Pergamon

Tetrahedron Letters, Vol. 37, No. 38, pp. 6831-6834, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01545-6

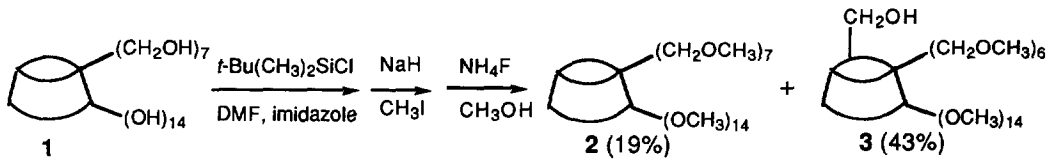
A Convenient Synthesis of Mono-6-hydroxy Permethylated β-Cyclodextrin *via tert*-Butyldimethylsilylation

Zhen Chen, Jerald S. Bradshaw,* and Milton L. Lee

Department of Chemistry and Biochemistry, Brigham Young University
Provo, UT 84602 U.S.A.

Abstract: A convenient method to prepare mono-6-hydroxy permethylated β-cyclodextrin (**3**) *via tert*-butyldimethylsilylation is described. Mono-6-*tert*-butyldimethylsilyl-β-cyclodextrin was prepared and treated with NaH and CH_3I in the same pot. The protecting group was removed by refluxing with NH_4F in CH_3OH to give **3** in an overall yield of 43%. Copyright © 1996 Elsevier Science Ltd

Recently, chemical modification of cyclodextrins with various functional groups has been extensively investigated. Cyclodextrins are very popular building blocks for supramolecular structures[1,2] and their derivatives are widely used in the fields of analytical chemistry[3] and as enzyme mimics.[4] However, selective modifications of the cyclodextrins are difficult to control because of problems arising from steric and statistical factors imposed by the torus structure and the large number of hydroxy groups. When a mono-functionalized cyclodextrin is desired, the ideal situation is to have only one reactive functional group in the cyclodextrin molecule with all other hydroxy groups blocked. In this case, positional isomers and homologous derivatives with a higher degree of substitution can be avoided. The mono-substituted product can easily be separated. Mono-6-hydroxy permethylated β-cyclodextrin is such a compound which has been used in the synthesis of photo- and electroactive receptors,[5] stationary phases for liquid chromatography,[6] stationary phases for gas and supercritical fluid chromatography,[7] and cyclodextrin dimers.[8] Unfortunately, the application of mono-6-hydroxy permethylated β-cyclodextrin is hindered by its inconvenient preparation. The generally used method for its preparation was reported by Tanaka *et al*,[6] although the experimental details and characterization of the product were not given. First, mono-(6-O-trityl)-β-cyclodextrin was prepared in about 30% yield by treating β-cyclodextrin with trityl chloride in pyridine.[9] Second, all the remaining hydroxy groups were methylated in dimethylformamide (DMF). Finally, the trityl group was removed in a two-phase system (concentrated HCl-$CHCl_3$). There are several disadvantages related to this synthetic method. The overall yield is not good (< 30%); one must use pyridine in the first step and the work up is very tedious; and acid is used in the last step. A convenient method to prepare mono-6-hydroxy permethylated β-cyclodextrin in a reasonable yield would be important for many workers in the field.



1 2 (19%) + 3 (43%)

Scheme 1. Synthesis of mono-6-hydroxy permethylated β-cyclodextrin (3).

We now describe a convenient synthesis of the title compound 3 *via tert*-butyldimethylsilylation. The strategy is shown in Scheme 1. The *tert*-butyldimethylsilyl group has proven to be a valuable protecting group in cyclodextrin chemistry.[10,11] It can be selectively attached to the primary 6-OH groups of the cyclodextrin glucose residues, and the silyl groups are stable under ordinary conditions. The silyl groups are easily removed using NH_4F, [12] avoiding the use of acid which can decompose the cyclodextrin. To a stirred mixture of β-cyclodextrin (4.54 g, 4 mmol) and imidazole (0.61 g, 6 mmol) in 100 ml of dry DMF, a solution of *tert*-butyldimethylsilyl chloride (1.24 g, 8 mmol) in 20 ml of dry DMF was added dropwise at rt under an Argon atmosphere. The mixture was stirred at rt while carefully monitoring the reaction by TLC on silica gel (1-BuOH/EtOH/H_2O: 5/4/3 by volume). The reaction reached equilibrium and no further apparent change occurred after 1 h. TLC showed three major components having R_f values of 0.41 (β-cyclodextrin), 0.63 and 0.72. After cooling to 0 °C, NaH (6.4 g, 260 mmol) was added and the mixture was stirred at 0 °C for 30 min then at rt for 1 h. After cooling to 0 °C, 34 ml of CH_3I (77 g, 545 mmol) was added dropwise. The mixture was kept for 1 h at 0 °C then for 24 h at rt. TLC ($CHCl_3$/CH_3OH: 10/1) showed three components with R_f values of 0.68 (permethylated β-cyclodextrin, by comparing with the standard sample), 0.72 and 0.78. Because there was no component having an R_f value smaller than that of permethylated β-cyclodextrin, all hydroxy groups must be methylated. Although the migration of *tert*-butyldimethylsilyl groups from O-2 to O-3 during the alkylation process is usual, the same groups at the 6 positions are stable.[13] The reaction mixture was treated using a procedure similar to that reported.[14] Excess NaH was decomposed by the addition of CH_3OH (15 ml) after cooling the system to 0 °C. The resulting mixture was poured into 400 ml of ice water with stirring and extracted with $CHCl_3$ (4 x 100 ml). The combined $CHCl_3$ layers were washed successively with 75 ml of a 3% aqueous solution of $Na_2S_2O_3$ to remove excess CH_3I and H_2O (3 x 75 ml) and then dried ($MgSO_4$). After concentrating and drying under vacuum overnight at 80 °C, a solid residue of 6.11 g was obtained. Trying to separate the three components at this stage by the usual column chromatography was very difficult because their polarities are very similar. The mixture was subjected to the deprotection step before separation was achieved.

The residue (6.11 g) was refluxed with 2.06 g of NH_4F in 200 ml of CH_3OH for 24 h and then concentrated.[12] The solution of the residue in ethyl acetate was filtered through celite, and the filtrate was concentrated. TLC ($CHCl_3$/CH_3OH: 10/1) revealed three components with R_f values of 0.68, 0.54, and 0.42, respectively. Column chromatography ($CHCl_3$/CH_3OH: 50/1) on silica gel easily gave pure permethylated β-

cyclodextrin (2) 1.08 g (19%, R_f = 0.68) and mono-6-O-hydroxy permethylated β-cyclodextrin (3) 2.43 g (43%, R_f = 0.54). When using one equivalent of *tert*-butyldimethylsilyl chloride in the first step, only 23% of **3** was isolated. The third spot, which is a mixture of isomeric dihydroxy compounds, was not isolated. Product **3** thus obtained was fully characterized by ^1H and ^{13}C NMR spectroscopy, FABMS and elemental analysis.[15]

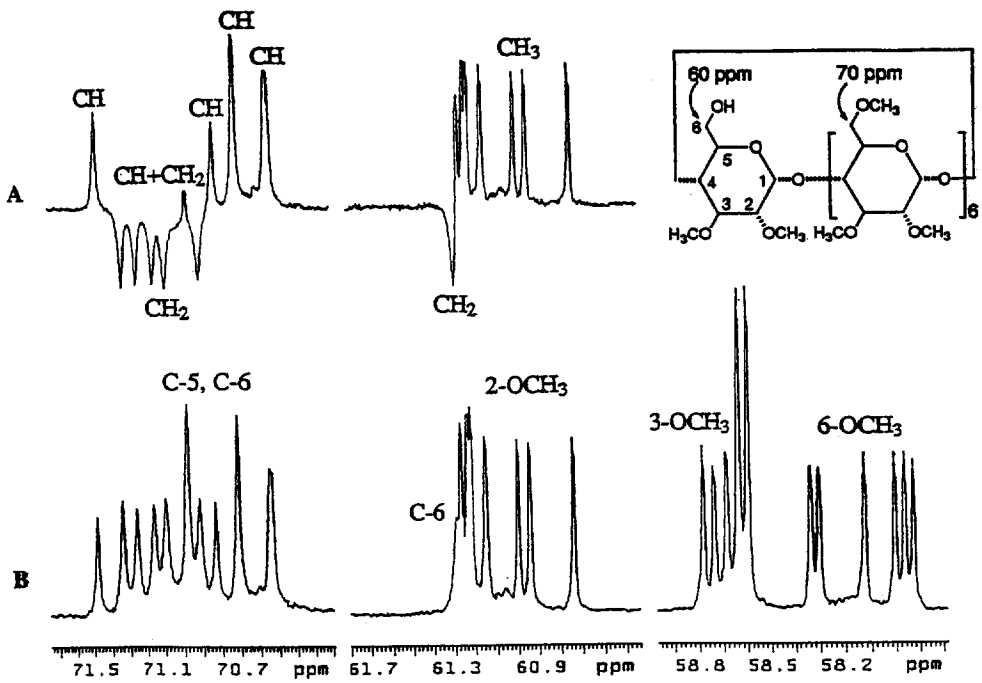


Figure **1**. Partial DEPT (A) and ^{13}C NMR (B) spectra of **3**.

Mono-6-hydroxy permethylated β-cyclodextrin (**3**) is an unsymmetric molecule. Figure **1** shows partial DEPT (A) and ^{13}C NMR (B) spectra of **3**. The DEPT spectrum is unique in that peaks corresponding to methyl and methine carbon atoms point up and those for methylene carbon atoms point down.[10] In general, the signal for the C-6 atom containing an OH group appears at about 60 ppm. O-Methylation of the hydroxy group is expected to shift the α-carbon to about 70 ppm.[16] In the DEPT spectrum of **3**, the signals for the six CH_2 carbon atoms containing OCH_3 groups at the 6-position appear at 70.8-71.3 ppm and there are six of these peaks when one accounts for the fact that the signals for one CH_2 and one CH appear at the same ppm. The remaining CH_2 carbon atom produces a signal at 61.3 ppm indicating a CH_2OH. The ^{13}C NMR spectrum shows seven signals each for the 2- and 3-OCH_3 groups but only six signals for the 6-OCH_3 groups. These spectral data clearly show that **3** is indeed the mono-6-hydroxy permethylated compound.

In conclusion, the details of the synthesis and characterization of mono-6-hydroxy permethylated β-

cyclodextrin (**3**) are reported. The method described here is superior to the earlier one.[6] The overall yield is higher, the first two steps are in one pot, and the final work up is simple. Compound **3** is not only an appropriate nucleophile, but it also can be transformed easily into the mono-tosylate, aldehyde, carboxylic acid and other mono derivatives on the primary side of the β-cyclodextrin. Thus, a wide application of compound **3** can be envisioned.

Acknowledgement: The authors thank Dr. Yoichi Habata for many helpful discussions, and Dr. Du Li for obtaining the high resolution NMR spectra.

REFERENCES AND NOTES

1. Wenz, G. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 803.
2. Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725.
3. Li, S.; Purdy, W. C. *Chem. Rev.* **1992**, *92*, 1457.
4. Tabushi, I: Functionalized cyclodextrins as artificial enzymes. In *Chemical approaches to understanding enzyme catalysis*; Green, B.; Ashani, Y.; Chipman, D. Eds.; Elevier, Amsterdam. 1982.
5. Brugger, N.; Deschenaux, R.; Ruch, T.; Ziessel, R. *Tetrahedron Lett.* **1992**, *33*, 3871.
6. Tanaka, M.; Kawaguchi, Y.; Niinae, T.; Shono, T. *J. Chromatogr.* **1984**, *314*, 193.
7. Yi, G-L.; Bradshaw, J. S.; Rossiter, B. E.; Malik, A.; Li, W.-B.; Lee, M. L. *J.Org.Chem.* **1993**, *58*, 4845.
8. Deschenaux, R.; Greppi, A.; Ruch, T.; Kriemler, H-P.; Raschdorf, F.; Ziessel, R. *Tetrahedron Lett.* **1994**, *35*, 2165.
9. Melton, L. D.; Slessor, K. N. *Carbohydr. Res.* **1971**, *18*, 29.
10. Pregel, M. J.; Buncel, E. *Can. J. Chem.* **1991**, *69*, 130.
11. Takeo, K.; Mitoh, H.; Uemura, K. *Carbohydr. Res.* **1989**, *187*, 203.
12. Chang, W-J.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177.
13. Icheln, D.; Gehrcke, B.; Piprek, Y.; Mischnick, P.; Konig, W.; Dessoy, M. A.; Morel, A. F. *Carbohydr. Res.* **1996**, *280*, 237.
14. Szejtli, J.; Liptak, A.; Jodal, I.; Fuged, P.; Nanasi, P.; Neszmelyi, A. *Starch* **1980**, *32*, 165.
15. Selected analytical data for **3**:
    ^{1}H NMR ($CDCl_3$) δ 5.2-4.9 (m, 7 H), 3.9-3.0 (m, 103 H), of which 3.34 (s), 3.45 (s) and 3.56 (s) are for three OCH_3 groups; ^{13}C NMR ($CDCl_3$) δ 98.04, 98.00, 97.98, 97.94, 97.92, 97.82, 81.41, 81.19, 81.10, 81.04, 81.00, 80.93, 80.90, 80.83, 80.81, 80.76, 80.69, 80.55, 80.08, 79.66, 79.49, 79.07, 78.86, 77.67, 76.52, 76.46, 76.26, 76.00, 70.83, 70.70, 70.61, 70.51, 70.44, 70.34, 70.27, 70.19, 70.07, 69.89, 60.67, 60.59, 60.57, 60.55, 60.48, 60.32, 60.27, 60.06, 58.12, 58.08, 57.97, 57.93, 57.68, 57.64, 57.47, 57.35, 57.31, 57.26; FABMS: m/z 1437, [M-H+Na]$^+$; Anal. Calcd for $C_{62}H_{110}O_{35}$: C, 52.61; H, 7.83. Found: C, 52.40; H, 7.67.
16. Boger, J.; Corcoran, R. J.; Lehn, J-M. *Helv. Chim. Acta* **1978**, *61*, 2190.

(*Received in USA* 18 *June* 1996; *revised* 29 *July* 1996; *accepted* 1 *August* 1996)