

Polyhydroxylated Tetrahydronaphthalene Ethers: Synthesis and Molecular Properties

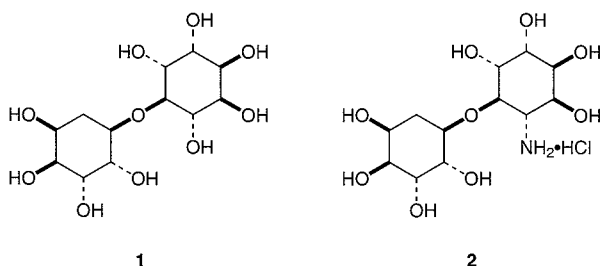
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Abstract: Polyhydroxylated tetrahydronaphthalene ethers **9a** and **10** were synthesized in five steps by a chemoenzymatic approach. The resulting ethers have shown interesting molecular properties which are discussed here.

Both natural and unnatural derivatives of carbohydrates have received much attention in recent years because of their therapeutic potential.¹ Recently, iterative procedures for the synthesis of inositol and aminocyclitol conjugates such as **1** and **2** have been developed and these compounds have been shown to bind calcium and assemble into helical structures.²

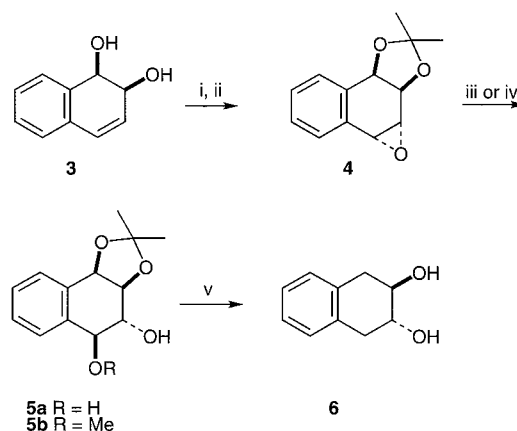


The inositol dimers and oligomers are synthesized by simple procedures and with full control of regio-, stereo- and enantioselectivity.³ The interesting biological and physical properties of this new class of compounds led us to extend this study to similar oligomers bearing an aromatic ring. We would expect that the structures containing both lipophilic and hydrophilic regions would exhibit interesting molecular properties. The presence of a π -system may also elicit π -stacking, or be amenable to the formation of metal π -complexes and thus lead to additional molecular properties.

The combination of biotransformations and chemical synthesis offers a unique opportunity to shorten routes to important targets in an environmentally conscious manner. The virtues of efficient, biocatalysis-based synthetic design have recently been reviewed.⁴ Oxidation of aromatic compounds by microorganisms results in enantiomerically pure *cis*-diols which are useful synthons for many natural products.^{4,5,6} Dihydronaphthalene *cis*-diol **3** was obtained by biooxidation of naphthalene in a moderate yield (5g/L) using toluene dioxygenase expressed in *Escherichia coli* JM109 (pDTG601). This particular biotransformation was first reported by Gibson⁷ who used *Pseudomonas putida* NCIB11 strain containing naphthalene dioxygenase but other microorganisms have also been used.⁸ The absolute configuration of the diol has been firmly established⁷ and the compound is commercially available.⁹

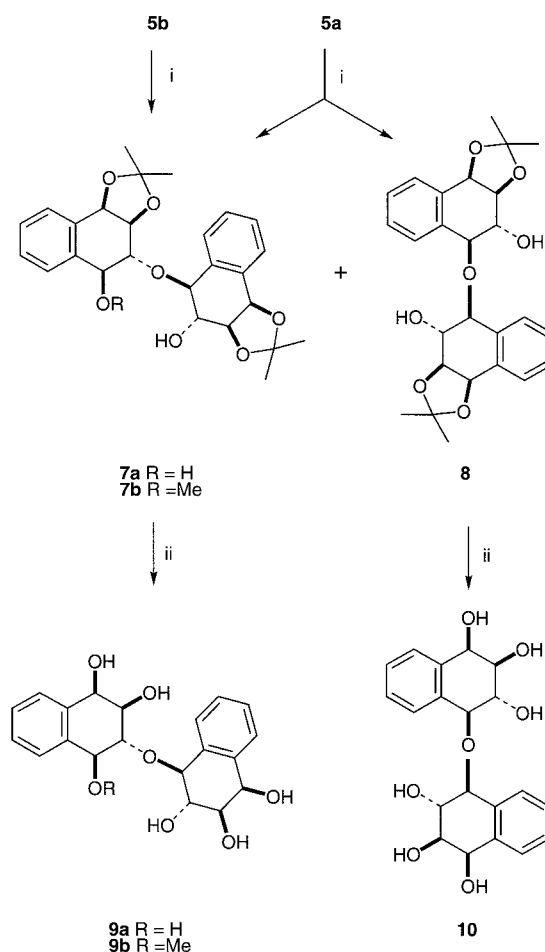
The coupling strategy is based on an iterative opening of epoxide **4** at the benzylic position by nucleophiles in the presence of a Lewis acid catalyst.

The diol **3** was protected as its isopropylidene derivative to allow the subsequent stereoselective epoxidation using *m*-chloroperbenzoic acid in methylene chloride,¹⁰ (Scheme 1) to afford **4**. Ring opening of **4** at the benzylic position was accomplished with KOH in wet DMSO solution at 75°C, to afford **5a** in 84% yield. The stereochemistry was confirmed by conversion of **5a** to (2*R*,3*R*)-dihydroxytetrahydronaphthalene (**6**) by hydrogenolysis and by comparison of the optical rotation with that reported for this compound in the literature.¹⁰



Reagents : i) *p*-TsOH, 2,2-DMP, acetone; ii) *m*-CPBA, CH₂Cl₂, 0°C to rt.; iii) KOH, DMSO, 75°C; iv) MeONa, MeOH, reflux; v) H₂/Pd(C), HCl, EtOH.

Scheme 1



Reagents : i) 4, BF₃·OEt₂, CH₂Cl₂, -20°C; ii) THF/TFA/H₂O 4/1/1, rt.

Scheme 2

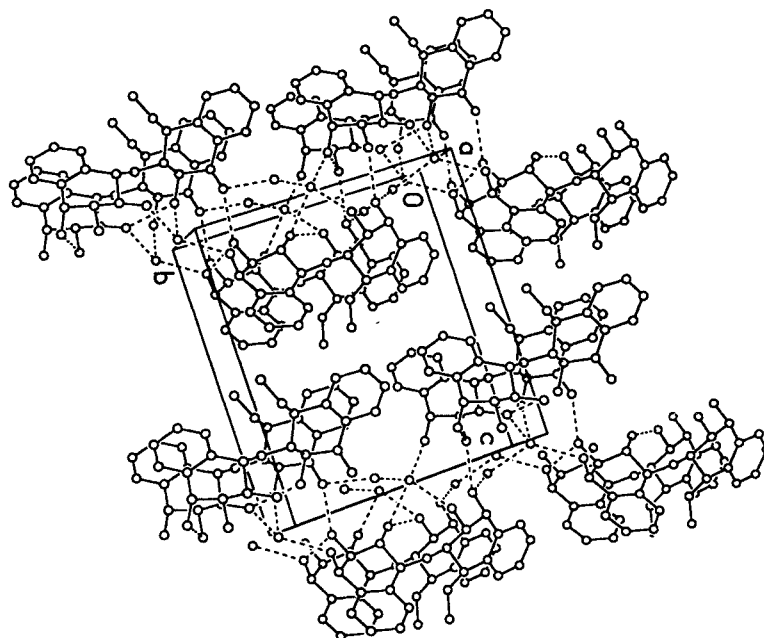


Figure 1

Ring opening of **4** with **5a** in the presence of boron trifluoride diethylether complex in methylene chloride at -20°C ,^{3a} gave the ethers **7a** and **8** in a 3:1 ratio in 50% yield. These regioisomers were readily separated by column chromatography on silica gel. The ^1H and ^{13}C NMR spectrum of ether **8** indicated the presence of a C_2 symmetry axis. Polyols **9a** and **10** were obtained separately by deprotection of the acetonides **7a** and **8** respectively in a mixture of THF/ H_2O /TFA (4/1/1) in excellent yields (90%).

To better control the selectivity of the coupling reaction, epoxide **4** was opened to afford a protected hydroxyl functionality at the benzylic position. Several nucleophiles (methanol, benzyl alcohol, *tert*-butanol, *p*-methoxybenzyl alcohol) were used for the ring opening of **4** with methanol giving the best results.

Treatment of **4** with sodium methoxide in methanol at reflux, afforded the alcohol **5b** in 95% yield. The stereochemistry of this compound was confirmed by deprotection and hydrogenolysis to **6**. The coupling reaction was performed under conditions described above and afforded **7b** in 56% yield (Scheme 1). Ether **7b** was also obtained in 57% yield in a one-step procedure from epoxide **4** in the presence of 0.5 equivalent of methanol and $\text{BF}_3\cdot\text{OEt}_2$ in dichloromethane at -78°C , and deprotected to give **9b** in 80% yield.

The stereochemistry of **9b** was confirmed by single crystal X-ray diffraction analysis, which clearly indicates an aggregate with strong hydrogen bonding. The three dimensional structure (Figure 1) shows sheets in the *ab* plane. These sheets formed three regions, a hydrophilic region that contains water molecules linked by hydrogen bonding, and two lipophilic regions composed of the aromatic portions of the molecules. This suggests that chelation of metals can occur via either hydroxyl groups or π chelation in the lipophilic regions.

In summary, we have developed a simple method to synthesize dimeric ethers of tetrahydronaphthalenetetrols. It is expected that this method will be easily extended to the preparation of trimers, tetramers, and higher oligomers. This particular strategy will be exploited in both solution and solid phase synthesis of libraries of this type of compounds. Further results on metal binding capabilities and other properties of these compounds will be reported in due course.

Illustrative Experimental Procedure:

Alcohol **5b** (1.043 g, 4.17 mmol) and epoxide **4** (0.777 g, 3.56 mmol) were dissolved in dry dichloromethane under an argon atmosphere. Boron trifluoride diethyletherate complex (12 μL , 0.08 mmol) was added and the mixture was stirred at -15°C for 1 hour, then at room temperature overnight. The mixture was poured into ethyl acetate and the organic phase was washed with a saturated sodium bicarbonate solution, brine, dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, ethyl acetate/hexane, 1/3) to afford ether **7b** (935 mg, 56%) as a white solid. $[\alpha]_{\text{D}}^{25} +133.5$ (c 1.04, CHCl_3); mp $175\text{--}177^{\circ}\text{C}$ (recrystallized from CH_2Cl_2 /hexane); IR (KBr) 3464, 2984, 2936, 1456, 1260, 1214, 1164, 1110, 1079, 872, 746; ^1H NMR (300 MHz, CDCl_3) δ 7.81 (m, 1H), 7.31–7.50 (m, 7H), 5.34 (d, $J = 7.7$ Hz, 1H), 5.23 (d, $J = 7.4$ Hz, 1H), 4.69 (bs, 1H, OH), 4.66 (m, 2H), 4.41 (d, $J = 9.3$ Hz, 1H), 4.36 (d, $J = 7.4$ Hz, 1H), 4.11 (dd, $J = 9.9, 8.2$ Hz, 1H), 3.77 (t, $J = 9.1, 1\text{H}$), 1.54 (s, 3H), 1.52 (s, 3H), 1.49 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl_3) δ 136.1, 135.6, 132.7, 132.2, 128.5, 128.2, 128.0, 127.8, 127.7, 124.9, 124.4, 110.5, 110.0, 82.5, 81.7, 80.9, 78.3, 78.1, 76.0, 74.1, 73.9, 60.2, 27.7, 27.1, 25.5, 25.1; HRMS (FAB) calcd for $(\text{C}_{27}\text{H}_{32}\text{O}_7\text{-H})$ 467.2070, Found 467.2074; Anal. calcd for $\text{C}_{27}\text{H}_{32}\text{O}_7$: C, 69.21; H, 6.88. Found: C, 69.13; H, 6.84.

Acknowledgements

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