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Selective synthesis and structure determination of $6^A,6^C,6^E$-tri(*O*-sulfonyl)-β-cyclodextrins

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Abstract

By reacting with a rigid disulfonyl chloride, β-cyclodextrin 6-tosylate is readily disulfonylated for the first time to give $6^A,6^C,6^E$-trisulfonylated β-cyclodextrins in good yields, which represents an efficient novel method for the regio-selective preparation of $6^A,6^C,6^E$-trifunctionalized β-cyclodextrins.

The modification of cyclodextrins offers huge opportunities for the investigations at the frontiers of chemistry ranging from supramolecular chemistry to analytical techniques. It also represents a great challenge for chemists since cyclodextrins consist of a large number of hydroxyl groups belonging to three types, namely the primary face 6-OH groups, the secondary face 3-OH and 2-OH groups, and their competition makes the selective modification of cyclodextrins extremely difficult.[1] During recent decades, methods for selective modification of one hydroxyl group on either face, two hydroxyl groups on the primary face and per-modification of either or both faces have been well established.[2] Modification of three hydroxyl groups also witnessed several examples. Early in 1970, Cramer et al. reported some mixtures of cyclodextrin-imidazole derivatives,[3] with an average substitution of three imidazole entities for the hydroxyl groups, presumably on the primary face. Cyclodextrin trisulfonates were prepared either by reacting cyclodextrin with 3 equiv. of sulfonyl chloride or by reacting a cyclodextrin disulfonate with 1 equiv. of sulfonyl chloride.[4] Cyclodextrin triazides were prepared by reacting cyclodextrin with LiN_3 in the presence of Ph_3P and CBr_4 in DMF.[5] These random cascade reactions usually produced mixtures of many regio-isomers with variable degrees of substitutions. Boger et al. reported a six-step procedure for the synthesis of symmetrical triamino α-cyclodextrins with the secondary face permethylated.[6,7] There is also documented an enzymatic method for a five-step synthesis of $6^A,6^C,6^E$-tri(*O*-methyl)-α-cyclodextrin from maltose.[8] Fujita et al. demonstrated a regio-specific tri-sulfonylation at the 3^A-, 3^C- and 3^E-OH groups of

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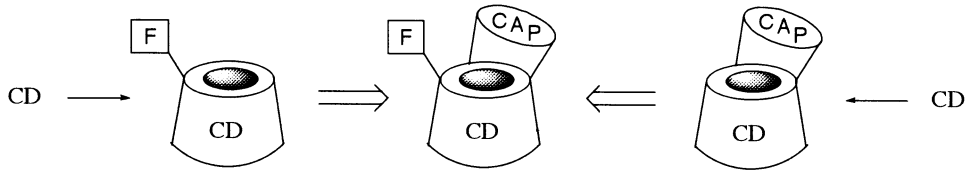
β-cyclodextrin,[9] which represents so far the only practicable method for the tri-modification of cyclodextrins. However, it is only confined to the 3-OH of β-cyclodextrin, and still confronts the competition from over- and under-substitutions. Therefore, a generally applicable method for the selective modification of three hydroxyl groups still remains to be developed. Herein we report our recent research into this subject. Our method involves the selective transannular disulfonylation of 6-tosyl cyclodextrin, affording 6^{A},6^{C},6^{E}-tri(*O*-sulfonyl)-β-cyclodextrins in good yields.

Transannular disulfonylation proved to be efficient in the selective modification of two primary hydroxyl groups of β-cyclodextrin.[10–13] Its combination with mono-functionalization methods may provide some new and generally applicable approaches to access trifunctionalized cyclodextrins (Scheme 1). We tried the mono-functionalization–capping strategy and found it worked well upon some mono-modified β-cyclodextrins as reactants. Among the various combinations of the 6-modified β-cyclodextrins with arenedisulfonyl chlorides examined in this research, the pairing of 6-tosyl β-cyclodextrin with dibenzofuran 2,8-disulfonyl chloride resulted in the expected trisulfonyl β-cyclodextrins in good yields. The reaction was carried out in pyridine in the presence of molecular sieves at rt for 2.5 h. The reaction mixture demonstrated very simple HPLC elution diagram, as can be seen in Fig. 1, in which a strong peak (I) is accompanied by a weak one (II) with the rest being negligible. Chromatography of this reaction mixture allowed the separation of the two fractions in 23 and 4.5% yields, respectively. FAB-MS of both fractions showed a peak at m/z 1603, consistent with that of the pseudo-molecular ion [M+Na] of the trisulfonyl products.



Scheme 1. The combination of mono-functionalization with the capping strategy may offer new and generally applicable approaches to the trifunctionalizations of cyclodextrins

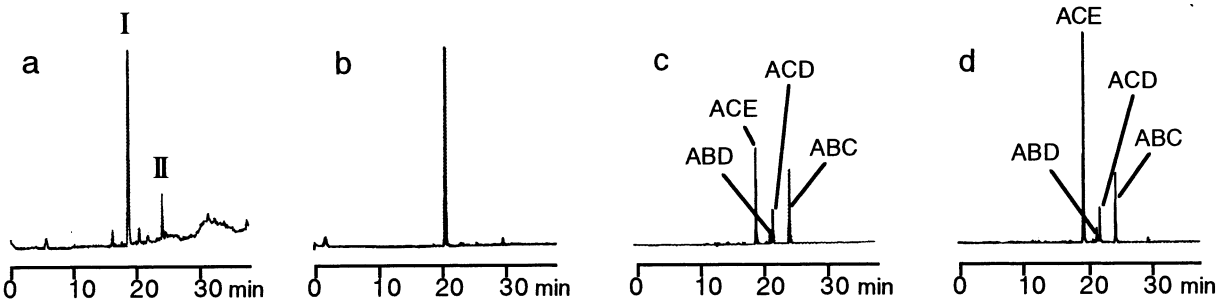
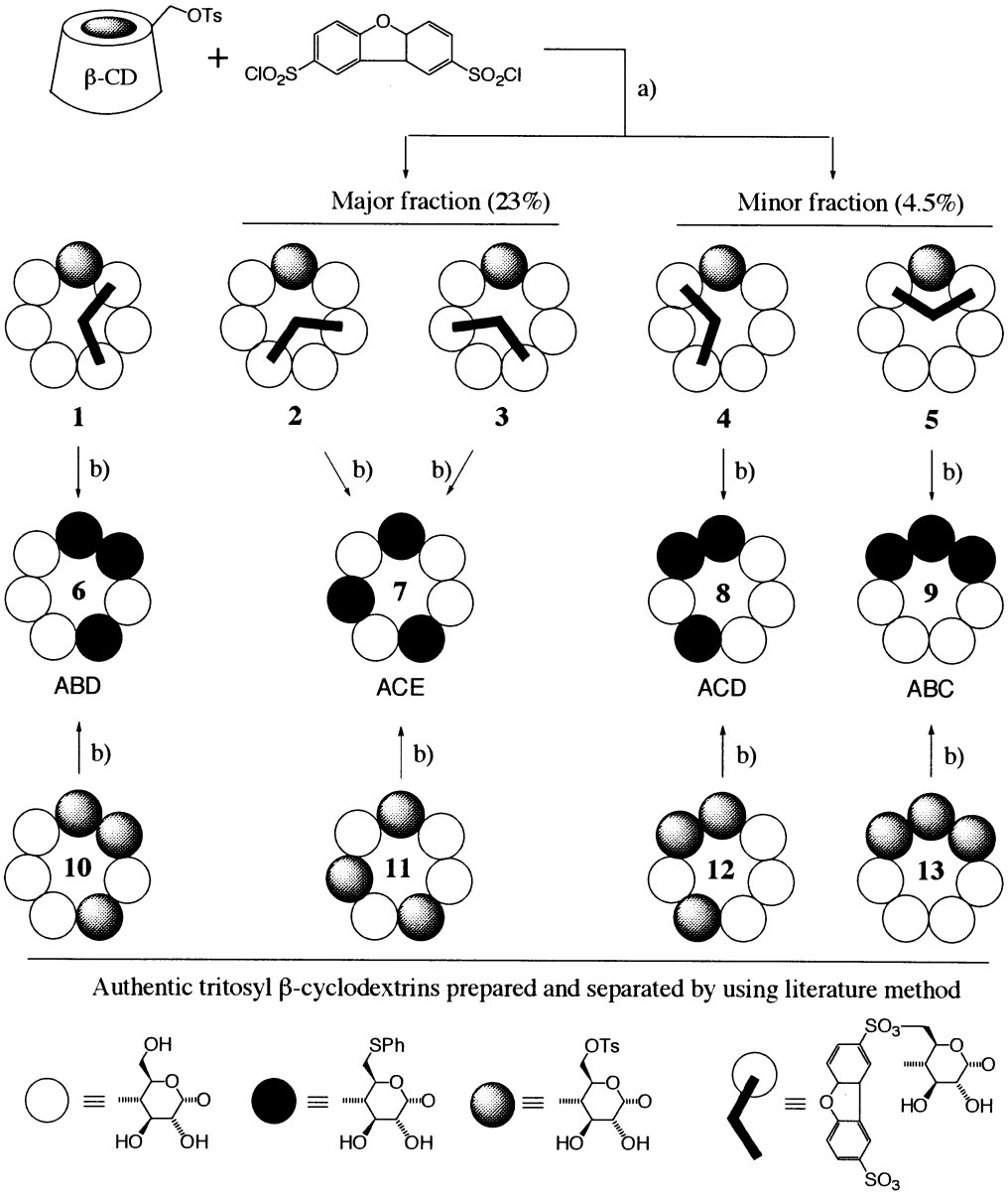


Figure 1. HPLC elution patterns of (a) the reaction mixture of 6-tosyl β-cyclodextrin and dibenzofuran 2,8-disulfonyl chloride, (b) reaction solution of phenyl mercaptan and the chromatographic fraction corresponding to the main peak of (a), (c) authentic isomeric tri(phenylmercapto) β-cyclodextrins prepared by literature procedure and (d) mixture of (b) and (c). A reversed phase ODS column was employed and eluted with a gradient from 20% aq. CH_3CN with CH_3CN concentration being increased at a rate of 0.67%/min. The elutes were detected at λ 210 nm

NMR spectra revealed that each fraction was actually a mixture of two regio-isomers. It was deemed necessary to identify the substitution patterns of the two fractions. Since dibenzofuran

2,8-disulfonyl chloride regio-specifically reacts with the 6^A- and 6^C-OH groups of β-cyclodextrin,[14] the capping of 6-tosyl β-cyclodextrin with this reagent produces theoretically five isomeric products **1**–**5** (Scheme 2). On being treated with phenyl mercaptan, compounds **1**, **4** and **5** afford **6**, **8** and **9**, respectively, while **2** and **3** result in the same homogeneously trifunctionalized cyclodextrin **7**. On the other hand, we were able to prepare and separate all the isomeric 6^A,6^X,6^Y-tri(*O*-tosyl) β-cyclodextrins **10**–**13** by following the literature procedures.[4] Subsequent treatment of these tritosylates with phenyl mercaptan produces compounds **6**–**9**, which were used as authentic samples to identify those obtained from the above capping reaction by comparing their retention times in the HPLC diagram.



Scheme 2. Synthesis of trisulfonyl β-cyclodextrins and determination of their substitution patterns (a) pyridine, molecular sieves, rt, 2.5 h; (b) DMF, PhSH, Cs_2CO_3

The reaction of the major fraction with phenyl mercaptan gave one product peak in the HPLC diagram, which has the same retention time as that of the tri(phenylmercapto) β-cyclodextrin obtained from the $6^A,6^C,6^E$-tritosylate **11**. This fact indicated that the major fraction and the authentic $6^A,6^C,6^E$-tritosylate **11** produce the same identical tri(phenylmercapto) β-cyclodextrins since **6**–**9** all showed different retention times from each other (Fig. 1). The minor fraction, after similar treatment, gave two product peaks in a 7/1 ratio, with the same retention times as those of the authentic $6^A,6^C,6^D$-and $6^A,6^B,6^C$-tri(phenylsulfide) **8** and **9**, respectively. Therefore we conclude that the major fraction consists of **2** and **3**, while the minor fraction contains mainly **4** contaminated with a trivial amount of compound **5**. It is interesting to note that the clockwise–counter-clockwise isomers **1** and **4** were produced in quite different amounts, which implies that the tosyl group may even encase its two neighboring 6-OH groups in quite a different reactivity from each other.

At present, the regio-isomers **2** and **3** can hardly be separated. Fortunately, it is not necessary to separate these two isomers from each other in terms of the preparation of homogeneously trifunctionalized cyclodextrin derivatives since they can both give the same product in subsequent transformations.

In conclusion, we have demonstrated that transannular disulfonylation can be carried out with 6-tosyl β-cyclodextrin and selectively afford the $6^A,6^C,6^E$-trisulfonates in good yields. Since β-cyclodextrin 6-tosylate is readily accessible,[15] this method is of synthetic significance in the preparation of homogeneously $6^A,6^C,6^E$-trifunctionalized β-cyclodextrins.

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References

1. Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer: Berlin, 1978.
2. Kahn, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977.
3. Cramer, F.; Mackensen, G. *Chem. Ber.* **1970**, *103*, 2138.
4. Fujita, K.; Tahara, T.; Koga, T. *Chem. Lett.* **1989**, 821.
5. Hanessian, S.; Benalil, A.; Laferriere, C. *J. Org. Chem.* **1995**, *60*, 4786.
6. Boger, J.; Brenner, D. G.; Knowles, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7630.
7. Coleman, A. W.; Ling, C.; Miocque, M. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1381.
8. Cottaz, S.; Driguez, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1088.
9. Fujita, K.; Tahara, T.; Yamamura, H.; Imoto, T.; Koga, T.; Fujioka, T.; Mihashi, K. *J. Org. Chem.* **1990**, *55*, 877.
10. Tabushi, I.; Yamamura, K.; Nabeshima, T. *J. Am. Chem. Soc.* **1984**, *106*, 5267.
11. Tabushi, I.; Nabeshima, T.; Fujita, K.; Matsunaga, A.; Imoto, T. *J. Org. Chem.* **1985**, *50*, 2638.
12. Breslow, R.; Canary, J. W.; Verney, M.; Waddell, S. T.; Yang, D. *J. Am. Chem. Soc.* **1990**, *112*, 5212.
13. Khan, A. R.; Forgo, P. F.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977.
14. Koga, K.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **2000**, *41*, 6855.
15. Byun, H.-S.; Zhong, N.; Bittman, R. *Org. Synth.* **1999**, *77*, 225.