Chapter 1
Iterative Strategies for the Synthesis of Deoxypropionates

This chapter gives an overview of iterative synthetic strategies for the construction of deoxypropionates. Non-catalytic methodologies are briefly summarized followed by an overview of enantioselective catalytic iterative methods. This chapter serves as an introduction to the following chapters in which the synthesis of methyl-branched lipids, (deoxy)propionates, from mycobacteria is described.

1.1 Introduction

Polypropionates (polyketides) are synthesized in nature by the polymerization of propionyl subunits via Claisen condensation reactions followed by reduction of the resulting keto-function. This results in a continuous methyl-hydroxy-methyl iteration with all possible stereo-configurations, coming in cyclic as well as and acyclic structures. A broad variety of synthetic methods for the construction of polypropionates has been described over the last decades.[1] Especially the chiral auxiliary based aldol condensation reaction, developed by Evans, has contributed to a large extend to the synthesis of polypropionates.[2]

Nature sometimes deviates from the polypropionate pattern (**1**, **2**, **3**, **4**, **5**, **6**, Figure 2) by formal removal of the hydroxyl group resulting in *syn* (**7**) or *anti* (**8**) 1,3,5,… *n*-polymethyl alkyl chains (Figure 1), the deoxypropionates. Deoxypropionates are the enzymatically dehydrated and reduced products of polypropionates and are widely distributed as individual and combined structures in natural products.

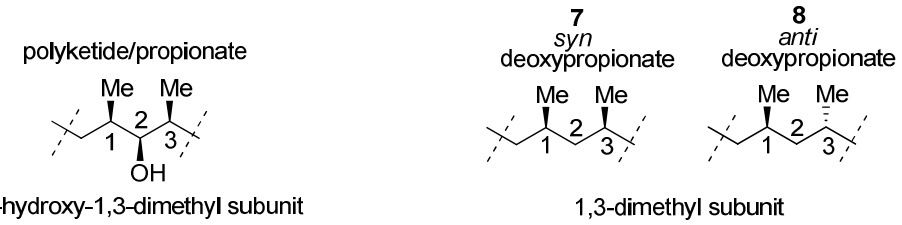


Figure 1: The polyketide/propionate structure compared to the related deoxypropionate structure.

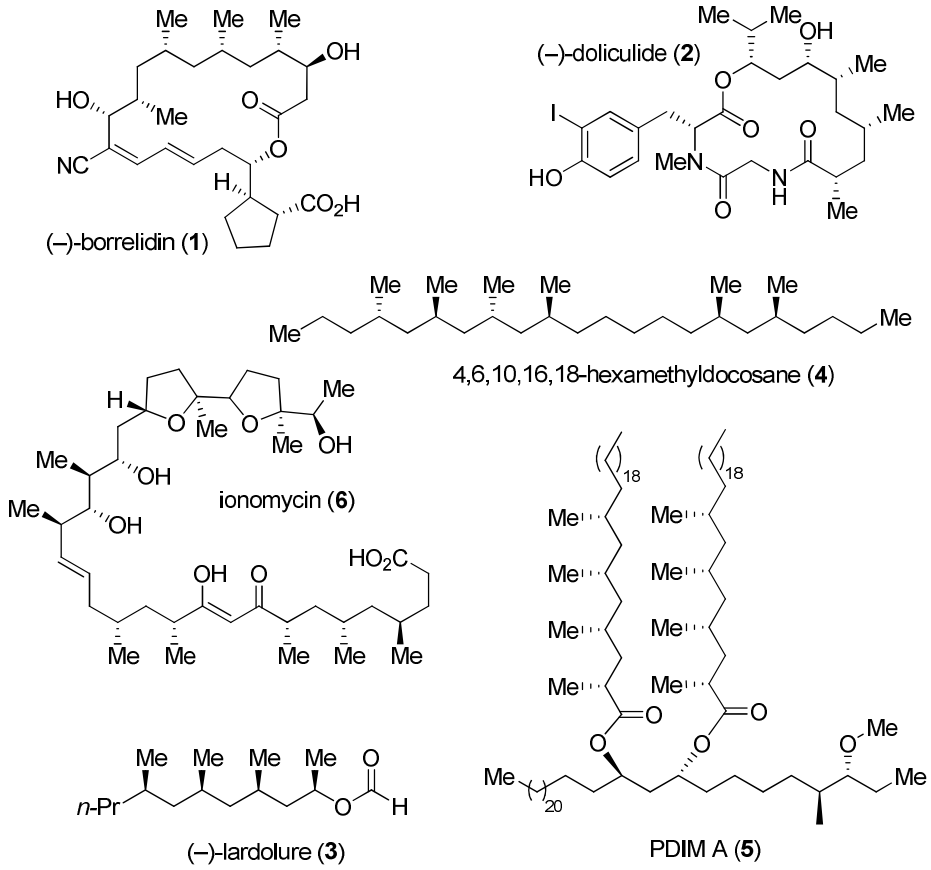
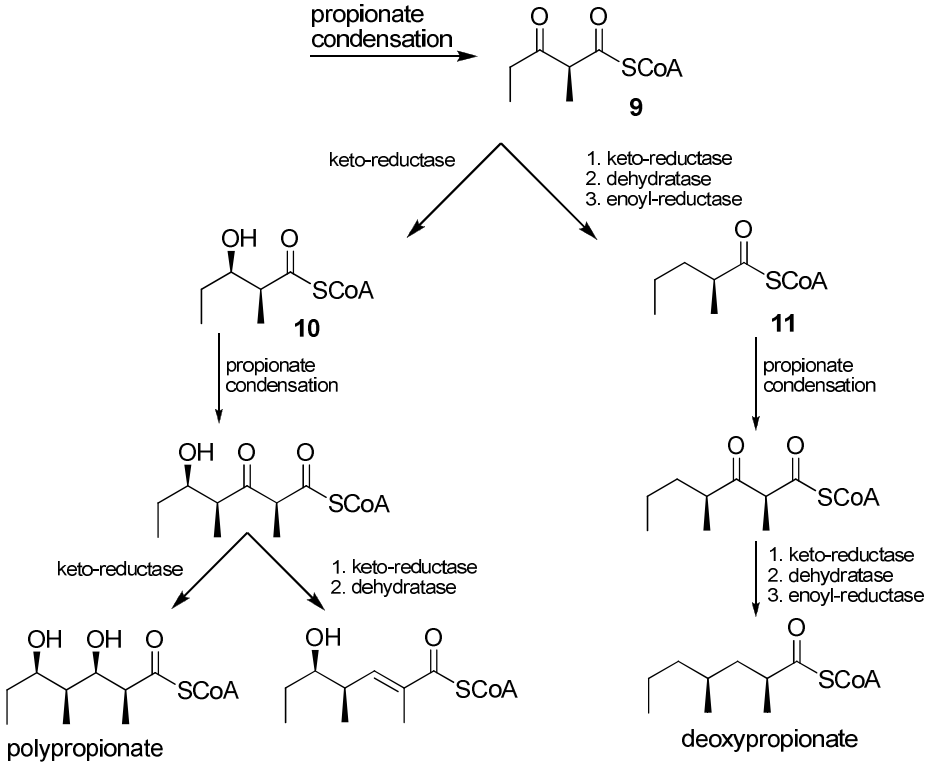


Figure 2: Examples of naturally occurring (deoxy)propionates.

Depending on the polyketide synthase involved, the resulting ketone functionality of the Claisen condensation (**9**) can be reduced to a β-hydroxy group by a keto-reductase resulting in **10** (Scheme 1).[3,4] A dehydratase can eliminate water resulting in the corresponding α,β-unsaturated thioester, which can then be reduced by an enoyl-reductase to the saturated thioester **11**. Repetition of the steps leads to (deoxy)propionate structures which can be found in a variety of natural products.[3,5-9] Finally, a thio-esterase hydrolyzes the polypropionate chain in the termination stage to the free (deoxy)propionate.

Deoxypropionates are synthesized by bacteria, fungi, and plants (Figure 2).[4] Many naturally occurring deoxypolypropionates have been isolated and a broad range of fascinating biological activities are associated with these structures *e.g.*; cytostatics: borrelidin (**1**)[5] and doliculide (**2**),[6] pheromones: lardolure (**3**)[7] and 4,6,10,16,18-hexamethyldocosane (**4**),[8] virulent markers: PDIM A (**5**),[9] and calcium ionophores: ionomycin (**6**).[10]



Scheme 1: Biosynthetic pathway for deoxypropionates.

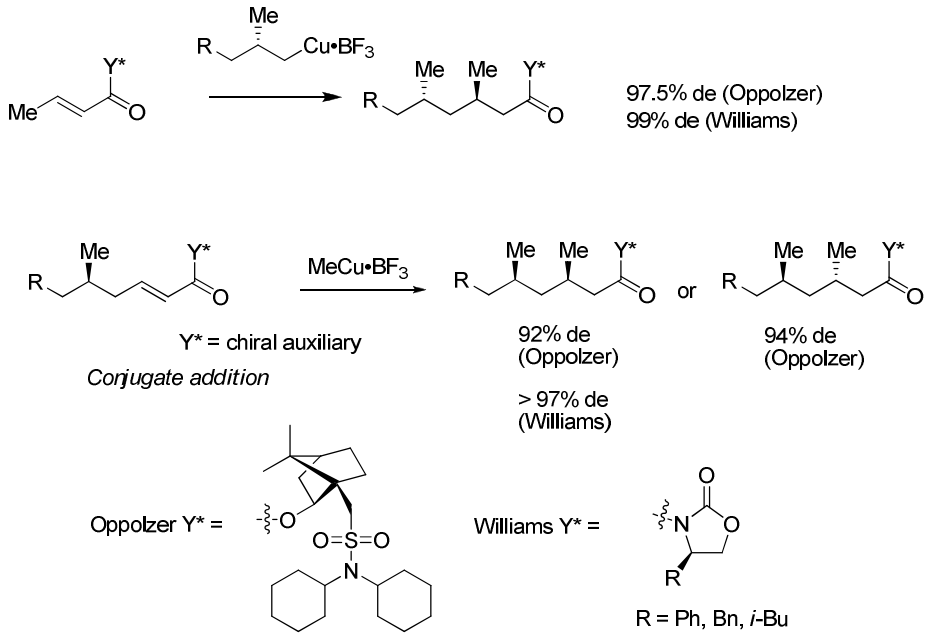
Hanessian *et. al.* have reviewed iterative synthetic methods for the construction of deoxypropionates in 2006.[11] Because of the abundant presence of deoxypropionate units in natural products, many synthetic strategies have been developed over the last three decades. These strategies are often based on the selective introduction of methyl substituents in an consecutive (iterative) fashion, either *syn* or *anti*, and can be divided in non-catalytic and catalytic strategies.

1.2 Noncatalytic methods for the construction of deoxypropionates

1.2.1 1,4-Addition reactions directed by chiral auxiliaries

The iterative synthesis of deoxypropionates was first reported by Oppolzer in 1986.[12] The 1,4-addition reaction of an enantiopure methyl-branched organocuprate species to a chiral α,β-unsaturated camphor derived ester was described (Scheme 2). In this reaction the *anti*-product was predominantly formed (de = 97.5%). The formation of the *syn*-product with the opposite enantiomer of the camphor sulfonamide or the organocuprate species was not reported. The 1,4-addition reaction of methylcuprate to a related camphor based substrate, already containing a methyl-branched stereocenter, resulted in excellent diastereomeric excess for both the *syn* (92% de) and *anti*-product (94% de).

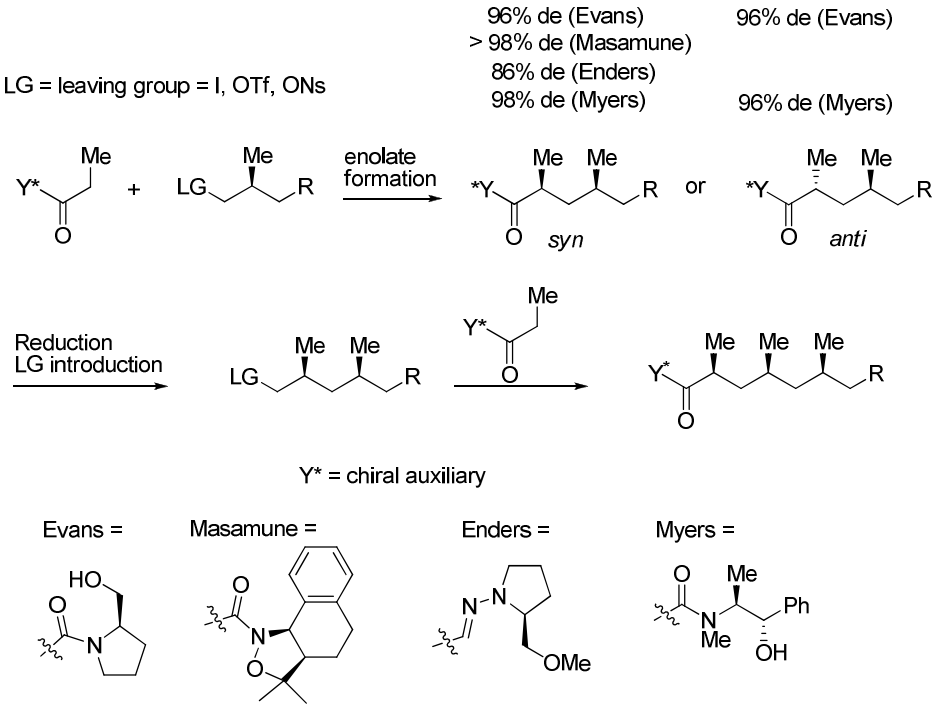
Williams reported a similar approach with α,β-unsaturated oxazolidinones. Enantiopure methyl-branched organocuprates were used as the Michael donor which resulted in excellent selectivities for the *anti*-dimethyl product (99% de).[13] The stereochemical outcome of this 1,4-addition reaction is dependent on both the chiral auxiliary and the already present stereocenter of the methyl-branched organocuprate. Addition of methylcuprate to a substrate containing a methyl-branched stereocenter resulted in a high diastereoselectivity for the *syn*-product (97% de).



Scheme 2: Iterative 1,4-addition reactions with chiral auxiliaries.

1.2.2 (Aza)enolate alkylation reactions directed by chiral auxiliaries

Well known chiral enolate alkylation strategies have been reported by Evans,[14] Masamune,[15] Enders[16] and Myers.[17] In all these strategies a chiral auxiliary containing propionyl enolate derivative acts as a nucleophile towards a substrate already containing one methyl-branched stereocenter (Scheme 3). The methyl-branched product of the alkylation reaction is reduced with simultaneous cleavage of the chiral auxiliary group to the corresponding alcohol which is subsequently turned into a leaving group. This newly formed substrate can readily be substituted in a second alkylation reaction with the same chiral enolate reagent as in the first alkylation reaction, making it an iterative sequence.



Scheme 3: Iterative enantiopure enolate alkylation reactions and chiral auxiliaries used.

Evans and co-workers applied this strategy in the total synthesis of ionomycin.[14] Their chiral amide enolate auxiliary strategy was proven highly selective and efficient. Both the *syn*- and *anti*-products of the 1,3-dimethyl deoxypropionate substructure could be constructed with high selectivity (96% de).

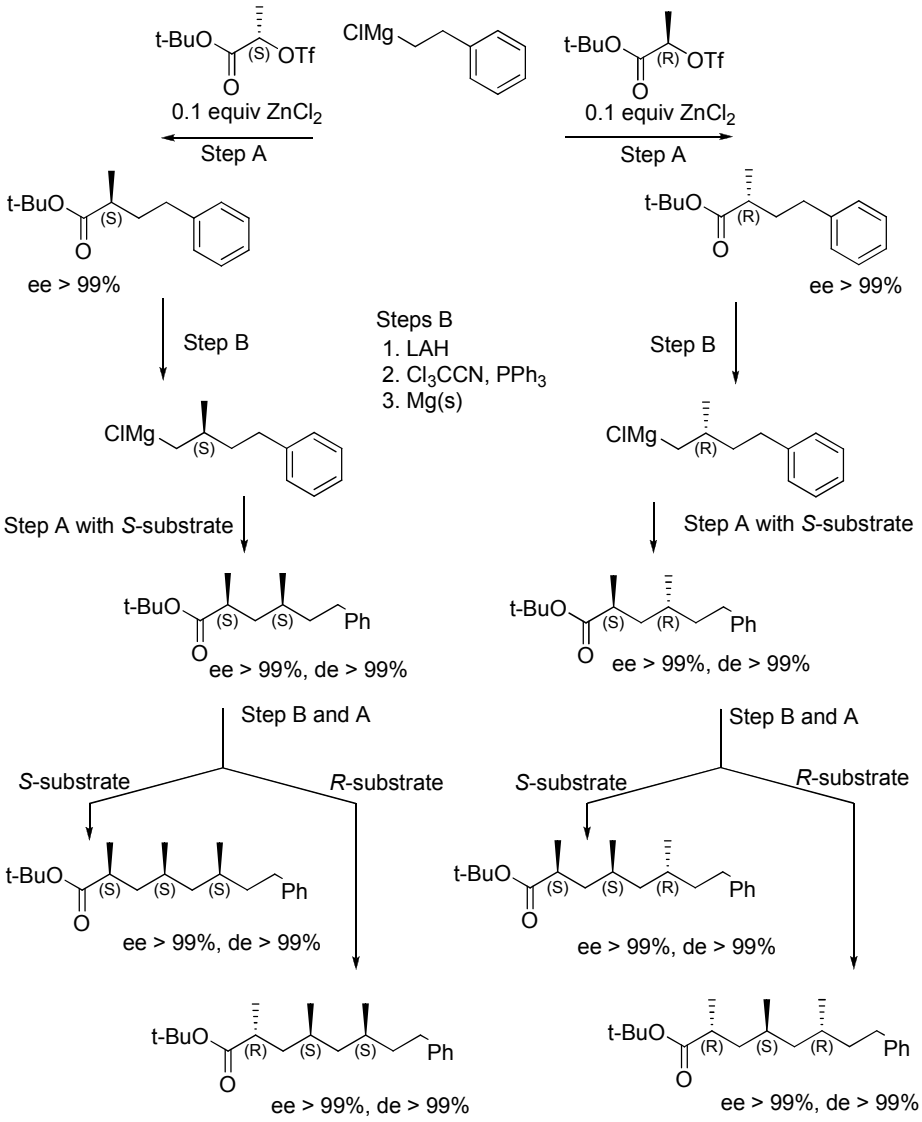
Masamune applied potassium enolates of non-racemic *N*-propionylisoxazolidines in the total synthesis of (+)-siphonarienone.[15b] The *syn*-selectivity for the dimethyl product of the reported alkylation was > 98%, whereas the *anti*-product of the same substrate was not reported.

The Enders lithioenamine (azaenolate) alkylation reaction, employing a chiral proline derived hydrazone auxiliary (SAMP/RAMP auxiliaries) was applied in the total synthesis of (+)-pectinatone.[16a] The dimethyl *syn*-deoxypropionate substructure was obtained with a de of 84%. The formation of the *anti*-product was not reported.

Myers and co-workers introduced an iterative alkylation reaction using the lithium propionamide enolate of (+)-pseudoephedrine (2 equiv of LDA). The iterative construction of all possible diastereomeric structures of 1,3,5-trimethyl deoxypropionates was reported.[17] All products were obtained with excellent diastereomeric ratio's ranging from 55:1 to 199:1.

1.2.3 Iterative zinc-catalyzed enantiospecific sp^3-sp^3 cross-coupling reactions

Recently, Breit reported a new method that allows for zinc-catalyzed enantiospecific sp^3-sp^3-coupling of a great variety of Grignard reagents with different α-hydroxy ester triflates derived from the chiral pool.[18] Starting from enantiopure lactic acid *tert*-butyl ester triflate affords chiral α-methyl-substituted esters with complete inversion of configuration. Although both enantiomers of lactic acid are commercially available, the *R*-enantiomer is very expensive. This new method was very recently used in an iterative fashion in the synthesis of all four possible diastereoisomers of trideoxypropionates (Scheme 4) with perfect stereocontrol.[19]

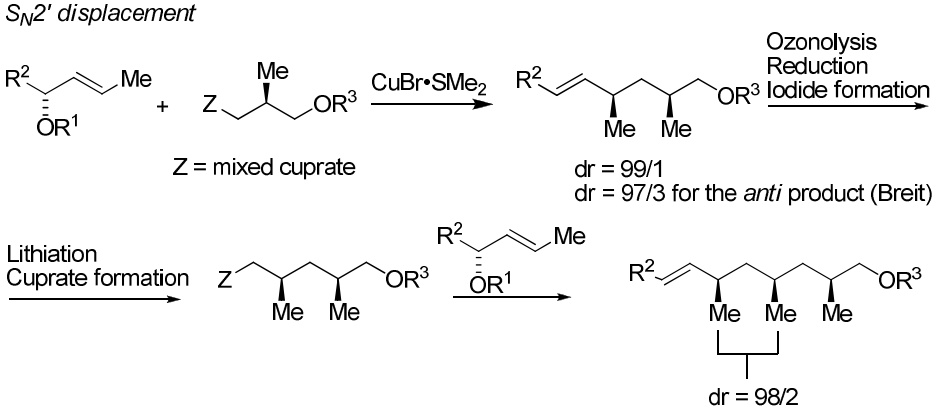


Scheme 4: Iterative zinc-catalyzed enantiospecific sp^3-sp^3 cross-coupling reactions.

The product of the alkylation reaction is derivatized into a Grignard reagent which is the alkylating agent in the second step of the iterative protocol. Enantiomeric and diastereomeric excess were > 99% in all cases.

1.2.4 Iterative asymmetric allylic alkylation reactions

Asymmetric allylic alkylation reactions in an iterative fashion for the construction of deoxypropionates have been reported by the groups of Breit[20] and Spino[21] (Scheme 5). The method reported by Spino starts with an enantiopure menthone derivative which undergoes S_N2' displacement by an enantiopure mixed organocuprate reagent with nearly perfect stereocontrol. The stereochemical outcome is exclusively dependent on the stereochemistry of the allylic carbonate.

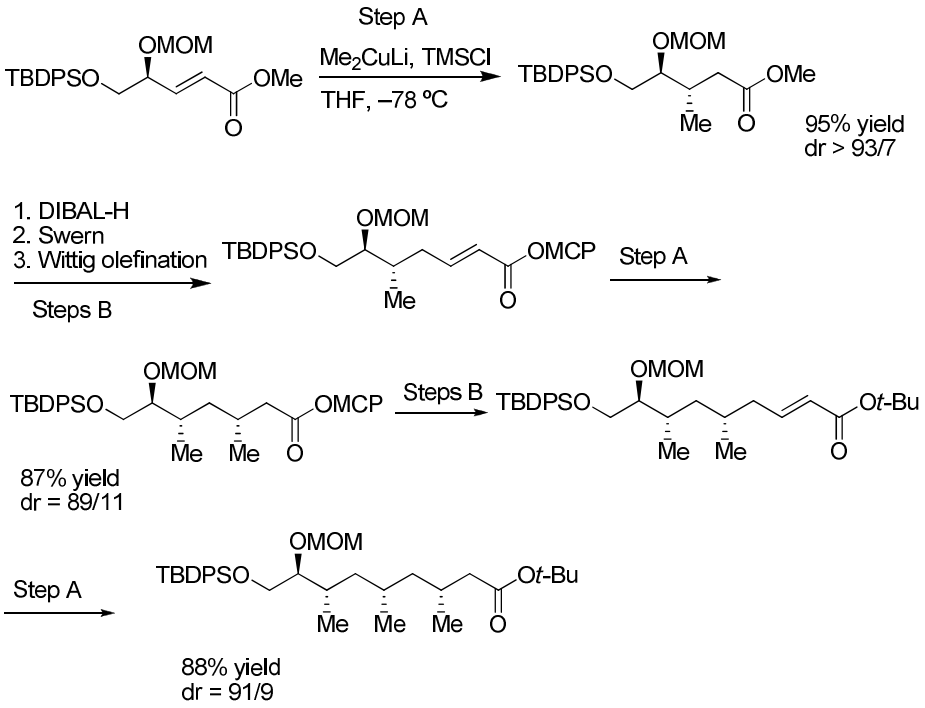


Scheme 5: Iterative allylic substitution reactions with enantiopure organocuprate reagents to enantiopure allylic esters.

Breit described the allylic alkylation reaction of enantiopure organocuprates on enantiopure *ortho*-diphenylphosphanylbenzoate (*o*-DPPB) allylic esters, containing an internal phosphorus ligand. The *o*-DPPB esters were obtained by enzymatic kinetic resolution. The stereochemical outcome of the reaction is completely dependent on the stereochemistry of the allylic *o*-DPPB-ester. In order to perform these reactions in an iterative fashion, the olefin product of the allylic alkylation reaction is transformed into an iodide derivative in several synthetic steps. The iodide is subsequently used as the substrate for a second allylic alkylation. Both iterative methods are highly selective but do require enantiopure reagents and substrates.

1.2.5 Substrate-controlled iterative 1,4-addition reactions

Hanessian and co-workers applied iterative substrate directed 1,4-addition reactions in a number of natural product syntheses.[11,22] The route started with an enantiopure α,β-unsaturated ester with a methoxymethyl (MOM) protected hydroxy stereocenter in the γ-position (Scheme 6). Both enantiomers of this substrate are readily available starting from either *L*-malic acid or *D*-glyceraldehyde.

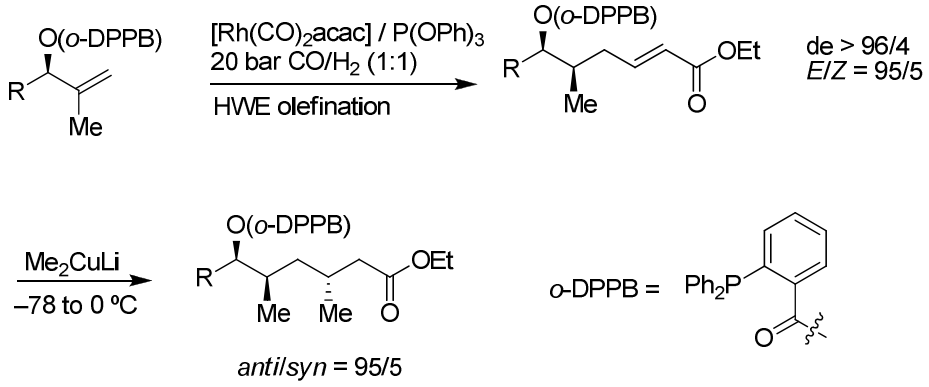


Scheme 6: Substrate-controlled iterative 1,4-addition reactions for the construction of all-*syn* deoxypropionates.

The 1,4-addition reaction with Me_2CuLi proceeds with excellent *anti*-selectivity for the formation of the vicinal hydroxy-methyl motif (dr > 93:7). The ester functionality of the product is reduced with DIBAL-H to the corresponding alcohol which is subsequently oxidized to the aldehyde by Swern oxidation. Wittig olefination of the aldehyde results in an α,β-unsaturated ester which can readily undergo a second 1,4-addition

reaction. The second 1,4-addition reaction with Me_2CuLi favors the *syn*-dimethyl deoxypropionate with a dr of 89:11 when the 1-methyl-1-cyclopentyl (MCP) ester is used.[23] A subsequent third iterative step (on an unsaturated *t*-butyl ester) resulted in a trimethyl deoxypropionate structure with an increased dr of 91:9 compared to the previous step. The strongly preferred *syn*-product formation is attributed to a preferred conformational effect in the transition-state in which 1,5-*syn*-pentane interactions are minimized or avoided (see Chapter 2).

Breit and co-workers[24] reported a substrate-controlled 1,4-addition reaction on α,β-unsaturated esters with a directing *ortho*-diphenylphosphanylbenzoate (*o*-DPPB) group at the ε-position (Scheme 7). This substrate was obtained from a hydroformylation-olefination reaction sequence. Addition of Me_2CuLi to the unsaturated system resulted in a dr of 95:5 favoring the *anti*-product. The coordinating effect for the introduction of a third methyl group was not investigated.

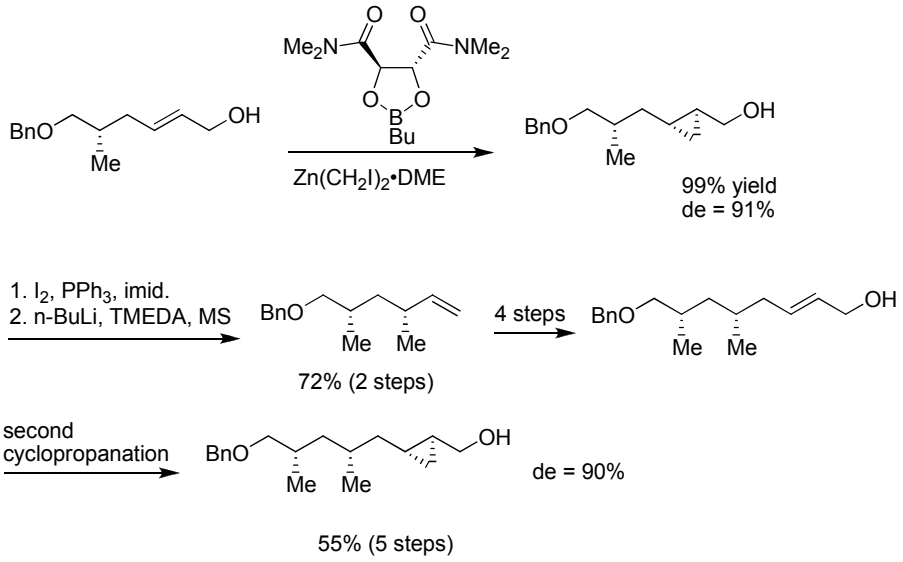


Scheme 7: Phosphine-directed 1,4-addition reaction favoring the *anti* deoxypropionate substructure.

1.2.6 Iterative cyclopropanation fragmentation

In 2001 Ghosh *et al.*[25] reported an enantioselective cyclopropanation fragmentation strategy for the construction of (–)-doliculide, an all-*syn* deoxypropionate-containing natural product with antitumor properties.[26] The synthesis started with an enantiopure methyl-branched allylic alcohol which was obtained in eight steps from Roche Ester (Scheme 8). Charette

asymmetric cyclopropanation[27] of the allylic alcohol resulted in the corresponding cyclopropane in high yield (99%) and good diastereomeric excess of 91%. Conversion of the iodide into the alcohol, followed by fragmentation of the cyclopropane ring upon treatment with *n*-BuLi/TMEDA and molecular sieves, resulted in the *syn*-dimethyl deoxypropionate substructure which was transformed into an allylic alcohol for subsequent cyclopropanation in four steps. The second cyclopropanation reaction resulted in the desired product with similar selectivity (de = 90%).



Scheme 8: Iterative enantioselective cyclopropanation/fragmentation strategy.

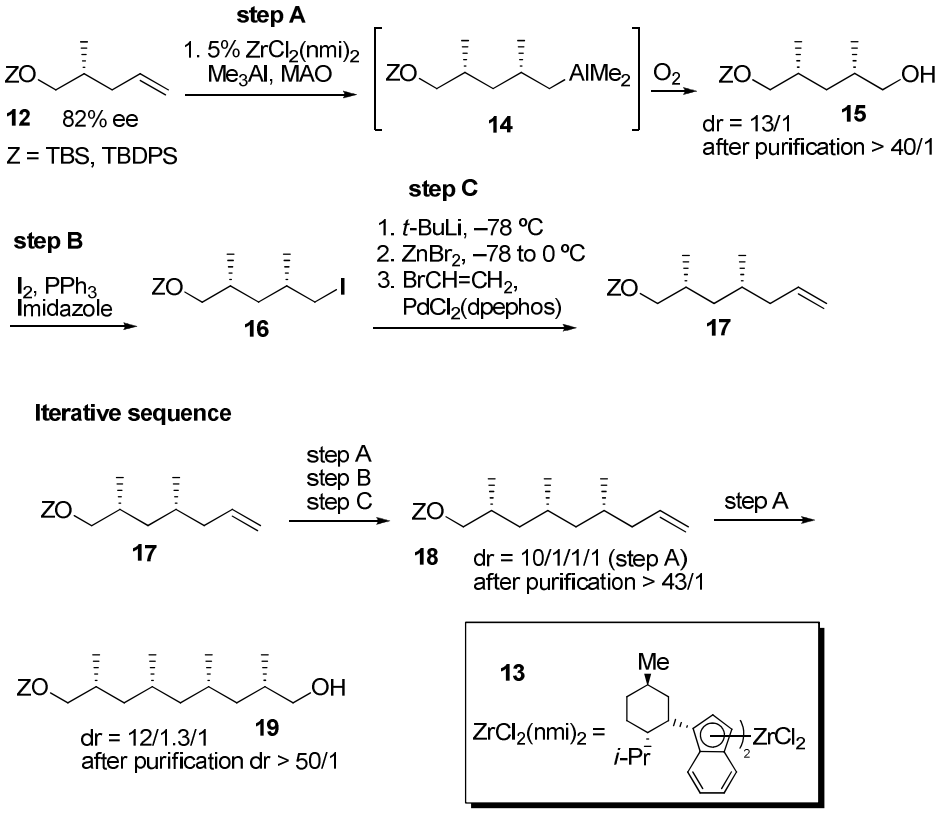
1.3 Catalytic asymmetric iterative strategies for deoxypropionates

1.3.1 Iterative zirconium-catalyzed asymmetric carboalumination

Negishi and co-workers have developed an iterative strategy for the construction of deoxypropionates based on the zirconium-catalyzed asymmetric carboalumination (ZACA)-reaction.[28a-l] In this protocol, an

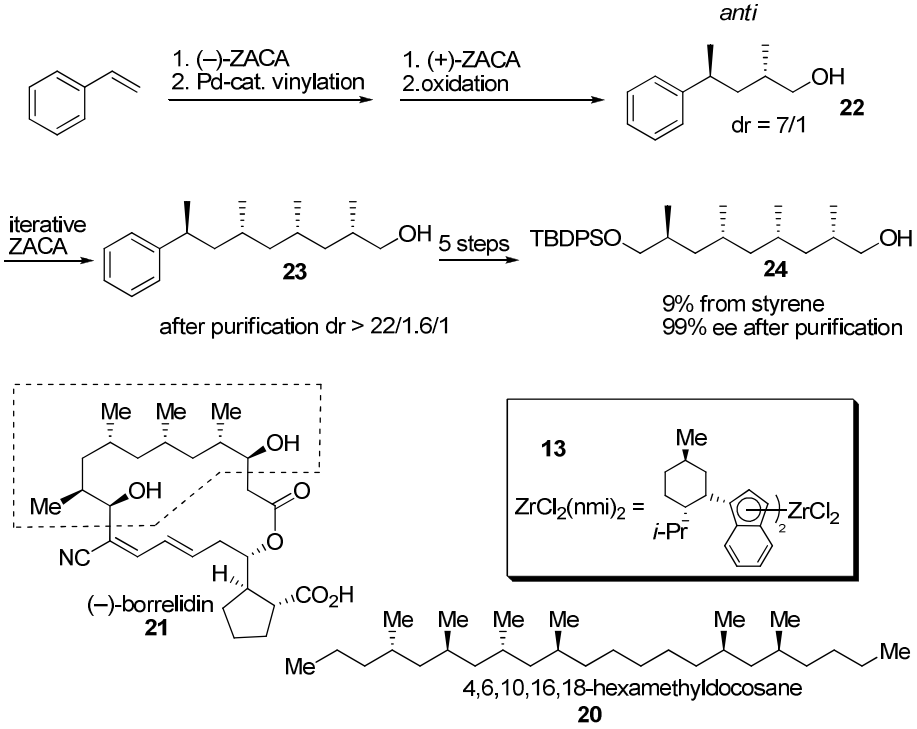
enantioselective carboalumination of a terminal olefin **12** is catalyzed by the enantiomerically pure zirconium complex **13** (Scheme 9) resulting in the carboaluminated product **14**. Subsequent oxidization by O_2 results in the primary alcohol **15** (step A). This alcohol is then transformed into the corresponding iodide **16** in step B. The iodide is lithiated with *t*-BuLi and treated with $ZnBr_2$ to form the corresponding organozinc species which in turn undergoes a palladium-catalyzed vinylation reaction to form terminal olefin **17** which is the substrate for a subsequent ZACA reaction (step C). The starting material in Scheme 9 can be made either from enantiomerically pure methyl-3-hydroxyisobutyrate (Roche ester) or *via* the ZACA protocol from protected allyl alcohol with an ee of 82%. Negishi and co-workers use enzymatic kinetic resolution to increase the ee from 82 to 98% (68% recovery at 75% conversion).[28c]

The iterative steps require separation of diastereomers in the alcohol stages by column chromatography. Diastereoselectivity for the second introduced methyl group is 13 : 1 for the *syn*-product and 1 : 8 for the *anti*-product (using *ent*-**13**). After purification, dr's are typically higher than 40 : 1. Although the ZACA iterative protocol is very elegant, stereoselectivities are not excellent and purification of diastereomers is therefore required leading to significant loss of material.



Scheme 9: Iterative ZACA (Zirconium catalyzed Asymmetric CarboAlumination reaction).

The ZACA iterative protocol was demonstrated in the total synthesis of (*S*,*R*,*R*,*S*,*R*,*S*)-4,6,8,10,16,18-hexamethyldocosane[28h] (**20**, Scheme 10), a natural product isolated from the cuticula of the cane beetle *Antitrogus parvulus* by Kitching and co-workers.[29]



Scheme 10: ZACA protocol for the synthesis of the upper part of borrelidin and 4,6,10,16,18-hexamethyldocosane.

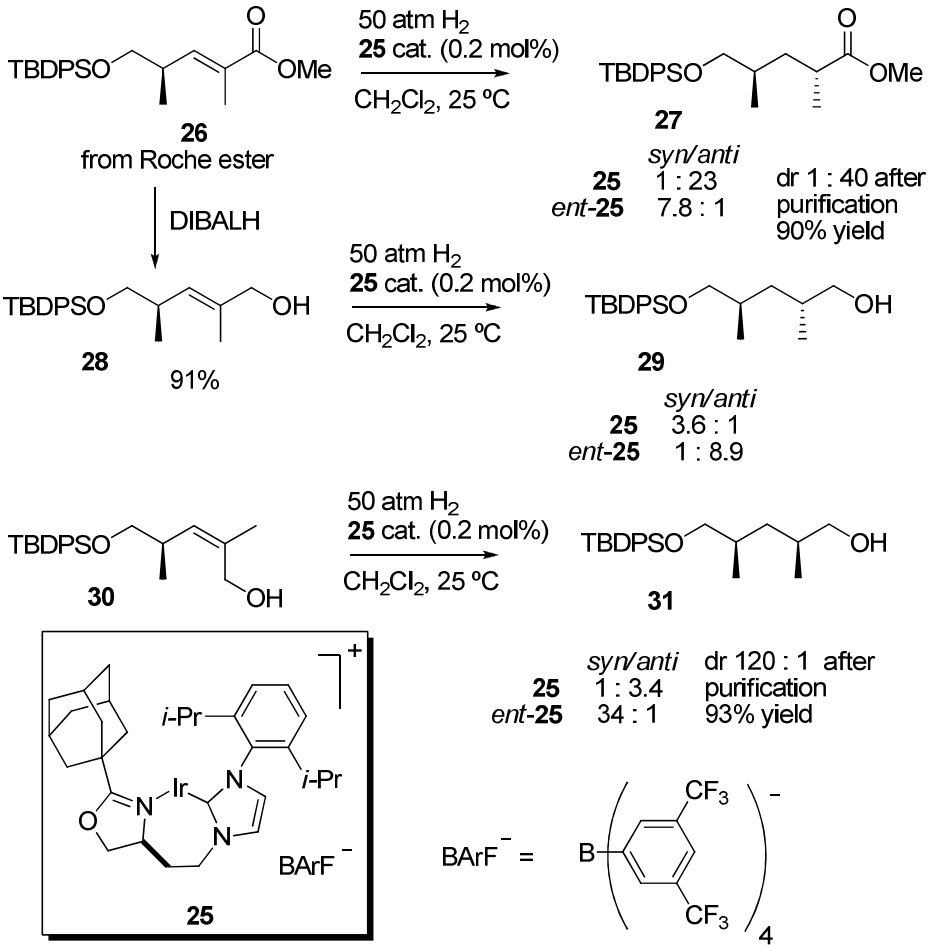
Another example of the application of the ZACA protocol was demonstrated in the synthesis of the upper part of borrelidin (**21**, Scheme 10).[28b] Styrene was chosen as the starting material in the synthesis of borrelidin. The *anti*-product **22** was obtained with a diastereomeric ratio of 7 : 1. Formation of the *syn*-product with *ent*-**13** resulted in a ratio of 1 : 4.6. In two following iterative steps minor diastereomers were separated from the major diastereomer. The phenyl ring was then completely oxidized to the acid and after several chemical transformations building block **24** was isolated in 9.3 % yield starting from styrene.

It is somewhat remarkable that styrene was chosen as the starting material because substrate **14** in Scheme 9 can also be made in the *anti*-fashion which was published by the same group[28c] one year before they published

the synthesis of the upper part of borrelidin. All the more so because the *anti* selectivity is higher (10 : 1) for the TBDPS protected substrate (compared to **22**) and this approach does not require oxidation of the phenyl group.

1.3.2 Iterative asymmetric hydrogenation reactions

In 2007, Burgess and co-workers reported an iterative strategy for the construction of deoxypropionates based on the enantioselective hydrogenation of tri-substituted alkenes.[30] A chiral version of the Crabtree[31] catalyst was used in combination with a carbene oxazoline ligand (**25**, Scheme 11).



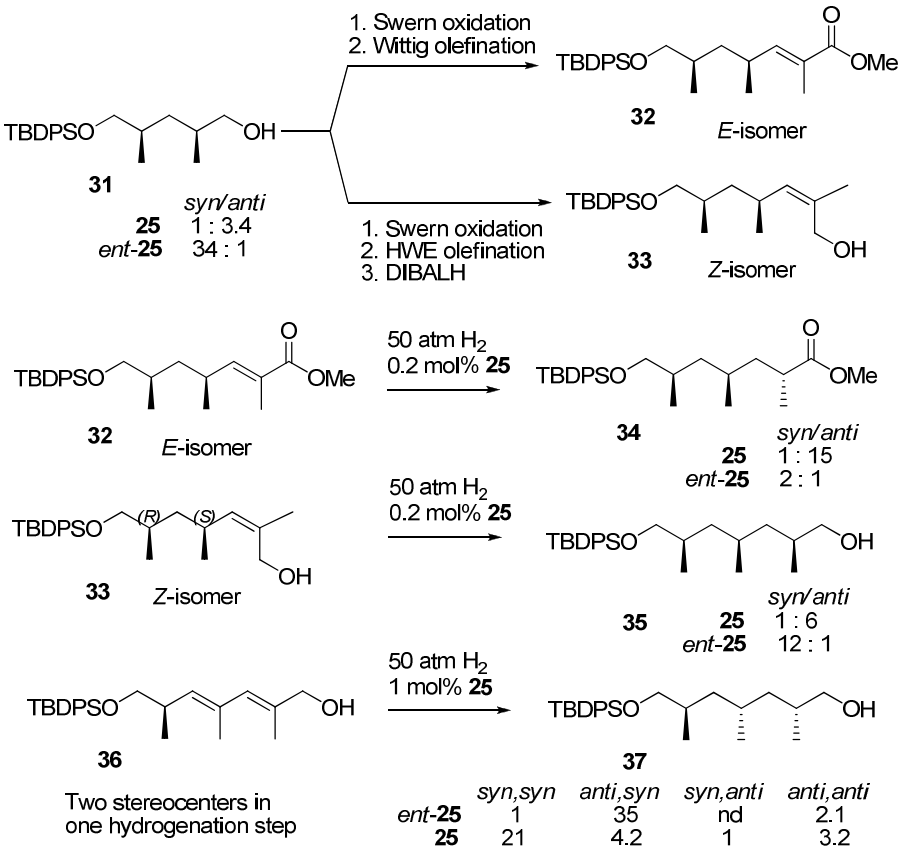
Scheme 11: Asymmetric hydrogenation of chiral tri-substituted alkenes.

Substrate **26**, which was prepared from the chiral pool compound Roche ester in 3 steps, was hydrogenated (50 atm. H_2, 0.2 mol% **25**, 25 °C for 4 h). The *syn*-product was obtained with catalyst **25** and the *anti*-product was obtained with *ent*-**25** with a dr of 23 : 1 for the *anti* and 7.8 : 1 for the *syn*-product, respectively. To improve the selectivity of the *syn*-product, the substrate was reduced with DIBAL-H into the corresponding allylic alcohol

28. It was found that the catalyst approaches these α,β-unsaturated esters and alcohols from opposite π-faces.[30b] However, the hydrogenation of the *E*-isomer of the resulting allylic alcohol proved not to be very selective for the *syn*-addition as a dr of 3.6 : 1 (with *ent*-**25**) was found. The *Z*-isomer of the allylic alcohol **30**, made from the *Z*-isomer of the unsaturated ester, was found to favor the *syn*-product **31** with a dr of 34 : 1 (120 : 1 after column chromatography). Hydrogenation of the *Z*-isomer of the unsaturated ester was not reported.

The products were reduced (for the esters, **27**) or oxidized (for the alcohols, **29**/**31**) to the corresponding aldehydes which can undergo subsequent Wittig or HWE (Horner-Wadsworth-Emmons) olefination reactions (Scheme 12) for the following iterative step. Wittig olefination leads predominantly to the *E*-isomer **32** (89% isolated) which can be used as a substrate for the *anti*-product **34**. HWE olefination has a preference for the *Z*-isomer (96% isolated) of the unsaturated ester which can be reduced to *Z*-allylic alcohol **33**, the substrate for *syn*-product **35** after hydrogenation.

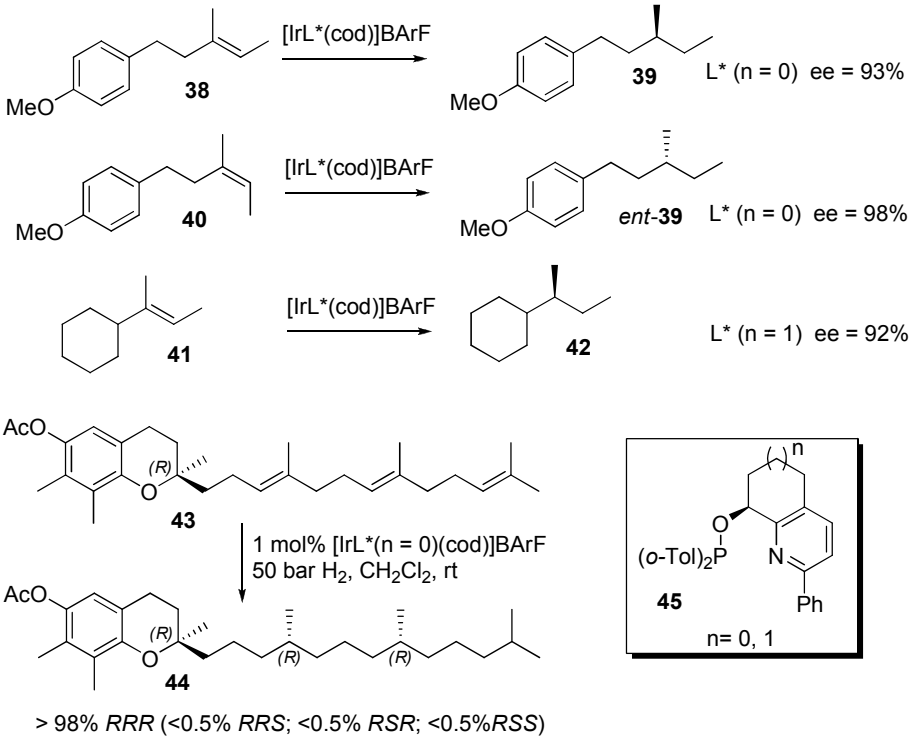
A direct route to products **34** and **35** was also investigated (Scheme 12). Diene substrate **36** could be prepared from substrate **26** by a reduction, olefination, reduction sequence. Diene **36** was hydrogenated using 1 mol% of catalyst **25** (contrary to the 0.2 mol% normally used). With catalyst *ent*-**25** the *anti*,*syn*-product **37** was isolated with a dr of 35 : 2.1 : 1 ratio and the major isomer could be separated from the minor ones. The all *syn*-product could also be obtained using **25** resulting in a dr of 21 : 4.2 : 3.2 : 1.



Scheme 12: Iterative strategy by subsequent catalytic asymmetric hydrogenation reactions.

One year earlier, the group of Pfaltz published[32] a somewhat similar approach involving enantioselective alkene reduction of γ-tocotrienyl acetate **43** to natural (*R*,*R*,*R*)-γ-tocopheryl acetate **44**, a Vitamine E derivative (Scheme 13). In this case iridium-catalyzed hydrogenation was found to perform best with P,N ligands (ligands with coordinating P and N atoms, **45**). With this catalytic system, unfunctionalized substrates **38**, **40** and **41** could be hydrogenated in high yield and enantioselectivities. Hydrogenation of completely unfunctionalized substrate **41** results in a remarkable high selectivity yielding 92% ee. It should be noted that the double bond of the alkene is the only functionality in the molecule!

Although the Pfaltz group does not describe an iterative approach for the construction of polydeoxypropionates, it elegantly demonstrates an approach for the construction of 1,5-dimethyl substituted structure. This saturated isoprenoid substructure is another common motif in natural products and can be found as well in components from *M. tuberculosis*.[33]



Scheme 13: Iridium-catalyzed asymmetric hydrogenation of unfunctionalized alkenes and dienes with P,N-ligands.

1.3.3 Iterative 1,4-addition reactions with Grignard reagents and the CuI/tol-BINAP catalytic system

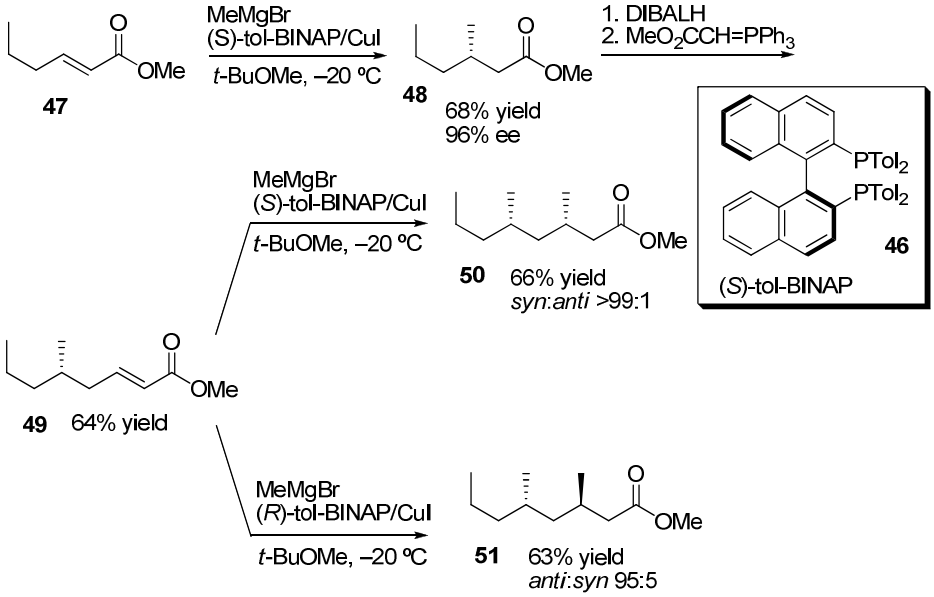
Loh and co-workers[34a,b,c] described an iterative protocol for the synthesis of deoxypropionates based on the copper-catalyzed 1,4-addition with Grignard reagents in 2007. CuI is used as the copper source and tol-BINAP (**46**) as the ligand. Although we found that MeMgBr works poorly in the reaction with unsaturated oxo-esters such as **47**, these authors found that

by switching to the CuI/tol-BINAP system, the desired product **48** could be obtained in high ee (96%) and a moderate yield of typically 65% (Scheme 14). Ester **48** was reduced with DIBAL-H to the corresponding aldehyde and treated with a Wittig reagent to obtain unsaturated ester **49** which can undergo a second copper-catalyzed 1,4-addition. The reduction-olefination step can be performed in one pot with an overall yield of 64%. This moderate yield can be explained by the fact that oxo-esters are sensitive to over-reduction, a problem which does not occur with thioesters (*vide infra*).

The authors report that the second 1,4-addition reaction results in dimethyl substituted ester **50** with a *syn*:*anti* selectivity of >99 : 1 and moderate yield.

Formation of *anti*-product **51** employing (*R*)-tol-BINAP resulted in an *anti*:*syn* ratio of 95:5. The CuI/tol-BINAP system also works on unsaturated thioesters as was demonstrated in 2007 by our group.[35] Secondly, in our experience the HWE olefination equivalent of the Wittig reaction is more selective and reduces reaction times for the formation of the *E*-isomer of the unsaturated ester.

Starting, however, with substrate **49** of 96% ee, makes it impossible to obtain a *syn*:*anti* selectivity of >99:1. The authors do not report separation or enrichment of diastereomers by chromatography. Neither is an incomplete reaction reported, which could also explain this outcome. The *syn*:*anti* ratio's are calculated from the integrals of the two diastereomers in ^{13}C-NMR, with a rather small signal to noise ratio and no comment is made about the relaxation time of the two different diastereomers.



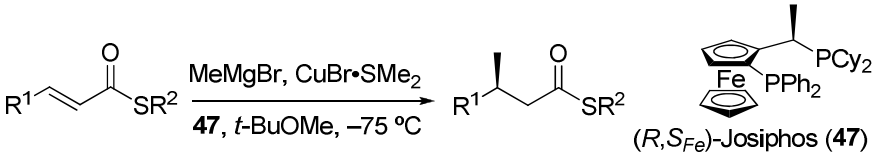
Scheme 14: Iterative 1,4-additions with CuI/tol-BINAP catalytic system.

1.3.4 Iterative 1,4-addition reactions on α,β-unsaturated thioesters for the construction of deoxypropionates

1.3.4.1 Enantioselective conjugate addition of Grignard reagents to α,β-unsaturated thioesters for the introduction of methyl substituents

Following the discovery of the copper-catalyzed 1,4-addition to acyclic enones[36] with Grignard reagents in 2004, our group found that the same catalytic system could be employed in the 1,4-addition reaction to unsaturated oxo-esters[37] in 2005. The catalytic system was based on the use of CuBr•SMe_2. The only limitation of unsaturated esters over enones was that the introduction of methyl groups *via* MeMgBr was troublesome. The less reactive methylmagnesium bromide could be used with high enantioselectivity but yields were typically around 20%. For an iterative and therefore linear approach to be successful, it is of utmost importance that all steps are highly selective and high yielding. In the same year[7a] this limitation was overcome by changing from an unsaturated oxo-ester to an

unsaturated thioester. Thioesters are more reactive[38] and can be compared to enones concerning reactivity towards methylmagnesium bromide in the copper-catalyzed 1,4-addition reaction. The introduction of a methyl substituent was demonstrated for a variety of substrates in high yield and high enantioselectivity (Table 1.1).



entry	R^1	R^2	yield (%)[c]	ee(%)[d]
1	*n*-Pent	Et	90	96
2[e]	*n*-Pent	Et	90	96
3[e]	*n*-Pent	Me	93	96
4[e]	*n*-Bu	Et	93	95
5[e]	*n*-Pr	Et	92	96
6[e]	Et	Et	92	92
7[e]	$BnO(CH_2)_3$	Et	94	95
8[e]	Ph	Et	88	95

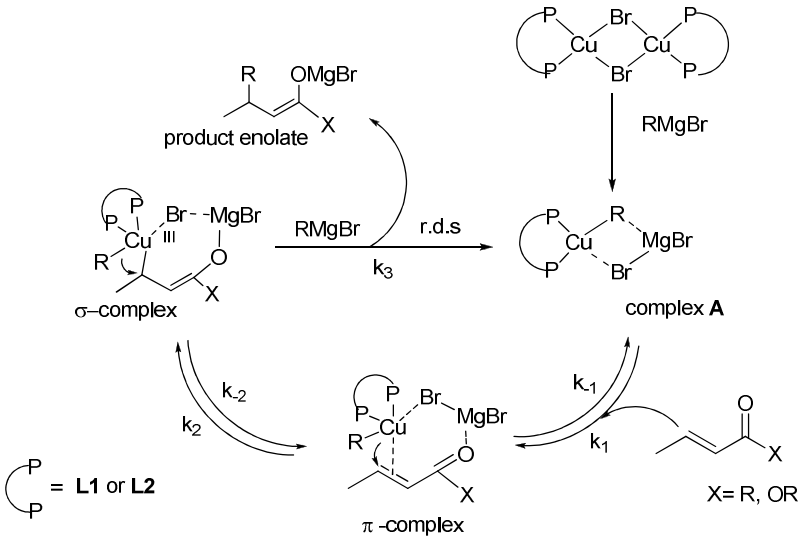
Table 1.1: Enantioselective 1,4-addition to unsaturated thioesters. [a] Conditions: 1.2 equiv. MeMgBr, $CuBr•SMe_2$ (5 mol %), (R,S_{Fe})-Josiphos (6 mol %), 2-5 h. [b] All conversions > 98% (GC-MS). [c] Isolated yields. [d] Regio- and enantioselectivity determined by chiral GC or HPLC. [e] With 1 mol % of $CuBr•SMe_2$ and 1.2 mol % of (R,S_{Fe})-Josiphos.

1.3.4.2 Proposed mechanism of the copper-catalyzed 1,4-addition reaction

In 2006 a detailed study was made to elucidate the reaction mechanism of the copper-catalyzed 1,4-addition with Grignard reagents.[39] In this exploration kinetic, spectroscopic and electrochemical analyses were applied.

The roles of the solvent, copper halide, and the Grignard reagent were examined. Kinetic studies support that the reductive elimination step is the rate-limiting step in which the chiral catalyst, the substrate, and the Grignard reagent are involved (Scheme 15). The CuBr/ligand complex exists as dimer or monomer complex in solution (solvent dependent). The

structure of the dimeric complex was proven by X-ray analysis. Upon addition of the Grignard reagent the dimeric complex is dissociated and a monomeric alkyl copper species, with the magnesium halide in close proximity, is formed. This heterodinuclear Cu,Mg complex is believed to be the active species. The newly formed species interacts with the unsaturated system and forms a π-complex followed by formation of a magnesium enolate through a Cu(III) intermediate. The product magnesium enolate is then released in the rate determining step involving a second equivalent of the Grignard reagent regenerating the active catalyst.



Scheme 15: Proposed catalytic cycle for the copper-catalyzed 1,4-addition with Grignard reagents.

1.3.4.3 Enolate trapping strategy in the synthesis of phaseolinic acid

The product of the copper-catalyzed 1,4-addition reaction is normally quenched with MeOH or a saturated solution of NH_4Cl (aq.) to yield the neutral thioester. The enolate can also be used for direct functionalization by trapping it with other electrophiles, *e.g.* alkyl halides or aldehydes. Trapping the enolate with an aldehyde results in two additional stereocenters (Scheme 16).[40] In an attempt to explain the stereochemical outcome of this trapping procedure, NMR studies were executed to obtain information about the geometry of the magnesium enolate. The NMR data

revealed that thioester enolate **54** predominantly exists as the *Z*-isomer. The *syn*-relation between the two newly formed stereocenters can be explained by the fact that the more favorable transition state has the alkyl moiety of the aldehyde and the phenyl group of the substrate both in an equatorial orientation in the activated complex (**55**). The stereochemical outcome of the two newly formed stereocenters relative to the original stereocenter of the methyl group (product of the asymmetric 1,4-addition) can be explained considering *syn*-pentane interactions. These interactions are minimized in case of a *re*-face attack of the enolate to the aldehyde. With the phenyl group pointing away from the aldehyde versus the methyl group (sterical hindrance), *syn*-pentane interactions or minimized and product **56** is favored in an all *syn*-fashion.

The *Z*-enolate of the thioester (sulfur on the same side as the alkyl group) was found to be the one reacting in our trapping studies with aldehydes and explained the stereochemical outcome of those reactions. This, however, contradicts with the hypothesis of a seven-membered ring intermediate with *E*-geometry of the enolate (Scheme 15). For the *Z*-enolate it is practically impossible to form the seven-membered ring (Figure 3). The geometry of oxo-ester enolates was, however, not investigated.

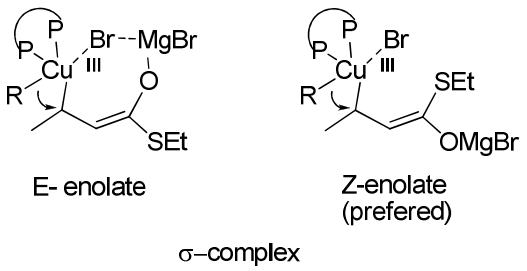
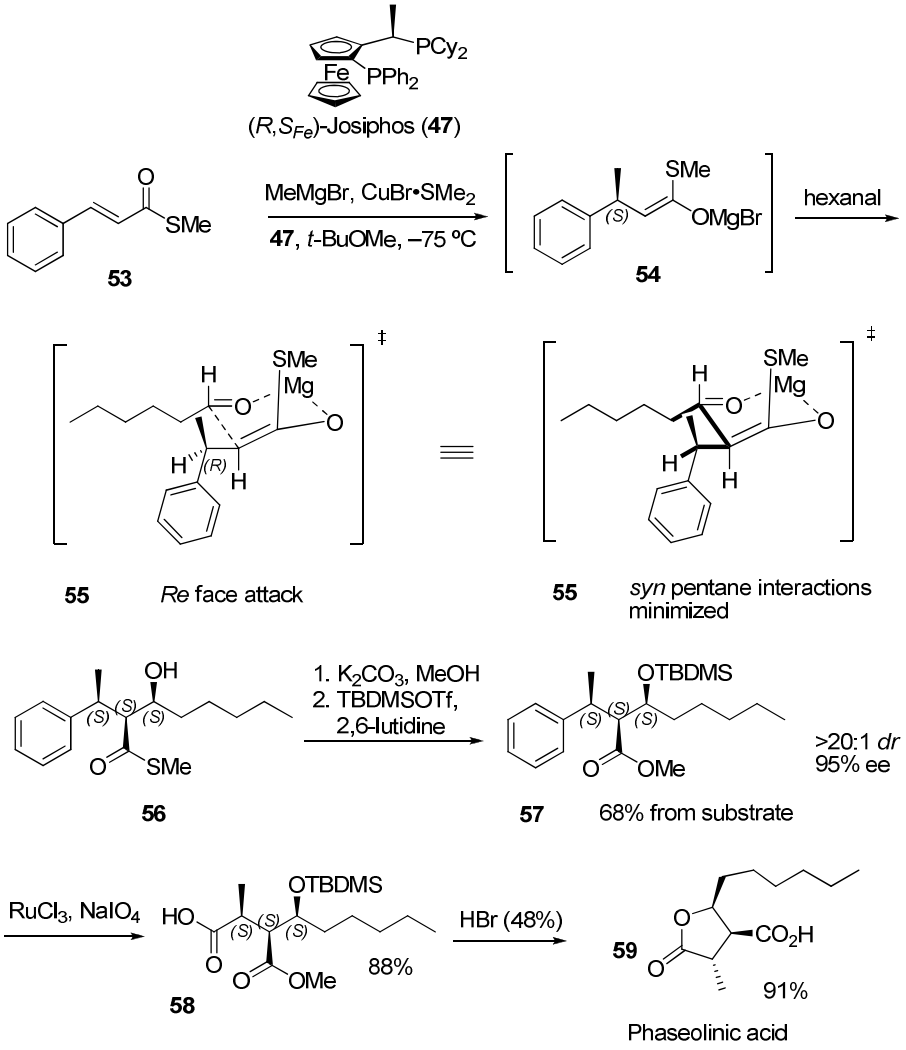


Figure 3: σ-Cu^{III} enolate geometries.

The trapping strategy was demonstrated in the synthesis of phaseolinic acid (Scheme 16).[40] Starting with the thioester of cinnamic acid (**53**) as the Michael acceptor, the CuBr/Josiphos catalyst was used in combination with methylmagnesium bromide. Instead of normal work up procedures, the enolate intermediate was quenched with hexanal to yield **56** in a dr > 20 : 1 and 95% ee. Alcohol **56** was subsequently protected as a *t*-butyldimethyl silyl ether to provide **57**.



Scheme 16: Enolate trapping of the 1,4-addition intermediate in the synthesis of phaseolinic acid.

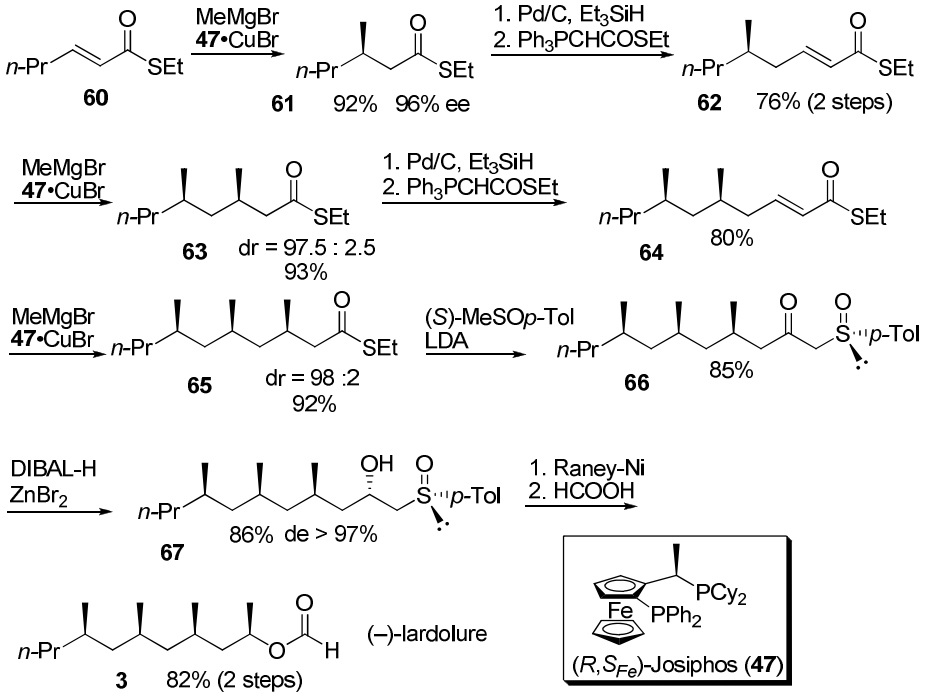
Phenyl group oxidation with $RuCl_3$ resulted in acid **58** without racemization of the *alpha*-stereocenter. In the last step Phaseolinic acid (**59**) was obtained from 58 under acidic deprotection and lactonization conditions (HBr) and thus from **53** in five steps in an overall yield of 54%.

1.3.4.4 Asymmetric catalytic iterative total synthesis of (–)-lardolure

The application of the iterative copper-catalyzed 1,4-addition was demonstrated for the first time in the synthesis of (–)-lardolure (**3**, Scheme 17).[7a] In this synthesis, three iterative steps are executed starting with a 1,4-addition on thioester **60** in 92% yield and an ee of 96%. The thioester product **61** was reduced with Pd/C and Et_3SiH (Fukayama conditions)[41] to the aldehyde which was subsequently treated with Wittig reagent $Ph_3PCHCOSEt$ to provide unsaturated thioester **62**. The second catalytic asymmetric 1,4-addition yields *syn*-product **63** when the same enantiomer of the Josiphos ligand **47** is used (dr = 97.5 : 2.5). Formation of the *anti*-product was also possible by switching to the enantiomer of the Josiphos ligand (*ent*-**47**). *Anti*-**63** was obtained with an *anti*:*syn* ratio of 95:5.

Subsequent reduction and olefination as before resulted in **64** in 80% yield over those two steps. The third methyl group was introduced under the same 1,4-addition conditions as before to provide **65**. Sulfinyl ketone **66** was obtained by an addition reaction of thioester **65** using the lithium anion of (*S*)-methyl-*p*-tolylsulfoxide. Substrate-controlled diastereoselective reduction of the ketone with DIBAL-H resulted in β-hydroxysulfoxide **67** (de > 97%). Finally, desulfurization of **67** followed by formylation led to the final product (–)-lardolure (**3**).

All steps in this iterative protocol are high yielding and enantioselectivities and diastereoselectivities are excellent. Enantioselectivity is even increased for the all-*syn* deoxypropionate when more iterative steps are executed as was also observed in the substrate-controlled iterative 1,4-addition strategy reported by Hanessian.[22b]



Scheme 17: Asymmetric iterative 1,4-addition in the synthesis of (–)-lardolure (**55**).

1.4 Synopsis

After the initial pioneering work on non-catalytic 1,4-addition strategies for the construction of deoxypropionates by Oppolzer[12] and later by Williams[13], several methods have been reported the last 20 years. Iterative enolate additions have been described by Evans,[14] Masamune,[15] Enders[16] and Myers[17] using a variety of chiral auxiliaries which resulted in excellent selectivities for both the formation of the *syn* and the *anti* deoxypropionate substructures. More recently, iterative approaches were reported by Breit[20] and Spino[21] based on allylic substitution reaction with enantiopure substrates and organocuprate reagents leading to excellent selectivities. Very recently, Breit and co-workers have developed an iterative zinc-catalyzed enantiospecific sp^3-sp^3 cross-coupling protocol which makes it

possible to introduce all possible diastereomers with perfect stereocontrol (>99%).[19] Hanessian has reported several natural product syntheses over the last decade based on the substrate-controlled preferred *syn*-formation of deoxypropionates with stoichiometric amounts of Me_2CuLi.[11,22] The cyclopropanation fragmentation strategy described by Ghosh offers an alternative indirect way for the construction of *syn*-deoxypropionates.[25]

The field of catalytic asymmetric iterative synthesis of deoxypropionates has seen tremendous progress over the last decade. This started with the introduction of the iterative zirconium-catalyzed carboalumination (ZACA) protocol in 2004 by Negishi and co-workers.[28a,d,k] High selectivities for both the *syn* and *anti* deoxypropionate motifs were obtained in several natural product syntheses. Undesired diastereomers could by separated by chromatography and enantiopure products could be isolated.

Copper-catalyzed iterative 1,4-addition reactions on unsaturated thioesters with MeMgBr described by Minnaard and Feringa started in 2005 with the asymmetric total synthesis of (–)-lardolure.[7a] Excellent enantioselectivities and diastereoselectivities were obtained in the construction of the all-*syn* deoxypropionate substructure. Both the *syn* and *anti* motif could be readily prepared in excellent yield and diastereoselectivity.

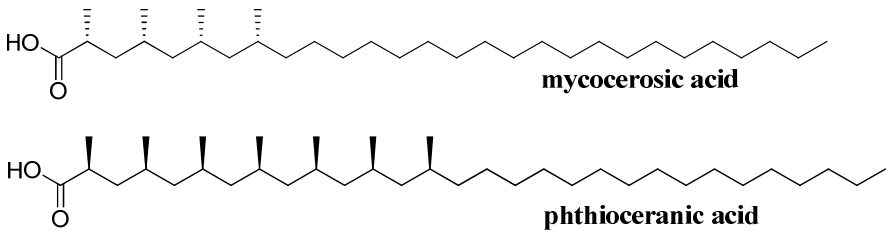
Burgess' hydrogenation strategy (2007), starting with an enantiopure substrate derived from Roche ester, proved to be highly selective in the synthesis of deoxypropionates.[30] This system also allowed for the introduction of two stereocenters in one reaction by hydrogenation of dienes and the *syn*-product could be obtained with good selectivity.

The iterative copper-catalyzed asymmetric 1,4-addition reaction with MeMgBr and CuI/tol-BINAP on oxo-esters was described by Loh *et al.* in 2007/2008. This method is highly selective for the construction of both the *syn* and *anti* motif of the deoxypropionates although yields are moderate.[34]

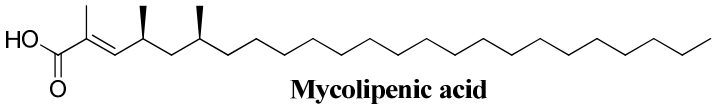
1.5 Outlook

In this thesis the application of the iterative copper-catalyzed 1,4-addition reaction is described in the total synthesis of methyl-branched lipids (deoxypropionates) from *Mycobacterium tuberculosis (M. tuberculosis)*. Next to the iterative construction of the deoxypropionate structure, several new synthetic strategies are developed and applied in the synthesis of these lipids.

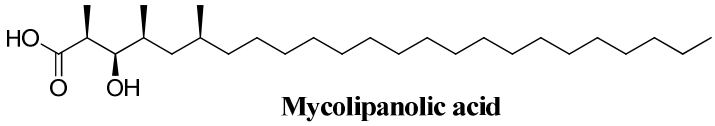
In ***Chapter 2*** the development and application of the iterative copper-catalyzed asymmetric conjugate addition (ACA) with MeMgBr is described. It will focus on the construction of functionalized deoxypropionates. The efficiency and selectivity of the methodology will be demonstrated in the synthesis of mycocerosic acid and phthioceranic acid, two multi-methyl-branched acids from *Mycobacterium tuberculosis* (*M. tuberculosis*).



In ***Chapter 3*** the first catalytic enantioselective synthesis of mycolipenic and mycolipanolic acid from *M. tuberculosis* is described. Iterative copper-catalyzed asymmetric conjugate addition reactions, selective olefination and an enantioselective aldol reaction are key strategic elements in the synthesis of both acids. The optical rotation and other spectroscopic data of the two synthetic acids are compared to the literature values reported for the naturally occurring acids.

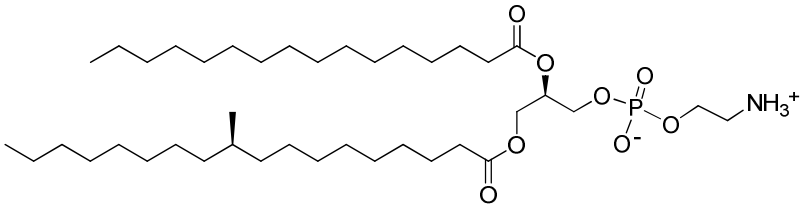


Mycolipenic acid



Mycolipanolic acid

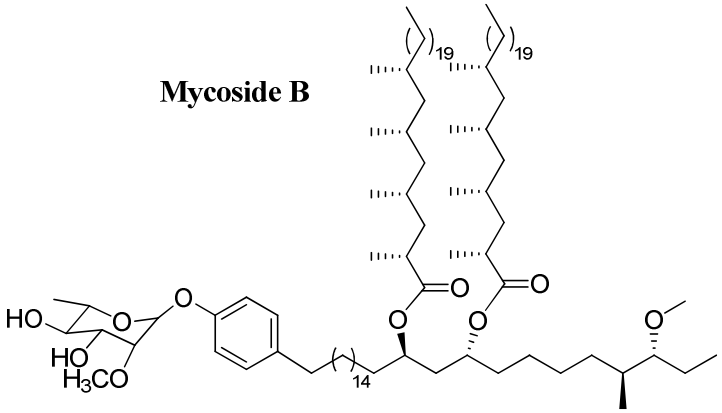
In ***Chapter 4*** the isolation, synthesis and characterization of a phospholipid from *M. tuberculosis* is described. This newly discovered glycerophospholipid containes two different acyl residues of which the relative position was unknown. The synthesis of both regioisomers is described together with the first enantioselective and catalytic synthesis of tuberculostearic acid, a methyl-branched acid which is characteristic in membrane lipids of mycobacteria. The position of the acyl residues is determined by comparison of spectroscopic and MS/MS data of the two synthetic compounds to the data of the isolated natural phospholipid.



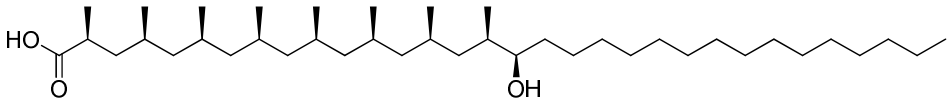
1-*O*-TBSA-2-*O*-palmitoyl-*sn*-phospholipid

In ***Chapter 5*** a new strategy for the construction of phenylphthiocerol, a substructure of the mycosides (phenolic glycolipids) is described. Mycosides are outer membrane lipids of mycobacteria and play an important role in their virulence. Hetero asymmetric allylic alkylation, cross-metathesis and Sharpless epoxidation reactions are key strategic elements in the synthesis towards phenylphthiocerol and eventually mycosides.

Mycoside B



In ***Chapter 6*** the synthesis of two diastereomers of octa-methyl-branched hydroxyphthioceranic acid is discussed. Copper-catalyzed asymmetric allylic alkylation and iterative conjugate addition reactions are key strategic elements in the synthesis. The synthetic acid is compared to the natural product isolated from *Mycobacterium tuberculosis.* Its unknown stereochemistry at the hydroxyl-bearing stereocenter is established by comparison of spectroscopic and chromatographic data of the two synthetic diastereomers and the natural isolate.



hydroxyphthioceranic acid

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