Efficient Monomodification of the Secondary Hydroxy Groups of β-Cyclodextrin

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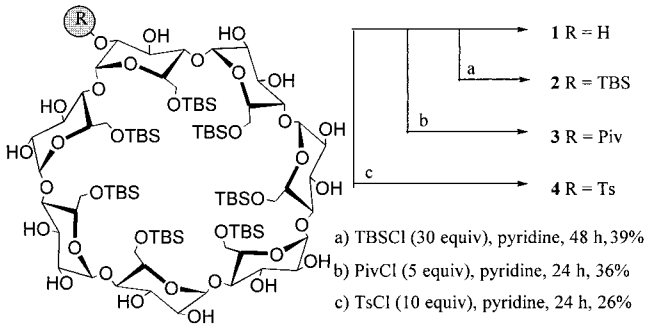
In conjunction with our research on functionalized monolayer surfaces,[1] we required access to a range of selectively modified cyclodextrin derivatives. The internal hydrophobic space and external hydrophilic hydroxy groups make cyclodextrins ideal tools for investigating enzyme mimics,[2] drug delivery systems,[3] catalytic reactions,[4] host−guest interactions,[5] and self-assembled monolayers.[6] The use of cyclodextrins for these applications has been hampered by poor solubility in many common solvents and the notoriously low selectivity and low efficiency of monomodification reactions. To expand the range of applications of cyclodextrin, the development of efficient and selective synthetic modifications of cyclodextrin is essential. Of particular interest are selective monomodifications of the secondary 2- and 3-hydroxy groups that form the rim of the larger face of cyclodextrin.[7]

The readily available heptakis-6-*O*-(*tert*-butyldimethylsilyl)-β-cyclodextrin **1**[8] shows unusual and interesting reactivity when treated with excess TBSCl in pyridine for 48 h, resulting in the conversion of **1** into a single octasilyl derivative **2** (39%) (Scheme 1).[9] We have shown that the silylation occurred at the more acidic C-2 position of the sugar (vide infra). To test the generality of this selective modification, we also studied the acylation[10] and sulfonation[11] of **1**. We have found that **1** reacts with 2,2,2-trimethylacetyl chloride (Piv-C1) to afford **3** in 36% yield. Similarly, treatment of **1** with 10 equiv of tosyl chloride in

Scheme 1



pyridine gave, after 24 h, monotosylate β-cyclodextrin **4** as the major product in 26% yield.

Compounds **2**−**4** are easily handled and purified by column chromatography. As with the silylation, sulfonation occurred at C-2 (vide infra). Acetylation (Ac_2O, pyridine) gave little or no selectivity.

To capitalize upon the selective silylation and to prove the regiochemistry of silylation, we investigated the methylation of the remaining C-2 and C-3 hydroxyl groups. Migration of the *tert*-butyldimethylsilyl group is known in cyclodextrin chemistry and has been examined systematically.[12] Under strongly basic conditions (MeI, NaH, THF), the 2-*O*-silyl group of polysilylated cyclodextrin will migrate to the 3-O position. The migration can be suppressed under nonpolar and weakly basic conditions ($MeSO_2CF_3$, 2,6-di-*tert*-butyl-pyridine, CH_2Cl_2).[13] Thus, if the initial silylation had occurred at the 2-hydroxy position, these two different reaction conditions would generate two different products. However, if selective silylation had occurred at C-3, these different reaction conditions would afford the same product. When we applied these two different methylation conditions to **2**, two different compounds, **5** and **6**, were generated (Scheme 2). They have the same mass (FAB[$M + Na^+$] = 2254) but different ^1H and ^{13}C NMR spectra. Compound **5** was not observed during the nonpolar methylation process. Thus, we conclude that the structure of **2** is correctly assigned as being the result of highly selective silylation at one of the seven possible C-2 hydroxy groups. The structure of compound **5** was further confirmed by its conversion to compound **7** (FAB($M + Na^+$) = 1700).[14] Compounds **5** and **6** can be readily formed from **2**, *providing a synthetic pathway for selectively generating a β-cyclodextrin with only one free secondary hydroxyl group, in either the 2- or 3-position.* Treatment of compounds **5** and **6** with tetrabutylammonium fluoride gave the versatile monofunctionalized β-cyclodextrins **8** and **9** in high yields.

While it is known that the ^{13}C resonance of the 2-OMe and 3-OMe group is around 58−61 ppm, the exact assignment of the methyl groups can be ambiguous. We are able to assign conclusively the two different types of OMe groups in the ^{13}C NMR of compounds **5** and **6**. In Figure 1, compound **6** shows six carbon peaks around 58 ppm and seven carbon peaks around 61 ppm, whereas compound **5** shows the reverse seven signals at ca. 58 ppm and six ca. 61 ppm.

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(9) Compound **2** can be directly generated by treating β-cyclodextrin itself with 15 equiv of TBSCl in pyridine for 48 h. If β-cyclodextrin is treated with only 7.7 equiv of TBSCl for 24 h, only compound **1** is formed. In contrast to many β-cyclodextrin derivatives, compound **1** is easily handled and purified with normal-phase chromatography.

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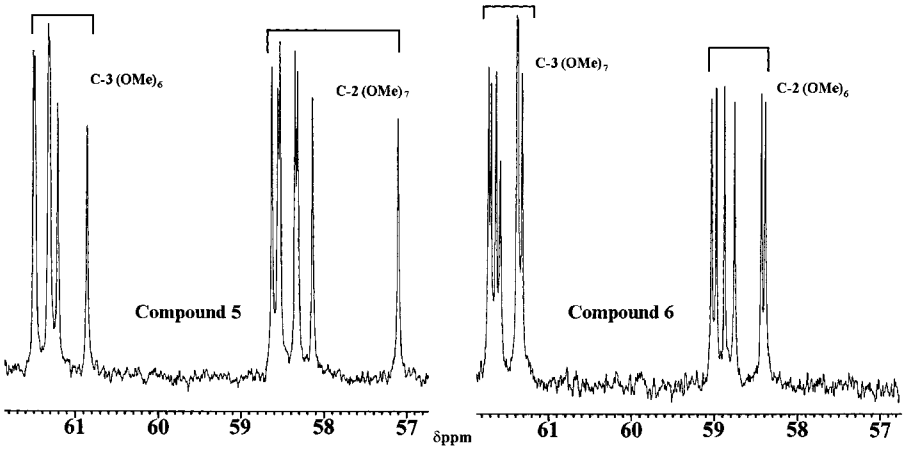
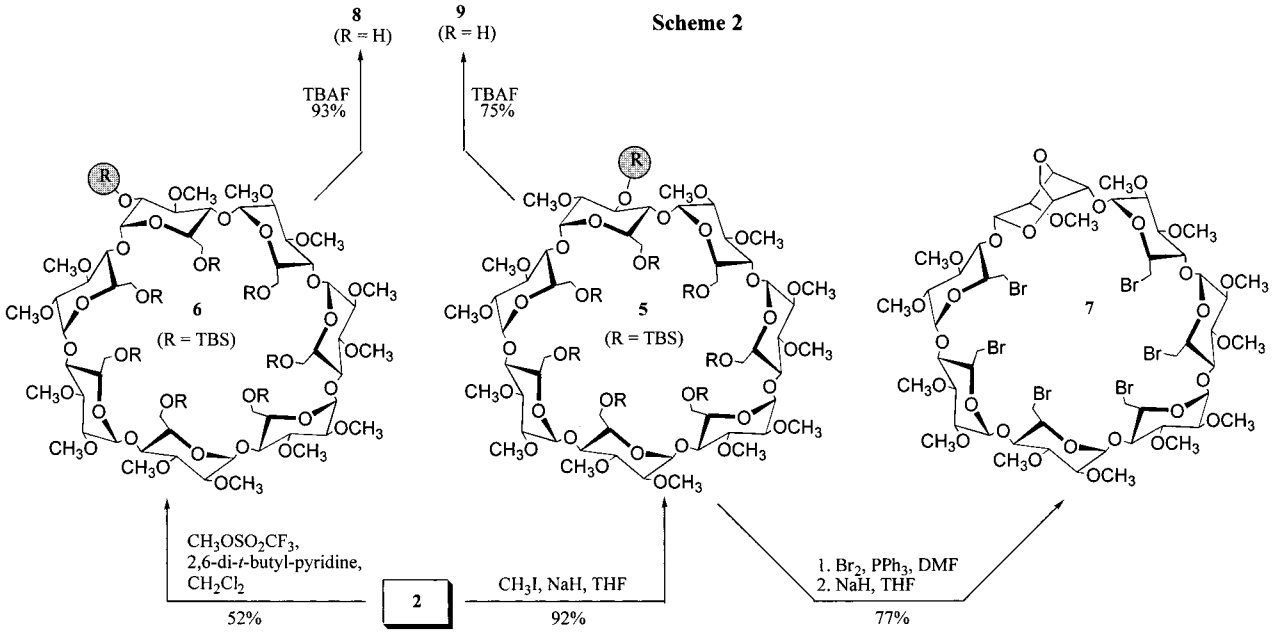


Figure 1. 100 MHz ^{13}C NMR spectra of **5** and **6**.

Scheme 2



Thus, by simply counting the signals in the ^{13}C NMR, we have been able to determine the substitution patterns on the modified cyclodextrins. The nonpolar methylation reaction was then applied to compound **3** and **4**. From the ^{13}C NMR signals, we concluded that the modifications occurred on the 2-OH. This general NMR interpretation method can be used for assigning the position of *any* 2- or 3-hydroxy monofunctionalized cyclodextrin by persilylating the primary alcohols and permethylating the remaining secondary hydroxy groups.

In conclusion, we have demonstrated a highly selective and synthetically practical monomodification strategy for the secondary face of β-cyclodextrin. Silylation, acylation, and sulfonation of heptakis-6-*O*-(*tert*-butyldimethylsilyl)cyclodextrin **1** occur efficiently and with high regioselectivity in all cases to afford a single regioisomer. Judicious choice of migrating silyl or nonmigrating conditions for methylation allows us to control precisely the position of the silyl group at the 2-O- or 3-O position. Thus, the corresponding free monohydroxy compounds can be generated selectively following protection of the remaining secondary alcohols as methyl ethers and subsequent desilylation. We believe that these compounds will find widespread use as versatile intermediates for the synthesis of novel cyclodextrin derivatives. By comparing the ^{13}C NMR spectra of compounds **5** and **6**, we were also able to accurately distinguish and assign the carbon signals of the 2-OMe and 3-OMe groups. The method may be useful for assigning the position of any functional group monofunctionalized on the secondary face of β-cyclodextrin following proper derivatization of the free alcohols.

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Supporting Information Available: Experimental procedures and NMR spectra for obtained compounds.

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