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Asymmetric Synthesis of (3R,5R)- and (3S,5S)-2,6-Dimethylheptane-3,5-diol, useful C_2 Chiral Auxiliaries.

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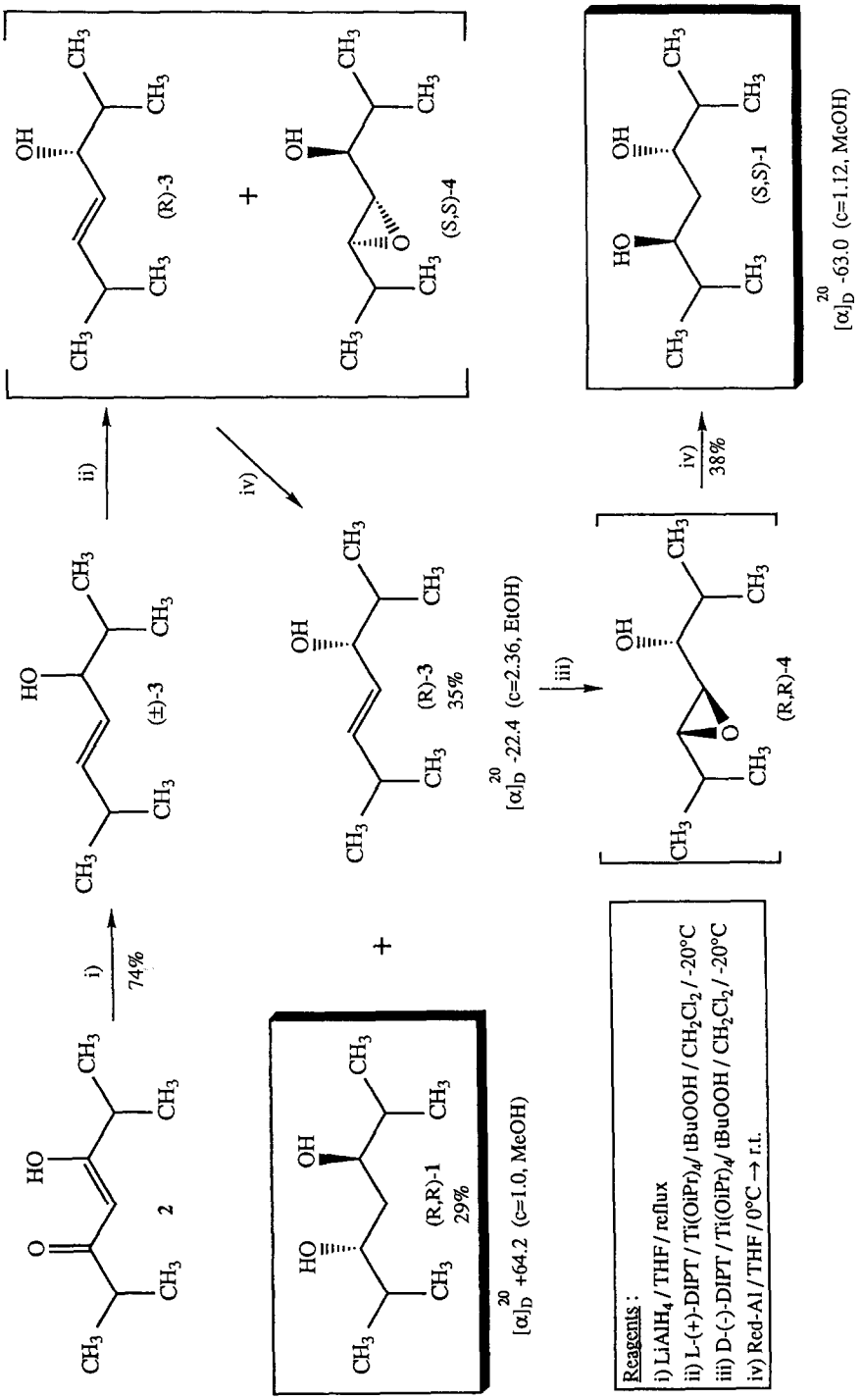
Abstract: (R,R)- and (S,S)-2,6-Dimethylheptane-3,5-diol, which are useful C_2 chiral auxiliaries, have been both synthesized in high optical purity from 2,6-dimethylheptane-3,5-dione, by using as key step a Sharpless kinetic resolution.

Enantiomerically pure 1,3 diols having a C_2 axis of symmetry are particularly useful as chiral auxiliaries in asymmetric synthesis.[1] Amongst these diols, 2,6-dimethylheptane-3,5-diol (**1**) shows distinct advantages over pentane-2,4-diol. Being bulkier than the latter, it generally shows better enantio- and diastereo-differentiating properties.[2] Moreover, it is much less volatile and can be easily recovered and recycled after hydrolysis of the acetal function. During the course of our work on the synthesis of scalemic α-halogenoaldehydes,[3] we needed a supply of enantiomerically pure (R,R)- and (S,S)-**1**. To the best of our knowledge, only one preparation procedure of these enantiomers has been reported,[4] through catalytic hydrogenation at high temperature and pressure of 2,6-dimethylheptane-3,5-dione (**2**) over Raney nickel modified with D- or L-tartaric acid. In our hands, this procedure could not be reproduced. Indeed, the attempted asymmetric reduction of pentane-2,4-dione repeatedly led to nearly racemic samples of pentane-2,4-diol. Thus we decided to synthesize (R,R)- and (S,S)-**1** by another approach, which had already been used for the synthesis of (2S,4S)- and (2R,4R)-non-8-ene-2,4-diol,[5] and which is outlined in scheme 1.

2,6-Dimethylheptane-3,5-dione (**2**)[4b] was reduced by $LiAlH_4$ into (±)-(E)-2,6-dimethylhept-4-en-3-ol [(±)-**3**)][6] in a 74% yield. The latter was submitted to a Sharpless kinetic resolution using L-(+)-DIPT and 0.5 eq of TBHP for 16 h, leading to a 53:47 mixture of (3S,5S)-2,6-dimethyl-4,5-epoxy-heptan-3-ol [(S,S)-**4**)] and 3 enriched in the R enantiomer. The two compounds were not separated, but directly submitted to a reduction with Red-Al,[7] affording after flash chromatography (R,R)-(+)-**1** [29% from (±)-**3**; $[\alpha]_D$ +64.2 (c=1.0, MeOH)], and (3R)-(-)-**3** [35%; $[\alpha]_D$ -22.4 (c=2.36, EtOH)]. The latter was submitted to another Sharpless kinetic resolution with D-(-)-DIPT, using 0.9 eq of TBHP. After 18 h, the 9:1 mixture of (R,R)-**4** and **3** thus obtained was treated with Red-Al. Work up and flash chromatography afforded (S,S)-(-)-**1** in a 13% yield from (±)-**3** {$[\alpha]_D$ -63.0 (c=1.12, MeOH)}. The yields reported in this paper are not optimized and could certainly be bettered.

In conclusion, the procedure described herein allows the easy synthesis in high optical purities (op>97%) of the two enantiomers of 2,6-dimethylheptane-3,5-diol, which are efficient and handy chiral auxiliaries. It is based on well-established reactions which do not require special equipment or extreme conditions as is the case with the synthesis previously described.[4]


i) 74%
ii)
iii)
iv)
iv) 38%
(±)-3
(R)-3
(S,S)-4
(R,R)-1
29%
(R)-3
35%
(R,R)-4
(S,S)-1
$[\alpha]_D^{20}$ +64.2 (c=1.0, MeOH)
$[\alpha]_D^{20}$ -22.4 (c=2.36, EtOH)
$[\alpha]_D^{20}$ -63.0 (c=1.12, MeOH)
Reagents :
i) $LiAlH_4$ / THF / reflux
ii) L-(+)-DIPT / $Ti(OiPr)_4$ / tBuOOH / CH_2Cl_2 / -20°C
iii) D-(-)-DIPT / $Ti(OiPr)_4$ / tBuOOH / CH_2Cl_2 / -20°C
iv) Red-Al / THF / 0°C → r.t.

Scheme 1

Experimental part

^{1}H NMR spectra were recorded on a BRUKER WM 250 spectrometer at 250 MHz and are reported in ppm from internal TMS on the δ scale. Data are reported as follows: chemical shift (multiplicity: s: singlet, bs: broad singlet, d: doublet, o: octet, m: multiplet, coupling constants in Hertz). Infrared spectra were taken with a BRUKER IFS 25 instrument as a film on a NaCl disk unless otherwise stated. EIMS were recorded on a VG Micromass 7070 spectrometer. Peak intensities are expressed as % relative to the base peak. Optical rotations were measured on a PERKIN-ELMER 141 polarimeter at 589 nm (sodium D line), in a 10 cm cell at 20 °C. Thin layer chromatography analyses were performed on 0.25 mm POLYGRAM silica gel SIL G precoated plates (MACHEREY NAGEL). Column chromatographies were performed over silica gel (MN Kieselgel 0.04-0.063 mm), using the flash technique. GC analyses were performed on a DELSI D200 apparatus equipped with a column of 10 % Carbowax 20 M on Chromosorb W, acid washed (2 m, 5 mm i. d.). During work up, organic solutions were dried over $MgSO_4$.

*$LiAlH_4$ reduction of 2,6-dimethylheptane-3,5-dione (**2**).*[6] To 4.39 g of $LiAlH_4$ in 35 ml of anhydrous Et_2O was added dropwise at 0 °C in 15 min, a solution of 2,6-dimethylheptane-3,5-dione[4b] (5.288 g, 33.8 mmol) in 35 ml of Et_2O and the resulting mixture was refluxed for 16 h. After cooling to 0 °C, 4 ml of H_2O were cautiously added followed by 4 ml of a 20% NaOH solution and 6 ml of H_2O. The mixture was filtered, the aqueous solution extracted with Et_2O and the aluminium salts repeatedly washed for 30-60 min with refluxing Et_2O. The combined organic extracts were washed with a saturated NaCl solution, dried, filtered and evaporated *in vacuo* to afford 4.135 g of residue. Flash chromatography of the latter on silica gel (hexane: ether, 85:15 to 20:80 afforded 3.549 g (74%) of (±)-(**3**), accompanied by *meso*-**1** (0.164 g) and (±)-**1** (0.208 g). (±)-**3**: oil; MS: m/z 142 ($M^{+\cdot}$, 4), 125 (1), 113 (11), 99 (100), 81 (43), 71 (9), 69 (9), 57 (25), 55 (22), 43 (96), 41 (27). IR: 3378, 3020, 2960, 2873, 1667, 1470-1456, 1385, 1367, 1099, 1017, 972 cm^{-1}. ^{1}H NMR: 5.59 (1H, dd, 15.5, 6.6 Hz, H-5), 5.40 (1H, ddd, 15.5, 7.3, 1.1 Hz, H-4), 3.76 (1H, bdd, 7.1, 6.1 Hz, H-3), 2.30 (1H, o, 6.7 Hz, H-6), 1.68 (1H, o, 6.6 Hz, H-2), 1.48 (1H, bs, OH), 1.0 (6H, d, 6.8 Hz, H-7+H-9), 0.91 (3H, d, 6.8 Hz) and 0.86 (3H, d, 6.8 Hz) (H-1+H-8).

*Kinetic resolution of (±)-**3**.* Under a nitrogen atmosphere, 2.08 g (14.6 mmol) of (±)-**3** dried on 3 Å molecular sieves were dissolved in dry CH_2Cl_2 containing 0.066 g of powdered 4 Å molecular sieves and 0.412 g of L-(+)-DIPT (1.76 mmol). Then, more CH_2Cl_2 was added until the substrate concentration reached 0.25 M and the reaction mixture was cooled to -20 °C. To this stirred mixture were added, 440 µl of $Ti(OiPr)_4$ (1.48 mmol), stirring was continued for 15 min, and then 2.4 ml of a dried solution of TBHP (3.0 M in toluene) were added. The reaction was allowed to proceed for 16 h at -18 °C under stirring. After usual work up, extraction with CH_2Cl_2, drying and evaporation of the solvent, 2.268 g of residue were obtained. GC analysis showed the presence of (R)-**3** and of (3S,5S)-**4** in a 53:47 ratio. This mixture was engaged without purification in the reduction step.

*Red-Al reduction of (S,S)-**4**.* Red-Al (5 eq, 3.5 M) in toluene was added to 20 ml of dry THF under nitrogen and the mixture of (R)-**3** and (S,S)-**4** in THF was slowly added under stirring at 0 °C. After 15 min, the reaction mixture ice bath was removed and the reaction was allowed to proceed at room temperature for three days. Usual work up and silica gel flash chromatography (hexane:ether 85:15 to 30:70) led to the isolation of (R)-(**3**) (35%) {$[\alpha]_D$ -22.4 (c=2.36, EtOH)}, unreacted (S,S)-**4** (7%) and (R,R)-(**1**) (29%). (R,R)-**1**: m. p. 88.5-89 °C (m. p. lit[4b]: 89-91 °C); $[\alpha]_D$ +64.2 (c=1.0, MeOH) {$[\alpha]_D$ lit[4] +64.5 (c=1.0, MeOH)}; MS: m/z 161 ($M^{+\cdot}$ + H·, 0.3), 142 (0.8), 117 (24), 99 (53), 81 (59), 73 (100), 70 (45), 55 (53), 43 (53); IR (KBr): 3350, 2975, 2875, 1470, 1430, 1406, 1360, 1330, 1150, 1105, 1045, 1005, 990, 900, 790, 660, 500 cm^{-1}; ^{1}H NMR: 3.65 (2H, m, H-3 + H-5), 2.13 (2H, bs, OH), 1.71 (2H, o, 6.7 Hz, H-2 + H-6), 1.60 (2H, dd, 6.4, 5.2 Hz, H-4), 0.96 (6H, d, 6.8 Hz) and 0.91 (6H, d, 6.8 Hz) (H-1, H-7, H-8 and H-9). (S,S)-**4**: oil; $[\alpha]_D$ -22.4 (c=2.36, EtOH); MS: m/z 141 ($M^{+\cdot}$ - OH·, 0.3), 115 (6), 97 (19), 86 (56), 73 (72), 71 (100), 69 (50), 57 (33), 55 (56), 43 (54), 41 (79); IR: 3455, 2960, 2875, 1470, 1385, 1368, 1250, 1080, 1030, 1000, 943,

926, 900, 875 cm^{-1}; ^1H NMR: 3.58 (1H, m, H-3), 2.86 (1H, dd, 2.8, 2.8 Hz, H-4), 2.81 (1H, dd, 7.0, 2.4 Hz, H-5), 1.84 (1H, d, 2.2 Hz, OH), 1.80 (1H, o, 6.7 Hz, H-2), 1.57 (1H, o, 6.8 Hz, H-6), 1.05-0.96 (12H, superposition of H-1, H-7, H-8 and H-9).

Kinetic resolution of (3R)-3 followed by Red-Al reduction. Using the same procedure as above, 1.21 g of (3R)-(-)-**3** {$[\alpha]_D$ -22.4} was submitted to a Sharpless kinetic resolution, but using D-(-)-DIPT and 0.9 eq of TBHP. After 18 h, the reaction mixture was treated in the usual way and the resulting mixture containing 90% of (R,R)-**4** by GC was directly reduced with Red-Al as described above. Silica gel flash chromatography of the resulting mixture afforded 0.515 g (38%) of (S,S)-**1**: m. p. 89.5-90 °C; $[\alpha]_D$ -63.0 (c=1.12, MeOH); {$[\alpha]_D$ lit.[4] -64.5 (c=1.0, MeOH)}; MS, IR and ^1H NMR: identical to those of (R,R)-**1**.

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