Tetrahedron Letters, Vol.32, No.46, pp 6737-6740, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

# A COMPLETE SET OF β-CYCLODEXTRINS $6^A,6^X$-DIACTIVATED BY TWO DIFFERENT SULFONYL GROUPS

Kahee Fujita,*[1a] Hatsuo Yamamura,[1b] and Taiji Imoto[1c]

Faculty of Pharmaceutical Sciences, Nagasaki University, Bunkyo-machi, Nagasaki 852, Japan, Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466, Japan, and Faculty of Pharmaceutical Sciences, Kyushu University, Maidashi, Higashi-ku, Fukuoka 812, Japan

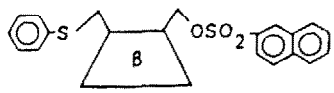
***Key Words:*** Cyclodextrin; Enzyme Model; Receptor Model; Unsymmetrically Bifunctional Cyclodextrin; $6^A$-O-(p-Nitrobenzenesulfonyl)-$6^X$-O-(β-naphthalenesulfonyl)-β-cyclodextrin

***Abstract:*** Each of $6^A$-O-(p-nitrobenzenesulfonyl)-$6^X$-O-(β-naphthalenesulfonyl)-β-cyclodextrins (X= B-G) was prepared by the reaction of 6-O-(β-naphthalenesulfonyl)-β-cyclodextrin with p-nitrobenzenesulfonyl chloride, isolated, and structurally determined through selective chemical conversion.

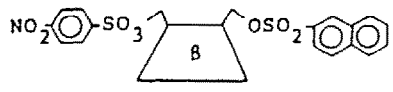
Unsymmetrically bifunctional cyclodextrins have attracted much attention because they are excellent mimics of enzymes or receptors.[2] Unfortunately, the position of the two functional groups in the reported compounds have not been unequivocally determined, being inferred only from the enzyme-like or receptor-like behavior of the compounds. Although a pioneering study has been reported on the preparation of a β-cyclodextrin derivative possessing two sulfonyl groups of different reactivities attached to the primary hydroxyl side of the macrocycle,[3] the regiochemical purity and the positions of attachment are not mentioned.

We have developed effective methods for the separation and unequivocal structure determination of symmetrically 6-O-disubstituted cyclodextrins.[4] We recently reported the synthesis of sets of structurally determined cyclodextrins having two different substituents, $6^A$-S-phenyl-$6^X$-O-(β-naphthalenesulfonyl)-$6^A$-thio-β-cyclodextrins (X = B-G, **1a-f**), and $6^A$-S-(*tert*-butyl)-$6^X$-S-phenyl-$6^A,6^X$-dithio-β-cyclodextrins (X = B-G).[5] These provide authentic compounds for regiochemical determination of unsymmetrically bifunctional cyclodextrins through appropriate chemical conversions.

In the present paper, we describe preparation of unsymmetrically disulfonylated cyclodextrins (**2a-f**) as the starting materials for the synthesis of unsymmetrically bifunctional cyclodextrins. Their regiochemistry is determined with the aid of the



1a-f



2a-f

disubstituted cyclodextrins **1a-f**. Compounds **2a-f** have two different sulfonyl groups at the 6-O positions and their reactivities are very different from one another in nucleophilic substitution reactions.

p-Nitrobenzenesulfonyl chloride (700 mg, $3.16 \times 10^{-3}$ mol) was added to a solution of 6-O-(β-naphthalenesulfonyl)-β-cyclodextrin (500 mg, $3.78 \times 10^{-4}$ mol) in dry pyridine (20 mL) under ice cooling and the mixture was stirred for 3 h in an ice bath. After usual workup procedure followed by concentration, the residue was chromatographed by a reverse-phase column with a gradient elution from water to aqueous ethanol to give the recovered starting material (161 mg, 32.2 %), **2a** (19 mg, 3.3 %), **2b** (22 mg, 3.9 %), **2c** (17 mg, 3.0 %), **2d** (28 mg, 4.9 %), **2e** (12 mg, 2.1 %), and **2f** (8 mg, 1.3 %). The numbers (**2a-f**) of the compounds are given in the order of increasing retention time in reverse-phase HPLC and a reverse-phase column chromatography (Figure 1).

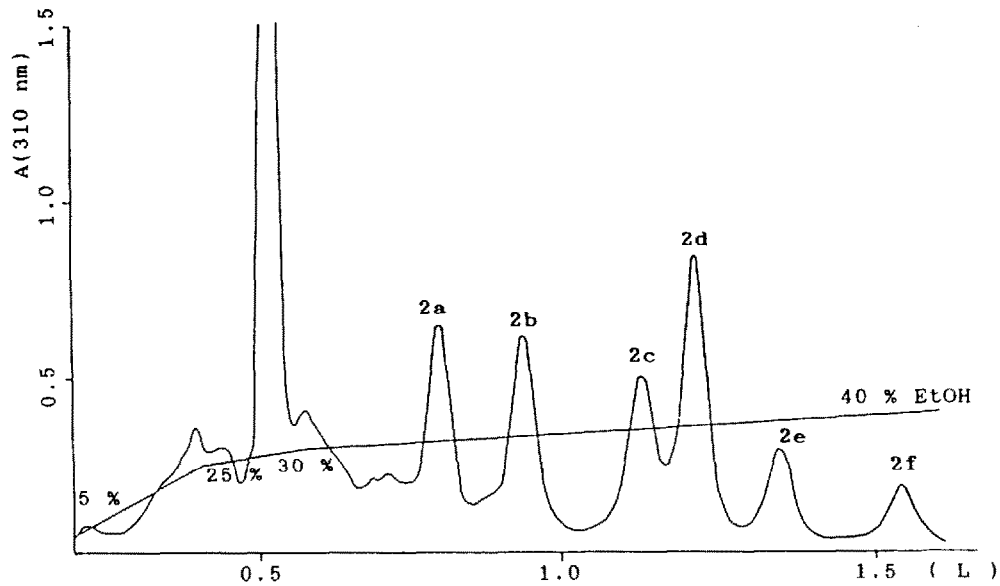
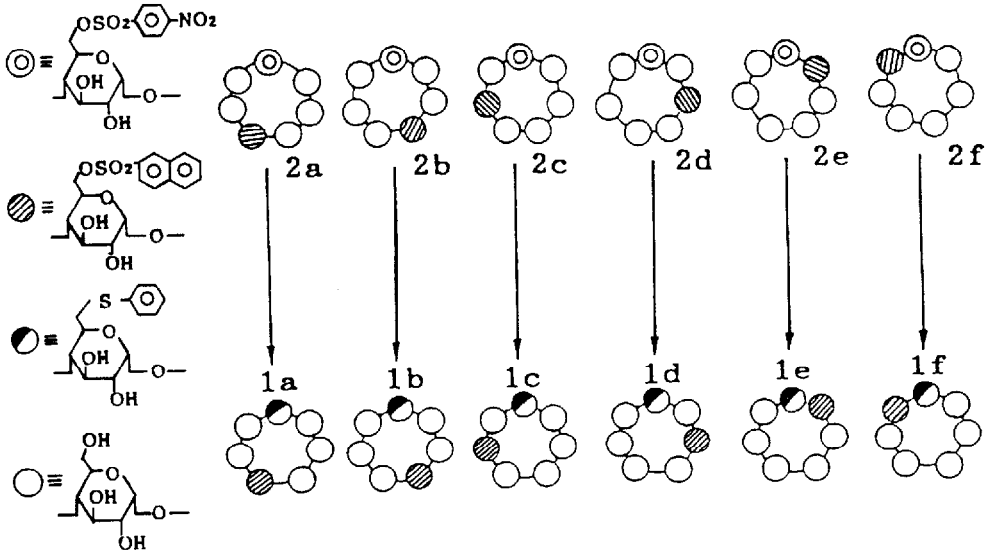



Figure 1. Reverse-phase column chromatography of $6^{A}$-O-(p-nitrobenzenesulfonyl)-$6^{X}$-O-(β-naphthalenesulfonyl)-β-cyclodextrins 2a-f. A gradient of ethanol (EtOH) was applied.

The fast-atom-bombardment (FAB) mass spectra of compounds **2a-f** demonstrate that they are unsymmetrically disulfonylated β-cyclodextrins. The $^1$H NMR spectra also show that each of the compounds **2a-f** has a p-nitrobenzenesulfonyl group and a β-naphthalenesulfonyl group attached to the cyclodextrin moiety. That the p-nitrobenzenesulfonyl group must be located on a 6-O position is reasonably deduced from many results of similar sulfonylation reactions in pyridine.[2-6]

The positional determination of the sulfonyl groups was carried out by selective nucleophilic substitution of the p-nitrobenzenesulfonyl group with thiophenol. A solution of **2b** (50 mg, $3.31\times10^{-5}$ mol), thiophenol (5.5 mg, $4.98\times10^{-5}$ mol), and $Cs_2CO_3$ (8.1 mg, $2.49\times10^{-5}$ mol) in dimethylformamide (1 mL) was stirred at room temperature for 3 h. After the reaction mixture was concentrated *in vacuo*, the residue was analyzed by reverse-phase HPLC and chromatographed by a reverse-phase column to give a major product **1b** (15 mg, 31.2 %). By comparing its HPLC retention time and $^1$H NMR spectrum with those of the authentic samples,[5a] **1b** was assigned to $6^A$-S-phenyl-$6^D$-O-(β-naphthalenesulfonyl)-$6^A$-thio-β-cyclodextrin. Therefore, **2b** was assigned to $6^A$-O-(p-nitrobenzenesulfonyl)-$6^D$-O-(β-naphthalenesulfonyl)-β-cyclodextrin. Similarly, structure determination of the other disulfonylated cyclodextrins was successfully carried out. The results are shown in Scheme 1.




**Scheme 1. Structure determination of $6^A$-O-(p-nitrobenzenesulfonyl)-$6^X$-O-(β-naphthalenesulfonyl))-β-cyclodextrin 2a-f through selective chemical conversion.**

These selective chemical conversions demonstrated that the unsymmetrically disulfonylated cyclodextrins can offer unsymmetrically bifunctional cyclodextrins having all types of regiochemistry that Tabushi[7] pointed out as R (recht angular), E (entgegen), and Z (zusammen) arrangement of two different functional groups.

***Acknowledgment.*** We thank Japan Maize Products Co. Ltd. (Nihon Shokuhin Kako) for a generous gift of $\beta$-cyclodextrin.

***References and Notes***

1. (a) Nagasaki University. (b) Nagoya Institute of Technology. (c) Kyushu University.
2. (a) Tabushi, I.; Nabeshima, T.; Kitaguchi, H.; Yamamura, K. *J. Am. Chem. Soc.* **1982**, *104*, 2017. (b) Tabushi, I.; Kuroda, Y.; Yamada, M.; Higashimura, H.; Breslow, R. *Ibid.* **1985**, *107*, 5545. (c) Tabushi, I.; Kuroda, Y.; Mizutani,T. *Ibid.* **1986**, *108*, 4514.
3. Tabushi, I.; Yamamura, K.; Nabeshima, T. *J. Am. Chem. Soc.* **1984**, *106*, 5267.
4. (a) Fujita, K.; Matsunaga, A.; Imoto, T. *Tetrahedron Lett.* **1984** 5533. (b) Fujita, K.; Matsunaga, A.; Imoto, T. *J. Am. Chem. Soc.* **1984**, *106*, 5740. (c) Fujita, K.; Yamamura, H.; Matsunaga, A.; Imoto, T. *ibid.* **1986**, *108*, 4509. (d) Fujita, K.; Yamamura, H.; Imoto, T.; Fujioka, T.; Mihashi, K. *J. Org. Chem.* **1988**, *53*, 1943.
5. (a) Fujita, K.; Matsunaga, A.; Yamamura, H.; Imoto, T. *J. Org. Chem.* **1988**, *53*, 4520. (b) Fujita, K.; Matsunaga, A.; Ikeda, Y.; Imoto, T. *Tetrahedron Lett.* **1985**, 6439. (c) Fujita, K.; Matsunaga, A.; Iomto, T.; Hirotsu, k.; Kamitori, S.; Higuchi, T. *J. Am. Chem. Soc.* **1985**, *107*, 1790.
6. (a) Croft, A. P.; Bartsch, R. A. *Tetrahedron* **1983**, *39*, 1417. (b) Melton, L. D.; Slessor, K. N. *Carbohydr. Res.* **1971**, *18*, 29.
7. Tabushi, I. *Tetrahedron* **1984**, *40*, 269.

(Received in Japan 5 August 1991)