SYNTHESIS OF HEPTA-ARBUtin-BRANCHED β-CYCLODEXTRINS AT THEIR PRIMARY SIDES VIA CLICK REACTION

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Experimental

1. General

β-CyD, 2-propynyl bromide and 4-hydroxyphenyl β-D-glucopyranoside (arbutin) were purchased from Tokyo Chemical Industry Co. (Tokyo, Japan). 1H NMR (600 MHz) and 13C NMR (150 MHz) spectra were recorded on a JEOL ECA-600 spectrometer at 600 MHz (1H), and 150 MHz (13C). The MALDI-TOF-MS spectra were recorded on a Voyager DE STR spectrometer. Microwave-assisted synthesis was performed using a CEM Microwave Synthesizer Discover®. All reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F254 precoated plates (0.25 mm). Column chromatography was conducted using silica gel 60 N (40–50 μm, Kanto Chemical Co., INC.).

2. Preparation of 3

After 1 (5.01 g, 18.4 mmol) in 0.5 M NaOH aq. solution (37 mL, 19 mmol) was stirred for 20 min at room temperature, the solvent was evaporated under reduced pressure. To the reaction residue was added DMF (70 mL) and 2-propynyl bromide (1.7 mL, 22.6 mmol). After the reaction mixture was stirred for 24 h, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica-gel (chloroform/methanol = 10/1) to afford 3 (4.67 g, 82% yield) as amorphous crystal. 1H NMR (CD3OD): δ 2.90 (1H, t, J = 2.8 Hz, CH2CCH), 3.38-3.47 (4H, m, H-2, 3, 4, 5), 3.69 (1H, dd, J = 5.5 Hz, J = 12.4 Hz, Ha -6), 3.88 (1H, dd, J = 2.1 Hz, J = 12.4 Hz, Hb-6), 4.66 (2H, d, J = 2.7 Hz, CH2CCH), 4.78 (1H, d, J = 7.6 Hz, H-1), 6.90 (2H, d, J = 9.0 Hz, Ph), 7.05 (2H, d, J = 8.9 Hz, Ph); 13C NMR (CD3OD): δ 57.2 (CH2CCH), 62.5 (C-6), 71.4 (C-5), 74.9 (C-4), 76.6 (CH2CCH), 77.9 (C-2), 78.1 (C-3), 80.0 (CH2CCH), 103.3 (C-1), 116.9, 119.1, 153.8, 154.5 (Ph).

3. Preparation of 4
To a solution of 3 (2 g, 6.8 mmol) in pyridine (5.5 mL) was added acetic anhydride (11.0 mL). After the reaction mixture was stirred for 24 h at room temperature, the reaction was then quenched by adding citric acid aq. solution (5 mL). The mixture was extracted with EtOAc (three times) and the combined organic solvent was dried over anhydrous Na$_2$SO$_4$. The organic solvent was filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica-gel (hexane/ethyl acetate = 3/1) to afford 4 (2.8g, 91% yield) as amorphous crystal. $^1$H NMR (CDCl$_3$): $\delta$ 2.04 (3H, s, Ac), 2.05 (3H, s, Ac), 2.08 (3H, s, Ac), 2.08 (3H, s, Ac), 2.52 (1H, t, $J$ = 2.1 Hz, CH$_2$CCH), 3.78-3.83 (1H, m, H-5), 4.16 (1H, dd, $J$ = 2.8 Hz, $J$ = 12.4 Hz, H$_a$-6), 4.29 (1H, dd, $J$ = 5.5 Hz, $J$ = 12.3 Hz, H$_b$-6), 4.65 (2H, d, $J$ = 2.1 Hz, CH$_2$CCH), 4.97 (1H, d, $J$ = 7.6 Hz, H-1), 5.16 (1H, t, $J$ = 9.0 Hz, H-4), 5.22-5.30 (2H, m, H-2, 3), 6.19 (2H, d, $J$ = 9.6 Hz, Ph), 6.96 (2H, d, $J$ = 9.0 Hz, Ph); $^{13}$C NMR (CDCl$_3$): $\delta$ 20.56, 20.59, 20.62, 20.67 (Ac), 56.3 (CH$_2$CCH), 61.9 (C-6), 68.3 (C-4), 71.2 (C-3), 71.9 (C-5), 72.7 (C-2), 75.5 (CH$_2$CCH), 78.5 (CH$_2$CCH), 100.0 (C-1), 115.9, 118.5, 151.5, 153.6 (Ph), 169.2, 169.4, 170.2, 170.6 (C=O).

4. Preparation of 7
Sodium ascorbate (8.4 mg, 0.042 mmol) and copper(II) sulfate (14.1 mg, 0.056 mmol) were added to a solution of 4 (217.1 mg, 0.45 mmol) and 6 (102.4 mg, 0.054 mmol) in THF (3.5 mL)–H$_2$O (3.5 mL). After the reaction mixture was heated up to 70 °C by microwave irradiation at 18 W for 40 min, the reaction was quenched by adding sat. NaCl aq. solution (3 mL). The mixture was extracted with EtOAc (three times), and the combined organic solvent was dried over anhydrous Na$_2$SO$_4$. The organic solvent was filtered and evaporated under reduced pressure. The crude product was purified by preparative silica-gel TLC (CH$_2$Cl$_2$/MeOH = 15/1) to afford 7 (263.2 mg, 93% yield) as a colorless oil. $^1$H NMR (CDCl$_3$): $\delta$ 2.02-2.08 (126H, m, Ac), 3.55 (7H, t, $J$ = 8.2 Hz, CD-4), 3.89-3.90 (7H, m, Arb-5), 4.16 (7H, m, CD-5, CD-6a), 4.29 (7H, dd, $J$ = 4.8 Hz, $J$ = 12.4 Hz, Arb-6a), 4.40-4.81 (14H, m, CD-5, CD-6a), 4.75 (7H, dd, $J$ = 3.41 Hz, $J$ = 10.4 Hz, CD-2), 4.76-4.84 (7H, m, CD-6b), 4.95-4.99 (14H, m, CH$_2$CCH), 5.01 (7H, d, $J$ = 8.2 Hz, Arb-1), 5.17 (7H, t, $J$ = 9.6 Hz, Arb-4), 5.22 (7H, t, $J$ = 7.5 Hz, Arb-3), 5.28-5.31 (7H, m, Arb-2), 5.47 (7H, d, $J$ = 3.4 Hz, CD-1), 6.83 (14H, d, $J$ = 8.9 Hz, Ph), 6.90 (14H, d, $J$ = 8.9 Hz, Ph), 7.56 (7H, s, CH$_2$CCHN); $^{13}$C NMR (CDCl$_3$): $\delta$ 20.58, 20.63, 20.64, 20.69, 20.72, 20.76 (Ac), 50.2 (CD-6), 61.8 (Arb-6), 62.0 (OCH$_2$-triazole), 68.3 (Arb-4), 69.8 (CD-5), 69.9 (CD-2), 70.4 (CD-3), 71.2 (Arb-3), 71.8 (Arb-5), 72.8 (Arb-2), 77.2 (CD-4), 96.1 (CD-1), 99.9 (Arb-1), 115.5, 118.5 (Ph), 125.9 (CH$_2$CCH), 143.6 (CH$_2$CCH), 151.3, 154.3 (Ph), 169.3, 169.3, 169.4, 170.2, 170.5, 170.6 (C=O); MALDI-TOF MS: m/z calcd for C$_{231}$H$_{273}$N$_{21}$O$_{119}$ •Na$: 5267.58; found 5265.24.

5. Preparation of 8
A 28% sodium methylate methanol solution (0.3 mL, 0.002 mmol) was added to a solution of 7 (266.2 mg, 0.05 mmol) in MeOH (5 mL). The resulting mixture was stirred for 16 h. The solvent was evaporated under reduced pressure. The crude product was purified by reprecipitation in MeOH to
afford 8 (157.2 mg, 88% yield) as amorphous crystal. (Data of $^1$H NMR and $^{13}$C NMR, see Reference 16)

6. Preparation of 10
To a solution of 9 (692 mg, 2.98 mmol) in DMF (10 mL) was added triphenylphosphine (1.17 g, 4.47 mmol) and iodine (1.14 g, 4.49 mmol) at 40 oC under an argon atmosphere. After the reaction mixture was stirred for 24 h, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica-gel (hexane/ethyl acetate = 8/1) to afford 10 (763.6 mg, 75% yield) as a colorless oil. $^1$H NMR (CDCl$_3$): $\delta$ 2.44 (1H, t, J = 1.4 Hz, CH$_2$CCH), 3.26 (2H, t, J = 6.9 Hz, ICH$_2$), 3.66-3.77 (14H, m, OCH$_2$CH$_2$), 4.21 (2H, d, J = 1.4 Hz, CH$_2$CCH); $^{13}$C NMR (CDCl$_3$): $\delta$ 2.9 (ICH$_2$), 58.4 (CH$_2$CCH), 69.0, 70.1, 70.4, 70.5, 70.6 (OCH$_2$CH$_2$), 71.9 (CH$_2$CH$_2$I), 74.5 (CH$_2$CCH), 79.6 (CH$_2$CCH).

7. Preparation of 12
The above similar procedure (preparation of 10) using 11 (341 mg, 0.83 mmol), triphenylphosphine (654 mg, 2.49 mmol) and iodine (631.1 mg, 2.49 mmol) in DMF (3.5 mL) afforded 12 (368 mg, 85% yield) as a colorless oil. $^1$H NMR (CDCl$_3$): $\delta$ 2.37 (1H, t, J = 2.1 Hz, CH$_2$CCH), 3.19 (2H, t, J = 6.8 Hz, ICH$_2$), 3.58-3.63 (28H, m, OCH$_2$CH$_2$), 3.69 (2H, t, J = 6.8 Hz, ICH$_2$CH$_2$), 4.13 (2H, d, J = 2.8 Hz, CH$_2$CCH); $^{13}$C NMR (CDCl$_3$): $\delta$ 2.9 (ICH$_2$), 58.3 (CH$_2$CCH), 69.1-70.6 (OCH$_2$CH$_2$), 71.9 (CH$_2$CH$_2$I), 74.5 (CH$_2$CCH), 79.6 (CH$_2$CCH).

8. Preparation of 13
The above similar procedure (preparation of 3) using sodium salt of 1 (100.6 mg, 0.37 mmol) and 10 (126.4 mg, 0.37 mmol) in DMF (2 ml) afforded 13 (135.8 mg, 76% yield) as a colorless oil. $^1$H NMR (CD$_3$OD): $\delta$ 2.75 (1H, d, J = 1.4 Hz, CH$_2$CCH), 3.24-3.29 (2H, m, H-3, 5), 3.30-3.34 (2H, m, H-2, 4), 3.52-3.58 (12H, m, OCH$_2$CH$_2$), 3.60 (1H, m, H-6), 3.70 (2H, d, J = 2.0 Hz, OCH$_2$CH$_2$), 3.78 (1H, d, J = 12.3 Hz, Hs-6), 3.96 (2H, d, J = 2.7 Hz, OCH$_2$CH$_2$), 4.07 (2H, s, CH$_2$CCH), 4.67 (1H, d, J = 7.6 Hz, H-1), 6.76 (2H, d, J = 6.9 Hz, Ph), 6.95 (2H, d, J = 7.6 Hz, Ph); $^{13}$C NMR (CD$_3$OD): $\delta$ 59.0 (CH$_2$CCH), 62.4 (C-6), 69.0, 70.0, 70.8, 71.21 (OCH$_2$CH$_2$), 71.25 (C-5), 71.38, 71.42, 71.6 (OCH$_2$CH$_2$), 74.8 (C-4), 75.9 (CH$_2$CCH), 77.8 (C-2), 77.9 (C-3), 80.5 (CH$_2$CCH), 103.1 (C-1), 116.2, 118.9, 153.0, 155.3 (Ph).

9. Preparation of 15
The above similar procedure (preparation of 3) using sodium salt of 1 (20.8 mg, 0.076 mmol) and 12 (37.5 mg, 0.072 mmol) in DMF (1 ml) afforded 15 (29.1 mg, 61% yield) as a colorless oil. $^1$H NMR (CDCl$_3$): $\delta$ 2.47 (1H, t, J = 2.0 Hz, CH$_2$CCH), 3.00 (1H, bs, H-5), 3.30 (1H, d, J = 6.9 Hz, H$_s$-6), 3.36-3.79 (31H, m, OCH$_2$CH$_2$, H$_s$-6), 3.98-4.04 (2H, m, OCH$_2$CH$_2$), 4.18 (2H, d, J = 2.0 Hz, CH$_2$CCH), 4.76 (1H, bs, H-1), 4.89 (1H, bs, H-4), 5.03 (1H, bs, H-2), 5.40 (1H, bs, H-3), 6.75 (2H, d, J = 8.9 Hz,
Ph), 6.93 (2H, d, J = 8.9 Hz, Ph); $^{13}$C NMR (CDCl$_3$): δ 58.3 (CH$_2$CCH), 61.3 (C-6), 69.0 (OCH$_2$CH$_2$), 69.4 (C-4), 69.7, 70.3, 70.4, 70.4, 70.4, 70.6 (OCH$_2$CH$_2$), 73.2 (C-5), 74.7 (CH$_2$CCH), 75.6 (C-2), 76.2 (C-3), 79.6 (CH$_2$CCH), 102.0 (C-1), 115.3, 118.3, 151.0, 154.0 (Ph).

10. Preparation of 14
The above similar procedure (preparation of 4) using 13 (297.4 mg, 0.61 mmol) and acetic anhydride (10 mL) in pyridine (5 mL) afforded 14 (378.1 mg, 95% yield) as amorphous crystal. $^1$H NMR (CDCl$_3$): δ 2.03 (3H, s, Ac), 2.04 (3H, s, Ac), 2.08 (3H, s, Ac), 2.09 (3H, s, Ac), 2.43 (1H, t, J = 2.8 Hz, CH$_2$CCH), 3.56-3.73 (12H, m, OCH$_2$CH$_2$), 3.79-3.82 (1H, m, H-5), 3.83-3.84 (2H, m, OCH$_2$CH$_2$), 4.08-4.09 (2H, m, OCH$_2$CH$_2$), 4.16 (1H, dd, J = 2.8 Hz, J = 12.4 Hz, H$_a$-6), 4.20 (2H, d, J = 2.8 Hz, CH$_2$CCH), 4.29 (1H, dd, J = 5.5 Hz, J = 12.4 Hz, H$_b$-6), 4.95 (1H, d, J = 7.6 Hz, H-1), 5.16 (1H, t, J = 9.6 Hz, H-4), 5.22-5.30 (2H, m, H-2, 3), 6.83 (2H, d, J = 9.0 Hz, Ph), 6.93 (2H, d, J = 8.9 Hz, Ph); $^{13}$C NMR (CDCl$_3$): δ 20.61, 20.62, 20.67, 20.7 (Ac), 58.4 (CH$_2$CCH), 61.9 (C-6), 68.0 (OCH$_2$CH$_2$), 68.3 (C-4), 69.1 (OCH$_2$CH$_2$), 69.8 (C-5), 70.4, 70.61, 70.62, 70.64, 70.8 (OCH$_2$CH$_2$), 71.2 (C-2), 72.0 (OCH$_2$CH$_2$), 72.8 (C-3), 74.5 (CH$_2$CCH), 79.7 (CH$_2$CCH), 100.3 (C-1), 115.4, 118.6, 151.0, 155.0 (Ph), 169.3, 169.4, 170.3, 170.6 (C=O).

11. Preparation of 16
The above similar procedure (preparation of 4) using 15 (29.1 mg, 0.056 mmol) and acetic anhydride (2 mL) in pyridine (1 mL) afforded 16 (32.9 mg, 90% yield) as a colorless oil. $^1$H NMR (CDCl$_3$): δ 2.03 (3H, s, Ac), 2.04 (3H, s, Ac), 2.08 (3H, s, Ac), 2.09 (3H, s, Ac), 2.45 (1H, t, J = 2.5 Hz, CH$_2$CCH), 3.64-3.73 (28H, m, OCH$_2$CH$_2$), 3.80-3.82 (1H, m, H-5), 3.82-3.85 (2H, m, OCH$_2$CH$_2$), 4.07-4.09 (2H, m, OCH$_2$CH$_2$), 4.16 (1H, dd, J = 2.5 Hz, J = 12.2 Hz, H$_a$-6), 4.20 (2H, d, J = 2.4 Hz, CH$_2$CCH), 4.29 (1H, dd, J = 5.1 Hz, J = 12.2 Hz, H$_b$-6), 4.95 (1H, d, J = 7.5 Hz, H-1), 5.16 (1H, t, J = 9.2 Hz, H-4), 5.21-5.28 (2H, m, H-2, 3), 6.82 (2H, d, J = 9.0 Hz, Ph), 6.92 (2H, d, J = 9.1 Hz, Ph); $^{13}$C NMR (CDCl$_3$): δ 20.6, 20.63, 20.67, 20.73 (Ac), 58.3 (CH$_2$CCH), 61.9 (C-6), 67.9 (OCH$_2$CH$_2$), 68.2 (C-4), 69.0 (OCH$_2$CH$_2$), 69.7 (C-5), 70.3-70.7 (OCH$_2$CH$_2$), 71.1 (C-2), 71.9 (OCH$_2$CH$_2$), 72.7 (C-3), 74.5 (CH$_2$CCH), 79.6 (CH$_2$CCH), 100.1 (C-1), 115.3, 118.5, 150.9, 154.8 (Ph), 169.1, 169.2, 170.3, 170.4 (C=O).

12. Preparation of 17
The above similar procedure (preparation of 7) using sodium ascorbate (5.7 mg, 0.029 mmol), copper(II) sulfate (9.5 mg, 0.035 mmol), 14 (200.6 mg, 0.306 mmol) and 6 (69.1 mg, 0.036 mmol) in THF (2.4 mL)-H$_2$O (2.4 mL) afforded 17 (221 mg, 94% yield) as amorphous crystal. $^1$H NMR (CDCl$_3$): δ 1.94-2.08 (126H, m, Ac), 3.51 (1H, t, J = 8.3 Hz, CD-4), 3.62-3.71 (84H, m, OCH$_2$CH$_2$), 3.81-3.82 (21H, m, Arb-5, OCH$_2$CH$_2$), 4.06 (14H, t, J = 4.8 Hz, OCH$_2$-triazole), 4.15 (7H, d, J = 11.6 Hz, Arb-6a), 4.29 (7H, dd, J = 5.5 Hz, J = 12.4 Hz, Arb-6b), 4.47-4.49 (7H, m, CD-5), 4.52-4.57 (14H, m, OCH$_2$CH$_2$), 4.72-4.74 (14H, m, CD-2, CD-6a), 4.85 (7H, d, J = 13.2 Hz, CD-6b), 4.95 (7H, d, J =
13. Preparation of 19
The above similar procedure (preparation of 7) using sodium ascorbate (0.9 mg, 0.005 mmol), copper(II) sulfate (1.6 mg, 0.006 mmol), 16 (32.9 mg, 0.040 mmol) and 6 (11.3 mg, 0.006 mmol) in THF (0.4 mL)-H2O (0.4 mL) afforded 19 (40.2 mg, 87% yield) as amorphous crystal. 1H NMR (CDCl3): δ 2.02 (21H, s, Ac), 2.03 (21H, s, Ac), 2.04 (21H, s, Ac), 2.06 (21H, s, Ac), 2.07 (21H, s, Ac), 2.08 (21H, s, Ac), 3.53 (7H, t, J = 8.2 Hz, CD-4), 3.61-3.72 (196H, m, OCH2CH2), 3.80-3.82 (7H, m, Arb-5), 3.82-3.84 (14H, m, OCH2CH2), 4.08 (14H, t, J = 4.8 Hz, OCH2-triazole), 4.16 (7H, dd, J = 2.1 Hz, J = 12.4 Hz, Arb-6a), 4.29 (7H, dd, J = 5.5 Hz, J = 12.4 Hz, Arb-6b), 4.43-4.44 (7H, m, CD-5), 4.48-4.52 (14H, m, OCH2CH2), 4.69-4.70 (14H, m, CD-2, CD-6a), 4.81 (7H, d, J = 13.1 Hz, CD-6b), 4.96 (7H, d, J = 8.3 Hz, Arb-1), 5.16 (7H, t, J = 9.6 Hz, Arb-4), 5.22-5.31 (14H, m, Arb-2, 3), 5.36 (7H, t, J = 9.0 Hz, CD-3), 5.51 (7H, d, J = 2.0 Hz, CD-1), 6.83 (14H, d, J = 9.0 Hz, Ph), 6.93 (14H, d, J = 9.0 Hz, Ph), 7.76 (7H, s, CH2CCHN); 13C NMR (CDCl3): δ 20.5, 20.60, 20.60, 20.65, 20.65, 20.7 (Ac), 49.9 (CD-6), 61.8 (Arb-6), 64.4 (OCH2-triazole), 67.8 (OCH2CH2), 68.2 (Arb-4), 69.7 (CD-5), 69.7 (OCH2CH2), 69.9 (Arb-5), 70.2 (CD-2), 70.3-70.5 (OCH2CH2), 70.7 (CD-3), 70.7 (OCH2CH2), 71.2 (Arb-2), 71.9 (OCH2CH2), 72.7 (Arb-3), 76.4 (CD-4), 96.2 (CD-1), 100.2 (Arb-1), 115.3, 118.6 (Ph), 125.6 (CH2CCH2), 144.8 (CH2CCH), 151.0, 154.9 (Ph), 169.2, 169.3, 170.2, 170.2, 170.3, 170.5 (C=O); MALDI-TOF MS: m/z calcd for C287H385N21O147•Na+: 6477.33; found 6479.71.

14. Preparation of 18
The above similar procedure (preparation of 8) using 17 (124.3 mg, 0.019 mmol) in the presence of NaOMe (0.3 mL of a 28% sodium methylate methanol solution, 0.002 mmol) in MeOH (1 mL)-THF (0.5 mL) afforded 18 (87.8 mg, 97% yield) as amorphous crystal. (Data of 1H NMR and 13C NMR, see Reference 18)

15. Preparation of 20
The above similar procedure (preparation of 8) using 19 (34.7 mg, 0.0045 mmol) in the presence of NaOMe (0.3 mL of a 28% sodium methylate methanol solution, 0.002 mmol) in MeOH (2.5 mL)-THF (2.5 mL) afforded 19 (24.5 mg, 91% yield) as amorphous crystal. (Data of 1H NMR and 13C NMR, see Reference 19)