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The Preparation of 2-O-Acetonyl-β-cyclodextrin as One Key Intermediate for Water Soluble β-Cyclodextrin Derivatives

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Abstact: 2-O-Acetonyl-β-cyclodextrin with a suitable average substitution degree of about 5.8, which could be used as a key intermediate for water soluble functional β-cyclodextrin derivatives, was prepared based on the proper oxidation of heptakis (6-O-dimethyl-*tert*-butylsilyl)-2-O -hydroxypropyl-β-cyclodextrin.

Keywords: 2-O-Acetonyl-β-cyclodextrin, key intermediate, water soluble.

Regioselective functionalization of the secondary hydroxyls on the more open side, which has been considered to be the real business end of doughnut-shaped cyclodextrins (CDs, including α, β, γ-CD, *etc.)*, is of much value for constructing potential artificial enzymes, molecular recognition sensors and other functional models[1-8]. These derivatives could also be used as potential drug carriers and food stabilizers[4-6]. For regio-selective functionalization of β-CD, particularly for the functionalization on the secondary hydroxyl side with a controlled degree of modification groups (mono-, di-, *etc.*)[1,4,5], a few inter -mediates, such as 2-O-tosyl-β-CD[7,8], per(2-O-tosyl)-β-CD[9], per(3,6-anhydro)-β-CD[10,11] and heptakis-2,3-epoxy-β-CD[12] had been developed. These intermediates are hardly soluble in water. Here we report the preparation of water soluble 2-O-acetonyl -β-CD **4** with a suitable average substitution degree of about 5.8 (**Scheme 1**), which could be used as a key intermediate for water soluble β-CD derivatives, for example **5**a.

For the preparation of **4**, β-CD was first converted to silanized derivative **1** by the reactive 6-hydroxyls[4,5]. **2** was prepared based on more acidic 2-hydroxyls compared with 3-hydroxyls[4,5] of **1**. In the formation of **3**, 3-hydroxyls and the other 2-hydroxyls of **2** could be retained under the oxidation by acetone with aluminium *iso*propoxide. This might be due to their relative rigid structures compared with the hydroxyls in hydroxypropyls of **2**.

5a, which could be prepared by the reaction of **4** with ethylenediamine, can also be used as a key intermediate based on its active amine. **5**b and **5**c were examples derivatived from **5**a. **5**b and **5**c both have a flexible chain that bonds an aryl moiety on the secondary side of β-CD. They might be able to simulate the "induced fit" of enzymes[13].

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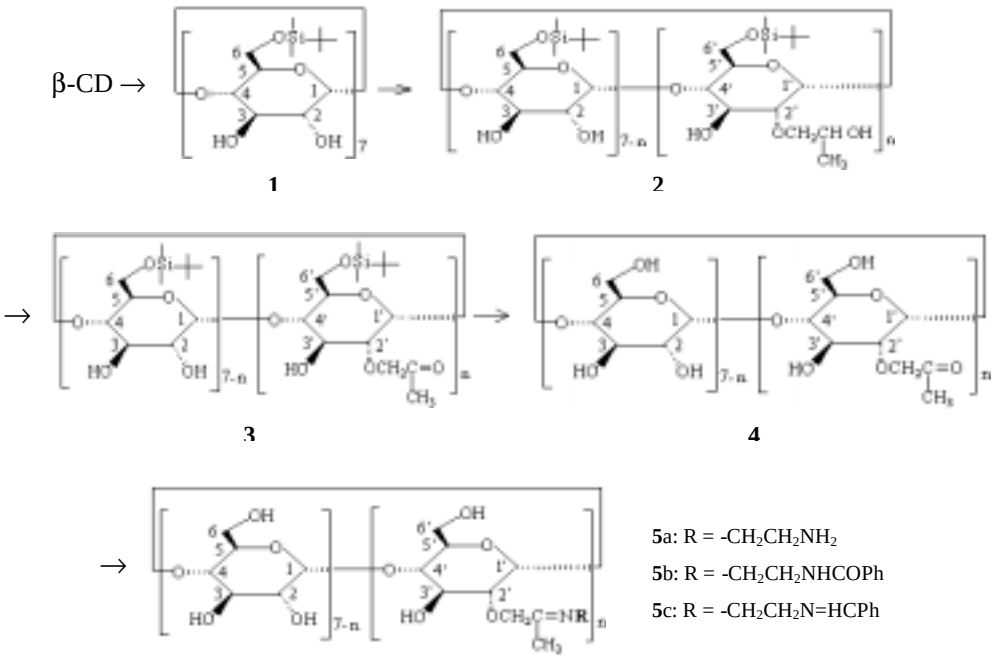
The *n* in **4**, **5**a, **5**b and **5**c was the corresponding to the average substitution degree of acetonyls or the acetonyl derivatives. The *n* values can be controlled by the ratio of reactants and monitored by the ^{1}H-NMR spectra of the products.

Scheme 1 The preparation route of 2-O-acetonyl-β-CD



Experimental

Commercially available β-CD was recrystallized from water and dried in *vacuo* at 100°C for 4 h. Pyridine and N,N-dimethylformamide (DMF) were dried over, and redistilled from CaH_2. Chloroform was dried over $CaCl_2$.

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Brucker AM-400 spectrometer (ppm; Me_4Si used as an internal reference). IR spectra were recorded on Shimaduzu IR-435 spectrometer.

Heptakis(6-O-dimethyl-tert-butylsilyl)-2-O-hydroxypropyl-β-CD ***2*** *(n=5.8):*

Heptakis (6-O-dimethyl-*tert*-butylsilyl)-β-CD **1** was prepared from β-CD according to reported method[14,15]. 0.07 equivalent sodium hydride (1.7 g) was added to a solution of 19.3 g of **1** in 400 mL of dry DMF at 0°C and the mixture was stirred for 2 h. Subsequently, 0.07 equivalent epoxy propane (4.1 g) was added dropwise in the period of 1 h at 0°C, then was warmed to room temperature and kept this temperature for about 12 h to form **2**. The solvent was removed in *vacuo* followed by a silica gel column chromatography with eluant of $CHCl_3$ / CH_3COCH_3 / PrOH / H_2O (40:15:5:3 by volume) to give pure **2** in 90 %. ^{1}H-NMR ($CDCl_3$, ppm) δ_H: 5.95 ~ 5.60 (br, 2-OH, 3-OH, 3′-OH), 5.26 ~ 4.84 (m, 7 H, H-1, 1′), 4.21 ~ 3.22 (m, about 65 H, H-2′, 2, 4, 6, 5, 3, 4′, 6′, 5′, 3′, and -H_2CCH(OH)-), 1.02 (d, 17.5 H, J=6.0 Hz, -CH(OH)CH_3), 0.85

(s, 63 H, $(H_3C)_3CSi$); ^{13}C-NMR (ppm) δ_C: 101.9~100.8 (C-1, 1′), 81.7~80.2 (C-4, 4′), 77.2~71.5 (-H_2**C**CH(OH)-, C-2′, 3, 2, 5, 3′, 5′), 66.4 (-**C**H(OH)CH_3), 61.2 (C-6, 6′), 24.4~-3.2 (-CH(OH)**C**H_3, $(H_3C)_3C(CH_3)_2Si$-). Anal. calcd. for $C_{101.4}H_{202.8}O_{40.8}Si_7$, C 53.48, H 8.91; found: C 53.39, H 8.97.

Heptakis(6-O-dimethy-tert-butylsilyl)-2-O-acetonyl-β-CD ***3*** *(n=5.8):*

The solution of **2** formed above was directly dispersed in about 2 parts of acetone (based on volume) with a catalytic amount of aluminium *iso*propoxide (about 7.0 equivalent based on **2**), and then refluxed for about 12 h. Most of the solvent was removed in *vacuo* followed by a silica gel column chromatography with eluant of $CHCl_3$ / CH_3COCH_3 / PrOH / H_2O (40:15:5:3 by volume) to obtain pure **3** in 80 %. ^{1}H-NMR ($CDCl_3$, ppm) δ_H: 5.96~5.61 (br, 2-OH, 3-OH, 3'-OH), 5.37~4.88 (m, 7 H, H-1, 1′), 4.67 (s, about 11.6 H, -OCH_2CO-), 4.22~3.20 (m, 42 H, H-2′, 2, 4, 6, 5, 3, 4′, 6′, 5′, 3′), 2.11 (s, about 17.4 H, -$COCH_3$), 0.86 (s, 63 H, $(H_3C)_3CSi$); ^{13}C-NMR (ppm) δ_C: 219.6 (-CO-), 101.9~100.8 (C-1, 1′), 81.7~80.2 (C-4, 4′), 78.7~71.4 (O**C**H_2CO-, C-2′, 3, 2, 5, 3′, 5′), 61.2 (C-6, 6′), 28.7 (-CO**C**H_3), 15~-3.2 $(H_3C)_3C(CH_3)_2Si$-). Anal. calcd. for $C_{101.4}H_{191.2}O_{40.8}Si_7$, C 53.75, H 8.45; found: C 53.66, H 8.52.

2-O-Acetonyl-β-CD ***4*** *(n=5.8):*

Compound **3** (14.5 g) was deprotected by treatment with 14 equivalent $BF_3{\cdot}Et_2O$ in 500 mL of $CHCl_3$ at room temperature overnight. The deprotection was quenched by ice-water. The mixture was concentrated in *vacuo*, followed by silica gel column chromatography with eluant of $CH_3COOCH_2CH_3$ / PrOH / H_2O (2:3:2 by volume) to give 76 % yield of **4**. ^{1}H-NMR (D_2O, ppm) δ_H: 5.36~4.85 (m, 7 H, H-1, 1′), 4.70 (s, 11.6 H, -OCH_2CO-), 4.25~3.20 (m, about 42 H, H-2′, 2, 4, 6, 5, 3, 4′, 6′, 5′, 3′), 2.12 (s, 17.4 H, -$COCH_3$); ^{13}C-NMR (ppm) δ_C: 220.6 (-CO-), 101.8~100.8 (C-1, 1′), 82.6~80.1 (C-4, 4′), 78.8~71.2 (OCH_2CO-, C-2′, 3, 2, 5, 3′, 5′), 61.1 (C-6, 6′), 28.7 (-$COCH_3$). IR, (KBr) ν / cm^{-1}: 1739 for -CO-. Anal. calcd. for $C_{59.4}H_{93.2}O_{40.8}$ •2 H_2O, C 47.69, H 6.56; found: C 47.61, H 6.67.

2-O-(2-Aminoethyl-imino-propyl)-β-CD ***5a*** *(n=5.8):*

Compound **4** (10.0 g) and 0.07 equivalent ethylenediamine reacted with a catalytic amount of acetic acid in 250 mL of DMF for 6 h at 80°C, followed by purification on a Sephadex G-25 column (Φ=3.5×50 cm, the eluent was distilled water) to get **5a** in 58 % yield. ^{1}H-NMR (D_2O, ppm) δ_H: 5.32~4.90 (m, 7 H, H-1, 1′), 4.62 (s, about 11.6 H, -OCH_2C=N-), 4.21~2.81 (m, about 54 H, H-2′, 2, 4, 6, 5, 3, 4′, 6′, 5′, 3′, and =NCH_2-), 2.58 (m, about 11.6 H, -CH_2NH_2), 1.77 (s, about 17.4 H, -(H_3C)C=N-), 1.25 (br, about 11.6 H, -NH_2); ^{13}C-NMR (D_2O, ppm) δ_C: 181.6 (C=N), 101.6~99.7 (C-1, 1′), 82.2~80.7 (C-4, 4′), 77.6~71.9 (O**C**H_2C=N-, C-2′, 3, 2, 5, 3′, 5′), 60.9 (C-6, 6′), 39.4 (=NCH_2-), 35.5 (-CH_2NH_2), 24.1 (-$(H_3$**C**$)$C=N-). Anal. calcd. for $C_{71.0}H_{128.0}O_{35.0}N_{11.6}$ • 2 H_2O, C 49.01, H 7.36, N 9.34; found: C 48.96, H 7.41, N 9.32.

2-O-[2-(N-Benzoyl-aminoethyl)-imino-propyl]-2-O-hydroxypropyl-β-CD ***5b*** *(n=5.8)*:

3.8 g of **5a** was dissolved in a mixture of 40 mL of freshly distilled pyridine and 60 mL of water. Then 0.07 equivalent benzoylchloride in 20 mL of acetonitrile was added dropwise in 10 minutes. After stirring for 12 h, the reaction solution was evaporated to

about 5 mL under 50°C in *vacuo*, followed by purification on a Sephadex G-25 column (Φ=3.5×50 cm, the eluent was distilled water) to get **5b** in 57 % yield. ^{1}H-NMR (D_2O, ppm) δ_H: 8.82 (br, about 5.8 H, -NHCO-), 8.12 ~ 7.41(m, about 29 H, aromatic protons), 5.32 ~ 4.92 (m, 7 H, H-1, 1'), 4.61 (s, about 11.6 H, -OCH_2C=N-), 4.23 ~ 2.67 (m, about 65 H, H-2', 2, 4, 6, 5, 3, 4', 6', 5', 3', and -CH_2CH_2-), 1.77 (s, about 17.4 H, -(H_3C)C=N-); ^{13}C-NMR (ppm) δ_C: 177.6 (C=N), 144.6, 133.5, 129.4, 128.6 (aromatic carbons), 101.9-99.8 (C-1, 1′), 82.4 ~ 79.7 (C-4, 4′), 77.4 ~ 65.5 (O**C**H_2C=N-, C-2′, 3, 2, 5, 3′, 5′), 60.4 (C-6, 6′), 56.1 (-**C**H_2-NHCO-), 39.6 (=NCH_2-), 24.2 (-(H_3**C**)C=N-). Anal. calcd. for $C_{111.6}H_{116.4}O_{40.8}N_{11.6}$ • 2 H_2O, C 58.05, H 5.05, N 7.04; found: C 57.97, H 5.15, N 7.00

2-O-[2-(N-Benzylidene-aminoethyl)-imino-propyl]-β-CD ***5c*** *(n=5.8)*:

7.6 g of **5**a and 0.07 equivalent benzaldehyde were dissolved in 20 mL of DMF and stirred for 2 h. 2 mL of 5 % HCl solution was added dropwise and the mixture stirred for another 2 h. The reaction solution was concentrated to about 5 mL under 50°C in *vacuo*, and then a Sephadex G-25 column (Φ=3.5×50 cm) was applied to furnish **5**c in 58 % yield. ^{1}H-NMR (D_2O, ppm) δ_H: 8.34 (s, about 5.8 H, -N=CH-), 7.85-7.37 (m, about 29 H, aromatic protons), 5.22 ~ 4.87 (m, 7 H, H-, 1, 1′), 4.62 (s, about 11.6 H, -OCH_2C=N-), 4.19 ~ 2.72 (m, about 65H, H-2′, 2, 4, 6, 5, 3, 4′, 6′, 5′, 3′, and -CH_2CH_2-), 1.76 (s, about 17.4 H, -(H_3C)C=N-); ^{13}C-NMR (D_2O, ppm) δ_C: 175.8 (-OCH_2**C**=N-), 152.1 (-N=**C**HPh), 136.1, 130.5, 128.7, 127.2 (aromatic carbons), 102.0 ~ 100.1 (C-1, 1′), 81.6 ~ 80.1(C-4, 4′), 76.6 ~ 65.1 (O**C**H_2 CN-, C-2′, 3, 2, 5, 3', 5′), 61.5 ~ 58.8 (C-6, 6′, -**C**H_2N=CHPh), 38.9 (=NCH_2-), 24.0 (-(H_3**C**)- CN-). Anal. calcd. for $C_{111.6}H_{116.4}O_{35.0}N_{11.6}$ • 2H_2O, C 60.49, H 5.26, N 7.34; found: C 60.41, H 5.30, N 7.31.

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References

1. C. J. Easton , S. F. Lincoln, *"Modified Cyclodextrins"*, Pub. Imperial College Press, London, **1999**.
2. D. Q. Yuan, R. G. Chen, H. M. Zhao, *You Ji Hua Xue (Chin. J. Org. Chem.)*, **1992**, (12), 126.
3. Y. Inoue, Y. Liu, L. H. Tong, B. J. Shen, D. S. Jin, *J. Am. Chem. Soc.*, **1993**, *115*, 10637.
4. J. Szejtli, *Proc. Int. Symp. Cyclodextin*, 4Th, Kluwer Dordrecht, **1988**.
5. J. Szejtli, *Minutes Int. Symp. Cyclodextin*, 6Th, Paris, Fr.: Stante, **1992**.
6. D. Bradley, *New Scientist*, **1992**, *1832*, 15.
7. A. Ueno, R. Breslow, *Tetrahedron Lett.*, **1982**, (23), 3451.
8. B. J. Shen, L. H. Tong, H. W. Zhang, D. S. Jin, *Youji Huaxue (Chin. J. Org. Chem.)*, **1991**, (11), 265.
9. A. W. Coleman, P. Zhang, H. Parrot-Lopez, C. C. Ling, M. Miocque, L. Mascrier, *Tetrahedron Lett.*, **1991**, 3997.
10. A. Gadelle, J. Defaye, *Angew. Chem. Int. Engl.*, **1991**, (1), 78.
11. P. R. Ashton, P. Ellwood, I. Staton, J. F. Stoddart, *Angew. Chem. Int. Ed. Engl.*, **1991**, (1), 81.
12. A. R. Khan, L. Barton, V. T. D'Souza, *J. Chem. Soc., Chem. Commun.*, **1992**, 1112.
13. A. Y. Hao, J. M. Lin, L. H. Tong, *J. Inclusion Phenomen.*, **1999**, *34*, 445.
14. A. W. Coleman, P. Zhang, C. C. Ling, H. Parot-Lopez, H. Galons, *Carbohydr. Res.*, **1992**, *224*, 307.
15. A. Y. Hao, X. L. Lin, L. M. Sun, J. H. Yang, *Synth. Commun.*, **2000**, *30* (20), 3703.

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