J Incl Phenom Macrocycl Chem (2009) 63:373–378
DOI 10.1007/s10847-008-9511-8

Facile direct acylation and acyl migration of β-cyclodextrin on the secondary hydroxyl face

Zhizhong Wang · Runhua Lu

Received: 28 August 2008 / Accepted: 15 October 2008 / Published online: 6 November 2008

Abstract A new convenient strategy for direct acylation of β-cyclodextrin on the secondary hydroxyl face was achieved by using the combination of *N*-benzoylimidazole and carbonate buffer in DMF, and the acyl migration between the C-2 and C-3 hydroxyl groups of β-cyclodextrin was found.

Keywords β-Cyclodextrin · Acylation · *N*-benzoylimidazole · Acyl migration

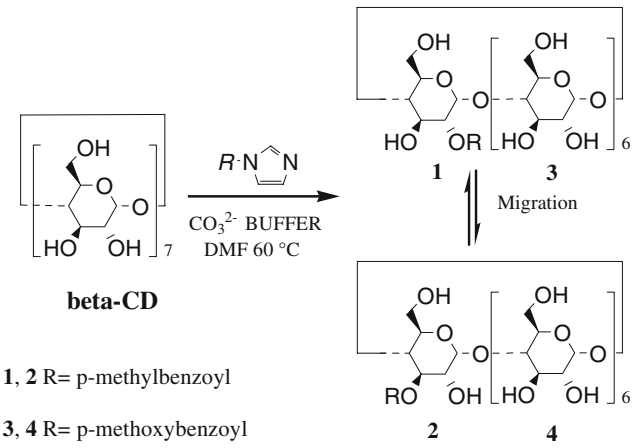
Introduction

Cyclodextrins (CDs) are well-known cyclic oligosaccharides consisting of six or more α-1, 4-linked D-glucopyranose units, which possess the secondary C-2 and C-3 hydroxyl groups on their more open face and the primary C-6 hydroxyl groups on the other face. Owing to their hydrophobic and optically active interior, derivatives of CDs have evolved into a versatile class of macrocyclic compounds with applications in artificial enzymes, sensors, drug delivery systems, and chiral reagents [1–6]. For example, 6-O-benzoyl-β-CDs as novel supramolecular photosensitizing hosts have recently excited considerable attention in photochirogenesis [7–10]. However the more open secondary hydroxyl face of CDs is stated to be catalytically very important [11–14], modifications of this face are believed to produce valuable derivatives for catalysis, enzyme mimic, chiral discrimination, etc.

Of the three types of hydroxyl groups present in β-CD, those at the 6-position are the most basic and often most nucleophilic, those at the 2-position are the most acidic, and those at the 3-position are the most inaccessible. Thus, under normal circumstances, an electrophilic reagent attacks the 6-position, and it is important to recognize that more reactive reagents will attack the hydroxyl groups less selectively. Selective introduction of functional groups to β-CD has been extensively studied for the primary hydroxyl face [15], but less well for the secondary hydroxyl face. The most commonly used method for selective introduction of one functional group at the secondary face is via activation of one hydroxyl group by sulfonylation. In recent years, research has focused on improving the preparation of mono-2-tosyl-β-CD as the key intermediate, and several successful strategies have been developed [16–24]. Only very few examples are known of the introduction of a single functional group at the secondary face of CDs without prior sulfonylation. Ding Rong and Valerian T. D'Souza functionalized the C-2 OH by deprotonation with NaH and subsequent reaction with an electrophilic reagent [17], this method needs the use of strong alkali as reactant and requires strict anhydrous conditions. Ai You Hao et al. monoacylated β-CD on the secondary hydroxyl side with acyl chloride in alkaline acetonitrile solution [25], which uses the toxic solvent and high reactive reagent. To our knowledge, this reaction gave a mixture of C-2, C-3, and C-6 positions. *N*-benzoylimidazole has been recently shown to be a highly selective acylating reagent [26, 27], however it has not excited considerable attention in cyclodextrin chemistry. Herein, the authors describe a convenient method for direct monobenzoylation of β-CD

Z. Wang · R. Lu
Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, Sichuan, People's Republic of China

R. Lu (✉)
Department of Applied Chemistry, College of Sciences, China Agricultural University, Beijing 100094, People's Republic of China
e-mail: lurh@cib.ac.cn



Scheme 1 Direct acylation of *β*-cyclodextrin with *N*-acylimidazole

on the secondary hydroxyl face (Scheme 1), and report the acyl migration between the C-2 and C-3 hydroxyl groups.

Experimental

Analytical and preparative high performance liquid chromatography (HPLC) column chromatographies were done using a Perkin-Elmer Series 200 HPLC system with an UV/Vis detector. A Kromasil 100-10-C18 column (4.6 mm × 250 mm) was used for the analytical HPLC, and a ZORBAX SB-C18 column (10 mm × 250 mm) was used for preparative HPLC. NMR spectra were recorded on Bruker AM-600 (^{1}H 600 MHz and ^{13}C 150 MHz) in DMSO-d_6 solutions with tetramethylsilane (TMS) as standard. The ESI-MS experiments were performed using a ThermoQuest Finnigan LCQ^{DECA} system equipped with an ESI source (ThermoQuest LC/MS Division, San Jose, CA, USA). About 0.2 M carbonate buffer (pH 9.9) was prepared by mixing equal volumes of 0.2 M sodium carbonate and 0.2 M sodium bicarbonate. All other chemicals were of commercial grade without further purification.

General experimental procedure

N-benzoylimidazole [28] was prepared in the following way: imidazole (3.52 mmol) was dissolved in redistilled dichloromethane (10 mL), and benzoyl chloride (1.76 mmol) was added dropwise while the solution was kept below 5 °C for 1 h. After standing for another 1 h at room temperature, the suspension was filtered to remove imidazole hydrochloride, and the filtrate was evaporated in vacuo at 30 °C until no solvent evaporated out. The residue was dissolved in DMF (60 mL), and *β*-CD (1.76 mmol) was added and stirred. After the stirred solution became clear, 12 mL of 0.2 M carbonate buffer

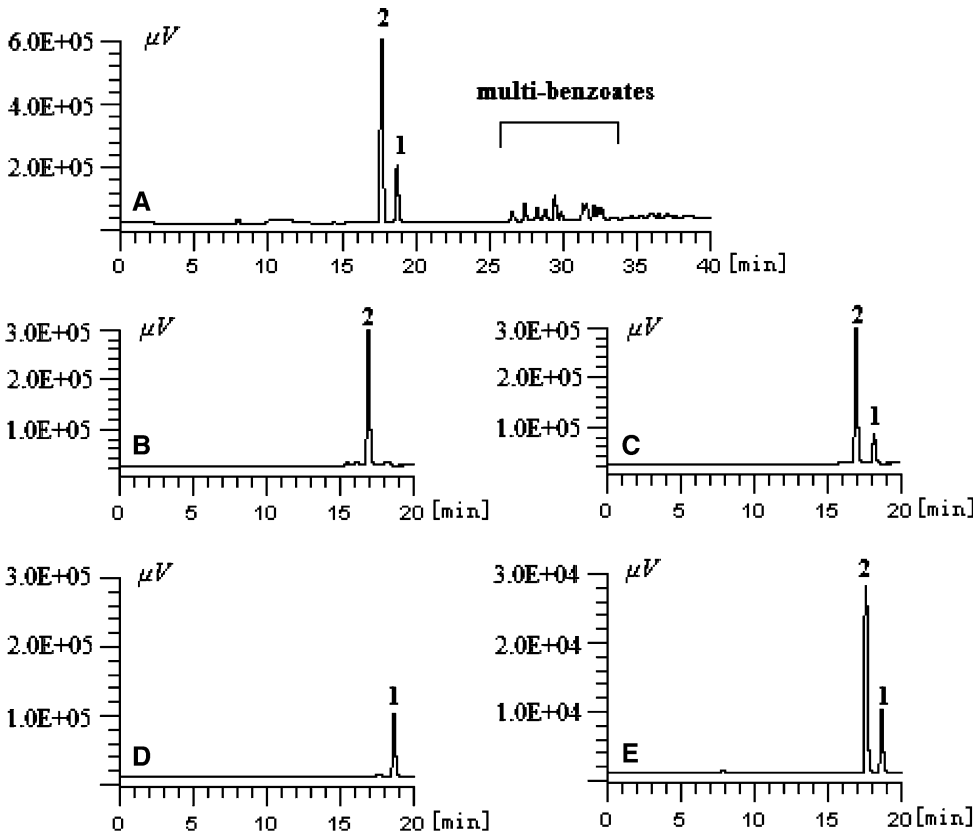


Fig. 1 HPLC analysis of the final reaction mixture of *β*-CD and *N*-(*p*-methylbenzoyl) imidazole, and the acyl migration process of the isolated solutions through preparative high performance liquid chromatography. Detection was done at 240 nm wavelength. Gradient elution was done from 10:90 to 40:60 MeOH–H_2O for 20 min, to 100:0 MeOH–H_2O for 20 min; flow rate of 0.8 mL/min. **a** The final reaction mixture; **b** isolated peak **2** initially; **c** 1 h after heated at 50 °C or 3 days after kept at temperature room for **2**; **d** isolated peak **1** initially; **e** 1 h after heated at 50 °C or 3 days after kept at temperature room for **1**. Compound numbers are presented corresponding peaks

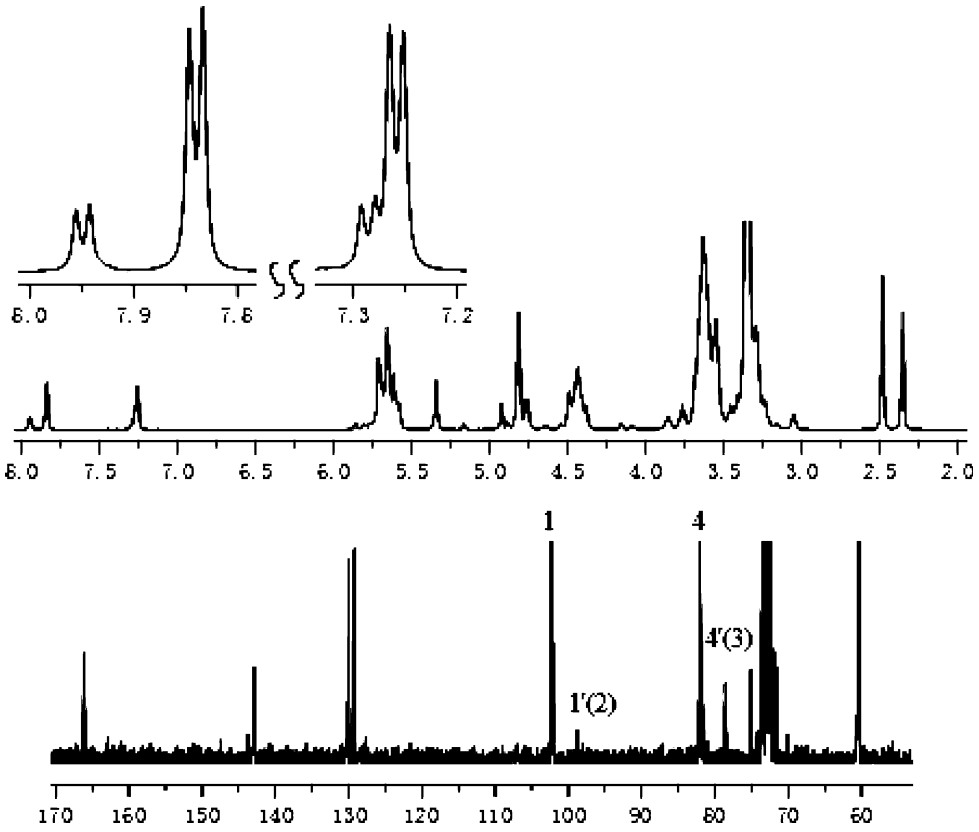


Fig. 2 The ^{1}H and partial ^{13}C NMR spectra of isomers (**1** and **2**) in DMSO-d_6. The numbers indicate the peak assignments

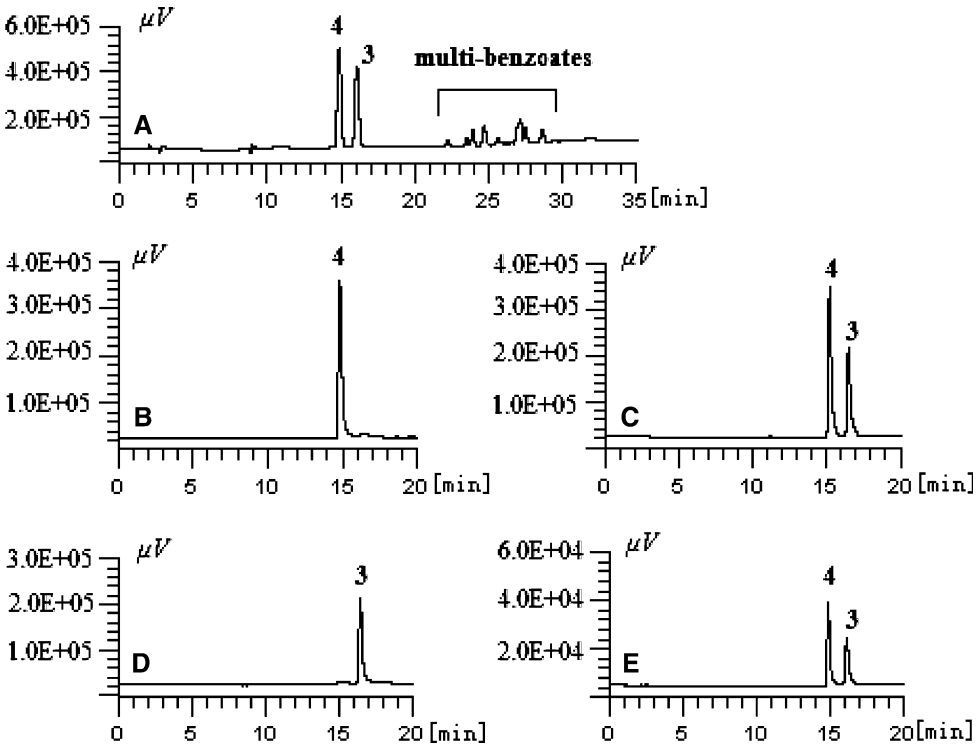


Fig. 3 HPLC analysis of the final reaction mixture of β-CD and *N*-(*p*-methoxybenzoyl) imidazole, and the acyl migration process of the isolated solutions through preparative high performance liquid chromatography. Detection was done at 255 nm wavelength. Gradient elution was done from 10:90 to 40:60 MeOH–H_2O for 20 min, to 100:0 MeOH–H_2O for 20 min; flow rate of 0.8 mL/min. **a** The final reaction mixture; **b** isolated peak **4** initially; **c** 2 h after heated at 50 °C or 7 days after kept at temperature room for **4**; **d** isolated peak **3** initially; **e** 2 h after heated at 50 °C or 7 days after kept at temperature room for **3**. Compound numbers are presented corresponding peaks

(pH 9.9) were added. The reaction mixture was heated at 60 °C for 2 h. Then the mixture was neutralized with 1 N HCl, evaporated in vacuo to a volume of ca. 5 mL, and 300 mL of acetone was added to precipitate cyclodextrin derivatives. The collected solid was subjected to a RP-18 column eluted with H_2O–MeOH; the eluent composition

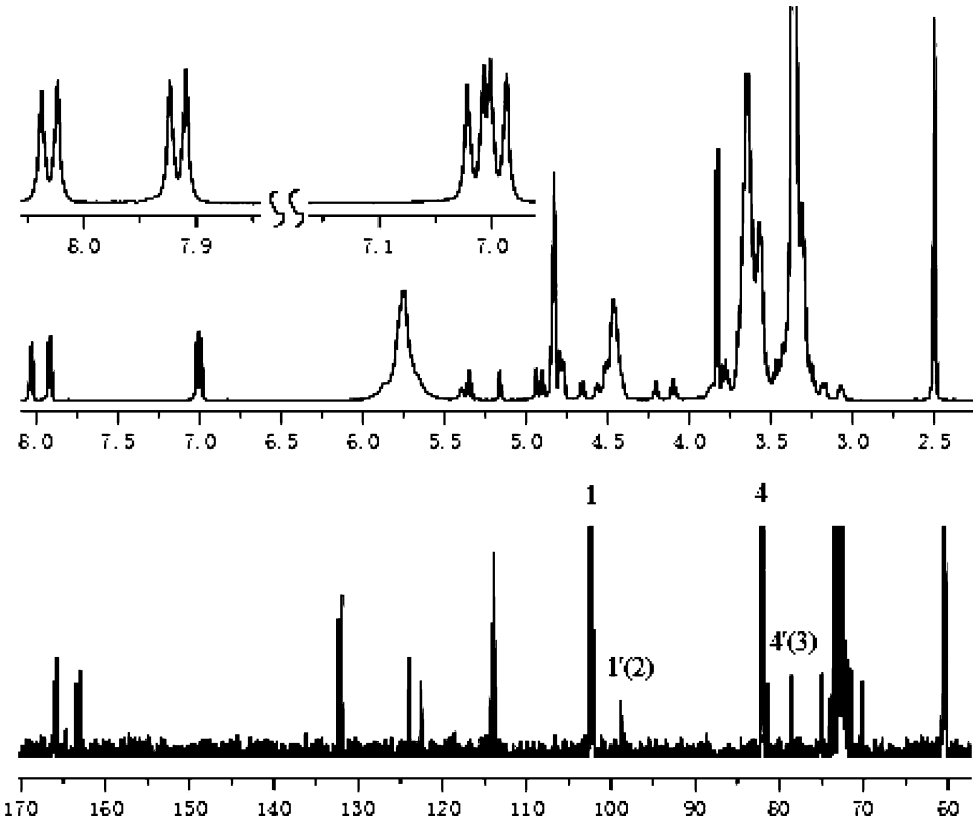


Fig. 4 The ^{1}H and partial ^{13}C NMR spectra of isomers (**3** and **4**) in DMSO-d_6. The numbers indicate the peak assignments

was gradually changed (MeOH–H_2O, 0–10%, 10%–20%, 20%–30%, 30%–50%) until the products were eluted. The residue obtained after removal of the solvent was triturated with acetone, filtered, washed with acetone and dried. Thus, isomers were obtained.

Result and discussion

In our previous work [29, 30], the authors found that carbonate buffer (pH 9.9) can efficiently activate the C-2 OH of β-CD, and regioselectively promote reactions at the 2-position. A mixture of β-CD, one molar equivalent of *N*-(*p*-methylbenzoyl)imidazole, and carbonate buffer in DMF was stirred at 60 °C for 2 h. The reaction was monitored using reversed-phase HPLC. As shown by the HPLC (Fig. 1a), the reaction is highly regio-selective, generating mainly 3-mono(O-*p*-methylbenzoyl)-β-CD (**2**), 2-mono(O-*p*-methylbenzoyl)-β-CD (**1**), and a little multi-benzoates.

Open reversed-phase column chromatographic separation of the above reaction mixture afforded a fraction containing **1** and **2** (total yield 44%); Rechromatography led to the same result and not to the pure isomers. This result was unexpected. Therefore this observation led to the assumption that acyl migration occur between the C-2 and C-3 hydroxyl groups [31, 32]. In order to prove the conclusion, the isolation of **1** and **2** was carried out using HPLC. On the preparative column with the elution of 20% aqueous MeOH, **1** and **2** showed good separations, and were collected respectively. Monitoring by HPLC of the two isolated solutions (Fig. 1b–e), it was surprise that the solution of **1** showed proportions of **2** increasing with time, and in the same way the solution of **2** showed proportions of **1** increasing with time. On the other hand, it is important to note that the rate of acyl migration is relatively slow in room temperature, and fast in higher temperature. Consequently, a systematic study on the rate, equilibrium and mechanism of acyl migration, is in progress.

The structures of **1** and **2** were confirmed using ESI-MS and NMR spectra. Their ESI-MS spectrum exhibited the molecular ion $[M + Na]^+$ at m/z 1275. As shown in Fig. 2, the ^{1}H and ^{13}C NMR spectra show peaks in pairs, these indicate there exist two isomers. ^{13}C NMR spectra is an effective technique for the analysis of cyclic oligosaccharides. As elegantly explained by Breslow [16], usually, arylation of a hydroxyl group of CDs leads to a downfield chemical shift of the carbon carrying the hydroxyl (α-carbon), but a small upfield chemical shift of β-carbon and a still smaller shift of γ-carbon. In the ^{13}C NMR spectra, no change in the shift of C-6 of the substituted glucose unit with respect to unsubstituted glucose units clearly indicate that the substituent is at the 2 and 3-positions other than at

the 6-position of β-CD. Because signals of C-4′(3), which are the substituted glucose unit at the 3-position, are higher than those of C-1′(2) which are the substituted glucose unit at the 2-position, quantities of **2** is more than **1**. This result is consistent with that of HPLC.

Using *N*-(*p*-methoxybenzoyl)imidazole as acylating reagent, the similar results were obtained (**3** and **4**, total yield 40%), shown in Figs. 3 and 4. Their ESI-MS spectrum exhibited the molecular ion $[M + Na]^+$ at m/z 1291.

Conclusion

A facile direct monobenzoylation of β-CD on the secondary hydroxyl face was developed by using the combination of *N*-benzoylimidazole and carbonate buffer in DMF, and the acyl migration between the C-2 and C-3 hydroxyl groups of β-CD was observed. Because the rate of acyl migration is relatively slow in room temperature, the authors are in the process of enantiodifferentiating photoisomerization of (Z)-cyclooctene included and sensitized by 2-O-modified β-CD or 3-O-modified β-CD.

Acknowledgment Financial support from the Chinese Natural Science Foundation (NO. 20772120) is gratefully acknowledged.

References

1. Breslow, R.: Biomimetic chemistry. Pure. Appl. Chem. **66**, 1573 (1994)
2. Breslow, R.: Biomimetic chemistry and artificial enzymes: catalysis by design. Acc. Chem. Res. **28**, 146 (1995)
3. Breslow, R., Dong, S.D.: Biomimetic reactions catalyzed by cyclodextrins and their derivatives. Chem. Rev. **98**, 1997–2011 (1998)
4. Stainer, C.A., Alderman, S.J., Claridge, T.D., Anderson, H.L.: Unidirectional photoinduced shuttling in a rotaxane with a symmetric stilbene dumbbell. Angew. Chem. Int. Ed. Engl. **41**, 1769–1772 (2002)
5. Hedges, A.R.: Industrial applications of cyclodextrins. Chem. Rev. **98**, 2035–2044 (1998)
6. Uekama, K., Hirayama, F., Irie, T.: Cyclodextrin drug carrier systems. Chem. Rev. **98**, 2045–2076 (1998)
7. Lu, R.H., Yang, C., Cao, Y.J., Wang, Z.Z., Wada, T., Jiao W., Mori, T., Inoue, Y.: Supramolecular enantiodifferentiating photoisomerization of cyclooctene with modified beta-cyclodextrins: critical control by a host structure. Chem. Commun. 374–376 (2008)
8. Fukuhara, G., Mori, T., Wada, T., Inoue, Y.: Entropy-controlled supramolecular photochirogenesis: enantiodifferentiating Z-E photoisomerization of cyclooctene included and sensitized by permethylated 6-O-modified-beta-cyclodextrins. J. Org. Chem. **71**, 8233–8243 (2006)
9. Tong, L.H., Lu, R.H., Inoue, Y.: Asymmetric photochemistry with native and modified cyclodextrins. Prog. Chem. **18**, 533–541 (2006)
10. Fukuhara, G., Mori, T., Wada, T., Inoue, Y.: Entropy-controlled supramolecular photochirogenesis: enantiodifferentiating Z-E photoisomerization of cyclooctene included and sensitized by permethylated 6-O-benzoyl-b-cyclodextrin. Chem. Commun. 4199–4201 (2005)
11. D'Souza, V.T., Bender, M.L.: Miniature organic models for enzymes. Acc. Chem. Res. **20**, 146 (1987)
12. Vanetten, R.L., Sebastian, J.F., Clowes, G.A., Bender, M.L.: Acceleration of phenyl ester cleavage by cycloamyloses. A model for enzymic specificity. J. Am. Chem. Soc. **89**, 3242–3253 (1967)
13. Vanetten, R.L., Clowes, G.A., Sebastian, J.F., Bender, M.L.: The mechanism of the cycloamylose-accelerated cleavage of phenyl esters. J. Am. Chem. Soc. **89**, 3253–3262 (1967)
14. Rama Rao, K., Srinivasan, T.N., Bhanumathi, N., Sattur, P.B.: Artificial enzymes: synthesis of imidazole substituted at C(2) of beta-cyclodextrin as an efficient enzyme model of chymotrypsin. J. Chem. Soc. Chem. Commun. 10 (1990)
15. Khan, A.R., Forgo, P., Stine, K.J., D'Souza, V.T.: Methods for selective modifications of cyclodextrins. Chem. Rev. **98**, 1977–1996 (1998)
16. Ueno, A., Breslow, R.: Selective sulfonation of a secondary hydroxyl group of beta-cyclodextrin. Tetrahedron Lett. **23**, 3451–3454 (1982)
17. Rong, D., D'Souza, V.T.: A convenient method for functionalization of the 2-position of cyclodextrins. Tetrahedron Lett. **31**, 4275–4278 (1990)
18. Law, H., Baussanne, I., Garc Fernandez, J.M., Defaye, J.: Regioselective sulfonylation at O-2 of cyclomaltoheptaose with 1-(p-tolylsulfonyl)-(1H)-1, 2, 4-triazole. J. Carbohydr. Res. **338**, 451–453 (2003)
19. Teranishi, K., Watanabe, K., Hisamatsu, M., Yamada, T.: Efficient regioselective synthesis of mono-2-O-sulfonyl-cyclodextrins by the combination of sulfonyl imidazole and molecular sieves. J. Carbohydr. Chem. **17**, 489–494 (1998)
20. Teranishi, K.: Practicable regiospecific bifunctionalization on the secondary face of alpha- and beta-cyclodextrins. Chem. Commun. 1255–1256 (2000)
21. Teranishi, K.: Regiospecific 2^A, 2^C-disulfonation of β-cyclodextrin. Tetrahedron Lett. **41**, 7085–7088 (2000)
22. Teranishi, K.: Regioselective 2^A, 2^D-disulfonyl capping of β-cyclodextrin for practical bifunctionalization on the secondary hydroxyl face. Tetrahedron Lett. **42**, 5477–5480 (2001)
23. Yu, H., Teramoto, A., Fukudome, M., Xie, R.G., Yuan, D.Q., Fujita, K.: A facile sulfonylation method enabling direct syntheses of per(2-O-sulfonyl)-β-cyclodextrins. Tetrahedron Lett. **47**, 8837–8840 (2006)
24. Strerath, M., Meng, M., Kubik, S.: Facile one-step synthesis of mono-2-(p-tolylsulfonyl)-β-cyclodextrin under aqueous conditions. Synthesis 348–350 (2007)
25. Hao, A.Y., Tong, L.H., Zhang, F.S., Gao, X.M.: Convenient preparation of monoacylated β-cyclodextrin (cyclomaltoheptaose) on the secondary hydroxyl side. J. Carbohydr. Res. **277**, 333–337 (1995)
26. Varela, O., Cicero, D., de Lederkremer, R.M.: A convenient synthesis of 4-thio-D-galactofuranose. J. Org. Chem. **54**, 1884–1890 (1989)
27. Horton, D., Priebe, W., Varela, O.: Selective acylation of 6-deoxyglycals. J. Carbohydr. Res. **144**, 317–324 (1985)
28. Holder, N.L., Fraser-Reid, B.: An improved synthesis of methyl 2-O-benzoyl-4,6-O-benzylidene-α-D-altropyranoside. Synthesis 83 (1972)
29. Wang, Z.Z., He, G.Y., Lu, R.H.: A convenient and economic method for the synthesis of mono-2-tosyl-β-cyclodextrin. Monatsh. Chem. **139**, 1109–1111 (2008)
30. Wang, Z.Z., Jiao, W., He, G.Y., Lu, R.H.: One-step regioselective green synthesis of 2,3-mannoepoxy-β-cyclodextrin under aqueous

conditions. Monatsh. Chem. (2008). doi: 10.1007/s00706-008-0010-9
31. Leung, D.K., Yang, Z.W., Breslow, R.: Selective disruption of protein aggregation by cyclodextrin dimers. Proc. Natl. Acad. Sci. USA **97**, 5050–5053 (2000)
32. Icheln, D., Gehrcke, B., Piprek, Y., Mischnick, P., Konig, W.A., Dessoy, M.A., Morel, A.F.: Migration of secondary tert-butyldimethylsilyl groups in cyclomalto-heptaose and -octaose derivatives. J. Carbohydr. Res. **280**, 237–250 (1996)