Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1173–1180

TETRAHEDRON: *ASYMMETRY*

Enzymatic resolution of the 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane (1,8-cineole) system

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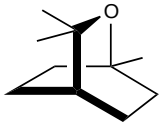
Received 1 April 2002; accepted 3 June 2002

Abstract—Regioselective oxidation of 1,8-cineole **1** with chromyl acetate according to a literature procedure gave the bicyclic 2-ketocineole **8** as the major product along with the symmetrical diketocineole **9**. The bicyclic monoketone was reduced with lithium aluminum hydride followed by exposure to acetyl chloride/DMAP to afford the *exo*-acetate (±)-**4b**. Pig liver esterase (PLE)-mediated hydrolysis of the racemic acetate provided the alcohol (−)-**2b** (45%) together with its antipodal acetate (+)-**4b** (43%) in greater than 99% enantiomeric purity, as determined by analysis of the Mosher's ester derivatives. Iodination of the alcohol *exo*-(+)-**2b**, obtained by hydrolysis of the resolved actetate with iodine/triphenylphosphine/imidazole, provided the corresponding *endo* iodide (−)-**12a**, which was easily dehydrohalogenated with DBU under solvent-free conditions to provide the corresponding cineolene (−)-**6** in an overall yield of 6 and 99% e.e.

1. Introduction

The 2- and 3-hydroxy and corresponding acetoxy derivatives of 1,8-cineole (eucalyptol) **1** are biologically significant congeners of the monoterpenoid 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane system.[1] The 2-*exo*-hydroxy derivative **2b** has recently been detected as the sole metabolic product when **1** was incubated with human liver microsomes under various concentrations and P_{450} levels.[2] In contrast, both the 2- and 3-hydroxylated products **2a**/**2b** and **3a**/**3b** were detected in the excretia of the brushtail opossum *Trichosurus vulpecula* when the animals were maintained on a diet of 0.5% **1**.[3] The individual enantiomeric 2- and 3-acetoxy derivatives **4a**/**4b** and **5a**/**5b** have been detected as the odiferous principles contained in the rhizomes of the galangal *Alpinia galanga*.[4] The rare cineolene (2,3-didehydro-1,8-cineole) **6** has been isolated by gas chromatography, along with **1** as a major constituent, from the essential oils of *Laurus nobilus* (Lauraceae). The biosynthesis of **6** in Lauraceae was presumed to involve either dehydrogenation of **1** or dehydration of **2a**/**2b** or **3a**/**3b**, all of



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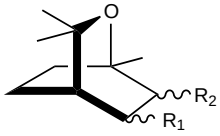
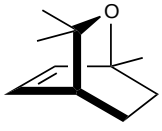


2a, R_1=*endo* OH, R_2=H
2b, R_1=*exo* OH, R_2=H

3a, R_1=H, R_2=*endo* OH
3b, R_1=H, R_2=*exo* OH

4a, R_1=*endo* OAc, R_2=H
4b, R_1=*exo* OAc, R_2=H

5a, R_1=H, R_2=*endo* OAc
5b, R_1=H, R_2=*exo* OAc



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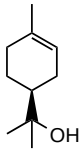

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PII: S0957-4166(02)00313-0

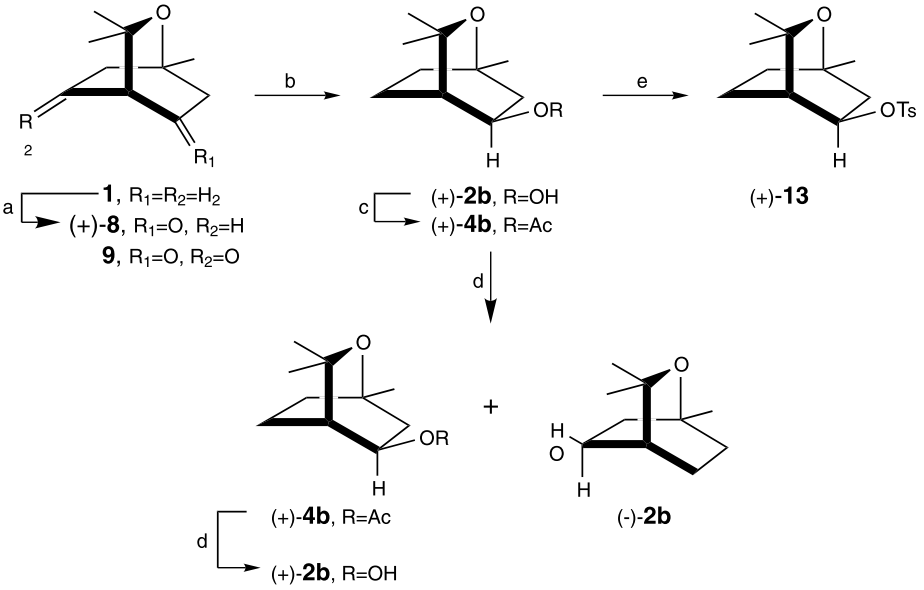
which are biosynthetic cyclization products of α-terpineol.[5] Although the chiral α-terpineol system **7** has served as a starting point for the synthesis of several of the corresponding cineole derivatives,[6] we are currently interested in the 1,8-cineole system as a synthon for chiral monoterpenoid synthetic intermediates.

Our interest in the synthetic potential of **1** was further driven by its relatively low cost and ready availability together with the ease at which **1** may be functionalized by oxidation at C-2 to afford both symmetrical and chemically resolvable products. Moreover, functionalization of such chiral intermediates at either C-2 or C-3 (or both) followed by regioselective opening of the 1,8-ether bridge will allow an entry into the series of extended menthane derivatives with control of the absolute stereochemistry. Herein, we report the highly efficient resolution of the 1,8-cineole system through the employment of porcine liver esterase (PLE) in conjunction with the racemic 3-acetoxy derivative as the substrate. The resolved compounds were then used as intermediates for the preparation of the naturally occuring cineolene derivative (−)-**6** through mild, selective halogenation followed by elimination.

2. Results and discussion

The synthetic scheme commences with the chromyl acetate-mediated oxidation of commercially available 1,8-cineole **1** to the corresponding racemic 2-keto derivative **8** (Scheme 1). Although the transformation was first described by Catalan,[7] the requirements of a useful reaction scale, high degree of purity and the necessary safety precautions connected with the preparation and use of oxochromium(VI) reagents[8] prompted us to develop an improved procedure (see Section 4). Slow addition of a freshly-prepared solution of chromyl acetate in acetic anhydride to a solution of **1** in glacial acetic acid effected oxidation at C-2 to provide **8** as the major product. Isolation of **8** entailed extractive workup to remove reduced chromium by-products followed by neutralization of the excess acetic anhydride and spinning band distillation. Flash column chromatography after distillation afforded ketone **8** (50%) and diketone **9** (8%).[9] The racemic ketone **8** was reduced with lithium aluminum hydride in diethyl ether to provide the racemic *exo*-alcohol **2b**[7] as the sole product in quantitative yield after purification by flash column chromatography. Treatment of the alcohol (±)-**2b** with acetyl chloride in the presence of 4-dimethylaminopyridine (DMAP) in dichloromethane at 0°C provided the racemic acetate (±)-**4b** in 70% yield after purification by flash column chromatography.

Based on our experience with the PLE-mediated desymmetrization of *meso*-spirocyclic diacetates, we elected to conduct the initial enzymatic hydrolysis studies under strictly aqueous conditions.[10] Incubation of the acetate (±)-**4b** with a commercially available preparation of porcine liver esterase (PLE) for 12 h at 37°C afforded a chromatographically-separable mixture of the alcohol (−)-**2b** (45, 90% of theoretical) and the acetate (+)-**4b** (43, 86% of theoretical). Despite the inherent hydrophobicity of terpene esters such as (±)-**4b**, the enzymatic reaction mixture formed a uniform suspension which was easily sampled and this could be monitored by thin-layer chromatography. Furthermore, only a single enzyme run was required to provide alcohol and acetate of high enantiomeric purity.[11] The (+)-acetate which was isolated from the lipase hydrolysis was saponified with lithium hydroxide in tetrahydrofuran/methanol/water at room temperature and thus provided the alcohol (+)-**2b** (80%) after silica gel column chromato-

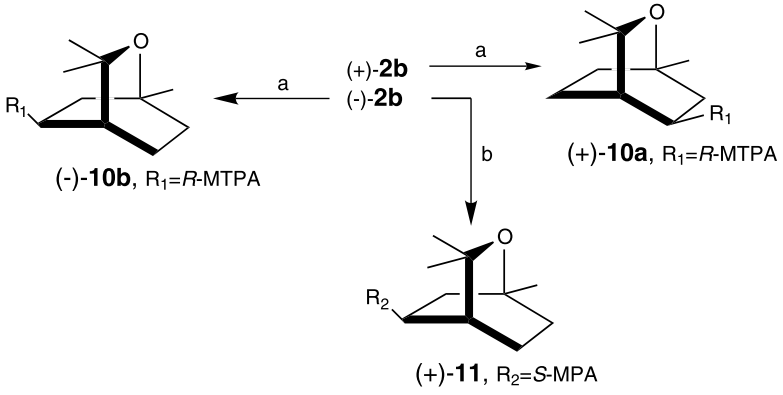


Scheme 1. *Reagents and conditions*: (a) $CrO_3/Ac_2O/AcOH/0$–5°C/20 h (50%); (b) $LiAlH_4/Et_2O$/reflux/1.5 h (99%); (c) $CH_3COCl/DMAP/CH_2Cl_2$/0°C–rt (70%); (d) pig liver esterase/H_2O/pH 7.00/37°C/12 h, (+)-**4b** (86.4%), (−)-**2b** (89.4%); (e) *p*-toluenesulfonyl chloride/DMAP/CH_2Cl_2/0°C/24 h (81%).

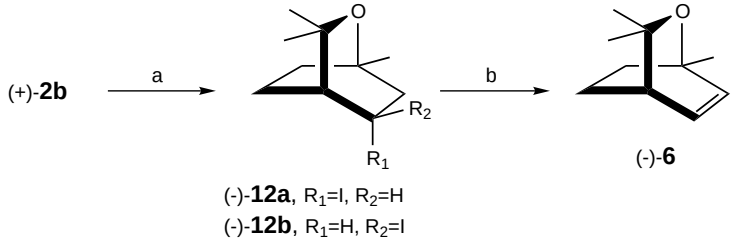
graphy. To confirm the enantiomeric purity, Mosher esters (+)-**10a** and (−)-**10b**[12] were prepared from each of the resolved (+)- and (−)-alcohols, respectively, using freshly-prepared (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl (MTPA) chloride and DMAP in dichloromethane. ^{19}F NMR analysis of each ester revealed >99% enantiomeric purity for both derivatives at a concentration of 10 mg/mL in $CDCl_3$. The absolute configuration of the alcohol (−)-**2b**, generated from the enzymatic reaction, was determined to be 1*R*,4*S*,5*R* by comparative ^1H and ^{13}C NMR analysis of its (*S*)-(+)-*O*-methyl mandelate ester (+)-**11** (Scheme 2).[4b] The spectral values were in agreement with those reported by Kubota for the *O*-methyl mandelate derivatives of the naturally-occuring acetoxycineoles.

Halogenation of the cineole nucleus and its derived alcohols en route to unsaturated cineole derivatives has been problematic due to a lack of selectivity together with the sensitivity of the 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane nucleus to cleavage and rearrangement.[13] The Garegg–Samuelsson iodination appeared to be particularly attractive since it has been employed successfully in the carbohydrate series to convert both primary and secondary hydroxyl groups to the corresponding iodides (Scheme 3).[14] Exposure of the alcohol (+)-**2b** to a mixture of iodine/triphenylphosphine/imidazole in benzene/acetonitrile at 78°C effected complete consumption of (+)-**2b** thereby forming the less polar (chromatographically more mobile) iodinated product, as indicated by monitoring the reaction by TLC. ^1H NMR analysis indicated that the chromatographically-homogenous product, obtained in 45% isolated yield, consisted of a mixture of *endo*- and *exo*-iodides (*endo*/*exo*, 2.5:1).

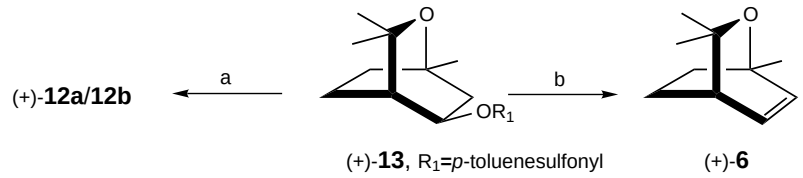
The lengthy purification steps required to remove both unreacted triphenylphosphine and triphenylphosphine oxide contributed to a considerable reduction in the yield of isolated purified product. A related iodination was examined in conjunction with the racemic series.[15] Iodine/chlorodiphenylphosphine/imidazole was employed with (±)-**2b** as the substrate and thereby afforded the *endo*- and *exo*-iodides in a similar ratio in 48% isolated yield albeit with simpler purification steps. The exclusive formation of the *endo*-iodide (±)-**12a** through the *p*-toluenesulfonyl ester (±)-**13** was also pursued. The *p*-toluenesulfonyl ester (±)-**13** was prepared in 81% yield by treating of the *exo*-alcohol (±)-**2b** with *p*-toluenesulfonyl chloride in the presence of 4-dimethylaminopyridine (DMAP). Interestingly, treatment of (±)-**13** with 5 equiv. of sodium iodide in refluxing acetone for 20 h resulted in a 36% isolated yield of *endo*- and *exo*-iodides with a reversed ratio of 1:2 (*endo*–*exo*) (Scheme 4). In general, dehydrohalogenation of the mixture of *endo*- and *exo*- (2.5:1, *endo*/*exo*) iodides (−)-**12a** and (−)-**12b** by heating with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided cineolene (−)-**6** (Scheme 3).[16] The initial dehydrohalogenation experiments in the (−)-**12a**/**12b** series employed toluene as a reaction solvent and 2 equiv. of DBU. Although elimination commenced at 100–102°C, as evidenced by a brown precipitate of DBU·HI, the iodides **12a**/**12b** were never completely consumed in the presence of the solvent. Moreover, monitoring the



Scheme 2. *Reagents and conditions*: (a) (*R*)-$C_6H_5COMeCF_3COCl$/DMAP/CH_2Cl_2/16 h/rt; (b) (*S*)-$C_6H_5COMeCOCl$/DMAP/CH_2Cl_2/16 h/rt.



Scheme 3. *Reagents and conditions*: (a) I_2/PPh_3/imidazole/benzene/CH_3CN/75°C/6 h (45%) or $I_2/ClPPh_2$/imidazole/toluene/rt/2 h (48%); (b) DBU/100°C/15 min then 115°C/20 min (99%).



Scheme 4. *Reagents and conditions*: (a) NaI/acetone/reflux/20 h (36%); (b) DBU/115–120°C/20 h (61%).

DBU-promoted elimination of **12a**/**12b** by ^{1}H NMR revealed that the *endo*-iodide **12a** was consumed faster than *exo*-**12b**. The most efficient dehydrohalogenation conditions entailed heating the mixture of **12a**/**12b** with 1.3 equiv. of DBU without a solvent which resulted in complete consumption of the iodides and a quantitative yield of cineolene (−)-**6**. Preliminary elimination experiments in the racemic series also employed *p*-toluenesulfonyl ester (±)-**13** as a substrate. The treatment of *p*-toluenesulfonyl ester (±)-**13** with DBU at 115–120°C for 20 h resulted in a 61% isolated yield of racemic cineolene (±)-**6** (Scheme 4).

3. Conclusion

Pig liver esterase (PLE) is effective for the enantioselective hydrolysis of a racemic mixture of cineolyl acetates. The enzyme was employed under strictly aqueous conditions and provided the products with high enantiomeric excess and chemical yield. The enzyme-mediated reaction was found to be selective for the (*R*)-ester, a result which is consistent with PLE selectivity for many similar types of substrates.[17] Both the iodination–dehydroiodination scheme in the chiral series and the *p*-toluenesulfonate elimination in the racemic series were found to be superior to both the previously reported xanthate pyrolysis and Bamford–Stevens protocols in yielding the desired cineolenes.

4. Experimental

4.1. General

NMR spectra were recorded on a Varian INOVA 500 instrument using $CDCl_3$ as solvent and internal standard unless otherwise indicated. Carbon signals marked with an asterisk represent methyl and methyne carbons as determined by APT experiments. Proton coupling constants (*J*) are reported in hertz (Hz). ^{19}F NMR spectra were recorded using trifluromethybenzene as an external standard. FTIR spectra were recorded with a Mattson Galaxy Series 5000 FT instrument. Optical rotation values were recorded with a Jasco DIP 360 polarimeter. Dichloromethane was distilled from CaH_2 and pyridine was distilled from barium oxide. All other reagents and solvents were ACS reagent grade and used as commercially available. Flash column chromatography was carried out using silica gel 60 (E. Merck 9385, 230–400 mesh).[18] Silica gel filtrations employed silica gel 60 (E. Merck 7734, 70–230 mesh). Celite filtrations employed Celite 521. Analytical thin-layer chromatographic (TLC) separations utilized 0.25 mm glass-backed silica gel plates (E. Merck 5715, silica gel 60 F_{254}). The TLC chromatograms were developed by dipping in 2% anisaldehyde in ethanol or 2.5% phosphomolybdic acid in ethanol followed by heating (hot plate). Solutions, reaction mixtures and chromatographic fractions were concentrated under vacuum using a standard rotary evaporator. Enzymatic reactions were conducted in a Lab-Line Model 3525 Incubator-Shaker. High-resolution mass spectroscopic analyses (HRMS) were performed by the Nebraska Center for Mass Spectrometry, University of Nebraska, Lincoln and the University of California Riverside Mass Spectrometry Facility.

4.2. (±)-1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane-5-one, 8

To a mechanically stirred solution of glacial acetic acid (90 mL, 1.57 mol) and acetic anhydride (18 mL, 1.98 mol) was added (Caution!) anhydrous chromium trioxide (37.5 g, 0.37 mol, technical flake) while cooling in an ice/water bath. The red–brown solution was stirred under an atmosphere of nitrogen for 1 h while cooling was continued. The flask was then fitted with a steel canula and a solution of chromyl acetate was added dropwise through the canula under nitrogen pressure to a stirred, cooled (ice/water bath) solution of 1,8-cineole **1** (18.4 g, 0.12 mol) and glacial acetic acid (30 mL). After the transfer of the chromyl acetate solution was complete, some residual chromium trioxide remained. The residual material was dissolved, while cooling, in additional acetic acid/acetic anhydride solution (20–30 mL) and then transferred via canula to the 1,8-cineole solution. After addition of the oxidant was complete, the resultant dark-green 1,8-cineole/oxidant solution was stored at 4°C for 20 h. A crushed ice/water mixture (1 L) was then added followed by extraction of the dark-green solution with diethyl ether (5×200 mL). The combined ether extracts containing the products along with residual acetic acid/acetic anhydride were neutralized by cautious addition of anhydrous sodium carbonate while stirring vigorously. The salts resulting from the neutralization were removed by vacuum filtration while washing with ether and the filtrate was dried over anhydrous sodium sulfate. Removal of the solvent followed by flash column chromatography (hexane/ether, 9:1) of the residual oil provided the racemic ketone **8** (10.08 g, 50%) along with diketone **9** (1.74 g, 8%) and unreacted 1,8-cineole (1.84 g, 10%). For **8**: R_f 0.23

(hexane/ether, 9:1); ^{1}H NMR (500 MHz, $CDCl_3$)[19] δ: 1.06 (s, 3H), 1.15 (s, 3H), 1.23 (s, 3H), 1.55 (m, 1H), 1.67 (m, 1H), 1.79 (m, 1H), 2.08 (dd, J=2.0, 3.8, 1H), 2.16 (m, 2H), 2.30 (dd, J=3, 18.8, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.3, 26.5, 27.2, 30.9, 49.2, 52.0, 73.8. IR ($CHCl_3$) 3437, 3033, 2456 cm^{-1}, 1725. HRMS (EI) m/z (M^+) calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1156.

4.3. (±)-*exo*-1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane-5-ol, (±)-2b

A suspension of lithium tetrahydroaluminate (0.64 g, 16.8 mmol) in ether (25 mL) was prepared in a 300 mL round-bottom flask fitted with a dry-ice cold finger condenser, mechanical stirrer and argon inlet. To the stirred suspension was added a solution of (±)-ketone **8** (1.13 g, 6.73 mmol) in dry ether (5.0 mL) under a stream of argon while cooling in an ice/water bath. After the addition of **8** was complete, the reaction mixture was refluxed (1.5 h) followed by cooling the reaction mixture (ice/water) prior to quenching. The vigorously stirred reaction mixture was then quenched by the addition of saturated aqueous sodium sulfate (20 mL) followed by extraction of the resultant white suspension with diethyl ether (3×25 mL). The ethereal extracts were combined, dried over anhydrous sodium sulfate, filtered and concentrated to provide (±)-**2b** as a chromatographically homogeneous oil (1.18 g, 99%) which was of sufficient purity to use in the acetylation step. R_f 0.16 (hexane/ether, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$)[19] δ: 1.11 (s, 3H), 1.23 (s, 3H), 1.37 (m, 2H), 1.43 (s, 3H), 1.53 (m, 1H), 1.58 (m, 1H), 1.68 (ddd, J=3.18, 6.06, 13.79, 1H), 2.04 (m, 2H), 4.14 (ddd, J=2.01, 6.08, 10.27, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.66, 27.08, 30.34, 30.74, 31.03, 40.97, 43.43, 70.46, 71.06, 73.69. IR ($CHCl_3$) 3613, 2957, 2462, 1623 cm^{-1}; HRMS (EI) m/z (M^+) calcd for $C_{10}H_{18}O_2$ 170.1306, found 170.1300.

4.4. (±)-*exo*-1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane-5-yl acetate, (±)-4b

To a stirred solution of (±)-alcohol **2b** (1.0 g, 5.87 mmol) and 4-dimethylaminopyridine (1.08 g, 8.81 mmol) dissolved in dichloromethane (10.0 mL) was added acetyl chloride (1.38 g, 17.6 mmol) while cooling at 0–5°C. The reaction mixture was warmed to room temperature followed by removal of the dichloromethane and excess acetyl chloride under vacuum. The residue was dissolved in diethyl ether, directly applied to a flash silica column and eluted with pentane/ether (9:1). Evaporation of the solvents provided the (±)-acetate **4b** as white crystals (0.88 g, 70%). Mp 41–43°C. R_f 0.42 (hexane/ether, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.13 (s, 3H), 1.24 (s, 3H), 1.36 (s, 3H), 1.47 (m, 2H), 1.63 (m, 1H), 1.75 (m, 2H), 2.06 (s, 3H), 2.11 (m, 2H), 4.99 (ddd, J=2.15, 4.55, 5.76, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.24, 21.71, 26.97, 30.34, 30.39, 30.62, 37.60, 40.47, 70.21, 73.01, 73.36. IR ($CHCl_3$) 3432, 3038, 1725, 1369 cm^{-1}. HRMS (EI) m/z (M^+) calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1416.

4.5. Enzymatic resolution of (±)-*exo*-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane-5-yl acetate: (−)-*exo*-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane-5-ol, (−)-2b and (+)-*exo*-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane-5-yl acetate, (+)-4b

Racemic ester (±)-**4b** (0.85 g, 4.71 mmol) was ground to a fine powder and added in one portion to phosphate buffer solution (pH 7.00, 15 mL). A suspension of porcine liver esterase (EC 3.1.1.1. Sigma Lot# 29F8055, 2530 units) was added to the buffer/substrate suspension and the reaction mixture was swirled in an incubator at 37°C for 12 h. The suspension was then saturated with brine (5.0 mL) followed by the addition of dichloromethane (5 mL). The suspension was vacuum-filtered through a Celite pad to remove proteinaceous material followed by extraction of the filtrate with dichloromethane (3×20 mL). The combined extracts containing the crude ester/alcohol mixture were dried over sodium sulfate and concentrated. Flash column chromatography (hexane/ether, 5:1) of the residual oil provided the ester (+)-**4b** (368 mg, 43%) and the alcohol (−)-**2b** (305 mg, 45%). For ester (+)-**4b**: mp 41–43°C; R_f 0.52 (hexane/ether, 1:1); $[\alpha]_D^{25}$ +55.8 (c=1.25, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.12 (s, 3H), 1.24 (s, 3H), 1.36 (s, 3H), 1.47 (m, 2H), 1.62 (m, 1H), 1.74 (m, 2H), 2.06 (s, 3H), 2.10 (m, 2H), 4.98 (ddd, J=2.13, 4.57, 5.9, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.25, 21.71, 27.07, 30.34, 30.40, 30.63, 37.55, 40.48, 70.19, 73.02, 73.34. IR ($CHCl_3$) 3434, 2974, 2461, 1725 cm^{-1}. HRMS (EI) m/z (M^+) calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1412. For alcohol (−)-**2b**: mp 90–92°C; R_f 0.21 (hexane/ether, 1:1); $[\alpha]_D^{25}$ −45.3 (c=1.24, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.11 (s, 3H), 1.24 (s, 3H), 1.38 (m, 2H), 1.43 (s, 3H), 1.57 (m, 2H), 1.69 (ddd, J=3.25, 6.11, 13.81, 1H), 4.15 (ddd, J=2.1, 4.23, 6.11, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.66, 27.11, 27.38, 30.37, 31.03, 40.99, 43.45, 70.43, 71.09. IR ($CHCl_3$) 2461, 1725, 1464, 1368 cm^{-1}. HRMS (EI) m/z (M^+) calcd for $C_{10}H_{18}O_2$ 170.1306, found 170.1301.

4.6. (+)-*exo*-1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane-5-ol, (+)-2b

exo-Acetate (+)-**4b** (315 mg, 1.48 mmol) was added to a solution of 1N aqueous lithium hydroxide (15 mL) in water/methanol/THF (4:3:5). The reaction mixture was stirred at room temperature (3 h) while monitoring by TLC. Brine (15 mL) was then added followed by extraction with THF (3×10 mL). The extracts were then combined and dried over anhydrous sodium sulfate (16 h). The drying agent was removed by filtration followed by removal of the solvent, reconstitution of the residue in dichloromethane (20 mL) and drying over anhydrous sodium sulfate. Removal of the drying agent and solvent followed by filtration through a short pad of silica gel provided the pure *exo*-alcohol (+)-**2b** (203 mg, 80%). Mp 90–92°C; $[\alpha]_D^{25}$ +49.8 (c=1.04, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.11 (s, 3H), 1.24 (s, 3H), 1.38 (m, 2H), 1.44 (s, 3H), 1.58 (m, 2H), 1.69 (ddd, J=3.25, 6.11, 13.84, 1H), 2.05 (m, 2H), 4.15 (ddd, J=2.12, 4.25, 6.08, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.67, 27.11, 30.34, 31.07, 40.93, 43.44, 70.45, 71.05,

73.67. IR ($CHCl_3$) 2974, 1462, 1365 cm^{-1}. HRMS (EI) m/z (M^+) calcd for $C_{10}H_{18}O_2$ 170.1306, found 170.1309.

4.7. (−)-*endo*-/*exo*-5-Iodo-1,3,3-trimethyl-2-oxabicyclo-[2.2.2]octane, (−)-12

Iodine (700 mg, 2.76 mmol) was added to a stirred solution of imidazole (376 mg, 5.52 mmol) and benzene/acetonitrile (2:1, 20 mL). To the brown–black solution, under a nitrogen atmosphere, was added triphenylphosphine (724 mg, 2.76 mmol) to give a yellow-white suspension. Alcohol (+)-**2b**, dissolved in benzene/acetonitrile (2:1, 1 mL) was then added to the reagent mixture which turned the suspension white. The reaction mixture was heated at 75°C for 6 h, during which time the mixture changed colour back to yellow. At the end of the reaction, the mixture was concentrated under vacuum and the residue was directly applied to a flash chromatography column eluting with hexane/ether (6:1). Concentration of the eluent gave the product (−)-**12a**/**12b** as a colorless oil along with triphenylphosphine. Addition of ether (1–5 mL) and iodomethane (1 mL, 16.1 mmol) precipitated the triphenylphosphine as the methiodide which was removed by filtration. Removal of the solvent furnished the *endo*- and *exo*-iodides (−)-**12a** and (−)-**12b** (173 mg, 45%) as an oily liquid which yellows on standing at room temperature. R_f 0.65 (hexane/ether, 1:1); $[\alpha]_D^{25}$ −30 ($c=1.23$, $CHCl_3$). FTIR ($CHCl_3$) 3045, 2976, 1437, 1176 cm^{-1}. For *endo*-(−)-**12a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.07 (s, 3H), 1.28 (s, 3H), 1.34 (s, 3H), 1.62 (m, 1H), 1.70 (m, 1H), 1.73 (m, 1H), 2.08 (m, 1H), 2.10 (m, 1H), 2.26 (m, 1H), 2.46 (m, 1H), 5.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.6, 26.57, 28.28, 28.85, 30.05, 31.45, 42.72, 46.87, 71.19, 74.44. For *exo*-(−)-**12b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.10 (s, 3H), 1.28 (s, 3H), 1.53 (m, 1H), 1.63 (m, 1H), 1.69 (s, 3H), 1.75 (m, 1H), 1.96 (m, 1H), 2.10 (m, 1H), 2.29 (m, 1H), 2.42 (m, 1H), 4.50 (dd, $J=9.63$, 9.99 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.36, 25.32, 26.88, 29.72, 29.98, 30.84, 42.12, 46.23, 72.09, 74.87. IR ($CHCl_3$) 3061, 2976, 1437, 1176 cm^{-1}.

4.7.1. (±)-*endo*-/*exo*-5-Iodo-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane, (±)-12: chlorodiphenylphosphine method.

To a solution of imidazole (160 mg, 2.35 mmol) in dry toluene (1.0 mL) was added chlorodiphenylphosphine (0.21 mL, 1.17 mmol) by syringe under an atmosphere of nitrogen. (±)-*exo*-Alcohol **2b** (100 mg, 0.59 mmol) dissolved in dry toluene (1.0 mL) was then added by syringe while stirring. A solution of iodine (298 mg, 1.17 mmol) was then added while stirring and the resultant brown solution was stirred at room temperature under nitrogen (2 h). When the reaction was complete the mixture was transferred to a separatory funnel and then washed with saturated sodium bicarbonate (5 mL). Ground iodine was added to the separatory funnel and shaken until the organic phase was colored with unreacted iodine. The organic layer was then separated, washed with 5% aqueous sodium thiosulfate (3×15 mL) and dried over anhydrous sodium sulfate. Removal of the solvent followed by flash column chromatography (hexane/ether, 6:1) of the residual oil provided (±)-**12** as an *endo*/*exo* mixture (79.5 mg, 48%; *endo*/*exo*, 2.5:1) which exhibited the same spectral characteristics as (−)-**12**.

4.7.2. Preparation of (±)-12. Sodium iodide/*exo*-*p*-toluenesulfonate method.

A solution of freshly ground dry *exo*-*p*-toluenesulfonate **13** (250 mg, 0.77 mmol) in dry acetone (2.0 mL) was added to a solution containing vacuum dried sodium iodide (578 mg, 3.85 mmol) in acetone (2.0 mL). The reaction mixture was heated under reflux under nitrogen for 20 h, during which time the reaction mixture became dark brown. The reaction mixture was filtered through a plug of glass wool followed by removal of the acetone. The residue was dissolved in dichloromethane (25 mL), washed with 5% aqueous sodium bicarbonate solution (25 mL) and then washed with a 5% aqueous sodium thiosulfate solution (2×25 mL). The organic layer was then dried over anhydrous sodium sulfate. Removal of the drying agent followed by flash column chromatography of the residual oil (hexane/ether, 20:1) afforded (±)-**12** as an *endo*/*exo* mixture (78.7 mg, 37%; *endo*/*exo*, 1:2) which exhibited the same spectral characteristics as (±)-**12** prepared by the arylphosphine/iodine methods described above.

4.8. (±)-5-*exo*-(*p*-Toluenesulfonyloxy)-1,3,3-trimethyl-2-oxabicyclo[2.2.2]-octane, 13

Racemic alcohol **2b** (579 mg, 3.4 mmol) and 4-dimethylaminopyridine (1.66 g, 13.6 mmol) was dissolved in dichloromethane (4 mL). The solution was then cooled to 0°C under nitrogen and *p*-toluenesulfonyl chloride (1.3 g, 6.8 mmol) dissolved in dichloromethane (2.0 mL) was added dropwise by syringe while stirring. Stirring was continued at room temperature for 24 h. The reaction mixture was then poured into a separatory funnel, washed with brine (3×25 mL) and dried over sodium sulfate. Removal of the drying agent and solvent followed by flash chromatography provided the *exo*-*p*-toluenesulfonate **13** (0.89 g, 81%). Mp 92–93°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.17 (s, 3H), 1.21 (s, 3H), 1.34 (m, 3H), 1.37 (s, 3H), 1.59 (m, 1H), 1.87 (ddd, $J=3.16$, 6.02, 14.4 Hz, 1H), 1.97 (dd, $J=10.5$, 14.4 Hz, 2H), 2.07 (m, 1H), 2.46 (s, 3H), 4.81 (ddd, $J=2.10$, 2.24, 4.41 Hz, 1H), 7.38 (d, $J=8.0$ Hz, 2H), 7.80 (d, $J=8.19$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.30, 26.81, 30.00, 30.67, 38.50, 38.65, 40.59, 70.18, 73.22, 80.55, 80.93, 127.75, 127.98, 129.64, 130.55, 134.59, 144.89. IR ($CHCl_3$) 2974, 2457, 1599, 1359 cm^{-1}. HRMS (CI) m/z (MNH_4^+) calcd for $C_{17}H_{28}NO_4S$ 342.1753, found 342.1753.

4.9. (−)-1,3,3-Trimethyl-2-oxabicyclo[2.2.2]oct-5-ene, (−)-6

A mixture of *endo*-iodide (−)-**12** (115 mg, 0.41 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (68 mg, 0.45 mmol) were mixed in a 5 mL round-bottomed flask connected directly to a 10 mL vacuum trap cooled to −78°C. The mixture was heated (oil bath) while stirring under nitrogen at 100°C for 15 min and then at 115°C for 20 min. During the heating the reaction mixture

became green-brown and viscous. The flask was cooled then vacuum (1.0 Torr) was applied to the apparatus followed by gentle warming of the flask (80–90°C). The olefin (−)-**6** (62 mg, 99%) was collected in the vacuum trap at −78°C as a clear colorless liquid: $[\alpha]_D^{25}$ −39.8 ($c=1.00$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.99 (s, 3H), 1.28 (s, 3H), 1.33 (s, 3H), 1.73 (m, 1H), 2.01 (m, 1H), 2.28 (m, 1H), 6.09 (d, $J=8.14$, 1H), 6.46 (dt, $J=1.39$, 8.08, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.59, 28.30, 29.29, 31.48, 36.65, 71.28, 74.47, 135.38, 135.6. IR ($CHCl_3$) 3611, 2462, 1461, 1378 cm^{-1}. HRMS (EI) m/z (M^+) calcd for $C_{10}H_{16}O$ 152.1201, found 152.1195.

4.9.1. Preparation of (±)-6 by DBU-promoted elimination of *exo*-*p*-toluenesulfonate, (±)-13. A mixture of the racemic 5-*exo*-tosylate (±)-**13** (671 mg, 2.07 mmol) and DBU (0.37 mL, 2.48 mmol) was placed in a 25 mL round-bottom flask fitted with a water-cooled cold-finger condenser. The mixture was heated (oil bath, 115–120°C) for 20 h while stirring, during which time the color of the mixture became dark brown. At the end of the reaction period the condenser was removed and the flask was fitted with a 10 mL vacumm trap cooled with dry ice. The product was then distilled into the trap under vacuum (1 Torr). The yield of pure (±)-cineolene **6** was 193.4 mg (61%) which had the same spectral properties as detailed for (−)-**6**.

4.10. (+)- and (−)-*exo*-1,3,3-Trimethyl-2-oxabicyclo-[2.2.2]oct-5-yl-*R*-α-methoxy-α-(trifluoromethyl)-phenylacetate. Mosher esters, (+)-10a and (−)-10b

Thionyl chloride (1.0 mL, 13.7 mmol) was added to (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (134 mg, 0.57 mmol). Finely ground sodium chloride (166 mg, 2.85 mmol) was added and the mixture was refluxed for 48 h. At the end of the reflux period, excess thionyl chloride was removed by short-path distillation at atmospheric pressure, which left a yellow residual oily acid chloride. The crude product was placed under vacuum (0.5 Torr) at 0°C (0.5 h). The oily acid chloride was then dissolved in dichloromethane (4.0 mL). Half the solution of the Mosher acid chloride (2.0 mL) was added to a stirred solution of the *exo*-alcohol (+)-**2b** (0.25 mmol) and 4-dimethylaminopyridine (0.76 mmol) in dichloromethane (0.5 mL). The other half of the acid chloride solution was added to the *exo*-alcohol (−)-**2b** under identical conditions. The esterification reactions were both stirred (16 h) followed by solvent removal under vacuum and direct flash column chromatography (hexane/ether, 2:1). **(+)-*exo*-Mosher ester**, **(+)-10a**: $[\alpha]_D^{25}$ +48.25 ($c=2.7$, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.03 (s, 1H), 1.13 (s, 3H), 1.18 (s, 3H), 1.28 (m, 1H), 1.46 (m, 1H), 1.55 (m, 1H), 1.64 (m, 1H), 1.68 (m, 1H), 1.82 (ddd, $J=3.16$, 6.29, 14.13, 1H), 2.10 (m, 1H), 2.20 (dd, $J=10.59$, 14.11, 1H), 3.57 (s, 3H), 5.25 (m, 2H), 7.41 (m, 3H), 7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.38, 26.88, 30.16, 30.22, 37.88, 40.17, 70.14, 73.11, 75.37, 74.44, 122.46, 124.75, 127.44, 128.64, 129.80, 132.53. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −72.67 (s, 3F) 99%; −72.76 (s, 3F) 1%. HRMS (EI) m/z (MH^+) calcd for $C_{20}H_{25}O_4F_3$ 386.1705, found 386.1709. **(−)-*exo*-Mosher ester**, **(−)-10b**: $[\alpha]_D^{25}$ −7.00 ($c=2.8$, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.10 (s, 3H), 1.13 (s, 3H), 1.22 (s, 3H), 1.28 (m, 1H), 1.46 (m, 1H), 1.55 (m, 1H), 1.64 (m, 1H), 1.74 (m, 1H), 1.68 (ddd, $J=3.16$, 6.29, 14.3), 2.13 (m, 1H), 2.21 (dd, $J=10.59$, 14.11, 1H), 3.54 (s, 3H), 5.25 (m, 1H), 7.41 (m, 3H), 7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.38, 26.88, 30.16, 30.22, 37.88, 40.17, 70.14, 73.11, 75.37, 74.44, 122.46, 124.75, 127.44, 128.64, 129.80, 132.53; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −72.68 (s, 3F) 1%, −72.7 (s, 3F) 99%. HRMS (EI) m/z (MH^+) calcd for $C_{20}H_{25}O_4F_3$ 386.1705, found 386.1718.

4.11. (+)-*exo*-1,3,3-Trimethyl-2-oxabicyclo[2.2.2]oct-5-yl-*S*-α-methoxyphenyl-acetate, (+)-(11)

(*S*)-(+)-α-Methoxyphenylacetic acid (60 mg, 0.36 mmol) was added to oxalyl chloride (1.0 mL, 11.3 mmol). The solution was stirred at room temperature (20 h) then heated under reflux (3 h). The excess oxalyl chloride was removed by short-path distillation at atmospheric pressure followed by application of vacuum (0.5 Torr) at 0°C. The product acid chloride was then dissolved in dichloromethane (1.0 mL) and slowly added to a solution of *exo*-alcohol (−)-**2b** (61.3 mg, 0.36 mmol) and DMAP (132 mg, 1.08 mmol) in dichloromethane (1.0 mL) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature (16 h) followed by removal of the reaction solvent and direct flash column chromatography (hexane/ether, 2:1) of the residue. The yield of the oily colorless mandelic acid ester (+)-**11** was 44 mg (38%). $[\alpha]_D^{25}$ +6.2 ($c=1.7$, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.05 (s, 3H), 1.18 (s, 3H), 1.20 (s, 3H), 1.38 (m, 1H), 1.48 (m, 2H), 1.58 (m, 1H), 1.1 (dd, $J=1.97$, 3.89, 1H), 2.03 (dd, $J=10.36$, 14.07, 2H), 4.72 (s, 3H), 5.03 (ddd, $J=2.15$, 4.51, 10.5, 1H), 7.35 (m, 3H), 7.42 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.24, 30.26, 30.66, 37.73, 40.21, 70.11, 73.19, 73.85, 83.01, 127.42, 128.84, 136.30. HRMS (EI) m/z (MH^+) calcd for $C_{19}H_{27}O_4$ 319.1901, found 319.1909.

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