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Synthesis of Homochiral 1,2-Diols from (-)-Fenchone and (+)-Camphor

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Abstract: (+)-(1*R*,2*S*)-1,2-dihydroxy-7,7-dimethylnorbornane (**3**) and (-)-(1*R*,2*R*)-1,2-dihydroxy-3,3-dimethylnorbornane (**12**) have been obtained from (-)-fenchone and (+)-camphor.

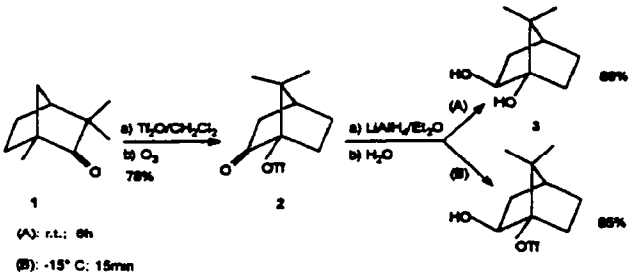
There are several reports on the use of acyclic and monocyclic homochiral 1,2-diols as chiral auxiliares and chiral ligands.[1] On the other hand, examples of bicyclic 1,2-diols are very rare, due to the difficulty of their preparation.[2] However, for the study of the mechanism of asymmetric reactions, it is convenient to have a series of scheletal isomers at ones disposal.

With regard to this, we report here on the preparation of novel homochiral 1,2-diols and derivatives, from the natural occurring ketones (-)-fenchone (**1**) and (+)-camphor (**5**) respectively.

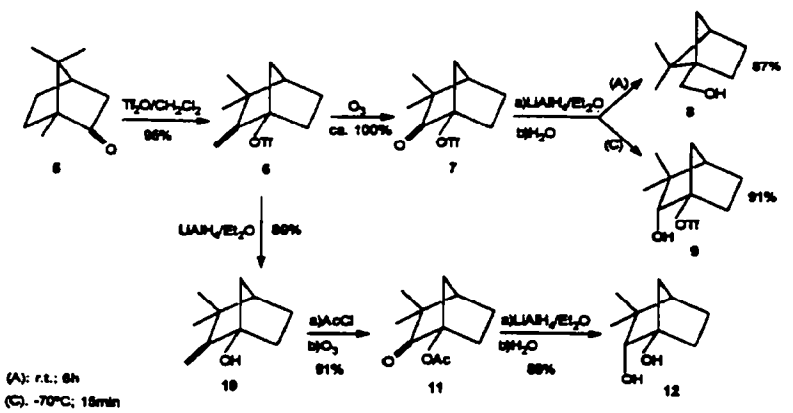
(+)-(1*R*,2*S*)-1,2-dihydroxy-7,7-dimethylnorbornane (**3**) was obtained straightforwardly from **1** as shown in scheme 1. The reaction of the 2-oxo triflate **2**[3] with $LiAlH_4$ in Et_2O for 6 h at r.t (path A) takes place with very high diastereoselectivity (> 98% d.e) and yield (89%). When the reaction was conducted at -15°C for 15 min (path B), the product was the 2-*exo*-hydroxy triflate **4** (> 98% d.e, 85%).[3] In the case of the 2-oxo triflate **7** (Scheme 2), the reaction takes place, *via* path A, with ring contraction[3] giving the alcohol **8**.[4] However, at -70°C (path C), the 2-*endo*-hydroxy triflate (**9**) was obtained (> 98% d.e, 91%). The preparation of (-)-(1*R*,2*R*)-1,2-dihydroxy-3,3-dimethylnorbornane (**12**)[5] was achieved by supression of the ring contraction employing the poorer leaving group acetate. Thus, the reduction of 2-oxo acetate **11**, prepared

as shown in scheme 2,[5,6] with $LiAlH_4$ yields **12** (> 98% d.e, 86%).

In summary we have presented a convenient method for the preparation of the homochiral 1,2-diols **3** and **12**. The applications of **3**, **12**, **4** and **9** as chiral auxiliares will be reported later.



SCHEME 1



SCHEME 2

EXPERIMENTAL

^1H NMR and ^{13}C NMR were recorded on Varian-XL 300 MHz spectrometer in deuterochloroform, and chemical shifts are expressed in ppm. IR spectra were recorded on Perkin-Elmer 781 spectrometer. Mass spectra were recorded on Varian-Mat 711 instrument. Optical rotations were measured on Perkin-Elmer 241 Polarimeter. Melting points were determined on Gallemkamp apparatus and are uncorrected. Capillary GLC data were recorded on Perkin-Elmer Sigma 300 (column type: OV-101, 25 m).

General procedure for the synthesis of the 2-oxo-1-norbornyl derivatives 2, 7 and 11.

Ozone was passed through a -40°C cooled solution of the corresponding 2-methylen-1-norbornyl derivative (20.0 mmol) in methanol (50 mL). After 2 h. (the reaction time was monitored by GLC), the cold solution was purged with nitrogen to remove the excess of ozone, and treated with dimethyl sulfide (2 mL). The reaction mixture was stirred for 10 minutes and allowed to warm up to room temperature. The resulting solution was diluted with water (100 mL) and extracted with CH_2Cl_2 (4x25 mL). The organic layer was washed with brine (2x25 mL) and dried over $MgSO_4$. The extract was concentrated under reduced pressure and the 2-oxo-1-norbornyl derivative was purified by elution chromatography (silicagel, pentane/CH_2Cl_2 4:1

for **2** and **7**, and silicagel, pentane/diethyl ether 4:1 for **11**).

(-)-(1*R*)-7,7-dimethyl-2-oxo-1-norbornyl triflate (2)

^{1}H NMR δ: 2.56 (1H, ddd, J=18.4 Hz, J=4.8 Hz, J=2.7 Hz), 2.35-2.10 (5H, m), 1.66 (1H, m), 1.14 (3H, s), 1.02 (3H, s); ^{13}C NMR δ: 205.6 (C2), 118.3 (CF_3, q, J=318.2 Hz), 103.0 (C1), 47.4 (C7), 41.3 (C3), 38.1 (C4), 26.9 (C5), 24.1 (C6), 18.5 (Me), 18.0 (Me); IR (CCl_4) ν: 2960, 1780 (CO), 1420 (SO_2), 1220 (CF_3), 1150 (SO_2), 1120 cm^{-1}; MS m/e (%B): 153 (M^+·-Tf, 12), 109 (12), 97 (19), 83 (10), 69 (43), 67 (25), 55 (100); mp: 81.4-82.9°C; $[\alpha]_D^{20}$: see lit.[3a]

(-)-(1*R*)-3,3-dimethyl-2-oxo-1-norbornyl triflate (7)

^{1}H NMR δ: 2.55 (1H, bd, J=10.0 Hz), 2.25 (1H, bs), 2.20-1.80 (5H, m), 1.13 (3H, s), 1.09 (3H, s); ^{13}C NMR δ: 210.5 (C2), 118.0 (CF_3 q, J=316.7 Hz), 98.3 (C1), 46.6 (C3), 41.4 (C4), 37.5 (C7), 28.3 (C6), 23.4 (C5), 23.3 (Me), 21.3 (Me); IR (CCl_4) ν: 2980, 1780 (CO), 1420 (SO_2), 1220 (CF_3), 1150 (SO_2), 1020, 930, 920 cm^{-1}; MS m/e (%B): 286 (M^+·, 24), 215 (30), 125 (50), 83 (37), 56 (69), 46 (100), 41 (33); mp: 39.0-39.7°C; $[\alpha]_D^{20}$: see lit.[3a]

(+)-(1*R*)-3,3-dimethyl-2-oxo-1-norbornyl acetate (11)

^{13}C NMR δ: 214.7 (C2), 169.6 (OCO), 88.7 (C1), 47.4 (C3), 42.9 (C4), 37.2 (C7), 28.5 (C6), 23.7 (C5), 23.0 (Me), 21.6 (Me), 21.2 (Me); $[\alpha]_D^{20}$ +24.5 (c=1.12, MeOH); ^{1}H NMR, IR, mp and MS see: lit.[5]

General procedure for the synthesis of the alcohols 3, 8 and 12.

To a 0°C cooled solution of LAH (20.5 mmol) in diethyl ether (30 mL) was slowly added a solution of the corresponding 2-oxo-1-norbornyl derivative (see scheme 2) (10.0 mmol) in diethyl ether, and stirred for 6 h (the reaction was monitored by GLC). The reaction mixture was treated with saturated solution of NH_4Cl (40 mL) and extracted with diethyl ether (5x20 mL). The organic layer was washed with brine (2x50 mL) and dried over $MgSO_4$. The extract was concentrated under reduced pressure and the corresponding 1,2-dihydroxynorbornane was purified by elution chromatography (silicagel, pentane/diethyl ether 20:1).

(+)-(1*R*,2*S*)-1,2-dihydroxy-7,7-dimethylnorbornane (3)

^{1}H NMR δ: 3.68 (1H, m), 2.78 (1H, bs), 2.64 (1H, bs), 1.84-1.75 (4H, m), 1.63 (1H, m), 1.18-1.13 (2H, m), 1.02 (3H, s), 0.92 (3H, s); ^{13}C NMR δ: 82.4 (C1), 75.7 (C2), 44.9 (C7), 40.6 (C4), 39.0 (C3), 30.7 (C5), 26.6 (C6), 19.5 (Me), 19.1 (Me); IR (CCl_4) ν: 3600 (OH), 2970, 1230, 1170, 1090 cm^{-1}; MS m/e (%B): 156 (M^+·, 29), 141 (11), 138 (4), 123 (34), 97 (85), 95 (49), 69 (50), 55 (60), 41 (100); mp: 200°C with decomposition; $[\alpha]_D^{20}$ +15.0 (c=0.84, MeOH).

(+)-5,5-dimethyl-1-hydroxymethylbicyclo[2.1.1]hexane (8)

^{13}C NMR δ: 62.6 (CH_2OH), 54.1 (C1), 44.7 (C5), 43.9 (C4), 37.0 (C6), 27.3 and 25.6 (C2 and C3), 19.5 (Me), 19.2 (Me); $[\alpha]_D^{20}$ +5.3 (c=0.76 MeOH); ^{1}H NMR, IR and mp: see lit.[4]

(-)-(1*R*,2*R*)-1,2-dihydroxy-3,3-dimethylnorbornane (12)

^{13}C NMR δ:84.8 (C1), 82.7 (C2), 44.6 (C4), 39.7 (C7), 38.6 (C3), 30.5 (C6), 25.5 (C5), 24.4 (Me), 20.3 (Me); $[\alpha]_D^{20}$ -8.7 (c=0.76, MeOH); ^{1}H NMR, IR, mp and MS see lit.[5]

General procedure for the synthesis of 2-hydroxy-1-norbornyl triflates 4 and 9.

To a -15°C (-70°C in the case of **9**) cooled suspension of LAH (10.2 mmol) in diethyl ether (30 mL), was added a solution of the corresponding 2-oxo-1-norbornyl triflate (10.0 mmol) in diethyl ether (15 mL) and stirred for 15 minutes, the reaction was monitored by GLC. The reaction mixture was treated with saturated solution of NH_4Cl (40 mL) and extracted with diethyl ether (5x20 mL). The organic layer was washed with brine (2x20 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, pure 2-hydroxy-1-norbornyl triflate was obtained without further purification.

(+)-(1*R*,2*S*)-7,7-dimethyl-2-hydroxy-1-norbornyl triflate (4)

^1H NMR δ: 4.22 (1H, dt, J=8.0 Hz, J=4.0 Hz), 2.53 (1H, d, J=4.5 Hz), 2.19-1.89 (4H, m), 1.81-1.73 (2H, m), 1.31 (1H, m), 1.19 (3H, s), 1.02 (3H, s); ^{13}C NMR δ: 118.2 (CF_3, q, J=320.8 Hz), 102.4 (C1), 73.8 (C2), 47.7 (C7), 39.6 (C3), 38.5 (C4), 28.8 (C5), 27.5 (C6), 19.6 (Me), 19.1 (Me); IR (CCl_4) ν: 3620 (OH), 3980, 1420 (SO_2), 1220 (CF_3), 1150 (SO_2), 1000, 950, 905 cm^{-1}; MS m/e (%B): 270 (M^+-H_2O, 2), 226 (3), 155 (5), 137 (32), 109 (32), 95 (68), 79 (12), 69 (78), 67 (44), 59 (36), 55 (52), 43 (68), 41 (100); $[\alpha]_D^{20}$ +33.7 (c=0.40 MeOH).

(-)-(1*R*,*S*)-3,3-dimethyl-2-hydroxy-1-norbornyl triflate (9)

^1H NMR δ: 3.76 (1H, s), 2.43 (1H, bs), 2.18 (1H, m), 2.02 (1H, bd, J=9.6 Hz), 1.77 (1H, d, J=9.6 Hz), 1.65-1.50 (4H, m), 0.95 (3H, s), 0.72 (3H, s); ^{13}C NMR δ: 118.2 (CF_3, q, J= 314.5 Hz), 104.3 (C1), 80.2 (C2), 43.1 (C4), 39.8 (C3), 37.4 (C7), 30.5 (Me), 25.0 (C6), 22.6 (C5), 20.4 (Me); IR (CCl_4) ν: 3580 (OH), 2440 (OH), 2960, 1420 (SO_2), 1250, 1220 (CF_3), 1155 (SO_2), 1020, 990, 935, 900 cm^{-1}; $[\alpha]_D^{20}$ -21.3 (c=0.74, MeOH).

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