Université de Montréal

Iterative Construction of Deoxypropionate Units; A Study of the "Anchor" and "Ester" Effects

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Iterative Construction of Deoxypropionate Units;
A Study of the "Anchor" and "Ester" Effects

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To my Parents
For their loving support

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Summary

There exist many natural products bearing *syn*-disposed 1,3-methyl groups on an acyclic carbon chains, also known as a deoxypropionate unit. Consequently, efforts have been devoted towards the development of methodologies in order to readily access such structural motifs. The iterative methodology developed by the Hanessian group takes advantage of substrate and conformational control. Addition of lithium dimethylcuprate to γ-alkoxy and δ-methyl-α,β-unsaturated esters, controlled by 1,2 and 1,3-induction, respectively, affords the desired structural unit in an iterative manner. This work studies the idea of conformational control and the introduction of anchoring groups towards the addition of lithium dimethylcuprate to α,β-unsaturated esters. Anchoring groups orient the acyclic chain of these esters in certain preferred conformations by avoiding high energy *syn*-pentane interactions with the pendant *C*-methyl groups. A variety of anchoring groups are surveyed. Some anchoring groups introduce *syn*-pentane interactions in all possible conformations, some anchoring groups introduce only one costly interaction, whereas other groups studied introduce no *syn*-pentane interactions. The diastereomeric ratios obtained upon conjugate cuprate additions to these substrates are compared and conclusions are drawn based on the results thus obtained. Another factor investigated is the 'ester' effect. It has been observed that the sterically larger ester groups lead to higher diastereoselectivities, compared to smaller esters. A variety of esters were surveyed. Finally, a variety of alkoxy substituents were studied in order to shed some light on the nature interaction of the alkoxy substituent with the reagent.

Key Words: acyclic stereoselection, conjugate addition, deoxypropionate, substrate control, *syn*-pentane interaction

Résumé

Il existe de nombreux produits naturels comportant des groupes de type 1,3-methyles *syn*, appelé unité désoxypropionate. En conséquence, de nombreux efforts ont été menés afin de développer des méthodologies donnant accès à facile ce type de motif. La méthodologie itérative développée au sein du groupe Hanessian est basée sur un contrôle conformationnel du substrat. L'addition de diméthylcuprate de lithium sur un ester α,β-insaturé substitué en γ-alkoxy et δ-méthyle, contrôlée respectivement par induction 1,2 et 1,3 permet de synthétiser l'unité structurale désirée de manière itérative. Le travail présenté dans ce mémoire étudie le concept de contrôle conformationnel et d'introduction de groupes d'ancrage pour l'addition de diméthylcuprate de lithium sur des esters α,β-insaturés. Les groupes d'ancrage doivent permettre de figer la molécule dans certaines conformations privilégiées par l'introduction d'intéractions de type *syn*-pentane avec les groupes *C*-méthyles. Différents groupes d'ancrage ont été évalués. Certains introduisent des intéractions *syn*-pentane dan toutes les conformations possibles, d'autres introduisent seulement une intéraction favorable et, enfin certains n'introduisent pas d'intéractions *syn*-pentane. Les ratios diastéréomériques obtenus à la suite de l'addition conjuguée du cuprate à ces substrats sont comparés et les conclusions sont basées sur les résultats obtenus. Un second facteur étudié est l'effet de l'ester. Il est montré que les esters plus volumineux donnent de meilleures diastéréosélectivités. Pour finir, différents éthers ont été étudiés dans le but de récolter de l'information sur la nature de l'intéraction entre le substituant alkoxy et le réactif.

Mots clés: désoxypropionate, interaction *syn*-pentane, stéréosélection acyclique, substrat dépendant

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Abbreviations

$[\alpha]_D$	optical rotation
AcCl	acetyl chloride
ACP	acyl carrier protein
AT	acyl transferase
Bn	benzyl
BOM	benzyloxymethyl
BOMCl	benzyloxymethyl chloride
calcd	calculated
CoA	co-enzyme A
COSY	correlation spectroscopy
d	doublet
kDa	kilodaltons
DCE	1,2-dichloroethane
dd	doublet of doublets
d.e.	diastereomeric excess
DEBS	deoxyerythronolide B synthase
6-dEB	6- deoxyerythronolide B
DH	dehydratase
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMS	methyl sulfide
DMSO	dimethyl sulfoxide
DPEphos	bis[2-(diphenylphosphanyl)phenyl]ether
o-DPPB	*ortho*-diphenylphosphanylbenzoyl
d.r.	diastereomeric ratio
d.s.	diastereoselectivity
dt	doublet of triplets
e.e.	enantiomeric excess

EI	electron impact
ER	enoyl reductase
EtOAc	ethyl acetate
eq.	equivalents
FAB	fast atom bombardment
FID	free induction decay
g	gram
GC	gas chromatography
h	hour
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
KHMDS	potassium hexamethyldisilazide
KS	keto reductase
LAB	lithium amidotrihydroborate
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LiTMP	lithium tetramethylpiperidide
m	multiplet
MAO	methylaluminoxane
MCP	1-methyl-1-cyclopentyl
Me	methyl
MEMCl	2-methoxyethoxymethyl chloride
MeOH	methanol
MHz	megahertz
min	minute

mL	milliliter
mmol	millimole
MOMCl	chloromethyl methyl ether
MPTA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
MsCl	methanesulfonyl chloride
NaHMDS	sodium hexamethyldisilazide
NEt_3	triethylamine
NMR	nuclear magnetic resonance
NMI	neomenthylindenyl
nOe	nuclear Overhauser effect
Ph	phenyl
PhMe	toluene
PKS	polyketide synthase
ppm	parts per million
py	pyridine
q	quartet
quin	quintet
RAMP	(*R*)-(+)-1-amino-2-(methoxymethyl)pyrrolidine
r.t.	room temperature
SAMP	(*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine
s	singlet
sec	seconds
t	triplet
T1	relaxation time
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl group
TBDPS	*tert*-butyldiphenylsilyl group
TBDPSCl	*tert*-butyldiphenylsilyl chloride
t-Bu	*tert*-butyl
TE	thioesterase

tert	tertiary
TESOTf	triethylsilyl trifluoromethanesulfonate
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
UV	ultraviolet
ZACA	zirconium catalyzed asymmetric carboalumination

Chapter I:

An introduction to deoxypropionate units

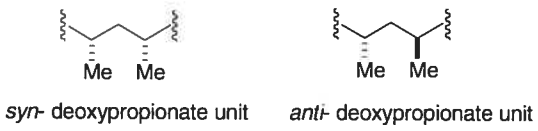
This chapter will focus on natural products that contain deoxypropionate subunits and the biosynthesis of natural products derived from the polyketide pathway. Also, discussed in this chapter are some of the iterative approaches to accessing deoxypropionate units. Aspects of conformational design that bias the molecules towards adapting certain energetically favored conformations and the implications that this may have in the synthesis of deoxypropionates will be highlighted.

I.1. Natural products with deoxypropionate motifs

The isolation, structural determination and synthesis of biologically active natural products are of continuing interest, due to the fundamental scientific understanding that is realized and the synthetic challenges involved. [1-3] Synthetically, natural products pose great challenges, none more so than the development of new methodology to access certain structural motifs. While describing the challenges that were encountered during the synthesis of vitamin B_{12}, Eschenmoser delineated the challenges that organic chemists confront while tackling natural product synthesis:

> *"Natural product synthesis poses the challenge to consider and develop new pathways of structural transformation. Natural products as targets for synthetic research possess a special fertility in this regard, because the structural channels of biosynthesis are not necessarily the conduits of organic synthesis."*
>
> *A. Eschenmoser*[4]

One such structural motif is a deoxypropionate unit, found in certain natural products, and biosynthetically produced through the successive decarboxylative condensation of small carboxylic acids as their Co-enzyme A esters (Figure 1).[5,6]



syn- deoxypropionate unit *anti*- deoxypropionate unit

Figure 1: Deoxypropionate units.

Many natural products harbor one or more deoxypropionate triads within their structural framework. A deoxypropionate unit is a three carbon unit, a deoxypropionate triad, is defined as consisting of a 2,4-dimethylpentane unit.[7] In natural products with more than one stereotriad, the methyl groups are generally in an all *syn*-orientation on a cyclic or acyclic framework, and there are only a few exceptions where the deoxypropionate unit has an *anti*- orientation.

Natural products harboring deoxypropionate units exhibit diverse biological activities.[8] For example, some cyclic and acyclic natural products with *syn*-oriented deoxypropionate units are the cytotoxic doliculide[9], TMC-151,[10] and the *Siphonaria*[11] family of natural products consisting of siphonarienal, siphonarienolone, pectinatone, which exhibit activity against Gram-positive bacteria, yeast and several human cancer cell lines (Figure 2).

Other natural products with *anti*-disposed deoxypropionate units such as venturicidine aglycone,[12] ionomycin,[13] and borrelidin[14] are featured in Figure 3. Ionomycin is a pharmacological tool routinely used for the intracellular transport of Ca^{2+}. Venturcidine aglycone possesses antifungal antibiotic activity with potential use in agriculture. Borrelidin possesses a wide array of biological activities including inhibition of cyclin-dependent kinase of *Saccharomyces cerevisiae* and potent antiangiogenesis activity in the rat aorta. The recently isolated cane beetle sex

pheromone, 4,6,8,10,16,18-hexamethyldocosane has only been isolated in very small amounts, and its biological activity has not yet been determined.[15]

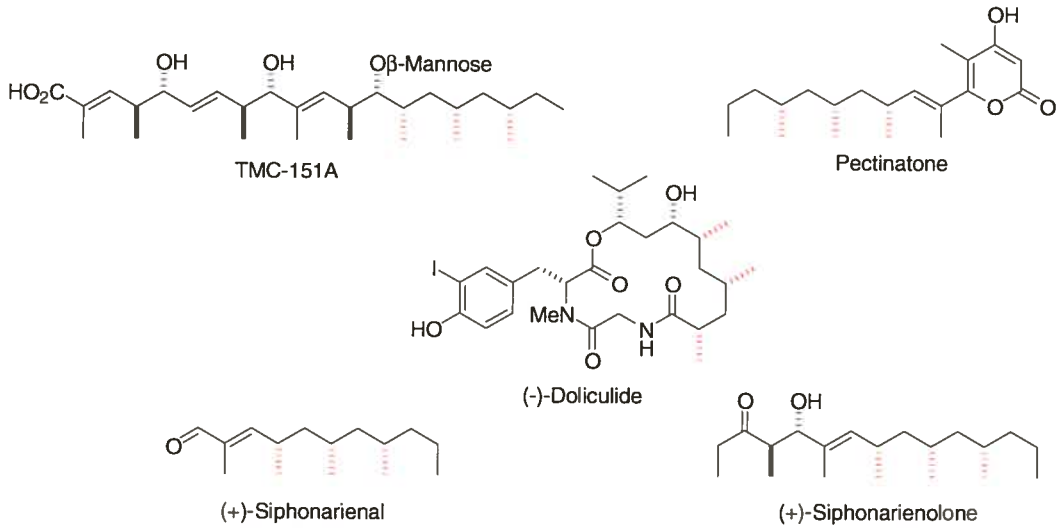


Figure 2: Natural products with *syn*-deoxypropionate units.

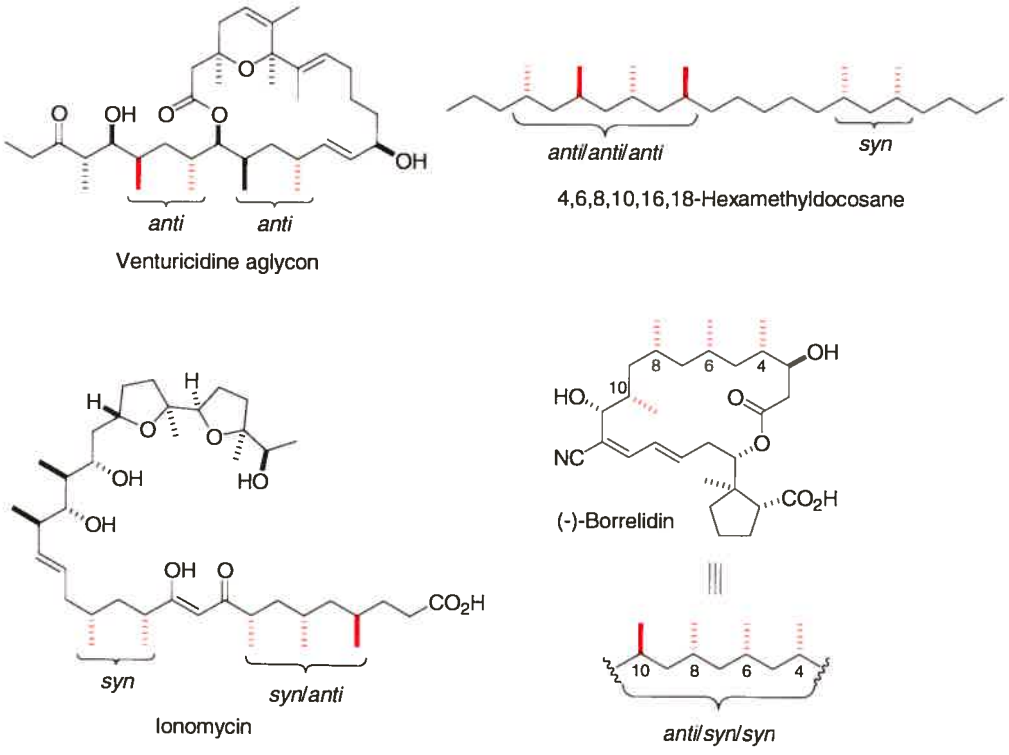


Figure 3: Natural products with *anti*-deoxypropionate triads.

Nature's preference for *syn*-2,4-dimethylpentane units probably originates from a preferred biosynthetic pathway in which energetically preferred conformations avoid undesirable high energy interactions.[7] Placing alternating methyl groups in an all *syn*- orientation decreases the number of high energy conformations by avoiding *syn*-pentane interactions. Thus as shown in Figure 4, the acyclic molecule pectinatone adopts a conformation devoid of *syn*-pentane interactions (see Section I .4). Similarly the chiral hydrocarbon chain in borrelidin, a macrocyclic structure, also exists in a folded conformation wherein *syn*-pentane interactions are avoided. We have found it convenient to display the acyclic chains on a virtual diamond lattice backbone, where the methyl groups are gauche with respect to each other.[14d] In fact the solid-state conformations of pectinatone and borrelidin as seen from their X-ray structures show quasi perfect congruence with the diamond lattice model.

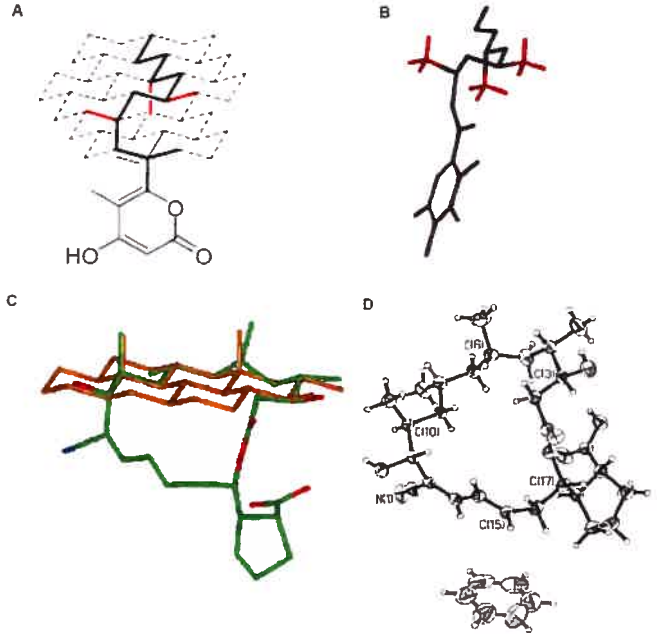


Figure 4: (A) Superimposition of the carbon backbone of (-)-pectinatone on a virtual diamond lattice; (B) X-ray crystal structure of pectinatone; (C) Superimposition of borrelidin on a virtual diamond lattice; (D) X-ray crystal structure of borrelidin.[14d]

I.2. Biosynthesis of polyketides

Polyketide is a term that defines a class of molecules produced through successive condensation of small carboxylic acids, such as acetates and propionates, as their Co-enzyme A thioesters.[5] Polyketide natural products are produced as secondary metabolites. They are structurally complex and diverse molecules displaying antibiotic, antifungal, antiparasitic, immunosuppressive, and antitumor activities (Figure 5).[6]

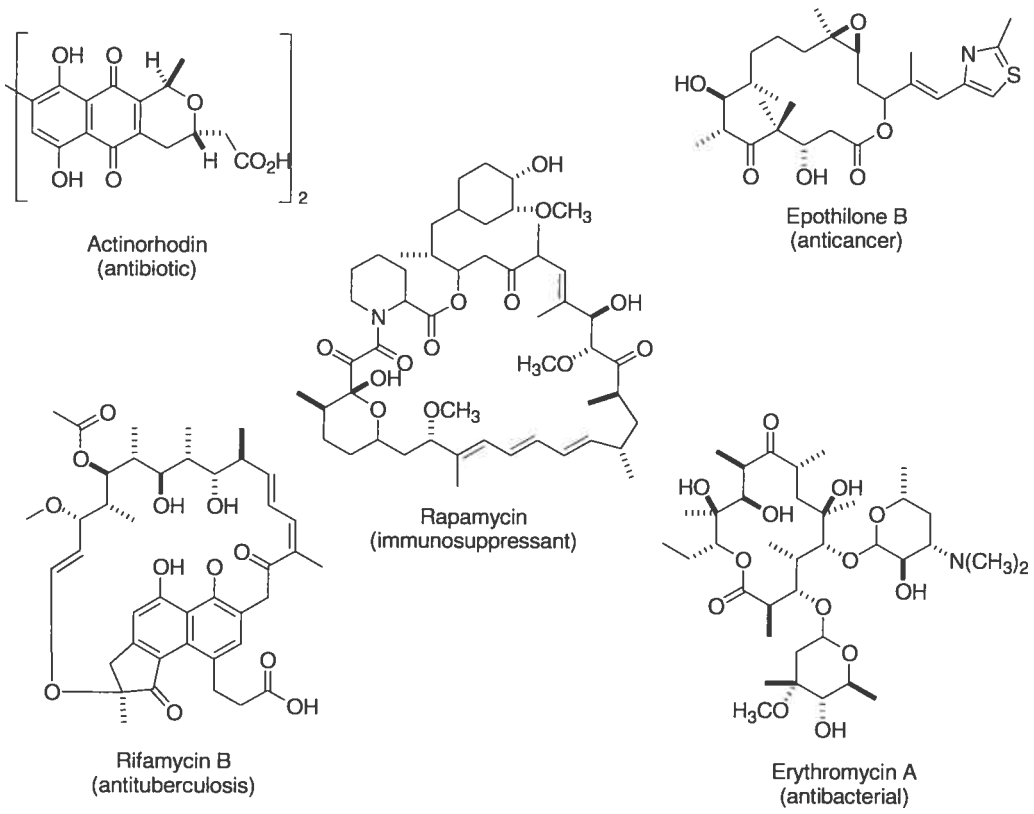


Figure 5: Examples of some polyketide (propionate) derived natural products.

Despite their structural complexity, the biosynthesis of polyketides proceeds through simple decarboxylative condensations of acetate or propionate units, paralleling the reiterative biosynthesis of fatty acids.[6] Structural complexity in polyketides arises after each condensation step as well as by enzymes that catalyze different chemical

transformations (such as cyclizations, oxidations, alkylations, glycosylations).[16] There are two types of polyketides, aromatic and complex. Aromatic polyketides are mainly assembled from the condensation of acetate units, whereas complex polyketides are composed of acetates, propionates, or butyrates. Aromatic polyketides are constructed through a reiterative process, wherein the β-carbonyl groups formed after each cycle are usually left unreduced. However, in complex polyketides the structural diversity arises from the various organic acid monomers available (Figure 6) and the extent of β-carbon processing (to carbonyl, hydroxyl, enoyl, or methylene groups), which varies from cycle to cycle.[5,17]

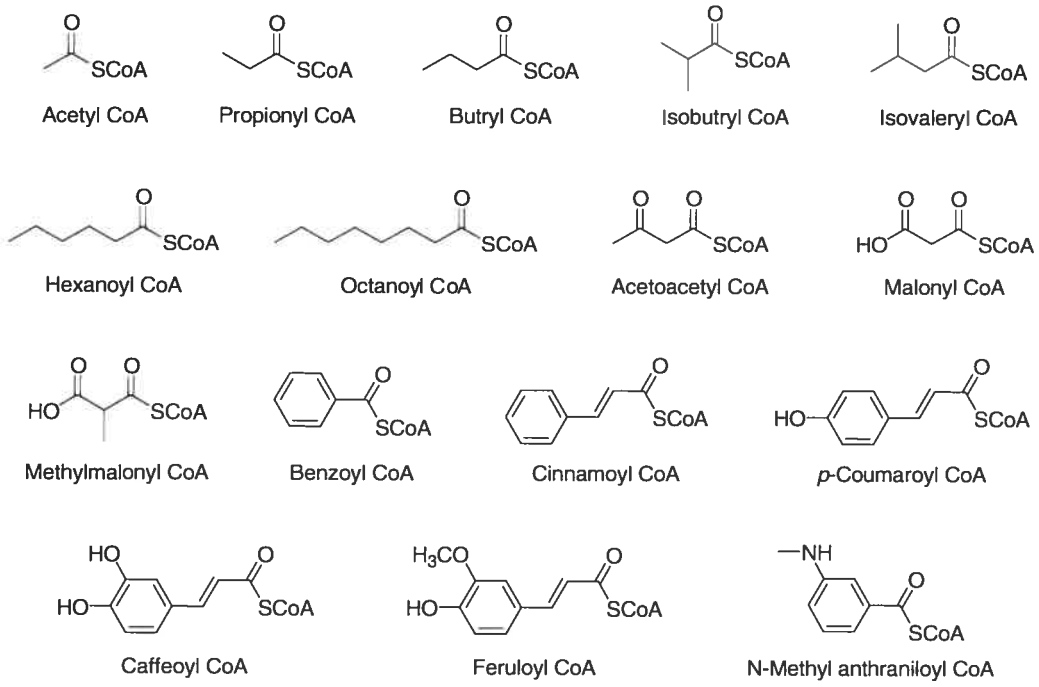


Figure 6: Starter and extender biosynthetic units.[18]

Birch and Donovan[19] proposed that polyketides are synthesized through the condensation of acetate units. Research conducted since their first hypothesis has drawn a substantial analogy between the formation of long chain fatty acids carried

out by fatty acid synthases and the synthesis of polyketides by polyketide synthases (PKS).[5]

Polyketide synthases (PKSs) are large multifunctional proteins, consisting mainly of three architecturally different types. Type I synthases are large multidomain proteins which carry all the active sites that are necessary for polyketide synthesis. These synthases are analogous to vertebrate fatty acid synthases, and are responsible for the biosynthesis of fungal polyketides. Type II synthases, on the other hand, have similar active sites distributed among smaller, monofunctional polypeptides. Type II synthases are analogous to bacterial fatty acid synthases, and are responsible for the biosynthesis of bacterial aromatic natural products such as actinorhodin (Figure 5). Type III synthases, also known as Modular PKSs, have multiple copies of active sites that are basically homologous to those found in fatty acid synthases.[20]

Modular PKSs are large multifunctional proteins that participate in the biosynthesis of complex macrolide antibiotics such as erythromycin A (Figure 5). They are organized into multiple active sites called modules, which are composed of catalytic active domains (100-400 amino acids each). [20,21] Each of these modules is responsible for one cycle of polyketide chain extension and functional group modification, which takes place within the individual domains of each of the modules. The modules generally have many domains, each minimally containing:

i) acyl transferase (AT): catalyses the loading of the starter, extender and intermediate extender units

ii) acyl carrier proteins (ACP): functions in holding the growing macrolide as thioesters and,

iii) β-keto acylthioester synthase (KS): catalyses chain extension

Other domains present in the various modules differ with regard to the amount of functional group manipulation that the growing polyketide macrolide undergoes. Some of the other domains comprise:

i) keto reductase (KS): catalyses reduction to the alcohol functionality

ii) dehydratase (DH): eliminates water to give the unsaturated thioester

iii) enol reductase (ER): catalyzes the final reduction

iv) thioesterase (TE): catalyzes macrolide release and ultimate cyclization

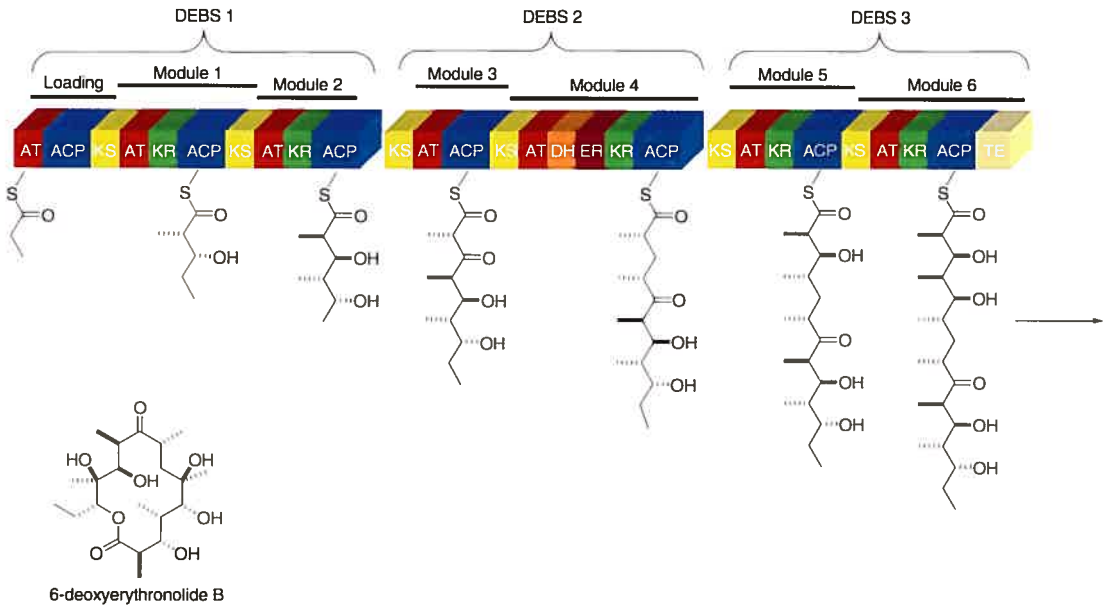


Figure 7: Predicted domain organization and biosynthetic intermediates of 6-deoxyerythronolide B synthase (DEBS).[22]

The most thoroughly studied modular PKS is 6-deoxyerythronolide B synthase (DEBS) from *Saccharopolyspora erythraea*, which catalyzes the formation of 6-deoxyerythronolide B (6-dEB), the parent macrolide aglycone of the antibiotic erythromycin A (Figure 7). The six modules of DEBS are organized into three large polypeptides, DEBS 1, DEBS 2, and DEBS 3. Each of these polypeptides consists of two modules and is about >300 kDa. In DEBS 1 there are additional AT and ACP domains, involved in the loading of the propionyl-CoA primer unit. In DEBS 3 the TE domain is linked in the release of the heptaketide from the PKS followed by concomitant formation of the 14-membered macrolactone ring.[22]

Deoxypropionates have been shown to share a common biosynthetic origin to metabolites such as erythromycin. Norte *et al.*[11c] propose that the metabolites isolated from *Siphonaria grisea* are biosynthetically obtained from propionyl-CoA, followed by successive condensations with methylmalonyl-CoA (Figure 8).

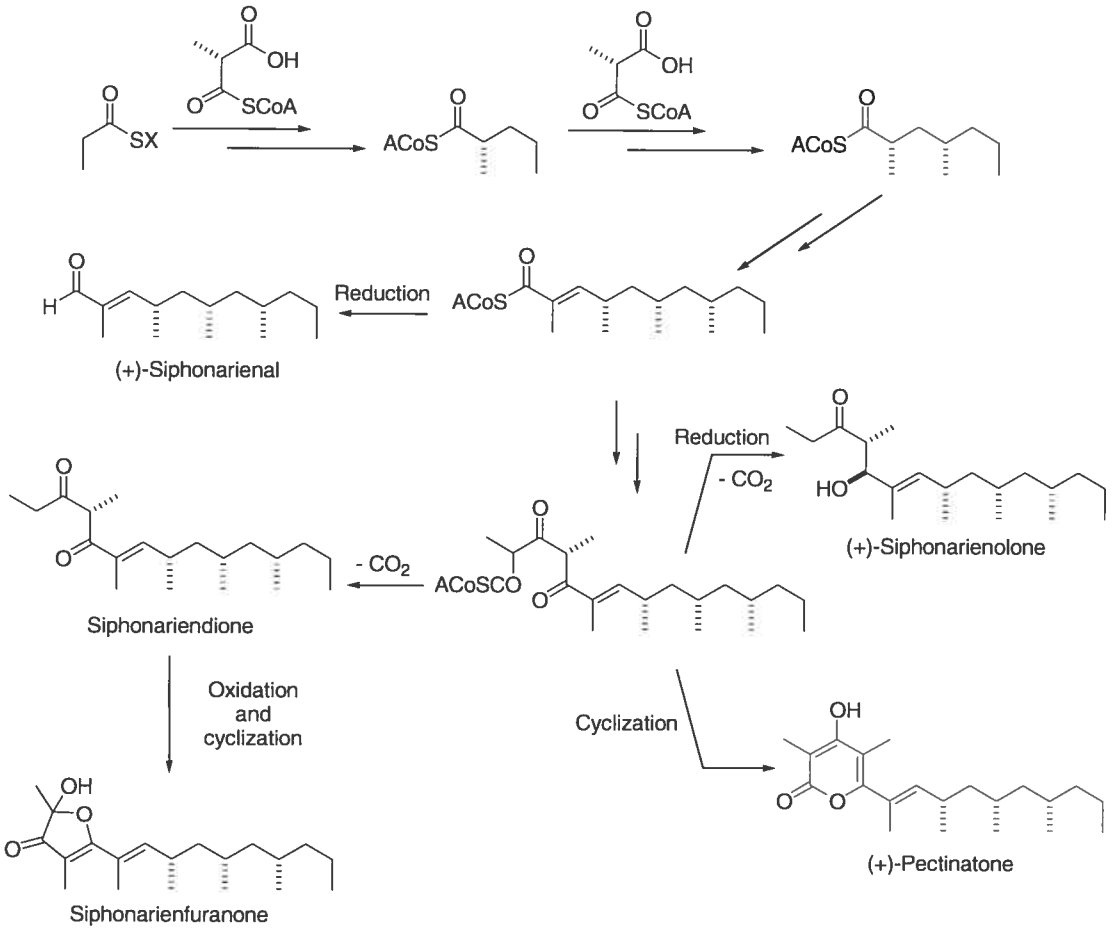


Figure 8: Proposed biosynthesis of deoxypropionate natural products.[11c]

I.3. Iterative synthetic methodologies towards deoxypropionate units

The isolation and structural determination of such a large number of natural products containing deoxypropionate units has led to the development of many methodologies allowing access to such structural motifs in an iterative fashion.[23] This section will discuss some examples wherein at least two deoxypropionate units can be accessed in an iterative fashion. The various synthetic methodologies are divided into four main categories, (a) methods wherein stereochemical control is introduced by utilizing chiral auxiliaries, (b) methods that make use of asymmetric

allylic substitution, (c) methods that use substrate control to direct the nucleophile, and finally, (d) catalytic methods.

I.3.1. 1,4-Conjugate addition using a camphorsulfonamide chiral auxiliary mediated

The methodology developed by Oppolzer[24] constitutes one of the earliest examples of stereocontrolled conjugate addition. Stereochemical bias is achieved by using a camphorsulfonamide chiral auxiliary. *Re*- or *si*- face attack of the nucleophile leads to the β-C alkylated ester, depending on which enantiomer of the chiral auxiliary is used (Figure 9).

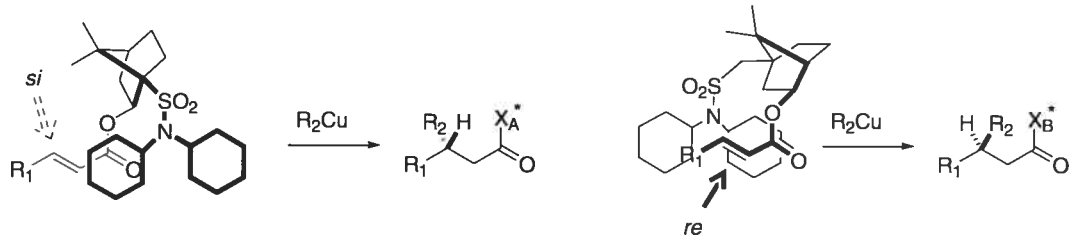
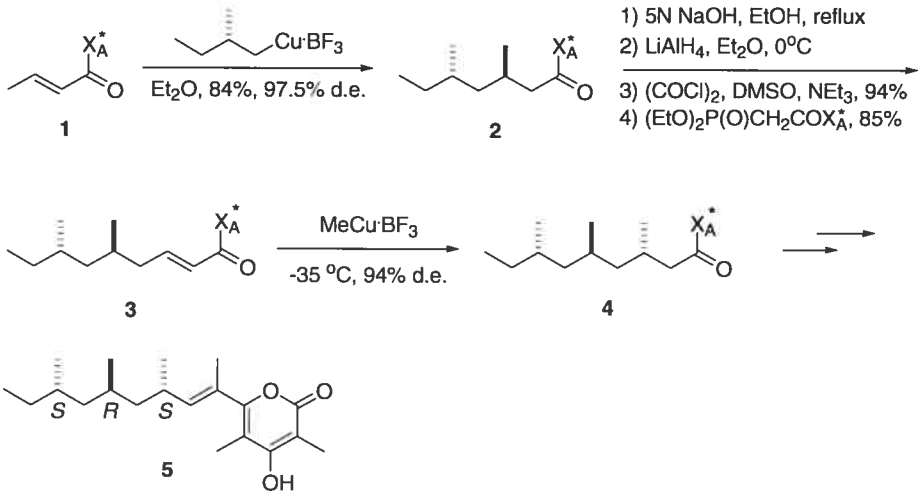


Figure 9: Chiral auxiliary mediated facial selectivity for 1,4-conjugate addition.[24]

Oppolzer utilized the camphorsulphonamide chiral auxiliary towards the synthesis of norpectinatone. Michael addition of the organocopper reagent bearing a resident *C*-methyl group to compound **1** gave the corresponding *anti*-deoxypropionate unit, with excellent d.e. (Scheme 1). Alkaline hydrolysis of substrate **2** was followed by reduction of the corresponding carboxylic acid to the alcohol. Swern oxidation to the aldehyde followed by chain extension with a phosphonate resulted in product **3**. Iteration of the 1,4-conjugate addition was accomplished at this stage by treatment of compound **3** with the methylcopper reagent in the presence of BF_3 affording product **4**, with *anti*/*anti*-deoxypropionate units. Further functional group manipulation afforded product **5**, which did not correspond to the spectroscopic data reported for norpectinatone. Towards that end, the (*S*, *R*, *R*)- diastereomer was also synthesized

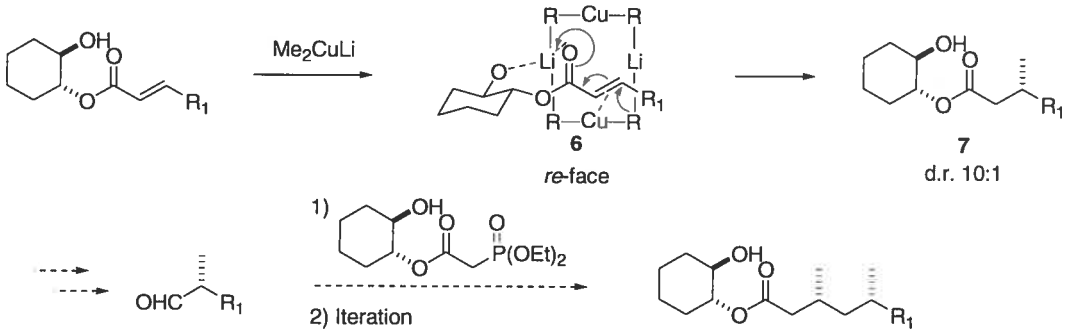
(not shown), but did not match the spectral data of norpectinatone either. Based on the above information it was concluded that the desired natural product has the all *syn*- stereochemistry.



Scheme 1: Oppolzer's camphorsulfonamide auxiliary based iterative 1,4-conjugate addition.[24]

I.3.2. Use of chiral cyclohexanediols as chiral auxiliaries

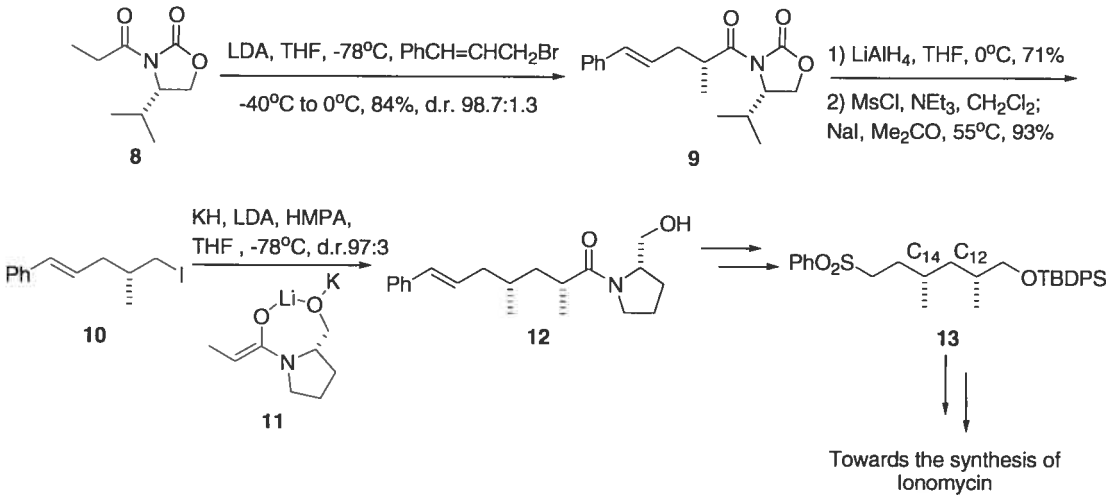
Sakai's[25] approach involved the use of chiral cyclohexanediols to obtain diastereoselective addition of lithium dimethylcuprate to α,β-unsaturated esters. The observed diastereoselectivity for the first cuprate addition leading to product **7** was 10:1 (Scheme 2). The proposed transition state involves chelation of the lithium ion in the square planar dimeric dialkylcuprate complex with the alcohol and the ester carbonyl, leading to the formation of the copper(I)-alkene π-complex (**6**). The double bond then receives the R substituent from the *re*-face in a stereocontrolled manner. An iterative sequence has been proposed by Sakai, but this methodology has not been applied in an iterative manner.



Scheme 2: Sakai's method to access deoxypropionates.[25]

I.3.3. Using Evans' oxazolidinone chiral auxiliary: Diastereoselective enolate alkylations

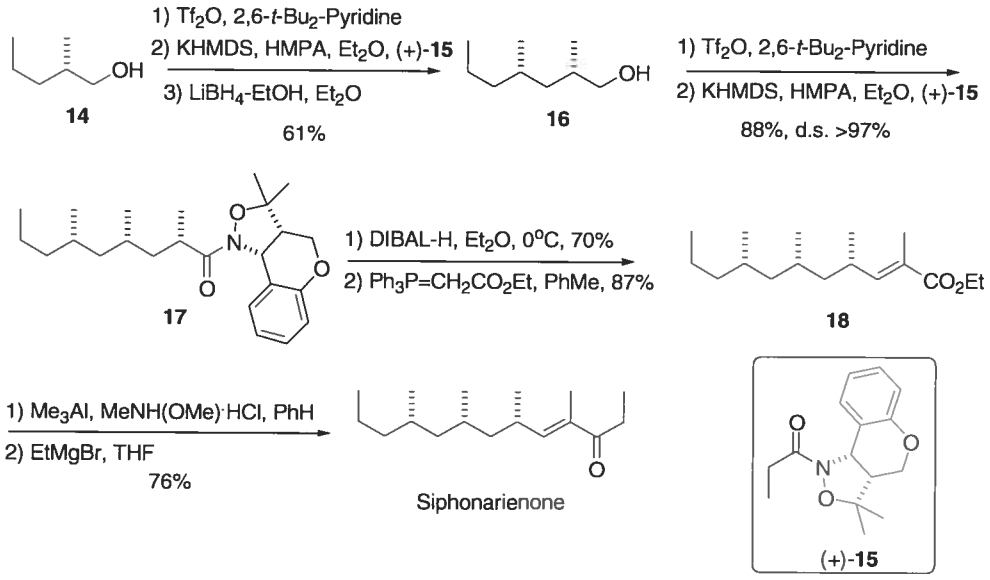
Towards the synthesis of ionomycin, Evans *et al.*[13c] made use of oxazolidinone-derived and prolinol amide-derived enolate alkylations. As shown in Scheme 3, which starts with oxazolidinone **8**, alkylation with cinnamyl bromide led to the installation of the first methyl group in product **9**. Standard functional group manipulation provided alkyl iodide **10**. Utilizing the alkyl iodide in the alkylation of the prolinol amide enolate (**11**) provided product **12**. The use of mixed bases and HMPA/THF as solvent is noteworthy.



Scheme 3: Evans' use of carboximide and prolinol amide-derived chiral auxiliaries.[13c]

The more nucleophilic prolinol amide enolate **11** was used in the second alkylation step, since oxazolidinone derived enolates (like **8**), are not sufficiently nucleophilic in order to react with alkyl iodides. With the C_{12}-C_{14} *syn*-deoxypropionate unit installed standard functional group manipulation provided product **13**, which was used to complete the synthesis of ionomycin.

I.3.4. Using Masamune's chiral auxiliary: Diastereoselective enolate alkylations



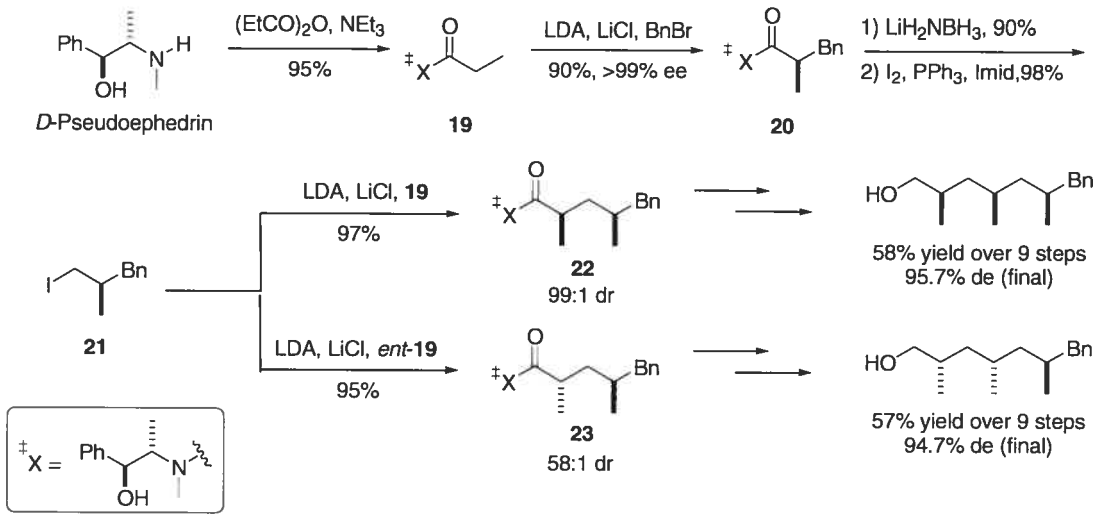
Scheme 4: Masamune's use of benzopyranoisoxazolidine chiral auxiliary.[26]

The benzopyranoisoxazolidine chiral auxiliaries used by Masamune[27] are accessed by a three step sequence, starting with *o*-allyloxybenzaldehyde and an oxime. The iterative approach to access deoxypropionate units was showcased by Abiko and Masamune[26] in achieving the first synthesis of (+)-siphonarienone (Scheme 4). Treatment of chiral alcohol **14** with triflic anhydride, followed by treatment of the corresponding triflate with the potassium enolate of (+)-**15**, provided the asymmetric alkylation product with high diastereoselectivity (d.s. >97%). Reduction of the isoxazolidine resulted in the corresponding alcohol (**16**),in a 67%

yield over three steps. Iteration of the process was achieved by conversion of the alcohol to the triflate followed by another alkylation with the potassium enolate of (+)-**15**, providing product **17** with high diastereoselectivity (d.s. >97%). With the two deoxypropionate units installed the stage was set for completion of the synthesis. Standard functional group manipulation led to the synthesis of (+)-siphonarienone.

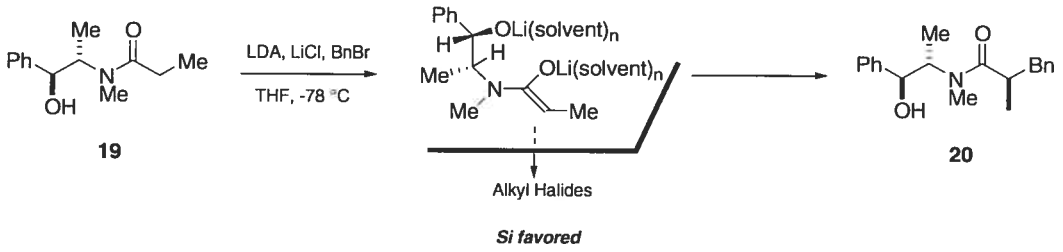
I.3.5. Diastereoselective enolate alkylations using pseudoephedrin as a chiral auxiliary

Myers *et al.*[28] used pseudoephedrin as a chiral auxiliary to access deoxypropionate units in an iterative manner. Use of *D*- or *L*- pseudoephedrin allows access to either *syn*- or *anti*- deoxypropionate units. Treatment of acid chlorides or anhydrides leads to the selectively *N*-acylated product **19** (Scheme 5). Since intramolecular *O*- to *N*-acyl transfer within pseudoephedrin β-amino acids occurs rapidly, and the *N*-acylated product is favored under neutral or basic conditions, products arising from (mono)acylation on the oxygen atom are not observed.[29] Treatment of compound **19** with lithium diisopropylamide results in the formation of the dianion, which is followed by alkylation in the presence of lithium chloride leading to product **20**, with excellent diastereomeric excess. Lithium chloride has been shown to accelerate the alkylation and also facilitates in driving the reaction to completion.[30] Iteration of the process proceeds by reduction of amide **20** to the corresponding alcohol with lithium amidotrihydroborate (LAB), followed by iodination to give product **21**. Alkyl iodide **21** is then treated with the enolate derived from **19** resulting in product **22**. Reactions producing *syn*- stereochemistry represent a matched case (**22**, d.r. 99:1), whereas reactions producing *anti*- stereochemistry, are an example of a mismatched case, as shown by the treatment of alkyl iodide **21** with the enolate derived from *L*-pseudoephedrin, resulting in a diastereomeric ratio of 58:1 for **23**.



Scheme 5: Myers' pseudoephedrin chiral auxiliary.[28]

Cleavage of the auxiliary can be accomplished by treatment with either strong acid (18N sulfuric acid) or base (tetra-*n*-butylammonium hydroxide). However, both acid and base hydrolysis has reportedly resulted in some epimerization.[30] In addition to hydrolysis, the pseudoephedrin amides can be transformed into aldehydes and ketones.

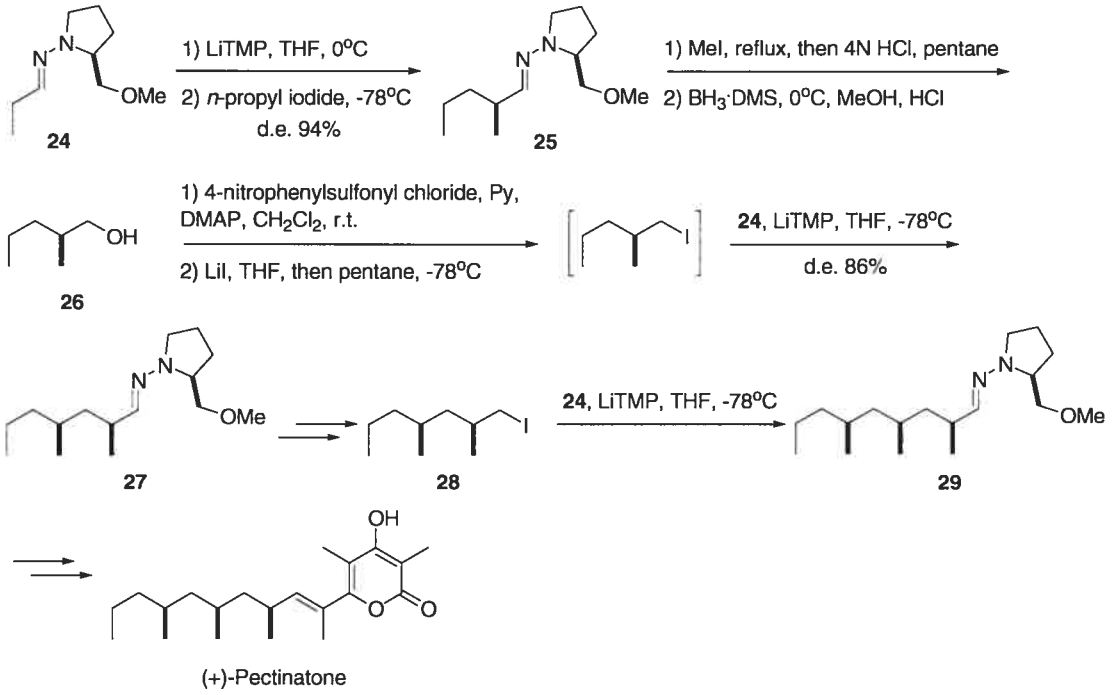


Scheme 6: Selectivity in pseudoephedrin amide alkylations.[29]

The basis for the selectivity can be explained by considering the reactive conformer shown in Scheme 6, wherein the solvent molecules and the lithium alkoxide may block the β-face of the (*Z*)-enolate, forcing the electrophile to come in from the α-face. The pseudoephedrin side-chain adopts a staggered conformation, with the C-H

bond α to the *N*-atom lying in the same plane as the enolate oxygen, in order to minimize allylic strain.[29]

I.3.6. Diastereoselective aza-enolate alkylations: Using Enders' SAMP or RAMP hydrazones as chiral auxiliaries

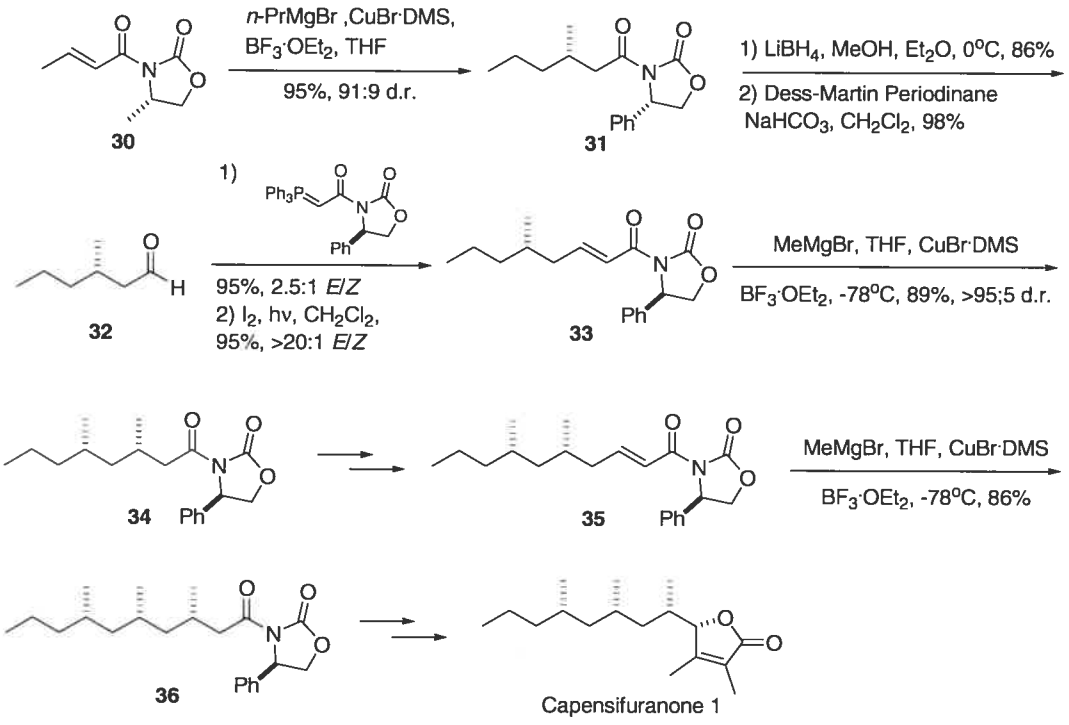


Scheme 7: Enders' aza-enolate alkylations.[31]

The aza enolates derived from SAMP or RAMP hydrazones are very reactive towards secondary iodides, β-branched iodides and bromides. Towards the synthesis of (+)-pectinatone, Enders and Birbeck[31] have shown that generation of the aza-enolate, alkylation, and cleavage of the hydrazone auxiliary can be carried out in an iterative fashion to generate deoxypropionate units. As shown in Scheme 7, generation of the aza-enolate followed by alkylation with *n*-propyl iodide provided the resulting hydrazone **25** with excellent diastereocontrol (d.e. 94%). Alcohol **26** was obtained by a two step protocol, which was followed by conversion of **26** to the

nosylate. *In situ* generation of the iodide and treatment with the enolate of **24** gave the corresponding hydrazone **27** in 86% d.e. Cleavage of the auxiliary followed by a second reiteration sequence gave hydrazone **29** (85% d.e., overall). Standard functional group manipulation gave the desired natural product (+)-pectinatone, harboring the all *syn*-deoxypropionate units.

I.3.7. Williams' oxazolidinone chiral auxiliary mediated 1,4-conjugate addition

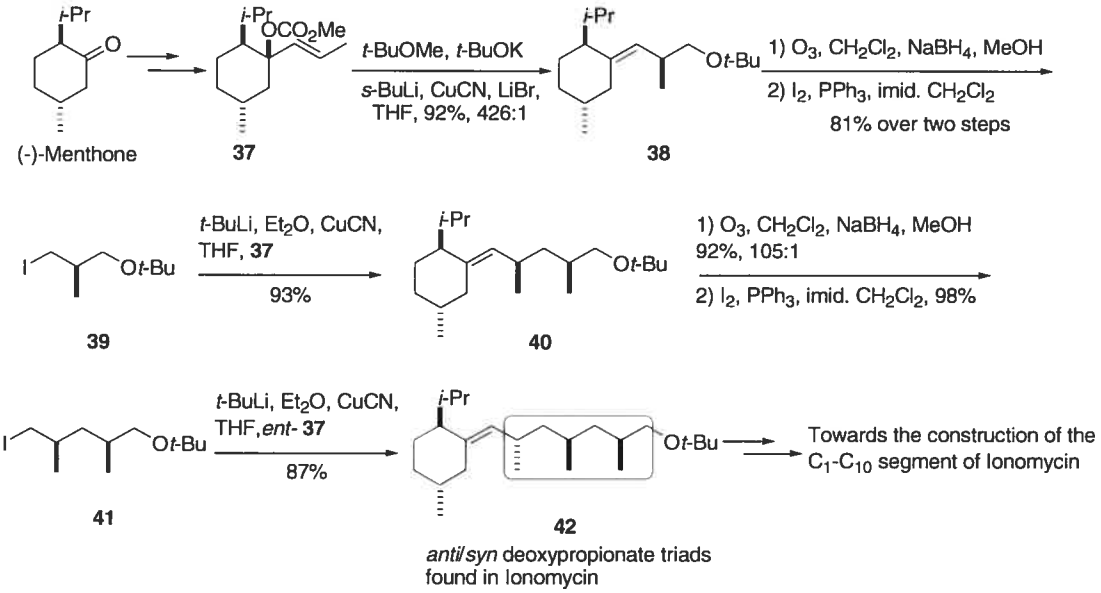


Scheme 8: Williams' iterative approach towards the synthesis of capensifuranone **1**.[33]

Hruby *et al.*[32] utilized 4-phenyl-1,3-oxazolindin-2-ones as chiral auxiliaries in the asymmetric addition of organocuprates to α,β-unsaturated substrates. The same chiral auxiliary was utilized by Williams *et al.*[33] in their synthesis of capensifuranone. As shown in Scheme 8, addition of the Yamamoto organocopper reagent[34] to compound **30** provided product **31** (d.r. 91:9). Removal of the chiral auxiliary ($LiBH_4$), followed by oxidation, afforded aldehyde **32**, which was further

homologated. Isomerization of the resulting *E/Z* mixture in the presence of iodine upon exposure to sunlight afforded product **33**. Iteration of the process by addition of the methylcopper regent provided intermediate **34** with excellent diastereocontrol. Removal of the auxiliary, followed by homologation of the substrate as described above, afforded product **35**. Addition of methylcopper reagent to substrate **35**, gave product **36** with two *syn/syn-* deoxypropionate units. Standard functional group manipulation afforded the desired final product.

I.3.8. Chiral auxiliary mediated S_N2' displacement



Scheme 9: S_N2' mediated displacement of allylic carbonates.[35]

Spino and Allan[35] access the deoxypropionate units by S_N2' displacement of a chiral allylic carbonate. The chiral carbonates can be derived from (+)- or (-)-menthone in one or two steps by the addition of alkenyl or alkynl metal reagents, respectively (Scheme 9).[36] Treatment of chiral carbonate **37** with an alkyl cuprate leads to the *anti*-addition product **38** with excellent stereoselectivity. Ozonolysis followed by reductive workup led to cleavage of the chiral auxiliary and to

conversion of the resulting chiral alcohol to iodide **39**, which was ready to be used in the first iteration step. Lithium-halogen exchange of iodide **39**, followed by addition of menthol derivative **37**, led to the installation of one deoxypropionate unit with high diastereocontrol. Reiteration of the process provided compound **42**, wherein the *anti/syn* deoxypropionate units of the C_1-C_{10} fragment of ionomycin have been installed with a high level of stereocontrol.

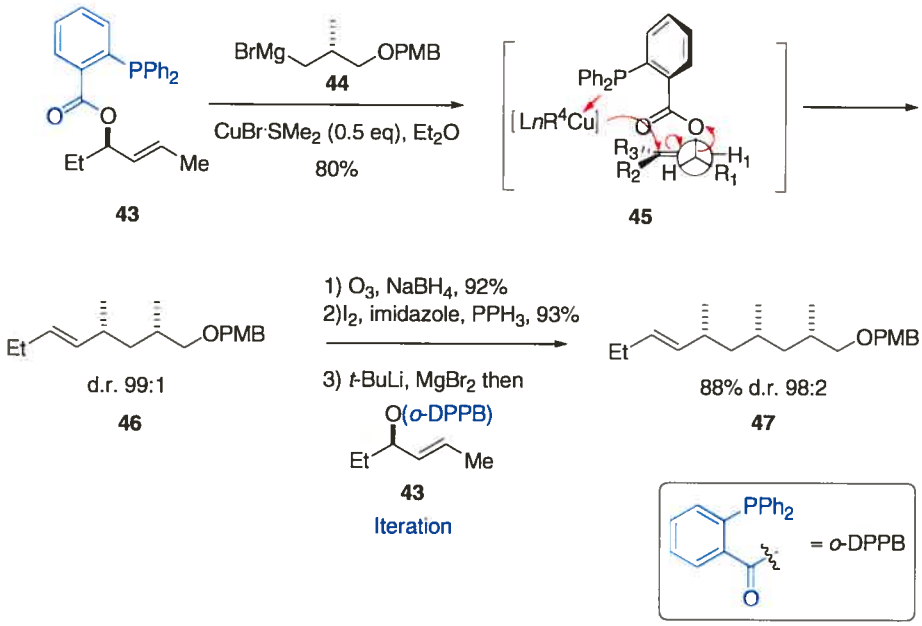
The high level of stereoselectivity is explained by the two rotamers shown in Figure 10. Rotamer **37A** has been calculated to be approximately 4 kcal/mol lower in energy than rotamer **37B**, and it has been hypothesized that the same energy difference would be expected to be maintained at the transition state during the cuprate addition, leading to the *anti*-addition product.[36]

Figure 10: Energy difference between the rotamers.[36]

I.3.9. Breit's reagent-directing group: Asymmetric allylic-substitution

Breit and Herber[37] report the use of *ortho*-diphenylphosphanylbenzoyl (*o*-DPPB) as a reagent-directing group for the addition of Gilman cuprates to allylic electrophiles in an iterative fashion. This method commences with a three step preparation of the *o*-DPPB electrophile **43** obtained from the corresponding racemic allylic alcohol (not shown). As shown in Scheme 10, this is followed by allylic substitution of the Grignard reagent **44**, already harboring a resident *C*-methyl group, to the electrophile giving one deoxypropionate unit in product **46** with excellent stereoselectivity (d.r. 99:1). The stereochemical outcome is explained through the coordination of the phosphane with the organocopper reagent, as indicated in **45**. The result of the coordination is that the nucleophile is delivered *syn*- with respect to the

leaving group.[38] The proposed directed delivery of the organocopper reagent has been proven by oxidizing the phosphane. The phosphane oxide substrate proceeds through a non-directed *anti*- attack of the nucleophile.



Scheme 10: Reagent directed allylic substitution.[37,38]

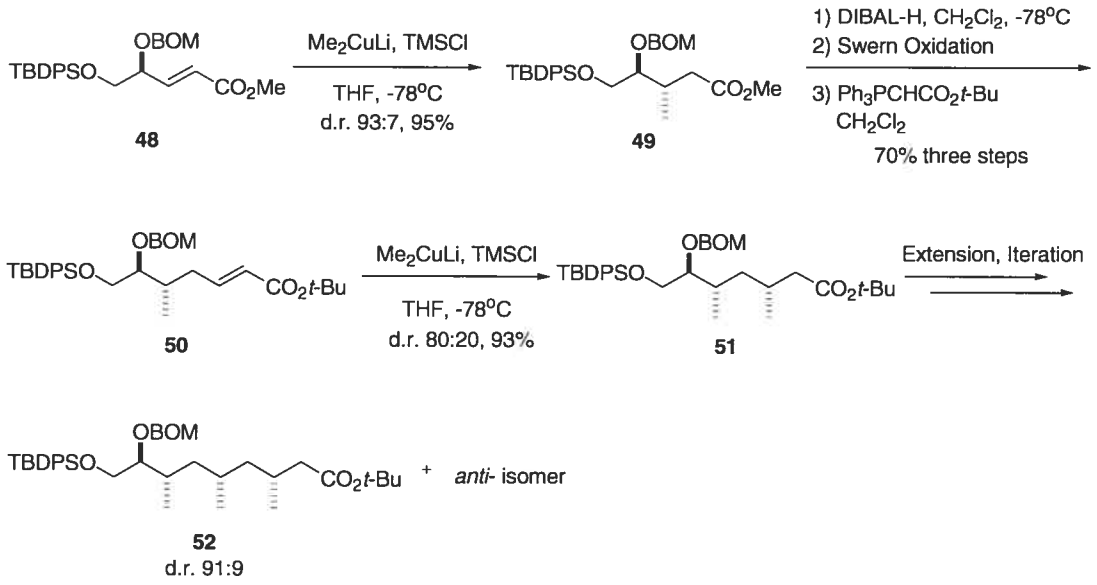
Iteration of the process begins with oxidative cleavage of the olefin by ozonolysis and reductive workup, followed by conversion to the iodide. Lithium-halogen exchange by treatment with *tert*-BuLi is followed by transmetallation with $MgBr_2 \cdot OEt_2$. Directed allylic substitution of the resulting Grignard reagent with **43** gave the *syn*/*syn* deoxypropionate **47** in a diastereomeric ratio of 98:2. Recently Breit and Herber[15] have utilized the same strategy in synthesizing sex pheromones of the cane beetle, 4,6,8,10,16,18-hexamethyldocosane, which feature *anti*/*anti*/*anti*- methyl stereochemistry in the 4,6,8,10 subunit.

Breit and Demel[39] have also used the *o*-DPPB group as a catalyst directing group in hydroformylation reactions. The use of the *o*-DPPB group has also been extended to a subsequent step wherein it is used as a reagent-directing group towards

the diastereoselective addition of lithium dimethylcuprates to α,β-unsaturated esters.[40]

I.3.10. Substrate control

Hanessian *et al.*[8, 14d] make use of substrate control for the iterative installation of deoxypropionate units. Previously it had been demonstrated that polypropionate subunits can be constructed from a series of 1,2-inductions by subjecting enantiopure γ-alkoxy-α,β-unsaturated esters to a conjugate addition of lithium dimethylcuprate followed by hydroxylation of the corresponding potassium enolate.[41] Homologation to a new γ-alkoxy enoate and reiteration afforded enantioenriched propionate units of a defined stereochemistry. For the construction of isotactic deoxypropionates, Hanessian *et al.* utilized a strategy similar to the construction of polypropionates (Scheme 11).



Scheme 11: Utilizing substrate control in the synthesis of deoxypropionates.[8, 14d]

Addition of the Gilman cuprate to γ-alkoxy-α,β-unsaturated ester **48** afforded ester **49** with a high level of stereocontrol, resulting from 1,2-induction.

Homologation of ester **49** to the δ-methyl-α,β-unsaturated ester **50**, followed by addition of lithium dimethylcuprate, led to product **51** with good selectivity. Further homologation and iteration led to product **52**. Substrates **52** and *ent*-**52** were intermediates in the synthesis of doliculide[8] and borrelidin[14d], respectively.

The 1,2-induction observed in the addition of the Gilman cuprate to γ-alkoxy-α,β-unsaturated esters is explained by the conformations shown in Figure 11. The observed *anti*- attack can be rationalized on the basis of the reactive conformer model **48A**, which is also in agreement with the proposed models of Yamamoto[42] and Morokuma.[43] There is a favorable interaction between the lone pair of electrons on the oxygen atom of the alkoxy substituent and the π-electrons of the double bond, leading to the "*O*-inside alkoxy" (OR) effect.[44]

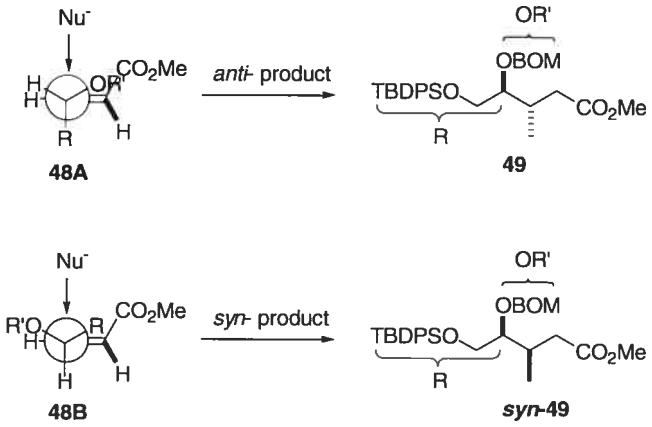


Figure 11: Proposed conformations for *anti* and *syn* attack.[41]

Also the *anti*-orientation of the R group, with regard to the trajectory of the nucleophile may stabilize the σ*C-Cu orbital in the d,π* complex-β-cuprio (III) adduct, through σ-bond donation. Conformer **48B** leading to the *syn*- product does not give the stabilizing interaction of the inside OR as in conformer **48A**.

Conjugate addition of lithium dimethylcuprate to δ-methyl-α,β-unsaturated esters, proceeding through 1,3-induction leading to the *syn*-addition products, is

explained by the proposed transition states in Figure 12. The backbone of the growing hydrocarbon chain folds in a manner wherein *syn*-pentane interactions are minimized. Superimposition of the energetically favored conformation on a diamond lattice assists in visualizing the backbone of the acyclic enoates.

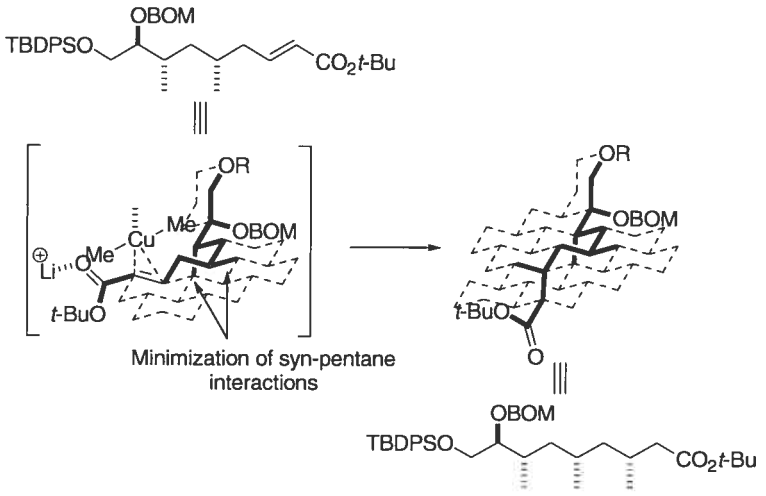
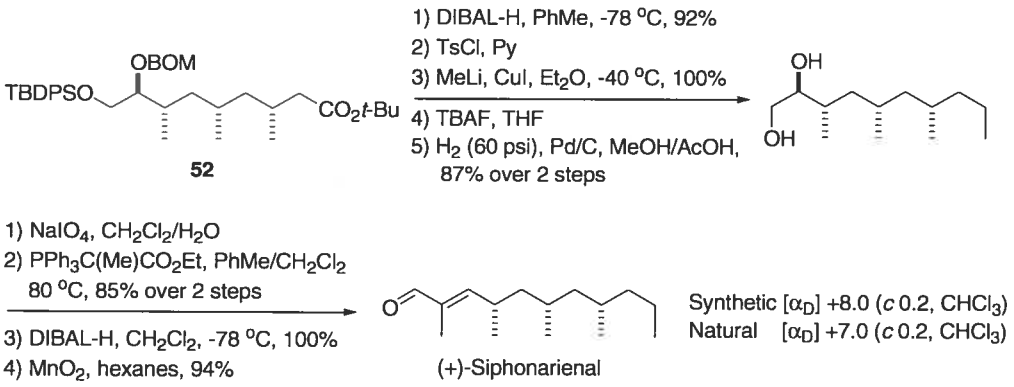


Figure 12: Minimization of *syn*-pentane interactions in the hydrocarbon chain backbone.[8, 14d]

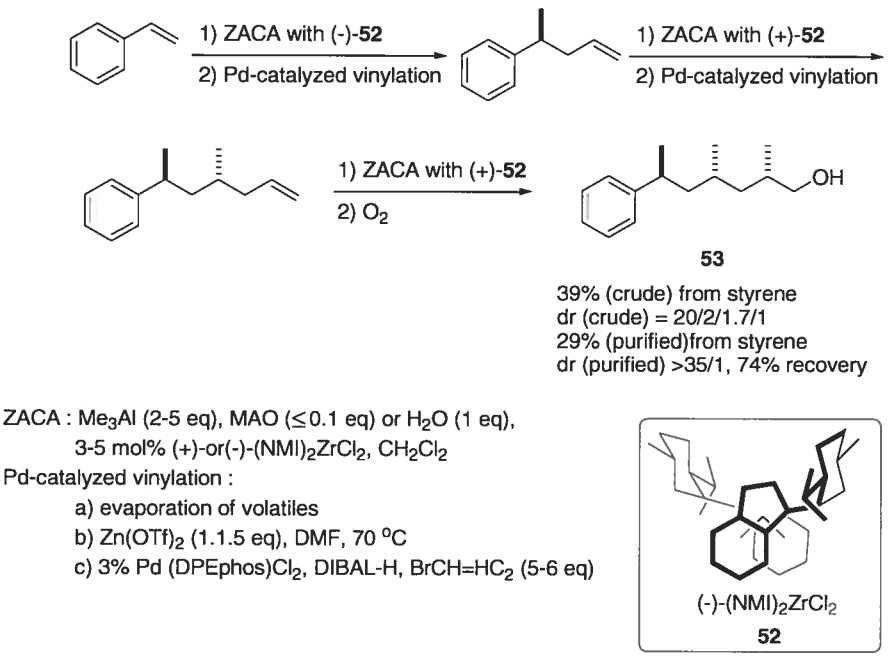


Scheme 12: Synthesis of (+)-siphonarienal from intermediate **52**.[14d]

The *syn*- selectivity of the conjugate additions of lithium dimethylcuprate was verified by the synthesis of (+)-siphonarienal. As shown in Scheme 12 compound **52**,

which serves as an intermediate towards the synthesis of borrelidin,[14d] is converted to (+)-siphonarienal. The physical constants thus obtained were identical to the reported values for (+)-siphonarienal. Furthermore upon completion of the synthesis of borrelidin the X-ray obtained showed that the methyl groups of the deoxypropionate chain were indeed syn with respect to each other.[14d]

I.3.11. Negishi's zirconium catalyzed method

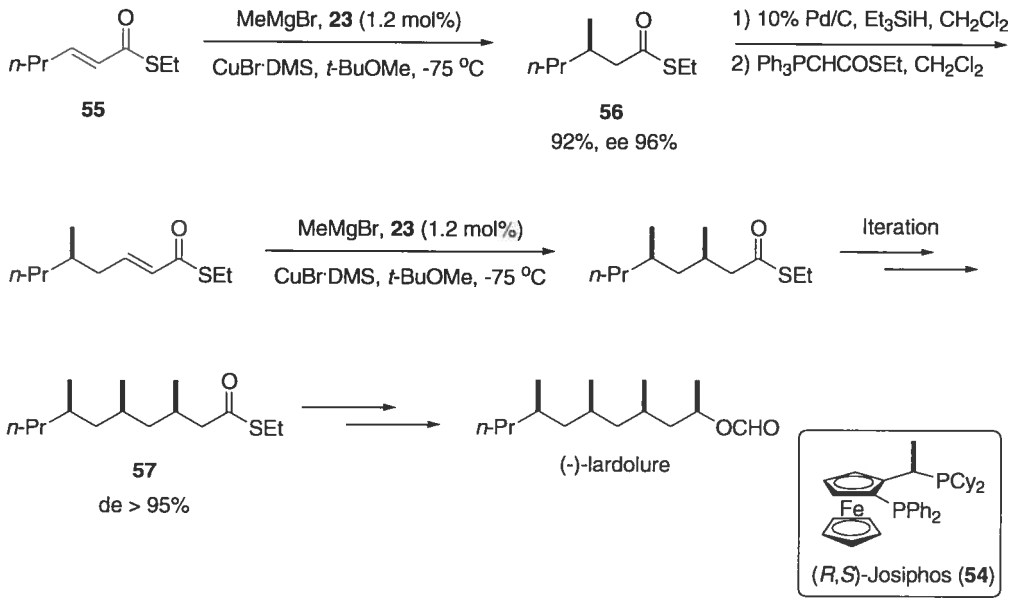


Scheme 13: Negishi's catalytic, iterative protocol for accessing deoxypropionates.[45]

Negishi *et al.*[45] prepared the deoxypropionate motif through an iterative sequence of Zr-catalyzed asymmetric carboalumination (ZACA) followed by palladium catalyzed vinylation. The ZACA is achieved by employing (+)- or (-)-dichlorobis(neomenthyl)zirconium (**52**) as the catalyst in the presence of Me_3Al and methylaluminoxane (MAO), which significantly accelerates the reactions. As shown in Scheme 13, starting from styrene, three cycles of iteration led to **53**, with a diastereomeric ratio of >35/1. This methodology has been applied by Negishi *et al.* in the synthesis of natural products such as siphonarienolone and some of its

structurally related analogues, and it has also been applied to the synthesis of borrelidin and ionomycin intermediates.

I.3.12. Feringa's catalytic addition of Grignard reagents in the presence of chiral ligands



Scheme 14: Feringa's catalytic method.[46]

Feringa *et al.*[46] have developed a highly efficient iterative, catalytic system to access the deoxypropionate motif in an enantio- and diastereoselective manner. They make use of conjugate addition to α,β-unsaturated thioesters, in the presence of a complex prepared in *situ* from CuBr·DMS (6 mol %) and Josiphos (**54**, 5 mol%). They have applied their methodology towards the synthesis of (-)-lardolure (Scheme 14). Conjugate addition with methylmagnesium bromide affords enantiopure **56** (96% e.e.). Iteration of the process begins with the conversion of the thioester to the aldehyde, followed by a Wittig reaction giving the desired α,β-unsaturated thioester. A second catalytic conjugate addition followed by another iteration sequence provides the polydeoxypropionate **57** with an overall d.e. >95%. This methodology

also allows access to *anti*-1,3-dimethyl arrays, by utilizing *ent*-**54** as the chiral catalyst, providing diastereomeric ratios of 95:5. The high diastereoselectivities obtained showcase the efficiency of the chiral catalyst to control the configuration of the new stereocenter, independent of the absolute configuration of the chain.

Towards the synthesis of (-)-doliculide, Gosh and Liu[9b] install the deoxypropionate units indirectly by utilizing Charette's cyclopropanation[47] followed by regioselective ring opening.[48]

I.4. Conformational design

Studies by Hoffmann *et al.*[7] indicate that 2,4-dimethylpentane units can be rendered monoconformational, despite the many degrees of rotational freedom, by anchoring an inductor group at one end of the molecule. As shown in Figure 13, compound **58** has two low energy conformations **58a** and **58b**.[49] Rotation about C_2-C_3 would lead to a destabilizing *syn*-pentane interaction (**58c**). Introducing substitution (X) at the terminal carbon atoms (**59**) could possibly destabilize one of the two conformers (**59a**, **59b**) to different extents. In certain cases the substitution could render the dimethylpentane segment monoconformational.

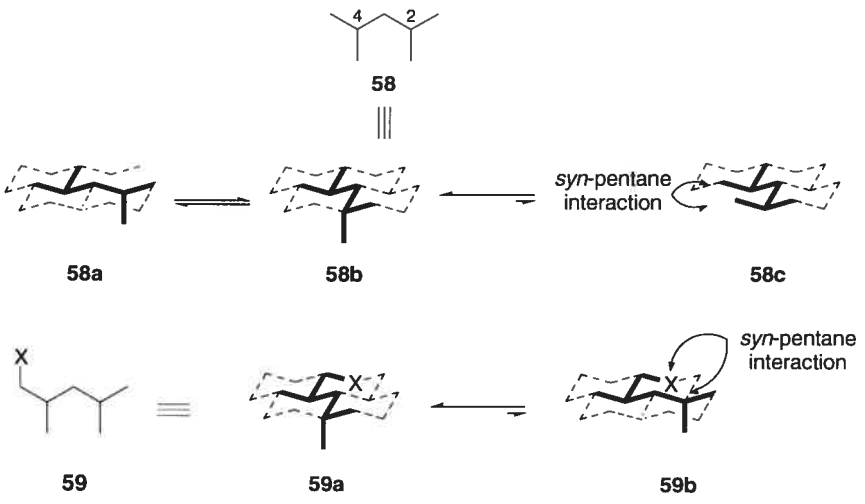


Figure 13: Biasing a conformation by introducing destabilizing interactions.[49]

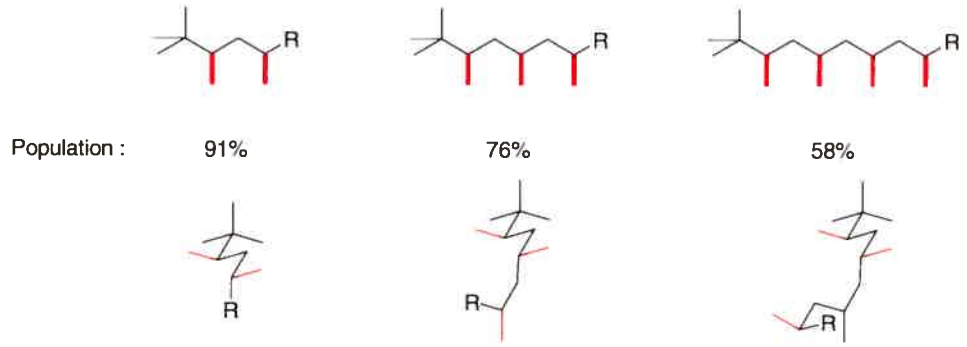


Figure 14: Calculated preference for attaining fully extended conformation.[7]

A dimethylpentane segment in a defined conformation can serve as an inductor group; affecting the conformation of the neighboring dimethylpentane segments. The inductor group would affect the conformation of neighboring segments in order to avoid destabilizing *syn*-pentane interactions. This conformational control is only possible if the dimethylpentane segment is isotactic (*syn*-methyl groups), not when it is syndiotactic (*anti*-methyl groups). Also, the conformational preference decreases as the number of adjacent dimethylpentane segments increases (Figure 14).

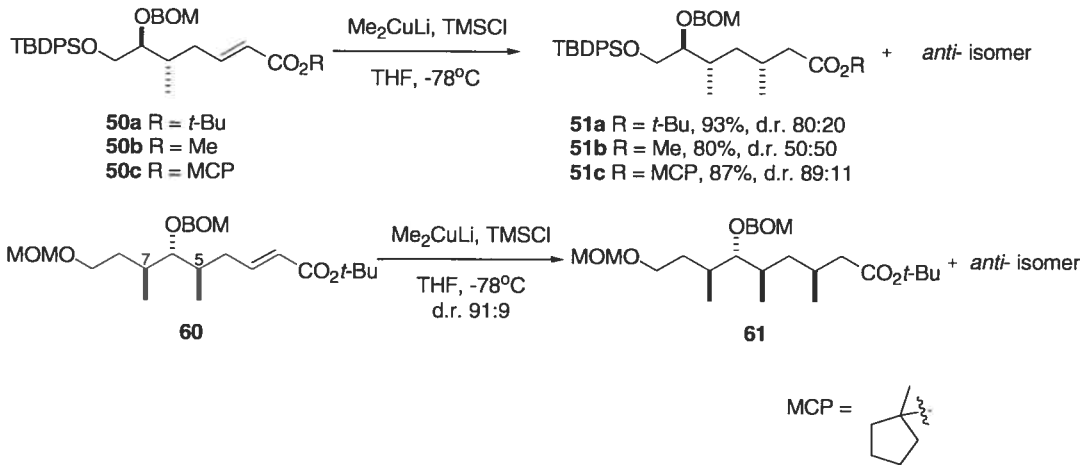
Chapter II:

Evaluating the "anchoring" and "ester" effects

In this chapter the prospect of conformational control and the introduction of anchoring groups in acyclic molecules are investigated. Anchoring groups bias the molecule towards certain energetically favored acyclic conformations thereby inducing stereochemical induction in the addition of lithium dimethylcuprate to α,β-unsaturated esters. The "anchoring" effect with an *iso*-propyl group in such enoates is assessed. Various esters and protecting groups are surveyed, and finally the degree of conformational induction offered by the *iso*-propyl anchor is investigated by extending the system to its limits.

II.1. Introduction to the "anchoring effect" and the "ester effect"

Work done in the Hanessian laboratories towards the total synthesis of doliculide[8] and borrelidin[14d] showed that anchoring an inductor group in δ-methyl-α,β-unsaturated esters led to the predominance of one reactive conformation over another. The result of this was that higher selectivities were obtained when treating δ-methyl-α,β-unsaturated esters with lithium dimethylcuprate. The term coined for this observation is the "anchoring effect". Another effect observed was the "ester effect", which indicated that changing the α,β-unsaturated ester to a bulkier ester led to better selectivities. Both these results are shown in Scheme 15. Conjugate addition of lithium dimethylcuprate to compounds **50a-c** led to diastereomeric ratios in the range of 50:50 to 89:11, depending on the nature of the ester substituent. Addition of the Gilman cuprate to compound **60** led to much higher selectivity of the *syn*- diastereomer.



Scheme 15: Previous results reported by Hanessian.[14d]

The only difference between substrates **50a** and **60** is the structural motif highlighted in red. Branching at C_7 (instead of having the $CH_2OTBDPS$) may destabilize one reactive conformer in **60** over another by introducing a *syn*-pentane interaction with the pendant methyl group at C_5, thereby leading to better selectivities. Branched groups at C_7 may serve as inductor groups, anchoring the molecule preferentially in one conformation over another (see also section I.4). Intrigued by these results, we wanted to further probe the anchoring effect at the extremities of α,β-unsaturated esters and to investigate the ester effect, while also determining what effect, if any, the nature of the alkoxy substituent had.

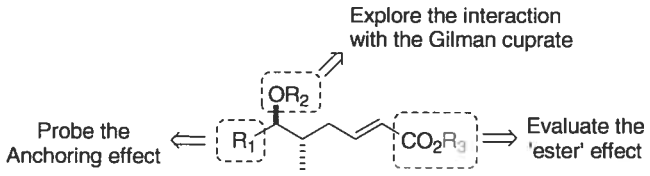


Figure 15: Studying the variables of the ε-alkyl, alkoxy-δ-methyl-α,β-unsaturated esters.

As shown in Figure 15, the substrate can be varied in three different positions, which would allow us to alter the electronics and the sterics of the system. This would consequently shed some light on the mechanism of addition of lithium dimethylcuprate to δ-methyl-α,β-unsaturated esters. To evaluate the role of the anchoring group (R_1), the nature of the alkoxy substituent (R_2), and the ester effect (R_3), we decided to systematically vary one parameter at a time. Most of the previous work had been done with the benzyloxymethyl (BOM) protecting group and with methyl- and *tert*-butyl esters, with the bulkier *tert*-butyl ester giving the best selectivities. Based on the results presented in Scheme 15, we decided to investigate the anchoring effect of a terminal *iso*-propyl group with the BOM protecting group and a variety of ester substituents.

II.2. Determination of diastereomeric ratios

An important aspect in developing diastereo- and enantioselective reactions is analyzing the ratios of products by a suitable method. Many different methods for determining product ratios have been used such as HPLC analysis, GC analysis and a variety of other chromatographic techniques. Sometimes, further chemical conversion to either known products or to MPTA esters, and NMR analysis thereof, has been used to determine the relative ratio of products formed. Also, analysis of ^{1}H NMR spectra has been widely used for determining diastereomeric ratios. Although diastereomers are often easily distinguished by routine ^{13}C NMR, this method is not suitable for quantitative analysis (*vide infra*).

During the course of this project, we tried many of the above techniques to determine the diastereomeric ratio of the products formed; however, none were found to be suitable for our molecules. Analysis by ^{1}H NMR provides no information in most cases, as the diastereomers do not have detectable chemical shift differences. We have, nonetheless, been able to detect the different diastereomers through ^{13}C NMR spectroscopy. Therefore in order to gain quantitative information from ^{13}C NMR spectra we decided to acquire the spectra using inverse gated proton decoupling experiments.[8] In examples where the diastereomers could be observed by both ^{1}H

NMR and ^{13}C NMR spectroscopy, both techniques have been used and the ratios obtained show excellent correlation.

II.2.1. Inverse gated proton decoupling experiments

Quantitative ^{13}C NMR can be useful in providing structural information in those cases where ^{1}H NMR spectra are harder to interpret due to overlap of the desired signals. Signals in ^{13}C NMR appear over a larger chemical shift range, facilitating the analysis of the spectra considerably. Quantitative ^{13}C NMR has been shown to be an indispensable tool in the quantitative determination of structural units in lignans.[50] However, routine ^{13}C NMR spectra are not amenable to quantitative analysis due to several factors that affect the intensity of the ^{13}C signals. First of all, the ^{13}C nuclei that have different relaxation times (T1) may not return to equilibrium between pulses, thereby not allowing the signals to achieve full amplitude. Secondly, the nuclear Overhauser enhancement (nOe) observed between the proton and carbon nuclei during the acquisition of a routine ^{13}C NMR increases the signal intensity (up to approx. 200%).[51] This increase in intensity is not proportional for all signals.[52] It is, however, possible to adjust the parameters of the ^{13}C NMR spectrum, thereby correcting for the above mentioned limitations in order to acquire a spectrum which can provide useful quantitative information regarding signal intensities.

The most important factor in the large variation of signal intensity between routine NMR's and the theoretical values is the variation of relaxation time.[53] The relaxation delay on routine spectra is not long enough. If the relaxation delay is long enough (approximately five times the value of the longest ^{13}C relaxation time[50]) each carbon then reaches equilibrium, so the effect of the effect of T1 on the intensity is removed. Different relaxation times of ^{13}C nuclei can be taken care of by using a pulse delay after acquisition in order to reestablish equilibrium.

The second factor affecting the signal intensities mentioned above is the nOe. Routine ^{13}C NMR spectra are subject to broad band decoupling (i.e. irradiation) of protons.[51] The effect of decoupling is two fold. First of all, by decoupling the protons, the ^{13}C NMR spectrum is simplified significantly resulting in singlets being

observed, as opposed to complex overlapping multiplets. The second effect of decoupling is that nOe is observed, which enhances the ^{13}C signal intensities (*vide supra*). Signal enhancement due to the nOe can be corrected for by applying inverse-gated proton decoupling (Figure 16). Inverse-gated decoupling is obtained by turning on or gating the broadband decoupling during acquisition and turning it off during the pulse delay (relaxation time). The build up of nOe is a slow process, and it builds up only slightly during the acquisition period and dies down immediately during the relaxation delay. Decoupling, on the other hand, is a fast process which is established almost immediately upon irradiation, resulting in signal intensities proportional to the number of carbon atoms that they represent.

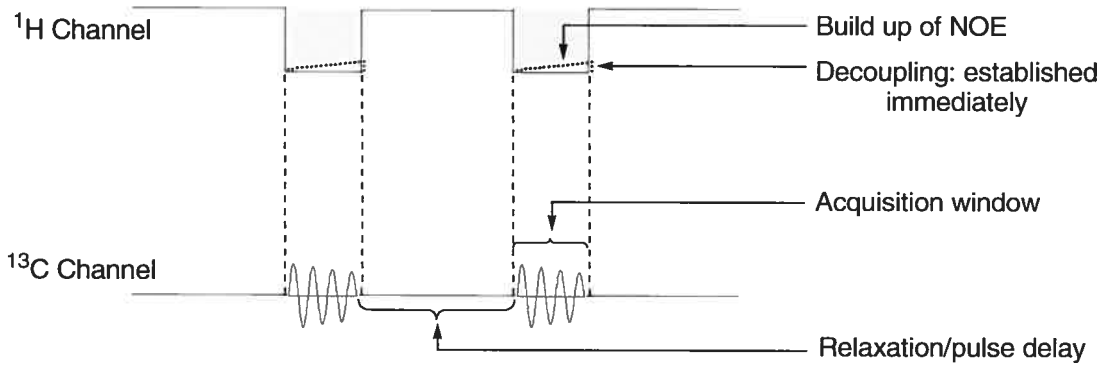


Figure 16: Inverse gated broadband proton decoupling pulse sequence.

Some other factors that affect the accuracy of quantitative ^{13}C NMR spectra are the number of data points acquired, the signal-to-noise ratio, and the amount of sample available for analysis. The number of data points used to acquire the spectrum is only important to the extent that the shape of the peak be accurately represented. The acquisition time is usually 1.5 sec and the data is zerofilled twice before fourier transform. The signal-to-noise ratio ideally should be at least 35/1, and approximately 50-100 mg of sample is sufficient.

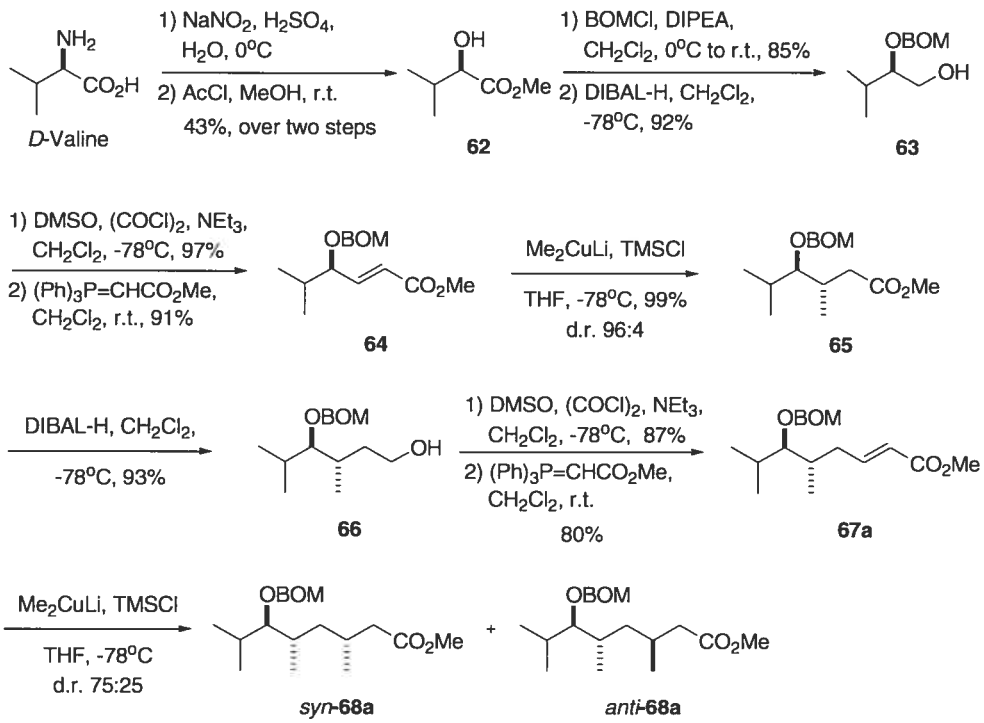
The inverse gated decoupling experiments performed for our molecules had a 30° pulse and 10 s relaxation delay. The signal-to-noise ratios obtained were well within the defined parameters for samples in the range of 100 mg.

II.3. Investigating the effects of the ester groups and the protecting groups

This section will deal with investigating the effects observed towards the *syn*-selective addition of lithium dimethylcuprate to α,β-unsaturated esters upon variation of the ester groups and the protecting groups.

II.3.1. Probing the 'ester' effect

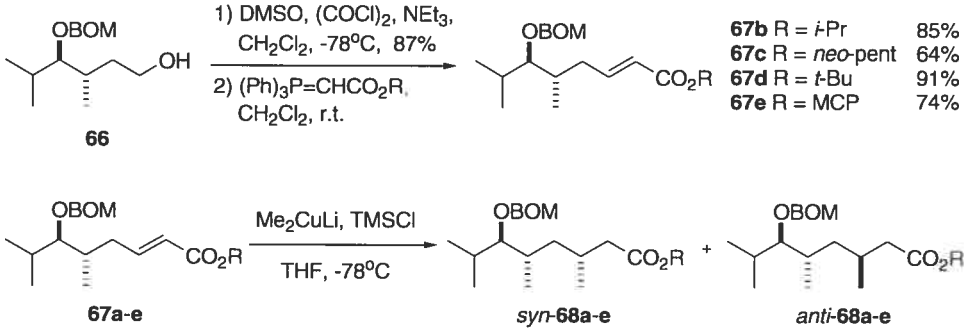
Following a literature procedure[54], *D*-valine was treated with sodium nitrite and H_2SO_4, to give the alcohol which was converted to the hydroxymethyl ester **62** (Scheme 16). Reduction of the ester with Dibal-H afforded alcohol **63**. Swern oxidation followed by Wittig homologation provided enoate **64**. Addition of lithium dimethylcuprate to substrate **64** gave ester **65** and the corresponding *anti*-diastereomer (not shown) in a diastereomeric ratio of 96:4 (obtained by inverse gated proton decoupling ^{13}C NMR). Reduction of ester **65**, providing alcohol **66**, was followed by Swern oxidation and Wittig homologation to the corresponding γ-methyl-α,β-unsaturated methyl ester **67a**. Addition of lithium dimethylcuprate to **67a** afforded products *syn*- and *anti*-**68a** with a diastereoselectivity of 75:25. This observed ratio was higher than the ratio obtained with substrate **50b** (Scheme 15), wherein there was no anchoring group. Therefore we decided to survey a variety of esters with the *iso*-propyl anchor and the benzyloxymethyl protecting group (R_1 = *iso*-propyl, R_2 = BOM, Figure 15) and to examine the effect different esters had on the selectivity of the cuprate additions.



Scheme 16: Synthesis of substrates with *iso*-propyl anchor.

The various esters were prepared by Swern oxidation of **66**, followed by homologation with the corresponding Wittig reagent afforded the α,β-unsaturated esters **67a-e**. As can be seen from the results in Table 1, conjugate cuprate addition to **67a** results in the lowest diastereomeric ratio (Table 1, entry 1, d.r. 75:25). Whereas substrates **67b** and **c** gave slightly better selectivities, and substrate **67d** gives very good selectivity with a d.r. of 89:11. Comparing these results to those from Scheme 15 (substrate **50a**, d.r. 80:20), the effect of the *iso*-propyl anchoring group can be seen clearly. The selectivities increase when the *iso*-propyl anchor is present, all other aspects of the substrate being the same. However, the best diastereomeric ratio was obtained with the 1-methyl-1-cyclopentyl (MCP) ester (Table 1, entry 5, d.r. 91:9). The precise effect of the ester group in the mechanism of conjugate cuprate additions is not clear, but it may be that the bulky ester group serves to hold the molecule in a preferred conformation or there may be an interaction of the ester carbonyl with the reagent. The diastereoselectivities obtained by the

addition of lithium dimethylcuprate to substrates **67a** and **67e** (methyl- and MCP-ester) range from 75:25 to 91:9, respectively. Although the role the ester serves is not entirely clear, there is indeed an effect on the diastereoselectivity of conjugate cuprate additions.



Entry	Substrate	R	d.r. (*syn/anti*)[a]	yield (%)[b]
1	**67a**	Me	75:25	80
2	**67b**	*i*-Pr	77:23	96
3	**67c**	*neo*-Pent	78:22	93
4	**67d**	*t*-Bu	89:11	87
5	**67e**	MCP	91:9	89

[a] determined by inverse gated proton decoupled ^{13}CNMR
[b] isolated yields after chromatography

Table 1: Addition of lithium dimethylcuprate to δ-methyl-α,β-unsaturated esters; probing the 'ester' effect.

Figure 17 shows the inverse gated proton decoupling ^{13}C NMR spectra obtained from the reactions featured in Table 1 (entries 1 and 5). Both ^{13}C NMR spectra show the expansions of the alkyl regions (approx. 50-15 ppm). Part A features the ^{13}C NMR spectrum of *syn*- and *anti*-**68a**, and part B shows *syn*- and *anti*-**68d**. The peaks for the minor and major diastereomers have been integrated and the signals for the minor diastereomer have been distinguished from the major diastereomer by placing a red arrow above the peaks. Upon comparing the two ^{13}C NMR spectra, one can see the

quantitative difference between the two spectra by comparing the differences observed in the integrated ratios.

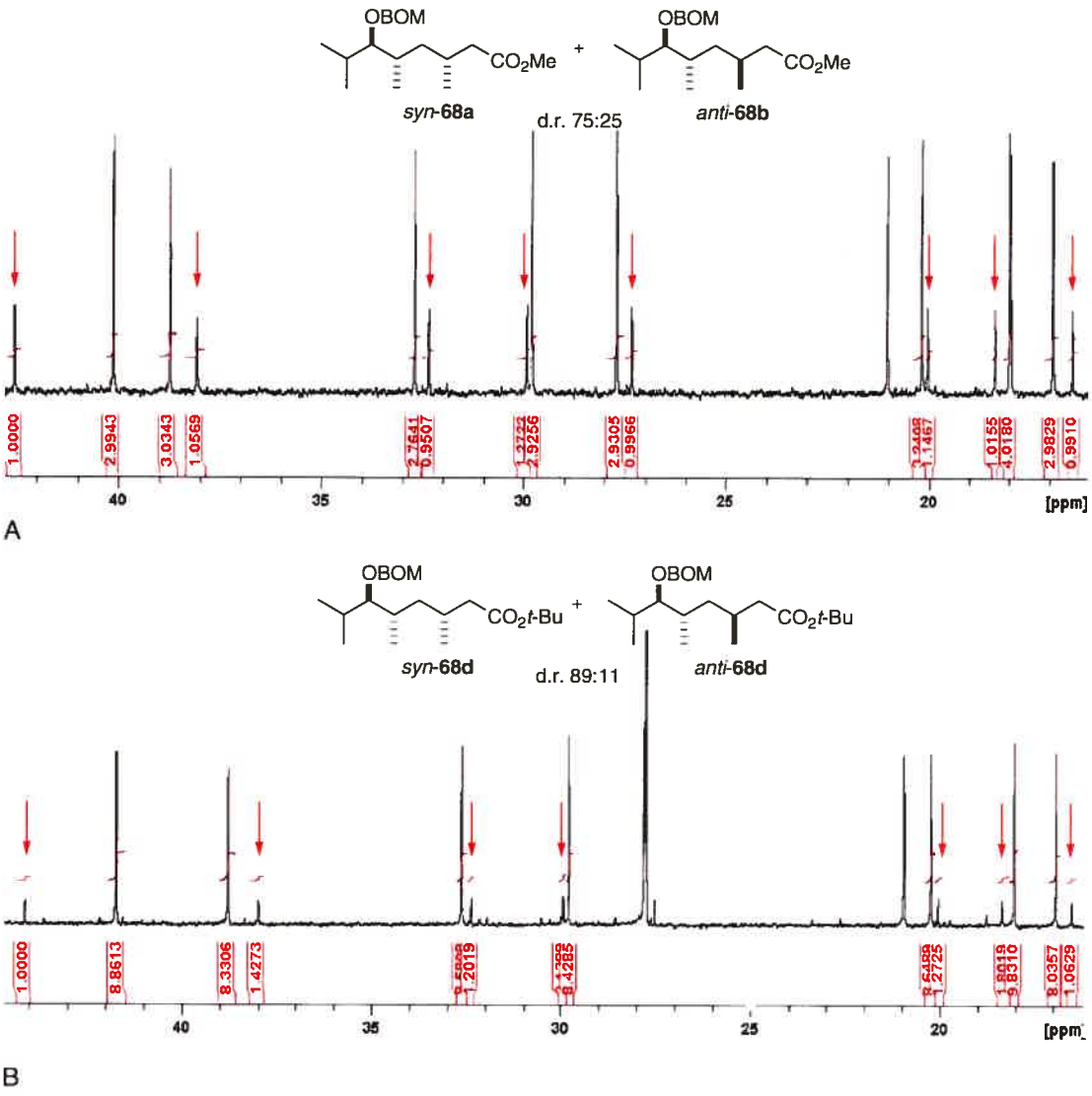
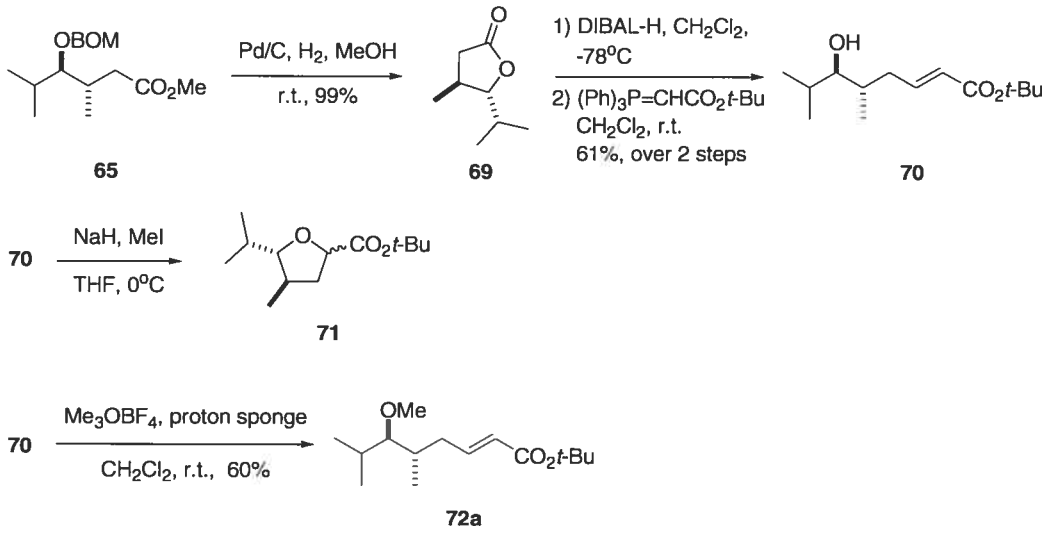


Figure 17: Inverse-gated proton decoupling ^{13}C NMR spectra of compounds (A) *syn*- and *anti*-**68a** and (B) *syn*- and *anti*-**68d**. The red arrow indicates the signals for the minor *anti*- diastereomer.

II.3.2. Effect of the nature of the protecting group

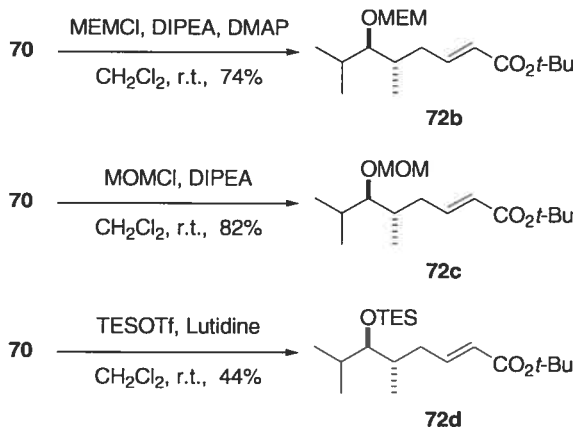
In order to evaluate the effect of the protecting group, we synthesized a series of differentially protected δ-methyl-α,β-unsaturated esters. By changing the protecting group a variety of parameters could be evaluated. Since silyl protecting groups are known to not chelate, having a silyl protecting group would indirectly indicate whether or not there is coordination of the BOM protecting group with the lithium dimethylcuprate species. Also, the necessity of steric bulk in the ε-position could be evaluated by changing the bulky BOM group to a smaller methyl ether.



Scheme 17: Synthesis of substrates towards the second cuprate addition: accessing the common hydroxy enoate intermediate **70**.

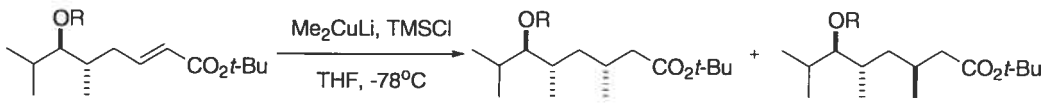
Hydrogenation of the BOM protecting group led to in *situ* cyclization affording lactone **69** in quantitative yield (Scheme 17). Reduction to the lactol with Dibal-H (1 eq.), followed by Wittig homologation, afforded the hydroxy enoate **70**. This enoate served as a common intermediate to provide the various protected ethers **72a-d**. Treatment of alcohol **70** with NaH and MeI gave product **71** resulting from an intermolecular etherification *via* conjugate alkoxide addition to the enoate. The

desired methyl ether (**72a**) was then prepared under non-basic conditions by treatment of alcohol **70** with Meerwein's reagent in the presence of proton sponge®.



Scheme 18: Synthesis of the differentially protected substrates towards the second cuprate addition.

Products **72b-d** were obtained by standard alcohol protection methodology as shown in Scheme 18. Conjugate addition of Gilman cuprate to the δ-methyl-α,β-unsaturated esters **72a-d**, resulted in a diastereomeric mixture of products **73a-d** (Table 2). Substrate **72a**, with the methyl ether gave provided products *syn*- and *anti*-**73a** in excellent diastereomeric ratio (Table 2, entry 1), similar to the diastereomeric ratios obtained from substrates **72b** and **72c** (Table 2, entries 2 and 3). From this result it seems that steric bulk does not have a substantial impact on the selectivities obtained. The d.r. obtained in entry 4 is in the same range as the other compounds shown in Table 2. If the OR group coordinated to the cuprate then it would be expected that the silyl ether would give lower selectivities. The diastereomeric ratios obtained by changing the protecting group were all quite similar to the diastereomeric ratios obtained with the OBOM protecting group (Table 1, entry4). It can be concluded that the nature of the protecting group, whether it be chelating or non-chelating or sterically large or small, is not that important in these conjugate additions.



72a-e *syn*-**73a-e** *anti*-**73a-e**

Entry	Substrate	R	d.r. (*syn*/*anti*)[a]	yield (%)[b]
1	**72a**	Me	90:10	60
2	**72b**	MEM	86:14	81
3	**72c**	MOM	86:14	78
4	**72d**	TES	82:18	84
5	**67d**	BOM	89:11	87

[a] determined by inverse gated proton decoupled ^{13}C NMR
[b] isolated yields after chromatography

Table 2: Second iterative addition of lithium dimethylcuprate.

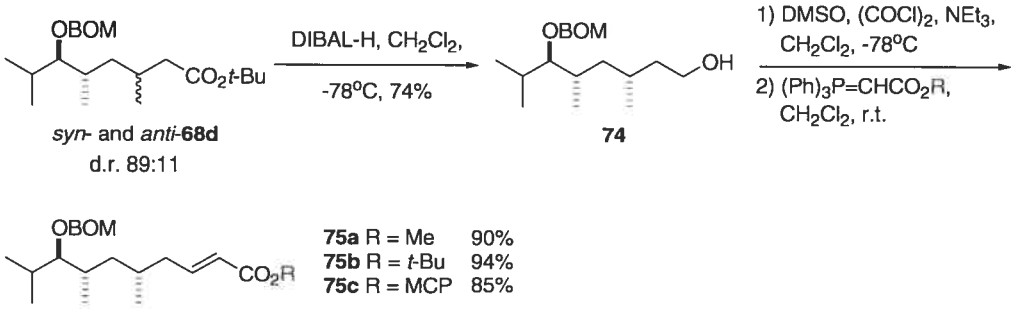
II.4. Substrate control; how far can we go?

Several conclusions can be drawn from the studies conducted in the previous section. First, a definitive ester effect was observed, with methyl esters giving the lowest selectivity and bulkier esters such as *tert*-butyl and MCP giving much more pronounced selectivities (Table 1). Second, the ether type protecting group does not significantly affect the observed selectivities for addition of lithium dimethlycuprate to δ-methyl-α,β-unsaturated esters (Table 2). Finally, the proposed anchor effect was also observed, when comparing the diastereoselectivities shown in Table 1 (entries 1, 4 and 5) with those shown in Scheme 15 for compounds **51a-c**. A marked increase in selectivity was observed in the substrates with the *iso*-propyl anchoring group. Based on these results, we decided to extend the iteration of deoxypropionate units.

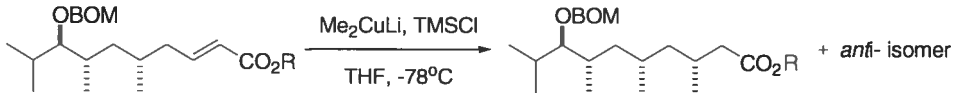
II.4.1. Third iterative cuprate addition

Reduction of the diastereomeric mixture of *syn*- and *anti*-**68d** with Dibal-H resulted in a mixture of both *syn*- and *anti*-alcohols in 74% combined yield (Scheme 19). Repeated chromatographic purification of the mixture did not result in complete separation of both diastereomers. Nonetheless enough pure **74** was obtained to

proceed with the synthesis. Oxidation of the alcohol followed by Wittig homologation gave diastereomerically pure enoates **75a-c**.



Scheme 19: Synthesis of substrates towards the third cuprate addition.



75a-c **76a-c**

Entry	Substrate	R	d.r. (*syn/anti*)[a]	yield (%)[b]
1	**75a**	Me	67:33	84
2	**75b**	*t*-Bu	87:13	97
3	**75c**	MCP	83:17	91

[a] determined by inverse gated proton decoupled ^{13}CNMR
[b] isolated yields after chromatography

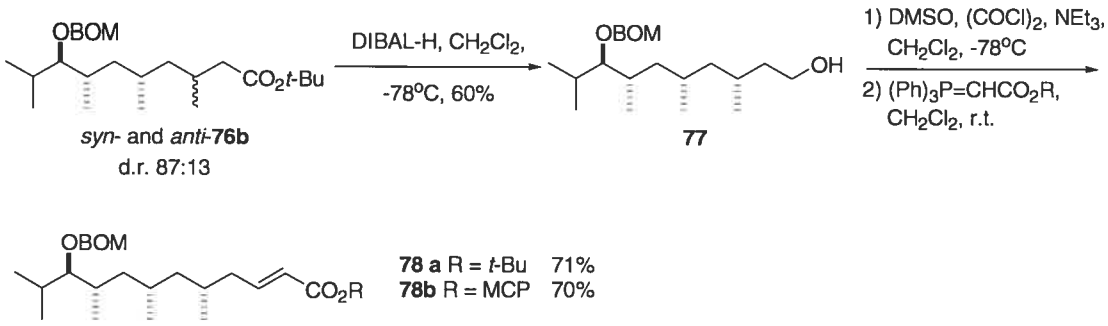
Table 3: Third iterative addition of lithium dimethylcuprate.

Addition of lithium dimethylcuprate to the δ-methyl-α,β-unsaturated esters (**75a-c**), gave the corresponding esters **76a-c**, with two deoxypropionate units installed in the growing hydrocarbon chain (Table 3). The ratios for the *syn*-selective cuprate additions are good, despite the fact that the conformational preference tends to decrease as the number of dimethylpentane segments increases (Figure 14).[7] The best selectivity was observed for the substrate with the *tert*-butyl ester (Table 3, entry 2), followed closely by the MCP ester (Table 3, entry 3). In this series, the effect of the

MCP ester seems to be diminishing beyond the second cuprate addition as the chain is extended.

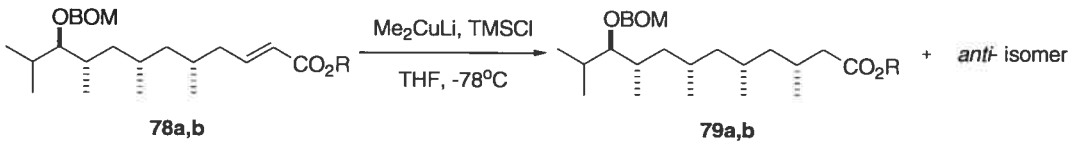
II.4.2. Extension of substrate control towards the fourth cuprate addition

Reduction of the diastereomeric mixture of *syn*- and *anti*- **76b** (d.r. 87:13), followed by chromatographic separation of the diastereomers, resulted in alcohol **77** (Scheme 20). Although, the diastereomers were not completely separated, enough amounts of **77** were obtained to proceed with the synthesis of the necessary substrates. Thus oxidation of **77**, followed by Wittig homologation, provided the α,β-unsaturated esters **78a** and **78b** in good yield.



Scheme 20: Synthesis of substrates towards the fourth cuprate addition.

As shown in Table 4, the diastereomeric ratios obtained from the *syn*-selective cuprate additions are surprisingly good. No of significant ester effect is observed, as both substrates give similar ratios. Comparing the results from the third iterative cuprate addition to those of the fourth addition, one can clearly see that the levels of 1,3-induction being observed have plateaued. Presumably, as the acyclic chain continues to grow, more degrees of rotational freedom are introduced, involving more conformers with similar energies, resulting in somewhat diminished selectivities.



78a,b **79a,b**

Substrate	R	d.r. (*syn/anti*)[a]	yield (%)[b]
78a	*t*-Bu	85:15	78
78b	MCP	83:17	92

[a] determined by ^{13}C inverse gated NMR
[b] isolated yields after chromatography

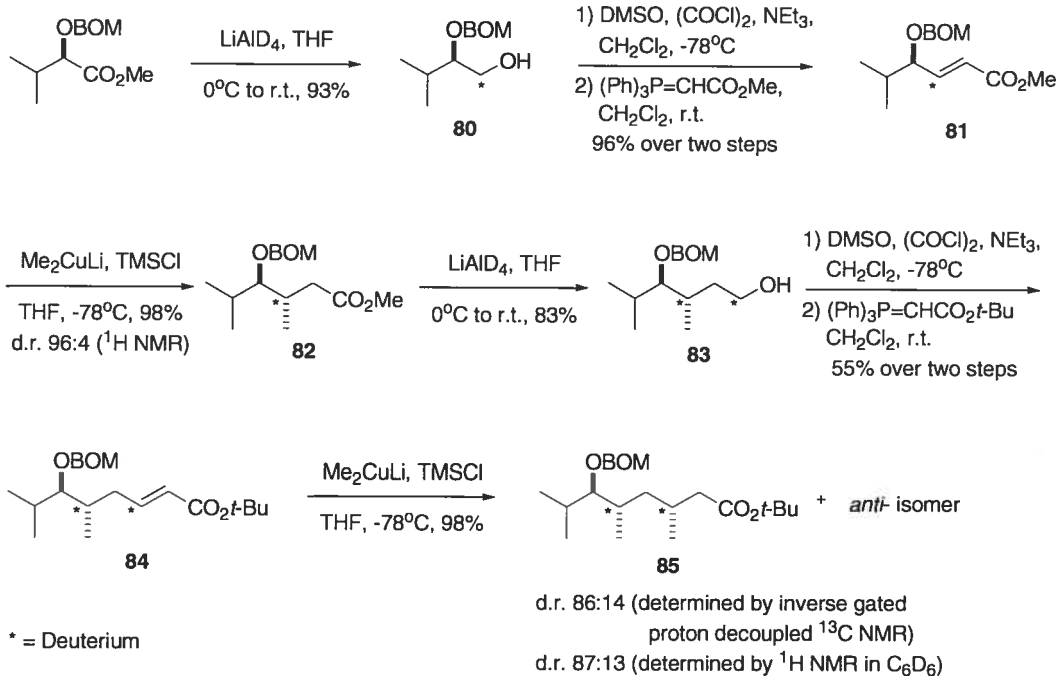
Table 4: Addition of lithium dimethylcuprate to δ-methyl-α,β-unsaturated esters; towards the third deoxypropionate triad.

II.5. Deuterium labeling studies

After having extended the acyclic conformational control towards the third deoxypropionate triad (i.e. after four iterative cuprate additions), we decided to revisit the first two cuprate additions by including a deuterium label in the β-position on the α,β-unsaturated ester. The expectation was that incorporating the deuterium label would simplify the ^1H NMR spectrum, which might allow determination of the d.r. by integration of the ^1H NMR. This would also reinforce the validity of the inverse gated proton decoupled ^{13}C NMR as an initial measure of diastereroselectivity.

II.5.1. Comparison of the deuterium labeled compounds with the non-deuterium labeled compounds

As indicated in Scheme 21, alcohol **80** was obtained by reduction of the corresponding methyl ester with lithium aluminum deuteride. Swern oxidation followed by the usual Wittig homologation provided enoate **81**. Addition of lithium dimethylcuprate gave product **82** in a diastereomeric ratio of 96:4 (obtained by ^1H NMR, minor diastereomer not shown).



Scheme 21: Deuterium labeling studies.

Comparing the ^{1}H NMR spectra of **82** with **65** (which has the same structure but without the deuterium label) shows that not only is the spectrum simplified for **82**, but inclusion of the deuterium label also allows for the determination of the d.r. by ^{1}H NMR (Figure 18). The inverse gated proton decoupling ^{13}C NMR for the diastereomeric mixture of *syn-* and *anti-* **65** gave a d.r. of 96:4, which is in excellent agreement with the observed ratio from the addition of lithium dimethylcuprate to **81**. Reduction of **82** with lithium aluminum deuteride gave the corresponding deuterium labeled alcohol **83**, which after functional group manipulation provided the δ-methyl-α,β-unsaturated ester **84**. Conjugate cuprate addition to **84** provided ester **85**, with a d.r. of 87:13 (based on ^{1}H NMR). The ratios obtained from the inverse gated ^{13}C NMR spectrum (d.r. 86:14) are in excellent agreement with the ratios obtained from ^{1}H NMR. Also noteworthy is the close correlation of the d.r.'s obtained from the addition of lithium dimethylcuprate to substrates 67d (Table 1, entry 5, d.r. 86:14) and 84 (Scheme 21, d.r. 84:16).

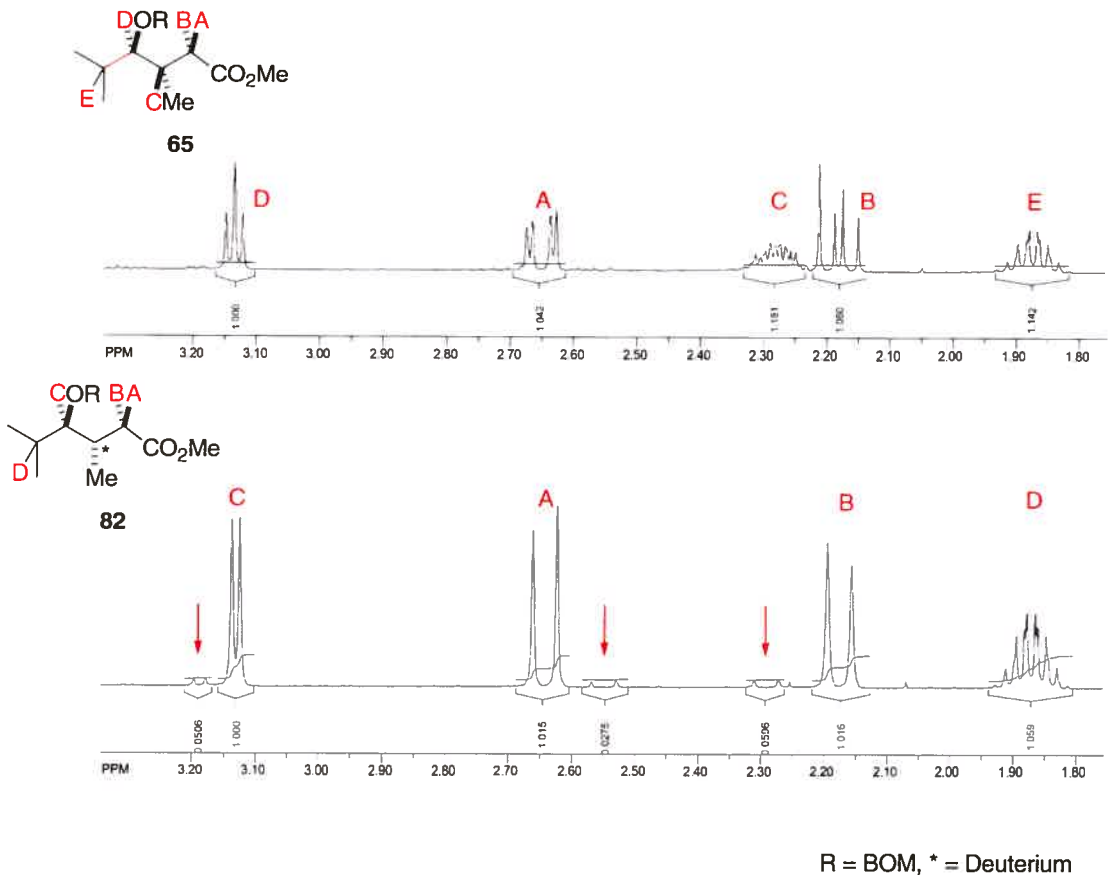


Figure 18: Comparison of the ^{1}H NMR spectra of compounds **65** and **85** (AV 400 MHz, $CDCl_3$). The red arrow indicates the minor *anti*- isomer.

II.6 Determining the conformation of the δ-methyl-α,β-unsaturated esters

As mentioned in Section I.1, the chiral hydrocarbon chain in borrelidin and pectinatone exists in conformations wherein *syn*-pentane interactions are minimized, by placing the methyl groups gauche with respect to each other. The same has been observed for other polyketide natural products.[7] However, the presence of these conformations in the solid state does not mean that the same will be observed in solution. Information regarding the solution state conformations can be acquired from vicinal ^{3}J coupling constants along the chiral hydrocarbon backbone. The ^{3}J coupling constants are a function of the dihedral angle, and so they are dependent on the conformation of the molecule.[7]

Hoffmann realized that if a small and large ^3J coupling constant was observed then it could be concluded that the molecule exists in a preferred conformation.[55] As shown in Figure 19, if the two conformations are present in a 1:1 ratio, then the vicinal coupling constants ($J_{1,2}$ and $J_{1,3}$) will have an average value of 6-7 Hz. However, if the two conformers are not in a 1: 1 ratio then there will be a departure from the average value of 6-7 Hz for $J_{1,2}$ and $J_{1,3}$. Work done previously in the Hanessian group also had shown that similar conclusions could be drawn.[14d] We performed NMR studies on several of our substrates in order to obtain the $^3J_{H,H}$ coupling constants.

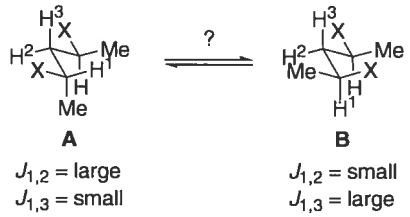


Figure 19: Conformational dependence based on vicinal coupling constants.[55]

The ^{1}H NMR spectrum of **67a** was unambiguously assigned by analysis of the ^{1}H NMR, ^{13}C NMR, DEPT135, HMQC and COSY45 experiments, as well as by homodecoupling analysis (Figure 20). Although the vicinal ^3J coupling constants could not be directly obtained from the ^{1}H NMR spectrum due to complex overlapping signals, we were able to obtain the desired information from ^{1}H-^{1}H homodecoupling experiments. The relevant coupling constants that would provide some information regarding the conformation of **67a** are $^3J_{ED}$ and $^3J_{EC}$. As can be seen in Figure 21, part A, the area of interest on the ^{1}H NMR does not provide any useful information due to the complex splitting pattern observed for protons C and D, and the overlap of protons G and E. However, upon irradiation of proton B, the spectrum is simplified significantly. Protons labeled C and D now appear as doublet of doublets allowing for the determination of the desired $^3J_{ED}$ and $^3J_{EC}$ coupling constants (Figure 21, part B).

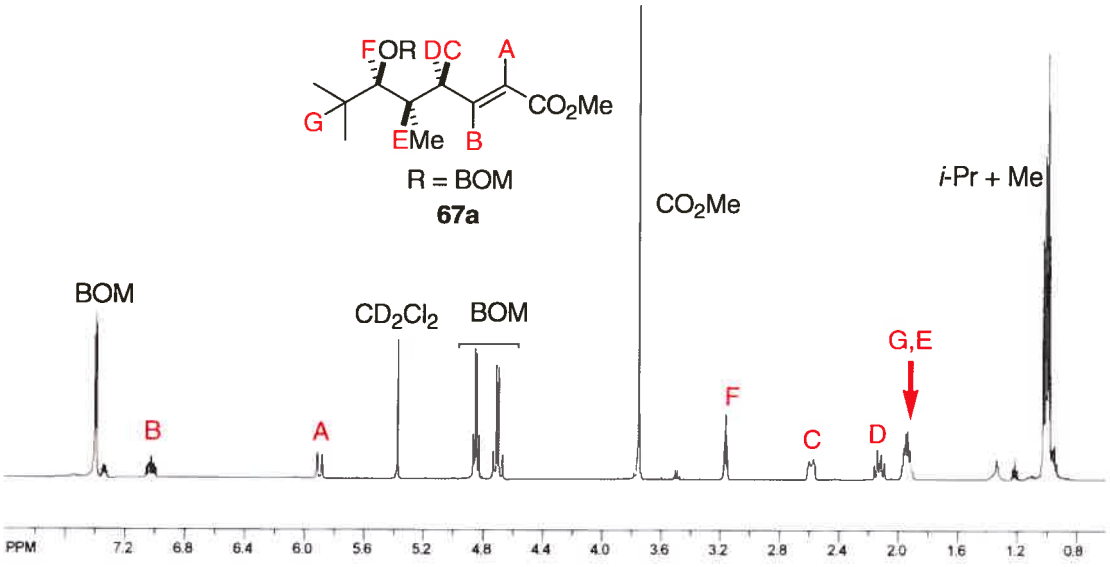


Figure 20: ^{1}H NMR spectrum of **67a** (AV 500 MHz, CD_2Cl_2).

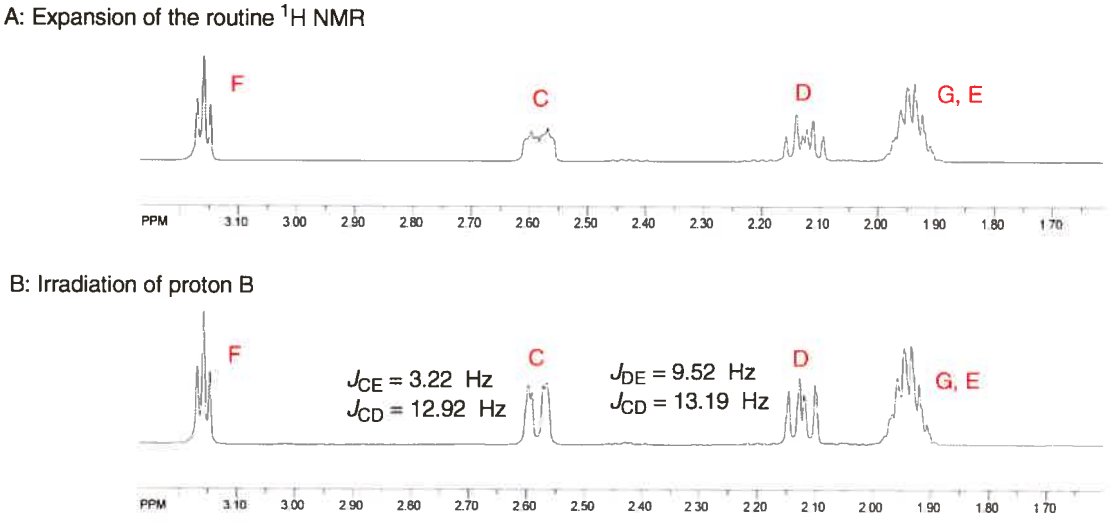


Figure 21: (**A**) Expansion of the routine ^{1}H NMR spectrum of **67a**; (**B**) ^{1}H NMR spectrum of **67a** upon irradiation of proton B.

The complete data obtained from the homodecoupling experiments are presented in Figure 22, where it can be seen that vicinal coupling constants are $^{3}J_{EC}$,

$_{ED}$ = 3.22 and 9.52 Hz. One large and one small coupling constant was observed, indicating the presence of a preferred conformation in solution on the NMR time scale. Based on the information obtained, it is not possible to state whether conformation A, B or C is preferred. The average values for $^3J_{EF}$ = 5.10 Hz would indicate that all three conformers exist in equilibrium.

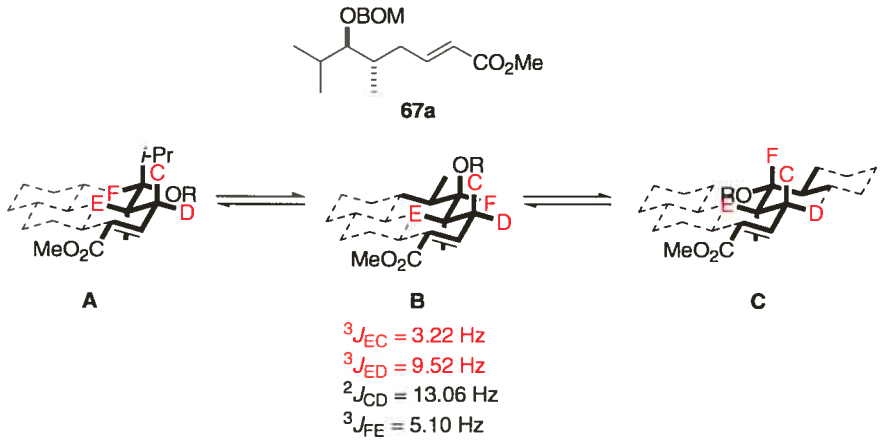


Figure 22: Homodecoupling data for **67a**.

Similarly, the coupling information for compounds **67d** and **75a** was also obtained. Analysis of the acquired information, presented in Figure 23, shows that there seems to be a preferred conformation even in solution. Since a preferred conformation can be observed on an NMR time scale at 25 °C, then it can be presumed that a similar conformation would be observed during the reactions which are performed at -78 °C.

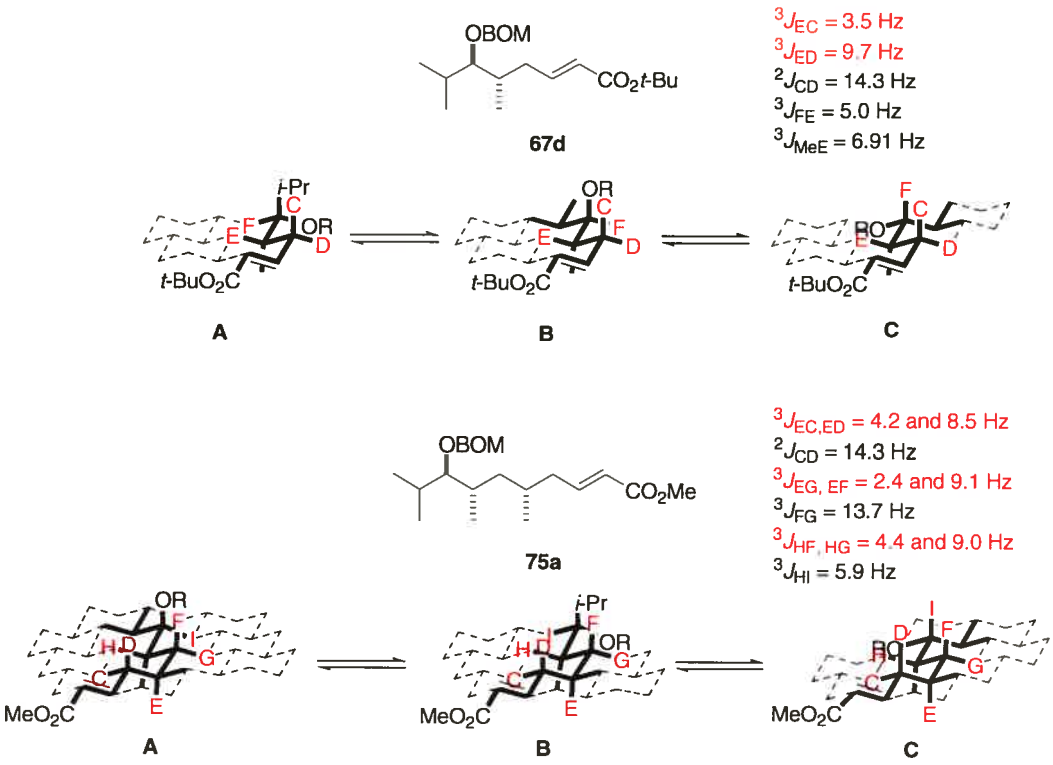


Figure 23: Homodecoupling data for **67d** and **75a**.

II.7. Conclusions

This chapter has focused on analyzing the effects of the *iso*-propyl anchor group in conjunction with different ester groups. Sections II.3.1 and II.3.2 probed the effect of different esters and protecting groups on the addition of lithium dimethylcuprate to δ-methyl-α,β-unsaturated esters. It was observed that bulky esters such as *tert*-butyl and MCP provide better selectivities, whereas smaller esters such as methyl esters result in lower diastereomeric ratios. The nature of the interaction of the ester group with the reagent or the precise role the ester plays in cuprate additions is not entirely clear; nonetheless a significant ester effect was observed. The conclusions drawn from the cuprate additions performed on the differentially protected δ-methyl-α,β-unsaturated esters were that steric bulk in the protecting group did not play a significant role in providing higher diastereoselectivites. Nor was chelation of the protecting group with the reagent a factor, as substantially

decreased selectivities were not observed with the silyl protecting group. The benzyloxymethyl group was found to be the best protecting group, as it consistently gave high selectivities.

The iteration of the deoxypropionate units providing two and three contiguous deoxypropionate units installed in a fully iterative manner by exploiting substrate and conformational control was described in Section II.4. A substantial ester effect was not observed in either the third or the fourth iterative cuprate addition. Nonetheless, substrate control was provided some diastereocontrol, despite the increased number of low energy conformers that would be a consequence of a growing acyclic chain.

Deuterium labeling studies showed an excellent correlation of the diastereomeric ratios obtained from the ^{1}H NMR spectra of the deuterated compounds compared to those measured by the inverse gated proton decoupling ^{13}C NMR experiments of the non-deuterated compounds.

Finally, homodecoupling studies provided some insight into the conformational preference of the chiral hydrocarbon backbone harboring deoxypropionate units within acyclic α,β-unsaturated esters on an NMR time scale.

Chapter III:

Investigating other anchoring groups

Chapter two focused on one anchoring group, *iso*-propyl, while other parameters were investigated, such as a variety of ester groups, alkoxy substituents. Also, the extent of substrate control was investigated, by performing four iterative cuprate additions with good diastereoselectivity. The focus of this chapter will be to investigate a variety of other anchors, while also probing the ester effect. In the previous chapter it was determined that the nature of the protecting group was not very important with the best alkoxy protecting group being the benzyloxymethyl, therefore in this chapter the effect of the nature of the alkoxy protecting group will not be further probed.

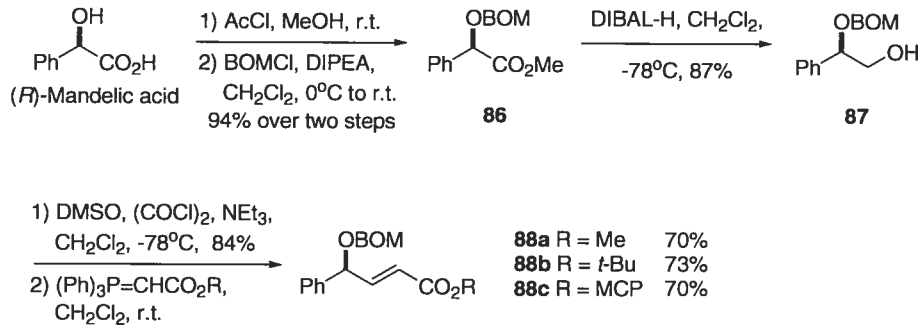
III.1. Investigating the effects of the phenyl anchoring group

Thus far, only sp^3 hybridized anchors have been investigated. Towards the synthesis of doliculide[8] and borrelidin[14d], the anchoring group utilized was $CH_2OTBDPS$, and the focus of the last chapter was a branched alkyl anchor, with the *iso*-propyl. We then decided to probe the effects of a phenyl anchor. Even though a phenyl group is sterically demanding, it could in principle adopt an orientations that would minimize unfavorable interactions.

III.1.1. Phenyl anchor; Addition of lithium dimethylcuprate to γ-alkoxy-α,β-unsaturated esters

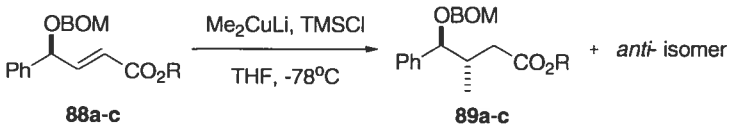
Synthesis of the desired substrates began with esterification of (*R*)-mandelic acid, followed by BOM protection leading to ester **86** (Scheme 22). Reduction to the

alcohol followed by Swern oxidation and Wittig homologation afforded products **88a-c** in good yield. Attempts to reduce ester **86** directly to the aldehyde failed, with some alcohol always being formed. Therefore, it was decided to reduce to the alcohol and then oxidize in order to avoid unnecessary loss of material.



Scheme 22: Phenyl anchor; synthesis of substrates towards the first cuprate addition.

As shown in Table 5, addition of lithium dimethylcuprate to the γ-alkoxy-α,β-unsaturated esters **88a-c** gave the desired esters **89a-c**, and the corresponding *anti*-isomer (not shown), with excellent d.r. The best diastereoselectivity was afforded by the substrates with the *tert*-butyl and the MCP esters, followed closely by the methyl ester. Cuprate additions to γ-alkoxy-α,β-unsaturated esters (i.e. the first cuprate additions) generally proceed with excellent stereoselectivity, as there is no pendant methyl group to afford energetically unfavorable *syn*-pentane interactions. Therefore, homologation of the substrates towards the installation of the second methyl, one deoxypropionate unit, would give better insight into the role of the phenyl anchor.



88a-c **89a-c**

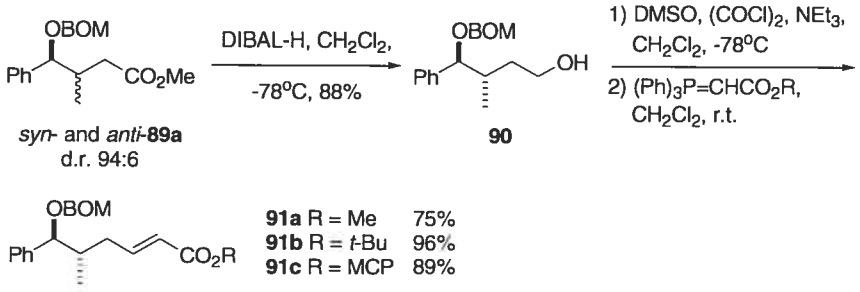
Substrate	R	d.r. (*anti/syn*)[a]	yield (%)[b]
88a	Me	94:6	97
88b	*t*-Bu	95:5	92
88c	MCP	95:5	89

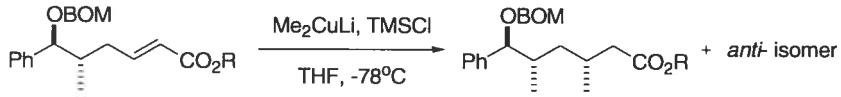
[a] determined by ^{1}H NMR
[b] isolated yields after chromatography

Table 5: Addition of lithium dimethylcuprate to γ-alkoxy-α,β-unsaturated esters.

III.1.2. Probing the effects of the phenyl anchor and the ester effect in the addition of lithium dimethylcuprate to δ-methyl-α,β-unsaturated esters

Reduction of the diastereomeric mixture of *syn*- and *anti*- methyl ester **89a**, followed by the usual three step homologative sequence led to α,β-unsaturated esters **91a-b** (Scheme 23). Addition of lithium dimethylcuprate to enoates **91a-c** afforded the corresponding cuprate adducts in excellent yield and moderate to good diastereomeric ratios. Noteworthy is the comparison of the diastereomeric ratios obtained by inverse gated proton decoupling ^{13}C NMR experiments with those obtained by ^{1}H NMR. An excellent correlation for the diastereomeric ratio's between the two techniques can be observed, thereby corroborating the diastereomeric ratios reported by the inverse-gated NMR technique. A dramatic ester effect is not observed, but the d.r. does indeed improve in going from the methyl ester to the *tert*-butyl or the MCP ester.





91a-c 92a-c

Substrate	R	d.r. (*syn/anti*)[a]	d.r. (*syn/anti*)[b]	yield (%)[c]
91a	Me	69:31	69:31	86
91b	*t*-Bu	84:16	81:19	85
91c	MCP	85:15	-	86

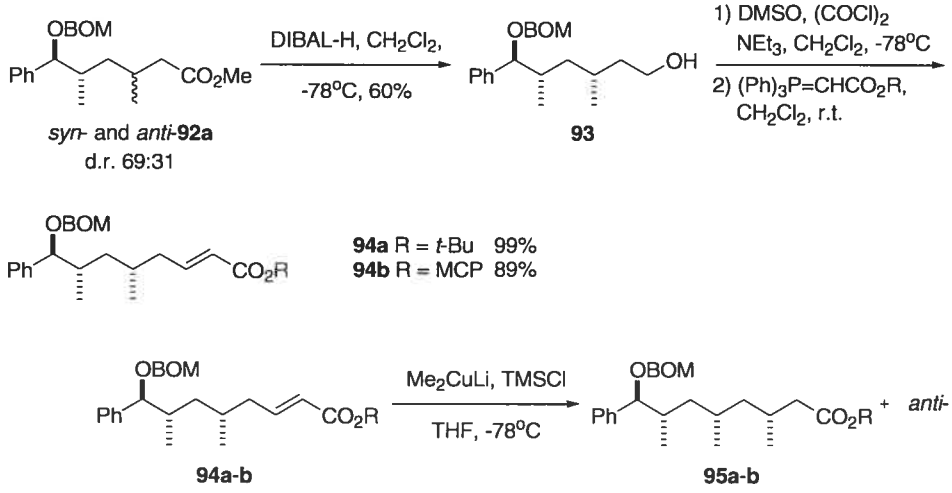
[a] determined by inverse gated proton decoupled ^{13}C NMR
[b] determined by ^{1}H NMR
[c] isolated yields after chromatography

Scheme 23: Effect of the phenyl anchor towards the addition of lithium dimethylcuprate on δ-methyl-α,β-unsaturated esters.

III.1.3. Probing the effects of the phenyl anchor and the ester effect in the third iterative cuprate addition

Despite the moderate levels of 1,3-induction observed with the phenyl anchored γ-methyl-α,β-unsaturated esters (Scheme 23), we decided to homologate the system towards the third iterative cuprate addition and observe the level of substrate control provided. As shown in Scheme 24, Dibal-H reduction of a diastereomeric mixture of *syn*- and *anti*-**92a**, followed by careful chromatographic purification of the resulting diastereomeric alcohols provided **93**. Oxidation, followed by Wittig homologation afforded enoates **94a** and **94b**. Addition of lithium dimethylcuprate to **94a** and **94b** gave products **95a** and **95b**, with the level of substrate control seeming to have plateaued, as in the case of the *iso*-propyl series (Section II.4.1 and II.4.2). Although the diastereoselectivity afforded by substrate

control is fairly good, the system seems to have reached its maximum. Also, as mentioned previously, the 'ester' effect is no longer being observed, in this case both the *tert*-butyl and MCP esters provide the same diastereomeric ratios.



Substrate	R	d.r. (*syn/anti*)[a]	yield (%)[b]
94a	*t*-Bu	79:21	90
94b	MCP	79:21	74

[a] determined by inverse gated proton decoupled ^{13}C NMR
[b] isolated yields after chromatography

Scheme 24: Third iterative cuprate addition with phenyl anchor.

III.2. Investigating the effects of the *tert*-butyl anchor

Having studied the *iso*-propyl and phenyl anchors in some detail, we had realized that the anchors studied thus far always allowed for conformations wherein there is at least one conformer that avoids a *syn*-pentane interaction. We therefore decided to investigate the *tert*-butyl anchor.

III.2.1. Studying the diastereoselectivities offered by the *tert*-butyl anchor

As shown in Figure 24, a *tert*-butyl anchor introduces an unavoidable *syn*-pentane interaction in the idealized conformations based on the virtual diamond lattice. The bonds colored in red in conformations A, B, and C indicate the observed

syn-pentane interactions. Of these conformations A and C are subject to *syn*-pentane interactions between appended *C*-methyl groups, while in B the interaction is with a chain element. These higher energy interactions cannot be avoided by rotating the bonds. Therefore we assumed that the selectivities for the second cuprate addition would be lower compared to the *iso*-propyl series.

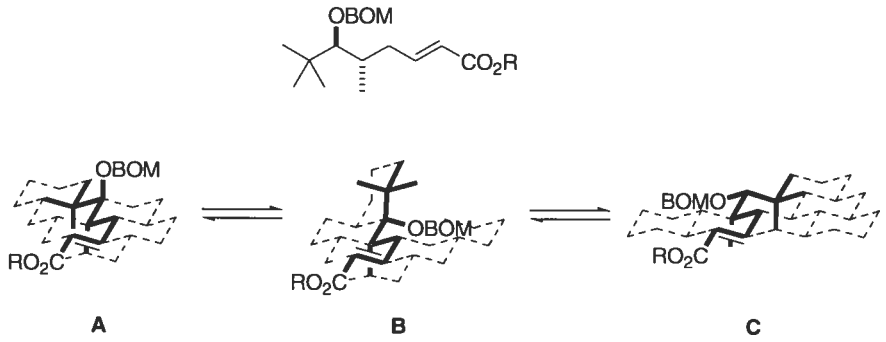
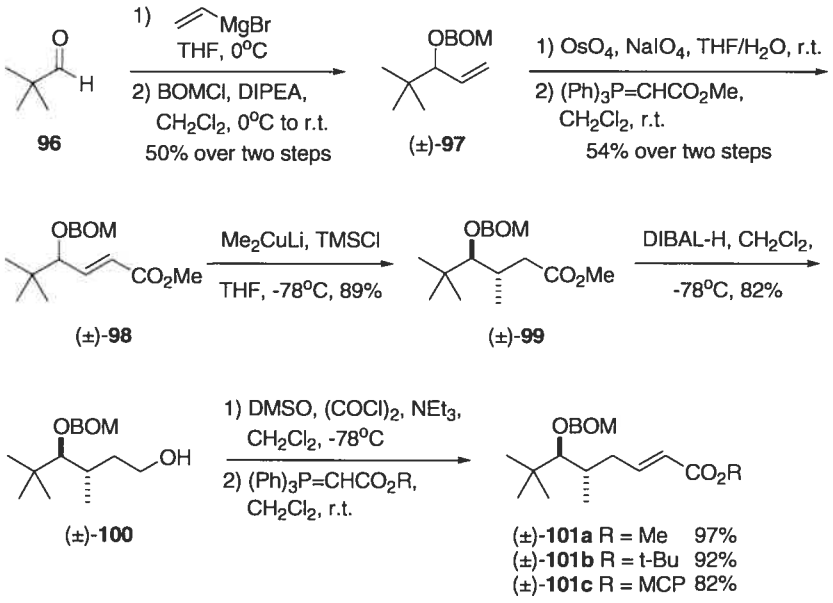
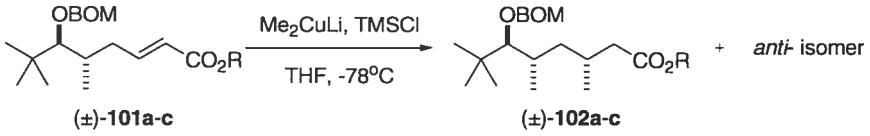


Figure 24: Unavoidable *syn*-pentane interaction with *tert*-butyl anchor.

Synthesis of the substrates commences with addition of vinylmagnesium bromide to dimethyl propionaldehyde (**96**), followed by BOM protection of the resulting vinyl alcohol to afford product (±)-**97** (Scheme 25). Osmium tetraoxide dihydroxylation followed by treatment with sodium periodate gave the corresponding aldehyde, which was subsequently treated with *tert*-butyl phosphonate, providing the γ-alkoxy-α,β-unsaturated ester (±)-**98**. Addition of lithium dimethylcuprate to substrate (±)-**98** afforded ester (±)-**99**. Neither ^{1}H NMR nor inverse gated proton decoupled ^{13}C NMR showed any presence of the minor diastereomer. Reduction of ester (±)-**99** with Dibal-H, followed by the usual homologation afforded the δ-methyl-α,β-unsaturated esters (±)-**101a-c**.



Scheme 25: Synthesis of substrates with *tert*-butyl anchor



Substrate	R	d.r. (*syn/anti*)[a]	d.r. (*syn/anti*)[b]	yield (%)[c]
(±)-**101a**	Me	64:36	63:37	76
(±)-**101b**	*t*-Bu	82:18	82:18	85
(±)-**101c**	MCP	81:19	82:18	73

[a] determined by inverse gated proton decoupled ^{13}C NMR
[b] determined by ^{1}H NMR
[c] isolated yields after chromatography

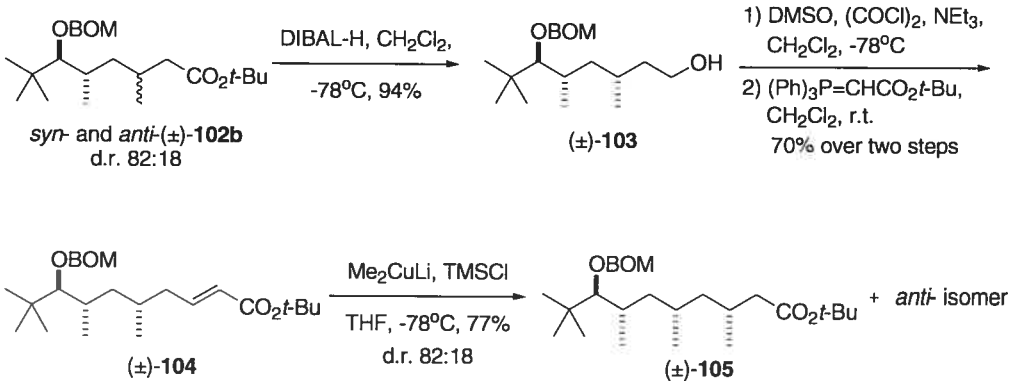
Table 6: Effect of the *tert*-butyl anchor towards the addition of lithium dimethylcuprate on δ-methyl-α,β-unsaturated esters.

As shown in Table 6, addition of lithium dimethylcuprate to substrates **(±)-101a-c**, provided esters **(±)-102a-c** and their corresponding *anti*- isomers (not shown) with surprisingly good diastereoselectivities. Also, noteworthy is the excellent correlation between the selectivities determined by inverse gated proton decoupled ^{13}C NMR and

^{1}H NMR analysis. Comparing the selectivities observed in Table 6 to those in Scheme 23, one can see that despite having different anchors, the diastereomeric ratios are quite similar. To further probe the effects of the *tert*-butyl anchor, or see if the anchor would have any effects, a third iteration was carried out.

III.2.2. Extension of the *tert*-butyl anchor towards the third cuprate addition

Reduction of a diastereomeric mixture of *syn*- and *anti*- esters **(±)-102a** with Dibal-H, followed by careful chromatographic purification of the diastereomeric alcohols afforded alcohol **(±)-103** (Scheme 26). Oxidation followed by Wittig homologation provided the δ-methyl-α,β-unsaturated-*tert*-butyl ester **(±)-104**. Addition of lithium dimethylcuprate to substrate **(±)-104** gave a diastereomeric mixture of ester **(±)-105** and the *anti*- isomer (not shown), in a diastereomeric ratio of 82:18. There is still a certain amount of 1,3-induction being observed, but the selectivities for the second and third cuprate additions with the *tert*-butyl anchor have not dropped as substantially as had been hypothesized earlier. In order to understand this discrepancy we decided to investigate the conformation of these molecules.



Scheme 26: Third iterative cuprate addition with *tert*-butyl anchor.

III.2.3. NMR studies towards investigating possible conformations

For the *tert*-butyl anchor we had hypothesized that the selectivities for the second and third cuprate additions would be less than what had been observed with

the *iso*-propyl and phenyl anchors. We had expected these results because having a *tert*-butyl anchor would introduce *syn*-pentane interactions in all possible conformations as depicted in Figure 24. However, the results obtained from Sections III.2.1 and III.2.2 showed good diastereomeric ratios. With the above results in hand we decided to look closely into the conformation these molecules may adapt in solution, as had been done in Chapter 2, Section II.6. The data obtained from the homodecoupling analysis performed on enoate **(±)-101a** is presented in Figure 25. As had been obtained previously (Section II.6) in this case too, for the vicinal couplings one large ($^3J_{ED}$ = 10.3 Hz) and one small ($^3J_{EC}$ = 2.6 Hz) coupling constant was obtained, indicating that there was a preferred conformation. However the small value for $^3J_{EF}$ indicates that conformation A is preferred over conformations B and C. In conformations B and C one can see that there is *syn*-pentane interaction with the appended *C*-methyl groups (indicated in green), however conformation A has a *syn*-pentane interaction with the chain element. From the coupling constant obtained for $^3J_{EF}$ it can be concluded that the *syn*-pentane interaction with the chain is not as high energy as the interaction observed in conformation B.

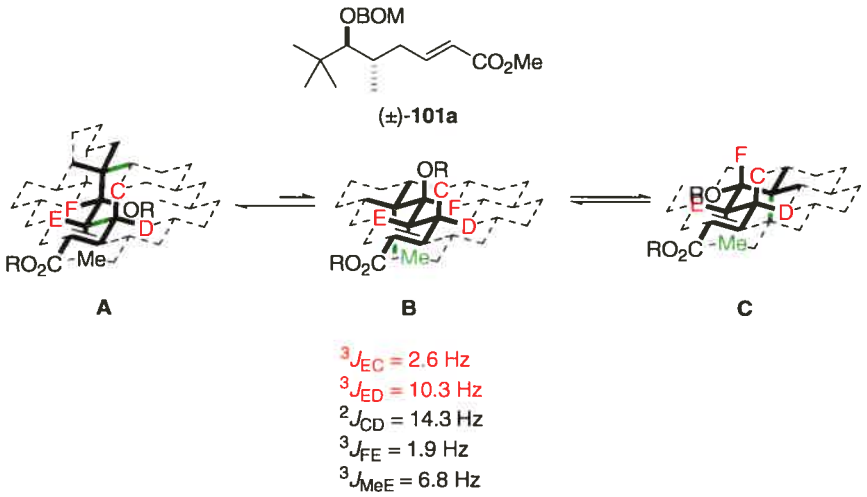


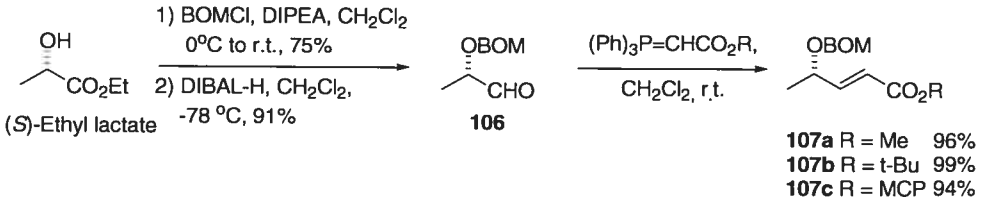
Figure 25: Data obtained from the homodecoupling analysis of **(±)-101a**.

The molecules studied in Section II.6 bearing the *iso*-propyl anchor have three low energy conformers (Figures 22 and 23), however in the case of the *tert*-butyl anchor only one such low energy conformer is preferred based on the coupling information obtained. The fact that there is only one low energy conformer within the *tert*-butyl series explains why lower selectivities for the second and third cuprate additions were not observed.

III.3. Investigating the effects of having no anchoring group

As a final proof of the proposed anchoring effect we had decided to study a series of molecules wherein no anchoring group was present. To this end we decided to investigate a methyl anchor. It had been hypothesized that the methyl end group would afford no anchoring to the molecule since it would not preferentially adopt any particular conformation.

III.3.1. Probing the ester effect towards the addition of lithium dimethylcuprate to γ alkoxy-α,β-unsaturated esters



Scheme 27: Synthesis of the methyl anchored γ-alkoxy-α,β-unsaturated esters.

Synthesis of the substrates began with BOM protection of the commercially available (*S*)-ethyl lactate. Reduction of the ethyl ester to the corresponding aldehyde followed by Wittig homologation afforded the enoates **107a-c** in excellent yield (Scheme 27). As shown in Table 7, addition of lithium dimethylcuprate to enoates **107a-c** afforded a diastereomeric mixture of esters **108a-c** and the *anti*- isomers (not shown). The diastereoselectivity is not excellent but a slight ester effect is observed,

with the *tert*-butyl ester, giving the best diastereomeric ratio. As has been observed with other anchors the MCP ester does not give selectivities better than the *tert*-butyl ester.

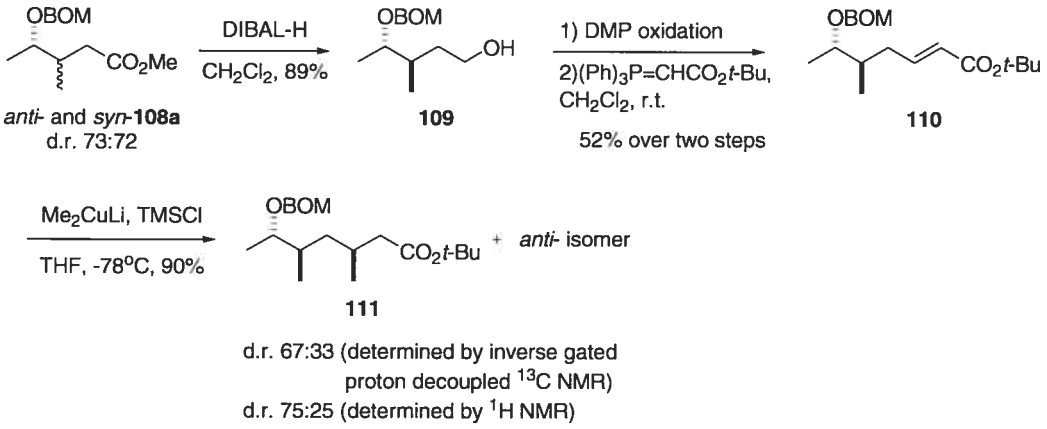
107a-c **108a-c**

Substrate	R	d.r. (*anti/syn*)[a]	d.r. (*anti/syn*)[b]	yield (%)[c]
107a	Me	73:27	72:28	99
107b	*t*-Bu	85:15	85:15	91
107c	MCP	80:20	82:18	92

[a] determined by inverse gated proton decoupled ^{13}C NMR
[b] determined by ^{1}H NMR
[c] isolated yields after chromatography

Table 7: Addition of lithium dimethylcuprate to methyl anchored γ-alkoxy-α,β-unsaturated esters.

III.3.2. Effect of no anchoring group towards the second cuprate addition



Scheme 28: Effect of the methyl anchor towards the second iterative cuprate addition.

As shown in Scheme 28, starting with a diastereomeric mixture of *syn*- and *anti*- esters **108a**, following standard functional group manipulation, enoate **110** was obtained in three steps. Addition of lithium dimethylcuprate to substrate **110** provided ester **111** and the minor *anti*- diastereomer (not shown) with a d.r. of 67:33 *syn*/*anti*. As had been expected the methyl anchor leads to a decrease in selectivity due to the loss of the anchoring effect that had been provided with the other anchors.

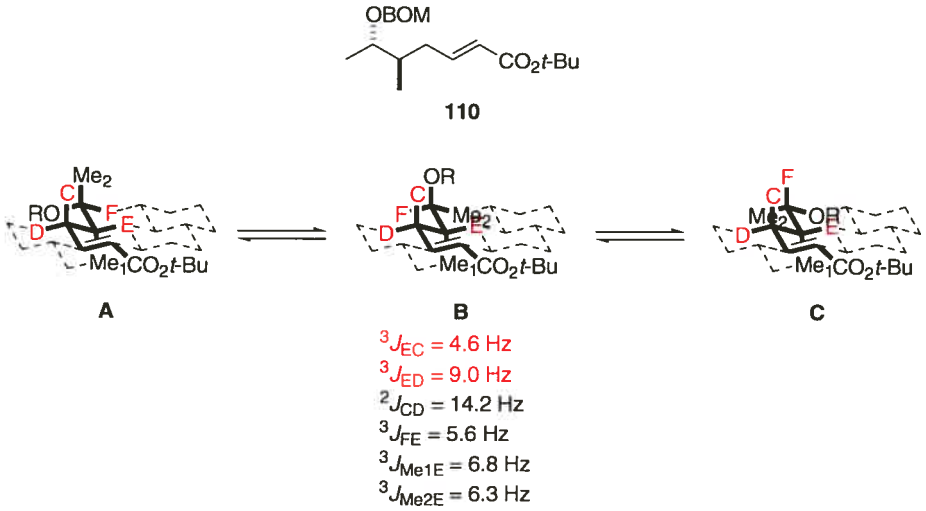


Figure 26: Data obtained from the homodecoupling analysis of **110**.

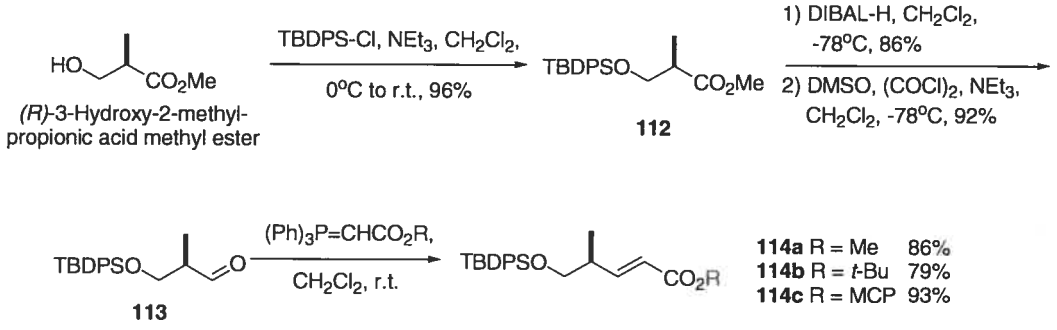
The homodecoupling analysis of enoate **110** as shown in Figure 26, indicates that there is not a very large gap between the vicinal coupling constants ($^3J_{EC}$ and $^3J_{ED}$) upon comparison with the data presented in Sections II.6 and III.2.3. This smaller $^3J_{EC}$ and $^3J_{ED}$ gap may be due to the lack of any anchoring group which consequently results in the lower selectivities observed for these molecules. Since an average coupling value of 5.6 Hz is observed for $^3J_{FE}$ it cannot be stated with certainty which of the three conformers shown in Figure 26 is preferred. Based on the 5.6 Hz value it may seem that all three conformers are present.

III.4. Studying the necessity of the benzyloxymethyl group

One of the conclusions made from the study of the alkoxy protecting groups was that the nature of the protecting group was not that important, and it had been observed that the BOM protecting group gave the best selectivities. We then decided to re-visit the BOM group, and see what the effect would be if instead of having γ-alkoxy-α,β-unsaturated esters we used γ-methyl-α,β-unsaturated esters.

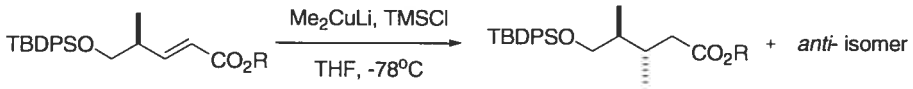
III.4.1. Probing the ester effect towards the addition of lithium dimethylcuprate to γ-methyl-α,β-unsaturated esters

Starting with commercially available (*R*)-3-hydroxy-2-methyl-propionic acid methyl ester, protection with TBDPSCl gave the silyl ether **112** in 96% yield (Scheme 29). Reduction to the alcohol, followed by Swern oxidation and Wittig homologation afforded the γ-methyl-α,β-unsaturated esters **114a-c** in excellent yield. We had hypothesized that the selectivities for the conjugate addition to enoates **114a-c** would proceed with very low diastereoselectivity. As previously mentioned (Section I.3.10, Figure 11), the high level of diastereocontrol observed in the addition of lithium dimethylcuprate to γ-alkoxy-α,β-unsaturated esters was due to the "inside alkoxy" effect. In substrates **114a-c**, loss of the alkoxy group altogether, would result in loss of the stabilization offered by the "inside alkoxy" effect, possibly resulting in lower selectivities.



Scheme 29: Synthesis of the γ-methyl-α,β-unsaturated esters.

As shown in Table 8, addition of lithium dimethylcuprate to the γ-methyl-α,β-unsaturated esters **114a-c** provided esters **115a-c** and the *anti-* isomer (not shown). Surprisingly, not only did the selectivities not drop, but a substantial ester effect was also observed, the MCP ester gave the best diastereomeric ratio (d.r. 94:6). The presence of a bulky $CH_2OTBDPS$ may account for the observed ester effect. Figure 27 shows the two conformations leading to the obtained major *anti-* and the minor *syn-* diastereomers. Conformation **114A** leading to the desired *anti-* product proceeds through the modified Felkin-Anh model.[56]



108a-c **109a-c**

Substrate	R	d.r. (*anti/syn*)[a]	yield (%)[b]
108a	Me	83:17	94
108b	*t*-Bu	91:9	90
108c	MCP	94:6	92

[a] determined by inverse gated proton decoupled ^{13}C NMR
[b] isolated yields after chromatography

Table 8: Addition of lithium dimethylcuprate to γ-methyl-α,β-unsaturated esters.

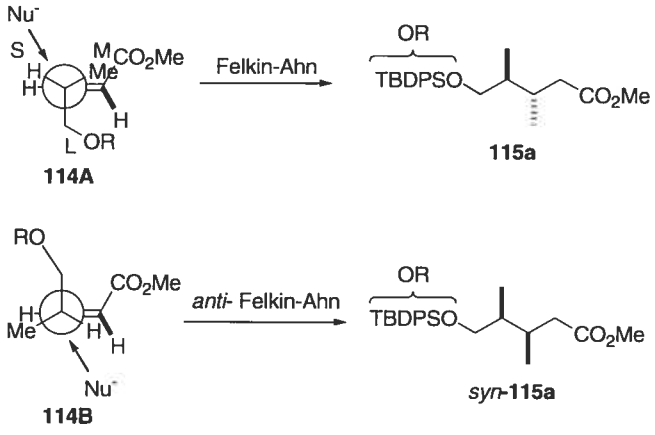
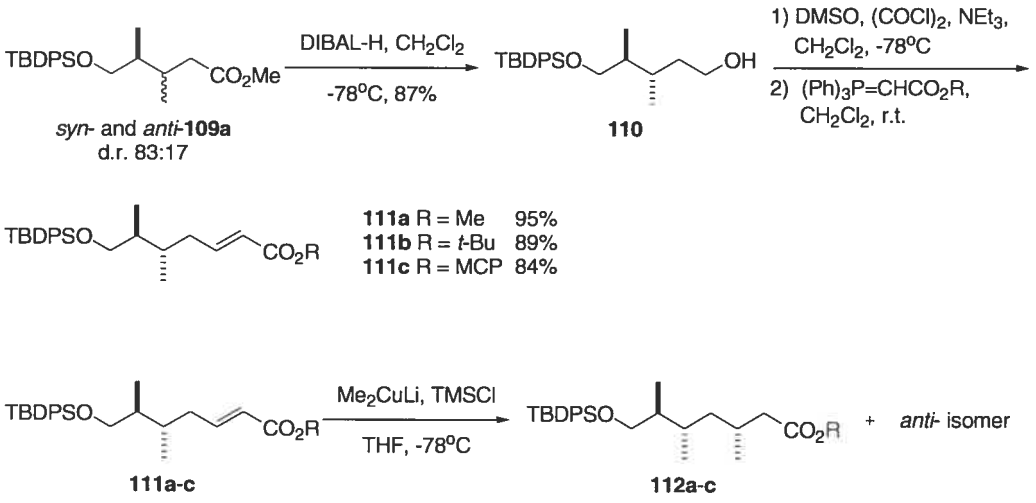


Figure 27: Modified Felkin-Ahn model for chiral Michael acceptors.

III.4.2. Effect of no alkoxy group towards the second cuprate addition

Iteration of the cuprate addition process begins with homologation of the substrate. Reduction of the diastereomeric mixture of *syn*- and *anti*- esters **115a** to the alcohol, followed by separation of the diastereomeric alcohols afforded **116** (Scheme 30). Usual oxidation and Wittig homologation afforded the δ-methyl-α,β-unsaturated esters **117a-c**. Addition of lithium dimethylcuprate to enoates **117a-c** afforded esters **118a-c** and the *anti*- isomers (not shown). The lower diastereoselectivity due to the loss of the alkoxy group can be seen clearly in the second cuprate addition. Furthermore, a substantial ester effect is not observed. Diastereoselectivities range from 67:33 to 74:26. Comparison of these ratios with those in Scheme 15 shows the difference in diastereoselectivity with and without the OBOM group.



Substrate	R	d.r. (*syn*/*anti*)[a]	yield (%)[b]
111a	Me	67:33	88
111b	*t*-Bu	70:30	83
111c	MCP	74:26	70

[a] determined by inverse gated proton decoupled ^{13}C NMR
[b] isolated yields after chromatography

Scheme 30: Probing the effect of the loss of the alkoxy substituent towards conjugate cuprate additions.

Based on these results it can be seen that depending on the substrate the benzyloxymethyl group also serves to anchor the molecule in a preferred conformation, leading to better diastereoselectivities.

III.5. Conclusions

The first section of this chapter dealt with the phenyl anchor. It was observed that the diastereoselectivities obtained with the phenyl anchor compared to the *iso*-propyl anchor were substantially lower (compare Tables 1 and 3 with Scheme 23 and 24). Also, upon performing iterative additions of lithium dimethylcuprate to the phenyl anchored substrates, the diastereoselectivities did increase in going from the smaller methyl ester to the bulkier *tert*-butyl and MCP esters, however not much difference was observed between the two bulky *tert*-butyl and MCP esters (Schemes 23 and 24).

The *tert*-butyl anchor was also investigated, in Section III.2. It had been anticipated that this anchor would provide decreased diastereoselectivities upon addition of lithium dimethylcuprate to the corresponding δ-methyl-α,β-unsaturated esters. The observed diastereoselectivities were indeed lower than the corresponding *iso*-propyl anchored substrates, but a significant difference between the phenyl anchor and the *tert*-butyl anchor was not observed. An NMR investigation of the conformation of the enoates sheds some light on the possible reasons.

The *tert*-butyl anchor was studied as an example of an anchor wherein all possible conformations would provide high energy *syn*-pentane interactions. We then decided to study a methyl anchor, wherein no conformation would lead to any *syn*-pentane interactions. Selectivities for the first cuprate additions were modest, however dropped for the second iterative cuprate addition.

Finally the necessity of the OBOM group was probed. Cuprate additions to the γ-methyl-α,β-unsaturated esters provided the corresponding γ-methyl-β-methyl products in excellent diastereomeric ratios. Also, an excellent ester effect was observed with the methyl ester giving the lowest selectivity and the MCP ester giving

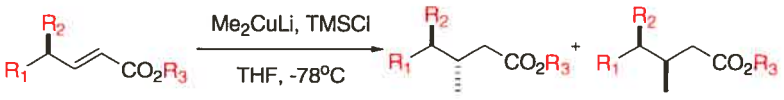
the best selectivity. However, iteration of the process provided products wherein both the diastereoselectivites were lowered and no ester effect was observed.

Chapter IV:

Synopsis

IV.1. Addition of lithium dimethylcuprate to γ-alkoxy- and γ-methyl-α,β-unsaturated esters

Addition of the Gilman cuprate to γ-methyl-α,β-unsaturated esters (i.e. the first cuprate addition) is generally not affected by variations in the anchoring group. The high *anti*-selectivity for these first cuprate additions is explained by the '*O*-inside alkoxy' effect (Chapter I, Section I.3.10). As shown in Table 9, the substitution was varied in three positions. The best selectivity was observed for substrate **64**, with the *iso*-propyl anchor (entry 1). Somewhat lower diastereomeric ratios are observed with the methyl anchored substrates (entries 6-8). It had been anticipated that the methyl anchor would not provide any anchoring effect therefore, was expected to result in lower selectivities. Also, the δ-methyl substrates **114a-c** (entries 9-11) had been hypothesized to give lower selectivities, in this case due to loss of the '*O*-inside alkoxy' effect. However, excellent diastereoselection was observed and a substantial ester effect was also observed. The best diastereoselectivity was observed with the MCP ester and the smaller methyl ester gave a lower diastereomeric ratio. The modified Felkin-Ahn model (Chapter III, Section III.4.1) explains the origin of the diastereocontrol.



major product *anti-* major product *syn-*

Entry	Substrate	R_1	R_2	R_3	d.r. (*anti/syn*)[a]	yield (%)[b]
1	**64**	*i*-Pr	OBOM	Me	96:4	99
2	**88a**	Ph	OBOM	Me	94:6[c]	97
3	**88b**	Ph	OBOM	*t*-Bu	95:5[c]	92
4	**88c**	Ph	OBOM	MCP	95:5[c]	89
5	(±)-**97**	*t*-Bu	OBOM	Me	>95:5	89
6	**107a**	Me	OBOM	Me	73:27	99
7	**107b**	Me	OBOM	*t*-Bu	85:15	91
8	**107c**	Me	OBOM	MCP	80:20	92
9	**114a**	$CH_2OTBDPS$	Me	Me	83:20	94
10	**114b**	$CH_2OTBDPS$	Me	*t*-Bu	91:9	90
11	**114c**	$CH_2OTBDPS$	Me	MCP	94:6	92

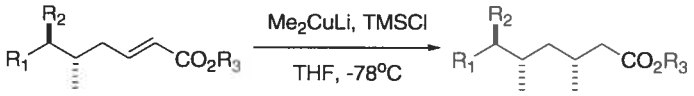
[a]determined by inverse gated proton decoupled ^{13}C NMR
[b] isolated yields after chromatography
[c]determined by ^{1}H NMR

Table 9: Addition of lithium dimethylcuprate to γ-alkoxy- and γ-methyl-α,β-unsaturated esters.

IV.2. Addition of lithium dimethylcuprate to δ-methyl-α,β-unsaturated esters

Table 10 shows the various substrates wherein lithium dimethylcuprate was added to δ-methyl-α,β-unsaturated esters. Substrate **67e** gave the highest diastereoselectivity (entry 5). The second cuprate additions shed light on the anchor effect vs. ester effect. It seems that although the anchoring group does indeed play a role in maintaining the molecule in a preferred conformation, it does not necessarily introduce such costly interactions. The ester effect seems to be the dominating factor, as a clear difference in diastereoselectivity is observed when changing from a smaller methyl ester to larger *tert*-butyl and MCP esters. The difference between *tert*-butyl and MCP esters on the other hand, is not very substantial both esters generally give

diastereomeric ratios in the same range. Substrates **67a**, **67d**, and **67e** show a clear ester effect (entries 1,4 and 5), related to the increase in the size of the ester.



Entry	Substrate	R_1	R_2	R_3	d.r. (*syn/anti*)	yield (%)[b]
1	**67a**	*i*-Pr	OBOM	Me	75:25	80
2	**67b**	*i*-Pr	OBOM	*i*-Pr	77:23	96
3	**67c**	*i*-Pr	OBOM	*neo*-Pent	78:22	93
4	**67d**	*i*-Pr	OBOM	*t*-Bu	89:11	87
5	**67e**	*i*-Pr	OBOM	MCP	91:9	89
6	**91a**	Ph	OBOM	Me	69:31	86
7	**91b**	Ph	OBOM	*t*-Bu	84:16	85
8	**91c**	Ph	OBOM	MCP	85:15	86
9	(±)-**101a**	*t*-Bu	OBOM	Me	64:36	76
10	(±)-**101b**	*t*-Bu	OBOM	*t*-Bu	82:18	85
11	(±)-**101c**	*t*-Bu	OBOM	MCP	81:19	73
12	**110**	Me	OBOM	*t*-Bu	67:33	90
13	**117a**	$CH_2OTBDPS$	Me	Me	67:33	88
14	**117b**	$CH_2OTBDPS$	Me	*t*-Bu	70:30	83
15	**117c**	$CH_2OTBDPS$	Me	MCP	74:26	70

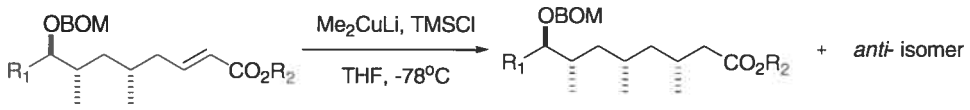
[a] determined by inverse gated proton decoupled ^{13}C NMR
[b] isolated yields after chromatography
[c] determined by ^{1}H NMR

Table 10: Comparison of the different anchors and esters towards the addition of lithium dimethylcuprate to δ-methyl-α,β-unsaturated esters.

Substrates **91a-c** show a less pronounced difference between the *tert*-butyl and MCP esters, but the selectivity observed with the methyl ester is nonetheless lower (entries 6-8). The *tert*-butyl anchored substrates were expected to result in considerably lower selectivities, but surprisingly afforded moderate to good diastereoselection (entries 9-11). Even though the ester effect seems to be the dominant effect the example with the methyl anchored substrate (entry 12) shows that loosing the anchoring group does indeed result in lower diastereomeric ratios. From these results

it can be concluded that the ester effect is certainly the more dominant effect being observed in the addition of lithium dimethylcuprate to δ- methyl-α,β-unsaturated esters.

IV.3. Third iterative addition of lithium dimethylcuprate to δ-methyl-α,β-unsaturated esters



Entry	Substrate	R_1	R_2	d.r. (*syn/anti*)[a]	yield (%)[b]
1	**75a**	*i*-Pr	Me	67:33	84
2	**75b**	*i*-Pr	*t*-Bu	87:13	97
3	**75c**	*i*-Pr	MCP	83:17	91
4	**94a**	Ph	*t*-Bu	79:21	90
5	**94b**	Ph	MCP	79:21	74
6	(±)-**103**	*t*-Bu	*t*-Bu	82:18	77

[a] determined by inverse gated proton decoupled ^{13}C NMR
[b] isolated yields after chromatography

Table 11: Comparison of the different anchors and esters towards the third iterative addition of lithium dimethylcuprate to δ-methyl-α,β-unsaturated esters.

As shown in Table 11 the selectivities observed towards the third iterative cuprate additions seem to have plateaued regardless of the nature of the anchoring group. Nonetheless the level of substrate and conformational control observed for the diastereoselective addition of lithium dimethylcuprate to acyclic δ-methyl-α,β-unsaturated esters is quite impressive. Another effect that was observed was the decreasing preference for *syn*-selective cuprate additions with the MCP ester in the growing acyclic chain. Addition of lithium dimethylcuprate to substrate **67e** gave the corresponding *syn*- and *anti*- esters in a diastereomeric ratio of 91:9, homologation and iteration thereof affords a diastereomeric ratio of 83:17 for substrate **75c** (Table

10, entry 5 and Table 11, entry 3). The same decrease in selectivity is observed for the phenyl anchored substrates (Table 1, entries 4 and 5).

Chapter V:

Experimental

V.1. General experimental notes

Reagents

All reagents were purchased from Aldrich, Sigma, Lancaster or Acros and were used without any further purification, unless otherwise noted. All commercially unavailable reagents were prepared following literature procedures.

Anhydrous reaction conditions

All anhydrous reactions were performed under an atmosphere of dry argon. The glass vessels, needles, and stirring bars were either oven-dried at 110-140 °C, or flame dried, and cooled to room temperature under a flow of argon. Solvents such as tetrahydrofuran, diethyl ether, dichloromethane and toluene were obtained from the Solvent Dispensing System (SDS), which filters the solvents over a column of alumina under an atmosphere of argon. Acetonitrile and NEt_3 were distilled over calcium hydride under an atmosphere of argon.

Temperature control

The temperatures indicated in the reaction schemes and in the procedures are all external temperatures.

-78 °C	dry ice-acetone bath
0 °C	ice-water bath
room temperature	ambient temperature without any control

Chromatography

Flash chromatography was carried out according to the procedure of Still,[57] using silica gel 60 (0.40-0.063 mm. 230-400 mesh ASTA) (E. Merck). Thin layer chromatography (TLC) was performed using commercially available, precoated glass backed Silica Gel 60 F_{254} plates with a thickness of 25 um. Visualization of the UV active compounds on the TLC plates was done with the aid of a UV254 lamp. The TLC plates were stained with either of the following stains:

- Cerium molybdate stain:[58] Prepared by dissolving 12 g ammonium molybdate, and 0.5 g ceric ammonium molybdate in 235 mL H_2O and 15 mL concentrated sulphuric acid.
- Potassium permanganate stain: Prepared by dissolving 1.5 g potassium permanganate, 10 g potassium carbonate and 1.25 mL 10% NaOH in 200 mL H_2O.

Instrumentation

Nuclear Magnetic Resonance Spectroscopy:

Routine nuclear magnetic resonance spectra were recorded on Bruker AMX 300 (^{1}H 300 MHz, ^{13}C 75 MHz), Bruker AV 300 (^{1}H 300 MHz, ^{13}C 75 MHz), Bruker ARX 400 (^{1}H 400 MHz, ^{13}C 100 MHz), and Bruker AV 400 (^{1}H 400 MHz, ^{13}C 100 MHz) instruments. The NMR experiments reported in Chapters II and III (^{1}H NMR, COSY45, *J*resolve and ^{1}H-^{1}H homodecoupling) were recorded on a Bruker AV 500 MHz instrument. Chemical shifts (δ) and coupling constants (J) are expressed in parts per million (ppm) and hertz (Hz) respectively. Abbreviations used describing the splitting of the peaks are as follows:

s	singlet
d	doublet
t	triplet

q	quartet
quin	quintet
dd	doublet of doublet
dq	doublet of quartet
m	multiplet

The ^{13}C NMR chemical shifts observed for minor diastereomers, obtained from the cuprate additions, are indicated in parentheses.

Infrared Spectrometry:

The infrared spectra (IR) were recorded on a Perkin-Elmer 781 or Paragon 1000 spectrophotometer as a thin film on a sodium chloride cell.

Polarimetry:

Optical rotations (α_D) were measured at the sodium line using a Perkin-Elmer 241 polarimeter at ambient temperature.

Mass spectra:

Low resolution and high resolution mass spectra were obtained from VG Micromass, Kratos MS-50 TCTA, or Ael-MS902 instruments. The data were obtained by ionization by electrospray, electron impact (EI) or fast atom bombardment (FAB). Most of the molecules reported herein did not ionize, consequently did not provide any valid mass spectral data. Therefore there very few mass spectra are reported.

V.2. Experimental procedures and data

General Procedure A: DIBAL-H reduction

To a solution of the ester in CH_2Cl_2 cooled to -78 °C, DIBAL-H (3 equivalents) was added. The reaction was stirred at -78 °C for 4 h before being quenched with a saturated Na/K tartrate solution. The reaction mixture was diluted with EtOAc and

stirred for 30 min at room temperature until a clear biphasic solution was observed. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered. After concentration, the resulting residue was purified by flash chromatography.

General Procedure B: Swern Oxidation

Oxalyl chloride (2.5 equivalents) was slowly added to a solution of DMSO (5 equivalents) in CH_2Cl_2 cooled to -78 °C. The mixture was allowed to stir at -78 °C for 20 min before addition of a solution of the alcohol in CH_2Cl_2. After 45 min NEt_3 (10 equivalents) was added and the reaction was warmed to room temperature. The reaction was quenched with a saturated solution of NH_4Cl, the aqueous layer was extracted three times with EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered and then concentrated. Flash chromatography afforded the desired aldehyde.

General Procedure C: Wittig reaction

A solution of the aldehyde in CH_2Cl_2 was charged with $Ph_3P{=}CHCO_2R$ (1.5 equivalents). The reaction mixture was stirred at room temperature for 18 h and then evaporated to dryness. The crude solid was triturated with hexanes/Et_2O (3:1), and the resulting slurry was filtered over a pad of celite. The filtrate was concentrated and purified by flash chromatography affording the enoate.

General Procedure D: cuprate addition

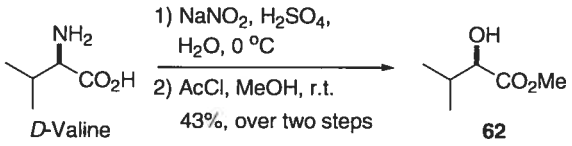
To a slurry of CuI (6 equivalents) in THF at -15 °C was added MeLi·LiBr (12 equivalents). The resulting colorless solution was stirred at this temperature for 20 min then cooled to -78 °C. Dropwise addition of TMSCl (18 equivalents) was followed by canulation of a solution of the α,β-unsaturated ester in THF at -78 °C. The reaction mixture was stirred at -78 °C for 3 h and quenched with solution of NH_4OH/NH_4Cl (1:1). The mixture was diluted with Et_2O and warmed to room temperature. The aqueous layer was extracted three times with Et_2O, the combined

organic extracts were washed with NH_4OH/NH_4Cl (1:1), brine, and dried over Na_2SO_4. The solution was filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography.

General Procedure E: Swern oxidation followed by Wittig reaction

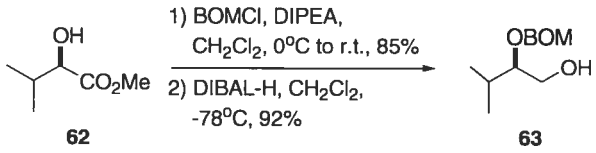
Oxalyl chloride (2.5 equivalents) was added to a solution of DMSO (5 equivalents) in CH_2Cl_2 at -78 °C. After 15 min, a solution of the alcohol in CH_2Cl_2 was added and stirred at -78 °C for 45 min. NEt_3 (10 equivalents) was then added and the reaction mixture was warmed to room temperature over 45 min. A saturated solution of NH_4Cl was added and the layers were separated. The aqueous layer was extracted three times with EtOAc, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude aldehyde was added to a solution of $Ph_3P{=}CHCO_2R$ (1.5 equivalents) in CH_2Cl_2, and the reaction mixture was stirred at room temperature for 18 h then evaporated to dryness. The crude solid was triturated with hexanes/Et_2O (3:1), and the resulting slurry was filtered over a pad of celite. The filtrate was concentrated and purified by flash chromatography.

2-Hydroxy-3-methylbutyric acid methyl ester (62)



The above compound was prepared according to a literature procedure.[54] All spectral and physical data were in accordance with the reported data.

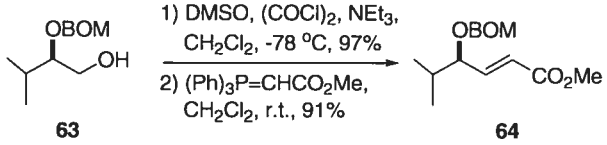
(2*R*)-2-Benzyloxymethoxy-3-methylbutan-1-ol (63)



62 63

The above compound was prepared according to a literature procedure.[54] All spectral and physical data were in accordance with the reported data.

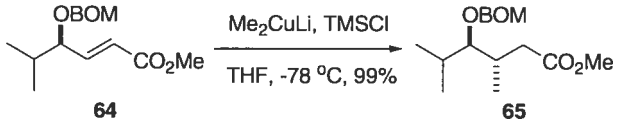
(*E*)-(4*R*)-4-Benzyloxymethoxy-5-methylhex-2-enoic acid methyl ester (64)



63 64

The above compound was prepared according to a literature procedure.[54] All spectral and physical data were in accordance with the reported data.

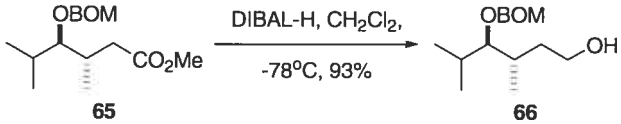
(3*S*, 4*R*)-4-Benzyloxymethoxy-3,5-dimethylhexanoic acid methyl ester (65)



64 65

The above compound was prepared according to a literature procedure.[54] All spectral and physical data were in accordance with the reported data.

(3*S*, 4*R*)-4-Benzyolmethoxy-3,5-dimethylhexan-1-ol (66)



65 66

Following general procedure A, reduction of compound **65** (1.51 g, 5.13 mmol) afforded alcohol **66** (1.26 g, 93%) after flash chromatographic purification with 10% EtOAc/hexanes.

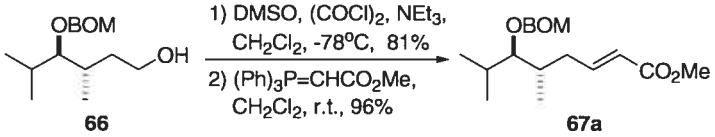
$[\alpha]_D$ -16.2 (c = 1.42, $CHCl_3$)

IR (thin film) 3410, 3032, 2961, 2876, 1455, 1384, 1366, 1207, 1159cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.23 (m, 5H), 4.85 (d, 1H, J = 6.9 Hz), 4.82 (d, 1H, J = 6.9 Hz), 4.71 (d, 1H, J = 11.8 Hz), 4.66 (d, 1H, J = 11.8 Hz), 3.76 (m, 1H), 3.62 (m, 1H), 3.15 (m, 1H), 2.02 (m, 1H), 1.93 (m, 2H), 1.79 (m, 1H), 1.56 (m, 1H), 0.98 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 138.3, 128.8 (2C), 128.2 (2C), 128.1, 97.2, 90.3, 70.6, 61.0, 34.9, 32.9, 30.9, 20.7, 18.7, 17.6

(*E*)-(5*S*, 6*R*)-6-Benzyloxymethoxy-5,7-dimethyloct-2-enoic acid methyl ester (36a)



66 67a

Following general procedures B and C, oxidation of alcohol **66** (1.55 g, 5.82 mmol) afforded the desired aldehyde (1.31 g, 81%). Wittig homologation of the aldehyde (0.10 g, 0.38 mmol) gave product **67a** (0.12 g, 96%) as a colorless oil after flash chromatography with 2% EtOAc/hexanes.

$[\alpha]_D$ -12.7 (c = 0.73, $CHCl_3$)

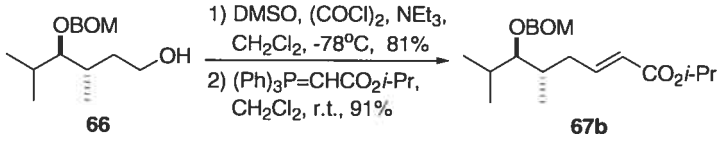
IR (thin film) 3032, 2962, 2876, 1725, 1656, 1497, 1455 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 (m, 5H), 6.99 (m, 1H), 5.85 (d, 1H, J = 15.6 Hz), 4.86 (d, 1H, J = 6.8 Hz), 4.83 (d, 1H, J = 6.8 Hz), 4.72 (d, 1H, J = 12.0 Hz), 4.68 (d, 1H, J = 12.0 Hz), 3.74 (s, 3H), 3.12 (t, 1H, J = 5.3 Hz), 2.55 (m, 1H), 2.05 (m, 1H), 1.90 (m, 2H), 0.95 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.4, 149.4, 138.3, 130.5 (2C), 128.8 (2C), 128.2, 122.5, 97.2, 89.6, 70.6, 51.8, 35.6, 35.5, 30.8, 20.7, 17.9, 17.5

HRMS (EI) *m/z* 321.2060 (calcd for 321.2066 $C_{19}H_{28}O_4$)

(*E*)-(5*S*, 6*R*)-6-Benzyloxymethoxy-5,7-dimethyloct-2-enoic acid isopropyl ester (67b)



66 67b

Following general procedures B and C, oxidation of alcohol **66** (1.55 g, 5.82 mmol) afforded the desired aldehyde (1.31 g, 81%). Wittig homologation of the aldehyde (0.20 g, 0.77 mmol) gave product **67b** (0.24 g, 91%) as a colorless oil after flash chromatography with 2% EtOAc/hexanes.

$[\alpha]_D$ -11.2 (c = 0.83, $CHCl_3$)

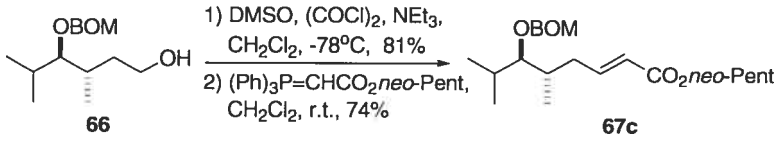
IR (thin film) 2964, 1715, 1653, 1454, 1372, 1310, 1270, 1220, 1178 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32 (m, 5H), 6.95 (m, 1H), 5.82 (d, 1H, J = 15.5 Hz), 5.08 (m, 1H), 4.83 (d, 1H, J = 6.9 Hz), 4.81 (d, 1H, J = 6.9 Hz), 4.70 (d, 1H, J = 11.9 Hz), 4.66 (d, 1H, J = 11.9 Hz), 3.12 (t, 1H, J = 5.3 Hz), 2.56 (m, 1H), 2.05 (m, 1H), 1.91 (m, 2H), 1.29 (m, 6H), 0.96 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.6, 148.7, 128.8 (2C), 128.1 (2C), 128.0, 123.4, 97.2 (2C), 89.7, 70.6, 67.8, 35.6, 35.4, 30.8, 22.3 (2C), 20.7, 18.0, 17.6

HRMS (EI) *m/z* 349.2389 (calcd for 349.2379 $C_{21}H_{32}O_4$)

(*E*)-(5*S*, 6*R*)-6-Benzyloxymethoxy-5,7-dimethyloct-2-enoic acid 2,2-dimethyl-propyl ester (67c)



66 67c

Following general procedures B and C, oxidation of alcohol **66** (1.55 g, 5.82 mmol) afforded the desired aldehyde (1.31 g, 81%). Wittig homologation of the aldehyde (0.20 g, 0.77 mmol) gave product **67c** (0.21 g, 74%) as a colorless oil after flash chromatography with 2% EtOAc/hexanes.

$[\alpha]_D$ -5.8 (c = 0.55, $CHCl_3$)

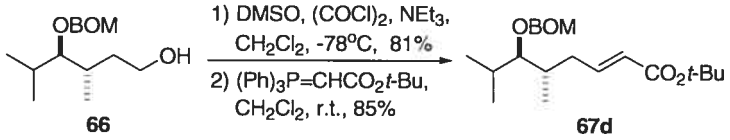
IR (thin film) 3100, 1715, 1650, 1498 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31 (m, 5H), 6.98 (m, 1H), 5.87 (d, 1H, J = 15.6 Hz), 4.84 (d, 1H, J = 6.9 Hz), 4.81 (d, 1H, J = 6.9 Hz), 4.71 (d, 1H, J = 11.9 Hz), 4.66 (d, 1H, J = 11.9 Hz), 3.84 (s, 2H), 3.12 (t, 1H, J = 5.3 Hz), 2.56 (m, 1H), 2.06 (m, 1H), 1.91 (m, 2H), 0.99 (m, 18H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.1, 149.0, 128.8 (2C), 128.1 (2C), 128.1, 122.9, 97.2, 89.7, 78.6, 73.9, 70.6, 35.6, 35.5, 31.8, 30.8, 26.9 (3C), 20.7, 18.0, 17.5

HRMS (EI) m/z 377.2706 (calcd for 377.2692 $C_{23}H_{36}O_4$)

(*E*)-(5*S*, 6*R*)-6-Benzyloxymethoxy-5,7-dimethyloct-2-enoic acid *tert*-butyl ester (67d)



66 67d

Following general procedures B and C, oxidation of alcohol **66** (1.55 g, 5.82 mmol) afforded the desired aldehyde (1.31 g, 81%). Wittig homologation of the aldehyde (0.20 g, 0.77 mmol) gave product **67d** (0.24 g, 85%) as a colorless oil after flash chromatography with 2% EtOAc/hexanes.

$[\alpha]_D$ -6.3 (c = 0.40, $CHCl_3$)

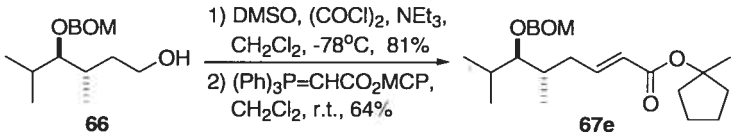
IR (thin film) 2967, 1712, 1651, 1455, 1366 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 5H), 6.87 (m, 1H), 5.77 (d, 1H, J = 15.5 Hz), 4.82 (d, 1H, J = 6.9 Hz), 4.80 (d, 1H, J = 6.8 Hz), 4.69 (d, 1H, J = 11.9 Hz), 4.65 (d, 1H, J = 11.9 Hz), 3.11 (t, 1H, J = 5.4 Hz), 2.52 (m, 1H), 2.02 (m, 1H), 1.90 (m, 2H), 1.49 (s, 9H), 0.95 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4, 147.7, 138.3, 128.8 (2C), 128.5 (2C), 128.0, 124.6, 97.2, 89.7, 80.4, 70.6, 35.6, 35.2, 30.8, 28.6 (3C), 20.7, 17.8, 17.5

HRMS (EI) *m/z* 363.2533 (calcd for 363.2535 $C_{22}H_{34}O_4$)

(*E*)-(5*S*, 6*R*)-6-Benzyloxymethoxy-5,7-dimethyloct-2-enoic acid 1-methylcyclopentyl ester (66e)



Following general procedures B and C, oxidation of alcohol **66** (1.55 g, 5.82 mmol) afforded the desired aldehyde (1.31 g, 81%). Wittig homologation of the aldehyde (0.20 g, 0.77 mmol) gave product **67e** (0.19 g, 64%) as a colorless oil after flash chromatography with 2% EtOAc/hexanes.

$[\alpha]_D$ -6.8 (c = 0.83, $CHCl_3$)

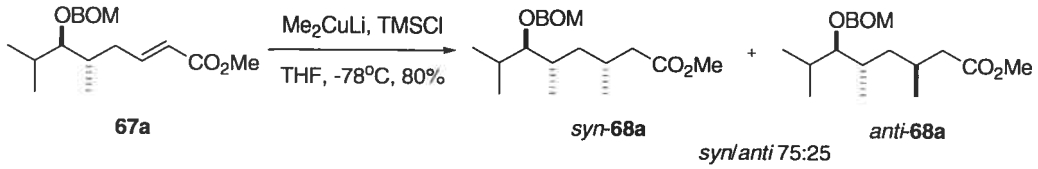
IR (thin film) 2963, 2875, 1712, 1652, 1455, 1374, 1320 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32 (m, 5H), 6.88 (m, 1H), 5.77 (d, 1H, J = 15.6 Hz), 4.82 (d, 1H, J = 6.9 Hz), 4.80 (d, 1H, J = 6.7 Hz), 4.69 (d, 1H, J = 11.9 Hz), 4.65 (d, 1H, J = 11.9 Hz), 3.11 (t, 1H, J = 5.3 Hz), 5.04 (m, 1H), 2.13 (m, 2H), 2.02 (m, 1H), 1.89 (m, 2H), 1.71 (m, 6H), 1.59 (s, 3H), 0.98 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.5, 147.8, 138.3, 128.8 (2C), 128.1 (2C), 128.0, 124.5, 97.2, 89.9, 89.7, 70.6, 39.6 (2C), 35.6, 35.3, 30.8, 24.9, 24.2 (2C), 20.7, 18.0, 17.5

HRMS (EI) *m/z* 389.2700 (calcd for 389.2692 $C_{24}H_{36}O_4$)

(3*R*, 5*S*, 6*R*)-6-Benzyloxymethoxy-3,5,7-trimethyl-octanoic acid methyl ester (68a)



67a *syn*-**68a** *anti*-**68a**

syn/*anti* 75:25

Compound **67a** (0.784 g, 2.45 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification of the product with 2% EtOAc/hexanes afforded the products *syn*-**68a** and *anti*-**68a** (0.66 g, 80% combined yield) in a ratio of 75:25 *syn*/*anti*.

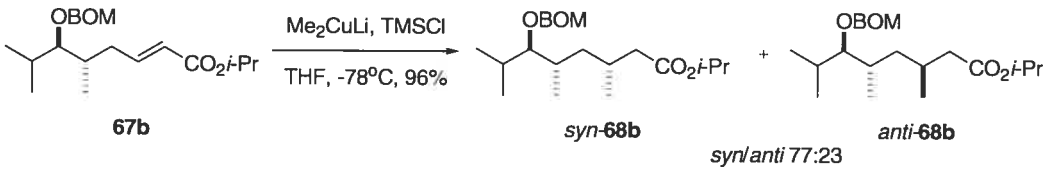
$[\alpha]_D$ -17.0 (c = 1.20, $CHCl_3$)

IR (thin film) 2961, 1738, 1455, 1382 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.32 (m, 5H), 4.34 (d, 1H, J = 6.9 Hz), 4.80 (d, 1H, J = 6.9 Hz), 4.71 (d, 1H, J = 11.9 Hz), 4.66 (d, 1H, J = 11.9 Hz), 3.68 (s, 3H), 3.11 (t, 1H, J = 5.3 Hz), 2.41 (dd, 1H, J = 3.7, 13. 9 Hz), 2.04 (m, 2H), 1.89 (m, 1H), 1.79 (m, 1H), 1.50 (m, 1H), 1.15 (m, 1H), 0.96 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 173.4 (173.2), 137.7, 128.0 (2C), 127.8 (2C), 127.5, (96.4) 96.2, (89.9) 89.3, 69.7, 51.0, (42.6) 40.1, 38.8 (38.1), 32.7 (32.4), (29.9) 29.8, 27.7 (27.3), 21.0, 20.0, (18.0) 17.9, 16.9 (16.4)

(3*R*, 5*S*, 6*R*)-6-Benzyloxymethoxy-3,5,7-trimethyloctanoic acid isopropyl ester (68b)



67b *syn*-**68b** *anti*-**68b**

syn/*anti* 77:23

Compound **67b** (0.10 g, 0.29 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification of the product with 2% EtOAc/hexanes afforded the products *syn*-**68b** and *anti*-**68b** (0.102 g, 96% combined yield) in a ratio of 77:23 *syn/anti*.

[α]$_D$ -16.1 (*c* = 1.18, $CHCl_3$)

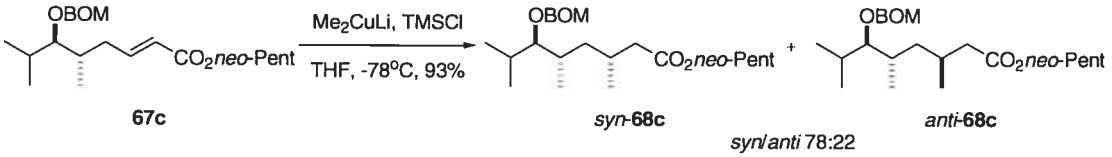
IR (thin film) 2963, 2934, 2876, 1731, 1498, 1455, 1374, 1259 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31 (m, 5H), 5.02 (m, 1H), 4.82 (d, 1H, *J* = 6.9 Hz), 4.79 (d, 1H, *J* = 6.9 Hz), 4.69 (d, 1H, *J* = 11.9 Hz), 4.65 (d, 1H, *J* = 11.9 Hz), 3.09 (t, 1H, *J* = 5.4 Hz), 2.35 (dd, 1H, *J* = 4.3, 14.2 Hz), 2.04 (m, 1H), 1.91 (m ,2H), 1.76 (m, 1H), 1.48 (m, 1H), 1.25 (m, 6H), 1.13 (m, 1H), 0.94 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 172.5 (172.3), 137.7, 128.0 (2C), 127.4 (2C), 127.2, (96.3) 96.2, (89.9) 89.4, 69.7, 67.0, (43.2) 40.7, 38.9 (38.0), 32.6 (32.4), (29.9) 29.8, 27.7 (27.5), 21.5, 21.5, 20.9, 20.2 (20.0), (18.4) 18.0, 17.0 (16.5)

HRMS (EI) *m/z* 365.2711 (calcd for 365.2692 $C_{22}H_{36}O_4$)

(3*R*, 5*S*, 6*R*)-6-Benzyloxymethoxy-3,5,7-trimethyloctanoic acid 2,2-dimethyl-propyl ester (68c)



67c — *syn*-**68c** — *anti*-**68c**

syn/anti 78:22

Compound **67c** (0.10 g, 0.27 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification of the product with 2% EtOAc/hexanes afforded the products *syn*-**68c** and *anti*-**68c** (0.097 g, 93% combined yield) in a ratio of 78:22 *syn/anti*.

[α]$_D$ -14.6 (*c* = 0.65, $CHCl_3$)

IR (thin film) 2960, 2874, 1736, 1463, 1367, 1254 cm^{-1}

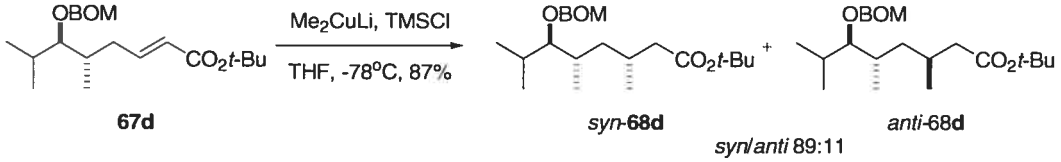
^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.33 (m, 5H), 4.82 (m, 2H), 4.71 (d, 1H, *J* = 11.9 Hz), 4.66 (d, 1H, *J* = 11.9 Hz), 3.78 (s, 2H), 3.10 (m, 1H), 2.44 (dd, 1H, *J* = 3.8, 14.1 Hz), 2.25 (m, Minor), 2.08 (m, 1H), 1.99 (dd, 1H, *J* = 9.5, 14.1 Hz), 1.90 (m,

1H), 1.80 (m, 1H), 1.49 (m, 1H), 1.37 (m, minor), 1.27 (m, minor), 1.17 (m, 1H), 1.00-0.91 (m, 21H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.2 (172.9), 137.7, 128.0 (2C), 127.3 (2C), 127.2, (96.3) 96.2, (89.9) 89.4, 73.3, 69.7, (42.9) 40.4, 38.7 (38.1), 32.7 (32.4), 30.9, (29.9) 29.8, 27.7 (27.4), 26.1 (3C), 21.1, 20.2 (20.1), (18.4) 18.0, 16.9 (16.4)

HRMS (EI) *m/z* 393.3019 (calcd for 393.3005 $C_{24}H_{40}O_4$)

(3*R*, 5*S*, 6*R*)-6-Benzyloxymethoxy-3,5,7-trimethyloctanoic acid *tert*-butyl ester (68d)



67d *syn*-**68d** *anti*-**68d**

syn/*anti* 89:11

Compound **67d** (0.10 g, 0.28 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification of the product with 2% EtOAc/hexanes afforded the products *syn*-**68d** and *anti*-**68d** (0.091 g, 87% combined yield) in a ratio of 89:11 *syn*/*anti*.

$[\alpha]_D$ -14.0 (c = 0.60, $CHCl_3$)

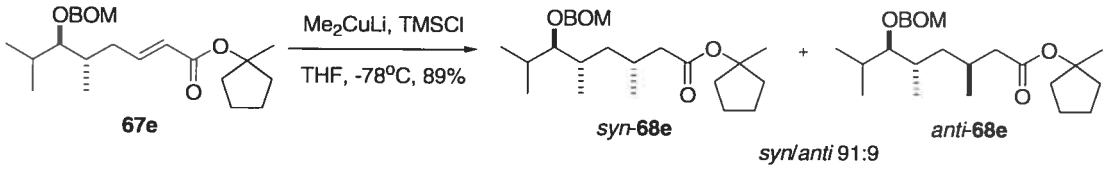
IR (thin film) 2963, 2932, 2875, 1729, 14.56, 1367, 1257 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31 (m, 5H), 4.82 (d, 1H, J = 6.9 Hz), 4.79 (d, 1H, J = 6.9 Hz), 4.69 (d, 1H, J = 12.0 Hz), 4.65 (d, 1H, J = 12.0 Hz), 3.09 (t, 1H, J = 5.2 Hz), 2.30 (dd, 1H, J = 4.4, 14.3 Hz), 2.01 (m, 1H), 1.87 (m, 2H), 1.77 (m, 1H), 1.49 (m, 1H) 1.46 (s, 9H), 1.12 (m, 1H), 0.94 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.2 (173.9), 138.5, 128.8 (2C), 128.1 (2C), 128.0, 97.1, 97.1, (90.6) 90.1, 80.4, 70.4, (44.9) 42.5, 39.6 (38.8), 33.5 (33.2), (30.7) 30.6, 28.5 (3C), 21.7, 21.0 (20.8), (19.2) 18.8, 17.7 (17.3)

HRMS (EI) *m/z* 379.2861 (calcd for 379.2848 $C_{23}H_{38}O_4$)

(3*R*, 5*S*, 6*R*)-6-Benzyloxymethoxy-3,5,7-trimethyloctanoic acid 1-methylcyclopentyl ester (68e)



Compound **67e** (0.10 g, 0.26 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification of the product with 2% EtOAc/hexanes afforded the products *syn*-**68e** and *anti*-**68e** (0.094 g, 89% combined yield) in a ratio of 91:9 *syn/anti*.

$[\alpha]_D$ -12.0 (c = 1.25, $CHCl_3$)

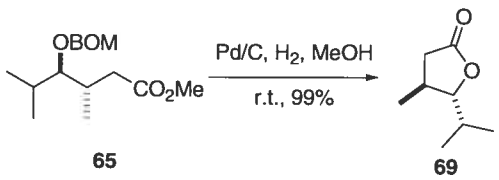
IR (thin film) 2962, 2874, 1727, 1498, 1455, 1374, 1270 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.31 (m, 5H), 4.82 (d, 1H, J = 6.9 Hz), 4.79 (d, 1H, J = 6.9 Hz), 4.69 (d, 1H, J = 12.0 Hz), 4.65 (d, 1H, J = 12.0 Hz), 3.09 (t, 1H, J = 5.2 Hz), 2.31 (dd, 1H, J = 4.7, 14.2 Hz), 2.11 (m, 2H), 1.99 (m, 1H), 1.88 (m, 2H), 1.70 (m, 7H), 1.55 (s, 3H), 1.47 (m, 1H), 1.10 (m, 1H), 0.95 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 172.6 (172.3), 137.7, 128.0 (2C), 127.6 (2C), 127.2, (96.3) 96.2, (89.9) 89.4, 89.1, 69.7, (44.0) 41.6, 38.8, 38.8, 38.8 (38.7), 32.6 (32.7), 29.9 (29.8), 27.9, 27.6, 24.0, 23.4, 20.9, 20.2 (20.0), (18.4) 18.0, 16.9 (16.5)

HRMS (EI) *m/z* 405.3017 (calcd for 405.3004 $C_{25}H_{40}O_4$)

(5*R*, 4*S*)-5-Isopropyl-4-methyl-dihydro-furan-2-one (69)



A solution of compound **65** (2.00 g, 6.79 mmol) and 10% Pd/C (0.400 g) in AcOH (10 mL) and MeOH (70 mL), was stirred for 18 h at room temperature under an

atmosphere of H_2. The reaction mixture was then filtered over a pad of celite. A solution of saturated $NaHCO_3$ was added to the filtrate, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (10% EtOAc/hexanes) afforded the lactone **69** (0.95 g, 99%) as a colorless oil.

$[\alpha]_D$ +17.4 (c = 0.39, $CHCl_3$)

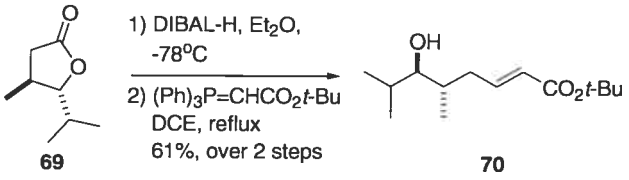
IR (thin film) 2964, 1738, 1454, 1369 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 3.86 (t, 1H, J = 6.1 Hz), 2.71 (dd, 1H, J = 8.6, 17.6 Hz), 2.37 (m, 1H), 2.19 (dd, 1H, J = 8.1, 17.5 Hz), 1.87 (m, 1H), 1.16 (d, 3H, J = 6.7 Hz), 1.02 (d, 3H, J = 6.9 Hz), 1.00 (d, 3H, J = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 177.2, 92.5, 37.7, 32.9, 32.0, 19.7, 19.1, 17.8

MS (ESI) m/z 143.1 $(M+H)^+$

(*E*)-(5*S*, 6*R*)-6-Hydroxy-5,7-dimethyloct-2-enoic acid *tert*-butyl ester (70)



69 **70**

A solution of lactone **69** (0.960 g, 6.75mmol) in Et_2O (70 mL) at -78 °C was charged with DIBAL-H (1.0 M in PhMe, 6.8 mL, 6.8 mmol). The mixture was stirred at -78 °C for 20 min before being quenched with a saturated solution of Na/K tartrate. The reaction mixture was diluted with 30 mL of EtOAc and stirred for 30 min at room temperature till a clear biphasic solution was observed. This was then extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and then concentrated. The lactol was taken to the next step without any further purification.

To a solution of the crude lactol in DCE (50 mL) was added $Ph_3P{=}CHCO_2t$-Bu (5.00 g, 13.5 mmol). The reaction mixture was refluxed for 4 h before concentrating *in*

vacuo. The concentrate was triturated with hexanes/Et_2O (3:1) and the resulting slurry was filtered over a pad of celite. Concentration of the filtrate followed by flash chromatographic purification afforded product **70** (0.90 g, 61%) as a colorless oil.

$[\alpha]_D$ -8.7 (c = 25.0, $CHCl_3$)

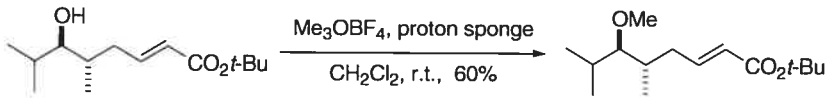
IR (thin film) 3473, 2968, 2934, 2876, 1715, 1697, 1651, 1459, 1392, 1368, 1319 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ(ppm) 6.87 (m, 1H), 5.78 (d, 1H, J = 15.5 Hz), 3.11 (t, 1H, J = 5.8 Hz), 2.50 (m, 1H), 2.05 (m, 1H), 1.79 (m, 2H), 1.48 (s, 9H), 0.93 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4, 147.4, 124.7, 80.7, 80.4, 36.0, 35.0, 30.4, 28.6 (3C), 20.4, 16.8, 16.2

HRMS (EI) m/z 243.1948 (calcd for 243.1960 $C_{14}H_{26}O_3$)

(*E*)-(5*S*, 6*R*)-6-Methoxy-5,7-dimethyloct-2-enoic acid *tert*-butyl ester (72a)



70 **72a**

To a solution of compound **70** (0.10 g, 0.41 mmol) in CH_2Cl_2 (5 mL) were added Me_3OBF_4 (0.61 g, 4.1 mmol) and proton sponge® (0.89 g, 4.1 mmol). The mixture was stirred at room temperature for 18 h, before being quenched with a saturated solution of NH_4Cl. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (5 % EtOAc/hexanes) afforded product **72a** (0.66 g, 60%) as a colorless oil.

$[\alpha]_D$ -2.8 (c = 3.60, $CHCl_3$)

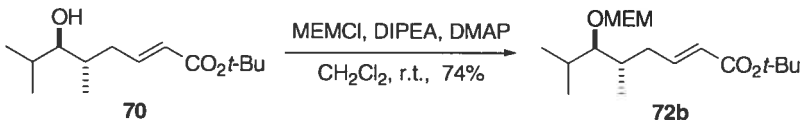
IR (thin film) 2965, 1716, 1652, 1460, 1367 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ(ppm) 6.83 (m, 1H), 5.74 (d, 1H, J = 15.5 Hz), 3.44 (s, 3H), 2.62 (t, 1H, J = 5.7 Hz), 2.43 (m, 1H), 1.96 (m, 1H), 1.80 (m, 2H), 1.46 (s, 9H), 0.90 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.9, 147.2, 123.9, 90.9, 79.8, 61.8, 35.4, 34.4, 30.4, 28.0 (3C), 20.2, 16.9, 16.8

MS (ESI) m/z 257.2 $(M+H)^+$

(*E*)-(5*S*, 6*R*)-6-(2-Methoxy-ethoxymethoxy)-5,7-dimethyloct-2-enoic acid *tert*-butyl ester (72b)



70 **72b**

A solution of **70** (0.20 g, 0.83 mmol), DIPEA (0.83 mL, 5.0 mmol) and DMAP (0.02 g, 0.16 mmol) in CH_2Cl_2 (8 mL) was cooled to 0 °C. After addition of MEMCl (0.28 mL, 2.5 mmol), the mixture was stirred at room temperature for 18 h. The reaction was quenched with a saturated solution of NH_4Cl, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4 and filtered. After concentration, the residue was purified by flash chromatography (20% EtOAc/hexanes) affording product **72b** (0.20 g, 74%) as a colorless oil.

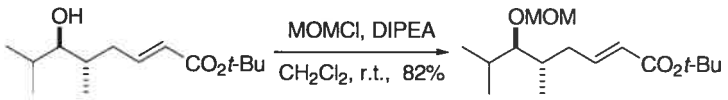
$[\alpha]_D$ -12.9 (c = 0.35, $CHCl_3$)

IR (thin film) 2967, 2932, 1714, 1652, 1458, 1368, 1319 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.79 (m, 1H), 5.71 (d, 1H, J = 15.5 Hz), 4.71 (s, 2H), 2.46 (m, 2H), 3.50 (t, 2H, J = 4.6 Hz), 3.34 (s, 3H), 3.01 (t, 1H, J = 5.4 Hz), 2.43 (m, 1H), 1.93 (m, 1H), 1.81 (m, 2H), 1.43 (s, 9H), 0.91 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.3, 147.7, 124.5, 98.0, 89.4, 80.3, 72.1, 68.0, 59.4, 35.5, 35.2, 30.7, 28.5 (3C), 20.7, 17.7, 17.4

(*E*)-(5*S*, 6*R*)-6-Methoxymethoxy-5,7-dimethyloct-2-enoic acid *tert*-butyl ester (72c)



70 **72c**

To a solution of compound **70** (0.20 g, 0.83 mmol) in CH_2Cl_2 (8 mL) were added DIPEA (0.83 mL, 5.0 mmol) and MOMCl (0.18 mL, 2.5 mmol) at 0 °C. The mixture was then stirred at room temperature for 18 h before being quenched with a solution of saturated NH_4Cl. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), the combined organic layers were dried over Na_2SO_4 and filtered. After concentration, purification by flash chromatography (10% EtOAc/hexanes) afforded product **72c** (0.19 g, 82%) as a colorless oil.

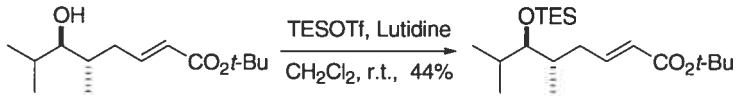
$[\alpha]_D$ -12.7 (c = 0.26, $CHCl_3$)

IR (thin film) 2930, 1715, 1651, 1462, 1368, 1319, 1154 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.83 (m, 1H), 5.74 (d, 1H, J = 15.5 Hz), 4.63 (s, 2H), 3.38 (s, 3H), 3.00 (t, 1H, J = 5.4 Hz), 2.46 (m, 1H), 1.97 (m, 1H), 1.83 (m, 2H), 1.46 (s, 9H), 0.91 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4, 147.7, 124.5, 99.2, 89.5, 80.4, 56.4, 35.5, 35.2, 30.7, 28.5 (3C), 20.7, 17.8, 17.4

(*E*)-(5*S*, 6*R*)-5,7-Dimethyl-6-triethylsilanoxyoct-2-enoic acid *tert*-butyl ester (72d)



70 **72d**

To a solution of compound **70** (0.097 g, 0.40 mmol) in CH_2Cl_2 (5 mL) were added lutidine (0.14 mL, 1.2 mmol) and TES-OTf (0.14 mL, 0.60 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h and was subsequently quenched with saturated NH_4Cl. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), and dried over Na_2SO_4. After concentration the residue was

purified by flash chromatography to yield product **72d** (0.10 g, 44%) as a colorless oil.

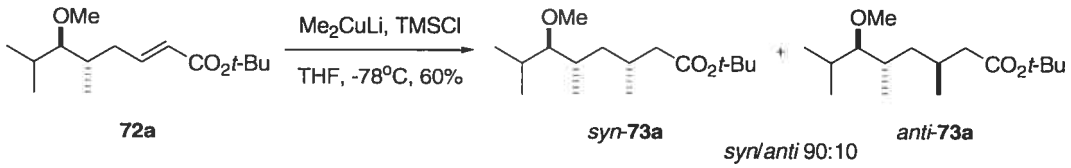
$[\alpha]_D$ -5.9 (c = 0.35, $CHCl_3$)

IR (thin film) 2960, 2878, 1716, 1653, 1460, 1367, 1318 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.87 (m, 1H), 5.76 (d, 1H, J = 15.5 Hz), 3.26 (t, 1H, J = 4.9 Hz), 2.45 (m, 1H), 1.93 (m, 1H), 1.78 (m, 2H), 1.50 (s, 9H), 1.01 (m, 9H), 0.90 (t, 9H, J = 6.3 Hz), 0.64 (q, 6H, J = 7.9 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.5, 148.2, 124.3, 82.4, 80.3, 36.7, 35.2, 31.7, 28.6 (3C), 20.7, 18.2, 17.6, 7.5 (3C), 6.0 (3C)

(3*R*, 5*S*, 6*R*)-6-Methoxy-3,5,7-trimethyloctanoic acid *tert*-butyl ester (73a)



Compound **72a** (0.069 g, 0.27 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**73a** and *anti*-**73a** (0.044 g, 60% combined yield) in a ratio of 90:10 *syn*/*anti*.

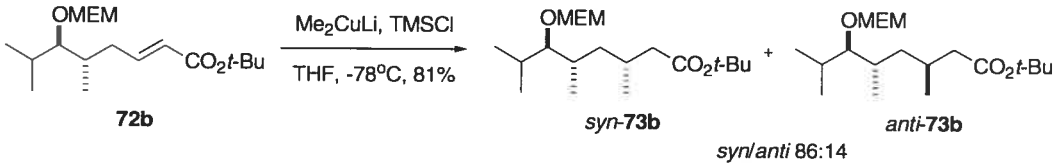
$[\alpha]_D$ -19.7 (c = 1.16, $CHCl_3$)

IR (thin film) cm^{-1} 2966, 2361, 1715, 1367

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.46 (s, 3H), 2.60 (m, 1H), 2.31 (dd, 1H, J = 4.5, 14.3 Hz), 2.12 (m, minor), 2.02 (m, 1H), 1.83 (m, 2H), 1.69 (m, 1H), 1.46 (s, 9H), 1.41 (m, 1H), 1.30 (m, minor), 1.19 (m, minor), 1.09 (m, 1H), 0.94 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.6 (172.3), 92.0 (91.9), 80.0 (2C), 61.4 (61.3), (44.2) 41.6, 38.3 (37.7), 32.7 (32.6), 30.2 (29.3), 27.7 (3C), 21.0, 20.0 (19.9), (18.3) 17.7, 16.9 (16.4)

(3*R*, 5*S*, 6*R*)-6-(2-Methoxy-ethoxymethoxy)-3,5,7-trimethyloctanoic acid *tert*-butyl ester (73b)



72b *syn*-**73b** *anti*-**73b**

syn/*anti* 86:14

Compound **72b** (0.10 g, 0.30 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**73b** and *anti*-**73b** (0.085 g, 81% combined yield) in a ratio of 86:14 *syn*/*anti*.

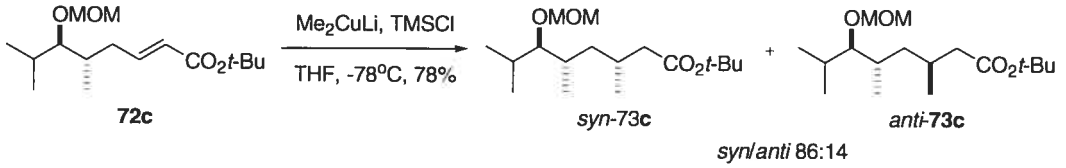
$[\alpha]_D$ -17.2 (c = 0.93, $CHCl_3$)

IR (thin film) 2962, 2931, 2876, 1729, 1459, 1367, 1257cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.74 (d, 1H, J = 6.9 Hz), 4.71 (d, 1H, J = 7.0 Hz), 3.72 (m, 2H), 3.53 (t, 2H, J = 4.7 Hz), 3.36 (s, 3H), 3.00 (t, 1H, J = 5.3 Hz), 2.26 (dd, 1H, J = 4.4, 14.3 Hz), 1.96 (m, 1H), 1.81 (m, 2H), 1.69 (m, 1H), 1.42 (s, 9H), 1.07 (m, 2H), 0.91 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.2 (172.9), 97.9, 97.8, (90.4) 89.9, 80.3, 72.1, 67.9, 59.4, (44.9) 42.4, 39.5 (38.7), 33.3 (33.1), (30.6) 30.5, 28.5 (3C), 21.7, 20.9 (20.7), (19.1) 18.7, 17.6 (17.2)

(3*R*, 5*S*, 6*R*)-6-Methoxymethoxy-3,5,7-trimethyloctanoic acid *tert*-butyl ester (73c)



72c *syn*-73**c** *anti*-**73c**

syn/*anti* 86:14

Compound **72c** (0.10 g, 0.35 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes

afforded the products *syn*-**73c** and *anti*-**73c** (0.083 g, 78% combined yield) in a ratio of 86:14 *syn*/*anti*.

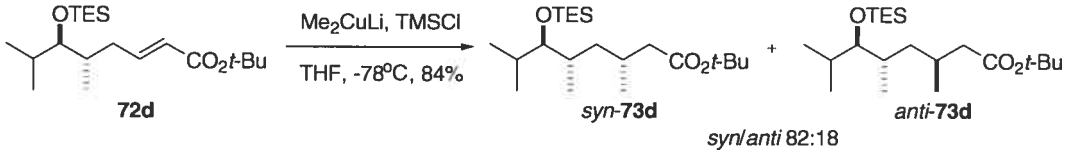
[α]$_D$ -22.1 (*c* = 1.51, $CHCl_3$)

IR (thin film) 2962, 1730, 1462, 1367 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.68 (d, 1H, *J* = 6.7 Hz), 4.66 (d, 1H, *J* = 6.7 Hz), 3.42 (s, 3H), 3.01 (t, 1H, *J* = 4.8 Hz), 2.31 (dd, 1H, *J* = 4.9, 14.3 Hz), 2.02 (m, 1H), 1.86 (m, 2H), 1.75 (m, 1H), 1.47 (s, 9H), 1.44 (m, 1H), 1.11 (m, 1H), 0.96 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.2 (172.9), (99.0) 98.9, (90.6) 90.1, 80.4, 56.4, 42.5, 39.5 (38.6), (33.3) 33.0, (30.6) 30.5, 28.5, 21.7 (3C), 20.9 (20.7), 19.1, (18.7) 18.7, 17.6 (17.2)

(3*R*, 5*S*, 6*R*)-3,5,7-Trimethyl-6-triethylsilanyloxyoctanoic acid *tert*-butyl ester (73d)



Compound **72d** (0.10 g, 0.28 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**73d** and *anti*-**73d** (0.088 g, 84% combined yield) in a ratio of 86:14 *syn*/*anti*.

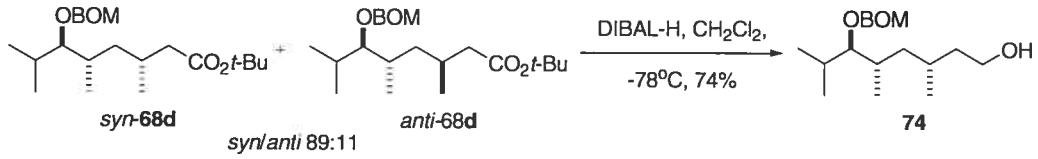
[α]$_D$ -5.9 (*c* = 0.35, $CHCl_3$)

IR (thin film) 2960, 1732, 1460, 1367 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.21 (t, 1H, *J* = 4.9 Hz), 2.31 (dd, 1H, *J* = 4.4, 14.2 Hz), 1.98 (m, 1H), 1.86 (m, 1H), 1.76 (m, 1H), 1.63 (m, 2H), 1.47 (s, 9H), 1.41 (m, 1H), 0.99 (m, 12H), 0.90 (m, 9H), 0.63 (q, 6H, *J* = 7.9 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.8 (172.4), (82.6) 82.2, 79.7, (44.5) 42.0, 39.1 (38.3), 34.2 (33.8), (30.8) 30.7, 28.1, 27.8 (3C), 21.2, 20.5 (20.3), (18.6) 18.0, 17.0 (16.4), 7.0 (3C), 5.4 (3C)

(3*R*, 5*S*, 6*R*)-6-Benzyloxymethoxy-3,5,7-trimethyloctan-1-ol (74)



Following general procedure A, the diastereomeric mixture of compounds *syn*-**68d** and *anti*-**68d** (1.04 g, 2.76 mmol) was reduced to give a mixture of diastereomeric alcohols. Careful chromatographic separation provided alcohol **74** (0.63 g, 74%) as a colorless oil.

$[\alpha]_D$ -20.6 (c = 0.73, $CHCl_3$)

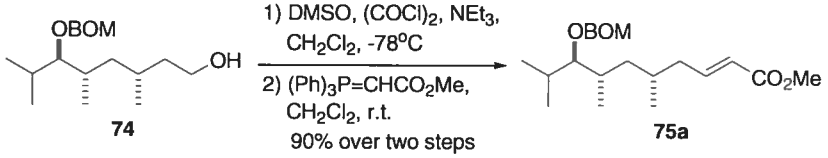
IR (thin film) 3402 2960, 2931, 2875, 1456, 1382, 1158 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 5H), 4.85 (d, 1H, J = 6.9 Hz), 4.81 (d, 1H, J = 6.9 Hz), 4.71 (d, 1H, J = 11.9 Hz), 4.67 (d, 1H, J = 11.9 Hz), 3.70 (m, 2H), 3.11 (t, 1H, J = 5.3 Hz), 1.87 (m, 2H), 1.69 (m, 2H), 1.49 (m, 2H), 1.27 (m, 1H), 1.10 (m, 1H), 0.97 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 138.5, 128.8 (2C), 128.1 (2C), 128.0, 97.0, 90.3, 70.5, 61.5, 40.3, 39.0, 33.4, 30.6, 27.7, 21.5, 21.1, 18.8, 17.8

HRMS (ESI) m/z 331.2238 (calcd for 331.2243 $C_{19}H_{32}O_3Na$)

(*E*)-(5*S*, 7*S*, 8*R*)-8-Benzyloxymethoxy-5,7,9-trimethyldec-2-enoic acid methyl ester (75a)



Following general procedure E, alcohol **74** (0.20 g, 0.65 mmol) provided product **75a** (0.21, 90% over two steps) after flash chromatographic purification with 2% EtOAc/hexanes.

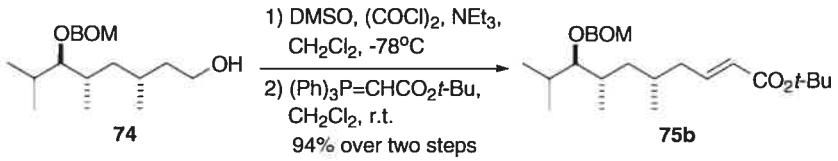
$[\alpha]_D$ -13.5 (c = 1.14, $CHCl_3$)

IR (thin film) 2959, 1726, 1458, 1382 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33(m, 5H), 6.98 (m, 1H), 5.85 (d, 1H, J = 15.6 Hz), 4.84 (d, 1H, J = 6.9 Hz), 4.80 (d, 1H, J = 6.9 Hz), 4.70 (d, 1H, J = 11.9 Hz), 4.66 (d, 1H, J = 11.9 Hz), 3.73 (s, 3H), 3.10 (t, 1H, J = 5.2 Hz), 2.31 (m, 1H), 1.84 (m, 4H), 1.50 (m, 1H), 1.12 (m, 1H), 0.96 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.6, 148.1, 137.7, 128.0 (2C), 127.3 (2C), 127.2, 121.8, 96.2, 89.4, 69.7, 51.9, 38.8, 38.0, 32.7, 29.8, 29.8, 20.6, 20.3, 18.0, 17.0

(*E*)-(5*S*, 7*S*, 8*R*)-8-Benzyloxymethoxy-5,7,9-trimethyldec-2-enoic acid *tert*-butyl ester (75b)



74 **75b**

Following general procedure E, alcohol **74** (1.01 g, 3.27 mmol) provided product **75b** ((*E*)- 1.07 g, (*Z*)- 0.150 g, 94%) after flash chromatographic purification with 2% EtOAc/hexanes.

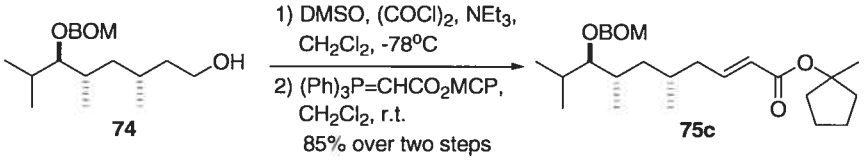
$[\alpha]_D$ -9.1 (c = 0.63, $CHCl_3$)

IR (thin film) 2961, 2931, 1715, 1653, 1457, 1368, 1321, 1256 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.36 (m, 5H), 6.87 (m, 1H), 5.78 (d, 1H, J = 15.5 Hz), 4.85 (d, 1H, J = 6.7 Hz), 4.82 (d, 1H, J = 6.8 Hz), 4.71 (d, 1H, J = 11.9 Hz), 4.68 (d, 1H, J = 11.9 Hz) 3.12 (t, 1H, J = 5.2 Hz), 2.31 (m, 1H), 1.97-1.90 (m, 3H), 1.64 (m, 1H), 1.52 (s, 9H), 1.53-1.52 (m, 1H), 1.14 (m, 1H), 0.99 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4, 147.2, 138.5, 128.7 (2C), 128.1 (2C), 128.0, 124.7, 97.0, 90.2, 80.3, 70.5, 39.5, 38.6, 33.4, 30.6, 30.5, 28.6 (3C), 21.5, 21.0, 18.8, 17.8

(*E*)-(5*S*, 7*S*, 8*R*)-8-Benzyloxymethoxy-5,7,9-trimethyldec-2-enoic acid 1-methylcyclopentyl ester (75c)



Following general procedure E, alcohol **74** (0.35 g, 0.30 mmol) provided product **75c** ((*E*)- 0.11 g, (*Z*)- 0.010 g, 85%) after flash chromatographic purification with 2% EtOAc/hexanes.

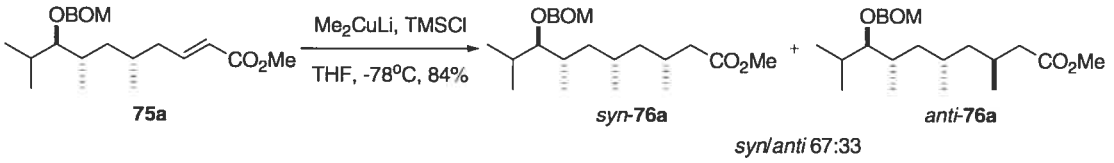
$[\alpha]_D$ -11.2 (c = 1.10, $CHCl_3$)

IR (thin film) 2962, 2874, 1714, 1653, 1498, 1455, 1375, 1321 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 5H), 6.86 (m, 1H), 5.77 (d, 1H, J = 15.6 Hz), 4.84 (d, 1H, J = 6.9 Hz), 4.80 (d, 1H, J = 6.9 Hz), 4.70 (d, 1H, J = 11.9 Hz), 4.66 (d, 1H, J = 11.9 Hz), 3.10 (m, 1H), 2.28 (m, 1H), 2.13 (m, 2H), 1.87 (m, 3H), 1.73 (m, 5H), 1.65 (m, 2H), 1.59 (s, 3H), 1.48 (m, 1H), 1.11 (m, 1H), 0.95 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.7, 146.5, 137.7, 128.0 (2C), 127.3 (2C), 127.2, 123.8, 96.2, 89.4, 89.1, 69.7, 38.8, 38.8, 38.7, 37.8, 32.6, 29.8, 29.7, 24.1, 23.4 (2C), 20.7, 20.2, 18.1, 17.0

(3*R*, 5*S*, 7*S*, 8*R*)-8-Benzyloxymethoxy-3,5,7,9-tetramethyldecanoic acid methyl ester (76a)



Compound **75a** (0.22 g, 0.61 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**76a** and *anti*-**76a** (0.26 g, 93% combined yield) in a ratio of 67:33 *syn*/*anti*.

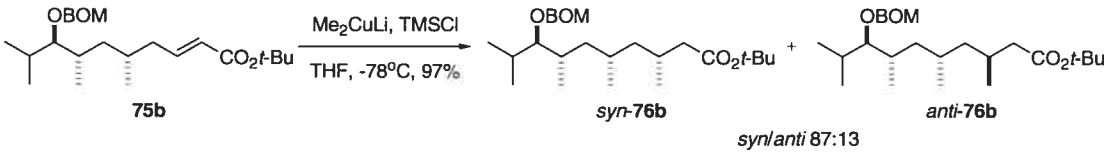
[α]$_D$ -26.2 (*c* = 0.98, $CHCl_3$)

IR (thin film) 2959, 1740, 1462 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.34 (m, 5H), 4.84 (d, 1H, *J* = 6.9 Hz), 4.81 (d, 1H, *J* = 6.9 Hz), 4.70 (d, 1H, *J* = 11.9 Hz), 4.67 (d, 1H, *J* = 11.9 Hz), 3.68 (s, 3H), 3.11 (m, 1H), 2.38 (dd, 1H, *J* = 3.9, 13.7 Hz), 2.22 (m, 1H), 2.04 (m, 2H), 1.89 (m, 1H), 1.56 (m, 2H), 1.38 (m, 2H), 1.08 (m, 1H), 0.94 (m, 15H)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 173.3 (173.2), 137.7, 128.0 (2C), 127.4 (2C), 127.2, (96.2) 96.1, (89.4) 89.2, 69.6, 51.0, 43.3 (42.5), 40.4, (39.9) 39.7, 32.6 (32.4), 29.8, 29.7, 27.5 (27.1), 20.9, 20.8, 20.3, (18.6) 18.1, 17.0 (16.8)

(3*R*, 5*S*, 7*S*, 8*R*)-8-Benzyloxymethoxy-3,5,7,9-tetramethyldecanoic acid *tert*-butyl ester (76b)



Compound **75b** (0.055 g, 0.14 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**76b** and *anti*-**76b** (0.054 g, 97% combined yield) in a ratio of 87:13 *syn*/*anti*.

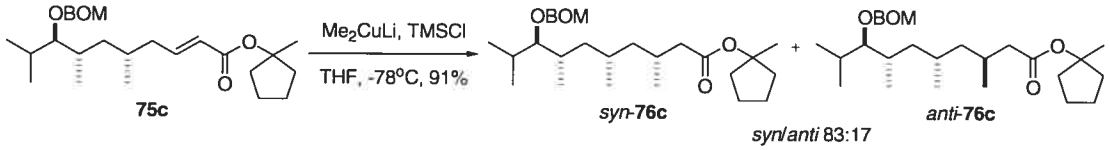
[α]$_D$ -21.1 (*c* = 1.10, $CHCl_3$)

IR (thin film) 2961, 2931, 2874, 1729, 1456 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.33 (m, 5H), 4.85 (d, 1H, *J* = 6.9 Hz), 4.81 (d, 1H, *J* = 6.9 Hz), 4.71 (d, 1H, *J* = 11.9 Hz), 4.67 (d, 1H, *J* = 11.9 Hz), 3.12 (t, 1H, *J* = 5.1 Hz), 2.29 (dd, 1H, *J* = 4.8, 14.3 Hz), 2.08 (m, 1H), 1.85 (m, 3H), 1.47 (s, 9H), 1.33 (m, 2H), 1.08 (m, 2H), 0.94 (m, 16H)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 173.2 (172.9), 138.0, 128.2 (2C), 127.6 (2C), 127.4, 96.3, (90.3) 90.0, 79.8, 69.9, (44.7) 44.2, (43.1) 42.8, 40.0, 33.4 (33.1), 29.9 (2C), 28.0 (3C), 27.6, 21.1, 20.9, 20.6, (19.3) 18.9, 17.8 (17.5)

(3*R*, 5*S*, 7*S*, 8*R*)-8-Benzyloxymethoxy-3,5,7,9-tetramethyldecanoic acid 1-methylcyclopentyl ester (76c)



Compound **75c** (0.073 g, 0.17 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**76c** and *anti*-**76c** (0.069 g, 91% combined yield) in a ratio of 83:17 *syn*/*anti*.

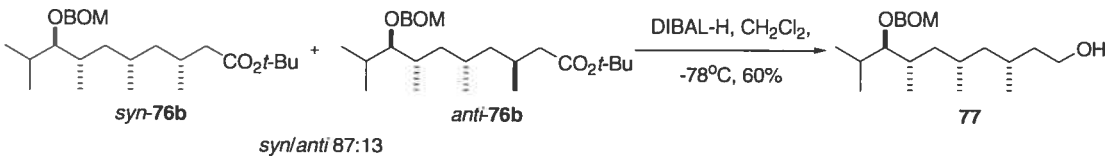
[α]$_D$ -18.2 (*c* = 1.20, $CHCl_3$)

IR (thin film) 2960, 2874, 1728, 1462 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.33 (m, 5H), 4.84 (d, 1H, *J* = 6.9 Hz), 4.81 (d, 1H, *J* = 6.9 Hz), 4.17 (d, 1H, *J* = 11.9 Hz), 4.67 (d, 1H, *J* = 11.9 Hz), 3.12 (m, 1H), 2.30 (dd, 1H, *J* = 4.7, 14.2 Hz), 2.09 (m, 4H), 1.64 (m, 2H), 1.71 (m, 6H), 1.57 (s, 3H), 1.45 (m, 1H), 1.31 (m, 1H), 1.20 (m, 1H), 1.07 (m, 2H), 0.94 (m, 15H)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 172.6 (172.3), 137.7, 128.0 (2C), 127.4 (2C), 127.2, (96.2) 96.1, (89.6) 89.2, 69.6, (43.9) 43.4, (42.5) 41.9, (39.9) 39.8, 38.7, 38.7, 32.6 (32.4), (29.8) 29.7, 27.7 (27.6), 27.4 (27.0), 24.0, 23.4, 20.9, 20.7, 20.4, 20.4, 20.3, (18.6) 18.1, 17.0 (16.8)

(3*R*, 5*S*, 7*S*, 8*R*)-8-Benzyloxymethoxy-3,5,7,9-tetramethyl-decan-1-ol (77)



Following general procedure A, the diastereomeric mixture of compounds *syn*-**76b** and *anti*-**76b** (0.23 g, 0.54 mmol) was reduced to give a mixture of diastereomeric alcohols. Careful chromatographic purification (2% EtOAc/hexanes) provided alcohol **77** (0.11 g, 60%) as a colorless oil.

[α]$_D$ -24.1 (*c* = 0.98, $CHCl_3$)

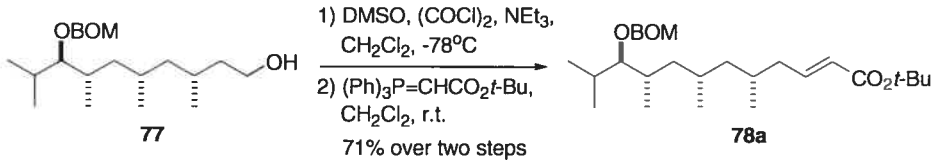
IR (thin film) 3400, 2959, 2929, 1456, 1380 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.33 (m, 5H), 4.85 (d, 1H, *J* = 6.9 Hz), 4.81 (d, 1H, *J* = 6.9 Hz), 4.69 (d, 1H, *J* = 11.9 Hz), 4.67 (d, 1H, *J* = 11.9 Hz), 3.69 (m, 2H), 3.12 (t, 1H, *J* = 5.1 Hz), 1.87 (m 2H), 1.65 (m, 3H), 1.44 (m, 2H), 1.28 (m, 2H), 1.04 (m, 1H), 0.93 (m, 16H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.7, 128.0 (2C), 127.4 (2C), 127.2, 96.1, 89.3, 69.7, 60.8, 44.1, 39.9, 38.6, 32.7, 29.7, 27.4, 26.7, 21.1, 20.5, 20.4, 18.1, 17.1

HRMS (ESI) *m/z* 373.27132 (calcd for 373.27079 $C_{22}H_{38}O_3Na$)

(*E*)-(5*R*, 7*S*, 9*S*, 10*R*)-10-Benzyloxymethoxy-5,7,9,11-tetramethyldodec-2-enoic acid *tert*-butyl ester (78a)



Following general procedure E, alcohol **77** (0.075 g, 0.21 mmol) provided product **78a** (0.068, 71% over two steps) after flash chromatographic purification with 2% EtOAc/hexanes.

[α]$_D$ -17.9 (*c* = 1.02, $CHCl_3$)

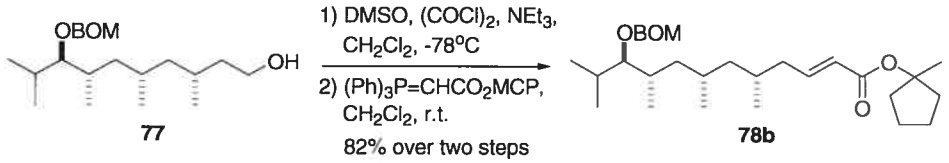
IR (thin film) 2960, 2930, 1715, 1653, 1457, 1368, 1321, 1288, 1250, 1158 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32 (m, 5H), 6.89 (m, 1H), 5.76 (d, 1H, *J* = 15.5 Hz), 4.85 (d, 1H, *J* = 6.9 Hz), 4.81 (d, 1H, *J* = 6.9 Hz), 4.71 (d, 1H, *J* = 11.9 Hz),

4.67 (d, 1H, J = 11.9 Hz), 3.11 (t, 1H, J = 5.1 Hz), 2.24 (m, 1H), 1.86 (m, 4H), 1.57 (m, 1H), 1.50 (s, 9H), 1.42 (m, 1H), 1.32 (m, 1H), 1.06 (m, 1H), 0.93 (m, 16H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.6, 146.3, 137.7, 128.0 (2C), 127.4 (2C), 127.2, 123.9, 96.1, 89.3, 79.6, 69.7, 43.2, 39.8, 38.0, 32.6, 29.7, 29.5, 27.9 (3C), 27.4, 20.9, 20.5, 20.4, 18.1, 17.1

(*E*)-(5*R*, 7*S*, 9*S*, 10*R*)-10-Benzyloxymethoxy-5,7,9,11-tetramethyldodec-2-enoic acid 1-methylcyclopentyl ester (78b)



77 78b

Following general procedure E, alcohol **77** (0.14 g, 0.30 mmol) provided product **78a** (0.11, 82% over two steps) after flash chromatographic purification with 2% EtOAc/hexanes.

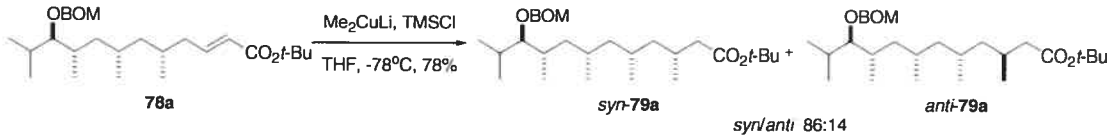
$[\alpha]_D$ -15.2 (c = 0.92, $CHCl_3$)

IR (thin film) 2958, 1714, 1652, 1456, 1375, 1321, 1168, 1121, 1040 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36 (m, 5H), 6.87 (m, 1H), 5.77 (d, 1H, J = 15.6 Hz), 4.85 (d, 1H, J = 6.9 Hz), 4.81 (d, 1H, J = 6.9 Hz), 4.71 (d, 1H, J = 11.9 Hz), 4.67 (d, 1H, J = 11.9 Hz), 3.11 (m, 1H), 2.25 (m, 1H), 2.12 (m, 2H), 1.98-1.87 (m, 2H), 1.85-1.68 (m, 6H), 1.65 (m, 3H), 1.60 (s, 3H), 1.42 (m, 1H), 1.32 (m, 1H), 1.07 (m, 1H), 1.87 (m 16H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.7, 146.4, 137.7, 128.0 (2C), 127.4 (2C), 127.2, 123.8, 96.10, 89.3, 89.1, 69.6, 43.2, 39.8, 38.8 (2C), 38.0, 32.6, 29.7, 29.5, 27.4, 24.1, 23.4 (2C), 20.3, 20.5, 20.4, 18.1, 17.1

(3*R*, 5*R*, 7*S*, 9*S*, 10*R*)-10-Benzyloxymethoxy-3,5,7,9,11-pentamethyldodecanoic acid *tert*-butyl ester (79a)



Compound **78a** (0.067 g, 0.15 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**79a** and *anti*-**79a** (0.057 g, 78% combined yield) in a ratio of 86:14 *syn/anti*.

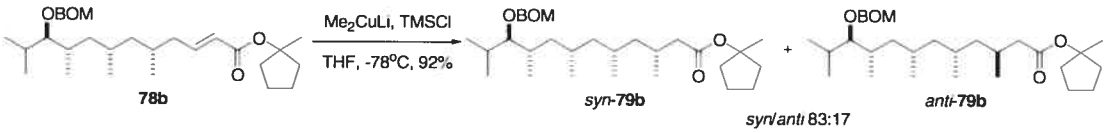
$[\alpha]_D$ -19.5 (c = 1.20, $CHCl_3$)

IR (thin film) 2960, 2930, 1730, 1456, 1367 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.34 (m, 5H), 4.85 (d, 1H, J = 6.9 Hz). 4.81 (d, 1H, J = 6.9 Hz), 4.70 (d, 1H, J = 11.9 Hz), 4.67 (d, 1H, J = 11.9 Hz), 3.12 (m, 1H), 2.28 (dd, 1H, J = 4.9, 14.2 Hz), 2.02 (m, 1H), 1.89 (m, 2H). 1.82 (m, 1H), 1.57 (m, 1H), 1.47 (s, 9H), 1.40 (m, 1H), 1.26 (m, 3H), 1.04 (m, 1H), 0.99-0.87 (m, 19H)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 172.5 (172.2), 137.8, 128.0 (2C), 127.4 (2C), 127.2, 96.1, (89.3) 89.2, 79.5, 69.6, (44.6) 44.4, (44.0) 43.7, 39.8, 32.7 (32.6), 29.7, (29.7) 29.6, 27.8 (3C), 27.7, 27.4, 27.3, 21.2, (20.9) 20.9, 20.6, 20.4, (18.7) 18.2, 17.0 (16.8)

(3*R*, 5*R*, 7*S*, 9*S*, 10*R*)-10-Benzyloxymethoxy-3,5,7,9,11-pentamethyldodecanoic acid 1-methylcyclopentyl ester (79b)



Compound **78b** (0.10 g, 0.21 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**79b** and *anti*-**79b** (0.094 g, 92% combined yield) in a ratio of 83:17 *syn/anti*.

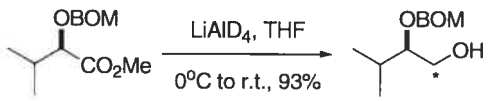
$[\alpha]_D$ -23.9 (c = 1.43, $CHCl_3$)

IR (thin film) 2960, 2874, 1729, 1456, 1376 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.34 (m, 5H), 4.85 (d, 1H, J = 6.9 Hz), 4.81 (d, 1H, J = 6.9 Hz), 4.71 (d, 1H, J = 11.9 Hz), 4.67 (d, 1H, J = 11.9 Hz), 3.12 (m, 1H), 2.30 (dd, 1H, J = 4.8, 14.2 Hz), 2.07 (m, 4H), 1.89 (m, 3H), 1.74-1.60 (m, 7H), 1.57 (s, 3H), 1.43 (m, 1H), 1.29 (m, 2H), 1.03 (m, 1H), 0.97 (m, 12H), 0.90 (m, 8H)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 172.8 (172.6), 138.0, 132.1, 128.2 (2C), 127.6 (2C), 127.4, 96.2, 89.3, 69.8, (44.8) 44.6, (44.1) 44.0, (43.0) 42.2, 40.0, 39.0, 38.9, 32.9 (32.8), 29.9, 27.9 (27.9), 27.6 (27.3), 27.5 (27.2), 24.2, 23.6 (2C), 21.5, (21.2) 21.1 20.8, 20.7, (18.9) 18.4, 17.3 (17.2)

(2*R*)-2-Benzyloxymethoxy-3-methylbutan-1-ol (80)



80

A solution of the methyl ester (0.998 g, 3.96 mmol) in THF (20 mL) cooled to 0 °C was charged with $LiAlD_4$ (0.170 g, 3.96 mmol). The reaction mixture was stirred at room temperature for 4 h before being quenched with a saturated solution of NH_4Cl. The resulting precipitate was filtered over a pad of celite and concentrated. Flash chromatographic purification with 20% EtOAc/hexanes afforded the deuterium labeled alcohol **80** (0.84 g, 93%) as a colorless oil.

$[\alpha]_D$ -60.5 (c = 1.07, $CHCl_3$)

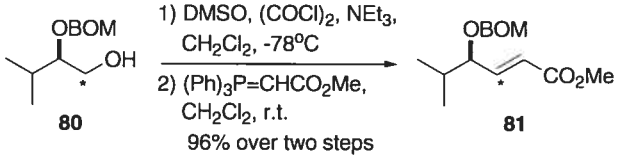
IR (thin film) 3440, 2962, 2877, 1455 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.36 (m, 5H), 4.96 (d, 1H, J = 6.9 Hz), 4.78 (d, 1H, J = 6.9 Hz), 4,77 (d, 1H, J = 11.7 Hz), 4.65 (d, 1H, J = 11.7 Hz), 3.38 (d, 1H, J = 5.8 Hz), 3.06 (brs, 1H), 1.89 (m, 1H), 0.98 (d, 3H, J = 5.7 Hz), 0.96 (d, 3H, J = 5.7 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 136.9, 128.2 (2C), 127.7, 127.6 (2C), 95.4, 87.1, 69.7, 62.6 (quin, J = 21.4 Hz), 29.8, 18.4, 17.9

HRMS (ESI) *m*/z 249.14302 (calcd for 249.14254 $C_{13}H_{18}D_2O_3Na$)

(*E*)-(4*R*)-4-Benzyloxymethoxy-5-methylhex-2-enoic acid methyl ester (81)



80 81

Following general procedure E, alcohol **80** (0.865 g, 3.84 mmol), provided product **81** ((*E*)- 0.82 g, (*Z*)- 0.13 g, 96%) after flash chromatographic purification (2% EtOAc/hexanes).

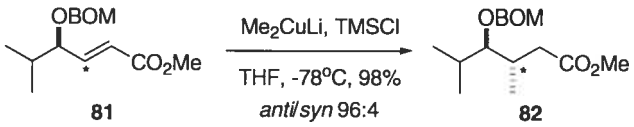
[α]$_D$ +102.7 (*c* = 1.13, $CHCl_3$)

IR (thin film) 2961, 1726, 1643, 1436 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 5H), 6.01 (s, 1H), 4.74 (m, 3H), 4.58 (d, 1H, *J* = 11.7 Hz), 4.06 (d, 1H, *J* = 5.6 Hz), 3.77 (s, 3H), 1.92 (m, 1H), 1.01 (d, 3H, *J* = 6.8 Hz), 0.96 (d, 3H, *J* = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.2, 146.1 (t, *J* = 23.6 Hz), 137.3, 128.1 (2C), 127.5 (2C), 127.4, 122.2, 92.4, 80.0, 69.4, 51.3, 32.2, 17.2 (2C)

(3*S*, 4*R*)-4-Benzyloxymethoxy-3,5-dimethylhexanoic acid methyl ester (82)



81 82

Compound **81** (0.721 g, 2.59 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded product **82** (0.75 g, 98%) in a ratio of 96:4 *anti*/*syn*.

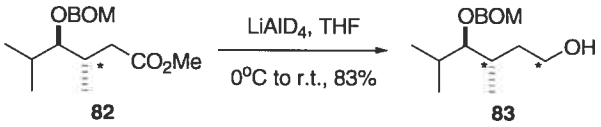
[α]$_D$ -16.3 (*c* = 1.17, $CHCl_3$)

IR (thin film) 2962, 1738, 1455 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 (m, 5H), 4.82 (d, 1H, J = 6.9 Hz), 4.79 (d, 1H, J = 6.9 Hz), 4.70 (d, 1H, J = 11.8 Hz), 4.65 (d, 1H, J = 11.8 Hz), 3.77 (s, minor), 1.99 (s, 3H), 3.19 (d, J = 7.5 Hz, minor), 3.15 (d, 1H, J = 5.3 Hz), 2.64 (d, 1H, J = 15.3 Hz), 2.55 (d, J = 15.7 Hz, minor), 2.29 (d, J = 15.5 Hz, minor), 2.18 (d, 1H, J = 15.3 Hz), 1.86 (m, 1H), 0.97 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.8, 137.5, 128.1 (2C), 127.4 (2C), 127.3, 96.4, 88.5, 69.8, 51.1, 36.7, 32.1 (t, J = 19.5 Hz), 30.1, 19.8, 17.4, 17.3

(3*S*, 4*R*)-4-Benzyloxymethoxy-3,5-dimethylhexan-1-ol (83)



82 83

A solution of ester **82** (0.10 g, 0.38 mmol) in THF (5 mL) cooled to 0 °C was charged with $LiAlD_4$ (0.016 g, 0.38 mmol). The reaction mixture was stirred at room temperature for 4 h before being quenched with a solution of saturated NH_4Cl. The resulting precipitate was filtered over a pad of celite, and the filtrate was concentrated. Flash chromatographic purification with 10% EtOAc/hexanes afforded the deuterium labeled alcohol **83** (0.083 g, 79%) as a colorless oil.

$[\alpha]_D$ -20.0 (c = 0.89, $CHCl_3$)

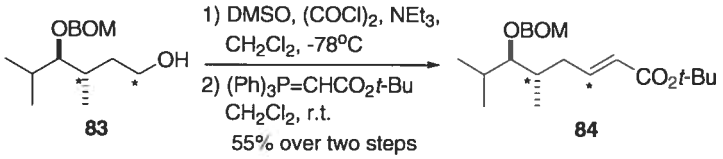
IR (thin film) 3404, 2961, 1455 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33 (m, 5H), 4.86 (d, 1H, J = 6.9 Hz), 4.83 (d, 1H, J = 6.9 Hz), 4.72 (d, 1H, J = 11.8 Hz), 4.67 (d, 1H, J = 11.8 Hz), 3.15 (d, 1H, J = 6.2 Hz), 2.40 (brs, 1H), 1.94 (m, 1H), 1.78 (d, 1H, J = 14.0 Hz), 1.54 (d, 1H, J = 14.0 Hz), 0.97 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.5, 128.1 (2C), 127.4 (2C), 127.3, 96.3, 89.5, 69.9, 59.4 (quin, J = 22.1 Hz), 33.7, 31.6 (t, J = 19.4 Hz), 30.1, 19.9, 18.0, 16.7

HRMS (ESI) m/z 292.19625 (calcd for 292.19591 $C_{16}H_{23}D_3O_3Na$)

(*E*)-(*5S*, *6R*)- 6-Benzyloxymethoxy-5,7-dimethyloct-2-enoic acid *tert*-butyl ester (84)



83 84

Following general procedure E, alcohol **83** (0.082 g, 0.30 mmol) provided product **84** (0.060 g, 55%) after flash chromatographic purification (2% EtOAc/hexanes).

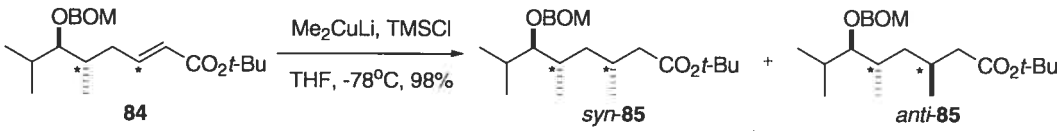
[α]$_D$ -13.2 (*c* = 1.18, $CHCl_3$)

IR (thin film) 2963, 1728, 1456, 1367 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.34 (m, 5H), 5.78 (s, 1H), 4.83 (d, 1H, *J* = 6.9 Hz), 4.81 (d, 1H, *J* = 6.9 Hz), 4.70 (d, 1H, *J* = 11.9 Hz), 4.66 (d, 1H, *J* = 11.9 Hz), 3.12 (d, 1H, *J* = 5.1 Hz), 2.53 (d, 1H, *J* = 14.3 Hz), 2.02 (d, 1H, *J* = 14.3 Hz), 1,92 (m, 1H), 1.51 (s, 9H), 0.95 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.7, 146.6 (t, *J* = 23.7 Hz), 137.5, 128.1 (2C), 127.4 (2C), 127.3, 123.7, 96.4, 88.8, 79.63, 69.8, 34.4 (t, *J* = 19.2 Hz), 34.3, 30.5, 27.8 (3C), 20.0, 17.2, 16.7

(*3R*, *5S*, *6R*)-6-Benzyloxymethoxy-3,5,7-trimethyloctanoic acid *tert*-butyl ester (85)



84 *syn*-85 *anti*-85

syn/*anti* 86:14

Compound **84** (0.060 g, 0.11 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**85** and *anti*-**85** (0.062 g, 98% combined yield) in a ratio of 86:14 *syn*/*anti*.

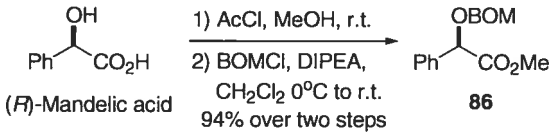
$[\alpha]_D$ -15.4 (c = 1.08, $CHCl_3$)

IR (thin film) 2963, 1723, 1455 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.33 (m, 5H), 1.84 (d, 1H, J = 6.9 Hz), 4.80 (d, 1H, J = 6.9 Hz), 4.10 (d, 1H, J = 11.9 Hz), 4.66 (d, 1H, J = 11.9 Hz), 3.10 (d, 1H, J = 6.0 Hz), 2.31 (d, 1H, J = 14.5 Hz), 1.90 (m, 2H), 1.47 (s, 10H), 1.12 (d, 1H, J = 13.7 Hz), 0.99 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 172.5 (172.2), 137.7, 128.0 (2C), 127.4 (2C), 127.2, (96.3) 96.2, (89.8) 89.4, 79.6, 69.7, (44.0) 41.6, 38.6 (37.8), 32.2 (t, J = 18.6 Hz), (29.9) 29.8, 27.7 (3C), 27.4 (t, J = 19.7 Hz), 20.8, 20.2 (20.0), (18.2) 18.1, 16.8 (16.4)

R-Benzyloxymethoxyphenylacetic acid methyl ester (86)



A solution of (*R*)-mandelic acid (4.00 g, 26.3 mmol) in MeOH (30 mL) cooled to 0 °C was charged with AcCl (0.930 mL, 13.1 mmol) and stirred at room temperature for 24 h. The reaction mixture was quenched with the addition of a solution of saturated NH_4Cl. Extraction with EtOAc (3 x 10 mL), was followed by dying over Na_2SO_4, filtration and concentration of the volatiles. A solution of the crude hydroxy ester in CH_2Cl_2 (50 mL) was cooled to 0 °C and charged with DIPEA (27.5 mL, 157.7 mmol) followed by the drop wise addition of BOMCl (18.30 mL, 78.87 mmol). The mixture was stirred at room temperature for 18 h and was quenched by the addition of a solution of saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded methyl ester **86** (7.07 g, 94% yield) as a colorless oil.

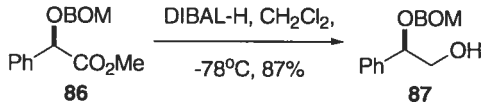
$[\alpha]_D$ -104.6 (c = 1.10, $CHCl_3$)

IR (thin film) 2953, 1751, 1456 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.52 (m, 2H), 7.37 (m, 8H), 5.26 (s, 1H), 4.96 (d, 1H, J = 7.1 Hz), 4.87 (d, 1H, J = 7.1 Hz), 4.73 (d, 1H, J = 11.7 Hz), 4.63 (d, 1H, J = 11.7 Hz), 3.72 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.6, 137.9, 136.5, 129.3, 129.2 (2C), 128.9 (2C), 128.4 (2C), 128.3, 127.9 (2C), 93.7, 77.4, 70.6, 52.8

(2*R*)-2-Benzyloxymethoxy-2-phenylethanol (87)



Following general procedure A, **86** (6.90 g, 24.1 mmol) was reduced to give alcohol **87** (5.41 g, 87%), upon purification by flash chromatography with 10% EtOAc/hexanes.

[α]$_D$ -157.0 (c = 1.15, $CHCl_3$)

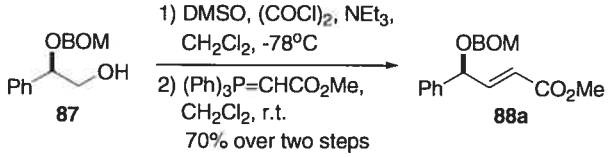
IR (thin film) 3436, 3032, 2886, 1495, 1454, 1383 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33, (m, 10H), 4.90-4.74 (m, 4H), 4.58 (m, 1H), 3.83-3.70 (m, 2H), 2.46 (brs, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 138.3, 137.3, 128.4 (2C), 128.3 (2C), 128.0, 127.9 (2C), 127.7, 126.9 (2C), 93.2, 80.3, 70.0, 67.1

HRMS (ESI) m/z 281.11482 (calcd for 281.11426 $C_{16}H_{18}O_3Na$)

(*E*)-(4*S*)-4-Benzyloxymethoxy-4-phenylbut-2-enoic acid methyl ester (88a)



Following general procedure E, alcohol **87** (0.22 g, 0.85 mmol) provided product **88a** (0.19 g, 70% over two steps) after flash chromatographic purification (2% EtOAc/hexanes).

$[\alpha]_D$ -57.9 (c = 0.86, $CHCl_3$)

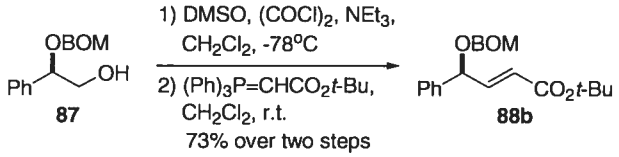
IR (thin film) 3065, 3032, 2951, 2890, 1724, 1660, 1603, 1496 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 10H), 7.01 (dd, 1H, J = 5.3, 15.6 Hz), 6.14 (dd, 1H, J = 1.6, 15.6 Hz), 5.34 (dd, 1H, J = 1.39, 5.3 Hz), 4.82 (d, 1H, J = 7.0 Hz), 4.75 (d, 1H, J = 7.0 Hz), 4.65 (d, 1H, J = 11.7 Hz), 4.57 (d, 1H, J = 11.7 Hz), 3.74 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.6, 147.2, 138.4, 137.4, 128.6 (2C), 128.3 (2C), 128.2, 127.9 (2C), 127.7, 127.3 (2C), 120.4, 92.0, 76.4, 69.7, 51.5

HRMS (ESI) m/z 335.12538 (calcd for 335.12469 $C_{19}H_{20}O_4Na$)

(*E*)-(4*S*)-4-Benzyloxymethoxy-4-phenylbut-2-enoic acid *tert*-butyl ester (88b)



Following general procedure E, alcohol **87** (0.25 g, 0.97 mmol) provided product **88b** (0.25 g, 73% over two steps) after flash chromatographic purification (2% EtOAc/hexanes).

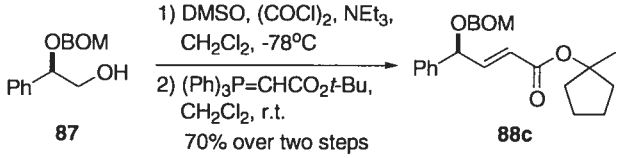
$[\alpha]_D$ -49.0 (c = 0.97, $CHCl_3$)

IR (thin film) 3032, 2979, 1715, 1656, 1495, 1455, 1392, 1368 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.22 (m, 10H), 6.90 (dd, 1H, J = 5.6, 15.6 Hz), 6.03 (dd, 1H, J = 1.6, 15.6 Hz), 5.32 (dd, 1H, J = 1.5, 5.6 Hz), 4.83 (d, 1H, J = 7.0 Hz), 4.75 (d, 1H, J = 7.0 Hz), 4.66 (d, 1H, J = 11.7 Hz), 4.58 (d, 1H, J = 11. 7 Hz), 1.49 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.4, 145.5, 138.7, 137.4, 128.6 (2C), 128.3 (2C), 128.1, 127.9 (2C), 127.6, 127.3 (2C), 122.9, 92.0, 80.4, 76.5, 69.6, 28.0 (3C)

(*E*)-(4*S*)-4-Benzyloxymethoxy-4-phenylbut-2-enoic acid 1-methylcyclopentyl ester (88c)



Following general procedure E, alcohol **87** (0.310 g, 1.20 mmol) provided product **88c** (0.32 g, 70% over two steps) after flash chromatographic purification (2% EtOAc/hexanes).

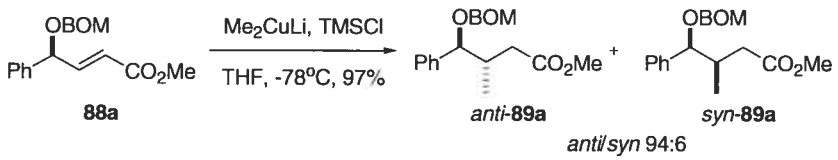
[α]$_D$ -42.3 (*c* = 0.84, $CHCl_3$)

IR (thin film) 2962, 1713, 1655, 1495, 1454, 1374, 1310 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 10H), 6.91 (dd, 1H, *J* = 5.5, 15.6 Hz), 6.04 (dd, 1H, *J* = 1.6, 15.6 Hz), 5.32 (dd, 1H, *J* = 1.3, 5.5 Hz), 4.82 (d, 1H, *J* = 7.0 Hz), 4.75 (d, 1H, *J* = 7.0 Hz), 4.65 (d, 1H, *J* = 11.7 Hz), 4.58 (d, 1H, *J* = 11.7 Hz), 2.12 (m, 2H), 1.75-1.69 (m, 4H), 1.64 (m, 2H), 1.58 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.6, 145.6, 138.7, 137.4, 128.6 (2C), 128.2 (2C), 128.1, 127.9 (2C), 127.6, 127.3 (2C), 122.7, 92.0, 89.9, 69.7, 39.0, 38.9, 24.3, 23.7 (2C)

(3*S*, 4*S*)-4-Benzyloxymethoxy-3-methyl-4-phenylbutyric acid methyl ester (89a)



Compound **88** (0.10 g, 0.32 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *anti*-**89a** and *syn*-**89a** (0.102 g, 97% combined yield) in a ratio of 94:6 *anti/ syn.*

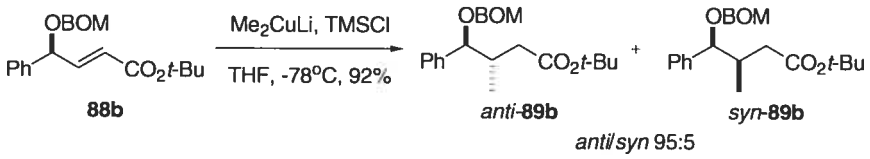
[α]$_D$ -11.7 (*c* = 0.77, $CHCl_3$)

IR (thin film) 3032, 2951, 1738, 1495, 1454, 1436, 1381 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.38-7.27 (m, 10H), 4.70 (m, 2H), 4.60 (d, 1H, *J* = 7.0 Hz), 4.48 (d, 1H, *J* = 11.7 Hz), 4.43 (d, 1H, *J* = 7.9 Hz), 3.69 (s, 3H), 3.69 (s, minor), 2.76 (dd, 1H, *J* = 4.8, 15.8 Hz), 2.45 (m, 1H), 2.26 (dd, 1H, *J* = 8.7, 15.2 Hz),1.06 (d, *J* = 6.6 Hz, minor), 7.18 (d, 3H, *J* = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.3 (173.0), 139.3 (139.5), 137.4, 128.1 (2C), 127.9 (2C), 127.6, 127.5 (2C), 127.4, 127.4 (2C), (92.3) 92.1, 81.9 (80.8), 69.5, 51.1, 37.5, 36.6 (36.4), 16.4 (15.2)

(3*S*, 4*S*)-4-Benzyloxymethoxy-3-methyl-4-phenylbutyric acid *tert*-butyl ester (89b)



88b *anti*-**89b** *syn*-**89b**

anti/*syn* 95:5

Compound **88b** (0.10 g, 0.28 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *anti*-**89b** and *syn*-**89b** (0.095 g, 92% combined yield) in a ratio of 95:5 *anti/ syn.*

[α]$_D$ -128.1 (*c* = 0.091, $CHCl_3$)

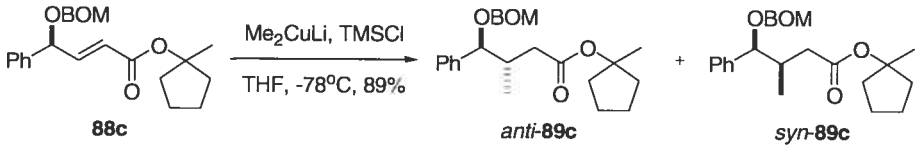
IR (thin film) 3032, 2977, 1728, 1495, 1455, 1367 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.48-7.23 (m, 10H), 4.72 (m, 2H), 4.60 (d, 1H, *J* = 6.9 Hz), 4.48 (d, 1H, *J* = 11.6 Hz), 4.42 (d, 1H, *J* = 7.9), 2.66 (dd, 1H, *J* = 5.0,

15.0 Hz), 2.40 (m, 1H), 2.14 (m, 1H), 1.48 (s, 9H), 1.04 (d, J = 6.8 Hz, minor), 0.84 (d, 3H, J = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.2, 139.9, 137.4, 128.0 (2C), 127.9, 127.6 (2C), 127.4 (2C), 127.4 (2C), 127.3, 92.1, 82.0, 79.7, 69.4, 39.1, 36.6, 27.8 (3C), 16.1

(3*S*, 4*S*)-4-Benzyloxymethoxy-3-methyl-4-phenylbutyric acid 1-methylcyclopentyl ester (89c)



88c *anti*-**89c** *syn*-**89c**

anti/*syn* 95:5

Compound **88c** (0.10 g, 0.26 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *anti*-**89c** and *syn*-**89c** (0.092 g, 89% combined yield) in a ratio of 95:5 *anti*/ *syn*.

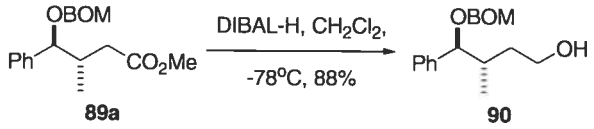
$[\alpha]_D$ -98.8 (c = 1.07, $CHCl_3$)

IR (thin film) 3032, 2964, 1727, 1495, 1454, 1374 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33 (m, 10H), 4.69 (d, 1H, J = 6.9 Hz), 4.60 (d, 1H, J = 6.9 Hz), 4.48 (d, 1H, J = 11.7 Hz), 4.42 (d, 1H, J = 6.8 Hz), 2.65 (dd, 1H, J = 5.0, 14.9 Hz), 2.38 (m, 1H), 2.13 (m, 2H), 1.72 (m, 6H), 1.65 (m, 2H), 1.59 (s, 3H), 0.90 (d, J = 6.9 Hz, minor), 0.83 (d, 3H, J = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 139.8, 137.4, 128.0 (2C), 127.9 (2C), 127.6 (2C), 127.4 (2C), 127.9, 127.3, 92.1, 89.3, 82.0, 69.5, 39.1, 38.8, 38.8, 36.6, 24.1, 23.5 (2C), 16.2

(3*S*, 4*S*)-4-Benzyloxymethoxy-3-methyl-4-phenylbutan-1-ol (90)



89a 90

Following general procedure A, **89a** (0.650 g, 1.98 mmol) was reduced to give alcohol **90** (0.520 g, 88%), upon purification by flash chromatography with 10% EtOAc/hexanes.

$[\alpha]_D$ -9.2 (c = 6.90, $CHCl_3$)

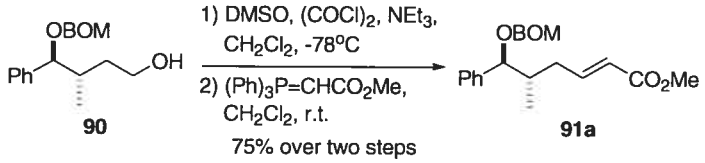
IR (thin film) 3402, 3031, 2884, 1495 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.38-7.28 (m, 10H), 4.74 (m, 2H), 4.63 (d, 1H, J = 6.9 Hz), 4.52 (d, 1H, J = 11.7 Hz), 4.45 (d, 1H, J = 7.4 Hz), 3.84-3.67 (m, 2H), 2.09-1.97 (m, 2H), 1.85 (s, 1H), 1.52 (m, 1H), 0.83 (d, 3H, J = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 141.6, 139.5, 128.8 (2C), 128.6 (2C), 128.3, 128.2 (2C), 128.1 (2C), 128.0, 93.0, 83.6, 70.4, 61.6, 37.2, 36.4, 17.1

HRMS (ESI) m/z 323.16177 (calcd for 323.16206 $C_{19}H_{24}O_3Na$)

(*E*)-(5*S*, 6*S*)-6-Benzyloxymethoxy-5-methyl-6-phenylhex-2-enoic acid methyl ester (91a)



90 91a

Following general procedure E, alcohol **90** (0.17 g, 0.56 mmol) provided product **91a** (0.15 g, 75% over two steps) after flash chromatographic purification (2% EtOAc/hexanes).

$[\alpha]_D$ -62.9 (c = 0.93, $CHCl_3$)

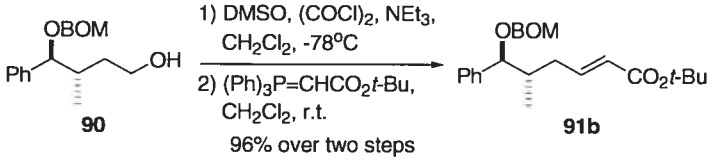
IR (thin film) 2951, 1723, 1656, 1495 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.40-7.29 (m, 10H), 7.03 (m, 1H), 5.91 (d, 1H, J = 15.7 Hz), 4.72 (m, 2H), 4.64 (d, 1H, J = 6.9 Hz), 4.52 (d, 1H, J = 11.7 Hz), 4.34

(d, 1H, J = 7.4 Hz), 3.76 (s, 3H), 2.77 (m, 1H), 2.19-1.09 (m, 2H), 0.79 (d, 3H, J = 6.6 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.4, 148.7, 140.7, 138.2, 128.9 (2C), 128.7, 128.3 (2C), 128.2 (2C), 128.2, 128.1 (2C), 122.8, 93.0, 82.8, 70.4, 51.9, 39.5, 36.1, 16.6

(*E*)-(5*S*, 6*S*)-6-Benzyloxymethoxy-5-methyl-6-phenylhex-2-enoic acid *tert*-butyl ester (91b)



Following general procedure E, alcohol **90** (0.15 g, 0.50 mmol) provided product **91b** (0.19 g, 96% over two steps) after flash chromatographic purification (2% EtOAc/hexanes).

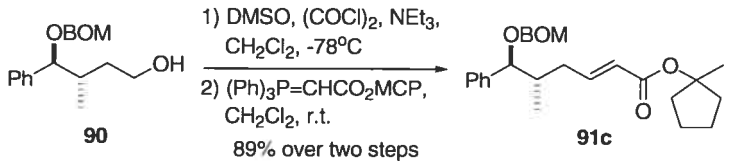
$[\alpha]_D$ -56.4 (c = 1.05, $CHCl_3$)

IR (thin film) 3032, 2977, 2932, 1713, 1651, 1495 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42-7.23 (m, 10H), 6.93 (m, 1H), 5.82 (d, 1H, J = 15.6 Hz), 4.72 (m, 2H), 4.63 (d, 1H, J = 6.9 Hz), 4.51 (d, 1H, J = 11.7 Hz), 4.42 (d, 1H, J = 7.2 Hz), 2.68 (m 1H), 2.09 (m, 2H), 1.52 (s, 9H), 0.78 (d, 3H, J = 6.4 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4, 147.1, 140.7, 138.2, 128.9 (2C), 128.7 (3C), 128.4 (2C), 128.1 (3C), 124.3, 93.0, 82.9, 80.5, 70.4, 39.5, 35.9, 28.6 (3C), 16.6

(*E*)-(5*S*, 6*S*)-6-Benzyloxymethoxy-5-methyl-6-phenylhex-2-enoic acid 1-methylcyclopentyl ester (91c)



Following general procedure E, alcohol **90** (0.17 g, 0.56 mmol) provided product **91c** (0.21 g, 96% over two steps) after flash chromatographic purification (2% EtOAc/hexanes).

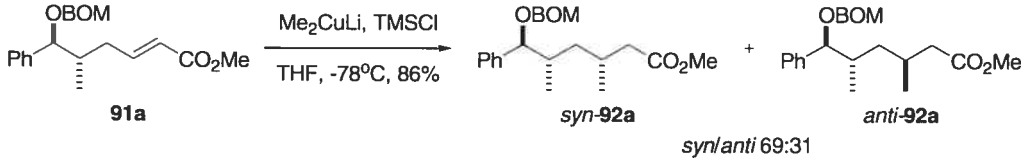
[α]$_D$ -53.1 (*c* = 1.14, $CHCl_3$)

IR (thin film) 3032, 2964, 2876, 1712, 1652 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.40-7.28 (m, 10H), 6.92 (m, 1H), 5.84 (d, 1H, *J* = 5.8 Hz), 4.72 (m, 2H), 4.63 (d, 1H, *J* = 6.9 Hz), 4.51 (d, 1H, *J* = 11.7 Hz), 4.43 (d, 1H, *J* = 7.2 Hz), 2.70 (m, 1H), 2.17-2.05 (m, 4H), 1.77-1.64 (m, 6H), 1.62 (s, 3H), 0.79 (d, 3H, *J* = 6.5 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.5, 147.1, 140.7, 138.2, 128.9 (2C), 128.7 (3C), 128.4 (2C), 128.1 (3C), 128.1 (2C), 124.8, 93.0, 90.0, 82.9, 70.4, 39.6, 39.5, 35.9, 24.9, 24.3, 16.6

(3*R*, 5*S*, 6*S*)-6-Benzyloxymethoxy-3,5-dimethyl-6-phenylhexanoic acid methyl ester (92a)



Compound **91a** (0.10 g, 0.28 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**92a** and *anti*- **92a** (0.089 g, 86% combined yield) in a ratio of 69:31 *syn/anti*.

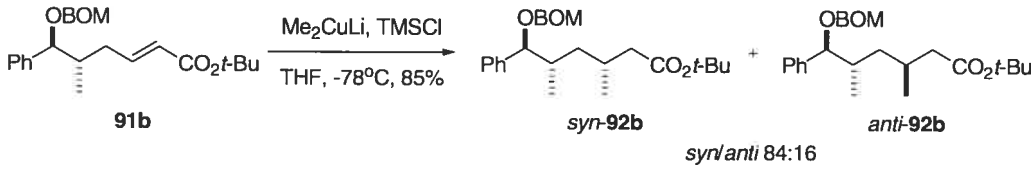
[α]$_D$ -71.5 (*c* = 1.23, $CHCl_3$)

IR (thin film) 3031, 2958, 1738 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.40-7.27 (m, 10H), 4.73 (m, 2H), 4.62 (d, 1H, J = 6.9 Hz), 4.45 (m, 2H), 3.66 (m, 3H), 2.39 (dd, 1H, J = 4.3, 14.5 Hz). 2.32-2.19 (m, minor), 2.11 (m, 1H), 2.02 (m, 1H), 1.90 (m, 1H), 1.69-1.61 (m, 1H), 1.10 (m, 1H), 1.01 (d, 3H, J = 6.5 Hz), 0.81 (d, 3H, J = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.6 (173.4), (140.8) 140.6, 137.7, 128.3 (2C), 128.0, 127.9 (2C), 127.8 (2C), 127.6, 127.5 (2C), 92.5, (83.3) 82.7, 69.7, 51.2, (42.7) 40.5, 40.1 (39.6), 36.9 (36.7), 28.0 (27.6), 21.1 (18.6), 16.2 (15.6)

(3*R*, 5*S*, 6*S*)-6-Benzyloxymethoxy-3,5-dimethyl-6-phenylhexanoic acid *tert*-butyl ester (92b)



91b *syn*-**92b** *anti*-**92b**

syn/*anti* 84:16

Compound **91b** (0.10 g, 0.25 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**92b** and *anti*-**92b** (0.089 g, 85% combined yield) in a ratio of 84:16 *syn/anti*.

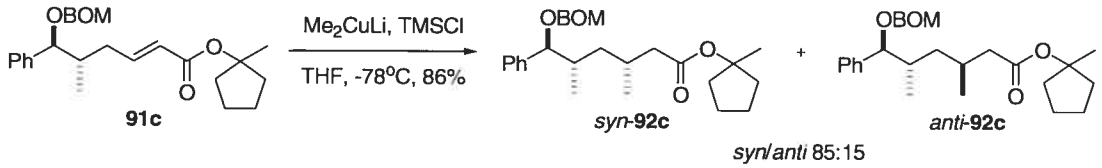
$[\alpha]_D$ -67.4 (c = 1.11, $CHCl_3$)

IR (thin film) 3032, 2965, 2932, 1727, 1495 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.37-7.26 (m, 10H), 4.72 (m, 2H), 4.62 (d, 1H, J = 6.9 Hz), 4.49 (d, 1H, J = 11.7 Hz), 4.41 (d, 1H, J = 6.9 Hz), 2.30 (dd, 1H, J = 4.4, 14.4 Hz), 2.17-2.01 (m, 1H), 2.02-1.86 (m, 2H), 1.66 (m, 1H), 1.46 (s, 9H), 1.13-1.03 (m, 1H), 0.99 (d, 3H, J = 7.0 Hz), 0.91 (d, J = 6.4 Hz, minor), 0.79 (d, 3H, J = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.4 (172.1), (140.4) 140.2, 137.5, 128.0 (2C), 127.8, 127.7 (2C), 127.6 (2C), 127.4, 127.3 (2C), 92.3, (83.1) 82.7, 79.6 (2C), 69.4, (44.1) 41.8, 39.9 (39.2), 36.6 (36.5), 27.8 (3C), 20.8 (18.4), 15.9 (15.3)

(3*R*, 5*S*, 6*S*)-6-Benzyloxymethoxy-3,5-dimethyl-6-phenylhexanoic acid 1-methylcyclopentyl ester (92c)



syn/*anti* 85:15

Compound **91c** (0.10 g, 0.24 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**92c** and *anti*-**92c** (0.089 g, 86% combined yield) in a ratio of 85:15 *syn*/*anti*.

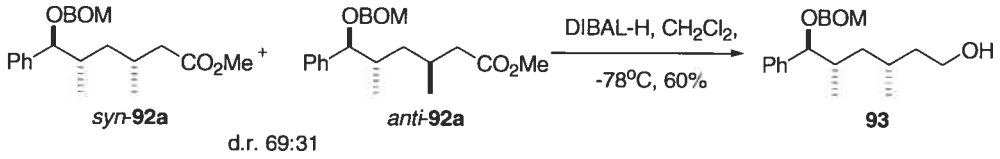
$[\alpha]_D$ -64.2 (c = 1.11, $CHCl_3$)

IR (thin film) 2962, 1726, 1496 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36-7.25 (m, 10H), 4.71 (m 2H), 4.61 (d, 1H, J = 6.9 Hz), 4.84 (d, 1H, J = 11.6 Hz), 4.41 (d, 1H, J = 6.9 Hz), 2.31 (dd, 1H, J = 4.3, 14.3 Hz), 2.11 (m, 3H), 1.91 (m, 2H), 1.72-1.61 (8H), 1.55 (s, 3H), 0.99 (d, 3H, J = 6.6 Hz), 0.79 (d, 3H, J = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.8 (172.7), (140.8) 140.9, 137.7, 128.2 (2C), 127.9 (2C), 127.8, 127.6 (2C), 127.5, 127.4 (2C), 92.5, 89.4, 82.9, 69.6, (44.2) 41.8, 40.2 (39.4), 39.4, 38.9, 36.8 (36.7), 28.0 (27.7), 24.2 (2C), 23.6, (20.7) 18.6, 16.1 (15.4)

(3*R*, 5*S*, 6*S*)-6-Benzyloxymethoxy-3,5-dimethyl-6-phenylhexan-1-ol (93)



Following general procedure A, the diastereomeric mixture of *syn*- and *anti*- esters **92a** (0.66 g, 1.8 mmol) was reduced to give a mixture of diastereomeric alcohols. Purification by flash chromatography (2% EtOAc/hexanes) gave the pure alcohol **93** (0.15 g) and a mixture of diastereomers (0.20 g) in 60% overall yield.

[α]$_D$ -51.7 (c = 1.09, $CHCl_3$)

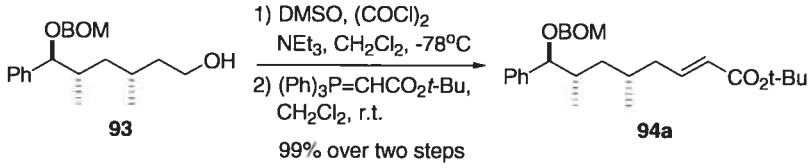
IR (thin film) 3402, 2931, 1454 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.38-7.27 (m, 10H), 4.73 (m, 2H), 4.63 (d, 1H, J = 6.9 Hz), 4.50 (d, 1H, J = 11.6 Hz), 4.44 (d, 1H, J = 6.6 Hz), 3.75-3.62 (m, 2H), 2.00 (m, 1H), 1.75-1.63 (m, 2H), 1.61-1.46 (m, 2H), 1.32 (m, 1H), 1.03 (m, 1H), 0.97 (m, 3H), 0.78 (m, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 141.0, 138.3, 128.8 (2C), 128.5 (2C), 128.4, 128.2 (2C), 128.1 (2C), 127.9, 93.1, 83.6, 70.2, 61.4, 41.1, 39.2, 37.4, 27.7, 21.4, 17.0

HRMS (ESI) m/z 365.20872 (calcd for 365.20722 $C_{22}H_{30}O_3Na$)

(*E*)-(5*S*, 7*S*, 8*S*)-8-Benzyloxymethoxy-5,7-dimethyl-8-phenyloct-2-enoic acid *tert*-butyl ester (94a)



Following general procedure E, alcohol **93** (0.071 g, 0.21 mmol) provided product **94a** (0.090 g, 99% over two steps) after flash chromatographic purification (2% EtOAc/hexanes).

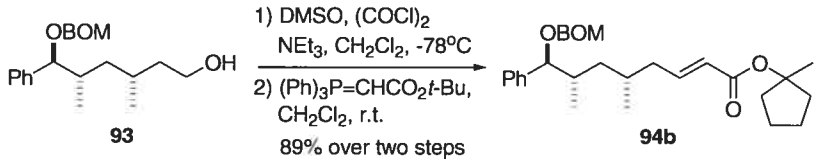
[α]$_D$ -41.1 (c = 0.95, $CHCl_3$)

IR (thin film) 3065, 3031, 2930, 1713, 1652 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37-7.29 (m, 10H), 6.87 (m, 1H), 5.75 (d, 1H, J = 15.5 Hz), 4.73 (m, 2H), 4.64 (d, 1H, J = 6.9 Hz), 4.51 (d, 1H, J = 11.6 Hz), 4.44 (d, 1H, J = 6.8 Hz), 2.27 (m, 1H), 2.03-1.85 (m, 2H), 1.86-1.65 (m, 2H), 1.51 (s, 9H), 1.04 (m, 1H), 0.96 (d, 3H, J = 6.4 Hz), 0.80 (d, 3H, J = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.6, 146.4, 140.2, 137.5, 128.0 (2C), 127.7 (2C), 127.6, 127.4 (2C), 127.3 (2C), 127.1, 123.9, 92.3, 82.6, 79.6, 69.4, 39.8, 38.0, 36.6, 29.9, 27.8 (3C), 20.5, 16.1

(*E*)-(5*S*, 7*S*, 8*S*)-8-Benzyloxymethoxy-5,7-dimethyl-8-phenyloct-2-enoic acid 1-methylcyclopentyl ester (94b)



Following general procedure E, alcohol **93** (0.071 g, 0.21 mmol) provided product **94b** (0.086 g, 89% over two steps) after flash chromatographic purification (2% EtOAc/hexanes).

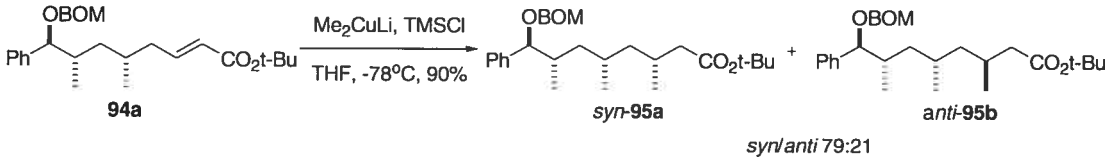
$[\alpha]_D$ -36.9 (c = 0.94, $CHCl_3$)

IR (thin film) 2960, 1713, 1652 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37-7.28 (m, 10H), 6.87 (m, 1H), 5.77 (d, 1H, J = 15.5 Hz), 4.73 (m, 2H), 4.64 (d, 1H, J = 6.9 Hz), 4.50 (d, 1H, J = 11.6 Hz), 4.44 (d, 1H, J = 6.8 Hz), 2.26 (m, 1H), 2.15 (m, 2H), 2.03-1.86 (m, 2H), 1.84-1.64 (m, 8H), 1.61 (s, 3H), 1.05 (m, 1H), 0.96 (d, 3H, J = 6.4 Hz), 0.80 (d, 3H, J = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.8, 146.4, 140.2, 137.5, 128.0 (2C), 127.7 (2C), 127.6, 127.4 (2C), 127.3 (2C), 127.1, 123.8, 92.3, 89.1, 82.6, 69.4, 39.8, 38.8 (2C), 38.0, 36.6, 29.9, 24.1, 23.5 (2C), 20.5, 16.1

(3*R*, 5*S*, 7*S*, 8*S*)-8-Benzyloxymethoxy-3,5,7-trimethyl-8-phenyloctanoic acid *tert*-butyl ester (95a)



Compound **94a** (0.060 g, 0.14 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**95a** and *anti*-**95a** (0.056 g, 90% combined yield) in a ratio of 79:21 *syn/anti*.

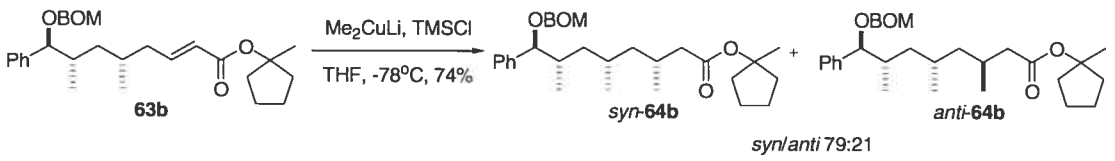
$[\alpha]_D$ -39.6 (c = 1.10, $CHCl_3$)

IR (thin film) 2960, 2930, 1728 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.37-7.27, (m, 10H), 4.74 (m, 2H), 4.64 (d, 1H, J = 6.9 Hz), 4.50 (d, 1H, J = 11.6 Hz), 4.44 (d, 1H, J = 6.8 Hz), 2.29 (dd, 1H, J = 4.9, 14.3 Hz), 2.08-1.96 (m, 2H), 1.90 (dd, 1H, J = 8.9, 14.3 Hz), 1.65 (m, 2H), 1.47 (s, 9H), 1.30 (m, 1H), 1.04-0.92 (m, 6H), 0.87 (m, 2H), 0.78 (d, 3H, J = 7.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 173.2 (173.0), 141.0, 138.3, 128.4 (2C), 128.4 (2C), 128.2, 128.2 (2C), 128.1 (2C), 127.8, 93.1, 83.6 (83.5), 80.3, 70.2, (44.0) 43.6, 42.1, (41.2) 40.9, 36.4 (36.3), 27.8 (3C), 27.7, 27.5 (27.5), 20.7, 16.1 (15.8)

(3*R*, 5*S*, 7*S*, 8*S*)-8-Benzyloxymethoxy-3,5,7-trimethyl-8-phenyloctanoic acid 1-methylcyclopentyl ester (95b)



Compound **94b** (0.086 g, 0.18 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes

afforded the products *syn*-**95b** and *anti*-**95b** (0.065 g, 74% combined yield) in a ratio of 79:21 *syn/anti*.

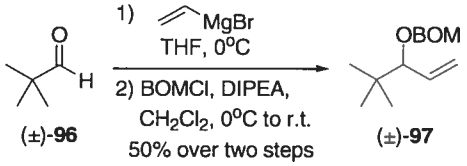
$[\alpha]_D$ -71.9 (c = 0.62, $CHCl_3$)

IR (thin film) 2959, 1727, 1454 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.37-7.27 (m, 10H), 4.75 (m, 2H), 4.64 (d, 1H, J = 6.9 Hz), 4.50 (d, 1H, J = 11.6 Hz), 4.44 (d, 1H, J = 6.8 Hz), 2.30 (dd, 1H, J = 4.8, 14.2 Hz), 2.19-1.96 (m, 4H), 1.90 (dd, 1H, J = 8.9, 14. 2 Hz), 1.80-1.62 (m, 8H), 1.57 (s, 3H), 1.30 (m, 1H), 1.05-0.92 (m, 7H), 0.84 (m, 1H), 0.78 (d, 3H, J = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 173.4 (173.1), 141.0, 138.3, 128.8 (2C), 128.6 (2C), 128.4, 128.4 (2C), 128.2, 128.2 (2C), 93.1, 89.9, (83.6) 83.5, 70.2, (44.7) 44.4, (43.5) 42.7, (41.7) 41.7, 39.6, 39.5, 39.5, 37.2, 28.4, 28.3, 24.8, 24.2 (2C), 21.5 (21.0), 16.9 (16.6)

(1-*tert*-Butyl-allyloxymethoxymethyl)-benzene ((±)-97)



A solution of 1.5 M vinylmagnesium bromide (46.4 mL, 69.7 mmol) in THF (250 mL) was cooled to 0 °C prior to the addition of 2,2-dimethyl-propionaldehyde, **65**, (6.39 mL, 58.1 mmol). The mixture was stirred at the same temperature for 4 hr before being quenched with a saturated solution of NH_4Cl. The aqueous layers were washed with EtOAc (3 x 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. A solution of the crude vinyl alcohol and DIPEA (40.45 mL, 232.2 mmol) in CH_2Cl_2 (150 mL) was cooled to 0 °C, followed by the drop wise addition of BOMCl (26.01 mL, 116.1 mmol). The reaction mixture was stirred at room temperature for 18 h and was quenched with a saturated solution of NH_4Cl. The aqueous layers were washed

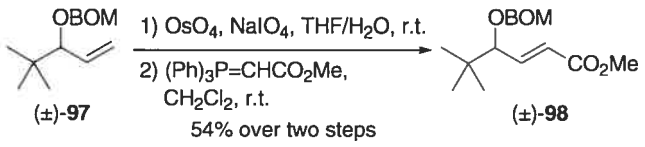
with EtOAc (3 x 25 mL), dried over Na_2SO_4 and concentrated. Flash chromatography (2% EtOAc/hexanes) gave the desired product, **(±)-97**, in 50% yield.

IR (thin film) 3032, 2956, 2872, 1498 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.40 (m, 5H), 5.79 (m, 1H), 5.34 (d, 1H, J = 10.4 Hz), 5.26 (d, 1H, J = 17.2 Hz), 4.86 (d, 1H, J = 6.9 Hz), 4.82 (d, 1H, J = 11.7 Hz), 4.75 (d, 1H, J = 6.9 Hz), 4.58 (d, 1H, J = 11.7 Hz), 3.78 (d, 1H, J = 8.2 Hz), 1.02 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.7, 135.0, 128.1 (2C), 127.6 (2C), 127.3, 118.9, 91.5, 85.0, 69.3, 34.0, 25.9 (3C)

4-Benzyloxymethoxy-5,5-dimethylhex-2-enoic acid methyl ester ((±)-98)



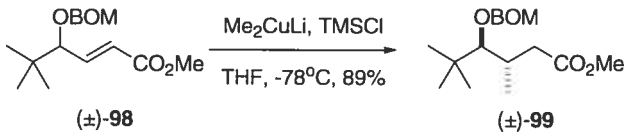
To a solution of substrate **(±)-97** (0.890 g, 3.80 mmol) in THF (5 mL) and H_2O (5 mL) at 0 °C, sodium periodate (2.03 g, 9.50 mmol) was added, followed by OsO_4 (0.24 mL, 0.19 mmol). The mixture was stirred at room temperature for 18 h. The reaction mixture was extracted with EtOAc (3 x 5 mL), dried over Na_2SO_4 and concentrated. A solution of the crude aldehyde in CH_2Cl_2 (10 mL) was charged with $Ph_3P{=}CHCO_2Me$ (1.91 g, 5.70 mmol), and stirred for 3 days at room temperature. The reaction mixture was evaporated to dryness, trituration of the crude solid with hexanes/Et_2O (3:1) resulted in a slurry which was filtered over a pad of celite. The filtrate was concentrated and purified by flash chromatography (2% EtOAc/hexanes) affording enoate **(±)-98** (o.60 g, 54%).

IR (thin film) 2955, 2872, 1726, 1657 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 (m, 5H), 6.91 (dd, 1H, J = 7.3, 15.8 Hz), 6.00 (dd, 1H, J = 1.0, 15.8 Hz), 4.73 (s, 3H), 4.56 (d, 1H, J = 11.7 Hz), 3.93 (dd, 1H, J = 0.9, 7.3 Hz), 3.77 (s, 3H), 0.99 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.1, 145.6, 137.3, 128.1 (2C), 127.5 (2C), 127.4, 123.2, 92.6, 83.1, 69.5, 51.3, 34.8, 25.8 (3C)

(3*S*, 4*S*)-4-Benzyloxymethoxy-3,5,5-trimethylhexanoic acid methyl ester ((±)-99)



(±)-**98** (±)-**99**

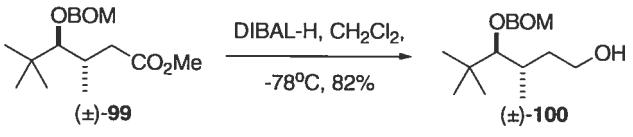
Compound (±)-**98** (0.27 g, 0.93 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification of the product with 2% EtOAc/hexanes afforded product (±)-**99** (0.26 g, 89%) as a single diastereomer.

IR (thin film) 2957, 2875, 1738, 1436 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 5H), 4.84 (d, 1H, J = 6.9 Hz), 4.76 (d, 1H, J = 6.9 Hz), 4.72 (d, 1H, J = 11.9 Hz), 4.65 (d, 1H, J = 11.9 Hz), 3.70 (s, 3H), 3.08 (d, 1H, J = 2.0 Hz), 2.69 (dd, 1H, J = 3.2, 15.8 Hz), 2.39 (m, 1H), 2.17 (dd, 1H, J = 10.2, 15.8 Hz), 1.10 (d, 3H, J = 7.0 Hz), 0.97 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.0, 137.5, 128.1 (2C), 127.4 (2C), 127.3, 96.7, 91.2, 69.9, 51.1, 37.3, 36.2, 30.4, 26.2 (3C), 21.6

(3*S*, 4*S*)-4-Benzyloxymethoxy-3,5,5-trimethylhexan-1-ol ((±)-100)



(±)-**99** (±)-**100**

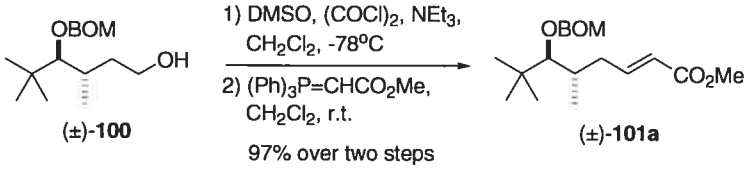
Following general procedure A, substrate (±)-**99** (0.481 g, 1.56 mmol) was reduced to give alcohol (±)-**100** (0.36 g, 82%), after chromatographic purification (10% EtOAc/hexanes).

IR (thin film) 3369, 2958, 2874, 1481 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33 (m, 5H), 4.87 (d, 1H, J = 6.9 Hz), 4.79 (d, 1H, J = 6.9 Hz), 4.72 (d, 1H, J = 11.9 Hz), 4.69 (d, 1H, J = 11.9 Hz), 3.77 (m, 1H), 3.68 (m, 1H), 3.12 (s, 1H), 2.22 (brs, 1H), 1.97 (m, 2H), 1.43 (m, 1H), 1.09 (d, 3H, J = 7.00 Hz), 0.98 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.6, 128.1 (2C), 127.4 (2C), 127.3, 96.6, 91.9, 69.9, 61.2, 36.1, 35.1, 30.3, 26.4 (3C), 21.3

(*E*)-(5*S*, 6*S*)-6-Benzyloxymethoxy-5,7,7-trimethyloct-2-enoic acid methyl ester ((±)-101a)



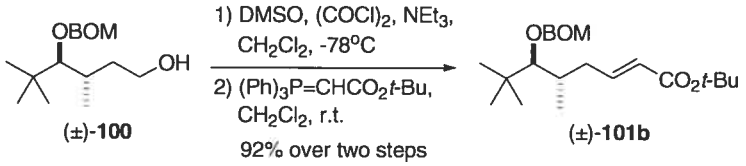
Following general procedure E, alcohol **(±)-100** (0.18 g, 0.65 mmol), provided product **(±)-101a** ((*E*)- 0.17 g, (*Z*)- 0.045 g, 97% over two steps) after flash chromatographic purification (2% EtOAc/hexanes).

IR (thin film) 3031, 2955, 2872, 1725, 1655, 1436 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (m, 5H), 7.03 (m, 1H), 5.86 (d, 1H, J = 15.6 Hz), 4.86 (d, 1H, J = 6.8 Hz), 4.77 (d, 1H, J = 6.8 Hz), 4.72 (d, 1H, J = 11.9 Hz), 4.65 (d, 1H, J = 11.9 Hz), 3.75 (s, 3H), 3.11 (s, 1H), 2.60 (m, 1H), 1.99 (m, 2H), 1.07 (d, 3H, J = 6.7 Hz), 0.97 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.7, 149.3, 137.6, 128.1 (2C), 127.3 (2C), 127.3, 121.2, 96.7, 91.4, 69.9, 51.0, 36.2, 35.2, 32.8, 26.2 (3C), 20.87

(*E*)-(5*S*, 6*S*)-6-Benzyloxymethoxy-5,7,7-trimethyloct-2-enoic acid *tert*-butyl ester ((±)-101b)



(±)-**100** (±)-**101b**

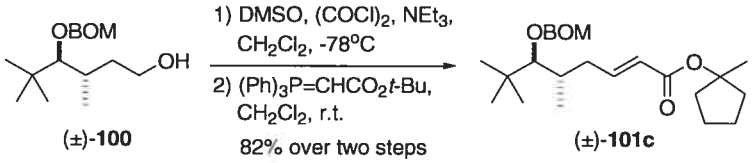
Following general procedure E, alcohol **(±)-100** (0.079 g, 0.29 mmol) provided product **(±)-101b** (0.098 g, 92% over two steps) after flash chromatographic purification (2% EtOAc/hexanes).

IR (thin film) 2961, 1713, 1652, 1456 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 5H), 6.91 (m, 1H), 5.77 (d, 1H, J = 15.6 Hz), 4.86 (d, 1H, J = 6.8 Hz), 4.77 (d, 1H, J = 6.9 Hz), 4.72 (d, 1H, J = 11.8 Hz), 4.65 (d, 1H, J = 11.9 Hz), 3.11 (s, 1H), 2.56 (m, 1H), 1.94 (m, 2H), 1.51 (s, 9H), 1.07 (d, 3H, J = 6.8 Hz), 0.96 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.8, 147.6, 137.6, 128.1 (2C), 127.4 (2C), 127.3, 123.3, 96.7, 91.4, 79.7, 69.9, 36.2, 34.9, 32.8, 27.8 (3C), 26.3 (3C), 20.9

(*E*)-(5*S*, 6*S*)-6-Benzyloxymethoxy-5,7,7-trimethyloct-2-enoic acid 1-methylcyclopentyl ester ((±)-101c)



(±)-**100** (±)-**101c**

Following general procedure E, alcohol **(±)-100** (0.079 g, 0.29 mmol), provided product **(±)-101c** (0.094 g, 82%, over two steps) after flash chromatographic purification (2% EtOAc/hexanes).

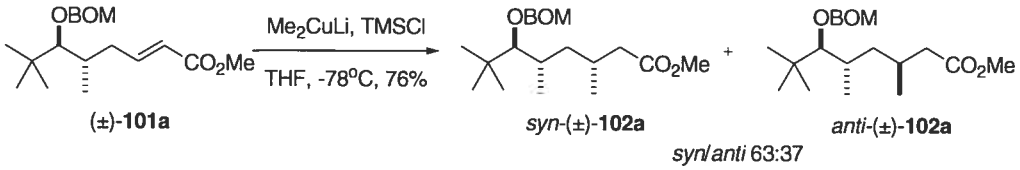
IR (thin film) 2960, 2873, 1714, 1455 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 5H), 6.91 (m, 1H), 5.78 (d, 1H, J = 15.6 Hz), 4.86 (d, 1H, J = 6.8 Hz), 4.77 (d, 1H, J = 6.8 Hz), 4.72 (d, 1H, J = 11.9 Hz),

4.65 (d, 1H, J = 11.9 Hz), 3.11 (s, 1H), 2.58 (m, 1H), 2.15 (m, 2H), 1.97 (m, 2H), 1.73 (m, 4H), 1.65 (m, 2H), 1.60 (s, 3H), 1.07 (d, 3H, J = 6.6 Hz), 0.96 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.9, 147.7, 137.6, 128.1 (2C), 127.4 (2C), 127.3, 123.2, 96.7, 91.4, 89.2, 69.9, 38.8 (2C), 36.2, 34.9, 32.8, 26.3 (3C), 24.1, 23.5 (2C), 20.9

(3*R*, 5*S*, 6*S*)-6-Benzyloxymethoxy-3,5,7,7-tetramethyloctanoic acid methyl ester ((±)-102a)



(±)-**101a** — *syn*-(±)-**102a** + *anti*-(±)-**102a**

syn/*anti* 63:37

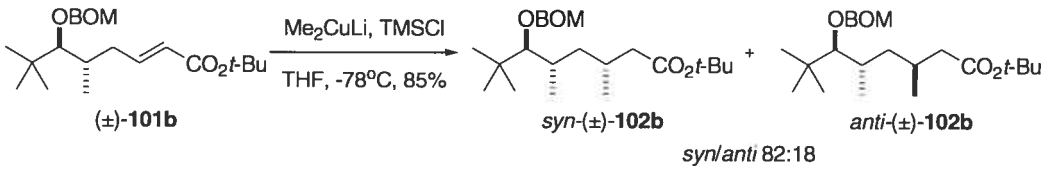
Compound **(±)-101a** (0.10 g, 0.30 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**(±)-102a** and *anti*-**(±)-102a** (0.080 g, 76% combined yield) in a ratio of 63:37 *syn/anti*.

IR (thin film) 2957, 2873, 1739, 1456 1362 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33 (m, 5H), 4.85 (m, 1H), 4.77 (m, 1H), 4.68 (m, 2H), 3.69 (s, 3H), 3.66 (s, minor), 3.11 (d, J = 1.7 Hz minor), 3.09 (d, 1H, J = 1.8 Hz), 2.46 (m, 1H), 2.24 (m, minor), 2.04 (m, 2H), 1.82 (m, minor), 1.58 (m, 1H), 1.45 (m, 1H), 1.23 (m, minor), 1.11 (m, 1H), 1.08 (d, 3H, J = 6.9 Hz), 0.99 (d, 3H, J = 5.8 Hz), 0.96 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.5 (173.2), 137.7, 128.0 (2C), 127.4 (2C), 127.2, 96.6 (96.6), 92.1 (92.0), 69.8, 51.0 (51.0), (42.8) 40.3, 39.1 (38.6), (36.3) 36.2, 30.9 (30.4), 28.2 (27.8), 26.5 (3C), 21.4 (20.7), 21.3 (18.5)

(3*R*, 5*S*, 6*S*)-6-Benzyloxymethoxy-3,5,7,7-tetramethyloctanoic acid *tert*-butyl ester ((±)-102b)



(±)-**101b** *syn*-(±)-**102b** *anti*-(±)-**102b**

syn/*anti* 82:18

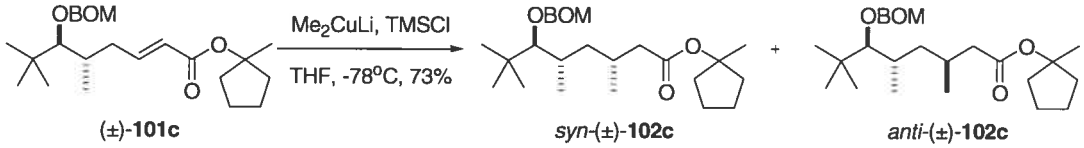
Compound (±)-**101b** (0.060 g, 0.16 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-(±)-**102b** and *anti*-(±)-**102b** (0.054 g, 85% combined yield) in a ratio of 82:18 *syn/anti*.

IR (thin film) 2960, 2873, 1729, 1456, 1367 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.31 (m, 5H), 4.85 (d, 1H, J = 6.8 Hz), 4.78 (d, 1H, J = 6.8 Hz), 4.74 (d, 1H, J = 11.8 Hz), 4.66 (d, 1H, J = 11.8 Hz), 3.12 (d, J = 1.5 Hz minor), 3.10 (d, 1H, J = 1.5 Hz), 2.39 (dd, 1H, J = 4.4, 14.3 Hz), 2.04 (m, 1H), 1.89 (dd, 1H, J = 9.4, 14.3 Hz), 1.83 (m, 1H), 1.57 (m, 1H), 1.48 (s, 9H), 1.15 (m, 1H), 1.08 (d, 3H, J = 6.9 Hz), 1.10 (d, 3H, J = 6.6 Hz), 0.96 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 172.6 (172.2), 137.7, 128.0 (2C), 127.4 (2C), 127.2, 96.6 (96.4), 92.1 (91.8), 79.7 (79.5), 69.8, (44.3) 41.8, 39.3 (38.5), (36.3) 36.3, 30.8 (30.4), 28.2 (27.9), 27.8 (3C), 26.6 (3C), 21.3 (20.8), 21.3 (20.7)

(3*R*, 5*S*, 6*S*)-6-Benzyloxymethoxy-3,5,7,7-tetramethyloctanoic acid 1-methylcyclopentyl ester ((±)-102c)



(±)-**101c** *syn*-(±)-**102c** *anti*-(±)-**102c**

syn/*anti* 82:18

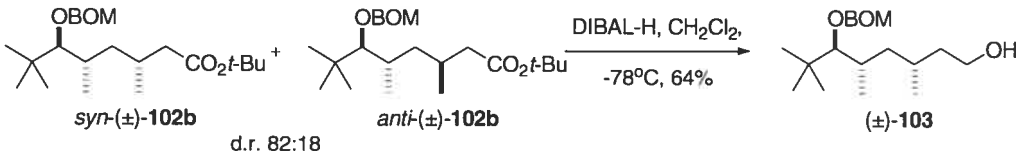
Compound (±)-**101c** (0.060 g, 0.15 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-(±)-**102c** and *anti*-(±)-**102c** (0.043 g, 73% combined yield) in a ratio of 82:18 *syn/anti*.

IR (thin film) 2959, 2874, 1728, 1456, 1374 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.34 (m, 5H), 4.85 (d, 1H, J = 6.8 Hz), 4.78 (d, 1H, J = 6.8 Hz), 4.72 (d, 1H, J = 11.8 Hz), 4.66 (d, 1H, J = 11.8 Hz), 2.40 (dd, 1H, J = 4.3, 14.2 Hz), 2.13 (m, 3H), 2.03 (m, 1H), 1.88 (dd, 1H, J = 9.5, 14.2 Hz), 1.79 (m, 1H), 1.72 (m, 7H), 1.57 (s, 3H), 1.56 (s, minor), 1.14 (m, 1H), 1.08 (d, 3H, J = 7.0 Hz), 0.99 (d, 3H, J = 6.6 Hz), 0.95 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 172.8 (172.4), 137.7, 128.0 (2C), 127.4 (2C), 127.2, 96.6 (96.4), 92.1 (91.8), 89.2 (89.1), 69.8, (44.2) 41.7, 39.2, 38.8, 38.8, 38.7, 36.3, 30.8 (30.4), 28.3 (27.9), 26.6 (3C), 24.0, 23.4 (2C), 21.3 (20.8)

(3*R*, 5*S*, 6*S*)-6-Benzyloxymethoxy-3,5,7,7-tetramethyloctan-1-ol ((±)-103)



syn-(±)-**102b** *anti*-(±)-**102b** d.r. 82:18 (±)-**103**

Following general procedure A, the diastereomeric mixture of *syn*- and *anti*- esters **(±)-102 b** (0.16 g, 0.42 mmol) was reduced. Chromatographic purification (5% EtOAc/hexanes) provided pure **(±)-103** (0.087 g), and mixtures of diastereomers (0.038 g) in 94% combined yield.

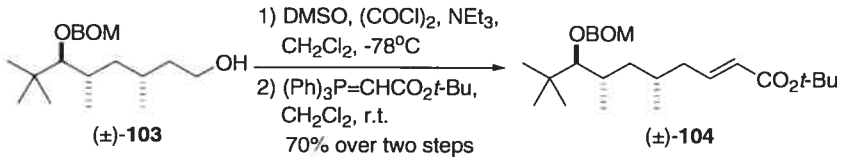
IR (thin film) 3368, 2956, 2872, 1456, 1362 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.35 (m, 5H), 4.86 (d, 1H, J = 6.8 Hz), 4.79 (d, 1H, J = 6.8 Hz), 4.72 (d, 1H, J = 11.9 Hz), 4.67 (d, 1H, J = 11.9 Hz), 3.76 (m, 1H), 3.63 (m, 1H), 3.11 (d, 1H, J = 1.9 Hz), 1.95-1.86 (m, 2H), 1.75 (m, 1H), 1.69-1.54 (m, 2H), 1.26 (m, 1H), 1.11 (m, 1H), 1.06 (d, 3H, J = 7.0 Hz), 0.97 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.7, 128.0 (2C), 127.4 (2C), 127.2, 96.6, 92.2, 69.9, 60.8, 39.7, 38.3, 36.3, 30.8, 27.2, 26.6 (3C), 21.6, 20.9

HRMS (ESI) *m/z* 345.24002 (calcd for 345.23936 $C_{20}H_{34}O_3Na$)

(*E*)-(5*S*, 7*S*, 8*S*)-8-Benzyloxymethoxy-5,7,9,9-tetramethyldec-2-enoic acid *tert*-butyl ester ((±)-104)



(±)-**103** (±)-**104**

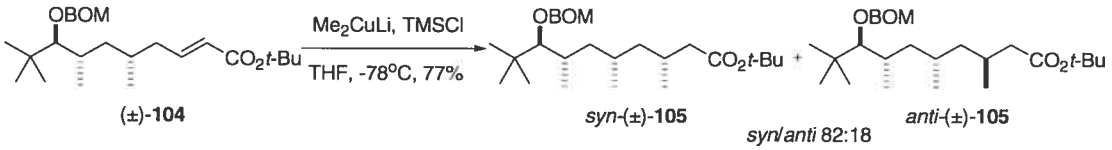
Following general procedure E, alcohol (±)-**103** (0.087 g, 0.27 mmol), provided product (±)-**104** (0.079 g, 79% over two steps) after flash chromatographic purification (2% EtOAc/hexanes).

IR (thin film) 2958, 2873, 1715, 1653, 1456, 1368 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 5H), 6.87 (m, 1H), 5.77 (d, 1H, J = 15.5 Hz), 4.85 (d, 1H, J = 6.9 Hz), 4.78 (m, 1H, J = 6.9 Hz), 4.71 (d, 1H, J = 11.8 Hz), 4.66 (d, 1H, J = 11.8 Hz), 3.09 (d, 1H, J = 1.9 Hz), 2.32 (m, 1H), 1.90 (m, 2H), 1.75 (m, 1H), 1.57 (m, 1H), 1,50 (s, 9H), 1,12 (m, 1H), 1,06 (d, 3H, J = 7.0 Hz), 0.95 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.6, 146.6, 137.7, 128.0 (2C), 127.4 (2C), 127.2, 123.9, 96.6, 92.2, 79.6, 69.8, 39.1, 38.0, 36.2, 30.9, 30.3, 27.8 (3C), 26.6 (3C), 21.4, 21.0

(3*R*, 5*S*, 7*S*, 8*S*)-8-Benzyloxymethoxy-3,5,7,9,9-pentamethyldecanoic acid *tert*-butyl ester ((±)-105)



(±)-**104** *syn*-(±)-**105** *anti*-(±)-**105**

syn/*anti* 82:18

Compound (±)-**104** (0.078 g, 0.19 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes

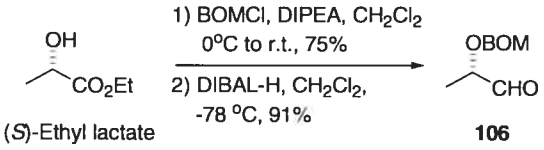
afforded the products *syn*-(±)-**105** and *anti*-(±)-**105** (0.062 g, 77% combined yield) in a ratio of 82:18 *syn/anti*.

IR (thin film) 2958, 2873, 1730, 1457, 1367 cm^{-1}

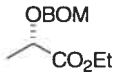
^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.34 (m, 5H), 4.84 (d, 1H, J = 6.9 Hz), 4.78 (d, 1H, J = 6.9 Hz), 4.71 (d, 1H, J = 11.9 Hz), 4.67 (d, 1H, J = 11.9 Hz), 3.10 (d, 1H, J = 1.9 Hz), 2.30 (dd, 1H, J = 4.8, 14.3 Hz), 2.09 (m, 1H), 1.90 (dd, 1H, J = 8.9, 14.3 Hz), 1.86 (m, 1H), 1.58 (m, 2H), 1.47 (s, 9H), 1.35 (m, 1H), 1.02 (d, 3H, J = 7.0 Hz), 1.02 (m, 1H), 0.97 (m, 16H)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 172.5 (172.2), 137.8, 128.0 (2C), 127.4 (2C), 127.2, 96.6, 92.2, 70.6, 69.8, (44.1) 43.5, (42.5) 42.0, (40.2) 40.0, 36.3 (2C), 30.8 (30.5), 28.0, 27.8 (3C), 26.7 (3C), 21.7, (21.3) 21.2, 20.8 (20.7)

(2*S*)-2-Benzyloxymethoxypropionaldehyde (106)



(2*S*)-2-Benzyloxymethoxypropionic acid ethyl ester



To solution of (*S*)-ethyl lactate (6.00 g, 50.8 mmol) in CH_2Cl_2 (250 mL) was cooled to 0 °C. DIPEA (53.08 mL, 304.8 mmol) was added followed by the drop wise addition of BOMCl (39.77 mL, 152.4 mmol). The mixture was stirred at room temperature for 18 h and was quenched by the addition of a saturated solution of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Flash

chromatography (10 % EtOAc/hexanes) afforded the corresponding ethyl ester (9.01 g, 75% yield) as a colorless oil.

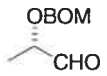
$[\alpha]_D$ –59.3(c = 1.80, $CHCl_3$)

IR (thin film) 2985, 1748, 1498, 1455, 1378 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.32 (m, 5H), 4.86 (s, 2H), 4.69 (d, 1H, J = 11.8 Hz), 4.65 (d, 1H, J = 11.8 Hz), 4.32 (q, 1H, J = 6.9 Hz), 4.20 (q, 2H, J = 7.1 Hz), 1.45 (d, 3H, J = 6.9 Hz), 1.28 (t, 3H, J = 7.1 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.6, 137.3, 128.0 (2C), 127.4 (2C), 127.3, 93.6, 71.3, 69.5, 60.5, 18.2, 13.8

HRMS (ESI) m/z 261.10973 (calcd for 261.10962 $C_{13}H_{18}O_4Na$)



106

To a solution of the ethyl ester in CH_2Cl_2 cooled to -78 °C, DIBAL-H (18.5 mL, 27.7 mmol) was added. The mixture was stirred at -78 °C for 4 h before being quenched with a saturated Na/K tartrate solution. The reaction mixture was diluted with EtOAc and stirred for 30 min at room temperature till a clear biphasic solution was observed. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered. After concentration, the resulting residue was purified by flash chromatography (10 % EtOAc/hexanes) affording aldehyde **106** (4.47 g, 91%) as a colorless oil.

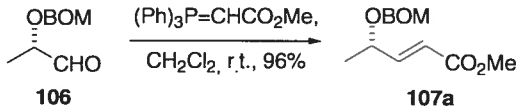
$[\alpha]_D$ –11.34 (c = 1.37, $CHCl_3$)

IR (thin film) 3033, 2892, 1735, 1454, 1380 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.67 (d, 1H, J = 1.5 Hz), 7.36 (m, 5H), 4.89 (s, 2H), 4.73 (d, 1H, J = 11.8 Hz), 4.67 (d, 1H, J = 11.9 Hz), 4.14 (dq, 1H, J = 1.5, 7.0 Hz), 1.35 (d, 3H, J = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.1, 137.0, 128.2 (2C), 127.5 (2C), 127.5, 93.8, 77.8, 69.7, 14.9

(*E*)-(4*S*)-4-Benzyloxymethoxypent-2-enoic acid methyl ester (107a)



Following general procedure C, aldehyde **106** (4.17 g, 21.5 mmol) provided product **107a** ((*E*)- 3.69 g, (*E*+*Z*)- 1.45 g, 96%) after flash chromatographic purification (2% EtOAc/hexanes).

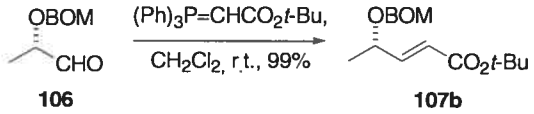
$[\alpha]_D$ –82.1 (*c* = 1.12, $CHCl_3$)

IR (thin film) 3090, 2951, 2889, 1727, 1662, 1498, 1454, 1436 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 (m, 5H), 6.90 (dd, 1H, *J* = 5.8, 15.7 Hz), 6.03 (dd, 1H, *J* = 1.3, 15.7 Hz), 4.81 (d, 1H, *J* = 7.1 Hz), 4.77 (d, 1H, *J* = 11.8 Hz), 4.61 (d, 1H, *J* = 11.8 Hz), 4.46 (m, 1H), 3.77 (s, 3H), 1.34 (d, 3H, *J* = 6.6 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4, 148.7, 137.3, 128.1 (2C), 127.6 (2C), 127.4, 120.2, 92.2, 70.8, 69.3, 51.3, 20.2

(*E*)-(4*S*)-4-Benzyloxymethoxypent-2-enoic acid *tert*-butyl ester (107b)



Following general procedure C, aldehyde **106** (0.15 g, 0.77 mmol) provided product **107b** ((*E*)- 0.14 g, (*E*+*Z*)- 0.084 g, 99%) after flash chromatographic purification (2% EtOAc/hexanes).

$[\alpha]_D$ –78.0 (*c* = 1.24, $CHCl_3$)

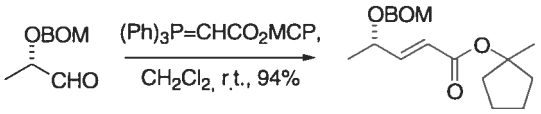
IR (thin film) 3005, 2978, 1715, 1659, 1498, 1455 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 (m, 5H), 6.78 (dd, 1H, *J* = 6.1, 15.7 Hz), 5.93 (dd, 1H, *J* = 11.4, 15.7 Hz), 4.81 (d, 1H, *J* = 7.1 Hz), 4.78 (d, 1H, *J* = 7.1 Hz),

4.68 (d, 1H, J = 11.7 Hz), 4.61 (d, 1H, J = 11.7 Hz), 4.42 (m, 1H), 1.51 (s, 9H), 1.33 (d, 3H, J = 6.6 Hz)

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.9, 149.9, 135.5 (4C), 133.5, 133.4, 129.6 (2C), 127.6 (4C), 122.7, 79.9, 67.5, 38.8, 28.1 (3C), 26.7 (3C), 19.2, 15.5

(*E*)-(4*S*)-4-Benzyloxymethoxypent-2-enoic acid 1-methylcyclopentyl ester (107c)



106 **107c**

Following general procedure C, aldehyde **106** (0.15 g, 0.77 mmol) provided product **107c** ((*E*)- 0.12 g, (*E*+*Z*)- 0.11 g, 94%) after flash chromatographic purification (2% EtOAc/hexanes).

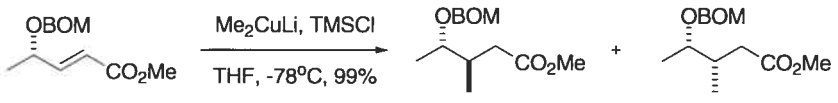
[α]$_D$ –75.3 (c = 1.43, $CHCl_3$)

IR (thin film) 3032, 2969, 1714, 1658, 1454, 1374 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 (m, 5H), 6.79 (dd, 1H, J = 6.0, 15.7 Hz), 5.95 (dd, 1H, J = 1.3, 15.7 Hz), 4.81 (d, 1H, J = 7.1 Hz), 4.78 (d, 1H, J = 7.1 Hz), 4.68 (d, 1H, J = 11.7 Hz), 4.61 (d, 1H, J = 11.7 Hz), 4.44 (m, 1H), 2.15 (m, 2H), 1.74 (m, 4H), 1.65 (m, 2H), 1.60 (s, 3H), 1.33 (d, 3H, J = 6.6 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.4, 147.2, 137.4, 128.1 (2C), 127.6 (2C), 127.4, 122.4, 92.2, 89.6, 70.9, 69.2, 38.8, 38.7, 24.0, 23.5 (2C), 20.3

(3*R*, 4*S*)-4-Benzyloxymethoxy-3-methylpentanoic acid methyl ester (108a)



107a *anti*-**108a** *syn*-**108a**

anti/*syn* 72:28

Compound **107a** (0.10 g, 0.40 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *anti*-**108a** and *syn*-**108a** (0.11 g, 99% combined yield) in a ratio of 72:28 *anti*/ *syn*.

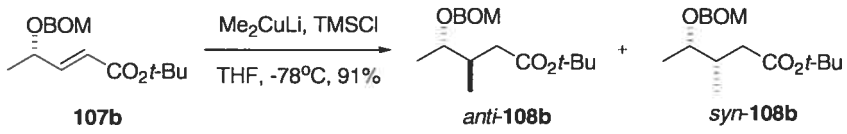
$[\alpha]_D$ +16.9 (c = 1.61, $CHCl_3$)

IR (thin film) 2974, 2885, 17 39, 1456, 1437, 1381 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.35 (nm 5H), 4.83 (m, 1H), 4.77 (m, 1H), 4.64 (s, 1H), 3.78 (m, minor), 3.69 (s, 3H), 3.68 (s, minor), 3.63 (m, 1H), 2.55 (m, 1H), 2.19 (m, 2H), 1.19 (d, 3H, J = 6.3 Hz), 1,17 (d, J = 6.4 Hz, minor), 1.00 (d, 3H, J = 6.4 Hz), 2.14 (d, J = 6.8 Hz, minor)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) (173.4) 173.3, (137.6) 137.6, 128.1 (2C), 127.5 (2C), 127.3, 92.9 (92.7), 76.2 (75.1), 69.2 (69.1), 51.0, 37.3 (36.6), 35.6 (34.8), 16.6 (15.9), 15.6 (14.7)

(3*R*, 4*S*)-4-Benzyloxymethoxy-3-methylpentanoic acid *tert*-butyl ester (108b)



107b — *anti*-**108b** — *syn*-**108b**

anti/*syn* 86:14

Compound **107b** (0.093 g, 0.32 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *anti*-**108b** and *syn*-**108b** (0.089 g, 91% combined yield) in a ratio of 86:14 *anti*/ *syn*.

$[\alpha]_D$ +10.5 (c = 1.22, $CHCl_3$)

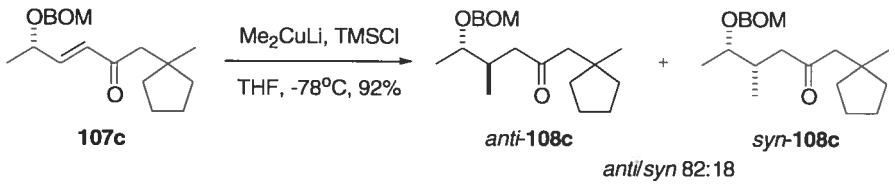
IR (thin film) 3032, 2977, 2884, 1730, 1498, 1456 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.35 (m, 5H), 4.84 (d, 1H, J = 7.1 Hz), 4.77 (d, 1H, J = 7.1 Hz), 4.66 (d, 1H, J = 11.9 Hz), 4.63 (d, 1H, J = 11.8 Hz), 3.75 (m, minor), 3.64 (m, 1H), 2.45 (dd, 1H, J = 5.0, 14.6 Hz), 2.17 (m, 1H), 2.05 (dd, 1H, J = 8.9,

14.6 Hz), 1.47 (s, 9H), 1.46 (s, minor), 1.18 (d, 3H, J = 6.3 Hz), 1.00 (d, 3H, J = 6.7 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) (172.4) 172.2, 137.6, 128.1 (2C), 127.4 (2C), 127.3, 92.8, 79.7, 76.1 (75.4), 69.2 (69.1), 38.8 (38.2), 35.5 (35.0), 27.8 (3C), 16.4 (16.7), 15.3 (14.6)

(4*R*, 5*S*)-5-Benzyloxymethoxy-4-methyl-1-(1-methylcyclopentyl)-hexan-2-one (108c)



107c *anti*-**108c** *syn*-**108c**

anti/*syn* 82:18

Compound **107c** (0.075 g, 0.24 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *anti*-**108c** and *syn*-**108c** (0.072 g, 92% combined yield) in a ratio of 86:14 *anti/ syn.*

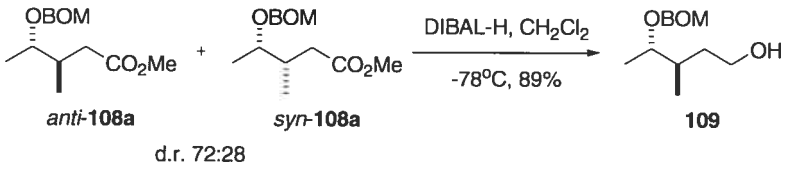
$[\alpha]_D$ +9.1 (c = 1.65, $CHCl_3$)

IR (thin film) 2968, 2877, 1727, 1454, 1376 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.35 (m, 5H), 4.84 (d, 1H, J = 7.1 Hz), 4.77 (d, 1H, J = 7.1 Hz), 4.64 (s, 2H), 3.75 (m, minor), 3.64 (m, 1H), 2.45 (dd, 1H, J = 4.8, 14.5 Hz), 2.25-2.03 (m, 4H), 1.80-1.61 (m, 6H), 1.57 (s, 3H), 1.18 (d, 3H, J = 6.3 Hz), 0.99 (d, 3H, J = 6.6 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) (172.5) 172.4, 137.6, 128.1 (2C), 127.5 (2C), 127.3, 92.6 (92.8), 76.2 (75.5), 69.2 (69.1), 38.8, 38.7, 38.7, 35.5 (35.0), 23.4 (2C), 16.5 (16.2), 15.3 (14.3)

(3*R*, 4*S*)-4-Benzyloxymethoxy-3-methylpentan-1-ol (109)



Following general procedure A, the diastereomeric mixture of *anti*- and *syn*- esters **108a** (3.48 g, 13.1 mmol) was reduced to give alcohol **109** (2.77 g, 87%) upon purification of the resulting diastereomeric alcohols by flash chromatography with 2% EtOAc/hexanes.

$[\alpha]_D$ +26.0 (c = 1.28, $CHCl_3$)

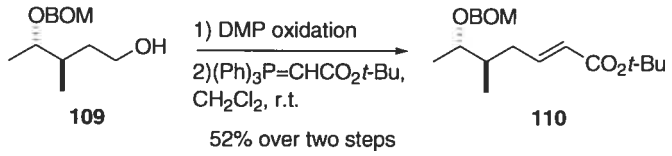
IR (thin film) 3402, 2964, 2880, 1454, 1380 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33 (m, 5H), 4.86 (d, 1H, J = 7.1 Hz), 4.80 (d, 1H, J = 7.1 Hz), 4.67 (d, 1H, J = 11.7 Hz), 4.64 (d, 1H, J = 11.7 Hz), 3.79-3.63 (m, 3H), 1.82 (m, 1H), 1.72 (m, 2H), 1.49 (m, 1H), 1.19 (d, 3H, J = 6.3 Hz), 0.98 (d, 3H, J = 6.9 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.5, 128.1 (2C), 127.5 (2C), 127.4, 92.8, 76.7, 69.2, 60.3, 35.1, 34.6, 16.0, 14.7

HRMS (ESI) *m/z* 261.14612 (calcd for 261.14509 $C_{14}H_{22}O_3Na$)

(*E*)-(5*R*, 6*S*)-6-Benzyloxymethoxy-5-methylhept-2-enoic acid *tert*-butyl ester (110)



To a solution of alcohol **109** (0.18 g, 0.75 mmol) in CH_2Cl_2 (15 mL) cooled to 0 °C pyridine (0.24 mL, 2.3 mmol) was added followed by the drop wise addition of Dess-Martin periodinane (0.38 g, 0.89 mmol). The mixture was stirred for 3 h at room temperature before being quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 x 5 mL), the combined organic layers were dried

over Na_2SO_4 and then concentrated. The crude aldehyde was taken onto the next step without any further purification. To a solution of the aldehyde from above in CH_2Cl_2 (15 mL) was added the *tert*-butyl phosphanylidene (0.34 g, 0.90 mmol). The reaction mixture was stirred at room temperature for 18 h and then evaporated to dryness. The crude solid was triturated with hexanes/Et_2O (3:1), and the resulting slurry was filtered over a pad of celite. The filtrate was concentrated and purified by flash chromatography (2% EtOAc/hexanes) affording enoate **110** ((*E*)- 0.11 g, (*Z*)- 0.20 g, 52% over two steps) as a colorless oil.

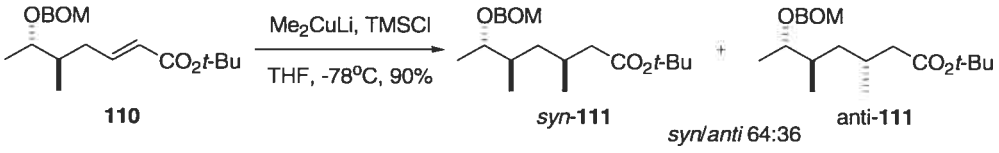
$[\alpha]_D$ +9.8 (c = 1.22, $CHCl_3$)

IR (thin film) 29c77, 2932, 2885, 1713, 1652, 1455, 1367 m^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 (m, 5H), 6.88 (m, 1H), 5.78 (d, 1H, J = 15.5 Hz), 4.85 (d, 1H, J = 7.1 Hz), 4.78 (d, 1H, J = 7.1 Hz), 4.64 (s, 2H), 3.64 (m, 1H), 2.42 (m, 1H), 2.03 (m, 1H), 1.82 (m, 1H), 1.50 (s, 9H), 1.18 (d, 3H, J = 6.3 Hz), 0.94 (d, 3H, J = 6.8 Hz)

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.8, 146.6, 137.8, 128.3 (2C), 127.7 (2C), 127.5, 124.2, 93.1, 79.9, 76.6, 37.8, 28.0 (3C), 16.4, 14.9

(3*S*, 5*R*, 6*S*)-6-Benzyloxymethoxy-3,5-dimethylheptanoic acid *tert*-butyl ester (111)



Compound **110** (0.090 g, 0.27 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**111** and *anti*-**111** (0.085 g, 90% combined yield) in a ratio of 64:36 *syn/anti*.

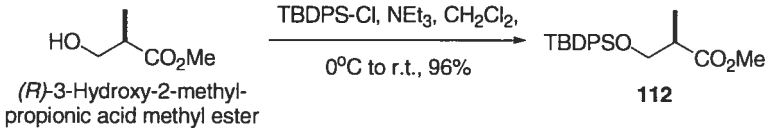
$[\alpha]_D$ +10.2 (c = 1.37, $CHCl_3$)

IR (thin film) 2970, 1882, 17.29, 1497, 1456 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.35 (m, 5H), 4.84 (d, J = 7.0 Hz, minor), 4.83 (d, 1H, J = 7.0 Hz), 4.79 (d, 1H, J = 7.0 Hz), 4.78 (d, J = 7.0 Hz, minor), 4.64 (s, 2H), 3.71 (m, 1H), 3.63 (m, minor), 2.25 (m, 1H), 2.16 (m, minor), 1.99 (m, 2H), 1.80 (m, 1H), 1.47 (s, 9H), 1.37 (m, 1H), 1.26 (m, minor), 1.17 (d, J = 6.4 Hz, minor), 1.13 (d, 3H, J = 6.4 Hz), 1.06 (m, 1H), 0.98 (d, 3H, J = 6.4 Hz), 0.94 (d, 3H, J = 6.8 Hz), 0.93 (d, J = 6.7 Hz, minor)

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 172.3 (172.1), 137.7, 128.1 (2C), 127.5 (2C), 127.3, (92.9) 92.8, 79.8, 75.9, 69.0, (43.8) 42.3, 39.8 (39.2), (34.9) 34.6, 27.8 (3C), 27.6 (27.6), 20.2 (18.6), (15.7) 15.0, 14.4 (13.9)

(2*R*)-3-(*tert*-Butyldiphenylsilanoxy)-2-methylpropionic acid methyl ester (112)



(R)-3-Hydroxy-2-methyl-propionic acid methyl ester

112

To a solution of (*R*)-3-hydroxy-2-methyl-propionic acid methyl ester (2.00 mL, 15.9 mmol) in CH_2Cl_2 (160 mL), were added triethylamine (5.30 mL, 38.11 mmol) and DMAP (0.20 g, 1.6 mmol). The reaction mixture was cooled to 0 °C followed by the addition of TBDPSCl (4.87 mL, 19.1 mmol), and stirred at room temperature for 18 h. The reaction mixture was quenched with a solution of saturated NH_4Cl, the aqueous layers were extracted with CH_2Cl_2 (3 x 20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by flash chromatography (10% EtOAc/hexanes) providing product **112** (5.50 g, 96%)

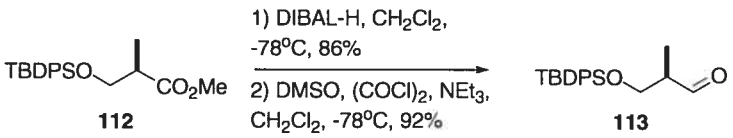
$[\alpha]_D$ -14.8 (c = 1.04, $CHCl_3$)

IR (thin film) 3072, 2933, 2859, 1742, 1473, 1429 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.68 (m, 4H), 7.43 (m, 6H), 3.82 (m, 1H), 3.79 (m, 1H), 3.71 (s, 3H), 2.70 (m, 1H), 1.18 (d, 3H, J = 7.0 Hz), 1.06 (s, 9H)

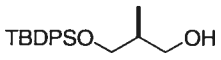
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 183.5, 136.0 (4C), 133.9 (2C), 130.1 (2C), 128.1 (4C), 66.3, 52.0, 42.8, 27.1 (3C), 19.6, 13.9

(2*R*)-3-(*tert*-Butyldiphenylsilanoxy)-2-methyl-propionaldehyde (113)



112 113

(2*S*)-3-(*tert*-Butyldiphenylsilanoxy)-2-methylpropan-1-ol



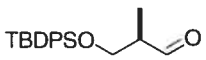
Following general procedure A compound **112** (5.50 g, 18.6 mmol) was reduced to give the corresponding alcohol (5.20 g, 86%), upon purification by flash chromatography with 10% EtOAc/hexanes.

[α]$_D$ -5.7 (*c* = 1.62, $CHCl_3$)

IR (thin film) 3370, 3072, 2958, 2858, 1472, 1478 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.70 (m, 4H), 7.44 (m, 6H), 3.75 (m, 1H), 3.70 (d, 2H, *J* = 6.0 Hz), 3.62 (m, 1H), 2.35 (brs, 1H), 2.01 (m, 1H), 1.09 (s, 9H), 0.86 (d, 3H, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 136.0 (4C), 133.5 (2C), 130.2 (2C), 128.2 (4C), 69.2, 68.1, 37.7, 27.3 (3C), 19.6, 13.6



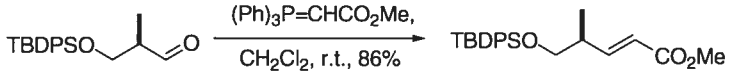
107

Following general procedure B, the alcohol from above (1.00 g, 2.69 mmol), provided aldehyde **113** (0.80 g, 92%) after flash chromatographic purification (2% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 9.80 (d, 1H, *J* = 1.4 Hz), 7.68 (m, 4H), 7.45 (m, 6H), 3.84 (m, 2H), 2.54 (m, 1H), 1.14 (d, 3H, *J* = 7.1 Hz), 1.08 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.9, 136.0 (4C), 133.6 (2C), 130.2 (2C), 128.1 (4C), 64.5, 49.2, 27.2 (3C), 19.7, 10.7

(*E*)-(4*S*)-5-(*tert*-Butyldiphenylsilanoxy)-4-methylpent-2-enoic acid methyl ester (114a)



113 **114a**

Following general procedure C, aldehyde **113** (9.01 g, 27.6 mmol) provided product **114a** (9.10 g, 86%) after flash chromatographic purification (2% EtOAc/hexanes).

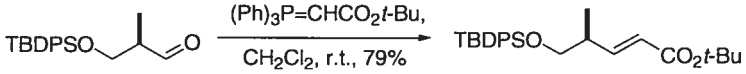
[α]$_D$ -15.1 (*c* = 1.15, $CHCl_3$)

IR (thin film) 2932, 2859, 1726, 1659, 1473, 1428 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (m, 4H), 7.43 (m, 6H), 6.98 (dd, 1H, *J* = 7.3, 15.8 Hz), 5.87 (dd, 1H, *J* = 1.3, 15.8 Hz), 3.76 (s, 3H), 3.60 (m, 2H), 2.58 (m, 1H), 1.09 (m, 12H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 167.0, 151.6, 135.5 (2C), 135.5 (2C) 133.4, 133.4, 129.6 (2C), 127.6 (4C), 121.1, 67.4, 51.3, 39.1, 26.7 (3C), 19.2, 15.5

(*E*)-(4*S*)-5-(*tert*-Butyldiphenylsilanoxy)-4-methylpent-2-enoic acid *tert*-butyl ester (114b)



113 **114a**

Following general procedure C, aldehyde **113** (0.402 g, 1.23 mmol) provided product **114b** (0.41 g, 79%) after flash chromatographic purification (2% EtOAc/hexanes).

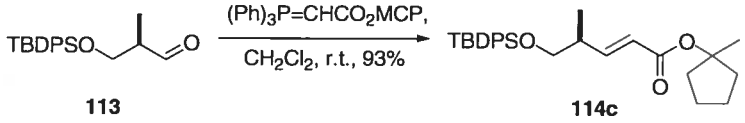
[α]$_D$ -13.7 (*c* = 1.05, $CHCl_3$)

IR (thin film) 2963, 1932, 2859, 1714, 1652, 1473, 1428 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68 (m, 4H), 7.43 (m, 6H), 6.98 (dd, 1H, J = 7.2, 15.8 Hz), 5.77 (dd, 1H, J = 1.3, 15.8 Hz), 3.59 (m, 2H), 2.57 (m, 1H), 1.51 (s, 9H), 1.10-1.07 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.4, 136.0 (4C), 134.0 (2C), 130.1 (2C), 128.1 (4C), 123.2, 80.4, 68.0, 39.3, 28.6 (3C), 27.2 (3C), 19.7, 16.0

(*E*)-(4*S*)-5-(*tert*-Butyldiphenylsilanoxy)-4-methylpent-2-enoic acid 1-methylcyclopentyl ester (114c)



113 **114c**

Following general procedure C, aldehyde **113** (0.402 g, 1.23 mmol) provided product **114c** (0.51 g, 93%) after flash chromatographic purification (2% EtOAc/hexanes).

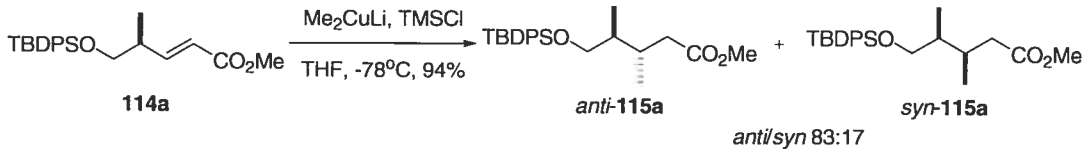
$[\alpha]_D$ -13.0 (c = 1.15, $CHCl_3$)

IR (thin film) 2962, 2859, 1714, 1654, 1472, 1428 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (m, 4H), 7.42 (m, 6H), 6.89 (dd, 1H, J = 7.2, 15.8 Hz), 5.79 (dd, 1H, J = 1.3, 15.8 Hz), 3.59 (d, 1H, J = 1.3 Hz), 3.58 (d, 1H, J = 1.0 Hz), 2.56 (m, 1H), 2.14 (m, 2H), 1.73 (m, 4H), 1.64 (m, 2H), 1.60 (s, 3H), 1.10-107 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.7, 150.5, 136.0 (4C), 134.0 (2C), 130.1 (2C), 128.1 (4C), 123.1, 90.0, 68.0, 39.6 (2C), 39.4, 27.2 (3C), 24.8, 24.2 (2C), 19.7, 16.0

(3*S*, 4*S*)-5-(*tert*-Butyldiphenylsilanoxy)-3,4-dimethylpentanoic acid methyl ester (115a)



Compound **114a** (5.20 g, 13.6 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *anti*-**115a** and *syn*-**115a** (5.10 g, 94% combined yield) in a ratio of 83:17 *anti/ syn.*

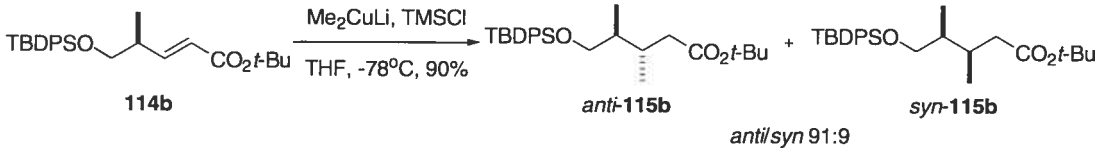
$[\alpha]_D$ +5.0 (c = 1.10, $CHCl_3$)

IR (thin film) 2961, 1727, 1472, 1428 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68 (m, 4H), 7.41 (m, 6H), 3.68 (s, 3H), 3.55 (m, 2H), 2.42 (dd, 1H, J = 4.2, 14.6 Hz), 2.20 (m, 1H), 2.07 (dd, 1H, J = 10.0 14.6 Hz), 1.71 (m, 1H), 1.08 (s, 9H), 0.93 (d, 3H, J = 6.8 Hz), 0.89 (d, 3H, J = 6.9 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.6 (174.2), 136.3 (4C), 134.7 (2C), 130.0 (2C), 128.1 (4C), (67.4) 67.0, 51.8, 40.5 (40.3), 38.4, 32.3 (31.4), 27.2 (3C), 19.7, 17.8 (15.3), 13.9 (12.3)

(3*S*, 4*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-3,4-dimethylpentanoic acid *tert*-butyl ester (115b)



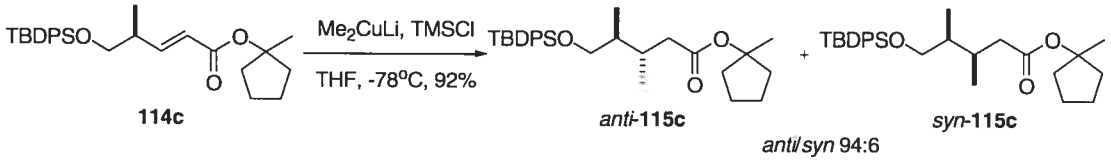
Compound **114b** (0.10 g, 0.24 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *anti*-**115b** and *syn*-**115b** (0.094 g, 90% combined yield) in a ratio of 91:9 *anti/ syn.*

$[\alpha]_D$ +3.9 (c = 1.11, $CHCl_3$)

IR (thin film) 2963, 1730, 1473, 1428 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.72 (m 4H), 7.45 (m, 6H), 3.56 (m, 2H), 2.37 (dd, 1H, J = 4.2, 14.4 Hz), 2.37 (m, 1H), 1.98 (dd, 1H, J = 10.0, 14.4 Hz), 1.74 (m, 1H), 1.49 (s, 9H), 1.11 (s, 9H), 0.97 (d, 3H, J = 6.9 Hz), 0.92 (d, 3H, J = 6.8 Hz)
^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 173.5 (173.2), 136.1 (4C), 134.3 (2C), 130.0 (2C), 128.0 (4C), 80.3, (67.4) 67.1, (41.9) 40.6, 39.8, 32.3 (31.6), 28.6 (3C), 27.3 (3C), 19.7, 17.7 (15.1), 13.9 (12.3)

(3*S*, 4*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-3,4-dimethylpentanoic acid 1-methylcyclopentyl ester (115c)



114c *anti*-**115c** *syn*-**115c**
anti/*syn* 94:6

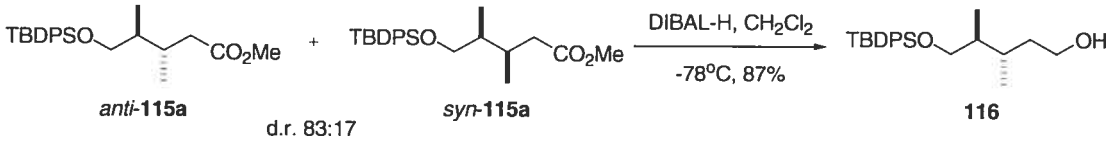
Compound **114c** (0.10 g, 0.22 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *anti*-**115c** and *syn*-**115c** (0.095 g, 92% combined yield) in a ratio of 94:6 *anti*/*syn*.

$[\alpha]_D$ +3.1 (c = 1.18, $CHCl_3$)

IR (thin film) 2959, 2859, 1739, 1428 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 7.70 (m, 4H), 7.42 (m, 6H), 3.53 (m, 2H), 2.35 (dd, 1H, J = 4.3, 14.4 Hz), 2.10 (m, 3H), 1.96 (dd, 1H, J = 10.1, 14.4 Hz), 1.67 (m, 7H), 1.56 (s, 3H), 1.07 (s, 9H), 0.93 (d, 3H, J = 6.9 Hz), 0.88 (d, 3H, J = 6.9 Hz),
^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 173.7 (173.2), 135.3 (2C), 135.3 (2C), 133.5, 133.5, 129.2, 129.2, 127.3 (4C), 89.1, (67.5) 67.1, (41.7) 40.5, 38.9, 38.9, 38.7, 32.3 (31.5), 26.5 (3C), 24.0, 23.4 (2C), 18.9, 16.9, 13.9 (12.2)

(3*S*, 4*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-3,4-dimethylpentan-1-ol (116)



Following general procedure A, the diastereomeric mixture of *anti*- and *syn*- esters **115a** (1.50 g, 3.76 mmol) was reduced to give pure **116** (1.22 g, 87%) upon purification (of the resulting diastereomeric alcohols) by flash chromatography with 2% EtOAc/hexanes.

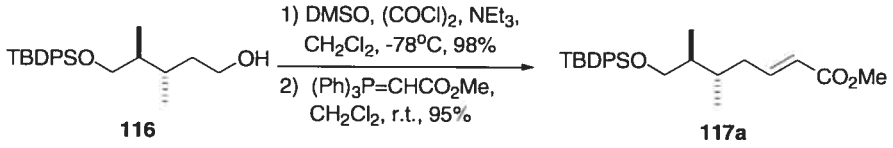
$[\alpha]_D$ -0.9 (c = 1.08, $CHCl_3$)

IR (thin film) 3340, 3072, 2859, 1472, 1428, 1390 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (m, 4H), 7.43 (m, 6H), 3.654 (m, 1H), 3.62 (m, 3H), 1.61-1.50 (m, 4H), 1.24 (m, 1H), 1.08 (s, 9H), 0.89 (m, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 136.1 (4C), 134.3 (2C), 130.0 (2C), 128.0 (4C), 67.1, 62.2, 40.8, 35.9, 31.1, 27.3 (3C), 19.7, 17.7, 13.6

(*E*)-(5*S*, 6*S*)-7-(*tert*-Butyldiphenylsilanyloxy)-5,6-dimethylhept-2-enoic acid methyl ester (117a)



Following general procedures B and C, oxidation of alcohol **116** (1.25 g, 3.37 mmol) afforded the desired aldehyde (1.22 g, 98%). Wittig homologation of the aldehyde (0.17 g, 0.46 mmol) gave product **117a** (0.19 g, 95%) as a colorless oil after flash chromatography with 2% EtOAc/hexanes.

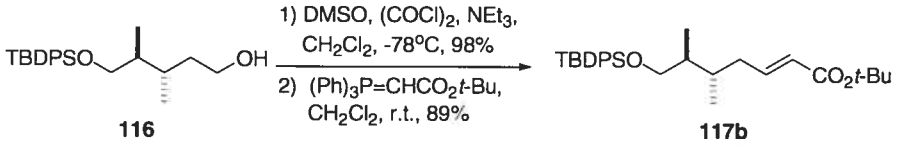
$[\alpha]_D$ +11.6 (c = 1.02, $CHCl_3$)

IR (thin film) 2959, 1726, 1657, 1428 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (m, 4H), 7.43 (m, 6H), 6.96 (m, 1H), 5.82 (d, 1H, J = 15.6 Hz), 3.76 (s, 3H), 3.56 (m, 2H), 2.27 (m, 1H), 1.97 (m, 1H), 1.83 (m, 1H), 1.69 (m, 1H), 1.07 (s, 9H), 0.90 (m, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.5, 149.7, 136.0 (4C), 134.3 (2C), 130.0 (2C), 128.0 (4C), 122.2, 66.9, 51.8, 40.5, 36.2, 34.3, 27.3 (3C), 19.7, 17.5, 14.0

(*E*)-(5*S*, 6*S*)-7-(*tert*-Butyldiphenylsilanyloxy)-5,6-dimethylhept-2-enoic acid *tert*-butyl ester (117b)



116 **117b**

Following general procedures B and C, oxidation of alcohol **116** (1.25 g, 3.37 mmol) afforded the desired aldehyde (1.22 g, 98%). Wittig homologation of the aldehyde (0.17 g, 0.46 mmol) gave product **117b** (0.19 g, 89%) as a colorless oil after flash chromatography with 2% EtOAc/hexanes.

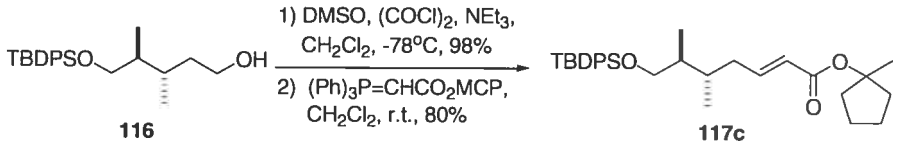
$[\alpha]_D$ +11.4 (c = 1.06, $CHCl_3$)

IR (thin film) 2962, 2932, 1714, 1652, 1473, 1428 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (m, 4H), 7.41 (m, 6H), 6.86 (m, 1H), 5.73 (d, 1H, J = 15.5 Hz), 3.57 (m, 2H), 2.22 (m, 1H), 1.93 (m, 1H), 1.82 m, 1H), 1.68 (m, 1H), 1.51 (s, 9H), 1.07 (s, 9H), 0.90 (m, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.5, 148.0, 136.0 (4C), 134.3 (2C), 130.0 (2C), 128.0 (4C), 124.4, 80.4, 66.9, 40.5, 36.1, 34.4, 28.6 (3C), 27.3 (3C), 19.7, 17.5, 14.1

(*E*)-(5*S*, 6*S*)-7-(*tert*-Butyldiphenylsilanyloxy)-5,6-dimethylhept-2-enoic acid 1-methylcyclopentyl ester (117c)



116 117c

Following general procedures B and C, oxidation of alcohol **116** (1.25 g, 3.37 mmol) afforded the desired aldehyde (1.22 g, 98%). Wittig homologation of the aldehyde (0.17 g, 0.46 mmol) gave product **117c** (0.18 g, 80%) as a colorless oil after flash chromatography with 2% EtOAc/hexanes.

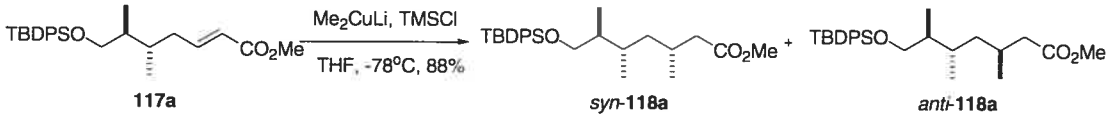
$[\alpha]_D$ +10.5 (c = 1.00, $CHCl_3$)

IR (thin film) 2961, 1714, 1652, 1428 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68 (m, 4H), 7.42 (m, 6H), 6.86 (m, 1H), 5.74 (d, 1H, J = 15.6 Hz), 3.55 (m, 2H), 2.24 (m, 1H), 2.16 (m, 2H), 1.94 (m, 1H), 1.71 (m, 8H), 1.60 (s, 3H), 1.07 (s, 9H), 0.89 (m, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.6, 148.0, 136.0 (4C), 134.3 (2C), 130.0 (2C), 128.0 (4C), 124.2, 89.9, 66.9, 40.5, 39.6 (2C), 36.1, 34.4, 27.3 (3C), 24.9, 24.2 (2C), 19.7, 17.5, 14.1

(3*R*, 5*S*, 6*S*)-7-(*tert*-Butyldiphenylsilanyloxy)-3,5,6-trimethylheptanoic acid methyl ester (118a)



117a *syn*-118a *anti*-118a

syn/*anti* 67:33

Compound **117a** (0.10 g, 0.24 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**118a** and *anti*-**118a** (0.091 g, 88% combined yield) in a ratio of 67:33 *syn/anti*.

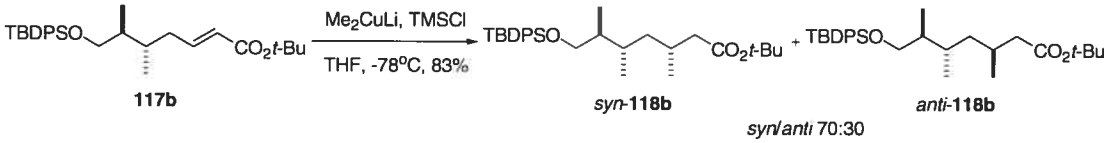
$[\alpha]_D$ -6.9 (c = 1.06, $CHCl_3$)

IR (thin film) 2959, 1740, 1428 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68, (m, 4H), 7.42 (m, 6H), 3.68 (s, minor), 3.65 (s, 3H), 3.61-3.46 (m, 2H), 2.41 (dd, 1H, J = 3.4, 13.8 Hz), 2.28-2.14 (m, 1H), 1.99 (m, 2H), 1.67 (m, 1H), 1.25 (m, 1H), 1.07 (s, 9H), 0.96-0.82 (m, 9H), 0.74 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.7 (173.5), 135.5 (4C), 133.9 (2C), 129.4 (2C), 127.5 (4C), (66.5) 66.3, 51.2, (40.7) 40.7, 40.2, 40.0 (39.2), 31.5 (31.0), 28.0 (27.8), 26.7 (3C), 20.9, 19.1, 17.1 (16.7,), 13.5 (13.2)

(3*R*, 5*S*, 6*S*)-7-(*tert*-Butyldiphenylsilanyloxy)-3,5,6-trimethylheptanoic acid *tert*-butyl ester (118b)



Compound **117b** (0.10 g, 0.21 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**118b** and *anti*-**118b** (0.086 g, 83% combined yield) in a ratio of 70:30 *syn/anti*.

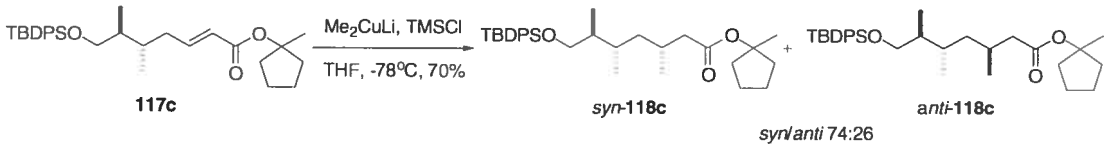
$[\alpha]_D$ -6.3 (c = 1.25, $CHCl_3$)

IR (thin film) 2961, 2859, 1729, 1473, 1428 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68 (m, 4H), 7.42 (m, 6H), 3.62-3.45 (m, 2H), 2.32 (dd, 1H, J = 4.2, 14.4 Hz), 1.97 (m, 1H), 1.82 (dd, 1H, J = 9.5, 14.4 Hz), 1.65 (m, 2H), 1.46 (s, 9H), 1.26 (m, 1H), 1.07 (s, 9H), 0.94 (d, 3H, J = 6.6 Hz), 0.87 (m, 6H), 0.74 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.6 (172.3), 135.3 (2C), 135.3 (2C), 133.7, 133.7, 129.2, 129.2, 127.2 (4C), (79.6) 79.5, (66.3) 66.2, 41.9, (40.6) 40.1, 39.9 (38.7), 31.4 (30.6), 28.0, 27.9 (3C), 26.6 (3C), 20.6, 18.9 (18.6), 16.9 (16.6), 13.4 (12.8)

(3*R*, 5*S*, 6*S*)-7-(*tert*-Butyldiphenylsilanyloxy)-3,5,6-trimethylheptanoic acid 1-methylcyclopentyl ester (118c)



Compound **117c** (0.10 g, 0.20 mmol) was subject to a cuprate addition following general procedure D. Flash chromatographic purification with 2% EtOAc/hexanes afforded the products *syn*-**118c** and *anti*-**118c** (0.072 g, 70% combined yield) in a ratio of 74:26 *syn/anti*.

$[\alpha]_D$ -8.2 (c = 1.07, $CHCl_3$)

IR (thin film) 2961, 1728, 1462, 1428 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68 (m, 4H), 7.42 (m, 6H), 3.62-3.40 (m, 2H), 2.33 (dd, 1H, J = 4.1, 14.3 Hz), 2.10 (m, 3H), 1.98 (m, 1H), 1.82 (dd, 1H, J = 9.6, 14.3 Hz), 1.72-1.62 (m, 8H), 1.56 (s, 3H), 1.07 (s, 9H), 0.94 (d, 3H, J = 6.6 Hz), 0.87 (m, 6H), 0.74 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.7 (172.5), 135.3 (2C), 135.3 (2C), 133.7, 133.6, 129.2, 129.2, 127.2 (4C), (89.1) 89.1, (66.3) 66.2, 41.7 (41.7), (40.6) 40.1, 39.9, 38.9 (38.8), (38.8) 38.7, 31.3 (30.6), 28.0 (27.8), 26.5 (3C), 24.0, 23.4 (2C), 20.7, 18.9 (18.6), 16.8 (16.5), 13.3 (12.8)

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