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CAN induced double ether ring formation: synthesis of *trans*- and *cis*-fused tricyclic ethers from 3-oxabicyclo[3.1.0]hexyl sulfides

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CAN oxidation of 3-oxabicyclo[3.1.0]hexy sulfides 4 and 5 possessing two hydroxy groups in the C-2 and C-4 side chains promoted a double ether ring formation along with a cleavage of the most substituted cyclopropyl bond to give tricyclic ketal adducts 8 and 10, which were converted to *trans*- and *cis*-fused tricyclic ethers 9 and 11 with high or moderate stereoselectivity by a TMSOTf-mediated trialkylsilane reduction.

Recently, a number of biologically active polyether toxins, such as the brevetoxins, ciguatoxins and halichondrins, have been isolated from marine organisms. The structural complexity and biological activities of these molecules have attracted the attention of synthetic chemists, and many new methods for the synthesis of cyclic ethers have been developed over the last few years.[1] Because these natural products have a unique ladder-like polycyclic molecular framework consisting of contiguous *trans*- and/or *cis*-fused polyether rings ranging in size from five- to nine-membered rings, several new synthetic methods have been aimed at the rapid construction of bi-, tri- and tetra-cyclic systems, including iterative strategies.[2]

We have already reported that the ceric(IV) ammonium nitrate (CAN) oxidation of cyclopropyl sulfides bearing a hydroxy group in a side chain promotes a S_N2-type nucleophilic substitution by the hydroxy group along with cleavage of the more substituted cyclopropyl carbon–carbon bond, giving rise to tetrahydrofuran and tetrahydropyran rings with perfect regio- and stereo-selectivity.[3] Our own interest in cyclic ether synthesis has recently been directed to a tandem synthesis of the polycyclic systems, using CAN induced double ether ring formation (**3** → **2**) and a Lewis acid-mediated trialkylsilane reduction (**2** → **1**), as shown in Scheme 1. We now report a stereoselective formation of the *trans*- and *cis*-fused tricyclic ether ring systems **1** containing five- and six-membered rings starting from 2α,4α- and 2β,4β-disubstituted 3-oxabicyclo-[3.1.0]hexyl sulfides **3**.

The several model compounds **4a**–**c** and **5b**–**c**, which possess different stereochemistry at C-2 and C-4, were synthesized to examine the applicability of the CAN-induced double ether ring formation (Table 1). Upon treatment of **4b** with CAN (8 equiv.) in dry MeOH in the presence of MS 3A at room temperature,[3] the *trans*-fused 6-6-5 tricyclic ketal **8b**† was obtained in 68% yield, and no other stereoisomers were detected (entry 2). Similarly, **4c** readily cyclized to the *cis*-fused 6-6-5 tricyclic ketal **8c**‡ in 62% yield under the same conditions (entry 3). In contrast to the *cis*-2,4-disubstituted diols **4b** and **4c**, the *trans*-2,4-disubstituted adduct **4a** gave no cyclized adducts. Indeed, only the bicyclic ketals **6** and **7** which were generated by an intermolecular nucleophilic substitution of a nitrate or methoxy group, were produced in 24 and 25% yields, respectively (entry 1). Although the different reactivity of **4a** compared with **4b** and **4c** is not clear at this stage, it is assumed that, in the case of **4a**, solvent and nitrate were introduced predominantly because the hydroxy group of the C-4 side chain, which is oriented axially in a preferred conformation (A), cannot attack the cyclopropyl carbon (C-5) from the proper back-side direction. In any event, these results demonstrate that the oxidative nucleophilic substitution by a hydroxy group to the cyclopropyl sulfides always occurs with perfect regio- and stereo-selectivity and that the sterically defined alignment of the nucleophile and fissile cyclopropyl bond is important for the ether ring formation.

Furthermore, both of the 6-6-5 triyclic ketals **8b** and **8c** were easily converted into the corresponding 6-6-5 tricyclic ethers **9b** and **9c** in good yields by known methods.[4] Specifically, the treatment of **8b** and **8c** with TMSOTf and Et_3SiH in CH_2Cl_2 at −78 °C resulted in stereoselective reduction, giving rise to the *trans-syn-cis*- and *cis-syn-cis*-fused 6-6-5 tricyclic products **9b**† and **9c**‡ as single isomers, respectively (entries 2 and 3). Finally, this method was applied to **5b** and **5c**, which possess two three-carbon side chains, with the aim of constructing a 6-6-6 tricyclic system. The same treatment of *cis*-2,4-disubstituted diols **5b** and **5c** as for **4a**–**c** gave the desired *trans-syn-trans*- and *cis-syn-trans*-fused 6-6-6 tricyclic ethers **11A**/**11B**[5] and **11C**† as the only products, respectively (entries 4 and 5).‡

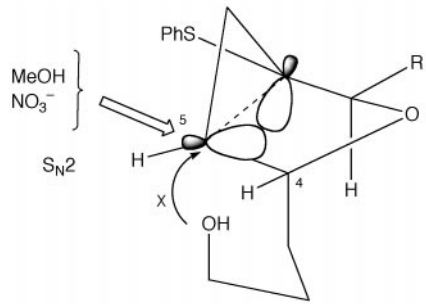
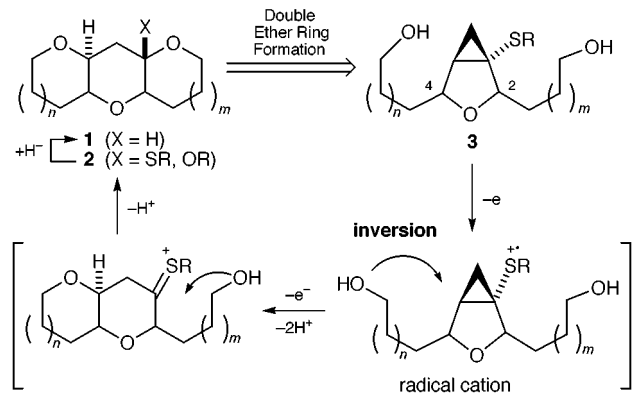
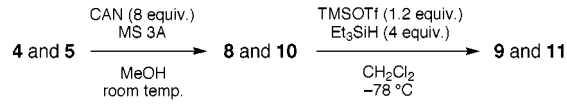


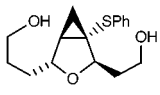
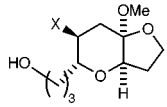
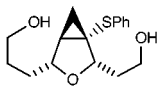
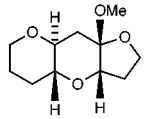
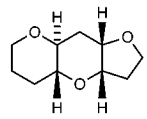
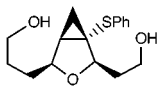
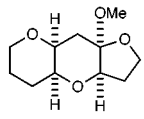
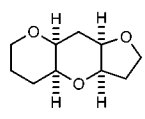
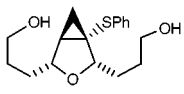
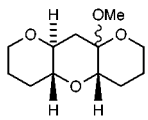
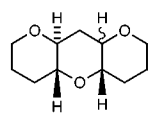
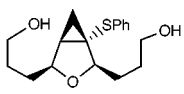
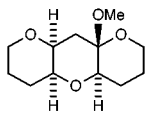
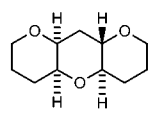
Fig. 1 Intermolecular nucleophilic ring-opening of **4a**.



Scheme 1

Table 1 Tricyclic ether formation from bicyclic sulfides **4a**,**b** and **5b**,**c**



Entry	Substrate	Cyclic acetals (% yield)	Cyclic ethers (% yield)
1	 **4a**	 **6** X = OMe (24) **7** X = ONO_2 (25)	–
2	 **4b**	 **8b** (68)	 **9b** (68)
3	 **4c**	 **8c** (62)	 **9c** (67)
4	 **5b**	 **10A/10B**[a] (60)	 **11A** (α-H) **11B** (β-H) (79)[b]
5	 **5c**	 **10C** (70)	 **11C** (88)

[a] **10A**:**10B** = 3:1. The ratio was calculated from isolated yields, but their stereochemistry could not be determined. [b] **11A**:**11B** = 3:1. The ratio was deduced from ^{1}H NMR analysis.

Since these tricyclic ether ring systems are frequently encountered constituents in polycyclic natural toxins, this method should be a versatile tool for the asymmetric synthesis of these biologically active natural products. More efficient synthesis of the starting bicyclic sulfides and further application to more advanced chiral fragments are under way in these laboratories.

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Notes and references

† Stereochemical assignments of these compounds were confirmed by NOE studies.

‡ Because the same treatment of the diastereomerically pure product **10A** also provided **11A** and **11B** with the same ratio (**11A**:**11B** = *ca.* 3:1), it appears that the stereochemistry of these diastereomers has no effect on the silane reduction.

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