A CATALYTIC BORYLATION-BASED APPROACH TO AUTOLYTIMYCIN AND ALLIED STUDIES

By

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ABSTRACT

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Since its discovery in 1999, Ir-catalyzed C–H activation/borylation has established itself as a potent tool for the construction of aromatic and heteroaromatic building blocks. Given their bench stability and versatility in chemical transformations, the use of boronates is synthetically advantageous. Catalysis by iridium features a regioselectiviy that is primarily directed by sterics, as opposed to electronics, complementing electrophilic aromatic substitution and functional group-directed metalation. Synthetic utilization of this characteristic allows access to structural moieties that are, in fact, relatively inaccessible via traditional routes. This last decade has been prolific with work on improvements, adaptations, and various applications of such borylations reported by many research groups.

Herein, a number of synthetic aspects of this chemistry are discussed. Halogen tolerance, for instance, allows for the preparation of multifunctional cross-coupling partners as useful building blocks. This feature is showcased in the diversity-oriented route to the COX-2 inhibitor DuP 697 and a series of analogs. The special regioselectivity attained on heteroaromatics has been utilized toward the development of a novel convergent route to the TMC-95 core. For this purpose, preparation of a key intermediate was made possible via a neutral and mild Ir-catalyzed *deborylation* method, developed in our laboratories, that allows the preparation of heteroaromatics with unusually placed boronate groups via diborylation/monodeborylation. In addition, the same gentle deborylation procedure was adapted for the preparation of deuterium-

labeled compounds in a site-selective manner, emphasizing the importance of the broad functional group tolerance of Ir-catalyzed C–H activation/borylation.

Perhaps the most attractive of its characteristics is that, given the cleanliness with which it proceeds, Ir-catalyzed C–H activation/borylation is amenable to one-pot transformations. This concept is highlighted in our synthetic approach to the Hsp90 inhibitor autolytimycin. Taking advantage of both the regioselectivity and halogen tolerance, our method enabled a highly convergent construction of the full carbon network of this natural product. We provide an illustration of a C–H activation/borylation-based three-step one-pot process, which is complemented by a *B*-alkyl sp^3–sp^2 Suzuki coupling on a highly inactivated aromatic chloride, an unprecedented transformation in complex molecule synthesis. The late-stage applicability of these boron-based methods lead to the preparation of highly elaborated 5-alkyl-3-amidophenols, motifs that are present in many natural products and that are difficult to obtain via conventional methods.

To Luis, Gloria, and Elsa.

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Å	angstrom
[α]	specific rotation
δ	chemical shift
μW	microwave
Ac	acetyl
APCI	atmospheric pressure chemical ionization
aq	aqueous
Ar	aryl
atm	atmospheres
B_2Pin_2	bis(pinacolato)diboron
BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOM	(benzyloxy)methyl
BOPCl	bis(2-oxo-3-oxazolidinyl)phosphonic chloride
BPin	pinacolboryl
BPS	*tert*-butyldiphenylsilyl
br	broad (spectral peak)
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
cat.	Catalytic

Cbz	benzyloxycarbonyl
CI	chemical ionization
COD	1,5-cyclooctadiene
Cy	cyclohexyl
d	doublet (spectral peak), day (reaction time)
DavePhos	2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	dimethylformamide
dmpe	1,2-bis(dimethylphosphino)ethane
DMPM	(3,4-dimethoxyphenyl)methyl

DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino) ferrocene
dr	diastereomeric ratio
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridine
EAS	electrophilic aromatic substitution
EDC, EDCI	3-(ethyliminomethyleneamino)-*N*,*N*-dimethylpropanamine hydrochloride
ee	enantiomeric excess
EI	electron ionization
ESI	electrospray ionization
Et	ethyl
eV	electron volt
EVE	ethyl vinyl ether
FAB	fast atom bombardment (an ionization technique)
GC	gas chromatography
H_2IMes	1,3-dimesityl-4,5-dihydroimidazol-2-ylidene
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	hydroxybenzotriazole
HRMS	high-resolution mass spectrometry
IMes	1,3-dimesitylimidazol-2-ylidene
Ind	indenyl

iPr	isopropyl
IPr	1,3-diisopropylimidazol-2-ylidene
JohnPhos	(2-biphenyl)di-*tert*-butylphosphine
lut	lutidine
mCPBA	*m*-chloroperbenzoic acid
Me	methyl
Mes	mesityl
MHz	megahertz
MOM	methoxymethyl
mp	melting point
ms	molecular sieves
MS	mass spectrometry
mtbe	methyl *tert*-butyl ether
nBu	*n*-butyl
NMR	nuclear magnetic resonance
OAc	acetate
ON	overnight
PEPPSI	pyridine-enhanced precatalyst preparation, stabilization, and initiation
Ph	phenyl
PinB	pinacolboryl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl

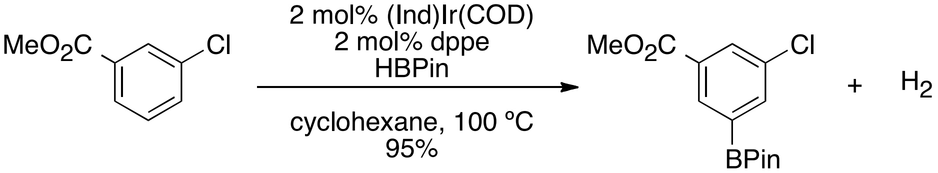
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PTS	polyoxyethanyl α-tocopheryl sebacate
py, pyr	pyridine, pyridyl
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
q	quartet (spectral peak)
QPhos	1,2,3,4,5-pentaphenyl-1'-(di-tert-butylphosphino)ferrocene
R	substituent
RCM	ring-closing metathesis
RRCM	relay ring-closing metathesis
RuPhos	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
rt	room temperature
s	singlet (spectral peak)
SAR	Structure-activity relationship
sBu	*sec*-butyl
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	triplet (spectral peak)
tAm	*tert*-amyl, *tert*-pentyl
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl

TEA	triethylamine
TES	triethylsilyl
tBu	*tert*-butyl
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time of flight
Trt	triphenylmethyl, trityl
Ts	tosyl
TSE	trimethylsilylethyl
UV	ultraviolet
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
xs	excess

Chapter 1. Introduction

1.1. Ir-catalyzed aromatic C–H activation/borylation

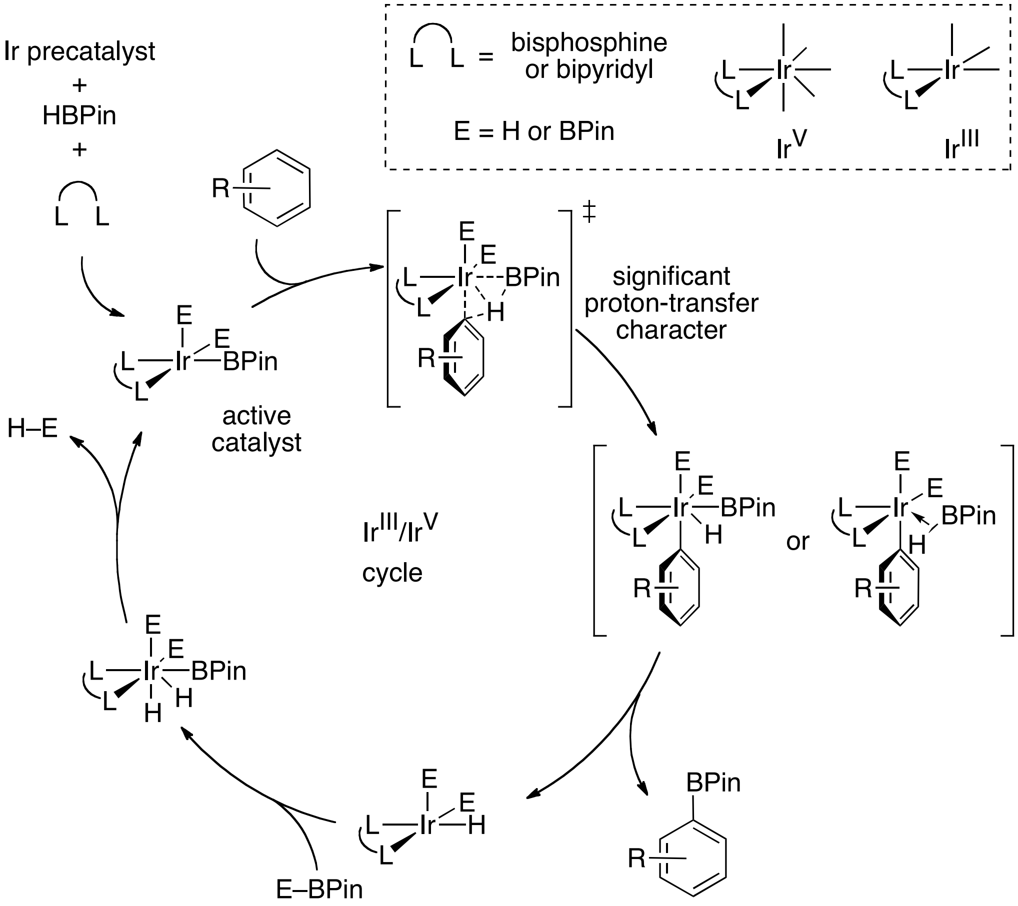
C–H activation/borylation[1] is a fairly recent and developing type of C–H activation[2] in which the thermodynamically favored conversion of a C−H bond into a C−B bond is effected by virtue of a transition metal.[3] In general, Re, Rh, Ru, Ir, and Pd have been utilized for selective C–H activation at aliphatic, benzylic, or aromatic positions.[1]



Scheme 1. Example of a C–H activation/borylation catalyzed by (Ind)Ir(COD)-dppe.

In 1999, the Smith[4] group demonstrated that aromatic C–H activation/borylation could be catalyzed by iridium species. Since then, there has been a significant advancement around this transformation, with important reports from the Smith,[5] Hartwig, Ishiyama, and Miyaura[6] groups and others,[7] which has resulted in the development of a well established method of high synthetic value.

Smith[5c] introduced the use of (Ind)Ir(COD) as precatalyst in combination with a bisphosphine ligand (usually dppe or dmpe) in borylation reactions with pinacolborane (HBPin) (Scheme 1). This represented a significant advance in terms of catalyst activity, turnover numbers, and product cleanliness. Subsequent improvement by Hartwig, Ishiyama, and Miyaura showed that the precatalyst $[Ir(OMe)COD]_2$ in combination with the bipyridyl ligand dtbpy, using bispinacolatodiboron (B_2Pin_2) as boron source, could effect borylation reactions at room temperature.[6c]



Scheme 2. Proposed catalytic cycle of Ir-catalyzed C–H activation/borylation.

The mechanism of the Ir-catalyzed C–H activation/borylation has been proposed to proceed via a Ir^{III}/Ir^{V} catalytic cycle depicted in Scheme 2,[5c,6g] where the active Ir^{III} catalyst is formed *in situ* from an Ir^{I} precatalyst and the boron source in the presence of the biphosphine or bipyridyl ligand. As reported by Smith,[51] experimental and theoretical data suggest that significant proton transfer character exists in the C–H activation transition state. After such C–H activation, the resulting Ir^{V} intermediate undergoes reductive elimination generating a C–B bond.

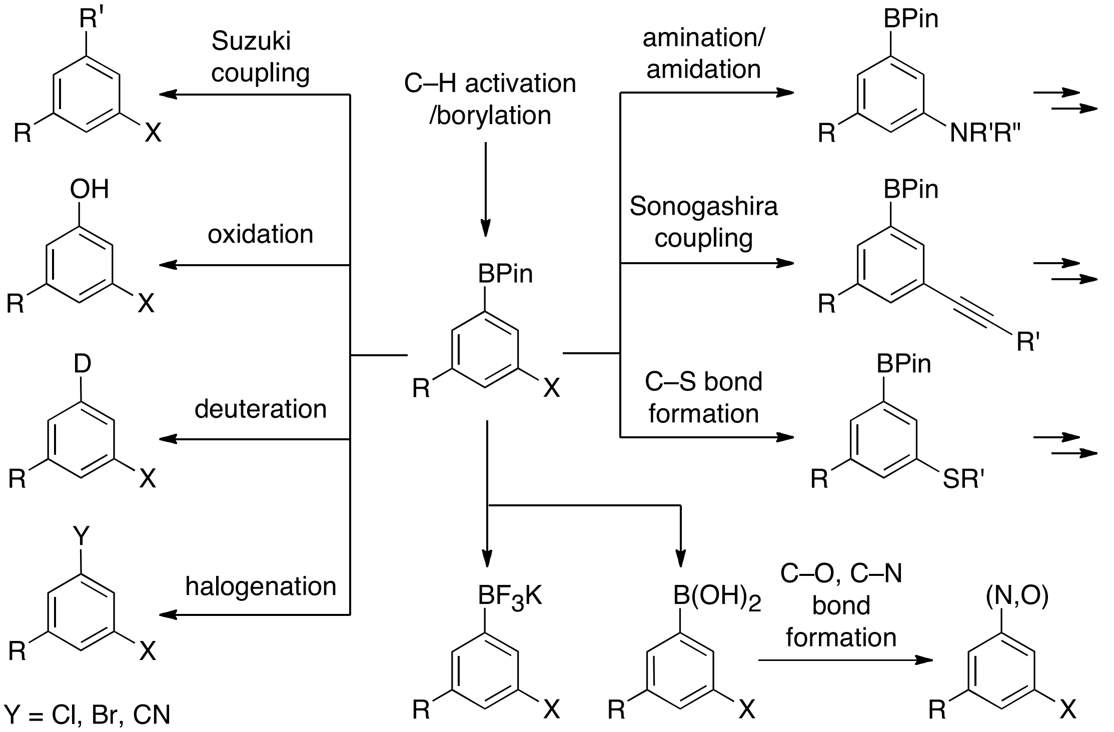
Installation of boron functionalities via C–H activation is a remarkable synthetic breakthrough. Arylboronic esters and acids[8] are versatile compounds heavily used in Pd- and Cu-catalyzed cross-coupling reactions leading to not only C–C but also C–N and C–O bond formations.[9] Other transformations include Rh-catalyzed additions[10] and Petasis reactions[11] (see also Scheme 3). Synthesis of these compounds is usually carried out from Grignard or lithium species generated via *ortho*-metallation or from halide-containing precursors via Miyaura coupling.[9] Direct borylation of arenes provides access to these synthetically valuable compounds without depending on the accessibility of the corresponding halides or organometallics.

1.2. Features of Ir-catalyzed C–H activation and their synthetic value.

Ir-catalyzed C–H activation/borylation possesses synthetically attractive attributes that have made it emerge as a versatile tool for organic chemistry. First of all, it displays a regioselectiviy that is mainly directed by sterics, as opposed to electronics, complementing electrophilic aromatic substitution and functional group-directed metalation chemistries. Thus, borylation of aromatic substrates typically occurs at the least hindered position as displayed in the example shown in Scheme 1, which makes C–H activation/borylation an excellent tool for the construction of 1,3,5-trisubstituted arenes.

The large number of aromatic and heteroaromatic substrates studied by our group and others[5-7] have demonstrated the broad functional-group tolerance of Ir-catalyzed C–H activation/borylation. Compounds containing amines, amides, esters, ethers, nitriles and halides have uneventfully been borylated, which suggests that this chemistry could even be employed in late-stages in complex molecule synthesis.

Most importantly, halogen tolerance expands the synthetic utility of borylated arenes. A halide-containing borylated compounds can be readily employed in an amidation,[5h] amination,[5f] Sonogashira coupling, or a C–S forming reaction at the halide position (Scheme 3), moreover the resulting boron-containing product can then be further manipulated.

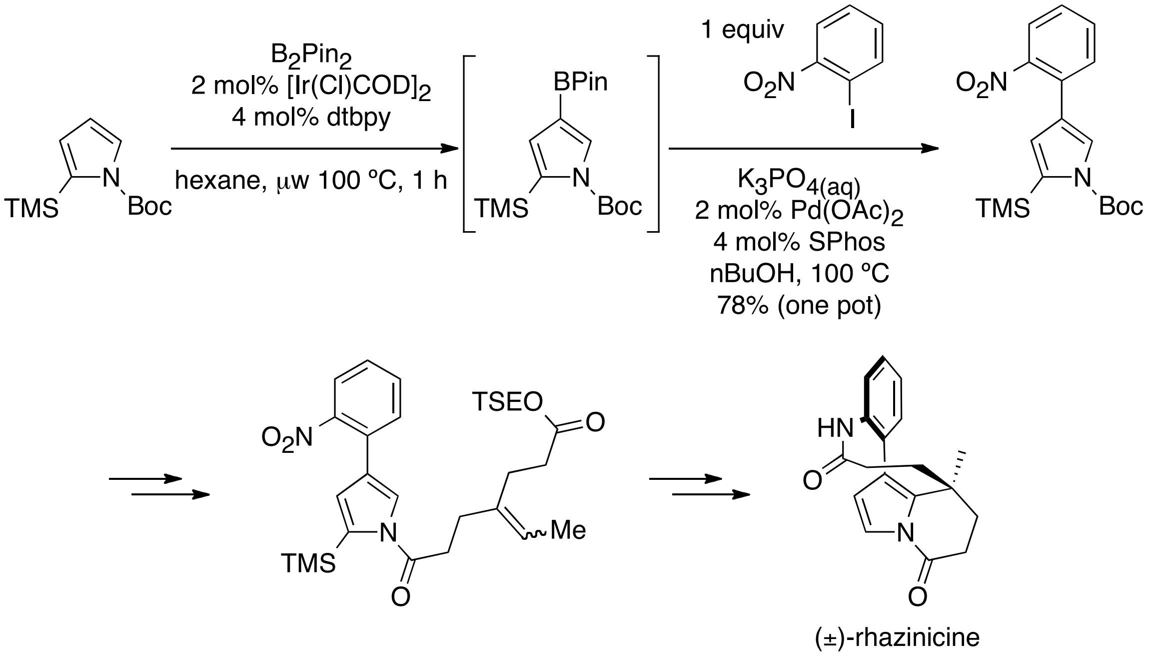


Scheme 3. Synthetic utility of borylated arenes.

Also, C–H activation/borylation proceeds with remarkable cleanliness, which makes it amenable to one-pot transformations. In fact, borylations have been successfully joined with subsequent reactions resulting in the rapid preparation of compounds difficult to access by other means. Some examples include one-pot borylation/oxidation,[5d] borylation-amination,[5f] and even the three-step borylation-amidation-oxidation.[5h]

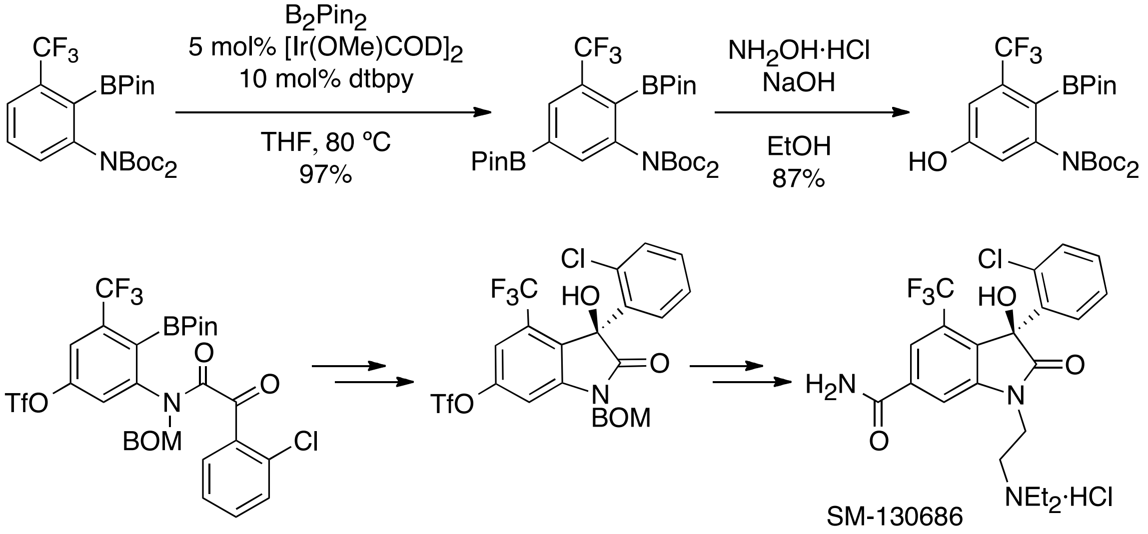
1.3. Applications of Ir-catalyzed C–H activation/borylation

Ir-catalyzed C–H activation/borylation has been featured in a number of recent reports of complex molecule synthesis. For instance, Gaunt's total synthesis of (±)-rhazinicine,[12] started with the borylation of a Boc-protected pyrrole, employing the economical (though less active) precatalyst $[Ir(Cl)COD]_2$ under microwave irradiation (Scheme 4). The pyrrole protecting group sterically directed the borylation to the C3 position,[5k] which would otherwise occur at the C2 position in the absence of Boc.[6d] The TMS group, on the other hand, was rather used to control the selectivity in the late-stage ring-forming Pd-catalyzed C–H alkenylation. The resulting borylated compound was subsequently subjected to Suzuki coupling to install the rhazinicine biaryl system in a one-pot manner with excellent yield to two steps.



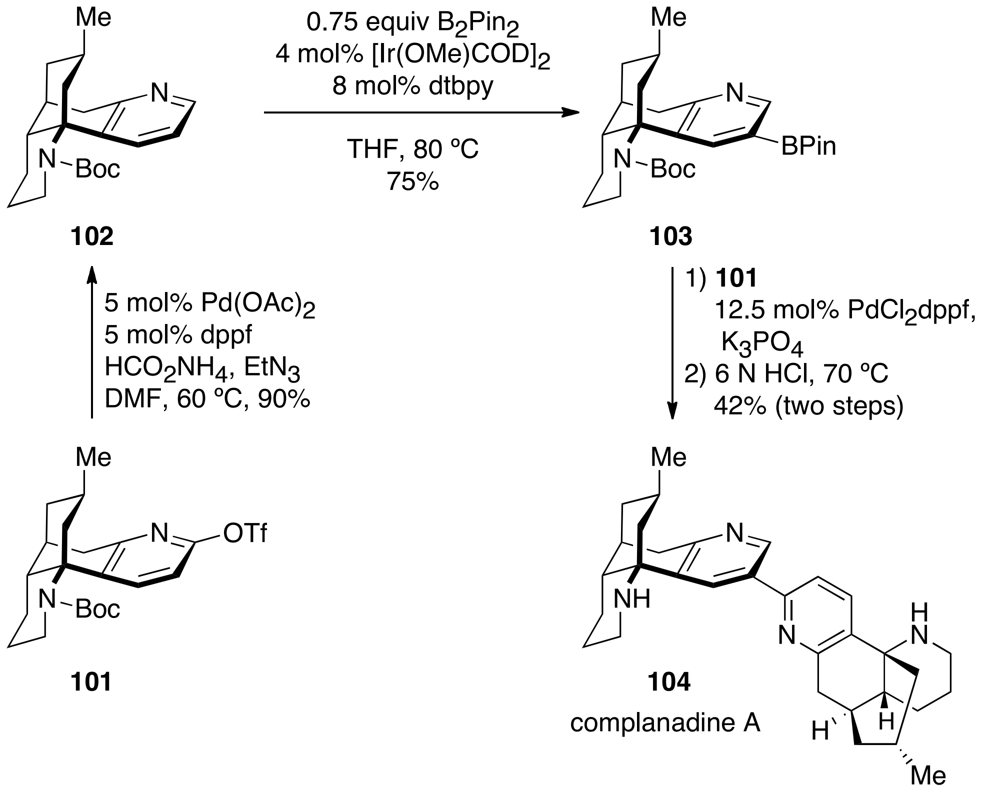
Scheme 4. Gaunt's synthesis of (±)-rhazinicine.

Shibasaki and Kanai[13] also utilized Ir-catalyzed C–H activation/borylation in their recent synthesis of SM-130686 (Scheme 5). Interestingly, the borylation substrate, prepared in four steps from a commercially available arylboronic acid, already contained a pinacolboryl group. The resulting diborylated arene was subjected to hydroxylamine-promoted oxidation,[14] which afforded a monooxidation of the most sterically available boron group with excellent yield and selectivity.



Scheme 5. Shibasaki and Kanai's total synthesis of SM-130686.

In the most recent illustration, Sarpong's total synthesis of complanadine A,[15] borylation took place, remarkably, at a late stage in the synthesis (Scheme 6). Thus, the triflate group of an advanced intermediate (**101**) was removed under Pd-catalyzed reducing conditions to afford **102**. Pyridine **102** was then subjected to Ir-catalyzed borylation to selectively afford a 3-borylated intermediate **103**. Most interestingly, this borylation product was used in a Suzuki coupling with the original advanced triflate **101**, followed by Boc deprotection to afford the desired natural product complanadine A in an outstandingly clever manner.



Scheme 6. Sarpong's synthesis of complanadine A.

These three applications of Ir-catalyzed borylation in the preparation complex molecules are great illustrations of its synthetic value, exploiting in all cases its remarkable regioselectivity. Besides, Gaunt also exemplified the amenability of Ir-catalyzed borylation to one-pot transformations, whereas Sarpong provided an excellent instance of its late-stage applicability.

Even though there are examples of the application of Ir-catalyzed C–H activation/borylation in the construction of complex molecules, reports of this sort are still rare. The three examples shown are, in fact, recent. Given the synthetic potential discussed herein and the considerable work on improvements and adaptations of this chemistry carried out in the last decade,[5-7] we anticipate that diverse applications will be reported in the near future.

In this thesis, four main projects will be discussed, which highlight different synthetic attributes of Ir-catalyzed C–H activation/borylation. For starters, halogen tolerance is featured in our diversity-oriented route to the COX-2 inhibitor DuP 697 and a series of analogs (Chapter 2), which we considered is just one demonstration of the exploitability of building blocks that are easily accessible via C–H activation/borylation.

A gentle Ir-catalyzed *deborylation* method developed in our laboratories has permitted the preparation of heteroaromatics with uncommonly placed boronate groups via diborylation/monodeborylation.[16] A particular tryptophan-based building block prepared in this manner has been utilized in model studies toward the development of a novel convergent route to the TMC-95 core (Chapter 3).

Furthermore, the same mild deborylation procedure was tailored for the synthesis of site-selective deuterium-labeled compounds from borylated arenes (Section 2.2). Considering that site-specific deuteration methods[17] usually require halogen/organometallic functionalities, the broad functional-group tolerance of Ir-catalyzed C–H activation/borylation is certainly valuable in the application of this method.

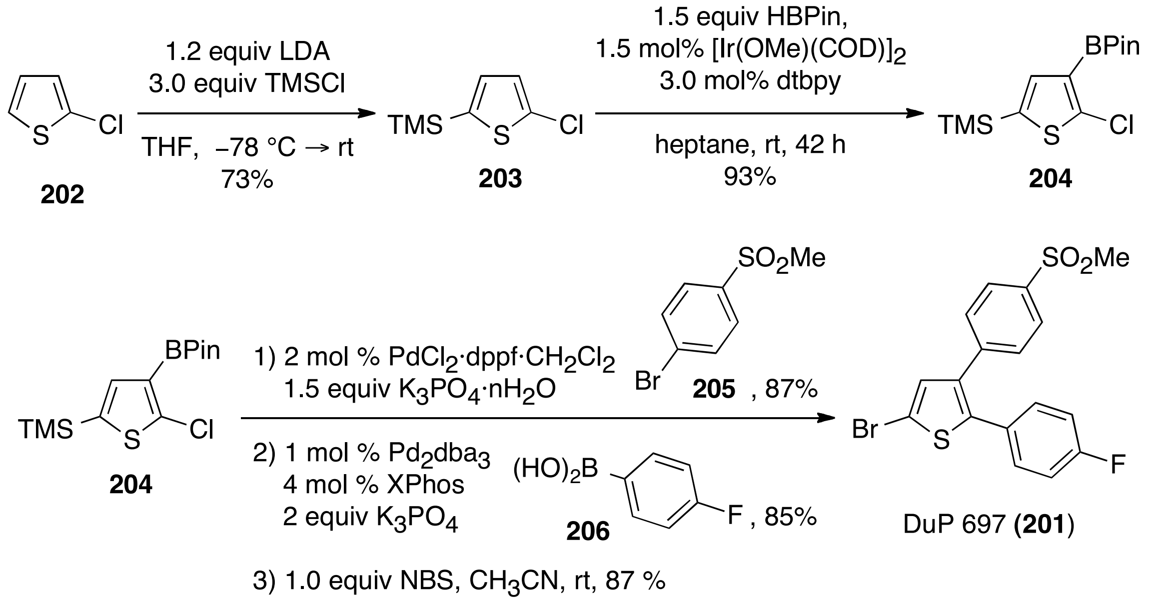
Finally, we aimed at evaluating the efficiency of our C–H activation/borylation/amidation/oxidation method in complex molecule synthesis, which turned out to be successful. Our efforts until now, have provided an unprecedented rapid assembly of the full carbon network of the Hsp90 inhibitor autolytimycin (Chapters 4–7).

Chapter 2. Synthesis of the COX-2 inhibitor DuP 697 and related studies

2.1. Synthesis of DuP 697 and analogs via C–H activation/borylation–Suzuki coupling

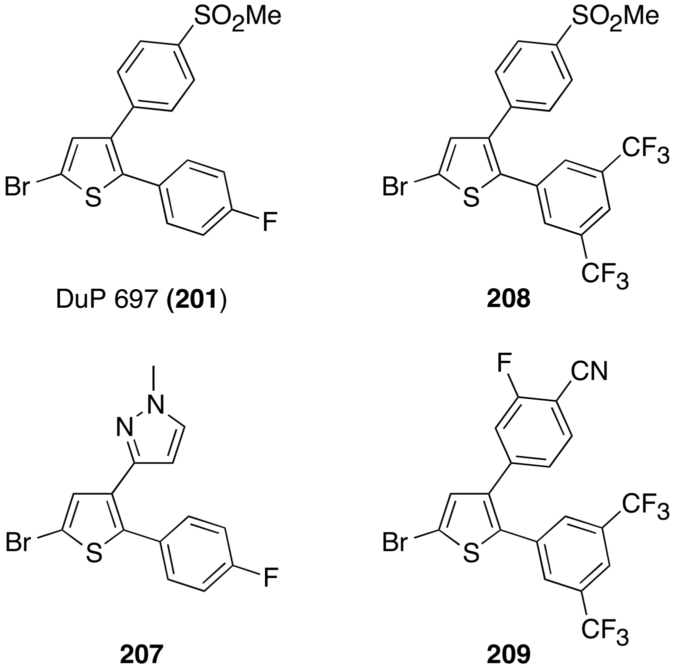
DuP 697 (**201**) is one of the first members of a series of 2,3-diarylthiophenes reported to selectively inhibit the cycloxygenase-2 (COX-2) enzyme.[18] COX-2 plays a key role in prostaglandin biosynthesis in inflammatory cells and in the central nervous system so its inhibition results in analgesic and anti-inflammatory activity.[19]

Scheme 7 shows our diversity-oriented route to DuP 697. Halogen tolerance, one of the most valuable features of Ir-catalyzed C–H borylation, makes possible the construction of **204**, a building block that contains both halogen and boron functionalities. Preparation of **204** and other synthetically useful thiophene-based scaffolds via C–H activation was reported recently by our group.[5i]



Scheme 7. C–H activation/borylation–Suzuki coupling-based synthesis of DuP 697.

Given the excellent chemoselectivity achievable in Suzuki couplings, it is possible to attach two different aromatic groups to the thiophene core. Coupling of **204** to an aromatic bromide (**205**) proceeds under standard conditions while the chloro substituent remains as a spectator. Then, a successive coupling with **206** at the less reactive chloro-substituted position can be carried out under conditions developed by Buchwald,[20] thus furnishing a diarylated thiophene. The TMS group, which was used as a steric director for the C–H activation/borylation step (**203** to **204**), can be easily replaced with a bromo substituent via electrophilic aromatic *ipso*-substitution as a final step. Preparation of DuP 697 (**201**) via this route was performed by Dr. Venkata Kallepalli,[16] who demonstrated a remarkable 42% overall yield for 5 steps from commercially available and inexpensive 2-chlorothiophene (**202**).



DuP 697 (**201**)

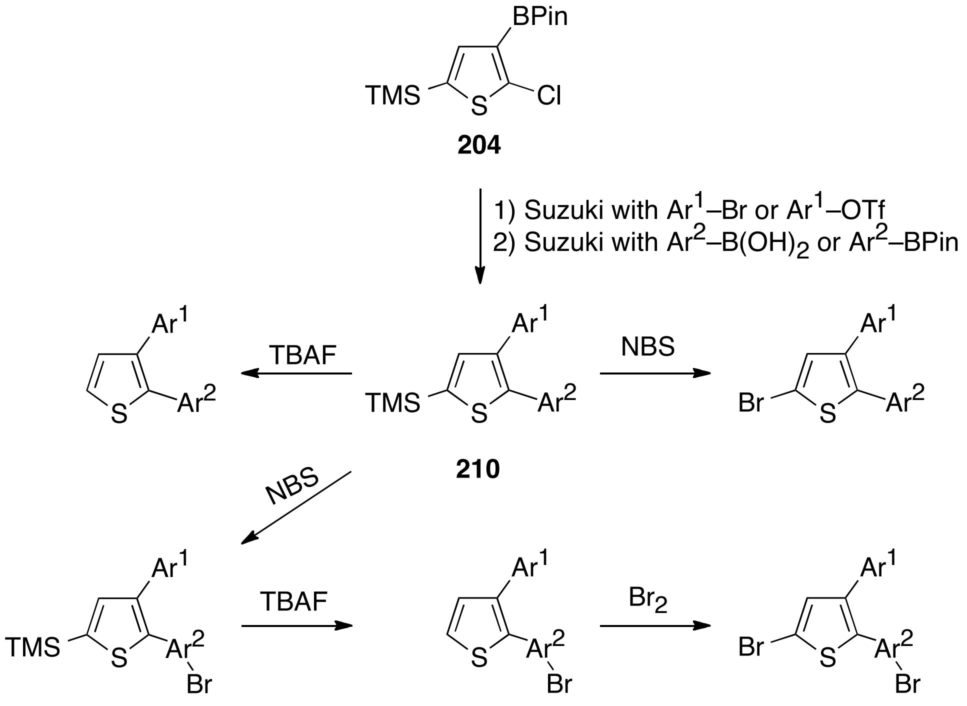
208

207

209

Figure 1. DuP 697 and three basic analogs.

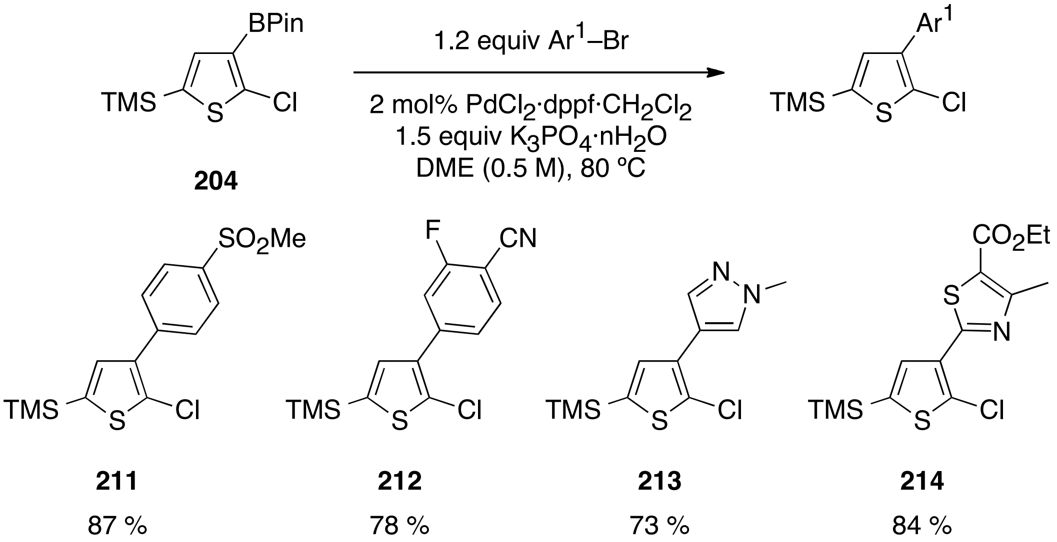
This route is characterized by its ability to generate a diverse array of analogs.[21] For instance, heterocycle- (**207**) and trifluoromethyl-containing[22] (**208**, **209**) versions of **201**, as the ones shown in Figure 1, are interesting in terms of their potentially enhanced bioactivity. We aimed at introducing as much variation as possible into our analog library and, thus, a series of compounds were prepared following the aforementioned sequence, where **204** was sequentially diarylated at the C3 and C2 positions to form intermediates **210** and, from there, various types of analogs were synthesized as displayed in Scheme 8.



Scheme 8. Preparation of various types of DuP 697 analogs.

For the installation of the first aryl substituent, conditions to which aromatic chlorides are known to show low or no reactivity[23] were required. We opted for $PdCl_2 \cdot dppf$ as catalyst since it is less air-sensitive and more efficient than other monodentate or bidentate phosphine ligand-containing systems.[24] Activation of aromatic chlorides by the Pd-dppf catalyst is limited to very few specific substrates[25] and there are previous examples in the literature where their *unreactivity* has been exploited for the preparation of chlorine-containing substances.[26]

Scheme 9 shows the preparation of a first set of monoarylated thiophenes with four diverse commercially available bromide partners. While the coupling reaction itself worked flawlessly and chemoselectively, it was found that TMS removal could occur when the reaction was run at temperatures higher than 80 ºC and after prolonged reaction times (> 12 h). Fortunately, full conversion was observed in all the cases usually after 2.5 hours to provide the desired Suzuki products with high yields.



204

211 87 %

212 78 %

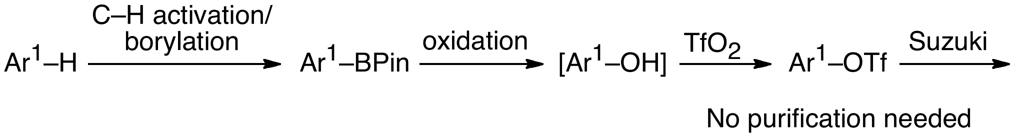
213 73 %

214 84 %

Scheme 9. Examples of 3-arylations in the preparation of DuP 697 analogs.

It is important to mention that the aryl partner used for the 3-arylation could as well be a triflate. In all cases, complete chemoselectivity was maintained. Mr. Hao Li demonstrated that while Suzuki couplings with aryl and heteroaryl triflates required additional time (2–6 h),[21] under these conditions there was no evidence of reaction at the chloro-substituted position in any case.

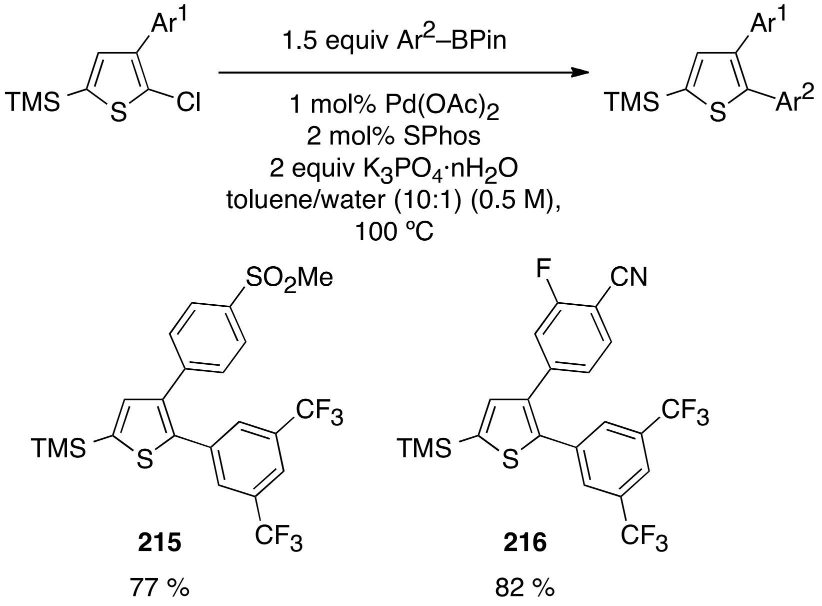
More importantly, the aryl triflates used in those couplings were generated from borylated arenes and directly used in the Suzuki reactions without need of purification (Scheme 10).



$$\mathrm{Ar^1{-}H} \xrightarrow{\text{C–H activation/ borylation}} \mathrm{Ar^1{-}BPin} \xrightarrow{\text{oxidation}} [\mathrm{Ar^1{-}OH}] \xrightarrow{\mathrm{TfO_2}} \mathrm{Ar^1{-}OTf} \xrightarrow{\text{Suzuki}}$$

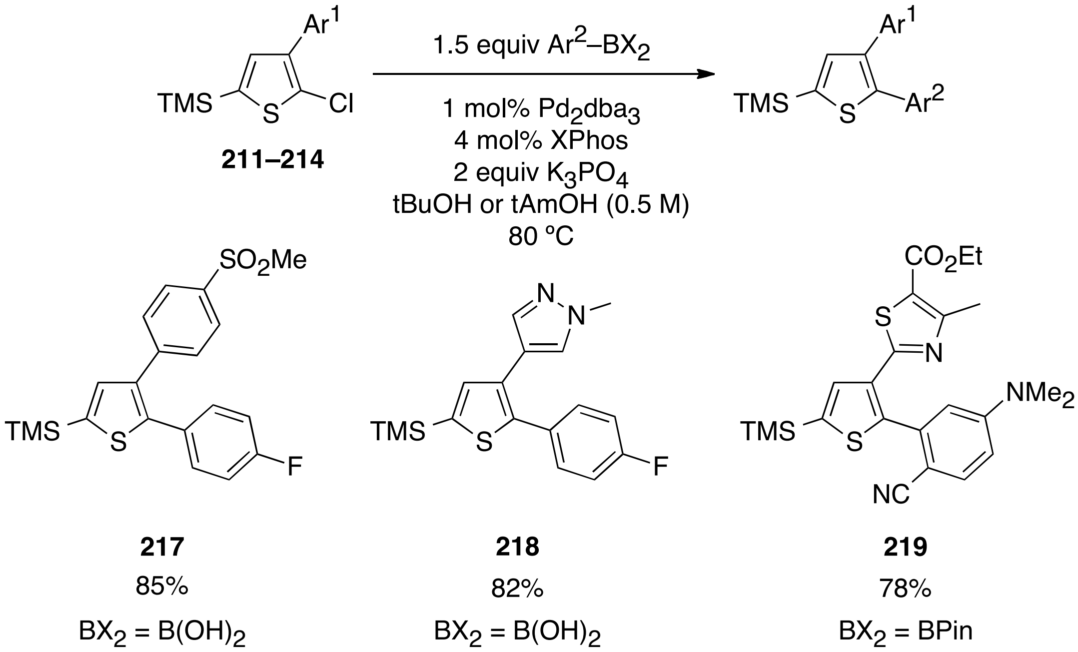
Scheme 10. C–H activation/borylation-based preparation of triflate Suzuki partners.

For the installation of the second aryl substituent, Buchwald's biaryl ligands[27] provided the right conditions to activate the chloro-substituted position. Among multiple examples found in the literature, two specific procedures, described below, were tested.



Scheme 11. 2-Arylations in the preparation of DuP 697 analogs via Suzuki coupling under "wet" conditions.

Under "wet conditions" with $Pd(OAc)_2$, SPhos, hydrated base, and toluene/water as solvent (Scheme 11), reactions were quite rapid (30 min to 1 h) but borylated partners (Ar^2-BPin) were particularly susceptible to protodeborylation. In some cases (e.g., **219**, *vide infra*), it appeared that the reaction did not proceed to completion because at a certain point there was no more borylated partner available. In instances where protodeborylation was not an issue, this procedure permitted a quick and efficient preparation of diaryl thiophenes such as **215** and **216**,[a] among others,[21] in good yields.



Scheme 12. 2-Arylation in the synthesis of DuP 697 analogs via Suzuki coupling under "dry" conditions.

On the other hand, under "dry conditions" with $Pd_2(dba)_3$, XPhos, anhydrous base, and a tertiary alcohol as solvent (Scheme 12), efficient but slower (2–6 h) reactions were observed. Nonetheless, the competing protodeborylation was slower too, allowing the full consumption of the chlorothiophene starting material with 1.5 equiv of borylated partner.

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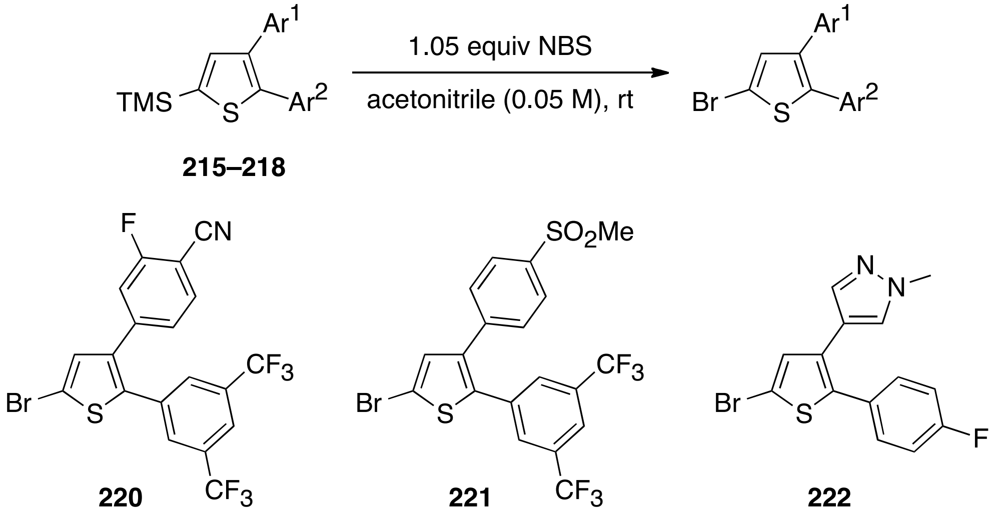
[a] Preparation of **215** and **216** was performed by Mr. Nathan Gesmundo.

Protodeborylation under Suzuki conditions is a well documented issue.[9] In the preparation of **219**, the boron-containing partner was fully consumed and its deborylated form was isolated during the purification stage. It appears likely that its tendency toward deborylation is the due to the presence of the cyano substituent *ortho* to the BPin group.[b]



215–218

220 66%

221 77%

222 76%

Scheme 13. Bromination step in the preparation of DuP 697 analogs

For the bromination step, in most cases, reaction of the diarylated compounds with 1 equiv of NBS in acetonitrile[28] efficiently gave the desired final bromination products via *ipso*-substitution (Scheme 13).[c] However, analogs with unusually placed bromo substituents (Scheme 14) were obtained quite efficiently due to the presence of specific electron-rich positions on the

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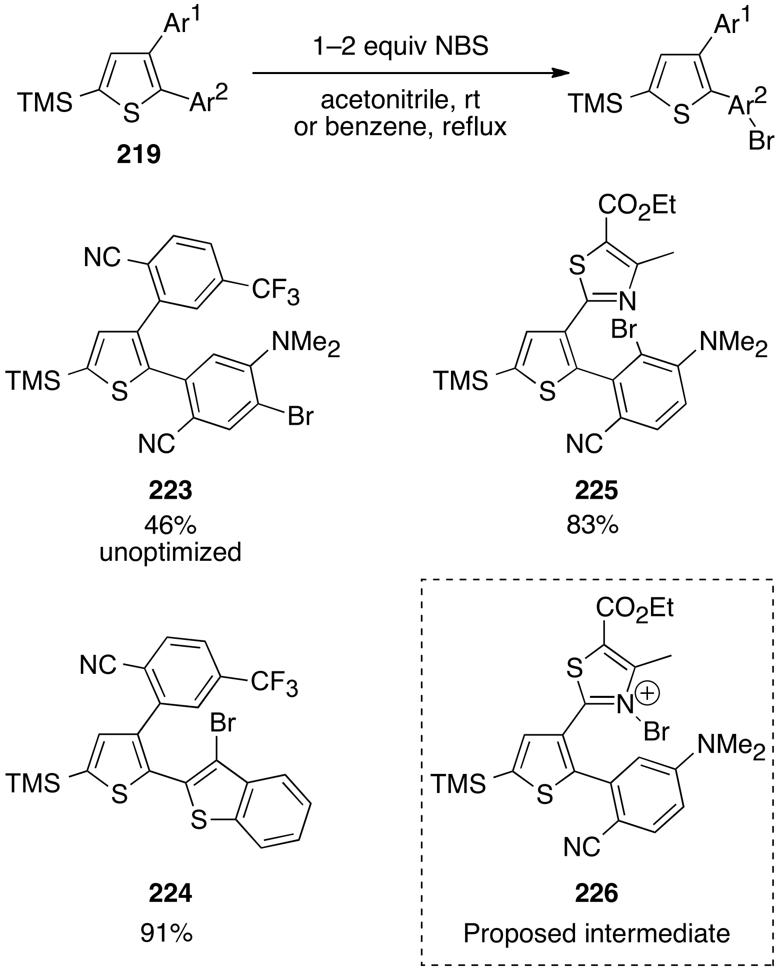
[b] 2-Alkenyl and 2-formyl arylboronic acids are known to readily undergo protodeborylation under Suzuki coupling conditions.[9] A similar behavior could be expected for a 2-cyano arylboronate.

[c] Acetonitrile significantly enhances the activity of NBS as a source of Br$^+$.[28]

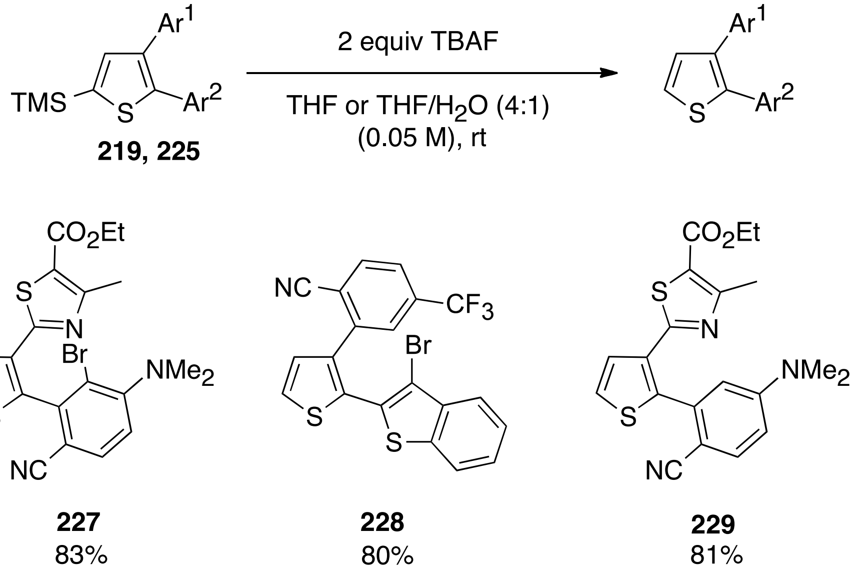
aryl substituents more reactive toward electrophilic aromatic substitution than the thiophene 5-position. Surprisingly, complete selectivity was observed in all cases and formation of other isomers was not detected.



Scheme 14. Bromination of diarylated thiophenes at unusual positions in the preparation of DuP 697 analogs.

Analog **225** presented an interesting case (when compared to **223**) since bromination occurred at the least sterically available position and this isomer was found to be the only product in the crude material by ^{1}H NMR. Moreover dibromination was not observed when excess NBS was employed. While it is reasonable that the single bromination on the dimethylamino-substituted ring would inactivate it toward a second *ortho*-substitution, survival of the TMS group was an interesting observation.[d]

The selectivity observed in the preparation of **225** could be explained in terms of a directed bromination. We consider that this reaction occurs most likely via intermediate **226**, where the *N*-bromo cation could presumably be stabilized by *both* sulfur atoms, partially distributing its positive charge through the thiophene ring as well. This would explain why the TMS group survives the reaction conditions. Interestingly, attempts to over-brominate isolated **225** (and **227**, *vide infra*) with NBS or Br_2 were unfruitful, which supports the proposed formation of an *N*-bromo intermediate that inactivates the system toward further substitution.



Scheme 15. Preparation of 5-unbrominated DuP 697 analogs.

Lastly, given that derivatives of DuP 697 where the bromo substituent is absent are known to be selective for COX-2,[18c,d] we also prepared a series of non-brominated analogs[21] via TBAF-

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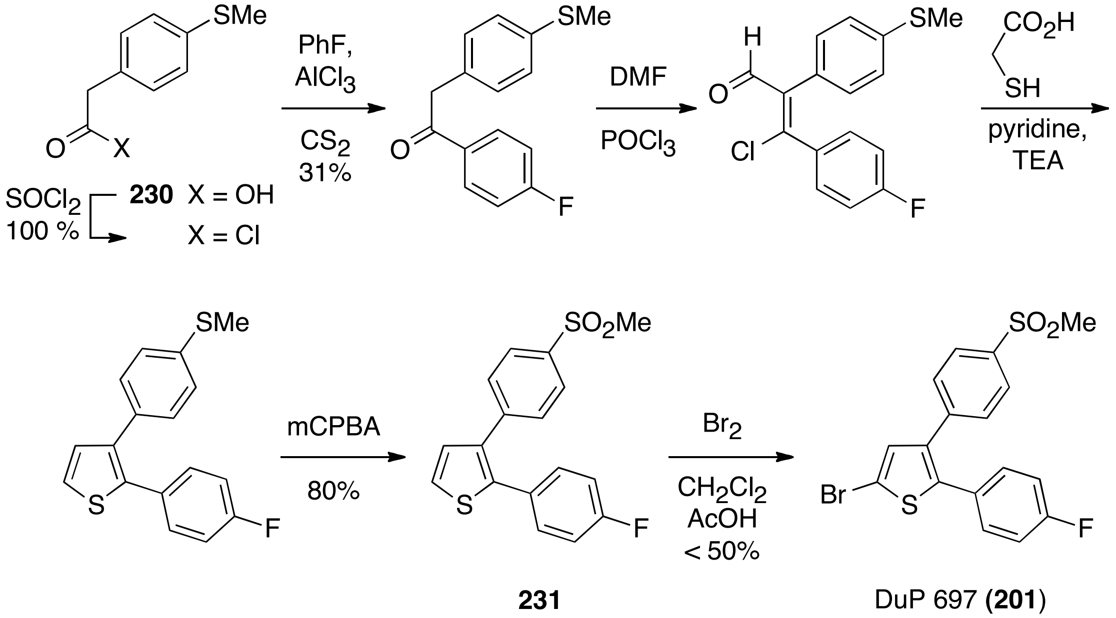
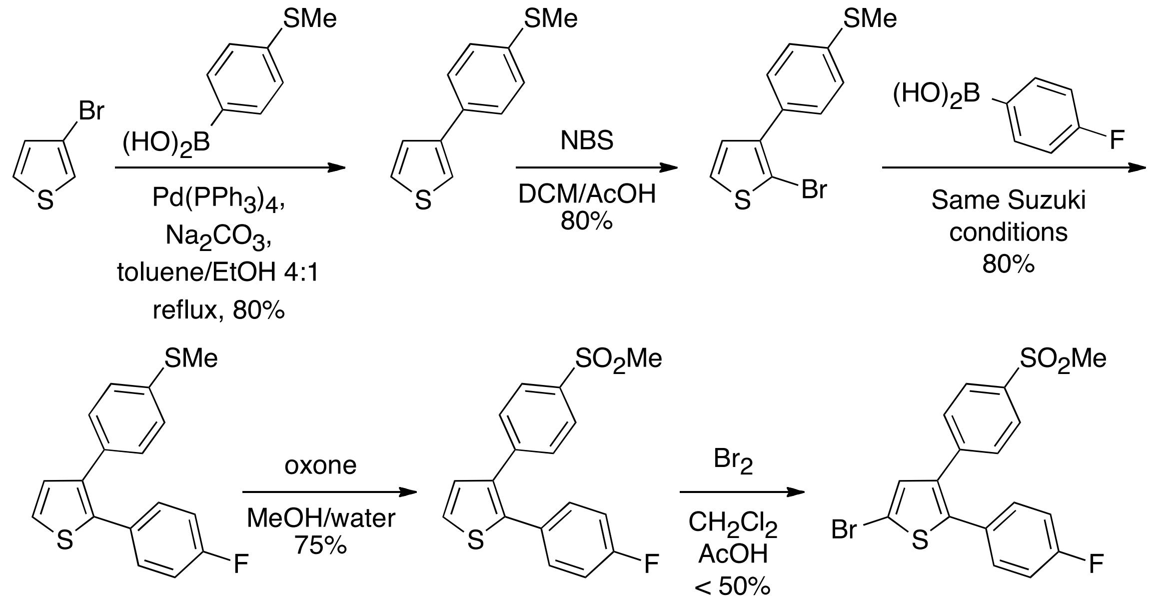
[d] The same was observed for **223** and **224**, compounds prepared by Mr. Hao Li.

mediated desilylation at C5 (Scheme 15). This transformation worked uneventfully and provided the desired analogs in very good yields.



Scheme 16. Original linear synthetic route to DuP 697.

The presented approach permitted the preparation of over 25 analogs, some of which exhibited good activity in a COX-2 screen.[29] Synthesis of these molecules would not have been viable by using the original synthetic route[18a] to DuP 697 (Scheme 16) or the second-generation route[18d] (Scheme 17). The original approach was rather linear, relied on the availability of appropriate arylated acetic acids (like **230**), and involved transformations, such as a Friedel-Crafts acylation, that are not functional group-tolerant. Furthermore, introduction of the aryl substituents occurred right at the beginning of the synthetic sequence and before the thiophene ring was formed, which is far from being SAR-friendly.



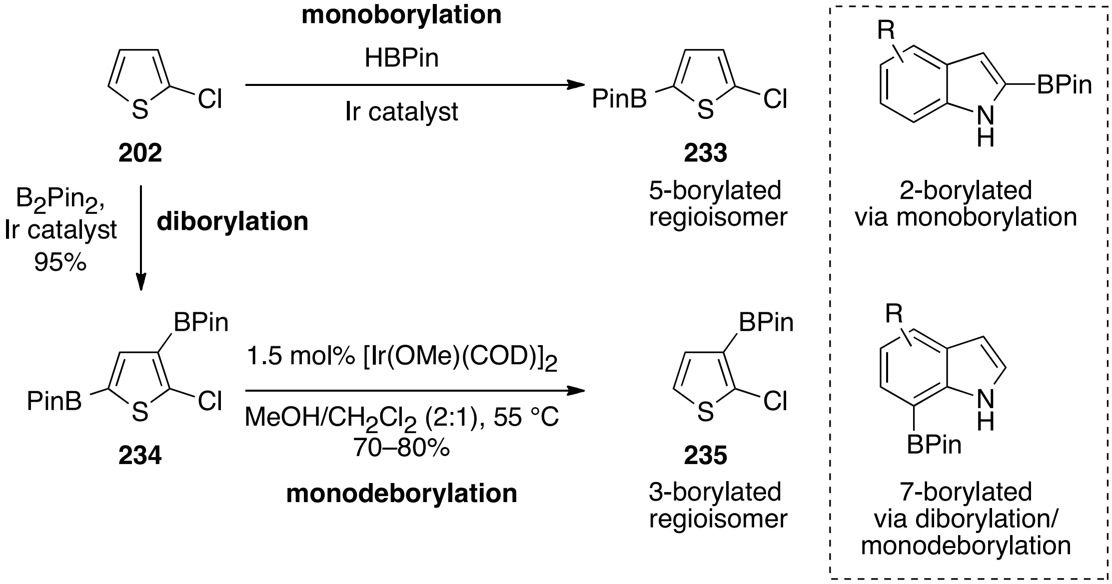
231 **232** DuP 697 (**201**)

Scheme 17. DuPont's improved route toward DuP 697.

Shown in Scheme 17 is an iterative bromination/Suzuki coupling-based approach to DuP 697 reported by DuPont.[18d] The key step, bromination at the thiophene 2-position (required for the second coupling), intrinsically relies on its being the most nucleophilic center in the structure. However, it is clear that an EAS reaction could as well occur on the aryl substituents. In fact, on the thiophene ring itself, 2- or 5-bromination could take place[30] and this would largely depend on the nature of the aryl substituent. An electron-poor aryl would be unreactive to EAS but would likely direct the bromination to the thiophene 5-position due to sterics. Conversely, an electron rich aryl could direct the substitution to the 2-position but would compete in the bromination reaction. This situation certainly limits the applicability of this route in the preparation of analogs. In this route to DuP 697 (Scheme 17), the authors introduced the electron-poor methanesulfonylphenyl substituent as a methylthiophenyl group (electron-rich, apparently to favor the subsequent 2-thiophene bromination) and performed an oxidation at a later stage. We found that installation of Ar^1 via Ar^1–X (X = Br, OTf) (Scheme 8) widely expands the diversity that can be introduced into the system. For instance, the thiazole bromide used in the preparation of **214** (Scheme 9) is commercially available, while the corresponding boron compounds are unknown.

Thus, the preparation of DuP 697 (**201**) and analogs hereby presented clearly serves as an example of the synthetic flexibility that can result from combining Ir-catalyzed C–H activation/borylation and Suzuki cross-couplings. An alternative preparation procedure will be presented in Section 2.3.

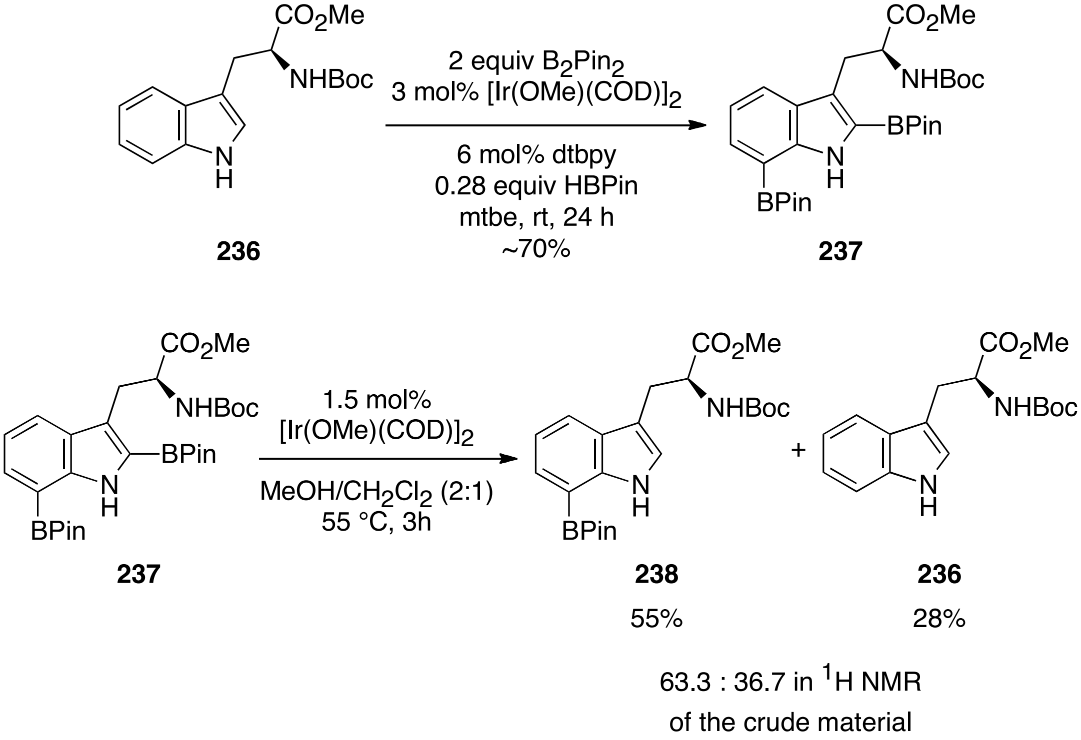
2.2. Access to uncommon borylated regioisomers and selective deuteration via C–H activation/borylation–deborylation



Scheme 18. Diborylation/monodeborylation of thiophenes and indoles.

Heterocycles react under Ir-catalyzed C–H activation/borylation conditions[5g,5i,6d,6h] generally faster than arenes and display heteratom-directed selectivities as exemplified by **233** (Scheme 18), prepared by monoborylation of 2-chlorothiophene **202**. Subjecting these substrates to stronger borylation conditions, higher temperature, or excess of HBPin/B_2Pin_2 leads to the formation of diborylated products, such as **234**. With molecules like **234** in hand, it was found by Dr. Venkata Kallepalli[16] that catalytic $[Ir(OMe)(COD)]_2$ in methanol/DCM (2:1) could efficiently perform a selective protodeborylation and, most interestingly, that the first pinacolboryl group installed via C–H activation/borylation becomes the first one to be removed in this process.

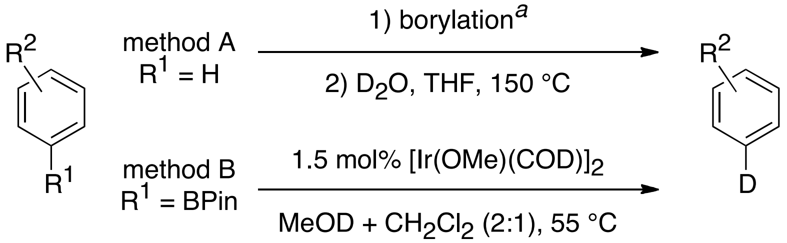
In this manner, monodeborylation of diborylated heterocycles allows access to uncommon boron-containing regioisomers. Of particular interest to us were 3-borylated thiophenes (See Section 2.3) and 7-borylated indoles (See Chapter 3).



Scheme 19. Preparation of a 7-monoborylated tryptophan derivative.

For purposes described in Chapter 3, we required an efficient preparation of a 7-monoborylated tryptophan derivative (Scheme 19, for the optimization see Table 2), attainable via deborylation of **237**. In order to facilitate the isolation of the desired product, it was preferred to allow the reaction to run for an extended period of time (3 h) to ensure full consumption of **237** even though dideborylation took place. Remaining **237** only complicated the isolation step. After 3 h, the crude material thus obtained consisted of a clean 63:37 mixture of desired product **238** and recovered **236**, which was easily separable by filtration through silica gel eluting with dichloromethane. Interestingly, 7% of dideborylation is observed after only 1 hour of reaction (Table 2), while half of the diborylated compound is still intact. Such an easy deborylation at the "less heteroaromatic" 7-position was intriguing, so we wondered if this method could be used for the deborylation of borylated arenes, as opposed to heteroarenes. In this endeavor, we explored the possibility of using deborylation as a method for deuterium labeling. This type of transformation had already been demonstrated by Dr. Feng Shi,[31] who found that crude materials from borylation reactions could be treated with D_2O (See Table 1, method A) at high temperature to afford the corresponding deuterated arenes. It was verified that high temperature was important to ensure a fast and complete conversion, so it was unclear if the drastically milder conditions presented above would work at all for this sort of substrates. However, we were glad to confirm that, in fact, subjection of purified borylated compounds to $[Ir(OMe)(COD)]_2$ using CD_3OD/DCM (2:1) as solvent (Table 1, method B) at 55 ºC, provided the desired deuterated products in good yield with percentages of deuterium incorporation (determined by GC-MS) higher than 95% in most cases. The required reaction times for each substrate were estimated by running the reaction in a mixture in $CD_3OD/CDCl_3$ (2:1) and monitoring the progress by ^1H NMR. When CD_3OD/DCM (2:1) was used, reactions were allowed to continue for slightly longer time to ensure full conversion. This *modus operandi* was preferred since monitoring the reaction by TLC, and thus exposing the reaction mixture to air, was *not* an option. Preliminary experiments established that solvent degassing was essential for this reaction to work. Furthermore, a number of experiments suggested that the catalyst effectively “died” due to exposure to air and no more conversion was detected. This fact implies that the transformation is truly catalyzed by Ir and that deoxygenation of the solvent is indispensable for the survival of the catalyst.

Table 1. Deuterodeborylation of various borylated arenes.



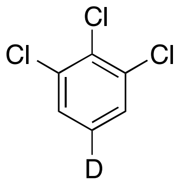
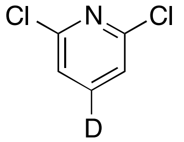
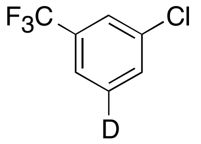
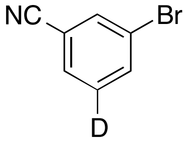
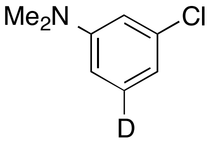
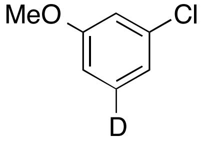
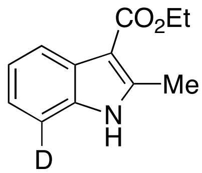
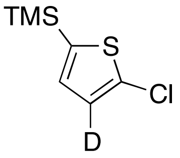
entry	product	Method A[31] borylation conditions[a]	 deuteration time[b]	 yield[c]	Method B deuteration time	 yield[c]
1		1.8 equiv HBPin, 3.25 h	1 h	95%	5.5 h	85%
2		1.8 equiv HBPin, 3.25 h	1 h	89%	19 h (69% conversion)	-
3		1.8 equiv HBPin, 3 h	1.5 h	67%	4 h	69%
4		1.5 equiv HBPin, 6 h	2 h	69%	8 h	74%

Table 1 (cont'd)

entry	product	Method A[31]			Method B	
		borylation conditions[a]	deuteration time[b]	yield[c]	deuteration time	yield[c]
5[d]		2.0 equiv HBPin, 18 h	2 h	92%	10 h	97%
6		1.5 equiv HBPin, 12 h	1 h	88%	6 h	67%
7					1.5 h	96%
8					0.5 h	89%

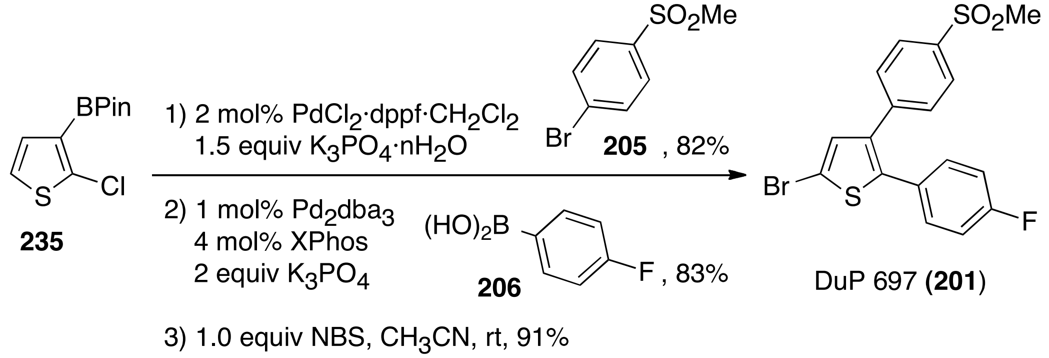
[a] 2 mol% (Ind)Ir(cod)-dmpe at 150 °C for entries 1–5; 1.5 mol% $[Ir(OMe)(COD)]_2$, 3 mol% dtbpy at room temperature for entry 6. [b] 0.5 mL D_2O (~11 equiv) and 3–4 mL THF or DME were added to borylation crude material. [c] Isolated yields, average of two runs. [d] Deuteration for method A was carried out in the presence of 0.5 equiv Ac_2O.

Two additional substrates (entries 7 and 8) were tested to demonstrate how deborylation of heteroarenes is intrinsically faster as compared to arenes, which turned out to be true. Interestingly, the pyridine substrate (entry 2) was slow and complete conversion was not achievable under our mild conditions. We have not yet elucidated the mechanism by which this reaction takes place and it is definitely worth taking note that a pyridine, which could potentially act as a ligand on iridium, displays lower reactivity.

In this manner, we have proven that C–H activation/borylation/deborylation is an efficient and mild approach to the synthesis of deuterium-labeled compounds. Comparable site-specific deuteration methods[17] usually require halogen/organometallic functionalities, which weakens their functional group-compatibility.

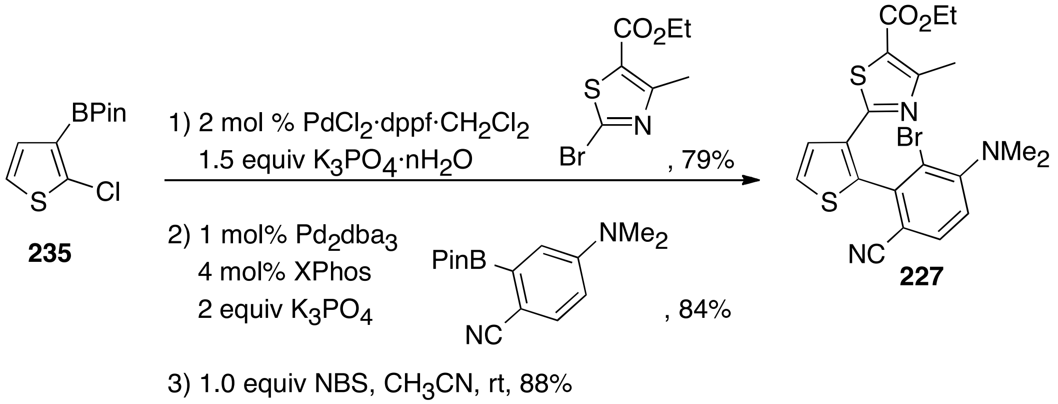
2.3. Second-generation approach to DuP 697 via C–H activation/borylation–deborylation–Suzuki coupling

Access to **235** via diborylation/monodeborylation (Scheme 18) was particularly appealing since we envisioned that it could provide an alternative route to DuP 697 (**201**). In fact, as shown in Scheme 20, building block **235** performed as productively as **204** (Scheme 7) in the two consecutive Suzuki couplings. The use of NBS in acetonitrile[28] proved its efficiency as compared to other traditional bromination conditions (like Br_2 in DCM/AcOH in Scheme 17), providing DuP 697 (**201**) in excellent yield, as in the case of the TMS-substituted substrate.



Scheme 20. Second-generation synthesis of DuP 697.

The use of **235** as starting material instead of **204** is, in addition, convenient since its preparation from **202** proceeds via relatively mild and scalable conditions preferable over silylation via deprotonation with LDA (Scheme 7, page 9).



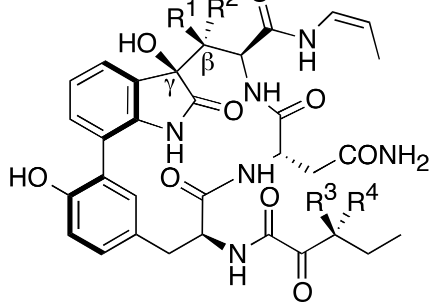
Scheme 21. Preparation of a DuP 697 analog via the second-generation approach.

The new route was tested via the synthesis of one analog. We were pleased to observe that the three-step sequence proceeded with outstanding yields. Not surprisingly, bromination took place displaying the same behavior as in TMS-substituted thiophenes, providing in the case of **227**, an unusually placed bromo substituent.

Chapter 3. Model studies for the synthesis of the TMC-95 core

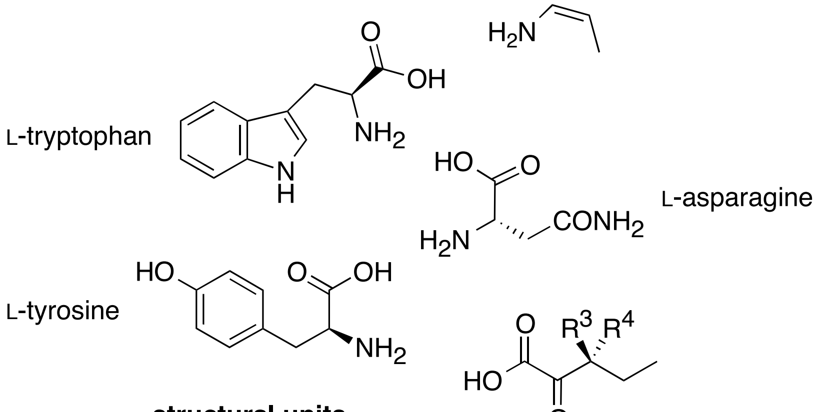
3.1. Target choice and significance

The isolation of TMC-95A−D (Figure 2) from the fermentation broth of *Apiospora montagnei* Sacc. TC 1093 was reported in 2000,[32] introducing a novel family of fungal metabolites with a distinctive cyclic peptide structure composed of L-tyrosine, L-aspargine, a highly oxidized L-tryptophan (containing a β,γ-diol), (*Z*)-1-propenylamine, and 3-methyl-2-oxopentanoic units.



TMC-95

	R^1	R^2	R^3	R^4
A	H	OH	CH_3	H
B	H	OH	H	CH_3
C	OH	H	CH_3	H
D	OH	H	H	CH_3



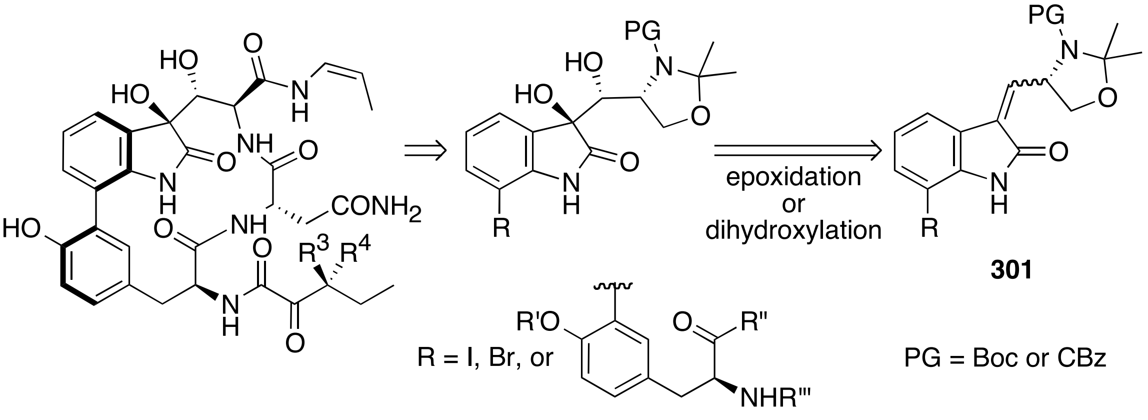
structural units

Figure 2. TMC-95 compounds and their structural units.

There is considerable interest in the TMC-95 family due to their remarkable activity and selectivity as proteasome inhibitors.[33] Such a bioactivity[32b] makes them promising as agents for the treatment of cancer, among other diseases.[34] Rapidly after their isolation, appeared reports of total syntheses[35] of TMC-95 A or mixtures of TMC-95 A and B by three different research groups and a quite a few studies on the preparation of analogs.[36] A substantial number of synthetic steps in those reports are spent in the construction of the indole moiety, as will be discussed in the following section. We hereby present our attempt to exploit Ir-catalyzed C–H activation/borylation as a tool to access these compounds in a more convenient way.

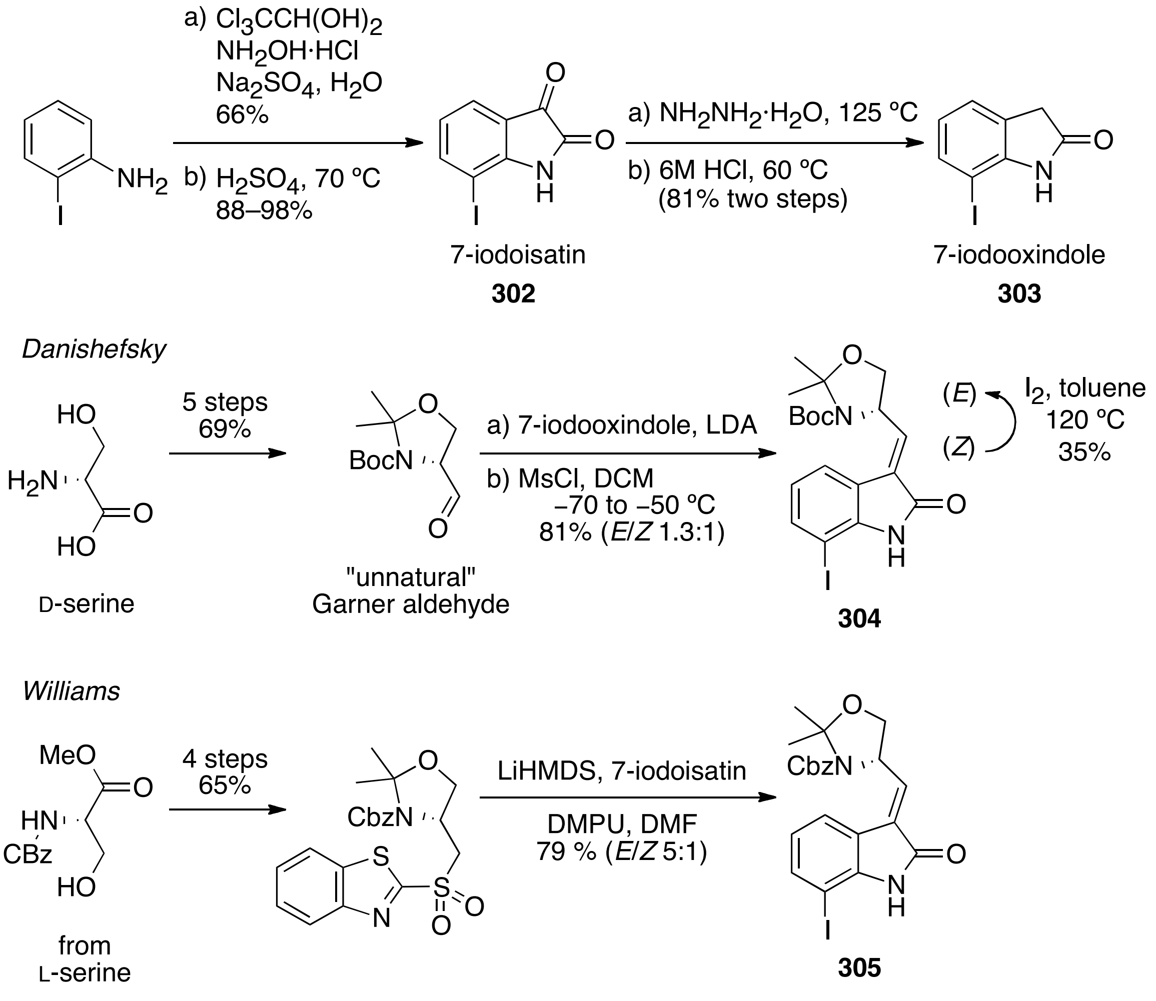
3.2. General analysis of the reported syntheses of TMC-95 compounds

Three research groups have reported total syntheses of TMC-95 compounds, describing two somewhat similar approaches for the synthesis of the β,γ-diol. Namely, Danishesfky[35a-c] and Williams[35d,e] employed a dihydroxylation reaction whereas Inoue and Hirama[35f,g] used an epoxidation (Scheme 22).

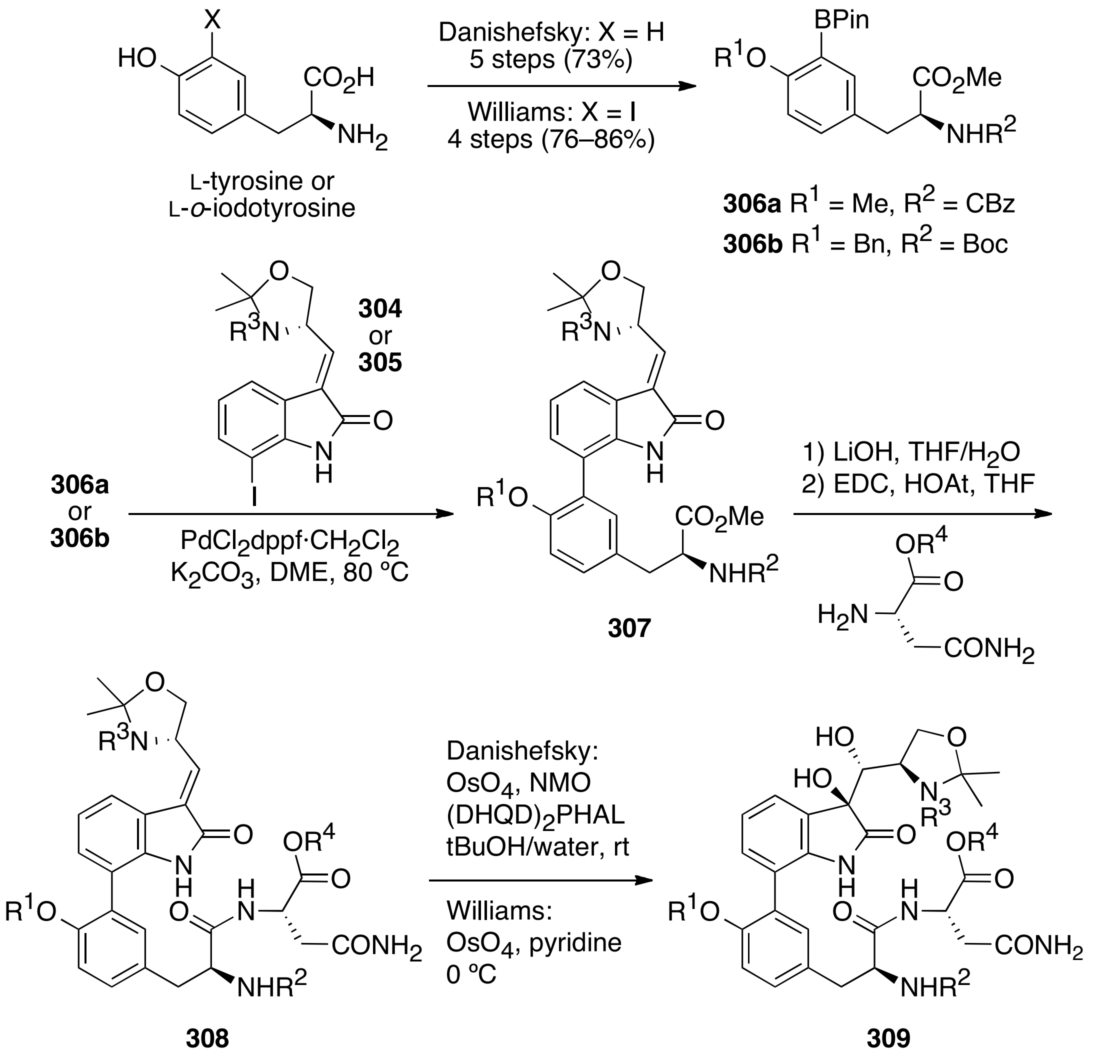


Scheme 22. Access to the β,γ-diol moiety in the total syntheses of TMC-95 compounds.

Preparation of intermediates **301**, however, was tackled in different ways by the three groups. Danishefsky's route (Scheme 23) started with the preparation of 7-iodooxindole (**303**) from *o*-iodoaniline, which was then deprotonated with LDA and added to an "unnatural" Garner aldehyde derived from D-serine. The resulting aldol adduct was mesylated to promote elimination and form the α,β-unsaturated amide. Modest levels of selectivity were observed (*E*/*Z* 1.3:1) in the elimination, thus requiring a recycling isomerization step. This 11-step process (without counting the recycling step) was improved by Williams, who modified it to start from a derivative of *natural* L-serine and to construct the double bond via Julia olefination of 7-iodoisatin (**302**), which gave better selectivity (*E*/*Z* 5:1) and resulted in a more attractive 7-step process.



Scheme 23. Danishefsky's preparation of the oxindole core from D-serine (middle) and Williams' modification from a derivative of L-serine (bottom).

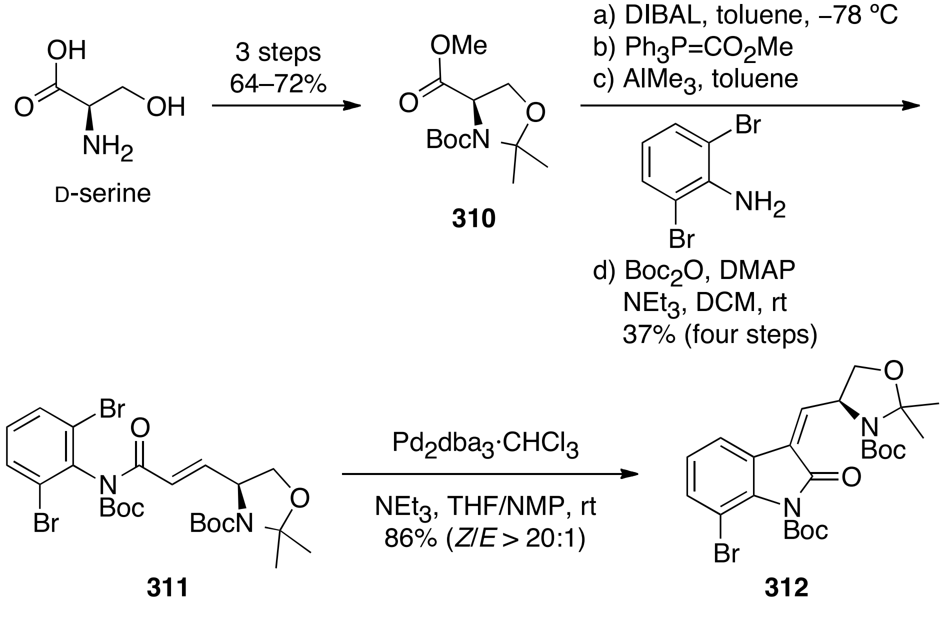


	R^1	R^2	R^3	R^4		yields	
Danishefsky	Me	Cbz	Boc	tBu	75%	85%	88% (5:1 desired/undesired)
Williams	Bn	Boc	CBz	Bn	90%	98%	87% (single isomer, desired)

Scheme 24. A Direct comparison between Danishefsky's and Williams' syntheses of TMC-95 compounds.

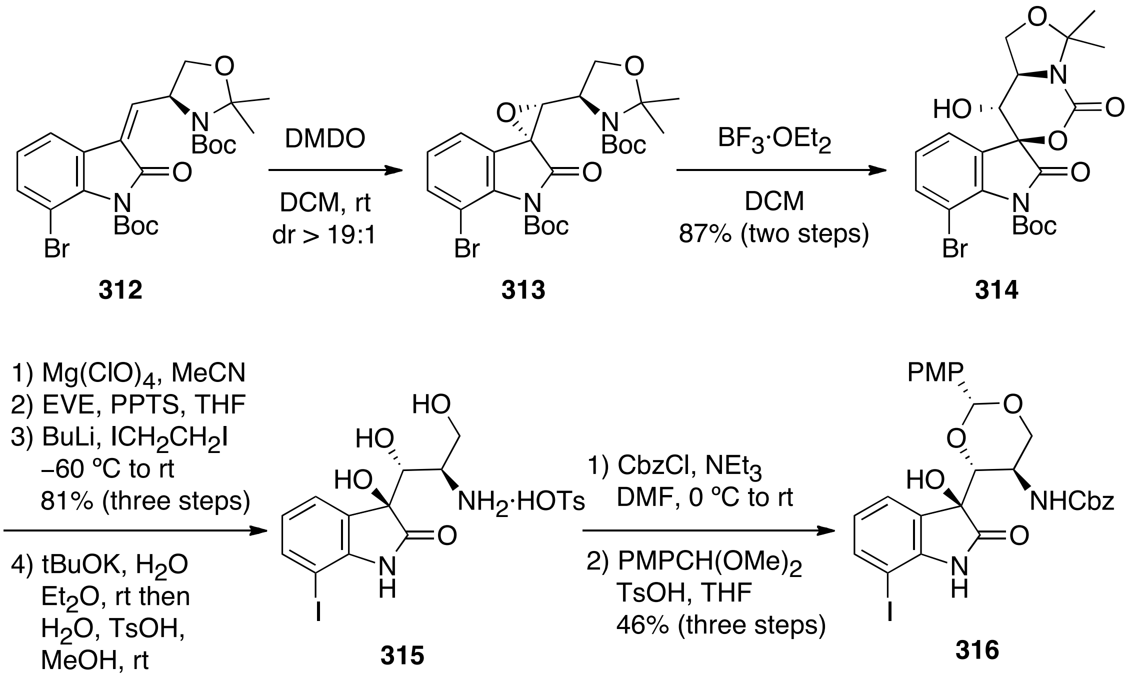
Both Danishefsky and Williams used the resulting intermediates **304** and **305** in the formation of the biaryl system via Suzuki coupling (Scheme 24). Borylated partners **306a** and **306b** were prepared respectively from L-tyrosine and L-*o*-iodotyrosine in a very similar manner. In fact, at this point the two syntheses become basically identical and the only difference is the protective groups employed. Scheme 24 shows a straight comparison between the two; Suzuki cross-coupling and attachment of the L-asparagine unit proceeded uneventfully in both cases, but a prominent difference was observed in the dihydroxylation step. In Danishefsky's case, reaction was run at room temperature to drive the reaction to full conversion and Sharpless' $(DHQD)_2PHAL$[37] was used to improve the selectivity levels, achieving a modest 5:1 ratio of desired and undesired isomers. Williams, on the other hand, reported that dihydroxylation with OsO_4 in pyridine allowed the reaction to occur at 0 ºC, which resulted in complete stereoselectivity.

From the advanced intermediates **309**, a final 1:1 mixture of TMC-95 A and B was obtained by Danishefsky[35a-c] after 13 additional steps, whereas Williams[35d,e] used 9 steps, both featuring entirely different approaches for the formation of the labile (*Z*)-1-propenylamine unit (see Figure 2), but those details will not be discussed here.



Scheme 25. Inoue and Hirama's preparation of the oxindole core from D-serine.

Conversely, instead of a dihydroxylation reaction, Inoue and Hirama[35f,g] employed a face-selective epoxidation for the installation of the β,γ-diol (*vide infra*), again on an α,β-unsaturated amide (**301** in Scheme 22). As shown in Scheme 25 the required *Z* (as opposed to *E*) unsaturated amide **312** was obtained from unnatural D-serine in 8 steps with high selectivity by virtue of a Heck coupling. It is important to mention that the use of exactly the same method was simultaneously attempted by Danishefsky[35a] to construct his intermediate (*E*)-α,β-unsaturated amide **304** with little success.



Scheme 26. Installation of the β,γ-diol moiety via epoxidation in Inoue and Hirama's total synthesis of TMC-95 A.

Thus, subjection of **312** to reaction with DMDO cleanly afforded the epoxidation product **313**, with high levels of selectivity, which was immediately activated by $BF_3 \cdot OEt_2$ to afford **314** in high yield over two steps. The newly stereoselectively installed oxygen atom at the indole 3-

position was originally on the *N*-Boc protective group. This transformation was out of the ordinary but, as shown in Scheme 26, required additional manipulation and hence more steps in comparison to Danishefsky and Williams' route. Moreover, the authors exchanged the 7-bromo for an iodo substituent *for an effective biaryl coupling* but no supporting details were given.[35f,g] Subsequent steps with **316** were performed in a similar manner as in the other two reports; specifically, Suzuki coupling, attachment of the L-asparagine unit, and manipulations, completing the total synthesis of TMC-95 A after 20 additional steps. An important contribution of Inoue and Hirama's synthesis was the installation of the (*Z*)-1-propenylamine unit from L-allothreonine benzyl ester; this creative idea was later exploited by Williams.[35e]

Besides the total synthesis work, there have been a considerable number of reports on the preparation of TMC-95 analogs, particularly coming from the Moroder[36a-f] group, who has worked on structural modifications based on the information provided by the crystal structure of the 20S proteasome–TMC-95 A complex.[38]

Moroder demonstrated that the intricate structure of TMC-95 A could be significantly reduced while maintaining good levels of activity.[36b] Scheme 27 shows the preparation of a simplified analog: First, Suzuki coupling of 7-bromo-L-tryptophan derivative **317**[e] with Danishefsky's[35a] intermediate **306a** afforded biaryl **318**[f] and to it was attached the L-serine unit. It is important to

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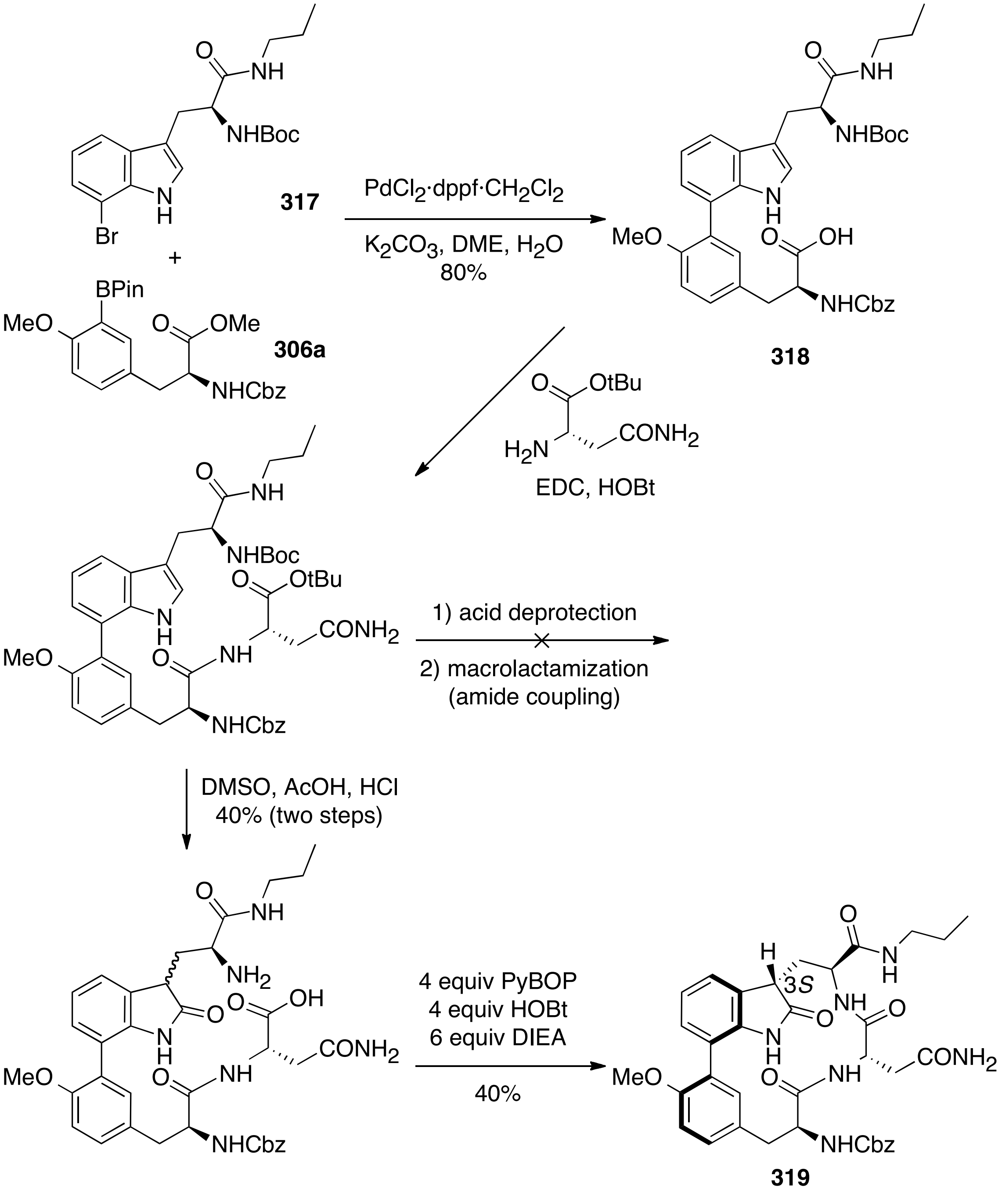
[e] See Scheme 29 for the method used to access 7-bromo-L-tryptophan.

[f] The authors did not discuss the methyl ester hydrolysis, which is not likely to occur under Suzuki conditions.

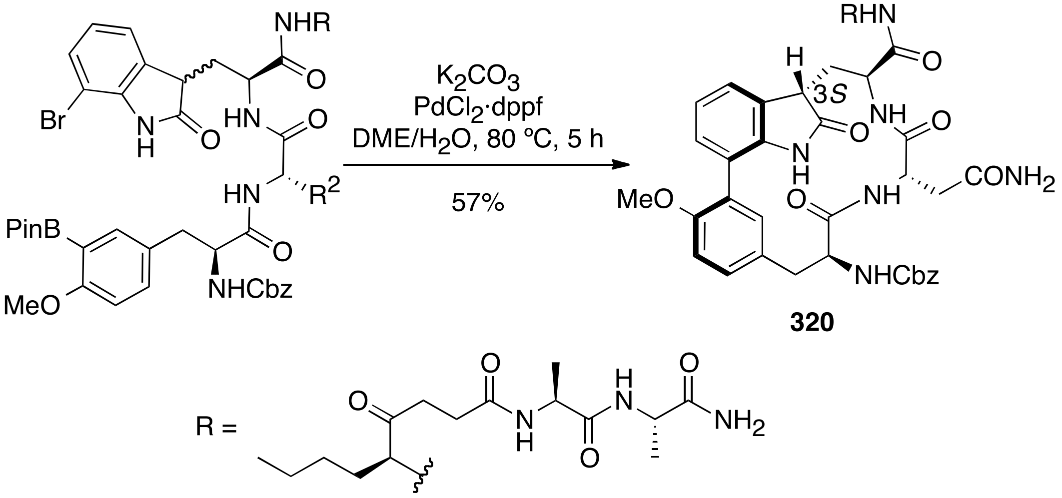
highlight that a macrolactamization intended for the preparation of a fully peptidic analog (i.e., non-oxidized indole moiety) would not proceed (middle), according to their later reports.[36a,36c]



Scheme 27. Preparation of a "simplified" TMC-95 analog by Moroder.

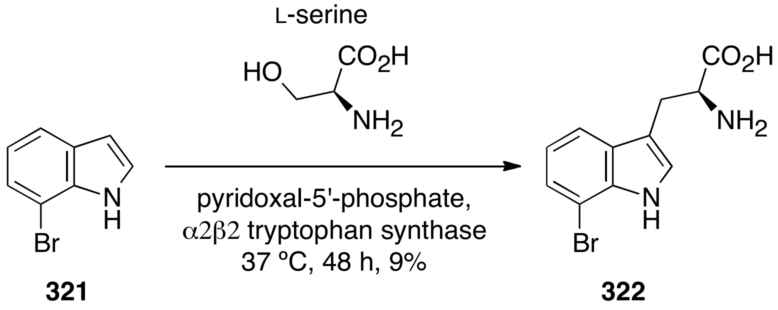
Oxidation of the indole ring under mild conditions[39] afforded a mixture of isomers and, interestingly, only the 3*S* diastereomer reacted to form the closed tripeptide **319**. From these results, Moroder concluded that an sp^3 center at the indole 3-position is required for the ring closure in this system.[36a]

Moroder developed an alternative route in which the macrocycle was closed using a Suzuki coupling.[36c] Conveniently, the base used in the coupling reaction simultaneously caused epimerization at the sp^3 oxindole 3-position leading to higher yields of the cyclized product **320** with a 3*S* stereocenter (Scheme 28). More importantly, it was proven that the mild procedure used for the oxidation of the indole ring[39] (*vide supra*) was completely innocuous to the boronic ester group.



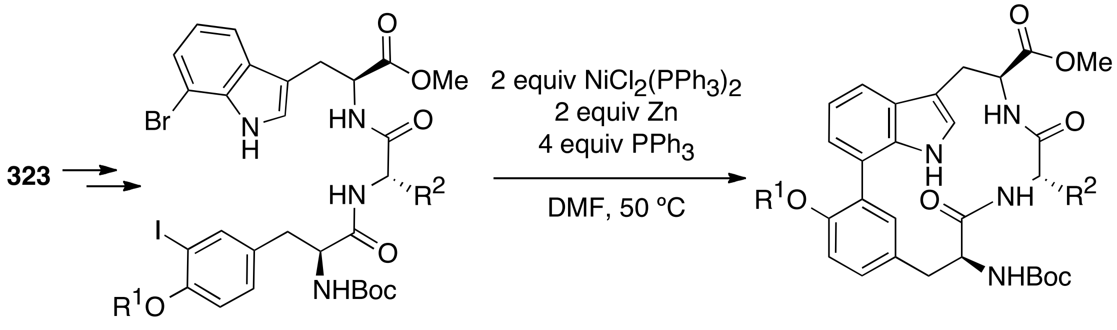
Scheme 28. Synthesis of Moroder's second-generation TMC-95 analog via a ring-closing Suzuki coupling.

In this manner, Moroder made evident that the synthetically challenging β,γ-diol moiety of the TMC-95 core could be evaded. A disadvantage in this process, however, is that 7-bromo-L-tryptophan (**322**), required for the preparation of starting materials like **317** (Scheme 27), is to be accessed via a low-yielding enzymatic procedure[40] (Scheme 29).



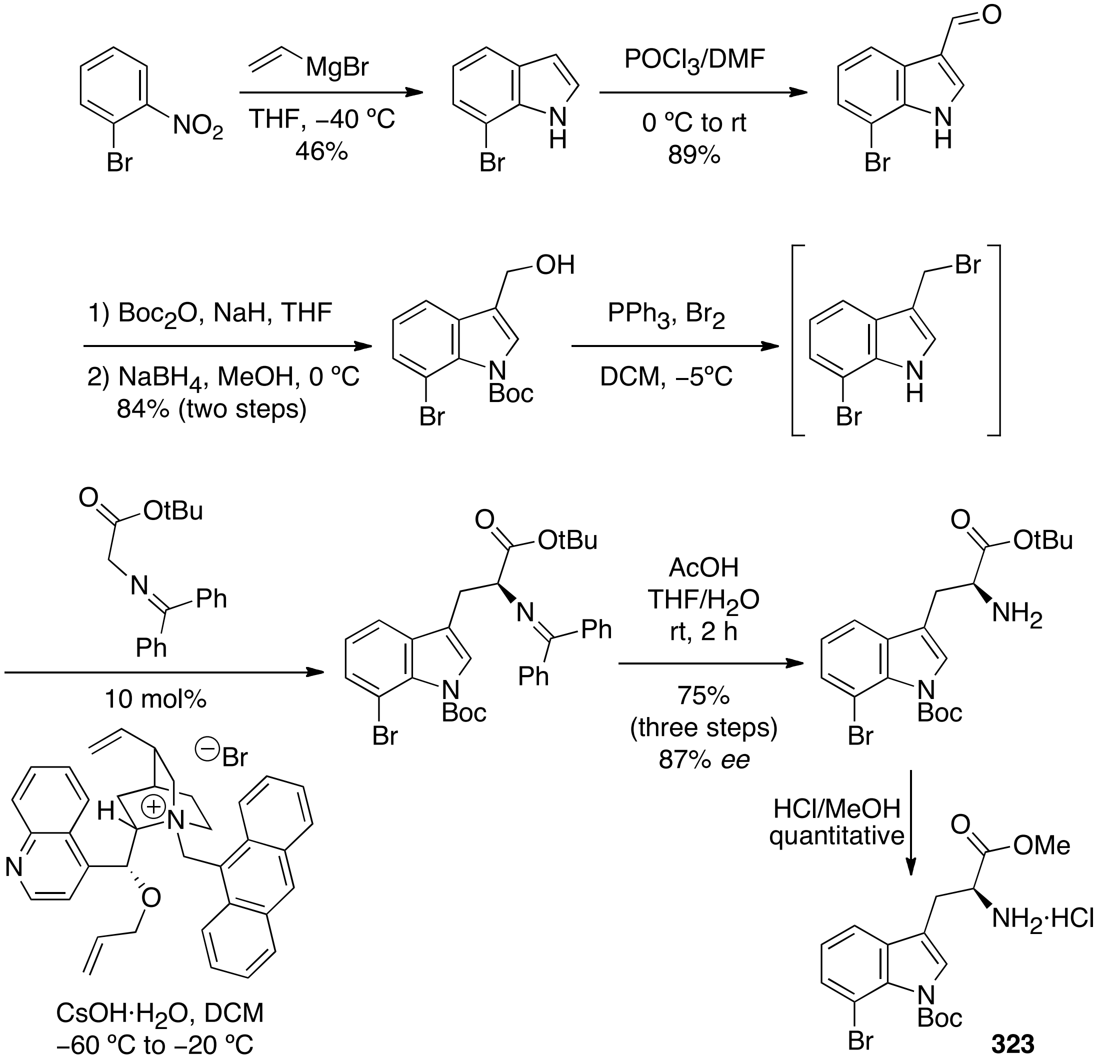
Scheme 29. Enzymatic preparation of 7-bromo-L-tryptophan.

On the other hand, an important contribution on the preparation of TMC-95 analogs has been made by the Vidal group.[36g,h] Vidal opted for a non-enzymatic preparation (Scheme 31) of a 7-bromo-L-tryptophan derivative (**323**) in seven steps, albeit with moderate enantioselectivity (87% *ee*), using Corey's method[41] for asymmetric enolate alkylation.



324 a R^1 = Bn, R^2 = Me: 13%
b R^1 = Bn, R^2 = iBu: 4%
c R^1 = Me, R^2 = iBu: 8%
d R^1 = Me, R^2 = Me: 10%

Scheme 30. Preparation of Vidal's strained TMC-95 analogs.



323

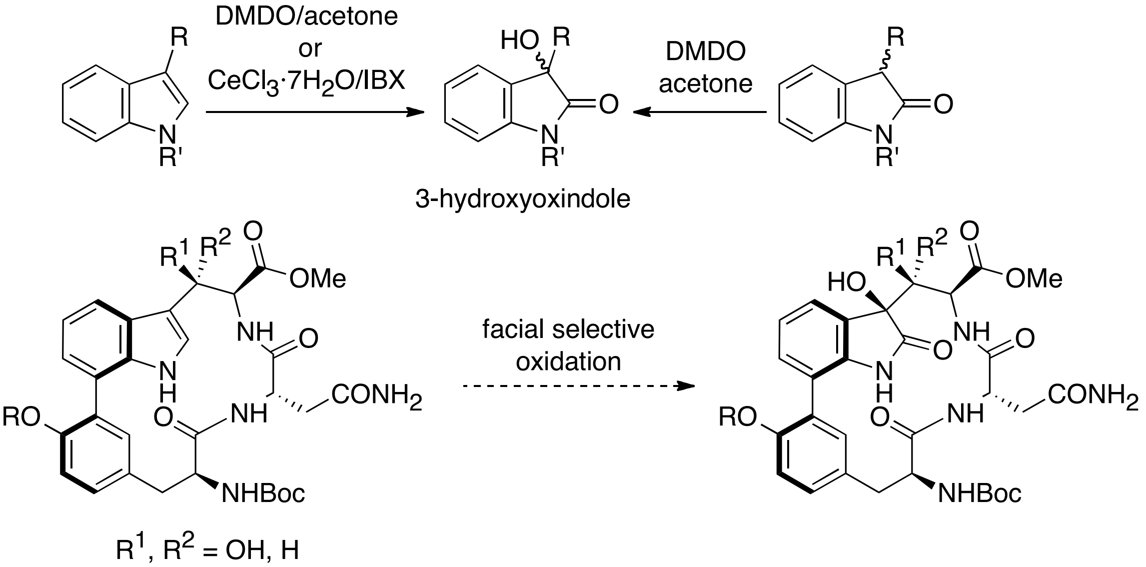
Scheme 31. Non-enzymatic preparation of a 7-bromo-L-tryptophan derivative.

Intermediate **323** was used in the preparation of fully peptidic TMC-95 analogs (Scheme 30).[36g] Nevertheless, the employed Ni-mediated ring closure method required two equivalents of nickel/zinc catalyst, low yields of cyclized products (4–13%) were obtained and, unfortunately, no information was given on the atroposelectivity of this ring-closure.

Vidal's peptidic analogs **324a–d** (Scheme 30) are exceptionally interesting since cyclization to form such a strained system did occur under metal-catalyzed conditions (compared to the attempted macrolactamization in Scheme 27). Possibly, this transformation could be improved via condition screening.

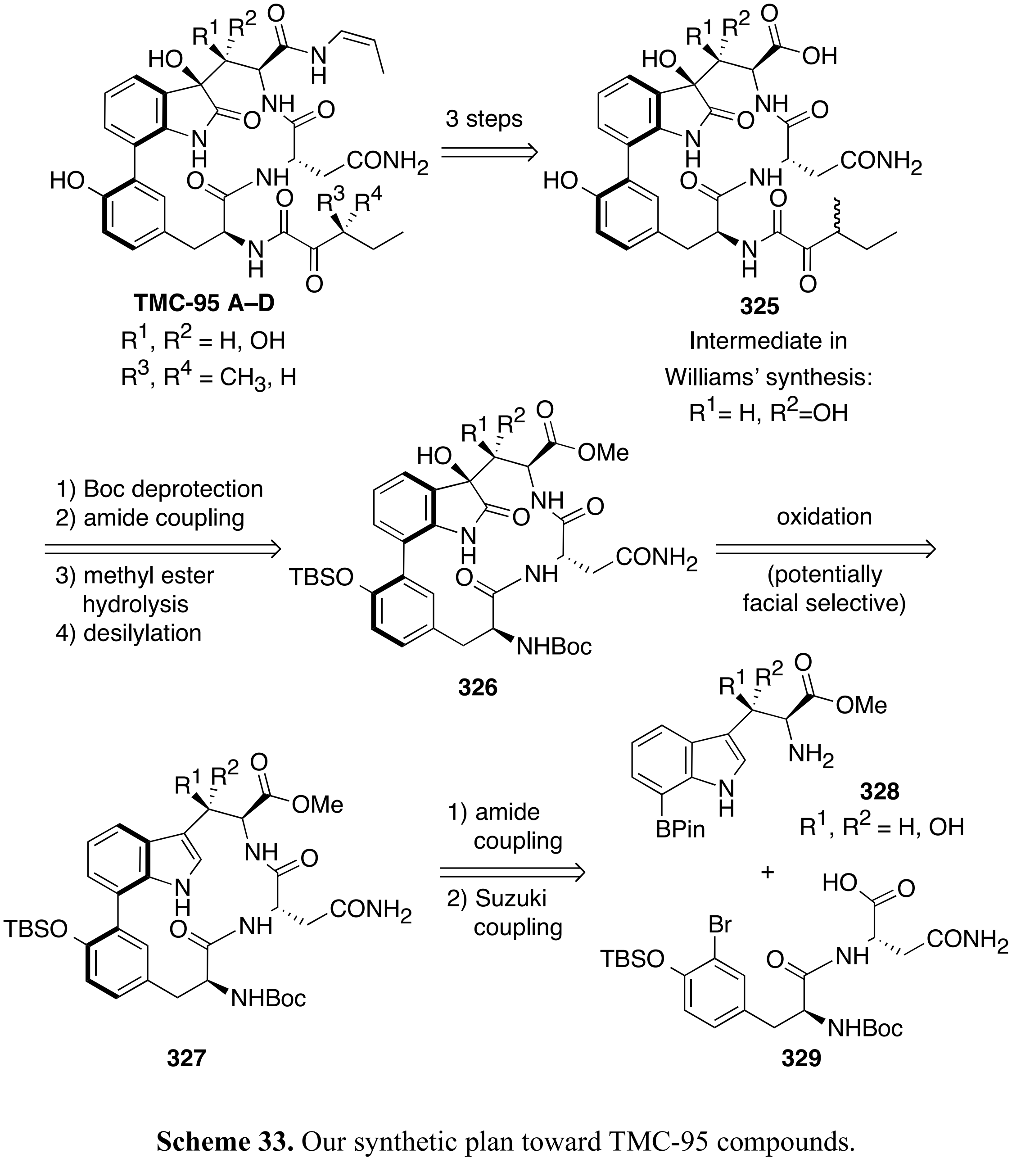
3.3. Our synthetic approach to the TMC-95 core

The 3-hydroxyoxindole core (Scheme 32) is a common moiety found in natural products like the maremycinsm,[42] convolutamydines,[43] celogentins[44] and several drug candidates,[45] and as such has been the target of important recently developed methods for asymmetric installation of oxygen at the oxindolic C3 position.[46] Recently, there have been reports on the discovery of mild conditions for the oxidation[47] of oxindoles and indoles (Scheme 32), using DMDO[47a] and $CeCl_3 \cdot 7H_2O$/IBX.[47b] While these methods do not offer any stereoselectivity, they happen to be interesting to us since it is conceivable that such mild procedures, applied to constrained molecules similar to Vidal's TMC-95 analog **324** (and maybe Moroder's **319**), could perform the oxidation in a facial selective fashion.



Scheme 32. Possible facial selective oxidation for the synthesis of TMC-95 compounds.

Our synthetic plan toward the TMC-95 family is shown in Scheme 33. Provided that a facial selective oxidation works as expected, it would be possible to transform intermediate **326**, in 4 functional group manipulations, to structure **325**, which is equivalent to one of Williams' intermediates,[35e] three steps away from the final 1:1 mixture of TMC-95 A and B.



Scheme 33. Our synthetic plan toward TMC-95 compounds.

We consider that it would be fascinating from a synthetic point of view if the strained intermediate **327** (Scheme 33) could be prepared in a convergent manner via two sequential steps: Amide coupling of **328** and **329**, followed by a ring-closing Suzuki coupling. Even though Moroder showed that formation of such strained compounds is not favorable (Scheme 27),[36a,36c] Vidal's reported low-yielding[g] Ni-promoted cyclizations[36g] (superstoichiometric amounts of Ni/Zn were used, see Scheme 30) encouraged us to adopt this approach in order to test the efficiency of newly developed catalyst systems for Suzuki couplings. More explicitly, Buchwald's biaryl ligands are known to outstandingly favor not only the oxidative addition and reductive elimination steps but *also* the transmetalation step;[27] since transmetalation is particularly what leads the cyclization *per se* in our system, we consider that this idea is worth testing.

We were especially motivated because of a very recent disclosure[48] of SPhos[49] conditions that avoid racemization in Suzuki couplings involving aminoacids. Another interesting recent report is the total synthesis of complestatin[50] by the Zhu group, which involves a ring closure of a similarly strained system via Suzuki coupling. This closure required 1 equiv of $PdCl_2 \cdot$dppf, and it is worthy of note that a comparable closure, in studies toward the synthesis of the same natural product, was reported about a decade ago[51] but the amount of catalyst was not specified.

The need of highly active catalysts for Suzuki coupling in our case, as opposed to traditional ones (i.e., $PdCl_2 \cdot$dppf, used in all the reported total syntheses of TMC-95 A–B and analogs, see

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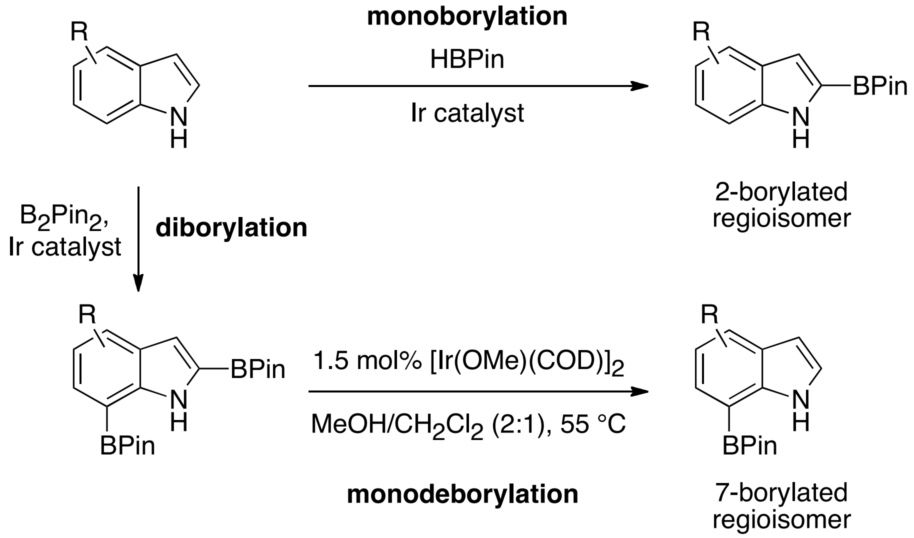
[g] The atroposelectivity in this ring-closing biaryl formation is also unknown.

Section 3.2), is evident. We plan to find suitable conditions for this transformation via high throughput screening of Pd sources, bases, solvents, concentration, and ligands. This study will be carried out at Merck in the following months.

If our attempts are unsuccessful, it is plausible that we could still perform the coupling under the same conditions used by Moroder[36c] (Scheme 28) after partial oxidation of the indole ring (see Scheme 27). Nonetheless, a facial selective 3-oxidation of the resulting cyclized oxindole using DMDO[47a] (see Scheme 32) has fewer chances to succeed; the substrate scope of this method unequivocally suggests that the process depends very much on the enolization of the amide, which is expected to be difficult in the constrained molecule.

Returning to our synthetic plan, preparation of dipeptide **329** did not appear to be a demanding task, so we aimed at developing a route as efficient as possible.



Scheme 34. Access to 7-borylated indoles via diborylation/monodeborylation.

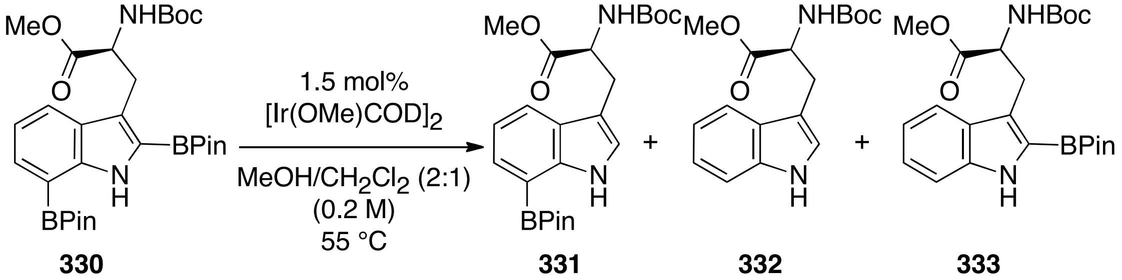
Finally, preparation of 7-borylated indoles by virtue of Ir-catalyzed diborylation followed by monodeborylation (Scheme 34) has previously been demonstrated by Dr. Venkata Kallepalli.[16]

Preparation of 7-substituted tryptophans can be complicated (see Scheme 29 and Scheme 31); our method appears as a most efficient approach for the preparation of **328**.

3.4. Results and discussion

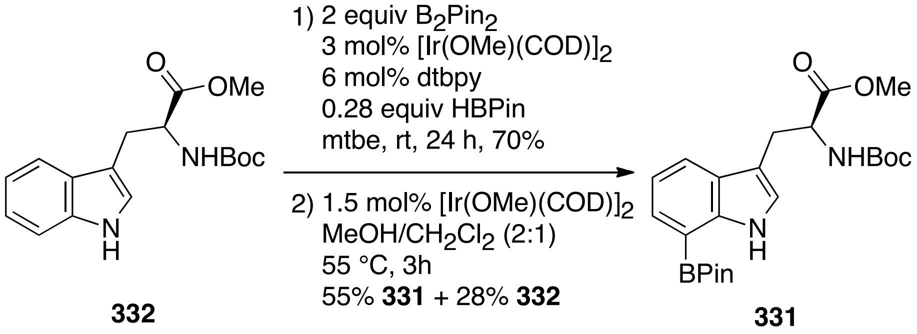
Our work started with a search for an efficient route to intermediate **328**, which contains an L-tryptophan-based structure with an additional hydroxy group at the β-position and a pinacolboryl substituent at the 7-position.

Table 2. Optimization study for the preparation of *N*-Boc 7-pinacolboryl-L-tryptophan methyl ester via Ir-catalyzed deborylation.



Reaction time	Relative amounts in crude material determined by ^{1}H NMR				Isolated yield of **331**
	330	**331**	**332**	**333**	
1 h	51.4	41.5	7.1	-	nd
2 h	12.3	69.5	18.2	-	56%
3 h	-	63.3	36.7	-	55%

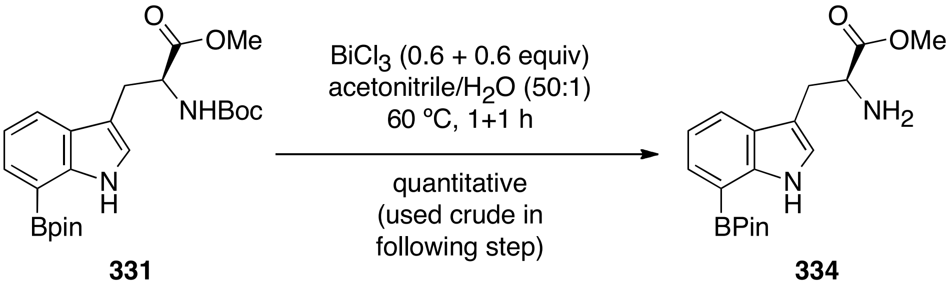
In order to optimize the preparation of this 7-borylated compound, we used the deborylation of *N*-Boc-2,7-dipinacolboryl-L-tryptophan methyl ester (**330**), accessible via Ir-catalyzed C–H activation/borylation, as a model (Table 2). Monitoring this reaction by ^{1}H NMR was not viable since the use of deuterated solvents (CD_3OD) would lead to the formation of deuterated compounds. On the other hand, TLC analysis would not provide quantitative information. Carrying out three different runs and stopping the reactions after 1, 2, and 3 hours respectively gave pretty valuable information. The fact that almost identical yields of the desired compound **331** were obtained after 2 or 3 hours was an interesting coincidence. From these numbers, it is likely that this procedure could be further optimized by carrying out the reaction for a specific reaction time in between 2 and 3 hours. However, letting the reaction run for 3 hours, and thus, ensuring that the diborylated starting material was fully consumed, was significantly more convenient since purification on silica gel became considerably easier.



Scheme 35. Preparation of a 7-pinacolboryl-L-tryptophan derivative.

Thus, the overall yield in the process of subjecting of *N*-Boc-L-tryptophan methyl ester (**332**) to diborylation, followed by deborylation (Scheme 35) can be calculated to be 54% for two steps based on recovered starting material. Most importantly, given their sufficiently different retention factors, **331** and **332** were easily separated by column chromatography silica gel eluting with dichloromethane.

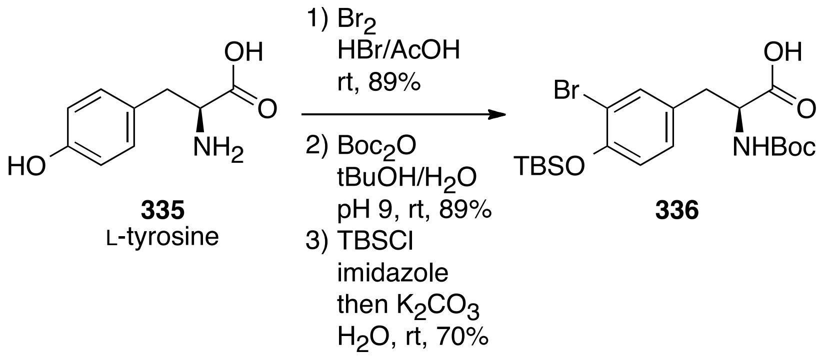
Subsequent Boc deprotection of **331** with $BiCl_3$[52] cleanly provided **334** (Scheme 36). While TFA is the most commonly used reagent for Boc deprotection in peptide chemistry, the use of tBu^+ scavengers (anisole, thioanisole) is recommended in the presence of tryptophan, methionine, and cysteine residues. While working on the preparation of tryptophan-containing dipeptides and tripeptides without boronate groups, Ms. Fang Yi Shen demonstrated that the use of $BiCl_3$ was more convenient than several TFA-based conditions. Application of the same procedure to the 7-borylated **331** was pleasingly efficient. However, we were unable to reproduce the original report, where catalytic $BiCl_3$ was used.[52] A stoichiometric amount added in portions gave the best results.



331 **334**

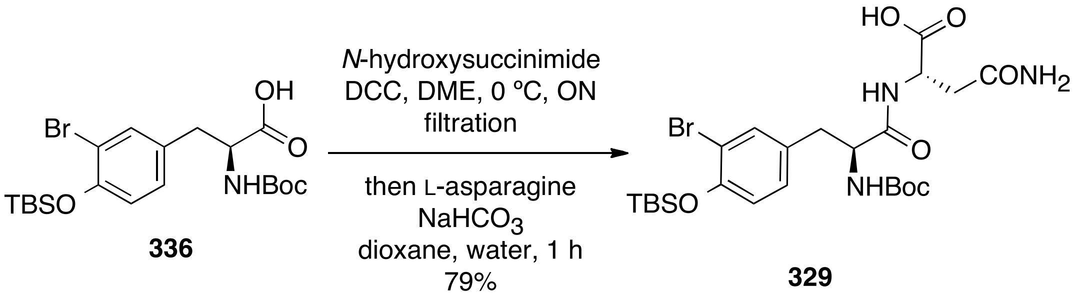
Scheme 36. $BiCl_3$-mediated deprotection of a 7-pinacolboryl-L-tryptophan derivative.

Since preparation of model building block **334** containing a BPin group and a free amine was viable, we simultaneously worked on the development of a route to dipeptide **329** (Scheme 33). Thus, repeating reported procedures,[53] L-tyrosine (**335**) was subjected to bromination, followed by Boc protection. Then, application of a TBS diprotection/monodeprotection procedure previously used on *N*-Boc-L-tyrosine[54] afforded intermediate **336** in good yields.



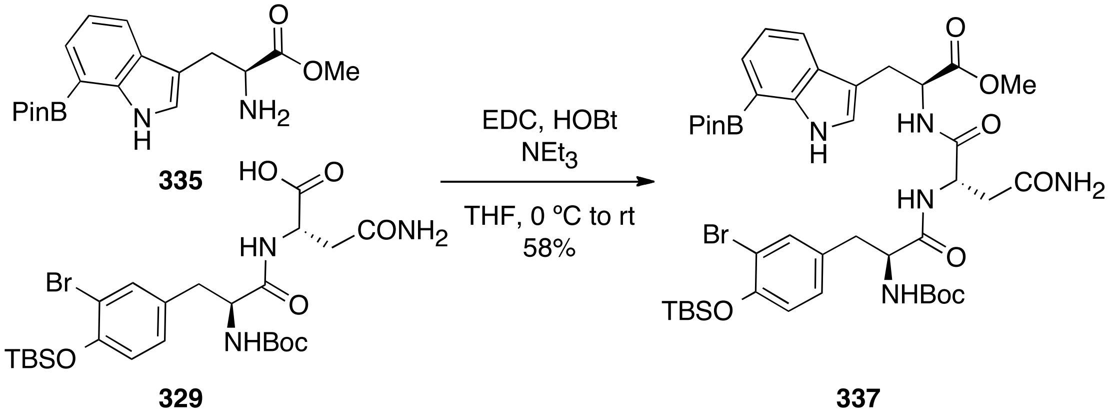
Scheme 37. Preparation of the tyrosine unit for the synthesis of the TMC-95 core.

Attachment of the L-asparagine unit was conveniently done in "one step" via activation of **336** as its hydroxysuccinimide ester followed by direct reaction with commercial L-asparagine monohydrate (Scheme 38). We found this method suitable for our purposes since there was no need to protect L-asparagine as an ester (or to deprotect it afterward) and dipeptide **329** was obtained already containing a free carboxylic acid and being ready for the formation of the tripeptide.



Scheme 38. Preparation of a tyrosine–asparagine didpeptide for the synthesis of the TMC-95 core.

Dipeptide **329** was further coupled with **335** (Scheme 39) in a moderate-yielding reaction to afford our first model tripeptide to be subjected to ring-closing Suzuki coupling. Even though preliminary Suzuki experiments with tripeptide **337** under conditions that are optimized to avoid recemization of aminoacids[48b] have failed to give the desired cyclization product, we have established a fast access to this advanced Suzuki substrate, in a way that sufficient amounts of this compound can be easily synthesized and used to find suitable coupling conditions via high throughput screening.



335

329

337

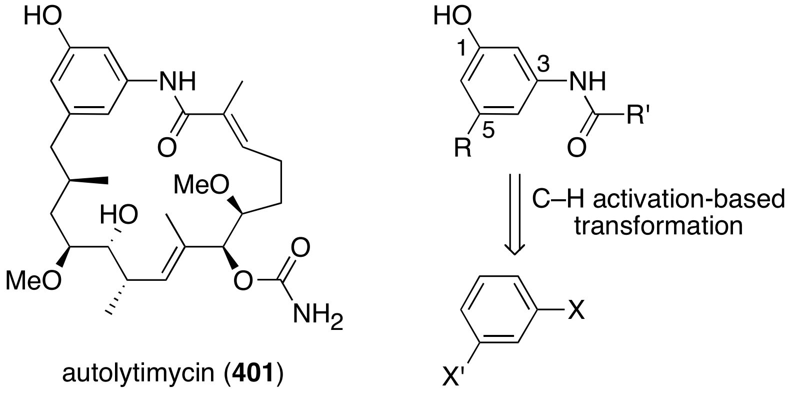
Scheme 39. Preparation of a model tripeptide for the synthesis of the TMC-95 core.

As presented in Section 3.2, preparation of 7-substituted derivatives of L-tryptophan (Scheme 29 and Scheme 31) can be a tedious task. Our rapid access to **335** provides an clear example of the synthetic utility of Ir-catalyzed C–H activation/borylation combined with deborylation and its capability to build unusual building blocks under gentle conditions. Furthermore, we consider that **335** could be useful in the preparation of TMC-95 analogs, which have attracted even more attention than the natural products themselves.[34]

Chapter 4. A synthetic approach to autolytimycin

4.1. Target choice and significance

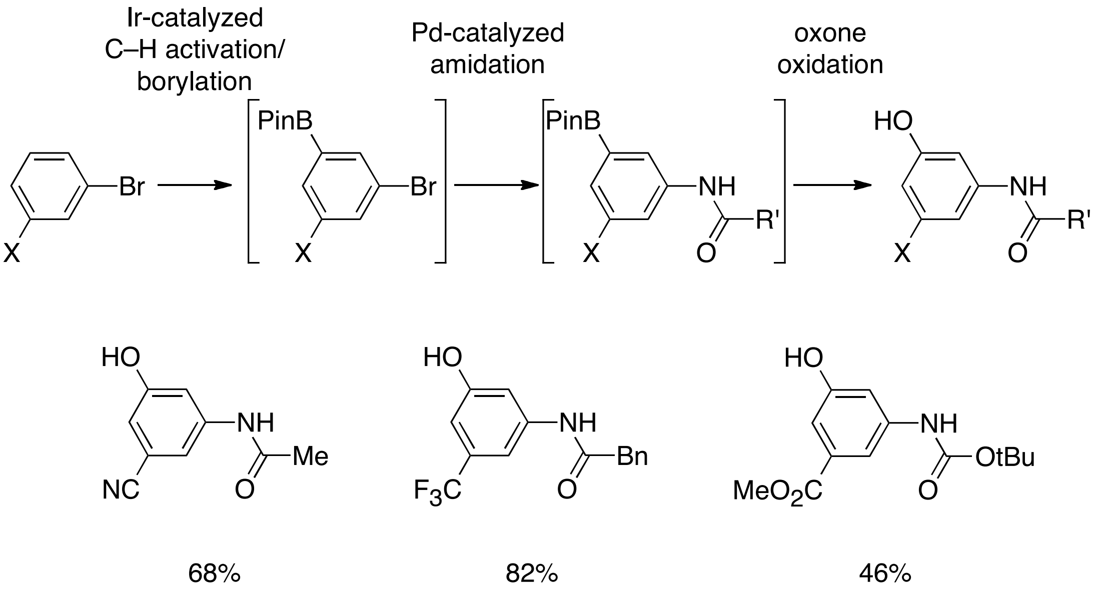
A synthetically appealing characteristic of Ir-catalyzed C–H activation/borylation is the cleanliness with which it proceeds; for instance, when HBPin is used as the boron source, hydrogen gas is the only byproduct generated. This makes it highly amenable to one-pot transformations, which is an important feature of our synthetic approach to the Hsp90 inhibitor autolytimycin (**401**).



autolytimycin (**401**)

Figure 3. The Hsp90 inhibitor autolytimycin and its 1,3,5-trisubstituted aromatic core.

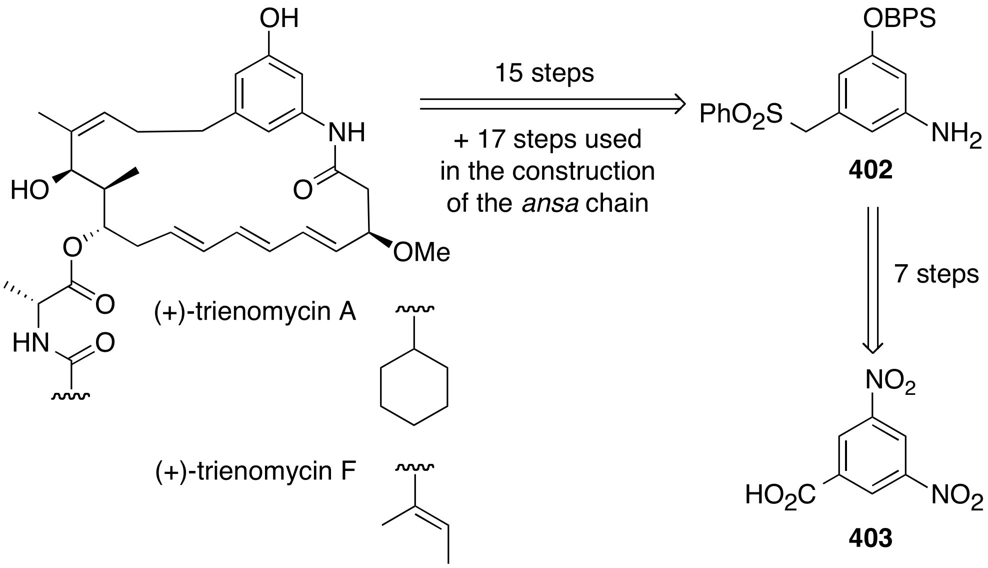
C–H activation/borylation is an excellent tool for the construction of 1,3,5-trisubstituted arenes (see Section 1.2) and exploiting it in one-pot transformations results in a rapid build-up of complexity. One specific important illustration is a recent report by our group on the preparation of 5-substituted 3-amidophenols from 3-substituted aryl halides via a one-pot C–H activation/borylation/amidation/oxidation[5h] (Scheme 40). This protocol has demonstrated a wide functional group tolerance and the isolated yields are reasonably high, taking into account that it involves three reactions in one step. We targeted autolytimycin (**401**) to prove the feasibility of using this method in a complex system.



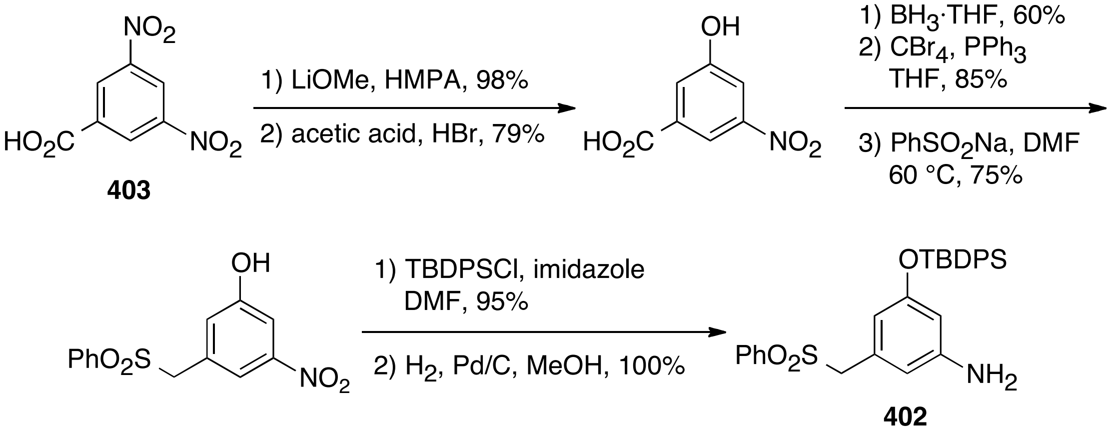
Scheme 40. One-pot C–H activation/borylation/amidation/oxidation.

The 1,3,5-trisubstituted aromatic core of autolytimycin is especially attractive since the three *meta* substituents are all *ortho*/*para*-directors in electrophilic aromatic substitution, which makes its preparation difficult by traditional methods. Autolytimycin's 5-alkyl-3-amidophenol moiety is also found in other natural products like the trienomycins and proansamitocyn.[55] Substituted versions are found in a considerable number of natural products biosynthesized from 3-amino-5-hydroxybenzoic acid (AHBA).[56]

Previously reported preparations[57] of natural products and analogs containing the same 1,3,5-trisubstitution have generally involved a sequence of manipulations to build suitable aromatic building blocks from commercially available compounds that already contain a 1,3,5-trisubstitution pattern. For instance, in Smith's unified synthetic route to trienomycins A and F,[57a] a total of seven steps (which is a substantial portion of steps in the linear sequence) are spent in manipulating the substituents on the aromatic core (Scheme 41).



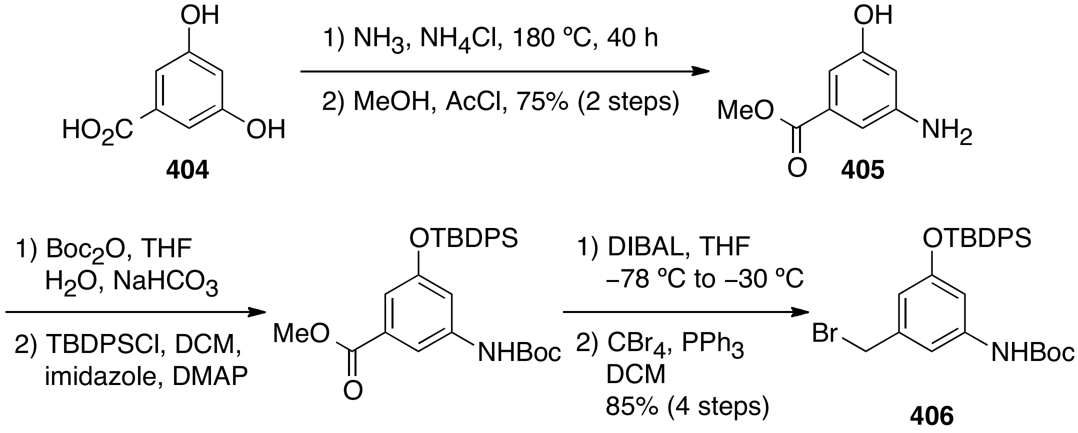
Scheme 41. Smith's synthetic route to trienomycins A and F.



Scheme 42. Preparation of a 5-alkyl-3-aminophenol from 3,5-dinitrobenzoic acid.

During the preparation of the required aromatic precursor, the electron-donating alkyl and amino substituents are to be temporarily masked as the electron-withdrawing carboxylate and nitro groups. Nitro groups can be displaced by reaction with lithium methoxide in HMPA,[58] which makes 3,5-dinitrobenzoic acid **403** a suitable starting material in this approach (Scheme 42). Reduction of the carboxylate and nitro groups and functional group manipulations, afforded the desired precursor **402** after seven steps. This route has also been used by the Blagg group in the development of a general route to simplified ansamycin antibiotics.[57b]

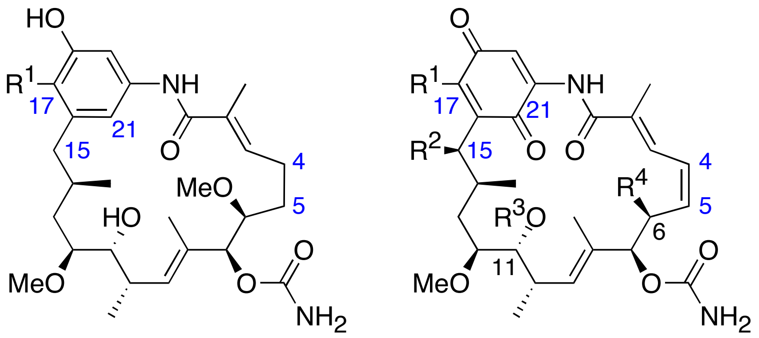
Alternatively, 3,5-dihydroxybenzoic acid (**404**) can also be used as starting material, since one of the hydroxyls can be directly transformed into an amino group by reaction with ammonia at high temperature, taking advantage of the potential ketonic character of resorcinols.[59] This method (Scheme 43) was used in the preparation of the aromatic core of *seco*-proansamitocin,[57c] as part of Kirschning's studies on the biosynthesis of maytansine and the ansamitocyns.[57c-f] While this approach is a more direct way compared to Scheme 42, given that the amino group is installed in a non-oxidized form, it still implies a series of manipulations to transform the carboxylate group into a synthetically adaptable alkyl chain.



Scheme 43. Preparation of a 5-alkyl-3-aminophenol from 3,5-dihydroxybenzoic acid.

We envisioned that if our one-pot C–H activation/borylation/amidation/oxidation method, could be combined with a subsequent *B*-alkyl Suzuki coupling, aided by the halogen tolerance in the Ir-catalyzed step, we could provide rapid access to 5-alkyl-3-amidophenols, in a route that would be flexible in terms of the alkyl group to be installed at the 5-position. Morover, if highly elaborated amides are used in this process, simple commercially available dihalogenated arenes could be rapidly elaborated into complex substituted phenols. Particularly important in the case of our target molecule, autolytimycin, its phenol moiety imparts its biological properties,[60] as will be discussed in the following section.

4.2. Autolytimycin and the geldanamycin family (C15-ansamycins)



R^1	
-OMe	reblastatin (**407**)
-H	autolytimycin (**401**)

R^1	R^2	R^3	R^4	
-OMe	-H	-H	-OMe	geldanamycin (**408**)
-H	-OMe	-Me	-OMe	herbimycin A (**409**)
-H	-H	-H	-OMe	herbimycin B
-H	-OMe	-H	-OMe	herbimycin C
-H	-OMe	-Me	-Me	macbecin I (**410**)
-H	-OMe	-Me	-Me	macbecin II (hydroquinone)

Figure 4. Autolytimycin, reblastatin, and the geldanamycin family.

Autolytimycin was first isolated in 2000[61] from *Streptomyces* sp. S6699, and was reported to inhibit the oncostatin M signaling pathway that promotes cartilage degradation, which is known to cause arthritis in mice. It was later named when an isolation from *Streptomyces autolyticus* JX-47 was reported in 2001.[62] Autolytimycin (**401**) belongs to a family of biosynthetically related natural compounds (Figure 1) produced by certain species of streptomyces.[63]

Unlike **401**, most of the members of the family contain an additional double bond between carbons 4 and 5, a benzoquinone ring instead of a phenol, and an oxygenated center at carbon 15. This C15 center has served as a disconnection point in all the previously reported total syntheses of these compounds. In most of the cases, two building blocks were attached via nucleophilic attack to an alkyl or aromatic aldehyde. A ring-closing amide formation, as well, has so far been an ever-present final key step (See Section 4.3 for detailed information).

Interest in these compounds is in part due to their heat shock protein 90 (Hsp90) inhibitory activity. Hsp90 has been identified as one of the most promising anticancer therapeutic targets[64] and members of the geldanamycin family have been referred to as natural prototypes for Hsp90 inhibition.[65]

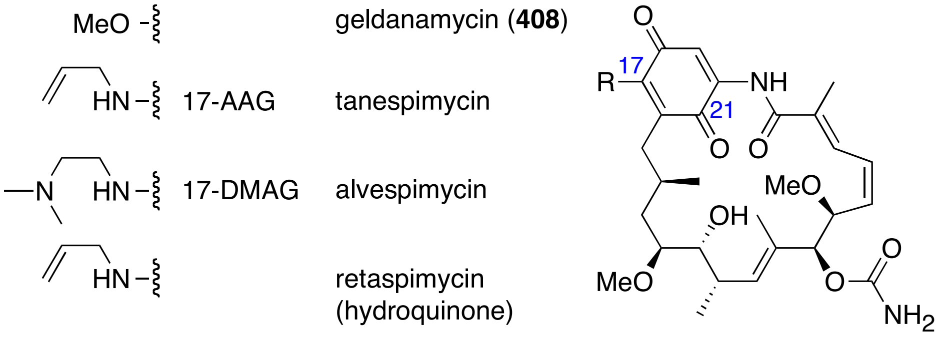


Figure 5. Geldanamycin and its analogs in clinical trials.

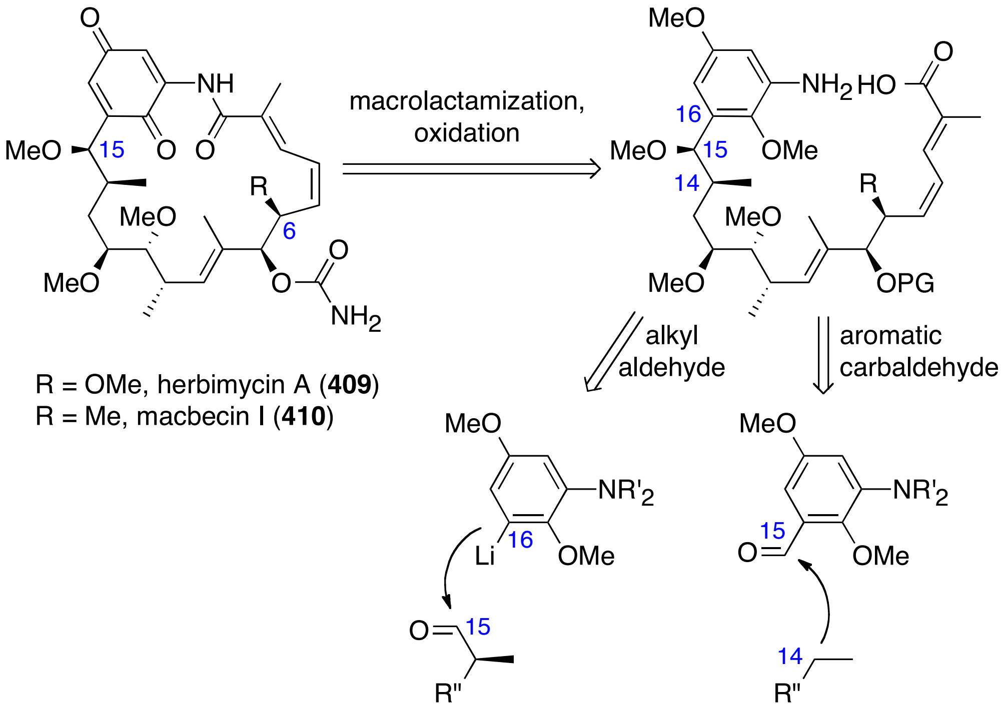
Geldanamycin, the most studied and accessible member in the list, possesses a center at carbon 17 that is susceptible to nucleophilic attack; three C17-substituted derivatives are currently in clinical trials[66] but unfortunately there are toxicity issues (namely, hepatoxicity) attributed to the benzoquinone core.

Autolytimycin, reblastatin, together with few non-natural non-benzoquinone (non-hepatoxic) ansamycins have been produced via genetic engineering;[60a-c] interestingly, these phenolic analogs show appreciably higher affinity for Hsp90 and it has been proposed that this is due to the absence of both the C21 oxygen and the C4–C5 double bond.[60d] We recognized that to provide access to autolytimycin via total synthesis in a flexible manner is highly desirable since it would allow the preparation of analogs that are not reachable through genetic engineering or functionalization of the natural products.

4.3. General analysis of the reported total syntheses of C15-ansamycins

Members of the geldanamycin family (Figure 4, page 51) have long been targets of total synthesis. Professor James Panek published a comprehensive review[63] on the biosynthesis, design, and preparation of ansamycin antibiotics, which included a complete inspection of the reported syntheses of these compounds. Very recently, Panek himself reported the first total synthesis of autolytimycin[67] applying an elegant, convergent route also used in the synthesis of reblastatin (*vide infra*).[68]

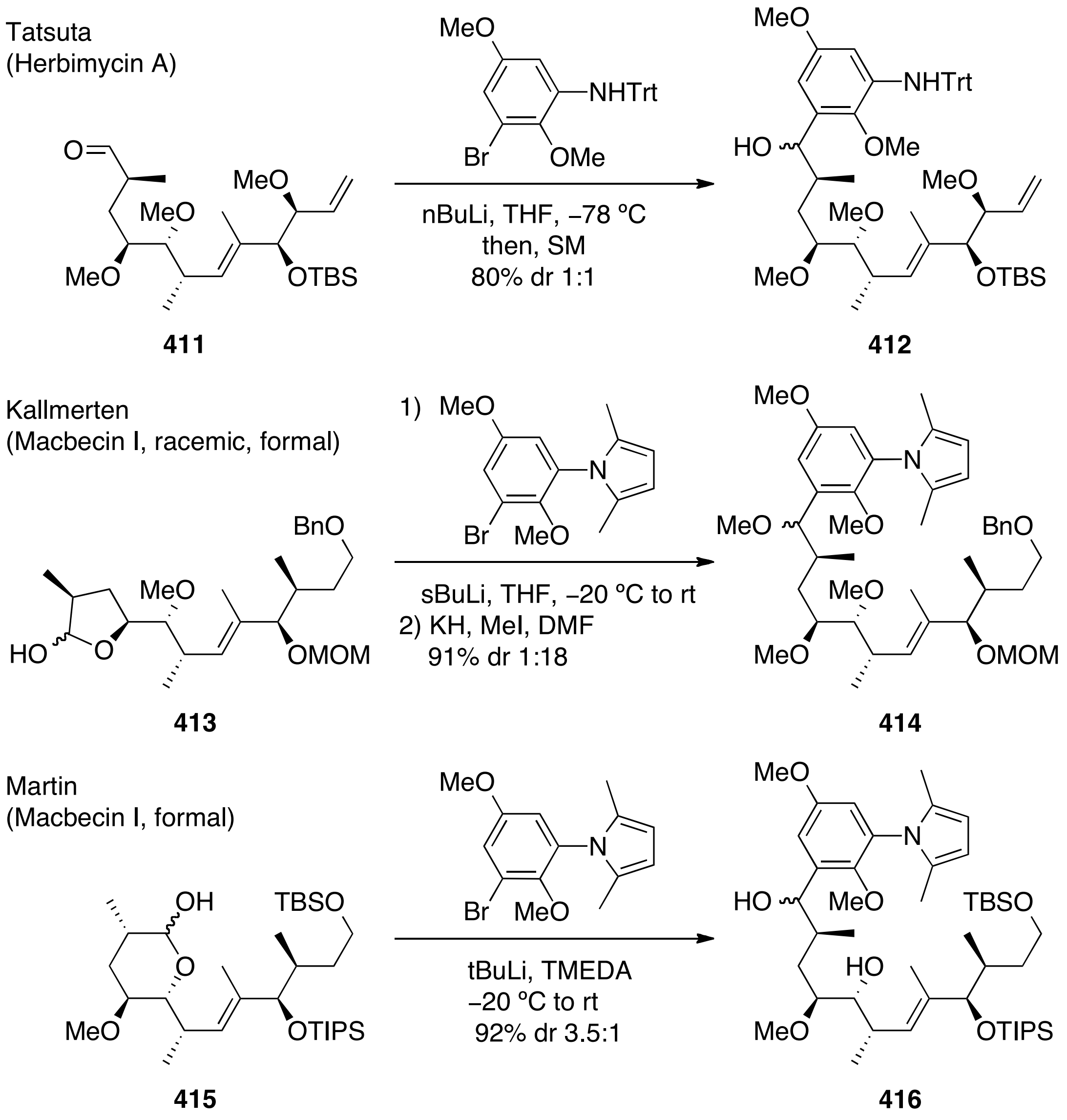
In all the reported total syntheses of C15-ansamycins (eleven in total), a ring-closing amide formation has been a key final step. Also, as mentioned previously, most of the members of the geldanamycin family possess an oxygenated center at carbon 15, which has served as a disconnection point in all of the cases, including two formal syntheses. Family members that have been synthesized multiple times are herbimycin A and macbecin I (Scheme 44).[69] In such syntheses, attachment of the aromatic moiety to the alkyl chain has always involved a nucleophilic attack to either an alkyl aldehyde or an aromatic carbaldehyde.



Scheme 44. General approach to C15-oxygenated C15-ansamycins.

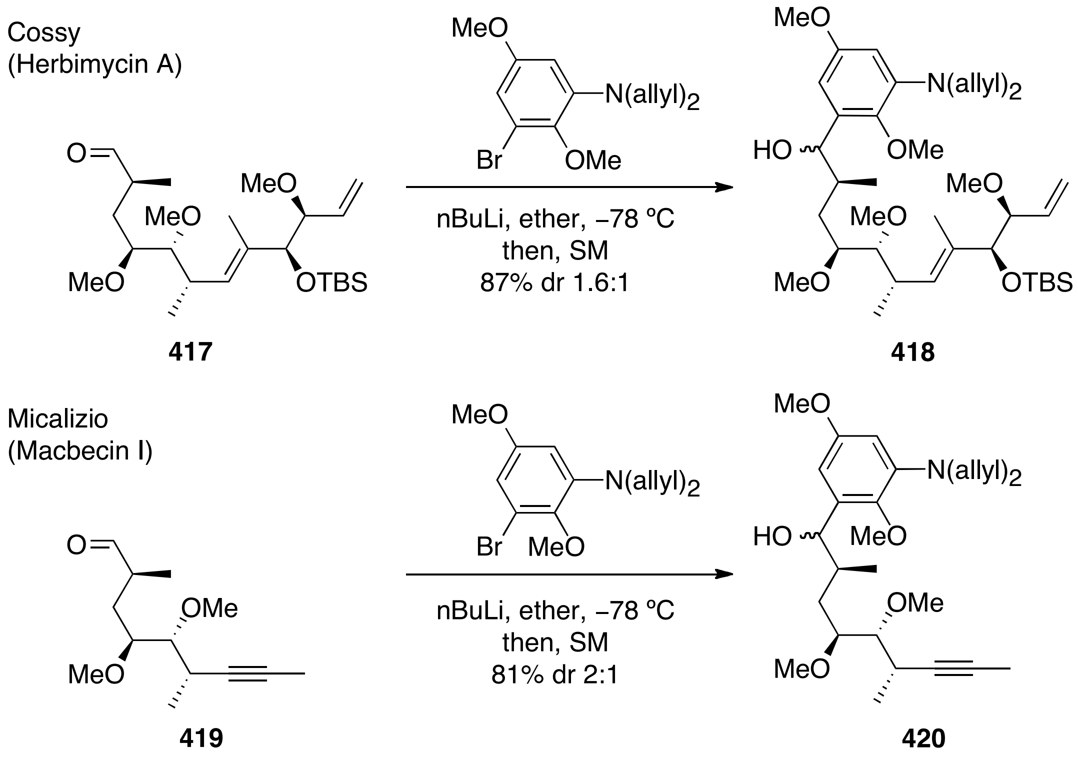
When an alkyl aldehyde is used, nucleophilic attack is expected to give the desired product based on the Felkin-Ahn model. However, in the first total synthesis of herbimycin A, Tatsuta[69e,69h] reported that the late-stage attachment of the aromatic ring (Scheme 45) provided **412** in good yield but without selectivity. After separation of diastereomers, the undesired isomer was oxidized and then subjected to asymmetric reduction using lithium aluminum hydride treated with a chiral amino alcohol (Chirald®)[70] for recycling purposes.

In order to achieve selectivity, a slight modification was introduced by Kallmerten[69c,d] in his racemic formal synthesis of macbecin I. Thus, subjection of a 5-membered lactol, instead of the free aldehyde, to a reaction with a similar aryllithium species afforded a 1:18 mixture of diastereomers. Unfortunately, it was the minor isomer that had the desired stereochemistry.



Scheme 45. Late stage attachment of aryl and alkyl fragments in the syntheses of herbimycin A and macbecin I.

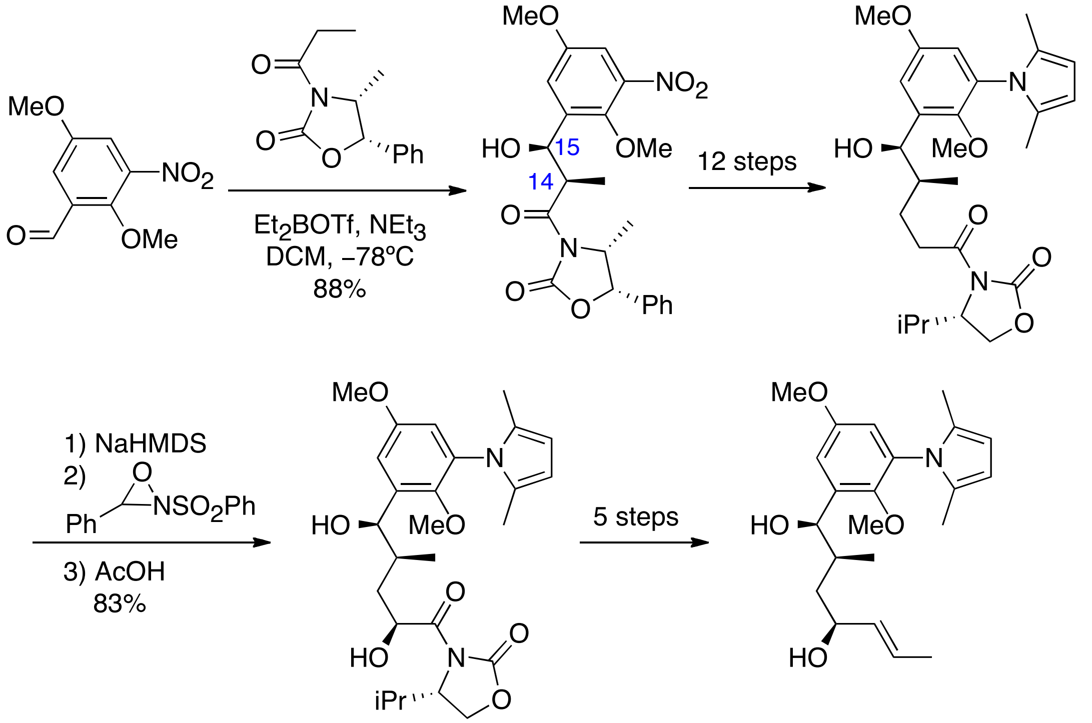
In his formal synthesis of macbecin I, Martin[69g,69j] carried out a yet another interesting modification. Subjecting a six-membered lactol instead of a five-membered one did the trick to favor the formation of the desired isomer, providing **416** with moderate selectivity (3.5:1) in good yield.



Scheme 46. Attachment of aryl and alkyl fragments in recent syntheses of herbimycin A and macbecin I.

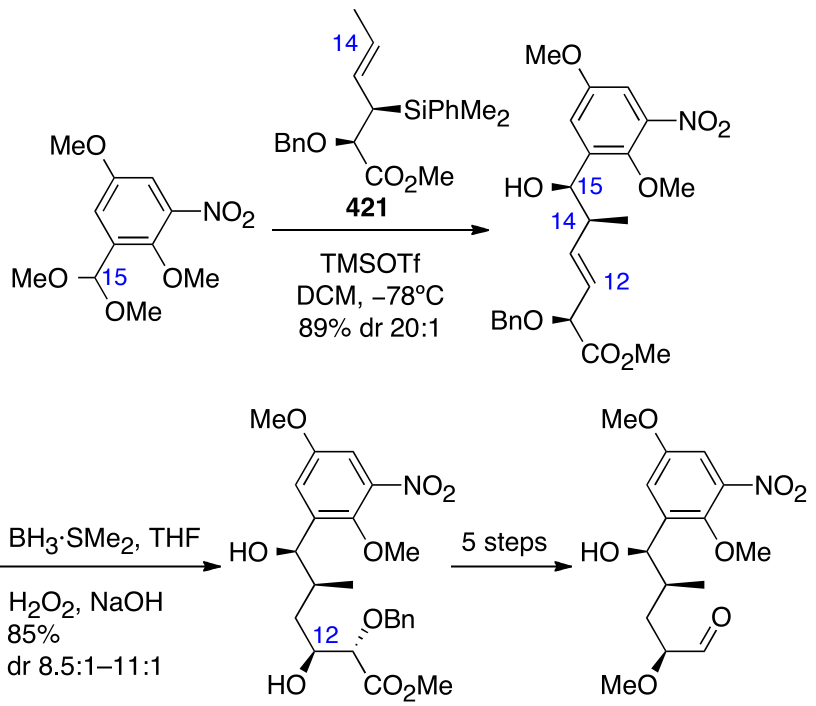
Even though the alkyl aldehyde approach suffers from low selectivity, it has been used in the recent total syntheses of herbimycin A and macbecin I by Cossy[69l] and Micalizio[69m] respectively (Scheme 46). In both cases, it was demonstrated that the free aldehyde (as opposed to a lactol) can be subjected to nucleophilic attack to provide the desired Felkin-Ahn product in moderate selectivity. Cossy's synthesis of herbimycin A involved an appealing construction of the *ansa* chain involving three asymmetric allylmetalation reactions, although in a rather linear fashion. Micalizio's synthesis of macbecin I, on the other hand, involved a very convergent approach, analogous to Panek's synthesis of reblastatin (*vide infra*).

In contrast, the aromatic carbaldehyde approach (see Scheme 44) has been utilized resulting in all cases in excellent selectivities. The very first total synthesis of a C15-ansamycin (macbecin I) by Baker[69a,b,71] involved the installation of the aromatic ring and the C14 and C15 stereocenters using an Evan's asymmetric aldol reaction (Scheme 47). This was, however, just the first step, and it was followed by a rather lengthy step-by-step elongation of the *ansa* chain.



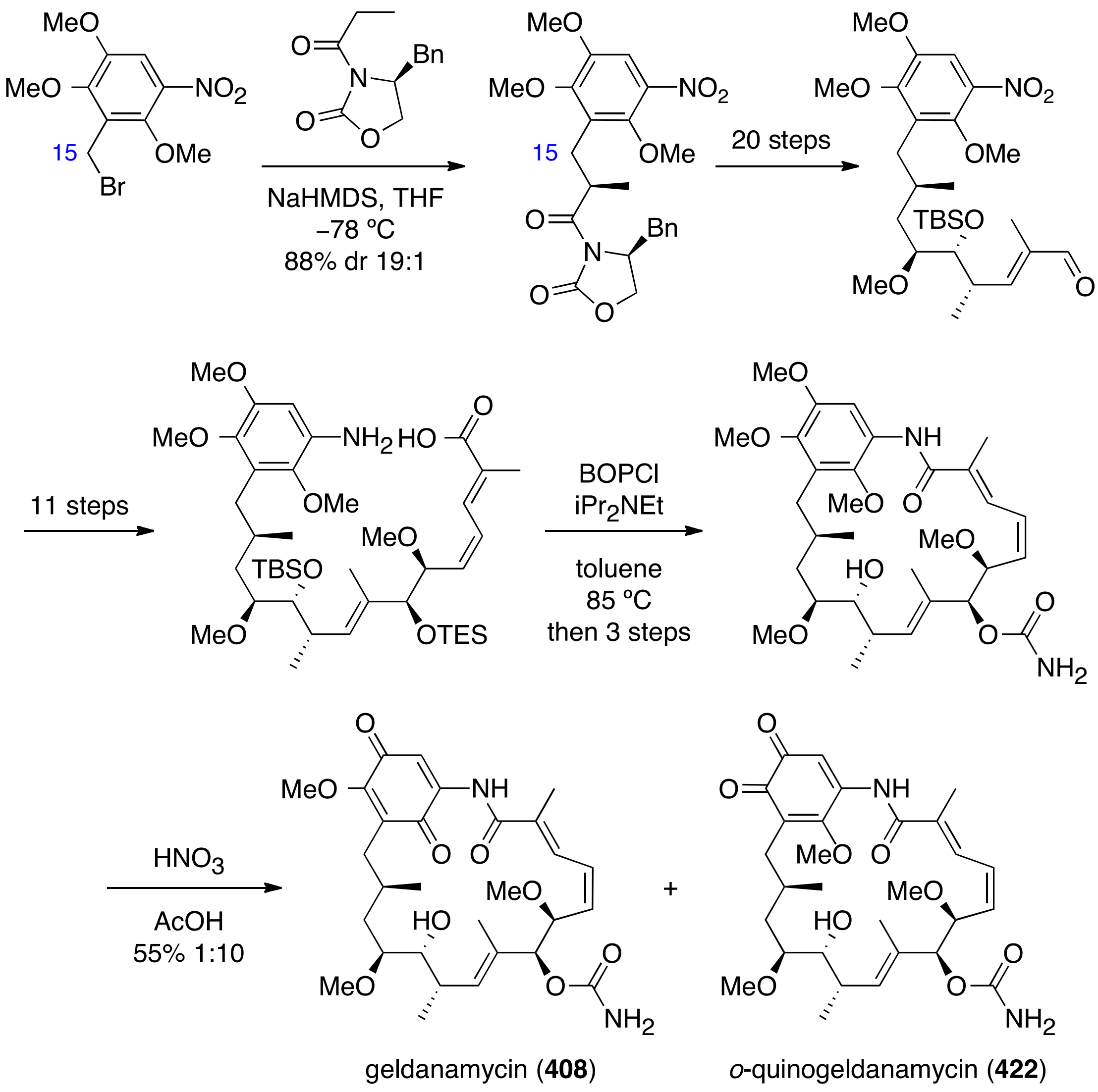
Scheme 47. First steps in Baker's first total synthesis of macbecin I.

A more convergent route to macbecin I was later reported by Evans,[69f,69i] which involved the installation of the seven stereocenters of the molecules through a series of chiral enolate-based reactions. However, a totally different approach was introduced by Panek in his total synthesis of macbecin I, in which six out of the seven stereocenters were installed by exploiting a chiral crotylsilane method developed in his group. Given the similarities between macbecin I and herbimycin A, the latter was also synthesized by the Panek group[69k] several years later, using the same left-hand-side intermediates. Attachment of the remaining sections of the ansa chain, nonetheless, was effected in a linear manner in both cases.



Scheme 48. First steps in Panek's total syntheses of macbecin I and herbimycin A.

In 2002, Andrus accomplished the first total synthesis of geldanamycin,[72] which was also the first preparation of a compound in the family that did not contain an oxygenated center at C15 (Scheme 49). Anyway, the same disconnection point was used to install the aromatic core, in a manner analogous to Baker's and Evans' syntheses of macbecin I (Scheme 47), but performing an asymmetric enolate benzylation instead of an asymmetric aldol reaction.

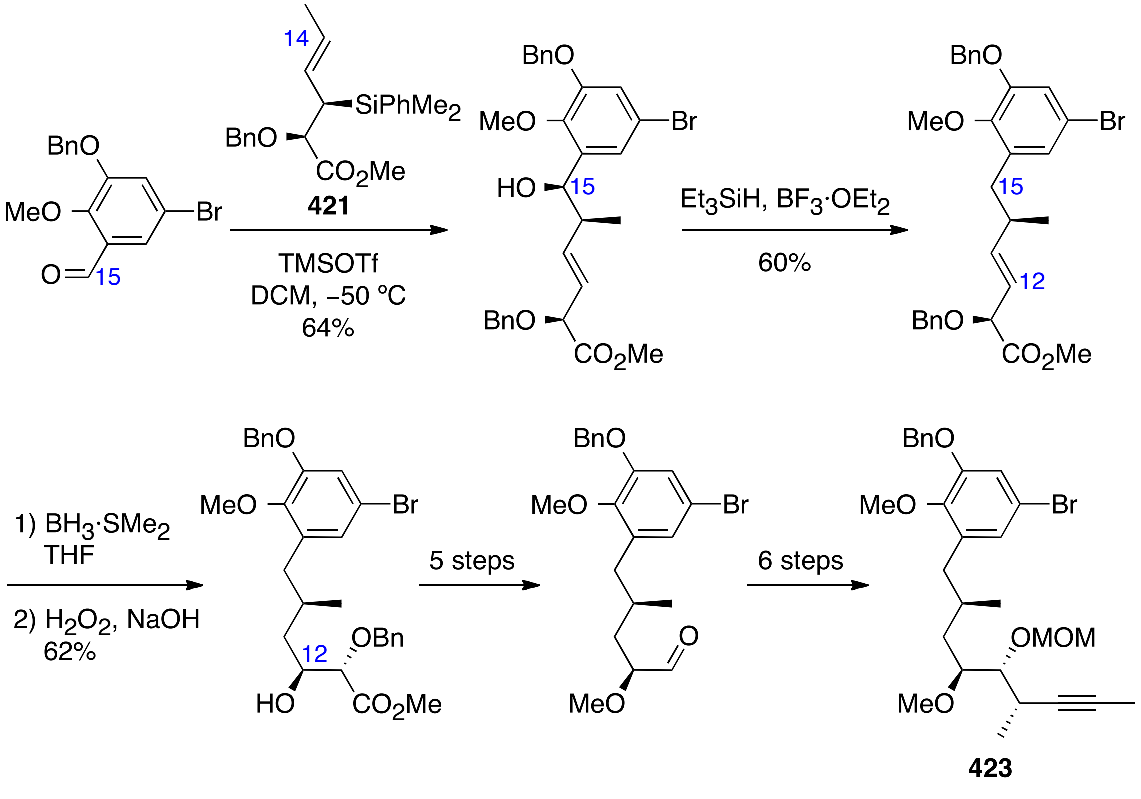


Scheme 49. Andrus' total synthesis of geldanamycin.

Andrus' approach, however, was severely linear and after 41 steps the overall yield was evidently low (0.05%). Furthermore, optimized conditions for the final oxidation step provided a 1:10 mixture of desired (**408**) and undesired (**422**) oxidized products. This problem was cleverly solved by Panek in his recent synthesis of geldanamycin (*vide infra*).

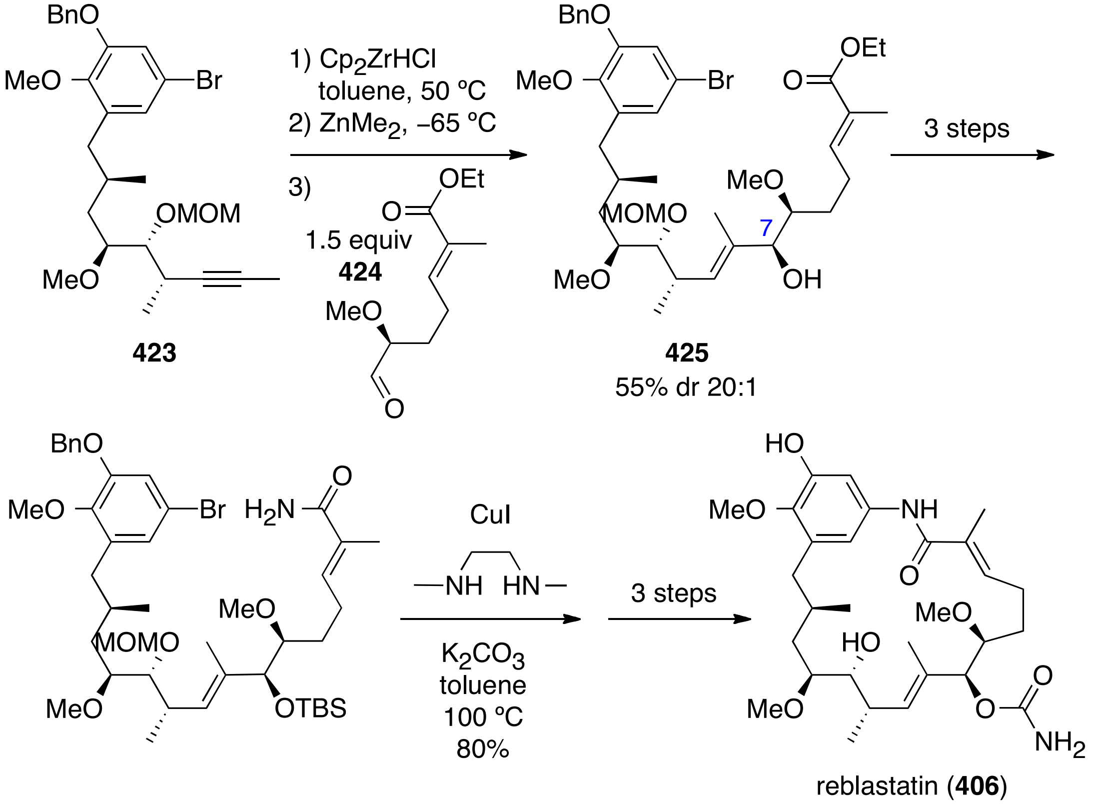
In recent years, the Panek group has demonstrated the utility of their chiral crotylsilane method, combined with a deoxygenation step, to provide access to C15-deoxygenated C15-ansamycins. This was first illustrated in the total synthesis of reblastatin **406**.[68]

The first total synthesis of reblastatin started with the reaction of the same chiral crotylsilane reagent employed in previous syntheses (**421**, compare to Scheme 48) on an appropriately modified aromatic carbaldehyde, followed by a deoxygenation at the benzylic position and installation of the C12 oxygenated center via hydroboration/oxidation as shown in Scheme 50. An additional eleven steps afforded a fully elaborated left-hand half **423**.



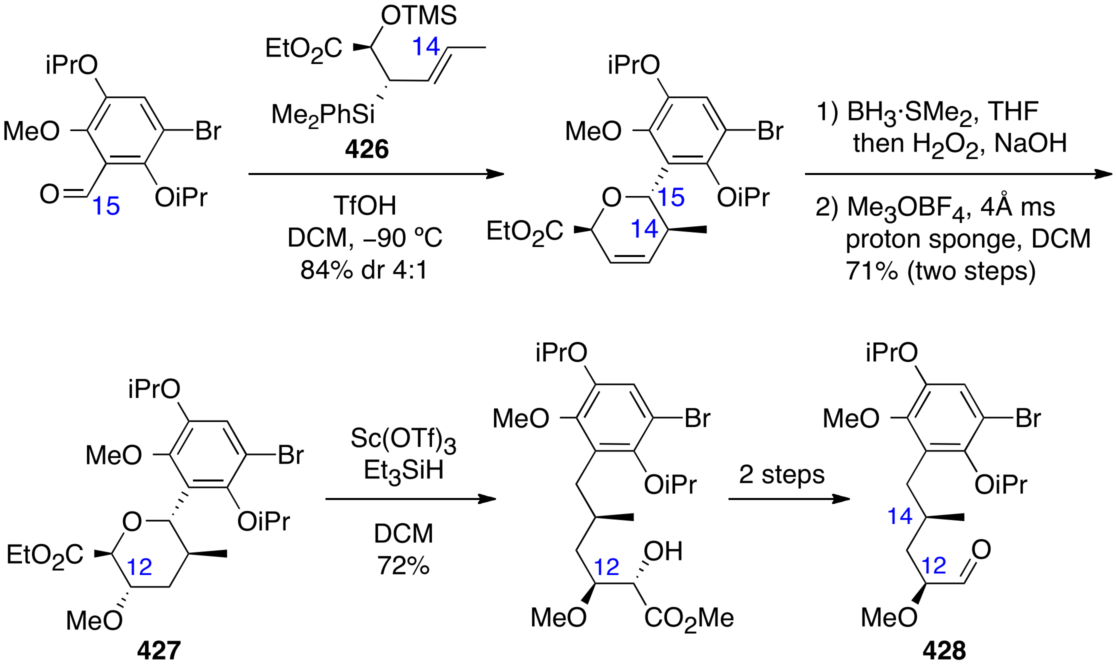
Scheme 50. Panek's synthesis of the left-hand portion of reblastatin.

Panek's synthesis of reblastatin[68] introduced a number of improvements with respect to previous synthetic approaches, starting from the fact that this new route was much more convergent. Thus, left-hand half **423**, was subjected to hydrozirconation/zincation before being added to a fully elaborated right-hand half aldehyde **424**, to provide **425** with excellent selectivity at C7, consistent with a Cram-chelate transition state (Scheme 51). The ring-closure was later effected via a Cu-catalyzed amidation reaction, which was the first example of this sort. Until this point all the previous syntheses had involved a macrolactamization.

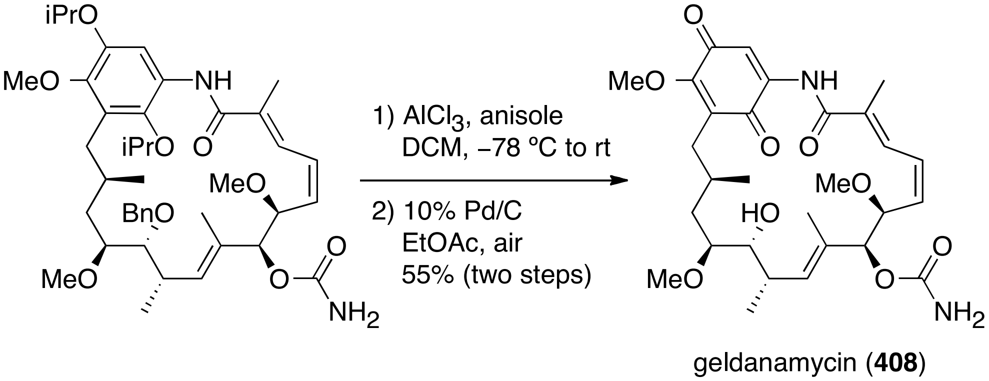


Scheme 51. Completion of the synthesis of reblastatin by Panek.

The Panek group also reported the second total synthesis of geldanamycin,[73] again by exploiting their chiral crotylsilane method. Since a deoxygenation step is required, their route was modified in order to reduce the number of steps. Thus, a tailored chiral crotylsilane **426** was employed, which provides a pyran ring as product. Hydroboration/oxidation and deoxygenation (in the form of a reductive pyran ring-opening) took place in a similar manner as in the case of reblastatin, to afford the corresponding left-hand half **428** comparatively in a lower number of steps (see Scheme 50).



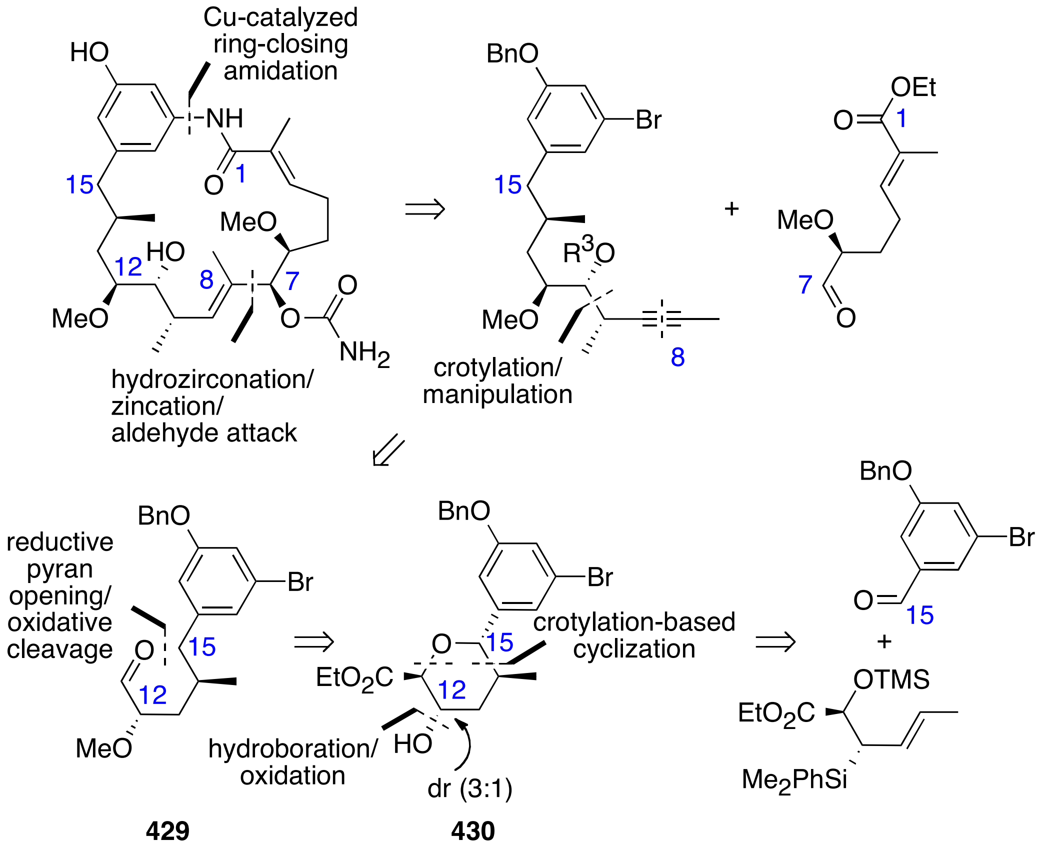
Scheme 52. First steps in Panek's total synthesis of geldanamycin.



Scheme 53. Final steps in Panek's total synthesis of geldanamycin.

Moreover, in the very final steps, deprotection of the diisopropyl and benzyl ethers, in the presence of the methyl ethers was accomplished with $AlCl_3$ to generate dihydrogeldanamycin, which was readily oxidized with catalytic palladium on carbon under an air atmosphere to give geldanamycin selectively (Scheme 53). In this manner, Panek provided a solution to the selectivity issues observed in the first total synthesis of geldanamycin (Scheme 49).

Very recently, Panek reported the first total synthesis of autolytimycin,[67] which is based on the tailored chiral crotylsilane **426**, which in the same publication was also employed in a second-generation synthesis of reblastatin. Scheme 54 shows the full retrosynthetic scheme for Panek's synthesis of autolytimycin, highlighting its convergency.

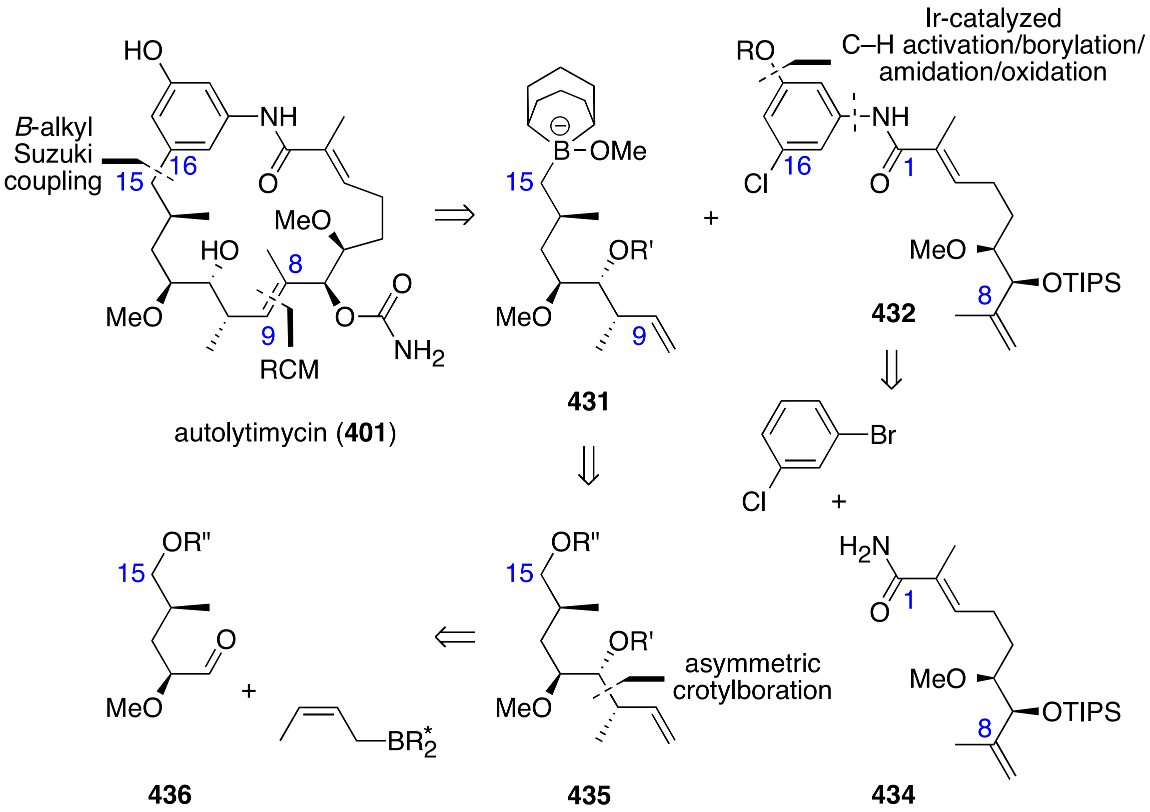


Scheme 54. Panek's route in the total synthesis of autolytimycin.

Among all the presented synthetic approaches to the C15-ansamycin compounds, Panek's approach is indeed superior in terms of convergency and rapid installation of stereochemistry. The use of chiral crotylsilanes has provided access to several members of the geldanamycin family, however, each synthesis starts over with a different aromatic core that eventually undergoes the same transformations. It is clear that an approach that introduces the aromatic moiety in a late stage would be significantly more attractive. On the other hand, the chiral crotylsilanes reagents introduce stereocenters in the molecule that are later destroyed. For instance, in the synthesis of autolytimycin (Scheme 54), intermediate **430** possesses four chiral centers, but after reductive pyran opening and oxidative cleavage only two stereocenters are left in intermediate **429**, one of which was installed via hydroboration with moderate selectivity (3:1).

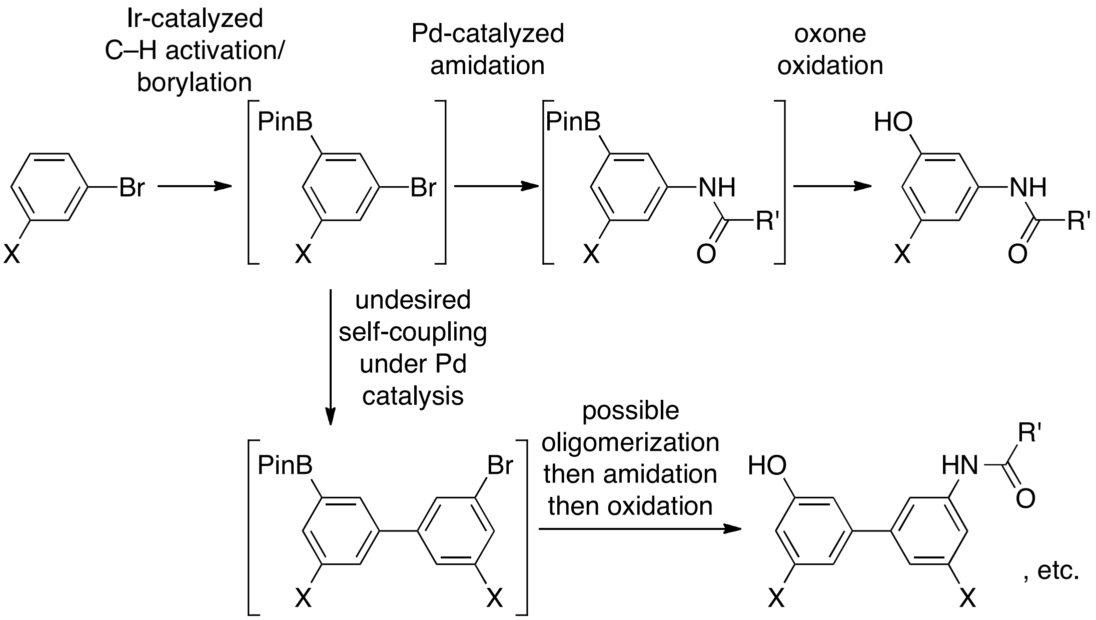
4.4. Our synthetic approach to autolytimycin

Our synthetic strategy toward autolytimycin (**401**) is shown in Scheme 55. The target molecule was split into two halves **431** and **432**. A *B*-alkyl Suzuki coupling[74] reaction appeared as an adequate method for the connection of the alkyl chain to the aromatic core and a ring-closing metathesis would allow the closure of the 19-membered macrocycle. Formation of alkylborane coupling partners such as **431** involves, in most of the cases, a hydroboration reaction[75] but the presence of a β-stereocenter suggested that preparation from an alkylmetal[76] intermediate would be more appropriate, since methods for asymmetric hydroboration have not yet been fully developed.[77] Though 9-BBN derivatives are frequently the reagents of choice,[78] we determined that alkyl partner **431** or any boron-containing alternative could be prepared at the appropriate moment from a stable precursor such as **435**.



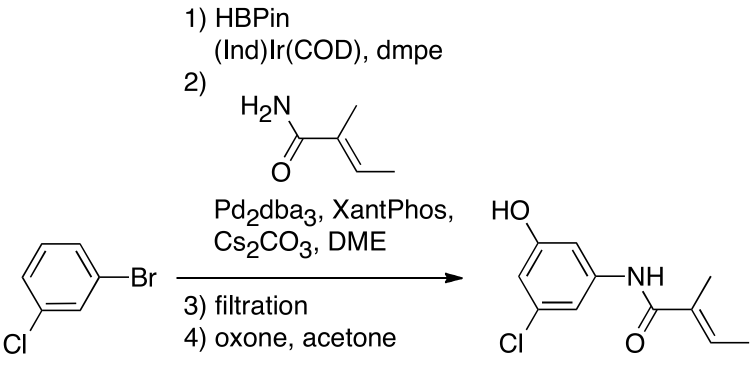
Scheme 55. Our synthetic approach to autolytimycin.

On the other hand, we planned to apply our one-pot C–H activation/borylation/ amidation/oxidation method[5h] to 3-bromochlorobenzene and amide **434** to access the necessary Suzuki partner amidochlorophenol **432**. Ir-catalyzed C–H activation allows the easy preparation of 1,3,5-trisubstituted arenes since its regioselectivity is driven by sterics, not by electronics and besides being amenable to one-pot transformations, it permits the presence of halogens that can then be used for further functionalization.



Scheme 56. Observed side reactions during Ir-catalyzed C–H activation/borylation/amidation/oxidation.

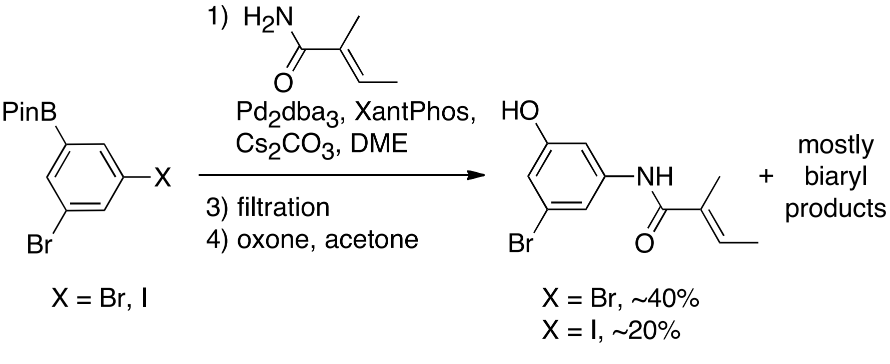
In the presence of halogens, however, it is necessary to suppress undesired self-Suzuki couplings and oligomerizations that might occur under palladium catalysis during the amidation step (Scheme 56). An opportune way to this is to moderately inactivate the Bpin group toward transmetalation under strictly dry conditions. Dr. Feng Shi[31] determined that 3-bromochlorobenzene is the most appropriate dihalogenated substrate for the three-step process, given the complete inactivity of aryl chlorides to the $Pd_2(dba)_3$/XantPhos catalyst system used in amidations. Subjection of 3-bromochlorobenzene to our one-pot protocol with a model α,β-unsaturated amide successfully provided chloroamidophenol **433** in high yield over three steps (Scheme 57), which bodes well for the employment of this chemistry in our total synthesis.



433

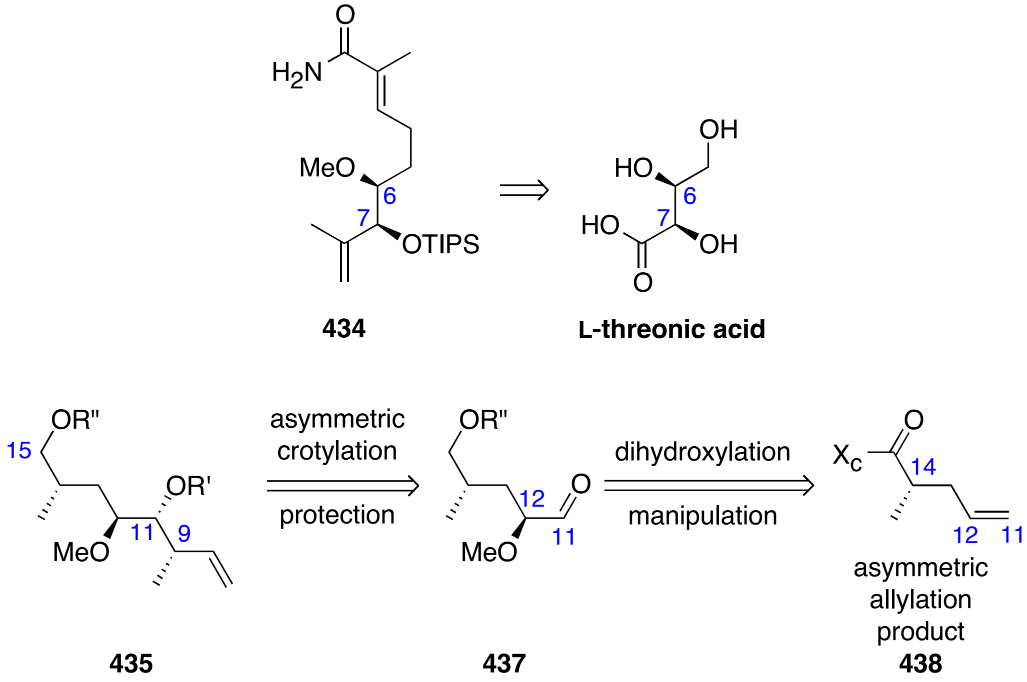
Scheme 57. One-pot Ir-catalyzed C–H activation/borylation/amidation/oxidation.

Thus, access to an amidochlorophenol is straightforward, however, the subsequent alkyl chain attachment has to be performed on this unactivated aromatic chloride. Although the Suzuki cross-coupling is the third most common C–C bond forming reaction used for the preparation of drug candidates,[79] sp^3–sp^2 couplings with aryl chlorides are rarely, if ever, used in the synthesis of elaborate structures. Attempts[31] to obtain the corresponding amido*bromo*phenol, starting from 1,3-dibromobenzene or 3-bromoiodobenzene resulted in significant formation of biaryl products, even when purified borylated compounds were subjected to just amidation/oxidation (Scheme 58).



Scheme 58. Attempts to replace the chloro with a bromo substituent in amidation/oxidation model studies.

Significant advances in the last decade[27,80] allow coupling reactions with chloroarenes, which were formerly known to be unreactive substrates. Therefore, despite having an aryl chloride electrophilic partner such as **432**, marked by the presence of two electron-rich substituents, we opted to take the opportunity to evaluate available methods for sp^3–sp^2 couplings and test their efficacy in this complex system.



Scheme 59. Flexible access to the stereochemistry on the building blocks for the construction of autolytimycin.

Having proposed an approach that introduces the aromatic moiety with reactions that do not create stereogenic centers, we aimed at developing a route to the *ansa* chain that is flexible from a stereochemical point of view. To install the stereocenters on carbons 6 and 7 we turned to the chiral pool (Scheme 59); L-threonic acid contains two chiral oxygenated centers with the same stereochemistry as **434**. Since by exploiting carbohydrate-based synthons[81] we could access variations of **434** with altered stereochemistry, this approach was certainly attractive. For our current target, L-threonic acid can be readily prepared from vitamin C.[82]

Intermediate **435**, on the other hand, bears four stereocenters that can be established by utilizing three (or only two) key stereo-defining steps (Scheme 4). The stereocenter located on C11 and the pendant chain moiety linked to it can be obtained via asymmetric crotylation of aldehyde **437**. The two oxygen atoms connected to carbons 11 and 12 and the stereocenter on C12 can be installed by applying a Sharpless dihydroxylation;[37] the hydroxyl groups delivered on the terminal alkene are distinct and can be differently functionalized. At this stage, the relative position of the C11–C12 double bond and the C14 stereocenter suggests the application of an asymmetric enolate allylation,[83] which lead us to recognize **438** as our initial target.

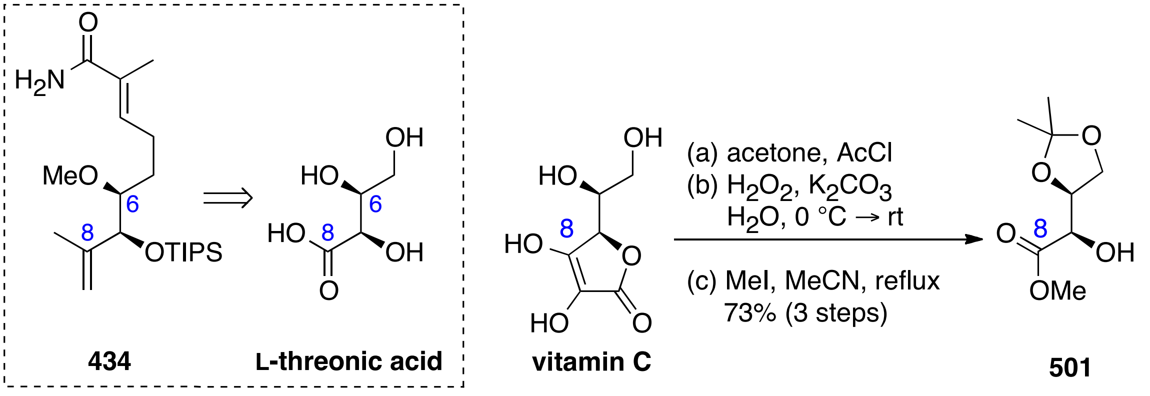
Chapter 5. A synthetic approach to autolytimycin: Synthesis of Suzuki partners

One of the main disconnections in our synthetic approach to autolytimycin is a *B*-alkyl Suzuki coupling involving two fully functionalized halves – an amide-containing aryl chloride and an alkyl-BBN adduct – that together form the complete carbon network of the natural product. The preparation of these two elaborated structures is presented in this chapter, which follows our retrosynthetic plan described in Section 4.6 (page 64).

5.1. Preparation of the aryl partner

5.1.1. Synthesis of the amide portion

According to the synthetic route developed by Dr. Feng Shi,[31] preparation of amide **434** started with the synthesis of 3,4-isopropylidene-L-threonic acid methyl ester (**501**)[h] in three high-yielding steps from vitamin C[82] (Scheme 60). In this manner, the two present stereocenters are acquired from the chiral pool, avoiding the need for asymmetric induction in the preparation of this half of the molecule.



Scheme 60. Preparation for 3,4-isopropylidene-L-threonic acid methyl ester.

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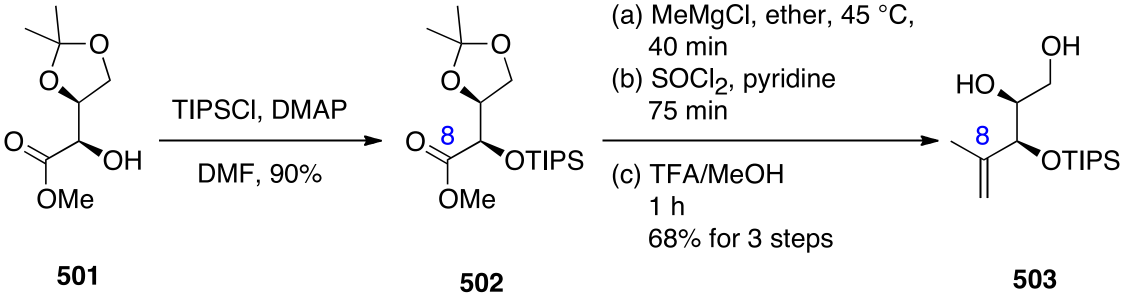
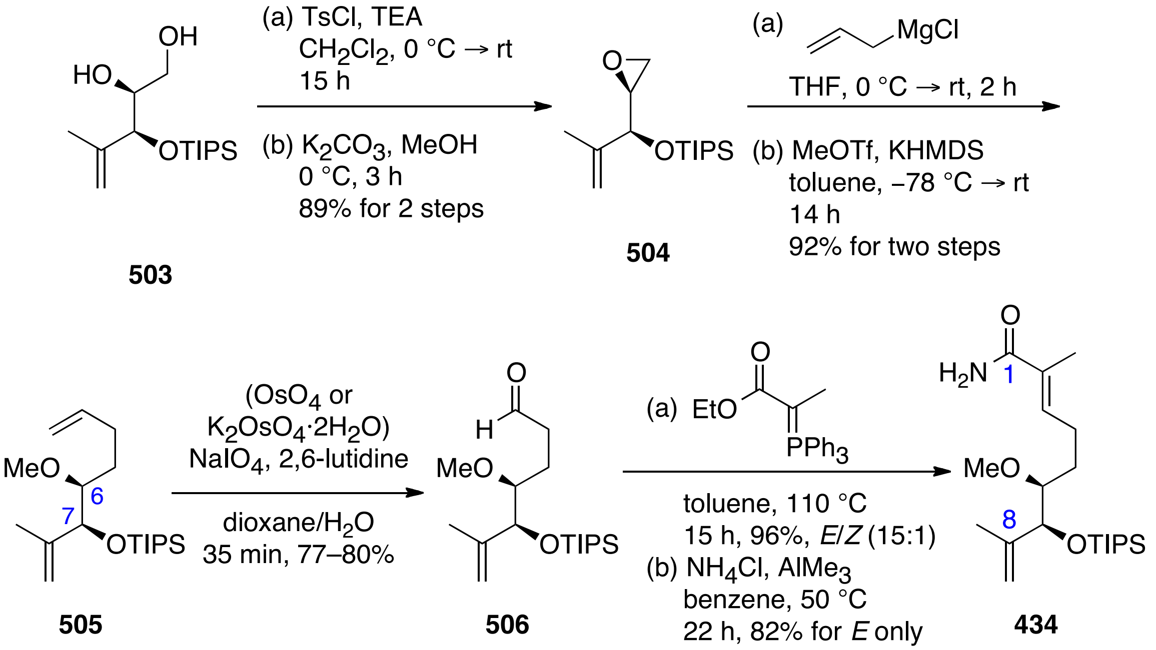
[h] Ester **501** is commercially available but its preparation in large scale from inexpensive vitamin C was significantly more convenient.

In order to transform the ester functionality at C8 into the required 2-propenyl group, **501** was TIPS-protected and afterward subjected to a double methyl Grignard addition, followed by dehydration, furnishing a 1,1-disubstituted olefin. Then, acid-promoted deprotection of the acetonide revealed diol **503** (Scheme 61). Dr. Monica Norberg[84] demonstrated that a series of reactions in the preparation of amide **434** could be performed sequentially using crude materials from the preceding step. In this particular case, the crude tertiary alcohol from the Grignard reaction of **502** can be directly dehydrated and subjected to deprotection, without purification of the intermediates. This *modus operandi* was successfully applied in multigram scale to afford **503** in 68% yield over three steps.



Scheme 61. Installation of the 1,1-disubstituted olefin moiety in construction of the amide portion of autolytimycin.

Installation of the (*E*)-α,β-unsaturated amide moiety involved four specific stages showed in Scheme 62. First, diol **503** was transformed into epoxide **504** via tosylation and treatment with a mild base for ring closure. A high yield was obtained, again, in a two-step process without purification of the primary tosylate intermediate. Second, the carbon chain was extended by epoxide opening with allylmagnesium chloride followed by methylation[85] to provide diene **505**. It is important to mention that our choice for this specific (and relatively expensive) methylation procedure was based on our need to avoid a silyl group migration from the C7 protected alcohol to the C6 alkoxide. The same issue determined our preference for the bulky TIPS protecting group.[31] For the third stage, a selective reaction of the monosubstituted olefin in the presence of the 1,1-disubstituted alkene was required. Interestingly, treatment of diene **505** with catalytic osmium tetroxide or potassium osmate[i] together with NaIO$_4$ and 2,6-lutidine[86] resulted in oxidative cleavage, furnishing aldehyde **506** in very good yield and with outstanding selectivity.[84] Even though electron-rich olefins generally react faster than electron-deficient alkenes in osmylation reactions, a number of exceptions to this rule are found in the literature.[87]



Scheme 62. Preparation of the amide portion in our route to autolytimycin.

Finally, the synthesis of amide **434** was completed after a Wittig olefination of aldehyde **506** with commercially available (carbethoxyethylidene)triphenylphosphorane, which gave

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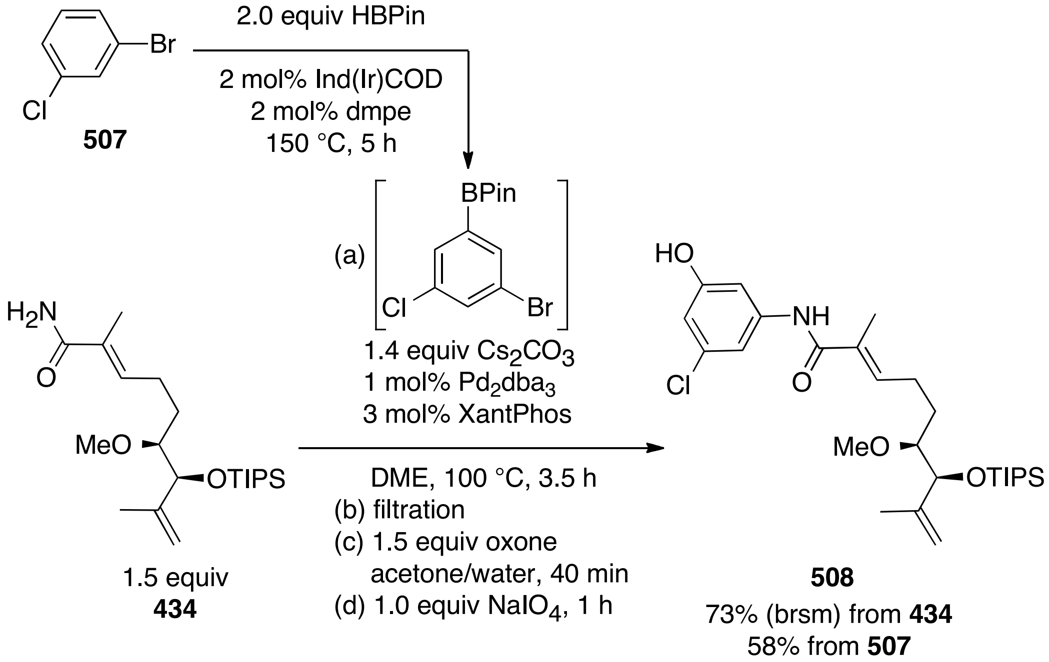
[i] Since osmium tetroxide solutions tend to deteriorate, the use of the non-volatile potassium osmate is preferable in terms of reproducibility.

inseparable isomers of the corresponding ethyl ester in a 15:1 *E*/*Z*. A subsequent Weinreb amidation[88] afforded the desired (*E*)-α,β-unsaturated amide in an 82% isolated yield.[j]

5.1.2. C–H activation/borylation/amidation/oxidation

With amide **434** in hand, Dr. Feng Shi[31] and Dr. Monica Norberg[84] confirmed the applicability of our one-pot C–H activation/borylation/amidation/oxidation method on an elaborated system (Scheme 63), to provide our desired *B*-alkyl Suzuki aryl chloride partner **508**.



Scheme 63. One-pot C–H activation/borylation/amidation/oxidation applied in our synthetic approach to autolytimycin.

Performing the three-step sequence gave very good results when the amide was used in excess; 1.5 equivalents were sufficient to keep the undesired Suzuki self-coupling, which was the major

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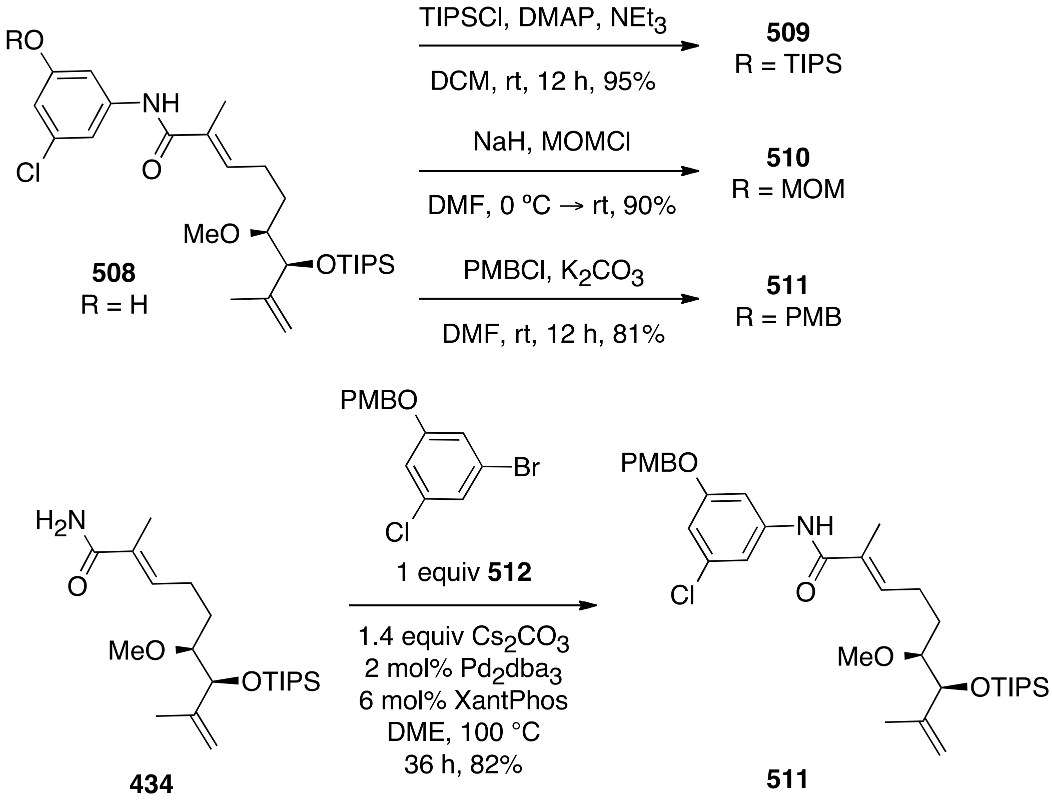
[j] Reaction performed by Dr. Monica Norberg.

side reaction,[k] within acceptable levels (~6%).[84] Most importantly, the excess of amide **434** was recovered in excellent yield. For reasons discussed in Chapter 6, the *B*-alkyl Suzuki coupling was studied on a series of protected amidochlorophenol substrates (**509**–**511**), which were easily obtained from **508** (Scheme 64).



Scheme 64. Preparation of protected amidochlorophenols in our route to autolytimycin.

An alternative route to protected amidochlorophenols was established by Dr. Monica Norberg. For instance, **511** could also be prepared in high yield by amidation of PMB-protected bromochlorophenol **512** with our elaborated amide **434**. Protected phenol **512** is accessible via a one-pot C–H activation/borylation/oxidation (Scheme 65), so essentially the same steps (borylation, amidation, oxidation, protection) are carried out, but in different order. This new

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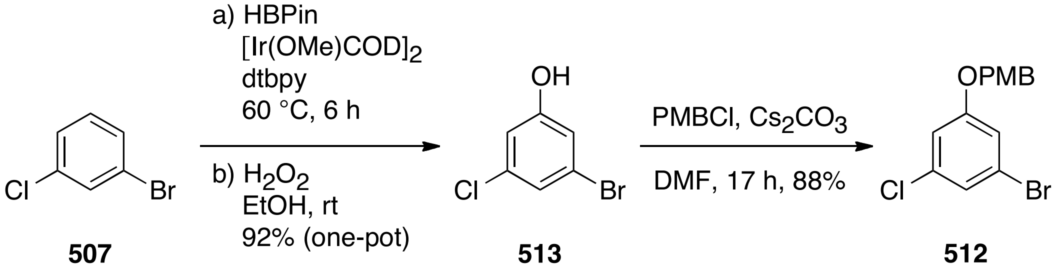
[k] See section 4.6 for a discussion.

route would be preferred for the preparation of protected Suzuki aryl chloride partners since undesired reactions and the use of an excess of amide in the preparation of **508** (Scheme 63) can be avoided.

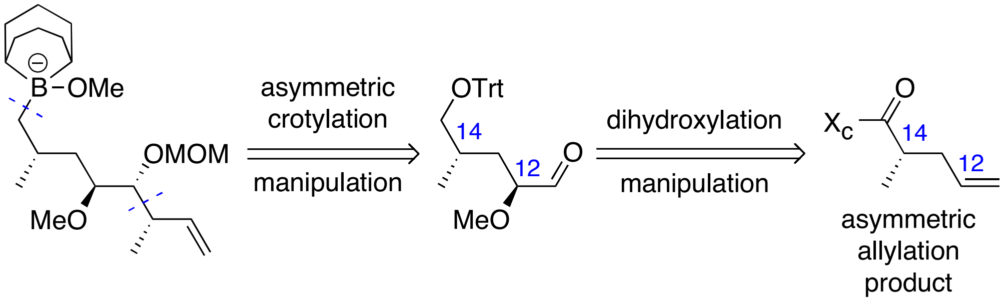


Scheme 65. Optimized preparation of PMB-protected 3-bromo-5-chlorophenol.

The late-stage installation of aromatic cores from diverse sources that are not necessarily 1,3,5-trisubstituted is valuable in terms of potential synthesis of analogs. There have been reports on the preparation of autolytimycin analogs with few non-natural aromatic cores via mutasynthesis (genetic engineering).[89] Total synthesis would significantly expand the scope of aromatic moieties that could be incorporated.

5.2. Synthesis of the alkyl partner

Unlike the amide-containing aryl chloride half of the molecule (**508**), the alkyl-BBN Suzuki partner **514** did require asymmetric induction in its preparation. The construction of this system with four chiral centers could be divided in two stages: the installation of stereocenters at C12 and C14, and an asymmetric crotylation.

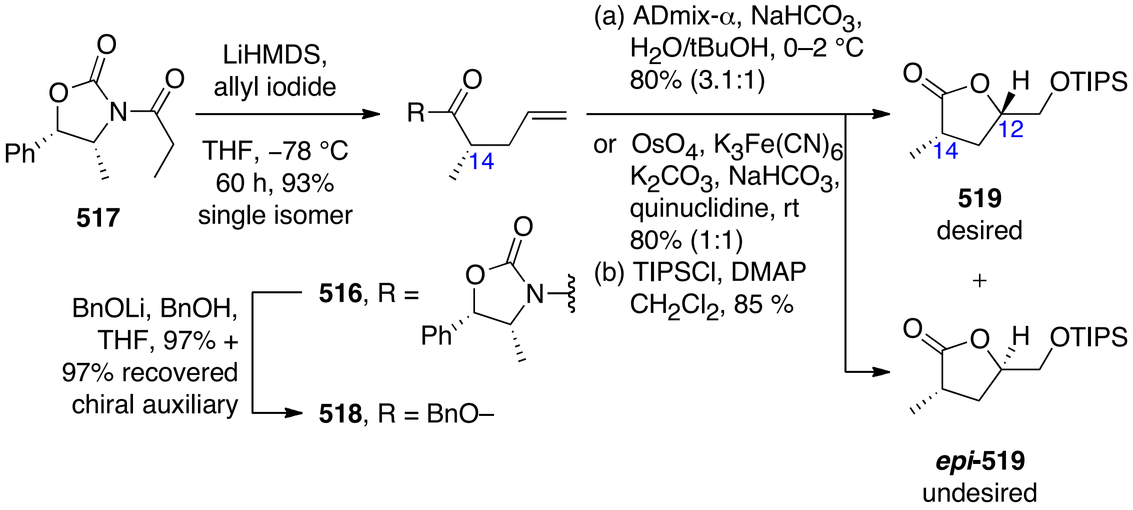


514 **515** **516**

Scheme 66. Two stages in the preparation of alkyl partner in our route to autolytimycin.

5.2.1. Installation of the C12 and C14 stereocenters

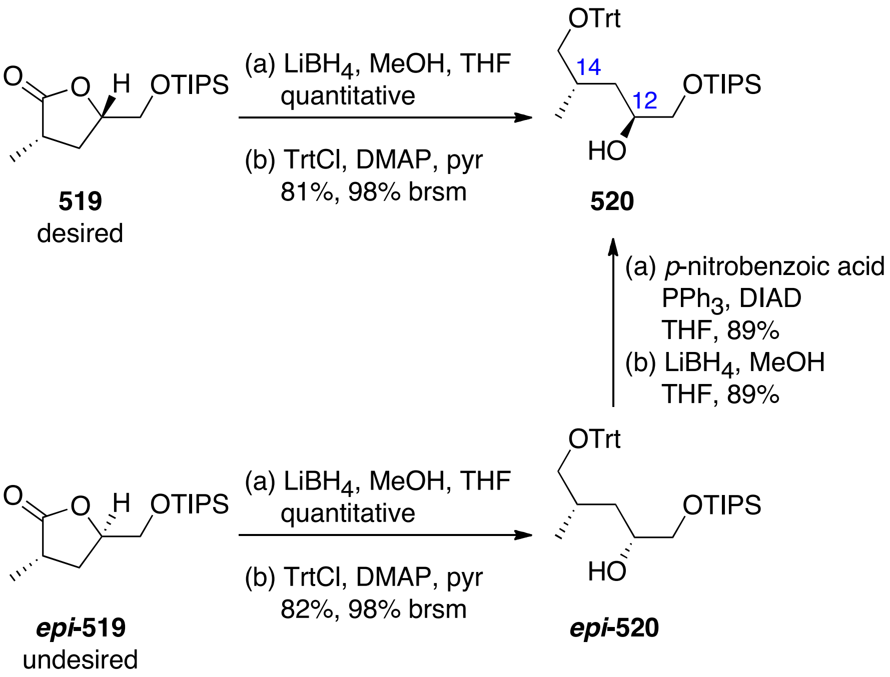
For our first stereo-defining step, Evans norephedrine-based enolate precursor **517**[90] was allylated using LiHMDS as a base (Scheme 7), which turned out to be a markedly slow and therefore extremely selective reaction that afforded **516** as a single diasteromer by NMR (>97:3).



Scheme 67. Installation of the C12 and C14 stereocenters of autolytimycin.

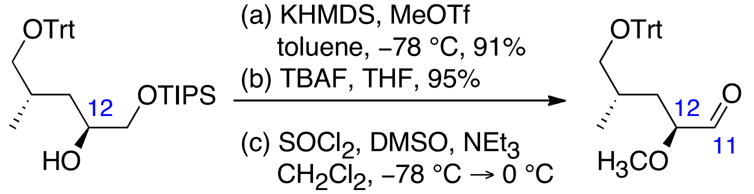
Then, in favor of the subsequent dihydroxylation step, we exploited a strategy previously reported by Carter and coworkers in their synthesis of the ABC ring system of azaspiracid:[91] the chiral auxiliary was replaced by a better leaving benzyloxy group to allow the kinetic-controlled formation of a five-membered lactone[37,92] after the asymmetric dihydroxylation. In accordance with their results, separation of the resulting diasteromers was viable after TIPS protection (i.e., **519** and ***epi*-519**).

While the bicarbonate-buffered medium used to avoid racemization of the C14 stereocenter is not expected to influence the stereoselectivity,[37] it is known that terminal alkenes can be poor substrates for Sharpless dihydroxylations. Optimized asymmetric conditions provided a modest 3.1:1 ratio of desired and undesired diastereomers. Isomer **519** was subjected to reductive lactone opening and selective trityl protection of the resultant primary alcohol to give the desired diprotected triol **520**.



Scheme 68. Protective group manipulations and recycling step in the synthesis of autolytimycin's alkyl half.

In an attempt to utilize the undesired material, the same steps were applied to ***epi*-519** simultaneously (Scheme 68). The resulting ***epi*-520** was esterified under Mitsunobu[93] conditions and treated with lithium borohydride to afford a product spectroscopically identical to **520**. This sequence demonstrates a viable way to recycle the undesired isomer. Given that non-asymmetric conditions can provide equal yields of a nearly 1:1 mixture of **519** and ***epi*-519**, (Scheme 67) asymmetric conditions can be avoided with only a minor decrease in the overall yield.



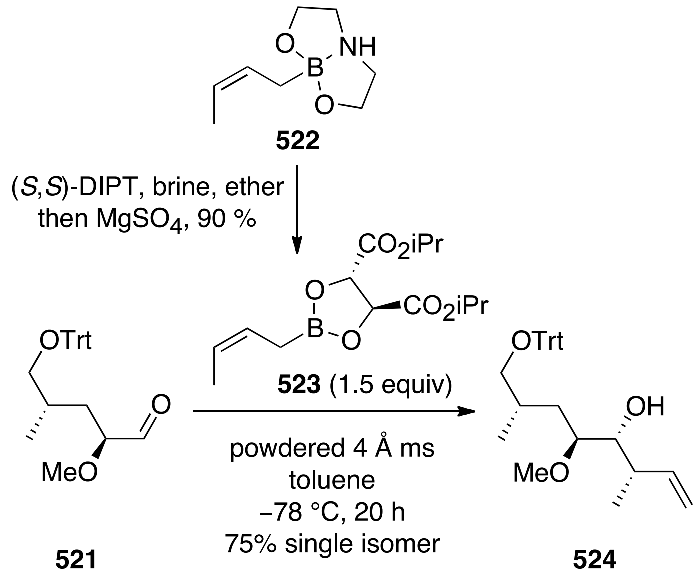
520 **521**

Scheme 69. Preparation of the crotylation substrate in the synthesis of autolytimycin.

Methylation[85] of **520** proceeded without complications and the C11 aldehyde was installed after TIPS deprotection and Swern oxidation, to efficiently provide intermediate **521** (Scheme 69). Again, this three-step process can be run on **520** with no purifications without affecting the final yield.

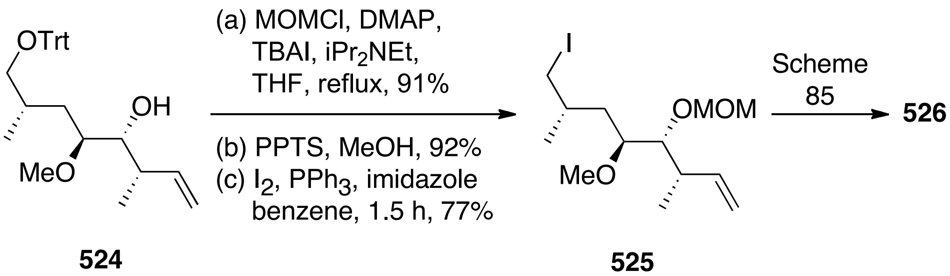
5.2.2. Asymmetric crotylation and final steps

For our last enantio-defining step – an asymmetric crotylation reaction – high selectivity was expected since the desired stereochemistry corresponds to a "match case" according to the anti-Felkin behavior of (*Z*)-crotylmetal reagents.[94] In order to provide large quantities of material and simplify its purification (i.e., avoid separation of diastereomers), we searched for a selective and scalable alternative. Roush's crotylboration[95] was found to be the most suitable since the chiral component, diisopropyl tartrate, is commercially available, inexpensive, and can be used as received. An optimum outcome was achieved when crystalline **522** was used as a precursor for (*S*,*S*)-(*Z*)-crotylboronate **523**.



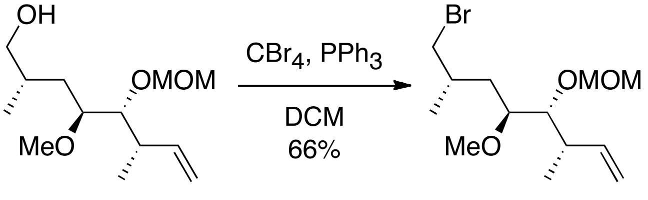
Scheme 70. Asymmetric crotylation in our synthetic route to autolytimycin.

Reaction in toluene under strict anhydrous conditions, making sure that all the crotylation agent was in the form of the tartrate ester,[96] afforded 75% of **524** as a single isomer (>97:3) at 60 mmol scale (~25 g of aldehyde). Reactions at small scale performed equally well with yields in the 70–80% range.



Scheme 71. Final steps in the preparation of the alkyl partner in our synthetic approach to autolytimycin.

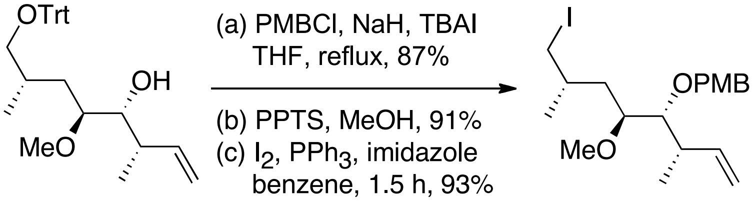
Finally, crotylation product **524** was manipulated to provide primary iodide **525** in three steps. We envisioned that **525** would be an appropriate precursor for the alkyl partner BBN adduct **526** to be employed in the following Suzuki reaction. As will be discussed in the following chapter, the coupling step required extensive experimentation and, as part of it, we studied the generation of BBN adduct **526** from alkyl bromide **528** as well.



527 **528**

Scheme 72. Preparation of a fully elaborated alkyl bromide to be tested in the generation of the BBN adduct in our synthetic approach to autolytimycin.

At the same time, it was necessary to evaluate the effects of the protective group in both the Suzuki coupling and the ring-closing metathesis steps. A specific modification that was done was the replacement of the MOM protecting group with a PMB (Scheme 73).



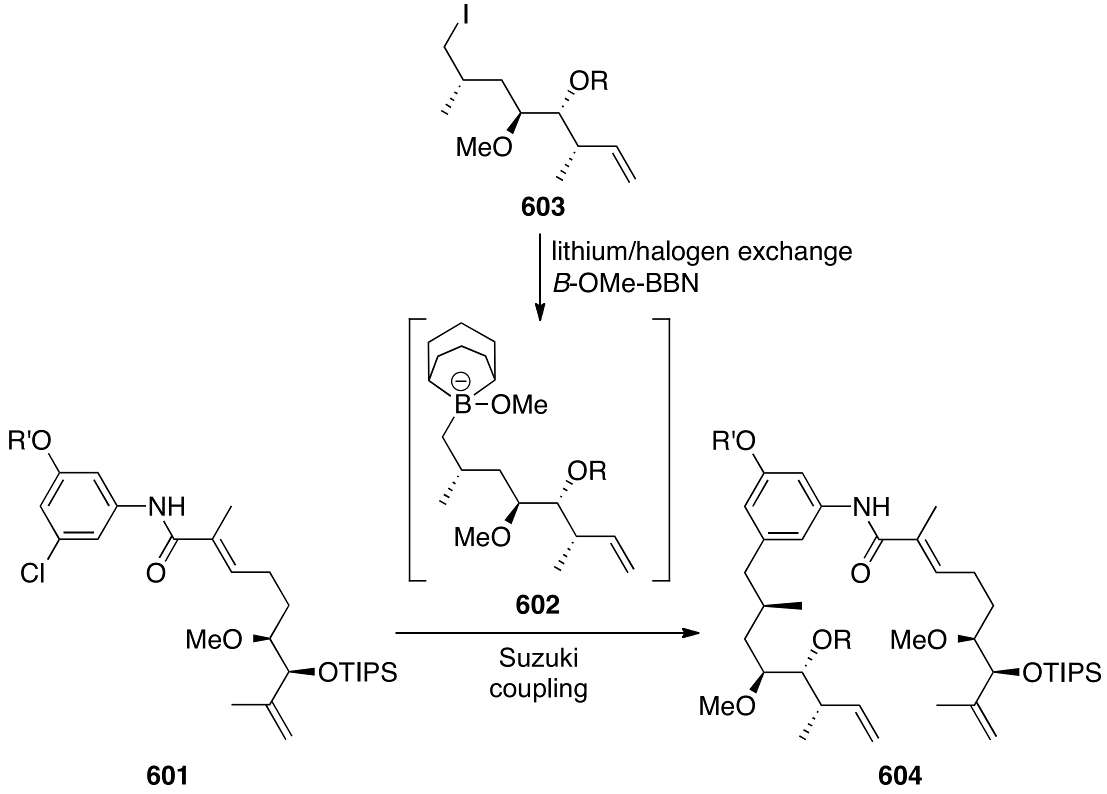
524 **529**

Scheme 73. Preparation of a modified alkyl partner in our synthetic approach to autolytimycin.

In conclusion, we have established of synthetic routes to access two fragments of the natural product autolytimycin containing its complete carbon network. Special considerations were taken in the design of the synthetic steps, in a way that could be adapted for the preparation of variations of the molecule with different stereochemistry.

Chapter 6. A synthetic approach to autolytimycin: *B*-alkyl sp^3–sp^2 Suzuki coupling

Following our retrosynthetic plan for the synthesis of the Hsp90 inhibitor autolytimycin described in Section 4.6 (page 64), the complete carbon network of this natural product is to be assembled in a convergent manner via a *B*-alkyl Suzuki coupling (Scheme 74) between two fully elaborated halves, whose preparation was presented in Chapter 5. Even though the generation of a BBN adduct from an advanced alkyl iodide (**603** → **602**) to be employed in a Suzuki coupling is well precedented in complex molecule synthesis,[97] the use of an electron-rich aryl chloride (**601**) as coupling partner was not. The application of this important C–C bond-forming reaction in our synthetic approach to autolytimycin will be presented in this chapter.

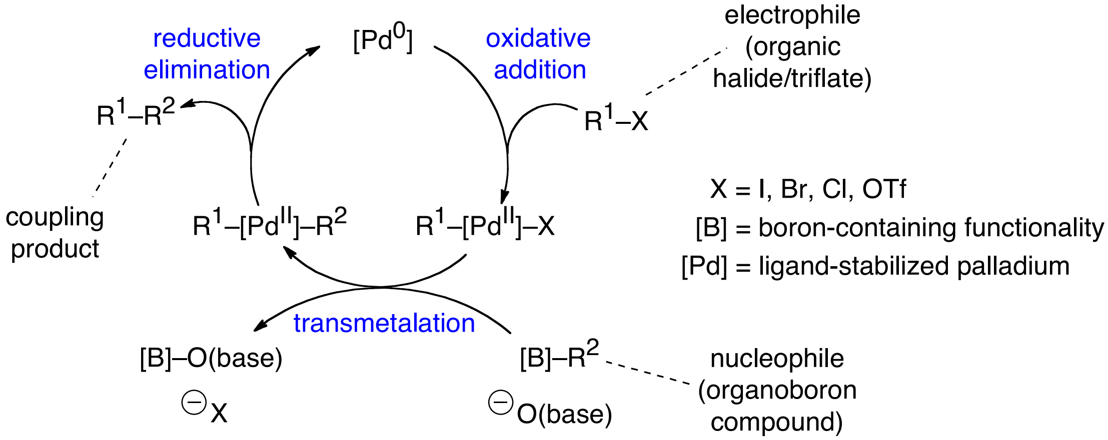


Scheme 74. The Suzuki coupling step in our synthetic approach to autolytimycin.

6.1. Literature precedence

6.1.1. The Suzuki cross-coupling

Cross-coupling reactions have had a tremendous impact in organic synthesis. The 2010 Nobel Prize in Chemistry was awarded to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki for the discovery and development of palladium-catalyzed coupling reactions. The Suzuki coupling is characterized by the use of organoboron compounds as nucleophilic partners in these reactions.[98] Given the low cost and toxicity, and bench stability of boron-containing compounds, the Suzuki coupling is usually the preferred method.[9]



Scheme 75. The Suzuki coupling catalytic cycle.

The Suzuki coupling follows the same catalytic cycle (Scheme 75) accepted as general for metal-catalyzed carbon–carbon bond-forming reactions.[99] In this way, a palladium(0) species oxidatively adds to an organic halide or triflate (electrophile), forming a Pd(II) intermediate that undergoes a transmetalation with the organoboron partner (nucleophile) to assemble a Pd(II) species containing both organic partners, which will form the desired coupling product via reductive elimination, process during which the active palladium(0) catalyst is regenerated.[1]

In traditional Suzuki systems, the oxidative addition step has been documented to be rate-limiting and it is known that aryl and vinyl halides that are activated by electron-withdrawing groups are more reactive toward oxidative addition than those with electron-donating groups.[100]

Currently it is accepted that, in coupling reactions, the identity of the rate-limiting step depends on the strength of the C–X bond in the organohalide, the reactivity of the organometallic partner in transmetalation, and other factors in a case-dependent manner.[101]

Since vinyl and aryl electrophiles easily undergo oxidative addition, the Suzuki coupling has conventionally been employed for sp^2–sp^2 bond-forming processes, as exemplified by its widespread use for the formation of biaryl systems.[102] However, besides aryl and vinyl electrophiles, there are plenty of literature examples where alkynyl, allyl, benzyl, and even alkyl halides and triflates participate in a Suzuki coupling under appropriate reaction conditions.[98b]

On the other hand, the order of reactivity of electrophiles toward oxidative addition has been established to be (under Pd(0)/PPh_3 conditions): [103]

$$\mathrm{I} > \mathrm{Br} > \mathrm{OTf} \gg \mathrm{Cl}$$

Thus, for many years, coupling reactions involved almost exclusively the reactive iodides, bromides, and triflates. However, thanks to the development of highly active catalyst systems

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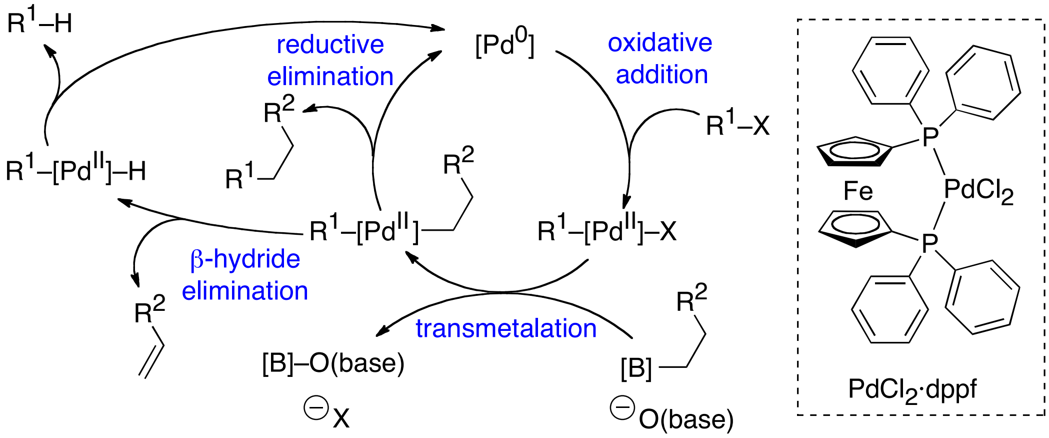
[1] It is also possible that the $^{-}X^*$ ligand on Pd could exchange with a ^{-}O(base) anion prior to the transmetalation *per se*.

bearing bulky phosphine/carbene ligands (See section 6.1.3), organic chlorides now are considered regular participants in this important reaction.

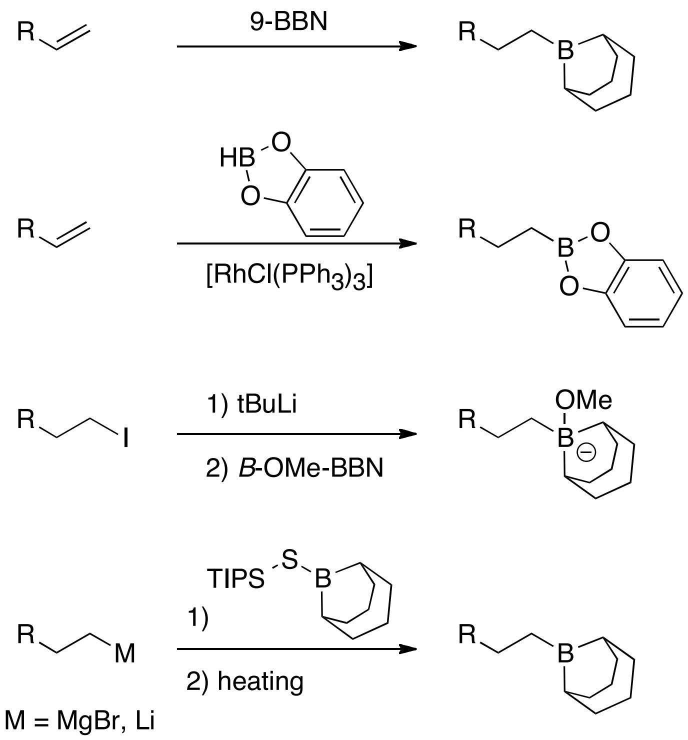
6.1.2. *B*-alkyl Suzuki coupling

The first examples of cross-coupling reaction using alkylboron compounds, specifically alkyl-BBN species generated via hydroboration, were reported by Suzuki and Miyaura in 1986.[104] Previously, coupling reactions involving alkyl groups bearing β-hydrogens had been limited due to the predisposition of alkylpalladium complexes to undergo β-hydride elimination (Scheme 76).



Scheme 76. Potential β-hydride elimination in the Suzuki coupling catalytic cycle involving alkylboron compounds.

Due to the steric requirements for β-hydride elimination,[105] its rate can be lowered by the use of excess ligand or by employing $PdCl_2$·dppf as a catalyst, which was successfully used by Hayashi[106] for coupling reactions with alkylmagnesiums and alkylzinc reagents. Because of its bite angle,[107] the bidentate bis(diphenylphosphino)ferrocene ligand (dppf) also induces rapid reductive elimination by enforcing a *cis* geometry between the two organic ligands (coupling partners) on the square planar Pd(II). This facilitates the formation the sp^3–sp^2 bond. Furthermore, the use of bulky ligands has also led to the development of efficient methods for sp^3–sp^3 Suzuki couplings.[108]



Scheme 77. Methods for the preparation of alkylboron Suzuki partners.

Access to alkylboron compounds to be used in coupling reactions (Scheme 77) usually implies a generation *in situ* via hydroboration[75] of from alkylmetal[76] species, due to purification difficulties. Alternatively, the more readily isolable alkylboronic acids[109] and trifluoroborates[110] can also be employed. The *B*-alkyl Suzuki coupling[74] has been extensively used in the area of total synthesis, as will be discussed in Section 6.1.4.

6.1.3. Aryl chlorides as electrophiles in *B*-alkyl Suzuki coupling

At present, numerous active catalyst systems have been developed that allow coupling reactions with aryl chlorides.[80] The reactivity of such systems is based on the use of bulky electron-rich ligands that readily allow the formation of monoliganded Pd(0) species (as opposed to diliganded) that are extremely active toward oxidative addition.[27] Shown in Figure 6 is a selection of bulky ligands that specifically includes those that have been shown to promote the formation of sp^3–sp^2 bonds.

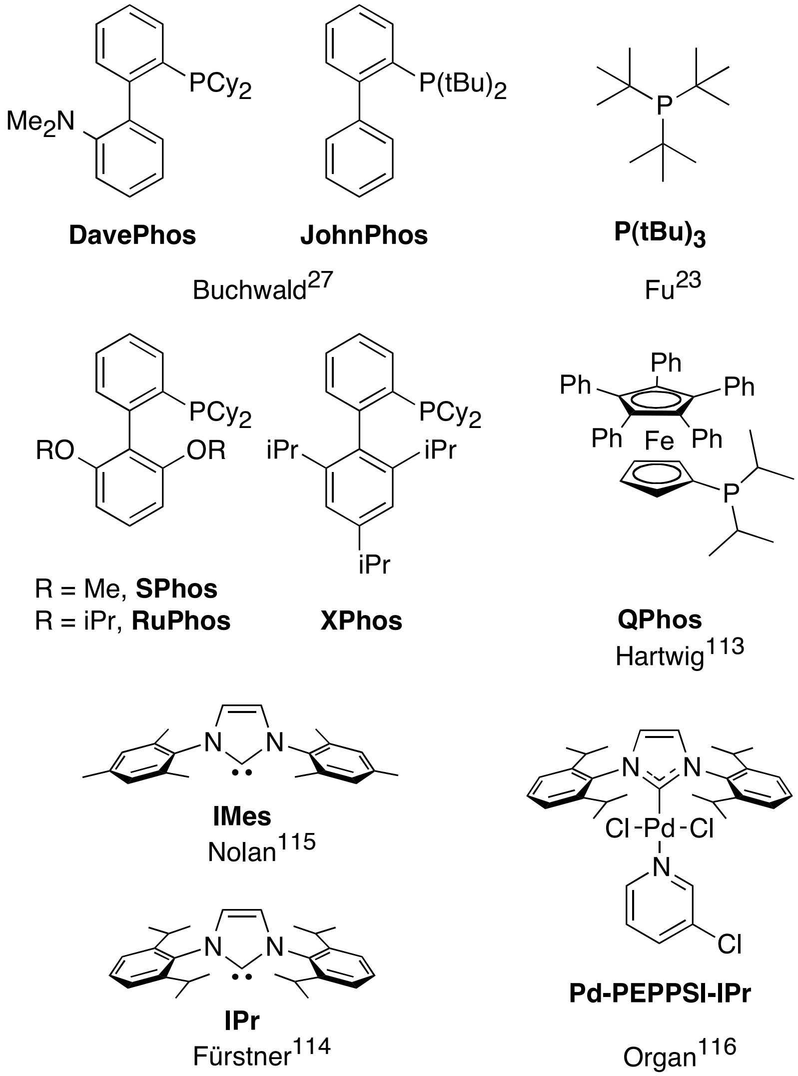
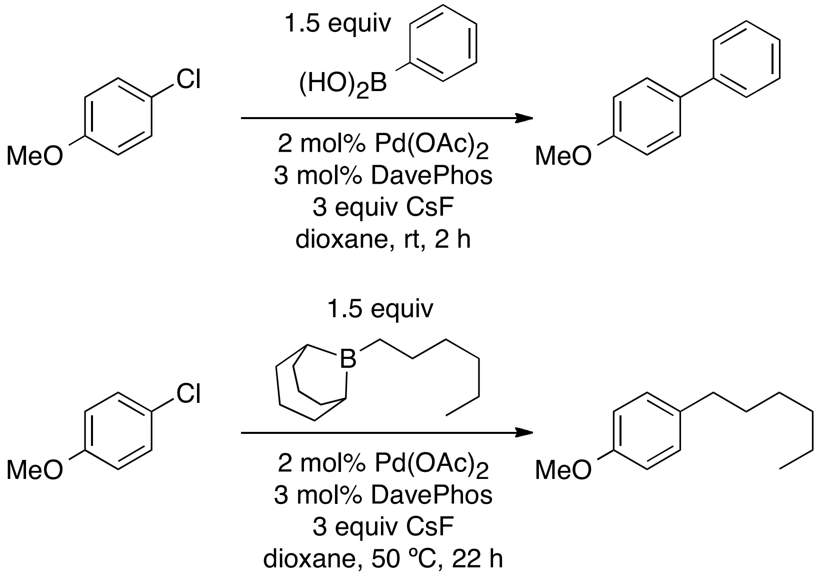


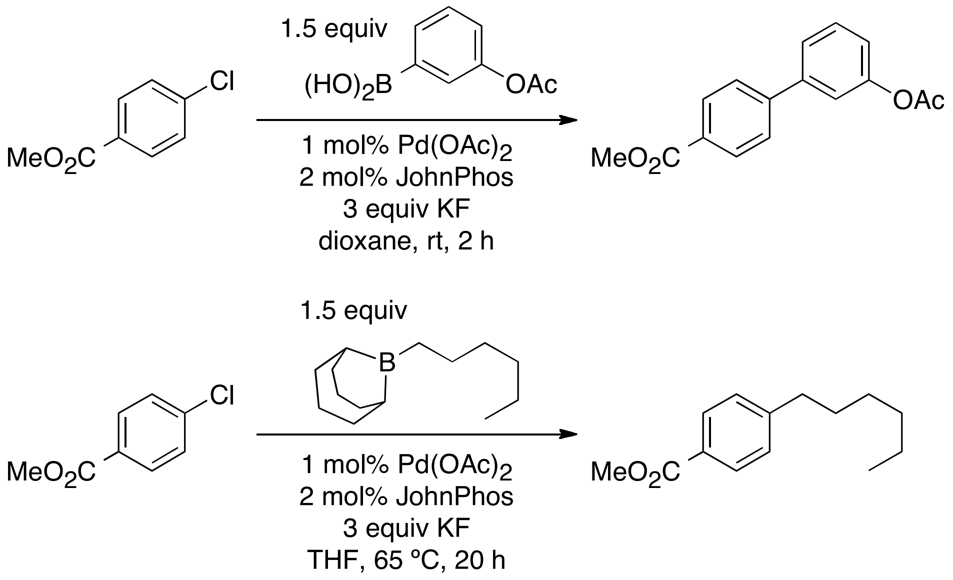
Figure 6. Selected examples of ligands that allow coupling reactions with aryl chlorides.

The first example of a successful coupling of an aromatic chloride with an alkylboron compound, specifically hexyl-BBN generated via hydroboration, was reported by Buchwald in 1998 when the highly active biaryl ligand DavePhos[111] was introduced (Scheme 78). Remarkably, DavePhos allowed the reaction of chloroarenes (even inactivated by electro-donating groups) and arylboron compounds to occur at room temperature. This, however, was not the case when an alkyl-BBN was used as the coupling partner, which suggests a lower propensity to transmetalation.



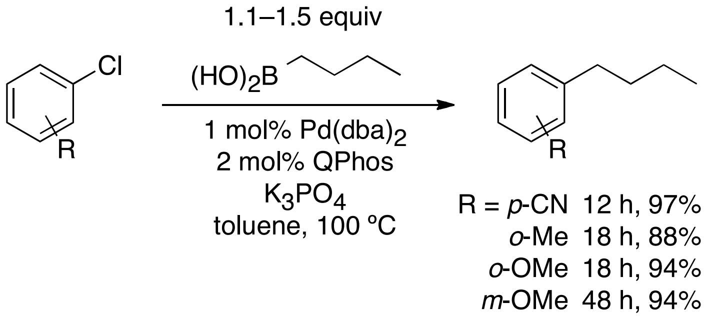
Scheme 78. Suzuki couplings on aryl chlorides using DavePhos.

Later, the Buchwald group reported that the dimethylamino group on DavePhos (originally assumed to be a bidentate ligand) was not required for high activity. This observation led to the development of a new highly active ligand named JohnPhos (See Figure 6).[112] Once again, as shown in Scheme 79, it is clear that arylboronic acids are significantly more reactive than alkyl-BNNs as partners.



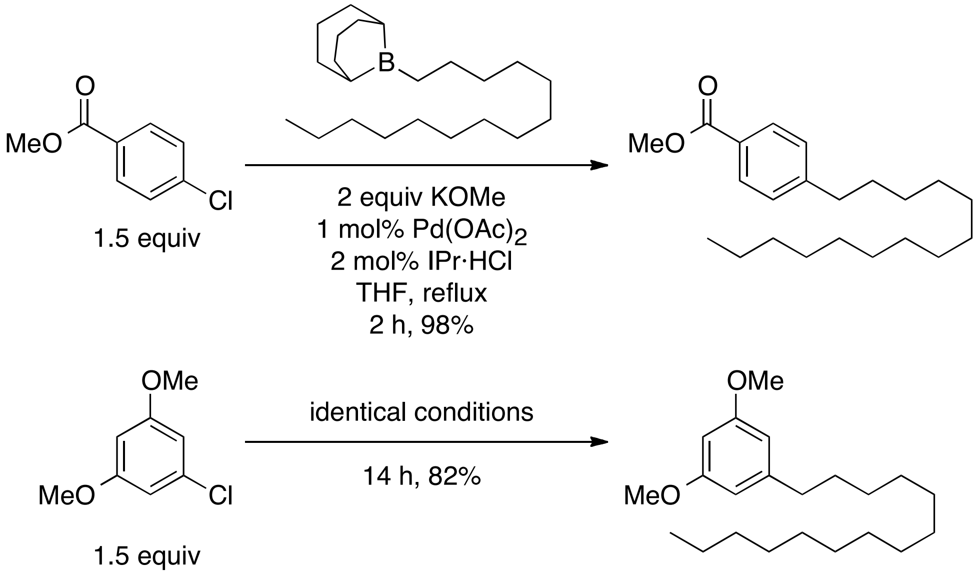
Scheme 79. Suzuki couplings on aryl chlorides using JohnPhos.

On the other hand, the massive ligand QPhos,[113] developed by Hartwig, for C–N, C–O, and C–C bond-forming reactions, has been shown to promote coupling reactions between aryl chlorides with alkyl boronic acids. Yet there are no reports of its use with alkyl-BBNs. From comparing the reaction times needed for various chloride substrates (Scheme 80), it is clear that the electronics of the substituents have a significant impact in the reaction rate, presumably affecting in the oxidative addition step.



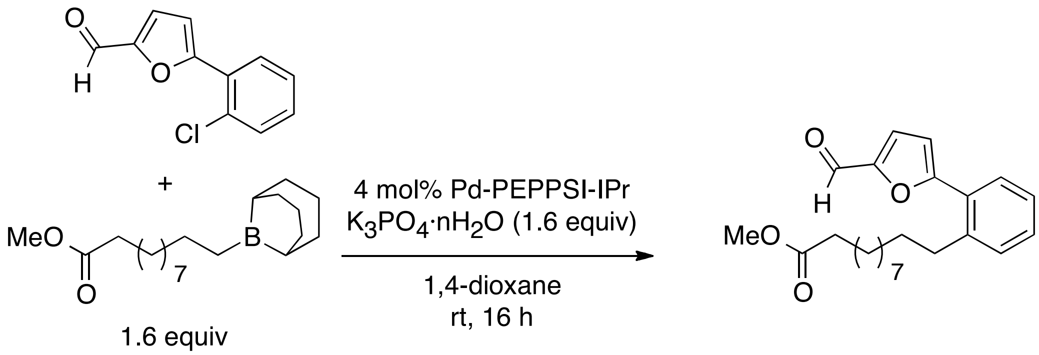
Scheme 80. Suzuki couplings of aryl chlorides and alkylboronic acids using QPhos.

Phosphines are not the only type of ligands that have been studied in *B*-alkyl Suzuki coupling with chloroarenes. Fürtsner[114] demonstrated that the N-heterocyclic carbene IPr (see Figure 6), generated *in situ* from its HCl salt in the presence of base, efficiently effected the coupling reaction of both activated and inactivated aromatic chlorides with alkyl-BBN partners generated via hydroboration. This result followed a previous report by Nolan,[115] where IMes (see Figure 6) was shown to activate aryl chlorides for reaction with arylboronic acids. As displayed in Scheme 81, the reaction rates are highly sensitive to the electronic effects of the ring substituents.



Scheme 81. *B*-alkyl Suzuki couplings of aromatic chlorides using the NHC ligand IPr.

The use of N-heterocyclic carbenes has been further improved by the Organ group with the development of the pyridine-enhanced precatalyst preparation, stabilization, and initiation ("PEPPSI") system.[116] Outstandingly, the use of this precatalyst allows reactions to proceed at room temperature.

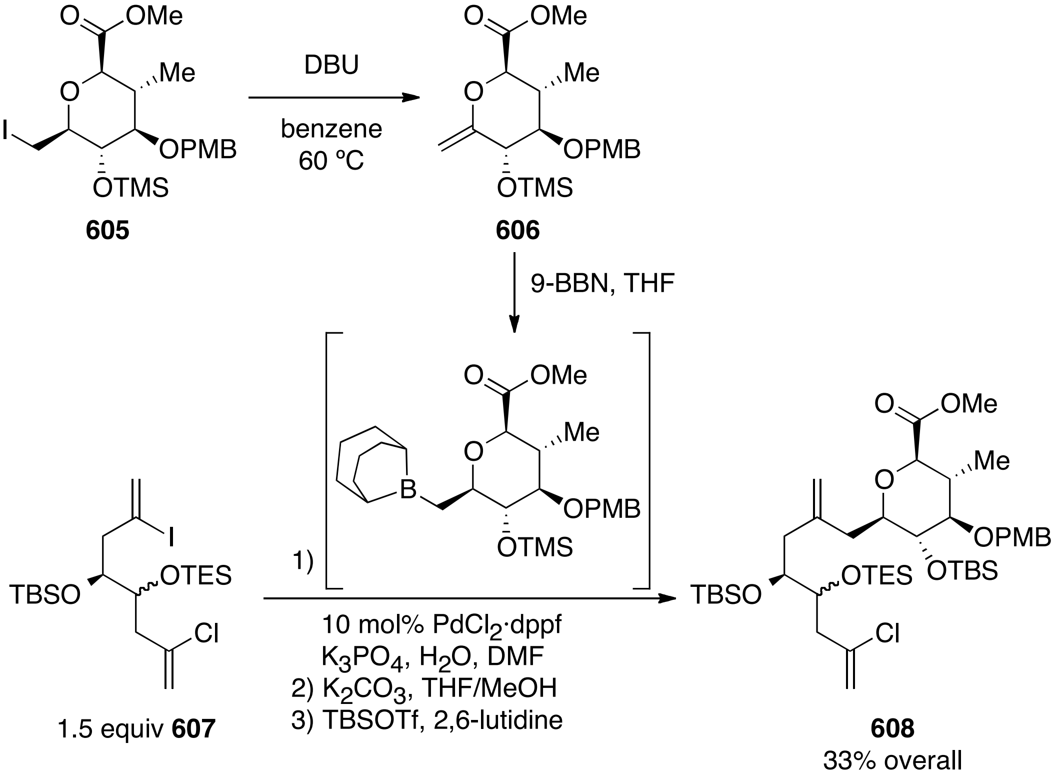


Scheme 82. Example of a *B*-alkyl Suzuki coupling with an aryl chloride using PEPPSI.

While there has been an explosive development of bulky ligands, both phosphine- and carbene-based, in the last decade, Buchwald's biaryl ligands have rapidly become the preferred alternative. Recently, Molander[110b] reported that by using parallel experimentation (high throughput screening) with multiple catalyst systems, SPhos and RuPhos generated the highest ratios of products in the coupling reactions of primary alkyltrifluoroborates with aryl chlorides. While there have been a considerable number of subsequent advances,[117] the use of aryl chlorides as partners for *B*-alkyl Suzuki coupling, especially in complex molecule synthesis, is still rare.

6.1.4. *B*-alkyl sp^3–sp^2 couplings in complex molecule synthesis

Due to the difficulty of purifying most alkylboranes, *B*-alkyl Suzuki couplings generally involve a prior *in situ* formation of the borane.[74] Literature examples that involve a hydroboration to prepare an alkyl-BBN species to be subjected to Suzuki coupling conditions are a considerable in number.[m] Specifically in complex molecule synthesis, such reported examples generally involve vinyl iodides,[118] vinyl bromides,[119] aryl bromides,[120] and aryl triflates[121] as coupling partners. Methods for *asymmetric* hydroboration have not yet been fully developed[77] but the present stereochemistry on the molecule can induce face selectivity in this process, resulting in well-defined new stereocenters. This concept is showcased in Paquette's synthetic studies toward altohyrtin A (Scheme 83) among several other examples.[122]



Scheme 83. A *B*-alkyl Suzuki coupling on a vinyl iodide featured in Paquette's synthetic studies toward altohyrtin A.

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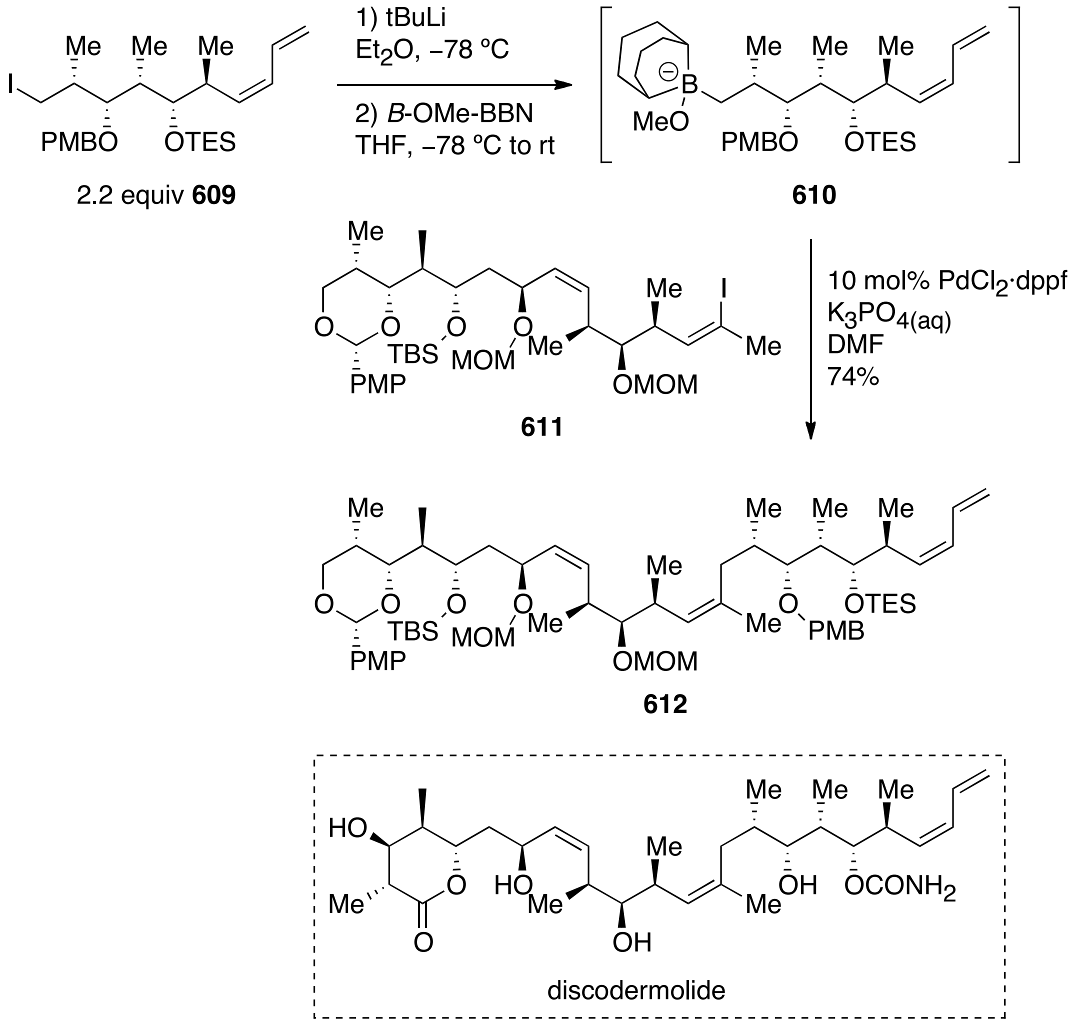
[m] The large number of examples found using Reaxys™ and Scifinder™ have been carefully reviewed and only few selected examples are cited here.

A notable application of the *B*-alkyl Suzuki coupling is presented in Marshall's total synthesis of discodermolide (Scheme 84).[97c] This is the first example of the generation of a BBN adduct from an elaborated alkyl iodide using lithium-halogen exchange followed by reaction with *B*-OMe-BBN. This concept however was first introduced in 1989 by Williard[97a] in his studies on the synthesis of the C10–C19 portion of amphidinolide A. Here a hydroboration would not have offered stereoselectivity and would have been incompatible with the diene moiety in **609**.



Scheme 84. *B*-alkyl Suzuki coupling step in Marshall's synthesis of discodermolide.

In general, literature examples[97] that feature non-hydroboration routes to alkyl-BBN coupling partners almost exclusively use alkyllithium-based BBN adducts, generated from alkyl iodides and Suzuki-coupled in a one-pot manner. It is important to mention that partners employed in those coupling reactions are vinyl bromides,[97a,b] vinyl iodides,[97c-p] and aryl iodides,[97q,r] substrates that are all exceedingly more reactive than aryl chlorides. Currently, there are plenty of active catalyst systems that allow coupling reactions with aryl chlorides. For some systems, examples of reactions with alkylboronic acids and alkylboron species (generated via hydroboration) have been reported, as discussed in section 6.1.3. To the best of our knowledge, however, there are no examples of the use of aryl chlorides as partners for *B*-alkyl Suzuki coupling in complex molecule synthesis. Despite this, it is known that aryl chlorides can be coupled with alkyl-BBN species (generated via hydroboration) and therefore, given the multiple reports on the generation of BBN adducts from elaborated alkyl iodides,[97] we envisaged that our desired reaction would be viable.

6.2. Preliminary results

Even though the *in situ* generation of a BBN adduct **526** from our fully elaborated iodide **525** via lithium-halogen exchange, followed by reaction with *B*-OMe-BBN, was not found to be problematic[n] the crucial sp^3–sp^2 coupling turned out to be a difficult step (Scheme 85). Optimized conditions allowed a maximum of 5% yield of the fully elaborated Suzuki product (**614**), accompanied by a bothersome undesired dechlorination side product (**615**).

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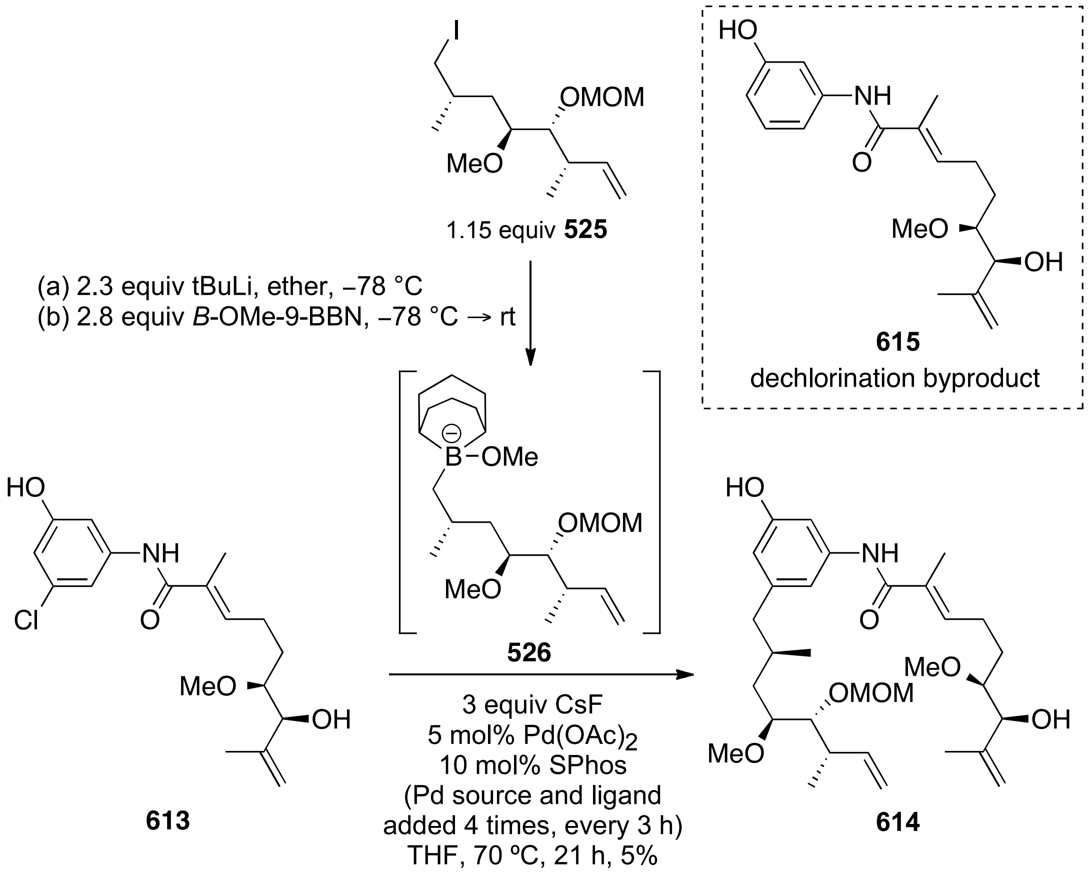
[n] This was demonstrated by Dr. Feng Shi[31] through ^{11}B NMR experiments.



Scheme 85. First productive real-system Suzuki coupling in our synthetic approach to autolytimycin.

By screening reactions conditions using model substrates (Figure 7),[o] it was found that protection of the phenol could have a potential benefit. Under basic conditions (required for efficient transmetalation among other advantages),[123] the phenol could be deprotonated, which would affect its solubility or perhaps make the aromatic ring more electron-rich, thereby lowering its reactivity toward oxidative addition. These statements, however, have not been experimentally verified.

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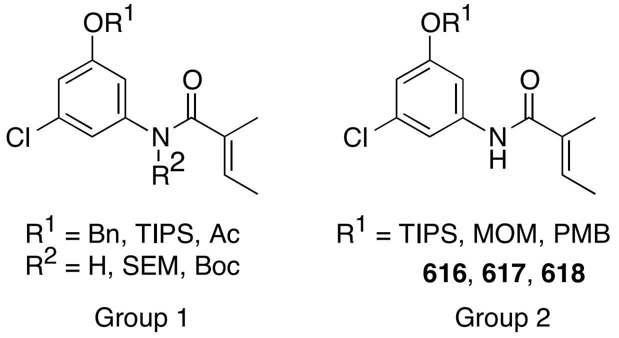
[o] Group 1 model substrates were studied by Dr. Feng Shi.[31]



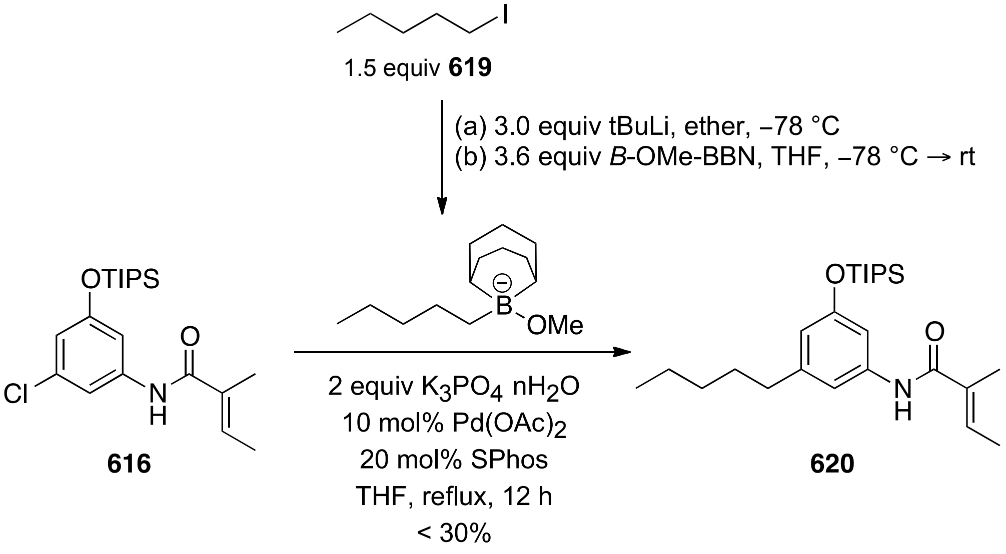
R^1 = Bn, TIPS, Ac
R^2 = H, SEM, Boc

Group 1

R^1 = TIPS, MOM, PMB
616, **617**, **618**

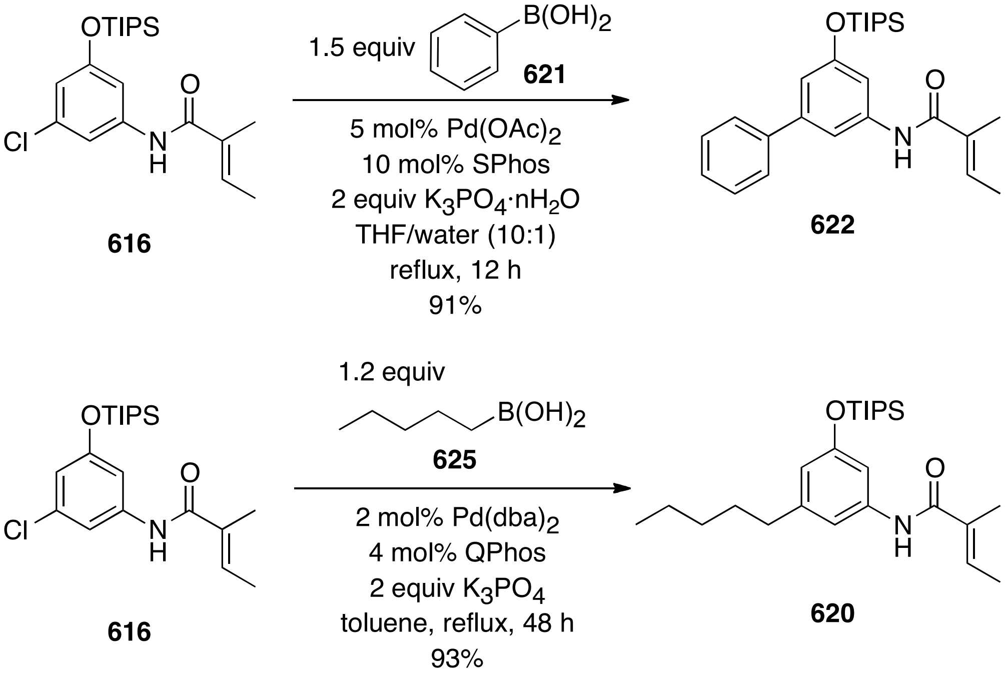
Group 2

Figure 7. Model amidochlorophenol substrates used to screen Suzuki coupling conditions in our synthetic route to autolytimycin.



Scheme 86. Modest results obtained with a model substrate in a preliminary screening.

Unfortunately, also a vast number of condition-exploring runs with these protected model substrates (Figure 7) only resulted in little, if any, formation of the desired product. The best conditions found to work (~30% conversion) in a model substrate (Scheme 86) were totally inefficient when applied to the fully elaborated system. Up to this point, our main concern was the low reactivity of these highly unactivated (electron-rich) chloride substrates, however, applying reported procedures for the coupling of aryl chlorides with arylboronic or alkylboronic acids on one of our model substrates afforded excellent yields of the coupled products (Scheme 87). The Pd(dba)$_2$/QPhos-promoted reaction was especially significant. Alkylboronic acids are known to be are less reactive towards transmetalation than arylboronic acids.[80] Under the original Suzuki conditions[75,124] for *B*-alkyl coupling reactions, several alkylboron compounds were compared; alkyl-BBN substrates were found to be the most active, while alkylboronic acids afforded 0% conversion even when TlOH was used as base.[p]



Scheme 87. Successful Suzuki coupling reactions on model amidochlorophenols.

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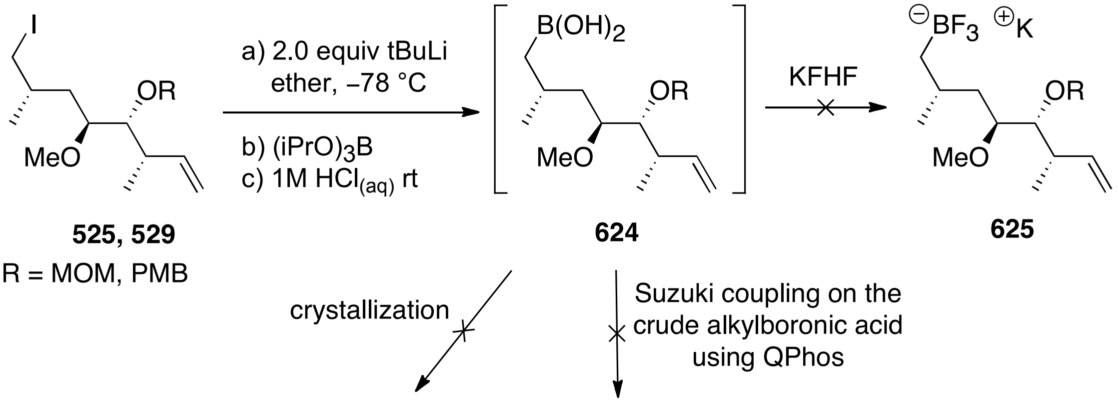
[p] Kishi[125] reported rate-enhanced sp^2–sp^2 Suzuki couplings in the presence of TlOH, presumably due to a fast hydroxyl-halogen exchange at Pd, prior to transmetalation.

Previously, the use of alkylboronic acids in Suzuki couplings usually required toxic thalium hydroxide[125] or thalium ethoxide[126] as additives,[q] so the high activity achieved with QPhos is remarkable. On the other hand, QPhos conditions have not been reported to work with alkyl-BBN substrates. It is known that different boron-containing compounds may display completely different behaviors in the transmetalation step. For instance, the best conditions found by the Fu group for sp^3–sp^3 couplings with alkyl-BBN[108a,b] reagents (generated via hydroboration) did not work at all for alkylboronic acids.[108c]

With these working conditions in hand, we attempted the preparation of a real-system boronic acids **624** from our fully elaborated primary iodides **525** and **529** with no success due to purification issues (Scheme 88). It is known that boronic acids exist in equilibrium with their trimeric cyclic anhydrides, boroxines,[109] and while simple boronic acids can be recrystallized from water, that was not the case in our system. Attempts to isolate the alkyl species as their trifluoroborates[110] **625** also failed.



Scheme 88. Attempts to prepare isolable alkylborons from our fully elaborated iodide.

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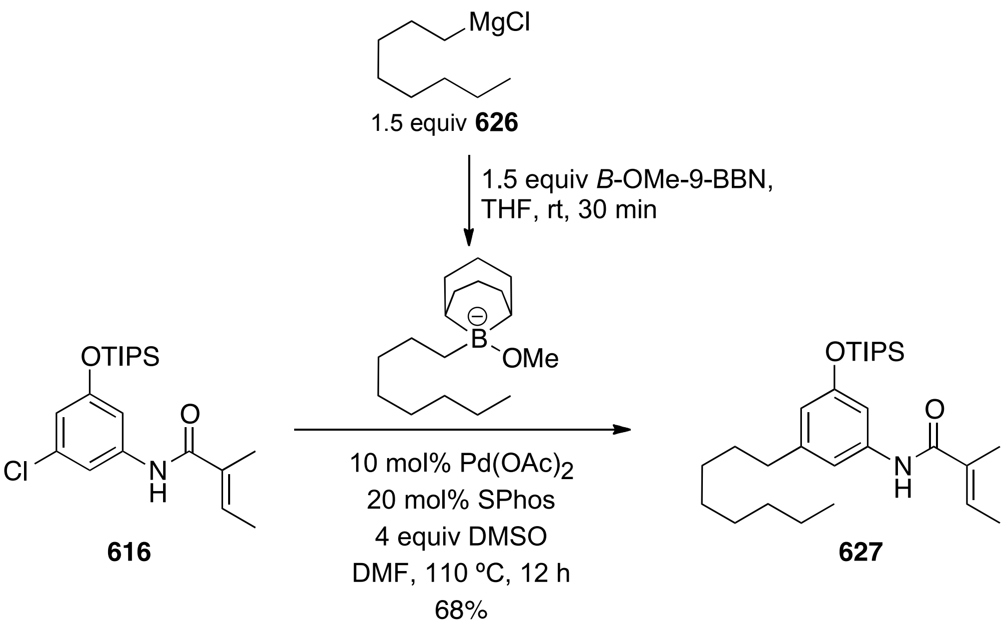
[q] The effect of thallium bases in our system was also evaluated by Dr. Feng Shi.**31**



Scheme 89. Successful Suzuki coupling on a model substrate via generation of the BBN adduct from a Grignard reagent.

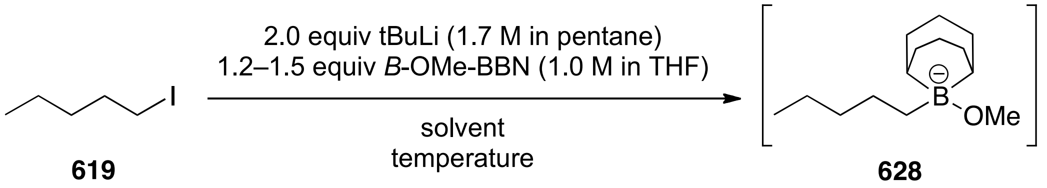
On the other hand, Dr. Monica Norberg[84] reported that generation of the BBN adduct from a Grignard reagent could provide a possible solution, although this reaction had to be performed at least at a 10 mmol scale for efficient formation of the alkylmagnesium species from an alkyl chloride. Previously, BBN adducts generated from Grignard reagents had been effectively used by Fürtsner.[127] Unfortunately, generation of the corresponding alkylmagnesium chloride species from our fully elaborated alkyl partner did not provide satisfactory results. Moreover, significant amounts of dechlorination product were observed, especially in the presence of a base. The best results were achieved when DMSO was used as an additive (Scheme 89). The use of DMSO as a palladium "stabilizer" has been previously reported by Sanford.[128] Even though, Soderquist's studies[123] have shown the importance of the base in Suzuki couplings for efficient transmetalation, among other benefits, in this case the absence of base was intriguingly beneficial (See page 113 for a discussion). Additionally Dr. Monica Norberg[84] demonstrated that solvent degassing was important to ensure that the catalyst is long-lived.

6.3. Evolution to a successful *B*-alkyl sp^3–sp^2 Suzuki coupling

Examination of the literature examples of generation of BBN adducts from alkyl iodides[97] showed that we were using the most common method for lithium-halogen exchange/reaction with *B*-OMe-BBN. Nonetheless, different authors preferred to use modified procedures. Thus, we started an investigation on the effects of the BBN adduct generation method in the Suzuki coupling step (Table 3). Until this point, we had only used Method C, with the corresponding addition of THF after *B*-OMe-BBN was added. This appears to improve the nucleophilicity of the generated alkyllithium species, presumably by breaking its polymeric aggregates.[129] In our case, however, it appeared that an optimum generation of the BBN adduct did not necessarily translate into a successful Suzuki coupling.

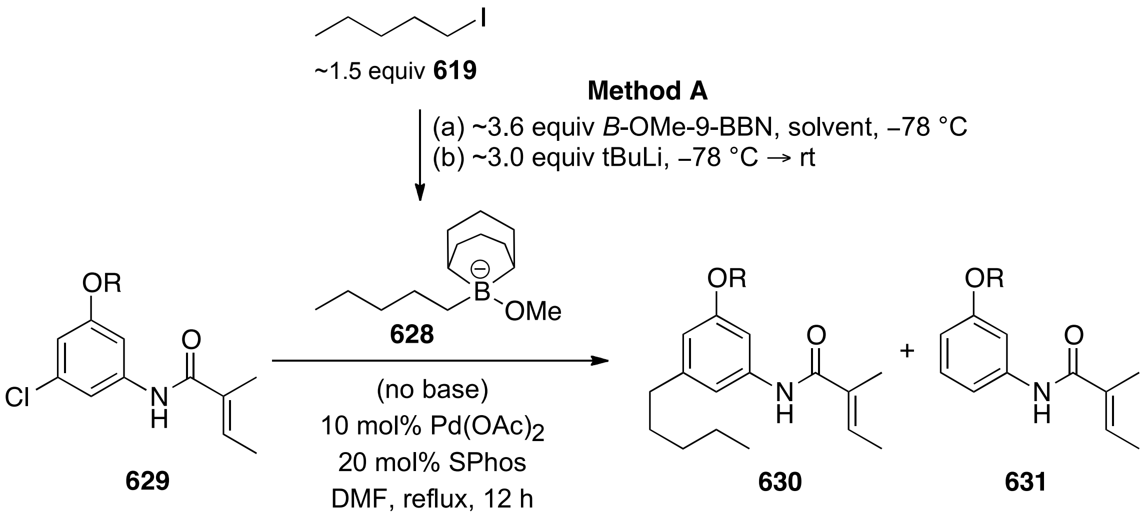
With Method A, the alkyl iodide was premixed with *B*-OMe-BBN before the lithium halogen exchange took place. Interestingly, when this reaction was performed in ether or pentane/ether (3:2), little or no conversion was observed in the Suzuki coupling (Table 4). On the other hand, reaction in THF gave promising results, although the dechlorination product was also formed, even in the absence of base.

Table 3. Evaluated methods for the generation of the BBN adduct from and alkyl iodide in Suzuki coupling studies.



	Description
Method A	**619** was premixed with *B*-OMe-BBN in THF, ether, or pentane/ether (3:2) (~0.1 M), then tBuLi was added at −78 ºC and the mixture was stirred at room temperature for ~1 hour.
Method B	**619**, dissolved in ether or pentane/ether (3:2) (~0.1 M), was treated with tBuLi at −78 ºC, the mixture was stirred at room temperature for ~1 hour, *B*-OMe-BBN was then added at −78 ºC, and finally the mixture was stirred at room temperature for ~2 hours.
Method C	**619**, dissolved in pentane/ether (3:2) or ether (~0.1 M) was treated with tBuLi at −78 ºC, *B*-OMe-BBN was added immediately, and the mixture was stirred at room temperature for ~1 hour. *Optional*: additional THF after *B*-OMe-BBN.

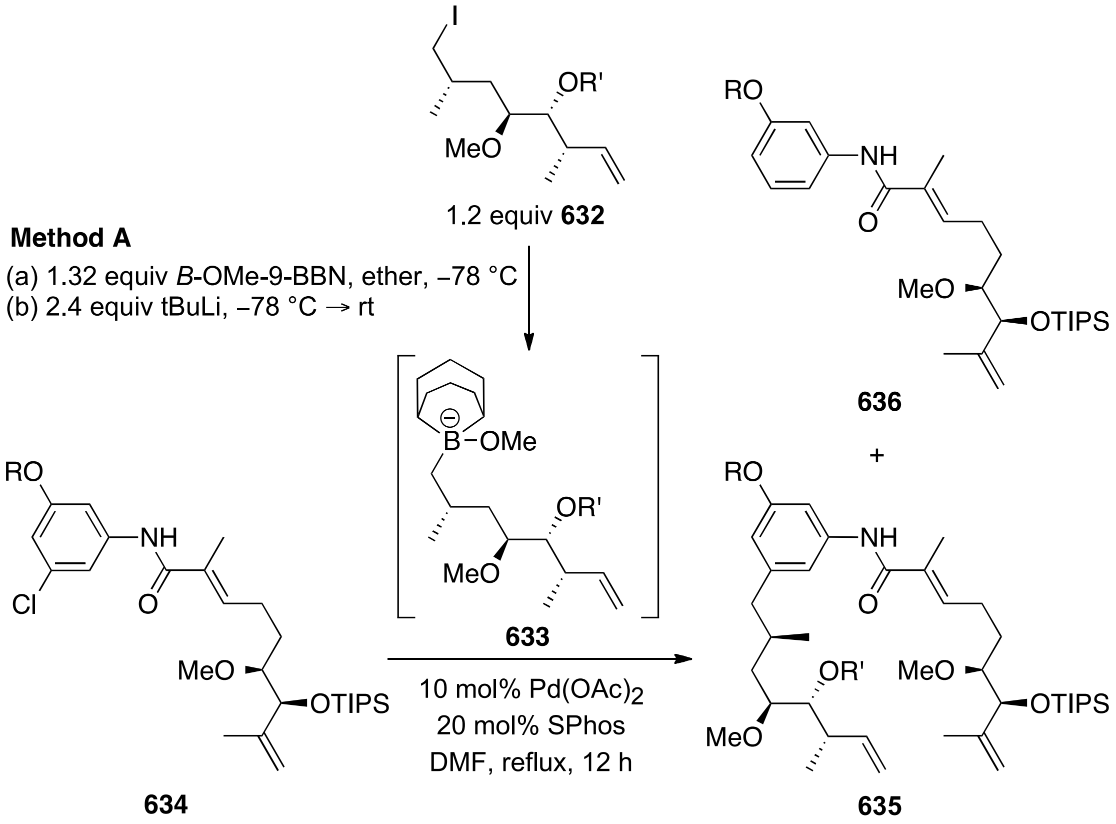
Table 4. Suzuki coupling results on model substrates using Method A for generation of the BBN adduct.



entry	Solvent used in BBN generation	R	Result
1	ether or pentane/ether (3:2)	MOM	No reaction
2	THF	TIPS	15% **630** + 30% **631**
3	THF	MOM	45% **630** + 20% **631**

Since the desired product was obtained in higher yield than the best previous result (Scheme 86), these conditions were applied to the fully elaborated substrates. Although in the model substrates the MOM-protected phenol afforded a higher yield of Suzuki product than the dechlorination product (Table 4, entry 3), in the fully elaborated system, the ratio was reversed (Table 5, entry 1). The same conditions were tested on slightly modified substrates in the presence of a base (Table 5, entries 2 and 3), different runs afforded different yields but the Suzuki/dechlorination ratio was maintained as ~1:2, as it was in most of the cases using Method A for the formation of the BBN adduct.

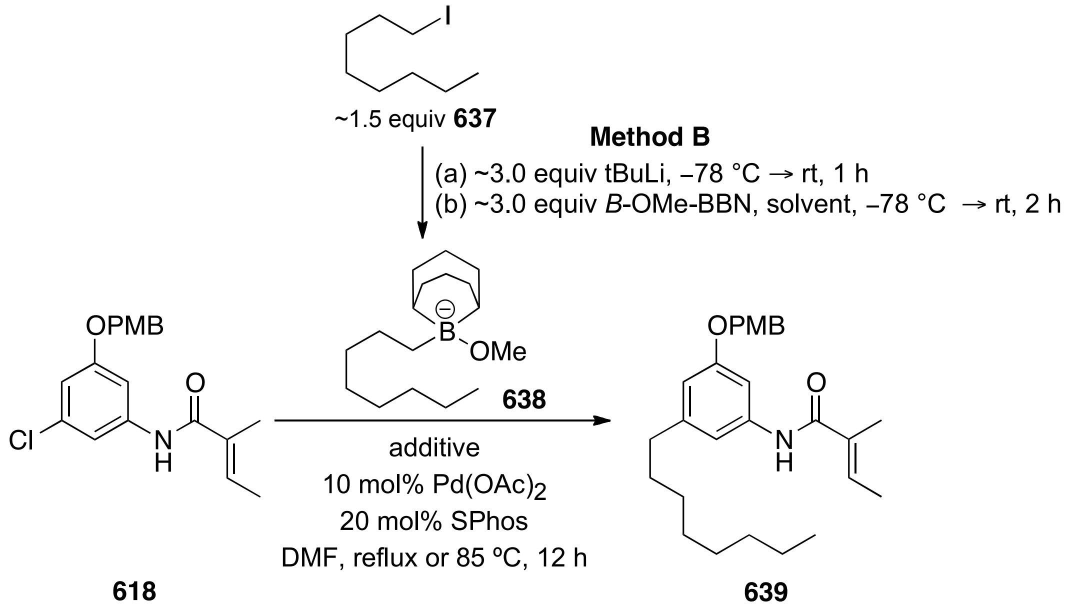
Table 5. Suzuki coupling results on the fully elaborated substrates using Method A for generation of the BBN adduct.



Entry	R	R'	additive	Result
1	MOM	MOM	-	~20% **635** + 46% **636**
2	PMB	MOM	2.0 equiv $K_3PO_4 \cdot nH_2O$	7% **635** + 15% **636**
3	PMB	PMB	2.0 equiv $K_3PO_4 \cdot nH_2O$	6–15% **635** + 15–30% **636**

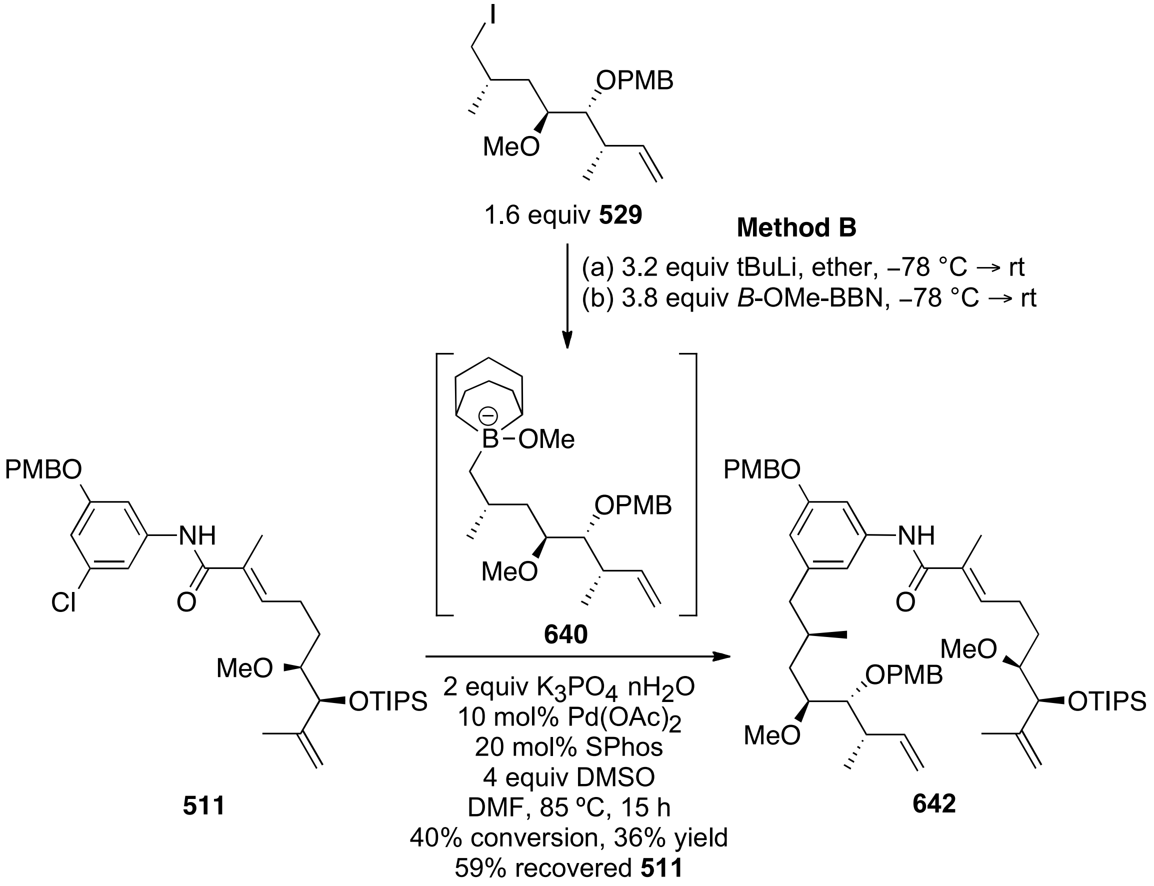
In Method B the use of THF was avoided, the lithium-halogen exchange step was allowed to run for extra time, and the reaction with *B*-OMe-BBN was also given enough time to proceed. Interestingly, dechlorination was never observed in this case (Table 6).

Table 6. Suzuki coupling results on model substrates using Method B for generation of the BBN adduct.



entry	Solvent used in the BBN generation	Temperature in Suzuki coupling	Additive	Isolated yield **639**
1	ether	110 ºC	-	18%
2	ether	100 ºC	4 equiv DMSO	38%
3	ether	85 ºC	4 equiv DMSO	45%
4	pentane/ether (3:2)	110 ºC	4 equiv DMSO	~5%
5	pentane/ether (3:2)	85 ºC	4 equiv DMSO and 2 equiv $K_3PO_4·nH_2O$	45%

When the lithium-halogen exchange was performed in ether, encouraging results were obtained. From comparing entries 1 and 2, we observed a positive effect of using DMSO as an additive. Another positive effect was attained by lowering the reaction temperature (entry 3). Recent reports[130] have revealed that DMF can act as a source of hydride in Pd-catalyzed dehalogenations at high temperature (150 ºC), we considered that a lower temperature would be safer, even though dechlorination was not observed in these cases. On the other hand, using pentane/ether (3:2) as a solvent in the lithium-halogen exchange resulted in extremely low conversions. Outstandingly, the yield was substantially increased by adding both DMSO and base as additives, without giving any dechlorination product.

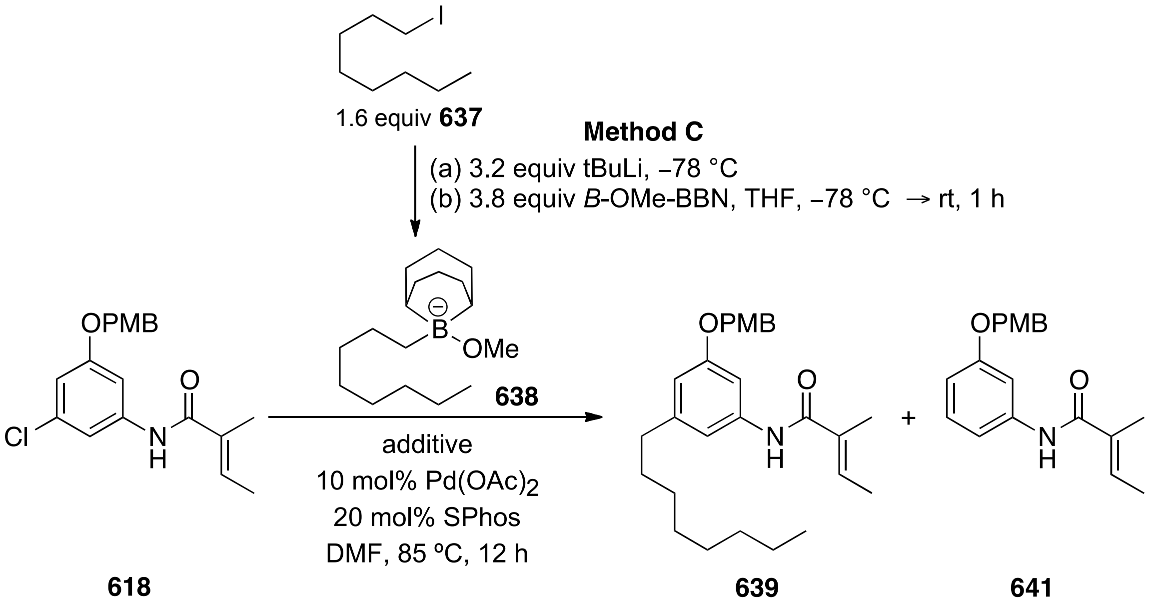


Scheme 90. Example of a set of partially optimized conditions for the *B*-alkyl Suzuki coupling in our synthetic route to autolytimycin.

From these results, we concluded that lithium halogen exchange in ether, followed by Suzuki coupling at 85 ºC in the presence of DMSO and base would afford the best result. Thus, the Suzuki coupling step was carried out with the fully elaborated substrates under these partially optimized conditions (Scheme 90). At this point, the main problem appeared to be the decomposition of the palladium catalyst to form palladium black, observable as the formation of black precipitate. In the presence of DMSO the decomposition occurred in a matter of hours instead of minutes. The results nonetheless were encouraging since a good yield based on recovered starting material is obtained (90%).

At this point, we wondered if an optimized formation of the BBN adduct would improve these results, thus we returned to Method C for the formation of the BBN adduct (Table 7). In Method C, the alkyl iodide, dissolved in ether or pentane/ether(3:2), is treated with tBuLi and *B*-OMe-BBN added rapidly one after the other, followed by the addition of THF. Surprisingly, when THF was not added at the end, the Suzuki coupling step proceeded with very poor conversions (~10%). At the same time, addition of THF when pentane/ether (3:2) was used as solvent in the exchanges, also resulted in low yields (Table 7, entry 1). Conversely, when ether was used as solvent, results were encouraging in the presence of both DMSO and base (entry 2) since dechlorination was not observed. These conditions are very similar to those originally found through screening (Scheme 86), which afforded about 30% of desired product (and no dechlorination) but were inefficient in the fully elaborated substrates. The differences, however, were the use of DMF as a solvent in the Suzuki coupling, the addition of DMSO, and solvent degassing. Surprisingly, elimination of the DMSO (entry 3) did not affect the result and comparable yields were obtained, so the increase of yield is either due to DMF or solvent degassing.

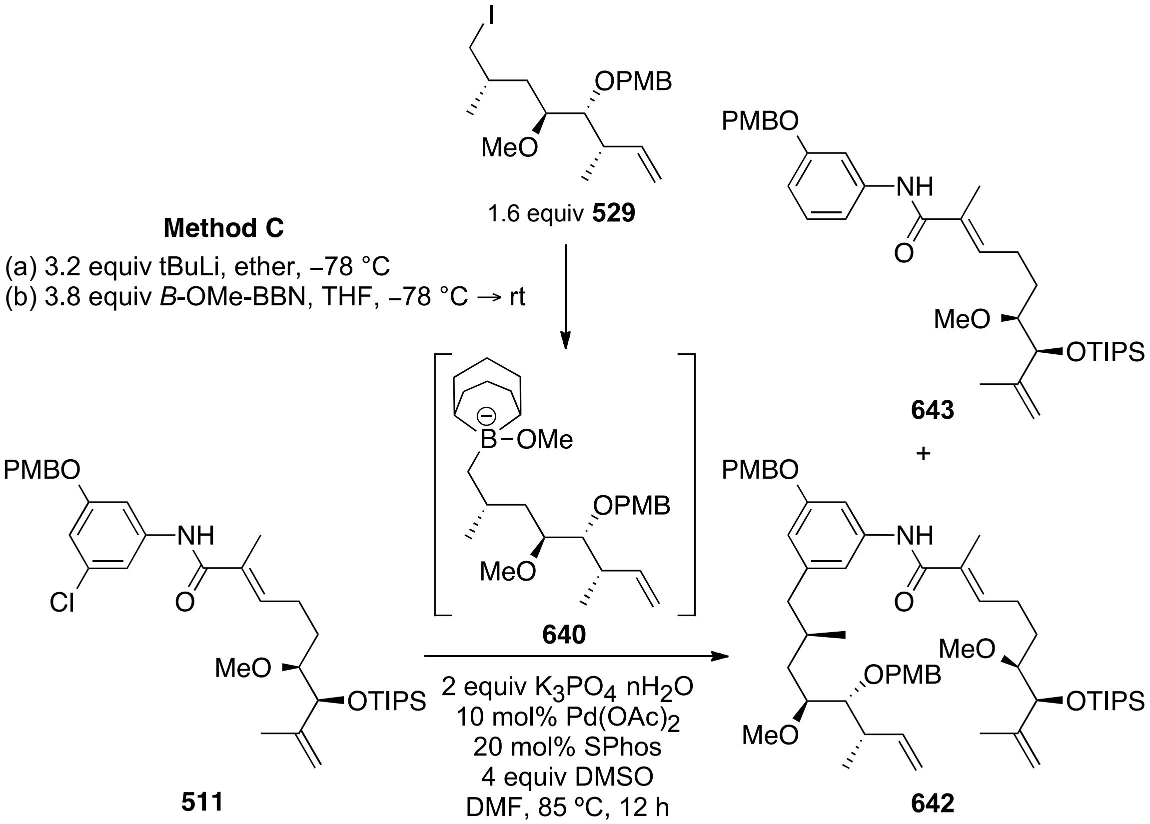
Table 7. Suzuki coupling results on model substrates using Method C for generation of the BBN adduct.



entry	Solvent used in the BBN generation	Concentration during BBN generation	additive	Result
1	pentane/ether (3:2)	0.1 M	2 equiv $K_3PO_4 \cdot nH_2O$	10% **639**
2	ether	0.1 M	2 equiv $K_3PO_4 \cdot nH_2O$ and 4 equiv DMSO	45% **639**
3	ether	0.1 M	2 equiv $K_3PO_4 \cdot nH_2O$	50% **639**
4	ether	0.5 M	2 equiv $K_3PO_4 \cdot nH_2O$	Full conversion 65% **639** + 10% **641**

On the other hand, we also recognized that the generation of BBN adducts from Grignard reagents (Scheme 89, which resulted in better conversions) was taking place at a higher concentration (0.5 M) than the lithium-halogen exchange (0.1 M). So we evaluated the effect of increasing the concentration (entry 4), which resulted in substantial enhancement in conversion (from ~50% to full conversion), even though dechlorination was formed in these circumstances. The same conditions were then tested on the fully elaborated substrates (Table 8).

Table 8. Suzuki coupling results on the fully elaborated substrates using Method C for generation of the BBN adduct.

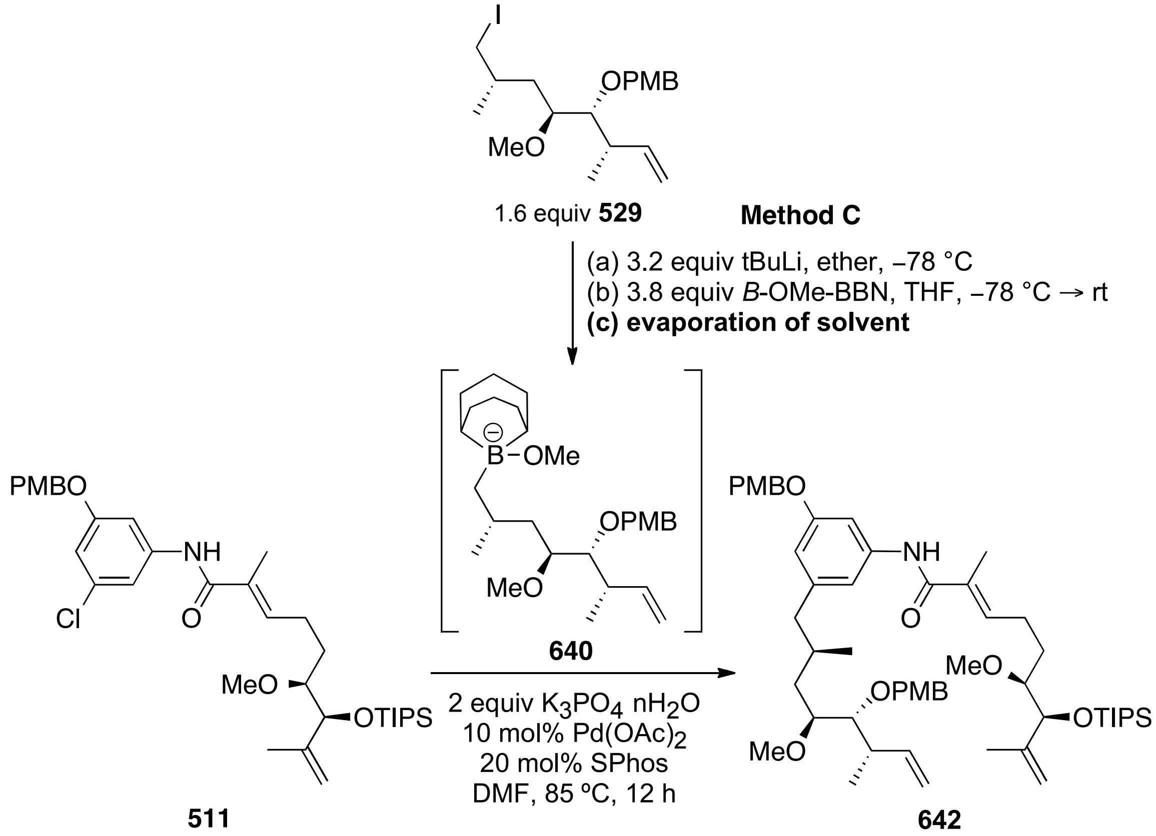


entry	Concentration during BBN generation	Result
1	0.1 M	30% conversion 24% **642**
2	0.5 M	0% **642** + ~10% **643**

Table 8 shows the results of applying Method C on the fully elaborated substrates. When the lithium-halogen exchange was carried out at low concentration (0.1 M) the following Suzuki reaction proceeded with moderate conversion, but a high concentration (0.5 M) in the halogen exchange severely affected the performance in the coupling step with only small amounts of the dechlorination product observed. This outcome somehow contradicts our conclusions from Table 7, but there are apparently considerable differences between our model and fully elaborated primary iodides.

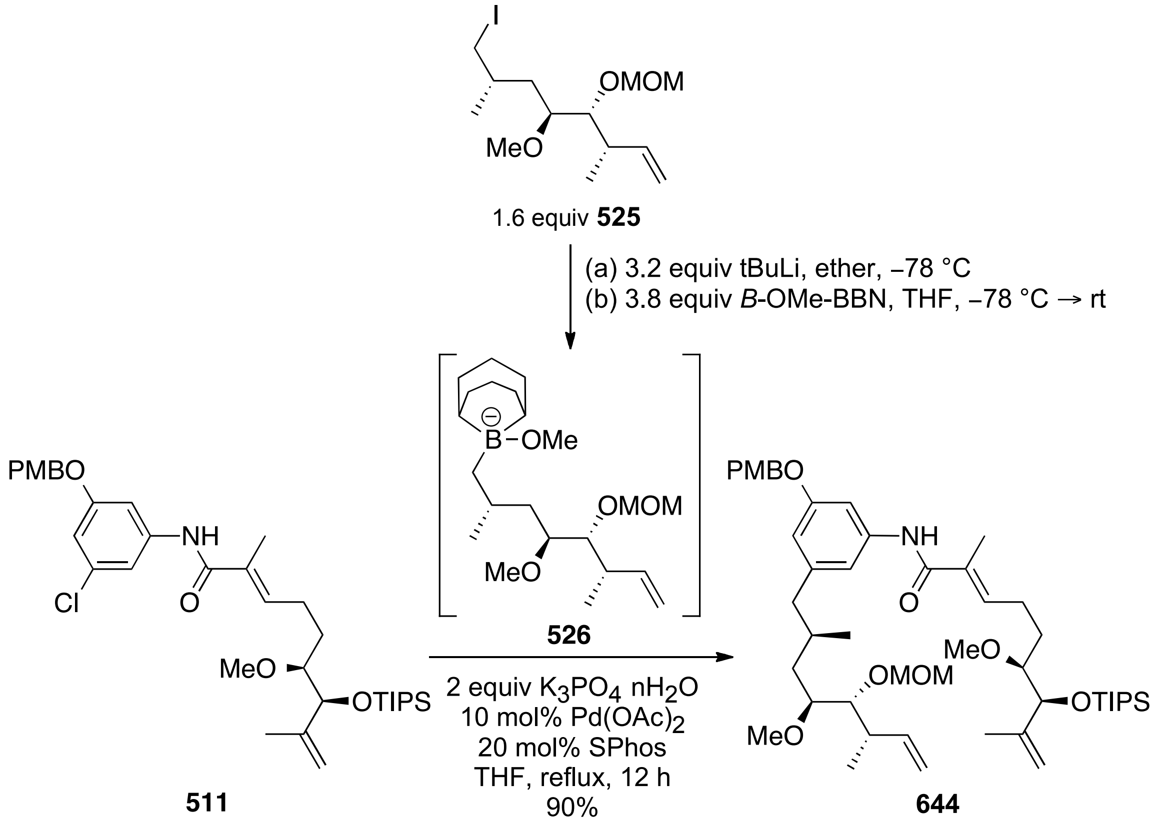
In general, these experiments suggested that the generation of the adduct should be better run at *low* concentrations, whereas the Suzuki coupling itself can be driven to full conversion at a *high* concentration. We figured that this *Catch-22* could be solved by evaporating the solvent with a nitrogen stream prior to the coupling reaction. Then, after addition of DMF (solvent in the Suzuki reaction), the coupling can take place at a concentration ten times higher than in previous cases. This modification was applied on the fully elaborated substrates (Table 9). Surprisingly all our initial attempts resulted in no reaction (entry 1), however addition of $Pd(OAc)_2$ and SPhos as a solution in THF resulted in a remarkable improvement, leading to complete formation of the desired product, which was also isolated in high yield. These intriguing results suggest that the formation of the active pre-catalyst $SPhos{\cdot}Pd(OAc)_2$ is difficult in the presence of the highly concentrated alkyl-BBN adduct. On the other hand, it is interesting that addition of the catalyst mixture as solutions in DMF and DMSO did not provide good results, in contrast with the use of THF as a solvent. In fact, Pd and ligand premixing in THF has been suggested by the Buchwald group for substrates that give poor or no conversions.[131] A subsequent improvement in this reaction has been the elimination of DMF as solvent to be replaced by only the THF solution of catalyst, which has resulted in amazing results (Scheme 91).

Table 9. Suzuki coupling results on the fully elaborated substrates at high concentration.



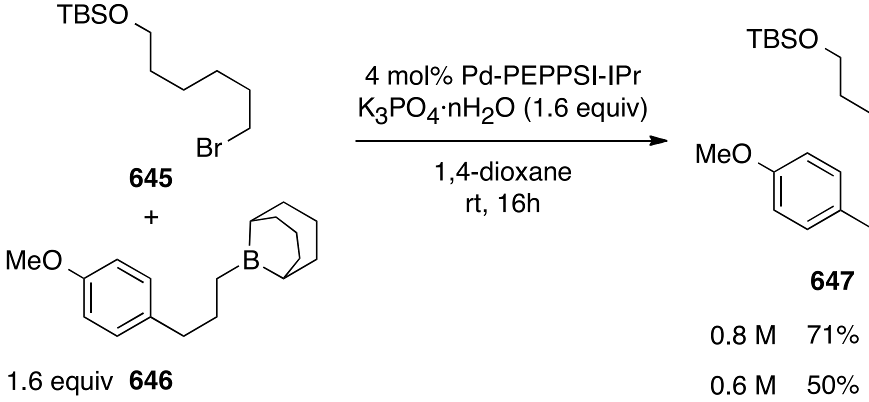
entry	palladium source and ligand addition mode	Result
1	As solids	0% conversion, no dechlorination.
2	As a degassed solution in THF	Full conversion No dechlorination 83% **643**

In summary, our preliminary experiments brought us to the realization that this transformation required unusual tweaking. In fact, concentration turned out to be essential in this transformation; the formation of the BBN adduct performed better at *low* concentration, whereas the Suzuki coupling itself required *high* concentration. Evaporation of the solvent with a nitrogen stream prior to the coupling reaction allowed us to meet this requirement, but premixing the palladium and the ligand in solution before being added to the reaction vessel was necessary for catalytic activity. By combining these factors, high-yielding conditions for the coupling reaction were found and applied to the fully elaborated Suzuki partners.



Scheme 91. Optimized Suzuki coupling conditions used in our route to autolytimycin.

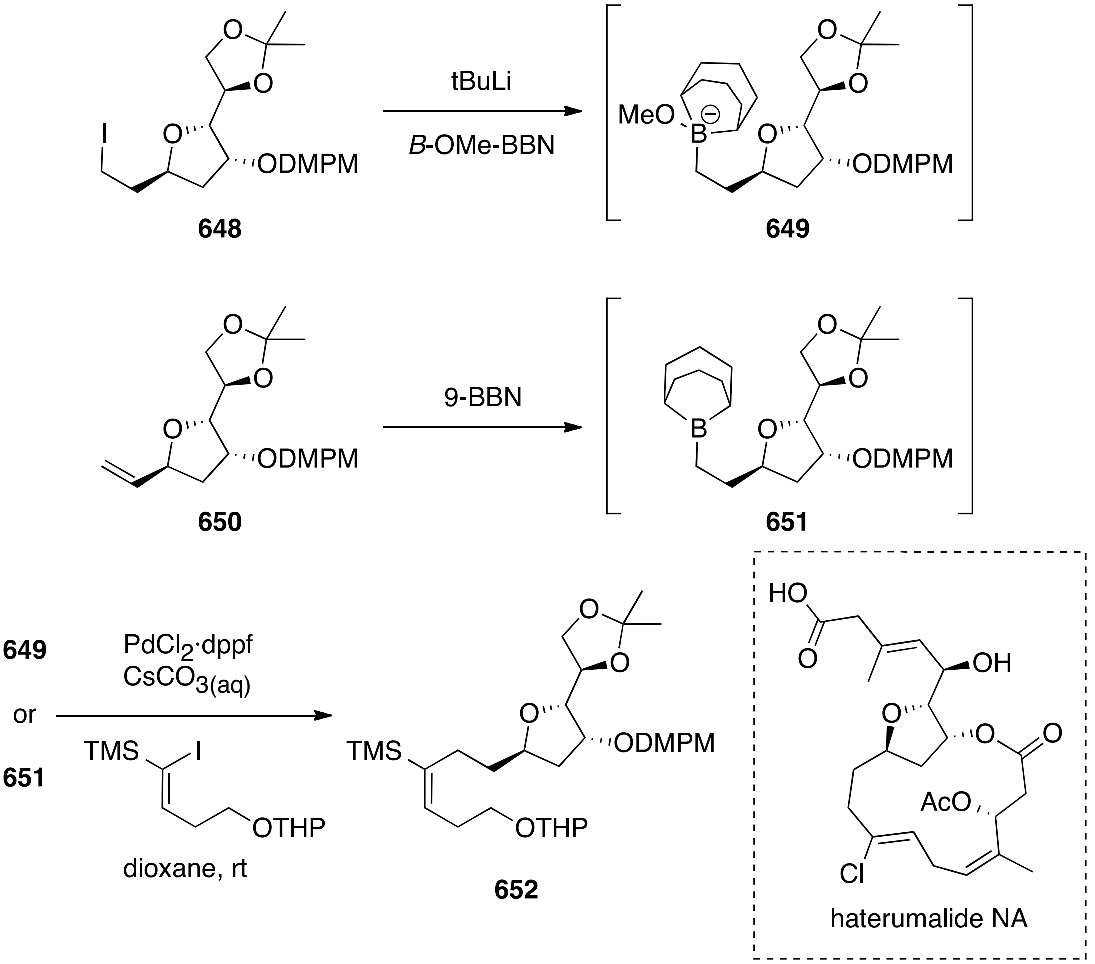
The remarkable effect of concentration on the reaction efficiency was surprising to us since we did not find literature cases where this matter was discussed. Interestingly, in a recent (2008) paper regarding the application of the Pd-PEPPSI catalyst system (see Figure 6, page 86) on sp^3–sp^3 Suzuki couplings, the Organ group reported that dilution had a detrimental effect on the yield.[116] Explicitly, in one reaction, changing the concentration from 0.8 M to 0.6 M lowered the yield from 71% to 50%. Additionally, no byproducts were found and starting materials were recovered. This proved that the diminution of yield was not due to undesired reactions but to incomplete conversion. It is essential to mention that it is specified in the supporting information that the employed alkyl-BBN species were generated using solid 9-BBN dimer (as opposed to 9-BBN solution in THF), which allows their preparation in high concentration. Nevertheless, it is still not clear which step of the catalytic cycle is affected by concentration.



Scheme 92. Concentration effect in a *B*-alkyl Suzuki coupling observed by the Organ group using the highly active Pd-PEPPSI system.

Also, in their recent (2008) total synthesis of haterumalide NA, the Kigoshi group[97n] vaguely discussed the effect that concentration might have had in one of their Suzuki couplings involving alkyl-BBN species. Specifically, when the generation of the alkyl partner was effected via hydroboration with solid 9-BBN dimer, the Suzuki coupling afforded quantitative yield, whereas the use of 9-BBN solution (dilute) lead to 0% conversion (Table 10). Interestingly, generation via lithium-halogen exchange followed by treatment with *B*-OMe-BBN (low concentration too) provided low conversion. It is highly probable that evaporation of the solvent at that stage would have solved the low conversion problem.

Table 10. Concentration effect in a *B*-alkyl Suzuki coupling observed in Kigoshi's total synthesis of haterumalide NA.

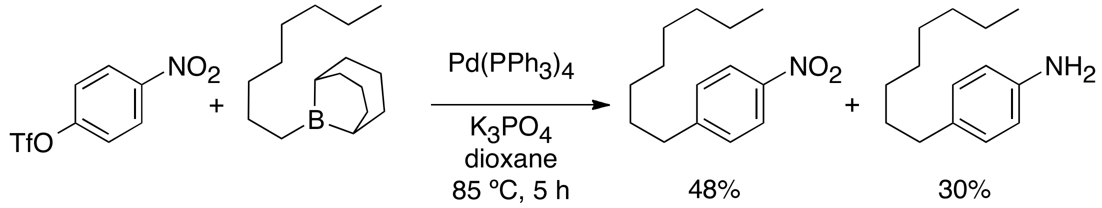


starting material	Conditions for the generation of the BBN adduct	Yield in Suzuki coupling
648	tBuLi, *B*-OMe-BBN	32%
649	9-BBN solution in THF	0%
649	Solid 9-BBN dimer	quantitative

It is interesting that while in the majority of the cases involving hydroboration in complex molecule synthesis 9-BBN solutions are used, in all the methods presented in section 6.1.3 (page 85), for the coupling of aryl chlorides and alkyl-BBN species, the starting materials are always prepared using solid 9-BBN dimer. The importance of concentration, especially for substrates of comparatively low reactivity in coupling reactions, is certainly an aspect that has not been discussed in the literature.

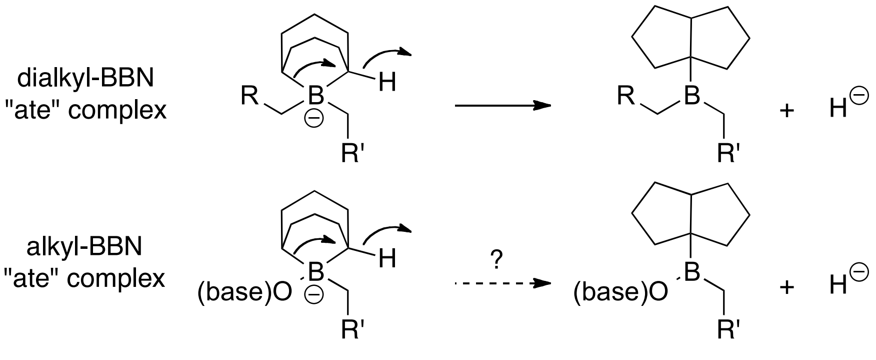
Another aspect of the reactions to discuss is the dehalogenation side reaction found in some of our experiments. Dehalogenation is a known issue[9] in some specific Suzuki couplings but the high levels observed in several of our runs, imply a source of hydride.

A number of reports[130] have shown that DMF can act as a source of hydride for Pd-catalyzed reductions/dehalogenations via formation of dimethylamine and carbon monoxide at high temperature (150 ºC). While our reactions were run at a significantly lower temperature, this could still be one of the possibilities. However, this would not explain why dehalogenation is observed in such high levels when the lithium-halogen exchange and reaction with *B*-OMe-BBN were performed in THF (Table 4, page 101) or when the BBN adduct was prepared from Grignard reagents.

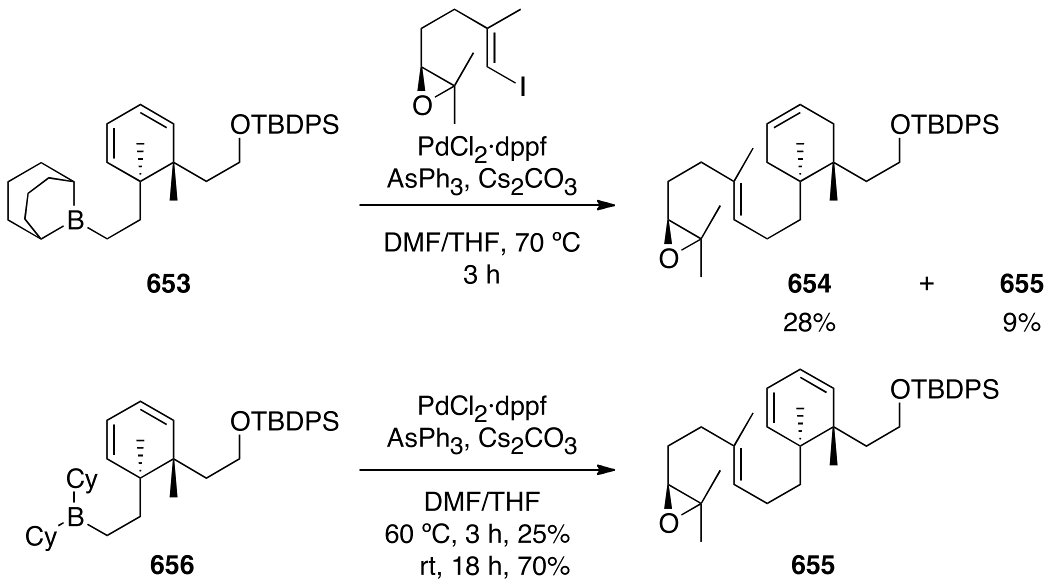


Scheme 93. Reduction of a nitro group under Suzuki coupling conditions with an alkyl-BBN species.

Interestingly, back in 1993, Suzuki reported the unexpected reduction of a nitro group[103a] during a coupling reaction between an alkyl-BBN and an aryl triflate (Scheme 93). This result was explained by suggesting that this transformation could occur via a reduction mechanism similar to the one observed for dialkyl-BBN "ate" complexes.[132] Dialkyl-BBN "ate" complexes (obtained via reaction of alkyl-BBN and alkyllithium species) can in fact act as reducing agents (Scheme 94) on carbonyl compounds[132b] and tertiary alkyl, benzyl and allyl halides.[132c,d] An analogous behavior has not been reported for their monoalkylated counterparts.



Scheme 94. Dialkyl-BBN "ate" complexes as sources of hydride.



Scheme 95. Reduction of a diene under Suzuki coupling conditions with an alkyl-BBN.

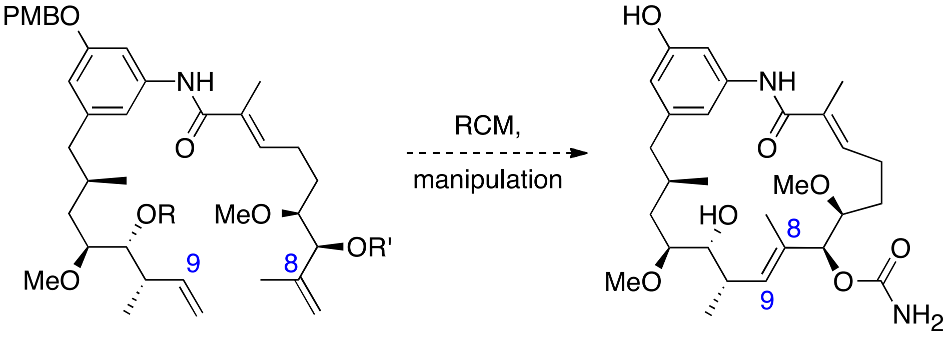
In addition, De Clerq[133] has also reported the reduction of a diene (Scheme 95) during the Suzuki coupling of a vinyl halide with an alkyl-BBN partner. Interestingly, by employing an alternative bulky borane Cy_2BH as a replacement for 9-BBN in the hydroboration reaction, the reduction during the Suzuki coupling was not observed. This specific result indicates that the source of hydride is likely related to the BBN species.

We observed dehalogenation during our Suzuki experiments, especially when the formation of the BBN adduct was performed in THF (Table 4, page 101). Organolithium species are notorious for having special behaviors in different solvents, for instance, it is known that tBuLi is a tetramer in hexane, a dimer in ether, and a monomer in THF.[129] It is conceivable that dialkyl-BBN "ate" complexes (Scheme 94) could form under special circumstances during the generation of the BBN adduct, which would later act as a hydride source. On the other hand, it has been recognized that Grignard reagents have a higher tendency to form dialkyl-BBN "ate" complexes.[78,134] There are quite a few metal-mediated dehalogenation methods[135] where hydride is provided from nucleophilic sources like sodium borohydride in the presence of a base.[136] This, in some way, correlates with the observation that in some of our experiments the absence of base was favorable to avoid the undesired dechlorination reaction. In this specific case, according to the mechanism shown in Scheme 94, the hydride transfer occurs from the BBN bridgehead hydrogen, which is in agreement with the fact that we did not observed the formation of any β-hydride elimination product, even in cases with high dehalogenation levels.

In conclusion, through extensive experimentation we have found a "tweaked" set of conditions that allow for an efficient *B*-alkyl Suzuki coupling Suzuki coupling on a highly inactivated amidochorophenol, which have been successfully used in our synthetic route to autolytimycin. This result establishes that the 5-alkyl-3-amidophenol moiety, which is found in a number of natural products, could be rapidly assembled by combining Ir-catalyzed C–H activation/borylation/amidation/oxidation and Suzuki coupling.

Chapter 7. A synthetic approach to autolytimycin: Ring-closing metathesis

Our synthetic route toward the Hsp90 inhibitor autolytimycin (**401**), illustrated in Section 4.6 (page 64), was designed aiming for high convergency. Having established a step sequence that allows a rapid connection of 5-alkyl-3-amidophenols from fully elaborated blocks (Chapters 5 and 6), ring-closing metathesis (RCM) presented the attractive option of bringing together the 19-membered macrocycle from a just-assembled intermediate containing the complete carbon network (**701**) of the natural product.



701

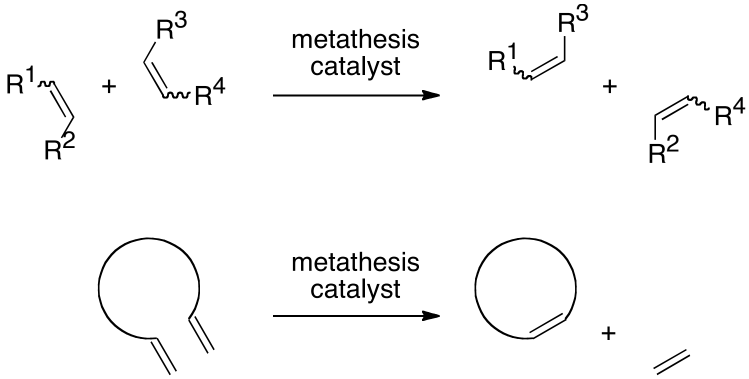
autolytimycin (**401**)

Scheme 96. The ring-closing metathesis step in our synthetic approach to autolytimycin.

Even though a compound containing a trisubstituted olefin flanked by five trisubstituted stereogenic centers, like **401**, was certainly expected to be a challenging RCM target, throughout the years numerous research groups have worked on improving metathesis reaction on relatively unreactive, sterically encumbered, and selectivity-lacking systems. Great advances in this area have been encouraged by application in complex molecule synthesis[137] and the development still continues. The ring closure of macrocycles by means of a metathesis reaction has been extensively used in total syntheses during the last decades.[138] The present chapter discusses our initial efforts to employ this important reaction in our synthetic approach to autolytimycin.

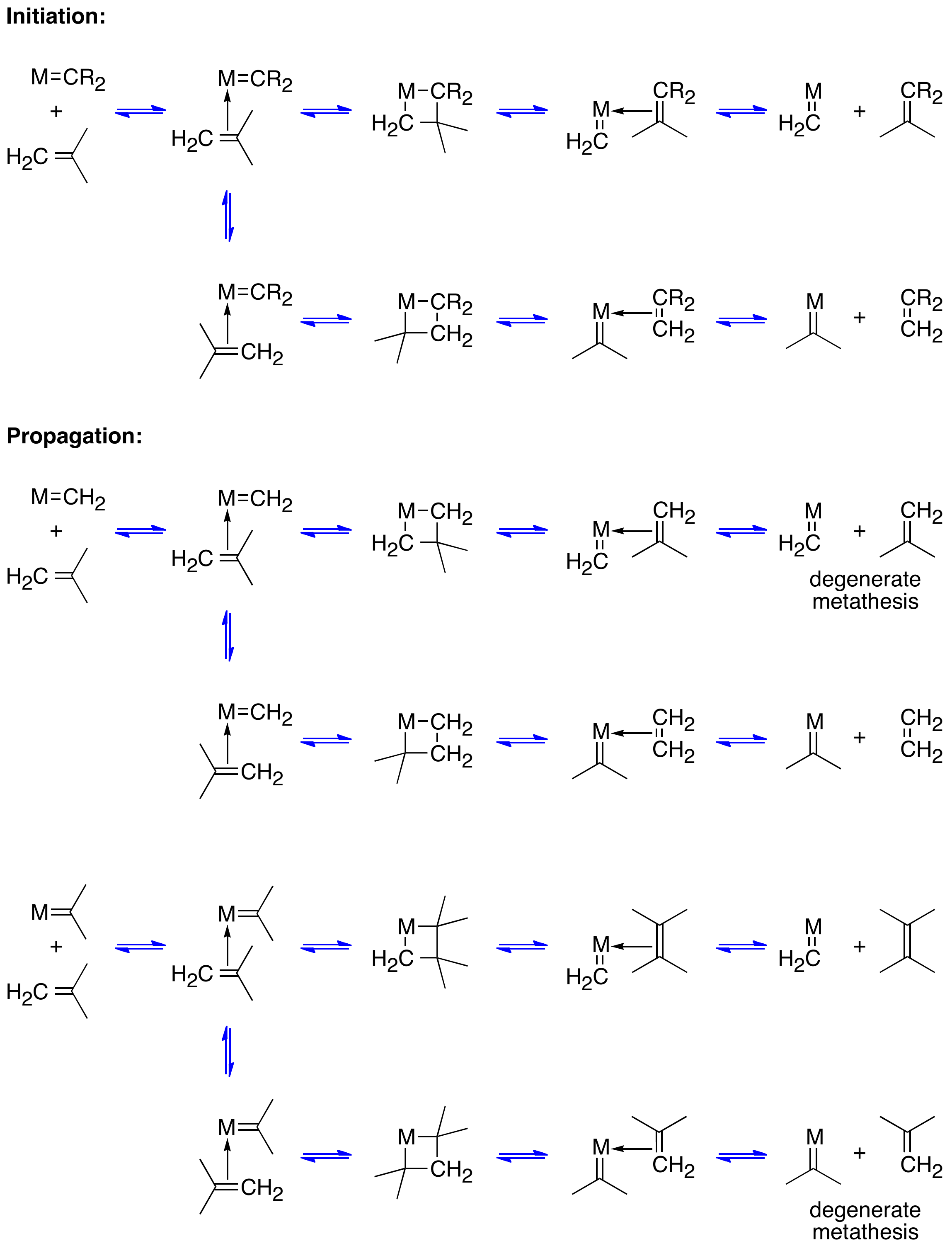
7.1. Literature precedence

Metathesis is among those remarkable chemical reactions that have fundamentally transformed the synthesis of complex molecules.[139] The 2005 Nobel Prize in Chemistry was awarded to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock for the development of the metathesis method in organic synthesis. Olefin metathesis is the most used form of this reaction, which, by definition, involves the redistribution of alkylidene fragments by the scission of carbon–carbon double bonds in alkenes,[140] as depicted in Scheme 97. Among its numerous variations, ring-closing metathesis (RCM) occupies a special place, having established itself as one of the preferred strategies for the preparation of cyclic compounds.[141]



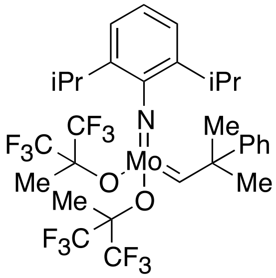
Scheme 97. Schematic illustration of a general metathesis and a ring-closing metathesis reactions.

Intuitively, metathesis was thought to occur through a process in which *two* olefins coordinated to a metal and *exchanged* alkylidene groups.[142] In the early seventies, Chauvin[143] proposed a mechanism that implicated the metal-driven fragmentation of one olefin at a time (a non-pairwise process) which, with further experimental evidence by Grubbs,[144] eventually became the widely

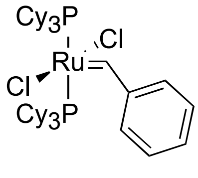


Scheme 98. Chauvin's mechanism, proposed in 1971, for the catalyzed olefin metathesis involving metal alkylidene and metallacyclobutane intermediates.

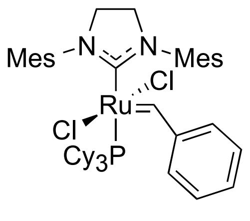
accepted mechanism for this reaction.[145] In due course, the understanding of the important role of metal alkylidenes led to the progressive development of metal carbene complexes able to catalyze olefin metathesis, with pioneering reports by Schrock[146] in 1990 ([Mo]-**I**) and Grubbs[147] in 1992 ([Ru]-**III**).



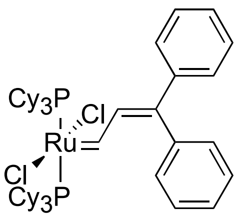
[Mo]-**I**[146]
Schrock's catalyst



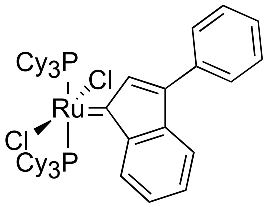
[Ru]-**I**[150]
1st generation
Grubbs catalyst



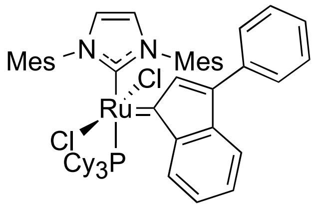
[Ru]-**II**[164]
2nd generation
Grubbs catalyst



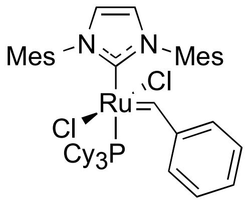
[Ru]-**III**[147]



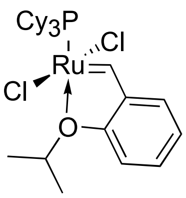
[Ru]-**IV**[159]



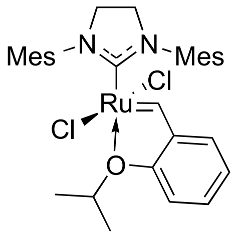
[Ru]-**V**[158]



[Ru]-**VI**[155, 156]



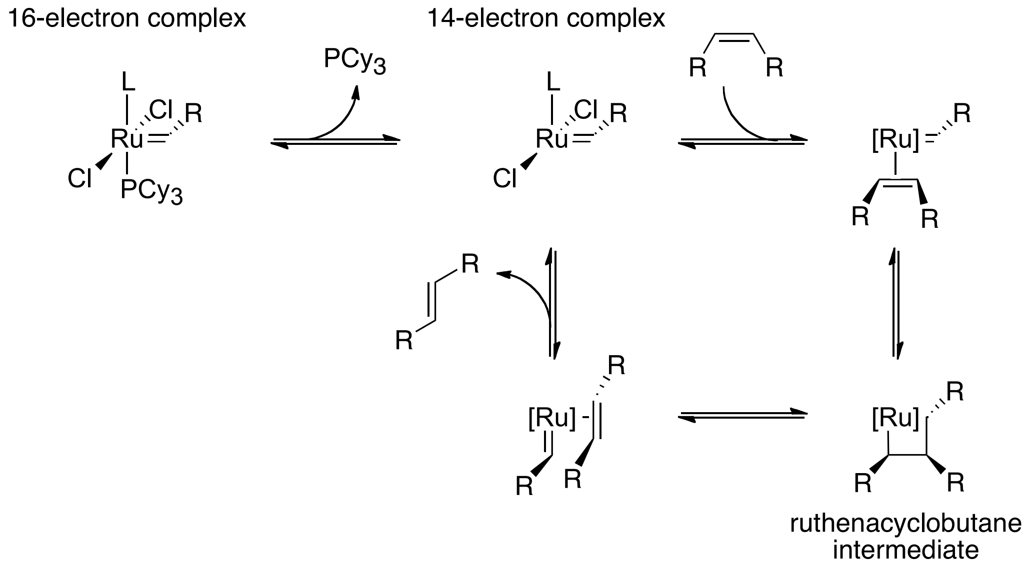
[Ru]-**VII**[167]
1st generation
Hoveyda-Grubbs
catalyst



[Ru]-**VIII**[170]
2nd generation
Hoveyda-Grubbs
catalyst

Figure 8. Metal–alkylidene complexes commonly used as metathesis catalysts.

While highly active and efficient on a number of substrates,[148] molybdenum catalyst [Mo]-**I** suffered from limited functional group compatibility and excessive oxygen and moisture sensitivity, which restricted its widespread use. Among the organic synthetic community, ruthenium catalysts promptly became popular and went through astonishing development over the years.[149] In 1995, the benzylidene complex [Ru]-**I** ("First-generation Grubbs' catalyst") was introduced[150] as an improved version of the previously reported[151] catalyst [Ru]-**III**. Although [Ru]-**I** seemed slightly less reactive than Schrock's [Mo]-**I**, its comparatively significant air and water stability made it persist in the organic synthesis arena.[152]



Scheme 99. Mechanism of the metathesis of a symmetrical *cis* olefin to its *trans* isomer.

At the end of 1998, a report by the Herrmann[153] group demonstrated that replacing the phosphine ligands of [Ru]-**I** with N-heterocyclic carbenes (NHC) noticeably improved its stability. Taking into account that the *actual* active metathesis catalyst (a 14-electron species) is formed *in situ* via a reversible ligand dissociation[154] (Scheme 99), the presence of a labile ligand (i.e., a phosphine) is still desirable. Promptly, many research groups almost simultaneously released a series of reports on the preparation and catalytic evaluation of mixed phosphine/NHC-containing complexes, all condensed within the year 1999. Of particular significance are the reports from the Nolan[155] and Grubbs[156] groups on the synthesis and applications of [Ru]-**VI** (See Figure 8), an improved catalyst featuring an IMes ligand. Among others,[157] complex [Ru]-**V**,[158] also bearing an IMes carbene, is a case worthy of note, being an enhanced version of the indenylidene complex [Ru]-**IV**,[159] whose structure (result of a rearrangement)[160] was initially misassigned[161] but rapidly corrected.[158b] In the same manner in which [Ru]-**IV** was shown to be as efficient as [Ru]-**I** at catalyzing metathesis reactions,[159] comparable results were found when their IMes-substituted versions, [Ru]-**V** and [Ru]-**VI** were put side by side.[162] Yet while others focused on the use of *unsaturated* NHC ligands,[163] Grubbs's[164] development of the highly active[165] [Ru]-**II** ("Second-generation Grubbs catalyst") totally changed the panorama with the incorporation of the *saturated* NHC ligand H_2IMes. This seemingly minor difference (compare [Ru]-**VI** and [Ru]-**II** in Figure 8) turned out to be the key to superior efficiency in various metathesis reaction types.[166] Furthermore, still in 1999, a serendipitous finding by the Hoveyda group[167] led to the development of catalyst [Ru]-**VII**, featuring a modification of enormous relevance for catalyst longevity.[168] The newly introduced 2-isopropoxybenzylidene ligand was able to stabilize the complex in its resting 16-electron state and to readily open a coordination site in the presence of the substrate.[169] Unsurprisingly, the development of the corresponding H_2IMes-containing catalyst [Ru]-**VIII** ("Second-generation Hoveyda–Grubbs catalyst"),[170] phosphine-free and extremely robust, was promptly reported.[r]

Even though the history of ruthenium-based catalysts seems to have followed a progressive evolution, it is important to consider that "there is no single best catalyst available, and it is unlikely that such a catalyst will be developed".[166] In fact, during more than one decade, an astonishing number (several hundred) of NHC-bearing ruthenium catalysts have been designed, developed, and fashioned according to specific needs.[171] Eventually, the commercial availability of a number of these catalysts[172] rapidly encouraged the use of metathesis in the preparation of complex molecules, especially macrocycles, having RCM as a late-stage key synthetic step.

In general, taking into account a considerable number of literature reports, the use of ring-closing metathesis for the formation of 5–8-membered rings commonly affords the thermodynamic *Z* olefins,[173] whereas larger rings are usually obtained as *E*/*Z* mixtures where the *E* isomer is dominant.[174] About RCM reactions forming 8–10-membered rings, it has been recently said that

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[r] [Ru]-**VII** and [Ru]-**VIII** are known for being reisolable once the metathesis reaction is complete, a valuable feature (especially with high catalyst loadings) attributable to a release-return ("boomerang") mechanism that allows the regeneration of the complexes.[168] A very recent report,[169] however, argues that the reisolation is possible due to an incomplete activation of the catalysts and that there is a lack of evidence supportive of a significant contribution of such mechanism at low catalyst loadings.

their “outcome depends on still imperfectly understood factors”,[175] presumably steric and conformational effects.

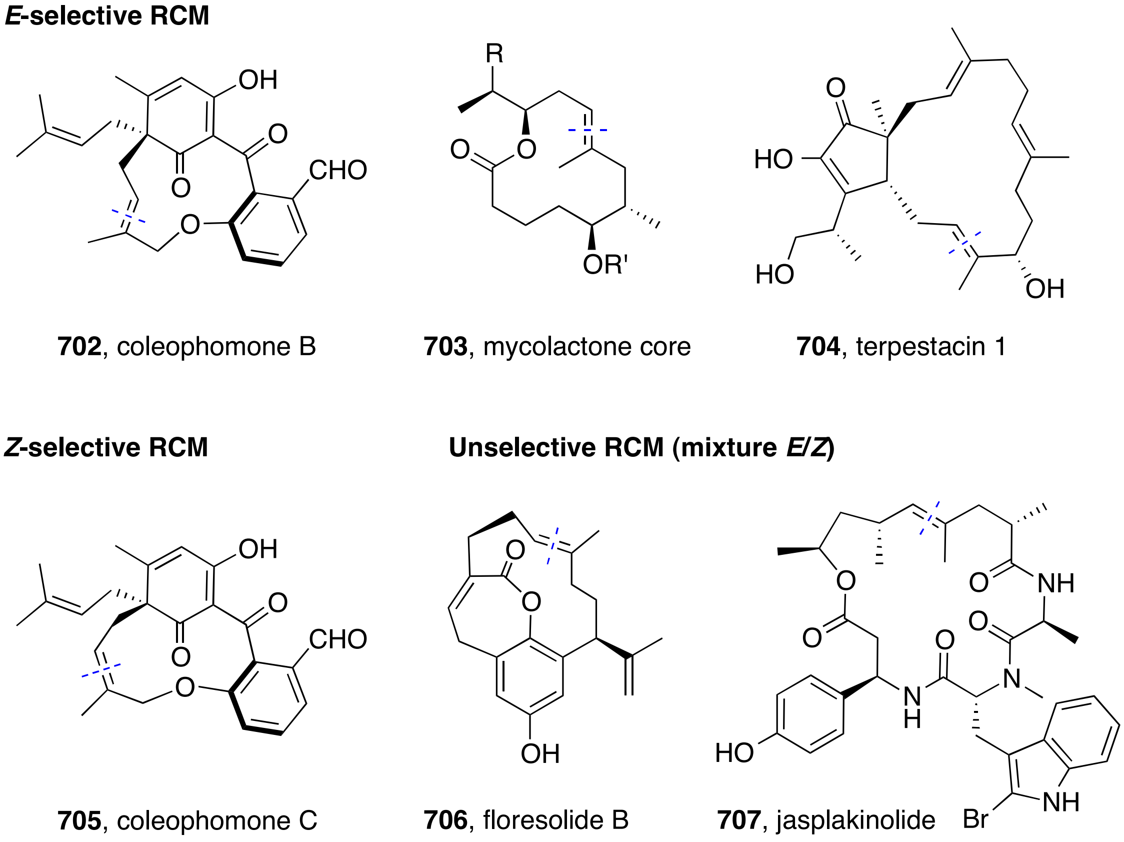
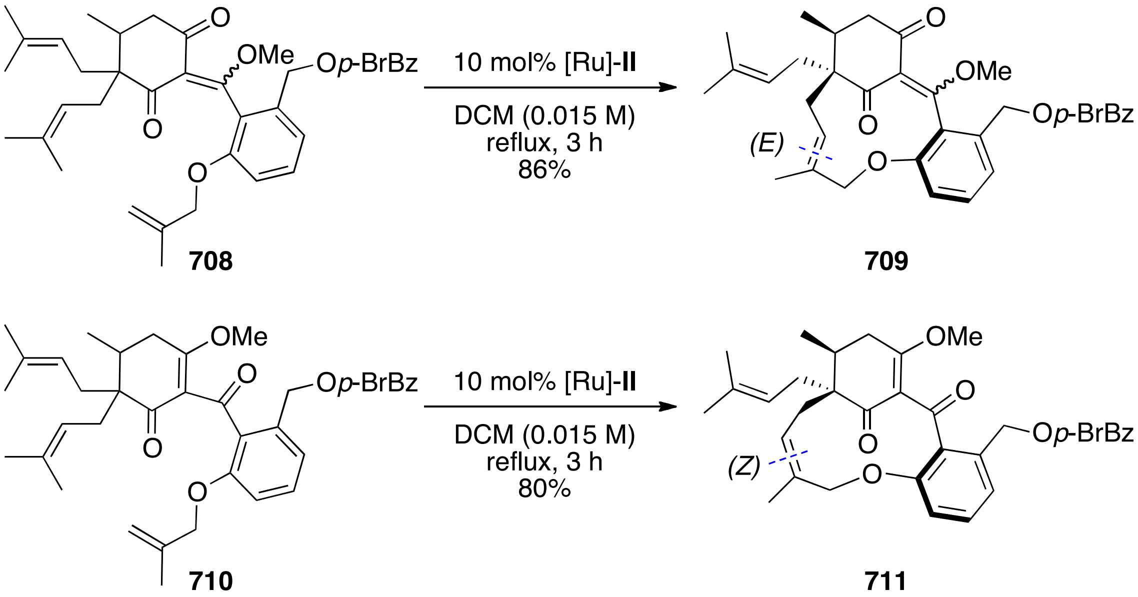


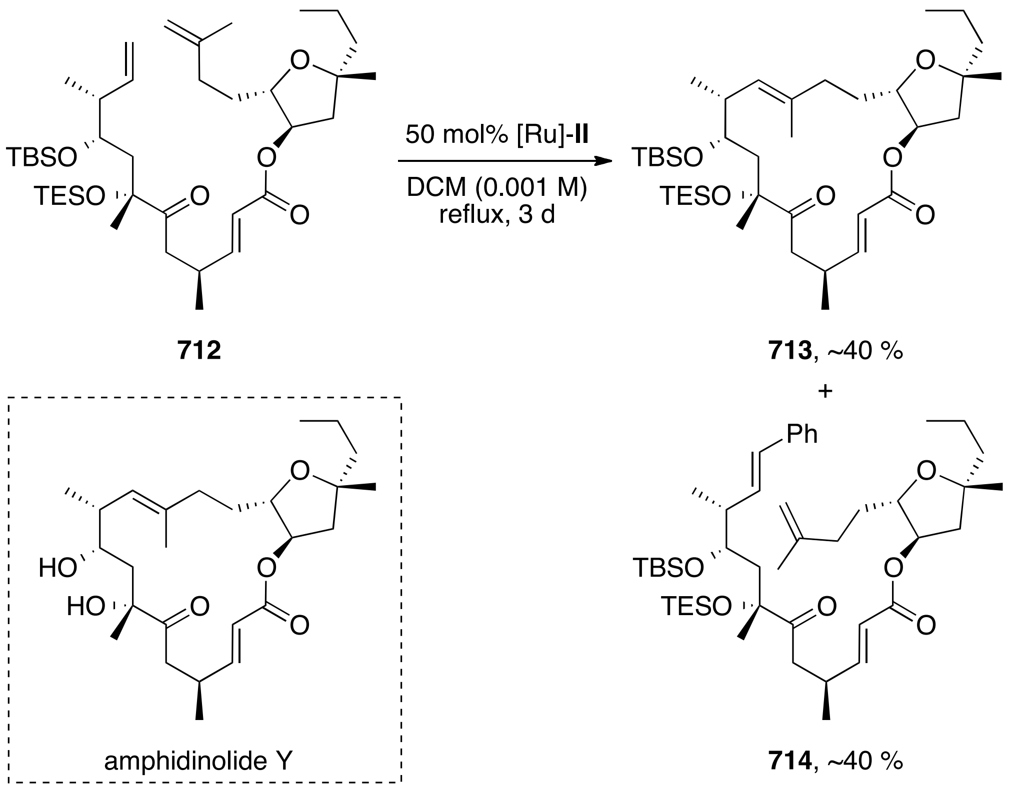
Figure 9. Literature examples of complex molecules containing a trisubstituted olefin formed via Ru-catalyzed RCM in total synthesis.

For our purposes, we became interested in RCM examples involving the assembly of larger (>10-membered) rings and the selectivities obtained on such ring closures. Applications of ring-closing metathesis in total synthesis have been reviewed at length[137-138] and due to the vast number of notable examples, cases involving the formation of *disubstitued* systems (assembled from two terminal olefinic ends) will not be discussed here. Instances of macrocycles formed via the RCM assembly of *trisubstituted* olefins are significantly fewer. Furthermore, recent ruthenium-mediated examples (Figure 9) as well as older reports featuring molybdenum catalysts[148b,c] appear to be limited to methyl-substituted alkenes. *E*/*Z* selectivity, as mentioned, is known to be an issue[176] but rather in a case-dependent even unpredictable fashion. This is clearly illustrated by comparing the apparently rigid 12-membered cyclic natural product floresolide B (**706**), synthesized via RCM (with lack of selectivity),[177] and the flexible-looking, also 12-membered, mycolactone core (**703**), reported to be closed via metathesis as a single isomer by two independent research groups.[178] In terms of selectivity, on the other hand, Nicolaou's total synthesis of coleophomones B and C[179] (**702** and **705**) is certainly out of the ordinary. This report shows how a subtle difference between two substrates (**708** and **710,** Scheme 100) allowed for the exclusive preparation of both geometrical isomers of the desired 11-membered ring with remarkable selectivity.



Scheme 100. Substrate-controlled *E*/*Z* selectivity in the key RCM step in Nicolaou's total synthesis of coleophomones B and C.

A meticulous literature search revealed that formation of trisubstituted olefins in larger macrocycles via RCM is even more infrequent. Among those few, the total synthesis of terpestacin[180] (Figure 9, **704**) reported by the Trost group is an important example that shows the application of ring-closing metathesis with complete *E* selectivity to assemble a product featuring three *E* olefins within a 15-membered ring.

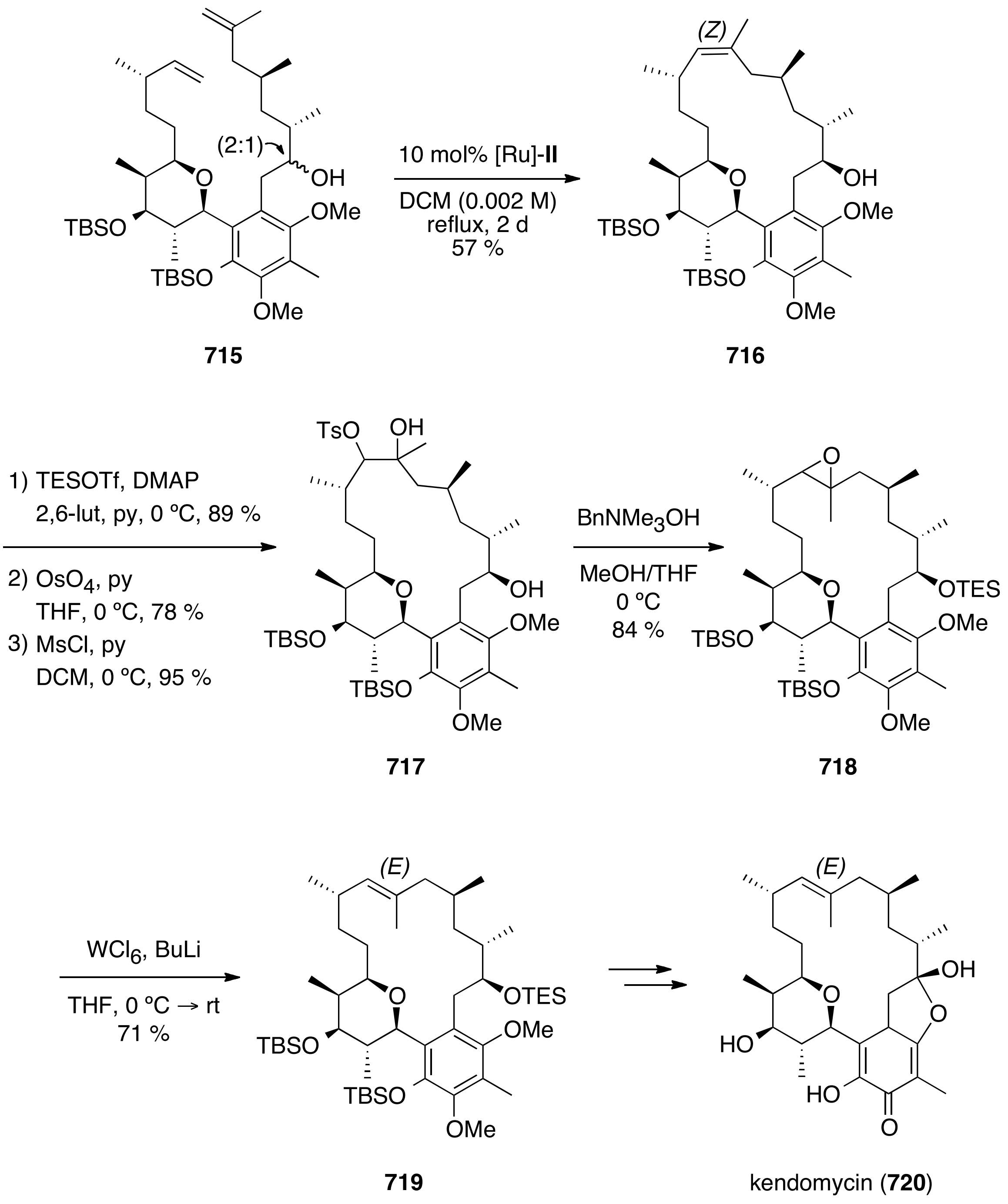


Scheme 101. Late-stage RCM in the total synthesis of amphidinolide Y.

Dai's total synthesis of amphidinolide Y[181] (Scheme 101) provides a case with a more sterically demanding substrate that actually required an excess of [Ru]-**II** catalyst in order to favor the formation of the product, **713**, which inopportunely was obtained as a 1:1 mixture with compound **714**, resulting from the incorporation of the ruthenium catalyst's alkylidene ligand into the system. The desired 17-membered macrocycle **713** was formed as the *E* olefin selectively, an outcome commonly supported by the notion that, in large rings, the *E* isomer tends to be dominant, most likely due to a more favored assembly of the corresponding ruthenacyclobutane intermediate (See Scheme 98 and Scheme 99). Nonetheless, the reported total synthesis of jasplakinolide[182] (Figure 9, **707**) provides just the right counterexample, since the RCM step provided the 19-membered in a totally unselective manner.

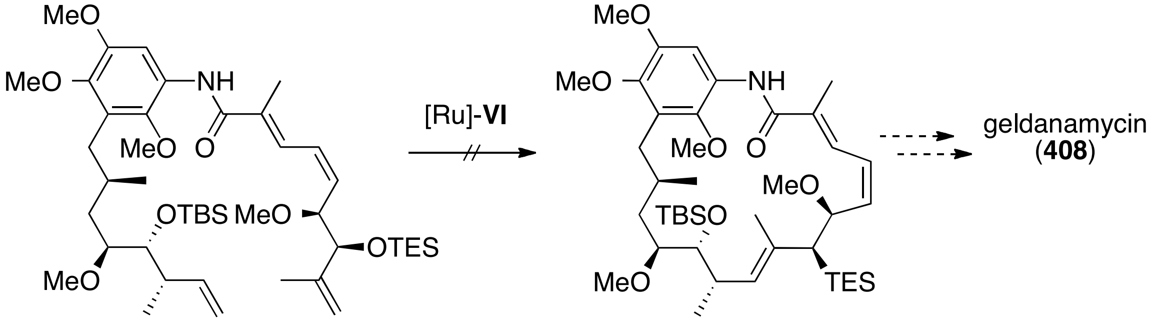
Another important report, the total synthesis of kendomycin by the Smith[183] group (Scheme 102), is surely attention-grabbing for many reasons. First of all, even though the RCM substrate employed (**715**) was a 2:1 mixture of epimers, the 16-membered ring-closed product was cleanly formed exclusively from one of them. In addition, the RCM reaction afforded the *Z* olefin selectively as a single product (**716**), which turned out to be the undesired isomer in this case. The authors evaluated a number of methods to obtain the olefin with the desired geometry. Their final route involved the isomerization of the RCM product via the formation of an epoxide and its corresponding deoxygenation.

With all these noteworthy applications reported within the last five years, we were encouraged to examine ring-closing metathesis in our synthetic route toward autolytimycin. It is important to mention that RCM had been previously employed in the synthesis of simplified ansamycins reported by the Blagg group.[57b] Although this reaction worked efficiently at forming *disubstituted* olefins from bare carbon chains without oxygenated centers, similarly productive results are not generally found for the construction of *trisubstituted* olefin-containing targets in the presence of multiple substituted centers. As shown up to this point, successful ring-closures of such macrocycles via metathesis in the literature basically involve systems that are not as sterically encumbered, comparatively speaking.



Scheme 102. Late-stage formation of a trisubstituted olefin via RCM and its isomerization in Smith's total synthesis of kendomycin.

Andrus' full paper on the synthesis of geldanamycin[72b] briefly describes the evaluation of a tentative RCM-based route (Scheme 103). The authors reported the lack of success in a number of metathesis experiments involving various solvents, concentrations, modes of addition, and additives. However, the report implies that only catalyst [Ru]-**VI** (See Figure 8, page 119) was studied at the time. In any case, considering especially the current availability of catalysts of much higher activity/stability and the structural differences between geldanamycin and autolytimycin (being the latter presumably more flexible, see Scheme 96), we decided to investigate ring-closing metathesis as our first alternative to assemble the autolytimycin macrocycle.



721

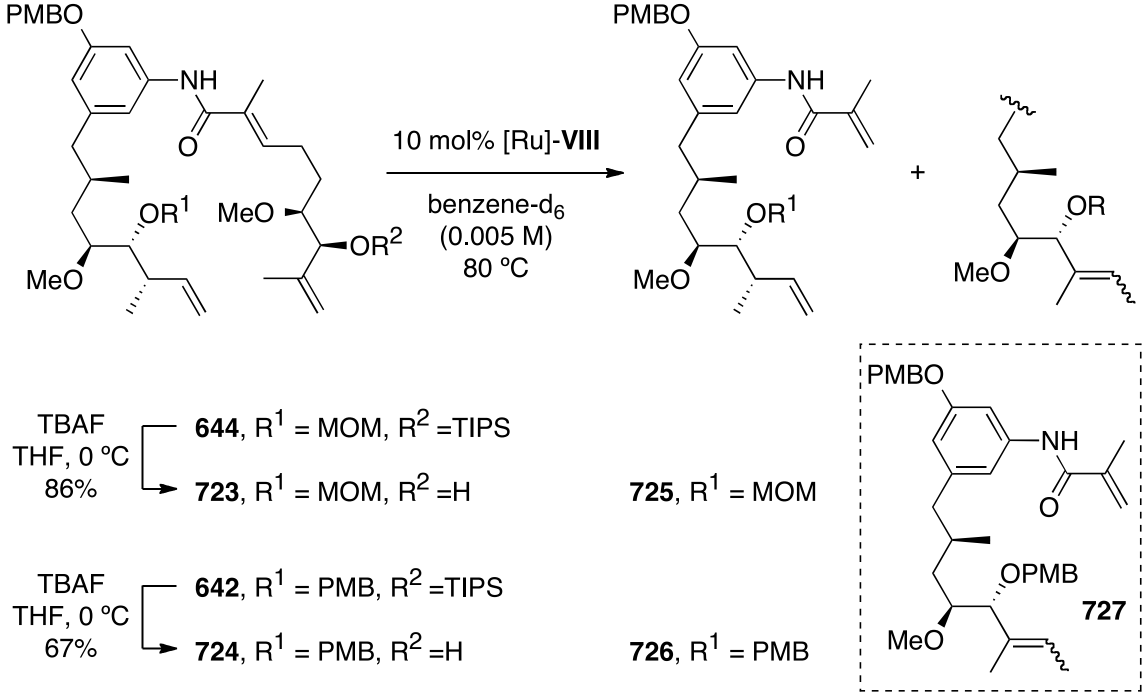
722

Scheme 103. Attempted RCM in Andrus' total synthesis of geldanamycin.

7.2. Results and discussion

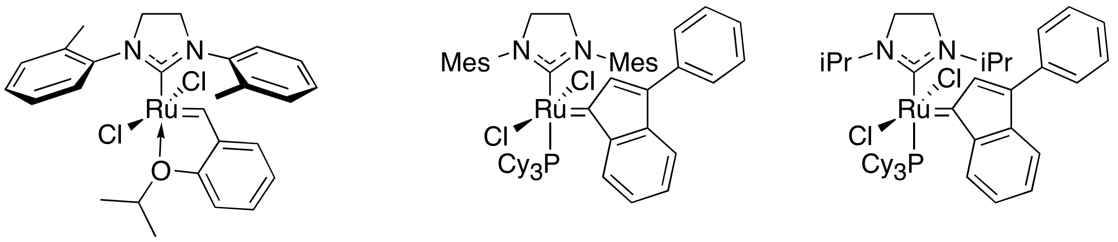
7.2.1. Preliminary results

For our first RCM experiments, the discussed robustness of the second-generation Hoveyda-Grubbs catalyst ([Ru]-**VIII**, Figure 8) and current reports on its superior performance[184] made [Ru]-**VIII** our initial metathesis catalyst of choice. In order to follow the progress of the reaction by NMR, our first experiments were performed in deuterated solvents, highly diluted, and under standard heating (80 ºC). Subjection of Suzuki product **644** (see preparation in Scheme 91) to these metathesis conditions (Scheme 104) gave little evidence of any reaction. Surprisingly, prolonged reaction times led to the exclusive consumption of the terminal olefin with respect to the disubstituted one (as determined by ^{1}H NMR). This observation was initially mistaken as a potential dimerization but was later identified to be the result of an olefin isomerization (*vide infra*). The selective reaction on the terminal olefin (left-hand side) made us consider that the presence of the bulky TIPS group might have hindered the reaction on the disubstituted alkene. Moreover, protective group-free allylic hydroxyl groups are known to display greatly accelerated rates of reaction with ruthenium alkylidenes.[185] Thus, Suzuki products **644** and **642** were subjected to TBAF-mediated TIPS deprotection to afford the new RCM substrates **723** and **724**.



Scheme 104. Earliest RCM results in our synthetic approach to autolytimycin.

To our dissapointment, RCM reactions on both substrates, **723** and **724**, demonstrated that the olefins in our system displayed a tendency to undergo *independent* reactions (Scheme 104). While the right-hand side olefin led to the loss of a six-carbon chain, the terminal olefin underwent isomerization. Forcing reaction conditions (20 mol% [Ru]-**II**, toluene, 110 ºC, 16 h) on substrate **724** later allowed the isolation of the major component, **727**, which confirmed both the six-carbon chain loss and the isomerization of the terminal olefin. Furthermore, higher catalyst loadings and temperatures drove an apparent decomposition of our substrate, leading to the formation of complex mixtures. Given this situation, we studied the use of a newly developed catalyst [Ru]-**IX,**[186] a modified second-generation Hoveyda–Grubbs catalyst, known for being efficient with encumbered olefins for possessing *o*-toluyl substituents in place of mesityls on the carbene ligand. Unfortunately, in our hands, this catalyst provided similar results and even a faster decomposition. Other modified Hoveyda–Grubbs-based catalysts[187] were not explored.



[Ru]-**IX**[186]
o-toluyl variant of
2nd generation Hoveyda-Grubbs

[Ru]-**X**[188, 189]
Neolyst™ M2

[Ru]-**XI**[190]

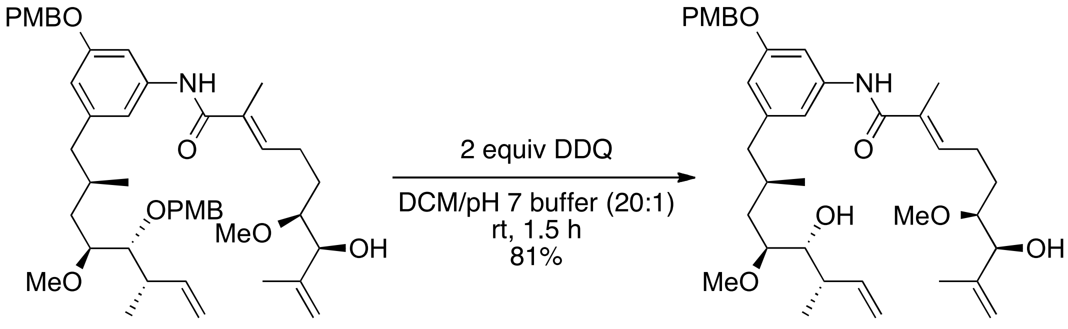
Figure 10. Recently developed metathesis catalysts.

In the search for catalysts known to have a higher thermal stability, we turned our attention to [Ru]-**X**, a commercially available catalyst known as Neolyst™ M2. This compound resulted interesting to us for being the H_2IMes-containing version of catalysts [Ru]-**IV** and [Ru]-**V** (Figure 8) and therefore, intuitively expected to be significantly active. In fact, [Ru]-**X** has been said to display an improved “performance, especially in ring-closing metathesis (RCM) of tri- and tetrasubstituted olefins”.[172b] We were surprised, however, to find out that literature reports involving [Ru]-**X** had been rather scarce until recent years, with reports from the Nolan[188] and

Grela[189] groups. We also decided to evaluate [Ru]-**V**, which was found to be as active as [Ru]-**X** for some substrates.[188a] During the course of our studies, the IPr version of Neolyst™ M2, [Ru]-**XI** (Figure 10), was reported to be more active in several metathesis reactions.[190] By that time, nevertheless, we had already realized that catalyst activity was not as critical for the success of the RCM in our system as the structural features of the substrate itself as will be discussed in the following pages.

In attempts to tune the conformation of the molecule, we evaluated a series of common solvents, toluene, benzene, and dichloromethane, together with uncommon ones, like the fluorinated[191] hexafluorobenzene and octafluorotoluene, and the ionic liquids [bmim]BF_4 and [bmim]PF_6.[192] These uncommon solvents have been reported to facilitate RCM reaction in difficult instances.[191-192] At the same time, the reactions were performed at temperatures from 40 to 110 ºC and the use of microwave irradiation (reported to have an effect on metathesis reactions)[193] allowed us to carry out the reactions at 150–180 ºC, but not even traces of the desired product were found in any case, while isomerization of the terminal olefin and the loss of a six-carbon chain were always present. Furthermore, under forcing conditions, especially at high temperature and high catalyst loading, the substrate appeared to decompose forming complex mixtures.

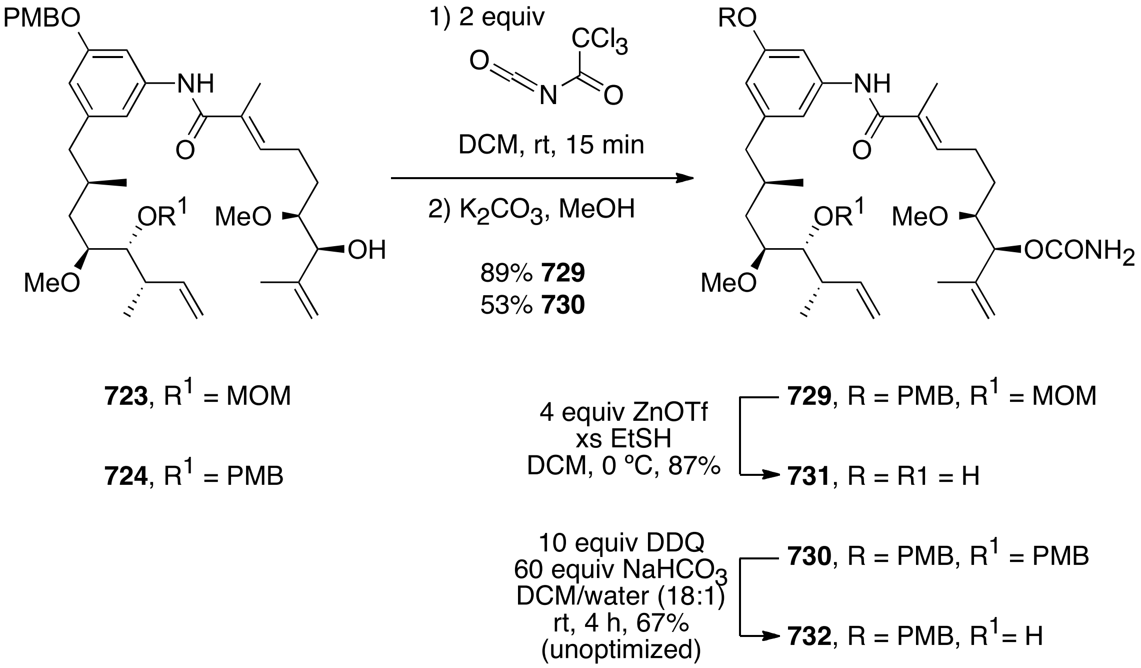
It is actually known that both first-generation,[194] and second-generation[195] ruthenium catalysts can gradually decompose by action of water and oxygen (and alcohols), forming ruthenium hydride species that are selective and effective at promoting alkene double-bond isomerization. Even though the use of degassed solvents and nitrogen sparging (a constant flow of nitrogen gas bubbling through the solution) somehow controlled the decomposition of the reaction mixture, the isomerization of the terminal olefin appeared unavoidable (see Section 7.2.3, page 144, for details). Among many solvents tested in our preliminary reactions, acetic acid[196] proved to be effective at controlling to a certain extent the olefin isomerization, which eventually occurred nonetheless after longer reaction times.



724 **728**

Scheme 105. Selective PMB deprotection of a secondary alcohol in the presence of a PMB-protected phenol.

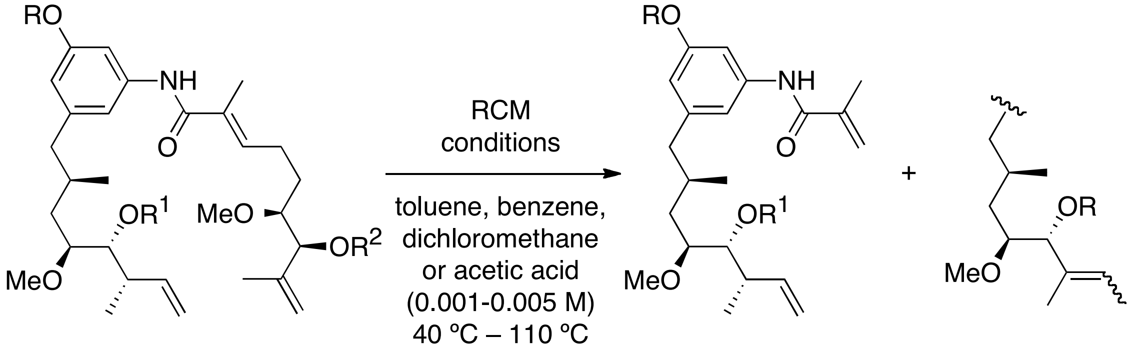
With these results in hand, we decided to continue with an evaluation of the effect of the protective groups on the RCM outcome. A summary of the results is presented in Table 11, page 134. Treating our substrate **724** with DDQ, a reagent commonly used for removal of PMB groups,[197] led to the exclusive deprotection of the secondary alcohol, leaving the phenolic one untouched, to provide **728** (Scheme 105). Interestingly, the result was the same even in the presence of a large excess of DDQ. The use of the deprotected substrate **728** in RCM, however, did not stop the isomerization of the olefin, nor favored the formation of the desired ring (Table 11, entry 5), so then we intended to lower the reactivity of the right-hand side olefin by installing a carbamate group (Scheme 106) to presumably avoid the bothersome six-carbon chain loss. All these cases (see Table 11, entries 6, 7, and 9) were apparently unreactive substrates that provided isomerization as the only detectable transformation after long reaction times. Equivalent results were observed both in the presence of a small MOM group (entry 6) and in absence of a protective group (entry 9).



Scheme 106. Preparation of carbamate-containing RCM substrates.

After some experimentation, we found out that simultaneous deprotection of both the phenolic PMB and the MOM groups was achievable under Lewis-acidic conditions in the presence of a thiol scavenger[198] to give compound **731** (Scheme 106). This product actually corresponded to the ring-opened form of our target molecule autolytimycin. Much to our dismay, the use of **731** as RCM substrate, also failed to provide the desired product (Table 11, entry 7) and isomerization was the only observable reaction. As mentioned, metathesis conditions on ring-opened autolytimycin containing a PMB-protected phenol (**732**, prepared via the selective PMB deprotection) afforded equal results (Table 11, entry 9).

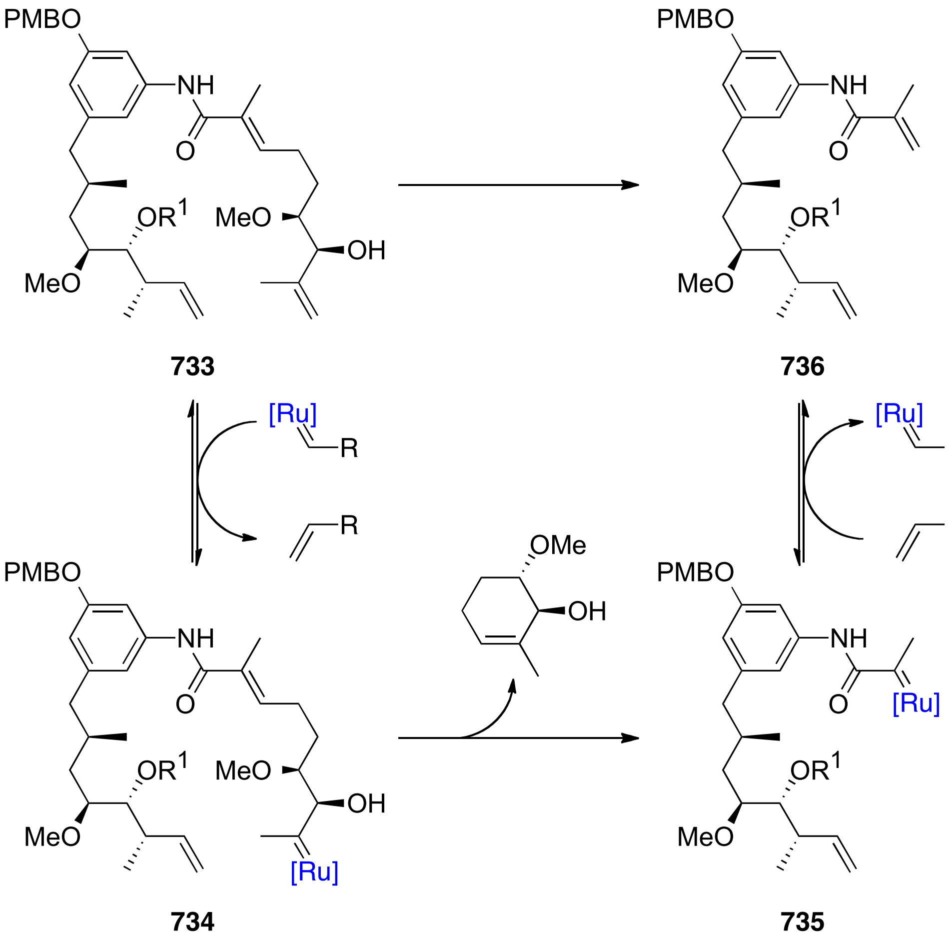
Table 11. Summary of synthesized RCM substrates and evaluated metathesis conditions.



Entry	R	R^1	R^2	Substrate	Evaluated catalysts	Results
1	PMB	MOM	TIPS	**644**	[Ru]-**VIII**	only isomerization
2	PMB	PMB	TIPS	**642**	-	-
3	PMB	MOM	H	**723**	[Ru]-**II**, **V**, **VIII**, **X**	six-carbon chain loss and isomerization
4	PMB	PMB	H	**724**	[Ru]-**II**, **VIII**, **X**	six-carbon chain loss and isomerization
5	PMB	H	H	**728**	[Ru]-**II**, **V**, **IX**, **X**	six-carbon chain loss and isomerization
6	PMB	MOM	$CONH_2$	**729**	[Ru]-**II**	only isomerization
7	H	H	$CONH_2$	**731**	[Ru]-**II**, **X**	only isomerization
8	PMB	PMB	$CONH_2$	**730**	-	-
9	PMB	H	$CONH_2$	**732**	[Ru]-**II**, **X**	only isomerization

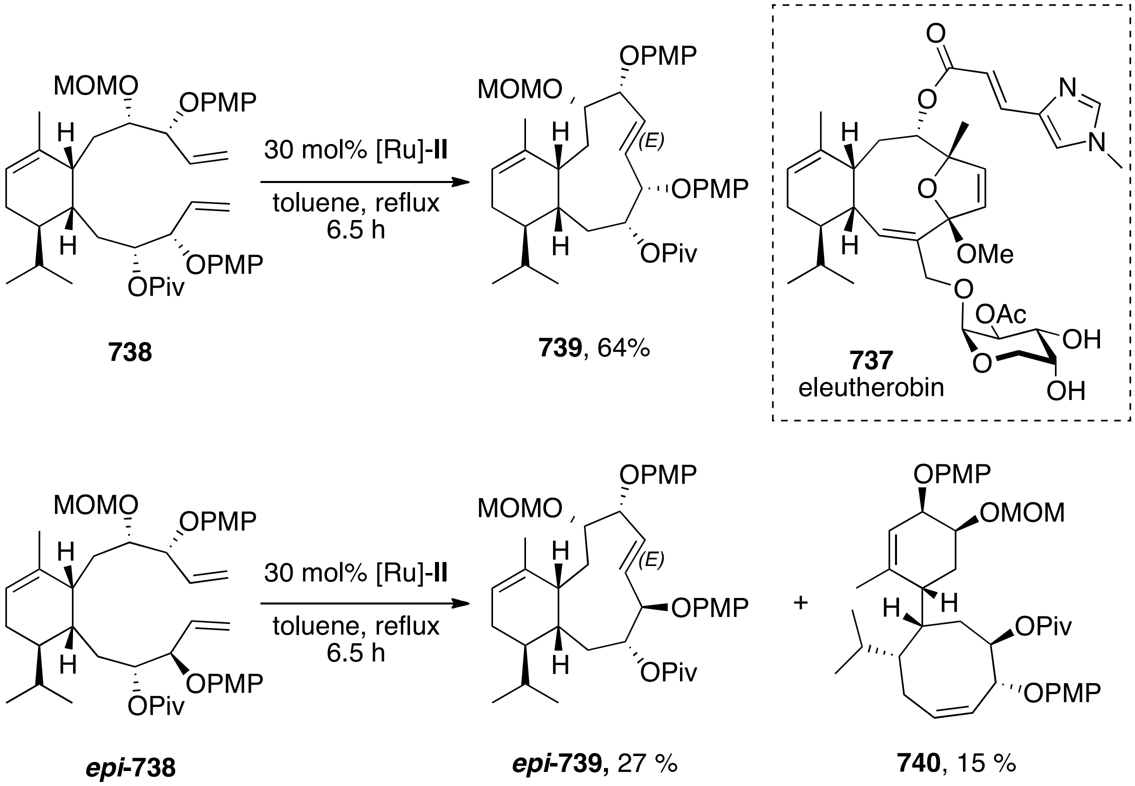
For reactions with substrates **723**, **724**, and **728**, for which transformations besides isomerization were observed, thorough analyses of crude materials and chromatography fractions by LC-MS were performed in an effort to find *traces* of the desired 19-membered ring, to no avail. In theory, the terminal olefin (left-hand side) is expected to be more accessible for reaction with ruthenium catalysts but for some reason it seemed to participate exclusively in isomerization.

Furthermore, when we take into account the mechanism (illustrated in Scheme 107) by which the bothersome six-carbon chain loss is expected to occur, intermediate **735**, for instance, could as well lead to the formation of a 13-membered ring, but no evidence of such ring closure was detected either. A possible explanation for this behavior would be that, when the ruthenium complex installs itself into the terminal olefininc end (left-hand side), it renders a non-productive intermediate, in which the metallic center is not able to encounter the other end.



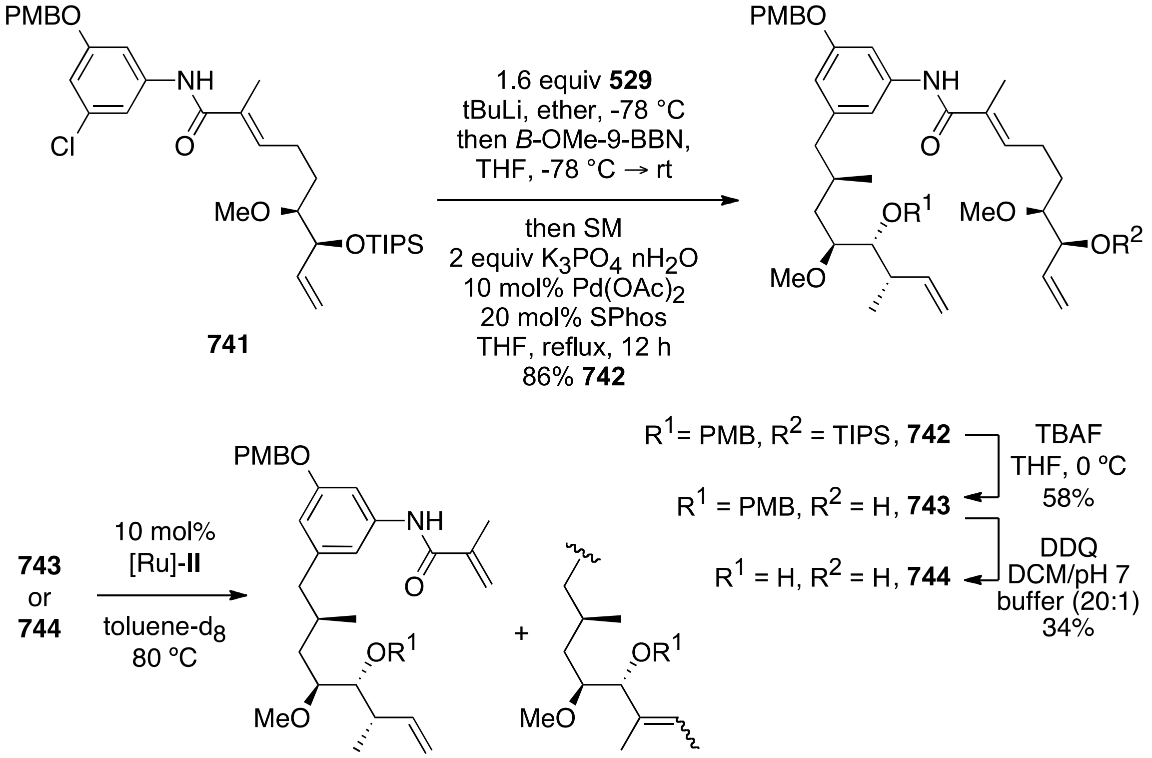
Scheme 107. Proposed mechanism for the six-carbon chain loss from RCM substrates.

Aware of the possibility that our desired *trisubstituted* olefin was too sterically hindered to be formed via an RCM, we evaluated the likelihood of forming a *disubstituted* olefin instead. As mentioned earlier, our desired alkene is flanked by five trisubstituted stereogenic centers, which makes it a relatively uncommon RCM target. We became interested in the reported formal synthesis of eleutherobin,[199] a fairly unique example of the formation of an olefin quite sterically encumbered, rather infrequent in the literature. The productive RCM of **738** (Scheme 108) permitted the formation of a disubstituted olefin flanked by four protected oxygenated centers (**739**). A fascinating detail in this report is that an epimer of the successful substrate (***epi*-738**), subjected to identical RCM conditions, displayed a totally different behavior; even though the expected 10-membered product (***epi*-739**) was formed, it was accompanied by compound **740**, whose intricate structure apparently formed via the unanticipated ring-opening metathesis of the present cyclohexene ring.



Scheme 108. Example of a successful RCM in a congested system featured in a formal synthesis of eleutherobin.

We then envisioned that the removal of the methyl substituent from the right-hand side olefin would make our substrate less demanding in terms of sterics. Thus, demethylated amidochlorophenol **741**[s] was subjected to *B*-alkyl Suzuki coupling, which proceeded with high efficiency, and subsequent protective group manipulations to afford the desired demethylated substrates (Scheme 109). During the course of our studies, a report by the Hierseman[200] group presented a case similar to ours, where the formation of a *trisubstituted* olefin was difficult but the ring was successfully formed after removal of a methyl substituent. Unfortunately, unlike in that report, our demethylated substrates exclusively favored the six-carbon chain loss previously observed in the original RCM substrates (see Table 11).



Scheme 109. Preparation and evaluation of demethylated RCM substrates.

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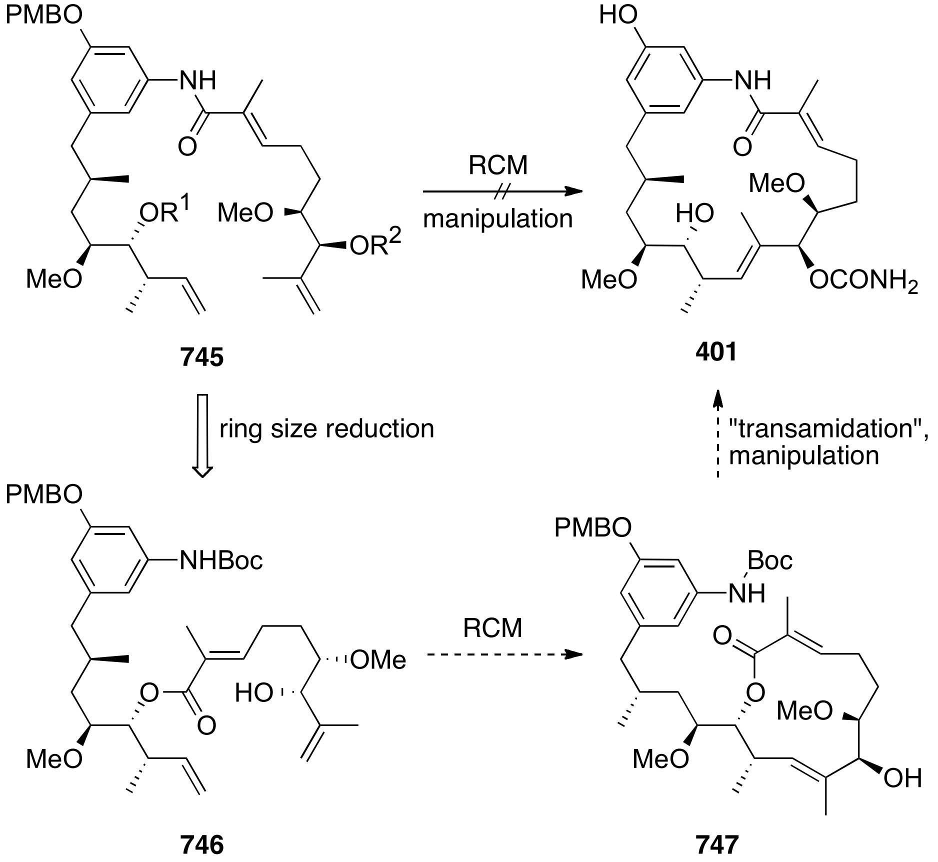
[s] Prepared by Dr. Monica Norberg[84]

Considering that the two olefinic ends appeared to have difficulties to find each other for reaction under metathesis conditions, we developed an approach to evaluate the effect of the ring size on the RCM. Our plan, depicted in Scheme 110, called for the disconnection of the amide bond and the formation of an ester in order to turn our RCM target into a 12-membered ring (**747**), thus presumably making the encounter of the two olefins more likely.



Scheme 110. Proposed facilitation of ring-closing metathesis via ring size reduction.

Before embarking into the synthesis of RCM substrate **746**, a more accessible compound, **749** (prepared via TIPS deprotection of **748**[t]), was used as a simplified model. Triene **749**, however, turned out to be a rather tough RCM substrate and actually required an excess of catalyst and

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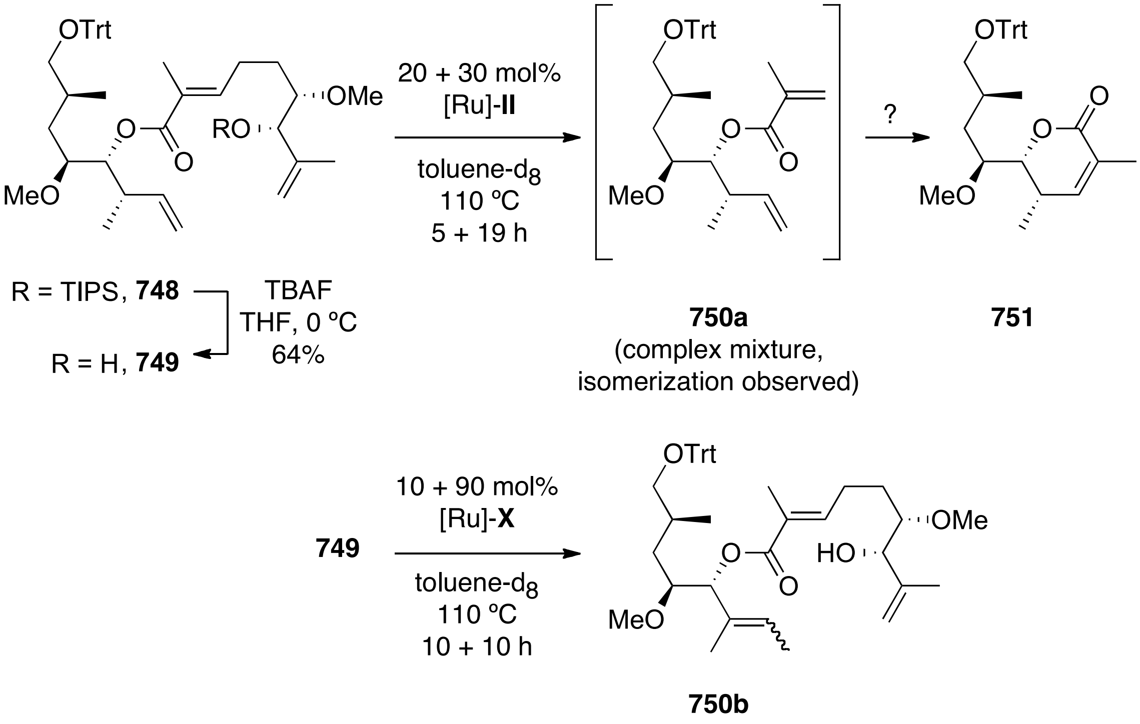
[t] Synthesized by Dr. Monica Norberg[84]

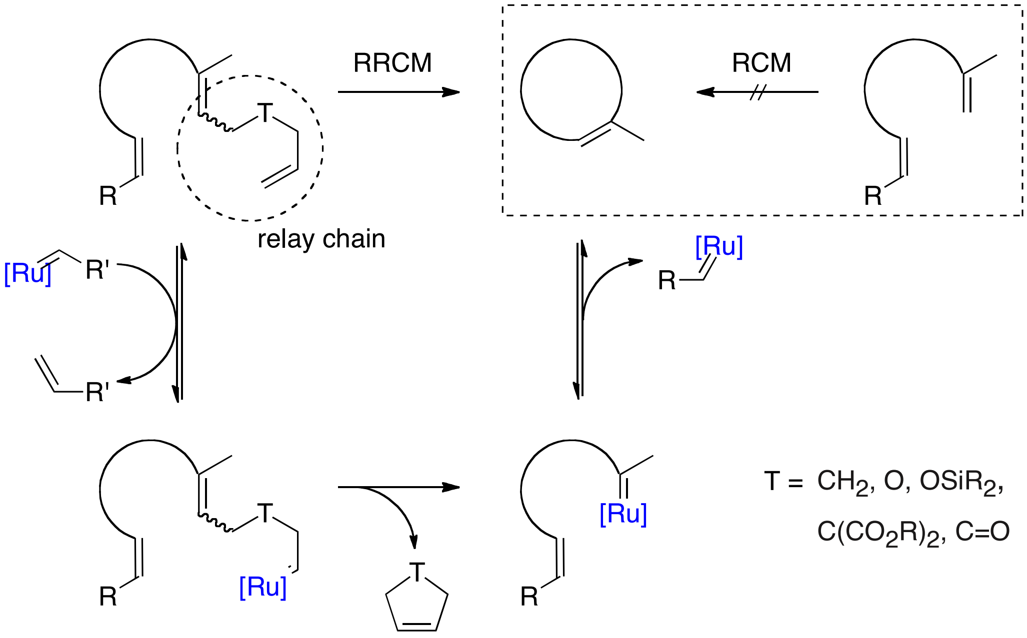
high temperature to give any evidence of conversion. As shown in Scheme 111, formation of the desired 12-membered ring was not observable and, depending on the catalyst used, either the terminal or the disubstituted olefin were consumed. This route was abandoned to pursue different alternatives aimed to solve both the isomerization of the terminal olefin and the bothersome six-carbon chain loss from the RCM substrates.



Scheme 111. Preparation and evaluation of a ring-reduced RCM substrate.

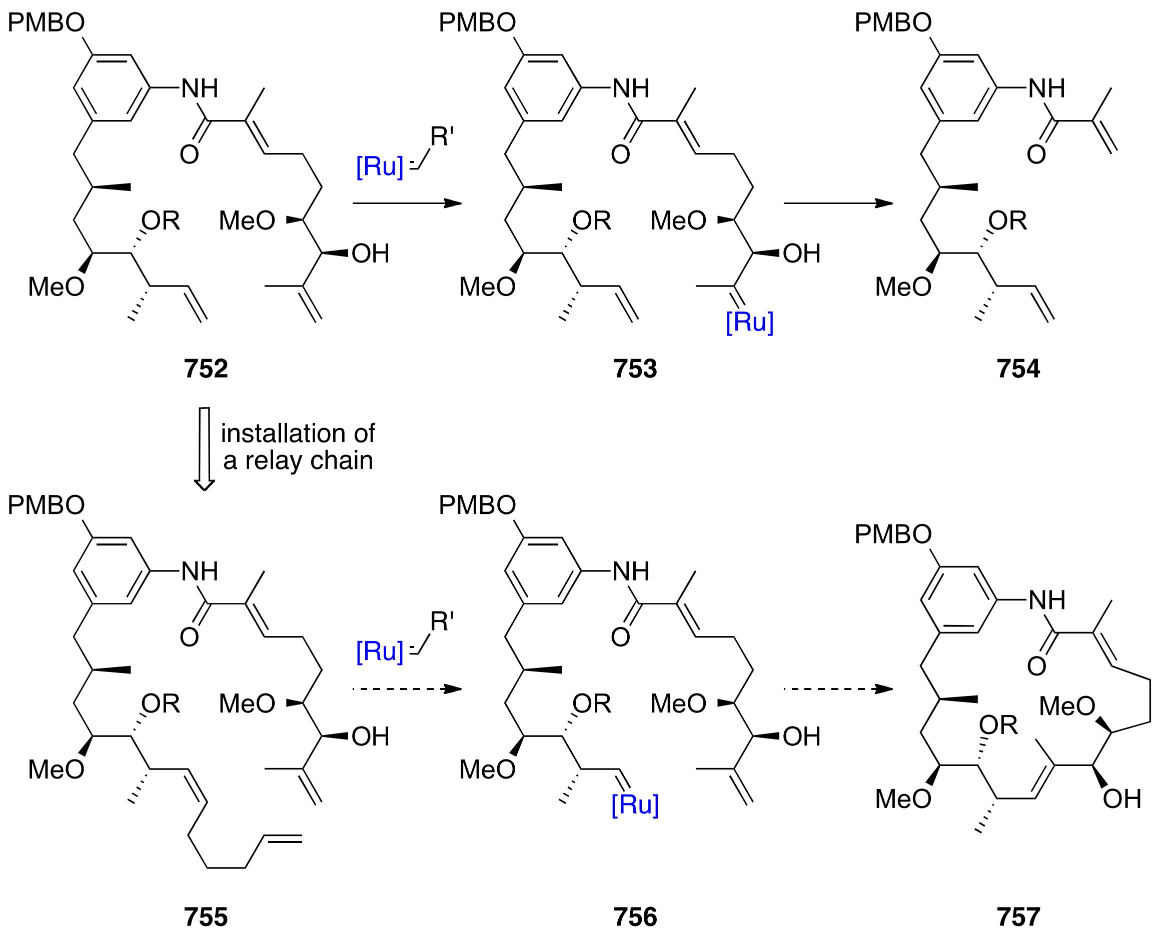
7.2.2. Relay RCM

Given our initial RCM results, we developed an RRCM-based tactic intended to suppress the undesired six-carbon chain loss from our metathesis substrates. Relay ring-closing metathesis (RRCM) was introduced a few years ago by Hoye[201] as an strategy to drive the ring formation from substrates that perform inneficiently in traditional RCM closures (including the formation of tetrasubstituted olefins) via a directed “metal movement through metathesis sequences” depicted in Scheme 112. This problem-solving approach has been certainly successful and has been since then exploited to resolve a number of metathesis issues encountered especially during the synthesis of complex natural and non-natural compounds.[202]



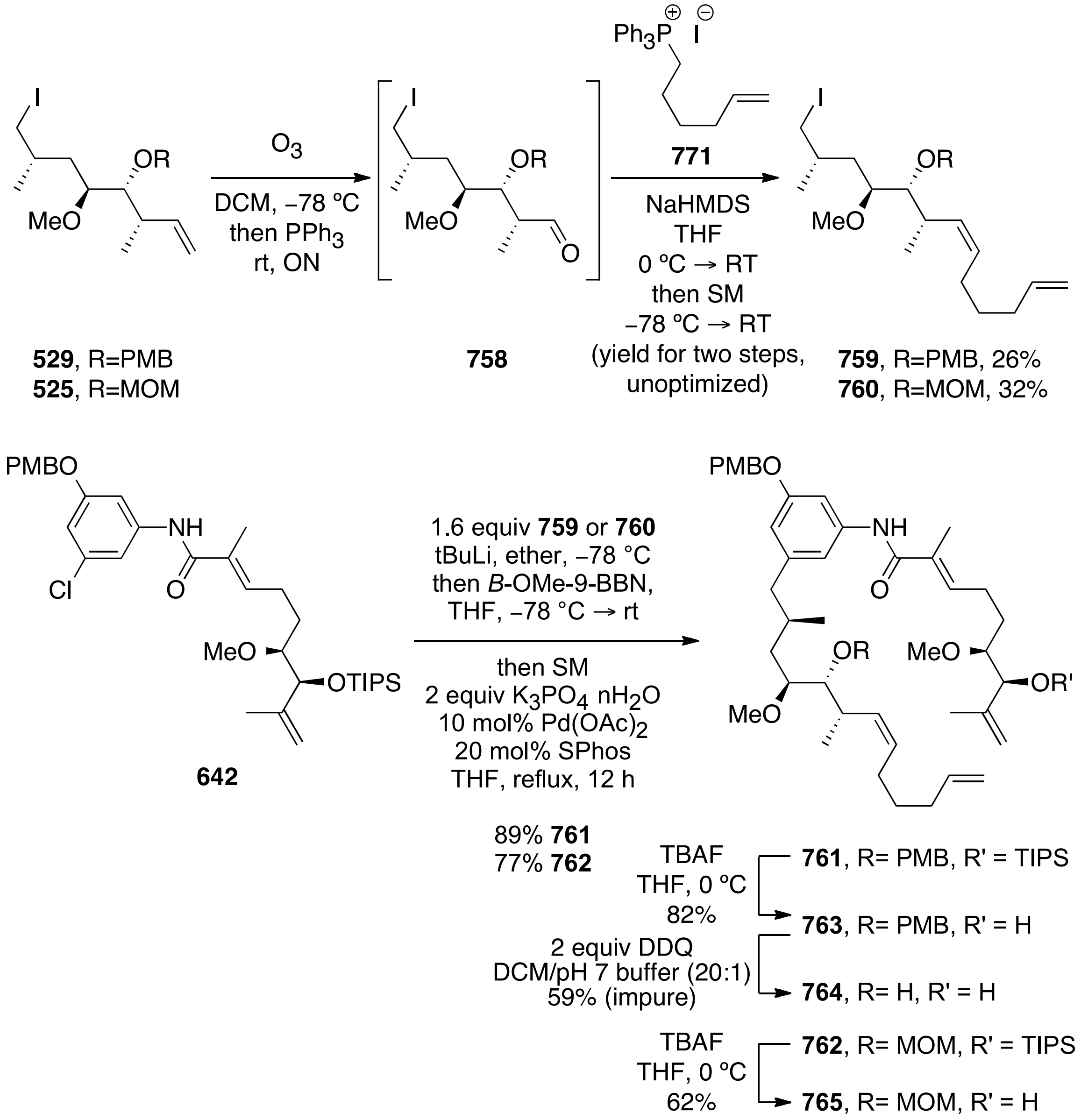
Scheme 112. Schematic representation of an RRCM and its corresponding RCM.

The RRCM strategy is typically employed to direct the metal center to install itself on a hard-to-access, sterically encumbered olefinic end. For our purposes, however, our disubstituted olefin appeared to be reactive enough and what we expected was to actually avoid its reaction with the catalyst as initiation step. Our rationalization called for the installation of a relay chain on the terminal olefin, as illustrated in Scheme 113, in order to direct the catalyst into the formation of intermediate **756**, which could then carry out the desired ring closure.



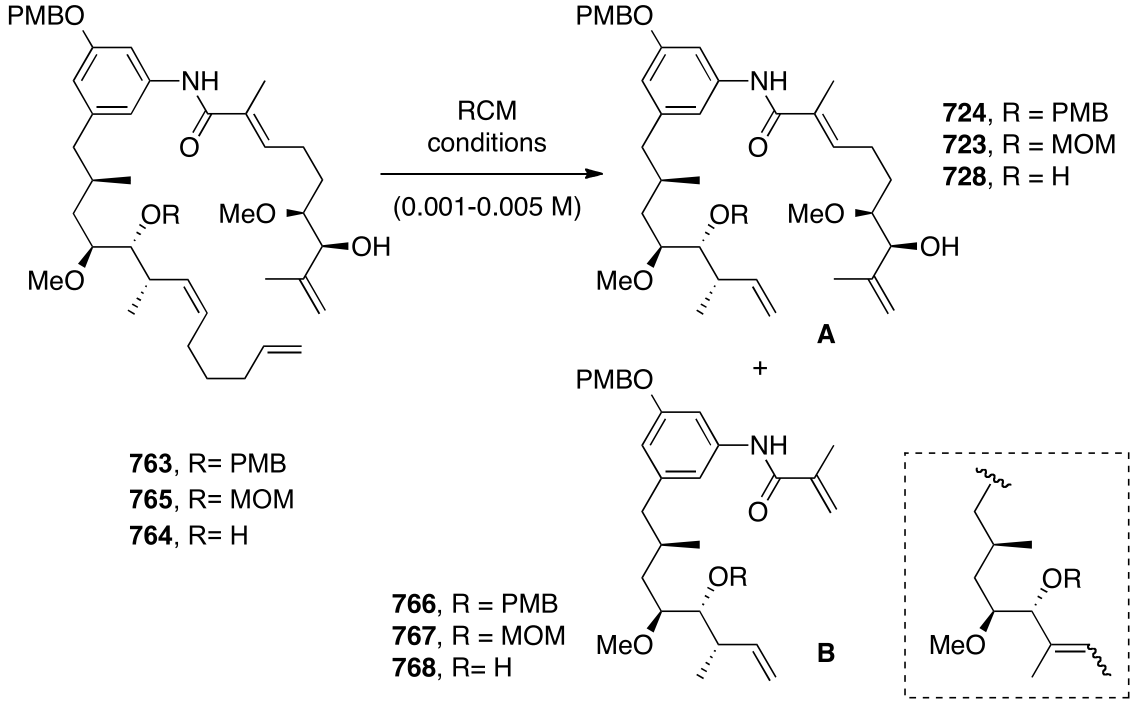
Scheme 113. RRCM-based strategy to avoid the undesired six-carbon chain loss from the RCM substrates.

Installation of the relay chain in our system was executed in a rather inefficient manner (Scheme 114). An appropriate route toward modified alkyl iodides **759** and **760** would be to perform the ozonolysis/Wittig olefination sequence before the installation of the iodide itself. But with ready access to both **525** and **529** (Scheme 71 and Scheme 73) in hand, we opted for this alternative to accelerate the synthesis of the RRCM substrates and test our hypothesis before trying to improve their preparation. The following steps, the corresponding *B*-alkyl Suzuki couplings and protecting group manipulations proceeded efficiently for the preparation of our RRCM substrates **763**, **764**, and **765**.



Scheme 114. Installation of a metathesis relay chain via an ozonolysis/Wittig olefination sequence and the preparation of the RRCM substrates.

Table 12. Metathesis reactions using RRCM substrates.



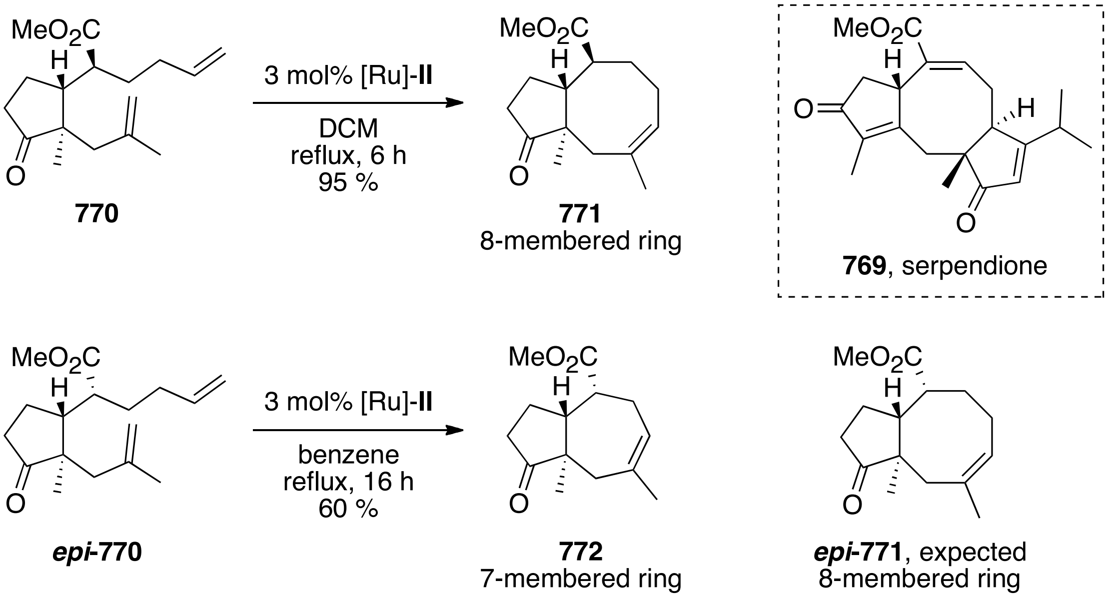
Entry	Substrate	Conditions	Conversion	Results
1	**763**	20 mol% [Ru]-**II** benzene-d_6, 80 ºC, 1 h	100%	~1:1 **A**:**B**
		+ 1.5 h		~2:3 **A**:**B**
2	**763**	10 mol% [Ru]-**X** DCM, 40 ºC, 10 h	100%	**A**, 60% isolated
3	**765**	10 mol% [Ru]-**II** benzene-d_6, 80 ºC, 1 h	100%	~3:2 **A**:**B**
4	**765**	10 mol%[Ru]-**II** toluene, N_2 sparging 80 ºC, 5 h	100%	Mostly **B** (TLC)
		+ 5 h		Isomerization and decomposition observed in crude material.
5	**764**	10 mol%[Ru]-**X** DCM, 40 ºC, 12 h	100%	Mostly **A**, ~50% isolated
6	**764**	10 mol%[Ru]-**X** toluene, N_2 sparging RT, 50, 80 ºC, 1 + 2 + 5 h	100%	Decomposition Mostly **B**, ~30% isolated (~50% isomerized)

PMB-protected RRCM substrate **763** was found to react rapidly under metathesis conditions but in a rather unproductive way (Table 12, entry 1), resulting in the "regeneration" of the original RCM substrate **724** and the formation of the six-carbon chain loss product **766**, both likely to be formed via a similar mechanism (see Scheme 107). The use of milder conditions (entry 2) provided the exclusive formation of **724** again and no further reaction was observed even after a long reaction time. Based on these results, we considered the possibility that the ring-closure might be hindered by the presence of the large PMB protective group, which justified the preparation of the MOM-protected (**765**) and deprotected (**764**) forms. Nonetheless, the reaction with **765** gave almost identical results (entry 3) and mild reaction conditions on **764** (entry 5) provided the original RCM substrate **728**. Attempts to force the ring-closure (entries 4 and 6) favored the 6-carbon chain loss and ultimately the decomposition of the reaction mixture. Interestingly, this decomposition and the isomerization of the terminal olefin were somehow controlled during the first hours of reaction (Table 12, entries 1, 3, and presumably 4). Longer reaction times and higher temperatures eventually led to the formation of isomerized products. Disappointingly, formation of the desired 19-membered product was not detected in any case. Even though our RRCM-based approach was unsuccessful, after these experiments we recognized that, in order to find improved RCM conditions, we needed to facilitate both the analysis of crude mixtures and the purification of products, by avoiding somehow the isomerization of the terminal olefin.

7.2.3. Suppressing isomerization

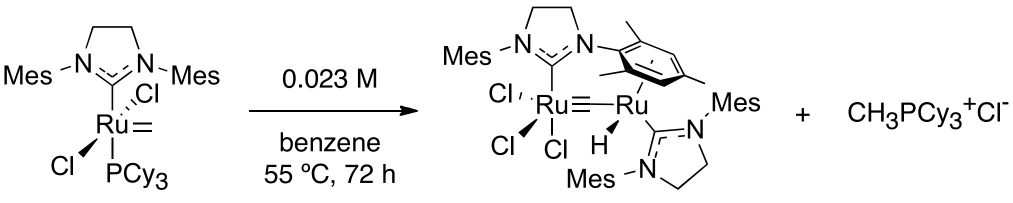
The isomerization of olefins under metathesis conditions is an issue well documented in the literature.[203] Even though the mechanism by which it occurs is not yet totally understood, it has been attributed to metal hydride species, formed via decomposition of the ruthenium catalyst.[204]

This aspect has also been reported to cause troubles in the synthesis of other complex molecules. Among several examples in the literature,[205] the studies toward the synthesis of serpendione[206] (**769**) provide a pretty attention-grabbing example. Two epimers, **770** and ***epi*-770**, independently subjected to identical ring-closing metathesis conditions gave two totally different results (Scheme 115); in one case, the desired 8-membered product **771** with high efficiency, whereas the other one gave a 7-membered ring **772** as the main product, resulting from an apparently highly efficient isomerization, followed by the corresponding ring closure. Interestingly, the authors also reported that using first-generation Grubbs catalyst ([Ru]-**I**) on ***epi*-770** exclusively afforded a dimer, which after being resubjected to reaction with second-generation Grubbs catalyst ([Ru]-**II**), gave a mixture or **772** and ***epi*-771**, where the 7-membered ring was still the major component.



Scheme 115. Isomerization-RCM sequence observed in the synthesis of serpendione.

This is yet another fascinating example of dissimilar behaviors of two closely related molecules under RCM conditions and definitely worthy of note is the predisposition of *one* of them to favor an isomerization prior to the RCM itself. Not surprisingly, it has been recognized that these *undesired* isomerization reactions can also be of synthetic utility.[207] However, this was not an isolated case. In a recent communication on the synthesis polyanthellin A,[208] a related side formation of an undesired 8-membered ring in place of a 9-membered using second-generation Hoveyda–Grubbs catalyst ([Ru]-**VIII**) was reported. Even in an older report by Overmann,[209] where [Mo]-**I** (Schrock's catalyst) was used, a similar transformation was observed.



773

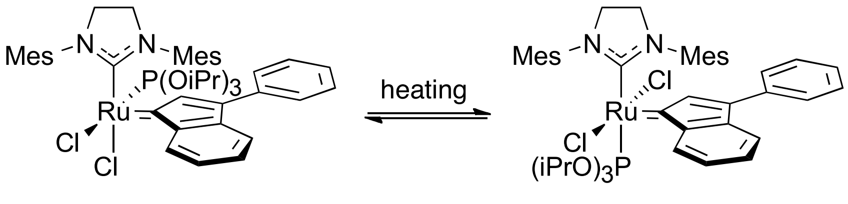
774 "Ru–H"
46 %

Scheme 116. Reported formation of a ruthenium hydride decomposition product from an NHC-containing ruthenium methylidene complex.

As mentioned earlier, it had been already shown that both first-generation,[194] and second-generation[195] ruthenium catalysts can slowly decompose by action of moisture and air, forming ruthenium hydride complexes that are active and selective alkene double-bond isomerization catalysts. A report by the Grubbs group,[210] however, has demonstrated that formation of ruthenium hydride species can occur *without* external agents other than the PCy_3 ligand already present in the complex (Scheme 116). Methylidene complex **773**, expected to form *in situ* during RCM reactions, can decompose thermally to form metal hydride **774** surprisingly at only 55 ºC.

Moreover, it was demonstrated that complex **774** indeed displays olefin isomerization activity in catalytic amounts.

Very recently, we became interested in a report by the Cazin group on the preparation and evaluation of a new catalyst named “Caz-1”.[211] In this newly reported communication it was stated that replacing the PCy_3 phosphine, common to numerous metathesis catalysts (see Figure 8, page 119), with a phosphite ligand permitted the formation of a complex of superior activity and longevity, existent in two isomeric forms (Scheme 117). Interestingly, the isolable-in-pure-form isomer of this catalyst was found to be in a rare *cis* conformation ([Ru]-**XII**) but both isomers were found to have identical activities upon heating during the metathesis reaction. Given that it had been acknowledged that the dissociated phosphine is involved in the decomposition of the ruthenium catalysts,[210] we rapidly decided to assess if the replacement of the phosphine with a phosphite could also imply some inhibition of the decomposition pathway leading to ruthenium hydride species, which would translate into control of olefin isomerization.



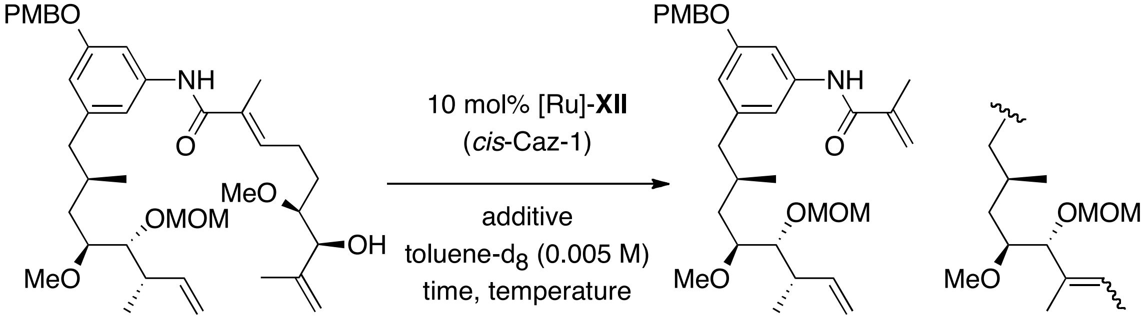
[Ru]-**XII**
cis-Caz-1

trans-Caz-1

Scheme 117. Catalyst *cis*-Caz-1 and its *trans* form.

Unfortunately, reaction of our RCM substrate **723** with *cis*-Caz-1 also resulted in the formation of significant amounts of the isomerization product (See Table 13, entry 1). Nevertheless, these new results show that *cis*-Caz-1 was in fact more active than any of the catalysts that we had tested previously, leading to complete consumption of the starting material, even at lower temperature (85 ºC), after just two hours. Moreover, the combination of lower temperature (85 ºC) and the use of *p*-benzoquinone[203] (a ruthenium hydride scavenger) as additive allowed an almost complete control over the isomerization of the terminal olefin (Table 13, entries 2 and 3). However, the only metathesis product observed was again **767** and no evidence of the formation of the desired 19-membered ring, even in trace amounts, was found under these improved conditions.

Table 13. RCM results using catalyst *cis*-Caz-1.

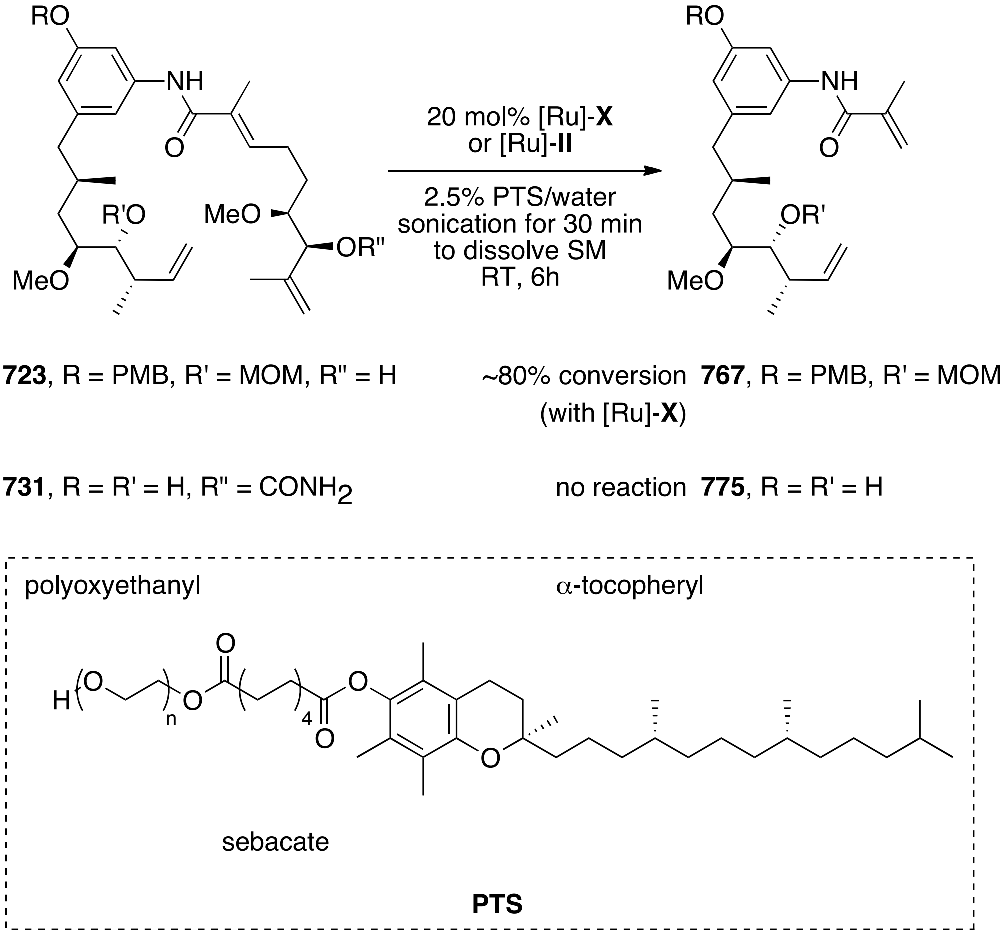


723

767

entry	time, temperature	Additive	% conversion	% isomerization
1	2 h, 100 ºC	None	100%	70%
2	2 h, 100 ºC	1 equiv *p*-benzoquinone	100%	35%
3	2 h, 85 ºC	1 equiv *p*-benzoquinone	100%	< 5%
	+10 h, 85 ºC			10%

We also attempted RCM reactions in aqueous conditions using the amphiphile PTS (Scheme 118), as recently reported by Lipshutz.[212] Even though these reactions did not provide any desired 19-membered macrocycle, this method proved to be certainly remarkable, especially because olefin isomerizarion appeared to be totally eradicated. To the best of our knowledge, there are no examples in the literature on the suppression of olefin isomerization by the use the PTS/water system as solvent. More interestingly, these conditions allowed [Ru]-**X** (Neolyst^{TM} M2), which usually requires high temperature for activation, to catalyze the reaction at room temperature.



723, R = PMB, R' = MOM, R" = H

~80% conversion (with [Ru]-**X**) **767**, R = PMB, R' = MOM

731, R = R' = H, R" = $CONH_2$

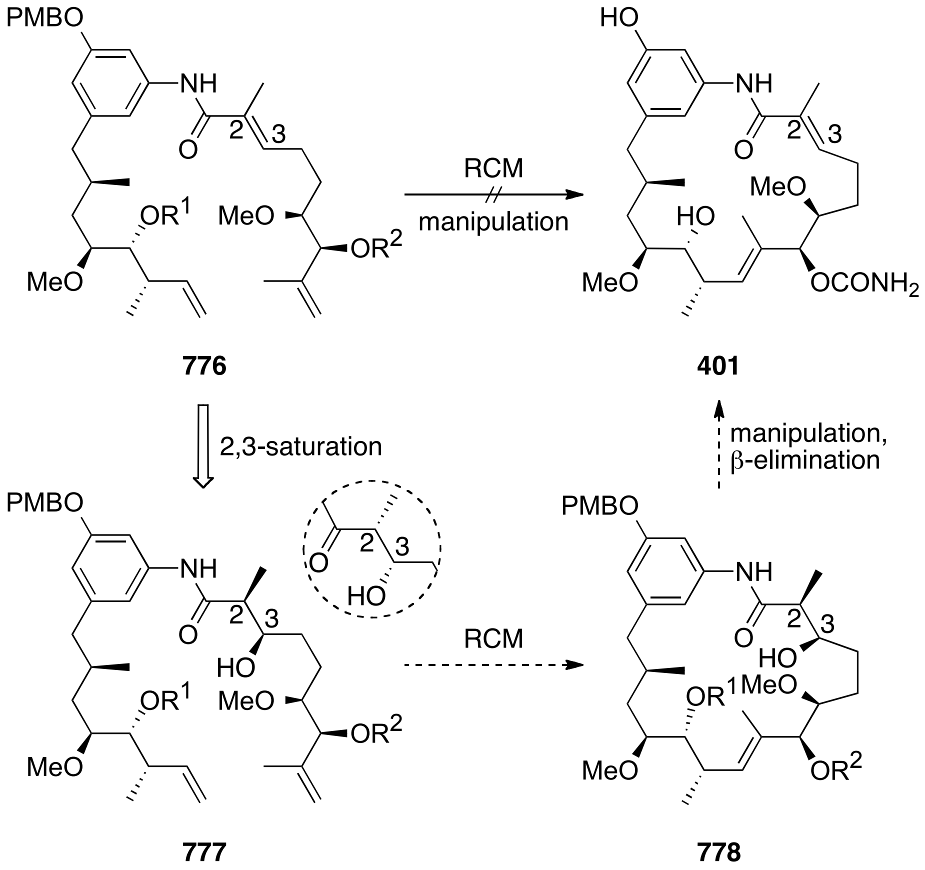
no reaction **775**, R = R' = H

Scheme 118. RCM under aqueous conditions using the nonioinic amphiphile PTS.

Unfortunately, the α-tocopheryl chain in PTS appeared to be a poor solvent for our polar substrates. Aware of this inconvenience, we opted for suspension of the substrate into the solvent system with the aid of sonication. This technique allowed the reaction of our original RCM substrate **723** (resulting in an fairly efficient six-carbon chain loss at room temperature), but completely failed when the significantly more polar ring-opened autolytimycin (**731**) was employed. These results call for further experimentation, particularly because of the unexpected prevention of olefin isomerization.

7.2.4. Removal of the C2–C3 double bond

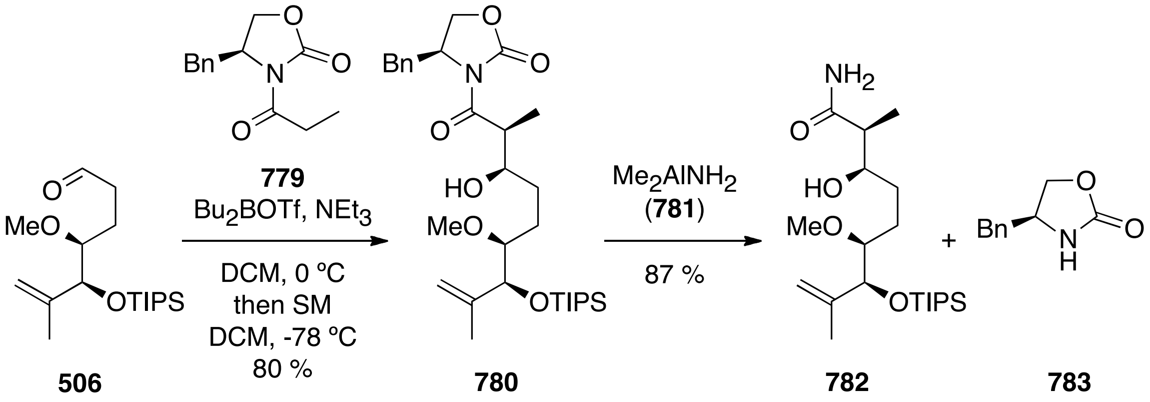
Since the six-carbon chain loss from the RCM substrates seemed unavoidable, the exclusion of the C2–C3 double bond appeared to be the most reasonable option. Given the apparent difficulty for ring closure in our system, we envisioned that this would also be a tactic to provide the structure with more flexibility.



Scheme 119. Proposed saturation of the C2–C3 double bond of the RCM substrate.

To study the behavior of the RCM substrate in absence of the C2–C3 double bond, we sought a new substrate amenable to a subsequent transformation meant to regenerate the α,β-unsaturated moiety and accessible without drastically altering our original synthetic route. A "formal hydration" of the double bond offered **777** (Scheme 119), or its diastereomer, as promising substrates. We found their *syn* aldol-like structure attractive in terms of ease of synthesis and the likelihood to productively restore the *E* α,β-unsaturated system.

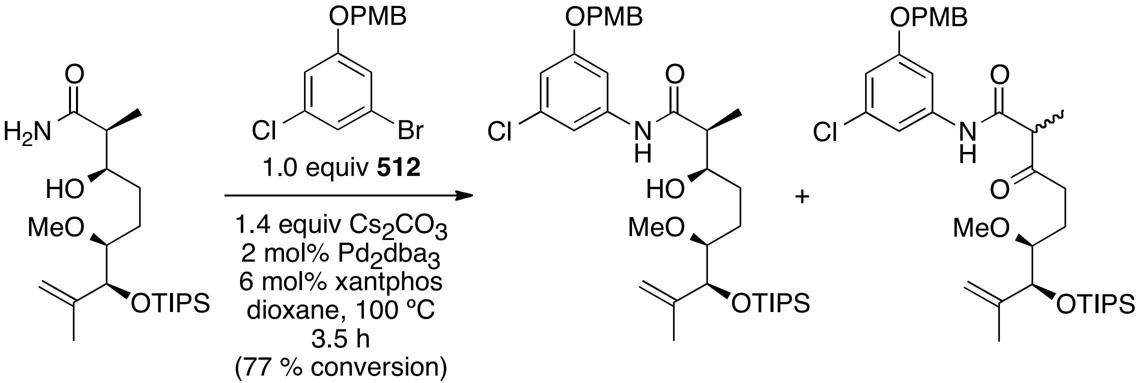
Thus, we proceeded with the synthesis of amide **782**, a "saturated" version of our original amide **434**, which also was prepared in two steps from aldehyde **506** (Scheme 62). An aldol reaction on **506** using Evans[213] phenylalanine-based enolate precursor **779** provided adduct **780** as a single diastereomer. We purposely opted for an asymmetric aldol reaction to avoid handling diastereomeric mixtures.



Scheme 120. Installation of the C2–C3 saturation on the amide portion.

Subsequent substitution of the chiral auxiliary with an amino group afforded **782** in very good yield and conveniently in one step using dimethylaluminum amide (**781**),[214] which had to be freshly prepared for best results. Even though the preparation of the Weinreb reagent Me_2AlNH_2 (to be used within two weeks)[215] was operationally tedious, other conditions like the combination of ammonium chloride and trimethylaluminum,[216] which we used in the synthesis of our original amide **434** (Page 72) did not provide satisfactory results.

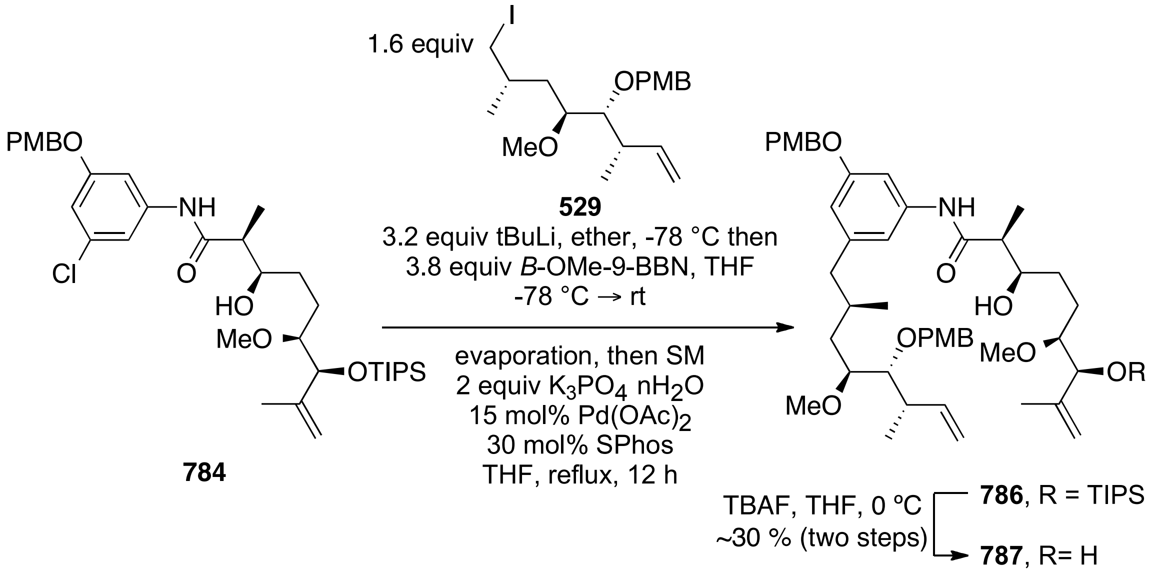
Amide **782** was then subjected to arylation under the same conditions used for the unsaturated substrate (Scheme 64). A decent, unoptimized yield was obtained by stopping the reaction at incomplete conversion (Scheme 121). For this transformation, Dr. Monica Norberg[84] had demonstrated the formation of an undesired oxidation product **785** after long reaction times and an excess of aryl bromide partner. This outcome was consistent with a recent report on the use of alcohols as sources of hydrogen for palladium-catalyzed dehalogenations.[217] The oxidation product, however, was not detected at all when the reaction was stopped after just a few hours. Furthermore, little conversion was observed after the third hour of the reaction, suggesting that the catalyst activity can be rapidly depleted. Taking into account the 77% conversion achieved, it is likely that this transformation could be driven to full conversion in a matter of hours, without the formation of the oxidation product, by adding extra catalyst.



782 **784** **785**, not observed

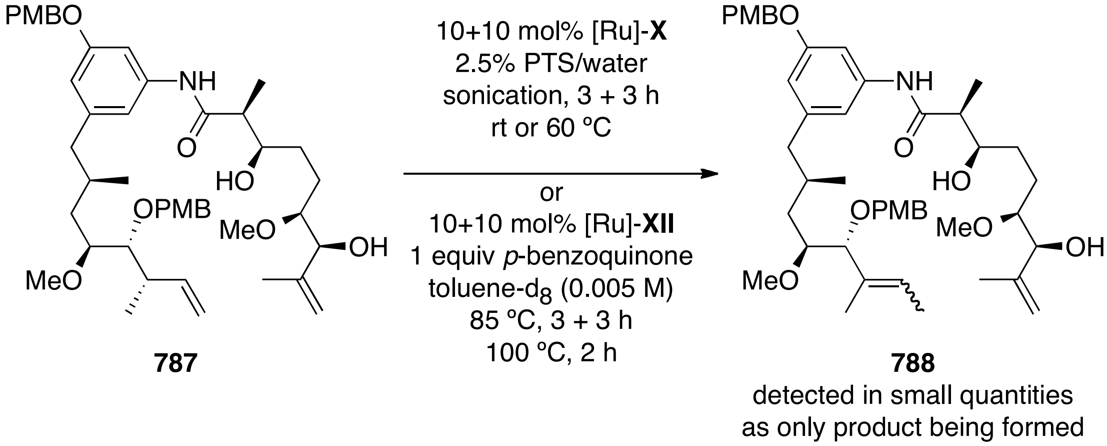
Scheme 121. Preparation of the 2,3-saturated aryl chloride Suzuki substrate.

On the other hand, the subsequent Suzuki coupling was severely affected by the presence of the β-hydroxy substituent. Reaction of the new amidochlorophenol **784**, under the very same conditions used on the initial unsaturated substrate, provided a fairly complex mixture after the workup step (filtration through silica gel), contrasting very much with the results of the original reaction (Scheme 91). The presence of peaks corresponding to propionyl groups in the ^{1}H NMR of the crude material suggests that the substrate might have undergone a retroaldol reaction under the coupling conditions. Such process is likely to have been triggered after reaction of the free β-alcohol with the excess of *B*-OMe-BBN remaining from the generation of the BBN adduct (see Section 6.3, page 98, for details on the Suzuki coupling step). This undesired retroaldol would also imply the *in situ* formation of species susceptible to further reactions (namely a boron enolate and an aldehyde), not only compromising the efficiency of the desired coupling but also complicating the purification process at the end. Retroaldol reactions were not observed in the presence of base at 100 ºC during the arylation step (Scheme 121), which supports the involvement of boron species in this case. Nonetheless, the current conditions allowed the Suzuki coupling reaction to occur to some extent and after column chromatography provided the desired product, although contaminated, and in poor yield.



Scheme 122. Preparation of the 2,3-saturated RCM substrate.

Even though a protective group on the β-alcohol intended to suppress the reaction with *B*-OMe-BBN is also likely to set the substrate up for β-elimination in the presence of base in boiling THF during the Suzuki step, this option is still to be taken into account for future work. For the time being, the current conditions provided sufficient material to test the behavior of the RCM substrate in absence of the C2–C3 double bond. Impure product **786** was directly subjected to TIPS deprotection which provided the new RCM substrate **787** with a reasonable level of purity.

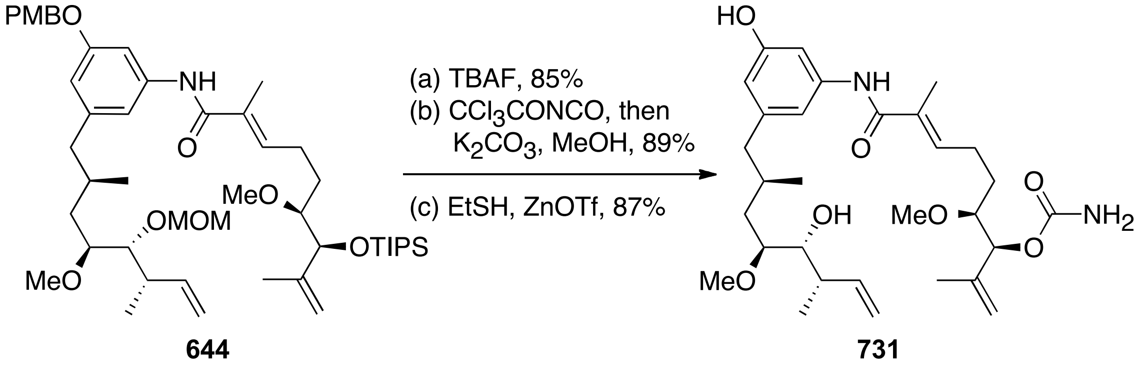


Scheme 123. RCM with 2,3-saturated RCM substrate.

In all cases, much to our dismay, subjection of the new RCM substrate to a series of metathesis reactions, including our best conditions to minimize isomerization (Scheme 123) (see Section 7.2.3), failed to provide the desired 19-membered macrocycle. In the case of the reaction using PTS in water, no reaction was detected most likely due to a solubility problem (see page 149 for details on this solvent system). For the reaction with *cis*-Caz-1 ([Ru]-**XII**), the starting material appeared to be unreactive, but addition of extra catalyst, longer reaction times, or higher temperature, led to the isomerization of the terminal olefin as the only detectable reaction. Interestingly, running the same conditions on the original and the new substrates side by side, gave the known six-carbon chain loss on the former, proving the activity of the catalysts. These results suggest that our new RCM substrate still requires some tuning, quite likely the modification of the present stereogenic centers.

7.3. Final remarks

Our projected goal to synthesize autolytimycin around its 5-alkyl-3-amidophenol moiety led us to develop a route based on C–H activation and coupling reactions that allows access to advanced intermediates convergently. Since the rapid formation of an intermediate containing the complete carbon network of autolytimycin is achievable, ring-closing metathesis came into sight as a quite convenient final key step to assemble its 19-membered macrocyle. Such transformation, however, turned out to be rather tough and still remains as *one* elusive synthetic step to overcome in this course. As indicated in Section 7.2, functional group manipulations that would be required to conclude the synthesis after a productive RCM are expected to take place uneventfully, as demonstrated with the preparation of "ring-opened autolytimycin" (Scheme 124, **731**).



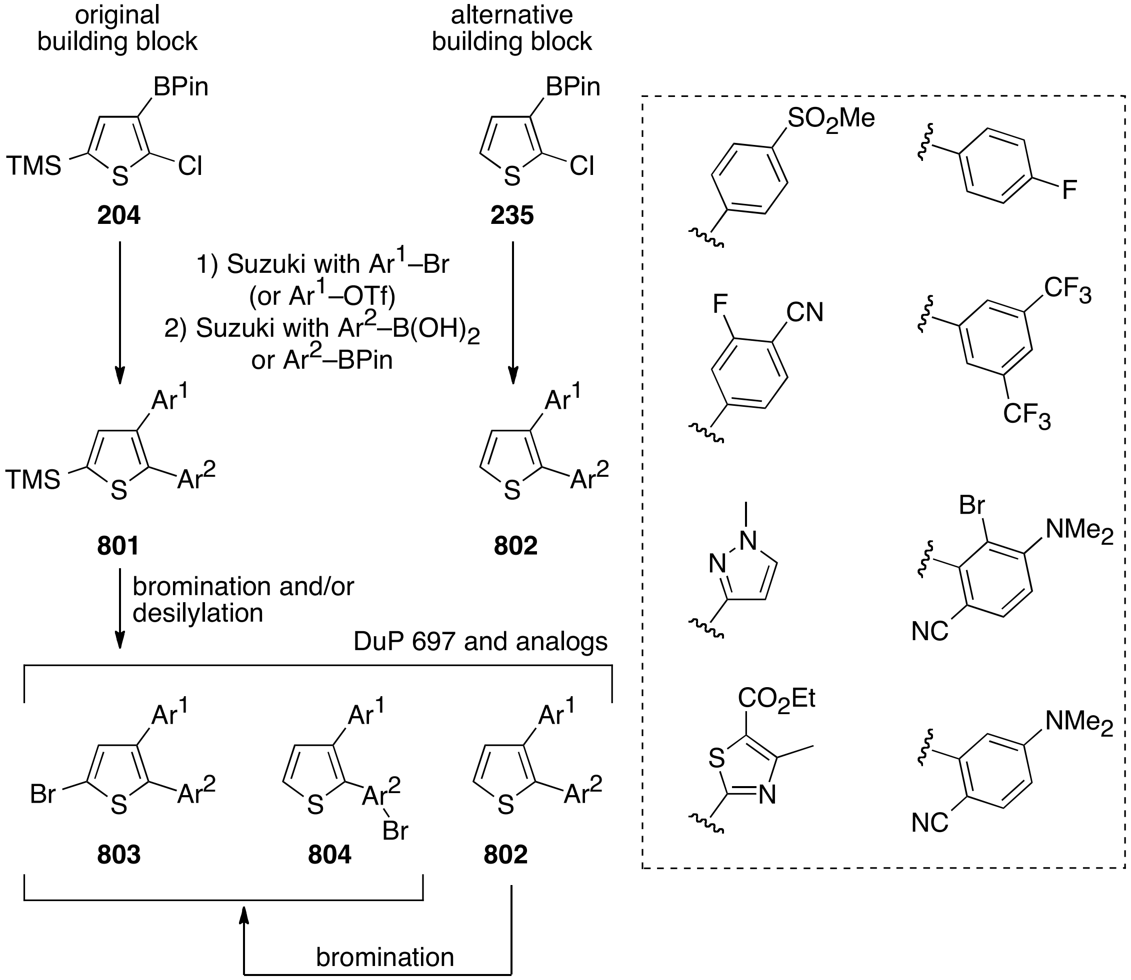
Scheme 124. Preparation of "ring-opened autolytimycin".

The unsatisfactory outcomes of a variety of RCM conditions and substrate modifications suggest that perhaps a different macrocyclization tactic must be assessed. Still, its known that the slightest variations on the structure of an RCM substrate can modify the conformational organization of the molecule, which is critical for the success of this reaction.[174] Examples in the literature have shown that alike substrates with minor differences in stereochemistry can display completely different behaviors under RCM conditions. For instance, the reaction of only one of the epimers subjected to RCM in the synthesis of kendomycin[183] (Scheme 102), the undesired RCM–ROM–RCM cascade observed with one epimer of the RCM substrate in the formal synthesis of eleutherobin[199b] (Scheme 108), or the formation of either an eight- or a seven-membered ring from two epimers in the synthesis of serpendione[206] (Scheme 115), just to mention a few. Considering the existence of effective synthetic methods for inversion of oxygenated stereocenters,[218] modifications of the stereochemistry are to be taken into account for future work in this project. Furthermore, Section 4.4 (See Scheme 59) discusses how our synthetic route is quite flexible in terms of the stereochemistry of the oxygenated centers in proximity to the olefin, making this alternative worth being explored.

Chapter 8. Summary and conclusions

8.1. Synthesis of the COX-2 inhibitor DuP 697 and analogs

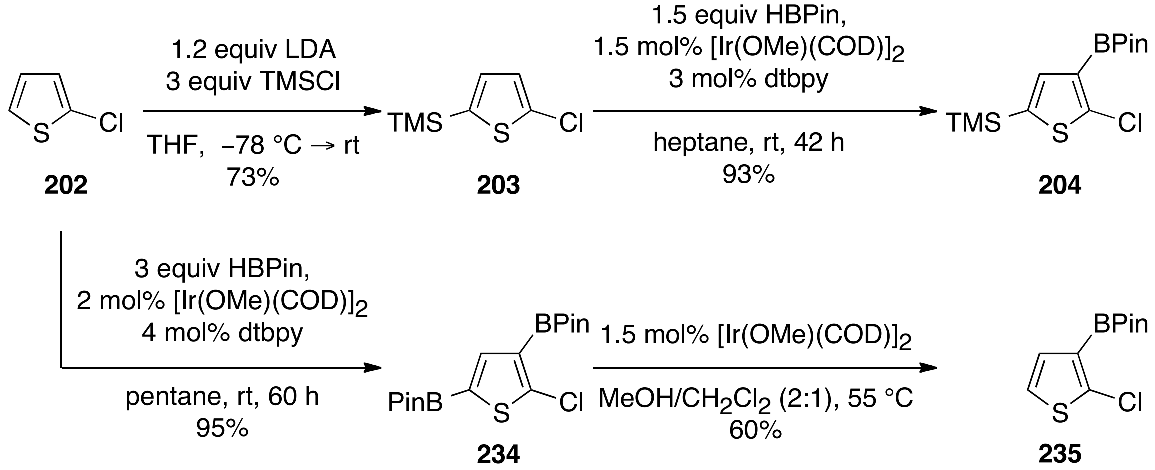
Ir-catalyzed C–H activation/borylation boasts an impressive set of synthetically useful features. Besides allowing the presence of varied functional groups, its halogen tolerance maximizes one's ability to construct valuable building blocks. This notion was illustrated in our diversity-oriented route to the COX-2 inhibitor DuP 697 and a series of analogs.



Scheme 125. Our original diversity-oriented route to DuP 697 and an alternative.

Building block **204** (Scheme 125) was used in the preparation of over 25 analogs,[21] following a sequence of two Suzuki couplings accompanied by bromination, desilylation, or a combination of both. Our experiments showed that the trimethylsilyl group, used as a steric director during the preparation of **204** (Scheme 126), was not a requirement for selectivity or reactivity in the concluding bromination step, so we envisioned an alternative route.

A neutral and mild Ir-catalyzed *deborylation* method developed by Drs. Venkata Kallepalli[16] and Feng Shi[31] in our lab, provided access to an alternative building block, **235**, which displayed flawless performance in the sequence of two Suzuki couplings and bromination, to access DuP 697 and one analog. The use of **235** as starting material instead of **204** is clearly an improvement since its preparation from 2-chlorothiophene (**202**) proceeds via gentle and scalable conditions that are preferable over silylation via deprotonation with LDA.

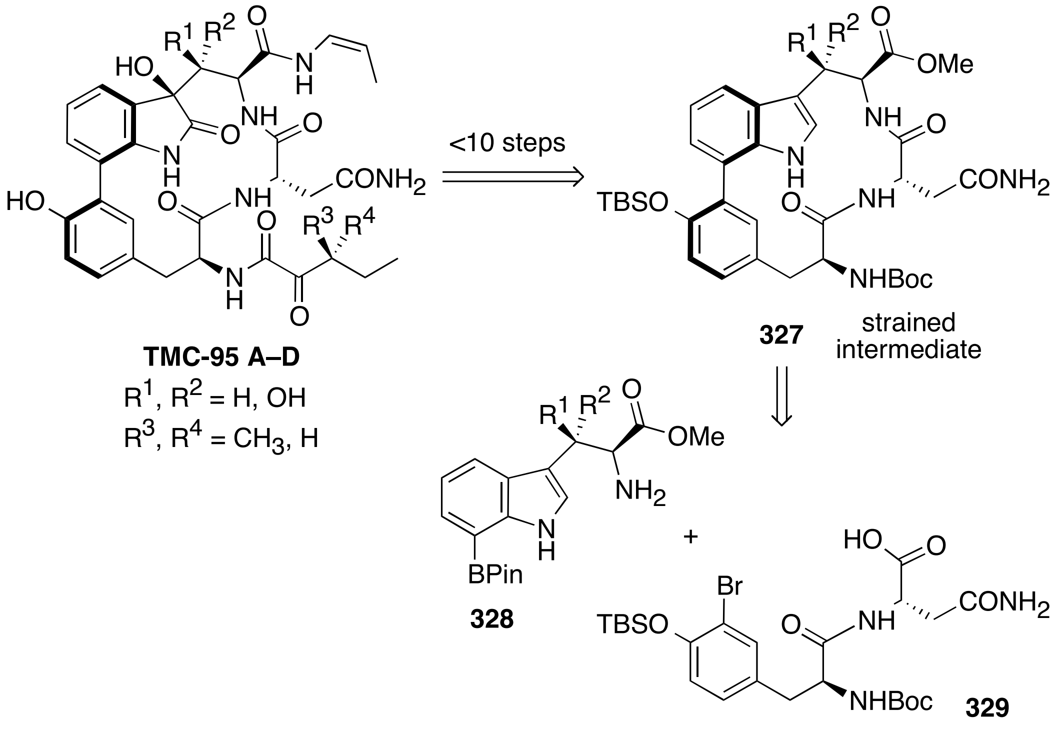


Scheme 126. Access to building blocks used in the preparation of DuP 697 analogs.

This synthesis of DuP 697 and analogs provided a well structured example of the flexibility that results from joining Ir-catalyzed C–H activation/borylation and Suzuki cross-couplings. Furthermore, the use of diborylation followed by monodeborylation to build special building blocks holds the promise of considerable synthetic utility.

8.2. Model Studies for the synthesis of the TMC-95 core

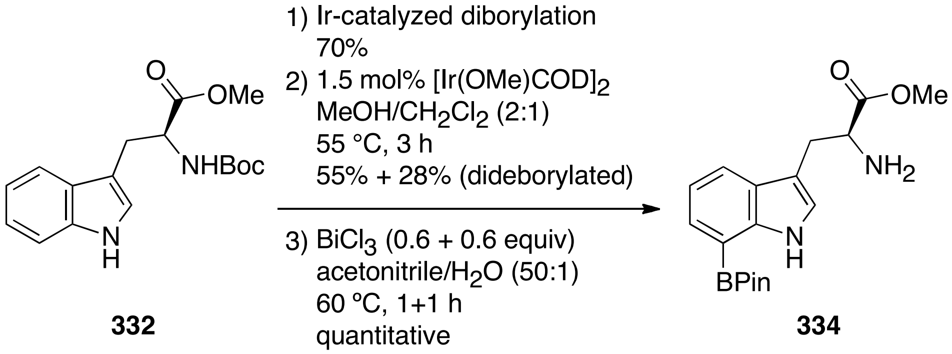
The concept of synthetically exploiting heteroaromatics with unusually placed boronate groups (prepared via diborylation/monodeborylation) was extended in our model studies to the synthesis of the TMC-95 core. TMC-95 compounds are selective proteasome inhibitors with strong bioactivity profiles,[32b] which has recently attracted significant interest.[34]



Scheme 127. Our synthetic plan toward the TMC-95 family.

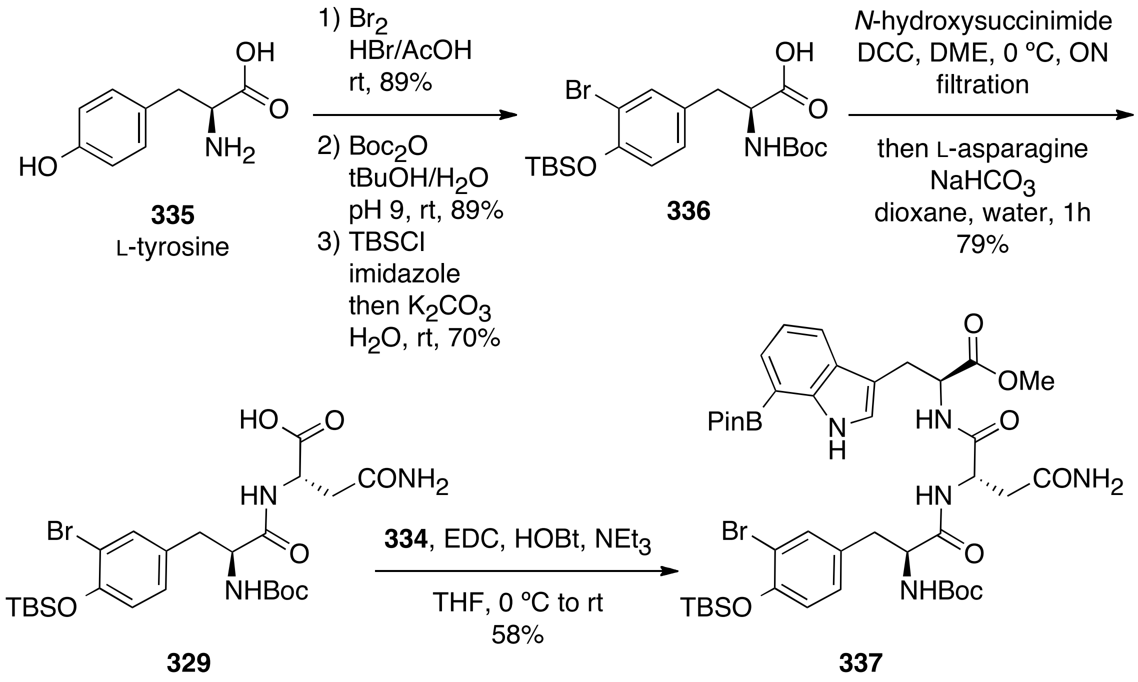
Previously reported total syntheses of TMC-95 compounds[35] have involved a considerable number of steps in the construction of the oxidized indole moiety. We have hereby proposed a synthetic approach to the TMC-95 core (Scheme 127) that aims at avoiding excessive manipulation and providing access to the final natural products conveniently from the natural aminoacid units.

A particular example in the literature[36g] reported the preparation of three purely peptidic analogs of TMC-95, comparable to our intermediate **327**, however, the tryptophan portion had to be prepared in a seven-step sequence and very low yields were observed in their Ni-catalyzed cyclization (4–13%) (See section 3.2 for details). We consider, nevertheless, that this was an important precedent since the cyclization to form such a strained system did happen and this is the type of reaction that could be improved via condition screening.



Scheme 128. Preparation of a triptophan-based building block for the synthesis of the TMC-95 core.

We demonstrated that preparation of **334**, our desired tryptophan-based building block containing a boronate group at the C7 position and a free amine, was feasible via diborylation/monodeborylation followed by a mild $BiCl_3$-mediated Boc deprotection procedure (Scheme 128). With **334** in hand, we rapidly developed a route to intermediate **329**, leading to a quick construction of a model tripeptide to be subjected to ring-closing Suzuki coupling. Additionally, access to a β-hydroxytryptophan derivative was achievable by employing a method developed by Crich.[219]



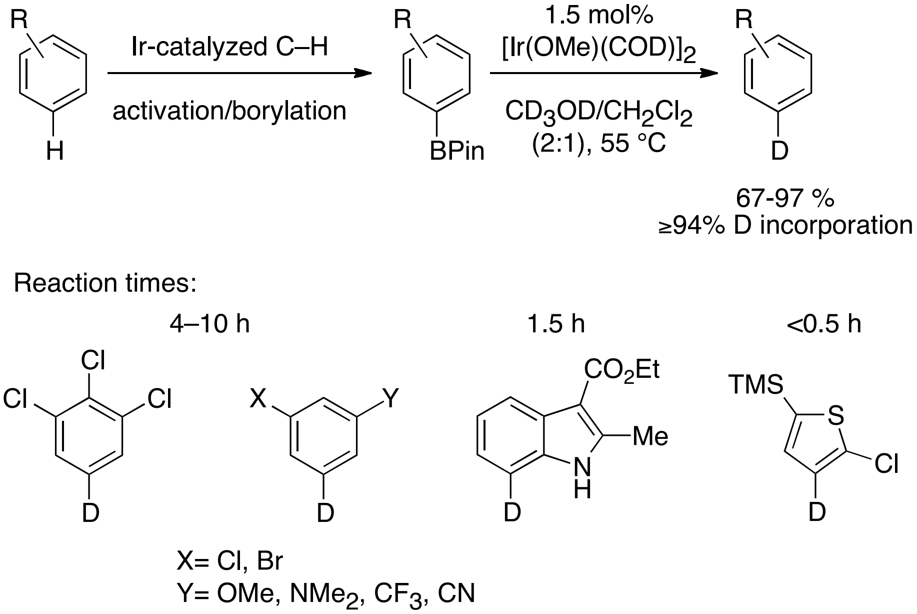
Scheme 129. Preparation of a model tripeptide for the synthesis of the TMC-95 core.

Preliminary Suzuki coupling experiments with intermediate **337** under standard conditions,[48b] however, have failed to give the desired cyclization product. Since we have demonstrated a rapid access to an advanced Suzuki substrate, we plan to find suitable conditions via high throughput screening of palladium sources, bases, solvents, concentration, and ligands. This study will be carried out at Merck in the following months.

In this manner, our model studies to the synthesis of the TMC-95 core provide an additional example of the synthetic utility of Ir-catalyzed C–H activation/borylation combined with deborylation and its capability to build unusual building blocks under gentle conditions. We consider that **334** could be significantly useful in the preparation of TMC-95 analogs, which have attracted even more attention than the natural products themselves.[34]

8.3. Mild site-selective deuteration of arenes

In a third application, our mild deborylation procedure, typically used on heteroaromatics, was adapted for the preparation of deuterium-labeled arenes (Scheme 130). While the method proved successful, slower transformations were observed and special care was necessary. Specifically, freeze-pump-thaw degassing and the use of an air-free flask were preferred to avoid any exposure of the reaction mixture to oxygen, presumably to ensure the survival of the catalyst. Also, to guarantee good levels of deuterium incorporation, the starting materials were carefully dried in a vacuum dessicator.

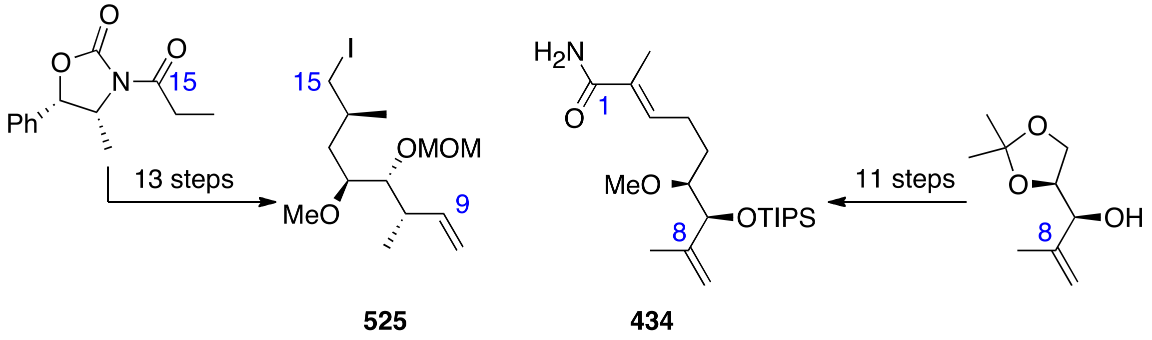


Scheme 130. Mild site-selective deuterium-labeling of arenes.

We demonstrated that C–H activation/borylation followed by deborylation in deuterated methanol at 50–60 ºC, allows for the synthesis of deuterium-labeled compounds in a convenient and gentle manner. Analogous site-specific deuteration methods[17] typically require halogen/organometallic functionalities. In this transformation, the broad functional group tolerance of Ir-catalyzed C–H activation/borylation is certainly valuable.

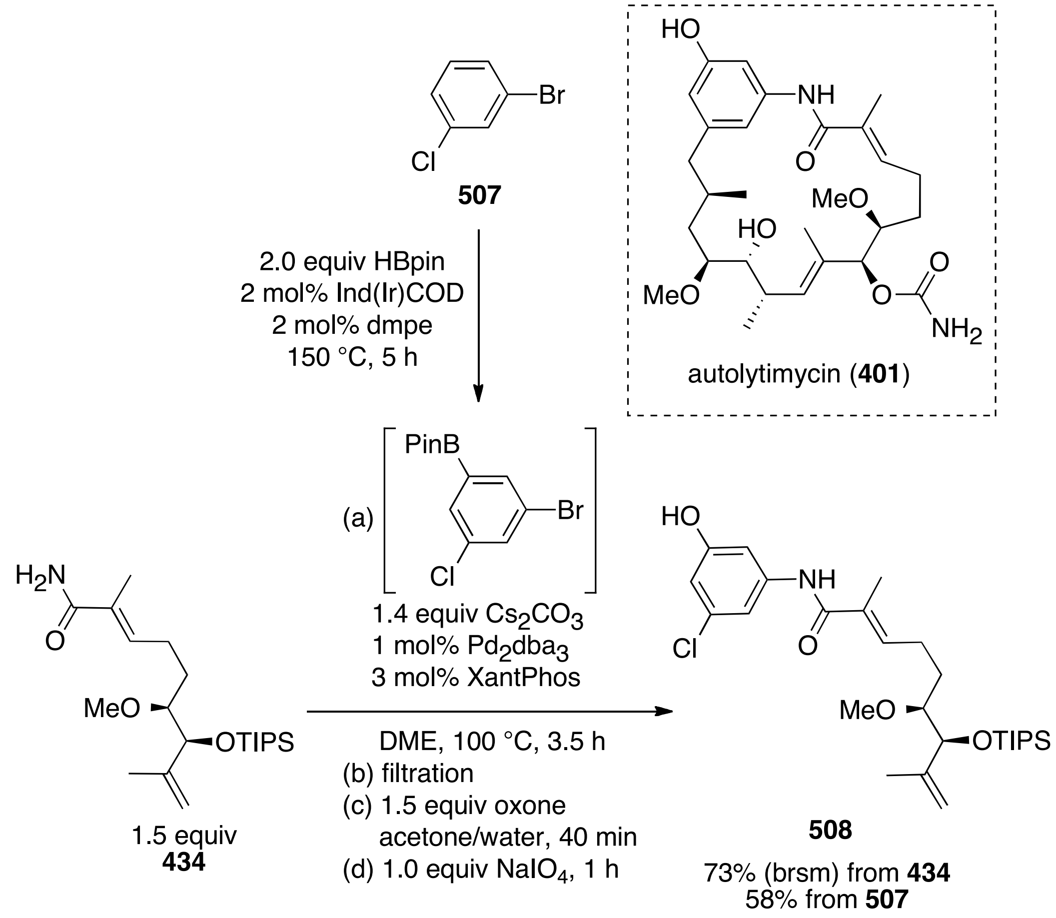
8.4. A synthetic approach to autolytimycin

Ir-catalyzed C–H activation provides an elegant tactic for the preparation of 1,3,5-trisubstituted arenes, even highly elaborated. Its halogen tolerance and amenability to one-pot transformations permitted the convergent construction of the full carbon network of the Hsp90 inhibitor autolytimycin.



Scheme 131. Summarized preparation of advances intermediates in our synthetic approach to autolytimycin.

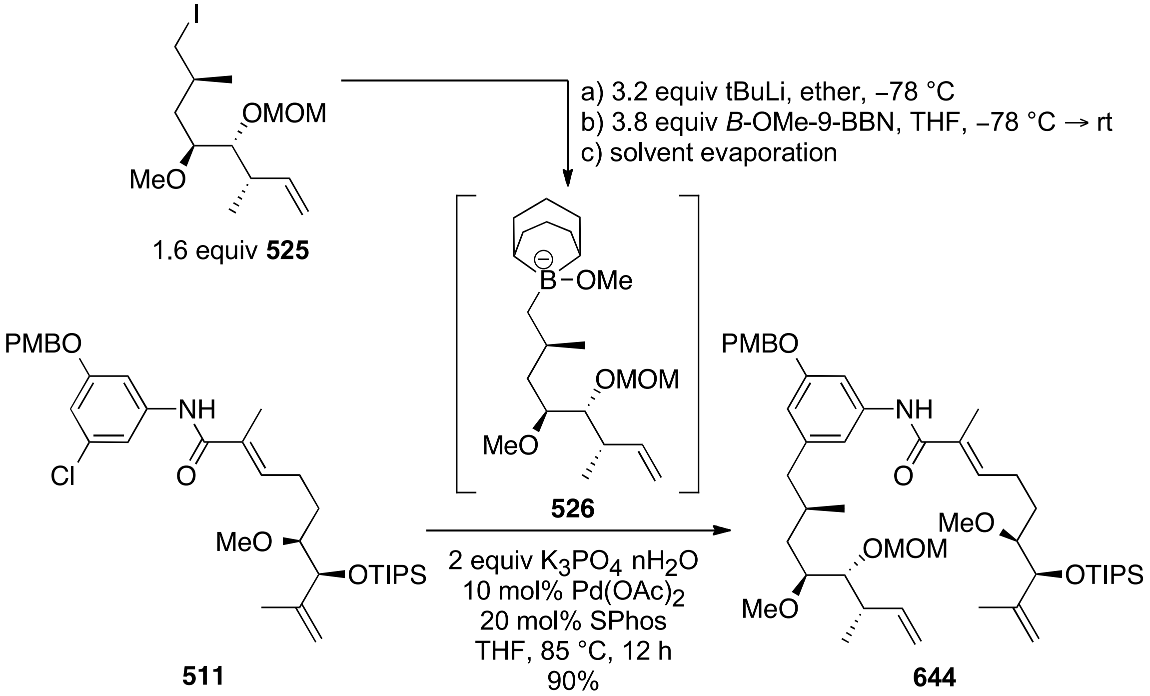
Syntheses of advanced intermediates were high-yielding and followed a plan that was flexible from a stereochemical point of view (Scheme 131). The key step in our route to this natural product was an application of a one-pot C–H activation/borylation/ amidation/oxidation, employing our advanced amide partner **434** (Scheme 132). During this three-step process, sufficient halogen differentiation was required to suppress undesired self-Suzuki couplings and oligomerizations, so 3-bromochlorobenzene (**507**) was the most appropriate dihalogenated substrate for this sequence. Nonetheless, the subsequent attachment of the alkyl chain had to be performed then on the resulting electron-rich, unactivated aromatic chloride.



Scheme 132. C–H activation/borylation/amidation/oxidation in our route to autolytimycin.

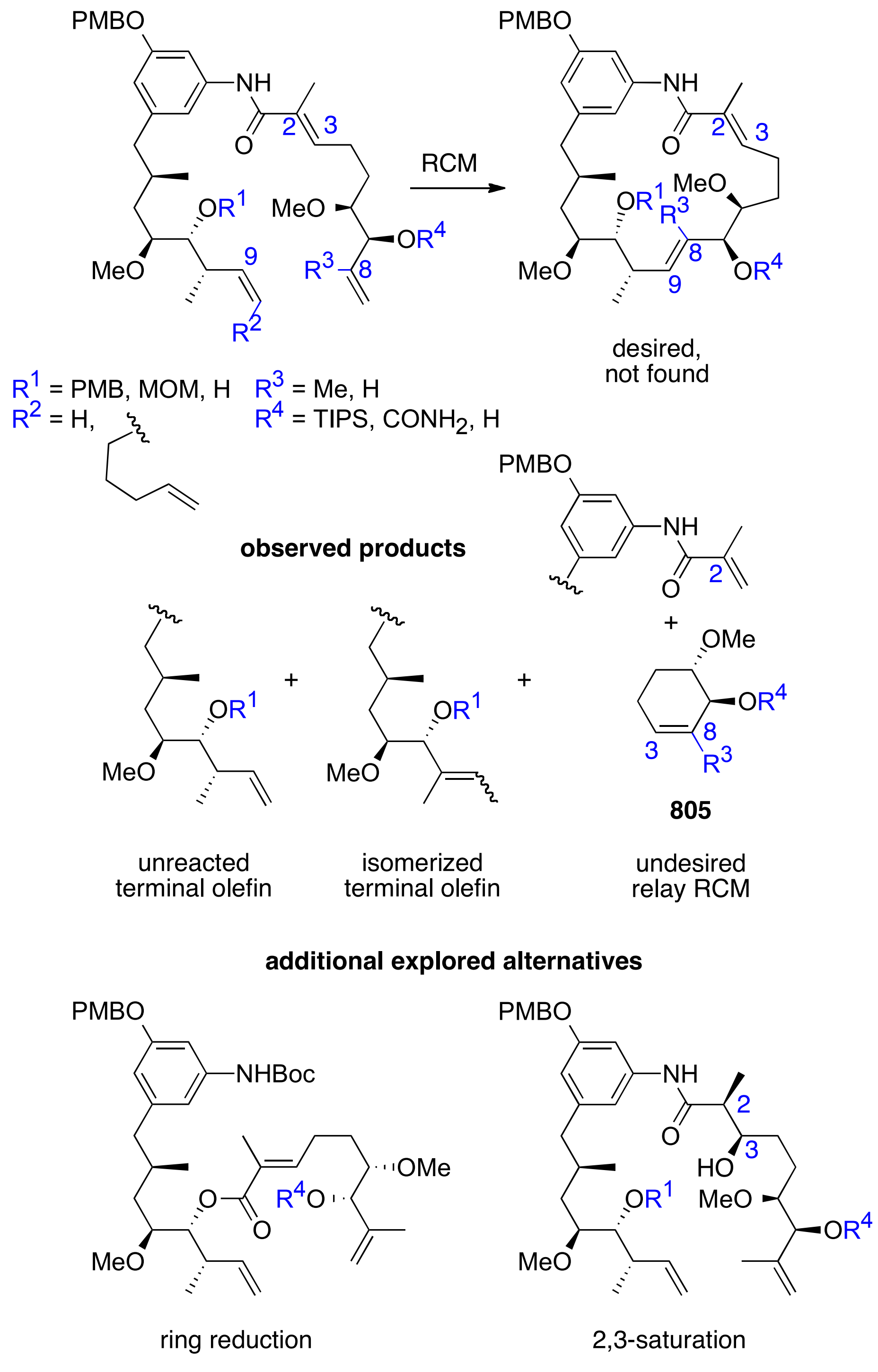
After protection, the advanced amidochlorophenol was subjected to a *B*-alkyl sp^3–sp^2 Suzuki coupling (Scheme 133). This transformation was unprecedented in complex molecule synthesis and required special tweaking to work appropriately. In fact, our results in real and model systems resulted mostly in extremely low conversions, dechlorination, and formation of only traces of, if any, desired product in a vast number of condition-exploring runs.

While investigating alternatives for the formation of the BBN adduct, our experiments showed that its generation worked better at *low* concentration, whereas the Suzuki coupling itself required a *high* concentration. To our delight, evaporation of the solvent with a nitrogen stream prior to the coupling reaction did the trick. Thus, the coupling reaction took place at a concentration about ten times higher than that initially investigated. Substantial changes in terms of conversion were realized in this way. Degassed solvents were indispensable to extending the catalyst life and, in addition, the catalytic efficiency was considerably improved by premixing the palladium source and the ligand in solution before being added to the reaction vessel. By combining these observations, high-yielding conditions for the coupling reaction between **511** and **525**, using $Pd(OAc)_2$ and SPhos, were found (Scheme 133).



Scheme 133. *B*-alkyl sp^3–sp^2 Suzuki coupling used in our route to autolytimycin.

Final functional group manipulations have been carried out uneventfully as shown in the preparation of **731** (ring-opened autolytimycin) (Scheme 124) but, unfortunately, effective conditions for the RCM step have not been found. Ring-closing metathesis has been attempted on a series of substrates (Scheme 134), using 6 different RCM catalysts, numerous solvents (including ionic liquids), and a broad range of temperatures.



Scheme 134. Summary of RCM attempts in our approach to autolytimycin.

During these RCM reactions, decomposition and olefin isomerization problems were to some extent solved via nitrogen sparging/solvent degassing, use of additives,[203] or by performing the reaction under aqueous conditions.[212] Yet success in forming the desired 19-membered macrocycle remains elusive. Perhaps the most notable problem is the inconvenient formation of six-membered ring undesired products (**805)**. Four modifications of the original substrate were presented, C8-demethylation, ring reduction (12-membered ring RCM substrate), attachment of a relay chain (for RRCM), and removal of the C2–C3 double bond. The first two were unsuccessful due to the formation of products **805**. Attempts to direct the catalyst to the terminal left-hand-side olefin via RRCM[201] were ineffective at stopping the closure of **805** or at forming the expected product. Removal of the C2–C3 double bond has not favored the formation of the desired macrocycle but additional experiments are to be performed bearing in mind this promising modification.

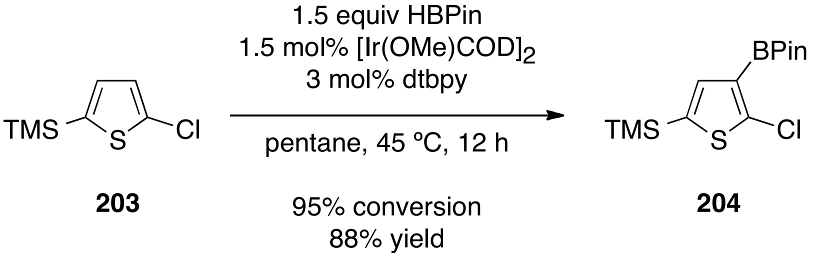
Chapter 9. Experimental details and characterization data

9.1. General considerations

Unless otherwise stated, starting materials were subjected to purification before use and yields refer to chromatographically and spectroscopically pure compounds. All reactions were carried out in oven-/flame-dried glassware and under nitrogen atmosphere, with the exception of those performed in unpurified solvents or aqueous conditions. All solvents were reagent grade. Acetone, pyridine, dioxane, and methanol were purchased and used as received. 1,2-Dimethoxyethane (DME), diethyl ether, and tetrahydrofuran (THF) were distilled from sodium/benzophenone under nitrogen atmosphere before use. Acetonitrile, triethylamine, dichloromethane, benzene, and toluene were distilled from calcium hydride under nitrogen atmosphere before use. Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were treated with calcium hydride, distilled, and stored over freshly activated 4Å molecular sieves. Freeze-pump-thaw method was the preferred technique for solvent degassing. Reactions were monitored by thin layer chromatography on precoated silica gel plates, using UV light or phosphomolybdic acid stain for visualization. Column chromatography was performed on 60 Å silica gel (230–400 mesh). NMR spectra were recorded on Varian spectrometers: Inova-300 (300.11 MHz for ^{1}H and 75.47 MHz for ^{13}C), Varian VXR-500 (499.74 MHz for ^{1}H and 125.67 MHz for ^{13}C), Varian Unity-500-Plus (499.74 MHz for ^{1}H, 125.67 MHz for ^{13}C, and 160.34 MHz for ^{11}B), or Varian Inova-600 (599.89 MHz for ^{1}H and 150.84 MHz for ^{13}C). ^{1}H and ^{13}C chemical shifts (in ppm) were referenced to residual solvent signals: $CDCl_3$ (δ 7.24 for ^{1}H and 77.0 for ^{13}C), CD_3OD (δ 3.31 for ^{1}H and 49.15 for ^{13}C), DMSO-d_6 (δ 2.49 for ^{1}H and 39.5 for ^{13}C), and acetone-d_6 (δ 2.04 for ^{1}H and 29.84 for ^{13}C). ^{11}B chemical shifts were referenced to neat $BF_3 \cdot Et_2O$ (δ 0.0 ppm) as external standard. Melting points were recorded on a MEL-TEMP® capillary melting point apparatus and are uncorrected. Optical rotations were measured using a Perkin Elmer 341 polarimeter. Low-resolution mass spectra were acquired using gas chromatography-mass spectrometry (GC-MS) on a HP 5890 series II GC coupled to a VG Trio-1 mass spectrometer operated in EI^{+} mode (70 eV). High-resolution mass spectra were acquired at the MSU Mass Spectrometry facility using a Waters GCT Premier GC/TOF instrument (EI, CI), a JEOL HX-110 double-focusing magnetic sector instrument (FAB), or a Waters QTOF Ultima mass spectrometer (APCI, ESI). $Pd_2(dba)_3$, $Pd(OAc)_2$, SPhos, XantPhos, and XPhos were purchased from Strem, dtbpy was purchased from Aldrich and used as received. $[Ir(OMe)(COD)]_2$ was prepared according to literature procedures.[220] For section 9.2: 5-trimethylsilyl-2-chlorothiophene (**203**) and diarylated thiophenes **215** and **216** were prepared by Mr. Nathan Gesmundo by the procedures described in Scheme 7 and Scheme 9. **235** was prepared according to the reported procedure.[16] Palladium precatalysts $Pd_2(dba)_3$, $PdCl_2 \cdot dppf \cdot CH_2Cl_2$, and $Pd(OAc)_2$, were purchased from Strem and used as received. Bromide coupling partners 4-bromo-1-methyl-1*H*-pyrazole and 2-bromo-4-methylthiazole-5-carboxylate were purchased from Aldrich and used as received. Boron coupling partners 4-(dimethylamino)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile and 4-fluorophenylboronic acid were obtained from Boropharm and Aldrich respectively and used as received. Commercial *N*-bromosuccinimide (Strem) was crystallized from water, thoroughly dried in a vacuum desiccator, and stored in a refrigerator protected from moisture and light. For section 9.3: Boronic esters

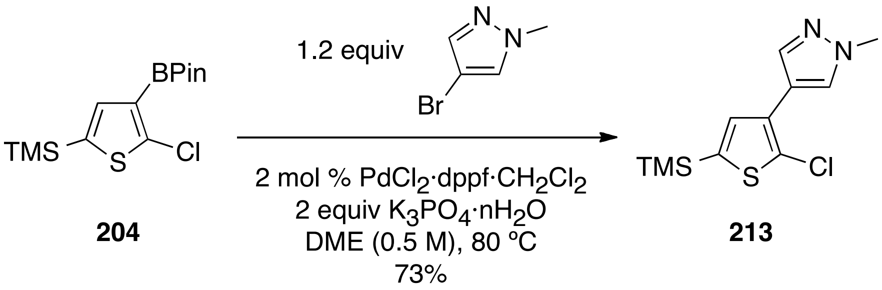
4,4,5,5-tetramethyl-2-(3,4,5-trichlorophenyl)-1,3,2-dioxaborolane, 2,6-Dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 2-(3-chloro-5-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 3-chloro-*N*,*N*-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline, 2-(3-chloro-5-methoxyphenyl)-4,4,5,5 -tetramethyl-1,3,2-dioxaborolane, and ethyl 2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-di-oxaborolan-2-yl)-1*H*-indole-3-carboxylate were obtained form Boropharm and dried in a vacuum dessicator overnight before use. 3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (purified by sublimation) was prepared by Mr. Hao Li and was dried in a vacuum dessicator overnight before use. For sections 9.5 and 9.6: Methylmagnesium iodide 3.0 M solution in THF and allylmagnesium chloride 2.0 M solution in THF were purchased from Aldrich and used as received. *n*-Butyllithium and *t*-butyllithium solutions were purchased from Aldrich and standardized by titration with diphenylacetic acid[221] prior to use. For Section 9.7: Metathesis catalysts were purchased from Strem and used as received.

9.2. Experimental details for Sections 2.1 and 2.3: DuP 697 and analogs

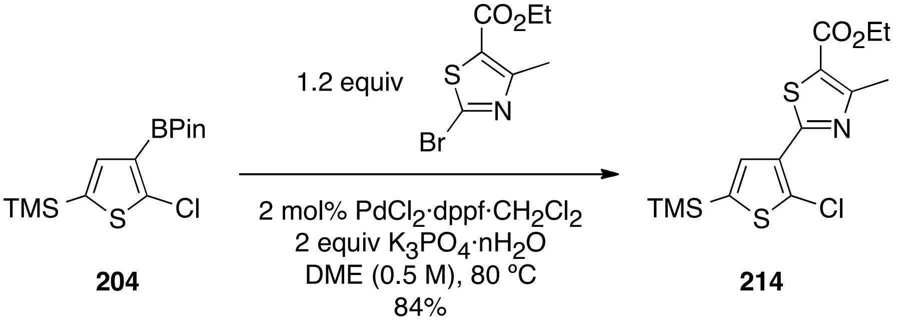


Preparation of (5-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl) trimethylsilane (**204**):[16] In a glove box, $[Ir(OMe)(COD)]_2$ (0.052 g, 0.079 mmol) and HBPin (1.15 mL, 7.86 mmol) were mixed in an air-free flask, forming a bright yellow transparent solution, and to it was added dtbpy (0.042 g, 0.157 mmol) using pentane (3.5 mL) to rinse the test tube used to weigh. To the resulting dark solution was added 5-trimethylsilyl-2-

chlorothiophene, **203**, (1.0 g, 5.24 mmol) using pentane (3.5 mL) to rinse the test tube used to weigh. The air-free flask was sealed and taken out of the box. The reaction mixture was heated at 45 °C overnight. After 13 hours, ^{1}H NMR of sample showed a 95:5 ratio of product to starting material. The reaction mixture was concentrated *in vacuo* and the resulting residue was filtered through a plug of silica gel, eluting with dichloromethane to afford borylation product **204** (1.46 g, 4.61 mmol, 88% yield) as a white solid; mp 67–68 °C (lit[16] 68–69 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (s, 1 H), 1.32 (s, 12 H), 0.26 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.7, 139.4, 139.4, 83.7, 24.8, −0.2; HRMS (ESI): *m/z* calculated for $C_{17}H_{34}O_5Si$ $[M+H]^+$ 385.1813, found 385.1811.

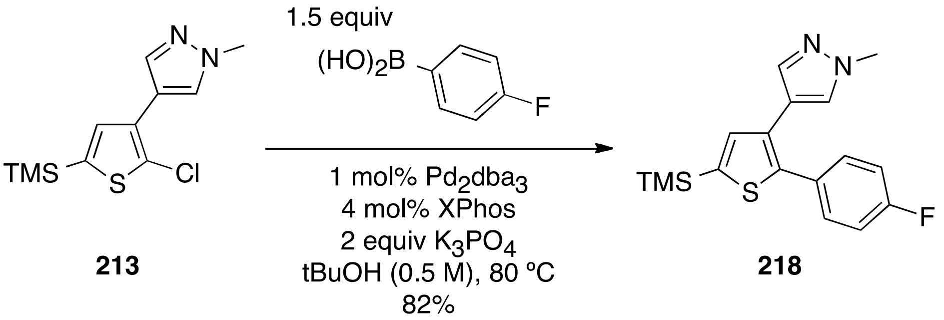


Preparation of **213**: In an air-free flask provided with a magnetic stir bar were mixed **204** (200.0 mg, 0.631 mmol), 4-bromo-1-methyl-1*H*-pyrazole (122.0 mg, 0.758 mmol), $K_3PO_4 \cdot nH_2O$ (235 mg, 0.95 mmol), and $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (10.4 mg, 12.6 µmol). The flask with the solid mixture was purged and refilled with nitrogen several times. Degassed DME (1.3 mL) was added under nitrogen atmosphere and the reaction mixture was heated up to 80 °C. The progress of the reaction was monitored by TLC (4:1 hexanes/EtOAc). Once finished, usually after 2.5 hours, the reaction mixture was filtered through a short plug of silica gel eluting with acetone. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography eluting with hexanes/EtOAc (9:1 → 3:1) to afford **213** (124.9 mg, 0.461 mmol, 73% yield) as a white solid. R_f = 0.3 (hexanes/ethyl acetate 5:1); mp 82–83 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (s, 1 H), 7.79 (s, 1 H), 7.13 (s, 1 H), 3.93 (s, 3 H), 0.29 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8, 137.8, 133.2, 133.2, 131.0, 128.0, 115.9, 39.1, –0.4; IR (neat): 3139, 3091, 3052, 2957, 2898, 1420, 1385, 1312, 1277, 1120, 984, 839, 804, 756 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{11}H_{16}N_2SiSCl$ $[M+H]^+$ 271.0492, found 271.0493.



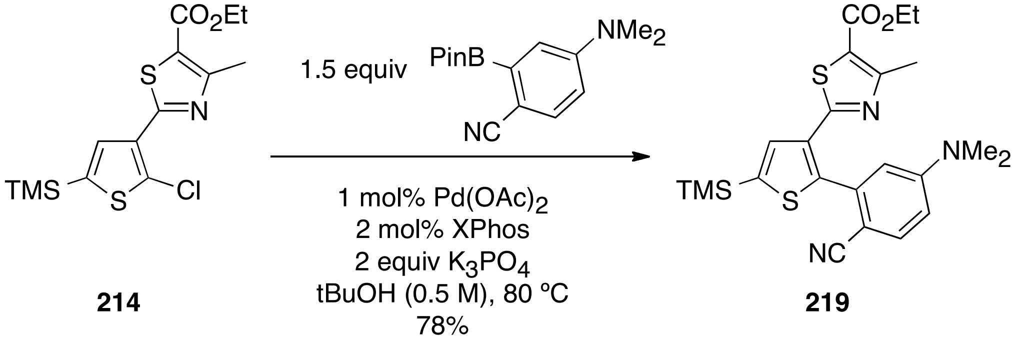
Preparation of **214**: In an air-free flask provided with a magnetic stir bar were mixed **204** (200.0 mg, 0.631 mmol), ethyl 2-bromo-4-methylthiazole-5-carboxylate (190.0 mg, 0.758 mmol), $K_3PO_4 \cdot nH_2O$ (235 mg, 0.95 mmol), and $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (10.4 mg, 12.6 μmol). The flask with the solid mixture was purged and refilled with nitrogen several times. Degassed DME (1.3 mL) was added under nitrogen atmosphere and the reaction mixture was heated up to 80 °C. The progress of the reaction was monitored by TLC (5:1 hexanes/EtOAc). Once finished, usually after 2.5 hours, the reaction mixture was filtered through a short plug of silica gel eluting with acetone. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography eluting with hexanes/EtOAc (19:1 → 5:1) to afford **214** (190.5 mg, 0.529 mmol, 84% yield) as a pale yellow solid. R_f = 0.54 (5:1 hexanes/EtOAc); mp 63–65 ºC; ^{1}H NMR

(500 MHz, $CDCl_3$) δ 7.75 (s, 1 H), 4.34 (q, *J* = 7.25 Hz, 2 H), 2.76 (s, 3 H), 1.38 (t, *J* = 7.25 Hz, 3 H), 0.32 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 161.6, 159.7, 139.4, 133.6, 133.6, 133.0, 121.7, 61.2, 17.3, 14.4, −0.4; IR (neat): 2988, 2959, 2927, 1715, 1539, 1522, 1371, 1321, 1259, 1093, 991, 843, 760 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{14}H_{19}NO_2SiS_2Cl$ $[M+H]^+$ 360.0315, found 360.0315.



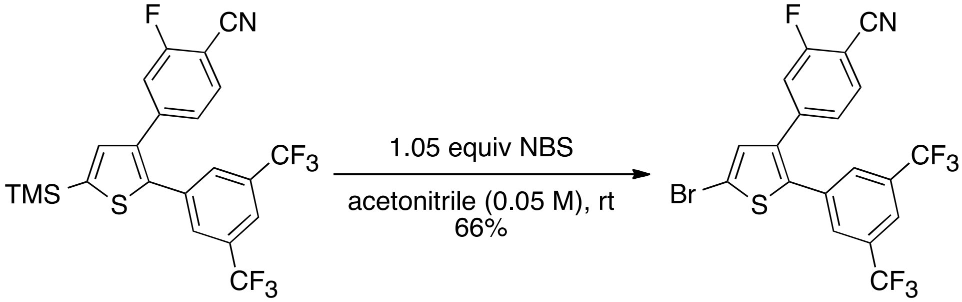
Preparation of **218**: To an air-free flask provided with a stir bar were added **213** (31.9 mg, 0.118 mmol), 4-fluorophenylboronic acid (24.7 mg, 0.177 mmol), anhydrous potassium phosphate (49.8 mg, 0.236 mmol), Pd_2dba_3 (1.1 mg, 1.18 μmol), and XPhos (2.2 mg, 4.7 μmol). The flask with the solid mixture was purged and refilled with nitrogen multiple times. To the flask was added degassed tBuOH (0.25 mL), and the resulting suspension was heated up to 80 °C. The progress of the reaction was monitored by TLC. After completion, usually after 6 hours, the reaction mixture was filtered through a short plug of silica gel eluting with acetone. The filtrate was concentrated *in vacuo* and the material was subjected to column chromatography eluting with hexanes/EtOAc (3:1 → 2:1) to afford **218** (31.8 mg, 0.096 mmol, 82% yield) as a very thick colorless oil. R_f = 0.21 (hexanes/EtOAc 3:1); ^1H NMR (500 MHz, $CDCl_3$): δ 7.37 (m, 3 H), 7.19 (s, 1 H), 7.15 (s, 1 H), 7.02 (m, 1 H), 3.82 (s, 3 H), 0.33 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$):

δ (163.4, 161.4) (d, ${}^{1}J_{C\text{–}F}$ = 247.7 Hz), 141.1, 138.2, 135.9, (131.0, 131.0) (d, ${}^{3}J_{C\text{–}F}$ = 8.7 Hz), (130.8, 130.8) (d, ${}^{4}J_{C\text{–}F}$ = 3.5 Hz), 130.6, 128.0, 117.5, (115.6, 115.5) (d, ${}^{2}J_{C\text{–}F}$ = 22.0 Hz), 38.9, –0.1; IR (neat): 3029, 2955, 2897, 2855, 1601, 1527, 1502, 1448, 1265, 1250, 1222, 1157, 1018, 983, 843, 821 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{17}H_{20}N_2SiSF$ $[M+H]^+$ 331.1101, found 331.1101.



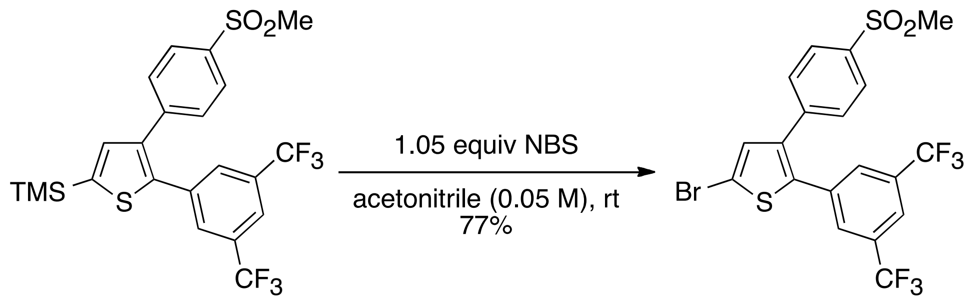
Preparation of **219**: To an air-free flask provided with a stir bar were added **214** (36.8 mg, 0.102 mmol), 4-(dimethylamino)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (22.3 mg, 0.153 mmol), anhydrous potassium phosphate (43 mg, 0.204 mmol), Pd_2dba_3 (1.0 mg, >1.02 μmol), and XPhos (2.0 mg, >4.08 μmol). The flask with the solid mixture was purged and refilled with nitrogen multiple times. To the flask was added degassed tBuOH (0.2 mL), and the resulting suspension was heated up to 80 °C. The progress of the reaction was monitored by TLC. After completion, usually after 6 hours, the reaction mixture was filtered through a short plug of silica gel eluting with acetone. The filtrate was concentrated *in vacuo* and the material was subjected to column chromatography eluting with hexanes/EtOAc (5:1 → 2:1) to afford **219** (37.4 mg, 0.080 mmol, 78% yield) as a pale yellow solid. R_f = 0.26 (hexanes/EtOAc 3:1); mp 177–178 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1 H), 7.54 (d, *J* = 9.0 Hz, 1 H), 6.70 (dd, *J* =

9.0, 3.0 Hz, 1 H), 6.66 (d, J = 3.0 Hz, 1 H), 4.25 (q, J = 7.0 Hz , 2 H), 3.03 (s, 6 H), 2.67 (s, 3 H), 1.30 (t, J = 7.0 Hz, 3 H), 0.36 (s, 9 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 163.7, 162.5, 159.6, 152.4, 144.5, 141.5, 137.8, 134.8, 134.6, 134.3, 122.2, 119.0, 113.9, 111.9, 99.1, 61.1, 40.0, 17.5, 14.3, −0.2; IR (neat): 2957, 2926, 2857, 2820, 2214, 1711, 1599, 1554, 1516, 1442, 1372, 1323, 1264, 1124, 1093, 1003, 843 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{23}H_{28}N_3O_2SiS_2$ [M+H]$^+$ 470.1392, found 470.1390.



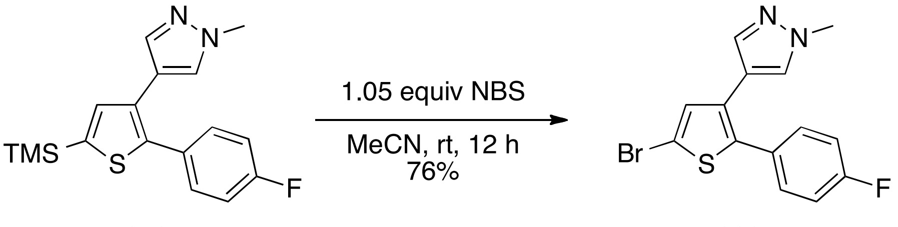
216 **220**

Preparation of **220**: To a solution of **216** (50.1 mg, 0.103 mmol) in acetonitrile (2.0 mL) was added *N*-bromosuccinimide (19.2 mg, 0.108 mmol) in one portion and the mixture was stirred at room temperature until TLC confirmed completion, usually after 12 hours. The reaction mixture was filtered through a short plug of silica gel eluting with dichloromethane. The filtrate was concentrated *in vacuo* and purified by column chromatography eluting with hexanes/EtOAc (19:1 → 5:1) to afford **220** (33.5 mg, 0.068 mmol, 66% yield) as a white solid. R_f = 0.57 (hexanes/ethyl acetate 5:1); mp 148–150 ºC; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.81 (s, 1H), 7.60 (s, 1 H), 7.55 (dd, J = 8.0, 6.5 Hz, 1H), 7.15 (s, 1 H), 7.07 (dd, J = 8.5, 1.5 Hz, 1H), 7.04 (dd, J = 8.0, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ (164.2, 162.1) (d, $^1J_{C\text{–}F}$ = 260.2 Hz), (141.4, 141.4) (d, $^3J_{C\text{–}F}$ = 8.4 Hz), 138.3, (137.3, 137.3) (d, $^4J_{C\text{–}F}$ = 2.3 Hz), 134.4, 133.9, (133.0, 132.7, 132.4, 132.2) (q, $^{2}J_{\mathrm{C-F}}$ = 33.8 Hz), 132.4, 129.0 (m), (126.0, 123.8, 121.6, 119.5) (q, $^{1}J_{\mathrm{C-F}}$ = 273.4 Hz), (125.3, 125.2) (d, $^{3}J_{\mathrm{C-F}}$ = 3.6 Hz), 122.1 (septet, $^{3}J_{\mathrm{C-F}}$ = 3.4 Hz), (116.8, 116.6) (d, $^{2}J_{\mathrm{C-F}}$ = 20.7 Hz), 114.6, 113.4, (101.0, 100.9) (d, $^{2}J_{\mathrm{C-F}}$ = 15.4 Hz); IR (neat): 2923, 2853, 2237, 1727, 1620, 1354, 1205, 1179, 1129 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{19}H_{8}BrF_{7}NS$ $[M+H]^{+}$ 493.9444, found 493.9448.



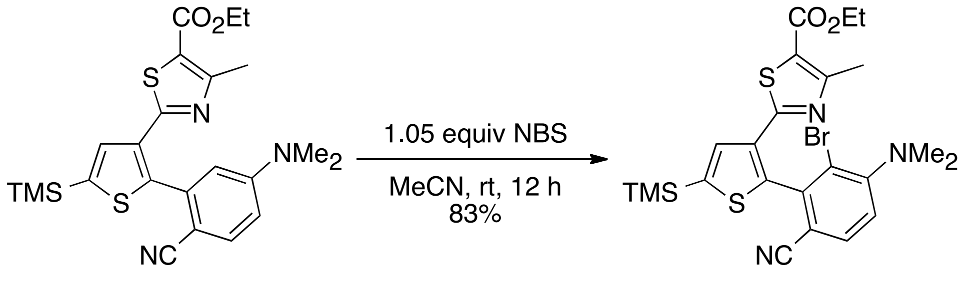
215 **221**

Preparation of **221**: To a solution of **215** (33.1 mg, 0.063 mmol) in acetonitrile (1.3 mL) was added *N*-bromosuccinimide (11.8 mg, 0.066 mmol) in one portion and the mixture was stirred at room temperature until TLC confirmed completion, usually after 12 hours. The reaction mixture was filtered through a short plug of silica gel eluting with dichloromethane. The filtrate was concentrated *in vacuo* and purified by column chromatography eluting with hexanes/EtOAc (5:1) to afford **221** (25.8 mg, 0.049, 77% yield) as a white solid. R_f = 0.21 (hexanes/ethyl acetate 5:1); mp 53–54 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.75 Hz, 2 H), 7.76 (s, 1 H), 7.55 (s, 2 H), 7.38 (d, *J* = 8.75 Hz, 2 H), 7.18 (s, 1 H), 3.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.1, 139.9, 138.7, 137.6, 134.7, (132.9, 132.5, 132.0, 131.6) (q, $^{2}J_{\mathrm{C-F}}$ = 34.1 Hz), 132.7, 129.9, 129.0 (m), (128.2, 124.6, 121.0, 117.3) (q, $^{1}J_{\mathrm{C-F}}$ = 273.3 Hz), 128.0, 121.7 (septet, $^{3}J_{\mathrm{C-F}}$ = 3.6 Hz), 114.2, 44.5; IR (neat): 3087, 2930, 1599, 1469, 1432, 1375, 1279, 1155, 1023, 957, 898, 866, 841, 790, 771, 738 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{19}H_{12}BrF_6O_2S_2$ $[M+H]^+$ 528.9366, found 528.9366.



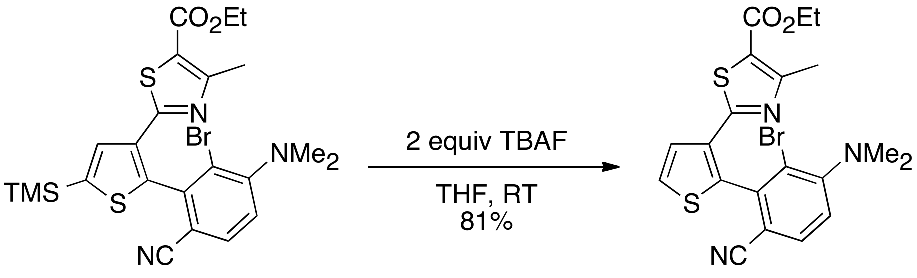
218 **222**

Preparation of **222**: To a solution of **218** (22.9 mg, 0.069 mmol) in acetonitrile (1.4 mL) was added *N*-bromosuccinimide (12.3 mg, 0.071 mmol) in one portion and the mixture was stirred at room temperature until TLC confirmed completion, usually after 12 hours. The reaction mixture was filtered through a short plug of silica gel eluting with dichloromethane. The filtrate was concentrated *in vacuo* and purified by column chromatography eluting with hexanes/EtOAc (5:1 → 2:1) to afford **222** (17.8 mg, 0.053, 76% yield) as a very thick colorless oil. R_f = 0.17 (hexanes/ethyl acetate 3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (m, 2 H), 7.29 (d, *J* = 0.5 Hz, 1 H), 7.09 (d, *J* = 0.5 Hz, 1 H), 7.05 (s, 1 H), 7.03 (m, 2 H), 3.81 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (163.7, 161.7) (d, $^1J_{C\text{–}F}$ = 247.9 Hz), 138.1, 136.8, 131.4, (131.3, 131.2) (d, $^3J_{C\text{–}F}$ = 8.4 Hz), 129.8, (129.6, 129.6) (d, $^4J_{C\text{–}F}$ = 3.2 Hz), 128.0, 116.5, (115.9, 115.7) (d, $^2J_{C\text{–}F}$ = 22.0 Hz), 111.1, 39.0; IR (neat): 3100, 3071, 2932, 2855, 1603, 1586, 1533, 1504, 1448, 1417, 1288, 1234, 1157, 1100, 1093, 985, 972, 841, 810 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{14}H_{11}N_2FSBr$ $[M+H]^+$ 336.9810, found 336.9810.



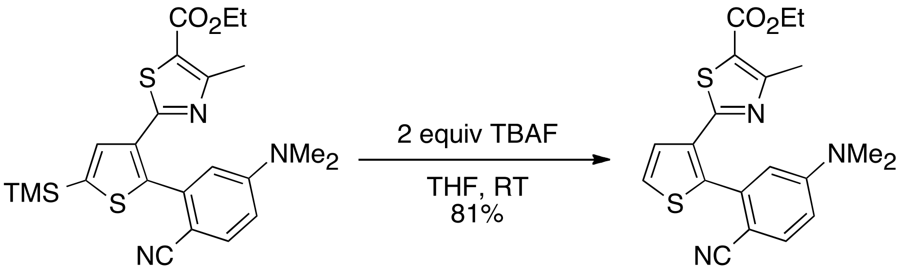
219 **225**

Preparation of **225**: To a solution of **219** (50.0 mg, 0.106 mmol) in acetonitrile (2.1 mL) was added *N*-bromosuccinimide (18.9 mg, 0.11 mmol) in one portion and the mixture was stirred at room temperature until TLC confirmed completion, usually after 12 hours. The reaction mixture was filtered through a short plug of silica gel eluting with dichloromethane. The filtrate was concentrated *in vacuo* and purified by column chromatography eluting with hexanes/EtOAc (7:1 to 5:1) to afford **225** (48.7 mg, 0.089 mmol, 83% yield) as white solid. R_f = 0.22 (hexanes/EtOAc 5:1); mp 134–136 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1 H), 7.65 (d, *J* = 8.5 Hz, 1 H), 7.14 (d, *J* = 8.5 Hz, 1 H), 4.23 (q, *J* = 7.3 Hz , 2 H), 2.92 (s, 6 H), 2.64 (s, 3 H), 1.28 (t, *J* = 7.3 Hz, 3 H), 0.38 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 162.3, 159.7, 156.8, 143.4, 142.7, 139.8, 134.9, 134.0, 132.9, 122.0, 121.5, 120.4, 116.9, 108.1, 61.0, 43.7, 17.4, 14.2, −0.2; IR (neat): 2954, 2924, 2853, 2224, 1717, 1653, 1578, 1523, 1501, 1456, 1437, 1261 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{23}H_{27}N_3O_2SiS_2Br$ $[M+H]^+$ 548.0497, found 548.0498.



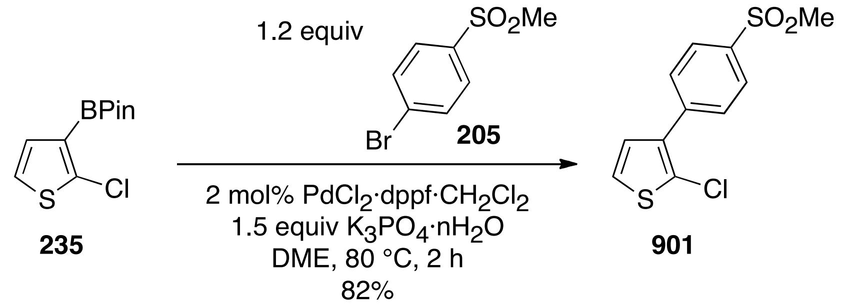
225 **227**

Preparation of **227**: To a solution of **225** (54.2 mg, 0.099 mmol) in THF (2.0 mL) was added tetrabutylammonium fluoride 1 M in THF (0.2 mL, 0.2 mmol) dropwise at room temperature. The completion of the reaction, usually after 2.5–3 hours, was confirmed by TLC. The reaction mixture was quenched with aqueous saturated sodium bicarbonate (5 mL) and extracted with ethyl acetate (3 × 5 mL); combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Desilylation product **227** (39.1 mg, 0.082 mmol, 83% yield) as a wax after purification by column chromatography eluting with hexanes/EtOAc (1:1 → 3:1). R_f = 0.4 (hexanes/EtOAc 3:1); mp 53–54 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 5.25 Hz, 1 H), 7.66 (d, *J* = 8.5 Hz, 1 H), 7.50 (d, *J* = 5.25 Hz, 1 H), 7.15 (d, *J* = 8.5 Hz, 1 H), 4.24 (q, *J* = 7 Hz, 2 H), 2.93 (s, 1 H), 2.62 (s, 1 H), 1.28 (t, *J* = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 162.3, 159.8, 156.8, 139.4, 138.5, 133.7, 132.9, 127.7, 126.9, 122.1, 121.7, 120.6, 116.9, 108.3, 61.1, 43.7, 17.4, 14.3; IR (neat): 3110, 2926, 2795, 2224, 1714, 1579, 1522, 1485, 1437, 1373, 1327, 1263, 1128, 1093 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{20}H_{19}N_3O_2S_2Br$ $[M+H]^+$ 476.0102, found 476.0105.

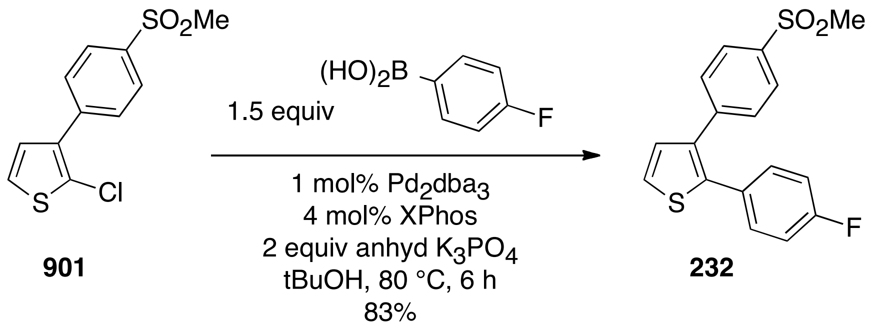


219 **229**

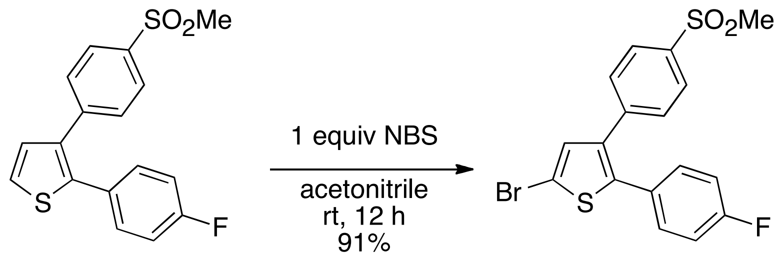
Preparation of **229**: To a solution of **219** (51 mg, 0.109 mmol) in THF (2.2 mL) was added tetrabutylammonium fluoride 1 M in THF (0.22 mL, 0.22 mmol) dropwise at room temperature. The completion of the reaction, usually after 2.5–3 hours, was confirmed by TLC. The reaction mixture was quenched with aqueous saturated sodium bicarbonate (5 mL) and extracted with ethyl acetate (3 × 5 mL); combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. Desilylation product **229** (35 mg, 0.088 mmol, 81% yield) was obtained as a white solid after purification by column chromatography eluting with hexanes/EtOAc (3:1). R_f = 0.25 (hexanes/EtOAc 3:1); mp 185 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 5.0 Hz, 1 H), 7.55 (d, J = 9.0 Hz, 1 H), 7.39 (d, J = 5.0 Hz, 1 H), 6.72 (dd, J = 9.0, 3.0 Hz, 1 H), 6.68 (d, J = 3.0 Hz, 1 H), 4.26 (q, J = 7.5, 2 H), 3.04 (s, 6 H), 2.66 (s, 3 H), 1.30 (t, J = 7.5, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 162.5, 159.6, 152.4, 139.5, 137.4, 134.6, 133.1, 128.3, 125.8, 122.3, 118.9, 114.1, 112.0, 99.5, 61.1, 40.0, 17.5, 14.3; IR (neat): 3108, 2964, 2928, 2859, 2213, 1716, 1701, 1684, 1653, 1601, 1558, 1522, 1506, 1437, 1373, 1263 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{20}H_{20}N_3O_2S_2$ $[M+H]^+$ 398.0997, found 398.0997.



Preparation of 2-chloro-3-(4-(methylsulfonyl)phenyl)thiophene (**901**): In a flame-dried air-free flask were mixed **235** (151 mg, 0.617 mmol), 1-bromo-4-(methylsulfonyl)benzene, **205**, (174 mg, 0.741 mmol), potassium phosphate n-hydrate (230 mg, 0.926 mmol), and PdCl2·dppf (9.04 mg, 0.012 mmol), together with a stir bar. The solid mixture was put under high vacuum and refilled with nitrogen several times. Degassed (freeze-pump-thaw) DME (1.25 mL) was added under nitrogen atmosphere. The reaction mixture was heated up to 80 °C. After 2h, TLC (hexanes/EtOAc 2:1) showed that the reaction was complete. The reaction mixture was passed through a short plug of silica gel eluting with acetone and the filtrate was concentrated and adsorbed into a minimum amount of silica gel. Column chromatography eluting with hexanes/EtOAc (2:1) afforded **901** (138 mg, 0.506 mmol, 82% yield) as an off-white solid. R_f = 0.27 (2:1 hexanes/EtOAc); mp 114–115 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, J = 8.2 Hz, 2 H), 7.75 (d, J = 8.2 Hz, 2 H), 7.20 (d, J = 5.9 Hz, 1 H), 7.06 (d, J = 5.9 Hz, 1 H), 3.08 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 139.6, 139.3, 136.2, 129.3, 128.0, 127.6, 126.8, 123.6; IR (neat) 2923, 2872, 1737, 1717, 1700, 1685, 1653, 1559, 1540, 1521, 1276, 1136, 1023, 837, 771 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{11}H_{10}O_2S_2Cl$ $[M+H]^+$ 272.9811, found 272.9813.

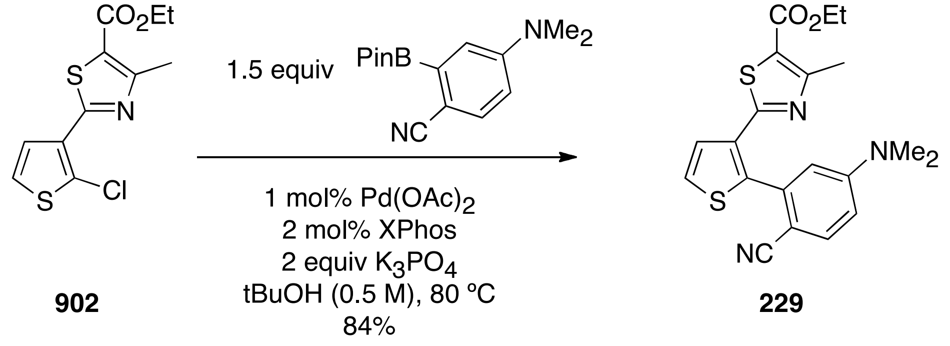


Preparation of 2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)thiophene (**232**): To an air-free flask was added **901** (44.4 mg, 0.163 mmol), (4-fluorophenyl)boronic acid, **206**, (34.2 mg, 0.244 mmol), anhydrous potassium phosphate (69.1 mg, 0.326 mmol), Pd$_2$dba$_3$ (1.5 mg, >1.628 μmol), and XPhos (3.1 mg, 6.51 μmol), and the solid mixture was purged *in vacuo* and refilled with nitrogen several times. To the flask was added degassed tBuOH (0.65 mL), and the resulting suspension was heated up to 80 °C for 6 h. The mixture was passed through silica gel eluting with acetone. The filtrate was concentrated and purified by column chromatography eluting with hexanes/EtOAc (2:1) to afford **232** (44.9 mg, 0.135 mmol, 83% yield) as an off-white solid. R_f = 0.38 (2:1 hexanes/EtOAc); mp 146–148 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.82 (d, J = 8.1 Hz, 2 H), 7.42 (d, J = 8.1 Hz, 2 H), 7.36 (d, J = 5.3 Hz, 1 H), 7.22 (dd, J = 8.7, 5.4 Hz, 1 H), 7.15 (d, J = 5.3 Hz, 1 H), 6.98 (dd, J = 8.7, 8.7 Hz, 1 H), 3.05 (s, 3 H); ^{13}C NMR (150 MHz, CDCl$_3$): δ (163.4, 161.7) (d, $^1J_{\text{C–F}}$ = 248.5 Hz), 142.0, 139.6, 138.7, 136.1, (131.2, 131.1) (d, $^3J_{\text{C–F}}$ = 8.1 Hz), 131.1, 129.8, (129.79, 129.77) (d, $^4J_{\text{C–F}}$ = 4.0 Hz), 127.5, 125.1, (115.95, 115.81) (d, $^2J_{\text{C–F}}$ = 22.2 Hz), 44.5; IR (neat) 3103, 3081, 3015, 2927, 1936, 1903, 1652, 1595, 1540, 1507, 1439, 1283, 1313, 1151, 1118, 1093, 962, 901, 882, 841, 774 cm^{-1}; HRMS (ESI): *m/z* calculated for [M+H]$^+$ 333.0419, found 333.0419.



232 **201**

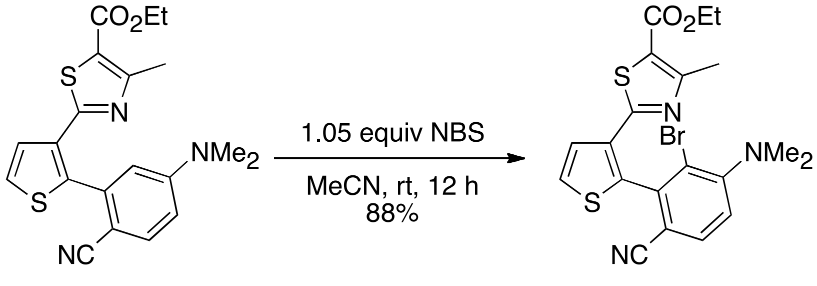
Preparation of DuP 697 (**201**): To a solution of **232** (23.2 mg, 0.070 mmol) in acetonitrile (1.5 mL) was added *N*-bromosuccinimide (13.0 mg, 0.073 mmol) in one portion and the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered through a short plug of silica gel eluting with dichloromethane. The filtrate was concentrated *in vacuo* and purified by column chromatography eluting with hexanes/EtOAc (4:1) to afford **201** (26.1 mg, 0.064 mmol, 91% yield) as a white solid. R_f = 0.3 (4:1 hexanes/EtOAc); mp 123–123.5 °C (lit[18a] 122–124 °C); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82 (d, J = 8.7 Hz, 2 H), 7.37 (d, J = 8.7 Hz, 2 H), 7.16 (m, 2 H), 7.11 (s, 1 H), 6.98 (m, 2 H), 3.05 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (163.6, 161.9) (d, $^1J_{C–F}$ = 249.5 Hz), 140.78, 140.77, 139.2, 136.5, 132.2, (131.1, 131.0) (d, $^3J_{C–F}$ = 8.2 Hz), 129.7, (128.55, 128.52) (d, $^4J_{C–F}$ = 3.6 Hz), 127.6, (116.16, 116.01) (d, $^2J_{C–F}$ = 21.9 Hz), 111.9, 44.4; HRMS (EI): *m/z* calculated for $C_{17}H_{12}O_2S_2BrF$ $[M]^+$ 409.9446, found 409.9452.



902 **229**

Preparation of **229**: To an air-free flask provided with a stir bar were added **902** (56.4 mg, 0.196

mmol), 4-(dimethylamino)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (42.7 mg, 0.294 mmol), anhydrous potassium phosphate (83 mg, 0.392 mmol), Pd_2dba_3 (2.0 mg, >1.96 μmol), and XPhos (4.0 mg, >7.84 μmol). The flask with the solid mixture was purged and refilled with nitrogen multiple times. To the flask was added degassed tBuOH (0.8 mL), and the resulting suspension was heated up to 80 °C. The progress of the reaction was monitored by TLC. After completion, usually after 6 hours, the reaction mixture was filtered through a short plug of silica gel eluting with acetone. The filtrate was concentrated *in vacuo* and the material was subjected to column chromatography eluting with hexanes/EtOAc (5:1 → 2:1) to afford **229** (65.1 mg, 0.164 mmol, 84% yield) as a white solid, spectroscopically identical to the compound obtained via desilylation (page 180). R_f = 0.25 (hexanes/ethyl acetate 3:1); mp 183–184 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, *J* = 5.0 Hz, 1 H), 7.55 (d, *J* = 9.0 Hz, 1 H), 7.39 (d, *J* = 5.0 Hz, 1 H), 6.72 (dd, *J* = 9.0, 3.0 Hz, 1 H), 6.68 (d, *J* = 3.0 Hz, 1 H), 4.26 (q, *J* = 7.5, 2 H), 3.04 (s, 6 H), 2.66 (s, 3 H), 1.30 (t, *J* = 7.5, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 162.5, 159.6, 152.4, 139.5, 137.4, 134.6, 133.1, 128.3, 125.8, 122.3, 118.9, 114.1, 112.0, 99.5, 61.1, 40.0, 17.5, 14.3.

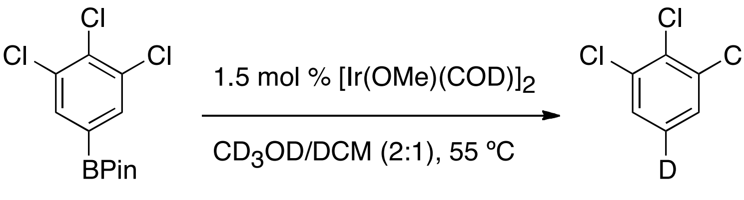


229 **227**

Preparation of **227**: To a solution of **229** (42.5 mg, 0.107 mmol) in acetonitrile (2.1 mL) was added *N*-bromosuccinimide (19.2 mg, 0.108 mmol) in one portion and the mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered through a short plug of silica gel eluting with dichloromethane. The filtrate was concentrated *in vacuo* and purified by column chromatography eluting with hexanes/EtOAc (1:1 → 3:1) to afford **227** (44.9 mg, 0.094 mmol, 88%), spectroscopically identical to the compound prepared via desilylation (page 179). R_f = 0.4 (hexanes/EtOAc 3:1); mp 53–54 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 5.25 Hz, 1 H), 7.66 (d, *J* = 8.5 Hz, 1 H), 7.50 (d, *J* = 5.25 Hz, 1 H), 7.15 (d, *J* = 8.5 Hz, 1 H), 4.24 (q, *J* = 7 Hz, 2 H), 2.93 (s, 1 H), 2.62 (s, 1 H), 1.28 (t, *J* = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 162.3, 159.8, 156.8, 139.4, 138.5, 133.7, 132.9, 127.7, 126.9, 122.1, 121.7, 120.6, 116.9, 108.3, 61.1, 43.7, 17.4, 14.3.

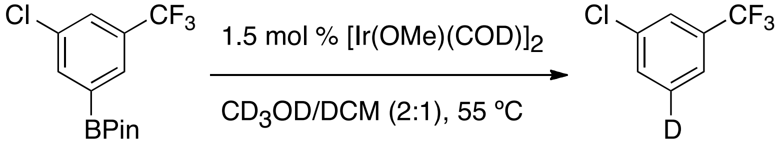
9.3. Experimental details for Section 2.2: Deborylation

General Procedure A. Deuterodeborylation for preparation of deuterated aromatics from purified boronic esters with CD_3OD: In an air-free flask provided with a stir bar, a solution of aryl boronic ester (dried overnight in a vacuum dessicator) in methanol-d_4/DCM 2:1 (0.2 M) was freeze-pump-thaw degassed (0.01 mmHg) three times and Ir catalyst (1.5 mol%) was added under nitrogen blanketing. The flask was sealed and heated in an oil bath to 55 °C. Required reaction times for each substrate were estimated by running the reaction in a J. Young tube at a 0.1 mmol scale using methanol-d_4/$CDCl_3$ 2:1 as solvent and monitoring the progress by ^{1}H NMR. Upon completion, the reaction mixture was concentrated, and the residue was directly subjected to column chromatography eluting with pentane or dichloromethane.



903 **904**

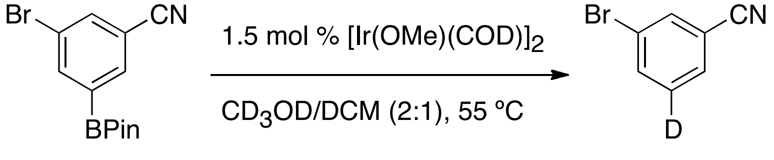
Preparation of 1,2,3-trichlorobenzene-5-d (**904**[31], Table 1, entry 1): General procedure A (page 185) was applied to 4,4,5,5-tetramethyl-2-(3,4,5-trichlorophenyl)-1,3,2-dioxaborolane (**903**) (61.5 mg, 0.2 mmol) with $[Ir(OMe)(COD)]_2$ (2.0 mg, 1.5 mol%) in CD_3OD/DCM (2:1) (1 mL). After 5.5 h, the reaction mixture was concentrated *in vacuo*. Column chromatography eluting with pentane afforded **904** (30.9 mg, 85% yield) as an off-white solid. mp 53–54 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (apparent s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.3, 131.5, 128.6, (127.4, 127.2, 127.0) (t, $J_{C\text{–}D}$ = 25 Hz); HRMS (EI): *m/z* calculated for $C_6H_2DCl_3$ $[M]^+$ 180.9363, found 180.9371.



905 **906**

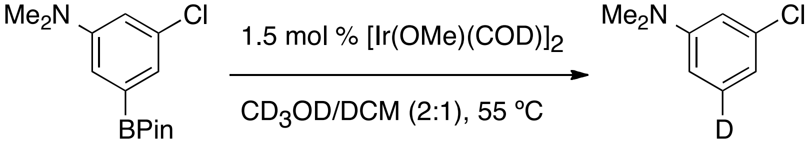
3-Chlorobenzotrifluoride-5-d (**906**[31], Table 1, entry 3): General procedure A (page 185) was applied to 2-(3-chloro-5-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**905**) (61.3 mg, 0.2 mmol) with $[Ir(OMe)(COD)]_2$ (2.0 mg, 1.5 mol%) in CD_3OD/DCM (2:1) (1 mL). After 4 h, the reaction mixture was concentrated. Column chromatography eluting with pentane afforded 27.5 mg of a colorless oil containing **906** (25.1 mg, 69% yield) and pentane. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (apparent s, 1 H), 7.54–7.48 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$):

δ 134.9, (132.7, 132.4, 132.2, 131.9) (q, J_{C-F} = 35 Hz), 131.9, (130.1, 129.9, 129.7) (t, J_{C-D} = 25 Hz), (126.6, 124.4, 122.3, 120.1) (q, J_{C-F} = 271 Hz), (125.73, 125.70, 125.66, 125.63) (q, J_{C-F} = 4 Hz), (123.37, 123.34, 123.31, 123.28) (q, J_{C-F} = 3.75 Hz).



907 **908**

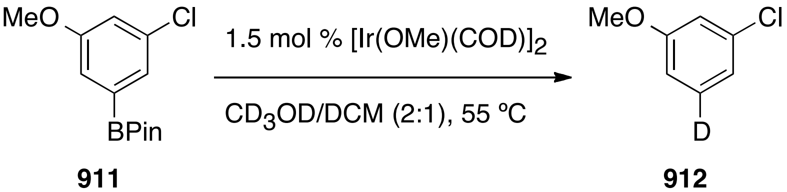
3-Bromobenzonitrile-5-d (**908**[31], Table 1, entry 4): General procedure A (page 185) was applied to 3-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (**907**) (61.6 mg, 0.2 mmol) with $[Ir(OMe)(COD)]_2$ (2.0 mg, 1.5 mol%) in CD_3OD/DCM (2:1) (1 mL). After 8 h, the reaction mixture was concentrated *in vacuo*. Column chromatography eluting with CH_2Cl_2 afforded **908** (27.2 mg, 74% yield) as an off-white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 2.0, 1.5 Hz, 1 H), 7.73 (apparent s, 1 H), 7.58 (apparent s, 1 H); ^{13}C NMR (125 MHz, CDCl3): δ 136.0, 134.7, 130.5, (130.5, 130.3, 130.1) (t, J_{C-D} = 25 Hz), 122.8, 117.2, 114.2; HRMS (EI): *m/z* calculated for C_7H_3DBrN $[M]^+$ 181.9590, found 181.9592.



909 **910**

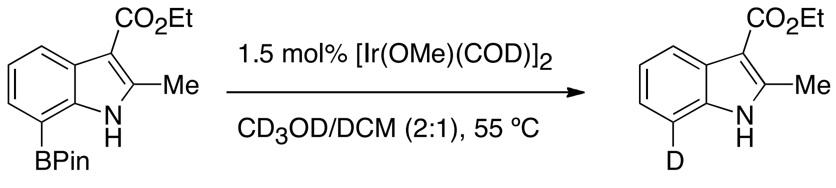
Preparation of 3-Chloro-N,N-dimethylaniline-5-d (**910**[31], Table 1, entry 5): General procedure A (page 185) was applied to 3-chloro-*N*,*N*-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)aniline (**909**) (56.2 mg, 0.2 mmol) with $[Ir(OMe)(COD)]_2$ (2.0 mg, 1.5 mol%) in CD_3OD/DCM (2:1) (1 mL). After 10 h, the reaction mixture was concentrated *in vacuo*. Column chromatography eluting with (pentane/CH_2Cl_2 3:1) afforded **910** (30.4 mg, 0.194 mmol, 97% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69–6.66 (m, 2 H), 6.58 (apparent s, 1 H), 2.94 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.4, 134.9, (129.8, 129.6, 129.4) (t, $J_{C\text{–}D}$ = 25 Hz), 116.0, 112.2, 110.4, 40.3; HRMS (ESI): *m/z* calculated for $C_8H_{10}DClN$ $[M+H]^+$ 157.0637, found 157.0636.



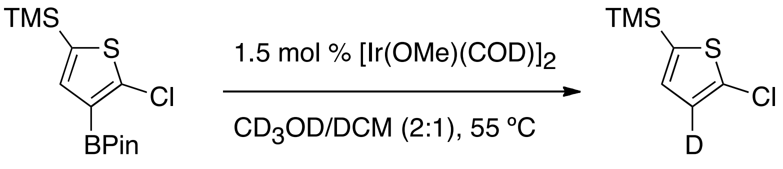
911 **912**

Preparation of 3-Chloroanisole-5-d (**912**[31], Table 1, entry 6): General procedure A (page 185) was applied to 2-(3-chloro-5-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**911**) (54.0 mg, 0.2 mmol) with $[Ir(OMe)(COD)]_2$ (2.0 mg, 1.5 mol%) in CD_3OD/DCM (2:1) (1 mL). After 6 h, the reaction mixture was concentrated *in vacuo*. Column chromatography eluting with dichloromethane afforded **912** (19.3 mg, 0.134 mmol, 67% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (apparent s, 1 H), 6.89 (t, J = 2.4 Hz, 1 H), 6.78 (apparent s, 1 H), 3.78 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 134.8, (130.1, 129.9, 129.7) (t, $J_{C\text{–}D}$ = 25 Hz), 120.7, 114.3, 112.4, 55.3; HRMS (EI): *m/z* calculated for C_7H_6DClO $[M]^+$ 143.0248, found 143.0255.



913 **914**

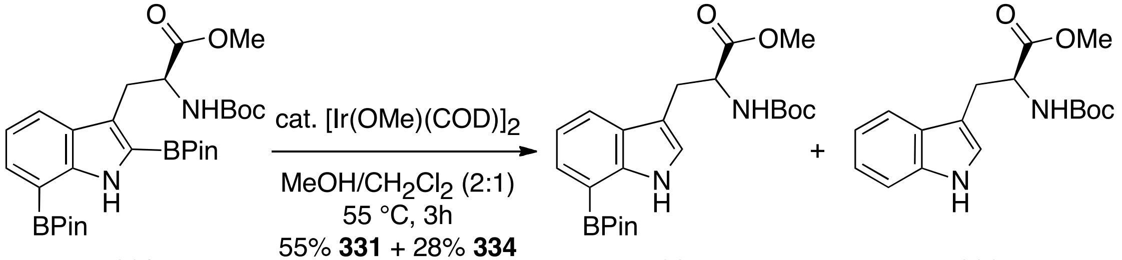
Preparation of ethyl 2-methylindole-3-carboxylate-7-d (**914**, Table 1, entry 7): General procedure A (page 185) was applied to ethyl 2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-3-carboxylate (**913**) (65.8, 0.2 mmol) with $[Ir(OMe)(COD)]_2$ (2 mg, 1.5 mol%) with a small modification. Before use, dried **913** was treated with a minimum amount of CD_3OD in the reaction air-free flask and the solvent was evaporated *in vacuo* twice, then CD_3OD/DCM (2:1) (1 mL) was added, the solution was degassed, and catalyst was added. After 1.5 h, the reaction mixture was concentrated *in vacuo*. Column chromatography eluting with dichloromethane afforded **914** (39.1 mg, 0.191 mmol, 96% yield) as an off-white solid. *N*-deuterated material was not observed after purification by column. mp 132–133 ºC; ^1H NMR (600 MHz, $CDCl_3$): δ 8.35 (br, 1 H), 8.09 (d, J = 7.4 Hz, 1 H), 7.20 (t, J = 7.4 Hz, 1 H), 7.17 (dd, J = 7.4, 1.6 Hz, 1 H), 4.39 (q, J = 7.3 Hz, 2 H), 2.73 (s, 3 H), 1.43 (t, J = 7.3 Hz, 3 H); ^2H NMR (76.75 MHz, pentane): δ 7.65; ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.1, 143.9, 134.4, 127.2, 122.2, 121.7, 121.3, 110.2 (t, $J_{C–D}$ = 24 Hz), 104.7, 59.5, 14.6, 14.2; IR (neat): 3301, 2976, 2914, 2860, 1662, 1595, 1541, 1456, 1438, 1223, 1183, 1097, 802 cm^{-1}; HRMS (EI): *m/z* calculated for $C_{12}H_{12}DNO_2$ $[M]^+$ 204.1009, found 204.1019.



204 **915**

Preparation of 2-chloro-5-(trimethylsilyl)thiophene-3-d (**915**, Table 1, entry 8): General procedure A (page 185) was applied to (5-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)trimethylsilane (**204**) (0.81 g, 2.56 mmol) with $[Ir(OMe)(COD)]_2$ (25.0 mg, 1.5 mol%) in CD_3OD/DCM (2:1) (12.8 mL). After 30 minutes, the reaction mixture was concentrated to about 5 mL, diluted with pentane (10 mL) and filtered through a short plug of silica gel packed with pentane. Fractions containing the product were mixed and carefully concentrated to afford 640 mg of a mixture of product and pentane (ca. 1:2 by ^{1}H NMR, calculated yield 89%). Further concentration *in vacuo* of a small portion of the material afforded pure **915** (after significant loss) as a colorless oil, which was used for characterization purposes. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.98 (s, 1 H), 0.28 (s, 9 H); ^{2}H NMR (76.75 MHz, pentane): δ 7.52; ^{13}C NMR (150 MHz, $CDCl_3$): δ 140.2, 134.4, 133.2, 127.2 (t, J_{C-D} = 26 Hz), −0.3; IR (neat): 3064, 2957, 2903, 1407, 1240, 1156, 1031, 999, 840, 760, 697, 674 cm^{-1}; HRMS (EI): *m/z* calculated for $C_7H_{10}DSiSCl$ $[M]^+$ 191.0102, found 191.0110.

9.4. Experimental details for Chapter 3: TMC-95 core



Preparation of 7-borylated L*-tryptophan derivative* **331**: To an air-free flask containing a degassed solution of **330**[u] (172.0 mg, 0.302 mmol) in methanol (1.0 mL) and dichloromethane (0.5 mL) was added in one portion [Ir(OMe)COD]$_2$ (3.0 mg, 4.52 μmol). The flask was purged and refilled with nitrogen three times and the resulting mixture was heated in oil bath at 55 °C for 3 hours. The reaction mixture was then concentrated *in vacuo* and filtered through a short plug of silica gel eluting with dichloromethane to remove the iridium residue. The crude material was adsorbed on a minimum amount of silica gel, dried *in vacuo*, and purified by column chromatography eluting with dichloromethane to afford *N*-Boc-L-tryptophan methyl ester, **332** (27.2 mg, 0.085 mmol, 28% recovered borylation substrate) and 7-borylated L-tryptophan derivative **331** (73.3 mg, 0.165 mmol, 55% yield) as a white solid, mp 178–178.5 ºC; R_f (**331**) = 0.33 (DCM); $[\alpha]^{20}_{D}$ +31.9º (*c* 1.22, CH$_2$Cl$_2$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.10 (br, 1 H), 7.65 (d, *J* = 7.9 Hz, 1 H), 7.62 (d, *J* = 7.1 Hz, 1 H), 7.11 (dd, *J* = 7.9, 7.1 Hz, 1 H), 7.04 (s, 1 H), 5.03 (d, *J* = 7.5 Hz, 1 H), 4.61 (dd, *J* = 7.5, 5.4 Hz, 1 H), 3.65 (s, 3 H), 3.32–3.26 (m, 2 H), 1.41 (s, 9 H), 1.37 (s, 12 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.7, 155.2, 141.3, 129.5, 126.6, 122.7, 122.3, 122.29, 119.1, 109.6, 83.8, 79.7, 54.2, 52.2, 28.3, 27.9, 25.0; IR (neat) 3447, 3052, 2977,

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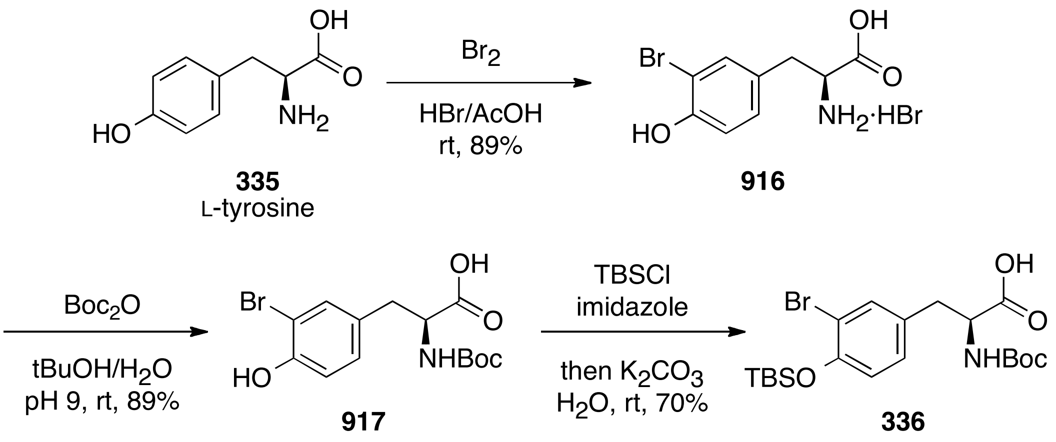
[u] Material prepared by Ms. Fang Yi Shen

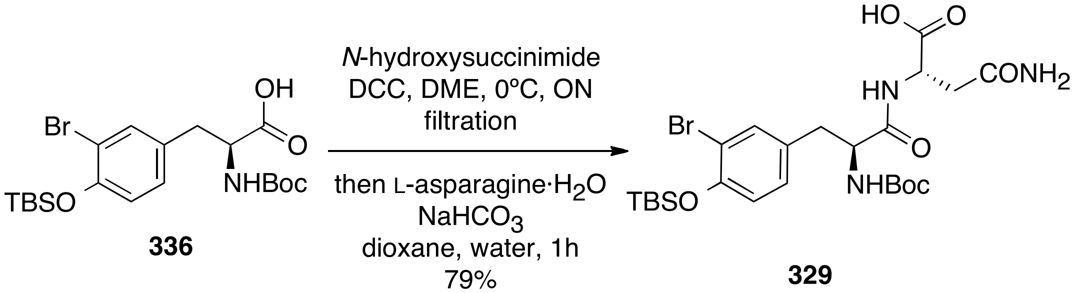
2931, 1741, 1714, 1591, 1543, 1506, 1435, 1373, 1329, 1294, 1205, 1166 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{23}H_{34}BN_2O_6$ $[M+H]^+$ 445.2510, found 445.2513.



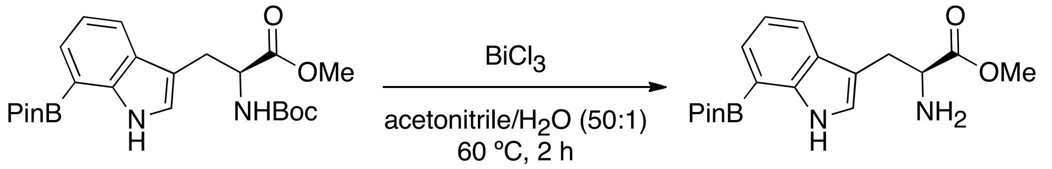
Preparation of (S)-3-bromotyrosine hydrobromide **916**:[53] Commercial solution of hydrogen bromide 33% w/v in acetic acid (135 mL, 552 mmol) was added dropwise to a suspension of (*S*)-tyrosine, **335**, (50.01 g, 276 mmol) in glacial acetic acid (225 mL) while stirring, followed by a solution of bromine (15.4 mL, 299 mmol) in acetic acid (102 mL), added dropwise using an addition funnel over several hours (overnight). The resulting mixture was stirred at room temperature for at least additional 24 hours. The precipitate was filtered and rinsed twice with glacial acetic acid and then with ether several times. The resulting paste was dried under high vacuum overnight and then in a vacuum dessicator in the presence of NaOH pellets. The product (*S*)-3-bromotyrosine hydrobromide, **916**, (84.09 g, 247 mmol, 89% yield discounting the weight of acetic acid present in the crude material) was obtained as an off-white solid (reported white)[53], mp (crude) 212–218 ºC (dec) (lit[53] mp 210–215 °C, dec); $[\alpha]^{20}_{D}$ +2.84° (*c* 8.84, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.43 (d, *J* = 2.0 Hz, 1 H), 7.10 (dd, *J* = 8.5, 2.0 Hz, 1 H), 6.90 (d, *J* = 8.5 Hz, 1 H), 4.20 (dd, *J* = 7.4, 5.8 Hz, 1 H), 3.21 (dd, *J* = 14.8, 5.8 Hz, 1 H), 3.07 (dd, *J* = 14.8, 7.4 Hz, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 171.2, 155.4, 135.2, 130.9, 128.0, 117.9, 111.4, 55.3, 36.2. This crude product was used directly in the following step without further purification.

Preparation of (S)-N-Boc-3-bromotyrosine (**917**):[53] To a suspension of (*S*)-3-bromotyrosine hydrobromide, **916**, (6.00 g, 17.60 mmol) in tBuOH (54 mL) and water (6 mL) was added aqueous NaOH (2 M) in small portions to adjust the pH to 9. Di-*tert*-butyl dicarbonate (4.61 g, 21.11 mmol) was added and the mixture was stirred at room temperature. After 30 minutes, the pH was readjusted to 9, by addition of aqueous NaOH (2 M), and more di-*tert*-butyl dicarbonate (2.304 g, 10.56 mmol) was added. The resulting mixture was stirred for additional 30 min at room temperature. The solution was transferred to a separatory funnel and washed with hexanes (2 × 150 mL). The aqueous phase was acidified to pH 2–3 by addition of 10% v/v aqueous HCl and extracted with ethyl acetate (3 × 150 mL). Combined organic phases were washed with water (2 × 400 mL) and brine (400 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford crude (*S*)-*N*-Boc-3-bromotyrosine, **917**, (5.62 g, 15.61 mmol, 89% yield) as a foam. $[\alpha]^{20}_{D}$ +11.54° (*c* 1.63, MeOH); ^{1}H NMR (500 MHz, acetone-d_6) δ 7.41 (d, *J* = 1.6 Hz, 1 H), 7.11 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 6.00 (br d, *J* = 8.0 Hz, 1 H), 4.37 (m, 1 H), 3.11 (dd, *J* = 14.0, 5.2 Hz, 1 H), 2.92 (dd, *J* = 14.0, 8.8 Hz, 1 H), 1.37 (s, 9 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 173.3, 156.2, 153.5, 134.6, 131.3, 130.5, 117.1, 110.0, 79.3, 55.6, 37.0, 28.6; HRMS (ESI): *m/z* calculated for $C_{14}H_{19}NO_5Br$ $[M+H]^+$ 360.0447, found 360.0447. This crude product was used directly in the following step without further purification.

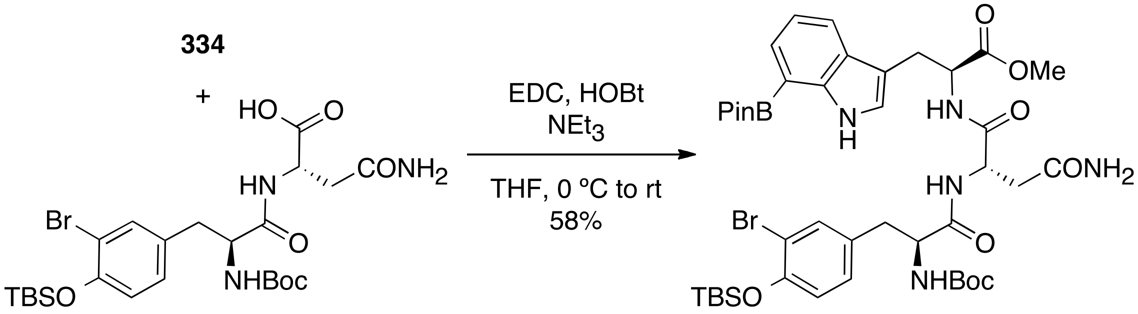
Preparation of (S)-O-TBS-N-Boc-3-bromotyrosine (**336**): To a solution of (*S*)-*N*-Boc-3-bromotyrosine, **917**, (1.30 g, 3.61 mmol) in DMF (15 mL) were successively added imidazole (0.74 g, 10.83 mmol) and TBSCl (1.20 g, 7.94 mmol). The resulting solution was stirred at room temperature overnight. The reaction mixture was then treated with water (15 mL), stirred for 30 min, and extracted with diethyl ether (3 × 30 mL). Combined ether layers were successively washed with 1N aqueous HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). Once dried over Na_2SO_4, the organic extract was concentrated *in vacuo*. The resulting yellowish oil was redissolved in THF (10 mL), treated with potassium carbonate 1 M in water (11 mL, 11 mmol), and stirred at room temperature for 1 hour. The mixture was acidified to pH 3 by addition of 1M aqueous HCl and then extracted with ethyl acetate (3 × 10 mL). The combined ethyl acetate layers were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with hexanes/EtOAc/HOAc 8:1.9:0.1 to provide (*S*)-*O*-TBS-*N*-Boc-3-bromotyrosine (**336**) as a slightly yellowish oil that became a foam under high vacuum and hardened upon standing to form a white solid (1.20 g, 2.53 mmol, 70% yield), mp 116–118 ºC; R_f = 0.35 (hexanes/EtOAc/HOAc 8:1.9:0.1); $[\alpha]^{20}_{D}$ +14.5° (*c* 0.54, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (apparent s, 1 H), 6.97 (dd, *J* = 8.1, 2.0 Hz, 1 H), 6.77 (d, *J* = 8.1 Hz, 1 H), 4.95 (d, *J* = 7.7 Hz, 1 H), 4.52 (m, 1 H), 3.11 (dd, *J* = 13.7, 4.4 Hz, 1 H), 2.94 (dd, *J* = 13.7, 6.3 Hz, 1 H), 1.41 (s, 9 H), 1.01 (s, 9 H), 0.21 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 155.4, 151.7, 134.1, 129.9, 129.1, 120.1, 115.3, 80.5, 54.3, 36.6, 28.3, 25.7, 18.3, 4.2; IR (neat) 3307, 2957, 2930, 2859, 1684, 1654, 1496, 1395, 1366, 1289, 1255, 1167, 1046 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{20}H_{33}NO_5BrSi$ $[M+H]^+$ 474.1311, found 474.1313.



Preparation of dipeptide **329**: To a stirring solution of **336** (0.996 g, 2.1 mmol) and *N*-hydroxysuccinimide (0.302 g, 2.63 mmol) in DME (21 mL) at 0 °C was added DCC (0.542 g, 2.63 mmol) in one portion. The containing flask was sealed and the reaction mixture was stirred at 0 ºC overnight. The resulting suspension was filtered and the solid (urea) was rinsed with cold DME (3 × 5 mL). The filtrate together with the rinses was concentrated *in vacuo*, redisolved in dioxane (9 mL), and cooled to about 10 °C. To this solution was added a solution of L-asparagine (1.67 g, 12.60 mmol) and sodium bicarbonate (1.06 g, 12.60 mmol) in water (6 mL) in small portions. After 1 h of vigorous stirring, most of the dioxane was removed under vacuum and the remaining aqueous phase was acidified to pH 3.5 and extracted three times with EtOAc. The combined extracts were washed with water and brine, dried over $MgSO_4$, and evaporated to yield a white foam that was subjected to flash chromatography eluting with hexanes/EtOAc/HOAc 8:1.9:0.1 to afford **336** (74 mg, 7.5% recovered starting material) and the desired dipeptide **329** (972 mg, 1.651 mmol, 79% yield) as a white solid, mp 147–147.5 ºC; R_f = 0.21 (hexanes/EtOAc/HOAc 8:1.9:0.1); $[\alpha]^{20}_{D}$ +16.5° (*c* 0.49, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (br, 1 H), 7.31 (s, 1H), 6.99 (br, 1 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 6.70 (dd, *J* = 8.0, 3.0 Hz, 1 H), 5.69 (br, 1H), 5.56 (br, 1H), 4.71 (m, 1 H), 4.40 (m, 1H), 3.06 (apparent d, *J* = 13.5 Hz, 1 H), 2.92–2.69 (m, 3 H), 1.26 (s, 9 H), 0.98 (s, 9 H), 0.16 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 172.3, 171.9, 156.1, 151.3, 134.2, 131.0, 129.2, 120.0, 115.1, 80.4, 55.6, 50.2, 37.3, 37.0, 28.3, 25.7, 18.3, 4.2; IR (neat) 3449, 3297, 3055, 2957, 2857, 1734, 1669, 1604, 1495, 1473, 1437, 1372, 1329, 1292, 1254, 1205, 1167, 1047 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{24}H_{39}N_3O_7BrSi$ $[M+H]^+$ 588.1741, found 588.1742.



331 **334**



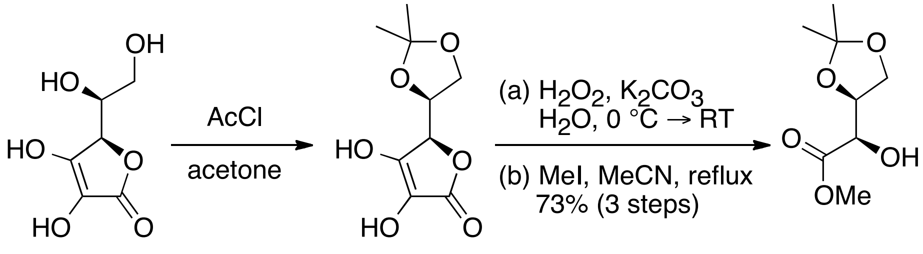
329 **337**

Preparation of 7-borylated L*-tryptophan derivative* **334**: To a solution of **331** (63.6 mg, 0.143 mmol) in acetonitrile (1.4 mL) and water (28 μL) was added $BiCl_3$ (27.1 mg, 0.086 mmol, 0.6 equiv) in one portion. The containing flask was sealed and placed in an oil bath at 60 ºC. The reaction mixture was stirred for 1 hour and then cooled to room temperature. A second batch of $BiCl_3$ (27.1 mg, 0.086 mmol, 0.6 equiv) was added and the suspension was stirred again at 60 ºC for 1 hour. The reaction was quenched with $NaHCO_3$ and the excess of solids was removed by filtration through a plug of celite eluting with acetonitrile. Concentration of the filtrate *in vacuo* provided a crude material (ca. 100 mg) consisting basically on Boc-deprotected product (**334**), acetonitrile, and presumably inorganic salts. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.40 (s, 1 H), 7.56 (d, $J \approx$ 8.0 Hz, 1 H), 7.49 (d, $J \approx$ 8.0 Hz, 1 H), 7.48 (s, 1 H), 7.06 (br, 2 H), 7.04 (t, $J \approx$ 8.0 Hz, 1 H), 4.66 (m, 1 H), 3.53 (s, 3 H), 3.50 (m, 2 H), 1.30 (s, 6 H), 1.29 (s, 6 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.2, 141.5, 129.7, 127.9, 126.1, 125.7, 121.8, 104.8, 84.0, 54.5, 54.2, 26.2, 25.0; HRMS (ESI): *m/z* calculated for $C_{18}H_{26}BN_2O_4$ $[M+H]^+$ 345.1986, found 345.1992. This crude material was used directly in the following step without further purification and assuming a quantitative yield.

Preparation of tripeptide **337**: To a stirred slurry of crude 7-borylated L-tryptophan derivative **334** (assumed to contain 49.3 mg of **334**, 0.142 mmol, 1.2 equiv) and dipeptide **329** (70.2 mg, 0.119 mmol) in THF (6 mL) were added EDC (45.8 mg, 0.239 mmol) and HOBT (36.6 mg, 0.239 mmol). The mixture was stirred and cooled to 0 °C under nitrogen atmosphere. Triethylamine (166 μL, 1.194 mmol) was added in one portion via syringe and the mixture was allowed to slowly warm to room temperature and stirred for 24 h. The reaction mixture was concentrated *in vacuo*, adsorbed onto a minimum amount of silica gel, dried under high vacuum, and directly subjected to column chromatography eluting with ether and then ether/EtOAc (1:1 → 0:1) to afford tripeptide **337** (63.1 mg, 0.069 mmol, 58% yield) as an off-white slightly orange solid, mp 131.5–133.5 ºC; R_f = 0.32 (EtOAc); $[\alpha]^{20}_D$ +20.5° (*c* 0.21, CH$_2$Cl$_2$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.22 (s, 1H), 7.76 (br d, J = 8.0 Hz, 1 H), 7.64 (d, J = 8.0 Hz, 1 H), 7.59 (d, J = 7.0 Hz, 1 H), 7.46 (br d, J = 6.5 Hz, 1 H), 7.27 (d, J = 2.0 Hz, 1 H), 7.11 (s, 1 H), 7.09 (dd, J =

8.0, 7.0 Hz, 1 H), 6.89 (dd, *J* = 8.5, 2.0 Hz, 1 H), 6.74 (d, *J* = 8.5 Hz, 1 H), 5.95 (br, 1 H), 5.52 (br, 1 H), 4.96 (br d, *J* = 7.5 Hz, 1 H), 4.76 (m, 1 H), 4.73 (m, 1 H), 4.26 (m, 1 H), 3.60 (s, 3 H), 3.27 (apparent d, *J* = 6.0 Hz, 2 H), 2.92 (dd, *J* = 14.0, 5.0 Hz, 1 H), 2.82 (m, 1 H), 2.79 (dd, *J* = 16.0, 4.0 Hz, 1 H), 2.46 (dd, *J* = 16.0, 6.5 Hz, 1 H), 1.37 (s, 9 H), 1.35 (s, 12 H), 1.00 (s, 9 H), 0.20 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 171.9, 171.4, 170.2, 155.5, 151.5, 141.2, 134.0, 130.5, 129.4, 129.0, 126.2, 123.3, 122.0, 120.1, 119.0, 115.3, 109.0, 83.8, 80.5, 55.6, 53.2, 52.4, 49.6, 36.5, 36.45, 28.2, 27.3, 25.7, 25.0, 18.3, −4.3; IR (neat) 3397, 2956, 2916, 2849, 1577, 1540, 1459, 1419, 1355 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{42}H_{62}BN_5O_{10}SiBr$ $[M+H]^+$ 914.3542, found 914.3549.

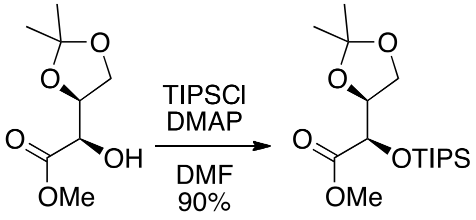
9.5. Experimental details for Chapter 5: Autolytimycin, Suzuki partners



vitamin C **918** **501**

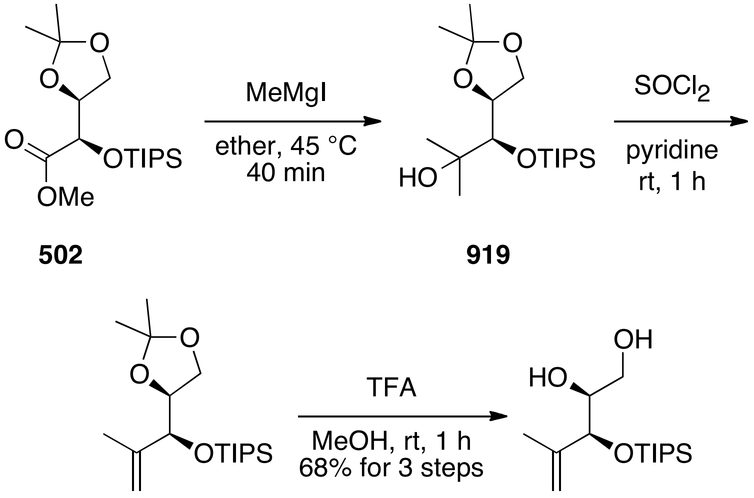
Preparation of 5,6-isopropylidene-L-ascorbic acid (**918**):[31] To a solution of vitamin C (110.02 g, 0.625 mol) in acetone (625 mL) was added acetyl chloride (10.5 mL, 0.147 mol and the resulting mixture was vigorously stirred at room temperature overnight. The abundant precipitate formed was collected by filtration and washed with ice cold acetone to remove the yellow color. The mother liquor was concentrated to about 200 mL and a second crop of precipitate was collected and washed. The mother liquor was again concentrated to about 100 mL and a third crop of precipitate was collected and washed. Combined solids were dried under high vacuum to afford crude **918** (110.06 g) as a beige solid, which was used directly in the following step without further purification.

Preparation of 3,4-isopropylidene-L-threonic acid methyl ester (**501**):[31] An aqueous (750 mL) solution of **918** (110 g, 0.51 mol) and K_2CO_3 (141 g, 1.018 mol) was cooled on an ice/water bath and ice-cold aqueous H_2O_2 30% w/v (200 mL) was added in portions along with ice, keeping the internal temperature below 30 °C. Upon complete addition, the reaction was stirred at room temperature for 15 h. Water was removed by rotary evaporation in a 60 °C water bath. Ethanol was added to help remove the excess of water by coevaporation. Finally, the residue was dried under high vacuum. The resulting dry solid was suspended in acetonitrile (~800 mL) using a mechanical stirrer. The suspension was treated with MeI (50 mL, >0.72 mol) and heated to reflux for 1 day. After being cooled to room temperature, it was concentrated to ~200 mL and CH_2Cl_2 (300 mL) was added to precipitate KI. The solid was filtered off and washed with CH_2Cl_2 and the combined filtrates were evaporated. Purification by column chromatography eluting with hexanes/EtOAc (1:1 → 1:1.5) afforded **501** (87.5 g, 73% over 3 steps) as a colorless oil. $R_f = 0.5$ (1:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 4.36 (dt, $J = 6.5$, 2.5 Hz, 1 H), 4.10 (dd, $J = 8.0$, 3.0 Hz, 1 H), 4.06 and 3.98 (d of ABq, $^3J = 7.0$ Hz, $J_{AB} = 8.5$ Hz, 2 H), 3.79 (s, 3 H), 2.93 (apparent d, $J = 8.0$ Hz, 1 H), 1.39 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 110.0, 76.2, 70.3, 65.6, 52.7, 26.1, 25.3.



501 **502**

Preparation of O-TIPS-3,4-isopropylidene-L-threonic acid methyl ester (**502**):[31,84] Triisopropylsilyl chloride (35.2 mL, 166 mmol) was added dropwise to a well stirred solution of **501** (10.52 g, 55.3 mmol) and DMAP (13.51 g, 111 mmol) in dry DMF (152 mL) at room temperature. After 20 h, TLC (hexanes/ether, 6:1) confirmed the complete consumption of the starting material. To the reaction mixture were added saturated aqueous $NaHCO_3$ (150 mL), ether (300 mL), and enough water to dissolve all solids. The phases were separated and the aqueous layer was extracted three times with ether. Water was added as needed to dissolve solids. Combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography eluting with hexanes/ether (6:1) provided **502** (17.21 g, 49.7 mmol, 90% yield) as clear oil. R_f = 0.30 (6:1 hexanes/ether); $[\alpha]^{20}_D$ +10.4 (*c* 1.17, EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ 4.41 (d, *J* = 5.5 Hz, 1 H), 4.25 (q, *J* = 6.5 Hz, 1 H), 4.05 and 3.97 (d of ABq, ^3J = 6.0 Hz, J_{AB} = 8.5 Hz, 2 H), 3.69 (s, 3 H), 1.32 (s, 3 H), 1.28 (s, 3 H), 1.12–0.95 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 109.7, 77.1, 73.2, 65.2, 51.8, 26.2, 25.1, 17.79, 17.76, 12.2.

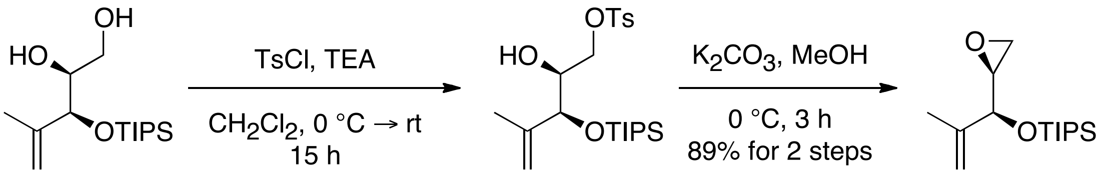


502 **919** **920** **503**

Preparation of tertiary alcohol **919**:[31,84] Commercial methylmagnesium iodide 3.0 M in THF (53.7 ml, 161 mmol) was diluted with ether (120 mL) in a three-necked round-bottomed flask, equipped with a reflux condenser, and a solution of **502** (17.43 g, 50.3 mmol) in ether (120 mL) was added via cannula at room temperature. Additional ether (40 mL) was used for rinsing. The resulting solution was heated in an oil bath at 45 °C for 40 minutes, cooled down to room temperature, and quenched with water. The resultant slurry was treated with saturated aqueous potassium sodium tartrate solution and vigorously stirred until all solids were dissolved (ca. 30 minutes). The phases were separated, more saturated aqueous potassium sodium tartrate solution was added to the aqueous layer to dissolve the solids, and the white aqueous phase was extracted four times with ether. Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting material was used in the following step without further purification.

Preparation of 1,1-disubstituted olefin **920**:[31,84] A solution of **919** (crude from previous step, assumed to be 17.43 g, 50.3 mmol) in pyridine (400 mL, no purification or drying needed) was cooled to 0 °C by an ice/water bath. To this solution was added $SOCl_2$ (7.42 ml, 102 mmol) dropwise via syringe and the mixture quickly turned yellow-orange. The reaction was then warmed to room temperature and stirred for 75 min. Upon completion, the reaction was quenched with half-saturated aqueous Na_2CO_3 at 0 °C and diluted with ether. The layers were separated and the aqueous layer was extracted with ether. Combined organic layers were washed with water, followed by 5% (w/v) aqueous $CuSO_4$ until the aqueous phase was no longer purple, and then water before being dried over $MgSO_4$. After concentration *in vacuo*, the crude material was subjected to the following step without further purification.

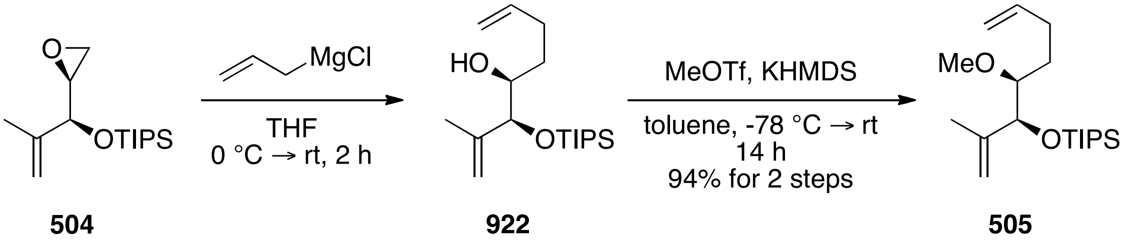
Preparation of diol **503**:[31,84] To a stirred solution of **920** (crude from previous step, assumed to be 16.53 g, 50.3 mmol) in methanol (300 mL, used as received) at 0 °C was added TFA (100 ml, 1295 mmol) dropwise. After 5 minutes at 0 °C, the reaction was stirred at room temperature for 1 h open to air, then saturated aqueous Na_2CO_3 solution was added until no more gas evolved. The resulting mixture was partitioned between half-saturated aqueous $NaHCO_3$ and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. Combined organic layers were dried over $MgSO_4$ and concentrated. The crude diol was purified by flash silica gel chromatography (hexanes/EtOAc, 3:2) to provide **503** (9.87 g, 34.2 mmol, 68% yield for three steps) as clear oil. $R_f = 0.5$ (3:2 hexanes/EtOAc); $[\alpha]^{20}_{D}$ −11.4 (*c* 2.33, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98 (m, 1 H), 4.92 (m, 1 H), 4.19 (d, *J* = 6.5 Hz, 1 H), 3.65–3.59 (m, 2 H), 3.49 (m, 1 H), ~2.65 (br, 1 H), ~2.05 (br, 1 H), 1.73 (dd, *J* = 1.5, 1.0 Hz, 3 H), 1.10–1.04 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 114.4, 77.6, 73.4, 63.0, 18.04, 18.00, 17.6, 12.4.



503 **921** **504**

Preparation of tosylate **921**:[31,84] To a solution of diol **503** (9.85 g, 34.1 mmol) in CH_2Cl_2 (115 mL) at 0 °C (ice/water bath) was added Et_3N (46.1 mL, 328 mmol, ~10 equiv) followed by TsCl (7.26 g, 38.1 mmol). The reaction mixture was left to slowly reach room temperature overnight and quenched with saturated $NaHCO_3$. After dilution with CH_2Cl_2, the layers were separated and the aqueous phase was extracted with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4. After concentration *in vacuo*, the crude material was immediately subjected to the following step without further purification.

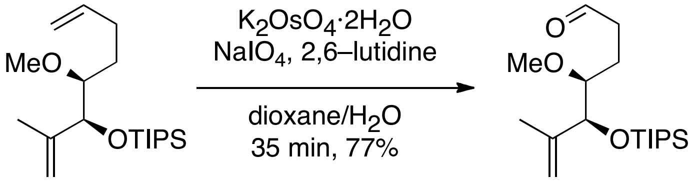
Preparation of epoxide **504**:[31,84] To a stirred solution of **921** (crude from previous step, assumed to be 15.11 g, 34.1 mmol) in commercial MeOH (171 mL) at 0 °C was added K_2CO_3 (8.02 g, 58.0 mmol) in one portion. The suspension was stirred at 0 °C for 2 h and poured into half-saturated aqueous NH_4Cl before being extracted three times with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (hexanes/CH_2Cl_2, 1.5:1) afforded **504** (8.26 g, 30.5 mmol, 89% yield for two steps) as a colorless oil. $R_f = 0.5$ (1.5:1 hexanes/CH_2Cl_2); $[\alpha]^{20}_{D}$ −8.6 (*c* 1.17, EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ 4.98 (m, 1 H), 4.86 (m, 1 H), 3.79 (d, *J* = 6.5 Hz, 1 H), 3.00 (ddd, *J* = 6.5, 4.0, 3.0 Hz, 1 H), 2.76 (dd, *J* = 5.0, 4.0 Hz, 1 H), 2.57 (dd, *J* = 5.0, 3.0 Hz, 1 H), 1.77 (m, 3 H), 1.10–1.02 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 112.2, 78.6, 56.0, 44.9, 18.7, 17.95, 17.90, 12.3.



Preparation of epoxide-opening product **922**:[84] To a stirred solution of **504** (8.25 g, 30.5 mmol) in THF (153 mL) at 0 °C was added allylmagnesium chloride (2.0 M in THF, 45.8 ml, 92 mmol). Upon finished addition the ice bath was removed. After 2h the reaction was quenched with water, then stirred with saturated aqueous Na_2CO_3 solution until a white slurry was formed, which was diluted with ether. The layers were separated and the aqueous layer was extracted with ether. Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dried *in vacuo* and used in the following step without further purification.

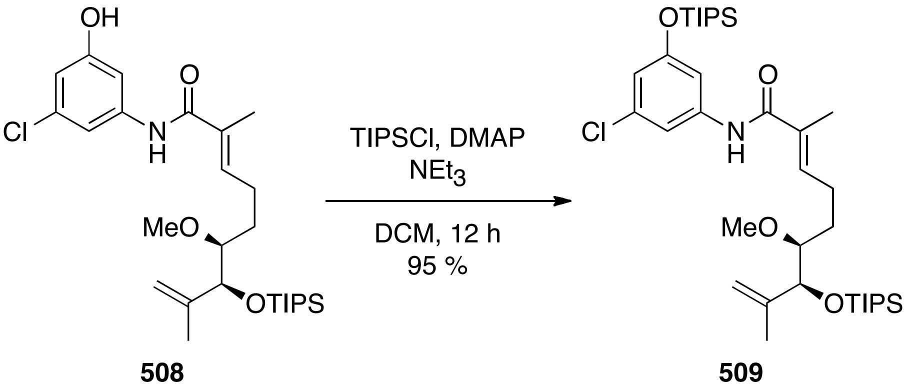
Preparation of diene **505**:[84] To a stirred solution of **922** (crude from previous step, assumed to be 9.53 g, 30.5 mmol) in toluene (191 mL) at −78 °C was added KHMDS (0.5 M in toluene, 183 mL, 92 mmol) dropwise via cannula. After 30 minutes, MeOTf (16.8 mL, 153 mmol) was added dropwise. The reaction mixture was left to slowly reach room temperature and quenched after 14 h with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with ether. Combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash silica gel chromatography (hexanes/CH_2Cl_2, 5:1) to provide **505** (9.34 g, 28.6 mmol, 94% yield for two steps) as clear oil. $R_f = 0.30$ (hexanes/CH_2Cl_2, 5:1);

$[\alpha]^{20}_{D}$ −11.1 (*c* 1.17, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddd, *J* = 17.0, 13.0, 6.5 Hz, 1 H), 5.01–4.86 (m, 4 H), 4.26 (d, *J* = 6.0 Hz, 1 H), 3.44 (s, 1 H), 3.16 (ddd, *J* = 9.0, 6.0, 4.0 Hz, 1 H), 2.20 (m, 1 H), 2.07 (m, 1 H), 1.72 (s, 3 H), 1.56 (m, 1H), 1.29 (m, 1 H), 1.10–1.00 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 138.9, 114.5, 112.8, 83.9, 77.2, 58.9, 30.1, 29.6, 19.0, 18.09, 18.05, 12.5.



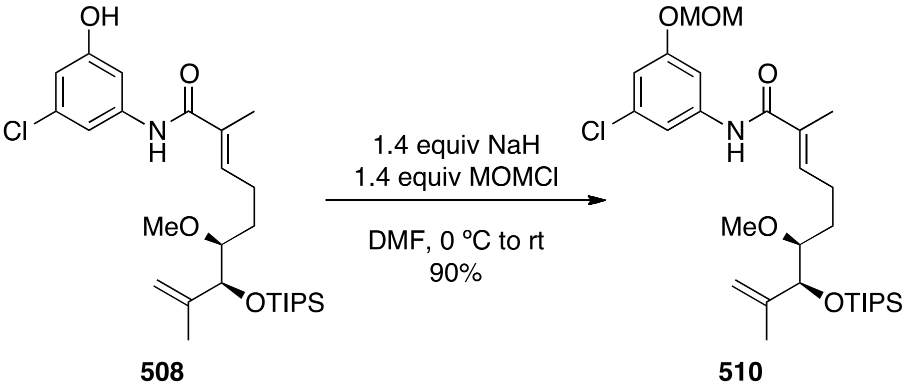
505 **506**

Preparation of aldehyde **506**[31,84]: To a vigorously stirring suspension of **505** (709.2 mg, 2.172 mmol), $NaIO_4$ (1.86 g, 8.69 mmol), and 2,6-lutidine (506 μL, 4.34 mmol) in dioxane (3.3 mL) in a cold water bath (10–15°C) was added a solution of potassium osmate dihydrate (8.00 mg, 0.022 mmol) in water (1.1 mL) dropwise forming a white slurry. The reaction mixture was stirred allowing it to warm to room temperature until TLC eluting with hexanes/DCM (5:1) showed full conversion; in this specific run, after 35 minutes. The reaction mixture was diluted with water and CH_2Cl_2, the phases were separated and the aqueous layer was extracted with CH_2Cl_2. Combined organic layers were dried over $MgSO_4$ and concentrated. The crude material was subjected to flash silica gel chromatography (hexanes/EtOAc, 15:1) to provide **506** (549.1 mg, 1.671 mmol, 77% yield) as light yellow oil. R_f = 0.30 (hexanes/EtOAc, 9:1); $[\alpha]^{20}_{D}$ −22.8 (*c* 1.17, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (t, *J* = 2.0 Hz, 1H), 4.95 (m, 1 H), 4.90 (m, 1 H), 4.27 (d, *J* = 6.0 Hz, 1H), 3.38 (s, 3 H), 3.16 ddd, *J* = 9.0, 6.0, 3.25 Hz, 1 H), 2.45 (m, 2 H), 1.87 (m, 1 H), 1.73 (s, 3 H), 1.57 (m, 1 H), 1.09–1.01 (m, 21 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 202.6, 144.8, 113.2, 83.8, 76.9, 58.7, 40.6, 23.1, 19.0, 18.1, 18.0, 12.4; HRMS (ESI): *m/z* calculated for $C_{18}H_{35}O_3Si$ $[M+H]^+$ 329.2512, found 329.2510.



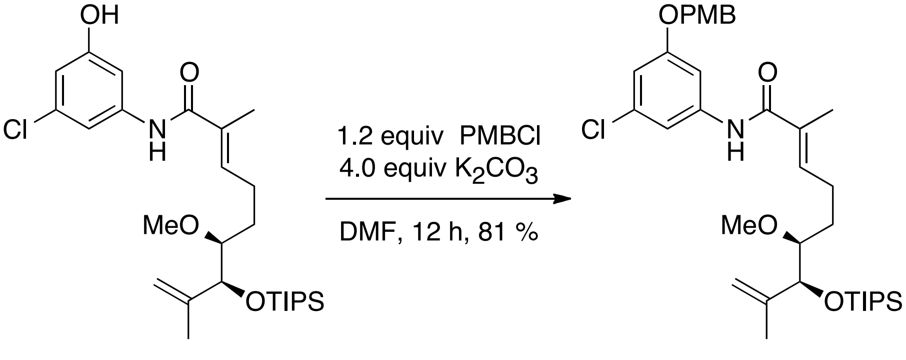
Preparation of TIPS-protected amidochlorophenol **509**:[31] To a solution of **508** (0.5g, 0.980 mmol) and 4-(dimethylamino)pyridine (0.024 g, 0.196 mmol) in dichloromethane (1.6 mL) were successively added triethylamine (0.152 mL, 1.078 mmol) and triisopropylsilyl chloride (0.208 mL, 0.980 mmol) at 0 °C and the mixture was stirred at room temperature for 12 hours. The reaction was quenched with water, extracted with ethyl acetate, dried over MgSO$_4$, and concentrated *in vacuo*. The product was purified by flash chromatography eluting with hexanes/ethyl acetate (9:1) affording **509** (0.620 g, 0.931 mmol, 95% yield) initially as a viscous oil that crystallized after few days forming waxy white needles. mp 52–53 °C. R_f = 0.35 (9:1 hexanes/ethyl acetate); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.27 (br, 1 H), 7.14 (t, *J* = 2 Hz, 1 H), 7.07 (t, *J* = 1.5 Hz, 1 H), 6.60 (t, *J* = 2 Hz, 1 H), 6.34 (m, 1 H), 4.95 (s, 1 H), 4.89 (s, 1 H), 4.31 (d, *J* = 6 Hz, 1 H), 3.44 (s, 3 H), 3.18 (m, 1 H), 2.27 (m, 2 H), 1.91 (s, 3 H), 1.73 (s, 3 H), 1.67 (m, 1 H), 1.33 (m, 1 H), 1.25 (m, 3 H), 1.10–1.03 (m, 39 H); ^{13}C NMR (62.8 MHz, CDCl$_3$): δ

167.5, 157.2, 144.9, 139.8, 136.9, 134.6, 131.9, 115.9, 112.9, 112.5, 109.7, 84.3, 76.2, 58.7, 29.0, 25.0, 19.2, 18.07, 18.04, 17.9, 12.8, 12.6, 12.4; HRMS (ESI): *m/z* calculated for $C_{36}H_{65}ClNO_4Si_2$ $[M+H]^+$ 666.4135, found 666.4141.



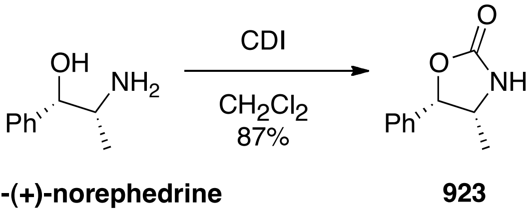
Preparation of *MOM-protected amidochlorophenol* **510**: Sodium hydride (30.7 mg, 0.768 mmol) (60% dispersion in mineral oil) was rinsed with pentane under nitrogen atmosphere and the solvent extracted via cannula several times. To the solid was added DMF (0.5 mL) and the resulting suspension cooled down to 0 °C. A solution of **508** (280 mg, 0.549 mmol) in DMF (3.5 mL) was added and the resulting solution stirred at 0 °C for some minutes. To the solution was added chloromethyl methyl ether (58.4 µL, 0.768 mmol) causing the immediate evolution of gas, the solution was allowed to warm to room temperature and quenched with water (1.4 mL). The solution was extracted with ether, dried over $MgSO_4$ and concentrated *in vacuo*. Absolute ethanol was added and the resulting solution pumped down several times. The crude material was purified by column chromatography eluting with hexanes/ethyl acetate (7:1) to afford **510** (273mg, 0.493 mmol, 90% yield) as a slightly yellowish oil. $R_f = 0.3$ (7:1 hexanes/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (br, 1 H), 7.26 (t, *J* = 2 Hz, 1 H), 7.17 (t, *J* = 2 Hz, 1 H), 6.78 (t, *J* = 2 Hz, 1 H), 6.35 (m, 1 H), 5.13 (s, 2 H), 4.95 (s, 1 H), 4.90 (s, 1 H), 4.31 (d, *J* = 5.5

Hz, 1 H) , 3.451 (s, 3 H) , 3.446 (s, 3 H), 3.18 (m, 1 H), 2.29 (m, 2 H), 1.91 (s, 3 H), 1.73 (s, 3 H), 1.67 (m, 1 H), 1.35 (m, 1 H), 1.12-1.00 (m, 21 H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 167.5, 158.2, 144.9, 139.8, 137.1, 135.1, 131.8, 113.5, 112.9, 112.5, 106.0, 94.5, 76.3, 58.8, 56.2, 29.0, 25.1, 19.2, 18.08, 18.04, 12.7, 12.4.

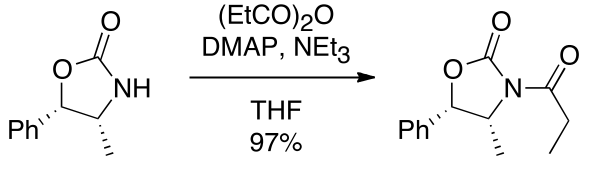


508 **511**

Preparation of PMB-protected amidochlorophenol **511**: To a suspension of **508** (460.6 mg, 0.903 mmol) and K_2CO_3 (499 mg, 3.61 mmol) in DMF (2 mL) was added 4-methoxybenzyl chloride (0.148 mL, 170 mg, 1.083 mmol) dropwise and the resulting mixture was stirred at room temperature. After 12 hours, TLC (hexanes/EtOAc 4:1) confirmed full consumption of the starting material. The reaction was quenched with brine and extracted three times with ethyl acetate. Combined organic layers were dried over $MgSO_4$ and concentrated. The excess of DMF was removed by adding small portions of ethanol and pumping down several times. Column chromatography eluting with hexanes/EtOAC (9:1 → 4:1) afforded PMB-protected chloroamidophenol **511** (461.0 mg, 0.731 mmol, 81% yield) as a white solid. R_f = 0.6 (1:1 hexanes/ether); mp 93–94 °C; $[\alpha]^{20}_{D}$ −8.3 (*c* = 0.33, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1 H), 7.31 (d, *J* = 8.7 Hz, 2 H), 7.29 (t, *J* = 2.1 Hz, 1 H), 7.07 (t, *J* = 1.8 Hz, 1 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 6.70 (t, *J* = 2.1 Hz, 1 H), 6.35 (qt, *J* = 1.3, 7.7 Hz, 1 H), 4.95–4.89 (m, 4 H), 4.31, (d, J = 5.6 Hz, 1 H), 3.80 (s, 3 H), 3.45 (s, 3 H), 3.18 (ddd, J = 8.8, 5.7, 2.8 Hz, 1 H), 2.34–2.21 (m, 1 H), 1.91 (d, J = 1.0 Hz, 3 H), 1.73 (s, 3 H), 1.67 (m, 1 H), 1.36 (m, 1 H), 1.10–1.03 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 159.9, 159.6, 144.9, 139.9, 137.1, 135.0, 131.8, 129.3, 128.4, 114.0, 113.0, 112.3, 111.4, 104.7, 84.3, 76.3, 70.1, 58.8, 55.3, 29.0, 25.1, 19.2, 18.1, 18.0, 12.7, 12.4; IR (neat): 3407, 2963, 2867, 1649, 1632, 1591, 1547, 1452, 1379, 1261, 1169, 1115, 1039, 801 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{35}H_{53}ClNO_5Si$ $[M+H]^+$ 630.3382, found 630.3408.

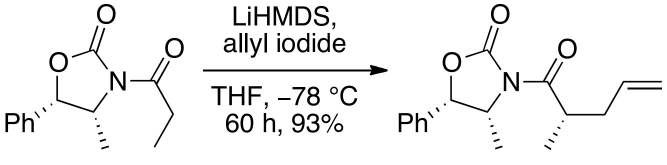


Preparation of (4S,5R)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (**923**[90a]): To a solution of (1*S*,2*R*)-(+)-norephedrine (20.0 g, 132.2 mmol) in CH_2Cl_2 (420 mL) was added carbonyl diimidazole (23.6 g, 145.6 mmol) in one portion and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated and the crude material was directly subjected to column chromatography eluting with hexanes/EtOAc (3:4). Concentration *in vacuo* afforded 20.4 g (87% yield) of **701** as white powder and colorless crystals. R_f = 0.36 (3:4 hexanes/EtOAc); mp 116–117 °C; $[\alpha]^{20}_D$ +169.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.20 (m, 5 H), 6.1 (br, 1 H), 5.73 (d, J = 7.5 Hz, 1 H), 4.23 (dq, J = 7.5, 6.5 Hz, 1 H), 0.83 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 134.9, 128.48, 128.45, 126.0, 81.0, 52.4, 17.5.



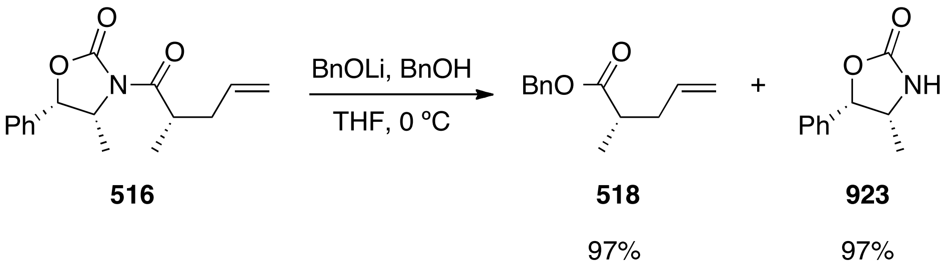
923 **517**

Preparation of Evans enolate precursor **517**[90b]: To a flask containing **923** (14.28 g, 80.6 mmol) in THF (30 mL) was added DMAP (0.25 g, 2.0 mmol) and triethylamine (14 mL, 108.0 mmol). The mixture was cooled down on an ice/water bath and propionic anhydride (21 mL, 222.5 mmol) was added dropwise. After 4 h of stirring at room temperature, the reaction mixture was poured onto half-saturated aqueous NaHCO$_3$ (100 mL), stirred for 1 h, and extracted with ethyl acetate. Combined organic extracts were washed with water and brine, and dried over MgSO$_4$. After evaporation of the solvent, the crude material was purified by column chromatography eluting with hexanes/EtOAc (5:1). Concentration under high vacuum, under vigorous magnetic stirring, afforded 18.40 g (97%) of **517** a slightly yellowish oil. $R_f = 0.35$ (5:1 hexanes/EtOAc); $[\alpha]^{20}_{D}$ +45.6° (*c* 1.842, CH$_2$Cl$_2$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.50–7.25 (m, 5 H), 5.68 (d, *J* = 6.6 Hz, 1 H), 4.77 (qd, *J* = 7.5, 6.6 Hz, 1 H), 3.01 and 2.93 (q of ABq, $^3J = 7.3$ Hz, $J_{AB} = 17.8$ Hz, 2 H), 1.19 (t, *J* = 7.3 Hz, 3 H), 0.91 (d, *J* = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.8, 153.1, 133.3, 128.7, 125.6, 79.0, 54.7, 29.2, 14.5, 8.3.

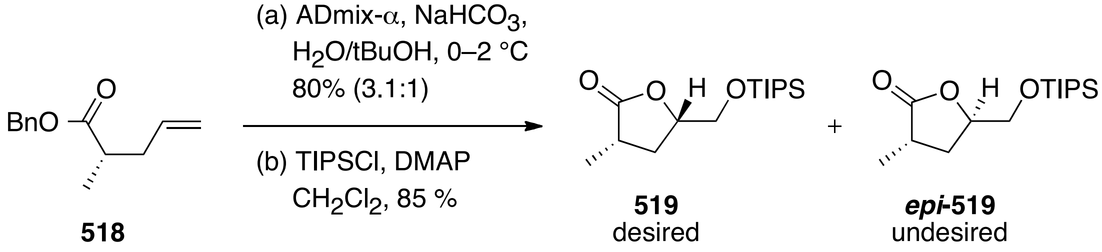


517 **516**

Preparation of asymmetric allylation product **516**: In a vacuum/flame-dried 1L round-bottomed flask, lithium bis(trimethylsilyl)amide 1M solution in hexanes (93 mL, 93 mmol) was diluted with THF (77 mL) and cooled down to −78 °C. After 30 minutes, a solution of Evans enolate precursor **517** (18.9 g, 81 mmol) in THF (170 mL) was added dropwise via cannula from a pear-shaped flask, which was rinsed twice using more THF (85 mL). After 45 minutes of stirring, a solution of allyl iodide (11.11 mL, 122 mmol) in THF (85 mL) was added slowly (0.5 mL/min) and the resulting mixture was stirred at −78 °C for 60 h or until the starting material (**517**) was completely consumed as determined by TLC (5:1 hexanes/EtOAc). The reaction was quenched with saturated aqueous $NaHCO_3$ (~500 mL), extracted with ether (3 × 600 mL), dried over $MgSO_4$, and concentrated. ^{1}H NMR of crude material showed a clean single diastereomer. The crude was subjected to column chromatography eluting with hexanes/EtOAc 5:1 to afford **516** (20.65 g, 76 mmol, 93% yield) as a white solid after removal of solvents under high vacuum. R_f = 0.47 (4:1 hexanes/EtOAc); mp 65–66 °C (lit[83] 69–70 °C); $[\alpha]^{20}_D$ +44.8° (*c* 1.167, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.32 (m, 3 H), 7.31–7.26 (m, 2 H), 5.78 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1 H), 5.64 (d, *J* = 7.5 Hz, 1 H), 5.02 (m, 2 H), 4.77 (dq, *J* = 7.5, 6.5 Hz, 1 H), 3.86 (sext, *J* = 6.5 Hz, 1 H), 2.47 (m, 1 H), 2.20 (m, 1 H), 1.17 (d, *J* = 6.5, 3 H), 0.84 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 152.7, 135.2, 133.4, 128.71, 128.66, 125.6, 117.1, 78.7, 54.8, 37.9, 37.1, 16.5, 14.6.

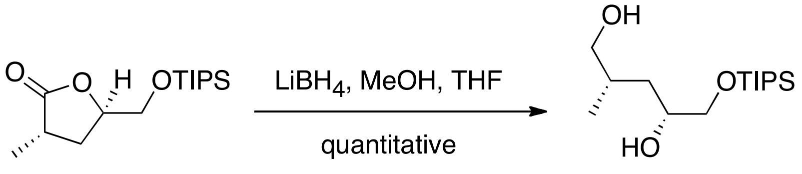


Preparation of benzyl ester **518**[91]: To a vacuum/flame-dried 2L round-bottomed flask containing benzyl alcohol (14.93 mL, 144 mmol) in THF (315 mL) at 0 °C was added *n*-butyllithium 1.6M in hexanes (59.0 mL, 94 mmol) dropwise. 30 minutes later, a solution of allylation product **518** (20.65 g, 76 mmol) in THF (63.0 mL) was added slowly, still at 0 °C. After 30 minutes, TLC (hexanes/EtOAc 3:1) showed that the starting material was fully consumed. The reaction was quenched with saturated aqueous NH_4Cl (450 mL), extracted three times with diethyl ether, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with hexanes/EtOAc (19:1 → 1:4) to afford **518** (14.97 g, 73.3 mmol, 97% yield) as a colorless liquid and **923** (12.99 g, 73.3 mmol, 97% recovered chiral auxiliary). R_f = 0.45 (19:1 hexanes/EtOAc); $[\alpha]^{20}_{D}$ +2.9° (*c* 1.667, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5 H), 5.76 (dddd, *J* = 17.1, 10.3, 7.0, 7.0 Hz, 1 H), 5.14 (s, 2 H), 5.05 (m, 2 H), 2.61 (sextet, *J* = 7.0 Hz, 1 H), 2.46 (m, 1 H), 2.23 (m, 1 H), 0.91 (d, *J* = 7.0, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 136.2, 135.4, 128.5, 128.1, 128.1, 116.9, 66.1, 39.3, 37.8, 16.5.



Preparation of lactones **519** *and* ***epi*-519**:[91] To a 3L round-bottomed flask containing a solution of **518** (36.5 g, 179 mmol) in water (890 mL) and tBuOH (890 mL) were sequentially added sodium bicarbonate ($NaHCO_3$, 60.0 g, 715 mmol), $(DHQ)_2PHAL$ (1.949 g, 2.502 mmol), potassium ferricyanide ($K_3Fe(CN)_6$, 247 g, 750 mmol), and potassium carbonate (K_3CO_3, 104 g, 750 mmol), and a mechanical stirrer was introduced in the flask. Once the mixture was well stirred, the 3L flask was immersed into an acetone bath (at 0 °C) equipped with a CryoCool chiller. After 30 minutes of stirring at 0–2 °C, potassium osmate dihydrate ($K_2OsO_2(OH)_4$, 0.369 g, 1.001 mmol) was added in one portion. The progress of the reaction was monitored by TLC (hexanes/EtOAc 3:1) of mini-worked-up samples. After 36 h, when the starting material (**516**) appeared to be completely consumed as determined by TLC, the reaction was quenched with sodium sulfite (Na_2SO_3, 376 g) and stirred for 1 h at room temperature. The resulting mixture was extracted with ethyl acetate (3 × 1.7 L), and the combined organic layers were washed with a small amount of brine (~100 mL). In order to recycle the chiral ligand $(DHQ)_2PHAL$, the organic extract was washed with 100 mL of 3% aqueous H_2SO_4 saturated with K_2SO_4. As precipitate formed, small amounts of water were added to dissolve the salts. The aqueous layer was separated and another 60 mL of saturated aqueous K_2SO_4 was used to wash the organic phase. The aqueous extract, containing $(DHQ)_2PHAL$, was stored for use in future reactions. The organic solution (more than 5 L) was dried over $MgSO_4$ and concentrated *in vacuo*. A ratio 3.1:1 of desired/undesired diastereomers was calculated by ^1H NMR. The crude material was subjected to column chromatography (hexanes/EtOAC 1:19 → 4:3) to provide recovered starting material **518** (1.12 g, 5.5 mmol, 3%) and the mixture of five-membered lactones contaminated with ~30% BnOH. The yield for this step was calculated to be 18.60 g (143 mmol, 80% yield). After drying, the impure mixture of lactones was dissolved in dichloromethane (600 mL) together with DMAP (98 g, 804 mmol) in a 2L round-bottomed flask. Triisopropylsilyl chloride (89 mL, 420 mmol) was added via syringe and the resulting solution was stirred at room temperature for 5 hours, when TLC of a mini-worked-up sample, eluting with EtOAc/hexanes (4:3), confirmed the consumption of the starting primary alcohols. The reaction was quenched with saturated aqueous $NaHCO_3$ (200 mL), extracted with CH_2Cl_2 (3 × 600 mL), dried over sodium sulfate, and concentrated *in vacuo*. A sequence of two column chromatographies eluting with hexanes/diethyl ether (9:1 → 2:1), afforded the desired TIPS-protected lactone **519** (32.84 g, 115 mmol, 64.2% yield) and its isomer ***epi*-519** (10.77 g, 37.6 mmol, 21.0% yield). (**519**): R_f = 0.51 (6:1 hexanes/EtOAc); $[\alpha]^{20}_{D}$ +5.7° (*c* 3.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.42 (ddt, *J* = 10.0, 6.0, 4.0 Hz, 1 H), 3.91 and 3.79 (d of ABq, ^3J = 4.0 Hz, J_{AB} = 11.0 Hz, 2 H), 2.67 (m, 1 H), 2.37 (ddd, *J* = 12.5, 9.0, 6.0 Hz, 1 H), 1.85 (dt, *J* = 10.0, 12.0 Hz, 1 H), 1.26 (d, *J* = 7.5 Hz, 3 H), 1.09–1.02 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.4, 78.3, 64.3, 35.4, 32.0, 17.90, 17.89, 15.4, 11.9. (***epi*-519**): R_f = 0.58 (6:1 hexanes/EtOAc); $[\alpha]^{20}_{D}$ −15.6° (*c* 3.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.51 (dddd, *J* = 9.0, 3.0, 3.0, 3.0 Hz, 1 H), 3.91 and 3.74 (d of ABq, ^3J = 3.5 and 3.0 Hz, J_{AB} = 11.0 Hz, 2 H), 2.80 (tq, *J* = 9.5, 7.5 Hz, 1 H), 2.43 (ddd, *J* = 12.5, 9.5, 3.0 Hz, 1 H), 1.93 (dt, *J* = 12.5, 9.0 Hz, 1

H), 1.24 (d, $J = 7.5$ Hz, 3 H), 1.07–1.01 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 77.7, 65.3, 34.2, 32.2, 17.91, 17.88, 16.4, 11.9.

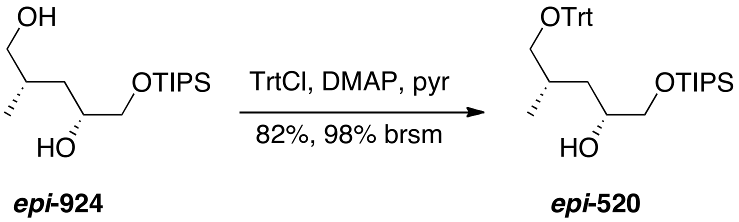


***epi*-519**
undesired

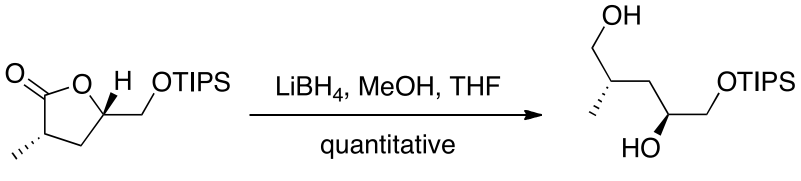
***epi*-924**

*Preparation of monoprotected triol **epi-924***. To a solution of ***epi*-519** (15.01 g, 52.4 mmol) in THF (260 mL) in a 2L round-bottomed flask connected to a nitrogen line was added MeOH (2.5 mL, 61.8 mmol). This solution was cooled to 0 °C and stirred for 10 minutes before $LiBH_4$ 2 M in THF (32.7 mL, 65.5 mmol) was added dropwise. Bubbling started after the first 10 mL was added. The solution was stirred 1 h at 0 °C and 2 h at room temperature. Full consumption of the starting material was confirmed by TLC (hexanes/ether 4:1). The reaction was carefully quenched with saturated aqueous NH_4Cl added in portions until no bubbling was observed. Then, water (85 mL) and glycerol (65 mL) were added and the solution was stirred at room temperature overnight. The resulting homogeneous solution was mixed with ethyl acetate (450 mL) and brine (150 mL) in a separatory funnel. The phases were separated and the aqueous layer was extracted three times with ethyl acetate. Combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Crude material contained ring-opening product ***epi*-924** (15.22 g, 52.4 mmol, 100% yield), pure enough to be directly used in the next reaction without further purification. $[\alpha]^{20}_{D}$ +9.6º (*c* 1.16, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (m, 1 H), 3.45–3.80 (2 overlapping d of ABq, can be viewed as 4 dd at 3.65 (dd, $J = 9.6, 3.6$ Hz, 1 H), 3.53 (dd, $J = 10.8, 4.8$ Hz, 1 H), 3.49 (dd, $J = 10.8, 6.5$ Hz, 1 H), and 3.48 (dd, $J = 9.6, 8.3$ Hz, 1 H)), 2.91

(br, 1 H), 2.64 (br, 1 H), 1.90 (m, 1 H), 1.45 (m, 2 H), 1.13–0.98 (m, 21 H), 0.94 (d, $J = 7$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.3, 67.7, 67.6, 36.5, 32.5, 17.9, 17.0, 11.9; HRMS (ESI): *m/z* calculated for $C_{15}H_{35}O_3Si$ $[M+H]^+$ 291.2355, found 291.2359.



Preparation of diprotected triol ***epi*-520**. A solution of trityl chloride (16.07 g, 57.6 mmol) and DMAP (160 mg, 1.310 mmol) in pyridine (50 mL) was added dropwise via addition funnel to a 1L round-bottomed flask containing crude ***epi*-924** (15.22 g, 52.4 mmol) in pyridine (40 mL) and the resulting mixture was stirred at room temperature for 3.5 days. The reaction was quenched with water (200 mL) and extracted with dichloromethane (5 × 0.2 L). Combined organic layers were repeatedly washed with aqueous $CuSO_4$ (5% w/v) (until the washings were light blue) and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was subjected to column chromatography eluting with hexanes/EtOAc (40:1 → 9:1 → 1:1) to afford ***epi*-520** as a colorless oil (22.89 g, 43.0 mmol, 82% yield) and ***epi*-924** (2.42 g, 8.33 mmol, 16% recovered starting material). R_f (***epi*-520**) = 0.3 (5:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +11.5 (*c* 1.275, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (m, 6 H), 7.27 (m, 6 H), 7.21 (m, 3 H), 3.66–3.58(m, 2 H), 3.41 (m, 1 H), 3.01 and 2.92 (d of ABq, $^3J = 5.6$ and 5.6 Hz, $J_{AB} = 8.8$ Hz, 2 H), 2.53 (s, 1 H), 1.91 (m, 1 H), 1.52 (m, 1 H), 1.31 (m, 1 H), 1.13–0.98 (m, 24 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 128.7, 127.7, 126.8, 86.2, 70.2, 67.9, 67.7, 37.0, 30.8, 18.4, 18.0, 11.9; IR (neat): 3390, 2943, 2866, 1490, 1462, 1449, 1384, 1100, 1068 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{34}H_{48}O_{3}SiLi$ [M+Li]$^{+}$ 539.3533, found 539.3529.

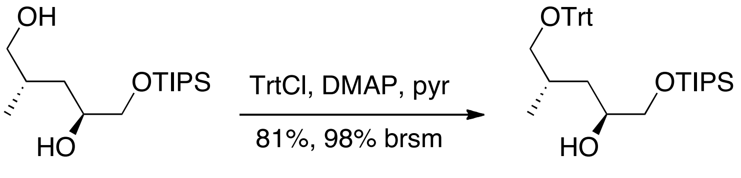


519
desired

924

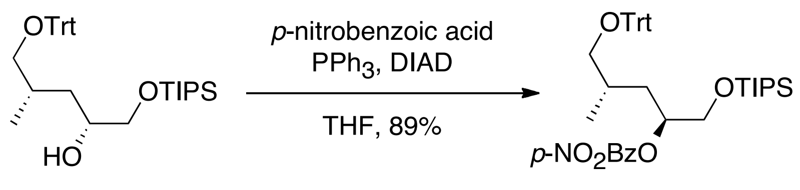
Preparation of monoprotected triol **924**. To a solution of **519** (22.79 g, 80 mmol) in THF (0.4 L) in a 2L round-bottomed flask connected to a nitrogen line was added MeOH (3.7 mL, 92 mmol). This solution was cooled to 0 °C and stirred for 10 minutes before $LiBH_4$ 2 M in THF (50 mL, 100 mmol) was added dropwise. Bubbling started after the first 15 mL was added. The solution was stirred 1 h at 0 °C and 2 h at room temperature. Full consumption of the starting material was confirmed by TLC (hexanes/ether 4:1). The reaction was carefully quenched with saturated aqueous NH_4Cl added in portions until no bubbling was observed. Then, water (130 mL) and glycerol (100 mL) were added and the solution was stirred at room temperature overnight. The resulting homogeneous solution was mixed with ethyl acetate (600 mL) and brine (200 mL) in a separatory funnel. The phases were separated and the aqueous layer was extracted three times with ethyl acetate. Combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Crude material contained ring-opening product **924** (23.11 g, 80 mmol, 100% yield), pure enough to be directly used in the next reaction without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (m, 1 H), 3.66–3.37 (m, 4 H), 3.16 (s, 2 H), 1.88–1.78 (m, 1 H), 1.39–1.29 (m, 2

H), 1.08–1.02 (m, 21 H), 0.90 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.2, 68.7, 67.8, 38.2, 34.6, 18.1, 17.9, 11.9.



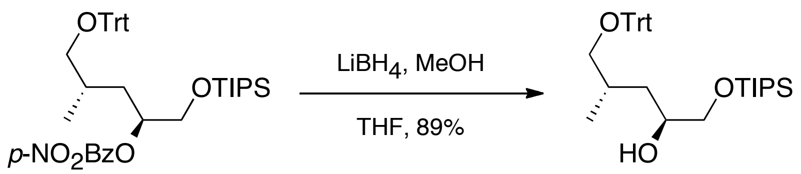
924 **520**

Preparation of diprotected triol **520**. A solution of trityl chloride (24.39 g, 88 mmol) and DMAP (250 mg, 2.044 mmol) in pyridine (80 mL) was added dropwise via addition funnel to a 1L round-bottomed flask containing crude **924** (23.11 g, 80 mmol) in pyridine (60 mL) and the resulting mixture was stirred at room temperature for 3.5 days. The reaction was quenched with water (250 mL) and extracted with dichloromethane (5 × 0.25 L). Combined organic layers were repeatedly washed with aqueous $CuSO_4$ (5% w/v) (until the washings were light blue) and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was subjected to column chromatography eluting with hexanes/EtOAc (40:1 → 9:1 → 1:1) to afford **520** as a colorless oil (34.19 g, 64.2 mmol, 81% yield) and **924** (3.92 g, 13.49 mmol, 17% recovered starting material). R_f (**520**) = 0.43 (9:1 hexanes/EtOAc); $[\alpha]^{20}_{D}$ −12.4 (*c* 2.17, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.45 (m, 6 H), 7.32–7.22 (m, 9 H), 3.78–3.72 (m, 1 H), 3.68 (dd, *J* = 9.5, 4.0 Hz, 1 H), 3.51 (dd, *J* = 9.5, 7.5 Hz, 1 H), 3.01–2.95 (m, 2 H), 2.57 (d, *J* = 3.5 Hz, 1 H), 2.10–2.03 (m, 1 H), 1.59 (ddd, *J* = 13.5, 9.5, 5.0 Hz, 1 H), 1.23 (ddd, *J* = 13.5, 9.0, 3.5 Hz, 1 H), 1.13–1.07 (m, 21 H), 1.01 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 128.7, 127.7, 126.8, 86.2, 69.7, 69.0, 68.0, 37.2, 30.5, 18.0, 17.2, 11.9; HRMS (ESI): *m/z* calculated for $C_{34}H_{48}O_3SiLi$ $[M+Li]^+$ 539.3533, found 539.3528.



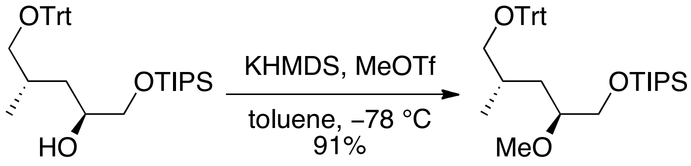
***epi*-520** **925**

Preparation of Mitsunobu product p-nitrobenzoate **925**. To a well stirred mixture of ***epi*-520** (26.14 g, 49.1 mmol), *p*-nitrobenzoic acid (32.8 g, 196 mmol), and triphenylphosphine (51.5 g, 196 mmol) in THF (0.5 L) at 0 °C was added diisopropyl azodicarboxylate (38.2 mL, 196 mmol) dropwise via syringe and the resulting solution was stirred at room temperature. After 12 h, full consumption of the starting material was confirmed by TLC (hexanes/EtOAc 20:1). The reaction mixture was concentrated *in vacuo*, the bright orange residue was redissolved in ether (300 mL) and to it was added petroleum ether (150 mL) in portions. The white precipitate was filtered out and the filtrate was concentrated and dried under high vacuum. The crude material was subjected to column chromatography eluting with hexanes/EtOAc (99:1 → 25:1) to afford **925** (29.67 g, 43.5 mmol, 89% yield) as a yellowish oil that became a waxy solid upon standing. R_f = 0.4 (25:1 hexanes/EtOAc); mp 53–56 ºC (wax); $[\alpha]^{20}_{D}$ −3.9 (*c* 1.07, pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.9 Hz, 2 H), 8.16 (d, *J* = 8.9 Hz, 2 H), 7.40 (m, 6 H), 7.24 (m, 6 H), 7.20 (m, 3 H), 5.30 (m, 1 H), 3.83 (apparent d, *J* = 5.0 Hz, 2 H), 2.96 (apparent d, *J* = 6.0 Hz, 2 H), 2.00 (ddd, *J* = 14.0, 9.9, 4.0 Hz, 1 H), 1.81 (m, 1 H), 1.53 (m, 1 H), 1.09–0.93 (m, 24 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 150.5, 144.3, 136.0, 130.7, 128.7, 127.7, 127.6, 126.8, 123.4, 86.3, 74.7, 74.6, 86.6, 65.1, 34.9, 30.6, 17.9, 17.1, 11.9; HRMS (ESI): *m/z* calculated for $C_{41}H_{51}NO_6SiNa$ $[M+Na]^+$ 704.3383, found 704.3380.



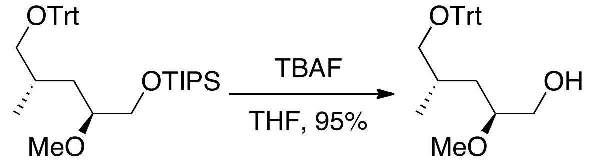
925 **520**

Preparation of diprotected triol **520** *from nitrobenzoate* **925**: To a solution of **925** (29.67 g, 43.5 mmol) in THF (220 mL) and methanol (2.2 mL, 54.4 mmol) at 0 °C was added $LiBH_4$ 2M in THF (27.2 mL, 54.4 mmol) dropwise. The temperature was kept at 0 °C for 1 h and increased to room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (30 mL), water (30 mL), and glycerol (30 mL), and stirred at room temperature. After 10 h, the reaction mixture was diluted with brine and water, extracted with ethyl acetate, and dried with Na_2SO_4. Column chromatography eluting with hexanes/dichloromethane (3:1 → 1:2) afforded **520** (20.62 g, 38.7 mmol, 89% yield) as a colorless oil spectroscopically identical to the material obtained by tritylation of **924** (page 218). R_f = 0.3 (5:1 hexanes/EtOAc); $[\alpha]^{20}_{D}$ −11.1 (*c* 1.23, EtOH); HRMS (ESI): *m/z* calculated for $C_{34}H_{48}O_3SiLi$ $[M+Li]^+$ 539.3533, found 539.3532.



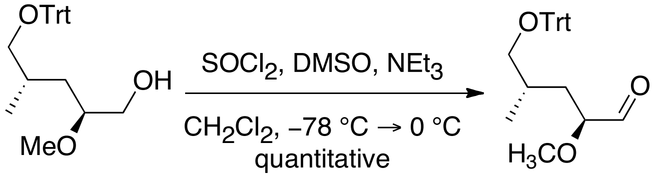
520 **926**

Preparation of methyl ether **926**: A solution of KHMDS (39.7 g, 199 mmol) in toluene (332 mL) (prepared in a glove bag) was added dropwise via cannula to a 2L round-bottomed flask containing a solution of **520** (35.37 g, 66.4 mmol) in toluene (332 mL) at −78 °C. When the addition was finished, the mixture was stirred for 15 additional minutes and methyl trifluoromethanesulfonate (32.9 mL, 299 mmol) was then added dropwise under vigorous stirring. The cold bath was removed and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ether, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography eluting with hexanes/dichloromethane (3:1 → 1:1) to afford **926** (33.04 g, 60.4 mmol, 91% yield) as a colorless oil. $R_f = 0.3$ (2:1 hexanes/dichloromethane); $[\alpha]^{20}_{D}$ −8.3 (*c* 1.25, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.20 (m, 15 H), 3.75 and 3.59 (d of ABq, ^3J = 5.5 and 5.0 Hz, J_{AB} = 10.0 Hz, 2 H), 3.42 (s, 3 H), 3.32–3.27 (m, 1 H), 3.01 and 2.92 (d of ABq, ^3J = 5.5 and 6.5 Hz, J_{AB} = 9.0 Hz, 2 H), 2.06–2.00 (m, 1 H), 1.56 (ddd, J = 13.0, 9.5, 4.5 Hz, 1 H), 1.36 (ddd, J = 13.0, 9.5, 4.0 Hz, 1 H), 1.11–1.07 (m, 21 H), 1.03 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 128.8, 127.6, 126.7, 86.1, 80.0, 68.8, 66.1, 58.1, 36.2, 30.5, 18.0, 17.4, 11.9.



926 **927**

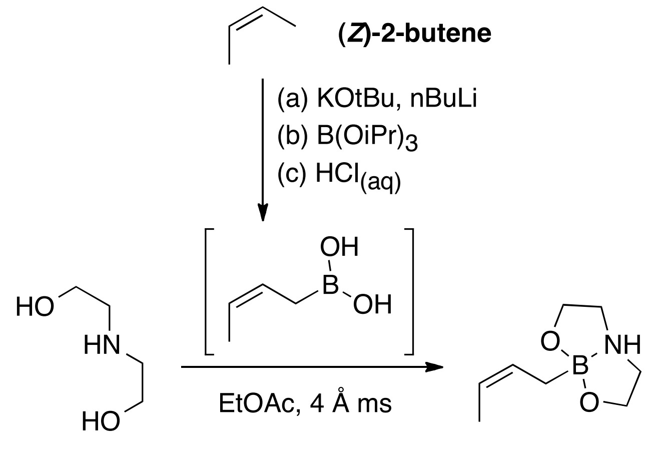
Preparation of primary alcohol **927**:[31] To a solution of **926** (33.04 g, 60.4 mmol) in THF (121 mL) at 0 °C was added TBAF (1.0 M in THF) (91 mL, 91 mmol) dropwise and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ether, dried over $MgSO_4$, and concentrated *in vacuo*. The product was purified by flash chromatography eluting with hexanes/EtOAc (3:2) to give **927** (22.41 g, 57.4 mmol, 95% yield) as a colorless oil. $R_f = 0.4$ (3:2 hexanes/EtOAc); $[\alpha]^{20}_{D}$ +1.9 (*c* 2.17, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.41 (m, 6 H), 7.29–7.25 (m, 6 H), 7.23–7.19 (m, 3 H), 3.64 (ddd, *J* = 11.0, 6.0, 3.5 Hz, 1 H), 3.41 (m, 1 H), 3.32 (s, 3 H), 3.27 (m, 1 H), 2.95 and 2.91 (d of ABq, $^3J = 6.0$ Hz, $J_{AB} = 9.0$ Hz, 2 H), 1.87 (m, 1 H), 1.79 (apparent t, *J* = 6.25 Hz, 1 H), 1.69 (ddd, *J* = 13.5, 7.0, 5.5 Hz, 1 H), 1.17 (ddd, *J* = 13.5, 8.0, 5.5 Hz, 1 H), 1.03 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 128.7, 127.7, 126.8, 86.2, 79.4, 68.4, 64.1, 57.0, 34.9, 30.7, 17.9.



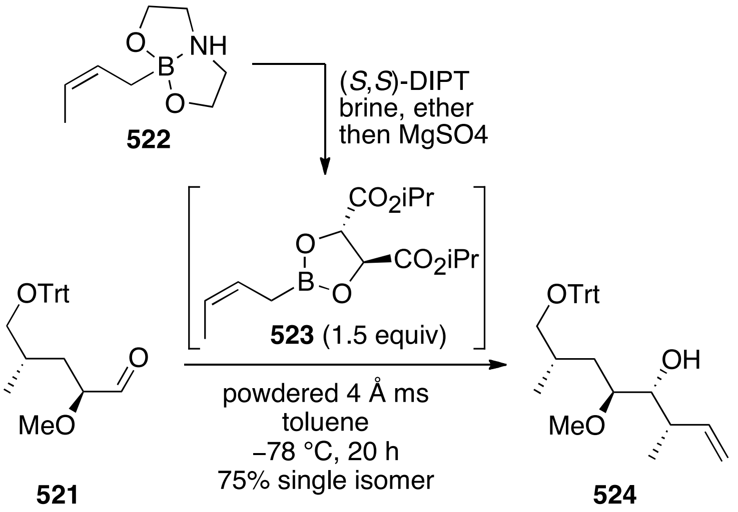
927 **521**

Preparation of aldehyde **521**:[31] A solution of DMSO (10.12 mL, 143 mmol) in CH_2Cl_2 (582 mL) was added slowly via syringe to a vacuum/flame-dried 2L round-bottomed flask containing oxalyl chloride (6.24 mL, 71.3 mmol) in CH_2Cl_2 (291 mL) at −78 °C. The transparent solution was stirred for 10 minutes and a solution of alcohol **927** (23.2 g, 59.4 mmol) in CH_2Cl_2 (116 mL) was added dropwise. The cloudy mixture was stirred for additional 10 minutes and triethylamine (41.4 mL, 297 mmol) was then added dropwise. After 10 minutes at −78 °C and 1 h at room temperature, the transparent reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted three times with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo* to afford crude **521** as a yellowish oil containing small amounts of CH_2Cl_2 and DMSO. Aldehyde

521 can be used crude (quantitative yield calculated by ^{1}H NMR) in the following step. Purification by column chromatography eluting with hexanes/EtOAc (5:1 → 1:1) afforded **521** (22.5 g, 57.9 mmol, 97% yield) as a colorless oil. $R_f = 0.5$ (5:1 hexanes/EtOAc); $[\alpha]^{20}_{D}$ −39.8 (*c* 1.10, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, *J* = 2.0 Hz, 1 H), 7.46–7.38 (m, 6 H), 7.31–7.25 (m, 6 H), 7.24–7.19 (m, 3 H), 3.57 (ddd, *J* = 8.5, 4.0, 2.0 Hz, 1 H), 3.37 (s, 3 H), 2.95 (d, *J* = 6.0 Hz, 2 H), 2.02 (m, 1 H), 1.74 (ddd, *J* = 14.0, 8.5, 5.0 Hz, 1 H), 1.40 (ddd, *J* = 12.0, 9.0, 4.0 Hz, 1 H), 0.98 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.9, 144.3, 128.7, 127.7, 126.9, 86.3, 84.0, 68.2, 58.2, 33.7, 30.2, 17.0; HRMS (ESI): *m*/*z* calculated for $C_{26}H_{28}O_3Na$ $[M+Na]^+$ 411.1936, found 411.1935.

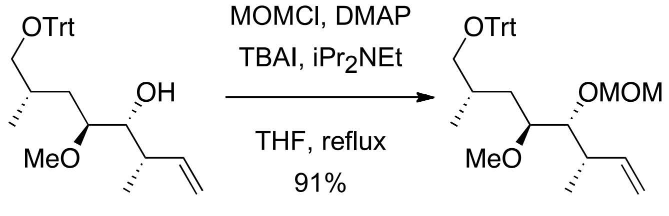


Preparation of (Z)-crotylboronic acid diethanolamine ester (**522**[95]): A 2L three-necked round-bottomed flask, provided with a jacketed addition funnel (without a pressure-equalizing arm) and a stir bar, was vacuum/flame-dried and charged with potassium *t*-butoxide (50.7 g, 424 mmol) under nitrogen atmosphere. THF (315 mL) was added via cannula and the resulting white suspension was vigorously stirred while the flask was evacuated and refilled with nitrogen several times and cooled down to −78 °C. The outer jacket of the addition funnel was filled with a dry ice/acetone mixture. (*Z*)-2-butene (25 g, 446 mmol) was cooled down to −78 °C in its metallic container (under nitrogen atmosphere) and transferred into the addition funnel via cannula. After the pre-cooled (*Z*)-2-butene was added to the suspension, the addition funnel was evacuated and refilled with nitrogen several times. *n*-Butyllithium 1.6M in hexanes (265 mL, 424 mmol) was then transferred via cannula into the addition funnel and added dropwise (very slowly) to the suspension. Upon complete addition, the bright yellow suspension was allowed to warm to −25 °C for 45 minutes and then cooled back down to −78 °C. The addition funnel was evacuated and refilled with nitrogen several times and its outer jacket was warmed to about −50 °C. Triisopropyl borate (99 mL, 424 mmol) (mp −59 °C) was transferred via cannula into the addition funnel and added dropwise (very slowly) to the reaction mixture. The resulting pale yellow suspension was maintained at −78 °C for 20 minutes and then it was rapidly poured into a separatory funnel containing aqueous HCl 1M saturated with NaCl (850 mL, 850 mmol). The pH of the aqueous phase was adjusted to 1 and the two transparent colorless layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 800 mL) and combined organic layers were treated with diethanolamine (35.7 g, 339 mmol) and stirred over freshly activated 4 Å molecular sieve beads (~100 g) under nitrogen atmosphere for 3 h. Filtration and concentration *in vacuo* afforded a white powdery solid. Recrystallization from dichloromethane/ether gave colorless crystals. Continuous subjection of the mother liquor to crystallization, filtration, and drying under vacuum afforded crotylation agent precursor **522** (22.35 g, 132 mmol, 39% combined yield) as a white solid. Yields varied from run to run. This solid was stored in the fridge in presence of drierite for several months without any detectable decomposition. mp (plates) 150–151 ºC (lit.[95] 156–157 ºC); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (m, 1 H), 5.31 (m, 1 H), 4.05 (br, 1 H), 4.01 (m, 2 H), 3.88 (m, 2 H), 3.19 (m, 2 H), 2.78 (m, 2 H), 1.61 (d, *J* = 6.5 Hz, 3 H), 1.45 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 132.8, 119.8, 62.9, 51.8, 12.5; ^{11}B NMR (62.8 MHz, CDCl$_3$) δ 13.1; IR (neat): 3133, 3004, 2860, 1638, 1473, 1355, 1272, 1210, 1103 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_8H_{19}BNO_3$ $[M+H_3O]^+$ 188.1458, found 188.1461.



Preparation of asymmetric crotylation product **524**[31]: To a suspension of (*Z*)-crotylboronic acid diethanolamine ester (**522**) (16.70 g, 99 mmol) and (−)-diisopropyl tartrate (23.14 g, 99 mmol) in diethyl ether (165 mL) was added brine (165 mL) and the mixture was stirred until two clear layers formed. After 5 minutes, the phases were separated and the aqueous layer was extracted with diethyl ether (4 × 150 mL). Combined organic extracts were washed with brine (300 mL) and transferred to a vacuum/flame-dried 2L round-bottomed flask containing $MgSO_4$ (50 g) and the suspension was vigorously stirred for 3 hours under nitrogen atmosphere. The solid was filtered off and rinsed with diethyl ether under nitrogen blanketing. The filtrate was directly placed into a vacuum/flame-dried three-necked 2L round-bottomed flask containing freshly activated powdered 4 Å molecular sieves (5.5 g, >60 mg/mmol of crotylation agent). The yield of (*S*,*S*)-(*Z*)-crotylboronate **523** was assumed to be 90% (26.50 g, 89 mmol). The solvent (diethyl ether) was carefully distilled off into a liquid-nitrogen-cooled trap using high vacuum and stirring at room temperature. Portions of dry toluene were added and pumped down under high vacuum several times to ensure that the reagent was dry and that all the active boronate was in the form of the tartrate ester derivative. Dry toluene (~400 mL) was added to the flask via cannula and the resulting suspension was cooled down below −78 °C. Aldehyde **521** (23.00 g, 59.2 mmol) (dried in a vacuum (0.01 torr) desiccator over drierite for 1 day before use) was added dropwise as a solution in toluene (200 mL). The reaction mixture was stirred at −78 °C and the progress of the reaction was monitored by TLC (hexanes/EtOAc 7:1). After 20 h, aqueous sodium hydroxide 2.0 M (89 mL, 178 mmol) (2 equiv with respect to crotylboronate) was added and the mixture was allowed to warm to 0 °C. The mixture was stirred for 1 hour and then filtered trough a pad of celite eluting with diethyl ether. Phases were separated and the aqueous layer was extracted three times with diethyl ether. Combined organic layers were dried over K_2CO_3, filtered, and concentrated. ^{1}H NMR of the crude material indicated a conversion of about 90% and confirmed the formation of a single diastereomer. Column chromatography eluting with hexanes/EtOAC (10:1) afforded asymmetric crotylation product **524** (19.74 g, 44.4 mmol, 75% yield) as a colorless oil. This reaction can be performed in small scale with equal results and yields in the 70–80% range. $R_f = 0.24$ (10:1 hexanes/EtOAc); $[\alpha]^{20}_{D}$ −14.4° (*c* 1.03, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.42 (m, 6 H), 7.29–7.25 (m, 6 H), 7.28–7.23 (m, 3 H), 5.62 (ddd, *J* = 17.0, 10.5, 8.5 Hz, 1 H), 5.03 (dd, *J* = 17.0, 1.5 Hz, 1 H), 5.00 (dd, *J* = 10.5, 1.5 Hz, 1 H), 3.59 (m, 1 H), 3.29 (s, 3 H), 3.23 (dt, *J* = 10.5, 2.7 Hz, 1 H), 2.98 and 2.88 (d of

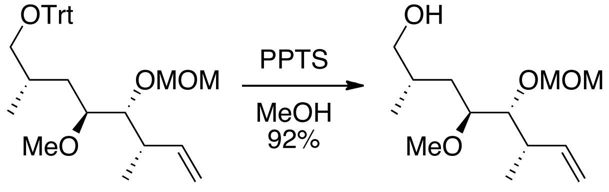
ABq, ${}^{3}J$ = 5.5 and 7.0 Hz, J_{AB} = 8.5 Hz, 2 H), 2.22 (m, 1 H), 2.10 (d, J = 2 Hz, 1 H), 2.03–1.95 (m, 1 H), 1.59 (ddd, J = 14.2, 10.5, 3.9 Hz, 1 H), 1.21 (ddd, J = 14.4, 10.0, 2.4 Hz, 1 H), 1.11 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 140.1, 128.8, 127.6, 126.8, 115.2, 86.1, 80.1, 73.4, 69.2, 57.0, 40.4, 31.5, 30.4, 17.2, 17.1; HRMS (ESI): *m/z* calculated for $C_{30}H_{36}O_3Na$ $[M+Na]^+$ 467.2562, found 467.2560.



524 **928**

Preparation of MOM-protected homoallylic alcohol **928**:[31] To a solution of **524** (4.09 g, 9.20 mmol) in dichloromethane (77 mL) were sequentially added DMAP (0.112 g, 0.920 mmol), *N*,*N*-diisopropylethylamine (9.64 mL, 55.2 mmol), chloromethyl methyl ether (2.096 mL, 27.6 mmol), and tetrabutylammonium iodide (0.340 g, 0.920 mmol) and resulting mixture was stirred at room temperature under nitrogen atmosphere. The progress of the reaction was monitored by TLC (hexanes/EtOAc 8:1) of mini-worked-up samples. After 24 h the reaction was quenched with saturated aqueous NH_4Cl. The two phases were separated, and the aqueous layer was extracted three times with ethyl acetate, dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified by flash chromatography eluting with hexanes/EtOAc (19:1 → 8:1) to give **928** (4.08 g, 8.35 mmol, 91% yield) as a colorless oil and recovered starting material **524** (0.123 g, 0.276 mmol, 3%). R_f (**928**) = 0.3 (8:1 hexanes/EtOAc); $[\alpha]^{20}_{D}$ +14.4° (*c* 2.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.38 (m, 6 H), 7.27–7.21 (m, 6 H), 7.20–7.15 (m, 3 H), 5.67

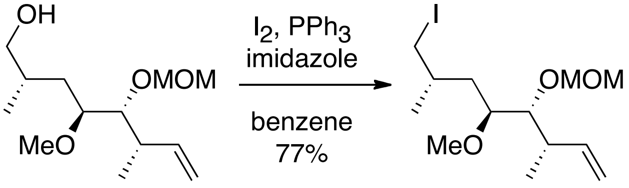
(ddd, $J = 17.0, 10.5, 8.5$ Hz, 1 H), 5.02–4.96 (m, 2 H), 4.78 and 4.59 (ABq, $J_{AB} = 6.5$ Hz, 2 H), 3.57 (dd, $J = 8.5, 2.0$ Hz, 1 H), 3.37 (s, 3 H), 3.26 (s, 3 H), 3.27 (overlapped m, 1 H), 2.99 and 2.84 (d of ABq, $^{3}J = 5.5$ and 7.5 Hz, $J_{AB} = 8.5$ Hz, 2 H), 2.25 (m, 1 H), 1.99 (m, 1 H), 1.59 (ddd, $J = 14.5, 10.5, 4.0$ Hz, 1 H), 1.19 (ddd, $J = 14.0, 10.0, 2.0$ Hz, 1 H), 1.09 (d, $J = 6.5$ Hz, 3 H), 0.96 (d, $J = 6.5$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 141.1, 128.8, 127.6, 126.7, 114.8, 97.4, 86.1, 80.7, 79.5, 69.1, 56.9, 56.0, 40.5, 33.3, 30.7, 17.4, 17.2; HRMS (ESI): *m/z* calculated for $C_{32}H_{40}O_4Na$ $[M+Na]^+$ 511.2824, found 511.2829.



928 **527**

Preparation of primary alcohol **527**:[31] To a solution of **928** (4.5 g, 9.21 mmol) in MeOH (65.8 mL) was added PPTS (pyridinium *p*-toluenesulfonate) (2.3 g, 9.21 mmol) at room temperature. The progress of the reaction was monitored by TLC (1:1 hexanes/EtOAc). After 24 h, the reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ether, dried over $MgSO_4$, and concentrated under vacuum. The crude material was subjected to column chromatography eluting with hexanes/EtOAc (1:1) to give **527** (2.08 g, 8.44 mmol, 92% yield) as a colorless oil. $R_f = 0.4$ (1:1 hexanes/EtOAc); $[\alpha]^{20}_{D}$ +9.6 (*c* 1.75, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (ddd, $J = 17.0, 10.5, 9.0$ Hz, 1 H), 5.03–4.98 (m, 2 H), 4.81 and 4.62 (ABq, $J_{AB} = 6.6$ Hz, 2 H), 3.63 (dd, $J = 9.0, 1.5$ Hz, 1 H), 3.49 and 3.39 (d of ABq, $^{3}J = 5.0$ and 6.0 Hz, $J_{AB} =$

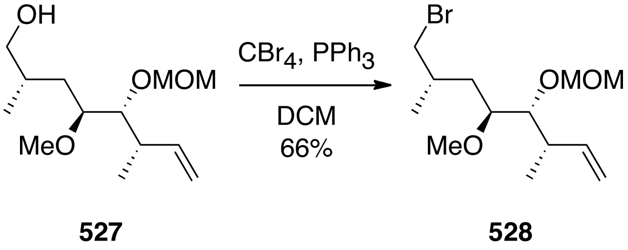
11.0 Hz, 2 H), 3.39 (s, 3 H), 3.33 (s, 3 H), 3.31 (overlapped m, 1 H), 2.32–2.24 (m, 1 H), 2.23 (br, 1 H), 1.74 (m, 1 H), 1.60 (ddd, $J = 15.0, 10.0, 6.5$ Hz, 1 H), 1.37 (ddd, $J = 15.0, 7.0, 1.5$ Hz, 1 H), 1.11 (d, $J = 6.5$ Hz, 3 H), 0.91 (d, $J = 6.5$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 115.1, 97.3, 82.2, 78.6, 68.5, 56.6, 56.0, 40.9, 33.8, 33.4, 17.7, 17.6; HRMS (ESI): *m/z* calculated for $C_{13}H_{27}O_4$ $[M+H]^+$ 247.1909, found 247.1912.



527 **525**

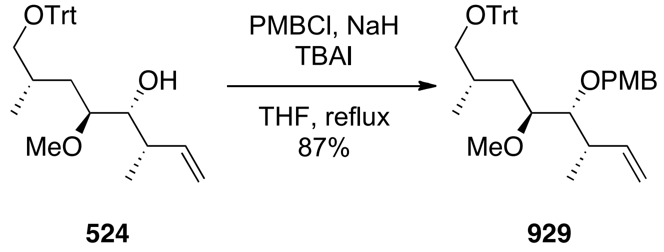
Preparation of alkyl iodide **525**: To a 25mL pear-shaped flask covered with aluminum foil, containing a solution of **527** (100.7 mg, 0.409 mmol) in benzene (4 mL), was added imidazole (41.7 mg, 0.613 mmol), triphenylphosphine (139 mg, 0.531 mmol), and iodine (135 mg, 0.531 mmol) and the resulting suspension was vigorously stirred at room temperature. After 1 h, the reaction mixture was a homogeneous bright yellow suspension. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$; the resulting two-phase system was stirred and, after some minutes, two colorless and clear phases formed. The phases were separated and the aqueous layer was extracted with ether. Combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was directly adsorbed in silica gel and subjected to column chromatography eluting with hexanes/EtOAc (10:1) to afford **525** (112.1 mg, 0.314 mmol, 77% yield) as a colorless oil. $R_f = 0.4$ (10:1 hexanes/EtOAc); $[\alpha]^{20}_D$ −11.3° (*c* 1.067, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (ddd, $J = 17.0, 10.5, 9.0$ Hz, 1

H), 5.03 (ddd, J = 17.0, 1.5, 1.0 Hz, 1 H), 5.01–4.98 (m, 1 H), 4.81 and 4.62 (ABq, J_{AB} = 7.0 Hz, 2 H), 3.60 (dd, J = 9.0, 2.0 Hz, 1 H), 3.40 (s, 3 H), 3.30 (s, 3 H), 3.28–3.25 (m, 2 H), 3.14 (dd, J = 9.5, 6.5 Hz, 1 H), 2.27 (m, 1 H), 1.70 (m, 1 H), 1.65 (ddd, J = 14.0, 10.5, 3.5 Hz, 1 H), 1.29 (ddd, J = 14.0, 9.5, 2.0 Hz, 1 H), 1.10 (d, J = 7.0 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 115.1, 97.4, 80.9, 78.8, 57.0, 56.1, 40.7, 36.1, 31.4, 20.0, 19.1, 17.7; HRMS (ESI): *m/z* calculated for $C_{13}H_{26}IO_3$ $[M+H]^+$ 357.0927, found 357.0929.



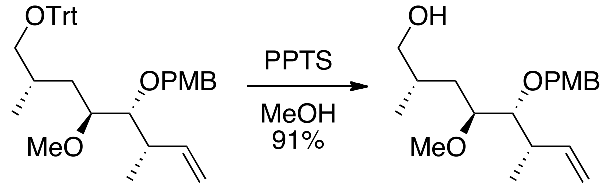
Preparation of alkyl bromide **528**: To a solution of **527** (48.3 mg, 0.196 mmol) and triphenylphosphine (61.7 mg, 0.235 mmol) in dichloromethane (0.65 mL) was added in portions carbon tetrabromide (68.3 mg, 0.206 mmol) and the solution was stirred at room temperature for 4 h. The reaction mixture was diluted with petroleum ether (0.65 mL), and filtered by suction washing with petroleum ether/ethyl acetate (10:1). The organic solution was evaporated and the crude material purified by column chromatography, eluting with hexanes/ethyl acetate (6:1) to give **528** (40 mg, 0.129 mmol, 66.0% yield) as a colorless oil. R_f = 0.4 (6:1 hexanes/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.67 (m, 1 H), 5.06-4.96 (m, 2 H), 4.81 (d, J = 6.5 Hz, 1 H), 4.62 (d, J = 6.5 Hz, 1 H), 3.61 (dd, J = 9, 2 Hz, 1 H), 3.44 (m, 1 H), 3.39 (s, 3 H), 3.31 (s, 3 H), 3.30 (m, 2 H), 2.27 (m, 1 H) , 2.03 (m, 1 H), 1.68 (m, 1 H), 1.33 (m, 1 H), 1.11 (d, J = 6.5

Hz, 3 H), 0.98 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.1, 115.3, 97.7, 81.1, 79.2, 57.2, 56.3, 42.9, 40.1, 34.9, 32.2, 18.4, 17.9.



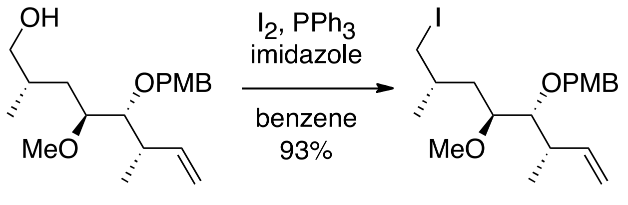
524 **929**

Preparation of **929**: To a 0 °C slurry of sodium hydride, suspension in mineral oil 60% w/w, (0.439 g, 10.96 mmol), TBAI (0.270 g, 0.731 mmol) and **524** (3.25 g, 7.31 mmol) in THF (25 mL) was added 4-methoxybenzyl chloride (1.095 mL, 8.04 mmol). The resulting suspension was refluxed at 70 °C for 16 hours. The reaction was quenched with aqueous saturated ammonium chloride (25 mL), extracted with EtOAc (3 × 50 mL), dried over MgSO4, and concentrated under vacuum overnight. The crude material was adsorbed on silica gel and purified by column chromatography eluting with hexanes/ether 9:1 to afford **929** (3.58 g, 6.34 mmol, 87% yield) as a colorless oil. R_f = 0.4 (hexanes/ether 9:1); $[\alpha]^{20}_{D}$ +12.9° (*c* 0.317, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.41 (m, 6 H), 7.27–7.21 (m, 6 H) , 7.23–7.17 (m, 5 H), 6.81 (d, *J* = 8.5, 2 H), 5.66 (m, 1 H), 5.00–4.93 (m, 2 H), 4.68 (d, *J* = 11 Hz, 1 H), 4.43 (d, *J* = 11 Hz, 1 H), 3.76 (s, 3 H), 3.36 (dd, *J* = 8.5, 2.5 Hz, 1 H), 3.55 (ddd, *J* = 10.0, 2.5, 2.5 Hz, 1 H), 3.29 (s, 3 H), 2.98 (dd, *J* = 9.0, 5.0 Hz, 1 H), 2.85 (dd, *J* = 8.5, 7.5 Hz, 1 H), 2.25 (m, 1 H), 2.01 (m, 1 H), 1.70 (m, 1 H), 1.22 (m, 1 H), 1.05 (d, *J* = 6.5 Hz, 3 H), 0.95 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 144.5, 141.5, 131.2, 129.5, 128.8, 127.6, 126.7, 114.6, 113.6, 86.1, 81.7, 81.1, 73.7, 69.1, 57.2, 55.2, 40.7, 33.4, 30.7, 17.3, 17.2; HRMS (ESI): *m/z* calculated for $C_{38}H_{44}O_4Na$ $[M+Na]^+$ 587.3137, found 587.3137.



929 **930**

Preparation of **930**: To a solution of **929** (3.44 g, 6.09 mmol) in MeOH (43.5 mL) was added PPTS (1.531 g, 6.09 mmol) at room temperature in one portion. The reaction was stirred for 24 hours at room temperature, quenched with aqueous saturated $NaHCO_3$, extracted with ether, dried over $MgSO_4$, and concentrated under vacuum. The crude material was purified by column chromatography eluting with hexanes/ethyl acetate (1:1) to give **930** (1.78 g, 5.52 mmol, 91% yield) as a colorless oil. $R_f = 0.35$ (1:1 hexanes/ethyl acetate); $[\alpha]^{20}_D$ −2.5° (*c* 0.317, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 5.65 (m, 1 H), 5.00 (m, 1 H), 4.97 (m, 1 H), 4.73 (d, *J* = 11 Hz, 1 H), 4.47 (d, *J* = 11 Hz, 1 H), 3.78 (s, 3 H), 3.49 (m, 1 H), 3.43-3.35 (m, 4 H), 3.35 (s, 3 H), 2.4 (t, 6 Hz, 1 H, exchangeable), 2.26 (m, 1 H), 1.775 (m, 1 H), 1.665 (m, 1 H), 1.39 (m, 1 H), 1.07 (d, *J* = 6.5 Hz, 3 H), 0.91 (d, *J* = 7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 141.2, 131.0, 129.5, 114.9, 113.7, 82.8, 81.0, 73.8, 68.6, 56.9, 55.3, 41.1, 33.9, 33.5, 17.8, 17.6; HRMS (ESI): *m/z* calculated for $C_{19}H_{31}O_4$ $[M+H]^+$ 323.2229, found 323.2222.

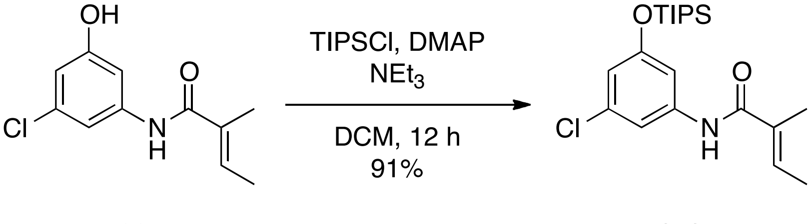


930 **529**

Preparation of **529**: To a 25mL pear-shaped flask covered with aluminum foil, containing a solution of **930** (100.7 mg, 0.409 mmol) in benzene (4 mL), was added imidazole (41.7 mg, 0.613 mmol), triphenylphosphine (139 mg, 0.531 mmol), and iodine (135 mg, 0.531 mmol) and the resulting brown suspension was vigorously stirred at room temperature. After 1 h, the reaction mixture was a homogeneous bright yellow suspension. *Note:* the workup and the purification are to be carried out in the dark. The reaction was quenched by the addition of saturated $Na_2S_2O_3$; the resulting two-phase system was stirred and, after some minutes, two colorless and clear phases formed. The phases were separated and the aqueous layer was extracted with ether. Combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated until some precipitate was observed. Petroleum ether (10 mL) was added and the suspension was filtered. The solids were washed with petroleum ether/ether (2:1) and the filtrate was directly adsorbed in silica gel. The product was purified by column chromatography eluting with hexanes/ether (5:1) to afford **529** (782.0 mg, 1.809 mmol, 93% yield) as a colorless oil. R_f = 0.8 (1:1 hexanes/ether); $[\alpha]^{20}_D$ +1.5° (*c* 0.733, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 5.66 (m, 1 H), 5.01 (m, 1 H), 4.98 (m, 1 H), 4.72 (d, *J* = 11 Hz, 1 H), 4.47 (d, *J* = 11 Hz, 1 H), 3.78 (s, 3 H), 3.40 (dd, *J* = 8.5, 2.5 Hz, 1 H), 3.34 (s, 3 H), 3.30 (ddd, *J* = 10, 2.5, 2.5 Hz, 1 H), 3.27 (dd, *J* = 9.5, 4.0 Hz, 1 H), 3.13 (dd, *J* = 9.5, 6.5 Hz, 1 H), 2.28 (m, 1 H), 1.78–1.70 (m, 2 H), 1.31 (m, 1 H), 1.08 (d, *J* = 7 Hz, 3 H), 0.92 (d, *J* =

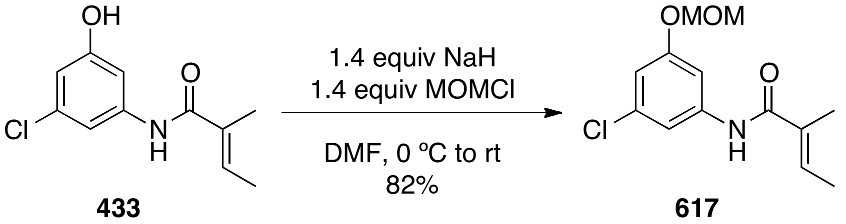
6.5 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 159.1, 141.2, 131.0, 129.6, 114.9, 113.7, 81.4, 81.2, 73.9, 57.2, 55.3, 40.9, 36.3, 31.6, 20.15, 19.0, 17.5; HRMS (ESI): *m/z* calculated for $C_{19}H_{29}IO_3Na$ $[M+Na]^+$ 455.1059, found 455.1074.

9.6. Experimental details for Chapter 6: Autolytimycin, Suzuki coupling



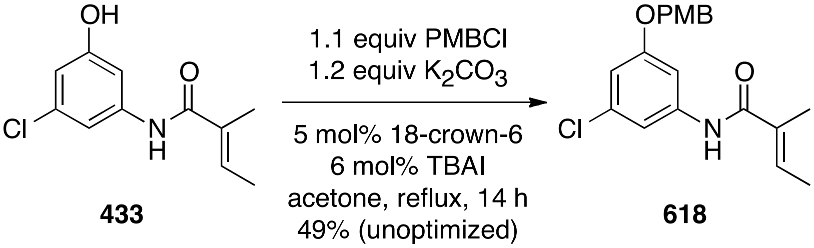
433 **616**

Preparation of TIPS-protected amidochlorophenol **616**:[31] To a solution of **433**[5h] (1.4g, 6.20 mmol) and DMAP (0.152 g, 1.241 mmol) in dichloromethane (10.5 mL) were successively added triethylamine (0.96 mL, 6.82 mmol) and triisopropylsilyl chloride (1.32 mL, 6.20 mmol) at 0 °C and the mixture was stirred at room temperature for 12 hours. The reaction was quenched with aqueous saturated sodium bicarbonate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). Combined organic extracts were dried over MgSO$_4$ and concentrated. Column chromatography eluting with 8:1 hexanes/EtOAc afforded TIPS-protected amidochlorophenol **616** (2.157 g, 5.65 mmol, 91% yield) as a white solid; mp 84.5–85.5 °C (lit.[31] 82–83 °C); $R_f = 0.33$ (8:1 hexanes/EtOAc). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.29 (br, 1 H), 7.14 (t, $J = 2.0$ Hz, 1 H), 7.09 (t, $J = 2.0$ Hz, 1 H), 6.60 (t, $J = 2.0$ Hz, 1 H), 6.48 (m, 1 H), 1.91 (apparent t, $J = 1.2$ Hz, 3 H), 1.80 (apparent d, $J = 7.0$ Hz, 3 H), 1.25 (m, 3 H), 1.10–1.07 (m, 18 H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 167.4, 157.2, 139.8, 134.6, 132.7, 131.7, 115.9, 112.5, 109.7, 17.9, 14.1, 12.6, 12.5; IR (neat): 3301, 2946, 2892, 2868, 1662, 1637, 1599, 1538, 1449, 1426, 1386, 1286, 1226, 1182, 1142, 1096, 1075, 1013, 953, 918, 901, 883, 860 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{20}H_{33}ClNO_2Si$ $[M+H]^+$ 382.1964, found 382.1960.

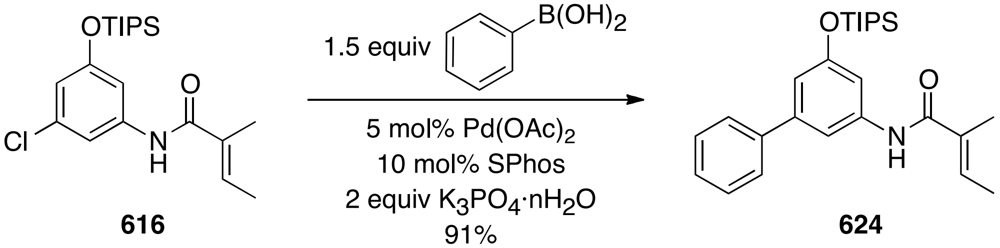


Preparation of MOM-protected amidochlorophenol **617**: Sodium hydride (12 mg, 0.298 mmol) (60% disersion in mineral oil) was rinsed twice with ~2mL dry pentane under nitrogen. Carefully, most of the solvent was removed via cannula and the rest evaporated under vacuum. To the residual white solid was added DMF (200 μL) and the resulting suspension was cooled to 0 °C. A solution of phenol **433** (48.0 mg, 0.213 mmol) in DMF (150 μL) was added and the resulting solution stirred at 0 °C for 30 minutes. To the solution was added chloromethyl methyl ether (23 μL, 0.298 mmol) causing the immediate evolution of gas. The solution was allowed to warm to room temperature and quenched with water (0.5 mL). The solution was extracted with ether, dried with $MgSO_4$ and concentrated *in vacuo*. The excess of DMF was removed by adding small portions of absolute ethanol and concentrating the resulting solutions under vacuum three times. Column chromatography eluting with hexanes/EtOAc (7:1) afforded **617** (47.2 mg, 0.175 mmol, 82 % yield) as a waxy white solid. mp 51.5–53 °C; $R_f = 0.30$ (7:1 hexanes/EtOAc). ^1H NMR (500 MHz, $CDCl_3$): δ 7.40 (br, 1 H), 7.27 (t, $J = 2.0$ Hz, 1 H), 7.17 (t, $J = 2.0$ Hz, 1 H), 6.77 (t, $J = 2.1$ Hz, 1 H), 6.48 (qq, $J = 1.5, 7.0$ Hz, 1 H), 5.12 (s, 2 H), 3.44 (s, 3 H), 1.90 (apparent t, $J = 1.5$ Hz, 3 H), 1.79 (apparent d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 158.1, 139.8, 135.0, 132.6, 131.8, 113.5, 112.4, 106.1, 94.5, 56.1, 14.1, 12.5; IR (neat):

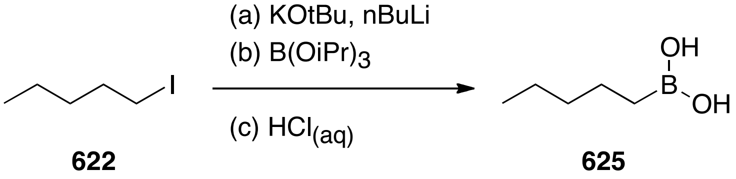
3307, 3128, 3088, 2955, 2827, 1664, 1636, 1602, 1534, 1457, 1427, 1397, 1317, 1274, 1234, 1211, 1154, 1082, 1025, 966, 924, 848 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{13}H_{17}ClNO_3$ $[M+H]^+$ 270.0891, found 270.0898.



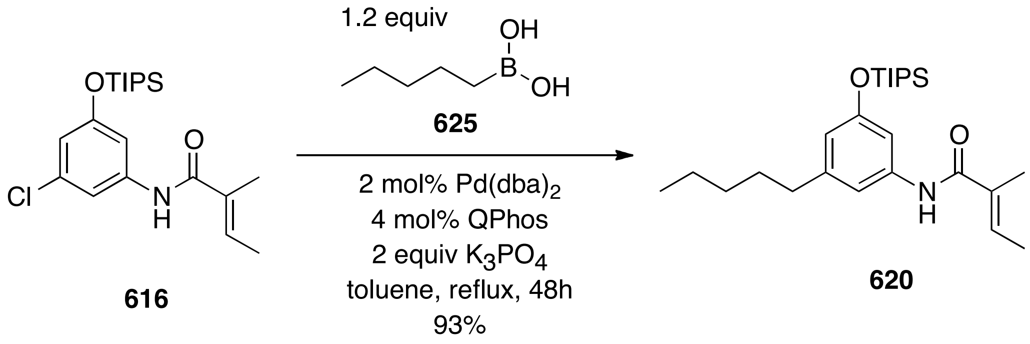
Preparation of PMB-protected amidochlorophenol **618** (Unoptimized. For a better procedure see the preparation of amidochlorophenol **511**, page 208): To a suspension of chloroamidophenol **433** (1.24 g, 5.49 mmol), potassium carbonate (0.911 g, 6.59 mmol), 18-crown-6 (0.087 g, 0.330 mmol), and TBAI (0.101 g, 0.275 mmol) in acetone (275 mL) was added 4-methoxybenzyl chloride (0.947 g, 6.04 mmol). The resulting mixture was heated to reflux for 14 h. The reaction mixture was concentrated, redissolved in dichloromethane, washed twice with water, then brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (hexanes/EtOAc 5:1) afforded **618** (0.93 g, 2.69 mmol, 48.9 % yield) as a white solid. mp 98–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (br, 1 H), 7.32 (d, *J* = 13.5 Hz, 2 H), 7.28 (t, *J* = 1.7 Hz, 1 H), 7.08 (t, *J* = 1.7 Hz, 1 H), 6.90 (d, *J* = 13.5 Hz, 2 H), 6.70 (t, *J* = 1.7 Hz, 1 H), 6.49 (qq, *J* = 1.5, 6.5 Hz, 1 H), 4.95 (s, 2 H), 3.80 (s, 3 H), 1.91 (apparent s, 3 H), 1.81 (apparent d, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 159.9, 159.6, 139.9, 135.0, 132.7, 131.8, 129.3, 128.3, 114.0, 112.4, 111.4, 104.7, 70.1, 55.3, 14.1, 12.5; IR (neat): 3314, 3078, 3004, 2933, 2836, 1661, 1589, 1539, 1514, 1456, 1420, 1377, 1269, 1173, 1024, 849, 824 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{19}H_{21}ClNO_3$ $[M+H]^+$ 346.1204, found 346.1199.



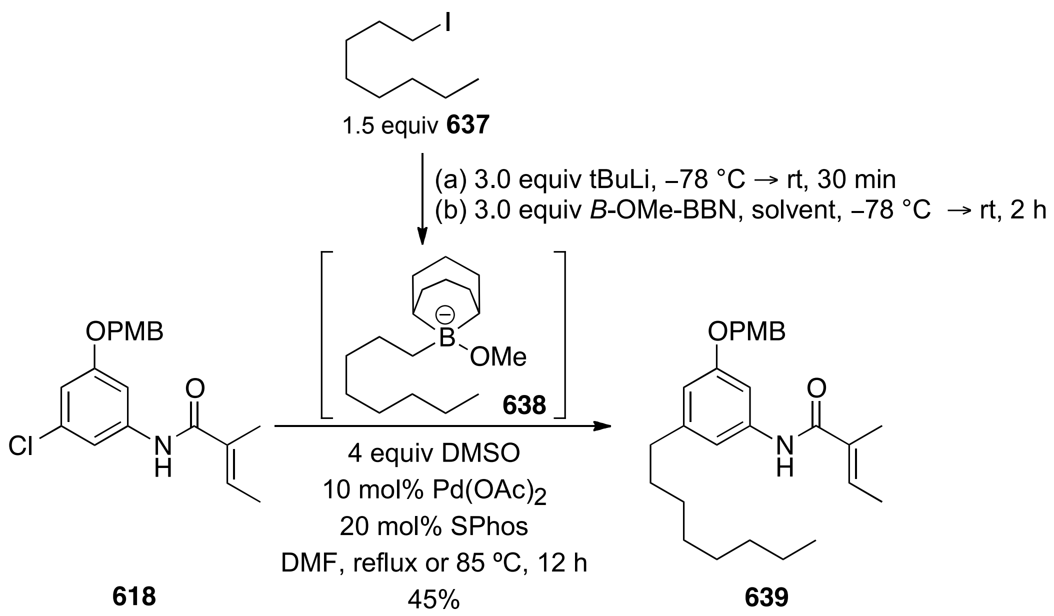
Preparation of Suzuki product **624**: A 10mL round-bottomed flask provided with a magnetic stirrer was charged with potassium phosphate hydrate (55.7 mg, 0.209 mmol), TIPS-protected amidochlorophenol **616** (40 mg, 0.105 mmol), palladium(II) acetate (1.2 mg, 5.24 µmol), SPhos (4.3 mg, 10.47 µmol), and phenylboronic acid (19.2 mg, 0.157 mmol). The flask was evacuated and refilled with nitrogen (this was repeated 2 additional times). Degassed water (25 µL) and THF (0.24 mL) were added and the reaction mixture was allowed to stir at reflux (70 °C) overnight. After the starting material was consumed as determined by TLC, the reaction solution was cooled to room temperature and then adsorbed onto silica gel directly. The product was isolated by flash chromatography eluting with hexanes/dichloromethane (1:2) to give **624** (40.2 mg, 0.095 mmol, 91%) as white waxy solid after removal of the solvent under high vacuum. R_f = 0.35 (1:2 hexanes/dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (s, 1 H), 7.05 (t, J = 2Hz, 1 H), 6.87 (s, 1 H), 6.48–6.43 (m, 2 H), 2.49 (t, J = 7.5Hz, 2 H), 1.91 (m, 3 H), 1.78 (d, J = 6.5Hz, 3 H), 1.56 (m, 2 H), 1.23 (m, 7 H), 1.13–1.03 (m, 18 H), 0.84 (t, J = 7.5Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 167.4, 156.4, 144.7, 138.8, 133.0, 130.9, 115.9, 112.5, 108.9, 35.9, 31.4, 30.9, 22.5, 18.0, 17.7, 14.1, 14.0, 12.7, 12.6.



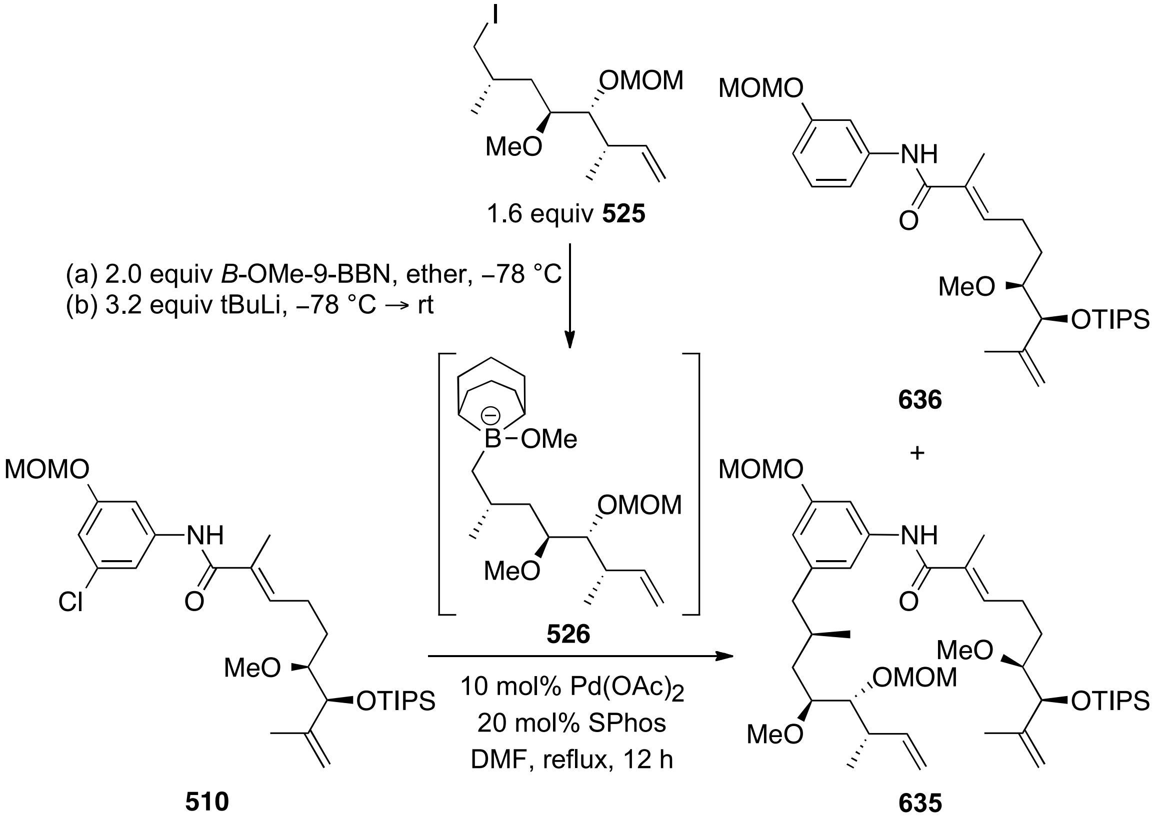
Preparation of pentylboronic acid (**625**): In a round-bottomed flask provided with a magnetic stirring bar, a solution of pentyl iodide (2 mL, 15.25 mmol) in diethyl ether (50.8 mL) was treated with *tert*-butyllithium 1.7M hexanes (18.0 mL, 30.5 mmol) (added dropwise) at −78 °C. After 20 minutes, triisopropyl borate (3.90 mL, 16.77 mmol) was added dropwise and the mixture was stirred for 20 minutes before being rapidly poured into a separatory funnel containing hydrochloric acid 1M saturated with NaCl (30.5 mL, 30.5 mmol). The aqueous layer was adjusted to pH 1 using HCl 2M, the phases were separated and the aqueous layer was extracted with diethyl ether four times. Combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. To the resulting orange solid was added water (50 mL) and the solution was boiled until it became homogeneous and transparent (slightly yellow). After being slowly cooled down to room temperature the formed solid was filtered out and dried under vacuum until it looked like dry white flakes, affording 1.05 g (9.05 mmol, 59.4% yield) of product. Note: Excess of vacuum makes the product "melt", probably forming oligomers and eliminating water. mp 91–92 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.31 (s, 2 H), 1.40–1.10 (m, 6 H), 0.85 (t, *J* = 7.25 Hz, 3 H), 0.56 (t, *J* = 7.75, 2 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 34.4, 23.8, 22.0, 15.4, 13.9; ^{11}B NMR (62.8 MHz, $CDCl_3$) δ 33.3.



Preparation of Suzuki product **620**: Inside the dry box, an air free flask provided with a magnetic stir bar was charged with **616** (50 mg, 0.131 mmol), $Pd(dba)_2$ (1.5 mg, 2.62 µmol), QPhos (3.7 mg, 5.24 µmol), anhydrous potassium phosphate (55.6 mg, 0.262 mmol), and pentylboronic acid, **625**, (18.4 mg, 0.158 mmol). Anhydrous toluene (300 µL) was added and the air free flask was sealed and removed from the dry box. The reaction mixture was stirred at 100 °C for 48 hours. After the starting material was consumed as determined by TLC, the reaction solution was cooled to room temperature and then adsorbed onto silica gel directly. The product was isolated by flash chromatography eluting with hexanes/ether (5:1) to give 51 mg (0.122 mmol, 93%) of **620** as white waxy solid after removal of the solvent under high vacuum. R_f = 0.35 (5:1 hexanes/ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (br, 1 H), 7.05 (t, J = 2 Hz, 1 H), 6.87 (s, 1 H), 6.47 (q, J = 6.5 Hz, 1 H), 6.44 (s, 1H), 2.49 (t, J = 7.5 Hz, 2 H), 1.91 (s, 3 H), 1.79 (d, J = 6.5 Hz, 3 H), 1.56 (p, 2 H), 1.32–1.20 (m, 7 H), 1.08 (d, J = 8 Hz, 18 H), 0.86 (t, J = 7 Hz, 3 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 167.4, 156.4, 144.8, 138.8, 133.0, 130.9, 115.9, 112.5, 108.9, 35.9, 31.4, 30.9, 22.5, 18.0, 14.1, 14.0, 12.7, 12.6.



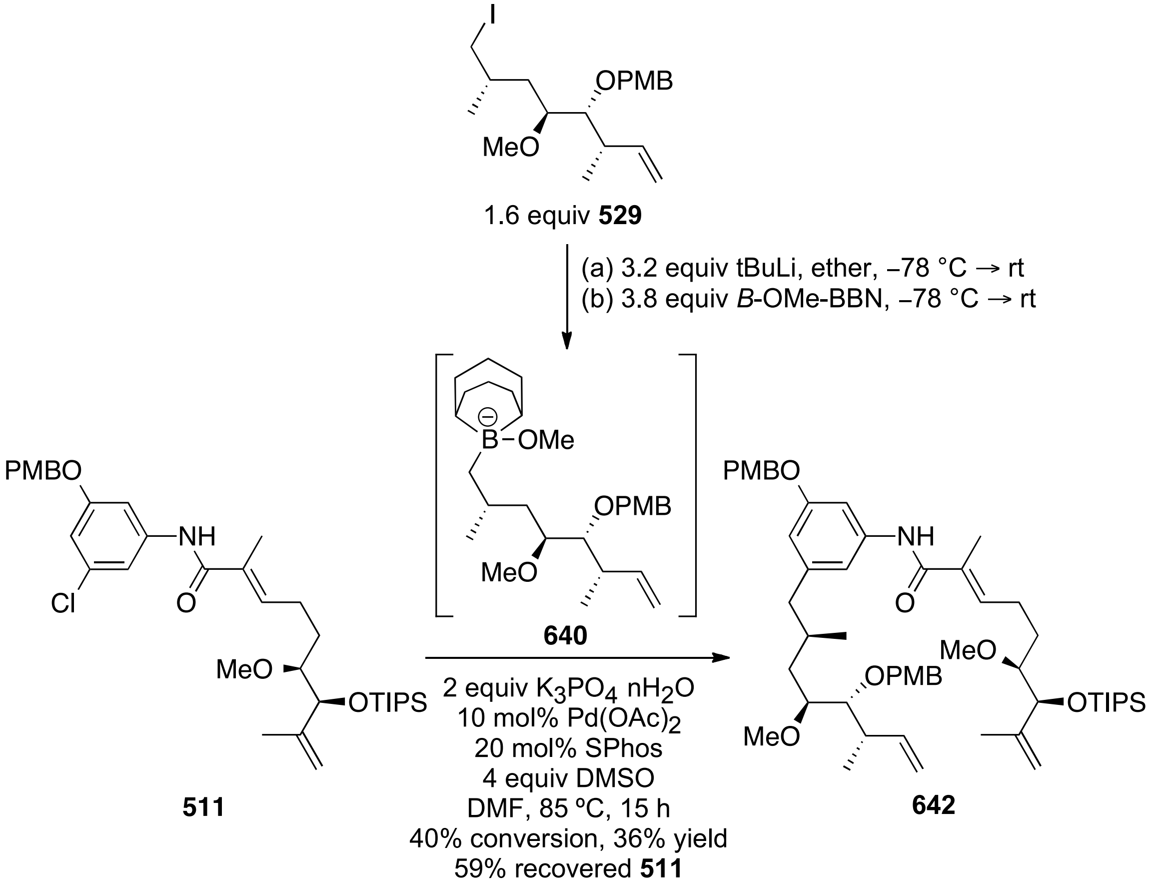
Preparation of Suzuki product **639** *under partially optimized conditions* (Table 6, entry 3): To a 25 mL pear-shaped flask provided with a magnetic stirrer, containing octyl iodide (66.2 μL, 0.367 mmol) in ether (400 μL) at −78 °C, was added *tert*-butyllithium 1.7 M in pentane (430 μL, 0.733 mmol) and the mixture was stirred at that temperature for 30 minutes. *B*-methoxy-9-borabicyclo[3.3.1]nonane (370 μL, >0.367 mmol) was added dropwise, followed by THF (400 μL) and the reaction mixture was stirred for 5 minutes more at −78 °C and then at room temperature for 1 h 45 m. DMF (1.6 mL) was added and the resulting clear colorless solution was freeze-pump-thaw degassed (0.01 atm) twice. A mixture of PMB-protected chloroamidophenol **618** (84.5 mg, 0.244 mmol), palladium(II) acetate (5.5 mg, 0.024 mmol), and SPhos (20.06 mg, 0.049 mmol) was added to the flask, followed by DMSO (70 μL, 0.977 mmol). A reflux condenser was attached under nitrogen atmosphere and the resulting mixture was refluxed overnight. After 12 h, the reaction mixture was passed through a small plug of silica gel, eluting with acetone. The resulting yellowish solution (~15 mL) was concentrated *in vacuo*. Ethanol was added and evaporated *in vacuo* a few times in order to eliminate the excess of DMF. Column hexanes/ether (2:1) afforded pure Suzuki product **639** (46.5 mg, 0.111 mmol, 45.4 % yield). R_f = 0.35 (2:1 hexanes/ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 2 H), 7.33 (br, 1 H), 7.26 (apparent s, 1 H), 6.89 (d, *J* = 8.5 Hz, 2 H), 6.83 (apparent s, 1 H), 6.55 (apparent s, 1 H), 6.48 (apparent q, *J* = 6.8 Hz, 1 H), 4.96 (s, 2 H), 3.80 (s, 3 H), 2.52 (t, *J* = 7.5 Hz, 2 H), 1.92 (s, 3 H), 1.80 (apparent d, *J* = 7.0 Hz, 3 H), 1.56 (p, 2 H), 1.33–1.18 (m, 10 H), 0.86 (t, *J* = 7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 159.4, 159.3,145.0, 139.0, 132.9, 131.1, 129.3, 129.1, 113.9, 112.3, 111.5, 103.5, 69.8, 67.5, 55.3, 36.1, 31.9, 31.2, 29.5, 29.3, 29.2, 22.7, 14.1, 12.5; HRMS (ESI): *m/z* calculated for $C_{27}H_{38}NO_3$ $[M+H]^+$ 424.2852, found 424.2849.



Preparation of dechlorination product **636** *under non-optimized Suzuki conditions* (Table 5, entry 1): To a 10mL pear-shaped flask provided with a magnetic stirrer, containing iodide **525** (67.1 mg, 0.188 mmol) in THF (1.5 mL) at −78 °C under nitrogen atmosphere, was added *B*-

methoxy-9-borabicyclo[3.3.1]nonane 1M in THF (210 μL, >0.207 mmol). Twenty minutes later, *tert*-butyllithium 1.7 M in pentane (225 μL, 0.377 mmol) was added dropwise and the reaction mixture was stirred for 5 minutes more at −78 °C and then at room temperature. After 30 minutes, DMF (2.4 mL) was added and the solution was frozen and degassed under vacuum (0.01 atm) twice, forming a clear and colorless solution (solution A). A mixture of MOM-protected phenol **511** (87mg, 0.157 mmol), palladium(II) acetate (3.5 mg, 0.016 mmol), and SPhos (12.9 mg, 0.031 mmol) was prepared in a flame-dried 25mL round-bottomed flask and it was purged and refilled with nitrogen three times. Solution A was then transferred via cannula at room temperature into the round-bottomed flask and the mixture was heated up to 110 °C. The progress of the reaction was monitored by TLC (7:1 hexanes/EtOAC). Complete consumption of the SM was achieved after 9 hours and the reaction mixture was concentrated. Absolute ethanol (~1.5 mL) was added and the suspension was concentrated *in vacuo* to remove the excess of DMF. This procedure was repeated twice. The black thick residue was redissolved in 1.5 mL of acetone, adsorbed onto ~300 mg of silica gel and directly purified by column chromatography eluting with hexanes/EtOAC 7:1 to afford impure **635** (24.4 mg, <0.033 mmol, <21% yield) (apparently contaminated with BBN-containing species) and pure dechlorination product **636** (37.2 mg, 0.072 mmol, 46% yield). Since better conditions were found (see following procedures), the preparation of this Suzuki product was not optimized. The dechlorination product was used for characterization purposes. R_f(**636**) = 0.35 (7:1 hexanes/ethyl acetate); $[\alpha]^{20}_{D}$ −9.3° (*c* 1.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (br, 1 H), 7.31 (t, *J* = 2.5 Hz, 1 H), 7.20 (t, *J* = 8.0 Hz, 1 H), 7.15 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1 H), 6.76 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1 H), 6.36 (m, 1 H), 5.16 (s, 2 H), 4.95 (s, 1 H), 4.89 (s, 1 H), 4.31 (d, *J* = 5.5 Hz, 1 H), 3.46 (s, 3 H), 3.45 (s, 3 H), 3.18 (m, 1 H), 2.35–2.20 (m, 2 H), 1.92 (s, 3 H), 1.73 (s, 3 H), 1.67 (m, 1

H), 1.35 (m, 1 H), 1.12–1.00 (m, 21 H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 167.5, 157.7, 144.9, 139.2, 136.6, 132.0, 129.7, 113.4, 112.9, 112.1, 108.0, 94.5, 84.3, 76.4, 58.8, 56.1, 29.1, 25.0, 19.2, 18.09, 18.05, 12.8, 12.4; IR (neat): 3310, 2942, 2867, 1662, 1603, 1540, 1490, 1446, 1386, 1269, 1151, 1084, 1014, 883 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{29}H_{50}NO_5Si$ [M+H]$^+$ 520.3453, found 520.3460.



1.6 equiv **529**

(a) 3.2 equiv tBuLi, ether, −78 °C → rt
(b) 3.8 equiv *B*-OMe-BBN, −78 °C → rt

511

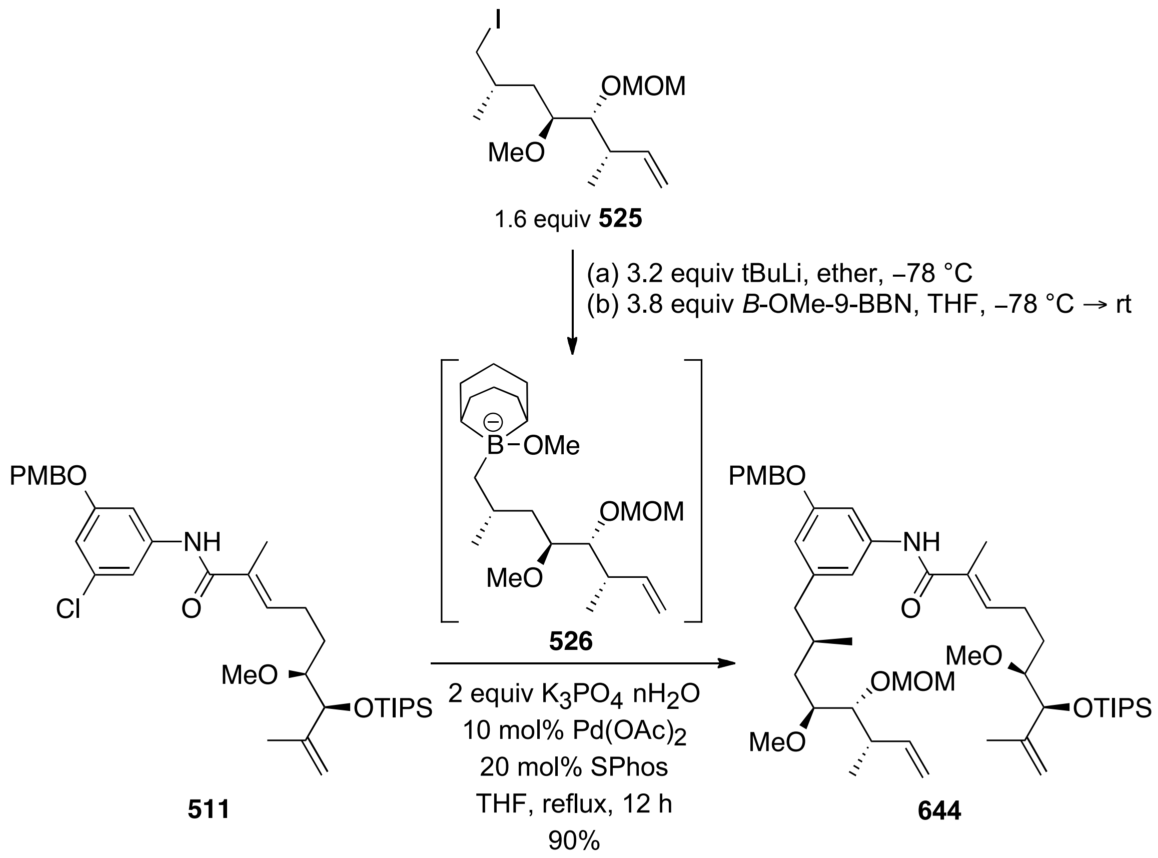
640

2 equiv K_3PO_4 nH_2O
10 mol% $Pd(OAc)_2$
20 mol% SPhos
4 equiv DMSO
DMF, 85 ºC, 15 h
40% conversion, 36% yield
59% recovered **511**

642

Preparation of Suzuki product **642** *under partially optimized conditions*: To a flame-dried 25mL pear-shaped flask provided with a magnetic stirrer, containing iodide **529** (109 mg, 0.252 mmol) in ether (1.6 mL) at −78 °C under dry nitrogen atmosphere, was added dropwise *tert*-butyllithium 1.7 M in pentane (300 μL, 0.503 mmol) and the resulting mixture was stirred at −78 °C for 5 minutes, at room temperature for 1 hour, and then cooled down again to −78 °C. *B*-

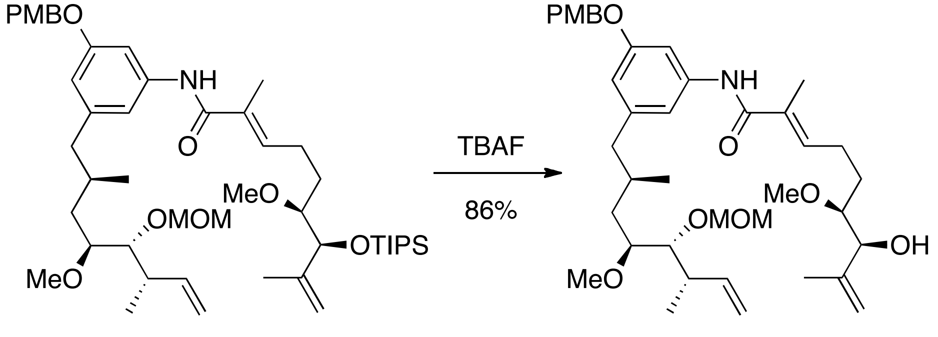
methoxy-9-borabicyclo[3.3.1]nonane 1M in THF (277 µL, 0.277 mmol) was added dropwise and the solution was stirred for 10 minutes more at −78 °C and then at room temperature for 1 hour. DMF (1.2 mL) was added and the solution was frozen and degassed under vacuum (0.01 atm) 3 times (Solution A). A mixture of amide **511** (122 mg, 0.194 mmol) and potassium phosphate hydrate (41.1 mg, 0.194 mmol) was prepared in a flame-dried three-necked 50mL round-bottomed flask provided with a reflux condenser and it was purged and refilled with nitrogen several times. Solution A was transferred via cannula at room temperature and the 25mL pear-shaped flask was rinsed with DMF (1.1 mL). The rinse was degassed 3 times as mentioned before and was transferred via cannula to the second flask. A solution of palladium acetate (4.4 mg, 0.019 mmol), SPhos (15.9 mg, 0.039 mmol), in DMSO (1.0 mL) was prepared in a small vial. The solution was degassed three times as mentioned before and added to the main reaction flask and the resulting brown suspension was refluxed at 85 °C for 15 hours. The reaction mixture was filtered though a thin pad of silica gel eluting with ether and ethyl acetate and the yellow filtrate was concentrated under vacuum. Ethanol was added and the solution was pumped down several times in order to get rid of the excess of DMF. NMR shows a conversion of 40% to the Suzuki coupling product and 0% of dehalogenation. Column chromatography eluting with hexanes/EtOAc (7:1) afforded **642** (62 mg, 35.6% yield) as a white solid and 59% of recovered **511**. R_f(**642**) = 0.3 (7:1 hexanes/ethyl acetate); $[\alpha]^{20}{}_{D}$ −13.7° (*c* 0.667, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (t, *J* = 2 Hz, 1 H), 7.34 (br, 1 H), 7.33 (d, *J* = 8.5 Hz, 2 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 6.72 (t, *J* = 2 Hz, 1 H), 6.56 (t, *J* = 2 Hz, 1 H), 6.35 (m, 1 H), 5.67 (m, 1 H), 5.02–4.94 (m, 3 H), 4.96 (s, 2 H), 4.89 (t, *J* = 1.5 Hz, 1 H) , 4.70 (d, *J* = 11 Hz, 1 H), 4.44 (d, *J* = 11 Hz, 1 H), 4.035 (d, *J* = 5.5 Hz Hz, 1 H) , 3.79 (s, 3 H) , 3.76 (s, 3 H), 3.45 (s, 3 H), 3.42–3.35 (m, 2 H), 3.33 (s, 3 H), 3.183 (m, 1 H), 2.63 (m, 1 H), 2.35 (m, 4 H), 1.98 (m, 1 H), 1.92 (s, 3 H), 1.76 (m, 1 H), 1.73 (s, 3 H), 1.66 (m, 1 H), 1.36 (m, 1 H), 1.24 (m, 1 H), 1.09–1.01 (m, 24 H), 0.77 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 159.4, 159.3, 159.1, 145.0, 143.4, 141.4, 139.0, 136.4, 132.1, 131.2, 129.5, 129.3, 129.2, 114.7, 113.9, 113.7, 113.1, 112.9, 112.2, 103.8, 84.3, 81.6, 81.3, 76.5, 73.8, 69.8, 58.8, 57.25, 55.3, 44.8, 40.8, 36.7, 31.2, 29.1, 25.0, 19.1, 18.8, 18.1, 18.05, 17.4, 12.8, 12.4; HRMS (ESI): *m/z* calculated for $C_{54}H_{82}NO_8Si$ $[M+H]^+$ 900.5810, found 900.5804.



Preparation Suzuki coupling product **644** *under optimized conditions*: Before use, iodide **525** was dried in a vacuum desiccator over drierite (0.01 torr) for 1 day. A vacuum/flame-dried 25mL pear-shaped flask, provided with a magnetic stirrer and connected to a nitrogen line, was charged with iodide **525** (226 mg, 0.635 mmol) and ether (2.6 mL) via syringe. The solution was stirred, cooled to −78 °C, and to it was added *tert*-butyllithium 1.7 M in pentane (750 μL, 1.27 mmol) (solution remains colorless and clear). After 3 minutes, *B*-methoxy-9-borabicyclo[3.3.1]nonane 1M in THF (1.51 mL, 1.51 mmol) was added (white precipitate forms), followed by THF (2.6 mL) (solution becomes clear/colorless rapidly). The solution was stirred for 10 minutes more at −78 °C (white precipitate forms) and then at room temperature for 20 minutes (solution becomes clear and colorless again). The solvent was blown off under a nitrogen gas stream. After all the solvent was evaporated, THF (1 mL) was added, followed by potassium phosphate hydrate (197 mg, 0.793 mmol) and amide **511** (250 mg, 0.397 mmol). The resulting suspension was freeze-pump-thaw degassed (0.01 torr) three times. In a small vial, a mixture of palladium(II) acetate (8.9 mg, 0.040 mmol) and SPhos (32.6 mg, 0.079 mmol) was dissolved in THF (1 mL). The vial was connected to the Schlenk line and the solution was freeze-pump-thaw degassed (0.01 torr) 3 times. The solution of catalyst was added quickly to the first mixture via syringe causing a sudden color change to dark orange-brown. A water-cooled condenser was attached under nitrogen atmosphere and the reaction mixture was refluxed for 12 hours. After full conversion was confirmed by TLC, the mixture was diluted with acetone and filtered through a short pad of silica gel eluting with acetone. After concentration of the filtrate, the crude material was purified by column chromatography eluting with hexanes/EtOAc (49:1 → 3:1) to afford Suzuki product **644** (294 mg, 0.357 mmol, 90% yield) as a white solid. When necessary, the product was washed with hexanes to remove any yellow/orange color. R_f = 0.29 (4:1 hexanes/EtOAc); mp 84–85 ºC; $[\alpha]^{20}_{D}$ +6.2° (c 0.5, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 1 H), 7.34 (br, 1 H), 7.34 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 6.73 (s, 1 H), 6.55 (s, 1 H), 6.35 (t, *J* = 7.4 Hz, 1 H), 5.67 (m, 1 H), 5.01 (d, *J* = 17.8 Hz, 1 H), 4.98 (d, *J* = 10.8 Hz, 1 H), 4.95 (s, 1 H), 4.95 (s, 2 H), 4.89 (s, 1 H), 4.82 (d, *J* = 6.8 Hz, 1 H), 4.61 (d, *J* = 6.8 Hz, 1 H), 4.30 (d, *J* = 6.0 Hz, 1 H), 3.79 (s, 3 H), 3.60 (dd, *J* = 8.8, 1.8 Hz, 1 H), 3.45 (s, 3 H), 3.39 (s, 3 H), 3.32 (m, 1 H), 3.30 (s, 3

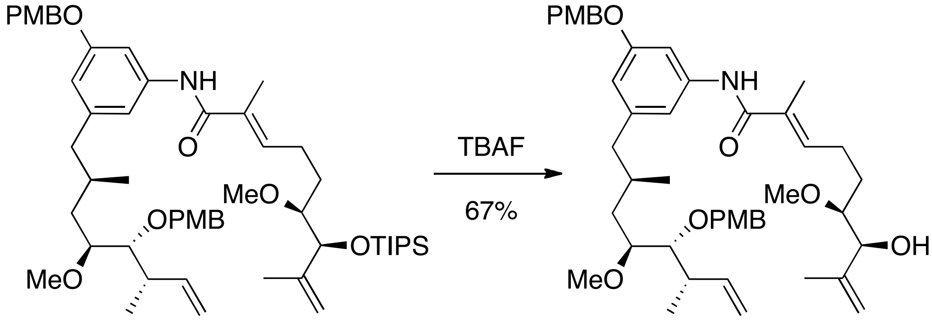
H), 3.18 (ddd, *J* = 8.8, 5.8, 2.7 Hz, 1 H), 2.65 (dd, *J* = 13.3, 4.9 Hz, 1 H), 2.37–2.19 (m, 4 H), 1.95 (m, 1 H), 1.92 (s, 3 H), 1.73 (s, 3 H), 1.72–1.62 (m, 2 H), 1.36 (m, 1 H), 1.22 (m, 1 H), 1.11 (d, *J* = 6.6 Hz, 3 H), 1.09–1.02 (m, 21 H), 0.75 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 159.4, 159.3, 145.0, 143.3, 141.0, 138.9, 136.4, 132.1, 129.3, 129.1, 114.9, 113.9, 113.0, 112.9, 112.3, 103.7, 97.4, 84.3, 80.9, 79.3, 76.5, 69.8, 58.8, 57.0, 56.1, 55.3, 44.7, 40.6, 36.7, 31.2, 29.1, 25.0, 19.1, 18.5, 18.1, 18.0, 17.6, 12.8, 12.4; IR (neat): 3245, 2962, 2924, 2866, 1656, 1614, 1557, 1541, 1516, 1458, 1437, 1380, 1260, 1096, 1033, 872, 801 cm^{-1}; HRMS (ESI): *m*/*z* calculated for $C_{48}H_{78}NO_8Si$ [M+H]$^+$ 824.5497, found 824.5494.

9.7. Experimental details for Chapter 7: RCM and final steps



644 **723**

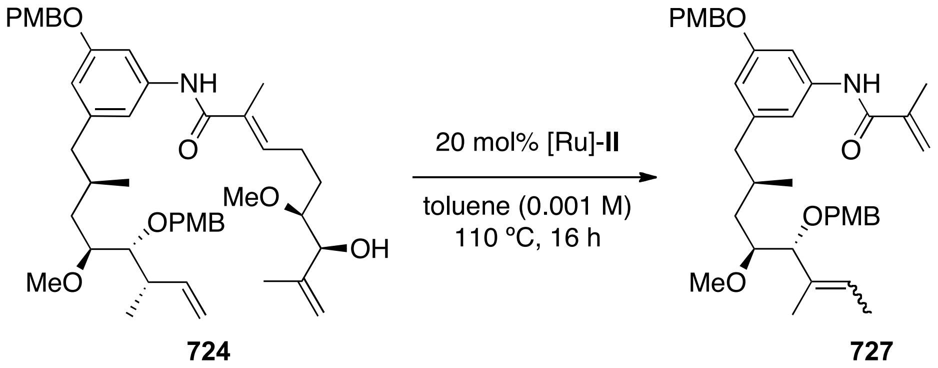
Preparation of RCM substrate **723**: To a pear-shaped flask containing a solution of Suzuki coupling product **644** (154.4 mg, 0.187 mmol) in THF (3.5 mL) at 0 °C was added TBAF 1M solution in THF (1.87 mL, 1.87 mmol) dropwise. After 1.5 hours, TLC (hexanes/EtOAc 1:1) showed that the reaction was complete. The reaction was quenched with 4 mL of saturated sodium bicarbonate and extracted with ethyl acetate several times. Combined organic layers were dried over $MgSO_4$ and concentrated. Purification by column chromatography eluting with hexanes/EtOAc (2:1 → 1:2) afforded **723** (108.1 mg, 0.162 mmol, 86% yield) as a clear colorless thick oil that formed a white wax upon standing. R_f = 0.4 (1:1 hexanes/EtOAc); $[\alpha]^{20}_{D}$ +19.8° (c 1.15, chloroform); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (s, 1 H), 7.34 (br, 1 H), 7.33 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 6.74 (s, 1 H), 6.55 (s, 1 H), 6.38 (t, *J* = 7.4 Hz, 1 H), 5.67 (m, 1 H), 5.03 (s, 1 H), 5.01 (d, *J* = 17.3 Hz, 1 H), 4.98 (d, *J* = 10.3 Hz, 1 H), 4.95 (s, 2 H), 4.95 (s, 1 H), 4.81 (d, *J* = 6.8 Hz, 1 H), 4.61 (d, *J* = 6.8 Hz, 1 H), 3.97 (dd, *J* = 6.6, 3.5 Hz, 1 H), 3.79 (s, 3 H), 3.59 (dd, *J* = 8.6, 1.9 Hz, 1 H), 3.44 (s, 3 H), 3.38 (s, 3 H), 3.34 (m, 1 H), 3.30 (s, 3 H), 3.26 (m, 1 H), 2.65 (dd, *J* = 13.5, 5.3 Hz, 1 H), 2.53 (OH) (d, *J* = 3.5 Hz, 1 H), 2.37–2.19 (m, 4 H), 1.95 (m, 1 H), 1.93 (s, 3 H), 1.75 (s, 3 H), 1.72–1.64 (m, 2 H), 1.60 (m, 1 H), 1.22 (m, 1 H), 1.11 (d, *J* = 7.0 Hz, 3 H), 0.76 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 159.4, 159.3, 144.3, 143.3, 141.0, 138.8, 136.0, 132.2, 129.3, 129.1, 114.9, 113.9, 113.9, 113.1, 112.3, 103.8, 97.4, 81.6, 80.9, 79.3, 77.1, 69.8, 58.3, 57.0, 56.1, 55.3, 44.7, 40.6, 36.6, 31.2, 29.1, 23.9, 18.6, 18.0, 17.5, 12.8; IR (neat): 3437, 3077, 2961, 1663, 1611, 1541, 1516, 1462, 1435, 1381, 1294, 1250, 1173, 1088, 1036, 909, 819 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{39}H_{58}NO_8$ $[M+H]^+$ 668.4162, found 668.4162.



642 **724**

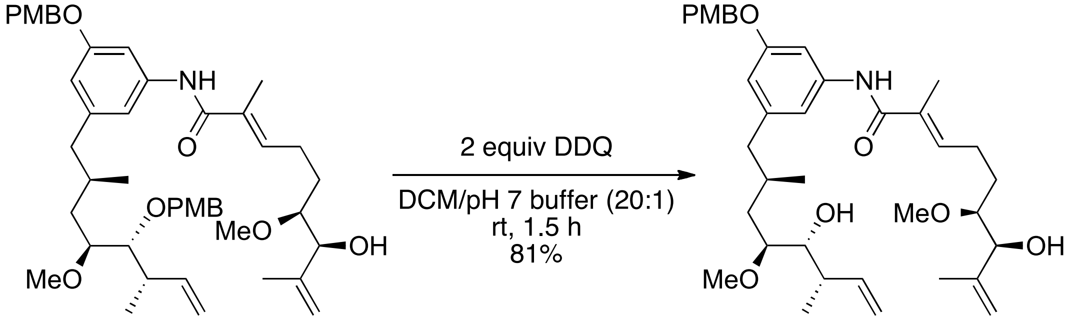
Preparation of RCM substrate **724**. To a pear-shaped flask containing a solution of Suzuki coupling product **642** (268.0 mg, 0.298 mmol) in THF (10.9 mL) at 0 °C was added TBAF (1M

THF) (3 mL, 3 mmol) dropwise. After 1.5 hours, TLC (hexanes/EtOAc 1:1) showed that the reaction was complete. The reaction was quenched with 10 mL of saturated sodium bicarbonate and extracted with ethyl acetate several times. Combined organic layers were dried over $MgSO_4$ and concentrated. The residue was adsorbed on silica gel and purified by column chromatography eluting with hexanes/ether 1:1 → 2:1 to afford **724** (148.2 mg, 67%) as a colorless oil. R_f = 0.3 (3:7 hexanes/ether); $[\alpha]^{20}_{D}$ -57.4° (*c* 0.467, benzene); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (t, *J* = 2 Hz, 1 H), 7.34 (br, 1 H), 7.33 (d, *J* = 8.5 Hz, 2 H), 7.22 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 6.72 (t, *J* = 2 Hz, 1 H), 6.56 (t, *J* = 2 Hz, 1 H), 6.37 (m, 1 H), 5.67 (m, 1 H), 5.04-4.94 (m, 4 H), 4.95 (s, 2H), 4.70 (d, *J* = 10.5 Hz, 1 H), 4.44 (d, *J* = 10.5 Hz, 1 H), 3.954 (m, 1 H), 3.79 (s, 3 H) , 3.76 (s, 3 H), 3.46(m, 1 H), 3.43 (s, 3 H), 3.41-3.32 (m, 2 H), 3.32 (s, 3 H), 3.26 (m, 1 H), 2.62 (m, 1 H), 2.52 (d, *J* = 4 Hz, 1 H, exchangeable), 2.26 (m, 4 H), 1.97 (m, 1 H), 1.92 (s, 3 H), 1.75 (s, 3 H), 1.67 (m, 1 H), 1.6 (m, 1 H), 1.24 (m, 2 H), 1.06 (d, *J* = 6.5 Hz, 3 H), 0.77 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 159.4, 159.3, 159.1, 144.3, 143.4, 141.4, 138.8, 135.9, 132.2, 131.2, 129.5, 129.3, 129.2, 114.7, 113.9, 113.9, 113.7, 113.1, 112.3, 103.9, 81.7, 81.7, 81.3, 73.8, 69.8, 58.3, 57.2, 55.3, 44.8, 40.8, 36.7, 31.2, 29.2, 23.9, 18.8, 18.0, 17.4, 12.8; HRMS (ESI): *m/z* calculated for $C_{45}H_{61}NO_8$ $[M+H]^+$ 744.4475, found 744.4448.



Formation of **727** *under RCM conditions*: To a flame-dried three-necked round-bottomed flask, provided with a condenser, containing a solution of RCM susbstrate **724** (8.4 mg, 0.011 mmol) in toluene (9 mL) under nitrogen atmosphere (SM in the three-necked flask was dried overnight in a vacuum dessicator) was added a solution of Grubbs 2nd generation catalyst [Ru]-**II** (1.9 mg, 2.2 µmol) in toluene (2.2 mL) via syringe and the resulting mixture was stirred at 110 °C. After 16 h, the dark green solution was filtered through a short plug of silica gel eluting with dichloromethane and concentrated *in vacuo*. Analysis of the crude material by ^{1}H NMR revealed the formation of one main product. Column chromatography eluting with hexanes/EtOAc (19:1 1:1) afforded impure **727** (2.2 mg, 3.66 µmol, 32.4% yield) as a dark green oil. R_f = 0.8 (hexanes/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (br, 1 H), 7.37 (apparent s, 1 H), 7.33 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8.5 Hz, 2 H), 6.88 (d, J = 8.5 Hz, 2 H), 6.83 (d, J = 8.5 Hz, 2 H), 6.70 (apparent s, 1 H), 6.54 (apparent s, 1 H), 5.74 (apparent s, 1 H), 5.48 (apparent q, J = 6.5 Hz, 1 H), 5.43 (apparent s, 1 H), 4.95 (s, 2 H), 4.39 (d, J = 11.5 Hz, 1 H), 4.14 (d, J = 11.5 Hz, 1 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.54 (d, J = 6.0 Hz, 1 H), 3.31 (m, 1 H), 3.27 (s, 3 H), 2.59 and 2.27 (d of ABq, ^3J = 5.5 and 3.75 Hz, J_{AB} = 13.0 Hz, 2 H), 2.04 (s, 3 H), ~1.94 (m, 1 H), 1.66 (d, J = 11.5 Hz, 3 H), 1.62 (s, 3 H), ~1.27 (m, 2 H), 0.81 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz,

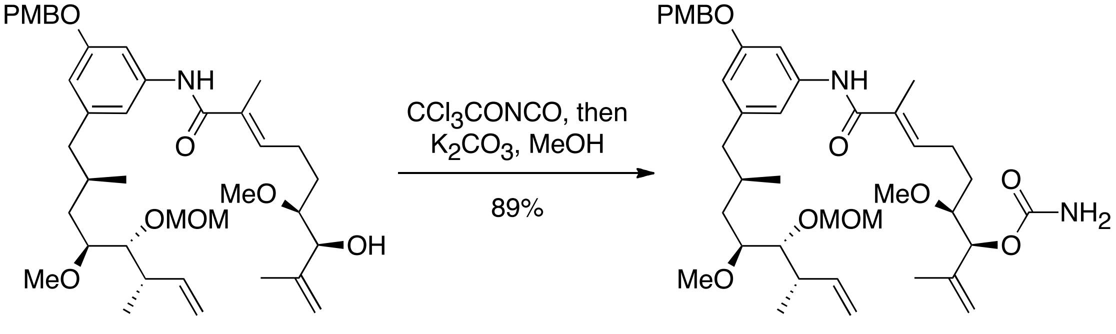
$CDCl_3$): δ 166.4, 159.5, 159.3, 158.9, 143.5, 141.1, 138.6, 133.3, 131.0, 129.3, 129.1, 126.0, 124.3, 119.6, 114.0, 113.6, 113.0, 112.6, 103.8, 86.2, 77.8, 69.8, 69.4, 58.1, 55.30, 55.26, 44.7, 38.8, 31.2, 19.0, 18.8, 13.3, 12.1; HRMS (ESI): *m*/*z* calculated for $C_{37}H_{48}NO_6$ $[M+H]^+$ 602.3482, found 602.3476.



724 **728**

Preparation RCM substrate **728**: To a solution of **724** (40.0 mg, 0.054 mmol) in dichloromethane (3.5 mL) and commercial pH 7 buffer (Orion) (~170 μL) was added solid DDQ (24.4 mg, 0.108 mmol) and the resulting dark mixture was stirred at room temperature for 1 h and 30 min. The reaction mixture was adsorbed on silica gel and directly purified by column chromatography eluting with ether/EtOAC (99:1 → 1:1) to give **728** (27.1 mg, 0.043 mmol, 81 % yield) as a slightly yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (br, 1 H), 7.33 (d, *J* = 8.75 Hz, 2 H), 7.31 (t, *J* = 2.0 Hz, 1 H), 6.88 (d, *J* = 8.75 Hz, 2 H), 6.76 (apparent s, 1 H), 6.54 (apparent s, 1 H), 6.38 (apparent t, *J* = 7.5 Hz, 1 H), 5.60 (m, 1 H), 5.06–4.98 (m, 2 H), 5.03 (apparent s, 1 H), 4.953 (s, 2 H), 4.947 (apparent s, 1 H), 3.97 (m, 1 H), 3.79 (s, 3 H), 3.60 (m, 1 H), 3.43 (s, 3 H), 3.32 (s, 3 H), 3,28–3.23 (m, 2 H), 2.57 (dd, *J* = 13.5, 5.5 Hz, 1 H), 2.55 (br, 1 H), 2.34–2.19 (m, 4 H), 2.09 (br, 1 H), 1.96 (m, 1 H), 1.93 (s, 3 H), 1.75 (s, 3 H), 1.72–1.57 (m, 3 H), 1.23 (m, 1 H), 1.11 (d, *J* = 6.5 Hz, 3 H), 0.79 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz,

$CDCl_3$): δ 167.3, 159.4, 159.2, 144.3, 143.2, 139.9, 138.8, 136.0, 132.2, 129.3, 129.1, 115.3, 113.94, 113.93, 113.1, 112.4, 103.8, 81.6, 80.1, 77.1, 73.3, 69.8, 58.3, 57.0, 55.3, 44.8, 40.4, 34.5, 30.9, 29.1, 23.9, 18.7, 18.0, 17.4, 12.8; HRMS (ESI): *m/z* calculated for $C_{37}H_{54}NO_7$ $[M+H]^+$ 624.3900, found 624.3907.

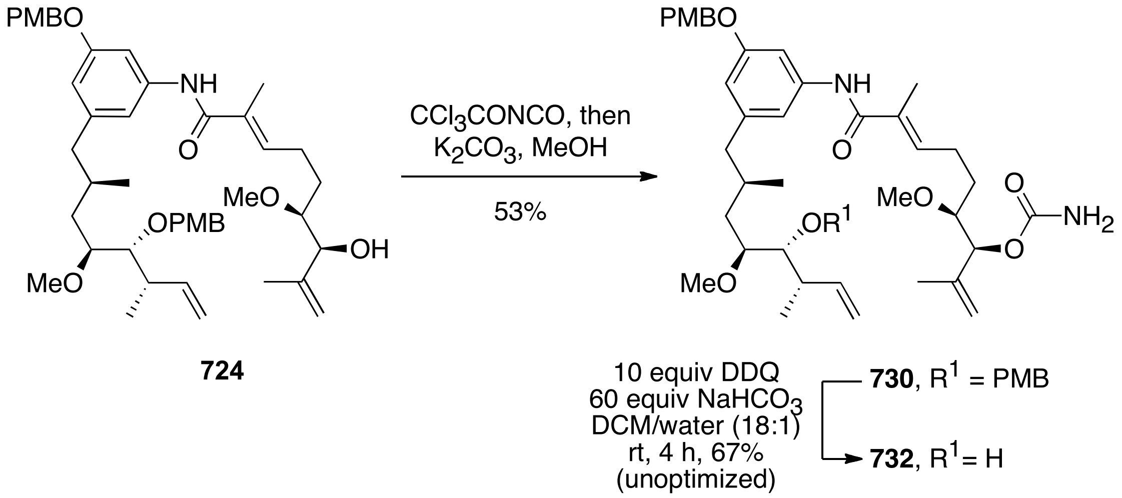


723

729

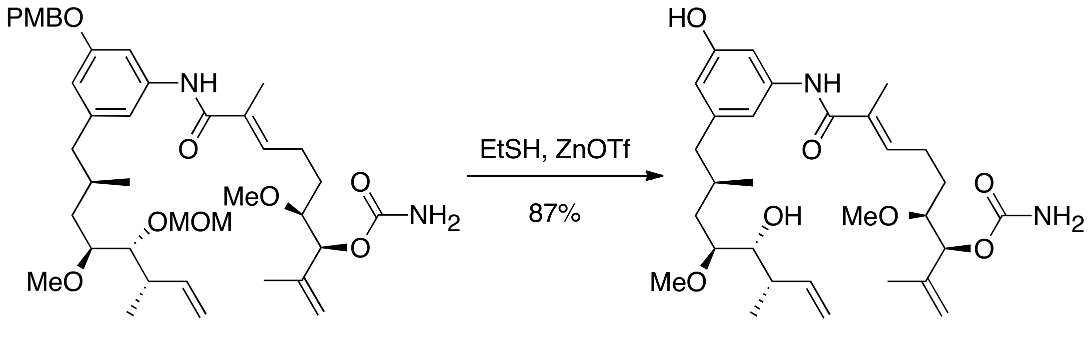
Preparation of allylic carbamate **729**. To a solution of **723** (60 mg, 0.090 mmol) in dichloromethane (11.8 mL) was added trichloroacetyl isocyanate (0.021 mL, 0.180 mmol). The reaction was stirred for 15 minutes and MeOH (14.75 mL) was added followed by potassium carbonate (57.1 mg, 0.413 mmol). The reaction was stirred for 30 minutes (monitored by TLC), before the solvent was evaporated *in vacuo*. The crude product was subjected to column chromatography eluting with ether to afford **729** (56.7 mg, 0.080 mmol, 89% yield) as a clear colorless thick oil. R_f = 0.3 (ether); $[\alpha]^{20}_D$ +4.0° (c 2.33, chloroform); ^1H NMR (600 MHz, $CDCl_3$) δ 7.59 (br, 1 H), 7.38 (s, 1 H), 7.34 (d, J = 8.6 Hz, 2 H), 6.89 (d, J = 8.6 Hz, 2 H), 6.79 (s, 1 H), 6.54 (s, 1 H), 6.33 (t, J = 7.3 Hz, 1 H), 5.66 (m, 1 H), 5.13 (d, J = 4.5 Hz, 2 H), 5.01 (s, 1 H), 5.00 (d, J = 17.5 Hz, 1 H), 4.98 (d, J = 10.5 Hz, 1 H), 4.97 (s, 1 H), 4.96 (s, 2 H), 4.80 (d, J = 6.6 Hz, 1 H), 4.72 (br, 2 H), 4.61 (d, J = 6.6 Hz, 1 H), 3.79 (s, 3 H), 3.59 (dd, J = 8.7, 2.0 Hz, 1

H), 3.42 (s, 3 H), 3.38 (s, 3 H), 3.37–3.31 (m, 2 H), 3.30 (s, 3 H), 2.63 (dd, *J* = 13.6, 5.4 Hz, 1 H), 2.39–2.22 (m, 4 H), 1.96 (m, 1 H), 1.93 (s, 3 H), 1.78 (s, 3 H), 1.73–1.57 (m, 3 H), 1.21 (m, 1 H), 1.10 (d, *J* = 6.9 Hz, 3 H), 0.76 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 159.4, 159.2, 156.0, 143.2, 141.2, 141.0, 139.0, 135.5, 132.6, 129.2, 129.1, 114.9, 113.9, 113.4, 113.1, 112.3, 103.8, 97.4, 81.1, 80.8, 79.4, 77.9, 69.7, 58.8, 57.0, 56.0, 55.3, 44.7, 40.5, 36.5, 31.0, 29.2, 24.5, 19.4, 18.5, 17.5, 12.9; IR (neat): 3317, 2921, 2851, 1733, 1718, 1653, 1609, 1540, 1516, 1457, 1435, 1379, 1301, 1249, 1134, 1095, 1036 cm^{-1}; HRMS (ESI): *m*/*z* calculated for $C_{40}H_{59}N_2O_9$ $[M+H]^+$ 711.4220, found 711.4221.



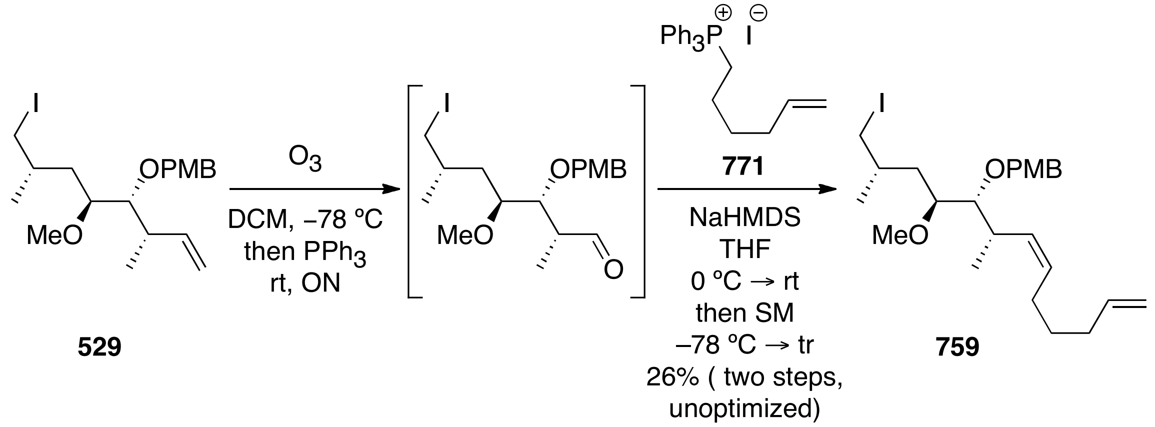
Preparation of allylic carbamate **732**: To a solution of **724** (23.7 mg, 0.032 mmol) in dry dichloromethane (5.5 mL) under inert atmosphere was added trichloroacetyl isocyanate (~8 µL, >0.064 mmol) and the resulting solution was stirred for 30 minutes. TLC (1:4 hexanes/ether) of a sample confirmed the complete consumption of the starting material. Methanol (6.6 mL) was added, followed by potassium carbonate (20.3 mg, 0.147 mmol), and the suspension was stirred for 30 minutes, time after which TLC confirmed the complete formation of a single new spot. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (4:1

hexanes/ether) to afford **730** (13.2 mg, 0.017 mmol, 52.7 % yield) as a colorless oil. This material was dissolved in dichloromethane (2 mL), placed in a sealed tube, and treated with water (110 μL) and solid sodium bicarbonate (85 mg, 1.006 mmol). While stirring, a freshly prepared solution of DDQ 0.1 M in CH_2Cl_2 (950 μL, 0.084 mmol) was added dropwise and after 2 hours, a second batch of DDQ 0.1 M in CH_2Cl_2 (950 μL, 0.084 mmol) was added. TLC (4:1 diethyl ether/hexanes and 4:1 diethyl ether/EtOAc), used to monitor the progress of the reaction, confirmed the formation of *one* major product. The reaction mixture was concentrated, adsorbed onto silica gel, and subjected to column chromatography eluting with ether/EtOAC (99:1 → 1:1) to give mono-deprotection product **732** (7.5 mg, 0.011 mmol, 67.1 % yield) as a yellowish oil. R_f = 0.30 (4:1 diethyl ether/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (br, 1 H), 7.36 (t, *J* = 2.0 Hz, 1 H), 7.34 (d, *J* = 8.75 Hz, 2 H), 6.89 (d, *J* = 8.75 Hz, 2 H), 6.81 (apparent s, 1 H), 6.53 (apparent s, 1 H), 6.33 (apparent t, *J* = 7.5 Hz, 1 H), 5.60 (m, 1 H), 5.13 (d, *J* = 4.5 Hz, 1 H), 5.05–4.97 (m, 2 H), 5.01 (apparent s, 1 H), 4.97 (apparent s, 1 H), 4.96 (s, 2 H), 4.74 (br, 2 H exchangeable), 3.79 (s, 3 H), 3.60 (m, 1 H), 3.42 (s, 3 H), 3.35 (m, 1 H), 3.32 (s, 3 H), 3.25 (m, 1 H), 2.63 (dd, *J* = 13.5, 5.5 Hz, 1 H), 2.36–2.2 (m, 4 H), 2.07 (d, *J* = 2.5, 1 H exchangeable), 1.96 (m, 1 H), 1.94 (s, 3 H), 1.78 (s, 3 H), 1.73–1.59 (m, 3 H), 1.17 (m, 1 H), 1.11 (d, *J* = 6.5 Hz, 3 H), 0.80 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.6, 159.2, 156.3, 156.0, 143.0, 141.2, 139.9, 139.0, 135.5, 132.7, 129.3, 129.1, 115.3, 113.9, 113.4, 113.1, 112.4, 103.7, 81.1, 80.1, 77.9, 73.3, 69.7, 58.8, 57.0, 55.3, 44.7, 40.4, 34.4, 30.8, 29.1, 24.6, 19.5, 18.7, 17.5, 13.0; HRMS (ESI): *m*/*z* calculated for $C_{38}H_{55}N_2O_8$ $[M+H]^+$ 667.3958, found 667.3959.



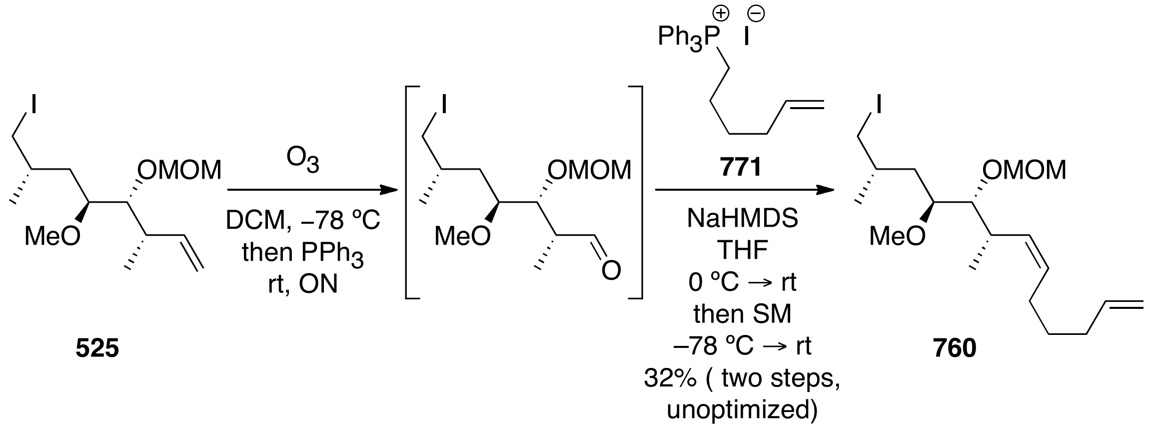
729 **731**

Preparation of ring-opened autolytimycin (**731**): Dry zinc triflate (14.0 mg, 0.039 mmol) was rapidly added to a vacuum-flame-dried small vial containing a solution of carbamoylation product **729** (7.0 mg, 9.85 μmol) and ethanethiol (10 μL, 0.135 mmol) in dichloromethane (0.1 mL) at 0 °C. The resulting mixture was stirred and after 5 minutes the cool bath was removed. After additional 15 minutes at room temperature, the suspension was diluted with dichloromethane (~1 mL). Saturated sodium bicarbonate (~1 mL) was added dropwise at 0 °C and the resulting mixture was filtered through celite eluting with dichloromethane. The organic phase was separated with a pipette and the aqueous layer was extracted with more dichloromethane. Combined organic layers were dried over Na_2SO_4 and concentrated. Purification by column chromatography eluting with ether/EtOAc (9:1) afforded ring-opened autolytimycin, **731** (4.7 mg, 8.6 μmol, 87% yield) as a clear colorless thick oil. R_f = 0.26 (4:1 diethyl ether/EtOAc); $[\alpha]^{20}_{D}$ −18.2° (c 0.39, chloroform); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (br, 1 H), 7.56 (s, 1 H), 7.39 (br, 1 H), 6.54 (s, 1 H), 6.42 (s, 1 H), 6.31 (t, *J* = 7.4 Hz, 1 H), 5.59 (m, 1 H), 5.12 (d, *J* = 4.4 Hz, 2 H), 5.02 (d, *J* = 17.3 Hz, 1 H), 5.01 (s, 1 H), 4.99 (d, *J* = 10.3 Hz, 1 H), 4.96 (s, 1 H), 4.91 (br, 2 H), 3.60 (dd, *J* = 9.2, 3.1 Hz, 1 H), 3.42 (s, 3 H), 3.36 (m, 1 H), 3.32 (s, 3 H), 3.25 (ddd, *J* = 10.8, 2.4, 2.4 Hz, 1 H), 2.63 (dd, *J* = 13.6, 5.4 Hz, 1 H), 2.36–2.18 (m, 4 H), 1.96 (m, 1 H), 1.93 (s, 3 H), 1.77 (s, 3 H), 1.74–1.58 (m, 3 H), 1.23 (br, 1 H), 1.14 (m, 1 H), 1.11 (d, *J* = 6.5 Hz, 3 H), 0.80 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 156.9, 156.2, 143.1, 141.2, 139.9, 138.6, 136.0, 132.5, 115.3, 113.3, 112.5, 112.1, 105.1, 81.1, 80.1, 77.7, 73.4, 58.8, 57.0, 44.5, 40.4, 34.2, 30.6, 29.0, 24.6, 19.5, 18.8, 17.5, 13.0; IR (neat): 3338, 2960, 2926, 2869, 2247, 1716, 1661, 1616, 1543, 1498, 1436, 1384, 1315, 1261, 1088, 911, 864, 838, 733 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{30}H_{47}N_2O_7$ [M+H]$^+$ 547.3380, found 547.3383.

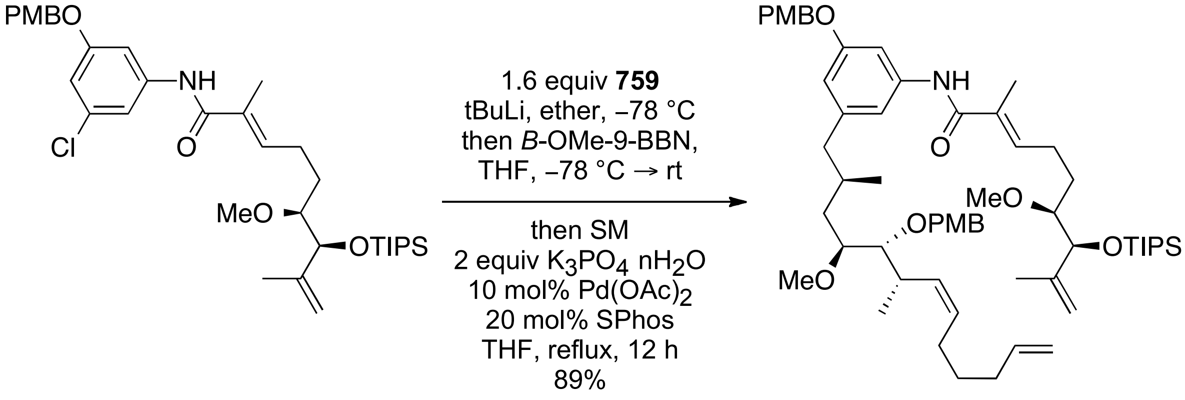


Preparation of relay chain-containing iodide **759**: A stirring solution of iodide **529** (0.365 g, 0.844 mmol) in dichloromethane (8.5 mL) at −78 °C (dry ice/acetone bath) was saturated with ozone until a blue color persisted. Once the completion of this step was confirmed by TLC (hexanes/EtOAc 9:1) and still at −78 °C, the solution was purged with nitrogen gas until the color dissipated and triphenylphosphine (0.244 g, 0.929 mmol) was added in one portion. The solution was allowed to slowly warm up to room temperature overnight. The reaction mixture was then concentrated and dried under high vacuum. At the appropriate time, the resulting residue was redissolved in THF (2.7 mL) to be used in the next step, assuming a quantitative yield of the aldehyde. Simultaneously, to a solution of 5-hexenyltriphenylphosphonium iodide[222] (**771**) (574.0 mg, 1.215 mmol) in THF (1.4 mL) at 0 ºC was slowly added NaHMDS

1M in THF (1.1 mL, 1.1 mmol) under inert atmosphere. The resulting red solution was stirred for 2 hours at room temperature and then cooled to −78 °C. The aforementioned solution of crude aldehyde was added dropwise and the reaction mixture was allowed to slowly warm up to room temperature overnight. After 12 hours, the reaction was quenched with aqueous saturated NH_4Cl (6 mL) and extracted three times with ether. Combined organic layers were washed with brine, dried over MgSO4, and concentrated. Purification by column chromatography, eluting with hexanes/EtOAc (50:1 → 7:1), afforded iodide **759** (111.7 mg, 0.223 mmol, 26.4 % yield), as a slightly yellowish oil, from the complex crude mixture. This procedure was not optimized. R_f = 0.21 (7:1 hexanes/ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.3 Hz, 2 H), 6.86 (d, *J* = 8.3 Hz, 2 H), 5.77 (ddt, *J* = 17.0, 11.5, 7.0 Hz, 1 H), 5.33 (ddd, *J* = 11.0, 7.5, 6.5 Hz, 1 H), 5.11 (m, 1 H), 4.98 (apparent d, *J* = 17.0 Hz, 1 H), 4.93 (apparent d, *J* = 11.5 Hz, 1 H), 4.77 (d, *J* = 10.75 Hz, 1 H), 4.46 (d, *J* = 10.75 Hz, 1 H), 3.78 (s, 3 H), 3.39 (dd, *J* = 9.0, 2.0 Hz, 1 H), 3.34 (s, 3 H), 3.31–3.26 (m, 2 H), 3.14 (dd, *J* = 8.5, 7.5 Hz, 1 H), 2.51 (m, 1 H), 2.10–1.92 (m, 4 H), 1.81–1.69 (m, 2 H), 1.49–1.35 (m, 2 H), 1.24 (m, 1 H), 1.02 (d, *J* = 6.5 Hz, 3 H), 0.92 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 138.5, 132.4, 131.1, 129.7, 129.5, 114.7, 113.7, 81.9, 81.6, 74.0, 57.2, 55.3, 36.1, 34.5, 33.4, 31.5, 29.0, 27.2, 20.1, 19.2, 18.6; IR (neat): 3079, 3006, 2960, 2926, 2881, 1615, 1514, 1456, 1377, 1302, 1248, 1173, 1100, 1038, 911, 804 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{24}H_{38}IO_3$ $[M+H]^+$ 501.1866, found 501.1871.



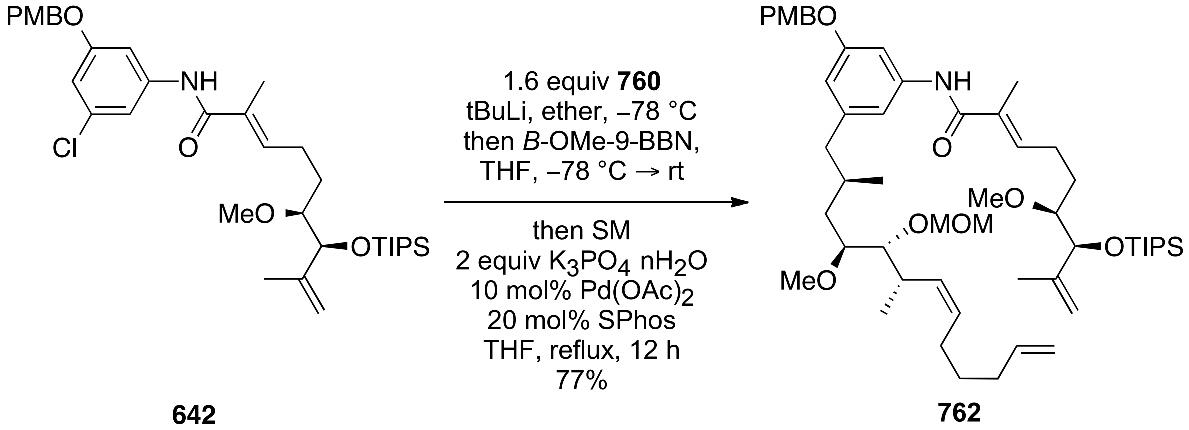
Preparation of relay chain-containing iodide **760**: A stirring solution of iodide **525** (1.764 g, 4.95 mmol) in dichloromethane (50 mL) at −78 °C (dry ice/acetone bath) was saturated with ozone until a blue color persisted. Once the completion of this step was confirmed by TLC (hexanes/EtOAc 9:1) and still at −78 °C, the solution was purged with nitrogen gas until the color dissipated and triphenylphosphine (1.429 g, 5.45 mmol) was added in one portion. The solution was allowed to slowly warm up to room temperature overnight. The reaction mixture was then concentrated and dried under high vacuum. At the appropriate time, the resulting residue was redissolved in THF (15.5 mL) to be used in the next step, assuming a quantitative yield of the aldehyde. Simultaneously, to a solution of 5-hexenyltriphenylphosphonium iodide[222] (**771**) (3.36 g, 7.12 mmol) in THF (8 mL) at 0 ºC was slowly added NaHMDS 1M in THF (6.4 mL, 6.4 mmol) under inert atmosphere. The resulting red solution was stirred for 2 hours at room temperature and then cooled to −78 °C. The aforementioned solution of crude aldehyde was added dropwise and the reaction mixture was allowed to slowly warm up to room temperature overnight. After 12 hours, the reaction was quenched with aqueous saturated NH_4Cl (60 mL) and extracted three times with ether. Combined organic layers were washed with brine, dried over MgSO4, and concentrated. Purification by column chromatography, eluting with hexanes/EtOAc (20:1 → 4:1), afforded iodide **760** (0.673 g, 1.585 mmol, 32 % yield) as a slightly yellowish oil from the complex crude mixture. This procedure was not optimized. R_f = 0.7 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.0, 11.5, 7.0 Hz, 1 H), 5.34 (ddd, *J* = 11.0, 7.5, 6.5 Hz, 1 H), 5.15 (m, 1 H), 4.99 (apparent d, *J* = 17.0 Hz, 1 H), 4.93 (apparent d, *J* = 11.5 Hz, 1 H), 4.83 (d, *J* = 10.75 Hz, 1 H), 4.62 (d, *J* = 10.75 Hz, 1 H), 3.58 (dd, *J* = 8.5, 1.0 Hz, 1 H), 3.41 (s, 3 H), 3.30 (s, 3 H), 3.29 (m, 1 H), 3.22 (m, 1 H), 3.14 (dd, *J* = 9.5, 6.0 Hz, 1 H), 2.51 (m, 1 H), 2.12–1.93 (m, 4 H), 1.71–1.63 (m, 2 H), 1.50–1.36 (m, 2 H), 1.22 (m, 1 H), 1.05 (d, *J* = 6.5 Hz, 3 H), 0.91 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 132.1, 129.6, 114.7, 97.5, 81.2, 79.3, 56.9, 56.1, 36.0, 34.2, 33.4, 31.2, 29.0, 27.2, 20.0, 19.3, 18.6; HRMS (ESI): *m/z* calculated for $C_{18}H_{34}IO_3$ $[M+H]^+$ 425.1553, found 425.1559.



642 **761**

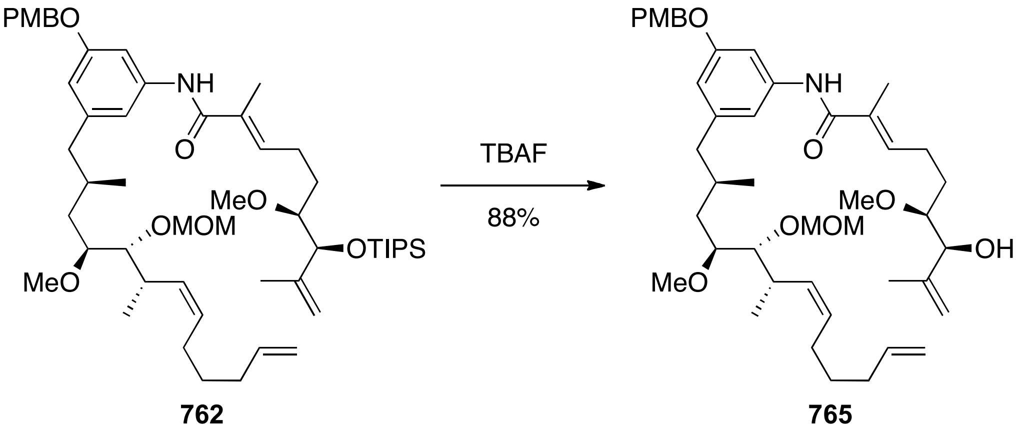
Preparation Suzuki product **761**: To a flame-dried 25mL pear-shaped flask provided with a magnetic stirrer, containing iodide **759** (165.0 mg, 0.381 mmol) in ether (1.2 mL) at −78 °C under nitrogen atmosphere, was added *tert*-butyllithium 1.7 M in pentane (450 μL, 0.762 mmol) (solution remains colorless and clear) and few minutes later, *B*-methoxy-9-borabicyclo[3.3.1]nonane 1M in THF (900 μL, <0.904 mmol) was added in one portion (white precipitate forms), followed by THF (1.2 mL) (solution rapidly becomes clear/colorless). The solution was stirred for 10 minutes more at −78 °C (white precipitate forms) and then at room temperature for 30 minutes (solution becomes clear/colorless). The solvent was blown off using nitrogen gas and a thin needle on the rubber cap. After the solvent was completely evaporated, THF (0.5 mL) was added, followed by potassium phosphate hydrate (118 mg, 0.476 mmol) and PMB-protected chloroamidophenol **642** (150.0 mg, 0.238 mmol). The mixture was freeze-pump-thaw degassed three times. A mixture of palladium(II) acetate (5.7 mg, 0.024 mmol) and SPhos (19.6 mg, 0.048 mmol) was dissolved in THF (1.2 mL). This solution was freeze-pump-thaw degassed three times and added in one portion to the first mixture causing a rapid color change to dark orange/brown. The reaction mixture was heated to reflux for 12 h. Once full conversion was confirmed by TLC (hexanes/EtOAc 9:1), the mixture was diluted with acetone and filtered through a short plug of silica gel eluting with additional acetone. After concentration, the product was purified by column chromatography eluting with hexanes/EtOAC (49:1 → 4:1) to afford Suzuki product **761** (190.9 mg, 0.212 mmol, 89% yield) as a white waxy solid. mp 46–47.5 °C. R_f = 0.3 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (t, *J* = 2 Hz, 1 H), 7.34 (d, *J* = 8.5 Hz, 2 H), 7.33 (br, 1 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 6.71 (t, *J* = 2 Hz, 1 H), 6.56 (t, *J* = 2 Hz, 1 H), 6.35 (m, 1 H), 5.77 (ddt, *J* = 17.0, 11.5, 7.0 Hz, 1 H), 5.31 (ddd, *J* = 11.0, 7.5, 6.5 Hz, 1 H), 5.17 (m, 1 H), 4.98 (apparent d, *J* = 17.0 Hz, 1 H), 4.96 (s, 2 H), 4.95 (overlapped s, 1 H), 4.92 (apparent d, *J* = 11.5 Hz, 1 H), 4.89 (apparent s, 1 H), 4.74 (d, *J* = 11 Hz, 1 H), 4.43 (d, *J* = 11 Hz, 1 H), 4.31 (apparent d, *J* = 5.5 Hz, 1 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.73 (m, 1 H), 3.45 (s, 3 H), 3.39 (m, 1 H), 3.33 (s, 3 H), 3.18 (m, 1 H), 2.64 (dd, *J* = 13.5, 5.0 Hz, 1 H), 2.51 (m, 1 H), 2.35–2.19 (m, 3 H), 2.08–1.95 (m, 4 H), 1.92 (s, 3 H), 1.86–1.77 (m, 2 H), 1.73 (s, 3 H), 1.71–1.56 (m, 2 H), 1.47–1.32 (m, 3 H), 1.08–1.02 (m, 21 H), 1.01 (d, *J* = 6.5 Hz, 3 H), 0.75 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ

167.5, 159.4, 159.3, 159.1, 145.0, 143.4, 138.9, 138.6, 136.4, 132.6, 132.1, 131.2, 129.63, 129.59, 129.3, 129.2, 114.6, 113.9, 113.7, 113.0, 112.9, 112.2, 103.7, 84.3, 82.0, 81.7, 76.5, 73.9, 69.7, 58.8, 57.2, 55.28, 55.25, 44.8, 36.5, 34.5, 33.4, 31.1, 29.1, 28.9, 27.1, 25.0, 19.1, 18.7, 18.6, 18.08, 18.05, 12.8, 12.4; HRMS (ESI): *m/z* calculated for $C_{59}H_{90}NO_8Si$ $[M+H]^+$ 968.6436, found 968.6431.



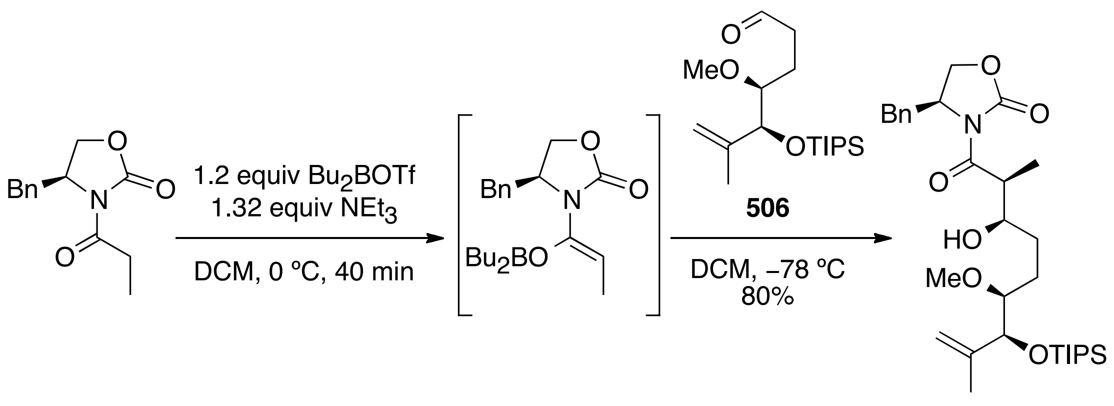
Preparation of Suzuki product **762**: To a flame-dried 25mL pear-shaped flask provided with a magnetic stirrer, containing iodide **760** (151.0 mg, 0.357 mmol) in ether (1.2 mL) at −78 °C under nitrogen atmosphere, was added *tert*-butyllithium 1.7 M in pentane (420 µL, 0.714 mmol) (solution remains colorless and clear) and 3 minutes later *B*-methoxy-9-borabicyclo[3.3.1]nonane 1M solution in THF (850 µL, >0.847 mmol) was added (white precipitate forms), followed by THF (1.2 mL) (solution rapidly becomes clear/colorless). The solution was stirred for 10 minutes more at −78 °C (white precipitate forms) and then at room temperature for 1 hour (solution becomes clear/colorless). The solvent was blown off using a stream of nitrogen gas and a thin needle on the rubber cap. After solvent was completely evaporated, THF (0.5 mL) was added, followed by potassium phosphate hydrate (118.0 mg, 0.476 mmol) and PMB-protected chloroamidophenol (150.0 mg, 0.238 mmol). The mixture was freeze-pump-thaw degassed three times. A mixture of palladium(II) acetate (5.7 mg, 0.024

mmol) and SPhos (19.6 mg, 0.048 mmol) was dissolved in THF (1.2 mL). This solution was freeze-pump-thaw degassed three times and added in one portion to the first mixture causing a rapid color change to dark orange/brown. The reaction mixture was heated to reflux for 12 h. TLC (9:1 hexanes/EtOAc) revealed almost complete conversion. The mixture was diluted with acetone and filtered through silica gel (wet with acetone) eluting with more acetone. After concentration, a 90% conversion was determined by ^{1}H NMR. The product was purified by column, eluting with hexanes/EtOAC (49:1 → 4:1) to afford **762** (163.0 mg, 0.183 mmol, 77 % yield) as a waxy solid. mp 50.5–52 °C. R_f = 0.27 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.32 (m, 4 H), 6.89 (d, *J* = 8.5 Hz, 2 H), 6.73 (apparent s, 1 H), 6.55 (apparent s, 1 H), 6.35 (m, 1 H), 5.78 (ddt, *J* = 17.0, 11.5, 7.0 Hz, 1 H), 5.32 (m, 1 H), 5.17 (m, 1 H), 4.98 (apparent d, *J* = 17.0 Hz, 1 H), 4.95 (s, 2 H), 4.95 (overlapped s, 1 H), 4.94 (apparent d, *J* = 11.5 Hz, 1 H), 4.89 (apparent s, 1 H), 4.83 (d, *J* = 11 Hz, 1 H), 4.61 (d, *J* = 11 Hz, 1 H), 4.31 (apparent d, *J* = 6.0 Hz, 1 H), 3.79 (s, 3 H), 3.58 (m, 1 H), 3.45 (s, 3 H), 3.39 (s, 3 H), 3.34 (m, 1 H), 3.30 (s, 3 H), 3.19 (m, 1 H), 2.65 (dd, *J* = 13.5, 5.0 Hz, 1 H), 2.52 (m, 1 H), 2.35–2.19 (m, 3 H), 2.11–1.93 (m, 4 H), 1.92 (s, 3 H), 1.74 (s, 3 H), 1.71–1.56 (m, 3 H), 1.48–1.31 (m, 3 H), 1.14 (m, 1 H), 1.11–0.98 (m, 24 H), 0.73 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 159.4, 159.2, 145.0, 143.3, 138.9, 138.6, 136.4, 132.3, 132.1, 129.4, 129.3, 129.1, 114.7, 113.9, 113.0, 112.9, 112.3, 103.6, 97.5, 84.3, 81.2, 79.7, 76.5, 69.7, 58.8, 56.9, 56.1, 55.3, 44.7, 36.5, 34.2, 33.4, 31.1, 29.1, 28.9, 27.2, 25.0, 19.1, 18.6, 18.5, 18.09, 18.05, 12.8, 12.4; HRMS (ESI): *m/z* calculated for $C_{53}H_{86}NO_8Si$ $[M+H]^+$ 892.6123, found 892.6125.



Preparation of RRCM substrate 765 as in print: *Preparation of RRCM substrate* **765**: To a pear-shaped flask containing a solution of Suzuki product **762** (68.4 mg, 0.077 mmol) in THF (2.5 mL) at 0 °C was added TBAF 1M in THF (770 μL, 0.770 mmol) dropwise. After 2 h at that temperature, TLC eluting with 3:1 hexanes/EtOAc confirmed the full consumption of the starting material. Still inside the cold bath, the reaction was quenched with 6 mL of cold aqueous saturated $NaHCO_3$ and the mixture was stirred for 5 minutes. The layers were separated and the aqueous phase was extracted with ether three times. Combined organic layers were dried over $MgSO_4$ and concentrated. The crude material was subjected to column chromatography eluting with hexanes/ether (3:7 → 3:17) (R_f = 0.18 → 0.4) to afford **765** (49.6 mg, 0.067 mmol, 88% yield) as a waxy solid after high vacuum. mp 53–55.5 °C; R_f = 0.4 (3:17 hexanes/ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.32 (m, 4 H), 6.89 (d, *J* = 8.5 Hz, 2 H), 6.74 (apparent s, 1 H), 6.55 (apparent s, 1 H), 6.38 (m, 1 H), 5.78 (ddt, *J* = 17.0, 11.5, 7.0 Hz, 1 H), 5.32 (m, 1 H), 5.17 (m, 1 H), 5.03 (apparent s, 1 H), 4.99 (apparent d, *J* = 17.0 Hz, 1 H), 4.95 (s, 2 H), 4.946 (overlapped s, 1 H), 4.94 (apparent d, *J* = 11.5 Hz, 1 H), 4.83 (d, *J* = 11 Hz, 1 H), 4.61 (d, *J* = 11 Hz, 1 H), 3.97 (m, 1 H), 3.79 (s, 3 H), 3.58 (m, 1 H), 3.45 (s, 3 H), 3.39 (s, 3 H), 3.29 (s, 3 H), 3.30–3.19 (m, 2 H), 2.65 (dd, *J* = 13.5, 5.0 Hz, 1 H), 2.55–2.48 (m, 2 H), 2.30–2.19 (m, 3 H), 2.11–1.95 (m, 4 H), 1.93 (s, 3 H), 1.75 (s, 3 H), 1.73–1.57 (m, 4

H), 1.43 (m, 1H), 1.13 (m, 1 H), 1.05 (d, *J* = 6.5 Hz, 3 H), 0.73 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 159.4, 159.2, 144.2, 143.3, 138.8, 138.6, 136.0, 132.3, 132.1, 129.4, 129.3, 129.0, 114.7, 114.0, 113.9, 113.0, 112.3, 103.6, 97.5, 81.6, 81.2, 79.6, 77.1, 69.7, 58.3, 57.0, 56.1, 55.3, 44.7, 36.4, 34.2, 33.4, 31.0, 29.1, 28.9, 27.1, 23.9, 18.6, 18.5, 17.9, 12.8; HRMS (ESI): *m/z* calculated for $C_{44}H_{66}NO_8$ $[M+H]^+$ 736.4788, found 736.4792.

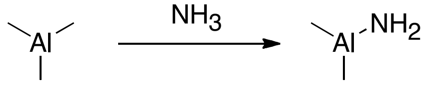


779

780

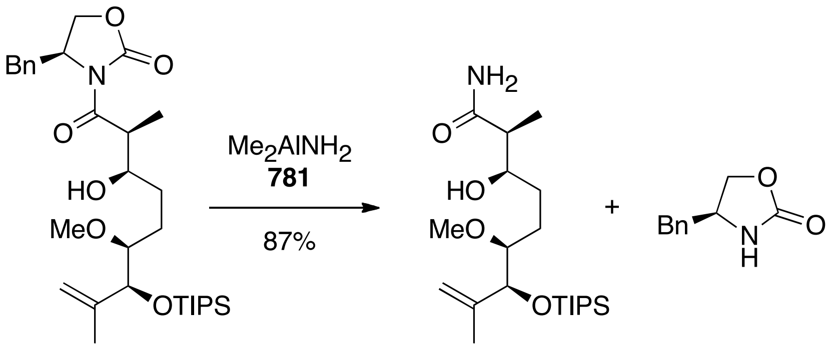
Preparation of aldol product **780**: A solution of (*S*)-4-benzyl-3-propionyloxazolidin-2-one (**779**)[213] (142 mg, 0.609 mmol, 1 equiv) in dichloromethane (2 mL) was cooled below 0 °C using an ice/water/salt bath. Dibutylboryl triflate 1M solution in dichloromethane (730 µL, 0.730 mmol, 1.2 equiv) was added dropwise, followed by triethylamine (113 µL, 0.804 mmol, 1.32 equiv). The bright yellow solution was stirred at 0 °C, on an ice/water bath, for 40 minutes and then cooled down to −78 °C on an acetone/dry ice bath. Then, a solution of aldehyde **506** (200 mg, 0.609 mmol) in dichloromethane (0.4 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 1.5 h after which it was slowly warmed up to −50 °C and stirred for 1.5 h; then again it was slowly warmed up to 0 °C and stirred for another 1.5 h. At this point, the reaction was carefully quenched with pH 7 buffer and MeOH (1:3) (0.6 mL), followed by 30%

H_2O_2 and MeOH (1:2) (1.8 mL) added dropwise. The cloudy mixture was stirred at 0 °C for 1 h and then warmed up to room temperature. The volatile material was removed *in vacuo* and the residue was extracted with dichloromethane. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Column chromatography eluting with hexanes/EtOAc (7:1 → 4:1) afforded **780** (272.1 mg, 0.484 mmol, 80% yield) as a clear colorless oil. R_f = 0.11 (7:1 hexanes/ethyl acetate); $[\alpha]^{20}_{D}$ +20.7° (*c* 2.039, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.29 (m, 2 H), 7.28–7.25 (m, 1 H), 7.20–7.17 (m, 2 H), 4.92 (s, 1 H), 4.86 (s, 1 H), 4.67 (dddd, *J* = 9.5, 7.5, 3.5, 3.0 Hz, 1 H), 4.24 (d, *J* = 6.25 Hz, 1 H), 4.19 and 4.16 (d of ABq, ^3J = 7.5 and 3.0 Hz, J_{AB} = 9.0 Hz, 2 H), 3.88 (m, 1 H), 3.74 (ddd, *J* = 14.0, 7.0, 3.0 Hz, 1 H), 3.44 (s, 3 H), 3.23 and 2.76 (d of ABq, ^3J = 3.5 and 9.5 Hz, J_{AB} = 13.25 Hz, 2 H), 3.17 (ddd, *J* = 8.5, 6.25, 3.0 Hz, 1 H), 3.07 (br, 1 H), 1.76–1.69 (m, 1 H), 1.71 (s, 3 H), 1.56 (m, 2 H), 1.28–1.20 (m, 1 H), 1.24 (d, *J* = 7.0 Hz, 3 H), 1.07–1.02 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.3, 153.0, 145.1, 135.1, 129.4, 128.9, 127.4, 113.1, 84.7, 77.6, 71.9, 66.1, 58.9, 55.1, 42.3, 37.8, 30.2, 26.8, 18.6, 18.1, 18.0, 12.5, 10.7; IR (neat): 3530, 2942, 2869, 1784, 1696, 1456, 1385, 1210, 1100, 884, 806 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{31}H_{51}NO_6SiNa$ $[M+Na]^+$ 584.3383, found 584.3384.

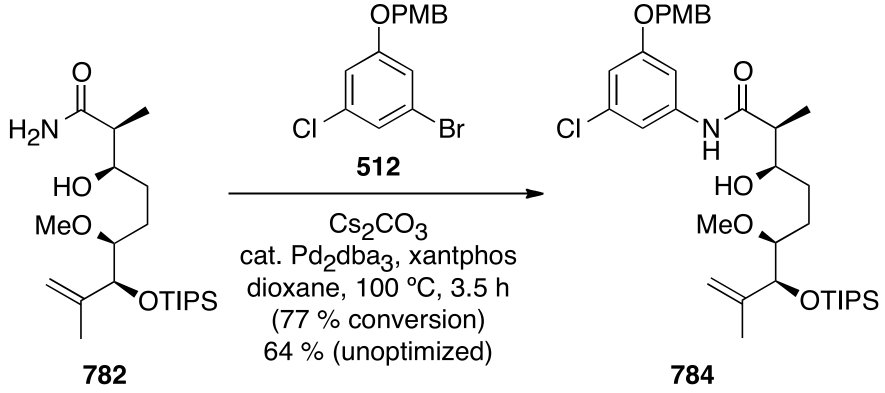


781

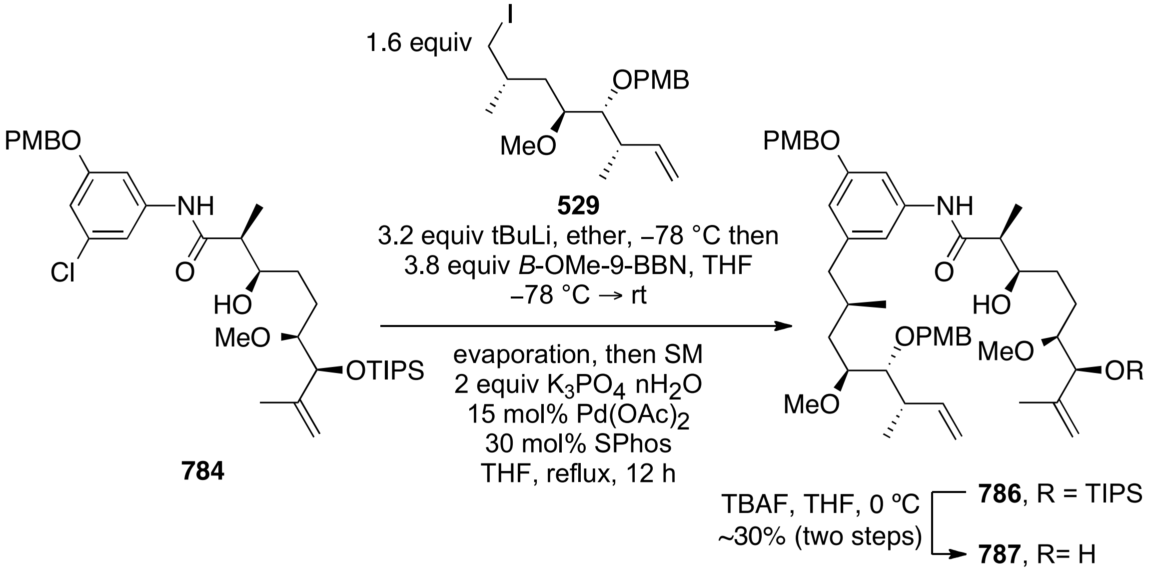
Preparation of dimethylaluminum amide (**781**):[215a] The glassware set-up for this reaction was first assembled and properly flame/vacuum-dried. A solution consisting of trimethylaluminum 25% in hexane (35 mL) and dry dichloromethane (25 mL) was placed in a 100mL three-necked round-bottomed flask. This flask was equipped with a dry ice condenser and a nitrogen gas inlet and was cooled in a dry ice/acetone bath. In another 100mL three-necked flask equipped with a dry ice condenser and a nitrogen gas inlet, were placed a few pieces of sodium metal. Both flasks were connected through a piece of plastic tubing, using flow controllers. The flask containing sodium was also cooled in the same dry ice-acetone bath and ammonia gas was then introduced. When more than 10 mL of the blue liquid ammonia solution accumulated in the flask, the addition of gas was stopped and the stopcocks between the liquid ammonia flask and the trimethylaluminum solution were opened to allow the dried ammonia gas to slowly distill into the reaction flask. When half the addition of ammonia was complete, the cooling bath was removed. Once the addition was complete, dry ice was no longer added to the condenser the mixture was allowed to stir at room temperature overnight under a nitrogen atmosphere until no more gas evolved. This reagent was immediately stored in the freezer as obtained. According to Weinreb,[223] the solution of **781** made by this procedure has a concentration of approximately 1.2 M and lasts for 2 weeks.



Preparation of amide **782**: To aldol product **780** (800 mg, 1.424 mmol) was added trimethylaluminum amide 1.2 M solution (3 mL, >3.56 mmol). The resulting homogeneous solution was stirred at room temperature for 7 hours. TLC (ether) showed that the reaction was complete. The reaction mixture was poured into a separatory funnel containing 2 mL of ice, 2 mL 1.0 M HCl, and 2 mL of ether. When methane production ceased the layers were separated, and the aqueous layer was extracted with two additional 4mL portions of ether, and two 4mL portions of ethyl acetate. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Column chromatography eluting with hexanes/EtOAc (1:1 → 1:2) afforded recovered chiral auxiliary (244.9 mg, 1.381 mmol, 97% yield), R_f = 0.3 (1:1 hexanes/ethyl acetate) and amide **782** (499.1 mg, 1.242 mmol, 87% yield) R_f = 0.08 (1:1 hexanes/ethyl acetate) as a colorless thick oil that solidified upon standing. mp 103–104 ºC; $[\alpha]^{20}_{D}$ −0.5° (*c* 1.182, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.18 (br, 1 H), 5.25 (br, 1 H), 4.92 (s, 1 H), 4.87 (s, 1 H), 4.29 (d, *J* = 6.5 Hz, 1 H), 3.78 (m, 1 H), 3.69 (d, *J* = 3.0 Hz, 1 H, exchangeable), 3.45 (s, 3 H), 3.21 (ddd, *J* = 8.0, 6.5, 3.0 Hz, 1 H), 2.42 (ddd, *J* = 8.5, 7.25, 3.0 Hz, 1 H), 1.76–1.69 (m, 1 H), 1.71 (s, 3 H), 1.56–1.50 (m, 2 H), 1.30 (m, 1 H), 1.15 (d, *J* = 7.0 Hz, 3 H), 1.07–1.01 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.1, 144.8, 113.3, 84.7, 76.9, 72.2, 58.7, 44.6, 29.5, 26.4, 18.6, 18.1, 18.0, 12.4, 11.6; IR (neat): 3345, 3177, 2926, 2867, 1684, 1636, 1458, 1420, 1373, 1253, 1094, 1063, 883, 822 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{21}H_{44}NO_4SiH$ $[M+H]^+$ 402.3040, found 402.3042.



Preparation of amide **784**[84]: Inside a glovebox, Pd_2dba_3 (21.0 mg, 0.023 mmol), XantPhos (39.8 mg, 0.069 mmol), anhydrous cesium carbonate (262.0 mg, 0.803 mmol), and 1,4-dioxane (1.15 mL) were premixed and stirred in an air-free flask for about 10 minutes. *o*-PMB-bromochlorophenol **512** (225.0 mg, 0.688 mmol) was added followed by amide **782** (230.3 mg, 0.573 mmol). The flask was sealed, taken out of the glovebox, and heated in an oil bath at 100 °C for 3.5 hours. The progress of the reaction was monitored by ^1H NMR analysis of worked-up samples (final yield was affected). No significant change was observed between samples taken after 2.5 hours (72% conversion) and 3.5 hours (77% conversion). The reaction was stopped at this point because of the risk of formation of an oxidation product (see page 151 for details). The mixture was cooled to room temperature, filtered through a short plug of celite eluting with ethyl acetate, and concentrated. The crude material was subjected to column chromatography eluting with hexanes/EtOAc (1:1 → 1:2) to afford amide **784** (239.3 mg, 0.369 mmol, 64% yield discounting the weight of ether present in the isolated material) and amide **782** (42.1 mg, 18% recovered starting material). R_f(**784**)= 0.27 (3:1 hexanes/EtOAc); $[\alpha]^{20}_D$ +14.3° (*c* 0.56, ether); ^1H NMR (500 MHz, $CDCl_3$): δ 8.61 (br, 1 H), 7.31 (d, *J* = 8.5 Hz, 2 H), 7.28 (t, *J* = 1.7 Hz, 1 H), 7.04 (t, *J* = 1.7 Hz, 1 H), 6.89 (d, *J* = 8.5 Hz, 2 H), 6.67 (t, *J* = 1.7 Hz, 1 H), 4.94 (s, 2 H), 4.87 (apparent s, 1 H), 4.84 (apparent s, 1 H), 4.30 (d, *J* = 6.7 Hz, 1 H), 4.17 (br, 1 H), 3.81 (m, 1 H), 3.80 (s, 3 H), 3.48 (s, 3 H), 3.24 (td, *J* = 6.7, 2.9 Hz, 1 H), 2.61 (qd, *J* = 7.1, 2.9 Hz, 1 H), 1.73 (m, 1 H), 1.70 (s, 3 H), 1.54 (m, 1 H), 1.42 (m, 1 H), 1.18 (d, *J* = 7.1 Hz, 3 H), 1.11–0.97 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4, 159.9, 159.6, 144.5, 140.1, 134.9, 129.3, 128.5, 114.0, 113.7, 112.2, 110.9, 104.6, 84.7, 76.7, 72.8, 70.1, 58.6, 55.3, 46.1, 28.9, 26.2, 18.4, 18.1, 18.0, 12.4, 11.9; IR (neat): 3415, 3310, 2941, 2865, 1669, 1591, 1542, 1516, 1458, 1377, 1302, 1251, 1201, 1173, 1011, 1036, 884, 824 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{35}H_{55}ClNO_6Si$ $[M+H]^+$ 648.3487, found 648.3490.



Preparation of Suzuki product **786**: To a flame-dried 10 mL pear-shaped flask, provided with a magnetic stirrer, containing iodide **529** (45.1 mg, 0.104 mmol) (dried in a vacuum desiccator over drierite overnight) in ether (0.4 mL) at –78 °C under nitrogen atmosphere, was added *tert*-butyllithium 1.7 M in pentane (125 μL, 0.208 mmol) (solution remains colorless and clear). A few minutes later, *B*-methoxy-9-borabicyclo[3.3.1]nonane 1M in THF (0.25 mL, 0.25 mmol) was added (white precipitate forms) followed by THF (0.35 mL) (solution becomes clear/colorless rapidly). The solution was stirred for 10 minutes more at –78 °C (white precipitae forms) and then at room temperature for 30 minutes (solution becomes clear/colorless again). The solution was transferred via cannula to a small air-free flask containing potassium phosphate hydrate (0.032 g, 0.130 mmol) and aryl chloride partner **784** (0.042 g, 0.065 mmol). The solvent was blown off using nitrogen and a thin needle on the rubber cap. After the solvent was evaporared, THF (200 μL) was added. The resulting mixture was freeze-pump-thaw degassed (0.01 torr) three times. In a small vial, a mixture of palladium(II) acetate (2.2 mg, 9.75 μmol) and SPhos (8.0 mg, 20 μmol) was dissolved in THF (0.4 mL). The vial was connected to the Schlenk line and the solution was freeze-pump-thaw degassed (0.01 torr) three times. The solution of catalyst was added quickly to the first mixture via syringe causing a sudden color change to dark orange-brown. The air-free flask was sealed under nitrogen atmosphere and the reaction mixture was refluxed for 12 hours. Once full conversion was confirmed by TLC (3:1 hexanes/EtOAc), the mixture was diluted with acetone and filtered through a short pad of silica gel eluting with acetone. After concentration of the filtrate, the residue was subjected to column chromatography eluting with hexanes/EtOAc (49:1 → 3:1). Fractions containing the main spot at $R_f = 0.29$ (4:1 hexanes/EtOAc) were combined and concentrated to afford the desired product **786** contaminated with an unidentified closely related compound in a 4:1 molar ratio. This material (~30 mg) was used in the following step without further purification.

Preparation of RCM substrate **787**: Approximately half of the impure Suzuki product **786** obtained in the previous step, dissolved in THF (1.1 mL), was treated at 0 ºC with TBAF 1M in THF (325 μL, 0.325 mmol), added dropwise. After 1.5 hours, TLC (1:1 DCM/ether) showed that the SM was fully consumed. The reaction was quenched with 2 mL of saturated sodium bicarbonate and extracted with ethyl acetate several times. Combined organic layers were dried over $MgSO_4$ and concentrated. Column chromatography eluting DCM/ether (2:1 → 1:2) afforded **787** (7.3 mg, 0.0095 mmol, 29.5 % yield) as a colorless thick oil. R_f (**787**) = 0.17 (1:1 DCM/ether); $[\alpha]^{20}_{D}$ +1.7° (*c* 0.32, ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (br, 1 H), 7.33 (d, *J* = 9.0 Hz, 2 H), 7.32 (t, *J* = 1.7 Hz, 1 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 9.0 Hz, 2 H), 6.71 (t, *J* = 1.7 Hz, 1 H), 6.55 (t, *J* = 1.7 Hz, 1 H), 5.66 (m, 1 H), 5.02–4.95 (m, 2 H), 4.85 (apparent s, 1 H), 4.94 (s, 2 H), 4.90 (apparent s, 1 H), 4.70 (d, *J* = 10.5 Hz, 1 H), 4.44 (d, *J* = 10.5 Hz, 2 H), 4.00 (m, 1 H), 3.85 (m, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.46 (s, 3 H), 3.41–3.35 (m, 2 H), 3.32 (s, 3 H), 3.32–3.28 (m, 1 H), 2.62 (dd, *J* = 13.3, 5.0 Hz, 1 H), 2.53–2.48 (m, 2 H), 2.28–2.22 (m, 2 H), 1.97 (br, 1 H), 1.76 (m, 1 H), 1.72 (s, 3 H), 1.62–1.48 (m, 4 H), 1.25–1.22 (m, 1 H), 1.22 (d, *J* = 7.5 Hz, 3 H), 1.07 (d, *J* = 7.5 Hz, 3 H), 0.76 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.7, 159.4, 159.3, 159.0, 144.0, 143.5, 141.3, 138.7, 131.1, 129.6, 129.3, 129.1, 114.7, 114.3, 113.9, 113.7, 113.0, 112.1, 103.8, 82.2, 81.5, 81.3, 77.2, 73.8, 72.8, 69.8, 58.5, 57.2, 55.29, 55.27, 46.1, 40.9, 36.6, 31.2, 30.3, 28.4, 26.8, 18.7, 17.7, 17.5, 11.6; IR (neat): 3311, 2953, 2925, 2869, 2852, 1653, 1615, 1558, 1541, 1516, 1457, 1375, 1249, 1172, 1146, 1096, 1036, 822 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{45}H_{64}NO_9$ $[M+H]^+$ 762.4581, found 762.4588.

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