Stereoselective Preparation of (1*S*,2*R*)- and (1*S*,2*S*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic Acids

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Starting with (1*S*)-ketopinic acid (7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptane-1-carboxylic acid), a facile high-yield synthesis of diastereomerically pure (1*S*,2*R*)- and (1*S*,2*S*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic acids, potentially useful as chiral auxiliaries, has been achieved: the key step for the latter (2-*endo* isomer) involves the base-catalyzed epimerization of the (1*S*,2*R*)-2-hydroxy isomer (2-*exo*-isomer), exclusively formed by the L-Selectride® reduction of alkyl ketopinate, *via* the retro-aldol reaction.

Keywords ketopinic acid; chiral auxiliary; reduction; 2-*exo*-hydroxyapocamphanecarboxylic acid; 2-*endo*-hydroxyapocamphanecarboxylic acid

Camphor-derived chiral auxiliaries have proved to be highly versatile in a number of asymmetric reactions.[1] We have recently reported the effective use of members of this class of carboxylic acids, such as (1*S*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxylic acid (ketopinic acid)[2] and the 2-alkoxy analogue [(1*S*,2*R*)-2-alkoxy-1-apocamphanecarboxylic acid],[3] as chiral templates in the diastereoselective preparation of chirons for 2-amino alcohols.

In the course of that study, we required a practical preparation of both 2-*exo*- and 2-*endo*-hydroxy-1-apocamphanecarboxylic acids, which are potentially highly promising chiral directors. This paper describes in detail the stereoselective preparation of the title compounds from commercially available ketopinic acid.[4]

Reduction of alkyl (1*S*)-ketopinate (**1a—c**) with L-Selectride® at −78 °C resulted in exclusive formation of (1*S*,2*R*)-2-hydroxy-1-apocamphanecarboxylates (2-*exo*-isomers)[5] (**2a—c**) (94—97% yields). On the other hand, the 2-*endo*-hydroxy derivative (**3a**) was obtained only with a poor ratio of *endo* to *exo* of 1:3 on treatment of the methyl ester (**1a**) with sodium borohydride,[6] while the use of cerium chloride as an additive improved the ratio to 2:1 in favor of the *endo* isomer.[5] The butyl ester (**1b**) gave a poorer *endo*:*exo* ratio of 1:3 even in the presence of cerium chloride. Thus, sodium borohydride reductions seem to be still impractical for the preparation of the 2-*endo*-alcohols (**3**).[7]

Base-catalyzed epimerization of the isomeric alcohols would be feasible by the retro-aldol type cleavage of the C_1–C_2 bond followed by recyclization. The equilibrium between the 2-*exo*- and 2-*endo*-alcohols thus attained would be biased greatly in favor of the *endo*-isomer due to the steric repulsion by the *gem*-dimethyl group at C_7. In practice, treatment of either isomer with catalytic amounts of bases such as potassium *tert*-butoxide and sodium hydride in *N*,*N*-dimethylformamide (DMF) under cooling gave predominantly the *endo*-isomer. Thus, starting from (1*S*,2*R*)-2-hydroxy *n*-butyl and *tert*-butyl esters (**2b** and **2c**), the (1*S*,2*S*)-derivatives (**3b** and **3c**) were obtained in 77% and 79% yields, respectively, in addition to the starting *exo*-isomers (11—12% yields) under the optimum conditions using *tert*-butoxide in DMF below 20 °C for 1 h. Under identical conditions, the *endo*-isomer (**3b**) was recovered in 83% yield in addition to the epimerized *exo*-isomer (**3a**) in 7.4% yield as would be expected after complete equilibration. This epimerization might involve the retro-aldol reaction as a key step, though an attempt to isolate the aldehydic intermediates was unsuccessful. As would be expected from the proposed mechanism, the 2-alkoxy derivatives were completely unreactive under the above equilibrium conditions.

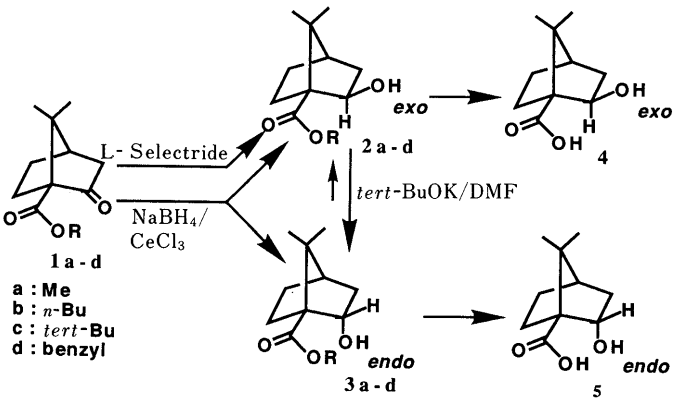

Chart 1

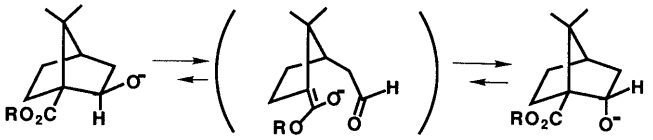

Chart 2

Based on the above findings, benzyl (1*S*)-ketopinate (**1d**) was reduced by L-Selectride® to the 2-*exo*-hydroxy isomer (**2d**) in 95% yield, which was then treated with potassium *tert*-butoxide in DMF to give 67% yield of the 2-*endo*-isomer (**3d**) in addition to the starting 2-*exo*-derivative (7%). The isomeric benzyl esters (**2d** and **3d**) thus obtained were hydrogenolyzed on 10% Pd–C to give cleanly the (1*S*,2*R*)-2-hydroxy (2-*exo*-isomer) and (1*S*,2*S*)-2-hydroxy (2-*endo*-isomer) carboxylic acids (**4** and **5**), respectively, in quantitative yields.

In conclusion, we present here facile practical routes to both 2-*exo*- and 2-*endo*-hydroxy-7,7-dimethylbicyclo[2.2.1]-heptane-1-carboxylic acids from readily available ketopinic acid.

Experimental

Melting points were determined on a Yanaco micro melting point apparatus and are given as read. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded in $CDCl_3$ at 400 MHz on a JEOL GSX400 instrument with tetramethylsilane as an internal standard. Optical rotations were measured in $CHCl_3$ with a JASCO DIP-370 polarimeter. Tetrahydrofuran (THF) and DMF were distilled from sodium/benzophenone and over calcium hydride, respectively.

Methyl (1*S*)-Ketopinate (1a) (1*S*)-Ketopinic acid (8.482 g, 46.6 mmol) was added to a mixture of thionyl chloride (17 ml, 0.23 mol) and methanol (43 ml), and the whole was stirred at room temperature overnight. Removal of the solvent followed by silica gel chromatography (CH_2Cl_2) gave methyl (1*S*)-ketopinate (**1a**) (8.311 g, 42.3 mmol, 91%) as colorless crystals, mp 37—39 °C, $[\alpha]_D^{27}$ +38.4° (c=0.86). MS (EI) m/z: 196.1120 (M^+, Calcd for $C_{11}H_{16}O_3$, 196.1099). ^{1}H-NMR δ: 1.09 (3H, s), 1.16 (3H, s), 1.42 (1H, ddd, J=3.7, 9.5, 12.5 Hz), 1.75—1.84 (1H, m), 1.96 (1H, d, J=18.3 Hz), 1.99—2.09 (1H, m), 2.12 (1H, t, J=4.4 Hz), 2.33—2.42 (1H, m), 2.54 (1H, dt, J=3.7, 18.3 Hz), 3.76 (3H, s).

Butyl (1*S*)-Ketopinate (1b) (1*S*)-Ketopinic acid (5.612 g, 30.8 mmol) was dissolved in thionyl chloride (95 ml) and the whole was refluxed for 1 h followed by concentration *in vacuo* to yield an oily residue, which was dissolved in THF (50 ml). The solution was treated with BuOH (11.5 ml, 2 eq), triethylamine (6.5 ml, 1.5 ml) and 4-*N*,*N*-dimethylaminopyridine (376 mg, 3.1 mmol) at room temperature overnight. Usual work up followed by silica gel chromatography (CH_2Cl_2) gave butyl (1*S*)-ketopinate (**10b**) (6.608 g, 27.7 mmol, 90%) as a colorless oil, $[\alpha]_D^{26}$ +29.8° (c=1.0). MS (EI) m/z: 238.1540 (M^+, Calcd for $C_{14}H_{22}O_3$, 238.1570). ^{1}H-NMR δ: 0.93 (3H, t, J=7.3 Hz), 1.09 (3H, s), 1.17 (3H, s), 1.35—1.45 (3H, m), 1.60—1.67 (2H, m), 1.76—1.83 (1H, m), 1.95 (1H, d, J=18.3 Hz), 1.98—2.08 (1H, m), 2.11 (1H, t, J=4.4 Hz), 2.33—2.41 (1H, m), 2.54 (1H, dt, J=4.0, 18.3 Hz), 4.17 (2H, t, J=7.0 Hz).

***tert*-Butyl (1*S*)-Ketopinate (1c)** A solution of (1*S*)-ketopinic acid (1.012 g, 5.6 mmol) in CH_2Cl_2 (38 ml) was saturated with isobutylene gas in the presence of five drops of concentrated H_2SO_4 and stirred at room temperature overnight. After addition of triethylamine (1.0 ml, 7.2 mmol), volatile compounds were removed *in vacuo* followed by silica gel column chromatography to yield a colorless oil (1.230 g, 5.2 mmol, 93%), $[\alpha]_D^{29}$ +38.8° (c=1.1). MS (EI) m/z: 238.1539 (M^+, Calcd for $C_{14}H_{22}O_3$, 238.1570). ^{1}H-NMR δ: 1.08 (3H, s), 1.15 (3H, s), 1.34—1.40 (1H, m), 1.48 (9H, s), 1.70—1.77 (1H, m), 1.92 (1H, d, J=18.3 Hz), 1.96—2.03 (1H, m), 2.08 (1H, t, J=4.4 Hz), 2.28—2.36 (1H, m), 2.47—2.54 (1H, m).

Benzyl (1*S*)-Ketopinate (1d) Analogously to the butyl ester (**1b**), this ester was obtained in 79% yield, as a colorless oil from (1*S*)-ketopinic acid (2.01 g, 11.0 mmol), benzyl alcohol (1.2 ml, 11.6 mmol), triethylamine (2.3 ml, 16.5 mmol) and 4-*N*,*N*-dimethylaminopyridine (673 mg, 5.5 mmol), $[\alpha]_D^{27}$ +24.3° (c=1.04). MS (EI) m/z: 272.1411 (M^+, Calcd for $C_{17}H_{20}O_3$, 272.1413). ^{1}H-NMR δ: 1.05 (3H, s), 1.14 (3H, s), 1.38—1.44 (1H, m), 1.83 (1H, ddd, J=14.3, 9.5, 4.8 Hz), 1.96 (1H, d, J=18.3 Hz), 1.99—2.07 (1H, m), 2.10 (1H, t, J=4.6 Hz), 2.36—2.43 (1H, m), 2.54 (1H, dt, J=18.3, 4.0 Hz), 5.20 (1H, d, J=12.5 Hz), 5.24 (1H, d, J=12.8 Hz), 7.28—7.38 (5H, m).

Reduction of 1 with L-Selectride®. General Procedure A 1 M solution of L-Selectride® (6.2 mmol) in THF was added dropwise to a solution of an alkyl (1*S*)-ketopinate (**1**) (5.2 mmol) in THF (8.4 ml) at −78 °C for 30 min and the mixture was kept at 0 °C for another 30 min. After quenching with a 6 M NaOH aqueous solution and a 30% H_2O_2 solution (4.5 ml), the mixture was extracted repeatedly with ethyl acetate. Removal of the solvent followed by chromatography on silica gel (CH_2Cl_2) gave the corresponding 2-*exo*-hydroxyapocamphanecarboxylate (**2**) quantitatively.

Methyl (1*S*,2*R*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate (2a) 97% yield, mp 58—59 °C (from hexane) (lit.[7] 44—45 °C)[8] $[\alpha]_D^{29}$ −30.6° (c=1.01). *Anal.* Calcd for $C_{11}H_{19}O_3$: C, 66.64; H, 9.15. Found: C, 66.61; H, 9.05. ^{1}H-NMR δ: 1.07 (3H, s), 1.08—1.16 (1H, m), 1.23 (3H, s), 1.28—1.34 (1H, m), 1.71—1.91 (4H, m), 2.08—2.15 (1H, m), 3.75 (3H, s), 3.78 (1H, s), 4.05 (1H, dd, J=7.8, 2.8 Hz).

***n*-Butyl (1*S*,2*R*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate (2b)** 89% yield as an oil, $[\alpha]_D^{28}$ −22.1° (c=1.02). MS (EI) m/z: 240.1725 (M^+, Calcd for $C_{14}H_{24}O_3$, 240.1726), ^{1}H-NMR δ: 0.95 (3H, t, J=7.3 Hz), 1.08 (3H, s), 1.10—1.14 (1H, m), 1.23 (3H, s), 1.27—1.33 (1H, m), 1.34—1.46 (2H, m), 1.61—1.92 (6H, m), 2.08—2.17 (1H, m), 3.90 (1H, br s), 4.05 (1H, dd, J=3.1, 7.9 Hz), 4.09—4.22 (2H, m).

***tert*-Butyl (1*S*,2*R*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate (2c)** 96% yield as an oil, $[\alpha]_D^{29}$ −30.7° (c=1.02). MS (EI) m/z: 184.1100 (M^+, Calcd for $C_{10}H_{16}O_3$, 184.1100). ^{1}H-NMR δ: 1.06 (3H, s), 1.08—1.12 (1H, m), 1.23 (3H, s), 1.24—1.30 (1H, m), 1.49 (9H, s), 1.68—1.75 (2H, m), 1.77—1.89 (2H, m), 2.05—2.12 (1H, m), 4.02 (1H, ddd, J=8.0, 4.0, 1.9 Hz), 4.11 (1H, s).

Benzyl (1*S*,2*R*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate (2d) 95% yield as an oil, $[\alpha]_D^{29}$ −14.3° (c=1.01). MS (EI) m/z: 274.1568 (M^+, Calcd for $C_{17}H_{22}O_3$, 274.1570). ^{1}H-NMR δ: 1.06 (3H, s), 1.08—1.14 (1H, m), 1.23 (3H, s), 1.30—1.37 (1H, m), 1.71—1.92 (4H, m), 2.11—2.18 (1H, m), 3.72 (1H, d, J=12.5 Hz), 4.07 (1H, ddd, J=7.7, 3.3, 1.8 Hz), 5.17 (1H, d, J=12.5 Hz), 5.21 (1H, d, J=12.5 Hz), 7.30—7.39 (5H, m).

Reduction of 1a with $NaBH_4/CeCl_3$. Methyl (1*S*,2*S*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate (3a) Sodium borohydride (0.16 g, 4.2 mmol) was added to a mixture of $CeCl_3 \cdot 7H_2O$ (0.36 g, 1.0 mmol) in H_2O (10 ml) and methyl (1*S*)-ketopinate (**1a**) (1.04 g, 5.3 mmol) in EtOH (6 ml) at −15 °C and the whole was stirred for 10 min. Usual work-up gave an oily product which was chromatographed on silica gel (CH_2Cl_2) to yield 0.42 g (40%) of the 2-*endo*-hydroxy compound (**3a**) in addition to the isomeric 2-*exo*-derivative (**2a**) (0.24 g, 23%). mp <30 °C (lit.[7] 54 °C),[8] $[\alpha]_D^{26}$ +37.5° (c=1.0). ^{1}H-NMR δ: 1.04 (3H, s), 1.06—1.07 (1H, m), 1.09 (3H, s), 1.35—1.43 (1H, m), 1.67—1.70 (1H, m), 1.84—1.96 (2H, m), 2.08 (1H, s), 2.27—2.35 (2H, m), 3.70 (3H, s), 4.73 (1H, dd, J=10.4, 2.6 Hz).

Base-Catalyzed Epimerization. General Procedure A solution of 2-*exo*-hydroxyapocamphane-1-carboxylates (**2**) (2 mmol) in DMF (12 ml) was stirred in the presence of potassium *tert*-butoxide (0.2 mmol) at room temperature or under cooling for 1 h. Usual work-up gave an equilibrium mixture of 2-*endo*- and 2-*exo*-alcohols, of which the former was predominant in a ratio of 7—9 : 1. The isomers were readily separated by chromatography on silica gel (CH_2Cl_2–AcOEt).

Methyl (1*S*,2*S*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate (3a) This was obtained in 63% yeild in addition to the starting *exo*-isomer (17%), and was identical with the 2-*endo*-isomer derived from sodium borohydride reduction.

***n*-Butyl (1*S*,2*S*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate (3b)** This was obtained in 76% yield in addition to the *exo*-isomer (11% yield) as an oil, $[\alpha]_D^{28}$ +32.0° (c=1.01). MS (EI) m/z: 240.1722 (M^+, Calcd for $C_{14}H_{24}O_3$, 240.1726). ^{1}H-NMR δ: 0.944 (1H, dd, J=2.2, 10.3 Hz), 1.04 (3H, s), 1.06—1.08 (1H, m), 1.10 (3H, s), 1.35—1.45 (3H, m), 1.59—1.70 (3H, m), 1.85—1.96 (2H, m), 2.17 (1H, br s), 2.27—2.36 (2H, m), 4.00—4.20 (2H, m), 4.73 (1H, dd, J=2.2, 10.3 Hz).

***tert*-Butyl (1*S*,2*S*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate (3c)** This was obtained in 78% yield in addition to the *exo*-isomer (12% yeild), mp 64.8—65.0 °C, $[\alpha]_D^{30}$ +33.3° (c=1.00). *Anal.* Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.74; H, 10.17. ^{1}H-NMR δ: 1.03 (3H, s), 1.00—1.05 (1H, m), 1.09 (s, 3H), 1.47 (9H, s), 1.65—1.66 (1H, m), 1.85—1.88 (2H, m), 2.17 (1H, br), 2.24—2.31 (2H, m), 4.66 (1H, dd, J=10.5, 3.1 Hz).

Benzyl (1*S*,2*S*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate (3d) This was obtained in 66% yield as a colorless oil, in addition to the *exo*-isomer (7% yield). $[\alpha]_D^{29}$ +29.6° (c=1.02). MS (EI) m/z: 274.1577 (M^+, Calcd for $C_{17}H_{22}O_3$, 274.1570). ^{1}H-NMR δ: 1.03 (3H, s), 1.04—1.09 (1H, m), 1.12 (3H, s), 1.35—1.41 (1H, m), 1.68 (1H, t, J=4.4 Hz), 1.84—2.00 (2H, m), 2.08 (1H, br s), 2.38—2.27 (2H, m), 4.76 (1H, dd, J=2.4, 9.7 Hz), 5.14 (1H, d, J=13.2 Hz), 5.17 (1H, d, J=13.2 Hz), 7.29—7.38 (5H, m).

(1*S*,2*R*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic Acid (4) A solution of benzyl (1*S*,2*R*)-2-hydroxyapocamphanecarboxylate (**2d**) (0.28 g, 1.0 mmol) in MeOH (5 ml) was stirred in the presence of 10% Pd–C (0.1 g) under hydrogen gas at room temperature overnight. Removal of the catalyst followed by evaporation *in vacuo* gave the acid (**4**) as a colorless homogeneous solid (0.19 g, 99% yield), mp 214—216 °C (in a sealed tube) (from hexane–EtOH) (lit.[7] 246—247 °C),[8] $[\alpha]_D^{27}$ −33.3° (c=1.0). *Anal.* Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.92; H, 8.60. ^{1}H-NMR δ: 1.10 (3H, s), 1.12—1.18 (1H, m), 1.26 (3H, s), 1.32—1.42 (1H, m), 1.75—1.96 (4H, m), 2.16—2.24 (1H, m), 4.10 (1H, dd, J=3.3 Hz, 8.1 Hz), 7.8 (2H, br).

(1*S*,2*S*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic Acid (5) Analogously to the above, this acid was obtained by hydrogenolysis of benzyl (1*S*,2*S*)-2-hydroxyapocamphanecarboxylate (**3d**) as a colorless solid in 99% yield, mp 256—257 °C (from CCl_4) (lit.[7] 264–265 °C), $[\alpha]_D^{28}$ +43.6° (c=1.0). *Anal.* Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.98; H, 8.70. ^{1}H-NMR δ: 1.05 (1H, d, J=3.7 Hz), 1.08 (3H, s), 1.09 (3H, s), 1.36—1.42 (1H, m), 1.72 (1H, t, J=4.4 Hz), 1.87—2.01 (2H, m), 2.30—2.39 (2H, m), 4.76 (1H, dd, J=3.3, 10.1 Hz), 6.6 (2H, br).

References and Notes

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