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ter Horst, Bjorn; Feringa, Ben L.; Minnaard, Adriaan J.

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Iterative strategies for the synthesis of deoxypropionates

Bjorn ter Horst, Ben L. Feringa* and Adriaan J. Minnaard*

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This feature article gives an overview of iterative synthetic methods for the construction of deoxypropionates, an important class of polyketides. The catalytic and non-catalytic methodologies discussed are based on highly stereoselective reactions which can be carried out in an iterative fashion. Non-catalytic methods are described first, followed by state of the art catalytic iterative protocols. The application of the iterative methods in the synthesis of natural products is discussed as well.

Introduction

Polypropionates, or polyketides, are synthesized in nature by the condensation of malonate and methylmalonate units *via* decarboxylative Claisen reactions (Scheme 1). Depending on the polyketide synthase involved, the resulting ketone functionality of the Claisen condensation product **3** can be reduced to a β -hydroxy group by a keto-reductase (KR) resulting in β -hydroxythioester **4**.^{1,2} A dehydratase (DH) can eliminate water resulting in the corresponding α,β -unsaturated thioester **5**, which can then be reduced by an enoyl-reductase (ER) to the saturated thioester **6**. Repetition of this cycle with a varying involvement of the KR, DH and ER enzyme units leads to an impressive variety of polypropionate structures. Finally, a thio-esterase hydrolytically detaches the chain to provide the free polypropionate.

When polyketide synthases are selective for the incorporation of methylmalonate units and fully reduce the intermediate

products, so-called deoxypropionate units are formed (Fig. 1). Both *syn* (**1**) and *anti* (**2**) 1,3,5... *n*-polymethyl alkyl chains are found as individual and combined structures in natural products (Fig. 2).

Polyketides containing deoxypropionate units are synthesized by bacteria, fungi, and plants (Fig. 2).¹ A broad range of fascinating biological activities are associated with these structures *e.g.*; cytostatics: borrelidin (**7**)³ and dolicolide (**8**),⁴ pheromones: lardolure (**9**),⁵ waxes: 4,6,8,10,16,18-hexamethyldocosane (**10**),⁶ and PDIM A (**11**),⁷ and calcium ionophores: ionomycin (**12**).⁸

A broad variety of synthetic methods for the construction of polypropionates has been described over the last decades.⁹ Especially the chiral auxiliary based aldol condensation reaction, developed by Evans and others, has contributed to a large extent to the synthesis of polypropionates.^{10,11} Because of the abundant presence of deoxypropionate units, many synthetic strategies have also been developed for this pattern. These strategies are often based on the selective introduction of methyl substituents in a consecutive (iterative) fashion, either *syn* or *anti*, and can be divided into non-catalytic and catalytic methodologies.

Stratingh Institute for Chemistry, University of Groningen,
Nijenborgh 4, 9747 AG, Groningen, The Netherlands.
E-mail: a.j.minnaard@rug.nl, b.l.feringa@rug.nl;
Fax: +31 50 363 4296; Tel: +31 05363 4235

Bjorn ter Horst

Bjorn ter Horst (1977) obtained his Master's degree in Organic Chemistry in 2005 at the University of Groningen, The Netherlands. Subsequently he carried out his PhD-research in the group of Minnaard and Feringa at the same university in the field of asymmetric catalysis and natural product synthesis.

Ben L. Feringa

Ben L. Feringa obtained his PhD degree in 1978 at the University of Groningen under the guidance of Professor Hans Wynberg. After working as a research scientist at Shell he was appointed full professor at the University of Groningen in 1988 and named the distinguished Jacobus H. van't Hoff Professor of Molecular Sciences in 2004. He was elected foreign honorary member of the American Academy of Arts and Sciences and member of the Royal Netherlands Academy of Sciences. His research interests include stereochemistry, organic synthesis, asymmetric catalysis, molecular switches and motors, self-assembly and nanosystems.

Scheme 1 Biosynthetic pathway for deoxypropionates.

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

Non-catalytic methods for the construction of deoxypropionates

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 to a chiral α,β -unsaturated camphor derived ester was developed (Scheme 2). In this reaction the *anti*-product was predominantly formed with a de of 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 stereocentre, resulted in an excellent diastereomeric excess for both the *syn*, 92% de, and *anti*-product, 94% de. The camphor based chiral auxiliary almost completely dictates the diastereochemical outcome of the reaction, whereas the influence of the already present methyl-branched stereocentre is minimal.

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 stereocentre already present in the methyl-branched organocuprate. Addition of methylcuprate to a substrate containing a methyl-branched stereocentre resulted in a high diastereoselectivity for the *syn*-product (>97% de).

(Aza) enolate alkylation reactions directed by chiral auxiliaries

Well known and widely used chiral enolate alkylation strategies have been reported by Evans,¹⁴ Masamune,¹⁵ Enders¹⁶ and Myers.¹⁷ In all of these strategies, a chiral auxiliary containing propionyl enolate acts as a nucleophile towards a substrate already containing one methyl-branched stereocentre (Scheme 3).

The methyl-branched product of the alkylation reaction is reduced with simultaneous cleavage of the chiral auxiliary to give the corresponding alcohol which is subsequently turned into a leaving group. This newly formed substrate can then 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.

Evans and co-workers applied this strategy in the total synthesis of ionomycin.¹⁴ Their chiral amide enolate auxiliary was shown to be 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 (+)-siphonariene.^{15b} The *syn*-selectivity for the dimethyl product of the alkylation was >98%, whereas the formation of the *anti*-product was not reported.

The Enders lithioenamine (aza enolate) alkylation reaction, employing a chiral proline derived hydrazone (SAMP/RAMP auxiliary) 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. Recently, Prandi and co-workers¹⁸ reported an efficient iterative procedure based on the Enders methodology which was used for the synthesis of all-*syn* polymethyl fatty acids like those in **11** with up to 4 methyl groups. These acids

Adriaan J. Minnaard

at the Max Planck Institute for Molecular Physiology in Dortmund, Germany. His work focuses on asymmetric catalysis and natural product synthesis.

Adriaan J. Minnaard received his PhD degree from Wageningen Agricultural University, The Netherlands and was a scientist at DSM-Research, from 1997 to 1999. Subsequently, he joined the University of Groningen in 1999 as an Assistant Professor in the department of Prof. Ben L. Feringa. In 2005, he was appointed Associate—and in 2009 Full—Professor in Bio-organic Chemistry. In 2006 he was a guest researcher in the group of Prof. H. Waldmann

Fig. 2 Examples of naturally occurring (deoxy)propionates.

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

function as close mimics of the methyl-branched fatty acids in *M. tuberculosis*.

Myers and co-workers introduced an iterative alkylation reaction using the lithium propionamide enolate of (+)-pseudoephedrine (with 2 equiv. of LDA). The iterative construction of all possible diastereomers of 1,3,5-trimethyl deoxypropionates was reported.¹⁷ All products were obtained

with excellent diastereomeric ratios ranging from 55:1 to 199:1.

Iterative zinc-catalyzed enantiospecific sp^3 – sp^3 cross-coupling

Recently, Breit *et al.* reported a new method that allows the zinc-catalyzed enantiospecific sp^3 – sp^3 -coupling of a large variety of Grignard reagents with different α -hydroxy ester triflates derived from the chiral pool.¹⁹ Starting from the triflate of enantiopure lactic acid *tert*-butyl ester, this coupling affords chiral α -methyl-substituted esters with complete inversion of configuration. Both enantiomers of lactic acid are commercially available (although the *R*-enantiomer is expensive). This new method was very recently used in an iterative fashion in the synthesis of all four possible diastereomers of trideoxypropionates (Scheme 4) with perfect stereocontrol.²⁰ The product of the alkylation reaction is converted 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.

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 Breit²¹ and Spino²² (Scheme 5). The method developed by Spino starts with an enantiopure menthone derivative which undergoes S_N2' displacement by an enantiopure mixed organocuprate reagent with near perfect stereocontrol. The stereochemical outcome is exclusively dependent on the stereochemistry of the allylic carbonate.

Breit described the allylic alkylation reaction of enantiopure *ortho*-diphenylphosphanylbenzoate (*o*-DPPB) allylic esters with enantiopure organocuprates. The *o*-DPPB esters were obtained by enzymatic kinetic resolution.

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

into an iodide derivative in several synthetic steps. The iodide is subsequently used as the substrate for a second allylic alkylation. Very recently, the method was used for the first synthesis and elucidation of the stereochemistry of vittatalactone, an aggregation pheromone of the striped cucumber beetle, *Acalymma vittatum*.²¹ⁱ Both iterative methods are highly selective but do require enantiopure reagents and substrates.

Substrate controlled iterative 1,4-addition reactions

Hanessian and co-workers applied iterative substrate controlled 1,4-addition reactions in a number of natural product syntheses.²³ The iterative sequence starts with an enantiopure α,β -unsaturated ester **13** with a methoxymethyl (MOM) protected hydroxy stereocentre in the γ -position (Scheme 6). Both enantiomers of this substrate are readily available starting from either L-malic acid or D-glyceraldehyde. The 1,4-addition reaction with Me_2CuLi proceeds with good *anti*-selectivity for the formation of the vicinal hydroxy-methyl motif (**14**, $dr > 93:7$). 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 α,β -unsaturated ester **15** which can readily undergo a second 1,4-addition reaction. The second 1,4-addition reaction with Me_2CuLi favours the *syn*-dimethyl deoxypropionate with a dr of

89:11 when the 1-methyl-1-cyclopentyl (MCP) ester is used.²⁴ 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 high selectivity for *syn*-product formation is attributed to a preferred conformation in the transition-state in which 1,5-*syn*-pentane interactions are minimized or avoided.

Breit and co-workers²⁵ reported a substrate controlled 1,4-addition reaction on α,β -unsaturated esters with a directing *o*-DPPB group, mentioned earlier, at the ε -position (Scheme 7). This substrate was obtained from a hydroformylation-olefination reaction sequence. Addition of Me_2CuLi to unsaturated ester **16** resulted in a dr of 95:5 favouring *anti*-product **17**. The coordinating effect on the selectivity for the introduction of a third methyl group was not investigated.

Iterative cyclopropanation fragmentation

In 2001, Ghosh *et al.*²⁶ reported an enantioselective cyclopropanation fragmentation strategy for the construction of (–)-dolicolide (**8**) (Fig. 2), an all-*syn* deoxypropionate containing natural product with antitumour properties.²⁷ The synthesis started with an enantiopure methyl-branched allylic alcohol **18** which was obtained in 8 steps from Roche ester (Scheme 8). Charette asymmetric cyclopropanation²⁸ of allylic alcohol **18** resulted in the corresponding cyclopropane **19** in high yield (99%) and good diastereomeric excess of 91%. Conversion of alcohol **19** into the corresponding iodide, followed by fragmentation of the cyclopropane ring upon treatment with *n*-BuLi/TMEDA in the presence of molecular sieves, resulted in the *syn*-dimethyl deoxypropionate **20** which was transformed into allylic alcohol **21** for subsequent cyclopropanation in 4 steps. The second cyclopropanation reaction resulted in product **22** with similar selectivity ($de = 90\%$).

Catalytic asymmetric iterative strategies for the synthesis of deoxypropionates

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.^{29a–l} In this protocol, an enantioselective carboalumination of a terminal olefin **23** is catalyzed by enantiomerically pure zirconium complex **24** (Scheme 9) resulting in the carboaluminated product **25**. Subsequent oxidation by O_2 results in the primary alcohol **26** (step A). This alcohol is then transformed into the corresponding iodide **27** 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 **28**, 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 used an enzymatic kinetic resolution to increase the *ee* from 82% to

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

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

Scheme 8 Iterative enantioselective cyclopropanation/fragmentation strategy.

98% (68% recovery at 75% conversion of alcohol **23**, Z = H, into its acetate).^{29c}

The iterative steps require separation of diastereomers at 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*-**24**). After purification, diastereomeric ratios 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. The ZACA iterative protocol was demonstrated in the total synthesis of **10**, Fig. 2,^{29h} a natural wax isolated from the cuticula of the cane beetle *Antitrogon parvulus* by Kitching and co-workers.⁶

Another example of the application of the ZACA protocol is the synthesis of the upper part of borrelidin (**7**, Scheme 10).^{29b} Styrene was chosen as the starting material. The *anti*-product **29** was obtained in a diastereomeric ratio of 7:1. Formation of the *syn*-product with *ent*-**24** resulted in a ratio of 1:4.6. In two subsequent iterative steps, minor diastereomers were separated by column chromatography from the major diastereomer **30**. The phenyl ring was then completely oxidized to the acid in two steps and after three additional transformations building block **31** was isolated in 9.3% yield starting from styrene.

It is not obvious why styrene was chosen as the starting material, since the same group had already reported that the *anti*-isomer of compound **26** could be prepared directly with higher selectivity (10:1).^{29c} Moreover, this approach does not require oxidation of the phenyl group.

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

Minnaard and Feringa reported in 2005 the iterative construction of 1,3-methyl arrays based on their enantioselective copper-catalyzed 1,4-addition reaction on unsaturated thioesters with MeMgBr and Josiphos ligand (**32**, Scheme 11).^{5a} The 1,4-addition reaction on substrate **33** resulted in methyl-substituted thioester **34** with excellent yield and selectivity (93% yield, 95% ee). Thioester **34** was subsequently reduced to the corresponding aldehyde followed by Wittig olefination with Ph₃PCHCOSEt to yield α,β -unsaturated thioester **35** in 80% yield over those two steps. Thioester **34** was used in a second 1,4-addition reaction resulting in either *syn*-product **36**, under the same conditions as the first 1,4-addition reaction, or *anti*-product **37** when the opposite enantiomer of ligand **32** was used. Both **36** and **37** could be obtained in high yield (>90%) with an excellent diastereomeric ratio of, respectively, 96:4 and 95:5. This strategy was applied in the synthesis of several naturally occurring deoxypropionates (*vide infra*).

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

Scheme 10 ZACA protocol for the synthesis of the upper part of borrelidin.

(–)-Lardolure

The application of the iterative copper-catalyzed 1,4-addition was demonstrated in the synthesis of (–)-lardolure (**9**, Scheme 12).^{5a} In this synthesis, three iterative steps are executed starting with a 1,4-addition on thioester **38** with Josiphos ligand **32** in 92% yield and an ee of 96%. Product **39** was reduced with Pd/C and Et_3SiH (Fukuyama conditions)³⁰ to the aldehyde which was subsequently treated with Wittig reagent $\text{Ph}_3\text{PCHCOSEt}$ to provide unsaturated thioester **40**. The second catalytic asymmetric 1,4-addition

Scheme 11 Iterative copper-catalyzed 1,4-addition reactions with MeMgBr .

yields *syn*-product **41** when the same enantiomer of the Josiphos ligand **32** is used (dr = 97.5:2.5).

Subsequent reduction and olefination as before resulted in **42** in 80% yield over those two steps. The third methyl group was introduced under the same 1,4-addition conditions as before to provide **43**. Sulfanyl ketone **44** was obtained by the addition of lithiated (*S*)-methyl-*p*-tolylsulfoxide to **43**. Substrate controlled diastereoselective reduction with DIBAL-H resulted in β -hydroxysulfoxide **45** (de > 97%). Finally, desulfurisation of **45** followed by formylation led to (–)-(**9**).

Scheme 12 Asymmetric iterative 1,4-addition reactions in the synthesis of (–)-lardulure.

All steps in this iterative protocol are high yielding and enantioselectivities and diastereoselectivities are excellent. Diastereoselectivity increases for the all-*syn* deoxypropionate upon addition of subsequent methyl substituents (Scheme 12). This increased selectivity was also observed in the synthesis of mycocerosic and phthioceranic acid (*vide infra*) and is probably the result of a distinct conformation in the transition-state in which 1,5-*syn*-pentane interactions³¹ are minimized or avoided as was also observed by Hanessian.^{23c}

Mycocerosic acid and PDIM A

Together with tuberculostearic acid,³² phthioceranic acid, mycolipenic acid and mycolipanic acid, mycocerosic acid (**46**) is one of the many methyl-branched fatty acids from *M. tuberculosis*. Mycocerosic acid was first studied by Marks and Polgar³³ in the fifties. In 1963 Polgar and Smith³⁴ elucidated its absolute stereochemistry by degradation studies, confirmed subsequently by the synthesis of mycocerosic acid starting from chiral pool compounds and *via* a route involving kinetic resolution.^{35,36} These studies confirmed that the natural product had an all-*R* configuration. Recent studies showed that mycocerosic acid is produced by the enzyme mycocerosic acid synthase (MAS). Rainwater and Kolattukudy³⁷ studied the biosynthesis of mycocerosic acid and found that MAS is specific for methylmalonyl-CoA and does not incorporate malonyl-CoA into fatty acids.

The Cu/Josiphos catalyzed iterative conjugate addition of MeMgBr to unsaturated thioesters was applied in the total synthesis of enantiopure **46** (Scheme 13). The starting material contains a functionality at the terminus of the unsaturated thioester that is robust under the iterative reaction conditions (conjugate addition, Pd-catalyzed reduction, and Wittig reaction). For this reason **47** was selected, being an unsaturated thioester with a protected hydroxyl group prepared from glycol in 3 steps. Substrate **47** gave excellent enantioselectivity (98% ee) and complete regioselectivity in the copper-catalyzed 1,4-addition with MeMgBr and 1 mol% of (*ent*)-**32**/CuBr (Scheme 13). Bifunctional building block **48** was reduced to the corresponding aldehyde followed by a Wittig reaction to give thioester **49**. The *syn*-selectivity of the second

conjugate addition, leading to dimethyl thioester (*ent*)-**50**, could be established by ¹H-NMR spectroscopy in comparison with dimethyl thioester *anti*-**50**, prepared using **32**. The ratio *syn/anti* was higher than 97 : 3. The reduction/olefination/1,4-addition sequence was applied four times in an iterative procedure to arrive at the tetramethyl substituted compound **51** in ten steps with excellent selectivity (dr > 96 : 4) and an overall yield of 21% from **47**. Twofold reduction of thioester **51** with DIBAL-H resulted in alcohol **52**, which was converted subsequently into **53** after treatment with TsCl. The introduction of the long alkyl chain was achieved by treatment of **53** with C₁₈H₃₇MgBr and 20 mol% of CuBr·SMe₂ to yield **54**, which was deprotected with TBAF to yield the tetramethyl substituted alcohol **55**. Oxidation of **55** gave mycocerosic acid (**46**) in 15 steps with an overall yield of 12% (86% on average).³⁸ The optical rotation (–6.4, *c* = 0.94, CHCl₃) of **46** was in accordance with the literature value for the isolated product (–5.62, *c* = 8.9, CHCl₃).³⁴ Double esterification of phthiocerol (**56**) with mycocerosic acid gave PDIM A (**11**) in 63% yield (15 steps and 5.6% overall yield) (Scheme 14).^{7a}

Phthioceranic acid

The iterative copper-catalyzed 1,4-addition protocol was further demonstrated in the synthesis of phthioceranic acid (**57**, Scheme 15), a heptamethyl-branched acid from *M. tuberculosis*. The synthesis of **57** also started with bifunctional substrate **47** which was submitted to an enantioselective 1,4-addition with MeMgBr, catalyzed by 1 mol% of **32**·CuBr in *t*-BuOMe at –78° C (95% yield, 98% ee). The product was reduced to the corresponding aldehyde which was subsequently used in the olefination step. By repeating this sequence of 1,4-addition, reduction and Wittig olefination (see Scheme 13), all 7 methyl groups were introduced in a 1,3-*syn*-fashion with excellent stereoselectivity and very high yield. Thus, heptamethyl-substituted thioester **58** was synthesized in 19 steps with 8% overall yield starting from **47**. The diastereoselectivity of all iterative conjugate addition reactions was > 96%, as determined from the ¹H-NMR, in which the *syn/anti* isomers were clearly distinguishable.

Scheme 13 Total synthesis of mycocerosic acid.

Scheme 14 Final step in the synthesis of PDIM A.

Thioester **58** was reduced with DIBAL-H to the corresponding alcohol, which was subsequently converted into a tosylate with 2 equivalents of TsCl and pyridine. The long aliphatic chain was introduced *via* a copper-catalyzed coupling reaction with $C_{14}H_{29}MgBr$ (3 equiv.) and 20 mol% of $CuBr \cdot SMe_2$. The resulting silyl ether **59** was deprotected with TBAF to give the corresponding alcohol, which was finally oxidized to compound **57** with catalytic $RuCl_3$ and $NaIO_4$ in 90% yield over two steps.

The overall yield of the synthesis is 4% over 24 steps. No minor diastereomers of **57** could be observed by 1H - or ^{13}C -NMR, most probably as a result of the chromatography steps which remove traces of minor diastereomers.³⁹

Mycolipenic and mycolipanic acid

The synthesis of mycolipenic acid (phthienoic acid, **60**, Scheme 16) started with a careful optimization of the iterative

Scheme 15 Key steps in the total synthesis of phthioceranic acid.

copper-catalyzed asymmetric 1,4-addition protocol reported previously.^{38–40} In the previous reported reduction/olefination sequence, a Fukuyama reduction with Pd/C and Et_3SiH was applied, followed by Wittig olefination. This typically resulted in a yield of 70% over two steps. It turned out, however, that reduction of thioester *ent*-**48** with DIBAL-H, followed by olefination with Horner–Wadsworth–Emmons (HWE) reagent $(EtO)_2P(O)CH_2COSEt$ (**61**), afforded unsaturated thioester *ent*-**49** in 80% yield over two steps (typically 80–90%). This improved sequence makes the methodology, as the steps are iterative, considerably more efficient. The second asymmetric 1,4-addition reaction was performed under the same conditions as the first addition.

Scheme 16 Optimized reduction/olefination and the synthesis of mycolipenic (**60**) and mycolipanolic acid (**66**).

Alcohol **62** was obtained after five synthetic steps and was oxidized to aldehyde **63** under neutral conditions with *N*-methylmorpholine oxide (NMO) in the presence of catalytic tetrapropylammonium perruthenate (TPAP) in 90% yield.⁴¹ No epimerization of the α methyl stereocentre was observed during this transformation. Aldehyde **63** was treated with Wittig reagent **64**, which resulted in the corresponding olefin with an *E/Z* ratio of 9:1; the desired *E*-isomer **65** was isolated in 65% yield.⁴² In the final step, ethyl ester **65** was hydrolyzed in a water–THF mixture with LiOH and mycolipenic acid **60** was obtained in 70% yield.⁴³ The optical rotation of the synthetic material, +16.4 ($c = 1.96$, CHCl₃), matched with that reported in the literature for the natural product isolated from *M. tuberculosis* (+19).^{44,45}

For the introduction of the *syn*-hydroxy-methyl unit in the synthesis of mycolipanolic acid (**66**), an Evans aldol reaction of the boron enolate of enantiopure oxazolidone **67** with aldehyde **63** was used.^{10,46} To prevent over-oxidation or epimerization at the α stereocentre, **63** was prepared

freshly by oxidation of alcohol **62** employing the NMO/TPAP procedure followed by quick purification over silica (Scheme 16). After the aldol reaction with **67** and work up, **68** was isolated in a moderate 45% yield with excellent stereocontrol (diastereomeric ratio of 45:1).⁴³ Removal of the chiral auxiliary with H₂O₂ and LiOH gave mycolipanolic acid **66** in 90% crude yield. The optical rotation of the methyl ester of synthetic **66**, -7.0 ($c = 0.2$, CHCl₃), is in agreement with the literature value of -7.19 .⁴⁷

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

Loh and co-workers^{48a–c} described an iterative protocol for the synthesis of deoxypropionates based on the copper-catalyzed 1,4-addition with Grignard reagents in 2007. CuI was used as the copper source and tol-BINAP (**69**) as the ligand. Where the Minnaard and Feringa group found that MeMgBr performed poorly in the reaction with unsaturated oxo-esters such as **70**, Loh showed that by switching to the CuI/tol-BINAP system, the desired product **71** could be obtained in high ee (96%) and a moderate yield of 68% (Scheme 17).

Ester **71** was reduced with DIBAL-H to the corresponding aldehyde and treated with a Wittig reagent to obtain unsaturated ester **72** 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 at elevated temperatures (olefination step). The authors report that the second 1,4-addition reaction results in dimethyl substituted ester **73** with an excellent *syn:anti* selectivity of > 99:1 and moderate yield (66%).

Scheme 17 Iterative 1,4-additions with CuI/tol-BINAP catalytic system.

Formation of *anti*-product **74** employing (*R*)-tol-BINAP was reported to result in an *anti*:*syn* ratio of 95:5. Starting with substrate **72** with 96% ee, however, it is not feasible to obtain a *syn*:*anti* selectivity higher than 99:1 of **73**. The authors do not report separation or enrichment of diastereomers by chromatography, neither is an incomplete reaction reported, which might explain this outcome. The *syn*:*anti* ratios are calculated from the integrals of the two diastereomers in ^{13}C -NMR, with a rather small signal to noise ratio.

The CuI/tol-BINAP system also works on unsaturated thioesters as was demonstrated in 2007 by the Minnaard and Feringa group.⁴⁹ In addition they reported that the HWE olefination is more selective towards the *E*-isomer compared to the corresponding Wittig reaction.⁴³

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.⁵⁰ A chiral version of the Crabtree⁵¹ catalyst (**75**) was used based on a carbene oxazoline ligand (Scheme 18).

Substrate **76**, which was prepared from Roche ester in 3 steps, was hydrogenated at 50 atm H_2 (0.2 mol% **75**, 25 °C for 4 h). The *syn*-product was obtained with catalyst **75** and *anti*-product **77** was obtained with *ent*-**75** 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, **76** was reduced

Scheme 18 Asymmetric hydrogenation of chiral tri-substituted alkenes.

with DIBAL-H into the corresponding allylic alcohol **78**. It was found that the catalyst approaches these α,β -unsaturated esters and alcohols from opposite π -faces.^{50b} However, 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 (**79**, with *ent*-**75**) was found. The *Z*-isomer of the allylic alcohol (**80**), made from the *Z*-isomer of the unsaturated ester, was found to favour *syn*-product **81** 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, **77**) or oxidized (for the alcohols, **79/81**) to the corresponding aldehydes which can undergo subsequent Wittig or Horner–Wadsworth–Emmons olefination reactions (Scheme 19) for the following iterative step. Wittig olefination leads predominantly to the *E*-isomer **82** (89% isolated) which can be used as a substrate for the *anti*-product **83**. HWE olefination has a preference for the *Z*-isomer (96% isolated) of the unsaturated ester which can be reduced to *Z*-allylic alcohol **84**, the substrate for *syn*-product **85** after hydrogenation.

A direct route to products **83** and **85** was also investigated. Diene substrate **86** could be prepared from substrate **76** by a reduction, olefination, reduction sequence. Diene **86** was hydrogenated using 1 mol% of catalyst **75** (rather than the 0.2 mol% normally used). With catalyst *ent*-**75** the *anti*,*syn*-product **87** 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 **75** resulting in a dr of 21:4.2:3.2:1.

One year earlier in 2006, the group of Pfaltz published⁵² a somewhat similar approach of enantioselective alkene reduction of γ -tocotrienyl acetate **88** to natural (*R,R,R*)- γ -tocopheryl acetate **89**, a vitamin E derivative (Scheme 20).

In this case iridium-catalyzed hydrogenation was found to give the highest selectivity with P,N ligands (ligands with coordinating P and N atoms). Although the Pfaltz group did not describe an iterative approach for the construction of polydeoxypropionates, their findings elegantly demonstrate an approach for the construction of 1,5-polymethyl structures. These occur in polypropionates from *Mycobacterium tuberculosis*⁵³ as well as in many isoprenoids.

Conclusions

After the initial pioneering work on non-catalytic 1,4-addition strategies for the construction of deoxypropionates by Oppolzer¹² and later by Williams,¹³ several alternative methods have been reported during the last 25 years. Iterative enolate additions have been described by Evans,¹⁴ Masamune,¹⁵ Enders¹⁶ and Myers.¹⁷ More recently, iterative approaches were reported by Breit,^{20,21} Spino,²² Hanessian²³ and Ghosh.²⁶

The field of iterative catalytic asymmetric synthesis of deoxypropionates has seen tremendous progress over the last 5 years. It started with the introduction of the iterative zirconium-catalyzed carboalumination (ZACA) protocol in 2004 by Negishi and co-workers.^{29a,d,k} High selectivities for both the *syn* and *anti* deoxypropionate motif were obtained in several natural product syntheses. Undesired diastereomers

Scheme 19 Iterative strategy by subsequent catalytic asymmetric hydrogenation reactions.

Scheme 20 Iridium-catalyzed asymmetric hydrogenation of γ -tocotrienyl acetate, introducing the 1,5-dimethyl substructure in a single step.

were removed by chromatography and therefore 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.^{5a} Excellent enantioselectivities and diastereoselectivities were obtained in the preparation of the all-*syn* deoxypropionate substructure. Both the *syn* and *anti* motif could be constructed in excellent yield and diastereoselectivity (de > 96%). The effectiveness and robustness of this iterative strategy were further demonstrated by the synthesis of mycocerosic and phthioceranic acid, a tetra- and heptamethyl-branched acid, respectively, from *M. tuberculosis*.^{38,39} Optimization of the reduction/olefination step in the iterative sequence was demonstrated by the synthesis of mycolipenic and mycolipanic acid.⁴³

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 also highly selective for the construction of both the *syn* and *anti* motif of the deoxypropionates although yields are moderate.⁴⁸

Burgess' asymmetric hydrogenation strategy (2007), starting with an enantiopure substrate derived from Roche ester, proved to be highly selective in the synthesis of deoxypropionates (dr's up to 34:1).⁵⁰ This system also allowed the introduction of two stereocentres in one reaction by hydrogenation of dienes and especially the *syn*-product could be obtained with good selectivity.

Almost all catalytic and non-catalytic strategies described in this article allow the selective introduction of the *syn* and *anti* deoxypropionate motif. The non-catalytic approaches do, however, require either chiral auxiliaries which have to be removed and reintroduced in the iterative sequence or require stoichiometric amounts of chiral substrate which results in significant loss of material. This problem is overcome with the catalytic strategies developed in recent years. Although all catalytic strategies are linear, selectivities and yields are excellent and the number of synthetic steps is minimized.

Future prospects for the synthesis of deoxypropionates are found in lower catalyst loadings, reactions at ambient temperatures and fewer synthetic steps. In addition, the procedures described here can be seen as a prelude for the iterative synthesis of fully functionalized polypropionates. Iterative catalytic approaches are in principle very suitable for an automated synthesis in which any number of methyl substituents in the desired stereochemical configuration can be synthesized on demand. Although these developments still require a considerable effort, the abundance and biological activity of (deoxy)propionates justify them.

Notes and references

- 1 Tolerance and specificity of polyketide synthases: C. Khosla, R. S. Gokhale, J. R. Jacobsen and D. E. Cane, *Annu. Rev. Biochem.*, 1999, **68**, 219.
- 2 (a) C. Khosla, *Chem. Rev.*, 1997, **97**, 2577; (b) L. Katz, *Chem. Rev.*, 1997, **97**, 2557; (c) A. J. Birch, *Science*, 1967, **156**, 202.
- 3 Borrelidin, isolation and activity: M. Lumb, P. E. Macey, J. Spyvee, J. M. Whitmarsh and R. D. Wright, *Nature*, 1965, **206**, 263.
- 4 Dolicolide, isolation and structure: H. Ishiwata, M. Nemoto, M. Ojika and K. Yamada, *J. Org. Chem.*, 1994, **59**, 4710.
- 5 Lardolure: (a) R. Des Mazery, M. Pullez, F. López, S. R. Harutyunyan, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2005, **127**, 9966; (b) K. Mori and S. Kuwahara, *Tetrahedron*, 1986, **42**, 5539; (c) N. Hanaki, K. Ishihara, M. Kaino, Y. Naruse and H. Yamamoto, *Tetrahedron*, 1996, **52**, 7297. For the stereochemistry of lardolure, see: (d) K. Mori and S. Kuwahara, *Tetrahedron*, 1986, **42**, 5545.
- 6 4,6,8,10,16,18-Hexamethyldocosane, isolation and structure: (a) S. Chow, M. T. Fletcher, L. K. Lambert, O. P. Gallagher, C. J. Moore, B. W. Cribb, P. G. Allsopp and W. Kitching, *J. Org. Chem.*, 2005, **70**, 1808; (b) M. T. Fletcher, S. Chow, L. K. Lambert, O. P. Gallagher, B. W. Cribb, P. G. Allsopp, C. J. Moore and W. Kitching, *Org. Lett.*, 2003, **5**, 5083.
- 7 (a) E. Casas-Arce, B. ter Horst, B. L. Feringa and A. J. Minnaard, *Chem.-Eur. J.*, 2008, **14**, 4157; (b) For a review on deoxypropionates in mycobacteria, see: D. E. Minnikin, L. Kremer, L. G. Dover and G. S. Besra, *Chem. Biol.*, 2002, **9**, 545.
- 8 Isolation: C.-M. Liu and T. E. Hermann, *J. Biol. Chem.*, 1978, **253**, 5892.
- 9 (a) K. C. Nicolaou and S. A. Snyder, *Classics in Total Synthesis II*, Wiley-VCH, Weinheim, 2003; (b) K. C. Nicolaou and E. J. Sorensen, *Classics in Total Synthesis*, Wiley-VCH, Weinheim, 1996; (c) E. J. Corey and X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley & Sons, New York, 1989.
- 10 For a review see: B. Schetter and R. Mahrwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 7506.
- 11 (a) D. A. Evans and T. R. Taber, *Tetrahedron Lett.*, 1980, **21**, 4675; (b) D. A. Evans, J. Bartoli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127.
- 12 (a) W. Oppolzer, R. Maretta and G. Bernardelli, *Tetrahedron Lett.*, 1986, **27**, 4713; (b) For a review on camphor derivatives as chiral auxiliaries, see: W. Oppolzer, *Tetrahedron*, 1987, **43**, 1969.
- 13 (a) D. R. Williams, W. S. Kissel, J. J. Li and R. J. Mullins, *Tetrahedron Lett.*, 2002, **43**, 3723; (b) D. R. Williams, A. L. Nold and R. J. Mullins, *J. Org. Chem.*, 2004, **69**, 5374.
- 14 D. A. Evans, R. L. Dow, T. L. Shih, J. M. Takacs and R. Zahler, *J. Am. Chem. Soc.*, 1990, **112**, 5290.
- 15 (a) A. Abiko, O. Moriya, S. A. Filla and S. Masamune, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 793; (b) A. Abiko and S. Masamune, *Tetrahedron Lett.*, 1996, **37**, 1081.
- 16 (a) A. A. Birkbeck and D. Enders, *Tetrahedron Lett.*, 1998, **39**, 7823; (b) For a review on hydrazones as chiral auxiliaries, see: A. Job, C. F. Janecek, W. Bettray, R. Peters and D. Enders, *Tetrahedron*, 2002, **58**, 2253.
- 17 A. G. Myers, B. H. Yang, H. Chen and D. Kopecky, *Synlett*, 1997, 457.
- 18 J. Guiard, A. Collmann, M. Gilleron, L. Mori, G. De Libero, J. Prandi and G. Puzo, *Angew. Chem., Int. Ed.*, 2008, **47**, 9734.
- 19 C. Studte and B. Breit, *Angew. Chem., Int. Ed.*, 2008, **47**, 5451.
- 20 G. J. Brand, C. Studte and B. Breit, *Org. Lett.*, 2009, **11**, 4668.
- 21 (a) B. Breit and C. Herber, *Angew. Chem., Int. Ed.*, 2004, **43**, 3790; (b) B. Breit, *Angew. Chem., Int. Ed.*, 1998, **37**, 525; (c) C. Herber and B. Breit, *Angew. Chem., Int. Ed.*, 2005, **44**, 5267; (d) C. Herber and B. Breit, *Eur. J. Org. Chem.*, 2007, 3512; (e) C. Herber and B. Breit, *Chem.-Eur. J.*, 2006, **12**, 6684; (f) P. Demel, M. Keller and B. Breit, *Chem.-Eur. J.*, 2006, **12**, 6669; (g) T. Reiss and B. Breit, *Chem.-Eur. J.*, 2009, **15**, 6345; (h) T. Reiss and B. Breit, *Org. Lett.*, 2009, **11**, 3286; (i) Y. Schmidt and B. Breit, *Org. Lett.*, 2009, **11**, 4767.
- 22 (a) C. Spino, C. Beaulieu and J. Lafreniere, *J. Org. Chem.*, 2000, **65**, 7091; (b) C. Spino and M. Allan, *Can. J. Chem.*, 2004, **82**, 177.
- 23 (a) S. Hanessian, Y. Yang, S. Giroux, V. Mascitti, J. Ma and F. Raepel, *J. Am. Chem. Soc.*, 2003, **125**, 13784; (b) S. Hanessian, S. Giroux and V. Mascitti, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 11996; (c) S. Hanessian, N. Chahal and S. Giroux, *J. Org. Chem.*, 2006, **71**, 7403; (d) For a review on the iterative synthesis of acyclic deoxypropionate units, see: S. Hanessian, S. Giroux and V. Mascitti, *Synthesis*, 2006, 1057.
- 24 The use of the MCP ester resulted in the highest diastereomeric ratio compared to other esters.
- 25 B. Breit and P. Demel, *Tetrahedron*, 2000, **56**, 2833.
- 26 A. K. Ghosh and C. Liu, *Org. Lett.*, 2001, **3**, 635.
- 27 H. Ishiwata, H. Sone, H. Kigoshi and K. Yamada, *Tetrahedron*, 1994, **50**, 12853.
- 28 A. B. Charette and H. Juteau, *J. Am. Chem. Soc.*, 1994, **116**, 2651.
- 29 (a) E. Negishi, Z. Tan, B. Liang and T. Novak, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5782; (b) T. Novak, Z. Tan, B. Liang and E. Negishi, *J. Am. Chem. Soc.*, 2005, **127**, 2838; (c) B. Liang, T. Novak, Z. Tan and E. Negishi, *J. Am. Chem. Soc.*, 2006, **128**, 2770; (d) Z. Tan and E. Negishi, *Angew. Chem., Int. Ed.*, 2004, **43**, 2911; (e) D. Y. Kondakov and E. Negishi, *J. Am. Chem. Soc.*, 1995, **117**, 10771; (f) D. Y. Kondakov and E. Negishi, *J. Am. Chem. Soc.*, 1996, **118**, 1577; (g) G. Zhu and E. Negishi, *Org. Lett.*, 2007, **9**, 2771; (h) G. Zhu, B. Liang and E. Negishi, *Org. Lett.*, 2008, **10**, 1099; (i) B. Liang and E. Negishi, *Org. Lett.*, 2008, **10**, 193; (j) Z. Xu and E. Negishi, *Org. Lett.*, 2008, **10**, 4311; (k) M. Magnin-Lachaux, Z. Tan, B. Liang and E. Negishi, *Org. Lett.*, 2004, **6**, 1425; (l) E. Negishi, *Pure Appl. Chem.*, 2001, **73**, 239.
- 30 T. Fukuyama and H. Tokuyama, *Aldrichimica Acta*, 2004, **37**, 87.
- 31 For a review on preferred conformations see: R. Göttlich, B. C. Kahrs, J. Krüger and R. W. Hoffmann, *Chem. Commun.*, 1997, 247.
- 32 B. ter Horst, C. Seshadri, L. Sweet, D. C. Young, B. L. Feringa, D. B. Moody and A. J. Minnaard, *J. Lipid Res.*, 2010, DOI: 10.1194/jlr.M001982.
- 33 G. S. Marks and N. Polgar, *J. Chem. Soc.*, 1955, 3851.
- 34 N. Polgar and W. Smith, *J. Chem. Soc.*, 1963, 3081.
- 35 (a) N. Polgar and W. Smith, *J. Chem. Soc.*, 1963, 3085; (b) N. Polgar and W. Smith, *Chem. Ind.*, 1961, 1958.
- 36 G. Odham, E. Stenhagen and K. Waern, *Ark. Kemi*, 1969, **31**, 533.
- 37 D. L. Rainwater and P. E. Kolattukudy, *J. Biol. Chem.*, 1985, **260**, 616.
- 38 B. ter Horst, B. L. Feringa and A. J. Minnaard, *Chem. Commun.*, 2007, 489.
- 39 B. ter Horst, B. L. Feringa and A. J. Minnaard, *Org. Lett.*, 2007, **9**, 3013.
- 40 (a) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard and B. L. Feringa, *Chem. Rev.*, 2008, **108**, 2824; (b) F. R. López, A. J. Minnaard and B. L. Feringa, *Acc. Chem. Res.*, 2007, **40**, 179; (c) T. Jerphagnon, M. G. Pizzuti, A. J. Minnaard and B. L. Feringa, *Chem. Soc. Rev.*, 2009, **38**, 1039.
- 41 For a review on NMO/TPAP oxidations, see: S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639.
- 42 The HWE equivalent of Wittig reagent **64** was also investigated, however, this always resulted in a lower E:Z ratio.
- 43 B. ter Horst, J. van Wermeskerken, B. L. Feringa and A. J. Minnaard, *Eur. J. Org. Chem.*, 2010, 38.
- 44 D. J. Millin and N. Polgar, *J. Chem. Soc.*, 1958, 1902.
- 45 N. Polgar, *J. Chem. Soc.*, 1954, 1008.
- 46 H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, 1957, **79**, 1920.
- 47 L. Coles and N. Polgar, *J. Chem. Soc. C*, 1968, 1541.
- 48 (a) S.-Y. Wang, S.-J. Ji and T.-P. Loh, *J. Am. Chem. Soc.*, 2007, **129**, 276; (b) S.-Y. Wang, T.-K. Lum, S.-J. Ji and T.-P. Loh, *Adv. Synth. Catal.*, 2008, **350**, 673; (c) T.-K. Lum, S.-Y. Wang and T.-P. Loh, *Org. Lett.*, 2008, **10**, 761.
- 49 B. Maciá Ruiz, K. Geurts, M. A. Fernández-Ibáñez, B. ter Horst, A. J. Minnaard and B. L. Feringa, *Org. Lett.*, 2007, **9**, 5123.
- 50 (a) J. Zhou and K. Burgess, *Angew. Chem., Int. Ed.*, 2007, **46**, 1129; (b) J. Zhou, J. W. Ogle, Y. Fan, V. Banphavichit, Y. Zhu and K. Burgess, *Chem.-Eur. J.*, 2007, **13**, 7162; (c) J. Zhou, Y. Zhu and K. Burgess, *Org. Lett.*, 2007, **9**, 1391.
- 51 R. H. Crabtree, *Acc. Chem. Res.*, 1979, **12**, 331.
- 52 S. Bell, B. Wustenberg, S. Kaiser, F. Menges, T. Netscher and A. Pfaltz, *Science*, 2006, **311**, 642.
- 53 R. P. van Summeren, D. B. Moody, B. L. Feringa and A. J. Minnaard, *J. Am. Chem. Soc.*, 2006, **128**, 4546.