Iterative strategies for the synthesis of deoxypropionates

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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-poly(methyl 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 doliculide (8),4 pheromones: lardolure (9),5 waxes: 4,6,8,10,16,18-hexamethylcicosane (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.
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. The 1,4-addition reaction of an enantiopure methyl-branched organocuprate to a chiral,a,b-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 diastereomical outcome of the reaction, whereas the influence of the already present methyl-branched stereocentre is minimal.

Williams reported a similar approach with a,b-unsaturated oxazolidinones. Enantiopure methyl-branched organocuprates were used as the Michael donor which resulted in excellent selectivities for the anti-dimethyl product (99% de). 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, Masamune, Enders and Myers. 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. 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 (+)-siphonarienone. 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. 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-workers 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
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.\textsuperscript{17} All products were obtained with excellent diastereomeric ratios ranging from 55:1 to 199:1.

**Iterative zinc-catalyzed enantiospecific sp\textsuperscript{3}–sp\textsuperscript{3} cross-coupling**

Recently, Breit \textit{et al.} reported a new method that allows the zinc-catalyzed enantiospecific sp\textsuperscript{3}–sp\textsuperscript{3}-coupling of a large variety of Grignard reagents with different α-hydroxy ester triflates derived from the chiral pool.\textsuperscript{19} Starting from the triflate of enantioselect lactide acid \textit{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 \textit{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.\textsuperscript{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 Breit\textsuperscript{21} and Spino\textsuperscript{22} (Scheme 5). The method developed by Spino starts with an enantiopure menthone derivative which undergoes \textit{S}_{2}’\textsuperscript{2} 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 \textit{ortho}-diphenylphosphanylbenzoate (**o-DPPB**) allylic esters with enantiopure organocuprates. 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 the corresponding enolate. This iterative alkylation protocol allows for the enantiopure enolate alkylation reactions to be performed, along with the use of various chiral auxiliaries.

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

Scheme 4: Iterative zinc-catalyzed enantiospecific sp³–sp³ cross-coupling reactions.
Wittig olefination of the aldehyde results in subsequently oxidized to the aldehyde by Swern oxidation. Reduced with DIBAL-H to the corresponding alcohol which is reaction. The second 1,4-addition reaction with Me₂CuLi ester can readily undergo a second 1,4-addition reaction. The second 1,4-addition reaction with Me₂CuLi favours the syn-dimethyl deoxypropionate with a dr of 89:11 when the 1-methyl-1-cyclopentyl (MCP) ester is used. 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-workers reported a substrate controlled 1,4-addition reaction on α,β-unsaturated esters with a directing α-DPPB group, mentioned earlier, at the ε-position (Scheme 7). This substrate was obtained from a hydroformylation-olefination reaction sequence. Addition of Me₂CuLi to unsaturated ester resulted in a dr of 95:5 favouring anti-product. The coordinating effect on the selectivity for the introduction of a third methyl group was not investigated.

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

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. 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 iterative methods are highly selective but do require enantiopure reagents and substrates.

Substrates for subsequent cyclopropanation in 4 steps. The second cyclopropanation reaction resulted in product 22 with similar selectivity (de = 90%).

Iterative cyclopropanation fragmentation

In 2001, Ghosh et al. reported an enantioselective cyclopropanation fragmentation strategy for the construction of (−)-doliculide (8) (Fig. 2), an all-syn deoxypropionate containing natural product with antitumour properties. The synthesis started with an enantiopure methyl-branched allylic alcohol 18 which was obtained in 8 steps from Roche ester (Scheme 8). Charette asymmetric cyclopropanation 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. 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 O₂ 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 ZnBr₂ 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 89:11 when the 1-methyl-1-cyclopentyl (MCP) ester is used.
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. 2,29b a natural wax isolated from the cuticula of the cane beetle Antitrogus 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 Ph3PCHCOEt 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).
The application of the iterative copper-catalyzed 1,4-addition was demonstrated in the synthesis of \((-\text{C}0)\)-lardolure (9, Scheme 12).\(^{5}\) 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\(_3\)SiH (Fukuyama conditions)\(^{30}\) to the aldehyde which was subsequently treated with Wittig reagent Ph\(_3\)PCHOSEt to provide unsaturated thioester 40. The second catalytic asymmetric 1,4-addition 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. Sulfinyl ketone 44 was obtained by the addition of lithiated (-S)-methyl-p-tolylsulfoxide to 43. Substrate controlled diastereoselective reduction with DIBAL-H resulted in \(\beta\)-hydroxysulfoxide 45 (de > 97%). Finally, desulfurisation of 45 followed by formylation led to \((-\text{C}0)\)-(-9).

\((-\text{Lardolure})\)

The application of the iterative copper-catalyzed 1,4-addition was demonstrated in the synthesis of \((-\text{Lardolure})\) (9, Scheme 12). 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\(_3\)SiH (Fukuyama conditions)\(^{30}\) to the aldehyde which was subsequently treated with Wittig reagent Ph\(_3\)PCHOSEt to provide unsaturated thioester 40. The second catalytic asymmetric 1,4-addition 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. Sulfinyl ketone 44 was obtained by the addition of lithiated (-S)-methyl-p-tolylsulfoxide to 43. Substrate controlled diastereoselective reduction with DIBAL-H resulted in \(\beta\)-hydroxysulfoxide 45 (de > 97%). Finally, desulfurisation of 45 followed by formylation led to \((-\text{Lardolure})\).
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 interactions are minimized or avoided as was also observed by Hanessian. 23c

Mycocerosic acid and PDIM A

Together with tuberculosarcic acid, 32 phthioceranic acid, mycolipenic acid and mycolipanolic acid, mycocerosic acid (46) is one of the many methyl-branched fatty acids from M. tuberculosis. Mycocerosic acid was first studied by Marks and Polgar 33 in the fifties. In 1963 Polgar and Smith 34 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 Kolattukudy 37 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 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 n-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 stereochemistry 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 12  Asymmetric iterative 1,4-addition reactions in the synthesis of (−)-lardolure.
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/C_{13}SMe_{2}. The resulting silylether 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 {\textsuperscript{1}}H- or {\textsuperscript{13}}C-NMR, most probably as a result of the chromatography steps which remove traces of minor diastereomers.

**Mycolipenic and mycolipanolic acid**

The synthesis of mycolipenic acid (phthienoic acid, 60, Scheme 16) started with a careful optimization of the iterative copper-catalyzed asymmetric 1,4-addition protocol reported previously. In the previous reported reduction/olefination sequence, a Fukuyama reduction with Pd/C and Et_{3}SiH 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 48 with DIBAL-H, followed by olefination with Horner-Wadsworth-Emmons (HWE) reagent (EtO)_{2}P(O)CH_{2}COSEt (61), afforded unsaturated thioester 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.
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. No epimerization of the alpha 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. 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. The optical rotation of the methyl ester of synthetic 66, $\alpha = 7.0$ (c = 0.2, CHCl$_3$), is in agreement with the literature value of $\alpha = 7.19$.47

Iterative 1,4-addition reactions with Grignard reagents and the Cul/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 Cul/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%).
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 13C-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.45

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 H2 (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 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.500 However, the E-isomer of the resulting allylic alcohol proved not to be very selective for the syn-addition as a dr of 36:1 (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 published42 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-polypropionates. These occur in polydeoxypropionates from Mycobacterium tuberculosis53 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-workers29a,dk. High selectivities for both the syn and anti deoxypropionate motif were obtained in several natural product syntheses. Undesired diastereomers
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 \((\text{C}0)\)-lardolure.5

Excellent enantioselectivities and diastereoselectivities were obtained in the preparation of the all-\(\text{syn}\) deoxypropionate substructure. Both the \(\text{syn}\) and \(\text{anti}\) 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 hepta-methyl-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 mycolipanolic acid.43

The iterative copper-catalyzed asymmetric 1,4-addition reaction with MeMgBr and Cul/tol-BINAP on oxo-esters was described by Loh \textit{et al.} in 2007/2008. This method is also highly selective for the construction of both the \(\text{syn}\) and \(\text{anti}\) 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 \(\text{syn}\)-product could be obtained with good selectivity.

Almost all catalytic and non-catalytic strategies described in this article allow the selective introduction of the \(\text{syn}\) and \(\text{anti}\) 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.