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Asymmetric Synthesis of Both Enantiomers of 4-Hexanolide, a Component of the Female Sex Pheromone from the Dermestid Beetle *Trogoderma Glabrum*

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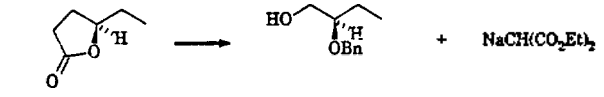
Optically active (R)- and (S)-2-benzyloxy-1-butanol have been prepared by a previously described asymmetric synthesis based on a chiral oxathiane and have been converted into (R)-(+)-4-hexanolide, a component of the pheromone secreted by the female of the dermestid beetle, and its enantiomer.

Introduction

(R)-(+)-4-hexanolide (**1**) is a component of the pheromone secreted by the female of the demestid beetle *Trogoderma glabrum*.[1] The beetle has been reported to respond to the (R)-isomer but to neither the (S)-isomer nor the racemate.[1]

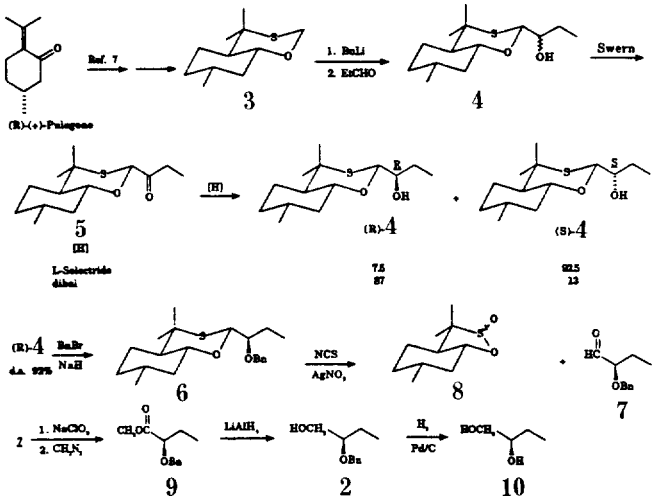
The preparation of optically active lactone **1** has received a great deal of synthetic attention, which may be categorized into three methods: 1) asymmetric reduction of suitable prochiral ketones with baker's yeast or chiral reducing agents,[2] 2) stereospecific synthesis from optically active starting materials such as glutamic acid[3a], D-(+)-ribolactone[3b], δ-D-(+)-gluconolactone[3c] and (R)-2,3-O-isopropylidene-D-glyceraldehyde[3d], 3) resolution of lactone precursors or lactones[4], and 4) other chiral methods such as Sharpless epoxidation[5a] or chiral sulfoxide methodology.[5b]

In the paper we report enantioselective syntheses of both enantiomers of 4-hexanolide, starting from 2-benzyloxy-1-butanol (**2**) which in turn, can be easily prepared based on chiral 1,3-oxathiane methodology.[6] As suggested in Scheme 1, the two-carbon homologation using malonate anion at the primary alcohol position followed by necessary manipulations of functional groups will lead to the product.



(R)-(+)-1 2

Scheme 1



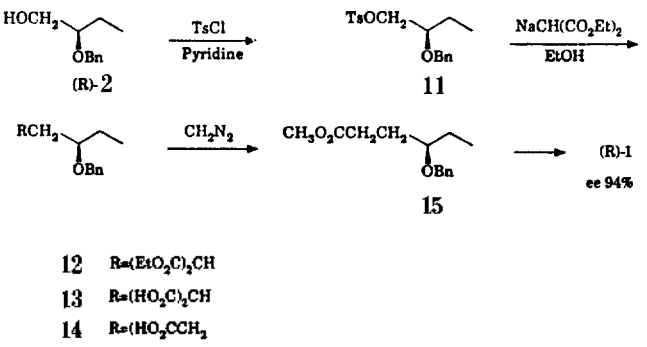
Scheme 2

Results and Discussion

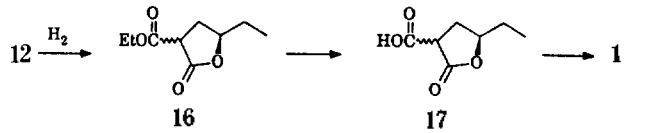
Optically active 2-alkoxy-1-butanol **2** was prepared starting from enantiomerically pure (2R, 4aS, 7R, 8aR)-4,4,7-trimethyl-4a,5,6,7,8,8a-hexahydrobenzoxathiane (**3**), as shown in Scheme 2. This oxathiane is obtained in three steps from the readily available (R)-(+)-pulegone.[7]

Treatment of oxathiane **3** with butyllithium followed by propionaldehyde gave a mixture of two diastereoisomers **4** in a nearly equal ratio. Subsequent Swern oxidation[8] of **4** and reduction of the resulting ethyl ketone **5** with L-Selectride (toluene, -78 °C) or dibal (toluene, -78 °C) gave the (S)- or (R)-carbinol in diastereomeric excess (d.e.) of 85% or 74%, respectively. The stereochemistry of reduction was determined by converting the oxathianyl alcohol **4** to 1,2-butanediol whose absolute configuration and sign of rotation were known in the literature (see below). In these reduction the formation of (S)- and (R)-isomer can be explained by Cram's chelate model and Cornforth's dipolar model, respectively.[9] Although the reductions are not completely stereoselective, the two diastereomers are easily separated and hence purified by flash chromatography[10] or HPLC on silica gel, presumably because intramolecular hydrogen bonding is more favorable, sterically, in one diastereomer ((R)-isomer, less polar) than in the other ((S)-isomer, more polar).

Benzylation of partially purified (R)-carbinol **4** (d.e. 92%) followed by cleavage of resulting benzyl ether **6** with N-chlorosuccinimide and silver nitrate[11] gave (R)-2-benzyloxy aldehyde **7** and sultines **8**. This aldehyde was in situ oxidized to acid with sodium chlorite[12] and esterified with diazomethane to methyl ester **9**. Separation of this ester from **8** using flash chromatography gave (R)-2-benzyloxy ester, $[\alpha]_D^{20}$ + 82.3 ($CHCl_3$), in overall yield of 80% from the oxathianyl alcohol (R)-**4**. Then, lithium aluminum hydride reduction gave (R)-(-)-2-benzyloxy alcohol **2**, $[\alpha]_D^{20}$-18.4($CHCl_3$).[13]



Scheme 3



Scheme 4

The enantiomeric purity of this alcohol was determined as follows.[14] Hydrogenolysis of **2** gave (R)-(+)-1,2-butanediol (**10**), $[\alpha]_D^{20}$ + 12.2 (c = 0.67, abs EtOH, lit. value, for (R)-isomer of 96% e.e. $[\alpha]_D^{20}$ + 11.92 (c = 2.13, EtOH)[13] which upon treatment with benzaldehyde gave a cis and trans mixture of 2-phenyl-1,3-dioxolanes. An examination of its proton NMR spectrum in the presence of chiral shift reagent Eu $(hfc)_3$ clearly showed 94% e.e., thus meaning no racemization during the reaction steps.

With 2-benzyloxy alcohol on hand, this alcohol was converted to the final product according to Scheme 3. Tosylation of (R)-alcohol **2**, followed by displacement of the tosyl group of tosylate **11** with sodio diethylmalonate gave the diester **12** in 86% yield. Saponification of **12** followed by decarboxylation of the resulting diacid **13** afforded a monoacid **14** in 91% yield from **12**. Finally, debenzylation of the methyl ester **15** obtained by methylation of **14** with diazomethane gave the final lactone **1**, $[\alpha]_D^{20}$ + 45.9 (MeOH). Similarly, starting from (S)-oxathianyl carbinol **4** (99% d.e.), (S)-lactone, $[\alpha]_D^{20}$-50.7 (MeOH) was obtained.

The enantiomeric purity of the lactone was determined by the method of Jakovac and Jones.[15] The (R)-lactone (oxathiane precursor d.e. 92%) and (S)-lactone (precursor d.e. 99%) was found to be 94% e.e. and 98% e.e., respectively.

Using another reaction sequences the (R)-diester **12** was converted to the (R)-lactone **1**, as shown in Scheme 4. Thus, the ester **12** (precursor d.e. 92%) was hydrogenolyzed to a mixture of two diastereomeric lactone **16**, which were hydrolyzed to acids **17**. Finally, decarboxylation by heating at 150-160 °C gave the (R)-lactone **1**, $[\alpha]_D^{20}$0 + 45.1 c = 1.89, MeOH) in 51% yield from **12**. The optical purity of this lactone was found to be 94% e.e. by the procedure of Jakovac and Jones.[15]

In summary, either enantiomer of 4-hexanolide was prepared from optically active 2-benzyloxy-1-butanol, which was easily available in high optical purity from chiral oxathiane auxiliary. The total yield was 30% in **12** steps or 36% in **11** steps from the oxathiane **3**.

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250

(250 MHz) spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used to designate the multiplicity of individual signals: s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = double doublet, dt = double triplet, m = multiplet. ^{13}C NMR were recored on a Bruker WM-250 (62.89 MHz) spectrometer using tetramethylsilane as an internal standard. ^1H NMR and ^{13}C NMR spectra were recorded in deuteriochloroform unless otherwise noted and are expressed in parts per million downfield from tetramethylsilane; couplings are in Hertz. Infrared(IR) spectra were recorded in carbon tetrachloride on a Beckman Model 4250 spectrophotometer. The following symbols are used to indicate approximate intensities of the IR absorption signals: W = weak, m = medium, s = strong, vs = very strong. Optical rotations were measured on a Perkin-Elmer Model 141 Polarimeter equipped with Na and Hg lights sources using a 10-cm thermostated cell at 20 °C.

2-(1R-Hydroxyethyl)-and 2-(1S-Hydroxyethyl)-1, 3-oxathiane (4). To a solution of 5.00g (25 mmol) of 1,3-oxathiane **3** in 100 m*l* of THF was added dropwise 16.4 m*l* (27.8 mmol) of 1.69 M butyllithium in hexanes over 5 min under nitrogen at -78 °C. After stirring for 10 hours, the solution was treated with 1.74g (30 mmol, 20% excess) of propionaldehyde in 20 m*l* of THF and the stirring was continued for 10 min at -78 °C. Then the reaction mixture was quenched with 20 m*l* of saturated ammonium chloride and 20 m*l* of water. The organic layer was separated, washed with brine and concentrated to give 6.32g (98% crude yield) of pale yellow oil as a mixture of diastereomer in a ratio of 53:47 ((R)-isomer: (S)-isomer), as determined by proton NMR spectrum. Purification by flash chromatography [hexanes-ethyl acetate (10:1)] gave 5.81 g of oil in 90% yield. (R)-isomer; ^1H NMR δ 4.68 (d, 1H, J = 7), 3.78 (m, 1H), 3.41 (dt, 1H, J = 10, 4), 2.97 (bs, 1H), 1.42 (s, 3H), 1.26 (s, 3H), 1.18 (d, 3H, J = 7), 0.93 (d, 3H, J = 7), and others; ^{13}C NMR δ 83.3, 76.9, 69.4, 50.7, 42.9, 41.6, 34.7, 31.3, 29.6, 24.3, 23.0, 22.1, 18.4; IR 3590 m, 2929 vs, 2960 vs, 1450 m, 1370 s, 1300 m, 1210 m, 1090 m, 1140 vs, 1080 s, 1060 vs, and other. (S)-isomer; ^1H NMR δ 4.91 (d, 1H, J = 4), 3.91 (double quartet, 1H, J = 6, 4), 3.44 (dt, 1H, J = 11, 4), 2.69 (bs, 1H), 1.41 (s, 3H), 1.28 (s, 3H), 1.23 (d, 3H, J = 7), 0.92 (d, 3H, J = 7), and others; ^{13}C NMR δ 83.1, 77.2, 69.3, 50.9, 42.6, 41.6, 41.6, 34.6, 31.3, 29.7, 24.3, 22.8, 22.1, 18.3; IR 3580 m, 2020 vs, 2860 s, 1450 m, 1370 m, 1150 vs, 1140 s, 1120 s, 1105 s, 1085 vs, 1060 vs, 1030 m, and others.

2-Propanoyl-1,3-oxathiane (5). To a solution of 3.12 g (40 mmol) of dimethyl sulfoxide in 100 m*l* of dry CH_2Cl_2 was added a solution of 6.30 g (4.24 m*l*, 30 mmol) of trifluoroacetic anhydride in 40 m*l* of dry CH_2Cl_2 over 10 min at -78 °C. After 30 min's stirring, the mixture was treated with a solution of 5.16 g (20 mmol) of alcohols **4** in 60 m*l* of CH_2Cl_2 over 30 min. The stirring was continued for additional 1 h. Then, 6.07 g (8.36 m*l*, 60 mmol) of triethylamine was added at -78 °C over 10 min and the mixture was allowed to warm to room temperature. Concentration of the yellow solution gave an oil, which was diluted with 200 m*l* of ether and washed successively with dilute HCl solution, 10% aqueous sodium carbonate and water. Drying, concentration and purification by flash chromatography provided 3.84 g (75%) of the ketone **5**, mp 48-49 °C. ^1H NMR δ 5.46 (s, 1H), 3.43 (dt, 1H, J = 11, 4), 2.68 (q, 2H, J = 7), 1.46 (s, 3H), 1.28 (s, 3H), 1.06 (t, 3H, J = 7), 0.94 (d, 3H, J = 7); ^{13}C NMR δ 206.1, 82.5, 77.0, 50.4, 43.9, 41.6, 34.6, 31.4, 31.3, 29.3, 24.3, 22.5, 22.0, 7.25; IR 2940 vs, 1720 vs, 1450 m, 1370 m, 1140 s, 1090 s, 1060 s, and others.

L-Selectride Reduction of 5. A solution of 2.56 g (10 mmol) of ketone **5** in 200 m*l* of dry toluene was treated with 15 m*l* of 1M solution of L-selectride in THF at -78 °C. After stirring for 4 h, the excess reducing agent was quenched with 10 m*l* of saturated NH_4Cl at -78 °C. Separation of toluene layer and concentration gave an oil. This oil was refluxed in 200 m*l* of 0.5M NaOH in methanol for several hours. The usual workup gave 2.34g (92%) of the (S)- and (R)-alcohols **4** in a ratio of 92.5:7.5.

Dibal reduction of 5. A solution of 1.28 g (5 mmol) of ketone **5** in 100 m*l* of dry toluene was treated with 7.5 m*l* of 1M dibal in hexanes at -78 °C. After stirring for 2h the solution was quenched with 5 m*l* of saturated NH_4Cl at -78 °C. The mixture was allowed to warm and the product was extracted with 2 × 50 m*l* of ether. Drying and concentration under reduced pressure gave 1.26 g (99% crude yield) of (R)- and (S)-alcohols **4** in a ratio of 87:13.

2-(1R-Benzyloxypropyl)-and 2-(1S-Benzyloxypropyl)-1,3-oxathiane (6). To a solution of 2.00 g (7.75 mmol) of alcohol **4** in 100 m*l* of THF was added 0.93 g (38.8 mmol) of NaH, followed by 1.52 g (8.91 mmol, 15% excess) of benzyl bromide. The mixture was refluxed under nitrogen for 10h. The excess NaH was quenched by dropwise addition of water. The organic layer was separated, dried and concentrated to give a crude oil, which was purified by flash chromatography [hexaneces-ethyl acetate (40:1)] to give 2.48 g (92%) of the benzyl ether as an oil. Similarly the (S)-isomer was prepared form the (S)-alcohol. (R)-isomer; ^1H NMR δ 7.39-7.27 (m, 5H), 5.03 (d, 1H, J = 7), 4.84, 4.60 (AB q, 2H, J = 12), 3.50-3.46 (m, 1H), 3.44 (dt, 1H, J = 7), 4.84, 4.60 (AB q, 2H, J = 12), 3.50-3.46 (m, 1H), 3.44 (dt, 1H, J = 11, 4), 1.41 (s, 3H), 1.27 (s, 3H), 0.94 (t, 3H, J = 7), 0.92 (d, 3H, J = 7), and others; ^{13}C NMR δ 138.9, 128.1, 127.8, 127.3, 82.4, 82.2, 77.1, 73.7, 50.7, 42.9, 41.8, 34.7, 31.4, 29.7, 24.3, 24.1, 22.8, 22.1, 9.79; IR 3100 w, 3080 m, 3040 m, 2980 s, 2940 vs, 2880 s, 1500 w, 1470 s, 1460 s, 1390 m, 1380m, 1370 m, 1210 m, 1210 m, 1190 m, 1155 vs, 1100 vs, 1070 vs, 1030 s, 1000 s, and others. (S)-isomer; ^1H NMR δ 7.40-7.24 (m, 5H), 5.01 (d, 1H, J = 5), 4.74, 4.59 (AB q, 2H, J = 12), 3.48-3.44 (m, 1H), 3.33 (dt, 1H, J = 10.4), 1.40 (s, 3H), 1.28 (s, 3H), 0.94 (t, 3H, J = 8), 0.92 (d, 3H, J = 7); ^{13}C NMR δ 138.8, 128.1, 127.9, 82.0, 81.8, 77.3, 72.5, 51.0, 42.5, 41.8, 34.8, 31.4, 29.8, 24.4, 24.1, 22.8, 22.1, 9.89; IR 3060 w, 3040 m, 2920 vs, 1460 s, 1380 m, 1210 m, 1190 m, 1150 s, 1090 vs, 1030 m, and others.

Methyl (R)-2-benzyloxybutanoate (9). A solution of 2.20 g (6.32 mmol) of (R)-benzyl ether **6** (precursor d.e. 92%) in 20 m*l* of acetone was added all at once to a stirred mixture of 2.52 g (18.9 mmol) of N-chlorosuccinimide, 2.67 g (15.7 mmol) of $AgNO_3$ and 1.57 g (18.9 mmol) of $NaHCO_3$ in 100 m*l* of 80% acetone in water at room temperature. A white precipitate was formed immediately. The mixture was stirred for 10 min, then treated with 3 m*l* of saturated Na_2SO_3 followed by 30 m*l* of saturated NaCl. AgCl was filtered and the filtrate was treated with 10 m*l* of 2-methyl-2-butene followed by a solution of 5.09 g (purity 80%, 45.9 mmol) of $NaClO_2$ and 5.72 g of KH_2PO_4 in 60 m*l* of water over 5 min at

room temperature. The stirring was continued for additional 30 min, then the organic solvent was removed under reduced pressure. The resulting aqueous solution was extracted with 3 × 50 m*l* of ether. The combined ethereal solution was dried and treated with excess ethereal diazomethane. After removal of ether, flash chromatography of the residue using hexances–ethyl acetate (10:1) provided 1.14 g (87%) of the ester [R_f = 0.30, hexanes–ethyl acetate (10:1)], $[\alpha]_D^{20}$ + 82.3 (c = 2.04, $CHCl_3$) and 1.07 g (85%) of sultines 8 (R_f = 0.20). Anal. Calc'd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.92; H, 7.84; ^{1}H NMR δ 7.36–7.30 (m, 5H), 4.70, 4.42 (ABq, 2H, J = 12), 3.90 (t, 1H, J = 6), 3.75 (s, 3H), 1.85–1.74 (m, 2H), 0.97 (t, 3H, J = 7); ^{13}C NMR δ 173.0, 137.8, 128.3, 127.9, 127.8, 79.3, 72.3, 51.6, 26.3, 9.70; IR 3040 m, 2980 s, 2960 vs, 2880 s, 1765 vs, 1750 s, 1470 s, 1460 s, 1440 s, 1400 m, 1340 m, 1300 s, 1270 s, 1200 vs, 1130 vs, 1090 s, 1080 s, 1050 s, 1030 s, and others. This ester was converted to (R)-1,2-butanediol (**10**), $[\alpha]_D^{20}$ + 12.2 (*c* = 0.67, abs EtOH) by $LiAlH_4$ reduction to alcohol **2**, $[\alpha]_D^{20}$–18.4 (*c* = 2.81, $CHCl_3$) followed by catalytic hydrogenolysis. Examination of the ^{1}H NMR spectrum of 2-phenyl-1,3-dioxolanes derived from diol in the presence of Eu $(hfc)_3$ showed that the diol's e.e. was 94%.[14]

(R)–2–benzyloxy–1–butanol (2). To a suspension of 190 mg (5 mmol) of $LiAlH_4$ in 50 m*l* of ether was added dropwise a solution of 1.04 g (5 mmol) of ester **9** (precursor d.e. 92%) in 20 m*l* of ether over 10 min at 0 °C. The excess $LiAlH_4$ was destroyed with sodium sulfate hydrate. The solid was filtered and the filtrate was concentrated. Kugelrohr distillation (120–130 °C, 0.2 mmHg) of the residue gave 0.86 g (96%) of the alcohol as a colorless oil, $[\alpha]_D^{20}$–18.4 (*c* = 2.81, $CHCl_3$); lit[13] for (R)-isomer of 96% e.e. $[\alpha]_D^{21}$–16.55 (*c* = 5.07, benzene); ^{1}H NMR δ 7.36–7.30 (m, 5H), 4.63, 4.54 (ABq, 2H, J = 12), 3.68, 3.55 (AB part of ABX). $HOCH_2CH(OBn)$–, 2H, J_{AB} = 11, J_{Bx} = 6, J_{BX} = 3), 3.51–3.41 (X part, $HOCH_2CH(OBn)$–, m, 1H), 2.02 (bs, 1H), 1.76–1.48 (m, 2H), 0.93 (t, 3H, J = 8); ^{13}C NMR δ 138.6, 128.5, 127.8, 127.7, 81.1, 71.5, 63.9, 23.6, 9.7. (S)-2-Benzyloxy-1-butanol was similarly prepared from methyl (S)-2-benzyloxybutanoate (precursor d.e. 99%). $[\alpha]_D^{20}$ + 21.0 (*c* = 2.15, $CHCl_3$).

2–Benzyloxybutyl–p–toluenesulfonate (11). A solution of 0.81 g (4.5 mmol) of alcohol **2** in 10 m*l* of pyridine was treated with 0.95 g (4.95 mmol) of p-toluenesulfonyl chloride at 0 °C. The resulting pale yellow solution was left overnight, then treated with 100 m*l* of ether and acidified with dilute HCl. The ethereal layer was separated, dried and concentrated to give 1.45 g (96%) of the tosylate as a colorless oil; ^{1}H NMR δ 7.77, 7.29 (ABq, 4H, J = 8), 7.35–7.24 (m, 5H), 4.57, 4.53 (ABq, 2H, J = 12), 4.06, 4.02 (AB part of ABX, $TsOCH_2$-CH–, 1H, J_{AB} = 11, J_{AX} = 2, J_{BX} = 3), 3.57–3.48 (X part, $TsOCH_2CH$–, m, 1H), 2.41 (s, 3H), 1.58–1.47 (m, 2H), 0.87 (t, 3H, J = 7); ^{13}C NMR δ 144.7, 138.1, 133.1, 129.8, 127.9, 127.7, 127.6, 77.6 72.1, 71.2, 24.2, 21.6, 9.4.

Diethyl (R)–3–Benzyloxy–1,1–pentanedicarboxylate (12). To a solution of sodium ethoxide in ethanol, prepared by dissolving 0.28 g (12 mmol) of sodium metal in 20 m*l* of ethanol was added 1.92 g (12 mmol) of diethyl malonate. The resulting solution was refluxed for 10 min. Then, a solution of 1.34 g (4 mmol) of (R)-tosylate **11** (oxathiane precursor d.e. 92%) in 10 m*l* of benzene was added over 5 min. The whole solution was refluxed for 30 h. The precipitate was filtered and the filtrate was concentrated to give an oil, which on kugelrohr distillation (130–140 °C, 0.02 mmHg) yield 1.15 g (89%) of the diester **12** as an oil, $[\alpha]_D^{20}$–29.1 (*c* = 2.76, $CHCl_3$). Anal. Calc'd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.72; H, 8.00; ^{1}H NMR δ 7.34–7.27 (m, 5H), 4.53, 4.40 (ABq, 2H, J = 11), 4.13 (q, 2H, J = 7), 4.10 (q, 2H, J = 7), 3.61 (dd, 1H, J = 9, 6), 3.43–3.33 (m, 1H), 2.23–2.01 (m, 2H), 1.69–1.57 (m, 2H), 1.24 (t, 3H, J = 7), 1.23 (t, 3H, J = 7), 0.93 (t, 3H, J = 8); ^{12}C NMR δ 169.7, 169.5, 138.6, 128.2, 127.8, 127.5, 77.7, 71.0, 61.2, 48.7, 32.8, 26.2, 14.1, 14.0, 9.16; IR 3040 m, 1980 s, 2940 s, 1760 vs, 1740 vs, 1380 s, 1330 s, 1305 s, 1265 s, 1230 s, 1180 s, 1155 vs, 1100 s, 1070 s, 1030 s, and others.

(R)–3–Benzyloxyl–1, 1–pentanedicarboxylic acid (13). A solution of 1.01 g (3.14 mmol) of the diester **12** and 0.83 g (12.6 mmol) of KOH in 30 m*l* of 80% ethanol in water was refluxed for 2h. Then, ethanol was distilled with water being added. The resulting aqueous solution was acidified with dilute HCl and extracted continuously with ether overnight. The ethereal extract was dried and concentrated to give 0.83 g (98%) of the diacid as a pale yellow oil, which was used for the next step without further purification; ^{1}H NMR δ 10.76 (bs, 2H), 7.30 (s, 5H), 4.58, 4.38 (ABq, 2H, J = 11), 3.67 (t, 1H, J = 7), 3.50–3.30 (m, 1H). 2.20–2.00 (m, 2H), 1.80–1.40 (m, 2H), 0.92 (t, 3H, J = 7).

(R)–4–Benzyloxy–1–hexanoic acid (14). A solution of 0.83 g (3.12 mmol, oxathiane precursor d.e. 92%) of the diacid **13** in 7 m*l* of 2,6-lutidine was refluxed for 2h. Then, the solution was treated with 50 m*l* of ether and acidified with dilute HCl. The product was extracted continuously with ether overnight. The ethereal extract was dried and concentrated to give 0.64 g (93%) of the monoacid as a pale yellow oil, $[\alpha]_D^{20}$–11.6 (*c* = 2.76, abs EtOH); ^{1}H NMR δ 9.70 (bs, 1H), 7.32 (s, 5H), 4.56, 4.48 (ABq, 2H, J = 11), 3.42–3.29 (m, 1H), 2.54–2.40 (m, 2H), 1.96–1.74 (m, 2H), 1.68–1.46 (m, 2H), 0.94 (t, 3H, J = 6); ^{13}C NMR δ 179.7, 138.6, 128.3, 127.7, 127.5, 79.0, 70.9, 30.1, 28.2, 26.1, 9.43.

Methyl (R)–4–benzyloxyhexanoate (15). A solution of 0.73 g (3.29 mmol) of the acid **14** (precursor d.e. 92%) in 20 m*l* of ether was treated with excess diazomethane. Concentration and Kugelrohr distillation (110–120 °C, 0.1 mmHg) of the residue provided 0.73 g (95%) of the methyl ester as a colorless oil, $[\alpha]_D^{20}$–22.5 (*c* = 3.02, $CHCl_3$). Anal. Calc'd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.94; H, 8.66; ^{1}H NMR δ 7.32–7.24 (m, 5H), 4.54, 4.45 (ABq, 2H, J = 11), 3.64 (s, 3H), 3.38–3.28 (m, 1H), 2.53–2.34 (m, 2H), 1.96–1.44 (m, 4H), 0.94 (t, 3H, J = 8); ^{13}C NMR δ 174.1, 138.9, 128.2, 127.7, 127.4, 79.1, 70.8, 51.4, 30.0, 28.5, 26.2, 9.43; IR 3040 w, 2980 m, 1750 vs, 1360 m, 1170 s, 1095 s, 1070 s, 1030 m, and others.

(R)–4–Hexanolide (1) by debenzylation of 15. A solution of 0.70 g (2.99 mmol) of the methyl ester **15** (precursor d.e. 92%) in 40 m*l* of methanol was hydrogenated at room temperature and 50 psi in the presence of 0.20 g of 10% Pd on carbon for 30 min. Removal of catalyst, concentration of the filtrate and Kugelrohr distillation (80–90 °C, 6 mmHg) of the residue gave 0.29 g (85%) of the lactone, $[\alpha]_D^{20}$ + 45.9 (*c* = 3.47, MeOH)[lit.[3a] $[\alpha]_D^{20}$ + 53.2 (*c* = 1, MeOH)]. The optical purity was found to be 93% e.e. by the procedure of Jakovac and Jones.[15] Similarly the (S)-lactone, $[\alpha]_D^{20}$–50.7 (*c* = 2.36, MeOH) was prepared from the (S)-alcohol **2** (oxathiane precursor d.e. 99%). The e.e. of the lactone was found to be

98%.

cis-and trans-2-Ethoxycarbonyl-4-hydroxyhexanoic acid lactone (16). A solution of 1.20 g (3.73 mmol) of the diethyl ester **12** in 30 m*l* of ethanol was hydrogenated at room temperature and 50 psi in the presence of 0.24 g of 10% Pd on carbon for one day. Filtration, concentration and Kugelrohr distillation (100–110 °C, 0.05 mmHg) provided 0.82 g (95%) of the lactones as an equal mixture of cis and trans isomer. Anal. Calc'd for $C_9H_{14}O_4$: C,58.05; H. 7.58. Found: C, 57.78; H, 7.56. ^{1}H NMR δ 4.62 (quintet, J = 7), 4.47–4.36(m) 1H; 4.29 (q, J = 7) 2H; 3.68–3.57 (m, 1H); 2.74–2.50 (m), 2.38–2.05 (m) 2H: 11.83 (q, J = 7), 1.73 (q, J = 7) 2H; 1.33 (t, J = 7), 1.31 (t, J = 7) 3H; 1.03 (t, J = 8), 1.02 (t, J = 8) 3H; ^{13}C NMR δ 171.8; 168.0; 81.4, 80.7; 62.1, 62.0; 47.5, 47.1; 31.8, 31.7; 28.5, 28.3; 14.1; 9.37.

cis-and trans-2-Carboxy-4-hydroxyhexanoic acid lactone (17). were prepared from a mixture of two ethyl esters **16** as described for the diacid **13**.

(R)-4-Hexanolide (1) by decarboxylation of 17. A mixture of 0.36 g (2.28 mmol) of the acids **17** (precursor d.e. 92%) was heated at 150–160 °C on a Kugelrohr distillation apparatus with a concomitant distillation of the lactone at 30 mmHg to give 0.25 g (96%) of the lactone, $[\alpha]_D^{20}$ + 45.1 (c = 1.89, MeOH). The optical purity of the lactone was found to be 94% by the procedure of Jacovac and Jones.[15]

(R)-1,2-butandiol (10). A solution of 150 mg (0.83 m mol) of benzyl ether **2** (precursor d.e. 92%) in 20 m*l* of methanol was hydrogenated at room temperature and 50 psi in the presence of 0.05 g of 5% palladium on carbon for 10h. The usual workup gave 65 mg (87%) of diol after kugelrohr distillation (95–100 °C, 10 m mHg), $[\alpha]_D^{20}$ + 12.2 (c = 0.67, abs EtOH); lit[13] for (R)-isomer of 96% e.e. $[\alpha]_D^{20}$ + 11.92 (c = 2.13, EtOH); ^{1}H NMR δ 3.70–3.60 (m, 2H), 3.51–3.41 (m, 1H), 2.86 (bs, 2H), 1.47 (apparent quintet, 2H, J = 7), 0.97 (t, 3H, J = 7).

Determination of the Enantiomeric Excess of the lactone. The enantiomeric excess of the lactone was determined according to a procedure introduced by Jakovac and Jones.[15] This procedure involves the treatment of a lactone with excess methyllithium followed by proton NMR examination of the resulting diol (in the present case, 2-methyl-2,5-heptanediol) in the presence of a chiral lanthanide shift reagent Eu(tfc)$_3$. Thus, this diol, in the absence of any chiral shift reagent, showed two distinct signals at 1.224 ppm and 1.215 ppm (CCl_4:CD_2Cl_2 = 1:1) due to the two diastereomeric methyl groups. In the presence of 15–20% of Eu(tfc)$_3$ each of the two methyl signals was observed to separate into two peaks, with the higher field signal later shown to be due to the (R)-isomer. Of the two methyl signals, the higher field on was more useful because it showed better sensitivity to the shift reagent.

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