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A reliable synthesis of 2- and 6-amino-β-cyclodextrin and permethylated-β-cyclodextrin

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Abstract—A new, reliable method for the introduction of an amine group at positions 2 or 6 of β-cyclodextrin and permethyl-β-cyclodextrin is described. It involves selective tosylation followed by azide substitution and almost quantitative reduction with triphenylphosphine followed by hydrolysis of the phosphinimine intermediate.

Cyclodextrins and their derivatives are of interest primarily because of their ability to form inclusion complexes with hydrophobic guest molecules such as Class II drugs.[1–3] The relatively low solubility of native cyclodextrins in water as well as in organic solvents, however, is the principal limitation to inclusion complexation processes and reactions. Moreover, this poor solubility in organic solvents, in particular, makes them difficult to modify chemically and purify.[4] A synthetic challenge is the selective modification of the three different types of hydroxyl group on the hydrophilic surface of the toroidal structure. The more reactive primary hydroxyl (position 6) presents at the smaller opening of the toroid while the less reactive secondary hydroxyls (positions 2 and 3) appear at the larger opening. A number of groups have made the more water soluble mono-6-amino-6-deoxy-β-cyclodextrin hydrochloride by tosylation of the primary (6-) hydroxyl and displacement with ammonia under pressure (10^6 N m^{-2}, 18 h)[5] or by displacement of tosylate by azide followed by catalytic hydrogenation.[6,7] These reports of both procedures indicate low yields, incomplete reactions and/or impure products. There has been no reported synthesis of the organic soluble permethylated derivative or of amination at the less reactive 2- or 3-positions. We now report a much-improved synthesis of mono-6-amino-6-deoxy-β-cyclodextrin and the first syntheses of the corresponding 2-amino constitutional isomer and of 2- and 6-amino-6-deoxypermethyl-β-cyclodextrin.

Our modified synthetic approach for mono-6-amino-6-deoxy-β-cyclodextrin **4a** consists of three steps from β-cyclodextrin, all of which proceed in much better yield than previously reported (Scheme 1). Mono-6-(*p*-toluenesulfonyl)-β-cyclodextrin **2**, prepared from β-CD **1** by a selective tosylation as previously reported by Brady,[8] was converted to the mono-6-azido-6-deoxy-β-cyclodextrin **3a** by excess sodium azide in water. Reduction of **3a** was achieved with triphenylphosphine in DMF followed by hydrolysis of the phosphinimine intermediate to provide **4a** in almost quantitative yield.[9] Titration of **4a** with dilute hydrochloric acid gave the highly water soluble mono-6-ammonium-β-CD chloride **5a**. The corresponding 2-amino isomer **8a** and hydrochloride **9a** were made by the same sequence of reactions but starting from the secondary tosylate prepared as described by Murakami and co-workers and in approximately the same yield.[10–13]

The monoazido-β-cyclodextrins **3a** and **7a** were permethylated to provide **3b**[14] and **7b**[15] and reduced with triphenylphosphine and water to provide amines **4b**[16] and **8b**.[17] Titration with hydrochloric acid yielded

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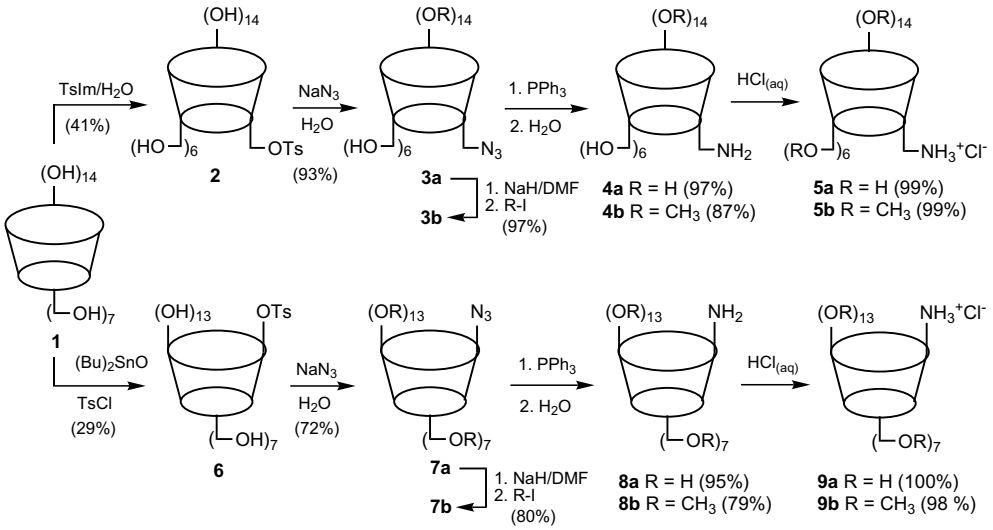

Scheme 1.

ammonium hydrochlorides **5b** and **9b**, which are soluble in water as well as in polar organic solvents.

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9. Mono-6-amino-6-deoxy-β-cyclodextrin **4a**: Triphenylphosphine (2.89 g, 11.0 mmol) was stirred with **3a** (11.60 g, 10.0 mmol) in DMF (20 mL) for 2 h. Deionized water (2.5 mL) was added and the solution refluxed for 30 min. Addition of acetone precipitated a white solid which was filtered, washed with acetone and dried under high vacuum for 16 h. Yield 11.0 g (97%); mp 215 °C (dec.). IR (KBr) *v*: 3428, 3311, 2928, 1659, 1438, 1414, 1389, 1369, 1334, 1156, 1080, 1030, 947, 755, 707, 609, 580 cm^{-1}. MS ESI (*m*/*z*): 1134.50 ($M+H^+$), calcd 1134.30. ^1H NMR (300 MHz, DMSO-d_6) δ: 3.34 (m, 30H, H-3,5, H-6, NH_2), 3.56–3.65 (m, 14H, H-2,4), 4.43–4.46 (m, 6H, OH-6), 4.83 (d, 6H, $J = 2.0$ Hz, H-1), 4.89 (d, 1H, $J = 2.0$ Hz, H-1′), 5.61–5.77 (m, 14H, OH-2,3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 41.7 (C-6′), 59.9 (C-6), 72.0 (C2), 72.4 (C-3), 73.0 (C-5), 81.5, 81.6, 82.8 (C-4), 101.9 (C-1).
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11. Mono-2-azido-2-deoxy-β-cyclodextrin **7a**: A mixture of **6** (5.0 g, 4.0 mmol) and sodium azide (3.90 g, 60 mmol) in water (20 mL) was stirred at 80 °C for 3 days. The resulting solution was then concentrated to half its volume and acetone (10 mL) added to precipitate a white solid which was redissolved in water (10 mL) and reprecipitated with acetone (10 mL). This process was repeated a further time to provide 3.25 g of product (yield 72%); mp 220 °C (dec.). MS ESI (*m*/*z*): calcd 1159 $[M]^+$, found 1158.6 $[M]^+$; calcd 1182 $[M+Na]^+$, found 1182.6 $[M+Na]^+$. Anal. for $C_{42}H_{69}O_{34}N_3{\cdot}4H_2O$; found C = 40.21%; H = 6.86%; N = 3.28%, calcd C = 40.19%; H = 6.25%; N = 3.41%. IR (KBr) *v*: 3229 (OH), 2928 (C-H); 2117 ($N_{3\,str}$); 1659, 1417, 1339 (C-H), 1155, 1079, 1022 (C–O_{str}). ^1H NMR (500 MHz, DMSO-d_6) δ: 3.60–3.67 (m, 14H, H-6), 3.81–3.95 (m, 28H, H-3,5, H-2,4), 4.5 (s, 7H, OH-6); 4.8 (m, 7H, H-1); 5.6–5.8 (br s, 13H, OH-2,3). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 59.9 (C-6); 61.4 (C-3′); 70.2 (C-5′); 72.0 (C-5); 72.2 (C-2); 73.0 (C-3); 80.2 (C-2′); 81.2 (C-4′); 81.7 (C-4); 102.8 (C-1); 103.2 (C-1′).
12. Mono-2-amino-2-deoxy-β-cyclodextrin **8a**: Yield 95%; mp. 223 °C (dec.). IR (KBr) *v*: 3246, 2928, 1645, 1417, 1368, 1156, 1001, 943, 858, 759, 709 cm^{-1}. MS ESI (*m*/*z*):1134.60 ($M+H^+$), calcd 1134.30. ^1H NMR (300 MHz, DMSO-d_6) δ: 3.30–3.36 (m, 14H, H-6), 3.60 (m, 30H, H-3,5, H-2,4, NH_2), 4.57 (br s, 7H, OH-6), 4.82 (d, 7H, $J = 2.84$ Hz, H-1), 5.73 (br s, 13H, OH-2,3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 59.8 (C-6), 71.5 (C-5′), 71.9 (C-5), 72.1 (C-2′), 72.2 (C-2), 72.7 (C-3′), 72.9 (C-3), 80.0 (C-4′), 81.4 (C-4), 101.8 (C-1), 103.8 (C-1′). Mono-2-ammonium-2-deoxy-β-cyclodextrin chloride **9a**: Yield 100%; mp 216 °C (dec.). IR (KBr dish) *v*: 3388, 2930, 1638, 1414, 1336, 1156, 1078, 1029, 947, 758, 708, 579 cm^{-1}. MS ESI (*m*/*z*): 1134.60 ($M+H^+$), calcd 1134.30. ^1H NMR (300 MHz, DMSO-d_6) δ: 3.31–3.44 (m, 14H, H-6), 3.61 (m, 31H, H-3,5, H-2,4, $^+NH_3$), 4.56 (br s, 7H, OH-6), 4.68–5.05 (m, 7H, H-1), 5.61–5.93 (m, 13H, OH-2,3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 60.2 (C-6), 72.0 (C-2′), 72.3 (C-5), 72.6 (C-2), 73.3 (C-3), 81.8 (C-4), 102.2 (C-1), 103.2 (C-1′).

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14. Mono-6-azido-6-deoxy-permethyl-β-cyclodextrin **3b**: Yield 97%; mp 106–108 °C; $[\alpha]_D = +157$ (*c* 0.01, $CHCl_3$). IR (KBr) *v*: 2929, 2834, 2104 (N_3), 1640, 1458, 1367, 1161, 1141, 1107, 1040, 970, 856, 756, 707, 558 cm^{-1}. Anal. for $C_{62}H_{109}N_3O_{34}\cdot 2H_2O$; found C = 50.38%, H = 7.70%, N = 2.76%, calcd C = 50.42%, H = 7.73%, N = 2.85%. MS ESI (*m*/*z*): 1462.60 ($M+Na^+$, 100), calcd 1462.68. ^1H NMR (300 MHz, $CDCl_3$) *δ*: 3.14–3.18 (m, 7H, H-5), 3.37 (s, 18H, 6-OCH_3), 3.48 (s, 21H, 3-OCH_3), 3.37–3.58 (m, 21H, H-3,6), 3.61 (s, 21H, 2-OCH_3), 3.68–3.92 (m, 14H, H-2,4), 5.03 (d, 1H, *J* = 3.6 Hz, H-1′), 5.10 (d, 6H, *J* = 3.6 Hz, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 52.0 (C-6′), 58.4–58.6 (2-OCH_3), 58.8 (6-OCH_3), 61.2, 61.3, 61.4 (3-OCH_3), 70.7, 70.8, 71.0 (C-5), 71.2, 71.3, 71.5 (C-6), 79.9, 80.0, 80.2, 88.3 (C-4), 81.3, 81.7 (C-2), 81.8, 82.0 (C-3), 98.3, 98.8, 99.0, 99.2 (C-1).
15. Mono-2-azido-2-deoxy-permethyl-β-cyclodextrin **7b**: Yield 80%; mp 73–75 °C. IR (KBr) *v*: 2879, 2108 (N_3), 1680, 1463, 1387, 1002, 950, 909, 857, 756, 705, 660, 555 cm^{-1}. MS ESI (*m*/*z*): 1462.60 ($M+Na^+$), calcd 1462.70. ^1H NMR (300 MHz, $CDCl_3$) *δ*: 3.12–3.16 (m, 7H, H-5), 3.34 (s, 21H, 6-OCH_3), 3.46 (s, 21H, 3-OCH_3), 3.42–3.57 (m, 21H, H-3,6), 3.60 (s, 18H, 2-OCH_3), 3.74–3.83 (m, 14H, H-2,4), 4.97 (d, 1H, *J* = 3.6 Hz, H-1′), 5.03–5.4 (m, 6H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 58.4 (2-OCH_3), 58.8 (6-OCH_3), 61.2 (3-OCH_3), 70.4, 70.8 (C-5), 71.2 (C-6), 78.5 (C-2′), 80.1 (C-4), 81.6 (C-2), 81.9 (C-3), 82.6 (C-3′), 98.8 (C-1), 99.8 (C-1′).
16. Mono-6-amino-6-deoxy-permethyl-β-cyclodextrin **4b**: A solution of triphenylphosphine (2.89 g, 11.0 mmol) and **3b** (14.41 g, 10.0 mmol) in acetone (25 mL) was stirred at room temperature for 2 h and then water (2.5 mL) added and the solution refluxed for 30 min. The acetone was removed and water (50 mL) added to precipitate to triphenylphosphine oxide which was removed by filtration. The aqueous filtrate was extracted (3 × 75 mL, CH_2Cl_2), and the combined organic extracts dried (Na_2SO_4) and concentrated to give a crude product which was recrystallized from CH_2Cl_2/hexane (1:5) to give pale yellow solid (12.31 g, 87%); mp 121–123 °C. IR (KBr) *v*: 3447 (NH_2), 2931, 2835, 1640, 1460, 1369, 1161, 1103, 1038, 970, 857, 755, 704, 544 cm^{-1}. MS ESI (*m*/*z*): 1414.50 ($M+H^+$), calcd 1414.70. ^1H NMR (500 MHz, DMSO-d_6) *δ*: 3.05–3.09 (m, 14H, H-3,5), 3.24 (s, 18H, 6-OCH_3), 3.30–3.46 (m, 16H, H-6 and NH_2), 3.39 (s, 21H, 3-OCH_3), 3.50 (s, 21H, 2-OCH_3), 3.79 (m, 14H, H-2,4), 5.05 (d, 6H, *J* = 3.6 Hz, H-1), 5.15 (d, 1H, *J* = 3.6 Hz, H-1′). ^{13}C NMR (125 MHz, DMSO-d_6) *δ*: 41.6 (C-6′), 57.9 (2-OCH_3), 58.1 (6-OCH_3), 60.6 (3-OCH_3), 70.4 (C-5), 71.1 (C-6), 79.6 (C-4), 81.3 (C-2), 81.6 (C-3), 97.7 (C-1). Mono-6-ammonium-6-deoxy-permethyl-β-cyclodextrin chloride **5b**: Yield 99%; mp 136–138 °C. IR (KBr) *v*: 3442 ($^+NH_3$), 2928, 1638, 1456, 1414, 1370, 1335, 1156, 1080, 1029, 756, 707, 579 cm^{-1}. MS ESI (*m*/*z*): 1414.60 (M^+), calcd 1414.70. ^1H NMR (300 MHz, DMSO-d_6) *δ*: 3.04–3.08 (m, 14H, H-3,5), 3.25 (s, 18H, 6-OCH_3), 3.31–3.47 (m, 17H, H-6 and $^+NH_3$), 3.40 (s, 21H, 3-OCH_3), 3.51 (s, 21H, 2-OCH_3), 3.80 (m, 14H, H-2,4), 5.06 (d, 6H, *J* = 3.6 Hz, H-1), 5.16 (d, 1H, *J* = 3.6 Hz, H-1′). ^{13}C NMR (75 MHz, DMSO-d_6) *δ*: 41.5 (C-6′), 57.8 (2-OCH_3), 58.2 (6-OCH_3), 60.7 (3-OCH_3), 70.5 (C-5), 71.2 (C-6), 79.7 (C-4), 81.4 (C- 2), 81.7 (C-3), 97.8 (C-1).
17. Mono-2-amino-2-deoxy-permethyl-β-cyclodextrin **8b**: Yield 79%; mp 93–95 °C. IR (KBr) *v*: 3510 (NH_2), 2930, 2834, 1680, 1460, 1368, 1140, 1101, 1036, 970, 857, 702, 544 cm^{-1}. MS ESI (*m*/*z*): 1414.50 ($M+H^+$), calcd 1414.70. ^1H NMR (300 MHz, $CDCl_3$) *δ*: 3.14–3.19 (m, 7H, H-5), 3.24 (t, 1H, *J* = 4.8 Hz, H-3′), 3.36 (s, 21H, 6-OCH_3), 3.48 (s, 21H, 3-OCH_3), 3.45–3.64 (m, 22H, H-3,6, NH_2), 3.62 (s, 18H, 2-OCH_3), 3.74–3.93 (m, 13H, H-2,4), 4.03 (dd, 1H, *J* = 3.21 Hz, H-4′), 4.96 (d, 1H, *J* = 3.6 Hz, H-1′), 5.04–5.14 (m, 6H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 58.4 (2-OCH_3), 58.8 (6-OCH_3), 61.3 (3-OCH_3), 70.9 (C- 5), 71.3 (C-6), 80.1 (C-4), 81.0 (C-2′), 81.7 (C-2), 82.4 (C-3), 98.8 (C-1), 102.5 (C-1′). Mono-2-ammonium-2-deoxy-permethyl-β-cyclodextrin chloride **9b**: Yield 98%; mp 108–110 °C. IR (KBr) *v*: 3491 ($^+NH_3$), 2930, 2834, 1641, 1461, 1369, 1193, 1140, 1089, 1038, 969, 857, 702, 544 cm^{-1}. MS ESI (*m*/*z*): 1414.60 (M^+), calcd 1414.70. ^1H NMR (300 MHz, $CDCl_3$) *δ*: 3.14–3.18 (m, 7H, H-5), 3.24 (t, 1H, *J* = 4.41 Hz, H-3′), 3.35 (s, 21H, 6-OCH_3), 3.48 (s, 21H, 3-OCH_3), 3.45–3.69 (m, 23H, H-3,6, $^+NH_3$), 3.61 (s, 18H, 2-OCH_3), 3.77–3.85 (m, 13H, H-2,4), 3.97 (dd, 1H, *J* = 3.21 Hz, H-4′), 5.03 (d, 1H, *J* = 2.82 Hz, H-1′), 5.07–5.13 (m, 6H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 58.8 (2-OCH_3), 59.6 (6-OCH_3), 62.0 (3-OCH_3), 71.6 (C-5), 72.0 (C-6), 80.9 (C-4), 82.4 (C-2), 82.7 9C-3, 83.5 (C-2′), 99.6 (C-1).