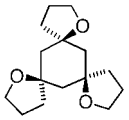
Synthesis and Conformational Properties of the Sterically Crowded D_{3d}-Symmetric all-*trans* Hexa(spirotetrahydrofuranyl)cyclohexane System**

Leo A. Paquette,* Jinsung Tae, Bruce M. Branan, Shawn W. E. Eisenberg, and John E. Hofferberth

In the preceding paper,[1] we introduced the belted trispiro ether **1** as a ligand capable of forming supramolecular complexes with alkali metal ions. This ionophore exhibits a distinct selectivity for Li^+, which is well accommodated by the



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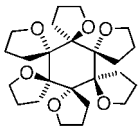

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conformer with oxygen atoms in the *syn*-axial positions. Very comparable spatial characteristics are resident in **2**, with the added feature that this functionalized molecular array in its O-axial conformation should be able to bind a metal ion on both of its electron-rich surfaces. Bifacial crown ethers are virtually unknown.[2]

MM3-based calculations indicate the global energy minimum of this rather crowded molecule to be **2-eq**, with **2-ax** comparatively destabilized by 4.6 kcal mol^{-1} (Figure 1 a). With the 1,3,5-oxygen triads present above and below the chairlike cyclohexane core in **2-ax**, the existing spatial characteristics are conducive to bifacial complexation. The possibility of gaining access to ladder polymers consisting of **2-ax** and alkali metal ions had given preliminary indication of being a realistic goal. The hypothetical $(\mathbf{2})_3 \cdot 4\,Li^+$ complex is shown as **3** in Figure 1 b.

On the basis of a significant number of experiments, it had become clear that the functionalized cyclohexanone **4**[3, 4] enters into 1,2-addition reactions with organometallic reagents from the direction *syn* to the methylene carbon atoms. Equatorial attack on the all-equatorial oxygen conformation of **4** is therefore overwhelmingly favored kinetically[5] (Scheme 1). As a consequence, the oxygen atom at this center must be introduced last. Therefore, tertiary carbinol **5b** was dehydrated and exposed to fluoride ion in order to generate homoallylic alcohol **6**. Following epoxidation of **6**, the readily separated oxirane **7** was oxidized to the aldehyde with tetra-*n*-propylammonium perruthenate[6] and treated with triethylamine to effect β elimination. The conversion of **9** into diol **10** was accomplished by sequential hydrogenation and hydride

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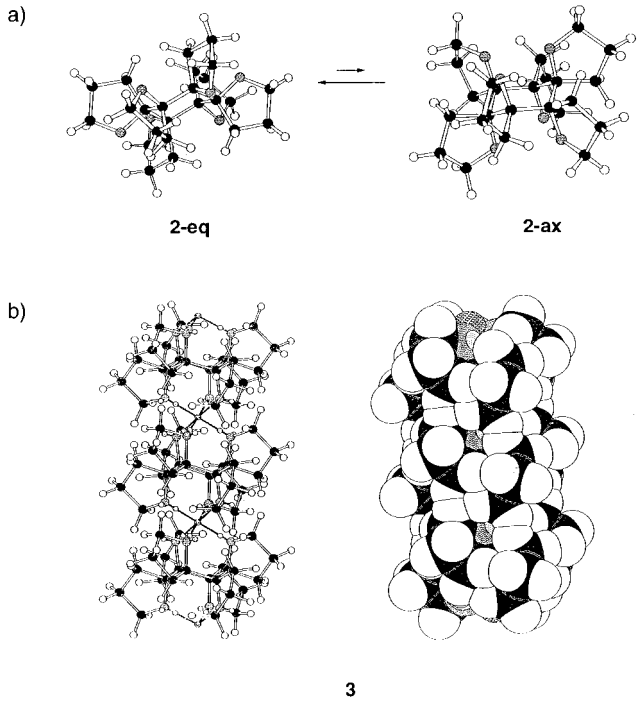
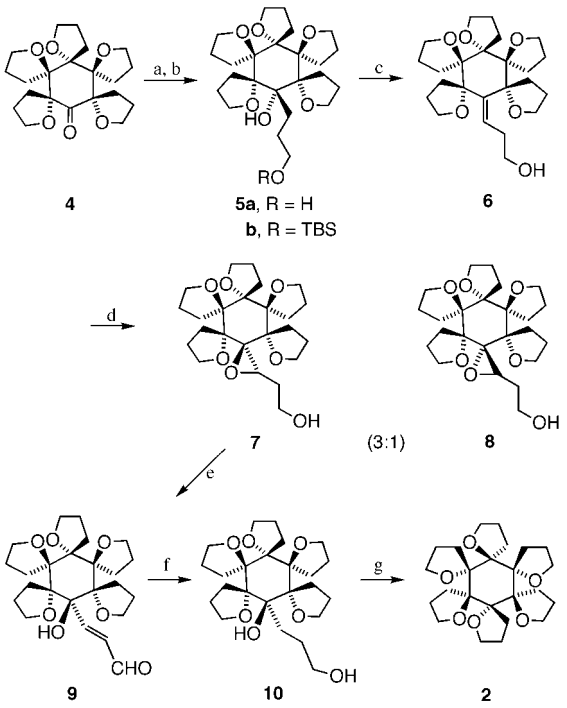


Figure 1. a) Ball-and-stick model of **2-eq** and **2-ax**, and their interconversion. b) Ball-and-stick (left) and space-filling models (right) of **3**, the hypothetical $(\mathbf{2})_3 \cdot 4\,Li^+$ complex.



Scheme 1. Synthesis of **2**: a) $CClMg(CH_2)_3OMgCl$, THF, −78 °C, 10 min, 91 %; b) TBSCl, Et_3N, DMAP, CH_2Cl_2, 20 °C, 18 h, 92 %; c) $SOCl_2$, pyridine, 0 °C, 40 min; TBAF, THF, 20 °C, 15 h, 90 % over 2 steps; d) MCPBA, $NaHCO_3$, CH_2Cl_2, 20 °C, 2 h, 97 %; e) TPAP, NMO, CH_2Cl_2/CH_3CN (9:1), 20 °C, 1 h, Et_3N, 30 min; f) 5 % Pd/C, 1 atm of H_2, C_2H_5OH, 10 °C, 1 h; $LiAlH_4$, THF, 20 °C, 3 h; g) TsCl, Et_3N, DMAP, CH_2Cl_2, 10 h at 20 °C, then 13 h at reflux, 42 % over 5 steps). DMAP = 4-dimethylaminopyridine, MCPBA = *meta*-chloroperbenzoic acid, NMO = *N*-methylmorpholine *N*-oxide, TBAF = tetrabutylammonium fluoride, TBSCl = *tert*-butyldimethylsilyl chloride, TPAP = tetrapropylammonium perruthenate, TsCl = *para*-toluenesulfonyl chloride.

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reduction. Transient formation of the primary monotosylate was followed by in situ cyclization[7] to deliver **2** as a colorless, crystalline solid (m.p. 249–251 °C, decomp.). X-Ray structural analysis of **2** confirmed its adoption of a somewhat flattened cyclohexane core and the equatorial disposition of all six C–O bonds, much as in the MM3-derived **2-eq** model. Figure 2

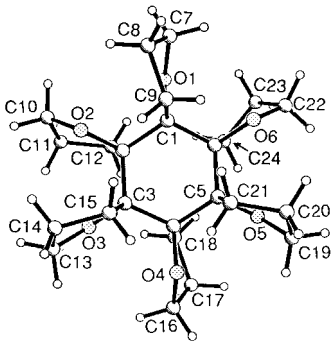


Figure 2. Molecular structure of **2** in the solid state. Selected bond lengths [Å] and angles [°]: O1–C1 1.455(2), O2–C2 1.447(2), O3–C3 1.446(3), O4–C4 1.449(2), O5–C5 1.446(2), O6–C6 1.448(3), C1–C2 1.571(3), O1–C7 1.431(3); C1-O1-C7 110.41(15), O1-C7-C8 104.85(8), C7-C8-C9 100.78(18), C8-C9-C1 105.53(7), C9-C1-C2 113.55(17), C6-C1-C2 112.51 (16).

shows a top view of the polyether which allows visual inspection of the conformations of the pendant heterocyclic rings.[8] The greatly simplified ^{1}H and ^{13}C NMR spectra (Table 1) testify to the inherently high symmetry of the compound.

Compound **2** is a fully substituted cyclohexane and is therefore a member of a class of compounds renown for their anomalous topological properties and unusually high barriers to conformational isomerization.[9] With respect to **2**, the barriers for the chair-to-chair interconversions for **11**–**13**[9, 10] seemed most meaningful. These data suggest that the **2-ax** $\rightleftharpoons$ **2-eq** equilibrium should be characterized by a barrier

Table 1. Selected spectroscopic data for compounds **2**, **4**, **5a**, and **7**.[a]

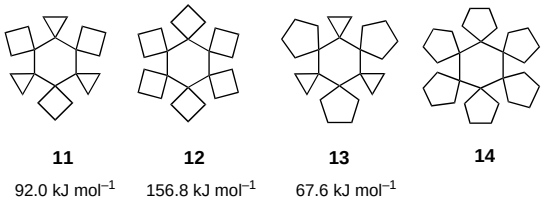
2: ^{1}H NMR (C_6D_6): $\delta = 3.58$ (t, $J = 6.7$ Hz, 12H), 2.49 (t, $J = 7.2$ Hz, 12H), 1.88 (quint., $J = 6.9$ Hz, 12H); ^{13}C NMR (C_6D_6): $\delta = 92.5$, 67.7, 30.4, 29.3; HR-MS: *m/z* calcd: 420.2512 [M^+]; found: 420.2485.

4: IR (film): $\tilde{\nu} = 1715$ cm^{-1}; ^{1}H NMR (C_6D_6): $\delta = 3.99$ (ddd, $J = 7.8$, 7.8, 4.7 Hz, 1H), 3.82 (ddd, $J = 7.8$, 7.8, 2.3 Hz, 1H), 3.78–3.51 (m, 7H), 3.50–3.45 (m, 1H), 3.25 (ddd, $J = 12.5$, 8.1, 6.7 Hz, 1H), 2.78–2.71 (m, 1H), 2.70–2.60 (m, 2H), 2.55–2.39 (m, 3H), 2.31–2.15 (m, 1H), 2.11–1.91 (m, 3H), 1.77–1.45 (m, 8H), 1.12 (ddd, $J = 12.6$, 8.6, 2.8 Hz, 1H); ^{13}C NMR (C_6D_6): $\delta = 207.4$, 94.9, 93.2, 92.2, 90.5, 88.8, 69.6, 69.3, 68.9, 68.1, 67.3, 32.5, 31.0, 30.7, 30.5, 29.3, 28.9, 28.2, 27.1, 26.4, 25.4; HR-MS: *m/z* calcd: 378.2042 [M^+]; found: 378.2030.

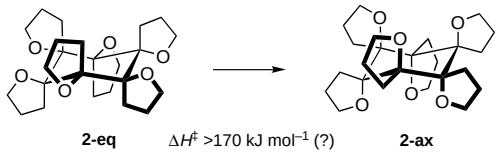
5a: ^{1}H NMR (C_6D_6): $\delta = 3.68$–3.49 (m, 13H), 3.01–2.93 (m, 2H), 2.81–2.71 (m, 2H), 2.56–2.47 (m, 3H), 2.40–2.35 (t, $J = 7.1$ Hz, 2H), 1.95–1.82 (m, 8H), 1.80–1.63 (m, 4H), 1.60–1.48 (m, 4H); ^{13}C NMR (C_6D_6): $\delta =$ 93.6, 92.4 (2 C), 81.6, 68.0, 67.4, 67.3, 64.0, 31.5, 30.7, 30.6, 30.5, 29.3, 28.2 (1 C unresolved); HR-MS: *m/z* calcd: 438.2618 [M^+]; found: 438.2614.

7: ^{1}H NMR (C_6D_6): $\delta = 4.28$ (s, 1H), 3.96 (dd, $J = 9.0$, 2.7 Hz, 1H), 3.73–3.46 (m, 12H), 2.69–2.52 (m, 2H), 2.50–2.35 (m, 6H), 2.14–1.90 (m, 10H), 1.89–1.73 (m, 4H); ^{13}C NMR (C_6D_6): $\delta = 92.12$, 92.08, 91.1, 89.3, 88.3, 68.9, 68.8, 67.9, 67.5, 67.4, 63.4, 62.3, 33.5, 32.8, 31.8, 30.6, 30.5, 30.4, 30.3, 29.4, 28.93, 28.86, 27.9, 27.4; HR-MS: *m/z* calcd: 436.2461 [M^+]; found: 438.2494.

[a] NMR spectra recorded at 300 (^{1}H) and 75 MHz (^{13}C). Correct elemental analyses have been obtained for most compounds.



significantly higher than that exhibited by **13** because of the constancy of the spiro substitution and the five-membered nature of its spirocyclic rings. In view of the fact that in going from **11** to **12** the barrier to inversion increases very significantly, the same should be true when proceeding from **13** to **14**, as a model for **2**. MM3 calculations on **12** and **14**[11] clearly point in this direction. Consequently, it was by no means certain that an inversion of **2-eq** to give **2-ax** (Scheme 2) as a prerequisite for bifacial complexation would take place.



Scheme 2. Inversion of **2-eq** to give **2-ax**.

Indeed, a variety of measurements revealed that **2-eq** exhibits no measurable capability for complexing lithium ions, even under forcing conditions ($LiBF_4$ in benzene/acetonitrile (1/1) at 175 °C in a sealed reaction vessel). Consequently, dynamic NMR studies were undertaken to check the possibility for high-temperature equilibration with **2-ax**. Strikingly, however, the ^{1}H (500 MHz) and ^{13}C NMR spectra (125 MHz) of **2-eq** in remained unchanged upon heating up to 300 °C in a sealed NMR tube. Whether this is due to an unprecedented high barrier to the inversion of **2-eq** or whether inversion takes place but remains undetected because of an insufficient population of **2-ax** at the temperatures employed remains an open question. Until [6.5]- and [6.6]rotane are prepared, it is highly probable that **2-eq** has the highest inversion barrier recognized to the present time. The steric overcrowding in **2** has been shown to be antithetical to bifacial complexation.

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[8] Crystal data for **2**: $C_{24}H_{36}O_6$, $M_r = 420.53$, monoclinic, space group $P2(1)/c$, $a = 8.4842(5)$, $b = 16.0451(9)$, $c = 14.9716(8)$ Å, $\beta = 93.964(1)^\circ$, $V = 2035.2(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.372$ Mg m^{-3}, $F(000) = 912$, $\mu(Mo_{K\alpha}) = 0.097$ mm^{-1}, $T = 173(2)$ K. A total of 12601 reflections were collected, of which 4732 were unique (R(int) = 0.0370). The refinement converged to $R1 = 0.0641$, w$R2 = 0.1248$, and $S = 1.072$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-111933. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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A New Approach to Glycopeptides**

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The importance of carbohydrates for a living organism goes far beyond the function of serving as an energy reservoir.[1] Carbohydrates are elementary building blocks of ribonucleic acids and glycoconjugates such as glycoproteins, -lipids, and -phospholipids,[2] and in most cases the carbohydrate portion of a given molecule is the carrier of the biological information.[3] As a component of the cell membrane, glycoconjugates fulfil important functions[2–4] during cell–cell recognition, cell–matrix interaction, and cell growth regulation, and thus also in the development of tumors.[5] Furthermore, they play a significant role in the interaction with biologically active factors such as enzymes, hormones, bacteriotoxins, and viruses.[1, 4]

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The substructure of a carbohydrate, which undergoes permanent change[6] during the life cycle of a cell, influences the biological properties of peptides and proteins.[1] In general, it increases their proteolytic stability,[7] improves their solubility and properties for transmembrane transport, and decreases their excretion rate[8] thus enhancing their bioavailability. Since glycosylations can cause restrictions of the conformational flexibility of peptides, they play a significant role in peptide folding processes.[9]

In many cases, the glycosylation of naturally occurring and non-natural peptides leads to a change in their activity profile. For instance, the analgesic activity of enkephalines[10] could be increased by glycosylation which is attributed, among others, to an improved passage of the glycosylated form across the blood/brain barrier.[11]

The convergent synthesis of *O*-glycosides by coupling reactions at the carbohydrate/peptide link is problematic because of the generally poor solubility of peptides under the glycosylation conditions and also because of regio- and stereochemical aspects.[9a, 12] Therefore, the method of choice[12] is an alternative synthetic strategy that involves the stepwise construction starting from O-glycosylated amino acid derivatives as well as small O-glycosylated peptide fragments, especially since further coupling reactions can be carried out enzymatically and in solid phase reactions.[14]

The conventional synthesis of glycosyl amino acids and peptides requires the orthogonal protection of the α-amino and the α-carboxylic functionalities. After glycosylation of the free hydroxy group, the carboxylic acid group is deprotected, activated, and the C-terminus is coupled with an amino ester.

The new protecting group/activation strategy described herein offers significant advantages: The introduction and cleavage of the protecting group occurs under mild conditions. This resolves the issue of the acid lability of the *O*-glycoside bond as well as the tendency of the *O*-glycosylated serine and threonine derivatives to undergo β-elimination in the presence of strong bases. As a result, the new strategy offers the possibility of a shorter reaction sequence. Moreover, the reaction can be monitored easily and quickly by ^{19}F NMR spectroscopy without any material loss.

Multifunctional α-amino acids such as serine, threonine, 4-hydroxyproline, and tyrosine react with hexafluoroacetone in very good yields to form 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones. The regioselective heterocyclization process in the case of serine and threonine not only allows the protection of the α-amino and the α-carboxylic groups in one step, but at the same time an additional activation of the carboxylic group. Since an excess of hexafluoroacetone is normally used, the hydroxy groups of serine, threonine, and 4-hydroxyproline in the crude product are partially present as hemiketals. The hexafluoroacetone can be cleaved by stirring a solution of the respective hemiketal in dichloromethane in the presence of silica gel at room temperature; the progress of the cleavage reaction can be monitored easily by ^{19}F NMR spectroscopy. The 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones obtained in this manner can be stored for several months when kept refrigerated in a moisture-free environment.[15]

The HFA-protected amino acids **5**–**8** (HFA = hexafluoroacetone) were allowed to react with 2,3,4,6-tetra-*O*-acetyl-α-

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