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„Total Synthesis of Cicutoxin and FR252921 *via* a Unified Pericyclic Approach“

verfasst von / submitted by

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Written by,

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Table of Contents

Abstract 4
Abstrakt 6
List of Abbreviation 8
Chapter 1. Introduction 12
1.1 Polyene Natural Products: Isolation and Bioactivity 12
1.2 General Strategies for the Syntheses of Polyene Natural Products 13
1.2.1 Carbonyl Olefinations 14
1.2.2 Transition Metal-Mediated Coupling Reactions 17
1.3 Polyene Synthesis: A 4π-Electrocyclic Ring opening Approach 21
1.3.1 Electrocyclic Reactions 21
1.3.2 4π-Electrocyclic Ring Closing Reactions 22
1.3.3 4π-Electrocyclic Ring Opening Reactions 24
Chapter 2. Objectives of this PhD Work 36
Chapter 3. Total Synthesis of Cicutoxin 37
3.1 Structure and Bioactivity 37
3.2 Previous Synthesis 38
3.2.1 Trippett *et al.*'s Racemic Synthesis 38
3.2.2 Gung *et al.*'s Asymmetric Synthesis 39
3.2.3 Brückner *et al.*'s Asymmetric Synthesis 40
3.3 Total Synthesis of Cicutoxin 41
3.3.1 Functionalization of Cyclobutenes 41
3.3.2 Retrosynthesis of Cicutoxin 43
3.3.3 Total Synthesis of Cicutoxin 44
3.4 Biological Studies 50
3.5 Conclusion 51
3.6 Perspective 51
Chapter 4. Total Synthesis of FR252921, FR252922 and FR256523 55

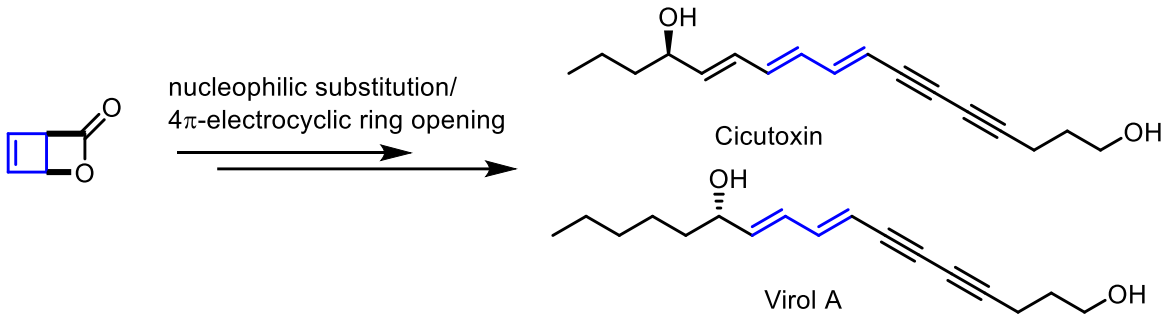
4.1 FR252921, FR252922 and FR256523: Structures and Bioactivities 55
4.2 FR252921: Previous Synthesis 56
4.2.1 Pohanka *et al.*'s Non-Stereospecific Semisynthesis of FR252921 and FR252922 56
4.2.2 Falck *et al.*'s Total Synthesis of FR252921 57
4.2.3 Cossy *et al.*'s Total Synthesis of FR252921 60
4.3 Synthesis of FR molecules, Analogues and Probes 64
4.3.1 Retrosynthesis 65
4.3.2 Optimization and Synthesis of Acid 4.071 68
4.3.3 Synthesis of Amine 4.072 69
4.3.4 Synthesis of Fragment 1 69
4.3.5 Synthesis of Fragment 2 81
4.3.6 Scalable Synthesis of Amines 96
4.3.7 Synthesis of Bisamides 97
4.3.8 Esterification 99
4.3.9 Macrocyclization 107
4.3.10 Deprotection 113
4.3.11 Biological Studies 115
4.4 Conclusion 120
4.5 Perspective 121
4.5.1 Analogues Simplification and Optimization 121
4.5.2 FR252921: An Ammonium Chelator? 122
Chapter 5. Synthetic Efforts towards Total Synthesis of Cyclamenol A 124
5.1 Structure and Bioactivity 124
5.2 Previous Synthesis 125
5.2.1 First Approach: Macrolactamization 125
5.2.2 Second Approach: Double Stille Coupling 129
5.2.3 Third Approach: McMurry Coupling or Pinacolization Approach 130
5.3 Synthetic Efforts towards Cyclamenol A 134
5.3.1 First Approach: Suzuki-Miyaura Macrocyclization/4π-Electrocyclic Ring Opening 134

5.3.2 Revised Approach Based on Ring-Closing Metathesis 143
5.4 Conclusion 148
5.5 Perspective 149
Chapter 6. Experimental Section 150
6.1 General Information 150
6.2 Total Synthesis of Cicutoxin 151
6.2.1 Functionalization of Cyclobutenes 151
6.2.2 Total Synthesis of Cicutoxin 154
6.3 Total Synthesis of FR252921, FR252922 and FR256523 167
6.3.1 Improved Synthesis of Acid 4.071 167
6.3.2 Synthesis of Salt 4.079 167
6.3.2 Synthesis of Aldehydes 169
6.3.3 Synthesis of Aldol Adducts 173
6.3.4 Synthesis of Fragment 2 176
6.3.5 Synthesis of Amines 185
6.3.6 Synthesis of Bisamides 187
6.3.7 Synthesis of Esters 192
6.3.8 Suzuki-Miyaura Macrocyclization/4π Electrocyclic Ring Opening 198
6.3.9 Mechanistic Study 203
6.3.10 Deprotection 206
6.3.11 Synthesis of the Probe 211
6.4 Synthetic Efforts towards Total Synthesis of Cyclamenol A 221
References 228

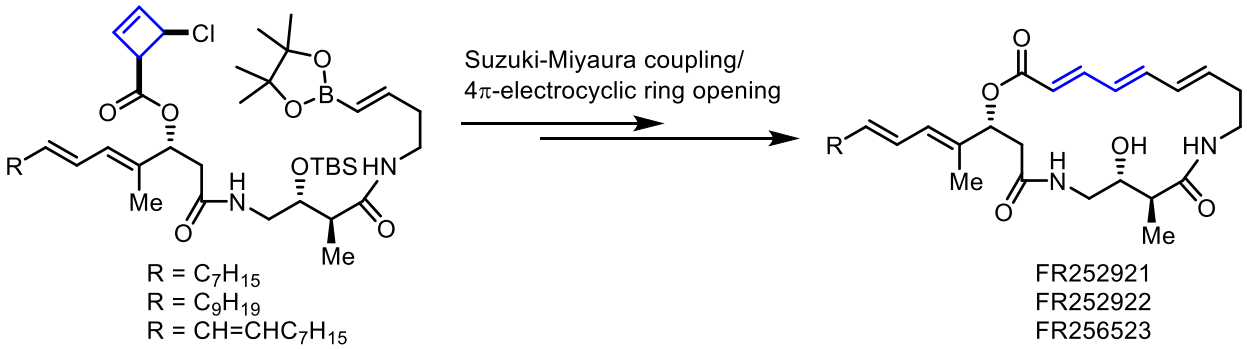
Abstract

The work in this thesis is devoted to the total syntheses of bioactive polyene natural products by using the cyclobutene moiety as a diene linchpin. We demonstrated that the 4π-electrocyclic ring opening of cyclobutene derivatives coupled with other reactions, such as nucleophilic substitution, Suzuki-Miyaura coupling, was a highly reliable and efficient method for the synthesis of polyenes.

In chapter 3, we achieved the divergent and efficient synthesis of polyenols, viz. cicutoxin and virol A, via a tandem nucleophilic substitution/4π-electrocyclic ring opening event.

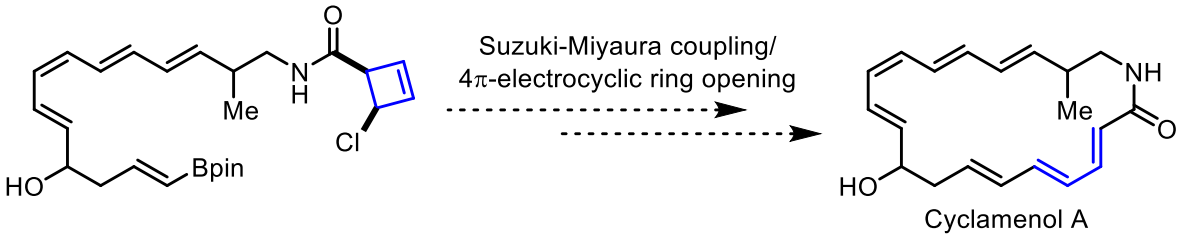


In chapter 4, we successfully devised a domino Suzuki-Miyaura coupling/4π-electrocyclic ring opening process, and applied it in the total synthesis of deceptively challenging immunosuppressants FR252921, FR252922 and FR256523. Our route was very convergent and allowed us to synthesize a range of analogues. Besides that, molecular probes were designed and synthesized for the identification of its molecular targets of this fascinating family of metabolites.



Abstract

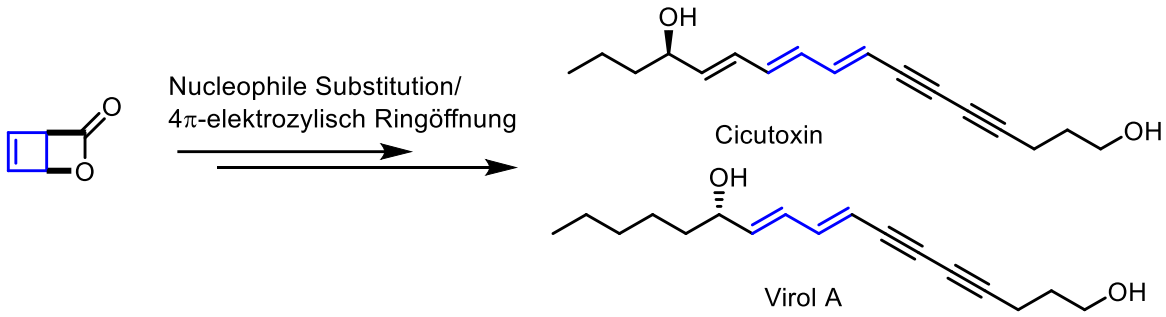
In chapter 5, we described our efforts towards the total synthesis of cyclamenol A. Our attempted Suzuki-Miyaura coupling/4π-electrocyclic ring opening approach is currently thwarted by our inability to obtain a suitable precursor for the macrocyclization.



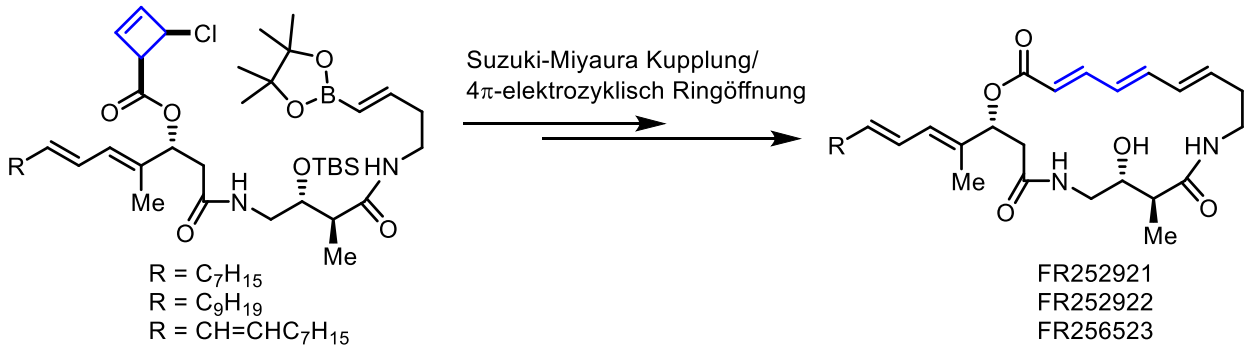
Abstrakt

Diese Arbeit ist den Totalsynthesen bioaktiver Polyen Naturstoffen mittels der Cyclobutengruppe als Dreh- und Angelpunkt gewidmet. Wir demonstrierten die hohe Zuverlässigkeit und Effizienz der 4π-elektrozyklisch Ringöffnung kombiniert mit anderen Reaktionen wie nukleophiler Substitution oder Suzuki-Miyaura Kupplung als Methode zur Synthese von Polyenen.

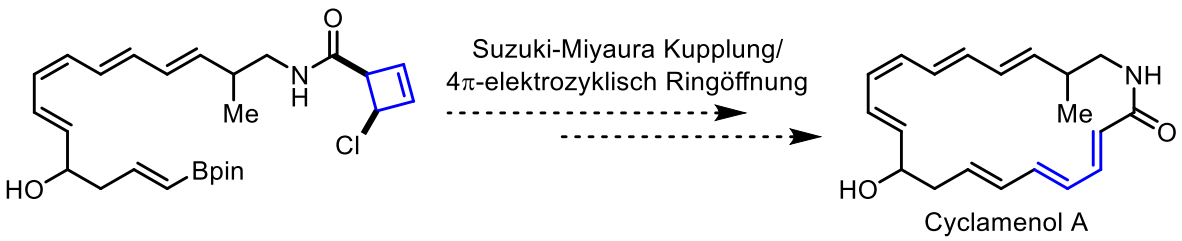
In Kapitel 3 erreichten wir die divergente und effiziente Synthese von den Polyenolen Cicutoxin und Virol A mittels eines Tandems nukleophilen Substitution/4π-elektrozyklisch Ringöffnungsereignis.



In Kapitel 4 entwickelten wir erfolgreich ein Domino Suzuki-Miyaura Kupplung/4π-elektrozyklisch Ringöffnungsverfahren und wandten dieses in der Totalsynthese der herausfordernden Immunsuppressiva FR252921, FR252922 und FR256523 an. Unsere Route war sehr konvergent und erlaubte uns eine Reihe von Analoga zu synthetisieren. Zusätzlich wurden molekulare Sonden für die Identifizierung der molekularen Ziele dieser faszinierenden Familie von Metaboliten entworfen und synthetisiert.



In Kapitel 5 beschreiben wir unsere Bemühungen in Richtung der Totalsynthese von Cyclamenol A. Unser versuchter Suzuki-Miyaura Kupplung/4π-elektrozyklisch Ringöffnungsansatz wurde gegenwärtig durch unser Unvermögen, eine passende Vorstufe für die Makrocyclisierung zu erhalten, durchkreuzt.



List of Abbreviation

ACN	acetonitrile
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl
Bn	benzyl
Bz	benzoyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
brsm	based on recovered starting material
C	concentration
CBS	Corey–Bakshi–Shibata catalyst
Conc.	concentrated
COD	1,5-cyclooctadiene
CsA	camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dba	dibenzylideneacetone
DCC	*N,N*'-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIC	N,N'-diisopropylcarbodiimide
DIPEA	diisopropyl-ethyl amine
d.r.	diastereomeric ratio
DMAP	dimethyl amino pyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	N, N'-dimethylpropyleneurea
DMSO	dimethylsulfoxide
DPBA	2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl

DPPA	diphenylphosphoryl azide
dppf	1,1'-ferrocenediyl-bis(diphenylphosphine)
E	electrophile
ee	enantiomeric excess
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	electron-donating group
EWG	electron-withdrawing group
equiv.	equivalent(s)
ent	enantiomer(ic)
ESI	electrospray ionization
Et	ethyl
FMO	frontier molecular orbital
Grubbs 2	Grubbs Catalyst™ 2nd Generation
h	hour(s)
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HBTU	N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate
HMPA	hexamethylphosphoramide
HOBt	hydroxybenzotriazole
HOMO	highest occupied molecular orbital
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
hv	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass
HWE	Horner-Wadsworth-Emmons
i	iso
Ipc	isopinocampheyl
KHMDS	potassium bis(trimethylsilyl)amide
LHMDS	lithium bis(trimethylsilyl)amide
M	molar (concentration)
Me	methyl
MIDA	N-methyliminodiacetic acid
min	minute(s)
MS	molecular sieves
MO's	molecular orbitals

MOM	methoxymethyl acetal
m/z	atomic mass units per charge
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
ND	not determined
NEt_3	triethylamine
NMM	N-methylmorpholine
NMP	N-methylpyrrolidine
NMR	nuclear magnetic resonance
N.R.	no reaction
Nu	nucleophile(s)
o	*ortho*
p	*para*
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
Ph	phenyl
pin	pinacol
Piv	pivaloate
Pr	propyl
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
quant.	quantitative
rac	racemic
RCM	ring-closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
rt	room temperature
s.m.	starting material
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	*tert*
t-AmOH	2-methylbutan-2-ol
TBAF	tetra-n-butylammonium fluoride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THP	tetrahydropyranyl
TLC	thin layer chromatography
TBS	*t*-butyl-dimethylsilyl

TBSOTf	*t*-butyl-dimethylsilyl trifluoromethane sulfonate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethane sulfonate
TMS	trimethylsilyl
Ts	toluenesulfonyl
sat.	saturated
2,2-DMP	2,2-dimethylpropane
9-BBN	9-borabicyclo[3.3.1]nonane
µW	microwave
UV	ultraviolet
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Chapter 1. Introduction

1.1 Polyene Natural Products: Isolation and Bioactivity

Polyene natural products are secondary metabolites containing conjugated alkenyl units (Figure 1.1). These compounds comprise a major family of metabolites with diverse structures and bioactivities and are isolated from bacteria, fungi, plants or marine organisms. [1]

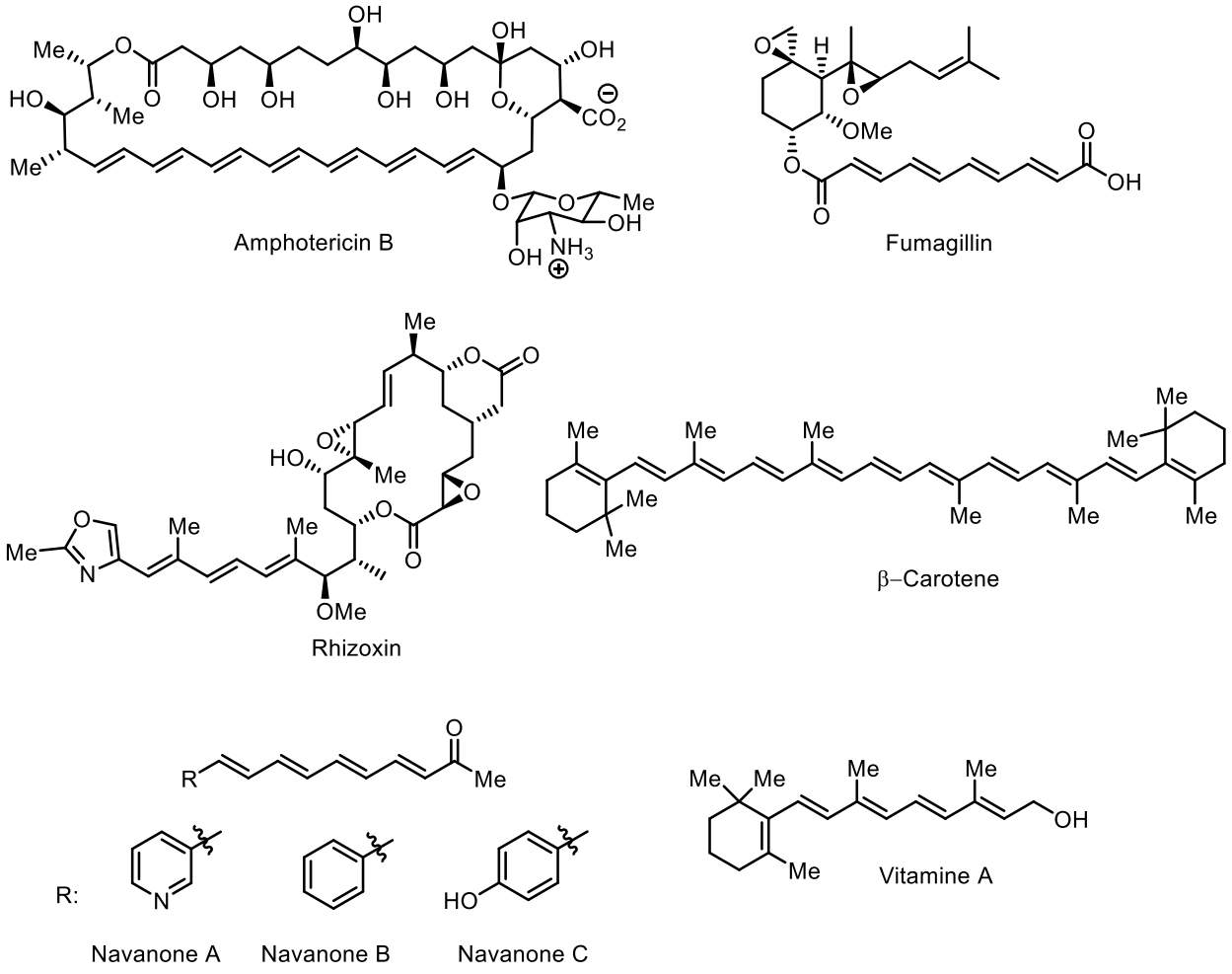


Figure 1.1 Examples of polyene natural products.

Among the bacterial polyene natural products, oxo polyene macrolides have arguably received the most attention from both synthetic chemists and biologists.[2] These natural products generally display up to seven conjugated C=C bonds and several 1,3- or 1,4- polyol motifs, and most of them possess potent

antifugal and antibiotic activities. One notable member from this family, amphotericin B (figure 1.1), has been widely used in the treatment of fungal infections.[3]

Polyene compounds have also been isolated from fungi. Prominent examples include fumigillin and rhizoxin (figure 1.1).[4,5] While fumigillin possesses amebicidal and antibacterial properties, rhizoxin has been found to display *in vivo* antitumor activity.

Plants are also a major source for polyene metabolites and pigments derived from carotenoids (such as β-carotene, figure 1.1), are arguably the most well-studied.[6] These pigments play crucial role in the light harvesting process during the photosynthesis.[7] In addition, they have been found to act as quenchers of reactive oxygen species.[8]

Marine organisms are also a source of polyene compounds which are typically toxic and vividly colored. Resulting from evolution, some marine organisms are known to secrete polyenes as a defense mechanism against predators. For instance, opisthobranchia, which lacks a hard shell, can secrete yellow navanones A, B, and C (figure 1.1) as alarm pheromones to its predators.[9]

Polyenes from animal sources generally display important functional properties. For instance, retinols, which include vitamin A (figure 1.1) and its analogues, have been found to play important roles in vision.[10] In addition, their usefulness as anti skin-aging agents is also being studied.[11]

1.2 General Strategies for the Syntheses of Polyene Natural Products

The efficient synthesis of polyene natural products still poses a big challenge to synthetic chemists,[1] as conjugated polyenes and the synthetic intermediates en route to those are sensitive to light, oxygen, heat and common agents, such as acids. Although the development of methodologies for the stereoselective construction of polyenes has progressed significantly in recent years, chemists are still limited to a traditional handful of approaches, namely carbonyl olefinations and transition metal-mediated coupling reactions (figure 1.2).[1]

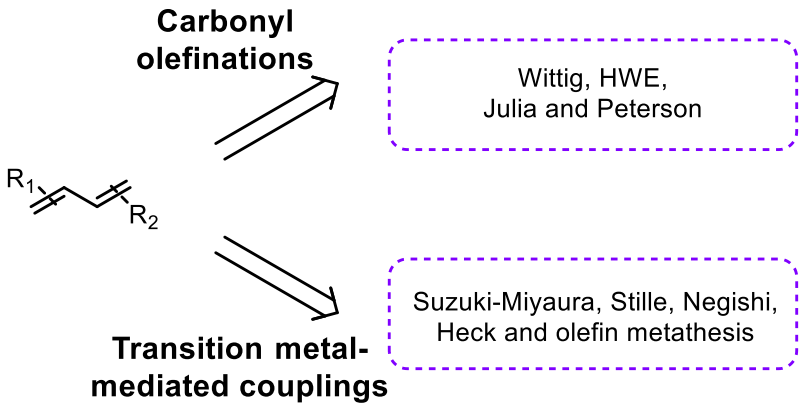


Figure1.2 Overview of traditional strategies for the synthesis of polyenes.

1.2.1 Carbonyl Olefinations

Among the full spectrum of carbonyl olefinations, the Wittig reaction and its modified version Horner–Wadsworth–Emmons (HWE) reaction (figure 1.3) have found extensive applications in the polyene natural products synthesis arena.[12,13] These reactions generally enjoy mild conditions and can afford high *E/Z* selectivity. However, a notable drawback of these reactions is their low atom economy since stoichiometric amounts of phosphine oxides or phosphonates are produced.

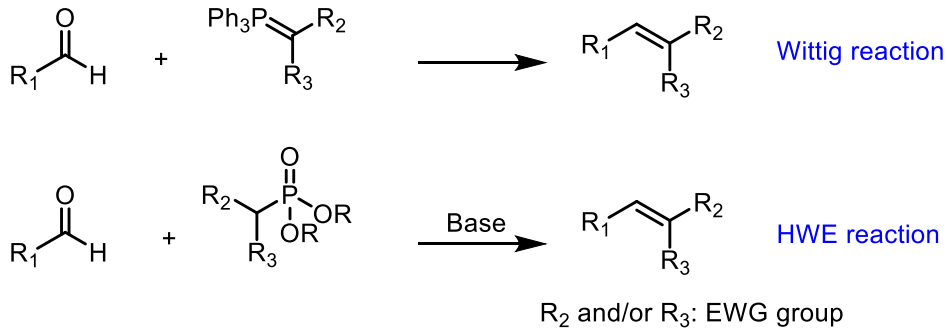


Figure 1.3 Wittig reaction and HWE reaction.

For example, the BASF synthesis of vitamin A utilizes a Wittig reaction on large scale to produce retinyl acetate **1.001**.[14]

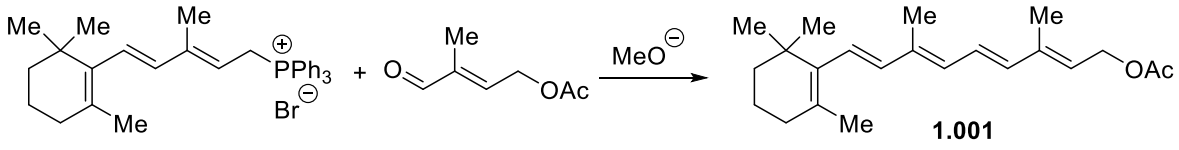


Figure 1.4 BASF's synthesis of retinyl acetate **1.001**.

The landmark synthesis of amphotericin B by Nicolaou and coworkers relies on the HWE reaction as a key macrocyclization event delivering product **1.002** in 70% yield.[15]

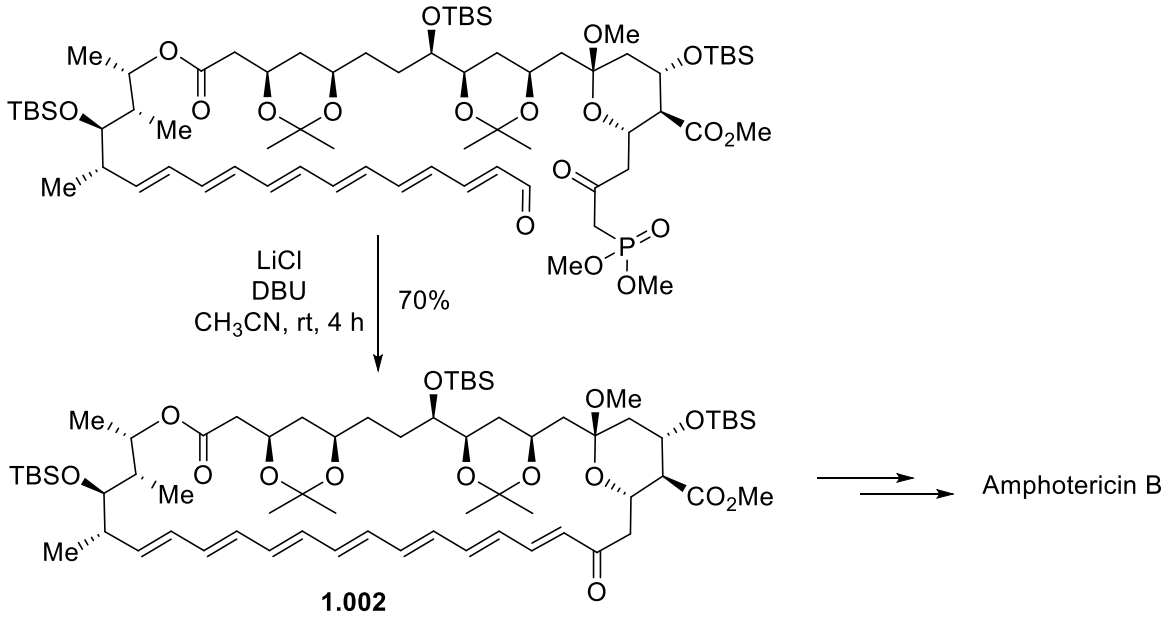


Figure 1.4 Nicolaou *et al.*'s synthesis of amphotericin B featuring a HWE macrocyclization.

The Julia and Peterson olefinations (figure 1.5) have also been used for polyene synthesis.[16,17] These reactions generally involve a two-step sequence. While Julia olefination usually favors the more stable *E* alkene isomer, Peterson olefination can be tuned to selectively deliver either *E* or *Z* alkene products depending on the reaction conditions. In addition, the modified Julia-Kocienski olefination (figure 1.5) which obviates the use of reducing reagents and enables the one pot synthesis of alkene, has found increasing application.[18]

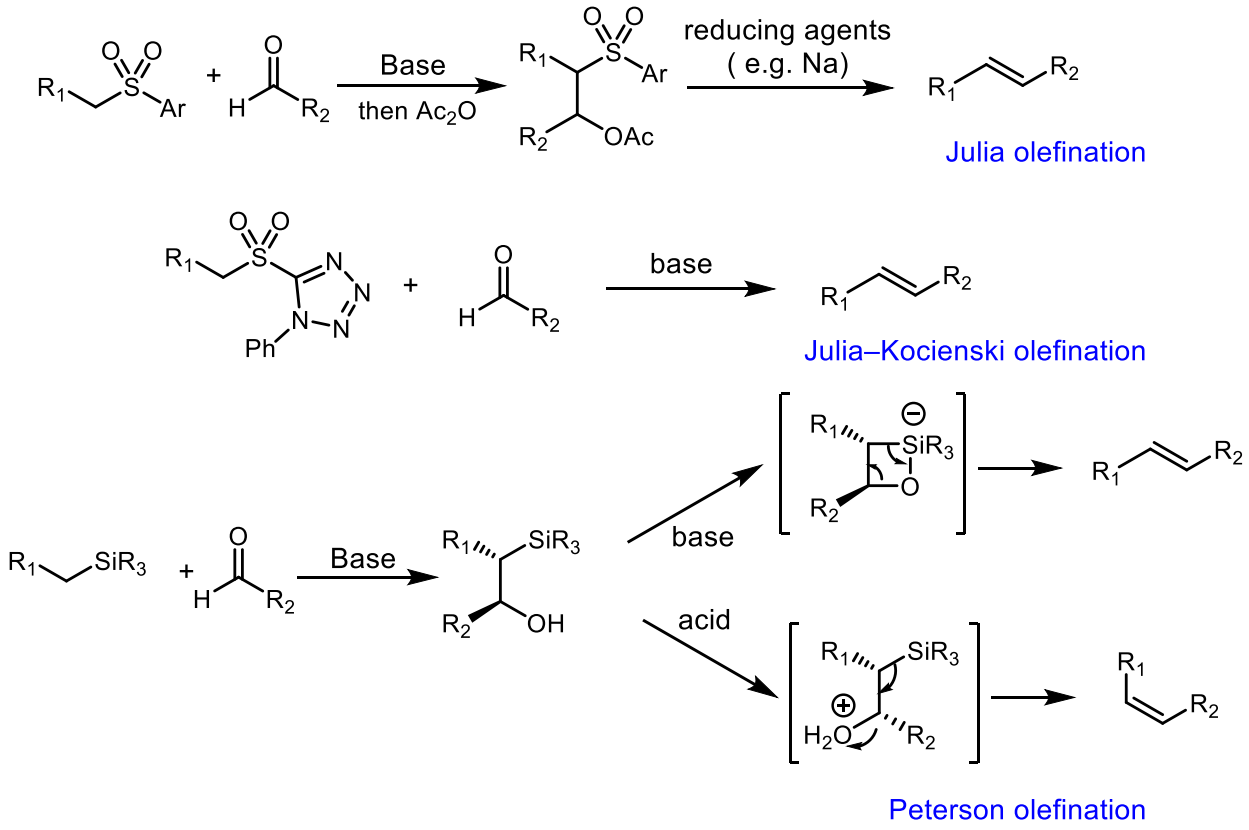


Figure 1.5 Julia, Julia-Kocienski and Peterson olefinations.

One example using these reactions can be found in the total synthesis of 2'-O-methylmyxalamide D (figure 1.6).[19] A key intermediate **1.003** was obtained in 41% yield with a *Z*/*E* selectivity = 25:1. Interestingly, the mechanistic origin of the *Z* selectivity remains unclear.

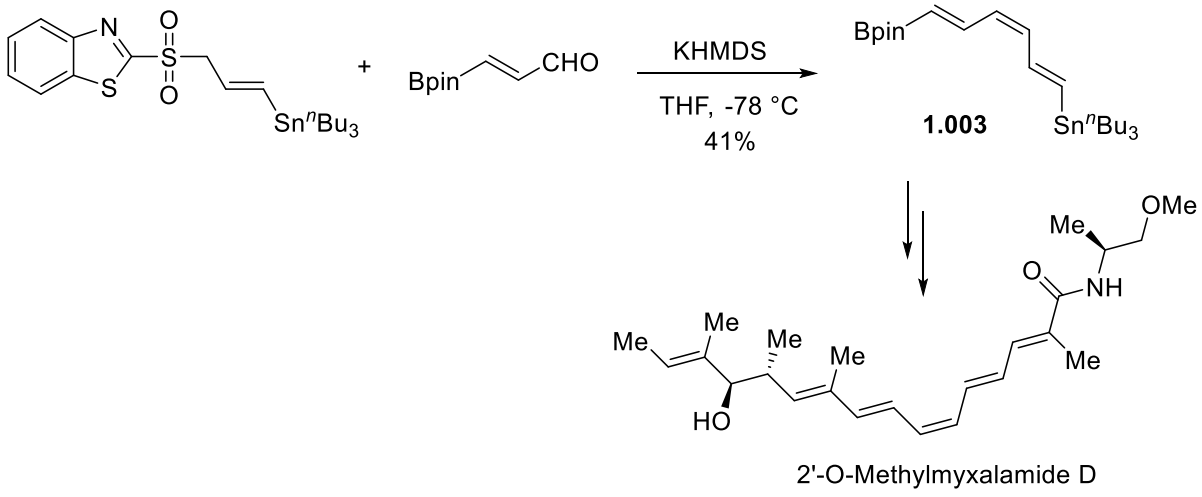


Figure 1.6 Julia olefination in the synthesis of 2'-O-methylmyxalamide D.

1.2.2 Transition Metal-Mediated Coupling Reactions

One of the most notable advances in organic synthesis in the last century is the development of transition metal-mediated cross coupling reactions.[20] Representative examples of these reactions include the Suzuki-Miyaura reaction,[21] the Stille reaction,[22] the Negishi reaction,[23] the Heck reaction[24]. Due to their excellent stereospecificity, mild conditions and wide functional group tolerance, these reactions have been widely used in the coupling of sp^2-sp^2 units.

Due to the non-toxic nature of boron reagents and its mild reaction conditions, Suzuki-Miyaura reaction has been widely used in the construction of polyene motifs.[1,21] Recently, Burke and coworkers synthesized a series of bifunctional halogen MIDA-boronate building blocks,[25] which allow the synthesis of polyene natural products in a nearly modulate fashion. For instance, the total synthesis of neurosporaxanthin β-D-glucopyranoside was accomplished by four iterative Suzuki-Miyaura cross couplings with only three bifunctional building blocks **BB1**, **BB2** and **BB3** (figure 1.7).[26]

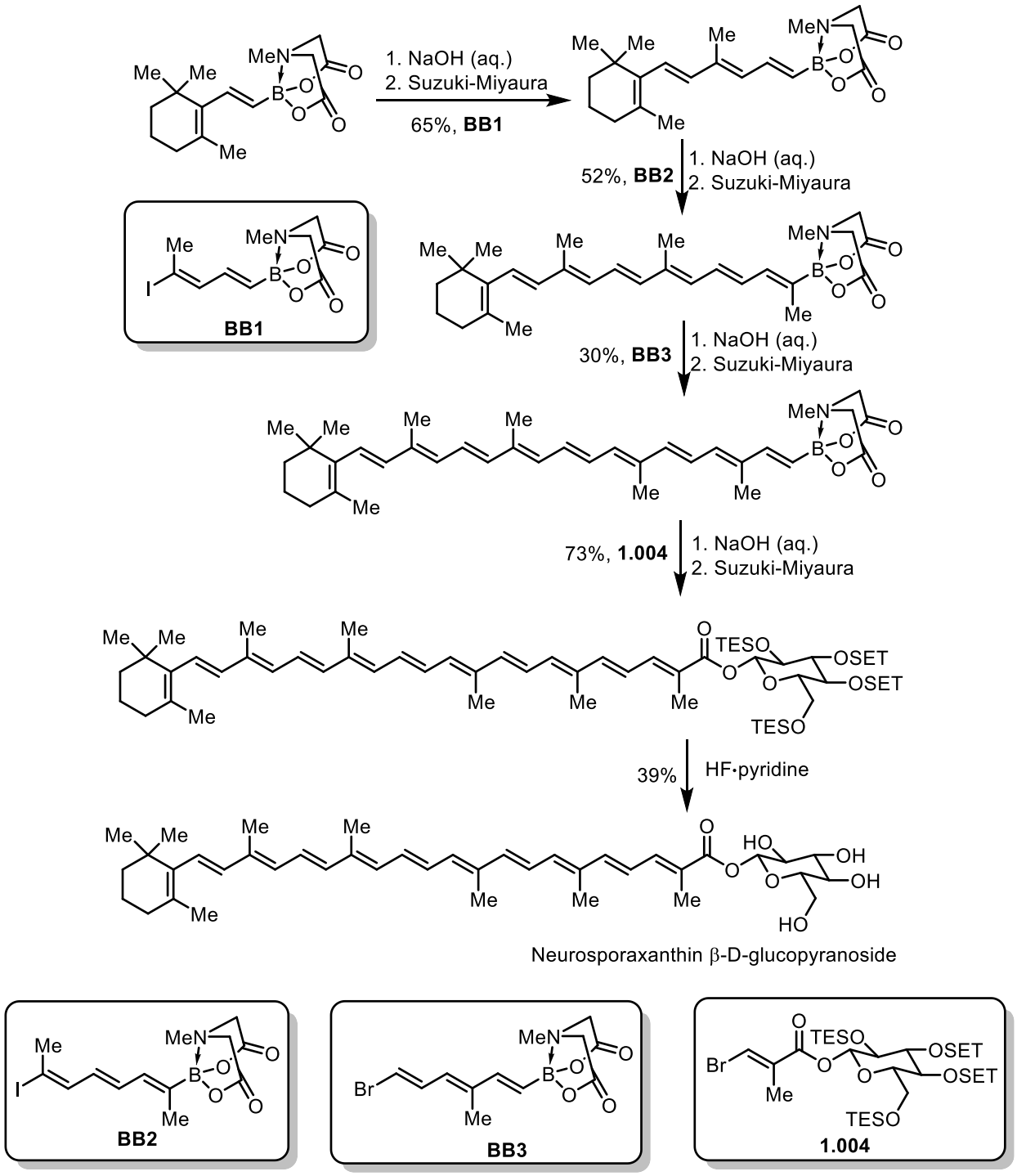


Figure 1.7 Burke *et al.*'s synthesis of neurosporaxanthin β-D-glucopyranoside.

The Stille reaction is also widely used for the assembly of poly-alkenyl units due to its mild reaction conditions and excellent stereospecificity. In Nicolaou *et al.*'s synthesis of rapamycin,[27] vinylenedistannane **1.005** was used as a vinyl linchpin to complete the triene segments and close the

macrocycle (figure 1.8). Although rapamycin was isolated in 28% yield, however, this reaction tolerated a wide variety of functional groups, including free alcohols, a ketoamide and a hemiketal.

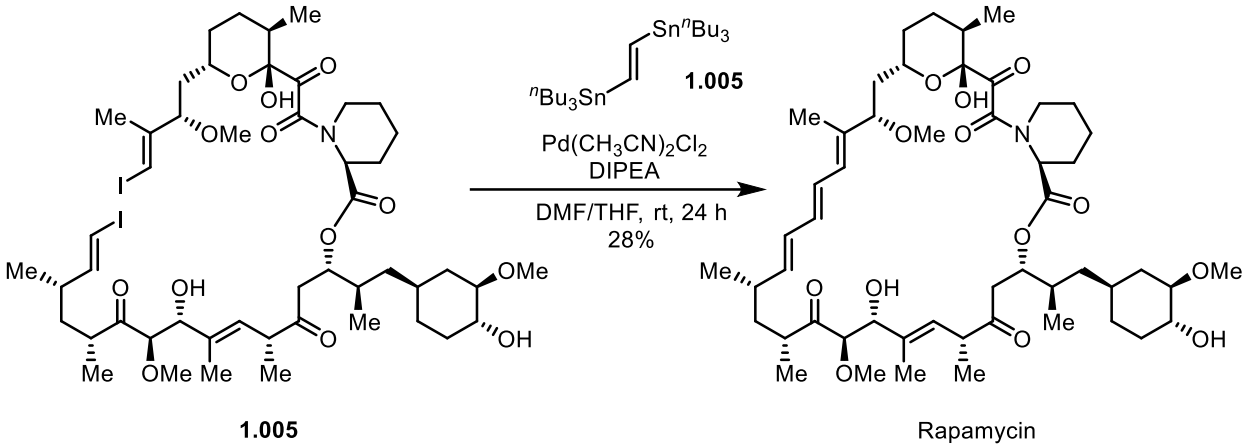


Figure 1.8 Nicolaou *et al.*'s synthesis of rapamycin.

The Negishi coupling is another important tool for stereospecific synthesis of polyenes. Negishi *et al.* utilized this reaction to synthesize β-carotene from precusor **1.006** (figure 1.9).[28] As a demonstration for the stereoselectivity, the β-carotene was obtained with ≥99% isomeric purity.

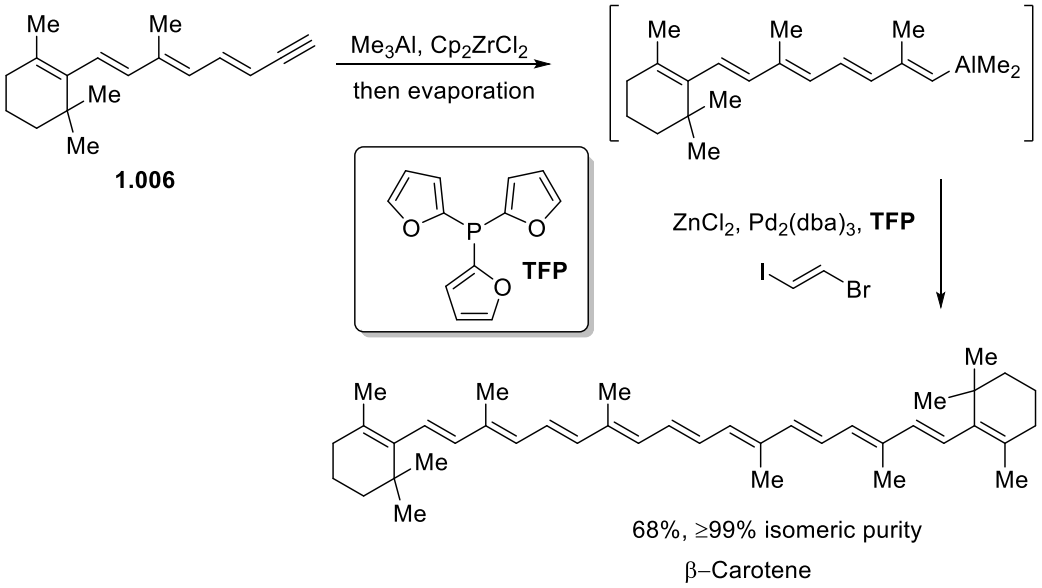


Figure 1.9 Negishi *et al.*'s synthesis of β-carotene.

The Heck reaction, although not frequently found in polyene synthesis, was used by the group of Whiting in their total synthesis of phthoxazolin A (figure 1.10).[29] In the reaction, the desired product **1.008** was

obtained in 43% yield through the intriguing Heck coupling of a vinyl boronate. However, Suzuki-type product **1.009** was also isolated, with a yield of 35%.

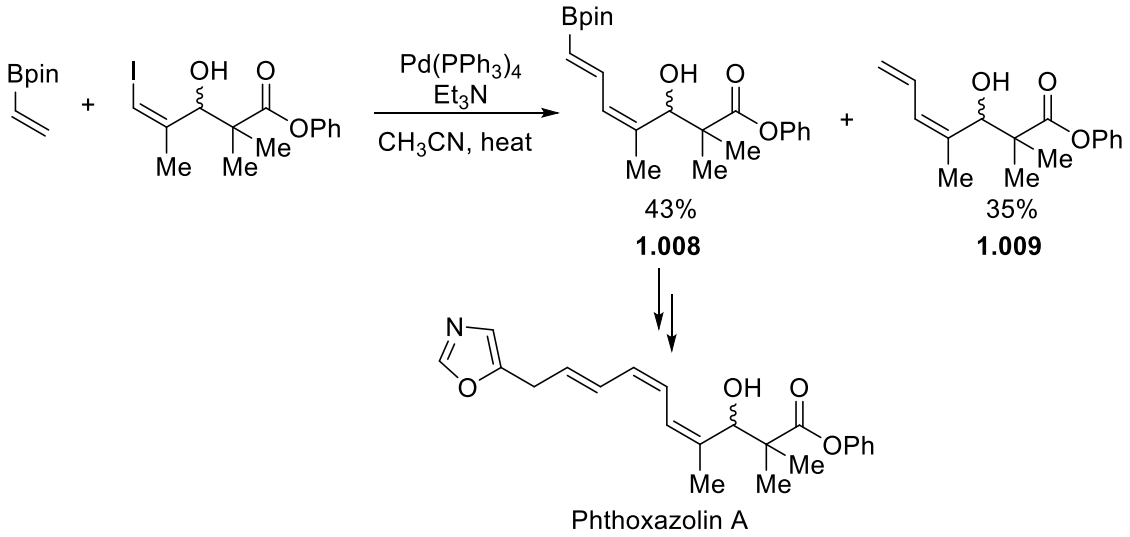


Figure 1.10 Whiting *et al.*'s synthesis of phthoxazolin A.

Nowadays, olefin metathesis plays an important role in the synthesis of polyenes.[30] As an example, the group of Fürstner elegantly utilized this reaction in their synthesis of iejimalide B (figure 1.11).[31] The highly unsaturated and functionalized precursor **1.010** was submitted to catalytic amount of ruthenium complex **1.010** for a ring closing metathesis event. Spectacularly, product **1.012** was formed at room temperature and isolated in 69% yield as a single *E*-isomer. TBS-deprotection then delivered iejimalide B in 80% yield.

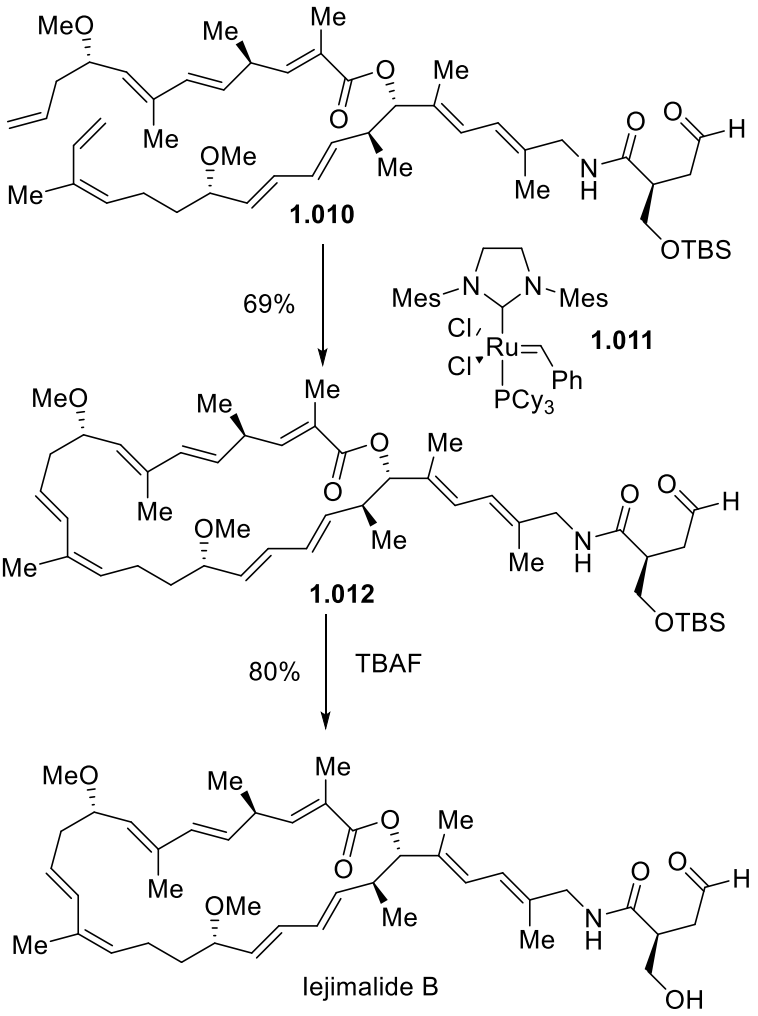


Figure 1.11 Fürstner *et al.*'s synthesis of iejimalide B.

1.3 Polyene Synthesis: A 4π-Electrocyclic Ring opening Approach

1.3.1 Electrocyclic Reactions

Pericyclic reactions generally exhibit excellent regio- and stereocontrol as a consequence of stringent frontier orbital requirements.[32] One important subclass of pericyclic reactions is termed electrocyclic reactions, in which π bonds are converted to σ bonds or vice versa in an intramolecular fashion.[33] Electrocyclic reactions can be triggered by either heat or light. The reactivity and stereospecificity of these processes can be predicted by frontier molecular orbital (FMO) theory (figure 1.12),[34] which considers two

relevant molecular orbitals, namely the highest-occupied molecular orbital (HOMO) and the lowest-unoccupied molecular orbital (LUMO). The bond-breaking and bond-forming events occur when the LUMO and the HOMO of the correct symmetry approach each other within a reasonable energy range. Electrocyclic reactions can be further classified, such as 4π-4 atom, 4π-5 atom, 6π-6 atom and 8π-8 atom electrocyclic reactions, according to the number of π-electrons and atoms involved in the transition state.

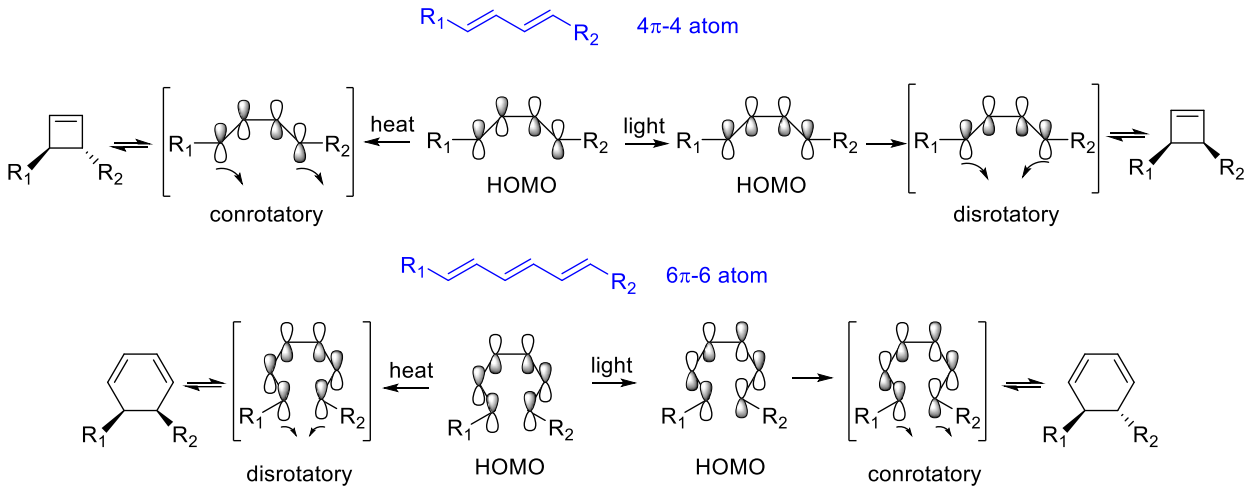


Figure 1.12 FMO theory for the prediction of electrocyclic reactions.

1.3.2 4π-Electrocyclic Ring Closing Reactions

4π-4 atom electrocyclic ring closing reactions deliver cyclobutene-type products. Under thermal conditions, this process is unfavorable compared to its reverse ring opening reaction due to the intrinsic ring strain of cyclobutenes.[35] However, cyclobutene derivatives can be formed upon exposure to light. For instance, upon UV irradiation, 2-pyrone is efficiently converted to a highly strained bicyclic lactone **1.013** in quantitative yield (figure 1.13).[36]

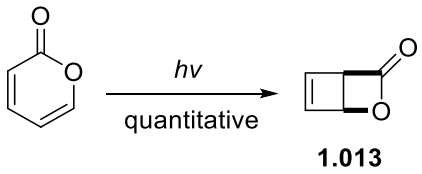


Figure 1.13 Photocyclization of 2-pyrone.

Light-triggered 4π-4 atom electrocyclization might also be involved in the biosynthesis of some natural products.[37] In their biomimetic total synthesis of salvileucalin C, Ding *et al.* first prepared the natural

product salvileucalin D. Upon UV irradiation of salvileucalin D, salvileucalin C was formed in 84% yield through a 4π-electrocyclic ring closing reaction (figure 1.14).[38]

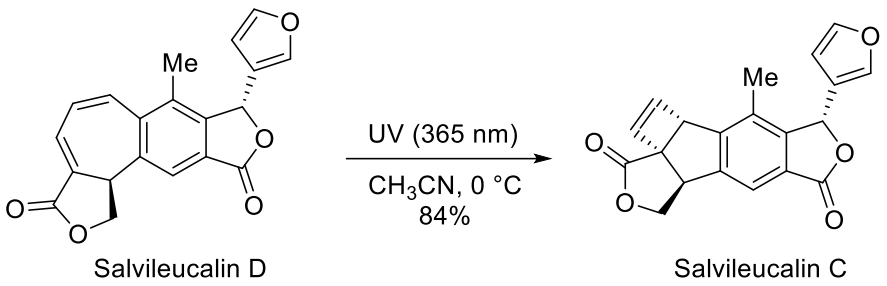


Figure 1.14 Ding *et al.*'s biomimetic synthesis of salvileucalin C.

4π-5 atom electrocyclic ring closing reactions are arguably most well studied by organic chemists. Two name reactions, viz. the Nazarov reaction and the Piancatelli reaction, base their key step on this process (figure 1.15) and have been extensively used in natural product total synthesis.[39,40,41,42]

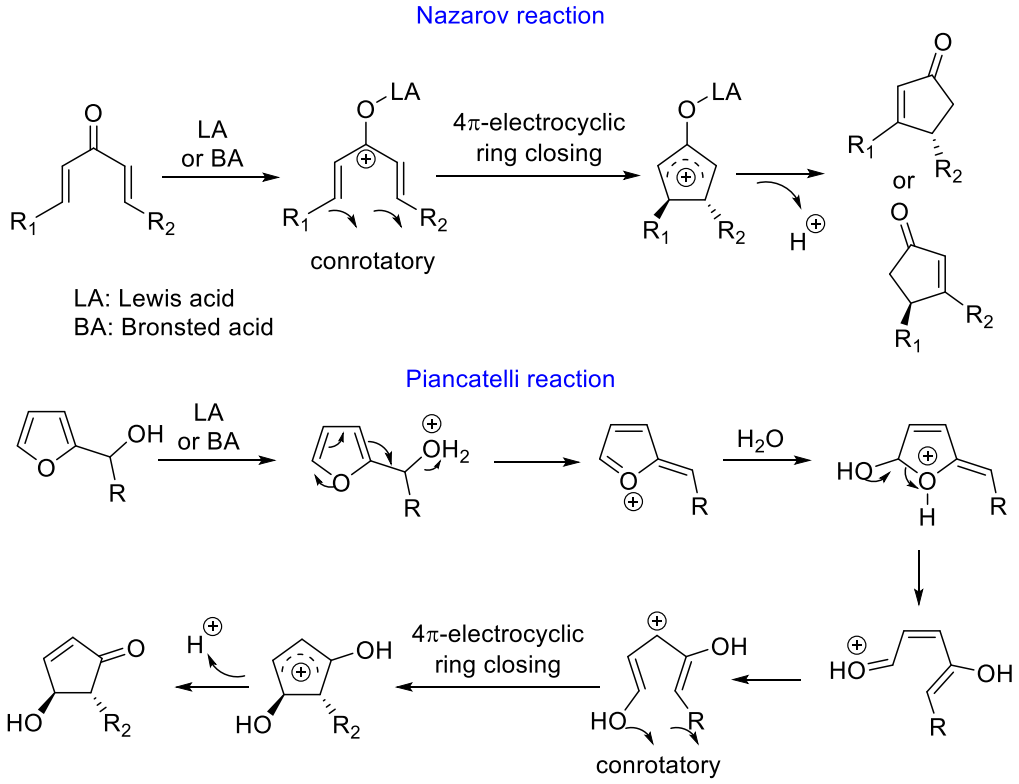


Figure 1.15 Nazarov reaction and Piancatelli reaction.

1.3.3 4π-Electrocyclic Ring Opening Reactions

1.3.3.1 Torquoselectivity

Due to the intrinsic ring strain of cyclobutenes, 4π-4 atom electrocyclic ring opening reactions are usually thermodynamically favored. The products formed from this process are 1,3-dienes, which are widely found in polyene natural products.[1] According to FMO theory, under thermal conditions a conrotatory ring opening of cyclobutenes is expected. For instance, while *cis*-3,4-dimethyl cyclobutene was heated to give product (*E,Z*)-hexadiene, *trans*-3,4-dimethyl cyclobutene gave the isomeric product (*E,E*)-hexadiene (figure 1.16).[43]

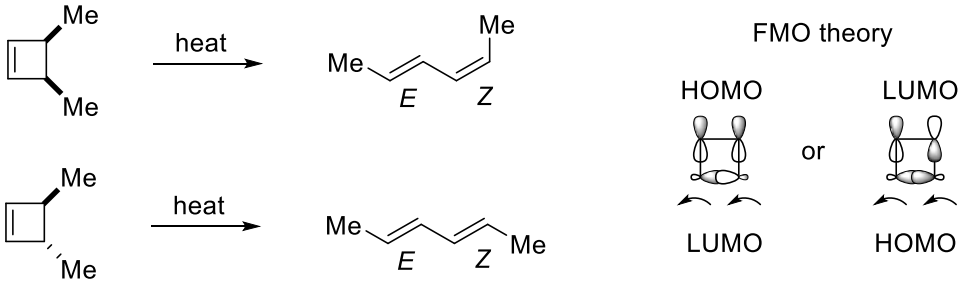


Figure 1.16 Thermal conrotatory ring opening of cyclobutenes.

Although FMO theory dictates the stereospecificity of the ring opening process, however, the absolute stereochemical outcome is not secured by this theory. As a conrotatory ring opening can occur in either a clockwise or counterclockwise fashion, two possible products could be obtained when unsymmetrically substituted cyclobutenes are used (figure 1.17).

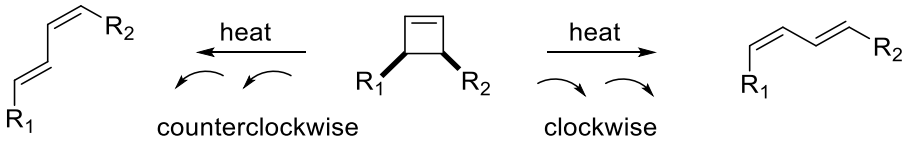


Figure 1.17 Products of conrotatory ring opening of unsymmetrically substituted cyclobutenes.

Based on their extensive experimental and computational studies on various cyclobutene derivatives,[44] Houk *et al.* proposed a set of torquoselectivity rules to predict the selectivity of the ring-opening process. The rules state that the electronic effects, rather than the steric effects are the major contributor for the observed torquoselectivity. In particular, a substituent on C3-position of the cyclobutene ring, can either rotate outwards or inwards during the ring-opening event. With donor substituents (e.g. hydroxy, alkoxy

and alkyl groups), outward ring opening is favored. For acceptor substituents, such as carbonyl derivatives, an inward ring opening is favored (figure 1.18).

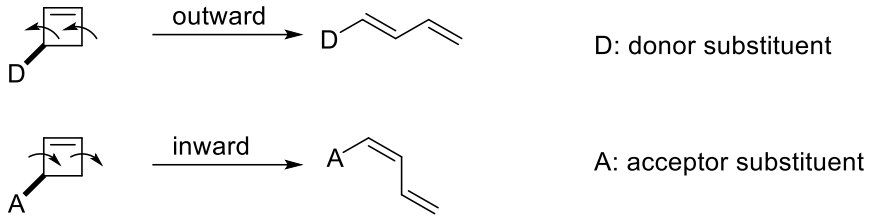


Figure 1.18 Torquoselectivity rule for the prediction of 4π-electrocyclic ring opening.

The torquoselectivity rule could be explained by FMO theory, with inward or outward conrotation of the breaking C3-C4 bond being dictated by secondary orbital interactions.[45] In qualitative terms, when a donor group (D) is placed on the C3-position, outward rotation leads to favorable mixing of the LUMO in the transition state (figure 1.19), therefore contributing to a lower activation barrier for the ring-opening event. In contrast, inward rotation will set up an unfavorable interaction between the donor group and the C3-C4 HOMO in the transition state. In the case of an acceptor group on the C3-position, the preference for the rotation is inversed. The empty orbital of the acceptor group will stabilize the HOMO of the C3-C4 bond with an inward rotation, which therefore becomes energetically more favorable (figure 1.19).[46]

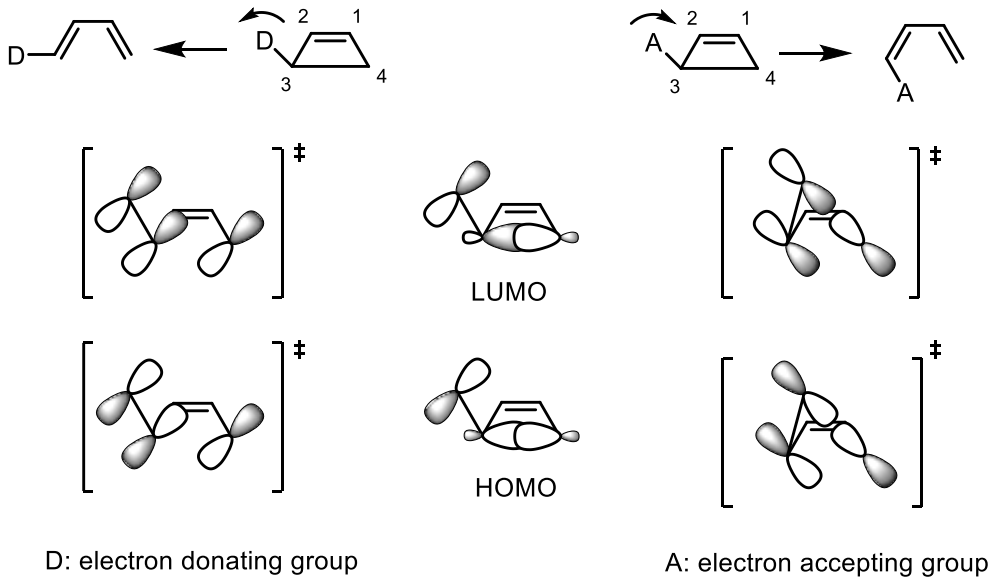


Figure 1.19 FMO theory for the elucidation of torquoselectivity rule.

This torquoselectivity rule was corroborated experimentally and was demonstrated to be operative in a variety of systems.[47] For instance, in the case of monosubstituted cyclobutene derivatives, while the opening of 3-methyl cyclobutene gave (*E,E*) pentadiene as a single isomer, the heating of 3-formyl cyclobutene afforded exclusively (*Z,E*)-penta-2,4-dienal as a single product (figure 1.20).[47m]

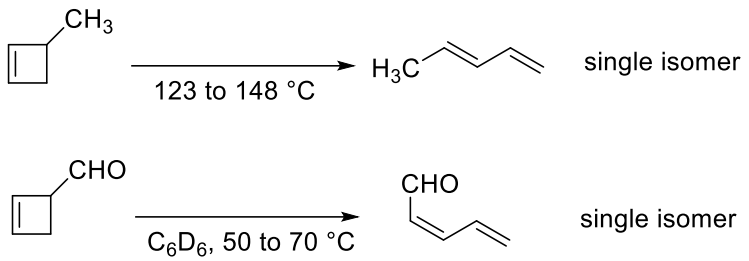


Figure 1.20 Ring opening of monosubstituted cyclobutenes.

The torquoselectivity rule also worked well for disubstituted cyclobutene derivatives. A notable example from the work of Houk *et al.* showed that the ring opening of 3-(*tert*-butyl)-3-methoxycyclobutene gave (*E*)-4-methoxy-5,5-dimethylhexa-1,3-diene as a single product, in spite of resulting in a sterically hindered *tert*-butyl group positioned *cis* to a vinyl group in the product. [47n]

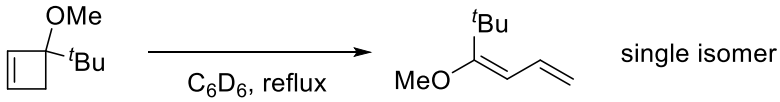


Figure 1.21 Ring opening of 3-(*tert*-butyl)-3-methoxycyclobutene.

Interestingly, when both donor and acceptor substituents were present respectively at the 3,4 positions of a cyclobutene derivative, a push-pull effect rendered the ring opening remarkably facile.[48] This could be explained by an enhanced stabilization of the transition state according to the torquoselectivity rule. For instance, *cis*-4-ethylcyclobut-2-ene-1-carbaldehyde undergoes 4π-electrocyclic ring opening at room temperature to give (2*Z*,4*E*)-hepta-2,4-dienal as a single isomer.[48d]

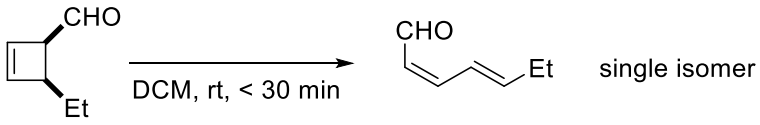


Figure 1.22 Ring opening of *cis*-4-ethylcyclobut-2-ene-1-carbaldehyde.

In case of substituents with similar electronic nature, the ring-opening event afforded mixtures. As an example, the *cis*-cyclobutene diester **1.014** was heated to give a mixture of product **1.015** and **1.016** in a 1.4:1 ratio (figure 1.23).[48d]

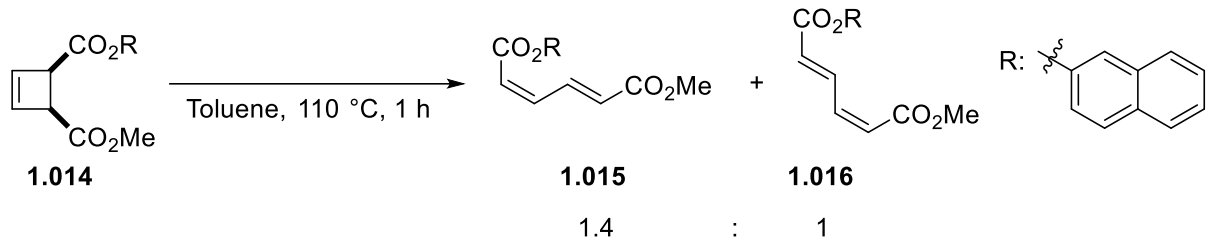


Figure 1.23 Ring opening of *cis*-cyclobutene diester **1.014**.

1.3.3.2 Applications in Total Synthesis

As demonstrated above, the ring opening of cyclobutene derivatives is an atom-economical and predictable process. Applications in the total synthesis of natural products are accordingly well documented.[37] For instance, upon heating of cyclobutenone **1.017**, Martin *et al.* could directly isolate cribrostatin 6 and quinone **1.021** in a ratio of 2:1 with a combined yield of 24%. This highly efficient process involved a 4π-electrocyclic ring opening of **1.017** to **1.018** and further radical cyclization to dihydroxyquinone **1.020**, which was oxidized easily to deliver product **1.021** and cribrostatin 6. In further optimization, the mixture of products was treated by Pd/C to deliver cribrostatin 6 in 26% overall yield (figure 1.24).[49]

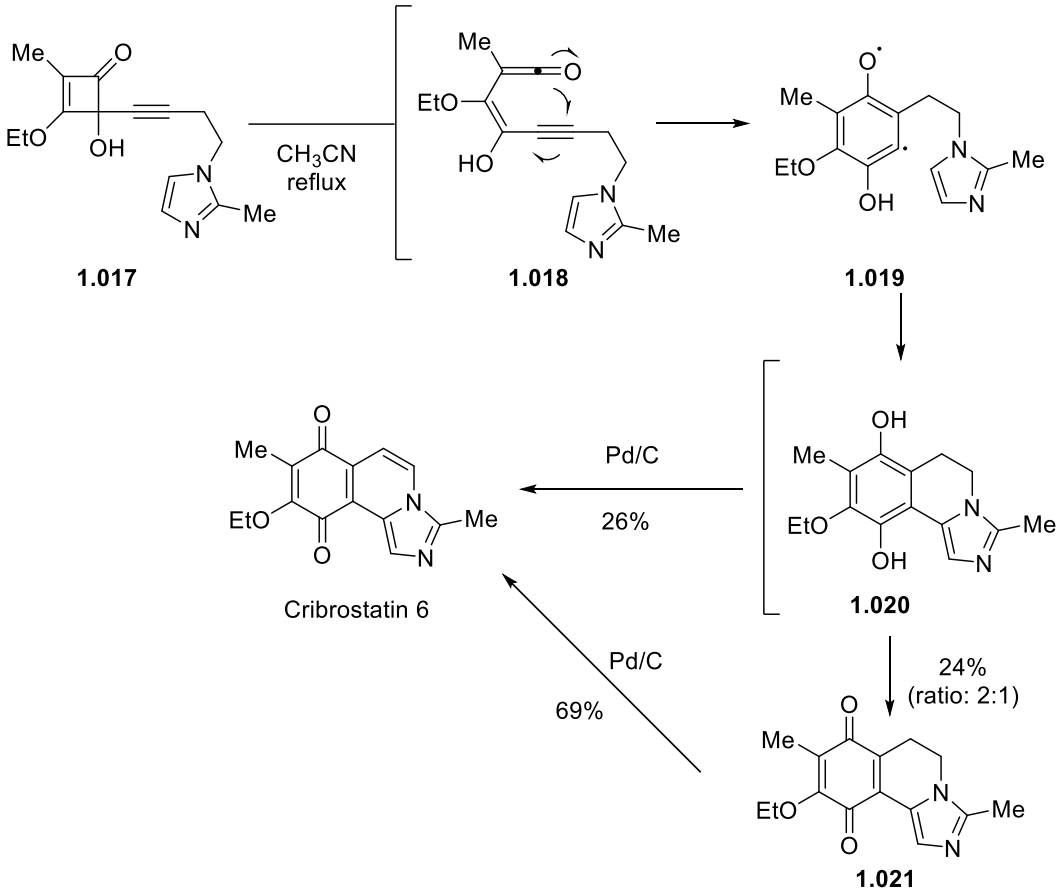


Figure 1.24 Martin *et al.*'s synthesis of cribrostatin 6.

Another example was showcased in Maimone *et al.*'s synthesis of podophyllotoxin (figure 1.25).[50] By treatment of bromopiperonal **1.022** with Corey-Chaykovsky reagent, the resulting epoxide underwent a further halogen-lithium exchange/epoxide-opening cascade reaction to afford benzocyclobutanol **1.023**. Benzocyclobutanol **1.023** was then deprotonated by KHMDS at -78 °C. Upon slow warming to 0 °C, a 4π-electrocyclic ring opening afforded putative *o*-quinodimethane potassium salt **1.024**, which was trapped by amide **1.025** through a cycloadditon reaction to afford salt **1.026**. Without isolation, the mixture was treated with super hydride and further ketalization afforded product **1.027** in 41% yield over 4 steps. A catalytic C-H arylation was conducted to give product **1.029**. Under acidic conditions, the ketal group of **1.029** was removed and an in situ lactone formation delivered podophyllotoxin in 43% yield along with 33% of C4-epi-podophyllotoxin.

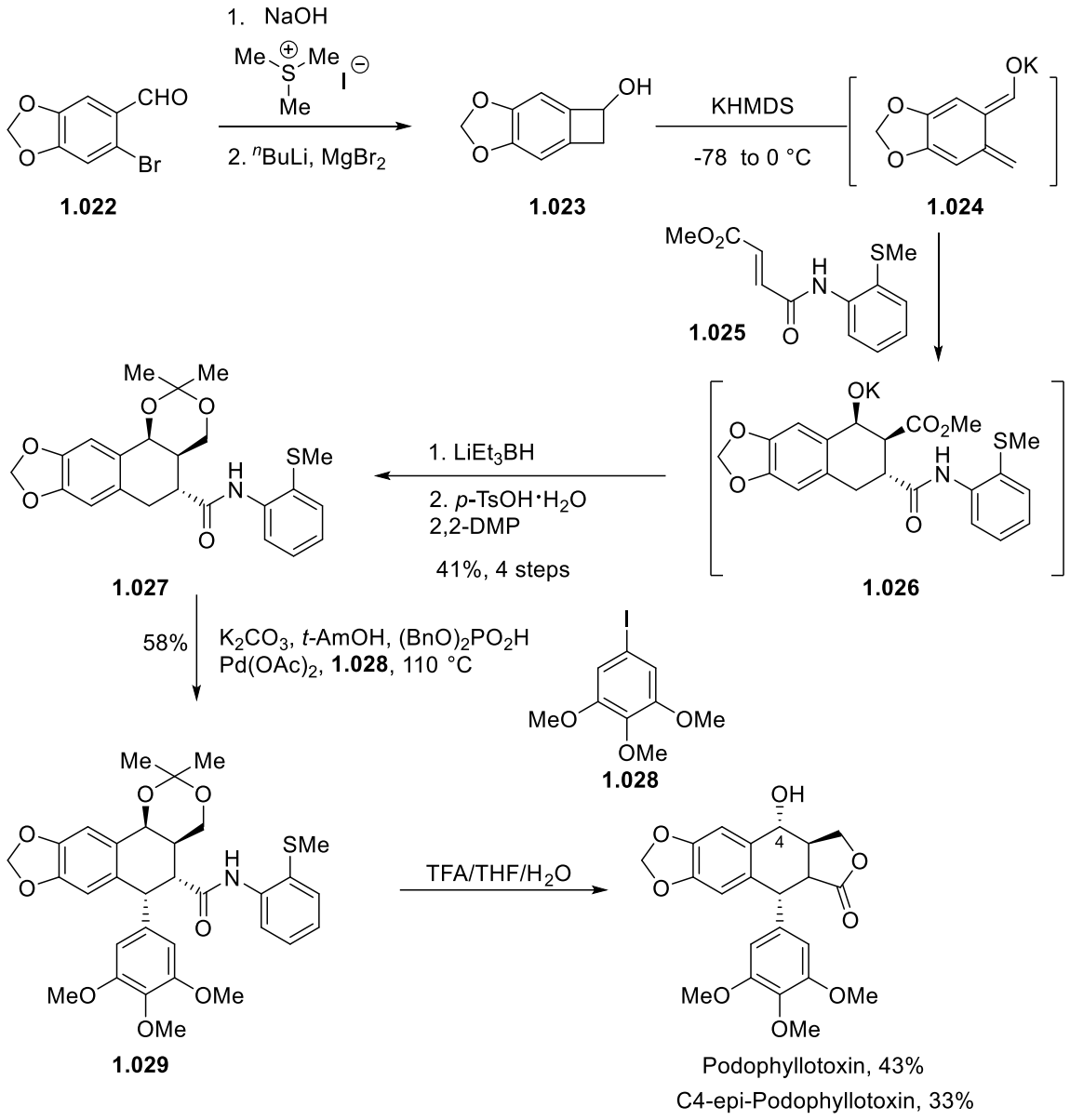


Figure 1.25 Maimone *et al.*'s synthesis of podophyllotoxin.

However, the use of a cyclobutene derivative as a diene linchpin in the polyene natural products synthesis is not widely explored.[1] An early example was demonstrated by Schreiber and Santini in their total synthesis of periplanone-B, a sex pheromone (figure 1.26).[51] Treatment of cyclohexenone **1.030** with propadiene under UV light delivered photoadducts **1.031** and **1.032** (2:1 ratio) in 72% yield. Without the need for separation, the mixture was converted to alcohols **1.033** which, upon anion accelerated Oxy-Cope rearrangement, converged to ketone **1.034**. Under heating, the embedded cyclobutene motif underwent a 4π-electrocyclic ring opening to deliver (*E,Z*)-dienic ketone **1.035** and (*E,E*)-dienic ketone

1.036 in a ratio of 2:1 with 77% combined yield. The (*E*,*Z*)-isomer **1.035** could be smoothly isomerized upon irradiation to **1.036**, which was used for the further functionalization to periplanone-B.

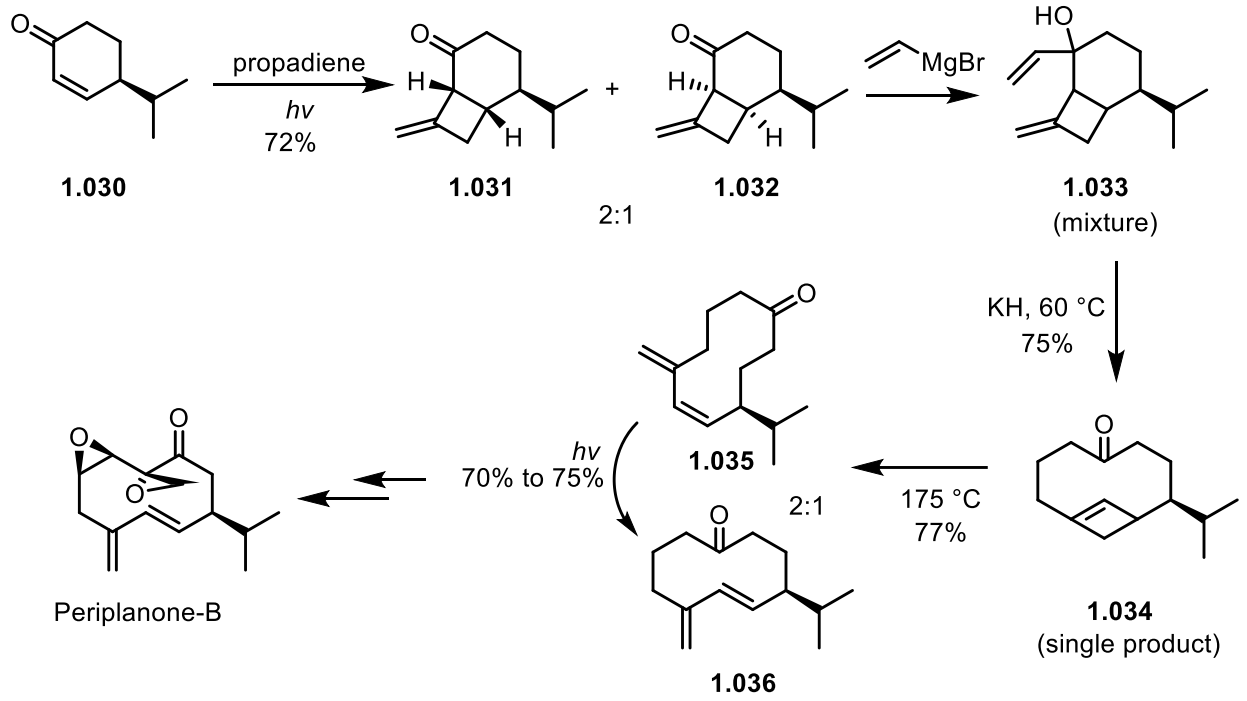


Figure 1.26 Schreiber *et al.*'s total synthesis of periplanone-B.

Our group has a long-standing interest in the synthesis and functionalization of cyclobutene derivatives.[52] Early research capitalized on the known photoisomerization of 2-pyrone to the bicylobutene lactone **1.013** in quantitative yield.[36] Lactone **1.013** was highly reactive towards various nucleophiles, leading to functionalized cyclobutene derivatives (figure 1.27).[52]

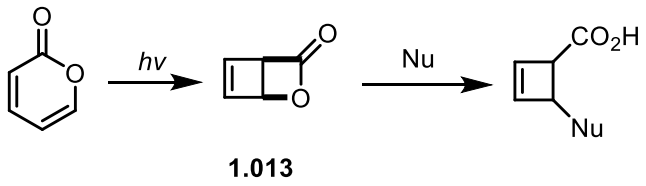
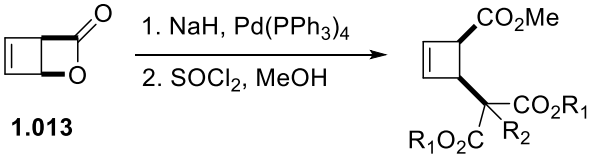


Figure 1.27 Formation and ring opening of bicyclobutenelactone **1.013**.

Under palladium catalysis, bicyclobutene lactone **1.013** reacted with malonate salts to deliver a range of cyclobutenes through a Tsuji-Trost reaction.[53] This transformation was highly stereospecific, as only the *cis*-configured products were obtained (figure 1.28) in the presence of catalytic amount of tetrakis-

(triphenylphosphine)palladium.[54] Further development of this transformation with chiral ligands led to enantioenriched cyclobutene derivatives, in an unusual diastereodivergent fashion.[55]



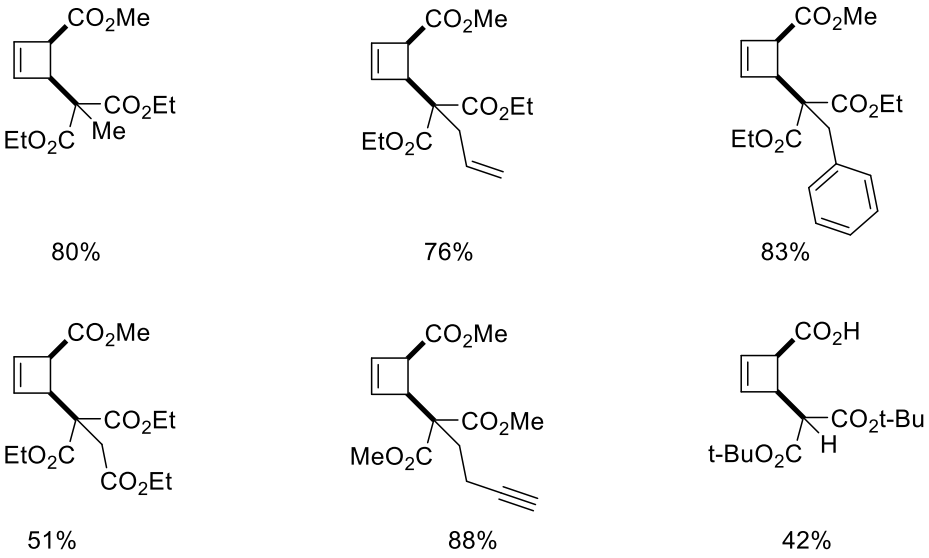


Figure 1.28 Palladium catalyzed ring opening of lactone **1.013**.

When the bicyclobutene lactone **1.013** was treated with sodium phenolates, (*Z,E*)-butadienoic acids were the isolated products (figure 1.29).[56]

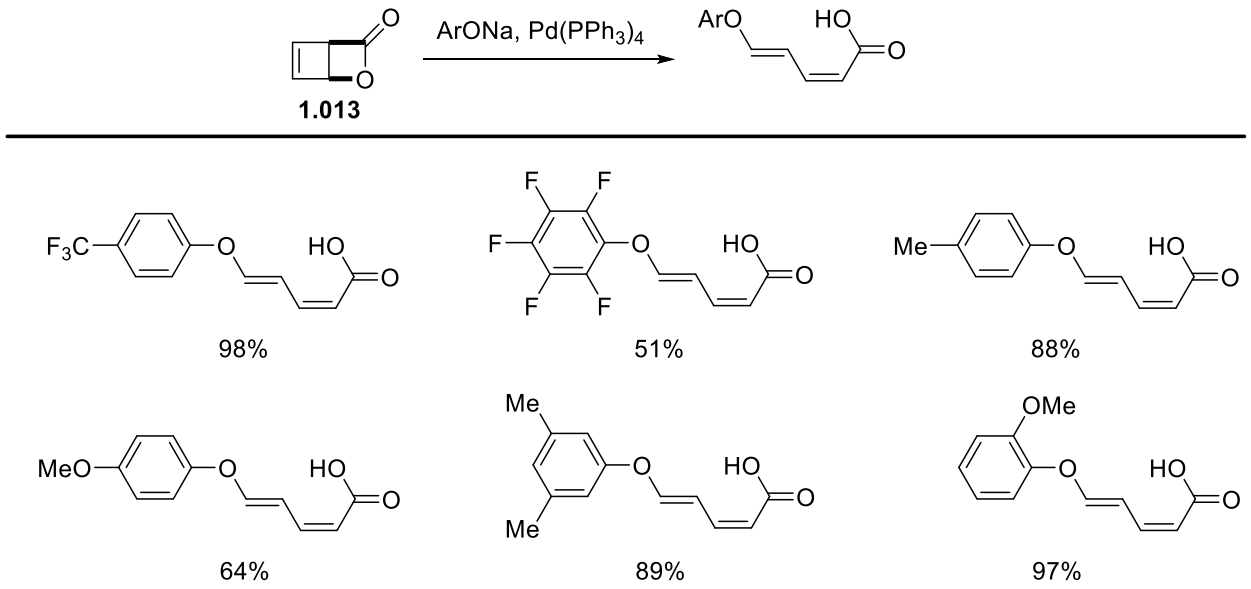


Figure 1.29 Synthesis of (*Z,E*)-butadienoic acids.

When trimethylsilyl azide was employed, (*E,E*)-azidodiene acid **1.037** was obtained (figure 1.30). [57] These highly steroselective and facile synthesis of functionalized dienes suggests the intermediacy of push-pull, unstable stereodefined cyclobutenes. This postulate was further corroborated by the observation of variable amounts of fleeting *trans*-azido-cyclobutene product **1.038** within the reaction mixtures.[57]

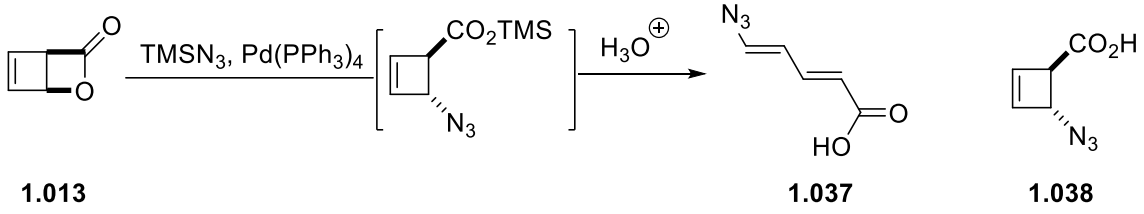


Figure 1.30 Synthesis of (*E,E*)-azidodiene acid **1.037**.

While simple treatment of bicyclobutene lactone **1.013** with halide salts gave *trans*-halogen substituted cyclobutene acids **1.040** and **1.042**, acidic hydrolysis of the lactone by dry HCl at low temperature gave the *cis*-chloro substituted acid **1.043** as the major product. These acids were kinetically stable. However, upon heating, dienic products were formed. With the exception of iodinated cyclobutene acid **1.039**, the opening of which resulted in a mixture of (*E,E*) and (*E,Z*) diene geometries, the other two acid **1.041** and **1.043**, upon heating, gave stereospecific (2*E*,4*E*)-5-bromopenta-2,4-dienoic acid **1.042** and (2*Z*,4*E*)-5-chloropenta-2,4-dienoic acid **1.044** respectively (figure 1.31).[58]

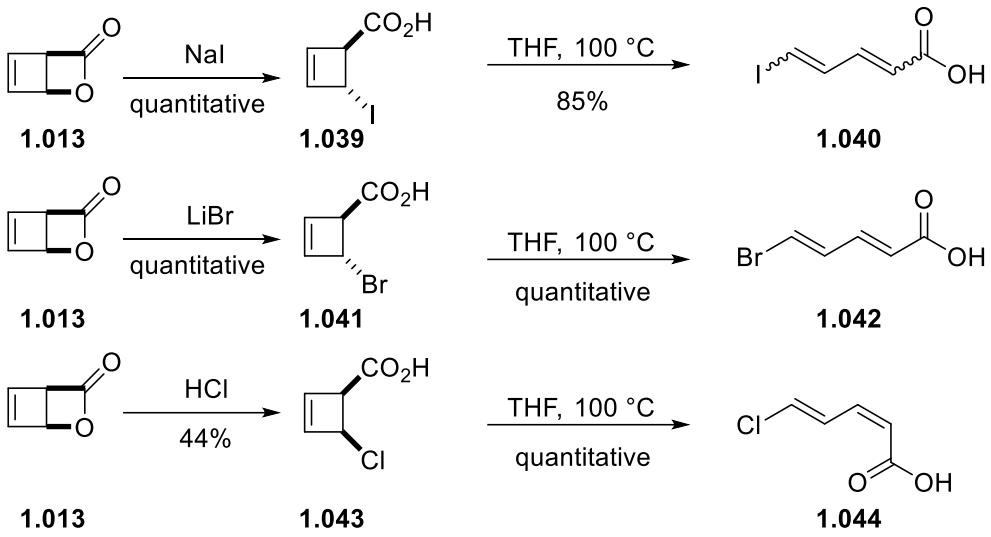


Figure 1.31 Synthesis of halogen substituted dienes.

These halogen substituted diene acid derivatives underwent various transition metal catalyzed cross coupling reactions, such as Suzuki-Miyaura, Sonogashira and Stille reactions, without loss of the diene geometry (figure 1.32).[58]

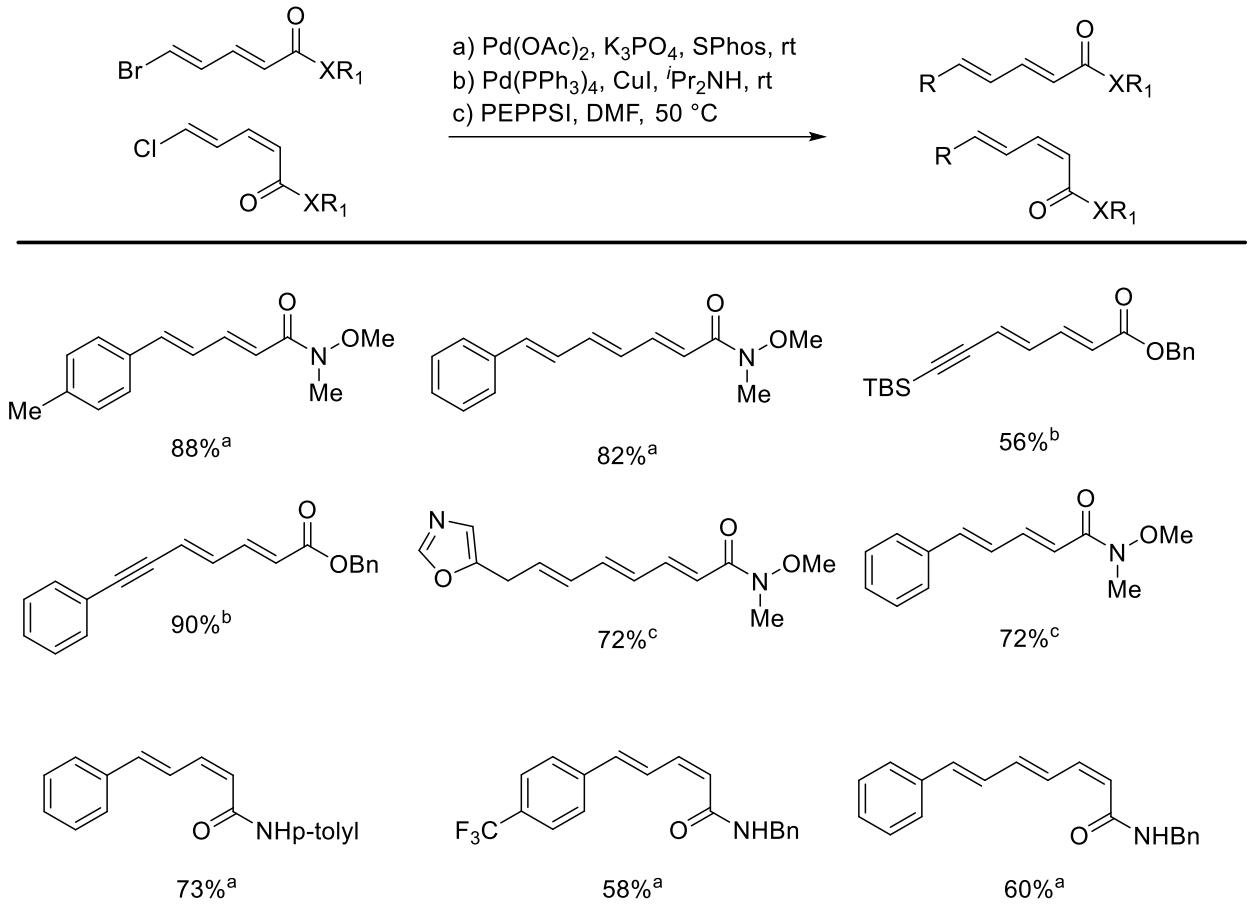


Figure 1.32 Cross-couplings of halogen-substituted dienes.

The application of these halogenated diene acids was demonstrated in the formal total synthesis of inthomycin C.[60] By treatment of bicyclobutene lactone **1.045** with lithium bromide, the resulting bromo-substituted cyclobutene acid **1.046** was converted to the Weinreb amide and further ring opened to deliver bromo-substituted diene amide **1.047** in 73% yield over 3 steps. A Stille reaction was conducted to afford triene amide **1.048** in 72% yield with excellent stereochemical fidelity. DIBAL-H reduction and Mukaiyama aldol addition gave the advanced intermediate **1.050**, which has previously been converted to inthomycin C (figure 1.33).[59]

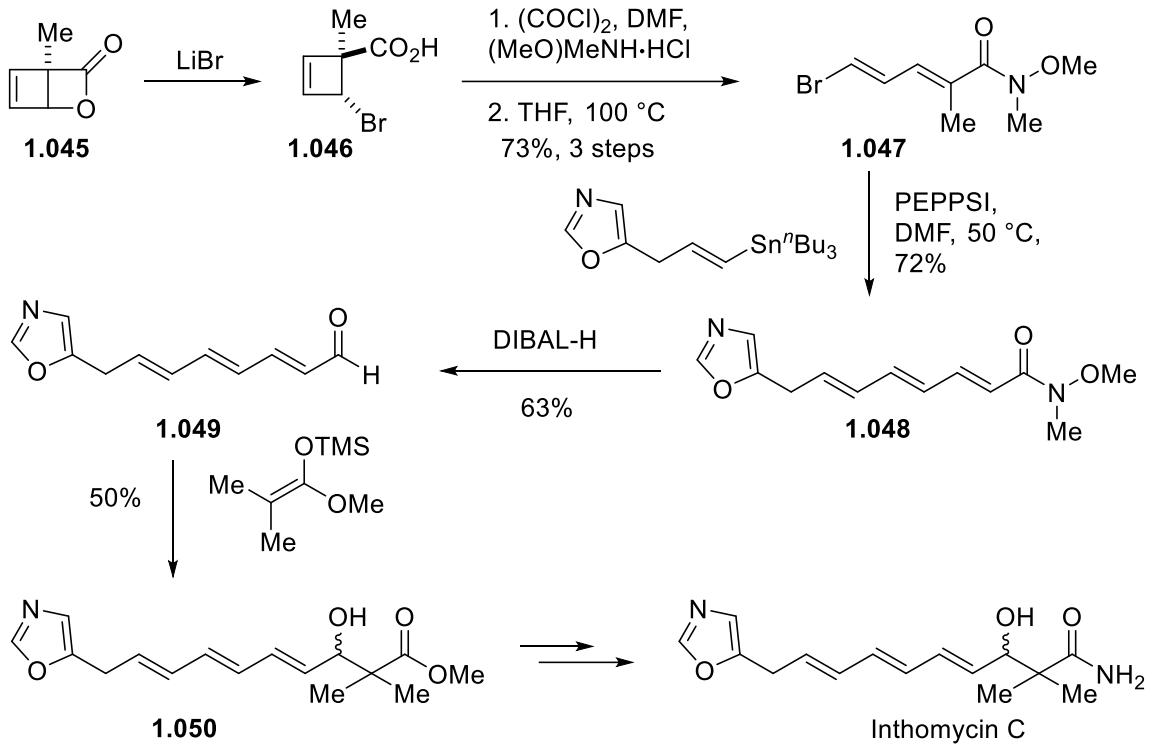


Figure 1.33 Formal synthesis of inthomycin C.

Chapter 2. Objectives of this PhD Work

As demonstrated in chapter 1, the 4π-electrocyclic ring opening of cyclobutene derivatives is a well-established and efficient pathway for the synthesis of dienes. Despite some applications based on this transformation,[37,51] the use of cyclobutenes as diene surrogates is not a common strategy in the total synthesis of polyene natural products.[58,60] One of the reasons could be the lack of efficient and modular syntheses/functionalizations of cyclobutene derivatives.[61] Therefore, the objectives of this work are to:

1) Develop methods for the functionalization of cyclobutene derivatives.

2) Apply 4π-electrocyclic ring opening of cyclobutenes in the total synthesis of bioactive polyene natural products.

Chapter 3. Total Synthesis of Cicutoxin

3.1 Structure and Bioactivity

Cicutoxin, a polyenic diol, was first isolated from the plant water hemlock by C. A. Jacobson in 1915.[62] It was described as "a yellowish liquid resin, viscous like ordinary cane sirup, polymerizing spontaneously into a semisolid body of a ruby-red to reddish brown color".[62] The nature of its chemical instability delayed its first structure determination until 1953,[63] followed by a very low yielding racemic synthesis in 1955.[64] The absolute configuration was established in 1999 along with its congeners virol A, virol B and virol C.[65] Interestingly, while the secondary alcohol in cicutoxin was identified to be *R*-configured, an *S* configuration is present in virol A, virol B and virol C (figure 3.1).

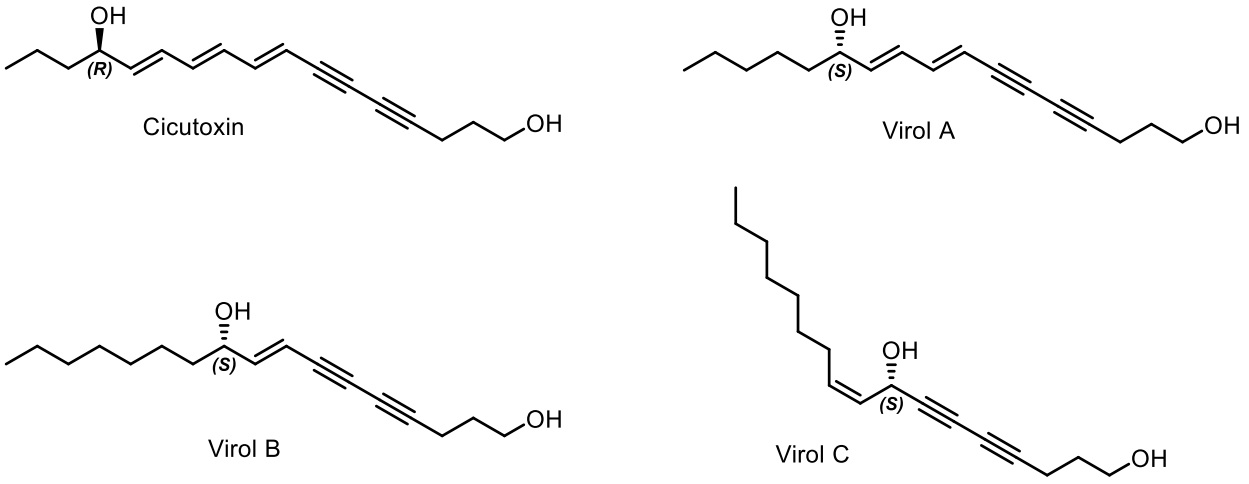


Figure 3.1 Structure of cicutoxin.

Cicutoxin and virol A were established to be responsible for the toxicity of water hemlock.[4] Whilst deaths due to the ingestion of this plant have been reported, no effective antidote was discovered yet.[66] Besides its high toxicity, cicutoxin displayed potent antileukemic activity.[67] Its potency in the inhibition of GABA antagonist, [^{3}H]EBOB's binding to GABA-gated Cl^- channels of GABA receptors was found to be correlated with its toxicity.[68]

3.2 Previous Synthesis

3.2.1 Trippett *et al.*'s Racemic Synthesis

The first total synthesis of cicutoxin was reported by the group of Trippett in 1955.[64] 3-Bromo-1-propanol **3.001** was readily protected as a THP ether to deliver bromo ketal **3.002**. The bromine atom was then displaced by the monosodium diacetylene **3.004**, prepared in one step from 1,4-dichlorobut-2-yne **3.003**, to afford diyne **3.005**. In parallel, ethoxyvinylacetylene **3.006** was deprotonated by phenyl lithium, and then reacted with hex-2-enal **3.007** to deliver dienynol **3.008**. The triple bond was then semireduced to afford alcohol **3.009**, the treatment of which with sulfuric acid afforded deca-2,4,6-trienal **3.010**.

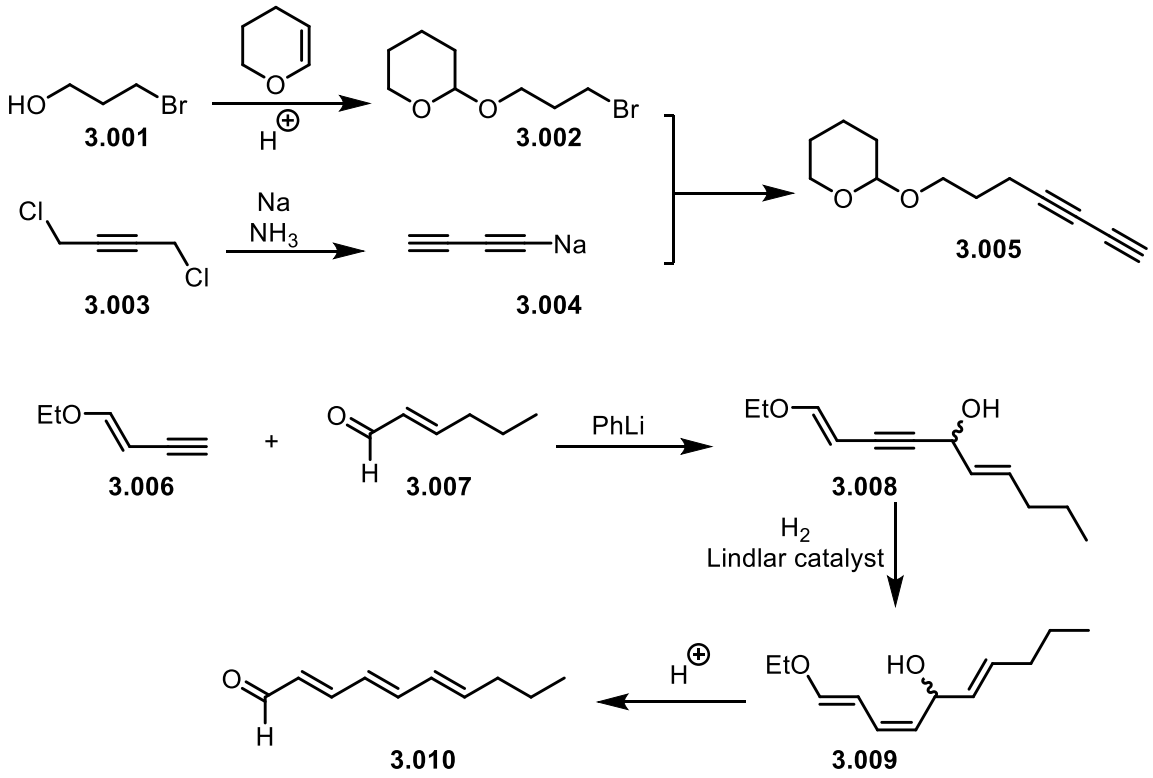


Figure 3.2 Synthesis of building blocks.

Diyne **3.005** was deprotonated by ethylmagnesium bromide, and then reacted with trienic aldehyde **3.010** to afford a putative alcohol **3.011**. Treatment of **3.011** with concentrated sulfuric acid delivered cicutoxin, although the yield was only 4%.

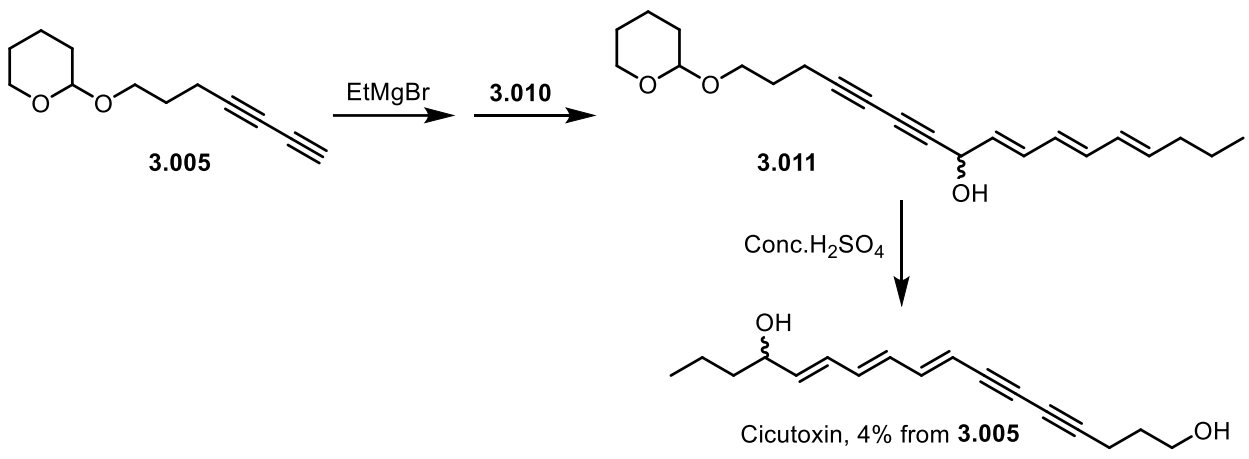


Figure 3.3 Trippett *et al.*'s racemic synthesis of cicutoxin.

3.2.2 Gung *et al.*'s Asymmetric Synthesis

In 2016, the group of Gung reported the first asymmetric total synthesis of cicutoxin.[69] In their original plan (figure 3.4), trienol **3.012** was oxidized and the resulting aldehyde was treated with propylmagnesiumbromide to afford alcohol **3.013**. Under Sonogashira conditions, **3.013** readily coupled with **3.005** to deliver **3.014** in 30% yield. However, attempted Lipase AK catalyzed kinetic resolution of **3.014** only resulted in decomposition.

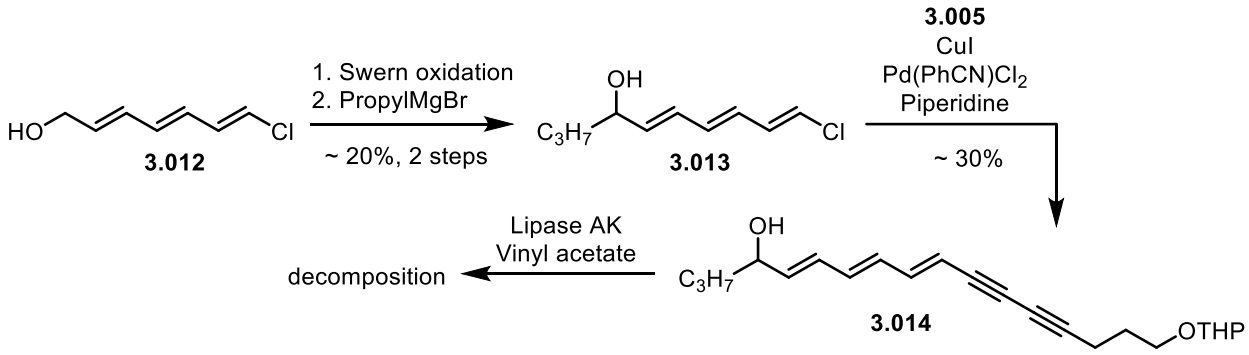


Figure 3.4 Original plan of Gung *et al.*.

Modifying their approach, Gung *et al.* instead decided to install the chiral center at an early stage before assembling the whole polyene skeleton (figure 3.5). Starting from enantiomerically pure (*R*)-1-hexyn-3-ol **3.015** and 1,4-diiodo-1,3-butadiene **3.016**, both prepared in one step, alcohol **3.017** was readily obtained in 63% yield. A further Sonogashira coupling with **3.005** delivered alcohol **3.018** in 74% yield. Then, after the triple bond was reduced by Red-Al, further removal of THP group by *p*-toluenesulfonic acid afforded cicutoxin in 38% yield over two steps.

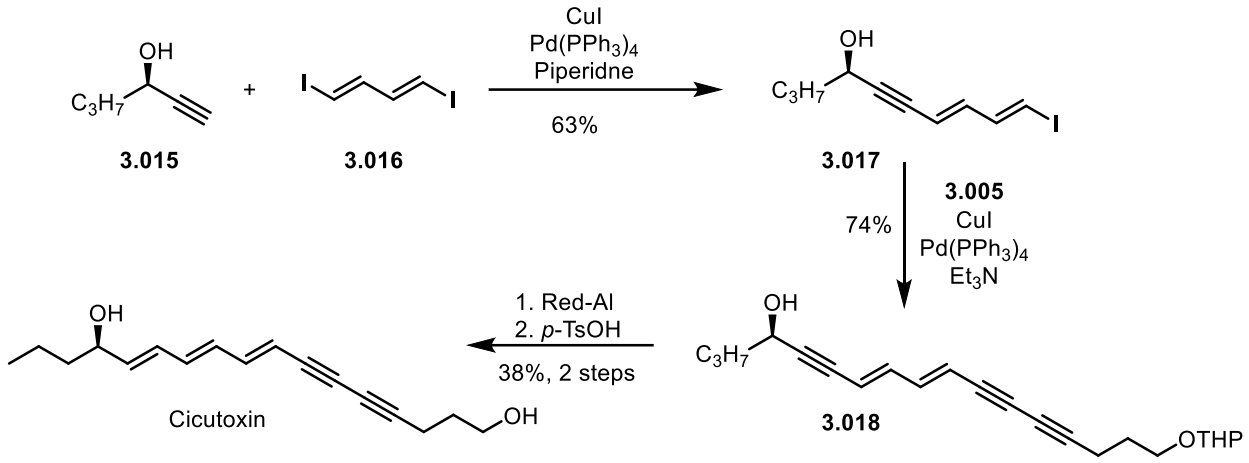


Figure 3.5 Gung *et al*.'s synthesis of cicutoxin.

3.2.3 Brückner *et al.*'s Asymmetric Synthesis

In 2011, the group of Brückner reported another asymmetric route to cicutoxin (figure 3.6).[70] Alcohol **3.019** was readily converted to its corresponding bromide **3.020** using the Appel reaction. **3.020** was then transformed to the symmetrical thioether **3.021** and further oxidized to sulfone **3.022**. Under the conditions of the Ramberg-Bäcklund reaction, trienic distannane **3.023** was readily obtained from **3.022** in 73% yield. The addition of the monoorganolithium reagent derived from **3.023** to Weinreb amide **3.024** delivered ketone **3.025**. CBS-reduction of this ketone afforded alcohol **3.026** in 84% yield and 82% ee. Finally, Stille coupling between **3.026** and diynol **3.027** delivered cicutoxin in 65% yield.

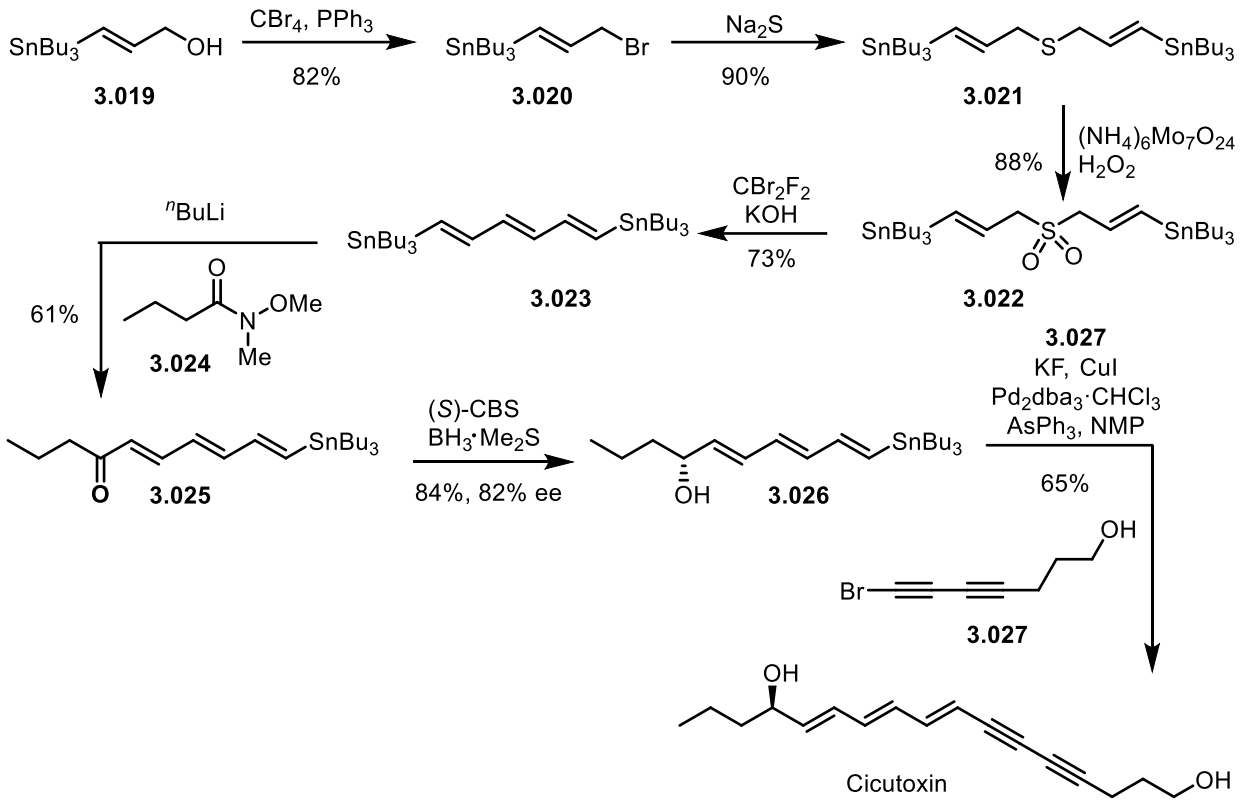


Figure 3.6 Brückner *et al.*'s synthesis of cicutoxin.

3.3 Total Synthesis of Cicutoxin

The results presented in this chapter were obtained in collaboration with Martin Berger.

3.3.1 Functionalization of Cyclobutenes

In 2015, we reported a methodology for the functionalization of cyclobutenes (figure 3.7).[60a] It was observed that bicyclobutene lactone **3.029**, obtained from 2-pyrone **3.028**, was reactive towards Grignard and zinc reagents in the presence of copper cyanide and lithium chloride. The *trans*-alkyl substituted cyclobutene acids **3.030** were readily formed in high yield regardless of bulky groups (**3.030h**). In addition, this transformation was compatible with ester, succinimide and TIPS ether functionalities (**3.030i, j, and k**). Interestingly, when the alkyl chain was a cyclopropyl group, we observed the formation of ring opened product **3.030b'**. The diene formation from substituted cyclobutene carboxylate was later calculated to be quite facile if the alkyl chain bears sp^2 or sp carbons at the substituted position.[71]

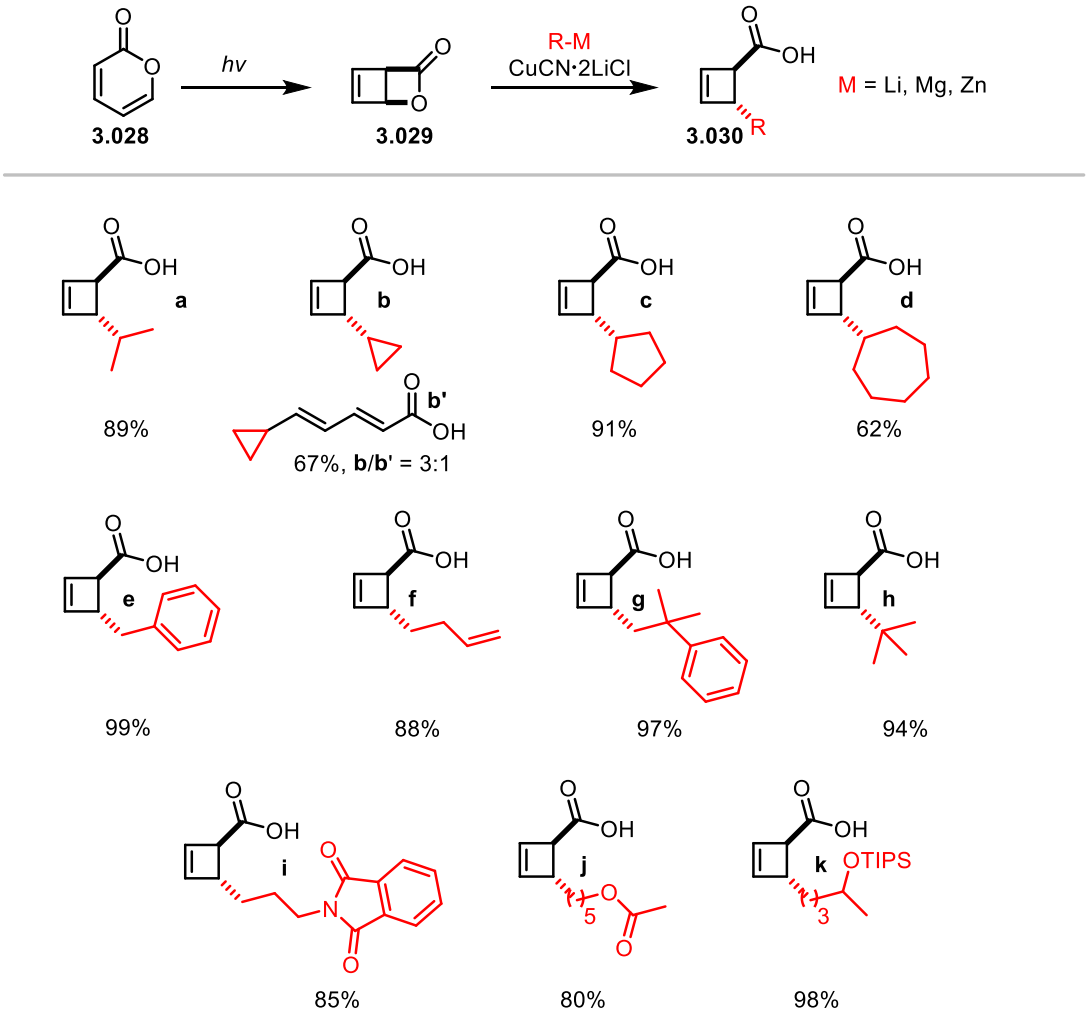


Figure 3.7 Functionalization of cyclobutenes.

The utility of this transformation was further demonstrated by Dr. Caroline Souris *et al.*'s work in the synthesis of (−)-Ieodomycin D and fragment **3.038** of macrolactin A (figure 3.8).[60a] Both of these syntheses relied on a key stereoselective 4π-electrocyclic ring opening step to unveil the diene units.

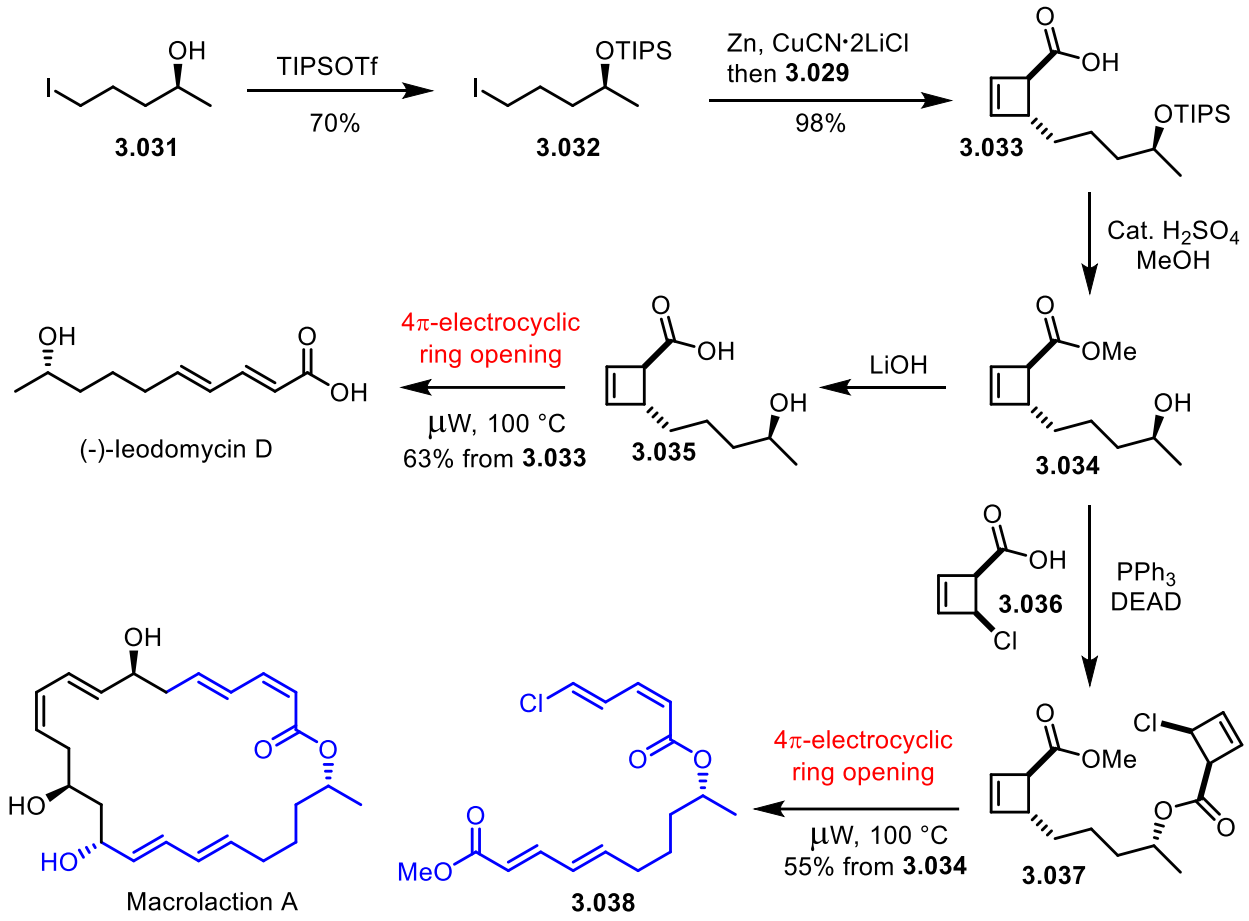


Figure 3.8 Synthesis of (−)-Ieodomycin D and fragment **3.038** of macrolaction A.

3.3.2 Retrosynthesis of Cicutoxin

The successful application of cyclobutene motifs as diene surrogates in the context of complex molecule synthesis prompted us to apply this transformation in a novel total synthesis of cicutoxin and virol A. It was envisioned that both cicutoxin and virol A could be synthesized from common intermediate **3.040**, a 4π-electrocyclic ring opening product of cyclobutene acid **3.039**. As **3.039** bears a diyne substituent, its ring opening was expected to be facile.[71] Acid **3.039** should be readily accessible from known diyne **3.005** and bicyclobutene lactone **3.029** (figure 3.9).

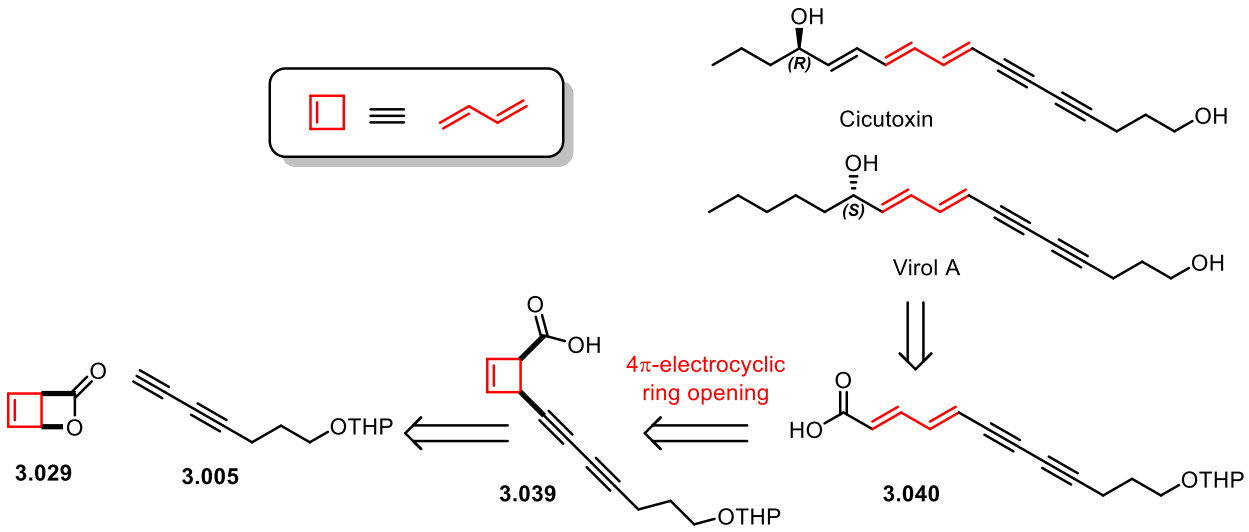
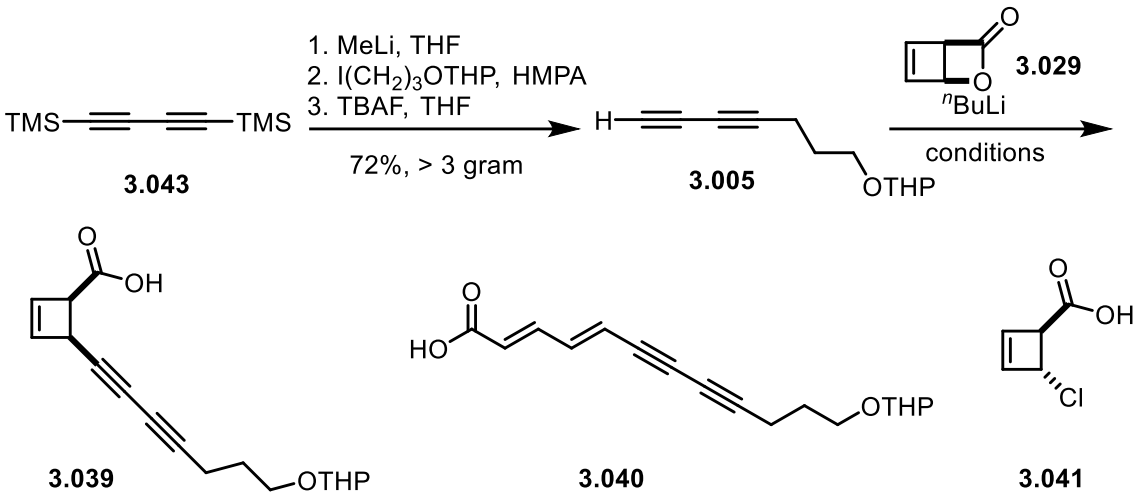


Figure 3.9 Retrosynthesis of cicutoxin and virol A.

3.3.3 Total Synthesis of Cicutoxin

The synthesis commenced with the commercially available 1,4-Bis-(trimethylsilyl)-1,3-butadiyne **3.043** (table 3.10). **3.043** was first mono desilylated by methyl lithium, and then reacted with THP-protected 3-iodo-1-propanol. Without isolation, the resulting diyne ether was treated with TBAF to deliver product **3.005** in 72% yield over 3 steps. Treatment of **3.005** with butyl lithium in the presence of a copper salt led to the corresponding organocopper reagent, which was anticipated to engage bicyclobutene lactone **3.029** to deliver product **3.039**. However, under our previous conditions of figure 3.7, a considerable amount of chlorosubstituted cyclobutene acid **3.041** was formed, along with desired product **3.039** (entry 1). The formation of **3.041** demonstrated the low nucleophilicity of the alkynyl cuprate reagent. We then screened different copper salts. When copper bromide was used,[72] **3.039** was only obtained in 14% yield (entry 2). Inspired by the work of B. H. Lipshutz *et al.*,[73] we then mixed 2.0 equivalents of ^{n}BuLi with 2.0 equivalents of **3.005** in the presence of 1.0 equivalent of copper cyanide at -78 °C to form a higher order cuprate (**3.005**)$_2$CuCNLi$_2$, to which **3.029** (1.0 equivalent) was added and the mixture was allowed to warm to room temperature. Pleasingly, the product **3.039** was formed cleanly in 70% yield, along with trace amount of (*E*,*E*)-dienic acid **3.040** (entry 3). Despite only 1.0 equivalent of **3.005** reacting in the transformation, 40% of **3.005** could be readily recovered after the work up.



Entry	Conditions	Comments
1	CuCN·2LiCl	**3.039**/**3.041** = 1:0.6
2	CuBr·Me_2S	**3.039** (14%)
3	CuCN	**3.039**+**3.040** (70%)

Table 3.10 Optimization for the synthesis of **3.039**.

When the mixture of **3.039** and **3.040** was allowed to stand at room temperature overnight, **3.040** was the only observed product (figure 3.11). Product **3.040** was then converted to Weinreb amide **3.041** in 79% yield. **3.041** was first reduced by DIBAL-H and without isolation, treatment of the crude aldehyde with phosphonate **3.042** smoothly afforded (*E*,*E*,*E*)-trienic ketone **3.043**.[74] This product was found to be always accompanied by isomeric (*Z*,*E*,*E*) ketone **3.044**. When all the operations were conducted with stringent exclusion of light, product **3.044** was not found any more; This suggests that either the intermediate or the product are sensitive to the light-promoted isomerization.

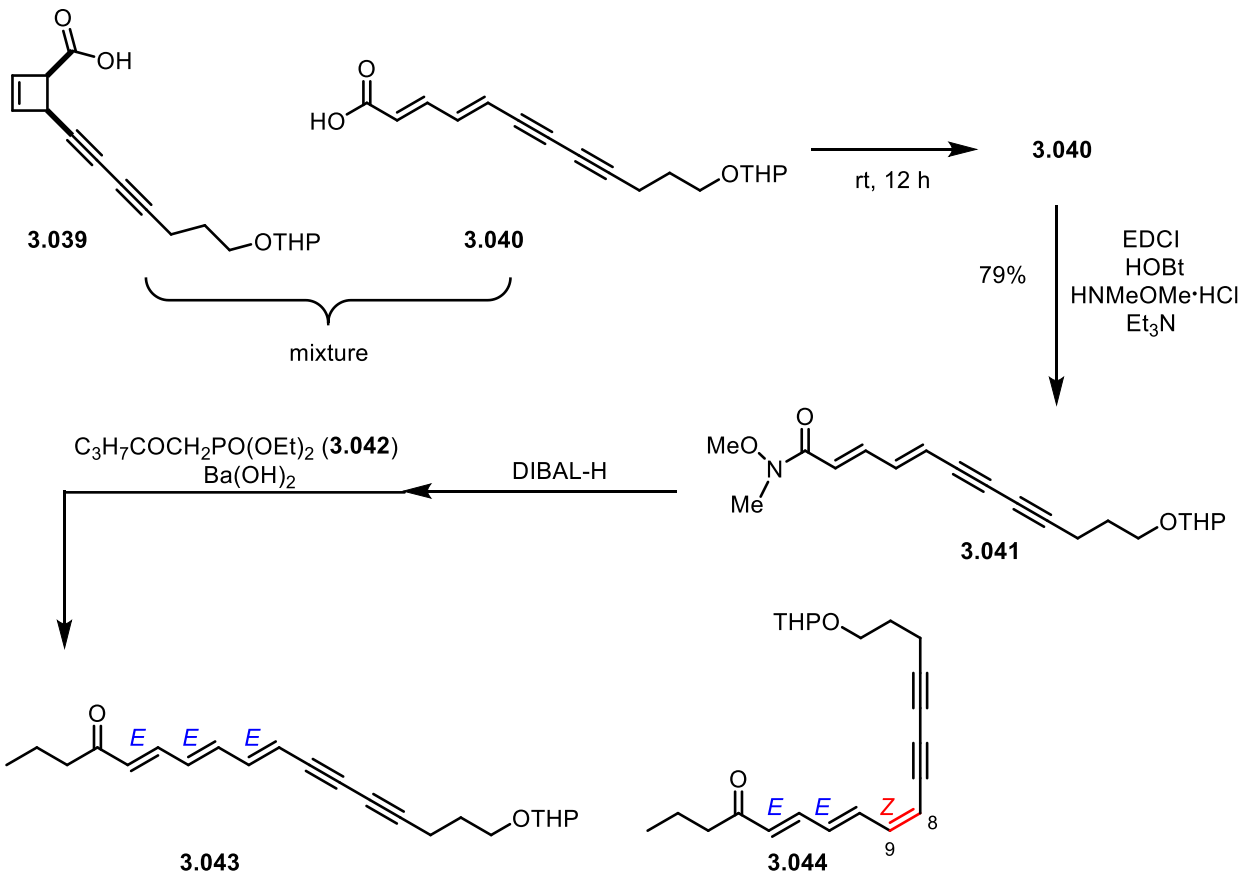


Figure 3.11 Synthesis of ketone **3.043**.

We studied this light-triggered isomerization of ketone **3.043** in more detail (figure 3.12). Pure **3.043** was first exposed to household light for 1 h, but unexpectedly, no isomerization was observed. When it was irradiated with UV light for 1 h, **3.044** began to form with the ratio of **3.043**/**3.044** being 12.4:1. Then the mixture was exposed to household light for another 12 h and the ratio increased to 2.77:1. The mixture was again irradiated with UV light for 14 h, however, the ratio only slightly increased to 2.63:1. Then the mixture was once again exposed to household light and, after 3 days, the ratio of **3.043**/**3.044** remained at 2.09:1. These experiments showed that the conversion of **3.043** to **3.044** is probably reversible under either UV light or household light. Product **3.043** is probably thermodynamically more stable than **3.044** as it was always observed as a major component in the mixture. Notably, this light-induced isomerization was quite clean, with no other products observed except for **3.043** and **3.044**.

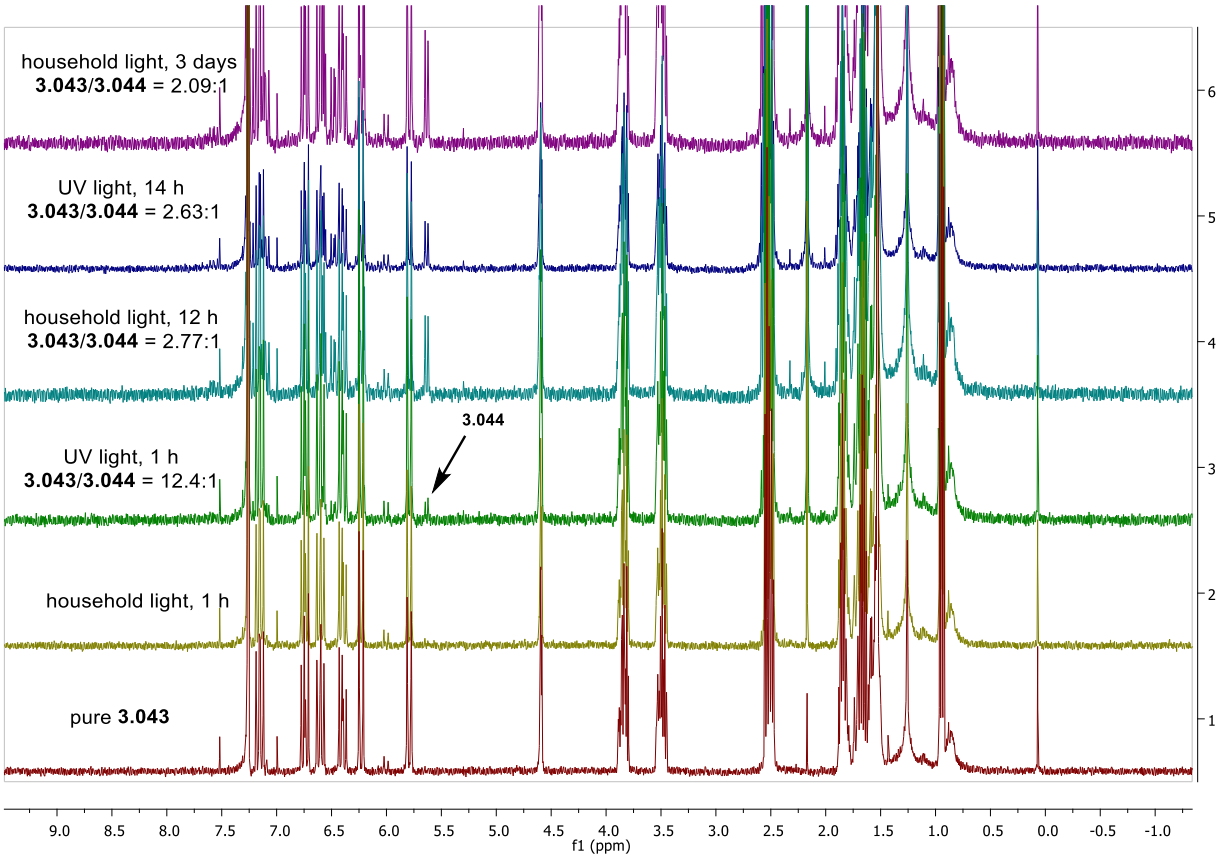


Figure 3.12 Isomerization of **3.043**.

Then the asymmetric reduction of ketone **3.043** was targeted. Inspired by the recent work reported by the group of Zhu (figure 3.13),[75] in which a variety of α,β-unsaturated ketones were asymmetrically reduced in high yield and ee, we planned to use their nickel complex for the asymmetric reduction of ketone **3.043**.

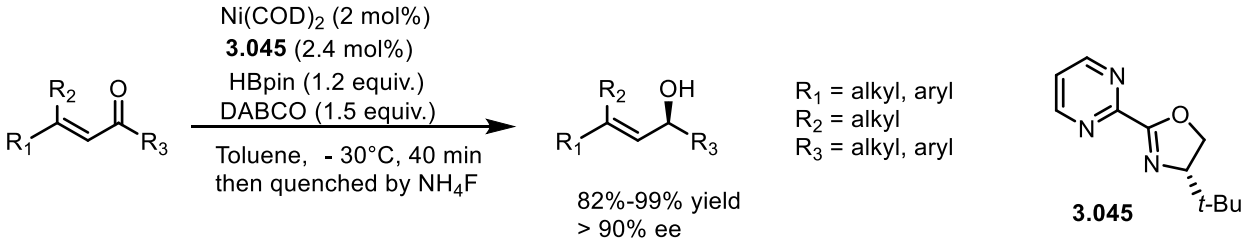


Figure 3.13 Zhao *et al.*'s protocol for the asymmetric reduction of ketones.

The Ligand ***ent*-3.045** was readily obtained from the pyrimidine **3.046** and amino alcohol **3.047** in one step in 71% yield (figure 3.14). Using the synthesized ligand ***ent*-3.045**, under the above conditions, ketone

3.048, a substrate in Zhu *et al.*'s work, was reduced to its corresponding alcohol **3.049** in quantitative yield. Then alcohol **3.049** was then transformed to its Mosher ester **3.050**.[76] By comparing with (*rac*)-**3.050** (not shown), derived from (*rac*)-**3.049**, the ee of alcohol **3.049** was determined to be > 90% by ^{1}H NMR (figure 3.14) which was comparable to Zhu *et al.*'s result: > 99% yield, > 99% ee.[75]

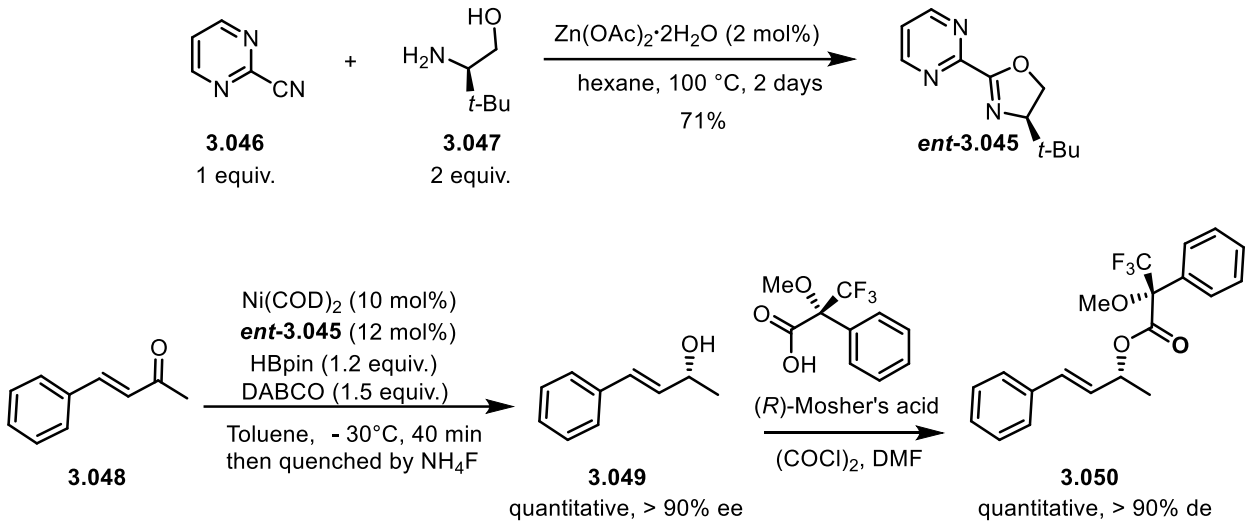


Figure 3.14 Repeating Zhao *et al.*'s reduction.

The success of our reduction on the known model substrate **3.048** above led us to attempt the reduction of ketone **3.043**. However, under the same conditions, even with increased catalyst loading, temperature and time, we never observed the reduction of the ketone **3.043** (figure 3.15). The main product remaining in the crude reaction was starting material. We believe this showcases the low reactivity of polyconjugated ketone **3.043**.

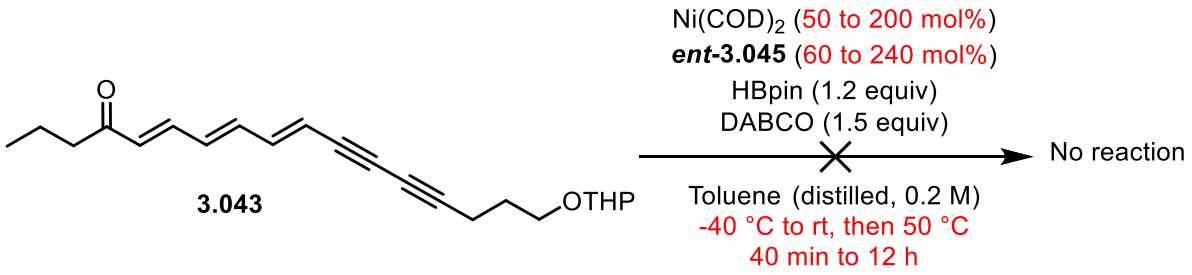
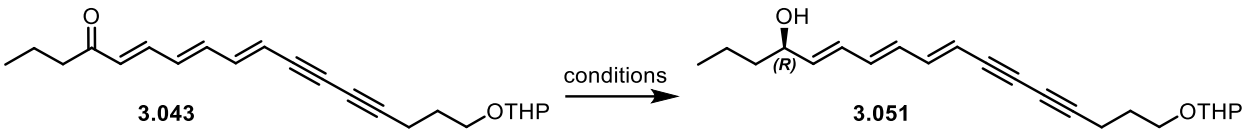


Figure 3.15 Attempted reduction of ketone **3.043**.

We then turned to the conditions of the Itsuno-Corey reduction (table 3.16).[77] Using the CBS reagent at 0 °C, the product **3.051** was readily isolated after 30 min, however, the *R*/*S* ratio was only 6.7:1 (entry 1). When the temperature was decreased to -78 °C, the reaction became quite sluggish, after 4 h, only 18%

of **3.051** was isolated. When the loading of the CBS reagent was increased to 2.0 equivalent and the temperature was kept at -50 °C, product **3.051** was readily isolated in 76% yield, with a ratio of *R*/*S* > 20:1. Clearly, the activity of the CBS reagent is sensitive to the reaction temperature. High enantioselectivity could be achieved with a high loading amount of the CBS reagent.



Entry	(*S*)-CBS reagent (equiv.)	BH_3 Me_2S (equiv.)	Temp./Time	Comments (Isolated yield, d.r.)
1	1	3	0 °C, 30 min	67%, *R*/*S* = 6.7:1
2	1	2	-78 °C, 4 h	18%[a], ND
3	2	2	-50 °C, 1.5 h	76%, *R*/*S* > 20:1

[a] 38% of **3.043** was recovered.

Table 3.16 Reduction of ketone **3.043** by the CBS reagent.

The optimized asymmetric reduction conditions were also applied in the total synthesis of virol A (figure 3.17).

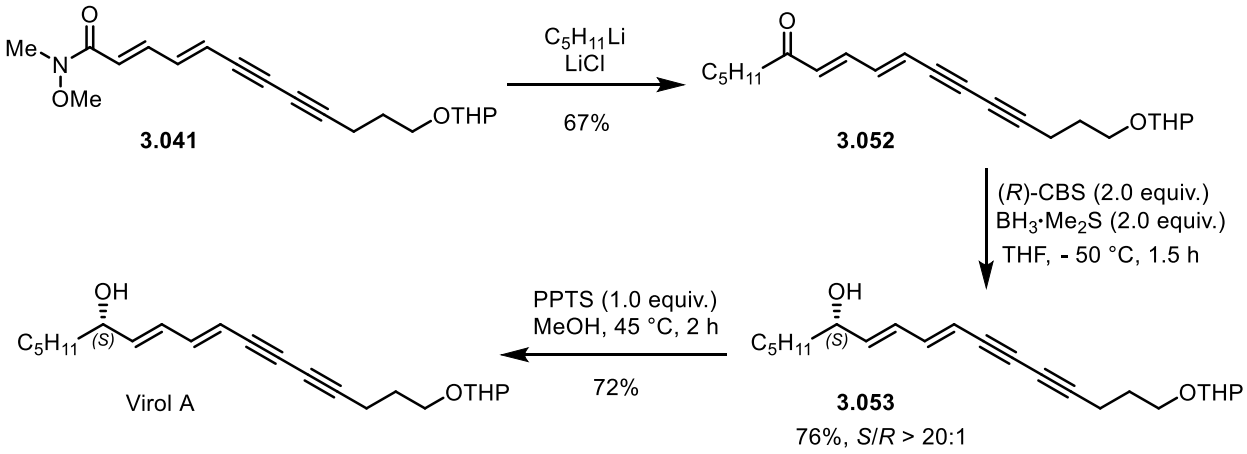


Figure 3.17 Total synthesis of virol A.

The THP group in **3.051** was then removed by the weak acid pyridinium *p*-toluenesulfonate (PPTS) in methanol at 45 °C. However, these conditions led to the isolation of byproduct O-Me cicutoxin in 53%

yield. When the stronger acid *p*-toluenesulfonic acid (PTSA) was used, the reaction could be carried out at room temperature, and cicutoxin was isolated in 60% (figure 3.18).

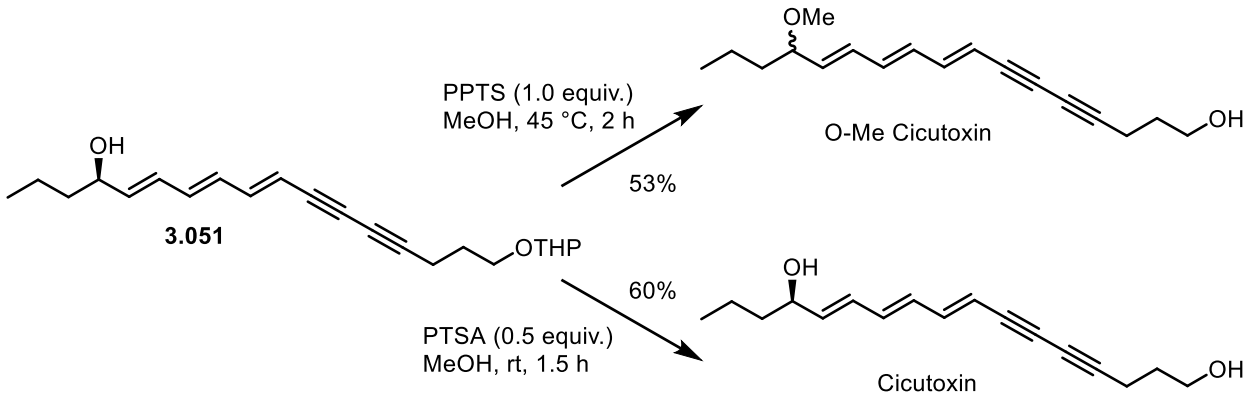


Figure 3.18 Total synthesis of cicutoxin.

In addition, reduction of the ketone **3.043** by sodium borohydride allowed us to isolated (*rac*)-**3.051**. Further removal of the THP group of (*rac*)-**3.051** led to (*rac*)-cicutoxin (figure 3.19). The flexibility of this route allowed us to obtain several products which would prove useful for the following structure-activity relationship study.

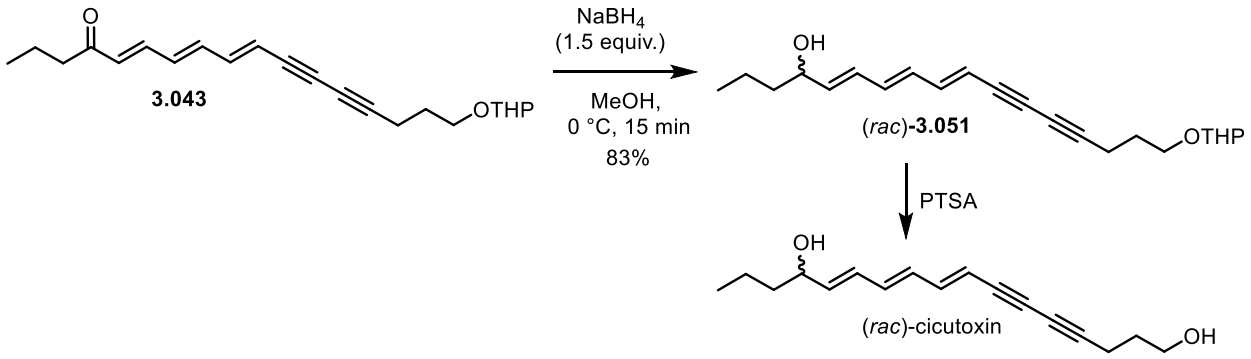


Figure 3.19 Total synthesis of (*rac*)-cicutoxin.

3.4 Biological Studies

Cicutoxin and virol A were reported to be detrimental to the central nervous system and inhibit GABA-gated Cl^- channels of GABA receptors.[68,78] In collaboration with the research group of Dr. Margot Ernst, Medical University of Vienna, we tested their effect on α1β3γ2 $GABA_A$ receptors, which are the major $GABA_A$ receptor isoforms in the adult mammalian brain.[79] It was observed that both cicutoxin and virol A, either enantioenriched or racemic, were potent inhibitors of $GABA_A$-induced chloride current. However,

the synthetic byproduct O-Me cicutoxin was inactive in the inhibition of chloride current, highlighting the crucial role of free hydroxyl group (figure 3.19).

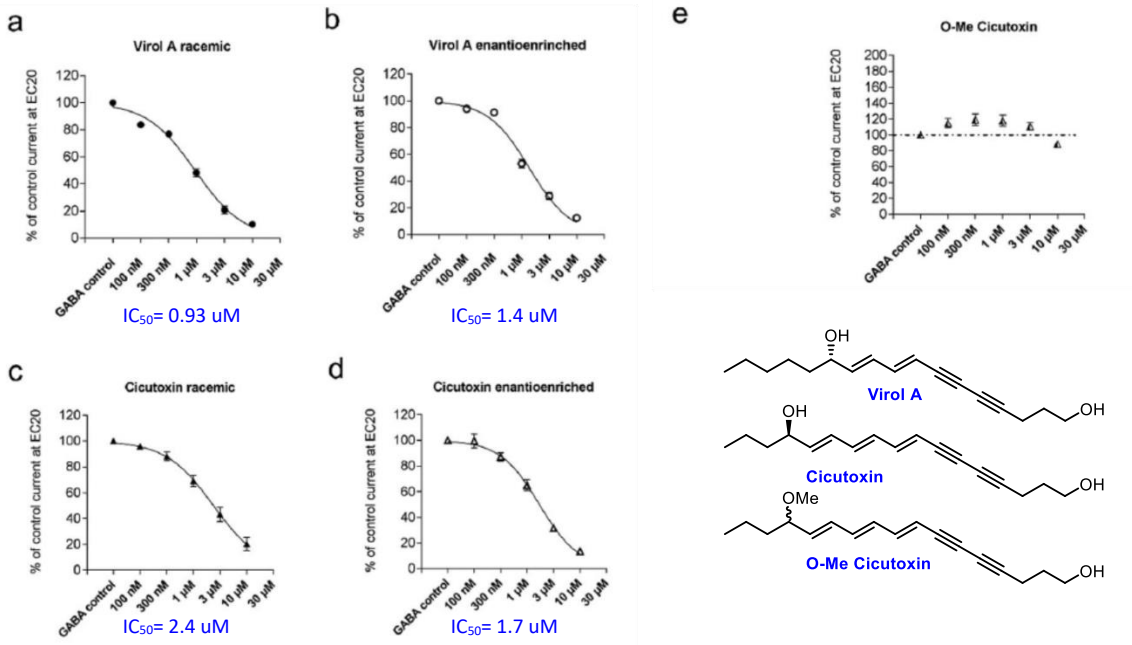


Figure 3.19 Inhibition of $GABA_A$-induced chloride current.

3.5 Conclusion

We developed a mild method for the expeditious preparation of *trans* cyclobutenes bearing various alkyl groups. This methodology was further extended to the total synthesis of cicutoxin and virol A. Our synthesis demonstrated that the ring opening of stereochemically defined cyclobutene could be quite facile and stereospecific. Compared to the prior syntheses of cicutoxin, our route was able to deliver both enantioenriched and racemic product due to a late stage reagent-controlled ketone reduction. Biological study showed that cicutoxin and virol A, either chiral or racemic, were potent in inhibiting the $GABA_A$-induced chloride current. However, the synthetic byproduct OMe-cicutoxin was completely inactive, highlighting the crucial role of free hydroxy group.

3.6 Perspective

Cyclobutene moiety as a reliable diene surrogate was showcased in the total syntheses of cicutoxin and virol A. It has been documented that the dienic carboxylates could be chemoselectively functionalized.[80] Early studies from the lab of K. B. Sharpless showed that both dienolate **3.054** and trienolate **3.056** could

be asymmetrically mono-dihydroxylated to afford diol ester **3.055** and **3.057** in high yield and enantioselectivity (figure 3.20).[80a]

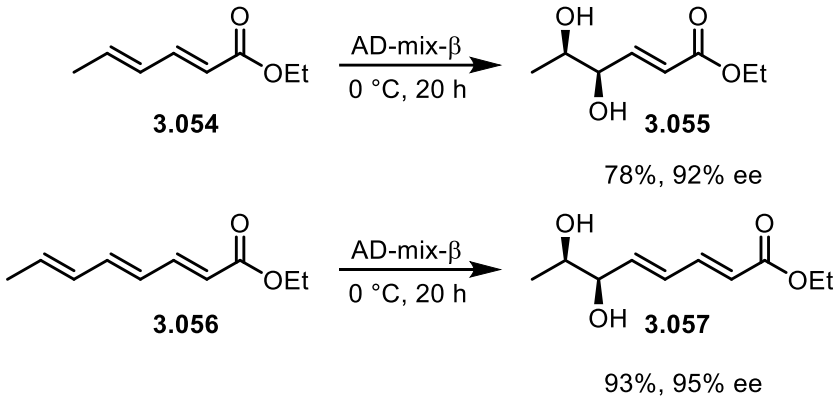


Figure 3.20 Chemo- and stereoselective dihydroxylation of dienolate and trienolate.

More impressively, A. B. Smith, III *et al.* demonstrated in their total synthesis of natural products lituarines A, B and C that the complex trienolate **3.058** could be iteratively and asymmetrically functionalized,[80f] either by dihydroxylation or epoxidation. Remarkably, all the stereochemical transformations were reagent-controlled (figure 3.21).

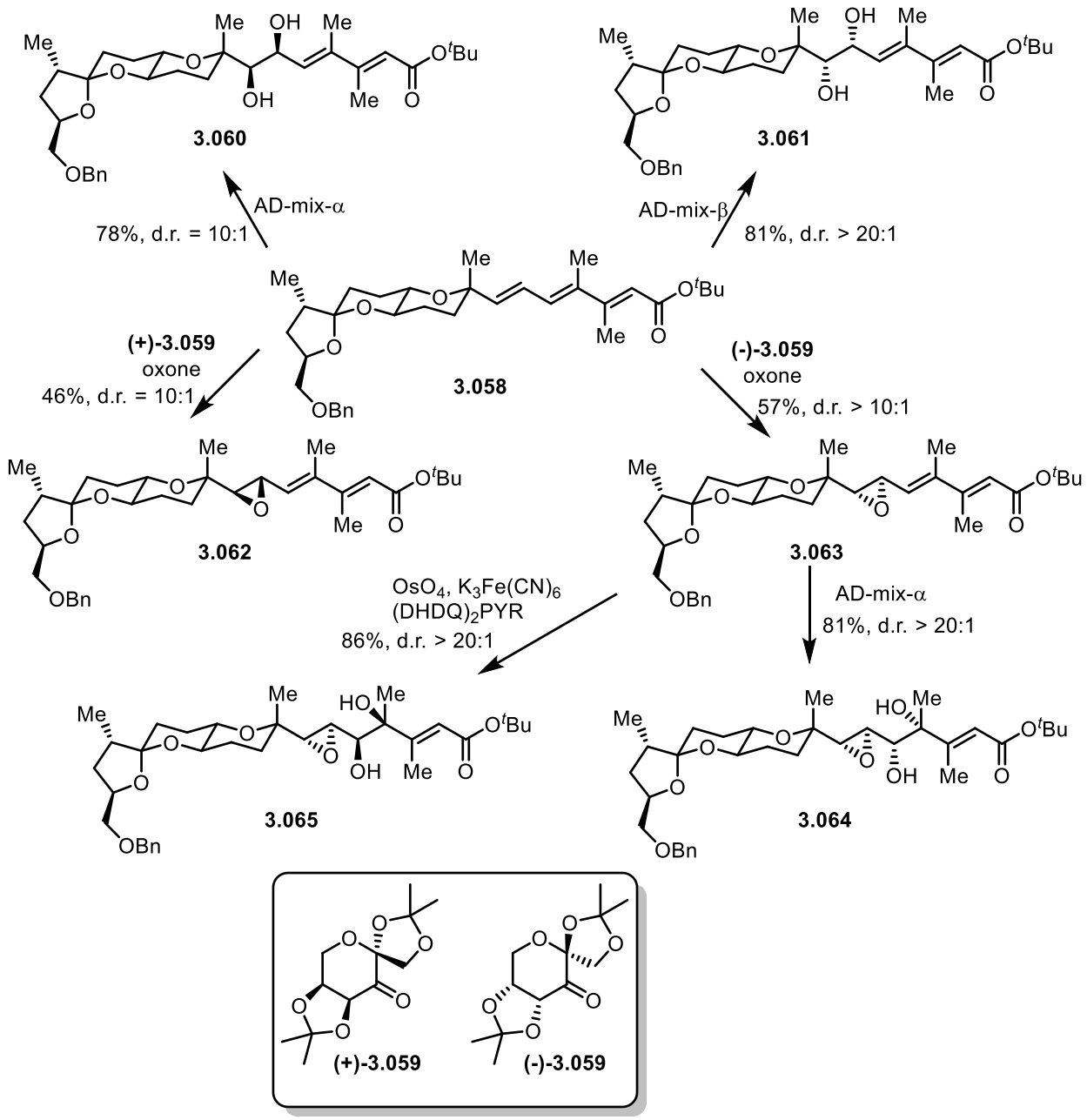


Figure 3.21 Iterative and chemoselective functionalizations of trienolate **3.058**.

As demonstrated above, the rich chemistry related to the C=C double bonds of the polyene could potentially extend our methodology to the synthesis of natural products beyond polyenes (figure 3.22).

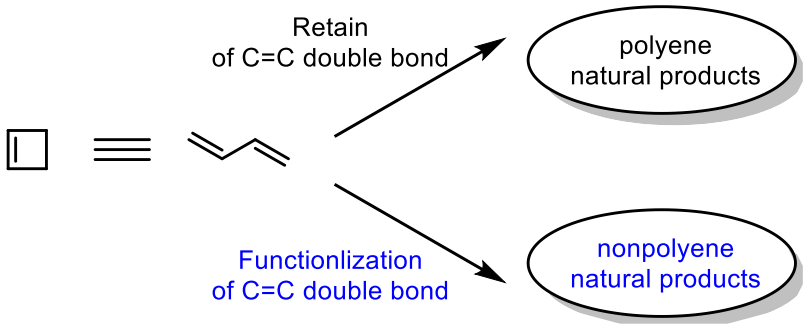


Figure 3.22 Possible extension of our methodology.

Chapter 4. Total Synthesis of FR252921, FR252922 and FR256523

4.1 FR252921, FR252922 and FR256523: Structures and Bioactivities

FR252921, FR252922 and FR256523 (henceforth FR molecules) are metabolites isolated by the then Fujisawa Company in 2003 (figure 4.1).[81] These compounds share a 19-membered (*E,E,E*)-trienic bislactam macrocyclic core and only differ on their side chains. Although their complete 2D structures were elucidated, the absolute stereochemistry at C12, C13 and C18 was not defined at that time. Initial biological assay showed that these compounds were potent immunosuppressants. All three compounds inhibited the lymphocyte proliferation when stimulated with lipopolysaccharides (LPS) and anti-CD3.[81] Further studies showed that FR252921 was an inhibitor for the generation of both interleukin 2 (IL-2) and interleukin 12 (IL-12). In contrast, the clinically used drug FK506 only inhibited the generation of IL-2.[82] *In vivo* study later demonstrated FR252921 synergistically improved the effect of FK506 and prolonged the allograft survival.[83]

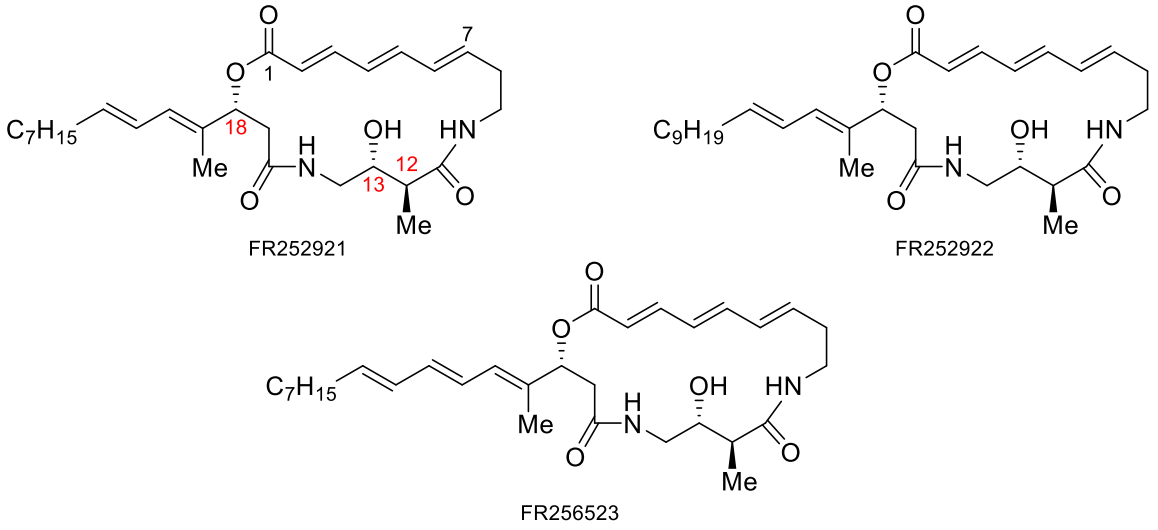


Figure 4.1 Structures of FR252921, FR252922 and FR256523.

4.2 FR252921: Previous Synthesis

Due to their potent biological activity and novel structures, the FR molecules rapidly drew the attention of synthetic chemists. A non-stereospecific synthesis was initially reported by the group of Pohanka.[84] The first total synthesis of FR252921 was reported by the group of Falck. Their work also established the absolute stereochemistry of FR252921.[85] Later, the group of Cossy reported their total synthesis of FR252921.[86] Besides that, one isomer synthesis, one formal synthesis and one synthetic approach were reported.[87,88,89]

4.2.1 Pohanka *et al.*'s Non-Stereospecific Semisynthesis of FR252921 and FR252922

The first non-stereospecific synthesis of FR252921 and FR252922 was reported by the group of Pohanka.[84] From the liquid culture broth of *Pseudomonas* sp. MF381-IODS, two pseudotrienic acids termed A and B were isolated. When the two acids were treated with dilute trifluoroacetic acid (TFA) during the purification step, two corresponding lactones were formed (figure 4.2). These lactones were shown to have the same bonding pattern as FR252921 and FR252922. Although this semisynthetic approach established a potentially intriguing biogenetic link between the FR molecules and the pseudotrienic acids, the question of stereoselective formation of the C18-stereocenter is not addressed.

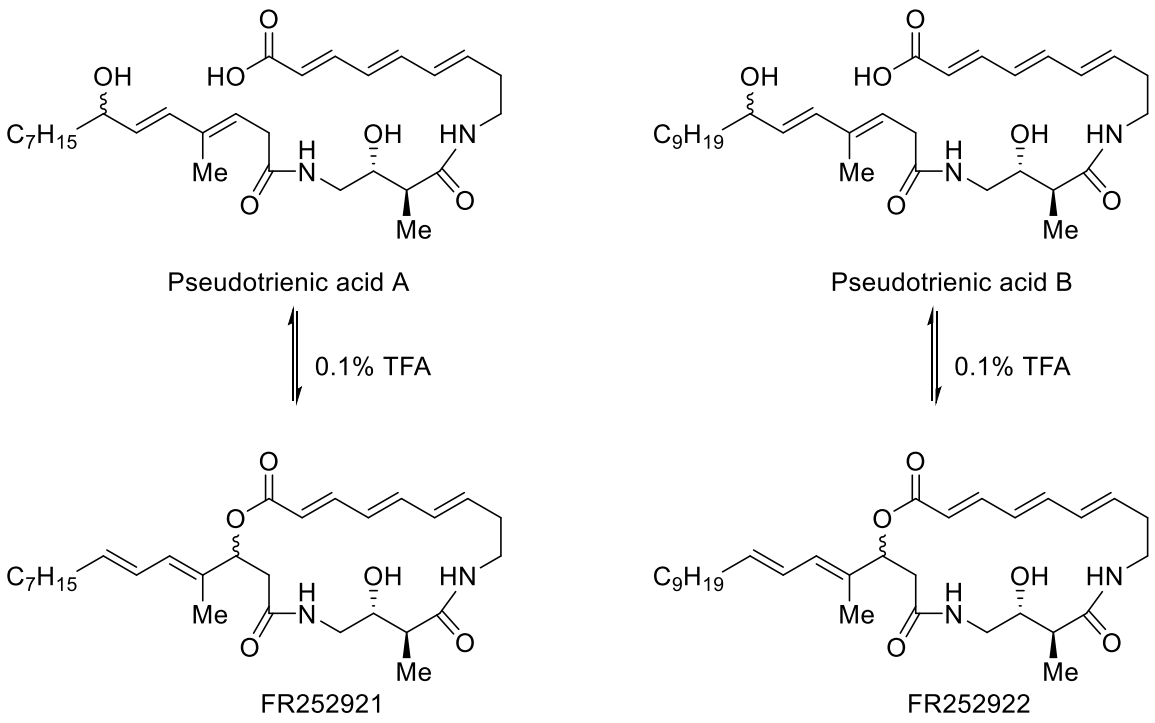


Figure 4.2 Pohanka *et al.*'s semisynthesis of FR252921 and FR252922.

4.2.2 Falck *et al.*'s Total Synthesis of FR252921

The first total synthesis of FR252921 was reported by the group of J. R. Falck. Through synthesizing four different diastereoisomers, those authors also established the absolute stereochemistry of C12, C13 and C18.[85]

The synthesis of dienic β-hydroxy acids was addressed first. Starting from the commercially available aldehyde **4.001**, the dienal **4.003** was readily obtained after three steps. Reformatsky reaction of aldehyde **4.003** with bromoacyloxazolidinone **4.004** in the presence of samarium iodide afforded aldol product **4.005** in 81% yield with a d.r. = 8:1. Following diastereomer separation, adduct **4.005** was readily hydrolyzed upon treatment with lithium peroxide to deliver free acid **4.006**. The same procedure was conducted on the minor diastereomer (not shown) to afford the enantiomer **4.007** (figure 4.3).

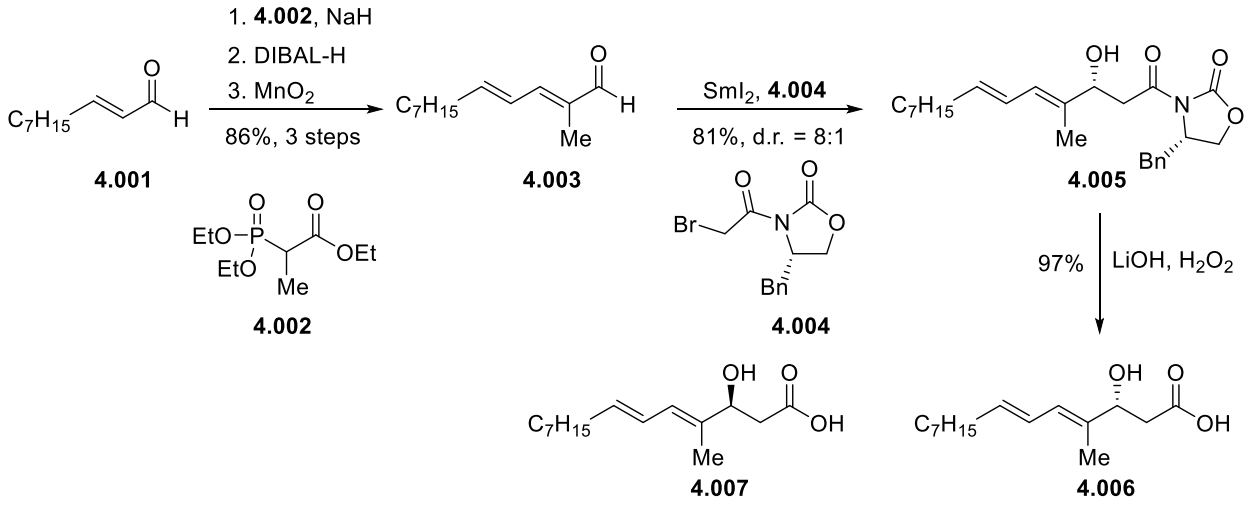


Figure 4.3 Synthesis of acid **4.006** and **4.007**.

Then the chiral γ-amino acid fragments were synthesized. Treatment of aldehyde **4.008** with oxazolidinone **4.009** in the presence of two equimolar amounts of $^{n}Bu_2BOTf$ gave *trans* aldol adduct **4.010** and *cis* aldol adduct **4.011** with a ratio of 1:1. Following a two-step sequence, the *anti* acid **4.012** and *syn* acid **4.013** were readily obtained in 89% yield (figure 4.4).

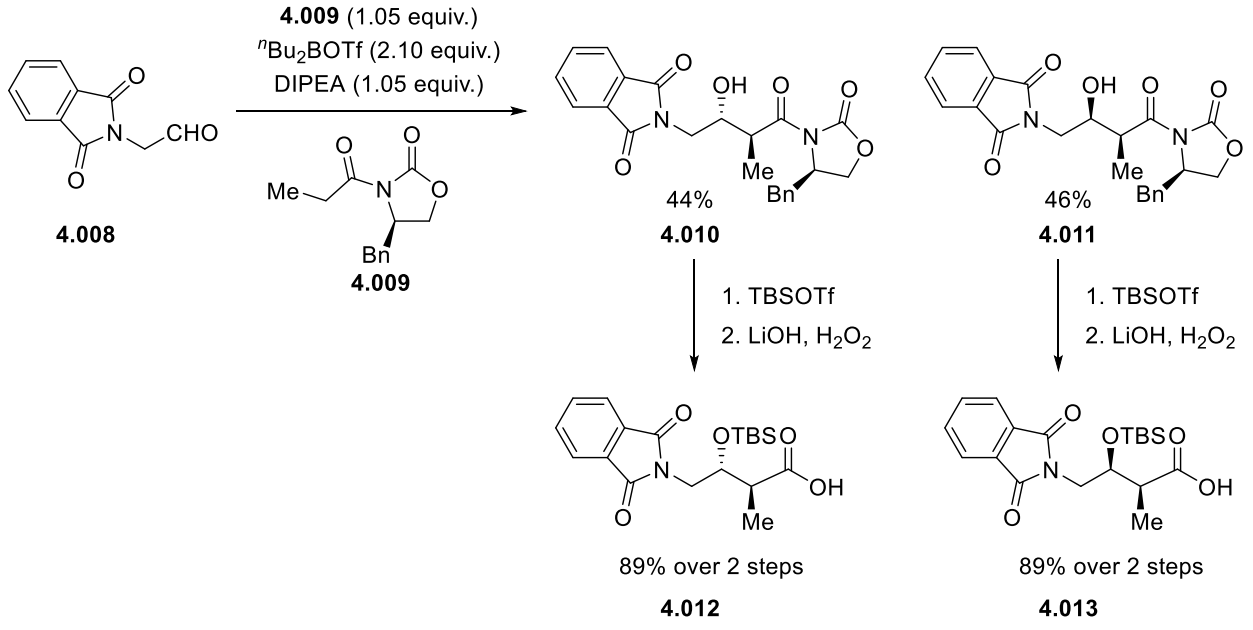


Figure 4.4 Synthesis of **4.012** and **4.013**.

The third segment of the synthesis was the trienic amine **4.020**. Hydrozirconation of homopropargyl tosylate **4.014**, followed by palladium catalyzed coupling with vinyl iodide **4.015** delivered diene tosylate

4.016 in 98% yield. **4.016** was readily converted to the azido aldehyde **4.017** after a 3-step sequence. Horner–Wadsworth–Emmons (HWE) reaction of **4.017** with the phosphonate **4.018** gave azido ester **4.019** in 95% yield. A final Staudinger reduction delivered amine **4.020** in 93% yield (figure 4.5).

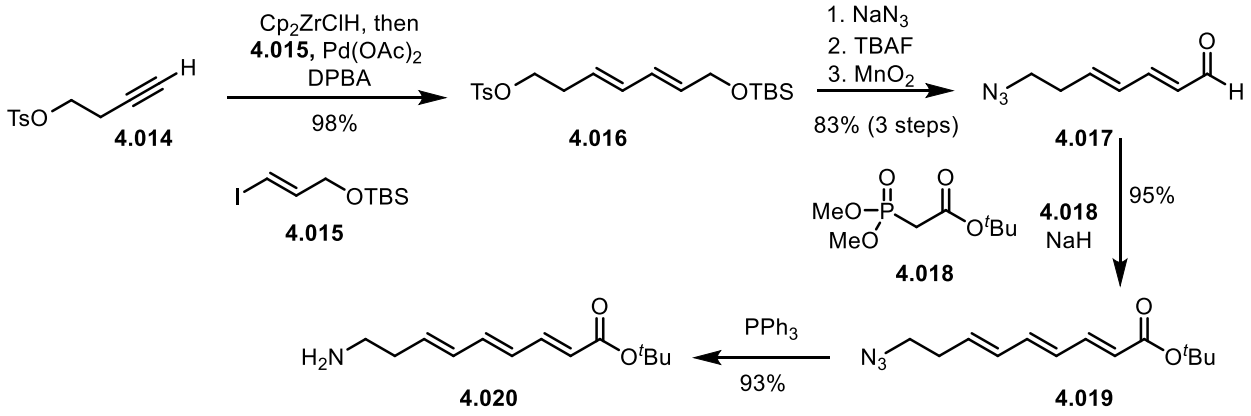


Figure 4.5 Synthesis of trienic amine **4.020**.

The assembling of the three fragments was straightforward. The acid **4.012** was coupled with amine **4.020**. The resulting amide was first treated with TBAF and then hydrazine to afford free aminoalcohol **4.021**. Coupling of **4.021** with acid **4.006** afforded bisamide **4.022**. *Tert*-butyl group deprotection unveiled acid **4.023**, which was submitted to Shiina macrolactonization conditions delivering the macrocycle **4.024**, albeit in only 10% to 15% yield. The three diastereoisomers **4.025**, **4.026**, **4.027** were also obtained following a protocol similar to that described above. The synthetic compounds were compared with the isolated sample of FR252921, which allowed an unambiguous assignment of the absolute stereochemistry of the natural product to compound **4.024** (figure 4.6).

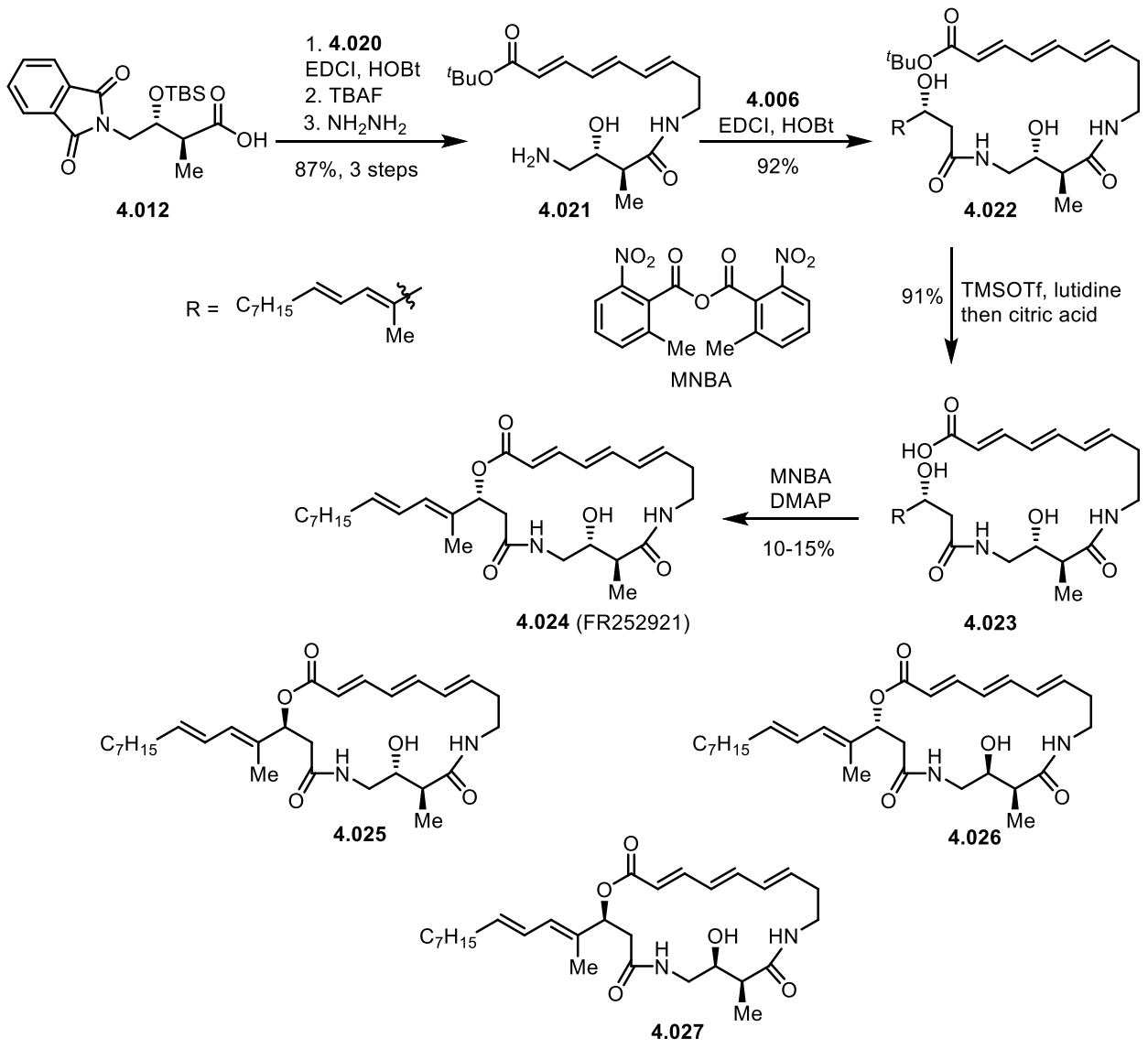


Figure 4.6 Falck *et al.*'s synthesis of FR252921.

4.2.3 Cossy *et al.*'s Total Synthesis of FR252921

Rapidly following Falck *et al.*'s synthesis, the group of Cossy reported their total synthesis of FR252921.[86] The chiral γ-amino acid fragment was synthesized in a different manner. The Boc protected glycine ester **4.028** was reduced by DIBAL-H to the corresponding aldehyde **4.029**. Crotylation of aldehyde **4.029** by the titanium-crotyl complex **4.030** delivered the *anti* carbamate **4.031** in 57% yield over two steps. Protection of the resulting product as N,O-acetonide, followed by ruthenium-catalyzed oxidative cleavage of the terminal olefin led to the desired γ-amino acid **4.033** in 75% yield over 2 steps (figure 4.7).

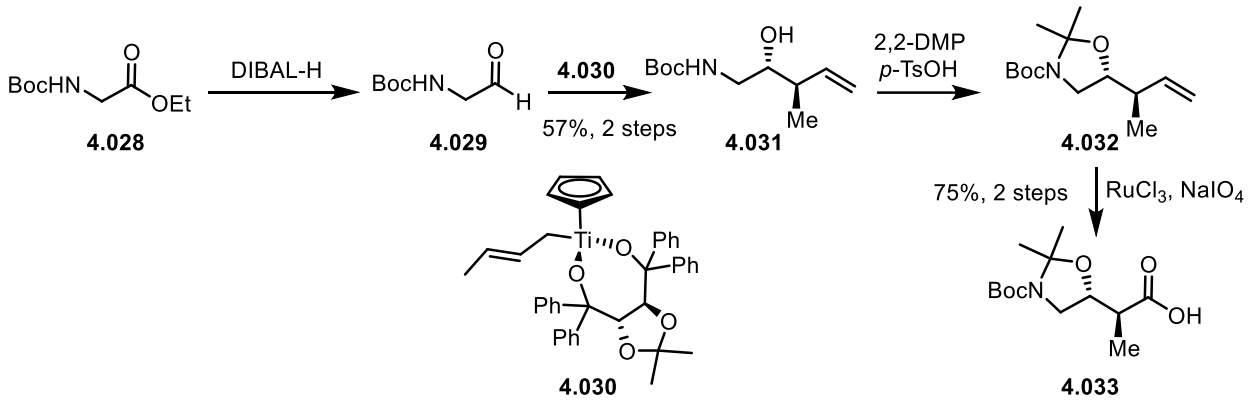


Figure 4.7 Synthesis of acid **4.033**.

The side chain was synthesized from (*E*)-3-iodo-2-methylacrylaldehyde **4.034**. Aldehyde **4.034** was converted to the β hydroxy ester **4.036** in 71% yield, > 95% ee upon the aldol addition of chiral titanium enolate **4.035**. Then, the Stille reaction was utilized to introduce another alkenyl unit to form dienic hydroxy ester **4.038** in 53% yield. Final hydrolysis of **4.038** by sodium hydroxide delivered the desired acid **4.006** in 99% yield (figure 4.8).

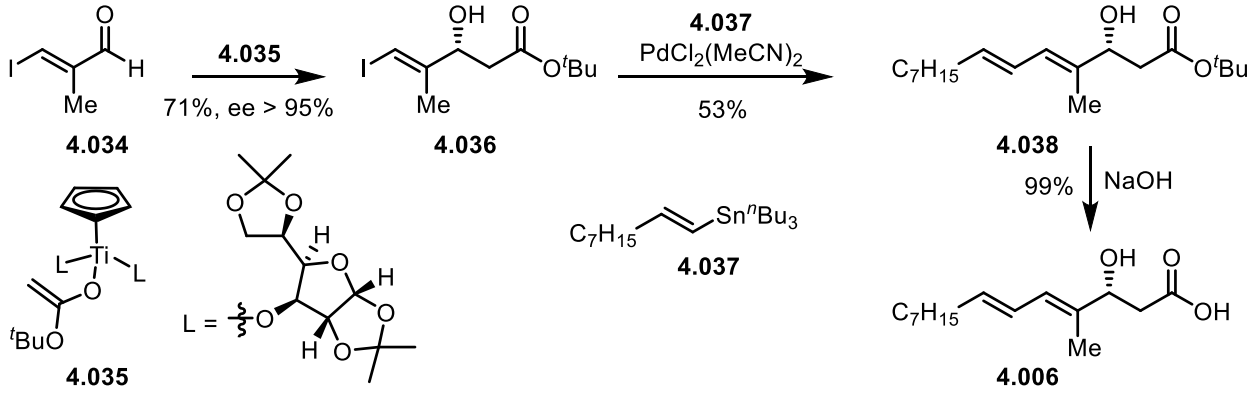


Figure 4.8 Synthesis of acid **4.006**.

Cossy *et al.*'s early attempts towards FR252921 involved several steps. The acid **4.033** was coupled with trienic amine **4.039** to afford amide **4.040**. The acetonide group of **4.040** was then removed, and the released hydroxy group was TIPS protected to afford **4.041**. Interestingly, the carbamate group in **4.041** was also TIPS protected. Treatment of **4.041** with TFA, then sodium carbonate, freed the amine **4.042**. Coupling of amine **4.042** and acid **4.006** delivered bisamide **4.043**. Hydrolysis of the ester in **4.043** readily afforded *seco* acid **4.044**. After a large number of conditions screened, it was observed that *seco* acid **4.044** readily cyclized under the condition of Yamaguchi macrolactonization. However, careful

characterization showed that the product was **4.046**, with a (*Z*)-C2-C3 bond. The desired (*E*,*E*,*E*)-product **4.047** was not obtained in the transformation (figure 4.9).

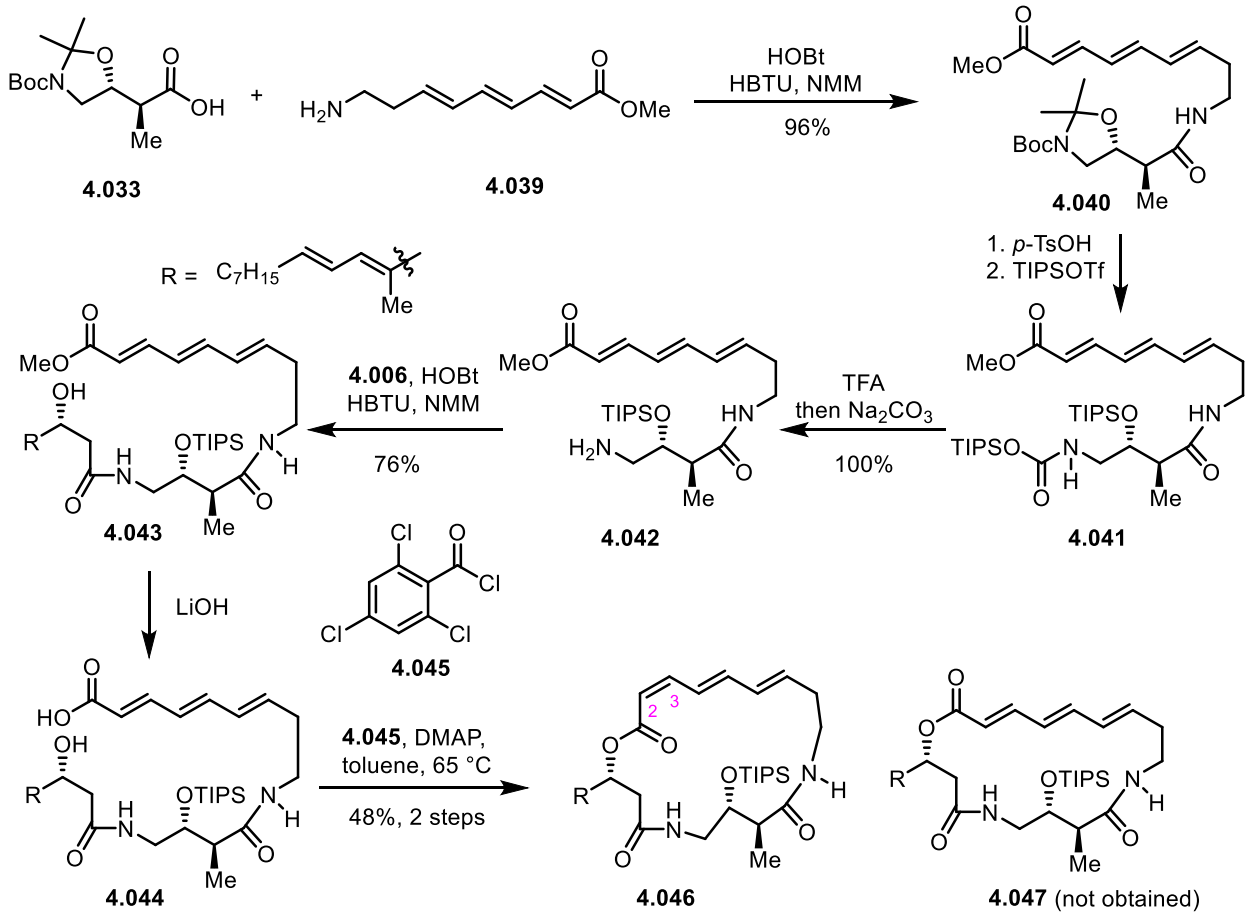


Figure 4.9 Cossy *et al.*'s early attempts towards FR252921.

A possible mechanism for the C2-C3 double bond isomerization was later proposed by Cossy *et al.*.[6b] According to this proposal, the *seco* acid **4.044** was first activated to form mixed anhydride **4.048**. The conjugate attack of DMAP at C3 of the anhydride **4.048** could deliver a putative ketene intermediate **4.049** after carboxylate elimination. The ketene was then internally captured by the pendant hydroxy group to afford intermediate **4.050**. The elimination of DMAP from compound **4.050** then regenerated the double bond. However, in this transformation, the *Z* isomer product **4.046** must be thermodynamically favored over the desired compound **4.047** (figure 4.10).

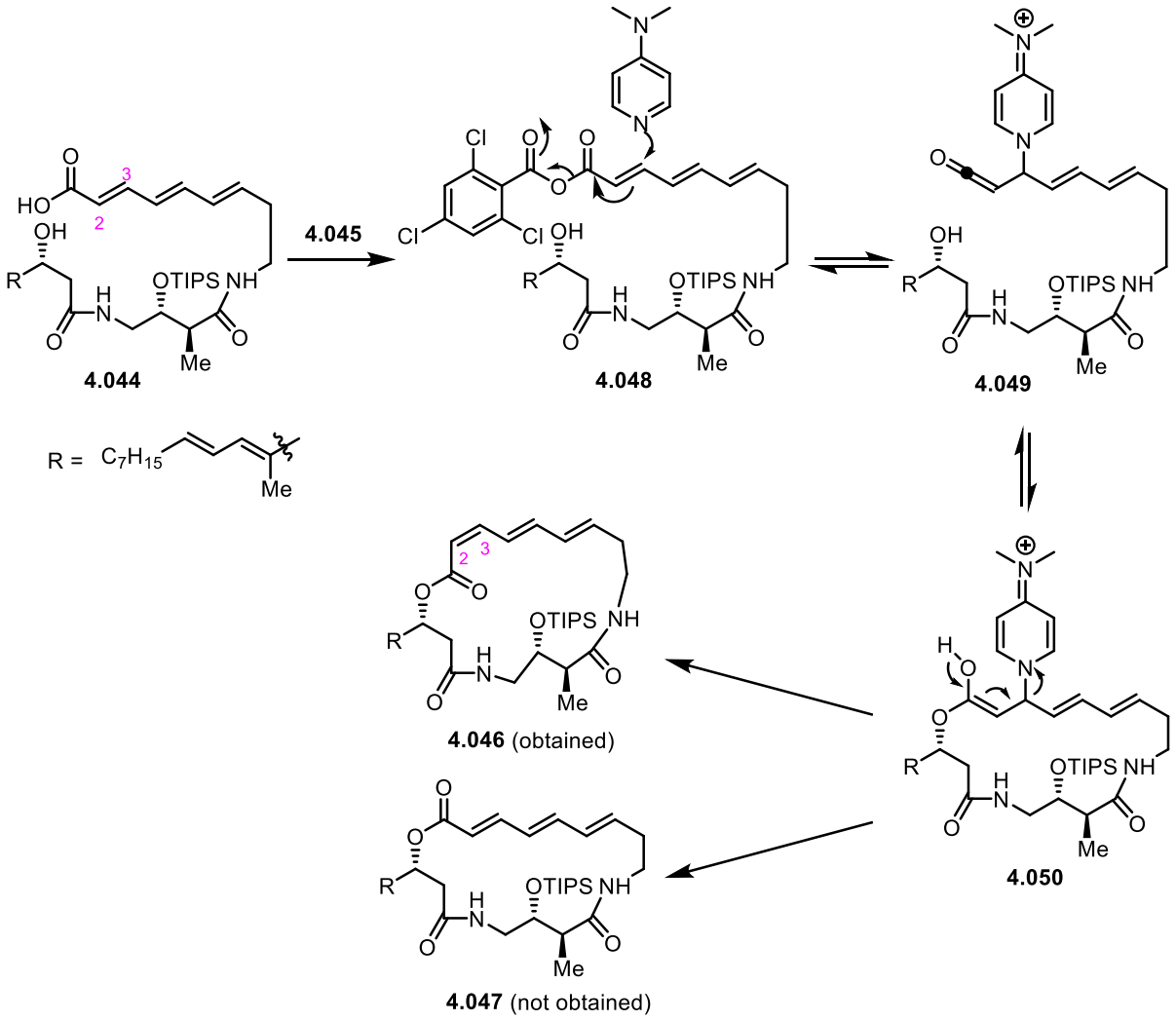


Figure 4.10 Possible mechanism for the isomerization of C2-C3 double bond proposed by Cossy *et al.*.

Suspecting the stereo-orientations at C12, C13 and C18 could be the reason behind the isomerization of C2-C3 double bond, Cossy *et al.* synthesized another two precursors **4.051** and **4.053** with variations of stereochemistry at C2, C3 and C18. These precursors were submitted to the Yamaguchi conditions as above. However, the only products obtained were again (*Z*)-C2-C3 double bond isomers **4.052** and **4.054** respectively. Ma *et al*. previously demonstrated the precursor **4.055** gave (*Z*)-C2-C3 isomer **4.056** under Yamaguchi conditions.[87] These combined evidence showed that the stereochemistry at C2, C3 and C18 was not responsible for the isomerization of the C2-C3 double bond (figure 4.11).

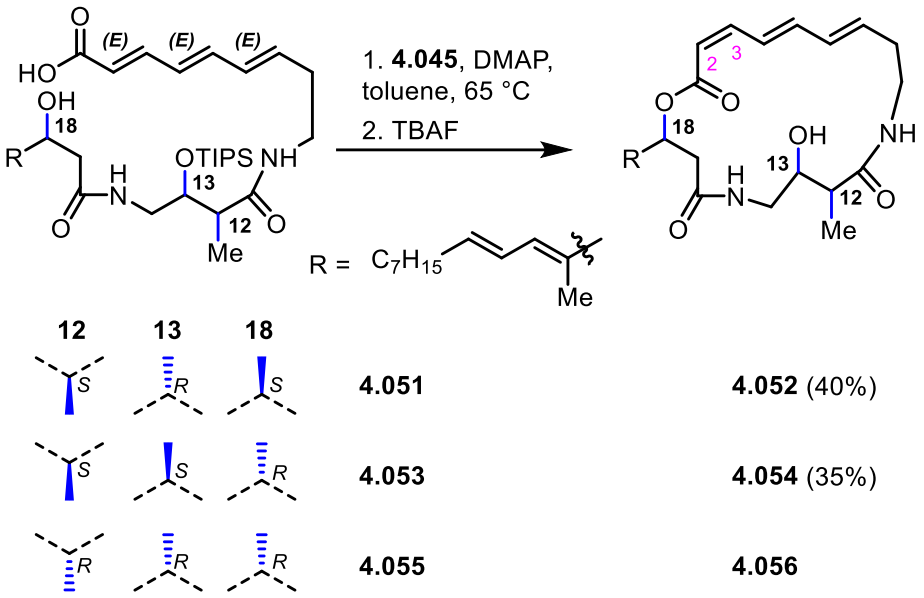


Figure 4.11 Macrolactonization using different diastereomeric precusors.

The effect of the protecting group TIPS was next investigated. Following the report of Falck *et al.*,[85] the precursor **4.023** was synthesized. *Seco* acid **4.023** was then submitted to the Shiina macrolactonization conditions used by Falck *et al.*.[85] However, contrary to Falck *et al.*'s result, this transformation only gave FR252921 in less than 5% yield. The product FR252921 was contaminated with considerable amounts of byproducts and could only be purified by reverse phase HPLC (figure 4.12).

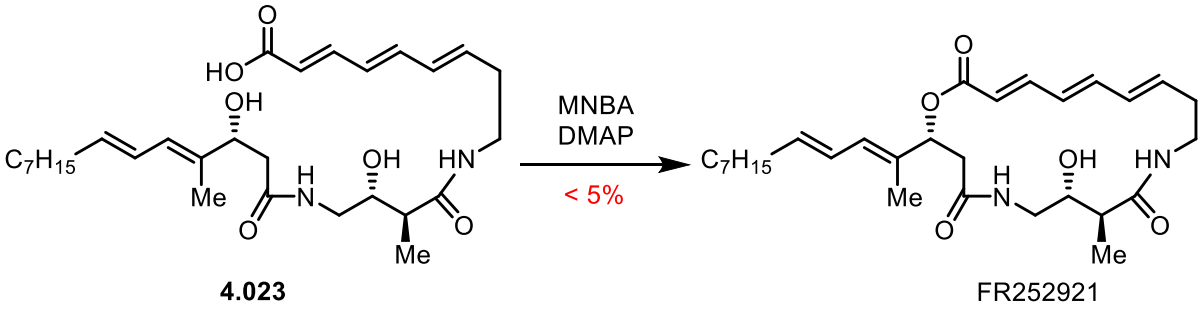


Figure 4.12 Cossy *et al.*'s final synthesis of FR252921.

4.3 Synthesis of FR molecules, Analogues and Probes

Results in this chapter were obtained in collaboration with Dr. Caroline Souris, Dr. Guilhem Coussanes, Dr. Paul Aillard and Dr. Dainis Kaldre.

4.3.1 Retrosynthesis

The cloud of isomerization obscured further investigation on the FR molecules. In response to this mystery, Dr. Boris Maryasin studied the stability of two simplified compounds **4.057** and **4.058** by theoretical calculation (figure 4.13). This study showed that the *Z* isomer **4.058** was more stable than the *E* isomer **4.057** due to an intramolecular hydrogen bonding between the carbonyl group of the ester and the neighboring amide hydrogen.

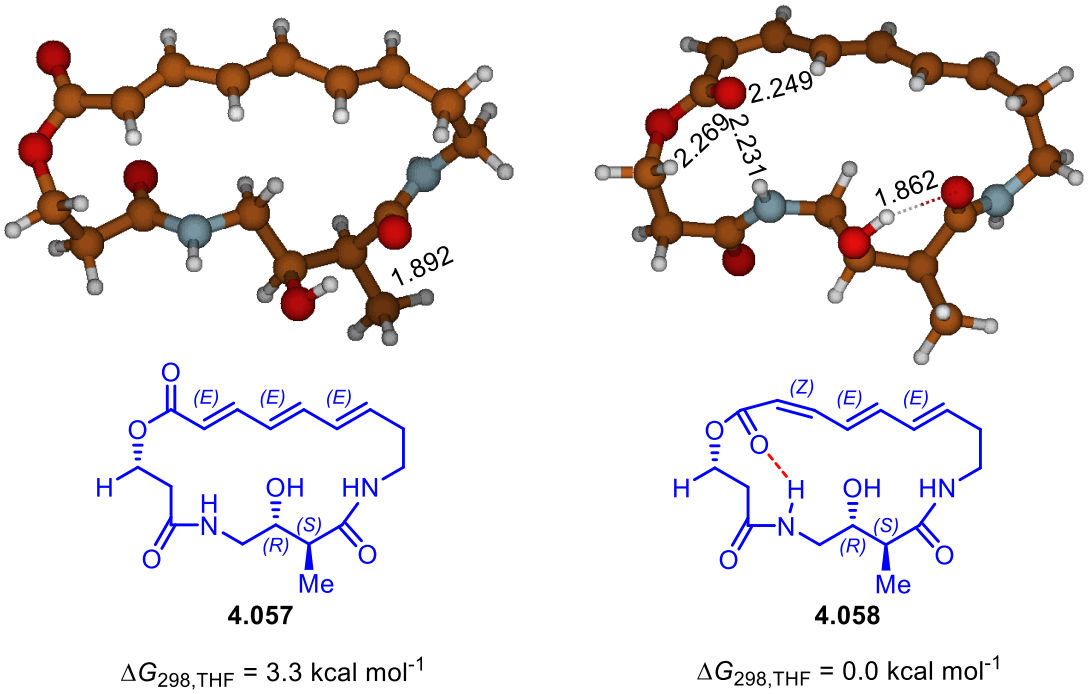


Figure 4.13 Stability explained by theoretical calculation.

The total synthesis of FR molecules could therefore be quite challenging as the naturally occurring (*E*)-C2-C3 isomer was proved to be thermodynamically less stable than its (*Z*)-C2-C3 isomer. As Cossy *et al.* concluded "the macrolactonization strategy is not suitable to prepare FR252921 in satisfying yields",[86a] and therefore new strategies for the construction of the (*E,E,E*)-trienic macrocycle needed to be developed. Towards this goal, the use of a novel 4π-electrocyclic ring opening approach was previously investigated in our group.[90]

During the functionalization of cyclobutene derivatives, Dr. Caroline Souris found that under Suzuki-Miyaura cross coupling conditions, (*E,E,E*)-trienic ester **4.061** could be readily formed from boronic ester **4.059** and *cis*-chlorocyclobutene ester **4.060** (figure 4.14).

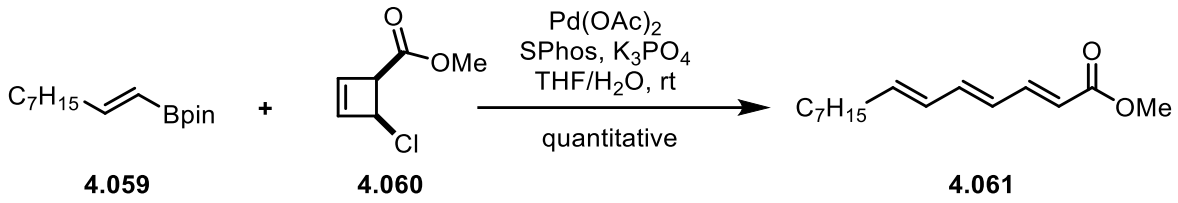


Figure 4.14 Stereoselective synthesis of triene **4.061** by Dr. Caroline Souris.

The streamlined and highly stereoselective formation of (*E*,*E*,*E*) trienic ester **4.061** is noteworthy. The direct 4π-electrocyclic ring opening of **4.060** should be excluded as it would afford a (*E*,*Z*) ester **4.061'-1**,[58] whose Suzuki-Miyaura coupling with **4.059** was expected to deliver a (*E*,*E*,*Z*) ester **4.061'-1**. Instead, under Suzuki-Miyaura cross coupling conditions, a stereoinvertive oxidative addition of palladium to the cyclobutene ester **4.061** was expected to form intermediate **4.062**.[55b,55c] From complex **4.062**, three possible pathways were proposed (figure 4.15).

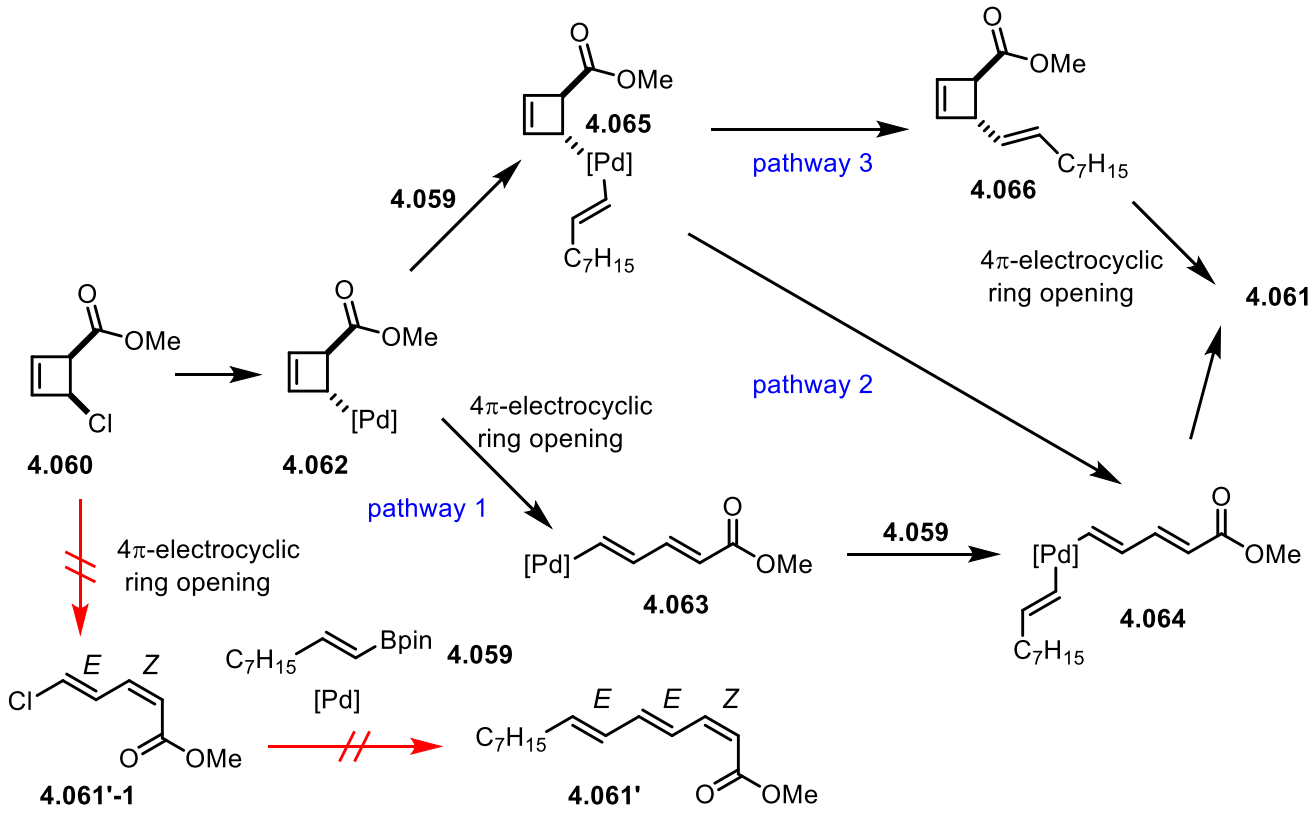


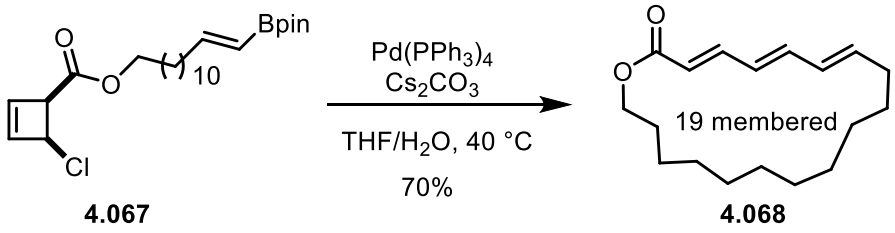
Figure 4.15 Possible pathways for the formation of **4.061** from **4.060**.

1) Complex **4.062** underwent a conrotatory 4π-electrocyclic ring opening to generate dienic palladium complex **4.063**.[55c] Transmetallation to intermediate **4.064** followed by reductive elimination released product **4.061** (pathway 1).

Alternatively, the complex **4.062** was stable enough to allow a transmetallation to form complex **4.065**.[55d,55e,57] Following this, two pathways were possible.

2) Complex **4.065** was not stable, and a subsequent 4π-electrocyclic ring opening delivered dienic complex **4.064**. Product **4.061** was formed after a reductive elimination (pathway 2).
3) Complex **4.065** was stable enough to allow a reductive elimination to generate *trans*-vinyl substituted cyclobutene ester **4.066**. A subsequent facile 4π-electrocyclic ring opening afforded product **4.061** (pathway 3).[71] Our mechanistic experiments (section 4.3.9) demonstrated that pathway 3 was the most likely pathway for the formation of **4.061**.

With the aim of developing an intramolecular variant of this novel transformation towards the FR molecules, Dr. Caroline Souris synthesized boronic ester **4.067**. After considerable screening, it was found that the combination of tetrakis(triphenylphosphine)palladium and cesium carbonate under Suzuki-Miyaura conditions delivered the 19-membered (*E,E,E*)-trienic lactone **4.068** in 70% yield (figure 4.16).[90]



4.067 **4.068**

Figure 4.16 Model macrocyclization by Dr. Caroline Souris.

This very promising model study prompted us to develop a tandem Suzuki-Miyaura/4π-electrocyclic ring opening process to the (*E,E,E*) trienic unit of the FR molecules. Our retrosynthesis is shown below (figure 4.17). Under Suzuki-Miyaura conditions, a putative intermediate **4.070** could be formed from bisamide **4.069** (pathway 3, figure 4.15). Intermediate **4.070**, according to our theoretical calculation,[71] was meta-stable, and a facile 4π-electrocyclic ring opening would release the 19-membered macrocycle. Simple disconnections from the amide and ester functionality within precursor **4.069** would lead to **4.071**, **4.072**, **fragment 1** and **fragment 2**.

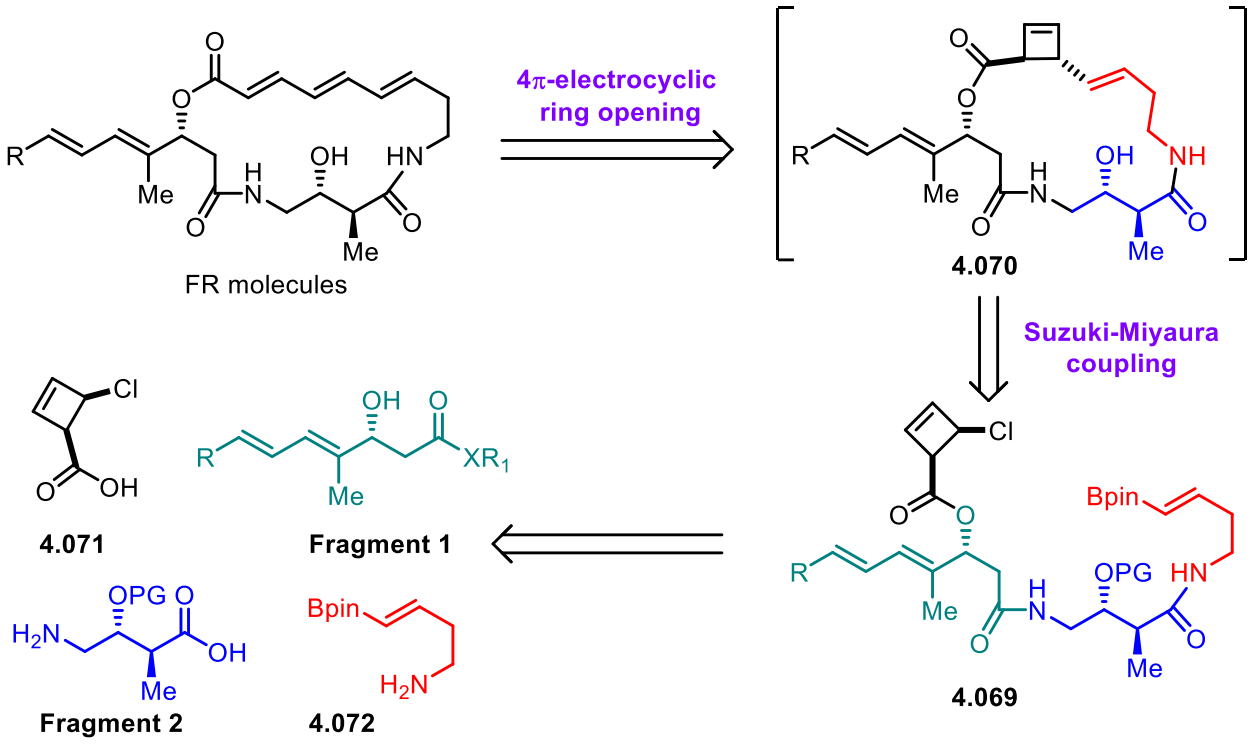


Figure 4.17 Retrosynthesis of the FR molecules.

4.3.2 Optimization and Synthesis of Acid 4.071

The synthesis of acid **4.071** has been reported by our group.[55b] Under UV irradiation, 2-pyrone **4.074** readily cyclized to bicyclobutene lactone **4.075** in quantitative yield. Pyrone **4.074**, though commercially available, is expensive (cheapest price: 116 £/g from TCI). However, it could be synthesized from coumalic acid **4.073** under flash vacuum pyrolysis. In our hands, 201.9 g (74%) of pyrone **4.074** could be readily obtained in a single run (figure 4.18).

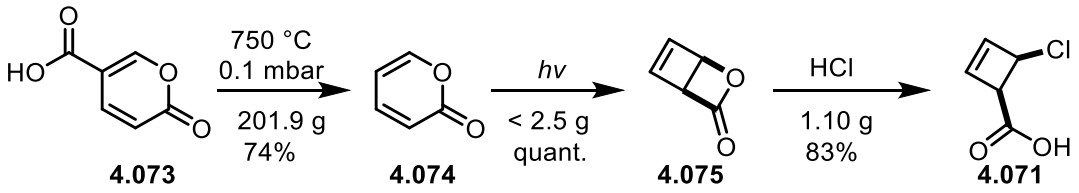


Figure 4.18 Improved synthesis of acid **4.071**.

The hydrolysis of bicyclobutene lactone **4.075** by dry HCl was reported to give acid **4.071** in 44% after recrystallization.[55b] In our hands, this procedure of purification was laborious and low yielding. Through screening different eluents, we found that by adding 3- 5% acetic acid to the mixed eluents (heptane/ethyl

acetate), the product **4.071**, a colorless solid, could be purified by column chromatography. This newly purification protocol increased the yield of **4.071** to 83% on a gram scale. The optimized synthetic route presented above secured a high yielding and scalable synthesis for the acid **4.071**.

4.3.3 Synthesis of Amine 4.072

The synthesis of amine **4.072** was developed by Dr. Caroline Souris before.[90] Curtius rearrangement of pent-4-ynoic acid **4.076** in *tert*-butanol delivered carbamate **4.077**. Hydroboration of **4.077** readily afforded boronic ester **4.078**. Though it had been observed that the deprotection of Boc group of **4.078** in TFA/DCM posed some compatible challenges with the boronate ester moiety,[90] in our hands, this transformation was quite clean using 10 equivalents of TFA. After removal of excess TFA, the salt **4.079** was obtained in quantitative yield. Amine **4.072** could be basified in situ from **4.079** when necessary. This synthetic route was amenable to upscaling, and product **4.079** was obtained in > 8 gram amount in a single batch.

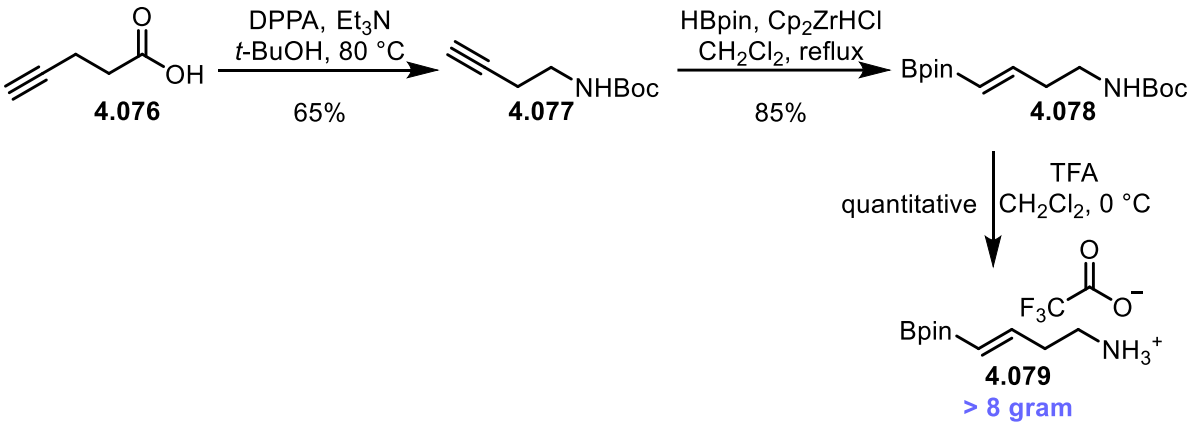


Figure 4.19 Scalable synthesis of **4.079**.

4.3.4 Synthesis of Fragment 1

4.3.4.1 Previous Efforts from Our Group

The synthesis of **fragment 1** proved to be nontrivial. Our plan for the introduction of chiral β-hydroxy group was based on a stereoselective acetate aldol reaction.[91] However, previous studies from Dr. Caroline Souris demonstrated that this transformation is challenging for the polyconjugated aldehyde electrophile.[90] Inspired by the work of Falck *et al.*,[85] Dr. Caroline Souris mixed the trienal **4.080** with bromoacetyloxazolidinone **4.081** or **4.082** in the presence of samarium iodide. However, no desired

product **4.083** was obtained. Instead, it was found that either the aldehyde **4.080** decomposed or the bromoacetyloxazolidinones were reduced to **4.084** (figure 4.20).[90]

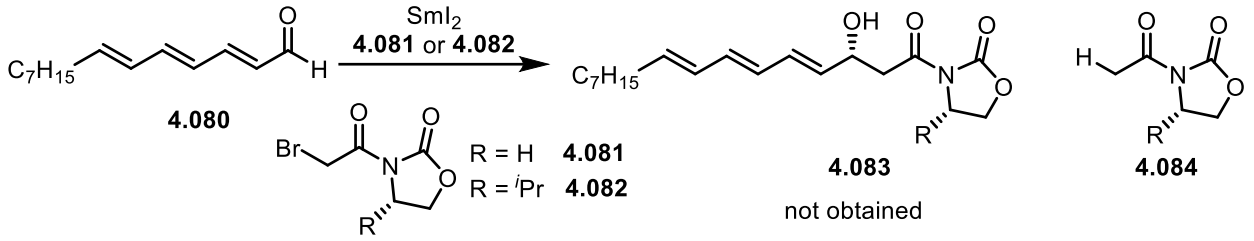
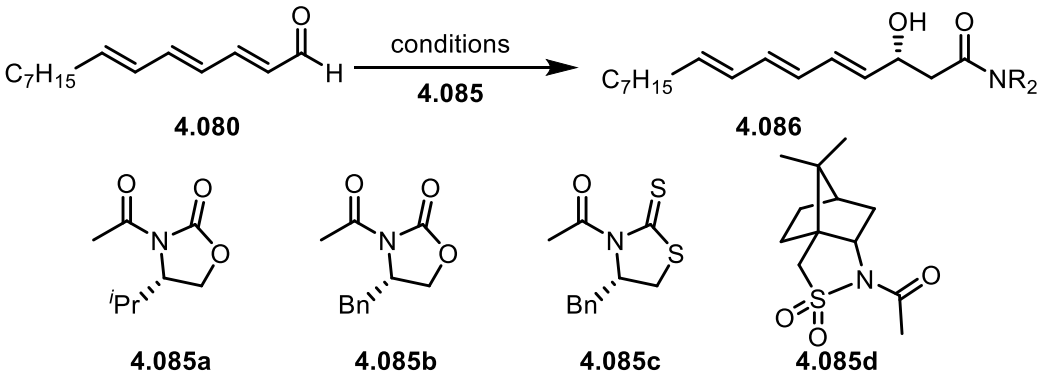


Figure 4.20 Acetate aldol reactions reported by Dr. Caroline Souris.

The failure of the above transformations led us to consider other types of aldol conditions (table 4.21).[90] However, none of the reactions afforded product **4.086** in practical yields.



Entry	Conditions	Solvent	T	4.085	Time	Comments
1	$TiCl_4$, DIPEA	DCM	-78 °C	**c**	18 h	N.R.
2	$TiCl_4$, DIPEA	DCM	-78 to -45 °C	**b**	18 h	N.R.
3	Bu_2BOTf, DIPEA	DCM	-78 °C	**c**	18 h	Decomposition
4	Cy_2BCl, DIPEA	DCM	-78 °C	**a**	18 h	**4.086a** (Traces)
5	$SnOTf_2$, DIPEA	DCM	-78 °C	**c**	18 h	N.R.
6	$MgBr_2(OEt_2)$, Et_3N, TMSCl	EtOAc	25 °C	**c**	48 h	N.R.
7	*n*BuLi	THF	-78 °C	**d**	96h	N.R.
8	^{n}BuLi then $Ti(O^iPr)_4$	THF	-78 °C	**c**	18 h	N.R.
9	^{n}BuLi then $SnBu_3Cl$	THF	-78 °C	**c**	18 h	N.R.

Table 4.21 Conditions screened by Dr. Caroline Souris.

After a large screening of conditions, the best result was obtained using a boron enolate (figure 4.22).[90] However, this reaction was still far from satisfactory, as the product **4.086a** was isolated in 69% yield with a moderate d.r. = 3.3:1.

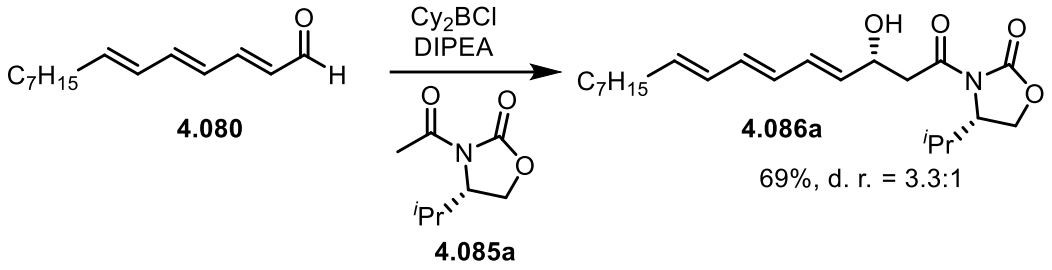


Figure 4.22 The best result obtained by Dr. Caroline Souris.

4.3.4.2 Improved Synthesis of Fragment 1

Although progress has been witnessed in the stereoselective acetate aldol reactions of chiral enolate precursors, the substrate scope is typically populated by aliphatic, aromatic or α,β-unsaturated aldehydes.[91] Polyconjugated aldehydes, such as dienals or trienals, are rarely observed as examples in the stereoselective acetate aldol reactions (figure 4.24).[91]

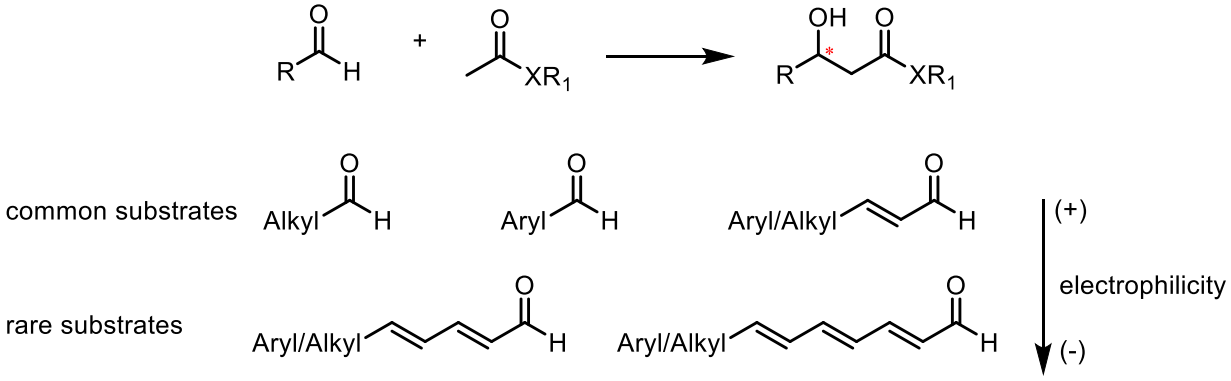


Figure 4.23 Substrate scope of stereoselective acetate aldol reactions.

The decreased electrophilicity of the carbonyl group along with the increased sensitivity of the conjugated polyene moiety within polyconjugated aldehydes are noteworthy hurdles for the successful execution of the aldol reactions of these substrates. For instance, during their total synthesis of JBIR-02, Gademann *et al.* found that while treatment of the N,O-silyl ketene acetal **4.087** with dienic aldehyde **4.088** and titanium tetrachloride resulted no conversion to the product **4.089**, use of the same conditions with (*E*)-3-bromo-2-methylacrylaldehyde **4.090** as a substrate instead delivered product **4.091** in 91% yield with d.r. > 50:1

(figure 4.24).[92] This example serves a clear demonstration of the intrinsic low reactivity of polyconjugated aldehydes in aldol reaction. Cossy *et al.* utilized a similar strategy to synthesize the acid **4.006** (figure 4.8).

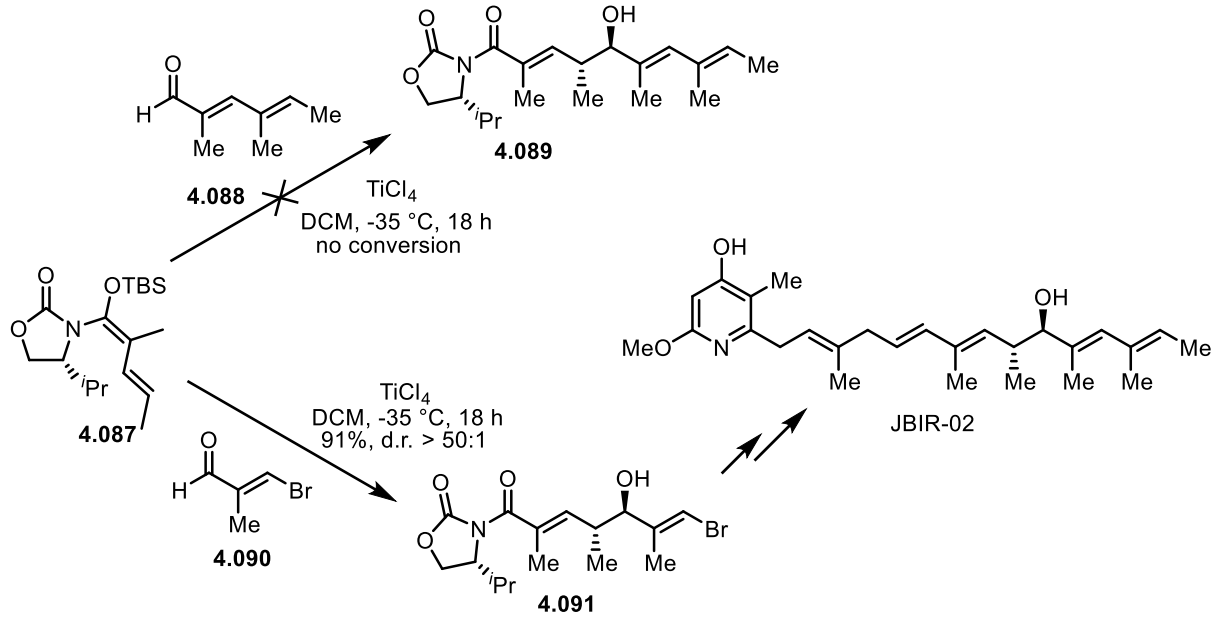


Figure 4.24 Low reactivity of the polyconjugated aldehyde demonstrated by Gademann *et al.*.

In our early foray, the aromatic aldehyde **4.092** was submitted to the conditions of Falck *et al.*.[85] Pleasingly, the aldol adduct **4.093** was obtained in > 50% yield (figure 4.25).

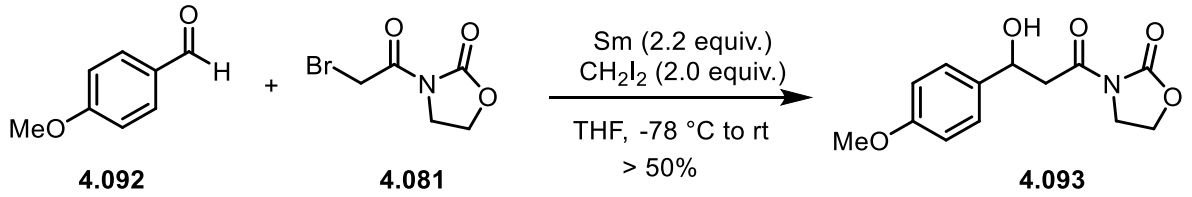


Figure 4.25 Attempted aldol reaction using aromatic aldehyde **4.092**.

The above reaction conditions were later used for the trienal **4.080**. When oxazolidinone **4.093** was used, the aldol product **4.094** was isolated in 31% yield albeit with a d.r. = 1:1. Suspecting the Bn group was inefficient for the transfer of chirality, we next synthesized the oxazolidinone **4.082** with an ^{i}Pr group. However, consistent with the result of Dr. Caroline Souris,[90] the aldol reaction using **4.082** only delivered traces of product **4.086a** (figure 4.26).

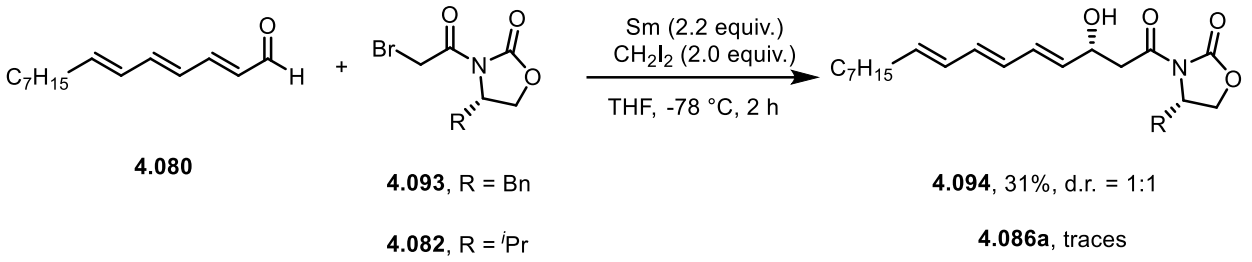


Figure 4.26 Attempted aldol reactions using the trienal **4.080**.

We next tried to use the conditions of Cossy *et al.* (figure 4.27).[86]

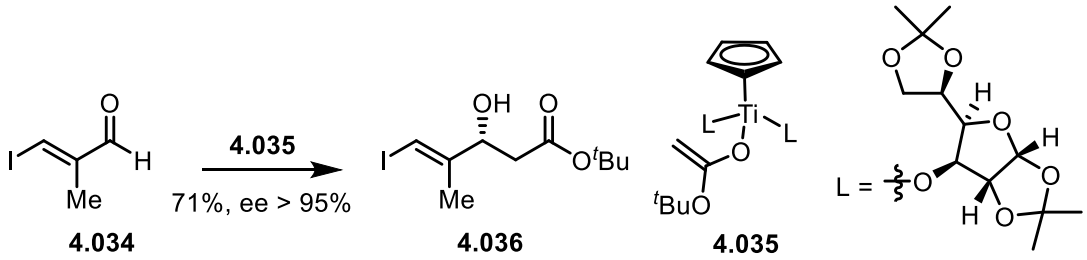


Figure 4.27 Cossy *et al.*'s synthesis of aldol adduct **4.036**.

Despite the fact that an enal **4.034** was successfully used in the transformation, the group of Kirschning had previously showed that the in situ generated enolate **4.035** also worked well on the trienic aldehydes. For instance, both trienic aldehyde **4.095** and **4.097** worked under the above conditions to deliver the desired aldol adduct **4.096** and **4.098** in good to excellent yield (figure 4.28).[93]

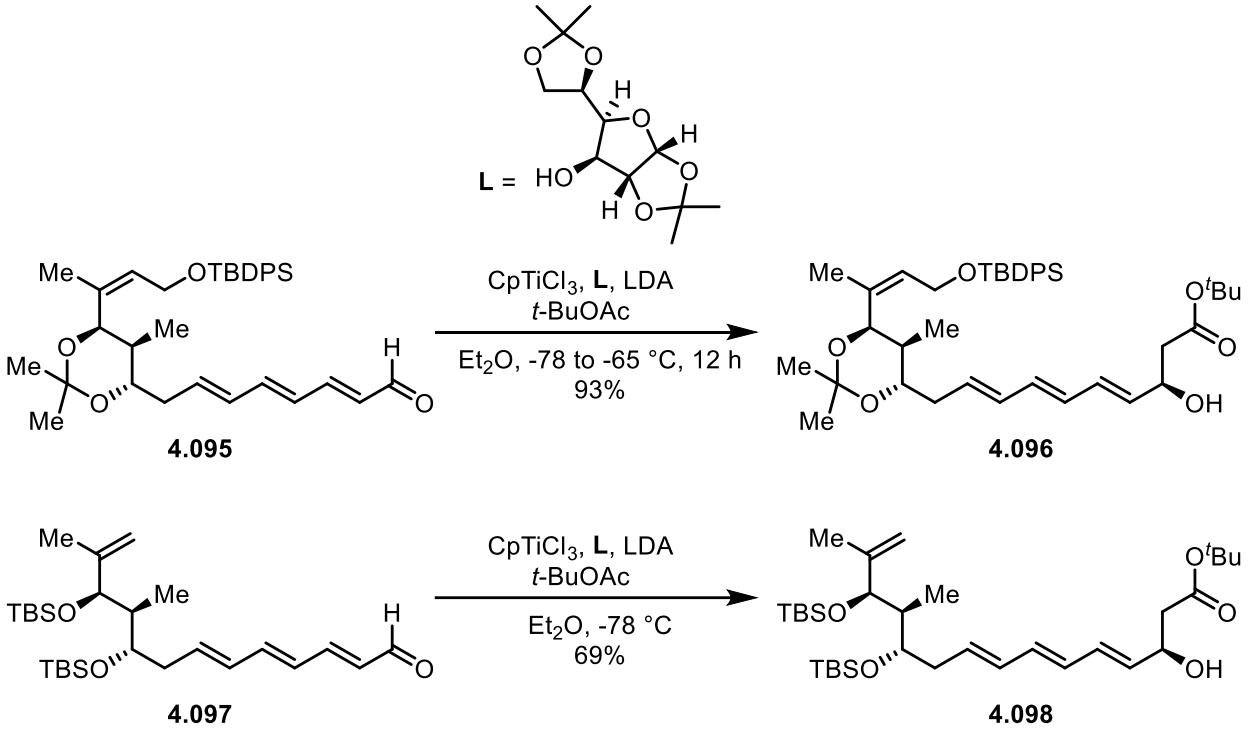


Figure 4.28 Examples from the group of Kirschning.

We then probed the above conditions on our trienic aldehyde **4.080**, unfortunately, in our hands, this reaction did not give any traces of the desired product **4.099**. Only some aldehyde **4.080** was recovered after work up (figure 4.29).

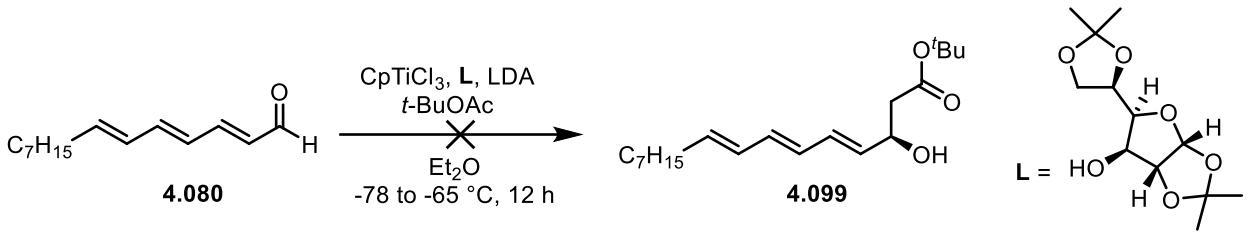


Figure 4.29 Attempted synthesis of **4.099**.

Despite the paucity of examples of stereoselective acetate aldol reactions on polyconjugated aldehydes, several transformations based on the use of chiral thiazolidinone auxiliaries caught our attention. Both the groups of Olivo and Hansen demonstrated that the bromo-dienic aldehyde **4.100** reacted readily with acetylthiazolidinone **4.101** in the presence of titanium tetrachloride and Hünig's *base*, to deliver product **4.102** in 75% to 86% yield with d.r. up to 15.3:1 (figure 4.30).[94]

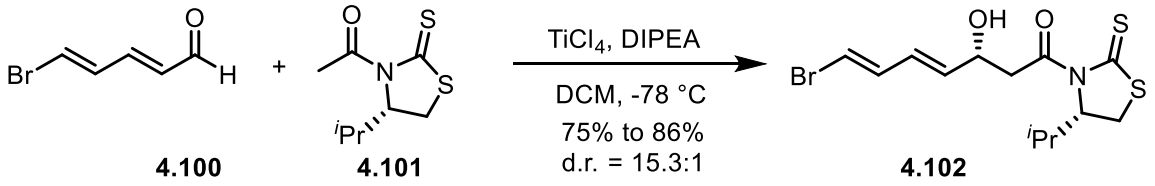


Figure 4.30 Acetate aldol reaction on the bromo-dienic aldehyde **4.100**.

However, this aldol reaction seemed to give inferior results when less active aldehydes were used. For instance, when (2*E*,4*E*)-hexa-2,4-dienal **4.103** was used in the same procedure, two aldol products **4.104** and **4.105** were isolated with a ratio of 1:1 (figure 4.31).[95]

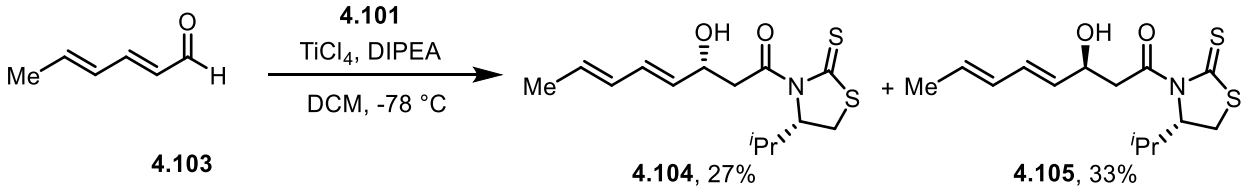
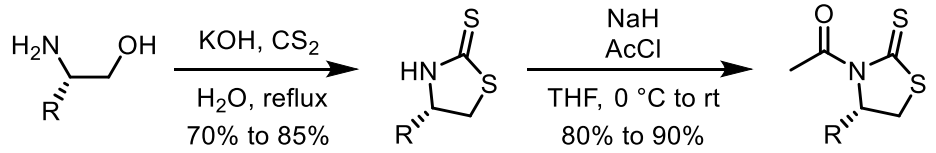


Figure 4.31 Inferior results for less active aldehyde **4.103**.

Nevertheless, these results encouraged us to synthesize a series of thiazolidinone auxiliaries which were readily accessible from the commercially available chiral amino alcohols (figure 4.32).



R = Bn, **4.106** | R = Bn, **4.109** | R = Bn, **4.085c**

R = ^{i}Pr, **4.107** | R = ^{i}Pr, **4.110** | R = ^{i}Pr, **4.101**

R = ^{t}Bu, **4.108** | R = ^{t}Bu, **4.111** | R = ^{t}Bu, **4.112**

Figure 4.32 Synthesis of acetylthiazolidinones.

M. T. Crimmins *et al.* found that in the presence of titanium tetrachloride (1.0 or 2.0 equiv.) and a base (sparteine, DIPEA or TMEDA, 1.0 equiv.), N-propionyl thiazolidinone **4.113** readily reacted with alkyl, aryl and alkenyl aldehydes to afford the "non Evans"-*syn* aldol adduct via a putative chelated transition state **TS 4.114** (figure 4.33).[96]

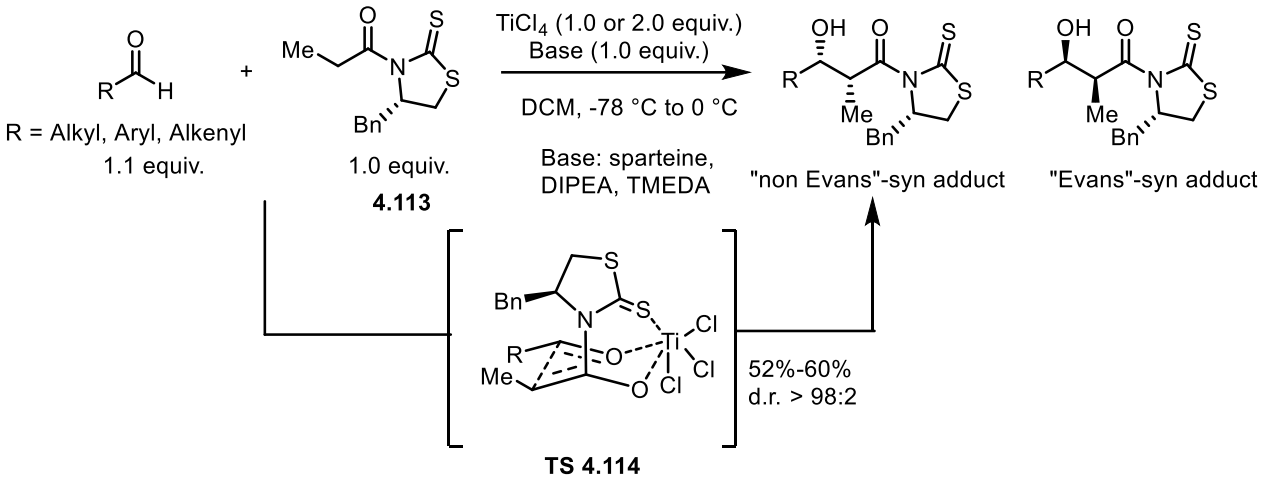
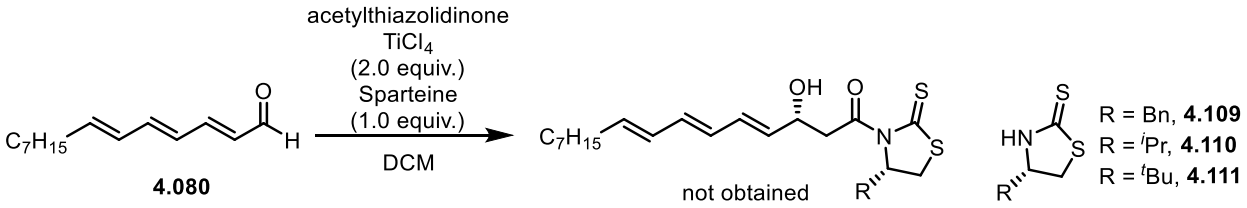


Figure 4.33 "Non Evans"-*syn* aldol reaction.

Inspired by this work, we decided to try the Crimmins procedure on our trienic aldehyde **4.080**. Unfortunately, none of the reactions below worked to deliver the desired aldol adduct. Instead, the hydrolyzed thiazolidinones were isolated after the work up (Table 4.34).

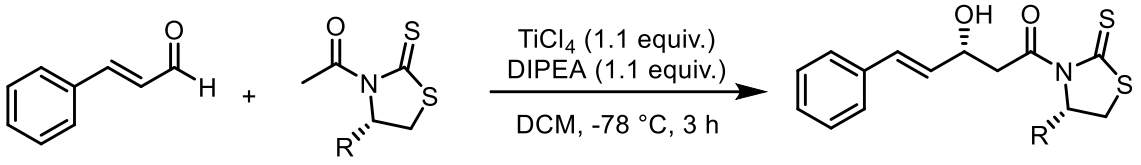


Entry	Acetylthiazolidinone	Temperature	Comments
1	**4.101** (2.0 equiv.)	0 °C	**4.110** (isolated)
2	**4.085c** (2.0 equiv.)	-20 °C	**4.109** (isolated)
3	**4.112** (2.0 equiv.)	-20 °C	Messy

Table 4.34 Attempted aldol conditions based on Crimmins *et al.*'s protocol.

Suspecting the reactions were thwarted by moisture, we carried out experiments in the presence or absence of 3 Å molecular sieves (table 4.35). Using cinnamaldehyde **4.115** as a model substrate, we found that in the absence of 3 Å MS, the hydrolyzed thiazolidinones were always detected in the reaction mixture (entry 1 and 2). However, once 3 Å MS were added, the hydrolyzed thiazolidinones were not present any more (entry 3 and 4). It was also observed that acetylthiazolidinone **4.085c** gave superior

results compared to acetylthiazolidinone **4.101**. Under the conditions of entry 4, the aldol adduct **4.116** was isolated in 77% yield.



1.0 equiv. **4.115**

1.1 equiv.
R = Bn, **4.085c**
R = ^{i}Pr, **4.101**

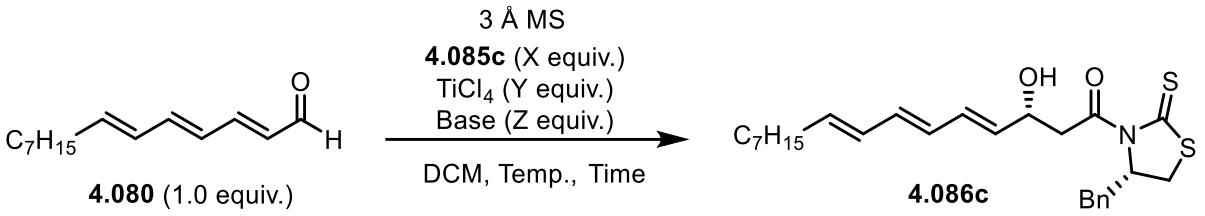
R = Bn, **4.116**
R = ^{i}Pr, **4.117**

Entry	Acetylthiazolidinone	3 Å MS	Comments
1	**4.101**	no	**4.117**, 51%[a], d.r. = 6.4:1. **4.110** (19%)[a]
2	**4.085c**	no	**4.116**, 62%[a], d.r. = 4.3:1. **4.109** (8%)[a]
3	**4.101**	Yes	**4.117**, 40%[a], d.r. = 5.4:1. **4.110** (0%)[a]
4	**4.085c**	Yes	**4.116**, 77%[b], d.r. = 6.7:1. **4.109** (0%)[a]

[a] ^{1}H NMR yield. [b] isolated yield.

Table 4.35 Influences of thiazolidinones and molecular sieves.

Then we focused on using the acetylthiazolidinone **4.085c** for our further optimization. Treatment of the trienal **4.080** under the conditions of entry 4 (table 4.35), however, did not lead to full conversion in a range of attempts (table 4.36).



Entry	X	Y	Base (Z)	Temp./Time	Comments[b]
1	1.0	1.1	Sparteine (1.1)	-70 °C, 15 h	48%, d.r. = 1.9:1
2[a]	1.0	1.1	Sparteine (1.1)	-70 °C, 15 h	48%, d.r. = 1.8:1
3	1.2	1.5	DIPEA (1.5)	-70 °C, 15 h	31%, d.r. = 5.8:1
4	1.2	1.5	DIPEA (1.5)	-78 to -45 °C, 2 h	51%, d.r. = 3.6:1
5	1.2	1.3	DIPEA (1.3)	-78 to -45 °C, 2.5 h	38%, d.r. = 3.0:1
6	1.2	2.0	DIPEA (2.0)	-78 to -60 °C, 2.5 h	31%, d.r. = 5.3:1
7	1.2	1.5	DIPEA (1.1)	-78 to -60 °C, 2.5 h	31%, d.r. = 6.8:1

All reactions were carried out on a 0.1 mmol scale. [a] DMPU (0.3 equiv.) used as additive. [b] Isolated yield for **4.086c**.

Table 4.36 Optimization of aldol reaction.

As can be seen from table 4.36, the use of sparteine as the base (entry 1 and 2) gave a moderate yield and the d.r. was low. The use of DMPU as the additive did not improve the result (entry 2). Instead, the use of DIPEA increased the d. r. to 5.8:1, albeit the yield was only 31% (entry 3). Considering most of the aldehyde **4.080** remained unreacted in these experiments, we accordingly increased the temperature to -45 °C. Although the yield increased to 51%, albeit the d.r. decreased to 3.6:1 (entry 4). The amount of titanium tetrachloride and base were then evaluated, however, no significant improvements were observed (entry 5 and 6). When we used slightly less DIPEA, the d.r. of the reaction increased to 6.8:1 (entry 7). Though the yield was only 31%, considering the unreacted aldehyde **4.080** could be recycled, we thus decided to use the conditions of entry 7 for our synthesis.

When the reaction was scaled up, we found that at -78°C, titanium tetrachloride (1.2 equiv.), DIPEA (1.2 equiv.) gave equal or superior results (figure 4.37) compared to the conditions of entry 7 (table 4.36). Though the yield was moderate, the d.r. was consistently high. The unreacted aldehyde **4.080** could be recycled for a second reaction without decreasing the yield and d.r. of the product (figure 4.37).

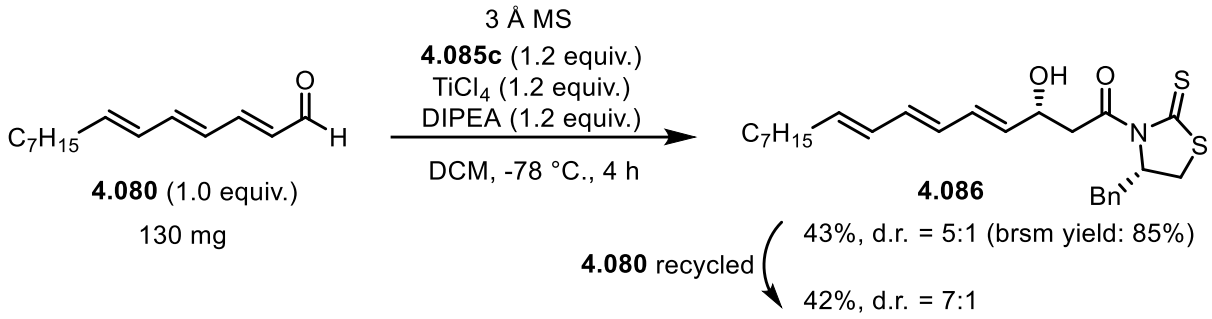


Figure 4.37 Aldol reaction on larger scale.

With the aim of synthesizing analogues with different side chains, a series of dienic or trienic aldehydes were then synthesized. Except for aldehyde **4.118m**,[97] other aldehydes were readily obtained following a 3-step sequence: Wittig/HWE, DIBAL-H reduction and MnO_2 oxidation (figure 4.38).

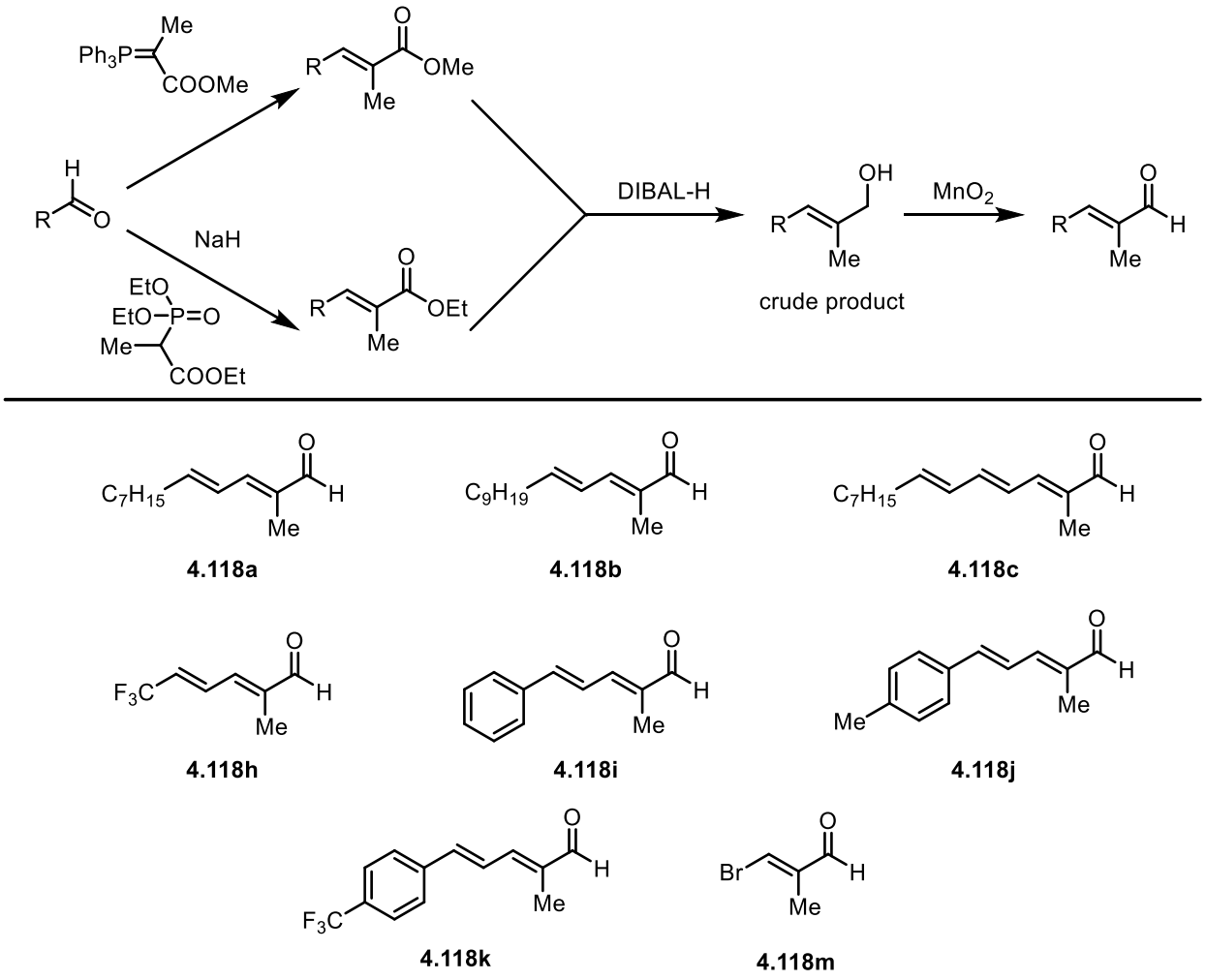
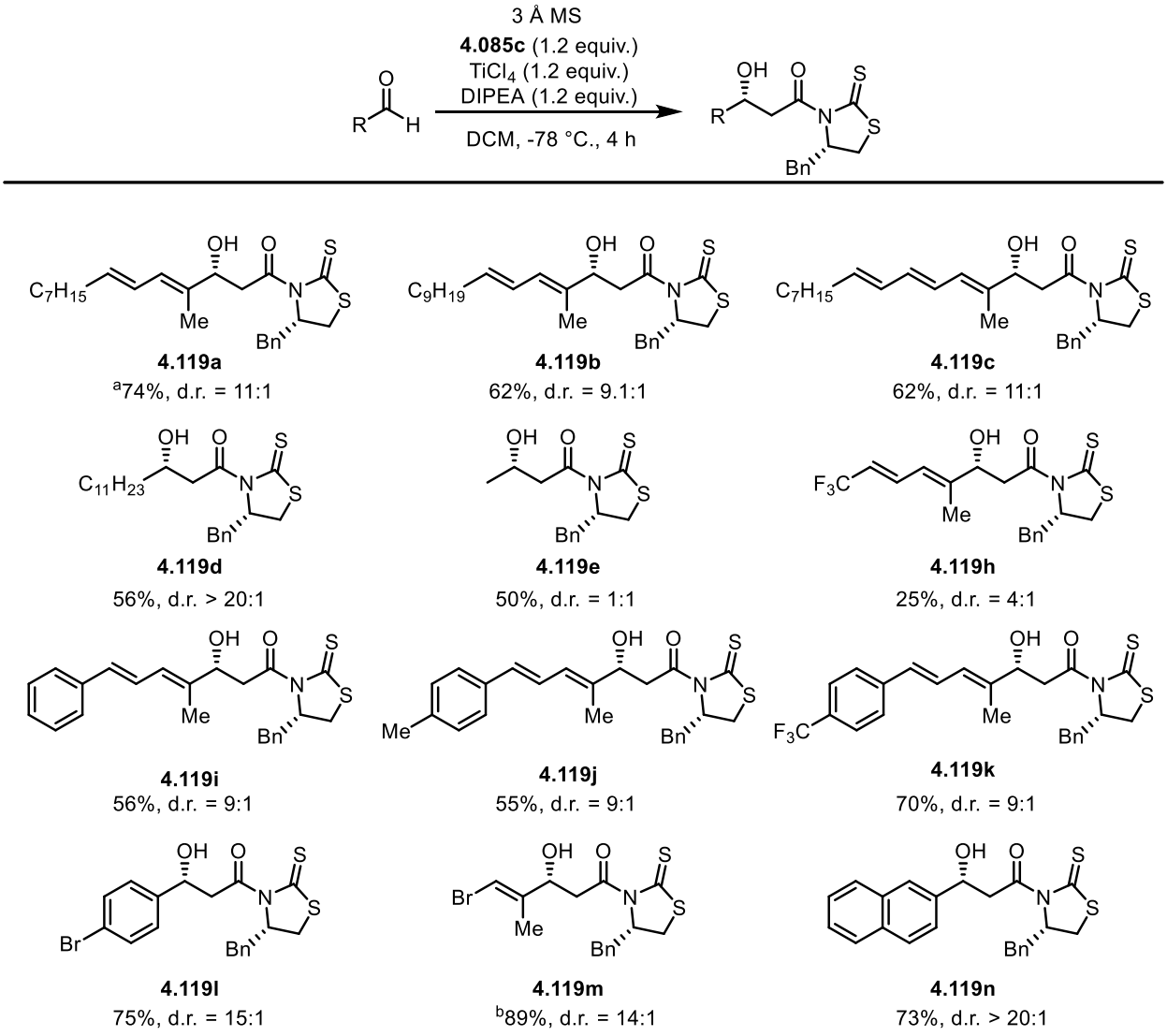


Figure 4.38 General procedures for the synthesis of aldehydes.

A variety of aldehydes were then submitted to the aldol conditions we developed above. Although the aldol reaction proved to be quite moisture sensitive, decent yield and d.r. could be obtained when activated 3 Å MS was added (figure 4.39). Aldol products with polyene side chains proved to be meta-stable, and were thus used in the next step without delay.



[a] 3.40 g obtained. [b] 2.88 g obtained.

Figure 4.39 Synthesis of aldol adducts.

4.3.5 Synthesis of Fragment 2

4.3.5.1 Previous Synthesis

Fragment 2 is a common motif widely found in a number of natural products (figure 4.40). Apart from its presence in the FR molecules and pseudotrienic acids,[81,84] it was also found in the structure of bistramide natural products, such as bistramide A.[98] It was previously known that this privileged structure motif is crucial to maintain the anti-cancer activity of bistramide A.[99]

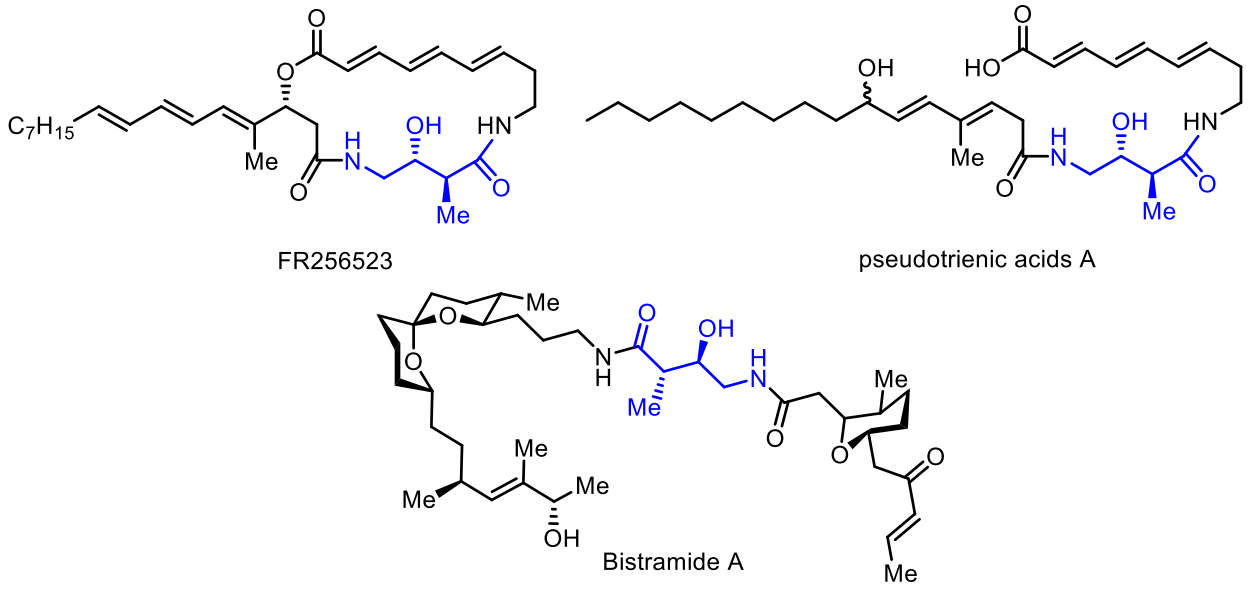


Figure 4.40 **Fragment 2** in natural products.

Fragment 2 was also frequently used as a building block for the synthesis of drugs (figure 4.41). For instance, amide **4.120** was used by Schreiber *et al.* for the synthesis of antimalarial agent **4.121**.[100] A similar amide **4.122** was used by Marcaurelle *et al.* in the assembly of the structurally related histone deacetylase inhibitor **4.123**.[101]

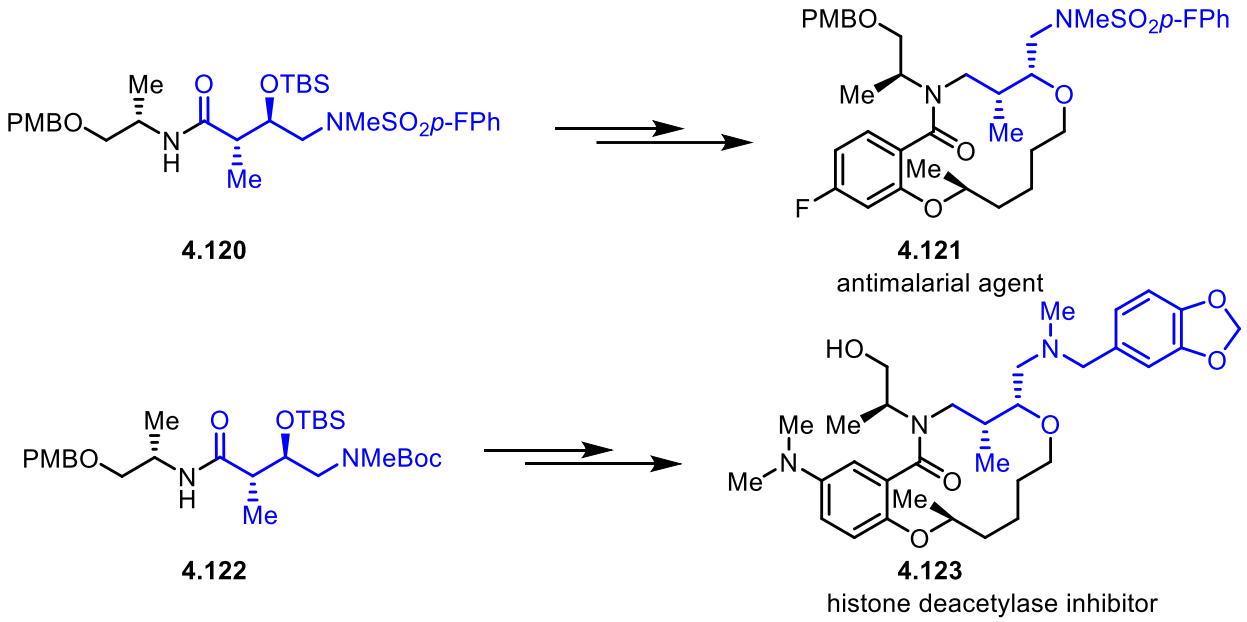


Figure 4.41 **Fragment 2** as a building block for drug synthesis.

Many groups have reported their own synthesis of **fragment 2**. Generally these routes are lengthy and laborious (figure 4.42).

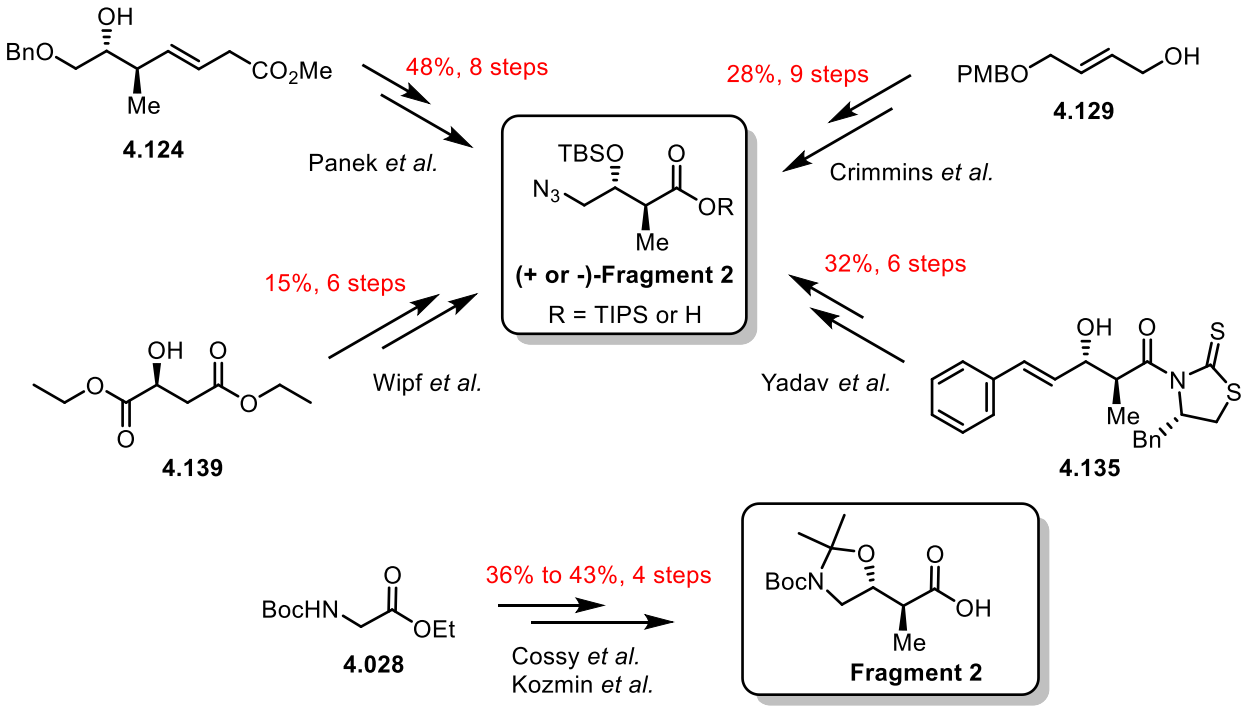


Figure 4.42 Overview of the prior synthesis of **fragment 2**.

The group of Panek started their synthesis from enatioenriched alcohol **4.124** (figure 4.43).[102] After a 3-step sequence, it was readily converted to product **4.125**. **4.125** was further converted to the azido alcohol **4.126**. Treatment of **4.126** under the conditions of Pinnick oxidation, followed by TIPS protection afforded final product **4.127** with 48% overall yield over 8 steps.

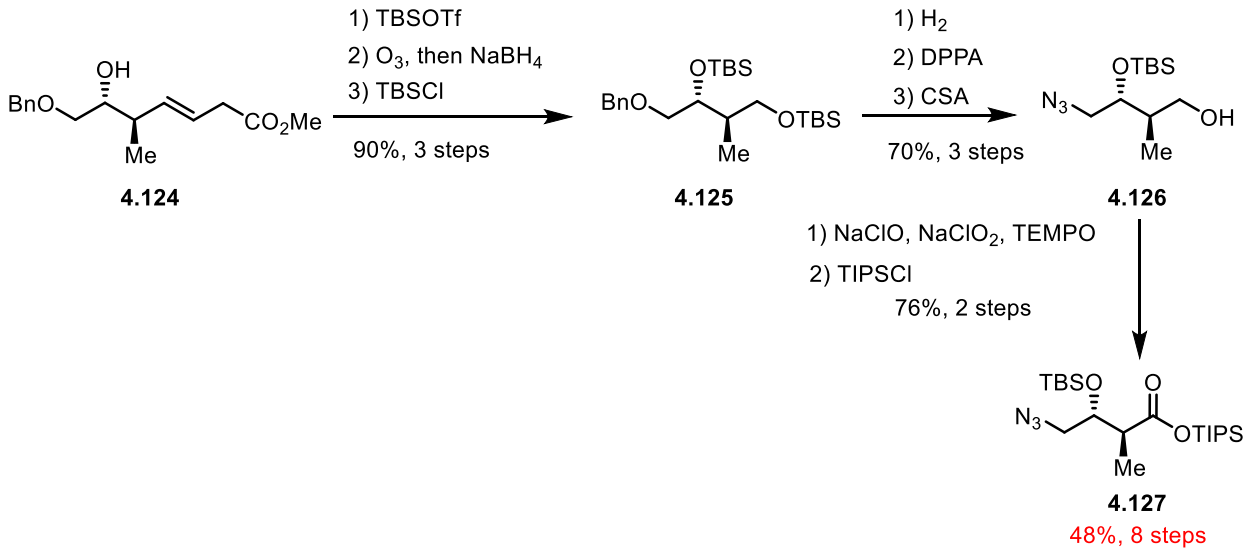


Figure 4.43 Panek *et al.*'s synthesis of **fragment 2**.

Kozmin *et al.* adopted Brown crotylation as the key step for the introduction of the chiral centers (figure 4.44).[103] Crotylation of aldehyde **4.029** by reagent **4.128** afforded product **4.031** in 64% yield. **4.031** was then protected as acetonide and oxidized by ruthenium trichloride and sodium periodate to deliver product **4.033**.

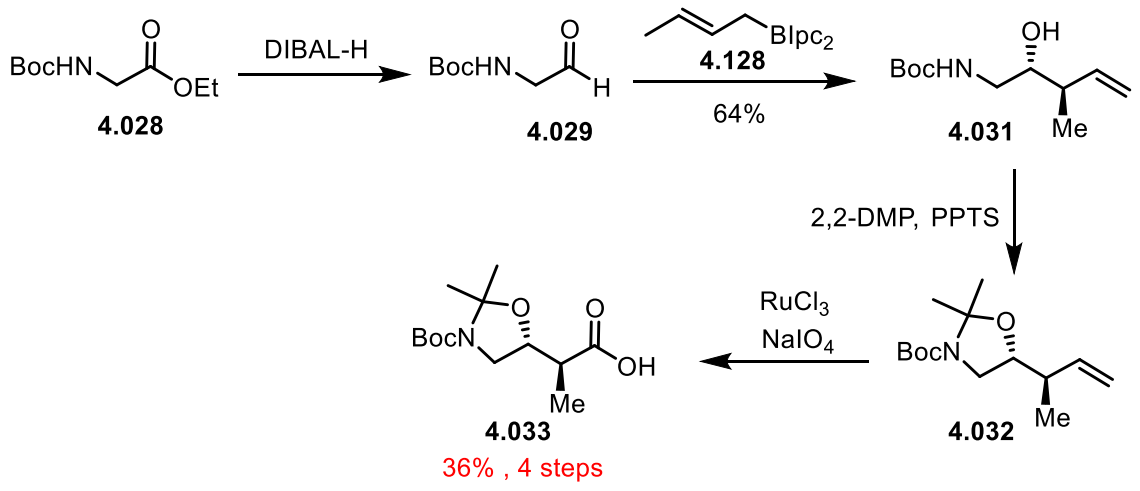


Figure 4.44 Kozmin *et al.*'s synthesis of **fragment 2**.

Crimmins *et al.* developed a novel strategy towards **fragment 2** (figure 4.45).[104] Commencing with allylic alcohol **4.129**, the epoxide **4.130** was readily obtained in 95% yield, with 98% ee by a Sharpless asymmetric epoxidation. Treatment of epoxide **4.130** with Gilman reagent afforded diol **4.131**, albeit with a moderate regioselectivity. Protection of diols as TBS ethers and further PMB removal by DDQ readily delivered alcohol **4.132**. Introduction of the azide group by DPPA and selective removal of the primary TBS group afforded product **4.133**. A final oxidation of the alcohol **4.133** afforded the product **4.134**. Although the chiral centers were introduced in a catalytic fashion, the whole route consisted of 9 steps and delivered product in only 28% overall yield.

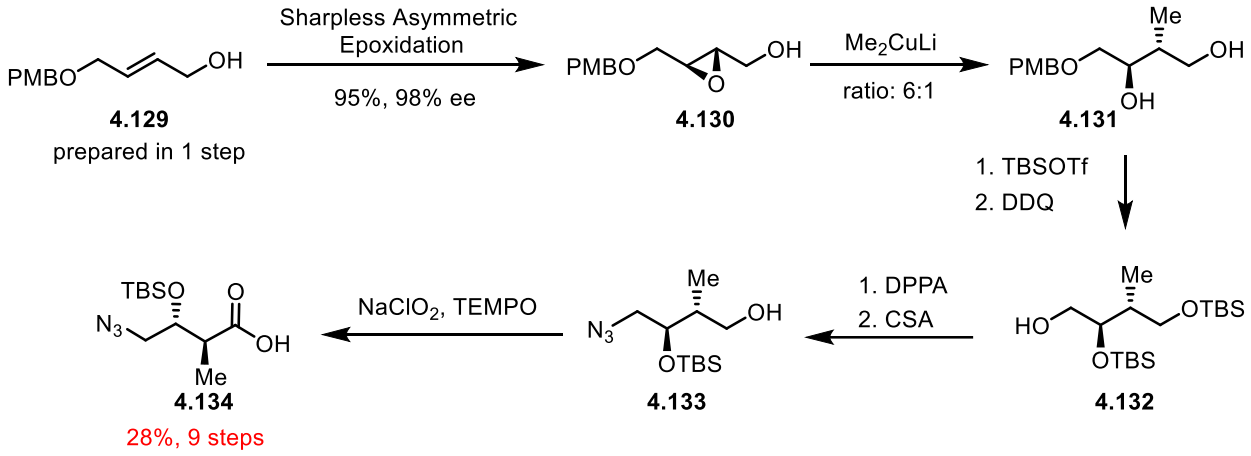


Figure 4.45 Crimmins *et al.*'s synthesis of **fragment 2**.

Yadav *et al.*'s synthesis of **fragment 2** relied on a key anti-aldol reaction developed by the group of Evans (figure 4.46).[105] Treatment of N-propionyl thiazolidinone **4.113** with cinnamalaldehyde **4.115** in the presence of magnesium dibromide, trimethylsilyl chloride and triethylamine delivered aldol adduct **4.135** in 94% yield. Then the thiazolidinone group was cleaved by the Weinreb amine and the resulting amide was further TBS-protected to afford product **4.136**. Ozonolysis of **4.136** with a reductive work up delivered hydroxy amide **4.137**. Introduction of the azide group by DPPA afforded azido amide **4.138**, which was hydrolyzed to release acid **4.134**. The whole route consisted of 6 steps, with 32% overall yield.

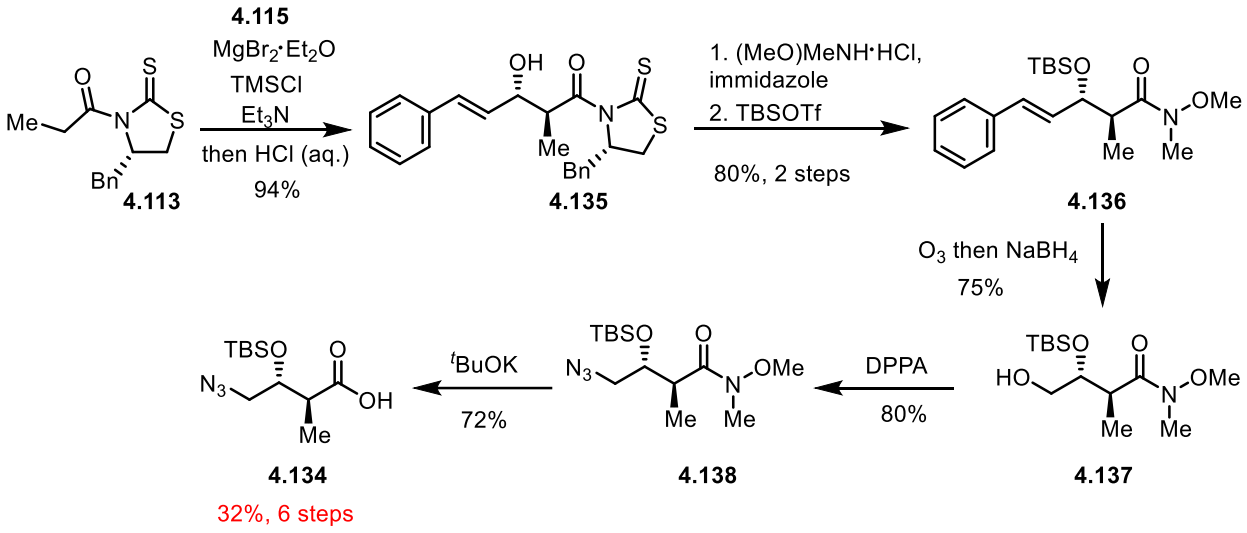


Figure 4.46 Yadav *et al.*'s synthesis of **fragment 2**.

Wipf *et al.* utilized a chiral pool strategy for the synthesis of **(*ent*)-fragment 2** (figure 4.47).[106] Starting from diethyl (*S*)-2-hydroxysuccinate **4.139**, the anti stereochemical relation of **4.140** was secured by a Fráter-Seebach alkylation. The ester neighboring the hydroxyl group was selectively reduced by borane to the alcohol, which was further converted to tosylate **4.141**. Displacement by azide afforded azido alcohol **4.142**. Protection of the alcohol by TBSCl and conversion to a silyl ester **(*ent*)-4.127** closed the route: The whole sequence consisted of 6 steps, albeit with a 15% overall yield.

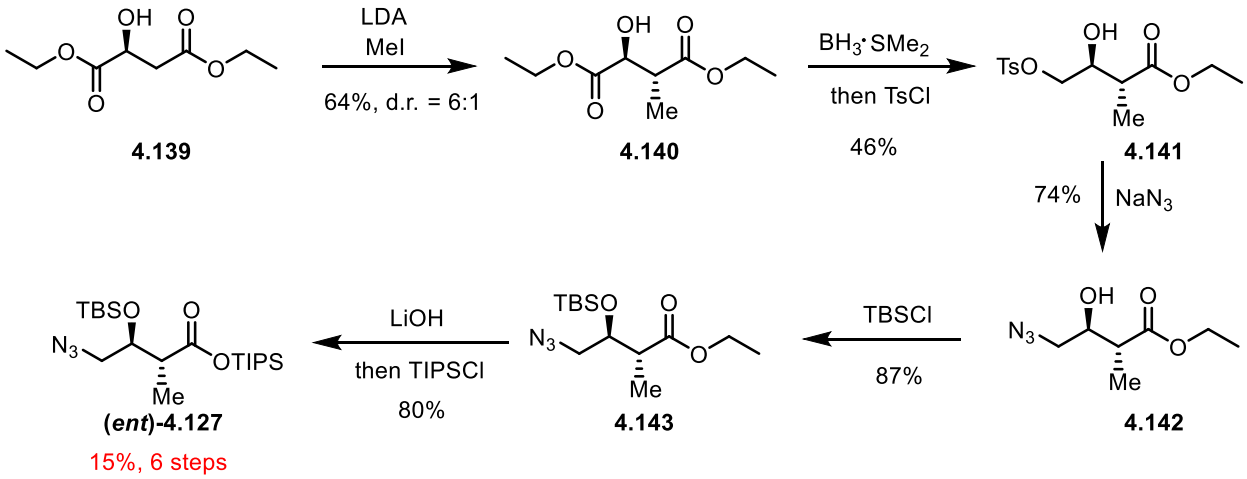


Figure 4.47 Wipf *et al.*'s synthesis of ***ent*-fragment 2**.

4.3.5.2 Optimization and Synthesis of Fragment 2

Our initial route towards **fragment 2** was based on Cossy *et al.*'s synthesis (figure 4.7),[86] but it presented several limitations. First, the carbamate protected glycinal **4.028** was unstable and difficult to handle. Second, the oxidation of **4.032** to carboxylic acid **4.033** suffered from poor reproducibility. In many conditions we screened, this reaction gave incomplete conversion and aldehyde **4.144** was observed as a side product (figure 4.48).[90]

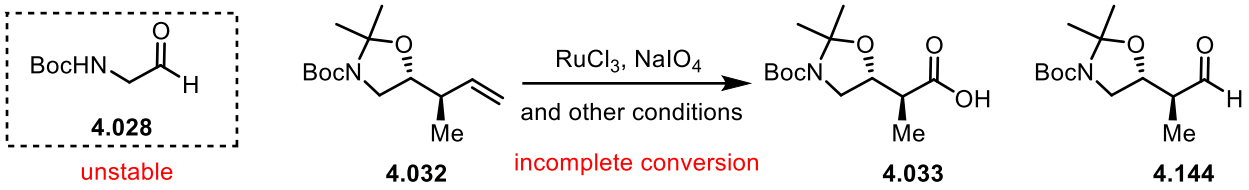
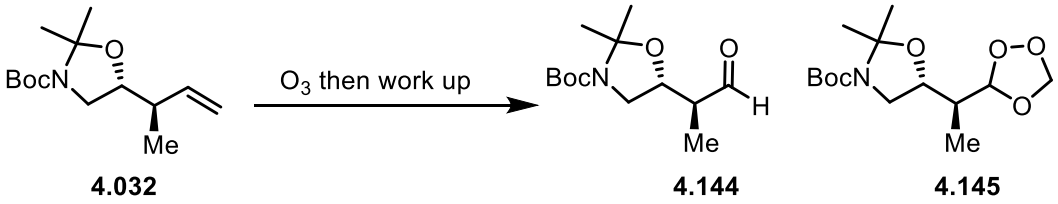


Figure 4.48 Observed limitations related to Cossy *et al.*'s route.

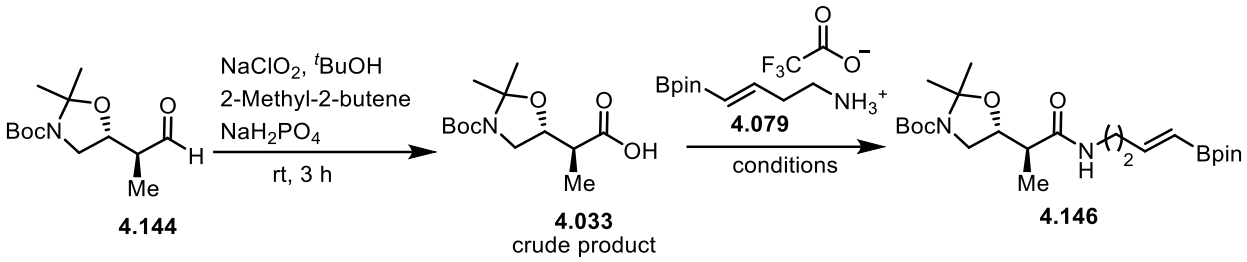
Since the direct oxidation of **4.032** to **4.033** was problematic, we opted for ozonolysis to obtain aldehyde **4.144** first (table 4.49). The ozonolysis worked well. While dimethyl sulfide proved to be less efficient for the work up as a mixture of ozonide **4.145** and aldehyde **4.144** was obtained (entry 1), triphenyl phosphine as a quencher cleanly afforded aldehyde **4.144** in 79% yield (entry 2).



Entry	Work up	Comments
1	Me_2S (10 equiv.), DCM, rt, 12 h	Mixture of **4.144** and **4.145**
2	PPh_3 (2 equiv.), DCM, rt, 3 h	**4.144** (79%)

Table 4.49 Optimization of ozonolysis.

Under the conditions of Pinnick oxidation,[107] aldehyde **4.144** was fully consumed after 3 h. The resulting acid **4.033** was confirmed by mass spectrometry, and used as crude product for the next step. The coupling of acid **4.033** and amine salt **4.079** was then evaluated. However, the initial screening conditions did not afford product **4.146** in more than 30% yield (table 4.50).



Entry	Conditions	comments
1	HATU (2.0 equiv.), Et_3N (20 equiv.) DCM, 0 to rt, 16 h	29%
2	HOBt (2.0 equiv.), EDCI (2.0 equiv.), Et_3N (20 equiv.) DCM, 0 to rt, 16 h	7%

Table 4.50 Early attempts for the synthesis of **4.146**.

As the route above became lengthy and poorly efficient, our next attempted foray to **fragment 2** featured a chiral pool strategy. We proposed the α-methylenation of commercially available *tert*-butyl (*R*)-4-hydroxy-2-oxopyrrolidine-1-carboxylate **4.147** to afford intermediate **4.148**. Conjugate reduction of the double bond could deliver carbamate **4.149**. Finally ring opening of lactam **4.149** was expected to release **fragment 2** (figure 4.51).

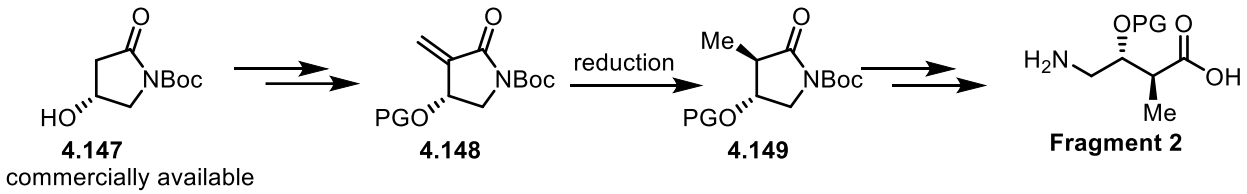


Figure 4.51 Chiral pool strategy to **fragment 2**.

4.147 was first protected as TBS ether **4.150**. The protection was quite slow, and only 40% of product **4.150** was isolated after 16 h. Most of carbamate **4.147** was recovered unreacted (figure 4.52).

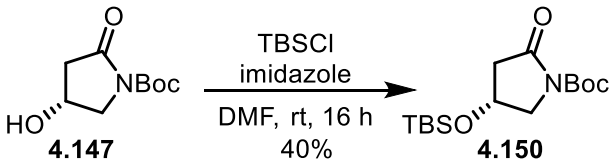


Figure 4.52 Synthesis of carbamate **4.150**.

The methylenation was next attempted using Eschenmoser's salt **4.151**.[108] However, under basic conditions, the desired product **4.152** was not observed. Instead, 20% of **4.150** was recovered, along with 50% of eliminated product **4.153** (figure 4.53). The structure of product **4.153** was deduced by mass spectrometry, although we were not able to distinguish between regioisomers **4.153a**/**4.153b**.

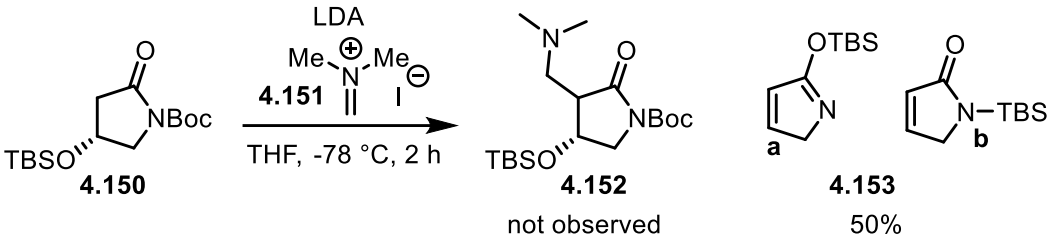


Figure 4.53 Attempted synthesis of **4.152**.

The isolation of product **4.153** was interesting, as the Boc group was removed. A possible mechanism for its formation is shown below (figure 4.54).

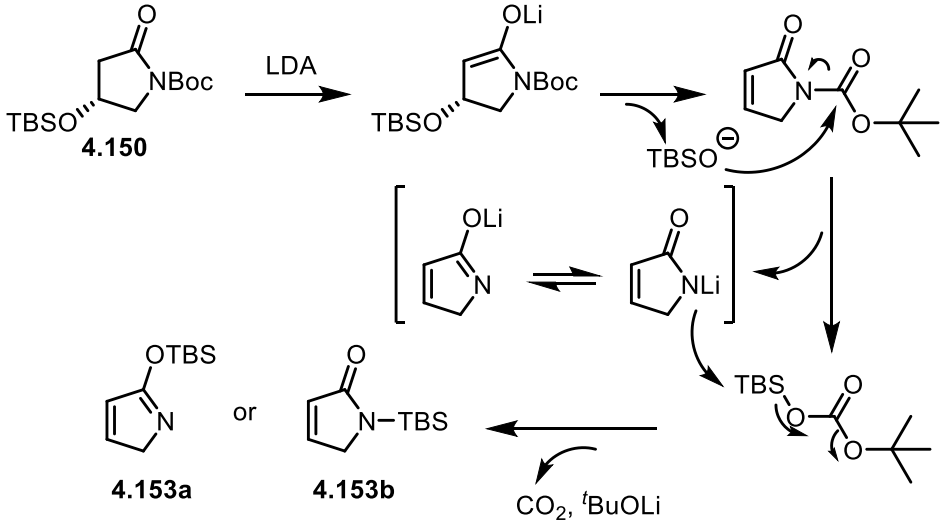


Figure 4.54 Possible mechanism for the formation of **4.153**.

The incorporation of a TBS group rendered the resulted product **4.150** prone to elimination under strong basic conditions. With 2.3 equivalent of LHMDS, compound **4.147** was expected to react with Eschenmoser's salt **4.151** to deliver product **4.154**. Although no eliminated product was isolated, the desired product **4.154** was not observed. Instead mainly starting material **4.147** was recovered (figure 4.55).

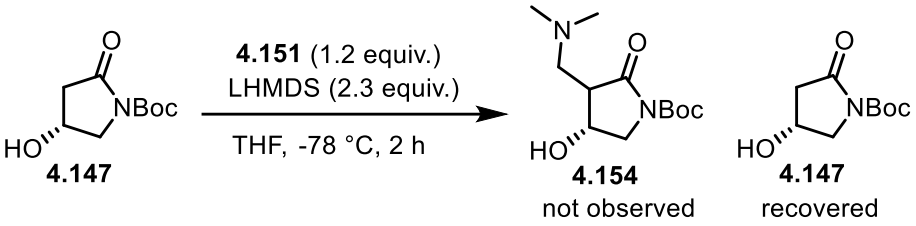
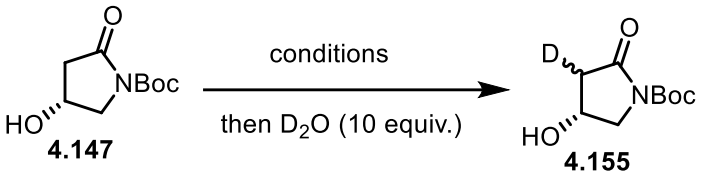


Figure 4.55 Attempted synthesis of **4.154**.

Suspecting double lithiation was not successful, we screened many lithiation conditions and quenched the reaction by D_2O. However, the deuterated product **4.155** was only observed as a trace product in many conditions (table 4.56). These reactions showed that the α-carbonyl proton was resistant to abstraction once the hydroxy group was deprotonated.



Entry	Conditions	Comments
1	NaH (1.2 equiv.), 0 °C, 1 h, THF, then ^{t}BuLi (1.2 equiv.), -78 °C, 30 min	Only **4.147**
2	MeMgBr(1.05 equiv.), -78 °C, 30 min, THF, then ^{t}BuLi (1.2 equiv.), -78 °C, 30 min	Mainly **4.147**, **4.155** (7%)
3	MeLi (1.05 equiv.), -78 °C, 30 min, THF, then ^{t}BuLi (1.2 equiv.), -78 °C, 30 min	Mainly **4.147**, **4.155** (13%)
4	NaH (1.2 equiv.), 0 °C, 30 min, THF, then ^{t}BuLi (1.2 equiv.), 0 °C, 30 min	Only **4.147**
5	MeLi (1.05 equiv.), 0 °C, 30 min, THF, then ^{t}BuLi (1.2 equiv.), 0 °C, 30 min	Only **4.147**
6	NaH (1.1 equiv.), 0 °C, 30 min, THF, then ^{n}BuLi (1.1 equiv.), 0 °C, 30 min	Only **4.147**
7	NaH (1.1 equiv.), 0 °C, 30 min, Et2O, then ^{t}BuLi (1.1 equiv.), -20 °C, 30 min	Mainly **4.147**, **4.155** (6%)

Table 4.56 Conditions for the double lithiation.

The results above were further confirmed by the direct methylation using methyliodide (figure 4.57).[109] The expected product **4.156** was not observed. Instead, the methylether **4.157** was isolated, along with unreacted **4.147**.

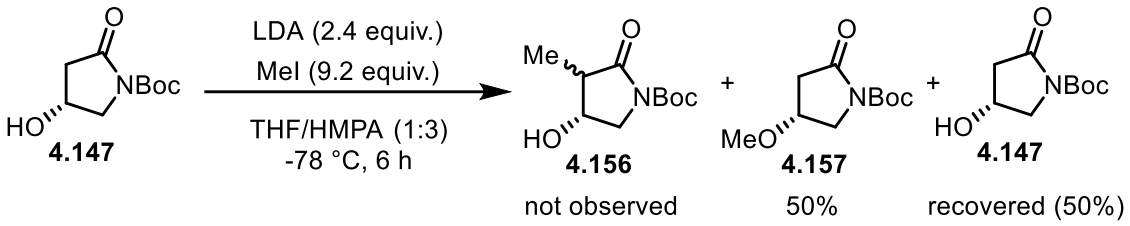


Figure 4.57 Attempted methylation under double lithiation conditions.

Our inability to methylate carbamate **4.147** led us to examine the route of Yadav *et al.* (figure 4.58).[105] Yadav *et al.* reported the product **4.134** was obtained in 32% overall yield. However, when we tried to up scale the reaction (> 2 gram scale), we found that the hydrolysis of **4.138** by ^{t}BuOK led to decreased yields and decomposition of the product. Later it was found that the strong base ^{t}BuOK led to TBS-removal to form the deprotected acid **4.159**. The tedious work up and unreliable yield for the hydrolysis of Weinreb amide **4.138** prompted us to replace it as a methyl ester **4.162**, readily prepared by cleaving the thiazolidinone group of **4.136** with MeOH instead of Weinreb amine salt. Further hydroxy group protection as TBS ether gave ester **4.160**. Azido ester **4.162** was then readily obtained in a 3-step sequence as before. Hydrolysis of **4.162** by a weaker base, lithium hydroxide, cleanly delivered product **4.134** in 90% yield. However, lactone **4.163** was frequently formed as a major product during the reductive ozonolysis step. **4.163** was shown to be volatile, rendering the lactonization of product **4.161** even more favorable, thus endowing our route with poor reproducibility.

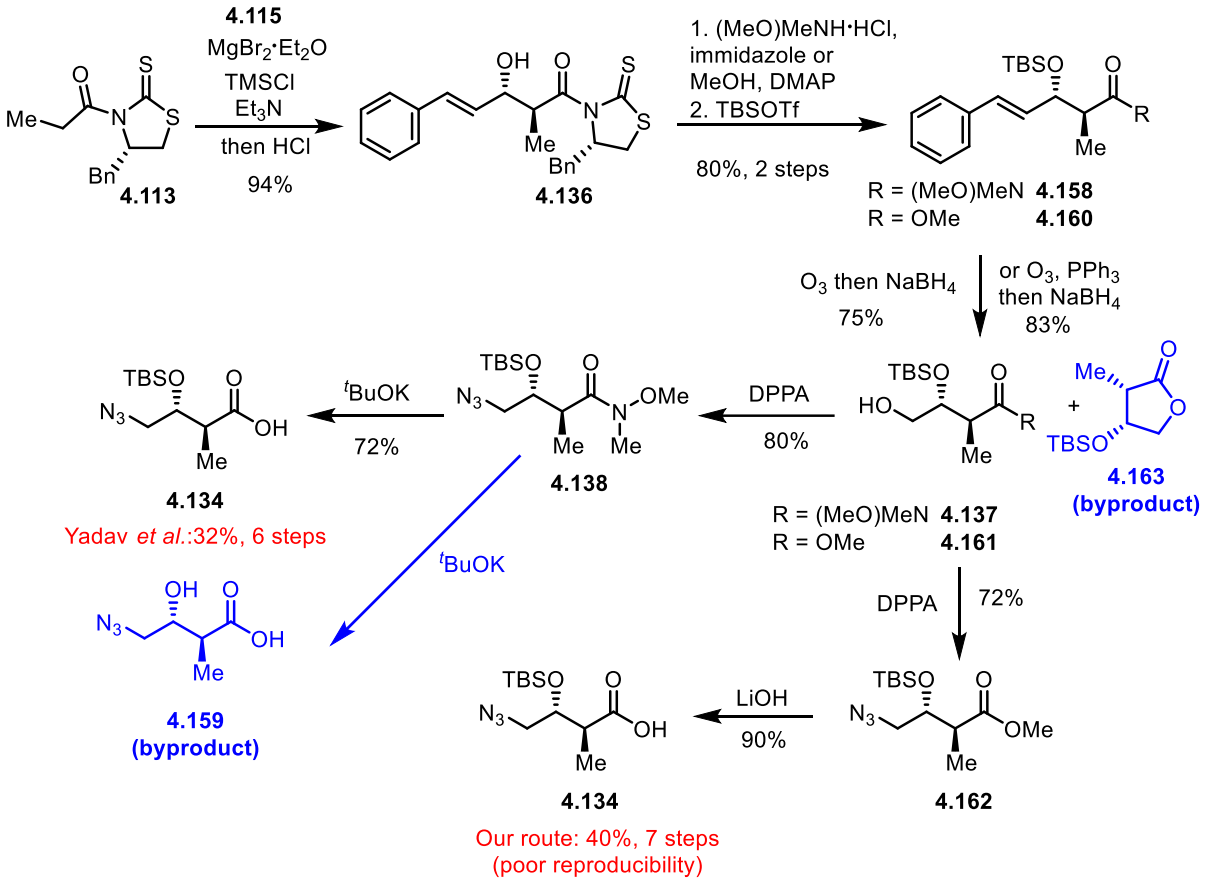


Figure 4.58 Yadav *et al.* and our modified route to acid **4.134**.

The intrinsic limitations of both Yadav *et al.*'s route and our modified sequence forced us to devise a novel solution to the efficient synthesis of **fragment 2**. After a comprehensive literature search, we decided to use the known product **4.165** as our starting point.[110] Commencing with **4.165**, a Fráter-Seebach alkylation could deliver ester **4.166** in one step.[111] Acid **4.134** should be easily obtained from **4.166** in two steps (figure 4.59).

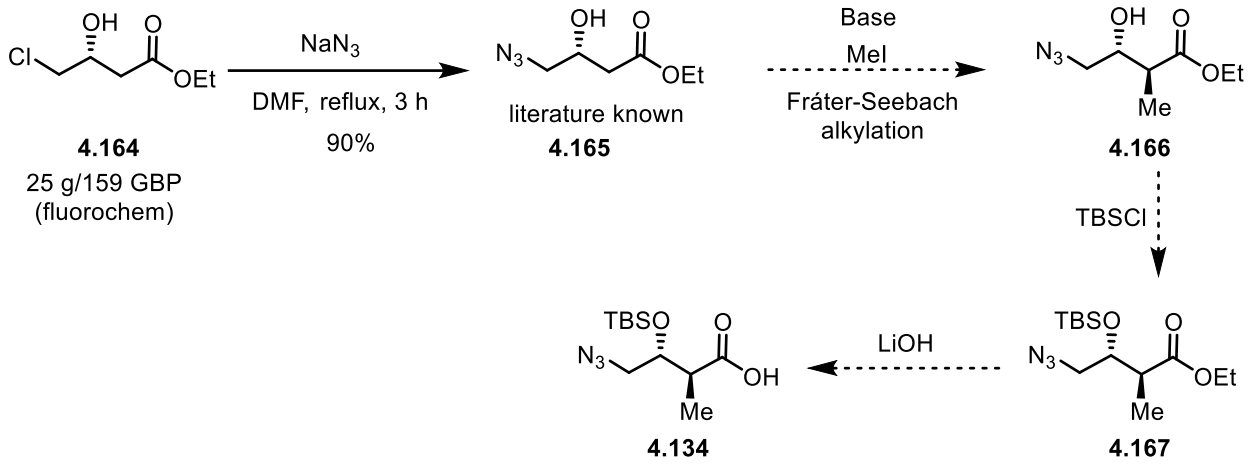
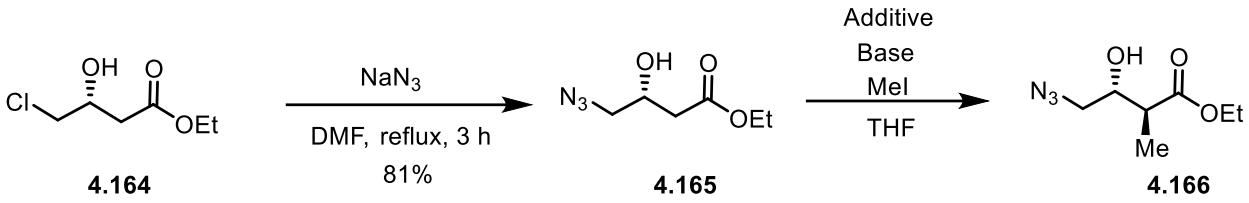


Figure 4.59 Our newly designed route to acid **4.134**.

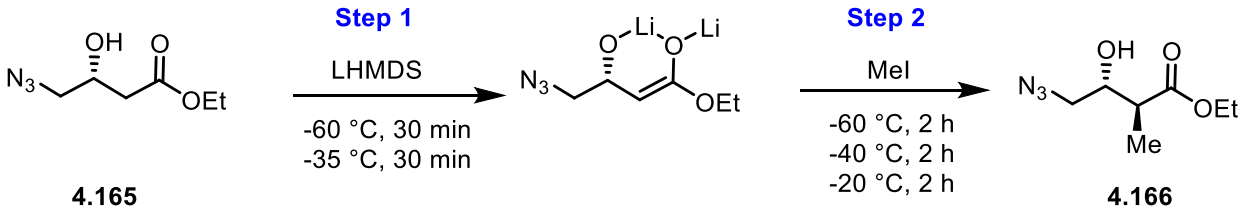
Azido ester **4.165** was easily prepared from commercially available ester **4.164** in 81% yield. We then studied its Fráter-Seebach alkylation, with parameters such as additives, bases and temperature (table 4.60). The addition of HMPA completely shut down the reaction (entry 1, 2 and 3). Though the addition of lithium chloride led to the formation of **4.166** in 70% yield, the d.r. was only 1:1. The d.r. of the product **4.166** was determined by transforming it to the corresponding diol (not shown).[112] In the absence of any additive, the use of LHMDS as the base afforded **4.166** in 60% yield with a d.r. > 20:1. However, the conversion was not complete (entry 5). When LDA was used as the base, the reaction led to mixtures of products (entry 6).



Entry	Base (2.2 equiv.)	MeI (equiv.)	Additive	Temp./Time	Comments
1	LDA	1.3	HMPA	-78 °C, 2 h	**4.165**
2	LHMDS	1.3	HMPA	-78 °C, 2 h	**4.165**
3	LHMDS	1.3	HMPA	-60 °C, 12 h then -40 °C, 8 h	**4.165**
4	LHMDS	2.0	LiCl	-78 °C to -20 °C, 4 h	**4.166** (70%, d.r. = 1:1) **4.165** (unreacted)
5	LHMDS	1.3	none	-78 °C to -5 °C, 4.5 h	**4.166** (60%, d.r. > 20:1) **4.165** (unreacted)
6	LDA	1.3	none	-78 °C to -5 °C, 4.5 h	messy

Table 4.60 Screening conditions for the Fráter-Seebach alkylation of **4.165**.

The incomplete conversions observed prompted us to study this reaction in more detail (table 4.61). Double lithiation at 0 °C or room temperature led to the recovery of **4.165** and no product **4.166** was observed (entry 1 and 2). When the double lithiation was conducted at low temperature, the product **4.166** was isolated in 53% yield, with a d.r. = 17.6:1 (entry 3). The use of 2.3 equiv. of LHMDS decreased the d.r. to 9.1:1, though the yield was increased to 61% (entry 4). As **4.165** was always observed after work up, we conducted the methylation step at a higher temperature (entry 6 and 7). However, neither conditions gave complete conversion. Therefore, the best result was obtained from the conditions of entry 3.



4.165 **4.166**

Entry	LHMDS (equiv.)	MeI (equiv.)	Step 1 (deviations)	Step 2 (deviations)	Comments (4.166/4.165), (yield), (d.r.)
1	2.1	2.0	0 °C /1 h	none	**4.165**
2	2.1	2.0	rt /1 h	none	**4.165**
3	2.1	2.0	none	none	3.4/1, 53%, 17.6:1
4	2.3	2.0	none	none	6.4/1, 61%, 9.1:1
5	2.1	3.3	none	none	5.8/1, ND, 9.6:1
6	2.1	2.0	none	0 °C for 6 h	5.6/1, ND, 8.8:1
7	2.1	2.0	none	-40 °C/12 h then -20 °C/12 h	5.2/1, ND, ND

Table 4.61 Optimization of Fráter-Seebach alkylation.

When the Fráter-Seebach alkylation of **4.165** was conducted on a large scale, the yield of **4.166** could be increased to 71% with a d.r. = 17.8:1. Azido acid **4.134** was then readily obtained from **4.166** in two steps. This optimized route led us to **fragment 2** in 56% yield over four steps (figure 4.61). In addition, acid **4.168**, which could be quite useful for structure-activity relationship (SAR) study of the natural product, was also obtained from **4.165** in two steps.

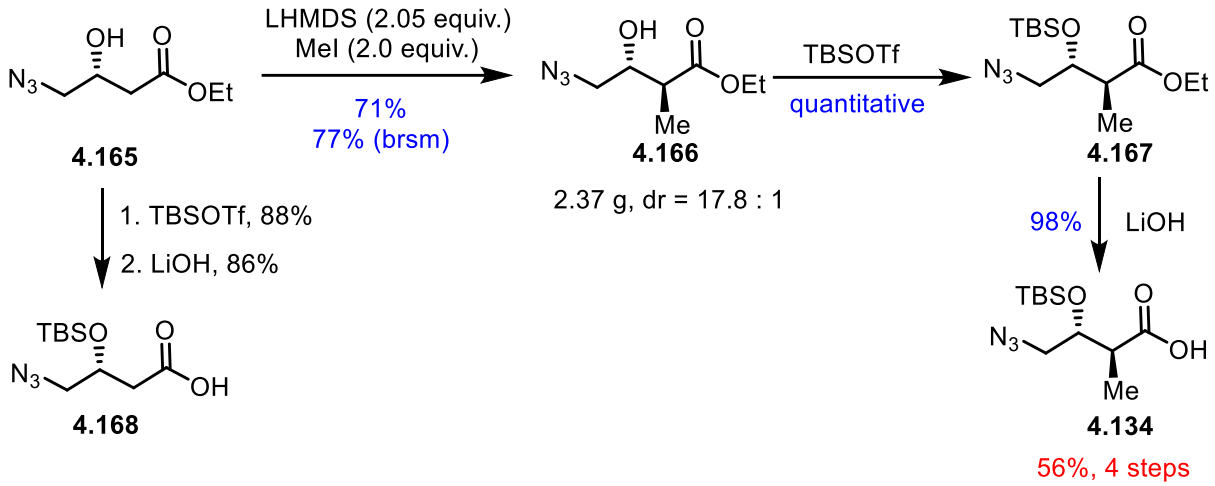


Figure 4.61 Optimized route for **fragment 2**.

To the best of our knowledge, our route to **fragment 2** is shortest and most efficient reported to date (figure 4.62). Other features of our sequence include high anti-selectivity, high atom economy, high reliability and facile derivatization. Besides that, ***ent*-4.134** could be readily synthesized from the commercially available ***ent*-4.164** (fluorochem: 100 g/ 38 GBP). Our route is likely to be of considerable use for a range of natural product and drug syntheses.

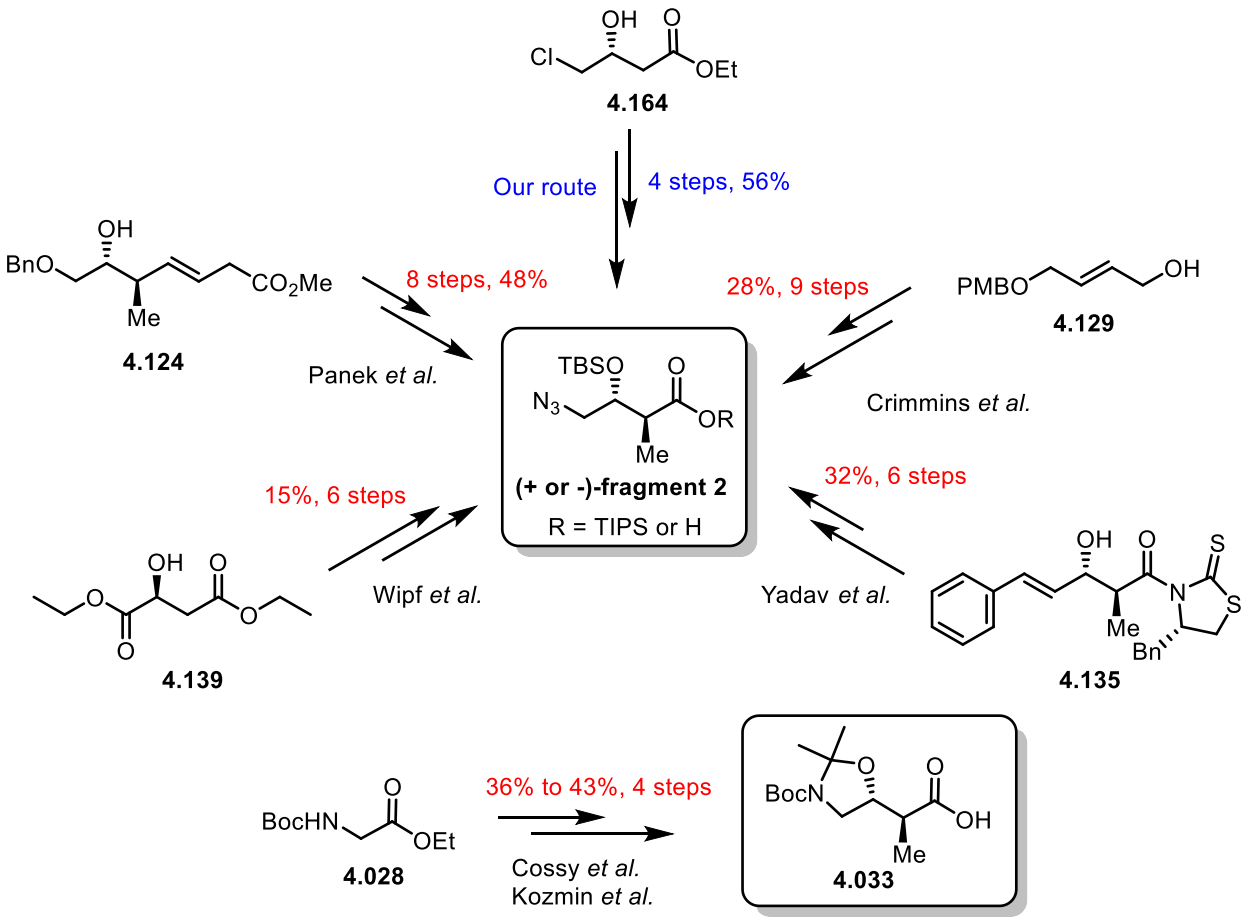


Figure 4.62 Comparison of our route to **fragment 2** with prior routes.

4.3.6 Scalable Synthesis of Amines

With all the motifs in hand, we started their assembly towards the FR molecules. Acid **4.134** was coupled with the amine salt **4.079** to afford the desired amide **4.169** in 92% yield. Reduction of azide by zinc delivered the amine **4.171** in quantitative yield on gram scale. The dimethyl amine **4.172** as well as the dehydroxy, demethyl salt **4.175** were obtained in a similar way (figure 4.63).

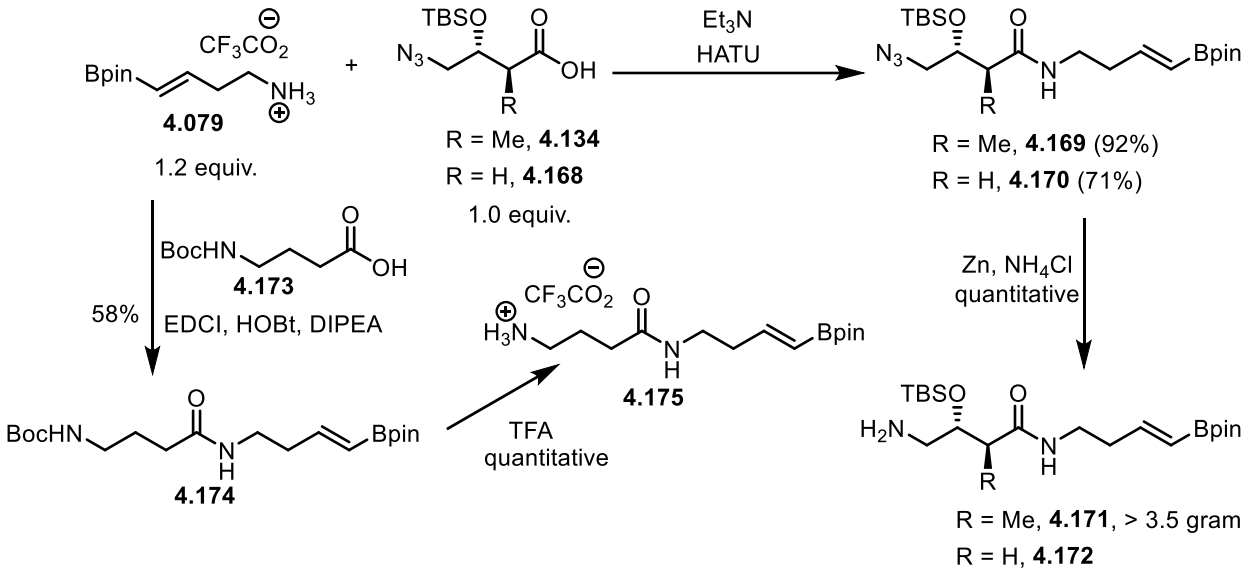


Figure 4.63 Scalable synthesis of amines.

4.3.7 Synthesis of Bisamides

Coupling of amine **4.171** with the **fragment 1** was next targeted. Initially we planned to hydrolyze the thiazolidinone group in **4.119c** to release the acid **4.176**. However, under basic conditions, only thiazolidinone **4.109** was isolated (figure 4.64).

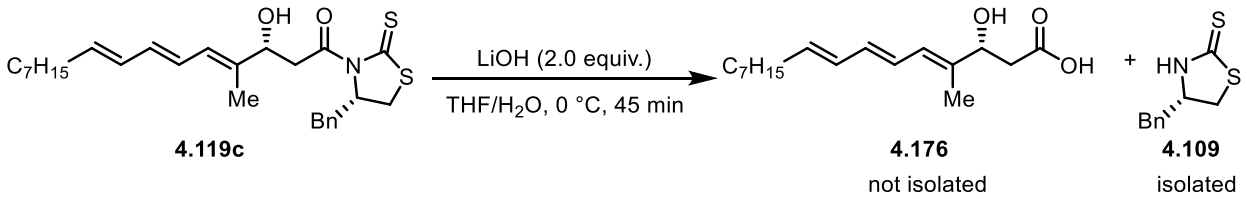


Figure 4.64 Attempted synthesis of acid **4.176**.

Suspecting the acid **4.176** was not stable for purification, we attempted to use it as a crude material. Aldol adduct **4.119c** was first hydrolyzed by lithium hydroxide and the crude product was dried and coupled directly with amine **4.171** in the next step. However, again the desired product **4.177c** was not observed (figure 4.65).

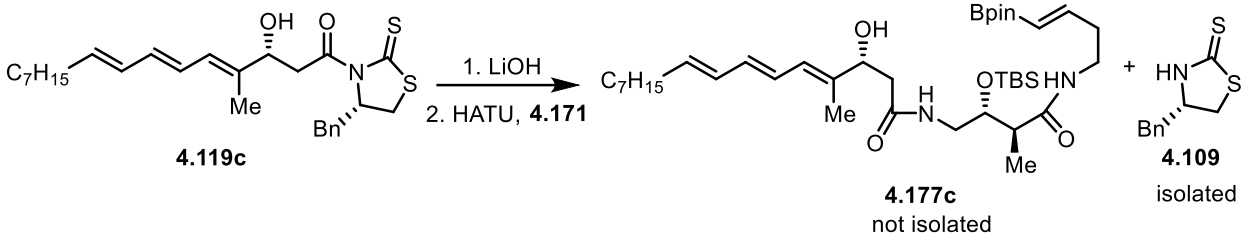


Figure 4.65 Attempted synthesis of **4.177c**.

Given the apparent sensitivity of β-hydroxy triene **4.119c**, we eventually found that the acyl transfer agent DMAP could facilitate the direct coupling of **4.119** and crude amines in one step.[113] This reaction was successfully reproduced over a range of substrates (figure 4.66).

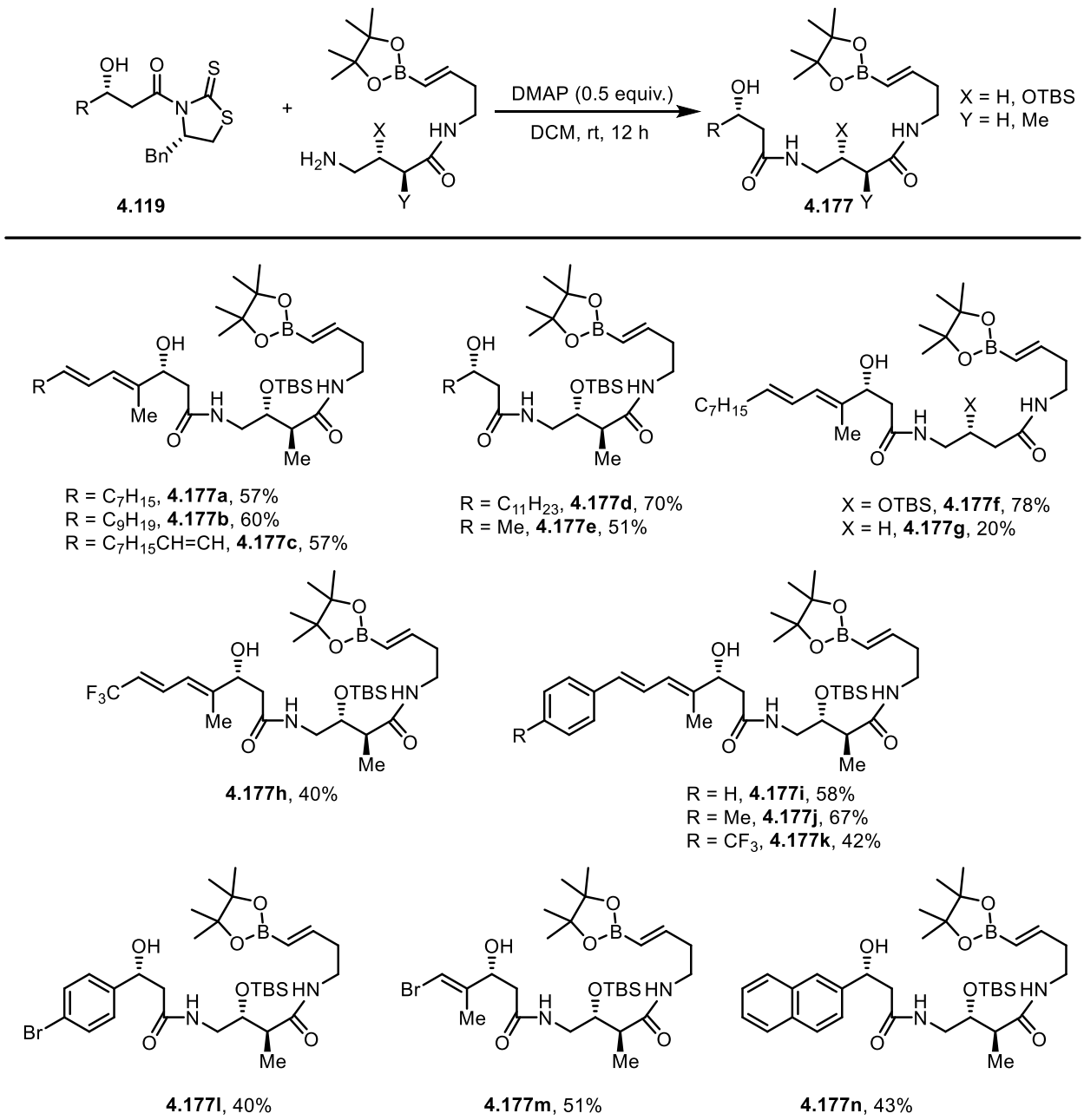
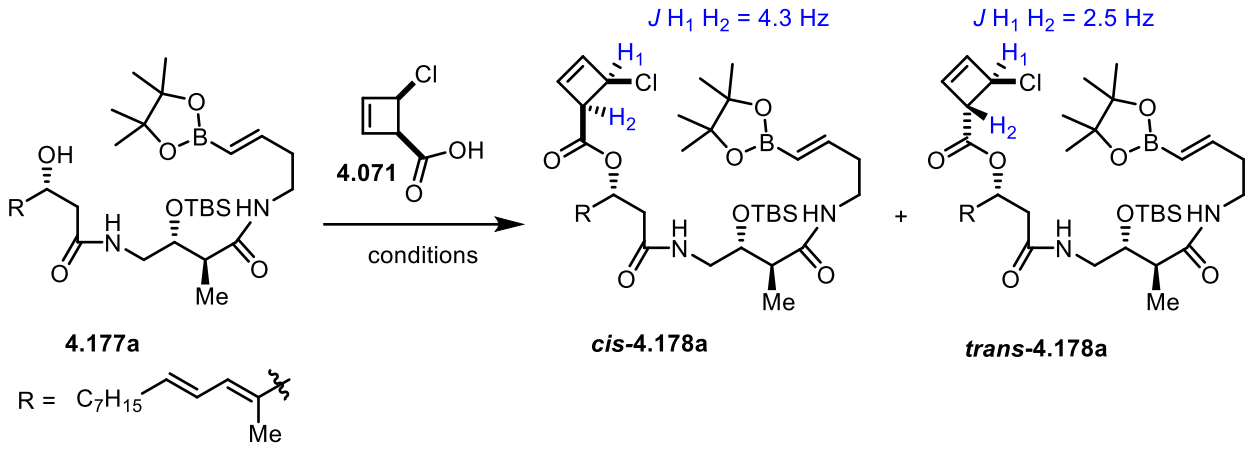


Figure 4.66 Synthesis of bisamides.

4.3.8 Esterification

The esterification of the bisamides **4.177a** with *cis*-chlorocyclotutene acid **4.071** proved to be challenging. After thorough screenings, carbodiimides emerged as superior reagents for the synthesis of ester ***cis*-4.178a** (entry 7 and 8, table 4.67, **Method A**). However, the yield was low, with a major side product being the stereoisomeric ***trans*-4.178a**. The *cis*-isomer and *trans*-isomer were separated by column

chromatography, and their structures were assigned by coupling constant analysis. In ***cis*-4.178a**, the coupling constant for H1 and H2 was calculated to be 4.3 Hz, typical for cis-chlorocyclotutene derivatives, while in the ***trans*-4.177a**, it was about 2.5 Hz, an indicator for the *trans*-relationship.[114]



Entry	Conditons	Comments (*cis*/*trans* or isolated yield)
1	MNBA, DMAP, Et_3N, DCM, rt	1:5
2	$Sc(OTf)_3$, $(p\text{-}NO_2PhCO)_2O$, CH_3NO_2, rt	Messy
3	PPh_3, DEAD, THF or Toluene, rt	Eliminated product observed
4	PyBOP, DIPEA, DCM, rt	Messy
5	HATU, DBU, DMF, rt	Not obtained
6	HBTU, DBU, DMF, rt	Not obtained
7	DIC, DMAP, DIPEA, DCM, rt	1: 1.2
8	EDCI, DMAP, DIPEA, DCM, rt	***cis*** (30%), ***trans*** (36%)[a]

Table 4.67 Conditions for the synthesis of ***cis*-4.178a**.

The formation of ***trans*-4.178a** posed a serious threat to our synthetic approach, since only a *cis*-arrangement of substituents around the cyclobutene moiety of **4.178a** would result in the desired (*E,E,E*)-triene geometric isomer upon stereoinvertive Suzuki-type coupling and conrotatory 4π-electrocyclic ring

opening. Fortunately, product ***cis*-4.178a** was found to be kinetically stable under the coupling conditions (figure 4.68).

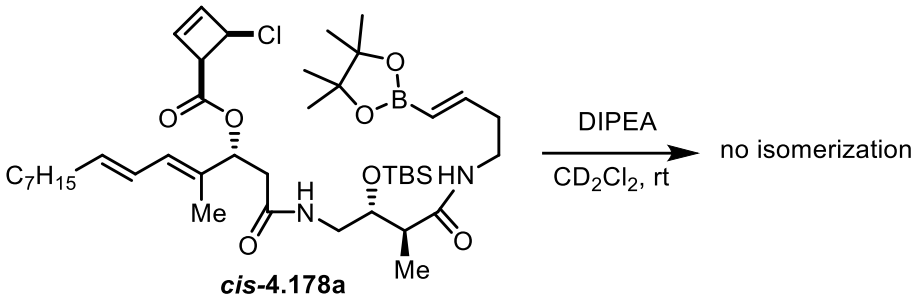


Figure 4.68 Stability of product ***cis*-4.178a**.

The stability of ***cis*-4.178a** under the basic conditions above implied that the isomerization occurred upon the activation of acid **4.071** (figure 4.69). For instance, acid **4.071** reacted readily with DIC to afford intermediate **4.179**. Attack of DMAP on the carbonyl of **4.179** generated an activated species **4.180**. The following attack of ROH released product ***cis*-4.178a**. However, once **4.179** was activated by DMAP, the proton H2 became quite acidic and prone to reversible deprotonation under basic conditions. **4.180** isomerized to the more thermodynamically stable intermediate **4.181** which was attacked by ROH to release ***trans*-4.178a**. Therefore the use of mild conditions for the activation of acid **4.071** and careful choices of base were crucial for the selective formation of ***cis*-4.178a**.

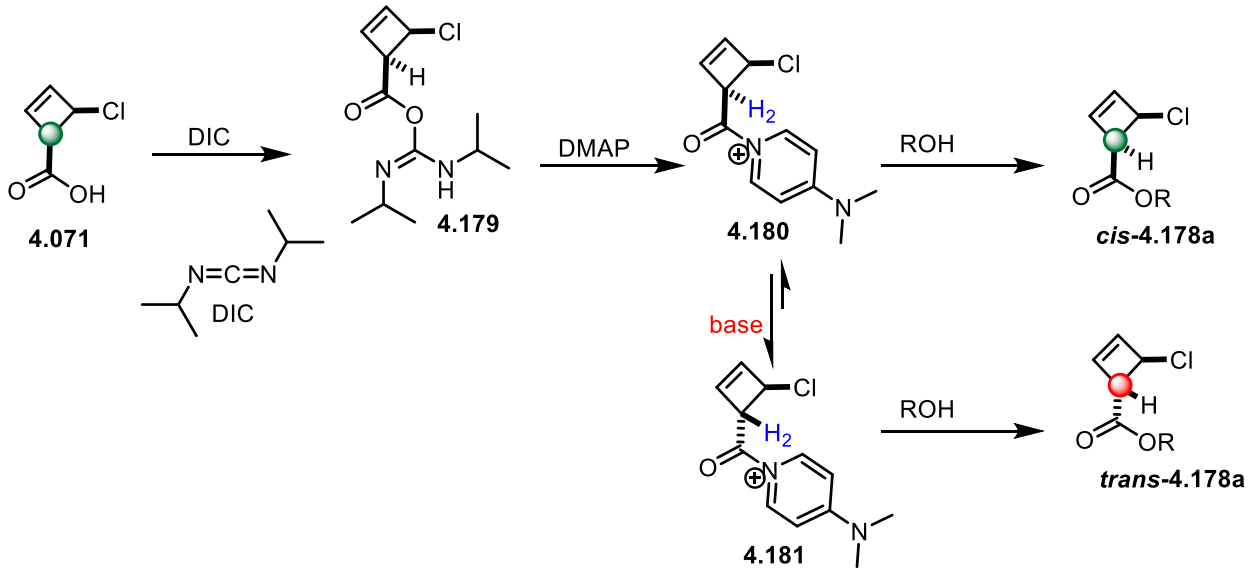


Figure 4.69 Mechanism for the isomerization.

In the meantime, Zhao *et al.* reported that a carboxylic acid could be activated by ynamide **4.182**,[115] to afford intermediate **4.183**. The interesting ketene aminol **4.183** could be isolated or treated directly with an amine to form amide product **4.184** (figure 4.70). The conditions of this protocol were very mild and little racemization was found when chiral amino acids were used.[115]

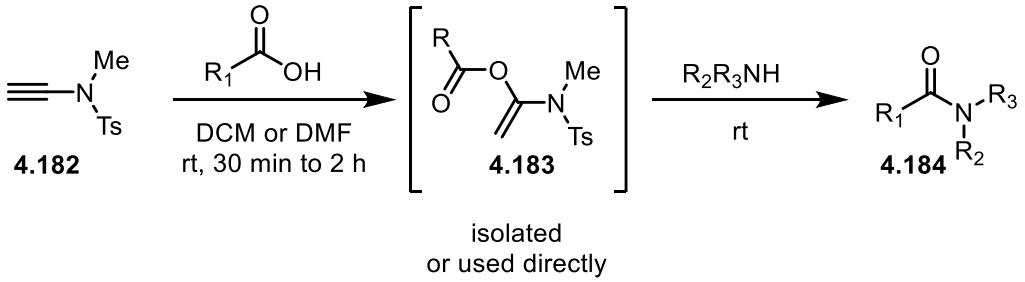
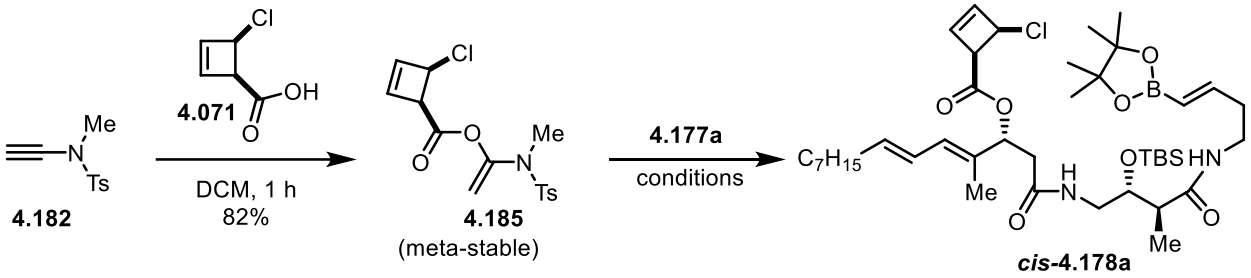


Figure 4.70 Zhao *et al.*'s protocol for activation of carboxylic acid.

Inspired by this work, we submitted the acid **4.071** to the above conditions developed by Zhao *et al.*. The adduct **4.185** was readily obtained in 82% yield without any isomerization. Though meta-stable, **4.185** could be purified by column chromatography. Unfortunately, treatment of **4.185** with bisamide **4.177a** under a variety of conditions, however did not lead to the formation of desired product ***cis*-4.178a** (table 4.71).

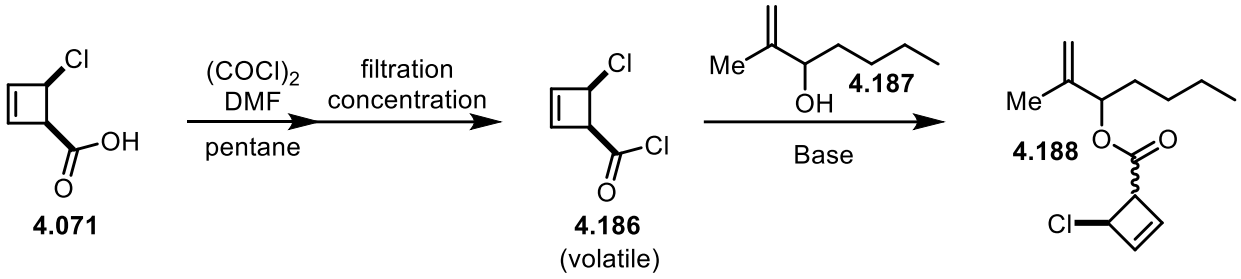


Entry	Conditions	Comments
1	DCM, rt, 48 h	Only s.m.
2	DMAP (0.1 equiv.), DCM, rt, 48 h	Mainly s.m.
3	DMF, rt, 5 h then 50 °C, 3 h	Messy

Table 4.71 Attempted synthesis of ***cis*-4.178a** from **4.185**.

Dr. Guilhem Coussanes used allylic alcohol **4.187** as a model substrate for the optimization of the esterification. Acid **4.071** was treated with catalytic amount of DMF and a large excess of oxalyl chloride (20 equiv.) in dry pentane for 1 h. Filtration and concentration led to the acid chloride **4.186**.[76] Then the

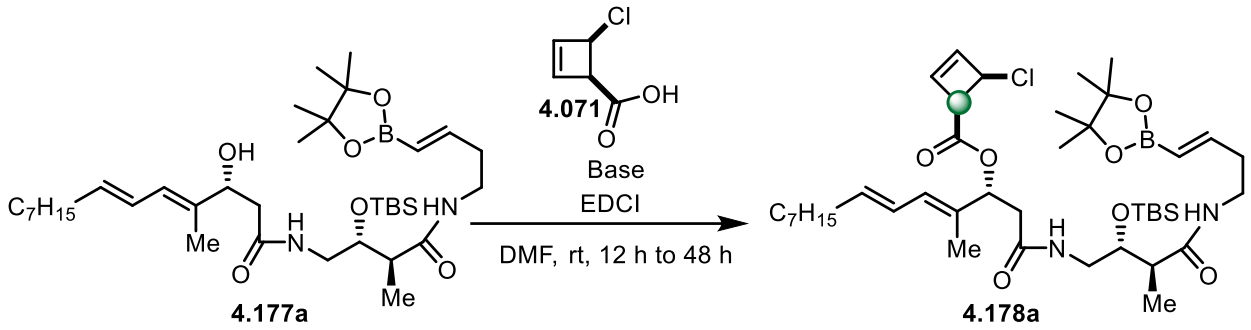
coupling of **4.186** with alcohol **4.187** was evaluated with different bases (table 4.72). The extent of *cis*/*trans* isomerization was highly related to the strength of the bases. With pyridine as the base, product **4.188** was formed with a *cis*/*trans* = 96:4 (entry 1, **Method B**). Stronger bases led to inferior results. Without any base, only traces of product was formed (entry 6). However, the volatility of acid chloride **4.186** rendered this transformation poorly reproducible.



Entry	Base	PKa	4.188 *cis/trans*
1	Pyridine	5.17	96:4
2	2,6-lutidine	6.77	40:60
3	Et_3N	10.78	30:70
4	DIPEA	11.02	30:70
5	Proton sponge	12.34	15:85
6	Without base		96:4 (trace amounts)

Table 4.72 Model study carried out by Dr. Guilhem Coussanes.

We then further evaluated the base's effects in the esterification conditions mediated by carbodiimides. Although a variety of bases were screened, the results did not improve significantly (table 4.73). The best yield was obtained when 3,5-dimethylpyridine was used (entry 8). However, ***cis*-4.178a** was isolated in 43% yield, along with 21% ***trans*-4.178a**.



entry	Base	PKa	Comments
1	pyridine	5.17	<20% conversion
2	4-Iodopyridine		<20% conversion
3[a]	2-Iodopyridine		Not observed
4[a]	2-fluoropyridne		Not observed
5	3-methylpyridine	5.68	70% conversion, ***cis/trans*** = 2.0:1
6	2-methylpyridine	5.97	<20% conversion
7	4-methylpyridine	6.02	57% conversion, ***cis/trans***= 3.5:1
8	3,5-dimethylpyridine	6.14	***cis*** (43%), ***trans*** (21%)
9	4-methoxylpyridine	6.62	Full conversion, ***cis/trans***= 1.5:1
10	DMAP	9.60	Full conversion, ***cis/trans***= 1:1

[a] DIC was used instead of EDCI.

Table 4.73 Further screening of the bases.

We next turned to the Ghosez's reagent as a potentially mild reagent for acid chloride synthesis, with the only by product being N,N-dimethylisobutyramide **4.189** (figure 4.74).[116]

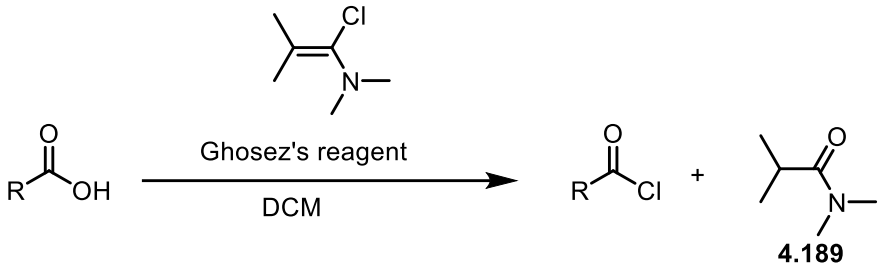
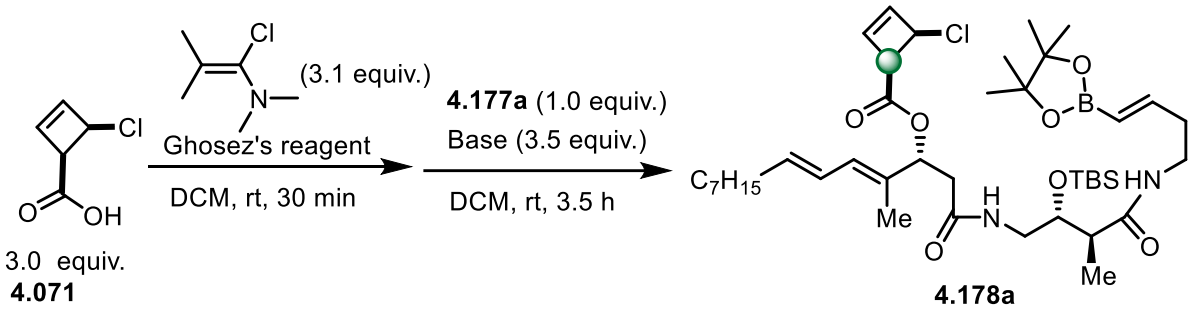


Figure 4.74 Formation of acid chloride by the Ghosez's reagent.

Cis-chlorocyclobutene acid **4.071** was successfully activated by using the commercially available Ghosez's reagent after 30 min at room temperature, however, the following esterification mediated either by pyridine or 3,5-dimethyl pyridine afforded the product with a *cis*/*trans* ratio = 1.9:1 (table 4.75).



Entry	Base	Comments
1	pyridine	Full conversion, ***cis*/*trans*** = 1.9/1
2	3,5-dimethyl pyridine	Full conversion, ***cis*/*trans*** = 1.9/1

Table 4.75 Attempted esterification using the commercially available Ghosez's reagent.

These observations were in contradiction with the result of **Method B** (entry 1, table 4.72). As Ghosez's reagent is prepared from amide **4.189** in the presence of phosgene and later triethylamine,[117] we surmised that commercial samples could be contaminated by triethylamine (figure 4.76). Since we demonstrated that triethylamine favors the formation of *trans*-isomer (entry 3, table 4.71), freshly distilled Ghosez's reagent was used in the following optimization.

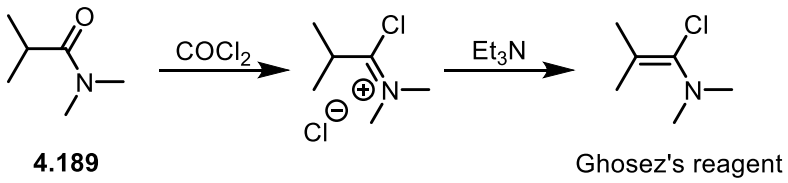


Figure 4.76 Reported synthesis of the Ghosez's reagent.

To make sure the acid chloride formation was not accompanied by any isomerization, we used ^{1}H NMR to monitor the process. ^{1}H NMR showed that this transformation was quite stereoselective and no *trans*-products were observed (figure 4.77).

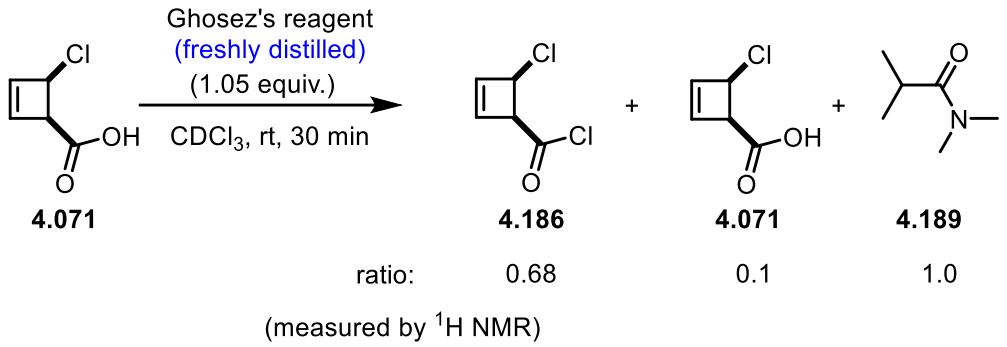
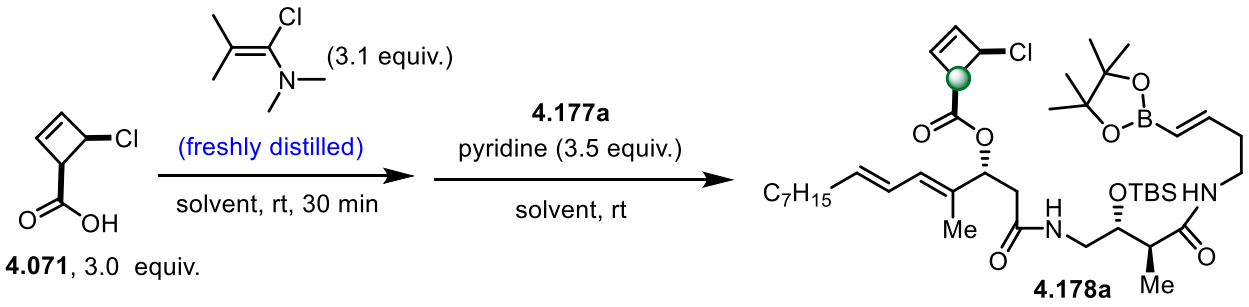


Figure 4.77 Stereoselective acid chloride formation.

Next, the freshly distilled Ghosez's reagent was employed for the esterification in chloroform or dichloromethane (table 4.78). In chloroform, full conversion could be achieved within 4 h. The product **4.178a** was isolated in 79% yield, with *cis/trans* = 8.8:1 (entry 1, **Method C**). This reaction could be readily carried out on gram scale with a slightly lower yield of 65%. The reaction in dichloromethane proved to be slow, though high *cis*/*trans* ratio was observed (entry 2).



Entry	Solvent	Comments
1[a]	$CHCl_3$, 4 h	Full conversion, 79%, ***cis*/*trans*** = 8.8:1
2	DCM, 7 h	60% conversion, ***cis*/*trans*** = 14:1

[a] 65% yield with 2.0 equiv. of the Ghosez's reagent, 1.29 g obtained.

Table 4.78 Optimization of conditions for the stereoselective esterification.

With the above conditions developed, a range of esterified products were obtained (figure 4.79).

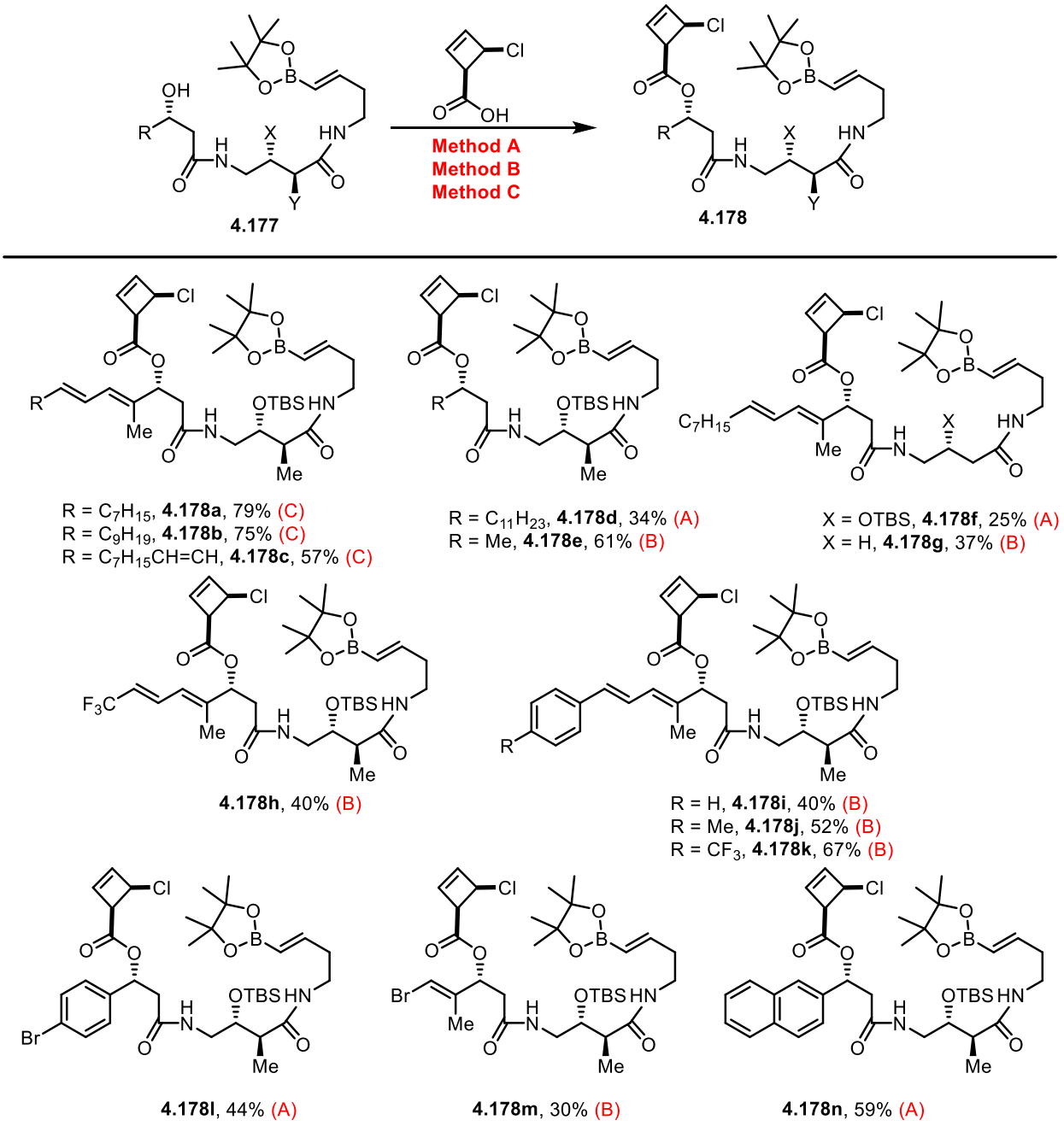
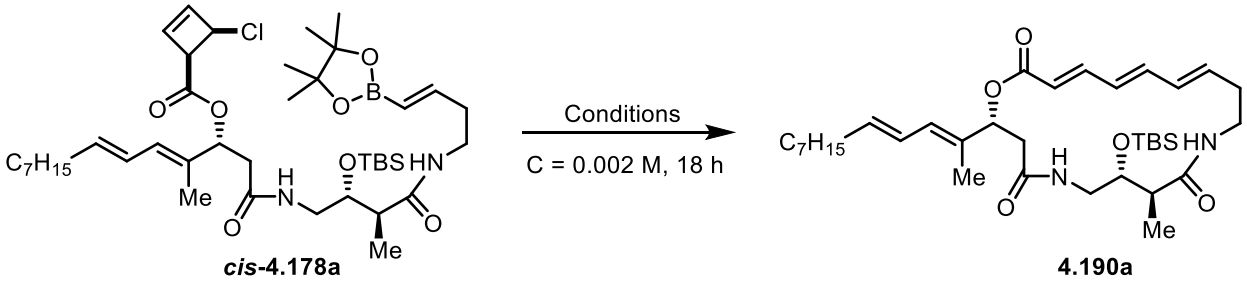


Figure 4.79 Esterified products.

4.3.9 Macrocyclization

The Key Suzuki-Miyaura macrocyclization was then attempted using substrate **4.178a** (table 4.80).[118] With ***cis*-4.178a**, it was found that the domino macrocyclization/ 4π-electrocyclic ring opening process smoothly took place in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium and cesium carbonate. Product **4.190a** was formed in 74% yield at room temperature after 18 h (entry 5). In addition,

67% yield of **4.190a** was isolated using $Pd(dppf)_2$, $AsPh_3$ and Cs_2CO_3 (entry 4).[119] The use of TlOEt as the base did not give any product (entry 3).[120] The combination of $Pd(OAc)_2$, SPhos and K_3PO_4 led to complex mixtures (entry 1 and 2).[121] Although ***cis*-4.178a** was used as diastereomeric mixture as it results from the coupling of an enantiopure bisamide with racemic *cis*-chlorocyclobutene acid **4.071**, the cyclization proceeded regardless of the absolute orientations of substituents on the cyclobutene motif.



Entry	Conditions	Comments
1	$Pd(OAc)_2$, SPhos, K_3PO_4, THF/H_2O, 40 °C	Messy
2	$Pd(OAc)_2$, SPhos, K_3PO_4, THF/H_2O, rt	Not observed
3	$Pd(PPh_3)_4$, TlOEt, THF/H_2O, rt	Not observed
4	$Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, DMF/THF/H_2O, rt	67%
5	$Pd(PPh_3)_4$, Cs_2CO_3, THF/H_2O, rt	74%

Table 4.80 Tandem Suzuki-Miyaura macrocyclization/4π-electrocyclic ring opening.

In agreement with our expectation, the isomeric precursor ***trans*-4.178a** did not deliver **4.190a**. As an example, when ***trans*-4.189a** was submitted to the same conditions of entry 5 (table 4.80), complex mixtures were obtained, and no desired product **4.190a** were observed on crude ^1H NMR (figure 4.81).

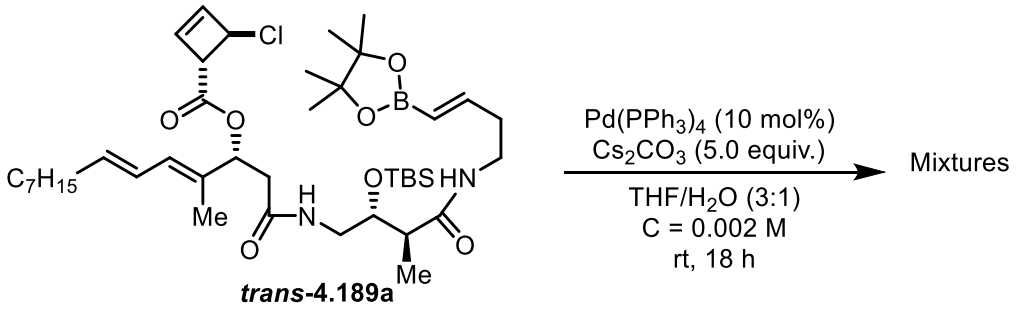


Figure 4.81 ***Trans*-4.189a** as a substrate led to complex mixtures.

Three possible pathways were proposed for the formation of macrocycle **4.190a** (figure 4.82). While both pathway 1 and 2 involved the intermediacy of a dienylpalladium complex **IV**, pathway 3 relied on a vinyl cyclobutene moiety **V**.

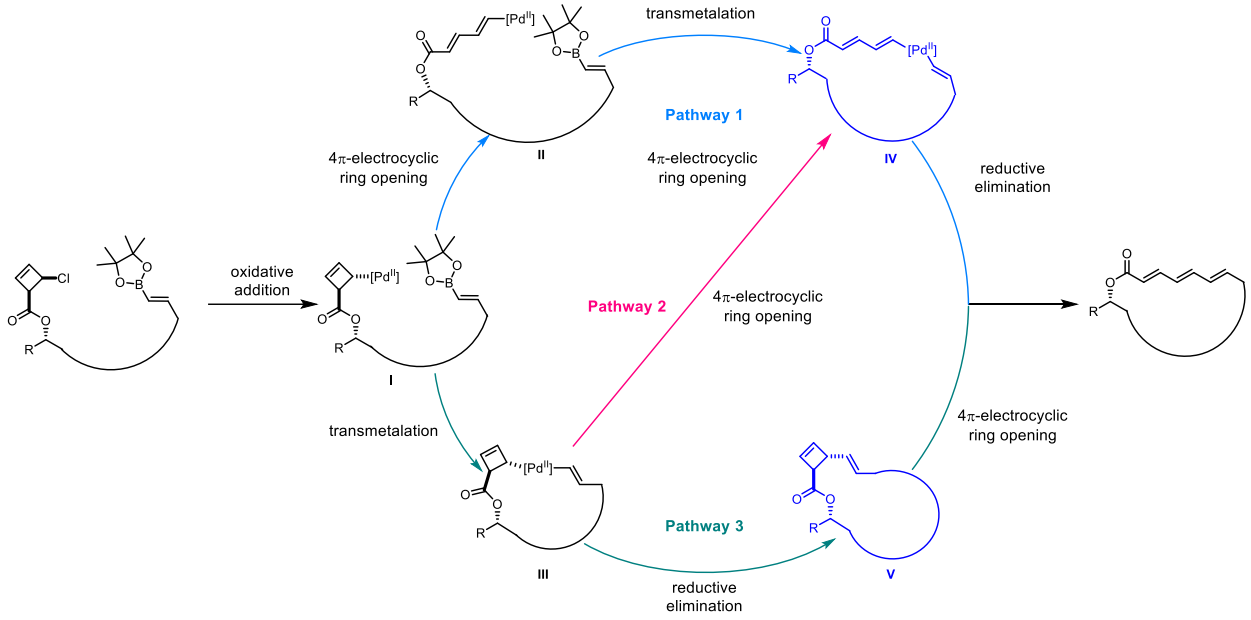
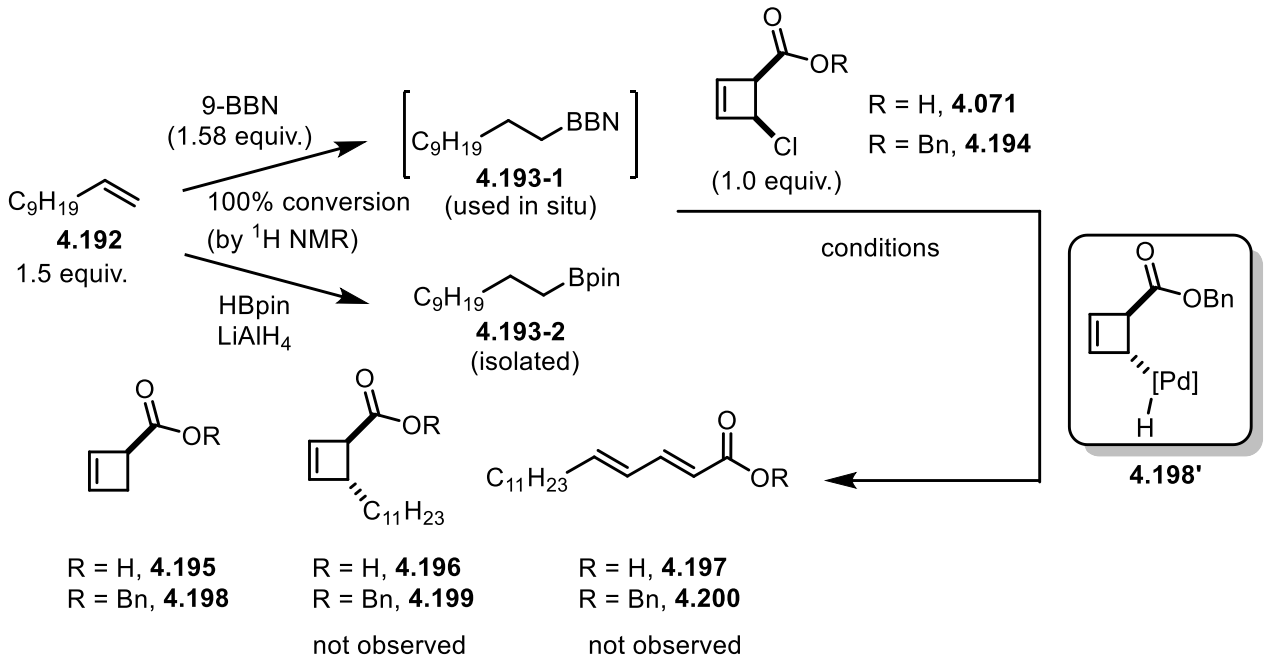


Figure 4.82 Possible pathways to the macrocycle **4.190a**.

To shed light on the mechanism of the formation of macrocycle **4.190a**, an alkyl boron intermediate **4.193-1** and pinacol boronic ester **4.193-2** was prepared through hydroboration of undec-1-ene **4.192** (table 4.83).[122] Those boron reagents was then treated with **4.071** or **4.194** under the same Suzuki-Miyaura coupling conditions used for the synthesis of macrocycle **4.190a**. In all the reactions screened, the expected product **4.196**, **4.197** or **4.199**, **4.200** was never observed. Instead, the reduced cyclobutene ester **4.198**, probably formed from the hydridopalladium species **4.198'** after a reductive elimination, was isolated in 20% yield (entry 5). These reactions suggest that the dienylpalladium intermediate **IV** was probably not involved in the formation of the macrocycle **4.190a,** thus excluding pathway 1 and 2 (figure 4.82)**. 4.190a** was most likely formed through a Suzuki-Miyaura coupling on the cyclobutene moiety and a sequential spontaneous 4π-electrocyclic ring opening of intermediate **V** (pathway 3, figure 4.82)**.**



Entry	Boron reagent	R	Conditions	Comments
1	**4.193-2**	Bn	$Pd(PPh_3)_4$, Cs_2CO_3, THF/H_2O, rt	Decomposition
2	**4.193-2**	Bn	$Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, DMF/THF/H_2O, rt	Decomposition
3	**4.193-1**	H	$Pd(PPh_3)_4$, Cs_2CO_3, THF/H_2O, rt	Decomposition
4	**4.193-1**	Bn	$Pd(PPh_3)_4$, Cs_2CO_3, THF/H_2O, rt	Decomposition
5	**4.193-1**	Bn	$Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, DMF/THF/H_2O, rt	**4.198** (20%)

Table 4.83 Mechanism elucidation.

The stability of product **4.190a** was tested. DMAP was earlier proposed to be responsible for the isomerization of the C2-C3 double bond during the activation of the acid in the macrolactonization, forays of Falck and Cossy.[85,86] In our hands, product **4.190a** appeared to be stable when it was treated with DMAP, as no isomerized product **4.190a'** was observed (figure 4.84). Therefore, we believed that the isomerization of the C2-C3 double bond probably occurred during the activation of the carboxylic acid.

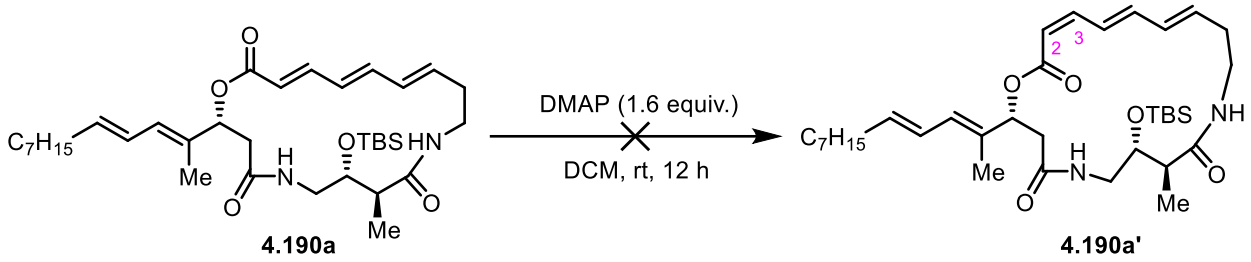


Figure 4.84 Stability of **4.190a**.

A variety of substrates were cyclized under the conditions of entry 5 (table 4.80), which allowed us to build a library of products for the following SAR study (figure 4.85). It is worth noting that this cyclization tolerated the aromatic bromide (**4.190l**) and vinyl bromide (**4.190m**). In both cases, no debrominated products were detected. The removal of methyl group at C12 did not influence the cyclization (**4.190f**). When the free hydroxy group at C13 was further removed, the cyclization still delivered product **FR4** in 58% yield.

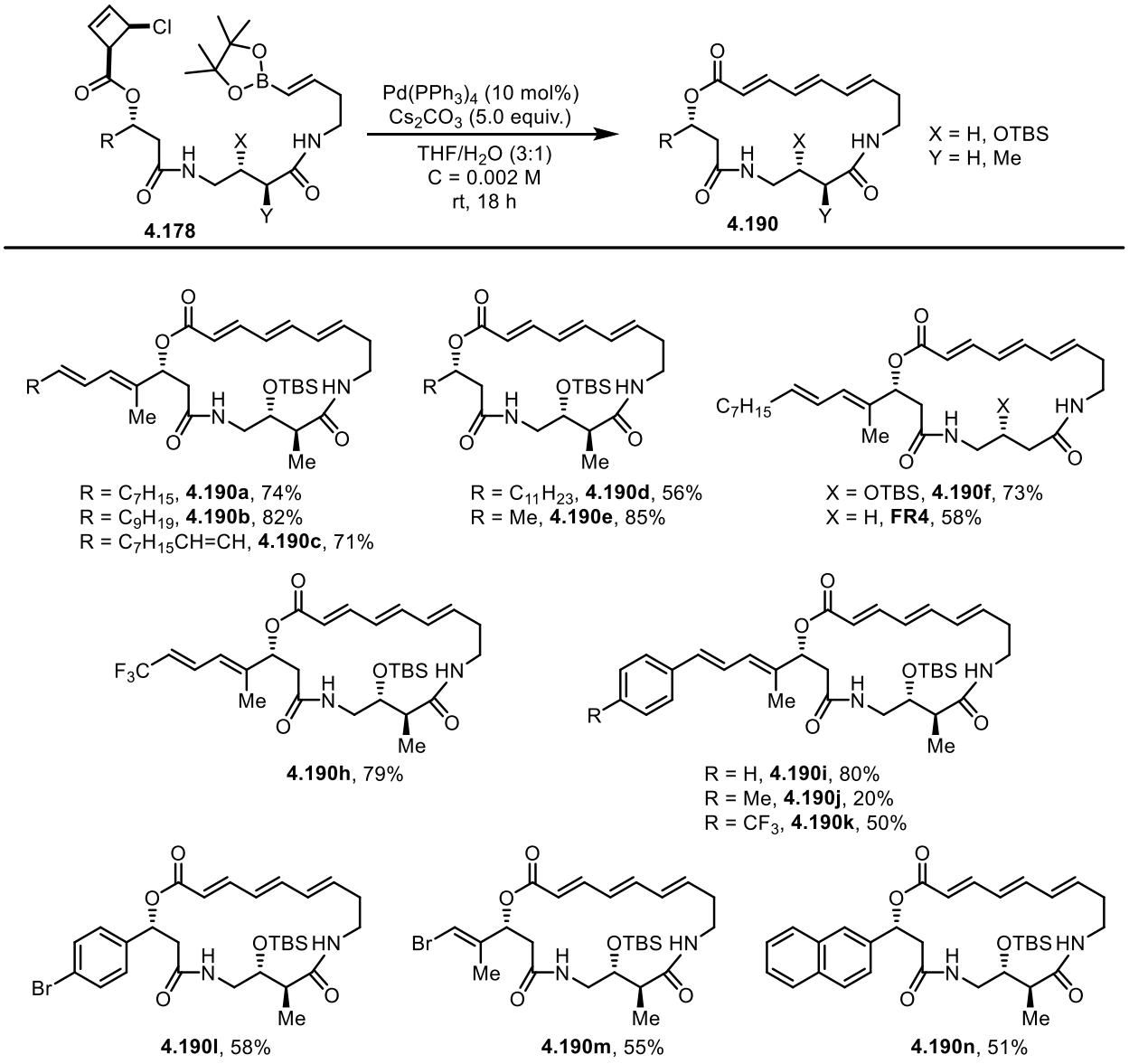
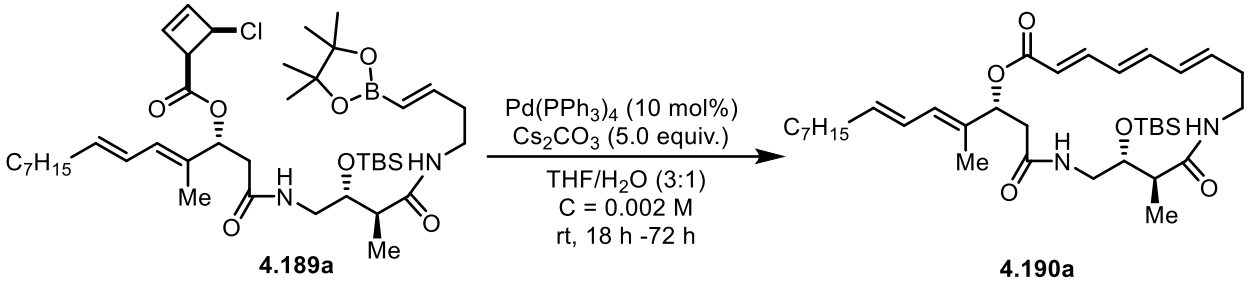


Figure 4.85 The library of cyclized products.

However, when we tried to scale up the cyclization above 100 mg, the yield of macrocycle **4.190a** dropped to ca. 25% yield. Increasing the reaction time to 72 h did not improve the yield (figure 4.86).



250 mg	25%
100 mg	23%
21.8 mg	74%

Figure 4.86 Attempted cyclization above 100 mg scale.

4.3.10 Deprotection

Although Falck *et al.* reported that the removal of TBS group of product **4.190a** by various fluoride reagents was accompanied by many side reactions,[85] in our hands, treatment of **4.190a** with TBAF (1.2 equiv.) in THF at 0 °C for 5 min cleanly delivered FR252921 in 90% yield, thus allowing us a 10-step Longest linear sequence to FR252921, with an overall yield of 14.9%. It was also interesting to note that ^{1}H NMR spectra of FR252921 before and after column showed a strong difference (figure 4.87). This observation implied that FR252921 might interact with a chemical species such as the tetrabutylammonium cation, within the crude mixtures.

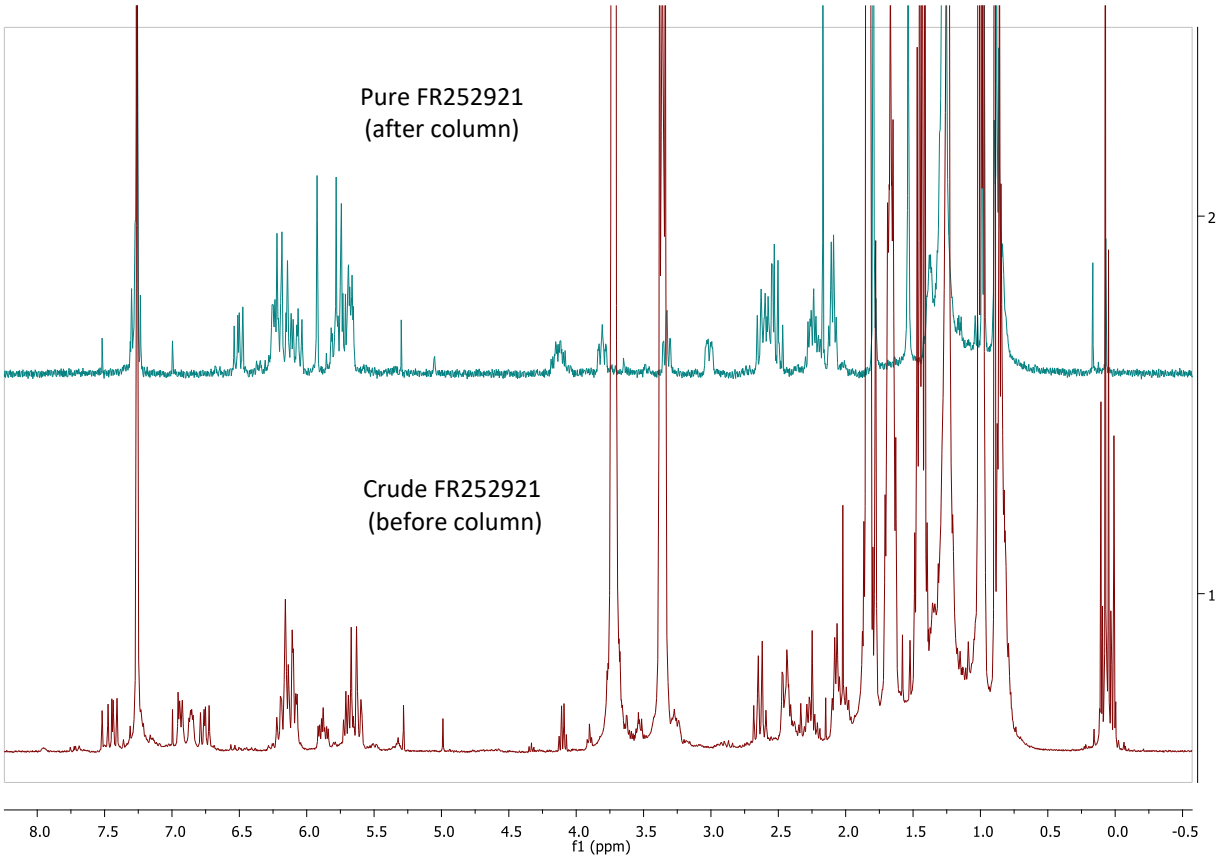


Figure 4.87 ^{1}H NMR spectra of FR252921: before and after column chromatography purification.

The deprotection conditions proved to be quite reproducible and worked for a variety of substrates, thus allowing us to build a library of macrocycles (figure 4.88).

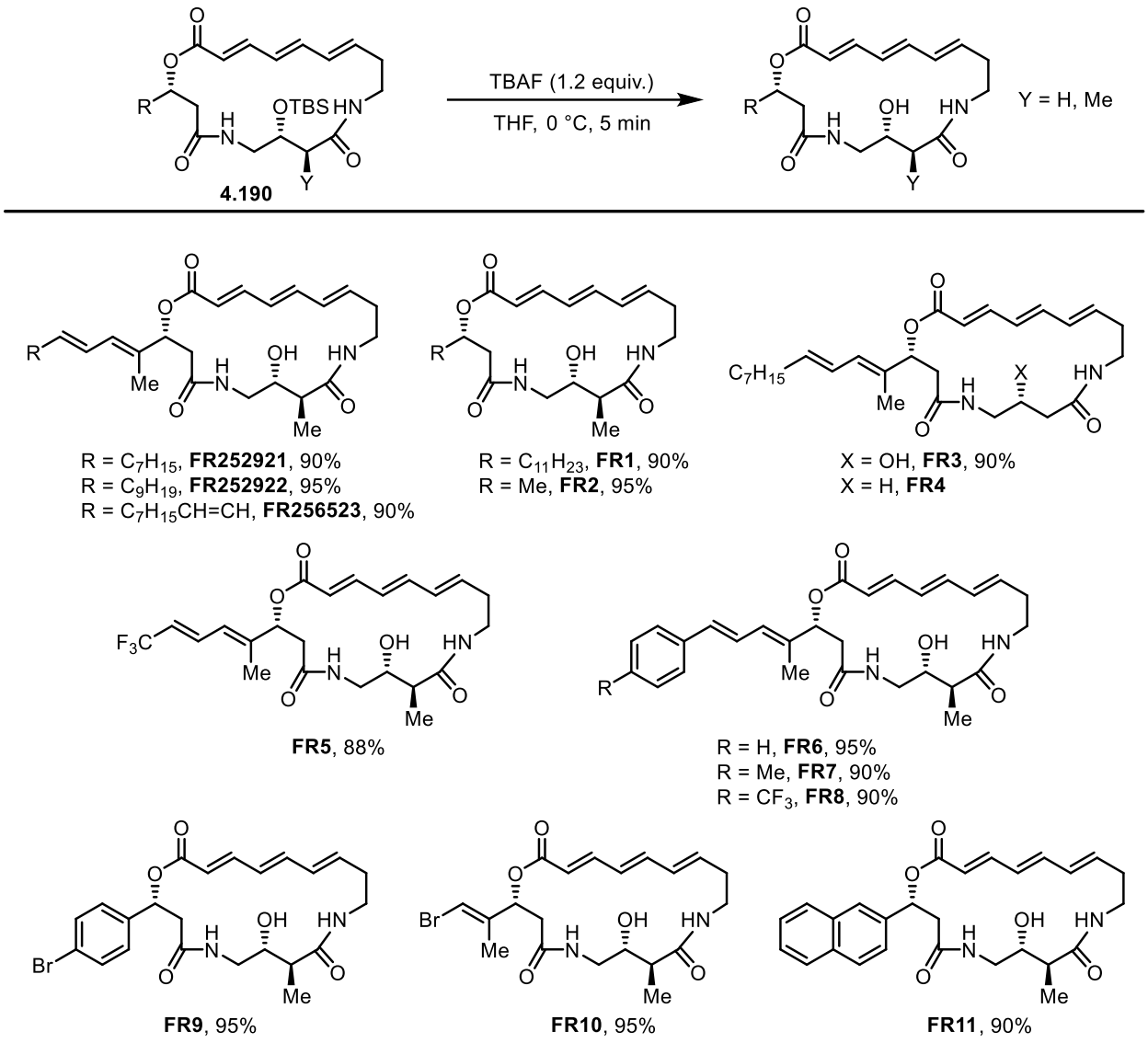


Figure 4.88 Deprotection of a library of macrocycles.

4.3.11 Biological Studies

The biological assays were performed by the group of Stefan Kubicek (CeMM, Vienna, Austria).

4.3.11.1 Immunosuppressive Activities

In collaboration with the group of Stefan Kubicek, the FR molecules and analogues were tested on the *EL4-T-lymphocyte* cells (figure 4.89). All the FR molecules inhibit the proliferation of *EL4-T-lymphocyte* cells with IC50 < 1 uM. When the sidechain is a long alkyl chain, **FR1** still maintains activity albeit at > 10-fold higher concentration (**FR1** vs FR252921). However, **FR2** with only a methyl group on the sidechain

completely loses its activity. While the C12 methyl group has very little effect on the biological activity (**FR3** vs FR252921), the further removal of C13 hydroxy group renders **FR4** inactive. Based on these initial results, we further synthesized analogues with different side chains. Among these analogues, **FR9** and **FR10**, with aromatic side chains, are inactive due to their poor solubility. While **FR6** is inactive, its congeners **FR7** and **FR8** retain the potency. **FR10** with only one double bond on the side chain is active albeit with an IC_{50} = 2.73 uM, about 10-fold higher than FR252921. Impressively, **FR5**, with a CF_3 group on the side chain, displays the most potent activity with an IC_{50} = 83 nM.

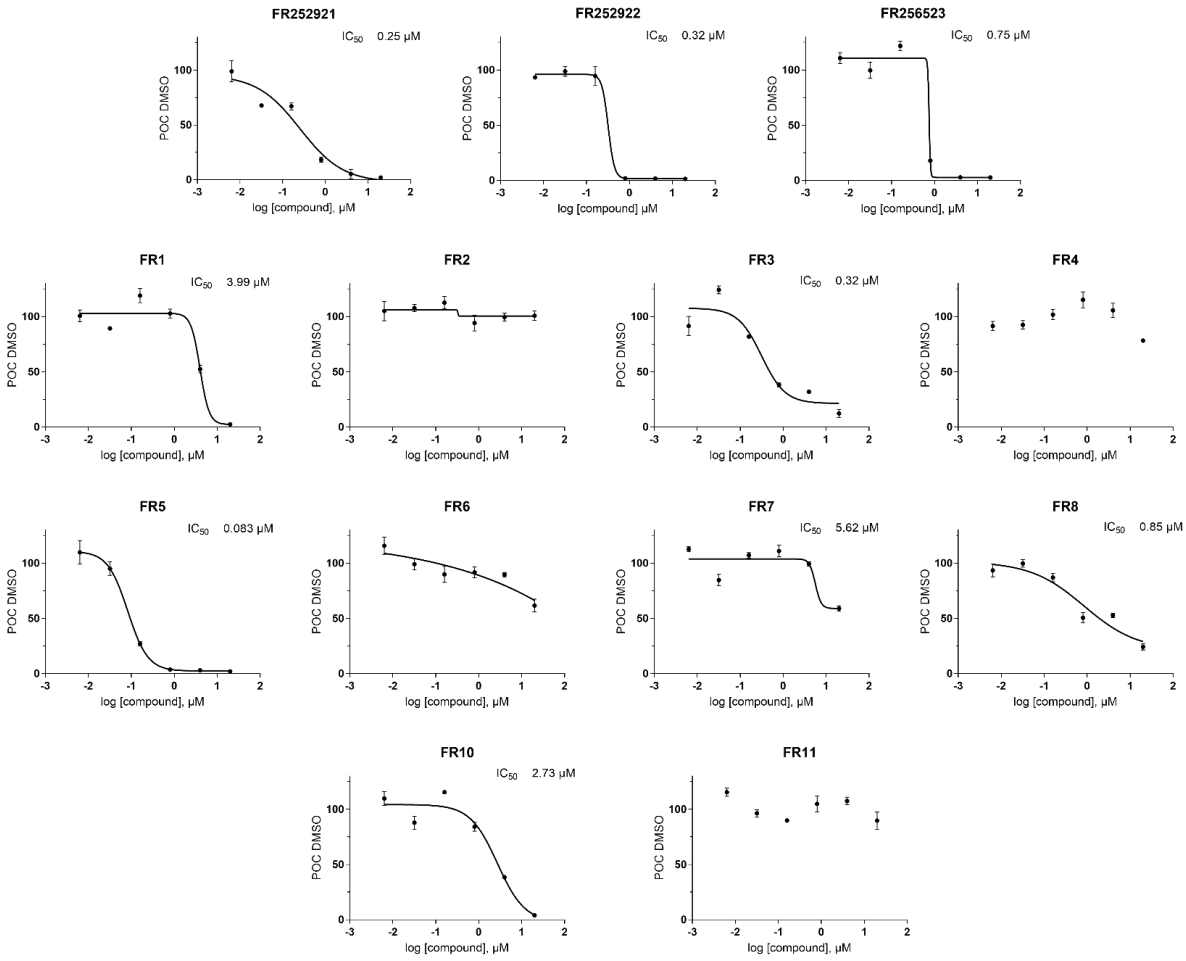


Figure 4.89 Dose-response curve of the FR molecules and analogues on *EL4 T-lymphocyte* cell line proliferation.

4.3.11.2 Design and Synthesis of Probes

These biological data enabled the establishment of the SAR for this class of metabolites (figure 4.89). Although the side chain is modifiable, our results suggest it should be lipophilic. While the C12 methyl group is not important, the C13 hydroxy group is crucial to maintain the activity. Based on this model, a biotin-tagged probe was designed in order to find its cellular targets and elucidate the mode of action of the FR molecules (figure 4.90).[123]

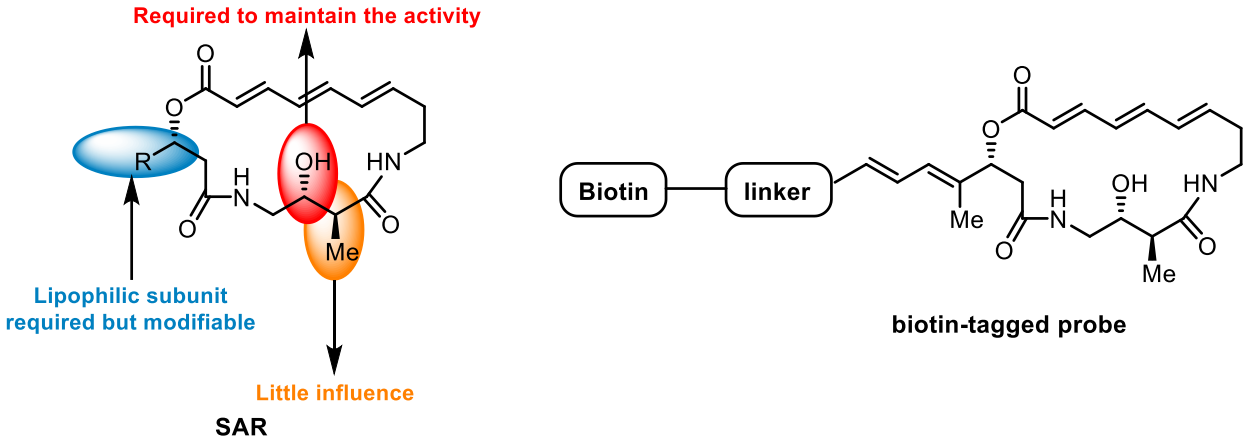


Figure 4.90 SAR and biotin-tagged probe.

We decided to incorporate an azide handle on the side chain, as the azide moiety was relatively stable and could be either reduced to amine for further coupling or used directly in a "click" type conjugation.[124] Commencing with alcohol **4.201** and crotonaldehyde **4.202**, aldehyde **4.203** was readily obtained under the cross olefin metathesis conditions.[125] **4.203** was then converted to dienic ester **4.204** under Wittig reaction conditions. Ester **4.204** was further transformed to azido aldehyde **4.206** over a 4-step sequence. Treatment of **4.206** with **4.085c** under aldol conditions delivered adduct **4.207** in 57% yield with d.r. = 6.4:1. Coupling of **4.207** with amine **4.171** in the presence of DMAP afforded bisamide **4.208** in 68% yield. Stereoselective esterification of **4.208** and acid **4.071** using the Ghosez's reagent delivered product **4.209** in 69% yield. The macrocyclization was carried on a 25 mg scale and delivered macrocycle **4.210** in 59% yield (figure 4.91).

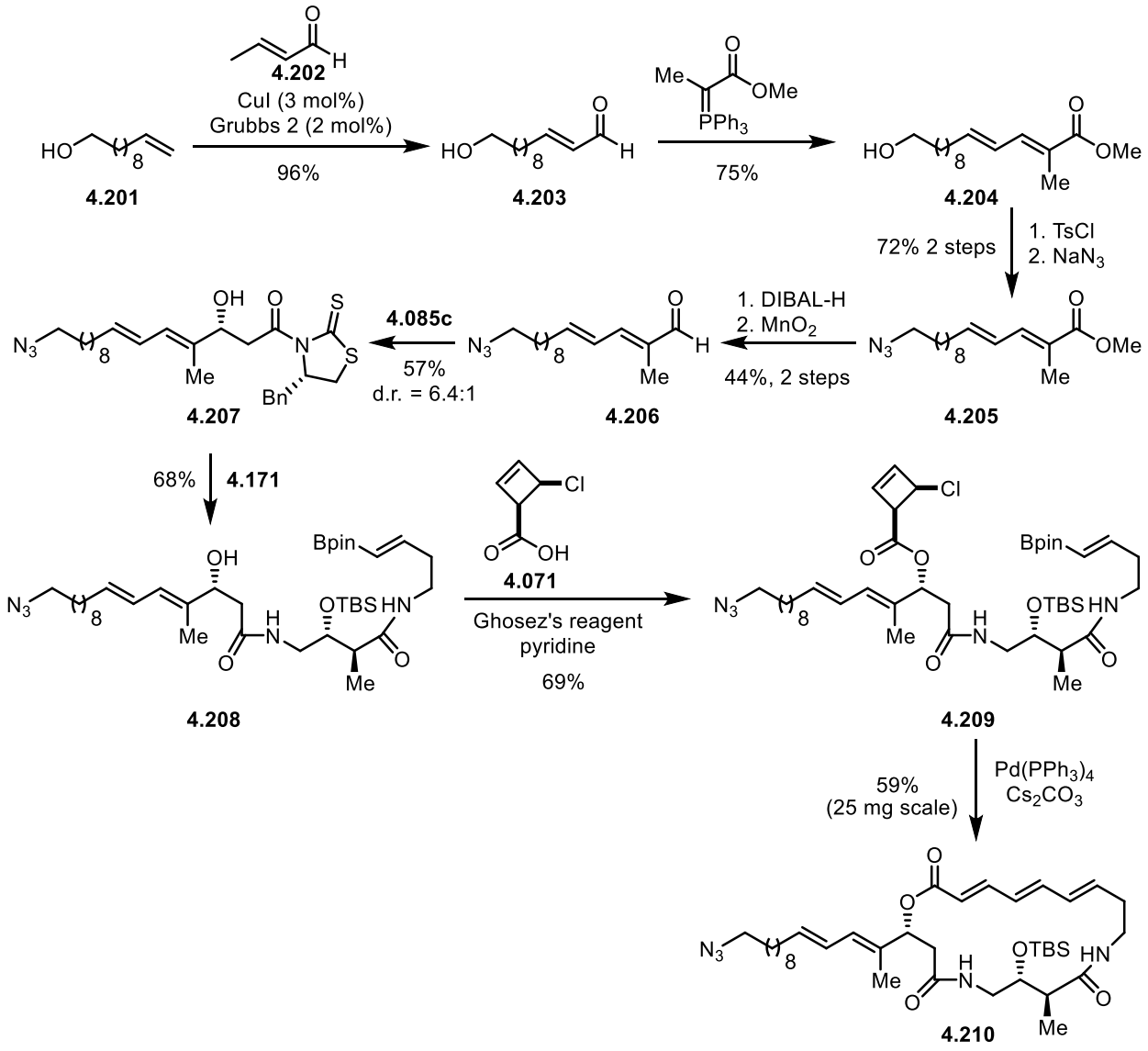


Figure 4.91 Synthesis of macrocycle **4.210**.

The incorporation of biotin was next targeted. Biotin was first activated by N-hydroxysuccinimide **4.211** to hydroxysuccinimide ester **4.212**, which was coupled by amine **4.213** to afford acid **4.214**. The acid **4.214** was further activated to hydroxysuccinimide ester **4.215** (figure 4.92).

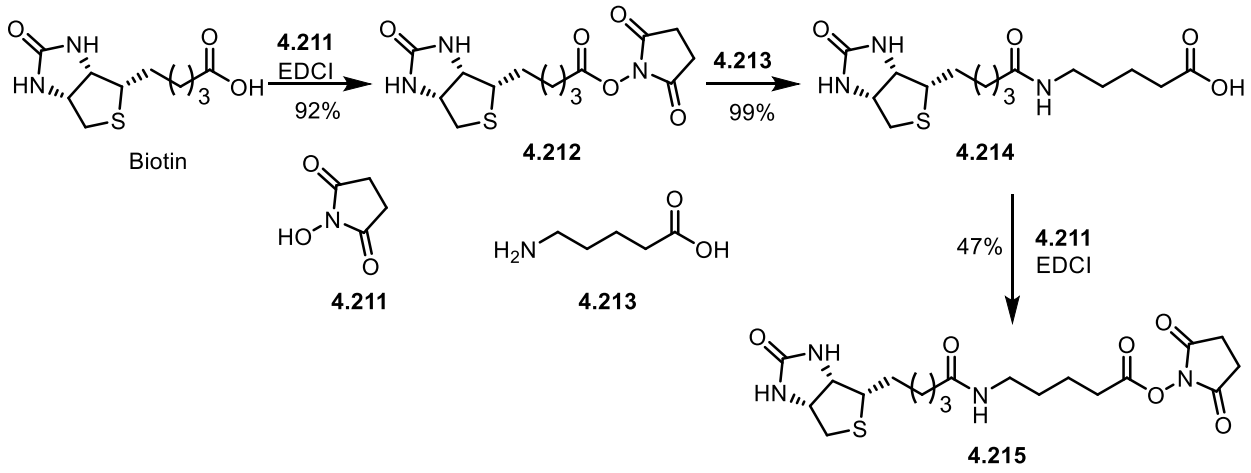


Figure 4.92 Synthesis of **4.215**.

The azidomacrocycle **4.210** was first reduced by triphenylphosphine to afford crude amine **4.216**. However, coupling of **4.216** with **4.215** only delivered product **4.217** in trace amounts (figure 4.93).

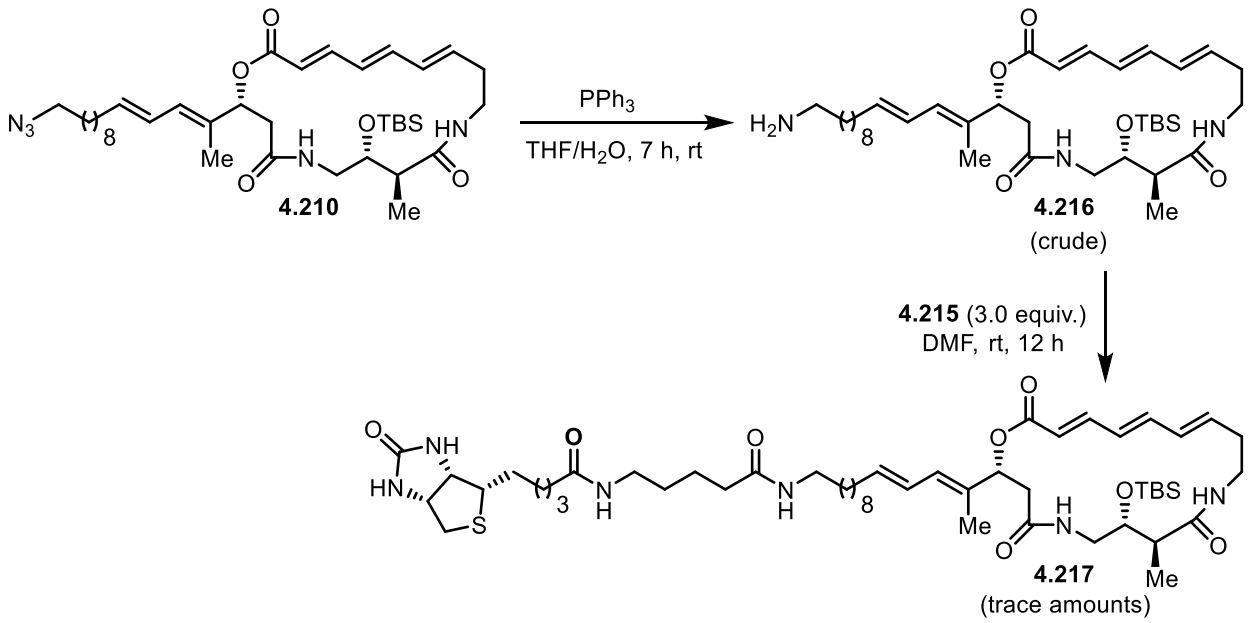


Figure 4.93 Attempted synthesis of **4.217**.

We then opted to use "click" chemistry for the incorporation of biotin on the side chain. Biotin was first functionalized with an alkyne moiety. Commencing with alcohol **4.218**, the crude amine **4.220** was readily obtained after three steps. Coupling of amine **4.220** with hydroxysuccinimide ester **4.212** delivered product **4.221** in 99% yield. The copper catalyzed alkyne azide cycloaddition was then utilized to couple **4.221** and **4.210**, delivering product **4.222** in 53% yield (figure 4.94).[124d] Removal of TBS by TBAF released

probe **4.223**. Initial study showed that probe **4.223** still maintained biological activity. Further application for target identification is currently underway in the lab of Stefan Kubicek.

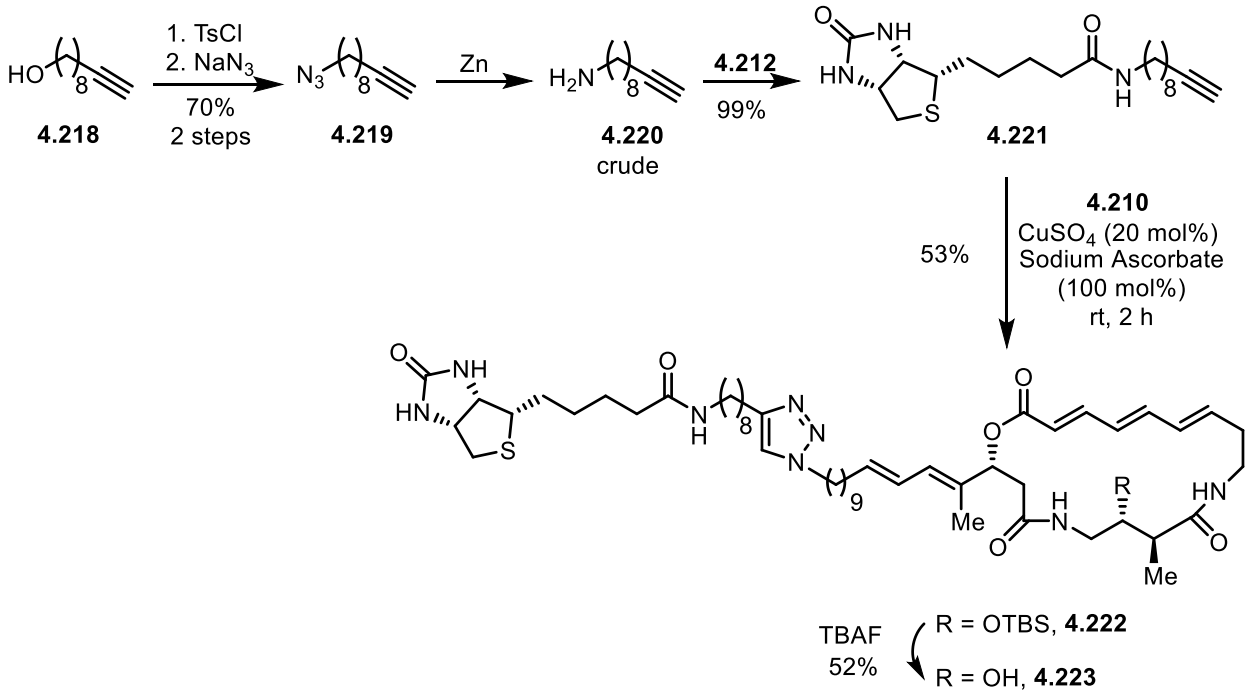


Figure 4.94 Synthesis of biotin-tagged probe **4.223**.

In the meantime, Dr. Guilhem Coussanes synthesized PROTAC-based probes in collaboration with the group of Georg Winter (CeMM, Vienna, Austria) (figure 4.95).[126]

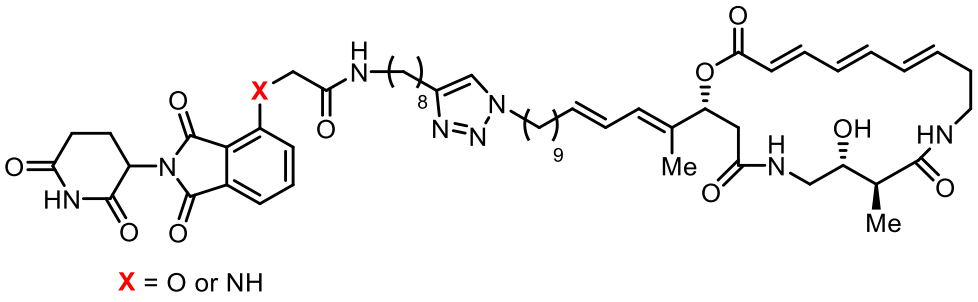


Figure 4.95 PROTAC-based probes.

4.4 Conclusion

We successfully achieved the total syntheses of the complex macrocyclic immunosuppressive natural products FR252921, FR252922 and FR256523 via a carefully designed intramolecular domino Suzuki-

Miyaura macrocyclization/4π-electrocyclic ring opening process. Remarkably, our strategy greatly supersedes more conventional, prior approaches featuring well-established macrolactonization methods which are conducive to deleterious C=C bond isomerization. Further highlights of this work include a novel and high-yielding synthesis of the useful **fragment 2** and the use of the Ghosez's reagent for stereoselective esterification of a pivotal *cis*-chlorocyclobutene carboxylate linchpin. Based on this short, 10-step (longest linear sequence) route, a range of compounds were synthesized and tested in a proliferation assay against *EL4-T-lymphocyte* cells, enabling the establishment of SAR correlations for this compound and the identification of a more potent analogue **FR5**. The biotin and PROTAC-based probes for the cellular target identification were designed and synthesized. Our work will pave the way for further biological studies and development of this fascinating class of secondary metabolites.

4.5 Perspective

4.5.1 Analogues Simplification and Optimization

Our convergent, efficient and derivatization-friendly route to the FR molecules enables the synthesis of analogues quite practical. In the future, we can synthesize C20-demethyl analogue **FR12** and test its effect on the proliferation of *EL4-T-lymphocyte* cells (figure 4.96). Once **FR12** proves to retain the bioactivity, the structure of potential bioactive analogues could be further simplified as **FR13** with both the side chain and the macrocyclic core simplification. The further simplified structures will endow the analogue synthesis more step-economy. Analogues with optimal pharmacological properties could be found as a result of optimizations.

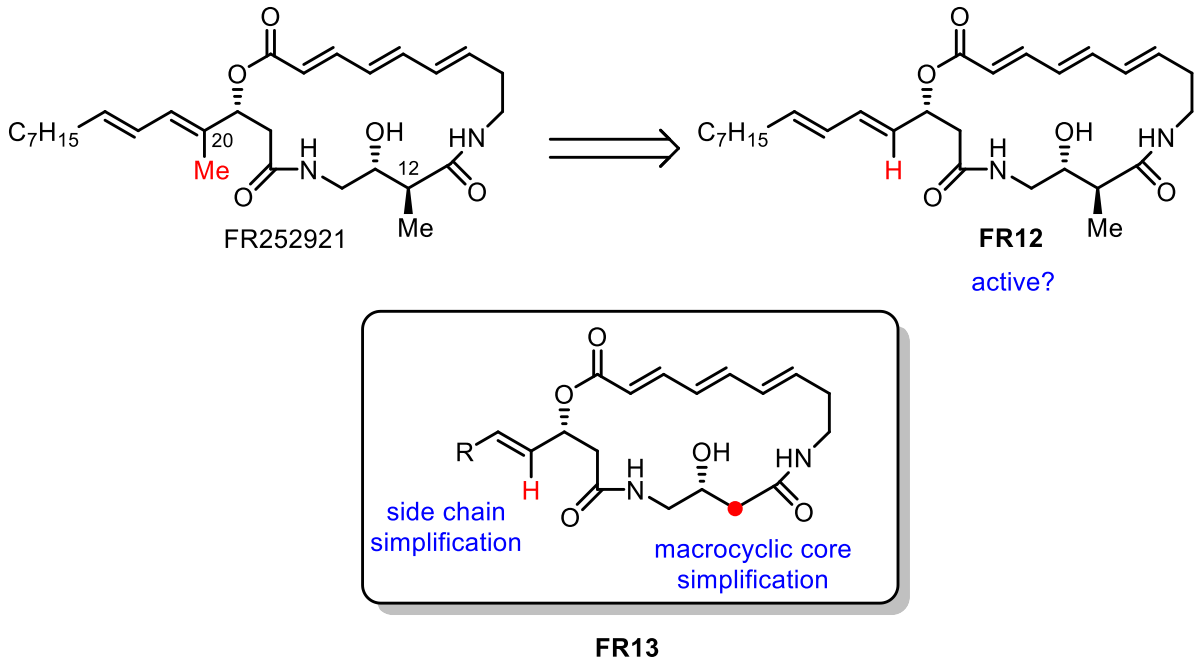


Figure 4.96 Analogues simplification and optimization.

4.5.2 FR252921: An Ammonium Chelator?

The fact that FR252921, obtained from the TBAF deprotection of **4.190a** (figure 4.88), displayed sharp different spectra before and after column chromatography purification is noteworthy. As FR252921 contains hydrogen bond donor moiety (hydroxy group, secondary amide), hydrogen bond acceptor moiety (ester, amide) and a macrocyclic tiene, its interaction with a proper cation species could be possible. Tetrabutylamonium cation, resulted from the work up of TBAF deprotection, was suspected to interact with the FR252921, although we can not rule out other factors such as anions' effect at the moment (figure 4.97). In fact, this postulate was initially supported by the separation of FR252921 using the reverse phase HPLC. When the eluent of acetonitrile + 10% of NH_4OAc (aq.) was used, FR252921 always showed a shoulder peak on the separation spectra. However, the same sample showed a single peak when NH_4OAc (aq.) was not used in the eluent. Can FR252921 be developed as a molecular sensor for ammoniums? Is this chelation effect related to its immunosuppressive bioactivity? Considering ammoniums are widely distributed in the cell and play important roles,[127] further studies on this interesting observation are needed.

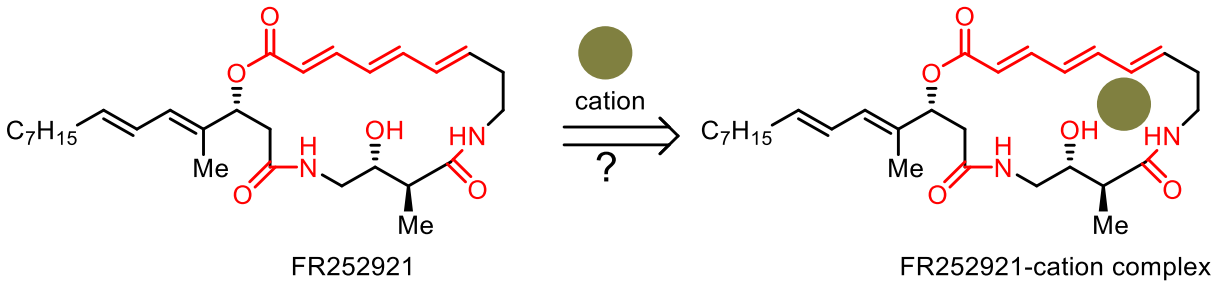


Figure 4.97 FR252921: An ammonium chelator

Chapter 5. Synthetic Efforts towards the Total Synthesis of Cyclamenol A

5.1 Structure and Bioactivity

Cyclamenol A is a 20-membered macrolactam isolated from *Streptomyces spec.* MHW 846 by chemists of the Bayer Corporation in 1994 (figure 5.1).[128] It is a highly unsaturated molecule with seven C=C double bonds, including one *Z*-configured C12-C13 double bond. The two conjugated polyene motifs are disconnected by a C8-C9 single bond, where a hydroxy group is positioned at C9. Its 2D structure was further confirmed by transforming cyclamenol A into derivatives **5.001**, **5.002**, **5.003**, **5.004** and **5.005**. Despite the fact that **5.001** and **5.005** were obtained as crystals in 20 mg and 40 mg respectively, the absolute configuration of C9 and C18 was not established yet.[128]

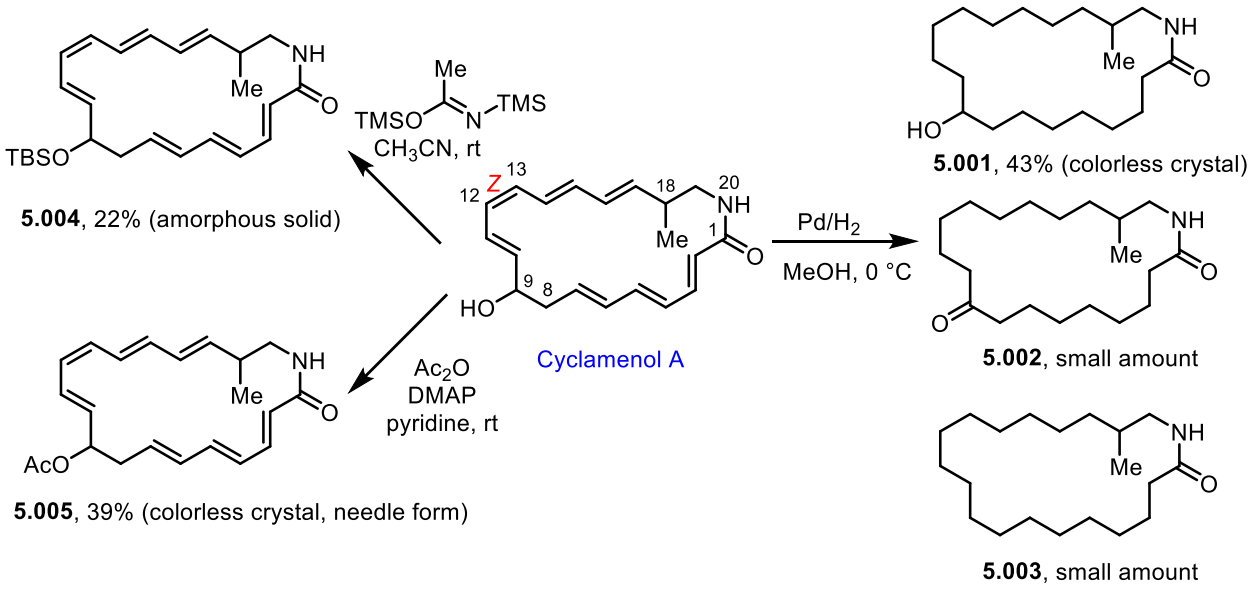


Figure 5.1 Structure and derivatives of cyclamenol A.

Biological studies showed that cyclamenol A was a potent inhibitor for the adhesion of leukocytes to endothelial cells, a process that can be triggered by inflammation, infection and tissue injuries.[128,129] Cyclamenol A blocks this process in an *ex vivo* model, in which a dose of 0.1 mg/kg could significantly reduce the leukocyte adhesion. When cyclamenol A was administered to hamsters with an

experimentally induced cardiac infarct, a dose of 1 mg/kg could reduce the infarct size by 19.0 ± 6.0% before occlusion and 12.2 ± 4.8% before reperfusion.[128] These studies showed that cyclamenol A could potentially be used in the treatment of acute inflammation and auto immune diseases.

5.2 Previous Synthesis

Till now, only the group of Waldmann reported a completed total synthesis of (9*S*,18*R*)-cyclamenol A.[130] Several approaches have been tried to close the 20-membered ring, albeit only one of them culminated in the synthesis of a diastereomer of cyclamenol A (figure 5.2).

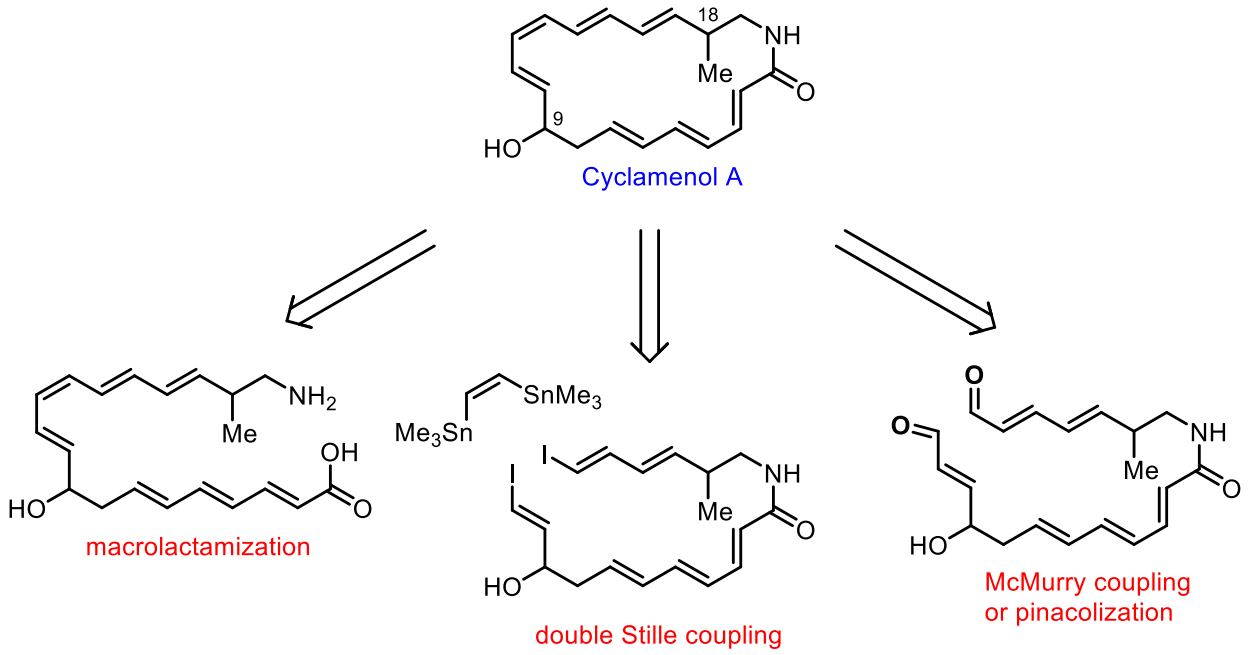


Figure 5.2 Approaches to cyclamenol A by Waldmann *et al.*

5.2.1 First Approach: Macrolactamization

The first approach reported by the Waldmann group was based on a late-stage macrolactamization strategy.[130a] It was envisioned that the 20-membered ring could be formed by an intramolecular amide bond formation from precursor **5.006** (figure 5.3). Disconnection of the C11-C12 bond led to segments **5.007** and **5.008**, which might be coupled together by a Sonogashira reaction. The *Z*-configured C12-C13 double bond was envisaged to result from *cis* reduction of a triple bond in the coupling product. Further disconnections of **5.007** and **5.008** led to segments **5.009**, **5.010**, **5.011** and **5.012**.

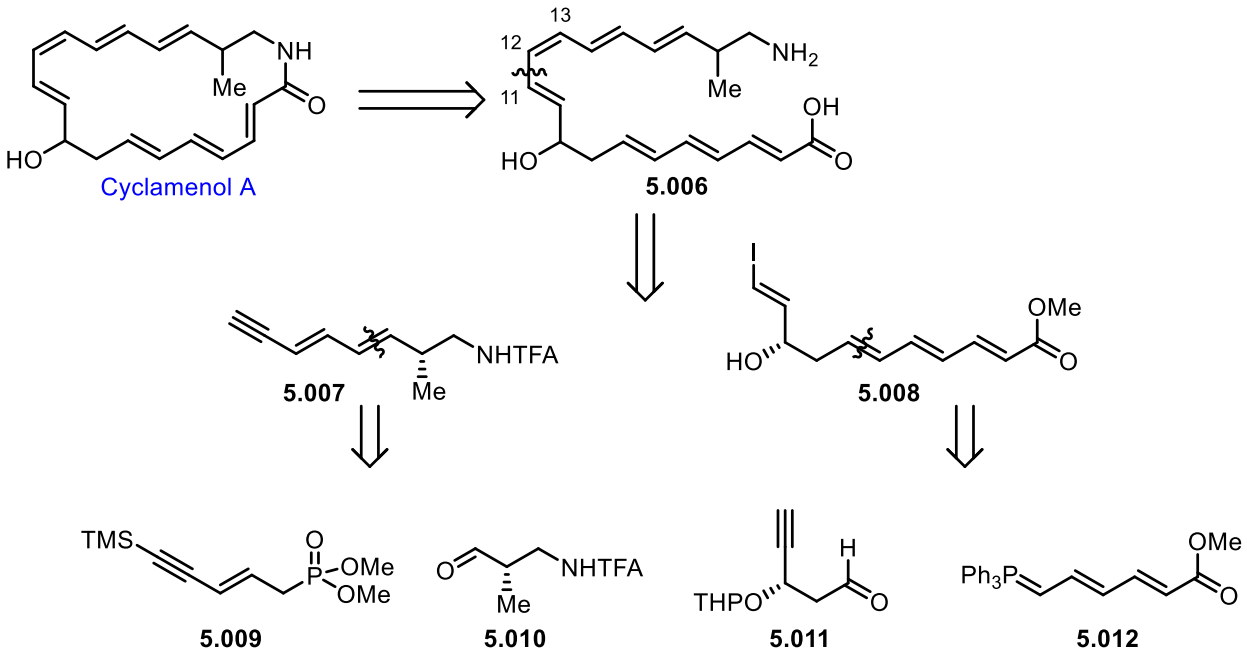


Figure 5.3 Retrosynthesis for the macrolactamization strategy.

Starting from malic acid **5.013**, acetonide **5.014** was readily obtained in 75% to 85% yield (figure 5.4). Reduction of carboxylic acid **5.014** by borane, followed by acidic work up, delivered lactone **5.015**. Then the free hydroxy group was protected as THP ether and further reduction of the lactone afforded hemiacetal **5.016** in 83% yield over two steps. Reaction of **5.016** with Bestmann-Ohira reagent **5.017** readily afforded alcohol **5.018**. Sequential one-pot Swern oxidation and Wittig olefination afforded, after removal of the THP protecting group, trienic alcohol **5.020** in 72% yield over three steps. Stereoselective palladium-catalyzed hydrostannation of **5.020** and subsequent treatment with iodine afforded vinyl iodide **5.008**.

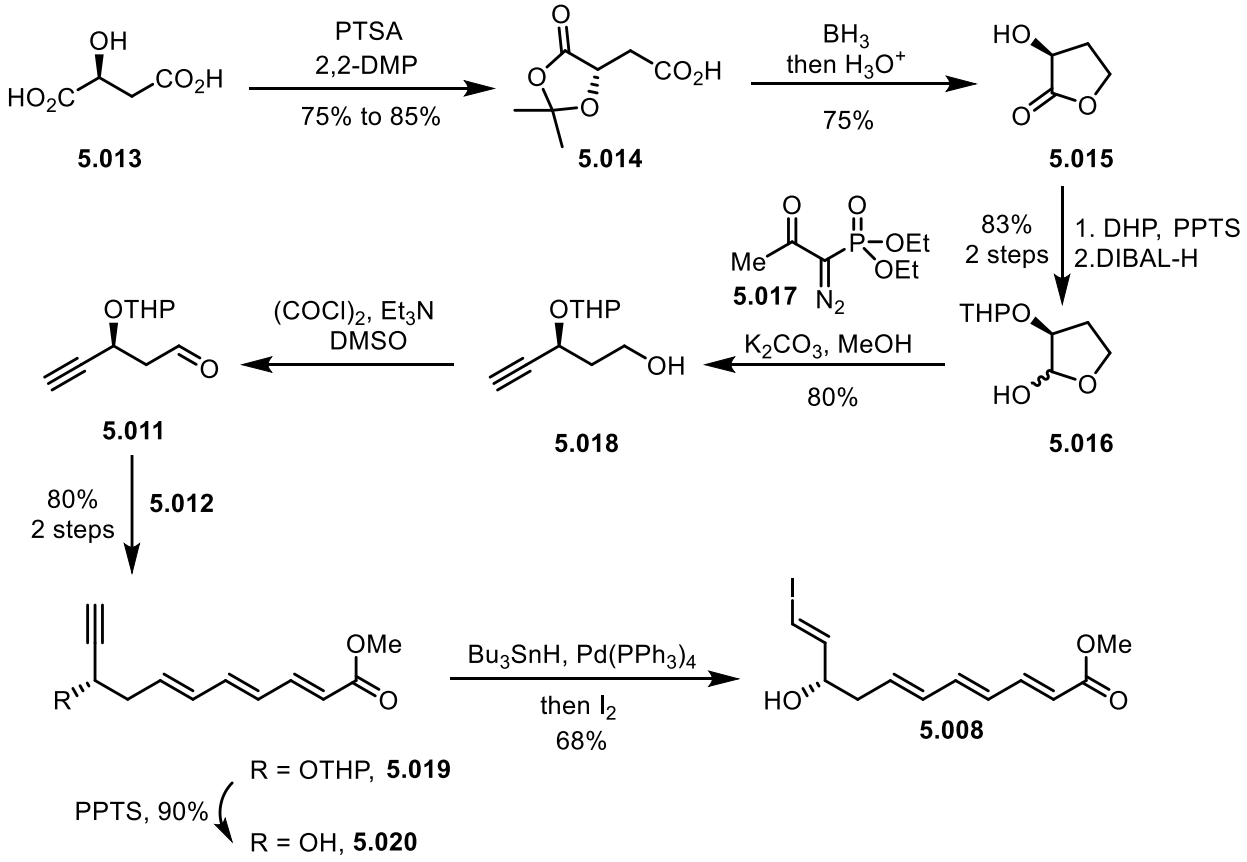


Figure 5.4 Synthesis of segment **5.008**.

Aminolysis of commercially available ester **5.023** afforded amide **5.024** (figure 5.5). **5.024** was readily reduced by borane to amine **5.025**, which was transformed into amide **5.026** in the presence of trifluoroacetic anhydride. Treatment of **5.026** under Swern oxidation conditions delivered the aldehyde **5.010**. Without isolation, the resulting aldehyde was mixed with the lithium salt of phosphonate **5.009**, readily obtained in two steps from (*E*)-1,3-dichloroprop-1-ene **5.021**, to afford amide **5.027**, with an *E*/*Z* ratio of 3:1. The *E/Z* ratio could be increased to 10:1 when isomeric mixtures of **5.027** were treated with catalytic amount of iodine in daylight. At this stage, the pure *E* isomer of **5.027** was separated by column chromatography. TMS deprotection by silver nitrate and potassium cyanide delivered segment **5.007**.

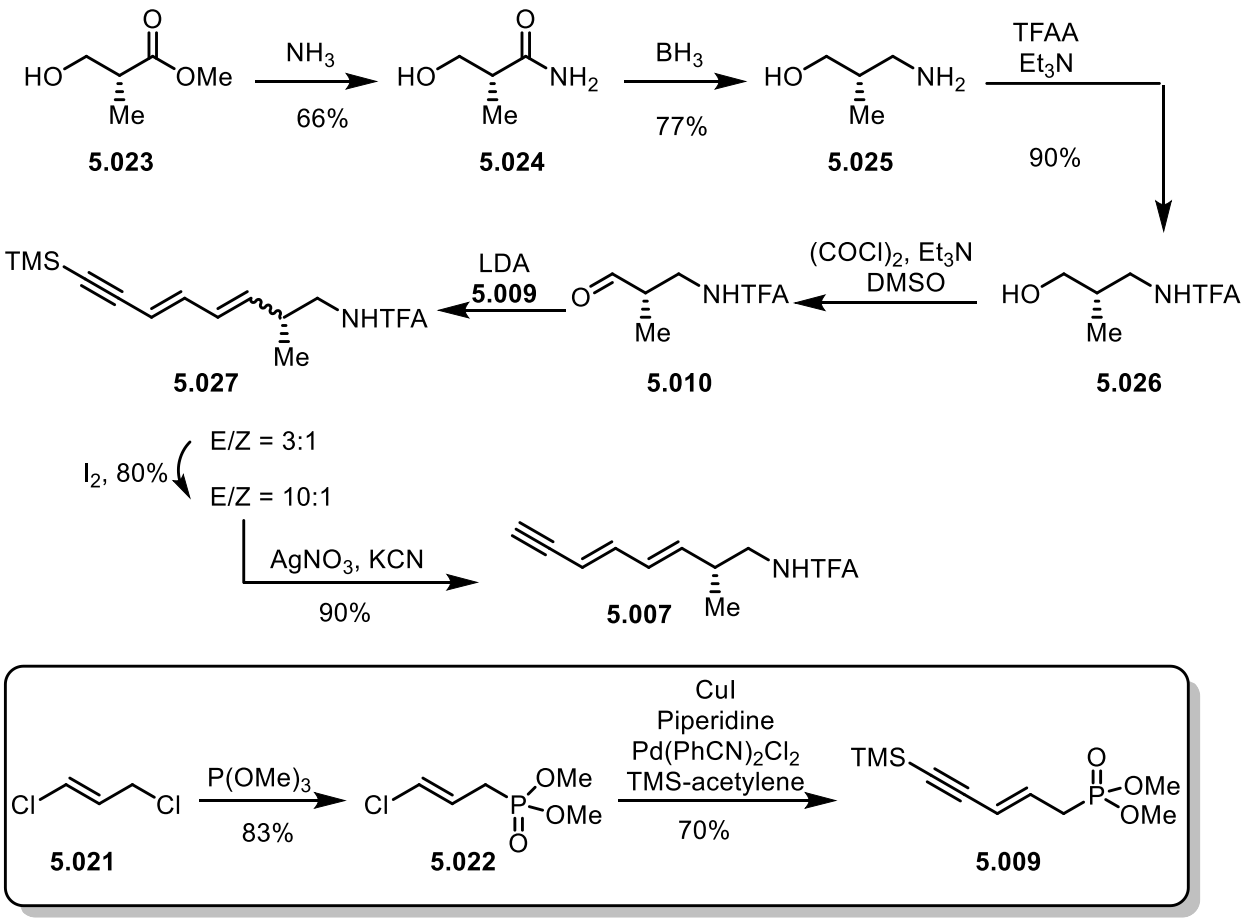


Figure 5.5 Synthesis of segment **5.007**.

The coupling of **5.007** and **5.008** under the Sonogashira reaction conditions readily delivered a fairly stable product **5.028** (figure 5.6). The stereoselective reduction of the triple bond by activated zinc in methanol afforded polyenic amide **5.029**. Treatment of **5.029** with lithium hydroxide released the free amine and acid moieties in the precursor **5.006**. Although various macrolactamization conditions were screened, the acid **5.006** proved entirely reluctant to cyclize and afford cyclamenol A.

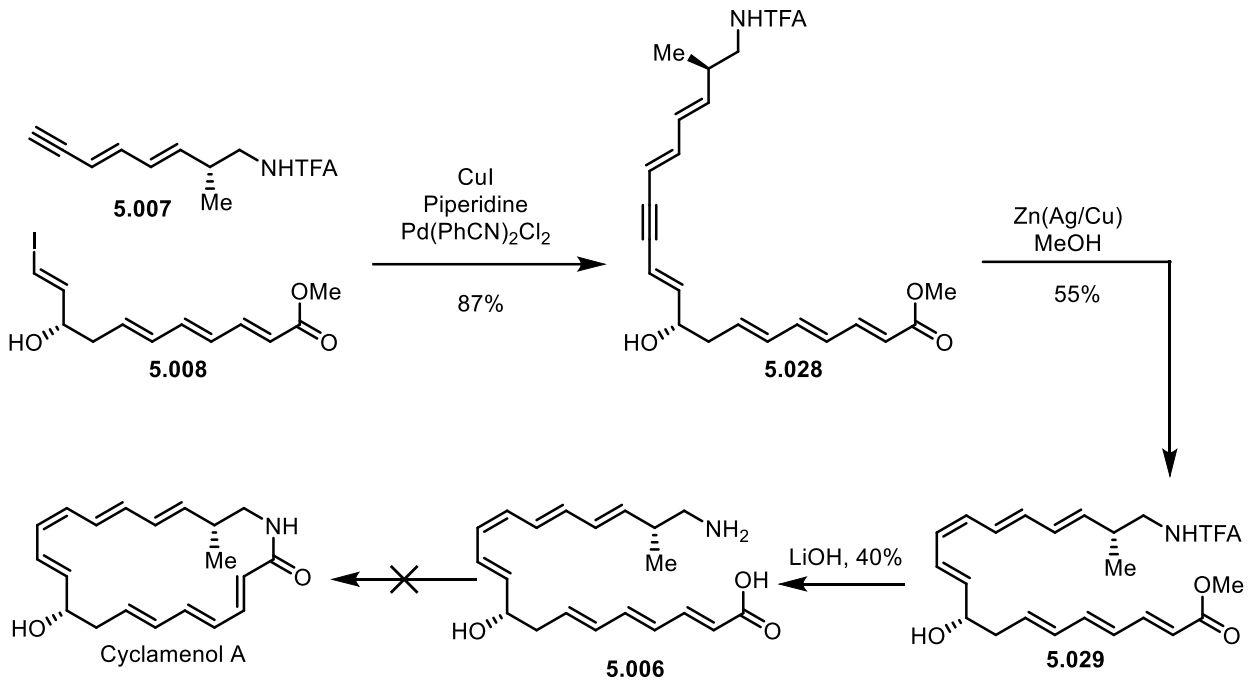


Figure 5.6 Attempt of macrolactamization failed to deliver cyclamenol A.

5.2.2 Second Approach: Double Stille Coupling

The double Stille coupling strategy was then envisioned by Waldmann *et al.* to close the 20-membered ring (figure 5.7).[130b] Carbamate **5.030** was readily obtained from ester **5.023** using a similar route as described in figure 5.5. Treatment of **5.030** under the Swern oxidation conditions, followed by Wittig olefination with phosphonium salt **5.032** afforded carbamate **5.034** after removal of the TMS group. Zirconium mediated stereoselective iodination of **5.034** readily delivered vinyl iodide **5.035**, whose Boc group was further removed to release the free amine **5.036**. Coupling of **5.036** with acid **5.037** (figure 5.4) in the presence of diethyl phosphorocyanidate afforded amide **5.038**. However, the coupling of **5.038** with bis(trimethylstannyl)ethylene **5.039** under a variety of Stille reaction conditions failed to deliver cyclamenol A.

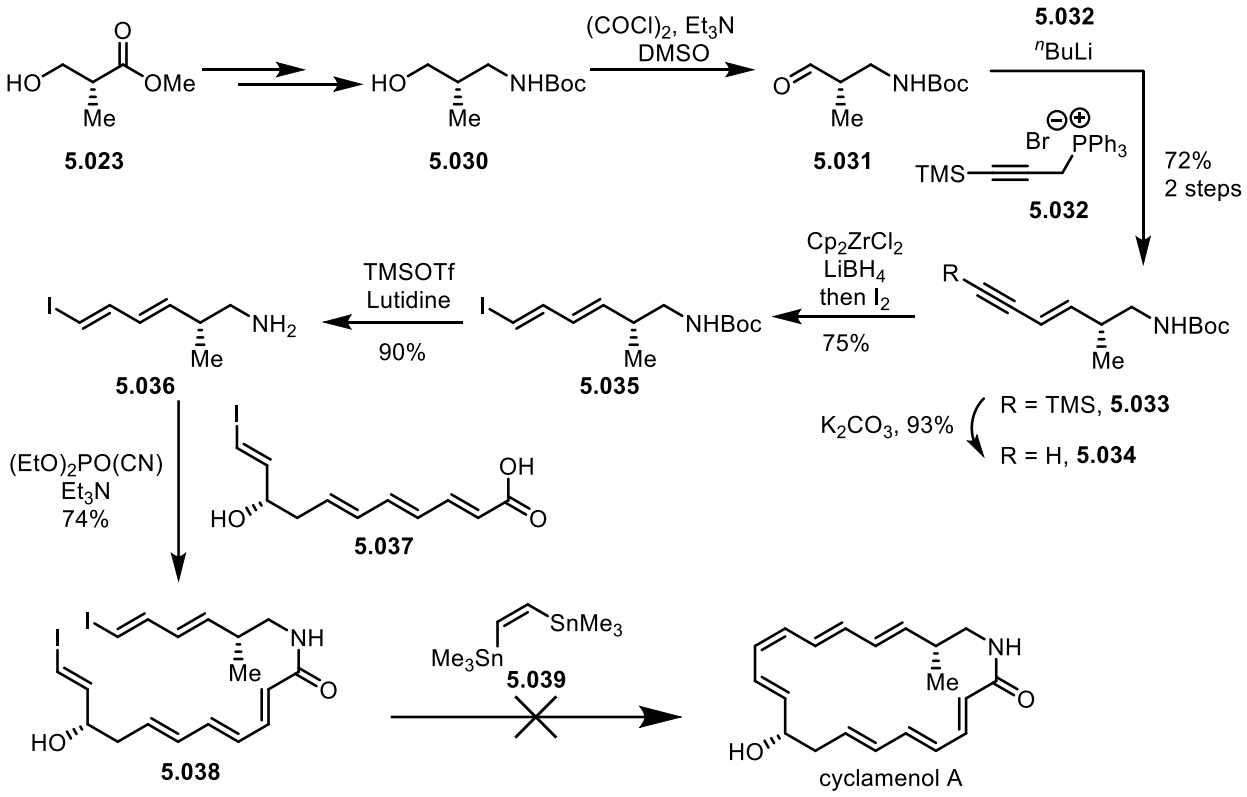


Figure 5.7 Attempt of double Stille coupling failed to deliver cyclamenol A.

5.2.3 Third Approach: McMurry Coupling or Pinacolization Approach

The failure of the two strategies above highlighted the challenges in the construction of the 20-membered ring. In a third trial, Waldmann *et al.* opted for a McMurry coupling or pinacolisation approach from precursor **5.040** to complete the synthesis of the macrocycle (figure 5.8).[130b,130c] Disconnection of the amide bond in **5.040** led to **5.041** and **5.042**, which could be built from segments **5.043**, **5.044**, **5.045**, **5.046** and **5.047**.

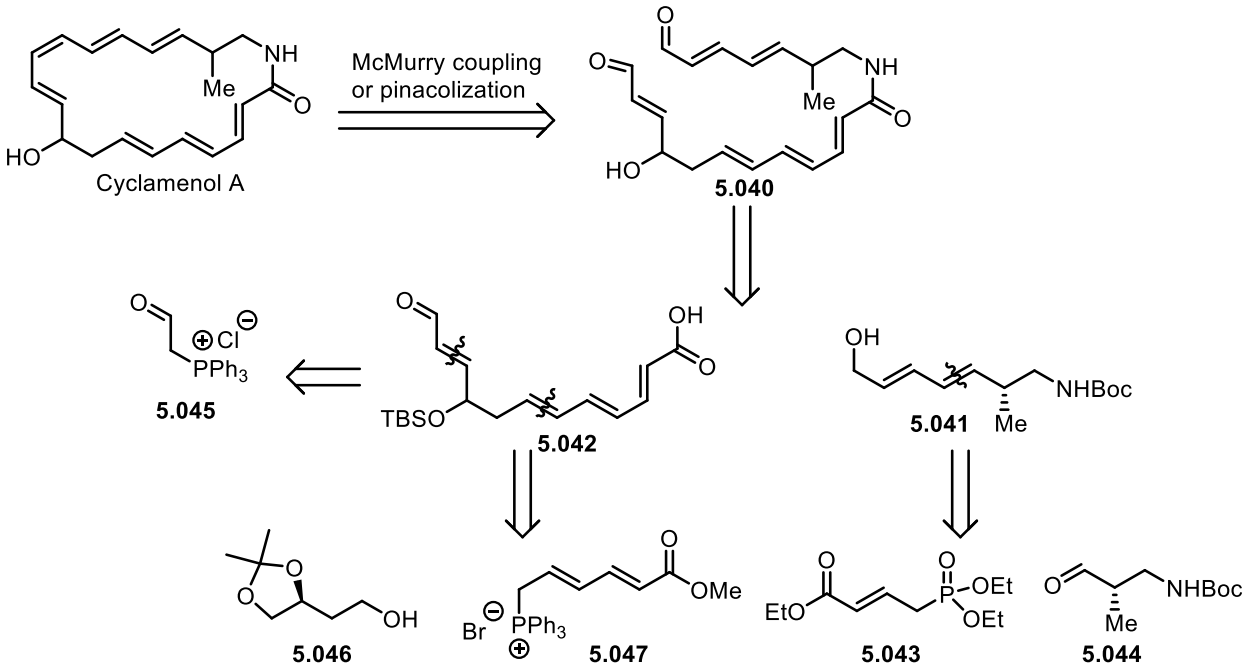


Figure 5.8 Retrosynthesis for the McMurry coupling or pinacolization strategy.

Starting from carbamate **5.030**, aldehyde **5.031** was readily obtained *via* Swern oxidation (figure 5.9). A HWE olefination of **5.031** with phosphonate **5.043** afforded dienic ester **5.048** in 83% yield over two steps. Reduction of the ester by DIBAL-H delivered alcohol **5.049**. Deprotection of Boc group by TFA, followed by a basic work up afforded amine **5.041**.

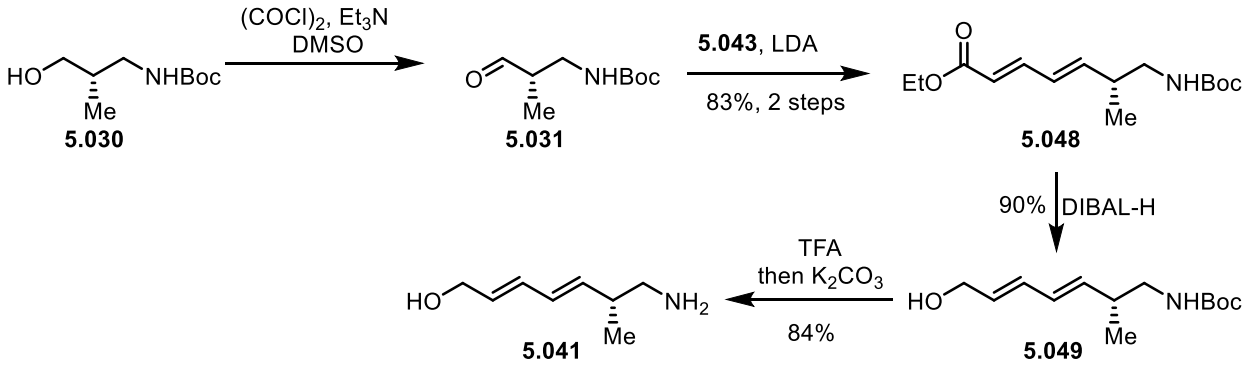


Figure 5.9 Synthesis of **5.041**.

Compound **5.046** was readily obtained from malic acid **5.013** in two steps (figure 5.10). Oxidation of **5.046** to the aldehyde **5.051**, followed by a Wittig olefination delivered trienic ester **5.052** in 85% yield. The ketal group was then removed. The resulting diol was rather unstable and immediately protected by TBS groups to afford bis-silyl ether **5.053**. The most labile TBS group of the primary alcohol was selectively removed

by pyridinium fluoride to deliver alcohol **5.054**. Swern oxidation of alcohol **5.054**, followed by a one pot Wittig olefination readily afforded aldehyde **5.055**. **5.055** was reduced under the Luche reduction conditions, and the resulting alcohol was further protected to deliver THP ether **5.056**. The protection of the resulting alcohol was proved to be necessary as it interfered with the following peptide bond formation step. Hydrolysis of the methyl ester by lithium hydroxide afforded segment **5.057**.

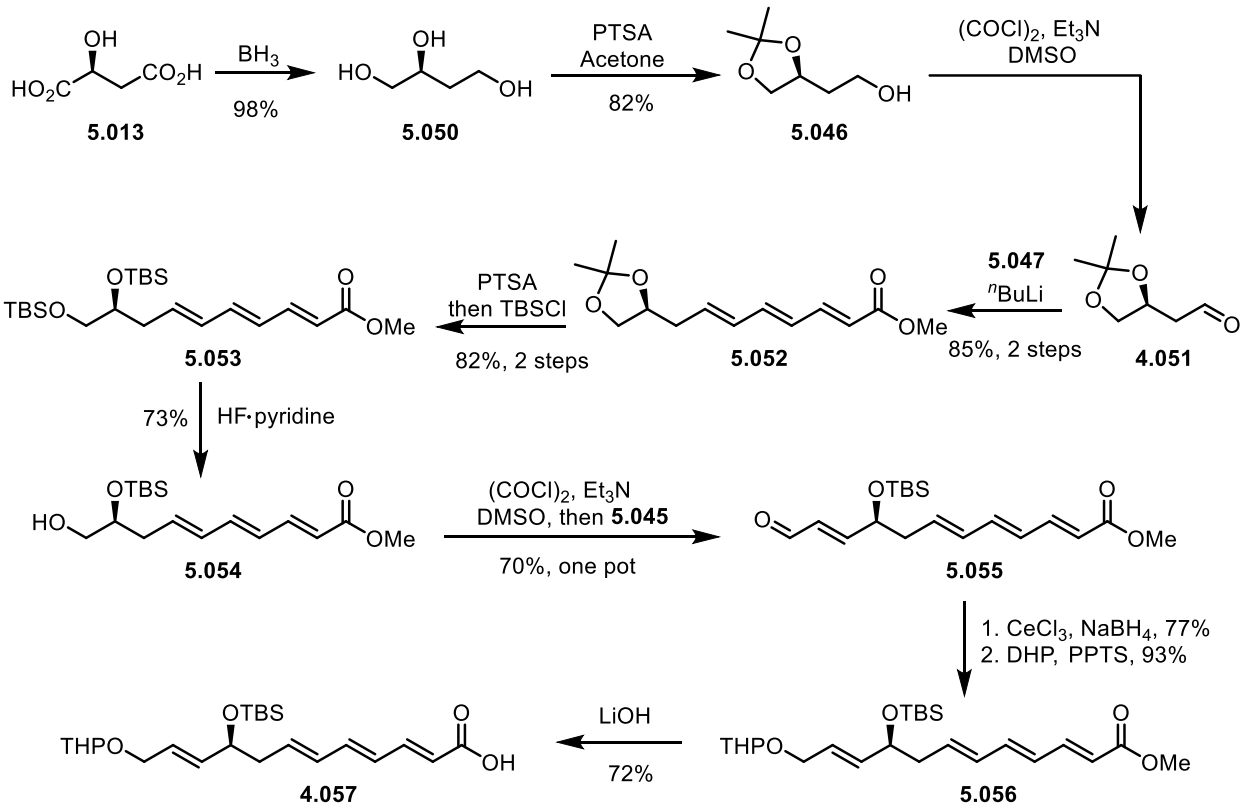


Figure 5.10 Synthesis of segment **5.057**.

5.2.3.1 McMurry Coupling

Acid **5.057** was then coupled with amine **5.041** in the presence of BOPCl, triethylamine and DMAP to deliver amide **5.058** (figure 5.11). The THP group was then removed, and the resulting diol was oxidized to bis-aldehyde **5.059**. However, under a variety of McMurry coupling conditions, the expected 20-membered macrolactam was not formed.[130b]

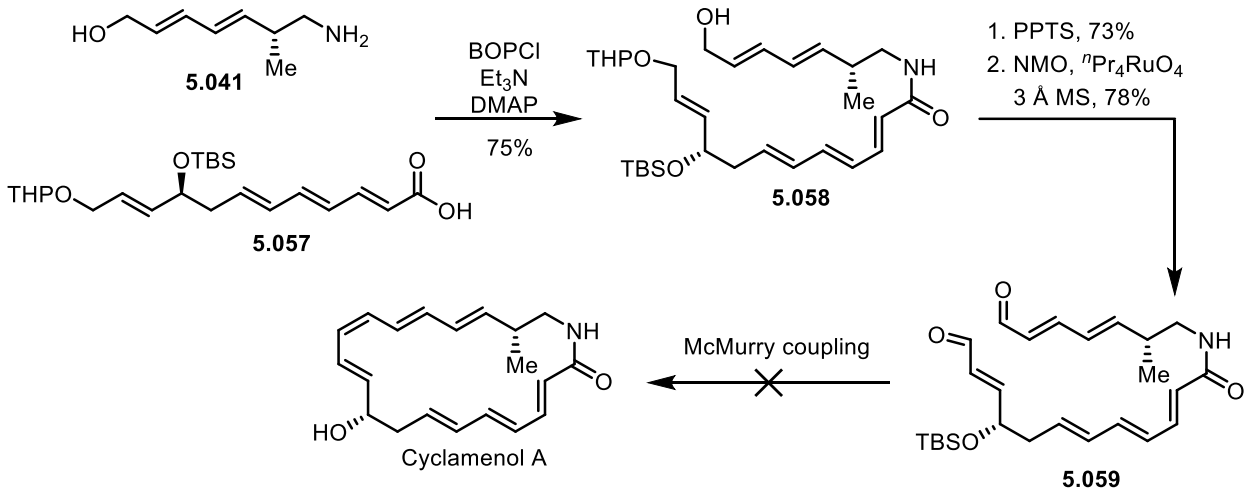


Figure 5.11 Attempted McMurry coupling failed to deliver cyclamenol A.

5.2.3.2 Pinacolization

With the crucial intermediate **5.059** in hand, Waldmann *et al.* then opted for a pinacolisation approach for the closure of the 20-membered ring (figure 5.12). After a number of screening conditions, it was found that the in situ prepared vanadium reagent $[V_2Cl_3(THF)_6][Zn_2Cl_2]$ in THF efficiently promoted the cyclization of the bis-aldehyde to afford cyclic pinacol **5.060**. Diol **5.060** was then converted to the thionocarbonate **5.061** by reaction with thiophosgene. Fragmentation of the thionocarbonate **5.061** generated a TBS-protected cyclamenol A (not shown), which proved to be rather sensitive to acids and bases. Numerous attempts of desilylation led to the decomposition of the TBS-protected cyclamenol A. Alternatively, the TBS group in **5.061** was first removed by TBAF to afford intermediate **5.062**, although the yield was only 26%. The fragmentation of the thionocarbonate in the presence of phospholidine **5.063** at low temperature released the *Z*-configured C12-C13 double bond. However, the optical rotation of the synthesized product was in sharp disagreement with that of the isolated sample. Therefore, the absolute configuration at C9 and C18 remains a mystery to date. [130b,130c]

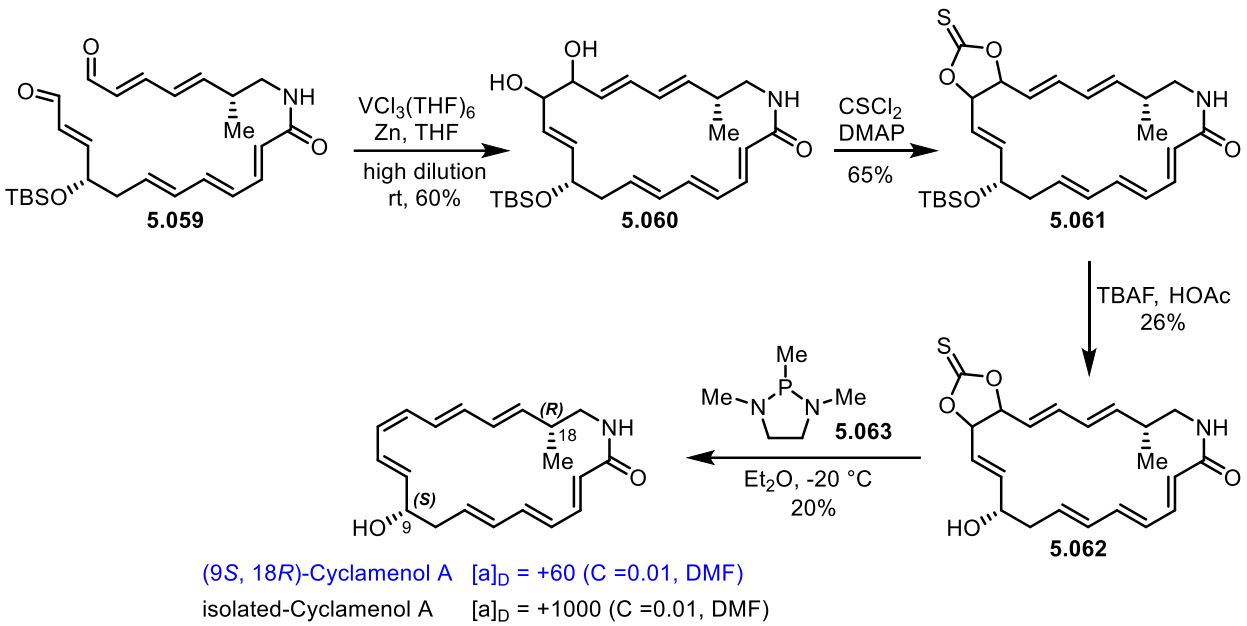


Figure 5.12 Ring closure by a pinacolization approach.

5.3 Synthetic Efforts towards Cyclamenol A

This work was carried out in collaboration with Dr. Guilhem Coussanes.

5.3.1 First Approach: Suzuki-Miyaura Macrocyclization/4π-Electrocyclic Ring Opening

5.3.1.1 Retrosynthesis

Encouraged by the successful application of the Suzuki-Miyaura macrocyclization/4π-electrocyclic ring opening in the synthesis of an (*E*,*E*,*E*)-trienic macrolactone unit (chapter 4), we envisioned that the 20-membered ring of cyclamenol A could be constructed in a similar fashion from precursor **5.064** (figure 5.13). Disconnection of the amide bond in **5.064** led to *cis*-chlorocyclobutene acid **5.065** and azide **5.066**. **5.066** was expected to be constructed from phosphonate **5.067** and aldehyde **5.068** using a HWE reaction. **5.068** was synthesized by a Suzuki-Miyaura coupling of Weinreb amide **5.070** and boronic ester **5.069**, both were readily available from acid **5.065** and chiral alcohol **5.071** respectively. This synthetic route was quite convergent, as cyclamenol A was evenly disconnected to three 5-carbon atoms units: **5.065** (X2), **5.067** and **5.069**.

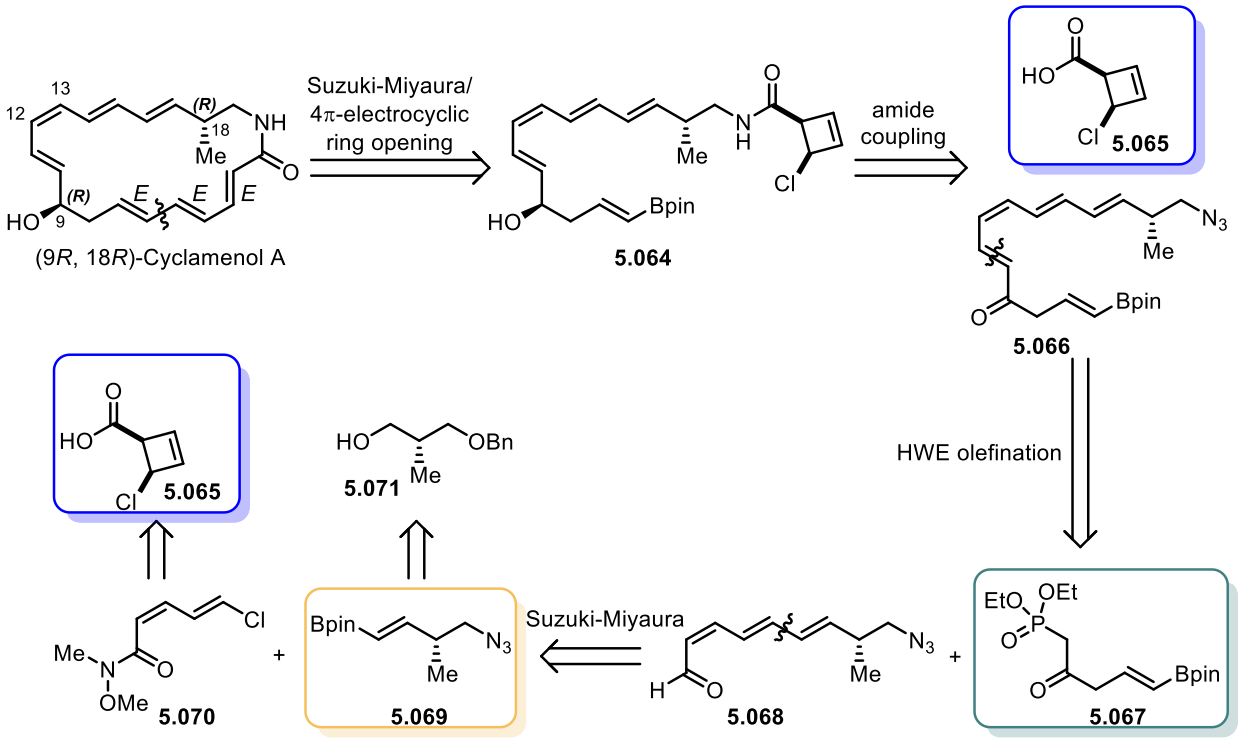


Figure 5.13 Retrosynthesis of cyclamenol A.

5.3.1.2 Synthesis of Fragment 5.070

The synthesis of Weinreb amide **5.070** was straightforward. Ring opening of bicyclobutenelactone **5.072** by dry hydrogen chloride led to *cis*-chlorocyclobutene acid **5.065** in 83% yield (figure 5.14). Microwave irradiation of acid **5.065** at 100 °C for 1 h afforded acid **5.073**, which was > 95% purity by ^{1}H NMR. The crude acid **5.073** was transformed into the Weinreb amide **5.070**. Although the reaction was clean by TLC, **5.070** was obtained in 25%-40% yield due to its volatility.

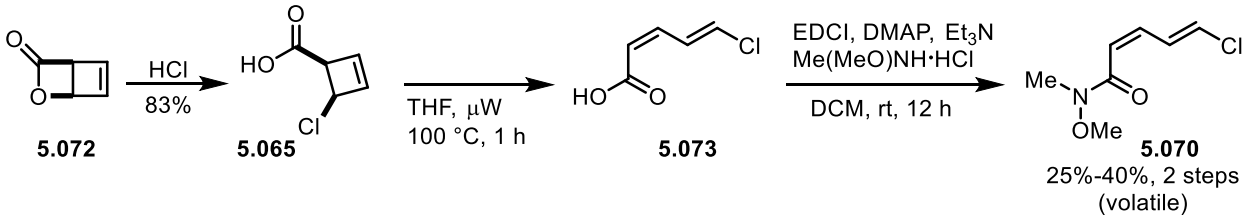


Figure 5.14 Synthesis of **5.070**.

5.3.1.3 Synthesis of Fragment 5.069

The enantiomerically pure alcohol **5.071** was received as a gift in bulk amount (500 g, 98% ee) from company Novartis (figure 5.15). Swern oxidation of **5.071** readily afforded aldehyde **5.074**. A two-step Corey-Fuchs reaction was utilized to deliver alkyne **5.075**.[131] The removal of benzyl group in **5.075** by DDQ led to alcohol **5.076**, which proved to be quite volatile. Therefore, **5.075** was converted to vinyl boronic ester **5.077** in the presence of Schwarz reagent, pinacolborane and triethylamine.[132] Removal of the benzyl group, followed by conversion of the hydroxy group to tosylate, then azide, led to product **5.069**. The whole synthetic route consisted of seven steps, the overall yield was 16% without much optimization.

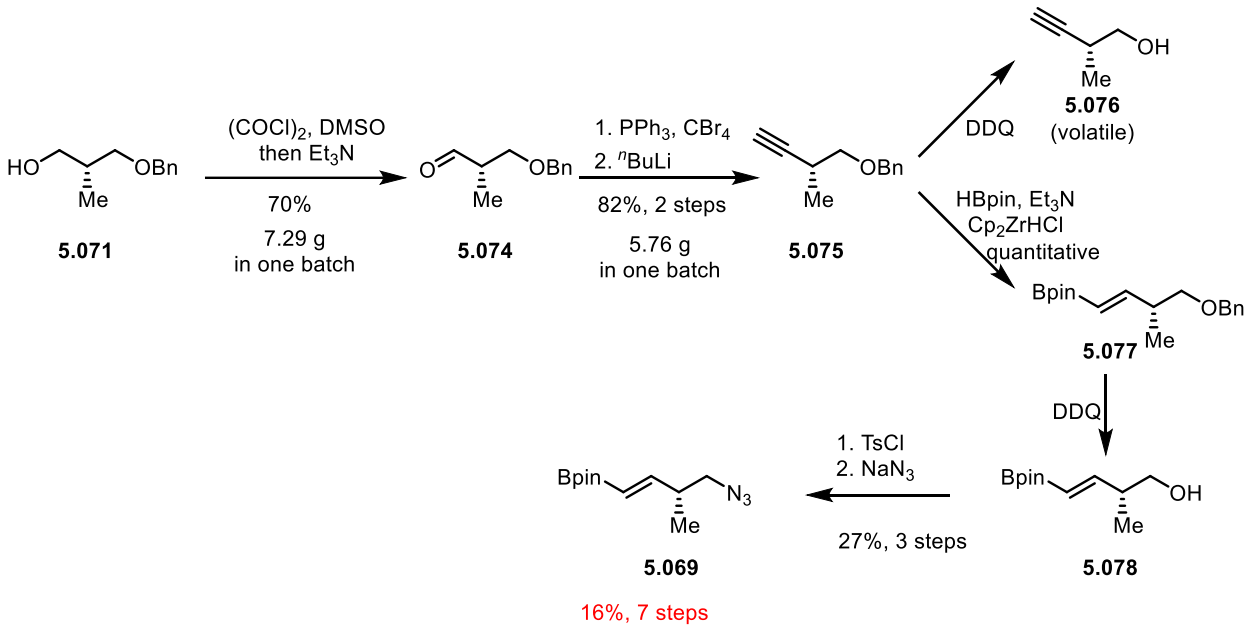


Figure 5.15 Synthesis of fragment **5.069**.

5.3.1.4 Synthesis of Fragment 5.067

Originally, we planned to use aldehyde **5.083** as a key building block for the synthesis of phosphonate **5.084** (figure 5.16). Protection of the commercially available alcohol **5.079** afforded TBS ether **5.080**. Hydroboration of alkyne delivered boronic ester **5.081**. Removal of TBS protecting group released alcohol **5.082**. However, the oxidation of alcohol **5.082** either under the Dess-Martin oxidation conditions or the Swern oxidation conditions, proved to be tricky.[133] In both conditions, the alcohol **5.082** was readily consumed, however, aldehyde **5.083** was never isolated cleanly. It seems that the aldehyde **5.083** is quite sensitive and decomposed during the reaction or work up.

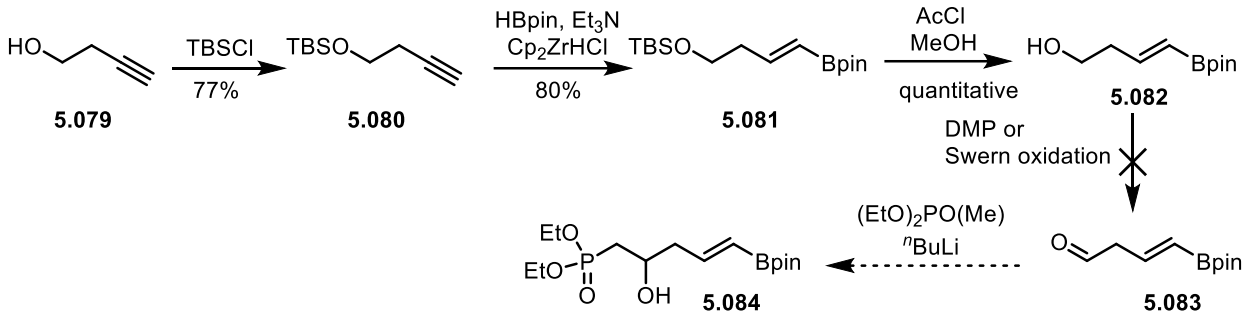


Figure 5.16 Attempt of synthesis of phosphonate **5.084**.

A second synthetic route was attempted. The nucleophilic ring opening of epoxide **5.085** by TMS-acetylene **5.086** readily delivered alcohol **5.087** in 90% yield (figure 5.17). Then the protection of hydroxy group as TBS ether, followed by the removal of terminal TMS group afforded alkyne **5.088**. Hydroboration of **5.088** readily delivered vinyl boronic ester **5.089**. The attempted Arbuzov reaction on **5.089** only resulted the recovery of starting material.[134] Then the TBS group was removed under acidic conditions to release alcohol **5.091**. However, Arbuzov reaction failed again on substrate **5.091**. Oxidation of alcohol **5.091** by Dess-Martin reagent only delivered trace amount of ketone **5.093**.

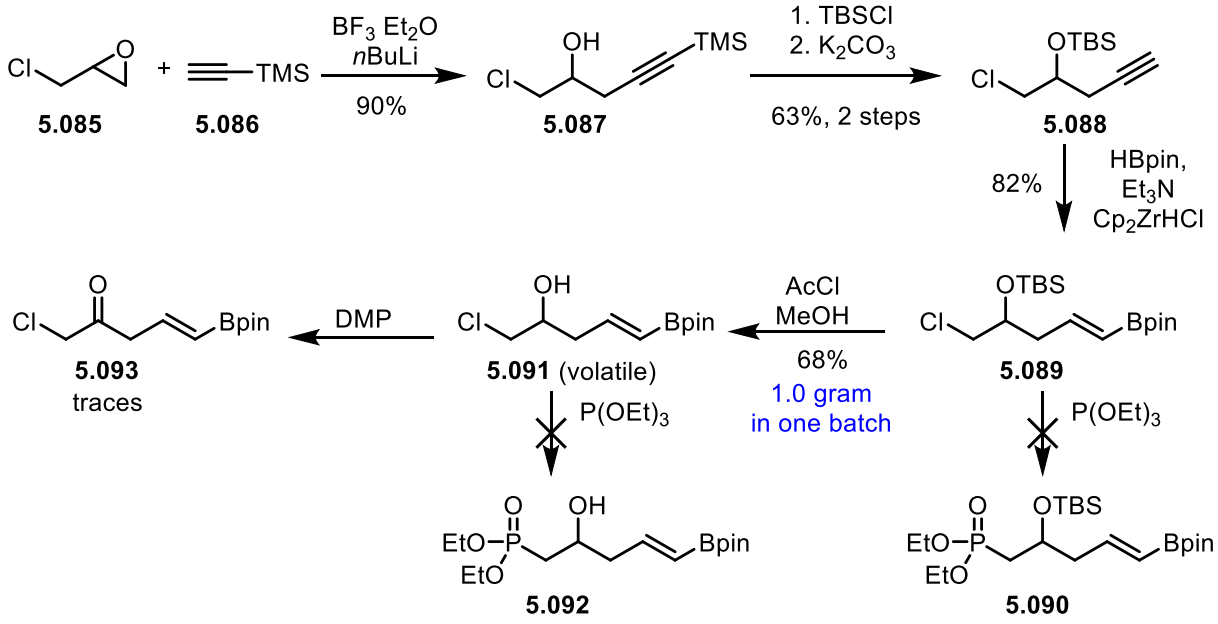
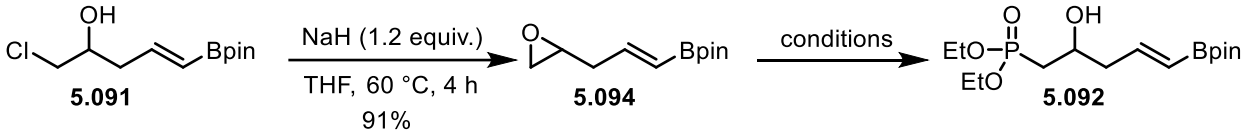


Figure 5.17 Attempt of synthesis of phosphonates.

The phosphonate **5.092** was therefore synthesized by another route (table 5.18). Treatment of β chloro alcohol **5.091** with sodium hydride at 60 °C for 4 h readily afforded epoxide **5.094** in 91% yield. The use of diethoxymethylphosphonate as the nucleophile under anionic conditions for the ring opening of epoxide

5.094 allowed the isolation of **5.092** in 31% yield. Alternatively, **5.092** could be obtained in 67% yield in the presence of zinc chloride as a Lewis acid.[135]



Entry	Conditions	Comments
1	$(EtO)_2P(O)Me$ (3.0 equiv.), ^nBuLi (3.0 equiv.) $BF_3{\cdot}Et_2O$ (5.0 equiv.), THF, -78 °C, 1.5 h	**5.092** (31%)
2	$ZnCl_2$ (1.2 equiv.), $P(OEt)_3$ (1.2 equiv.) Neat, rt, 5 h	**5.092** (67%)

Table 5.18 Synthesis of phosphonate **5.092**.

Even though phosphonate **5.092** was successfully obtained, the whole synthetic route was a bit long (7 steps, 19% yield). Later, the route was shortened to 4 steps (figure 5.19). The ring opening of epichlorohydrin **5.085** by the vinyl Grignard reagent led to alcohol **5.096** in 80% yield. An olefin cross metathesis of **5.096** with vinyl boronic ester **5.097** afforded alcohol **5.091**.[136] The phosphonate **5.092** was obtained in two steps from **5.091** following the same transformation as above (table 5.18). The overall yield of **5.092** was increased to 34%.

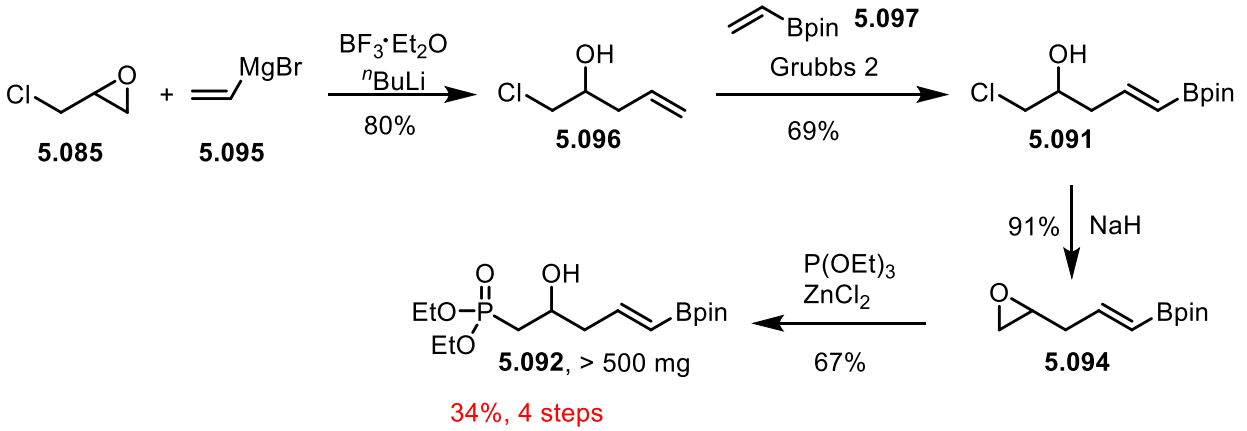
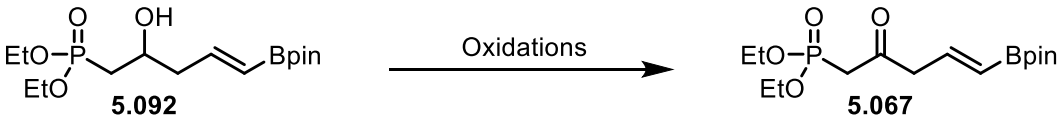


Figure 5.19 Optimized route to phosphonate **5.092**.

With sufficient amount of **5.092** in hand, the oxidation of the free hydroxy group was tried. However, this transformation proved to be quite challenging. Under many conditions, the decomposition of product **5.067** or incomplete conversion was observed (table 5.20).

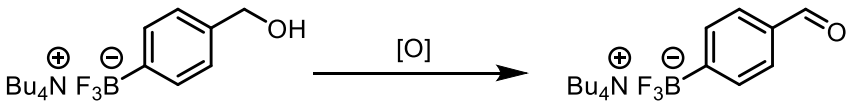


5.092 **5.067**

Entry	Oxidations	Comments (by ^{1}H NMR)
1	$(COCl)_2$, DMSO, Et_3N, -78 °C to rt, DCM	**5.092**
2	PCC, DCM, rt	decomposition
3	PCC, DMF, rt	**5.092**
4	TPAP, NMO, DCM, rt	**5.092**
5	DMP, DCM, 0 °C to rt	decomposition

Table 5.20 Attempt of synthesis of **5.067**.

In fact, boronic esters are generally incompatible with oxidative conditions. In order to address this issue, novel boron reagents have been developed recently. The group of Molander demonstrated that organotrifluoroborates were stable enough under various oxidative conditions. As an example, borate **5.098** was readily oxidized to **5.099** in high yield under three different sets of conditions (table 5.21).[137]



5.098 **5.099**

entry	conditions	Isolated yield of 5.099
1	1%TPAP, NMO	91%
2	Swern oxidation	90%
3	Dess-Martin oxidation	86%

Table 5.21 Oxidation of organotrifluoroborate **5.098**.

In addition, N-methyliminodiacetic acid (MIDA) boronates have been developed by the group of Burke as important building blocks and are capable of undergoing various transformations, including oxidations.[138] For instance, MIDA boronate **5.100** was readily oxidized to the acid **5.101** in the presence of chromium

trioxide and sulfuric acid. Alternatively, under Swern oxidation conditions, the corresponding aldehyde **5.102** was formed (figure 5.22).[138a]

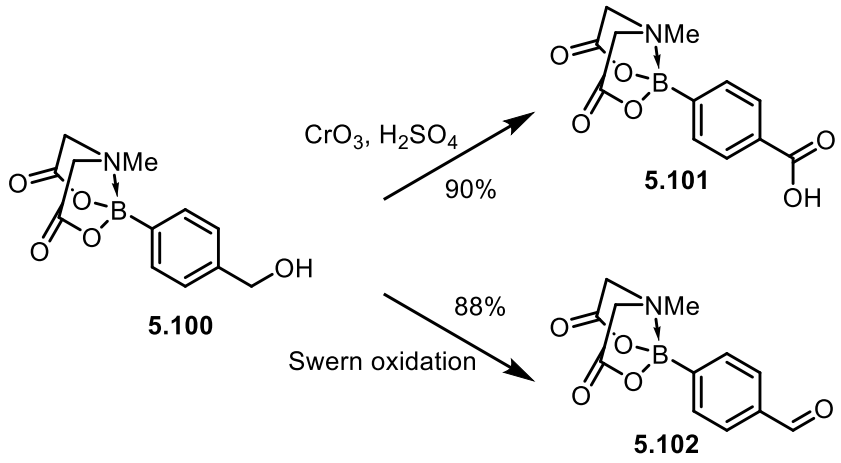


Figure 5.22 Oxidation of MIDA boronate **5.100**.

The sharp difference between MIDA boronates and pinacolboronic esters under oxidative conditions was demonstrated in the work of David M. Perrin *et al.* (figure 5.23).[139] For instance, the dihydroxylation of vinyl MIDA boronate **5.103** by osmium tetroxide delivered diol **5.104** without any impingement on the MIDA boronate motif. However, under the same conditions, the pinacolboronic ester **5.105** was oxidized preferentially to ketone **5.107** via a putative C-B bond oxidized intermediate **5.106**.[139]

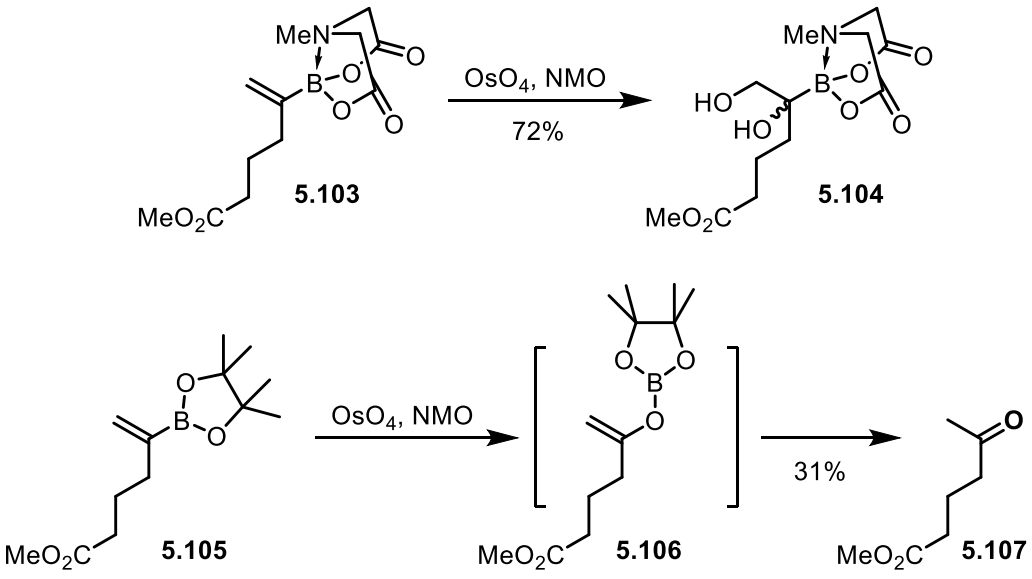


Figure 5.23 Instability of pinacolboronic esters under oxidative conditions.

Inspired by these results, we assumed that the occupation of the vacant orbital of boron atom might be crucial for the success of the oxidation (figure 5.24).

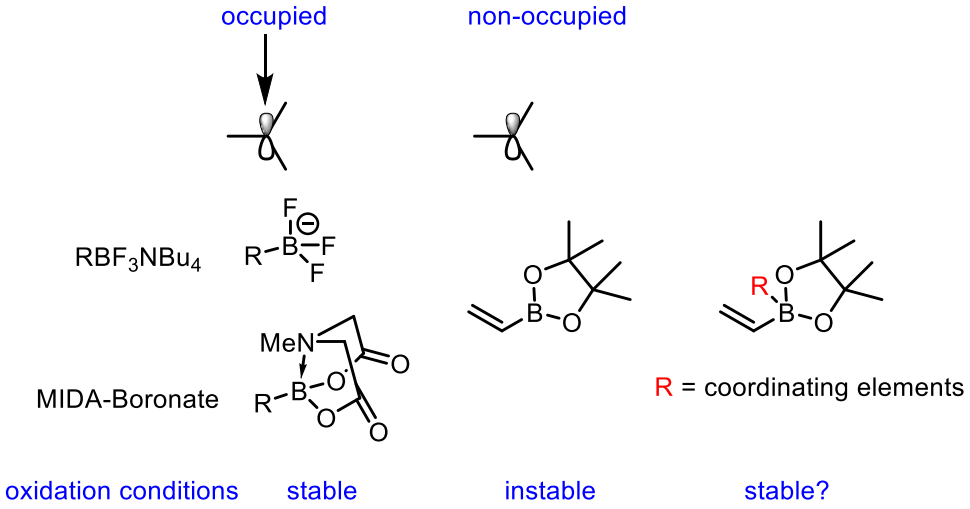
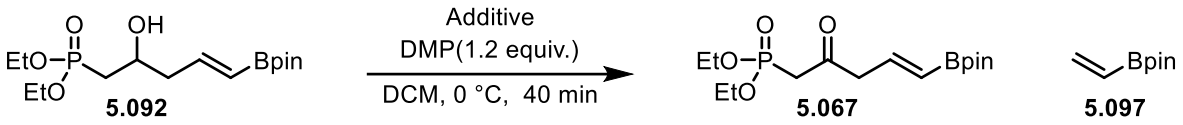


Figure 5.24 Stability of boron reagents towards oxidations.

The stability of pinacolboronic ester towards oxidation conditions could be increased if a suitable coordinating element occupied the vacant orbital of boron atom. With this idea in mind, we screened the conditions again for the oxidation of **5.092** (table 5.25). The Dess-Martin reagent was chosen as the oxidant due to its mild reaction conditions.[133a] When TBAF was used as an additive, the oxidation only resulted in decomposition (entry 1). However, with vinylpinacolboronic ester **5.097** as an additive, the reaction cleanly led to product **5.067** (entry 2). Further decreasing the amount of **5.097** to 2.5 equivalent did not influence the reaction (entry 3). However, with only 1.0 equivalent of **5.097**, incomplete conversion was observed (entry 4). In the absence of **5.097**, decomposition was the only observed result (entry 5). These experiments demonstrated the crucial role of vinylboronic ester **5.097**, which could act as a sacrificing reagent in the oxidative conditions although we do not have convincing evidence. The purification of **5.067** by column chromatography on silica gel resulted in its decomposition. Therefore the crude phosphonate **5.067** was used for the following HWE olefination.



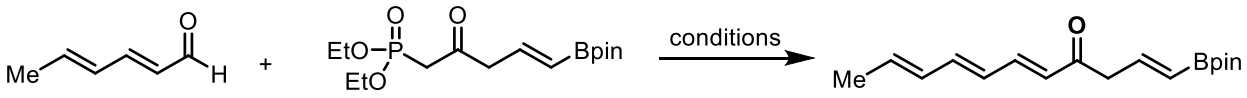
5.092 **5.067** **5.097**

Entry	Additive	Comments (by ^{1}H NMR)
1	TBAF (10 equiv.)	Decomposition
2	**5.097** (5.0 equiv.)	Full conversion, **5.067**
3	**5.097** (2.5 equiv.)	Full conversion, **5.067**
4	**5.097** (1.0 equiv.)	59% conversion, **5.067**
5	**5.097** (0 equiv.)	Decomposition

Table 5.25 Synthesis of fragment **5.067**.

5.1.3.5 Attempted Synthesis of 5.066

To optimize the conditions of HWE olefination, model aldehyde **5.108** was used. However, under various conditions,[140] the only observed result was the decomposition of phosphonate **5.067**. Crude ^{1}H NMR showed that **5.067** easily underwent deboronation under these conditions.



5.108 **5.067** (crude) **5.109**

Entry	Conditions	Comments
1	LiCl, DBU, CH_3CN, rt	Decomposition
2	NaH, THF, rt	Decomposition
3	$Ba(OH)_2$, THF/H_2O (40:1), rt to 50 °C	Decomposition
4	Cs_2CO_3, ^{i}PrOH, rt	Decomposition

Table 5.26 HWE reaction using model substrate **5.108**.

These results were further confirmed using substrate **5.068**, readily prepared by Suzuki-Miyaura cross coupling of **5.070** and **5.069** (figure 5.27).[141] **5.068** was reduced by DIBAL-H to the aldehyde **5.105**, which

was directly used as a crude substrate in the following HWE olefination. However, under either anhydrous or aqueous conditions,[140a,140b] no desired product **5.066** was formed.

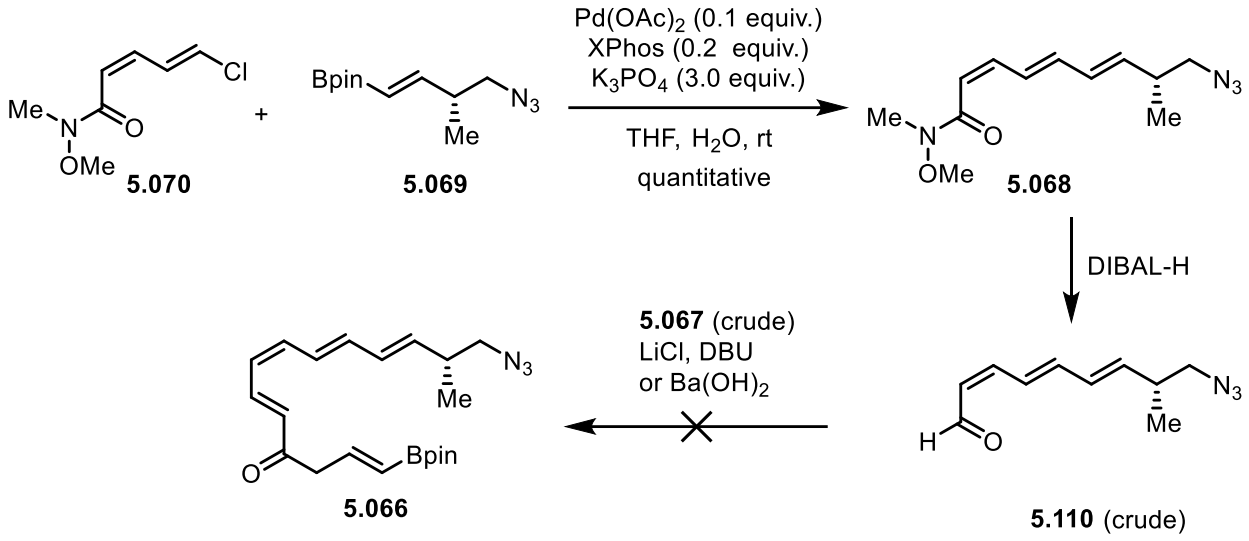


Figure 5.27 Attempt of synthesis of **5.066**.

5.3.2 Revised Approach Based on Ring-Closing Metathesis

5.3.2.1 Retrosynthesis

Our inability to achieve the synthesis of **5.066** by a HWE olefination highlighted the sensitivity of the phosphonate **5.067**. To circumvent the use of **5.067** while using other building blocks in hand, we decided to attempt a ring-closing metathesis (RCM) approach from precursor **5.111** (figure 5.28).[30] CBS reduction of the ketone **5.112** was expected to introduce the chiral hydroxy group. **5.112** could be formed by a Suzuki-Miyaura coupling from amide **5.113** and ketone **5.114**, which should be readily accessible from **5.069**, **5.070**, **5.115** and **5.116**. Among these four building blocks, **5.069** and **5.070** have already been obtained before.

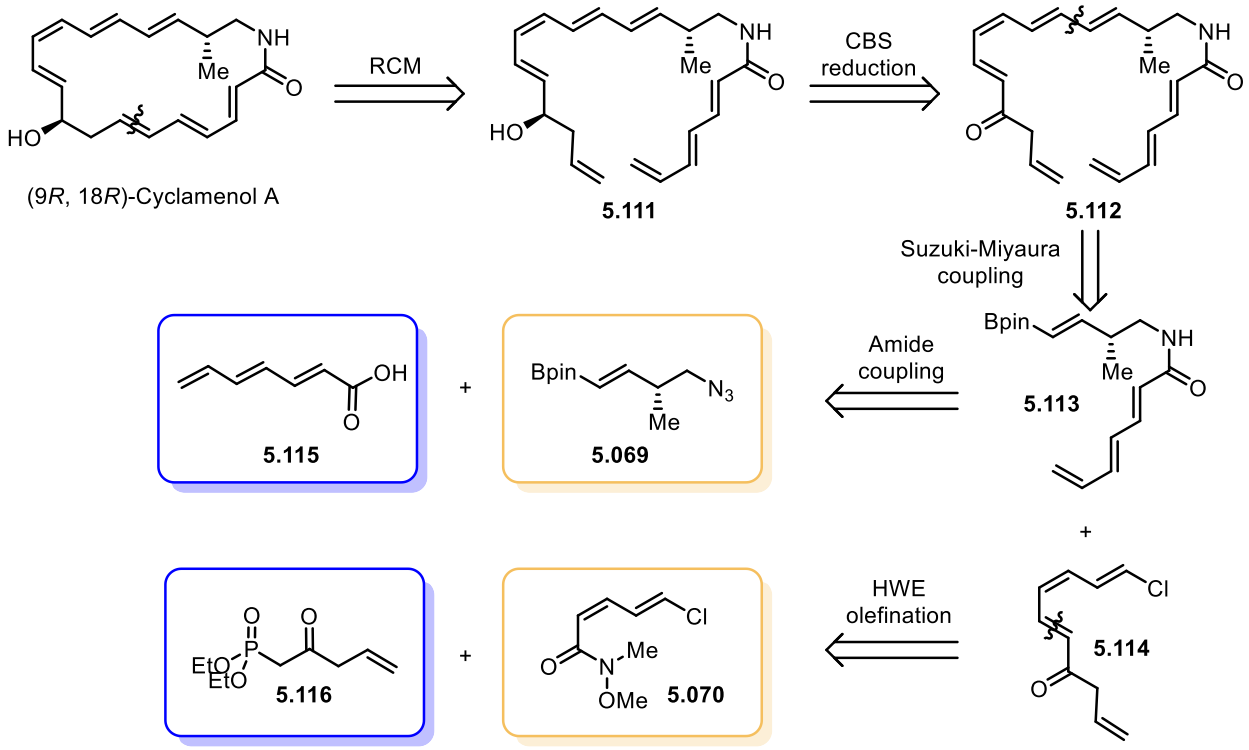


Figure 5.28 Retrosynthesis based on RCM strategy.

5.3.2.2 Synthesis of Fragment 5.113

Mixtures of **5.117** and **5.115** were readily obtained from bicyclobutene lactone **5.072** in the presence of vinyl Grignard reagent, copper cyanide and lithium chloride (figure 5.29).[60a] Heating of the mixture at 60 °C led to the formation of **5.115** as the sole product. Then **5.115** was coupled with amine **5.118** which was obtained from the azide **5.069**, to deliver product **5.113**, with 11% yield. Product **5.113** proved to be rather unstable even stored in the freezer.

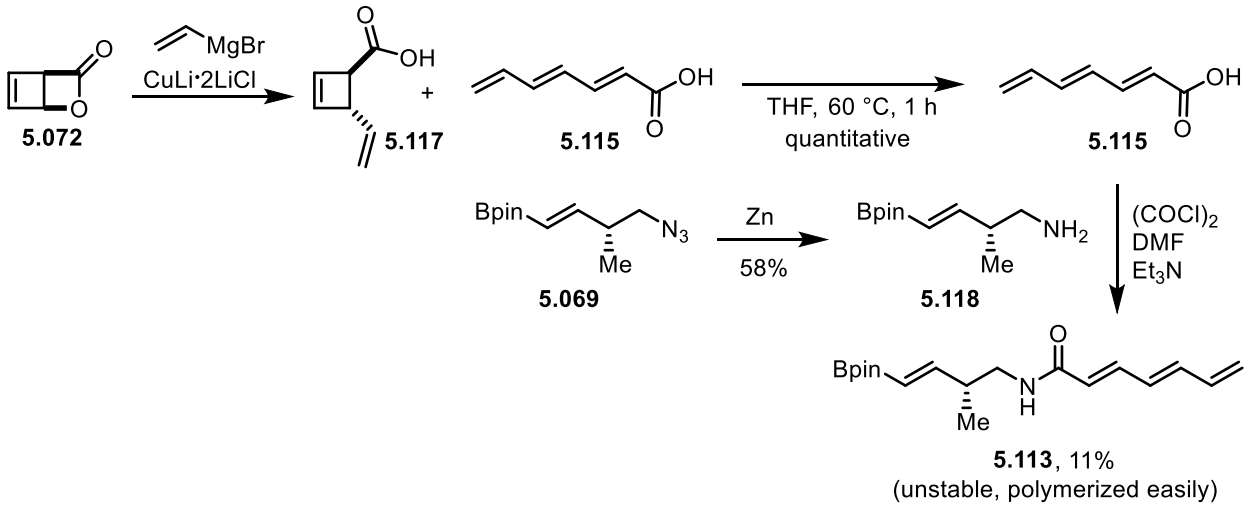


Figure 5.29 Synthesis of fragment **5.113**.

As methyl-substituted trienic carbonyl derivatives were found in some natural products,[142] a methyl substituted acid **5.120** was then prepared (figure 5.30). Although the Wittig olefination afforded trienic ester **5.119** in an *E*/*Z* ratio ranging from 7:1 to 9:1, after hydrolysis, the pure *E* isomer of **5.120** could be easily crystallized from the mixture of regioisomers.[142c]

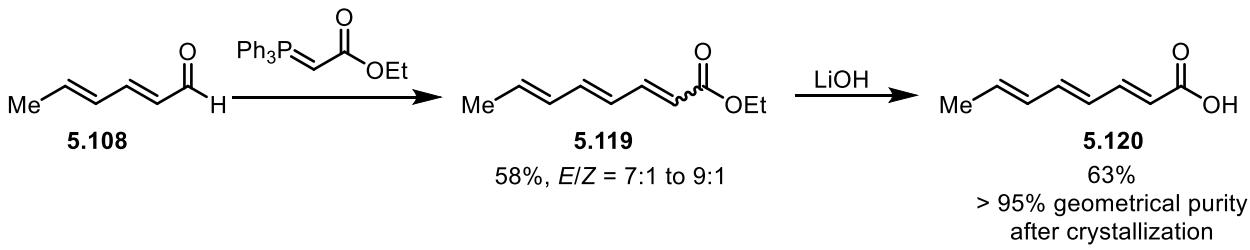
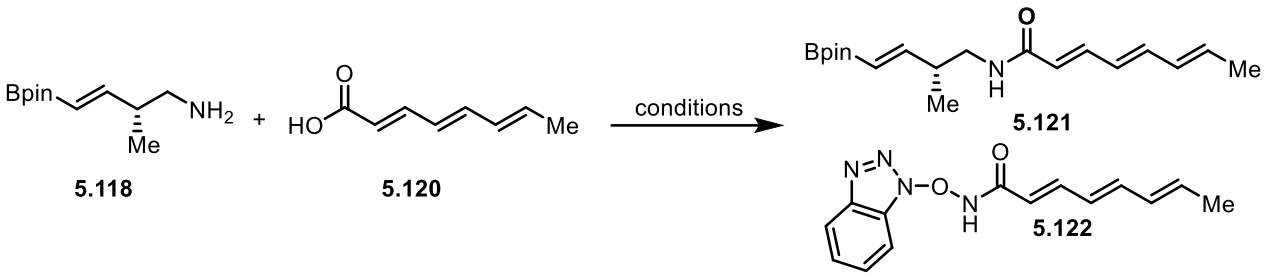


Figure 5.30 Synthesis of acid **5.120**.

The coupling of acid **5.120** and amine **5.118** was then attempted (table 5.31). When EDCI and HOBt were used, the major isolated product was activated ester **5.122**, with only traces of desired product **5.121** (entry 1). This result demonstrated the poor electrophilicity of ester **5.122**. Replacement of HOBt with DMAP as a stronger acyl transfer agent under the same conditions afforded product **5.121** in 30% yield (entry 2). The best result was obtained when oxalyl chloride, DMF, DMAP and DIPEA were used, albeit the yield was only 41% (entry 4).



Entry	Conditions	Comments
1	EDCI, HOBt, Et_3N, DMF, rt, 12 h	**5.121** (traces), **5.122** (36%)
2	EDCI, DMAP, Et_3N, DMF, rt, 10 h	**5.121** (30%)
3	BOPCl, DMAP, DIPEA, THF, rt, 12 h	**5.121** (36%)
4	$(COCl)_2$, DMF, DMAP, DIPEA, DCM, rt, 12 h	**5.121** (41%)

Table 5.31 Screening of amide coupling conditions.

5.3.2.3 Synthesis of Fragment 5.114

Treatment of acid chloride **5.123** with triethylamine afforded a putative ketene intermediate **5.124** which was trapped by the benzyl alcohol to release desired β,γ-unsaturated ester **5.125** and undesired α,β-unsaturated ester **5.126** in 79% overall yield, with a ratio of 7.1:1 (figure 5.32).[143]

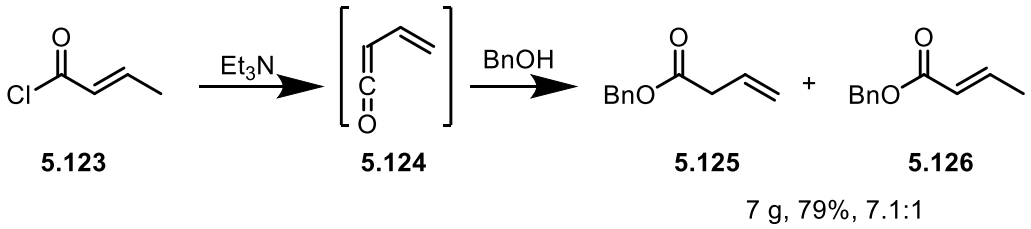
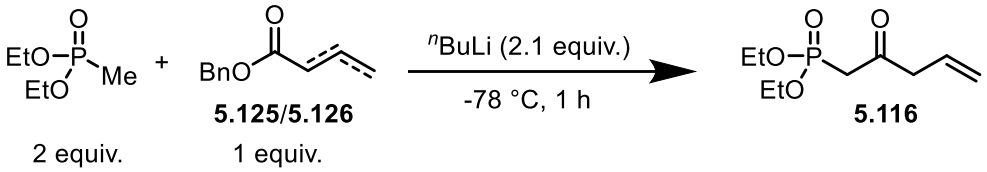


Figure 5.32 Synthesis of ester **5.125**.

Under anionic conditions, the coupling of diethoxymethylphosphonate with mixtures of **5.125** and **5.126** was attempted (table 5.33). While the use of THF as the solvent resulted in the recovery of **5.125**, phosphonate **5.116** was readily obtained in 28% yield when toluene was used as the solvent. Despite the low yield for this transformation, phosphonate **5.116** could be rapidly obtained in only two steps from the cheap acid chloride **5.123**.



Entry	Solvent	Comments
1	THF	**5.125** (recovered)
2	Toluene	**5.116** (28%)

Table 5.33 Synthesis of phosphonate **5.116**.

Then the HWE olefination of phosphonate **5.116** with crude aldehyde **5.127**, obtained from Weinreb amide **5.070**, was evaluated (figure 5.34). However, under the basic reaction conditions, no desired product **5.114** was detected. It was observed that phosphonate **5.116** swiftly decomposed.

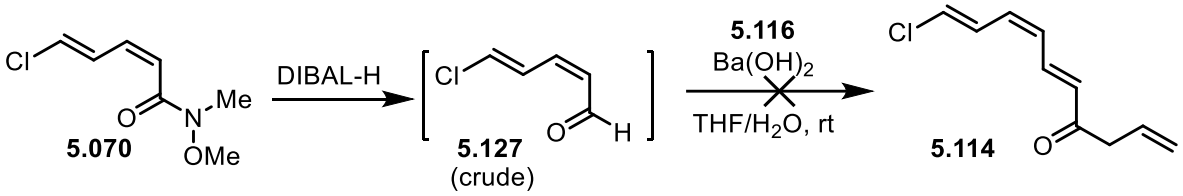


Figure 5.34 Attempt of synthesis of **5.114**.

Alternatively, phosphonate **5.129** was readily synthesized from chloro amide **5.128** (figure 5.35). The HWE olefination, same as above, of **5.129** with crude aldehyde **5.127** delivered isomerized (*E*,*E*,*E*) product **5.131** instead of the desired (*E*,*Z*,*E*) product **5.130**. The isomerized product **5.131** was always obtained even though all operations were conducted under the stringent exclusion of light.

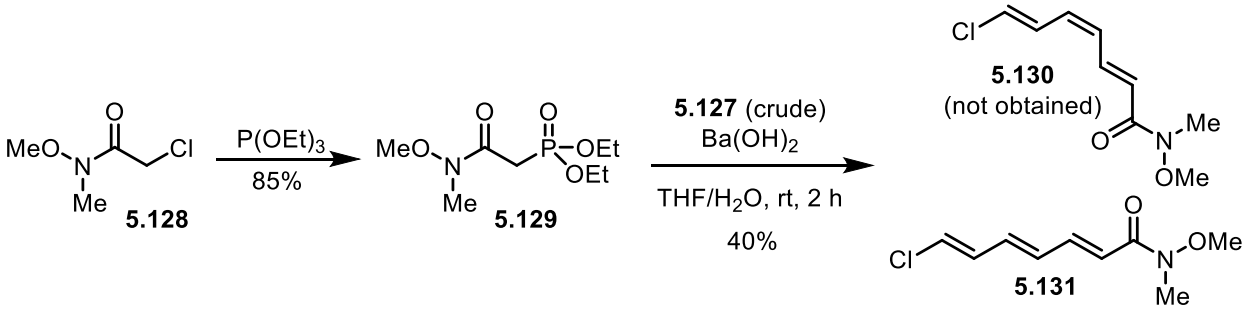


Figure 5.35 Attempt of synthesis of **5.130**.

Despite isomerization, product **5.131** was reacted with allyl Grignard reagent to afford ketone **5.132** in quantitative yield (figure 5.36). Suzuki-Miyaura coupling of **5.132** and amide **5.121** afforded product

5.133,[141] albeit with the migration of terminal double bond to the conjugated position. The excess of **5.132** was also recovered, however, it turned out to be product **5.134** with a migrated double bond. These results confirmed our original fears that the terminal double bond in compound **5.132** was prone to migrate into conjugation under basic conditions.

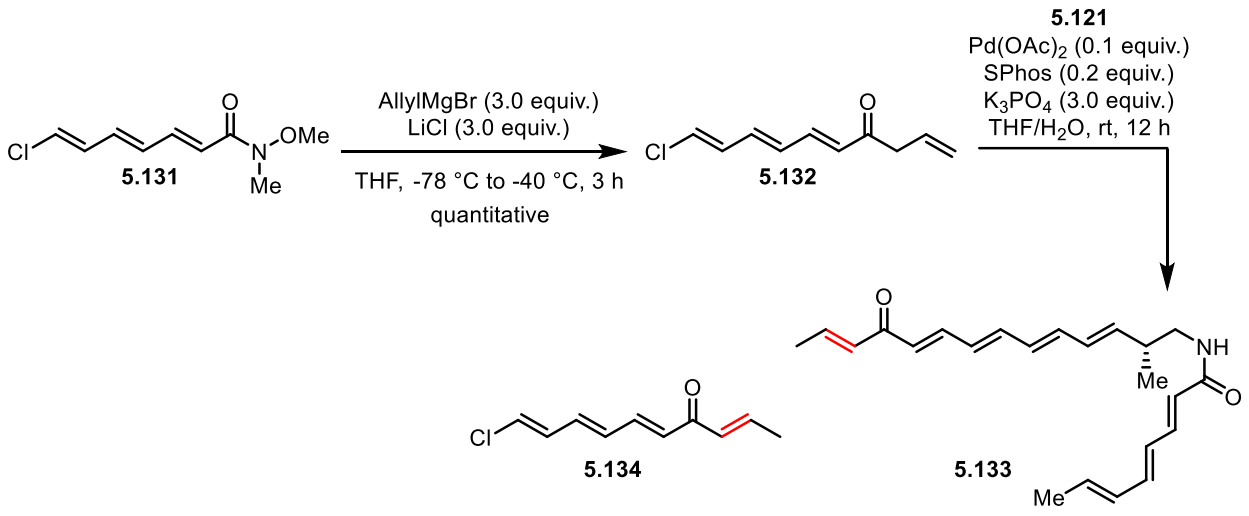


Figure 5.36 Evaluation of the Suzuki-Miyaura coupling.

Due to time limitations, we did not further pursue our efforts towards the total synthesis of cyclamenol A.

5.4 Conclusion

Cyclamenol A is a highly strained 20-membered macrolactam with six *E*-configured double bonds and one *Z*-configured double bond. Previous studies from the group of Waldmann showcased it was quite challenging to close the ring. Although a diastereoisomer of cyclamenol A was synthesized by Waldmann *et al.*, this natural product still hasn't been conquered by synthetic chemistry. In response to this, we proposed a novel and convergent Suzuki-Miyaura coupling/4π-electrocyclic ring opening process for the closure of the 20-membered ring. However, due to our inability to obtain a stable boronic ester precursor, we could not test our proposed ring-closure event (figure 5.37).

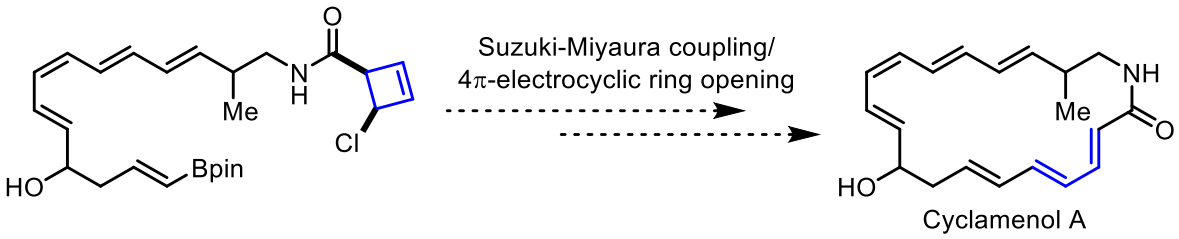


Figure 5.37 Our proposal to the ring closure of cyclamenol A.

5.5 Perspective

As described in our trials, we found that pinacol boronic esters were not stable under various oxidation or HWE olefination conditions. One possible way to circumvent this challenge would be to replace the pinacol boronate moiety with a MIDA boronate or trifluoroborate salt, groups which have proved to be much more stable to subsequent transformations. Therefore, compound **5.135** could be a potential precusor for our proposed Suzuki-Miyaura macrocyclization. In addition, as cyclamenol A is a highly strained macrocycle, reactions resulting in a large entropy gain, such as RCM, could also be viable solutions for the ring closure.

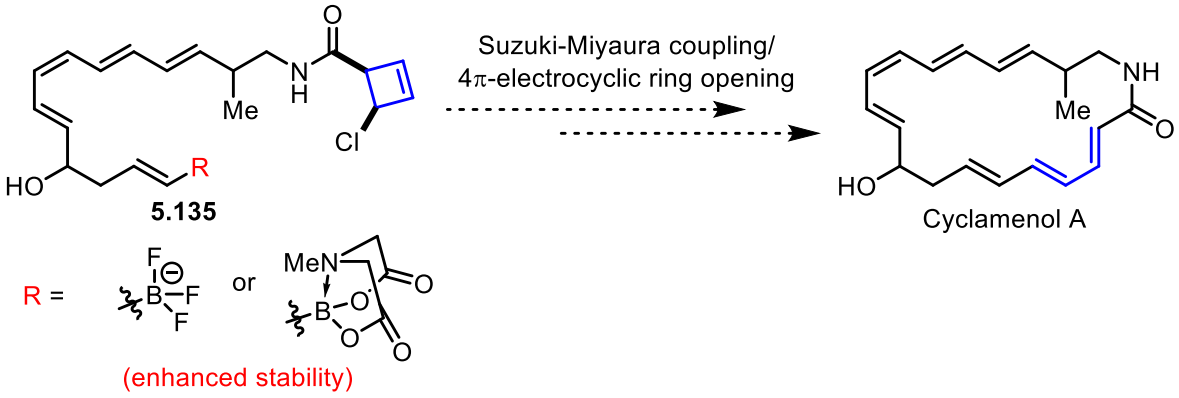


Figure 5.38 MIDA boronate or trifluoroborate salt as the cyclization precursor.

Chapter 6. Experimental Section

6.1 General Information

Unless otherwise stated, all glassware was oven dried before use and all reactions were carried out under an Argon atmosphere using standard Schlenk-techniques. Dry solvents were purchased from Acros Organics or Sigma-Aldrich and used without further purification. All reagents were purchased from commercial sources and were used without further purification unless otherwise stated. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminum plates coated with Kieselgel F254 with 0.2 mm thickness. Visualization was achieved by ultraviolet light (254 nm) or by staining with potassium permanganate. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck ans co.). Neat infra-red spectra were recorded using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Mass spectra were obtained using a Finnigan MAT 8200 (70 eV), an Agilent 5973 (70 eV), using electrospray ionization (ESI) or electron impact ionization (EI). Microwave reactions were performed using a Discover SP CEM microwave. All ^{1}H NMR, ^{13}C NMR NMR were recorded on a BrukerAV-400, AV-500, AV-600 or AV-700 spectrometer in Chloroform-*d*1 or DMSO-*d*6. Chemical shifts are given in parts per million (ppm), referenced to tetramethylsilane using the solvent peak as internal standard ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm; CD_3SOCD_3: ^{1}H = 2.50 ppm, ^{13}C = 39.52 ppm). Coupling constants were quoted in Hz. ^{1}H NMR splitting patterns were designated as singlet (s), broad (brd), doublet (d), triplet (t), quartet (q), pentet (p), sextet (se), septet (sep), octet (o) or combinations thereof. Splitting patterns that could not be interpreted were designated as multiplet (m).

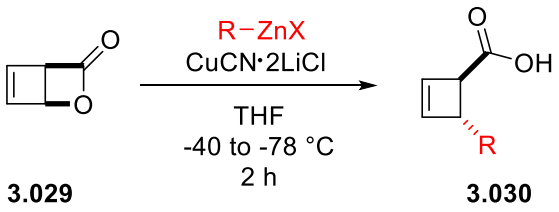
6.2 Total Synthesis of Cicutoxin

6.2.1 Functionalization of Cyclobutenes

6.2.1.1 Preparation of the Organozinc reagents

Metallic zinc powder was stirred with 0.05 N HCl (aq.) for 5 min, filtered off and washed with Pentane and then Et_2O. The activated zinc powder was then kept under vacuum for 12 h. In a flame dried flask were charged under argon dry DMF (1 M), I_2 (0.05 equiv.), and zinc dust (1.5 equiv.). The mixture was stirred at room temperature until the red colour of I_2 disappeared (ca. 2 min) (for larger sizes of zinc, the mixture was heated at 80 °C to accelerate the reaction of I_2 with zinc). The halide reagent (1.0 equiv.) was added and the mixture stirred at 80 °C for 3 h.

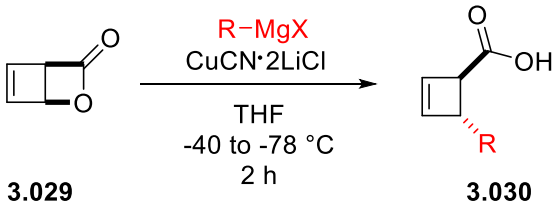
6.2.1.2 General Procedures Using Organozinc Reagents (GP1)



3.029 **3.030**

The organozinc reagent was prepared as described above. In a separated flame dried flask, CuCN (217 mg, 2.43 mmol, 1.0 equiv.) and LiCl (206 mg, 4.86 mmol, 2.0 equiv.) were stirred in THF (5 mL) for 15 min until complete dissolution of the salts. The organozinc solution (1.0 equiv.) was further diluted with THF (4 mL) and added dropwise to the solution of CuCN·2LiCl at -20 °C. The resulting mixture was stirred for 60 min at -20 °C, cooled down to -78 °C and an ethereal solution of lactone **3.029** (24.3 mL, 0.20 M, 4.86 mmol, 2.0 equiv.) was added dropwise. The resulting mixture was warmed to -30 °C for 3 h and 1 N HCl was added (5 mL) dropwise. The solution was allowed to warm up to room temperature and diluted in EtOAc (10 mL). The organic layer was washed with a saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), washed with brine, dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure to afford the desired product cyclobutene product **3.030**.

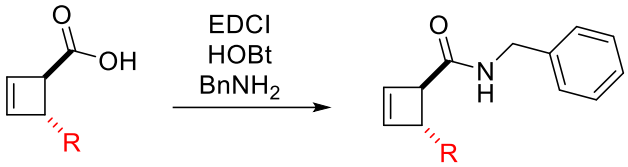
6.2.1.3 General Procedures Using Grignard Reagents (GP2)



3.029 **3.030**

In a flame dry flask, CuCN (143 mg, 1.6 mmol, 3.0 equiv.) and LiCl (135 mg, 3.2 mmol, 6.0 equiv.) were charged. The flask was put under vacuum and backfilled with Argon three times. THF (5 mL) was added to the solids. The suspension was stirred for 20 min at rt until a greenish solution was obtained. The solution was cooled down to -40 °C and the solution of the desired Grignard reagent RMgX (1.6 mmol, 3.0 equiv.) in THF (5 mL) was added. The mixture was then stirred of 40 min at -40 °C, and then cooled down to -78 °C. After 15 min, an ethereal solution of lactone **3.029** (3.5 ml, 0.15 M, 0.52 mmol, 1.0 equiv.) was added dropwise to the solution. The resulting mixture was warmed to -30 °C for 3 h and 1 N HCl was added (5 mL) dropwise. The solution was allowed to warm up to room temperature and diluted in EtOAc (10 mL). The organic layer was washed with a saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), washed with brine, dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure to afford the desired product cyclobutene product **3.030**.

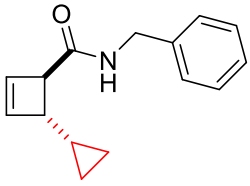
6.2.1.4 General Procedures for Amide Formation



3.030 **3.030'**

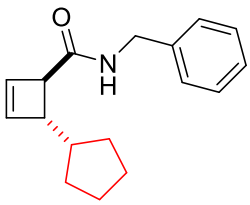
To a stirred solution of *trans*-**3.030** (200 mg, 1.50 mmol, 1.0 equiv.) in dry DCM (24 mL), under argon cooled at 0 °C, EDCI (318 mg, 1.66 mmol, 1.1 equiv.), HOBt (135 mg, 1.66 mmol, 1.1 equiv.) and benzyl amine (180 µL, 1.66 mmol, 1.1 equiv.) were added in this order and the resulting mixture was stirred at room temperature. After 18 h, an aqueous solution of $NaHCO_3$ (15 mL) was added. The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-pentane/EtOAc : 7/3 to 1/1) to yield pure product.

6.2.1.5 Substrate Scope



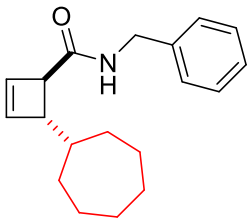
3.030b'

GP2, isolated as a 3:1 mixture of cyclobutene/diene, colorless oil, Y = 67%. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.26 (m, 5H), 6.26 (dt, *J* = 2.8, 0.7 Hz, 1H), 6.11 (dt, *J* = 2.8, 0.6 Hz, 1H), 5.87 (brd, 1H), 4.47 (d, *J* = 5.8 Hz, 2H), 3.23 (brd, 1H), 2.68 (d, *J* = 7.2 Hz, 1H), 1.01-0.93 (m, 1H), 0.52-0.40 (m, 2H), 0.21-0.19 (m, 2H) ppm. **^{13}C NMR (100MHz, $CDCl_3$):** δ 172.7, 143.0, 138.8, 134.7, 129.0 (2C), 128.1 (2C), 127.8, 54.0, 52.7, 43.8, 13.4, 3.4, 2.5 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{15}H_{17}NONa$) requires 250.1202, found 250.1205.



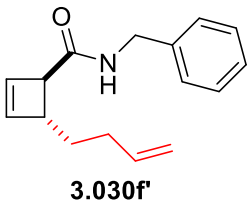
3.030c'

GP2, colorless solid, Y = 91%. **FTIR ($CHCl_3$, cm^{-1})**: 3284, 2948, 1642, 1541, 1228, 697. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.26 (m, 5H), 6.38 (dt, *J* = 2.8, 0.7 Hz, 1H), 6.12 (dt, *J* = 2.8,0.6 Hz, 1H), 5.85 (brd, 1H), 4.45 (dd, *J* = 5.7, 2.0 Hz, 2H), 3.17-3.16 (m, 1H), 2.80 (dt, *J* = 8.4, 1.0 Hz, 1H), 2.00 (sex, *J* = 7.8 Hz, 1H), 1.82-1.68 (m, 2H), 1.65-1.50 (m, 4H), 1.36-1.21 (m, 2H) ppm. **^{13}C NMR (100MHz, $CDCl_3$):** δ 173.0, 144.8, 138.8, 133.9, 129.1 (2C), 128.1 (2C), 127.8, 54.8, 53.3, 43.8, 43.2, 31.0, 30.2, 26.1, 26.0 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{17}H_{21}NONa$) requires 278.1515, found 278.1518.



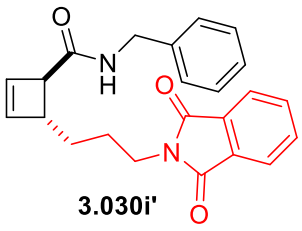
3.030d'

GP2, colorless solid, Y = 62%. **FTIR ($CHCl_3$, cm^{-1})**: 3282, 2918, 2851, 1739, 1641, 1537, 1497, 1222, 696. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.26 (m, 5H), 6.43 (dt, *J* = 2.8, 0.7 Hz, 1H), 6.12 (dt, *J* = 2.8, 0.6 Hz, 1H), 5.88 (brd, 1H), 4.45 (d, *J* = 5.8 Hz, 2H), 3.18-3.17 (m, 1H), 2.69 (dt, *J* = 9.2, 1.2 Hz, 1H), 1.90-1.84 (m, 1H), 1.78-1.61 (m, 4H), 1.54-1.38 (m, 4H), 1.33-1.15 (m, 4H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 173.1, 144.8, 138.8, 134.0, 129.0 (2C), 128.0 (2C), 127.8, 56.4, 53.3, 43.8, 43.7, 32.8, 32.3, 28.9, 28.6, 27.1, 27.0 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{19}H_{25}NONa$) requires 306.1828, found 306.1831.

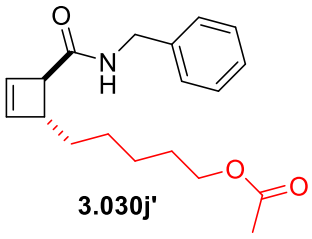


3.030f'

GP2, colorless oil, Y = 88%. **FTIR ($CHCl_3$, cm^{-1})**: 3282, 2921, 1739, 1642, 1539, 1229, 911, 698. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.26 (m, 5H), 6.42 (dt, *J* = 2.8, 0.7 Hz, 1H), 6.10 (dt, *J* = 2.8, 0.6 Hz, 1H), 5.89 (brd, 1H), 5.86-5.76 (m, 1H), 5.04-4.99 (m, 1H), 4.97-4.93 (m, 1H), 4.45 (d, *J* = 5.8 Hz, 2H), 3.15 (brd, 1H), 2.93-2.89 (m, 1H), 2.18-2.12 (m, 2H), 1.77-1.64 (m, 2H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 172.7, 145.2, 138.7, 138.6, 133.8, 129.1(2C), 128.1(2C), 127.8, 115.3, 54.4, 49.6, 43.8, 33.3, 32.4 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{16}H_{19}NONa$) requires 264.1359, found 264.1347.



GP1, colorless solid, Y = 85%. **FTIR ($CHCl_3$, cm^{-1})**: 3287, 2927, 1706, 1645, 1396, 1034, 720, 699. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.84-7.82 (m, 2H), 7.72-7.69 (m, 2H), 7.34-7.27 (m, 5H), 6.39 (dt, *J* = 2.8, 0.7 Hz, 1H), 6.10 (dd, *J* = 2.8, 0.7 Hz, 1H), 5.96 (brd, 1H), 4.44, (d, *J* = 5.8 Hz, 2H), 3.71 (dt, *J* = 7.0, 2.5 Hz, 2H), 3.16-3.15 (m, 1H), 2.95-2.92 (m, 1H), 1.81-1.74 (m, 2H), 1.71-1.61 (m, 2H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 172.5, 168.8 (2C), 144.7, 138.8, 134.2 (2C), 134.0, 132.5 (2C), 129.0 (2C), 128.1(2C), 127.8, 123.6 (2C), 54.1, 49.2, 43.8, 38.1, 31.1, 27.2 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{23}H_{22}N_2O_3Na$) requires 397.1522, found 397.1531.



GP1, colorless solid, Y = 80%. **FTIR ($CHCl_3$, cm^{-1})**: 2929, 1737, 1644, 1534, 1240, 1035, 699. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35-7.25 (m, 5H), 6.40 (d, *J* = 2.8 Hz, 1H), 6.09 (d, *J* = 2.8 Hz, 1H), 5.94 (brd, 1H), 4.45 (d, *J* = 5.8 Hz, 2H), 4.04 (t, *J* = 6.7 Hz, 2H), 3.13 (brd, 1H), 2.89-2.87 (m, 1H), 2.03 (s, 3H), 1.67-1.58 (m, 4H), 1.45-1.33 (m, 4H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 172.8, 171.5, 145.3, 138.8, 133.7, 129.0 (2C), 128.0 (2C), 127.8, 64.7, 54.5, 50.0, 43.8, 34.0, 28.8, 27.8, 26.2, 21.3 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{19}H_{25}NO_3Na$) requires 338.1726, found 338.1722.

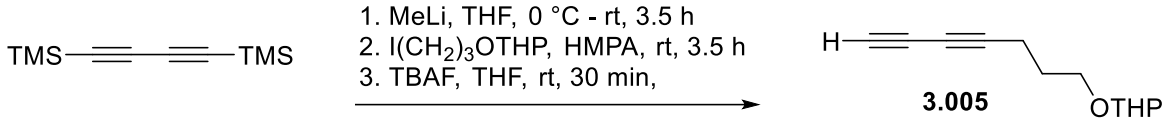
6.2.2 Total Synthesis of Cicutoxin

6.2.2.1 Synthesis of 3.005

3-Iodopropan-1-ol (0.48 mL, 5.0 mmol, 1.0 equiv.), pyridinium p-toluenesulfonate (PPTS) (188.0 mg, 0.75 mmol, 0.15 equiv.) and 3, 4-Dihydro-2H-pyrane (DHP) (0.68 mL, 7.5 mmol, 1.5 equiv.) were dissolved in dry DCM (10 mL) in a 25 mL round bottom flask. After purging with Argon, the mixture was stirred for 1.5 h at room temperature while covered with aluminium foil. The mixture was concentrated under reduced pressure and loaded directly on a column (silica gel, 0-3 % Et_2O in heptane) to give the product **A** in 88% yield. The procedure was adapted[1] and the spectral data are in accordance with the literature[2]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.62-4.59 (m, 1H), 3.91-3.84 (m, 1H), 3.81 (dt, *J* = 10.0, 5.9 Hz, 1H), 3.56-3.49 (m, 1H),

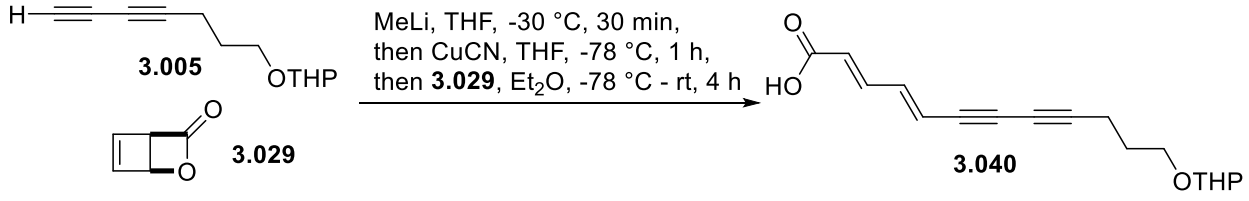
[1] Gorske, B. C., Mbofana, C. T., Miller, S. J. *Org. Lett.* **2009**, *11,* 4318-4321.
[2] Miura, K., Fujisawa, N., Saito, H., Wang, D., Hosomi, A. *Org. Lett.* **2001**, *3,* 2591-2594.

3.54 (dt, *J* = 10.0, 5.9 Hz, 1H), 3.30 (td, *J* = 6.9, 1.1 Hz, 2H), 2.13-2.06 (m, 2H), 1.86-1.76 (m, 1H), 1.76-1.66 (m, 1H), 1.62-1.48 (m, 4H) ppm.



1, 4-Bis-(trimethylsilyl)-1, 3-budadiyne (5.15 g, 5.3 mL, 26.5 mmol, 1.0 equiv.) was dissolved in dry THF (50 mL) in a flame-dried Schlenk tube. MeLi (1.6 M in ether, 16.6 mL, 26.5 mmol, 1.0 equiv.) was added dropwise at 0 °C and stirred for 3.5 hours at room temperature. Iodide **A** (7.16 g, 26.5 mmol, 1.0 equiv.), dissolved in hexamethylphosphoramide (HMPA) (9.2 mL, 53 mmol, 2.0 equiv.), was added dropwise and stirred overnight at room temperature. The mixture was quenched with brine (50 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was redissolved in dry THF (50 mL), and tetra-n-butylammonium fluoride (TBAF) (1 M in THF, 79.5 mL, 79.5 mmol, 3.0 equiv.) was added slowly at room temperature and stirred for 30 min. After removal of the solvent in vacuo, the crude product was dissolved in CH_2Cl_2 (100 mL) and washed with water (100 mL). After extracting the aqueous layer with CH_2Cl_2 (100 mL), the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Column chromatography (silica gel, 0-3% EtOAc in heptane) afforded 3.67 g (72%) of the product **3.005** as a red oil. The spectral data are in accordance with the literature[3]. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 4.61-4.57 (m, 1H), 3.91-3.78 (m, 2H), 3.56-3.44 (m, 2H), 3.40 (bt, *J* = 7.0 Hz, 2H), 1.95 (t, *J* = 1.2 Hz, 1H), 1.87-1.79 (m, 3H), 1.75-1.62 (m, 1H), 1.61-1.48 (m, 4H) ppm.

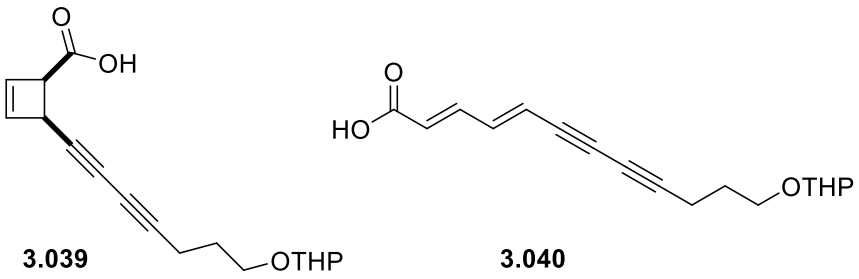
6.2.2.2 Synthesis of 3.041

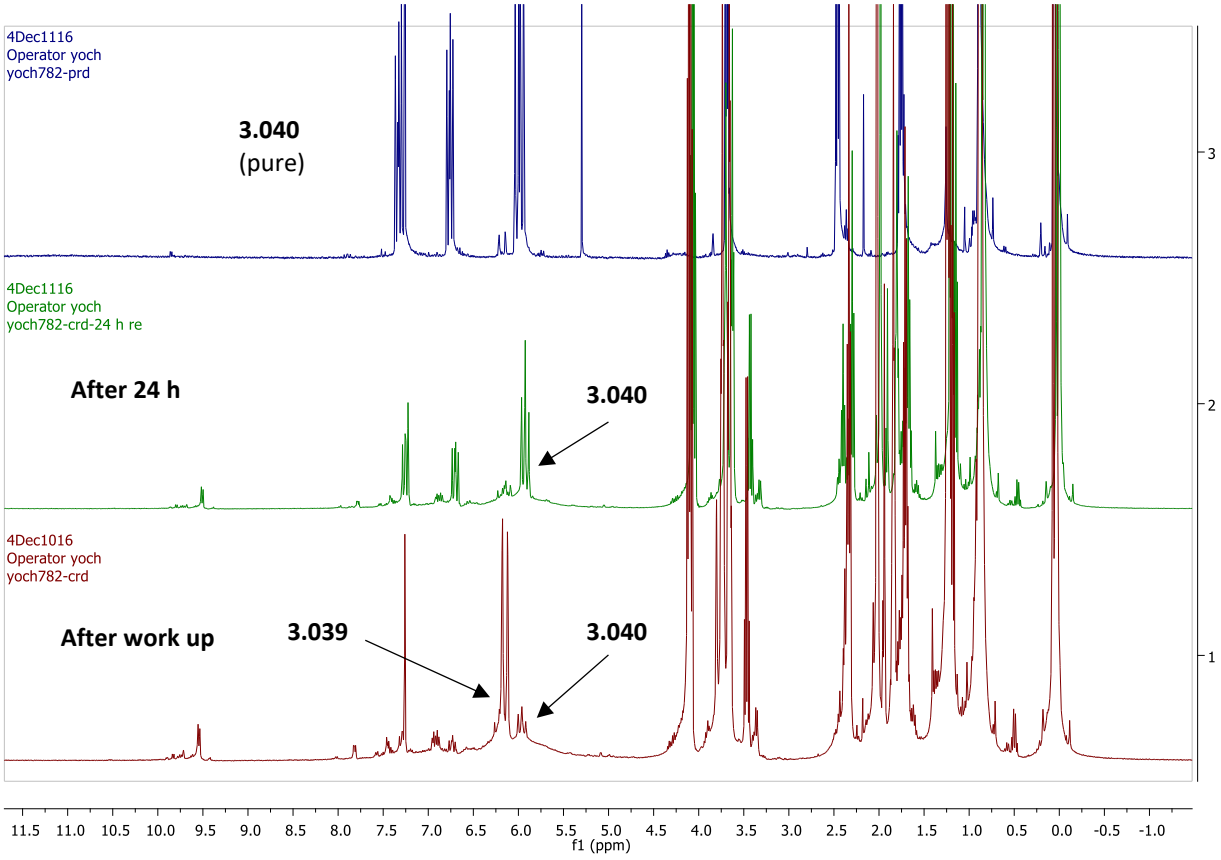


Diyne **3.005** (700 mg, 3.64 mmol, 2.0 equiv.) was dissolved in dry THF (4.0 mL) in a flame-dried Schlenk tube and cooled to -40 °C. MeLi (1.6 M in ether, 2.4 mL, 3.64 mmol, 2.0 equiv.) was added and the mixture was stirred for 30 minutes, before added via canula to a solution of CuCN (163.0 mg, 1.82 mmol, 1.0

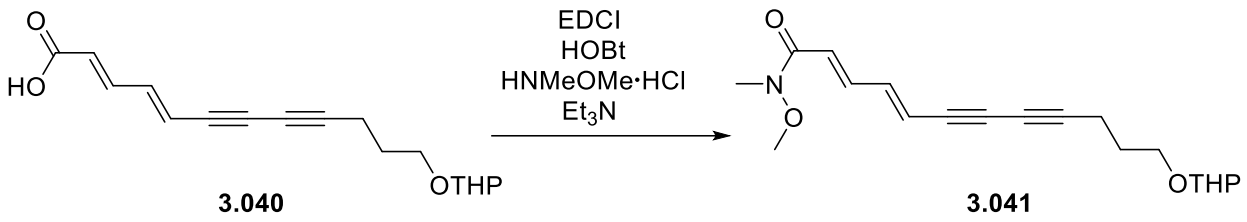
[3] Uwai, K., Oshima, Y. *Tetrahedron* **1999**, *55*, 9469-9480.

equiv.) dry THF (4.0 mL) at -78 °C, which was stirred for 1 h at -78 °C. Lactone **3.029** (0.1 M in ether, 18.2 mL, 1.82 mmol, 1.0 equiv.) was added dropwise and the mixture was allowed to slowly warm up to room temperature. The slurry was quenched after warming to room temperature with water (80 mL), acidified to pH = 2 with 1 N HCl (aq.) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude mixture was allowed to stay at room temperature for 1 day. Purification by column chromatography (silica gel, EtOAc/heptane/HOAc = 20:77:3) afforded 429 mg (82%) of product **3.040** as white solid. **FTIR ($CHCl_3$, cm^{-1}):** 2950, 2925, 2854, 1673, 1618, 1344, 1275, 1263, 1138, 1075, 1034, 1001, 764, 751, 528. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.23 (dd, *J* = 15.3, 11.6 Hz, 1H), 6.76 (dd, *J* = 15.4, 11.5 Hz, 1H), 6.01 (d, *J* = 15.5 Hz, 1H), 5.97 (d, *J* = 15.3 Hz, 1H), 4.60 (m, 1H), 3.89-3.79 (m, 2H), 3.54-3.50 (m, 1H), 3.48 (dt, *J* = 9.9, 6.1 Hz, 1H), 2.50 (bt, *J* = 7.0 Hz, 2H), 1.88-1.78 (m, 3H), 1.74-1.68 (m, 1H), 1.62-1.49 (m, 4H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 169.7, 144.9, 140.9, 122.4, 119.7, 99.0, 88.0, 81.7, 73.4, 65.8, 65.4, 62.4, 30.8, 28.5, 25.6, 19.7, 16.9 ppm. **HRMS (ESI) (m/z):** calculated for $[M - H^+]^-$ $(C_{17}H_{19}O_4)^-$ requires 287.1289, found 287.1281.





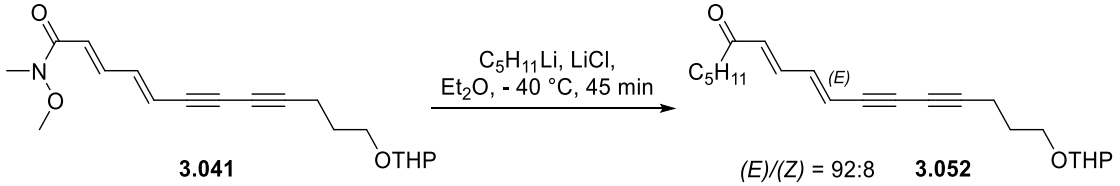
As can be seen from the crude ^{1}H NMR spectrum, the ring opened product **3.040** was formed already after the work up, despite **3.039** was the major product. After 24 h at room temperature, compound **3.040** was the major product which can been seen on crude ^{1}H NMR spectrum. Due to the meta-stability of **3.039** and also its close Rf to **3.040**, we are not able to isolate the clean **3.039**.



3.040 **3.041**

Carboxylic acid **3.040** (270 mg, 0.936 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (5 mL) in a flame-dried Schlenk tube. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDCI) (215 mg, 1.12 mmol, 1.2 equiv.) and 1-Hydroxybenzotriazole hydrate (HOBt) (88% w/w, 172 mg, 1.12 mmol, 1.2 equiv.) was added at room temperature and the mixture stirred for 30 min. After addition of *N, O*-Dimethylhydroxylamine hydrochloride (137 mg, 1.40 mmol, 1.5 equiv.) and Et_3N (0.26 mL, 1.87 mmol, 2.0 equiv.), the mixture was kept stirring for 12 h and quenched with sat. $NaHCO_3$ (aq.) (15 mL). The mixture was extracted with CH_2Cl_2 (2 x 15 mL), the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel, 50% EtOAc in heptane) afforded 245 mg (79%) of the Weinreb amide **3.041** as a yellow oil. **FTIR ($CHCl_3$, cm^{-1}):** 2938, 2871, 2225, 1651, 1607, 1462, 1440, 1416, 1380, 1261, 1202, 1179, 1136, 1120, 1075, 1034, 996, 869, 816. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.31 (dd, *J* = 15.1, 11.4 Hz, 1H), 6.80 (dd, *J* = 15.5, 11.5 Hz, 1H), 6.55 (d, *J* = 15.2 Hz, 1H), 5.96 (d, *J* = 15.5 Hz, 1H), 4.61-4.58 (m, 1H), 3.89-3.79 (m, 2H), 3.71 (s, 3H), 3.54-3.50 (m, 1H), 3.48 (dt, *J* = 9.9, 6.1 Hz, 1H), 3.26 (s, 3H), 2.49 (bt, *J* = 7.0 Hz, 2H), 1.88-1.78 (m, 3H), 1.74-1.68 (m, 1H), 1.61-1.49 (m, 4H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 166.5, 142.0, 141.6, 121.8, 117.7, 99.0, 87.2, 80.5, 73.8, 65.8, 65.5, 62.4, 62.1, 32.6, 30.8, 28.6, 25.6, 19.7, 16.9 ppm. **HRMS (ESI) (m/z):** calculated for $[M + Na^+]^+$ $(C_{19}H_{25}NNaO_4)^+$ requires 354.1679, found 354.1676.

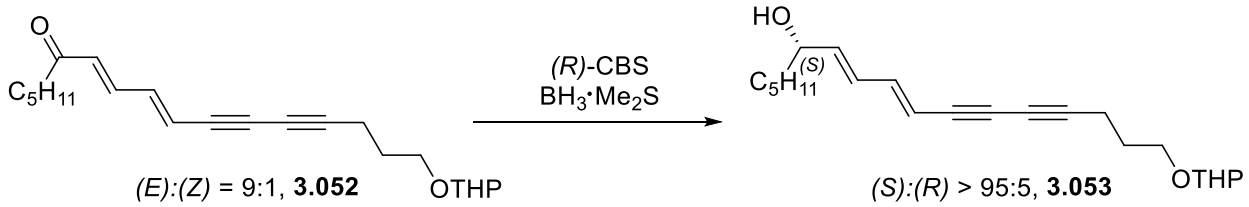
6.2.2.3 Synthesis of 3.053



3.041 *(E)*/*(Z)* = 92:8 **3.052**

A flame-dried Schlenk flask was charged with 1-Iodopentane (26 µL, 0.2 mmol, 3.0 equiv.) and dry Et_2O (1 mL). After cooling to -78 °C, ^{t}BuLi (1.7 M in pentane, 0.24 mL, 0.4 mmol, 6.0 equiv.) was added dropwise, and the mixture was stirred for 1 h at -78 °C. A separate flame-dried Schlenk was charged with Weinreb amide **3.041** (22.1 mg, 0.067 mmol, 1.0 equiv.), LiCl (14.1 mg, 0.333 mmol, 5.0 equiv.) and dry Et_2O (0.5 mL) and cooled to -40 °C. The pentyllithium solution was added via canula and the mixture was stirred for

45 minutes at -40 °C. The mixture was quenched with brine and water (5 mL, 1:1) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. Purification by prepTLC (aluminium oxide, 30% EtOAc in heptane) afforded 15.2 mg (67%) of desired ketone **3.052** as a yellow oil, containing 8% of isomerization product. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.12 (dd, *J* = 15.5, 11.3 Hz, 1H), 6.74 (dd, *J* = 15.4, 11.3 Hz, 1H), 6.23 (bd, *J* = 15.4 Hz, 1H), 6.00 (d, *J* = 15.5 Hz, 1H), 4.61-4.58 (m, 1H), 3.88-3.78 (m, 2H), 3.54-3.45 (m, 2H), 2.55 (t, *J* = 7.44 Hz, 2 H), 2.47 (bt, *J* = 6.84 Hz, 2H), 1.89-1.78 (m, 3H), 1.74-1.68 (m, 1H), 1.65-1.48 (m, 6H), 1.36-1.24 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 200.5, 141.9, 140.2, 131.6, 119.0, 99.0, 87.8, 81.2, 73.7, 65.8, 65.4, 62.4, 41.3, 31.6, 30.8, 28.5, 25.6, 24.0, 22.6, 19.6, 16.9, 14.1 ppm.



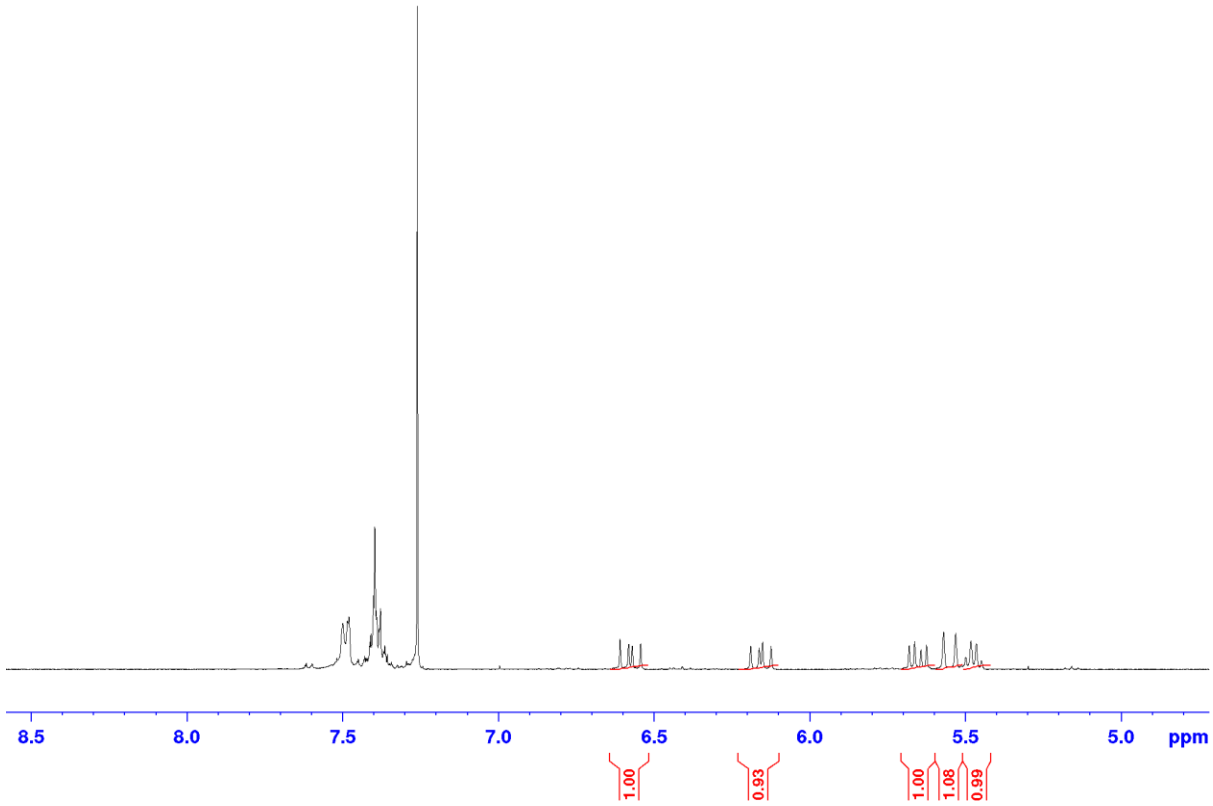
(E):(Z) = 9:1, **3.052** *(S):(R)* > 95:5, **3.053**

A flame-dry Schlenk tube was charged with a solution of *(R)-(+)*-2-Methyl-CBS-oxazaborolidine [(*R*)-CBS] (1 M in THF, 76 µL, 0.076 mmol, 2.0 equiv.), then a solution of ketone **3.052** (*(E):(Z)* = 9:1, 13.0 mg, 0.038 mmol, 1.0 equiv.) in dry THF (0.5 mL) was added. The mixture stirred at -50 °C for 10 min. Then BH_3-Me_2S complex (7 µL, 0.076 mmol, 2.0 equiv.) was added. The mixture was stirred vigorously at -50 °C for 1.5 h. After quenching with sat. NH_4Cl (aq.) (1 mL), the aqueous layer was extracted with EtOAc (2 x 4 mL), the combined organic layers were dried with $MgSO_4$ and filtered. Concentration under reduced pressure and column chromatography (silica gel, 50% EtOAc in heptane) afforded 10.0 mg (76%) of the desired product **3.053** as a colorless oil. The spectral data are in accordance with the literature[3]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.67 (dd, *J* = 15.6, 10.9 Hz, 1H), 6.29 (dd, *J* = 15.3, 10.9 Hz, 1H), 5.84 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.61 (d, *J* = 15.4 Hz, 1H), 4.61-4.58 (m, 1H), 4.21-4.14 (m, 1H), 3.90-3.78 (m, 2H), 3.55-3.43 (m, 2H), 2.47 (bt, *J* = 7.0 Hz, 2H), 1.90-1.65 (m, 4H), 1.64-1.19 (m, 13H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm. Specific rotation is in accordance with the literature[3]: **$[\alpha]_D$** = + 9.6 (c = 0.5, $CHCl_3$), **$[\alpha]_D$ (Lit.)** = + 10.8 (c = 1.1, $CHCl_3$).

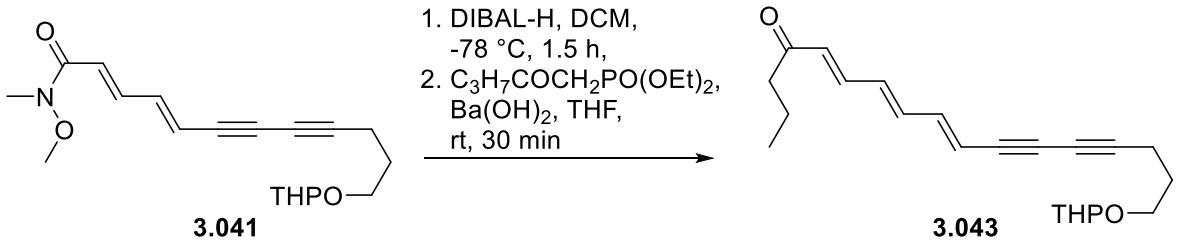
Determination of enantiomeric excess using Mosher ester method:

A dry schlenk tube was charged with *(R)*-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (9.9 mg, 41.8 µmol) and dissolved in dry pentane (1.5 mL). $(COCl)_2$ (697 mmol, 59 µL) was added, followed by addition of dry DMF (1 drop). The mixture was stirred for 30 minutes at room temperature and filtered through a plug of cotton. Removal of the solvent at 100 mbar (40 °C waterbath) afforded the acid chloride, which

was redissolved in $CDCl_3$ (0.7 mL). After addition of Et_3N (5.8 µL, 42 µmol), the solution was added to 3.6 mg of crude alcohol **3.053**. Addition of DMAP (8.5 mg, 0.7 µmol) led to completion of the ester formation within 15 min. ^{1}H NMR data of olefinic signals of Mosher ester: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.56 (dd, *J* = 15.6, 10.9 Hz, 1H), 6.14 (dd, *J* = 15.2, 10.9 Hz, 1H), 5.64 (dd, *J* = 15.2, 7.1 Hz, 1H), 5.54 (d, *J* = 15.6 Hz, 1H) ppm.

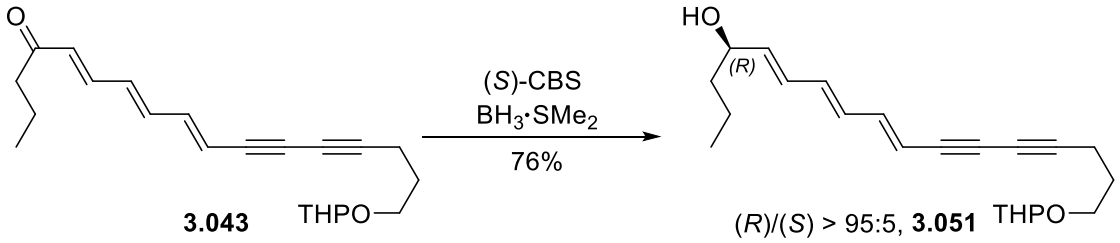


6.2.2.4 Synthesis of 3.051



The following reaction was performed in the shadows, since light may cause double bond isomerization of the following intermediates: A flame-dried Schlenk was charged with Weinreb amide **3.041** (38.3 mg, 0.116 mmol, 1.0 equiv.) and dry CH_2Cl_2 (1 mL). After cooling to -78 °C, a solution of DIBAL-H in CH_2Cl_2 (1 M

in CH_2Cl_2, 0.23 mL, 0.23 mmol, 2.0 equiv.) was added and the mixture was stirred for 1.5 h at -78 °C. After quenching with EtOAc (0.5 mL), the solution was allowed to warm up to room temperature. Sat. Na-K-tartrate (10 mL) and water (5 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated to give the crude aldehyde as yellow oil. A flame-dried Schlenk tube was charged with phosphonate (51.6 mg, 0.232 mmol, 2.0 equiv.) in dry THF (0.5 mL). Anhydrous barium hydroxide (79.5 mg, 0.464 mmol, 4.0 equiv.) was added and the mixture was stirred for 30 min at room temperature. A solution of crude aldehyde in THF (1 mL) and water (25 µL) was added dropwise and stirred for 30 min at room temperature. Water (10 mL) was added and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel prewashed with Et_3N/EtOAc/heptane 5:20:80, elution with 20% EtOAc in heptane) afforded 20.6 mg (52%) of product **3.043** as a yellow oil and single isomer. **FTIR ($CHCl_3$, cm^{-1}):** 2932, 2873, 1682, 1661, 1602, 1563, 1366, 1261, 1201, 1183, 1156, 1136, 1121, 1062, 1035, 1020, 1001. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.15 (dd, *J* = 15.5, 11.3 Hz, 1H), 6.74 (dd, *J* = 15.4, 11.3 Hz, 1H), 6.60 (dd, *J* = 14.8, 11.4 Hz, 1H), 6.40 (dd, *J* = 14.8, 11.3 Hz, 1H), 6.23 (bd, *J* = 15.4 Hz, 1H), 5.79 (d, *J* = 15.4 Hz, 1H), 4.60-4.58 (m, 1H), 3.88-3.79 (m, 2H), 3.54-3.44 (m, 2H), 2.53 (t, *J* = 7.4 Hz, 2H), 2.47 (bt, *J* = 7.1 Hz, 2H), 1.87-1.78 (m, 3 H), 1.74-1.68 (m, 1H), 1.65 (aqq. hex, *J* = 7.4 Hz, 2H), 1.60-1.49 (m, 4H), 1.25 (brd, 2H), 0.94 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 200.5, 143.1, 141.1, 139.6, 133.4, 131.1, 114.5, 99.0, 87.2, 80.3, 74.4, 65.8, 65.7, 62.4, 43.0, 30.8, 28.6, 25.6, 19.6, 17.9, 16.9, 14.0 ppm. **HRMS (ESI) (m/z):** calculated for $[M + Na^+]^+$ $(C_{22}H_{28}O_3Na)^+$ requires 363.1931, found 363.1931.



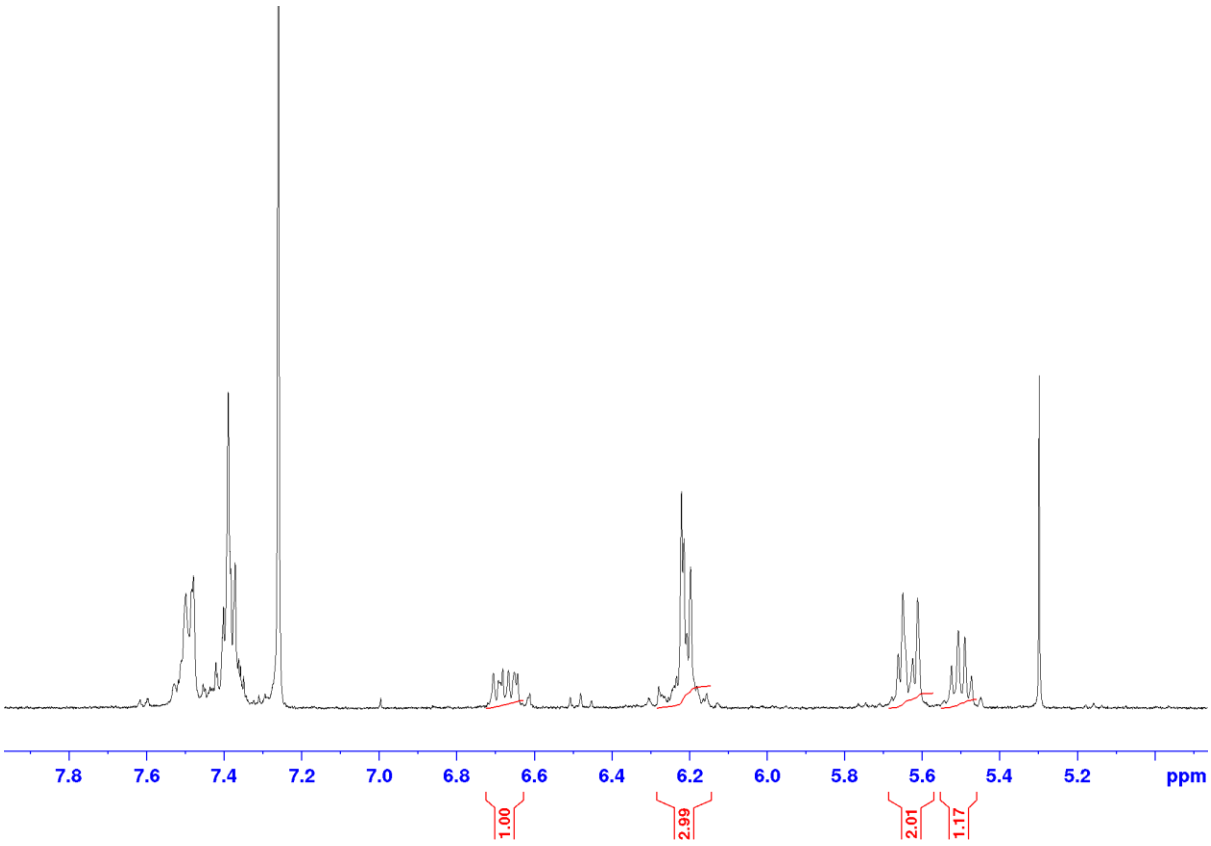
A flame-dry Schlenk tube was charged with a solution of *(S)*-2-Methyl-CBS-oxazaborolidine [(*S*)-CBS] (21.2 mg, 0.076 mmol, 2.0 equiv.), then a solution of ketone **3.043** (13.0 mg, 0.038 mmol, 1.0 equiv.) in dry THF (0.5 mL) was added. The mixture stirred at -50 °C for 10 min. Then BH_3-Me_2S complex (7.0 µL, 0.076 mmol, 2.0 equiv.) was added. The mixture was stirred vigorously at -50 °C for 1.5 h. After quenching with sat. NH_4Cl (aq.) (1 mL), the aqueous layer was extracted with EtOAc (2 x 4 mL), the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography

(silica gel, 50% EtOAc in heptane) afforded 10.0 mg (76%) of the desired product **3.051** as a colorless oil. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.70 (dd, *J* = 15.4, 10.6 Hz, 1H), 6.33-6.21 (m, 3H), 5.81 (dd, *J* = 15.2, 6.5 Hz, 1H), 5.60 (d, *J* = 15.4 Hz, 1H), 4.60-4.58 (m, 1H), 4.22-4.16 (m, 1H), 3.88-3.79 (m, 2H), 3.54-3.45 (m, 2H), 2.47 (btd, *J* = 7.1, 3.1 Hz, 2 H), 1.87-1.78 (m, 3H), 1.74-1.67 (m, 1H), 1.61-1.49 (m, 6H), 1.47 (d, *J* = 4.2 Hz, OH), 1.46-1.31 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$):** δ 144.3, 139.3, 135.4, 131.7, 129.9, 110.2, 99.0, 85.7, 77.9, 75.0, 72.4, 65.9, 65.8, 62.4, 39.5, 30.8, 28.7, 25.6, 19.7, 18.7, 16.8, 14.1 ppm. **FTIR ($CHCl_3$, cm^{-1}):** 3422, 2954, 2930, 2871, 1455, 1441, 1354, 1287, 1200, 1157, 1136, 1121, 1073, 1063, 1034, 1022, 995. **HRMS (ESI) (m/z):** calculated for $[M + Na^+]^+$ ($C_{22}H_{30}O_3Na)^+$ requires 365.2087, found 365.2096. The spectra data is in accordance with the literature[4].

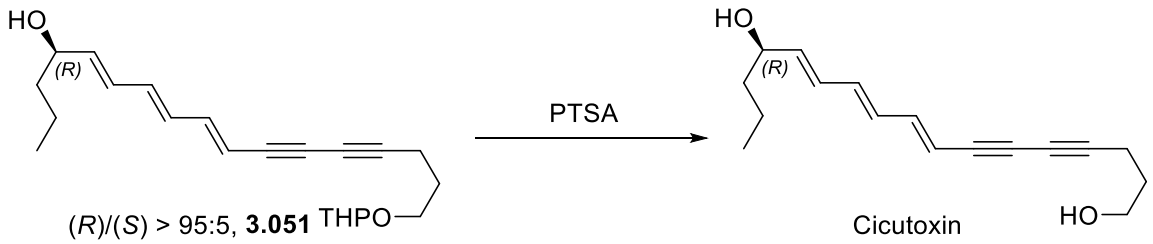
Determination of enantiomeric excess using Mosher ester method:

A dry schlenk tube was charged with *(S)*-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (12.0 mg, 51.1 µmol, 5.0 equiv.) and dissolved in dry pentane (1.5 mL). $(COCl)_2$ (22 µL, 0.255 mmol, 25 equiv.) was added, followed by addition of dry DMF (1 drop). The mixture was stirred for 30 min at room temperature and filtered through a plug of cotton. Removal of the solvent at 100 mbar (40 °C, waterbath) afforded the acid chloride. Then the above alcohol **3.051** (3.5 mg, 10.2 µmol, 1.0 equiv.) which was dissolved in CH_2Cl_2 (0.7 mL) was added to the acid chloride, followed by the addition of DMAP (1.2 mg, 10.2 µmol, 1.0 equiv.) and Et_3N (8.6 µL, 61.3 µmol, 6.0 equiv.). The mixture stirred vigorously at room temperature for 30 min leading to the complete consumption of alcohol **3.051**. Then the solvent was removed, flash column chromatography (silica gel, 20% EtOAc in heptane) gave the Mosher ester (5.0 mg, 88%) as a colorless oil. ^{1}H NMR data of olefinic signals of Mosher ester: **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.71-6.64 (m, 1H), 6.28-6.16 (m, 3H), 5.66-5.61 (m, 2H), 5.50 (dd, *J* = 13.7, 7.0 Hz, 1H) ppm.

[4] Gung B. W., Omollo A. O. *Eur. J. Org. Chem.* **2009**,1136-1138.



6.2.2.5 Synthesis of Cicutoxin



To a solution of alcohol **3.051** (7.0 mg, 20.4 µmol, 1.0 equiv.) in MeOH (2.0 mL) in a glass vial covered by aluminium foil was added p-toluenesulfonic acid (PTSA) (1.8 mg, 10.2 µmol, 0.5 equiv.) and the mixture was stirred for 1.5 h at room temperature. The crude mixture was quenched by sat. $NaHCO_3$ (aq.) (1.0 mL), after concentrating, the water phase was extracted by EtOAc (3 x 10 mL). The combined organic phase was washed by brine, dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel prewashed with Et_3N/EtOAc/heptane 5:20:80, elution with 20% EtOAc in heptane) afforded 2.8 mg (53%) cicutoxin as a colorless oil. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.70 (dd, *J* = 15.4, 10.7 Hz, 1H), 6.37-6.21 (m, 3H), 5.82 (dd, *J* = 15.2, 6.6 Hz, 1H), 5.60 (d, *J* = 15.4 Hz, 1H), 4.22-4.16 (m, 1H), 3.76 (bq, *J* = 5.8 Hz, 2H), 2.49 (bt, *J* = 7.0 Hz, 2H), 1.81 (app. pent., *J* = 6.5 Hz, 2 H), 1.60-1.48 (m, 2H), 1.46

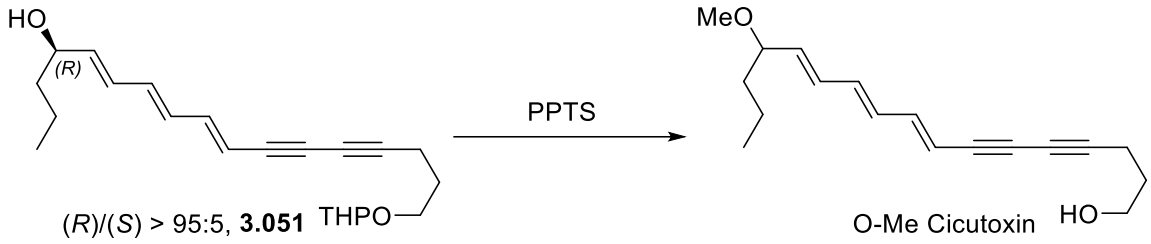
(d, *J* = 4.2 Hz, OH), 1.45-1.33 (m, 3H), 0.93 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$):** δ 144.4, 139.4, 135.4, 131.7, 129.9, 110.1, 85.3, 77.7, 75.2, 72.4, 66.0, 62.4, 39.5, 31.1, 18.7, 16.4, 14.1 ppm. **FTIR ($CHCl_3$, cm^{-1}):** 3348, 2956, 2930, 2871, 1061, 995, 751. **HRMS (ESI) (m/z):** calculated for $[M + Na^+]^+$ $(C_{17}H_{22}O_2Na)^+$: 281.1512, found 281.1512. **$[\alpha]_D$** = -17.1 (c = 0.17, MeOH), **$[\alpha]_D$ (Lit.)** = - 14.9 (c = 1.12, MeOH)[5]

Comparison of spectra of synthetic cicutoxin with that of the isolated cicutoxin

^{1}H NMR (500 MHz, $CDCl_3$) (isolated)[5]	^{1}H NMR (600 MHz, $CDCl_3$) (synthetic)	^{13}C NMR (125 MHz, $CDCl_3$) (isolated)[5]	^{13}C NMR (150 MHz, $CDCl_3$) (synthetic)
6.69 (dd, *J* = 15.5, 10.5 Hz, 1H)	6.70 (dd, *J* = 15.4, 10.7 Hz, 1H)	144.4	144.4
6.24 (dd, *J* = 15.0, 10.5 Hz, 2H)	6.37-6.21 (m, 3H)	139.3	139.4
6.32 (dt, *J* = 15.5, 10.5 Hz, 1H)		135.4	135.4
5.82 (dd, *J* = 15.5, 7.0 Hz, 1H)	5.82 (dd, *J* = 15.2, 6.6 Hz, 1H)	131.6	131.7
5.61 (d, *J* = 15.5 Hz, 1H)	5.60 (d, *J* = 15.4 Hz, 1H)	129.8	129.9
4.19 (m, 1H)	4.22-4.16 (m, 1H)	110.0	110.1
3.76 (t, *J* = 6.0 Hz, 2H)	3.76 (bq, *J* = 5.8 Hz, 2H)	85.3	85.3
2.48 (dt, *J* = 7.0, 1.0 Hz, 2H)	2.49 (bt, *J* = 7.0 Hz, 2 H)	77.7	77.7
1.79 (m, 2H)	1.81 (app. pent., *J* = 6.5 Hz, 2 H)	75.1	75.2
1.54 (m, 2H)	1.60-1.48 (m, 2H)	72.3	72.4
	1.46 (d, *J* = 4.2 Hz, OH)	65.9	66.0
1.39 (m, 2H)	1.45-1.33 (m, 2H and OH)	61.4	62.4
0.92 (m, *J* = 7.0 Hz, 3H),	0.93 (t, *J* = 7.3 Hz, 3H)	39.4	39.5
		31.0	31.1
		18.7	18.7
		16.3	16.4
		14.0	14.1

[5] Ohta, T. *et al. Tetrahedron,* **1999**, *55*, 12087–12098.

6.2.2.6 Syntehsis of O-Me Cicutoxin

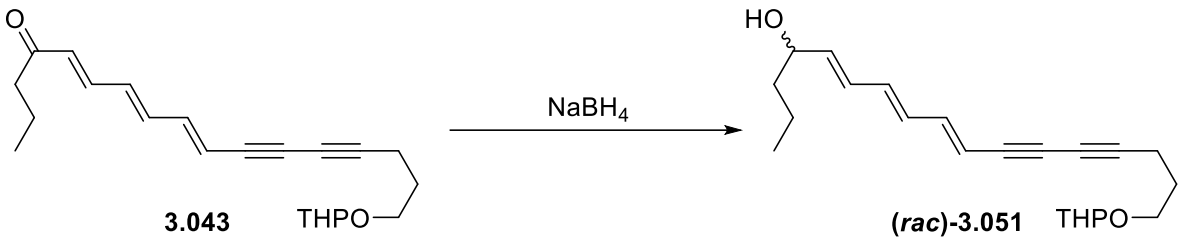


To a solution of alcohol **3.051** (2.1 mg, 6.1 µmol, 1.0 equiv.) in MeOH (0.5 mL) in a glass vial covered by aluminium foil was added pyridinium p-toluenesulfonate (PPTS) (1.5 mg, 6.1 µmol, 1.0 equiv.) and the mixture was stirred for 2 h at 45 °C. The crude mixture was quenched by sat. $NaHCO_3$ (aq.) (1.0 mL), after concentrating, the water phase was extracted by EtOAc (3 x 10 mL). The combined organic phase was washed by brine, dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel prewashed with Et_3N/EtOAc/heptane 5:20:80, elution with 20% EtOAc in heptane) afforded O-Me cicutoxin 1.0 mg (60%) as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 3366, 2958, 2930, 2871, 1111, 1084, 996, 764, 750. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.71 (dd, *J* = 15.4, 10.8 Hz, 1H), 6.33 (dd, *J* = 14.8, 10.6 Hz, 1H), 6.24 (dd, *J* = 14.8, 11.0 Hz, 1H), 6.20 (dd, *J* = 15.2, 10.7 Hz, 1H), 5.65 (dd, *J* = 15.2, 7.9 Hz, 1H), 5.61 (d, *J* = 15.4 Hz, 1H), 3.78-3.74 (bq, *J* = 5.8 Hz, 2H), 3.59 (bq, *J* = 7.0 Hz, 1H), 3.26 (s, 3H), 2.49 (td, *J* = 7.0, 0.7 Hz, 2H), 1.81 (app. pent., *J* = 6.5 Hz, 2H), 1.62-1.55 (m, 1H), 1.48-1.41 (m, 1H), 1.40-1.29 (m, 3H), 0.90 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$):** δ 144.5, 137.6, 135.4, 131.8, 131.6, 110.0, 85.3, 81.9, 77.7, 75.2, 66.0, 61.6, 56.5, 37.8, 31.1, 18.7, 16.4, 14.2 ppm. **HRMS (ESI) (m/z):** calculated for $[M + Na]^+$ $(C_{18}H_{24}O_2Na)^+$ requires 295.1669, found: 295.1662.

Although the compound O-Me cicutoxin was claimed in the literature[6], the reported characterization data (^{13}C NMR was not provided, HRMS was not in agreement with the structure and ^{1}H NMR was not in full agreement with our isolated product.) is not consistent with our product.

[6] Uwai K. *et al*. *J. Med. Chem.*, **2000**, *43*, 4508-4515.

6.2.2.7 Synthesis of (*rac*)-Cicutoxin

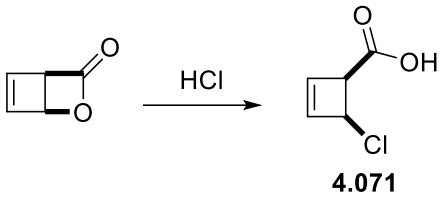


To a solution of ketone **3.043** (17.0 mg, 50 µmol, 1.0 equiv.) in MeOH (1 mL) in a glass vial, covered with aluminium foil, was added $NaBH_4$ (2.8 mg, 0.26 mmol, 1.5 equiv.) and the mixture was stirred for 15 min at 0 °C. Then the mixture was carefully quenched by addition of sat. NH_4Cl (aq.) (2 mL), and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed by brine and dried with $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel prewashed with Et_3N/EtOAc/heptane 5:20:80, elution with 30% EtOAc in heptane) afforded **(*rac*)-3.051** (14.2 mg, 83%) as a colorless oil.

(*rac*)-Cicutoxin: Racemic cicutoxin was prepared according to the procedure described for (*R*)-cicutoxin.

6.3 Total Synthesis of FR252921, FR252922 and FR256523

6.3.1 Improved Synthesis of Acid 4.071

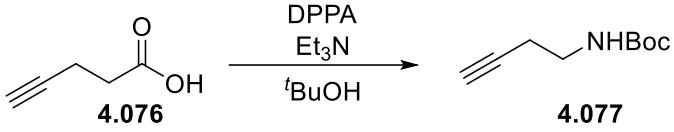


4.071

The acid **4.071** has been synthesized before by our group[7]. We describe herein an improved synthesis of **4.071** through modification of the purification conditions.

The bicyclobutene lactone (0.3 M, 34 mL, Et_2O) was stirred with activated 3 Å molecular sieves (10 g) at -20 °C for 15 min. Then dry HCl (2 M in Et_2O, 20 mL) was added. The solution was then stirred vigorously at -20 °C for another 24 h. The mixture was then allowed to warm to rt, concentrated. Purification by column chromatography (silica gel, Heptane/EtOAc = 4:1, 3% AcOH as additive) afforded 1.10 g (83%) of **4.071** as a colorless powder.

6.3.2 Synthesis of Salt 4.079

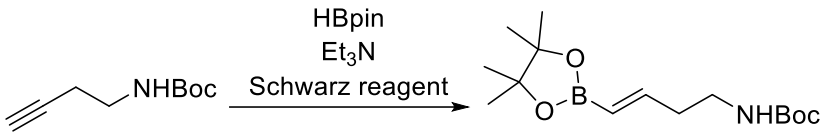


4.076 **4.077**

To a two necked 250 mL round bottom flask was added 10 g 3 Å molecular sieves, pent-4-ynoic acid **4.076** (4.80 g, 48.9 mmol, 1.0 equiv.) and ^tBuOH (150 mL). The solution was stirred at room temperature for 30 min. Then diphenyl phosphoryl azide (DPPA) (11.6 mL, 54 mmol, 1.1 equiv.) and Et_3N (7.5 mL, 54 mmol, 1.1 equiv.) were added. The resulted mixture was heated to reflux for 12 h. Then the mixture were concentrated under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 3:1) afforded 5.38 g (65%) of the desired product **4.077** as a colorless oil. The spectral data is in accordance with the literature[8].

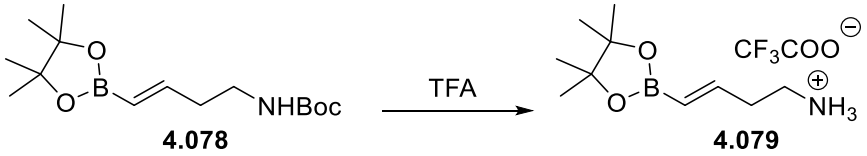
[7] Audisio, D., Luparia, M., Oliveira, M. T., Klütt, D., Maulide, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 7314-7317.

[8] Adriaenssens, L., Sánchez, J. L. A., Barril, X., O´Sullivan, C. K., Ballester, P. *Chem. Sci.* **2014**, *5*, 4210-4215.



4.077 **4.078**

In a dry flask, tert-butyl but-3-yn-1-ylcarbamate **4.077** (8.40 g, 49.7 mmol, 1.0 equiv.) was charged. The flask was flushed over 5 min with Argon. Pinacol borane (8.6 mL, 59.6 mmol, 1.2 equiv.) was added, followed by Cp_2ZrHCl (Schwarz reagent) (1.28 g, 4.97 mmol, 10 mol%) and Et_3N (0.70 mL, 4.97 mmol, 10 mol%). The mixture was stirred at 60°C for 16 h. Then the reaction mixture was cooled down to room temperature. The mixture were concentrated under reduced pressure. Purification by column chromatography (silica gel, Pentane/EtOAc: 7/3) afforded 12.6 g (85%) of the desired hydroborated product **4.078** as a white solid after stored in refridge. **FTIR ($CHCl_3$, cm^{-1}):** 3339, 2978, 1714, 1639, 1359, 1144, 850. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 6.53 (dt, *J* = 17.9, 6.7, 1H) 5.49 (d, *J* = 17.9, 1H), 4.56 (brd, 1H), 3.24-3.17 (m, 2H), 2.33 (app. q, *J* = 6.6, 2H), 1.41 (s, 9H), 1.25 (s, 12H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$)** δ 156.0, 150.7, 121.5, 83.4, 79.3, 39.3, 36.3, 28.7, 25.1 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{15}H_{28}BNO_4Na$) requires 320.2002, found 320.2003.

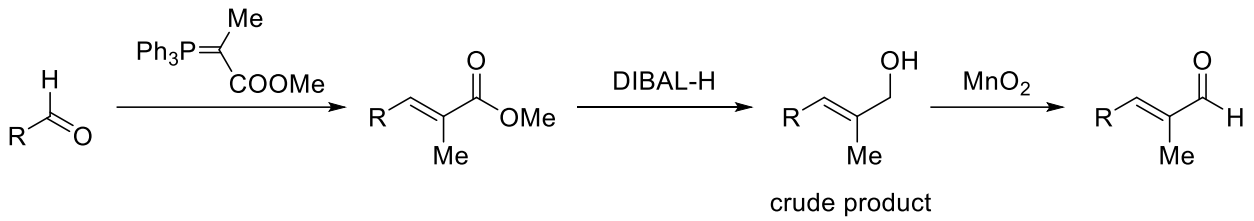


4.078 **4.079**

To a stirred solution of tert-butyl (*E*)-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)carbamate **4.078** (8.30 g, 27.9 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) was added trifluoroacetic acid (TFA) (21.3 mL, 115 mmol, 10 equiv.). The resulting mixture was vigorously stirred at room temperature for 1 h. Then CH_2Cl_2 and TFA was removed under vacuum to give the crude amine salt **4.079** (8.60 g) as a yellowish oil which was used in the next step without further purification.

6.3.2 Synthesis of Aldehydes

6.3.2.1 General Procedure 1 (GP1)

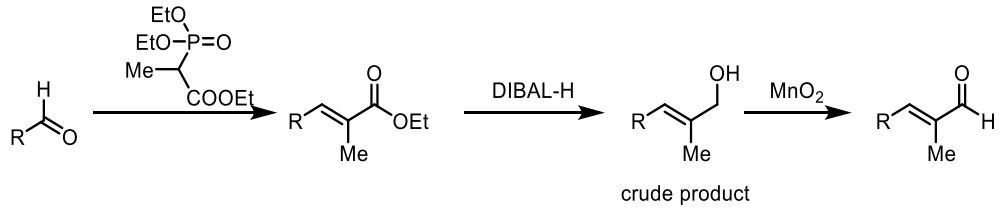


1) At room temperature, the aldehyde (1.0 equiv.) was dissolved in toluene and Wittig reagent (1.1 equiv.) was added. Reaction was stirred at 80 °C for 12 h, then cooled to room temperature and the solvent was evaporated under vacuo. Crude product was purified by column chromatography on silica gel to give the pure ester or directly used in the next step after simple filtration over silica.

2) The ester obtained was then dissolved in CH_2Cl_2. At 0 °C, diisobutylaluminium hydride (DIBAL-H) (2.5 equiv.) was dropwise added. After 1 h, the mixture was first carefully quenched by Rochelle salt solution. The resulting mixture was allowed to stir vigorously till the organic and aqueous phases separated. Then the mixture was extracted by CH_2Cl_2 3 times. The combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used directly in the next step without further purification.

3) The crude alcohol (1.0 equiv.) was dissolved in CH_2Cl_2, and then activated MnO_2 (15 equiv.) was added. The mixture was stirred vigorously for 5 h. Then the mixture was filtrated, the filtration was concentrated under reduced pressure. Purification by column chromatography on silica gel delivered the desired aldehyde.

6.3.2.2 General Procedure 2 (GP2)

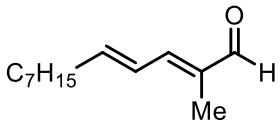


1) At 0 °C, the phosphonate (1.2 equiv.) was dissolved in THF, then NaH (1.3 equiv.) was dropwise added. The mixture was stirred for 30 min. The the aldehyde (1.0 equiv.) in THF solution was added, and the

mixture was stirred for another 2 h. The reaction was carefully quenched by sat. NH_4Cl. The aqueous phase was extracted by EtOAc 3 times. The combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Crude product was purified by column chromatography on silica gel to give the pure ester.

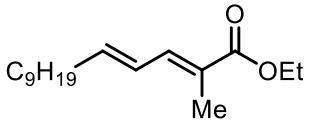
2) The ester obtained was then dissolved in CH_2Cl_2. At 0 °C, diisobutylaluminium hydride (DIBAL-H) (2.5 equiv.) was dropwise added. After 1 h, the mixture was first carefully quenched by Rochelle salt solution. The resulting mixture was allowed to stir vigorously till the organic and aqueous phases separated. Then the mixture was extracted by CH_2Cl_2 3 times. The combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used directly in the next step without further purification.

3) The crude alcohol (1.0 equiv.) was dissolved in CH_2Cl_2, and then activated MnO_2 (15 equiv.) was added. The mixture was stirred vigorously for 5 h. Then the mixture was filtrated, the filtration was concentrated under reduced pressure. Purification by column chromatography on silica gel delivered the desired aldehyde.



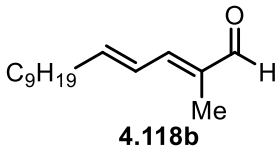
4.118a

Yield: 63% over 3 steps (GP2). The spectra data is in accordance with the literature[9].



4.118b'

Yield: 92% (GP2). **FTIR ($CHCl_3$, cm^{-1}):** 2925, 1706, 1234. **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 6.25 (ddt, *J* = 14.9, 10.8, 1.3 Hz, 1H), 6.02 (d, *J* = 10.8 Hz, 1H), 5.78-5.64 (m, 1H), 4.05 (s, 2H), 2.11 (q, *J* = 7.0 Hz, 2H), 1.78 (s, 3H), 1.46-1.34 (m, 2H), 1.28 (d, *J* = 13.8 Hz, 12H), 0.88 (t, *J* = 6.9 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.7, 135.5, 134.8, 125.9, 125.6, 68.9, 33.1, 32.1, 29.7, 29.7, 29.6, 29.5, 29.4, 22.8, 14.2, 14.2 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{17}H_{30}O_2Na$) requires 289.2138, found 289.2135.

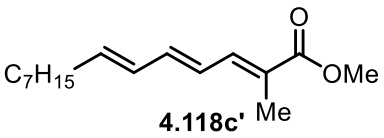


4.118b

Yield: 76% over 2 steps (GP1). **FTIR ($CHCl_3$, cm^{-1}):** 2924, 2854, 1682, 1635, 1463, 1206, 966. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.42 (s, 1H), 6.81 (d, *J* = 11.1 Hz, 1H), 6.51 (ddt, *J* = 15.1, 11.1, 1.4 Hz, 1H), 6.27-6.20 (m, 1H), 2.26-2.21 (m, 2H), 1.83 (d, *J* = 0.7 Hz, 3H), 1.50-1.43 (m, 2H), 1.30-1.27 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm. **^{13}C NMR (100 MHz;**

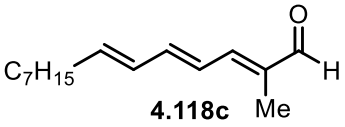
[9] Falck, J. R., He, A., Fukui, H., Tsutsui, H.; Radha, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4527-4529.

$CDCl_3$): δ 195.2, 149.4, 146.1, 136.1, 126.0, 33.6, 32.0, 29.66, 29.58, 29.44, 29.37, 28.9, 22.8, 14.2, 9.5 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{15}H_{26}ONa$) requires 245.1876, found m/z 245.1876.



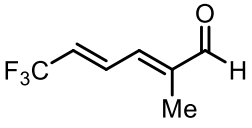
4.118c'

Yield: 91% (GP1). **FTIR ($CHCl_3$, cm^{-1}):** 2926, 2855, 1708, 1614, 1435, 1249, 1225, 1098, 990, 750.**^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.22-7.20 (m, 1H), 6.50 (dd, *J* = 14.8, 10.6 Hz, 1H), 6.38 (dd, *J* = 14.8, 11.4 Hz, 1H), 6.18 (dd, *J* = 15.1, 10.5 Hz, 1H), 5.94-5.86 (m, 1H), 3.75 (s, 3H), 2.14 (dd, *J* = 14.3, 7.1 Hz, 2H), 1.95 (d, *J* = 1.1 Hz, 1H), 1.43-1.40 (m, 2H), 1.29-1.28 (m, 8H), 0.88 (t, *J* = 6.0 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.1, 140.16, 139.89, 138.9, 130.4, 126.0, 125.7, 51.9, 33.1, 32.0, 29.33, 29.29, 29.20, 22.8, 14.2, 12.8 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{16}H_{26}O_2Na$) requires 273.1831, found: 273.1820.



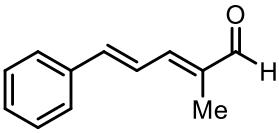
4.118c

Yield: 62% over 2 steps (GP1). **FTIR ($CHCl_3$, cm^{-1}):** 2926, 2855, 1678, 1611, 1195, 998, 837. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.43(s, 1H), 6.85 (dd, *J* = 10.9, 1.3 Hz, 1H), 6.66-6.51 (m, 2H), 6.23 (ddt, *J* = 15.1, 10.0, 1.3 Hz, 1H), 6.04-5.97 (m, 1H), 2.20-2.14 (m, 2H), 1.85 (d, *J* = 1.0 Hz, 3H), 1.46-1.39 (m, 2H), 1.33-1.26 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 194.8, 149.1, 142.1, 142.0, 137.0, 130.3, 125.3, 33.2, 31.9, 29.31, 29.27, 29.1, 22.8, 14.2, 9.6 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{15}H_{24}ONa$) requires 243.1719, found 243.1715.



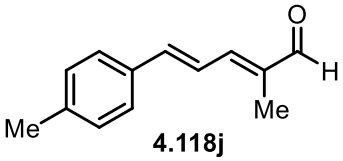
4.118h

Yield: 53% over 3 steps (GP1). **(Volatile). ^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.55 (s, 1H), 7.21 (m, 1H), 6.84 (d, *J* = 11.3 Hz, 1H), 6.13 (m, 1H), 1.94 (s, 3H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 194.15, 142.37, 131.45 (q, *J* = 6.8 Hz), 125.50 (q, *J* = 34.3 Hz), 9.90 ppm.



4.118i

Yield: 54% over 3 steps (method A). The spectra data is in accordance with the literature[10].

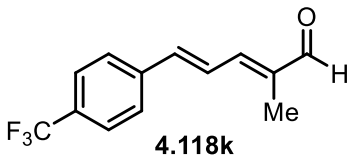


4.118j

Yield: 73% over 3 steps (GP1). **FTIR ($CHCl_3$, cm^{-1}):** 1671, 1619, 1192, 1180, 1012, 965, 803. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.50 (s, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.15-7.20 (m, 3H), 7.01 (d, *J* = 11.2 Hz, 1H), 6.97 (d, *J* = 15.4 Hz, 1H), 2.38 (s, 3H), 1.95 (s, 3H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 194.8,

[10] Riveira, M. J. *et al. Org. Biomol. Chem.* **2011**, *9*, 3170-3175.

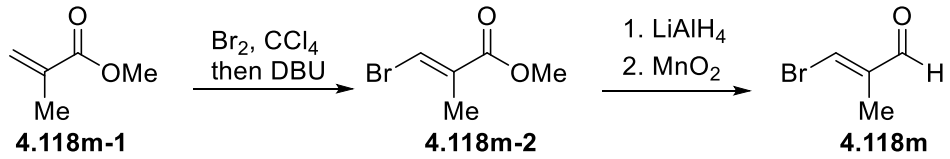
149.0, 141.2, 139.7, 133.3, 129.6, 127.4, 122.5, 21.4, 9.7 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{13}H_{14}NaO$) requires 209.0937, found 209.0936.



4.118k

Yield: 35% over 3 steps (GP1). **FTIR ($CHCl_3$, cm^{-1}):** 1671, 1621, 1322, 1193, 1164, 1121, 1066, 966, 803. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.53 (s, 1H), 7.61-7.64 (m, 3H), 7.30 (dd, *J* = 15.5, 11.2 Hz, 2H), 6.99-7.04 (m, 2H), 1.97 (s, 3H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 194.6, 147.4, 139.4, 138.9, 127.5, 125.82 (q, *J* = 3.8 Hz), 125.6, 9.8 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{13}H_{11}F_3NaO$) requires 263.0654, found *m/z* 263.0652.

6.3.2.3 Procedure for the Aldehyde 4.118m[11]



4.118m-1 **4.118m-2** **4.118m**

To a solution of dimethyl acrylate **4.118m-1** (5.00 g, 44.9 mmol, 1.0 equiv.) in CCl_4 solution (40 mL) cooled in an ice-water bath was slowly added a solution of bromine (2.8 mL, 54.9 mmol, 1.1 equiv.) in CCl_4 (10 mL). The mixture was then stirred for 2 h at 25 °C. The reaction mixture was cooled to 0 °C again and DBU (11.2 mL, 74.9 mmol, 1.5 equiv.) was added dropwise. The resultant mixture was stirred at this temperature for 15 min, and then at 25 ºC for 5 h. The reaction was acidified with an aqueous solution of 1 N HCl to pH 1-2. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give the bromo ester **4.118m-2** as a colorless oil (6.00 g, 67%), which was used for next without further purification.

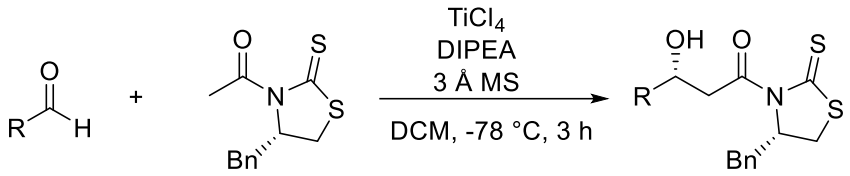
To a solution of the bromo ester **4.118m-2** (6.00 g, 33.5 mmol, 1.0 equiv.) in dry CH_2Cl_2 (50 mL) cooled in an ice-water bath (0 °C) was added $LiAlH_4$ (3.82 g, 101 mmol, 3.0 equiv.). The resultant suspension was stirred at the same temperature for 2 h. The reaction was quenched by careful addition of saturated aqueous sodium potassium tartrate (Rochelle's salt) (50 mL) and the resulting mixture was vigorously stirred at room temperature for 1 h. The mixture was diluted with water and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was washed with brine, dried

[11] Wang, Y., Dai, W. M. *Eur. J. Org. Chem.* **2014**, 323-330.

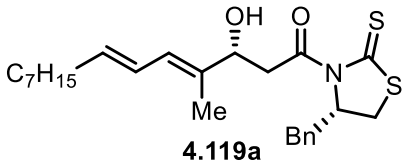
over anhydrous MgSO4, and concentrated under reduced pressure to give the corresponding allylic alcohol (1.50 g, 26%) which was used directly in the following step.

A suspension of the above allylic alcohol (1.50 g, 8.98 mmol, 1.0 equiv.) and activated MnO_2 (7.80 g, 89.8 mmol, 10 equiv.) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 1 h. The reaction mixture was filtered through a pad of Celite with washing by CH_2Cl_2. The combined filtrate was concentrated under reduced pressure, after column chromatography (Et_2O) to give aldehyde **4.118m-2** (700 mg, 52%). **4.118m-2** was volatile, and should be handled with great care. The spectra data is in accordance with the literature[12].

6.3.3 Synthesis of Aldol Adducts



To a flame-dried schlenk tube was added thiazolidine (1 equiv.) and CH_2Cl_2. At -78 °C, $TiCl_4$ (1 M in CH_2Cl_2, 1.1 equiv.) was added and the mixture stirred for 10 min. Afterwards DIPEA (1.1 equiv.) was added slowly and the solution was stirred for 30 min at -78 °C. Then the aldehyde (1.1 equiv.) dissolved in CH_2Cl_2 was added dropwise to the mixture. The solution was stirred at -78 °C for 3 h. Then the reaction was quenched with sat. NH_4Cl (aq.) at -78 °C and allowed to reach room temperature. The aqueous layer was extracted 3 times with CH_2Cl_2. The organic layers were combined, washed by brine, dried over Na_2SO_4 and concentrated in vacuum. The crude oil was purified by column chromatography (silica gel, Heptane/EtOAc = 9:1 to 7:3).

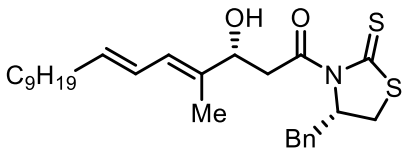


4.119a

Yield: 3.40 g, 74%, d.r. = 7.7:1. **FTIR ($CHCl_3$, cm^{-1}):** 2924, 2854, 1693, 1343, 1163, 1137, 1044, 965. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.36-7.34 (m, 2H), 7.30-7.27 (m, 3H), 6.25 (ddt, *J* = 14.9, 10.8, 1.3 Hz, 1H), 6.11 (d, *J* = 10.9 Hz, 1H), 5.75-5.70 (m, 1H), 5.39-5.36 (m, 1H), 4.64 (d, *J* = 9.6 Hz, 1H), 3.55 (dd, *J* = 17.4, 2.5 Hz, 1H), 3.44-3.39 (m, 2H), 3.24 (dd, *J* = 13.2, 3.8 Hz, 1H), 3.05 (dd, *J* = 13.2, 10.6 Hz, 1H), 2.90 (d, *J* = 11.5 Hz, 1H), 2.54 (d, *J* = 3.3 Hz, 1H), 2.12-2.01 (m, 2H), 1.78 (s, 3H), 1.39-1.36 (m, 2H), 1.31-1.25 (m, 8H), 0.88 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 201.5, 173.0,

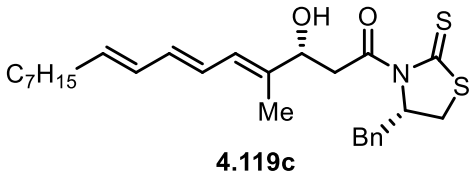
[12] Koukal, P., Ulč, J., Nečas, D., Kotora, M. *Eur. J. Org. Chem.* **2016**, 2110-2114.

136.6, 136.3, 135.1, 129.6, 129.1, 127.4, 125.9, 125.8, 72.8, 68.6, 44.5, 36.9, 33.2, 32.3, 32.0, 29.5, 29.33, 29.31, 22.8, 14.3, 13.0 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{25}H_{35}NO_2S_2Na$) requires m/z 468.2001, found m/z 468.1988. $[\alpha]_D^{20}$ = +155 (c = 0.94, $CHCl_3$).



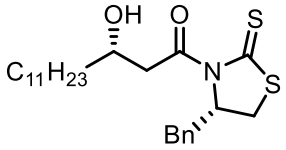
4.119b

Yield: 360 mg, 62%, d.r = 9.1:1. **FTIR ($CHCl_3$, cm^{-1}):** 2924, 2853, 1696, 1343, 1164, 1137, 1045, 966. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.36-7.34 (m, 2H), 7.30-7.27 (m, 3H), 6.24 (dd, *J* = 15.0, 10.8 Hz, 1H), 6.11 (d, *J* = 10.9 Hz, 1H), 5.75-5.70 (m, 1H), 5.39-5.36 (m, 1H), 4.64 (d, *J* = 9.6 Hz, 1H), 3.55 (dd, *J* = 17.4, 2.5 Hz, 1H), 3.44-3.39 (m, 2H), 3.24 (dd, *J* = 13.2, 3.8 Hz, 1H), 3.05 (dd, *J* = 13.2, 10.6 Hz, 1H), 2.90 (d, *J* = 11.5 Hz, 1H), 2.54 (d, *J* = 3.6 Hz, 1H), 2.12-2.09 (m, 2H), 1.78 (s, 3H), 1.39-1.37 (m, 2H), 1.26 (brd, 12H), 0.88 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 201.5, 173.0, 136.6, 136.3, 135.1, 129.6, 129.1, 127.4, 125.9, 125.7, 72.8, 68.6, 44.5, 36.9, 33.1, 32.3, 32.0, 29.70, 29.7, 29.5, 29.5, 29.4, 22.8, 14.3, 13.0 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{27}H_{39}NO_2S_2Na$) requires 496.2314, found 496.2316. $[\alpha]_D^{20}$ = +153 (c = 1.09, $CHCl_3$).



4.119c

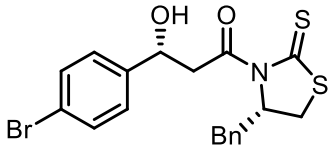
Yield: 170 mg, 62%, d.r. = 11:1. **FTIR ($CHCl_3$, cm^{-1}):** 2924, 2854, 1739, 1695, 1345, 1164, 1137, 1045, 987. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.37-7.33 (m, 2H), 7.30-7.26 (m, 3H), 6.33 (dd, *J* = 14.4, 10.8 Hz, 1H), 6.25-6.08 (m, 3H), 5.76-5.68 (m, 1H), 5.40-5.35 (m, 1H), 4.65 (d, *J* = 9.4 Hz, 1H), 3.57 (dd, *J* = 17.4, 2.8 Hz, 1H), 3.46-3.38 (m, 2H), 3.24 (dd, *J* = 13.2, 3.8 Hz, 1H), 3.05 (dd, *J* = 13.2, 10.5 Hz, 1H), 2.90 (d, *J* = 11.6 Hz, 1H), 2.59 (d, *J* = 3.5 Hz, 1H), 2.12-2.07 (m, 2H), 1.80 (d, *J* = 0.6 Hz, 3H), 1.40-1.37 (m, 2H), 1.32-1.27 (m, 8H), 0.88 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 201.5, 172.9, 137.1, 136.6, 135.9, 134.0, 130.6, 129.6, 129.1, 127.4, 126.03, 125.97, 72.9, 68.6, 44.5, 37.0, 33.0, 32.3, 32.0, 29.4, 29.3, 22.8, 14.2, 13.2 ppm**. HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{27}H_{37}NO_2S_2Na$) requires 494.2158, found 494.2163. $[\alpha]_D^{20}$ = +106 (c = 1.00, $CHCl_3$).



4.119d

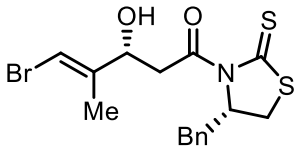
Yield: 678 mg, 60%, d.r. = >20:1. **FTIR ($CHCl_3$, cm^{-1}):** 2924, 2852, 1741, 1697, 1455, 1363, 1342, 1262, 1164, 1044, 701. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39-7.26 (m, 5H), 5.41 (ddd, *J* = 10.6, 6.9, 4.1 Hz, 1H), 4.14 (brd, 1H), 3.65 (dd, *J* = 17.8, 2.4 Hz, 1H), 3.49-3.35 (m, 1H), 3.23 (dd, *J* = 13.2, 3.9 Hz, 1H), 3.13 (dd, *J* = 17.8, 9.4 Hz, 1H), 3.05 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.90 (d, *J* = 11.6 Hz, 1H), 2.68 (d, *J* = 3.8 Hz, 1H), 1.63-1.18 (m, 20H), 0.88 (t, *J* = 6.9 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 201.6, 173.5, 136.6, 129.6, 129.1, 127.4, 68.5, 68.0, 46.1, 37.0, 36.6, 32.2, 32.1, 29.81, 29.78, 29.8, 29.7, 29.7, 29.5, 25.7, 22.8, 14.3 ppm.

HRMS (ESI) (m/z): calculated for $[M+Na]^+$ ($C_{24}H_{37}NO_2S_2Na$) requires 458.2158, found 458.2159. $[\alpha]_D^{20}$ = +176 (c = 1.12, $CHCl_3$).



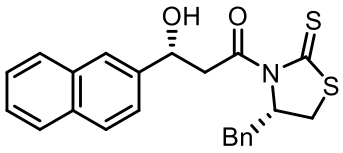
4.119l

Yield: 480 mg, 75%, d.r. = 15:1. **FTIR ($CHCl_3$, cm^{-1}):** 1689, 1488, 1342, 1258, 1163, 1044, 749. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.53-7.46 (m, 2H), 7.38-7.34 (m, 2H), 7.31-7.28 (m, 5H), 5.40 (ddd, *J* = 10.8, 7.0, 4.1 Hz, 1H), 5.29-5.19 (m, 1H), 3.82 (dd, *J* = 17.6, 2.6 Hz, 1H), 3.49 (dd, *J* = 17.6, 9.4 Hz, 1H), 3.40 (dd, *J* = 11.6, 7.2 Hz, 1H), 3.25 (dd, *J* = 13.2, 4.0 Hz, 1H), 3.11 (d, *J* = 4.0 Hz, 1H), 3.06 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.92 (d, *J* = 11.6 Hz, 1H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 201.5, 172.6, 141.5, 136.4, 131.8, 129.6, 129.1, 127.6, 127.5 121.7, 69.5, 68.4, 47.4, 37.0, 32.3 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{19}H_{18}NO_2BrS_2Na$) requires 459.9834, found 459.9831. $[\alpha]_D^{20}$ = +177 (c = 1.15, $CHCl_3$).



4.119m

Yield: 2.88 g, 89%, d.r. = 14:1. **FTIR ($CHCl_3$, cm^{-1}):** 1689, 1342, 1294, 1257, 1164, 1137, 1044. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.41-7.26 (m, 5H), 6.43-6.34 (m, 1H), 5.39 (ap ddd, *J* = 10.6, 6.8, 4.2 Hz, 1H), 4.68 (dt, *J* = 9.6, 2.7 Hz, 1H), 3.66 (dd, *J* = 17.5, 2.5 Hz, 1H), 3.43 (ddd, *J* = 11.6, 7.2, 0.8 Hz, 1H), 3.36 (dd, *J* = 17.5, 9.6 Hz, 1H), 3.23 (dd, *J* = 13.2, 4.0 Hz, 1H), 3.05 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.92 (d, *J* = 11.6 Hz, 1H), 2.84 (d, *J* = 3.9 Hz, 1H), 1.84 (d, *J* = 1.1 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 201.6, 172.4, 141.9, 136.4, 129.6, 129.1, 127.5, 105.7, 71.7, 68.5, 44.2, 37.0, 32.4, 16.1 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{16}H_{18}NO_2BrS_2Na$) requires 423.9834, found 423.9834. $[\alpha]_D^{20}$ = +143 (c = 1.20, $CHCl_3$).

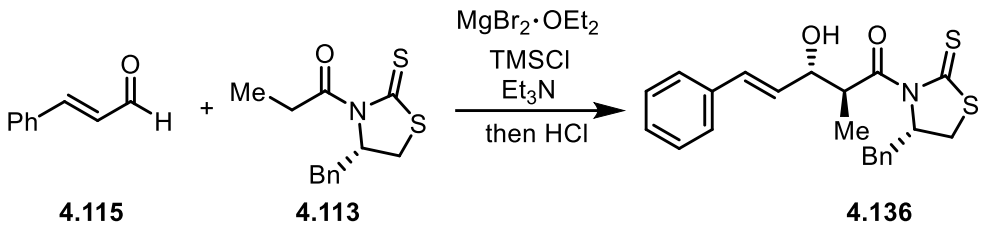


4.119n

Yield: 378 mg, 73%, d.r. = >20:1. **FTIR ($CHCl_3$, cm^{-1}):** 1690, 1343, 1258, 1165, 1137, 1044, 747, 702. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.85 (ddd, *J* = 12.9, 10.0, 4.7 Hz, 4H), 7.49 (tdd, *J* = 8.7, 7.7, 3.4 Hz, 3H), 7.36 (dd, *J* = 9.4, 5.5 Hz, 2H), 7.33-7.27 (m, 3H), 5.46 (dt, *J* = 9.3, 2.8 Hz, 1H), 5.39 (ddd, *J* = 10.8, 7.1, 4.0 Hz, 1H), 3.89 (dd, *J* = 17.6, 2.6 Hz, 1H), 3.67 (dd, *J* = 17.6, 9.5 Hz, 1H), 3.36 (dd, *J* = 11.6, 7.2 Hz, 1H), 3.27 (dd, *J* = 13.1, 3.9 Hz, 1H), 3.20 (d, *J* = 3.9 Hz, 1H), 3.06 (dd, *J* = 13.1, 10.5 Hz, 1H), 2.89 (d, *J* = 11.6 Hz, 1H) ppm.**^{13}C NMR (151 MHz, $CDCl_3$)**: δ 201.5, 172.8, 139.9, 136.5, 133.4, 133.1, 129.6, 129.1, 128.6, 128.2, 127.8, 127.4, 126.4, 126.1, 124.6, 124.0, 70.3, 68.5, 47.5, 36.9, 32.3 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{23}H_{21}NO_2S_2Na$) requires 430.0906, found 430.0908. $[\alpha]_D^{20}$ = +157 (c = 1.23, $CHCl_3$).

6.3.4 Synthesis of Fragment 2

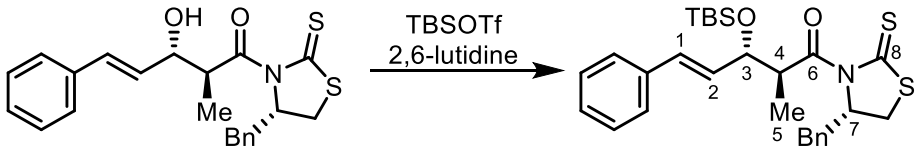
6.3.4.1 Route 1



4.115 **4.113** **4.136**

Compound **4.136** was prepared as described in the literature[13].

To a 100 mL flame dried flask were added $MgBr_2$-OEt_2 (632 mg, 2.45 mmol, 0.1 equiv.) and acylthiazolidinethione **4.113** (6.50 g, 24.5 mmol, 1 equiv.). Then EtOAc (61 mL) was added, sequentially followed by aldehyde **4.115** (3.4 mL, 26.9 mmol, 1.1 equiv.), Et_3N (6.8 mL, 49.0 mmol, 2.0 equiv.) and freshly distilled TMSCl (4.7 mL, 36.8 mmol, 1.5 equiv.). The cloudy, yellow reaction mixture was stirred at room temperature for 24 h. The suspension was filtered directly through a plug of silica gel (5.0 cm x 5.0 cm) and eluted with Et_2O. The eluent was concentrated in vacuo. The unpurified mixture was dissolved in THF (100 mL) and treated with 1.0 N HCl (20 mL). After stirring 1 h, the mixture was diluted with Et_2O (200 mL) and water (200 mL). The layers were separated and the organic layer was extracted sequentially with saturated $NaHCO_3$ (100 mL) and brine (50mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude oil was purified by column chromatography (silica gel, Heptane/EtOAc = 4:1 to 2:1) to afford 9.16 g (94%) of **4.136** as a yellowish oil. The ^{1}H NMR data is in agreement with the literature[13].

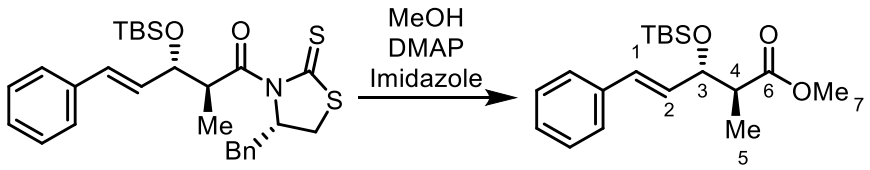


4.136 **4.136-1**

To a stirred solution of **4.136** (630 mg, 1.58 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL) at -78 °C was added 2,6-lutidine (0.28 mL, 2.38 mmol, 1.5 equiv.). Then TBSOTf (0.44 mL, 1.90 mmol, 1.2 equiv.) was dropwise added. The resultant mixture was stirred at -78 °C for 30 min. Then the reaction was quenched by 1 N HCl (3 mL), and extracted by CH_2Cl_2 (3 x 10 mL). The collected organic phase was washed by brine, dried over

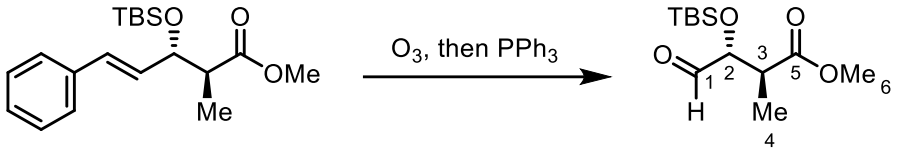
[13] Evans, D. A., Downey, C. W., Shaw, J. T., Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127-1130.

Na_2SO_4, filtered and concentrated in vacuo. The mixture was purified by column chromatography (silica gel, Heptane/EtOAc = 20:1) to afford 760 mg (94%) of **4.136-1** as a yellow foam. **FTIR ($CHCl_3$, cm^{-1}):** 2953, 2929, 1695, 1259, 1164, 836. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.28 (m, 10H, **ArH**), 6.54 (d, *J* = 15.9 Hz, 1H, **H1**), 6.06 (dd, *J* = 15.9, 7.9 Hz, 1H, **H2**), 5.26-5.21 (m, 1H, **H7**), 4.55-4.44 (m, 2H), 3.34-3.28 (m, 2H), 3.06 (dd, *J* = 13.1, 10.6 Hz, 1H), 2.88 (d, *J* = 11.5 Hz, 1H), 1.17 (d, *J* = 6.5 Hz, 3H, **H5**), 0.85 (s, 9H, **TBS-H**), 0.07 (s, 3H, **TBS-H**), 0.02 (s, 3H, **TBS-H**) ppm.**^{13}C NMR (100 MHz, $CDCl_3$)**: δ 201.4 (**C8**), 177.3 (**C6**), 136.9 (**Ar-C, quaternary**), 136.6 (**Ar-C, quaternary**), 132.7, 130.5, 129.6, 129.0, 128.8, 128.0, 127.3, 126.7, 78.3 (**C3**), 69.2 (**C7**), 46.2 (**C4**), 36.7 (**C**H2), 32.5 (**C**H2), 25.9 (**TBS-C**), 18.1 (**TBS-C**), 14.6 (**C5**), -3.6 (**TBS-C**), -3.7 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{28}H_{37}NO_2S_2SiNa$) requires 534.1927, found 534.1927. **$[\alpha]_D^{20}$** = +172 (c = 0.80, $CHCl_3$).



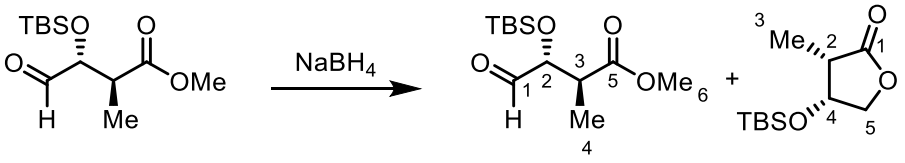
4.136-1 **4.160**

To a stirred solution of **4.136-1** (525 mg, 1.03 mmol, 1.0 equiv.) in MeOH (15 mL) was added DMAP (125 mg, 1.03 mmol, 1.0 equiv.) and imidazole (698 mg, 10.3 mmol, 10 equiv.). The mixture was stirred at room temperature for 13 h till the starting material **4.136-1** was not observed on crude ^{1}H NMR. Then MeOH was removed under reduced pressure. The crude mixture was acidified by 1 N HCl (30 mL), extracted by EtOAc (3 x 15 mL). The collected organic phase was washed by brine, dried over $MgSO_4$ filtered and concentrated. The mixture was purified by column chromatography (silica gel, Heptane/EtOAc = 20:1) to afford 350 mg (quantitative) of **4.160** as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 2953, 2930, 2857, 1740, 1254, 1061, 836, 777. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39-7.31 (m, 4H, **ArH**),7.27-7.25 (m, 1H, **ArH**), 6.53 (d, *J* = 15.9 Hz, 1H, **H1**), 6.06 (dd, *J* = 15.9, 7.6 Hz, 1H, **H2**), 4.42 (t, *J* = 8.2 Hz, 1H, **H3**), 3.70 (s, 3H, **H7**), 2.68-2.61 (m, 1H, **H4**), 1.08 (d, *J* = 7.1 Hz, 3H, **H5**), 0.87 (s, 9H, **TBS-H**), 0.06 (s, 3H, **TBS-H**), 0.03 (s, 3H, **TBS-H**) ppm.**^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.5 (**C6**), 136.8 (**ArC, quaternary**), 132.1, 130.3, 128.7, 127.8, 126.7, 76.3 (**C3**), 51.7 (**C7**), 47.5 (**C4**), 25.9 (**TBS-C**), 18.2 (**TBS-C**), 13.3 (**C5**), -3.8 (**TBS-C**), -5.0 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{19}H_{30}O_3SiNa$) requires 357.1856, found 357.1858. **$[\alpha]_D^{20}$** = +64.6 (c = 0.98, $CHCl_3$).



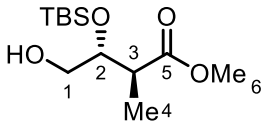
4.160 **4.160-1**

To a 25 mL two-necked round bottom flask was added **4.160** (34 mg, 0.10 mmol, 1.0 equiv.) and CH_2Cl_2 (3 mL). Then the solution was cooled to -78 °C and bubbled with O_3 till the color of the solution changed to blue. The remaining O_3 was bubbled out by O_2 till the color of the solution changed back to colorless. Then PPh_3 (53 mg, 0.20 mmol, 2.0 equiv.) was added. The mixture was stirred for 15 h and allowed to warm to room temperature. The crude mixture was concentrated and purified by column chromatography (silica gel, Heptane/EtOAc = 20:1 to 10:1) to afford 24 mg (92%) of the product **4.160-1** as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 2953, 2930, 2857, 1740, 1254, 1061, 836, 777. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.63 (d, *J* = 1.5 Hz, 1H, **H1**), 4.03 (dd, *J* = 4.8, 1.5 Hz, 1H, **H2**), 3.68 (s, 3H, **H6**), 2.97-2.91 (m, 1H, **H3**), 1.21 (d, *J* = 7.1 Hz, 3H, **H4**), 0.90 (s, 9H, **TBS-H**), 0.08 (s, 3H, **TBS-H**), 0.07 (s, 3H, **TBS-H**) ppm.**^{13}C NMR (100 MHz, $CDCl_3$)**: δ 203.1 (**C1**), 172.9 (**C5**), 79.1 (**C2**), 52.0 (**C6**), 43.6 (**C3**), 25.7 (**TBS-C**), 18.2 (**TBS-C**), 13.0 (**C5**), -4.4 (**TBS-C**), -5.0 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{12}H_{24}O_4SiNa$) requires 283.1336, found 283.1329. **$[\alpha]_D^{20}$** = +49.1 (c = 1.22, $CHCl_3$).



4.160-1 **4.161** **4.163**

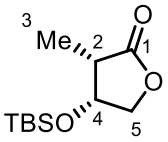
To a stirred solution of **4.160-1** (24 mg, 0.092 mmol, 1.0 equiv.) in MeOH (1.5 mL) at 0 °C was added $NaBH_4$ (8.4 mg, 0.22 mmol, 2.4 equiv.). The resultant mixture was stirred at 0 °C for 10 min before quenched by sat. NH_4Cl (aq.). Then MeOH was removed and the aqueous phase was extracted by EtOAc (3 x 5 mL). The collected organic phase was washed by brine, dried over Na_2SO_4, filtered and concentrated. The product **4.161** was formed, together with **4.163**.



4.161

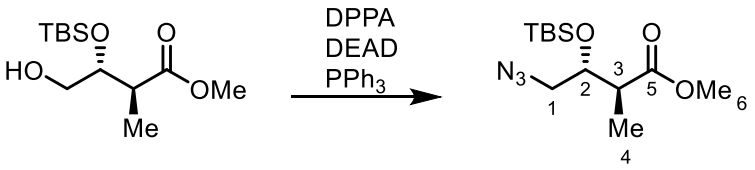
FTIR ($CHCl_3$, cm^{-1}): 3465, 2953, 2931, 2858, 1740, 1256, 1112, 1062, 836, 778. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.96-3.93 (m, 1H), 3.68 (s, 3H, **H6**), 3.62 (d, *J* = 3.9 Hz, 1H), 3.60 (dd, *J* = 3.9, 1.8 Hz, 1H), 2.84-2.77 (m, 1H), 1.87 (dd, *J* = 7.1, 5.8 Hz, 1H, **H3**), 1.13 (d, *J* = 7.1 Hz, 3H, **H4**), 0.88 (s, 9H, **TBS-H**), 0.09 (s, 3H, **TBS-H**), 0.06 (s, 3H, **TBS-H**) ppm.**^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.5 (**C5**), 74.4 (**C2**), 63.7 (**C1**), 51.8 (**C6**), 43.2 (**C3**), 25.8

(**TBS-C**), 18.1 (**TBS-C**), 13.2 (**C4**), -4.4 (**TBS-C**), -4.9 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{12}H_{26}O_4SiNa$) requires 285.1493, found 285.1496. $[\alpha]_D^{20}$ = +32.3 (c = 1.08, $CHCl_3$).



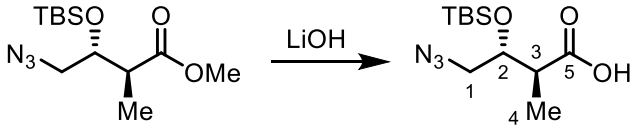
4.163

Volatile. **FTIR ($CHCl_3$, cm^{-1}):** 2929, 2857, 1755, 1255, 1173, 993, 841, 779. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.46-4.44 (m, 1H, **H4**), 4.26 (dd, *J* = 9.9, 3.5 Hz, 1H, **H5**), 4.14 (dd, *J* = 9.9, 0.8 Hz, 1H, **H5**), 2.59-2.52 (m, 1H, **H2**), 1.21 (d, *J* = 7.2 Hz, 3H, **H3**), 0.89 (s, 9H, **TBS-H**), 0.09 (s, 6H, **TBS-H**) ppm. $[\alpha]_D^{20}$ = +52.8 (c = 0.95, $CHCl_3$).



4.161 **4.162**

To a stirred solution of **4.161** (2.61 g, 9.95 mmol, 1.0 equiv.) in THF (30 mL) was sequentially added PPh_3 (3.13 g, 11.9 mmol, 1.2 equiv.), DEAD (2.2 mL, 11.9 mmol, 1.2 equiv.), DPPA (2.6 mL, 11.9 mmol, 1.2 equiv.). The mixture was stirred vigorously for 12 h and allowed to warm to room temperature. Then the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography (silica gel, Heptane/EtOAc = 5:1) to afford 2.06 g (72%) of the product **4.162** as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 2951, 2935, 2859, 2103, 1741, 1257, 1104, 839. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.04-4.01 (m, 1H, **H2**), 3.68 (s, 3H, **H6**), 3.39 (dd, *J* = 12.8, 3.7 Hz, 1H, **H1**), 3.22 (dd, *J* = 12.8, 5.3 Hz, 1H, **H1**), 2.81-2.74 (m, 1H, **H3**), 1.12 (d, *J* = 7.2 Hz, 3H, **H4**), 0.88 (s, 9H, **TBS-H**), 0.12 (s, 3H, **TBS-H**), 0.07 (s, 3H, **TBS-H**) ppm.**^{13}C NMR (100 MHz, $CDCl_3$)**: δ 174.6 (**C5**), 73.3 (**C2**), 54.2 (**C1**), 51.8 (**C6**), 44.2 (**C3**), 25.8 (**TBS-C**), 18.0 (**TBS-C**), 12.6 (**C4**), -4.2 (**TBS-C**), -5.0 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{12}H_{25}O_3N_3SiNa$) requires 310.1557, found 310.1563. $[\alpha]_D^{20}$ = +25.9 (c = 1.14, $CHCl_3$).

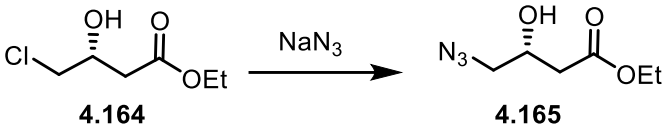


4.162 **4.134**

To the solution of ester **4.162** (270 mg, 0.94 mmol, 1.0 equiv.) in THF/MeOH/H_2O (4 mL/4 mL/2 mL) was added LiOH (112 mg, 4.68 mmol, 5.0 equiv.). The resultant mixture was stirred at room temperature for 13 h. Then the organic solvents were removed under reduced pressure. The remaining aqueous phase was acidified by 1 N HCl to pH = 2-3. The aqueous phase was extracted by EtOAc (5 x 5 mL). The collected organic phase was washed by brine, dried over Na_2SO_4, filtered and concentrated. The crude mixture was

purified by column chromatography (silica gel, Heptane/EtOAc = 5:1 to 21) to afford 233 mg (90%) of the product **4.134** as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 2930, 2858, 2101, 1709, 1256, 1104, 837, 777. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.04-4.00 (m, 1H, **H2**), 3.44 (dd, *J* = 12.8, 4.0 Hz, 1H, **H1**), 3.26 (dd, *J* = 12.8, 5.4 Hz, 1H, **H1**), 2.83-2.76 (m, 1H, **H3**), 1.17 (d, *J* = 7.2 Hz, 3H, **H4**), 0.90 (s, 9H, **TBS-H**), 0.14 (s, 3H, **TBS-H**), 0.10 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 179.5 (**C5**), 73.2 (**C2**), 54.2 (**C1**), 44.0 (**C3**), 25.8 (**TBS-C**), 18.1 (**TBS-C**), 12.7 (**C4**), -4.2 (**TBS-C**), -5.0 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{11}H_{23}O_3N_3SiNa$) requires 296.1401, found 296.1403. **$[\alpha]_D^{20}$** = +16.1 (c = 1.02, $CHCl_3$).

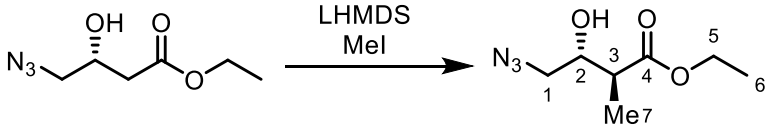
6.3.4.2 Route 2



4.164 **4.165**

Compound **4.165** was prepared as described in the literature[14].

NaN_3 (4.32 g, 66.4 mmol, 2.0 equiv.) was added to the stirred solution of ethyl (*R*)-(γ)-4-chloro-3-hydroxybutanoate **4.164** (5.54 g, 33.2 mmol, 1.0 equiv.) in DMF (80 mL), then the mixture was heated to 100 °C for 3 h. Once peaks of compound **4.164** disappeared on crude ^{1}H NMR, the mixture was cooled to room temperature and the salt was filtered. The remaining salt was washed wish EtOAc (30 mL). The collected organic phase was concentrated to give a crude oil. Purification by column chromatography (silica gel, Heptane/EtOAc = 2:1) afforded 4.66 g (81%) of the product **4.165** as a light yellowish oil. The spectral data is in accordance with the literature[14]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.24-4.16 (m, 3H), 3.40-3.31 (m, 2H), 3.16 (d, *J* = 4.2 Hz, 1H), 2.55 (d, *J* = 4.4 Hz, 1H), 2.53 (d, *J* = 1.6 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm. **$[\alpha]_D^{20}$** = +4.4 (C = 1.2, MeOH). Lit. **$[\alpha]_D^{20}$** = +7.5 (C = 3.65, MeOH)[14].



4.165 **4.166**

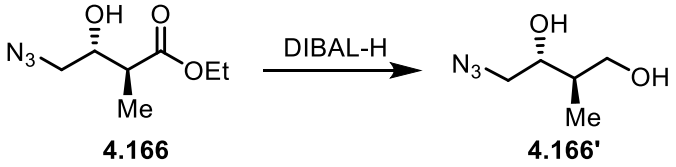
The solution of ethyl (*R*)-4-azido-3-hydroxybutanoate **4.165** (3.10 g, 17.9 mmol, 1.0 equiv.) in THF (10 mL) was dropwise added to the solution of LHMDS (1.0 M in THF, 36.7 mL, 2.05 equiv.) at -60 °C, and the

[14] Nishiguchi, S. *et al. Tetrahedron* **2010**, *66*, 314-320.

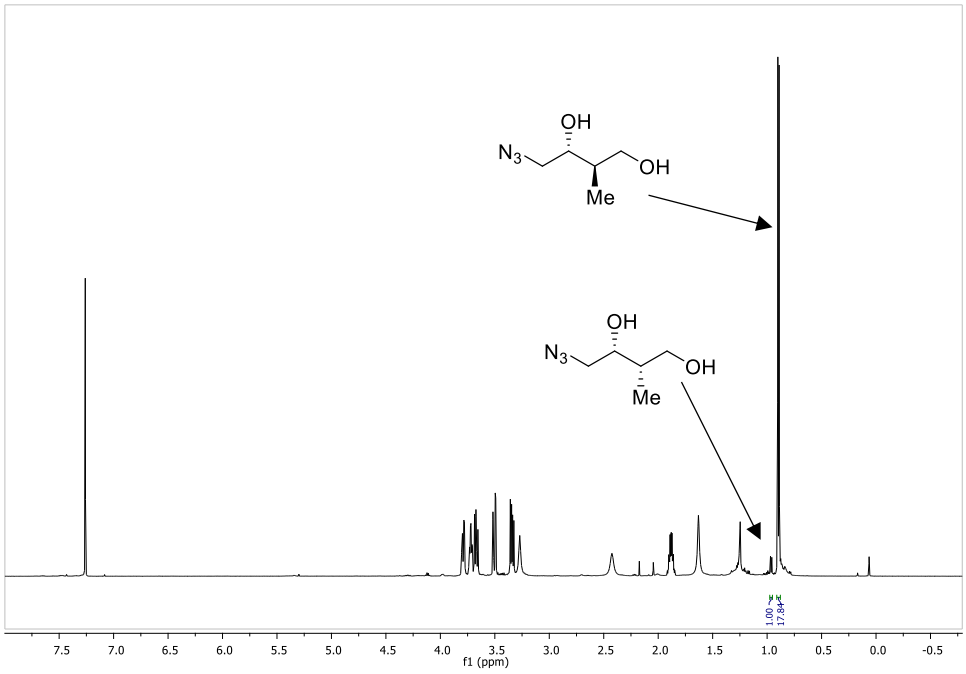
resulting mixture was stirred vigorously for 30 min. Then the temperature was increased to -35 °C and the mixture was stirred for another 30 min. The temperature was cooled down to -60 °C again, and then MeI (2.2 mL, 35.8 mmol, 2.0 equiv.) was added. The mixture was stirred at -60 °C for 2 h, then -40 °C for 2 h and -20 °C for another 2 h. Then the mixture was quenched by 15% Citric acid (aq.) (50 mL) to adjust the pH around 3-4. The aqueous layer was extracted with EtOAc (3 x 40 mL), the combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 4:1) afforded 2.38 g (71%, d.r. = 17.8:1) of the desired product **4.166** as a colorless oil. In addition, 260 mg (8%) of S.M. **4.165** was also recovered. **FTIR ($CHCl_3$, cm^{-1}):** 2101, 1724, 1459, 1262, 1186. **^{1}H NMR (600 MHz, $CDCl_3$):** δ = 4.19 (q, *J* = 7.1Hz, 2H, **H5**), 3.89-3.85 (m, 1H, **H2**), 3.43 (dd, *J* = 12.7, 3.8 Hz, 1H, **H1**), 3.35 (dd, *J* = 12.7, 6.2 Hz, 1H, **H1**), 3.16 (d, *J* = 6.1 Hz, 1H, **OH**), 2.71-2.62 (m, 1H, **H3**), 1.29 (t, *J* = 7.1 Hz, 3H, **H6**), 1.22 (d, *J* = 7.2 Hz, 3H, **H7**). **^{13}C NMR (151 MHz, $CDCl_3$):** δ = 175.5 (**C4**), 72.8 (**C2**), 61.2 (**C5**), 54.5 (**C1**), 42.6 (**C3**), 14.3 (**C6**, **C7**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_7H_{13}N_3O_3Na$) requires 210.0849, found 210.0848. **$[\alpha]_D^{20}$** = +2.45 (c = 1.02, $CHCl_3$). The spectra data is in accordance with the literature[15]. Enantiomer of **4.166**: **$[\alpha]_D^{22}$** = -2.5 (c = 1.02, CH_2Cl_2)[15].

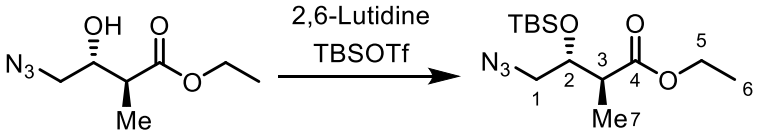
[15] Wipf, P., Uto, Y., Yoshimura, S. *Chem. Eur. J.* **2002**, *8*, 1670-1681.

The d.r. of compound **4.166** was determined by the reduction of the ester to the corresponding alcohol **4.166'**[16].



4.166 **4.166'**



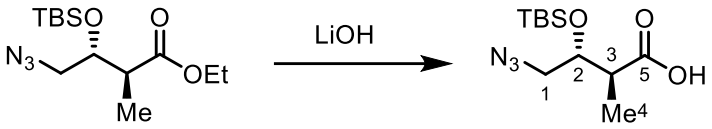


4.166 **4.167**

To a stirred solution of Ethyl (2*S*,3*R*)-4-azido-3-hydroxy-2-methylbutanoate **4.166** (2.11 g, 11.3 mmol, 1.0 equiv.) and 2,6-Lutidine (2.6 mL, 22.5 mmol, 2.0 equiv.) in CH_2Cl_2 (22 mL) at 0 °C was added TBSOTf (3.4 mL, 14.7 mmol, 1.3 equiv.). The mixture was stirred vigorously for 30 min at 0 °C, then quenched by sat. NH_4Cl (aq.) (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentration under reduced pressure. Purification

[16] Szpilman, A. M., Cereghetti, D. M., Wurtz, N. R., Manthorpe, J. M., Carreira, E. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4335-4338.

by column chromatography (silica gel, Heptane/EtOAc = 15:1) afforded 3.33 g (98%) of the desired product **4.167** as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 2165, 2029, 1960, 1900, 1217, 773. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 4.13 (q, *J* = 7.1Hz, 2H, **H5**), 4.06-4.00 (m, 1H, **H2**), 3.40 (dd, *J* = 12.8, 3.8 Hz, 1H, **H1**), 3.23 (dd, *J* = 12.8, 5.5 Hz, 1H, **H1**), 2.78-2.71 (m, 1H, **H3**) 1.27 (t, *J* = 7.1 Hz, 3H, **H6**), 1.12 (d, *J* = 7.2 Hz, 3H, **H7**), 0.89 (s, 9H, **TBS-H**), 0.13 (s, 3H, **TBS-H**), 0.08 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.1 (**C4**), 73.2 (**C2**), 60.7 (**C5**), 54.3 (**C1**), 44.3 (**C3**), 25.8 (**TBS-C**), 18.0(**TBS-C**), 14.3(**C6**), 12.6(**C7**), -4.2 (**TBS-C**), -5.0 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{13}H_{27}O_3N_3SiNa$) requires 324.1714, found 324.1707. **$[\alpha]_D^{20}$** = +26.8 (c = 0.91, $CHCl_3$).

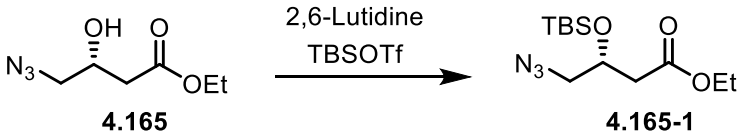


4.167 **4.134**

Ethyl (2*S*,3*R*)-4-azido-3-((tert-butyldimethylsilyl)oxy)-2-methylbutanoate **4.167** (3.00 g, 9.95 mmol, 1.0 equiv.) was dissolved in THF/MeOH/H_2O (20 mL/20 mL/10 mL), then LiOH H_2O (2.09 g, 49.8 mmol, 5.0 equiv.) was added. The resulting mixture was stirred at room temperature for 13 h. Then MeOH was removed under vacuum and the mixture was acidified by 1 N HCl to pH = 2-3. The aqueous phase was extracted by EtOAc (5 x 10 mL). The combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentration under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 5:1 to 2:1) afforded 2.62 g (96%) of the desired product **4.134** as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 2930, 2858, 2101, 1709, 1256, 1104, 837, 777. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.04-4.00 (m, 1H, **H2**), 3.44 (dd, *J* = 12.8, 4.0 Hz, 1H, **H1**), 3.26 (dd, *J* = 12.8, 5.4 Hz, 1H, **H1**), 2.83-2.76 (m, 1H, **H3**), 1.18 (d, *J* = 7.2 Hz, 3H, **H4**), 0.90 (s, 9H, **TBS-H**), 0.14 (s, 3H, **TBS-H**), 0.10 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 178.9 (**C5**), 73.2 (**C2**), 54.3 (**C1**), 44.0 (**C3**), 25.8 (**TBS-C**), 18.1 (**TBS-C**), 12.8 (**C4**), -4.2 (**TBS-C**), -5.0 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{11}H_{23}O_3N_3SiNa$) requires 296.1401, found 296.1403. **$[\alpha]_D^{20}$** = +22.1 (c = 1.10, $CHCl_3$). The spectra data is in agreement with **route 1** and the literature[17]. Lit. **$[\alpha]_D^{25}$** = +22.5 (c = 1.7, $CHCl_3$)[17].

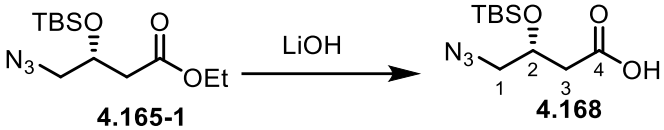
[17] Yadav J. S., Chetia, L. *Org. Lett.* **2007**, *9*, 4587-4589.

6.3.4.3 Synthesis of 4.168



4.165 **4.165-1**

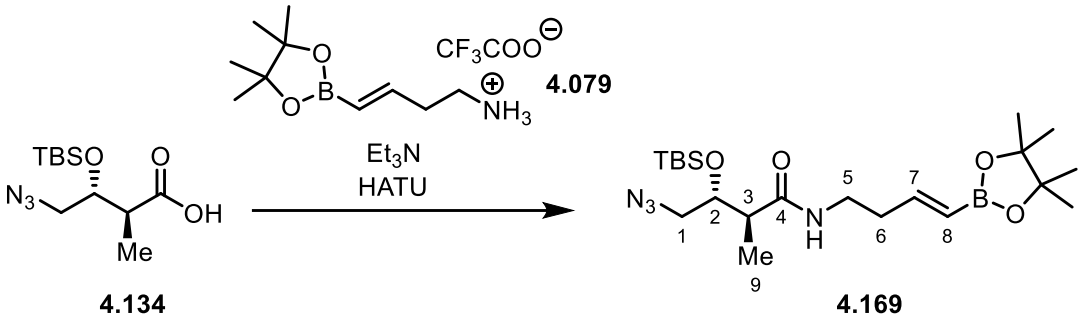
To a stirred solution of Ethyl (*R*)-4-azido-3-hydroxybutanoate **4.165** (485 mg, 2.8 mmol, 1.0 equiv.) and 2,6-Lutidine (0.65 mL, 5.6 mmol, 2.0 equiv.) in CH_2Cl_2 (5 mL) at 0 °C was added TBSOTf (1.0 mL, 4.2 mmol, 1.5 equiv.). The mixture was stirred vigorously for 30 min at 0 °C, then quenched by sat. NH_4Cl (aq.) (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentration under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 15:1) afforded 710 mg (88%) of the desired product **4.165-1** as a colorless oil. The spectral data were in accordance with the literature[14]. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.28-4.22 (m, 1H), 4.19-4.07 (m, 2H), 3.37 (dd, *J* = 12.5, 4.4 Hz, 1H), 3.23 (dd, *J* = 12.5, 5.3 Hz, 1H), 2.53 (dd, *J* = 6.3, 3.8 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H) ppm.



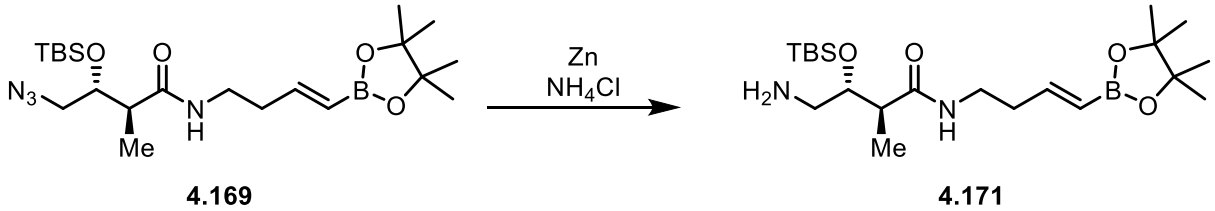
4.165-1 **4.168**

To a stirred solution of ethyl (*R*)-4-azido-3-((tert-butyldimethylsilyl)oxy)butanoate **4.165-1** (645 mg, 2.24 mmol, 1.0 equiv.) in THF/MeOH/H_2O (2/2/1, 11 mL) at 0 °C was added LiOH H_2O (471 mg, 11.2 mmol, 5.0 equiv.). The resulting mixture was stirred vigorously for 4 h at room temperature before MeOH was removed under vacuum. The mixture was acidified by 1 N HCl (aq.) to pH = 2-3. The aqueous phase was extracted by EtOAc (5 x 10 mL). The combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 3:1) afforded 500 mg (86%) of the desired product **4.168** as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 2930, 2858, 2104, 1712, 1285, 1256, 1110, 837, 778. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.32-4.19 (m, 1H, **H2**), 3.38(dd, *J* = 12.6, 4.5 Hz, 1H, **H1**), 3.26 (dd, *J* = 12.6, 5.2 Hz, 1H, **H1**), 2.60 (qd, *J* = 15.7, 6.1 Hz, 2H, **H3**) 0.89 (s, 9H, **TBS-H**), 0.13 (s, 3H, **TBS-H**), 0.10 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 175.9 (**C4**), 68.6 (**C2**), 56.4 (**C1**), 39.8 (**C3**), 25.8 (**TBS-C**), 18.0 (**TBS-C**), -4.6 (**TBS-C**), -4.9 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{10}H_{20}O_3N_3Si$) requires 258.1279, found 258.1277. **$[\alpha]_D^{20}$** = +3.03 (c = 1.22, $CHCl_3$).

6.3.5 Synthesis of Amines

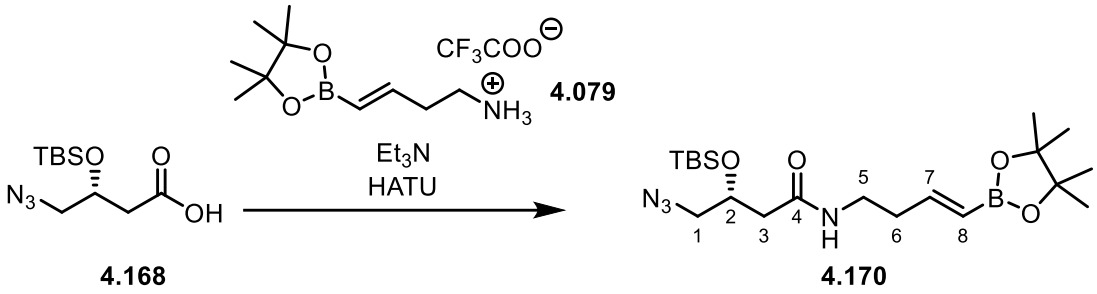


The crude amine salt **4.079** (3.58 g, 11.5 mmol, 1.2 equiv.) and the acid **4.134** (2.62 g, 9.55 mmol, 1.0 equiv.) were dissolved in CH_2Cl_2 (50 mL). At 0 °C, Et_3N (13.3 mL, 95.5 mmol, 10 equiv.) was added, followed by O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (4.36 g, 11.5 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature overnight. Then the reaction was quenched by 1 N HCl (aq.) (20 mL). The aqueous phase was extracted by CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 4:1 to 1:1) afforded 4.00 g (92%) of the product **4.169** as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 2977, 2932, 2102, 1643, 1361, 1101. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.54 (dt, *J* = 18.0, 6.5 Hz, 1H, **H7**), 5.95 (s, 1H, **NH**), 5.50 (d, *J* = 18.0 Hz, 1H, **H8**), 3.91-3.89 (m, 1H, **H2**), 3.49-3.42 (m, 2H, **H1** & **H6**), 3.24-3.18 (m, 2H, **H1** & **H6**), 2.44 (p, J = 7.0 Hz, 1H, **H3**), 2.37-2.33 (m, 2H, **H5**), 1.26 (s, 12H, **Bpin-H**), 1.09 (dd, J = 7.1, 1.5 Hz, 3H, **H9**), 0.88 (s, 9H, **TBS-H**), 0.12 (s, 3H, **TBS-H**), 0.06 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.0 (**C4**), 150.4 (**C7**), 121.3 (**C8**, deduced from HSQC), 83.3 (**Bpin-OC**), 73.6 (**C2**), 54.7 (**C1**), 45.5 (**C3**), 38.0 (**C6**), 35.7 (**C5**), 25.9 (**TBS-C**), 24.9 (**Bpin-CH_3**), 18.1 (**TBS-C**), 15.0 (**C9**), -4.3 (**TBS-C**), -4.9 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{21}H_{41}O_4N_4BSiNa$) requires 475.2882, found 475.2886. **$[\alpha]_D^{20}$** = +6.56 (c = 0.90, $CHCl_3$).



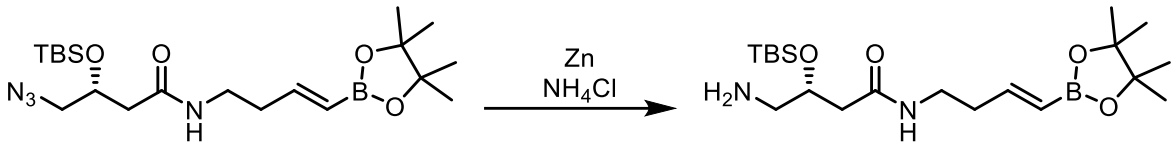
To a solution of amide **4.169** (4.00 g, 8.84 mmol, 1.0 equiv.) in THF/MeOH/H_2O (30 mL/30 mL/ 30 mL) was added activated zinc (2.32 g, 35.4 mmol, 4.0 equiv.) and NH_4Cl (3.79 g, 70.8 mmol, 8.0 equiv.). The mixture

was stirred vigorously at room temperature for 3 h. Then the organic solvents were removed under vacuum. The remaining aqueous phase was basified by sat. Na_2CO_3 (aq.) (10 mL) to pH around 9, and extracted by CH_2Cl_2 (5 x 15 mL). The combined organic layers were washed by brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product **4.171** (3.77 g, quantitative yield) was used in the next step without further purification.



4.168 **4.170**

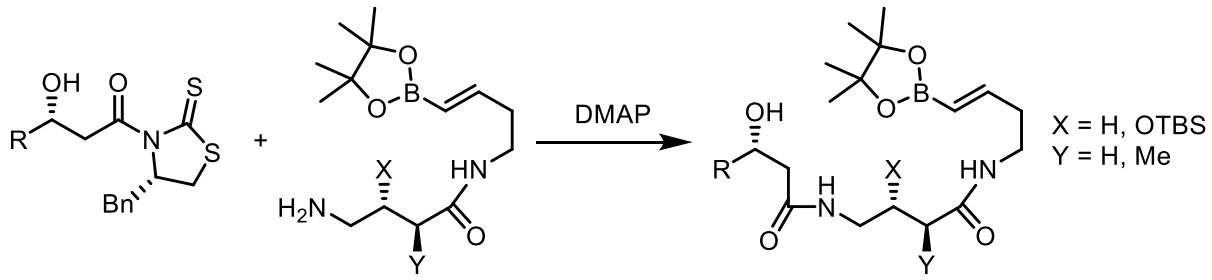
The crude amine salt **4.079** (675 mg, 2.17 mmol, 1.2 equiv.) and the acid **4.168** (470 mg, 1.8 mmol, 1.0 equiv.) were dissolved in CH_2Cl_2 (10 mL). At 0 °C, trimethylamine (Et_3N) (2.5 mL, 18 mmol, 10 equiv.) was added, followed by O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (961 mg, 2.53 mmol, 1.4 equiv.). The resulting mixture was allowed to warm to room temperature overnight. Then the reaction was quenched by 1 N HCl (aq.) (20 mL). The aqueous phase was extracted by CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 4:1 to 1:1) afforded 561 mg (71%) of the product **4.170** as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 3309, 2930, 2858, 2102, 1642, 1552, 1360, 1322, 1256, 1145, 1096, 971, 838, 778. **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 6.54 (dt, *J* = 17.8, 6.4 Hz, 1H, **H7**), 5.79 (s, 1H, **NH**), 5.52 (d, *J* = 18.0 Hz, 1H, **H8**), 4.33-4.21 (m, 1H, **H2**), 3.45-3.40 (m, 1H, **H6**), 3.38 (dd, J = 12.7, 3.5 Hz, 1H, **H1**), 3.31-3.26 (m, 1H, **H6**), 3.18 (dd, *J* = 12.6, 4.8 Hz, 1H, **H1**), 2.41 (dd, *J* = 14.4, 5.4 Hz, 1H, **H3**), 2.38-2.35 (m, 2H, **H5**), 2.34 (dd, *J* = 14.2, 6.1 Hz, 1H, **H3**), 1.27 (s, 12H, **Bpin-H**), 0.89 (s, 9H, **TBS-H**), 0.12 (s, 3H, **TBS-H**), 0.08 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 170.0 (**C4**), 150.2 (**C7**), 121.7 (**C8**, deduced from HSQC), 83.4 (**Bpin-OC**), 69.3 (**C2**), 56.4 (**C1**), 42.2 (**C3**), 38.1 (**C6**), 35.6 (**C5**), 25.9 (**TBS-C**), 24.9 (**Bpin-CH_3**), 18.1 (**TBS-C**), -4.6 (**TBS-C**), -4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{20}H_{39}O_4N_4BSiNa$) requires 461.2726, found 461.2701. **$[\alpha]_D^{20}$** = -9.71 (c = 1.03, $CHCl_3$).



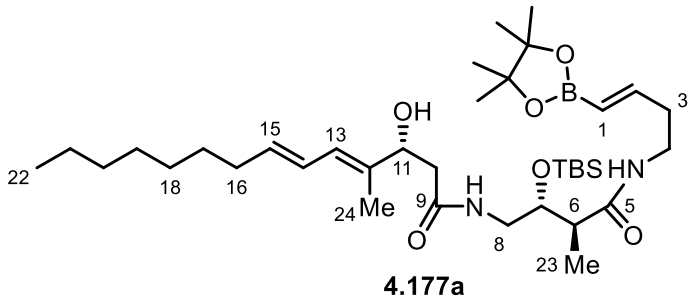
4.170 **4.171**

To a solution of amide **4.170** (561g, 1.28 mmol, 1.0 equiv.) in THF/MeOH/H_2O (3 mL/3 mL/ 3 mL) was added activated zinc (167 mg, 2.56 mmol, 4.0 equiv.) and NH_4Cl (274g, 5.12 mmol, 8.0 equiv.). The mixture was stirred vigorously at room temperature for 3 h. Then the organic solvents were removed under vacuum. The remaining aqueous phase was basified by sat. Na_2CO_3 (aq.) (10 mL) to pH around 9, and extracted by CH_2Cl_2 (5 x 15 mL). The combined organic layers were washed by brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product **4.171** (quantitative yield) was used in the next step without further purification.

6.3.6 Synthesis of Bisamides

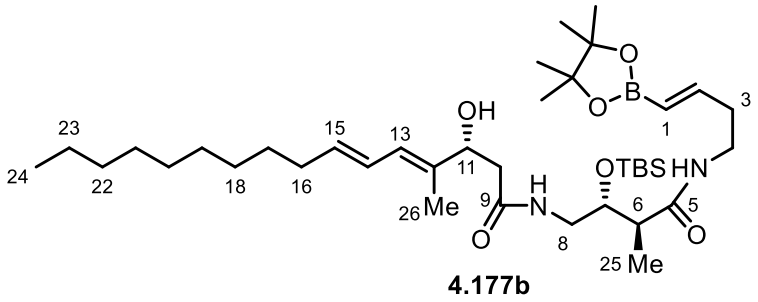


Aldol adduct (1.0 equiv.) and the crude amine (1.3 equiv.) were dissolved in CH_2Cl_2 (0.1 M). DMAP (0.5 equiv.) was then charged and the reaction mixture was vigorously stirred overnight at room temperature. The reaction was quenched with water and extracted 3 times with CH_2Cl_2. The resulting organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting crude oil was purified by column chromatography (silica gel, Heptane/EtOAc = 2:1, then Heptane/Isopropanol = 20:1 to 3:1).



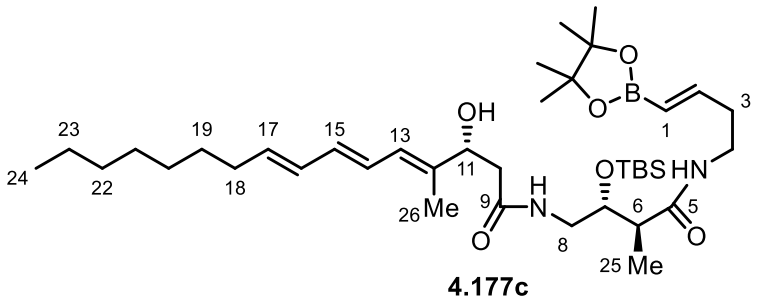
4.177a

Yield: 1.02 g, 57%. **FTIR ($CHCl_3$, cm^{-1}):** 2926, 2855, 1642, 1537, 1360, 1144, 836. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.55 (dt, *J* = 18.0, 6.5 Hz, 1H, **H2**), 6.38 (brd, 1H, **NH**), 6.22 (dd, *J* = 15.0, 10.9 Hz, 1H, **H14**), 6.11 (brd, 1H, **NH**), 6.08 (d, *J* = 10.9 Hz, 1H, **H13**), 5.76-5.66 (m, 1H, **H15**), 5.52 (d, *J* = 18.0 Hz, 1H, **H1**), 4.43 (d, *J* = 8.4 Hz, 1H, **H11**), 3.90-3.87 (m, 1H, **H7**), 3.74-3.69 (m, 1H, **H8**), 3.49 (brd, 1H, **OH**), 3.47-3.41 (m, 1H, **H3**), 3.30-3.24 (m, 1H, **H3**), 2.96-2.92 (m, 1H, **H8**), 2.44-2.34 (m, 5H, **H4**, **H6** & **H10**), 2.09 (q, *J* = 7.2 Hz, 2H, **H16**), 1.74 (s, 3H, **H24**), 1.38-1.36 (m, 2H, **H17**), 1.30-1.25 (m, 20H, **Bpin-CH_3** & **H18-H21**), 1.13 (d, *J* = 7.2 Hz, 3H, **H23**), 0.90 (s, 9H, **TBS-H**), 0.88 (t, *J* = 7.1 Hz, 3H, **H22**), 0.15 (s, 3H, **TBS-H**), 0.08 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.5 (**C5**), 172.3 (**C9**), 150.4 (**C2**), 136.1 (**C15**), 135.4 (**C12**), 125.8 (**C13**), 125.7 (**C14**), 121.7 (**C1**, deduced from HSQC), 83.4 (**Bpin-OC**), 73.7 (**C11**), 72.1 (**C7**), 44.8 (**C6**), 42.9 (**C8**), 41.6 (**C10**), 37.9 (**C3**), 35.8 (**C4**), 33.2 (**C16**), 32.0, 29.6, 29.3 (d), 26.0 (**TBS-C**), 24.9 (**Bpin-CH_3**), 22.8, 18.1 (**TBS-C**), 15.3 (**C23**), 14.3 (**C22**), 12.8 (**C24**), -4.4 (**TBS-C**), -4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** exact mass calculated for $[M+Na]^+$ ($C_{36}H_{67}N_2O_6BNa$) requires 685.4754, found 685.4759. **$[\alpha]_D^{20}$** = +12.3 (c = 0.50, $CHCl_3$).



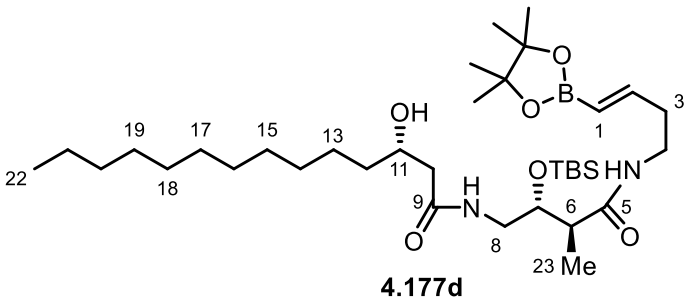
4.177b

Yield: 240 mg, 60%. **FTIR ($CHCl_3$, cm^{-1}):** 2927, 2854, 1643, 1548, 1361, 1324, 1145, 837. **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 6.55 (dt, *J* = 18.0, 6.5 Hz, 1H, **H2**), 6.48-6.44 (m, 1H, **NH**), 6.23-6.15 (m, 2H, **H14**, **NH**), 6.07 (d, *J* = 10.9 Hz, 1H, **H13**), 5.72-5.67 (m, 1H, **H15**), 5.51 (d, *J* = 18.0 Hz, 1H, **H1**), 4.43 (d, *J* = 8.7 Hz, 1H, **H11**), 3.89-3.86 (m, 1H, **H7**), 3.74-3.69 (m, 1H, **H8**), 3.47-3.42 (m, 1H), 3.29 -3.24 (m, 1H, **H3**), 2.94-2.89 (m, 1H, **H8**), 2.45-2.34 (m, 5H, **H4**, **H6** & **H10**), 2.11-2.07 (m, 2H, **H16**), 1.74 (s, 3H, **H26**), 1.37-1.36 (m, 2H, **H17**), 1.25 (brd, 24H, **Bpin-CH_3** & **H18-H23**), 1.13 (d, *J* = 7.2 Hz, 3H, **H25**), 0.89 (s, 9H, **TBS-H**), 0.87(t, *J* = 7.1 Hz, 3H, **H24**), 0.15 (s, 3H, **TBS-H**), 0.08 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 174.6 (**C5**), 172.3 (**C9**), 150.4 (**C2**), 136.0 (**C15**), 135.4 (**C12**), 125.8 (**C13**), 125.7 (**C14**), 121.7 (**C1**, deduced from HSQC), 117.4, 83.4 (**Bpin-OC**), 73.7 (**C11**), 72.1(**C7**), 44.7 (**C6**), 42.9 (**C8**), 41.6 (**C10**), 37.9(**C3**), 35.8 (**C4**), 33.2 (**C16**), 32.0, 29.71, 29.66, 29.55, 29.48, 29.38, 26.0 (**TBS-C**), 24.9 (**Bpin-CH_3**), 22.8, 18.1 (**TBS-C**), 15.4 (**C25**), 14.3 (**C24**), 12.8 (**C26**), -4.4 (**TBS-C**), -4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{38}H_{71}N_2O_6BNa$) requires 713.5067, found 713.5072. **$[\alpha]_D^{20}$** = +31.5 (c = 0.55, $CHCl_3$).



4.177c

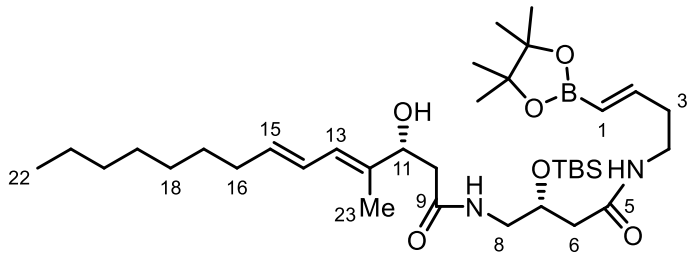
Yield: 86 mg, 57%. **FTIR ($CHCl_3$, cm^{-1}):** 2927, 1642, 1542, 1360, 1322, 1144, 988, 837, 778. **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 6.54 (dt, *J* = 17.9, 6.6 Hz, 1H, **H2**), 6.45 (brd, 1H, **NH**), 6.29 (dd, *J* = 14.6, 11.1 Hz, 1H, **H14**), 6.21-6.03 (m, 4H, **H13**, **H15**, **H16** & **NH**), 5.73-5.68 (m, 1H, **H17**), 5.51 (d, *J* = 18.0 Hz, 1H, **H1**), 4.46 (brd, 1H, **H11**), 3.87 (brd, 1H, **H7**), 3.74-3.69 (m, 1H, **H8**), 3.64 (d, *J* = 10.7 Hz, 1H, **OH**), 3.46-3.40 (m, 1H, **H3**), 3.28 -3.24 (m, 1H, **H3**), 2.91 (brd, 1H, **H8**), 2.44-2.33 (m, 5H, **H4**, **H6** & **H10**), 2.10-2.06 (m, 2H, **H18**), 1.76 (s, 3H, **H26**), 1.37-1.36 (m, 2H, **H19**), 1.25 (brd, 20H, **Bpin-CH_3** & **H20-H23**), 1.12 (d, *J* = 7.2 Hz, 3H, **H25**), 0.90-0.86 (m, 12H, **TBS-H** & **H24**), 0.14 (s, 3H, **TBS-H**), 0.08 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 174.6 (**C5**), 172.2 (**C9**), 150.4 (**C2**), 137.4 (**C12**), 135.9 (**C17**), 133.8, 130.6, 126.1, 125.7 (**C14**), 121.5 (**C1**, deduced from HSQC), 83.4 (**Bpin-OC**), 73.6 (**C11**), 72.1 (**C7**), 44.8 (**C6**), 42.9 (**C8**), 41.6 (**C10**), 37.9 (**C3**), 35.8 (**C4**), 33.0 (**C18**), 32.0, 29.4, 29.3 (**C19**), 26.0 (**TBS-C**), 24.9 (**Bpin-CH_3**), 22.8, 18.1 (**TBS-C**), 15.4 (**C25**), 14.3 (**C24**), 13.0 (**C26**), -4.4 (**TBS-C**), -4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{38}H_{69}N_2O_6BNa$) requires 711.4910, found 711.4916. **$[\alpha]_D^{20}$** = +23.2 (c = 1.12, $CHCl_3$).



4.177d

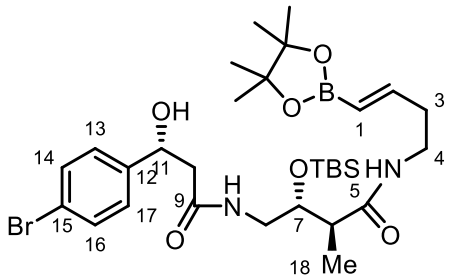
Yield: 115 mg, 70%. **FTIR ($CHCl_3$, cm^{-1}):** 2927, 2855, 1642, 1542, 1360, 1322, 1144, 837, 778. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.54 (dt, *J* = 18.0, 6.4 Hz, 1H, **H2**), 6.45-6.37 (m,1H, **NH**), 6.24 -6.19 (m, 1H, **NH**), 5.51 (d, *J* = 18.0 Hz, 1H, **H1**), 3.96 (brd, 1H, **H11**), 3.88-3.86 (m, 1H, **H7**), 3.83-3.81 (m, 1H, **OH**), 3.713.67 (m, 1H, **H8**), 3.48-3.42 (m, 1H, **H3**), 3.28-3.23 (m, 1H, **H3**), 2.95-2.90 (m, 1H, **H8**), 2.45-2.41 (m, 1H, **H6**), 2.37-2.32 (m, 3H, **H4** & **H10**), 2.23 (dd, J = 15.3, 9.3 Hz, 1H, **H10**), 1.53-1.48 (m, 1H), 1.44-1.37 (m, 2H), 1.30-1.23 (m, **29H**), 1.14 (d, J = 7.2 Hz, 3H, **H23**), 0.89 (s, 9H, **TBS-H**), 0.87 (t, J = 6.9 Hz, 3H, **H22**), 0.15 (s, 3H, **TBS-H**), 0.09 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.7 (**C5**), 172.9 (**C9**), 150.4 (**C2**), 121.4 (**C1**, deduced

from HSQC), 83.4 (**Bpin-OC**), 72.1 (**C7**), 68.7 (**C11**), 44.7 (**C6**), 42.9 (**C8**), 42.6 (**C10**), 37.9 (**C3**), 37.0, 35.8 (**C4**), 32.0, 29.80, 29.77, 29.74, 29.73, 29.71, 29.5, 26.0 (**TBS-C**), 25.7, 24.91 (**Bpin-CH_3**), 24.88, 22.8, 18.1 (**TBS-C**), 15.5 (**C23**), 14.3 (**C22**), -4.4 (**TBS-C**), -4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{35}H_{69}N_2O_6BSiNa$) requires 675.4910, found 675.4910. **$[\alpha]_D^{20}$** = +25.9 (c = 0.59, $CHCl_3$).



4.177f

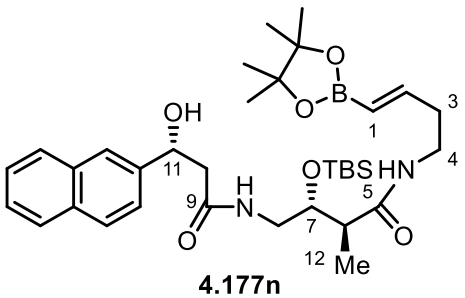
Yield: 216 mg, 78%. **FTIR ($CHCl_3$, cm^{-1}):** 2927, 2855, 1642, 1551, 1360, 1322, 1145, 967, 836, 779. **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 6.55 (dt, *J* = 18.0, 6.4 Hz, 1H, **H2**), 6.45 (brd, 1H, **NH**), 6.33 (brd, 1H, **NH**), 6.21 (dd, *J* = 14.5, 11.0 Hz, 1H, **H14**), 6.07 (d, *J* = 10.8 Hz, 1H, **H13**), 5.72-5.67 (m, 1H, **H15**), 5.51 (d, *J* = 18.0 Hz, 1H, **H1**), 4.43 (d, *J* = 8.9 Hz, 1H, **H11**), 4.18-4.15 (m, 1H, **H7**), 3.59-3.55 (m, 1H, **H8**), 3.43-3.38 (m, 2H, **H3** & **OH**), 3.30-3.25 (m, 1H, **H3**), 3.11-3.07 (m, 1H, **H8**), 2.44 (dd, *J* = 15.1, 9.2 Hz, 1H, **H10**), 2.40-2.31 (m, 4H, **H4**, **H6** & **H10**), 2.26 (dd, *J* = 14.0, 5.0 Hz, 1H, **H6**), 2.09 (q, *J* = 7.1 Hz, 2H, **H16**), 1.73 (s, 3H, **H23**), 1.38-1.35 (m, 2H, **H17**), 1.25 (brd, 20H, **Bpin-CH_3** & **H18-H21**), 0.88-0.86 (m, 12H, **TBS-H** & **H22**), 0.10 (s, 3H, **TBS-H**), 0.08 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 172.6 (**C5**), 170.4 (**C9**), 150.4 (**C2**), 136.1 (**C15**), 135.4 (**C12**), 125.8 (**C13**), 125.7 (**C14**), 121.6 (**C1**, deduced from HSQC), 83.4 (**Bpin-OC**), 73.8 (**C11**), 68.4 (**C7**), 44.2 (**C8**), 42.4 (**C6**), 41.7 (**C10**), 38.2 (**C3**), 35.6 (**C4**), 33.1 (**C6**), 32.0, 29.6, 29.3 (d), 25.9 (**TBS-C**), 24.9 (**Bpin-CH_3**), 22.8, 18.1 (**TBS-C**), 14.2 (**C22**), 12.7 (**C24**), -4.7 (**TBS-C**), -4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{35}H_{65}N_2O_6BNa$) requires 671.4597, found 671.4603. **$[\alpha]_D^{20}$** = +25.6 (c = 1.20, $CHCl_3$).



4.177l

Yield: 120 mg, 40%. **FTIR ($CHCl_3$, cm^{-1}):** 1739, 1641, 1535, 1361, 1321, 1143, 849, 778. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.46 (d, *J* = 8.3 Hz, 2H, **H14** & **H16**), 7.26 (d, *J* = 8.3 Hz, 2H, **H13** & **H17**), 6.54 (dt, *J* = 18.0, 6.4 Hz,

1H, **H2**), 6.42 (brd,1H, **NH**), 6.13 (brd, 1H, **NH**), 5.51 (d, *J* = 18.0 Hz, 1H, **H1**), 5.08-5.06 (m, 1H, **H11**), 4.47 (d, *J* = 3.2 Hz, 1H, **OH**), 3.86-3.83 (m, 1H, **H7**), 3.70-3.66 (m, 1H, **H8**), 3.45-3.40 (m, 1H, **H3**), 3.29-3.23 (m, 1H, **H3**), 2.95-2.90 (m, 1H, **H8**), 2.53-2.52 (m, 2H, **H6** & **H10**), 2.37-2.32 (m, 3H, **H4** & **H10**), 1.24 (s, 12H, **Bpin-CH_3**), 1.12 (d, *J* = 7.2 Hz, 3H, **H18**), 0.89 (s, 9H, **TBS-H**), 0.14 (s, 3H, **TBS-H**), 0.09 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: 174.6 (**C5**),171.8 (**C9**), 150.4 (**C2**), 142.2 (**C12**), 131.7 (**C14** & **C16**), 127.6 (**C13** & **C17**), 121.5 (**C1**, deduced from HSQC), 121.4 (**C15**), 83.4 (**Bpin-OC**), 72.0 (**C7**), 70.3 (**C11**), 44.8 (**C6**), 44.7 (**C10**), 42.9 (**C8**), 37.9 (**C3**), 35.8 (**C4**), 26.0 (**TBS-C**), 24.91(**Bpin-CH_3**), 24.89 (**Bpin-CH_3**), 18.1 (**TBS-C**), 15.4 (**C18**), -4.4 (**TBS-C**), -4.8 (**TBS-C**) ppm.**HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{30}H_{50}N_2O_6BBrSiNa$) requires 677.2586, found 677.2566. **$[\alpha]_D^{20}$** = +40.3 (c = 1.10, $CHCl_3$).



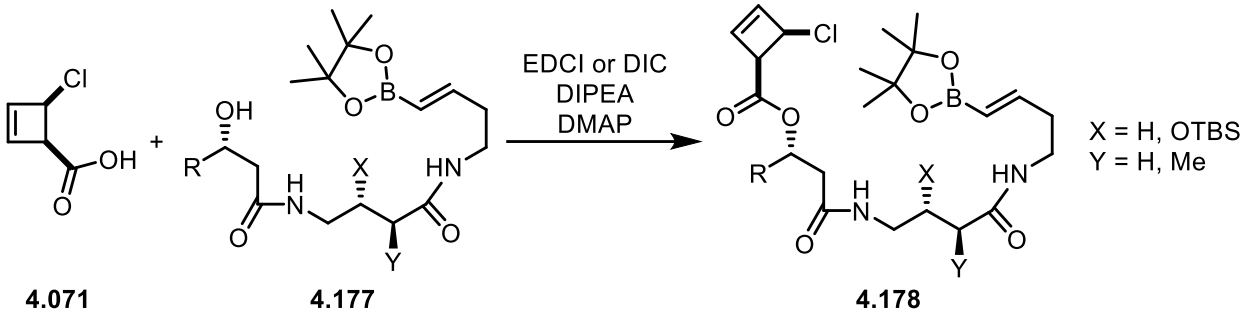
4.177n

Yield: 164 mg, 43%. **FTIR ($CHCl_3$, cm^{-1}):** 2952, 1642, 1545, 1360, 1322, 1143, 836, 778. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.85-7.82 (m, 4H, **ArH**), 7.49-7.46 (m, 3H, **ArH**), 6.54 (dt, *J* =18.1, 6.5, 1H, **H2**), 6.38-6.36 (m, 1H), 5.95-5.93 (t, *J* = 5.6 Hz, 1H), 5.51 (d, *J* = 18.0 Hz, 1H, **H1**), 5.30-5.27 (m, 1H), 4.27 (d, *J* = 3.1 Hz, **OH**), 3.83-3.79 (m, 1H, **H7**), 3.73-3.68 (m, 1H, **H8**), 3.42-3.36 (m, 1H, **H3**), 3.24-3.19 (m, 1H, **H3**), 2.93-2.88 (m, 1H, **H8**), 2.72-2.64 (m, 2H, **H10**), 2.35-2.29 (m, 2H, **H4**), 2.16-2.11 (m, 1H, **H6**), 1.24 (s, 12H, **Bpin-CH_3**), 1.01 (d, *J* = 7.1 Hz, 3H, **H12**), 0.87 (s, 9H, **TBS-H**), 0.12 (s, 3H, **TBS-H**), 0.06 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 174.5 (**C5**), 171.8 (**C9**), 150.4 (**C2**), 140.5, 133.4, 133.0, 128.5, 128.2, 127.8, 126.4, 126.1, 124.6, 123.9, 121.8 (**C1**, deduced from HSQC), 83.4 (**Bpin-OC**), 72.0 (**C7**), 71.1 (**C11**), 44.9 (**C10**), 44.6 (**C6**), 42.8 (**C8**), 37.9 (**C3**), 35.8 (**C4**), 26.0 (**TBS-C**), 24.9 (**Bpin-CH_3**), 18.1 (**TBS-C**), 15.2 (**C12**), -4.4 (**TBS-C**), -4.9 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{34}H_{53}N_2O_6BSiNa$) requires 647.3658, found 647.3669. **$[\alpha]_D^{20}$** = +38.4 (c = 1.47, $CHCl_3$).

6.3.7 Synthesis of Esters

6.3.7.1 General Procedures

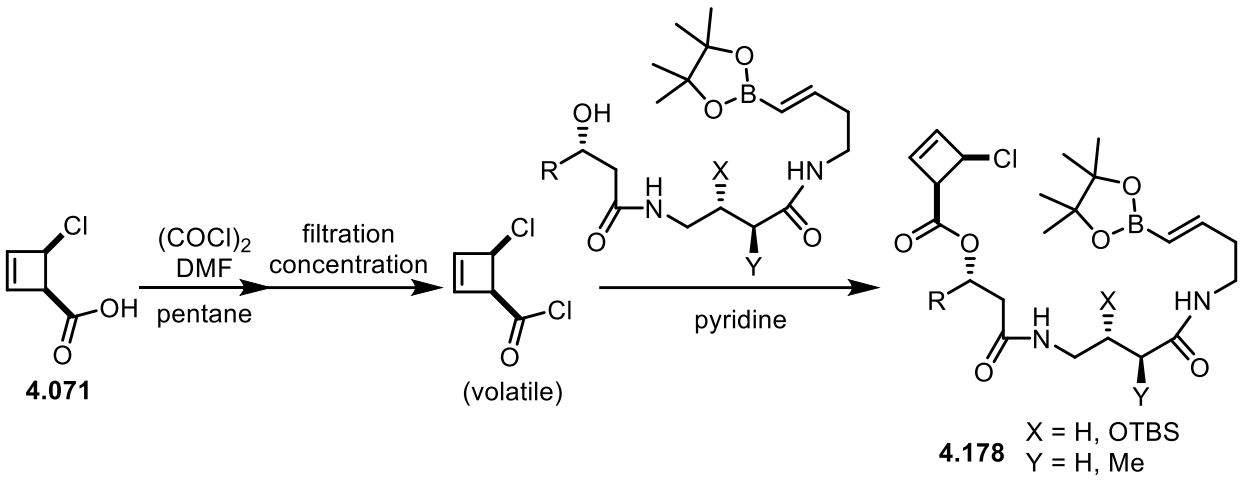
Method A



4.071 **4.177** **4.178**

The acid **4.071** (2.0 equiv.), EDCI or DIC (2.0 equiv.) and DIPEA (2.5 equiv.) were dissolved in CH_2Cl_2 at room temperature. Then amide alcohol dissolved in CH_2Cl_2 was added, followed by DMAP (0.2 equiv.). The mixture was vigorously stirred at room temperature overnight. Then the reaction was quenched by sat. NH_4Cl (aq.). The aqueous phase was extracted by CH_2Cl_2 (3 times). The combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (silica gel, Heptane/EtOAc = 4:1 to 1:1) afforded the *cis*-isomer as mixture of diastereomers.

Method B

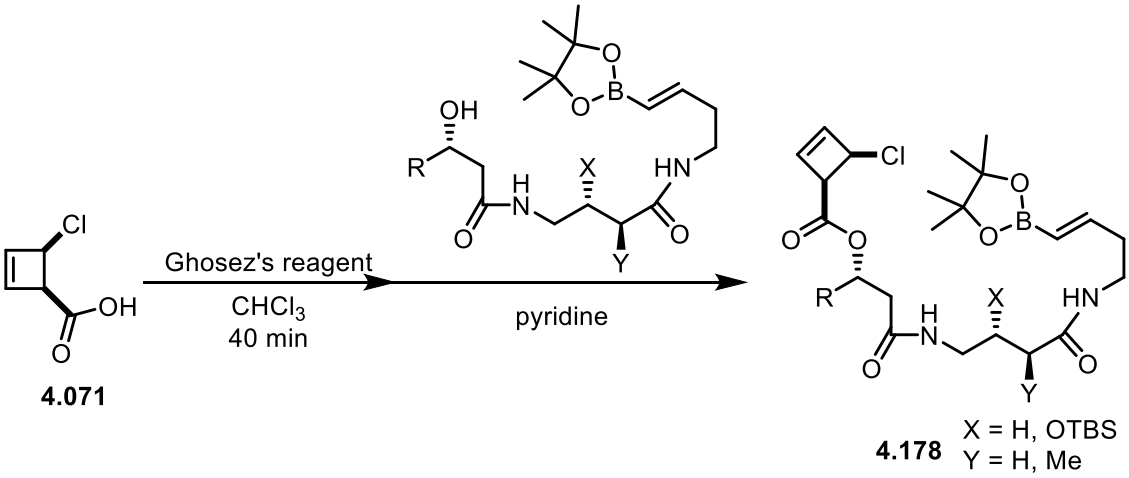


4.071 (volatile) **4.178**

Oxalyl chloride (10 equiv.) was added to a solution of cyclobutene acid **4.071** (3.0 equiv.) and DMF (1.0 equiv.) in pentane (0.05 M) at 0°C. A white precipitate formed immediately. After 1 h at room

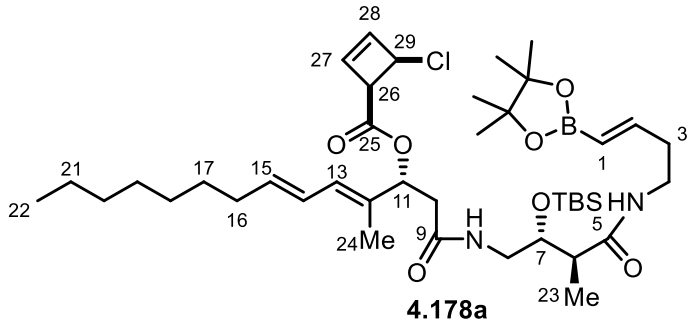
temperature, the mixture was filtered and carefully concentrated in vacuo. The crude acyl chloride was then dissolved in CH_2Cl_2 and added to a solution of amide alcohol (1.0 equiv.) in CH_2Cl_2 and pyridine (4.0 equiv.) at 0° C. The reaction was allowed to reach room temperature and stirred overnight. The reaction was quenched with water and extracted 3 times with CH_2Cl_2. The resulting organic layers were combined, dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 7:3 to 1:1) afforded the *cis*-isomer as mixture of diastereomers.

Method C



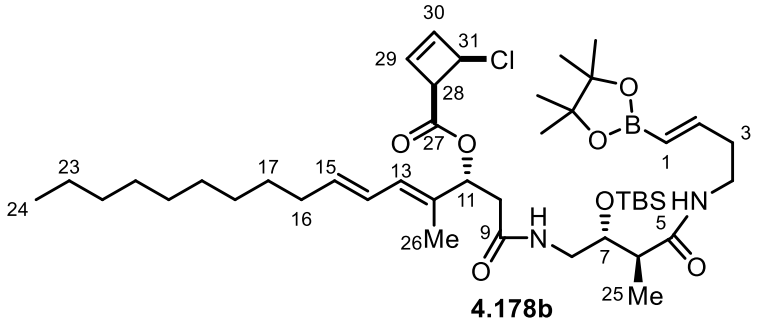
To the solution of acid **4.071** (3.0 equiv.) in $CHCl_3$ was added freshly distilled Ghosez's reagent (3.1 equiv.). The solution was stirred vigorously at room temperature for 40 min. Then the amide alcohol (1.0 equiv.) dissolved in $CHCl_3$ was added, followed by pyridine (3.5 equiv.). The resulting solution was vigorously stirred for another 4 h at room temperature. The reaction was quenched with water and extracted 3 times with CH_2Cl_2. The resulting organic layers were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 7:3 to 1:1) afforded the *cis*-isomer as mixture of diastereoisomers.

6.3.7.2 Substrate Scope



4.178a

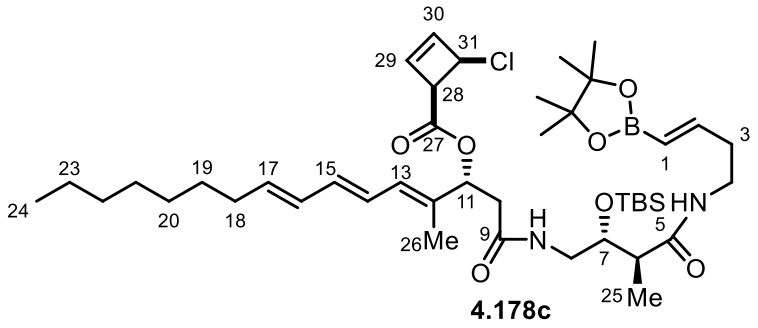
Yield: 20.4 mg, 79%, mixture of diastereoisomers (method C). **FTIR ($CHCl_3$, cm^{-1}):** 2929, 2856, 1738, 1645, 1539, 1361. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.54 (dt, *J* = 17.9, 6.2 Hz, 1H, **H2**), 6.27-6.24 (m, 2H, **H27** & **H28**), 6.21-6.18 (m, 1H, **NH** (next to C5)), 6.16-6.11 (m, 3H, **H13**, **H14**, **NH** (next to C9)), 5.74-5.69 (m, 1H, **H15**), 5.63 (dd, *J* = 7.9, 5.4 Hz, 1H, **H11**), 5.50 (d, *J* = 18.1 Hz, 1H, **H1**), 5.08 (d, *J* = 4.3 Hz, 1H, **H29**), 4.07 (d, *J* = 4.3 Hz, 1H, **H26**), 3.82-3.79 (m, 1H, **H7**), 3.78-3.73 (m, 1H, **H8**), 3.43-3.40 (m, 1H, **H3**), 3.29-3.23 (m, 1H, **H3**), 2.81-2.76 (m, 1H, **H8**), 2.66 (dd, *J* = 14.4, 7.9 Hz, 1H, **H10**), 2.49 (dd, *J* = 14.4, 5.4 Hz, 1H, **H10**), 2.38-2.33 (m, 3H, **H4** & **H6**), 2.07 (q, *J* = 7.2 Hz, 2H, **H16**), 1.77 (s, 3H, **H24**), 1.36-1.34 (m, 2H, **H17**), 1.25 (brd, 20H, **Bpin-CH_3** + **H18-H21**), 1.09 (d, *J* = 7.2 Hz, 3H, **H23**), 0.89-0.86 (m, 12H, **H22** & **TBS-H**), 0.14 (s, 3H, **TBS-H**), 0.07 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.6 (**C5**), 169.3 (**C9**), 168.8 (**C25**), 150.4 (**C2**), 140.6 (**C27**), 137.2 (**C28**), 136.6 (**C15**), 130.7 (**C12**), 129.0 (**C13**), 125.4 (**C14**), 121.3 (**C1**, deduced from HSQC), 83.3 (**Bpin-OC**), 77.0 (**C11**), 72.0 (**C7**), 56.3 (**C29**), 54.0 (**C26**), 44.5 (**C6**), 43.0 (**C8**), 40.9 (**C10**), 38.0 (**C3**), 35.8 (**C4**), 33.2 (**C16**), 31.9, 29.42, 29.36, 29.30, 26.0 (**TBS-C**), 24.9 (**Bpin-CH_3**), 22.8, 18.1 (**TBS-C**), 15.5 (**C23**), 14.3 (**C22**), 12.7 (**C24**), -4.4 (**TBS-C**), -4.9 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{41}H_{70}N_2O_7BClSiNa$) requires 799.4626, found 799.4620.



4.178b

Yield: 15.4 mg, 75%, mixture of diastereoisomers (method C). **FTIR ($CHCl_3$, cm^{-1}):** 2954, 1738, 1646, 1542, 1360, 1323, 1144, 837, 778. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.55 (dt, *J* = 17.9, 6.4 Hz, 1H, **H2**), 6.27-6.25 (m,

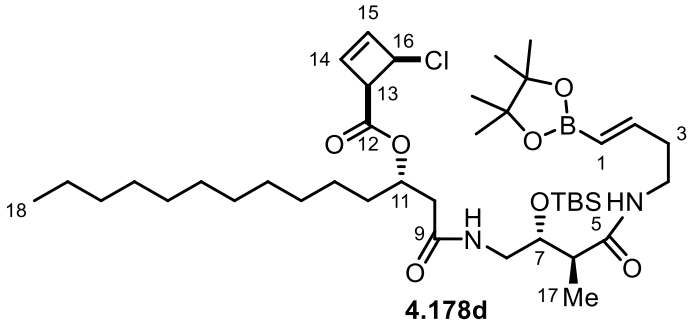
2H, **H29** & **H30**), 6.21-6.18 (m, 1H, **NH** (next to C5)), 6.17-6.11 (m, 3H, **H13**, **H14**, **NH** (next to C9)), 5.75-5.70 (m, 1H, **H15**), 5.63 (dd, *J* = 7.7, 5.4 Hz, 1H, **H11**), 5.50 (d, *J* = 18.1 Hz, 1H, **H1**), 5.08 (d, *J* = 4.2 Hz, 1H, **H31**), 4.07 (d, *J* = 4.3 Hz, 1H, **H28**), 3.82-3.79 (m, 1H, **H7**), 3.78-3.73 (m, 1H, **H8**), 3.46-3.40 (m, 1H, **H3**), 3.29-3.23 (m, 1H, **H3**), 2.81-2.77 (m, 1H, **H8**), 2.66 (dd, *J* = 14.4, 7.9 Hz, 1H, **H10**), 2.50 (dd, *J* = 14.4, 5.4 Hz, 1H, **H10**), 2.37-2.34 (m, 3H, **H4** & **H6**), 2.09-2.05 (m, 2H, **H16**), 1.77 (s, 3H, **H25**), 1.37-1.34 (m, 2H, **H17**), 1.25 (brd, 24H, **Bpin-CH₃** + **H18-H23**), 1.09 (d, *J* = 7.2 Hz, 3H, **H25**), 0.90 (s, 9H,**TBS-H**), 0.86 (t, *J* = 7.2 Hz, 3H, **H24**), 0.14 (s, 3H, **TBS-H**), 0.07 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, CDCl₃):** δ 174.6 (**C5**), 169.3 (**C9**), 168.8 (**C27**), 150.4 (**C2**), 140.6 (**C29**), 137.3 (**C30**), 136.6 **(C15**), 130.8 (**C12**), 129.0 (**C13**), 125.4 (**C14**), 121.3 (**C1**, deduced from HSQC), 83.3 (**Bpin-OC**), 77.0 (**C11**), 72.0 (**C7**), 56.4 (**C29**), 54.0 (**C30**), 44.5 (**C6**), 43.0 (**C8**), 40.9 (**C10**), 38.0 (**C3**), 35.9 (**C4**), 33.2 (**C16**), 32.0, 31.1, 29.70, 29.65, 29.5 (**C17**), 29.44, 29.43, 26.0 (**TBS-C**), 24.9 (**Bpin-CH₃**), 22.8, 18.1 (**TBS-C**), 15.5 (**C25**), 14.3 (**C24**), 12.7 (**C26**), 4.3 (**TBS-C**), -4.9 (**TBS-C**) ppm.



4.178c

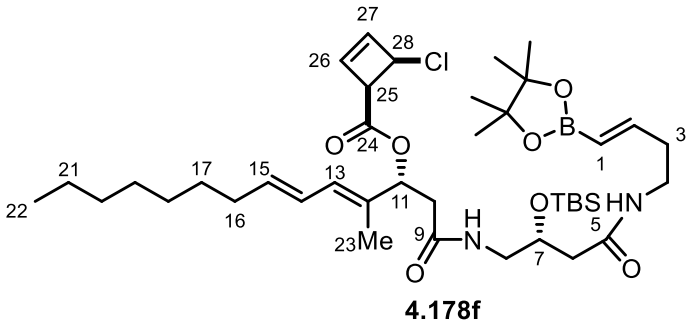
Yield: 32.5 mg, 57%, mixture of diastereoisomers (method C). **FTIR (CHCl₃, cm^{-1}):** 2948, 1736, 1646, 1541, 1360, 1324, 1169, 1144, 989, 837, 776. **^{1}H NMR (600 MHz, CDCl₃):** δ 6.55 (dt, *J* = 17.8, 6.4 Hz, 1H, **H2**), 6.27-6.16 (m, 7H, **H13**, **H14**, **H15**, **H29**, **H30**, **NH, NH**), 6.08 (dd, *J* = 15.0, 9.8 Hz, 1H, **H16**), 5.74-5.69 (m, 1H, **H17**), 5.67-5.65 (m, 1H, **H11**), 5.51 (d, *J* = 17.9 Hz, 1H, **H1**), 5.08 (d, *J* = 3.9 Hz, 1H, **H31**), 4.07 (d, *J* = 4.0 Hz, 1H, **H28**), 3.81-3.76 (m, 2H, **H7** & **H8**), 3.44-3.40 (m, 1H, **H3**), 3.26-3.23 (m, 1H, **H3**), 2.79-2.76 (m, 1H, **H8**), 2.67 (dd, *J* = 14.4, 7.8 Hz, 1H, **H10**), 2.51 (dd, *J* = 14.4, 5.7 Hz, 1H, **H10**), 2.35-2.31 (m, 3H, **H4** & **H6**), 2.10-2.06 (m, 2H, **H18**), 1.80 (s, 3H, **H26**), 1.38-1.36 (m, 2H, **H19**), 1.25 (brd, 20H, **Bpin-CH₃** + **H20-H23**), 1.08 (d, *J* = 7.1 Hz, 3H, **H25**), 0.89-0.86 (m, 12H, **TBS-H** & **H24**), 0.14 (s, 3H, **TBS-H**), 0.06 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, CDCl₃):** δ 174.7 (**C5**), 169.2 (**C9**), 168.8 (**C21**), 150.4 (**C2**), 140.6 (**C29**), 136.63 (**C30**), 136.58 (**C17**), 135.0, 132.6 (**C12**), 130.4 (**C16**), 128.9, 125.5, 121.5 (**C1**, deduced from HSQC), 83.3 (**Bpin-OC**), 76.8 (**C11**), 72.0 (**C7**), 56.4 (**C31**), 54.0 (**C28**), 44.6 (**C6**), 42.9 (**C8**), 40.9 (**C10**), 38.0 (**C3**), 35.9 (**C4**), 33.0 (**C18**), 32.0, 29.4 (**C19**), 29.30, 29.28, 26.0 (**TBS-C**), 24.9 (**Bpin-CH₃**), 22.8, 18.1 (**TBS-C**), 15.5 (**C25**), 14.2

(**C24**), 12.9 (**C26**), -4.4 (**TBS-C**), -4.9 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{43}H_{74}N_2O_7BClSiNa$) requires 827.4939, found 827.4946.



4.178d

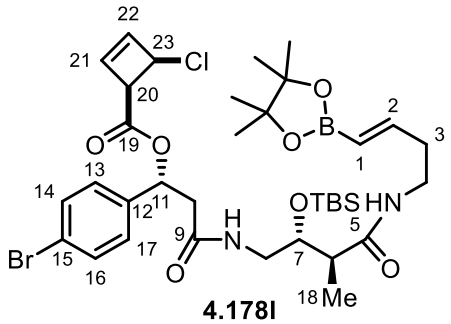
Yield: 38 mg, 34%, mixture of diastereoisomers (method A). **FTIR ($CHCl_3$, cm^{-1}):** 2926, 2855, 1735, 1643, 1540, 1359, 1324, 1144, 837, 776. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.55 (dt, *J* = 18.0, 6.5 Hz, 1H, **H2**), 6.27-6.21 (m, 4H, **H14**, **H15**, **NH**, **NH**), 5.51 (d, *J* = 18.0 Hz, 1H, **H1**), 5.24-5.20 (m, 1H, **H11**), 5.10 (d, *J* = 4.3 Hz, 1H, **H16**), 4.10 (d, *J* = 4.3 Hz, 1H, **H13**), 3.87-3.85 (m, 1H, **H7**), 3.75-3.70 (m, 1H, **H8**), 3.46-3.41 (m, 1H, **H3**), 3.28-3.23 (m, 1H, **H3**), 2.88-2.84 (m, 1H, **H8**), 2.51 (dd, *J* = 14.4, 6.7 Hz, 1H, **H10**), 2.47 (dd, *J* = 14.4, 5.0 Hz, 1H, **H10**), 2.42 (dd, *J* = 7.1, 4.9 Hz, 1H, **H6**), 2.37-2.34 (m, 2H, **H4**), 1.64-1.59 (m, 1H), 1.37-1.33 (m, 2H), 1.25-1.24 (m, 29H), 1.13 (d, *J* = 7.1 Hz, 3H, **H17**), 0.90 (s, 9H, **TBS-H**), 0.87 (t, *J* = 7.1 Hz, 3H, **H18**), 0.15 (s, 3H, **TBS-H**), 0.09 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.5 (**C5**), 169.9 (**C9**), 169.5 (**C12**), 150.4 (**C2**), 140.6 (**C14**), 136.7 (**C15**), 121.7 (**C1**, deduced from HSQC), 83.4 (**Bpin-OC**), 72.7 (**C11**), 72.1 (**C7**), 56.5 (**C16**), 54.0 (**C13**), 44.6 (**C6**), 43.1 (**C8**), 41.5 (**C10**), 38.0 (**C3**), 35.8 (**C4**), 34.0, 32.0, 29.78, 29.77, 29.7, 29.6, 29.50, 29.49, 26.0 (**TBS-C**), 24.92 (**Bpin-CH_3**), 24.91 (**Bpin-CH_3**), 22.8, 18.1 (**TBS-C**), 15.5 (C17), 14.3 (**C18**), -4.3 (**TBS-C**), -4.9 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{40}H_{72}N_2O_7BClSiNa$) requires 789.4783, found 789.4764.



4.178f

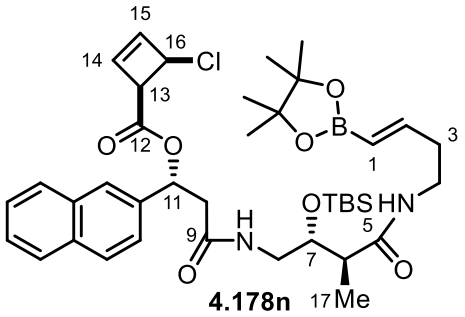
Yield: 23 mg, 25%, mixture of diastereoisomers (method A). **FTIR ($CHCl_3$, cm^{-1}):** 2927, 1738, 1642, 1554, 1359, 1323, 1145, 835, 777. **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 6.55 (dt, *J* = 17.9, 6.5 Hz, 1H, **H2**), 6.34 (t, *J* = 5.5

Hz, 1H, **NH**), 6.26-6.25 (m, 2H, **H26** & **H27**), 6.19-6.12 (m, 2H, **H13** & **H14**), 6.02 (dd, *J* = 7.8, 4.4 Hz, 1H, **NH**), 5.74-5.71 (m, 1H, **H15**), 5.65 (dd, *J* = 7.7, 5.6 Hz, 1H, **H11**), 5.51 (d, *J* = 18.0 Hz, 1H, **H1**), 5.08 (d, *J* = 4.3 Hz, 1H, **H28**), 4.12-4.11 (m, 1H, **H7**), 4.07 (d, *J* = 4.3 Hz, 1H, **H25**), 3.65-3.61 (m, 1H, **H8**), 3.41-3.35 (m, 1H, **H3**), 3.31-3.25 (m, 1H, **H3**), 2.99-2.95 (m, 1H, **H8**), 2.70 (dd, *J* = 14.4, 7.9 Hz, 1H, **H10**), 2.52 (dd, *J* = 14.4, 5.7 Hz, 1H, **H10**), 2.38-2.35 (m, 2H, **H4**), 2.28 (dd, *J* = 13.8, 6.0 Hz, 1H, **H6**), 2.22 (dd, *J* = 13.8, 5.2 Hz, 1H, **H6**), 2.09-2.05 (m, 2H, **H16**), 1.78 (s, 3H, **H23**), 1.37-1.35 (m, 2H, **H17**), 1.26 (brd, 20H, **Bpin-CH_3** + **H18-H21**), 0.89-0.86 (m, 12H, **H22** & **TBS-H**), 0.11 (s, 3H, **TBS-H**), 0.08 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 170.3 (**C5**), 169.7 (**C9**), 168.8 (**C24**), 150.4 (**C2**), 140.5 (**C26**), 137.4 (**C27**), 136.6 (**C15**), 130.7 (**C12**), 129.3 (**C13**), 125.4 (**C14**), 121.3 (**C1**, deduced from HSQC), 83.3 (**Bpin-OC**), 77.1 (**C11**), 68.4 (**C7**), 56.4 (**C28**), 54.0 (**C25**), 44.1 (**C8**), 42.3 (**C6**), 40.9 (**C10**), 38.3 (**C3**), 35.7 (**C4**), 33.2 (**C16**), 31.9, 29.42, 29.36, 29.30, 25.9 (**TBS-C**), 24.9 (**Bpin-CH_3**), 22.8, 18.1 (**TBS-C**), 14.3 (**C22**), 12.7 (**C23**), 4.6 (**TBS-C**), -4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{40}H_{68}N_2O_7BClSiNa$) requires 785.4470, found 785.4477.



4.178l

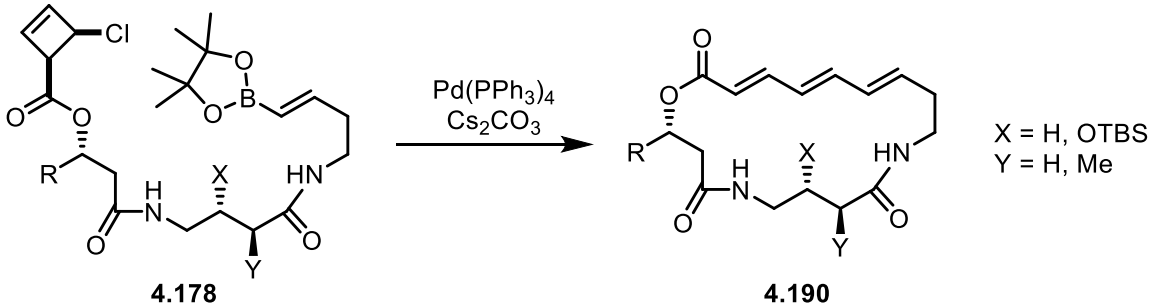
Yield: 57.3 mg, 44%, mixture of diastereoisomers (method A). **FTIR ($CHCl_3$, cm^{-1}):** 3337, 2969, 1741, 1637, 1560, 1463, 1362, 1250, 1167, 1143, 836, 776. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.46 (d, *J* = 8.5 Hz, 2H, **H14** & **H16**), 7.30 (d, *J* = 8.4 Hz, 2H, **H13** & **H17**), 6.54 (dt, *J* = 18.0, 6.5 Hz, 1H, **H2**), 6.29-6.24 (m, 2H, **H21, H22**), 6.16 (t, *J* = 7.1 Hz, 1H, **H11**), 6.14-6.12 (m, 1H, **NH**), 6.03 (t, *J* = 5.5 Hz, 1H, **NH**), 5.51 (d, *J* = 18.0 Hz, 1H, **H1**), 5.06 (d, *J* = 4.2 Hz 1H, **H23**), 4.08 (d, *J* = 4.2 Hz, 1H, **H20**), 3.73-3.69 (m, 1H, **H8**), 3.66-3.63 (m, 1H, **H7**), 3.45-3.38 (m, 1H, **H3**), 3.27-3.22 (m, 1H, **H3**), 2.91 (dd *J* = 14.2, 7.5 Hz, 1H, **H10**), 2.75-2.70 (m, 1H, **H8**), 2.61 (dd, *J* = 14.2, 6.8 Hz, 1H, **H10**), 2.36-2.33 (m, 2H, **H4**), 1.94-1.90 (m, 1H, **H6**), 1.25 (s, 12H, Bpin-CH_3), 1.14 (d, *J* = 7.2 Hz, 3H, **H18**), 0.88 (s, 9H, **TBS-H**), 0.12 (s, 3H, **TBS-H**), 0.06 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 174.5 (**C5**), 168.7 (**C9**), 168.5 (**C19**), 150.3 (**C2**), 140.7 (**C21**), 138.1 (**C12**) 136.4 (**C22**), 131.7 (**C14** & **C16**), 129.1 (**C13** & **C17**), 122.5 (**C15**), 121.4 (**C1**, deduced from HSQC), 83.4 (**Bpin-OC**), 73.4 (**C11**), 71.9 (**C7**), 56.4 (**C23**), 53.8 (**C20**), 44.5 (**C6**), 43.5 (**C10**), 42.8 (**C8**), 38.0 (**C3**), 35.8 (**C4**), 26.0 (**TBS-C**), 24.9 (**Bpin-CH_3**), 18.1 (**TBS-C**), 15.4 (**C18**), -4.4 (**TBS-C**), -4.9 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{35}H_{53}N_2O_7BClBrSiNa$) requires 789.2479, found 789.2485.



4.178n

Yield: 55.5 mg, 59%, mixture of diastereoisomers (method A). **FTIR ($CHCl_3$, cm^{-1}):** 2950, 1737, 1643, 1540, 1359, 1323, 1168, 1143, 837, 777. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.89-7.82 (m, 4H, **ArH**), 7.56-7.55 (m, 1H, **ArH**), 7.50-7.47 (m, 2H, **ArH**), 6.51 (dt, *J* = 18.0, 6.5 Hz, 1H, **H2**), 6.38 (t, *J* = 7.3 Hz, 1H, **H11**), 6.29-6.27 (m, 1H, **H15**), 6.24-6.23 (m, 1H, **H14**), 6.13-6.11 (m, 1H, **NH**), 5.57 (t, *J* = 5.6 Hz, 1H, **NH**), 5.48 (d, *J* = 18.0 Hz, 1H, **H1**), 5.08 (d, *J* = 4.2 Hz, 1H, **H16**), 4.11 (d, *J* = 4.2 Hz, 1H, **H13**), 3.72-3.68 (m, 1H, **H8**), 3.47-3.45 (m, 1H, **H7**), 3.30-3.22 (m, 1H, **H3**), 3.14-3.09 (m, 1H, **H3**), 3.07 (dd, *J* = 13.8, 6.8 Hz, 1H, **H10**), 2.76 (dd, *J* = 13.8, 7.8 Hz, 1H, **H10**), 2.65-2.61 (m, 1H, **H8**), 2.33-2.25 (m, 2H, **H4**), 1.42-1.38 (m, 1H, **H6**), 1.26 (s, 12H, **Bpin-CH_3**), 0.84 (s, 9H, **TBS-H**), 0.61 (d, *J* = 7.1 Hz, 3H, **H17**), 0.08 (s, 3H, **TBS-H**), -0.04 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.6 (**C5**), 168.8 (**C9**), 168.7 (**C19**), 150.5 (**C2**), 140.6 (**C14**), 136.4, 136.2, 133.2, 133.0, 128.42, 128.41, 127.8, 126.8, 126.6, 126.5, 121.3 (**C1**, deduced from HSQC), 83.4 (**Bpin-OC**), 74.3 (**C11**), 71.8 (**C7**), 56.3 (**C16**), 53.9 (**C13**), 44.1 (**C6**), 43.7 (**C10**), 42.4 (**C8**), 37.9 (**C3**), 35.8 (**C4**), 25.9 (**TBS-C**), 24.9 (**Bpin-CH_3**), 18.0 (**TBS-C**), 15.0 (**C17**), -4.5 (**TBS-C**), -5.0 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{39}H_{56}N_2O_7BClSiNa$) requires 761.3531, found 761.3541.

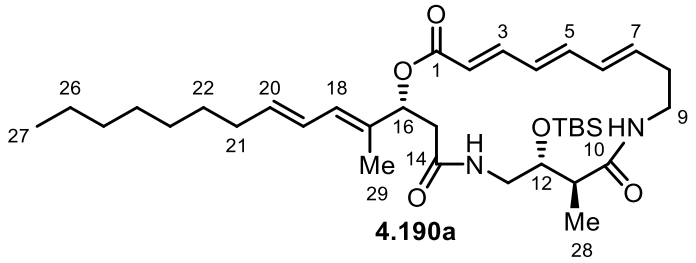
6.3.8 Suzuki-Miyaura Macrocyclization/4π Electrocyclic Ring Opening



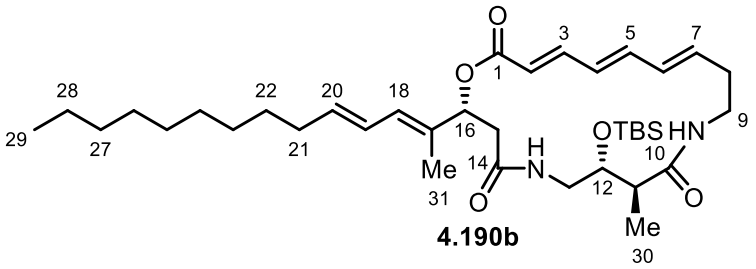
4.178 **4.190**

To a solution of the substrate (1.0 equiv.) in THF/H_2O (3/1) (0.002 M, degassed by bubbling with Argon for 10 min) was added Cs_2CO_3 (5.0 equiv.). The mixture was stirred at room temperature for 5-10 min, then $Pd(PPh_3)_4$ (10 mol%) was added. The vessel was then covered by aluminum foil and stirred at room

temperature for 18-24 h. The reaction was quenched by sat. NH_4Cl, extracted with CH_2Cl_2 (5 times). The combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 2:1 to 1:1) afforded the desired product.

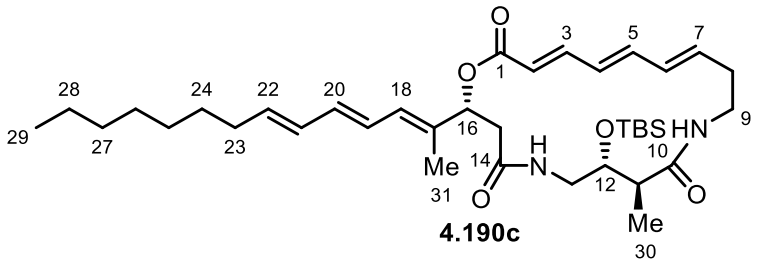


Yield: 20.6 mg, 74%, colorless powder. **FTIR ($CHCl_3$, cm^{-1}):** 3336, 2926, 2854, 1702, 1617, 1534, 1253, 1229, 1102, 1012, 835, 775. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.26 (dd, *J* = 15.3, 11.3 Hz, 1H, **H3**), 6.46 (dd, *J* = 14.8, 10.9 Hz, 1H, **H5**), 6.23-6.14 (m, 2H, **H4** & **H19**), 6.12-6.08 (m, 2H, **H18** & **H6**), 6.05 (brd, 1H, **NH**), 5.98 (brd, 1H, **NH**), 5.93-5.88 (m, 1H, **H7**), 5.76-5.70 (m, 2H, **H2** & **H20**), 5.63 (dd, *J* = 11.1, 3.1 Hz, 1H, **H16**), 4.11-4.05 (m, 1H, **H9**), 4.01 (brd, 1H, **H12**), 3.49-3.44 (m, 1H, **H13**), 2.96 (d, *J* = 13.9, 1H, **H9**), 2.55-2.39 (m, 5H, **H8**, **H11**, **H13** & **H15** x 2), 2.22-2.16 (m, 1H, **H8**), 2.11-2.08 (m, 2H, **H21**), 1.78 (s, 3H, **H29**), 1.39-1.36 (m, 2H, **H22**), 1.30-1.25 (m, 8H, **H23-H26**), 1.13 (d, *J* = 7.3 Hz, 3H, **H28**), 0.89-0.84 (m, 12H, **TBS-H** & **H27**), 0.08 (s, 3H, **TBS-H**), 0.05 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.1 (**C10**), 169.9 (**C14**), 166.3 (**C1**), 146.7 (**C3**), 143.2 (**C5**), 138.8 (**C7**), 136.7 (**C20**), 132.1 (**C17**), 131.5 (**C6**), 127.6 (**C4**), 126.5 (**C18**), 125.6 (**C19**), 119.5 (**C2**), 77.2 (**C16**), 72.3 (**C12**), 45.3 (**C11**), 43.0 (**C13**), 42.2 (**C15**), 37.4 (**C9**), 34.4 (**C8**), 33.2 (**C21**), 32.0, 29.8, 29.5, 29.3, 25.8 (**TBS-C**), 22.8, 18.0 (**TBS-C**), 14.3 (**C27**), 13.3 (**C29**), 12.4 (**C28**), -4.5 (**TBS-C**), -4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{35}H_{58}N_2O_5SiNa$) requires 637.4007, found 637.4008. **$[\alpha]_D^{20}$** = -78.7 (c = 0.85, $CHCl_3$).



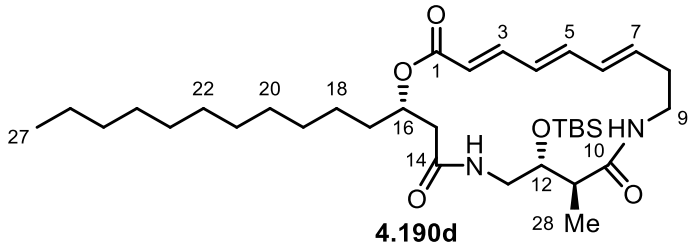
Yield: 8.2 mg, 82%, colorless powder. **FTIR ($CHCl_3$, cm^{-1}):** 3354, 2926, 2854, 1703, 1616, 1532, 1463, 1255, 1103, 1012, 836, 779. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.23 (dd, *J* = 15.5, 11.2 Hz, 1H, **H3**), 6.44 (dd, *J* = 14.9, 10.8 Hz, 1H, **H5**), 6.22 (dd, *J* = 14.8, 10.9 Hz, 1H, **H19**), 6.16 (dd, *J* = 14.9, 11.3 Hz, 1H, **H4**), 6.12-6.08 (m,

2H, **H6** & **H18**), 5.99 (brd, 1H, **NH**), 5.93-5.88 (m, 1H, **H7**), 5.81 (brd, 1H, **NH**), 5.76-5.70 (m, 2H, **H2** & **H20**), 5.63 (dd, *J* = 11.2, 3.0 Hz, 1H, **H16**), 4.10-4.03 (m, 1H, **H9**), 4.00 (brd, 1H, **H12**), 3.49-3.44 (m, 1H, **H13**), 2.96 (d, *J* = 13.9, 1H, **H9**), 2.54-2.39 (m, 5H, **H8**, **H11**, **H13** & **H15** x 2), 2.22-2.16 (m, 1H, **H8**), 2.12-2.08 (m, 2H, **H21**), 1.79 (s, 3H, **H31**), 1.38-1.36 (m, 2H, **H22**), 1.30-1.25 (m, 12H, **H23-H28**), 1.13 (d, *J* = 7.3 Hz, 3H, **H30**), 0.89-0.85 (m, 12H, **TBS-H** & **H29**), 0.08 (s, 3H, **TBS-H**), 0.05 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151MHz, $CDCl_3$):** δ 174.1 (**C10**), 169.8 (**C14**), 166.4 (**C1**), 146.6 (**C3**), 143.2 (**C5**), 138.8 (**C7**), 136.7 (**C20**), 132.0 (**C17**), 131.5 (**C6**), 127.6 (**C4**), 126.5 (**C18**), 125.6 (**C19**), 119.5 (**C2**), 77.2 (**C16**), 72.3 (**C12**), 45.3 (**C11**), 43.0 (**C13**), 42.3 (**C15**), 37.5 (**C9**), 34.5 (**C8**), 33.2 (**C21**), 32.0, 29.71, 29.66, 29.51, 29.48, 29.38, 25.8 (**TBS-C**), 22.8, 18.0 (**TBS-C**), 14.3 (**C29**), 13.4 (**C31**), 12.4 (**C30**), -4.5 (**TBS-C**), -4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{37}H_{62}N_2O_5SiNa$) requires 665.4320, found 665.4319. **$[\alpha]_D^{20}$** = -71.9 (c = 0.16, $CHCl_3$).



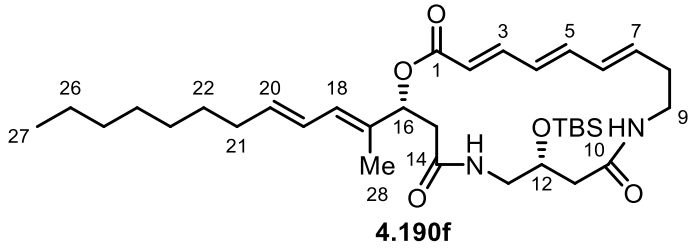
4.190c

Yield: 8.0 mg, 71%, colorless powder. **FTIR ($CHCl_3$, cm^{-1}):** 3327, 2926, 2855, 1709, 1617, 1533, 1252, 1229, 1100, 1011, 987, 835. **^{1}H NMR (700 MHz, $CDCl_3$):** δ 7.25 (dd, *J* = 15.6, 11.2 Hz, 1H, **H3**), 6.46 (dd, *J* = 14.8, 10.7 Hz, 1H, **H5**), 6.29 (dd, *J* = 14.8, 10.9 Hz, 1H, **H19**), 6.22 (dd, *J* = 14.8, 10.3 Hz, 1H, **H20**), 6.18-6.14 (m, 2H, **H4** & **H18**), 6.12-6.08 (m, 2H, **H21** & **H6**), 5.98 (brd, 1H, **NH**), 5.93-5.89 (m, 1H, **H7**), 5.81 (brd, 1H, **NH**), 5.74-5.70 (m, 2H, **H2** & **H22**), 5.65 (dd, *J* = 11.0, 3.0 Hz, 1H, **H16**), 4.11-4.04 (m, 1H, **H9**), 4.01 (brd, 1H, **H12**), 3.50-3.45 (m, 1H, **H13**), 2.97 (d, *J* = 13.8, 1H, **H9**), 2.54-2.52 (m, 2H, **H8** & **H15**), 2.49-2.46 (m, 1H, **H11**), 2.44-2.39 (m, 2H, **H13** & **H15**), 2.22-2.16 (m, 1H, **H8**), 2.11-2.08 (m, 2H, **H23**), 1.81 (s, 3H, **H31**), 1.39-1.37 (m, 2H, **H24**), 1.28-1.25 (m, 8H, **H25-H28**), 1.13 (d, *J* = 7.3 Hz, 3H, **H30**), 0.89-0.85 (m, 12H, **TBS-H** & **H29**), 0.08 (s, 3H, **TBS-H**), 0.05 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (176 MHz, $CDCl_3$):** δ 174.0 (**C10**), 169.8 (**C14**), 166.3 (**C1**), 146.7 (**C3**), 143.2 (**C5**), 138.9 (**C7**), 136.1 (**C22**), 134.5 (**C20**), 133.9 (**C17**), 131.5 (**C6**), 130.6 (**C21**), 127.6 (**C4**), 126.5 (**C18**), 125.8 (**C19**), 119.5 (**C2**), 77.1 (**C16**), 72.3 (**C12**), 45.3 (**C11**), 43.0 (**C13**), 42.3 (**C15**), 37.5 (**C9**), 34.5 (**C8**), 33.0 (**C21**), 32.0, 29.8, 29.4, 29.3, 25.8 (**TBS-C**), 22.8, 18.0 (**TBS-C**), 14.3 (**C29**), 13.6 (**C31**), 12.3 (**C30**), -4.5 (**TBS-C**), -4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{37}H_{60}N_2O_5SiNa$) requires 663.4164, found 663.4147. **$[\alpha]_D^{20}$** = -96.9 (c = 1.09, $CHCl_3$).



4.190d

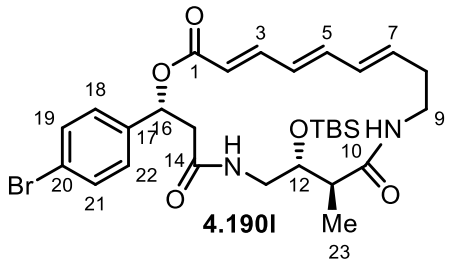
Yield: 5.2 mg, 56%, colorless powder. **FTIR ($CHCl_3$, cm^{-1}):** 3322, 2925, 2854, 1705, 1617, 1535, 1465, 1253, 1233, 1102, 1013, 836, 777. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.21 (dd, *J* = 15.3, 11.2 Hz, 1H, **H3**), 6.45 (dd, *J* = 14.9, 10.9 Hz, 1H, **H5**), 6.15 (dd, *J* = 14.8, 11.2 Hz, 1H, **H4**), 6.08 (dd, *J* = 14.9, 10.9 Hz, 1H, **H6**), 6.00 (brd, 1H, **NH**), 5.92-5.87 (m, 1H, **H7**), 5.84 (brd, 1H, **NH**), 5.71 (d, *J* = 15.4 Hz, 1H, **H2**), 5.28-5.24 (m, 1H, **H16**), 4.07-4.00 (m, 1H, **H9**), 3.94 (brd, 1H, **H12**), 3.39-3.34 (m, 1H, **H13**), 2.99-2.96 (m, 1H, **H9**), 2.53-2.50 (m, 2H, **H8** & **H15**), 2.48-2.45 (m, 2H, **H11** & **H13**), 2.25 (dd, *J* = 13.8, 10.3 Hz, 1H, **H15**), 2.22-2.15 (m, 1H, **H8**), 1.73-1.67 (m, 1H, **H17**), 1.62-1.57 (m, 1H, **H17**), 1.38-1.37 (m, 2H), 1.25 (m, 16H), 1.12 (d, *J* = 7.3 Hz, 3H, **H28**), 0.89-0.86 (m, 12H, **TBS-H** & **H27**), 0.07 (s, 3H, **TBS-H**), 0.05 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.2 (**C10**), 170.1 (**C14**), 167.0 (**C1**), 146.6 (**C3**), 143.1 (**C5**), 138.7 (**C7**), 131.6 (**C6**), 127.6 (**C4**), 119.7 (**C2**), 73.7 (**C16**), 72.3 (**C12**), 45.3 (**C11**), 43.4 (**C15**), 43.0 (**C13**), 37.5 (**C9**), 35.0 (**C17**), 34.5 (**C8**), 32.1, 29.80, 29.77, 29.73, 29.66, 29.59, 29.50, 25.8 (**TBS-C**), 25.6, 25.0, 22.8, 18.0 (**TBS-C**), 14.3 (C27), 12.9 (C28), -4.4 (**TBS-C**), -4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{34}H_{60}N_2O_5SiNa$) requires 627.4164, found 627.4157. **$[\alpha]_D^{20}$** = -5.8 (c = 0.76, $CHCl_3$).



4.190f

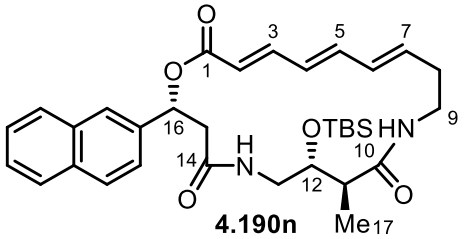
Yield: 17.3 mg, 73%, colorless powder. **FTIR ($CHCl_3$, cm^{-1}):** 3315, 2925, 2855, 1709, 1640, 1548, 1254, 1230, 1087, 1006, 975, 836, 777. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.26 (dd, *J* = 15.3, 11.3 Hz, 1H, **H3**), 6.48 (dd, *J* = 14.8, 10.9 Hz, 1H, **H5**), 6.21 (dd, *J* = 14.9, 10.8 Hz, 1H, **H19**), 6.14 (dd, *J* = 14.8, 11.3 Hz, 1H, **H4**), 6.12 (d, *J* = 10.8 Hz, 1H, **H18**), 6.08 (brd, 1H, **NH**), 6.06 (dd, *J* = 14.8, 11.4 Hz, 1H, **H6**), 5.92-5.88 (m, 1H, **H7**), 5.79 (brd, 1H, **NH**), 5.76-5.72 (m, 1H, **H20**), 5.70 (d, *J* = 15.3 Hz, 1H, **H2**), 5.62 (dd, *J* = 11.0, 2.9 Hz, 1H, **H16**), 4.19-4.15 (m, 1H, **H12**), 4.06-4.00 (m, 1H, **H9**), 3.36-3.32 (m, 1H, **H13**), 2.96 (d, *J* = 13.9, 1H, **H9**), 2.70 (dt, *J* = 13.5, 3.8 Hz, 1H, **H13**), 2.53 (dd, *J* = 13.9, 3.3 Hz, 1H, **H15**), 2.52-2.49 (m, 1H, **H8**), 2.45 (dd, *J* = 13.6, 11.3 Hz, 1H, **H15**), 2.35 (dd, *J* = 15.6, 4.3 Hz, 1H, **H11**), 2.28-2.24 (m, 1H, **H8**), 2.17 (dd, *J* = 15.6, 7.8 Hz, 1H, **H11**),

2.11-2.08 (m, 2H, **H21**), 1.79 (s, 3H, **H28**), 1.39-1.37 (m, 2H, **H22**), 1.30-1.25 (m, 8H, **H23-H26**), 0.88 (t, *J* = 7.1 Hz, 3H, **H27**), 0.82 (s, 9H, **TBS-H**), 0.04 (s, 3H, **TBS-H**), 0.03 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 170.9 (**C10**), 169.5 (**C14**), 166.3 (**C1**), 146.2 (**C3**), 142.8 (**C5**), 138.8 (**C7**), 136.8 (**C20**), 132.0 (**C17**), 131.9 (**C6**), 127.5 (**C4**), 126.7 (**C18**), 125.6 (**C19**), 119.7 (**C2**), 76.6 (**C16**), 69.4 (**C12**), 45.8 (**C13**), 42.9 (**C11**), 42.3 (**C15**), 37.5 (**C9**), 34.6 (**C8**), 33.2 (**C21**), 32.0, 29.8, 29.5, 29.33, 29.32, 25.9 (**TBS-C**), 25.0, 22.8, 18.1 (**TBS-C**), 14.2 (**C27**), 13.3 (**C28**), -4.49 (**TBS-C**), -4.53 (**TBS-C**) ppm.



4.190l

Yield: 44.6 mg, 58%, colorless powder. **FTIR ($CHCl_3$, cm^{-1}):** 3354, 2926, 2857, 1707, 1614, 1533, 1253, 1229, 1102, 1009, 835, 775. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.50 (d, *J* = 8.5 Hz, 2H, **H19** & **H21**), 7.31 (dd, *J* = 15.4, 11.2 Hz, 1H, **H3**), 7.28 (d, *J* = 8.5 Hz, 2H, **H18** & **H22**), 6.47 (dd, *J* = 14.9, 10.8 Hz, 1H, **H5**), 6.22 (dd, *J* = 11.4, 3.3 Hz, 1H, **H16**), 6.19 (dd, *J* = 14.8, 11.2 Hz, 1H, **H4**), 5.96-5.91 (m, 3H, **H6**, **H7** & **NH**), 5.74 (d, *J* = 15.3 Hz, 1H, **H2**), 5.74 (brd, 1H, **NH**), 4.08-4.04 (m, 2H, **H9** & **H12**), 3.56-3.51 (m, 1H, **H13**), 2.98 (d, *J* = 13.9, 1H, **H9**), 2.72 (dd, *J* = 13.9, 3.4 Hz, 1H, **H15**), 2.56 (dd, *J* = 13.9, 11.6 Hz, 1H, **H15**), 2.56-2.53 (m, 1H, **H8**), 2.49-2.46 (m, 2H, **H11** & **H13**), 2.23-2.17 (m, 1H, **H8**), 1.13 (d, *J* = 7.3 Hz, 3H, **H23**), 0.86 (s, 9H, **TBS-H**), 0.06 (s, 3H, **TBS-H**), 0.05 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 173.7 (**C10**), 169.1 (**C14**), 166.2 (**C1**), 147.2 (**C3**), 143.6 (**C5**), 139.3 (**C7**), 138.8 (**C17**), 131.9 (**C19** & **C21**), 131.4 (**C6**), 127.9 (**C18** & **C22**), 127.4 (**C4**), 122.2 (**C20**), 119.0 (**C2**), 73.8 (**C16**), 72.1 (**C12**), 45.3 (**C11**), 45.1 (**C15**), 42.8 (**C13**), 37.4 (**C9**), 34.6 (**C8**), 25.8 (**TBS-C**), 18.0 (**TBS-C**), 11.6 (**C23**) -4.5 (**TBS-C**), 4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{29}H_{41}N_2O_5SiBrNa$) requires 627.1860, found 627.1862. **$[\alpha]_D^{20}$** = -104 (c = 0.23, $CHCl_3$).



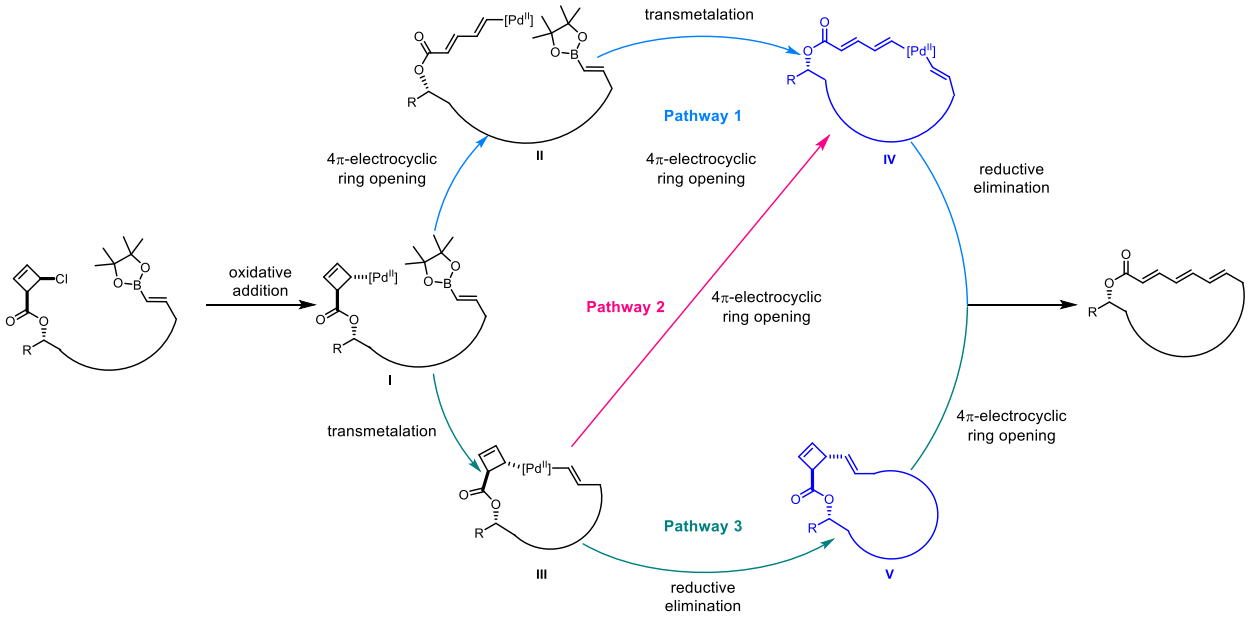
4.190n

Yield: 22.1 mg, 51%, colorless powder. **FTIR ($CHCl_3$, cm^{-1}):** 3320, 2927, 2855, 1705, 1615, 1532, 1253, 1229, 1102, 1016, 836, 776. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.86-7.82 (m, 4H, **ArH**), 7.52-7.41 (m, 4H, **H3** & **ArH**),

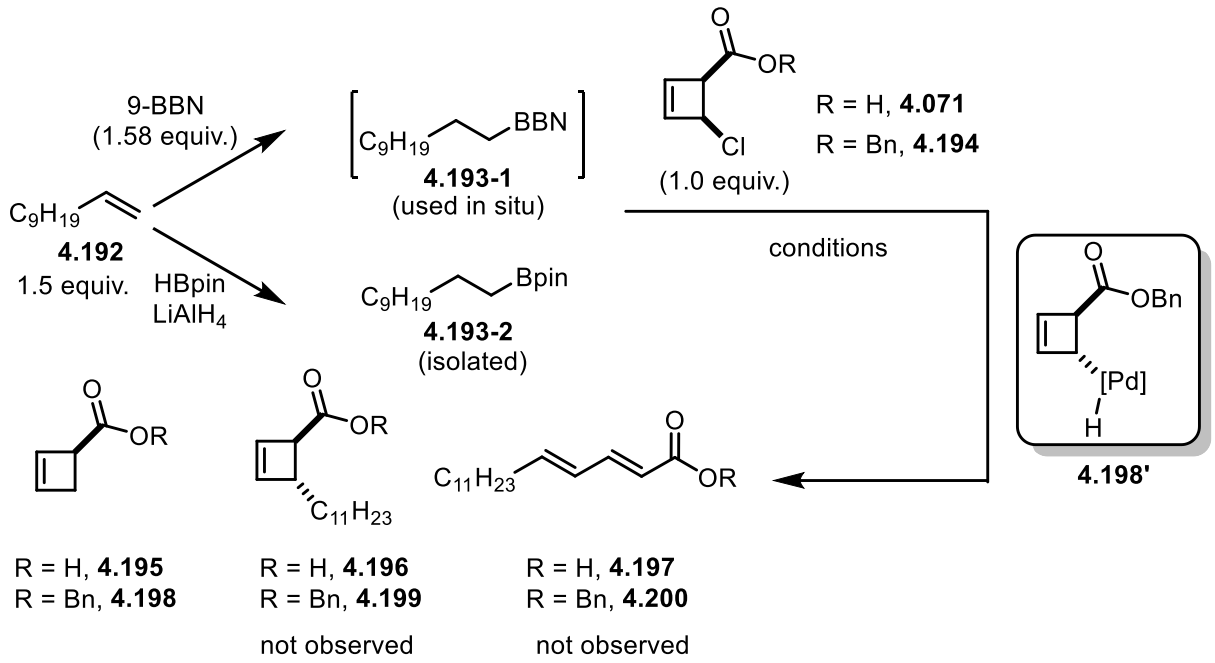
6.55-6.51 (m, 1H, **H5**), 6.44 (dd, *J* = 11.4, 2.8 Hz, 1H, **H16**), 6.21 (dd, *J* = 14.5, 11.5 Hz, 1H, **H4**), 6.13 (dd, *J* = 14.7, 10.8 Hz, 1H, **H6**), 6.21-6.13 (brd, **NH**), 6.06 (brd, 1H, **NH**), 5.96-5.92 (m, 1H, **H7**), 5.78 (d, *J* = 15.3 Hz, 1H, **H2**), 4.11-4.07 (m, 2H, **H9** & **H12**), 3.59-3.54 (m, 1H, **H13**), 2.97 (d, *J* = 13.8, 1H, **H9**), 2.82 (d, *J* = 13.3 Hz, 1H, **H15**), 2.75-2.71 (m, 1H, **H15**), 2.57-2.46 (m, 3H, **H8**, **H11** & **H13**), 2.25-2.18 (m, 1H, **H8**), 1.15 (d, *J* = 7.3 Hz, 3H, **H17**), 0.88 (s, 9H, **TBS-H**), 0.10 (s, 3H, **TBS-H**), 0.06 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.1 (**C10**), 169.6 (**C14**), 166.4 (**C1**), 147.2 (**C3**), 143.6 (**C5**), 139.1, 137.2, 133.3, 133.2, 131.5 (**C6**), 128.6, 128.2, 127.8, 127.6 (**C4**), 126.5, 126.3, 125.0, 124.1, 119.2 (**C2**), 74.6 (**C16**), 72.3 (**C12**), 45.3 (**C11**), 45.2 (**C15**), 43.0 (**C13**), 37.4 (**C9**), 34.5 (**C8**), 25.8 (**TBS-C**), 18.0 (**TBS-C**), -4.5 (**TBS-C**), -4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{33}H_{44}N_2O_5SiNa$) requires 599.2912, found 599.2914. **$[\alpha]_D^{20}$** = -135 (c = 0.67, $CHCl_3$).

6.3.9 Mechanistic Study

Three possible pathways were proposed for the formation of macrocycle **4.190a**. While both pathway 1 and 2 involved the intermediacy of a dienylpalladium complex **IV**, pathway 3 relied on a vinyl cyclobutene moiety **V**.



To shed light on the mechanism, following studies were carried out.



Entry	Boron reagent	R	Conditions	Comments
1	**4.193-2**	Bn	$Pd(PPh_3)_4$, Cs_2CO_3, THF/H_2O, rt	Decomposition
2	**4.193-2**	Bn	$Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, DMF/THF/H_2O, rt	Decomposition
3[a]	**4.193-1**	H	$Pd(PPh_3)_4$, Cs_2CO_3, THF/H_2O, rt	Decomposition
4[a]	**4.193-1**	Bn	$Pd(PPh_3)_4$, Cs_2CO_3, THF/H_2O, rt	Decomposition
5[a]	**4.193-1**	Bn	$Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, DMF/THF/H_2O, rt	**4.198** (20%)

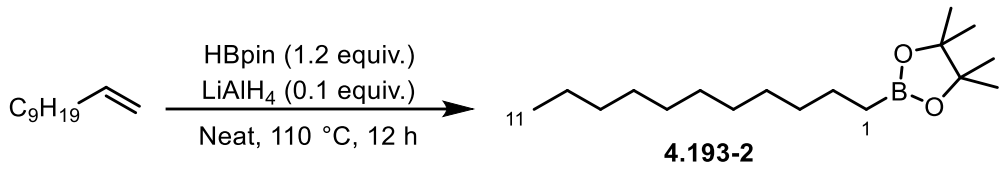
[a] 100% conversion was achieved measured by ^1H NMR.

In all the reactions screened, the expected product **4.196**, **4.197** or **4.199**, **4.200** was never observed. The reactions of entry1-4 only resulted in the decomposition of the starting materials. Instead, the reduced cyclobutene ester **4.198**, probably formed from the hydridopalladium species **4.198'** after a reductive elimination, was isolated in 20% yield under the conditons of entry 5.

Conclusion:

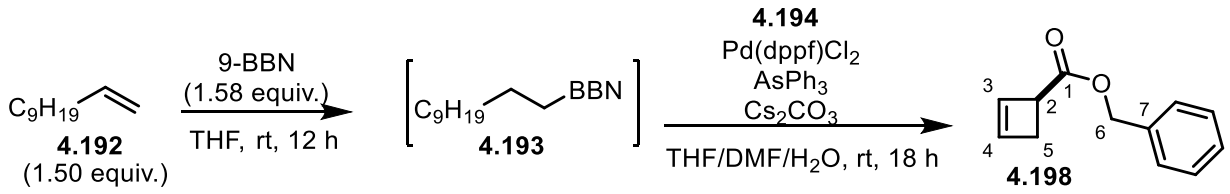
These reactions suggest that the dienylpalladium intermediate **IV** was probably not involved in the formation of the macrocycle **4.190a,** thus excluding pathway 1 and 2**. 4.190a** was most likely formed

through a Suzuki-Miyaura coupling on the cyclobutene moiety and a sequential spontaneous 4π-electrocyclic ring opening of intermediate **V** (pathway 3)**.**



4.193-2

To a flame dried Schlenk tube charged with $LiAlH_4$ (9.5 mg, 0.25 mmol, 0.1 equiv.) was added sequentially undec-1-ene **4.192** (0.51 mL, 2.5 mmol, 1.0 equiv.) and HBpin (0.44 mL, 3.0 mmol, 1.2 equiv.). The mixture was heated at 110 °C for 12 h. Then the mixture was diluted with CH_2Cl_2 (2.0 mL), and filtered through a pad of silica gel. Purification by column chromatography (silica gel, Heptane/EtOAc = 30:1) afforded 347 mg (52%) of product **4.193-2** as a colorless oil.[18] **FTIR ($CHCl_3$, cm^{-1}):** 3674, 2188, 2011, 1737, 1365, 1217, 1057, 809, 681. **^{1}H NMR (400 MHz, $CDCl_3$):** 1.44-1.34 (m, 2H), 1.25-1.24 (m, 28H), 0.87 (t, *J* = 6.7 Hz, 3H, **H11**), 0.76 (t, *J* = 7.7 Hz, 2H, **H1**). **^{13}C NMR (100 MHz, $CDCl_3$):** 83.0 (**Bpin-OC**), 32.6, 32.1, 29.82, 29.79, 29.74, 29.57, 29.51, 25.0, 24.2, 22.8, 14.2. **HRMS (ESI) (m/z):** calculated for $[M+H]^+$ ($C_{17}H_{36}O_2B_1$) requires 283.2803, found 283.2803.



4.198

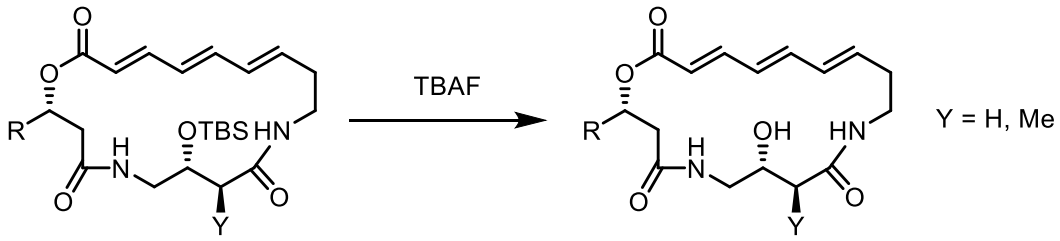
To a stirred solution of alkene **4.192** (31 uL, 0.15 mmol, 1.5 equiv.) in THF (1.0 mL) at 0 °C was 9-BBN (22 uL, 0.16 mmol, 1.6 equiv.). The mixture was then allowed to warm to room temperature and stirred for another 12 h. ^{1}N NMR showed the alkene **4.192** was fully consumed.

In a separated flask charged with **4.194** (22.3 mg, 0.10 mmol, 1.0 equiv.), Cs_2CO_3 (163 mg, 0.50 mmol, 5.0 equiv.), $Pd(dppf)Cl_2$ (7.3 mg, 0.01 mmol, 10 mmol%) and $AsPh_3$ (10.1 mg, 0.033 mmol, 33 mmol%) was added DMF (1.5 mL) and H_2O (0.5 mL). The mixture was stirred vigorously at room temperature. Then the above boron reagent was added to the mixture. The reaction was stirred vigorously at room temperature for 18 h before quenched by sat. NH_4Cl (aq.). The reaction was extracted with CH_2Cl_2 (5 X 5 mL). The combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 10:1) afforded 3.8 mg (20%) of

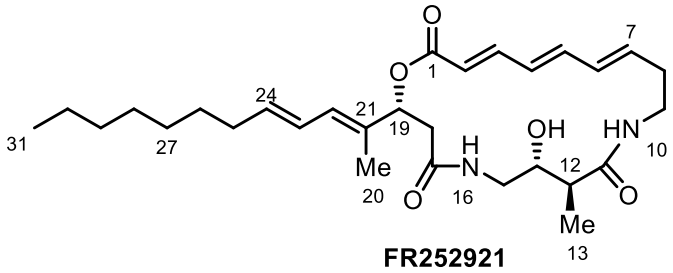
[18] Bismuto, A., Cowley, M. J., Thomas, S. P. *ACS Catal.* **2018**, *8*, 2001-2005.

product **4.198**. **FTIR ($CHCl_3$, cm^{-1}):** 3026, 3035, 2931, 1732, 1377, 1155, 1084, 1026, 697. **^{1}H NMR (400 MHz, $CDCl_3$):** 7.39-7.31 (m, 5H, **ArH**), 6.23-6.22 (m, 1H, **H4**), 6.06 (dd, *J* = 2.7, 0.9 Hz, 1H, **H3**), 5.14 (s, 2H, **H6**), 3.74-3.72 (m, 1H, **H2**), 2.83 (ddd, *J* = 13.6, 4.4, 0.8 Hz, 1H, **H5**), 2.76 (ddd, *J* = 13.6, 1.9, 0.9 Hz, 1H, **H5**). **^{13}C NMR (100 MHz, $CDCl_3$):** 173.2 (**C1**), 139.4, 136.2 (**C7**), 135.0, 128.7, 128.3, 128.2, 66.4 (**C6**), 46.1 (**C4**), 34.7 (**C5**). **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{12}H_{12}O_2Na$) requires 211.0730, found 211.0727.

6.3.10 Deprotection



Protected alcohol (1.0 equiv.) was dissolved in THF (1 mL) and cooled down to 0 °C. TBAF (1 M in THF, 1.2 equiv.) was then charged and the reaction was monitored by TLC (Heptane/EtOAc = 3:7). **Generally, within 5 min the reaction is finished.** The reaction was then quenched with a drop of saturated NH_4Cl, concentrated in vacuo and directly purified by chromatography (silica gel, $CHCl_3$/MeOH = 20:1).



Yield: 8.8 mg, 90%, colorless powder.

Rf = 0.46 ($CHCl_3$/MeOH = 10:1).

FTIR ($CHCl_3$, cm^{-1}): 3316, 2923, 1704, 1642, 1536, 1379, 1254, 1063, 1006, 965.

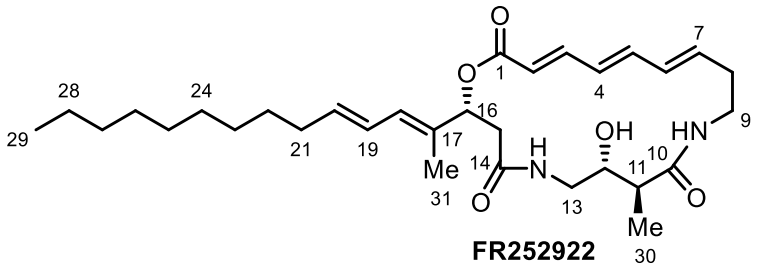
HRMS (ESI) (m/z): calculated for $[M+Na]^+$ ($C_{29}H_{44}N_2O_5Na$) requires 523.3142, found 523.3140.

Lit. $[\alpha]_D^{20}$ = -220 (c = 0.2, DMSO)[19,9] found $[\alpha]_D^{20}$ = -178 (c = 0.21, DMSO).

[19] Fujine, K. *et al. J. Antibiot.* **2003**, *56*, 55-61.

		^{1}H NMR [$(CD_3)_2SO$, (ppm)] (synthetic)	^{1}H NMR [$(CD_3)_2SO$, (ppm)] (literature)[9]	^{13}C NMR [$(CD_3)_2SO$, (ppm)] (synthetic)	^{13}C NMR [$(CD_3)_2SO$, (ppm)] (literature)[9]
1	C			165.40	165.4
2	CH	5.65 (d, *J* = 15.3 Hz)	5.65 (d, *J* = 16 Hz)	118.23	118.2
3	CH	7.36 (ddd, *J* = 15.3, 11.4, 0.7 Hz)	7.35 (dd, *J* = 16, 12 Hz)	147.37	147.4
4	CH	6.26 (dd, *J* = 14.8, 11.4 Hz)	6.26 (dd, *J* = 15, 11 Hz)	126.46	126.5
5	CH	6.56 (dd, *J* = 14.8, 10.8 Hz)	6.56 (dd, *J* = 15, 11 Hz)	143.82	143.8
6	CH	6.15 (dd, *J* = 15.1, 10.9 Hz)	6.15 (dd, J = 15, 11 Hz)	131.43	131.4
7	CH	5.85 (ddd, *J* = 15.1, 10.5, 4.8 Hz)	5.85 (ddd, *J* = 15, 11, 5 Hz)	139.09	139.1
8	CH_2	2.33 (m, 1H) 2.22 (m, 1H)	2.36-2.17 (4H, m)	32.09	32.1
9	CH_2	3.43 (m, 1H) 3.18 (m, 1H)	3.45-3.42 (m) 3.21-3.15 (m)	37.12	37.1
10	NH	7.61 (dd, *J* = 6.2, 6.2 Hz)	7.63 (t, *J* = 6 Hz)		
11	C			173.75	173.7
12	CH	2.27 (m, 1H)	2.36-2.17 (4H,m)	44.44	44.4
13	CH_3	0.89 (d, *J* = 7.1 Hz)	0.88 (d, *J* = 8 Hz)	10.56	10.5
14	CH	3.58 (dddd, *J* = 10.6, 6.4, 4.0, 2.3 Hz)	3.61-3.56 (m)	70.69	70.7
	OH	5.05 (d, *J* = 4.0 Hz)	5.06 (d, *J* = 4 Hz)		
15	CH_2	2.98 (ddd, *J* = 13.3, 5.3, 2.2 Hz) 2.78 (ddd, *J* = 13.3, 10.8, 4.9 Hz)	2.98-2.94 (m) 2.82-2.76 (m)	42.42	42.4
16	NH	7.87 (dd, *J* = 5.3, 4.9 Hz)	7.90 (t, *J* = 5 Hz)		
17	C			169.41	169.4
18	CH_2	2.71 (dd, *J* = 13.9, 11.6 Hz) 2.29 (dd, *J* = 13.9, 2.7 Hz)	2.70 (dd, *J* = 14, 12 Hz) 2.36-2.17 (4H, m)	40.60	40.7
19	CH	5.29 (dd, *J* = 11.6, 2.7 Hz)	5.29 (d, *J* = 10 Hz)	76.21	76.2
20	CH_3	1.72 (d, *J* = 1.4 Hz)	1.72 (s)	12.96	12.9
21	C			133.02	133.0
22	CH	6.01 (dq, *J* = 11.0, 1.4 Hz)	6.01 (d, *J* = 11 Hz)	125.42	125.4
23	CH	6.24 (ddt, *J* = 15.0, 11.0, 1.4 Hz)	6.24 (dd, *J* = 15, 11 Hz)	125.77	125.8
24	CH	5.72 (dt, *J* = 15.0, 7.2 Hz)	5.71 (dt, *J* = 15, 7 Hz)	135.57	135.6
25	CH_2	2.08 (td, *J* = 7.1, 7.2 Hz)	2.10-2.05 (m)	32.35	32.3

26	CH_2	1.35 (m)	1.36-1.18 (10H, m)	28.86	28.9
27	CH_2	1.25 (m)		28.61	28.59
28	CH_2	1.25 (m)		29.56	28.55
29	CH_2	1.24 (m)		31.25	31.3
30	CH_2	1.26 (m)		22.10	22.1
31	CH_3	0.85 (t, 7.1 Hz)	0.85 (t, *J* = 8 Hz)	13.97	14.0



FR252922

Yield: 6.5 mg, 95%, colorless powder.

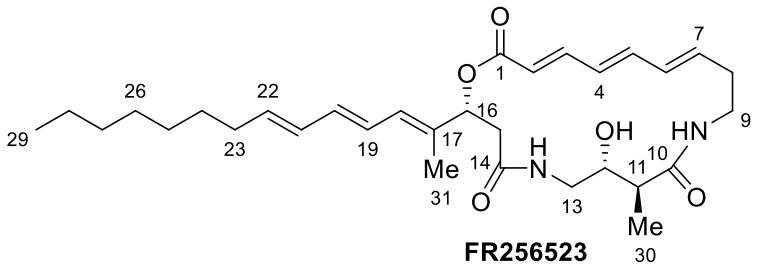
Rf = 0.39 ($CHCl_3$/MeOH = 10:1).

HRMS (ESI) (m/z): calculated for $[M+Na]^+$ ($C_{31}H_{48}N_2O_5Na$) requires 551.3455, found 551.3460.

Lit. $[\alpha]_D^{20}$ = -235 (C = 0.2, DMSO)[19], found $[\alpha]_D^{20}$ = -201 (C = 0.08, DMSO).

FTIR ($CHCl_3$, cm^{-1}): 3320, 2924, 2854, 1706, 1641, 1542, 1458, 1265, 1008, 967.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (dd, *J* = 15.2, 11.4 Hz, 1H, **H3**), 6.50 (dd, *J* = 14.9, 10.9 Hz, 1H, **H5**), 6.27-6.12 (m, 4H, **H4, H18, H19, NH**), 6.07 (dd, *J* = 14.9, 11.8 Hz, 1H, **H6**), 6.00 (s, 1H, **OH**), 5.80-5.69 (m, 4H, **H2, H20, NH, H7**), 5.67 (dd, *J* = 11.4, 3.2 Hz, 1H, **H16**), 4.17-4.10 (m, 1H, **H9**), 3.82-3.78 (m, 1H, **H13**), 3.32 (td, *J* = 10.4, 2.5 Hz, 1H, **H12**), 3.01 (d, *J* = 14.0, 1H, **H9**), 2.65-2.48 (m, 2H, **H8**, **H13**), 2.56 (dd, *J* = 13.9, 3.1 Hz, 1H, **H15**), 2.50 (dd, *J* = 13.8, 11.4 Hz, 1H, **H15**), 2.29-2.25 (m, 1H, **H11**), 2.24-2.20 (m, 1H, **H8**), 2.11-2.07 (m, 2H, **H21**), 1.79 (s, 3H, **H31**), 1.37-1.36 (m, 2H, **H22**), 1.25 (brd, 12H, **H23-H28**), 0.98 (d, *J* = 7.1 Hz, 3H, **H30**), 0.87 (t, *J* = 7.1 Hz, 3H, **H29**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 176.0 (**C10**), 169.4 (**C14**), 165.4 (**C1**), 144.6 (**C3**), 140.8 (**C5**), 136.7 (**C7**), 136.0 (**C20**), 133.0 (**C6**) , 131.9 (**C17**), 128.7 (**C4**) , 126.7 (**C18**), 125.6 (**C19**), 121.3 (**C2**) , 76.1 (**C16**), 71.6 (**C12**), 44.0 (**C13**), 43.0 (**C11**), 41.9 (**C15**), 36.9 (**C9**), 34.6 (**C8**), 33.2 (**C21**), 32.0, 29.71, 29.66, 29.5, 29.4, 22.8, 14.3 (**C29**), 13.3 (**C31**), 11.0 (**C30**) ppm.



FR256523

Yield: 4.7 mg, 90%, colorless powder.

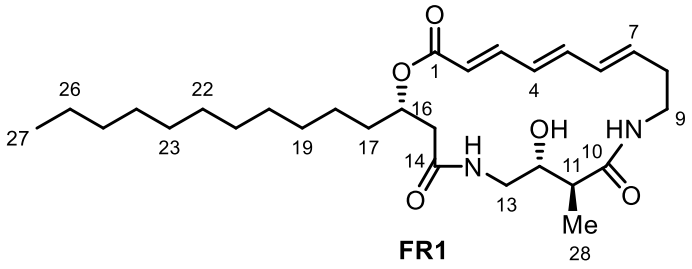
Rf = 0.40 ($CHCl_3$/MeOH = 10:1).

FTIR ($CHCl_3$, cm^{-1}): 3310, 2924, 1704, 1642, 1538, 1256, 1008, 987.

HRMS (ESI) (m/z): calculated for $[M+Na]^+$ ($C_{31}H_{46}N_2O_5Na$) requires 549.3299, found 549.3300.

Lit. $[\alpha]_D^{20}$ = -72 (C = 0.2, DMSO)[19], found $[\alpha]_D^{20}$ = -106 (c = 0.19, DMSO).

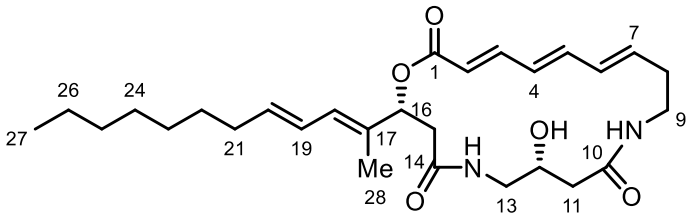
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (dd, *J* = 15.5, 11.2 Hz, 1H, **H3**), 6.51 (dd, *J* = 14.8, 10.9 Hz, 1H, **H5**), 6.31-6.16 (m, 5H, including **H4, H19, H18**), 6.12-6.05 (m, 2H, **H6**,), 6.00 (s, 1H), 5.81-5.68 (m 5H, including **H2**, **H7**, **NH** (Between C9 and C10), **H16**), 4.17-4.10 (m, 1H, **H9**), 3.82-3.78 (m, 1H, **H13**), 3.32 (td, *J* = 10.3, 2.6 Hz, 1H, **H12**), 3.02-3.00 (m, 1H, **H9**), 2.65-2.48 (m, 4H, **H13, H15, H15, H8**), 2.29-2.16 (m, 2H, **H11**, **H8**), 2.10-2.07 (m, 2H, **H23**), 1.81 (s, 3H, **H31**), 1.40-1.36 (m, 2H, **H24**), 1.28-1.25 (m, 8H, **H25-H28**), 0.98 (d, *J* = 7.1 Hz, 3H, **H30**), 0.87 (t, *J* = 6.9 Hz, 3H, **H29**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 176.0 (**C10**), 169.4 (**C14**), 165.4 (**C1**), 144.8 (**C3**), 140.9 (**C5**), 136.2, 136.1, 134.4, 133.8 (**C17**), 133.0 (**C6**), 130.6, 128.7 (**C4**), 126.7 (**C18**), 125.8 (**C19**), 121.2 (**C2**), 76.1 (**C16**), 71.6 (**C12**), 44.1 (**C13**), 43.0 (**C11**), 42.0 (**C15**), 36.9 (**C9**), 34.6 (**C8**), 33.0 (**C23**), 32.0, 29.4, 29.31, 29.30, 22.8, 14.3 (**C29**), 13.5 (**C31**), 11.0 (**C30**) ppm.



FR1

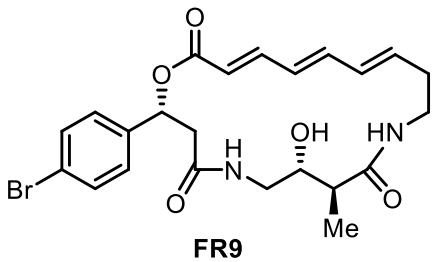
Yield: 2.9 mg, 90%, colorless powder. **FTIR ($CHCl_3$, cm^{-1}):** 3317, 2922, 1703, 1642, 1536, 1242, 1221, 1008, 775. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.22 (dd, *J* = 15.3, 11.3 Hz, 1H, **H3**), 6.48 (dd, *J* = 14.9, 10.8 Hz, 1H, **H5**), 6.22 (d, *J* = 8.4 Hz, 1H, **NH**), 6.18 (dd, *J* = 14.8, 11.3 Hz, 1H, **H4**), 6.06 (dd, *J* = 15.0, 10.9 Hz, 1H, **H6**), 5.90 (brd, 1H, **OH**), 5.79-5.76 (m, 1H, **H7**), 5.76 (d, *J* = 15.4 Hz, 1H, **H2**), 5.68 (d, *J* = 7.6 Hz, 1H, **NH**), 5.39-5.34

(m, 1H, **H16**), 4.11-4.04 (m, 1H, **H9**), 3.78-3.74 (m, 1H, **H13**), 3.34-3.30 (m, 1H, **H12**), 3.04 (d, *J* = 13.7 Hz, 1H, **H9**), 2.63-2.53 (m, 3H, **H8**, **H13**, **H15**), 2.35 (dd, *J* = 13.9, 11.1 Hz, 1H, **H15**), 2.27-2.20 (m, 2H, **H8, H11**), 1.72- 1.68 (m, 1H, **H17**), 1.62-1.58 (m, 1H, **H17**), 1.37-1.32 (m, 2H), 1.24 (brd, 16H), 0.97 (d, *J* = 7.1 Hz, 3H, **H28**), 0.87 (t, *J* = 6.8 Hz, 3H, **H27**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 176.0 (**C10**), 169.8 (**C14**), 166.1 (**C1**), 144.4 (**C3**), 140.6 (**C5**), 135.8 (**C7**), 133.0 (**C6**), 128.8 (**C4**), 121.4 (**C2**), 72.5 (**C16**), 71.6 (**C12**), 43.9 (**C13**), 43.0 (**C11**), 42.8 (**C15**), 36.9 (**C9**), 34.9 (**C8**) , 34.6 (**C17**), 33.5, 32.0, 29.80, 29.77, 29.71, 29.65, 29.50, 25.4, 22.8, 14.3 (**C27**), 11.2 (**C28**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{28}H_{46}N_2O_5Na$) requires 513.3299, found 513.3297. **$[\alpha]_D^{20}$** = -49 (c = 0.11, $CHCl_3$).



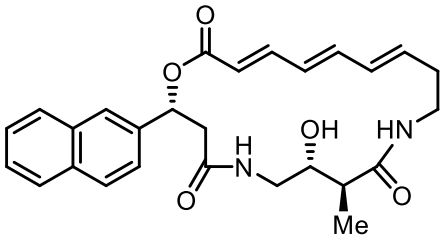
FR3

Yield: 3.7 mg, 90%, colorless powder. **FTIR ($CHCl_3$, cm^{-1}):** 3290, 2924, 1705, 1638, 1549, 1436, 1230, 1020, 1005, 963, 775. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.29 (dd, *J* = 15.2, 11.4 Hz, 1H, **H3**), 6.59 (d, *J* = 9.4 Hz, 1H, **OH**), 6.56 (dd, *J* = 14.8, 10.9 Hz, 1H, **H5**), 6.24-6.19 (m, 2H, **H19**, **NH**), 6.14-6-07 (m, 3H, **H4**, **H6, H18**), 5.89-5.84 (m, 1H, **H7**), 5.78-5.72 (m, 2H, **H20, NH**), 5.70-5.66 (m, 2H, **H2, H16**), 4.13-4.06 (m, 1H, **H9**), 3.66-3.62 (m, 1H, **H12**), 3.36-3.32 (m, 1H, **H13**), 2.98 (dd, *J* = 12.2, 4.2 Hz, 1H, **H9**), 2.66 (t, *J* = 11.8 Hz, 1H, **H13**), 2.58-2.50 (m, 3H, **H8, H15, H15**), 2.38-2.31 (m, 1H, **H8**), 2.20-2.16 (m, 1H, **H11**), 2.12-2.08 (m, 3H, **H21, H11**), 1.80 (s, 3H, **H28**), 1.39-1.36 (m, 2H, **H22**), 1.30-1.25 (m, 8H, **H23-H26**), 0.88 (t, *J* = 7.1 Hz, 3H, **H27**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 173.9 (**C10**), 169.3 (**C14**), 166.2 (**C1**), 145.2 (**C3**), 141.9 (**C5**), 137.5 (**C7**), 137.0 (**C20**), 133.2 (**C6**), 131.5 (C**17**), 128.0 (**C4**), 126.9 (**C18**), 125.5 (**C19**), 120.5 (**C2**), 76.2 (**C16**), 68.1 (**C12**), 45.3 (**C13**), 41.6 (**C15**), 38.7 (**C11**), 36.9 (**C9**), 34.5 (**C8**), 33.2 (**C21**), 32.0, 29.5, 29.3, 22.8, 14.3 (**C27**), 13.3 (**C28**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{28}H_{42}N_2O_5Na$) requires 509.2986, found 509.2985. **$[\alpha]_D^{20}$** = -195 (c = 0.13, $CHCl_3$).



FR9

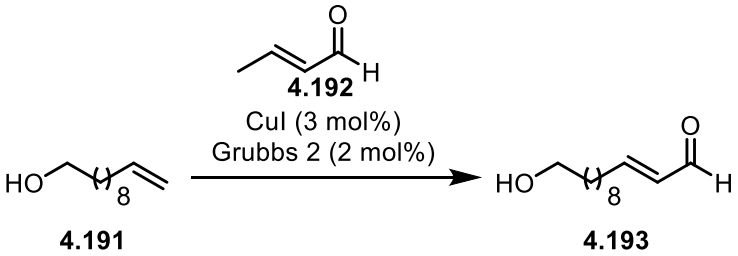
Yield: 14.6 mg, 95%, colorless powder. **Insoluble in most of solvents**, such as $CHCl_3$, DMF, MeOH, H_2O, DMSO, THF. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{23}H_{27}BrN_2NaO_5$) requires 513.0996, found 513.0990.



FR11

Yield: 8.2 mg, 90%, colorless powder. **Insoluble in most of solvents**, such as $CHCl_3$, DMF, MeOH, H_2O, DMSO, THF. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{27}H_{30}N_2NaO_5$) requires 485.2047, found 485.2045.

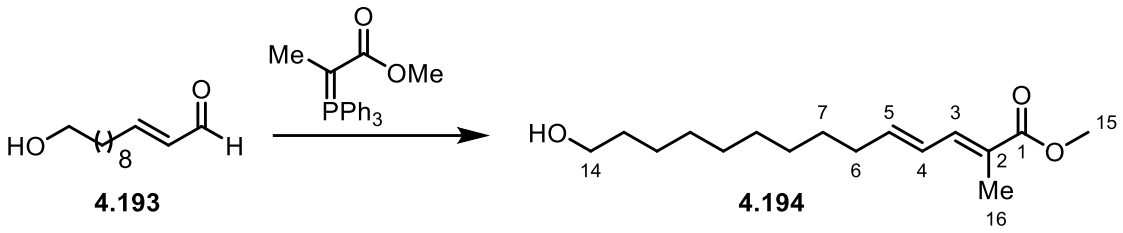
6.3.11 Synthesis of the Probe



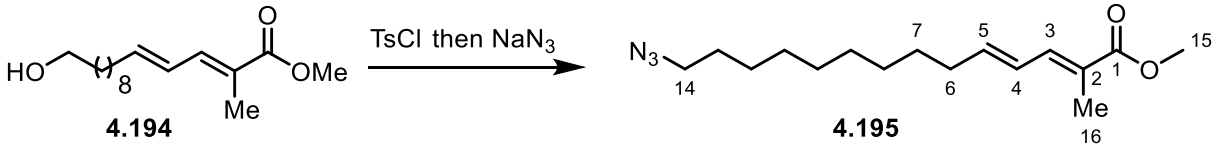
The procedure for the synthesis of **4.193** was adapted from the literature[20].

A flame dried pear-shaped flask with a rubber septum containing a stirring bar was charged with alcohol **4.191** (2.00 g, 11.7 mmol, 1.0 equiv.), aldehyde **4.192** (4.12 g, 58.7 mmol, 5.0 equiv.), Grubbs catalyst II (199 mg, 0.235 mmol, 2.0 mol%), CuI (67.1 mg, 0.352 mmol, 3.0mol%) and Et_2O (117 mL, 0.1 M) under an argon atmospherethe. The septum was then replaced by a reflux condenser. The mixture was heated at 40 °C for 3 h. The reaction mixture was cooled to room temperature and passed through a short column of silica gel with diethyl ether. After evaporation of the solvent, the crude product was purified by column chromatography (silica gel, Heptane/EtOAc = 2:1) to afford 2.23 g (96%) of aldehyde **4.193**. The spectra data is in agreement with the literature[20].

[20] Nishimura, T., Sawano, T., Hayashi, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 8057-8059.



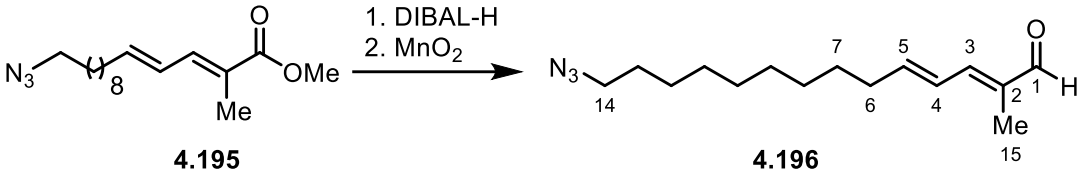
At room temperature, the aldehyde **4.193** (2.23 g, 11.2 mmol, 1.0 equiv.) was dissolved in toluene (40 mL) and Wittig reagent (5.09 g, 14.6 mmol, 1.3 equiv.) was added. Reaction was stirred at 80 °C for 12 h, then cooled to room temperature and the solvent was evaporated under vacuo. Crude product was purified by column chromatography (silica gel, Heptane/EtOAc = 2:1) to afford 2.25 g (75%) of ester **4.194**. **FTIR ($CHCl_3$, cm^{-1}):** 3385, 2927, 2854, 1709, 1639, 1436, 1238, 1107, 973, 750. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.16 (d, *J* = 11.3 Hz, 1H, **H3**), 6.33 (ddt, *J* = 15.0, 11.2, 1.4 Hz, 1H, **H5**), 6.11-6.04 (m, 1H, **H4**), 3.75 (s, 3H, **H15**), 3.64 (dd, *J* = 11.8, 6.5 Hz, 2H, **H14**), 2.18 (q, *J* = 7.1 Hz, 2H), 1.92 (d, *J* = 0.88 Hz, 3H), 1.60-1.53 (m, 2H), 1.44-1.30 (m, 12H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.3 (**C1**), 143.5, 139.1, 126.1, 124.8, 63.2 (**C15**), 51.9 (**C14**), 33.4, 32.9, 29.6, 29.52, 29.51, 29.3, 29.1, 25.9, 12.7 (**C16**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{16}H_{28}NaO_3$) requires 291.1931, found 291.1929.



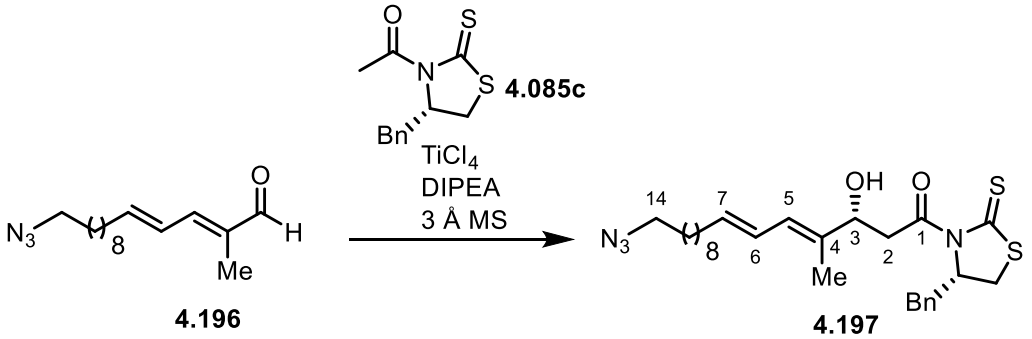
To a solution of **4.194** (2.25 g, 8.38 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was added TsCl (2.40 g, 12.6 mmol, 1.5 equiv.), followed by pyridine (1.4 mL, 16.8 mmol, 2.0 equiv.). The mixture was stirred at room temperature for 12 h before 1 N HCl (aq.) (20 mL) was added. The aqueous phase was extracted by CH_2Cl_2 (3 x 20 mL). The resulting organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting crude product was used directly in the next step.

The above crude product was dissolved in DMF (30 mL). To this solution was added NaN_3 (991 mg, 15.2 mmol, 1.8 equiv.). The mixture was then heated at 70 °C for 8 h before DMF was removed. To the mixture was added H_2O/CH_2Cl_2 (20/20 mL). The aqueous phase was extracted by CH_2Cl_2 (3 x 20 mL). The resulting organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, Heptane/EtOAc = 2:1) to afford 1.82 g (91%) of ester **4.195**. **FTIR ($CHCl_3$, cm^{-1}):** 3385, 2927, 2854, 1709, 1639, 1436, 1238, 1107, 973, 750. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.16 (d, *J* = 11.4 Hz, 1H, **H3**), 6.33 (ddt, *J* = 15.0, 11.3, 1.4 Hz, 1H, **H5**), 6.11-6.03 (m, 1H, **H4**), 3.75 (s, 3H, **H15**), 3.25 (t, *J* = 7.1 Hz, 2H, **H14**), 2.18 (q, *J* = 7.1 Hz, 2H), 1.93 (d, *J* = 0.88 Hz,

3H), 1.63-1.58 (m, 2H), 1.44-1.30 (m, 12H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 169.3 (**C1**), 143.5, 139.0, 126.1, 124.9, 51.9 (**C15**), 51.6 (**C14**), 33.4, 29.51, 29.47, 29.28, 29.25, 29.1, 29.0, 26.8, 12.7 (**C16**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{16}H_{27}N_3NaO_2$) requires 291.1995, found 316.1995.

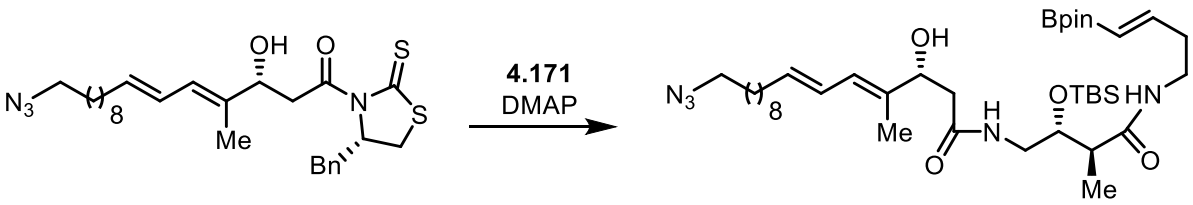


DIBAL (25% in Hexane, 6 mL, 7.5 mmol,) was added to a solution of methyl ester **4.195** (0.88 g, 3.0 mmol) in CH_2Cl_2 (15 mL) at 0°C. After 2 h, the reaction was quenched with MeOH (5 mL), poured into 1 M HCl solution and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuo to give crude allylic alcohol in nearly quantitative yield which was used without further purification in the next step. MnO_2 (1.83 g, 21 mmol) and $MgSO_4$ (3 g) were added to a mixture of the crude allylic alcohol in CH_2Cl_2 (15 mL) and stirred at room temperature for 12 h. The reaction mixture was filtrated over Celite® and the filter cake was washed with CH_2Cl_2. The resulting filtrate was concentrated in vacuo and purified by chromatography (silica gel, Heptane/EtOAc = 5:95 to 10:90) to afford the desired product **4.196** (375 mg, 47% over 2 steps). **FTIR ($CHCl_3$, cm^{-1}):** 2928, 2854, 2094, 1680, 1635, 1352, 1292, 1208, 966. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.41 (s, 1H, **H1**), 6.82 (d, *J* = 11.1 Hz, 1H, **H3**), 6.52 (dd, *J* = 15.0, 11.2 Hz, 1H, **H4**), 6.23 (dt, *J* = 15.0, 7.3 Hz, 1H, **H5**), 3.26 (t, *J* = 6.9 Hz, 2H, **H14**), 2.24 (q, *J* = 7.3 Hz, 2H), 1.83 (s, 3H, **H15**), 1.62-1.57 (m, 2H), 1.47-1.44 (m, 2H), 1.37-1.30 (m, 10H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 195.4 (**C1**), 149.6, 146.1, 126.0, 51.6 (**C14**), 29.51, 29.46, 29.32, 29.25, 28.95, 28.89, 26.8, 9.5 (**C15**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{15}H_{25}N_3NaO$) requires 286.1890, found 286.1886.



To a flame-dried schlenk tube was added thiazolidine **4.085c** (519 mg, 2.07 mmol, 1.1 equiv.) and CH_2Cl_2 (8 mL). At -78 °C, $TiCl_4$ (0.23 mL, 2.07 mmol, 1.1 equiv.) was added and the mixture stirred for 10 min. Afterwards DIPEA (0.36 mL, 2.07 mmol, 1.1 equiv.) was added slowly and the solution was stirred for 30

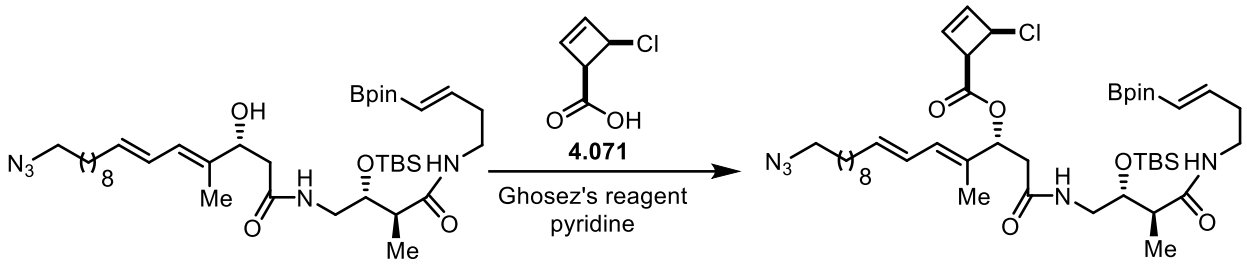
min at -78 °C. Then the aldehyde **4.196** (470 mg, 1.88 mmol, 1.0 equiv.) dissolved in CH_2Cl_2 (2 mL) was added dropwise to the mixture. The solution was stirred at -78 °C for 3 h. Then the reaction was quenched with sat. NH_4Cl (aq.) at -78 °C and allowed to reach room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed by brine, dried over Na_2SO_4, filtered and concentrated in vacuum. The crude oil was purified by column chromatography (silica gel, Heptane/EtOAc = 9:1 to 7:3) to afford 550 mg (57%) of product **4.197**. **FTIR ($CHCl_3$, cm^{-1}):** 2925, 2854, 2094, 1693, 1343, 1292, 1257, 1163, 1137, 1045, 966, 892. **^{1}H NMR (400 MHz, $CDCl_3$):** δ7.37-7.28 (m, 5H, **ArH**), 6.25 (dd, *J* = 14.9, 10.8 Hz, 1H, **H5**), 6.11 (d, *J* = 10.8 Hz, 1H), 5.72 (dt, *J* = 14.4, 7.2 Hz, 1H, **H7**), 5.41-5.35 (m, 1H), 4.63 (d, *J* = 9.4 Hz, 1H), 3.56 (dd, *J* = 17.4, 2.7 Hz, 1H), 3.46-3.38 (m, 2H), 3.27-3.22 (m, 3H), 3.05 (dd, *J* = 13.1, 10.5 Hz, 1H), 2.90 (d, *J* = 11.6 Hz, 1H), 2.53 (d, *J* = 2.1 Hz, 1H), 2.11 (q, *J* = 7.0 Hz, 2H), 1.78 (s, 3H), 1.63-1.54 (m, 2H), 1.38-1.29 (m, 12H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 201.5, 173.0, 136.6, 136.1, 135.2, 129.6, 129.1, 127.4, 125.94, 125.87, 72.9, 68.6, 51.6, 44.5, 37.0, 33.1, 32.3, 29.54, 29.50, 29.29, 29.27, 29.0, 26.8, 13.0 ppm.**HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{27}H_{38}N_4NaO_2S_2$) requires 537.2328, found 537.2327. **[α]D^{20}** = +130.1 (c = 1.00, $CHCl_3$).



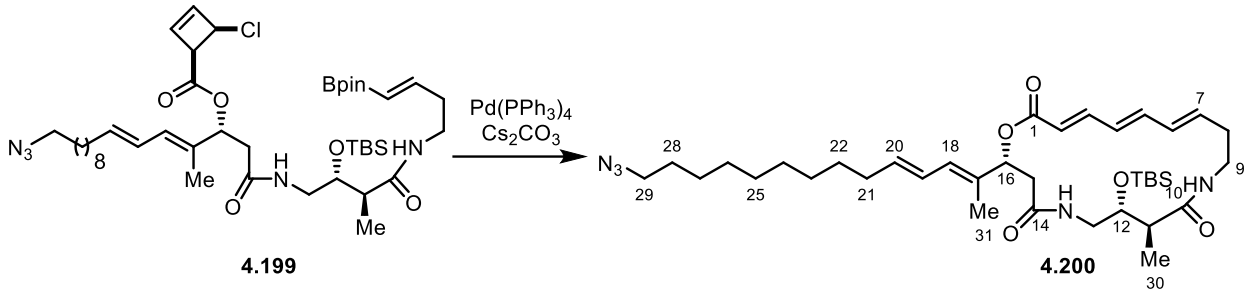
4.197 **4.198**

Aldol adduct **4.197** (550 mg, 1.28 mmol, 1.0 equiv.) and the crude amine **4.171** (546 mg, 1.28 mmol, 1.0 equiv.) were dissolved in CH_2Cl_2 (10 mL). DMAP (130 mg, 1.28 mmol, 1.0 equiv.) was then charged and the reaction mixture was vigorously stirred overnight at room temperature. The reaction was quenched with water and extracted with CH_2Cl_2 (3 x 10 mL). The resulting organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude oil was purified by column chromatography (silica gel, Heptane/EtOAc = 2:1, then Heptane/Isopropanol = 20:1 to 3:1) to afford 530 mg (68%) of bisamide **4.198**. **FTIR ($CHCl_3$, cm^{-1}):** 3338, 2928, 2855, 2095, 1642, 1541, 1464, 1359, 1322, 1253, 1144, 837, 778. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.54 (dt, *J* = 18.0, 6.4 Hz, 1H), 6.44 (brd, 1H), 6.21 (dd, *J* = 15.0, 10.8 Hz, 1H), 6.15-6.11 (m, 1H), 6.07 (d, *J* = 10.8 Hz, 1H), 5.69 (dt, *J* = 14.8, 7.0 Hz, 1H), 5.51 (d, *J* = 18.0 Hz, 1H), 4.44-4.41 (m, 1H), 3.90-3.86 (m, 1H), 3.74-3.67 (m, 1H), 3.58-3.55 (m, 1H), 3.46-3.36 (m, 1H), 3.31-3.28 (m, 1H), 3.25 (t, *J* = 6.9 Hz, 2H), 2.96-2.90 (m, 1H), 2.45-2.32 (m, 5H), 2.09 (q, *J* = 7.1 Hz, 2H), 1.73 (s, 3H), 1.62-1.55 (m, 2H), 1.23-1.38 (m, 24H), 1.13 (d, *J* = 7.1 Hz, 3H), 0.88 (m, 9H), 0.15 (s, 3H), 0.08

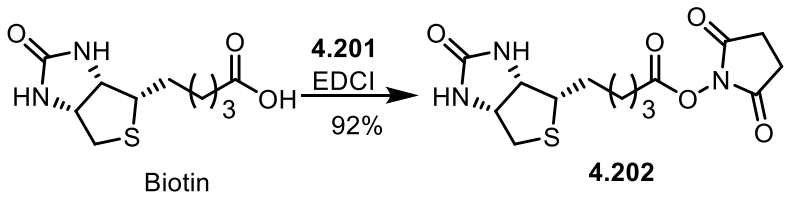
(s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 174.5, 172.2, 150.3, 136.1, 135.8, 125.9, 125.7, 83.4, 73.7, 72.2, 51.6, 44.8, 42.9, 41.7, 37.9, 35.7, 33.1, 29.52, 29.50, 29.28, 29.25, 29.0, 26.8, 26.0, 24.9, 18.1, 15.3, 12.8, -4.4, -4.8 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{38}H_{70}BN_5NaO_6Si$) requires 754.5081, found 754.5096. **[α]D^{20}** = +27.6 (c = 1.00, $CHCl_3$).



To the solution of acid **4.071** (90.4 mg, 0.682 mmol, 2.0 equiv.) in $CHCl_3$ (3.0 mL) was added freshly distilled Ghosez's reagent (95 uL, 0.716 mmol, 2.1 equiv.). The solution was stirred vigorously at room temperature for 40 min. Then the amide alcohol **4.198** (250 mg, 0.341 mmol, 1.0 equiv.) dissolved in $CHCl_3$ (2.0 mL) was added, followed by pyridine (69 uL, 0.853 mmol, 2.5 equiv.). The resulting solution was vigorously stirred for another 4 h at room temperature. The reaction was quenched with water and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed by brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 7:3 to 1:1) afforded 200 mg (69%) of the *cis*-isomer **4.199** as mixture of diastereoisomers. **FTIR ($CHCl_3$, cm^{-1}):** 3327, 2929, 2855, 2095, 1736, 1646, 1539, 1461, 1360, 1323, 1257, 1169, 1144, 839, 776. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.55 (dt, *J* = 18.0, 6.4 Hz, 1H), 6.10-6.27 (m, 6H), 5.72 (dt, *J* = 13.9, 6.9 Hz, 1H), 5.63 (dd, *J* = 7.8, 5.4 Hz, 1H), 5.51 (d, *J* = 18.0 Hz, 1H), 5.08 (d, *J* = 4.3 Hz, 1H), 4.08 (d, *J* = 4.3 Hz, 1H), 3.83-3.72 (m, 2H), 3.46-3.38 (m, 1H), 3.31-3.28 (m, 1H), 3.26 (t, *J* = 7.0 Hz, 2H), 2.82-2.76 (m, 1H), 2.66 (dd, *J* = 14.4, 8.0 Hz, 1H), 2.50 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.41-2.33 (m, 3H), 2.07 (q, *J* = 7.1 Hz, 2H), 1.77 (s, 3H), 1.62-1.54 (m, 2H), 1.36-1.25 (m, 24H), 1.10 (d, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 174.7, 169.4, 168.8, 150.3, 140.6, 137.1, 136.6, 130.9, 128.9, 125.5, 83.4, 77.0, 72.1, 56.4, 54.0, 51.6, 44.6, 43.0, 40.9, 38.0, 35.8, 33.1, 29.53, 29.50, 29.40, 29.33, 29.26, 29.0, 26.8, 26.0, 24.9, 18.1, 15.5, 12.8, -4.3, -4.9 ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{43}H_{73}BClN_5NaO_7Si$) requires 868.4953, found 868.4961.

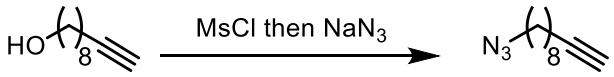


To a solution of the substrate **4.199** (30 mg, 0.039 mmol, 1.0 equiv.) in THF/H_2O (3/1) (20 mL, 0.002 M, degassed by bubbling with Argon for 10 min) was added Cs_2CO_3 (63 mg, 0.20 mmol, 5.0 equiv.). The mixture was stirred at room temperature for 5-10 min, then $Pd(PPh_3)_4$ (4.5 mg, 0.0039 mmol, 10 mol%) was added. The vessel was then covered by aluminum foil and stirred at room temperature for 18 h. The reaction was quenched by sat. NH_4Cl, extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 2:1 to 1:1) afforded 14 mg (59%) of the desired product **4.200**. **FTIR ($CHCl_3$, cm^{-1}):** 3345, 2927, 2854, 2094, 1705, 1617, 1537, 1462, 1433, 1254, 1230, 1103, 1012, 836. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.24 (dd, *J* = 15.4, 11.2 Hz, 1H, **H3**), 6.45 (dd, *J* = 14. 8, 10.8 Hz, 1H, **H5**), 6.22 (dd, *J* = 14. 9, 10.9 Hz, 1H, **H19**), 6.16 (dd, *J* = 14. 7, 11.2 Hz, 1H, **H4**), 6.12-6.07 (m, 2H, **H6, H18**), 6.00 (d, *J* = 7.7 Hz, 1H, **NH**), 5.93-5.88 (m, 1H, **H7**), 5.83 (brd, 1H, **NH**), 5.76-5.70 (m, 2H, **H20, H2**), 5.63 (dd, *J* = 11.1, 2.9 Hz, 1H, **H16**), 4.10-4.03 (m, 1H, **H9**), 4.00 (brd, 1H, **H12**), 3.49-3.44 (m, 1H, **H13**), 3.25 (t, *J* = 7.0 Hz, 2H, **H29**), 2.96 (d, *J* = 13.9 Hz, 1H, **H9**), 2.54-2.39 (m, 5H, **H8**, **H11, H13, H15, H15**), 2.22-2.15 (m, 1H, **H8**), 2.10 (q, *J* = 7.2 Hz, 2H, **H21**), 1.79 (s, 3H, **H31**), 1.62-1.57 (m, 2H), 1.38-1.29 (m, 12H), 1.13 (d, *J* = 7.2 Hz, 3H, **H30**), 0.87 (s, 9H, **TBS-H**), 0.08 (s, 3H, **TBS-H**), 0.05 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 174.1 (**C10**), 169.8 (**C14**), 166.4 (**C1**), 146.6 (**C3**), 143.2 (**C5**), 138.8 (**C7**), 136.6 (**C20**), 132.1 (**C17**), 131.5 (**C6**), 127.6 (**C4**), 126.6 (**C18**), 125.7 (**C19**), 119.5 (**C2**), 77.2 (**C16**), 72.3 (**C12**), 51.6 (**C29**), 45.3 (**C11**), 43.0 (**C13**), 42.3 (**C15**), 37.5 (**C9**), 34.5 (**C8**), 33.1 (**C21**), 29.8, 29.55, 29.52, 29.47, 29.29, 29.28, 29.0, 26.8, 25.9 (**TBS-C**), 25.0, 18.0 (**TBS-C**), 13.4 (**C31**), 12.4 (**C30**, deduced from HSQC), -4.5 (**TBS-C**), -4.8 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{37}H_{61}N_5NaO_5Si$) requires 706.4334, found 706.4337. **[α]D^{20}** = -53.2 (c = 0.71, $CHCl_3$).



The procedure for the synthesis of compound **4.202** was adapted from the literature[21].

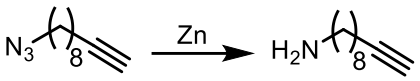
To a solution of D-biotin (7.00 g, 28.7 mmol, 1.0 equiv.) in DMF (75 mL) was added N-hydroxysuccinimide **4.201** (3.96 g, 34.4 mmol, 1.2 equiv.) and EDCI (6.59 g, 34.4 mmol, 1.2 equiv.). The reaction was allowed to proceed overnight. The resulting mixture was dried in vacuo to remove DMF. The gel-like residue was recrystallized from EtOH/Acetic acid/H_2O (95:1:4) to afford biotin-NHS **4.202** as a white solid. The spectra data is in agreement with the literature[21].



To a solution of **4.208** (2.00 g, 13.0 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was added Et_3N (3.6 mL, 25.9 mmol, 2.0 equiv.). The solution was then cooled to 0 °C in an ice bath and then MsCl (1.2 mL, 15.6 mmol, 1.2 equiv.) dissolved in CH_2Cl_2 (5 mL) was added dropwise. The reaction was stirred at 0 °C for 0.5 h and then at room temperature for 4 hours. The crude reaction was filtered through Celite, washed with CH_2Cl_2 (30 mL). The filtrate was washed with sat. $NaHCO_3$ (20 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude product was used directly in the next step.

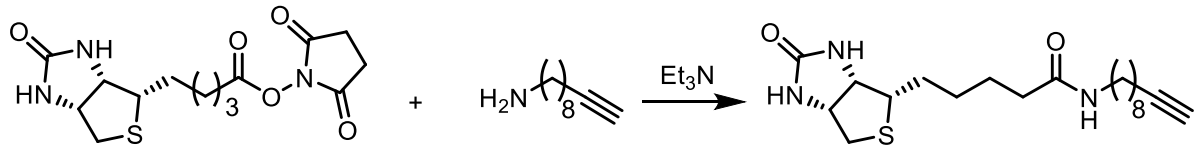
The above crude product was dissolved in DMF (30 mL). To this solution was added NaN_3 (1.69 mg, 25.9 mmol, 2.0 equiv.). The mixture was then heated at 70 °C for 8 h before DMF was removed. To the mixture was added H_2O/CH_2Cl_2 (20/20 mL). The aqueous phase was extracted by CH_2Cl_2 (3 x 20 mL). The resulting organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, Heptane/EtOAc = 2:1) to afford 1.40 g (60%) of ester **4.209**. The spectra data is in agreement with the literature[22].

[21] Shi, H., Liu, K., Xua, A., Yao, S. Q. *Chem. Commun.* **2009**, *0*, 5030-5032.
[22] Kojima, N. *et al. Bioorg. Med. Chem.* **2015**, *23*, 1276-1283.



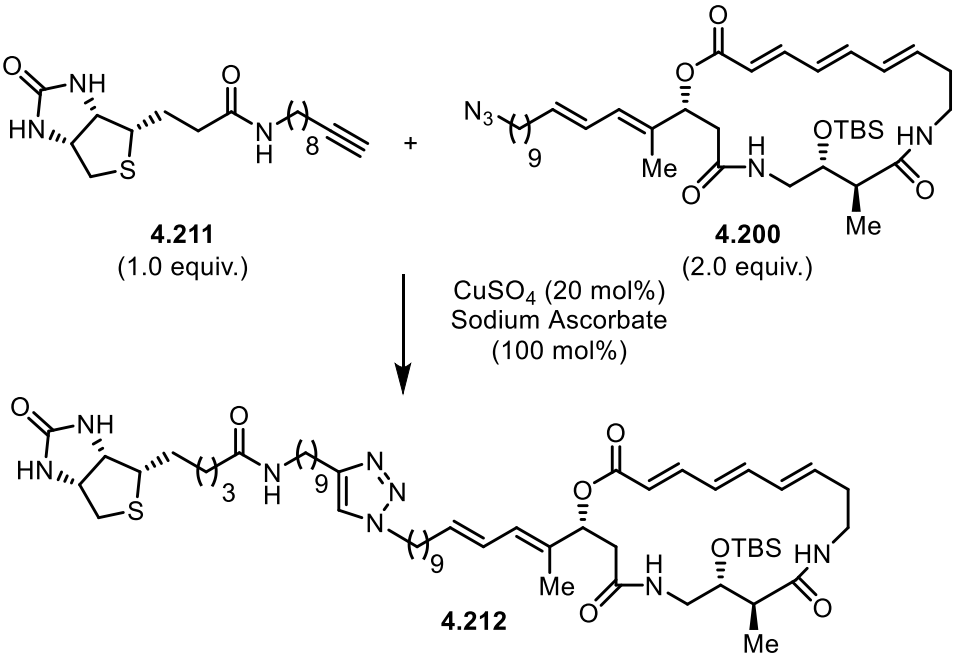
4.209 **4.210** crude

To a solution of amide **4.209** (1.35 g, 7.53 mmol, 1.0 equiv.) in THF/MeOH/H_2O (15 mL/15 mL/ 15 mL) was added activated zinc (1.97 g, 30.1 mmol, 4.0 equiv.) and NH_4Cl (3.22 g, 60.2 mmol, 8.0 equiv.). The mixture was stirred vigorously at room temperature for 3 h. Then the organic solvents were removed under vacuum. The remaining aqueous phase was basified by sat. Na_2CO_3 (aq.) (10 mL) to pH around 9, and extracted by CH_2Cl_2 (5 x 15 mL). The combined organic layers were washed by brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product **4.210** was used in the next step without further purification.

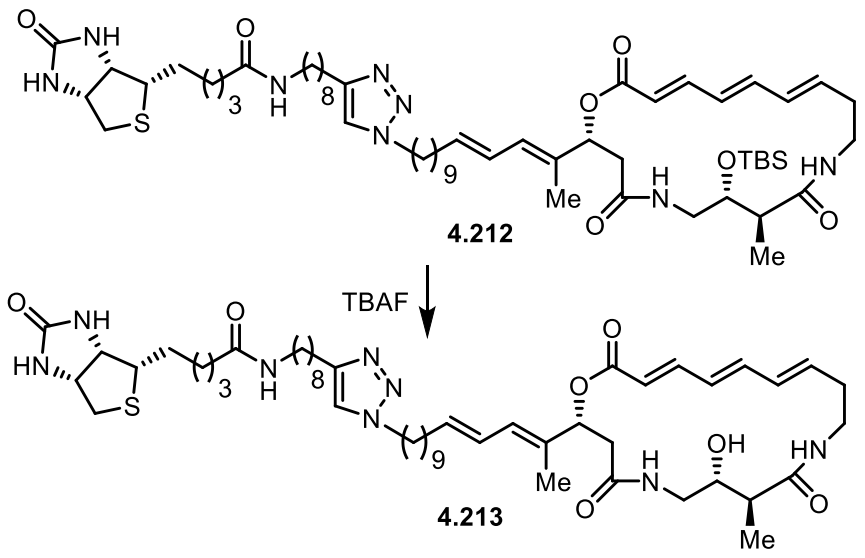


4.202 **4.210** **4.211**

To a solution of **4.202** (150 mg, 0.439 mmol, 1.0 equiv.) in DMF (4.0 mL) were added **4.210** (101 mg, 0.659 mmol, 1.5 equiv.) and Et_3N (0.22 mL, 1.32 mmol, 3.0 equiv.). The mixture was stirred vigorously at room temperature for 12 h. The resulting solid formed during the reaction was filtered and washed by MeOH/CH_2Cl_2 (10:1). After concentration in vacuo, the white solid **4.211** was used in the next step without further purification.

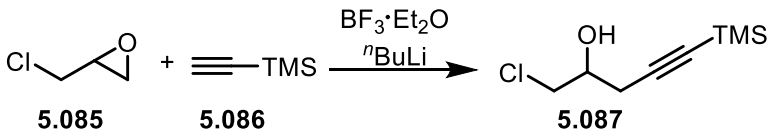


The mixture of **4.211** (6.6 mg, 0.018 mmol, 1.0 equiv.), **4.200** (24 mg, 0.035 mmol, 2.0 equiv.), copper sulfate pentahydrate (1.8 mg, 0.0070 mmol, 0.4 equiv.), sodium ascorbate (6.9 mg, 0.035 mmol, 2.0 equiv.) in ^{t}BuOH/H_2O (1:2, 1.5 mL) was stirred vigorously at room temperature. Once starting material **4.211** disappeared on HRMS (about 4 h), the mixture was extracted with $CHCl_3$ (5 X 5 mL). The combined organic layers were washed by brine (2 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, CH_2Cl_2/MeOH = 4:1) afforded 9.9 mg (53%) of the desired product **4.212**. The product **4.212** was poorly soluble in $CHCl_3$, but slightly soluble in MeOH. **FTIR ($CHCl_3$, cm^{-1}):** 2926, 2855, 1699, 1647, 1230, 781, 732. **^{1}H NMR (600 MHz, CD_3OD):** δ 7.32 (dd, *J* = 15.3, 10.9 Hz, 1H), 6.44 (dd, *J* = 14.9, 10.7 Hz, 1H), 6.10 (dd, *J* = 15.0, 11.0 Hz, 1H), 5.45 (dd, *J* = 11.5, 3.2 Hz, 1H), 1.00 (d, *J* = 7.1Hz, 3H), 0.78 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H). **^{13}C NMR (151MHz, CD_3OD)**: δ 176.82, 176.79, 176.0, 173.2, 169.2, 167.0, 150.1, 146.2, 141.3, 138.2, 134.1, 133.5, 129.2, 128.7, 127.8, 124.0, 120.3, 79.5, 74.3, 64.2, 62.5, 57.9, 52.1, 41.9, 41.2 ppm. (Due to the complexity of ^{1}H NMR and ^{13}C spectrum, only characteristic peaks are shown here). **HRMS (ESI) (m/z):** exact mass calculated for $[M+Na]^+$ ($C_{57}H_{94}O_7N_8S_1Si_1Na$) requires 1085.6628, found 1085.6628.



4.212 (4.2 mg, 0.0039 mmol, 1.0 equiv.) was dissolved in THF (1 mL) and cooled down to 0 °C. TBAF (1 M in THF, 11.8 uL, 3.0 equiv.) was then charged and the reaction was monitored by TLC (CH_2Cl_2/MeOH = 4:1). After 30 min, the reaction was then quenched with a drop of saturated NH_4Cl, concentrated in vacuo and directly purified by chromatography (silica gel, $CHCl_3$/MeOH = 8:1). **4.213** was obtained in 0.93 mg and contaminated with $^{n}Bu_4N^+X^-$. **FTIR ($CHCl_3$, cm^{-1}):** 2926, 2855, 1699, 1647, 1230, 781, 732. **^{1}H NMR (600 MHz, CD_3OD):** δ 7.32 (dd, *J* = 15.3, 10.9 Hz, 1H), 6.44 (dd, *J* = 14.9, 10.7 Hz, 1H), 6.10 (dd, *J* = 15.0, 11.0 Hz, 1H), 5.45 (dd, *J* = 11.5, 3.2 Hz, 1H), 1.00 (d, *J* = 7.1Hz, 3H), 0.78 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H). **^{13}C NMR (151 MHz, CD_3OD)**: δ 176.82, 176.79, 176.0, 173.2, 169.2, 167.0, 150.1, 146.2, 141.3, 138.2, 134.1, 133.5, 129.2, 128.7, 127.8, 124.0, 120.3, 79.5, 74.3, 64.2, 62.5, 57.9, 52.1, 41.9, 41.2 ppm. (Due to the complexity of $_1$H NMR and $_{13}$C spectrum, only characteristic peaks are shown here). **HRMS (ESI) (m/z):** exact mass calculated for $[M+Na]^+$ ($C_{51}H_{80}O_7N_8S_1Na$) requires 971.5763, found 971.5771.

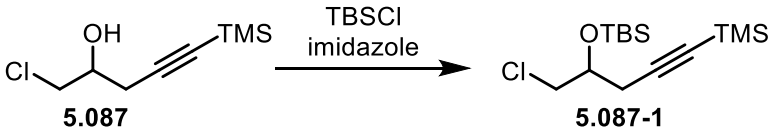
6.4 Synthetic Efforts towards Total Synthesis of Cyclamenol A



5.085 **5.086** **5.087**

The procedure for the synthesis of compound of **5.087** was adapted from the literature[23].

To a solution of **5.086** (21.2 mL, 150 mmol, 1.5 equiv.) in THF (100 mL) was added ^{n}BuLi (2.5 M in hexane, 60 mL, 1.5 equiv.) dropwise at -78 °C. After 30 minutes, boron trifluoride etherate (12.3 mL, 100 mmol, 1.0 equiv.) was added and the mixture was stirred for another 30 min. A solution of **5.085** (7.8 mL, 100 mmol, 1.0 equiv.) in THF (20 mL) was then dropwise added. The mixture was allowed to warm to -20 °C over 3 h before carefully quenched by 1 N HCl (aq.) (150 mL). The aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic phases were washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 5:1) afforded 17.2 g (90%) of the desired product **5.087**. The spectra data is in agreement with the literature[23].

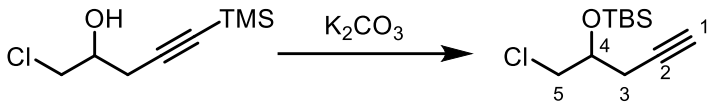


5.087 **5.087-1**

The procedure for the synthesis of compound **5.087-1** was adapted from the literature[24].

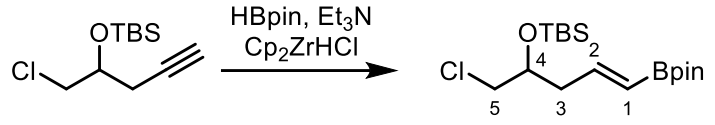
To a solution of 5.087 (3.00 g, 15.7 mmol, 1.0 equiv.) in DMF (20 mL) was added TBSCl (3.56 g, 23.6 mmol, 1.5 equiv.) and imidazole (2.14 g, 31.5 mmol, 2.0 equiv.). The mixture was stirred vigorously at room temperature for 2 h before quenched by sat. NH_4Cl (aq.) (30 mL). DMF was removed under reduced pressure. The remaining aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc =20:1) afforded 4.30 g (90%) of the desired product **5.087-1**. The spectra data is in agreement with the literature[24].

[23] Kobayashi, Y., Yoshida, S., Asano, M., Takeuchi, A., Acharya, H. P. *J. Org. Chem.* **2007**, *72*, 1707-1716.
[24] Bräse, S., Schömenauer, S., McGaffin, G., Stolle, A., Meijere, A. *Chem. Eur. J.* **1996**, *2*, 545-555.



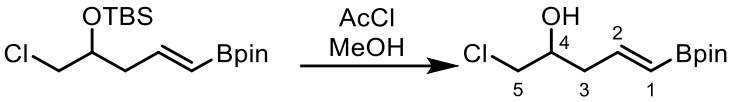
5.087-1 **5.088**

To a stirred solution of **5.087-1** (4.68 g, 5.51 mmol, 1.0 equiv.) in MeOH (5.0 mL) was added K_2CO_3 (992 mg, 11.0 mmol, 2.0 equiv.). The mixture was stirred vigorously at room temperature for 2 h before MeOH was removed. The remaining mixture was dissolved in Sat. NH_4Cl (5 mL). The aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford 960 mg (75%) of the desired product **5.088**. Product **5.088** was used in the next step without further purification. **^{1}H NMR (400 MHz, $CDCl_3$):** 4.02-3.96 (m, 1H, **H4**), 3.62 (dd, *J* = 11.0, 5.2 Hz, 1H, **H5**), 3.54 (dd, *J* = 11.1, 5.4, 1H, **H5**), 2.55-2.41 (m, 2H, **H3**), 2.01 (t, *J* = 2.7 Hz, 1H, **H1**), 0.90 (s, 9H, **TBS-H**), 0.12 (s, 6H, **TBS-H**).



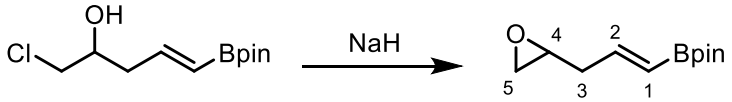
5.088 **5.089**

In a dry flask, alkyne **5.088** (850 mg, 3.65 mmol, 1.0 equiv.) was charged. The flask was flushed over 5 min with argon. Pinacol borane (0.64 mL, 4.38 mmol, 1.2 equiv.) was added, followed by Cp_2ZrHCl (188 mg, 0.73 mmol, 20 mol%) and Et_3N (0.10 mL, 0.73 mmol, 20 mol%). The mixture was stirred at 60°C for 16 h. Then the reaction mixture was cooled down to room temperature. The mixture were concentrated under reduced pressure. Purification by column chromatography (silica gel, Hentane/EtOAc = 10:1) afforded 1.04 g (79%) of the desired product **5.089** as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 2978, 2955, 2930, 2892, 2857, 1641, 1469, 1362, 1323, 1254, 1144, 1102, 1003, 970, 835, 776. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.56 (dt, *J* = 17.9, 7.0 Hz, 1H, **H2**), 6.52 (dt, *J* = 17.9, 1.4 Hz, 1H, **H1**), 3.94-3.89 (m, 1H, **H4**), 3.47-3.39 (m, 2H, **H5**), 2.53-2.46 (m, 1H, **H3**), 2.42-2.34 (m, 1H, **H3**), 1.26 (s, 12H, **Bpin-H**), 0.89 (s, 9H, **TBS-H**), 0.09 (S, 3H, **TBS-H**), 0.07 (s, 3H, **TBS-H**) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.3 (**C2**), 122.7 (**C1**), 83.3 (**Bpin-C**), 72.1 (**C4**), 48.6 (**C5**), 41.9 (**C3**), 25.9 (**TBS-C**), 24.9 (**Bpin-C**), 18.3 (**TBS-C**), -4.4 (**TBS-C**), -4.5 (**TBS-C**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{17}H_{34}O_3Cl_1B_1Si_1Na$) requires 383.1951, found 383.1943.



5.089 **5.091** (volatile)

To a stirred solution of **5.089** (2.15 g, 5.96 mmol, 1.0 equiv.) in MeOH (10 mL) at room temperature was added acetyl chloride (0.21 mL, 2.98 mmol, 0.5 equiv.). The mixture was stirred vigorously for 30 min before the solvent was removed under reduced pressure. Purification by column chromatography (silica gel, Hentane/EtOAc = 5:1) afforded 1.00 g (68%) of the desired product **5.091** as a colorless oil[25]. Caution: Product **5.091** is volatile, and can be removed at 40 °C, 70 mbar. **FTIR ($CHCl_3$, cm^{-1}):** 3450, 2979, 1641, 1364, 1324, 1144, 1003, 970, 849. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.58 (dt, *J* = 18.0, 6.9 Hz, 1H, **H2**), 5.58 (dt, *J* = 17.9, 1.4 Hz, 1H, **H1**), 3.97-3.90 (m, 1H, **H4**), 3.63 (dd, *J* = 11.1, 3.7 Hz, 1H, **H5**), 3.50 (dd, *J* = 11.1, 6.7 Hz, 1H, **H5**), 2.45 (td, *J* = 6.7, 1.4 Hz, 1H, **H3**), 2.19 (d, *J* = 4.9 Hz, 1H, **H3**), 1.26 (s, 12H, **Bpin-H**) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 148.2 (**C2**), 83.4 (**Bpin-OC**), 70.5 (**C4**), 49.7 (**C5**), 40.9 (**C3**), 24.9 (**Bpin-C**) ppm (The signal of C1 was too weak to be detected on the ^{13}C NMR). **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{11}H_{20}O_3Cl_1B_1Na$) requires 269.1086, found 269.1083.

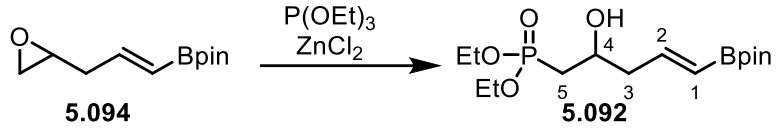


5.091 **5.094**

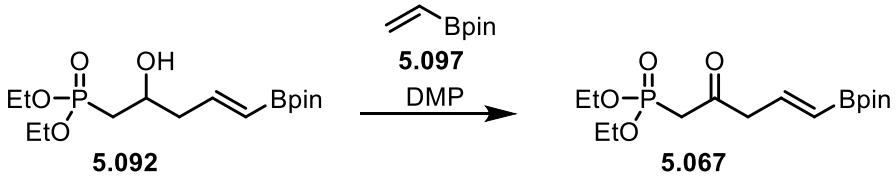
To a stirred solution of 5.091 (1.00 g, 4.06 mmol, 1.0 equiv.) in THF (10.0 mL) was added NaH (60% in paraffin liquid, 195 mg, 4.87 mmol, 1.2 equiv.). The mixture was then heated at 60 °C for 4 h before cooling down to room temperature. At 0 °C, sat. NH_4Cl (10 mL) was slowly added to the reaction. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Hentane/EtOAc = 5:1) afforded 780 mg (91%) of the desired product **5.094** as a colorless liquid[26]. Caution: Product **5.094** is volatile, and the solvent should be removed at 40 °C, 160 mbar. **FTIR ($CHCl_3$, cm^{-1}):** 2979, 2932, 1641, 1361, 1324, 1145, 972, 849, 773. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.62 (dt, *J* = 18.0, 6.4 Hz, 1H, **H2**), 5.59 (dt, *J* = 18.0, 1.4 Hz, 1H, **H1**), 3.04- 2.99 (m, 1H, **H4**), 2.77-2.75 (m, 1H, **H5**), 2.51-2.44 (m, 2H, **H5** & **H3**), 2.36-2.29 (m, 1H, **H3**), 1.26 (s, 12H, **Bpin-H**) ppm.**^{13}C NMR (100 MHz, $CDCl_3$)**: δ 148.0 (**C2**), 83.4 (**Bpin-C**), 50.9 (**C4**), 46.8 (**C5**), 38.7 (**C3**), 24.9 (**Bpin-C**) ppm (The signal of C1 was too weak to be detected

[25] Khan, A. T., Mondal, E. *Synlett*, **2003**, 694-698.
[26] F. Mayer, S. F., Steinreiber, A., Orru, R. V. A., Faber, K. *J. Org. Chem.* **2002**, *67*, 9115-9121.

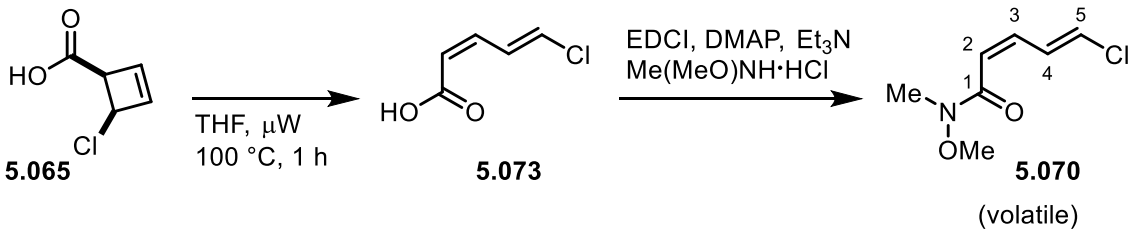
on the ^{13}C NMR). **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{11}H_{19}O_3B_1Na$) requires 233.1319, found 233.1321.



Under neat conditions, the mixture of **5.094** (380 mg, 1.81 mmol, 1.0 equiv.), $P(OEt)_3$ (0.33 mL, 1.90 mmol, 1.05 equiv.) and anhydrous $ZnCl_2$ (264 mg, 1.90 mmol, 1.05 equiv.) was stirred vigorously at room temperature till the mixture became viscous. Then CH_2Cl_2 (2.0 mL) was added so that the mixture was stirred again for another 1 h before the solvent was removed. Purification by column chromatography (silica gel, EtOAc + 5% MeOH) afforded 420 mg (67%) of the desired product **5.092** as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 3393, 2972, 2928, 1740, 1640, 1365, 1228, 1217, 1145, 1028, 968. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.60 (dt, *J* = 18.0, 6.8 Hz, 1H, **H2**), 5.54 (dt, *J* = 18.0, 1.4 Hz, 1H, **H1**), 4.17-4.07 (m, 5H, CH_3**CH_2**O & **H4**), 3.44 (brd, 1H, **OH**), 2.51-2.34 (m, 2H), 2.04-1.85 (m, 2H), 1.34 (dt, *J* = 7.1, 2.1 Hz, 6H, **CH_3**CH_2O), 1.26 (s, 12H, **Bpin-H**).**^{13}C NMR (100 MHz, $CDCl_3$)**: 149.0 (**C2**), 121.7 (**C1**), 83.4 (**Bpin-C**), 65.88, 65.83, 62.1, 62.0, 44.7, 44.6, 33.8, 32.4, 24.9 (**Bpin-C**), 16.62, 16.58, 16.56, 16.51. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{15}H_{30}O_6B_1P_1Na$) requires 371.1765, found 371.1765.

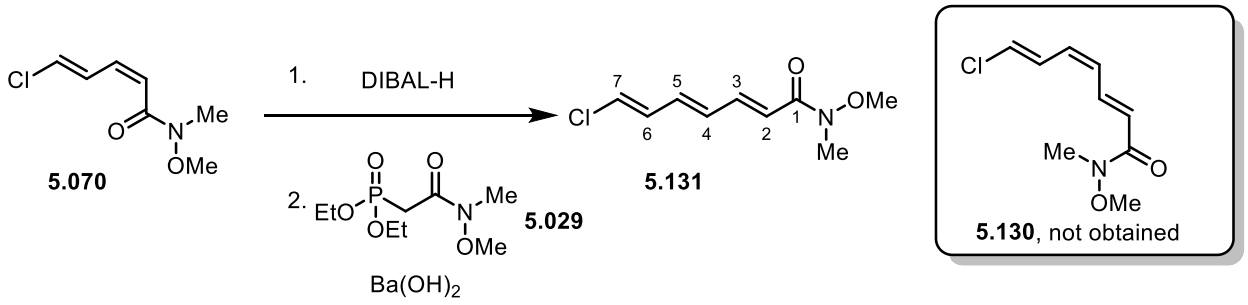


To a solution of **5.092** (310 mg, 0.89 mmol, 1.0 equiv.) in CH_2Cl_2 (4.0 mL) was added 5.097 (0.38, 2.23 mmol, 2.5 equiv.). At 0 °C, Dess-Martin reagent (DMP) (453 mg, 1.07 mmol, 1.2 equiv.) was added. The mixture was stirred vigorously at 0 °C for 40 min before quenched by sat. $Na_2S_2O_3$ (aq.) (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford crude product **5.067**. Caution: Product **5.067** is not stable on silica gel column, and should be used in the next step directly. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.65 (dt, *J* = 17.9, 6.7 Hz, 1H), 5.56 (dt, *J* = 17.9, 1.5 Hz, 1H), 4.19-4.08 (m, 5H), 3.47 (dd, *J* = 6.7, 1.5 Hz, 1H), 3.09 (d, *J* = 22.8 Hz, 2H), 1.33 (t, *J* = 7.0 Hz, 6H), 1.26 (s, 12H) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{15}H_{28}O_6B_1P_1Na$) requires 369.1609, found 369.1610.



The acid **5.065** (200 mg, 1.51 mmol) was dissolved in THF (3.0 mL). Then the solution was heated in the microwave at 100 °C for 1 h before the solvent was removed. The crude solid **5.073** was used in the next step without further purification.

To a flame-dried flask was added **5.073** (200 mg, 1.51 mmol, 1.3 equiv.), EDCI (318 mg, 1.66 mmol, 1.1 equiv.) and Et_3N (0.42 mL, 3.02 mmol, 2.0 equiv.) and CH_2Cl_2 (3.0 mL). The mixture stirred at room temperature for 10 min. Then Weinreb amine salt (221 mg, 2.26 mmol, 1.5 equiv.) and DMAP (37 mg, 0.30 mmol, 20 mol%) in CH_2Cl_2 (2 mL) was added. The mixture was stirred vigorously at room temperature for 12 h before quenched by sat. NH_4Cl (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 1:1) afforded 79 mg (30%) of the desired product **5.070** as a colorless oil. Caution: Product **5.070** was volatile. **FTIR ($CHCl_3$, cm^{-1}):** 2029, 1739, 1368, 1217, 1202, 781. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.86 (t, *J* = 12.3 Hz, 1H, **H3**), 6.51 (d, *J* =13.4 Hz, 1H), 6.44 (t, *J* = 11.6 Hz, 1H), 6.23 (d, *J* = 11.0 Hz, 1H), 3.69 (s, 3H, **OMe**), 3.24 (s, 3H, **NMe**) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)**: 137.9, 130.6, 129.3, 116.7, 61.9 (**OMe**), 31.1 (**NMe**) (the signal of C1 was too weak to be detected on ^{13}C NMR) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_7H_{10}O_2Cl_1N_1Na$) requires 198.0292, found 198.0291.

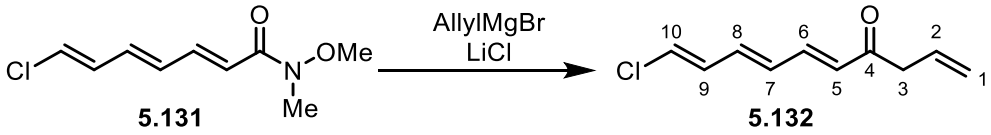


All the operations were carried out with exclusion of light. The vessels were covered by aluminium foil.

To a stirred solution of **5.070** (140 mg, 0.80 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL) at -78 °C was dropwise added DIBAL-H (1.0 M in hexane, 1.2 mL, 1.5 equiv.). The solution was allowed to warm to -50 °C over 2 h

before quenched by sat. Rochelle salt solution (4 mL). The suspension was stirred vigorously till organic phase was clearly separated from aqueous phase. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford crude aldehyde **5.127** (0.34 mmol, 42%) which was used in the next step without further purification. Caution: Product **5.127** was volatile!

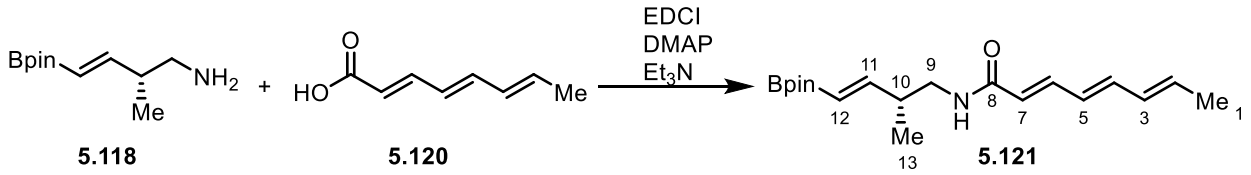
To a flask charged with phosphonate **5.029** (97.6 mg, 0.41 mmol, 1.2 equiv.) and $Ba(OH)_2$ (87 mg, 0.51 mmol, 1.5 equiv.) was added THF (1.5 mL) at room temperature. The suspension was vigorously stirred for 30 min before a solution of crude aldehyde **5.127** (0.34 mmol, 1.0 equiv.) in THF/H_2O (1.5 mL/ 38 uL, 40:1) was added. The resulting mixture was stirred for another 12 h before quenched by sat. NH_4Cl (4 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 3:1) afforded 23 mg (33%) of product **5.131** as a white crystal. Desired product **5.130** was not obtained. **FTIR ($CHCl_3$, cm^{-1}):** 1964, 1649, 1607, 1564, 1380, 1002, 838, 625. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.32 (dd, *J* = 15.1, 11.1 Hz, 1H, **H3**), 6.56-6.45 (m, 3H, **H2, H5, H7**), 6.40-6.35 (m, 2H, **H4, H6**), 3.71 (s, 3H, **OMe**), 3.10 (s, 3H, **NMe**) ppm. **^{13}C NMR (151MHz, $CDCl_3$)**: 167.0 (**C1**), 142.5 (**C3**), 135.2 (**C5**), 133.3 (**C7**), 131.4 (**C4**), 124.6 (**C6**), 120.2 (**C2**), 62.0 (**OMe**), 32.6 (**NMe**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_9H_{12}O_2Cl_1N_1Na$) requires 224.0449, found 224.0450.



5.131 **5.132**

LiCl (9.5 mg, 0.22 mmol, 3.0 equiv.) was flamed dried under vacuo in a Schlenk tube before cooled down to room temperature. Then **5.131** (15 mg, 0.074 mmol, 1.0 equiv.) in THF (1.0 mL) was added. The mixture was cooled to -78 °C before allylMgBr (1.0 M in Et_2O, 0.22 mL, 3.0 equiv.) was added dropwise. The reaction was allowed to warm to -40 °C over 2.5 h before quenched by sat. NH_4Cl (4 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 3:1) afforded 14 mg (quantitative yield) of product **5.132** as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 2924, 1675, 1624, 1558, 1292, 1000, 748, 730. **^{1}H NMR (700 MHz, $CDCl_3$):** δ 7.18 (dd, *J* = 15.4, 11.1 Hz, 1H, **H6**), 6.58-6.51 (m, 2H), 6.44-6.42 (m, 1H), 6.34-6.30 (m, 1H), 6.24 (d, *J* = 15.4 Hz, 1H, **H5**), 5.98-5.92 (m, 1H, **H2**), 5.20 (dq, *J* = 10.2, 1.3 Hz, 1H, **H1**), 5.17 (dq, *J* = 17.2, 1.5 Hz, 1H, **H1**), 3.33 (dt, *J* = 6.9, 1.4 Hz, 2H, **H3**) ppm. **^{13}C NMR (176 MHz, $CDCl_3$)**: 197.8 (**C4**), 142.1 (**C6**), 137.0, 133.2, 131.1 (**C2**), 131.0, 129.6

(**C5**), 125.8, 119.0 (**C1**), 46.1 (**C3**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{10}H_{11}O_1Cl_1Na$) requires 205.0391, found 205.0394.



5.118 **5.120** **5.121**

To a flame-dried flask was added **5.120** (26 mg, 0.18 mmol, 1.3 equiv.), EDCI (33 mg, 0.17 mmol, 1.2 equiv.) and Et_3N (40 uL, 0.28 mmol, 2.0 equiv.) and DMF (0.5 mL). The mixture stirred at room temperature for 10 min. Then amine **5.118** (30 mg, 0.14 mmol, 1.0 equiv.) and DMAP (6.9 mg, 0.057 mmol, 40 mol%) in DMF (0.5 mL) was added. The mixture was stirred vigorously at room temperature for 12 h before quenched by sat. NH_4Cl (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were washed by brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, Heptane/EtOAc = 1:1) afforded 14.1 mg (30%) of the desired product **5.121** as a colorless oil. **FTIR ($CHCl_3$, cm^{-1}):** 3287, 2975, 2923, 1639, 1612, 1548, 1364, 1324, 1146, 1002, 971, 849. **^{1}H NMR (700 MHz, $CDCl_3$):** δ 7.21 (dd, *J* = 14.8, 11.3 Hz, 1H, **H6**), 6.50-6.45 (m, 2H, **H11** & **H4**), 6.17-6.11 (m, 2H, **H3** & **H5**), 5.91-5.86 (m, 1H, **H2**), 5.77 (d, *J* = 14.9 Hz, 1H, **H7**), 5.48 (d, *J* = 18.1 Hz, 1H, **H12**), 5.44 (brd, 1H, **NH**), 3.48-3.45 (m, 1H, **H9**), 3.16-3.12 (m, 1H, **H9**), 2.49-2.44 (m, 1H, **H10**), 1.81 (d, *J* = 6.8 Hz, 3H, **H1**), 1.27 (s, 12H, **Bpin-CH_3**), 1.04 (d, *J* = 6.8 Hz, 3H, **H13**) ppm. **^{13}C NMR (176 MHz, $CDCl_3$)**: δ 166.3 (**C8**), 156.2 (**C4**), 141.3 (**C6**), 140.0 (**C11**), 134.1 (**C2**), 131.4 (**C3**), 127.8 (**C5**), 122.8 (**C7**), 119.1 (**C12**, deduced from HSQC), 83.4 (**Bpin-OC**), 44.2 (**C9**), 39.8 (**C10**), 24.95 (**Bpin-CH_3**), 24.94 (**Bpin-CH_3**), 18.6 (**C1**), 17.3 (**C13**) ppm. **HRMS (ESI) (m/z):** calculated for $[M+Na]^+$ ($C_{19}H_{30}O_3B_1N_1Na$) requires 354.2211, found 354.2215. **$[\alpha]_D^{20}$** = +42.5 (c = 0.84, $CHCl_3$).

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