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Selective Discrimination of Cyclodextrin Diols Using Cyclic Sulfates

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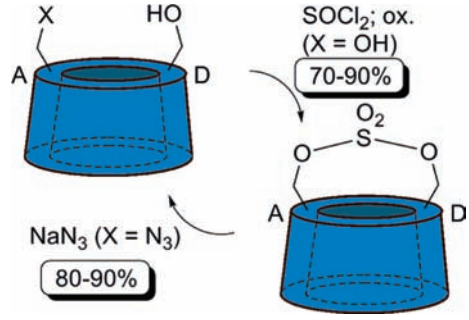
ABSTRACT



A method for selective monofunctionalition of readily available cyclodextrin diols ($2^{A-F},3^{A-F},6^{B,C,E,F}$-hexadeca-*O*-benzyl-α-cyclodextrin and $2^{A-G},3^{A-G},6^{B,C,E-G}$-nonadeca-*O*-benzyl-*β*-cyclodextrin) by regioselective nucleophilic opening of their cyclic sulfates is presented. Although the A and D products are nonequivalent in *β*-cyclodextrin, only the A product is formed.

Cyclodextrins (cycloamyloses) are an important group of molecules because of their ability to form complexes with small lipophilic molecules, their low toxicity, and comparatively low cost. They are widely used for drug and perfume formulation[1,2] and host−guest and biomimetic chemistry.[3] The interest in modified cyclodextrins is also high. However, the many similar alcohol functionalities in the cyclodextrin molecule make selective substitution of a few hydroxyl groups a difficult if not impossible task.[4,5] New synthetic methods to modify selectively the cyclodextrin are therefore of high interest and can frequently lead to compounds not hitherto available.[6]

Such a method is the synthesis of **1** reported by Pearce and Sinaÿ some years ago (Figure 1).[7] They found that DIBAL treatment of perbenzylated cyclodextrin gave the A,D diol **1** in excellent yield. Monodebenzylation is also described but is less effective. Sollogoub and Sinaÿ have shown that the remarkable regioselectivity is due to the process being

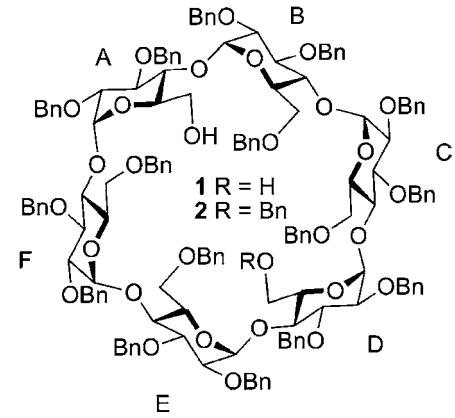


Figure 1. Partially benzylated cyclodextrins obtained from the DIBAL debenzylation of perbenzyl α-cyclodextrin.

(1) Hedges, A. R. *Chem. Rev.* **1998**, *98*, 2035–2044.
(2) Uekama, K.; Hirayama, F.; Irie, T. *Chem. Rev.* **1998**, *98*, 2045–2076.
(3) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997–2011.
(4) Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977–1996.
(5) Sollogoub, M. *Eur. J. Org. Chem.* **2009**, 1295–1303.

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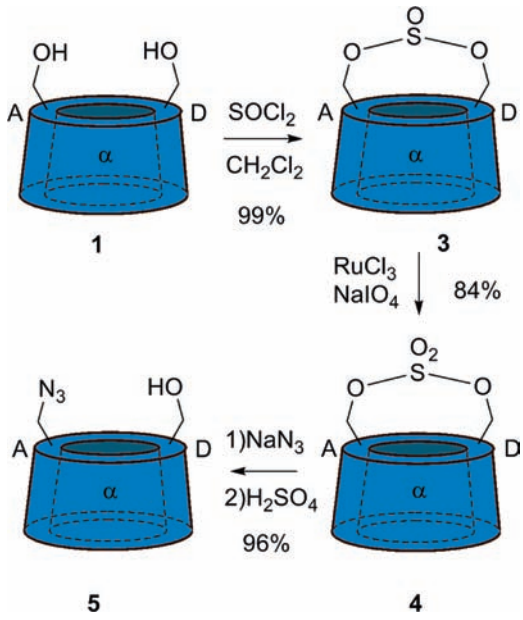
sterically demanding requiring coordination of DIBAL to both ring-oxygen and the oxygen that is debenzylated.[8] Sollogoub has subsequently shown how the methodology can provide a series of debenzylation patterns at the primary rim.[9,10]

While **1** is a valuable building block, it remains a challenge to discriminate between the two alcohols. Monosilylation of **1** (with TBSCl) proceeds with low selectivity, making synthesis of unsymmetrical derivatives from **1** an unsatisfactory process.[11] Recently, Guieu and Sollogoub have in a remarkable study shown that unsymmetrical amino alcohols[12] can be prepared regioselectively by DIBAL debenzylation of a monoazide. Nevertheless, synthesis of the monoazide precursor has the drawback of starting from **2** and not **1**.

Our approach to the problem uses selective substitution of cyclic sulfate bridging **1**. 1,2-Cyclic sulfates have been used by Gao and Sharpless to convert diols into epoxide-like functionalities that can only undergo monosubstitution.[13] Several bridged derivatives of **1** have been made in good yield,[14,15] but never with only a single atom between the 6^A and 6^D oxygen atoms.

However, we were delighted to find that the cyclic sulfite **3** is formed in excellent yield when 6 equiv of $SOCl_2$ was dropwise added to a solution of **1** in dichloromethane (Scheme 1). A molecular model of **3** (Chembio3D Ultra 11.0)

Scheme 1. Synthesis of Sulfate **4** and Its Reaction with NaN_3



shows that the A,D glucose residues are slightly twisted. Oxidation of **3** with $RuCl_3/NaIO_4$ gave as expected the sulfate **4** in 84% yield. Reaction of **4** with NaN_3 in DMF at 50 °C for 4 h followed by aqueous H_2SO_4 at room temperature for 15 min gave the monoazide **5** in excellent yield. The azide in compound **5** was reduced to an amino group (PBu_3), and the product (**6**) obtained was identical to the one obtained by Guieu and Sollogoub upon selective debenzylation of 6-azido-6-deoxyperbenzyl-α-cyclodextrin.

The ring opening could also be carried out with other nucleophiles (Figure 2). Ammonia gave **6** directly but in

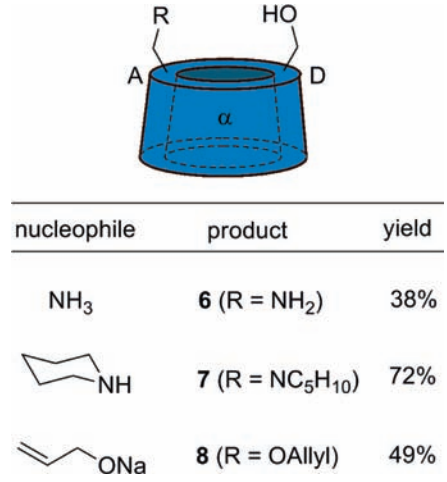


Figure 2. Products formed from reaction of **4** with nucleophiles.

lower yield (38%). Reaction with piperidine worked better, giving piperidino derivative **7** in 72% yield. Ring opening of the sulfite with an *O*-nucleophile, sodium allylate, gave the *O*-allyl derivative **8** in comparatively low yield (49%). Clearly, the cyclic sulfate can be opened with nucelophiles other than azide and most successfully with substituted amines.

The *β*-cyclodextrin analogue of **1**, the diol **9**, differs from **1** in that the unprotected alcohols are nonequivalent. Because of this lack of symmetry, the product obtained by selective substitution of one of the alcohols will differ from that obtained by substitution of the other. Opening of a cyclic sulfate of **9** may give two products. However, encouraged by the surprising observation by Guieu and Sollogoub[10] that the benzylated *β*-cyclodextrin monoazide exclusively debenzylates to the A,D isomer, we nevertheless investigated this transformation (Scheme 2). From **9**, the corresponding

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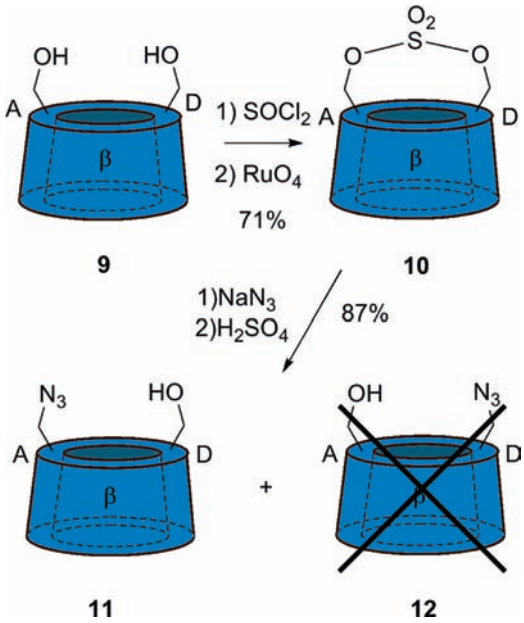
Scheme 2. Synthesis and Selective Reaction with Azide of Perbenzyl β-Cyclodextrin $6^A,6^D$-Sulfate (**10**)



cyclic sulfate **10** was obtained similarly first by reaction with $SOCl_2$ (dropwise addition over 3 h) followed by oxidation with $RuCl_3/NaIO_4$ in $CH_2Cl_2/MeCN/H_2O$ (1:1:2). This gave a 71% yield of **10** from **9**. Reaction of **10** with NaN_3 in DMF at 55 °C (18 h) and subsequent hydrolysis with aqueous H_2SO_4 in THF (0.5 h, 25 °C) only gave a single product **11** in 87% yield with none of the alternatively isomer **12** being observed. The structure of **11** was determined by reduction of the azide to an amino group with PBu_3 and comparison with the analytic data of the identical amino alcohol obtained by Guieu and Sollogoub.[12,16]

An explanation for this remarkable regioselectivity can be found by examination of molecular models (Chembio3D Ultra 11.0). A model of **10** shows that the sulfate bridge forces the glucose residues E−G to twist out of the plane of the ring. The result is that S_N2 substitution at the D residue becomes obstructed by the ring oxygen of the E residue (Figure 3). No such obstruction takes place at the A residue as the B and C residues are in the ring-plane (Figure S1, Supporting Information).

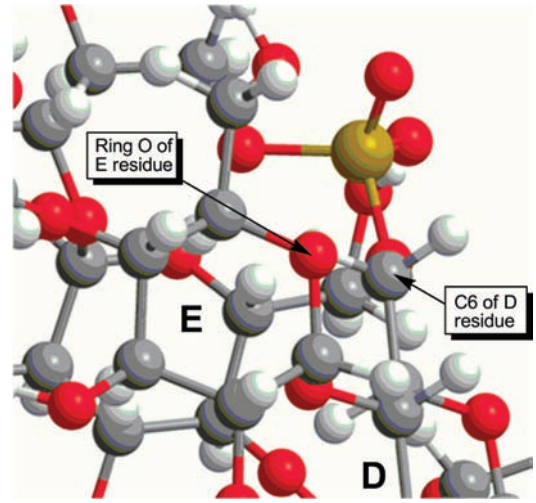


Figure 3. Chembio3D model of **10** (benzyl groups removed for clarity) showing that SN_2 substitution at the 6^D-sulfate is obstructed by $O5^E$.

The chemistry presented here opens an efficient route to difunctional cyclodextrin derivatives of interest, for instance, in the enzyme model research. The method is a useful alternative to the DIBAL reduction of azides[10] having the advantage of starting from the more readily available diols **1** and **9**.

Acknowledgment. We thank the Lundbeck Foundation for financial support.

Supporting Information Available: Experimental procedures for the transformation of **1** to **5** and **9**−**11**, Figure S1 showing the lack of hindrance at the A ring in **10**, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The R_f values and NMR spectra were identical. Most significant is the observation that the seven anomeric carbon signals (99.5, 99.3, 98.7, 98.6, 98.3, 98.2 97.6) are identical to those reported in ref 12. Since ^{13}C is very sensitive to structural changes in carbohydrates, this leaves no doubt about the structure.