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PREPARATION OF VINYL STANNANES, THEIR SUBSEQUENT REACTIONS, AND CHEMISTRY DEVELOPED THEREIN.

presented by

JILL A. MUCHNIJ

has been accepted towards fulfillment
of the requirements for the

Doctoral degree in Chemistry

Major Professor's Signature

9/29/08

Date

PREPARATION OF VINYL STANNANES, THEIR SUBSEQUENT REACTIONS, AND CHEMISTRY DEVELOPED THEREIN.

By

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ABSTRACT

PREPARATION OF VINYL STANNANES, THEIR SUBSEQUENT REACTIONS, AND CHEMISTRY DEVELOPED THEREIN.

By

Jill A. Muchnij

Investigation into the hydrostannation of alkynes, specifically the examination of the directing effects of oxygen containing functional groups linked to the alkyne moiety was initiated. Palladium catalyzed conditions revealed an increased formation of the internal stannane regioisomer when the proposed palladacycle intermediate could form. Diminished selectivities were observed in the presence of free hydroxyl groups which arose from solvation inhibiting palladacycle formation. The results of this project sparked the idea of a multi-step one pot reaction utilizing a hydrostannation reaction. A one-pot hydrostannation/Stille reaction and a Stille/Diels-Alder reaction are both known reactions and therefore a one-pot hydrostannation/Stille/Diels-Alder reaction is a logical extension. However in the course of developing a viable synthetic route to the triene required for the Diels-Alder reaction, it was discovered that the dienophile did not survive the hydrostannation step. It was unclear whether the 1,4-reduction of the α,β-unsaturated ester resulted from reaction with tributyltin hydride or polymethylhydrosiloxane, both are hydride donors. Further exploration of the palladium catalyzed reduction of α,β-unsaturated compounds revealed that polymethylhydrosiloxane was the reducing agent. This reaction could be exploited in the reduction of many α,β-unsaturated compounds, however, α,β-unsaturated aldehydes tended to over reduce.

Re-examination of a one-pot reaction involving a hydrostannation step led to the development of a one-pot Stille/hydrostannation that terminates in the formation of a vinyl stannane. The Stille coupling generates the trialkyltin halide that is then recycled into trialkyltin hydride which subsequently is utilized in the hydrostannation reaction. One difficulty that was overcome was the Stille coupling was unsuccessful in the presence of a terminal alkyne. Therefore, the alkyne needed to be protected during the Stille coupling and unprotected in the hydrostannation step. Fortunately, incorporation of the deprotection step into the one-pot Stille/deprotection/hydrostannation reaction was successful.

To Ron and My Parents

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ABBREVIATIONS

Δ	Heat
18-C-6	18-crown-6
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
aq	aqueous
BHT	tert-butylhydroxytoluene
Bn	benzyl
BORSM	based on recovered starting material
b.p.	boiling point
BPS	tert-butyldiphenylsilyl
Bu	butyl
calcd	calculated
cat	catalytic
Cbz	benzyloxycarbonyl
CMD	chemical manganese dioxide
CSA	camphorsulfonic acid
CuTC	copper thiophenecarboxylate
dba	dibenzylideneacetone
DBATO	bis(dibutylacetoxytin) oxide
DCC	dicyclohexylcarbodiimide
DEAD	diethylazodicarboxylate

decomp	decomposition
DIBAL	diisobutylaluminum hydride
DMAP	dimethylaminopyridine
DME	dimethoxymethyl ether
DMF	dimethylformamide
DMSO	dimethylsulfoxide
E	entgegend
EH	Zn(2-ethylhexanoate)$_2$
EI	electron impact
Et	ethyl
eq.	equivalents
equiv.	equivalents
GC	gas chromatography
h	hours
HRMS	high resolution mass spectroscopy
IBX	iodoxybenzoic acid
imid.	imidazole
Int	internal
i-Pr	isopropyl
M	molar
Me	methyl
MHz	megahertz
min	minutes

mL	milliliter
mm	millimeter
mmol	millimole
$MoBI_3$	$Mo(CO)_3(NCtBu)_3$
m.p.	melting point
MS	molecular sieves
NBS	N-bromosuccinimide
NMP	N-methylpyrrolidine
NMR	nuclear magnetic resonance
NR	no reaction
ON	overnight
PCC	pyridinium chlorochromate
Ph	phenyl
PMHS	polymethylhydrosiloxane
p-TSA	p-toluenesulfonic acid
pyr.	pyridine
quant.	quantitative yield
ref	reference
rt	room temperature
sat.	saturated
SM	starting material
TASF	tris(dimethylamino)sulfur trimethylsilyl difluoride
TBAF	tetrabutylammonium fluoride

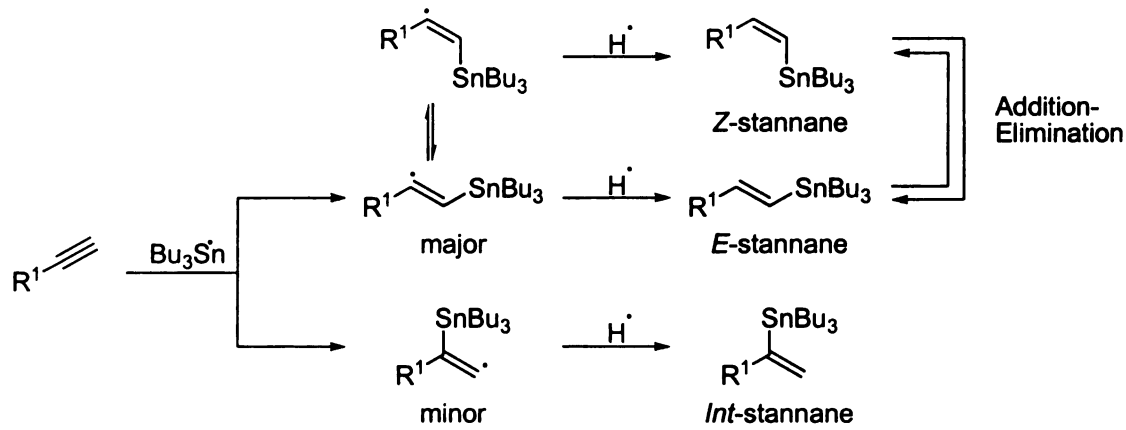
TBS	tert-butyldimethylsilyl
t-Bu	tertiary-butyl
TEA	triethylamine
TES	triethylsilyl
Tf	triflate
TFP	trifurylphosphine
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
v/v	volume/volume
W	watts
wt%	weight percent
Z	zusammen

Chapter 1: The preparation of vinyl stannanes

1.1 The generation of vinyl stannane isomers

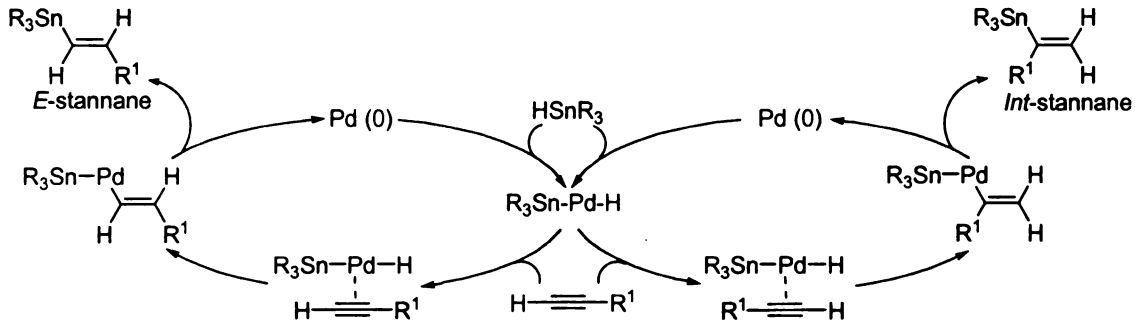
A myriad of conditions exist for the formation of vinyl stannanes.[1] The most straight forward conditions employ the addition of trialkyltin hydride across an alkyne producing the desired vinyl stannane. E-, Z-, and internal vinyl stannanes can be formed from the hydrostannation of a terminal alkyne. Under free radical conditions all three isomers can be isolated; however, the vinyl radical is stabilized alpha to R^1 and favors formation of the E- and Z-isomers

Scheme 1. Hydrostannation Pathways via Tin Radicals



(Scheme 1).[2] Changing the reaction conditions from a free radical to a palladium catalyzed process allows for the formation of the E- and internal vinyl stannane isomers exclusively (Scheme 2). Formation of the Z-vinyl stannane can still occur when the reactions are run at elevated temperatures and/or prolonged reaction times, due to tin radical formation. Other metals[3] have also been used to catalyze the hydrostannation of alkynes, but the most selective are palladium and molybdenum.[4,9]

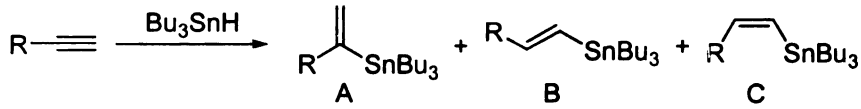
Scheme 2. Palladium Mediated Hydrostannation Pathways



1.2 Increasing the regioselectivity in the hydrostannation of 1-alkynes

The product distribution between E-, Z-, and internal vinyl stannanes is directly affected by the reaction conditions employed and the nature of the substituents connected to the alkyne (Table 1). To make the hydrostannation of alkynes a more synthetically useful reaction a method with high regioselectivity

Table 1. Reaction Conditions Effect on Regioselectivity



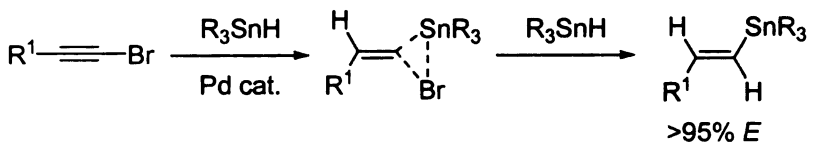
Entry	R	Conditions	Ratio A	Ratio B	Ratio C	Yield	Ref
1	-$C(CH_3)(OH)CH_2CH(CH_3)_2$	$PdCl_2(PPh_3)_2$, Et_2O, rt	1	24	0	66%	5
2	-CH_2OTHP	$PdCl_2(PPh_3)_2$,[a] THF, rt	2	1	0	68%	9
3	-Ph	AIBN, toluene 6 °C	0	1	3.2	83%	6
4	-Ph	$PdCl_2(PPh_3)_2$, benzene, 0 °C	1	1.2	0	82%	7
5	-Ph	$ZrCl_4$, toluene, 0 °C	0	1	19	73%	8

[a]in situ generated Bu_3SnH

would be ideal. As mentioned previously, palladium catalyzed hydrostannations of 1-alkynes result in the formation of E- and internal vinyl stannanes. It is

possible to increase the regioselectivity for E-vinyl stannane by modifying the 1-alkyne to a 1-bromoalkyne in conjunction with excess of tin hydride (Scheme 3). The reaction is thought to proceed through a 1-bromo-1-stannyl alkene that is further reduced by the tin hydride to a 1-stannyl alkene.[9,10]

Scheme 3. Terminal Bromoalkyne Directed Regioselectivity



1.3 Conclusions

In the hydrostannation of terminal alkynes three regioisomers can be formed. The regioselectivity of the hydrostannation is both reagent and substrate dependent. In the palladium mediated hydrostannation of terminal alkynes the E- and internal stannanes are formed and modification of the terminal alkyne to 1-bromoalkyne allows for selective E-stannane formation.

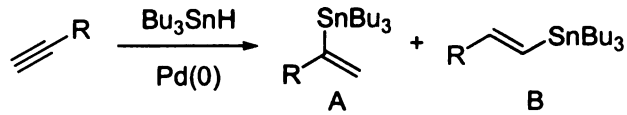
Further examination of the regioselectivity of the palladium mediated hydrostannation would increase the synthetic utility of vinyl stannanes because there would be greater predictability in the regiochemical outcome. Using this knowledge to combine the hydrostannation with subsequent one-pot transformations will be discussed in the remaining chapters.

Chapter 2: Examination of the affect of oxo-substitution on the regiochemical outcome in the hydrostannation of 1-alkynes

2.1 The known regiochemical effects of oxo-substitution

The regioselectivity of palladium mediated alkyne hydrostannations is normally considered substrate dependent (Table 2). However, predicting the regioselectivity is often difficult. Guibé has shown that the presence of a

Table 2. Substrate Directed Hydrostannation

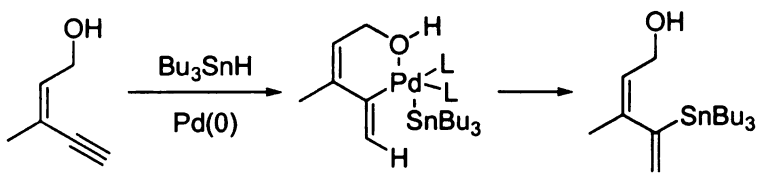


Entry	R	Ratio A	Ratio B	% yield
1	$-CO_2Me$	100	0	94
2	$-CH(n\text{-}C_5H_{11})_2$	0	100	90
3	$-CH_2OPh$	91	9	85

polarizing function group attached to a terminal alkyne in the palladium mediated hydrostannation is selective for the internal stannane (Table 2, entry 1).[9] Conversely, the E-stannane is formed selectively when large, bulky groups were placed in the propargylic position (Table 2, entry 2). Utilizing 1-bromoalkynes allows for E-stannane regioselectivity in palladium mediated hydrostannations, however, this method requires the modification of the terminal alkyne in a separate step. The hydrostannations of propargyl and vinylogous propargylic alcohols and their derivatives have also been examined (Table 2, entry 3).[11] Pancrazi has identified that the presence of an oxygen in the substrate allows for not only some inductive polarization of the alkyne but also the formation of a

palladacycle intermediate (Scheme 4).[12] These factors increase the regioselectivity for the formation of the internal stannane. Interestingly, Alami

Scheme 4. Oxygen Directed Hydrostannation through Palladacycle Intermediate



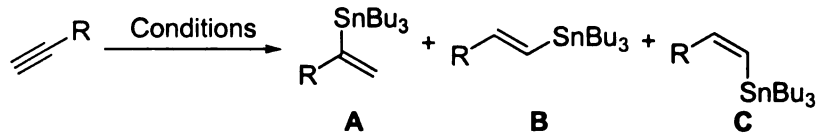
has shown that the hydrostannation of Z-enynes, in comparison to E-enynes, is highly regioselective for the internal stannane.[13] This propensity is not tied to the chelating ability of the substituents on the alkene. These results seem to bring into question how effectively a remote oxygen can direct the regiochemical outcome of the palladium mediated hydrostannation. These individual results clearly do not give a full picture on the regioselectivity of the palladium mediated hydrostannation. The results are gleaned from a variety of reaction conditions. The palladium source and the type of organotin hydride utilized are only two of many variables in the reaction conditions. Therefore we sought to hydrostannate a series of oxygen containing alkynes, under palladium catalysis, in an orderly progression. This data should give a clearer look into the directing effects of the oxygen functionality.

2.2 The systematic examination of the regioselectivity in the hydrostannation of 1-alkynes

As a point of comparison for the oxygen substituted alkynes, three straight chain alkyl substituted terminal alkynes were examined under the palladium mediated hydrostannation conditions and the ratio of the internal to E-stannane was consistent with all three alkynes, 1:2, (Table 3, entries 1-3). Having

identified the baseline ratio of hydrostannation products under palladium catalysis without an oxygen functionality, the systematic evaluation of a progression of different hydroxyalkynes and their derivatives was begun.

Table 3. Examination of Oxygen Functionality on Hydrostannation Selectivity

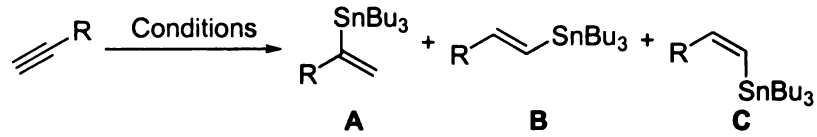


A **B** **C**

Entry	R	Conditions[a]	Ratio A	Ratio B	Ratio C	% yield
1	$-C_3H_7$	1	1	2.2	0	
2	$-C_4H_9$	1	1	1.8	0	
3	$-C_5H_{11}$	1	1	1.9	0	
4	$-CH_2OH$	1	1.3	1	0	60
5		2	1	9	2	52
6	$-(CH_2)_2OH$	1	1	1.6	0	69
7		2	1	80	19	90
8	$-(CH_2)_3OH$	1	1	2.5	0	56
9		2	0	9	1	70
7	$-(CH_2)_4OH$	1	1	3	0	95
8		2	0	5.4	1	64
9	$-(CH_2)_2OAc$	1	1.3	1	0	94
10		2	0	9.7	1	69
11	$-(CH_2)_3OAc$	1	1	1.4	0	60
12		2	1	18.6	1.5	75
13	$-(CH_2)_4OAc$	1	1	1.3	0	90
14		2	0	4	1	61
15	$-CH_2OMe$	1	16.7	5.7	1	49
16		2	1	7.8	1.8	82
17	$-(CH_2)_2OMe$	1	6.6	6.5	1	77
18		2	0	19	1	50

[a]Conditions 1: 1.5 equiv. Bu_3SnH, 0.8 mol% $PdCl_2(PPh_3)_2$, THF, 0 °C, 45 min; Conditions 2: 1.5 equiv. Bu_3SnH, 8 mol% AIBN, benzene, 80 °C, 3 h.

Table 3 (cont'd).



A B C

Entry	R	Conditions[a]	Ratio A	Ratio B	Ratio C	% yield
19	-$(CH_2)_3OMe$	1	1	1.4	0	81
20		2	2	20	1	46
21	-$(CH_2)_4OMe$	1	1	2.7	0	73
22		2	1	16	1	48
23	-CH_2OTBS	1	2.4	1	0	69
24		2	3.5	24.3	1	74
25	-$(CH_2)_2OTBS$	1	1	1.4	0	63
26		2	0	11	1	76
27	-$(CH_2)_3OTBS$	1	1	1.6	0	51
28		2	0	4.8	1	58
29	-$(CH_2)_4OTBS$	1	1	1.5	0	60
30		2	0	4.8	1	78
31	-CH_2OTMS	1	1.9	1	0	49
32	-CH_2OTIPS	1	3	1	0	79
33	-CH_2ODPMS	1	4.5	1	0	29

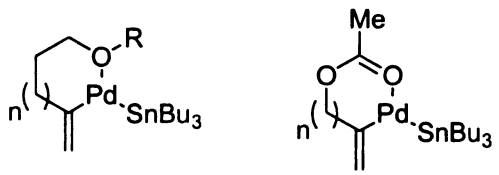
[a]Conditions 1: 1.5 equiv. Bu_3SnH, 0.8 mol% $PdCl_2(PPh_3)_2$, THF, 0 °C, 45 min; Conditions 2: 1.5 equiv. Bu_3SnH, 8 mol% AIBN, benzene, 80 °C, 3 h.

2.2.1 The examination of the hydrostannation of a series of free alcohols

Upon hydrostannation, propargyl alcohol showed a slight propensity for the internal stannane (1.3:1), while reactions of -ynols with increasing chain lengths up to 5-hexyn-1-ol showed a reversal in the regioselectivity (Table 3, entries 4-8). The proposed palladacycle intermediate that would form in each case, to favor internal stannane formation, appears to be feasible (ring sizes 5-7),

however, the preference for E-stannane indicates the directing effect from the formation of the stable palladacycle was minimal (Scheme 5). The free radical hydrostannation of the same alkynes, another point of comparison, not surprisingly favors the formation of E-stannane.

Scheme 5. Ethereal and Ester Palladacyle Intermediates



2.2.2 The examination of the hydrostannation of a series of acetate substituted alkynes

Propargyl acetate, the analogous starting point in the examination of a series of acetate functionalized hydroxyalkyne derivatives, was not stable under the reaction conditions.[9] The hydrostannation of 1-acetoxy -3-butyne proved to be selective for internal stannane, 1.3:1 (Table 3, entry 9). Inversion of the regioselectivity was observed with greater chain lengths, however the ratio of 1:1.3 (internal:E-stannane) remained steady as the chain increased from three to four methylene units (Table 3, entries 9-14). The difference between the acetate and alcohol series is considerable, with the free alcohol the internal stannane formation is reduced three-fold in comparison to the acetate. Perhaps the acetate helps to stabilize the palladacycle intermediate allowing for greater directing effects from the oxygen functionality or the acetate could polarize the alkyne allowing for greater internal stannane formation.

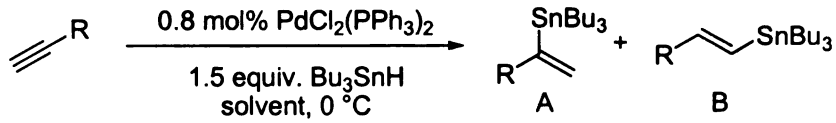
2.2.3 The examination of the hydrostannation of a series of ether containing alkynes

The series beginning with the hydrostannation of methyl propargyl ether again begins with the preference for the internal stannane and increasing the chain length (Table 3, entries 15-22) allows for the inversion of selectivity increasing to 3.5:1 in favor of the E-stannane in the hydrostannation of 6-methoxy-1-hexyne. The directing effect of the methyl ethers is not as pronounced as the acetates but clearly there is an appreciable difference relative to the free alcohols.

2.2.4 The examination of the effect of solvent in the hydrostannation of alcohols and ethers

The proposed palladacyle intermediate requires coordination between the oxygen functionality and the palladium catalyst. However, THF is a solvent where hydrogen bonding is possible between the solvent and the oxygen functionality. The effect of the solvent was examined in the hydrostannation of propargyl alcohol and methyl propargyl ether. In the case of propargyl alcohol the palladacycle intermediate could be disrupted by solvation of the free alcohol while methyl propargyl ether would not solvate and thereby be available for formation of the paladacyle. When the solvent was changed to benzene (non-coordinating) in the hydrostannation of propargyl alcohol, the propensity for internal stannane formation was increased. However, when methyl propargyl ether was examined under the same conditions there was no appreciable difference between THF and benzene (Table 4). This confirms that the solvation of the free hydroxyl group affects the regiochemical outcome of the hydrostannation and possibly disrupts the proposed palladacycle intermediate.

Table 4. Effect of Solvent on Regioselectivity



Entry	R	Solvent	Ratio A	Ratio B	yield
1	$-CH_2OH$	THF	1.3	1	60%
2	$-CH_2OH$	benzene	2.1	1	61%
3	$-CH_2OMe$	THF	2.5	1	49%
4	$-CH_2OMe$	benzene	2	1	61%

2.2.5 The examination of the hydrostannation of a series of silyl ether containing alkynes

Silyl ethers are typically considered non-chelating and therefore could also be used to examine the directing effect and the formation of the palladacycle intermediate. A series of TBS-ethers was prepared and subjected to the hydrostannation conditions. Upon hydrostannation, the TBS protected propargyl alcohol (Table 3, entry 23) a 2.4:1 ratio of internal stannane to E-stannane was observed, however, the other silyl ethers examined showed the same 1:1.5 ratio of internal to E-stannane regioselectivity. This suggests the palladacycle intermediate was stabilized by the TBS-ethers allowing for greater formation of the internal stannane as compared to the analogous free alcohols.

The use of silyl groups as protecting groups has become common place in organic synthesis and therefore, several groups were examined in this study. A comparison between TMS-, TBS-, TIPS-, and DPMS- protected propargyl alcohols revealed that TMS, TBS, and TIPS all behave similarly in the reaction affording a ~2.5:1 mixture of the vinyl tins with preference for the internal

stannane (Table 3, entries 31, 23, 32). The DMPS ether resulted in an increased preference for the internal stannane, 4.5:1, presumably due to the electron withdrawing nature of the protecting group (Table 3, entry 33).

2.3 Conclusions

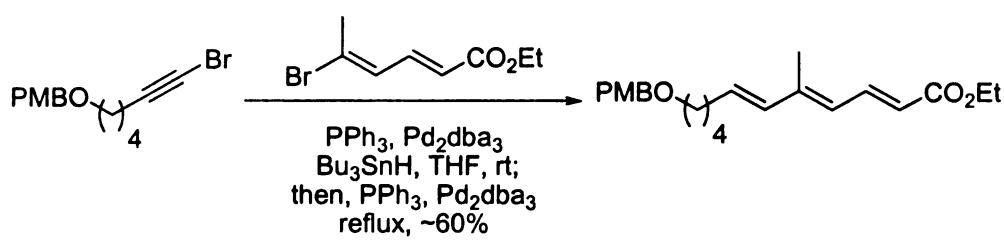
Examination of a series of hydroxyalkynes and their derivatives showed that the proposed palladacycle intermediate appears to be formed when the oxygen functionality is not solvated as in the case of the free hydroxyls. The acetates, methyl ethers, and silyl ethers all show an increased preference for internal stannane formation in comparison to the alcohols. However, each functionality shows a different degree of preference for the formation of the palladacycle intermediate and thereby preference for internal stannane formation.

Chapter 3: Towards the development of a one-pot hydrostannation/Stille coupling/Diels-Alder reaction

3.1 Combining the hydrostannation reaction with the Stille coupling to develop a one-pot protocol

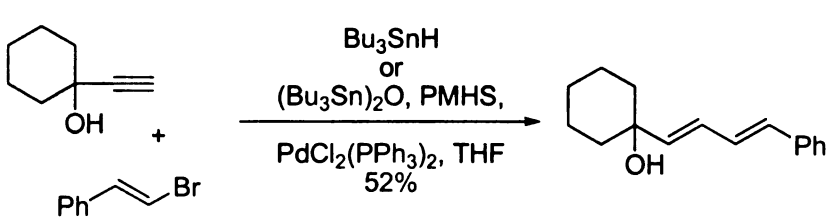
The Stille reaction is an important carbon-carbon bond forming reaction in organic synthesis, typically employing vinyl stannanes which are commonly accessed through the hydrostannation of an alkyne. Classically, the formation of the vinyl stannane and its utilization in a Stille coupling have been performed separately. These two reactions have been combined into a stepwise one-pot procedure utilizing tin hydride by Pattenden (Scheme 6).[10] The Maleczka group

Scheme 6. Pattenden's One-Pot Hydrostannation/Stille Coupling



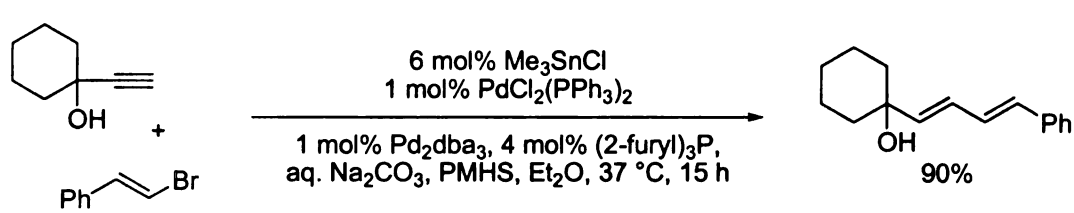
followed up this initial disclosure with the development of a one-pot hydrostannation/Stille coupling employing tributyltin hydride, or preparing the tin hydride in situ from bistributyltin oxide and PMHS (Scheme 7).[14] However, there are drawbacks to each of these reaction conditions, triorganotin hydrides are prone to dimerization or decomposition and the formation of tributyltin hydride

Scheme 7. Maleczka's One-Pot Hydrostannation/Stille Coupling



from bistributyltin oxide requires a two-fold excess of tin oxide, or the use of elevated reaction temperatures (>200 °C). Ideally a method with a stable triorganotin compound that can be easily converted to a triorganotin hydride would be highly useful. This one-pot hydrostannation/Stille coupling was further elaborated into a catalytic tin method that still utilized a triorganotin oxide intermediate. By utilizing catalytic tributyltin chloride in the presence of stoichiometric amounts of PMHS and aq. Na_2CO_3, the hydrostannation/Stille coupling was presumed to proceed through a tin oxide which was more easily converted to tributyltin hydride in the presence of PMHS. However, it was determined that the cross-coupling reaction was sluggish (48-72 h) with tributyltin chloride and allowed for nonproductive reaction pathways to occur. These problems were solved by switching to trimethyltin chloride resulting in decreased reaction times, greater tin turnovers, and higher yields (Scheme 8).[15]

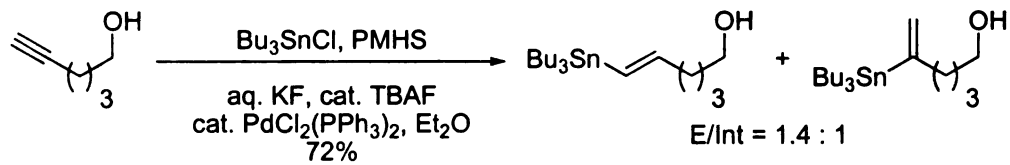
Scheme 8. Hydrostannation/Stille Coupling Catalytic in Tin



Subsequently, the Maleczka group developed a method for the in situ formation of triorganotin hydride from triorganotin chlorides via fluoride activation of PMHS by KF. Beyond formation of the polycoordinate silicon, the KF may also be reacting with the triorganotin chloride to form an ate complex which subsequently is converted to the triorganotin hydride. This triorganotin hydride

can then be utilized in hydrostannation of alkynes, whether under palladium catalysis or free radical conditions (Scheme 9).[5]

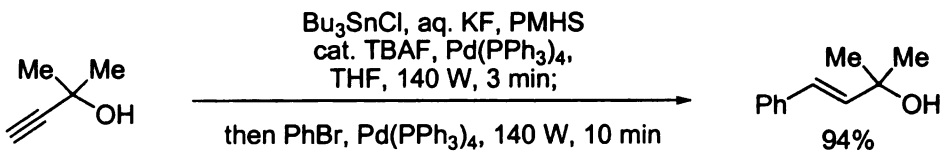
Scheme 9. Fluoride Activation for in situ Generation of R_3Sn-H form R_3Sn-Cl



Application of the "Sn-F" method of generating triorganotin hydride in situ with the one-pot catalytic hydrostannation/Stille coupling resulted in nearly identical results as the "Sn-O" approach.[16] An advantage to the "Sn-F" method is the resting state of the trimethyltin is a tin fluoride which is insoluble in most solvents. This allows for the easy removal of tin from the reaction medium via filtration. Whereas in the "Sn-O" method the water soluble tin carbonate is found in the aqueous layer creating disposal issues due to the toxicitiy of the trimethyltin species.[17]

The Maleczka group also extended the "Sn-F" approach to a one-pot hydrostannation/Stille coupling non catalytic in tin under the assistance of microwave irradiation. In a simple appliance-type microwave a palladium catalyzed hydrostannation utilizing Bu_3SnCl, KF, and PMHS was complete in 3 min under 140 W of irradiation, followed by subjection of the vinyl stannane in a Stille coupling in 10 min under 140 W of irradiation. This method allowed for the conversion of 1-alkynes to 1,3-dienes or styrenes in just minutes and if purification is considered, from start to finish the pure products are obtained in approximately 2.5 h (Scheme 10).[18]

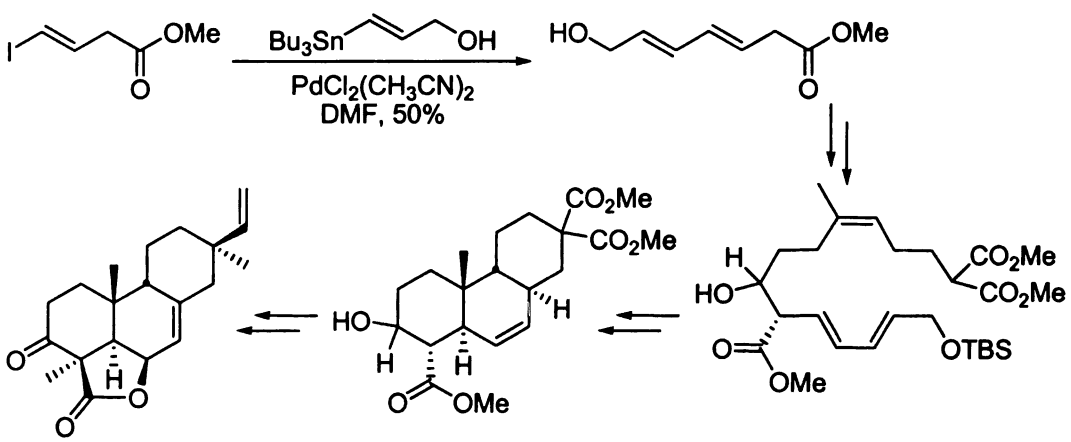
Scheme 10. Microwave Promoted One-Pot Hydrostannation/Stille Coupling



3.2 The one-pot Stille/Diels-Alder reaction

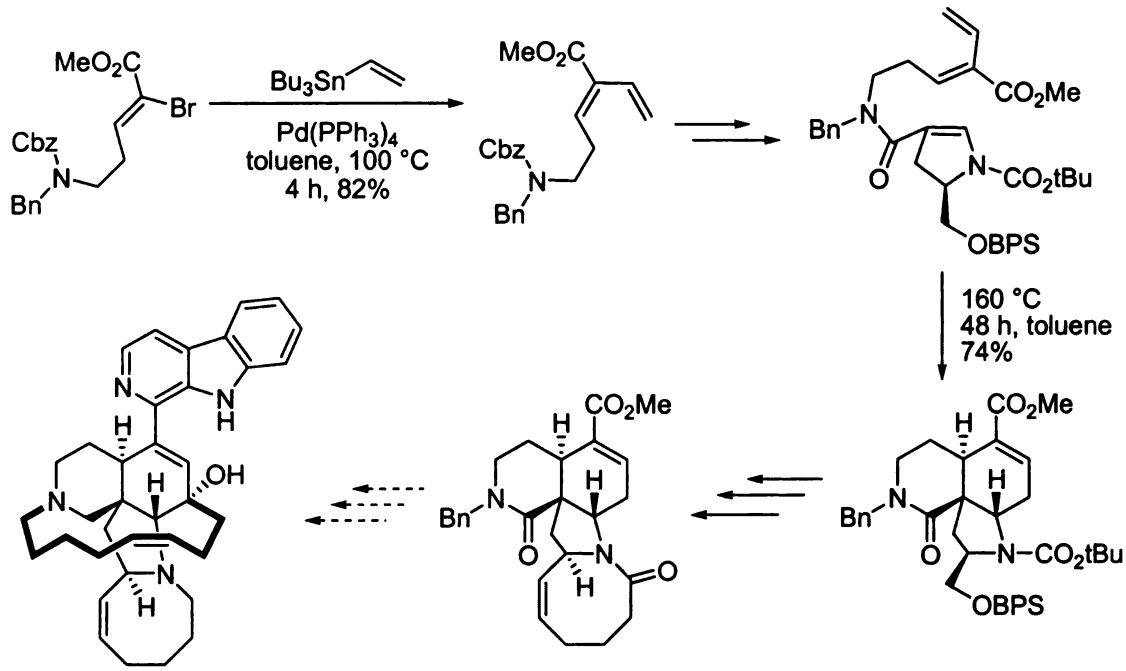
The Diels-Alder reaction, a cycloaddition between a 1,3-diene and a dienophile, has been extensively used in complex natural product synthesis.[19] The 1,3-diene can be installed via a Stille coupling. An excellent example of the stepwise utilization of these two reactions can be seen in the synthesis of

Scheme 11. Momilactone A Synthesis via a Stille and Diels-Alder Reaction



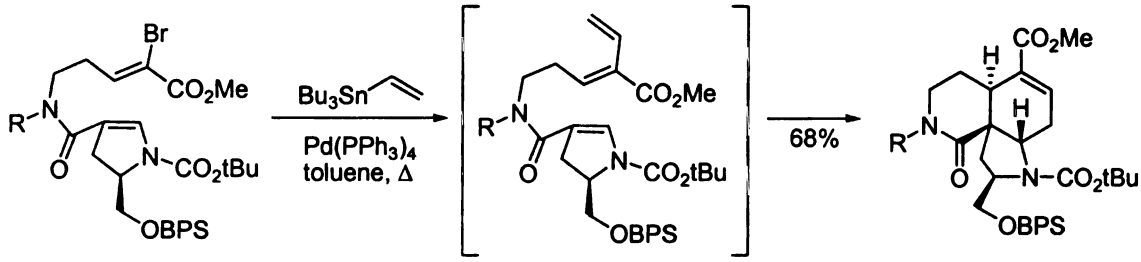
(±)-momilactone A (Scheme 11).[20] Martin's initial synthetic plan for manzamine A was based on a stepwise application of the Stille and Diels-Alder reactions, where the diene was installed into a key building block via a Stille coupling followed by incorporation of the dienophile and a thermally promoted Diels-Alder reaction (Scheme 12).[21,22] However, modification of the synthetic scheme allowed for a one-pot Stille/Diels-Alder reaction. By installing the diene later in the synthesis the two individual reactions could be combined in a domino-like

Scheme 12. Stepwise Stille Coupling Diels-Alder Approach for Manzamine A



process where the newly formed diene undergoes the cycloaddition under the Stille coupling reaction conditions (Scheme 13).[21]

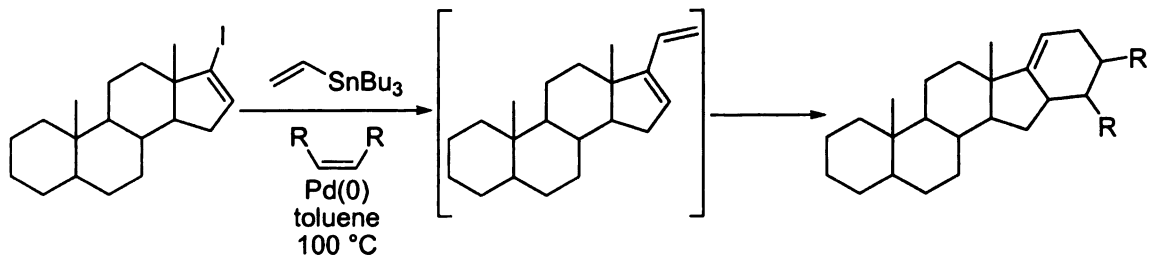
Scheme 13. One-Pot Stille Coupling / Diels-Alder



While Martin's chemistry illustrates the evolution of synthetic thought, several other groups have examined the utility of one-pot Stille/Diels-Alder reactions. The one-pot synthesis of pentacyclic steroids utilizing the Stille coupling followed by Diels-Alder cycloaddition was examined by Skoda-Földes. The diene, formed via a Stille coupling, could be isolated and subsequently

reacted with a dienophile to form the cycloadduct. However, the cycloadduct could also be formed from the reaction of the vinyl iodide with vinyl tributylstannane in the presence of the dienophile with Pd(0) as the catalyst (Scheme 14). The one-pot reaction usually underwent the Stille coupling readily,

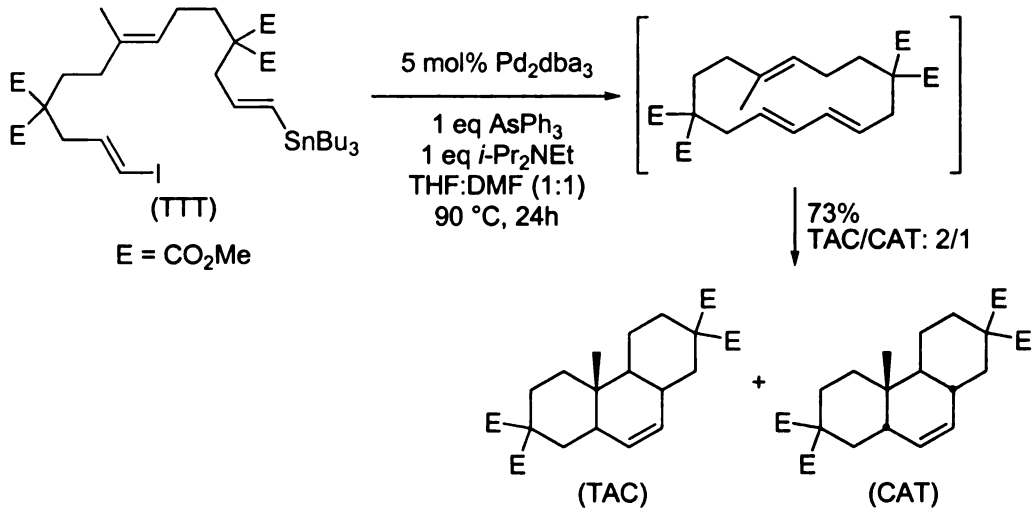
Scheme 14. Pentacyclic Steroids via a One-Pot Stille/Diels-Alder



but the Diels-Alder reaction did not go to completion after 4.5 h and therefore diene was recovered in all examples. The choice of the Pd catalyst system (Pd_2dba_3 + PPh_3 (1:8), Pd_2dba_3 + $AsPh_3$ (1:8), $Pd(PPh_3)_4$) affected the rate of the conversion of the starting material presumably due to coordination of the dienophile to the Pd thereby slowing the rate of oxidative addition in the Stille reaction. While the yield of the Diels-Alder product varied greatly (10-98%) the highest yields were afforded whem employing $Pd(PPh_3)_4$ as the catalyst.[23]

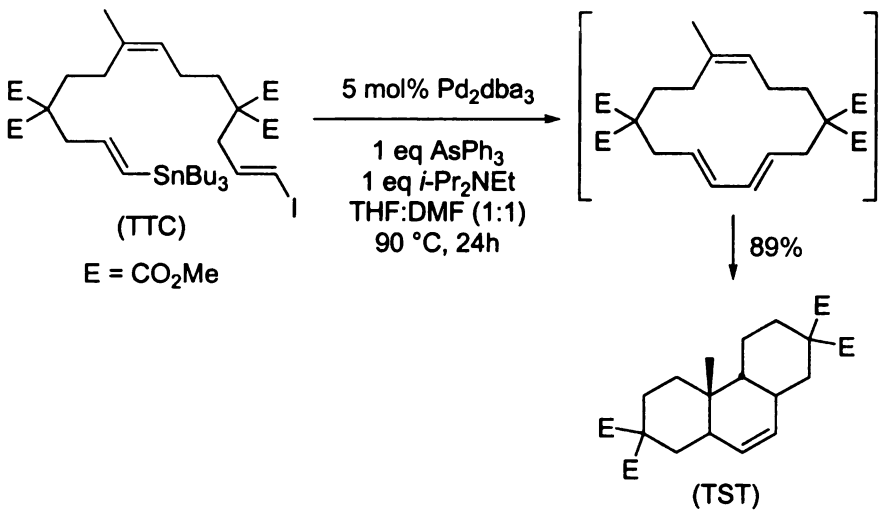
Deslongchamps demonstrated that the one-pot Stille/Diels-Alder reaction could be applied to the formation of macrocyclic trienes that undergo intramolecular Diels-Alder cycloadditions. A combination of Pd_2dba_3 and triphenylarsine promoted the coupling of a vinyl iodide and vinyl tin for the formation of the macrocyclic trienes which subsequently underwent cycloaddition under the thermal reaction conditions (Scheme 15).

Scheme 15. One-Pot Stille/Intramolecular Diels-Alder



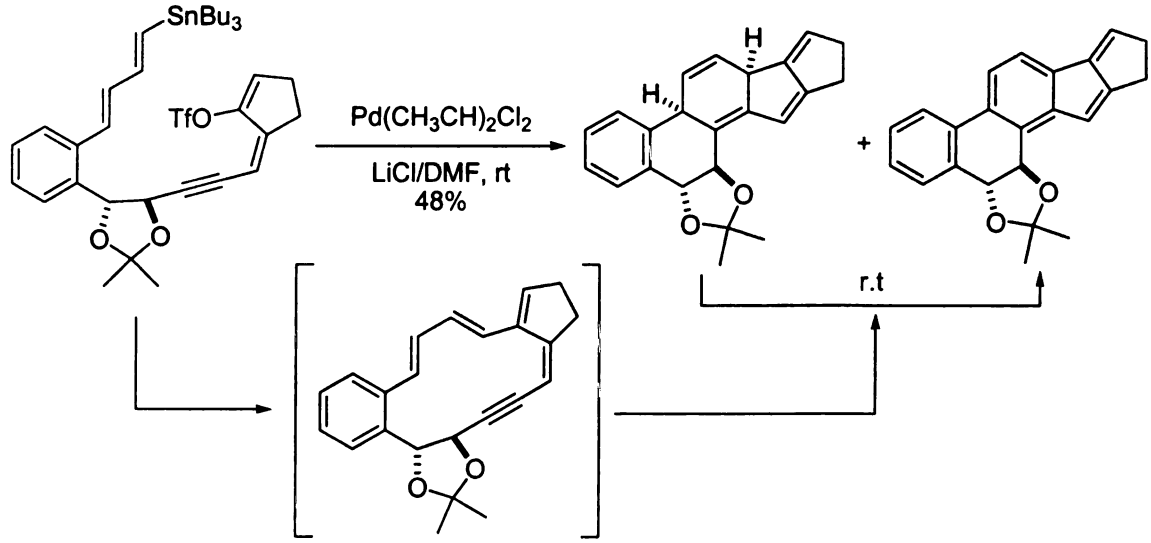
The optimized tandem Stille/Diels-Alder of the all trans triene (TTT) was an improvement over previous methods of forming the macrocycle, the TTT macrocycle has been known to be among the most difficult to close. Five other substrates were examined and it was found that while all substrates formed the macrocycle, only one other substrate, TTC, underwent Diels-Alder cycloaddition to form the tricycle under the Stille reaction conditions (Scheme 16).[24]

Scheme 16. Only Other Successful Stille/Intramolecular Diels-Alder



Suffert developed a system that forms a pentacyclic core following the Stille coupling/Diels-Alder cycloaddition (Scheme 17). Under surprising mild conditions, rt, not only did the Stille coupling proceed, but so did the Diels-Alder cycloaddition. The product began oxidatively aromatizing immediately, during the reaction, purification, and storage. Because other Stille/Diels-Alder reactions require high temperatures Suffert initially proposed the palladium catalyst facilitated the cycloaddition. However, all attempts to form the Diels-Alder precursor via a different method to then subject to the Stille/Diels-Alder reaction conditions were unsuccessful. Therefore the role the palladium catalyst plays in the Diels-Alder reaction has not been determined.[25]

Scheme 17. Suffert's One-Pot Stille/Diels-Alder

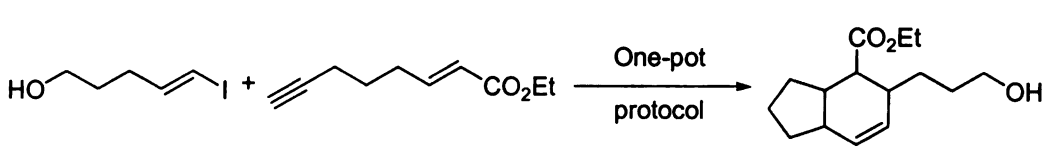


3.3 Development of a model system to test the feasibility of a one-pot hydrostannation/Stille/Diels-Alder reaction

The Maleczka group has developed a one-pot hydrostannation/Stille reaction and there are several examples in literature (shown above) of one-pot

Stille/Diels-Alder reactions, therefore a logical extension of these chemistries is the development of a one-pot hydrostannation/Stille/Diels-Alder reaction. Planning for a spontaneous Diels-Alder in conjunction with the Stille coupling required the Diels-Alder to be an intramolecular process. Due to the substantial investigations into the intramolecular Diels-Alder for the formation of [5,6] ring systems, the model system was developed with a three carbon tether between the diene and dienophile.[26,27,28,29,30,31,32] Since both the vinyl tin and the vinyl iodide would be prepared via a hydrostannation, the tin isomers would need to greatly favor one isomer or be separable. One of the diene vinyl groups would be formed in the one-pot protocol, however, the other (the vinyl iodide) would be isolated and purified prior to the one-pot reaction. While the best way to force the hydrostannation to proceed in high regioselectivity is to bulk up the alkyne, this could potentially inhibit the Stille coupling as well as the Diels-Alder reaction. Therefore, at least in the development of the targeted protocol, an alkyne was chosen with a hydroxyl group remote from the alkyne so that the hydroxyl would not effect the ratio of hydrostannation products but could still facilitate in the separation of the products (Scheme 18).[33]

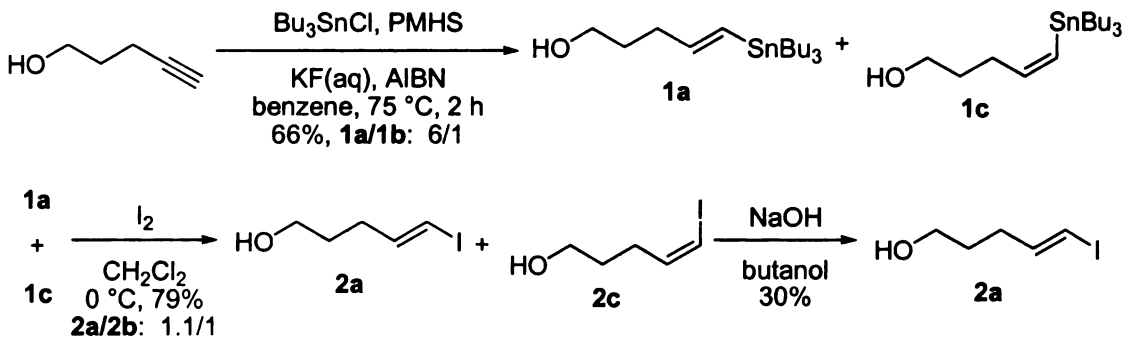
Scheme 18. Model System for One-Pot Hydrostannation/Stille/Diels-Alder



3.3.1 Synthesis of model for the examination of each proposed step in the one-pot hydrostannation/Stille/Diels-Alder reaction

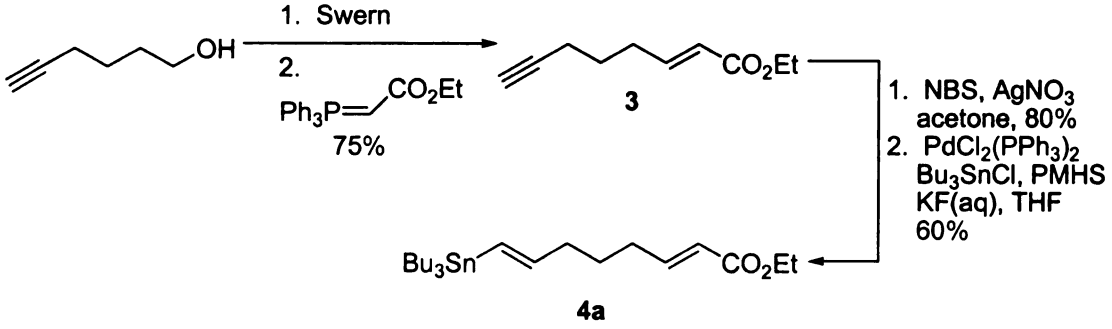
The synthesis of the model system began with the hydrostannation of 4-pentyn-1-ol. This was accomplished utilizing the in situ generation of tributyltin hydride from tributyltin chloride under free radical conditions. The resulting vinyl stannanes were then converted to the vinyl iodides through simple tin-halogen exchange. The E- and Z-isomers were inseparable through both steps, yet pure E-vinyl iodide was acquired through selective consumption of the Z-vinyl iodide with a NaOH/butanol solution (Scheme 19).[34]

Scheme 19. Synthesis of Vinyl Iodide for Model System



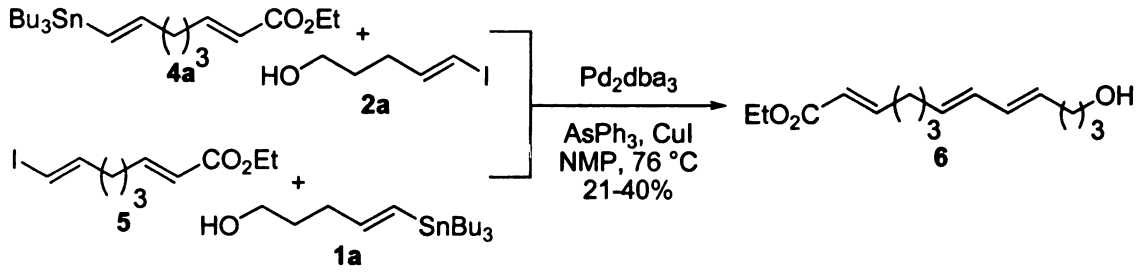
The coupling partner in the proposed Stille coupling was synthesized from 5-hexyn-1-ol. After formation of the vinyl ester from a tandem Swern-Wittig reaction, the alkyne was brominated to increase the propensity for terminal vinyl stannane formation in the subsequent hydrostannation (Scheme 20). Combining

Scheme 20. Synthesis of Vinyl Stannane for Model System



the vinyl iodide with the vinyl stannane under slightly modified Stille-coupling conditions, addition of CuI to increase the rate of transmetallation, afforded the desired diene, albeit in 40% yield (Scheme 21). Attempts to increase the yield by using Liebeskind's catalyst, CuTC, were unsuccessful.[35] After switching the coupling partners so that the ester containing molecule was the electrophile (by the reaction of the vinyl tin with I_2) and the vinyl tin compound was the molecule containing the alcohol the subsequent Stille coupling was attempted (Scheme 21). In this new system the same reaction conditions that were successful before were again (21% yield), while attempts to increase the yield by changing the catalyst system were not successful (i.e., $PdCl_2(TFP)_2$ in DMF and CuI/NaCl in NMP).

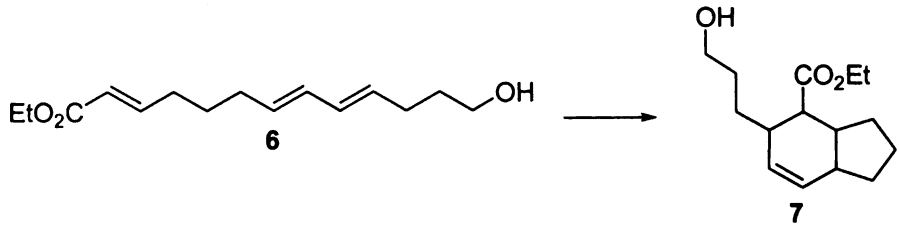
Scheme 21. Diels-Alder Precursor via a Stille Coupling



3.3.2 Examination of the isolated Diels-Alder step

With the fully elaborated diene **6** in hand, investigation into the cyclization of this Diels-Alder precursor was initiated. Simple thermal reactions whether neat or in the presence of solvent (benzene or NMP) did not proceed. Irradiation with a commercially available domestic microwave did not induce cyclization. Attempts to utilize Lewis acid catalysts were also unsuccessful ($AlCl_3$, $TiCl_4$, and $LiClO_4$/CSA) (Table 5).

Table 5. Examination of Diels-Alder Reaction Conditions



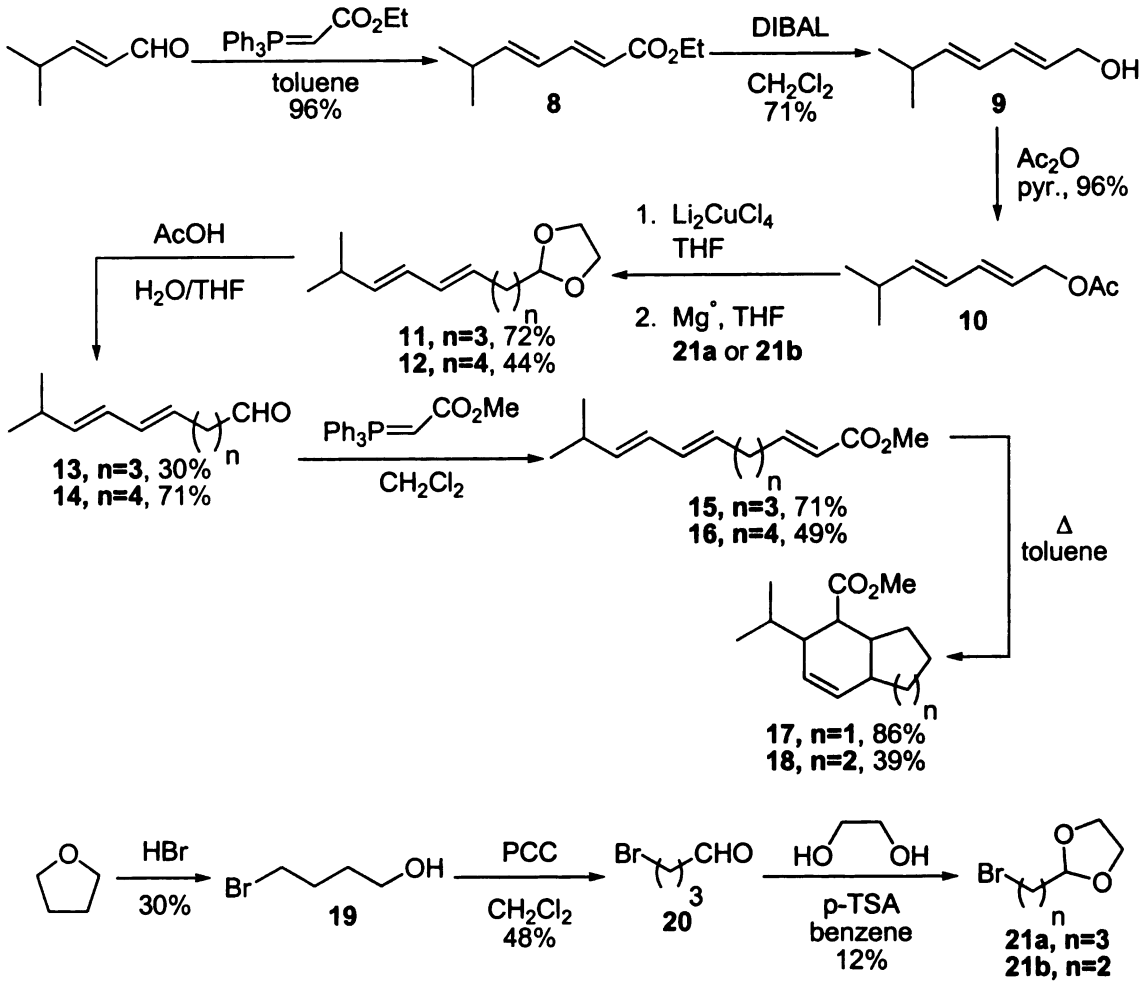
Entry	Additive/conditions	Temperature	Time	yield
1	benzene	180 °C	3 days	SM
2	Microwave, NMP	500W-600W	5-10 min	SM
3	Microwave, neat	500W	5-30 min	SM
4	Microwave, neat	500W-1000W	5-30 min	SM
5	Microwave, neat	1000W	30 min	Decomp
6	1.0 eq $AlCl_3$, CH_2Cl_2	rt	2 days	SM
7	0.2 eq $TiCl_4$, CH_2Cl_2	50 °C	3 days	SM
8	5M $LiClO_4/Et_2O$ 0.1 eq CSA/THF	rt	3 days	SM

Three factors were identified as possible hindrances to the cyclization: 1) an unidentified operational error during the sequence, 2) the presence of a free hydroxyl group, and 3) the ester group was not lowering the LUMO of the dienophile enough to facilitate cyclization.

3.3.3 Synthesis of a known 5,6 ring system closed by a Diels-Alder cycloaddition

To remove doubt over the substrates' inherent inability to undergo the cycloaddition other model systems were sought. A known system that cyclized readily that was closely related to the desired Diels-Alder was identified in literature.[29] The Roush group had previously studied a series of intramolecular Diels-Alder reactions and completed one with a similar core to our system. Roush's Diels-Alder precursor was also comprised of a vinyl ester dienophile,

Scheme 22. Roush's Approach to an Intramolecular Diels-Alder



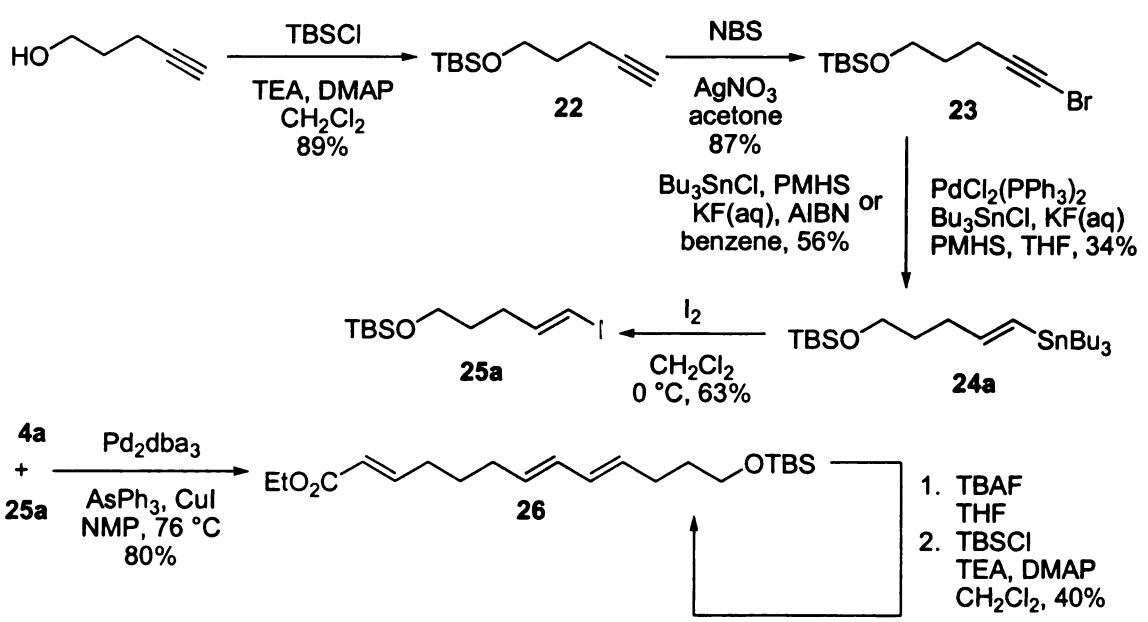
and a three carbon tether between the diene and the dienophile, where as the side chain on the diene was an isopropyl.[29] The synthesis of Roush's methyl (*E,E,E*)-deca-2,7,9-trienoate, **15**, began with a Wittig reaction of 4-methyl pentenal, to give the dienoate, **8**, in 96% yield. Reduction of the ester with DIBAL (71%) and subsequent reaction with acetic anhydride yielded the acylated product, **10** (96%). Cuprate addition of the acetal allowed for chain elongation and hydrolysis of the acetal formed the aldehyde, **13**. The Diels-Alder proceeded well upon heating in toluene to afford the expected cyclized 5,6-fused ring system, 86% yield (Scheme 22). The 6,6-fused ring system was also

synthesized by following the same synthetic route by changing to the acetal Grignard reagent, **21a**, that was elaborated from tetrahydrofuran (Scheme 22).[27,28,29,30,31,32]

3.3.4 Examination of Diels-Alder precursor, modifications thereof and further attempts to cyclize

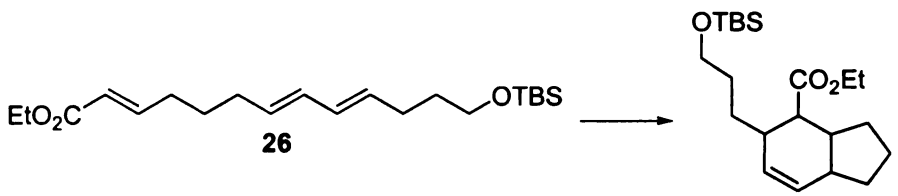
Having established a successful cycloaddition protocol for **15**, exploration into the role of the free hydroxyl group in **6** was examined next. The synthesis of the diene containing portion of the molecule was revised with the protection of the hydroxyl as a TBS silyl ether. Synthesis of the protected Diels-Alder precursor **26** began with the silylation of 4-pentynol. To increase the propensity for E-stannane formation the alkyne was brominated[9,10] and then subjected to hydrostannation conditions (both free radical and palladium catalyzed). The vinyl stannane was subsequently converted to the vinyl iodide and coupled with the stannyl ester fragment under the established reaction conditions. The material

Scheme 23. Synthesis of Silicon Protected Diels-Alder Precursor



was purified by deprotection of the silyl ether with TBAF and reprotected with TBSCl (Scheme 23). However, subsequent attempts to induce the Diels-Alder reaction with **26** again failed (heat/toluene, $MeAlCl_2$, Me_2AlCl, $AlCl_3$, and $LiClO_4$/CSA) (Table 6).

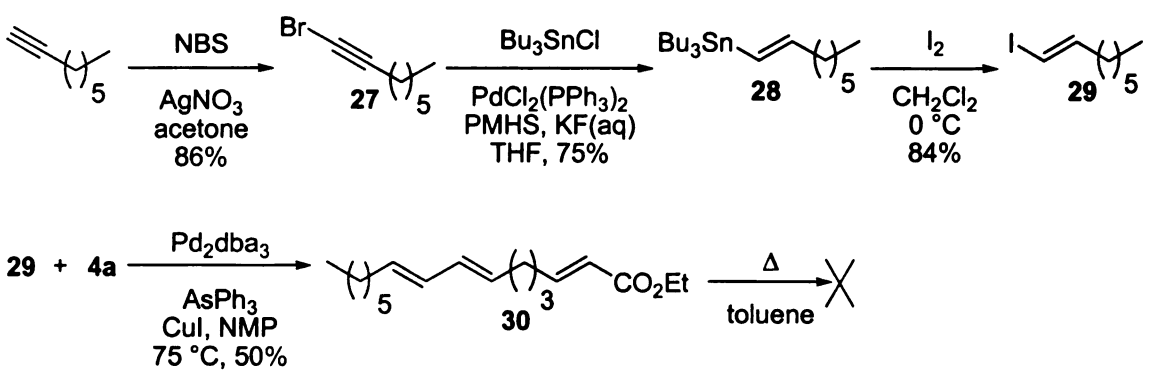
Table 6. Examination of Diels-Alder Conditions for Substrate 26



Entry	Additive/conditions	Temperature	Time	Yield
1	toluene	180 °C	3 days	SM
2	0.9 eq $MeAlCl_2$, CH_2Cl_2	25-50 °C	3 days	SM
3	0.1 eq $AlCl_3$, CH_2Cl_2	rt	5 days	decomp
4	5M $LiClO_4/Et_2O$ 0.1 eq CSA/THF	rt	3 days	SM
5	1.3 eq Me_2AlCl, CH_2Cl_2	25-50 °C	4 days	SM

Because modification of the hydroxyl side chain to a silyl ether did not facilitate the cyclization, the side chain was again modified to a straight chain alkyl. 1-Octyne was employed as the starting point, which was brominated prior

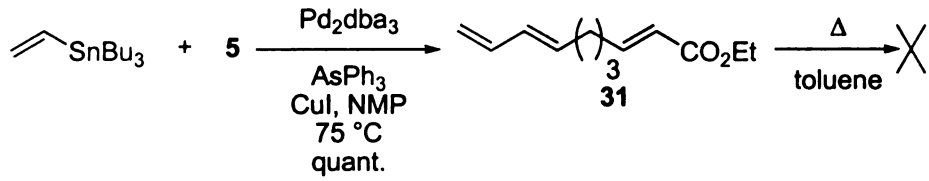
Scheme 24. Synthesis of Straight Chain Diels-Alder Precursor



to hydrostannation. Conversion to the vinyl halide then allowed for Stille coupling. The Diels-Alder reaction of the formed triene, **30**, was again unsuccessful (Scheme 24).

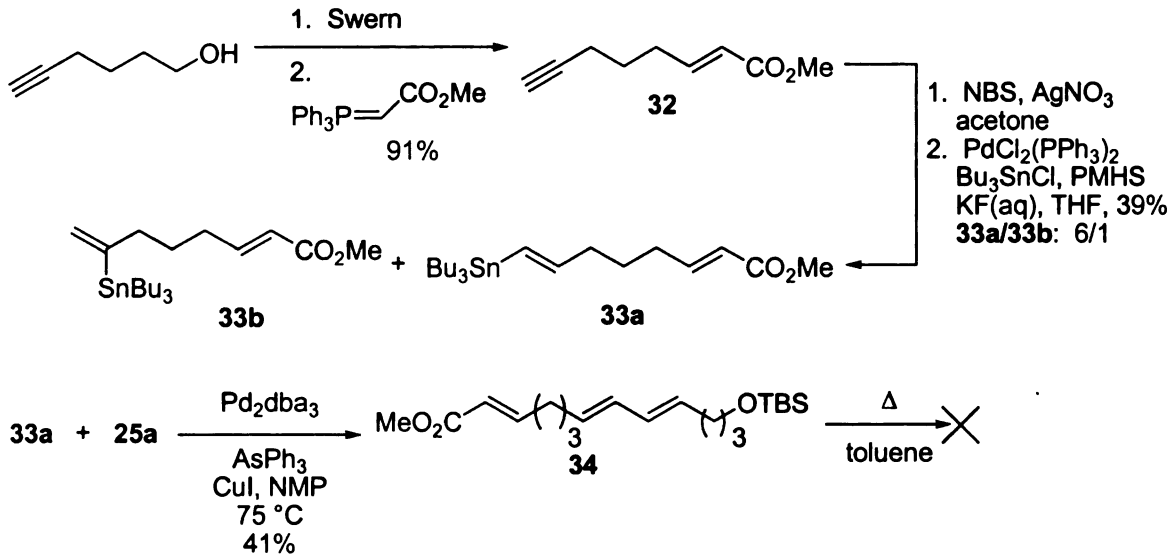
While all attempts to modify the side chain of the dienophile resulted in no net cyclization, the triene was modified one last time, via a Stille coupling of vinyl tributyltin with vinyl iodide **5**. Unfortunately, the unsubstituted triene **31** would also not undergo the thermally promoted Diels-Alder cycloaddition (Scheme 25). The composition of the side chain does not appear to be a factor in the Diels-Alder cycloaddition.

Scheme 25. Synthesis of Unsubstituted Triene **31** for Diels-Alder



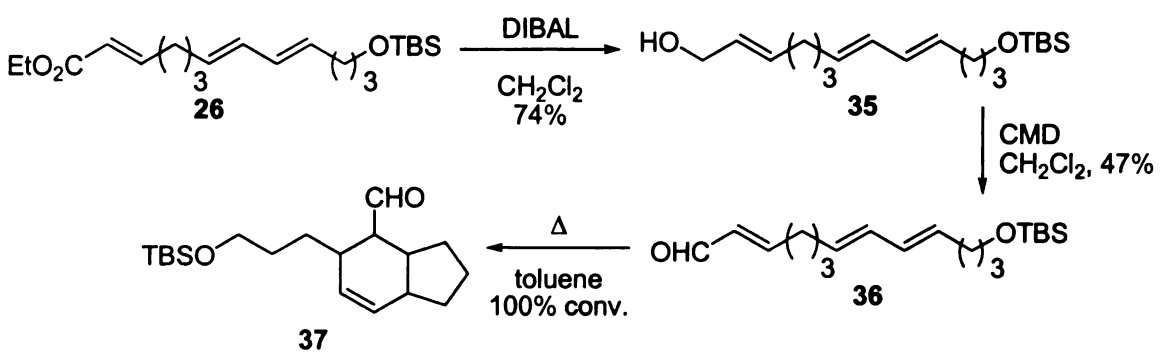
The third potential problem with the Diels-Alder was then examined, the reactivity of the vinyl ester. Since Roush's substrate, **15**, was successfully cyclized and contained a methyl ester, the synthesis of a methyl ester derivative was begun. Additionally, the methyl ester derivative of **31** was successfully cyclized by Roush.[28,29] Following the reaction scheme previously developed modifying the Wittig reagent from an ethyl to a methyl ester allowed for the synthesis of the triene, **34**. However, the cycloaddition was unsuccessful (Scheme 26). With the failure of the methyl ester derivative to cyclize, it was determined that the dienophile needed to be more reactive. Increasing the electron withdrawing nature of the substitution on the dieneophile would lower

Scheme 26. Synthesis of Methyl Ester Triene for Diels-Alder



the LUMO and by increasing the energy gap between the diene and dienophile would promote the Diels-Alder reaction. An aldehyde is more electron withdrawing than an ester and therefore a vinyl aldehyde should be more reactive in the Diels-Alder reaction. To examine this dienophile the Diels-Alder precursor with the TBS-protected alcohol, **26**, was subjected to DIBAL to afford the allylic alcohol, **35**, that was subsequently oxidized with chemical manganese dioxide[36] (CMD) to afford the aldehyde, **36**. Heating this substrate in toluene

Scheme 27. Synthesis and Diels-Alder Reaction of Aldehyde Triene 36

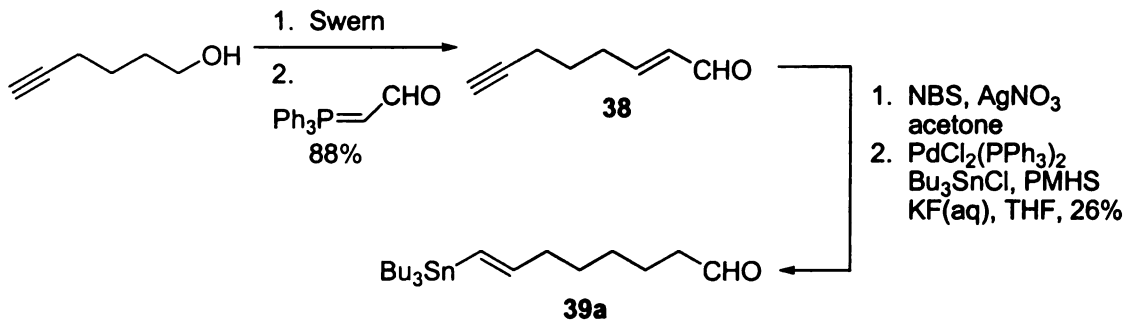


afforded the expected 5,6-fused ring system, **37** (Scheme 27). Therefore, the presence of the ester was the complication in the Diels-Alder reaction that was readily overcome by conversion to the aldehyde.

3.3.5. Attempts to form the Diels-Alder precursor with the aldehyde installed early in the synthesis

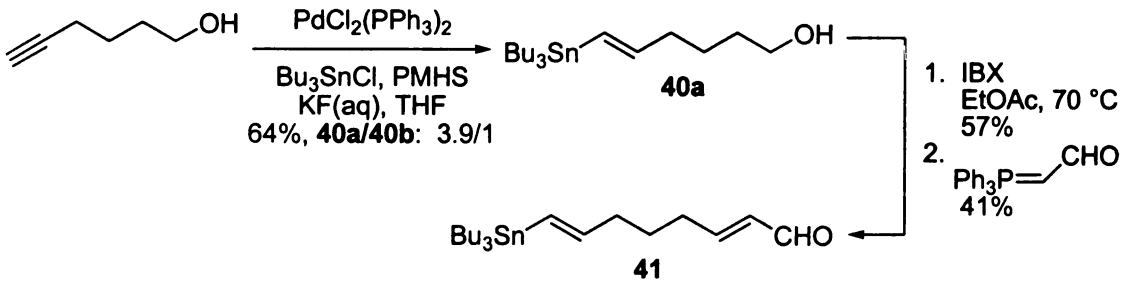
Modification of the previously developed synthesis of **3**, allowed for formation of the α,β-unsaturated aldehyde, **38**. However, the olefin was reduced in the hydrostannation step (Scheme 28). This substrate was a dead-end as the

Scheme 28. Hydrostannation Also Resulting in 1,4-Reduction



planned hydrostannation/Stille/Diels-Alder would not be possible with **39a**. Where as **41** could be converted to the vinyl halide necessary for the Stille coupling while circumventing the hydrostannation step, the α,β-unsaturated

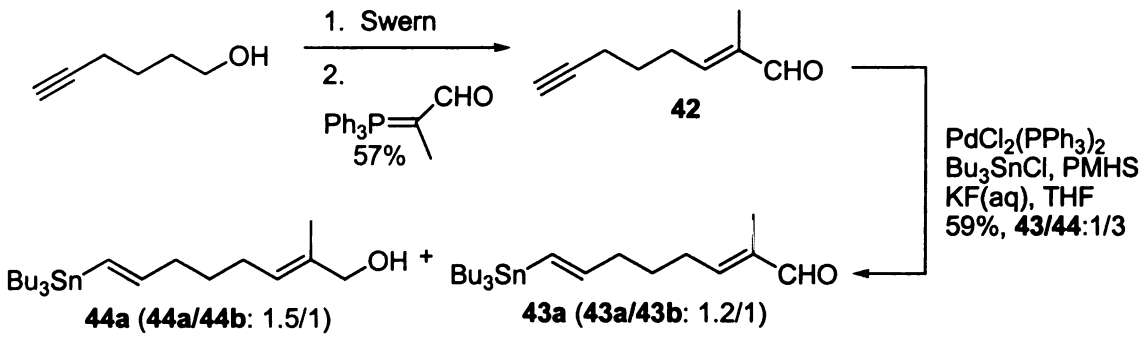
Scheme 29. Synthesis of Compound 41



aldehyde would still be subjected to the hydrostannation conditions in a one-pot reaction (Scheme 29).

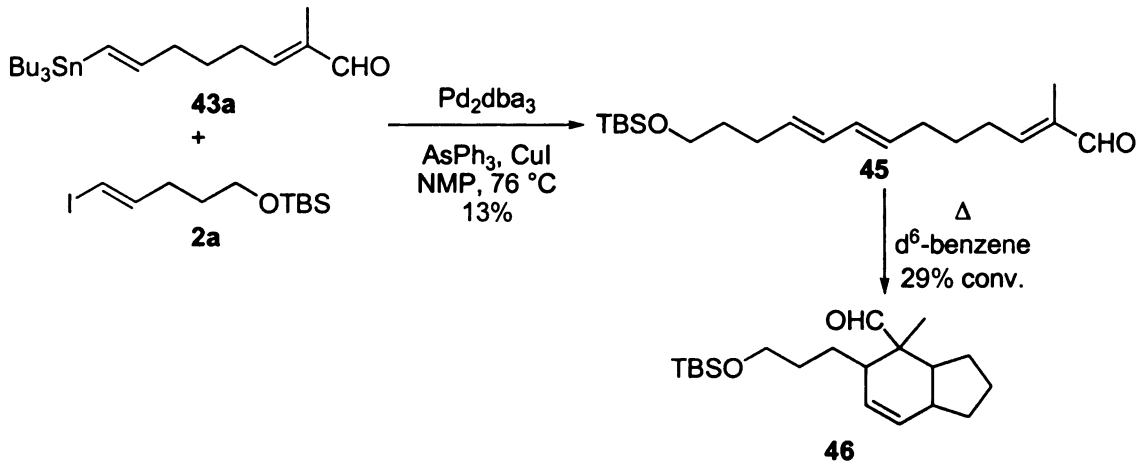
The reduction of the α,β-unsaturated aldehyde, **38**, is presumed to be from the tributyltin hydride that is formed in situ from tributyltin chloride in the hydrostannation step. It was reasonable then that increasing the steric bulk around the aldehyde could inhibit the reduction. Simply changing the Wittig reagent to triphenylphosphoranylidiene methyl acetaldehyde allowed for formation of the hydrostannation precursor, **42**. While olefin reduction was not a problem with the increased sterics, the aldehyde was now reduced (Scheme 30).

Scheme 30. Hydrostannation Resulting in 1,2-Reduction



The aldehyde **43a** was separated and subjected to Stille coupling with **2a** affording the Diels-Alder precursor, **45** (Scheme 31). The Diels-Alder reaction was successful under thermal conditions as monitored by proton NMR. While the Diels-Alder was successful, all attempts to combine the Stille and Diels- Alder reactions in a stepwise one-pot reaction were unsuccessful. While the envisioned end product was achieved, the desired one-pot hydrostannation/Stille/Diels-Alder was not realized due to the unfortunate fact that the α,β-unsaturated aldehyde needed for the Diels-Alder reaction would not

Scheme 31. Synthesis and Diels-Alder of Aldehydic Triene 45



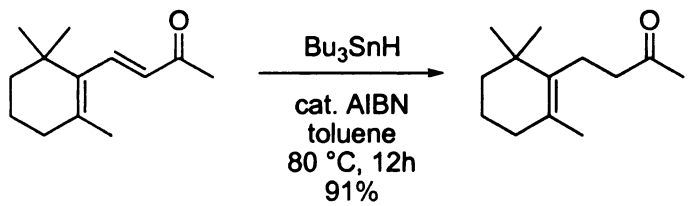
survive the reaction conditions of the hydrostannation. Therefore the one-pot hydrostannation/Stille/Diels-Alder reaction originally envisioned here is not feasible.

Chapter 4: The conjugate reduction of α,β-unsaturated compounds

4.1 Tin hydride as a reducing agent in the reduction of α,β-unsaturated compounds

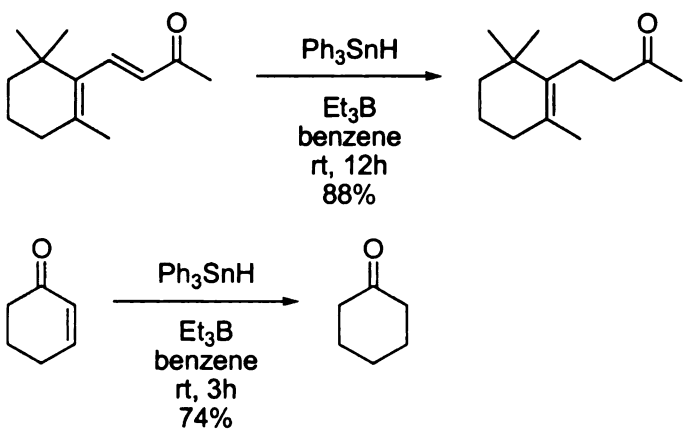
Trialkyltin hydrides have been utilized in the reduction of α,β-unsaturated carbonyl compounds under a variety of conditions, including free radical, Lewis acidic, and metal mediated. Free radical trialkyltin hydride reductions have been well documented (Scheme 32),[37,38,39,40] however, in the absence of a radical

Scheme 32. Free Radical Trialkyltin Hydride 1,4-Reduction



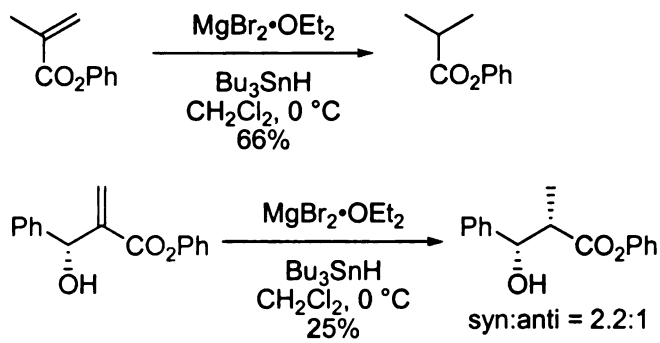
initiator reaction time is considerable (70 h).[41] Conjugate reductions with trialkyltin hydrides have also been induced by Lewis acids. For example, triethylborane in conjunction with triphenyltin hydride has been successfully utilized in the room temperature reduction of α,β-unsaturated carbonyl compounds (Scheme 33).[42] Triethylborane is a known radical initiator, however,

Scheme 33. Lewis Acid Promoted 1,4-Reduction with Triphenyltin Hydride



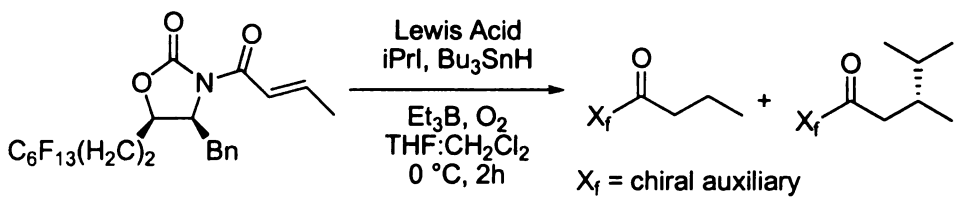
the reduction induced by other Lewis acids is thought to proceed through an ionic mechanism. Nagano not only employed $MgBr_2 \cdot OEt_2$ in straight forward conjugate reductions but also in chelation controlled reductions which resulted in mixtures of diastereomers (Scheme 34).[43] Several Lewis acids were also

Scheme 34. Magnesium Bromide Promoted 1,4-Reduction with Bu_3Sn-H



screened in the reduction of an α,β-unsaturated compound which contains a fluorous oxazolidinone chiral auxiliary. The fluorous auxiliary was utilized to facilitate the removal of tin after the reaction was complete by fluorous solid phase extraction. The aim of the research was the conjugate addition of an isopropyl group in preference to direct reduction, however, there was significant

Table 7. Lewis Acid Assisted 1,4-Reduction in Presence of Fluorous Auxiliary

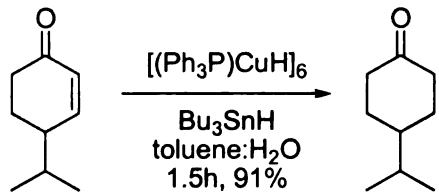


Entry	Lewis acid	%yield	%yield
1	$ZrCl_4$	45	44
2	$Dy(OTf)_3$	25	60
3	$Fe(ClO_4)_3$	22	34
4	$Sc(OTf)_2$	16	62
5	$Cu(OTf)_2$	12	31

reduction product formed with several Lewis acids (Table 7).[44] It is unclear whether the radical or ionic mechanism is at play in the formation of the reduction product.

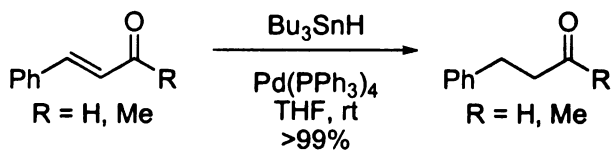
Metal mediated reductions with trialkyltin hydrides have also been developed, palladium appears to be the most widely studied,[45] however, copper

Scheme 35. Regeneration of Stryker's Reagent with Tributyltin Hydride



has also been utilized. Instead of using either stoichiometric amounts of Stryker's reagent or catalytic Stryker's reagent under a hydrogen atmosphere, tributyltin hydride can serve as the stoichiometric source of hydride with Stryker's reagent as the catalyst (Scheme 35).[46] Palladium mediated trialkyltin hydride reductions of α,β-unsaturated carbonyl compounds most commonly employ palladium (0). Keinan showed that tributyltin hydride in the presence of

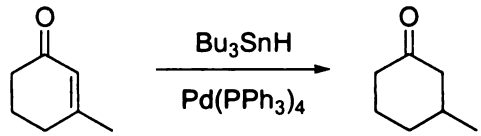
Scheme 36. Palladium Mediated 1,4-Reduction Utilizing Tributyltin Hydride



$Pd(PPh_3)_4$ exhibits hydride donor capabilities that had previously not been seen without the presence of a highly polar medium (containing an additive, i.e., $ZnCl_2$) or highly electrophilic partners (Scheme 36).[47,48] Guibé utilized a coactivating agent, $ZnCl_2$ in THF, or a proton donor, acetic acid in benzene, in the $Pd(PPh_3)_4$ catalyzed reduction of α,β-unsaturated carbonyls with tributyltin hydride. They

found that utilizing $ZnCl_2$ allowed for greater substrate scope than acetic acid and that less reactive enones required the use of greater amounts of $ZnCl_2$ (Scheme

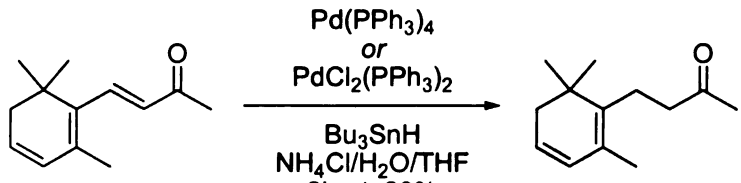
Scheme 37. Zinc Chloride Assisted Palladium Mediated 1,4-Reduction



AcOH/benzene: 23%
$ZnCl_2$/THF: 95%

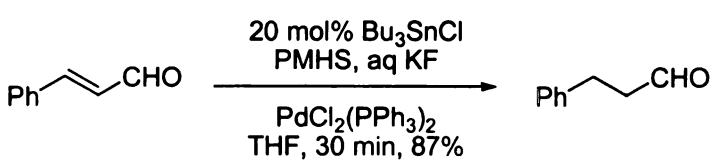
37).[49,50,51] When the radical triphenyltin hydride reduction proved poor yielding, Bäckvall turned to the $Pd(PPh_3)_4$ catalyzed reduction with tributyltin hydride in a NH_4Cl/H_2O/THF solution (Scheme 38).[52] Serra, however, utilized the

Scheme 38. Palladium Mediated 1,4-Reduction Under Aqueous Conditions



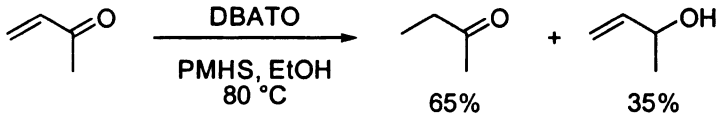
more stable palladium (II) catalyst to produce the same results (Scheme 38).[53] In the course of studying the use of catalytic tributyltin chloride and stoichiometric PMHS to form tributyltin hydride in situ, it was found that under palladium catalysis cinnamaldehyde could be reduced to hydrocinnamaldehyde at a rate that showed 4 turnovers of the catalytic tin(Scheme 39).[54]

Scheme 39. Palladium Mediated 1,4-Reduction Catalytic in Tin



While trialkyltin hydrides have previously been generated in situ by the reaction of siloxanes with organostannoxanes[55] or dialkyltin diacylates,[56] Lipowitz developed a system where bis(dibutylacetoxytin) oxide was used catalytically in conjunction with stoichiometric PMHS. Within this work there was only one example of a successful conjugate reduction (Scheme 40). Methyl vinyl ketone

Scheme 40. In Situ Generated Tin Hydride from Catalytic DBATO and PMHS

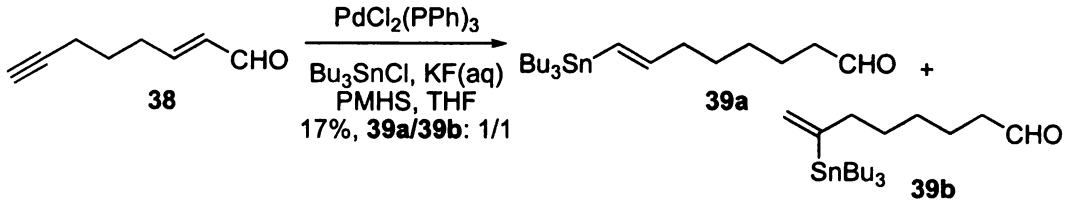


was reduced to the allylic alcohol (65% yield) and the aliphatic ketone (35% yield). Interestingly, when the tin was replaced with Pd/C, 100% yield of the aliphatic ketone was realized (Scheme 43).[57]

4.2 Examination of Bu_3SnH as the source of the hydride

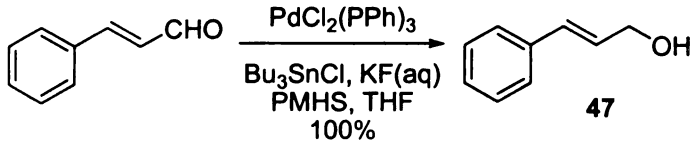
During our study into the feasibility of a one-pot hydrostannation/Stille/Diels-Alder protocol (Chapter 3), it was established that for the proposed Diels-Alder reaction to be successful the dienophile must be an aldehyde. Unexpectedly, in the process of preparing the requisite triene via palladium catalyzed hydrostannation of alkyne **38**, concomitant 1,4-reduction of the α,β-unsaturated aldehyde also occurred (Scheme 41). As shown in Scheme

Scheme 41. Unexpected 1,4-Reduction During a Hydrostannation Reaction



28 and 30, either the olefin or the aldehyde (1,2- or 1,4-reduction) would be reduced based on the substitution on the olefin. Because the reduction of the α,β-unsaturated aldehyde was initially seen in conjunction with the hydrostannation of an alkyne, the initial premise was that the reduction was a result of a palladium mediated tin hydride reduction. Thus to test the feasibility of this speculation, cinnamaldehyde was subjected to the palladium catalyzed hydrostannation conditions affording allylic alcohol **47** in 100% yield in lieu of the expected hydrocinnamaldehyde (Scheme 42). Lowering the tin loading to 20 mol%, from 100 mol%, resulted in the reaction not going to completion.

Scheme 42. Attempted Reduction Under Hydrostannation Conditions



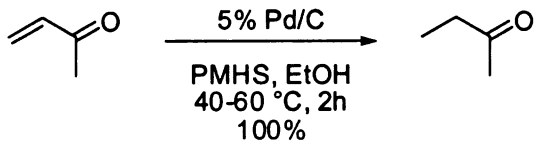
Examination of a variety of α,β-unsaturated carbonyl compounds (i.e., ethyl cinnamate, 2-chlorocinnamic acid, 2-cyclohexen-1-one, phorone, benzalacetone, and α-methylcinnamaldehyde) under the original reaction conditions resulted in inconsistent reductions. Reducing the tin loading again only resulted in lower conversion rates.

4.3 Determination of PMHS as the hydride source in the conjugate reduction

Another possibility for the source of the reduction was the PMHS present in the reaction. PMHS has been utilized as a hydride source in a variety of reduction reactions including 1,4-reductions. Lipowitz showed that a palladium

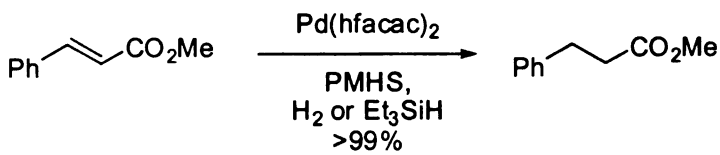
mediated (5% Pd/C) reduction of methyl vinyl ketone with PMHS was high yielding (Scheme 43).[57] Crabtree found that PMHS was capable of stabilizing

Scheme 43. Palladium Catalyzed 1,4-Reduction with PMHS



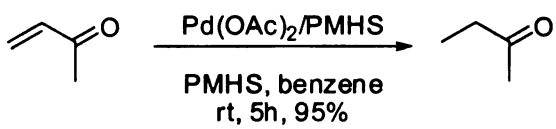
$Pd(hfcac)_2$ a catalyst that performs conjugate reductions with H_2 or silanes as the stoichiometric reductant (Scheme 44).[58] More recently, Chauhan found that

Scheme 44. Palladium Colloid Catalyzed 1,4-Reduction



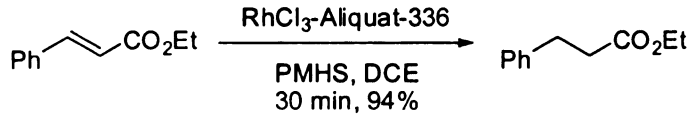
$Pd(OAc)_2$ reacts with PMHS to form reactive palladium nanoparticles that with either excess PMHS or H_2 reduce olefins.[72,59] The methodology was extended to the reduction of α,β-unsaturated carbonyl compounds (Scheme 45), however,

Scheme 45. Palladium PMHS Nanoparticle Catalyzed 1,4-Reduction



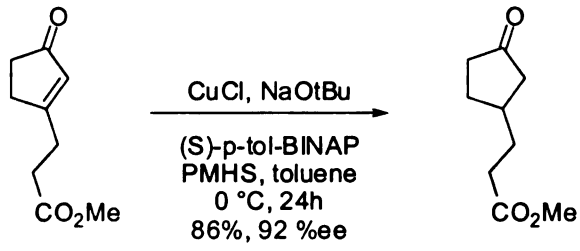
attempts to reproduce Chauhan's nanoparticle reductions were unsuccessful. Metals other than palladium have been examined in conjunction with 1,4-reductions involving PMHS. Pri-Bar found that rhodium with Aliquat® 336 reduced multiple bonds including those of α,β-unsaturated carbonyl compounds selectively (Scheme 46).[60] Copper has been utilized by both Lipshutz and Buchwald in chiral conjugate reductions where the β-postion was substituted

Scheme 46. Pri-Bar's Rhodium Catalyzed 1,4-Reduction with PMHS



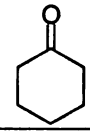
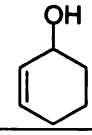
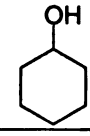
(Scheme 47).[61,62,63,64,65,66] Mimoun screened a variety of metal catalysts in the reduction of cyclohexenone in the presence of PMHS and $NaBH_4$ and found that catalytic $RuCl_2(PPh_3)_2$, $Ni(2\text{-}EH)_2$, $Pd(OAc)_2(PPh_3)_2$, and $Cu(2\text{-}EH)_2$ all afforded

Scheme 47. Asymmetric Copper Catalyzed Conjugate Reduction with PMHS



some conversion to the aliphatic ketone with varying degrees of selectivity (Table 8).[67] Therefore it appeared to be reasonable that the PMHS present in the reaction was the hydride source, substantiated by the fact that the elimination of

Table 8. Metal Screening for Conjugate Reduction of Cyclohexenone

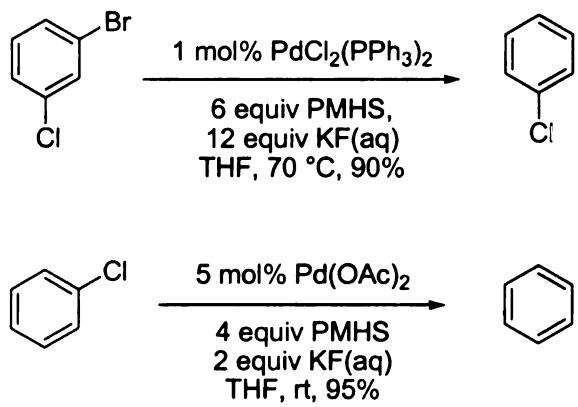
Entry	Catalyst	%conversion	Selectivity (%)		
					
1	$RuCl_2(PPh_3)_2$	92	40	46	13
2	$Ni(2\text{-}EH)_2$	46	68	20	11
3	$Pd(OAc)_2(PPh_3)_2$	100	92	2	6
4	$Cu(2\text{-}EH)_2$	55	98	0	1

tributyltin chloride from the reactions resulted in greater conjugate reduction. Regrettably the reaction was not selective, affording mixtures of the 1,2- and 1,4-reduction products.

4.4 Examination of $Pd(OAc)_2$ as the catalyst

Initial work on the hydrodehalogenation of aryl bromides and iodides by Maleczka and Rahaim found that the reduction proceeded well with $PdCl_2(PPh_3)_2$ as the catalyst.[68] However, this system required a large excess of both PMHS and KF (6 equiv and 12 equiv, respectively). To extend this methodology to aryl chlorides it was found that the use of phosphine-free Pd was necessitated and $Pd(OAc)_2$ was found to be ideal (Scheme 48).[69] This change in catalyst also facilitated the employment of lowered concentrations of PMHS and KF required

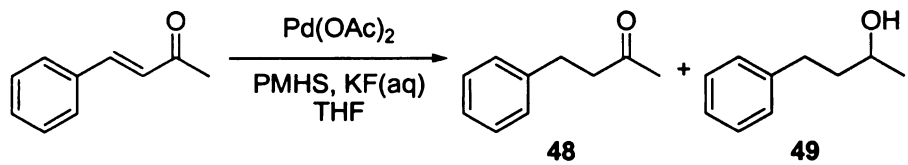
Scheme 48. Palladium Mediated Hydrodehalogenation with PMHS



for the hydrodehalogenation as stated earlier. PMHS has also been observed to react with $Pd(OAc)_2$ to form highly active palladium nanoparticles, which have been shown to perform a variety of reduction chemistries.[70,71,72] Therefore, it appeared that the $PdCl_2(PPh)_3$ catalyst utilized in the observed conjugate reduction might be replaced with $Pd(OAc)_2$ to a positive end. This change in catalyst did result in consistent product formation. The reduction of benzalacetone with 5 mol% $Pd(OAc)_2$, 4 equiv PMHS, 2 equiv KF, 5 mL THF, and 2 mL H_2O (the conditions employed in the hydrodehalogenation of aryl chlorides)

resulted in the desired ketone, **48**, (60%) and the aliphatic alcohol, **49**, (32%) (Scheme 49).

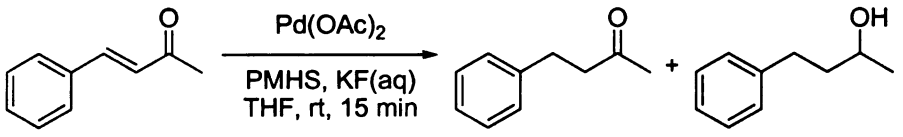
Scheme 49. Conjugate Reduction Under Hydrodehalogenation Conditions



4.5 Optimization of the reaction conditions for the reduction of benzalacetone

Attempting to optimize the reaction conditions, the $Pd(OAc)_2$ loading was reduced keeping all other conditions consistent, establishing that loadings lower than 3 mol% resulted in lower conversion rates. Keeping the catalyst loading at 3 mol%, the PMHS and KF concentrations were reduced while still keeping the ratio of PMHS to KF at a 2:1 ratio. This resulted in increased conversion to the aliphatic ketone. While the reaction was consistently complete in 15 minutes, reducing the KF loading below 0.25 equiv resulted in longer reaction times as did the absence of activator. Without fluoride activation the reaction proceed slowly only reaching 50% conversion at 24 h. Decreasing the concentration of the reaction, and either increasing or decreasing the amount of water resulted in lower conversion to the aliphatic ketone (Table 9). The optimized conditions to come out of these studies were 3 mol% $Pd(OAc)_2$, 0.25 equiv KF, 1 equiv PMHS, 5 mL THF, and 2 mL H_2O (entry 7).

Table 9: Examination of the Reduction of Benzalacetone with KF as the Activator of PMHS



entry	mol% $Pd(OAc)_2$	equiv KF	equiv PMHS	mL THF	mL H_2O	% conversion ketone	% conversion alcohol
1	5	2	4	5	2	65.2	28.3
2	4	2	4	5	2	63.7	31.3
3	3	2	4	5	2	62.3	27.6
4	1	2	4	5	2	56.4	19.0
5	3	1	2	5	2	65.7	30.3
6	3	0.5	1	5	2	69.5	28.7
7	3	0.25	1	5	2	75.7	19.9
8	3	0.25	1	5	1	64.6	33.3
9	3	0.25	1	5	3	72.7	26.0
10[a]	3	0.01	4	5	2	66.5	33.5
11[a]	3	0.01	4	10	2	63.5	36.5
12[b]	3	-	1	5	2	50.3	-

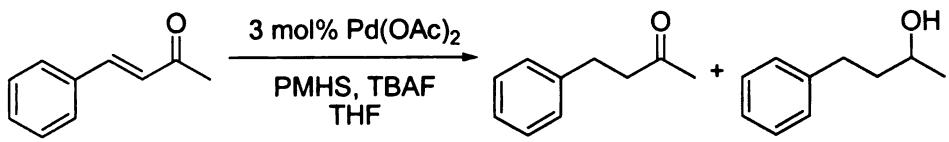
[a]run for 2 h, [b]run for 24 h

4.6 Examination of TBAF and Triton® B as activators of PMHS

KF is only one of many additives that have been used to activate PMHS. Fluoride has been the most common additive for promoting the transfer of nonsiloxane groups from organosiloxanes (i.e., hydride). TBAF, KF, CsF, and TASF have all been utilized to promote the transfer of phenyl from phenyltriethoxysilane in the palladium catalyzed conjugate addition to cyclohexenone via a hyper-coordinate silicon.[73] Catalytic amounts of TBAF have also been utilized with PMHS, without the presence of an added catalyst, to promote the reduction of the carbonyl group of ketones, carboxylic acids, esters, and aldehydes.[74,77] While fluoride additives have been the most common additive, Triton® B has also been shown to effectively activate PMHS in the

reduction of carbonyl compounds.[77] Therefore, TBAF and Triton® B were examined as activators in our 1,4 reductions.

Table 10: Examination of TBAF as the Activator in the Reduction of Benzalacetone



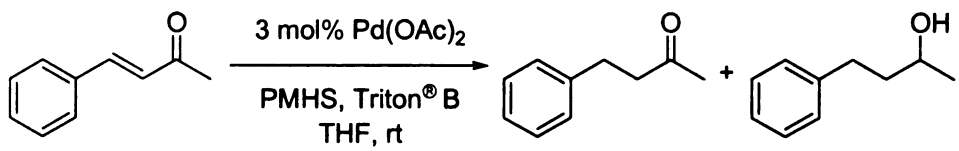
entry	mol % TBAF	equiv PMHS	% conversion ketone	% conversion alcohol
1[a]	1 drop	2	87.0	13.0
2[a]	1 drop	5	84.5	15.5
3[a,b]	1	5	69.9	30.1
4[a,b]	2	5	57.5	42.5
5[a,b]	3	5	71.8	28.2
6[c]	4	5	100	-
7[c]	5	5	78.3	21.7
8[c]	4	3	84.7	15.3
9[c]	4	2	75.6	24.4
10[c]	4	1	66.3	9.5

[a]run at rt, [b]sol-gel formation, [c]run at -78 °C

Utilizing KF as an activator required water to dissolve the KF so that the activator was accessible in the reaction. Previously our group has utilized TBAF as a phase transfer catalyst to promote the transfer of the fluoride ion into the THF layer. We hypothesized that TBAF could be utilized as the primary activator of PMHS in the conjugate reduction and remove the necessity of adding additional water in the reaction.[75] Initial attempts to incorporate TBAF into the previously developed conditions resulted in high conversion to the desired ketone (85-92%) and low conversion to the aliphatic alcohol (7-15%) with only one drop of TBAF and a variety of PMHS concentrations (Table 10). However, 1 drop of 1.0M TBAF in THF is not exact in terms of the actual quantity of TBAF delivered

to the reaction. Therefore, 1-6 mol% of TBAF was examined. In these cases it was found that sol-gel formed at room temperature. Interestingly, lowering the temperature to -78°C eliminated the problem. Due to the cryogenic conditions, the reaction was run under N_2, however, this does not constitute an anhydrous system because the 1.0M TBAF solution in THF contains water.[75] It was determined that 4 mol% TBAF was ideal with 5 equiv PMHS, 3 mol% $Pd(OAc)_2$ in 5 mL THF at -78°C (entry 6). Slightly longer reaction times were observed in the reduction of benzalacetone with TBAF (2 h) than with KF (15 min). Interestingly, the addition of 6 mol% PPh_3 to the reaction resulted in 79% conversion to the allylic alcohol. This result emphasizes the need to form phosphine-free palladium/PMHS nanoparticles in the conjugate reduction.

Table 11: Examination of Triton® B as the Activator in the Reduction of Benzalacetone



entry	mol% Triton® B	equiv PMHS	% conversion ketone	% conversion alcohol
1	4	2	72.5	27.5
2	3	2	77.3	22.7
3[b]	3	2	73.7	26.3
4	2	2	83.3	16.7
5	1	2	45.1	10.7
6	1	3	87.2	12.8
7[a]	1	3	85.5	14.5
8	1	4	79.4	20.6
9	1	5	73.3	26.7

[a]run at -78 °C, [b]activator was concentrated prior to reaction

The third activator of PMHS that was examined was Triton® B, which is a cost effective and fluoride free alternative to TBAF (Table 11).[76] First looking at the activator loading, the conversion to desired ketone dropped off noticeably at 1 mol% Triton® B (entry 5). However, simply increasing the concentration of PMHS to 3 equivalents returned the conversion to the ketone to 87% (entry 6). While the reduction was not noticeably hampered by cryogenic conditions, the reaction could be run at room temperature (2 h) because no sol-gel formation was observed. There also appeared to be no concern for the presence of water. Therefore this activator, unlike KF and TBAF, allowed for an anhydrous reaction system. While Lawrence concentrated the commercially available methanol solution of Triton® B (40 w/w%) to afford the pure ammonium salt,[77] it was found that this step was not necessary under our conditions. The optimized Triton® B conditions were determined to be 3 mol% $Pd(OAc)_2$, 1 mol% Trition® B, and 3 equiv PMHS in 5 mL THF. A related activator, benzyltrimethylammonium chloride, afforded 80% conversion to the desired ketone, however, the reaction time was quite long, 18 h.

4.7 Examination of substrate scope

Having established three sets of reaction conditions for the 1,4-reduction of enones, substrate screening was initiated to determine the scope of these reduction systems. Reduction of ethyl cinnamate (Table 12, entry 1) resulted in 100% conversion with all three conditions and nearly quantitative yield of the intact ester. A second aromatically activated substrate, cinnamamide (entry 2) underwent 79-100% conversion, however, purification by flash chromatography

resulted in loss of product (53-58% yield). Non-activated substrates were also reduced readily, phorone (entry 3), with KF and Triton® B as activators, was reduced to the fully saturated ketone. Utilization of TBAF as the activator resulted in formation of both the mono-reduced product (73%) and the fully saturated ketone (22%).

Table 12: Examination of Ketone Substrate Scope

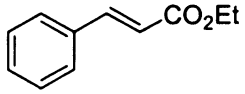
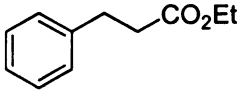
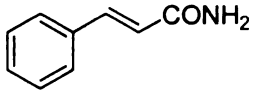
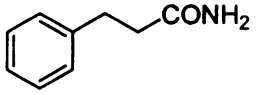
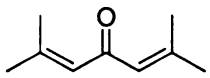
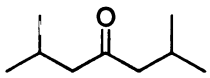
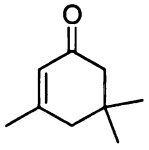
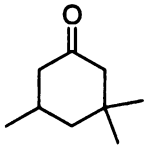
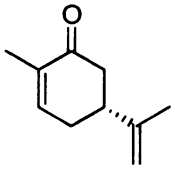
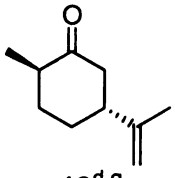
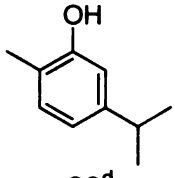
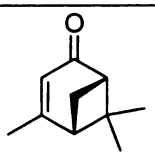
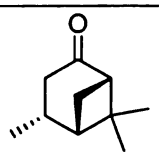
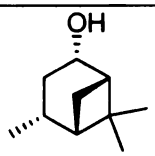
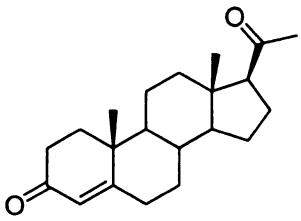
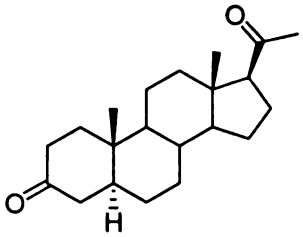
entry	substrate	Conditions[a]	Products[b]	
1				
		KF	100	
		TBAF	100	
		Triton® B	100	
2				
		KF	100	
		TBAF	79	
		Triton® B	97	
3				
		KF	99	
		TBAF	22[c]	
		Triton® B	100	
4				
		KF	94[e]	
		TBAF	29	
		Triton® B	98	
5				
		KF	40[d,g]	60[d]
		TBAF	65[d,h]	8[d]
		Triton® B	89[d,i]	2[d]

Table 12 (cont'd).

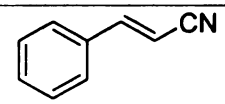
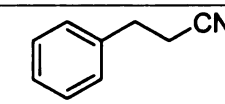
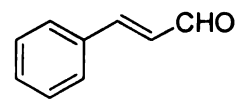
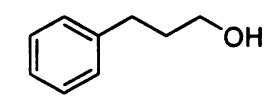
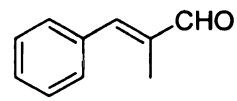
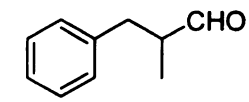
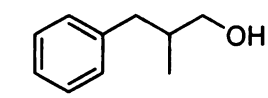
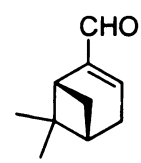
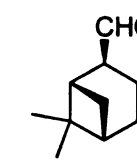
entry	substrate	Conditions[a]	Products[b]	
6				
		KF	100[f]	-
		TBAF	95	-
		Triton® B	62[d]	28[d,j]
7				
		KF	78	
		TBAF	50	
		Triton® B	100	

[a]KF: 3 mol% $Pd(OAc)_2$, 0.25 equiv KF, 1 equiv PMHS, 5 mL THF, 2 mL H_2O, TBAF: 3 mol% $Pd(OAc)_2$, 4 mol% TBAF, 5 equiv PMHS, 5 mL THF, Triton® B: 3 mol% $Pd(OAc)_2$, 1 mol% Triton® B, 3 equiv PMHS, 5 mL THF, [b]% conversion, [c]mono-olefin was major product, 73%, [d]isolated yield, [e]0.5 equiv KF, [f]0.5 equiv KF, 2 equiv PMHS, [g]11:1 trans, [h]9:1 trans, [i]7:1 trans, [j]5:1 α-OH

Several cyclic enones were also examined with favorable results. The reduction of 3,5,5-trimethylcyclohexenone (entry 4) also shows variability in the reduction of the enone with TBAF, only 29% conversion whereas with KF and Triton® B 94-98% conversion was observed. The reduction of (R)-carvone (entry 5) resulted in two products with the activator determining whether the enone reduction product or the rearrangement product (carvacrol) was major. The formation of carvacrol is known to occur under acidic,[78] basic,[79] hydrogenation[80,81] and high temperature[82,83] conditions via a radical based mechanism. Under the KF conditions the rearrangement pathway is favored, affording the phenol in 60%, while TBAF and Triton® B only produce trace amounts (8% and 2%). Additionally, it should be noted that the remote olefin is

not reduced and that the ketone product is diastereomerically enriched (>7:1 trans). The increased steric hindrance of (1S)-verbenone (entry 6) yielded only one diastereomer as determined by NMR. Reduction with both KF and TBAF resulted in near quantitative conversion to the ketone, while Triton® B also resulted in some alcohol formation (28%). The reduction of progesterone (entry 7) with TBAF was low yielding (50%) while KF and Triton® B were more efficient (78-100%).

Table 13: Examination of Aldehyde Substrate Scope

Entry	substrate	conditions[a]	Products[b]	
1				
		KF	86[c]	
		TBAF	76[c]	
		Triton® B	57[c]	
2				
		KF	30	
		TBAF	100	
		Triton® B	71	
3				
		KF	38[d,f]	47[d,f]
		TBAF	39[d]	55[d]
		Triton® B	20[c]	55[c]
4				
		KF	94[e,f]	
		TBAF	100[g]	
		Triton® B	66[c,h]	

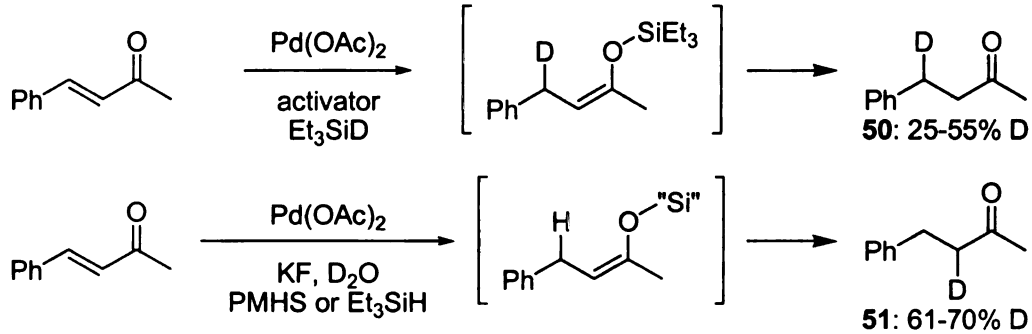
[a]KF: 3 mol% $Pd(OAc)_2$, 0.25 equiv KF, 1 equiv PMHS, 5 mL THF, 2 mL H_2O, TBAF: 3 mol% $Pd(OAc)_2$, 4 mol% TBAF, 5 equiv PMHS, 5 mL THF, Triton® B: 3 mol% $Pd(OAc)_2$, 1 mol% Triton® B, 3 equiv PMHS, 5 mL THF, [b]% conversion, [c]isolated yield, [d]% yield by nmr, mesitylene internal standard, [e]ratio of isomers 13:1, [f]0.5 equiv KF, 2 equiv PMHS, [g]ratio of isomers 54:1, [h]ratio of isomers 13:1

Cinnamonitrile (Table 13, entry 1) reduced cleanly to the saturated nitrile, while cinnamaldehyde (entry 2) was over reduced to the alcohol (30-100%). The increased steric hindrance around the olefin allowed for the formation of the conjugate reduction product of α-methylcinnamaldehyde (entry 3) as well as the alcohol. Here use of Triton® B resulted in greater conversion to the alcohol (55%) in comparison to TBAF (19%). The reduction of (S)-myrtenal (entry 4) proceeded smoothly to the saturated aldehyde in a 13:1 ratio of isomers.

4.8 Deuterium labeling study in the conjugate reduction of benzalacetone

To probe the mechanism of these palladium mediated 1,4-reductions a number of deuterium labeling experiments were conducted. Employing deuteriotriethylsilane in the Pd-catalyzed (3 mol%) reduction of benzalacetone via KF and Triton® B activation afforded deuterium incorporation at the β-carbon (55% and 25%, respectively). Application of D_2O in the KF reduction utilizing either triethylsilane (61% D) or PMHS (70% D) resulted in deuterium incorporation at the α-carbon. These results are consistent with hydrosilation followed by hydrolysis of the silyl enol ether intermediate (Scheme 50). The

Scheme 50. Deuterium Labeling Study to Establish Potential Mechanism



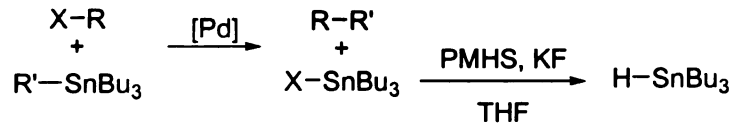
development of three methods to reduce α,β-unsaturated carbonyl compounds in a 1,4-manner has been achieved. While the 1,2-reduction has not been completely suppressed, most substrates only showed 1,4-reduction. The three methods were all equally successful with different advantages to each method. KF and TBAF are common fluoride activators, however due to the ability of TBAF to polymerize PMHS at room temperature cryogenic conditions are necessary (-78 °C). In contrast, the KF activated reduction is performed at room temperature. Triton® B is instead a fluoride free activator and the reduction is under anhydrous conditions. In all three cases the activator is employed in substoichiometric or catalytic concentrations.

Chapter 5: Development of a one-pot Stille/hydrostannation protocol

5.1 Recycling trialkyltin halides in a one-pot hydrostannation/Stille reaction

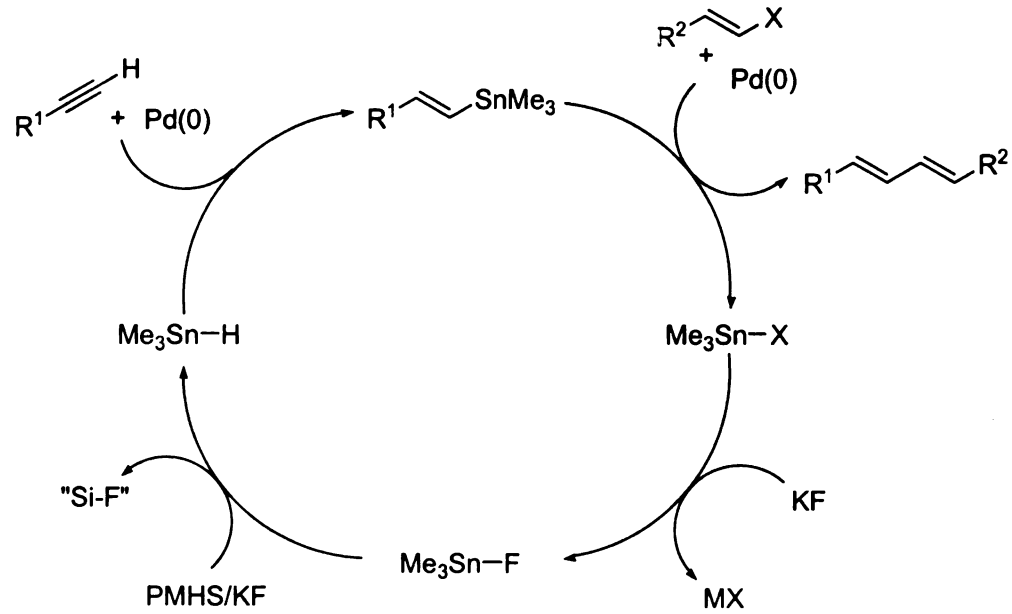
Vinyl tin compounds are very useful in synthetic organic chemistry and therefore their preparation is also important. Typically vinyl tins are prepared

Scheme 51. Potential Funneling to Tin Hydride from a Stille Coupling



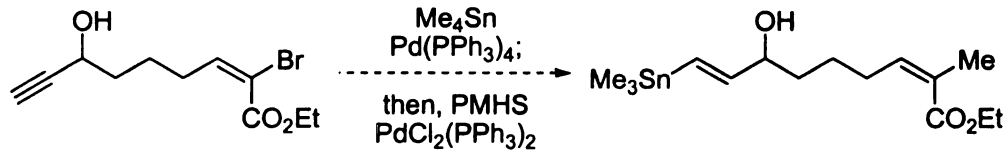
from the hydrostannation of alkynes with a triorganotin hydride. As mentioned in Chapter 2, the Maleczka group has developed a method to produce triorganotin hydride in situ from triorganotin chloride.[5,54] While this method employs commercially available tributyltin chloride, it is possible to envision that the tributyltin halide that is converted to tributyltin hydride could be the stoichiometric byproduct of a Stille coupling (Scheme 51). Additionally, the one-pot

Scheme 52. One-Pot Hydrostannation/Stille Coupling Catalytic in Tin



hydrostannation/Stille coupling developed by the Maleczka group was further elaborated into a catalytic variant in which trimethyltin chloride is converted to trimethyltin hydride in situ [14,15,16,18,84] Subsequent addition to an alkyne produces the vinyl tin component for the Stille coupling which then regenerates the trimethyltin halide that re-enters the reaction sequence (Scheme 52). While this protocol shows that the triorganotin halide that is generated in the Stille coupling can be recycled into triorganotin hydride through consumption of the vinyl tin. The question arises, would it be possible for the terminal product to be the hydrostannation product? In other words, could we develop a Stille coupling/hydrostannation sequence where between steps the trialkyltin is recycled in situ to trialkyltin hydride (Scheme 53)?

Scheme 53. Envisioned One-Pot Stille Coupling/Hydrostannation

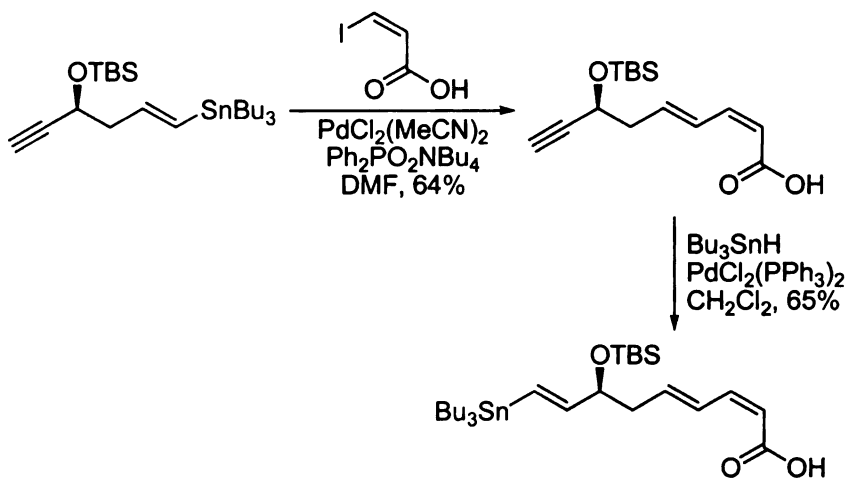


5.2 Initial model development

The model that was envisioned for the development of a one-pot Stille/hydrostannation protocol was one where the Stille coupling and the hydrostannation occur on different functionalized appendages of the same compound. There are limited literature examples of a Stille coupling followed immediately by a hydrostannation reaction. In the synthesis of (-)-macrolactin A, Smith's group employed a Stille coupling between a vinyl iodide and a vinyl tin that is tethered to an alkyne for the subsequent hydrostannation (Scheme 54).[85]

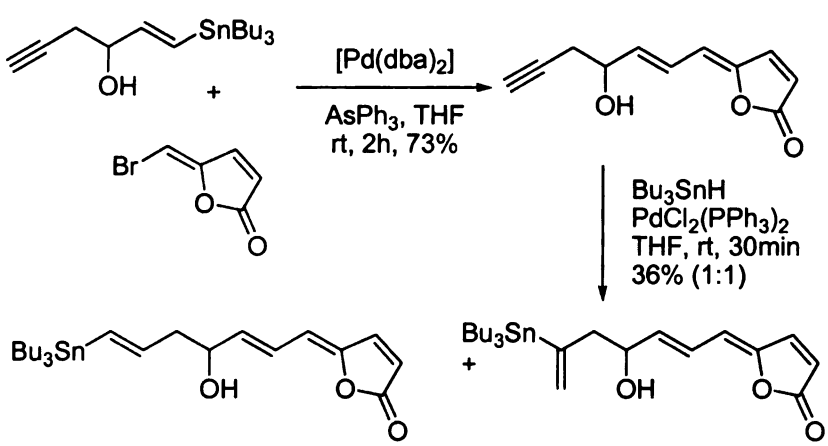
In similar manner, Sorg et. al. explored the use of a Stille coupling employing a vinyl bromide and a vinyl tin that is tethered to an alkyne that was subsequently

Scheme 54. Sequential Stille Coupling Hydrostannation Towards Macrolactin A



hydrostannated (Scheme 55).[86] These examples show that combining the Stille coupling with the hydrostannation in a one-pot system would be synthetically useful and would also reduce the total amount of tin necessary for the overall transformation.

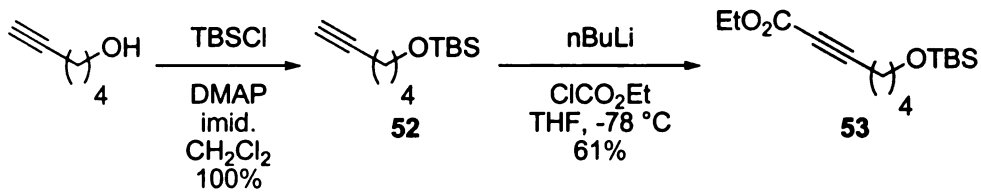
Scheme 55. Sorg's Sequential Stille Coupling Hydrostannation



Having established a literature precedence for the stepwise Stille coupling hydrostannation reaction, a model needed to be developed to probe the

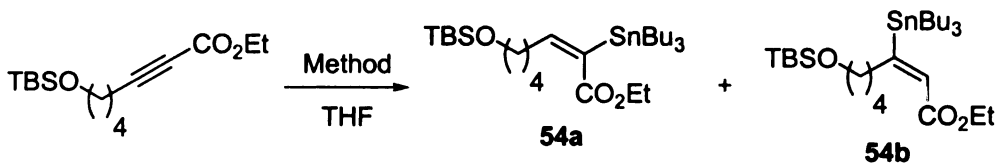
feasibility of combing the two reactions in a one-pot process. The initial model system would couple a vinyl halide and a vinyl tin in a Stille coupling, followed by in situ generation of tin hydride and subsequent hydrostannation of an alkyne. The vinyl halide would be easily accessible via hydrostannation of an alkyne followed by subsequent tin halogen exchange. Thus the model system would require two alkynes with altered reactivities, or the installation of each alkyne just

Scheme 56. Synthesis of Alkyne **53** for Model System



prior to their application. The route chosen would be the introduction of the alkyne for the hydrostannation late in the synthesis, utilizing Carreira's alkynylation of an aldehyde.[87,88,89,90,91] The synthesis began with O-silylation of 5-hexyn-1-ol to allow for the deprotonation of the alkyne and addition of ethyl chloroformate (Scheme 56). The alkyne could then be modified to the vinyl tin

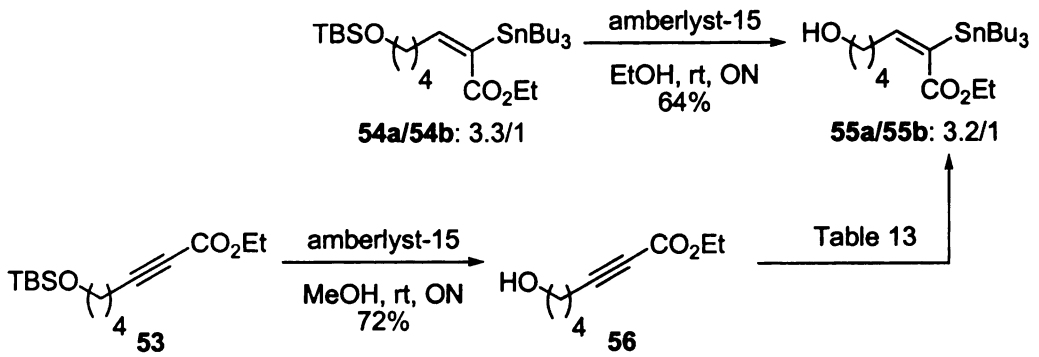
Table 14. Examination of Hydrostannation Conditions on Alkyne **53**



Entry	Method	Ratio (a:b)	% yield
1	1.2 equiv. Bu_3SnCl, 1 mol% $PdCl_2(PPh_3)_2$, 3 equiv. KF(aq), 2 equiv. PMHS, THF, rt	2.5:1	84
2	2 mol% $MoBl_3$, 3 equiv. Bu_3SnH, 9 mol% hydroquinone, THF, 55 °C	3.7:1	79
3	2 mol% $MoBl_3$, 1.3 equiv. Bu_3SnF, 1.3 equiv. PMHS, 9 mol% hydroquinone, THF, 55 °C	3.3:1	88

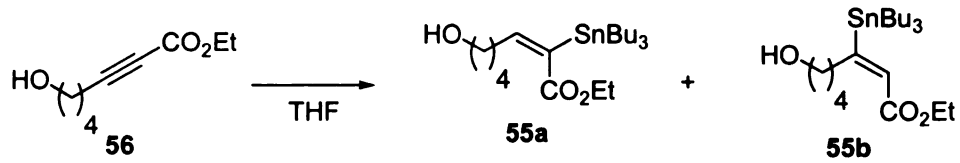
that would eventually be converted to the vinyl halide for the Stille coupling. The hydrostannation proceeded under a variety of conditions to afford the vinyl tin with varying degrees of regioselectivity (Table 14). The hydrostannation was more selective for the desired E-stannane when $MoBI_3$ was employed as the catalyst. This was expected based on the work of Kazmaier,[92,93,94] whose

Scheme 57. Synthetic Routes to Vinyl Tin **55**



conditions were examined in the hydrostannation (entry 2). TBAF deprotection of the silyl ether resulted in low yield (15%) of the desired alcohol, however, the deprotection was achieved in quantitative yield with Amberlyst-15 (Scheme 57).[95] Deprotection of **53** followed by hydrostannation resulted in the same vinyl tin compounds, **55a** and **55b** (Scheme 57). The method of hydrostannation was again investigated and the desired E-stannane was produced more selectively with $MoBI_3$ (Table 15). The separation of the tin isomers was made easier by the presence of the free hydroxyl group. Oxidation with IBX[96,97] (64-94%) or under Swern conditions (93%) resulted in the aldehyde that could then undergo alkynylation.

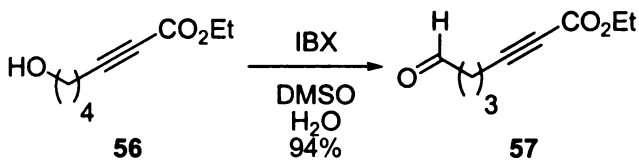
Table 15. Examination of Hydrostannation Conditions on Alkyne **56**



Entry	Method	Ratio (a:b)	% yield
1	1.2 equiv. Bu_3SnCl, 1 mol% $PdCl_2(PPh_3)_2$, 3 equiv. KF(aq), 2 equiv. PMHS, THF, rt	1.7:1	72
2	2 mol% $MoBl_3$, 3 equiv. Bu_3SnH, 9 mol% hydroquinone, THF, 55 °C	3.8:1	92
3	2 mol% $MoBl_3$, 1.3 equiv. Bu_3SnF, 1.3 equiv. PMHS, 9 mol% hydroquinone, THF, 55 °C	3.4:1	81

Unfortunately, the $Zn(OTf)_2$ mediated alkynylation of the resultant aldehyde was unsuccessful. Most successful applications of Carreira's chemistry have been early in syntheses on relatively simple substrates.[98] Because the aldehyde examined contained an ester and a tin moiety, either functional group could be affecting the alkynylation. Taking a step back, the hydroxy ester that was hydrostannated was instead first oxidized to the aldehyde (Scheme 58), but

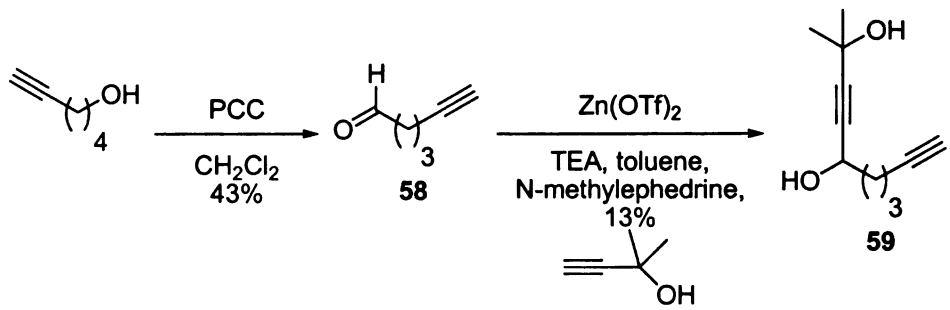
Scheme 58. IBX oxidation of Alkyne **56**



again the $Zn(OTf)_2$ mediated alkynylation was unsuccessful. The alkynylation of 5-hexynal under Carreira's conditions resulted in low yield (<13%) of the expected product (Scheme 59). Protection of the alkyne with TMSCl prior to the

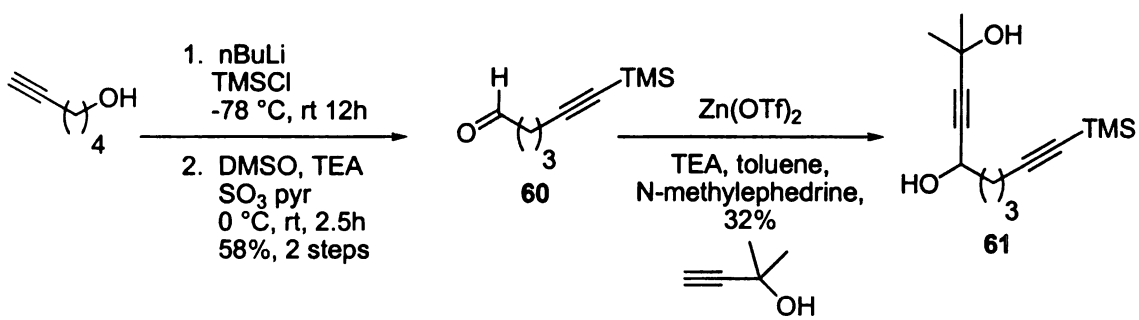
oxidation resulted in an aldehyde, which when subjected to alkynylation with $Zn(OTf)_2$ gave a slightly higher yield (32%) of the addition product than was

Scheme 59. Low Yielding Carreira Alkynylation Strategy



observed with the unprotected alkyne (Scheme 60). The TMS-alkyne was desilylated and the secondary alcohol was silylated with TBSCl. Deprotonation of the alkyne would be followed by the addition of the ester via reaction with ethyl chloroformate (Scheme 61).

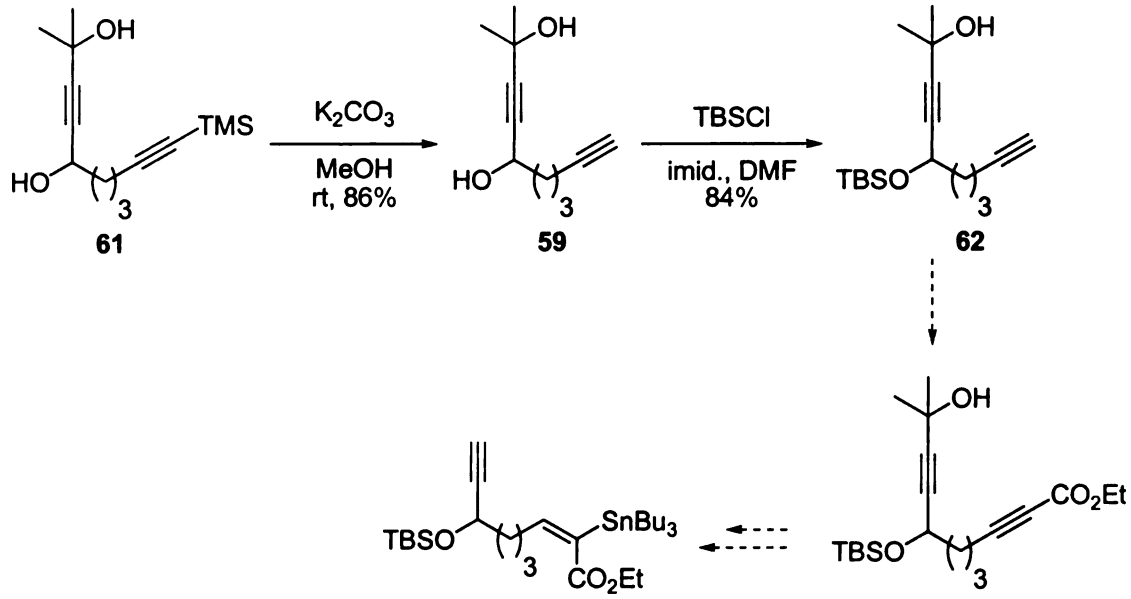
Scheme 60. Application of Protected Alkyne in Carreira Alkynylation



While this substrate could be further elaborated to the vinyl halide, via hydrostannation and tin-halogen exchange, necessary for the Stille coupling and the second alkyne could then be deprotected under basic conditions to afford the alkyne for hydrostannation, the large number of steps and the observed low

yields made this route poor for our methodology study. Ideally, the key substrates should be accessible in as few steps as possible with high yield.

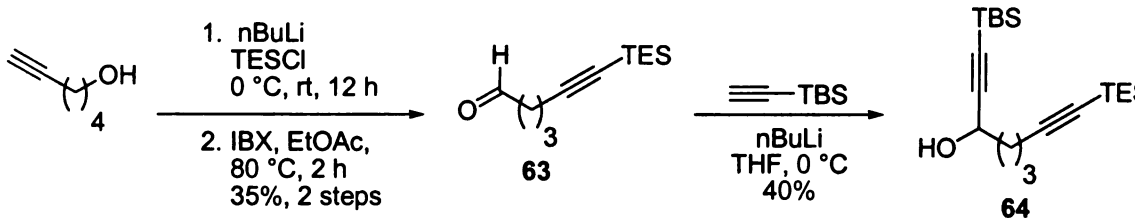
Scheme 61. Revised Route to Alkynyl Vinyl Stannane for Model Study



5.3 Potential models where both alkynes are introduced with different protecting groups

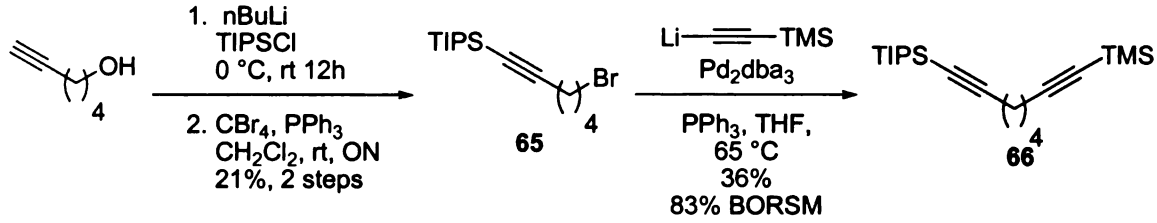
Reaction of lithium acetylides has been a well documented method of introducing alkynes to molecules. This method can be utilized in the formation of di-alkynes that are differentiated by protective group manipulation. The

Scheme 62. Synthesis of Differentially Protected Dialkyne **64**



conversion of 5-hexyn-1-ol to **63**, involved the IBX oxidation of the TES-protected molecule followed by the alkynylation of the resultant aldehyde (Scheme 62). This molecule as well as **66**, formed from the protection of 5-hexyn-1-ol and conversion of the alcohol to the alkyl bromide followed by Fu's sp-sp^3 cross-coupling conditions to form the di-alkyne[99] (Scheme 63), contain two silylprotected alkynes that could be modularly reacted to allow further elaboration of one alkyne into a suitable Stille coupling precursor without modification of the alkyne required for the planned in situ hydrostannation. While each of these compounds were synthesized, the manipulation of the silyl-protecting groups was not extensively studied owing to the limited literature methods to selectively deprotect one silyl group over another.[100] Also it would be determined later that elaboration of these substrates to vinyl tin compounds result in inseparable tin isomers.

Scheme 63. Synthesis of Differentially Protected Dialkyne **66**

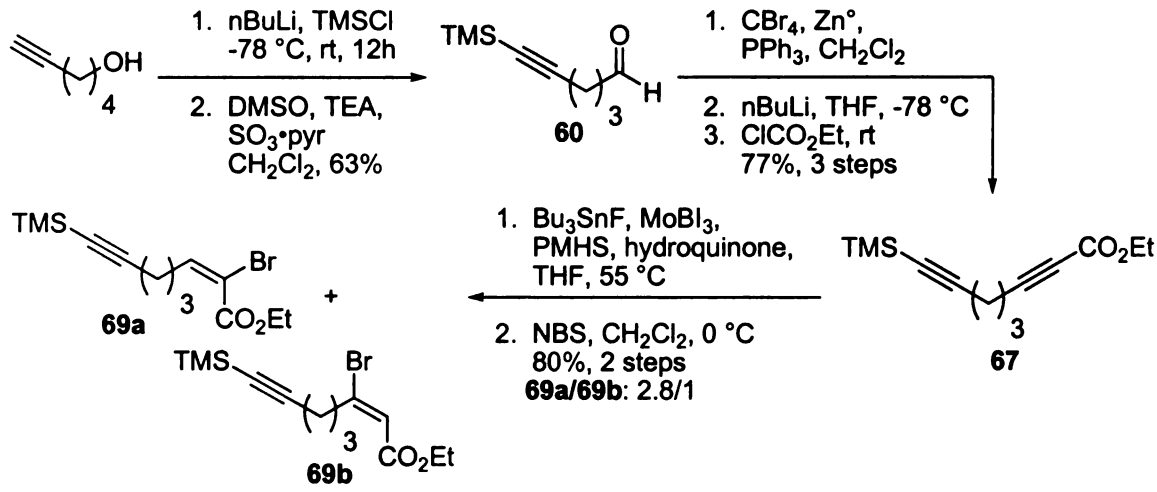


5.4 Formation of an alkyne containing substrate for the investigation of the one-pot Stille coupling/hydrostannation

The Corey-Fuchs reaction[101] could also allow for the introduction of a protected alkyne in a way such that the final product contains two chemically differentiable alkynes. Starting from 5-hexyn-1-ol, protection of the alkyne

followed by oxidation could be performed without intermediate purification. Conversion of the aldehyde to the alkyne could actually be achieved by quenching of the lithium acetylide with ethyl chloroformate to afford the alkynyl ester. Mo-catalyzed (2 mol%) hydrostannation occurred at the expected alkyne,[9] adjacent to the ester and treatment with NBS afforded the desired vinyl bromide (Scheme 64). While NMR of the crude reaction mixture suggested α-bromoester formation, all purification efforts resulted in a 1:1 mixture of vinyl bromide regioisomers.

Scheme 64. Synthesis of Alkynyl Vinyl Bromide **69**



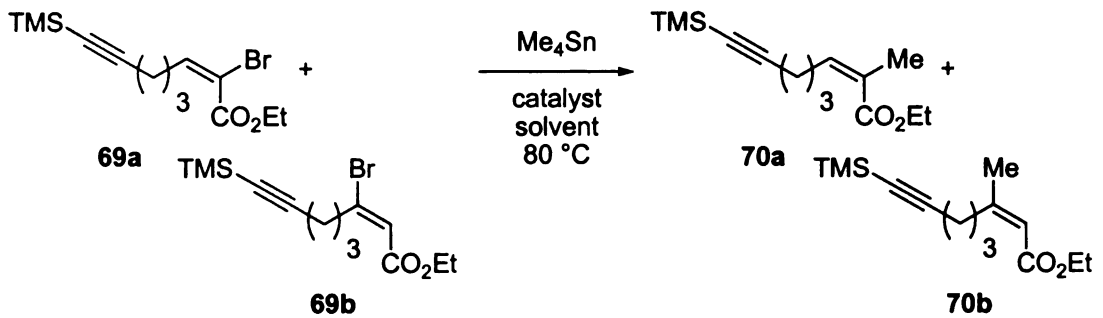
5.5 Examination of the Stille coupling of a vinyl bromide

5.5.1 Examination of the Stille coupling

The vinyl bromide mixture was then subjected to a variety of Stille coupling conditions with tetramethyl tin as the coupling partner (Table 16). Examination of several reaction conditions produced unpredictable results. Several catalysts as well as solvents resulted in 9-49% yield, the exception being the use of CuTC where no reaction occurred (Table 16, entry 9). The more

successful reaction conditions were examined further with the addition of the hydrostannation step.

Table 16. Examination of Cross Coupling Conditions for Tetramethyltin and **69**



Entry	Catalyst	Me_4Sn (equiv)	Solvent	Time (h)	Yield **70a**	Yield **70b**	SM
1	5 mol% Pd_2dba_3[a]	3	NMP	15	24	-	34
2	5 mol% $Cl_2Pd(PhCN)_2$	3	NMP	15	17	-	10
3	5 mol% $Pd(PPh_3)_4$	3	THF	15	9	-	37
4	1.4 mol% $Pd(PPh_3)_4$	1.13	HMPA	48[b]	16	33	-
5	0.7 mol% $Pd(CH_2Ph)(PPh_3)_2Cl$	1.13	HMPA	55[b]	14	31	-
6	5 mol% $Pd(CH_2Ph)(PPh_3)_2Cl$	3	THF	72	12	-	-
7	5 mol% $PdCl_2(PPh_3)_2$	3	THF	15	17	-	41
8	5 mol% $PdCl_2(PPh_3)_2$	3	THF	72	14	27	-
9	10 equiv CuTC	3	THF	20[c]	N.R.		38

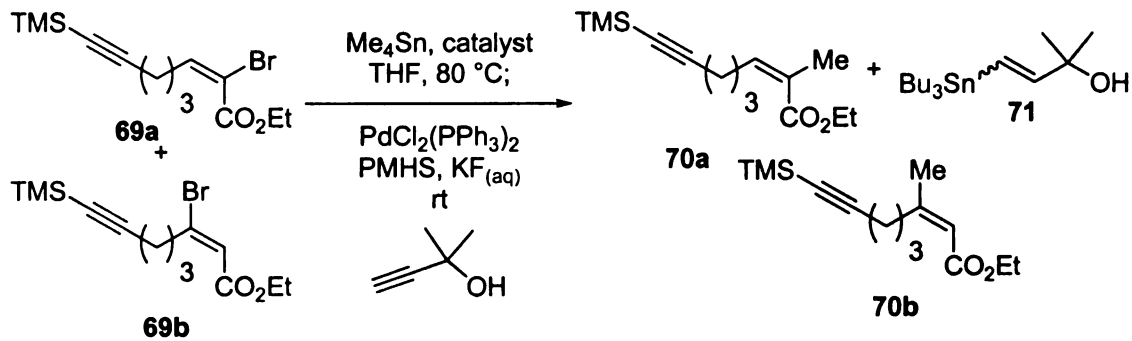
[a]10 mol% $AsPh_3$, 10 mol% CuI; [b]Temperature = 65 °C; [c]Temperature = 20 °C

5.5.2 Examination of the Stille coupling with the addition of an external alkyne

To extend the reaction to a one-pot Stille/hydrostannation reaction the Pd_2dba_3 and $PdCl_2(PPh_3)_2$ catalyzed reactions were examined with the addition of an alkyne as well as PMHS, and $KF_{(aq)}$. The results were again quite unpredictable, however, there was hydrostannation observed in two cases (Table 17, entries 1 and 6). Running the reaction with all reagents present at the

beginning of the sequence resulted in substantial polymerization of the reaction mixture and difficulty in the isolation of the products (Table 17, entry 3). The presence of the two vinyl bromide isomers further complicated analysis of the reaction.

Table 17. Examination of Conditions for a One-Pot Stille/Hydrostannation



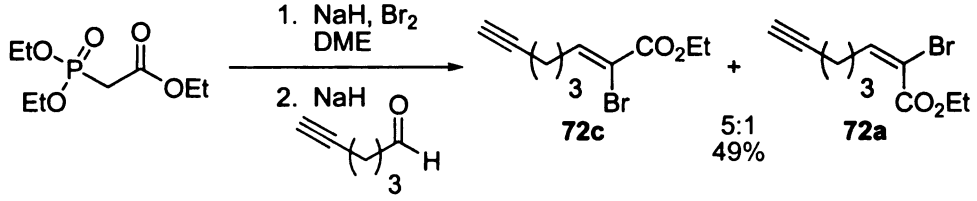
Entry[a]	Catalyst	Me_4Sn (equiv)	Time (h)	Yield **70a**	Yield **70b**	Yield **71**
1	5 mol% Pd_2dba_3[b]	3	48	-	15	100 E
2	5 mol% Pd_2dba_3[b]	1	48	-	49	-
3	5 mol% $PdCl_2(PPh_3)_2$[c]	1.2	24	3	15	-
4	5 mol% $PdCl_2(PPh_3)_2$	2	72	41	30	-
5	3 mol% $PdCl_2(PPh_3)_2$	3	72	5.5	58	-
6	1 mol% $PdCl_2(PPh_3)_2$	3	72	-	49	53 Z

[a]2nd step: 2 mol% $PdCl_2(PPh_3)_2$, 2 equiv PMHS, 3 equiv KF, 1 equiv alkyne; [b]10 mol% $AsPh_3$, 10 mol% CuI; [c]not run stepwise, polymerized overnight

5.5.3 Preparation of Stille Coupling precursor via an alternate route

Because the results for the Stille coupling/hydrostannation were convoluted due to the presence of two vinyl bromide isomers, another method to synthesize the substrate was examined. Reaction of 5-hexynal with a phosphonate ester resulted in the vinyl bromide directly (Scheme 65). However, the vinyl bromides were formed as a 1:5 mixture of E:Z isomers. This method unfortunately did not eliminate the formation of a mixture of isomers, therefore, a new model needed to be examined.

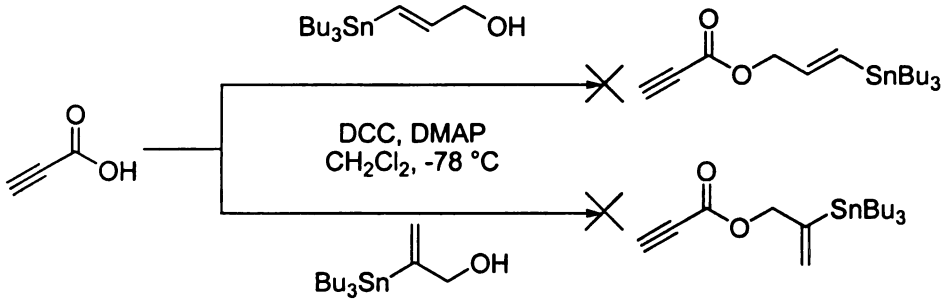
Scheme 65. Revised Synthesis of Alkynyl Vinyl Bromide



5.6 Development of heteroatom tethered substrates

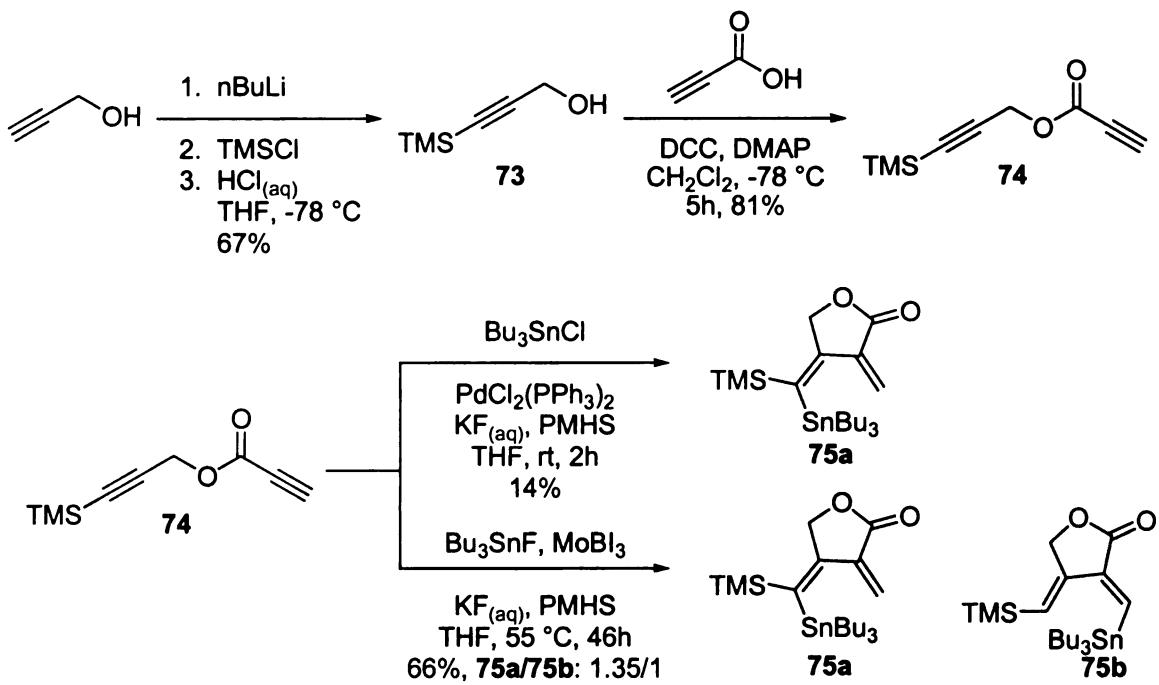
Another method to install two chemically differentiable alkynes is to tether the two alkynes with a heteroatom (i.e., ethers, esters, amines, and amides). Ideally, the vinyl tin or vinyl halide could be generated prior to tethering to the alkyne. Coupling of the vinyl tin with propynoic acid utilizing DCC resulted in no product formation (Scheme 66). Attempting to install the vinyl tin or vinyl

Scheme 66. Attempted Tethering of Propynoic Acid and a Vinyl Tin



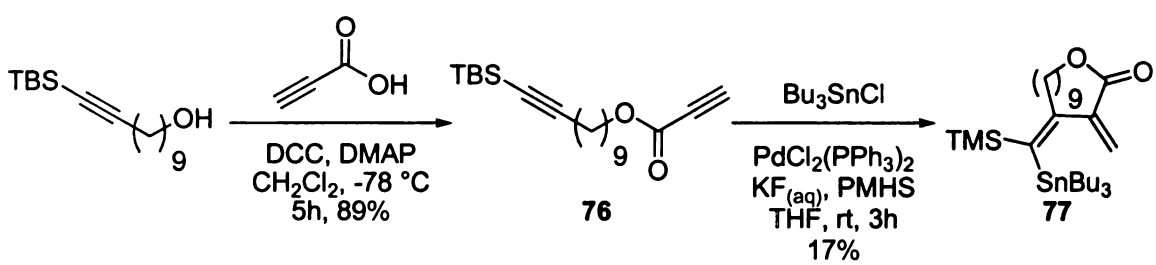
halide after the esterification step required differentiable alkynes. Protecting the alkyne of propargyl alcohol followed by DCC coupling resulted in a substrate with the two alkynes tethered by an ester. Hydrostannation of the substrate utilizing palladium (1 mol%) or molybdenum (2 mol%) catalysis resulted in a cyclized product that would not be suitable for the planned Stille/hydrostannation reaction (Scheme 67). While there is literature precedence for 5-membered ring formation during the hydrostannation of di-alkynes,[102] it was unclear if a larger

Scheme 67. Synthesis of Tethered Dialkyne **74** and Undesired Cyclized Product



alkyl tether would inhibit ring formation by distancing the alkynes spatially from one another. Unfortunately the undesired ring formation was not alleviated (Scheme 68).

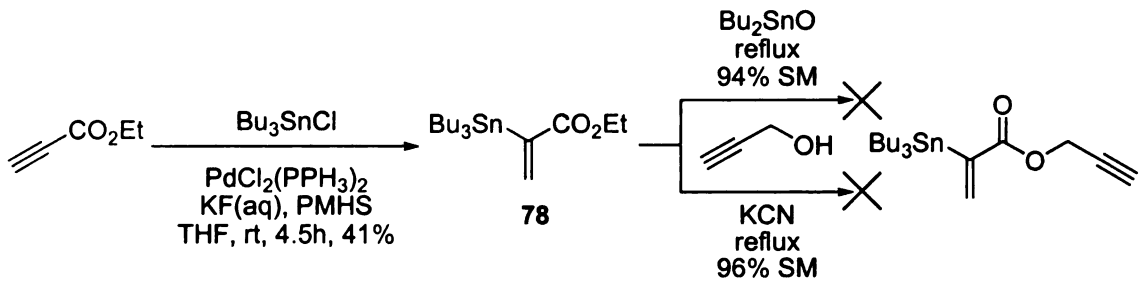
Scheme 68. Synthesis of Undesired Cyclized Product **77**



Instead of forming the ester linkage through DCC coupling of an acid and an alcohol, transesterification could be utilized. After forming a vinyl tin compound, **78**, via palladium mediated hydrostannation (1 mol%), attempts to transesterify the ester with propargyl alcohol and dibutyltin oxide[103] or KCN[104] resulted only in recovery of starting material (Scheme 69). A very versatile

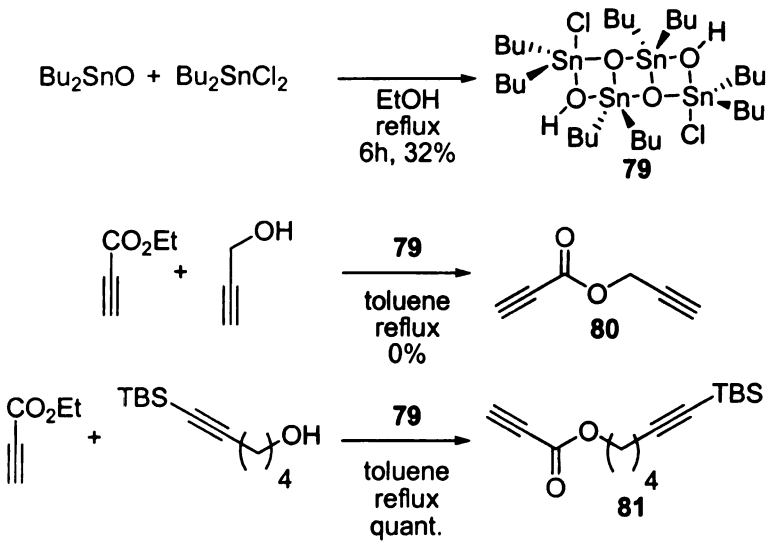
reagent for the transesterification of esters is a catalyst developed by Otera.[105,106] The catalyst was utilized in a test reaction, the transesterification of propargyl

Scheme 69. Attempted Transesterification with Dibutyltin Oxide and KCN



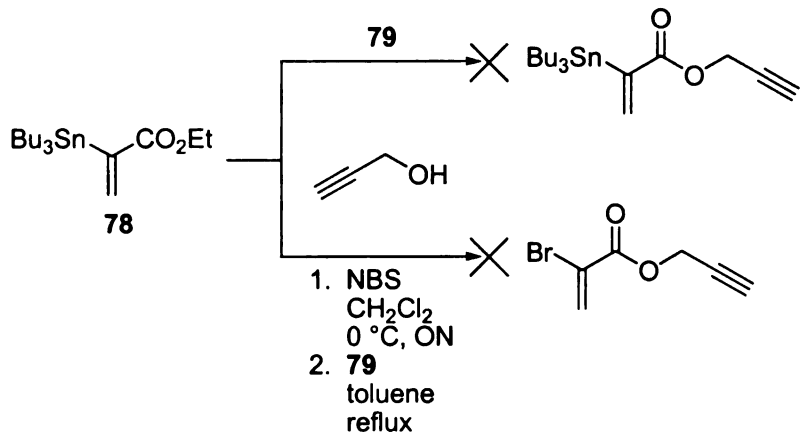
alcohol and ethyl propiolate. Product formation was suggested by ^{1}H NMR of the crude reaction mixture, however the volatility of the product made isolation difficult. The product from the transesterification with a less volatile alcohol was

Scheme 70. Transesterification with Otera's Catalyst



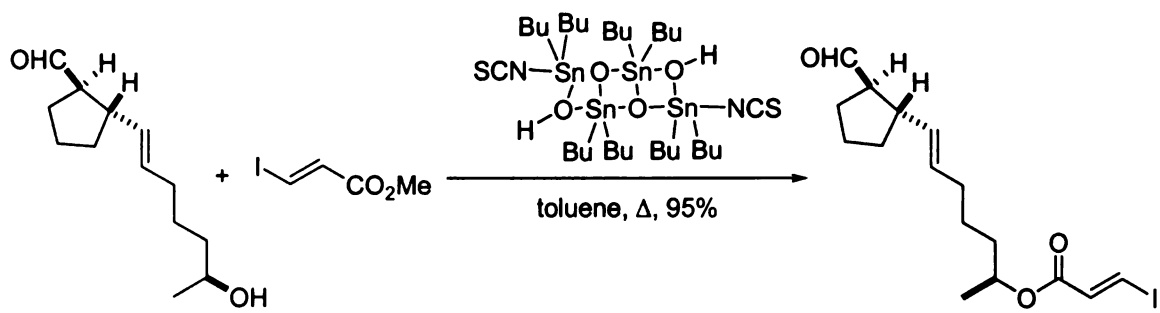
successful, indicating that the catalyst was active (Scheme 70). Utilizing Otera's catalyst, 10 mol%, (a distannoxane) in the transesterification of **78** and propargyl alcohol was unsuccessful, as was the transesterification of the vinyl bromide (Scheme 71). The failure of the transesterification with Otera's catalyst was

Scheme 71. Unsuccessful Transesterification of a Vinyl Tin Containing Ester



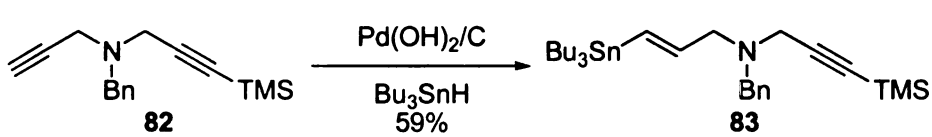
surprising due to the success of a related system by Schreiber, where the ester utilized contained a vinyl iodide (Scheme 72).[107]

Scheme 72. Transesterification of a Vinyl Iodide Containing Ester



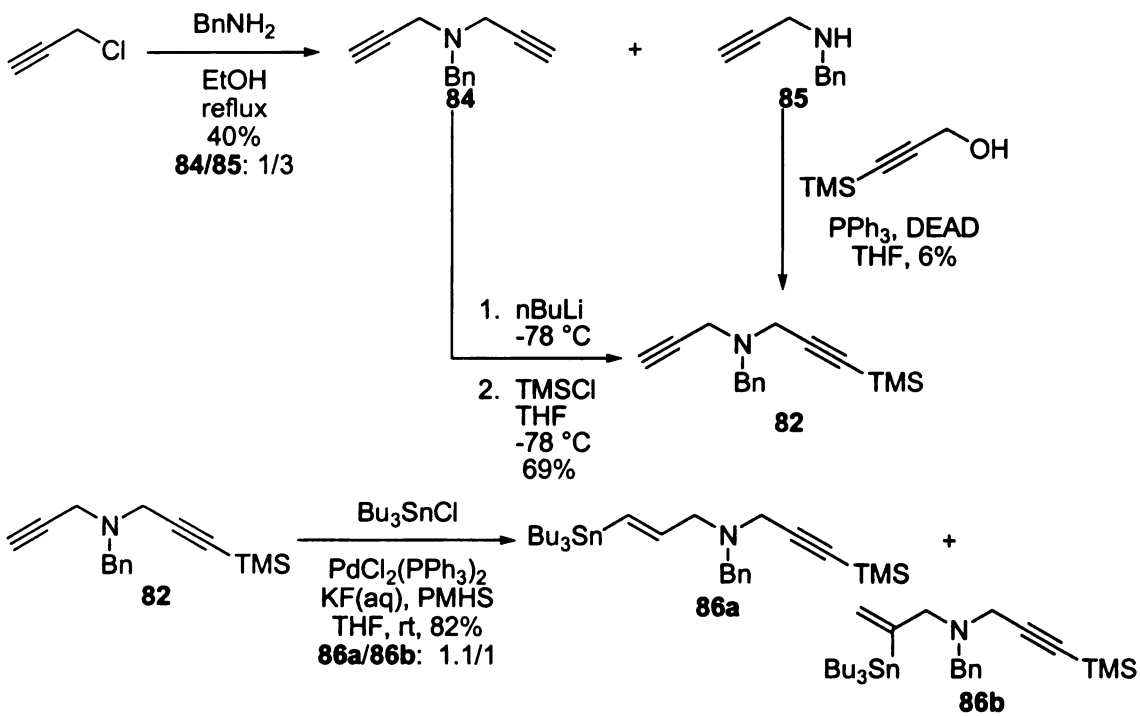
Lautens has shown that the hydrostannation of a specific tertiary amine linked di-alkyne could proceed without ring formation (Scheme 73). This phenomenon is isolated to this particular amine, other related amines did cyclize under the reaction conditions.[102] The synthesis of the desired amine was

Scheme 73. Successful Hydrostannation of Dialkyne



relatively straightforward requiring two steps to form the hydrostannation precursor. Pd-mediated hydrostannation (0.8 mol%) and deprotection of the alkyne proceeded without difficulty albeit in low overall yield (from propargyl chloride), 0.3%, (Scheme 74). Due to the low overall yield of the reaction scheme this route was abandoned.

Scheme 74. Synthesis and Hydrostannation of Amine Tethered Dialkyne

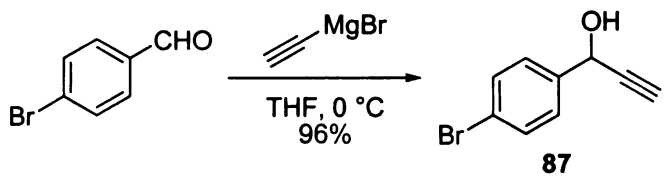


5.7 Attempted utilization of aryl bromides in the Stille coupling

The synthesis of vinyl halides or vinyl tin compounds in the presence of an alkyne that could be utilized in the examination of a Stille/hydrostannation reaction was shown to be low yielding and laborious. Changing gears from examining vinyl halides to looking at aryl halides allowed for the aryl halide to not be synthesized but rather be present from the beginning. Many aryl halides are commercially available and therefore the installation of the alkyne was all that

would be required. The alkynylation of an aryl aldehyde allows for formation of the Stille/hydrostannation precursor in one step (Scheme 75). Both the

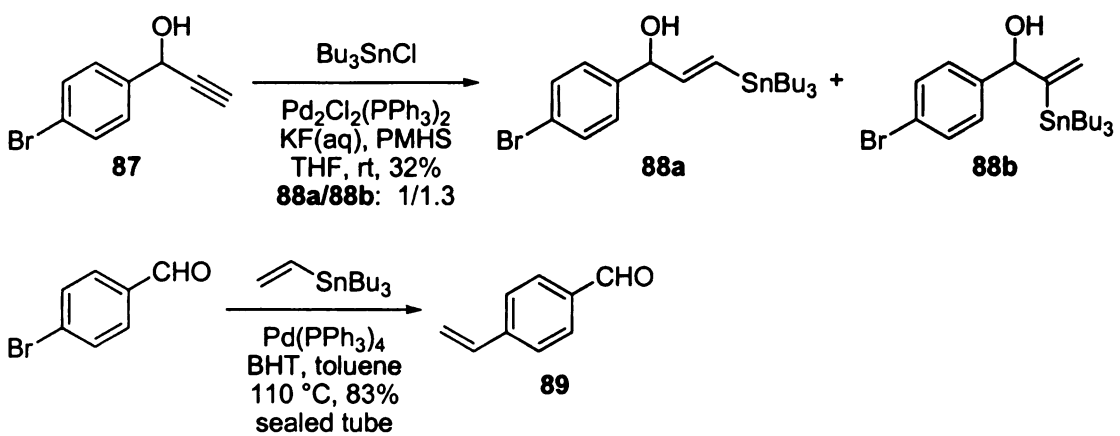
Scheme 75. Synthesis of Stille/Hydrostannation Precursor **87**



87

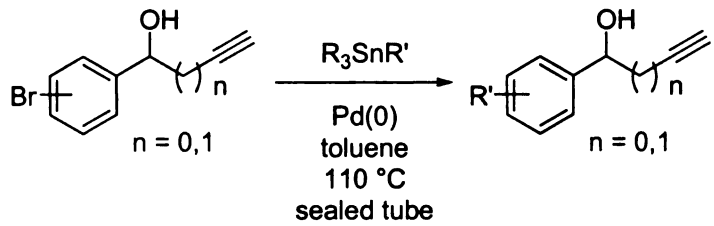
hydrostannation of **87** and the Stille coupling of p-bromobenzaldehyde were examined to allow for easier identification of the product expected in the Stille/hydrostannation reaction (Scheme 76). Attempts at the Stille coupling of

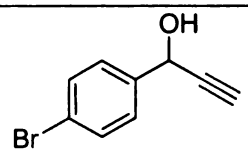
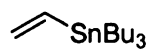
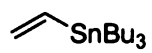
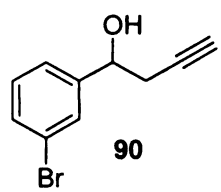
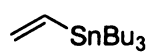
Scheme 76. Independent Synthesis of Expected Product Fragments



the aryl bromide **87** with several tin compounds only resulted in decomposition of the starting material utilizing several catalysts (Table 18). Increasing the distance between the aryl group and the alkyne by one carbon was examined.

Table 18. Examination of Stille Reaction Conditions in the Presence of an Alkyne

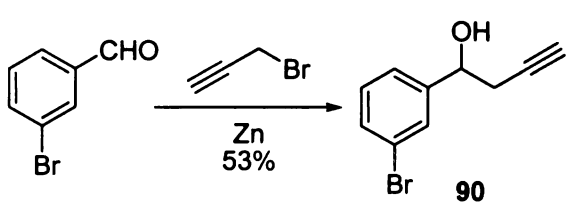


Entry	Substrate	Catalyst	Sn reagent[a]	product
1	 **87**	5 mol% Pd_2dba_3		Decomp.
2		2 mol% $Pd(PPh_3)_4$		Decomp.
3		2 mol% $Pd(PPh_3)_4$	$Bu_3Sn-SnBu_3$	Decomp.
4		2 mol% $Pd(PPh_3)_4$	Me_3Sn-Ph	Decomp.
5	 **90**	2 mol% $Pd(PPh_3)_4$		Decomp.

[a] 1.1 equiv

The second substrate was synthesized from propargyl bromide and m-bromobenzaldehyde (Scheme 77). The Stille coupling was again unsuccessful under a variety of conditions (Table 18).

Scheme 77. Synthesis of Stille/Hydrostannation Precursor **90**

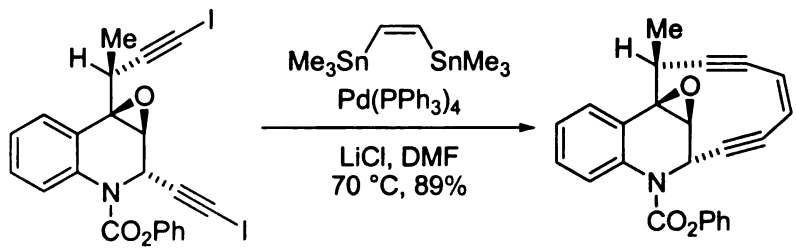


5.8 Development of a one-pot Stille coupling/hydrostannation

5.8.1 Literature precedence for the observed decomposition

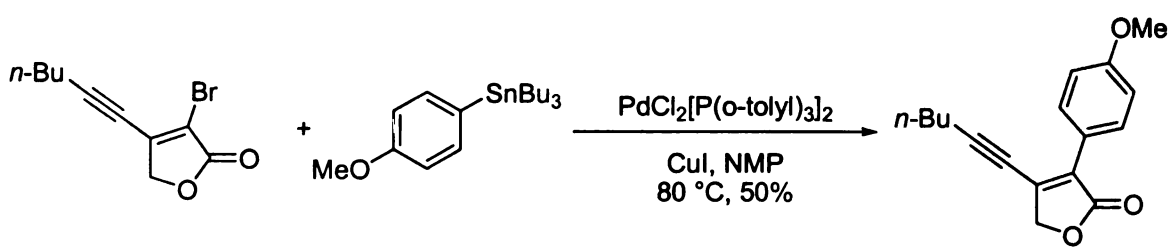
While the attempted Stille coupling of **87** resulted in decomposition, there are many examples of Stille couplings succeeding in the presence of alkynes. These fall into three categories; the alkyne can be present as the electrophile (alkynyl halide),[108,109] the alkyne can be internal,[110,111,112,113] and if the alkyne was terminal it must be protected (silyl alkyne).[114,115,116,117,118] A double Stille coupling

Scheme 78. Stille Coupling Employed in the Synthesis of Dynemicin Analogues



of alkynyl iodides has been employed in the synthesis of dynemicin analogues to install an enediyne (Scheme 78).[108] The presence of an internal alkyne was tolerated in the Stille coupling of a vinyl bromide with an aromatic tin (Scheme 79).[112] The most prophetic example of a silyl alkyne present during a Stille

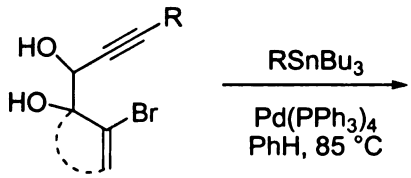
Scheme 79. Example of an Internal Alkyne Tolerated in a Stille Coupling

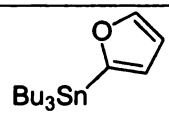
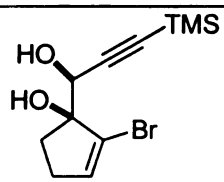
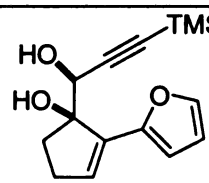
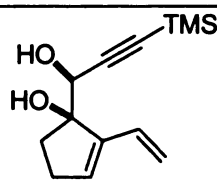
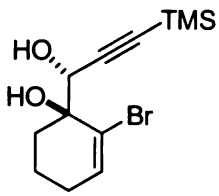
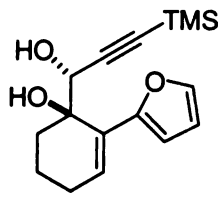
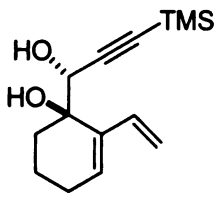
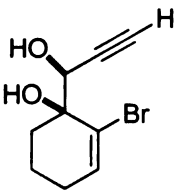
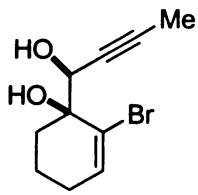
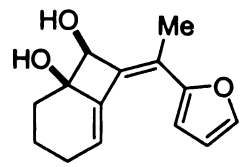
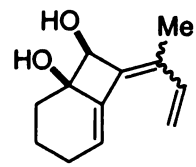
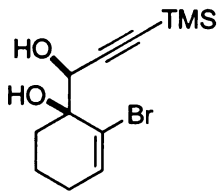
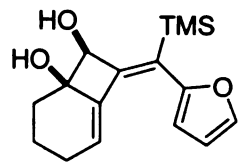
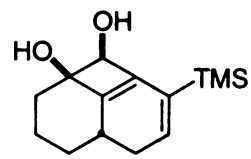


coupling is found in the work of Suffert. The Stille coupling of the same vinyl bromide with a pendant alkyne that was terminal, internal, and silylated were directly compared. The reaction proceeded in the internal and silylated cases

with several different tributyltin coupling partners. However, with the terminal alkyne only decomposition was observed (Table 19).[114]

Table 19. Examination of Alkyne Functional Groups in Stille Couplings

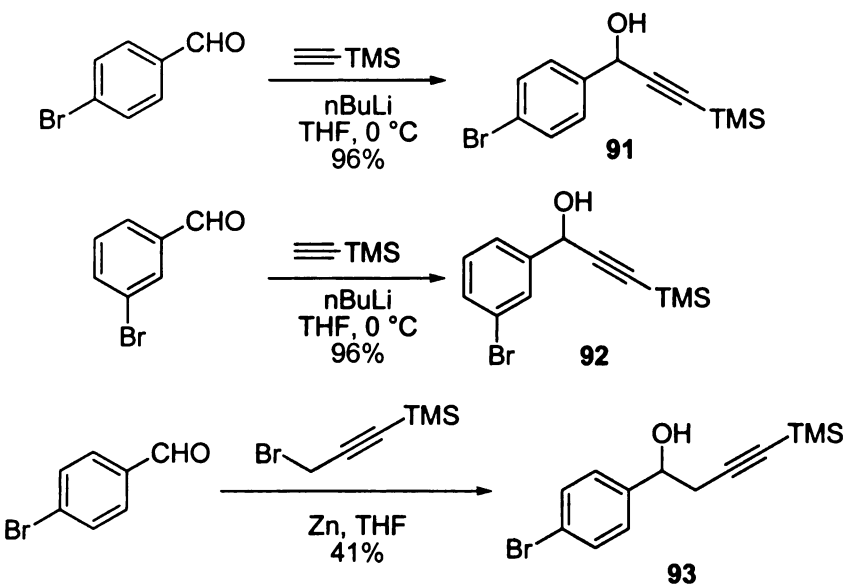


Entry	SM	 Products	 Products
1		 71%	 37%
2		 60%	 57%
3		—	Decomp.
4		 11%	 30%
5		 84%	 35%

5.8.2 Modification of substrate to contain a silyl alkyne

Due to the observed decomposition of the substrate containing the terminal alkyne, the substrate was modified to contain a silyl alkyne. Both meta- and para-substituted aryl bromides were prepared in a similar manner as previously (Scheme 80).

Scheme 80. Synthesis of TMS Protected Stille/Hydrostannation Precursors

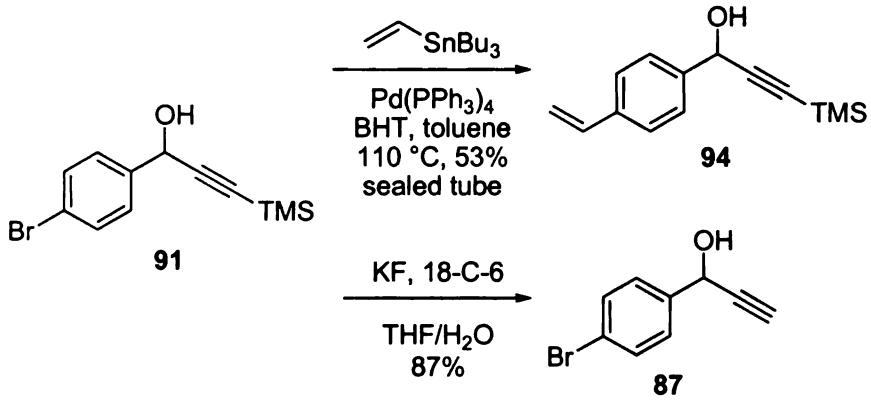


5.8.3 Stille coupling of substrate in the presence of a silyl alkyne

Having obtained the Stille coupling electrophiles in one step from commercially available aldehydes, the preparation of the aryl electrophiles was considerably easier than the synthesis of the vinyl electrophiles previously studied. Initial examination of the Stille coupling was done with vinyl tributyltin and **91**. The Stille coupling was successful in 53% yield. In order to add a hydrostannation step the alkyne needed to be deprotected. Reaction with

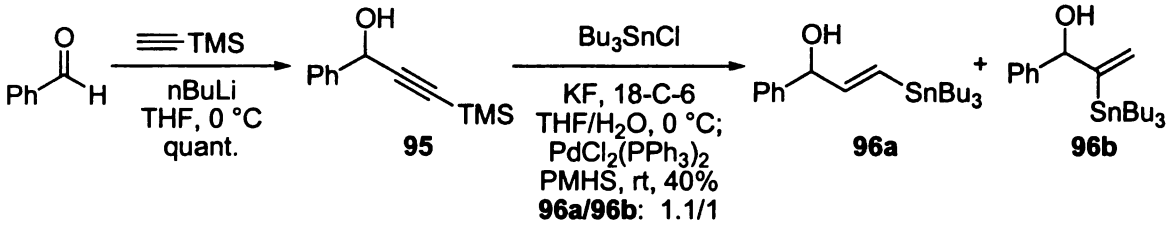
aqueous KF in THF was unsuccessful, however, the utilization of KF and 18-crown-6 resulted in the free alkyne which could be hydrostannated under standard conditions (Scheme 81).

Scheme 81. Stille Coupling of Precursor **91** Followed by TMS Deprotection



We then asked if the deprotection followed by hydrostannation could occur in one-pot. A concern was if during the deprotection hexabutylditin would form and inhibit the hydrostannation step. To examine this directly, benzaldehyde was alkynylated with TMS-acetylene and subjected to the deprotection conditions in the presence of tributyltin chloride followed by the addition of PMHS and palladium catalyst (1 mol%) to afford the vinyl stannane (Scheme 82).

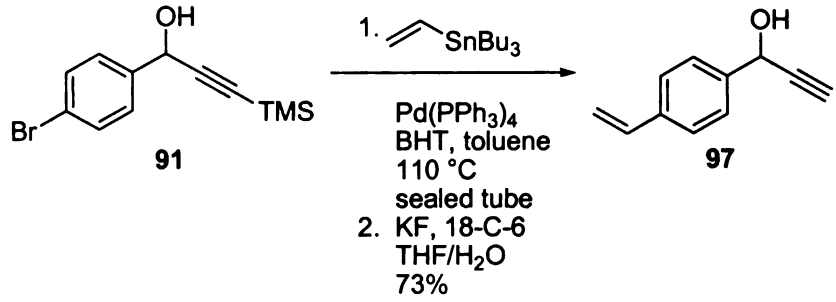
Scheme 82. Attempted One-Pot TMS Deprotection/Hydrostannation



With the deprotection and hydrostannation appearing to proceed without difficulty it was necessary to determine if the Stille coupling would influence the deprotection reaction unfavorably. Combining the Stille coupling (1.1 equiv

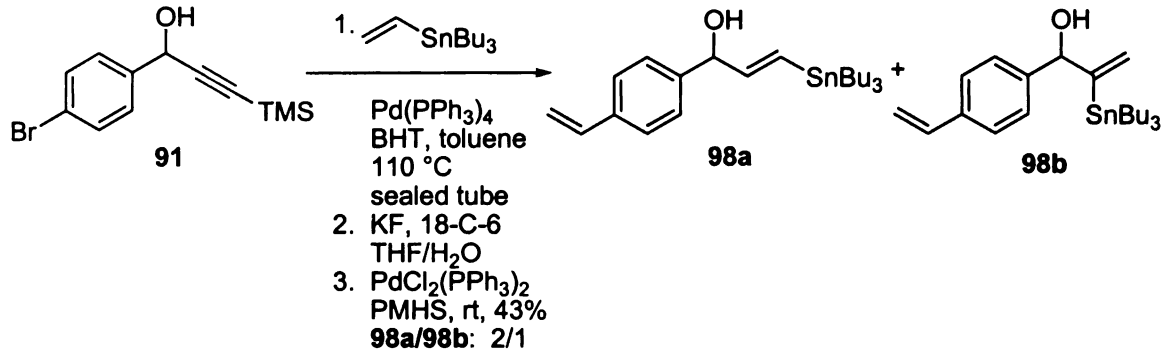
tributylvinyltin) with the deprotection in one-pot allowed for formation of the free alkyne without difficulty (Scheme 83). With the first two steps and the second

Scheme 83. Attempted One-Pot Stille Coupling/TMS Deprotection



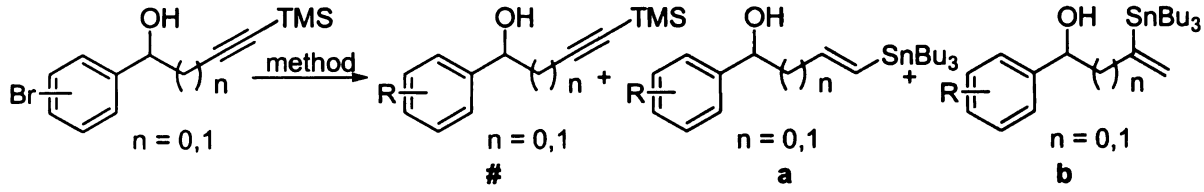
two steps examined together the three steps were combined in one-pot to afford the desired product in good yield, 43% (Scheme 84).

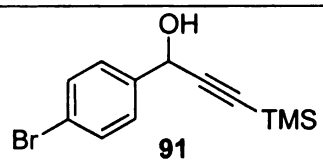
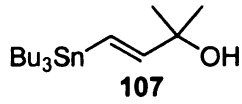
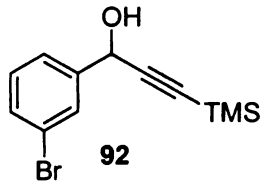
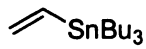
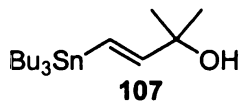
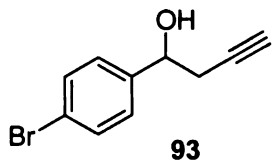
Scheme 84. One-Pot Stille/TMS Deprotection/Hydrostannation



Two other substrates were examined, meta-substitution and para-substitution with the alkyne separated from the alcohol by an additional carbon, whose syntheses have been shown previously (Scheme 80). In addition to the utilization of vinyltributyltin as the Stille coupling partner the use of a substituted E-tributylvinyltin was also examined. The Stille couplings of each substrate proceeded well as did the combined one-pot Stille/hydrostannation reaction

Table 20. Broadening of One-Pot Stille/Deprotection/Hydrostannation Reaction



Entry	Substrate	Vinyl Sn	Method[a]	#	a	b
1	 **91**		A	**94** 53%	-	-
2			B	-	**98a/98b** 43%, 2/1	
3		 **107**	A	**99** 53%	-	-
4			B	-	-	**100b** 12%
5	 **92**		A	**101** 57%	-	-
6			B	-	**102a/102b** 35%, 1.2/1	
7		 **107**	A	**103** 36%	-	-
8			B	-	-	**104b** 19%
9	 **93**		A	**105** 44%	-	-
10			B	-	-	**106b** 2.8%

[a]Method A: 1 equiv aryl bromide, 2 mol% $Pd(PPh_3)_4$, BHT (cat), 1.1 equiv vinyltin, toluene, 110 °C; Method B: 1 equiv aryl bromide, 2 mol% $Pd(PPh_3)_4$, BHT (cat), 1.1 equiv vinyltin, toluene, 110 °C; then, 3.3 equiv KF and 3.3 equiv 18-C-6 in THF/H_2O (98/2), 0 °C, 5 h; then, 1 mol% $PdCl_2(PPh_3)_2$, 2 equiv PMHS, rt, ON.

(Table 20). The one-pot reaction does appear to proceed more favorably with vinyl tributyltin as the Stille coupling partner than with **107**.

5.9 Conclusions and future work in the one-pot Stille/hydrostannation reaction

The one-pot Stille/hydrostannation reaction was developed and shown through the use of three aryl bromide electrophiles as well as two vinyl tin compounds to be of reasonable scope. The success of this method allowed for reduced handling of the toxic tin intermediates which are typically considered waste. Normally in the Stille coupling the tin halide formed is considered a by product that is disposed of and the tin hydride that is utilized in a hydrostannation is added to the reaction, here the by product is recycled and utilized in the hydrostannation successfully. While it was necessary to utilize a protected alkyne in the Stille coupling the deprotection step was readily incorporated into the one-pot reaction resulting in a one-pot 3 step reaction.

Future work should focus on the optimization of these results. For example, greater than 1 equiv of vinyl tin was necessary in the Stille coupling but the conditions were not fully optimized. The concentration of KF and 18-crown-6 as well as the necessity of the addition of Pd (II) catalyst prior to the hydrostannntion need to be examined further.

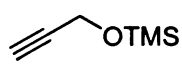
Experimental

Materials and Methods

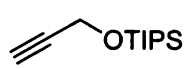
All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen, with magnetic stirring, and monitored by thin-layer chromatography with 0.25-mm pre-coated silica gel plates, unless otherwise noted. Tetrahydrofuran was freshly distilled from sodium/benzophenone under nitrogen. Methylene chloride, benzene, toluene, TMSCl, and Et_3N, were freshly distilled from calcium hydride. Palladium (II) acetate was purchased from Strem and used without purification. Flash chromatography was performed with silica gel 60 Å (230-400 mesh) purchased from Silicycle. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Infrared spectra were obtained on a Nicolet IR/42 spectrometer; ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini-300, Varian UnityPlus-500 or a Varian Unity$^+$-500 spectrometer (300.1, 500.0, 499.7 MHz for ^1H, respectively, and 75.5, 125.7, 125.7 MHz for ^{13}C, respectively), with chemical shifts reported relative to the residue peaks of solvent chloroform (δ 7.24 for ^1H and 77.0 for ^{13}C). Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected; high-resolution mass spectra were obtained either at the University of South Carolina, Department of Chemistry and Biochemistry, Mass Spectrometry Laboratory or at the Michigan State University Mass Spectrum Facility.

Chapter 2 Experimental

General procedure for the preparation of silyl protected alcohols: The silyl chloride (1.8 mmol) was added to a solution of the alcohol (2 mmol) in CH_2Cl_2 (10 mL) containing imidazole (2.4 mmol) and DMAP (cat) at 0 °C. The solution was stirred for 20 min. then allowed to warm to room temperature and stirred until the reaction was judged complete by tlc. The reaction was poured into a sat. $NH_4Cl_{(aq)}$ solution and the layers were separated. The organic phase was washed with $NH_4Cl_{(aq)}$ and then the combined aqueous layers were extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography afforded the pure silyl alcohol product.

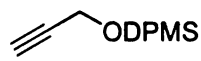


Preparation of trimethyl(prop-2-ynyloxy)silane: Following the general procedure propargyl alcohol (0.48 mL, 8 mmol) was protected with TMSCl (0.92 mL, 7.2 mmol) to afford 0.72 g (70% yield) of trimethyl(prop-2-ynyloxy)silane (silica gel; 98/2 hexanes/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (d, J = 2.2 Hz, 2H), 2.37 (t, J = 2.2 Hz, 1H), 0.14 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.1, 73.0, 50.8, -0.4. Spectral data were consistent with those obtained from commercially available material.



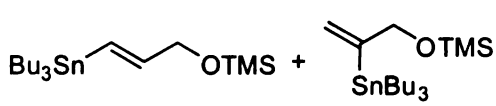
Preparation of triisopropyl(prop-2-ynyloxy)silane: Following the general procedure propargyl alcohol (0.12 mL, 2 mmol) was protected with TIPSCl (0.38 mL, 1.8 mmol) to afford 0.2086 g (54.6% yield) of triisopropyl(prop-2-

ynyloxy)silane (silica gel; 98/2 hexanes/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (d, *J* = 2.2 Hz, 2H), 2.36 (t, *J* = 2.2 Hz, 1H), 1.05 (m, 21H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.4, 72.5, 51.7, 17.8, 11.9. Spectral data were consistent with those previously reported.[119]



Preparation of methyldiphenyl(prop-2-ynyloxy)silane: Following the general procedure propargyl alcohol (0.24 mL, 4 mmol) was protected with DPMSCl (0.74 mL, 3.6 mmol) to afford 0.7850 g (86.4% yield) of methyldiphenyl(prop-2-ynyloxy)silane (silica gel; 98/2 hexanes/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dm, *J* = 7.7 Hz, 4H), 7.44 (m, 6H), 4.41 (d, *J* = 2.7 Hz, 2H), 2.44 (t, *J* = 2.2 Hz, 1H), 0.78 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 134.4, 130.0, 127.9, 81.7, 73.4, 51.6, -2.8. Spectral data were consistent with those previously reported.[120,121]

General procedure for the palladium mediated hydrostannation with tributyltin hydride in THF: Tributyltin hydride (0.75 mmol) was added dropwise to a 0 °C solution of the alkyne (0.5 mmol) and $PdCl_2(PPh_3)_2$ (0.004 mmol) in THF (2.5 mL). The reaction was stirred until complete as judged by tlc. The solvent was evaporated and the crude product was purified by flash chromatography to afford the vinyl stannanes.



Preparation of (E)-trimethyl(3-(tributylstannyl)allyloxy)silane and trimethyl(2-(tributylstannyl)allyloxy)silane (Table 3, entry 31): Following the general procedure, trimethyl(prop-2-ynyloxy)silane (0.0674 g, 0.5 mmol) was hydrostannated to afford 0.0102 g (49% yield) of the vinyl stannanes (silica gel, 1% TEA; hexanes). ^{1}H NMR of the crude product showed a 1/1.9 ratio of E/internal stannane **E:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (dm, *J* = 19.0 Hz, 1H), 6.07 (dm, *J* = 19.0 Hz, 1H), 4.14 (dd, *J* = 3.0, 1.1 Hz, 2H), 1.45 (m, 6H), 1.27 (m, 6H), 0.86 (m, 15H), 0.11 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 127.8, 66.4, 29.1, 27.3, 13.7, 9.4, -0.3. **Internal:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (dt, *J* = 2.4, 1.9 Hz, ^3J = 70 Hz, 1H), 5.17 (dt, *J* = 2.4, 1.9 Hz, ^3J = 30Hz, 1H), 4.23 (t, *J* = 1.6 Hz, 2H), 1.46 (m, 6H), 1.28 (m, 6H), 0.90 (m, 15H), 0.12 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 122.1, 69.0, 29.1, 27.1, 13.7, 9.6, -0.5.

IR (neat) 1076, 841 cm^{-1}.

HRMS (EI): m/z calcd for $C_{14}H_{31}OSiSn$ (M^+ - Bu): 363.1166. Found: 363.1168.

Preparation of (E)-triisopropyl(3-(tributylstannyl)allyloxy)silane and triisopropyl(2-(tributylstannyl)allyloxy)silane (Table 3, entry 32): Following the general procedure, triisopropyl(prop-2-ynyloxy)silane (0.1034 g, 0.49 mmol) was hydrostannated to afford 0.1930g (79% yield) of the vinyl stannanes (silica gel, 1% TEA; hexanes). ^{1}H NMR of the crude product showed a 1/3 ratio of E/internal stannane **E:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (dt, *J* = 19.0, 1.5 Hz, 1H), 6.04 (dt, *J* = 19.0, 3.8 Hz, 1H), 4.25 (dd, *J* = 3.8, 1.6 Hz, ^3J = 12 Hz, 2H),

1.44 (m, 6H), 1.23 (m, 12H), 1.04 (m, 12H), 0.86 (m, 18H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 119.0, 69.7, 29.1, 27.4, 18.0, 13.7, 12.1, 9.4. **Internal:** ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (dt, *J* = 2.7, 2.2 Hz, ^3J = 68 Hz, 1H), 5.16 (dt, J = 3.0, 1.9 Hz, ^3J = 30 Hz, 1H), 4.34 (t, *J* = 1.9 Hz, ^3J = 12Hz, 2H), 1.44 (m, 6H), 1.28 (m, 12H), 1.04 (m, 12H), 0.86 (m, 18H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 121.8, 69.7, 30.6, 27.4, 18.1, 13.7, 12.1, 9.9, 9.4.

IR (neat) 1067, 816 cm^{-1}.

HRMS (EI): m/z calcd for $C_{20}H_{43}OSiSn$ (M^+ - Bu): 447.2105. Found: 447.2122.

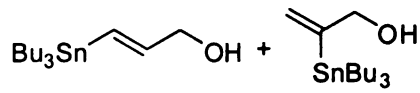
Preparation of (E)-methyldiphenyl(3-(tributylstannyl)allyloxy)silane and methyldiphenyl(2-(tributylstannyl)allyloxy)silane (Table 3, entry 33):

Following the general procedure, methyldiphenyl(prop-2-ynyloxy)silane (0.1267 g, 0.5 mmol) was hydrostannated to afford 0.0790 g (29% yield) of the vinyl stannanes (silica gel, 1% TEA; 95/5 hexanes/ethyl acetate). ^1H NMR of the crude product showed a 1/4.5 ratio of E/internal stannane **E:** ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (m, 5H), 7.45 (m, 5H), 6.25 (dm, *J* = 19.0 Hz, 1H), 6.17 (dm, *J* = 19.0 Hz, 1H), 4.34 (dd, *J* = 2.8, 1.4 Hz, 2H), 1.54 (m, 6H), 1.34 (m, 6H), 0.95 (m, 15H), 0.72 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 137.6, 134.0, 129.8, 127.8, 127.7, 67.0, 29.1, 27.3, 13.7, 9.5, -2.8. **Internal:** ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 5H), 7.39 (m, 5H), 5.90 (dt, *J* = 2.5, 2.0 Hz, ^3J = 67.0 Hz, 1H), 5.21 (dt, *J* = 2.5, 1.9 Hz, ^3J = 30.0 Hz, 1H), 4.37 (t, *J* = 1.9 Hz, ^3J = 13 Hz, 2H), 1.44 (m, 6H), 1.24 (m, 6H), 0.87 (m, 15H), 0.65 (s, 3H), ^{13}C NMR (75 MHz,

$CDCl_3$) δ 154.3, 136.0, 134.4, 129.8, 127.8, 122.4, 69.8, 29.1, 27.4, 13.7, 9.5, -3.0.

IR (neat) 1074, 788 cm^{-1}.

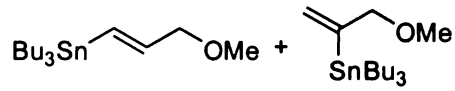
HRMS (EI): m/z calcd for $C_{24}H_{35}OSiSn$ (M^+ - Bu): 487.1479. Found: 487.1470.



Preparation of (E)-3-(tributylstannyl)prop-2-en-1-ol and 2-(tributylstannyl)prop-2-en-1-ol (Table 4, entry 1): Following the general procedure, propargyl alcohol (0.03 mL, 0.5 mmol) was hydrostannated to afford 0.1041 g (60% yield) of the vinyl stannanes (silica gel, 1% TEA; 80/20 pet. ether/ether). ^1H NMR of the crude product showed a 1/1.3 ratio of E/internal stannane **E:** ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (tm, *J* = 30.2 Hz, 2H), 4.14 (d, *J* = 2.8 Hz, 2H), 1.65 (bs, 1H), 1.45 (q, *J* = 7.7 Hz, 6H), 1.28 (quint., *J* = 7.7 Hz, 6H), 0.86 (t, *J* = 7.1 Hz, 15H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 128.2, 66.3, 29.0, 27.3, 13.7, 9.4. **Internal:** ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (tq, *J* = 2.2, 63.7 Hz, 1H), 5.21 (tq, *J* = 2.2, 29.7 Hz, 1H), 4.25 (tt, *J* = 1.6, 14.3 Hz, 2H), 1.71 (bs, 1H), 1.47 (quint., *J* = 7.1 Hz, 6H), 1.29 (quint., *J* = 7.1 Hz, 6H), 0.86 (t, *J* = 7.1 Hz, 15H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 122.8, 69.5, 29.1, 27.3, 13.7, 9.4. Spectral data were consistent with those previously reported.[9]

(E)-3-(tributylstannyl)prop-2-en-1-ol and 2-(tributylstannyl)prop-2-en-1-ol (Table 4, entry 2): Following the general procedure changing the solvent to benzene, propargyl alcohol (0.03 mL, 0.5 mmol) was hydrostannated to afford 0.1059 g (61% yield) of the vinyl stannanes (silica gel, 1% TEA; 80/20 pet.

ether/ether). ^{1}H NMR of the crude product showed a 1/2.1 ratio of E/internal stannane



(E)-tributyl(3-methoxyprop-1-enyl)stannane and tributyl(3-methoxyprop-1-en-2-yl)stannane (Table 4, entry 3): Following the general procedure, methyl propargyl ether (0.04 mL, 0.5 mmol) was hydrostannated to afford 0.0885 g (49% yield) of the vinyl stannanes (silica gel, 1% TEA; 99/1 pet. ether/ether). ^{1}H NMR of the crude product showed a 1/2.5 ratio of E/internal stannane **E:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (dt, *J* = 18.9, 1.1 Hz, 1H), 6.02 (dt, *J* = 19.2, 5.0 Hz, 1H), 3.93 (dd, *J* = 1.4, 4.9 Hz, 2H), 3.32 (s, 3H), 1.44 (m, 6H), 1.27 (m, 6H), 0.87 (m, 15H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 131.3, 76.3, 57.8, 29.1, 27.3, 13.7, 9.4. **Internal:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (m, ^3J = 116.7 Hz, 1H), 5.24 (m, ^3J = 64.9 Hz, 1H), 4.00 (t, *J* = 1.6 Hz, 2H), 3.32 (s, 3H), 1.44 (m, 6H), 1.27 (m, 6H), 0.87 (m, 15H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 124.6, 79.7, 57.7, 29.1, 27.4, 13.7, 9.5.

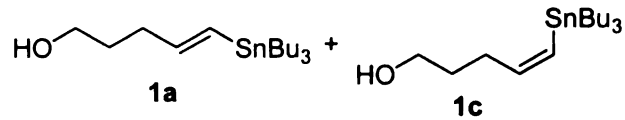
IR (neat) 1111 cm^{-1}.

HRMS (EI): m/z calcd for $C_{12}H_{25}OSiSn$ (M^+ - Bu): 305.0929. Found: 305.0933.

(E)-tributyl(3-methoxyprop-1-enyl)stannane and tributyl(3-methoxyprop-1-en-2-yl)stannane (Table 4, entry 4): Following the general procedure changing the solvent to benzene, methyl propargyl ether (0.04 mL, 0.5 mmol) was hydrostannated to afford 0.1102 g (61% yield) of the vinyl stannanes (silica gel,

1% TEA; 99/1 pet. ether/ether). ^{1}H NMR of the crude product showed a 1/2 ratio of E/internal stannane.

Chapter 3 Experimental

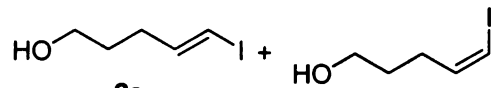


1a **1c**

Preparation of (E)- and (Z)-5-(tributylstannyl)pent-4-en-1-ol: A solution of 4-pentyn-1-ol (1.13 mL, 15 mmol), Bu_3SnCl (4.89 mL, 18 mmol), $KF_{(aq)}$ (2.6142 g, 45 mmol), PMHS (1.09 mL, 18 mmol), and AIBN (cat.) in benzene (75 mL) was immersed in a 75 °C oil bath. The reaction was stirred for 2 h and then cooled to room temperature. NaOH (0.5M, 15 mL) was added and the resulting solution was stirred for 2 h. The solution was filtered and the layers were separated. The aqueous layer was back extracted with ether. The combined organics were dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 1% TEA; 95/5 hexanes/ethyl acetate) to afford 4.44 g (65.5% yield) of the inseparable vinyl stannanes. ^1H NMR of the crude product showed a 6/1 ratio of E/Z stannane. **1a:** ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (tm, *J* = 33.0, 2H), 3.64 (q, *J* = 6.6 Hz, 2H), 2.20 (m, 2H), 1.67 (quint., *J* = 6.6 Hz, 2H), 1.55 (s, 1H), 1.45 (m, 6H), 1.26 (m, 6H), 0.87 (m, 15H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 128.1, 62.4, 34.1, 31.8, 29.1, 27.2, 13.7, 9.3, **1c:** ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (dt, *J* = 7.142, 12.1 Hz, 1H), 5.80 (d, *J* = 12.6 Hz, 1H), 3.64 (q, *J* = 4.9 Hz, 2H), 2.09 (q, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 7.1 Hz, 2H), 1.46 (m, 6H), 1.28 (m, 6H), 0.87 (m, 15H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 128.7, 62.7, 33.3, 32.8, 29.2, 27.3, 13.7, 10.2.

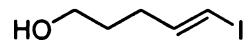
IR (neat) 3318 cm^{-1}.

HRMS (EI): m/z calcd for $C_{13}H_{27}OSn$ (M^+-Bu): 319.1084. Found: 319.1091.



2a **2c**

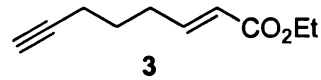
Preparation of (E)- and (Z)-5-iodopent-4-en-1-ol: The vinyl tin, **1a** and **1c**, (2.52 g, 6.7 mmol) was dissolved in CH_2Cl_2 (40 mL) at 0 °C. I_2 (2.16 g, 8.5 mmol) in CH_2Cl_2 (24 mL) was added dropwise making sure the purple color did not persist. The reaction was quenched with $Na_2S_2O_{3\,(aq)}$ and then diluted with ether and water. The layers were separated and the organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 85/15 hexanes/ethyl acetate) to afford 1.1192 g (79% yield) of the inseparable vinyl iodides. ^{1}H NMR of the crude product showed a 1.1/1 ratio of E/Z stannane. **2a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (dt, *J* = 7.1, 14.3 Hz, 1H), 6.01 (dt, *J* = 1.1, 14.3 Hz, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 2.13 (dq, *J* = 1.1, 7.1 Hz, 2H), 1.64 (quint., *J* = 7.1 Hz, 2H), 1.26 (s, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 75.0, 61.3, 32.1, 30.9. Spectral data were consistent with those previously reported.[122,123] **2c:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (t, *J* = 7.1 Hz, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.21 (q, *J* = 6.0 Hz, 2H), 1.68 (quint., *J* = 6.6 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 82.9, 61.5, 31.0, 30.5. Spectral data were consistent with those previously reported.[124]



2a

Preparation of (E)-5-iodopent-4-en-1-ol: NaOH (0.2068 g, 5.17 mmol) was dissolved in butanol (10 mL) and the mixture of E- and Z-vinyl iodides, **2a** and **2c** (1.5000 g, 7.08 mmol) was added. The resulting solution was refluxed until no Z

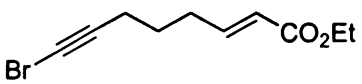
isomer was observed. After cooling to room temperature, the reaction was diluted with ether and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 85/15 hexanes/ethyl acetate) to afford 0.4597 g (30.6% yield) of the E-vinyl iodide. The spectral data was consistent with that shown above.



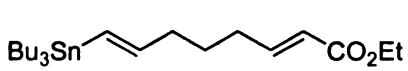
3

Preparation of (E)-ethyl oct-2-en-7-ynoate: The oxalyl chloride (1.07 mL, 12.24 mmol) was added to CH_2Cl_2 (75 mL) and the solution was cooled to -78 °C. A solution of DMSO (1.60 mL, 22.44 mmol) and CH_2Cl_2 (5 mL) was prepared and added dropwise. After 10 min of stirring, a solution of CH_2Cl_2 (1.5 mL) and 5-hexyn-1-ol (1.13 mL, 10.2 mmol) was added. After another 10 min of stirring, TEA (10 mL, 71.4 mmol) was added and the reaction stirred an additional 10 min. The cooling bath was removed and the solution was stirred for 10 min. Following addition of triphenylphosphoranylidene acetic acid ethyl ester (5.33 g, 15.3 mmol) the reaction was stirred overnight. The solvent was removed under reduced pressure without heating and ether was added. The solid residue, triphenylphosphine oxide, was scrapped from the sides of the flask and the resulting solution was stirred for 2 h. After filtering through a pad of silica gel (collecting fractions to avoid recovering triphenylphosphine oxide), the solution was concentrated and purified by flash chromatography (silica gel; 98/2 hexanes/ethyl acetate) to afford 1.2673 g (75% yield) of the ester. ^1H NMR (300 MHz, $CDCl_3$) δ 6.88 (dt, J = 6.6, 15.9 Hz, 1H), 5.79 (dt, J = 1.6, 15.4 Hz, 1H),

4.12 (q, J = 7.1 Hz, 2H), 2.27 (dq, J = 1.1, 7.1 Hz, 2H), 2.17 (td, J = 2.7, 7.1 Hz, 2H), 1.92 (t, J = 2.7 Hz, 1H), 1.63 (quint., J = 7.1 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 147.7, 122.0, 83.3, 68.9, 60.1, 30.8, 26.6, 17.7, 14.1. Spectral data were consistent with those previously reported.[125]



Preparation of (E)-ethyl 8-bromooct-2-en-7-ynoate: Added to a solution of dry acetone (80 mL) and **3** (3.3244 g, 20 mmol) was NBS (3.9132 g, 22 mmol) and $AgNO_3$ (0.3504 g, 2.1 mmol). After stirring 24 h, the solution was diluted with ether and washed with water. The aqueous layer was extracted with ether and the combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 98/2 hexanes/ethyl acetate) to afford 4.46 g (91% yield) of the bromoalkyne. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (dt, J = 6.6, 15.9 Hz, 1H), 5.79 (d, J = 15.4 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.24 (quint., J = 7.1 Hz, 2H), 2.19 (t, J = 7.1 Hz, 2H), 1.63 (quint., J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 147.6, 122.0, 79.2, 60.1, 38.6, 30.9, 26.4, 19.0, 14.2.
IR (neat) 2226, 1719 cm^{-1}.



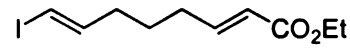
4a

Preparation of (2E,7E)-ethyl 8-(tributylstannyl)octa-2,7-dienoate: A solution of $PdCl_2(PPh_3)_2$ (0.0145 g, 0.02 mmol), (E)-ethyl 8-bromooct-2-en-7-ynoate (0.4970 g, 2.04 mmol), Bu_3SnCl (0.66 mL, 2.45 mmol), $KF_{(aq)}$ (0.3556 g, 6.12 mmol), PMHS (0.18 mL, 3.06 mmol), and TBAF (cat.) in THF (6 mL) was stirred

for 2.5 h. NaOH (1M) was added and stirred for 30 min. The solution was then filtered and extracted with ether and water. The organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 1% TEA; 95/5 hexanes/ethyl acetate) to afford 0.5651 g (60.6% yield) of the vinyl stannane. ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (dt, *J* = 7.1, 15.4 Hz, 1H), 5.87 (tm, *J* = 36.3 Hz, 2H), 5.76 (dt, *J* = 1.1, 15.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.14 (m, 4H), 1.44 (m, 8H), 1.24 (m, 9H), 0.84 (m, 15H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 149.0, 148.3, 128.3, 121.4, 60.0, 37.0, 31.4, 29.1, 27.2, 22.6, 14.2, 13.6, 9.3.

IR (neat) 1723 cm^{-1}.

HRMS (EI): m/z calcd for $C_{18}H_{33}O_2Sn$ (M^+ - Bu): 401.1503. Found: 401.1521.

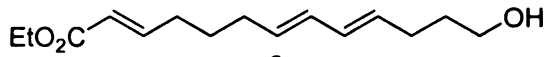


5

Preparation of (2E,7E)-ethyl 8-iodoocta-2,7-dienoate: The vinyl tin, **4a**, (1.5923 g, 3.48 mmol) was dissolved in CH_2Cl_2 (25 mL) at 0 °C. I_2 (0.8636 g, 3.40 mmol) in CH_2Cl_2 (20 mL) was added dropwise making sure the purple color did not persist. The reaction was quenched with $Na_2S_2O_{3\,(aq)}$ and then diluted with ether and water. The layers were separated and the organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 85/15 hexanes/ethyl acetate) to afford 0.9439 g (92% yield) of the vinyl iodide. ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (dt, *J* = 7.1, 15.4 Hz, 1H), 6.43 (dt, *J* = 7.1, 14.3 Hz, 1H), 5.97 (d, *J* = 14.3 Hz, 1H), 5.76 (dm, *J* = 15.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.16 (q, *J* = 7.1 Hz, 2H), 2.03 (q, *J* = 7.1 Hz,

2H), 1.53(m, 2H), 1.23 (t, J = 7.1 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 148.0, 145.4, 121.8, 75.3, 60.1, 35.2, 31.1, 26.4, 14.2.

IR (neat) 1719 cm^{-1}.

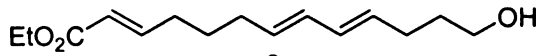


6

Preparation of (2E,7E,9E)-ethyl 13-hydroxytrideca-2,7,9-trienoate: In a round bottom flask with a condenser attached was placed NMP (5 mL) along with Pd_2dba_3 (0.0092 g, 0.01 mmol) and $AsPh_3$ (0.0123 g, 0.04 mmol). After stirring for 10 min at room temperature, the vinyl iodide **2a** (0.1546 g, 0.73 mmol) was added and the flask was immersed in a 70 °C oil bath. Immediately following immersion the tributylvinyl tin **4a** (0.2280 g, 0.50 mmol) and CuI (0.0019 g, 0.01 mmol) were added and the reaction stirred for 24 h. A sat. $KF_{(aq)}$ solution was added and stirred for 20 min at room temperature. Ether was added and the layers were separated. The aqueous layer was extracted with ether and the combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.0502 g (39.9% yield) of the triene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (dt, J = 6.9, 15.7 Hz, 1H), 6.00 (m, 2H), 5.79 (dd, J = 1.5, 15.6 Hz, 1H), 5.55 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.64 (t, J = 6.3 Hz, 2H), 2.16 (m, 4H), 2.07 (q, J = 7.3 Hz, 1H), 1.65 (m, 2H), 1.53 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 148.9, 131.7, 131.6, 130.9, 130.8, 121.6, 62.5, 60.1, 32.3, 31.9, 31.6, 28.9, 27.7, 14.3.

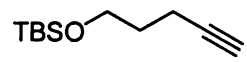
IR (neat) 3457, 1719 cm^{-1}.

HRMS (EI): m/z calcd for $C_{15}H_{25}O_3$ (M^++H): 253.1804. Found: 253.1813.



6

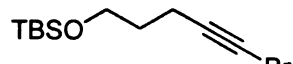
Preparation of (2E,7E,9E)-ethyl 13-hydroxytrideca-2,7,9-trienoate: In a round bottom flask with a condenser attached was placed NMP (15 mL) along with Pd_2dba_3 (0.0485 g, 0.05 mmol) and $AsPh_3$ (0.0668 g, 0.22 mmol). After stirring for 10 min at room temperature, the vinyl iodide **5** (1.2000 g, 4.08 mmol) was added and the flask was immersed in a 70 °C oil bath. Immediately following immersion the vinyl tin **1a** (1.0301 g, 2.74 mmol) and CuI (0.0152 g, 0.05 mmol) were added and the reaction stirred for 24 h. A saturated KF solution was added and stirred for 20 min at room temperature. Ether was added and the layers were separated. The aqueous layer was extracted with ether and the combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.1455 g (21% yield) of the triene **6**. The spectral data was consistent with that shown above.



22

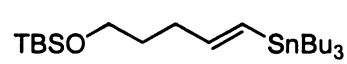
Preparation of 1-(tertbutyldimethylsiloxy)-4-pentyne: TBSCl (2.55 g, 16.5 mmol) was added to a solution of 4-pentyn-1-ol (1.4 mL, 15 mmol) in CH_2Cl_2 (25 mL) containing Et_3N (2.5 mL, 18 mmol) and DMAP (0.1843 g, 1.5 mmol) at 0 °C. The solution was stirred for 20 min and then allowed to warm to room temperature. The reaction mixture was added to a sat. solution of NH_4Cl and the layers were separated. The organic phase was washed with NH_4Cl and the combined aqueous layers were extracted with ether. The combined organic

layers were dried with $MgSO_4$, filtered, and concentrated to afford a colorless liquid. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to yield 2.50 g (89% yield) of silyl ether **22**. ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (t, *J* = 6.0 Hz, 2 H), 2.29 (td, *J* = 2.7, 7.1 Hz, 2 H), 1.95 (t, *J* = 2.7 Hz, 1 H), 1.75 (m, 2 H), 0.92 (s, 9 H), 0.08 (s, 6 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.3, 68.2, 61.4, 31.5, 25.9, 18.3, 14.8, -5.4. Spectral data were consistent with those previously reported.[126]



23

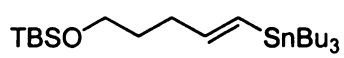
Preparation of 1-bromo-5-(tertbutyldimethylsiloxy)-1-pentyne: NBS (2.6021g, 14.6 mmol) and $AgNO_3$ (0.1993 g, 1.17 mmol), were added to a solution of dry acetone and 1-(tertbutyldimethylsiloxy)-4-pentyne (2.45 g, 12.2 mmol). After stirring for 1 h at room temperature, the reaction mixture was diluted with ether (200 mL) and washed with water (2 x 50 mL). The aqueous layer was extracted with ether, the organics were combined, dried with $MgSO_4$, filtered and concentrated. The crude product, **23**, (3.09 g, 87% yield) was determined to be pure by GC analysis. ^1H NMR (300 MHz, $CDCl_3$) δ 3.70 (t, *J* = 6.0 Hz, 2 H), 2.32 (t, *J* = 7.1 Hz, 2 H), 1.73 (quint, *J* = 6.0 Hz, 2 H), 0.92 (s, 9 H), 0.08 (s, 6 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.9, 61.3, 37.7, 31.3, 25.9, 16.1, 14.1, -5.4. Spectral data were consistent with those previously reported.[126]



24a

Preparation of 1-(tributylstannyl)-5-(tertbutyldimethylsiloxy)-1(E)-pentene: A solution of $PdCl_2(PPh_3)_2$ (0.082 g, 0.116 mmol), 1-bromo-5-

(tertbutyldimethylsiloxy)-1-pentyne, **23**, (3.09 g, 11.6 mmol), Bu_3SnCl (3.78 mL, 13.92 mmol), $KF_{(aq)}$ (2.02 g in 5 mL H_2O), PMHS (1.05 mL, 17.4 mmol), and cat. TBAF in THF (32.5 mL). The reaction was followed by tlc; upon completion, 10% NaOH was added and stirred for 0.5 h. The solution was filtered and extracted with ether and water. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The resulting liquid was purified by flash chromatography (silica gel, 1% TEA; 95/5 hexanes/ethyl acetate) to afford 1.89 g (34% yield) of vinyl stannane **24a**. ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (m, 2H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.20 (m, 2H), 1.63-1.41 (m, 8H), 1.28 (m, 6H), 0.87 (m, 24H), 0.03 (s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 127.5, 62.6, 34.0, 31.6, 29.1, 27.3, 26.0, 18.4, 13.7, 9.4, -5.3. Spectral data were consistent with those previously reported.[5]



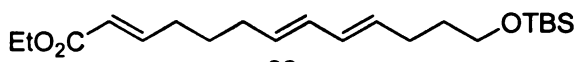
24a

Preparation of tert-butyl-dimethyl-(5-tributylstannanyl-pent-4-enyloxy)-silane A solution of 1-(tert-butyldimethylsiloxy)-4-pentyne, **22**, (5.98 g, 30 mmol), Bu_3SnCl (9.76 mL, 36 mmol), $KF_{(aq)}$ (5.2690 g, 90 mmol), PMHS (2.18 mL, 36 mmol), and AIBN (cat) in benzene (150 mL) was immersed in a 75 °C oil bath. The reaction was stirred for 2 h. The reaction was cooled to room temperature and 0.5 M NaOH (30 mL) was added and the reaction was stirred for 2 h. The mixture was filtered and the layers separated. The aqueous layer was extracted with ether. The organics were combined, dried with $MgSO_4$, filtered, and concentrated. The product was purified by flash chromatography (silica gel, 1%

TEA; 95/5 hexanes/ethyl acetate) to afford 8.2638 g (56.3% yield) of vinyl stannane **24a**. Spectral data was consistent with that shown above.

25a

Preparation of 1-(t-butyldimethylsiloxy)-5-iodo-4-pentene: A solution of I_2 (2.54 g, 10 mmol) in CH_2Cl_2 (60 mL) was added dropwise to vinyl tin **24a** (4.9937 g, 10 mmol) in CH_2Cl_2 (75 mL) at 0 °C until the purple color persisted. The reaction was quenched with aqueous sodium thiosulfate. The solution was diluted with ether and water. The layers were separated, the organics were dried, filtered, and concentrated. The crude product was purified with flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 2.0527 g (63% yield) of vinyl iodide **25a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (dt, *J* = 7.1, 14.3, 1H), 5.97 (dt, *J* = 1.1, 14.8, 1H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.10 (dq, *J* = 1.1, 7.1 Hz, 2H), 1.58 (quint., *J* = 7.1 Hz, 2H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 74.6, 68.2, 32.4, 31.6, 25.9, 18.3, -5.4. Spectral data were consistent with those previously reported.[127]



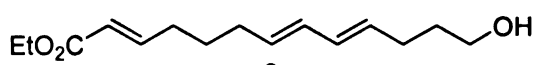
26

Preparation of 13-(tert-butyl-dimethyl-silanyloxy)-trideca-2,7,9-trienoic acid ethyl ester: A solution of Pd_2dba_3 (43 mg, 0.0437 mmol), $AsPh_3$ (175 mg, 0.175 mmol), and CuI (8.3 mg, 0.0438 mmol) in NMP (12 mL) was stirred for 10 min. The vinyl iodide, **25a**, (1.052 g, 3.26 mmol) was added and the flask was immersed in a 70 °C oil bath. Immediately following immersion, vinyl tin **4a** (1.00 g, 2.19 mmol) was added and stirred for 62 h. Ether was added, the layers were

separated, and the aqueous layer was back extracted. The organics were combined, dried with $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (silica gel; 98/2 hexanes/ethyl acetate) afforded 0.640 g (80% yield) of a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (dt, *J* = 6.6, 15.9 Hz, 1H), 6.50 (dt, *J* = 7.7, 14.3 Hz, 1H), 5.97 (d, *J* = 14.3 Hz, 1H), 5.79 (d, *J* = 14.3 Hz, 1H), 4.93 (m, 2H), 4.15 (m, 2H), 3.58 (t, *J* = 6.0 Hz, 2H), 2.19 (m, 4H), 2.07 (m, 2H), 1.56 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 148.8, 146.2, 140.9, 132.2, 128.6, 121.5, 82.4, 74.5, 62.5, 61.9, 60.1, 32.4, 31.4, 25.9, 18.3, 14.2, -5.3.

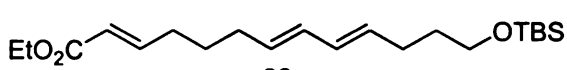
IR (neat) 1719, 1101 cm^{-1}.

MS (EI): m/z calcd for $C_{21}H_{39}O_3Si$ (M^++H): 367.3. Found: 367.2.



6

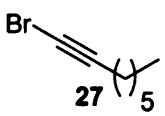
Deprotection of 13-(tert-Butyl-dimethyl-silyloxy)-trideca-2,7,9-trienoic acid ethyl ester: A solution of **26** (0.0500 g, 0.136 mmol) and TBAF (0.079 mL, 0.273 mmol) in THF (5 mL) was stirred for 5 h. After quenching with water the solution was poured into ether and extracted with water. The crude product was purified by flash chromatography (silica gel; 70/30 hexanes/ethyl acetate) to afford g (% yield) of triene **6**. Spectral data was consistent with that shown above.



26

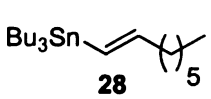
Preparation of 13-(tert-Butyl-dimethyl-silanyloxy)-trideca-2,7,9-trienoic acid ethyl ester: TBSCl (0.3135 g, 2.0 mmol) was added to a solution of triene **6**

(0.3936 g, 1.56 mmol) in CH_2Cl_2 (10 mL) containing DMAP (cat.) and imidazole (0.1539 g, 2.26 mmol) at 0 °C. The reaction was stirred for 1h and then allowed to warm to room temperature. After another hour the reaction mixture was added to a sat. solution of NH_4Cl and the layers were separated. The organic phase was washed with NH_4Cl and the combined aqueous layers were extracted with ether. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to afford a colorless liquid. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to yield 0.2292 g (40% yield) of triene **26**. Spectral data was consistent with that shown above.



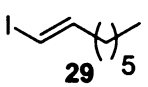
27

Preparation of 1-bromooct-1-yne: Octyne (2.67 mL, 18.1 mmol), NBS (3.5952 g, 19.9 mmol), and $AgNO_3$ (0.2763 g, 1.6 mmol) in acetone (100 mL) were stirred for 3 h at room temperature. The reaction was diluted with ether and washed with water. The aqueous layer was extracted with ether. The combined organics were dried and concentrated. The crude product was purified by flash chromatography (silica gel; hexanes) to afford 2.9432 g (86% yield) of bromide **27**. ^1H NMR (300 MHz, $CDCl_3$) δ 2.18 (t, J = 7.1 Hz, 2H), 1.49 (quint., J = 7.1 Hz, 2H), 1.27 (m, 6H), 0.87 (t, J = 7.1 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.4, 37.4, 31.3, 28.5, 28.3, 22.5, 19.7, 14.0. Spectral data were consistent with those previously reported.[128,129,130]



28

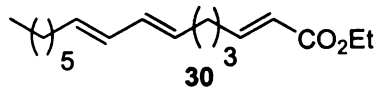
Preparation of (E)-oct-1-enyltributylstannane: A solution of $PdCl_2(PPh_3)_2$ (0.0993 g, 0.133 mmol), 1-bromobut-1-yne, **27**, (2.4907 g, 13.2 mmol), Bu_3SnCl (4.34 mL, 16.0 mmol), $KF_{(aq)}$ (2.3182 g in 7 mL H_2O), PMHS (1.59 mL, 26.6 mmol), and cat. TBAF in THF (45 mL). The reaction was stirred for 4 h and then 10% NaOH was added and stirred for 0.5 h. The solution was filtered and extracted with ether and water. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The resulting liquid was purified by flash chromatography (silica gel, 1% TEA; pentane) to afford 3.9956 g (75.2% yield) of vinyl tin **28**. ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (m, 2H), 2.11 (tq, *J* = 6.6, 31.9 Hz, 2H), 1.48 (quint., *J* = 7.7 Hz, 8H), 1.30 (m, 12H), 0.87 (t, *J* = 7.1 Hz, 18H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 126.9, 37.9, 31.8, 29.1, 28.8, 27.4, 27.3, 22.6, 14.1, 13.7, 9.4.



29

Preparation of (E)-1-iodobut-1-ene: A solution of I_2 (0.6330 g, 2.5 mmol) in CH_2Cl_2 (10 mL) was added dropwise to vinyl tin **28** (1.0040 g, 2.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C until the purple color persisted. The reaction was quenched with sat. $Na_2S_2O_{3(aq)}$. The solution was diluted with ether and water. The layers were separated; the organics were dried, filtered, and concentrated. The crude product was purified with flash chromatography (silica gel; pentane) to afford 0.5014 g (84% yield) of iodide **29**. ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (dt, *J* = 7.1, 14.3 Hz, 1H), 5.94 (dt, *J* = 1.1, 14.3 Hz, 1H), 2.03 (q, *J* = 7.1 Hz, 2H), 1.56 (m, 2H), 1.3 (m, 6H), 0.90 (t, *J* = 7.1 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ

146.8, 74.2, 36.0, 31.6, 28.6, 28.3, 22.5, 14.0. Spectral data were consistent with those previously reported.[131]

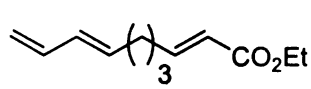


30

Preparation of (2E,5E,7E)-ethyl deca-2,5,7-trienoate: Pd_2dba_3 (0.0211 g, 0.023 mmol) and $AsPh_3$ (0.0279 g, 0.091 mmol) in NMP (7 mL) were stirred at room temperature for 10 min. The vinyl iodide, **29**, (0.4045 g, 1.7 mmol) was added and the flask was immersed in 60 °C oil bath. Immediately following immersion, vinyl tin **4a** (0.7766 g, 1.7 mmol) was added followed by CuI (0.0044 g, 0.023 mmol). After stirring for 15 h, sat. $KF_{(aq)}$ was added and stirred for 20 min at room temperature. Ether was added and the layers were separated. The organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.2361 g (49.9% yield) of triene **30**. ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (dtd, *J* = 2.2, 6.0, 15.9 Hz, 1H), 5.97 (m, 2H), 5.78 (d, *J* = 15.4 Hz, 2H), 5.58 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.12 (m, 6H), 1.26 (m, 10H), 0.85 (m, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 148.9, 133.1, 131.2, 130.9, 130.0, 121.5, 60.1, 33.1, 32.6, 31.7, 29.3, 28.9, 27.7, 27.2, 22.6, 14.3, 14.1.

IR (neat) 1719 cm^{-1}.

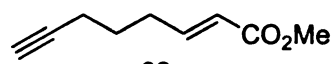
HRMS (EI): m/z calcd for $C_{18}H_{31}O_2$ (M^++H): 279.2324. Found: 279.2328.



31

Preparation of (2E,5E)-ethyl octa-2,5,7-trienoate: Pd_2dba_3 (0.0167 g, 0.0182 mmol) and $AsPh_3$ (0.0223 g, 0.0728 mmol) in NMP (7 mL) were stirred at room

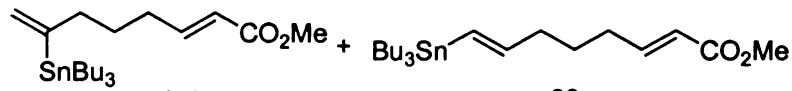
temperature for 10 min. The vinyl iodide, **5**, (0.3996 g, 1.36 mmol) was added and the flask was immersed in 60 °C oil bath. Immediately following immersion, tributylvinyl tin (0.2886 g, 0.91 mmol) was added followed by CuI (0.0035 g, 0.0182 mmol). After stirring for 15 h, sat. KF was added and stirred for 20 min at room temperature. Ether was added and the layers were separated. The organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.1898 g (107% yield) of the impure triene **31**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93(m, 1H), 6.47 (dt, *J* = 7.3, 14.2 Hz, 1H), 6.28 (dt, *J* = 6.8, 17.1 Hz, 1H), 6.01 (dt, *J* = 1.5, 14.5 Hz, 1H), 5.80 (dt, *J* = 1.5, 15.6 Hz, 1H), 5.08 (d, *J* = 15.1 Hz, 1H), 4.96 (d, *J* = 8.3 Hz, 1H), 4.16 (q, *J* = 7.3 Hz, 2H), 2.12 (m, 4H), 1.56 (q, *J* = 7.3 Hz, 2H), 1.26 (t, *J* = 7.3 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 148.0, 145.6, 133.7, 128.6, 122.0, 115.1, 60.2, 35.3, 31.2, 26.6, 14.3. Spectral data were consistent with those previously reported.[132]



32

Preparation of (E)-methyl oct-2-en-7-ynoate: Oxalyl chloride (0.63 mL, 7.2 mmol) was added to CH_2Cl_2 (42 mL) and the solution was cooled to -78 °C. A solution of DMSO (0.94 mL, 13.2 mmol) and CH_2Cl_2 (3 mL) was prepared and added dropwise. After 10 min of stirring, a solution of 5-hexyn-1-ol (0.66 mL, 6 mmol) and CH_2Cl_2 (1 mL) was added. After another 10 min of stirring, TEA (5.85 mL, 42 mmol) was added and the reaction stirred an additional 10 min. The cooling bath was removed and the solution stirred 10 min. Following the addition of the wittig reagent (3.0092 g, 9 mmol) the reaction stirred overnight at room

temperature. After concentration of the reaction, the flask was filled with ether and the solid was scraped off the sides of the flask. The solution was filtered through a pad of silica gel. The solute was concentrated and purified by flash chromatography (silica gel; 95/5 hexanes/ethyl acetate) to afford 0.8302 g (90.9% yield) of ester **32**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (dt, *J* = 7.1, 15.4 Hz, 1H), 5.82 (d, *J* = 15.9 Hz, 1H), 3.68 (s, 3H), 2.29 (q, *J* = 7.1 Hz, 2H), 2.18 (dt, *J* = 2.7, 7.1 Hz, 2H), 1.94 (t, *J* = 2.2 Hz, 1H), 1.65 (quint., *J* = 7.1 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 148.1, 121.6, 83.4, 69.0, 51.4, 30.9, 26.6, 17.7. Spectral data were consistent with those previously reported.[133]

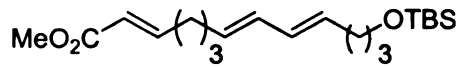


33b **33a**

Preparation of (2E,7E)-methyl 8-(tributylstannyl)octa-2,7-dienoate and (E)-methyl 7-(tributylstannyl)octa-2,7-dienoate: NBS (0.9763 g, 5.49 mmol) and $AgNO_3$ (0.0745 g, 0.439 mmol) were added to a solution of alkyne **32** (0.7589 g, 4.99 mmol) in acetone (20 mL). The resulting solution was stirred at room temperature for 1 h. It was diluted with ether and washed with water. The aqueous layer was extracted with ether. The combined organics were combined, dried over $MgSO_4$, and concentrated. The crude bromoalkyne (1.4768 g, 6.4 mmol) was dissolved in THF (20 mL). $PdCl_2(PPh_3)_2$ (0.0454 g, 0.064 mmol), Bu_3SnCl (2.08 mL, 7.7 mmol), $KF_{(aq)}$ (1.1155 g, 19.2 mmol), PMHS (0.76 mL, 12.8 mmol), and TBAF (cat.) were added and the reaction stirred for 5 h. 10% NaOH was added and stirred for 0.5 h. The solution was filtered and extracted with ether and water. The combined organic layers were dried with $MgSO_4$,

filtered, and concentrated. The resulting liquid was purified by flash chromatography (silica gel, 1% TEA; 90/10 hexanes/ethyl acetate) to afford 1.0927 g (38.5% yield) of vinyl tin **33**. ^{1}H NMR of the crude product showed a 6/1 ratio of E/internal stannane. **33a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (dt, *J* = 6.8, 15.6 Hz, 2H), 5.88 (s, 1H), 5.80 (d, *J* = 15.6 Hz, 1H), 3.70 (s, 3H), 2.17 (m, 4H), 1.45 (m, 8H), 1.28 (m, 6H), 0.85 (t, *J* = 7.7 Hz, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 149.5, 148.3, 128.4, 121.0, 51.4, 40.6, 37.0, 31.5, 29.1, 27.2, 13.7, 9.4, **33b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (dt, *J* = 6.8, 15.6 Hz, 2H), 5.64 (s, 1H), 5.11 (s, 1H), 3.70 (s, 3H), 2.25 (m, 4H), 1.53 (m, 8H), 1.28 (m, 6H), 0.85 (t, *J* = 7.7 Hz, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 154.6, 149.3, 125.5, 121.0, 51.4, 40.6, 37.0, 31.7, 29.1, 27.4, 13.7, 9.6.

IR (neat) 1728 cm^{-1}.



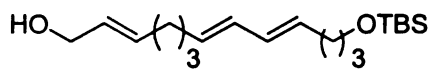
34

Preparation of (2E,5E,7E)-methyl 9-(tert-butyldimethylsilyloxy)nona-2,5,7-trienoate: Pd_2dba_3 (0.0366 g, 0.04 mmol) and $AsPh_3$ (0.0490 g, 0.16 mmol) in NMP (10 mL) was stirred at room temperature for 10 min. The vinyl iodide, **25a**, (0.9789 g, 3 mmol) was added and the flask was immersed in 80 °C oil bath. Immediately following immersion, vinyl tin **33a** (0.8787 g, 1.98 mmol) was added followed by CuI (0.0076 g, 0.04 mmol). After stirring for 26 h, sat. KF was added and stirred for 20 min at room temperature. Ether was added and the layers were separated. The organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica

gel; 98/2 hexanes/ethyl acetate) to afford 0.2792 g (41% yield) of triene **34**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (dt, *J* =7.1, 15.4 Hz, 1H), 6.49 (dt, *J* = 7.1, 14.3 Hz, 2H), 5.96 (dt. *J* = 1.1, 14.3 Hz, 1H), 5.80 (dm, *J* = 15.4 Hz, 2H), 4.94 (m, 2H), 3.69 (s, 3H), 3.60 (m, 2H), 2.11 (m, 2H), 1.57 (m, 2H), 1.24 (m, 4H), 0.86 (s, 9H), 0.01 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 149.3, 132.3, 131.1, 131.1, 130.4, 121.1, 62.5, 51.4, 32.4, 31.6, 28.9, 27.7, 26.0, 18.3, 17.5, -5.3.

IR (neat) 1734, 1103, 837 cm^{-1}.

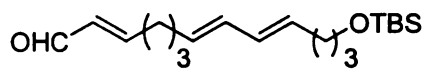
HRMS (EI): m/z calcd for $C_{20}H_{37}O_3Si$ (M^++H): 353.2512. Found: 353.2512.



35

Preparation of (2E,5E,7E)-9-(tert-butyldimethylsilyloxy)nona-2,5,7-trien-1-ol: DIBAL (0.53 mL, 1M in hexanes, 0.53 mmol) was added dropwise to a solution of ester **34** (0.0969 g, 0.26 mmol) in CH_2Cl_2 (2 mL) at -78 °C. The reaction stirred for 7 h before sat. Rochelle's salt was added and stirred at room temperature overnight. The layers were separated and the aqueous layer was extracted with ether. The combined organics were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.0621 g (73.6% yield) of alcohol **35**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (m, 2H), 5.64 (m, 3H), 5.54 (m, 1H), 4.06 (d, *J* = 4.9 Hz, 2H), 3.59 (dt, *J* = 5.4, 6.3 Hz, 2H), 2.10 (m, 4H), 1.58 (quint, *J* = 7.3 Hz, 2H), 1.45 (quint, *J* = 7.3 Hz, 2H), 1.28 (bs, 1H), 1.24 (t, *J* = 6.8 Hz, 2H), 0.87 (s, 9H), 0.02 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.0, 131.9, 131.8, 130.7, 130.6, 129.2, 63.8, 62.6, 32.5, 32.0, 31.6, 28.8, 28.8, 25.9, 18.3, -5.3.

IR (neat) 3335, 1100 cm^{-1}.

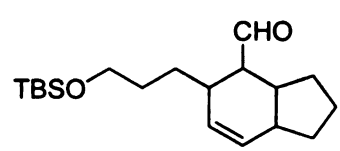


36

Preparation of (2E,5E,7E)-9-(tert-butyldimethylsilyloxy)nona-2,5,7-trienal: The allylic alcohol (0.0480 g, 0.148 mmol) 4Å MS (0.03 g), and CMD (0.0680 g, 0.77 mmol) in CH_2Cl_2 (12 mmol) were stirred overnight at room temperature. The solution was then filtered through a celite plug, concentrated, and purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.0225 g (47% yield) of aldehyde **36**. ^1H NMR (300 MHz, $CDCl_3$) δ 9.48 (dt, *J* = 1.1, 8.2 Hz, 1H), 6.82 (dt, *J* = 6.6, 15.9 Hz, 1H), 6.03 (m, 4H), 5.55 (m, 1H), 3.58 (m, 2H), 2.21 (m, 6H), 1.58 (m, 4H), 0.87 (s, 9H), 0.02 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.0, 158.4, 133.1, 132.5, 131.4, 130.7, 130.3, 62.5, 32.4, 32.0, 31.9, 28.8, 27.5, 25.9, 18.3, -5.3.

IR (neat) 1700 cm^{-1}.

MS (EI): m/z calcd for $C_{19}H_{35}O_2Si$ (M^++H): 323.2. Found: 323.2.



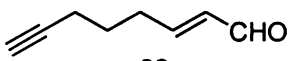
37

Preparation of 5-(3-(tert-butyldimethylsilyloxy)propyl)-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carbaldehyde: The aldehyde (0.0076 g, 0.024 mmol) was placed in toluene (1 mL) in a sealed tube and heated to 180 °C for 5 days. After cooling to room temperature the solution was concentrated to afford 0.0070 g (100% conversion) of bicycle **37**. ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (d, *J* = 2.4 Hz, 1H), 5.87 (d, *J* = 9.8 Hz, 1H), 5.65 (ddd, *J* = 2.4, 3.9, 10.3 Hz, 1H), 3.54 (dt, *J*

= 2.0, 6.3 Hz, 2H), 2.72 (m, 1H), 2.56 (ddd, J = 2.4, 6.3, 11.2 Hz, 1H), 2.42 (s, 1H), 2.02 (m, 1H), 1.90-1.00 (m, 10H), 0.86 (s, 9H), 0.01 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.0, 130.0, 129.7, 63.1, 56.7, 45.4, 39.8, 37.0, 30.8, 29.0, 28.3, 27.6, 25.9, 22.4, 18.3, -5.3.

IR (neat) 1701, 1101, 835 cm^{-1}.

HRMS (EI): m/z calcd for $C_{19}H_{35}O_2Si$ (M^++H): 323.2406. Found: 323.2363.

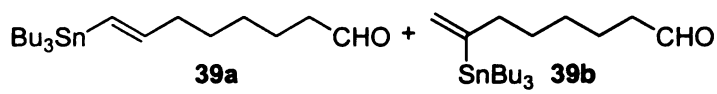


38

Preparation of (E)-oct-2-en-7-ynal: Oxalyl chloride (3.93 mL, 45.1 mmol) was added to CH_2Cl_2 (150 mL) and the solution was cooled to -78 °C. A solution of DMSO (6.40 mL, 90.2 mmol) and CH_2Cl_2 (60 mL) was prepared and added dropwise. After 10 min of stirring, a solution of 5-hexyn-1-ol (4.49 mL, 41 mmol) and CH_2Cl_2 (60 mL) was added. After another 10 min of stirring, TEA (28.6 mL, 205 mmol) was added and the reaction stirred an additional 10 min. The cooling bath was removed and the solution was warmed to room temperature. The reaction was diluted with CH_2Cl_2, washed with 0.1M HCl, water, and brine. The combined aqueous layers were extracted with CH_2Cl_2, the organics were dried over Na_2SO_4 and filtered. After concentration, the crude product was passed through a plug of silica gel. The aldehyde was then dissolved in THF and the triphenylphosphoranylidene acetaldehyde (1.00 g, 3.3 mmol) was added. The reaction was then heated to reflux for 48 h. After concentration of the reaction, the flask was filled with ether and the solid (triphenylphosphine oxide) was scraped off the sides of the flask. The solution was filtered through a pad of silica gel. The solute was concentrated and purified by flash chromatography

(silica gel; 95/5 hexanes/ethyl acetate) to afford 4.4044 g (87.9% yield) of aldehyde **38**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.43 (d, *J* = 7.7 Hz, 1H), 6.77 (dt, *J* = 7.1, 15.4 Hz, 1H), 6.06 (dd, *J* = 7.7, 15.4 Hz, 1H), 2.40 (q, *J* = 7.1 Hz, 2H), 2.18 (dt, *J* = 2.7, 6.6 Hz, 2H), 1.92 (m, 1H), 1.66 (quint., *J* = 7.1 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 157.1, 133.3, 69.2, 31.3, 26.3, 22.5, 17.7.

IR (neat) 3291, 2118, 1692 cm^{-1}.

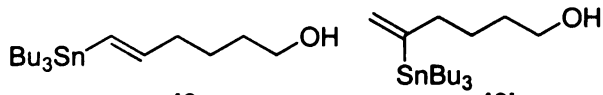


39a **39b**

Preparation of (E)-8-(tributylstannyl)oct-7-enal and 7-(tributylstannyl)oct-7-enal: NBS (0.1958 g, 1.1 mmol) and $AgNO_3$ (0.0149 g, 0.088 mmol) were added to a solution of alkyne **38** (0.1250 g, 1 mmol) in acetone (5 mL). The resulting solution was stirred at room temperature for 2 h. It was diluted with ether and washed with water. The aqueous layer was extracted with ether. The combined organics were dried over $MgSO_4$, and concentrated. The crude bromoalkyne was dissolved in THF (5 mL). $PdCl_2(PPh_3)_2$ (0.0071 g, 0.01 mmol), Bu_3SnCl (0.33 mL, 1.2 mmol), $KF_{(aq)}$ (0.1743 g, 3 mmol), and PMHS (0.06 mL, 1 mmol) were added and the reaction stirred for 8 h. 10% NaOH was added and stirred for 0.5 h. The solution was filtered and extracted with ether and water. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The resulting liquid was purified by flash chromatography (silica gel, 1% TEA; 90/10 hexanes/ethyl acetate) to afford 0.1080 g (26% yield) of vinyl tin **39a**. ^{1}H NMR of the crude reaction showed a 7/1 ratio of E/internal stannane. **39a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H), 5.88 (m, 2H), 2.40 (t, *J* = 7.1 Hz, 2H), 2.11 (m, 2H), 1.61 (m, 2H), 1.46 (m, 4H), 1.30 (m, 12H), 0.86 (t, *J* = 7.1 Hz, 15H), ^{13}C NMR (75

MHz, $CDCl_3$) δ 202.8, 149.2, 127.5, 43.9, 31.6, 29.1, 27.4, 27.3, 22.6, 14.1, 13.7, 9.3, **39b:** ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (d, *J* = 1.6 Hz, 1H), 5.63 (tm, *J* = 70.3 Hz, 1H), 5.08 (tm, *J* = 31.3 Hz, 1H), 2.40 (t, *J* = 7.1 Hz, 2H), 2.22 (t, *J* = 7.7 Hz, 2H), 1.61 (quint., *J* = 7.1 Hz, 2H), 1.46 (quint., *J* = 8.2 Hz, 4H), 1.30 (m, 12H), 0.86 (t, *J* = 7.1 Hz, 15H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 155.2, 124.9, 43.9, 41.0, 29.3, 29.1, 28.8, 27.4, 21.9, 13.6, 9.6.

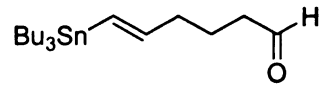
IR (neat) 1726 cm^{-1}.



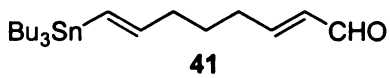
40a **40b**

Preparation of (E)-6-(tributylstannyl)hex-5-en-1-ol and 5-(tributylstannyl)hex-5-en-1-ol: A solution of $PdCl_2(PPh_3)_2$ (0.0175 g, 0.025 mmol), 5-hexyn-1-ol (0.28 mL, 2.5 mmol), Bu_3SnCl (0.81 mL, 3 mmol), $KF_{(aq)}$ (0.4358 g, 7.5 mmol), and PMHS (0.30 mL, 5.0 mmol) in THF (25 mL) was stirred for 19 h. NaOH (1M) was added and stirred for 30 min. The solution was then filtered and extracted with ether and water. The organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 1% TEA; 85/15 hexanes/ethyl acetate) to afford 0.6220 g (64% yield) of vinyl tin **40**. 1H NMR of the crude reaction showed 3.9/1 ratio of E/internal stannane. **40a:** ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (m, 2H), 3.63 (q, *J* = 5.5 Hz, 2H), 2.14 (q, *J* = 6.6 Hz, 2H), 1.46 (m, 9H), 1.29 (sept., *J* = 7.1 H, 6H), 0.86 (t, *J* = 7.7 Hz, 15H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 127.6, 62.9, 54.1, 32.2, 29.1, 27.3, 25.0, 13.7, 9.3. **40b:** ^1H NMR (300 MHz, $CDCl_3$) δ 5.65 (tm, *J* = 69.8 Hz, 1H), 5.10 (tm, *J* = 37.9 Hz, 1H), 3.62 (q, *J* = 6.6 Hz, 2H),

2.25 (t, 7.1 Hz, 1H), 1.46 (m, 10H), 1.30 (m, 8H), 0.87 (t, J = 7.1 Hz, 15H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 125.0, 62.8, 40.9, 32.3, 29.1, 27.4, 25.5, 13.7, 9.5. Spectral data were consistent with those previously reported.[134]



Preparation of (E)-6-(tributylstannyl)hex-5-enal: To a solution of **40a** (0.2779 g, 0.71 mmol) in toluene:DMSO (2:1) was added IBX (0.2599 g, 0.93 mmol). The solution was heated to 70 °C for 30 min. The reaction was diluted with ether and washed with 5% $NaHCO_3$, H_2O, and brine. The solution was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 1% TEA; 90/10 hexanes/ethyl acetate) to afford 0.1561 g (57% yield) of (E)-6-(tributylstannyl)hex-5-enal. ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 5.89 (m, 2H), 2.42 (dt, J = 0.6, 7.7 Hz, 2H), 2.15 (m, 2H), 1.72 (quint., J = 7.7 Hz, 2H), 1.46 (quint., J = 7.7 Hz, 6H), 1.29 (sept., J = 7.7 Hz, 6H), 0.86 (t, J = 7.1 Hz, 15H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 147.8, 129.0, 43.2, 37.0, 29.1, 27.2, 21.1, 13.7, 9.4.

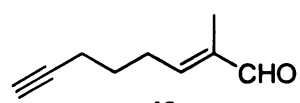


41

Preparation of (2E,7E)-8-(tributylstannyl)octa-2,7-dienal: (E)-6-(Tributylstannyl)hex-5-enal (0.1413 g, 0.36 mmol) and triphenylphosphoranylidene acetaldehyde (0.1111 g, 0.36 mmol) were placed in THF and heated to reflux for 49 h. The solution was cooled and concentrated. The crude product was purified by flash chromatography (silica gel, 1% TEA; 90/10 hexanes/ethyl acetate) to afford 0.0617 g (41% yield) of aldehyde **41**. ^1H

NMR (500 MHz, $CDCl_3$) δ 9.49 (d, *J* = 7.8 Hz, 1H), 6.83 (dt, *J* = 6.8, 15.6 Hz, 1H), 6.10 (ddt, *J* = 1.5, 7.8, 15.6 Hz, 1H), 5.90 (tm, *J* = 35.6 Hz, 2H), 2.33 (q, *J* = 6.8 Hz, 2H), 2.16 (tm, *J* = 7.3 Hz, 2H), 1.61 (quint, *J* = 7.3 Hz, 2H), 1.47 (quint., *J* = 7.3 Hz, 6H), 1.29 (q, *J* = 7.3 Hz, 6H), 0.87 (t, *J* = 7.3 Hz, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.1, 158.6, 148.0, 133.1, 128.9, 37.0, 32.0, 29.1, 27.2, 27.0, 13.7, 9.4.

IR (neat) 1699 cm^{-1}.

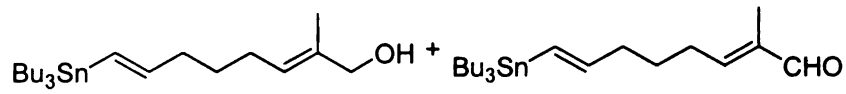


42

Preparation of (E)-2-methyloct-2-en-7-ynal: Oxalyl chloride (1.61 mL, 18.4 mmol) was added to CH_2Cl_2 (115 mL) and the solution was cooled to -78 °C. A solution of DMSO (2.62 mL, 37.0 mmol) and CH_2Cl_2 (10 mL) was prepared and added dropwise. After 10 min of stirring, a solution of 5-hexyn-1-ol (1.85 mL, 16.8 mmol) and CH_2Cl_2 (35 mL) was added. After another 10 min of stirring, TEA (11.71 mL, 84 mmol) was added and the reaction stirred an additional 10 min. The cooling bath was removed and the solution was allowed to warm to room temperature. The solution was diluted with CH_2Cl_2, washed with 0.1M HCl, water, and brine. The combined aqueous layers were back extracted with CH_2Cl_2, the organics were dried with Na_2SO_4, and concentrated. The crude product was passed through a silica gel plug and then concentrated. The aldehyde was dissolved in benzene (180 mL) and the triphenylphosphoranylidene methyl acetaldehyde (4.4 g, 13.8 mmol) was added. After refluxing for 17 h, the solution was cooled and concentrated. The crude

product was purified by flash chromatography (silica gel; 85:15 hexanes/ethyl acetate) to afford 1.2942 g (57% yield) of aldehyde **42**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (s, 1H), 6.45 (dt, *J* = 1.1, 7.1 Hz, 1H), 2.47 (q, *J* = 7.1 Hz, 2H), 2.24 (dt, *J* = 2.2, 7.1 Hz, 2H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.70 (s, 3H), 1.72 (t, *J* = 7.1 Hz, 2H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 153.0, 139.9, 83.2, 69.1, 27.6, 27.0, 17.9, 9.1.

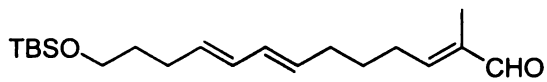
IR (neat) 2100, 1709 cm^{-1}.



44a **43a**

Preparation of (2E,7E)-2-methyl-8-(tributylstannyl)octa-2,7-dien-1-ol and (2E,7E)-2-methyl-8-(tributylstannyl)octa-2,7-dienal: A solution of $PdCl_2(PPh_3)_2$ (0.0071 g, 0.01 mmol), the aldehyde, **42**, (0.1312 mL, 1.0 mmol), Bu_3SnCl (0.33 mL, 1.2 mmol), $KF_{(aq)}$ (0.1743 g, 3.0 mmol), and PMHS (0.12 mL, 2.0 mmol) in THF (5 mL) was stirred for 26 h. NaOH (1M) was added and stirred for 30 min. The solution was then filtered and extracted with ether and water. The organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 1% TEA; 85/15 hexanes/ethyl acetate) to afford 0. 0598 g (14% yield) of a 1.15/1 mixture of E/internal vinyl stannanes and 0.1931 g (45% yield) of the allylic alcohol 1.9/1 mixture of E/internal vinyl stannanes. **43a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (s, 1H), 6.48 (m, 1H), 5.91 (m, 2H), 2.33 (m, 2H), 1.72 (s, 3H), 1.47 (m, 6H), 1.28 (m, 10H), 0.87 (t, *J* = 7.1 Hz, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3, 154.7, 148.2, 139.5, 128.7, 37.2, 29.2, 29.1, 27.3, 27.2, 13.7, 9.6, 9.4, **43b:** ^{1}H NMR

(300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 6.48 (m, 1H), 5.66 (tm, *J* = 38.5 Hz, 1H), 5.13 (tm, *J* = 15.9 Hz, 1H), 2.17 (m 2H), 1.72 (s, 3H), 1.47 (m, 6H), 1.28 (m, 10H), 0.94 (t, *J* = 7.1 Hz, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3, 154.7, 154.5, 139.5, 125.6, 40.8, 29.2, 29.1, 27.3, 27.2, 13.7, 9.6, 9.4. IR (neat) 1692 cm^{-1}. **44a:** ^1H NMR (500 MHz, $CDCl_3$) δ 5.90 (m, 2H), 5.40 (t, *J* = 7.3 Hz, 1H), 3.99 (s, 2H), 2.13 (q, *J* = 6.3 Hz, 2H), 2.02 (q, *J* = 7.8 Hz, 2H), 1.64(s, 3H), 1.46 (quint., *J* = 7.3 Hz, 9H), 1.28 (quint., *J* = 7.3 Hz, 6H), 0.87 (t, *J* = 7.3 Hz, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 134.9, 127.6, 126.3, 69.1, 37.4, 29.1, 28.7, 27.3, 27.0, 13.7, 13.7, 9.4, **44b:** ^1H NMR (500 MHz, $CDCl_3$) δ 5.66 (td, *J* = 2.9, 70.3 Hz, 1H), 5.40 (t, *J* = 7.3 Hz, 1H), 5.09 (td, *J* = 2.9, 28.0 Hz, 1H), 3.97 (s, 2H), 2.23 (t, *J* = 7.3 Hz, 2H), 2.02 (q, *J* = 7.8 Hz, 2H), 1.64 (s, 3H), 1.46 (quint., *J* = 7.8 Hz, 9H), 1.30 (quint., *J* = 7.3 Hz, 6H), 0.87 (t, *J* = 7.3 Hz, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 134.8, 126.1, 124.9, 69.0, 40.9, 29.4, 29.1, 27.4, 27.2, 13.7, 13.6, 9.6. IR (neat) 3316 cm^{-1}.



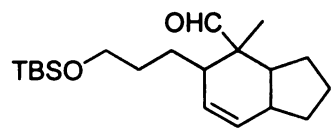
45

Preparation of (2E,7E,9E)-13-(tert-butyldimethylsilyloxy)-2-methyltrideca-2,7,9-trienal: Pd_2dba_3 (0.0238 g, 0.026 mmol) and $AsPh_3$ (0.0318 g, 0.104 mmol) in NMP (4 mL) were stirred at room temperature for 10 min. The vinyl iodide, **2a**, (0.6363 g, 1.95 mmol) was added and the flask was immersed in 64 °C oil bath. Immediately following immersion, vinyl tin **43** (0.5554 g, 1.3 mmol) was added in solution with NMP (3 mL) via cannula followed by CuI (0.0050 g, 0.026 mmol). After stirring for 16 h, sat. KF was added and stirred for 20 min at

room temperature. Ether was added and the layers were separated. The organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 98/2 hexanes/ethyl acetate) to afford 0.0558 g (13% yield) of triene **45**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (s, 1H), 6.46 (t, *J* = 6.6 Hz, 1H), 5.99 (dm, *J* = 14.3, 2H), 5.56 (m, 1H), 4.99 (m, 1H), 3.58 (m, 2H), 2.34 (m, 2H), 2.11 (quint., *J* = 7.1 Hz, 4H), 1.72 (s, 3H), 1.58 (m, 4H), 0.87 (s, 9H), 0.02 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 154.6, 139.5, 134.8, 132.5, 130.9, 130.3, 62.5, 32.4, 32.1, 29.7, 28.9, 28.0, 25.9, 18.3, 9.2, -5.3.

IR (neat) 1692 cm^{-1}.

HRMS (EI): m/z calcd for $C_{20}H_{37}O_2Si$ (M^++H): 337.2563. Found: 337.2534.



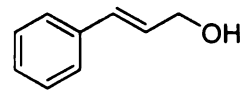
46

Preparation of 5-(3-(tert-butyldimethylsilyloxy)propyl)-4-methyl-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carbaldehyde: The triene, **45**, (0.0511 g, 0.15 mmol) was dissolved in d^6-benzene in a sealed tube and heated to 150 °C for 19 h then 180 °C for 3 h. Examination of the reaction by NMR showed that there was 29% conversion to **46**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 5.83 (d, *J* = 10.2 Hz, 1H), 5.62 (dm, *J* = 9.7 Hz, 1H), 3.54 (dt, *J* = 2.6, 6.2 Hz, 2H), 2.35 (m, 1H), 2.12 (m, 1H), 1.85 (m, 2H), 1.2-1.8 (m, 9H), 0.99 (s, 3H), 0.86 (s, 9H), 0.01 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 129.2, 128.8, 65.8, 63.1, 30.4, 53.4, 45.1, 42.9, 40.5, 31.6, 29.1, 26.0, 22.6, 14.1, 1.0, -5.3.

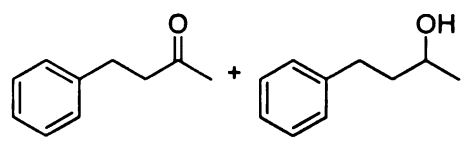
IR (neat) 1719, 1100, 802 cm^{-1}.

HRMS (EI): m/z calcd for $C_{20}H_{37}O_2Si$ (M^++H): 337.2563. Found: 337.2570.

Chapter 4 Experimental



Preparation of (E)-3-phenylprop-2-en-1-ol: A solution of cinnamaldehyde (0.13 mL, 1.0 mmol), $PdCl_2(PPh_3)_2$ (0.0070 g, 0.01 mmol), Bu_3SnCl (0.33 mL, 1.2 mmol), $KF_{(aq)}$ (0.1743 g, 3.0 mmol), PMHS (0.12 mL, 2.0 mmol), and THF (10 mL) was stirred at room temperature for 45 min. The reaction was quenched by the addition of 2M NaOH and stirred for 30 min. The organics were separated and washed with water. The combined organics were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (silica gel; 75/25 hexanes/ethyl acetate) afforded 0.1356 g (100% yield) of the allylic alcohol. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.65 (d, J = 15.9 Hz, 1H), 6.40 (dt, J = 5.5, 15.9 Hz, 1H), 4.36 (d, J = 5.5 Hz, 2H), 1.50 (s, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 131.1, 128.6, 128.5, 127.7, 126.4, 63.7. Spectral data were consistent with commercially available material.



48 **49**

Preparation of 4-phenylbutan-2-one and 4-phenylbutan-2-ol: An oven dried 25 mL round bottom flask was charged with benzalacetone (0.1462 g, 1.0 mmol), THF (5 mL), and $Pd(OAc)_2$ (0.0112 g, 0.05 mmol). The flask was sealed and flushed with N_2. While flushing, KF (0.1162 g, 2.0 mmol) dissolved in degassed H_2O (2 mL) and added via syringe. PMHS (0.24 mL, 4.0 mmol) was then injected dropwise into the reaction mixture. The reaction was stirred 15 min.,

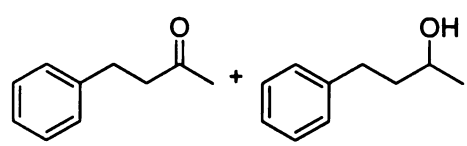
then the layers were separated and the aqueous layer was extracted with ether. The combined organics were dried with $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) afforded 0.0889 g (60% yield) of ketone **48** and 0.0486 g (32% yield) of alcohol **49**. **48:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (dt, *J* = 7.1, 25.8 Hz, 5H), 2.93 (t, *J* = 7.1 Hz, 2H), 2.78 (t, *J* = 7.1 Hz, 2H), 2.16 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 140.9, 128.4, 128.2, 126.0, 45.0, 30.0, 29.6. Spectral data were consistent with commercially available material. **49:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 5H), 3.86 (quint., *J* = 6.0 Hz, 1H), 2.75 (m, 2H), 1.80 (m, 2H), 1.65 (bs, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 128.3, 128.2, 125.7, 67.3, 40.7, 32.0, 23.3. Spectral data were consistent with commercially available material.

General procedure for the reduction activated by KF: The enone (1 mmol) and THF (5 mL) were placed in a round bottom flask. Added to the solution was $Pd(OAc)_2$ (0.0067 g, 0.03 mmol), KF (0.0145 g, 0.25 mmol) dissolved in degassed H_2O (2 mL), and PMHS (0.06 mL, 1 mmol). The reaction was allowed to stir at room temperature until complete as judged by tlc, GC, or ^{1}H NMR. NaOH (2M) was added slowly to the reaction (gas evolution) and allowed to stir for at least 30 min. The layers were separated and the aqueous layer was extracted with ether. The combined organics were dried with $MgSO_4$, filtered, and concentrated.

General procedure for the reduction activated by TBAF: The enone (1 mmol), THF (5 mL), and $Pd(OAc)_2$ (0.0067 g, 0.03 mmol) were placed in a round

bottom flask. The solution was cooled to –78°C followed by addition of TBAF (0.04 mL, 0.04 mmol) as a 1M THF solution and PMHS (0.3 mL, 5 mmol). The reaction was allowed to stir until complete as judged by tlc, GC, or ^{1}H NMR, a few drops of NaOH (2M) was added to the flask and it was allowed to warm to room temperature. Additional NaOH was added and the resulting solution was stirred for at least 30 min. The layers were separated and the aqueous layer was extracted with ether. The combined organics were dried with $MgSO_4$, filtered, and concentrated.

General procedure for the reduction activated by Triton®B: The enone (1 mmol) and THF (5 mL) were placed in a round bottom flask. Added to the solution was $Pd(OAc)_2$ (0.0067 g, 0.03 mmol), Triton®B (0.0042 g, 0.01 mmol, 40%w/w in MeOH), and PMHS (0.18 mL, 3 mmol). The reaction was allowed to stir at room temperature until complete as judged by tlc, GC, or ^{1}H NMR. NaOH (2M) was added slowly to the reaction (gas evolution) and allowed to stir for at least 30 min. The layers were separated and the aqueous layer was extracted with ether. The combined organics were dried with $MgSO_4$, filtered, and concentrated.

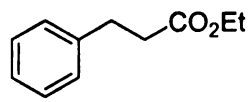


48 **49**

Reduction of benzalacetone with KF as the activator: Following the KF general procedure, benzalacetone (0.1462 g, 1 mmol) was reduced and monitored by GC. The reaction was complete in 15 min, 75.7% conversion to 4-phenylbutan-2-one, **48**, and 19.9% conversion to 4-phenylbutan-2-ol, **49**.

Reduction of benzalacetone with TBAF as the activator: Following the TBAF general procedure, benzalacetone (0.1462 g, 1 mmol) was reduced and monitored by ^{1}H NMR. The reaction was complete in 2 h, 100% conversion to 4-phenylbutan-2-one.

Reduction of benzalacetone with Triton® B as the activator: Following the Triton® B general procedure, benzalacetone (0.1462 g, 1 mmol) was reduced and monitored by ^{1}H NMR. The reaction was complete in 2 h, 87.2% conversion to 4-phenylbutan-2-one and 12.8% conversion to 4-phenylbutan-2-ol.

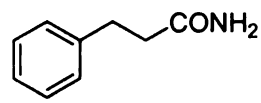


Reduction of ethyl cinnamate with KF as the activator: Following the KF general procedure, ethyl cinnamate (0.17 mL, 1 mmol) was reduced and monitored by GC. The reaction was complete in 1.5 h, 100% conversion to ethyl 3-phenylpropanoate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (m, 5H), 3.99 (q, *J* = 7.1 Hz, 2H), 2.82 (t, *J* = 8.2 Hz, 2H), 2.48 (t, *J* = 8.2 Hz, 2H), 1.09 (t, *J* = 7.1 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 140.5, 128.4, 128.3, 126.2, 60.3, 35.9, 31.0, 14.2. Spectral data were consistent with commercially available material.

Reduction of ethyl cinnamate with TBAF as the activator: Following the TBAF general procedure, ethyl cinnamate (0.17 mL, 1 mmol) was reduced and monitored by ^{1}H NMR. The reaction was complete in 2 h, 100% conversion to ethyl 3-phenylpropanoate.

Reduction of ethyl cinnamate with Triton® B as the activator: Following the Triton® B general procedure, ethyl cinnamate (0.17 mL, 1 mmol) was reduced

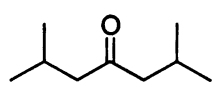
and monitored by ^{1}H NMR. The reaction was complete in 4 h, 100% conversion to ethyl 3-phenylpropanoate.



Reduction of cinnamamide with KF as the activator: Following the KF general procedure, cinnamamide (0.1472 g, 1 mmol) was reduced and monitored by GC. The reaction was complete in 1.5 h, 100% conversion to 3-phenylpropanamide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (m, 5H), 5.95 (bs, 1H), 5.48 (bs, 1H), 2.79 (t, *J* = 7.7 Hz, 2H), 2.35 (t, *J* = 7.7 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 140.6, 128.5, 128.2, 126.2, 37.4, 31.3. Spectral data were consistent with commercially available material.

Reduction of cinnamamide with TBAF as the activator: Following the TBAF general procedure, cinnamamide (0.1472 g, 1 mmol) was reduced and monitored by NMR. The reaction was complete in 4 h, 78.7% conversion to 3-phenylpropanamide.

Reduction of cinnamamide with Triton® B as the activator: Following the Triton® B general procedure, cinnamamide (0.1477 g, 1 mmol) was reduced and monitored by NMR. The reaction was complete in 2 h, 100% conversion to 3-phenylpropanamide.

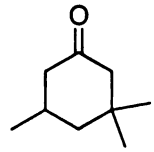


Reduction of phorone with KF as the activator: Following the KF general procedure, phorone (0.1382 g, 1 mmol) was reduced and monitored by ^{1}H NMR. The reaction was complete in 15 min, 97.6% yield as determined by ^{1}H NMR with

an internal standard (mesitylene, 0.14 mL, 1 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (d, *J* = 6.6 Hz, 4H), 2.10 (sept., *J* = 6.6 Hz, 2H), 0.88 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6, 52.2, 24.4, 22.5. Spectral data were consistent with commercially available material.

Reduction of phorone with TBAF as the activator: Following the TBAF general procedure, phorone (0.1382 g, 1 mmol) was reduced and monitored by ^{1}H NMR. At 4 h there was 73.4% conversion to 2,6-dimethylhept-5-en-4-one and 22.1% conversion to 2,6-dimethylheptan-4-one. **2,6-dimethylhept-5-en-4-one:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (s, 1H), 2.21 (t, *J* = 6.6 Hz, 2H), 2.04-2.11 (m, 1H), 2.09 (s, 3H), 1.82 (s, 3H), 0.86 (dd, *J* = 3.3, 6.6 Hz, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 154.6, 124.1, 53.3, 27.6, 25.0, 22.6, 20.6. Spectral data were consistent with those previously reported.[135,136]

Reduction of phorone with Triton® B as the activator: Following the Triton® B general procedure, phorone (0.1382 g, 1 mmol) was reduced and monitored by ^{1}H NMR. The reaction was complete in 4 h, 100% conversion to 2,6-dimethylheptan-4-one.

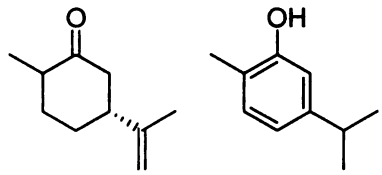


Reduction of 3,5,5-trimethylcyclohexenone with KF as the activator: Following the KF general procedure, 3,5,5-trimethylcyclohexenone (0.15 mL, 1 mmol) was reduced and monitored by ^{1}H NMR. At 15 min there was 94.3% conversion and purification by flash chromatography (silica gel, 90/10 hexanes/ethyl acetate) afforded 66.5% yield of 3,3,5-trimethylcyclohexanone. ^{1}H

NMR (300 MHz, $CDCl_3$) δ 2.26 (d, *J* = 11.5 Hz, 1H), 2.11 (d, *J* = 13.2 Hz, 1H), 2.00 (dm, *J* = 13.2 Hz, 2H), 1.85 (d, *J* = 13.2 Hz, 1H), 1.53 (dt, *J* = 3.3, 13.2 Hz, 1H), 1.24 (t, *J* = 13.2 Hz, 1H), 0.98 (m, 6H), 0.83 (s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 54.1, 49.2, 47.3, 35.3, 32.0, 29.6, 25.7, 22.4. Spectral data were consistent with commercially available material.

Reduction of 3,5,5-trimethylcyclohexenone with TBAF as the activator: Following the TBAF general procedure, 3,5,5-trimethylcyclohexenone (0.15 mL, 1 mmol) was reduced and monitored by ^1H NMR. At 4 h there was 29.2% conversion to 3,3,5-trimethylcyclohexanone.

Reduction of 3,5,5-trimethylcyclohexenone with Triton® B as the activator: Following the Triton® B general procedure, 3,5,5-trimethylcyclohexenone (0.15 mL, 1 mmol) was reduced and monitored by ^1H NMR. At 4h there was 92.5% conversion to 3,3,5-trimethylcyclohexanone and 7.4% conversion to 3,3,5-trimethylcycloxhexan-1-ol. Purification of the crude material by flash chromatography (silica gel, 90/10 hexanes/ethyl acetate) to afford 0.0765 g (54.6% yield) of 3,3,5-trimethylcyclohexanone and 0.0100 g (7.0% yield) of 3,3,5-trimethylcyclohexan-1-ol. **3,3,5-trimethylcyclohexan-1-ol**: ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (q, *J* = 2.7 Hz, 1H), 1.92 (m, 1H), 1.70 (dm, *J* = 13.2 Hz, 1H), 1.50 (dt, *J* = 2.2, 14.3 Hz, 1H), 1.38 (dm, *J* = 12.6 Hz, 1H), 1.31 (bs, 1H), 1.26 (m, 3H), 1.07 (s, 3H), 0.85 (s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.9, 49.2, 45.2, 41.6, 35.0, 39.6, 28.2, 23.0, 22.4. Spectral data were consistent with those previously reported.[137]

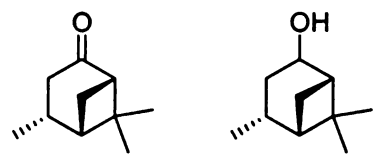


Preparation of (5R)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone and 5-isopropyl-2-methylphenol (carvacrol): Following the KF general procedure, R-carvone (0.16 mL, 1 mmol) was reduced and monitored by ^{1}H NMR. The reaction was complete in 2 h, 39.9% conversion to the ketone and 56.4% conversion to carvacrol. Purification of the crude product with flash chromatography (silica gel, 90/10 hexanes/ethyl acetate) afforded 0.0672 g (39.8% yield) of the ketone and 0.0894 g (59.5% yield) of carvacrol. **(5R)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (d, *J* = 8.2 Hz, 2H), 2.34 (m, 2H), 2.09 (m, 2H), 1.91 (d, *J* = 3.3, 13.2 Hz, 1H), 1.71 (s, 3H), 1.62 (dm, *J* = 11.0 Hz, 1H), 1.36 (td, *J* = 3.8, 12.6 Hz, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.87 (m, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7, 130.1, 109.6, 46.6, 45.4, 35.1, 32.7, 31.6, 19.3, 14.3. Spectral data were consistent with commercially available material. **carvacrol:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.65 (s, 1H), 4.69 (bs, 1H), 2.81 (sept., *J* = 7.1 Hz, 1H), 2.20 (s, 3H), 1.21 (d, *J* = 7.1 Hz, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 148.4, 130.8, 120.8, 118.7, 113.0, 33.6, 24.0, 15.3. Spectral data of carvacrol were consistent with commercially available material.

Preparation of (5R)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone and 5-isopropyl-2-methylphenol (carvacrol): Following the TBAF general procedure, R-carvone (0.16 mL, 1 mmol) was reduced and followed by ^{1}H NMR. The

reaction was complete at 2 h, purification by flash chromatography (silica gel, 90/10 hexanes/ethyl acetate) to afford 0.1233 g (80.3% yield) of the ketone and 0.0126 g (8.4% yield) of carvacol.

Preparation of (5R)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone and 5-isopropyl-2-methylphenol (carvacrol): Following the Triton® B general procedure, R-carvone (0.16 mL, 1 mmol) was reduced and followed by ^{1}H NMR. The reaction was complete at 4 h, purification by flash chromatography (silica gel, 90/10 hexanes/ethyl acetate) to afford 0.1352 g (88.8% yield) of the ketone and 0.0029 g (1.9% yield) of carvacol.

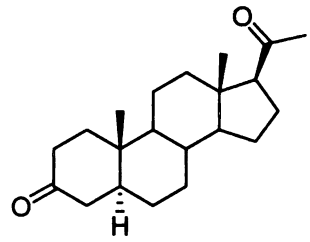


Preparation of (1S,4R,5S)-4,6,6-trimethylbicyclo[3.1.1]heptan-2-one: Following the KF general procedure, 1S-verbenone (0.15 mL, 1 mmol) was reduced and followed by ^{1}H NMR. The reaction was complete at 2 h, 100% conversion, the crude product was purified by flash chromatography (silica gel, 90/10 hexanes/ethyl acetate) to afford 0.1483 g (97.4% yield) of the ketone. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (dd, *J* = 11.5, 19.8 Hz, 1H), 2.54 (m, 2H), 2.34 (m, 1H), 2.15 (d, *J* = 4.4 Hz, 1H), 2.09 (m, 1H), 1.36 (d, *J* = 9.9 Hz, 1H), 1.30 (s, 3H), 1.13 (d, *J* = 7.7 Hz, 3H), 0.97 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.3, 57.9, 47.3, 41.3, 40.2, 31.0, 28.3, 26.9, 24.5, 20.9. Spectral data were consistent with those previously reported.[138]

Preparation of (1S,4R,5S)-4,6,6-trimethylbicyclo[3.1.1]heptan-2-one: Following the TBAF general procedure, 1S-verbenone (0.15 mL, 1 mmol) was

reduced and followed by ^{1}H NMR. The reaction was complete at 4 h, the crude product was purified by flash chromatography (silica gel, 90/10 hexanes/ethyl acetate) to afford 0.1481 g (97.3 % yield) of the ketone.

Preparation of (1S,4R,5S)-4,6,6-trimethylbicyclo[3.1.1]heptan-2-one and (1S,4R,5S)-4,6,6-trimethylbicyclo[3.1.1]heptan-2-ol: Following the Triton® B general procedure, 1S-verbenone (0.15 mL, 1 mmol) was reduced and followed by ^{1}H NMR. The reaction was complete at 4 h, purification of the crude product was purified by flash chromatography (silica gel, 90/10 hexanes/ethyl acetate) to afford 0.0826 g (54.3 % yield) of the ketone and 0.0373 g (24.2% yield) of the alcohol. **(1S,4R,5S)-4,6,6-trimethylbicyclo[3.1.1]heptan-2-ol:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (t, *J* = 2.7 Hz, 1H), 4.19 (dd, *J* = 2.2, 15.9 Hz, 1H), 2.48 (dt, *J* = 9.3, 15.4 Hz, 1H), 2.29 (dt, *J* = 6.6, 9.9 Hz, 1H), 1.99 (m, 1H), 1.78 (m, 1H), 1.70 (t, *J* = 1.6 Hz, 1H), 1.62 (m, 1H), 1.46 (m, 1H), 1.22 (s, 3H), 1.17 (s, 3H), 1.03 (d, *J* = 7.1 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 73.4, 48.9, 47.9, 38.2, 36.3, 34.5, 31.7, 29.0, 24.1, 21.8. Spectral data were consistent with those previously reported.[139]

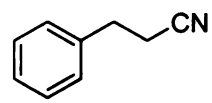


Reduction of progesterone with KF as the activator: Following the KF general procedure, progesterone (0.3145 g, 1 mmol) was reduced and followed by ^{1}H NMR. At 2 h there was 78% conversion to the ketone. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68-2.13 (m, 4H), 2.08 (s, 3H), 2.02-1.09 (m, 19H), 0.99 (s, 3H), 0.59

(s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.2, 209.7, 63.6, 56.3, 54.3, 44.8, 44.0, 41.9, 38.8, 37.0, 35.8, 35.4, 32.9, 32.0, 31.4, 27.8, 26.4, 24.3, 22.7, 20.9, 18.8, 18.0. Spectral data were consistent with commercially available material.

Reduction of progesterone with TBAF as the activator: Following the TBAF general procedure, progesterone (0.3145 g, 1 mmol) was reduced and followed by ^1H NMR. At 2 h there was 50% conversion to the ketone.

Reduction of progesterone with Triton® B as the activator: Following the Triton® B general procedure, progesterone (0.3145 g, 1 mmol) was reduced and followed by ^1H NMR. The reaction was complete in 2 h, 100% conversion to the ketone.

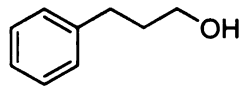


Preparation of 3-phenylpropanenitrile: Following the KF general procedure utilizing increased concentrations of KF (0.0290 g, 0.5 mmol) and PMHS (0.12 mL, 2 mmol), cinnamonitrile (0.13 mL, 1 mmol) was reduced and followed by ^1H NMR. The reaction was complete in 2 h. Purification of the crude product by flash chromatography (silica gel, 90/10 hexanes/ethyl acetate) afforded 0.1130 g (86.1% yield) of 3-phenylpropanenitrile. ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H), 3.00 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 128.9, 128.3, 127.3, 119.2, 31.6, 19.4. Spectral data were consistent with commercially available material.

Preparation of 3-phenylpropanenitrile: Following the TBAF general procedure, cinnamonitrile (0.13 mL, 1 mmol) was reduced and followed by ^1H

NMR. The reaction was complete in 2 h, purification of the crude product by flash chromatography (silica gel, 90/10 hexanes/ethyl acetate) afforded 0.0996 g (75.9% yield) of 3-phenylpropanenitrile.

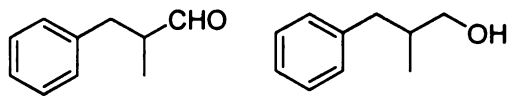
Preparation of 3-phenylpropanenitrile: Following the Triton® B general procedure utilizing increased concentrations of Triton B (0.0084 g, 0.02 mmol) and PMHS (0.36 mL, 6 mmol), cinnamonitrile (0.13 mL, 1 mmol) was reduced and monitored by ^{1}H NMR. The reaction was complete in 4 h, purification of the crude product by flash chromatography (silica gel, 90/10 hexanes/ethyl acetate) afforded 0.1139 g (86.8% yield) of 3-phenylpropanenitrile.



Preparation of 3-phenylpropan-1-ol: Following the KF general procedure, cinnamaldehyde (0.13 mL, 1 mmol) was reduced and followed by ^{1}H NMR. At 2 h there was 30% conversion to the alcohol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, *J* = 6.6 Hz, 2H), 7.06 (d, *J* = 7.1 Hz, 3H), 3.52 (t, *J* = 6.6 Hz, 2H), 2.56 (t, *J* = 8.0 Hz, 2H), 1.75 (quint., *J* = 7.7 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 128.3, 128.2, 125.7, 61.9, 34.1, 32.0. Spectral data were consistent with commercially available material.

Preparation of 3-phenylpropan-1-ol: Following the TBAF general procedure, cinnamaldehyde (0.13 mL, 1 mmol) was reduced and followed by ^{1}H NMR. At 2 h there was 100% conversion to the alcohol.

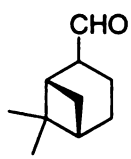
Preparation of 3-phenylpropan-1-ol: Following the Triton® B general procedure, cinnamaldehyde (0.13 mL, 1 mmol) was reduced and followed by ^{1}H NMR. At 4 h there was 71% conversion to the alcohol.



Preparation of 2-methyl-3-phenylpropanal and 2-methyl-3-phenylpropan-1-ol: Following the KF general procedure the reaction was run in d^8-THF utilizing increased concentrations of KF (0.0290 g, 0.5 mmol) and PMHS (0.12 mL, 2 mmol), α-methylcinnamaldehyde (0.14 mL, 1 mmol) was reduced and monitored by ^{1}H NMR. ^{1}H NMR of the crude reaction at 2 h with an internal standard (mesitylene, 0.14 mL, 1 mmol) indicated 47.0% yield of the aldehyde and 37.5% yield of the alcohol. **2-methyl-3-phenylpropanal:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.22 (m, 5H), 3.08 (dd, *J* = 5.5, 12.6 Hz, 1H), 2.62 (m, 2H), 1.07 (d, *J* = 6.6 Hz, 3H). Spectral data were consistent with those previously reported.[140] **2-methyl-3-phenylpropan-1-ol:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.1 Hz, 2H), 7.16 (t, *J* = 7.7 Hz, 3H), 3.47 (td, *J* = 6.0, 11.0 Hz, 2H), 2.73 (dd, *J* = 6.6, 13.7, 1H), 2.40 (dd, *J* = 7.7, 13.2 Hz, 1H), 1.92 (oct., *J* = 6.6 Hz, 1H), 1.61 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 3H). Spectral data were consistent with those previously reported.[141]

Preparation of 2-methyl-3-phenylpropanal and 2-methyl-3-phenylpropan-1-ol: Following the TBAF general procedure the reaction was run in d^8-THF, α-methylcinnamaldehyde (0.14 mL, 1 mmol) was reduced and monitored by ^{1}H NMR. ^{1}H NMR of the crude reaction with an internal standard (mesitylene, 0.14 mL, 1 mmol) indicated 42.6% yield of the aldehyde and 51.0% yield of the alcohol.

Preparation of 2-methyl-3-phenylpropanal and 2-methyl-3-phenylpropan-1-ol: Following the Triton® B general procedure, α-methylcinnamaldehyde (0.14 mL, 1 mmol) was reduced and monitored by ^{1}H NMR. The reaction was complete in 4 h, the crude product was purified by flash chromatography (silica gel, 90/10 hexanes/ethyl acetate) to afford 0.0705 g (47.6% yield) of the alcohol and 0.0323 g (21.8% yield) of the aldehyde.



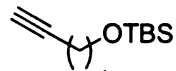
Preparation of (1S,5S)-6,6-dimethylbicyclo[3.1.1]heptane-2-carbaldehyde: Following the KF general procedure utilizing increased concentrations of KF (0.0290 g, 0.5 mmol) and PMHS (0.12 mL, 2 mmol), S-myrtenal (0.15 mL, 1 mmol) was reduced. The reaction was complete in 2 h, ^{1}H NMR showed 100% conversion to the saturated aldehyde (10:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 2.74 (t, *J* = 8.2 Hz, 1H), 2.20 (m, 1H), 2.07 (m, 2H), 1.82 (m, 3H), 1.54 (m, 1H), 1.22 (s, 3H), 1.16 (m, 1H), 0.84 (s, 3H). Spectral data were consistent with those previously reported.[142]

Preparation of (1S,5S)-6,6-dimethylbicyclo[3.1.1]heptane-2-carbaldehyde: Following the TBAF general procedure, S-myrtenal (0.15 mL, 1 mmol) was reduced. The reaction was complete in 2 h, ^{1}H NMR showed 100% conversion to the saturated aldehyde.

Preparation of (1S,5S)-6,6-dimethylbicyclo[3.1.1]heptane-2-carbaldehyde: Following the Triton® B general procedure, S-myrtenal (0.15 mL, 1 mmol) was reduced. The reaction was complete in 4 h, purification by flash chromatography

(silica gel, 90/10 hexanes/ethyl acetate) afforded 0.0998 g (65.6% yield) of the aldehyde.

Chapter 5 Experimental



52

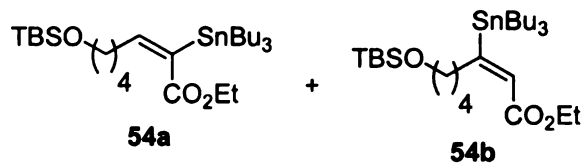
Preparation of tert-butyl(hex-5-ynyloxy)dimethylsilane: TBSCl (50.4946 g, 335 mmol) was added in small portions to a solution of 5-hexyn-1-ol (34.0 mL, 305 mmol) in CH_2Cl_2 (500 mL) containing TEA (51.0 mL, 366 mmol) and DMAP (3.7262 g, 30.5 mmol) at 0 °C. The solution was stirred for 20 min. and then allowed to warm to room temperature while stirring. The reaction mixture was poured into a sat. $NH_4Cl_{(aq)}$ solution and the layers were separated. The organic phase was washed with NH_4Cl and the combined aqueous layers were extracted with ether. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 64.31 g (100% yield) of silyl ether **52**. ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 (t, J = 3.8 Hz, 2H), 2.18 (m, 2H), 1.90 (s, 1H), 1.58 (m, 2H), 1.24 (m, 2H), 0.86 (s, 9H), 0.01 (s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.4, 68.2, 62.5, 31.8, 25.9, 25.0, 22.6, 18.2, -5.4. Spectral data were consistent with those previously reported.[143,144]

53

Preparation of ethyl 7-(tert-butyldimethylsilyloxy)hept-2-ynoate: A solution of nBuLi (100 mL, 160 mmol; 1.6 M in THF) was added to a THF (400 mL) solution of alkyne **52** (28.32 g, 133.3 mmol) at -78 °C under N_2. The resulting

mixture was stirred for 30 min. Ethyl chloroformate (15.3 mL, 160 mmol) in THF was added and stirred for 1 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ and extracted with ethyl acetate. The extract was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 46.2937 g (61% yield) of the ester. ^1H NMR (300 MHz, $CDCl_3$) δ 4.17 (q, *J* = 7.1 Hz, 2H), 3.59 (t, *J* = 6.0 Hz, 2H), 2.33 (t, *J* = 6.6 Hz, 2H), 1.60 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.85 (s, 9H), 0.01 (s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 89.1, 73.2, 62.3, 61.7, 31.7, 25.8, 24.1, 18.4, 18.2, 14.0, -5.4.

IR (neat) 2238, 1717, 1076, 839 cm^{-1}.



54a **54b**

Preparation of (E)-ethyl 7-(tert-butyldimethylsilyloxy)-2-(tributylstannyl)hept-2-enoate and (E)-ethyl 7-(tert-butyldimethylsilyloxy)-3-(tributylstannyl)hept-2-enoate via palladium mediated hydrostannation with Bu_3SnCl: The alkyne, **53**, (25.00 g, 87.9 mmol), $PdCl_2(PPh_3)_2$ (0.6168 g, 0.88 mmol), Bu_3SnCl (28.6 mL, 105.5 mmol), $KF_{(aq)}$ (15.3206 g, 263.6 mmol), PMHS (10.5 mL, 175.8 mmol), and THF (600 mL) were stirred at room temperature for 1 h. A 2M NaOH solution was added slowly and stirred for 30 min. The layers were separated and the aqueous layer was extracted with ether. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 1% TEA; 90/10 hexanes/ethyl acetate) to afford 42.4205 g (84% yield) of the vinyl stannanes. ^1H NMR of the

crude reaction showed a 2.5/1 ratio of **54a/54b**. **54a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (tt, *J* = 7.1, 30.2 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.58 (t, *J* = 6.0 Hz, 2H), 2.41 (q, *J* = 6.0 Hz, 2H), 1.46 (m, 10H), 1.25 (m, 12H), 0.86 (m, 21H), 0.01 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 153.3, 135.8, 63.0, 59.9, 32.4, 31.7, 28.9, 27.3, 25.9, 25.5, 18.3, 14.4, 13.7, 10.2, -5.3. **54b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (t, *J* = 32.4 Hz, 1H), 4.12 (q, *J* = 7.1, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 2.84 (t, *J* = 7.7 Hz, 2H), 1.45 (m, 10H), 1.26 (m, 12H), 0.92 (m, 12H), 0.86 (s, 9H), 0.01 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 164.2, 127.7, 63.1, 59.6, 35.1, 33.0, 30.6, 29.0, 27.5, 26.0, 18.3, 14.3, 13.7, 9.9, -5.3.

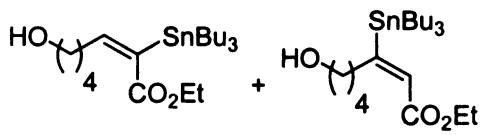
IR (neat) 1717, 1100, 837 cm^{-1}.

MS (EI): m/z calcd for $C_{23}H_{47}O_3SiSn$ (M^+ - Bu): 519.2. Found: 519.2 .

Preparation of (E)-ethyl 7-(tert-butyldimethylsilyloxy)-2-(tributylstannyl)hept-2-enoate and (E)-ethyl 7-(tert-butyldimethylsilyloxy)-3-(tributylstannyl)hept-2-enoate via molybdenum mediated hydrostannation with Bu_3SnH: The alkyne, **53**, (0.2845 g, 1 mmol), hydroquinone (0.0100 g, 0.09 mmol), and $MoBI_3$ (0.0086 g, 0.02 mmol) were dissolved in THF (1 mL). Then Bu_3SnH (0.8 mL, 3 mmol) was added slowly, the tube was sealed, and the mixture was warmed to 55 °C. When complete by tlc, the reaction was cooled to room temperature, concentrated, and purified by flash chromatography (silica gel, 1% TEA; 90/10 hexanes/ethyl acetate) to afford 0.4364 g (76 % yield) of the vinyl stannanes. ^{1}H NMR of the crude reaction showed a 3.7/1 ratio of **54a/54b**.

Preparation of (E)-ethyl 7-(tert-butyldimethylsilyloxy)-2-(tributylstannyl)hept-2-enoate and (E)-ethyl 7-(tert-butyldimethylsilyloxy)-3-

(tributylstannyl)hept-2-enoate via molybdenum mediated hydrostannation with Bu_3SnF: The alkyne, **53**, (0.5000 g, 1.76 mmol), hydroquinone (0.0176 g, 0.16 mmol), $MoBl_3$ (0.0151 g, 0.04 mmol), Bu_3SnF (0.8166 g, 2.64 mmol), and PMHS (0.16 mL, 2.64 mmol) were dissolved in THF (1.76 mL). The tube was sealed and the mixture was warmed to 55 °C for 1 h. The reaction was cooled to room temperature, concentrated, and purified by flash chromatography (silica gel, 1% TEA; 90/10 hexanes/ethyl acetate) to afford 0.8939 g (88% yield) of the vinyl stannanes. ^1H NMR of the crude reaction showed a 3.3/1 ratio of **54a/54b**.



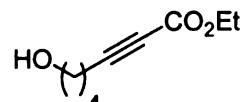
55a **55b**

Preparation of (E)-ethyl 7-hydroxy-2-(tributylstannyl)hept-2-enoate and (E)-ethyl 7-hydroxy-3-(tributylstannyl)hept-2-enoate: The silyl ether, **54a/54b**:3.3/1, (0.5909 g, 1.03 mmol) and amberlyst-15 (0.60 g) were placed in MeOH (8 mL). The mixture stirred at room temperature for 2 h. The solution was filtered through a plug of celite and concentrated. The crude product was purified by flash chromatography (silica gel, 1% TEA; 90/10 hexanes/ethyl acetate) to afford 0.3048 g (64% yield) of the alcohols (**55a/55b**: 3.2/1) which were separable. **55a**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (tt, *J* = 7.1, 30.8 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.54 (t, *J* = 6.6 Hz, 2H), 2.42 (q, *J* = 7.1 Hz, 2H), 1.36 (m, 10H), 1.15 (m, 9H), 0.78 (m, 15H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 153.1, 136.0, 62.5, 60.0, 32.1, 31.6, 28.9, 27.2, 25.3, 14.4, 13.7, 10.2. **55b**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (t, *J* = 32.5 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.67 (q, *J* = 6.6 Hz, 2H), 2.83 (t, *J* = 7.7 Hz, 2H), 1.91 (bs, 1H), 1.58 (m, 2H), 1.47 (m,

8H), 1.26 (m, 9H), 0.87 (m, 15H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 164.2, 127.7, 62.0, 59.7, 34.4, 32.1, 28.9, 27.3, 25.3, 14.3, 13.6, 9.8.

IR (neat) 3484, 1717 cm^{-1}.

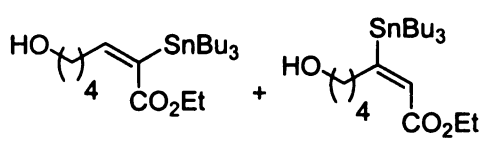
MS (EI): m/z calcd for $C_{17}H_{33}O_3Sn$ (M^+ - Bu): 405.1. Found: 405.2.



56

Preparation of ethyl 7-hydroxyhept-2-ynoate: The silyl ether, **53**, (0.1500 g, 0.53 mmol) was stirred in MeOH (1 mL) overnight with Amberlyst-15 (0.15 g). The reaction mixture was filtered through celite, concentrated, and purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 0.0650 g (72% yield) of alcohol **56**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (q, J = 7.1 Hz, 2H), 3.63 (m, 2H), 2.35 (m, 2H), 1.65 (m, 5H), 1.26 (m, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 88.9, 73.4, 62.0, 61.8, 31.6, 23.8, 18.4, 14.0.

IR (neat) 3405, 2236, 1701 cm^{-1}.



55a **55b**

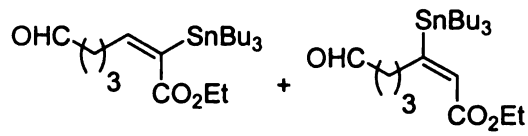
Preparation of (E)-ethyl 7-(tert-butyldimethylsilyloxy)-2-(tributylstannyl)hept-2-enoate and (E)-ethyl 7-(tert-butyldimethylsilyloxy)-3-(tributylstannyl)hept-2-enoate via palladium mediated hydrostannation with Bu_3SnCl: The alkyne, **56**, (0.1220 g, 0.72 mmol), $PdCl_2(PPh_3)_2$ (0.0051 g, 0.007 mmol), Bu_3SnCl (0.23 mL, 0.86 mmol), $KF_{(aq)}$ (0.1255 g, 2.16 mmol), PMHS (0.09 mL, 1.44 mmol), and THF (5 mL) were stirred at room temperature for 1 h. A 2M

NaOH solution was added slowly and stirred for 30 min. The layers were separated and the aqueous layer was extracted with ether. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 1% TEA; 80/20 hexanes/ethyl acetate) to afford 0.2414 g (72% yield) of the vinyl stannanes. ^1H NMR of the crude reaction showed a 1.7/1 ratio of **55a/55b**. Spectral data was consistent with that shown above.

Preparation of (E)-ethyl 7-(tert-butyldimethylsilyloxy)-2-(tributylstannyl)hept-2-enoate and (E)-ethyl 7-(tert-butyldimethylsilyloxy)-3-(tributylstannyl)hept-2-enoate via molybdenum mediated hydrostannation with Bu_3SnH: The alkyne, **56**, (0.2845 g, 1 mmol), hydroquinone (0.0100 g, 0.09 mmol), and $MoBI_3$ (0.0086 g, 0.02 mmol) were dissolved in THF (1 mL). Then Bu_3SnH (0.8 mL, 3 mmol) was added slowly, the tube was sealed, and the mixture was warmed to 55 °C. When complete by tlc, the reaction was cooled to room temperature, concentrated, and purified by flash chromatography (silica gel, 1% TEA; 80/20 hexanes/ethyl acetate) to afford 0.4364 g (75.8% yield) of the vinyl stannanes. ^1H NMR of the crude reaction showed a 3.8/1 ratio of **55a/55b**.

Preparation of (E)-ethyl 7-(tert-butyldimethylsilyloxy)-2-(tributylstannyl)hept-2-enoate and (E)-ethyl 7-(tert-butyldimethylsilyloxy)-3-(tributylstannyl)hept-2-enoate via molybdenum mediated hydrostannation with Bu_3SnF: The alkyne, **56**, (2.0000 g, 11.75 mmol), hydroquinone (0.1175 g, 1.06 mmol), $MoBI_3$ (0.1008 g, 0.24 mmol), Bu_3SnF (5.4440 g, 17.6 mmol), and PMHS (1.05 mL, 17.6 mmol) were dissolved in THF (11.75 mL). The tube was

sealed and the mixture was warmed to 55 °C for 1 h. The reaction was cooled to room temperature, concentrated, and purified by flash chromatography (silica gel, 1% TEA; 80/20 hexanes/ethyl acetate) to afford 3.5034 g (64 % yield) of the vinyl stannanes. ^{1}H NMR of the crude reaction showed a 3.4/1 ratio of **55a/55b**.

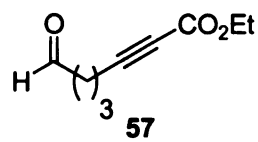


Preparation of (E)-ethyl 7-oxo-2-(tributylstannyl)hept-2-enoate and (E)-ethyl 7-oxo-3-(tributylstannyl)hept-2-enoate via IBX oxidation: IBX (0.0770 g, 0.28 mmol) was dissolved in DMSO (1 mL), then the alcohol, **55**, (0.1172 g, 0.25 mmol) was added to the reaction. After stirring overnight, the solution was diluted with H_2O. The resulting solution was filtered and extracted with ether. The organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 0.1078 g (94% yield) of the aldehydes. **(E)-ethyl 7-oxo-2-(tributylstannyl)hept-2-enoate:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.8 Hz, 1H), 5.95 (t, *J* = 7.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.44 (dt, *J* = 1.8, 7.1 Hz, 2H), 1.75 (m, 2H), 1.57 (m, 2H), 1.45 (m, 6H), 1.27 (m, 9H), 0.89 (m, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 171.0, 151.1, 137.5, 60.0, 43.2, 31.2, 28.9, 27.2, 21.5, 14.4, 13.6, 10.3. **(E)-ethyl 7-oxo-3-(tributylstannyl)hept-2-enoate:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.1 Hz, 1H), 5.95 (t, *J* = 31.3 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.86 (tt, *J* = 7.7, 27.5 Hz, 2H), 2.45 (dt, *J* = 1.1, 7.7 Hz, 2H), 1.72 (quint., *J* = 7.7 Hz, 2H), 1.47 (m, 6H), 1.29 (m, 9H), 0.91 (m, 15H), ^{13}C

NMR (125 MHz, $CDCl_3$) δ 202.1, 172.3, 164.0, 128.8, 59.6, 43.5, 34.3, 29.0, 27.2, 21.8, 14.3, 13.6, 10.0.

IR (neat) 1717 cm^{-1}.

Preparation of (E)-ethyl 7-oxo-2-(tributylstannyl)hept-2-enoate and (E)-ethyl 7-oxo-3-(tributylstannyl)hept-2-enoate via Swern oxidation: The oxalyl chloride (1.82 mL, 20.8 mmol) was added to CH_2Cl_2 (130 mL) and the solution was cooled to -78 °C. A solution of DMSO (2.71 mL, 38.2 mmol) in CH_2Cl_2 (10 mL) was prepared and added dropwise. After stirring for 10 min, a solution of the alcohol, **55**, (8.0248 g, 17.4 mmol) in CH_2Cl_2 (3 mL) was added. After another 10 min of stirring, TEA (12.1 mL, 86.7 mmol) was added and the reaction was stirred an additional 10 min. The cooling bath was removed and the reaction was stirred for 10 min. The solution was then diluted with CH_2Cl_2 and washed with water and brine. The combined aqueous layers were extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 1% TEA; 90/10 hexanes/ethyl acetate) to afford 7.40 g (93% yield) of the aldehydes.

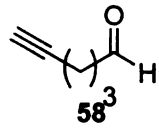


57

Preparation of ethyl 7-oxohept-2-ynoate: IBX (2.4320 g, 8.68 mmol) was dissolved in DMSO (30 mL), then the alcohol, **56**, (1.3000 g, 7.89 mmol) was added to the reaction. After stirring overnight, the solution was diluted with H_2O. The resulting solution was filtered and extracted with ether. The organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by

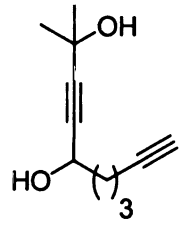
flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 0.9613 g (72% yield) of aldehyde **57**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.38 (t, *J* = 7.1 Hz, 2H), 1.86 (t, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 153.6, 87.6, 74.0, 61.8, 42.3, 19.9, 17.9, 14.0.

IR (neat) 2238, 1717 cm^{-1}.



58

Preparation of 5-hexynal: Pyridinium chlorochromate (8.6g, 40 mmol) was added to a stirred solution of 5-hexyn-1-ol (2.23 mL, 20 mmol) in CH_2Cl_2 (60 mL). After 1h the mixture was filtered through a pad of celite and silica gel. Concentration of the filtrate afforded the crude product which was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.8211 g (42.7% yield) of aldehyde, **58**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 2.48 (t, *J* = 7.1 Hz, 2H), 2.13 (t, *J* = 7.0 Hz, 2H), 1.88 (s, 1H), 1.71 (quint., *J* = 7.1 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 83.0, 69.2, 42.3, 20.6, 17.5. Spectral data were consistent with those previously reported.[145,146,147]

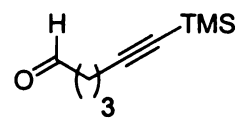


59

Preparation of 2-methyldeca-3,9-diyne-2,5-diol: A 10 mL flask was charged with $Zn(OTf)_2$ (0.3797 g, 1.04 mmol), N-methylephedrine (0.2175 g, 1.21 mmol),

toluene (0.9 mL), and TEA (0.15 mL, 1.07 mmol). The resulting mixture was vigorously stirred for 2h at room temperature before 2-methylbut-3-yn-2-ol (0.11 mL, 1.09 mmol) was added via syringe in one portion. After 15 min of stirring the reaction was cooled to 0 °C and **58** (0.05 mL, 0.52 mmol) was added. After stirring for 8h, the reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (5 mL). The reaction mixture was poured into a separatory funnel containing ether (15 mL). The layers were separated and the aqueous layer was extracted with ether. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.0171 g (13.8% yield) of **59**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (td, *J* = 2.0, 6.8 Hz, 1H), 2.93 (bs, 2H), 2.20 (tt, *J* = 2.4, 6.8 Hz, 2H), 1.94 (td, *J* = 1.0, 2.4 Hz, 1H), 1.77 (m, 2H), 1.64 (m, 2H), 1.48 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 89.8, 84.0, 82.8, 68.8, 65.0, 61.7, 36.5, 31.3, 24.1, 18.0.

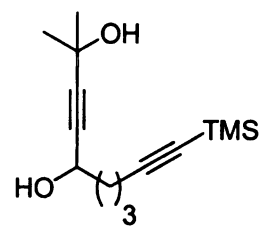
IR (neat) 3391, 2223 cm^{-1}.



60

Preparation of 6-trimethylsilanyl-hex-5-ynal: To a solution of 5-hexyn-1-ol (7.43 mL, 66.7 mmol) in dry THF (200 mL) was added nBuLi in hexanes (100 mL, 60 mmol) at –78°C. After the mixture reacted for 1 h, TMSCl (42.3 mL, 333.3 mmol) was added and stirred for 30 min, and then room temperature for 12h. Then, 10% HCl (55 mL) was added and stirred for 1 h, neutralized with sat $NaHCO_3$ and extracted with ethyl acetate. The solution was washed with water,

dried, filtered, and concentrated. The residue was passed through a short plug of silica with 3/1 hexanes/ethyl acetate and concentrated. To a solution of the TMS-hexynol in dry CH_2Cl_2 (300 mL) was added DMSO (15.14 mL, 213.3 mmol), triethylamine (29.73 mL, 213.3 mmol), and SO_3•pyr (31.832g, 200 mmol) at 0 °C. After stirring at room temperature for 2.5 h the reaction was quenched with NH_4Cl and the mixture was extracted with CH_2Cl_2. The organics were washed with water, dried, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 8.9330 g (71.4% yield) of aldehyde **60**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 2.55 (t, J = 6.0 Hz, 2H), 2.27 (t, J = 6.9 Hz, 2H), 1.81 (quint, J = 7.1 Hz, 2H), 0.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 105.5, 85.4, 42.3, 20.6, 18.8, -0.3. Spectral data were consistent with those previously reported.[148,149]



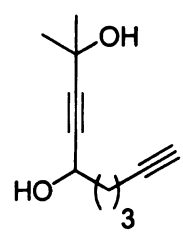
61

Preparation of 2-Methyl-10-trimethylsilanyl-deca-3,9-diyne-2,5-diol: A 100 mL flask was charged with $Zn(OTf)_2$ (1.6589 g, 4.6 mmol), N-methylephedrine (0.8924 g, 5.0 mmol), toluene (12 mL), and triethylamine (0.69 mL, 5.0 mmol). The resulting mixture was vigorously stirred for 2h at room temperature before 2-methylbut-3-yn-2-ol (0.48 mL, 5.0 mmol) was added via syringe in one portion. After 15 min of stirring **60** (0.48 mL, 5.0 mmol) was added in one portion. After stirring for 8h, the reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (5 mL).

The reaction mixture was poured into a separatory funnel containing ether (15 mL). The layers were separated and the aqueous layer was extracted with ether. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.3310 g (32.0% yield) of dialkyne **61**. ^1H NMR (300 MHz, $CDCl_3$) δ 4.40 (t, *J* = 6.6 Hz, 1H), 2.50 (bs, 2H), 2.25 (t, *J* = 6.7 Hz, 2H), 1.77 (m, 2H), 1.66 (q, *J* = 6.6 Hz, 2H), 1.49 (s, 6H), 0.12 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.8, 89.7, 85.0, 82.8, 65.1, 61.8, 36.7, 31.3, 24.2, 19.5, 0.1.

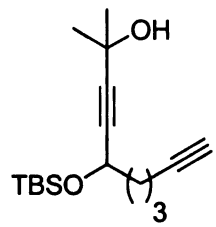
IR (PTFE card, neat) 3276, 2172, 841 cm^{-1}.

HRMS (EI): m/z calcd for $C_{14}H_{25}O_2Si$ (M^++H): 253.1624. Found: 253.1638.



59

Preparation of 2-methyl-deca-3,9-diyne-2,5-diol: To a solution of the silyl alkyne, **61**, (0.0526 g, 0.2 mmol) in methanol (0.5 mL) was added K_2CO_3 (0.0276 g, 0.2 mmol). The reaction was stirred at room temperature until complete by tlc before ether was added. The resulting precipitate was removed by filtration through celite. Concentration of the filtrate resulted in the crude product which was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.0324g (86% yield) of **59**. Spectral data were consistent with that shown previously.

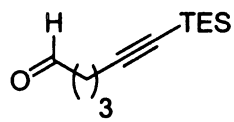


62

Preparation of 5-(tert-butyl-dimethyl-silanyloxy)-2-methyl-deca-3,9-diyn-2-ol: Added to a solution of the alcohol, **59**, (0.0204 g, 0.11 mmol) and imidazole (0.0290 g, 0.44 mmol) in DMF (0.11 mL) at 0 °C was TBSCl (0.0206 g, 0.12 mmol). The reaction was stirred for 20 min before allowing the reaction to warm to room temperature. When the reaction was complete it was poured into a solution of sat. $NH_4Cl_{(aq)}$. The layers were separated, the organics were washed with $NH_4Cl_{(aq)}$ and the combined aqueous layers were back extracted with ether. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.0271 g (83.7% yield) of silyl ether **62**. ^1H NMR (300 MHz, $CDCl_3$) δ 4.37 (t, *J* = 6.3 Hz, 1H), 2.20 (t, *J* = 2.7, 6.6 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.73 (m, 2H), 1.64 (m, 2H), 1.48 (s, 6H), 0.88 (s, 9H), 0.10 (d, *J* = 7.7 Hz, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 88.8, 84.2, 83.6, 68.5, 65.1, 62.4, 37.5, 31.4, 31.3, 25.8, 24.2, 18.2, 18.1, -4.4, -5.0.

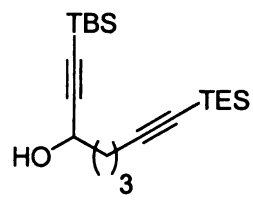
IR (neat) 3312, 2120, 1092, 837 cm^{-1}.

HRMS (EI): m/z calcd for $C_{17}H_{29}OSi$ ($[M-OH]^+$): 277.1988. Found: 277.1978.



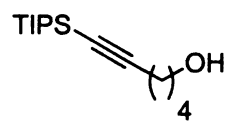
63

Preparation of 6-(triethylsilyl)hex-5-ynal: To a solution of 5-hexyn-1-ol (4.64 mL, 41.6 mmol) in dry THF (125 mL) was added nBuLi (62.4 mL, 99.9 mmol; 1.6M in hexanes) at 0 °C. After stirring for 1 h, TESCl (35 mL, 208.0 mmol) was added and stirred for 30 min, and then room temperature for 12 h. Then 10% HCl (35 mL) was added and stirred for 1 h. The solution was neutralized with $NaHCO_3$ and extracted with ethyl acetate. The combined organics were washed with water, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by passing through a short column (silica gel; 70/30 hexanes/ethyl acetate). The alcohol was dissolved in ethyl acetate (125 mL) and IBX (15.0290 g, 53.7 mmol) was added. The resulting suspension was immersed in an 80 °C oil bath and stirred vigorously open to the atmosphere for 2 h. The reaction was cooled to room temperature and filtered through a medium glass frit. The filter cake was washed with ethyl acetate (3x 100 mL) and the combined filtrates were concentrated. Purification by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 2.9666 g (33.5% yield) of aldehyde **63**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.80 (t, *J* = 6.6 Hz, 2H), 0.93 (t, *J* = 7.7 Hz, 9H), 0.53 (q, *J* = 7.7 Hz, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 106.9, 82.9, 42.6, 21.1, 19.2, 7.4, 4.4.
IR (neat) 2174, 1711, 1013 cm^{-1}.



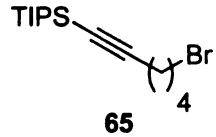
64

Preparation of 1-(tert-butyldimethylsilyl)-8-(triethylsilyl)octa-1,7-diyn-3-ol: TBS-acetylene (0.58 mL, 3.09 mmol) and nBuLi (1.5 mL, 2.38 mmol; 1.6M in hexanes) were added simultaneously and dropwise over 5 min to cold (-10 °C) THF (11.6 mL). After stirring for 10 min, **63** (0.5000 g, 2.38 mmol) in THF (2.4 mmol) was added via cannula. The resulting solution was stirred for 30 min at 0 °C and then treated with sat. $NH_4Cl_{(aq)}$ (5 mL). The aqueous layer was extracted with ether. The combined organic layers were concentrated, diluted with ether (5 mL) and then washed with water (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (90/10 hexanes/ethyl acetate) to afford 0.3325 g (39.8% yield) of dialkyne **64**. ^1H NMR (500 MHz, $CDCl_3$) δ 4.39 (t, *J* = 6.3 Hz, 1H), 2.28 (t, *J* = 7.3 Hz, 2H), 1.80 (m, 3H), 1.69 (q, *J* = 6.8 Hz, 2H), 0.96 (t, *J* = 7.8 Hz, 9H), 0.91 (s, 9H), 0.55 (q, *J* = 7.8 Hz, 6H), 0.08 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.8, 107.1, 87.9, 82.2, 62.4, 36.7, 26.0, 24.4, 19.5, 16.4, 7.4, 4.5, -4.7. IR (neat) 3341, 2174, 1251, 835 cm^{-1}.



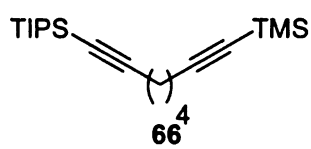
Preparation of 6-(triisopropylsilyl)hex-5-yn-1-ol: To a solution of 5-hexyn-1-ol (5.58 mL, 50.0 mmol) in dry THF (150 mL) was added nBuLi (75.0 mL, 120.0 mmol; 1.6M in hexanes) at 0 °C. After stirring for 1 h, TIPSCl (42.8 mL, 200 mmol) was added and stirred for 30 min, and then room temperature for 12 h. The solution was diluted with ethyl acetate and washed with water, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash

chromatography (silica gel; 50/50 hexanes/ethyl acetate) to afford 2.9235 g (23% yield) of 6-(triisopropylsilyl)hex-5-yn-1-ol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (t, *J* = 6.0 Hz, 2H), 2.24 (t, *J* = 7.1 Hz, 2H), 1.98 (s, 1H), 1.60 (m, 4H), 0.99 (s, 21H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.7, 80.3, 62.1, 31.7, 25.1, 19.5, 18.5, 11.2. Spectral data were consistent with those previously reported.[150]



65

Preparation of (6-bromohex-1-ynyl)triisopropylsilane: To a solution of the 6-(triisopropylsilyl)hex-5-yn-1-ol (2.5037 g, 9.8 mmol) and CBr_4 (4.5611 g, 13.75 mmol) in CH_2Cl_2 (16 mL) at room temperature was added a solution of triphenylphosphine (3.0921 g, 11.8 mmol) in CH_2Cl_2 (6 mL). The reaction stirred for 12 h, after which time the CH_2Cl_2 was removed under reduced pressure. Hexanes was added and the resulting heterogenous solution was filtered and concentrated. Purification by vacuum distillation (b.p. = 135 °C, 0.1 mm Hg) afforded 2.8000 g (89.7% yield) of bromide **65**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (t, *J* = 7.1 Hz, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.99 (quint., *J* = 7.1 Hz, 2H), 1.66 (quint. *J* = 7.1 Hz, 2H), 1.02 (m, 21H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.9, 81.0, 33.3, 31.5, 27.1, 19.0, 18.6, 11.3. Spectral data were consistent with those previously reported.[150]



66

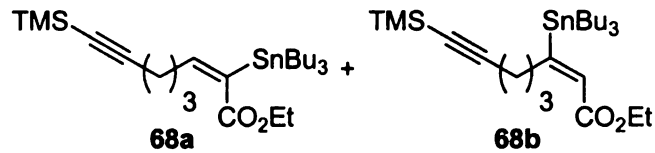
Preparation of triisopropyl(8-(trimethylsilyl)octa-1,7-diynyl)silane: A solution of TMS-acetylene (0.14 mL, 1.0 mmol) and nBuLi (0.69 mL, 1.1 mmol; 1.6M in hexanes) in THF (2.5 mL) at 0 °C was prepared and added via cannula dropwise to a 65 °C solution of THF (3.75 mL), Pd_2dba_3 (0.0230 g, 0.025 mmol), PPh_3 (0.0263 g, 0.1 mmol), and alkyl bromide, **65**, (0.4753 g, 1.5 mmol). The mixture was refluxed for 21 h. After cooling to room temperature, the mixture was quenched with sat. $NH_4Cl_{(aq)}$, washed with brine, extracted with ether and the combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 95/5 hexanes/ethyl acetate) to afford 0.1191g, (35.6% yield) of diyne **66**. ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (m, 4H), 1.61 (m, 4H), 1.03 (m, 21H), 0.11 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.5, 107.0, 84.7, 80.4, 27.8, 27.5, 19.3, 19.3, 18.6, 11.3, 0.11. Spectral data were consistent with those previously reported.[151]

67

Preparation of ethyl 8-(trimethylsilyl)octa-2,7-diynoate: A flask was charged with Zn dust (5.4391 g, 83.2 mmol), PPh_3 (21.8172 g, 83.2 mmol), CBr_4 (27.5849 g, 83.2 mmol), and CH_2Cl_2 (300 mL). The resulting suspension was stirred at room temperature overnight. To this solution was added a solution of the aldehyde, **60**, (6.8787 g, 40.9 mmol) in CH_2Cl_2 (100 mL). After stirring for 8 h, the mixture was diluted with hexanes (1 L) and filtered to remove the insoluble material. The filtrate was concentrated and purified by flash chromatography (silica gel; 95/5 hexanes/ethyl acetate) to afford the dibromide which was

dissolved in THF (110 mL). After cooling to -78 °C, the reaction was stirred for 1 h and then at room temperature for 1 h. After the addition of ethyl chloroformate (7.9 mL, 82.55 mmol) the reaction was stirred at room temperature overnight. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ and extracted with ether. The combined organics were washed with brine and dried over Na_2SO_4. After filtration and concentration the crude product was purified by flash chromatography (silica gel; 95/5 hexanes/ethyl acetate) to afford 6.4432 g (89% yield) of ester **67**. ^1H NMR (300 MHz, $CDCl_3$) δ 4.17 (q, *J* = 7.1 Hz, 2H), 2.42 (t, *J* = 7.1 Hz, 2H), 2.31 (t, *J* = 7.1 Hz, 2H), 1.74 (quint., *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.10 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 105.3, 88.1, 85.6, 73.5, 61.8, 26.5, 19.0, 17.6, 14.0, 0.02.

IR (neat) 2240, 2176, 1711 cm^{-1}.

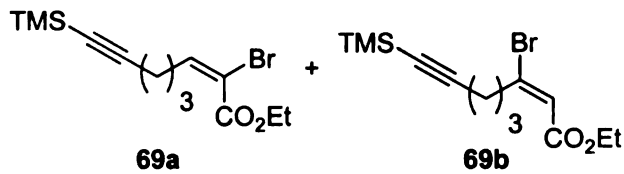


Preparation of (E)-ethyl 2-(tributylstannyl)-8-(trimethylsilyl)oct-2-en-7-ynoate and (E)-ethyl 3-(tributylstannyl)-8-(trimethylsilyl)oct-2-en-7-ynoate: The alkyne, **67**, (0.1400 g, 0.50 mmol), $MoBl_3$ (0.0043 g, 0.01 mmol), and hydroquinone (0.0046 g, 0.045 mmol) were dissolved in THF (1.5 mL). Bu_3SnF (0.2105 g, 0.65 mmol) and PMHS (0.04 mL, 0.65 mmol) were added and the tube was sealed. The tube was then lowered into a 55 °C oil bath and stirred for 8 h. The solution was allowed to cool to room temperature and the solution was concentrated. Purification by flash chromatography (silica gel, 1% TEA; 95/5 hexanes/ethyl acetate) afforded 0.2292 g (80% yield) of the vinyl stannanes. ^1H

NMR of the crude reaction showed a 2.8/1 ratio of **68a/68b**. **68a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (t, *J* = 7.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.46 (m, 2H), 2.20 (m, 2H), 1.44 (m, 6H), 1.26 (m, 11H), 0.88 (m, 15H), 0.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 151.6, 136.9, 107.0, 84.6, 60.0, 31.3, 28.9, 28.4, 27.2, 19.5, 14.4, 13.7, 10.3, 0.1. **68b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.90 (m, 2H), 2.20 (m, 2H), 1.44 (m, 6H), 1.26 (m, 11H), 0.88 (m, 15H), 0.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 164.0, 128.4, 120.1, 84.5, 59.6, 34.6, 29.0, 28.4, 27.3, 20.0, 14.3, 13.6, 9.9, 0.1.

IR (neat) 2176, 1717, 844 cm^{-1}.

MS (EI): m/z calcd for $C_{21}H_{39}O_2SiSn$ (M^+ - Bu): 471.2. Found: 471.2.

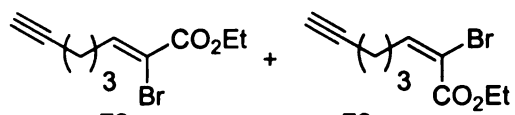


69a **69b**

Preparation of (E)-ethyl 2-bromo-8-(trimethylsilyl)oct-2-en-7-ynoate and (E)-ethyl 3-bromo-8-(trimethylsilyl)oct-2-en-7-ynoate: NBS (0.7186 g, 4.04 mmol) was added to a 0 °C solution of stannane, **68**, (2.0281 g, 3.85 mmol) in dry CH_2Cl_2 (20 mL) and stirred for 3 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification of the crude product by flash chromatography (silica gel; 95/5 hexanes/ethyl acetate) afforded 1.2200 g (100% yield) of the inseparable vinyl bromides. ^{1}H NMR of the crude reaction showed a 2.8/1 ratio of **69a/69b**. **69a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (t, *J* = 7.7 Hz,

1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.54 (q, *J* = 7.1 Hz, 2H), 2.23 (q, *J* = 7.1 Hz, 2H), 1.63 (quint., *J* = 7.7 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.9 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 146.9, 111.5, 105.8, 84.9, 61.7, 30.2, 27.1, 19.1, 13.8, 0.1, **69b:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.13 (t, *J* = 7.7 Hz, 2H), 2.23 (q, *J* = 7.1 Hz, 2H), 1.81 (quint., *J* = 7.7 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.9 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 148.3, 123.5, 114.0, 84.8, 60.1, 36.6, 27.1, 18.8, 13.7, 0.1.

IR (neat) 1720 cm^{-1}.



72c **72a**

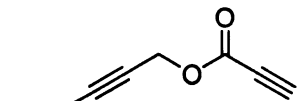
Preparation of (E)-ethyl 2-bromooct-2-en-7-ynoate and (E)-ethyl 3-bromooct-2-en-7-ynoate: Triethyl phosphonoacetate (0.62 mL, 3.1 mmol) was added dropwise to a slurry of 60% NaH (0.1248 g, 3.1 mmol) in DME (3 mL) at 20 °C. The solution was stirred for 1 h and Br_2 (0.16 mL, 3.1 mmol) was added keeping the temperature below 25 °C. The addition of Br_2 was exothermic and the color was immediately discharged. After the addition, the solution was warmed to 40 °C (briefly) then cooled to 10 °C and 60% NaH (0.1248 g, 3.1 mmol) was added all at once. The solution was gradually warmed to room temperature, during which rapid gas evolution took place. 5-Hexynal, **58**, (0.3055 g, 3.1 mmol) was added dropwise at such a rate as to maintain the temp below 30 °C. When complete (20 h), CH_2Cl_2 and water were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organics were washed with water. After drying over $MgSO_4$, the

solution was filtered and concentrated. The crude product was purified by flash chromatography (silica gel; 98/2 hexanes/ethyl acetate) to afford 0.3817 g (49% yield) of the vinyl bromides. **72c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.1 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.43 (q, *J* = 7.7 Hz, 2H), 2.23 (dt, *J* = 2.5, 7.1 Hz, 2H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.71 (quint., *J* = 7.7 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 144.7, 117.1, 83.3, 69.1, 62.4, 31.0, 26.3, 18.1, 14.1, **72a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (t, *J* = 7.7 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.58 (q, *J* = 7.7 Hz, 2H), 2.21 (dt, *J* = 2.5, 7.1 Hz, 2H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.66 (quint., *J* = 7.7 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 147.0, 117.1, 83.3, 69.0, 62.1, 30.3, 27.4, 18.0, 14.1. IR (neat) 2120, 1717 cm^{-1}.

73

Preparation of 3-(trimethylsilyl)prop-2-yn-1-ol: nBuLi (200 mL, 320 mmol; 1.6M in hexanes) was added dropwise to a stirred solution of propargyl alcohol (8.5 mL, 145.5 mmol) in THF (400 mL) at -78 °C. After 20 min, TMSCl (55 mL, 436.4 mmol) was added dropwise. The solution was allowed to warm to room temperature and HCl (2M) was added. After 16 h, the layers were separated and the aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; hexanes then ether) to afford 12.54 g (67% yield) of alcohol, **73**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (s, 2H), 1.95 (bs, 1H),

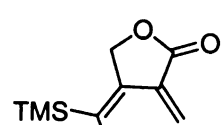
0.14 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.0, 90.3, 51.3, -0.30. Spectral data were consistent with those previously reported.[152]



74

Preparation of 3-(trimethylsilyl)prop-2-ynyl propiolate: A round bottom flask at -78 °C was charged with the alcohol, **73**, (0.6412 g, 5 mmol), DCC (6 mL, 6 mmol; 1M in hexanes), DMAP (0.0305 g, 0.25 mmol), and CH_2Cl_2 (50 mL). Propiolic acid (0.62 mL, 10 mmol) was added and the reaction was slowly warmed to room temperature. The solid was filtered off (through a pad of silica gel) and the filtrate was concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/diethyl ether) to afford 0.7253 g (80.5% yield) of ester **74**. ^1H NMR (300 MHz, $CDCl_3$) δ 4.73 (s, 2H), 2.92 (s, 1H), 0.14 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 97.3, 93.4, 75.7, 74.0, 54.2, -0.5.

IR (neat) 2189, 2124, 1719, 849 cm^{-1}.



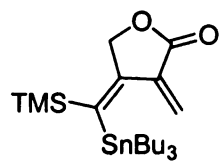
75a

Preparation of (E)-3-methylene-4-((tributylstannyl)(trimethylsilyl)methylene)dihydrofuran-2(3H)-one: A solution of $PdCl_2(PPh_3)_2$ (0.0070 g, 0.01 mmol), alkyne, **74**, (0.1888 g, 1 mmol), Bu_3SnCl (0.33 mL, 1.2 mmol), $KF_{(aq)}$ (0.1743 g, 3 mmol), and PMHS (0.12 mL, 2 mmol) in THF (7 mL) was stirred for 2 h at room temperature. The solution was

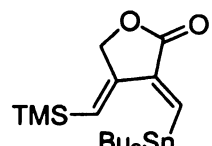
poured into ether and extracted with ether and water. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.0699 g (14.2% yield) of the vinyl stannane, **75a**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 13.2 Hz, 1H), 6.73 (d, *J* = 13.2 Hz, 1H), 4.72 (s, 2H), 1.45 (m, 6H), 1.26 (m, 6H), 0.95 (m, 6H), 0.85 (t, *J* = 7.1 Hz, 9H), 0.15 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 145.3, 140.7, 99.2, 91.8, 53.0, 28.9, 27.2, 13.6, 10.1, -0.3.

IR (neat) 1723, 847 cm^{-1}.

HRMS (EI): m/z calcd for $C_{21}H_{41}O_2SiSn$ (M^++H): 473.1898. Found: 473.1924.



75a

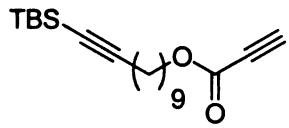


75b

Preparation of (E)-3-methylene-4-((tributylstannyl)(trimethylsilyl)methylene)dihydrofuran-2(3H)-one and (3Z,4Z)-3-((tributylstannyl)methylene)-4-((trimethylsilyl)methylene)dihydrofuran-2(3H)-one: The alkyne, **74**, (0.1809 g, 1 mmol), $MoBl_3$ (0.0086 g, 0.02 mmol), and hydroquinone (0.0099 g, 0.09 mmol) were dissolved in THF (3 mL). Bu_3SnF (0.4018 g, 1.3 mmol) and PMHS (0.08 mL, 1.3 mmol) were added and the tube was sealed. The tube was lowered into a 55 °C oil bath and stirred for 46 h. The solution was allowed to cool to room temperature and the solution was concentrated. The crude product was purified by flash chromatography (silica gel, 1% TEA; 95/5 hexanes/ethyl

acetate) to afford 0.3887 g (82.4% yield) of the vinyl stannanes. **75b:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 12.2 Hz, 1H), 6.74 (d, *J* = 12.2 Hz, 1H), 4.73 (s, 2H), 1.47 (m, 6H), 1.26 (hex., *J* = 7.3 Hz, 6H), 0.96 (dd, *J* = 8.3, 8.3 Hz, 6H), 0.86 (t, *J* = 7.324 Hz, 9H), 0.16 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 158.8, 134.6, 99.0, 92.1, 52.8, 29.1, 27.3, 13.7, 11.0, -0.32.

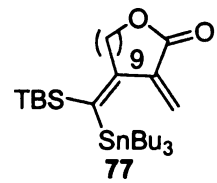
IR (neat) 2180, 1719, 1252, 849 cm^{-1}.



76

Preparation of 11-(tert-butyldimethylsilyl)undec-10-ynyl propiolate: A round bottom flask at -78 °C was charged with 11-(tert-butyldimethylsilyl)undec-10-yn-1-ol (1.0740 g, 3.8 mmol), DCC (0.9904 g, 4.8 mmol), DMAP (0.0244 g, 0.2 mmol), and CH_2Cl_2 (20 mL). Propiolic acid (0.49 mL, 8 mmol) was added and the reaction was slowly warmed to room temperature. The solid was filtered off (through a pad of silica gel) and the filtrate was concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/diethyl ether) to afford 1.0984 g (86.4% yield) of ester **76**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (t, *J* = 6.8 Hz, 2H), 2.84 (s, 1H), 2.18 (t, *J* = 6.8 Hz, 2H), 1.63 (quint., *J* = 6.8 Hz, 2H), 1.46 (quint, *J* = 6.8 Hz, 2H), 1.34 (m, 4H), 1.26 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 108.1, 82.3, 74.8, 74.4, 66.4, 29.3, 29.0, 28.9, 28.6, 28.6, 28.3, 26.0, 25.7, 19.7, 16.5, -4.5.

IR (neat) 2172, 2120, 1717 cm^{-1}.

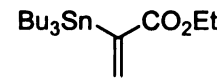


77

Preparation of (Z)-3-methylene-4-((tributylstannyl)(trimethylsilyl)methylene)oxacyclotridecan-2-one: A solution of $PdCl_2(PPh_3)_2$ (0.0070 g, 0.01 mmol), alkyne, **76**, (0.3205 g, 0.96 mmol), Bu_3SnCl (0.33 mL, 1.2 mmol), $KF_{(aq)}$ (0.1743 g, 3 mmol), and PMHS (0.12 mL, 2 mmol) in THF (7 mL) was stirred for 3 h at room temperature. The solution was poured into ether and extracted with ether and water. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.1027 g (17.1% yield) of vinyl stannane, **77**. ^1H NMR (500 MHz, $CDCl_3$) δ 6.88 (td, *J* = 2.7, 53.8 Hz, 1H), 5.88 (td, *J* = 2.7, 24.2 Hz, 1H), 4.09 (t, *J* = 6.6 Hz, 2H), 2.19 (t, *J* = 6.6 Hz, 2H), 1.63 (quint., *J* = 6.8 Hz, 2H), 1.46 (m, 6H), 1.35 (m, 4H), 1.29 (m, 14H), 0.95 (dd, *J* = 7.8, 8.3 Hz, 6H), 0.90 (s, 9H), 0.86 (t, *J* = 7.3 Hz, 9H), 0.05 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 146.1, 139.8, 108.2, 82.3, 64.8, 29.4, 29.3, 29.0, 28.9, 28.8, 28.7, 28.7, 27.3, 26.1, 26.1, 19.8, 16.5, 13.7, 10.1, -4.4.

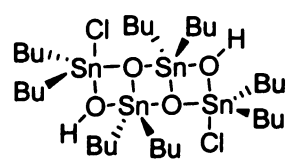
IR (neat) 1719, 837 cm^{-1}.

MS (EI): m/z calcd for $C_{28}H_{53}O_2SiSn$ (M^+-Bu): 569.3. Found: 569.3.



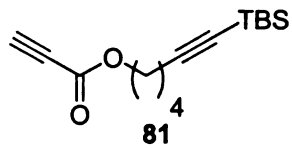
78

Preparation of ethyl 2-(tributylstannyl)acrylate: A solution of $PdCl_2(PPh_3)_2$ (0.2078 g, 0.30 mmol), ethyl propiolate (3.0 mL, 29.6 mmol), Bu_3SnCl (9.64 mL, 35.5 mmol), $KF_{(aq)}$ (5.1597 g, 88.8 mmol), and PMHS (3.53 mL, 59.2 mmol) in THF (200 mL) was stirred for 5 h at room temperature. The solution was poured into ether and extracted with ether and water. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 4.7565 g (41.3% yield) of vinyl stannane **78**. ^1H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, J = 2.7 Hz, $^3J_{Sn}$ = 53.8 Hz, 1H), 5.88 (d, J = 2.7 Hz, $^3J_{Sn}$ = 28.0 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 1.45 (m, 6H), 1.27 (m, 9H), 0.94 (m, 6H), 0.86 (t, J = 7.1 Hz, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 146.2, 139.7, 60.5, 28.9, 27.2, 14.3, 13.6, 10.1. IR (neat) 1719 cm^{-1}.



79

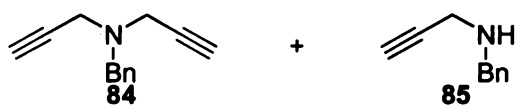
Preparation of Otera's catalyst: A mixture of Bu_2SnO (14.90 g, 60 mmol), Bu_2SnCl_2 (6.10 g, 20 mmol), and 95% EtOH (200 mL) was refluxed for 6h. The transparent solution was concentrated to give a white powder. This was pulverized and then was exposed to the ambient atmosphere overnight in order to convert the partially formed ethoxydistannoxane to the corresponding hydrowydistannoxane. Recrystallization (hexane, 0 °C) of the crude product afforded 6.8228 g (31.9% yield) of the pure product. m.p.:118-121 °C (lit m.p.: 109-121 °C). Physical data was consistent with those previously reported.[106,153]



81

Preparation of 6-(tert-butyldimethylsilyl)hex-5-ynyl propiolate: A toluene (5 mL) solution of ethyl propiolate (0.1 mL, 1 mmol), 6-(tert-butyldimethylsilyl)hex-5-yn-1-ol (2.1240 g, 10 mmol), and Otera's catalyst **79** (0.1069 g, 0.1 mmol) was refluxed for 24 h. The solution was concentrated and the crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.2633 g (100% yield) of ester **81**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (t, *J* = 6.6 Hz, 2H), 2.85 (s, 1H), 2.24 (t, *J* = 6.9 Hz, 2H), 1.78 (m, 2H), 1.57 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 106.8, 83.3, 74.7, 74.5, 65.8, 27.4, 26.0, 24.9, 19.4, 16.4, -4.5.

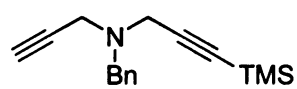
IR (neat) 2174, 2120, 1719, 1233, 839 cm^{-1}.



84 85

Preparation of N-benzyl-N-(prop-2-ynyl)prop-2-yn-1-amine and N-benzylprop-2-yn-1-amine: Propargyl chloride (3.6 mL, 50 mmol) in absolute EtOH (12 mL) was added dropwise to a stirred solution of benzyl amine (27.3 mL, 250 mmol) in absolute EtOH (50 mL). After the addition was complete, the solution was heated to reflux for 32 h. The solution was concentrated and the residue was partitioned between ether (36 mL) and NaOH (24 mL, 5M). The organic layer was washed with brine, dried over K_2CO_3, filtered, and concentrated. The residue was distilled under aspirator vacuum to separate benzyl amine (bp 70-80 °C) and the other components (>80 °C). The higher

boiling fractions were subjected to column chromatography (silica gel; 1/1 hexanes/ethyl acetate then ethyl acetate then 1/1 ethyl acetate/methanol) to afford 0.8888 g (9.7% yield) of the dialkylated product, **84**, and 2.1586 g (29.9% yield) of the monoalkylated product, **85**. **84:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5H), 3.72 (t, *J* = 20.5 Hz, 2H), 3.45 (td, *J* = 2.4, 19.0 Hz, 4H), 2.30 (t, *J* = 20.0 Hz, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.4, 129.2, 128.3, 127.4, 78.7, 73.2, 57.0, 41.7. Spectral data were consistent with those previously reported.[154] **85:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5H), 3.91 (t, *J* = 20.0 Hz, 2H), 3.44 (td, *J* = 2.4, 20.0 Hz, 2H), 2.29 (t, *J* = 20.0 Hz, 1H), 1.95 (bs, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 128.3, 127.1, 81.9, 71.5, 52.1, 37.2. Spectral data were consistent with those previously reported.[155]

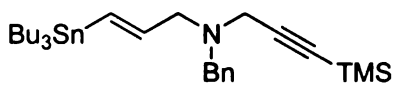


82

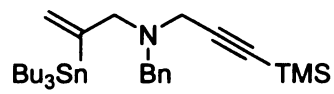
Preparation of N-benzyl-N-(prop-2-ynyl)-3-(trimethylsilyl)prop-2-yn-1-amine: To a solution of **85** (1.03 g, 6.89 mmol), PPh_3 (1.8064 g, 6.89 mmol), and 3-(trimethylsilyl)prop-2-yn-1-ol, **73**, (1.3248 g, 10.33 mmol) in THF (65 mL) was added a solution of DEAD (1.08 mL, 6.89 mmol) in THF (10 mL) at 0 °C over 15 min. The mixture was stirred at room temperature overnight and then concentrated. The crude product was purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 0.1113 g (6.1% yield) of tertiary amine **82**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 5H), 3.74 (s, 2H), 3.45 (m, 4H), 2.31 (t, *J* = 2.4 Hz, 1H), 0.24 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 129.3,

128.3, 127.4, 101.0, 90.1, 78.9, 73.2, 56.9, 43.0, 41.9, 0.02. Spectral data were consistent with those previously reported.[102]

Preparation of N-benzyl-N-(prop-2-ynyl)-3-(trimethylsilyl)prop-2-yn-1-amine: A solution of nBuLi (1.85 mL, 3.0 mmol, 1.6M in hexanes) in THF (27 mL) was cooled to -78 °C. This was then added via cannula to a solution of alkyne, **84**, (0.50 g, 2.7 mmol) in THF (27 mL) at -78 °C. The resulting solution was stirred for 30 min and TMSCl (0.52 mL, 4.1 mmol) was added. The resulting solution was stirred for 1 h and then quenched with sat. $NH_4Cl_{(aq)}$. The aqueous layer was extracted with ethyl acetate and the combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 88/12 hexanes/ethyl acetate) to afford 0.4796 g (68.8% yield) of tertiary amine **82**. The spectral data were consistent with that shown above.



86a



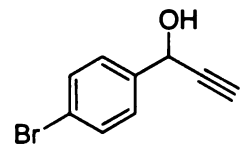
86b

Preparation of N-benzyl-2-(tributylstannyl)-N-(3-(trimethylsilyl)prop-2-ynyl)prop-2-en-1-amine: A solution of $PdCl_2(PPh_3)_2$ (0.0016 g, 0.002 mmol), alkyne, **82**, (0.0658 g, 0.23 mmol), Bu_3SnCl (0.08 mL, 0.28 mmol), $KF_{(aq)}$ (0.0409 g, 0.70 mmol), and PMHS (0.03 mL, 0.47 mmol) in THF (1 mL) was stirred for 4 h at room temperature. The solution was poured into ether and extracted with ether and water. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.1154 g (82.0% yield) of vinyl

stannane **86** (1.1:1 mixture of **86a**:**86b**). **86a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H), 6.18 (d, *J* = 19.2 Hz, 1H), 5.99 (dt, *J* = 6.0, 19.2 Hz, 1H), 3.60 (d, *J* = 3.3 Hz, 2H), 3.20 (m, 4H), 1.45 (m, 6H), 1.28 (m, 6H), 0.86 (m, 15H), 0.19 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 138.9, 132.6, 129.6, 128.5, 127.3, 101.4, 90.4, 60.7, 57.3, 42.7, 29.4, 27.5, 14.0, 9.8, 0.5, **86b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H), 5.88 (tm, *J* = 65.4 Hz, 1H), 5.25 (tm, *J* = 27.5 Hz, 1H), 3.60 (d, *J* = 3.3 Hz, 2H), 3.20 (m, 4H), 1.45 (m, 6H), 1.28 (m, 6H), 0.86 (m, 15H), 0.19 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 138.9, 132.6, 129.6, 128.5, 128.4, 101.3, 90.4, 63.4, 58.2, 41.7, 29.4, 27.7, 14.0, 9.7, 0.4.

IR (neat) 2164, 1250, 847 cm^{-1}.

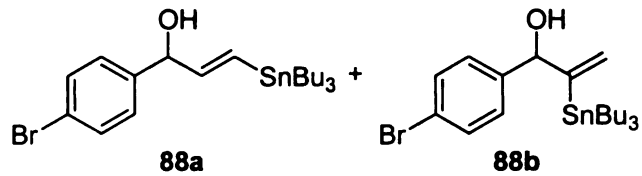
MS (EI): m/z calcd for $C_{28}H_{50}NSiSn$ (M^{+}+H): 548.3. Found: 548.2.



87

Preparation of 1-(4-bromophenyl)prop-2-yn-1-ol: A solution of p-bromobenzaldehyde (1.4280 g, 7.7 mmol) in THF (20 mL) was cooled to 0 °C. The alkynyl magnesium bromide (20 mL, 10 mmol; 0.5M in THF) was added via syringe and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ and extracted with ether. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 1.5623 g (96% yield) of alcohol **87**. m.p. = 45-48 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J*

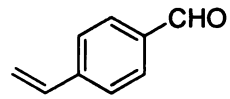
= 8.3 Hz, 2H), 5.41 (d, *J* = 5.9 Hz, 1H), 2.66 (d, *J* = 2.0 Hz, 1H), 2.27 (bs, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 131.7, 128.3, 122.5, 82.9, 75.2, 63.6. IR (PTFE card, neat) 3293, 2120 cm^{-1}.



88a **88b**

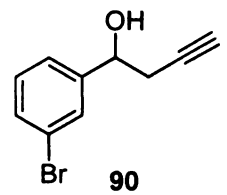
Preparation of (E)-1-(4-bromophenyl)-3-(tributylstannyl)prop-2-en-1-ol and 1-(4-bromophenyl)-2-(tributylstannyl)prop-2-en-1-ol: A solution of $PdCl_2(PPh_3)_2$ (0.0070 g, 0.01 mmol), alkyne, **87**, (0.2174 g, 1 mmol), Bu_3SnCl (0.33 mL, 1.2 mmol), $KF_{(aq)}$ (0.1743 g, 3 mmol), and PMHS (0.12 mL, 2 mmol) in THF (10 mL) was stirred for 2 h at room temperature. The solution was poured into ether and extracted with ether and water. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.1638 g (31.7% yield) of the vinyl stannanes. 1H NMR of the crude reaction showed a 1/1.3 ratio of **88a/88b**. **88a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 2.0, 6.8 Hz, 2H), 7.24 (dt, *J* = 2.0, 7.8 Hz, 2H), 6.29 (d, *J* = 18.6 Hz, 1H), 6.10 (dd, *J* = 5.4, 19.0 Hz, 1H), 5.12 (s, 1H), 2.13 (bs, 1H), 1.48 (quint., *J* = 7.8 Hz, 6H), 1.29 (m, 6H), 0.89 (m, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 141.8, 131.5, 131.0, 129.4, 128.1, 121.3, 29.0, 27.2, 13.7, 9.5, **88b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 5.88 (t, *J* = 61.5 Hz, 1H), 5.32 (t, *J* = 28.8 Hz, 1H), 5.25 (s, 1H), 1.99 (s, 1H), 1.32 (m, 6H), 1.22 (sept., *J* = 7.3

Hz, 6H), 0.83 (t, J = 7.3 Hz, 9H), 0.73 (t, J = 7.3 Hz, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 142.0, 131.3, 128.2, 125.1, 121.2, 80.13, 28.9, 27.4, 13.7, 10.0. IR (neat) 3230 cm^{-1}.



89

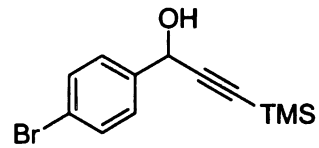
Preparation of 4-vinylbenzaldehyde: To a solution of p-bromobenzaldehyde (0.1850 g, 1 mmol), $Pd(PPh_3)_4$ (0.0231 g, 0.02 mmol), and a few crystals of BHT in toluene (2 mL) was added tributylvinyltin (0.32 mL, 1.1 mmol). The resulting solution was heated to reflux for 3 h. Sat. $KF_{(aq)}$ was added and stirred for 15 min. The reaction was diluted with ether and washed with water. The organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 95/5 hexanes/ethyl acetate) to afford 0.1092 g (82.6% yield) of the styrenyl product, **89**. ^1H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 6.74 (dd, J = 10.7, 17.6 Hz, 1H), 5.89 (d, J = 17.6 Hz, 1H), 5.41 (d, J = 10.7 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.6, 143.4, 135.8, 135.6, 130.0, 126.7, 117.4. Spectral data were consistent with those previously reported.[156,157]



90

Preparation of 1-(3-bromophenyl)but-3-yn-1-ol: Activated Zn powder (2.3540 g, 36 mmol) was placed in a flame dried round bottom flask (500 mL) fitted with a magnetic stir bar. Then m-bromobenzaldehyde (5.5073 g, 30 mmol) and

propargyl bromide (4.0 mL, 36 mmol) were added via a dropping funnel (added over 1.5 h). The resulting mixture was vigorously stirred at room temperatue. After a total of 3 h, sat. $NH_4Cl_{(aq)}$ was poured into the mixture and stirred for several minutes. Ether was added and the organic layer was separated and dried over $MgSO_4$. After filtration and concentration, the crude product was purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 2.2681 g (33.9% yield) of aryl bromide **90**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.40 (d, *J* = 6.3 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 4.80 (t, *J* = 5.9 Hz, 1H), 2.59 (m, 2H), 2.49 (m, 1H), 2.07 (t, *J* = 2.4 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 130.9, 130.0, 128.8, 124.3, 122.5, 94.7, 78.5, 71.4, 29.3. Spectral data were consistent with those previously reported.[158]



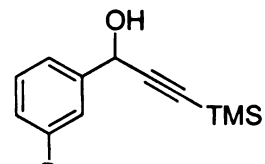
91

Preparation of 1-(4-bromophenyl)-3-(trimethylsilyl)prop-2-yn-1-ol: To a flask charged with TMS-acetylene (2.3 mL, 16.05 mmol) and THF (18 mL) at 0 °C was added nBuLi (10.1 mL, 16.2 mmol; 1.6M in hexanes) dropwise. The solution stirred for 30 min. The flask was then cooled to -78 °C and a solution of p-bromobenzaldehyde (2.7753 g, 15 mmol) in THF (6 mL) was added dropwise. The reaction was slowly warmed to room temperature and stirred an additional 1 h. The reaction was diluted with ether and poured into ice-water. The aqueous layer was extracted with ether. The combined organics were washed with water and dried over $MgSO_4$. After filtration and concentration, the crude product was

purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 4.0690 g (95.8% yield) of aryl bromide **91**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 5.38 (d, *J* = 5.9 Hz, 1H), 2.28 (bs, 1H), 0.18 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 131.6, 128.4, 122.3, 104.4, 92.1, 64.3, -0.2.

IR (PTFE card, neat) 3314, 2174, 1250, 843 cm^{-1}.

HRMS (EI): m/z calcd for $C_{12}H_{15}BrOSi$ (M^+): 284.0056. Found: 284.0048.



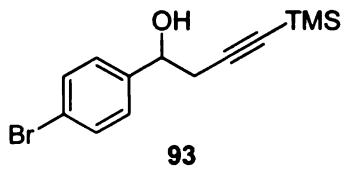
92

Preparation of 1-(3-bromophenyl)-3-(trimethylsilyl)prop-2-yn-1-ol: To a flask charged with TMS-acetylene (2.3 mL, 16.05 mmol) and THF (18 mL) at 0 °C was added nBuLi (10.1 mL, 16.2 mmol; 1.6M in hexanes) dropwise. The solution stirred for 30 min. The flask was then cooled to -78 °C and a solution of m-bromobenzaldehyde (1.76 mL, 15 mmol) in THF (6 mL) was added dropwise. The reaction was slowly warmed to room temperature and stirred an additional 1 h. The reaction was diluted with ether and poured into ice-water. The aqueous layer was extracted with ether. The combined organics were washed with water and dried over $MgSO_4$. After filtration and concentration, the crude product was purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 4.1023 g (96.4% yield) of aryl bromide **92**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.48 (m, 2H), 7.27 (d, *J* = 7.8 Hz, 1H), 5.43 (d, *J* = 5.9 Hz, 1H), 2.40

(bs, 1H), 0.23 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 131.3, 130.1, 129.8, 125.3, 122.5, 104.2, 92.3, 64.2, -0.3.

IR (neat) 3341, 2176, 1258, 1044, 847 cm^{-1}.

HRMS (EI): m/z calcd for $C_{12}H_{15}BrOSi$ (M^+): 284.0056. Found: 284.0051.

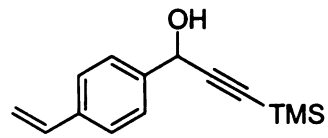


93

Preparation of 1-(4-bromophenyl)-4-(trimethylsilyl)but-3-yn-1-ol: Activated Zn powder (2.12 g, 32.4 mmol) was placed in a flame dried round bottom flask (500 mL) fitted with a magnetic stir bar. Then p-bromobenzaldehyde (5.02 g, 27 mmol) and TMS-propargyl bromide (4.6 mL, 32.4 mmol) were added via a dropping funnel (added over 1 h). The resulting mixture was vigorously stirred at room temperature. After a total of 3 h, sat. $NH_4Cl_{(aq)}$ was poured into the mixture and stirred for several minutes. Ether was added and the organic layer was separated and dried over $MgSO_4$. After filtration and concentration, the crude product was purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 3.3350 g (41.3% yield) of aryl bromide **93**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 4.80 (m, 1H), 2.61 (d, *J* = 5.4 Hz, 1H), 2.45 (m, 1H), 2.59 (d, *J* = 6.8 Hz, 1H), 0.13 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 131.4, 127.5, 121.6, 102.3, 88.4, 71.6, 31.1, -0.5. Spectral data were consistent with those previously reported.[159]

General procedure for the Stille coupling of an aryl bromide: To a solution of the aryl bromide (1 mmol), $Pd(PPh_3)_4$ (0.0231 g, 0.02 mmol), and a few

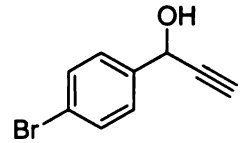
crystals of BHT in toluene (2 mL) was added tributylvinyltin (0.32 mL, 1.1 mmol). The resulting solution was heated at 110 °C. When the reaction was complete as determined by GC, sat. $KF_{(aq)}$ was added and stirred for 15 min. The reaction was diluted with ether and washed with water. The organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 95/5 hexanes/ethyl acetate) to afford the Stille coupling product.



94

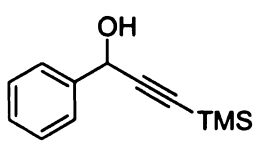
Preparation of 3-(trimethylsilyl)-1-(4-vinylphenyl)prop-2-yn-1-ol: Following the general procedure for the Stille coupling of aryl bromides, the aryl bromide, **91**, (0.2856 g, 1 mmol) was reacted with tributylvinyltin (0.32 mL, 1.1 mmol) for 3 h. The crude product was purified by flash chromatography (silica gel; 95/5 hexanes/ethyl acetate) to afford 0.1222 g (52.6% yield) of the styrenyl product, **94**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 2H), 6.70 (dd, *J* = 10.7, 17.6 Hz, 1H), 5.75 (d, *J* = 17.6 Hz, 1H), 5.42 (d, *J* = 5.9 Hz, 1H), 5.25 (d, *J* = 10.7 Hz, 1H), 2.25 (bs, 1H), 0.19 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8, 137.7, 136.3, 126.9, 126.4, 114.3, 104.8, 91.6, 64.7, -0.2. IR (neat) 3407, 2183, 1252, 849 cm^{-1}.

HRMS (EI): m/z calcd for $C_{14}H_{18}OSi$ (M^+): 230.1127. Found: 230.1126.



87

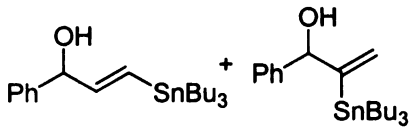
Preparation of 1-(4-bromophenyl)prop-2-yn-1-ol: The silyl alkyne, **91**, (0.0480g, 0.18 mmol) was dissolved in THF/H_2O (0.5 mL; 98/2 v/v) and immersed in a 0 °C ice bath. Added dropwise was a solution of KF (0.0110 g, 0.20 mmol) and 18-C-6 (0.0513 g, 0.20 mmol) in THF/H_2O (0.7 mL; 98/2 v/v). The reaction was allowed to slowly warm to room temperature over 4 h. The solution was diluted with water and extracted with ether. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 0.0310 g (86.6% yield) of aryl bromide, **87**. The spectral data was consistent with that shown above prepared via an alternate method.



95

Preparation of 1-phenyl-3-(trimethylsilyl)prop-2-yn-1-ol: To a flask charged with TMS-acetylene (3.8 mL, 26.75 mmol) and THF (30 mL) at 0 °C was added nBuLi (16.9 mL, 27 mmol; 1.6M in hexanes) dropwise. The solution stirred for 30 min. The flask was then cooled to -78 °C and a solution of benzaldehyde (2.5 mL, 25 mmol) in THF (10 mL) was added dropwise. The reaction was slowly warmed to room temperature and stirred an additional 1 h. The reaction was diluted with ether and poured into ice-water. The aqueous layer was extracted with ether. The combined organics were washed with water and dried over $MgSO_4$. After filtration and concentration, the crude product was purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 5.1076 g (100% yield) of alcohol **95**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 7.8 Hz, 2H),

7.37 (t, J = 7.3 Hz, 2H), 7.32 (d, J = 7.3 Hz, 1H), 5.44 (s, 1H), 2.25 (bs, 1H), 0.19 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 128.6, 128.3, 126.7, 104.9, 91.6, 65.0, -0.2. Spectral data were consistent with those previously reported.[160]

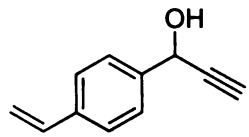


96a **96b**

Preparation of (E)-1-phenyl-3-(tributylstannyl)prop-2-en-1-ol and 1-phenyl-2-(tributylstannyl)prop-2-en-1-ol: The silyl alkyne, **95**, (0.2043g, 1 mmol) and Bu_3SnCl (0.27 mL, 1 mmol) was dissolved in THF/H_2O (8 mL; 98/2 v/v) and immersed in a 0 °C ice bath. Added dropwise was a solution of KF (0.1162 g, 2 mmol) and 18-C-6 (0.5286 g, 2 mmol) in THF/H_2O (22 mL; 98/2 v/v). The reaction was allowed to slowly warm to room temperature over 4 h. $PdCl_2(PPh_3)_2$ (0.0070 g, 0.01 mmol) and PMHS (0.12 mL, 2 mmol) were added and then the solution was stirred for 40 h. The solution was diluted with water and extracted with ether. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 0.1699 g (40.1% yield) of the vinyl stannanes. ^{1}H NMR of the crude reaction showed a 1.1/1 ratio of **96a/96b**. **96a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.34 (d, J = 4.4 Hz, 2H), 7.31 (d, J = 4.4 Hz, 2H), 6.29 (d, J = 19.0 Hz, 1H), 6.15 (dd, J = 5.4, 19.0 Hz, 1H), 5.15 (s, 1H), 2.0 (s, 1H), 1.47 (m, 6H), 1.27 (m, 6H), 0.85 (m, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 142.8, 136.0, 128.4, 127.5, 126.4, 77.5, 29.0, 27.3, 13.7, 9.5. **96b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.34

(d, J = 4.395 Hz, 2H), 7.31 (d, J = 4.395 Hz, 2H), 5.90 (t, J = 1.465 Hz, 1H), 5.32 (t, J = 1.465 Hz, 1H), 5.15 (s, 1H), 2.0 (s, 1H), 1.47 (m, 6H), 1.20 (m, 6H), 0.85 (m, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 143.0, 128.3, 127.3, 126.5, 124.3, 80.5, 28.9, 27.3, 13.7, 9.9.

IR (neat) 3374 cm^{-1}.

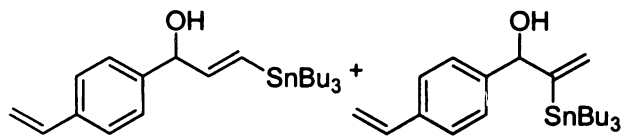


97

Preparation of 1-(4-vinylphenyl)prop-2-yn-1-ol: To a solution of the aryl bromide, **91**, (0.2820 g, 1 mmol), $Pd(PPh_3)_4$ (0.0231 g, 0.02 mmol), and a few crystals of BHT in toluene (2 mL) was added tributylvinyltin (0.32 mL, 1.1 mmol). The resulting solution was heated at 110 °C for 3 h. After cooling to room temperature, THF/H_2O (8 mL; 98/2 v/v) was added and the solution was immersed in an ice bath. A solution of KF (0.1917 g, 3.3 mmol) and 18-C-6 (0.8723 g, 3.3 mmol) in THF was added dropwise and stirred at 0 °C for 5 h. The reaction was diluted with water and extracted with ether. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 0.1148 g (72.9% yield) of the styrenyl product, **97**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 6.71 (dd, J = 10.7, 17.6 Hz, 1H), 5.75 (d, J = 17.6 Hz, 1H), 5.43 (s, 1H), 5.26 (d, J = 10.7 Hz, 1H), 2.65 (s, 1H), 2.34 (bs, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 137.9, 136.3,

126.8, 126.5, 114.5, 83.4, 74.8, 64.2. Spectral data were consistent with those previously reported.[161]

General Procedure for the one-pot Stille/hydrostannation reaction: To a solution of the aryl bromide (1 mmol), $Pd(PPh_3)_4$ (0.0231 g, 0.02 mmol), and a few crystals of BHT in toluene (2 mL) was added the vinyltin (1.5 mmol). The resulting solution was heated at 110 °C. After cooling to room temperature, THF/H_2O (8 mL; 98/2 v/v) was added and the solution was immersed in an ice bath. A solution of KF (0.1917 g, 3.3 mmol) and 18-C-6 (0.8723 g, 3.3 mmol) in THF was added dropwise and stirred for 5 h. After warming to room temperature, $PdCl_2(PPh_3)_2$ (0.0070 g, 0.01 mmol) was added and PMHS (0.12 mL, 2 mmol) was added slowly. After stirring overnight, the reaction was diluted with water and extracted with ether. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography to afford the vinyl stannanes.



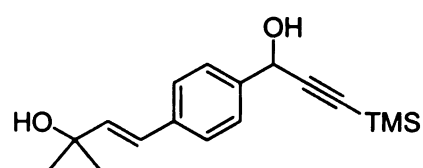
98a **98b**

Preparation of (E)-3-(tributylstannyl)-1-(4-vinylphenyl)prop-2-en-1-ol and 2-(tributylstannyl)-1-(4-vinylphenyl)prop-2-en-1-ol: Following the general procedure for the one-pot Stille/hydrostannation reaction, the aryl bromide, **91**, (0.2892 g, 1 mmol), was reacted with tributylvinyltin (0.44 mL, 1.5 mmol). The crude product was purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 0.1980 g (43.2% yield) of the vinyl stannanes

(**98a/98b**: 2/1). **98a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 6.70 (dd, *J* = 10.7, 17.6 Hz, 1H), 6.27 (d, *J* = 19.0 Hz, 1H), 6.15 (dd, *J* = 6.3, 18.1 Hz, 1H), 5.74 (d, *J* = 17.6 Hz, 1H), 5.21 (d, *J* = 10.7 Hz, 1H), 5.15 (t, *J* = 4.4 Hz, 1H), 1.97 (bs, 1H), 1.47 (m, 6H), 1.28 (m, 6H), 0.86 (m, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 142.4, 136.9, 136.5, 128.8, 126.6, 126.3, 113.8, 77.4, 29.1, 27.2, 13.7, 9.5. **98b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 6.69 (dd, *J* = 10.7, 17.6 Hz, 1H), 5.89 (t, *J* = 1.5 Hz, 1H), 5.71 (d, *J* = 17.6 Hz, 1H), 5.31 (t, *J* = 1.5 Hz, 1H), 5.29 (s, 1H), 5.20 (d, *J* = 10.7 Hz, 1H), 1.93 (s, 1H), 1.32 (m, 6H), 1.21 (m, 6H), 0.83 (m, 9H), 0.74 (m, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 142.6, 136.8, 136.6, 126.6, 126.2, 124.5, 113.6, 80.4, 29.0, 27.3, 13.6, 10.0.

IR (neat) 3348 cm^{-1}.

HRMS (EI): m/z calcd for $C_{19}H_{29}OSn$ (M^+ - Bu): 393.1244. Found: 393.1242.



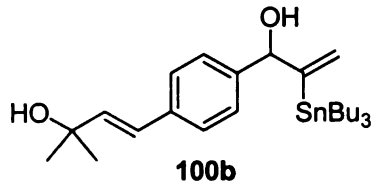
99

Preparation of (E)-4-(4-(1-hydroxy-3-(trimethylsilyl)prop-2-ynyl)phenyl)-2-methylbut-3-en-2-ol: Following the general procedure for the Stille coupling of aryl bromides, the aryl bromide, **91**, (0.2908 g, 1 mmol) was reacted with (E)-2-methyl-4-(tributylstannyl)but-3-en-2-ol (0.4758 g, 1.5 mmol) for 7 h. The crude product was purified by flash chromatography (silica gel; 60/40 hexanes/ethyl acetate) to afford 0.1555 g (52.5% yield) of the Stille coupling product, **99**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 6.56

(d, J = 16.1 Hz, 1H), 6.33 (d, J = 16.1 Hz, 1H), 2.45 (bs, 1H), 1.68 (bs, 1H), 1.40 (s, 6H), 0.18 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 138.0, 137.1, 127.0, 126.8, 125.9, 105.0, 91.5, 71.1, 64.6, 29.8, -0.2.

IR (neat) 33316, 2175, 843 cm^{-1}.

HRMS (EI): m/z calcd for $C_{17}H_{24}O_2Si$ (M^+): 288.1546. Found: 288.1545.

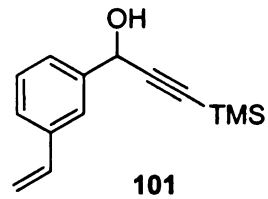


100b

Preparation of (E)-4-(4-(1-hydroxy-2-(tributylstannyl)allyl)phenyl)-2-methylbut-3-en-2-ol: Following the general procedure for the one-pot Stille/hydrostannation reaction, the aryl bromide, **91** (0.1028 g, 0.35 mmol), was reacted with **107** (0.1987 g, 0.53 mmol). The crude product was purified by flash chromatography (silica gel; 60/40 hexanes/ethyl acetate) to afford 0.0200 g (12% yield) of the vinyl stannane. **100b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 4H), 6.56 (dd, J = 8.3, 16.1 Hz, 1H), 6.33 (dd, J = 8.3, 16.1 Hz, 1H), 5.89 (tm, J = 61.5 Hz, 1H), 5.31(tm, J = 30.8 Hz, 1H), 5.28 (s, 1H), 1.55 (bs, 1H), 1.50 (bs, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.32 (m, 6H), 1.22 (m, 6H), 0.88 (m, 6H), 0.82 (t, J = 7.3 Hz, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 137.5, 137.3, 136.1, 128.5, 126.7, 126.4, 126.3, 126.1, 71.0, 29.9, 29.0, 27.3, 13.6, 10.0.

IR (neat) 3395 cm^{-1}.

HRMS (EI): m/z calcd for $C_{22}H_{35}O2Sn$ (M^+ - Bu): 451.1663. Found: 451.1652.

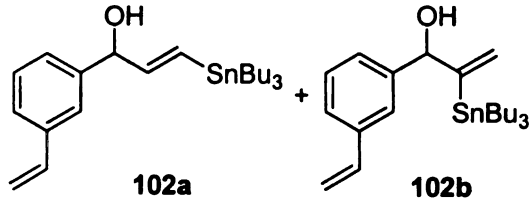


101

Preparation of 3-(trimethylsilyl)-1-(3-vinylphenyl)prop-2-yn-1-ol: Following the general procedure for the Stille coupling of aryl bromides, the aryl bromide, **92**, (0.2845 g, 1 mmol) was reacted with vinyltributyl tin (0.44 mL, 1.5 mmol) for 24 h. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.1310 g (56.6% yield) of the Stille coupling product, **101**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.42 (m, 1H), 7.33 (m, 2H), 6.72 (dd, *J* = 10.7, 17.6 Hz, 1H), 5.76 (dd, *J* = 1.0, 17.6 Hz, 1H), 5.43 (d, *J* = 6.3 Hz, 1H), 5.26 (d, *J* = 11.2 Hz, 1H), 2.30 (bs, 1H), 0.20 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 137.9, 136.5, 128.7, 126.2, 126.1, 124.5, 114.3, 104.9, 91.7, 64.9, -0.2.

IR (neat) 3372 cm^{-1}.

HRMS (EI): m/z calcd for $C_{14}H_{18}OSi$ (M^+): 230.1127. Found: 230.1133.



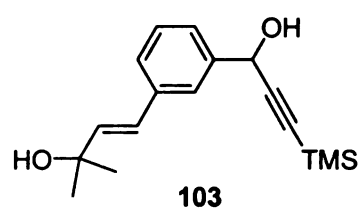
102a **102b**

Preparation of (E)-3-(tributylstannyl)-1-(3-vinylphenyl)prop-2-en-1-ol and 2-(tributylstannyl)-1-(3-vinylphenyl)prop-2-en-1-ol: Following the general procedure for the one-pot Stille/hydrostannation reaction, the aryl bromide (0.2863 g, 1 mmol), was reacted with vinyltributyl tin (0.44 mL, 1.5 mmol). The crude product was purified by flash chromatography (silica gel; 80/20

hexanes/ethyl acetate) to afford 0.1605 g (35.3% yield) of vinyl stannanes (**102a/102b**: 1.2/1). **102a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.30 (m, 2H), 7.24 (m, 1H), 6.70 (dd, *J* = 10.7, 17.6 Hz, 1H), 6.28 (dd, *J* = 1.5, 19.0 Hz, 1H) 6.16 (dd, *J* = 5.4, 19.0 Hz, 1H), 5.73 (d, *J* = 17.1 Hz, 1H), 5.23 (dd, *J* = 1.0, 10.7 Hz, 1H), 5.15 (t, *J* = 4.4 Hz, 1H), 2.03 (bs, 1H), 1.47 (m, 6H), 1.27 (m, 6H), 0.85 (m, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 143.0, 137.8, 136.7, 128.8, 128.6, 125.9, 125.4, 124.3, 114.0, 77.5, 29.1, 27.2, 13.7, 9.5. **102b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.28 (m, 2H), 7.20 (m, 1H), 6.69 (dd, *J* = 11.2, 17.6 Hz, 1H), 5.93 (t, *J* = 1.5 Hz, 1H), 5.73 (d, *J* = 17.6 Hz, 1H), 5.33 (t, *J* = 1.5 Hz, 1H), 5.30 (m, 1H), 5.22 (d, *J* = 11.2 Hz, 1H), 2.03 (s, 1H), 1.25 (m, 12H), 0.85 (m, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 143.2, 137.6, 136.8, 128.5, 126.0, 125.3, 124.5, 124.2, 113.8, 80.5, 31.6, 22.7, 14.1, 9.9.

IR (neat) 3372 cm^{-1}.

HRMS (EI): m/z calcd for $C_{19}H_{29}OSn$ (M^+ - Bu): 393.1244. Found: 393.1235.



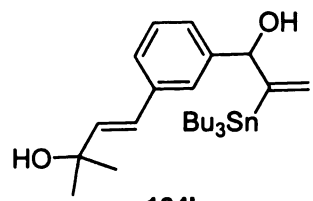
103

Preparation of (E)-4-(3-(1-hydroxy-3-(trimethylsilyl)prop-2-ynyl)phenyl)-2-methylbut-3-en-2-ol: Following the general procedure for the Stille coupling of aryl bromides, the aryl bromide, **92**, (0.2886 g, 1 mmol) was reacted with **107** (0.4758 g, 1.5 mmol) for 20 h. The crude product was purified by flash chromatography (silica gel; 60/40 hexanes/ethyl acetate) to afford 0.1061 g (36.1% yield) of the Stille coupling product, **103**. ^{1}H NMR (500 MHz, $CDCl_3$) δ

7.54 (s, 1H), 7.38 (m, 1H), 7.30 (s, 1H), 7.29 (s, 1H), 6.56 (d, J = 16.1 Hz, 1H), 6.36 (d, J = 16.1 Hz, 1H), 5.41 (s, 1H), 2.58 (bs, 1H), 1.78 (bs, 1H), 1.39 (s, 6H), 0.18 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 138.0, 137.3, 128.8, 126.5, 126.0, 125.7, 124.6, 105.0, 91.5, 71.1, 64.8, 29.8, -0.2.

IR (neat) 3355, 2174, 1250, 845 cm^{-1}.

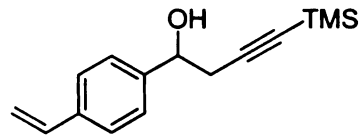
HRMS (EI): m/z calcd for $C_{17}H_{24}O_2Si$ (M^+): 288.1546. Found: 288.1537.



104b

Preparation of (E)-4-(3-(1-hydroxy-2-(tributylstannyl)allyl)phenyl)-2-methylbut-3-en-2-ol: Following the general procedure for the one-pot Stille/hydrostannation reaction, the aryl bromide, **92**, (0.2811 g, 1 mmol), was reacted with **107** (0.4758 g, 1.5 mmol). The crude product was purified by flash chromatography (silica gel; 60/40 hexanes/ethyl acetate) to afford 0.0955 g (19.0% yield) of the vinyl stannanes. **104b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10-7.40 (m, 4H), 6.56 (dd, J = 5.4, 16.1 Hz, 1H), 6.33 (d, J = 16.1 Hz, 1H), 5.91 (tm, J = 19.5 Hz, 1H), 5.32 (tm, J = 19.0 Hz, 1H), 5.28 (s, 1H), 2.02 (s, 1H), 2.00 (bs, 1H), 1.40 (d, J = 3.9 Hz, 6H), 1.32 (m, 6H), 1.22 (m, 6H), 0.86 (m, 6H), 0.82(t, J = 7.3 Hz, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 143.3, 137.5, 137.0, 128.5, 127.4, 126.4, 125.6, 124.5, 124.4, 80.5, 71.0, 29.9, 28.9, 27.3, 13.7, 10.0.

IR (neat) 3386 cm^{-1}.

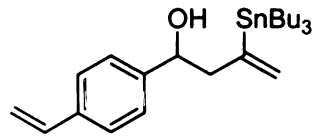


105

Preparation of 4-(trimethylsilyl)-1-(4-vinylphenyl)but-3-yn-1-ol: Following the general procedure for the Stille coupling of aryl bromides, the aryl bromide, **93**, (0.2948 g, 1 mmol) was reacted with vinyltributyl tin (0.44 mL, 1.5 mmol) for 24 h. The crude product was purified by flash chromatography (silica gel; 90/10 hexanes/ethyl acetate) to afford 0.1061 g (43.8% yield) of the Stille coupling product, **105**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 6.69 (dd, 10.7, 17.6 Hz, 1H), 5.74 (d, *J* = 17.6 Hz, 1H), 5.21 (d, *J* = 10.7 Hz, 1H), 4.80 (m, 1H), 2.61 (d, *J* = 5.9 Hz, 2H), 2.45 (bs, 1H), 0.14 (s, 9H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 137.2, 136.4, 131.4, 127.5, 126.2, 125.9, 113.9, 102.8, 88.0, 72.0, 31.1, -0.03.

IR (neat) 3403, 2176, 1250, 841 cm^{-1}.

HRMS (EI): m/z calcd for $C_{15}H_{20}OSi$ (M^+): 244.1283. Found: 244.1288.



106b

Preparation of 3-(tributylstannyl)-1-(4-vinylphenyl)but-3-en-1-ol: Following the general procedure for the one-pot Stille/hydrostannation reaction, the aryl bromide, **93**, (0.3092 g, 1 mmol), was reacted with vinyltributyl tin (0.44 mL, 1.5 mmol). The crude product was purified by flash chromatography (silica gel; 80/20 hexanes/ethyl acetate) to afford 0.0129 g (2.8% yield) of the vinyl stannanes. **106b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.3, 35.2 Hz, 4H),

6.69 (dd, J = 10.7, 17.6 Hz, 1H), 5.84 (t, J = 1.0 Hz, 1H), 5.72 (d, J = 17.6 Hz, 1H), 5.35 (d, J = 3.4 Hz, 1H), 5.21 (d, J = 10.7 Hz, 1H), 4.62 (d, J = 9.8 Hz, 1H), 2.70 (dd, J = 3.9, 15.1 Hz, 1H), 2.51 (dd, J = 9.8, 13.7 Hz, 1H), 2.25 (s, 1H), 1.49 (m, 6H), 1.28 (m, 6H), 0.90 (m, 15H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 143.7, 136.8, 136.5, 129.5, 125.9, 125.5, 113.6, 72.3, 30.3, 29.3, 27.4, 13.7, 9.9. IR (neat) 2918 cm^{-1}.

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