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Enzymatic desymmetrization of *meso*-1α,4α-dihydroxy-*cis*-decalins

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Abstract—The stereoselective acetylation of *meso*-decalindiols **1** and **2** by vinyl acetate in the presence of *Candida antarctica* lipase gave monoester (1*R*,4*S*,4a*R*,8a*S*)-**5** and (1*R*,4*S*,4a*R*,8a*S*)-**6** in high enantiomeric excess (ee ⩾98%). The hydrolysis of the corresponding *meso*-diacetates **3** and **4** in the presence of porcine liver esterase in phosphate buffer provided the opposite enantiomers.

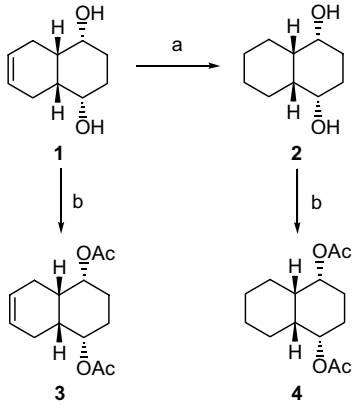
1. Introduction

The decalin ring system is an important structural feature often encountered in many natural products especially in terpenoid compounds.[1–5] Decalins exist in two stereoisomeric configurations; *cis*-decalin in which the substituents are on the same side of the ring junction, and *trans*-decalin in which they are on the opposite sides. The *trans* junction is more common but the *cis* junction is found in a significant number of natural products. Given the importance of the *cis*-decalin ring systems, the development of their synthesis has been the subject of considerable interest.[6–20] Herein we report the enzymatic desymmetrization of *meso*-1α,4α-dihydroxy-*cis*-decalins.

2. Results and discussion

2.1. Substrate preparation

Diol **1** was prepared in three steps from *cis*-1,3-butadiene and *p*-benzoquinone according to a known procedure.[21] Hydrogenation of **1** in ethyl acetate over palladium on carbon gave the saturated diol **2** (Scheme 1).[22] Corresponding diacetates **3** and **4** were prepared by the acetylation of **1** and **2** with acetic anhydride in pyridine.



Scheme 1. Reagents and conditions: (a) H_2, Pd/C, EtOAc; (b) Ac_2O, pyridine.

2.2. Enzymatic desymmetrizations

Initially, a wide range of lipases and esterases were screened for activity with the *meso*-substrates **1**–**4**. First, diols **1** and **2** were subjected to the enzyme-catalyzed esterification by treatment with *Pseudomonas cepacia* lipase (PCL) in vinyl acetate (solvent and acyl donor) to give optically active esters (1*R*,4*S*,4a*R*,8a*S*)-**5** and (1*R*,4*S*,4a*R*,8a*S*)-**6** in high yield (85%) and high enantiomeric excess (⩾98%) along with traces of the corresponding achiral diesters **3** and **4** (Scheme 2). Only one enantiomer of monoacetate **5** or **6** was detected by chiral GC but the reaction was slow (~3 days). The use of *Candida antarctica* lipase B (CAL-B) as catalyst at 40 °C gave the same yields and enantiomeric excesses in a shorter reaction time (1 day).

In general, the esterification (transesterification) of *meso*-diols and the hydrolysis of the corresponding *meso*-diesters are complementary and give the opposite enantiomers. Unexpectedly, many enzymes including

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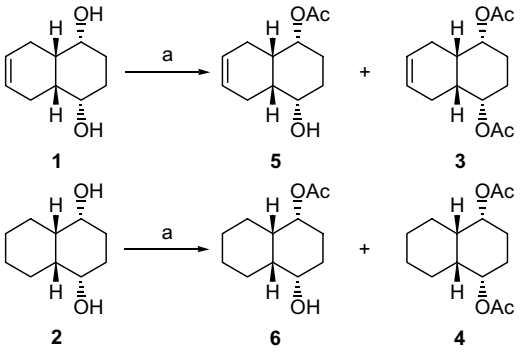
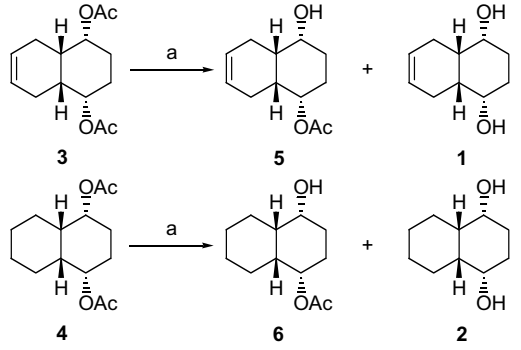


Scheme 2. Reagents and conditions: (a) *Pseudomonas cepacia* lipase, vinyl acetate, rt or *Candida antarctica* lipase B, vinyl acetate, 40 °C.

PCL and CAL-B showed no or very little hydrolytic activity in the presence of diesters **3** and **4**. Hydrolysis of diesters **3** and **4** by pig liver esterase (PLE) in a phosphate buffer provided enantiomerically pure (ee $\geqslant$98%) monoesters (1*S*,4*R*,4a*S*,8a*R*)-**5** and (1*S*,4*R*,4a*S*,8a*R*)-**6** (60–70% yield) and the corresponding achiral diols **1** and **2** (30–40% yield) indicating that monoacetates were also substrates (Scheme 3).



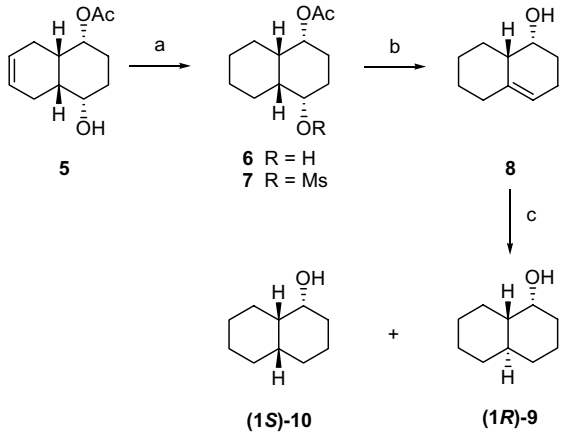
Scheme 3. Reagents and conditions: (a) pig liver esterase, phosphate buffer, pH 7.

The absolute configurations of monoesters **5** and **6** were determined by chemical correlation with compounds **9** and **10** of known absolute configurations (Scheme 4). Hydrogenation of **5** in the presence of 10% Pd/C gave the saturated compound **6**, which was then treated with mesyl chloride in pyridine to yield **7**. Treatment of **7** with $LiAlH_4$ reduced the acetyl and mesylate groups to give **8**.[23] Hydrogenation of **8** in the presence of 10% Pd/C gave the saturated compounds **9**, $[\alpha]_D^{22} = -35.3$ (*c* 0.22, EtOH); lit.[24] $[\alpha]_D^{25} = -34.5$ (*c* 1.1, EtOH) for the (1*R*)-enantiomer, and **10**, $[\alpha]_D^{22} = +24.0$ (*c* 1.25, $CHCl_3$); lit.[25] $[\alpha]_D^{21} = -22.0$ (*c* 1.0, $CHCl_3$) for the (1*S*)-enantiomer.

3. Experimental

3.1. General

NMR spectra were recorded on a Varian Inova AS400 spectrometer (400 MHz). Infrared spectra were recorded on a Bomem MB-100 spectrometer. Optical rotations were measured using a JASCO DIP-360 digital polarimeter (*c* as gram of compound per 100 mL). Flash column chromatography was carried out using 40–63 μm (230–400 mesh) silica gel. Lipase PS from *P. cepacia* was a gift from Amano International Enzyme Co. *C. antarctica* lipase B (chirazyme L-2) was obtained from Boehringer Mannheim and pig liver esterase from Sigma Chem. Co. The enantiomeric excesses (ee) were determined by GC analysis on a Chiraldex B-DM (β-cyclodextrin dimethyl) capillary column (30 m × 0.25 mm) using racemic compounds as references.



Scheme 4. Reagents and conditions: (a) (i) H_2, Pd/C, EtOAc; (ii) MsCl, Et_3N, CH_2Cl_2; (b) $LiAlH_4$, THF; (c) H_2, Pd/C, EtOAc.

3.2. (1*R*,4*S*,4a*R*,8a*S*)-Decahydronaphthalene-1,4-diol 2

A solution of *meso*-diol **1** (417 mg, 2.48 mmol) in ethyl acetate (10 mL) was stirred at rt with 10% Pd-on-carbon (125 mg) under hydrogen (40 psi) for 4 h. The catalyst was removed by filtration on Celite and the solvent evaporated to give **2** (417 mg, quantitative yield) as a white solid: mp 93–94 °C; lit.[22] mp 93–94 °C; IR (KBr) 3456, 2945, 1726, 1448, 1027, 949 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (m, 14H), 2.79 (s, 2H), 3.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 26.0, 27.4, 39.2, 72.6.

3.3. Preparation of diacetates 3 and 4: general procedure

To a stirred solution of diol **1** or **2** (3.8 mmol) in pyridine (5 mL) was added acetic anhydride (3 equiv) and the solution stirred overnight at rt. The solvent was co-evaporated with hexanes and CH_2Cl_2. The crude product was purified by flash chromatography (hexanes/EtOAc, 6:1) to give diester **3** or **4** (87–90%).

3.3.1. (1*R*,4*S*,4a*R*,8a*S*)-4-(Acetyloxy)-1,2,3,4,4a,5,8,8a-octahydronaphthalen-1-yl acetate 3. White solid: mp 56–57 °C; lit.[21] mp 56–57 °C; IR (KBr) 3449, 2933, 1735, 1234, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.52 (m, 2H), 1.80 (m, 14H), 4.93 (m, 2H), 5.52 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 25.0, 27.4, 35.0, 73.6, 125.4, 170.7.

3.3.2. (1*R*,4*S*,4a*R*,8a*S*)-4-(Acetyloxy)-decahydronaphthalen-1-yl acetate 4. Colorless oil; IR (NaCl) 3449, 2933, 1735, 1375, 1234, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.50 (m, 14H), 1.92 (m, 6H), 4.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 25.2, 26.1, 29.2, 39.0, 72.5, 170.3; HRMS (CI, NH_3) calcd for $C_{14}H_{26}NO_4$ $(M+NH_4)^+$: 272.1862. Found: 272.1865.

3.4. Enzymatic acylation of diols 1 and 2: general procedure

To a stirred solution of diol **1** or **2** (0.63 mmol) in vinyl acetate (5 mL) was added the lipase (50 mg, PCL at rt or CAL-B at 40 °C). The reaction course was monitored by TLC and when the substrate had disappeared (~3 days with PLC, ~1 day with CAL-B), the mixture was filtered and the solvent evaporated. The crude product was purified by flash chromatography (CH_2Cl_2/acetone, 98:2) to give **5** or **6** (85%) as colorless oils.

3.4.1. (1*R*,4*S*,4a*R*,8a*S*)-4-Hydroxy-1,2,3,4,4a,8,8a-octahydronaphthalen-1-yl acetate 5. $[\alpha]_D^{22} = +44.7$ (*c* 2.1, $CHCl_3$); IR (NaCl) 3371, 3020, 2917, 1732, 1435, 1375, 1248, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.44 (m, 2H), 1.70 (m, 2H), 1.87 (s, 3H), 2.01 (m, 6H), 2.41 (s, 1H), 3.74 (m, 1H), 4.86 (m, 1H), 5.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 24.3, 25.8, 26.7, 28.2, 34.8, 36.7, 72.1, 74.3, 126.0, 126.9, 170.9; HRMS (CI, NH_3) calcd for $C_{12}H_{18}O_3$ $(M+H)^+$: 211.1334. Found: 211.1338.

3.4.2. (1*R*,4*S*,4a*R*,8a*S*)-4-Hydroxydecahydronaphthalen-1-yl acetate 6. $[\alpha]_D^{22} = -26.5$ (*c* 4.0, $CHCl_3$); IR (NaCl) 3448, 2864, 1734, 1447, 1376, 1251, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (m, 2H), 1.60 (m, 13H), 2.03 (s, 3H), 3.80 (m, 1H), 4.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 24.1, 25.1, 27.0, 38.1, 40.6, 72.7, 74.7, 170.8; HRMS (CI, NH_3) calcd for $C_{12}H_{20}O_3$ $(M+NH_4)^+$: 230.1756. Found: 230.1760.

3.5. Enzymatic hydrolysis of diesters 3 and 4: general procedure

In a typical experiment, a suspension of ester **3** or **4** (0.40 mmol) was hydrolyzed with PLE (10 mg) in a phosphate buffer (5 mL, pH 7) at 38 °C. The reaction was monitored by TLC, and terminated when the substrate had disappeared (~48 h). The mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic phases dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (hexanes/EtOAc, 3:1) to give monoesters **5** and **6** (57–63%) as colorless oils and diols **1** and **2** (25–35%). Monoester **5**: $[\alpha]_D^{22} = -44.7$ (*c* 1.3, $CHCl_3$), ee ⩾98%, spectral data as above. Monoester **6**: $[\alpha]_D^{22} = +26.5$ (*c* 1.2, $CHCl_3$), ee ⩾98%, spectral data as above.

3.6. Determination of absolute configuration by chemical correlation

3.6.1. Reduction of 5 to 6. A solution of **5** (459 mg, 2.18 mmol; from CAL-B or PCL acylation) in ethyl acetate (10 mL) was stirred at rt with 10% Pd-on-carbon (160 mg) under hydrogen (40 psi) for 4 h. The catalyst was then removed by filtration on Celite and the solvent evaporated. The crude product was purified by flash chromatography (hexanes/EtOAc, 3:1) to give **6** (519 mg, 87%) as a colorless oil: $[\alpha]_D^{22} = -26.5$ (*c* 2.1, $CHCl_3$).

3.6.2. (1*R*,4*S*,4a*R*,8a*S*)-4-[(Methylsulfonyl)oxy]-decahydronaphthalen-1-yl acetate 7. To a stirred solution of **6** (243 mg, 1.14 mmol) and triethylamine (796 μL, 5.70 mmol) in anhydrous CH_2Cl_2 (20 mL) under a dry atmosphere at 0 °C was added dropwise a solution of mesyl chloride (352 μL, 4.56 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred overnight at rt, diluted with ethyl acetate (25 mL), then washed with 3 M HCl (2 × 20 mL), saturated $NaHCO_3$ (25 mL), brine (2 × 20 mL), dried over $MgSO_4$, and evaporated. The crude product was purified by flash chromatography (hexanes/EtOAc, 1:1) to yield **7** (301 mg, 91%) as a colorless oil: $[\alpha]_D^{22} = -17.2$ (*c* 2.1, $CHCl_3$); IR (NaCl) 3017, 2869, 1730, 1448, 1372, 1254, 1029, 930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (m, 2H), 1.55 (m, 10H), 1.88 (m, 2H), 1.98 (s, 3H), 2.94 (s, 3H), 4.71 (m, 1H), 4.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 23.8, 27.7, 28.4, 38.1, 38.9, 73.5, 83.2, 170.5; HRMS (CI, NH_3) calcd for $C_{13}H_{22}O_5S$ $(M+NH_4)^+$: 308.1532. Found: 308.1536.

3.6.3. (1*R*,8a*S*)-1,2,3,5,6,7,8,8a-Octahydronaphthalen-1-ol 8. To a solution of **7** (103 mg, 0.35 mmol) in anhydrous THF (4 mL) was added dropwise a solution of $LiAlH_4$ (1 M in THF, 1,79 mL, 1.79 mmol) and the mixture was stirred at rt under dry atmosphere for 4 h. The mixture was cooled to 0 °C and carefully quenched by dropwise addition of water (100 μL), followed by a 0.15 M NaOH solution (100 μL). The white inorganic precipitate was filtered off and washed with ethyl ether. The combined filtrates were dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (hexanes/EtOAc, 2:1) to give **8** (47 mg, 88%) as a colorless oil:[23] $[\alpha]_D^{22} = +22.0$ (*c* 1.0, $CHCl_3$); IR (NaCl) 3361, 2927, 2851, 1457, 1374, 1258, 1043, 947 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.15–2.17 (m, 14H), 3.86 (m, 1H), 5.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 22.1, 26.4, 28.1, 28.2, 28.7, 35.7, 43.0, 69.4, 118.4, 139.1.

3.6.4. Reduction of olefin 8. A solution of **8** (40 mg, 0,26 mmol) in diethyl ether (10 mL) was stirred at rt with 10% Pd-on-carbon (50 mg) under hydrogen (55 psi) for 2 h. The catalyst was removed by filtration on Celite and the solvent evaporated. The crude product was purified by flash chromatography (hexanes/Et_2O, 3:1) to give **9** (11 mg, 27%) and **10** (25 mg, 62%) as white solids.

3.6.5. (1*R*,4a*S*,8a*S*)-Decahydronaphthalen-1-ol 9. Mp 72–73 °C; $[\alpha]_D^{22} = -35.3$ (*c* 0.22, EtOH); lit.[24] $[\alpha]_D^{25} = -34.5$ (*c* 1.1, EtOH); IR (KBr) 3374, 2924, 2841, 1445, 1319, 1057, 1011, 942 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.92–1.85 (m, 17H), 3.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0, 26.4, 26.8, 29.7, 33.7, 33.9, 34.4, 35.6, 47.2, 70.7.

3.6.6. (1*R*,4a*R*,8a*S*)-Decahydronaphthalen-1-ol 10. Mp 67–69 °C; $[\alpha]_D^{22} = +24.0$ (*c* 1.25, $CHCl_3$); lit.[25] $[\alpha]_D^{21} = -22.0$ (*c* 1.0, $CHCl_3$); IR (KBr) 3318, 2926, 2856, 1448, 1089, 1061, 1030, 938 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.06–1.84 (m, 17H), 3.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 21.8, 24.5, 24.6, 26.5, 29.6, 32.0, 36.0, 43.1, 73.8.

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