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Facile Stereoselective Syntheses of Four of the Six 1, 2, 3, 4-Cyclohexanetetrols: Increasing the Accessibility of Cyclitols for Probing the Molecular Recognition of Saccharides

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FACILE STEREOSELECTIVE SYNTHESES OF FOUR OF THE SIX 1, 2, 3, 4-CYCLOHEXANETETROLS: INCREASING THE ACCESSIBILITY OF CYCLITOLS FOR PROBING THE MOLECULAR RECOGNITION OF SACCHARIDES.

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New and stereoselective syntheses of (1,2,3/4)-, (1,2/3,4)-, (1,4/2,3)-, and (1,2,4/3)-cyclohexanetetrols (**1**, **2**, **3**, and **4** respectively) are described. The known syn and anti 1,4-cyclohex-2-enediols **9** and **10** were used as starting materials. Diols **9** and **10** were allow to react with OsO_4 to directly form **3** and **1** respectively. Diols **9** and **10** were epoxidized with MCPBA, which yielded **4** and **2** after acid catalyzed epoxide opening.

Unlike nucleotides,[1] saccharides and alcohols have not been extensively investigated as targets for complexation by artificial receptors.[2] This is likely due to the non-planar shape of saccharides, which has resulted in predominately macrocyclic host designs.[3] Another complexity in saccharide binding is the large number of stereoisomers possible for just one of the simplest monomeric units pyranose.

One possible way to decrease the complexity of molecular recognition studies of saccharides is to analyze simpler guests such as

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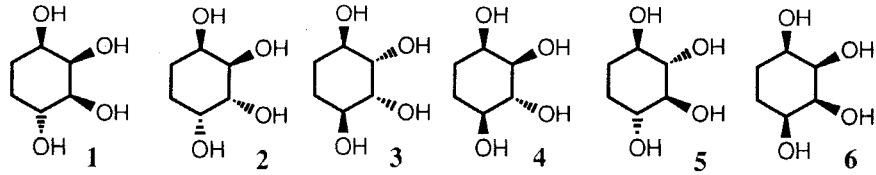
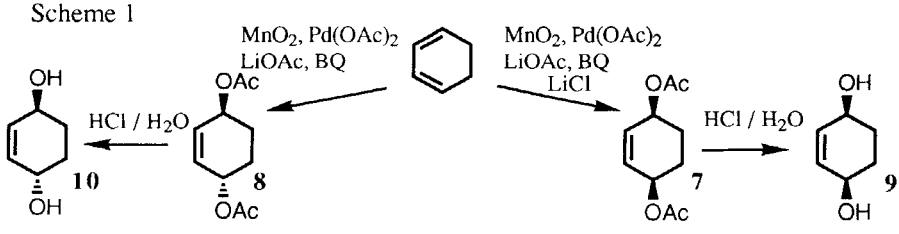
cyclohexanediols, triols and tetrols (cyclitols). The number of host-guest geometries will be reduced due to the smaller number of hydroxyls compared to saccharides. Indeed, studies of cyclitol recognition has yielded insight into the selectivities observed for saccharide binding.[4,5]

Although cyclohexanediols are commercially available,[6] and the synthesis of cyclohexanetriols is relatively straightforward,[7] the synthesis of the cyclohexanetetrols is more challenging.[8] Compounds **1**, **2**, **3** and **4** have been previously synthesized from the products of singlet oxygen addition to 1,3-cyclohexadiene.[8d] However, these synthetic procedures involve peroxide rearrangements and reductions with chromatographic separations of isomers. Similarly, multiple step synthetic procedures starting from inositols have been reported for the synthesis of tetrols **5** and **6**.[9]



Herein, simple stereoselective procedures for the synthesis of four (**1**, **2**, **3**, and **4**) of the six 1,2,3,4-cyclohexanetetrols are described. The facile syntheses were made possible by the elegant stereoselective preparation of *cis*- and *trans*-1,4-dihydroxy-2-cyclohexene (**9** and **10**) from 1,3-cyclohexadiene reported by Backvall (Scheme 1).[10]

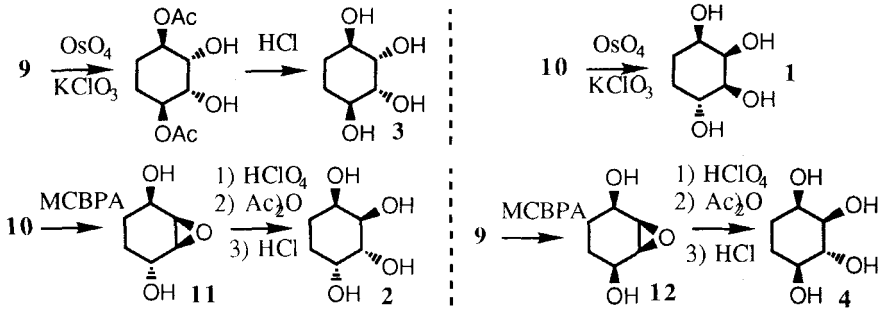
Scheme 1



The syntheses of cyclohexanetetrols **1** and **3** are the shortest (Scheme 2). Oxidation of **10** with 2 mole % OsO_4 (regenerated with

either $KClO_3$ or $NaClO_3$) lead to product **1**. Oxidation of **9** can yield two isomers **3** and **6**. However, due to the anti-addition of osmium tetroxide to allylic alcohols or acetates,[11] only product **3** was observed. Compound **9** was allowed to react with osmium tetroxide for five days, but gave **3** in only 20 % yield. However, treatment of diacetate **7** with OsO_4 gave (1,4/2,3)-1,4-diacetoxy-2,3-cyclohexanediol, which gave **3** in a 77% overall yield after hydrolysis of the acetates.

Scheme 2



The syntheses of **2** and **4** are also quite simple due to the symmetry elements present in **9** and **10** (Scheme 2). Compound **10** was allowed to react with *m*-chloroperbenzoic acid to give **11**. The hydrolytic opening of the epoxide **11**, however, gave isomers **2** and **5**. Compound was separated from **5** by formation of tetra-acetates followed by silica gel chromatography. After purification of the tetra-acetate of **2**, hydrolysis in aqueous acid yielded **2** (24 % from **10**). Similarly, treatment of **9** with MCBPA yielded **12**,[12] which when treated with acid gave **4** in 26% overall yield.

In summary, these quick syntheses of cyclohexanetetrols should allow a more facile analysis of the selectivity of binding monosaccharides with synthetic receptors. In addition, the synthetic elaborations on **7** and **8** demonstrate the great utility of the stereoselective oxidation of 1,3-cyclohexadiene,[10] and could serve as examples for further elaboration to more complex structures such as conduritols and aminocyclitols.

Experimental: ^1H NMR and ^{13}C NMR spectra were obtained using a Bruker AC-250 Spectrometer. High resolution mass spectra were recorded with a CEC 21-110B instrument in either the EI or CI mode. Melting points were measured with a Hoover Uni-Melt capillary melting point apparatus (not calibrated). Ether and THF were distilled from deep blue solutions resulting from benzophenone and sodium. All column chromatography was done with Silica Gel 40μ from Scientific Adsorbents Inc. *Cis*- and *trans*-1,4-dihydroxy-2-cyclohexene (**7** and **8**) were prepared from cyclohexadiene following Backvall's procedure.[10]

***d,l*-(1,2,3/4)-Cyclohexanetetrol (1)**

A 100 mL round bottom flask was charged with compound **10** (0.5 g, 4.4 mmol) in 5 mL H_2O and 5 mL THF. To this solution was added 1 mL of OsO_4 (2.5% in 2-methyl-2-propanol, 0.09 mmol) solution. The mixture was allowed to stir for 30 min., and then $NaClO_3$ (0.56 g, 5.27 mmol) was added over 40 min. The reaction was stirred at room temperature for 48 h. The OsO_4 was quenched with a saturated $NaHSO_3$ solution and the solvent reduced on a rotary evaporator to remove THF. The resulting aqueous solution was lyophilized to give a grayish solid, which was extracted in Soxhlet apparatus with methanol for 24 h to yield a white solid (0.5 g, 77%). The tetrol was further purified by sublimation at 100 °C. Mp 152 - 153 °C (lit.[13] 152.5 - 154.5 °C). ^1H NMR (D_2O, 500 MHz): δ 4.01 (dt, J's = 2.75 Hz, 1.5 Hz, C_2-H, 1 H), 3.75 (ddd, J's = 11.5 Hz, 3.0 Hz, 5.0 Hz, C_1-H, 1 H), 3.60 (ddd, J's = 11.5 Hz, 9.5 Hz, 5.0 Hz, C_4-H, 1 H), 3.38 (dd, J's = 10.0 Hz, 3.0 Hz, C_3-H, 1 H), 1.91 (ddd, J's = 13.0 Hz, 8.5 Hz, 4.0 Hz, CH_2, 1 H), 1.68 (m, CH_2, 2 H), 1.25 (m, CH_2, 1 H). $^{13}C\{^1H\}$ NMR (D_2O, 125 Hz): δ 77.2, 75.9, 72.5, 71.9, 30.6, 27.9. HRMS-CI calcd for $C_6H_{13}O_4$: 149.0814 (M^+ + H); found: 149.0818.

(1,4/2,3)-Cyclohexanetetrol (3)

Compound **7** (0.2 g, 1 mmol) was dissolved in 2 mL THF and 2 mL water, treated with 0.25 mL of OsO_4 (2.5% in 2-methyl-2-propanol, 0.025 mmol) solution and 0.13 g (1.21 mmol) of $NaClO_3$ in exactly the same manner as described for **1**. After Soxhlet extraction a yellow oil (0.24 g, 100%) was isolated. A ^1H NMR spectrum was in agreement with

(1,4/2,3)-1,4-diacetoxy-2,3-cyclohexanediol. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.85 (m, C<u>H</u>OAc, 2 H), 3.81 (m, C<u>H</u>OH, 2 H), 1.99 (s, 2 OAc, 6 H), 1.78 - 1.50 (m, CH2-5,6, 4 H). The oil was dissolved in 10 mL of 4 N HCl and stirred at reflux for 6 h. The HCl was evaporated and water added. The mixture was lyophilized to yield a white solid (0.5 g, 77%), which was purified by sublimation at 100 °C. Mp 205 -207 °C (lit.[14] 210 °C). ^{1}H NMR (D_2O, 500 MHz): δ 3.85 (br, $C_{1,4}$-H, 2 H), 3.78 (m, $C_{2,3}$-H, 2 H), 1.78 (m, CH_2-eq, 2 H), 1.63 (m, CH_2-a, 2 H). $^{13}C\{^1H\}$ NMR (D_2O, 125 Hz): δ 75.5, 72.3, 28.4. MS-CI m/z 149 (M^+ + H), 131, 113. HRMS-CI calcd for $C_6H_{13}O_4$: 149.0814 (M^+ + H); found: 149.0818.

***d,l*-(1,2/3,4)-Cyclohexanetetrol (2)**

Compound **10** (5.38 g, 47.2 mmol) in 20 mL of EtOAc was added dropwise to a stirred and cooled (0°C) solution of *m*-chloroperoxybenzoic acid (19.5 g, 56.6 mmol) in 40 mL dry ether under nitrogen. The mixture was stirred at 0 °C for 12 h. The reaction was neutralized with $Ca(OH)_2$ and filtered. The precipitate was washed with ether, and the combined organic solutions were dried (Na_2SO_4) and evaporated to give a light yellow liquid **11** (4.4 g, 72 %). ^{1}H NMR (CD_3CN, 250 MHz): δ 3.94 (m, CH-(O), 1 H), 3.82 (m, CH-(O), 1 H), 3.20 (m, C<u>H</u>OH, 1 H), 3.11 (m, C<u>H</u>OH, 1 H), 2.97 (br., OH, 1 H), 2.66 (br., OH, 1 H), 1.84 (m, CH_2, 1 H), 1.58 (m, CH_2, 1 H), 1.17 (m, CH_2, 2 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 Hz): δ 66.8, 64.1, 58.5, 55.4, 28.4, 23.2. Compound **11** (4 g, 30.8 mmol) was not characterized further, but instead dissolved in 30 mL THF and 20 mL of 3 N $HClO_4$. The mixture was stirred at room temperature overnight. The mixture was neutralized with NH_4OH and concentrated on a rotary evaporator to remove THF. The aqueous solution was lyophilized to give a light yellow solid. The ^{1}H NMR in D_2O showed mostly one tetrol (**2**), with a very small amount of a second tetrol (**5**). This mixture of tetrols was dried in vacuum overnight and then dissolved in 50 mL dry pyridine under nitrogen. Acetic anhydride (17.6 g, 172 mmol) was added dropwise through an addition funnel over 20 min. The reaction was stirred at room temperature for 36 h. The mixture was poured into water and extracted with ether (50 mL x 4).

The combined ether solution was washed with 1 N HCl, water, saturated $NaHCO_3$ solution, and then dried (Na_2SO_4) and evaporated. The residue was purified by silica gel chromatography with 20% methylene chloride in ether to give a white powder (3.9 g, 36% yield from **11**). The ^1H NMR spectrum was correct for a tetra-acetate. Mp 104 - 106 °C, (lit.[15] 104 -110°C). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.40 (br., AcOC<u>H</u>-2,3, 2 H), 5.21 (m, AcOC<u>H</u>-1,4, 2 H), 2.08 (s, OAc, 3 H), 2.01 (s, OAc, 3 H), 1.92 (m, CH_2, 2 H), 1.79 (m, CH_2, 2 H). The tetraacetate was hydrolyzed to the corresponding tetrol by stirring with 200 mL 4 N HCl at room temperature for 16 h. The mixture was evaporated and dried in vacuum over P_2O_5 to remove water and HCl, giving a light yellow syrup which was crystallized by addition of methanol and chloroform. The precipitate was filtered and further purified by sublimation to give a white solid (1.70 g, 92% from tetraacetate). Mp 208 - 209 °C (lit.[8] 209 - 211 °C). ^1H NMR (D_2O, 500 MHz): δ 4.02 (br., d, J = 3.0 Hz, $C_{1,4}$-H, 2 H), 3.79 (br., $C_{2,3}$-H, 2 H), 1.75 (m, CH_2-eq, 2 H), 1.65 (m, CH_2-a, 2 H). $^{13}C\{^1H\}$ NMR (D_2O, 125 Hz): δ 74.1, 71.8, 27.4. MS-CI m/z 149 (M^+ + H), 131, 113. HRMS-CI calcd for $C_6H_{13}O_4$: 149.0814 (M^+ + H); found: 149.0824.

***d,l*-(1,2,4/3)-Cyclohexanetetrol (4)**

Compound **9** (5.12 g, 45 mmol) and *m*-chloroperoxybenzoic acid (15.5 g) were treated in exactly the same manner as discussed for **2**, yielding 4.5 g of **12** (77%). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.61 (br., CH-2,3, 2 H), 3.01 (s, C<u>H</u>OH, 2 H), 2.90 (br., OH, 2 H), 1.19 (m, CH_2-5,6, 4 H). $^{13}C\{^1H\}$ NMR (CD_3CN, 75 Hz): δ 65.6, 58.1, 28.1. This compound was not characterized further. Compound **12** (4.48 g, 34.5 mmol) was dissolved in 30 mL THF and 20 mL of 3 M $HClO_4$. The resulting tetrol was converted to the tetra-acetate in the same manner as described for **2** to give 4.1 g of product, 38% yield from **12**. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.45 (m, CH-2,3, 2 H), 4.90 (m, CH-1,4, 2 H), 2.09 (s, $OCOCH_3$, 1 H), 2.00 (s, $OCOCH_3$, 1 H), 1.98 (s, $OCOCH_3$, 1 H), 1.95 (s, $OCOCH_3$, 1 H),.2.00 - 1.60 (m, CH_2-5,6, 4 H). Finally, tetrol **4** was formed from the tetra-acetate as described for **2** (1.68 g, 88% from tetra-acetate). Mp 135 - 136 °C (lit.[8] 139 -140.5 °C). ^1H NMR (D_2O, 500 MHz): δ 4.02 (br., C_1-H, 1 H), 3.52 (t, J's =

9.5 Hz, C_3-H, 1 H), 3.46 (ddd, J's = 10.5 Hz, 10.0 Hz, 4.5 Hz, C_4-H, 1 H), 3.41 (dd, J's = 9.5 Hz, 3.0 Hz, C_2-H, 1 H), 1.78 (m, CH_2-eq, 2 H), 1.35 (ddd, J's = 9.25 Hz, 7.75 Hz, 3.5 Hz, CH_2-a, 2 H). $^{13}C\{^1H\}$ NMR (D_2O, 125 Hz): δ 77.5, 76.8, 75.3, 72.1, 29.1, 28.7. MS-CI m/z 149 (M^+ + H), 113. HRMS-CI calcd for $C_6H_{13}O_4$: 149.0814 (M^+ + H); found: 149.0814.

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