Synthesis of cycloheptane-1,2,3,4-tetraols as cyclitol mimetics

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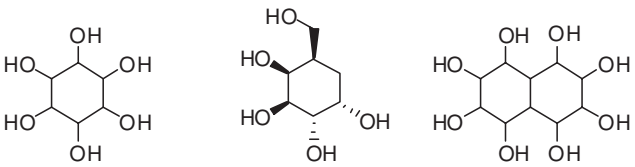
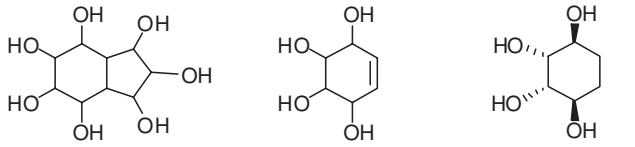
Acidic hydrolysis and acetylation of epoxidation products **11a/b** of 1,4-diacetoxy-2-cycloheptene afforded unsymmetrical 1,2,3,4-tetraacetoxycycloheptane (**12**). OsO_4-*cis*-hydroxylation and acetylation of 1,4-diacetoxy-2-cycloheptene gave two symmetrical 1,2,3,4-tetraacetoxycycloheptanes (**14**/**15**). Deacetylation of 1,2,3,4-tetraacetoxy cycloheptanes gave cycloheptane-1,2,3,4-tetraols as cyclitol mimetics.

Keywords: endoperoxide, cyclitol, carbasugar, inositol, conduritol

Cyclitol is a generic term used to describe polyhydroxycycloalkanes. Many biologically important molecules and natural products contain polyhydroxylated carbocycles.[1,2] Several of them have been used as sweeteners, antibiotics, antiviral, antidiabetes and anticancer agents.[3] The inositols (**1**) and their derivatives figure prominently in numerous biological processes.[4] The better known carbosugar of natural occurrence is pseudo-α-galactose (**2**).[4] Many analogues and structural variants of **1** and **2** have been synthesised and their biological activities, particularly glycosidase inhibition have been evaluated.[6,7] The synthesis of polycyclitols like **3** and **4** as new structural variants embodying the characteristic features present in **1** and **2** has recently been achieved.[8]



1 **2** **3**



4 **5** **6**

Conduritols (**5**) (six diastereomers designed A-F are known) have generated a great deal of synthetic interest.[4] Dihydroconduritol-A (**6**) was found and isolated by Zeying and Mingzhe from the plant *Toxocarpus* (from the Asclepiadacea family) which grows in China and some areas of India.[9] They have named the naturally occurring compound toxocarol and reported that this plant is being used in those areas for treatment of fractures, contusions, ulcers and cancers of the cervix, uterus and lung.[9] A new and stereocontrolled short method for the synthesis of **6** was described by Balci *et al.*[10] Various methods are already available for the construction of functionalized five- and six-membered rings but only a few approaches have been reported for the synthesis of seven- and eight-membered ring cyclitols.[2] The ring-closing metathesis is commonly used for the synthesis of new polyhydroxylated seven- and eight-membered carbocyles starting from D-arabinose.[2b,11] Considering the fundamental importance of the cyclitols, we have studied the synthesis of seven-membered cyclitol mimics. We would like to report herein our approaches to the efficient synthesis of cycloheptane cyclitol analogues. Our synthetic strategy is based on the introduction of the two oxygen functionalities by photooxygenation of 1,3-cycloheptadiene. The other oxygen functionalities are introduced by classical peracid epoxidation and OsO_4-hydroxylation reactions.

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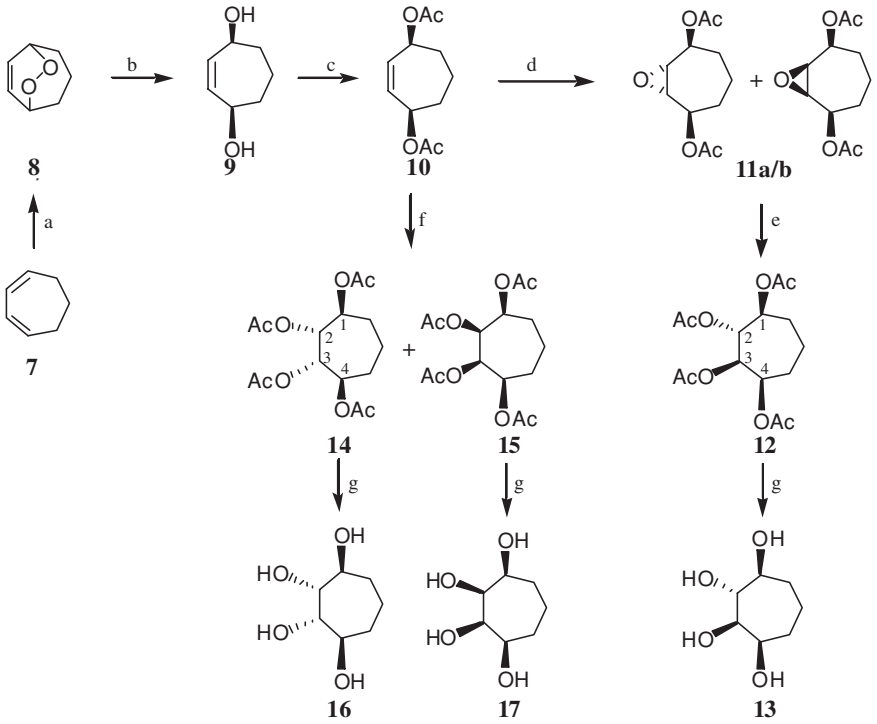
Results and discussion

Firstly, 1,3-cycloheptadiene (**7**) was submitted to photooxygenation using tetraphenyl-porphyrin (TPP) as a sensitiser.[12] The endoperoxide **8**, obtained in a quantitative yield, can be readily reduced by Zn–AcOH to the corresponding *cis*-diol **9** at room temperature.[12] The acetylation of the cyclohepten-1,4-diol (**9**) with an excess of acetic anhydride in pyridine resulted in the formation of the diacetate **10** in 95% yield. The various reactions of the diacetete **10** were investigated. Treatment of **10** with *m*-chloroperbenzoic acid (*m*-CPBA) gave the isomeric epoxy diacetates **11a/b** in a 3:1 ratio.[12b] Treatment of this mixture with dilute aqueous acid gave a regioselective ring opening of the epoxides to afford, after acetylation, **12** as the sole product (75% yield).[13,4d] The ^{1}H NMR spectrum of **12** in $CDCl_3$ consists of four singlets at 2.04–1.98 ppm (OAc protons), multiplets at 1.96–1.52 ppm (methylenic protons) and four multiplets at 5.21–4.91 ppm (OC-H protons) as it is an unsymmetrical structure. The ^{13}C NMR spectrum consisting of four carbonyl carbons and eleven aliphatic carbon signals is completely in agreement with the proposed structure. Deacetylation of **12** with ammonia in methanol afforded the cycloheptanetetraol **13**[14] in 99% yield. Compound **13** has been fully characterised from the spectroscopic data.

After successful isolation and characterisation of **13**, we next turned our attention to the synthesis of symmetrical cycloheptane-1,2,3,4-tetraol cyclitol mimetics. Since both faces of the alkene unit in **10** are not equivalent, two isomeric *cis*-hydroxylation products can be expected. To investigate introducing two hydroxyl groups in a *cis* configuration to the double bond in *cis*-1,4-diacetoxy-2-cycloheptene (**10**), we treated the diacetate **10** with catalytic amounts of OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant. After the reaction was complete, within 14 h, the crude product was acetylated with acetic anhydride-pyridine.

The OsO_4-catalysed *cis*-hydroxylation and the acetylation furnished a (68:32) mixture of the two symmetrical 1,2,3,4-tetracetoxycycloheptanes **14** and **15**, which could be best separated by column chromatography on silica gel. The relative configurational assignments of **14** and **15** are easily determined by ^{1}H and ^{13}C NMR spectral data. The ^{13}C NMR spectra of **14** and **15** are completely in agreement with these symmetrical structures. The OC-H protons of **14** and **15** give rise to a well-resolved AB system. The A part (low field) of the AB system for the compounds showed the coupling constant of $J_{1,2} = J_{3,4} = 7.3$ Hz to identify the existence of the 1,2-*trans* OAc-groups in **14** and $J_{1,2} = J_{3,4} = 2.8$ Hz supported the pressure of the 1,2-*cis* OAc-groups in **15**. These values were consistent with the data for similar compounds and in agreement with the twist chair conformation described



Scheme 1 Reagents and conditions: (a) TPP, O_2, CH_2Cl_2, *hν*; (b) Zn, AcOH, CH_2Cl_2; (c) Ac_2O-pyridine; (d) *m*-CPBA, CH_2Cl_2; (e) 0.02 M H_2SO_4, H_2O, then Ac_2O-pyridine, 75%; (f) OsO_4, NMO, acetone-H_2O, then Ac_2O-pyridine, total yield for 14 and 15: 74%; (g) NH_3, MeOH.

for seven-membered rings.[14,15] All data showed that the four acetoxyl groups of the molecule **15** are located on the same side of the seven-membered ring. These spectroscopic observations indicated that the *anti*-face of the cycloheptene double bond is considerably more accessible than the *syn*-face, which is blocked by the 1,4-*cis*-acetoxyl groups. Finally, deacetylation of **14** and **15** as described above gave the free tetraols **16** and **17**.

In conclusion, we have reported here a new approach for the synthesis of seven-membered cyclitols from easily available 1,3-cycloheptadiene, with advantages in terms of simplicity, efficiency and good chemical yields.

Experimental

General. All substances reported in this paper are in their racemic form. Solvents were concentrated at reduced pressure. Melting points were determined on a Buchi 539 capillary melting apparatus and are uncorrected. IR spectra were obtained from KBr pellets or film on a Mattson 1000 FT–IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on 200 (50) and 400 (100)-MHz Varian spectrometers and are reported in δ units with $SiMe_4$ as internal standard. Elemental analyses were carried out on a Carlo Erba 1108 model CHNS-O analyser.

(1S(R),2R(S),3R(S),4R(S))-1,2,3,4-tetraacetoxycycloheptane (**12**): The epoxy-diacetate mixture **11a/b** (370 mg, 1.62 mmol) was dissolved 0.02 M H_2SO_4 (90 ml) and the resulting solution was refluxed for 24 h. After removal of the solvent, the residue was added on to a short silica gel column (10 g) and eluted with CH_3OH (75 ml) to furnish the crude product. Later, Ac_2O (1.65 g, 16.16 mmol) was added to a stirred sample of the crude product in 1.30 g pyridine. The reaction mixture was stirred at room temperature for 24 h. The mixture was cooled to 0 °C and acidified by 1M HCl solution, and extracted with CH_2Cl_2 (3 × 50 ml). The combined extracts were washed with $NaHCO_3$ solution (3 × 20 ml) and water (20 ml) and dried ($MgSO_4$). Removing the solvent under reduced pressure gave the crude product (400 mg) as a viscous oil. Chromatography of the crude product over thin layer silica gel eluting with ethyl acetate/hexane (40:60) gave the tetraacetate **12** (310 mg, 75%). The product was recrystallised from ether/hexane to give **12** as white crystals: m.p. 72–73 °C. IR (KBr) 3023, 2946, 2869, 1751, 1434, 1373, 1234, 1033, 979, 925, 755. ^{1}H NMR (400 MHz, $CDCl_3$): 5.21 (*t*, *J* = 6.7 Hz, A part of AB-system, OCH, 1H), 5.15–5.12 (*m*, OCH, 1H), 5.07 (*dd*, *J* = 6.7 Hz, 1.5 Hz, B part of AB-system, OCH, 1H), 4.91 (*ddd*, *J* = 9.5 Hz, 7.1 Hz, 2.5 Hz, OCH, 1H), 2.04 (*s*, CH_3, 3H), 2.03 (*s*, CH_3, 3H), 2.00 (*s*, CH_3, 3H), 1.98 (*s*, CH_3, 3H), 1.96–1.82 (*m*, CH_2, 2H), 1.80–1.68 (*m*, CH_2, 3H), 1.61–1.52 (*m*, CH_2, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.91, 171.77, 171.39, 171.28, 76.82, 75.28, 74.90, 73.53, 31.46, 30.72, 22.99, 22.71 (2C), 21.47 (2C). Anal. calcd. for $C_{15}H_{22}O_8$: C 54.5, H 6.7; found: C 54.3, H 6.6.

(1S(R),2R(S),3R(S),4R(S))-cycloheptane-1,2,3,4-tetraol (**13**): The tetraacetate **12** (146 mg, 0.44 mmol) was dissolved in absolute methanol (15 ml). Dry NH_3 was passed through the solution while the mixture was stirred for 3 hours at room temperature. Evaporation of methanol and the acetamide formed gave **13** (colourless oil, 70 mg, 99%). Crystallisation of the tetraol with various solvents failed. IR (KBr) 3337, 2939, 1666, 1450, 1280, 1033. ^{1}H NMR (400 MHz, D_2O) 3.81 (*td*, *J* = 5.0 Hz, 2.3 Hz, OCH, 1H), 5.32 (*dd*, *J* = 6.2 Hz, 2.3 Hz, OCH, 1H), 3.44 (*br.t*, *J* = 6.8 Hz, OCH, 1H), 3.43–3.83 (*m*, OCH, 1H), 1.81–1.46 (*m*, CH_2, 5H), 1.32–1.28 (*m*, CH_2, 1H). ^{13}C NMR (100 MHz, D_2O) 76.83, 75.96, 74.19, 71.33, 31.92, 30.33, 19.34. Anal. calcd. for $C_7H_{14}O_4$: C 51.8, H 8.7; found: C 51.6, H 9.0.

(1S(R),2R(S),3S(R),4R(S))-1,2,3,4-tetraacetoxycycloheptane (**14**) *and (1S(R),2S(R), 3R(S),4R(S))-1,2,3,4-tetraacetoxycycloheptane* (**15**): To a solution of *N*-methylmorpholine *N*-oxide 790 mg 6.75 mmol in water 5 ml was added the solution of diacetate **10** (1.01 g, 4.76 mmol) in acetone (16 ml). After the flask had been cooled to –5 °C, OsO_4 (5 ml, 1% in acetone) was added under nitrogen at room temperature. After 13 h, the reaction was complete. $NaHSO_3$ (1.04 g, 10 mmol), Florisil (5g) and water (7 ml) were added, the slurry was stirred for 7 h, and the mixture was filtered through a pad of 0.5 g of Celite in a 50 ml sintered-glass funnel. The Celite cake was washed with acetone (150 ml). After the solvent was removed *in vacuo*, 860 mg (73%) of the crude product was obtained. Then, the crude product (860 mg) was dissolved in pyridine (3g) and Ac_2O (2.5 g, 24.49 mmol) and stirred for 3 days at room temperature. The mixture was cooled to 0 °C 1 M HCl solution (100 ml) added, and the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic extracts were washed with $NaHCO_3$ solution (50 ml) and water (50 ml) and then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue (1.01 g) was chromatographed over silica gel (65 g). Elution with ethylacetate/hexane (40:60) gave as the first fraction the tetraacetate **14** (590 mg, 51%): White crystals. M.p. 48–49 °C (recrystallised from ether/hexane): (1*S*(*R*),2*R*(*S*),3*S*(*R*),4*R*(*S*))-1,2,3,4-tetraacetoxycycloheptane (**14**): IR (KBr) 3023,

2946, 2884, 1753, 1438, 1376, 1246, 1230, 1069, 1038. ^{1}H NMR (400 MHz, $CDCl_3$) 5.35 (*d*, *J* = 7.3 Hz, A part of AB-system, OCH, 2H), 5.12 (*dt*, *J* = 7.3 Hz, 4.5 Hz, B part of AB-system, OCH, 2H), 2.06 (*s*, CH_3, 6H), 2.04 (*s*, CH_3, 6H), 1.96–1.83 (*m*, CH_2, 4H), 1.81–1.74 (*m*, CH_2, 1H), 1.60–1.54 (*m*, CH_2, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 170.18, 169.91, 72.87, 71.07, 31.37, 21.32, 21.09, 17.58. Anal. calcd. for $C_{15}H_{22}O_8$: C 54.5, H 6.7; found: C 54.3, H 7.0. Continued elution with the same solvent mixture afforded the tetraacetate **15** as the second fraction (270 mg, 23%): White crystals. M.p. 92–93 °C (recrystallised from ether/hexane): (1*S*(*R*),2*S*(R),3*R*(*S*),4*R*(*S*))-1,2,3,4-tetraacetoxycycloheptane (**15**): IR (KBr) 3016, 2954, 2885, 1743, 1434, 1373, 1241, 1234, 1149, 1049, 1025. ^{1}H NMR (400 MHz, $CDCl_3$) 5.25 (*dd*, *J* = 2.8 Hz, 0.9 Hz, A part of AB-system, OCH, 2H), 5.19–5.15 (*m*, OCH, 2H), 2.07 (*s*, CH_3, 6H), 2.00 (*s*, CH_3, 6H), 1.99–1.91 (*m*, CH_2, 1H), 1.90–1.80 (*m*, CH_2, 4H), 1.51–1.44 (*m*, CH_2, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 170.24, 170.04, 72.83, 71.33, 29.04, 21.18, 21.04, 17.95. Anal. calcd. for $C_{15}H_{22}O_8$: C 54.5, H 6.7; found: C 54.3, H 6.6.

(1S(R),2R(S),3S(R),4R(S))-cycloheptane-1,2,3,4-tetraol (**16**): **16** was synthesised by ammonolysis of **14** (416 mg, 1.26 mmol) as described above in the synthesis of **12** (colourless oil, 204 mg, 99%): IR (KBr) 3386, 2923, 1658, 1427, 1265, 1072, 1025. ^{1}H NMR (400 MHz, D_2O) 3.73 (*d*, *J* = 6.2 Hz, A part of AB-system, OCH, 2H), 3.69–3.65 (*m*, OCH, 2H), 1.77–1.70 (*m*, CH_2, 2H), 1.56–1.41 (*m*, CH_2, 3H), 1.34–1.28 (*m*, CH_2, 1H). ^{13}C NMR (100 MHz, D_2O) 75.51, 71.52, 33.12, 17.92. Anal. calcd. for $C_7H_{14}O_4$: C 51.8, H 8.7, found: C 51.7, H 8.9.

(1S(R),2S(R),3R(S),4R(S))-cycloheptane-1,2,3,4-tetraol (**17**): **17** was synthesised by ammonolysis of **15** (colourless oil, 256 mg, 0.76 mmol) as described above in the synthesis of **12** (125 mg, 99%): IR (KBr) 3409, 2939, 1450, 1280, 1141, 1072. ^{1}H NMR (400 MHz, D_2O) 3.80–3.72 (*m*, OCH, 4H), 1.77–1.70 (*m*, CH_2, 2H), 1.64–1.54 (*m*, CH_2, 3H), 1.27–1.12 (*m*, CH_2, 1H). ^{13}C NMR (100 MHz, D_2O) 75.51, 72.28, 30.77, 17.28. Anal. calcd. for $C_7H_{14}O_4$: C 51.8, H 8.7, found: C 51.6, H 8.8.

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