A Practical Method for the Synthesis of Homochiral 2,10-Camphanediols

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The esters **3a** and **3b** are conveniently prepared from (+)-ketopinic acid (7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxylate, **1**) and are subsequently reduced to afford *exo*- and *endo*-2,10-camphanediols [1-(hydroxymethyl)-7,7-dimethylbicyclo [2.2.1]heptan-2-ols, **4a** and **4b**, respectively] in good overall yield. The alkylation of ester **3a** with buyllithium gives only *exo*-10,10-dibutyl-2,10-camphanediol [*exo*-1-(1-butyl-1-hydroxypentyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol, **5**] in good yield.

Homochiral diols have been widely employed in asymmetric synthesis, for example, diastereo-differentiating reactions of chiral acetals derived from chiral diols[1-6] and enantioselective nucleophilic additions of chiral alkoxytitanium(IV) complexes where chiral diols were used as alkoxy ligands.[7] On the other hand, functionalized camphor skeletons have been proved to be highly versatile in numerous asymmetric reactions contributing to high asymmetric induction synthesis.[8-10] These results encouraged us to report the synthesis of homochiral *exo*-2,10-camphanediol **(4a)**, *endo*-2,10-camphanediol **(4b)** and *exo*-10,10-dibutyl-2,10-camphanediol **(5)**.

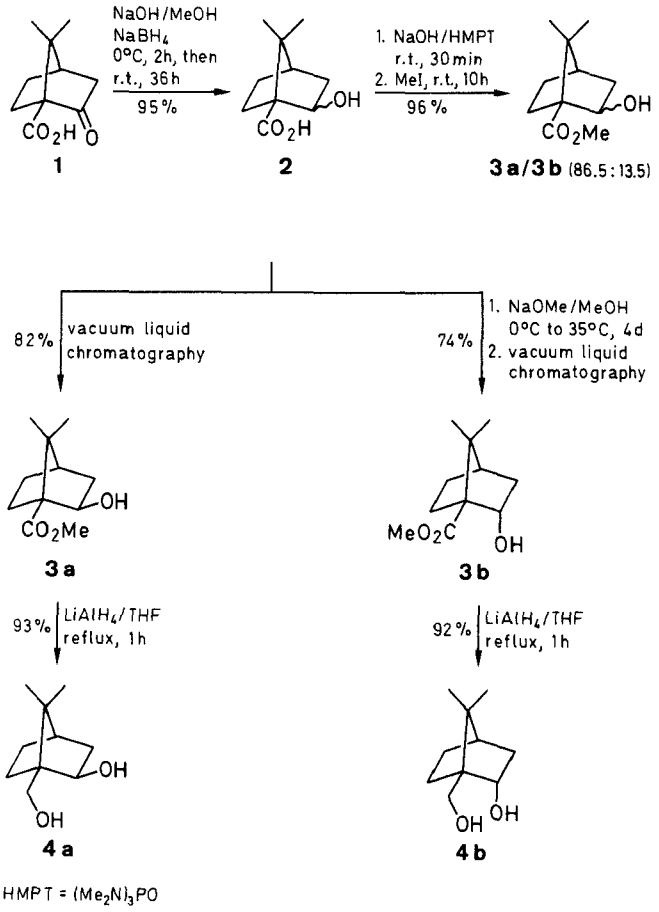
Reduction of (+)-ketopinic acid **(1)** is undoubtedly the best route for preparing 2,10-camphanediols.[11-14] Kuusinen[11] has reported the method of catalyzed hydrogenation of (+)-ketopinic acid **(1)**, where high pressure is used in the hydrogenation process and it is difficult to obtain homochiral diol **4a** and **4b**, thus the synthetic application is limited. Here sodium borohydride is used to reduce (+)-ketopinic acid **(1)** and an efficient Vacuum Liquid Chromatography[15] is used to separate the isomer of methyl *exo*-2-hydroxy-1-apocamphanecarboxylate **(3a)**. Also, methyl *endo*-2-hydroxy-1-apocamphanecarboxylate **(3b)** could be conveniently obtained by base-catalyzed epimerization[7] of the mixture **3**. Compounds **3a** and **3b** are further reduced with lithium aluminum hydride to afford 2,10-camphanediol **(4a)** and **(4b)**, respectively (Scheme **1**). ^{1}H-NMR spectra of **4b** and **3b** show the two doublet–doublet couplings of H-2, thus the stereochemistry of C-2 in **4b** and **3b** could be easily assigned by extra *W*-coupling between H-2 and H-6.[16] While **3a** reacts with butyllithium to give *exo*-10,10-dibutyl-2,10-camphanediol **(5)** (Scheme **2**). Comparison with published methods, the following advantages are noticeable:

i) it uses readily available starting materials, mild reaction conditions and the products are efficiently separated.

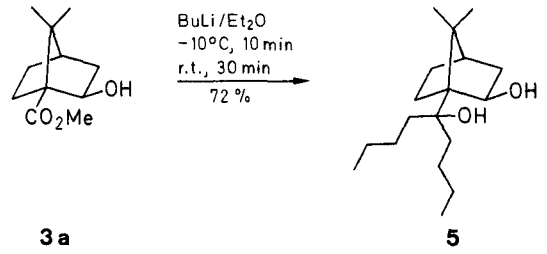
ii) *exo*-2,10-camphanediol **(4a)** is obtained in a higher overall yield (72%) and specially *endo*-2,10-camphanediol **(4b)** in an overall yield of 64% from (+)-ketopinic acid **1**, respectively.

iii) The alkyl group R is easily introduced to C-10 of **3a** and therefore variation of R should aid in the design of a chiral auxiliary with maximum efficiency during chirality transfer.

We herein present an useful method for synthesis of 2,10-camphanediols and their derivatives.



Scheme 1



Scheme 2

Melting points were measured on electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on Microlab 620 MX spectrophotometer, ^{1}H-NMR and ^{13}C-NMR on A Bruker WP 200 or WM 300 spectrometer, mass spectra on HD–DIS instrument, microanalyses on Carlo Erba–1106 element analyser, optical rotations on a Perkin–Elmer 241 polarimeter. The ratios **(3a/3b)** were measured on SC–7 GC instrument with chromosorb W. AW DMCS column. Vacuum liquid chromatography (VLC) was performed on Qingdao silica gel H (10–40/μm) and EtOAc/petroleum ether as eluent. (+)-Ketopinic acid **(1)**[17] is prepared from (+)-camphor.

Table. Spectroscopic Data of Products **3–5**

Product	IR (neat/KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C-NMR ($CDCl_3$) δ	MS (70 eV) m/z (%)
3a	3460, 3383 (OH), 1730, 1714 (CO_2Me)	1.08 (s, 3H), 1.12 (m, 1H), 1.22 (s, 3H), 1.32 (m, 1H), 1.76 (m, 2H), 1.87 (m, 2H), 2.13 (m, 1H), 3.73 (s, 3H), 3.88 (s, 1H, OH), 4.06 (m, 1H)	20.6, 21.9, 27.5, 30.8, 39.7, 45.7, 49.4, 51.4, 58.5, 77.8	198 (M^+, 3), 170 ($M^+ - H_2O$, 72), 41 (100)
3b	3460 (OH), 1726, 1711 (CO_2Me)	1.04 (s, 3H), 1.10 (s, 3H), 1.34 (m, 2H), 1.69 (t, 1H, J = 4.1), 1.90 (m, 3H, OH), 2.32 (m, 2H), 3.71 (s, 3H), 4.73 (ddd, 1H, J = 10.0, 3.5, 1.5)	19.6, 21.5, 23.6, 28.4, 37.2, 46.4, 50.9, 51.4, 59.7, 73.8	198 (M^+, 2), 170 ($M^+ - H_2O$, 50), 41 (100)
4a	3380 (OH)	0.89 (s, 3H, 3 × H8), 1.08 (m, 2H, $H6_\beta$, $H5_\beta$), 1.17 (s, 3H, 3 × H9), 1.48 (m, 1H, $H6_\alpha$), 1.76 (m, 4H, $H3_\alpha$, $H3_\beta$, H4, $H5_\beta$), 2.85 (s, 1H, OH), 3.24 (s, 1H, OH), 3.72 (d, 1H, $J_{10,10}$ = 11.1, H10), 3.93 (d, 1H, $J_{10,10}$ = 10.8, H10), 3.98 (dd, 1H, $J_{2,3_\alpha}$ = 7.8, J_{3_β} = 3.9, H2)	20.6 (C_8), 20.9 (C_9), 26.8 (C_5), 29.9 (C_6), 40.3 (C_3), 46.0 (C_4), 46.4 (C_7), 52.9 (C_1), 63.1 (C_{10}), 78.3 (C_2)	152 ($M^+ - H_2O$, 2), 108 (100)
4b[18]	3380 (OH)	0.91 (s, 3H), 0.93 (s, 3H), 0.99 (dd, 1H, J = 13.3, 3.1), 1.38 (m, 2H), 1.63 (t, 1H, J = 4.4), 1.82 (m, 1H), 2.11, (s, 2H, OH), 2.29 (m, 2H), 3.69 (d, 1H, J = 10.3), 3.84 (d, 1H, J = 10.2), 4.46 (ddd, 1H, J = 10.0, 3.5, 2.0)	25.5, 26.6, 28.7, 33.3, 42.4, 49.4, 51.2, 55.4, 67.0, 76.3	171 ($M^+ + 1$, 1), 153 ($M^+ + 1 - H_2O$, 10), 108 (100)
5	3248 (OH)	0.93 (m, 10H), 1.08 (m, 2H), 1.14 (s, 3H), 1.30 (m, 6H), 1.38 (s, 3H), 1.49 (t, 1H, J = 4.2), 1.71 (m, 5H), 2.24 (m, 1H), 2.28 (s, 2H, OH), 4.16 (dd, 1H, J = 7.8, 3.5)	14.1, 14.2, 23.2, 23.7, 24.8, 26.4, 26.5, 27.1, 29.4, 36.3, 38.2, 40.7, 48.2, 48.5, 57.9, 79.9, 80.3	265 ($M^+ + 1 - H_2O$, 18), 247 ($M^+ + 1 - 2 \times H_2O$, 100)

Methyl *exo*-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate (3a):

exo-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic Acid (**2**):

(+)-Ketopinic acid (**1**; 9.1 g, 50 mmol) is treated with NaOH (2.1 g, 55 mmol) in MeOH (100 mL) and $NaBH_4$ (1.0 g, 26 mmol) is added to the solution over 2 h at 0 °C under N_2. The mixture is allowed to warm and stirred at r.t. for 16 h, and then cooled to 0 °C and an additional $NaBH_4$ (1.0 g, 26 mmol) is introduced in 2 h. The mixture is continued to react at r.t. for 16 h, cooled to 0 °C again and acidified with 6N HCl to PH 4. The solvent is removed under vacuum and H_2O (50 mL) is added. The H_2O layer is extracted with Et_2O (40 mL), acidified and extracted with Et_2O (2 × 30 mL) again. The combined Et_2O layer is washed with brine (2 × 20 mL), dried (Na_2SO_4). The solvent is evaporated under vacuum to give acid **2**, yield: 8.7 g (95%).

Methyl exo-2-Hydroxy-7,7-dimethyl bicyclo[2.2.1]heptane-1-carboxylate (**3a**):

A 6N. NaOH (8 mL) is added to a solution of **2** (8.3 g, 45 mmol) in HMPT (125 mL), and the mixture is shaked for 30 min. MeI (14 mL, 225 mmol) is then poured and stirred at r.t. for 10 h. A 5% HCl (250 mL) is added, the mixture is extracted with Et_2O (5 × 50 mL). The combined Et_2O is successively washed with H_2O (2 × 40 mL), saturated Na_2SO_3 (40 mL) and H_2O (2 × 30 mL), dried (Na_2SO_4). The solvent is removed at reduced pressure to give a crude ester **3**, Yield: 8.6 g (96%); **3a/3b** (86.5: 13.5). The mixture **3** (5.0 g) is separated by VLC to give **3b**, Yield: 0.5 g (10%), oil and **3a**, yield: 4.1 g (82%); mp 57–58 °C (Lit.[11] mp 44–45 °C); $[\alpha]_D^{25}$ − 29.0° (c = 0.94, EtOH).

$C_{11}H_{18}O_3$	calc.	C 66.64	H 9.15
(198.3)	found	66.30	9.45

Methyl *endo*-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylate (3b):

A 2.5 M NaOMe in MeOH (18 mL) is added to a solution of the mixture **3** (3.5 g, 18.7 mmol) in abs. MeOH (80 mL) at 0 °C under N_2. The mixture is allowed to warm to 35 °C and stirred for 4d, monitored by GC analyses. A sat. aq NH_4Cl (50 mL) and Et_2O (100 mL) is added to the mixture at 0 °C. The Et_2O layer is separated, and the H_2O layer is extracted with Et_2O (2 × 50 mL). The combined organic layer is washed with H_2O (40 mL), brine (2 × 40 mL), dried (Na_2SO_4). The solvent is evaporated at reduced pressure and a crude **3** (**3a/3b**, 6.1 : 93.9) is purified by VLC to give endo isomer **3b**; yield: 2.6 g (74%); oil (Lit.[11] mp 53.5–54.0 °C); $[\alpha]_D^{25}$ + 33.2° (c = 1.02, EtOH).

***exo*-1-(Hydroxymethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol (4a); Typical Procedure:**

A solution of ester **3a** (2.5 g, 12.6 mmol) in THF (20 mL) is added dropwise to a mixture of $LiAlH_4$ (1.0 g, 25.0 mmol) and THF (60 mL) at − 5 °C under N_2, then the cooling bath is removed and the mixture is refluxed for 1 h. A 10% NaOH (5 mL) is added at − 5 °C, and the mixture is filtered and washed with Et_2O (5 × 20 mL). The combined Et_2O is dried (Na_2SO_4) and evaporated at reduced pressure. The residue is recrystallized from petroleum ether to give **4a**; yield: 2.0 g (93%); mp 257.5–259 °C (Lit.[11] mp 262–263 °C, Lit.[13] 232–235 °C); $[\alpha]_D^{25}$ − 38.2° (c = 0.97, EtOH).

$C_{10}H_{18}O_2$	calc.	C 70.55	H 10.66
(170.3)	found	70.82	10.44

Ester **3b** (1.5 g, 7.6 mmol) is reduced according to above procedure to give **4b**; yield: 1.2 g (93%); mp 229–231 °C (Lit.[11] mp 248–249 °C, Lit.[18] mp 180 °C); $[\alpha]_D^{25}$ + 30.0° (c = 1.04, EtOH).

$C_{10}H_{18}O_2$	calc.	C 70.55	H 10.66
(170.3)	found	70.35	10.86

***exo*-1-(1-butyl-1-hydroxypentyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol (5):**

BuLi in hexane (7 mL, 10.5 mmol) is added dropwise in a solution of ester **3a** (0.60 g, 3.0 mmol) in abs. Et_2O (10 mL) at − 10 °C under N_2 and is stirred for 10 min. The mixture is then allowed to warm and stirring is continued at r.t. for 30 min. Et_2O (20 mL) and H_2O (10 mL) are added at 0 °C, and the organic layer is then separated, washed with brine (2 × 10 mL) and dried (Na_2SO_4). The solution is concentrated at reduced pressure and the residue is distilled by bulb-to-bulb distillation at 150–155 °C/0.25 mbar to give diol **5**; yield: 0.61 g (72%); mp 107–108 °C; $[\alpha]_D^{25}$ − 10.0° (c = 1.15, EtOH).

$C_{18}H_{34}O_2$	calc.	C 76.54	H 12.13
(282.5)	found	76.49	12.55

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