyl acetate (100 mL, 1108 mmol) and 2 g of pulverized 4 Å MS. The reaction progress was monitored by GC analysis [50 °C, hold 4 min, 10 °C/min to 110 °C; acetate ~8.80 min, alcohol ~5.90 min]. After 72 h the ratio of alcohol to acetate was ~1:1. This mixture was filtered through a medium glass sintered funnel, washed with pentane, and concentrated by careful evaporation to afford 23 g of a 1:1 mixture of acetate and alcohol. To the 1:1 mixture was added THF (100 mL), Et_3N (18.2 mL, 130 mmol), DMAP (183.3 mg, 1.5 mmol) and succinic anhydride (8.22 g, 82.2 mmol). This mixture was heated to reflux for 4 h, cooled and quenched with 75 mL of $NaHCO_3$. The solution was stirred vigorously for 1 h before being diluted with ether. The two phases were separated and the organics were washed with 10% HCl, brine, dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by distillation (50 °C, 0.5 mmHg) to afford the (*R*)-acetate (**213**) (12.38 g, 96%) as a clear oil. $[\alpha]_D$ = +130.4, *c* = 2.575 $CHCl_3$, (lit.[5] $[\alpha]_D$ = +117.5, *c* = 2.30 $CHCl_3$). The aqueous phase was carefully acidified with 12 M HCl to pH 1.0 and then was extracted with EtOAc. The combined organics were dried ($MgSO_4$), filtered, and concentrated to afford the (*S*)-succinate (**214**) (15.60 g, 92%) as a solid. Note the succinate was stored until needed.



212

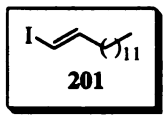
Preparation of (*R*)-4-TMS-3-butyn-2-ol (212) (Scheme 87). To a solution of the (*R*)-acetate (**213**) (9.08 g, 49.26 mmol) in hexanes (70 mL) at –78 °C was added DIBAL (74 mL of a 1M solution in hexanes, 74 mmol). This solution was stirred at –78 °C for 30 min and then was poured into a rapidly stirred mixture of Rochelle's salt (300 mL) and ether (200 mL). Once the ether layer clarified it was separated, dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified

by distillation (65 °C at 0.5 mmHg) to afford (*R*)-4-TMS-3-butyn-2-ol (**212**) (5.63 g, 80%) as a clear oil. $[\alpha]_D$ = +27.1, *c* = 2.30 $CHCl_3$. (lit.[5] $[\alpha]_D$ = +23.8, *c* = 2.02 $CHCl_3$.). For spectroscopic data see page 269.



34

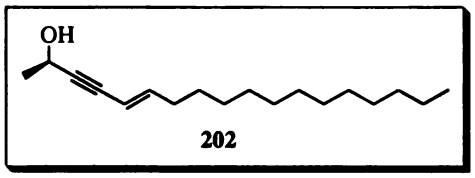
Preparation of (*R*)-3-butyn-2-ol (34) (Scheme 87). To a solution of (*R*)-4-TMS-3-butyn-2-ol (**212**) (4.31 g, 30.3 mmol) in ether (40 mL) was added TBAF (36.35 mL of a 1M solution in THF, 36.35 mmol) at 0 °C. This mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of a small amount of sat. aq. NH_4Cl. The phases were readily separated and the organics dried ($MgSO_4$). The resulting solution was distilled at atmospheric pressure at 40 °C to remove all the ether. Once most of the ether was distilled off, the remaining solution was distilled at 85 °C to afford (*R*)-3-butyn-2-ol (**34**) as solution in THF (3.71%), which corresponds to a 68% yield. This solution was used for future reactions.



201

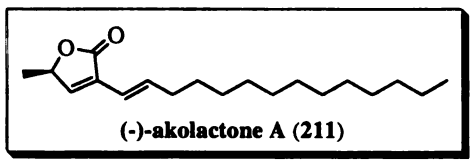
Procedure for the hydrozirconation and Zr/I_2 exchange. Preparation of 1-iodo-tetradec-1-ene (201) (Scheme 88). Super-hydride (51.45 mL of a 1M THF solution, 51.45 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (15.04 g, 51.45 mmol) in THF (120 mL) in a flask wrapped in foil. After 1 h, 1-tetradecyne (5.0 g, 25.73 mmol) in THF (150 mL) was added dropwise and stirring continued for 4 h. The reaction was then cooled to 0 °C and a solution of I_2 (6.53 g, 25.73 mmol) in CH_2Cl_2 (~200 mL) was added dropwise until a brown-orange color persisted. The mixture was diluted with CH_2Cl_2 (~100 mL) and was washed with aq. sat. $Na_2S_2O_3$. The phases were then separated and the combined organics were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; hexane] to afford of 1-iodo-tetradec-1-ene (**201**) (7.95 g, 96%) as a light yellow oil. IR

(neat) 2939, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.32 Hz, 3 H), 1.10-1.50 (m, 20 H), 2.06 (q, *J* = 7.07 Hz, 2 H), 5.99 (d, *J* = 14.35 Hz, 1 H), 6.53 (dt, *J* = 7.14, 14.28 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.11, 22.69, 28.35, 28.93, 29.36, 29.54, 29.64, 29.66, 29.69, 29.71, 31.92, 36.05, 74.23, 146.73; HRMS (EI) *m/z* 322.1158 [(M^+), calcd. for $C_{14}H_{27}I$ 322.1156].



202

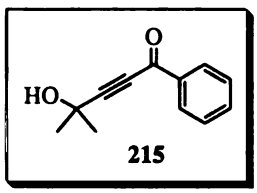
The chiral synthesis of Akolactone A. Preparation of (*R*)-octadec-5-en-3-yn-2-ol (202) (Scheme 88). To a solution of THF/NMP (180 mL; 1:1) was added CsF (9.11 g, 60 mmol), (R)-3-butyn-2-ol (**34**) (22.67 g of 3.71% solution in THF, 12.0 mmol), PMHS (1.44 mL, 24 mmol), CuTc (4.56 g, 24 mmol), 1(*E*)-iodo-tetradec-1-ene (**201**) (5.80 g, 18 mmol), and $PdCl_2(PPh_3)_2$ (421.1 mg, 0.6 mmol). This mixture was stirred at room temperature until complete by TLC analysis (hexanes/EtOAc 90/10). Once complete (7 h), the reaction was diluted with Et_2O and then washed with sat. aq. NH_4OH. The phases were then separated and the combined organics were washed with H_2O (2X), brine (2X), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography [silica gel; 90:10 hexane/EtOAc] to afford (*R*)-octadec-5-en-3-yn-2-ol (**202**) (2.80 g, 88%) as a solid. $[\alpha]_D$ = +12.8, *c* = 0.392 $CHCl_3$. (mp. 32-34 °C). For spectroscopic data see page 262-263.



(-)-akolactone A (211)

Representative procedure for the Pd catalyzed Cyclocarbonylation via Alper's protocol. Preparation of 5-methyl-3-tetradec-1-enyl-5H-furan-2-one (37) ((-)-Akolactone A) (Scheme 88). Under an Ar atmosphere, (*R*)-

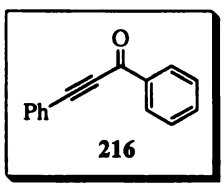
octadec-5-en-3-yn-2-ol (**202**) (1.06 g, 4 mmol), Pd_2dba_3 (146.4 mg, 0.16 mmol) and dppb (136.4 mg, 0.32 mmol) were added to an oven dried stainless steel autoclave. Degassed (~2 h with N_2) CH_2Cl_2 (40 mL) was added and the autoclave was sealed in under an Ar atmosphere. The vessel was purged 6X with CO (200 psi each time). It was then charged with CO (600 psi) and then H_2 (200 psi). The vessel was placed in oil bath and the internal temperature was maintained at 95 °C for 48 h. The reaction vessel was cooled to room temperature before opening. Once opened, the reaction was concentrated and the resulting residue was purified by column chromatography [silica gel; 92:8 Hexane/EtOAc] to afford 5-methyl-3-tetradec-1-enyl-5H-furan-2-one (**211**)[233] (1.02 g, 88%) as a clear oil. $[\alpha]_D$ = -12.7, *c* = 0.4 $CHCl_3$ (lit. $[\alpha]_D$ = -13.2 , *c* = 0.1 $CHCl_3$)[233]; IR (neat) 1767, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.1 Hz, 3 H), 1.16-1.36 (br s, 18 H), 1.42 (m, 5 H), 2.16 (q, *J* = 6.9 Hz, 2 H), 5.02 (qd, *J* = 1.7, 7.4 Hz, 1 H), 6.09 (d, *J* = 17.23 Hz, 1 H), 6.79 (dt, *J* = 7.1, 15.8 Hz, 1 H), 7.03 (d, *J* = 1.80 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.0, 19.1, 22.6, 28.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 33.4, 76.9, 118.2, 129.3, 138.7, 146.8, 171.9; HRMS (EI) *m/z* 292.2402 [(M^+), calcd. for $C_{19}H_{32}O_2$ 292.2403].



215

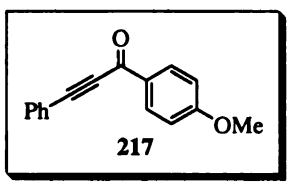
Representative procedure for a PMHS/CsF mediated Sonogashira coupling with acyl chlorides. Preparation of 4-hydroxy-4-methyl-1-phenyl-pent-2-yn-1-one (215) (Scheme 89, entry 1). To 30 mL of NMP was added CsF (1.52 g, 10.0 mmol), 2-methyl-3-butyn-2-ol (**1**) (0.20 mL, 2.0 mmol), and PMHS (0.24 mL, 4.0 mmol). After the initial reaction subsided, CuCl (40 mg, 0.4 mmol) was added followed by benzoyl chloride (0.26 mL, 2.2 mmol). The reaction was then heated to ~80 °C for 5 h. Once complete, the reaction

was diluted with water and then extracted with ether (2x). The combined organics were dried ($MgSO_4$), filtered and, concentrated. The resulting residue was purified by column chromatography [silica gel; 90:10 hexane/EtOAc] to afford 4-hydroxy-4-methyl-1-phenyl-pent-2-yn-1-one[235] (**215**) (173 mg, 46%) as a yellow oil.



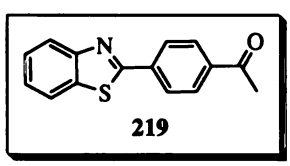
216

Preparation of 1,3-diphenyl-propynone (216) (Scheme 89, entry 2). Applying the above conditions to phenyl acetylene (**73**) (0.22 mL, 2.0 mmol) and benzoyl chloride (0.26 mL, 2.2 mmol) after column chromatography [silica gel; 95:5 hexane/EtOAc] to afford 1,3-diphenyl-propynone[236] (**216**) (275 mg, 67%) as an oil.



217

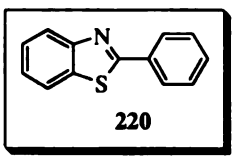
Preparation of 1-(4-methoxy-phenyl)-3-phenyl-propynone (217) (Scheme 89, entry 3). Applying the above conditions to phenyl acetylene (**73**) (0.22 mL, 2.0 mmol) and 4-methoxybenzoyl chloride (0.30 mL, 2.2 mmol) after column chromatography, [silica gel; 90:10 Hexane/EtOAc] to afford 1-(4-methoxy-phenyl)-3-phenyl-propynone[237] (**217**) (324 mg, 69%) as a white crystalline solid.



219

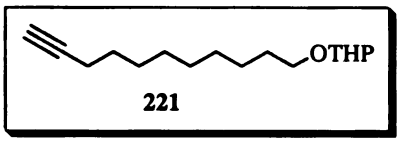
General procedure for the coupling of benzothiazole under CsF/PMHS conditions. Preparation of 1-(4-benzothiazol-2-yl-phenyl)-ethanone (219) (Scheme 90). To a solution of NMP (20 ml) was added CsF (760 mg, 5.0 mmol), benzothiazole (**218**) (0.22 mL, 2.0 mmol), PMHS (0.24 mL, 4.0 mmol), CuCl (5.0 mg, 0.05 mmol), 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**184**) (418 mg, 1.0 mmol), and $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol). This mixture was then allowed to stir for 17 h at room temperature. The reaction was then washed with H_2O (20 mL) and separated. The organics were then

washed with brine, dried ($MgSO_4$), and concentrated. The resulting residue diluted with a minimum amount of EtOH/$PhCH_3$ (5/2) and cooled to –5 °C to promote crystallization. The solid was then dried under vacuum to afford 1-(4-benzothiazol-2-yl-phenyl)-ethanone (**219**) (146 mg, 58%); (mp 181 °C, lit mp 182-183 °C).[238]



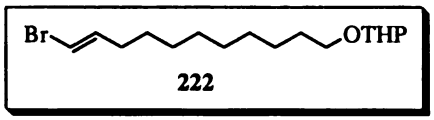
220

Preparation of 2-phenyl-benzothiazole (220) (Scheme 90). Applying the above conditions to benzothiazole (**218**) (0.22 mL, 2.0 mmol) and iodobenzene (0.11 mL, 1.0 mmol) afforded after recrystallization from EtOH/H_2O (2:1) 2-phenyl-benzothiazole (**220**) (110 mg, 52%); (mp 112 °C, lit mp 113-113.5 °C).[238]



221

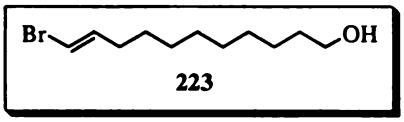
Procedure for synthesis of (*E*)-11-bromo-undec-10-en-1-ol. Preparation of 2-undec-10-ynyloxy-tetrahydro-pyran (221) (Scheme 91). A solution of 10-undecyn-1-ol (5.0 g, 29.71 mmol) and DHP (4.07 mL, 44.57 mmol) in hexane (10 mL) was added to a suspension of Amberlyst A-15 (1.25 g) in hexanes (10 mL). This mixture was stirred for 1 h. The reaction was then filtered through celite and the filtrate was concentrated. The resulting residue was purified by column chromatography [silica gel; 95:5 hexane/EtOAc] to afford 2-undec-10-ynyloxy-tetrahydro-pyran[239] (**221**) (6.60 g, 88%) as a clear oil.



222

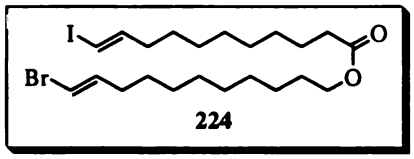
Preparation of 2-(11-bromo-undec-10-enyloxy)-tetrahydro-pyran (222) (Scheme 91). Cp_2ZrCl_2 (1.46 g, 5 mmol) and THF (20 mL) were added to a flame dried flask filled with Ar. Super hydride (5.0 mL of a 1M solution in THF, 5.0 mmol) was added dropwise at room temperature. This mixture was stirred at room temperature for 1 h. Next 2-undec-10-ynyloxy-tetrahydro-pyran (**221**) (631 mg, 2.5 mmol) in THF (5 mL) was added at 25 °C and this mixture was stirred for 20 min. NBS (900 mg, 5 mmol) was then added and stirring was continued for 15 min. The reaction was then portioned between 90/10 hexane/EtOAc and sat. aq. $NaHCO_3$. The aqueous layer was extracted with 90/10 hexane/EtOAc. The combined organics were washed with brine, dried ($MgSO_4$), and filtered through a plug of celite and silica gel. The filtrate was concentrated and purified by column chromatography [silica gel; 95:5 hexane/EtOAc] to afford 2-(11-bromo-undec-10-enyloxy)-tetrahydro-pyran (**222**) (800 mg, 96%) as an oil. IR (neat) 2928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20-1.90 (m, 20 H), 2.02 (q, J = 7.0 Hz, 2 H), 3.36 (m, 1 H), 3.48 (m, 1 H), 3.72 (m, 1 H), 3.84 (m, 1 H), 4.56 (m, 1 H), 5.98 (d, J = 13.5 Hz, 1 H),

6.15 (dt, J = 7.1, 13.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 22.6, 25.4, 26.1, 28.5, 29.2, 29.4, 30.7, 31.5, 32.3, 62.1, 67.5, 98.6, 103.9, 138.1; HRMS (EI) *m/z* 332.1341 [(M^+), calcd. for $C_{16}H_{29}BrO_2$ 332.1351].



223

Preparation of (*E*)-11-bromo-undec-10-en-1-ol (223) (Scheme 91). A solution of 2-(11-bromo-undec-10-enyloxy)-tetrahydro-pyran (**222**)(800 mg, 2.4 mmol) and CBr_4 (40 mg, 0.12 mmol) in dry MeOH (10 mL) was refluxed at 65 °C for 3 h. The solution was cooled to room temperature and poured into 5% $NaHCO_3$ (10 mL) and then was extracted with ether (3x). The organics were washed with brine, dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by column chromatography [silica gel; 90:10 hexane/EtOAc] to afford (*E*)-11-bromo-undec-10-en-1-ol (**223**) (574 mg, 96%) as a white solid (mp = 42 °C). IR (neat) 3335 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20-1.45 (m, 11 H), 1.52-1.64 (m, 4 H), 2.05 (q, J = 7.0 Hz, 2 H), 3.66 (t, J = 6.6 Hz 2 H), 6.03 (dt, J = 1.2, 13.5 Hz, 1 H), 6.18 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 28.6, 28.9, 29.3, 29.4, 29.5, 32.8, 32.9, 63.0, 103.9, 138.3; HRMS (EI) *m/z* 249.0848 [(M^+), calcd. for $C_{11}H_{21}BrO$ 249.0854.



224

Procedure for the DCC mediated coupling. Preparation of (*E*)-11-iodo-undec-10-enoic acid (*E*)-11'-bromo-undec-10'-enyl ester (224) (Scheme 91). (*E*)-11-iodo-undec-10-enoic acid (**98**) (2.02 g, 6.5 mmol), (*E*)-11-bromo-undec-10-en-1-ol (**223**) (1.47 g, 5.9 mmol), DCC (6.5 mL of a 1M solution in CH_2Cl_2, 6.5 mmol), and 4-methylaminopyridine (144 mg, 1.18 mmol) were added to 50 mL of CH_2Cl_2. This mixture was allowed to stir at 25 °C for 5 h. The reaction was then filtered through a

plug of celite and the filtrated was concentrated. The resulting residue was purified by column chromatography [silica gel; 95:5 hexane/EtOAc] to afford (*E*)-11-iodo-undec-10-enoic acid (*E*)-11'-bromo-undec-10'-enyl ester (**224**) (3.07 g, 96%) as a yellow oil. IR (neat) 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20-1.45 (m, 22 H), 1.52-1.67 (m, 4 H), 2.02 (q, *J* = 7.0 Hz, 4 H), 2.27 (t, *J* = 6.6 Hz, 2 H), 4.04 (t, *J* = 6.7 Hz 2 H), 5.91 (m, 2 H), 6.15 (dt, *J* = 7.1, 13.5 Hz, 1 H), 6.18 (dt, *J* = 7.1, 13.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 25.8, 28.2, 28.4, 28.5, 28.7, 28.8, 28.9, 29.0, 29.1, 29.1, 29.3, 32.8, 34.2, 34.8, 35.9, 64.2, 74.3, 103.9, 138.0, 146.5, 173.7; HRMS (EI) *m/z* 541.1156 [(M^+), calcd. for $C_{22}H_{38}BrIO_2$ 541.1176].

Procedure for the Pd catalyzed hydrostannation of acetylene gas. Preparation of vinyltributylstannane (Scheme 92). Acetlyene gas was bubbled through a cooled solution of THF. This was done by filling a graduated cylinder with 50 mL THF and once ~30 mL of acetylene was obtained; the solution was transferred via cannula to the reaction flask. The amount of acetylene used was about 250 mmol. To the main reaction flask was added $PdCl_2(PPh_3)_2$ (702 mg, 1 mmol), PMHS (9 mL, 150 mmol), KF (17.48 g, 300 mmol) (dissolved into ice-cold water). While this mixture was stirring, a solution of Bu_3SnCl (27.1 mL, 100 mmol) in THF (50 mL) was added slowly over ~30 min and was then allowed to sir at 25 °C for 2 h. Once the addition began, the flask became warm and the color went from yellow to orange to a brownish color after 2 h. Once complete, the reaction was diluted with Et_2O and washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The crude ^1H NMR indicated some residual PMHS, but overall was very clean. The residue was then purified by vacuum distillation [104-106 °C, @ 2.5 mmHg] to afford vinyltributylstannane as a clear liquid (24.73 g, 78%).

COMPOUND DIRECTORY

Compound	Page	Compound	Page	Compound	Page
2	107-108	**68**	160-161	**127**	206-207
3	108-109	**70**	161	**128**	207-208
5	109-110	**72**	161	**129**	208
7	110	**74**	162	**130**	208-209
9	110-111	**75**	162-163	**140**	209-210
11	111	**76**	163-164	**141**	
13	112	**78**	164	**142**	211
15	112-113	**81**	167	**143**	214
16	119	**82**	168	**144**	215-216
18	123-124	**83**	168	**137**	216-217
19	125	**84**	168-169	**145**	217
20	129-130	**85**	169	**146**	218-219
21	130	**86**	169-170	**147**	219
23	131	**87**	171	**148**	219-220
24	132	**88**	170	**150**	221-222
25	132-133	**89**	170	**151**	222
27	133-134	**90**	172-173	**136**	222-223
29	134	**91**	174	**153**	223-224
31	134-135	**97**	177	**135**	225
33	135-136	**92**	180	**155**	225
35	136-137	**93**	180	**156**	225
36	137-138	**94**	180-181	**169**	237
37	138	**96**	180	**170**	237
38	138-139	**98**	182	**172**	238-239
39	154	**99**	182-183	**173**	239
40	139	**101**	183-184	**178**	247
41	155	**103**	184-185	**179**	249-250
42	139-140	**104**	185-186	**180**	251-252
43	141	**105**	185	**181**	252
45	142	**106**	186-187	**182**	252
46	142-143	**107**	187	**183**	252
47	143	**108**	188	**184**	254-255
48	143	**109**	188-189	**185**	255
49	148	**110**	189-190	**186**	255
50	148-149	**114**	197-198	**187**	256
52	149	**115**	197	**190**	256
54	149-150	**116**	204-205	**191**	257
56	150	**119**	200-201	**192**	257
57	153	**120**	201-202	**193**	258
59	155	**121**	202	**194**	259
61	156	**122**	202-203	**195**	259
62	156-157	**123**	203	**196**	260
64	161-162	**124**	204	**197**	260

66	160	**125**	206	**198**	260-261
Compound	**Page**	**Compound**	**Page**	**Compound**	**Page**
199	261	**208**	267	**222**	275-276
200	262	**209**	267-268	**223**	276-277
201	271-272	**210**	268	**224**	277
202	262-263	**211**	268-269		
203	263-264	**212**	269		
204	264	**215**	273-274		
205	264	**216**	274		
206	265	**217**	274		
207	266-267	**221**	275		

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(70) The use of 1-bromoalkynes can improve the regioselectivity see ref 24 for further information and Scheme 19.

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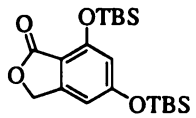

137c

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