Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 11, pp. 3255-3262, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00426-0

Synthesis of (*S*)- and (*R*)-3-Hydroxyhexadecanoic Acid

Barbara Jakob, Gundula Voss and Hans Gerlach*

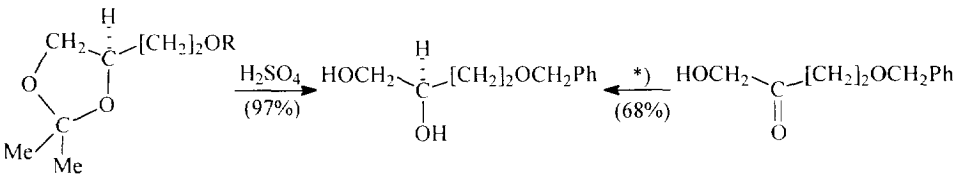
Laboratory of Organic Chemistry, University of Bayreuth, D-95440 Bayreuth, Germany

Abstract: Diol (*R*)-(+)-**3** is prepared either from the hydroxyketone **2** by reduction with fermenting baker's yeast or by hydrolysis of the dioxolane (*R*)-(+)-**1** which is available from dimethyl D-malate as starting material. (*R*)-(+)-**3** could be converted stereoselectively into (*R*)-(+)-**4**. Reaction of (+)-**4** with dodecylmagnesium bromide yielded the alcohol (*S*)-(−)-**5** with >99% ee. Its acetylation gave (*S*)-(+)-**6** and hydrogenolysis gave the primary alcohol (*S*)-(+)-**7** which could be oxidized selectively to (*S*)-(+)-**8** with $NaIO_4/RuCl_3$. Alkaline hydroysis of (+)-**8** yielded 3-hydroxyhexadecanoic acid (*S*)-(+)-**9** which could be esterified to give the methyl ester (*S*)-(+)-**10** with >99% ee. Starting with the dioxolane (*S*)-(−)-**1**, derived from dimethyl L-malate, the 3-hydroxyhexadecanoic acid (*R*)-(−)-**9** and its methyl ester (*R*)-(−)-**10** could be synthesized via the intermediates (*S*)-(−)-**3**, (*S*)-(−)-**4**, (*R*)-(+)-**5**, (*R*)-(−)-**6**, (*R*)-(−)-**7** and (*R*)-(−)-**8**.

Optically active 3-hydroxyalkanoic acids and their derivatives occur widely in biological systems. For instance (*S*)-3-hydroxyhexadecanoic acid is a constituent of pahutoxin[1], a defense substance isolated from fish, and (*R*)-3-hydroxyhexadecanoic acid is a constituent of the extracellular glycolipids from the red yeast *Rhodotorula*[2] and of eupassofilin from a higher plant[3]. It is well known that (*R*)-3-hydroxyalkanoic acids are bound to the acyl carrier protein in the pathway for fatty acid synthesis and that (*S*)-3-hydroxyalkanoic acids exist in the fatty acid metabolism pathway as esters of coenzyme A. Although various methods of synthesizing these important 3-hydroxyalkanoic acids have been proposed, no practical way for the preparation of enantiomerically pure compounds has been reported. The enantioselective hydrogenation of methyl 3-oxoalkanoates with D- and L-tartaric acid-NaBr-modified Raney nickel[4] gave methyl (*S*)- and (*R*)-3-hydroxyhexadecanoate with 83% and 87% ee. In a study[5] of the reduction of 3-oxoalkanoic acids with fermenting baker's yeast (*R*)-3-hydroxyhexadecanoic acid with 98% ee was isolated in 42% yield. In the present work we describe a practical synthesis of enantiomerically pure (*S*)- and (*R*)-3-hydroxyhexadecanoic acid via (*R*)- and (*S*)-oxiranes which are easily prepared from commercially available D- and L-malic acid derivatives of natural origin.

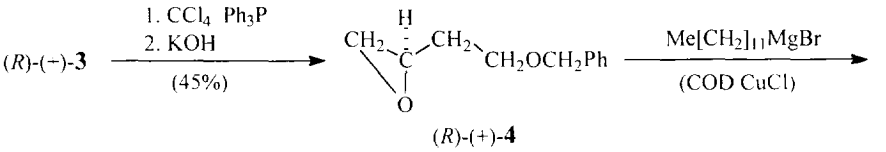
The key intermediate for the synthesis of (*S*)-3-hydroxyhexadecanoic acid acids is the enantiomerically pure diol (*R*)-(+)-**3**. This diol is available with 95% ee from 4-benzyloxy-1-hydroxy-2-butanone (**2**) by reduction with actively fermenting baker's yeast. (*R*)-(+)-**3** with > 99% ee can be prepared from the dioxolane (*R*)-(+)-**1**, which is easily available enantiomerically pure from dimethyl D-malate via (*R*)-(+)-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol[6] and formation of the benzyl ether. The conversion of the diol (*R*)-(+)-**3** into the oxirane (*R*)-(+)-**4** could be performed without loss of enantiomerical purity according to Liu and Coward[7]. Reaction of (+)-**3** with Ph_3P/CCl_4 produced a mixture of regioisomeric chlorohydrins which could be smoothly transformed into (+)-**4** by treatment with potassium hydroxide. Reaction of the enantiomerically pure oxirane (*R*)-(+)-**4** with

dodecylmagnesium bromide in the presence of 1,5-cyclooctadienecopper(I) chloride as catalyst[8] yielded the alcohol (*S*)-(−)-**5** in 92% yield. Esterification of (−)-**5** with (+)-MTPA gave only one of the diastereoisomeric Mosher esters with >99% de showing that the formation of (+)-**4** from (+)-**3** and the subsequent reaction with the Grignard reagent to produce (−)-**5** are completely stereospecific. Reaction of (−)-**5** with acetic anhydride produced the acetate (*S*)-(+)-**6** and hydrogenolysis of the benzyl ether group gave the primary alcohol (*S*)-(+)-**7**. It could be selectively oxidized with ruthenium(III) chloride and sodium periodate according to Sharpless et al.[9] to provide (*S*)-(+)-3-acetoxyhexadecanoic acid (+)-**8** in 98% yield. Alkaline hydrolysis gave the hydroxy acid (+)-**9** which could be converted into the methyl ester (*S*)-(+)-**10** with trimethyl orthoformate. Esterification of (+)-**10** with (+)-MTPA gave only one of the diastereoisomeric Mosher esters with >99% de.

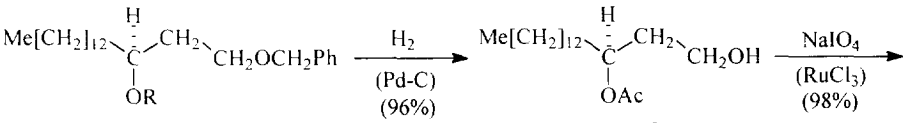


(*R*)-(+)-**1** R = CH_2Ph (*R*)-(+)-**3** **2**

*) fermenting baker's yeast

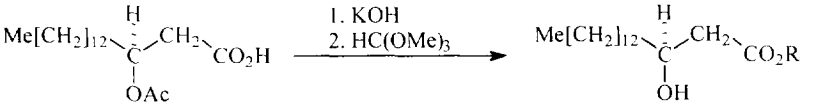


(*R*)-(+)-**4**



(*S*)-(−)-**5** R = H (92%)
(*S*)-(+)-**6** R = Ac (100%)

(*S*)-(+)-**7**



(*S*)-(+)-**8**

(*S*)-(+)-**9** R = H (83%)
(*S*)-(+)-**10** R = Me (96%)

With dimethy L-malate as starting material the single enantiomer dioxolane (*S*)-(–)-**1** could be prepared in a few steps via (*S*)-(–)-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol[6] and subsequent formation of the benzyl ether. Hydrolysis of (–)-**1** gave the diol (*S*)-(–)-**3** with >99% ee which could be converted stereoselectively into the oxirane (*S*)-(–)-**4** accoding to the method of Liu and Coward[7]. Reaction with dodecylmagnesium bromide produced the alcohol (*R*)-(+)-**5** with >99% ee. Application of the reactions as in the enantiomeric series provided the acetate (*R*)-(–)-**6**, the primary alcohol (*R*)-(–)-**7**, the acetoxy acid (*R*)-(–)-**8**, the (*R*)-(–)-3-hydroxyhexadecanoic acid (–)-**9**, and its methyl ester (*R*)-(–)-**10** with >99% ee.

EXPERIMENTAL SECTION

^{1}H (270.17 MHz) and ^{13}C (67.94 MHz) NMR spectra were recorded on a Jeol JNM-EX 270 instrument (d in ppm referenced to residual solvent signal, with chemical shifts referred to TMS; *J* in Hz, multiplicities as determined from DEPT spectra). Optical rotations were measured on a Perkin Elmer 241 polarimeter. IR spectra were recorded on a Perkin Elmer Paragon 1000 FT IR spectrometer. Melting points were determined on a Büchi 510 melting point apparatus. Column chromatography: Kieselgel 60 (from Merck). Kieselgel 60 F_{254} glass plates (from Merck) were used for TLC, compounds were visualized by conc. H_2SO_4/5 min 160 °C. All solvents were distilled before use. Diethyl ether and THF were filtered through ICN Alumina B prior to use. Elemental analyses were performed by the microanalytical laboratory of Ilse Beetz, D-96317 Kronach.

(R)-(+)-4-(2-Benzyloxyethyl)-2,2-dimethyl-1,3-dioxolane (+)-**1**: A solution of 19.13 g (131 mmol) of (*R*)-(+)-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (prepared from dimethyl D-malate as described in ref.[6] for the (*S*)-(–)-enantiomer from dimethyl L-malate) was added dropwise with stirring to a suspension of 6.80 g (170 mmol, 60% dispersion in oil, washed twice with cyclohexane) of sodium hydride in 200 ml of THF at room temp. under N_2. Then 25.0 ml (27.5 g, 217 mmol) of benzylchloride was added dropwise and the resulting mixture was heated under reflux for 16 h. Subsequently 100 ml of water was added, the solvent was evaporated and the mixture was extracted twice with 500 ml of diethyl ether. The extracts were dried (Na_2SO_4), and the solvent was evaporated. The residue (40.6 g) was distilled to give 29.65 g (95%) of (+)-**1**, colorless liquid, b.p. 81-83 °C/0.001 Torr, $[\alpha]_D^{20}$ = +0.33 (*c* = 10.5, $CHCl_3$) [ref.[10] –1.6 (*c* = 1.156, $CHCl_3$) for (–)-**1**]. -^{1}H NMR and ^{13}C NMR spectra identical to those reported in ref.[10].

(S)-(–)-4-(2-Benzyloxyethyl)-2,2-dimethyl-1,3-dioxolane (–)-**1**: Analogously prepared as described above for (+)-**1** from 11.90 g (81.5 mmol) of (*S*)-(–)-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol[6] to give 16.56 g (86%) of (–)-**1**, colorless liquid, b.p. 98-102 °C/0.05 Torr, $[\alpha]_D^{20}$ = –0.35 (*c* = 11.0, $CHCl_3$) [ref.[10] –1.6 (*c* = 1.156, $CHCl_3$).

4-Benzyloxy-1-hydroxy-2-butanone **2**: 3.08 ml (9.60 g, 60 mmol) of bromine was added at once to a solution of 10.68 g (60 mmol) of 1-phenylmethoxy-3-butanone (Fluka) in 36 ml of dry methanol at 4 °C. After 1.5 h the color of bromine had disappeared. Then 120 ml of 1 M K_2CO_3 was added, the mixture was concentrated in vacuo and extracted twice with 300 ml of diethyl ether/toluene (1:1). The extracts were washed twice with 50 ml of 1 M K_2CO_3, dried (Na_2SO_4), and the solvent was evaporated. The residue (19.88 g dimethylacetal) was dissolved in 240 ml of THF and 120 ml of 1 M H_2SO_4 and the mixture was heated at reflux temp. for 1.5 h. Then the mixture was concentrated in vacuo and extracted with cyclohexane/diethyl ether (1:1). The extracts were washed with 2 M $KHCO_3$, dried (Na_2SO_4), and the solvent was evaporated to give 13.4 g of crude bromo ketone. The residue and 10.08 g (120 mmol) of potassium formate was dissolved in 60 ml of methanol and heated at reflux temp. for 2 h. Then 180 ml of diethyl ether was added, the resulting suspension was filtered and

the filtrate was concentrated. The residue (12.02 g) was chromatographed on 600 g of silica gel (cyclohexane/AcOEt, 2:1) to afford 7.52 g (65%) of **2** as a colorless oil, R_f = 0.20, b.p. 105-115 °C/0.001 Torr. - IR ($CHCl_3$): $\tilde{\nu}$ = 3502 cm^{-1} (OH), 1723 (CO). - ^1H NMR ($CDCl_3$): d = 2.69 (t, J = 6.0 Hz, 2 H, 3-H), 3.10 (t, J = 4.8 Hz, 1 H, OH), 3.77 (t, J = 6.0 Hz, 2 H, 4-H), 4.29 (d, J = 4.8 Hz, 2 H, CH_2OH), 4.51 (s, 2 H, OCH_2Ph), 7.22-7.40 (5 H, Ph). - ^{13}C NMR ($CDCl_3$): d = 39.0, 64.9, 68.8, 73.3 (4 t, C-1,3,4, OCH_2Ph), 127.6, 127.8, 128.4, 137.6 (Ph), 208.4 (s, C=O). - $C_{11}H_{14}O_3$: calcd. 194.0943; found 194.0943.

(R)-(+)-4-Benzyloxy-1,2-butanediol (+)-**3**: A solution of 4.98 g (21.1 mmol) of (+)-**1** in 70 ml of THF and 50 ml of 1 N H_2SO_4 was heated under reflux for 1 h. Then the mixture was concentrated in vacuo and subsequently extracted twice with 350 ml of AcOEt. The extracts were dried (Na_2SO_4) and the solvent was distilled off to give 4.00 g (97%) of (+)-**3** with >99% ee as a colorless oil. An analytical sample was distilled, b.p. 130 °C/0.001 Torr, $[\alpha]_D^{20}$ = +22.7 (c = 5.16, EtOH).

*(R)-(+)-**3** by reduction of **2** with fermenting baker's yeast*: A solution of 6.85 g (35.3 mmol) of **2** in 7 ml of ethanol was added dropwise into an actively fermenting mixture of 82 g of baker's yeast, 82 g of sucrose, and 820 ml of water and kept for one day. An analogous fermenting mixture was added the second day and the suspension was frequently shaken. The third day the mixture was centrifugated (40 min, 1000 rpm) and the water layer was decanted and concentrated in vacuo. The residue (33.58 g) was suspended in 150 ml of ethanol/diethyl ether (1:1). The resulting mixture was filtered through a cotton plug to remove the insoluble constituents. Evaporation of the solvent afforded 22.5 g of an oily product. The deposited yeast particles were separately suspended in 200 ml of water and treated as above to give additional 1.0 g of oily product. Chromatography of the combined residues (23.5 g) on 400 g of silica gel (cyclohexane/AcOEt, 1:1) afforded 4.96 g (68%) of (+)-**3** with 95% ee as a colorless oil, R_f = 0.20 (cyclohexane/AcOEt, 1:1), b.p. 125-135 °C/0.001 Torr, $[\alpha]_D^{20}$ = +21.35 (c = 4.67, EtOH), –5.5 (c = 1.5, $CHCl_3$) [ref.[11] –4.2 (c = 1.1, $CHCl_3$)]. - ^1H NMR and ^{13}C NMR ($CDCl_3$) spectra are identical with those reported in ref.[11]. (+)-**3** was treated with (+)-MTPA to furnish the bisester with a 1-H dd-signal at d = 4.70 ppm in the ^1H NMR ($CDCl_3$). An additional 1-H dd-signal at δ = 4.64 ppm of the distereoisomeric ester had 2.5% of its intensity. The nonpolar fractions afforded 1.36 g (20%) of the starting material **2**, R_f = 0.40 (cyclohexane/AcOEt, 1:1).

(S)-(–)-4-Benzyloxy-1,2-butanediol (–)-**3**: Analogously prepared as described above for (+)-**3** from 4.00 g (18.0 mmol) of (–)-**1** to give 3.20 g (96%) of (–)-**3**, colorless oil, $[\alpha]_D^{20}$ = –22.6 (c = 5.16, EtOH), +2.2 (c = 5.27, $CHCl_3$) [ref.[10] –5.2 (c = 18, $CHCl_3$)].

(R)-(+)-2-(2-Benzyloxyethyl)-oxirane (+)-**4**: A solution of 6.18 g (31.5 mmol) of (+)-**3** in 50 ml of CCl_4 was added to 9.60 g (36.6 mmol) of Ph_3P in 70 ml of CCl_4 and the mixture was heated at reflux temp. for 18 h. After cooling the mixture was concentrated in vacuo and the residue was chromatographed on 1000 g of silica gel (cyclohexane/AcOEt, 2:1) to give 3.61 g of a mixture of chlorhydrins, R_f = 0.35 and 0.45. 20 ml of DMSO and 60 ml of 0.5 N KOH was added and the mixture was heated to 55 °C for 45 min. After cooling the reaction mixture was extracted three times with 250 ml of diethyl ether. The combined extracts were washed with 100 ml of H_2O, dried (Na_2SO_4), and the solvent was evaporated. The residue (2.9 g) was chromatographed on 300 g of silica gel (cyclohexane/AcOEt, 2:1) to give 2.515 g (45%) of (+)-**4** as a colorless oil, R_f = 0.55, b.p. 62-65 °C/0.01 Torr, $[\alpha]_D^{23}$ = +15.4 (c = 4.8, $CHCl_3$) [ref.[7] +16.9 (c = 2.51, $CHCl_3$)]. ^1H and ^{13}C NMR spectra are identical to those given in ref.[7].

(S)-(–)-2-(2-Benzyloxyethyl)-oxirane (–)-**4**: Analogously prepared as described above for (+)-**4** from 9.165 g (42.7 mmol) of (–)-**3** to give 6.52 g (52%) of (–)-**4**, b.p. 57-60 °C/0.005 Torr, $[\alpha]_D^{23}$ = –15.6 (c = 5.1, $CHCl_3$)

[ref.[7] −14.5 (*c* = 2.51, $CHCl_3$)].

(S)-(−)-1-Benzyloxy-3-hexadecanol (−)-**5**: A solution of 5.00 ml (5.19 g, 20.8 mmol) of 1-bromododecane and 0.1 ml of 1,2-dibromoethane in 60 ml of THF was added dropwise within 5 h under N_2 to a suspension of 1.50 g (61.7 mmol) of magnesium turnings in 20 ml of boiling THF. Then the Grignard reagent was cooled to −16 °C and 3.021 g (16.95 mmol) of (+)-**4** and 700 mg (1.69 mmol) of 1,5-cyclooctadienecopper(I) chloride was added. After stirring the mixture for 16 h at room temp. 17 ml of 2 N H_2SO_4 was added and the THF was distilled off in vacuo. The residue was extracted twice with 250 ml of toluene/diethyl ether (1:1) and the combined extracts were washed with 100 ml of 2 M $KHCO_3$, dried (Na_2SO_4), and the solvent was evaporated. The residue (7.46 g) was chromatographed on 500 g of silica gel (cyclohexane/AcOEt, 9:1) to give 5.44 g (92%) of (−)-**5** as colorless crystals, R_f = 0.21. An analytical sample was distilled, b.p. 156-157 °C/0.001 Torr, m.p. 35.3-35.9 °C, $[\alpha]_D^{20}$ = −7.5 (*c* = 2.43, $CHCl_3$). - IR (CCl_4): $\tilde{\nu}$ = 3631 cm^{-1}, 3600-3400 (OH). - ^1H NMR ($CDCl_3$): δ = 0.86 (m, 3 H, H-16), 1.20-1.50 (24 H, 4-H to H-15), 1.70 (dd, *J* = 5.0, 2.0 Hz, 1 H, H-2), 1.73 (dd, *J* = 5.0, 6.3 Hz, 1 H, H-2), 2.81 (m, 1 H, OH), 3.63 (dt, *J* = 9.2, 6.3 Hz, 1 H, H-1), 3.71 (dt, *J* = 9.2, 5.3 Hz, 1 H, H-1), 3.78 (m, 1 H, H-3), 4.51 (s, 2 H, OCH_2Ph), 7.25-7.34 (5 H, Ph). - ^{13}C NMR ($CDCl_3$): d = 14.1 (q, C-16), 22.6, 25.6, 29.3, 29.57, 29.59, 29.61, 29.63, 29.64, 29.65, 29.66, 31.9, 36.4, 37.4 (13 t, C-2,4 to C-15), 69.2 (t, C-1), 71.3 (d, C-3), 73.2 (t, OCH_2Ph), 127.58, 127.64, 128.4, 137.9 (Ph). - $C_{23}H_{40}O_2$ (348.57): calcd. C 79.25, H 11.57; found C 79.33, H 11.55. - (−)-**5** was treated with (+)-MTPA to furnish the ester with a OCH_3 signal at δ = 3.53 in the ^1H NMR ($CHCl_3$) spectrum. The signal at δ = 3.49 of the diastereomeric ester could not be detected.

(R)-(+)-1-Benzyloxy-3-hexadecanol (+)-**5**: Analogously prepared as described above for (−)-**5** with the Grignard reagent made from 5.00 ml (5.19 g, 20.8 mmol) of 1-bromododecane, 1.50 g (61.7 atom-gram) of magnesium turnings in 80 ml of THF and 3.021 g (16.95 mmol) of (−)-**4** in the presence of 700 mg (1.69 mmol) of 1,5-cyclooctadienecopper(I) chloride catalyst. The residue (7.2 g) was chromatographed on 500 g of silica gel (cyclohexane/AcOEt, 9:1) to yield 5.53 g (94%) of (+)-**5** as colorless crystals, R_f = 0.17. An analytical sample was distilled, b.p. 169-170 °C/0.002 Torr, m.p. 34.6-35.5 °C, $[\alpha]_D^{20}$ = +7.9 (*c* = 2.97, $CHCl_3$). - $C_{23}H_{40}O_2$ (348.57): calcd. C 79.25, H 11.57; found C 79.34, H 11.55. - (+)-**5** was treated with (+)-MTPA to furnish the ester with a OCH_3 signal at δ = 3.49 in the ^1H NMR ($CHCl_3$) spectrum. The signal at δ = 3.53 of the diastereomeric ester could not be detected.

(S)-(−)-1-Benzyloxy-3-hexadecyl Acetate (+)-**6**: A mixture of 5.213 g (14.95 mmol) of (−)-**5**, 20 ml of acetic anhydride and 20 ml of pyridine was stirred at room temp. for 21 h. Toluene was added and the solvent and excess reagent were evaporated in vacuo. The residue (5.91 g) was chromatographed on 500 g silica gel (cyclohexane/AcOEt, 9:1) to afford 5.83 g (100%) of (+)-**6** as a colorless oil, R_f = 0.36. An analytical sample was distilled, b.p. 168-169 °C/0.001 Torr, $[\alpha]_D^{20}$ = +12.5 (*c* = 2.84, $CHCl_3$). - IR (CCl_4): $\tilde{\nu}$ = 1738 cm^{-1} (C=O). - ^1H NMR ($CDCl_3$): = δ 0.86 (m, 3 H, 16-H), 1.20-1.40 (22 H, 5-H to 15-H), 1.45-1.55 (2 H, 4-H), 1.78 (ddd, *J* = 15.8, 6.6, 1.6 Hz, 1 H, 2-H), 1.89 (ddm, *J* = 15.8, 6.6 Hz, 1 H, 2-H), 1.98 (s, 3 H, CH_3CO_2), 3.44 (dt, *J* = 9.2, 6.6 Hz, 1 H, 1-H), 3.49 (dt, *J* = 9.2, 6.6 Hz, 1 H, 1-H), 4.46 (s, 2 H, OCH_2Ph), 5.00 (tt, *J* = 6.6, 5.9 Hz, 1 H, 3-H), 7.23-7.33 (5 H, Ph). - ^{13}C NMR ($CDCl_3$): δ = 14.1 (q, C-16), 21.1 (q, CH_3CO_2), 22.6, 25.2, 26.9, 29.3, 29.45, 29.47, 29.53, 29.61, 29.63, 29.65, 31.9, 34.3, 34.4 (13 t, C-2,4 to C-15), 66.7 (t, C-1), 71.9 (d, C-3), 73.0 (t, OCH_2Ph), 127.5, 127.6, 128.3, 138.3 (Ph), 170.7 (s, $MeCO_2$). - $C_{25}H_{42}O_3$ (390.61): calcd. C 76.87, H 10.84; found C 76.97, H 10.75.

(R)-(−)-1-Benzyloxy-3-hexadecyl Acetate (−)-**6**: Analogously prepared as described above for (+)-**6** from a mixture of 5.099 g (14.63 mmol) of (+)-**5**, 20 ml of acetic anhydride and 20 ml of pyridine to give 5.70 g (100%) of (−)-**6** as a colorless oil, R_f = 0.38 (cyclohexane/AcOEt, 9:1), b.p. 156-157 °C/0.002 Torr, $[\alpha]_D^{23}$ = −13.2 (*c* = 3.58, $CHCl_3$). - $C_{25}H_{42}O_3$ (390.61): calcd. C 76.87, H 10.84; found C 76.76, H 10.74.

(S)-(+)-1-Hydroxy-3-hexadecyl Acetate (+)-**7**: A solution of 5.568 g (14.26 mmol) of (+)-**6** in 300 ml of MeOH and 2 ml of acetic acid was stirred with 600 mg of Pd/C (5%, Fluka) under H_2 (1 bar) for 2 h. The mixture was filtered through celite and the solvent was distilled off in vacuo and the residue (4.63 g) was chromatographed on 500 g silica gel (cyclohexane/AcOEt, 4:1) to give 4.13 g (96%) of (+)-**7** as a colorless oil, R_f = 0.17. An analytical sample was distilled, b.p. 129-130 °C/0.005 Torr, $[\alpha]_D^{20}$ = +10.5 (*c* = 1.57, $CHCl_3$). - IR (CCl_4): $\tilde{\nu}$ = 3636 cm^{-1}, 3600-3400 (OH), 1736, 1722 (C=O). - ^1H NMR ($CDCl_3$): d = 0.85 (m, 3 H, 16-H), 1.10-1.40 (22 H, 5-H to 15-H), 1.44-1.64 (2 H, 4-H), 1.63 (ddt, *J* = 14.5, 9.6, 4.3 Hz, 1 H, 2-H), 1.82 (dddd, *J* = 14.5, 9.6, 5.9, 3.3 Hz, 1 H, 2-H), 2.05 (s, 3 H, CH_3CO_2), 2.35 (m, 1 H, OH), 3.45-3.60 (2 H, 1-H), 5.02 (m, 1 H, 3-H). - ^{13}C NMR ($CDCl_3$): δ = 14.0 (q, C-16), 21.0 (q, CH_3CO_2), 22.6, 25.3, 29.27, 29.31, 29.43, 29.47, 29.55, 29.56, 29.57, 29.59, 31.8, 34.5, 37.4 (13 t, C-2,4 to C-15), 58.5 (t, C-1), 71.6 (d, C-3), 171.8 (s, $MeCO_2$). - $C_{18}H_{36}O_3$ (300.49): calcd. C 71.95, H 12.08; found C 72.03, H 12.13.

(R)-(−)-1-Hydroxy-3-hexadecyl Acetate (−)-**7**: Analogously prepared as described above for (+)-**7** from a mixture of 5.507 g (14.63 mmol) of (−)-**6** and 600 mg of Pd/C (5%, Fluka) in 300 ml of MeOH and 2 ml of acetic acid. The residue (4.70 g) was chromatographed on 500 g of silica gel (cyclohexane/AcOEt, 4:1) to give 4.05 g (96%) of (−)-**7** as a colorless oil, R_f = 0.14. An analytical sample was distilled, b.p. 135-136 °C/0.002 Torr, $[\alpha]_D^{20}$ = −11.5 (*c* = 2.88, $CHCl_3$). - $C_{18}H_{36}O_3$ (300.49): calcd. C 71.95, H 12.08; found C 71.86, H 12.04.

(S)-(+)-3-Acetoxyhexadecanoic Acid (+)-**8**: A solution of 3.950 g (13.15 mmol) of (+)-**7** in 28 ml of CCl_4 was added within 7 h at 20 °C with stirring to a solution of 8.50 g (39.7 mmol) of sodium periodate and 110 mg (0.53 mmol) of ruthenium(III) chloride hydrate in 56 ml of acetonitrile, 28 ml of CCl_4 and 84 ml of water. The mixture was stirred for additional 16 h. Then the mixture was concentrated in vacuo, 120 ml of 2 N H_2SO_4 was added and the mixture was extracted twice with 300 ml of AcOEt. The combined extracts were dried (Na_2SO_4), the solvent was evaporated and the residue (4.47 g) was chromatographed on 500 g of silica gel (cyclohexane/AcOEt/AcOH, 80:20:2) to give 4.05 g (98%) of (+)-**8** as colorless crystals, R_f = 0.21. An analytical sample was distilled, b.p. 164-165 °C/0.002 Torr, m.p. 46.0-46.7 °C (ref.[12] 44-45 °C), $[\alpha]_D^{20}$ = +2.7 (*c* = 1.35, $CHCl_3$) [ref.[12] +2.70 (*c* = 1.0, $CHCl_3$)]. - IR (CCl_4): $\tilde{\nu}$ = 3500-2500 cm^{-1} (CO_2H), 1746, 1716 (C=O). - ^1H NMR ($CDCl_3$): δ = 0.83 (m, 3 H, 16-H), 1.20-1.30 (22 H, 5-H to 15-H), 1.56 (m, 2 H, 4-H), 1.99 (s, 3 H, CH_3CO_2), 2.52 (dd, *J* = 15.8, 5.6 Hz, 1 H, 2-H), 2.59 (dd, *J* = 15.8, 7.3 Hz, 1 H, 2-H), 5.16 (quint, *J* = 6.3 Hz, 1 H, 3-H), 11.20 (m, 1 H, CO_2H). - ^{13}C NMR ($CDCl_3$): d = 14.0 (q, C-16), 21.0 (q, CH_3CO_2), 22.6, 25.0, 26.8, 29.28, 29.29, 29.41, 29.48, 29.56, 29.59, 29.62, 31.9, 33.9, 38.8 (13 t, C-2,4 to C-15), 70.3 (d, C-3), 170.6 (s, $MeCO_2$), 176.5 (s, CO_2H). - $C_{18}H_{34}O_4$ (314.47): calcd. C 68.75, H 10.90; found C 68.77, H 10.83.

(R)-(−)-3-Acetoxyhexadecanoic Acid (−)-**8**: Analogously prepared as described above for (+)-**8** from a solution of 3.820 g (12.71 mmol) of (−)-**7**, 8.25 g (38.6 mmol) of sodium periodate and 107 mg (0.52 mmol) of ruthenium(III)-chloride hydrate in 56 ml of acetonitrile, 56 ml of CCl_4 and 84 ml of water. The residue (4.07 g) was chromatographed on 500 g of silica gel (cyclohexane/AcOEt/AcOH, 80:20:2) to give 3.76 g (94%) of (−)-**8** as colorless crystals, R_f = 0.18. An analytical sample was distilled, b.p. 164-165 °C/0.002 Torr, m.p. 45.5-46.2 °C (ref.[12] 44-45 °C), $[\alpha]_D^{20}$ = −3.1 (*c* = 3.71, $CHCl_3$) [ref.[12] −2.98 (*c* = 1.0, $CHCl_3$)]. - $C_{18}H_{34}O_4$ (314.47): calcd. C 68.75, H 10.90; found C 68.83, H 10.80.

(S)-(+)-3-Hydroxyhexadecanoic Acid (+)-**9**: A solution of 3.815 g (12.13 mmol) of (+)-**8** in 120 ml of methanol and 40 ml of 5 N KOH was heated under reflux for 45 min. After cooling to room temp. 20 ml of 10 N H_2SO_4 was added and the mixture was extracted twice with 300 ml of cyclohexane/diethyl ether (1:1). The combined extracts were dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on 450 g of silica gel (cyclohexane/AcOEt/AcOH, 67:33:2) to give 2.76 g (83%) of (+)-**9** as colorless crystals, R_f = 0.32. An analytical sample was crystallized from the tenfold amount of acetone, m.p. 78.7-79.5 °C (ref.[12] 77.0 °C), $[\alpha]_D^{20}$ = +12.4 (*c* = 1.97, $CHCl_3$) [ref.[12] +13.9 (*c* = 1, $CHCl_3$)]. - IR ($CHCl_3$): $\tilde{\nu}$ = 3600-3450 cm^{-1} (OH), 3450-2500 (CO_2H), 1709 (C=O). - ^1H NMR (CD_3OD): δ = 0.89 (m, 3 H, 16-H), 1.20-1.40 (23 H, 5-H to 15-H, OH), 1.46 (m, 2 H, 4-H), 2.35 (dd, *J* = 15.2, 7.9 Hz, 1 H, 2-H), 2.44 (dd, *J* = 15.2, 5.0 Hz, 1 H, 2-H), 3.96 (m, 1 H, 3-H), >8 (br, 1 H, CO_2H). - ^{13}C NMR (CD_3OD): δ = 14.4 (q, C-16), 23.7, 26.7, 30.5, 30.69, 30.73, 30.74, 30.78, 30.79, 30.80, 30.81, 33.1, 38.1, 43.2 (13 t, C-2,4 to C-15), 69.3 (d, C-3), 175.7 (s, CO_2H). - $C_{16}H_{32}O_3$ (272.43): calcd. C 70.54, H 11.84; found C 70.58, H 11.82.

(R)-(–)-3-Hydroxyhexadecanoic Acid (–)-**9**: Analogously prepared as described above for (+)-**9** from a solution of 3.500 g (11.13 mmol) of (–)-**8** in 120 ml of methanol and 40 ml of 5 N KOH. The residue was chromatographed on 450 g of silica gel (cyclohexane/AcOEt/AcOH, 67:33:2) to give 2.76 g (91%) of (–)-**9** as colorless crystals, R_f = 0.30. An analytical sample was sample was distilled, b.p. 150-155 °C/0.002 Torr, m.p. 79.2-79.6 °C (ref.[2] 77-79 °C), $[\alpha]_D^{20}$ = –12.6 (*c* = 2.08, $CHCl_3$) [ref.[2] –13.8 (*c* = 2.4, $CHCl_3$)]. - $C_{16}H_{32}O_3$ (272.43): calcd. C 70.54, H 11.84; found C 70.55, H 11.86.

(S)-(+)-Methyl 3-Hydroxyhexadecanoate (+)-**10**: A solution of 1.480 g (5.43 mmol) of (+)-**9**, 4.00 ml (3.88 g, 36.5 mmol) of trimethyl orthoformate and 840 mg (4.4 mmol) of *p*-toluenesulfonic acid in 45 ml of methanol was heated at reflux for 45 min. After cooling to room temp. the solvent was evaporated, 100 ml of water was added and the mixture was extracted twice with 300 ml of cyclohexane/diethyl ether (1:1). The extracts were dried (Na_2SO_4), the solvent was evaporated and the residue (1.59 g) was chromatographed on 250 g of silica gel (cyclohexane/AcOEt, 4:1) to provide 1.49 g (96%) of (+)-**10** as colorless crystals, R_f = 0.30, crystallized from 8 ml of acetone, m.p. 49.6-50.3 °C, $[\alpha]_D^{20}$ = +13.5 (*c* = 2.09, $CHCl_3$). - IR (CCl_4): $\tilde{\nu}$ = 3600-3450 cm^{-1} (OH), 1729 (C=O). - ^1H NMR ($CDCl_3$): δ = 0.86 (m, 3 H, 16-H), 1.20-1.60 (24 H, 4-H to 15-H), 2.39 (dd, *J* = 16.5, 8.9 Hz, 1 H, 2-H), 2.50 (dd, *J* = 16.5, 3.3 Hz, 1 H, 2-H), 2.82 (d, *J* = 4.0 Hz, 1 H, OH), 3.69 (s, 3 H, OCH_3), 3.98 (m, 1 H, 3-H). - ^{13}C NMR ($CDCl_3$): δ = 14.1 (q, C-16), 22.7, 25.5, 29.3, 29.50, 29.54, 29.56, 29.62, 29.63, 29.65, 29.66, 31.9, 36.5, 41.1 (13 t, C-2,4 to C-15), 51.7 (q, OCH_3), 68.0 (d, C-3), 173.5 (s, CO_2Me). - $C_{17}H_{34}O_3$ (286.46): calcd. C 71.28, H 11.96; found C 71.28, H 11.85. - (+)-**10** was treated with (+)-MTPA to furnish the ester with a CO_2CH_3 signal at δ = 3.56 in the ^1H NMR ($CHCl_3$) spectrum. The signal at δ = 3.64 of the diastereomeric ester could not be detected.

(R)-(–)-Methyl 3-Hydroxyhexadecanoate (–)-**10**: Analogously prepared as described above for (+)-**10** from a solution of 2.100 g (7.71 mmol) of (–)-**9**, 6.00 ml (5.81 g, 54.8 mmol) of trimethyl orthoformate and 1.30 g (6.83 mmol) of *p*-toluenesulfonic acid in 65 ml of methanol. The residue was chromatographed on 250 g of silica gel (cyclohexane/AcOEt, 4:1) to provide 2.15 g (97%) of (–)-**10** as colorless crystals, R_f = 0.28, crystallized from 10 ml of acetone, m.p. 49.6-50.3 °C (ref.[2] 49-50 °C), $[\alpha]_D^{20}$ = –13.8 (*c* = 1.48, $CHCl_3$) [ref.[2] –14.3 (*c* = 2.5, $CHCl_3$)]. - $C_{17}H_{34}O_3$ (286.46): calcd. C 71.28, H 11.96; found C 71.32, H 11.88. - (–)-**10** was treated with (+)-MTPA to furnish the ester with a CO_2CH_3 signal at δ = 3.64 in the ^1H NMR ($CHCl_3$) spectrum. The signal at δ = 3.56 of the diastereomeric ester could not be detected.

Mosher esters have been prepared according to Dale and Mosher[13] with (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (Fluka).

Acknowledgement: We thank the *Fonds der Chemischen Industrie* for support.

References and Notes

1. D. B. Boylan, P. J. Scheuer, *Science* **1967**, *155*, 52 - 56.
2. A. P. Tulloch, J. F. T. Spencer, *Can. J. Chem.* **1964**, *42*, 830 - 835.
3. W. Herz, R. P. Sharma, *J. Org. Chem.* **1976**, *41*, 1015 - 1020.
4. M. Nakahata, M. Imaida, H. Ozaki, T. Harada, A. Tai, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2186 - 2189.
5. M. Utaka, H. Watabu, H. Higashi, T. Sakai, S.Tsuboi, S. Torii, *J. Org. Chem.* **1990**, *55*, 3917 - 3921.
6. B. Küchler, G. Voß, H. Gerlach, *Liebigs Ann. Chem.* **1991**, 545 - 552.
7. C. Liu, J. K. Coward, *J. Org. Chem.* **1991**, *56*, 2262 - 2264.
8. G. Voß, H. Gerlach, *Liebigs Ann. Chem.* **1982**, 1466 - 1477.
9. P. Carlsen, T. Katshuki, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936 - 3938.
10. T. M. Willson, P. Kocienski, K. Jarowicki, K. Isaac, P. M. Hitchcock, A. Faller, S. F. Campbell, *Tetrahedron* **1990**, *46*, 1767 - 1782.
11. A. Börner, J. Ward, W. Ruth, J. Holz, A. Kless, D. Heller, H. B. Kagan, *Tetrahedron* **1994**, *35*, 10419 - 10430.
12. A. Yoshikawa, T. Sugimora, A. Tai, *Agric. Biol. Chem.* **1989**, *53*, 37 - 40.
13. J. A. Dale, H.S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512-519.

(*Received in UK* 27 *August* 1996; *accepted* 8 *October* 1996)