Synthesis of Enantiomers of 1,2-Heptanediol

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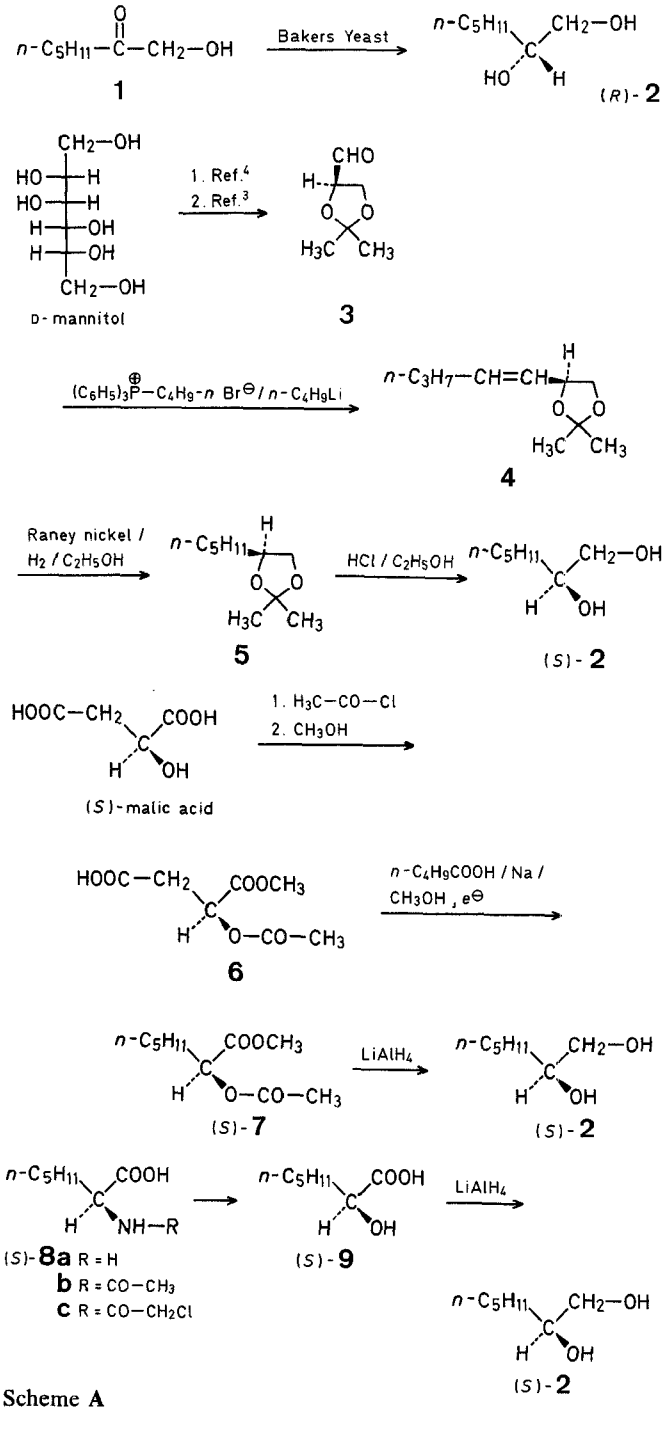
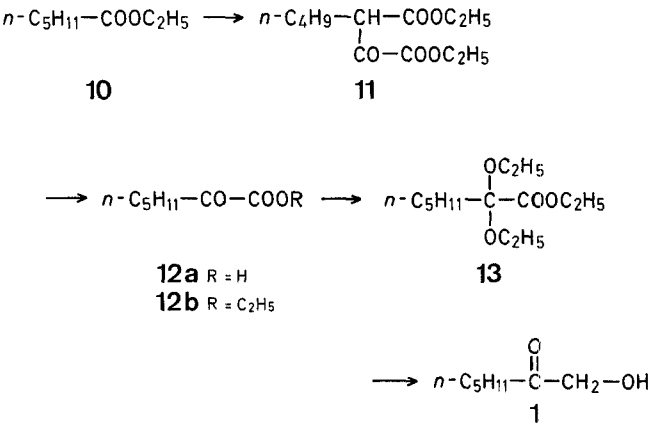
The (*S*)- and (*R*)-1,2 enantiomers of heptanediol **(2)** are chiral synthons for complex molecules[1]. We now describe reactions which enable us to prepare (*S*)- and (*R*)-**2** in high yields and with good optical purities. Various routes are indicated in Scheme **A**. (*R*)-(−)-1,2-Heptanediol [(*R*)-**2**] is obtained optically pure in 60% yield by a bakers yeast reduction of the α-ketol **1**. This ketol was prepared from chloroacetaldehyde and *n*-pentyl magnesium halide in poor yield[2]. We set up an improved preparation in four steps (Scheme **B**) starting from ethyl *n*-hexanoate **(10)** and giving an overall yield of 43% (based on **10**).



Scheme **A**



Scheme **B**

For the synthesis of (*S*)-**2** we investigated various processes involving chiral syntheses, resolutions, or asymmetric syntheses. The best results were obtained by chiral syntheses starting from easily available materials belonging to the chiral pool[3]. At first, D-mannitol is transformed into 1,2,5,6-di-*O*-isopropylidenemannitol[4]. Subsequent cleavage by lead(IV) acetate gives (*R*)-1,2-*O*-isopropylideneglyceraldehyde **(3)**[4]. In order to avoid any racemization, this aldehyde is immediately used for the next step that is, the reaction with a Wittig reagent. The olefin **4** is isolated [mainly in the (*Z*)-configuration] in 51% yield. (*S*)-Heptanediol **(2)** is obtained from **4** in 78% yield after catalytic reduction and hydrolysis. The compound is optically pure[12]. Another route to optically pure (*S*)-**2** started from (*S*)-malic acid. Its acetate monomethyl ester **6** was used in a mixed Kolbe reaction with *n*-pentanoic acid. Crude (*S*)-**7** was reduced by lithium aluminium hydride to (*S*)-1,2-heptanediol **(2)** which was obtained in 48% yield and 100% optical purity (according to maximum optical rotation reported in literature). (*S*)-Hydroxyheptanoic acid **(9)** is also an alternative starting material for the production of (*S*)-**2** by lithium aluminium hydride reduction.

The acid (*S*)-**9** can be resolved[5] or obtained by nitrous deamination of (*S*)-2-aminoheptanoic acid **(8a)**. Optically pure (*S*)-**8a** is prepared by enzymatic hydrolysis of a racemic **8b** or **8c**[6]. We checked the validity of the route (*S*)-**8a**→(*S*)-**2** with respect to the three previous ones. Its major inconvenience is a loss of optical purity during the nitrous deamination of (*S*)-**8a**. In our hands by using the standard procedure, we never obtained (*S*)-**9** with an optical purity higher than 70%. In order to prepare (*S*)-**2** from (*R*)-**2** or vice-versa, we investigated the possibility of configuration inversion on 1-acetoxy-2-tosyloxyheptane. By using procedures known for cleanly inverting the stereochemistry on some sugar diols[7], we always obtained about 30% racemization. In conclusion the best ways for obtaining optically pure (*R*)-**2** and (*S*)-**2** are the bakers yeast reduction of **1** and a chiral synthesis starting from either D-mannitol or (*S*)-malic acid respectively.

As an example of the utility of (*S*)- or (*R*)-**2**, the preparation of a chiral Wittig reagent from (*S*)-2-hydroxy-1-iodoheptane which should be useful for the introduction of the side chains of prostaglandins with the desired (15*S*)-configuration could be envisaged. For a previous approach to the introduction of an unsaturated side chain with an asymmetric centre in prostaglandin synthesis see Ref.[13].

In this respect, a model reaction using the readily available 1,2-butanediol was studied (Scheme **C**). The diol **2** ($R^1 = C_2H_5$) was

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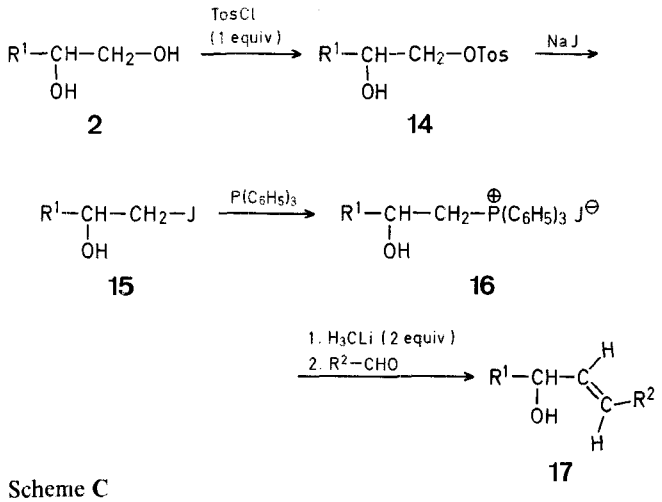
converted to 1-iodo-2-hydroxybutane via 1-tosyloxy-2-hydroxybutane (**14**) and then to a crystalline phosphonium salt **16**. Wittig reactions of **16** with 2-methylpropanal or cyclopentanecarboxaldehyde gave the corresponding olefins (**17**) in 30% yields[14]. Using the same reaction sequence with $R^1 = n\text{-}C_5H_{11}$, the yield of the step **15**→**16** was increased to 85–90% by using two equivalents of triphenylphosphine in nitromethane at 80–85 °C during 60 h[15]. The Wittig reaction of **16** with cyclohexanecarboxaldehyde gave again the olefin **17** in 30% yield[15].



Scheme C

1-Hydroxy-2-oxoheptane (1):

2-Oxoheptanoic Acid (**12a**): To a solution of sodium (6.35 g, 0.28 mol) in absolute ethanol (95 ml) at room temperature is quickly added a mixture of diethyl oxalate (165 g, 1.1 mol) and ethyl hexanoate (39.75 g, 0.25 mol). Then ethanol (b.p. <60 °C/100 torr) and oxalate (b.p. <90 °C/15 torr and 3 torr) are removed under reduced pressure. Acetic acid (16.5 ml) and water (20 ml) are added to the solid residue. The solution is extracted with ether (2 × 150 ml) and the organic layer is washed with water (100 ml), saturated sodium hydrogen carbonate solation (50 ml), and water (2 × 50 ml), successively. The solvent is evaporated under reduced pressure. To the residual oil is added water (150 ml) and concentrated hydrochloric acid (75 ml) and the whole mixture is refluxed for 6 h. The excess hydrochloric acid is neutralized by addition of concentrated ammonia solution at 20 °C and the theoretical quantity of barium sulfate to neutralize *2-oxoheptanoic acid* (**12a**) is slowly introduced. The insoluble barium salt is separated and washed with water (50 ml). This salt is added to excess 2 normal hydrochloric acid and **12a** is distilled; yield: 23 g (64%); b.p. 111–113 °C/18 torr (Lit.[9], b.p. 108–111 °C/17 torr[9]).

Ethyl 2-Oxoheptanoate (**12b**): A solution of **12a** (125 g, 0.87 mol), *p*-toluenesulfonic acid (0.5 g) in absolute ethanol (65 ml) and toluene (17.5 ml) is refluxed for 6 h. Then the mixture is distilled (b.p. <77 °C/760 torr); after addition of triethanolamine (0.4 ml), **12b** is distilled; yield: 140 g (94%); b.p. 97–102 °C/11 torr.

$C_9H_{16}O_3$	calc.	C 62.76	H 9.36
(172.2)	found	62.81	9.29

Ethyl 2,2-Diethoxyheptanoate (**13**): To a 30% hydrogen chloride solution in ethanol (12.5 ml) is added a solution of **12b** (24 g, 0.14 mol) and ethyl orthoformate (50 g, 0.34 mol) in ethanol (50 ml). After three days at 20 °C, ethanol is evaporated under reduced pressure and the acetal ester **13** distilled; yield: 26.9 g (78%); b.p. 85–87 °C/0.3 torr.

$C_{13}H_{26}O_4$	Calc.	C 63.88	H 10.64
(246.3)	found	63.40	10.81

1-Hydroxy-2-oxoheptane (**1**): To a solution of ester **13** (26.5 g, 0.11 mol) in anhydrous ether (100 ml) is slowly added a 0.9 molar ether solution of lithium aluminium hydride (66 ml). The mixture is stirred at room temperature for 12 h. Ethyl acetate (~ 15 ml), water (80 ml), and excess 2 normal sulfuric acid (30 ml) are then added successively. The mixture is stirred for 30 min at 20 °C, extracted with ether (5 × 30 ml), the extract is dried with magnesium sulfate, evaporated under reduced pressure. The product **1** is distilled; yield: 13 g (91%); b.p. 90–92 °/15 torr; analytically pure by G.L.C. analysis (15% Carbowax 20 M).

Bakers Yeast Reduction of 1[2]:

A mixture of sugar (500 g) and fresh bakers yeast (500 g) in water (5000 ml) gives after 45 min at 30–32 °C a rapid evolution of carbon dioxide. A solution of **1** (50 g, 0.38 mol) in ethanol (50 ml) is then added. The mixture is stirred for 3 days at room temperature, filtered through celite, and the water evaporated in vacuo. The oily residue is extracted with ethanol (2 × 200 ml) and then with ether (1 × 100 ml). The combined extracts are evaporated and the residue distilled twice to give *(R)-1,2-heptanediol* (**2**); yield: 28.2 g (56%); b.p. 68–70 °C/0.04 torr; $[\alpha]_D^{22}$: +16.8° (*c* 11.8, ethanol); Ref.[2], $[\alpha]_D$: +16.5°.

Wittig Reaction of (*R*)-1,2-*O*-Isopropylideneglyceraldehyde (3):

1,2,5,6-Di-*O*-isopropylidene-D-mannitol is oxidized with lead(IV) acetate according to Ref.[4] to give **3**; yield: 69%. *n*-Butyltriphenylphosphonium bromide (44.8 g, 0.11 mol; prepared according to Ref.[8]; m.p. 239–241 °C) is suspended in ether (500 ml) and treated with a 1.86 normal hexane solution of *n*-butyllithium (65 ml) at 25 °C. After 2 h at 25 °C, freshly prepared **3** (9 g, 0.07 mol; b.p. 40–44 °C/11 torr) in ether (100 ml) is added. The mixture is stirred at 25 °C for 12 h, benzene (300 ml) is added, and the mixture is refluxed for 10 h. The cooled solution is poured into water (50 ml), filtered, and extracted with ether (3 × 25 ml). Drying with magnesium water and evaporation of the solvents gives **4** as an oil. Hexane (25 ml) is added to the oil, the solution is filtered, and passed through a column of basic alumina to give pure **4**; yield: 6.07 g (51%); $[\alpha]_D^{23}$: +5.57° (neat).

$C_{10}H_{18}O_2$	calc.	C 70.54	H 10.66
(170.2)	found	70.50	10.78

I.R. (film): $\nu = 1660\ cm^{-1}$.

^{1}H-N.M.R. (CCl_4): δ = 0.9 (m, 3H); 1.1–2.4 (m, 10 H); 3.2–3.6 (m, 1H); 3.7–4.1 (m, 1H); 4.4–4.9 (m, 1H); 5.1–5.8 ppm (m, 2H).

(*S*)-1,2-Heptanediol (2):

The alkene **4** (5.8 g, 0.034 mol) in ethanol (40 ml) is hydrogenated at 1 atmosphere hydrogen pressure in the presence of Raney-nickel (0.3 g) at 60 °C for 24 h. The catalyst is filtered, the solvent evaporated, and the oily residue **5**[10] is dissolved in ethanol (100 ml). A few drops of concentrated hydrochloric acid are added, the mixture is refluxed for 6 h, the solvent is evaporated, and (*S*)-**2** is distilled; yield: 3.25 g (78%); b.p. 118–120 °C/10 torr; $[\alpha]_D^{22}$: −16.1° (*c* 11.7, ethanol).

(*S*)-1,2-Heptanediol (2) from (*S*)-Malic Acid:

A solution of malic acid (10 g, 0.08 mol) in acetyl chloride (30 ml) is refluxed for 3 h. After evaporation in vacuo of volatile products, methanol (5 ml) is added to the residue and the mixture is warmed for 30 min at 50 °C; compound **6** is recrystallized from ethyl acetate, yield: 11.1 g (73%); m.p. 48–50 °C.

$C_7H_{10}O_6$	calc.	C 44.22	H 5.30
(190.2)	found	44.32	5.25

^{1}H-N.M.R. ($CDCl_3$): δ = 2.87 (d, 2H); 4.10 (s, 6H); 5.40 (t, 1H); 9.4 ppm (s, 1H).

Compound **6** (10 g, 0.05 mol) and pentanoic acid (25 ml) are added to methanol (160 ml) and sodium (0.1 g) in a refrigerated electrolytic cell. Electrolysis is performed with a stabilized current (60 V, 1.5 to 2 A) for 50 h. Evaporation of volatile products gives a residue which is diluted with ether (300 ml) and washed with 0.5 normal sodium hydroxide solution (50 ml) and water (2 × 25 ml) successively. After drying with magnesium sulfate and evaporation of ether, the oil (*S*)-7 obtained is reduced as usual with lithium aluminium hydride and (*S*)-**2** distilled; yield based upon **6**: 48%; $[\alpha]_D^{22}$: −16.6° (*c* 11.9, ethanol).

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[1] See Refs.[13,15].

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