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CHAPTER 1

Asymmetric Synthesis of α-Unsubstituted β-Hydroxy Acids

Jan Spengler[1,*] and Fernando Albericio[1,2]

[1]Institute for Research in Biomedicine, Barcelona Science Park, University of Barcelona, Baldiri Reixac 10, E-08028 Barcelona, Spain and [2]Department of Organic Chemistry, University of Barcelona, Martí i Franqués 1-11, E-08028 Barcelona, Spain

Abstract: α-Unsubstituted β-hydroxy acids (3-hydroxycarboxylic acids) are constituents of various natural products with pharmacological and other technical properties of interest. They are also important intermediates in organic synthesis. This article reviews various possible routes for asymmetric synthesis of enantiopure or enantiomerically enriched α-unsubstituted β-hydroxy acids.

Keywords: 3-hydroxycarboxylic acids, asymmetric aldol reactions, acetate aldol reactions, Reformatsky reaction, asymmetric reduction, Arndt-Eistert homologation, Wolff-rearrangement, beta-lactones, cyclic sulfites, reductive cleavage, green plastics, statines, 3-hydroxytetradecanoic acid, Mukaiyama aldol reaction, chiral auxiliaries, chiral catalysts, 3-oxo-carboxylic acids, BINAP, asymmetric conjugate radical addition, catalytic desymmetrization.

1. INTRODUCTION

Chiral α-unsubstituted β-hydroxy acids (3-hydroxy carboxylic acids, $R^1R^2C^*(OH)\text{-}CH_2\text{-}CO_2H$) are constituents of various natural products with pharmacological and other technical properties of interest. They are also important intermediates in organic synthesis. Fig. (**1**) shows several representative members of natural products containing the α-unsubstituted β-hydroxy acid unit[1].

β-Hydroxy acids with long aliphatic side chains are often present in lipids, such as lipid A, which is one of the lipophilic components of lipopolysaccarides in the cell

***Address correspondence to Jan Spengler:** Institute for Research in Biomedicine, Barcelona Science Park, University of Barcelona, Baldiri Reixac 10, E-08028 Barcelona, Spain; Tel: ++34 93 4037127, Fax: ++34 93 4037126; E-mail: jan.spengler@irbbarcelona.org
Dedicated to Prof. Klaus Burger on the occasion of his 75th birthday

[1] The aim of the following listing is to provide most concisely an orientation over the different and diverse areas of organic synthesis in which the chemistry of α-unsubstituted β-hydroxy acids is of importance. Therefore, details about properties, like biological activities, resources, *etc.* and other examples may be obtained by following the literature within the citations given in the whole review.

Atta-ur-Rahman (Ed)

surface of Gram-negative bacteria [1].

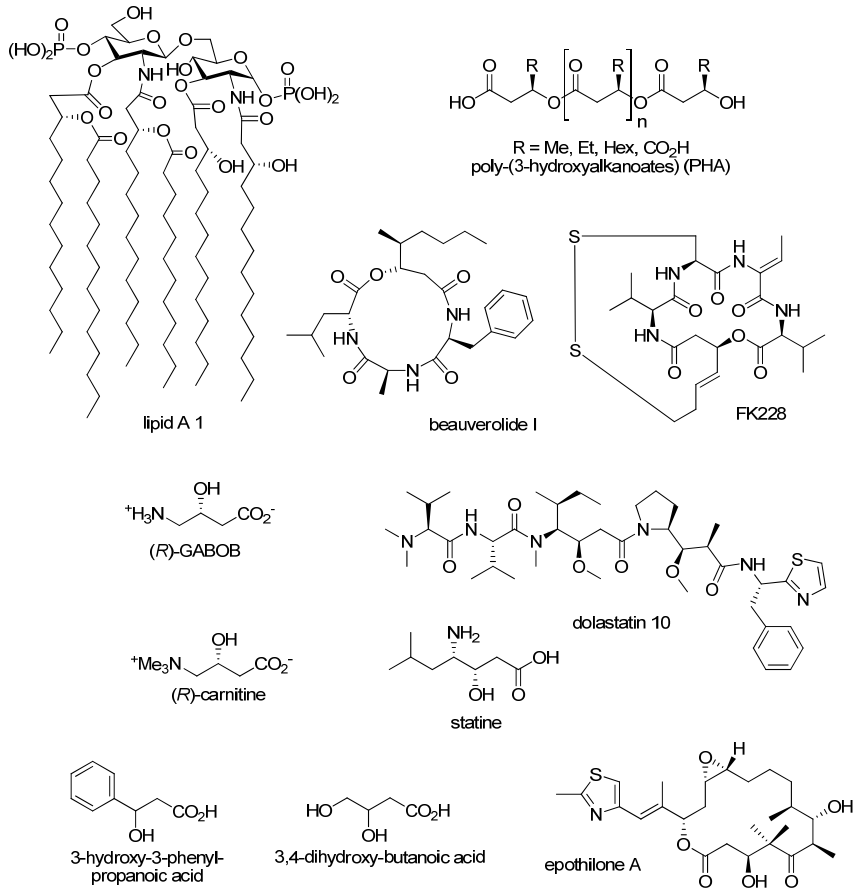


Figure 1: α-Unsubstituted β-hydroxy acids in natural products.

A number of biologically active depsipeptides isolated from (mostly marine) organisms contain β-hydroxy acids [2, 3]. Beauveriolide I, a reducer of lipid droplet formation in macrophages that does not show cytotoxic effects, is a 4-membered cyclodepsipeptide of which the β-hydroxy acid building block bears a branched aliphatic side chain [4]. In contrast, the structure of the β-hydroxy acid constituent with a terminal thiol function and a *trans*-C=C bond in the HDAC-inhibiting cyclodepsipeptide FK228 is much more complex [5]. Dolastatin 10 is a linear depsipeptide that exhibits cytotoxic anti-miotic activity [6]. The centrally situated β-hydroxy acid of dolastatin belongs to the statine family, which share the common structural feature of an additional chiral centre bearing a γ-amino

substituent [7]. The γ-amino β-hydroxy acids, such as GABOB and carnitine, which act as neuromodulators in the mammalian central nervous system and are involved in the energy metabolism, respectively, can be considered statines without a side chain at the γ-carbon [8].

Poly[(*R*)-3-hydroxyalkanoates] (PHAs), found in bacteria, supposedly evolved before poly-peptides, -saccharides and -nucleic acids, as storage materials and amphiphilic macromolecules [9]. The physical properties of PHAs, their biodegradability and enhanced production by metabolic engineering make them attractive candidates for the development of "green" plastics [10]. However, industrially appliable biotechnological processes that would allow production of enantiomerically pure *R*-3-hydroxyalkyl carboxylic acids from renewable natural resources are not available so far. A review article analyzes advances towards the production of these acids, including chemical and enzymatic degradation of PHA´s, *de novo* biosynthesis and metabolic pathway engineering [11].

Simple α-unsubstituted β-hydroxy acids are abundant metabolic products. For example, 3-hydroxy-3-phenylpropionic acid is found in plants [12] and in *E. coli* [13], and 3,4-dihydroxybutanoic acid in coffee [14]. Clinically, the excretion patterns of these products can indicate certain metabolic defects [15].

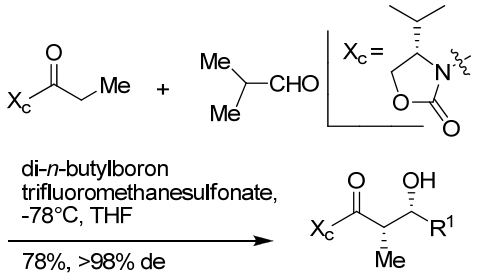
Several (anticancer) macrolides have the formal structure of α-unsubstituted β-hydroxy ω-lactones [16,17]. Thus, the synthesis of such complex structures requires the highly diastereoselective generation of the α-unsubstituted β-hydroxy acid motif.

The α-unsubstituted β-hydroxy acid motif has spurred organic chemists to develop around twenty synthetic routes that differ significantly from those used to synthesize β-hydroxy carboxylic acids with substituents at the α-carbon. Not all the synthetic strategies reviewed in the following chapters may be of general interest; however, some of their synthetic potential probably remains underestimated. Although some articles have briefly reviewed a range of synthetic approaches to α-unsubstituted β-hydroxy acids in the introduction paragraphs, only one author has discussed in depth the relevant synthetic methodologies in terms of scalability for technical production of 3-hydroxytetradecanoic acid [18].

Here we provide, to the best of our knowledge, the most comprehensive review to date of synthetic routes toward enantiomerically pure or enantiomerically enriched α-unsubstituted β-hydroxy acids to help organic chemists plan syntheses involving α-unsubstituted β-hydroxy acid as targets or intermediates.

2. ALDOL REACTIONS WITH CHIRAL AUXILIARIES

Since the first report in 1981 by Evans, intensive research has given rise to a large number of chiral auxiliaries, metal and organic catalysts that can produce *syn*- or *anti*-propionate units in high yields and with excellent diastereoselectivities (Scheme **1**) [19,20].



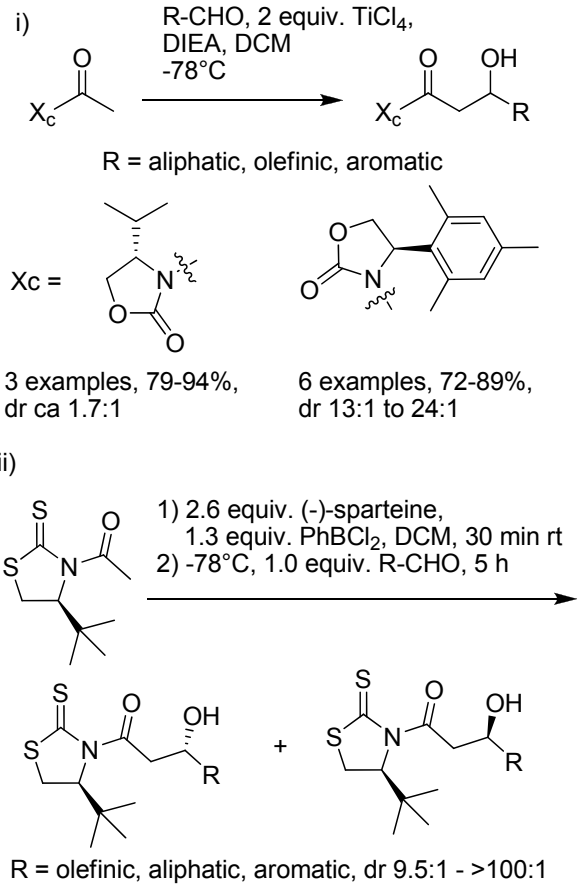
Scheme 1: Aldol reactions with chiral auxiliaries.

2.1. Direct Addition of Unsubstituted Acetyl Units

The synthesis of optically enriched α-unsubstituted β-hydroxy acids can be achieved by asymmetric aldol reactions. The level of diastereofacial selectivity observed in the metal-assisted aldolizations of the chiral acetyl-derived enolates depends on the metallic Lewis acid, the chiral auxiliary and the aldehyde. In general, the diastereoselectivities achieved in acetyl-based aldol condensations are only moderate when compared with the levels attainable for propionate aldol condensations (Scheme **1**). Several examples for stereoselective acetate aldol reactions from metal enolates that render α-unsubstituted β-hydroxy acids can be found in a recent review article [21].

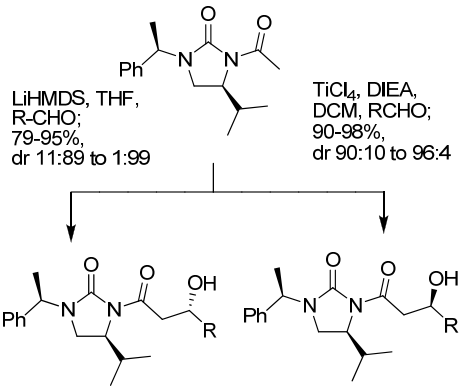
For example, in the titanium-assisted aldol reaction, Evans auxiliary yielded separable diastereomers in a ca. 1.7:1 ratio [22], but an improved mesityl-substituted auxiliary furnished dr's up to 24:1 (Scheme **2**, entry i) [23]. The

recently developed chiral *N*-acetyl-4-*tert*-butyl-1,3-thiazolidine-2-thione auxiliary can be synthesized on a multi-gram scale. Optimized conditions for the addition of the boron-enolate to aliphatic and aromatic aldeydes in the presence of sparteine gave a dr between 9.5:1 and >100:1 (Scheme **2**, entry ii) [24,25]. Also known are chiral acetate enolates of tin [26] and lithium [27,28] (see also on Reformatsky Reactions Chapter **3**).



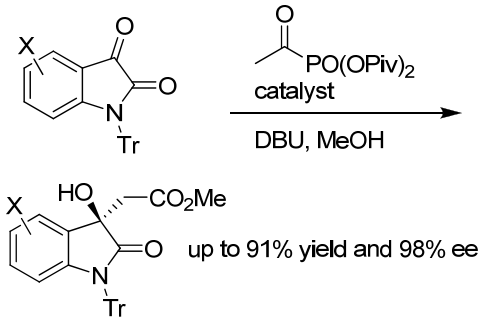
Scheme 2: Acetate aldol reactions: i) metal-assisted, ii) *via* borone enolates.

A reversal of selectivity in acetate aldol reaction has been observed when either lithium or titanium enolates were generated from imidazolidinone acetamide. A variety of aromatic and sterically demanding aliphatic aldehydes could be reacted to give the *syn*- and the *anti*-products with high diastereomeric ratios especially for aromatic aldehydes (Scheme **3**) [29].



Scheme 3: Reversal of selectivity in acetate aldol reactions depending on the metal.

The first report on an organocatalyzed acetate aldol reaction uses acetylphosphonate as surrogate for acetate or acetamide. So react isatin and acetylphosphonate in the presence of cinchona alkaloid derivatives highly enantioselectively. The phosphonate was transformed in the ester or amide, by methanolysis or aminolysis, respectively (Scheme **4**) [30].

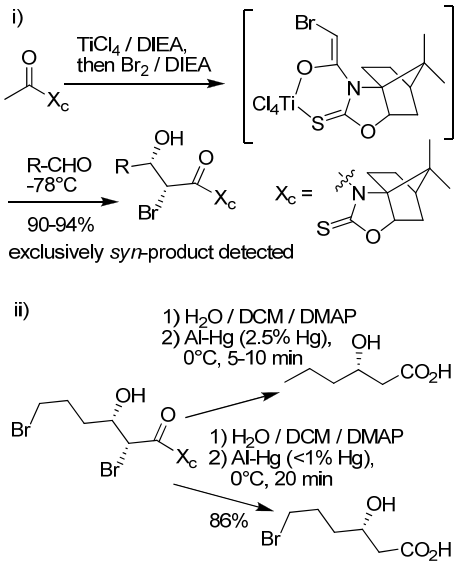


Scheme 4: The first organocatalyzed acetate aldol reaction.

2.2. Addition of Acetyl Units with Removable Substituent at the α-Position

Aldol reactions that yield products with removable substituents at the α-position produce considerably higher diastereoselectivities than those using genuine acetyl units. Hydrogenolysis of α-methylthio-β-hydroxy [19] and α-bromo-β-hydroxy carboxylates [31] has been reported to afford the corresponding β-hydroxy carboxylates. Debromination can be performed selectively under radical conditions with *n*-Bu_3SnH when C=C double bonds are present. However, requirement of excess amounts of the tin compound and difficult separation from

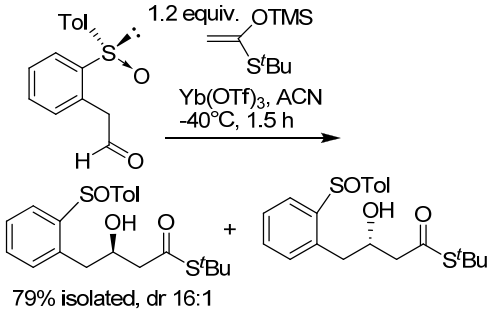
the (toxic) tin by-products limit the utility of this method [32]. The recently reported Al-Hg amalgam-promoted chemoselective debromination allows a clean transformation of 2-bromo-3-hydroxycarbonyl groups into α-unsubstituted β-hydroxy acids in the presence of carbon double bonds as illustrated by Scheme **5**. The α-bromo compound, which participated in the ensuing highly stereoselective reaction with aldehydes, could be prepared *in situ* by treatment of the titanium enolate generated from the camphor-based *N*-acetyloxazolidinethione with bromine (Scheme **5**, entry i) [33]. For debromination, the prior removal of the chiral auxiliary (with DMAP) was found to be essential. The reactivity of the Al-Hg amalgam can be tuned that it allows reductive cleavage of C-Br bonds α to the carboxyl group alone even in the presence of other reactive C-Br bonds (Scheme **5**, entry ii) [34].



Scheme 5: Synthesis (i) and debromination (ii) of α-bromo-β-hydroxy carboxylates.

2.3. Mukaiyama Aldol Reaction with Chiral Electrophiles

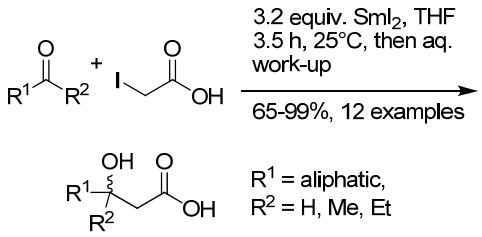
The remote stereoselective control by a chiral sulfinyl group was used in Mukaiyama aldol reactions [35]. This special approach gave, for instance, (*R*)-3-hydroxy-4-phenylbutyric acid from the (*S*)-2-[2-(*p*-tolylsulfinyl)phenyl]acetaldehyde and *O*-silyl ketenethioacetal in a dr up to 16:1 (Scheme **6**). The sulfinylgroup was later removed reductively [36].



Scheme 6: Remote stereocontrol in the Mukaiyama aldol reaction.

3. REFORMATSKY REACTIONS

The classical Reformatsky reactions consist of the zinc-induced formation of β-hydroxyalkanoates from α-halo esters and aldehydes or ketones [37]. Clear proof of the efficiency and the excellent functional group tolerance of Reformatsky-type reactions is provided by a recently reported preparation of racemic α-unsubstituted β-hydroxy acids by reaction of iodoacetic acid with aldehydes or ketones in the presence of SmI_2 (Scheme **7**) [38].

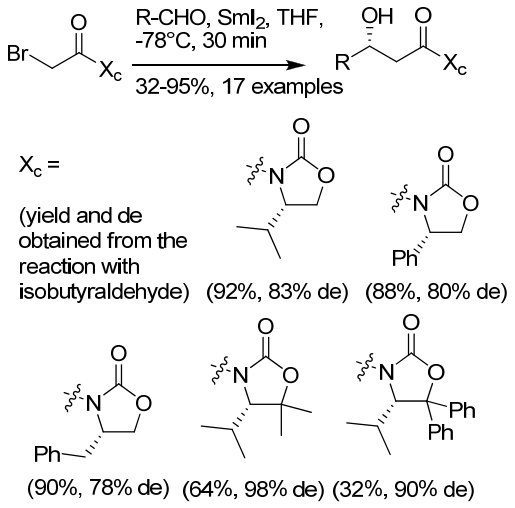


Scheme 7: SmI_2 - mediated Reformatsky reaction.

3.1. Reformatsky Reactions with Chiral Auxiliaries

With the aim to achieve stereoselectivity in the Reformatsky reactions, chiral auxiliaries have been used [39]. For example, a samarium-mediated Reformatsky reaction was run with several chiral auxiliary-bound α-bromo acetic acids. The 4-substituted (Evans-type) and 5,5-disubstituted ("SuperQuat") oxazolidinones were reacted with aliphatic and aromatic aldehydes (17 reactions) to furnish products in 32-95% yield with de values between 49% and >99% (Scheme **8**). The esters and the free acids were obtained by transesterification and hydrolysis, respectively [40]. This protocol was applied successfully to the synthesis of a segment of the macrolide

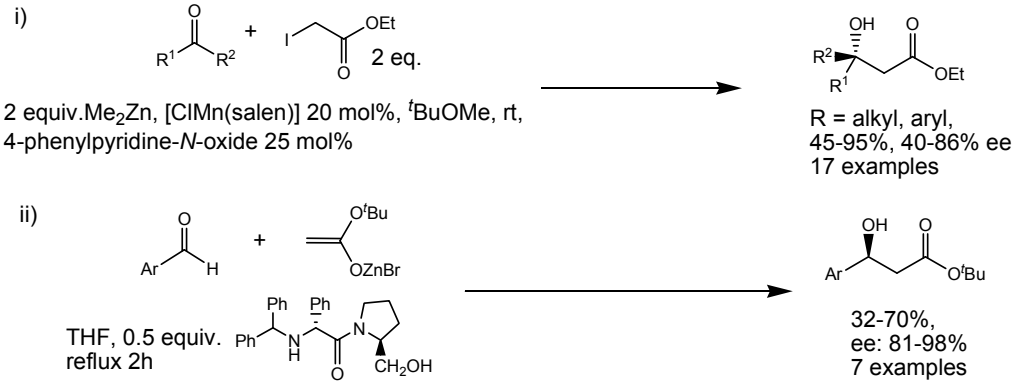
borrelidin [17]. Employing the Evans chiral auxiliary, the *erythro* and the *threo* analogs of *N*-Boc-isostatine and *N*-Boc-dolaisoleucine could be obtained [41].



Scheme 8: SmI_2 -mediated Reformatsky reactions with chiral auxiliaries.

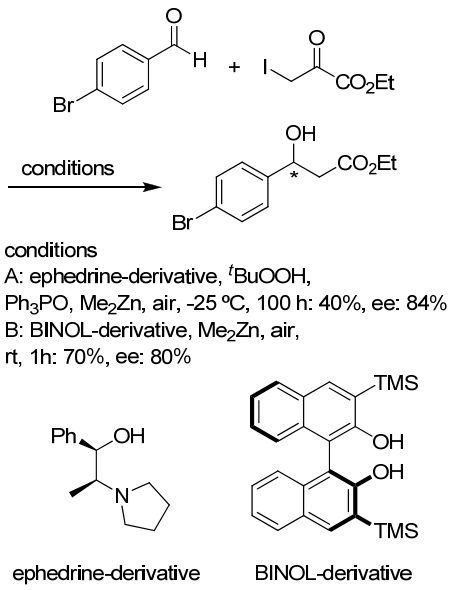
3.2. Catalytic Asymmetric Reformatsky Reactions

The zinc-mediated Reformatsky reaction was performed enantioselectively in the presence of chiral ligands. The chiral catalyst [ClMn(salen)] (20 mol%) induced up to 86% ee (Scheme **9**, entry i) [42], and with a D-phenylglycinyl prolinol-derived ligand (0.5 eq.), up to 98% ee (Scheme **9**, entry ii) [43]. In both cases, the type of ester proved to influence the degree of stereoselectivity.



Scheme 9: Enantioselectivity in Reformatsky reactions induced by chiral catalysts with salen (i) and peptide (ii) ligands.

Further improvement of catalytic enantioselective Reformatsky reaction was achieved with ephedrin [44] and BINOL [45] derivatives that effectively catalyze the Me_2Zn-promoted addition of ethyl iodoacetate to aromatic aldehyde in the presence of air or *tert*.-butyl hydroperoxide with ee´s up to 84% (Scheme **10**). For aliphatic aldehydes, the ee´s were lower. This trend was also observed for a Cu(I) promoted reaction [46] and when a bisoxazolidinine as chiral ligand was used [47].



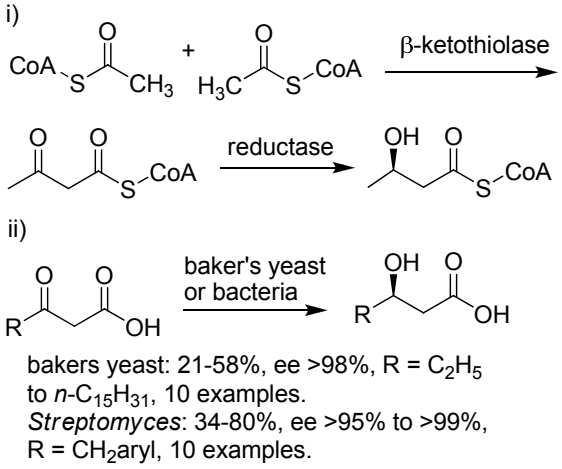
Scheme 10: Influence of the type of chiral catalysts on reaction time and yield in enantioselective Reformatsky reactions.

4. ASYMMETRIC REDUCTION OF 3-OXO-CARBOXYLIC ACIDS

4.1. *De Novo* Microbial Production and Enzymatic Reduction

Reduction of acetoacetyl-CoA by acetoacetyl-CoA reductase is part of the metabolic pathway of polyhydroxybutyrate (PHB) production in bacteria [9,10]. The first reaction of the biosynthesis is condensation between two acetyl-CoAs leading to acetoacetyl-CoA by the catalysis of β-ketoacyl-CoA thiolase. The second reaction is reduction of acetoacetyl-CoA to (*R*)-3-hydroxybutyryl-CoA by NADPH-dependent acetoacetyl-CoA dehydrogenase (Scheme **11**, entry i). Finally, the (*R*)-3-hydroxybutyryl-CoA is polymerized into PHB by P(3HB) polymerase. The degradation then starts with a depolymerization by

depolymerase. All these enzymes are expressed in single recombinant bacteria to produce (*R*)-3-hydroxybutyric acid [48,49]. Fermenting baker's yeast can also reduce a number of aliphatic 3-oxo-carboxylic acids to the corresponding (*R*)-β-hydroxy acids with high ee [50]. Furthermore, using engineered *Streptomyces coelicolor* bacteria, aryl-substituted 3-oxo-carboxylic acids were reduced enantioselectively (Scheme **11**, entry ii) [51]. Use of isolated carbonyl reductases in the reduction of aromatic β-ketonitriles have completely eliminated the competing α-ethylation, which is often observed with whole cell biocatalysis [52]. Enzyme combinations have been applied to the synthesis of both isomers of 3-heteroaryl-3-hydroxypropanoic acids [53].

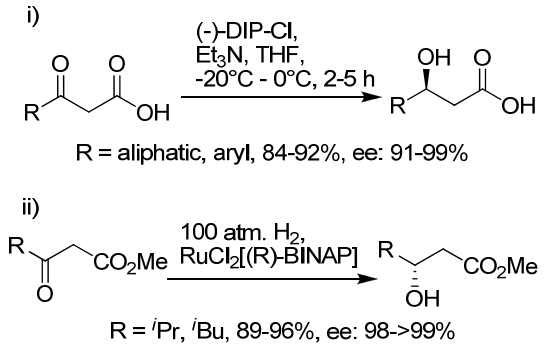


Scheme 11: Part of the biosynthesis of polyhydroxybutyrate (PHB) in bacteria (i); enantioselective reduction of 3-oxo-carboxylic acids by yeast or bacteria (ii).

4.2. Chemical Reduction

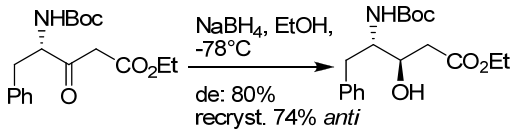
Reduction of 3-oxo carboxylic acids with commercially available chiral *B*-chlorodiisopinocampheylborane (DIP-Cl™) yields enantioselectively β-hydroxy acids [54]. For the reduction of eight ketoacids with aromatic and aliphatic substituents, good yields (87-92%) and high ee (91-99%) are reported while the reduction of the carboxylic acid esters proceeds much more slowly (Scheme **12**, entry i).

The Noyori catalyst, $RuCl_2$[(*R*)-BINAP], can be used for the catalytic reduction of esters of 3-oxo carboxylic acids with H_2 [55]. A high yield and ee >98% can be achieved with H_2 pressures of 100 atm (Scheme **12**, entry ii) [56].



Scheme 12: Enantioselectivity in reduction (i) and catalytic hydrogenation (ii) of 3-oxo-carboxylic acids.

In the synthesis of statine analogues, the NHBoc substituent at the γ-position induces stereoselectivity. Thus, reduction of the β-oxo group with borohydride yields the *anti*-product preferentially (Scheme **13,** see also chapter 6.3.) [57,58].



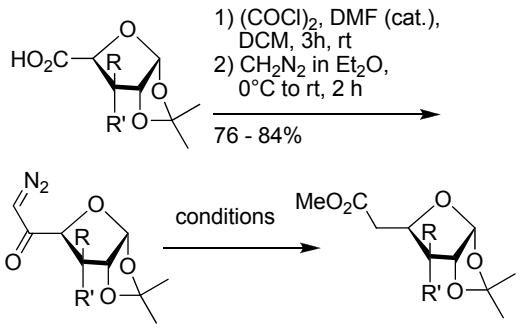
Scheme 13: Induction of stereoselectivity from the γ-position.

5. ARNDT-EISTERT HOMOLOGATION OF A-HYDROXY ACID DERIVATIVES

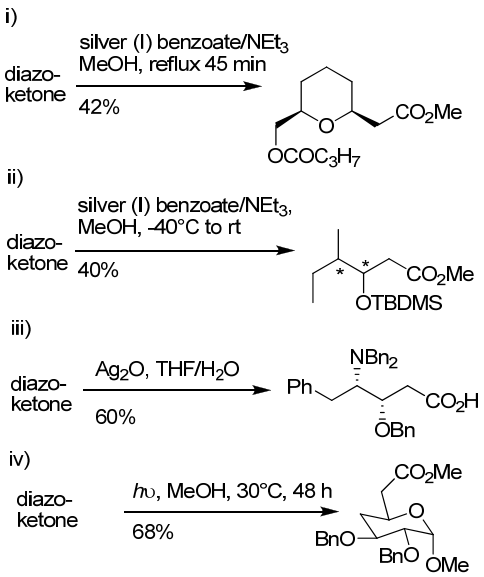
The Arndt-Eistert homologation reaction is a synthetic application of the Wolff-rearrangement. In general, it proceeds with retention of stereochemistry and has become a standard protocol for the homologation of α-amino acids to β-amino acids [59]. Similarly, the homologation of α-hydroxy acids can yield β-hydroxy acids in two steps. The first step, conversion of the carboxylic acids to the diazoketones, proceeds, on the whole, in good yields. The second step is the Wolff–rearrangement. The synthesis of intermediates of carbonolide B and other sugar carboxylic acids proceed at room temperature by the catalysis of Ag^+ with good yield (Scheme **14**) [60].

A wide variety of conditions is reported for the Wolff-rearrangement of diazoketones. A methyl tetrahydropyran-2-yl acetate was obtained by refluxing its diazoketone

precursor in methanol in the presence of silver (I) benzoate/triethylamine catalyst (Scheme **15**, entry i) [61]. On the other hand, isoleucic acid homologs were obtained from the diazoketones at –40°C in MeOH (Scheme **15**, entry ii) [62]. The rearrangement in water in the presence of Ag_2O at ambient temperature gave statine analogues (Scheme **15**, entry iii) [63,64]. For the synthesis of the carbohydrate moiety of a natural product, ambruticin, the rearrangement was induced photochemically without Ag^+ (Scheme **15**, entry iv) [65].

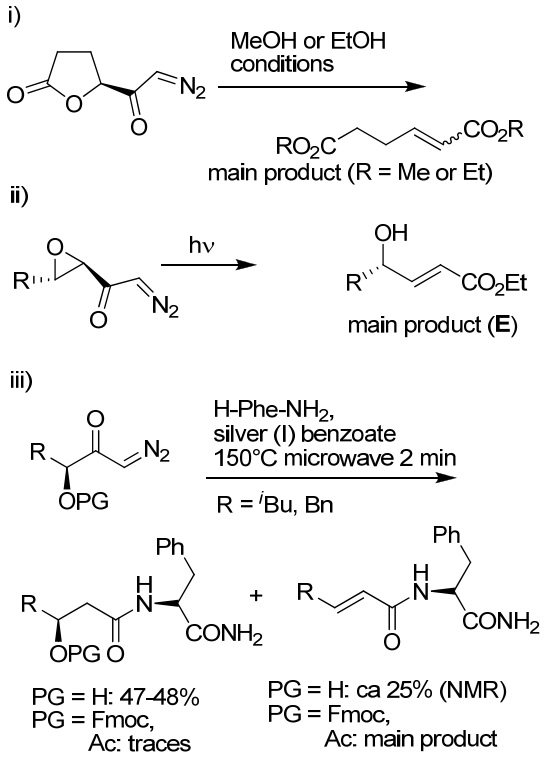


Scheme 14: The Arndt-Eistert homologation of α-hydroxy acids.



Scheme 15: Examples of Wolff–rearrangement of diazoketones catalyzed by Ag^+ or light.

The Arndt-Eistert homologation is useful when the α-hydroxy acid is readily available. However, the scope of its application is limited. There are reports on undesired β-elimination that occurs with a lactonic acid (Scheme **16**, entry i) [66] and α,β-epoxy diazomethyl ketones (Scheme **16**, entry ii) [67] under Arndt-Eistert conditions. A recent study demonstrates that the outcome of the rearrangement depends on the reaction conditions, the nucleophile to be added to the ketene intermediate and the substituent of the O^{α}-functionality. In this case, the optimal conditions for Ag^{+}- catalyzed Wolff-rearrangement of the diazoketones of leucic and phenyllactic acid were found to be microwave shock heating. β-Hydroxy products were produced in preference to α,β-unsaturated product when O^{α}-unprotected diazoketones were used in combination with amines as nucleophiles while acyl-type O^{α}-protecting groups yielded elimination products almost exclusively. Decreasing nucleophilicity of the trapping nucleophile diminished the yield of the homologation products (Scheme **16**, entry iii) [68].

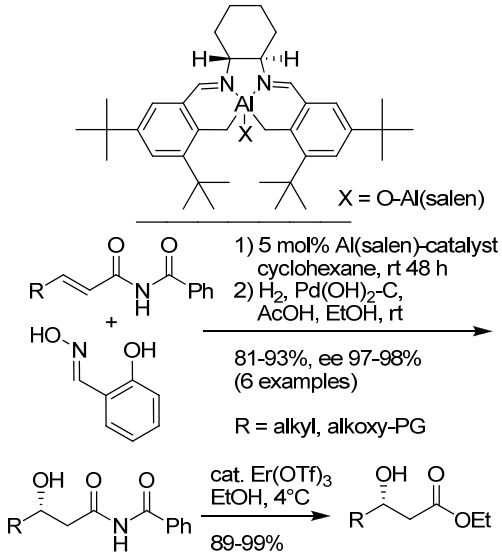


Scheme 16: Examples of undesired β-eliminations as side or main reaction under conditions of Wolff–rearrangement.

6. B-HYDROXY ACIDS FROM *E*-OLEFINS

6.1. Asymmetric Nucleophile Conjugate Addition with C-O Bond Formation

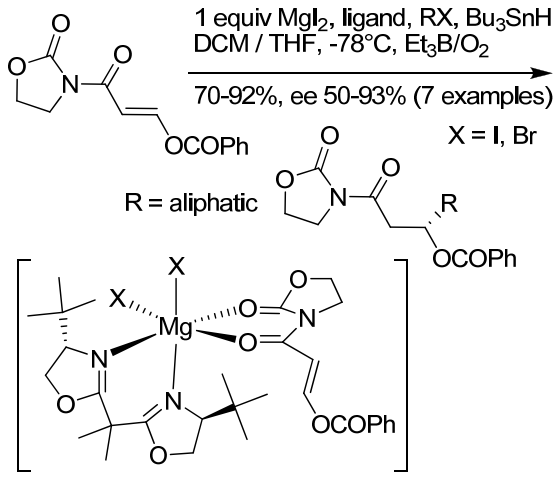
Enantioface differentiation with *E*-olefins requires a source of chiral induction. Conjugate addition of oxime nucleophiles on (*E*)-α,β-unsaturated imides is a formal hydratation, because catalytic reduction of the oxime O-N linkage gives rise to a hydroxy group. When catalyzed by a chiral salen-Al complex, this reaction permits highly enantioselective conjugate addition of salicylaldehyde oxime. Ethanolysis of the β-hydroxy imides in the presence of $Er(OTf)_3$ gave β-hydroxy acids (Scheme **17**) [69].



Scheme 17: Conjugate addition of oxime nucleophiles to *E*-olefins.

6.2. Asymmetric Conjugate Radical Addition with C-C Bond Formation

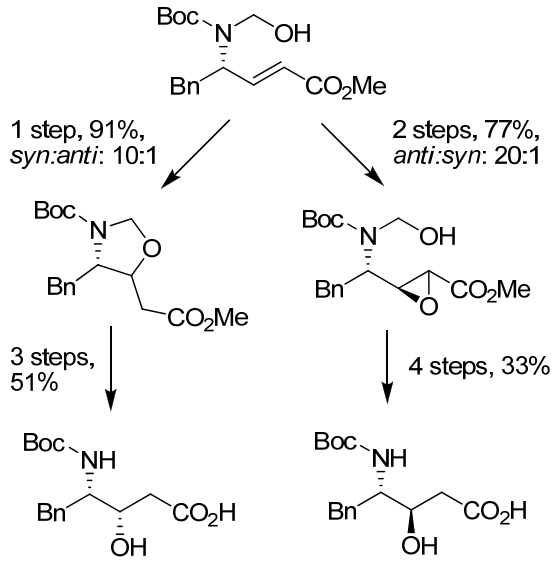
Enantioselective conjugate radical additions were performed with β-acyloxy acrylates such that the side-chain would be attached to the acrylates. Higher yields and ee values were obtained when an equimolar amount of a Lewis acid was used. From a mechanistic viewpoint, it is envisaged that both carbonyl groups of the acrylate and the oxazolidinone are coordinated with the Lewis acid (MgI_2) that is chelated with the chiral bis(oxazoline) ligand and that the conjugate radical addition takes place from the less hindered side (Scheme **18**) [70].



Scheme 18: Asymmetric conjugate radical addition with *C-C* bond formation.

6.3. Chiral Induction from nearby Substituents

The *syn*- and *anti* derivatives of 4-amino-3-hydroxy-5-phenylpentanoic acids (see also chapter 4.2.) have been prepared from the corresponding γ-amino-α,β-unsaturated ester. The Boc-protected γ-amino group could be used for chiral induction. After *N*-hydroxymethylation, the synthesis could be conducted to the *syn*-derivative *via* an oxazoline, and to the *anti*-derivative *via* an epoxide (Scheme **19**) [71].

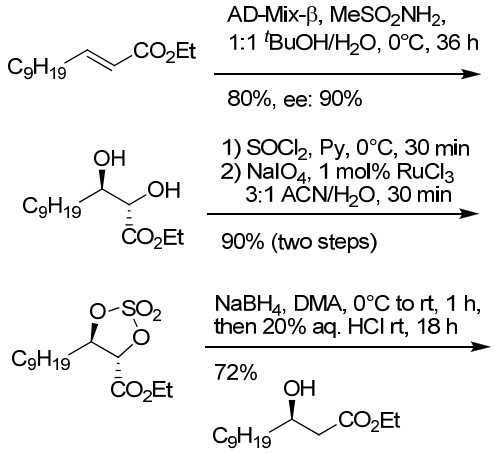


Scheme 19: Intramolecular chiral induction in hydroxylation of *E*-olefin.

7. β-HYDROXY ACIDS FROM 2,3-DIHYDROXY ACIDS

7.1. Regioselective Reductive Cleavage on Cyclic Sulfates

Application of the Sharpless asymmetric dihydroxylation [72] to the C=C double bond of (*E*)-α,β-unsaturated dodecanoic acid ester yielded the *syn*-diol, which was converted *via* the cyclic sulfite to the corresponding cyclic sulfate. The regioselective reductive cleavage of the sulfate yielded (*R*)-3-hydroxydecanoic acid ester (Scheme **20**) [73].



Scheme 20: Regioselective reductive cleavage on cyclic sulfates.

7.2. Regioselective Substitution - Reductive Cleavage

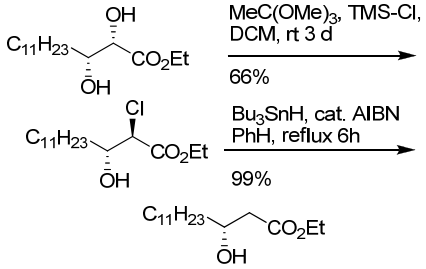
Two hydroxy groups of α,β-dihydroxy esters (the Sharpless asymmetric dihydroxylation products from (*E*)-α,β-unsaturated esters) can also be differenciated from each other as follows: treatment with trimethyl orthoacetate followed by chlorotrimethylsilane yielded α-chloro-β-hydroxy ester, an S_N2-product, in a regio- and stereoselective manner. The chlorine atom was then removed by the tri-*n*-butyltin hydride-mediated radical reaction (Scheme **21**) [1].

8. β-HYDROXY ACIDS FROM DIOLS

8.1. Regioselective Oxidation of 1,3-Diols

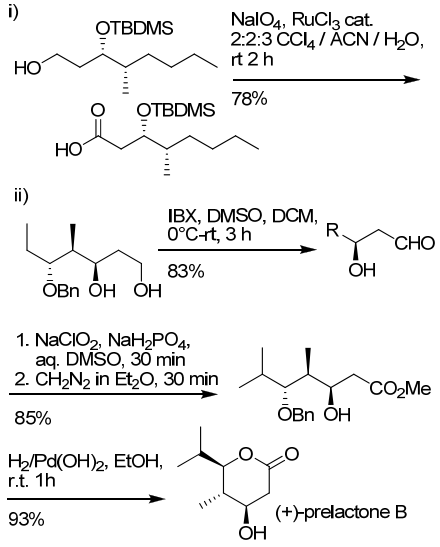
Oxidation of 1,3-diols to 3-hydroxy carboxylic acids can be performed either directly or stepwise *via* an aldehyde. The ruthenium (VIII)-mediated oxidation of

(3*S*,4*S*)-3-hydroxy-4-methyloctanol yielded (3*S*,4*S*)-3-hydroxy-4-methyloctanoic acid, a constituent of the cyclodepsipeptide beauveriolide I (Scheme **22**, entry i) [4].



Scheme 21: Regioselective substitution of 2,3-dihydroxy acids followed by reductive cleavage.

The linear β-hydroxy acid precursor of prelactone B was constructed from a 1,3-diol by stepwise oxidation. The first regioselective oxidation of the primary hydroxy group yielded an aldehyde, which was isolated and then oxidized. The methyl ester was obtained after *in situ* esterification (Scheme **22**, entry ii) [74].

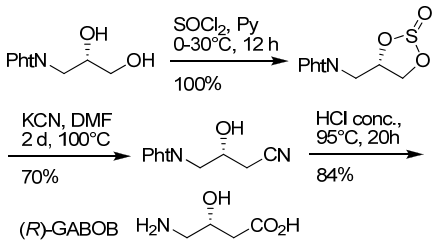


Scheme 22: Regioselective oxidation of 1,3-diols; directly (i) or stepwise (ii).

8.2. Nucleophilic Ring-Opening of Cyclic Sulfites with C_1 Homologation

1,2-Diols react with thionyl chloride to give cyclic sulfites and the thiaheterocycles thus obtained have found versatile use in organic synthesis [75]. As already shown in Chapter 7.1., they can be further oxidized to cyclic sulfates.

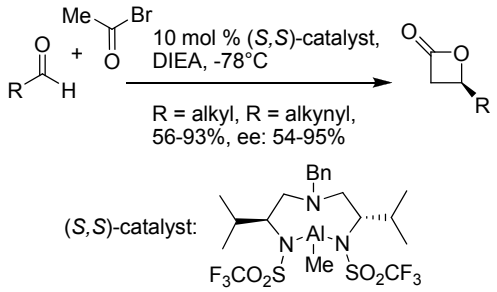
However, the cyclic sulfite, obtained quantitatively as a diastereomeric mixture from 1-phthalimido-(*R*)-propane-2,3-diol, underwent nucleophilic ring-opening by cyanide. After acidic hydrolysis of the resulting β-hydroxy nitrile, (*R*)-4-amino-3-hydroxybutyric acid (GABOB) was obtained (Scheme **23**) [8].



Scheme 23: Nucleophilic ring-opening of cyclic sulfites.

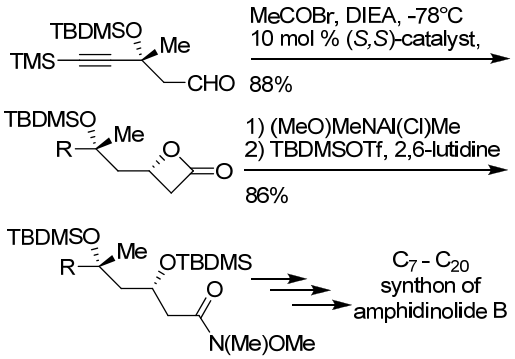
9. RING-OPENING OF β-LACTONES *VIA* NUCLEOPHILIC ADDITION-ELIMINATION

Optically active β-lactones (2-oxetanones) offer considerable versatility as intermediates for organic synthesis [76]. The catalytic asymmetric acyl halide – aldehyde cyclocondensation reaction gives highly enantiomerically enriched β-lactones (Scheme **24**) [77].



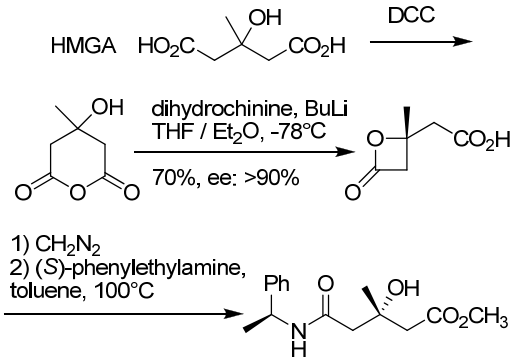
Scheme 24: Synthesis of enantiomerically enriched β-lactones.

β-Lactones can be viewed as "activated aldol products" and as such, should give access to a variety of β-hydroxy ester or amide adducts by their ring-opening *via* nucleophilic addition at the carbonyl function. Thus, starting from aldehydes, α-unsubstituted β-hydroxy carboxamides were obtained after two high-yielding synthetic steps [78]. This route was followed during the synthesis of the C_7-C_{20} synthon of amphidinolide B (Scheme **25**) [79].



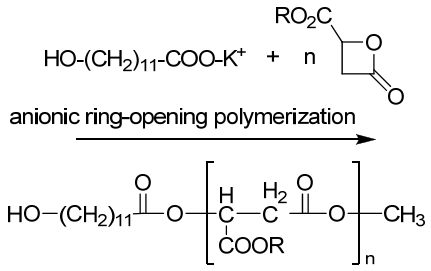
Scheme 25: β-Lactones as "activated" aldol products.

3-Hydroxy-3-methylglutaric acid (HMGA, dicrotalic acid), which represents as HMG- CoA a key intermediate in biosynthesis, is a prochiral molecule. Thus, its regioselective derivatization at the carboxy termini should lead to chiral compounds. Such regioselectivity can be achieved *via* its β-lactone: HMGA was converted into its anhydride. Treatment with a chiral base, dihydrochinine, yields the (*R*)-β-lactone. With dihydrochinidin, the (*S*)-β-lactone was similarly obtained. The carboxylic group was then esterified (in case it could act as a nucleophile). Nucleophilic addition of (*S*)-phenethylamine afforded the corresponding HMGA-amide. Check of the optical purity revealed >90% ee for the β-lactonization step (Scheme **26**) [80].



Scheme 26: 3-Hydroxy-3-methylglutaric acid as building block for the synthesis of β-methyl-β-hydroxy acids.

Nucleophilic addition of carboxylate anions to β-lactones can be used for ring-opening polymerization; biocompatible polymalates were prepared in this way. It proceeds with inversion of configuration but without any racemization (Scheme **27**) [81].

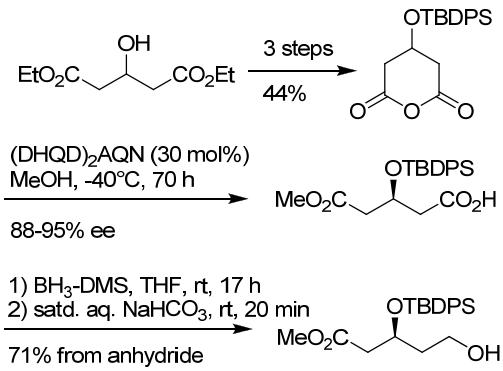


Scheme 27: Ring-opening polymerization of β-lactones.

10. OTHER STRATEGIES

10.1. Catalytic Desymmetrization

Commercially available diethyl 3-hydroxyglutarate can be transformed to a *meso*-anhydride on a multi-gram scale. Catalytic desymmetrization of the *O*-TBDPS-protected *meso*-anhydride with $(DHQD)_2AQN$ in the presence of MeOH gave the (*S*)-monomethyl ester with 88-95% ee. Reduction of the acid function with borane-dimethylsulfide complex followed by aqueous work-up gave an enantiomerically enriched alcohol from the cyclic *meso*-anhydride in good overall yield (Scheme **28**). A more elaborate structure was constructed by manipulating the primary alcohol function [82].

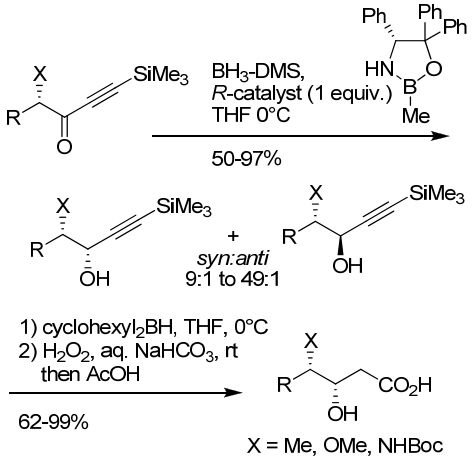


Scheme 28: Catalytic desymmetrization of 3-hydroxyglutarate.

10.2. Stereoselective Reduction of 1-Trimethylsilyl-1-alkyn-3-ones

Chiral 4-substituted 1-trimethylsilyl-1-alkyn-3-ones can be diastereoselectively reduced with chiral boranes to the corresponding 1-trimethylsilyl-1-alkyn-3-ols in

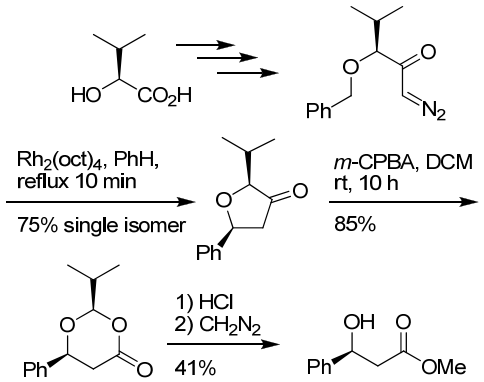
good yield. Hydroboration followed by oxidative work-up gave the corresponding carboxylic acids. A number of statine analogues were synthesized following this approach (Scheme **29**) [**Error! Bookmark not defined.**].



Scheme 29: Stereoselective reduction of 1-trimethylsilyl-1-alkyn-3-ones.

10.3. Stereoselective Dirhodium(II)-Catalyzed *C-H* Insertion

L-α-Isovalerianic acid was transformed to an α-alkoxydiazoketone. The conditions for the Rh-catalyzed C-H insertion were optimized such that the 2,4-*cis*-configuration could be established exclusively with cyclization. Baeyer-Villinger oxidation of the furanone gave the 2-isopropyl-6-phenyl-1,3-dioxan-4-one, which was converted to the (*R*)-3-hydroxy-3-phenylpropanoate after acidic hydrolysis and methyl ester formation (Scheme **30**) [83].

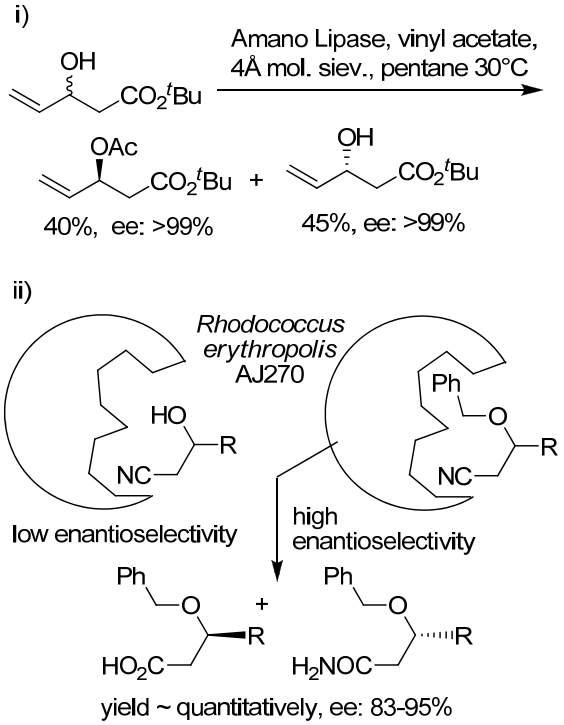


Scheme 30: Stereoselective dirhodium(II)-catalyzed *C-H* insertion.

11. ENZYMATIC RESOLUTION OF RACEMIC PRECURSORS

Racemic 3-hydroxypent-4-enoic acid *tert*-butyl ester was kinetically resolved by Amano PS lipase. Both the *O*-acetylated (*S*)-isomer and the unreacted (*R*)-isomer were obtained in good yield and very high enantiomeric purity (Scheme **31**, entry i). The (*S*)-isomer was further transformed to a branched aliphatic α-unsubstituted β-hydroxy acid building block of a cyclodepsipeptide, plusbacin A_3, by alkene cross metathesis reaction [84].

Enantioselective transformations of β-hydroxy nitriles were achieved by whole cells of *Rhodococcus erythropoli*s AJ270. The enantioselectivity of the nitrile hydrolysis increased dramatically after *O*-benzyl protection of the substrates. With eight distinct nitriles, pairs of β-benzoxy acids and amides of opposite configuration were obtained each in ee between 83% and 95% and nearly quantitative yield (*R* + *S*) (Scheme **31**, entry ii) [85]. Immobilized enzymes were applied for the hydrolytic resolution of 3-hydroxy-3-phenylpropionates [46].

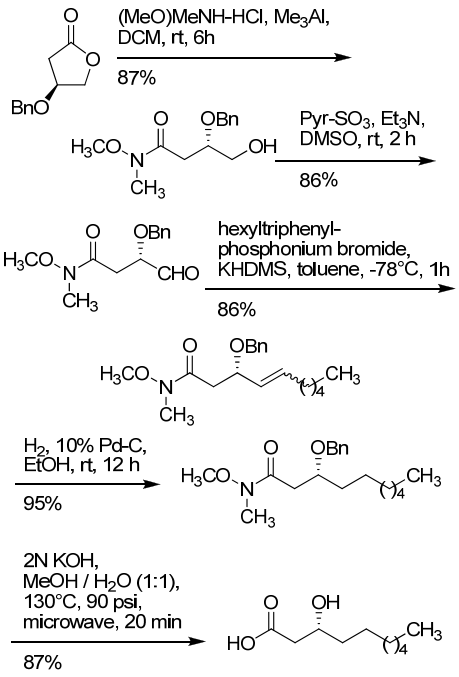


Scheme 31: Enzymatic resolution of racemic precursors.

12. CHIRAL POOL-DERIVED β-HYDROXY CARBOXYLIC ACIDS

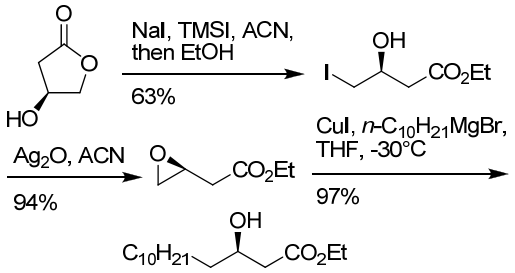
12.1. From (*S*)-3-Hydroxy-γ-butyrolactone

The nucleophilic ring-opening of *O*-benzyl-protected (*S*)-3-hydroxy-γ-butyrolactone with the Weinreb amine yielded the β-benzyloxy amide with a primary hydroxy function at the γ-carbon. Parikh-Doering oxidation gave an aldehyde precursor for the Wittig reaction with hexyltriphenylphosphonium bromide. Hydrogenation of the double bond proceeded with simultaneous cleavage of the *O*-benzyl protecting group. Finally, the Weinreb amide was hydrolyzed with the assistance of microwave heating to give (*R*)-3-hydroxydecanoic acid (Scheme **32**) [86].



Scheme 32: β-Hydroxy carboxylic acids from (*S*)-3-hydroxy-γ-butyrolactone *via* Wittig reaction.

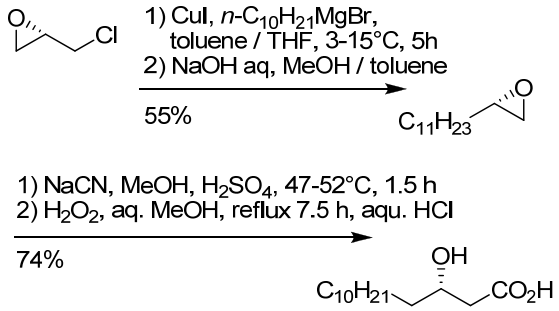
The nucleophilic ring-opening of (*S*)-3-hydroxy-γ-butyrolactone with iodotrimethylsilane gave iodohydrin, which, on treatment with Ag_2O, yielded the (*S*)-3,4-epoxybutanoate. The Grignard reaction with decylmagnesium bromide took place chemo- and regioselectively. The (*R*)-3-hydroxy acid ester was obtained in a three-step overall yield of 57% (Scheme **33**) [87].



Scheme 33: β-Hydroxy carboxylic acids from (*S*)-3-hydroxy-γ-butyrolactone *via* Grignard-Reaction.

12.2. From Epichlorohydrin

Chiral epichlorhydrin was first subjected to chemo- and regioselective ring-opening with $C_{10}H_{21}MgBr$ followed by alkaline-induced epoxide formation. The epoxide was then ring-opened with NaCN to the β-hydroxy nitrile. Basic hydrolysis in the presence of H_2O_2 yielded the corresponding acid (Scheme **34**) [88].



Scheme 34: Chiral epichlorohydrin as building block for β-hydroxy carboxylic acids.

CONCLUSION

It has been surprising to find such a microcosm of synthetic methods for the asymmetric construction of α-unsubstituted β-hydroxy acids and derivatives reported. The structural motif, $R^1R^2C^*(OR^3)$-CH_2-COR^4, constitutes part of many structurally diverse natural products, and this has indeed challenged the minds of chemists. We hope that this, to the best of our knowledge comprehensive, review helps to make the best choice between the synthetic routes in this impressive array.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

The author(s) confirm that this chapter content has no conflict of interest.

DISCLOSURE

The chapter submitted for series eBook titled **"Advances in Organic Synthesis, Volume 4"** is an update of our article published in **CURRENT ORGANIC SYNTHESIS, Volume 5, Number 2, 2008**, with additional text and references.

LIST OF ABBREVIATIONS

Ac = acetyl

ACN = acetonitrile

AIBN = azobisisobutyronitrile

aq. = aqueous

BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Bn = benzyl

Boc = *tert*-butyloxycarbonyl

cat. = catalytic

CoA = coenzyme A

DCC = *N,N*'-dicyclohexyl carbodiimide

DCM = dichloromethane

de = diasteriomeric excess

$(DHQD)_2AQN$ = dihydroquinidine - anthranyl ligand

DIEA = diisopropylethylamine

DMAP = 4-(*N,N*-dimethylamino)pyridine

DMS = dimethyl sulfide

DMF = *N,N*-dimethylformamide

DMSO = dimethyl sulfoxide

dr = diasteriomeric ratio

ee = enantiomeric excess

Et = ethyl

equiv. = equivalent

Fmoc = 9-fluorenylmethoxycarbonyl

HDAC = histone deacetylase

hν = light

IBX = *o*-iodoxybenzoic acid

KHDMS = potassium bis(trimethylsilyl)amide

Me = methyl

MeOH = methanol

m-CPBA = *m*-chloroperbenzoic acid

PG = protecting group

PhH = benzene

recryst. = recrystallization

rt = ambient temperature

satd. = saturated

TBDMS = *tert*-butyldimethylsilyl

Tf = trifluoromethanesulfonyl

THF = tetrahydrofuran

TMS = trimethylsilyl

X_c = chiral auxiliary

REFERENCES

[1] Oikawa, M.; Kusumoto, S. On a practical synthesis of β-hydroxy fatty acid derivatives. Tetrahedron: Asymmetry, 1995, 6, 961-969.

[2] Sarabia, F.; Chammaa, S.; Sánchez Ruiz, A.; Martín Ortiz, L.; López Herrera, F.J. Chemistry and biology of cyclic depsipeptides of medicinal and biological interest. Curr. Med. Chem., 2004, 11, 1309- 1332.

[3] Hamada, Y.; Shioiri, T. Recent Progress of the Synthetic Studies of Biologically Active Marine Cyclic Peptides and Depsipeptides. Chem. Rev., 2005, 105, 4441- 4482.

[4] Tian, H.; Jiao, X.; Xie, P.; Liang, X. Total synthesis of beauveriolide I. Tetrahedron Lett,. 2005, 46, 8579-8581.

[5] Yurek-George, A.; Habens, F.; Brimmell, M.; Packham, G.; Ganesan, A. Total Synthesis of Spiruchostatin A, a Potent Histone Deacetylase Inhibitor. J. Am. Chem. Soc., 2004, 126, 1030-1031.

[6] Mordant, C.; Reymond, S.; Tone, H.; Lavergne, D.; Touati, R.; Ben Hassine, B.; Ratovelomanana-Vidal, V.; Genet, J.-P. Total synthesis of dolastatin 10 through ruthenium-catalyzed asymmetric hydrogenations. Tetrahedron 2007, 63, 6115-6123.

[7] Alemany, C.; Bach, J.; Garcia, J.; Lopez, M.; Rodriguez, A.B. A Synthetic Approach to 3-Hydroxy 4-Substituted Carboxylic Acids based on the Stereoselective Reduction of 1-Trimethylsilyl-1-alkyn-3-ones. Tetrahedron, 2000, 56, 9305-9312.

[8] Lohray, B.B.; Reddy, A.S.; Bhushan, V. An efficient synthesis of (3R)-4-amino-3-hydroxybutyric acid (GABOB) *via* cyclic sulfite methodology. Tetrahedron: Asymmetry, 1996, 7, 2411-2416.

[9] Seebach, D.; Fritz, M.G. Detection, synthesis, structure, and function of oligo(3-hydroxyalkanoates): contributions by synthetic organic chemists. Int. J. Biol. Macromol., 1999, 25, 217-236.

[10] Reddy, C.S.K.; Ghai, R.; Rashmi, K.; Kalia, V.C. Polyhydroxyalkanoates: an overview. Bioresour. Technol., 2003, 137-146.

[11] Ren, Q.; Ruth, K.; Thony-Meyer, L.; Zinn, M. Enatiomerically pure hydroxycarboxylic acids: current approaches and future perspectives. Applied Microbiol. Biotechnol., 2010, 87, 41-52.

[12] Jarvis, A.P.; Schaaf, O.; Oldham, N.J. 3-Hydroxy-3-phenylpropanoic acid is an intermediate in the biosynthesis of benzoic acid and salicylic acid but benzaldehyde is not. Planta, 2000, 212, 119-126.

[13] Burlingame, R.; Chapman, P.J. Catabolism of phenylpropionic acid and its 3-hydroxy derivative by Escherichia coli. J. Bacteriol., 1983, 155, 113-121.

[14] Bahre, F.; Maier, H.G. New non-volatile acids in coffee. Deut. Lebensm.-Rundsch., 1999, 95, 399-402.

[15] Rizzo, C.; Bertini, E.; Piemonte, F.; Leuzzi, V.; Sabetta, G.; Federici, G.; Luchetti, A.; Dionisi-Vici, C. Oxidative abnormalities in Menkes disease. J. Inherit. Metab. Dis., 2000, 23, 349-351.

[16] Watkins, E.B.; Chittiboyina, A.G.; Avery, M.A. Recent developments in the syntheses of the epothilones and related analogues. Eur. J. Org. Chem., 2006, 4071-4084.

[17] Nagamitsu, T.; Takano, D.; Fukuda, T.; Otoguro, K.; Kuwajima, I.; Harigaya, Y.; Omura, S. Total Synthesis of (-)-Borrelidin. Org. Lett., 2004, 6, 1865-1867.

[18] Ikunaka, M. A process in need is a process indeed: scalable enantioselective synthesis of chiral compounds for the pharmaceutical industry. Chem. Eur. J., 2003, 9, 378-388.

[19] Evans, D.A.; Bartroli, J.; Shih, T.L. Enantioselective aldol condensations. 2. Erythro-selective chiral aldol condensations *via* boron enolates. J. Am. Chem. Soc., 1981, 103, 2127-2129.

[20] Geary, L.M.; Hultin, P.G. The state of the art in asymmetric induction: the aldol reaction as a case study. Tetrahedron: Asymm., 2009, 20, 131-173.

[21] Ariza, X.; Garcia, J.; Romea, P.; Urpi, F. Stereoselective acetate aldol reactions from metal enolates. Synthesis, 2011, 2175-2191.

[22] Le Sann, C.; Munoz, D.M.; Saunders, N.; Simpson, T.J.; Smith, D.I.; Soulas, F.; Watts, P.; Willis, C.L. Assembly intermediates in polyketide biosynthesis: enantioselective syntheses of β-hydroxycarbonyl compounds. Org. Biomol. Chem., 2005, 3, 1719-1728.

[23] Crimmins, M.T.; Shamszad, M. Highly Selective Acetate Aldol Additions Using Mesityl-Substituted Chiral Auxiliaries. Org. Lett., 2007, 9, 149-152.

[24] Zhang, Y.; Phillips, A.J.; Sammakia, T. Highly Selective Asymmetric Acetate Aldol Reactions of an N-Acetyl Thiazolidinethione Reagent. Org. Letters 2004, 6, 23-25.

[25] Zhang, Y.; Sammakia, T. Double Diastereoselective Acetate Aldol Reactions with Chiral N-Acetyl Thiazolidinethione Reagents. J. Org. Chem., 2006, 71, 6262-6265.

[26] Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. New C-4-chiral 1,3-thiazolidine-2-thiones: excellent chiral auxiliaries for highly diastereo-controlled aldol-type reactions of acetic acid and α,β-unsaturated aldehydes. J. Org. Chem., 1986, 51, 2391-2393.

[27] Braun, M.; Devant, R. The (R)- and (S)-2-acetoxy-1,1,2-triphenylethanols - effective synthetic equivalents of a chiral acetate enolate. Tetrahedron Lett., 1984, 25, 5031-5034.

[28] Saito, S.; Hatanaka, K.; Kano, T.; Yamamoto, H. Diastereoselective aldol reaction with an acetate enolate: 2,6-bis(2-isopropylphenyl)-3,5-dimethylphenol as an extremely effective chiral auxiliary. Angew. Chem. Int. Ed., 1999, 37, 3378-3381.

[29] Khatik, G.L.; Kumar, V.; Nair, V.A. Reversal of selectivity in acetate aldol reactions of N-acetyl-(S)-4-isopropyl-1-[(R)-1-phenylethyl]imidazolidin-2-one. Org. Lett., 2012, 14, 2442-2445.

[30] Guang, J.; Guo, Q.; Zhao, J.C.-G. Acetylphosphonate as a Surrogate of Acetate or Acetamide in Organocatalyzed Enantioselective Aldol Reactions. Org. Lett., 2012, 14, 3174-3177.

[31] Fleming, P.R.; Sharpless, K.B. Selective transformations of threo-2,3-dihydroxy esters. J. Org. Chem., 1991, 56, 2869-2875.

[32] Corey, E.J.; Choi, S. Highly enantioselective routes to Darzens and acetate aldol products from achiral aldehydes and tert-butyl bromoacetate. Tetrahedron Lett., 1991, 32, 2857-2860.

[33] Wang, Y.-C.; Su, D-W.; Lin, C.-M.; Tseng, H.L.; Li, C.-L.; Yan, T.-H. Toward the Development of a General Chiral α-Substituted Acetate Enolate Synthon for Aldolization. DMAP- and NEt3-Promoted Oxazolidinethione "Deacylation". J. Org. Chem., 1999, 64, 6495-6498.

[34] Wang, Y.-C.; Yan, T.-H. A new approach for the chemoselective debromination of chiral bromohydrins. Toward the development of a very general approach to enantiopure α-unsubstituted β-hydroxy acids. J. Org. Chem., 2000, 65, 6752-6755.

[35] Mukaiyama, T.; Kobayashi, S.; Sano, T. Asymmetric aldol-type reaction between both achiral ketene silyl acetals of acetic acid esters and aldehydes by the use of a chiral promoter. Tetrahedron, 1990, 46, 4653-4662.

[36] Garcia Ruano, J.L.; Fernandez-Ibanez, M.A.; Maestro, M.C. Remote stereocontrol by the sulfinyl group: Mukaiyama aldol reactions of (S)-2-[2-(p-tolylsulfinyl)phenyl]acetaldehyde in the asymmetric synthesis of β-hydroxy acids and 1,3-diols. Tetrahedron, 2006, 62, 12297-12305.

[37] Ocampo, R.; Dolbier, Jr., W.R. The Reformatsky reaction in organic synthesis. Recent advances. Tetrahedron, 2004, 60, 9325-9374 and references therein.

[38] Concellón, J.M.; Concellón, C. Aldol-type Reactions of Unmasked Iodoacetic Acid with Carbonyl Compounds Promoted by Samarium Diiodide: Efficient Synthesis of Carboxylic 3-Hydroxyacids and Their Derivatives. J. Org. Chem., 2006, 71, 4428-4432.

[39] Ribeiro, C.M.R.; Cordeiro de Farias, F.M. Chiral ligands in the asymmetric Reformatsky reaction. Mini-Rev. Org. Chem., 2006, 3, 1-10.

[40] Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. Asymmetric Samarium-Reformatsky Reaction of Chiral α-Bromoacetyl-2-oxazolidinones with Aldehydes. J. Org. Chem., 2000, 65, 1702-1706.

[41] Nelson, C.G.; Burke, T.R. Samarium iodide-mediated Reformatsky reactions for the stereoselective preparation of β-hydroxy-γ-amino acids: Synthesis of isostatine and dolaisoleucine. J. Org. Chem., 2012, 77, 733-738.

[42] Cozzi, P.G. A catalytic, Me2Zn-mediated, enantioselective Reformatskii reaction with ketones. Angew. Chem. Int. Ed., 2006, 45, 2951-2954.

[43] Shin, E.-K.; Kim, H.J.; Kim, Y.; Kim, Y.; Park, Y.S. D-Phg-L-Pro Dipeptide-derived prolinol ligands for highly enantioselective Reformatskii reactions. Tetrahedron Lett., 2006, 47, 1933-1935.

[44] Cozzi, P.G.; Benfatti, F.; Capdevila, M.G.; Mignogna, A. Me2Zn mediated, tert-butylhydroperoxide promoted, catalytic enantioselective Reformatsky reaction with aldehydes. Chem. Comm., 2008, 3317-3318.

[45] Fernandez-Ibanez, M.A.; Macia, B.; Minnaard, A.J.; Feringa, B.L. Catalytic enantioselective Reformatsky reaction with aldehydes. Angew. Chem. Int. Ed., 2008, 47, 1317-1319.

[46] Benfatti, F.; Cozzi, P.G. Copper-promoted enantioselective Reformatsky-type reaction with ketones. Tetrahedron: Asymm., 2010, 21, 1503-1506.

[47] Wolf, C.; Moskowitz, M. Catalyzed Enantioselective Reformatsky Reaction. J. Org. Chem,. 2011, 76, 6372-6376.

[48] Gao, H.-J.; Wu, Q.; Chen, G.-Q. Enhanced production of D-(-)-3-hydroxybutyric acid by recombinant Escherichia coli. FEMS Microbiol. Lett., 2002, 213, 59-65.

[49] Lee, S.Y.; Lee, Y.; Wang, F. Chiral compounds from bacterial polyesters: sugars to plastics to fine chemicals. Biotechnol. Bioeng., 1999, 65, 363-368.

[50] Utaka, M.; Watabu, H.; Higashi, H.; Sakai, T.; Tsuboi, S.; Torii, S. Asymmetric reduction of aliphatic short- to long-chain β-keto acids by use of fermenting bakers' yeast. J. Org. Chem., 1990, 55, 3917-3921.

[51] Booker-Milburn, K.I.; Gillan, R.; Kimberley, M.; Taguchi, T.; Ichinose, K.; Stephenson, G.R.; Ebizuka, Y.; Hopwood, D.A. Enantioselective reduction of β-keto acids with engineered Streptomyces coelicolor. Angew. Chem. Int. Ed., 2005, 44, 1121-1125.

[52] Ankati, H.; Zhu, D.; Yang, Y.; Biehl, E.R.; Hua, L. Asymmetric Synthesis of Both Antipodes of β-Hydroxy Nitriles and β-Hydroxy Carboxylic Acids *via* Enzymatic Reduction or Sequential Reduction/Hydrolysis. J. Org. Chem., 2009, 74, 1658-1662.

[53] Brem, J.; Tosa, M.I.; Paizs, C.; Vass, E.; Irimie, F.D. Enzyme-catalyzed synthesis of (R)- and (S)-3-hydroxy-3-(10-alkyl-10H-phenothiazin-3-yl)propanoic acids. Tetrahedron: Asymm., 2010, 21, 365-373.

[54] Wang, Z.; Zhao, C.; Pierce, M.E.; Fortunak, J.M. Enantioselective synthesis of β-hydroxy carboxylic acids: direct conversion of β-oxocarboxylic acids to enantiomerically enriched β-hydroxy carboxylic acids *via* neighboring group control. Tetrahedron: Asymmetry, 1999, 10, 225-228.

[55] Keegan, D.S.; Hagen, S.R.; Johnson, D.A. Efficient asymmetric synthesis of (R)-3-hydroxy- and alkanoyloxytetradecanoic acids and method for the determination of enantiomeric purity. Tetrahedron: Asymmetry, 1996, 7, 3559-3564.

[56] Albert, M.; Seebach, D.; Duchardt, E.; Schwalbe H. Synthesis and NMR analysis in solution of oligo(3-hydroxyalkanoic acid) derivatives with the side chains of alanine, valine, and leucine (β-depsides): coming full circle from PHB to β-peptides to PHB. Helv. Chim. Acta, 2002, 85, 633-658.

[57] Wagner, B.; Gonzalez, C.I.; Dau, M.E.T.H.; Zhu, J. Total synthesis and conformational studies of hapalosin, N-desmethylhapalosin and 8-deoxyhapalosin. Bioorg. Med. Chem., 1999, 7, 737-747.

[58] Adrio, J.; Cuevas, C.; Manzanares, I.; Joullie, M.M. Total synthesis and biological evaluation of Tamandarin B analogues. J. Org. Chem., 2007, 72, 5129-5138.

[59] Kirmse, W. 100 years of the Wolff rearrangement. Eur. J. Org. Chem., 2002, 2193-2256.

[60] Tilekar, J.N.; Patil, N.T.; Dhavale, D.D. Synthesis of C1-C6 segment of carbonolide B: Wolff rearrangement of sugar α-diazo ketones. Synthesis, 2000, 395-398.

[61] Jones, J.B.; Hinks, R.S. Enzymes in organic synthesis. 36. Synthesis of optically active civet constituent from an enzyme-generated chiral synthon. Can. J. Chem., 1987, 65, 704-707.

[62] Murai, A.; Amino, Y.; Ando, T. Absolute configuration of the β-hydroxyl fatty acid constituent of permetin A. J. Antibiot., 1985, 38, 1610-1613.

[63] Kondekar, N.B.; Kandula, S.R.V.; Kumar, P. Application of the asymmetric aminohydroxylation reaction for the syntheses of HIV-protease inhibitor, hydroxyethylene dipeptide isostere and γ-amino acid derivative. Tetrahedron Lett., 2004, 45, 5477-5479.

[64] Ko, S.Y. Unusual Regioselection in the Mitsunobu Reactions of syn-2,3-Dihydroxy Esters: Synthesis of Statine and Its Diastereomer. J. Org. Chem., 2002, 67, 2689-2691.

[65] Kende, A.S.; Fujii,Y.; Mendoza, J.S. Total synthesis of natural ambruticin. J. Am. Chem. Soc., 1990, 112, 9645-9646.

[66] Pirillo, D.; Leggeri, P.; Traverso, G. Synthesis of S-(+)-4-carboxymethylene-4-butanolide by the Arndt-Eistert rearrangement. Farmaco Ed. Sci., 1984, 39, 963-967.

[67] Thijs, L.; Dommerholt, F.J.; Leemhuis, F.M.C.; Zwanenburg, B. A general stereospecific synthesis of γ-hydroxy-α,β-unsaturated esters. Tetrahedron Lett., 1990, 31, 6589-6592.

[68] Spengler, J.; Ruiz-Rodriguez, J.; Burger, K.; Albericio F. Homologation of α-hydroxy acids to α-unsubstituted β-hydroxy carboxamides *via* Arndt-Eistert reaction. Tetrahedron Lett., 2006, 47, 4557-4560.

[69] Vanderwall, C.D.; Jacobson, E.N. Enantioselective Formal Hydration of α,β-Unsaturated Imides by Al-Catalyzed Conjugate Addition of Oxime Nucleophiles. J. Am. Chem. Soc., 2004, 126, 14724-14725.

[70] Sibi, M.P.; Zimmerman, J.; Rheault, T. Enantioselective conjugate radical addition to β-acyloxy acrylate acceptors: An approach to acetate aldol-type products. Angew. Chem. Int. Ed., 2003, 42, 4521-4523.

[71] Yoo, D.; Song, J.; Kang, M.S.; Kang, E.-S.; Kim, Y.G. Stereodivergent approach to both syn- and anti-isomers of γ-amino-β-hydroxy acids: (3S,4S)- and (3R,4S)-AHPPA derivatives. Tetrahedron: Asymm., 2011, 22, 1700-1704.

[72] Becker, H.; Sharpless, K.B. A new ligand class for the asymmetric dihydroxylation of olefins. Angew. Chem. Int. Ed., 1996, 35, 448-451.

[73] Schneekloth, J.S.; Sanders, J.L.; Hines, J.; Crews, C.M. Neurotrophic peptide aldehydes: Solid phase synthesis of fellutamide B and a simplified analog. Bioorg. Med. Chem. Lett., 2006, 16, 3855-3858.

[74] Yadav, J.S.; Bhaskar Reddy, K.; Sabitha, G. An efficient synthesis of (+)-prelactone B. Tetrahedron Lett., 2004, 45, 6475-6476.

[75] Byun, H.-S.; He, L.; Bittman, R. Cyclic Sulfites and Cyclic Sulfates in Organic Synthesis. Tetrahedron, 2000, 56, 7051-7091.

[76] Yang, H.W.; Romo, D. Methods for the synthesis of optically active β-lactones (2-oxetanones). Tetrahedron, 1999, 55, 6403-6434.

[77] Nelson, S.G.; Peelen, T.J., Wan, Z. Catalytic Asymmetric Acyl Halide-Aldehyde Cyclocondensations. A Strategy for Enantioselective Catalyzed Cross Aldol Reactions. J. Am. Chem. Soc., 1999, 121, 9742-9743.

[78] Nelson, S.G.; Spencer, K.L.; Cheung, W.S.; Mamie, S.J. Divergent reaction pathways in amine additions to β-lactone electrophiles. An application to β-peptide synthesis. Tetrahedron, 2002, 58, 7081-7091.

[79] Gopalarathnam, A.; Nelson, S.G. Amphidinolide B: Asymmetric Synthesis of a C7-C20 Synthon. Org. Lett., 2006, 8, 7-10.

[80] Hashimoto, K.; Kitaguchi, J.; Mizuno, Y.; Kobayashi, T.; Shirahama, H. A new reagent for the preparation of chiral HMGA (3-hydroxy-3-methylglutaric acid) esters and amides. Synthesis of (R)- and (S)-β-carboxymethyl-β-methyl-β-lactones by asymmetric desymmetrization of HMGA anhydride. Tetrahedron Lett., 1996, 37, 2275-2278.

[81] Coulembier, O.; Degée, P.; Cammas-Marion, S.; Guérin, P.; Dubois, P. New Amphiphilic Poly[(R,S)-β-malic acid-b-ε-caprolactone] Diblock Copolymers by Combining Anionic and Coordination-Insertion Ring-Opening Polymerization. Macromolecules, 2002, 35, 9896-9903.

[82] Wipf, P.; Grenon, M. Toward the total synthesis of lophotoxin - New methodologies and synthetic strategies. Can. J. Chem., 2006, 84, 1226-1241.

[83] Yakura, T.; Tanaka, T.; Ikeda, M.; Uenishi, J. Asymmetric synthesis of β-hydroxy acid *via* stereoselective dirhodium(II)-catalyzed C-H insertion of α-alkoxydiazoketone. Chem. Pharm. Bull., 2003, 51, 471-473.

[84] Wohlrab, A.; Lamer, R.; VanNieuwenhze, M.S. Total synthesis of plusbacin A3: a depsipeptide antibiotic active against vancomycin-resistant bacteria. J. Am. Chem. Soc., 2007, 129, 4175-4177.

[85] Ma, D.-Y., Zheng, Q.-Y., Wang, D.-X., Wang, M.-X. Dramatic Enhancement of Enantioselectivity of Biotransformations of β-Hydroxy Nitriles Using a Simple O-Benzyl Protection/Docking Group. Org. Lett., 2006, 8, 3231-3234.

[86] Jaipuri, F.A.; Jofre, M.F.; Schwarz, K.A.; Pohl, N.L. Microwave-assisted cleavage of Weinreb amide for carboxylate protection in the synthesis of a (R)-3-hydroxyalkanoic acid. Tetrahedron Lett., 2004, 45, 4149-4152.

[87] Huang, G.; Hollingsworth, R.I. An efficient synthesis of (R)-3-hydroxytetradecanoic acid. Tetrahedron: Asymmetry, 1998, 9, 4113-4115.

[88] Matsuyama, K.; Ikunaka, M. A practical enantioselective synthesis of (S)-3-hydroxytetradecanoic acid. Tetrahedron: Asymmetry, 1999, 10, 2945-2950.