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Optically Active Bicyclo[2.2.2]octane Derivatives; Synthesis of (1S,4R,6R)-6-Hydroxybicyclo[2.2.2]octan-2-one from Its Enantiomer.

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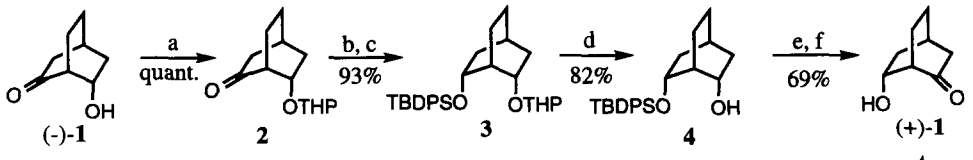
Abstract: (1S, 4R, 6R)-6-Hydroxybicyclo[2.2.2]octan-2-one, (+)-**1**, is synthesized from its enantiomer in 6 steps using a combination of orthogonal protecting groups and red-ox chemistry.

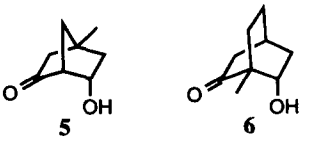
Biotransformations provide enantiomerically pure or highly enriched compounds which are frequently used as starting materials in organic synthesis.[1-4] Although optically active ketoalcohol (-)-**1** is available via bakers' yeast reduction of the corresponding prochiral diketone, its enantiomer (+)-**1** can not be prepared with this method.[5,6]Since it is important to have access to both enatiomers particularly for synthesis of biologically relevant compounds this encouraged us to synthesize (+)-**1** using (-)-**1** as a starting material following the sequence presented below (See scheme). This methodology could probably also be applied on similar bicyclic ketols such as **5** and **6**, which would give access to the enantiomers of the earlier synthesized terpenes starting from these compounds.[7-9]

The hydroxyl group of (-)-**1** was protected as the THP-ether and then the resulting ketone was stereospecifically reduced by $NaBH_4$ to give the 6R-isomer of the THP protected diol only. Protection of the new hydroxyl group as the diphenyl-t-butylsilyl (TBDPS) ether followed by selective removal of the THP-protection gave the new alcohol **4**. Surprisingly, the deprotection procedure using p-toluensulphonic acid (PTS) and methanol was not as selective as one would expect from the literature.[10,11] We only got 40% of the desired product and some of the material was further deprotected to give the meso-diol. A very selective deprotection was achieved by simply using the sterically more demanding 2-propanol as solvent instead of methanol. Subsequent oxidation of alcohol **4** followed by deprotection gave (+)-**1** in 53% over all yield. All stereocenters were inverted using this methodology. The e.e. was slightly higher for (+)-**1** (94.4%) compared to (-)-**1** (92.5%). This might be due to some small enrichment when the diastereomeric THP-protected compounds (**2** and **3**) were chromatographed.



(-)-**1** **2** **3** **4** (+)-**1**

Scheme. (a) PPTS, DHP, CH_2Cl_2; (b) $NaBH_4$, THF:MeOH; (c) TBDPSCl, imidazole. DMF; (d) PTS, iPrOH:Et_2O; (e) DMSO, $(COCl)_2$, Et_3N; (f) Bu_4NF



5 **6**

Experimental

General. GC chromatographic analyses were performed on a Varian 3400 gas cromatograph equipped with a DBwax (J&W Scientific) capillary column (30 m, 0.25 mm i.d., 0.25 μm stationary phase). Optical rotations were measured with a Perkin Elmer 141 polarimeter at the sodium D-line and at ambient temperature using $CHCl_3$ as solvent. Infrared spectra were recorded with a Perkin Elmer 298 infrared spectrometer and NMR spectra with a Varian Gemini 300 MHz spectometer using $CDCl_3$ ($CHCl_3$ δ 7.26 (^1H) and 77.0 (^{13}C)) as solvent. Flash chromatography employed Matrex Amicon normal phase silica gel 60 (0.035-0.070 mm). Ethyl acetate and heptane was distilled prior to chromatography. Methylene chloride (CH_2Cl_2) and dimethylformamide (DMF) was distilled from calcium hydride, tetrahydrofuran (THF) and diethylether was distilled from sodium-benzophenone ketyl. All reactions were performed in septum-capped, oven dried flasks under an atmospheric pressure of nitrogen.

(1R,4S,6S)-6-(2-Tetrahydropyranyloxy)-bicyclo[2.2.2]octan-2-one (2). DHP (1.8 ml, 21.4 mmol) was added to a solution of ketoalcohol (+)-**1** (1.0 g, 7.14 mmol) in CH_2Cl_2 (50 ml). The mixture was cooled to 0°C followed by addition of pyridiniumtosylate (PPTS) (cat. amt.). After 8 h at room temperature ice was added, the phases were separated and the organic phase was washed with aqueous saturated sodiumhydrogen carbonate (2x10 ml), dried (Na_2SO_4) and the solvent was removed at reduced pressure. The residue (1.76 g) was chromatographed (SiO_2, heptane:ethyl acetate 70:30, R_f 0.26) to give (**2**) as an oil (1.6 g, quantitative yield). The diastereomeric ratio was 46:54 according to GC analysis. $[\alpha]_D^{22}$-9.5 (c 2.70, $CHCl_3$), IR 1725 cm^{-1} (C=O). NMR ($CDCl_3$) δ 4.73 (t, 0.5 H, J=3.0 Hz, H-2'), 4.68 (t, 0.5 H, J=3.6 Hz, H-2'), 4.21 (dt, 0.5 H, J_1=9.1 Hz, J_2=3.1 Hz, H-6), 4.12 (ddd, 0.5 H, J_1=8.8 Hz, J_2=3.7 Hz, J_3=2.4 Hz, H-6), 3.84 (m, 1H, H-6'α), 3.48 (m, 1H, H-6'β), 2.59 (m, 1H, H-1), 2.01-2.35 (m, 4H, H-3, H-4, $H\text{-}5_{endo}$), 1.40-1.84 (m, 11H, $H\text{-}5_{exo}$, H-7, H-8, H-3', H-4', H-5'). HREIMS Calcd. for $C_{13}H_{20}O_3$ 224.1412. Observed 224.1413.

(1R,2R,4S,6S)-2-(t-Butyldiphenylsilyloxy)-6-(2-tetrahydropyranyloxy)-bicyclo[2.2.2]octane (3). The THP ether (**2**) (470 mg, 2.10 mmol) was dissolved in THF (188 ml) and methanol (24 ml) whereafter $NaBH_4$ (220 mg, 5.81 mmol) was added all at once. After 35 h at room temperature the mixture was concentrated at reduced pressure and diluted with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure to give the monoprotected diol (452 mg, 95%) as an oil. GC analysis showed complete absence of (**2**). IR (KBr) 3520 cm^{-1}. This crude product was dissolved in DMF (1 ml) whereafter diphenyl-t-buthylsilylchloride (740 mg, 2.69 mmol) and imidazole (410 mg, 6.02 mmol) where added and the mixture was kept at room temperature for five days.[12] The solution turned inhomogeneous shortly after mixing. The mixture was diluted with ether, washed five times with water and dried (Na_2SO_4). Concentration at reduced pressure followed by chromatography (SiO_2, heptane:ethyl acetate 95:5, R_f 0.26) gave **3** as a colourless oil (909 mg, 98%). IR analysis showed no OH-absorption. $[\alpha]_D^{22}$+7.3 (c 3.85, $CHCl_3$). NMR ($CDCl_3$) δ 7.81 (m, 1H, $H_{Ar\text{-}ortho}$), 7.73 (m, 3H, $H_{Ar\text{-}ortho}$), 7.37 (m, 6H, $H_{Ar\text{-}meta}$, $H_{Ar\text{-}para}$), 4.87 (t, 0.5 H, J = 3.7 Hz, H-2'), 4.79 (t, 0.5 H, J = 3.6 Hz, H-2'), 3.88-4.07 (m, 3H, H-2, H-6, H-6'α), 3.49 (m, 1H, H–6'β), 1.40-2.06 (m, 12H, H-1, H-3, H-4, H-5, H-3', H-4', H-5'), 1.08-1.35 (m, 4H, H-7, H-8), 1.07 (S, broad, 9H, $-CH_3$). HRCIMS (NH_3) Calcd. for

$C_{29}H_{41}O_3Si$ (M+1) 465.2825. Observed 465.2823.

(1R,2R,4S,6S)-2-(Diphenyl-t-butylsilyloxy)bicyclo[2.2.2]octan-6-ol (4). Compound **3** (612 mg, 1.32 mmol) was dissolved in freshly distilled 2-propanol (20 ml) and ether (10 ml) followed by addition of p-toluensulphonic acid (PTS) (20 mg, 0.10 mmol). The mixture was kept at room temperature for 20 h, then ice was added and most of the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and washed with aqueous saturated sodium hydrogen carbonate. The aqueous phase was re-extracted with ethyl acetate. The combined organic phase was washed with brine and dried (Na_2SO_4). Concentration at reduced pressure followed by chromatography (SiO_2, heptane:ethyl acetate 9:1, R_f 0.27) gave **4** (413 mg, 82%) as a colourless oil which crystalized in the refridgerator (mp 64-65 °C) $[\alpha]_D^{22}$ -9.2 (c 1.65, $CHCl_3$). IR (KBr) 3300-3500 cm^{-1}(broad). NMR ($CDCl_3$) δ 7.70 (m, 2H, $H_{Ar\text{-}ortho}$), 7.67 (m, 2H, $H_{Ar\text{-}ortho}$), 7.41 (m, 6H, $H_{Ar\text{-}meta}$, $H_{Ar\text{-}para}$), 4.32 (d, 1H, J = 9.9 Hz, OH), 4.07 (m, 1H, H-2 or H-6), 3.90 (m, 1H, H-2 or H-6), 2.11 (m, 1H, H-5_{endo}), 2.01 (m, 1H, H-1), 1.59-1.70 (m, 4H, H-3, H-4, H-5_{exo}), 1.09-1.40 (m, 4H, H-7, H-8), 1.09 (S, 9H, -CH_3). CIMS (NH_3) 381 (M+1). HREIMS Calcd. for $C_{20}H_{23}O_2Si$ (M-tBu) 323.1467. Observed 323.1470.

(1S,4R,6R)-6-Hydroxybicyclo[2.2.2]octan-2-one ((+)-1). Dry DMSO (0.84 g, 10.7 mmol) diluted with CH_2Cl_2 (1.4 ml) was added dropwise to a solution of freshly distilled oxalyl chloride (0.28 ml, 3.25 mmol) in CH_2Cl_2 (2.9 ml) at -60°C.[13] The temperature was rised to -5°C and then **4** (413 mg, 1.09 mmol) in CH_2Cl_2 (1.2 ml) was added. The mixture was kept for 10 min at -5°C, then cooled to -15°C followed by addition of freshly distilled triethyl amine (1.86 ml, 13.3 mmol). The mixture was kept 10 min at -15°C then 30 min at room temperature. Water was added and the organic phase was separated. The aquous phase was re-extracted twice with CH_2Cl_2. The combined organic phase was washed subsequently with brine, 0.1 M HCl, aquous saturated sodium hydrogen carbonate, brine and dried (Na_2SO_4). Concentration at reduced pressure gave a crude oil which was filtered through a pad of silica to give the protected ketoalcohol as an oil (400 mg, 97%). IR (KBr) 1725 cm^{-1} (C=O). The oil (390 mg, 1.03 mmol) was diluted with THF (20 ml) and cooled to 0°C. One drop of glacial acetic acid was added followed by addition of tetrabutyl ammonium fluoride (1.54 ml, 1.54 mmol, 1M in hexane). The mixture was kept at room temperature for 40 h wherafter it was concentrated at reduced pressure to approximately 5ml. The residue was diluted with ethyl acetate and washed with aquous saturated sodium hydrogen carbonate. The aqueous phase was re-extracted twice with ethyl acetate and the combined organic phase was dried (Na_2SO_4). Concentration at reduced pressure, followed by chromatography (SiO_2, heptane:ethyl acetate 1:2, R_f 0.21) gave (+)-**1** as a white solid (102 mg, 71%) (mp 160-161°C), $[\alpha]_D^{22}$+6.8 (c 1.15, $CHCl_3$) (lit.[5] for (-)-**1**: $[\alpha]_D^{22}$ -6.5 (c 1.0, $CHCl_3$)). IR and NMR data were identical with those of (-)-**1**. Anal. Calcd. for $C_8H_{12}O_2$: C 68.55; H 8.63. Found C 68.6; H 8.7.

The determination of the enantiomeric purity was done by GC analysis of the Mosher esters of (+)- and (-)-**1** and was found to be 94.4% and 92.5%, respectively. A mixture of the two samples gave only two peaks. Note that (+)-**1** was prepared from the same batch of yeast reduction as (-)-**1** to acertain that no racemization had occured by migration of the protecting groups.

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