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Synthesis and configurational assignment of (*R*) and (*S*)-2-bromohexadecanoic acids

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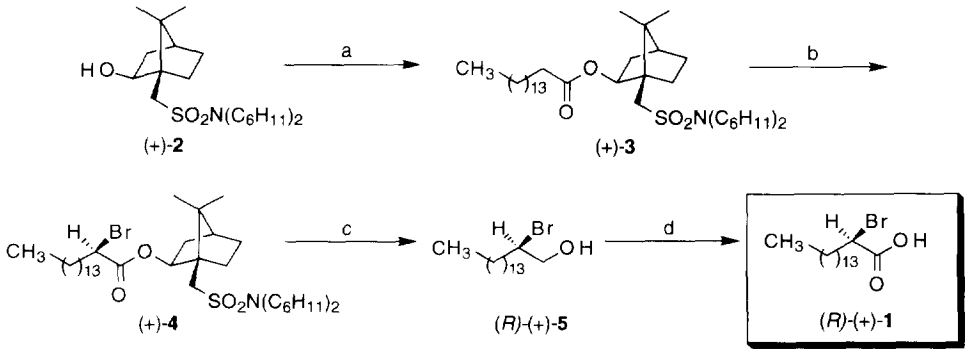
Abstract: Synthesis of both enantiomers of 2-bromohexadecanoic acid is described by diastereoselective bromination of esters (+)- and (-)-**3** followed by removal of the chiral auxiliary. The absolute configuration of the acids is confirmed by an independent chemical synthesis from chiral pool precursors.

In our ongoing studies on the β-oxidation of fatty acids precursors in the biosynthesis of lepidopteran sex pheromones, we became interested in the design and synthesis of potential inhibitors of this process.[1-3] In this context, we found (±)-2-bromohexadecanoic acid (**1**) to be a potent inhibitor in our model biological system. In order to gain insight into the stereoselectivity of this action, both enantiomers of this acid were required to be separately tested in our bioassay. Although the preparation of (+)-**1** was described in the literature by enantioselective lipase-catalyzed esterification of (±)-**1** with *n*-butanol,[4] neither its absolute configuration nor its enantiomeric excess were definitely proved. On the other hand, since (−)-**1** was obtained as the corresponding butyl ester, a hydrolytic system should be developed to avoid the epimerization at the stereogenic carbon. In this regard, the strongly acidic proton at this position may be readily epimerized even under mild conditions, as previously shown for related examples.[5] In this paper we wish to report on the total synthesis of both enantiomers of 2-bromohexadecanoic acid **1**, the quantification of their enantiomeric excess by GC with an appropriate chiral capillary column and the unambiguous assignment of their absolute configurations by chemical synthesis from chiral pool precursors.

Homochiral 2-bromocarboxylic acids can be easily prepared from the corresponding α-amino acids by a classical and well established enantioselective diazotisation and bromide displacement process.[6,7] Recently, this method has been successfully applied to the synthesis of (*R*)-2-bromodecanoic acid from commercially available (*R*)-2-aminodecanoic acid.[8] Although the preparation of the homochiral 2-aminohexadecanoic acids required in our case is decribed in the literature by a multistep procedure based on the enantioselective enzymatic resolution of the corresponding racemic N-acyl derivatives,[9] we were interested in a diastereoselective approach based on chiral auxiliaries.[10]



a: hexadecanoyl chloride, toluene, AgCN (97%). b: 1) LDA, hexane, -78°C; 2) TMSCl, THF; 3) NBS (72%). c: $NaBH_4$, $CaCl_2$, THF (60%). d: $NaIO_4$, $RuCl_3$ cat., $CCl_4/CH_3CN/H_2O$ (73%)

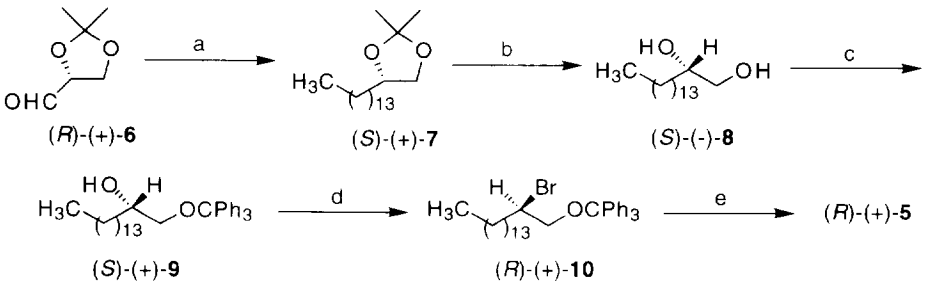
SCHEME 1

In this context, we selected isoborneol derivatives (+) and (-)-**2**, introduced by Oppolzer,[11] which have found application, among others, in the diastereoselective α-halogenation of ester derivatives as precursors of homochiral epoxides.[12,13] Thus, generation of the lithium enolate of (+)-**3**, obtained by reaction of hexadecanoyl chloride with chiral auxiliary (+)-**2** and LDA followed by quenching with TMSCl, and *in situ* reaction with NBS afforded a mixture of bromoesters (+)-**4** in 70-80% diastereomeric excess, based on the relative integrations of the CH-Br proton by ^1H NMR (Scheme 1).[14]Attempts to remove the chiral auxiliary by hydrolysis were unsuccessful. Thus, under basic conditions (LiOOH-THF [5] or LiOH-THF-H_2O[15]) mixtures of partially epimerized **4** and racemized 2-bromohexadecanoic acid were obtained. On the other hand, acid treatment (AcOH-6N HCl[16], HCl-dioxane, or HCl(g)-Et_2O) was hampered by solubility problems of our substrate. Finally, hydrolysis under more drastic conditions (AcOH-CH_3SO_3H, 90°C[17]) led to a complex mixture of products. In the light of these results we decided to remove the chiral isoborneol auxiliary by reduction of (+)-**4** to *R*(+)-**5**, under the conditions previously described by Oppolzer ($NaBH_4$-$CaCl_2$),[13] followed by oxidation of the resulting bromoalcohol to 2-bromohexadecanoic acid *R*(+)-**1**. Thus, by using this reduction procedure, bromoalcohol (*R*)-(+)-**5** was obtained in 68% yield with unchanged chirality at the stereogenic center, as revealed by derivatization to the corresponding MTPA ester.[18] Concerning the oxidation step, a major problem associated with our compound is the presence of a readily epimerizable position next to the newly formed carboxylic function. Among the methods described in the literature for the oxidation of alcohols,[19] Sharpless oxidation of (*R*)-(+)-**5** was considered the most suitable, due to its well precedented compatibility with epimerizable stereogenic centers.[20] Thus, under the standard reaction conditions for this process ($NaIO_4$-$RuCl_3$ cat, CCl_4, CH_3CN, H_2O), alcohol (*R*)-(+)-5 was oxidized to bromoacid (*R*)-(+)-**1** without racemization at C-2 (see below) in 84% yield ($[\alpha]^{25}_D$ +13.8 (c 0.45, $CHCl_3$)).

An unanticipated difficulty in this study was the determination of the enantiomeric purity of the resulting bromoacid (*R*)-(+)-**1**. Initial attempts by derivatization with (*S*)-(+)-methyl mandelate under standard conditions (DCC, DMAP, CH_2Cl_2, 1h, rt)[21] showed an unexpectedly low ee, an indication that partial racemization had taken place in the course of the derivatization reaction. This hypothesis was confirmed when commercially available (*S*)-(-)-2-bromopropionic acid was reacted under the above conditions to yield a mixture of diasteromeric esters of only 10% de.[22] Finally, the enantiomeric purity of (*R*)-(+)-**1** could be determined by derivatization with diazomethane and GC analysis of the corresponding methyl esters on a chiral capillary

column containing a 1:1 mixed phase of SE-54 and heptakis(2,3-di-O-pentyl)-6-*tert*-butyldimethylsilyl-β-cyclodextrin.[23] The enantiomeric excess of (*R*)-(+)-**1** thus calculated was 70%, which is in agreement with that calculated for (*R*)-(+)-**5** via Mosher ester analysis. Similarly, starting from chiral auxiliary (-)-**2**, enantiomeric bromoacid (*S*)-(-)-**1** was obtained in comparable overall chemical yields and enantiomeric excess.

Although the diastereoselectivity of the halogenation of the enolates generated from esters **3** can be explained on the basis of the mechanistic model proposed by Oppolzer,[13] we were interested in the development of an alternative synthesis which would enable us to unambiguously confirm the above assignments. Thus, the absolute configuration of bromoacids **1** was confirmed through the enantioselective route outlined in Scheme 2, in which the synthesis of (*R*)-(+)-**5** starting from (*R*)-(+)-glyceraldehyde[24] (**6**) was envisaged.



a: 1) 1-tridecylphosphonium iodide, BuLi, THF, -78°C (85%, *Z*/*E* 3/1); 2) H_2, Pd/C, MeOH (95%)
b: 2N HCl, THF-H_2O, rt (95%). c: Ph_3CCl, DMAP, pyr (87%). d: 1)Tf_2O, CH_2Cl_2, -78°C;
2) LiBr, CH_3CN . e: 1N HCl, acetone-H_2O (53% steps d and e)

SCHEME 2

The key step in this sequence was the stereocontrolled introduction of the bromine atom at the C2 position of trityl derivative (*S*)-(+)-**9**. The best results were obtained by conversion of the secondary alcohol into the corresponding triflate followed by *in situ* displacement with an equimolar amount of LiBr in CH_3CN. As expected,[25] the reaction took place with inversion of configuration at the stereogenic center to give bromide (*R*)-(+)-**10**, which, after trityl removal, afforded bromoalcohol (*R*)-(+)-**5**, identical to that obtained by the above synthetic route.

In summary, we have prepared both enantiomers of 2-bromohexadecanoic acid under non epimerizable conditions and unambiguously assigned for the first time their absolute configuration. Studies addressed to the stereoselectivity of our biological system towards these compounds are currently underway.

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Experimental

General. Elemental analyses were determined on Carlo Erba models 1107 and 1500. IR spectra were recorded on a Bomem MB-120 with Fourier transform instrument. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions on a Varian Gemini 200 and a Varian Unity 300 spectrometers, operating at 200 and 300 MHz for ^1H and 50 and 75 MHz for ^{13}C, respectively. The values are expressed in δ scale relative to internal Me_4Si. Optical rotations were measured on a Perkin Elmer 141 polarimeter. Commercial analytical-grade reagents were obtained from commercial suppliers (Aldrich Chemie, Fluka Chemie, Janssen Chimica) and were used directly without further purification. Solvents were distilled prior to use and dried by standard methods.[26] GC analyses were performed on a Carlo Erba 4130 instrument equipped with a FID detector, using a fused silica capillary column SPB-5 30m x 0.25 mm i.d. using hydrogen as carrier gas. For chiral GC (compounds (*R*)-(+)-**1** and (*S*)-(-)-**1** methyl esters), a HP 5890 chromatograph equipped with a Chrom-Card (Fisons) data acquisition system and a Silica Siemens capillary column 20m x 0.25 mm with a 1:1 mixed phase (0.28% SE-54: 0.28 heptakis(2,3-di-O-pentyl)-6-*tert*-butyldimethylsilyl-β-cyclodextrin) was used. Column temperature: isotherm 155°C, carrier gas: 11 psi, injector temp 270°C.[23] Retention times: (*S*)-(-)-**1** methyl ester, 107 min; (*R*)-(+)-**1** methyl ester, 111 min. Enantiomeric purity of compounds **5** and **8** was determined by derivatization *via* a modified Mosher ester procedure.[18]

(*1R,2S,4S*)-(+)-1-Dicyclohexylsulfamoylmethyl-7,7-dimethylbicyclo[2.2.1]hept-2-yl hexadecanoate ((+)-3). To a solution of 540 mg (1.36 mmole) of 10-dicyclohexylsulfamoyl-D-isoborneol in 3 ml of anh. toluene containing 277 mg (2 mmole) of silver cyanide was added dropwise under argon a solution of 681 mg (2.8 mmole) of palmitoyl chloride in 6 ml of anhydrous toluene. The mixture was refluxed for 6 h, cooled and diluted with ether. After treatment with 2N NaOH soln., the solid (sodium palmitate) was filtered off and washed with ether. The organic extract was washed with brine and dried (Na_2SO_4) to afford 840 mg (97%) of ester (+)-**3**, pure enough to be used in the following step of the synthetic sequence. $[\alpha]_D^{25}$ +23.1 (c 1.56, $CHCl_3$). Anal. Calcd. for $C_{38}H_{69}NO_4S$: C, 71.76%; H, 10.93%; N, 2.20%; S, 5.04%. Found: C, 71.64%; H, 10.88%; N, 2.24%, S, 4.82%. IR (film): 2925, 2852, 1737, 1465, 1454 cm^{-1}. ^1H-NMR (200 MHz, $CDCl_3$): δ 4.89 (dd, J= 8.4; 3.2 Hz; 1H; O-CH); 3.2 (m; 3H; 2CH cyclohexyl + H-CHSO$_2$); 2.61 (d, J=13.2 Hz; 1H; H-CHSO$_2$), 2.40 (t; J=7.6 Hz; 2H; CH$_2$-CO); 1.94 (m; 2H; CH$_2$-CH$_2$-CO); 1.8-1.5 (b; 20H; 10CH$_2$), 1.20 (b; 31H, 12CH$_2$ + 7H bicyclo); 0.94 (s; 3H; CH$_3$); 0.84 (s; 3H; CH$_3$); 0.84 (t; J=6.3 Hz; 3H; H$_2$C-CH$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.0 (CO), 78.3 (CH-O); 57.4 (CH cyclohexyl); 53.6 (CH$_2$-SO$_2$); 49.3 (q); 49.0 (q); 44.4 (CH); 39.6; 34.6; 32.7; 31.9; 30.1; 29.6; 29.5; 29.4; 29.3; 29.2; 27.0; 26.5; 25.2; 24.8; 22.6; 20.4 (CH$_3$); 20.0 (CH$_3$); 14.1 (CH$_3$).

(*1S,2R,4R*)-(-)-1-Dicyclohexylsulfamoylmethyl-7,7-dimethylbicyclo[2.2.1]hept-2-yl hexadecanoate ((-)-3). Following identical procedure and starting from 433 mg (1.09 mmole) of 10-dicyclohexylsulfamoyl-L-isoborneol, ester (-)-**3** was obtained in 98% yield (680 mg).

$[\alpha]_D^{25}$ -23.1 (c 1.54; $CHCl_3$). Anal. Calcd. for $C_{38}H_{69}NO_4S$: C, 71.76%; H, 10.93%; N, 2.20%; S, 5.04%. Found: C, 71.73%; H, 11.08%, N, 2.15%; S, 4.82%.

(*2R,1'R,2'S,4'S*)-(+)-1'-Dicyclohexylsulfamoylmethyl-7',7'-dimethylbicyclo-[2.2.1]hept-2'-yl 2-bromohexadecanoate ((+)-4). To 0.15 ml of a 1.95N LDA solution in hexane (0.30 mmole) was added dropwise, at -78°C under argon, 189 mg (0.30 mmole) of ester (+)-**4** in 1 ml of anh. THF. The mixture was stirred for 10 min and then 70 µl of trimethylsilyl chloride (0.55 mmole) in 1 ml of anh. THF was added. The reaction mixture was further stirred for 20 min and then 64 mg (0.36 mmole) of N-

bromosuccinimide were added. The mixture was allowed to warm up to room temperature and the reaction was monitored by TLC until completion. After 1 h at room temperature, the reaction was quenched by addition of saturated NH_4Cl aqueous solution The aqueous layer was extracted with ether and the organic layer washed with brine and dried (Na_2SO_4). The solvent was removed and the crude purified by flash column chromatography eluting with hexane:ethyl acetate 9:1 to yield 160 mg (75%, 70% de) of **(+)-4**. $[\alpha]^{25}_D$ +26.1 (c 3,90, $CHCl_3$). Anal. Calcd. for $C_{38}H_{68}BrNO_4S$: C, 63.84%; H, 9.59%. Found: C, 63.72%; H, 9.62%. IR (film): 2925; 2852; 1733 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.93 (dd; J=7.8; 2.7 Hz; 1H; CH-O); 4.21 (dd; J=8.7; 5.7 Hz; 1H; CH-Br major diastereomer); 4.14 (dd; J=8.4; 6.0 Hz; 1H; CH-Br minor diastereomer); 3.26-3.19 (c; 3H; 2CH cyclohexyl + H-C<u>H</u>-SO_2); 2.63 (d; J=6.6 Hz; 1H; <u>H</u>-CH-SO_2); 2.61 (d; J=6.6 Hz; 1H; <u>H</u>-CH-SO_2); 1.97 (m; 2H; C<u>H</u>$_2$-CHBr); 1.73-1.58 (c; 20H; 10CH_2 cyclohexyl); 1.21 (b; 31H; 12CH_2 + 7H bicyclo); 0.98 (s; 3H; CH_3); 0.85 (s; 3H; CH_3); 0.84 (t; J=6.8 Hz; 3H; H_2C-C<u>H</u>$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.0 (CO); 80.2 (CH-O); 57.4 (2CH cyclohexyl); 53.6 (CH_2-S); 49.5 (q); 49.2 (q); 48.0 (CH-Br); 44.3 (CH); 39.3 (<u>C</u>H_2-CBr); 35.2; 33.2; 32.3; 31.9; 30.4; 29 6; 29.5; 29.4; 29.35; 29.32; 28.6; 27.2; 27.0; 26.4; 25.2; 22.6; 20.4 (CH_3); 20.0 (CH_3); 14.1 (CH_3).

(2*S*,1'*S*,2'*R*,4'*R*)-(-)-1'-Dicyclohexylsulfamoylmethyl-7',7'-dimethylbicyclo-[2.2.1]hept-2'-yl 2-bromohexadecanoate ((-)-4). Following the same procedure, from 505 mg of ester (-)-**3** 420 mg (72%, 81% de) of ester (-)-**4** was obtained. $[\alpha]^{25}_D$-26.0 (c 1.44, $CHCl_3$).

(*R*)-(+)-2-Bromo-1-hexadecanol ((*R*)-(+)-5). *Method A.* In a 25 ml Schlenk flask was placed under argon 20 mg (0.5 mmole) of $NaBH_4$. The flask was cooled at 0°C and then 44 mg (0.4 mmole) of anh. $CaCl_2$ and 0.5 ml of anh. THF were added. The resulting suspension was stirred for 30 min. and cooled to -10°C. Then, 185 mg (0.37 mmole) of bromoester (+)-**4** in 2 ml of anh. THF was slowly added. The reaction mixture was brought to room temperature and stirred for 10 h. After quenching with 1N HCl and extracting with ether, the organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded a crude, which was purified by flash column chromatography eluting with hexane:ethyl acetate 9:1 to yield 107 mg (70% recovery) of the chiral auxiliary and 81 mg (68%, 70% ee) of alcohol **(*R*)-(+)-5**. $[\alpha]^{25}_D$ +12.6 (c 1.66, $CHCl_3$). Anal. Calcd. for $C_{16}H_{33}BrO$: C, 59.80%; H, 10.35%. Found: C, 59.76%; H, 10.40%. mp: 30-31°C. IR (film): 3650-3200; 2923; 2852 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.13 (m; 1H; CH-Br); 3.76 (m; 2H; CH_2-O); 1.98 (m; 1H; <u>H</u>-CH-CBr); 1.83 (m; 2H; H-C<u>H</u>-CBr + O<u>H</u>); 1.50 (m; 1H; H-C4); 1.40 (m; 1H; H-C4); 1.23 (sa; 22H; 11CH_2); 0.86 (t; J=6.9 Hz; 3H; CH_3). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 67.3 (CH_2-O); 60.2 (CH-Br); 35; 32; 29.6; 29.5; 29.4; 29.3; 28.9; 27; 23; 14.1.

Method B. A solution of 496 mg (0.99 mmole) of alcohol (*S*)-(+)-**9** in 3 ml of anh. CH_2Cl_2 was placed under argon in a Schlenk flask. Then, 2,6-lutidine (138µl, 1.18 mmole) and a solution of 195µl (1.18 mmole) of triflic anhydride in 1 ml of anh. CH_2Cl_2 were added at -78°C. The mixture was stirred for 20 min., warmed to 0°C and then 86 mg (0.99 mmol) of LiBr, previously dried at 200°C for 12 h, in 2 ml of anh. CH_3CN was added. The reaction mixture was further stirred for 3 h, quenched with water and extracted with CH_2Cl_2. The organic phases were washed with brine, dried (Na_2SO_4), and evaporated to afford a mixture of (*R*)-(+)-**10**, bromoalcohol (*R*)-(+)-**5**, and triphenylmethanol in a relative ratio of 2:1:1. A sample of pure (*R*)-(+)-**10** was obtained by chromatography on alumina (act III) eluting with mixtures of hexane:toluene. $[\alpha]^{25}_D$ +6.3 (c 0.9, $CHCl_3$). HRMS Calcd. for $C_{35}H_{47}BrO$: 563.668; Found: 563.650. mp: 61-63°C. IR (film): 3080; 3063; 3031; 3022; 2923; 2852; 1595; 1490; 1465; 1448; 1064; 786; 775; 763 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): ∂ 7.48-7.19 (m; 15H; 3Ph); 3.94 (m; 1H; CH-Br); 3.37 (dd, J= 10.0; 5.7 Hz; 1H; <u>H</u>CH-O); 3.32 (dd, J= 10.0; 6.3 Hz; 1H; HC<u>H</u>-O); 1.92 (m, 1H; <u>H</u>CH-CH_2Br); 1.77 (m; 1H; HC<u>H</u>-CH_2Br); 1.23 (b; 24H;

$12CH_2$); 0.86 (t; J= 6.9 Hz; 3H; CH_3). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 143.8 (3 *ipso*-C ar.), 128.6 (6 *o*-CH ar.); 127.8 (6 *m*-CH ar.); 127.0 (3 *p*-CH ar.); 86.7 ($\underline{C}Ph_3$); 67.4 (CH_2-O); 54.5 (CH-Br); 35.4; 31.9; 29.6; 29.5; 29.4; 29.3; 28.9; 27.1; 22.7; 14.1. The above crude mixture was dissolved in 40 ml of a 1:1 mixture of acetone and 2N HCl, and heated to reflux for 12 h. After cooling, the reaction mixture was extracted with ether and the organic phase washed with 0.5N NaOH aq. solution and brine, dried (Na_2SO_4), and evaporated to give a solid which, after purification by flash chromatography on elution with hexane/EtOAc 9:1 afforded bromoalcohol (*R*)-(+)-**5** (170 mg, 68% ee, 53% overall yield from (*S*)-(+)-**9**).

(*S*)-(-)-2-Bromo-1-hexadecanol ((*S*)-(-)-5). Following method A, 204 mg of (-)-**4** afforded 55mg (60%) of (*S*)-(-)-**5**. $[\alpha]^{25}_D$ -13.5 (c 1.14, $CHCl_3$).

(*R*)-(+)-2-bromohexadecanoic acid ((*R*)-(+)-1). A solution of 25 mg (0.08 mmole) of alcohol (*R*)-(+)-**5** in 0.5 ml CCl_4 and 0.5 ml CH_3CN was treated with 0.75 ml H_2O, 68 mg (0.32 mmole) $NaIO_4$ and 6 mg $RuCl_3$•3 H_2O. The resulting heterogeneous mixture was vigorously stirred at room temperature and monitored by TLC until consumption of the starting material. The reaction mixture was then diluted with 5 ml CH_3CN, the remaining solids were centrifuged off, and the solution was evaporated to dryness under reduced pressure to give a solid, which was taken up in 15 ml CH_2Cl_2 and washed with water. The organic phase was dried (Na_2SO_4), filtered and evaporated to give crude acid, which was purified by boiling in hexane in the presence of charcoal. Filtration and evaporation afforded (*R*)-(+)-**1** as a white solid (22 mg, 84%, 70% ee, based on chiral GC of the methyl ester). $[\alpha]^{25}_D$ +13.8 (c 0.45; $CHCl_3$). IR(film): 3300-2500, 2848, 1701 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.91 (bs; 1H; COOH); 4.22 (t; J=7,4 Hz; 1H; CH-Br); 2.01 (m; 2H; $C\underline{H}_2$-CHBr); 1.24 (sa; 24H; $12CH_2$); 0,86 (t; J=6,7 Hz; 3H; CH_3). ^{13} C-NMR (50 MHz, $CDCl_3$): δ 175.6(CO); 45.3(CH-Br); 34.6($\underline{C}H_2$-CBr); 31.9, 29.6, 29.5, 29.4, 29.3, 28.8, 27.2, 22.6, 14.1(CH_3).

(*S*)-(-)-2-bromohexadecanoic acid ((*S*)-(-)-1). Following the same procedure, 34 mg (0.11 mmole) of (*S*)-(-)-**5** afforded acid (*S*)-(-)-**1** (26 mg, 73%, 55% ee); $[\alpha]^{25}_D$ -10.0 (c 1.35, $CHCl_3$).

(*S*)-(+)-2,2-Dimethyl-4-tetradecyl-1,3-dioxolane ((*S*)-(+)-7). To a solution of 2.54 g (45 mmole) of 1-tridecylphosphonium iodide, previously dried at 100°C for 15 h at 0.1 mm Hg, in 100 ml of anh. THF was added, at -30°C under argon, 30 ml of a 1.5M BuLi soln. in hexane (45 mmole). The resulting deep red solution was stirred at -50°C for 1 h and cooled to -78°C. Then, a solution of 4.43 g (34.1 mmole) of aldehyde (**R**)-(+)-**6**, obtained from D-mannitol as previously described,[24] in 30 ml of anh. THF was slowly added and the reaction mixture further stirred for 1 h at -78°C. The mixture was poured into ice-water and extracted with hexane. The organic phases were washed with brine and dried ($MgSO_4$). After filtration and evaporation of the solvent, the crude was purified by column chromatography on neutral alumina (act. III) eluting with hexane to afford 8.62 g (85%) of a 3:1 *Z*/*E* mixture of alkenes. Anal. Calcd. for $C_{19}H_{36}O_2$: C, 76.97%; H, 12.24%. Found: C, 77.08%; H, 12.28%. IR (film): 2923, 2854, 1465, 1456, 1369, 1060 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.85-5.65 (m; 1H; CH=C); 5.65-5.56 (m; 1H; CH=C *E* isomer); 5.48-5.31 (m; 1H; CH= (*Z* and *E* isomers); 4.84 (m, 1H; CH-C=C *Z* isomer); 4.44 (m, 1H; CH-C=C *E* isomer); 4.03 (dd; J=7.9 Hz; 6.0 Hz; 1H; HC<u>H</u>-O); 3.52 (t; J=7.9 Hz; 1H; <u>H</u>CH-O *Z* isomer); 3.49 (t; J=7.9 Hz; 1H; <u>H</u>CH-O *E* isomer); 2.06 (m; 2H; CH_2-C=C); 1.39 (s; 3H; CH_3); 1.37 (s; 3H; CH_3); 1.23 (b; 20H; $10CH_2$); 0.85 (t; J=6.5 Hz; CH_2-C<u>H</u>$_3$). ^{13}C-NMR (50 MHz, $CDCl_3$): (*Z*)-**11** δ 135.2 (CH=); 126.9 (CH=); 108.9 (quat. C); 72.0 (CH-O); 69.4 (CH_2-O); 31.9; 29.6; 29.4; 29.3; 29.1; 27.7; 26.8 (CH_3); 26.0 (CH_3); 22.6; 14.1 (CH_2-$\underline{C}H_3$).

The above mixture of alkenes (4.79 g, 16.2 mmole) was dissolved in 40 ml of methanol and hydrogenated with 479 mg of 10% Pd/C under atmospheric pressure at room temperature. When the theoretical amount of hydrogen was adsorbed, the reaction mixture was filtered over Celite which was washed with

methanol. The solvent was stripped off to furnish 4.57 g (95%) of dioxolane (*S*)-(+)-**7**. $[\alpha]^{25}_D$ +7.4 (c 1.04, hexane). Anal. Calcd. for $C_{19}H_{38}O_2$: C, 76.45%; H, 12.83%. Found: C, 76.81%; H, 12.72%. IR (film): 3010; 2985; 1465; 1456 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.03 (m; 2H; O-CH_2); 3.47 (m; 1H; O-CH); 1.7-1.4 (m; 2H; O-C-CH_2); 1.38 (s; 3H; C-CH_3); 1.33 (s; 3H; C-CH_3); 1.23 (b; 24H; 12CH_2); 0.86 (t; J=6.4 Hz; 3H; CH_2-C$\underline{H}_3$). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 108.5 (quat. C); 76.2 (O-CH); 69.5 (O-CH_2); 33.6; 31.9; 29.6; 29.5; 29.3; 27.0 (CH_3); 25.8 (CH_3); 22.7; 14.1 (CH_2-$\underline{C}H_3$).

(*S*)-(-)-1,2-Hexadecanediol ((*S*)-(-)-8). A solution of 423 mg (1.4 mmole) of dioxolane (*S*)-(+)-**7** in 10 ml of THF was mixed with 10 ml of a 2N HCl soln. and the mixture stirred at room temperature for 2 h. The solvent was evaporated off and the residue extracted with diethyl ether. The organic phase was washed with $NaHCO_3$ sat soln. and brine and dried (Na_2SO_4). After filtration and removal of the solvent, crude diol (*S*)-(-)-**8** was obtained (331 mg, 91%, >98%ee by ^{1}H NMR analysis of Mosher ester), pure enough to be used in the following step without further purification. $[\alpha]^{25}_D$ -9.0 (c 0.9, EtOH); lit[27] $[\alpha]^{28}_{546.1}$ = -5.25. mp: 63-65°C. IR (film): 3470, 3460-3000, 2952, 2917, 2848 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.74-3.60 (m; 2H; CH_2-O); 3.41 (m; 1H; CH-O); 1.96 (d; J=4.2 Hz; 1H; CH-O$\underline{H}$); 1.83 (t; J=5.6 Hz; 1H; CH_2-O$\underline{H}$); 1.23 (b; 26H; 13CH_2); 0.86 (t; J=6.4 Hz; 3H; CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 72.3 (CHOH); 66.8 (CH_2OH); 33.2; 31.9; 29.7; 29.6; 29.5; 29.4; 25.5; 22.7; 14.1 (CH_3).

(*S*)-(+)-1-triphenylmethoxyhexadecan-2-ol, (*S*)-(+)-9. To a solution of diol (*S*)-(-)-**8** (110 mg, 0.43 mmole) in 3 ml of anh. pyridine were added trityl chloride (140 mg, 0.50 mmole) and a catalytic amount of dimethylaminopyridine. The mixture was refluxed for 3 h, poured into a mixture of 2N HCl and ice and extracted with ether. The organic phases were washed with brine and dried (Na_2SO_4). The solvent was evaporated off, and the crude purified by column chromatography on neutral alumina (act. III) eluting with toluene:hexane 6:4 to obtain alcohol (*S*)-(+)-**9** (187 mg, 87%). $[\alpha]^{25}_D$ +7.4 (c 2.03, $CHCl_3$). Anal. Calcd. for $C_{35}H_{48}O_2$: C, 83.95%; H, 9.66%. Found: C, 83.99%; H, 9.77%. mp: 53-54°C. IR (film): 3600-3400; 3080 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.51-7.26 (m; 15H; arom.); 3.79 (m; 1H; C$\underline{H}$-OH); 3.22 (dd; J=9.4 Hz; 3.2 Hz; 1H; $\underline{H}$CH-O); 3.06 (dd; J=9.4 Hz; 7.6 Hz; 1H; HC$\underline{H}$-O); 2.37 (d; J=3.6 Hz; 1H; OH); 1.27 (b; 26H; 13CH_2); 0.90 (t; J=6.0 Hz; 3H; CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 143.9 (3 *ipso*-C ar.); 128.6 (6 *o*-CH ar.); 127.8 (6 *m*-CH ar.); 127.0 (3 *p*-CH ar.); 86.6 (CPh_3); 71.0 (CH-O); 67.8 (CH_2-O); 33.3; 31.9; 29.7; 29.65; 29.59; 29.4; 25.5; 22.7; 14.2 (CH_3).

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