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Asymmetric synthesis of (*R*)- and (*S*)-4-methyloctanoic acids. A new route to chiral fatty acids with remote stereocenters

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ABSTRACT

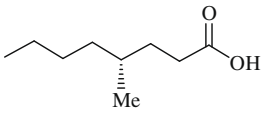
The enantioselective synthesis of both enantiomers of 4-methyloctanoic acid, one major aggregation pheromone component of the rhinoceros beetles of the genus *Oryctes* and an important aroma compound, is described. The key step of the synthesis is based on a stereospecific alkylation with an alcohol-protected alkyl iodide using a pseudoephedrine derivative as a chiral auxiliary followed by subsequent removal of the auxiliary. Both enantiomers are obtained in excellent yields and enantioselectivities (93–94% ee). The strategy outlined allows preparation of a wide variety of enantiopure methyl-branched saturated and unsaturated fatty acids.

1. Introduction

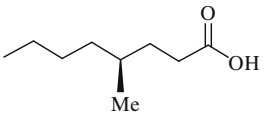
Rhinoceros beetles are one of the most important pests of coconuts, oil palms, and date palms in Middle-East, North Africa, South, and Southeast Asia.[1,2] The adults burrow galleries into the growing points of palms killing the mature trees by defoliation or producing wounds that favor entry points for palm weevils or lethal diseases.[3,4] The main pheromone components emitted by males of most of the rhinoceros beetles of the genus *Oryctes* are 4-methyloctanoic acid **1** and its corresponding ethyl ester.[5] The acid has been described also as an important aroma compound of Turkish tobacco,[6] Italian cheese,[7] and in perinephric fats of various red meat species.[8]

Several approaches have been reported for the synthesis of racemic 4-methyloctanoic acid.[3,9–12] However, the optically active (*R*)- and (*S*)-4-methyloctanoic acids **1** have only been obtained by the use of citronellol as chiral starting material[3,13], liquid chromatographic separation of diastereomeric phenylglycinol amides[13] or phenylethylamides,[14] or enzymatic resolution of the racemic material,[15–17] but no asymmetric synthesis involving induction of chirality has been reported so far.

We report herein the first asymmetric synthesis of both enantiomers of 4-methyloctanoic acid, (*R*)- and (*S*)-**1**, using a pseudoephedrine amide as a chiral auxiliary. The structure of these compounds is apparently simple but the distance between the stereocenter and the functional group turns the synthesis into a challenge. Moreover, conservation of the chirality at the α-carbon to the carbonyl during the synthesis was an additional subject of concern. The selected methodology has been based on the fact that pseudoephedrine amides undergo efficient and highly diastereoselective alkylation reactions with a wide range of alkyl iodides[18–21] giving rise to a variety of compounds with different functional groups, such as alcohols, carboxylic acids, aldehydes, and ketones.[21] Therefore, these chiral auxiliaries appeared to be suitable for our purposes. Our approach involves two key steps: (1) stereospecific alkylation of pseudoephedrinepropionamides **2** with 1-benzyloxy-3-iodopropane **3** followed by removal of the auxiliary, and (2) Wittig reaction of the α-substituted aldehyde **6**. Both steps occurred with excellent yields and full preservation of chirality with the acids (*R*)-**1** and (*S*)-**1** being obtained in 41–55% overall yields and 93–94% ee.



(*R*)-**1**



(*S*)-**1**

2. Results and discussion

The starting amides (*R,R*)-(−)- and (*S,S*)-(+)-pseudoephedrinepropionamides **2** are enantiomerically pure and commercially available (99% ee, Aldrich).

Alkylation with 1-benzyloxy-3-iodopropane **3**, obtained by a modification of Corey's procedure in 92% yield[22], using 1.9 equiv of LDA in the presence of anhydrous LiCl, afforded stereospecifically (*S,R,R*)-**4** and (*R,S,S*)-**4** in 90–98% yields (Scheme 1).

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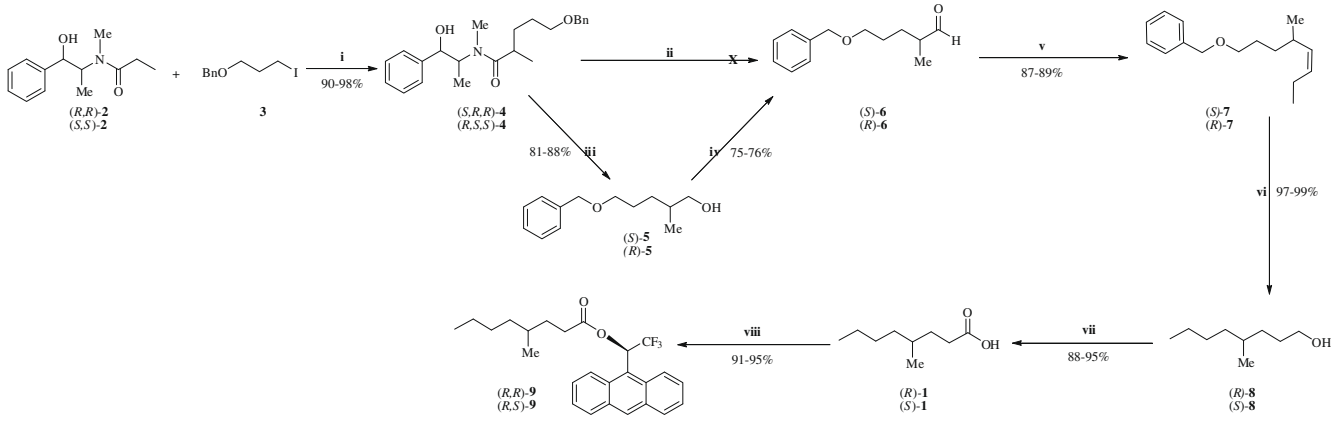

Scheme 1. Asymmetric synthesis of 4-methyloctanoic acid **1**. Reagents and conditions: (i) LDA/THF, LiCl; (ii) $LiAlH(OEt)_3$, −78 °C, TFA, 0 °C; (iii) LDA/THF, $BH_3{\cdot}NH_3$, 0 °C; (iv) $(COCl)_2/CH_2Cl_2$, DMSO, DIPEA, −78 °C; (v) $CH_3CH_2CH_2PPh_3Br$, KO^tBu/THF; (vi) H_2, Pd/C, EtOH, rt.; (vii) CrO_3, H_2SO_4, 0 °C; (viii) EDC·HCl, Et_3 N, DMAP/CH_2Cl_2, rt.

The absolute configuration of the newly generated stereocenter was assumed to follow the general rule proposed by Myers et al.[18]; the major alkylation product resulting from electrophilic attack on the putative (*Z*)-enolate from the same face (1,4-*syn*) as the C–Me group of the auxiliary when the enolate is drawn in a planar, extended conformation.

Attempts to directly convert amide (*S,R,R*)-**4** to aldehyde (*S*)-**6** by using lithium triethoxyaluminum hydride[23] under different conditions (solvent, reagents stoichiometry, etc) failed. This reagent is prepared in situ by reaction of lithium aluminum hydride with ethyl acetate in 1:1.5 molar ratio, and has been used successfully to prepare aldehydes in good yields and enantioselectivity.[18] In our hands, however, the starting amide (*S,R,R*)-**4** was recovered unchanged in most cases along with the expected aldehyde (*S*)-**6** but in poor yields (less than 40%) and with loss of enantiomeric purity. Therefore, we decided to reduce amides (*S,R,R*)-**4** and (*R,S,S*)-**4** to the corresponding alcohols (*S*)-**5** and (*R*)-**5** in the presence of lithium amidotrihydroborate.[24] This reducing agent was prepared in situ by reaction of LDA with borane-ammonia complex in THF at 0 °C. The reaction provided the expected alcohols **5** in 81–88% yields without apparent epimerization. Swern oxidation[19] of alcohols (*S*)-**5** and (*R*)-**5** furnished aldehydes (*S*)-**6** and (*R*)-**6** in 75–76% yields. Wittig reaction with propyltriphenylphosphonium bromide/K^tBuO in THF afforded benzyl-protected (*S*)- and (*R*)-(*Z*)-4-methyl-5-octanol **7** in 87–89% yields without loss of enantiomeric purity, as determined by the specific rotation values of alcohols (*R*)-**8** and (*S*)-**8** in comparison to the literature.[25] This step allows the possibility to prepare a large variety of 4-methyl Δ-5 fatty acids of *cis* stereochemistry of different chain lengths.

Hydrogenation of compounds **7** with Pd/C promoted reduction of the double bond and concomitant removal of the benzyl protecting group to produce the corresponding alcohols **8** in almost quantitative yields. Finally, oxidation with Jones reagent[26] afforded the desired (*R*)-**1** and (*S*)-**1** acids in 88–95% yields and with specific rotations consistent with those reported previously.[14]

Determination of diastereomeric/enantiomeric purity of the different intermediates **4**–**8** was based in most cases on their specific rotation values and subsequent comparison with those from the literature. Direct calculation of the enantiomeric purity of diastereomers **4** and enantiomers **1**, **7**, and **8** was not possible by chiral GC on a Cydex-B column because of the very low volatility of the compound (in the case of diastereomers **4**) or due to the enhanced separation difficulty induced by the remote location of the stereogenic center from the functional group (in the case of compounds **1**, **7**, and **8**). Finally, unequivocal determination of the enantiomeric purity of acids **1** was obtained by derivatization with (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol, a known reagent for the resolution of enantiomers by ^{19}F NMR and/or HPLC analysis of the corresponding diastereomers[27], in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl)/Et_3 N/DMAP in CH_2Cl_2 (Scheme 1).

Derivatization occurred in excellent yields (91–95%) and the resulting esters **9** were initially analyzed by ^{19}F NMR in the presence of tris[3-(trifluoromethylhydroxymethylen)-(+)-camphorato] europium (III)[28] but without success. However, HPLC analysis on a Chiralcel OD column under isocratic conditions (hexane:2-propanol 95:5, flow rate 1 ml/min) resulted in a baseline separation of both diastereomers (*R,R*)-**9** (de 94%) and (*R,S*)-**9** (de 93%) (Fig. 1).

Considering that no racemization occurred during the derivatization step, the enantiomeric purity of (*R*)-**1** and (*S*)-**1** was 94% and 93% ee, respectively, which agrees with the calculated values based on the specific rotation data previously obtained.

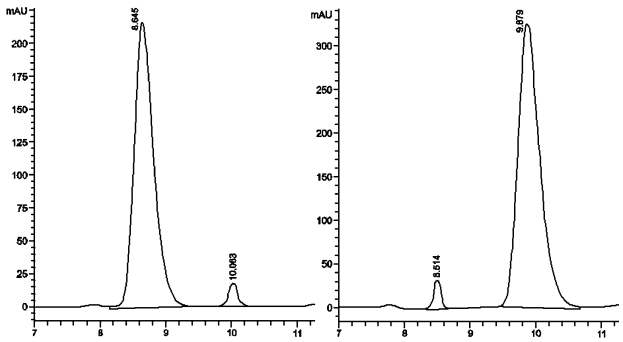

Figure 1. Enantiomeric resolution of derivatives **(*R,R*)-9** (left) and **(*R,S*)-9** (right) by chiral HPLC using a Chiralcel OD column (250 mm × 4.6 mm i.d.).

3. Conclusion

The first asymmetric synthesis of (*R*)- and (*S*)-4-methyloctanoic acid has been achieved in good overall chemical yields and enantioselectivities by induction of chirality through Myers alkylation methodology. The strategy outlined here allows the preparation of a wide variety of enantiopure methyl-branched saturated and unsaturated fatty acids just by the simple choice of the alkylating electrophile with different chain lengths and the required ylid for the hydrophobic part of the molecule.

4. Experimental

4.1. General

n-Butyllithium (1.6 or 2.5 M in hexane), (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol, (*1R,2R*)-(−)- and (*1S,2S*)-(+)-pseudoephedrinepropionamide, were purchased from Aldrich. All reactions employing organometallic compounds were carried out under argon atmosphere. All solvents were dried and distilled according to standard procedures. IR spectra were recorded on a Bomen MB-120 or on a Nicolet Avatar 360 FT-IR spectrometer. NMR spectra were recorded at 300, 400, or 500 MHz for ^{1}H, 75 or 100 MHz for ^{13}C, and 282 MHz for ^{19}F, on a Varian Unity 300, Varian Mercury 400, or Varian Inova 500 spectrometer. Mass spectra (MS) were obtained on a Fisons MD 800 instrument and high resolution mass spectra LC/ESI-MS were run on a UPLC Acquity (Waters USA) coupled to a mass spectrometer LCT Premier XE (Waters USA) with a TOF analyzer using a BEH C18 1.7 μm (2.1 × 50 mm) column. Elemental analyses were determined on a Carlo Erba-1106, Carlo Erba EA-1108, or Perkin Elmer CHN 2400 analyzer. Optical rotations were measured on a Perkin–Elmer 341 polarimeter.

4.2. Synthesis of acids (*R*)-1 and (*S*)-1

4.2.1. 1-Benzyloxy-3-iodopropane 3 [29]

This compound was prepared by a modified procedure to that described by Corey.[22] To a stirred, cooled (0 °C) solution of 3.00 g (18.05 mmol) of 3-benzyloxy-1-propanol, 10.41 g (39.71 mmol) of recrystallized triphenylphosphine, and 2.70 g (39.71 mmol) of imidazole in 40 ml of acetonitrile and 80 ml of Et_2O was slowly added 10.08 g (39.71 mmol) of iodine. After being stirred for 2 h, the reaction mixture was diluted with ether and sequentially washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $CuSO_4$, and water. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 4.58 g (92%) of 1-benzyloxy-3-iodopropane **3** as a yellow oil, which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H); 4.53 (s, 2H); 3.56 (t, J = 5.7 Hz, 2H); 3.32 (t, J = 6.9 Hz, 2H); 2.11 (tt, J_1 = 6.9 Hz, J_2 = 5.7 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2 (C); 128.4 (CH); 127.6 (CH); 73.1 (CH_2); 69.5 (CH_2); 33.5 (CH_2); 3.5 (CH_2) ppm. IR (film) ν: 3089, 3067, 3030, 2936, 2883, 2854, 1494, 1447, 1368, 1174, 1096, 1021, 735, 693 cm^{-1}. MS (EI): *m/z* (%) 277 (M+1, 28); 276 (M^+, 1); 275 (M-1, 20); 217 (15); 169 (43); 149 (42); 130 (59); 127 (40); 121 (53); 105 (57); 90 (100); 80 (24); 77 (99); 75 (20); 74 (22); 71 (11); 65 (99); 63 (42); 50 (82); 41 (95).

4.2.2. (2*S*)-*N*-Methyl-*N*-[(1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-2-methyl-5-benzyloxypentamide (*S,R,R*)-4

A solution of *n*-butyllithium in hexanes (1.5 M, 41 ml, 61.50 mmol) was added to a suspension of lithium chloride (8.31 g, 196.04 mmol) and diisopropylamine (9.4 ml, 66.33 mmol) in THF (40 ml) at −78 °C. The resulting suspension was briefly warmed to 0 °C and then cooled to −78 °C. An ice-cooled solution of (1*R*,2*R*)-(−)-pseudoephedrinepropionamide (7.16 g, 32.35 mmol) in THF (90 ml) was added via cannula. The mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, and at room temperature for 5 min. The mixture was cooled to 0 °C, and iodide **3** (4.26 g, 15.43 mmol) was added neat to the reaction mixture. After being stirred at 0 °C for 2 h and room temperature overnight, the mixture was treated with saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification of the residue by flash column chromatography (hexane:AcOEt; 3:2) afforded amide (*S,R,R*)-**4** as a highly viscous yellow oil (4.86 g, 90%). $[\alpha]_D^{20} = -55.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$), (major rotamer): δ 7.29 (m, 10H); 4.50–4.61 (m, 1H); 4.48 (s, 2H); 4.44 (m, 1H); 3.49 (m, 2H); 3.42 (t, J = 6.3 Hz, 2H); 2.81 (s, 3H); 2.63 (m, 1H); 1.38–1.74 (m, 4H); 1.1 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$), (major rotamer): δ 178.8 (C); 142.5 (C); 138.5 (C); 128.7 (CH); 128.3 (CH); 128.2 (CH); 127.6 (CH); 127.5 (CH); 126.3 (CH); 76.4 (CH); 72.9 (CH_2); 70.2 (CH_2); 57.8 (CH); 36.3 (CH); 33.1 (CH_3); 30.6 (CH_2); 27.5 (CH_2); 17.3 (CH_3); 14.4 (CH_3) ppm. IR (film) ν: 3369, 3034, 2975, 2940, 2861, 1614, 1451, 1111, 731, 695 cm^{-1}. MS (EI) *m/z* (%): 351 (M-18, 12); 237 (39); 205 (48); 148 (54); 147 (71); 146 (70); 131 (63); 92 (58); 91 (100); 77 (30); 71 (10); 58 (57); 56 (60). HRMS Calcd for $C_{23}H_{32}NO_3$ (M^+): 370.2382; Found: 370.2388.

4.2.3. (2*S*)-5-Benzyloxy-2-methyl-1-pentanol (*S*)-5[30]

A solution of *n*-butyllithium in hexanes (2.5 M, 9.5 ml, 23.84 mmol) was added dropwise to a cold (−78 °C) solution of diisopropylamine (3.6 ml, 25.10 mmol) in THF (25 ml). The solution was warmed to 0 °C and stirred for 10 min, and then the borane-ammonia complex (0.82 g, 23.84 mmol) was added in a single portion. The reaction was stirred at 0 °C for an additional 15 min and then warmed to room temperature for 15 min. The reaction was re-cooled (0 °C) for the dropwise addition of amide (*S,R,R*)-**4** (2.20 g, 5.96 mmol) in THF (15 ml), and then warmed to room temperature until the reaction was completed by TLC (2 h). The mixture was cooled to 0 °C and 3 N HCl was added carefully. The slurry was stirred for 30 min at 0 °C and extracted with ether. The combined organics were washed with 1 N HCl, 1 N NaOH, brine, dried over $MgSO_4$, filtered, concentrated, and purified on column chromatography (hexane:ether; 7:3) to give (*S*)-**5** (1.00 g, 81%) as a pale yellow oil, $[\alpha]_D^{20} = -9.4$ (*c* 6.6, $CHCl_3$); lit.[30] = −8.7 (*c* 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 5H); 4.50 (s, 2H); 3.46 (m, 4H); 1.43–1.78 (m, 3H); 1.10–1.28 (m, 2H); 0.92 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5 (C); 128.3 (CH); 127.6 (CH); 127.5 (CH); 72.9 (CH_2); 70.6 (CH_2); 68.1 (CH_2); 35.6 (CH); 29.5 (CH_2); 27.1 (CH_2); 16.5 (CH_3) ppm. IR (film) ν: 3395, 2898, 1455, 1357, 1095, 905, 725 cm^{-1}. MS (EI) *m/z* (%): 208 (M^+, 30); 147 (18); 108 (77); 107 (91); 105 (61); 104 (58); 99 (68); 92 (86); 91 (100); 89 (49); 83 (54); 69 (64); 65 (72); 55 (63)

4.2.4. (2*S*)-5-Benzyloxy-2-methyl-1-pentanal (*S*)-6[31]

DMSO (264 μl, 3.72 mmol) was added to oxalyl chloride (224 μl, 2.65 mmol) in cold (−78 °C) dichloromethane (18 ml), and the mixture was stirred for 10 min before alcohol (*S*)-**5** (0.37 g, 1.78 mmol) was added. After stirring for an additional 20 min, diisopropylethylamine (924 μl, 5.30 mmol) was added in a single portion, and the cold bath was subsequently removed. The reaction was allowed to warm for 30 min before being quenched via the addition of water. The product was extracted with ether and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure using an ice bath. The crude mixture was flashed through a silica chromatographic column eluting with pentane:ether (9:1) to give a pale yellow oil (0.27 g, 75%). $[\alpha]_D^{20} = +9.3$ (*c* 1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.62 (d, J = 1.8 Hz, 1H); 7.32 (m, 5H); 4.50 (s, 2H); 3.49 (t, J = 6.0 Hz, 2H); 2.36 (tqd, $J_1 = J_2$ = 6.9 Hz, J_3 = 1.8 Hz, 1H); 1.41–1.88 (m, 4H); 1.11 (d, J = 3.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.0 (C); 138.4 (C); 128.4 (CH); 127.6 (CH); 127.5 (CH); 72.9 (CH_2); 69.9 (CH_2); 46.0 (CH); 27.1 (CH_2); 13.3 (CH_3) ppm. IR (film) ν: 2935, 2862, 1729, 1456, 1361, 1119, 742 cm^{-1}. MS (EI) *m/z* (%): 206 (M^+, 9); 188 (3); 173 (11); 115 (44); 107 (82); 99 (40); 91 (100); 79 (60); 69 (78); 65 (68); 57 (61); 43 (39).

4.2.5. (4*S*)-1-Benzyloxy-4-methyl-5-octene (*S*)-7

n-Propyltriphenylphosphonium bromide (1.02 g, 2.65 mmol) was added in one portion to a cooled (0 °C) suspension of K^{t}BuO (0.30 g, 2.65 mmol) in THF (4 ml). The suspension turned bright yellow, was warmed to room temperature, and was stirred for 45 min. Aldehyde (*S*)-**6** (0.38 g, 1.85 mmol) was dissolved in THF (2 ml) and added to the reaction mixture at room temperature. Stirring was continued for 45 min, the reaction quenched with water and extracted with hexane. The combined organics were washed with brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed (hexane:ether; 98:2) to give (*S*)-**7** (0.37 g, 87%) as a colorless oil, $[\alpha]_D^{20} = -4.4$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.37 (m, 5H); 5.32 (m, 1H); 5.09 (m, 1H); 4.51 (s, 2H); 3.46 (t, *J* = 6.6 Hz, 2H); 2.44 (m, 1H); 2.03 (m, 2H); 1.14–1.71 (m, 4H); 0.96 (t, *J* = 7.5 Hz, 3H); 0.95 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6 (C); 135.3 (CH); 130.3 (CH); 128.3 (CH); 127.6 (CH); 127.4 (CH); 72.8 (CH_2); 70.6 (CH_2); 33.9 (CH_2); 31.5 (CH); 27.8 (CH_2); 21.5 (CH_3); 20.8 (CH_2); 14.6 (CH_3) ppm. IR (film) *v*: 2956, 2859, 2236, 1456, 1359, 1104, 734 cm^{-1}. MS (EI) *m/z* (%): 232 (M^+, 1); 203 (3); 175 (10); 141 (62); 123 (68); 107 (44); 91 (100); 81 (71); 67 (60); 55 (67). Elem. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.59; H, 10.33.

4.2.6. 4-Methyl-1-octanol (*R*)-8[25]

Compound (*S*)-**7** (0.15 g, 0.65 mmol) was dissolved in EtOH (5 ml) and stirred under a balloon of H_2 for 2 h at room temperature with a catalytic amount of Pd/C (10% active, ~5 mg). After filtration through Celite, the filtrate was concentrated to afford alcohol (*R*)-**8** (93 mg, 99%) as a pale yellow oil without need of further purification. $[\alpha]_D^{20} = +0.5$ (*c* 1.4, $CHCl_3$); lit.[25] +0.6 (*c* 1.6, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (t, *J* = 6.9 Hz, 2H); 1.06–1.67 (m, 11H); 0.85–0.90 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.4 (CH_2); 36.6 (CH_2); 32.9 (CH_2); 32.6 (CH); 30.3 (CH_2); 29.2 (CH_2); 23.0 (CH_2); 19.6 (CH_3); 14.1 (CH_3) ppm. IR (film) *v*: 3335, 2956, 2928, 2871, 1460, 1378, 1058 cm^{-1}. MS (EI) *m/z* (%): 126 [(M-18)$^+$, 1]; 98 (17); 84 (33); 69 (100); 56 (80); 43 (43); 41 (50).

4.2.7. (4*R*)-4-Methyloctanoic acid (*R*)-1[14]

To a solution of alcohol (*R*)-**8** (47 mg, 0.33 mmol) in acetone (2 ml), previously cooled to 0 °C, was added dropwise 0.4 ml (1.1 mmol) of Jones reagent over a period of 30 min. The mixture was stirred for one additional hour at room temperature and then 2-propanol (2 ml) and ether (50 ml) were added. The organic layer was decanted, washed with brine, and the solvent removed in vacuo. The crude mixture was purified by column chromatography eluting with CH_2Cl_2:MeOH (98:2) to obtain (*R*)-**1** (46 mg, 88%) as a pale yellow oil. $[\alpha]_D^{20} = -1.5$ (*c* 1.4, $CHCl_3$); lit.[14] = −1.53 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (m, 2H); 1.68 (m, 1H); 1.45 (m, 2H); 1.10–1.33 (m, 6H); 0.87–0.90 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.3 (C); 36.3 (CH_2); 32.3 (CH); 31.8 (CH_2); 31.6 (CH_2); 29.1 (CH_2); 22.9 (CH_2); 19.2 (CH_3); 14.1 (CH_3) ppm. IR (film) *v*: 3091, 2957, 2926, 2865, 1710, 1458, 1286, 1218, 1110, 939 cm^{-1}. MS (EI) *m/z* (%): 159 (M^+, 1); 129 (24); 101 (95); 99 (97); 83 (90); 73 (100); 69 (77); 60 (87); 59 (76); 57 (99).

4.2.8. (2*R*)-*N*-Methyl-*N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-2-methyl-5-benzyloxypentamide (*R*,*S*,*S*)-4

Compound (*R*,*S*,*S*)-**4** was prepared in the same way as (*S*,*R*,*R*)-**4** starting from (*1S*,*2S*)-(+)-pseudoephedrinepropionamide (4.57 g, 20.65 mmol), LiCl (5.33 g, 125.82 mmol), DIPA (6 ml, 42.27 mmol), *n*-BuLi (1.5 M, 26.2 ml, 39.32 mmol), and iodide **3** (2.72 g, 9.83 mmol) to obtain amide (*R*,*S*,*S*)-**4** (3.56 g, 98%) as a pale yellow oil. $[\alpha]_D^{20} = +55.7$ (*c* 1.26, $CHCl_3$). HRMS Calcd for $C_{23}H_{32}NO_3$ (M^+): 370.2382; Found: 370.2385. The spectroscopic data are identical to those of (*S*,*R*,*R*)-**4**.

4.2.9. (2*R*)-5-Benzyloxy-2-methyl-1-pentanol (*R*)-5[32]

Following the procedure described above for (*S*)-**5** and starting from (*R*,*S*,*S*)-**4** (3.00 g, 8.12 mmol), DIPA (4.8 ml, 34.10 mmol), *n*-BuLi (2.2 M, 14.8 ml, 32.48 mmol), and $BH_3{\cdot}NH_3$ (1.11 g, 32.48 mmol), the corresponding alcohol (*R*)-**5** (1.49 g, 88%) was obtained as a yellow oil after purification on column chromatography. $[\alpha]_D^{20} = +9.5$ (*c* 1.0, $CHCl_3$); lit.[32] = +8.2 (*c* 6.8, $CHCl_3$). The spectroscopic data are identical to those of (*S*)-**5**.

4.2.10. (2*R*)-5-Benzyloxy-2-methyl-1-pentanal (*R*)-6[31]

A procedure identical to that described above for (*S*)-**6** was followed. Thus, from alcohol (*R*)-**5** (1.45 g, 6.97 mmol), DMSO (1 ml), oxalyl chloride (886 μl, 10.47 mmol), and DIPEA (3.3 ml, 18.75 mmol), aldehyde (*R*)-**6** (1.09 g, 76%) was obtained as a pale yellow oil after purification by column chromatography. $[\alpha]_D^{20} = -9.1$ (*c* 1.0, $CHCl_3$). The spectroscopic data are identical to those of (*S*)-**6**.

4.2.11. (4*R*)-1-Benzyloxy-4-methyl-5-octene (*R*)-7

Compound (*R*)-**7** was prepared in the same manner as (*S*)-**7** starting from (*R*)-**6** (0.95 g, 4.61 mmol), propyltriphenylphosphonium bromide (2.54 g, 6.60 mmol), and KO*t*Bu (0.74 g, 6.60 mmol) to give (*R*)-**7** (0.95 g, 89%) as a colorless oil. $[\alpha]_D^{20} = +4.5$ (*c* 1.0, $CHCl_3$). Elem. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.86; H, 10.37. The spectroscopic data are identical to those of (*S*)-**7**.

4.2.12. (4*S*)-4-Methyl-1-octanol (*S*)-8[25]

Following the procedure described above for (*R*)-**8** and starting from (*R*)-**7** (0.69 g, 8.12 mmol) and Pd/C (10% active, ~20 mg), the corresponding alcohol (*S*)-**8** (0.41 g, 97%) was obtained as a pale yellow oil, without need of further purification. $[\alpha]_D^{20} = -0.5$ (*c* 1.4, $CHCl_3$); lit.[25] = −0.5, (*c* 1.8, MeOH). The spectroscopic data are identical to those of (*R*)-**8**.

4.2.13. (4*S*)-4-Methyloctanoic acid [(*S*)-1][14]

Following similar procedure as for (*R*)-**1**, oxidation of alcohol (*S*)-**8** (0.22 g, 1.51 mmol) with Jones reagent (1.8 ml, 5.03 mmol) afforded the expected acid (*S*)-**1** (0.23 g, 98%) as a pale yellow oil, after purification on column chromatography. $[\alpha]_D^{20} = +1.5$ (*c* 1.4, $CHCl_3$); lit.[14] = +1.45 (*c* 1.1, $CHCl_3$). The spectroscopic data are identical to those of (*R*)-**1**.

4.3. Synthesis of derivatives (*R*,*R*)-9 and (*R*,*S*)-9

4.3.1. (1*R*,4*R*)-[1-(9-Anthryl)-2,2,2-trifluoro]ethyl 4-methyloctanoate (*R*,*R*)-9

To a solution of carboxylic acid (*R*)-**1** (13.40 mg, 0.08 mmol) in CH_2Cl_2 (1 ml) was added (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (25 mg, (0.09 mmol). Then, EDC·HCl (51 mg, 0.26 mmol), Et_3 N (25 μl, 0.17 mmol) and DMAP (15 mg, 0.12 mmol) were added and the mixture was stirred at room temperature for 24 h. Dichloromethane was then added and the organic phase was washed with brine to afford (*R*,*R*)-**9** (30 mg, 91%) as a yellow oil, after solvent evaporation. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76 (d, *J* = 9.0 Hz, 1H); 8.57 (s, 1H); 8.38 (d, *J* = 9.0 Hz, 1H); 8.04 (t, *J* = 7.5 Hz, 2H); 7.84 (q, *J* = 8.0 Hz, 1H); 7.64 (t, *J* = 7.5 Hz, 1H); 7.57 (t, *J* = 8.0 Hz, 1H); 7.50 (dt, J_1 = 7.5 Hz, J_2 = 7.0 Hz, 2H); 2.39–2.58 (m, 2H); 1.03–1.71 (m, 9H); 0.81–0.91 (m, 6H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −72.3 (d, *J* = 7.5 Hz, 3F, $-CF_3$) ppm. HPLC analysis on a Chiralcel OD column under isocratic conditions using a mixture of hexane:isopropanol 95:5 (flow rate 1 ml/min) gave a diastereomeric purity of (*R*,*R*)-**9** of 94%.

4.3.2. (1*R*,4*S*)-[1-(9-Anthryl)-2,2,2-trifluoro]ethyl 4-methyloctanoate [(*R*,*S*)-9]

A similar procedure to that described for (*R*,*R*)-**9** was followed. Thus, starting from carboxylic acid (*S*)-**1** (15 mg, 0.09 mmol), (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (29 mg, 0.10 mmol), EDC·HCl (57 mg, 0.30 mmol), Et_3N (30 μl, 0.20 mmol), and DMAP (16 mg, 0.13 mmol), diastereomer (*R*,*S*)-**9** (35 mg, 95%) was obtained as a yellow oil. The spectroscopic data are identical to those of (*R*,*R*)-**9**. HPLC analysis on a Chiralcel OD column under isocratic conditions using a mixture of hexane:2-propanol 95:5 (flow rate 1 ml/min) gave a diastereomeric purity of (*R*,*S*)-**9** of 93%.

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