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Asymmetric synthesis of monohydroxy tetradecanoic acids and their methyl esters

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Abstract—Methyl 3-, 6- and 13-oxo tetradecanoates were reduced by $NaBH_4$ in the presence of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (DIPGH) and (−)-menthol together with isovaleric and pivalic acids in THF solution. The highest enantiomeric purity was found for the 13-hydroxy ester isomer of 96% ee. Enantiomeric excess (ee, %) was determined by chiral HPLC and ^1H NMR with shift reagent, $Eu(tfc)_3$.

1. Introduction

Long chain hydroxy fatty acids are widely distributed in nature since they have been investigated as components of animals, plants and microorganism[1] and more recently, they have gained great attention because of their uses in industrial and cosmetics areas. Among them chiral hydroxy aliphatic acids are more valuable by possessing at least one stereogenic carbon atom. Most of the naturally occurring hydroxy acids are optically active, and they are essential biological molecules as well as intermediates for organic synthesis.[2]

Monohydroxy tetradecanoic acid and their methyl ester isomers with a hydroxy group in various positions are important amongst them. Methyl 3-, 6-, 13-monohydroxy tetradecanoates and their acids are preferred in this work. It has been well documented that (*R*)-(−)-3-hydroxy tetradecanoic acid is a major fatty acid composing 'lipid-A' in endotoxin[3] and 13-hydroxy tetradecanoic acid was found in white-fir bark.[4]

(*S*)-Enantiomer of methyl 3-hydroxy tetradecanoate was obtained with a 85% enantiomeric excess by using a modified Raney-Nickel catalyst[5,6] and with a 98.7% enantiomeric excess with a chiral ruthenium catalyst.[7] These experiments were carried out by hydrogenation at higher hydrogen pressures. In another experiment[8] (*S*)-3-hydroxy-tetradecanoic acid was obtained by a multi-step synthesis in an overall yield of 27%. In the literature, there is no data about the asymmetric synthesis of 6-, and 13-tetradecanoic acids and their methyl esters.

This study aimed to synthesize the enantiomers of 3-, 6-, 13-hydroxy-tetradecanoic acids and their methyl esters with high enantiomeric excess at atmospheric pressure by asymmetric reduction with chirally modified $NaBH_4$. This reduction method is applied for the long chain keto esters for the first time. Realization of this asymmetric reduction at normal atmospheric pressure together with inexpensive auxiliaries make it competitive with other reduction methods.

İn the literature no study was found about the synthesis of these enantiomers obtained by the method applied in this work. In previous studies[9,10] some aromatic ketones were reduced by modified $NaBH_4$ with 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose,[9] (*S*)-(−)-1-(2-chlorophenyl)-2,2-dimethylpropane-1,3-diol[10] and nonchiral acids.

Auxiliaries for the asymmetric reduction in this study are L-(−)-menthol **1** and, 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (DIPGH) **2**, isovaleric **3** and pivalic acids **4** (Scheme 1). The optimal reduction conditions giving the highest enantiomeric purity were determined. The natural alcohol, L-(−)-menthol, has not been used as an auxiliary before in modified $NaBH_4$ reductions.

Due to the lack in the literature of the spectroscopic and chromatographic analysis of these enantiomeric hydroxy tetradecanoic acid methyl ester isomers, the

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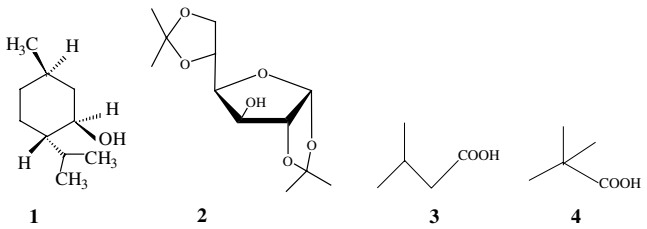
synthesized enantiomers were checked by chiral HPLC and chiral ^{1}H NMR-shift studies in order to identify them and supply pure reference compounds.



1 2 3 4

Scheme 1.

2. Results and discussion

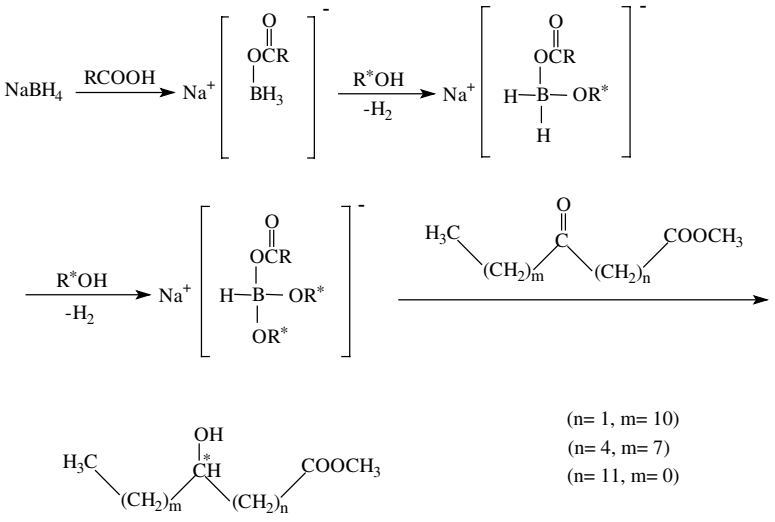
3-, 6- and 13-Monoketo tetradecanoic acid methyl esters carrying keto group at the ends and at the middle of the chain with 14 carbon atoms were chosen as prochiral compounds in order to study the influence of the keto position on the asymmetric reduction and enantiomeric excess. Chirally modified $NaBH_4$ was preferred as the reducing agent and it was prepared from chiral alcohols having at least one hydroxyl group and branched carboxylic acids. Naturally occurring **1** and sterically bulky **2**–**4** were used as auxiliaries.

According to the previous racemic reduction by $NaBH_4$[11] 1 mol of $NaBH_4$ was sufficient for the reduction of 1 mol of keto ester. Two and four moles of chiral monoalcohols **1** and **2** and 1 mol of carboxylic acids **3** and **4** were taken for the preparation of 1 mol chiral $NaBH_4$. The increasing yield of $NaBH_4$ reduction in acidic medium has been established in the previous study.[11] In other reports[9,12] on $NaBH_4$ reductions, different acids were studied too, where the formation of a sodium carboxyborohydride was reported (Scheme 2).

The induction effects of the chiral alcohols **1** and **2** and the carboxylic acids **3** and **4** were examined in different mole ratios as shown in Tables 1–3. Herein, the asymmetric reductions were investigated in terms of the positional effect, reduction yield and enantiomeric excess. Different ratios of organic acids and chiral alcohols changed the yield of the asymmetric reductions and the enantiomeric excesses. For the reduction yield of 3-keto ester, **1** was more dominant than **2** and **4** was more effective than **3** (Table 1, entry 6).

The reduction of 3-keto ester, in the presence of **2** results in considerably higher stereoselectivities (50–57% ee) (Table 1, entries 1–8). Especially **2** together with **4** showed more induction. The excess of chiral alcohol had no effect on the enantiomeric excess for the 3-keto position. **4** had together with **2**, an ee value of 57% for the molar ratio of $NaBH_4$–chiral alcohol **2**–acid **4** and 56% for 1:4:1, respectively (Table 1, entries 4 and 8). Compound **1** being less sterically hindered showed a positive reduction effect and **2** being more sterically hindered had a positive induction effect. 13-keto ester having its keto groups at the end of the chain gave a reduction yield of 75% for the ratio 1:2 of $NaBH_4$ and **1** (Table 2, entry 2). Their ratio of 1:4 decreased the reduction yield (57%, Table 2, entry 6). The pivalic acid was better than **3** for the reduction yield. $NaBH_4$ had together with **2** lower reduction yields for their ratios of 1:2 and 1:4. The effects of the acids **3** and **4** were similar on reduction. The highest enantiomeric excess of % 96 ee was obtained for the (*S*)-13-hydroxy ester from the ratio of $NaBH_4$:**2**:**4** = 1:2:1 (Table 2, entry 4). 6-Keto isomer with a keto position on the middle of the chain delivered lower reduction and enantiomeric excesses for all entries (Table 3).

This work demonstrates the importance of the positional effect. At the position of lower steric hinderance the highest enantiomeric excess and asymmetric reduction yield were observed, namely the prochiral 13-keto isomer corroborates this, being located at the end of the carbon chain at the ($\omega - 1$) position. The 3-keto isomer



Scheme 2.

Table 1. Effects of different organic acids, chiral alcohols and their molar ratios on the asymmetric reduction of 3-keto tetradecanoic acid methyl ester

Entry	$NaBH_4$:acid:chiral alcohol	Yield (%)	$[\alpha]_D^{20}$ (*c* 1, $CHCl_3$)	Ee[c] (%)	Absolute configuration[d]
1	$NaBH_4$:**3**:**1**[a]	5	+9.2	50	*S*
2	$NaBH_4$:**4**:**1**[a]	36	+9.8	53	*S*
3	$NaBH_4$:**3**:**2**[a]	24	+9.8	53	*S*
4	$NaBH_4$:**4**:**2**[a]	20	+10.5	57	*S*
5	$NaBH_4$:**3**:**1**[b]	20	+9.8	53	*S*
6	$NaBH_4$:**4**:**1**[b]	54	+9.9	54	*S*
7	$NaBH_4$:**3**:**2**[b]	33	+9.6	52	*S*
8	$NaBH_4$:**4**:**2**[b]	28	+10.3	56	*S*

Reaction condition:
[a] THF (20 mL), $NaBH_4$ (3.9 mmol), organic acid (3.9 mmol), chiral alcohol (7.8 mmol), keto ester (3.9 mmol); rt, 4 days.
[b] $NaBH_4$ (3.9 mmol), organic acid (3.9 mmol), chiral alcohol (15.6 mmol), keto ester (3.9 mmol); rt, 4 days.
[c] Enantiomeric excess (ee, %) was determined by ^1H NMR-shift reagent and chiral HPLC method.
[d] These configurations were determined due to the sign of the optical rotations measured in this work.

Table 2. Effects of different organic acids, chiral alcohols and their molar rations on asymmetric reduction of 13-keto tetradecanoic acid methyl ester

Entry	$NaBH_4$:acid:chiral alcohol	Yield (%)	$[\alpha]_D^{20}$ (*c* 1, $CHCl_3$)	Ee[c] (%)	Absolute configuration[d]
1	$NaBH_4$:**3**:**1**[a]	51	+20.0	87	*S*
2	$NaBH_4$:**4**:**1**[a]	75	+20.7	90	*S*
3	$NaBH_4$:**3**:**2**[a]	18	+20.7	90	*S*
4	$NaBH_4$:**4**:**2**[a]	4	+22.1	96	*S*
5	$NaBH_4$:**3**:**1**[b]	29	+21.6	94	*S*
6	$NaBH_4$:**4**:**1**[b]	57	+21.6	94	*S*
7	$NaBH_4$:**3**:**2**[b]	5	+17.9	78	*S*
8	$NaBH_4$:**4**:**2**[b]	14	+17.9	78	*S*
9	$NaBH_4$:**no acid**:**1**	33	+6.9	30	*S*

Reaction condition:
[a] THF (20 mL), $NaBH_4$ (3.9 mmol), organic acid (3.9 mmol), chiral alcohol (7.8 mmol), keto ester (3.9 mmol); rt, 4 days.
[b] THF (20 mL), $NaBH_4$ (3.9 mmol), organic acid (3.9 mmol), chiral alcohol (15.6 mmol), keto ester (3.9 mmol); rt, 4 days.
[c] Enantiomeric excess (ee, %) was determined by chiral HPLC.
[d] Absolute configuration was determined according to the sign of the optical rotations measured in this work.

Table 3. Effects of different organic acids, chiral alcohols and their molar rations on asymmetric reduction of 6-keto tetradecanoic acid methyl ester[a]

Entry	$NaBH_4$:acid:chiral alcohol	Yield (%)	$[\alpha]_D^{20}$ (*c* 1, $CHCl_3$)	Ee[b] (%)	Absolute configuration[c]
1	$NaBH_4$:**3**:**1**	7	+6.3	48	*S*
2	$NaBH_4$:**4**:**1**	5	+6.5	49	*S*
3	$NaBH_4$:**3**:**2**	2	+6.5	49	*S*
4	$NaBH_4$:**4**:**2**	12	+6.5	49	*S*

Reaction condition:
[a] THF (20 mL), $NaBH_4$ (3.9 mmol), organic acid (3.9 mmol), chiral alcohol (7.8 mmol), keto ester (3.9 mmol); rt, 4 days.
[b] Enantiomeric excess (ee, %) was determined by ^1H NMR-shift reagent.
[c] Absolute configuration was determined according to the sign of the optical rotations measured in this work.

carries the keto group at the β-position, between the ester and long chained methylene groups and is more sterically hindered than the 13-keto isomer. Therefore reduction yield and enantiomeric excess obtained are lower for the β-position.

The 6-keto isomer has its keto group close to the middle of the chain and is hindered from one side by the ester group carrying four methylenes and the other side by seven methylenes with a methyl group at the end. This position caused a lower reduction yield and enantiomeric excess because of steric hinderance from both sides. The configuration of the mentioned enantiomeric hydroxy esters were assigned as *S* from the literature values[5–7,13,14] of 3-hydroxy tetradecanoic acid where a positive rotation was measured for the (*S*)-configuration. In this present study the optical rotation signs for all enantiomeric 3-, 6-, 13-monohydroxy methyl esters and acids are positive, therefore they were assigned the (*S*)-configuration.

In the literature there are no data on the optical rotation for the 3-, 6-, 13-monohydroxy tetradecanoic acid methyl esters and 6-, 13-monohydroxy tetradecanoic acids. The specific rotations of the mentioned isomers from different enantiomeric excesses are determined for the first time in this study (Tables 1–4).

The enantiomeric excesses were determined for the third and sixth positions by the ^1H NMR-shift method with $Eu(tfc)_3$. The difference in the chemical shift of methoxy singlet was distinguishable for the enantiomeric methyl

Table 4. (*S*)-Enantiomeric enriched 3-, 6- and 13-hydroxy tetradecanoic acids

Enantiomeric enriched hydroxy acid isomers	En (°C)	n_D^{85}	$[\alpha]_D^{20}$ (*c* 1, $CHCl_3$)	Ee (%)	Absolute configuration
3-Hydroxy tetradecanoic acid	76.5–77	1.4365	+9.1[a]	57	*S*
6-Hydroxy tetradecanoic acid	66–67	1.4424	+4.1	49	*S*
13-Hydroxy tetradecanoic acid	58–59	1.4448	+20.8	96	*S*

[a] {Lit.[6] $[\alpha]_D^{25}$ +16.1 (*c* 1, $CHCl_3$), lit.[8] $[\alpha]_D^{25}$ +16.0 (*c* 1.03, $CHCl_3$)}.

esters in the presence of the chiral shift reagent, which produced a difference of 9–25 Hz for enantiomeric pairs of (*R*)- and (*S*)-configurations. Based on the intensity of each signal, the value of ee% was calculated. The methoxy signal of 13-hydroxy isomer could not be split by ^{1}H NMR shift, therefore its ee% was determined by chiral HPLC. The enantiomeric 3-hydroxy methyl ester isomer gave also positive results with chiral HPLC, but we are not successful with the sixth position. The ee% calculated from the chiral HPLC chromatogram of 3-hydroxy isomer was in agreement with the value of ^{1}H NMR shift.

(*S*)-Hydroxy esters of high enantiomeric excesses were hydrolyzed to their (*S*)-hydroxy acids (Table 4).

3. Experimental

Enantiomerically pure L-(−)-menthol was obtained from Merck. 1,2:5,6-Di-*O*-isopropilidene-D-glucofuranose was prepared according to the literature method.[15] From the keto tetradecanoic acid methyl ester isomers used in the asymmetric reduction reaction, 3- and 13-keto esters were synthesized by acetoacetester[16] and 6-keto ester by Blaise reactions,[17] respectively. Melting points were determined with Gallenkamp model melting point apparatus and were uncorrected. Refractive indices were measured with 60/70 Model Abbe refractometer. The optical rotations were measured with a AA-10 Automatic Polarimeter. IR was run on Mattson 1000 series FTIR (as 1% KBr tablets). All asymmetric reduction reactions were carried out at room temperature. The enantiomeric purity was checked by ^{1}H NMR-shift and chiral HPLC methods as methyl esters. ^{1}H NMR Spectrometer Bruker Model 400 MHz, chemical shifts were given in ppm relative to internal standard TMS ($\delta = 0$ ppm). $Eu(tfc)_3$ = Tris[3-(trifluoromethyl-hydroxymethylene)-*d*-camphorato]europium (III) was used as shift reactive in ^{1}H NMR method. HPLC chromatography were undertaken with Hewlett–Packard 6890 Model. A chiral column Chiralcell OD (0.46 × 25 cm), 30 °C, was used for the ee determinations. Cyclohexane and isopropanol (95/5, v/v) were used as flowing phase, flow speed: 0.5 mL/min, detected at 254 nm.

General procedure for asymmetric reduction of prochiral keto esters by chiral modified $NaBH_4$: To a stirred suspension of $NaBH_4$ (3.9 mmol) in THF (5 mL) was added a solution of the acid (3.9 mmol) in THF (5 mL). The solution was stirred 30 min and evolution of H_2 was observed. Then the chiral alcohol (7.8 mmol or 15.6 mmol) in THF (5 mL) was added. After stirring 4 h, the keto ester (3.9 mmol) was added to the reaction solution all at once. The mixture was stirred for 4 days. The end of the reaction was controlled by TLC (developing solvent: toluene/ethyl acetate = 8:2).

The reaction mixture was hydrolyzed by 1 N HCl solution. The solution was extracted with ether. Ether phase which was separated, washed with distilled water. After drying over anhydrous $NaSO_4$, the unreacted keto ester, chiral alcohol and enantiomeric pure hydroxy esters were purified by column chromatography (developing solvent: toluene/ethyl acetate = 8:2).

The enantiomeric excesses of products were measured by ^{1}H NMR and chiral HPLC methods.

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