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Design and synthesis of a *trans*-fused polycyclic ether skeleton as an α-helix mimetic scaffold

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Abstract—Inspired by the common skeletal feature of potent marine toxins, a ladder-like polycyclic ether scaffold was designed as the basis for the synthesis of structurally defined α-helix mimics. A synthetic route to *trans*-fused 6/6/6/6/6 pentacyclic ether skeletons is presented, involving the iterative assembly of tetrahydropyran rings via the SmI_2-mediated coupling reaction of α-sulfonyl ketones with aldehydes.

The potent ladder-like polycyclic ether marine toxins are based on a common *trans*/*syn*-fused cyclic ether array, with ring sizes ranging from five to nine members.[1] Among these potent toxins, brevetoxins[2,3] and ciguatoxins[4,5] (Fig. 1) are believed to bind to a common site (site 5) on the α subunit of voltage-sensitive sodium channels (VSSCs),[6] where the α subunit consists of 24 transmembrane helices. Although the three-dimensional structure of the receptor site in the VSSC remains unknown, and the extremely limited availability of the toxins has hampered further biological investigation, recent studies have suggested a relationship between the size of the polycyclic ether skeleton and the inhibitory activity against the binding of labeled brevetoxins with the VSSC.[7] It appears that both the length and the relatively straight conformation of the cyclic ether skeletons are critical factors in this relationship, and are required for the binding and modulation of the VSSC function.[8] The interactions between the polycyclic ethers and the receptor site are surmised to be primarily hydrophobic and to be supplemented by hydrogen bonding between skeletal oxygen atoms and the OH/NH groups of the α-helical peptides.[8] In addition to this hydrogen bonding, axially oriented CH groups adjacent to the skeletal oxygen atoms are also expected to play an important role in molecular recognition of the aromatic amino acid residues through CH/π interactions, as exemplified by the crystal structures of complexes between the carbohydrate-binding proteins and specific substrates.[9,10]

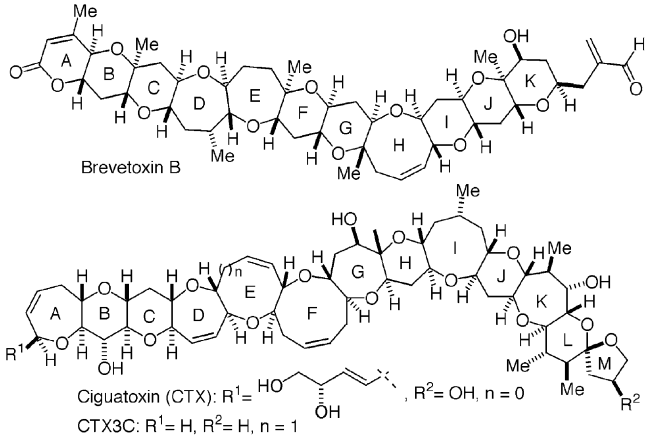

Figure 1. Structures of brevetoxin B, ciguatoxin and CTX3C.

On analysis of the mode of action of these ladder-like toxins, it was noticed that the *trans*-fused cyclic ethers may be topologically analogous to the α-helical peptides. In the 6/6/6 tricyclic system (Fig. 2a), the distance between skeletal oxygen atoms on the same side (4.8 Å) in the cyclic ethers is almost identical to the interval

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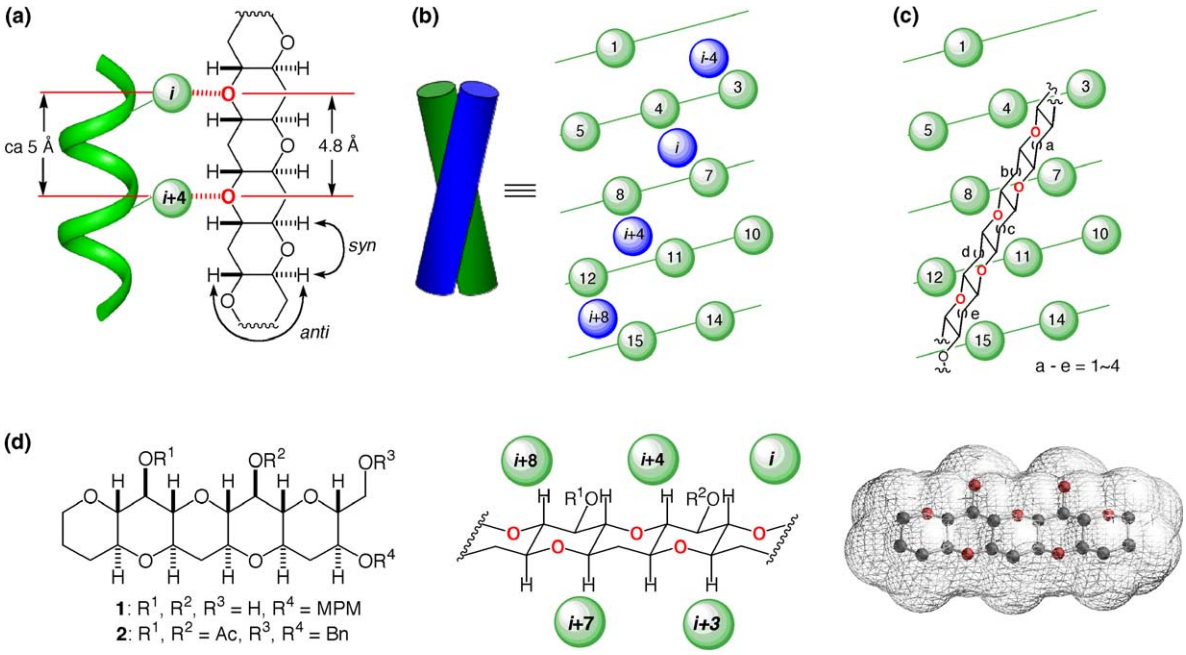


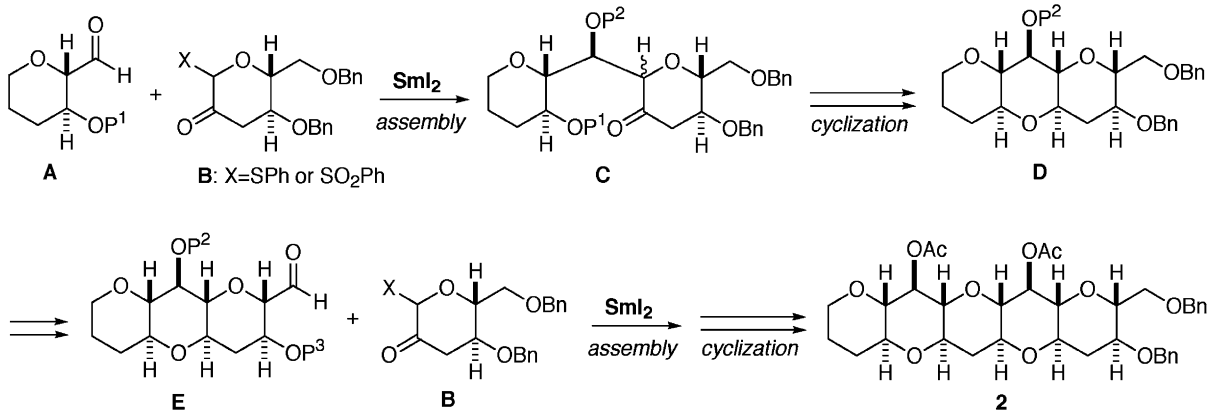
Figure 2. (a) Structural features of a cyclic ether skeleton and an α-helix; (b) Typical helix–helix interaction, showing projection of the surface defined by the ridges and grooves of two helices (green and blue); (c) Hypothetical binding model for the cyclic ether with an α-helix; (d) Design of cyclic ether **1** as an α-helix mimetic scaffold. The water-accessible surface (Connolly surface) for the skeletal cyclic ether part of **1** was generated by Chem 3D Ver. 5.0 using a probe radius of 1.4 Å.

between side-chains in the α-helical peptides in the canonical *i*, *i*+4 relationship (ca. 5 Å). As illustrated in Figure 2b, a typical mode of packing between α-helices (green and blue) involves insertion of the ridges of one helix (blue) into the grooves of an adjacent helix (green).[11] Inspired by this potentially analogous topology, the hypothetical binding model shown in Figure 2c was derived. In this model, the ladder-like polycyclic ether fits into the grooves of the helix.

As a first step in the investigation of this model, a 6/6/6/6/6 pentacyclic ether skeleton (**1**) was designed as a structurally defined α-helix mimetic scaffold[12] having two equatorial hydroxyl groups separated by a distance of 4.8 Å (Fig. 2d). Installation of a variety of substituents (R^1 and R^2) is possible via the hydroxyl groups, and the consequent undulation of the molecular surface is expected to be analogous to the ridges formed by side-chains of α-helices in the *i*, *i*+4 relationship.

The strategy for the iterative synthesis of the cyclic ether scaffolds is outlined in Scheme 1. A SmI_2-mediated Reformatsky-type reaction of α-ketosulfide **B** with aldehyde **A** was employed for the assembly of the two hydropyrans.[13] Subsequent hydroxy-ketone cyclization of the compound **C** would afford tricyclic **D**.[14] After conversion of **D** into aldehyde **E**, the second assembly of two cyclic ethers **E** and **B** followed by the hydroxy-ketone cyclization would yield the 6/6/6/6/6/6 cyclic ether skeleton **2** with two equatorial hydroxy groups.

The key coupling component, α-ketosulfide **8**, was synthesized from tri-*O*-acetyl-D-glucal **3** (Scheme 2). Reduction of **3** with triethylsilane and $BF_3{\cdot}Et_2O$ followed by



Scheme 1. Strategy for iterative synthesis of cyclic ether skeleton **3**.