Synthesis of (±)-*trans*-cyclohexa-3,5-diene-1,2-diol derivatives from *myo*-inositol

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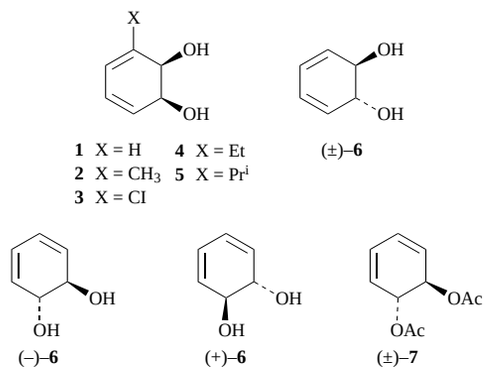
***myo*-Inositol 8 has been converted to biscyclohexylidene ketals 9–11. The inseparable mixture of isomers 9 and 11 has been utilised as such to obtain the synthetically useful (±)-*trans*-cyclohexa-3,5-diene-1,2-diol derivative 24 *via* the intermediates 14 and 15. The *trans*-diol derivative 24 has also been converted to synthetically useful epoxide derivative 25 in high yield and selectivity.**

Introduction

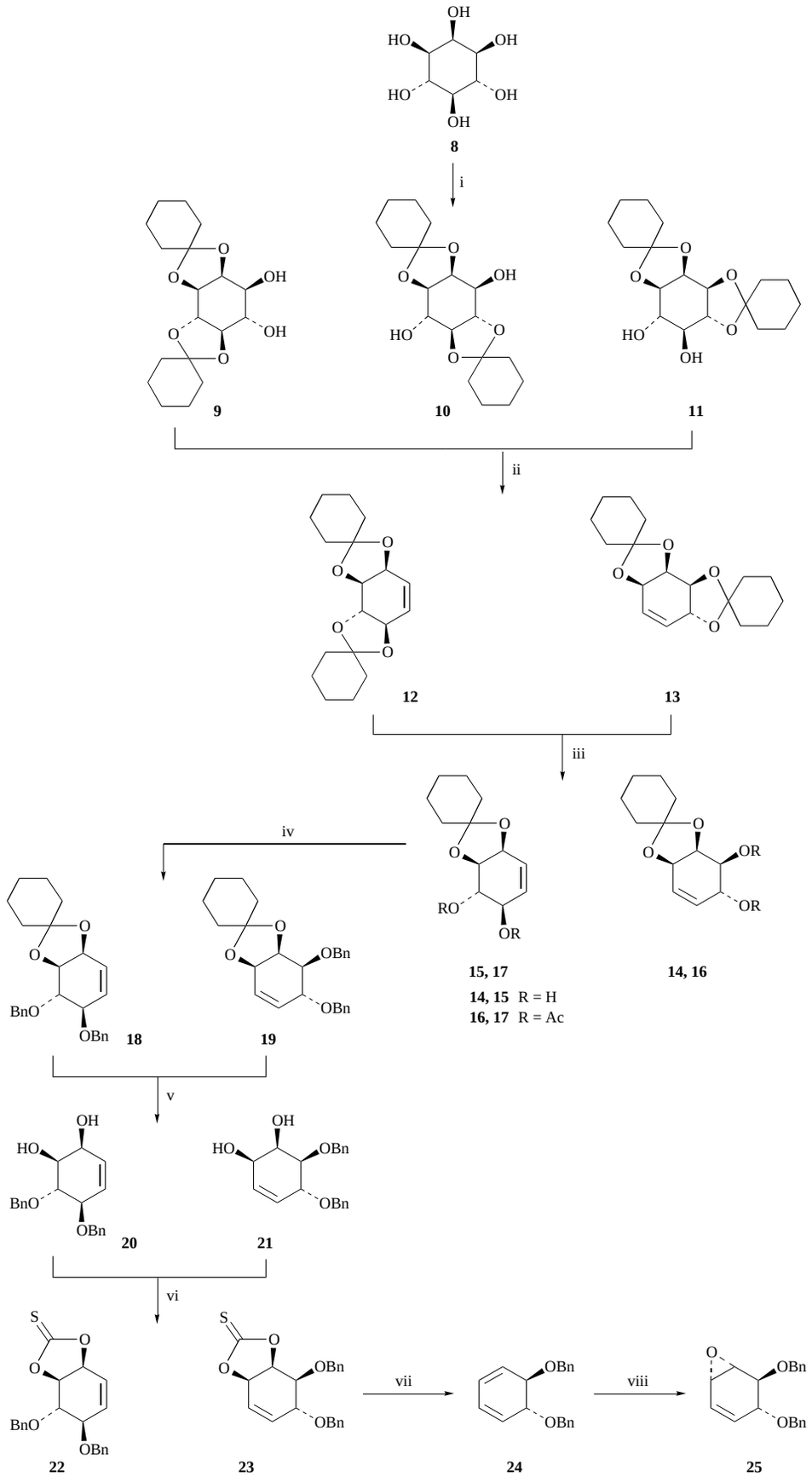
Metabolism of aromatic compounds by bacteria was studied at the beginning of this century by Stormer.[1] Oxidation of benzene to catechol was subsequently reported as early as 1913.[2] *cis*-Cyclohexadiene-1,2-diol **1** was isolated for the first time by Gibson in 1968 from the metabolism of benzene by certain soil bacteria[3–5] and likewise was chiral *cis*-diol **2** from toluene.[6,7] Subsequently several alkylbenzenes, halogenobenzenes and other aromatics were oxidised to chiral *cis*-diols **3**–**5**.[8–10] Extensive use of *cis*-diol **1** as a building block in enantiospecific syntheses is best known from the work of Ley and his group.[11,12]

On the other hand the utility of bacteria to produce the analogous enantiomerically pure *trans*-cyclohexa-3,5-diene-1,2-diols (+)- and (−)-**6** from benzene has not been very good. Metabolism of benzene oxide with liver microsomes *in vivo* is known to result in the formation of isomer (+)-**6** at an estimated optical purity of 50%.[13,14] Enzyme-catalysed hydrolysis of *trans*-diol diacetate (±)-**7** was selected for resolution to obtain isomers (−)-**6** and (+)-**6** (97% ee) in an overall yield of 15 and 47%, respectively.[15] The absolute stereochemistry of isomers (−)-**6** and (+)-**6** was determined by converting them to the known (−)- and (+)-*trans*-1,2-dihydroxycyclohexane,[13,16,17] respectively. Enantiomerically pure isomers (+)-**7** and (−)-**7** have also been obtained from lipase-effected enantioselective hydrolysis of (±)-4,5-diacetoxycyclohex-1-ene.[18] Racemic *trans*-cyclohexa-3,5-diene-1,2-diol diacetate (±)-**7** has been prepared synthetically from benzene *via* successive Birch reduction, bromination, *trans*-hydroxylation, dehydrobromination and acetylation.[19] Diol (±)-**6** was synthetically exploited for the synthesis of racemic conduramines,[20] conduritols,[21] inosamine,[22] fortamine,[23] aminocyclitol antibiotics of the 2-deoxystreptamine type,[24] *chiro*-inositol 2,3,5-trisphosphate,[25] *myo*-inositol 1,4,5-trisphosphate[26] and fluoroinositol phosphate analogues.[27]



Results and discussion

We felt the need to develop a chemical route to obtain enantiomerically pure *trans*-cyclohexa-3,5-diene-1,2-diol derivatives from (*meso*)-*myo*-inositol[28] in large quantities because of their utility in the total synthesis of natural products (Scheme 1). *myo*-Inositol **8** was converted to a mixture of bis-cyclohexylidene ketals **9**, **10**, **11** in 38, 26 and 19% yield, respectively, by reaction with cyclohexanone in *N*,*N*-dimethylformamide (DMF) at 100 °C for 12 h containing toluene-*p*-sulfonic acid (*p*-TsOH).[29] Alternatively it could be made by reaction of *myo*-inositol **8** with 1-ethoxycyclohexene containing a catalytic amount of *p*-TsOH in DMF at 100 °C for 2 h.[30] From the so-obtained bis-ketals **9**–**11**, crystalline 1,4-diol **10** was separated by crystallisation[29] to leave a residue containing diastereoisomeric 1,2-diols **9** and **11** in the ratio 2:1 (by ^{1}H NMR spectroscopy). Reaction of 1,2-diols **9** and **11** with Ph_3P (3 mol equiv.), imidazole (3 mol equiv.) and iodine (3 mol equiv.) in toluene at reflux for 6 h gave the cyclohexene bis-cyclohexylidene ketals **12** and **13** (mp 66–68 °C) in 74% yield;[31] formation of the cyclohexene double bond was evident from the appearance of multiplets in the ^{1}H NMR spectrum between δ 5.6–6.25, integrating for two protons. Compounds **12** and **13** were allowed to react further at 0–5 °C with a catalytic amount of *p*-TsOH in CH_2Cl_2 for 4 h to obtain the cyclohexene diols **14** and **15** in 78% yield as a solid (mp 96–98 °C) due to selective deprotection of the *trans*-cyclohexylidene ketal. Products **14** and **15** were characterised from the ^{1}H NMR spectrum where cyclohexylidene protons appeared between δ 1.2–1.8, integrating for ten protons. From a mixture of compounds **14** and **15** we planned to obtain the *trans*-cyclohexa-3,5-diene-1,2-diols. Diols **14** and **15** were therefore treated with Ac_2O–pyridine to obtain the di-*O*-acetyl derivatives **16** and **17** in quantitative yield. However, attempted selective deprotection of the *cis*-cyclohexylidene protecting group of compounds **16** and **17** by reaction with *p*-TsOH in CH_2Cl_2 at 0 °C resulted in the formation of phenolic compounds. Attempts to deprotect the cyclohexylidene ketal in ethylene glycol–*p*-TsOH and HCl–methanol also met with failure. It was hence decided to protect the alcohols **14** and **15** as their benzyl ethers by reaction with $C_6H_5CH_2Br$–NaH–DMF at 0 °C, to obtain the dibenzyl ether derivatives **18** and **19** in 98% yield. The mixture of compounds **18** and **19** was then subjected to deprotection of the cyclohexylidene ketal in *p*-TsOH–CH_2Cl_2–methanol at 0 °C to room temp. for 4 h to obtain the diol derivatives **20** and **21** in 90% yield, which were characterised from their ^{1}H NMR spectrum. The mixture of diols **20** and **21** was further treated with 1,1′-thiocarbonyldimidazole[32] in toluene at reflux for 1 h to obtain the cyclic thiocarbonate derivatives **22** and **23** in high yield, and these were subsequently subjected to *syn* elimination by being refluxed in trimethyl phosphite for 2 h to obtain *trans*-(±)-cyclohexa-3,5-diene-1,2-diol bisbenzyl ether **24** as a syrup in



Scheme 1 *Reagents and conditions*: i, cyclohexanone, DMF, *p*-TsOH, 100 °C, 12 h; ii, PPh_3, I_2, imidazole, toluene, reflux, 6 h, iii, *p*-TsOH (cat.), CH_2Cl_2, 5 °C, 4 h; iv, BnBr, NaH, DMF; v, *p*-TsOH, CH_2Cl_2–MeOH; vi, 1,1′-thiocarbonyldiimidazole, toluene, reflux, 1 h; vii, $P(OMe)_3$, reflux, 2 h; viii, MCPBA, CH_2Cl_2, $NaHCO_3$, room temp., 4h

90% yield. Compound **24** was characterised from the appearance of cyclohexadiene protons (4 H) at δ 5.83 as a singlet and the H-5, H-6 protons at δ 4.37 as a singlet in the ^{1}H NMR spectrum. The *trans*-1,2-diol derivative **24** on reaction with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 at room temperature for 4 h gave the epoxide **25** due to stereoselective epoxida-

tion of the double bond *anti* to the adjacent benzyl ether. Compound **25** was fully characterised from the ^{1}H NMR spectrum.

Experimental

^{1}H NMR spectra were measured with a Varian Gemini (200 MHz) spectrometer, with tetramethylsilane as internal standard for solutions in deuteriochloroform; coupling constants (*J*) are given in Hz. IR spectra were taken with a Perkin-Elmer 283 spectrometer. UV spectra were measured with a Shimadzu 160-A spectrometer. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C on rotary evaporator.

(±)-(3α,4β,5α,6α)-3,4 : 5,6-Bis(cyclohexylidenedioxy)cyclohexene 12 and (±)-(3α,4α,5α,6β)-3,4 : 5,6-bis(cyclohexylidenedioxy)cyclohexene 13

To a solution of diols **9** and **11** (5.0 g, 4.7 mmol) in toluene (40 cm^3) were added triphenylphosphine (11.55 g, 44.1 mmol) and imidazole (2.29 g, 44.1 mmol) and the mixture was heated to 60 °C. Iodine (11.2 g, 44.1 mmol) was added portionwise during 15 min and the reaction mixture was refluxed for 4 h, when TLC (hexane–ethyl acetate, 3 : 1) indicated completion of the reaction from the appearance of a faster moving spot; it was then cooled to room temperature, a further batch of iodine (14.94 g, 58.8 mmol) was added followed by aq. NaOH (1 M; 50 cm^3) and the mixture was stirred for 30 min at room temperature. The toluene phase was washed successively with water, 5% aq. sodium thiosulfate, saturated aq. $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated to obtain a solid residue, which was filtered on a bed of silica gel (eluted with 25% ethyl acetate in hexane) to obtain the *title compounds* (3.33 g, 74%), which solidified on storage, mp 66–68 °C (Found: C, 70.45; H, 8.46. $C_{18}H_{26}O_4$ requires C, 70.56; H, 8.55%); δ_H 1.3–1.8 (20 H, m, cyclohexylidene), 3.35–4.8 (4 H, m, 3-, 4-, 5- and 6-H) and 5.6–6.25 (2 H, m, 1- and 2-H).

(±)-(1α,2β,5α,6α)-5,6-(Cyclohexylidenedioxy)cyclohex-3-ene-1,2-diol 14 and (±)-(1β,2α,5α,6α)-5,6-(cyclohexylidenedioxy)-cyclohex-3-ene-1,2-diol 15

To a solution of compounds **12** and **13** (3.30 g, 10.8 mmol) in CH_2Cl_2 (10 cm^3) was added catalytic amount of *p*-TsOH (30 mg) and the mixture was stirred at 0–5 °C for 4 h. After completion of the reaction the mixture was neutralised with triethylamine. The reaction mixture was concentrated, and filtered on a bed of silica gel (eluted with 50% ethyl acetate in hexane) to obtain the *title compounds* **14** and **15** (1.91 g, 78%) as an inseparable mixture of solids, mp 96–98 °C (Found: C, 63.65; H, 7.95. $C_{12}H_{18}O_4$ requires C, 63.70; H, 8.02%); ν_{max}($CHCl_3$) 3500 cm^{-1} (OH); δ_H 1.2–1.8 (10 H, m, cyclohexylidene), 3.4–4.7 (4 H, m, 1-, 2-, 5- and 6-H) and 5.5–6.0 (2 H, m, 3- and 4-H).

(±)-(3α,4β,5α,6α)-3,4-Bis(benzyloxy)-5,6-(cyclohexylidenedioxy)cyclohexene 18 and (±)-(3β,4α,5α,6α)-3,4-bis(benzyloxy)-5,6-(cyclohexylidenedioxy)cyclohexene 19

To hexane-washed NaH (0.35 g, 14.4 mmol) in DMF (10 cm^3) was added a solution of compounds **14** and **15** (1.3 g, 5.75 mmol) in DMF (5 cm^3) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C and benzyl bromide (2.24 g, 14.4 mmol) was added dropwise. The reaction mixture was stirred for 30 min at room temperature. After completion of the reaction the mixture was quenched with methanol followed by ice–water and extracted into CH_2Cl_2. The organic phase was washed with water, dried (Na_2SO_4), and concentrated to obtain *title compounds* **18** and **19** (2.28 g, 98%) as a syrup (Found: C, 76.39; H, 7.84. $C_{26}H_{30}O_4$ requires C, 76.82; H, 7.44%); δ_H 1.3–1.7 (10 H, m, cyclohexylidene), 3.5–4.6 (4 H, m, 3-, 4-, 5- and 6-H), 4.6–4.85 (4 H, m, $C_6H_5CH_2$ × 2), 5.5–5.9 (2 H, m, 1- and 2-H) and 7.25–7.45 (10 H, m, ArH).

(±)-(1α,2α,5α,6β)-5,6-Bis(benzyloxy)cyclohex-3-ene-1,2-diol 20 and (±)-(1α,2α,5β,6α)-5,6-bis(benzyloxy)cyclohex-3-ene-1,2-diol 21

To a solution of compounds **18** and **19** (2.2 g, 5.4 mmol) in CH_2Cl_2–CH_3OH (60 and 10 cm^3) was added a catalytic amount of *p*-TsOH (20 mg) and the mixture was stirred for 3 h at 0 °C before being warmed to room temperature and stirred for another 1 h. The reaction mixture was neutralised with triethylamine and concentrated to obtain a residue, which was filtered on a bed of silica gel (eluted with 50% ethyl acetate in hexane) to obtain the *title compounds* (1.65 g, 90%) as a syrup (Found: C, 73.06; H, 7.26. $C_{20}H_{24}O_4$ requires C, 73.14; H, 7.37%); δ_H 2.5–2.8 (2 H, br s, OH), 3.55–4.3 (4 H, m, 1-, 2-, 5- and 6-H), 4.45–4.95 (4 H, m, $C_6H_5CH_2$ × 2), 5.7–5.9 (2 H, m, 3- and 4-H) and 7.2–7.35 (10 H, m, ArH).

(±)-(3aα,6α,7β,7aα)-6,7-Bis(benzyloxy)-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxole-2-thione 22 and (±)-(3aα,6β,7α,7aα)-6,7-bis(benzyloxy)-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxole-2-thione 23

To a solution of compounds **20** and **21** (1.6 g, 4.91 mmol) in dry toluene (10 cm^3) was added 1,1′-thiocarbonyldiimidazole (1.31 g, 7.36 mmol) and the mixture was refluxed under nitrogen for 1 h. After completion of the reaction the mixture was diluted with toluene (20 cm^3) and then concentrated to obtain a residue, which was filtered on a bed of silica gel (eluted with 25% ethyl acetate in hexane) to obtain the *title compounds* (1.71 g, 95%) as a syrup (Found: C, 67.99; H, 5.86. $C_{21}H_{20}O_4S$ requires C, 68.47; H, 5.47%); δ_H 3.7–4.2 (2 H, m, 6- and 7-H), 4.6–5.3 (6 H, m, 3a- and 7a-H, $C_6H_5CH_2$ × 2), 5.8–6.2 (2 H, m, 4- and 5-H) and 7.2–7.35 (10 H, m, ArH).

(±)-*trans*-5,6-Bis(benzyloxy)cyclohexa-1,3-diene 24

Thiocarbonate derivatives **22** and **23** (1.65 g, 4.48 mmol) were refluxed for 2 h in trimethyl phosphite (0.94 g, 6.72 mmol) under nitrogen. After completion of the reaction the mixture was made alkaline by the addition of aq. NaOH and was extracted into CH_2Cl_2. The organic phase was washed with water (50 cm^3 × 3), dried (Na_2SO_4), and concentrated to obtain the *title compound* (1.17 g, 90%) as a syrup (Found: C, 82.03; H, 6.81. $C_{20}H_{20}O_2$ requires C, 82.15; H, 6.89%); M^+, 292; λ_{max}(MeOH) 259 nm; δ_H 4.37 (2 H, s, 5- and 6-H), 4.55 (4 H, s, $C_6H_5CH_2$ × 2), 5.83 (4 H, s, 1-, 2-, 3- and 4-H) and 7.2–7.35 (10 H, m, ArH).

(±)-(3β,4α,5β,6β)-3,4-Bis(benzyloxy)-5,6-epoxycyclohexene 25

To a solution of compound **24** (1.0 g, 3.42 mmol) in CH_2Cl_2 (200 cm^3) were added MCPBA (0.59 g, 3.42 mmol) and $NaHCO_3$ (0.28 g, 3.42 mmol) and the mixture was stirred at room temperature for 4 h. After completion of the reaction the mixture was diluted with CH_2Cl_2 (50 cm^3) and washed successively with saturated aq. $NaHCO_3$ and water. The organic phase was dried (Na_2SO_4) and concentrated to obtain the *title compound* (0.97 g, 92%) as a syrup (Found: C, 77.83; H, 6.47. $C_{20}H_{20}O_3$ requires C, 77.90; H, 6.54%); δ_H 3.2–3.5 (2 H, m, 5- and 6-H), 3.84 (1 H, d, $J_{3,4}$ 7.7, 3-H), 4.19 (1 H, d, $J_{3,4}$ 7.7, 4-H), 4.65–4.95 (4 H, m, $C_6H_5CH_2$ × 2), 5.92 (2 H, AB-type doublet, *J* 8.8, 1- and 2-H) and 7.25–7.4 (10 H, m, ArH).

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