Pergamon

Tetrahedron Letters 42 (2001) 5477–5480

TETRAHEDRON LETTERS

Regioselective $2^A,2^D$-disulfonyl capping of β-cyclodextrin for practical bifunctionalization on the secondary hydroxyl face

Katsunori Teranishi

Faculty of Bioresources, Mie University, 1515 Kamihama, Tsu, Mie 514-8507, Japan

Received 17 May 2001; revised 7 June 2001; accepted 8 June 2001

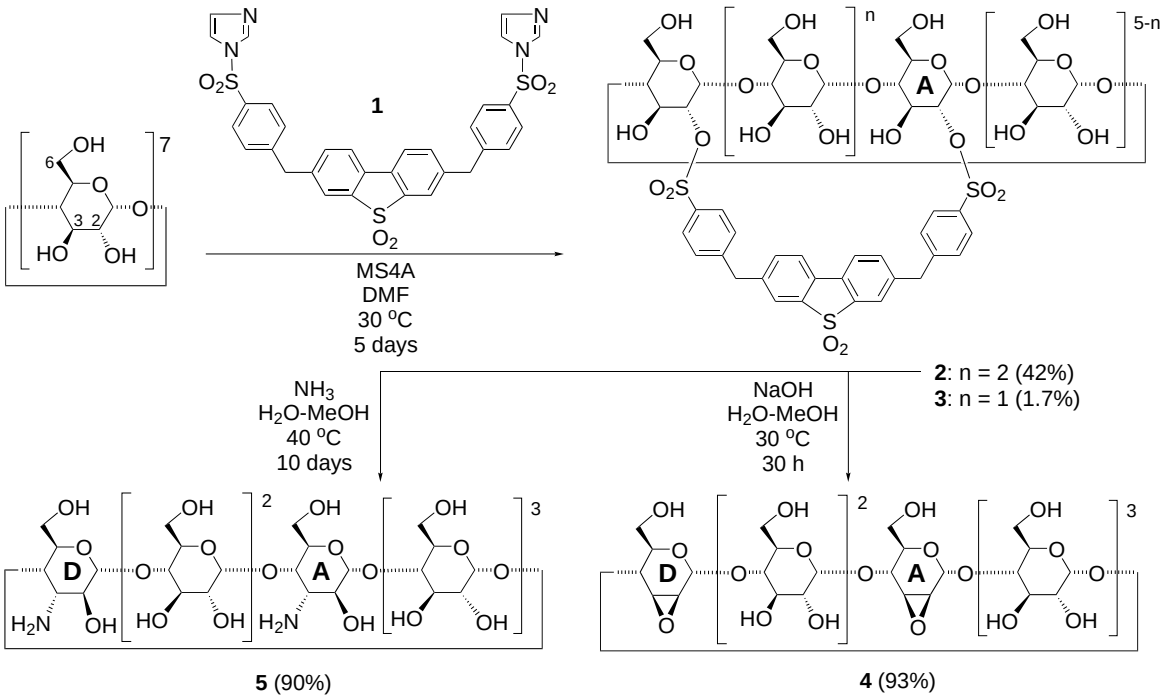
Abstract—A useful technique to bifunctionalize the secondary hydroxyl face of β-cyclodextrin is described. Regioselective $2^A,2^D$-disulfonylation of β-cyclodextrin was achieved by reacting β-cyclodextrin with a combination of a novel disulfonyl imidazole reagent and molecular sieves in DMF. The resulting disulfonate was converted to $2^A,3^A,2^D,3^D$-dimannoepoxy-β-cyclodextrin and $3^A,3^D$-diamino-$3^A,3^D$-dideoxy-($2^AS,3^AS$),($2^DS,3^DS$)-β-cyclodextrin, which contains two functional groups on the periphery of the molecule. © 2001 Elsevier Science Ltd. All rights reserved.

Cyclodextrins, cyclic α-1,4-linked oligosaccharides, have optically active and hydrophobic cavities within their bucket-like structures, with primary hydroxyl groups at the C-6 positions and secondary hydroxyl groups at the C-2 and C-3 positions. The remarkable properties afforded by the cyclodextrins' cavity result in their functions as chiral host molecules or as transporters of hydrophobic molecules. β-Cyclodextrin, a cyclodextrin that consists of seven D-glucopyranose units, and its derivatives have been investigated extensively and used as a miniature molecular mimic of enzyme. In order to increase the functionality of this cyclodextrin, selective modifications of the primary and/or the secondary hydroxyl groups have been investigated, and a variety of sulfonylations of the hydroxyl group(s) have been extensively applied as effective functionalization methods.[1] However, specific positioning and degrees of sulfonylation are difficult to control due to the large number of the hydroxyl groups in the cyclodextrin. Although several selective disulfonylations of the two primary hydroxyl groups by bridging the cyclodextrin molecules with disulfonyl chlorides have been developed to modify the primary hydroxyl face of the cyclodextrin,[2] selective disulfonylation of the secondary hydroxyl face has proven to be more challenging. It has been reported that disulfonyl reactions of β-cyclodextrin with *p*-toluenesulfonyl chloride afforded the regioisomeric $2^A,2^B$-, $2^A,2^C$-, and $2^A,2^D$-disulfonates (the glucose units are designated with letters A through G, clockwise, as viewed from the primary hydroxyl face).[3] Well-designed reactions of the cyclodextrins with sulfonyl imidazole reagents and molecular sieves in *N*,*N*-dimethylformamide (DMF) have been reported for regioselective monosulfonation of the C-2 hydroxyl group,[4] and have proven to be especially useful since the mild non-alkaline reaction conditions do not induce the decomposition of the sulfonates, and since the reactions are independent from the sulfonyl group type. Recently, successful regioselective $2^A,2^B$- and $2^A,2^C$-disulfonylations using disulfonyl imidazole reagents and molecular sieves have been reported.[5] In this Letter, a highly regioselective synthesis of $2^A,2^D$-disulfonylated β-cyclodextrin is described to provide a useful method for the effective bifunctionalization of the secondary hydroxyl face on the A and D glucose units (Scheme 1).

A novel disulfonyl imidazole reagent **1** was readily synthesized by the following procedures: Chlorosulfonic acid (16 ml) was added at 0°C to 4,4′-dibenzyldiphenyl (8.0 g), which was prepared by Wolff–Kishner reduction of 4,4′-dibenzoylbiphenyl.[6] The mixture was maintained at 0°C for 4 h, periodically stirred, followed by the addition of a second portion of chlorosulfonic acid (16 ml) at 0°C. The mixture was maintained at 0°C for 2 h, then poured over ice (300 ml). The precipitate was filtered, washed with cold water, and then dried under reduced pressure. The crude product was treated with imidazole (4.0 g) and triethylamine (8.0 ml) in dichloromethane (120 ml) at room temperature for 30 min. The reaction mixture was purified by silica gel column chromatography (dichloromethane/ethyl acetate (2:1), dichloromethane/ethyl acetate (1.5:1)) to yield the crude product (5.9 g), which was further purified by crystallization from chloroform to give pure reagent **1** (3.1 g).[7]

Keywords: β-cyclodextrin; regioselective disulfonylation.

PII: S0040-4039(01)01025-5



Scheme 1.

A mixture of β-cyclodextrin (3.0 g, 2.64 mmol), which was dried under vacuum at 120°C for 12 h, reagent **1** (0.58 g, 0.884 mmol), and freshly activated powder molecular sieves 4A (6.0 g) in DMF (300 ml) was stirred at 30°C for 5 days and monitored by HPLC analysis. When the sulfonyl reagent **1** was determined to be exhausted, HPLC analysis of the mixture confirmed that $2^{A},2^{D}$-disulfonate **2** and $2^{A},2^{C}$-disulfonate **3** were afforded in 53% and 3.5% yields, based on reagent **1**, respectively. However, $2^{A},2^{B}$-, 6-, and 3-sulfonate(s) were not detected by HPLC analysis of the reaction mixture nor by NMR analysis of the isolated products. After removing the molecular sieves by filtration, the filtrate was concentrated under reduced pressure, then dissolved in DMF (5 ml), followed by the addition of water (100 ml). Purification of the solution was carried out by chromatography using a simple open reverse-phase column (24×120 mm, Fuji Silisia Chromatorex-ODS DM1020T gel, 0–35% aqueous MeOH) to yield unreacted β-cyclodextrin (1.7 g),[8] disulfonate **2** (0.61 g, 42% yield based on reagent **1**), and disulfonate **3** (0.025 g, 1.7% yield based on reagent **1**). Disulfonates **2** and **3** were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, MALDI-TOF-MS, and subsequent derivative reactions.

Both the MALDI-TOF-MS spectra of disulfonates **2** and **3** exhibited molecular ions $[M+Na]^{+}$ at m/z 1677.3. The partial ^{1}H and ^{13}C NMR spectra of the disulfonates **2** and **3** are shown in Fig. 1. Peak integrations of the ^{1}H NMR spectra and the MALDI-TOF-MS spectra indicate that the disulfonation on one cyclodextrin molecule was executed by a single molecule of reagent **1**. Spectral assignments of disulfonates **2** and **3** were performed using ^{1}H-^{1}H COSY. The ^{1}H NMR spectra show appreciable downfield-shifts of the H-2 and H-3 protons of the two glucose units of **2** and **3**, respectively. In particular, the H-2 protons show a larger downfield-shift than the H-3 protons. The ^{13}C NMR spectra assigned from ^{1}H-^{13}C COSY and DEPT experiments demonstrated an upfield shift of the C-1 and C-3 carbon peaks and a downfield shift of the C-2 carbon peaks of the two glucose units of disulfonates **2** and **3**. These ^{1}H and ^{13}C NMR data, which do not conflict with the known shift effect of C-2 sulfonates,[9] indicate that the two sulfonyl groups are located at the C-2 oxygen of the two glucose units. Although the regiochemistry of the disulfonyl groups of disulfonate **2** could not be determine from NMR experiments, that of disulfonate **3** was readily assigned using 2D ROESY NMR. In the 2D ROESY NMR spectrum of disulfonate **3,** cross peaks were observed between a H-4A proton of the sulfonylated glucose unit A and the H-1B proton of the unsulfonylated glucose unit B and between the H-4B proton of the unit B and the H-1C proton of the sulfonylated glucose unit C; therefore, the structure of disulfonate **3** was determined as $2^{A},2^{C}$-disulfonate. Treatment of disulfonate **2** with NaOH (16 equiv.) in a mixture of water and MeOH at 30°C for 30 h, followed by open column chromatography on silica gel (CH_3CN, CH_3CN/water (6:1), CH_3CN-water (6:2)), yielded dimannoepoxy-β-cyclodextrin **4** in 93% yield. ^{1}H and ^{13}C NMR spectra for cyclodextrin **4** were in agreement with the published spectra for $2^{A},3^{A},2^{D},3^{D}$-dimannoepoxy-β-cyclodextrin,[3] suggesting that the structure of disulfonate **2** is $2^{A},2^{D}$-disulfonylated β-cyclodextrin.

One of the several functionalization of cyclodextrins is the introduction of amino group(s) onto the rim of

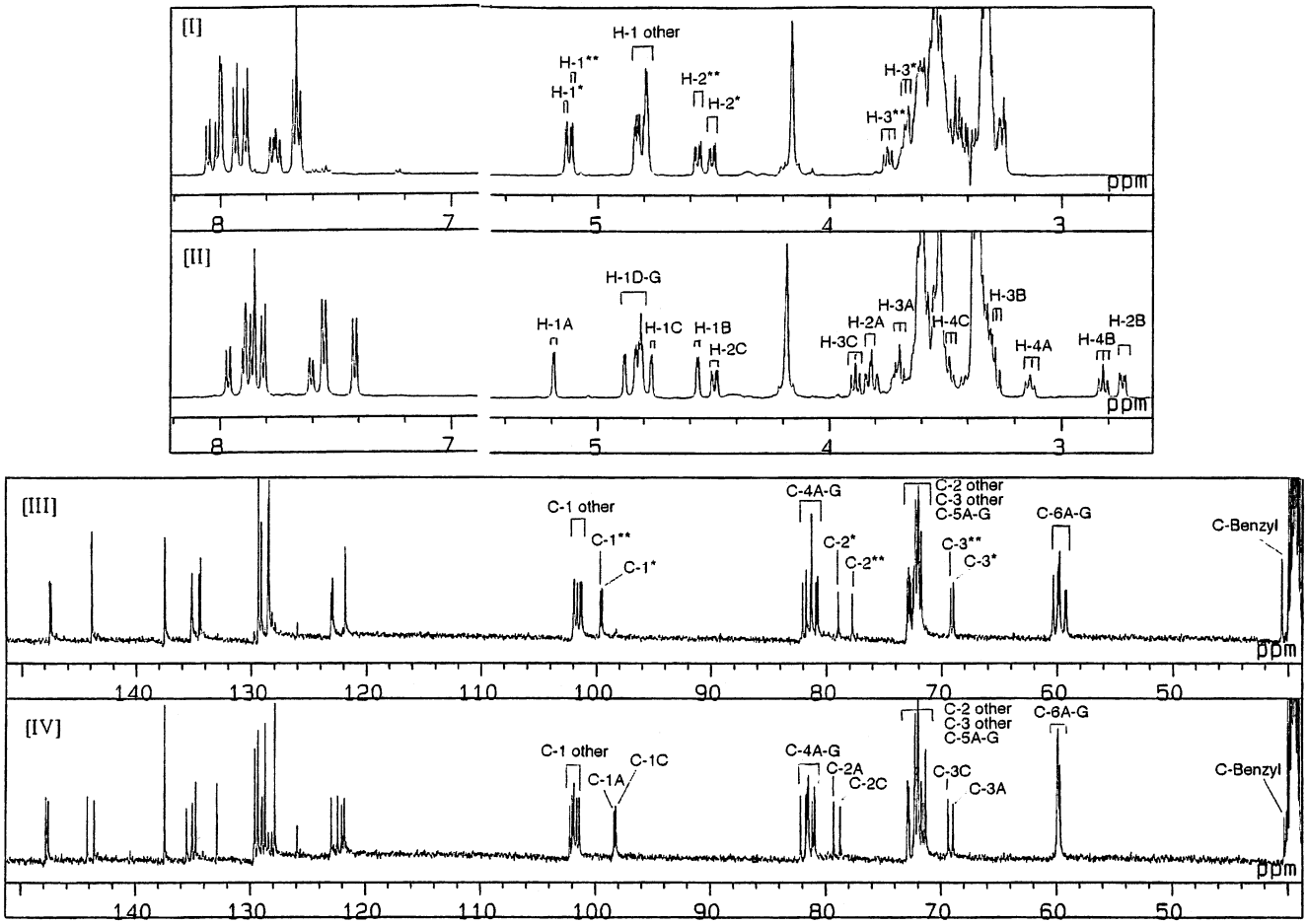


Figure 1. Partial ^{1}H and ^{13}C NMR spectra of **2** and **3** (50°C, DMSO-d_6 containing 5% D_2O, ref, DMSO: δ 2.49 for ^{1}H and 39.5 for ^{13}C). The assigned signals are numbered according to the usual convention shown in Scheme 1, and the symbols * and ** for **2** refer to the sulfonylated glucose units. The letters A, B, and C for **3** are assignments of glucose units. [I] ^{1}H NMR of **2**; [II] ^{1}H NMR of **3**; [III] ^{13}C NMR of **2**; [IV] ^{13}C NMR of **3**.

cyclodextrin molecules. Treatment of disulfonate **2** (0.46 g) with 28% aqueous NH_3 (14 ml) and MeOH (6 ml) at 40°C for 10 days, followed by ion-exchange column chromatography (Sephadex-CM C-25), readily yielded 3^{A},3^{D}-diamino-3^{A},3^{D}-dideoxy-($2^{A}S$,$3^{A}S$),($2^{D}S$, $3^{D}S$)-β-cyclodextrin **5** in 90% yield, which was characterized by ^{1}H and ^{13}C NMR spectroscopy and MALDI-TOF-MS.[10]

Acknowledgements

I am grateful for Grant-in-Aid for Scientific Research (No. 12045237 and 11660106) from the Japanese Ministry of Education, Science, and Culture. The NMR instrument used in this research was installed at the Cooperative Research Center of Mie University.

References

1. For reviews see: Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977–1996.
2. (a) Tabushi, I.; Shimokawa, K.; Shimizu, N.; Shirakata, H.; Fujita, K. *J. Am. Chem. Soc.* **1976**, *98*, 7855–7856; (b) Tabushi, I.; Kuroda, Y.; Shimokawa, K. *J. Am. Chem. Soc.* **1979**, *101*, 1614–1615; (c) Tabushi, I.; Kuroda, Y.; Yokota, K.; Yuan, L. C. *J. Am. Chem. Soc.* **1981**, *103*, 711–712; (d) Tabushi, I.; Nabeshima, T.; Kitaguchi, H.; Yamamura, K. *J. Am. Chem. Soc.* **1982**, *104*, 2017–2019; (e) Tabushi, I.; Yamamura, K.; Nabeshima, T. *J. Am. Chem. Soc.* **1984**, *106*, 5267–5270; (f) Fujita, K.; Matsunaga, A.; Imoto, T. *J. Am. Chem. Soc.* **1984**, *106*, 5740–5741; (g) Tabushi, I.; Nabeshima, T.; Fujita, K.; Matsunaga, A.; Imoto, T. *J. Org. Chem.* **1985**, *50*, 2638–2643; (h) Breslow, R.; Canary, J. W.; Varney, M.; Waddell, S. T.; Yang, D. *J. Am. Chem. Soc.* **1990**, *112*, 5212–5219; (i) Koga, K.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **2000**, *41*, 6855–6857.
3. (a) Fujita, K.; Ishizu, T.; Oshiro, K.; Obe, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2960–2962; (b) Ohta, K.; Fujita, K.; Shimada, H.; Ikegami, Y.; Nogami, Y.; Koga, T. *Chem. Pharm. Bull.* **1997**, *45*, 631–635.
4. (a) Teranishi, K.; Watanabe, K.; Hisamatsu, M.; Yamada, T. *J. Carbohydr. Chem.* **1998**, *17*, 489–494; (b) Teranishi, K.; Tanabe, S.; Hisamatsu, M.; Yamada, T. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 1249–1252.

5. (a) Teranishi, K. *J. Chem. Soc., Chem. Commun.* **2000**, 1255–1256; (b) Teranishi, K.; Hisamatsu, M.; Yamada, T. *Tetrahedron Lett.* **2000**, *41*, 933–936; (c) Teranishi, K. *Tetrahedron Lett.* **2000**, *41*, 7085–7088.
6. Schlenk, W.; Brauns, M. *Chem. Ber.* **1915**, *48*, 716–728.
7. Analytical data for **1**: colorless needles. mp 143–145°C. ^{1}H NMR δ ($CDCl_3$, 20°C): 4.14 (4H, s), 7.10 (2H, s), 7.31 (2H,s), 7.39 (4H, d, $J=7.9$ Hz), 7.39 (2H, d, $J=7.9$ Hz), 7.60 (2H, s), 7.70 (2H, d, $J=7.9$ Hz), 7.90 (4H, d, $J=7.9$ Hz), and 8.02 (2H, s).
8. β-Cyclodextrin recovered could be reused in this sulfonyl reaction with no problems.
9. Ueno, A.; Breslow, R. *Tetrahedron Lett.* **1982**, *23*, 3451–3454.
10. Data for **5**; ^{1}H NMR δ (50°C, DMSO-d_6 containing 5% D_2O, ref, DMSO: δ 2.49): 2.70–2.78 (2H, m, C*H*-NH_2), 3.2–4.0(m), 4.54–4.58 (2H, m, C-1H), 4.75 (1H, d, $J=3.6$ Hz, C-1H), 4.76 (1H, d, $J=3.6$ Hz, C-1H), 4.80 (1H, d, $J=2.4$ Hz, C-1H), 4.83 (1H, d, $J=3.7$ Hz, C-1H), and 4.86 (1H, d, $J=3.1$ Hz, C-1H).^{13}C NMR δ (50°C, DMSO-d_6 containing 5% D_2O, ref, DMSO: δ 39.50): 52.61 (*C*HNH_2), 52.83 (*C*HNH_2), 59.74–60.18 (C-6), 71.71–73.23, 76.73, 76.89, 79.35, 79.53, 79.77, 79.92, 81.20, 81.37, 81.68, 101.54 (C-1), 101.82 (C-1), 101.85 (C-1), 102.0 (C-1), 102.03 (C-1), 103.76 (C-1), and 104.01 (C-1). MALDI-TOF-MS m/z: 1155.8 $[M+Na]^+$.