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Asymmetric synthesis of long chain β-hydroxy fatty acid methyl esters as new elastase inhibitors

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ABSTRACT

Herein, β-hydroxy methyl esters with an even carbon chain length of 12–20 **1b**–**5b** were synthesized by three different asymmetric reduction methods I, II III from their corresponding β-keto methyl esters **1a**–**5a** with the aim of determining their elastase activities. In method I, chiral catalyst **A** was prepared from chiral ligand (*R*)-binaphthol **1**, while in method II, chiral catalyst **B** was synthesized from (2*R*,3*R*)-diisopropyl tartrate **2**. Chiral catalyst **B** has not previously been used in asymmetric borane reductions or in the asymmetric synthesis of chiral β-hydroxy methyl esters. In method III, an asymmetric reduction was catalysed by (*R*)-Me-CBS oxazaborolidine **3**. Hydride transfer was carried out in all of these methods by $BH_3{\cdot}SMe_2$. Chiral hydroxy methyl esters with an (*S*)-configuration were synthesized by method I and with an (*R*)-configuration via methods II and III. The chiral hydroxy methyl esters obtained were analysed by chiral HPLC for their ee % values. Methods I, II and III were applied to long chain β-keto methyl esters for the first time. The reduction methods I, II and III were examined in terms of reaction yield and enantiomeric excess according to carbon chain length and the variable ratio of chiral catalysts to β-keto methyl ester. The highest enantiomeric excess of 90% ee was found in method III for 12 and 14 carbon numbers.

1. Introduction

The asymmetric synthesis of enantiomerically enriched long chain β-hydroxy fatty acids has gained great importance since these compounds can be useful synthons for synthesis of pharmaceuticals, vitamins, flavours, antibiotics and pheromones.[1] (*R*)-β-Hydroxyalkanoic acids represent an important class of biologically active compounds often found in lipopeptides exhibiting antimicrobial, insecticidal and antiviral activities.[2,3] It is well known that (*R*)-β-hydroxyalkanoic acid exists in the pathway of fatty acid synthesis as an adduct of ACP and (*S*)-β-hydroxyalkanoic acid as an ester of CoA. (*R*)-(−)-β-Hydroxytetradecanoic acid is the major fatty acid component of lipid A in endotoxin.[4] The choline ester of (*S*)-β-acetoxyhexadecanoic acid is a fish toxin[5] while β-hydroxyeicosanoic acid is found in a different microorganism.[6]

Hydroxy fatty acid isomers play an important role in cancer chemotherapy, but in the literature there is no data on their anti-elastase activity. Elastase activity has gained increasing interest in recent years due to its important role in diseases of the lung, arteries, skin and ligaments. Elastase inhibition activity is a useful and protective tool against these diseases. α-Hydroxy acids (AHAs) have become increasingly popular as skin rejuvenating agents. β-Hydroxy fatty acids are formed during mitochondrial β-oxidation of fatty acids and are related to disorders in fatty acid oxidation.

According to the literature, no β-hydroxy fatty acid isomers have been examined for their elastase activity except for our published study[7] which reports the excellent elastase inhibition of racemic 3–13 monohydroxy eicosanoic acid isomers. Until now, there has been no report on the elastase activity of chiral β-hydroxy acid methyl ester isomers.

Herein our aim was to synthesize chiral β-hydroxy methyl esters with a 12–20 carbon chain length **1b**–**5b** in order to analyse them for their elastase activity in relation to the enantiomeric purity of their (*R*)- and (*S*)-enantiomers.

Enantiomerically pure β-hydroxy esters can be obtained from the corresponding prochiral β-keto esters by asymmetric reduction. Previously, the asymmetric reduction of β-keto esters was carried out by using modified Raney-Nickel,[8,9] chiral ruthenium (II) complexes[10] at higher hydrogen pressures and chiral modified $NaBH_4$ at atmospheric pressure.[11] In these studies, (*S*)-β-hydroxy tetradecanoic acid methyl ester was obtained with 85% ee by using a modified Raney-Nickel catalyst and with 98.7% ee using a chiral ruthenium catalyst. We have also studied the asymmetric reduction of methyl β-keto tetradecanoate with modified $NaBH_4$ at atmospheric pressure and synthesized the (*S*)-enantiomer of methyl β-hydroxy tetradecanoate with 57% ee.[11]

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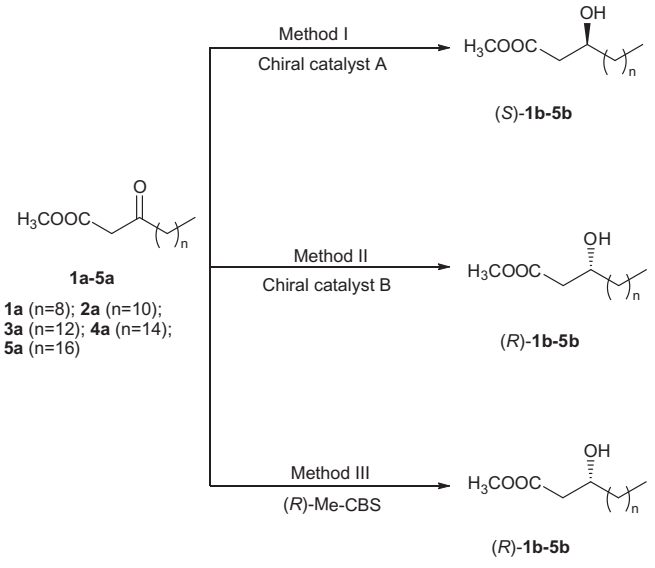
In the recent years, chiral oxazaborolidines and chiral organo aluminium compounds have been used as chiral catalysts in the asymmetric borane reduction of prochiral ketones. Organo-aluminium compounds, which are easily available and inexpensive, have been reported to accelerate the catalytic asymmetric borane reduction of ketones.[12,13] Uang et al. have employed chiral BINOL derivatives in the asymmetric reduction of aromatic prochiral ketones.[14,15] In our previous work, we have also used BINOL induced asymmetric Meerwein–Ponndorf–Verley reductions for the mono methyl 3-, 7- and 13-oxo tetradecanoates.[16] Asymmetric borane reduction with CBS is one of the most useful methods for the synthesis of chiral alcohols.[17]

Herein the (*R*)- and (*S*)-enantiomers of methyl β-hydroxyalkanoates **1b**–**5b** were synthesized with high enantiomeric excess by three different asymmetric reduction methods (I, II and III) which were also compared with each other in this work (Scheme 1). To the best of our knowledge, there has been no study on the synthesis of chiral β-hydroxy esters with 12, 14, 16, 18 and 20 carbon chain lengths using the methods applied herein and their elastase activities.

2. Results and discussion

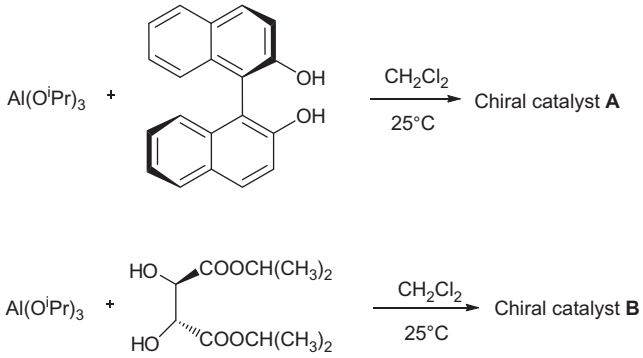
Long chain chiral β-hydroxy acids and their methyl esters are important components of biological molecules. For their asymmetric synthesis their corresponding β-keto acid methyl esters **1a**–**5a** with 12, 14, 16, 18 and 20 carbon chain lengths were chosen as prochiral compounds.

Herein we had two aims; the first was to synthesize chiral β-hydroxy methyl esters **1b**–**5b** with high enantiomeric excess and to examine the influence of the carbon length on the asymmetric reduction. The second aim was to study the elastase activity of these isomers **1b**–**5b** and analyse the effect of (*R*)- and (*S*)-enantiomers with different enantiomeric purities on elastase inhibition, outlined in our previous publication.[7] Three methods I, II and III were chosen for the asymmetric reduction reaction (Scheme 1).



Scheme 1. The three asymmetric reduction methods I, II and III.

In method I, chiral (*R*)-BINOL **1** and in method II, (2*R*,3*R*)-diisopropyl tartrate **2** were chosen as chiral ligands for the preparation of chiral catalysts **A** and **B**. The chiral catalysts **A** and **B** were prepared from 21 mol % of **1** or **2** and 10 mol % of aluminium tri-isopropoxide (Scheme 2). It should be noted that chiral ligand **2** has not been used before as a ligand in an asymmetric borane reduction.



Scheme 2. Synthesis of chiral catalysts **A** and **B**.

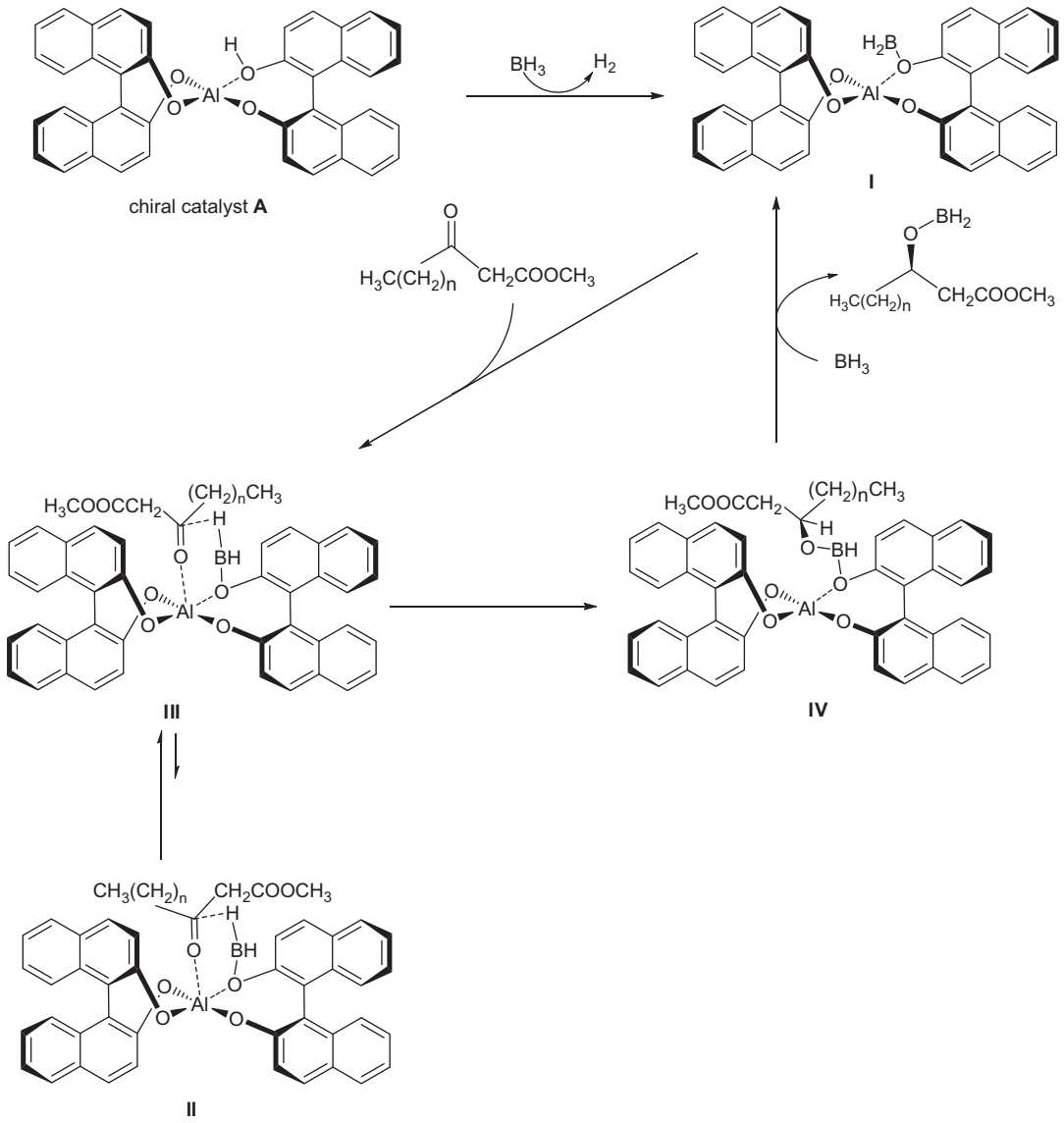
In methods I, II and III, $BH_3{\cdot}SMe_2$ was used as a hydride transfer agent in the presence of the chiral catalysts. The mechanism in Scheme 3 was based on Uang et al. postulated working model.[14,15] Chiral β-hydroxy methyl esters with an (*S*)-configuration were obtained via chiral catalyst **A** and with an (*R*)-configuration with chiral catalyst **B**. Chiral catalyst **A** is more sterically hindered than chiral catalyst **B**; therefore the enantiomeric excesses of method I were higher than method II (Table 1). Due to the steric hinderance of the long chain methylene groups and naphthyl group, the hypothetical transition structure **III** would be more favourable than **II** for method I, which gave hydroxy esters with an (*S*)-configuration. The postulated model **II** was preferred in method II because of the less sterically hindered structure of (2*R*,3*R*)-diisopropyl tartrate. Therefore, the hypothetical transition structure **II** could explain why the products had an (*R*)-configuration in method II (See Figs. 1 and 2).

The ratio of catalyst **A** (or **B**) to β-keto ester as (0.1:1; 0.5:1 and 1:1) was examined and the results are shown in Table 1. Different ratios of chiral catalysts **A** and **B** changed the enantiomeric excess and yield of the asymmetric reduction of the β-keto esters. The highest enantiomeric excess was observed for the ratio: chiral catalyst **A** (or **B**): β-keto ester = 1:1 (Table 1). The enantiomeric excess increased but the reduction yield decreased when increasing the amount of chiral catalyst **A** (or **B**). However, the carbon chain length did not have a significant effect on the reduction yields or ee values.

The ratio of catalyst **A**: β-keto ester = 1:1 gave the highest enantiomeric excess of 81% ee for (*S*)-**1b** and the lowest of 65% ee for (*S*)-**4b** and (*S*)-**5b** (Table 1, entries 1, 4 and 5). The same molar ratio of chiral catalyst **B**: β-keto ester = 1:1 was used for the asymmetric reduction of **1a** and gave an enantiomeric excess of 67% ee (Table 1, entry 1).

The CBS-oxazaborolidine catalyst obtained from (*S*)-(diphenylhydroxymethyl)pyrrolidine with BH_3 is an effective catalyst for the asymmetric borane reduction of ketones.[17,18] However, this catalyst is air and moisture sensitive.[19] Therefore, modified catalysts have been developed and successfully applied to enantioselective reductions.[20]

In method III, (*R*)-Me-CBS **3** was preferred for the asymmetric reduction of β-keto esters and β-hydroxy esters with high ee values being obtained. The results are summarized in Table 1. The general mechanistic model of Corey helps to explain the selectivity obtained in the catalytic reduction (Scheme 4). The first step of the reaction involves the coordination of BH_3 to the nitrogen atom of the oxazaborolidine CBS. This coordination serves to activate BH_3 as a hydride donor and to enhance the Lewis acidity of the catalyst's endocyclic boron. The strongly Lewis acidic complex readily



Scheme 3. Postulated working model for method I.

binds to the β-keto ester at the sterically more accessible electron lone pair. As a result, the stable six-membered transition state obtained leads to high ee values. In method I, a six-membered coordination state was also formed (Scheme 4), although the metals in the cyclic transition state are not the same in methods I, II and III. This may influence the balance and stability of the ring system, in a negative fashion. Furthermore, the Lewis acid ability of the aluminium as in methods I and II is weaker than the boron in method III; this coordination state may be formed with more difficulty than in method III because of the steric hindrance of the chiral aluminium catalyst. Therefore the ee values of method I and II were lower than those of III.

The highest enantiomeric excess of 90% ee was found for (*R*)-**1b** and (*R*)-**2b** in method III (Table 1, entries 1 and 2) and the lowest enantiomeric excess of 49% ee for (*R*)-**4b** and (*R*)-**5b** in method I (Table 1, entries 4 and 5).

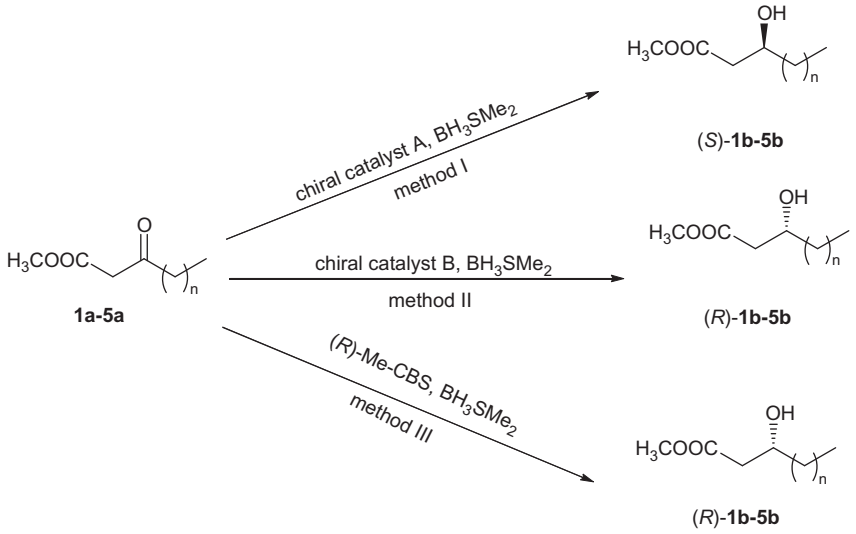
3. Conclusion

In the asymmetric reduction of β-keto methyl esters with the chain length of 12, 14, 16, 18 and 20 carbon atoms, their different methods marked as I, II and III were used. In method I, chiral catalyst **A** from $Al(O^iPr)_3$-**1** and in method II, chiral catalyst **B** from $Al(O^iPr)_3$-**2** were prepared (Scheme 2). Chiral catalyst **B** was used for the first time in such reductions. Method III was achieved by using the known (*R*)-Me-CBS **3**.

The configuration of the mentioned chiral β-hydroxy esters was assigned as (*S*) in the presence of chiral catalyst **A**, as (*R*) with chiral catalyst **B** and as (*R*) with (*R*)-Me-CBS. The absolute configuration of the chiral β-hydroxy methyl esters **1b**–**5b** was determined by comparing the sign of their specific rotation with the literature values.[11,21,22] The starting β-keto methyl esters herein were synthesized by using acetoacetate chemistry.

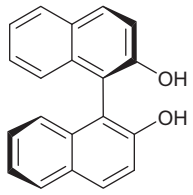
The different ratios of catalyst **A** (or **B**):β-keto ester (0.1:1; 0.5:1; 1:1) were studied in methods I and II as seen in Table 1. The highest enantiomeric excesses were observed from the ratio of the catalyst to β-keto ester = 1:1 (Table 1). The results showed that the enantiomeric excess increased while the reduction yield decreased when increasing the amounts of the chiral catalyst. The reduction yields and the enantiomeric excesses of method III were better than those obtained with methods I and II. This could be explained by the fact that the Lewis acid ability of the boron in

Table 1
Asymmetric reduction of prochiral β-keto ester isomers with methods I, II and III

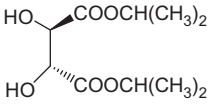


Entry	β-Hydroxy ester	Yield[a] (%)					% ee[gh] (config.)				
		Method I			Method II	Method III	Method I			Method II	Method III
1	**1b**	65[b]	55[c]	40[d]	40[e]	80[f]	53(*S*)[b]	69(*S*)[c]	81(*S*)[d]	67(*R*)[e]	90(*R*)[f]
2	**2b**	60[b]	50[c]	40[d]	40[e]	80[f]	53(*S*)[b]	65(*S*)[c]	67(*S*)[d]	63(*R*)[e]	90(*R*)[f]
3	**3b**	50[b]	40[c]	30[d]	30[e]	70[f]	51(*S*)[b]	65(*S*)[c]	67(*S*)[d]	63(*R*)[e]	85(*R*)[f]
4	**4b**	50[b]	40[c]	30[d]	30[e]	70[f]	49(*S*)[b]	58(*S*)[c]	65(*S*)[d]	63(*R*)[e]	75(*R*)[f]
5	**5b**	50[b]	40[c]	30[d]	30[e]	70[f]	49(*S*)[b]	58(*S*)[c]	65(*S*)[d]	63(*R*)[e]	75(*R*)[f]

[a] Isolated yield of products.
[b] Molar ratio of chiral catalyst A: β-keto ester = 0.1:1 (method I).
[c] Molar ratio of chiral catalyst A: β-keto ester = 0.5:1 (method I).
[d] Molar ratio of chiral catalyst A: β-keto ester = 1:1 (method I).
[e] Molar ratio of chiral catalyst B: β-keto ester = 1:1 (method II).
[f] Molar ratio of (*R*)-Me-CBS: β-keto ester = 0.1:1 (method III).
[g] The ee values were determined by HPLC analysis using Chiralcel OD column.
[h] Absolute configuration of the products was determined by comparing the sign of their specific rotation with the literature value.[11,21,22,24–26]



(*R*)-(+)-1,1'-Binaphthyl-2,2'-diol **1**



(2*R*,3*R*)-Diisopropyl tartrate **2**

Figure 1. Chiral ligands used in method I and II.

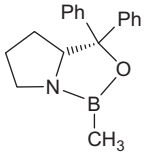


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Figure 2. Chiral catalysts used in method III.

the oxazaborolidine catalyst is stronger than the aluminium of the chiral catalysts **A** or **B**. In all three methods, the size of the carbon chain lengths had no significant effect on the reduction yields or enantiomeric excesses.

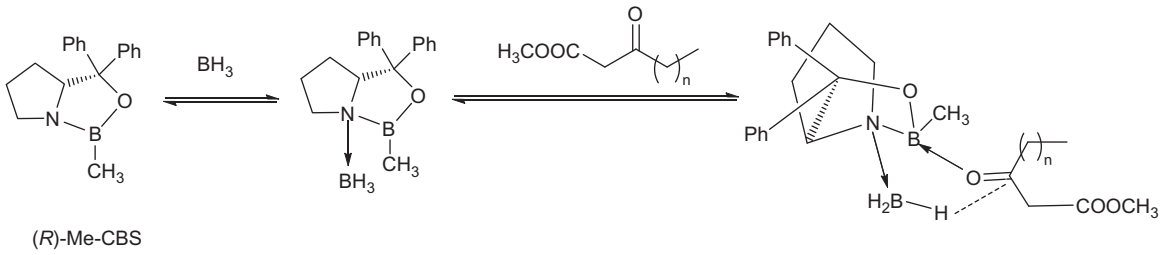
The methods used herein were carried out at atmospheric pressure. Method I and II were accomplished by inexpensive materials, but the ee values were not better than those in method III. (*R*)-Me-CBS is more expensive than $Al(O^iPr)_3$ but method III might be the preferred option in order to achieve high ee values (Table 1).

The enantiomeric purity of chiral β-hydroxy methyl ester isomers were checked by chiral HPLC with Chiralcel OD column (Table 1). The chiral hydroxy esters **1b**–**5b** synthesized with (*R*)- and (*S*)-configuration were characterized by IR, ^1H NMR and their measured specific rotations. Chiral hydroxy esters **1b**–**5b** with (*R*)- and (*S*)-configurations will be analysed for their elastase activity.

4. Experimental

4.1. General

The chemicals used herein were commercially available from Merck and Fluka. The β-keto methyl ester isomers used as starting materials were synthesized by acetoacetate chemistry.[23] The reactions were purified by flash column chromatography on silica gel (Merck; 230–400 mesh) with hexane-acetone and hexane-ethyl-acetate. ^1H NMR spectra were recorded at 400 MHz using TMS as the internal standard in $CDCl_3$. IR were run on a Mattson 1000 series FTIR (as 1% KBr tablets). Melting points were determined with Büchi Melting Point B-540. The specific rotations were measured with an optical activity AA-55 digital polarimeter at room temperature. The enantiomeric excesses (ee) of the chiral β-hydroxy es-



Scheme 4. Postulated working model for method III.

ters were determined with a Shimadzu/DGU-20A$_5$ HPLC apparatus fitted with a Chiralcel OD (0.46 × 25 cm) chiral column. Hexane and isopropanol (98/2, v/v) were used as the mobile phase, flow rate: 1.0 ml/min, wavelength: 210 nm. All reactions were performed under an inert atmosphere (nitrogen).

4.2. General procedure for the asymmetric reduction of prochiral β-keto esters using methods I and II

To a mixture of Al(O^{i}Pr)$_3$ (1.95 mmol) and (R)-BINOL **1** (3.9 mmol) in 5 ml dichloromethane stirred for 1 h, β-keto ester **1a–5a** (1.95 mmol) was added under N_2 at room temperature. After stirring for 0.5 h, the reaction mixture was heated to 40 °C and a borane dimethylsulfide complex (2.3 ml, 1 M in CH_2Cl_2) was added. After stirring for 1 h, the reaction mixture was treated with 1 M HCl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude product containing the hydroxy ester was purified by flash column chromatography (hexane/acetone 9:1, v/v).

4.3. General procedure for the asymmetric reduction of prochiral β-keto esters using method III

To a solution of (*R*)-Me-CBS **3** (0.195 mmol, 0.2 ml of 1 M solution in toluene) was added $BH_3{\cdot}SMe_2$ (2 M in THF, 2.93 mmol, 1.5 ml) and the mixture was stirred under a nitrogen atmosphere at room temperature, then cooled to 0 °C. After 10 min stirring, the solution of β-keto methyl ester **1a–5a** (1.95 mmol) in 5 ml of THF was added dropwise within 45 min at 0 °C. The reaction mixture was stirred for 1 h and then quenched with 2 M HCl. The solution was extracted with ether (3 × 20 ml). The organic layers were washed with water and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/ethylacetate 7:3,v/v).

4.4. Spectroscopic data of chiral β-hydroxy methyl ester isomers synthesized

4.4.1. β-Hydroxydodecanoic acid methyl ester 1b

[24]Mp 28–29 °C, $[\alpha]_D^{25} = -15.7$ (*c* 1, $CHCl_3$); lit[24] $[\alpha]_D^{30} = -15.5$ (c 1.17, $CHCl_3$), IR (KBr, cm^{-1}): 3407, 2858, 2925, 1739, 1152 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm): 0.88 (t, 3H, *J* = 6.8, –C*H*$_3$), 1.26–1.59 (m, 16H, (–C*H*$_2$)$_8$), 2.40 (dd, 1H, *J* = 16.4, *J* = 8.9), 2.51(dd, 1H, *J* = 16.4, *J* = 3.2), 2.75 (s, 1H, –OH), 3.71 (s, 3H, –OC*H*$_3$), 3.96–4.03 (m, 1H, –C*H*(OH). HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2:98, flow rate: 1.0 ml/min, wavelength: 210 nm; R_t (retention time): 8.024 min for the (*R*)-isomer, 10.234 min for the (*S*)-isomer; purity: 94.3% for (*R*), 4.3% for (*S*).

4.4.2. β-Hydroxytetradecanoic acid methyl ester 2b

[11,25]Mp 33–34 °C, (lit.[25] mp 33–34 °C). $[\alpha]_D^{25} = -16.0$ (*c* 1, $CHCl_3$), (lit.[11] $[\alpha]_D^{25} = -10.5$). IR (KBr, cm^{-1}): 3407, 2925, 2858, 1743, 1186 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 0.88 (t, 3H, *J* = 7.1, –C*H*$_3$), 1.26–1.58 (m, 20H, (–C*H*$_2$)$_{10}$), 2.44 (dd, 1H, *J* = 16.3, *J* = 8.9), 2.55 (dd, 1H, *J* = 16.3, *J* = 3.3), 2.94(s, 1H, –OH), 3.71 (s, 3H, –OC*H*$_3$), 4.0 (m, 1H, –C*H*(OH)). HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2:98, flow rate: 1.0 ml/min, wavelength: 210 nm; R_t (retention time): 8.063 min for (*R*)-isomer, 10.522 min for (*S*)-isomer; purity: 94.3% for (*R*), 4.3% for (*S*).

4.4.3. β-Hydroxyhexadecanoic acid methyl ester 3b

[21]Mp 49–50 °C, (lit.[21] mp 49–50 °C). $[\alpha]_D^{25} = -15.2$ (*c* 1, $CHCl_3$), IR (KBr, cm^{-1}): 3407, 2946, 2865, 1754, 1186 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm): 0.88 (t, 3H, *J* = 6.9, –C*H*$_3$), 1.26–1.60 (m, 24H, (–C*H*$_2$)$_{12}$), 2.36 (dd, 1H, *J* = 16.3, *J* = 8.9), 2.56 (dd, 1H, *J* = 16.3, *J* = 3.3), 2.94 (s, 1H, –O*H*), 3.71 (s, 3H, –OC*H*$_3$), 4.0 (m, 1H, –C*H*(OH). HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2:98, flow rate: 1.0 ml/min, wavelength: 210 nm; R_t (retention time): 7.736 min for the (*R*)-isomer, 10.080 min for the (*S*)-isomer; purity: 92.1% for (*R*), 6.7% for (*S*).

4.4.4. β-Hydroxyoctadecanoic acid methyl ester 4b

[26]Mp 51–52 °C, (lit.[26] mp 51.1–51.4 °C). $[\alpha]_D^{25} = -12.3$ (*c* 1, $CHCl_3$), IR (KBr, cm^{-1}): 3407, 2930, 2863, 1754, 1186 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm): 0.88 (t, 3H, *J* = 6.9, –C*H*$_3$), 1.26–1.60 (m, 28H, (–C*H*$_2$)$_{14}$), 2.41 (dd, 1H, *J* = 16.4, *J* = 8.9), 2.56 (dd, 1H, *J* = 16.4, *J* = 3.3), 2.92 (s, 1H, –O*H*), 3.72 (s, 3H, –OC*H*$_3$), 4.0 (m, 1H, –C*H*(OH). HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2:98, flow rate: 1.0 ml/min, wavelength: 210 nm; R_t (retention time): 7.442 min for the (*R*)-isomer, 9.761 min for the (*S*)-isomer; purity: 87.4% for (*R*), 12.6% for (*S*).

4.4.5. β-Hydroxyeicosanoic acid methyl ester 5b

[22]Mp 56–57 °C, (lit.[22] mp 56.5–57.5 °C). $[\alpha]_D^{25} = -12.2$ (*c* 1, $CHCl_3$), IR (KBr, cm^{-1}): 3407, 2930, 2863, 1754, 1186 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm): 0.88 (t, 3H, *J* = 6.9, –C*H*$_3$), 1.26–1.58 (m, 32H, (–C*H*$_2$)$_{16}$), 2.44(dd, 1H, *J* = 16.4, *J* = 8.9), 2.60 (dd, 1H, *J* = 16.3, *J* = 3.3), 2.94 (s, 1H, –O*H*), 3.72 (s, 3H, –OC*H*$_3$), 4.1 (m, 1H, –C*H*(OH). HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 2:98, flow rate: 1.0 ml/min, wavelength: 210 nm; R_t (retention time): 7.086 min for the (*R*)-isomer, 9.213 min for the (*S*)-isomer; purity: 87.4% for (*R*), 12.6% for (*S*).

Acknowledgments

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