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Developing Chiral Synthons for Polyketide-Based Natural Product Synthesis *via* Stereospecific Oxonia-Cope Rearrangement

By

Yi-Hung Chen
B.S., National Tsing Hua University, 1999

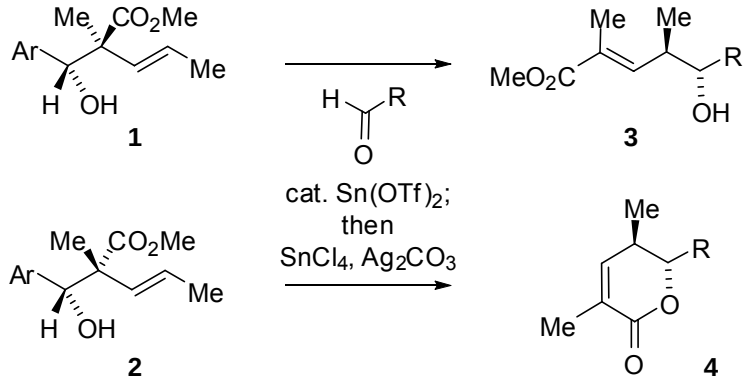
Advisor: Frank E. McDonald, Ph.D.

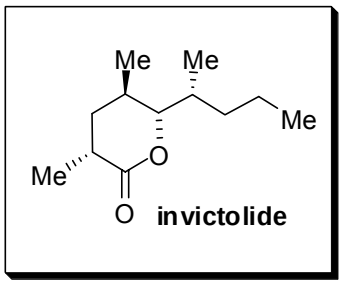
An Abstract of
A dissertation submitted to the Faculty of the Graduate School of Emory University in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

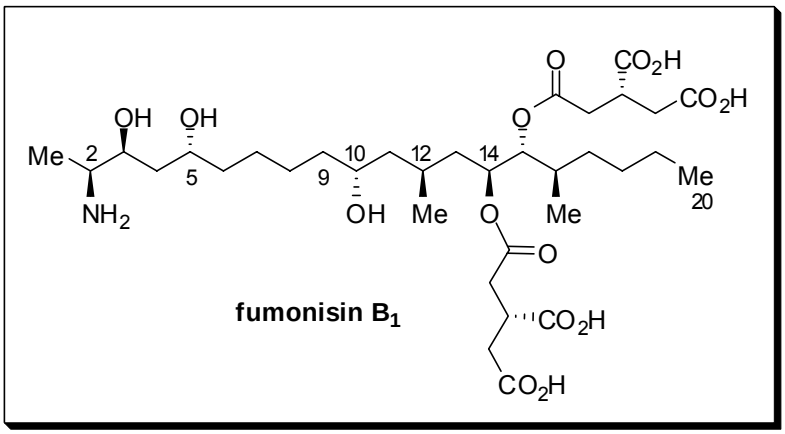
Department of Chemistry
2007

Abstract

Homoallylic alcohols **1** and **2** underwent stereospecific Lewis acid-catalyzed transfer of the bispropionate unit with different aldehydes. By applying this powerful methodology, the synthesis of (-)-invictolide was accomplished in a very concise manner beginning with **2** and (*R*)-2-methylpentanal. We are currently working on the total synthesis of polyketide-derived mycotoxins from simple precursors, including fumonisin B_1. The key features of our synthesis are the use of oxonia-Cope rearrangements to introduce C5 and C14 stereocenters and construct C1-C9 and C10-C20 carbon skeletons.







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First and foremost, I would like to thank Prof. Frank E. McDonald for all his guidance and unwavering support through my study at Emory University. He gave me enough freedon to develop on my own as an independent researcher. He has always steered me down the right path. I have been fortunate to have such a great mentor.

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I would like to give my thanks for all the past and present members of the McDonald laboratory. In addition, I would like to thank my friends at Emory, who have made this period of time more enjoyable and memorable.

I owe all to my parents for their love and unconditional support in whatever I have strived to achieve. Finally, I want to thank my fiancée, Hsiao-Pei, who has always been standing beside me. It is her love, devotion and encourangement that have made this achievement possible and meaningful.

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Abbreviations

Ac	acetate
Anal. Calcd.	analysis calculated
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu (*n*-Bu)	normal butyl
Calcd.	calculated
CSA	camphorsulfonic acid
d	doublet
DCC	dicyclohexyl carbodiimide
dr	diastereomeric ratio
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EDTA	ethylenediaminetetraacetic acid
er	enantiomeric ratio
EI	electronic ionization
Et	ethyl
g	gram
HRMS	high resolution mass spectroscopy

i-Pr	*iso*-Propyl
IR	infrared
L	liter
LDA	lithium diisopropylamide
M	molarity
m	multiplet
mix.	mixture
Me	methyl
mg	milligram
mL	milliliter
mmol	millimole
Ms	methanesulfonyl, mesyl
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
PPTS	pyridinium *p*-Toluenesulfonate
Py.	pyridine
q	quartet
quint	quintet
rt	room temperature
s	singlet

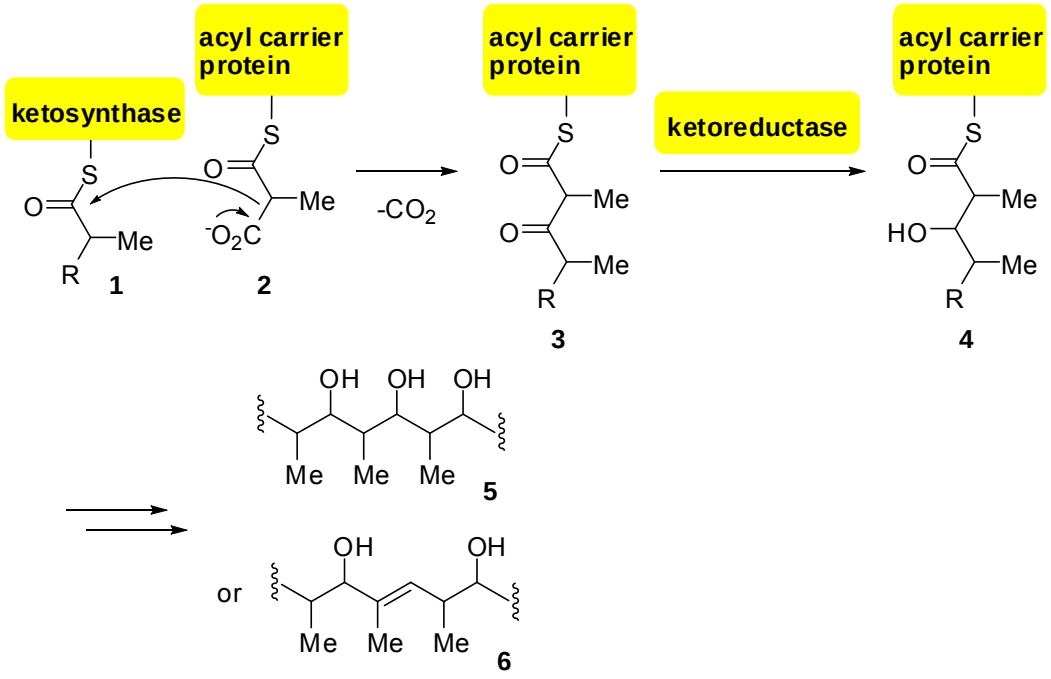
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	dimethylbutylsilyl
Tf	trifluoromethanesulfonyl, triflyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TIPS	triisopropylsilyl

Chapter 1. *Developing Chiral Synthons for Polyketide-Based Natural Product Synthesis via Stereospecific Oxonia-Cope Rearrangements.*

1.1. Introduction and Background.

Polyketides are a broad range of natural products, which are important lead targets for antibiotics and antitumor drugs. In the work on studying polyketide biosynthesis, a combination of synthetic, enzymological, and molecular genetic approaches identified converting the simple building blocks for acetate and propionate components of complex natural products *via* iterative sequence of Claisen-type condensations (**1** + **2** → **3**, **Figure 1**), along with reduction or dehydration to afford a variety of substructures (**5** or **6**).[1]

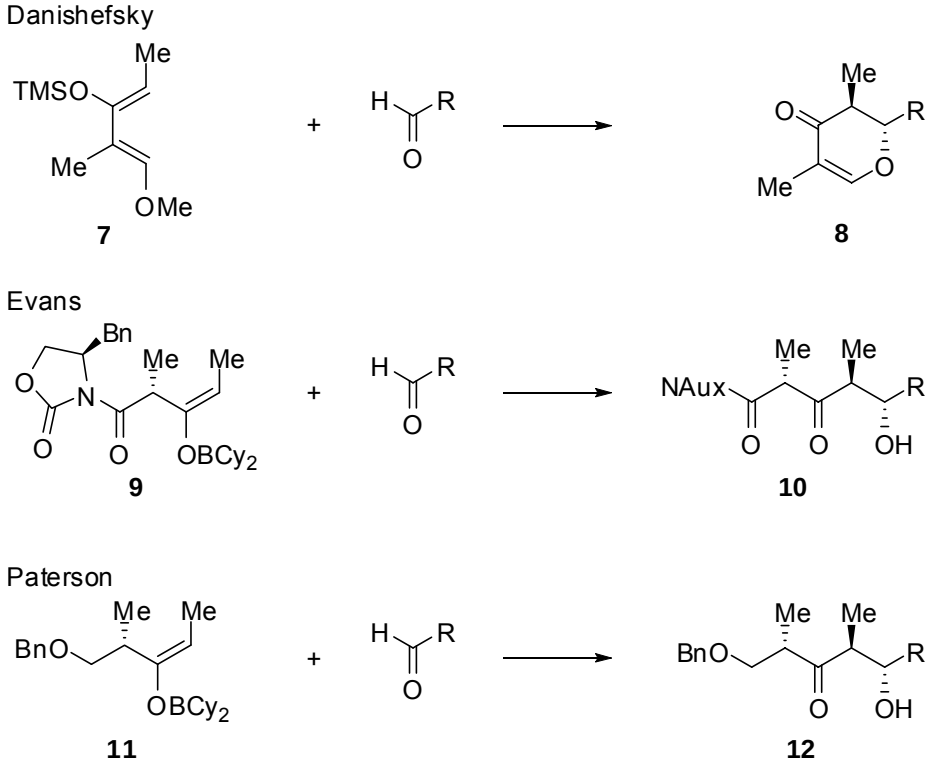
Figure 1. Biosynthesis of Polyketides Substructures



Moreover the Claisen-type or aldol reactions which provide β-hydroxy carbonyl compounds with one or two new stereocenters are particularly valuable

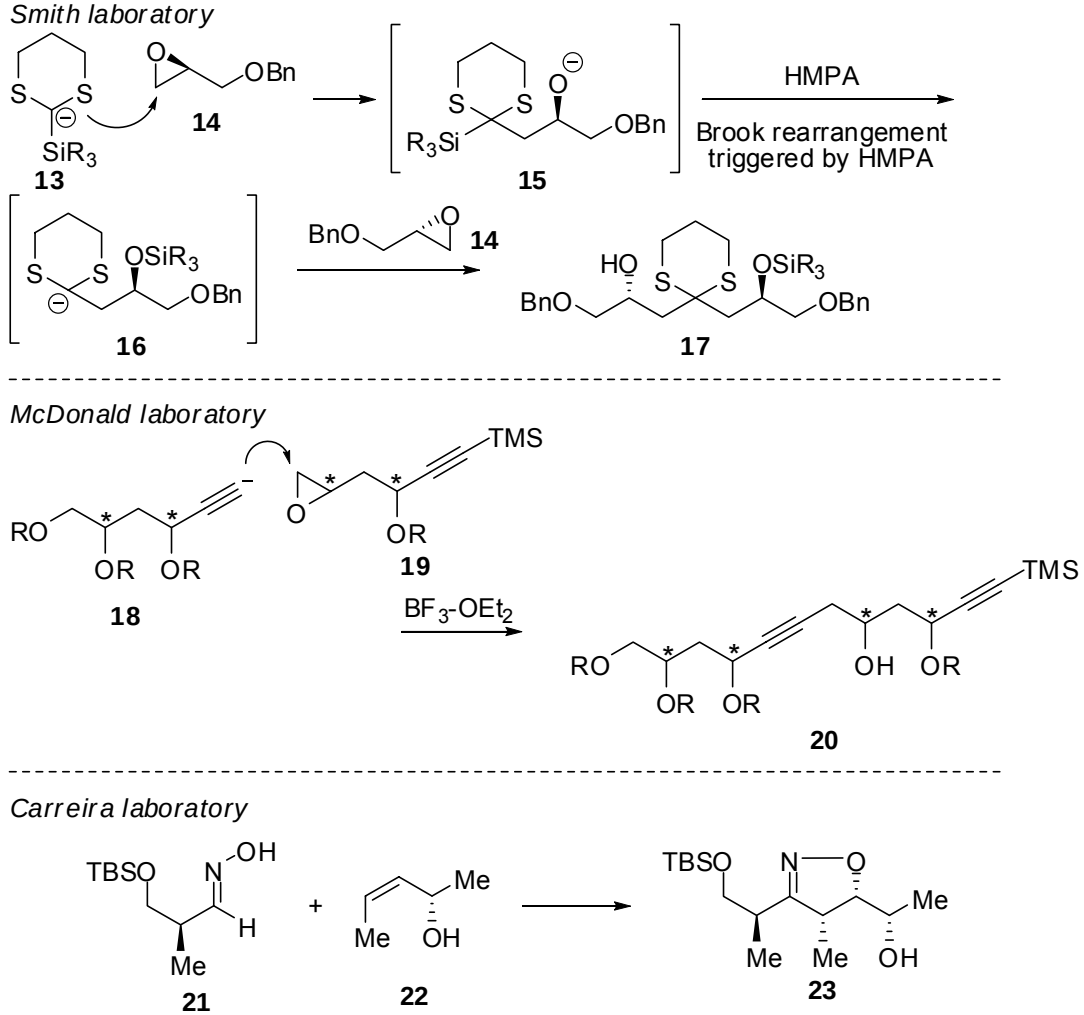
for synthetic chemists to pursue polyketide synthesis.[2] However aldol or aldol-related transformations usually provide two (acetate) or three (propionate) carbons at a time to the growing carbon skeleton, so that tedious transformations and manipulating protecting groups are required for these approaches in complex molecule synthesis. In order to make the synthesis more efficient, many laboratories have reported different strategies that would allow the incorporation of larger modules, such as four- or five-carbon building blocks in the course of the synthesis. Well known examples are the Danishefsky diene **7**,[3] Evans β-keto imide derived enolates **9**,[4] and Paterson aldol reactions[5] in which bispropionate fragments are employed in those transformations (**Figure 2**).

Figure 2. Bispropionate Transfer



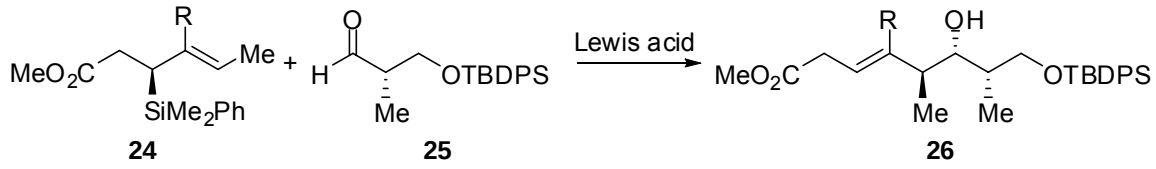
Some other non-traditional approaches including highly selective vinylogous Mukaiyama aldol reactions which introduced a combined acetate-propionate (or bispropionate) building blocks are extremely useful for synthesis.[6] Although carbonyl addition reactions were generally employed, several alternative approaches have been disclosed. For example, dithiane chemistry allowed for bidirectional fragment coupling with various functional groups.[7] As shown in **Figure 3**, Smith and co-workers reported that the lithiated silyl dithiane **13** reacted with a simple epoxide **14** to afford oxyanion intermediate **15**. The resulting intermediate was treated with hexamethylphosphoramide (HMPA) to trigger 1,4-Brook rearrangement and generate a new reactive anion **16**, which subsequently participated in the second epoxide addition to furnish a mono-protected 1, 5-diol **17**. Smith's synthesis of spongistatins, which are extraordinarily potent anti-tumor macrolides, highlighted the merit of this transformation.[7b,7c] The McDonald laboratory presented that Lewis acid activated nucleophilic epoxide opening with nucleophile **18**[8] to provide diyne **20** with four stereocenters, which are useful building blocks for polyketide construction. The application of this chemistry has been demonstrated in total synthesis of the polyene-polyol macrolide RK-397.[8b] The general stereo- and regioselective cycloaddition of chiral nitrile oxide **21** and allylic alcohol **22** provided isoxazoline **23**[9] which can be further converted to the β-hydroxy ketone. Carreira *et al.* have demonstrated this powerful cycloaddition in the total synthesis of erythronolide A.[9b]

Figure 3. Non-Aldehyde Addition Approaches



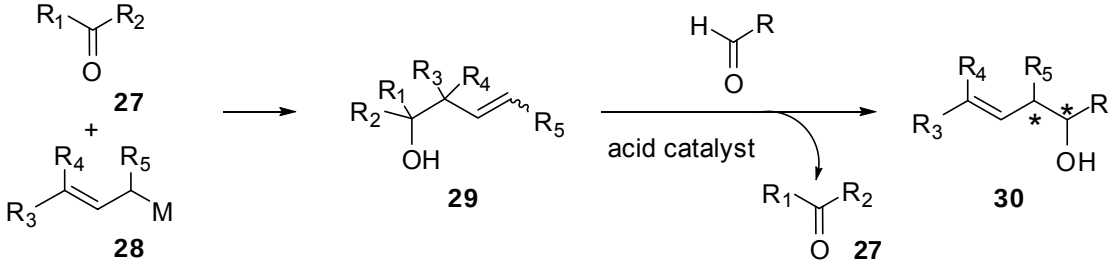
The preparation of homoallylic or homopropargylic alcohols can serve as aldol surrogates upon fuctionalization of the double or triple bonds. In addition to widely-used allyl-, crotyl- and allenyl-metal protocols,[10] Panek *et al.* introduced chiral crotylsilane **24** as a powerful reagent for the incorporation of six-carbon fragments as shown in **Figure 4**.[11]

Figure 4. Panek Chiral *(E)*-Crotylsilane Reagent



The allylic rearrangements pioneered by the Nokami[12] and Loh[13] laboratories (**Figure 5**), in which a chiral non-racemic homoallylic alcohol condensed with aldehydes to accomplish transfer of crotyl and other allylic units with a 2-oxonia-[3,3]-sigmatropic rearrangement mechanism, have been reported in recent years. As shown in **Figure 5**, the preparation of highly enantiomerically pure allyl-donor reagents **29** is easy and no allylic metal nucleophiles are involved in the main transformation. The absolute configuration of homoallylic alcohol **30** is predictable and extremely stereospecific under very mild reaction conditions.

Figure 5. Allylic Transfer *via* 2-Oxonia-[3, 3]-Sigmatropic Rearrangement



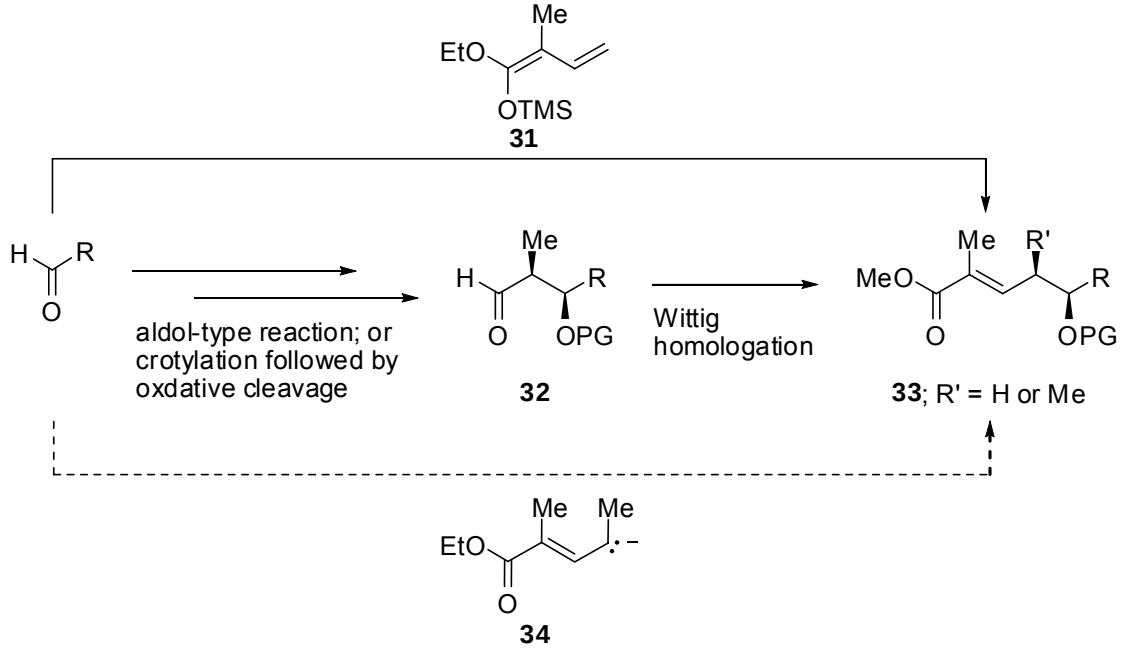
The McDonald laboratory is interested in developing novel methodology for polyketides synthesis in a non-aldol fashion, reducing the required number of carbon-carbon bond forming steps by relying on larger building block incorporation. In this chapter, we present the development of novel synthons for the stereospecific introduction of bispropionate segments *via* oxonia-Cope rearrangements.[14]

1.2. Results and Discussions.

1. 2. 1. Initial Study of Allylic Rearrangement

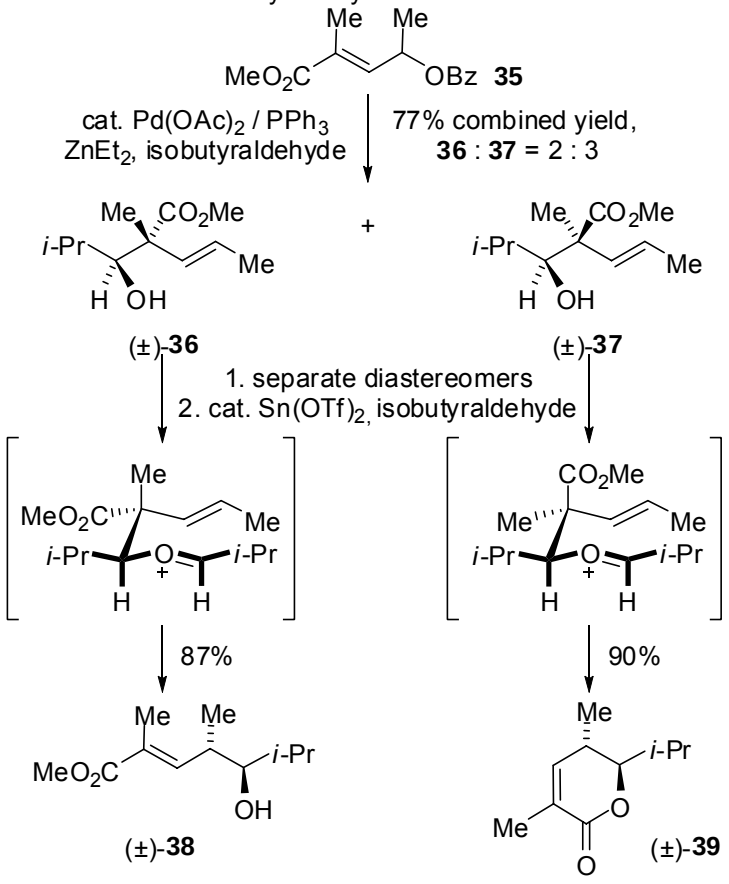
The bispropionate motif **33** is a valuable synthetic subunit (**Figure 6**) which can be further functionalized by highly selective substrate-directable reactions. Traditionally **33** could be synthesized *via* an asymmetric aldol reaction followed by reduction and Wittig type olefination,[15] or alternatively by asymmetric crotylation followed by oxdative cleavage and olefination.[16] More recently, the progresses in catalytic asymmetric vinylogous aldol reactions can provide combined acetate-propionate adduct **33** efficiently. Bluet and Campagne reported the first vinylogous aldol reaction with simple ester-derived silyl dienol ether **31** in 1999.[17] We sought to explore the chemical equivalent of bispropionate anion **34** for synthesis of the common structural motif in many biologically active natural products. Furthermore, the chemistry would be extended to generate both *syn*- and *anti* isomers.

Figure 6. Preparation of Acetate-Propionate Building Block



We first examined the reductive coupling of allylic benzoate **35**[14] with isobutyraldehyde, using Tamaru's conditions of palladium/phosphine catalyst and diethylzinc,[18] but found none of the desired γ-adduct, and only the separable mixture of α-addition products **36** and **37** were obtained (**Scheme 1**). By using non-racemic benzoate **35** which was prepared from ethyl-(*S*)-lactate, we could not alter the diastereomeric ratio of **36** / **37**, and only racemic γ-adducts were formed. However, inspired by Nokami's allylic transfer chemistry,[19] both homoallylic alcohol diastereomers **36** and **37** underwent stereospecific oxonia-[3,3]-Cope-rearrangement to provide the desired γ-adducts **38** and **39**, respectively, with the lactone of **39** spontaneously forming due to the presence of the *Z*-alkene.

Scheme 1. Initial Study of Allylic Transfer Reactions.

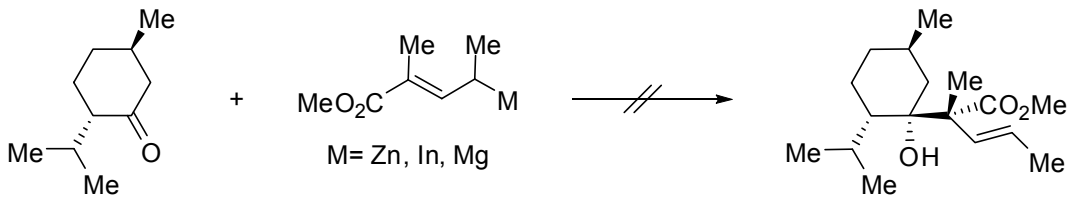


However, several limitations of this method were evident from these experiments including the preparation of non-racemic compounds **36** - **39**, and the absence of any stereoselectivity in the initial reductive coupling of **35**. Since isobutyraldehyde was produced as a byproduct in the allylic rearrangements of **36** and **37**, it was impractical to interchange a second aldehyde into the allylic rearrangement step from **36** or **37** due to a competing reaction with isobutyraldehyde. A possible solution to these problems was to use a chiral and non-racemic ketone (menthone for example) as a reductive coupling substrate. Considering the possibly low reactivity of homoallylic alcohol formation because of steric effects, aldehydes which would either be deactivated after the allylic rearrangement step, or would be removed by a secondary reaction in the course of allylic rearrangement could be coupled with a bispropionate synthon.

1. 2. 2. Design of Bispropionate Synthons

We aimed to develop a new generation of bispropionate synthons, which permitted the direct synthesis of a broad spectrum of dipropionate subunits with a simple protocol. Initially, we screened different kinds of bispropionyl-metal reagent condensation with (-)-menthone **40** to form a chiral, non-racemic reagent **41**. However formation of the C-C bond between two quaternary centers was extremely difficult, so desired product was not obtained (**Figure 7**).

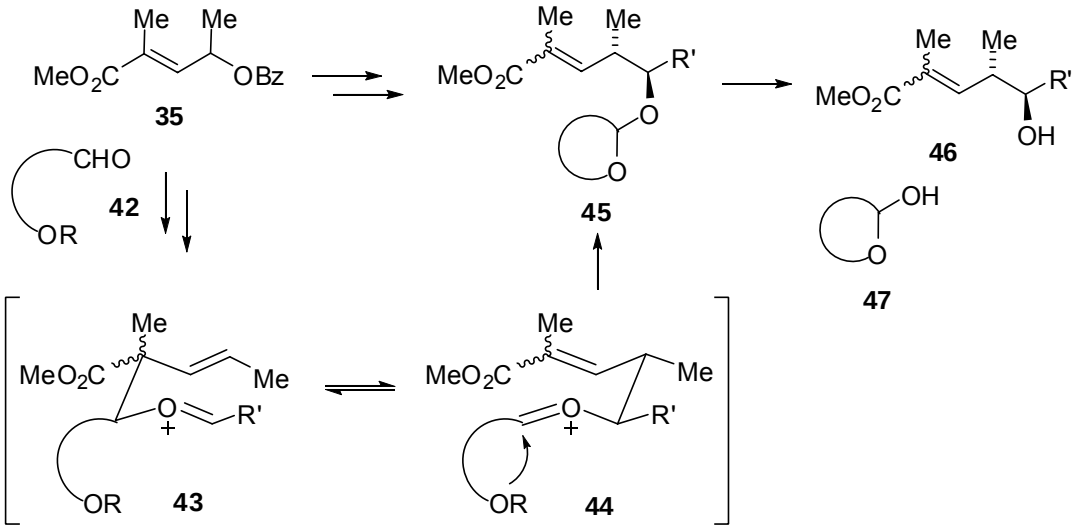
Figure 7. Preparation of Chiral Non-racemic Homoallylic Alcohol



40 **41**

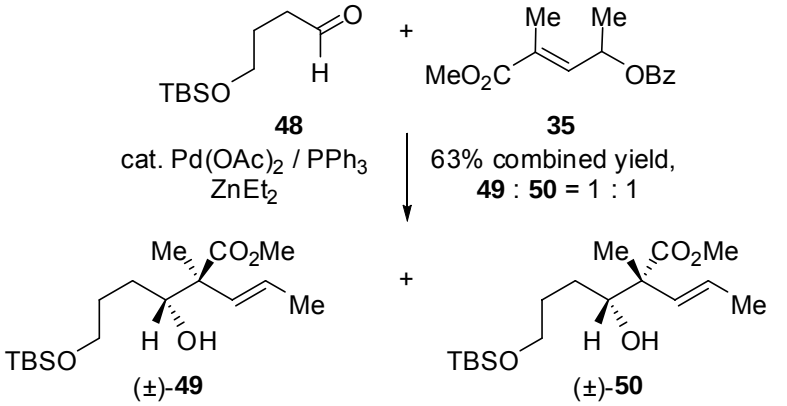
Thus a second-generation reagent was proposed, in which the aldehyde for reductive coupling with **35** was tethered to a hydroxyl group such as **42**, so that the equilibrium in the [3,3]-rearrangement between **43** and **44** might be driven to product **45** or **46** (**Figure 8**). The byproduct aldehyde would be deactivated as the lactol **47**.

Figure 8. Design of Bispropionate Synthons



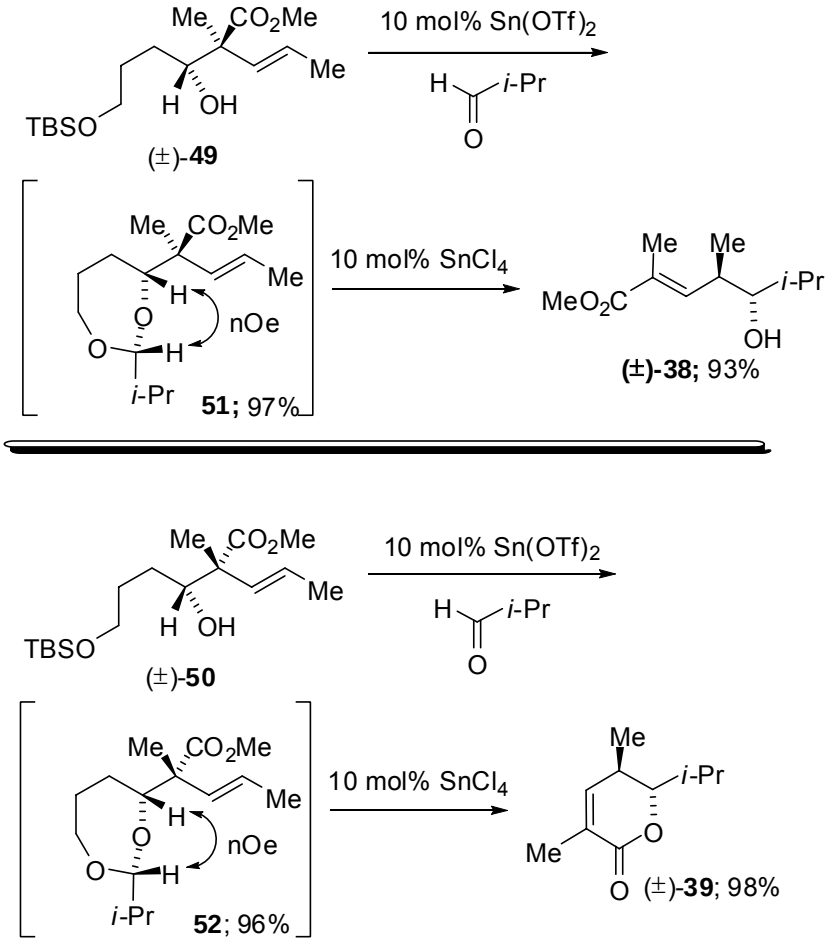
Under the same palladium-catalyzed reductive coupling conditions,[18] allylbenzoate **35** condensed with aldehyde **48** to afford separable diastereomers **49** and **50** in 63% yield (1 : 1 diastereomeric ratio, **Scheme 2**).

Scheme 2. Preparation of Racemic Bispropionate Synthons **49** and **50**



Under acid-promoted rearrangement conditions in the presence of a catalytic amount of $Sn(OTf)_2$, carbinol **49** gave the seven-membered ring acetal **51** in almost quantitative yield with isobutyraldehyde (**Scheme 3**). However, the acetals further transformed into the desired bispropionate adduct **38** in good yield with a catalytic amount of $SnCl_4$. Identical reaction conditions with diastereomer **50** provided cyclic lactone **39**, again via cyclic acetal intermediate **52**. Acetals **51** and **52** were stable intermediates and could be isolated by chromatography. Moreover, the relative stereochemistry for both acetals was assigned based on nuclear Overhauser effect (nOe) study.

Scheme 3. Allylic Rearrangement with Synthons **49** and **50**

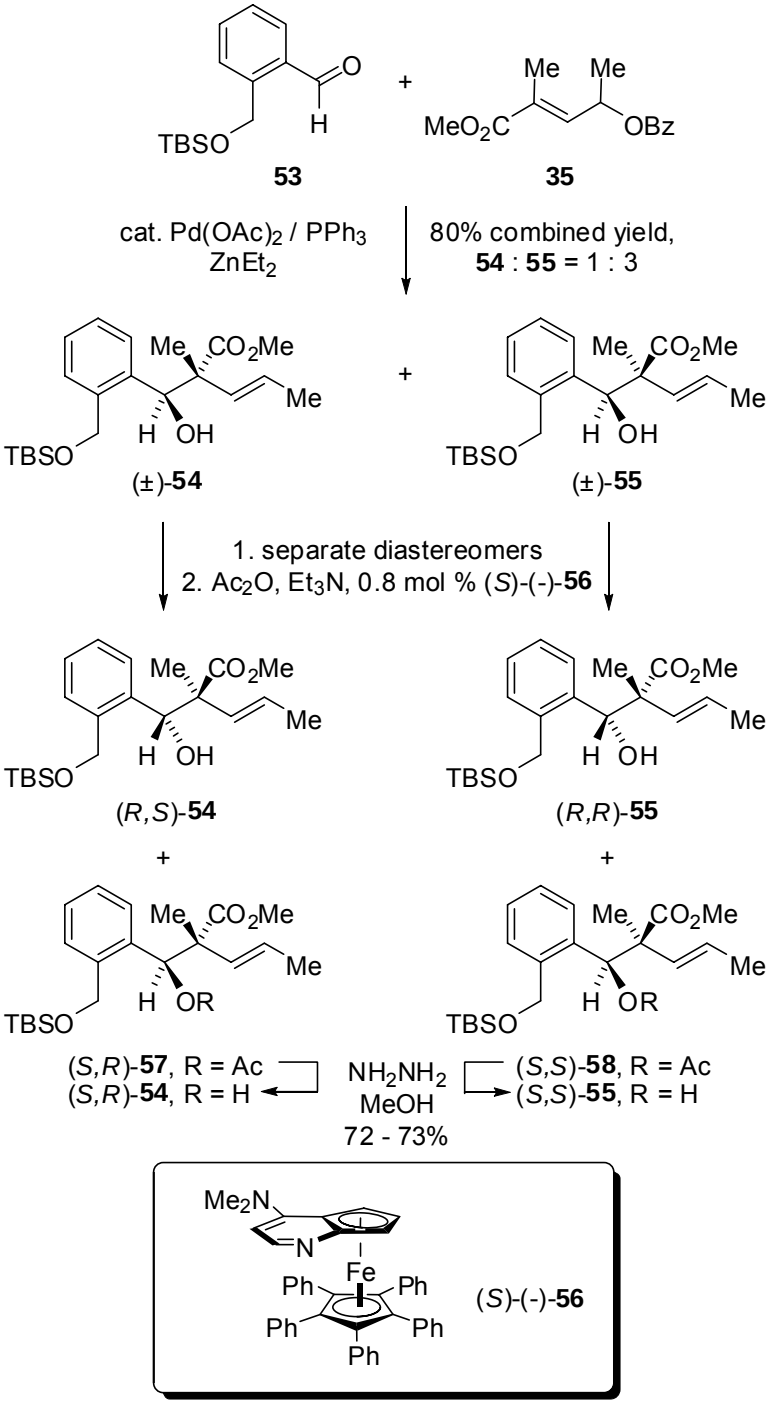


To our delight, the acetals were further transformed into the desired bispropionate adducts in excellent yield, resolving the by-product issue by the intramolecular oxonia-Cope rearrangement.

The remaining puzzle was the preparation of chiral, non-racemic synthons. Enzymatic and non-enzymatic methodologies[20] failed to resolve the recemic homoallylic alcohol **49** and **50**. Both alcohols were oxidized to β-keto ester but they could not be reduced selectively by chiral oxazaborolidine catalyst or *B*-chlorodiisopinocampheylborane. The last stereochemical hurdle stimulated the design of aryl carbinols bispropionate synthons **54** and **55** as shown in **Scheme 4**. Under the same palladium-catalyzed "umpolung" (reversal of polarity) reaction, allylbenzoate **35** condensed with benzaldehyde **53**[21] to afford separable diastereomers **54** and **55** in 80% yield and 1 : 3 diastereoselectivity (**Scheme 4**). Each racemic diastereomer was submitted to non-enzymatic kinetic resolution, catalyzed by Fu's planar-chiral modified DMAP catalyst (*S*)-(-)-C_5Ph_5-DMAP **56**.[22] It has been reported that the catalyst could resolve a wide arrary of arylalkylcarbinols with excellent stereoselection, and the selectivity factor increased with increasing steric demand of the alkyl group. The alcohols (*R, S*)-**54** and (*R, R*)-**55** were each obtained in excellent enantiomeric purity from resolution of each racemate. The absolute stereochemistry of carbinols (*R*, *S*)-**46** and (*R*, *R*)-**47** was confirmed by Mosher ester analysis,[23] which is consistent with Fu's prediction and the enantiomeric purity was determined by chiral-HPLC analysis. The corresponding acetates (*S, R*)-**57** and (*S, S*)-**58** were easily converted into the alcohols (*S*, *R*)-**54** and (*S*, *S*)-**55** by hydrazine in methanol.[24]

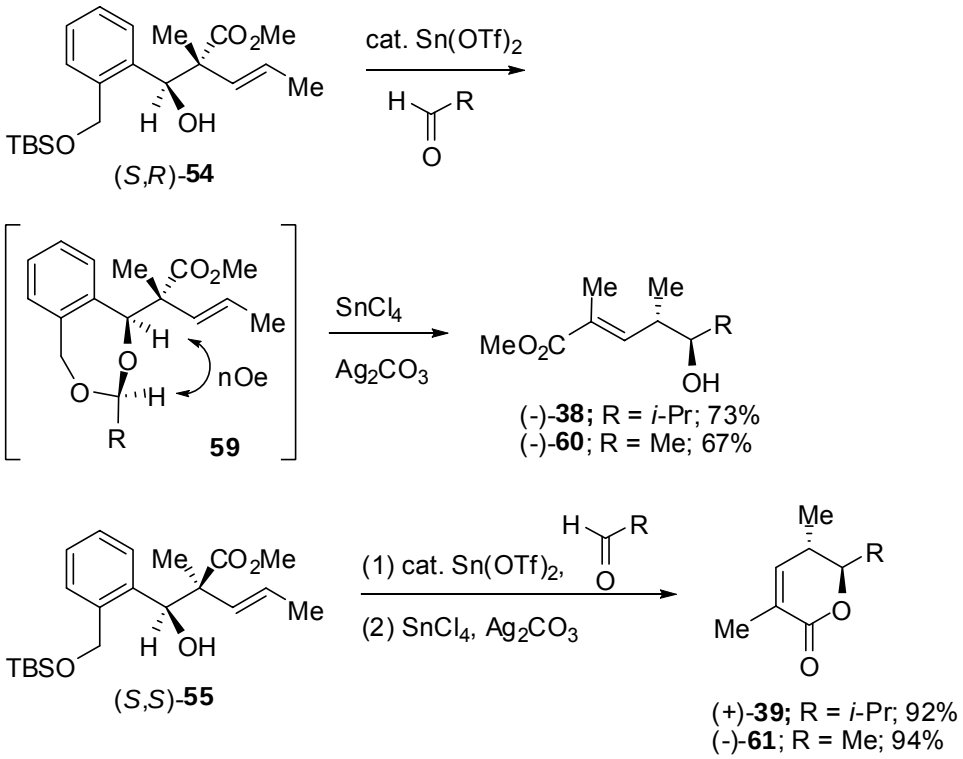
With each of the four possible isomers in pure form, we focused on the optimization of the bispropionate transfer reaction with a variety of aldehydes, including *alpha*-chiral aldehydes.

Scheme 4. Preparation of Chiral Non-racemic Bispropionate Synthons **54** and **55**



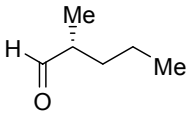
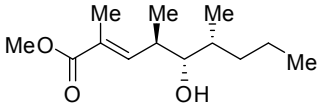
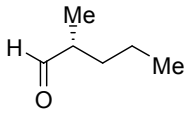
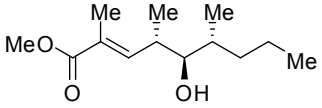
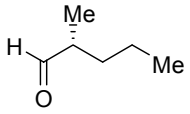
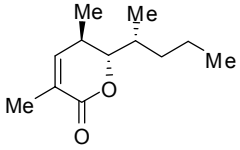
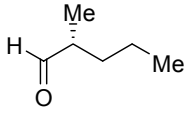
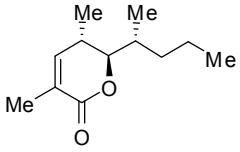
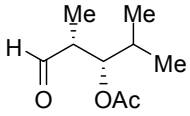
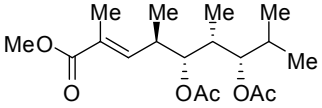
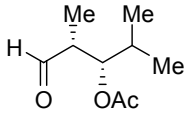
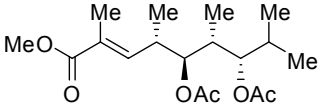
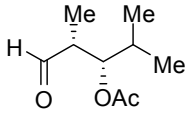
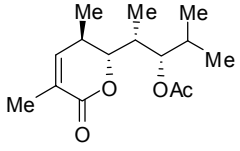
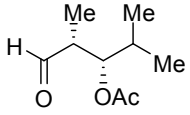
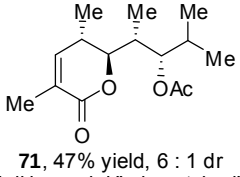
Both arylalkylcarbinols (*S,R*)-**54** and (*S,S*)-**55** underwent acid-promoted seven-membered ring acetal formation in the presence of catalytic amount of $Sn(OTf)_2$ to give excellent yield with isobutyraldehyde and acetaldehyde (**Scheme 5**). However, the acetal intermediates could not be converted to the bispropionate adducts with 10 mol% of $SnCl_4$ at 0 ˚C (identical conditions used in the catalyzed rearrangement of acetals **51** and **52**, **Scheme 3**). Increasing Lewis acid loading or raising the temperature provided the desired products in low yield along with by-products that could not be separated. Optimization revealed that the best results were obtained by the addition of Ag_2CO_3 as a halide scavenger as shown in **Scheme 5**. Arylacetals derived from (*S, R*)-**54** and (*S, S*)-**55** with $SnCl_4$ and Ag_2CO_3 furnished the bispropionates in good to excellent yield and high enantiomeric purity, which was confirmed by Mosher ester or HPLC analysis.

Scheme 5. Initial Results with Simple Aldehydes



Having achieved chirality transfer to the bispropionate products, we turned our attention to α-chiral aldehyde substrates (**Table 1**). In the case of α-chiral aldehydes **62** and **63**, catalytic TMSOTf was used in the first step, to minimize epimerization of the chiral aldehyde. Identical reaction conditions for all four diastereomers **54-55** provided acyclic and cyclic bispropionates. We were particularly pleased to see that (α-chiral aldehydes) were compatible with this methodology, without significant epimerization of the chiral center arising from the aldehyde. We also realized that the purification of acetal intermediates was not necessary, and the crude intermediates could be used for the rearrangement.

Table 1. *Synthesis of Bispropionates with Chiral Aldehyde **62** and **63***

synthon	aldehyde	Procedure[a]	product (isolated yield, dr)
(*R*, *S*)-**54** (87% ee)	 **62** (96% ee)	A	 **64**, 75% yield, 12 : 1 dr
(*S*, *R*)-**54** (85% ee)		A	 **65**, 78% yield, 10 : 1 dr
(*R*, *R*)-**55** (89% ee)		A	 **66**, 89% yield, 14 : 1 dr
(*S*, *S*)-**55** (90% ee)		A	 **67**, 85% yield, 14 : 1 dr
(*R*, *S*)-**54** (87% ee)	 **63** (85% ee)	B	 **68**, 69% yield Felkin model "matched"
(*S*, *R*)-**54** (85% ee)		B	 **69**, 62% yield, 9 : 1 dr Felkin model "mismatched"
(*R*, *R*)-**55** (89% ee)		A	 **70**, 80% yield Felkin model "matched"
(*S*, *S*)-**55** (90% ee)		A	 **71**, 47% yield, 6 : 1 dr Felkin model "mismatched".

[a] Procedure A: TMSOTf (10 mol%), CH_2Cl_2. -78 ˚C, 4 h, pyridine quench; then $SnCl_4$ (0.6 equiv), Ag_2CO_3 (2 equiv), $MeNO_2/CH_2Cl_2$, 20 ˚C. Procedure B: same as procedure A, except followed by Ac_2O, pyridine.

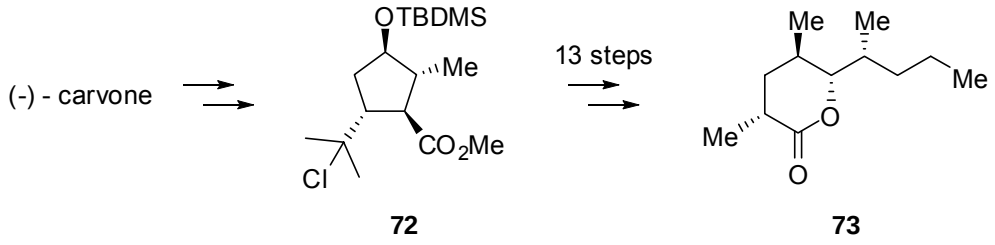
The study with (*R*)-2-methylpentanal (**62**) and (2*R*, 3*S*)-3-acetoxy-2,4-dimethylpentanal (**63**) revealed that the bispropionate transfer reaction occurred without observable double diastereoselection from aldehyde **62**, but some diminution in yield and stereoselectivity was observed for Felkin model "mismatched" cases with aldehyde **63** (i.e., from (*S*, *R*)-**54** and (*S*, *S*)-**55**). The diacetate products **68** and **69** were prepared from the acetylation of the product mixture because of partial acetyl migration after the rearrangement. Moreover, it has been observed that isolation yields of the acyclic alcohols were consistently lower than those for lactones even though rearrangement occurred observably faster for acetals derived from synthons **54**. We suspect that the acyclic products seemed to decompose upon prolonged contact with the Lewis acids that promote this rearrangement.

1. 2. 3. Total Synthesis of (-)-invictolide.

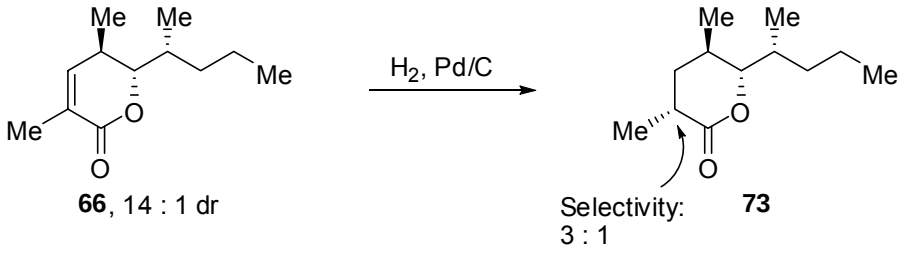
To demonstrate the effectiveness of this strategy, we present the synthesis of (-)-invictolide **73** which is a component of queen recognition pheromone of *Solenopsis invicta*. The structure of (-)-invictolide **73** has been determined by Tumlinson and co-workers based on spectroscopic analysis and synthesis.[25] Several syntheses have been reported in the literature including the most recent example from Honda's group in 1996 (**Scheme 6**).[26] In that work, the Multi-substituted cyclopentane **72** derived from (-)-carvone was converted to (-)-invictolide in 13 steps.

Scheme 6. Synthesis of (-)-invictolide **73**.

(1) Honda's Synthesis



(2) Our Synthesis



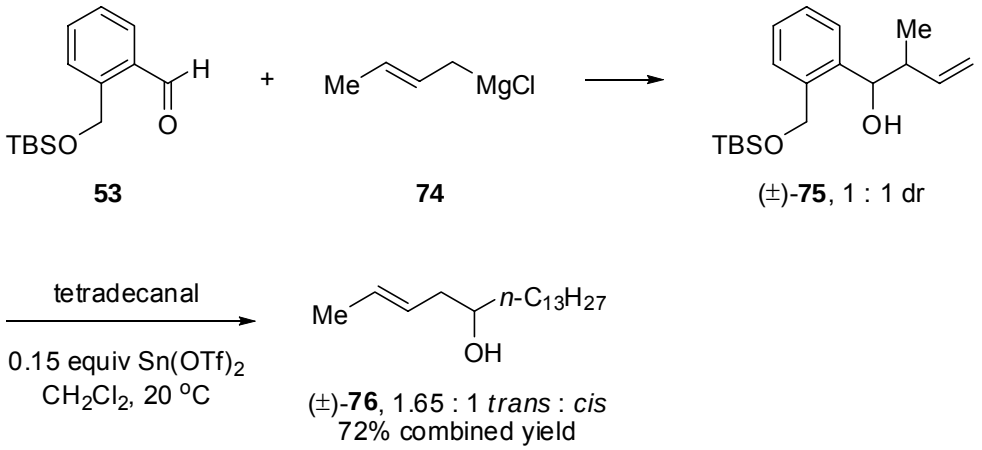
Our synthesis was very concise from lactone **66,** which was synthesized from (*R*, *R*)-**55** and (*R*)-2-methylpentanal (**62**), by Pd-C catalyzed hydrogenation of **66**. This result also validated the structural assignment for our lactone products.

1. 2. 4. New Crotyl Reagents

With the successful development of aryl carbinol bispropionate synthons, we considered thorough investigation of the synthetic potential of the allylic rearrangement mechanism, expanding the functional group and stereochemistry patterns on the bispropyl-donor reagent. Because some simple patterns such as bisacetate are common substructures in biologically active natural products, it is valuable to develop highly selective reagents for the rapid introduction of bisacetate motif. Having realized the shortcomings of the methods developed by Nokami and Loh for the preparation of linear *cis*-crotyl groups, we anticipated the improvement by modifying our arylaldehyde based system (**Scheme 7**). At this

stage, we generally screened reactions on racemic compounds for convenience. In our approach, the addition of linear crotyl moiety to tetradecanal with $Sn(OTf)_2$ catalysis without isolation of an acetal intermediate furnished a mixture of *cis* and *trans* homoallylic alcohol **76**. Although the crotyl donor reagent was a mixture of both *syn* and *anti*-isomer (1:1), the alkene stereochemistry of linear crotyl adduct **76** was not 1 : 1. It was rationalized that the *anti*-isomer (leading to *trans*-alkene) is more reactive than the *syn*-isomer under the same conditions. We will further optimize the reaction conditions for improving efficiency of *cis*-alkene product formation.

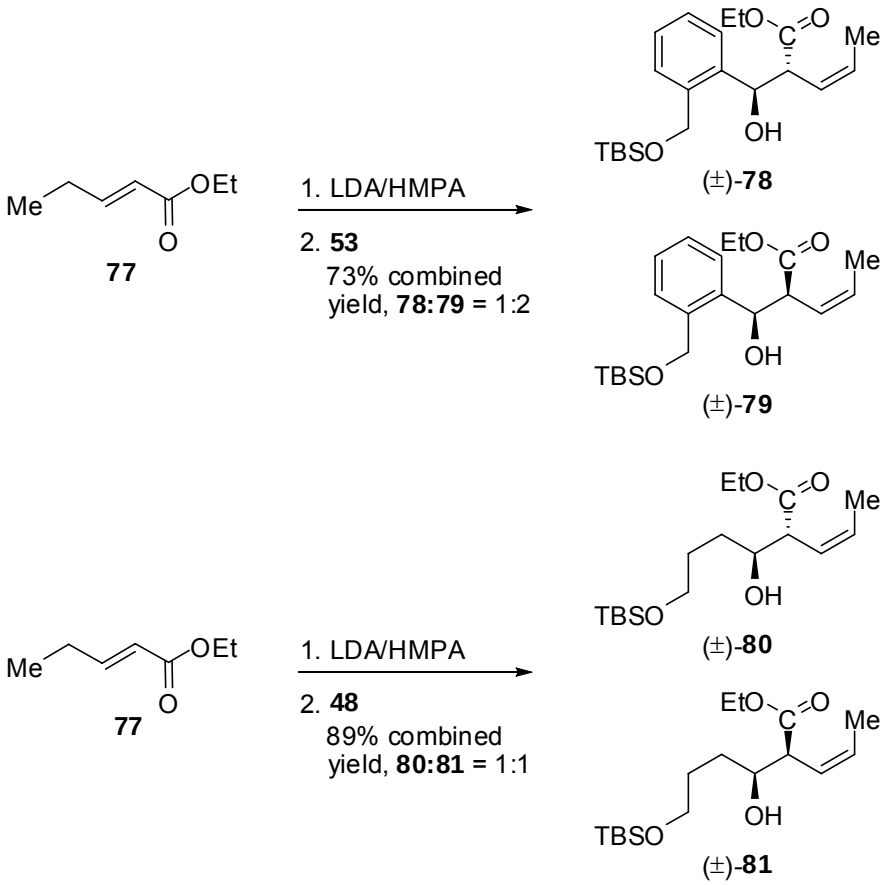
Scheme 7. Aryl Crotyl Donor Reagent



We envisioned that this methodology would be even more powerful if it could be extended to *cis*-alkene compounds **78-81** that would provide *syn*-bisacetate adducts (**Scheme 8**). The preparation of (*Z*)-configured bisacetate donor commenced with ethyl (*E*)-2-pentenoate **77**.[27] The deconjugative aldol reaction of aldehyde **53** provided separable diastereomeric mixtures **78** and **79** in 73% yield (1:2 diastereomeric ratio). Under the same deconjugative aldol

condition, pentenoate **77** condensed with butanal **48** to afford diastereomers **80** and **81** in 89% combined yield.

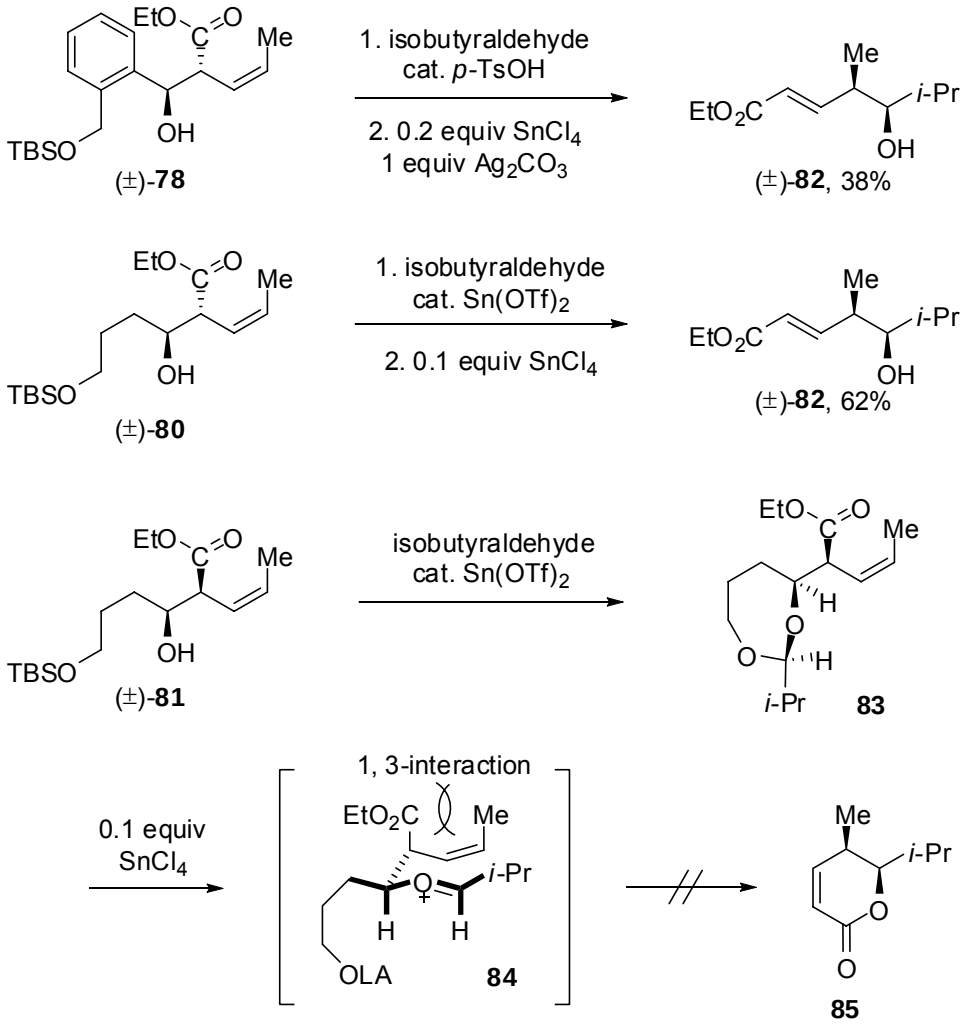
Scheme 8. Preparation of Compound **78-81**



Both *anti*-isomers **78** and **80** under acid-promoted acetal formation conditions were allowed to react with isobutyraldehyde in almost quantitative yield based on TLC-analysis. Those intermediates were further transformed into the corresponding *syn*-adduct **82** with catalytic amount of $SnCl_4$ in 38% and 62% yield respectively as shown in **Scheme 9**. It is worthy to note that the diastereomer **81** could not rearrange to the desired γ-adduct because of sterically demanding ethyl ester and methyl groups at axial positions in a chair-like

transition state **84,** even though the acetal intermediate **85** was formed in the first step.

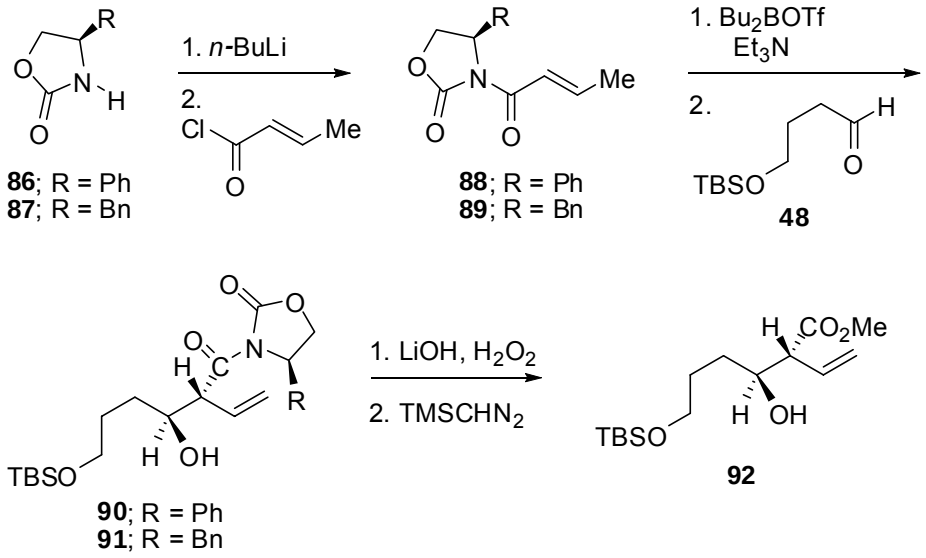
Scheme 9. Preparation of *Syn*-bisacetate Substrate



In connection with our recent studies on the total synthesis of fumonisin B_1 which will be discussed carefully in chapter two of this dissertation, we anticipated that the chiral non-racemic homoallylic alcohol **92** might be generated from chiral crotonate imides **88** and **89** (**Scheme 10**).[28] Aldol reaction of the derived dibutylboryl enolates proceeded with complete α-addition to give imides

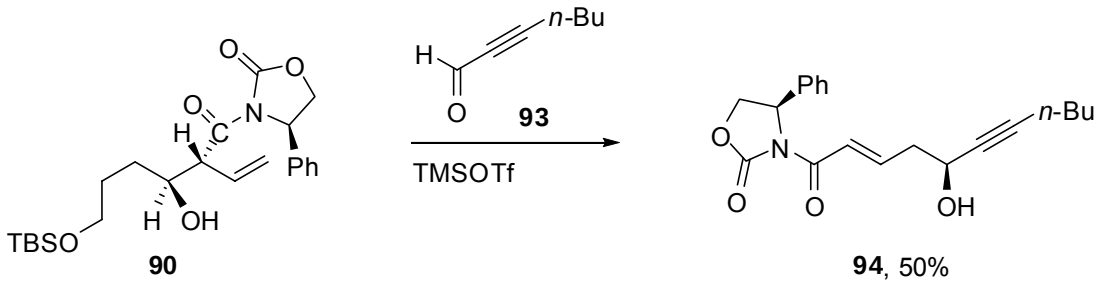
90 and **91** in good yield. These crotonate aldol adducts were further converted to methyl-ester **92** under peroxide-mediated hydrolysis followed by methylation.

Scheme 10. Evans Deconjugative Aldol Reactions



To this stage, we and others[12] had observed that oxonia-Cope rearrangement could not be applied to sterically hindered or α,β-unsaturated aldehydes. However, we discovered the first successful transformation with an unsaturated aldehyde **93** and imide **90** as shown in **Scheme 11**. In this case, substoichiometric trimethylsilyl triflate (TMSOTf) catalyzed the initial acetal intermediate formation, which upon addition of full equivalent of TMSOTf promoted the rearrangement to occur through oxonium ion transition state. The reaction was done in one pot fashion without isolation of the acetal intermediate and provided enyne **94** in moderate yield.

Scheme 11. Oxonia-Cope Rearrangement with Imide **90**



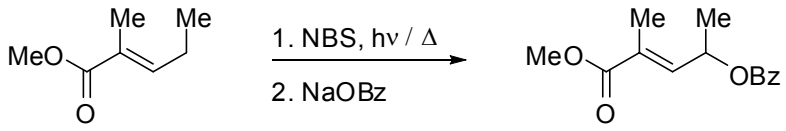
1.3. Conclusions.

In conclusion, we have established a family of new propionate synthons, and have demonstrated the remarkably efficient and stereospecific transformation to provide synthetically useful bispropionate or bisacetate substructures under very mild conditions. We also showed that this powerful transformation could be applied to propionate-based natural product syntheses in a concise manner. Further optimization and application of the methodology towards the synthesis of other polyketide-based natural product (i.e. fumonisin B_1) will be discussed in next chapter.

1.4. Experimental Section.

General. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C), NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$) with residual chloroform (δ 7.26 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR), or deuterated benzene (C_6D_6) with residual benzene (δ 7.16 ppm for ^{1}H NMR and δ 128.4 ppm for ^{13}C NMR) taken as the standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m,

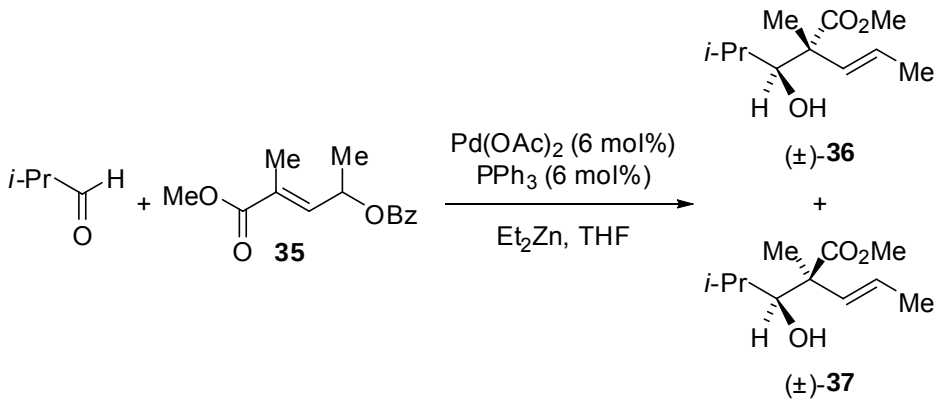
multiplet. IR spectra were collected on a Mattson Genesis II FT-IR spectrometer as neat films. Mass spectra (high resolution APCI) was recorded on a Finnigan LTQ-FTMS Mass spectrometer. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatography using Chiralpak AS-RH (15 cm) and Chiralpak AS (25 cm) columns. Elemental analyses were performed by Atlantic Microlab Inc, P. O. Box 2288, Norcross, Georgia. Optical rotations were measured using a Perkin-Elmer 341 polarimeter. Analytical Thin Layer Chromatography (TLC) was performed on precoated glass backed plates purchased from Whatman (silica gel 60F254; 0.25mm thickness). Flash column chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from EM Science. All reactions were carried out with anhydrous solvents in oven-dried or flame-dried and argon-charged glassware. All anhydrous solvents except as mentioned were dried with 4 Å molecular sieves (beads) purchased from Sigma-Aldrich and tested for trace water content with Coulometric KF Titrator from Denver Instruments. All solvents used in extraction procedures and chromatography were used as received from commercial suppliers without prior purification. All reagents were purchased from Sigma-Aldrich or Strem Chemicals.



35

2-methyl-4-(benzoyloxy)-pent-2-enoic acid methyl ester (35). In a 250 mL round-bottom flask with reflux condenser, *N*-bromosuccinimide (NBS, 9.18 g, 51.2 mmol) was added to a solution of methyl *trans*-2-methyl-2-pentenoate (6.02 g, 46.5 mmol) in CCl_4 (70 mL) at room temperature. The resulting solution was irradiated with a 150 W bulb for 3 h, allowing the reaction mixture to boil to reflux temperature. After cooling, the reaction mixture was diluted with hexane (50 mL) and passed through a short plug of silica. The solvents were removed by rotary evaporation, and the crude mixture containing an allylic bromide was used for the next step, without further purification.

The allylic bromide intermediate was dissolved in DMF (80 mL), and sodium benzoate (9.02 g, 62.5 mmol) was added at room temperature. The resultant solution was stirred at 100 °C for 3 h, cooled to room temperature and diluted with water (200 mL). The allylic benzoate was extracted with ethyl acetate and the organic layer was dried over $MgSO_4$ followed by concentration to afford a yellowish oil. The residue was purified by flash chromatography on silica gel (EtOAc/Hexane = 1:6) to yield compound **35** (7.62 g, 66% for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, 2H, *J* = 8.2, 1.2 Hz), 7.56 (tt, 1H, *J* = 7.0, 1.2 Hz), 7.44 (dd, 2H, *J* = 8.2, 7.0 Hz), 6.75 (dq, 1H, *J* = 8.4, 1.4 Hz), 5.90-5.83 (m, 1H), 3.75 (s, 3H), 1.99 (d, 3H, *J* = 1.4 Hz), 1.47 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 165.8, 139.9, 133.0, 130.1, 129.6, 129.3, 128.3, 68.2, 52.0, 19.7, 12.9; HRMS (APCI): *m/z* calcd. for $C_{14}H_{17}O_4$ (M^+) 249.1127, found 249.1120; FT-IR (KBr) 2988, 2934, 2849, 1718, 1660, 1602, 1451 cm^{-1}.

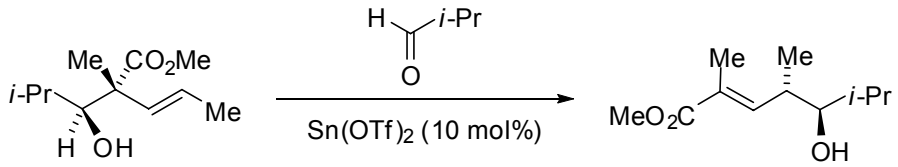


2-(1-Hydroxy-2-methyl-propyl)-2-methylpent-3-enoic acid methyl ester (36, 37). $Pd(OAc)_2$ (67 mg, 0.3 mmol) was dissolved in ***freshly distilled THF*** (33 mL) under argon, and cooled to 0 °C. PPh_3 (79 mg, 0.3 mmol), a solution of isobutyraldehyde (410 mg, 5.68 mmol) and allylic benzoate **35** (1.28 g, 5.16 mmol) in THF (12 mL) were added under argon followed by dropwise addition of diethylzinc (25.80 mL, 1 M in hexane, 25.8 mmol). The mixture was stirred at 0 °C for 5 min and room temperature for 20 h. The reaction was quenched by dropwise addition of 5 % HCl at 0 °C ***(Caution: evolution of ethane gas)*** and diluted with ether. After the mixture was warmed to room temperature the layers were separated and aqueous layer was extracted with ether. The combined organic solution was washed with saturated brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (Ether/Pentane = 1:4) to afford homoallylic alcohol

36 (318 mg, 1.59 mmol) and the diastereomer **37** (477 mg, 2.38 mmol) in 77% combined yield.

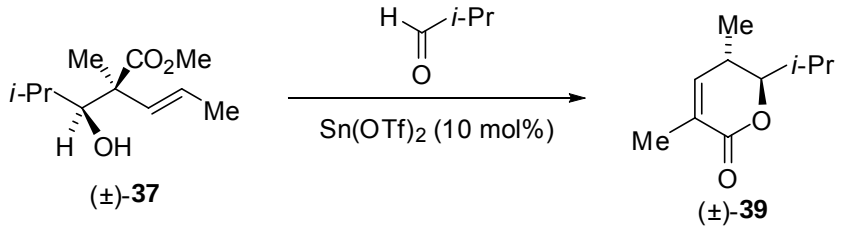
(±)-**36**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (dq, 1H, *J* = 15.6, 1.4 Hz), 5.62 (m, 1H), 3.68 (s, 3H), 3.58 (d, 1H, *J* = 5.2 Hz), 2.31 (bs, 1H), 1.80~1.72 (m, 1H), 1.73 (dd, 3H, *J* = 6.0, 1.4 Hz), 1.29 (s, 3H), 0.92 (d, 3H, *J* = 6.8 Hz), 0.88 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 132.1, 127.0, 80.1, 52.5, 52.0, 30.3, 20.8, 18.3, 18.1, 16.4; HRMS (APCI): *m/z* calcd. for $C_{11}H_{21}O_3$ (M^+) 201.1485, found 201.1482; FT-IR (KBr) 3520, 3030, 2957, 2918, 2883, 1725, 1451 cm^{-1}.

(±)-**37**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (dq, 1H, *J* = 16.0, 1.6 Hz), 5.60~5.51 (m, 1H), 3.69 (s, 3H), 3.55 (d, 1H, *J* = 4.4 Hz), 2.49 (bs, 1H), 1.83~1.73 (m, 1H), 1.71 (dd, 3H, *J* = 6.4, 1.6 Hz), 1.29 (s, 3H), 0.94 (d, 3H, *J* = 6.8 Hz), 0.85 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 132.3, 125.9, 80.8, 52.7, 52.1, 30.1, 21.9, 18.2, 17.7, 17.2; HRMS (APCI): *m/z* calcd. for $C_{11}H_{21}O_3$ (M^+) 201.1485, found 201.1483; FT-IR (KBr) 3509, 3030, 2988, 2922, 2880, 1725, 1451 cm^{-1}.



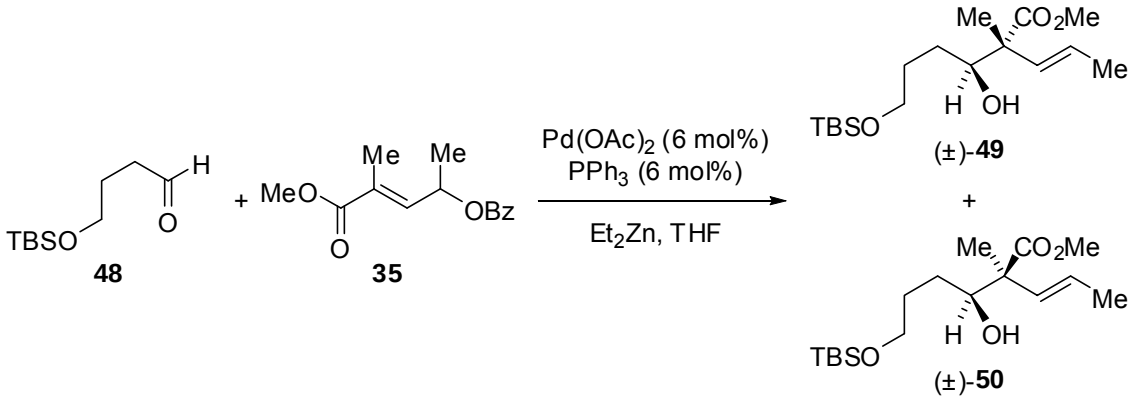
(±)-**36** (±)-**38**

5-Hydroxy-2,4,6-trimethylhept-2-enoic acid methyl ester (38). $Sn(OTf)_2$ (18 mg, 0.042 mmol) was added to a solution of alcohol (±)-**36** (84 mg, 0.42 mmol) and freshly distilled isobutyraldehyde (47 μL, 0.50 mmol) in CH_2Cl_2 (4.0 mL) under argon at room temperature. The resulting solution was stirred at room temperature for 4 h and passed through a short plug of silica (EtOAc/Hexane = 1:4). The solvents were removed by rotary evaporation and the residue was purified by flash chromatography on silica gel (Ether/Pentane = 1:1) to yield alcohol **38** (74 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (dq, 1H, *J* = 10.4, 1.6 Hz), 3.72 (s, 3H), 3.22 (t, 1H, *J* = 5.6 Hz), 2.72-2.67 (m, 1H), 1.87 (d, 3H, *J* = 1.2 Hz), 1.73-1.65 (m, 1H), 1.59 (br s, 1H), 1.01 (d, 3H, *J* = 6.8 Hz), 0.93 (d, 3H, *J* = 6.8 Hz), 0.90 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 143.8, 127.9, 80.1, 51.7, 36.5, 30.9, 19.6, 16.8, 16.7, 12.7; HRMS (APCI): *m/z* calcd. for $C_{11}H_{21}O_3$ (M^+) 201.1491, found 201.1485; FT-IR (KBr) 3497, 2960, 2874, 1712, 1648, 1285 cm^{-1}.



6-Isopropyl-3,5-dimethyl-5,6-dihydropyran-2-one (39). The same procedure for compound **38** was followed using $Sn(OTf)_2$ (64 mg, 0.15 mmol), alcohol **37** (300 mg, 1.50 mmol), freshly distilled isobutyraldehyde (0.16 mL, 1.8 mmol). The residue was purified by flash chromatography on silica gel (Ether/Pentane = 1:5)

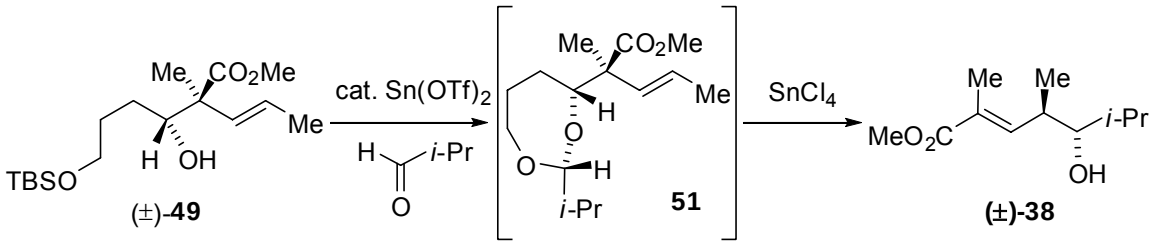
to yield δ-lactone **39** (227 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32-6.30 (m, 1H), 3.85 (dd, 1H, *J* = 10.0, 2.8 Hz), 2.58-2.52 (m, 1H), 1.96-1.90 (m, 1H), 1.87 (dd, 3H, *J* = 2.0, 1.2 Hz), 1.06 (d, 3H, *J* = 4.0 Hz), 1.04 (d, 3H, *J* = 4.0 Hz), 0.94 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 146.1, 127.1, 87.8, 31.1, 28.9, 19.6, 16.8, 16.4, 15.3; HRMS (APCI): *m/z* calcd. for $C_{10}H_{17}O_2$ (M^+) 169.1229, found 169.1222; FT-IR (KBr) 2968, 2880, 1718, 1459 cm^{-1}.



Homoallylic alcohol (49, 50). The same procedure for compound **36** and **37** was followed using $Pd(OAc)_2$ (40 mg, 0.18 mmol) , PPh_3 (47 mg, 0.18 mmol), aldehyde **40** (605 mg, 2.99 mmol), allylic benzoate **27** (817 mg, 3.29 mmol) and diethylzinc (15.00 mL, 1 M in hexane, 15 mmol). The residue was purified by flash chromatography on silica gel to yield **49** (310 mg) and diastereomer **50** (313 mg) in 63% combined yield.

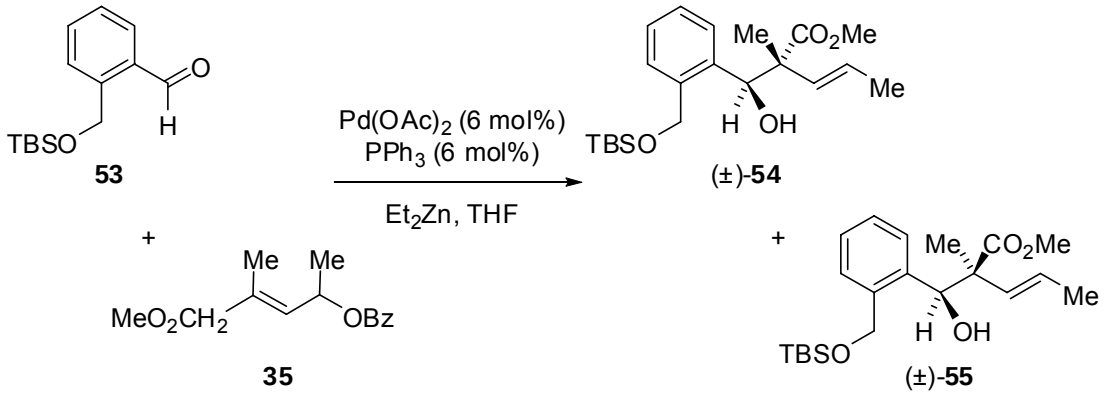
(±)-**49**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.73 (dq, 1H, *J* = 16.2, 1.8 Hz), 5.62-5.56 (m, 1H), 3.78 (dd, 1H, *J* = 10.2, 1.2 Hz), 3.69 (s, 3H), 3.68-3.61 (m, 2H), 2.83 (bs, 1H), 1.77-1.71 (m, 1H), 1.74 (dd, 3H, *J* = 6.0, 1.8 Hz), 1.64-1.47 (m, 2H), 1.36-1.29 (m, 1H), 1.25 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

(±)-**50**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.59-5.49 (m, 2H), 3.86 (dd, 1H, *J* = 10.2, 5.4 Hz), 3.69 (s, 3H), 3.66-3.63 (m, 2H), 2.85 (d, 1H, *J* = 5.4 Hz), 1.74-1.71 (m, 1H), 1.69 (dd, 3H, *J* = 6.0, 1.2 Hz), 1.62-1.57 (m, 2H), 1.25-1.20 (m, 1H), 1.25 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 131.7, 126.5, 75.8, 63.1, 53.6, 52.0, 29.9, 28.1, 25.9, 18.2, 15.1, -5.4.



5-Hydroxy-2,4,6-trimethylhept-2-enoic acid methyl ester (38). $Sn(OTf)_2$ (13 mg, 0.03 mmol) was added to a solution of alcohol **49** (100 mg, 0.30 mmol) and freshly distilled isobutyraldehyde (24 mg, 0.33 mmol) in CH_2Cl_2 (3.0 mL) under argon at room temperature. The resulting solution was stirred at room temperature for 1 h and passed through a short plug of silica (EtOAc/Hexane = 1:8). The solvents were removed by rotary evaporation and the crude cyclic acetal **51** was used for the next step without further purification. The crude acetal **51** was dissolved in $MeNO_2$ (1.5 mL) and CH_2Cl_2 (1.5 mL) under argon, and $SnCl_4$ (0.03 mL, 1 M in CH_2Cl_2, 0.03 mmol) were added at 0 ˚C. The resulting solution was stirred at 0 ˚C for 5 h before quenching with saturated aqueous $NaHCO_3$ (3 mL). The salts were filtered off with Celite and the extractions were performed with CH_2Cl_2. The combined organic layers were dried

($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (Ether/Pentane = 1:1) to yield alcohol **38** (47 mg, 90%).

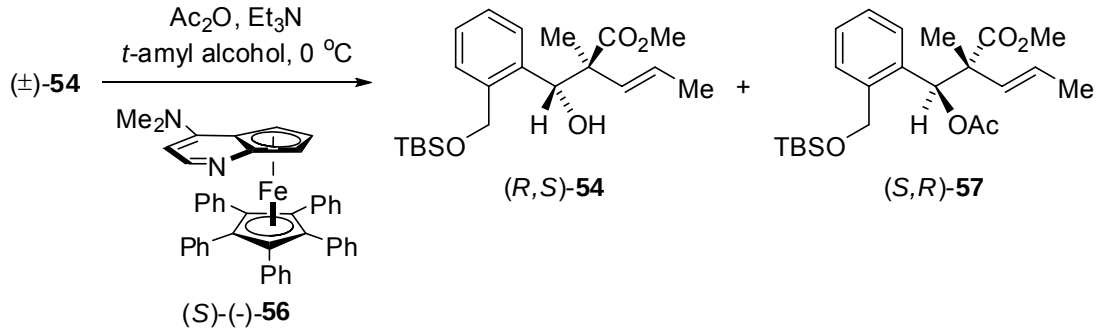


2-{[2-(*tert*-Butyldimethylsilanyloxymethyl)-phenyl]-hydroxymethyl}-2-methylpent-3-enoic acid methyl ester (54, 55). $Pd(OAc)_2$ (61 mg, 0.27 mmol) was dissolved in ***freshly distilled THF*** (30 mL) under argon, and cooled to 0 °C. PPh_3 (71 mg, 0.27 mmol), a solution of aldehyde **53** (1.11 g, 4.43 mmol) and allylic benzoate **35** (1.10 g, 4.43 mmol) in THF (10 mL) were added under argon followed by dropwise addition of diethylzinc (22.15 mL, 1 M in hexane, 22 mmol). The mixture was stirred at 0 °C for 5 min and room temperature for 20 h. The reaction was quenched by dropwise addition of 5 % HCl at 0 °C ***(Caution: evolution of ethane gas)*** and diluted with ether. After the mixture was warmed to room temperature the layers were separated and aqueous layer was extracted

with ether. The combined organic solution was washed with saturated brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (Ether/Pentane = 1:6 with 1~2% methanol) to afford homoallylic alcohol **54** (348 mg, 0.92 mmol) and the diastereomer **55** (984 mg, 2.60 mmol) in 80% combined yield.

(±)-**54**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 1H, *J* = 7.2 Hz), 7.36 (dd, 1H, *J* = 7.6, 1.6 Hz), 7.29-7.20 (m, 2H), 5.90 (dq, 1H, *J* = 16.0, 1.8 Hz), 5.47-5.38 (m, 1H), 5.21 (s, 1H), 4.79 (dd, 2H, *J* = 12.8 Hz), 3.73 (s, 3H), 1.75 (dd, 3H, *J* = 6.4, 1.8 Hz), 1.17 (s, 3H), 0.93 (s, 9H), 0.099 (s, 3H), 0.097 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 138.9, 137.0, 129.4, 128.1, 127.7, 127.3, 127.2, 126.5, 73.9, 63.1, 53.5, 52.4, 25.9, 18.7 (two overlapping carbons), 18.3, -5.3; HRMS (APCI): *m/z* calcd. for $C_{21}H_{35}O_4Si$ (M^+) 379.2305, found 379.2299; FT-IR (KBr) 3475, 3034, 2953, 1724, 1462, 1253 cm^{-1}; Anal. calcd. for $C_{21}H_{34}O_4Si$: C, 66.62; H, 9.05, found: C, 66.78; H, 9.10.

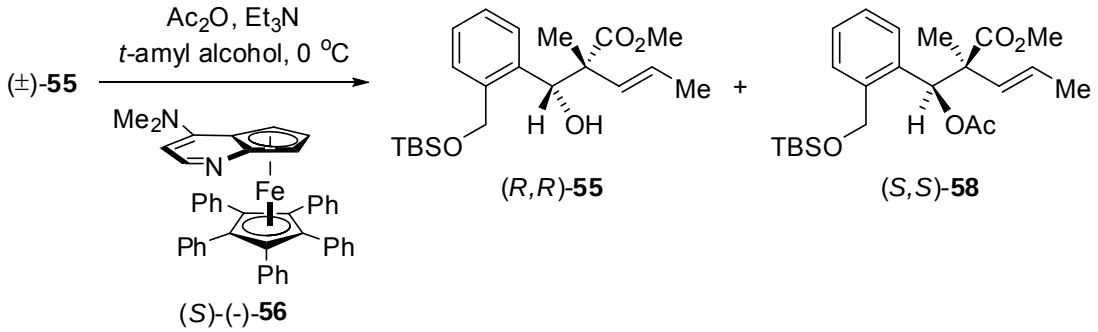
(±)-**55**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.31 (m, 2H), 7.19-7.15 (m, 2H), 5.34 (dq, 1H, *J* = 15.6, 1.4 Hz), 5.27-5.22 (m, 1H), 5.23 (s, 1H), 4.64 (dd, 2H, *J* = 13.2 Hz), 3.67 (s, 3H), 1.52 (dd, 3H, *J* = 6.0, 1.4 Hz), 1.17 (s, 3H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 138.8, 137.0, 131.6, 127.6, 127.5, 127.0, 126.6, 126.4, 73.2, 62.9, 54.8, 52.2, 25.9, 18.3, 18.2, 16.0, -5.3; HRMS (APCI): *m/z* calcd. for $C_{21}H_{35}O_4Si$ (M^+) 379.2305, found 379.2299; FT-IR (KBr) 3497, 3034, 2953, 1725, 1459, 1254 cm^{-1}; Anal. calcd. for $C_{21}H_{34}O_4Si$: C, 66.62; H, 9.05, found: C, 66.77; H, 9.18.



Kinetic resolution of 54. The racemic homoallylic alcohol (±)-**54** (1.42 g, 3.75 mmol), catalyst (*S*)-(-)-C_5Ph_5-DMAP **56** (20 mg, 0.03 mmol) and triethylamine (0.39 mL, 2.8 mmol) in *tert*-amyl alcohol (8.8 mL) was gently heated to dissolve the catalyst. After the catalyst was completely dissolved, the purple solution was cooled in an ice bath and acetic anhydride (0.27 mL, 2.8 mmol) was added by syringe. The resulting solution was stirred at 0 °C for 114 h and quenched with methanol (2.5 mL). The mixture was passed through a short plug of silica (EtOAc/Hexane = 1:2, then 10% triethylamine in EtOAc) to separate the alcohol and the acetate from the catalyst. The solution of alcohol and acetate was concentrated and the residue was purified by flash chromatography (Ether/Pentane = 1:4), which provided 740 mg of acetate (*S*, *R*)-**57** in 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 1H, *J* = 7.6 Hz), 7.29 (ddd, 1H, *J* = 6.8, 6.8, 1.6 Hz), 7.23 (dd, 1H, *J* = 7.6, 1.6 Hz), 7.16 (t, 1H, *J* = 6.8 Hz), 6.22 (s, 1H), 5.98 (dq, 1H, *J* = 16, 1.6 Hz), 5.39-5.31 (m, 1H), 4.97 (AB, 2H, *J* = 13.6 Hz), 3.69 (s,

3H), 2.01 (s, 3H), 1.78 (dd, 3H, *J* = 6.0, 1.6 Hz), 1.15 (s, 3H), 0.97 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 169.5, 139.9, 133.1, 129.0, 128.3, 128.2, 127.6, 126.1, 125.8, 74.3, 62.1, 52.6, 52.3, 26.0, 20.9, 18.4, 18.3, 18.2, -5.3, -5.4; HRMS (APCI): *m/z* calcd. for $C_{23}H_{37}O_5Si$ (M^+) 421.2410, found 421.2399; FT-IR (KBr) 3034, 2953, 1741, 1231 cm^{-1}; $[\alpha]^{25}_D$ = +17.1 (c = 1.1, $CHCl_3$).

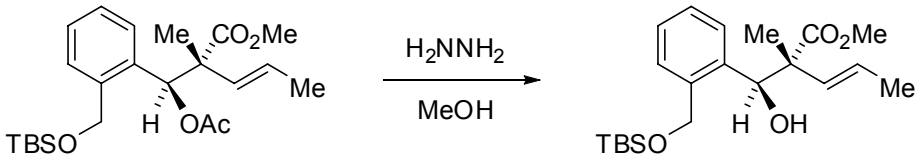
636 mg of alcohol (*R*, *S*)-**54** was isolated in 45% yield and reverse phase HPLC analysis of the alcohol revealed 87% ee (Chiralpak AS-RH); $[\alpha]^{25}_D$ = -74.3 (c = 1.2, $CHCl_3$).



Kinetic resolution of 55. The kinetic resolution procedure was followed using the racemic homoallylic alcohol (±)-**55** (1.01 g, 2.67 mmol), catalyst (*S*)-(-)-C_5Ph_5-DMAP **56** (18 mg, 0.03 mmol), triethylamine (0.27 mL, 2.0 mmol), *tert*-amyl alcohol (5.5 mL) and acetic anhydride (0.19 mL, 2.0 mmol). Reaction time: 119 h. The crude mixture was purified by flash chromatography (Ether/Pentane = 1:3), which provided 499 mg of acetate (*S*, *S*)-**58** in 44% yield. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.57 (d, 1H, *J* = 8.0 Hz), 7.33-7.27 (m, 2H), 7.22-7.19 (m, 2H), 6.24 (s, 1H), 5.36-5.30 (m, 2H), 4.90 (AB, 2H, *J* = 13.6 Hz), 3.74 (s, 3H), 2.00 (s, 3H), 1.59 (d, 3H, *J* = 4.8 Hz), 1.35 (s, 3H), 0.97 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 169.2, 139.9, 132.7, 130.0, 128.0, 127.3, 127.2, 125.9, 125.6, 73.4, 61.8, 53.7, 52.2, 26.0, 20.9, 18.4, 18.2, 16.1, -5.3, -5.5; HRMS (APCI): *m/z* calcd. for $C_{23}H_{37}O_5Si$ (M^+) 421.2410, found 421.2397; FT-IR (KBr) 3034, 2995, 1745, 1231 cm^{-1}; $[\alpha]^{25}_D$ = -50.0 (c = 0.23, $CHCl_3$).

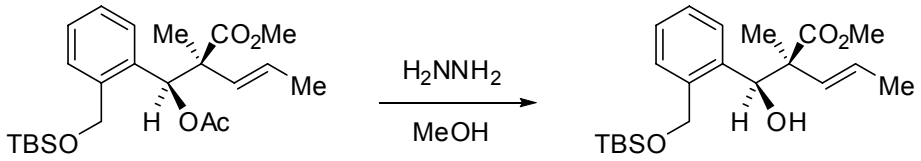
461 mg of alcohol (*R*, *R*)-**55** was isolated in 46% yield and reverse phase HPLC analysis of the alcohol revealed 89% ee (Chiralpak AS-RH); $[\alpha]^{25}_D$ = +16.0 (c = 0.3, $CHCl_3$).



(*S*,*R*)-**57** (*S*,*R*)-**54**

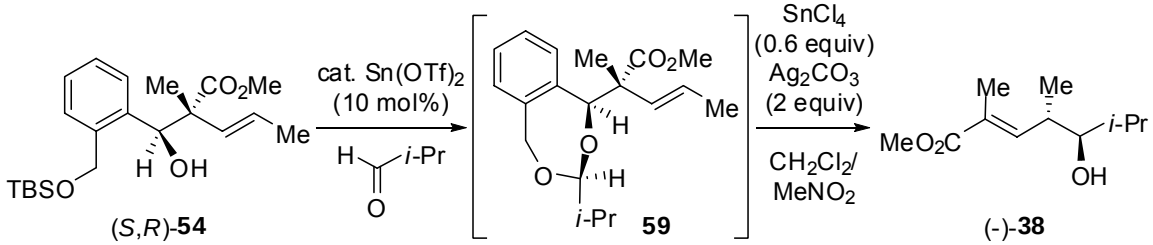
Basic methanolysis of 57. Acetate (*S*, *R*)-**57** (665 mg, 1.58 mmol) was dissolved in methanol (7 mL) under argon at 0 °C, and anhydrous hydrazine (0.99 mL, 31 mmol) was added. The reaction was maintained at 0 °C for additional 3 h before quenching with saturated $CuSO_4$ (5 mL). The precipitate was filtered off and the extractions were performed with ether. The combined organic layers were dried over $MgSO_4$ and concentrated to afford yellowish oil. The crude product was purified by flash chromatography on silica gel

(Ether/Pentane = 1:4) to yield alcohol (*S*, *R*)-**54** (438 mg, 73%); reverse phase HPLC analysis of the alcohol revealed 85 % ee (Chiralpak AS-RH); $[\alpha]^{25}_{D}$ = +72.0 (c = 2.8, $CHCl_3$).



(*S*,*S*)-**58** (*S*,*S*)-**55**

Basic methanolysis of 58. Acetate (*S*, *S*)-**58** (463 mg, 1.10 mmol) was dissolved in methanol (5 mL) under argon at 0 ^{o}C, and anhydrous hydrazine (0.69 mL, 22 mL) was added. The reaction was maintained at 0 ^{o}C for additional 3 h before quenching with saturated $CuSO_4$ (4 mL). The precipitate was filtered off and the extractions were performed with ether. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a yellowish oil. The crude product was purified by flash chromatography on silica gel (Ether/Pentane = 1:3) to yield alcohol (*S*, *S*)-**55** (314 mg, 75%); reverse phase HPLC analysis of the alcohol revealed 90% ee (Chiralpak AS-RH); $[\alpha]^{25}_{D}$ = -17.7 (c = 2.8, $CHCl_3$).

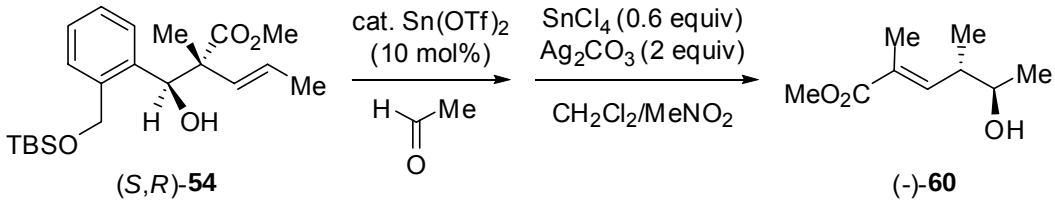


(*S*,*R*)-**54** **59** (-)-**38**

(4*S*, 5*R*)-5-Hydroxy-2,4,6-trimethylhept-2-enoic acid methyl ester (38). General procedure for bispropionate transfer (simple aldehydes, Scheme 5): $Sn(OTf)_2$ (13 mg, 0.032 mmol) was added to a solution of alcohol (*S*, *R*)-**54** (120 mg, 0.32 mmol) and freshly distilled isobutyraldehyde (27 mg, 0.38 mmol) in CH_2Cl_2 (3.2 mL) under argon at room temperature. The resulting solution was stirred at room temperature for 1 h and passed through a short plug of silica (EtOAc/Hexane = 1:4). The solvents were removed by rotary evaporation and the crude cyclic acetal **59** was used for the next step without further purification. The crude acetal **59** was dissolved in $MeNO_2$ (1.6 mL) and CH_2Cl_2 (1.6 mL) under argon, and Ag_2CO_3 (174 mg, 0.64 mmol) and $SnCl_4$ (0.19 mL, 1 M in CH_2Cl_2, 0.2 mmol) were added at room temperature. The resulting solution was stirred at room temperature for 75 min before quenching with saturated aqueous $NaHCO_3$ (3 mL). The salts were filtered off with Celite and the extractions were performed with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (Ether/Pentane = 1:1) to yield alcohol **38** (47 mg, 73%); $[\alpha]^{25}_D$ = -12.8 (c = 0.7, $CHCl_3$); Mosher ester analysis of the alcohol revealed 11:1 er (83% ee).

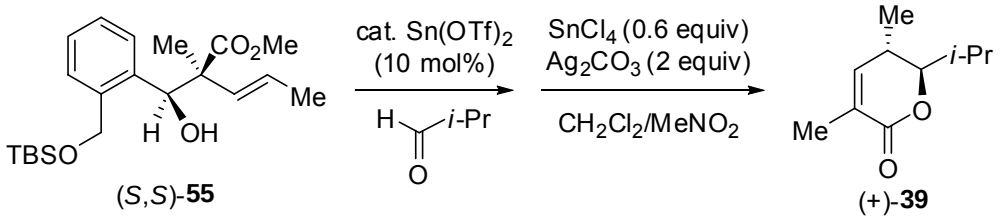
Acetal **59** is a single diastereomer and the relative stereochemistry was confirmed by nOe (nuclear Overhauser effect) experiment. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.17 (m, 3H), 7.14-7.12 (m, 1H), 5.93 (dq, 1H, *J* = 16, 1.6 Hz), 5.47-5.39 (m, 1H), 5.24 (s, 1H), 4.83 (AB, 2H, *J* = 13.0 Hz), 4.54 (d, 1H, *J* = 5.6 Hz), 3.71 (s, 3H), 1.87-1.79 (m, 1H), 1.68 (dd, 3H, *J* = 6.4, 1.6 Hz), 1.42 (s, 3H),

0.91 (d, 6H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 138.8, 137.2, 131.7, 129.6, 127.6, 127.3, 126.6, 125.9, 107.7, 85.6, 69.4, 53.2, 52.2, 33.1, 18.2, 17.8, 17.6, 17.0. HRMS (APCI): *m/z* calcd. for $C_{19}H_{27}O_4$ (M^+) 319.1909, found 319.1904; FT-IR (KBr) 2956, 1732, 1452, 1243 cm^{-1}.

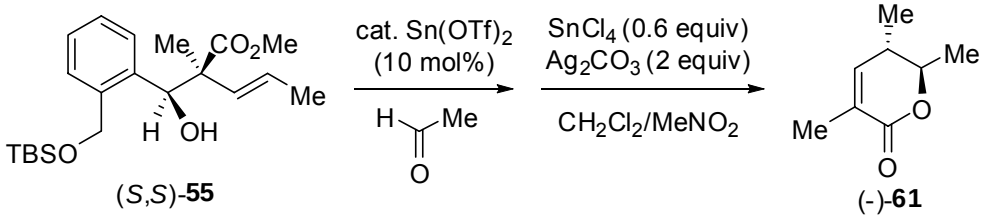


(*S*,*R*)-**54** (-)-**60**

(4*S*, 5*R*)-5-Hydroxy-2,4-dimethylhex-2-enoic acid methyl ester (60). The general procedure was followed using $Sn(OTf)_2$ (13 mg, 0.03 mmol), alcohol (*S*, *R*)-**54** (100 mg, 0.26 mmol), acetaldehyde (14 mg, 0.32 mmol), Ag_2CO_3 (143 mg, 0.52 mmol) and $SnCl_4$ (0.13 mL, 1 M in CH_2Cl_2, 0.1 mmol). The residue was purified by flash chromatography on silica gel (Ether/Pentane = 1:1) to yield homoallylic alcohol **60** (30 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (dq, 1H, *J* = 10.4, 1.4 Hz), 3.75 (s, 3H), 3.73-3.67 (m, 1H), 2.57-2.48 (m, 1H), 1.88 (d, 3H, *J* = 1.4 Hz), 1.20 (d, 3H, *J* = 6.4 Hz), 1.03 (d, 3H, *J* = 6.4 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 168.5, 143.8, 128.8, 71.3, 51.8, 40.9, 20.7, 16.1, 12.8; HRMS (APCI): *m/z* calcd. for $C_9H_{17}O_3$ (M^+) 173.1178, found 173.1173; FT-IR (KBr) 3459, 2972, 2876, 1710, 1648, 1436, 1243 cm^{-1}; $[\alpha]^{25}_D$ = -28 (c = 0.13, $CHCl_3$); Mosher ester analysis of the alcohol revealed 11:1 er (83% ee).

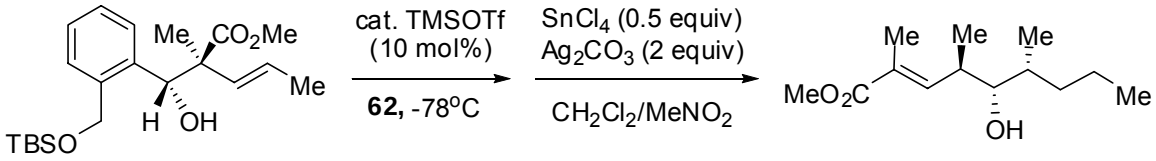


(5*S*, 6*R*)-6-Isopropyl-3,5-dimethyl-5,6-dihydropyran-2-one (39). The general procedure was followed using $Sn(OTf)_2$ (8 mg, 0.02 mmol), alcohol (*S*, *S*)-**55** (76 mg, 0.20 mmol), freshly distilled isobutyraldehyde (15 mg, 0.20 mmol), Ag_2CO_3 (109 mg, 0.40 mmol) and $SnCl_4$ (0.12 mL, 1 M in CH_2Cl_2, 0.1 mmol). The residue was purified by flash chromatography on silica gel (Ether/Pentane = 1:5) to yield δ-lactone **39** (31 mg, 92%); $[\alpha]^{25}_D$ = +23.5 (c = 1.4, $CHCl_3$); normal phase HPLC analysis of the lactone revealed 89 % ee (Chiralpak AS).



(5*S*, 6*R*)-3,5,6-trimethyl-5,6-dihydropyran-2-one (61). The general procedure was followed using $Sn(OTf)_2$ (8 mg, 0.02 mmol), alcohol (*S*, *S*)-**55** (55 mg, 0.13 mmol), acetaldehyde (8 mg, 0.2 mmol), Ag_2CO_3 (72 mg, 0.26 mmol) and $SnCl_4$ (0.07 mL, 1 M in CH_2Cl_2, 0.1 mmol). The residue was purified by flash chromatography on silica gel (Ether/Pentane = 1:2) to yield δ-lactone **61** (17 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33-6.32 (m, 1H), 4.16-4.09 (m, 1H), 2.43-2.36 (m, 1H), 1.91-1.90 (m, 3H), 1.40 (d, 3H, *J* = 6.0 Hz), 1.09 (d, 3H, *J* = 7.2

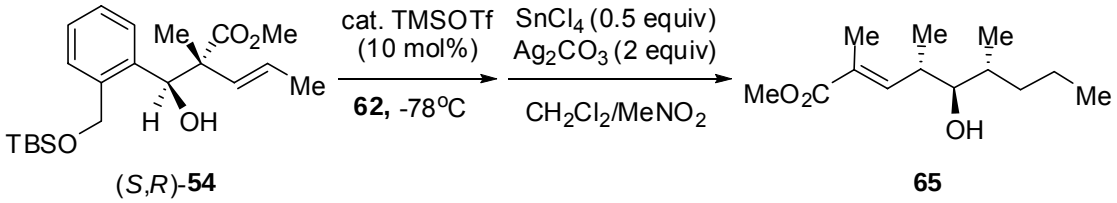
Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 145.6, 127.3, 80.1, 35.6, 19.1, 16.8, 16.4; HRMS (APCI): *m/z* calcd. for $C_8H_{13}O_2$ (M^+) 141.0916, found 141.0909; FT-IR (KBr) 2980, 2883, 1718, 1451 cm^{-1}; $[\alpha]^{25}_D$ = -45 (c = 0.1, $CHCl_3$); normal phase HPLC analysis of the lactone revealed 88% ee (Chiralpak AS).



(*R*,*S*)-**54** **64**

(4*R*, 5*S*, 6*R*)-5-Hydroxy-2,4,6-trimethylnon-2-enoic acid methyl ester (64). General procedure A for bispropionate transfer to *alpha*-chiral aldehydes (Table 1): Alcohol (*R*, *S*)-**54** (50 mg, 0.13 mmol) and (2*R*)-2-methylpentanal **62** (16 mg, 0.16 mmol) were dissolved in CH_2Cl_2 (1.3 mL), cooled to -78 °C, and TMSOTf (3 mg, 0.01 mmol) was added dropwise. The resulting solution was stirred at -78 °C for 4 h and quenched with pyridine (10 μL). The reaction mixture was passed through a short plug of silica (EtOAc/Hexane = 1:4). The solvents were removed by rotary evaporation and the residue was used for the next transformation without further purification. The crude acetal intermediate was dissolved in $MeNO_2$ (0.7 mL) and CH_2Cl_2 (0.7 mL) under argon, and Ag_2CO_3 (72 mg, 0.26 mmol) and $SnCl_4$ (0.065 mL, 1 M in CH_2Cl_2, 0.07 mmol) were added at room temperature. The resulting solution was stirred at room temperature for 75 min before quenched with saturated aqueous $NaHCO_3$ (3 mL). The salts were filtered off with celite and the extractions were performed with CH_2Cl_2. The

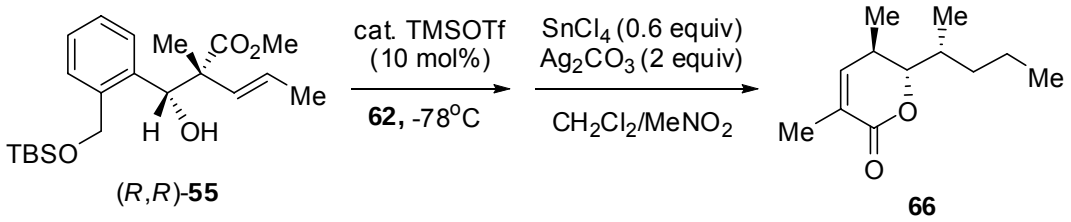
combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (Ether/Pentane = 1:3) to yield homoallylic alcohol **64** (22 mg, 75%). ^{1}H NMR analysis of the alcohol revealed 12:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dq, 1H, *J* = 10.0, 1.2 Hz), 3.73 (s, 3H), 3.35 (dd, 1H, *J* = 7.4, 4.0 Hz), 2.73-2.67 (m, 1H), 1.88 (d, 3H, *J* = 1.2 Hz), 1.64-1.58 (m, 1H), 1.46 (br s, 1H), 1.39-1.18 (m, 4H), 0.97 (d, 3H, *J* = 6.8 Hz), 0.92-0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 144.7, 128.2, 78.1, 51.8, 36.8, 36.2, 34.7, 20.2, 16.4, 14.3, 12.9, 12.8; HRMS (APCI): *m/z* calcd. for $C_{13}H_{25}O_3$ (M^+) 229.1804, found 211.1693 (M^+-H_2O); FT-IR (KBr) 3494, 2963, 2879, 1710, 1645, 1438, 1240 cm^{-1}.



(*S*,*R*)-**54** **65**

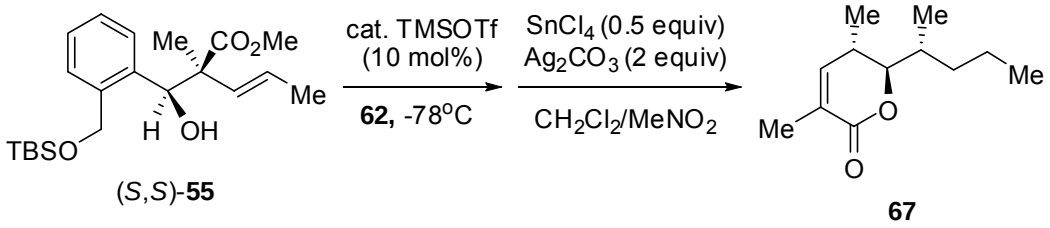
(4*S*, 5*R*, 6*R*)-5-Hydroxy-2,4,6-trimethylnon-2-enoic acid methyl ester (65). The general procedure A was followed using TMSOTf (4 mg, 0.02 mmol), alcohol (*S*, *R*)-**54** (68 mg, 0.18 mmol), (2*R*)-2-methylpentanal **62** (22 mg, 0.22 mmol), Ag_2CO_3 (99 mg, 0.36 mmol) and $SnCl_4$ (0.09 mL, 1 M in CH_2Cl_2, 0.09 mmol). The residue was purified by flash chromatography on silica gel (Ether/Pentane = 1:3) to yield homoallylic alcohol **65** (32 mg, 78%). ^{1}H NMR analysis of the alcohol revealed 10:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (dq, 1H, *J* = 10.0, 1.6 Hz), 3.74 (s, 3H), 3.29 (dd, 1H, *J* = 6.0, 5.6 Hz), 2.77-2.70 (m, 1H), 1.88 (d, 3H, *J* =

1.6 Hz), 1.56-1.40 (m, 3H), 1.27-1.10 (m, 2H), 1.03 (d, 3H, *J* = 7.2 Hz), 0.91 (t, 3H, *J* = 7.2 Hz), 0.88 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 143.9, 128.1, 79.9, 52.0, 36.5, 36.1, 33.5, 20.3, 17.2, 16.5, 14.7, 12.9; HRMS (APCI): *m/z* calcd. for $C_{13}H_{25}O_3$ (M^+) 229.1804, found 211.1692 (M^+-H_2O); FT-IR (KBr) 3497, 2961, 2876, 1710, 1648, 1436, 1239 cm^{-1}.



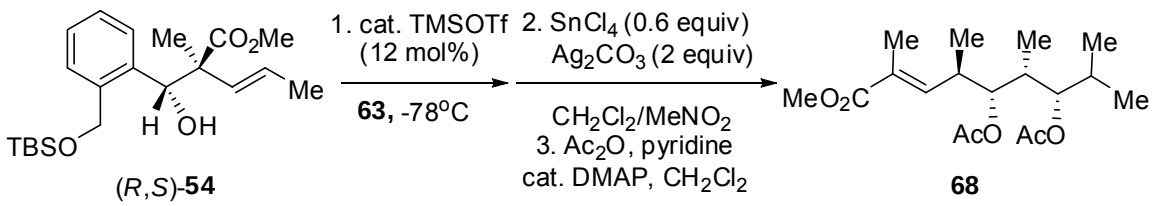
(*R*,*R*)-**55** **66**

(5*R*, 6*S*, 1'*R*)-3,5-Dimethyl-6-(1'-methylbutyl)-5,6-dihydropyran-2-one (66). The general procedure A was followed using TMSOTf (7 mg, 0.03 mmol), alcohol (*R*, *R*)-**55** (107 mg, 0.28 mmol), (2*R*)-2-methylpentanal **62** (38 mg, 0.38 mmol), Ag_2CO_3 (154 mg, 0.56 mmol) and $SnCl_4$ (0.17 mL, 1 M in CH_2Cl_2, 0.2 mmol). The residue was purified by flash chromatography on silica gel (Ether/Pentane = 1:5) to yield δ-lactone **66** (50 mg, 89%). ^{1}H NMR analysis of the lactone revealed 14:1 dr; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34-6.33 (m, 1H), 3.97 (dd, 1H, *J* = 10.8, 2.4 Hz), 2.66-2.58 (m, 1H), 1.91-1.90 (m, 3H), 1.76-1.70 (m, 1H), 1.52-1.29 (m, 4H), 1.05 (d, 3H, *J* = 7.2 Hz), 0.94 (d, 3H, *J* = 6.8 Hz), 0.90 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 146.4, 127.1, 86.1, 35.6, 33.4, 31.0, 20.4, 16.8, 16.2, 14.1, 13.1; FT-IR (KBr) 2961, 1718, 1459, 1382 cm^{-1}; HRMS (APCI): *m/z* calcd. for $C_{12}H_{21}O_2$ (M^+) 197.1542, found 197.1534; $[\alpha]^{25}_D$ = -28.9 (c = 0.40, $CHCl_3$).



(*S*,*S*)-**55** **67**

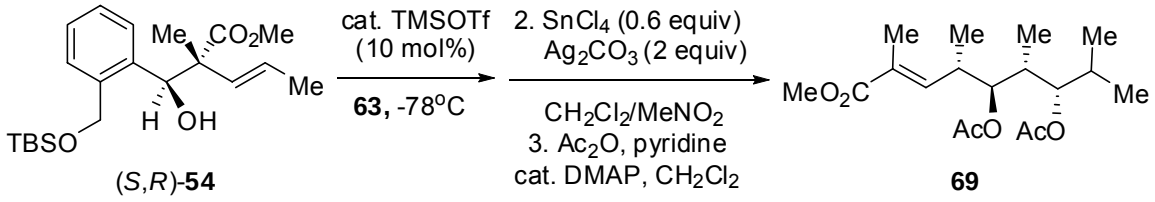
(5*S*, 6*R*, 1'*R*)-3,5-Dimethyl-6-(1'-methylbutyl)-5,6-dihydropyran-2-one (67). The general procedure A was followed using TMSOTf (3 mg, 0.01 mmol), alcohol (*S*, *S*)-**55** (50 mg, 0.13 mmol), (2*R*)-2-methylpentanal **62** (16 mg, 0.16 mmol), Ag_2CO_3 (72 mg, 0.26 mmol) and $SnCl_4$ (0.065 mL, 1 M in CH_2Cl_2, 0.07 mmol). The residue was purified by flash chromatography on silica gel (Ether/Pentane = 1:5) to yield yield δ-lactone **67** (22 mg, 85%). ^{1}H NMR analysis of the lactone revealed 14:1 dr; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35-6.33 (m, 1H), 3.92 (dd, 1H, *J* = 9.6, 3.2 Hz), 2.69-2.60 (m, 1H), 1.90-1.89 (m, 3H), 1.82-1.77 (m, 1H), 1.52-1.18 (m, 4H), 1.07 (d, 3H, *J* = 7.2 Hz), 1.05 (d, 3H, *J* = 6.8 Hz), 0.90 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 146.1, 127.0, 88.2, 33.7, 32.0, 30.7, 20.4, 16.8, 16.7, 16.6, 14.2; FT-IR (KBr) 2964, 1718, 1459, 1135 cm^{-1}; HRMS (APCI): *m/z* calcd. for $C_{12}H_{21}O_2$ (M^+) 197.1542, found 197.1535.



(*R*,*S*)-**54** **68**

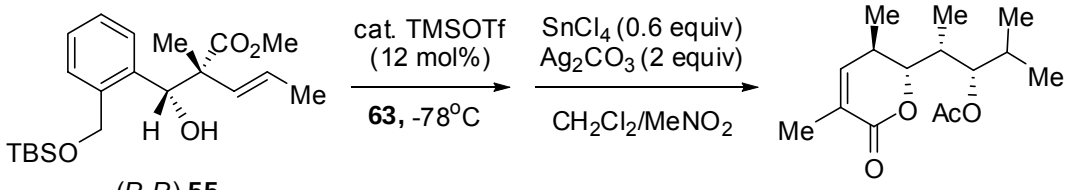
(4*R*, 5*R*, 6*R*, 7*S*)-5,7-Diacetoxy-2,4,6,8-tetramethylnon-2-enoic acid methyl ester (68). General procedure B for bispropionate transfer (Table 1): Alcohol (*R*, *S*)-**54** (60 mg, 0.16 mmol) and (2*R*, 3*S*)-3-acetoxy-2,4-dimethylpentanal **63** (30 mg, 0.17 mmol) were dissolved in CH_2Cl_2 (1.6 mL), cooled to -78 °C, and TMSOTf (5 mg, 0.02 mmol) was added dropwise. The resulting solution was stirred at -78 °C for 4 h and quenched with pyridine (10 µL). The reaction mixture was passed through a short plug of silica (EtOAc/Hexane = 1:4). The solvents were removed by rotary evaporation and the residue was used for next transformation without further purification. The crude acetal intermediate was dissolved in $MeNO_2$ (0.8 mL) and CH_2Cl_2 (0.8 mL) under argon atmosphere, and Ag_2CO_3 (88 mg, 0.32 mmol) and $SnCl_4$ (0.1 mL, 1 M in CH_2Cl_2, 0.1 mmol) were added at room temperature. The resulting solution was stirred at room temperature for 1.5 h before quenching with saturated aqueous $NaHCO_3$ (3 mL). The salts were filtered off with celite and the extractions were performed with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/Hexane = 1:2) to yield homoallylic alcohol (35 mg, 73%). ^1H NMR analysis of the alcohol revealed a 3:2 mixture indicating partial migration of the acetate protective group. The alcohol mixture (26 mg, 0.09 mmol) in a flask was charged with argon and added CH_2Cl_2 (1 mL), pyridine (29 µL, 0.36 mmol), acetic anhydride (25 µL) and DMAP (1 mg, 0.005 mmol) at 0 °C. After the addition, the resulting solution was allowed to warm to room temperature and

stirred for another 2 h before quenching with water. The extractions was performed with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/Hexane = 1 : 4) to yield diacetate **68** in 95 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (dq, 1H, *J* = 10.8, 1.6 Hz), 4.81 (dd, 1H, *J* = 8.0, 4.4 Hz), 4.62 (dd, 1H, *J* = 8.0, 3.6 Hz), 3.75 (s, 3H), 3.11-3.05 (m, 1H), 2.10 (s, 3H), 2.08 (s, 3H), 1.93(d, 3H, *J* = 1.6 Hz), 1.94-1.97 (m, 2H), 0.94 (d, 3H, *J* = 6.8 Hz), 0.87 (d, 3H, *J* = 6.8 Hz), 0.84 (d, 3H, *J* = 6.8 Hz), 0.77 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.7, 168.5, 141.9, 128.4, 77.9, 51.9, 36.8, 34.7, 29.6, 20.9, 20.8, 19.0, 18.4, 16.7, 12.7, 9.5; HRMS (APCI): *m/z* calcd. for $C_{18}H_{31}O_6$ (M^+) 343.2121, found 283.1905 (M^+-HOAc); FT-IR (KBr) 2972, 1738, 1237 cm^{-1}; $[\alpha]^{25}_D$ = -15.9 (c = 1.04, $CHCl_3$).



(4*S*, 5*S*, 6*R*, 7*S*)-5,7-Diacetoxy-2,4,6,8-tetramethylnon-2-enoic acid methyl ester (69). The general procedure B was followed using TMSOTf (2 mg, 0.009 mmol), alcohol (*S*, *R*)-**54** (35 mg, 0.09 mmol), (2*R*, 3*S*)-3-acetoxy-2,4-dimethylpentanal **63** (19 mg, 0.11 mmol) Ag_2CO_3 (50 mg, 0.18 mmol) and $SnCl_4$ (54 µL, 1 M in CH_2Cl_2, 0.05 mmol). Reaction time: 4 h. The residue was not purified and used for acetylation to provide diacetate **69** in 62 % yield. ^{1}H NMR

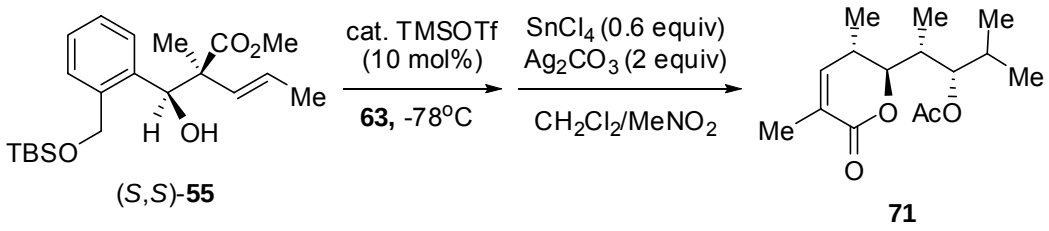
analysis of the diacetate revealed 9:1 dr. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.68 (dq, 1H, *J* = 10.8, 1.8 Hz), 4.82 (dd, 1H, *J* = 9.6, 4.2 Hz), 4.78 (dd, 1H, *J* = 10.2, 2.4 Hz), 3.75 (s, 3H), 2.95-2.91 (m, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.94-1.89 (m, 1H), 1.87 (d, 3H, *J* = 1.8 Hz), 1.85-1.80 (m, 1H), 0.96 (d, 3H, *J* = 7.2 Hz), 0.89 (d, 3H, *J* = 6.6 Hz), 0.87 (d, 3H, *J* = 7.2 Hz), 0.85 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 170.8, 168.5, 141.7, 128.3, 76.3, 76.2, 51.9, 36.0, 35.0, 30.0, 21.1, 21.0, 19.6, 18.8, 16.9, 12.5, 9.8; HRMS (APCI): *m/z* calcd. for $C_{18}H_{31}O_6$ (M^+) 343.2121, found 283.1906 (M^+-HOAc); FT-IR (KBr) 2971, 1737, 1238 cm^{-1}; $[\alpha]^{25}_D$ = +25.3 (c = 0.32, $CHCl_3$).



(*R*,*R*)-**55** **70**

(5*R*, 6*S*, 1'*R*, 2'*S*)-3,5-Dimethyl-6-(1',3'-dimethyl-2'-acetoxybutyl)-5,6-dihydropyran-2-one (70). The general procedure A was followed using TMSOTf (5 mg, 0.02 mmol), alcohol (*R*, *R*)-**55** (62 mg, 0.16 mmol), (2*R*, 3*S*)-3-acetoxy-2, 4-dimethylpentanal **63** (30 mg, 0.17 mmol) Ag_2CO_3 (88 mg, 0.32 mmol) and $SnCl_4$ (0.1 mL, 1 M in CH_2Cl_2, 0.1 mmol). Reaction time: 1.5 h. The residue was purified by flash chromatography on silica gel (EtOAc/Hexane = 1:4) to yield δ-lactone **70** (35 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33-6.32 (m, 1H), 4.94 (dd, 1H, *J* = 6.4, 5.6 Hz), 4.09 (dd, 1H, *J* = 10.4, 2.8 Hz), 2.66-2.61 (m, 1H), 2.12 (s, 3H), 2.05-1.90 (m, 2H), 1.88 (dd, 3H, *J* = 2.4, 1.6 Hz), 1.07 (d, 3H, *J* = 7.2

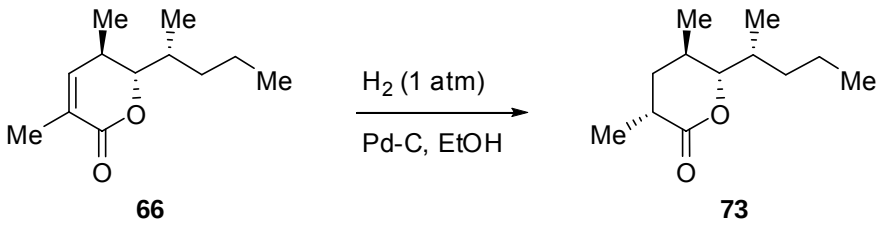
Hz), 0.99 (d, 3H, *J* = 7.2 Hz), 0.90 (d, 3H, *J* = 6.8 Hz), 0.88 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 165.2, 145.5, 127.1, 84.6, 79.3, 35.4, 31.0, 28.9, 21.0, 19.4, 17.2, 16.8, 16.4, 8.5 ; FT-IR (KBr) 2968, 1718, 1243 cm^{-1}; HRMS (APCI): *m/z* calcd. for $C_{12}H_{21}O_2$ (M^+) 269.1753, found 269.1748; $[\alpha]^{25}_D$ = -18.4 (c = 0.50, $CHCl_3$).



(*S*,*S*)-**55** **71**

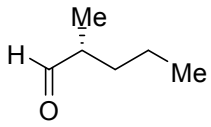
(5*S*, 6*R*, 1'*R*, 2'*S*)-3,5-Dimethyl-6-(1',3'-dimethyl-2'-acetoxybutyl)-5,6-dihydropyran-2-one (71). The general procedure A was followed using TMSOTf (3 mg, 0.01 mmol), alcohol (*S*, *S*)-**55** (40 mg, 0.11 mmol), (2*R*, 3*S*)-3-acetoxy-2, 4-dimethylpentanal **63** (22 mg, 0.13 mmol), Ag_2CO_3 (61 mg, 0.22 mmol) and $SnCl_4$ (0.13 mL, 1 M in CH_2Cl_2, 0.1 mmol). Reaction time: 8 h. The residue was purified by flash chromatography on silica gel (EtOAc/Hexane = 1:4) to yield δ-lactone **71** (13 mg, 42%). ^{1}H NMR analysis of the lactone revealed 6:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33-6.32 (m, 1H), 4.90 (dd, 1H, *J* = 9.6, 1.8 Hz), 3.93 (dd, 1H, *J* = 10.8, 3.6 Hz), 2.97-2.94 (m, 1H), 2.11-2.07 (m, 1H), 2.06 (s, 3H), 1.93-1.89 (m, 1H), 1.87 (d, 3H, *J* = 1.2 Hz), 1.14 (d, 3H, *J* = 7.2 Hz), 1.05 (d, 3H, *J* = 7.2 Hz), 0.90 (d, 3H, *J* = 7.2 Hz), 0.89 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 165.4, 146.2, 126.9, 86.8, 75.6, 34.5, 30.5, 29.9, 21.2,

19.0, 16.8, 16.4, 10.9; FT-IR (KBr) 2968, 1722, 1245 cm^{-1}; HRMS (APCI): *m/z* calcd. for $C_{12}H_{21}O_2$ (M^+) 269.1753, found 269.1748.



66 **73**

(-)-Invictolide (73). A solution of the unsaturated lactone **66** (27 mg, 0.14 mmol) and a catalytic amount of 5% Pd on carbon (4 mg) in ethanol (0.3 mL) was stirred at room temperature for 12 h under one atmosphere of hydrogen (balloon). The reaction mixture was passed through a short plug of silica (Ether/Pentane = 1:10) and the solvents were removed by a rotary evaporator to provide a mixture of (-)-invictolide **73** and its 3-epimer (2.33:1) as colorless oil (27 mg, 99%). The ^{1}H- and ^{13}C-NMR spectra were fully consistent with those reported by Hoffmann et al.[26h] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (dd, 1H, *J* = 9.6, 2.0 Hz), 2.69-2.59 (m, 1H), 2.02-1.87 (m, 1H), 1.67 (t, 2H, *J* = 8.0 Hz), 1.51-1.29 (m, 5H), 1.21 (d, 3H, *J* = 7.2 Hz), 0.97 (d, 3H, *J* = 6.8 Hz), 0.91 (d, 3H, *J* = 6.8 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 176.8, 85.6, 36.0, 35.3, 33.5, 32.5, 28.3, 20.4, 17.6, 16.5, 14.1, 12.2; HRMS (APCI): *m/z* calcd. for $C_{12}H_{23}O_2$ (M^+) 199.1698, found 199.1693.



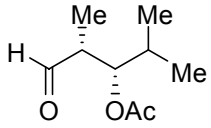
62

(2*R*)-2-methylpentanal (62). *n*-BuLi (4.63 mL, 2.5 M in hexane, 11.6 mmol) was added to a solution of LiCl (1.42 g, 33.5 mmol) and diisopropylamine (1.75 mL, 12.5 mmol) in THF (7 mL) at -78 °C and the reaction was warmed briefly to 0 °C and then recooled to -78 °C. A solution of (1*R*,2*R*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methylpentanamide[29] was added dropwise to the reaction flask. The reaction mixture was stirred at -78 °C for 1 h, 0 °C for 15 min and at room temperature for 5 min and finally cooled to 0 °C whereupon MeI (1.39 mL, 22.3 mmol) was added. The reaction was stirred at 0 °C for 55 min and then quenched by the addition of saturated aqueous ammonium chloride solution. The resulting mixture was extracted with ethyl acetate and the combined organic extracts were dried over sodium sulfate and concentrated to afford yellow oil. Purification of the residue by flash column chromatography on silica gel (EtOAc/Hexane = 1:1) to yield amide (1.38 g, 93%). ^{1}H NMR (3:1 rotamer ratio, * denotes minor rotamer peaks, 400 MHz, C_6D_6) δ 7.35-7.06 (m, 5H), 5.38 (br s, 1H), 4.59 (t, 1H, *J* = 6.8 Hz), 4.28* (dd, 1H, *J* = 8.0, 2.4 Hz), 4.06-3.96 (m, 1H), 2.87* (s, 3H), 2.83-2.74* (m, 1H), 2.21 (s, 3H), 2.26-2.14 (m, 1H), 1.86-1.70 (m, 2H), 1.35-1.11 (m, 2H), 1.32* (d, 3H, *J* = 6.8 Hz), 1.09 (d, 3H, *J* = 7.2 Hz), 0.91 (d, 3H, *J* = 6.4 Hz), 0.83 (t, 3H, *J* = 7.2 Hz), 0.71* (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (3:1 rotamer ratio, * denotes minor rotamer peaks, 100 MHz, C_6D_6) δ 178.5, 177.5*, 144.3, 143.3*, 129.0, 128.3*, 127.7*, 127.6, 127.0, 76.8, 75.7*, 61.0,

58.8*, 37.8*, 36.9, 36.8, 36.2*, 34.4, 27.4*, 21.4*, 21.3, 18.7*, 18.1, 16.0*, 14.8, 14.7. HRMS (APCI): *m/z* calcd. for $C_{16}H_{26}NO_2$ (M^+) 264.1964, found 264.1954; FT-IR (KBr) 3370, 3030, 2961, 1613, 1451 cm^{-1}.

To a solution of diisopropylamine (1.72 mL, 12.3 mmol) in THF (12.5 mL) was added *n*-BuLi (4.76 mL, 2.5 M in hexane, 11.4 mmol) at -78 °C. The resulting solution was stirred at -78 °C for 10 min, then warmed to 0 °C, and held at that temperature for 10 min. Borane-ammonia complex (402 mg, 11.7 mmol) was added under argon and the suspension was stirred at 0 °C for 15 min, then warmed to room temperature. After 15 min at room temperature, the suspension was cooled to 0 °C followed by dropwise addition of a solution of amide (0.77 g, 2.9 mmol) in THF (8.5 mL). Then the reaction was warmed to room temperature and stirred for additional 2 h before cooling to 0 °C, where excess borane was quenched by careful addition of 3 N aqueous hydrochloric acid solution (5 mL). The mixture was stirred for 30 min at 0 °C and then extracted with ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (5 mL), 2 N aqueous sodium hydroxide solution (5 mL), and brine (5 mL). The ether extracts were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (Ether/Pentane = 1:2) to yield (2*R*)-2-methylpentanol (219 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53-3.40 (m, 2H), 1.67-1.59 (m, 1H), 1.42-1.06 (m, 4H), 0.92-0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.4, 35.5, 35.4, 20.0, 16.5, 14.3; $[\alpha]^{25}_D$ = +10.5 (c = 0.85, $CHCl_3$); Mosher ester analysis of the alcohol revealed 98:2 er.

Oxalyl chloride (0.23 mL, 2.6 mmol) was dissolved in CH_2Cl_2 (11 mL), and a solution of DMSO (0.30 mL, 4.3 mmol) in CH_2Cl_2 (0.75 mL) was added at -78 °C. The resulting solution was stirred at -78 °C for 15 min followed by dropwise addition of (2*R*)-2-methyl-1-pentanol (219 mg, 2.14 mmol) in CH_2Cl_2 (2.5 mL). The resulting white heterogeneous mixture was stirred at -78 °C for 2 h, and Et_3N (0.90 mL, 6.4 mmol) was added. After 5 min at -78 °C, the mixture was warmed to room temperature for 1.5 h and 5 mL of H_2O was added. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was passed through a short plug of silica (Ether/Pentane = 1:1). The aldehyde **62** was used for next step without further purification. (150 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, 1H, *J* = 1.6 Hz), 2.38-2.32 (m, 1H), 1.72-1.30 (m, 4H), 1.09 (d, 3H, *J* = 7.2 Hz), 0.93 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 46.1, 32.6, 20.1, 14.0, 13.2; FT-IR (KBr) 2864, 2715, 1710, 1388 cm^{-1}; $[\alpha]^{25}_D$ = -27.4 (c = 0.42, acetone).



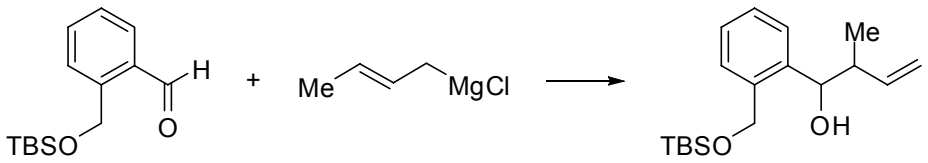
63

(2*R*, 3*S*)-3-Acetoxy-2,4-dimethylpentanal (63). To a solution of (3*S*, 4*S*)-2,4-dimethyl-3-hydroxy-5-hexene[30] (519 mg, 4.05 mmol) in CH_2Cl_2 (12 mL) was added pyridine (0.98 mL, 12 mmol), acetic anhydride (0.76 mL, 8.1 mmol) and DMAP (25 mg, 0.20 mmol) at 0 °C. The resulting solution was allowed to warm to

room temperature and stirred for another 2 h before quenched with water. The extractions was performed with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/Hexane = 1 : 8) to yield acetate (681 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74-5.65 (m, 1H), 5.09-4.99 (m, 2H), 4.71 (dd, 1H, *J* = 7.6, 5.6 Hz), 2.49-2.43 (m, 1H), 2.07 (s, 3H), 1.94-1.86 (m, 1H), 0.97 (d, 3H, *J* = 6.8 Hz), 0.88 (d, 3H, *J* = 3.8 Hz), 0.87 (d, 3H, *J* = 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 140.5, 114.7, 80.4, 39.7, 29.5, 20.9, 19.7, 16.5, 15.2; FT-IR (KBr) 2972, 1741, 1239 cm^{-1}; HRMS (APCI): *m/z* calcd. for $C_{10}H_{19}O_2$ (M^+) 171.1385, found 171.1380; $[\alpha]^{25}_D$ = -17.8 (c = 0.84, $CHCl_3$).

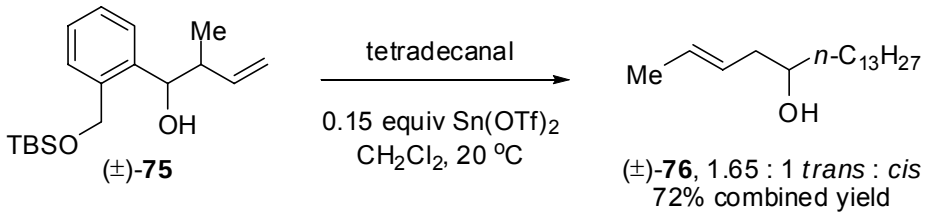
A solution of (3*S*, 4*S*)-2,4-dimethyl-3-acetoxy-5-hexene (576 mg, 3.34 mmol) in 1 : 1 CH_2Cl_2 : MeOH (24 mL, 0.08 M) was added pyridine (0.16 mL, 2 mmol) at room temperature under argon. The resulting solution was cooled to -78 °C and bubbled into O_3 until starting material was consumed. Me_2S (5 mL, 60 mmol) was added to the flask and the reaction was allowed to warm slowly to room temperature over a period of 18 h. The crude mixture was concentrated and diluted with ethyl acetate (40 mL). The organic layer was washed with water and brine followed by drying over $MgSO_4$, filtered and concentrated. The crude aldehyde **63** (495 mg, 86%) was used in the next transformation without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (d, 1H, *J* = 1.2 Hz), 5.14 (dd, 1H, *J* = 8.0, 4.0 Hz), 2.70-2.64 (m, 1H), 2.04 (s, 3H), 1.96-1.90 (m, 1H), 1.08 (d, 3H, *J* = 6.8 Hz), 0.95 (d, 3H, *J* = 6.8 Hz), 0.93 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 170.7, 76.3, 48.6, 29.8, 20.7, 19.0, 18.3, 7.4; FT-IR (KBr) 2972,

2880, 1733, 1374 cm^{-1}; HRMS (APCI): *m/z* calcd. for $C_{10}H_{19}O_2$ (M^+) 173.1178, found 173.1173.

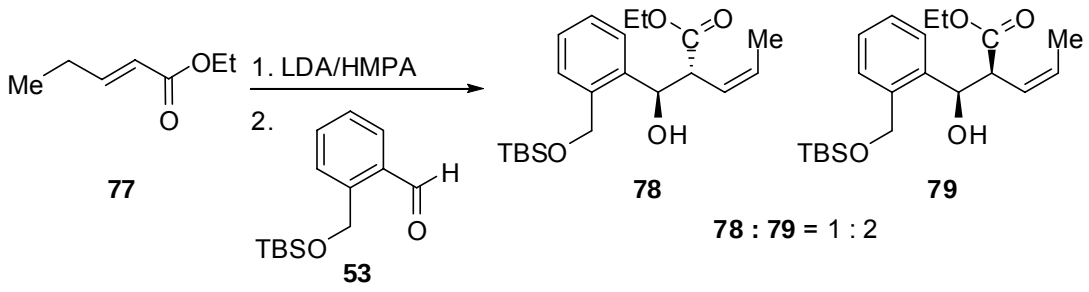


53 **74** (±)-**75**

1-(2-((*tert*-Butyldimethylsilyloxy)methyl)phenyl)-2-methylbut-3-en-1-ol (75). To a solution of magnesium turnings (60 mg, 2.4 mmol) and $HgCl_2$ (trace) in anhydrous THF (6 mL) was added crotyl chloride (0.25 mL, 2.4 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 10 min and room temperature for 1.5 h. After the Grignard reagent was formed, the solution was re-cooled to 0 °C followed by dropwise addition of a solution of aldehyde **53** (298 mg, 1.19 mmol) in THF (1 mL). The reaction was stirred vigorously at 0 °C for 2 h and quenched with ethyl acetate (1 mL) and NH_4Cl (1 mL). The extractions was performed with ether and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel to yield homoallylic alcohol **75** (322 mg, 88%) in 1 : 1 diastereomeric ratio.



Homoallylic Alcohol (76). $Sn(OTf)_2$ (17 mg, 0.04 mmol) was added to a solution of alcohol (±)-**75** (100 mg, 0.33 mmol) and tetradecanal (58 mg, 0.27 mmol) in CH_2Cl_2 (3.0 mL) under argon at 0 °C. The resulting solution was stirred at 0 °C for 2 h and room temperature for 13 h. The solution was passed through a short plug of silica (EtOAc/Hexane = 1:4). The solvents were removed by rotary evaporation and the residue was purified by flash chromatography on silica gel to yield alcohol **76** (52 mg, 72%). ^{1}H NMR spectrum showed that the product was 1.65 : 1 mixture of *trans* and *cis* isomers.

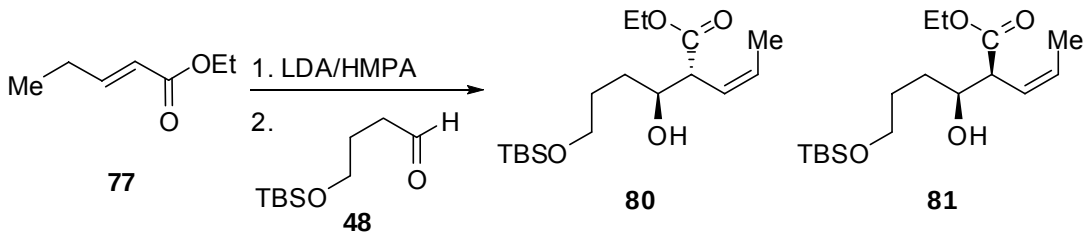


(*Z*)-Alkene (78) and (79). To a solution of diisopropylamine (0.37 mL, 2.6 mmol) in THF (3.5 mL) at 0 ˚C was added *n*-BuLi (1.05 mL, 2.5 M in hexane, 2.6 mmol). After stirring for 15 min, the reaction was cooled to -78 ˚C and HMPA (0.46 mL, 2.6 mmol) was added and held at that temperature for 30 min before adding a solution of ester **77** (306 mg, 2.38 mmol) in THF (1.5 mL). The dienoate was allowed to form over 30 min followed by the addition of solution of aldehyde **53** (536 mg, 2.14 mmol) in THF (1.5 mL). The resulting solution was stirred at -78 ˚C for 3 h and quenched with NH_4Cl (2 mL) and allowed to warmed to room temperature. The extractions was performed with ethyl acetate and the combined

organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel to yield **78** (84 mg, 0.22 mmol) and **79** (170 mg, 0.44 mmol) in 31% combined yield.

78. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (m, 1H), 7.31-7.21 (m, 3H), 5.75-5.66 (m, 2H), 5.34 (dd, 1H, *J* = 5.6, 2.8 Hz), 4.82 (d, 2H, *J* = 4.4 Hz), 4.08-4.03 (m, 2H), 3.88 (dd, 1H, *J* = 9.2, 5.6 Hz), 3.35 (d, 1H, *J* = 2.8 Hz), 1.38 (dd, 3H, *J* = 6.8, 1.6 Hz), 1.13 (t, 3H, *J* = 7.2 Hz), 0.93 (s, 9H), 0.12 (s, 6H).

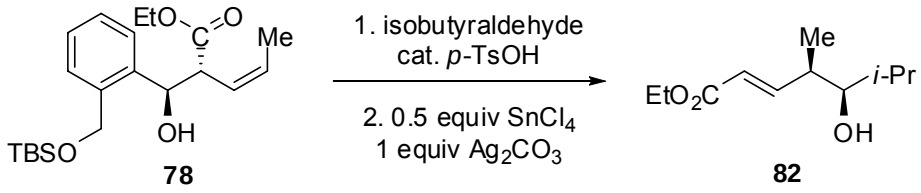
79. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.21 (m, 4H), 5.51-5.46 (m, 1H), 5.32-5.26 (m, 1H), 5.21 (dd, 1H, *J* = 9.6, 4.8 Hz), 4.90 (d, 1H, *J* = 12.4 Hz), 4.74 (d, 1H, *J* = 12.4 Hz), 4.21 (q, 2H, *J* = 7.2 Hz), 3.91 (dd, 1H, *J* = 9.6, 8.8 Hz), 3.34 (d, 1H, *J* = 4.8 Hz), 1.45 (dd, 3H, *J* = 6.8, 1.6 Hz), 1.28 (t, 3H, *J* = 7.2 Hz), 0.93 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H).



(*Z*)-Alkene (80) and (81). The procedure for *Z*-alkene **78** was followed using (*E*)-2-crotonate **77** (306 mg, 2.40 mmol), *n*-BuLi (1.08 mL, 2.5 M in hexane, 2.7 mmol). diisopropylamine (0.38 mL, 2.7 mmol), HMPA (0.47 mL, 2.70 mmol), aldehyde **48** (304 mg, 1.50 mmol). Reaction time: 2 h under -78 ˚C. The residue was purified by flash chromatography on silica gel to yield **80** (222 mg, 0.670 mmol) and **81** (220 mg, 0.670 mmol) in 89% combined yield.

80. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.76 (m, 1H), 5.62-5.55 (m, 1H), 4.16 (q, 2H, *J* = 7.6 Hz), 3.98-3.93 (m, 1H), 3.68-3.59 (m, 1H), 3.42 (ddd, 1H, *J* = 10, 4.8, 0.8 Hz), 3.10 (d, 1H, *J* = 3.6 Hz) 1.74-1.43 (m, 4H), 1.69 (dd, 3H, *J* = 6.4, 1.6 Hz), 1.26 (t, 3H, *J* = 7.2 Hz), 0.89 (s, 9H), 0.046 (s, 6H).

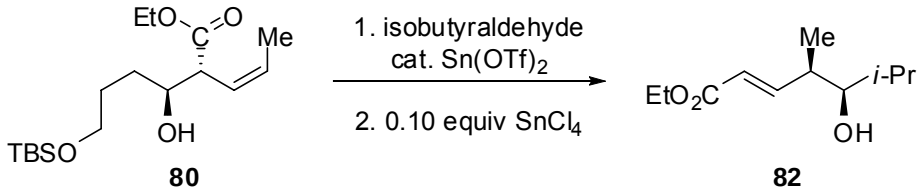
81. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71-5.67 (m, 1H), 5.41-5.35 (m, 1H), 4.19-4.12 (m, 2H), 3.87-3.83 (m, 1H), 3.65 (t, 1H, *J* = 5.6 Hz), 3.41 (t, 1H, *J* = 9.2 Hz), 3.20 (d, 1H, *J* = 5.2 Hz) 1.72-1.61 (m, 3H), 1.70 (dd, 3H, *J* = 6.8, 2.0 Hz), 1.39-1.35 (m, 1H), 1.26 (t, 3H, *J* = 7.2 Hz), 0.89 (s, 9H), 0.053 (s, 6H).



78 **82**

(±)-5-Hydroxy-4,6-dimethyl-hept-2-enoic acid ethyl ester (82). *p*-Toluenesulfonic acid monohydrate (4 mg, 0.02 mmol) was added to a solution of alcohol **78** (79 mg, 0.21 mmol) and freshly distilled isobutyraldehyde (21 µL, 0.23 mmol) in CH_2Cl_2 (2.0 mL) under argon at room temperature. The resulting solution was stirred at room temperature overnight and passed through a short plug of silica (EtOAc/Hexane = 1:8). The solvents were removed by rotary evaporation and the crude cyclic acetal was used for the next step without further purification. The crude acetal was dissolved in $MeNO_2$ (1.0 mL) and CH_2Cl_2 (1.0 mL) under argon, and $SnCl_4$ (0.1 mL, 1 M in CH_2Cl_2, 0.1 mmol) and Ag_2CO_3 (66 mg, 0.24 mmol) were added at room temperature. The resulting solution was

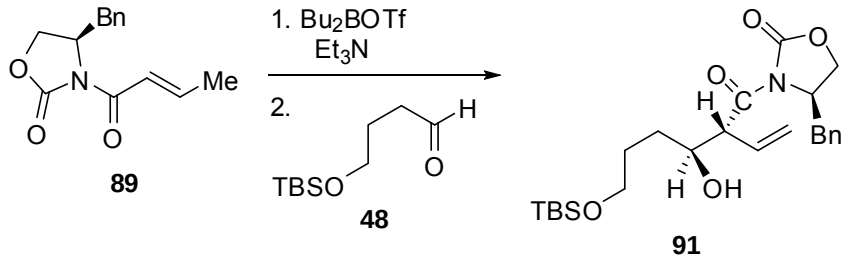
stirred at room temperature for 30 min before quenching with saturated aqueous $NaHCO_3$ (3 mL). The salts were filtered off with Celite and the extractions were performed with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel to yield alcohol **82** (17 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (dd, 1H, *J* = 15.4, 7.6 Hz), 5.86 (dd, 1H, *J* = 15.4, 0.8 Hz), 4.19 (q, 2H, *J* = 7.0 Hz), 3.29-3.25 (m, 1H), 2.54-2.49 (m, 1H), 1.75-1.70 (m, 1H), 1.29 (t, 3H, *J* = 7.0 Hz), 1.10 (d, 3H, *J* = 6.8 Hz), 0.94 (d, 3H, *J* = 4.0 Hz), 0.92 (d, 3H, *J* = 4.0 Hz);



80 **82**

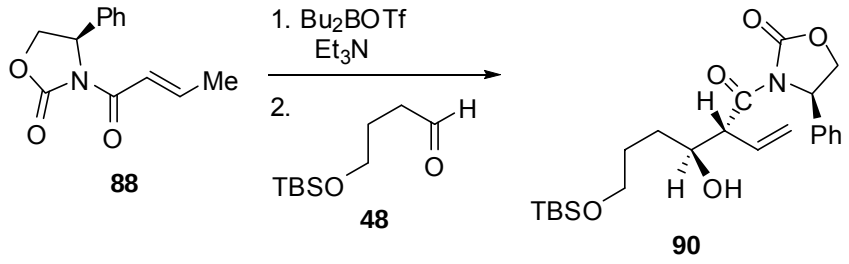
(±)-5-Hydroxy-4, 6-dimethyl-hept-2-enoic acid ethyl ester (82). $Sn(OTf)_2$ (42 mg, 0.10 mmol) was added to a solution of alcohol **80** (222 mg, 0.670 mmol) and freshly distilled isobutyraldehyde (67 µL, 0.33 mmol) in CH_2Cl_2 (6.7 mL) under argon at room temperature. The resulting solution was stirred at room temperature for 1 h and passed through a short plug of silica (EtOAc/Hexane = 1:8). The solvents were removed by rotary evaporation and the crude cyclic acetal was used for the next step without further purification. The crude acetal was dissolved in $MeNO_2$ (2.0 mL) and CH_2Cl_2 (2.0 mL) under argon, and $SnCl_4$ (0.067 mL, 1 M in CH_2Cl_2, 0.07 mmol) were added at 0 ˚C. The resulting solution was stirred at 0 ˚C for 1 h before quenching with saturated aqueous $NaHCO_3$ (5

mL). The salts were filtered off with Celite and the extractions were performed with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel to yield alcohol **82** (84 mg, 62%).



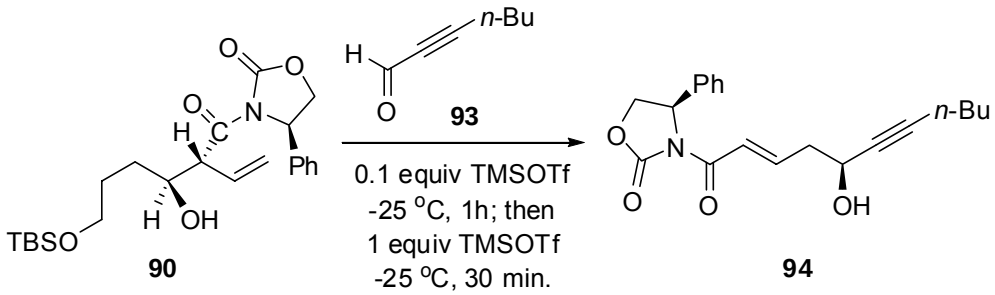
(*R*)-4-Benzyl-3-((2*R*,3*S*)-6-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2-vinylhexanoyl)oxazolidin-2-one (**91**)**.** To a stirred solution of imide **89** (2.40 g, 9,13 mmol) in CH_2Cl_2 (40 mL) was added Bu_2BOTf (10.76 mL, 1.0 M solution in CH_2Cl_2, 10.8 mmol) at -78 ˚C. The mixture was stirred for 5 min and then treated with freshly distilled triethylamine (1.91 mL, 13.7 mmol). After 1 h at -78 ˚C and 15 min at 0 ˚C the solution was recooled to -78 ˚C and treated with freshly prepared aldehyde **48** (2.77g, 13.7 mmol). The solution was kept for 2 h at -78 ˚C and 1.5 h at 0 ˚C, and then partitioned between 200 mL each NH_4Cl and (ethyl acetate / hexane = 1 : 1). The organic phase was washed brine and concentrated to an oil which was dissolved in ether (50 mL) and cooled to 0 ˚C. The resulting solution was treated with pH 7 buffer (8.6 mL) and 30% H_2O_2 (8.6 mL) at 0 ˚C. After stirring rapidly for 1 h the mixture was partitioned between 300 mL of water and 300 mL of a 1:1 mixture of ethyl acetate and hexane. The organic phase was washed with $NaHCO_3$ and brine then dried over sodium sulfate and concentrated

to afford yellow oil. Purification of the residue by flash column chromatography on silica gel (EtOAc/Hexane = 1:4) to yield alcohol **91** (3.51 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 3H), 7.21-7.19 (m, 2H), 6.09-6.00 (m, 1H), 5.40-5.36 (m, 2H), 4.73-4.68 (m, 1H), 4.55 (dd, 1H, *J* = 8.8, 3.6 Hz), 4.23-4.15 (m, 2H), 4.01 (m, 1H), 3.65 (t, 2H, *J* = 6.0 Hz), 3.35 (bs, 1H), 3.26 (dd, 1H, *J* = 12.8, 3.2 Hz), 2.75 (dd, 1H, *J* = 13.6, 9.6 Hz), 1.69-1.55 (m, 4H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 152.9, 135.0, 131.5, 129.4, 128.9, 127.4, 121.1, 71.6, 66.0, 63.1, 55.2, 52.5, 37.5, 31.2, 29.0, 25.9, 18.3, -5.4; HRMS (APCI): *m/z* calcd. for $C_{24}H_{38}O_5NSi$ (M^+) 448.2514, found 448.2510; FT-IR (KBr) 3399, 2953, 2358, 1783, 1693 cm^{-1}; $[\alpha]^{25}_D$ = -6.2 (c = 0.4, $CHCl_3$).



(*R*)-3-((2*R*,3*S*)-6-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-2-vinylhexanoyl)-4-phenyloxazolidin-2-one (**90**)**.** The procedure for alcohol **91** was followed using crotonyl oxazolidinone **88** (500 mg, 2.16 mmol), dibutylboron trifluoromethane sulfonate (2.38 mL, 1.0 M solution in CH_2Cl_2, 2.4 mmol), triethylamine (0.42 mL, 3.0 mmol) and aldehyde **48** (874 mg, 4.32 mmol). Reaction time: 1.5 h at -78 ˚C and 1 h at 0 ˚C. The residue was purified by flash chromatography on silica gel (Ether/Pentane = 1:1) to yield alcohol **90** (522 mg, 56%). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.40-7.38 (m, 3H), 7.25-7.21 (m, 2H), 5.88-5.79 (m, 1H), 5.45 (dd, 1H, *J* = 8.6, 4.0 Hz), 5.31-5.22 (m, 2H), 4.69 (t, 1H, *J* = 8.6 Hz), 4.58 (dd, 1H, *J* = 9.2, 4.0 Hz), 4.24 (dd, 1H, *J* = 8.6, 4.0 Hz), 4.01-3.96 (m, 1H), 3.63 (td, 2H, *J* = 6.4, 1.6 Hz), 3.27 (d, 1H, *J* = 2.4 Hz), 1.70-1.51 (m, 4H), 0.88 (s, 9H), 0.05 (s, 6H)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 153.1, 138.5, 131.0, 129.2, 128.8, 125.6, 121.3, 71.2, 69.7, 63.1, 57.6, 52.3, 30.9, 29.0, 25.9, 18.3, -5.4.



(*R*)-3-((*S*,*E*)-5-Hydroxyundec-2-en-6-ynoyl)-4-phenyloxazolidin-2-one (**94**)**:** Alcohol **90** (100 mg, 0.230 mmol) and aldehyde **93** (55 mg, 0.50 mmol) were dissolved in CH_2Cl_2 (2.0 mL), cooled to -25 °C, and TMSOTf (4 µL, ~0.02 mmol) was added dropwise. The resulting solution was stirred at -25 °C for 1 h and more TMSOTf (42 µL, 0.23 mmol) was added at the same temperature. The reaction mixture was further stirred for 30 min at -25 °C and quenched with saturated aqueous $NaHCO_3$ (3 mL). The extractions were performed with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel to yield enyne **94** (40 mg, 50%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 6H), 7.16-7.08 (m, 1H), 5.49 (dd, 1H, *J* = 8.8, 3.6 Hz), 4.71 (t, 1H, *J* = 8.8 Hz), 4.43

(m, 1H), 4.30 (dd, 1H, *J* = 8.8, 3.6 Hz), 2.64 (td, 2H, *J* = 6.6, 1.2 Hz), 2.18 (td, 2H, *J* = 6.8, 2.0 Hz), 1.49-1.32 (m, 4H), 0.88 (t, 3H, *J* = 7.2 Hz).

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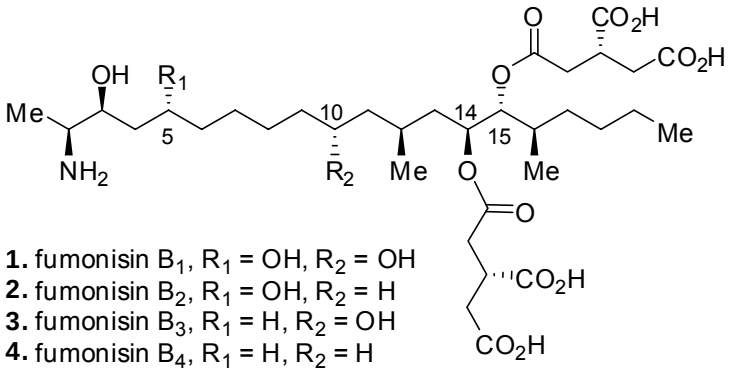
Chapter 2. *Towards the Total Synthesis of Mycotoxin Fumonisin B_1.*

2.1. Introduction and Background.

Fumonisins (**Figure 1)** are polyketide-derived mycotoxins produced by *Fusarium moniliforme*[1] and related filamentous fungi, which are widespread pathogens of corn and other grains. Dietary consumption of fumonisin-contaminated corn products have been associated with increased incidence of human esophageal cancer.[2] Fumonisin B_1 (**1**) has also been associated with disease syndromes in animals with the consumption of *F. moniliforme*-contaminated corn, such as hepatotoxicity and carcinogenicity in rats[3] and equine leukoencephalomalacia (disease of the central nervous system) in horses.[4] Moreover, it is relatively heat stable and persists through most of the conditions used in food manufacturing, so its presence in food is a potential risk to human health.

Figure 1. Structure of B-series Fumonisins



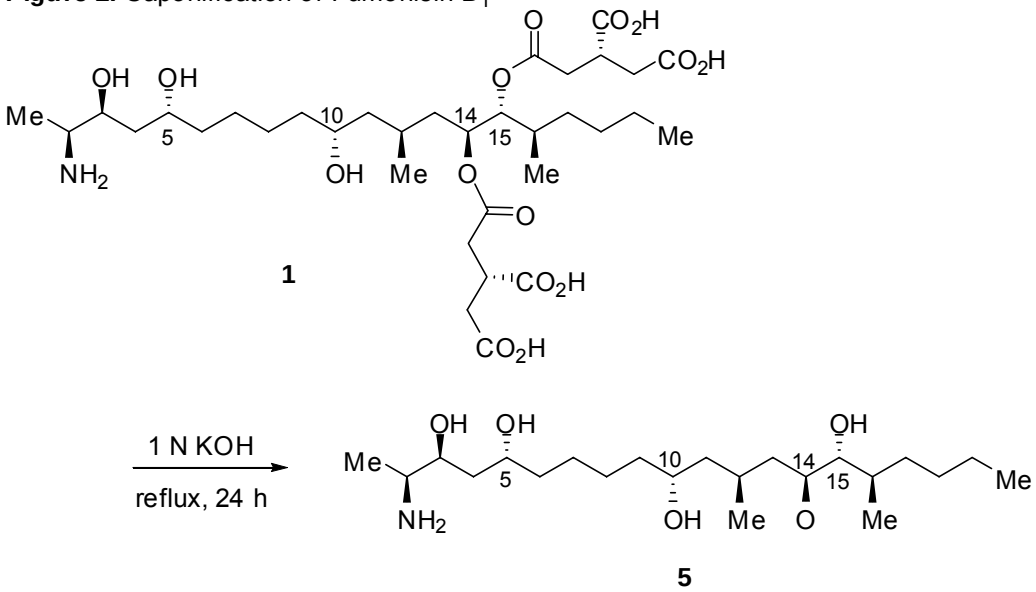
1. fumonisin B_1, R_1 = OH, R_2 = OH
2. fumonisin B_2, R_1 = OH, R_2 = H
3. fumonisin B_3, R_1 = H, R_2 = OH
4. fumonisin B_4, R_1 = H, R_2 = H

Regarding the mechanism of action on the molecular level, the Merrill laboratory reported that fumonisins can inhibit the sphinganine *N*-acyltransferase (ceramide synthase) and disrupt sphingolipid metabolism which might be

responsible for several fatal animal diseases.[5] However, since sphingolipids can regulate cell growth and apoptosis, the study of fumonisins and their relative compounds for inhibition of sphinganine *N*-acyltransferase is an attractive project for new antitumor drug discovery. Ironically, the hydrolyzed product of fumonisin B_1 at C-14 and C-15 of the backbone (i.e. aminopentol **5**) has low mycotoxin activity.[6] In a short-term liver cancer initiation model, the aminopentol **5** failed to promote cancer, but revealed greater cytotoxicity than the parent natural product fumonisin B_1 (**1**).[7]

The chemical structure of the fumonisin B_1 (**1**) backbone has been elucidated by Hoye's laboratory from aminopentol **5,** obtained by saponification of the ester linkage with aqueous potassium hydroxide (**Figure 2**).[8] The absolute configuration "*R*" at the tricarballylic acid moiety of fumonisins has been determined by Kishi's laboratory.[9]

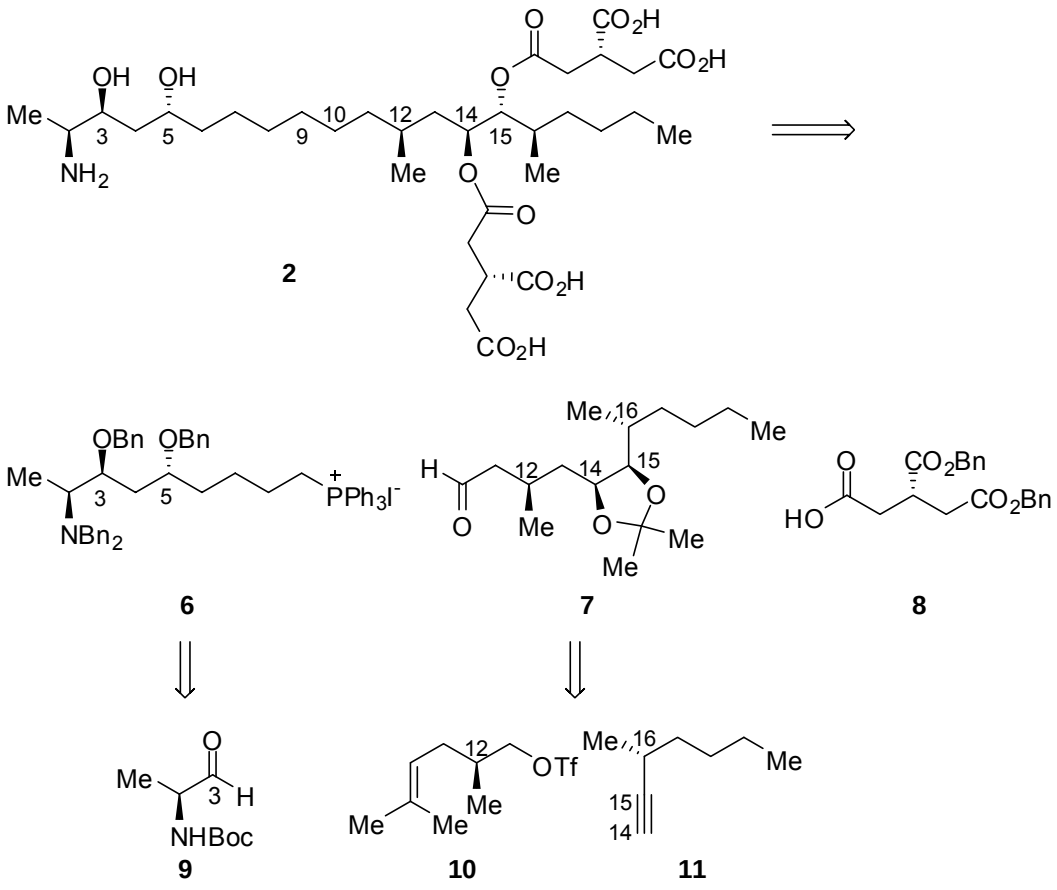
Figure 2. Saponification of Fumonisin B_1



Kishi *et al* reported the first total synthesis of fumonisin B_2,[10] and it is also the only total synthesis in the fumonisin family to date. The general features of

Kishi's fumonisin B_2 **2** synthesis are outlined retrosynthetically in **scheme 1**. They assembled fumonisin B_2 in a convergent manner from the left hand segment phosphine **6**, the right hand segment aldehyde **7** and the benzyl protected tricarballylic acid **8**. Fragments **6** and **7** were connected by Wittig reaction to provide the twenty carbon backbone followed by the installation of the acid **8**[9] segment on to the main skeleton. In the synthetic direction, the installation of C-3 and C-5 hydroxyl stereocenters of phosphine **6** through iterative asymmetric allylation,[11] followed by oxidative cleavage and two-carbon chain elongation (i.e. Horner-Wadsworth-Emmons olefination) could furnish the nine carbons skeleton. Subsequent conversion of the α,β-unsaturated ester to segment **6** could be

Scheme 1. Kishi's Synthesis of Fumonisin B_2

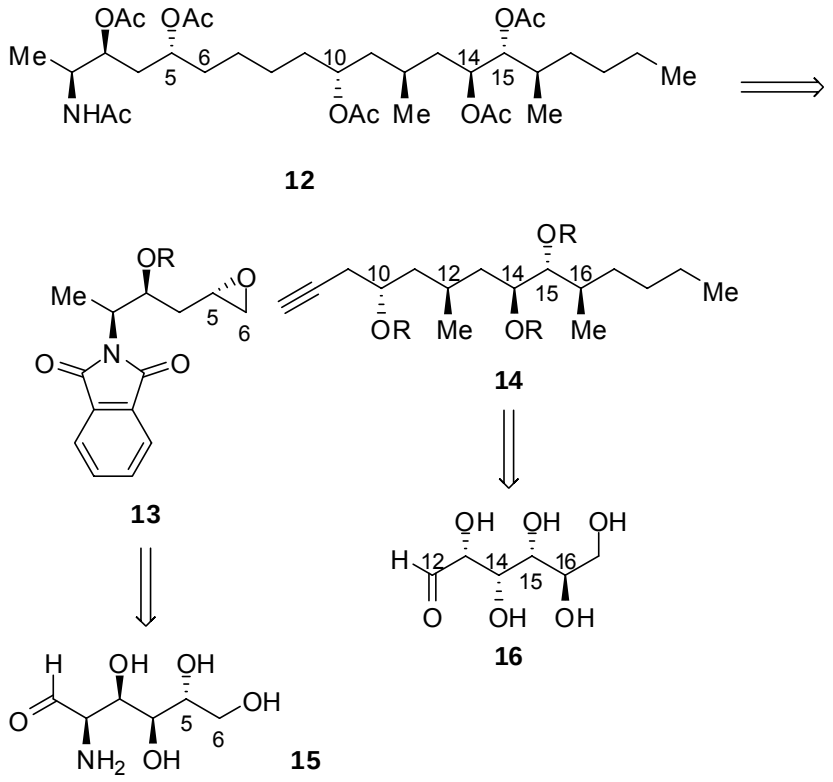


achieved through hydrogenation (Lindlar catalyst) followed by standard functional group manipulations. In the selection of suitable chiral starting materials for the preparation of aldehyde **7**, Myers' pseudoephedrine-based asymmetric alkylation[12] played a pivotal role for C-12 and C-16 methyl group. The union of intermediates **10** and **11** through alkyne-triflate coupling gave the main carbon skeleton. A sequence of functional group manipulations would set the stage for selective introduction of the vicinal hydroxyl groups at C-14 and C-15 on the backbone by applying a iodo-lactonization and ring opening strategy. Appropriate modifications could then complete the synthesis of key intermediate **7**. Both segment **6** and segment **7** required more than 15 steps from commercially available materials.

Gurjar's laboratory reported the first total synthesis of hexaacetyl fumonisin B_1 compound **12**,[13] which was targeted since that aminopentol backbone **5** showed a broader spectrum of activity than the parent natural product. The general strategy for the construction of compound **12** is based on the retrosynthetic analysis shown in **Scheme 2**. The convergent strategy identifies epoxide **13** and alkyne **14** as the key intermediates which could be generated from D-glucosamine **15** and D-glucose **16,** respectively. The carbohydrate chirons have been utilized on countless occasions as part of highly successful syntheses of complex natural products. Accordingly, this decision means that most of asymmetric transformations would be directed by the internal chirality. However, it still required rather lengthy functional group manipulations for both epoxide **13** and alkyne **14** fragments. The developed route required

more than twelve steps for epoxide **13** and more than twenty operations for alkyne **14**. Having accomplished the crucial C-C bond coupling between **13** and **14**, a five step modification was required to complete the synthesis of fumonisin B_1 backbone **12**.

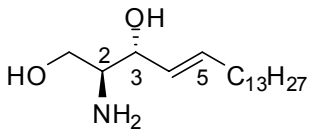
Scheme 2. Gurjar's Synthesis of Fumonishin B_1 Backbone



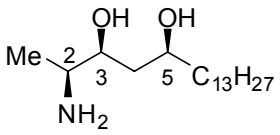
A class of 1-deoxy-5-hydroxysphingosine analogs enigmol **18** and isoenigmol **19** were reported by Liotta and Merrill's laboratories as shown in **Figure 3**.[14] The C-1 hydroxy group of sphingoshine **17** was moved to C-5 to maintain similar lipophilicity and avoid phosphorylation *in vivo* of the primary hydroxyl substituent. Studies of cytotoxicity against cancer cell lines HT-29 (colon) and DU-145 (prostate) revealed that these reagents were more potent than sphingosine **17** and demonstrated little host toxicity, thereby leading to the

expectation that they could be developed into highly valuable new reagents for the treatment of cancer.

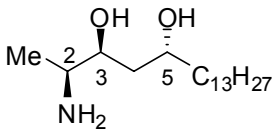
Figure 3. Structures of 1-Deoxy-5-Hydroxysphingolipid Analogues



17. sphingosine



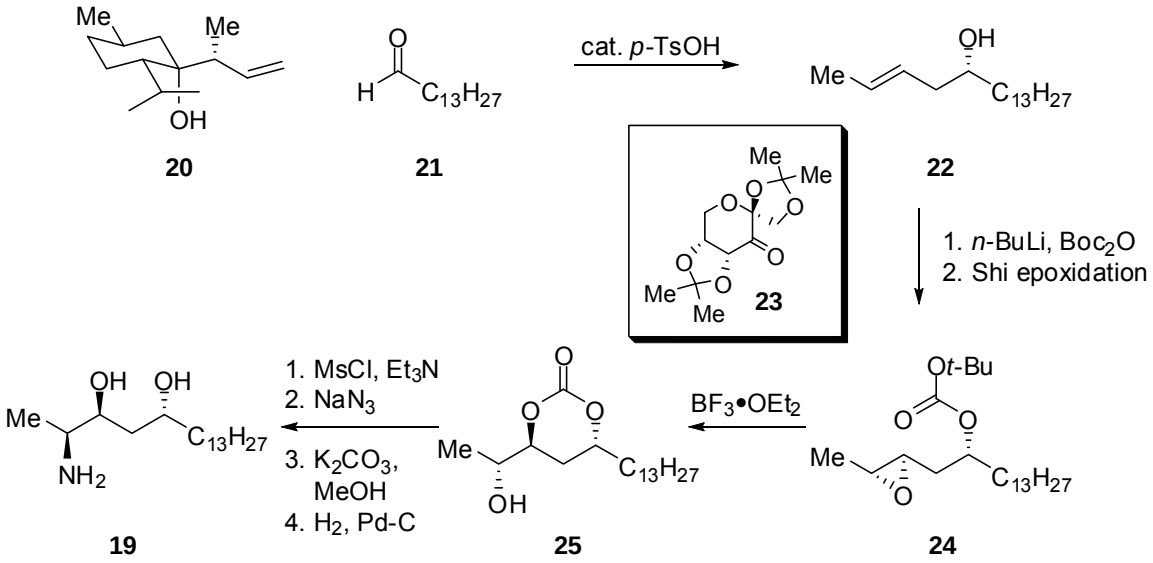
18. enigmol



19. (2*S*, 3*S*, 5*R*)-isoenigmol

The McDonald laboratory accomplished enantioselective syntheses of both unnatural enigmol **18** and isoenigmol **19** from simple and readily available commercially available starting materials.[15] The robust and highly stereo- and regioselective synthetic sequence provided gram-scale both enigmol and isoenigmol for further biological study. The general features of the efficient synthesis of sphingolipid analogs *via* 2-oxonia-Cope rearrangement is outlined in **Scheme 3**. The synthesis of isoenigmol commences with a stereospecific crotyl group transfer to tetradecanal **21** by employing Nokami's menthone-derived reagent **20**.[16] An important task remaining is the stereocontrolled introduction of amino- and hydroxyl-groups at C-2 and C-3. Conversion of the homoallylic alcohol into the corresponding *tert*-butyl carbonate followed by Shi epoxidation[17] with fructose-derived catalyst **23** furnished intermediate **24** in good yield. During the course of Lewis acid-promoted oxacyclization reaction,[18] cyclic carbonate alcohol **25** could be isolated as a single diastereomer. From this stage, alcohol **25** was converted into mesylate for the stereospecific substitution with azide. Isoenigmol **19** could be obtained after basic methanolysis of the cyclic carbonate and hydrogenation of the azide.

Scheme 3. The synthesis of isoenigmol



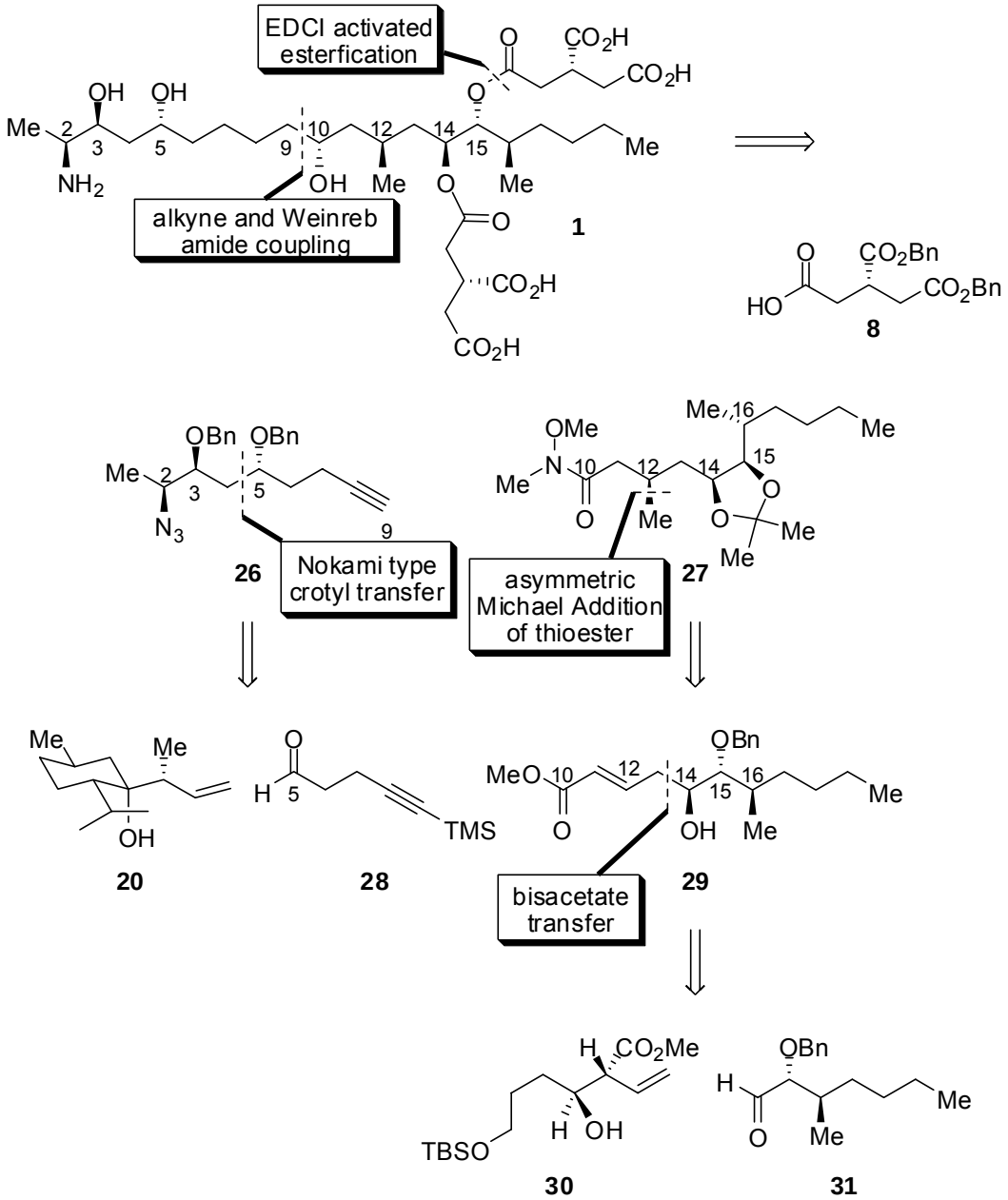
This chapter discusses the current status of development of a novel, efficient, and general method for the synthesis of fumonisins and structurally related AAL-toxins.[19] The main strategy is based on novel synthons which have been described in chapter 1, and the synthetic sequence of isoenigmol **19** because of similarity between the aminodiol headgroup of isoenigmol **19** and fumonisin B_1. We believe that the study of structure-activity relationships (SAR) of these toxins could identify more important anti-tumor reagents and this idea will rely on a well developed synthetic route. In this chapter, we will discuss the highly convergent synthetic strategies for fumonisin B_1 and the aminopentol backbone. The synthesis also demonstrates the value of using our bisacetate synthon for natural product synthesis.

2.2. Retrosynthetic Analysis.

The key features of our synthesis of fumonisin B_1 are outlined retrosynthetically in **Scheme 4**. Since its high aqueous solubility and highly sensitive to acidic conditions, we chose Kishi's strategies to reserve the benzyl protected tricarboxylic acid **8**[9] incorporation until the final stage of the synthesis. In the forward direction, it was anticipated that the fusion of alkyne **26** and Weinreb amide **27** might be achieved efficiently.[20] The secondary alcohol chirality at C-10 could be controlled with Noyori asymmetric transfer hydrogenation,[21] Alpine-borane reduction,[22] or oxazaborolidine-catalyzed reduction,[23] which are particularly selective for alkynyl ketones. A sequence of functional group manipulations would set the stage for a global deprotection, with concomitant azide and alkyne reduction upon treatment with hydrogen in the presence of palladium catalyst. For alkyne **26**, we anticipated that all transformations for enigmol **18** and isoenigmol **19** could be compatible with aldehyde **28**. Because we were concerned about the chemoselective reduction of the ketone carbonyl at C-10 in presence of azido group at late stage, evaluation of several conditions was necessary. Moreover, we thought to take advantage of the stability of azido group under acidic or basic conditions to minimize the protective group manipulations. Preparation of Weinreb amide **27** was the highlight of our bisacetate transfer strategy. It was projected that intermediate **27** could be elaborated in a straightforward way from methyl ester **29** *via* asymmetric Michael addition, diol protection and Weinreb amide formation. Intermediate **29** could conceivably be derived from allylic group transfer with methyl ester **30** and

aldehyde **31**. It is instructive to note that the 2-oxonia-[3, 3]-Cope rearrangement has not only created a stereocenter at C-14, but is also a linchpin for joining the left hand alkyne **26** and methyl group incorporation at C-12. The execution of this concise and convergent strategy is described in next section.

Scheme 4. Retrosynthesis of Fumonisin B_1

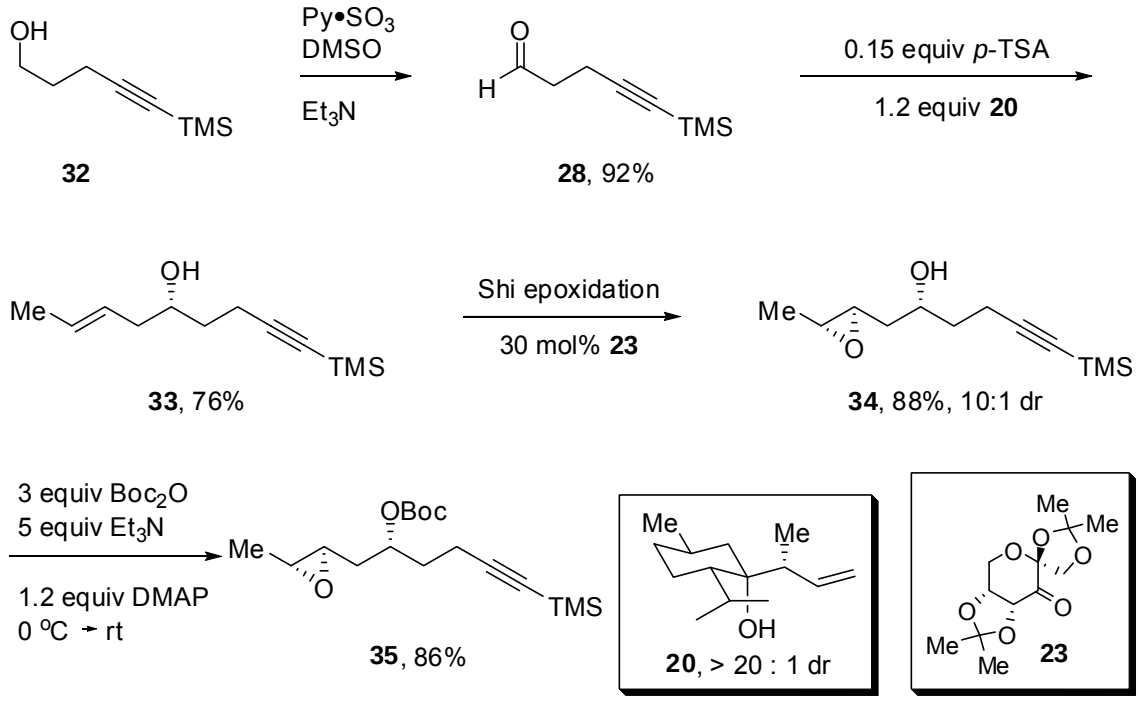


2.3. Total Synthesis of Fumonisin B_1.

*2. 3. 1. Synthesis of Alkyne **26**: C1-C9 Subunit of Fumonisin B_1.*

The construction of intermediate epoxide **35** is summarized in **Scheme 5**. Through a previously established synthetic pathway,[15] homoallylic alcohol **33** can be prepared in enantiomerically pure fashion from Nokami crotyl transfer to aldehyde **28** which was prepared from commercially available 5-trimethylsilyl-4-pentyn-1-ol **32** using a Parikh-Doering oxidation.[24] The alcohol **33** was smoothly converted to epoxide **35** in 10 : 1 diastereomeric ratio with chiral ketone catalyst **23** and stoichiometric oxidant, Oxone®. Interestingly, the trimethylsilyl group, which was important to reduce volatility of these synthetic intermediates, was compatible with the pH 10-11 solution required for Shi epoxidation. It is necessary to use more than one equivalent of 4-(*N, N*-dimethylamino)pyridine

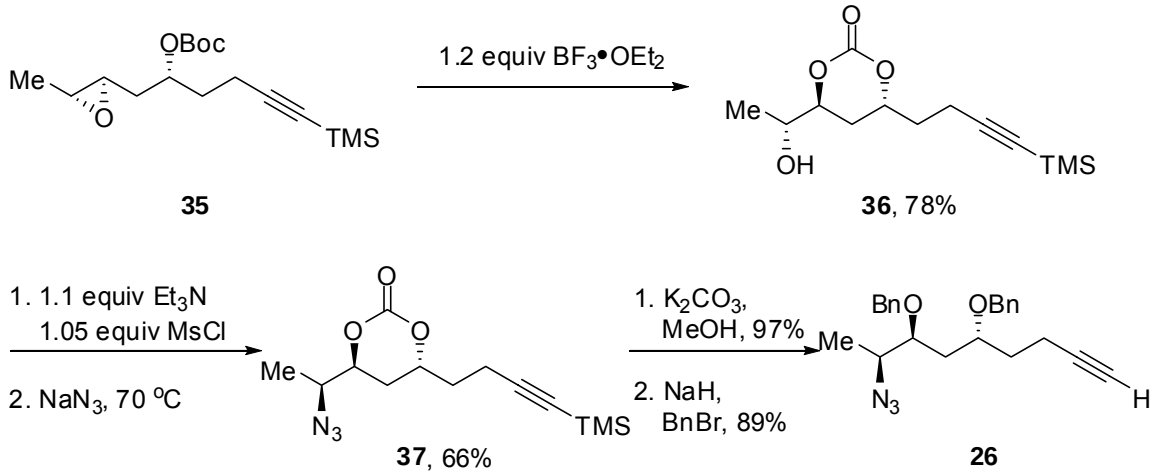
Scheme 5. Synthesis of Epoxide **35**.



(DMAP) for the *tert*-butyl carbonate **35** preparation. It is noteworthy that we changed the order of steps (**Scheme 3**) to incorporate the epoxide earlier and the reaction conditions for generation of *tert*-butyl carbonate **35**. Exposure of **34** to *n*-butyllithium and di-*tert*-butyldicarbonate resulted in a very low yield.

The relationship between epoxy-carbonate **35** and the targeted alkyne **26** is actually very close; the Lewis acid-promoted cyclization with freshly distilled boron trifluoride etherate afforded cyclic carbonate alcohol **36**, which could be separated from minor diastereomer in 78% yield (**Scheme 6**). The introduction of the azido group was accomplished as described earlier *via* formation of mesylate, followed by stereospecific substitution with sodium azide to provide azido-carbonate **37**. The yield for this two-step sequence is modest. A straight forward two-step sequence of reactions *via* basic methanolysis of the cyclic carbonate and alkynylsilane followed by benzylation of two hydroxyl groups completed the synthesis of C1-C9 subunit of fumonisin B_1 in excellent yield.

Scheme 6. Synthesis of Alkyne **26**.



35

36, 78%

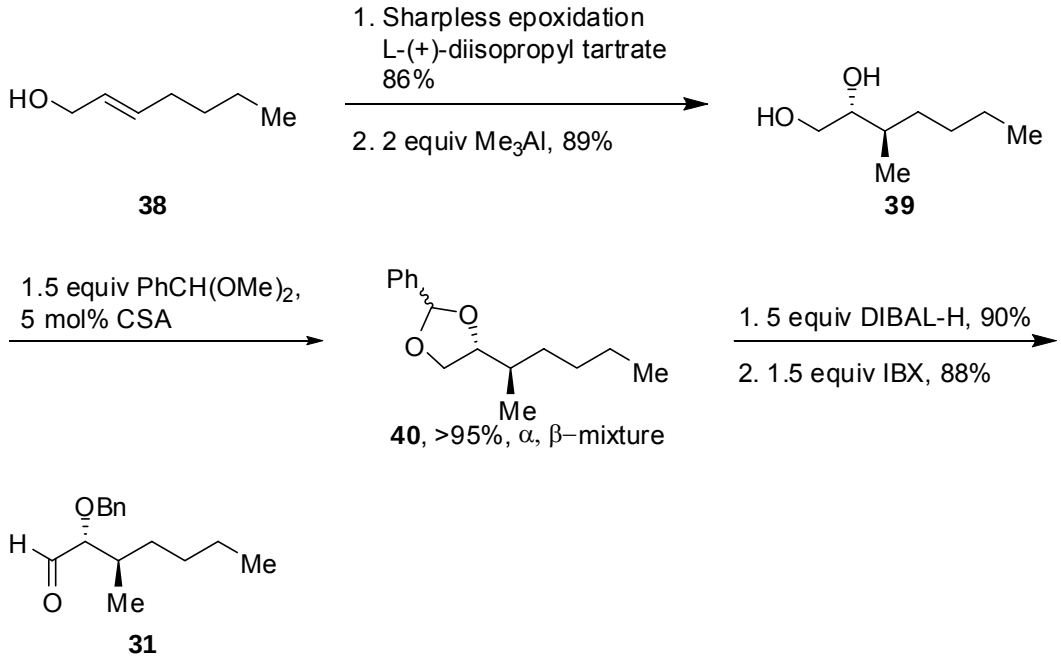
37, 66%

26

*2. 3. 2. Synthesis of Amide **27**: C10-C20 Subunit of Fumonisin B_1.*

With the synthesis of one fragment accomplished, our attention was then changed to the synthesis of amide **27**. As shown in **Scheme 7**, the synthesis of aldehyde **31** corresponding to C14-C20 of fumonisin B_1 commenced with the asymmetric epoxidation of *trans*-2-hepten-1-ol **38** with (+)-diisopropyl tartrate as the chiral ligand.[25] Regio- and stereoselective epoxide opening with exposure of epoxy alcohol to trimethylaluminium in hexane resulted in the formation of diol compound **39** with inversion of the configuration at C-3.[26] The diol **29** reacted smoothly with benzaldehyde dimethylacetal in the presence of a catalytic amount of camphorsulfonic acid (CSA) to give benzylidene acetal **40** in very good yield. Regioselective reductive cleavage of the benzylidene acetal occurred under Lewis-acidic reducing agent diisobutylaluminum hydride (DIBAL-H) to give the primary alcohol. An *o*-iodoxybenzoic acid (IBX) oxidation[27] of the primary alcohol

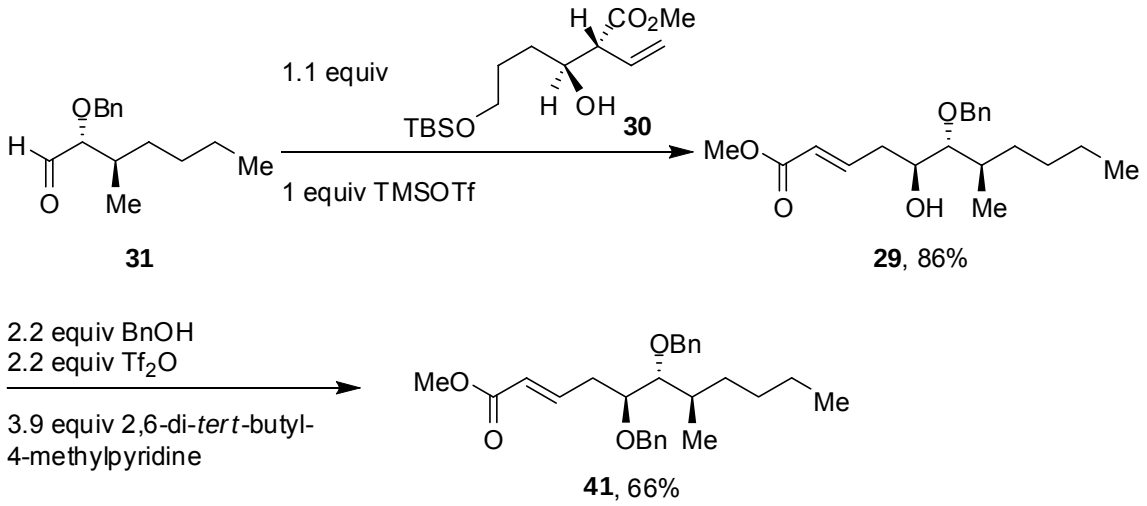
Scheme 7. Synthesis of Aldehyde **31**.



completed the synthesis of aldehyde **31**. It was difficult to identify the diastereoselectivity of the epoxide opening product and benzylidene acetal from ^{1}H NMR spectra, but we could assign the primary alcohol derived from DIBAL-H reduction as a single diastereomer. The oxidation with IBX occurred without observable epimerization of the α-chiral center of aldehyde **31**, and the crude product was used for next transformation without further purification.

The key transformation in the conversion of aldehyde **31** into methyl ester **29** is shown in **Scheme 8**. This case, building on the more modest examples of chapter 1, provides striking testimony to the value of the oxonia-Cope rearrangement for the construction of polyketide subunits. The reaction condition was optimized by using substoichiometric TMSOTf for the cyclic acetal intermediate formation, and subsequent addition of stoichiometric TMSOTf completed the rearrangement in one pot. Compound **29** can be protected in the form of dibenzyl ether under the condition with benzyl triflate that was generated in situ to furnish **41** in 66% yield.[28]

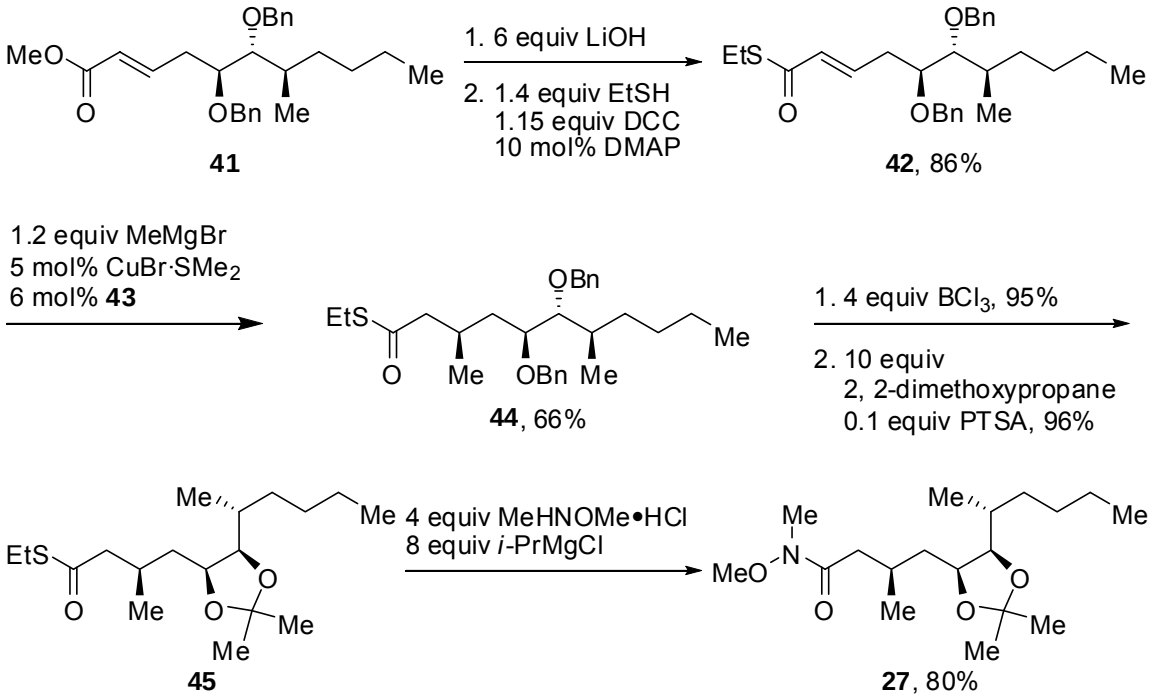
Scheme 8. Synthesis of Methylester **41**.

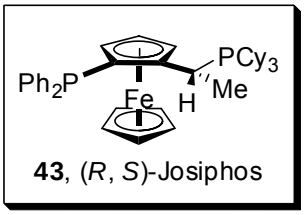


The linchpin fragment would allow the last stereocenter of amide **27** to be introduced with a copper-catalyzed enantioselective conjugate addition as shown in **Scheme 9**. Recently, the Feringa laboratory has reported an inexpensive catalytic enantioselective conjugate addition reactions to simple α,β-unsaturated methyl esters with Josiphos as the chiral ligand.[29] However, the poor results obtained in the 1,4-additions using methyl Grignard reagent was a serious limitation for this method. They subsequently reported reaction conditions for conjugate addition with methyl Grignard reagent and equally accessible α,β-unsaturated thioesters.[30] It was addressed that the reduced electron delocalization in the thioester moiety resulted in a higher reactivity toward conjugate addition. To set the stage for the crucial 1,4-addition, the methyl ester **41** was converted into thioester **42**. The asymmetric Michael addition occurred smoothly by using Feringa's methodology with (*R*, *S*)-Josiphos **43**, methyl magnesium bromide reagent and copper bromide to afford four contiguous stereocenters in **44**. After removal of the benzyl protective groups from **44** with boron trichloride, subjection of the resultant diol to acid-catalyzed acetonide formation provided thioester **45** in very good yield. At this stage, comparison could be made with the Kishi's advanced intermediate toward fumonisin B_2 synthesis by lithium aluminum hydride (LAH) reduction of compound **45** to the corresponding alcohol. The ^{1}H NMR spectrum of crude alcohol from reduction matched with Kishi's tabulated data, and confirmed the correct relative stereochemical relationships. We considered utilizing Fukuyama's palladium-catalyzed coupling of thioester **45** with alkyne **26**,[31] but the azide-alkyne Huisgen

cycloaddition was the potential problem under the coupling condition. Thus the thioester **45** was converted into Weinreb amide **27** by reaction with hydroxy-amine salt.[32]

Scheme 9. Synthesis of Key Intermediate 27.

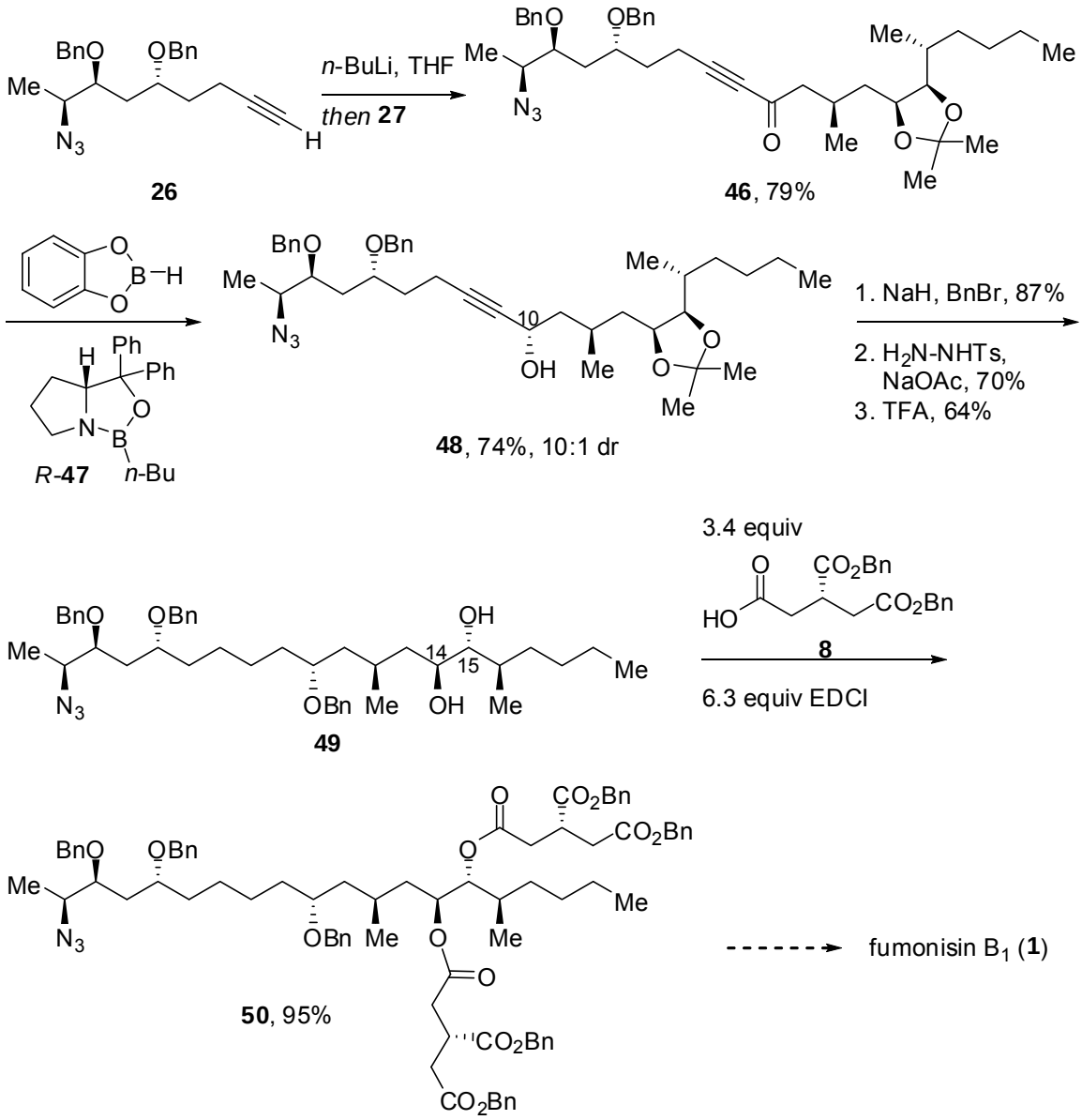




2. 3. 3. Synthesis of Fully Protected Fumonisin B_1.

The retrosynthetic analysis summarized in **scheme 4** identifies alkyne **26** and Weinreb amide **27** as crucial intermediates for fumonisin B_1 (**1**). We adopted one of the most reliable and widely used synthetic methods of metal acetylide coupling with Weinreb amide. As shown in **scheme 10**, the coupling of compounds **26** and **27** can be achieved with equimolar quantity in excellent yield. It was anticipated that the evaluation of reaction conditions was necessary for the asymmetric α,β-ynone reduction to introduce C-10 stereocenter. Indeed, only the catalytic asymmetric ketone reduction with chiral oxazaborolidine catalyst **47**[33] and catecholborane afforded good yield and stereoselectivity, furnishing alcohol **48** with all stereocenters for fumonisin B_1. The final stages of the synthesis of fumonisin B_1 required attachment of acid **8** to C-14 and C-15 of the backbone. To accomplish this important transformation, the hydroxy group at C-10 was first protected as benzyl ether. The alkyne can be selectively reduced with diimide without reaction of the azide or hydrogenolysis of the propargylic oxygen. Solvolysis of the remaining acetonide with trifluoroacetic acid (TFA) afforded diol **49,** which reacted with acid **8** using dehydrating reagent 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (EDCI) and DMAP, to give fully protected fumonisin B_1 **50**. Unfortunately, we have not yet been able to successfully conduct hydrogenolytic removal of the three benzyl ethers, four benzyl esters and hydrogenation of the azide to amine, despite similar precedent from Kishi's fumonisin B_2 synthesis[10] with removal of two, rather than three benzyl ethers.

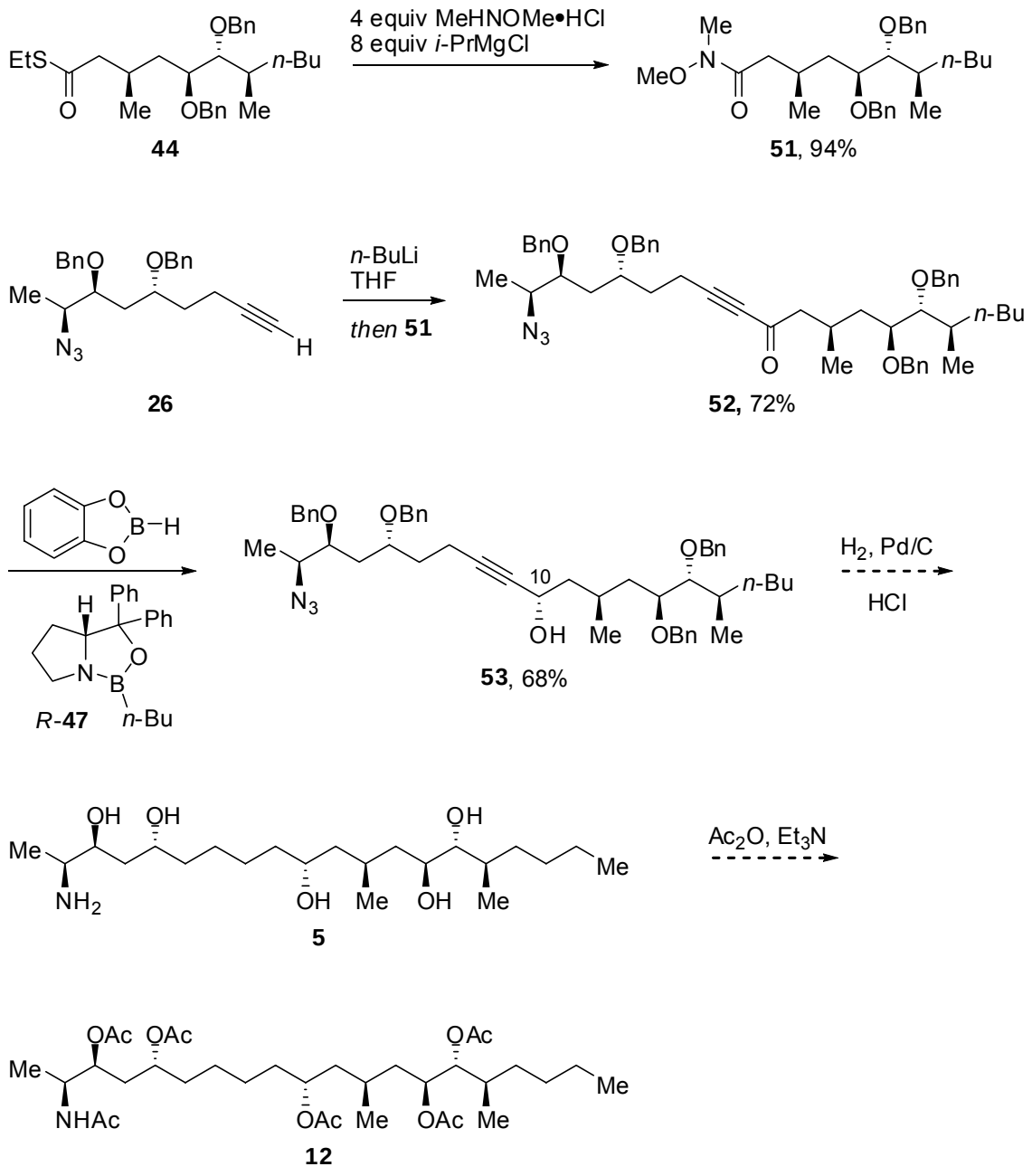
Scheme 10. Synthesis of Fully Protected Fumonisin B_1 50.



2. 3. 4.Towards the Synthesis of Aminopentol Hexaacetate Derivative.

All of the processes that we have addressed so far for fumonisin B_1 synthesis have proceeded smoothly except the global deprotection and concomitant azide reduction of compound **50**. The product from the final step is not clear based on ^{1}H NMR spectrum at this time. Obviously, during the course of study simplifying substrate without the side chains at C-14 and C-15 hydroxy groups can help us to understand if it is necessary to change protective groups on tricarballylic acid moiety. Moreover, the abundance of the natural source and high carcinogenicity of fumonisin B_1 and B_2 diminished the importance of pursuing the total synthesis and advanced biological test. Prof. Merrill's laboratory has reported that the acylated aminopentol **5** was more cytotoxic to a human colonic cancer cell line than the parent natural product fumonisin B_1.[5c] Therefore we shifted our attention to the synthesis of aminopentol hexaacetate derivative **12** as shown in **Scheme 11**. Under the same condition for the preparation of Weinreb amide **27**, the desired amide **51** was produced in good yield, which reacted with lithium acetylide generated from alkyne **26** to give ynone **52**. Asymmetric ketone reduction with chiral oxazaborolidine catalyst **47** and catecholborane was applied to introduce the required stereocenter at C-10. Although the prospects for global deprotection and reduction with hydrogen and palladium catalyst seem excellent, the last two steps did not provide the fully protected aminopentol **12** which has been reported by Gurjar and co-workers.[13] It was difficult to interpret the product based on the spectrum of crude mixture.

Scheme 11. Synthesis of Aminopentol Hexaacetate Derivative 12.

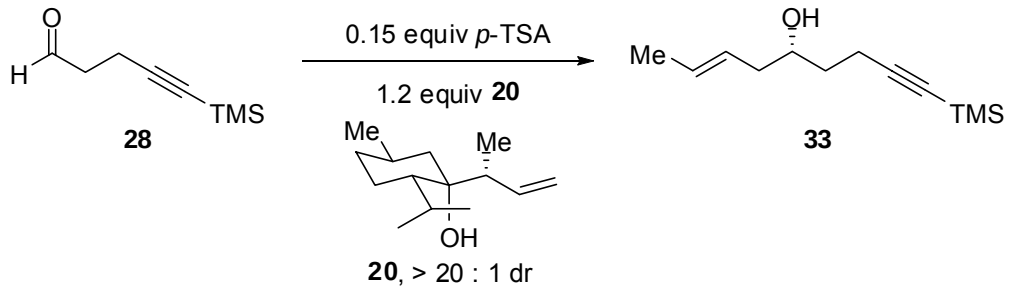


2.4. Conclusions. In conclusion, the 2-oxonia-[3,3]-sigmatropic rearrangement has involved into a powerful tool for the elaboration of polyketide-based natural product synthesis. This transformation as a vinylogous aldol equivalent can provide access to bisacetate compounds under Lewis acid condition. By applying this methodology, the synthesis of main skeleton of fumonisin B_1 was accomplished in a convergent and very concise manner.

2.5. Experimental Section.

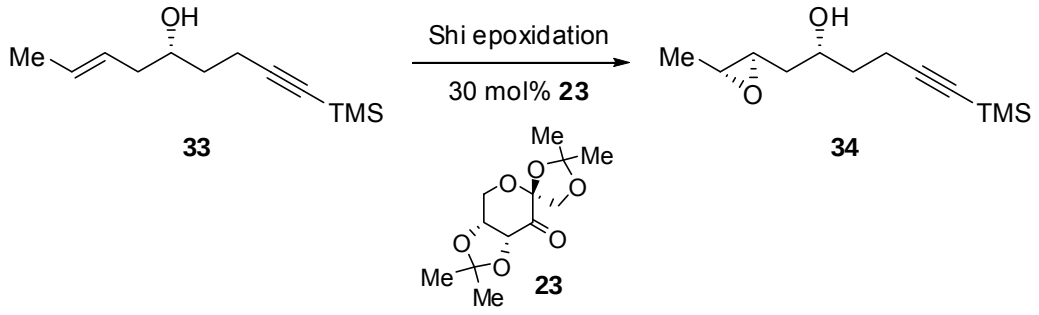
General. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C), INOVA-600 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C), NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$) with residual chloroform (δ 7.26 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR), or deuterated benzene (C_6D_6) with residual benzene (δ 7.16 ppm for ^{1}H NMR and δ 128.4 ppm for ^{13}C NMR) taken as the standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were collected on a Mattson Genesis II FT-IR spectrometer as neat films. Mass spectra (high resolution APCI) was recorded on a Finnigan LTQ-FTMS Mass spectrometer. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatography using Chiralpak AS-RH (15 cm) and Chiralpak AS (25 cm) columns. Optical rotations were measured using a Perkin-Elmer 341 polarimeter. Analytical Thin Layer Chromatography (TLC) was performed on precoated glass backed plates purchased from

Whatman (silica gel 60F254; 0.25mm thickness). Flash column chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from EM Science. All reactions were carried out with anhydrous solvents in oven-dried or flame-dried and argon-charged glassware. All anhydrous solvents except as mentioned were dried with 4 Å molecular sieves (beads) purchased from Sigma-Aldrich and tested for trace water content with Coulometric KF Titrator from Denver Instruments. All solvents used in extraction procedures and chromatography were used as received from commercial suppliers without prior purification. All reagents were purchased from Sigma-Aldrich or Strem Chemicals.



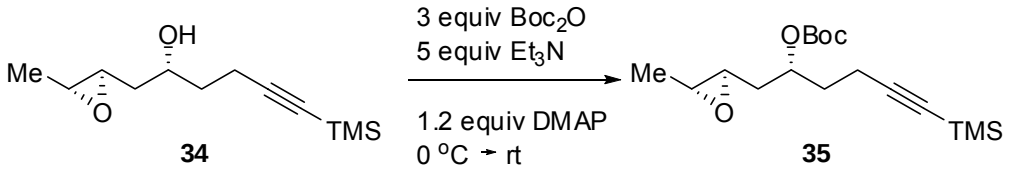
(*R*,*E*)-1-(Trimethylsilyl)non-7-en-1-yn-5-ol (33). In a 50 mL round-bottom flask, *p*-toluenesulfonic acid monohydrate (*p*-TSA) (336 mg, 1.77 mmol) was added to a solution of 5-(trimethylsilyl)pent-4-ynal **28** (1.82 g, 11.8 mmol) and crotyl donor reagent **20** (2.98 g, 14.1 mmol) in CH_2Cl_2 (20 mL) under argon at room temperature. The resulting solution was stirred at room temperature for 5 h and quenched with saturated $NaHCO_3$ (5 mL). The extractions were performed with CH_2Cl_2 and organic layer was dried over $MgSO_4$ followed by concentration to afford yellowish oil. The residue was purified by flash chromatography on silica

gel (ether/pentane = 1:5) to yield compound **33** (2.14 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61-5.52 (m, 1H), 5.47-5.39 (m, 1H), 3.75-3.70 (m, 1H), 2.37 (t, 2H, *J* = 6.8 Hz), 2.26-2.20 (m, 1H), 2.14-2.07 (m, 1H), 1.69 (dd, 3H, *J* = 6.0, 1.2 Hz), 1.74-1.59 (m, 3H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.1, 126.7, 107.0; 85.1, 70.2, 40.5, 35.1, 18.1, 16.5, 0.1; HRMS (APCI): *m/z* calcd. for $C_{12}H_{23}OSi$ (M^+) 211.1513, found 211.1511; FT-IR (KBr) 3392, 3023, 2959, 2920, 2174, 1441 cm^{-1}; $[\alpha]^{25}_D$ = +7.4 (c = 1.9, $CHCl_3$).



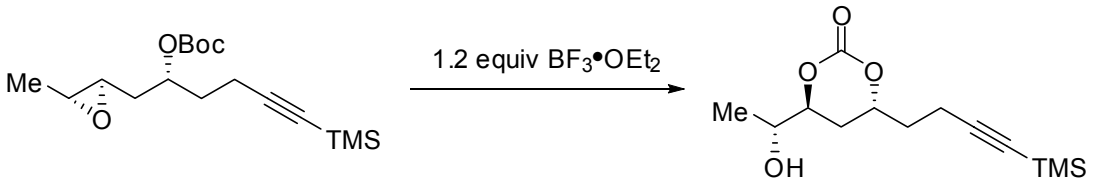
(*R*)-1-((2*R*,3*R*)-3-Methyloxiran-2-yl)-6-(trimethylsilyl)hex-5-yn-2-ol (34). The homoallylic alcohol **33** (1.50 g, 7.13 mmol) was taken into acetonitrile (53 mL) and dimethoxymethane (106 mL). A solution of 0.05 M $Na_2B_4O_7{\cdot}10H_2O$ in $4*10^{-4}$ M ethylenediaminetetraacetic acid (EDTA) (103 mL) was added followed by tetrabutyl ammonium hydrogen sulphate (86 mg, 0.21 mmol) and Shi ketone **23** (0.55 g, 2.1 mmol). The resulting solution was cooled to 0 ˚C. A solution of Oxone® (7.01 g, 11.4 mmol) in $4*10^{-4}$M EDTA (32 mL) and a solution of K_2CO_3 (6.59 g, 47.8 mmol) in water (32 mL) were added simultaneously over a period of 1.5 h. After complete addition, the reaction was maintained at 0 ˚C for additional 30 min before quenching with hexane. The precipitated was filtered of and the

extractions were performed with hexane. The combined organic layer was dried over Na_2SO_4 and concentrated to afford the crude mixture. The mixture was purified by flash chromatography on silica gel (ether/pentane = 1:1) to yield epoxy alcohol **34** (1.46 g, 88%). ^{1}H NMR analysis of the product revealed ~10:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04-4.00 (m, 1H), 2.85-2.83 (m, 1H), 2.80 (dq, 1H, *J* = 1.8, 5.2 Hz), 2.43 (d, 1H, *J* = 3.6 Hz), 2.38 (ddd, 2H, *J* = 2.4, 6.6, 6.6 Hz), 1.88 (ddd, 1H, *J* = 14.4, 3.6, 3.6 Hz) 1.71 (ddd, 2H, *J* = 7.2, 6.6, 6.0 Hz), 1.52 (ddd, 1H, *J* = 14.4, 7.8, 7.8 Hz), 1.32 (d, 3H, *J* = 5.2 Hz), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.7, 85.4, 69.7, 57.7, 54.2, 39.0, 35.6, 17.5, 16.3, 0.1; HRMS (APCI): *m/z* calcd. for $C_{12}H_{23}O_2Si$ (M^+) 227.1462, found 227.1460; FT-IR (KBr) 3437, 2959, 2358, 2173, 1438 cm^{-1}.



***tert*-Butyl-(*R*)-1-((2*R*,3*S*)-3-methyloxiran-2-yl)-6-(trimethylsilyl)hex-5-yn-2-yl carbonate (35).** In a 250 mL round-bottom flask, a solution of *t*-butyl dicarbonate (Boc_2O) (4.22 g, 19.4 mmol) in CH_2Cl_2 was added slowly to a solution of alcohol **34** (1.46 g, 6.45 mmol), DMAP (951 mg, 7.74 mmol), and triethylamine (4.48 mL, 32.3 mmol) in CH_2Cl_2 (130 mL) under argon at 0 ˚C. The resulting solution was stirred at 0 ˚C to room temperature over 20 h and quenched with saturated $NaHCO_3$. The extractions were performed with CH_2Cl_2 and organic layer was dried over Na_2SO_4 followed by concentration to afford yellowish oil. The residue

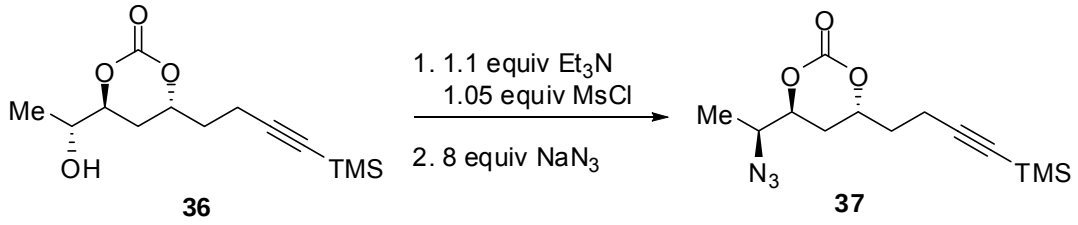
was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:6) to yield compound **35** (1.82 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93-4.87 (m, 1H), 2.78-2.72 (m, 2H), 2.32 (t, 2H, *J* = 7.6 Hz), 1.97-1.79 (m, 4H), 1.49 (s, 9H), 1.30 (d, 3H, *J* = 5.2 Hz), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 105.7, 85.3, 82.1, 74.0, 55.9, 54.0, 36.4, 32.8, 27.8, 17.5, 16.1, 0.1; HRMS (APCI): *m/z* calcd. for $C_{17}H_{31}O_4Si$ (M^+) 327.1986, found 327.1985; FT-IR (KBr) 2963, 2176, 1740, 1279 cm^{-1}.



35 **36**

(4*S*,6*R*)-4-((*R*)-1-Hydroxyethyl)-6-(4-(trimethylsilyl)but-3-ynyl)-1,3-dioxan-2-one (36). The *t*-butyl carbonate **35** (1.82 g, 5.57 mmol) was taken into CH_2Cl_2 (113 mL) was cooled to -40 ˚C followed by dropwise addition of freshly distilled boron trifluoride etherate (0.85 mL, 6.7 mmol) under argon. The solution was stirred for additional 1 h at -40 ˚C before quenching with saturated $NaHCO_3$ and allowed to warm to room temperature. The extractions were performed with ethyl acetate and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:1) to yield cyclic carbonate **36** (1.18 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03-4.98 (m, 1H), 4.88 (ddd, 1H, *J* = 6.2, 6.4, 13.4 Hz), 4.07-4.00 (m, 1H), 2.45-2.35 (m, 3H), 1.84-1.62 (m, 4H), 1.36 (d, 3H, *J* = 6.8 Hz),

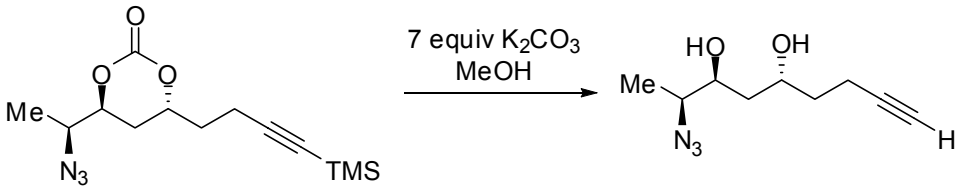
0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 106.2, 86.5, 76.8, 76.0, 67.7, 36.0, 35.9, 16.5, 14.9, -0.1; HRMS (APCI): *m/z* calcd. for $C_{13}H_{23}O_4Si$ (M^+) 271.1360, found 271.1359; FT-IR (KBr) 3459, 2957, 2174, 1795 cm^{-1}; $[\alpha]^{25}_D$ = -44.2 (c = 0.42, $CHCl_3$).



36 **37**

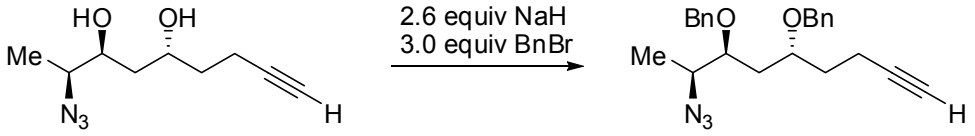
(4*S*,6*R*)-4-((*S*)-1-Azidoethyl)-6-(4-(trimethylsilyl)but-3-ynyl)-1,3-dioxan-2-one (37). In a 100 mL round-bottom flask, methane sulfonyl chloride (MsCl) (0.14 mL, 1.9 mmol) was added slowly to a solution of carbonate **36** (480 mg, 1.75 mmol), and triethylamine (0.27 mL, 1.9 mmol) in CH_2Cl_2 (15 mL) under argon at 0 ˚C. The resulting solution was stirred at 0 ˚C for 2 h and quenched with water. The extractions were performed with CH_2Cl_2 and organic layer was dried over Na_2SO_4 followed by concentration to afford crude mesylate. The residue was then dissolved in anhydrous dimethylformamide (DMF) (15 mL) followed by the addition of NaN_3 (0.92 g, 14 mmol). The resulting mixture was stirred at 70 ˚C for 24 h and quenched with water (30 mL). The extractions were performed with ether and organic layer was dried over Na_2SO_4 followed by concentration to afford colorless oil. The crude mixture was purified by flash chromatography on silica gel (ether/pentane = 1:2 → 1:1) to yield compound **37** (340 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92-4.80 (m, 2H), 3.78-3.72 (m, 1H), 2.42 (t, 2H, *J* =

6.4 Hz), 2.07-1.99 (m, 1H), 1.89-1.75 (m, 3H), 1.39 (d, 3H, *J* = 6.4 Hz), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 104.7, 86.5, 76.1, 75.7, 58.2, 33.0, 32.3, 16.6, 14.7, 0.1; HRMS (APCI): *m/z* calcd. for $C_{13}H_{22}N_3O_3Si$ (M^+) 296.1425, found 296.1422; FT-IR (KBr) 2959, 2174, 2103, 1799 cm^{-1}; $[\alpha]^{25}_D$ = -111.2 (c = 0.41, $CHCl_3$).



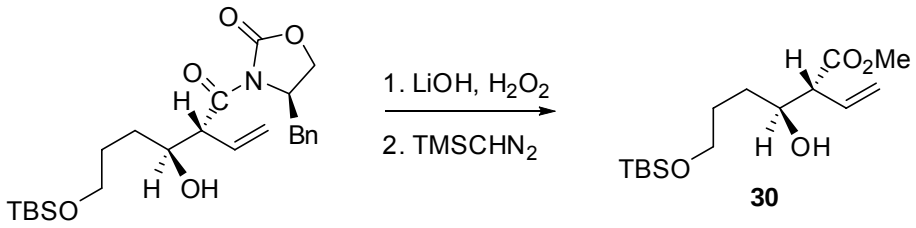
37

(2*S*,3*S*,5*R*)-2-Azidonon-8-yne-3,5-diol. The carbonate **37** (300 mg, 1.02 mmol) was taken into methanol (10 mL) and added K_2CO_3 (983 mg, 7.11 mmol) at room temperature. The solution was stirred 6 h at room temperature before quenching with saturated water. The extractions were performed with ethyl acetate and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:1.5) to yield the product (195 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84-3.77 (m, 1H), 3.76-3.68 (m, 2H), 2.73 (bs, 1H), 2.36 (ddd, 2H, *J* = 2.4, 6.8, 6.8 Hz), 2.30 (bs, 1H), 2.01 (t, 1H, *J* = 2.4 Hz), 1.88-1.70 (m, 2H), 1.67 (t, 2H, *J* = 6.8 Hz), 1.16 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.7, 72.9, 70.3, 69.5, 59.7, 35.4, 32.9, 17.1, 15.2; HRMS (APCI): *m/z* calcd. for $C_9H_{16}N_3O_2$ (M^+) 198.1237, found 198.1242; FT-IR (KBr) 3401, 3299, 2926, 2102 cm^{-1}; $[\alpha]^{25}_D$ = -60.8 (c = 0.59, $CHCl_3$).



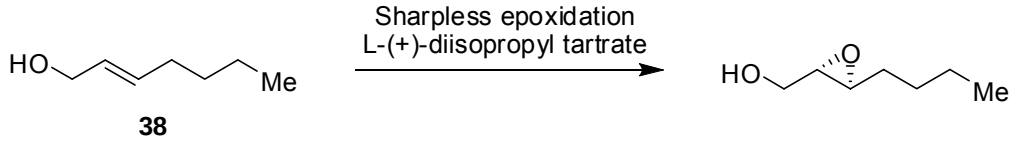
26

((2*S*,3*S*,5*R*)-2-azidonon-8-yne-3,5-diyl)bis(oxy)bis(methylene)dibenzene (26). In a 50 mL round-bottom flask, sodium hydride (98 mg, 60% dispersion in mineral oil, 2.4 mmol) was added to a solution of (2*S*,3*S*,5*R*)-2-azidonon-8-yne-3,5-diol (185 mg, 0.93 mmol) and tetrabutylammonium iodide (11 mg, 0.03 mmol) in THF (10 mL) under argon at 0 ˚C. The resulting solution was stirred at 0 ˚C for 10 min and room temperature for 30 min before adding benzyl bromide (0.34 mL, 2.8 mmol) at room temperature. The resulting solution was stirred at room temperature for 3 h and quenched with saturated NH_4Cl. The extractions were performed with ether and organic layer was dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography on silica gel (ether/pentane = 1:10) to yield compound **26** (312 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 10H), 4.71 (d, 1H, *J* = 11.4 Hz), 4.65 (d, 1H, *J* = 11.4 Hz), 4.56 (d, 1H, *J* = 5.0 Hz), 4.53 (d, 1H, *J* = 5.0 Hz), 3.70-3.63 (m, 2H), 3.55 (ddd, 1H, *J* = 4.4, 4.0, 8.0 Hz), 2.34-2.22 (m, 2H), 2.00-1.93 (m, 1H), 1.94 (t, 1H, *J* = 2.8 Hz), 1.74-1.66 (m, 2H), 1.61-1.52 (m, 1H), 1.25 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.3, 128.4, 128.4, 128.0, 127.7, 127.6, 127.5, 83.0, 78.6, 76.5, 72.3, 71.1, 69.2, 58.8, 35.6, 32.6, 15.5, 15.4; HRMS (APCI): *m/z* calcd. for $C_{23}H_{28}N_3O_2$ (M^+) 378.2176, found 378.2174; FT-IR (KBr) 2929, 2099, 1453 cm^{-1}; $[\alpha]^{25}_D$ = -42.6 (c = 0.47, $CHCl_3$).



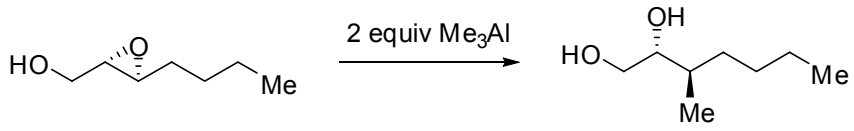
(2*R*,3*S*)-Methyl-6-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2-vinylhexanoate (30). To a solution of imide (7.50 g, 16.8 mmol) in dioxane (148 mL) was added H_2O_2 (23.6 mL, 30% in water, 201 mmol) and LiOH (1.41 g, 58.6 mmol) at 0 ˚C. The resulting solution was stirred at 0 ˚C for 1 h and room temperature for 1.5 h and then partitioned between saturated NH_4Cl (200 mL) and CH_2Cl_2 (200 mL). The aqueous layer was acidified to pH = 3 and the extractions were performed with ethyl acetate and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. A solution of the crude acid in benzene (180 mL) and methanol (45 mL) was added (trimethylsilyl)diazomethane (20.9 mL, 2 M in diethyl ether, 42 mmol) *via* syringe at room temperature. The resulting solution was stirred at room temperature for 2 h and concentrated to afford yellowish oil. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:6) to yield compound **30** (3.95 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (ddd, 1H, *J* = 10.0, 10.0, 16.8 Hz), 5.31-5.20 (m, 2H), 3.97-3.94 (m, 1H), 3.72 (s, 3H), 3.65 (t, 2H, *J* = 6.0 Hz), 3.12 (d, 1H, *J* = 3.6 Hz), 3.09 (dd, 1H, *J* = 4.8, 9.2 Hz), 1.72-1.45 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 132.0, 120.0, 71.3, 63.1, 55.9, 52.0, 31.3, 29.0, 25.9, 18.3, -5.4; HRMS (APCI): *m/z* calcd. for $C_{15}H_{31}O_4Si$ (M^+) 303.1986, found 303.1984;

FT-IR (KBr) 3461, 2953, 2930, 2858, 1737, 1471 cm^{-1}; $[\alpha]^{25}_D$ = +42.6 (c = 0.32, $CHCl_3$).



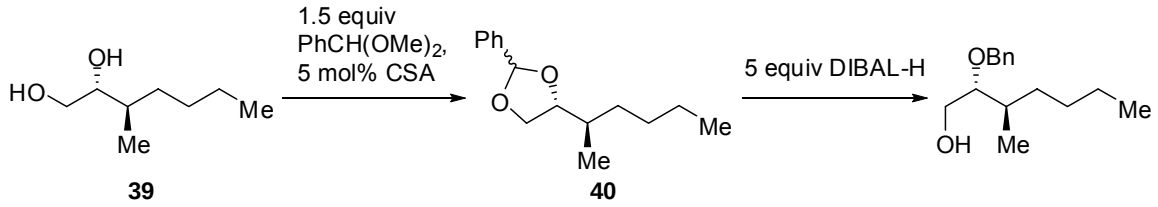
38

((2*S*,3*S*)-3-butyloxiran-2-yl)methanol. In a 250 mL round-bottom flask, L-(+)-diisopropyl tartrate (616 mg, 1.60 mmol) and titanium tetraisopropoxide (642 mg, 1.30 mmol) were added to a solution of 4Å molecular sieve (3.75 g) in CH_2Cl_2 (45 mL) under argon at -20 ˚C and the solution was stirred for 15 min. The resulting solution was treated with *tert*-butylhydroperoxide (4.78 mL, 5.5 M in decane, 26.3 mmol) at -20 ˚C and stirred for another 30 min before the addition of alcohol **38** (1.50 g, 12.6 mmol). The reaction was run at -20 ˚C for 12 h, quenched with citric acid (276 mg, 1.3l mmol), and diluted with ether (90 mL) and acetone (90 mL). The reaction mixture was stirred at 0 ˚C for 30 min and filtered through Celite. The solution was concentrated and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:1.5) to yield epoxide (1.41 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93-3.90 (ddd, 1H, *J* = 2.4, 5.4, 12.6 Hz), 3.65-3.61 (m, 1H), 2.97-2.95 (m, 1H), 2.93-2.92 (m, 1H), 1.64-1.56 (m, 2H), 1.49-1.30 (m, 4H), 0.92 (t, 3H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.7, 58.5, 56.0, 31.2, 28.0, 22.4, 13.9; FT-IR (KBr) 3429, 2958, 2931, 1744, 1467 cm^{-1}; $[\alpha]^{25}_D$ = -28.5 (c = 4.16, $CHCl_3$).



39

(2*R*,3*R*)-3-methylheptane-1,2-diol (39). In a 250 mL round-bottom flask, the epoxy alcohol (1.50 g, 10.9 mmol) in anhydrous hexane (12 mL) was added slowly to a solution of trimethyl aluminum (22 mL, 1.0 M in hexane, 22 mmol) under argon at 0 ˚C. After stirring for 1 h at 0 ˚C, the resulting mixture was diluted with CH_2Cl_2 (100 mL), treated with NaF (10 g, 240 mmol) and water (200 mL). Vigorous stirring of the resulting suspension was continued at room temperature for 30 min. The semi-solid was filtered through Celite. The extractions were performed with ethyl acetate and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:1.5) to yield the product (1.42 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73-3.69 (m, 1H), 3.54-3.49 (m, 2H), 2.05 (d, 1H, *J* = 3.0 Hz), 1.86-1.85 (m, 1H), 1.57-1.51 (m, 2H), 1.40-1.12 (m, 5H), 0.93-0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.2, 64.6, 36.1, 32.1, 29.2, 22.9, 15.2, 14.1; FT-IR (KBr) 3391, 2928, 2860, 1462 cm^{-1}; $[\alpha]^{25}_D$ = +11.4 (c = 2.69, $CHCl_3$).

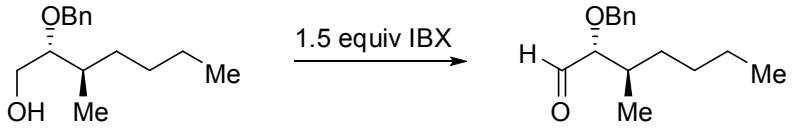


39 **40**

(2*R*,3*R*)-2-(benzyloxy)-3-methylheptan-1-ol. The diol **39** (1.05 g, 7.18 mmol) was dissolved in anhydrous acetonitrile (21 mL) and added benzaldehyde dimethyl acetal (1.64 g, 10.8 mmol) and CSA (85 mg, 0.36 mmol) at 0 ˚C. The mixture was stirred at 0 ˚C for 30 min and room temperature for 1 h. The reaction was quenched with water. The extractions were performed with ethyl acetate and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (ether/pentane = 1:8) to yield the product (1.60 g, 95%). ^{1}H NMR analysis of the product revealed ~1:1 dr. HRMS (APCI): *m/z* calcd. for $C_{15}H_{23}O_2$ (M^+) 235.1693, found 235.1691.

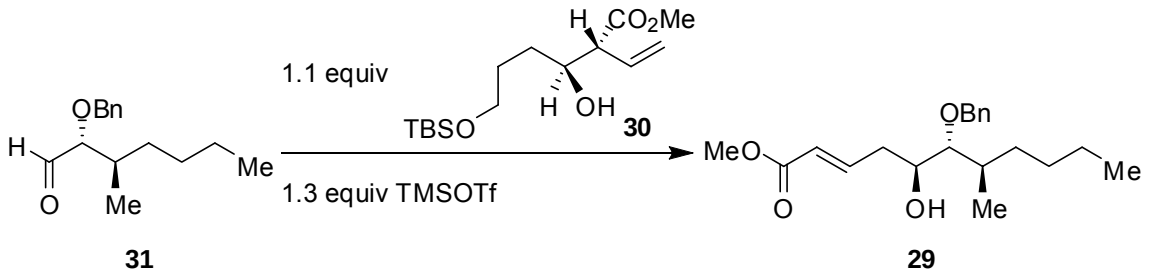
The benzylidene acetal **40** (1.45g, 6.19 mmol) was dissolved in anhydrous toluene (35 mL) under argon and added DIBAL-H (31.0 mL, 1.0 M in CH_2Cl_2, 31 mmol) *via* syringe pump over 1 h at 0 ˚C. The resulting solution was further stirred at 0 ˚C for 2 h and quenched with ethyl acetate and saturated Rochelle's salt. Vigorous stirring of the resulting mixture was continued at room temperature for 20 min. The extractions were performed with ethyl acetate and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (ether/pentane = 1:3→1:2) to yield the product (1.32 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 4.64 (d, 1H, *J* = 11.0 Hz), 4.52 (d, 1H, *J* = 11.0 Hz), 3.71-3.58 (m, 2H), 3.39-3.35 (m,

1H), 1.90-1.84 (m, 1H), 1.57 (bs, 1H), 1.49-1.42 (m, 1H), 1.39-1.12 (m, 5H), 0.91-0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.5, 127.8, 127.7, 83.8, 71.9, 61.5, 33.6, 32.5, 29.5, 22.9, 14.7, 14.1; HRMS (APCI): *m/z* calcd. for $C_{15}H_{25}O_2$ (M^+) 237.1849, found 237.1848; FT-IR (KBr) 3414, 2956, 2872, 1607, 1455 cm^{-1}; $[\alpha]^{25}_D$ = -13.2 (c = 0.55, $CHCl_3$).



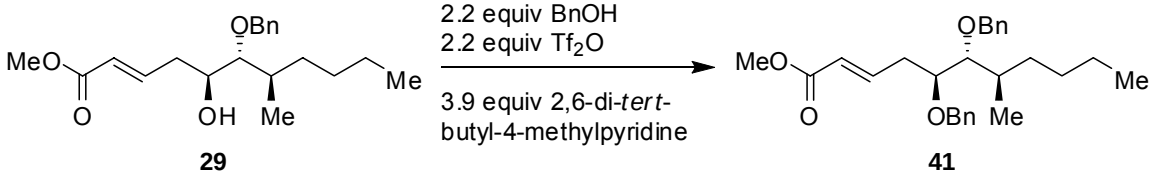
31

(2*R*,3*R*)-2-(benzyloxy)-3-methylheptanal (31). In a 50 mL round-bottom flask, the alcohol (306 mg, 1.29 mmol) in DMSO (1 mL) was added to a solution of IBX (542 mg, 1.94 mmol) in DMSO (3 mL) under argon at room temperature. After stirring for 2 h at room temperature, the reaction was quenched with water (15 mL). The precipitate was filtered off and the extractions were performed with ether. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The aldehyde **31** was used for next step without further purification (268 mg, 88%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, 1H, *J* = 2.8 Hz), 7.36-7.29 (m, 5H), 4.68 (d, 1H, *J* = 12.0 Hz), 4.49 (d, 1H, *J* = 12.0 Hz), 3.54 (dd, 1H, *J* = 6.0, 2.8 Hz), 1.99-1.93 (m, 1H), 1.53-1.47 (m, 1H), 1.32-1.16 (m, 5H), 0.96 (d, 3H, *J* = 7.2 Hz), 0.87 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 137.5, 128.5, 127.9, 127.9, 87.5, 72.8, 35.0, 31.4, 29.2, 22.8, 15.6, 14.0; HRMS (APCI): *m/z* calcd. for $C_{15}H_{23}O_2$ (M^+) 235.1693, found 235.1692; FT-IR (KBr) 2957, 2930, 2860, 1731, 1455 cm^{-1}.



(5*S*,6*R*,7*R*,*E*)-Methyl-6-(benzyloxy)-5-hydroxy-7-methylundec-2-enoate (29). Alcohol **30** (380 mg, 1.26 mmol) and aldehyde **31** (268 mg, 1.14 mmol) were dissolved in CH_2Cl_2 (11 mL), cooled to -25 °C, and TMSOTf (51 mg, 0.23 mmol) was added dropwise. The resulting solution was stirred at -25 °C for 1 h and more TMSOTf (280 mg, 1.25 mmol) was added at the same temperature. The reaction mixture was further stirred for 30 min between -25 and -15 °C and quenched with saturated aqueous $NaHCO_3$ (3 mL) at -15 °C. The resulting solution was stirred at room temperature for another 15 min. The extractions were performed with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography silica gel (ether/pentane = 1:3→1:2) to yield the product **29** (328 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 7.04 (ddd, 1H, *J* = 7.6, 7.8, 15.6 Hz), 5.92 (dt, 1H, *J* = 15.6, 1.2 Hz), 4.69 (d, 1H, *J* = 11.2 Hz), 4.61 (d, 1H, *J* = 11.2 Hz), 3.93-3.87 (m, 1H), 3.73 (s, 3H), 3.28 (dd, 1H, *J* = 4.8, 5.4 Hz), 2.54-2.48 (m, 1H), 2.44-2.36 (m, 1H), 1.78-1.59 (m, 3H), 1.40-1.16 (m, 5H), 0.95 (d, 3H, *J* = 6.8 Hz), 0.90 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 146.3, 138.5, 128.5, 127.7, 127.6, 123.3, 86.8, 74.7, 71.1, 51.5, 35.4, 35.0, 31.9, 29.4, 23.0, 16.3, 14.1; HRMS (APCI): *m/z* calcd. for $C_{20}H_{31}O_4$ (M^+) 335.2217,

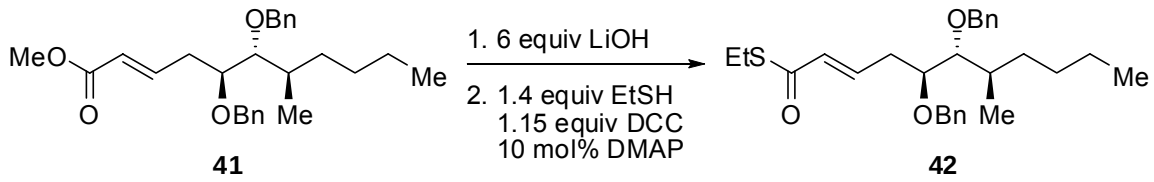
found 335.2215; FT-IR (KBr) 3430, 2954, 2861, 1723, 1656 cm^{-1}; $[\alpha]^{25}_D$ = -23.0 (c = 0.55, $CHCl_3$).



29 **41**

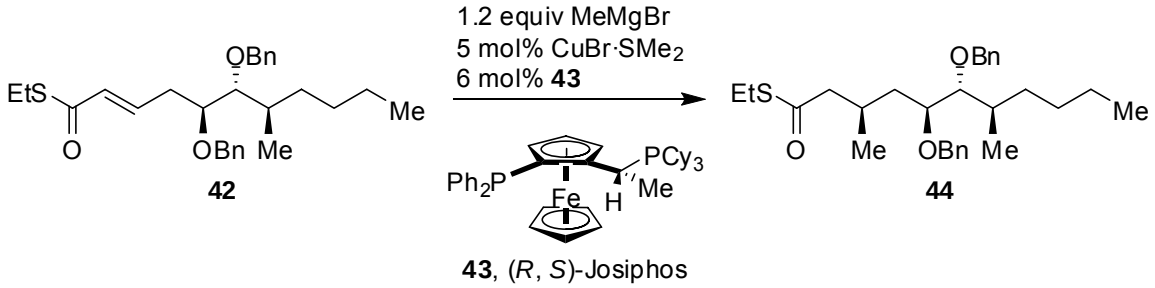
(5*S*,6*R*,7*R*,*E*)-Methyl-5,6-bis(benzyloxy)-7-methylundec-2-enoate (41). In a 50 mL round-bottom flask, a solution of triflic anhydride (578 mg, 2.05 mmol) in CH_2Cl_2 (6 mL) was added to a solution of benzyl alcohol (222 mg, 2.05 mmol) and 2,6-di-*tert*-butyl-4-methyl-pyridine (507 mg, 2.42 mmol) in CH_2Cl_2 (3 mL) at -78 °C under argon and the solution was stirred for 5 min. The resulting solution was treated with a solution of homoallylic alcohol **29** (310 mg, 0.93 mmol) and 2,6-di-*tert*-butyl-4-methyl-pyridine (254 mg, 1.21 mmol) in CH_2Cl_2 (4 mL). The reaction was run at -78 ˚C to 0 ˚C over 1.5 h, kept at 0 ˚C for 1 h and quenched with saturated NH_4Cl. The extractions were performed with CH_2Cl_2 and organic layer was dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography on silica gel (ether/pentane = 1:4) to yield compound **41** (260 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-6.98 (m, 11H), 5.90 (d, 1H, *J* = 15.6 Hz), 4.77 (d, 1H, *J* = 11.2 Hz), 4.61-4.47 (m, 3H), 3.74 (s, 3H), 3.71-3.65 (m, 1H), 3.41 (dd, 1H, *J* = 6.4, 5.2 Hz), 2.67-2.44 (m, 2H), 1.74-1.57 (m, 2H), 1.41-1.09 (m, 5H), 0.93-0.87 (m, 6H);); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 147.0, 138.8, 138.0, 128.4, 128.3, 127.9, 127.8, 127.7,

127.5, 122.6, 83.8, 79.2, 74.2, 71.7, 51.4, 35.0, 33.0, 32.0, 29.3, 13.0, 16.6, 14.1; HRMS (APCI): *m/z* calcd. for $C_{27}H_{37}O_4$ (M^+) 425.2686, found 425.2684; FT-IR (KBr) 2953, 2929, 2860, 1723, 1657, 1092 cm^{-1}; $[\alpha]^{25}_D$ = -14.1 (c = 0.50, $CHCl_3$).



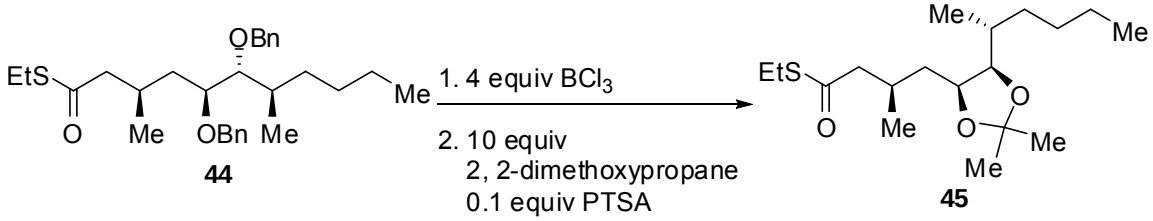
(5*S*,6*R*,7*R*,*E*)-*S*-ethyl-5,6-bis(benzyloxy)-7-methylundec-2-enethioate (42). Methyl ester **41** (300 mg, 0.710 mmol) was dissolved in THF (3 mL), and the resulting solution was added water (1 mL), methanol (1 mL) and lithium hydroxide (102 mg, 4.26 mmol) at room temperature. The resulting solution was stirred at 40 ˚C overnight and was acidified to pH = 3 at 0 ˚C. The extractions were performed with dichloromethane and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude acid was dissolved in CH_2Cl_2 (5 mL) and subsequent addition of ethanethiol (72 µL, 0.92 mmol), DMAP (9 mg, 0.07mmol) and dicyclohexyl carbodiimide (DCC) (209 mg, 1.01 mmol) at 0 ˚C. The resulting mixture was allowed to slowly warm to room temperature overnight. The mixture was then filtered through Celite, and precipitate was washed with dichloromethane. The filtrate was washed with saturated $NaHCO_3$, water, and brine, then dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography on silica gel (ether/pentane = 1:20→1:15→1:10) to yield compound **42** (278 mg, 86%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.08 (m, 10H), 7.03-6.90 (m, 1H), 6.16 (d, 1H, *J* =

15.0 Hz), 4.76 (d, 1H, *J* = 10.8 Hz), 4.60-4.54 (m, 3H), 3.71-3.64 (m, 1H), 3.38 (dd, 1H, *J* = 6.4, 5.0 Hz), 2.95 (q, 2H, *J* = 7.2 Hz), 2.63-2.49 (m, 2H), 1.71-1.57 (m, 2H), 1.39-1.12 (m, 5H), 1.29 (t, 3H, *J* = 7.2 Hz), 0.91-0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 142.8, 130.4, 128.8, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.5, 83.8, 79.2, 74.2, 71.8, 35.0, 33.0, 32.0, 29.2, 23.0, 16.5, 14.8, 14.1; HRMS (APCI): *m/z* calcd. for $C_{28}H_{39}O_3S$ (M^+) 455.2614, found 455.2613; FT-IR (KBr) 3029, 2929, 1671, 1632 cm^{-1}; $[\alpha]^{25}_D$ = -5.9 (c = 0.75, $CHCl_3$).



(3*R*,5*S*,6*R*,7*R*)-S-ethyl-5,6-bis(benzyloxy)-3,7-dimethylundecanethioate (44). $CuBr{\cdot}SMe_2$ (8 mg, 0.04 mmol) and (*R*, *S*)-Josiphos **43** (29 mg, 0.048 mmol) in ^{t}BuOMe (7 mL) was stirred at room temperature under argon for 30 min. The mixture was cooled to -78 ˚C and a solution of methyl Grignard reagent (0.30 mL, 3.0 M in ether, 0.9 mmol) was added dropwise. After stirring for 10 min at -78 ˚C, a solution of thioester **42** (320 mg, 0.70 mmol) in ^{t}BuOMe (0.7 mL) was added *via* syringe pump over 1 h. After the addition, the resulting solution was further stirred at -78 ˚C for 2.5 h, then quenched by MeOH and allowed to warm to room temperature. Saturated NH_4Cl solution was added and the extractions were

performed with ether. The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:10) to yield compound **44** (217 mg, 66%). ^{1}H NMR (600 MHz, , $CDCl_3$) δ 7.39-7.07 (m, 10H), 4.85 (d, 1H, *J* = 11.4 Hz), 4.67 (d, 1H, *J* = 11.4 Hz), 4.55 (d, 1H, *J* = 11.4 Hz), 4.48 (d, 1H, *J* = 11.4 Hz), 3.61 (dt, 1H, *J* = 9.6, 2.4 Hz), 3.42 (dd, 1H, *J* = 7.8, 2.4 Hz), 2.86 (q, 2H, *J* = 7.2), 2.52 (dd, 1H, *J* = 4.8, 9.4 Hz), 2.34-2.29 (m, 1H), 2.24 (dd, 1H, *J* = 9.4, 11.4 Hz), 1.78-1.56 (m, 3H), 1.47-1.43 (m, 1H), 1.32-1.20 (m, 3H), 1.24 (t, 3H, *J* = 7.2 Hz), 1.19-1.12 (m, 2H), 1.00 (d, 3H, *J* = 6.6 Hz), 0.91-0.84 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 139.1, 138.4, 128.4, 128.2, 128.1, 127.9, 127.6, 127.4, 83.4, 78.7, 74.2, 71.4, 50.4, 36.7, 35.1, 32.6, 29.0, 28.1, 23.3, 23.1, 20.9, 16.5, 14.8, 14.2; ; HRMS (APCI): *m/z* calcd. for $C_{29}H_{46}NO_3S$ ($M+NH_4^+$) 488.3193, found 488.3188; FT-IR (KBr) 3028, 2929, 1687, 1454 cm^{-1}.

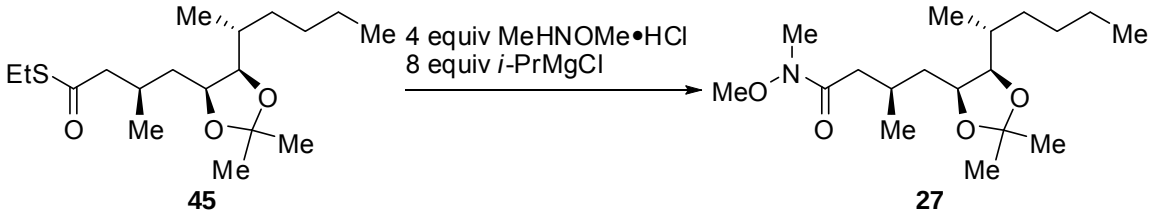


(*R*)-S-ethyl-4-((4*S*,5*R*)-5-((*R*)-hexan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-methylbutanethioate (45). In a 25 mL round-bottom flask, boron trichloride (1.12 mL, 1.0 M in heptane, 1.1 mmol) was added to a solution of dibenzylether **44** (132 mg, 0.28 mmol) in CH_2Cl_2 (4.5 mL) at -45 °C under argon. The resulting

solution was stirred at -45 ˚C to-20 ˚C over 2 h and quenched with methanol (2 mL) at -78 °C followed by warming to room temperature. The extractions were performed with CH_2Cl_2 and organic layer was dried over Na_2SO_4 followed by concentration to afford crude mixture. ^{1}H NMR analysis of crude diol revealed 10:1 dr. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:2) to yield diol (77 mg, 95%). ^{1}H NMR analysis of the crude product revealed ~10:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (d, 1H, *J* = 9.6 Hz), 3.37 (dd, 1H, *J* = 3.6, 6.0 Hz), 2.88 (dq, 2H, *J* = 1.6, 7.2 Hz), 2.63 (dd, 1H, *J* = 6.4, 10.8 Hz), 2.45 (dd, 1H, *J* = 6.4, 10.8 Hz), 2.38 (bs, 1H), 2.36-2.29 (m, 1H), 2.04 (bs, 1H), 1.70-1.63 (m, 1H), 1.57-1.49 (m, 2H), 1.43-1.09 (m, 6H), 1.24 (t, 3H, *J* = 7.6 Hz), 1.03 (d, 3H, *J* = 6.8 Hz), 0.89 (t, 3H, *J* = 7.2 Hz), 0.83 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 79.0, 69.6, 50.3, 36.8, 34.9, 32.1, 28.8, 27.3, 23.4, 23.0, 21.4, 15.3, 14.7, 14.1; FT-IR (KBr) 3399, 2957, 1688 cm^{-1}; FT-IR (KBr) 3399, 2957, 1688 cm^{-1}.

To a solution of diol (74 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL) was added 2,2-dimethoxypropane (270 mg, 2.55 mmol) and *p*-TSA (5 mg, 0.03 mmol) at room temperature under argon. The resulting solution was stirred at room temperature for 2 h and quenched with saturated $NaHCO_3$. The extractions were performed with CH_2Cl_2 and organic layer was dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:8) to yield compound **45** (80 mg, 96%) as single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (ddd, 1H, *J* = 2.8, 4.6, 9.6 Hz), 3.72 (dd, 1H, *J* = 4.6, 7.6 Hz), 2.87 (q, 2H, *J* = 7.2 Hz), 2.66 (dd, 1H, *J* = 5.2,

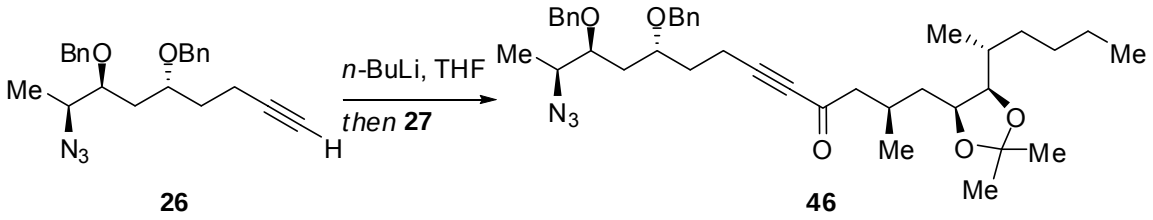
10.4 Hz), 2.43 (dd, 1H, *J* = 8.0, 10.4 Hz), 2.33-2.28 (m, 1H), 1.72-1.57 (m, 2H), 1.50-1.07 (m, 7H), 1.42 (s, 3H), 1.32 (s, 3H), 1.26 (t, 3H, *J* = 7.2 Hz), 1.03 (d, 3H, *J* = 7.2 Hz), 0.90 (t, 3H, *J* = 6.8 Hz), 0.82 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 107.5, 82.7, 75.5, 49.6, 35.7, 33.5, 32.1, 28.7, 28.5, 27.9, 26.2, 23.3, 23.0, 20.8, 15.7, 14.8, 14.2; FT-IR (KBr) 2958, 1689, 1655 cm^{-1}; $[\alpha]^{25}_D$ = -46.5 (c = 0.75, $CHCl_3$).



45 **27**

Weinreb amide (27). In a 25 mL round-bottom flask, Me(MeO)NH_2Cl (264 mg, 2.64 mmol) was added to a solution of thioester **45** (218 mg, 0.66 mmol) in THF (6.6 mL) under argon and the suspension was at cooled to -30 °C. The resulting mixture was added *i*-PrMgCl (2.6 mL, 2.0 M in THF, 5.28 mmol) dropwise at -30 ˚C. After completion of addition, the reaction was allowed to slowly warm to 0 °C over 2 hours, and then the reaction was diluted with ethyl acetate and sequentially washed with 1 M NaOH (2 × 15 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:2) to yield amide **27** (172 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14-4.09 (m, 1H), 3.76-3.70 (m, 1H), 3.68 (s, 3H), 3.17 (s, 3H), 2.57-2.54 (m, 1H), 2.31-2.26 (m, 2H), 1.87-1.60 (m, 3H), 1.52-1.08 (m, 6H), 1.42 (s,

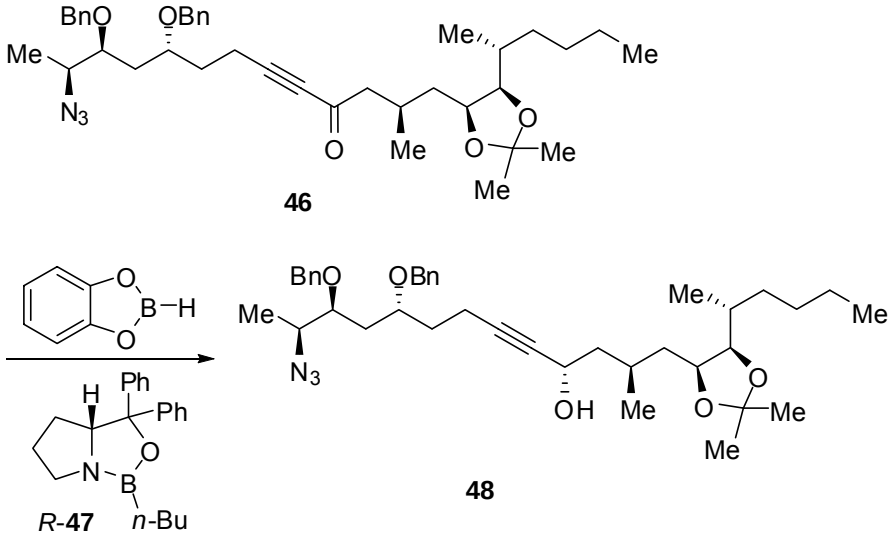
3H), 1.31 (s, 3H), 1.04 (d, 3H, *J* = 6.8 Hz), 0.90 (t, 3H, *J* = 6.8 Hz), 0.84 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 107.4, 82.7, 75.8 (75.7), 67.9, 61.1, 37.6, 35.9, 33.5, 32.1, 28.6 (28.5), 26.9, 26.3 (26.2), 25.6, 23.0, 21.2, 15.9 (15.8), 14.2 ; HRMS (APCI): *m/z* calcd. for $C_{18}H_{36}NO_4$ (M^+) 330.2639, found 330.2636; FT-IR (KBr) 2956, 2872, 1666 cm^{-1}; $[\alpha]^{25}_D$ = -50.0 (c = 0.30, $CHCl_3$).



26 **46**

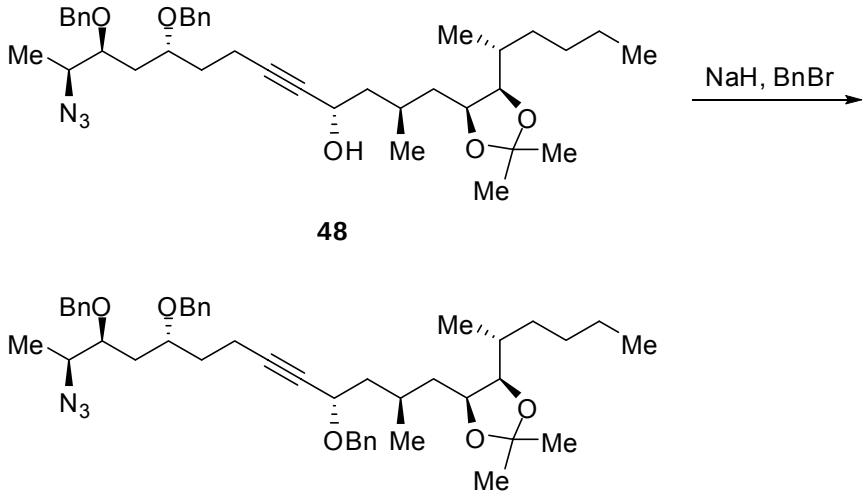
Ynone (46). To a solution of alkyne (82 mg, 0.22 mmol) in THF (2 mL) was added *n*-BuLi (84 µL, 2.5 M in hexane, 0.2 mmol) at -78 °C under argon. After 5 min at -78 °C, the mixture was warmed to 0 °C and stirred for 30 min. The mixture was then chilled to -78 °C, and the solution of amide **27** (45 mg, 0.14 mmol) in THF (0.5 mL) was added slowly. The resulting solution was stirred at -78 °C for 5 min and 0 °C for 1.5 h and then quenched with saturated NH_4Cl. The extractions were performed with ether and organic layer was dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:6) to yield compound **46** (71 mg, 79%) and recovered alkyne **26** (25 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 10H), 4.70 (d, 1H, *J* = 11.6 Hz), 4.65 (d, 1H, *J* = 11.6 Hz), 4.54 (d, 1H, *J* = 11.6 Hz), 4.51 (d, 1H, *J* = 11.6 Hz), 4.05 (ddd, 1H, *J* =

2.8, 3.8, 9.4 Hz), 3.73-3.65 (m, 2H), 3.56-3.49 (m, 2H), 2.66 (dd, *J* = 8.8 14.0 Hz), 2.48-2.41 (m, 1H), 2.38-2.28 (m, 3H), 2.00-1.93 (m, 1H), 1.72-1.10 (m, 13H), 1.42 (s, 3H), 1.32 (s, 3H), 1.24 (d, 3H, *J* = 6.0 Hz), 1.01 (d, 3H, *J* = 6.4 Hz), 0.90 (t, 3H, *J* = 7.2 Hz), 0.81 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.7, 138.5, 138.1, 128.4, 128.4, 128.1, 127.8, 127.6, 127.6, 107.5, 91.9, 82.7, 81.7, 78.4, 76.3, 75.5 (75.4), 72.1, 71.1, 58.9 (58.8), 51.2, 35.7, 35.2, 33.5, 32.1, 31.9, 28.7, 28.5, 26.6, 26.2, 23.0, 22.0 (21.9), 15.9, 15.8, 15.6 (15.5), 14.2 (14.1); FT-IR (KBr) 2930, 2099, 1669 cm^{-1}; $[\alpha]^{25}_D$ = -50.8 (c = 2.6, $CHCl_3$).



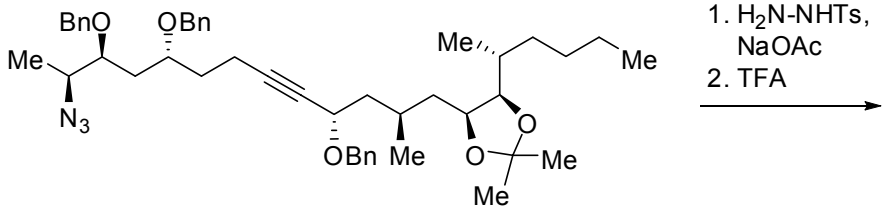
Alcohol (48). In a 10 mL round-bottom flask, ynone **46** (30 mg, 0.05 mmol) was treated with oxazaborolidine **47** (50 µL, 0.5 M in toluene, 0.03 mmol) under argon. The toluene was removed *in vacuo*, CH_2Cl_2 (0.25 mL) was added, and the solution was cooled to -78 °C. A solution of catecholborane (60 µL, 1.0 M in THF, 0.06 mmol) was then added dropwise. After stirring for 5 h at -78 °C, the reaction was quenched with methanol (0.2 mL) and the solution was warmed to room

temperature. The solution was diluted with ether (1 mL) and washed with 2:1 1 N NaOH-saturated $NaHCO_3$. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:5) to yield compound **48** (24 mg, 74%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.28 (m, 10H), 4.70 (d, 1H, *J* = 11.4 Hz), 4.64 (d, 1H, *J* = 11.4 Hz), 4.55 (d, 1H, *J* = 11.4 Hz), 4.53 (d, 1H, *J* = 11.4 Hz), 4.37-4.34 (m, 1H), 4.11-4.08 (m, 1H), 3.71 (dd, 1H, *J* = 4.8, 7.2 Hz), 3.68-3.64 (m, 1H), 3.60-3.59 (m, 1H), 3.54 (ddd, 1H, *J* = 4.2, 4.2, 8.0 Hz), 2.35-2.22 (m, 2H), 1.96-1.84 (m, 3H), 1.73-1.56 (m, 4H), 1.48-1.08 (m, 9H), 1.41 (s, 3H), 1.31 (s, 3H), 1.24 (d, 3H, *J* = 6.0 Hz), 0.99 (d, 3H, *J* = 6.6 Hz), 0.90 (t, 3H, *J* = 7.2 Hz), 0.81 (d, 3H, *J* = 6.6 Hz).



Tribenzylether. In a 10 mL round-bottom flask, sodium hydride (2 mg, 60% dispersion in mineral oil, 0.04 mmol) was added to a solution of propargylic alcohol **48** (18 mg, 0.03 mmol) and tetrabutylammonium iodide (trace) in THF

(0.5 mL) under argon at 0 ˚C. The resulting solution was stirred at 0 ˚C for 10 min and room temperature for 30 min before adding benzyl bromide (7 mg, 0.042 mmol) at room temperature. The resulting solution was stirred at room temperature overnight and quenched with saturated NH_4Cl. The extractions were performed with ether and organic layer was dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:8) to yield compound **26** (18 mg, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.19 (m, 15H), 4.75 (d, 1H, *J* = 11.6 Hz), 4.69 (d, 1H, *J* = 11.6 Hz), 4.63 (d, 1H, *J* = 11.6 Hz), 4.57-4.50 (m, 2H), 4.44 (d, 1H, *J* = 11.6 Hz), 4.15-4.05 (m, 2H), 3.70-3.59 (m, 3H), 3.54 (ddd, 1H, *J* = 3.6, 3.6, 7.8 Hz), 2.36-2.25 (m, 2H), 2.00-1.91 (m, 3H), 1.73-1.56 (m, 4H), 1.39-1.09 (m, 9H), 1.41 (s, 3H), 1.31 (s, 3H), 1.23 (d, 3H, *J* = 6.4 Hz), 0.92-0.88 (m, 6H), 0.77 (d, 3H, *J* = 6.8 Hz).

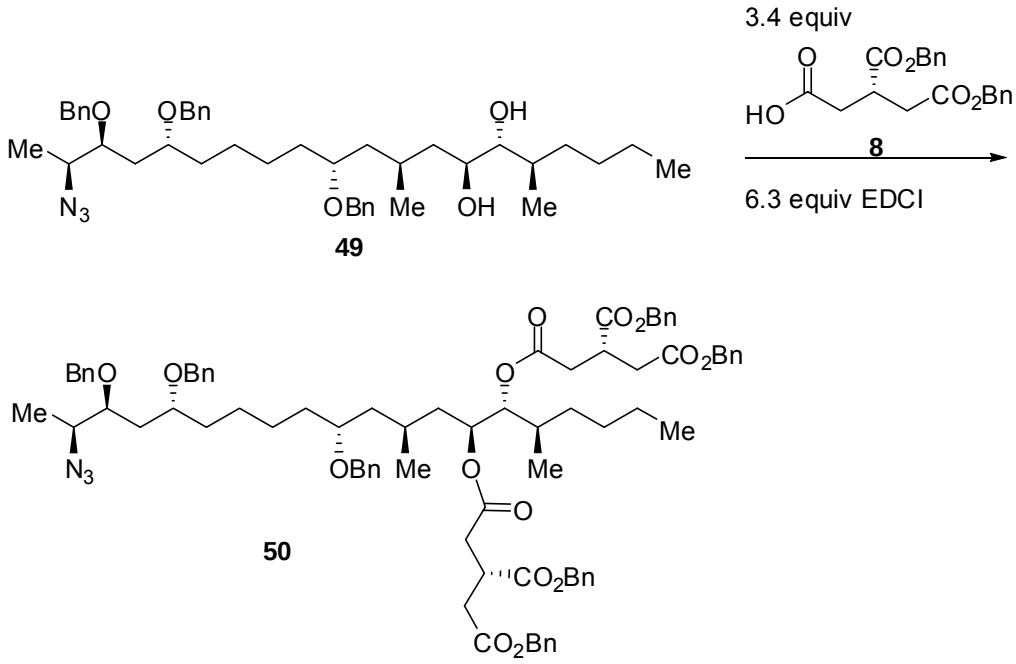


49

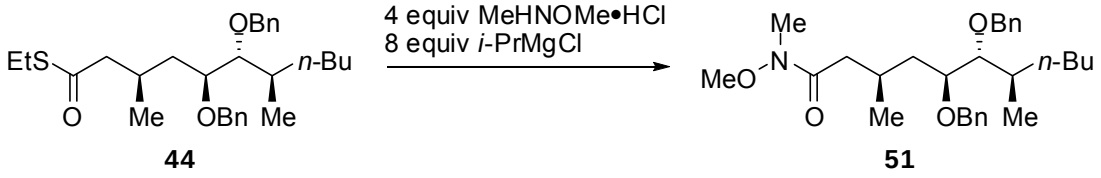
Diol (49). The alkyne (18 mg, 0.024 mmol) and *p*-toluenesulfonhydrazide (221 mg, 1.15 mmol) in dimethoxy ethane (7 mL) was heated to reflux. The solution of

sodium acetate (118 mg, 1.44 mmol) in water (1 mL) was added over 5 h using a syringe pump. The reaction was refluxed overnight and was then poured onto water and partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography on silica gel (ether/pentane = 1:6) to yield alkane (12 mg, 70%). ^{1}H NMR (600 MHz, , $CDCl_3$) δ 7.39-7.27 (m, 15H), 4.70 (d, 1H, *J* = 11.4 Hz), 4.64 (d, 1H, *J* = 11.4 Hz), 4.56-4.48 (m, 3H), 4.45 (d, 1H, *J* = 11.4 Hz), 4.12-4.09 (m, 1H), 3.71 (dd, 1H, *J* = 5.4, 7.6 Hz), 3.66-3.64 (m, 1H), 3.55-3.52 (m, 1H), 3.50-3.47 (m, 1H), 3.41-3.39 (m, 1H), 1.98-1.87 (m, 2H), 1.76-1.19 (m, 18H), 1.43 (s, 3H), 1.32 (s, 3H), 1.24 (d, 3H, *J* = 6.0 Hz), 1.15-1.10 (m, 2H), 0.95 (d, 3H, *J* = 6.6 Hz), 0.90 (t, 3H, *J* = 7.2 Hz), 0.81 (d, 3H, *J* = 6.6 Hz).

To a solution of the acetonide (11 mg, 0.015 mmol) in THF (0.2 mL) was added an 80 % TFA solution in water (1.2 mL) at 0 ˚C. Then mixture was stirred at room temperature for 1 h and the solvent was removed *in vacuo*. The residue was azeotroped four times with toluene and purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:2) to yield compound **49** (7 mg, 64%). ^{1}H NMR (400 MHz, , $CDCl_3$) δ 7.38-7.27 (m, 15H), 4.68 (d, 1H, *J* = 11.6 Hz), 4.65 (d, 1H, *J* = 11.6 Hz), 4.56-4.48 (m, 3H), 4.48 (d, 1H, *J* = 11.6 Hz), 3.82-3.76 (m, 1H), 3.68-3.63 (m, 1H), 3.57-3.50 (m, 1H), 3.47-3.32 (m, 3H), 1.96-1.90 (m, 2H), 1.76-1.06 (m, 20H), 1.24 (d, 3H, *J* = 6.0 Hz), 0.96 (d, 3H, *J* = 6.6 Hz), 0.92 (t, 3H, *J* = 7.2 Hz), 0.88 (d, 3H, *J* = 6.6 Hz).

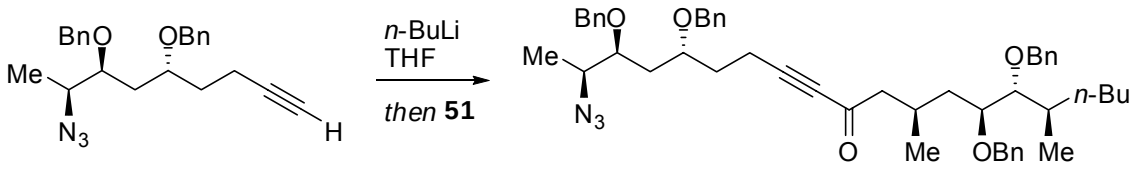


Fully protected FB_1 (50). To a solution of diol **49** (5 mg, 0.007 mmol) and the tricarballylic acid **8** (0.02 mmol) in CH_2Cl_2 (0.3 mL) was added DMAP (6 mg, 0.04 mmol) and EDCI (9 mg, 0.04 mmol) in that order. The mixture was stirred under argon over 15 h and was loaded on a column that was packed with silica gel and 2% Et_3N in hexane. Elution with 10 to 20% ethyl acetate and 2% Et_3N in hexane provided **50** (9 mg, 95%). ^{1}H NMR (600 MHz, , $CDCl_3$) δ 7.38-7.27 (m, 35H), 5.14-4.99 (m, 9H), 4.90 (dd, 1H, *J* = 3.0, 5.8 Hz), 4.69 (d, 1H, *J* = 11.4 Hz), 4.63 (d, 1H, 12.0 Hz), 4.55-4.51 (m, 3H), 4.37 (d, 1H, *J* = 11.4 Hz), 3.67-3.62 (m, 1H), 3.56-3.52 (m, 1H), 3.43-3.36 (m, 2H), 3.32-3.22 (m, 2H), 2.84-2.59 (m, 8H), 1.92-1.87 (m, 1H), 1.73-0.98 (m, 21H), 1.23 (d, 3H, *J* = 6.0 Hz), 0.88 (d, 3H, *J* = 6.6 Hz), 0.86-0.82 (m, 6H).



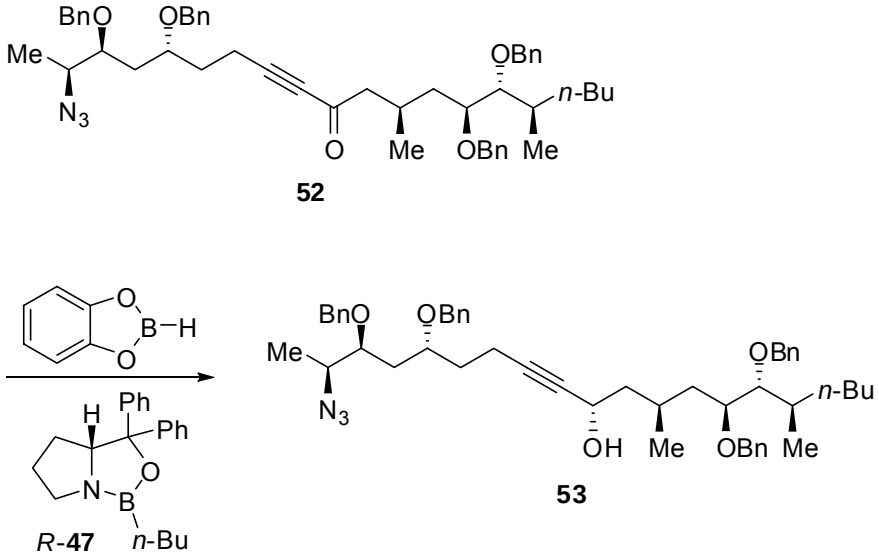
44 **51**

Weinreb amide (51). In a 10 mL round-bottom flask, $Me(MeO)NH_2Cl$ (56 mg, 0.56 mmol) was added to a solution of thioester **44** (66 mg, 0.14 mmol) in THF (1.4 mL) under argon and the suspension was at cooled to -30 °C. The resulting mixture was added *i*-PrMgCl (0.56 mL, 2.0 M in THF, 1.12 mmol) dropwise at -30 ˚C. After completion of addition, the reaction was allowed to slowly warm to 0 °C over 2 hours, and then the reaction was diluted with ethyl acetate and sequentially washed with 1 M NaOH (2 × 5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:4) to yield amide **51** (62 mg, 94%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43-7.07 (m, 10H), 4.85 (d, 1H, *J* = 11.4 Hz), 4.66 (d, 1H, *J* = 11.4 Hz), 4.55 (d, 1H, *J* = 11.4 Hz), 4.50 (d, 1H, *J* = 11.4 Hz), 3.67-3.65 (m, 1H), 3.58 (s, 3H), 3.42 (dd, 1H, *J* = 2.4, 4.8 Hz), 3.16 (s, 3H), 2.42-2.30 (m, 2H), 2.25-2.20 (m, 1H), 1.76-1.15 (m, 9H), 1.02 (d, 3H, *J* = 6.6 Hz), 0.90-0.86 (m, 6H).



26 **52**

Ynone (52). To a solution of alkyne (64 mg, 0.22 mmol) in THF (2 mL) was added *n*-BuLi (68 µL, 2.5 M in hexane, 0.17 mmol) at -78 °C under argon. After 5 min at -78 °C, the mixture was warmed to 0 °C and stirred for 30 min. The mixture was then chilled to -78 °C, and the solution of amide **51** (62 mg, 0.13 mmol) in THF (0.5 mL) was added slowly. The resulting solution was stirred at -78 °C for 5 min and 0 °C for 1.5 h and then quenched with saturated NH_4Cl. The extractions were performed with ether and organic layer was dried over Na_2SO_4 followed by concentration to afford crude mixture. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:7) to yield compound **52** (73 mg, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38-7.07 (m, 20H), 4.86 (d, 1H, *J* = 11.4 Hz), 4.71-4.64 (m, 3H), 4.56-4.45 (m, 4H), 3.68-3.66 (m, 1H), 3.62-3.58 (m, 1H), 3.53-3.48 (m, 2H), 3.44 (dd, 1H, *J* = 1.8, 4.8 Hz), 2.48-2.36 (m, 3H), 2.28-2.19 (m, 2H), 1.98-1.93 (m, 1H), 1.81-1.76 (m, 1H), 1.75-1.11 (m, 11H), 1.24 (d, 3H, *J* = 6.0 Hz), 1.00 (d, 3H, *J* = 6.6 Hz), 0.92-0.84 (m, 6H).



Alcohol (53). In a 10 mL round-bottom flask, ynone **52** (25 mg, 0.03 mmol) was treated with oxazaborolidine **47** (30 µL, 0.5 M in toluene, 0.015 mmol) under argon. The toluene was removed *in vacuo*, CH_2Cl_2 (0.25 mL) was added, and the solution was cooled to -78 °C. A solution of catecholborane (36 µL, 1.0 M in THF, 0.04 mmol) was then added dropwise. After stirring for 5 h at -78 °C, the reaction was quenched with methanol (0.2 mL) and the solution was warmed to room temperature. The solution was diluted with ether (1 mL) and washed with 2:1 1 N NaOH-saturated $NaHCO_3$. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:5) to yield compound **53** (16 mg, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41-7.07 (m, 20H), 4.85 (d, 1H, *J* = 11.4 Hz), 4.69 (d, 1H, *J* = 11.4 Hz), 4.66-4.46 (m, 6H), 4.31-4.27 (m, 1H), 3.67-3.40 (m, 5H), 2.32-2.22 (m, 2H), 1.96-1.91 (m, 2H), 1.74-1.16 (m, 14H), 1.24 (d, 3H, *J* = 6.6 Hz), 0.96 (d, 3H, *J* = 6.6 Hz), 0.89-0.85 (m, 6H).

2.6. Citations.

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