SUPPORTING INFORMATION

A Practical Total Synthesis of Globo-H for Use in Anticancer Vaccines

Insik Jeon,[1] Karthik Iyer,[1] and Samuel J. Danishefsky[1,2,*]

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Ethyl 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl-(1→2)-3,4-carbonyl-6-*O*-tri-isopropylsilyl-*β*-D-galactopyranosyl-(1→3)-6-*O*-tri-isopropylsilyl-2-deoxy-2-phenylsulfonlyamino-1-thio-*β*-D-galactopyranoside (7).[1] A solution of thiofucosyl donor **15** (2.38g, 4.41 mmol) and freshly activated 4 Å molecular sieves (2 g) in CH_2Cl_2/Et_2O (50 mL/25 mL) was stirred at rt for 1 h, then cooled to –78 °C. To the cooled solution was added AgOTf (3.4 g, 13.22 mmol) and 2,6-di-*tert*-butylpyridine (2.92 mL, 13.92 mmol). After 10 min, freshly distilled *p*-TolSCl (619.3 μL, 4.41 mmol) was added. After 40 minutes, the characteristic yellow color of *p*-TolSCl in the reaction solution disappeared, indicating depletion of *p*-TolSCl. A solution of acceptor **4** (2.85 g, 4.41 mmol) in CH_2Cl_2/Et_2O (6 mL/3 mL) was added dropwise via a syringe. The reaction mixture was warmed to rt under stirring over 3 h, and stirred for an additional 1 h at rt. The mixture was filtered over Celite and further washed with CH_2Cl_2. After evaporation of solvent in vacuo, the mixture was diluted with ethyl acetate then washed with a saturated aqueous solution of $NaHCO_3$, water, and brine and dried over $MgSO_4$. After removal of the solvent, the crude was purified via silica gel flash chromatography using 10-15% EtOAc/hexane to give 3.66 g (78%) of α-trisaccharide **6**.[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.29 (m, 15H,), 6.35 (d, *J* = 5.0 Hz, 1H), 5.01 (d, *J* = 3.7 Hz, 1H), 4.99 (d, *J* = 11.6 Hz, 1H), 4.92 (d, *J* = 4.7 Hz, 1H), 4.87 (d, *J* = 5.0 Hz, 1H), 4.84 (d, *J* = 11.6 Hz, 2H), 4.75 (d, *J* = 11.8 Hz, 1H), 4.71 (dd, *J* = 8.2, 3.6 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 2H), 4.54 (d, *J* = 6.3 Hz, 1H), 4.44 (m, 1H), 4.12-4.00 (m, 5H), 3.92-3.83 (m, 7H), 3.68 (m, 1H), 2.66 (d, *J* = 2.2 Hz, 1H), 1.15-1.07 (m, 45H); ESI-MS calcd for $C_{58}H_{86}O_{14}Si_2Na^+$ 1085.55 $(M + Na)^+$, found 1085.39. A mixture of trisaccharide glycal **6** (1 g, 0.94 mmol) and benzenesulfonamide (887 mg, 5.64 mmol) was azeotroped with C_6H_6 once and further dried on high vacuum for 1 h. It was dissolved in freshly distilled Et_2O (40 mL), and freshly activated 4 Å molecular sieves (1 g) was added. The resulting mixture was stirred at rt for 1 h, then cooled to –5 °C. To the solution was added I(*sym*-coll)$_2$$ClO_4$ (925 mg, 1.974 mmol) and the mixture was further stirred at –5 °C for 12 h. After filtration on Celite pad, the crude was washed with saturated $Na_2S_2O_3$ solution, saturated $CuSO_4$, brine and dried over $MgSO_4$. After concentration, the crude material, containing iodosulfonamide **17**, was immediately subjected to the next step without purification. To a solution of EtSH (695 μL, 9.4 mmol) in DMF (5 mL) was added lithium bis-(trimethylsilyl)amide (LHMDS, 1.0 M in THF, 4.7 mL, 4.7 mmol) at –45 °C. After 15 min of stirring, the solution was transferred dropwise via a cannula to a flask containing iodosulfonamide **17** in DMF (25 mL) at –45 °C. The reaction mixture was allowed to warm to rt and stirred for a total of 3 h. After dilution with saturated NH_4Cl, the crude was extracted four times with ethyl acetate. The combined extracts were washed with water and brine and dried over $MgSO_4$. Concentration and purification by silica gel chromatography (15-25% EtOAc in hexane) afforded 903 mg (75% over two steps) of DEF donor **7**. ^{1}H NMR (500 MHz, $CDCl_3$) δ7.90 (d, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.40-7.28 (m, 15H), 5.43 (s, 1H), 5.00 (d, *J* = 3.6 Hz, 1H), 4.98 (d, *J* = 11.6 Hz, 1H), 4.91 (d, *J* = 8.8 Hz, 1H), 4.84 (d, *J* = 7.9 Hz, 1H), 4.82 (d, *J* = 7.9 Hz, 1H), 4.74 (d, *J* = 11.8 Hz, 1H), 4.67-4.62 (m, 4H), 4.37 (d, *J* = 10.2 Hz, 1H), 4.12-4.08 (m, 4H), 4.00 (q, *J* = 6.5 Hz, 1H), 3.94-3.77 (m, 6H), 3.71 (s, 1H), 3.60-3.56 (m, 1H), 3.47 (m, 1H), 2.82 (m, 1H), 2.48-2.44 (m, 1H), 2.32-2.28 (m, 1H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.15-1.05 (m, 45H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.5, 140.7, 138.9, 138.8, 132.9, 129.0, 128.8, 128.6, 128.5, 128.4, 128.2, 128.0, 127.8, 127.8, 127.6, 99.7, 98.1, 83.8, 81.5, 79.4, 77.8, 76.7, 75.1, 74.4, 73.2, 73.1, 71.7, 71.7, 69.8, 68.1, 68.0, 62.2, 62.0, 55.4, 23.8, 18.2, 18.2, 18.1, 17.0, 14.7, 12.3, 12.1, 11.9; ESI-MS calcd for $C_{66}H_{97}O_{16}NS_2Si_2K^+$ 1318.54 $(M + K)^+$, found 1318.58.

4-Pentenyl 2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-*β*-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-*β*-D-glucopyranoside (8).[2] A solution of thiogalactosyl donor **16** (3.97g, 5.86 mmol) and freshly activated 4 Å molecular sieves (4 g) in CH_2Cl_2/ Et_2O (100 mL/50 mL) was stirred at rt for 1 h, then cooled to –78 °C. To the cooled solution was added AgOTf (4.52 g, 17.6 mmol) and 2,6-di-*tert*-butylpyridine (3.9 mL, 17.6 mmol). After 10 min, freshly distilled *p*-TolSCl (824 μL, 5.86 mmol) was added. After 10 minutes, the characteristic yellow color of *p*-TolSCl in the reaction solution disappeared, indicating depletion of *p*-TolSCl. A solution of acceptor **12** (4.65 g, 4.88 mmol) in CH_2Cl_2/ Et_2O (10 mL/5 mL) was added dropwise via a syringe. The reaction mixture was warmed to rt under stirring over 3 h, and then stirred for an additional 1 h at rt. The mixture was filtered over Celite and further washed with CH_2Cl_2. After evaporation of solvent in vacuo, the mixture was diluted with ethyl acetate then washed with a saturated aqueous solution of $NaHCO_3$, water, and brine and dried over Mg_2SO_4. After removal of the solvent, the crude was purified via silica gel flash chromatography using 15% EtOAc/hexane to give 5.55 g (76 %) of α-trisaccharide **13**. This PMB protected **13** (5.25 g, 3.49 mmol) in CH_2Cl_2 (130 mL) at 0 ^oC was treated with phosphate buffer (20 mL, pH 7.2) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.19 g, 5.24 mmol, 1.5 equiv.) and stirred at 0 ^oC for 5 h. The reaction mixture was diluted with saturated $NaHCO_3$ and further stirred at rt for 1 h. The mixture was extracted twice with CH_2Cl_2, then washed with brine, dried over $MgSO_4$, and concentrated to dryness. The crude material was purified by flash column chromatography using 16% EtOAc/hexane to give 4.06 g (84 %) of ABC acceptor **8**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 - 7.16 (m, 45 H), 5.89-5.81 (m, 1H), 5.13 (d, *J* = 3.1 Hz, 1H), 5.10 (d, *J* = 11.4 Hz, 1H), 5.06-4.99 (m, 2H), 4.91-4.85 (m, 2H), 4.81-4.71 (m, 6H), 4.85-4.49 (m, 5H), 4.43-4.38 (m, 3H), 4.31 (s, 2H), 4.19-4.03 (m, 5H), 3.99-3.95 (m, 3H), 3.84-3.80 (m, 2H), 3.76 (d, *J* = 10.0 Hz, 1H), 3.64-3.32 (m, 9H), 3.22 (dd, *J* =10.0, 5.0 Hz, 1H), 2.22-2.17 (m, 2H), 1.82-1.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 139.5, 138.8, 138.7, 138.7, 138.6, 138.5, 138.4, 138.3, 138.2, 138.1, 128.5, 128.4, 128.31, 128.30,128.28, 128.26, 128.24,128.15, 128.14, 128.06, 128.05, 127.82, 127.77, 127.73, 127.65, 127.64, 127.61, 127.58, 127.57, 127.52, 127.45, 127.2, 114.9, 103.6, 102.8, 99.7, 83.0, 81.8, 81.6, 79.4, 77.7, 75.3, 75.2, 75.2, 75.1, 75.0, 74.9, 73.2, 73.14, 73.08, 73.06, 73.00, 72.2, 70.0, 69.29, 69.25, 68.4, 67.8, 67.7, 60.4, 30.3, 29.0; ESI-MS calcd for $C_{86}H_{94}O_{16}Na^+$ 1405.64 $(M + Na)^+$; found: 1406.02.

4-Pentenyl 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl-(1→2)-3,4-carbonyl-6-*O*-tri-isopropylsilyl-*β*-D-galactopyranosyl-(1→3)-6-*O*-tri-isopropylsilyl-2-deoxy-2-phenylsulfonlyamino-*β*-D-galactopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-*β*-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-*β*-D-glucopyranoside (9).[2] The DEF donor **7** (2.13 g, 1.66 mmol) and ABC acceptor **8** (1.15 g, 0.831 mmol) were combined, azeotroped twice with anhydrous benzene (2 × 20 mL) and placed under high vacuum for 5 h. The mixture was then dissolved in CH_2Cl_2 (20 mL) and Et_2O (40 mL), treated with freshly activated 4 Å molecular sieves (2 g) and 2,6-di-*tert*-butylpyridine (734 μL, 3.32 mmol), then cooled to −78 ^oC. Methyl triflate (4.0 equiv, 365 μL) was added in one portion and the reaction was allowed to warm to rt slowly overnight. The reaction was quenched by the addition of Et_3N (5 mL), and filtered through Celite with Et_2O. The filtrate was washed with saturated $NaHCO_3$, and brine, and dried over $MgSO_4$. Concentration and purification by silica gel chromatography (15-20% EtOAc/hexane) afforded 1.551 g (72%) of hexasaccharide **9**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66 (d, J = 7.3 Hz, 2H), 7.35-6.94 (m, 63H), 5.77-5.69 (m, 1H), 5.10 (s, 1H), 5.02-4.99 (m, 2H), 4.95-4.91 (m, 3H), 4.89-4.87 (m, 1H), 4.84-4.51 (m, 11H), 4.43-4.31 (m, 4H), 4.26-4.19 (m, 3H), 4.11-3.13 (m, 40H), 2.98-2.95 (m, 1H), 2.78-2.77 (m, 1H), 2.66-2.64 (m, 1H), 2.09-2.04 (m, 2H), 1.68-1.62 (m, 2H), 1.13 (d, *J* = 6.4 Hz, 3H), 1.03-0.97 (m, 42H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 155.7, 141.0, 139.6, 139.2, 138.99, 138.96, 138.9, 138.8, 138.7, 138.6, 138.4, 138.3, 138.2, 132.3, 129.1, 128.9, 128.78, 128.75, 128.6, 128.54, 128.46, 128.43, 128.40, 128.37, 128.32, 128.30, 128.26, 128.16, 128.13, 127.96,

127.89, 127.86, 127.85, 127.8, 127.72, 127.66, 127.61, 127.59, 127.55, 127.5, 127.4. 115.1, 103.8, 103.4, 102.9, 99.9, 99.4, 98.1, 83.5, 81.9, 81.6, 80.7, 79.6, 79.2, 78.5, 78.1, 77.9, 77.7, 76.7, 75.6, 75.5, 75.4, 75.3, 75.2, 75.0, 74.2, 73.4, 73.3, 73.2, 72.8,72.2, 72.1, 71.6, 71.5, 69.6, 69.53, 69.46, 68.5, 68.4, 68.3, 68.0, 67.8, 62.2, 62.0, 56.3, 30.4, 29.2, 18.27, 18.25, 18.21, 18.18, 18.1, 17.9, 17.1, 12.12, 12.09; ESI-MS calcd for $C_{150}H_{185}NO_{32}SSi_2Na^+$ 2623.20 $(M + Na)^+$; found: 2624.41.

4-Pentenyl 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-*β*-D-galactopyranosyl-(1→3)-4,6-*O*-tri-acetyl-2-acetylamino-2-deoxy-*β*-D-galactopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-α-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-*β*-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-*β*-D-glucopyranoside (10).[2] TBAF (1.0 M in THF, 37.34 mL, 60 equiv.) was added to a solution of the hexasaccharide **9** (1.62 g, 0.622 mmol) and acetic acid (2.14 mL, 60 equiv.) in THF (35 mL). The reaction was stirred at rt for 3 days, poured into ice water and extracted with EtOAc. The organic extracts were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to an oil which was purified through a short plug of silica gel with EtOAc. The resulting triol was dissolved in anhydrous MeOH (20 mL) and sodium methoxide was added (0.75 mL of a 25% solution in MeOH). The reaction was stirred at rt for 18 h, neutralized with Dowex-H^+, filtered with MeOH washings and concentrated. THF (5 mL) and condensed liquid NH_3 (~70 mL) were added at –78 °C to the resulting white solid. Sodium (~1.2 g) was added and the resulting blue solution stirred at –78 °C for 2 h. The reaction was quenched with anhydrous MeOH (~30 mL), brought to rt and concentrated under a stream of dry N_2 to a volume of ~15 mL. The reaction was neutralized with Dowex-H^+, filtered with MeOH washing and concentrated to a white solid. The white solid was dissolved in pyridine (10 mL) and CH_2Cl_2 (10 mL) and cooled to 0 °C. A crystal of DMAP was added followed by acetic anhydride (10 mL). The ice bath was removed and the reaction stirred at rt overnight. The mixture was diluted with EtOAc and washed with water, saturated $NaHCO_3$ and brine, dried over $MgSO_4$. Concentration followed by purification by flash column chromatography (gradient elution 60% EtOAc/CH_2Cl_2) gave **10** as a white solid (470 mg, 42%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.74 (d, *J* = 6.5 Hz, 1H), 5.80-5.73 (m, 1H), 5.58 (d, *J* = 2.8 Hz, 1H), 5.44 (d, *J* = 3.4 Hz, 1H), 5.39 (d, *J* = 3.2 Hz, 1H), 5.27 (dd, *J* = 10.9, 3.0 Hz, 1H), 5.24-5.08 (m, 6H), 5.04-4.92 (m, 6H), 4.87 (t, *J* = 8.0 Hz, 1H), 4.74 (dd, *J* = 10.9, 2.5 Hz, 1H), 4.52-4.40 (m, 6H), 4.36 (t, *J* = 6.1 Hz, 1H), 4.26 (dd, *J* = 10.6, 3.4 Hz, 1H), 4.18-4.04 (m, 8H), 3.99 (d, *J* = 1.9 Hz, 1H), 3.95 (t, *J* = 6.3 Hz, 1H), 3.88-3.82 (m, 3H), 3.76-3.74 (m, 1H), 3.61-3.59 (m, 1H), 3.49-3.46 (m, 1H), 3.06-3.01(m, 1H), 2.15-2.14 (m, 12H), 2.10-2.03 (m, 29H), 2.00 (s, 3H), 1.96 (s, 2×3H), 1.95 (s, 3H), 1.90 (s, 3H), 1.71-1.59 (m, 2H), 1.14 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.5, 171.7, 171.0, 170.81, 170.78, 170.75, 170.7, 170.60, 170.59, 170.5, 170.3, 170.0, 169.8, 169.7, 169.2, 138.0, 115.3, 102.2, 101.5, 100.7, 99.5, 99.0, 94.6, 76.3, 73.9, 73.6, 73.4, 72.8, 72.6, 72.1, 72.0, 71.8, 71.5, 71.1, 70.91, 70.86, 70.4, 70.3, 69.5, 69.4, 69.1, 68.3, 68.2, 67.8, 67.5, 64.7, 62. 5, 62.0, 61.6, 61.4, 61.2, 56.4, 30.0, 28.8, 23.3, 21.10, 21.09, 21.03, 21.00, 20.98, 20.95, 20.91, 20.89, 20.87, 20.83, 20.82, 20.80, 20.74, 20.68, 16.1; ESI-MS calcd for $C_{77}H_{107}NO_{47}Na^+$ 1820.59 $(M + Na)^+$; found: 1821.17.

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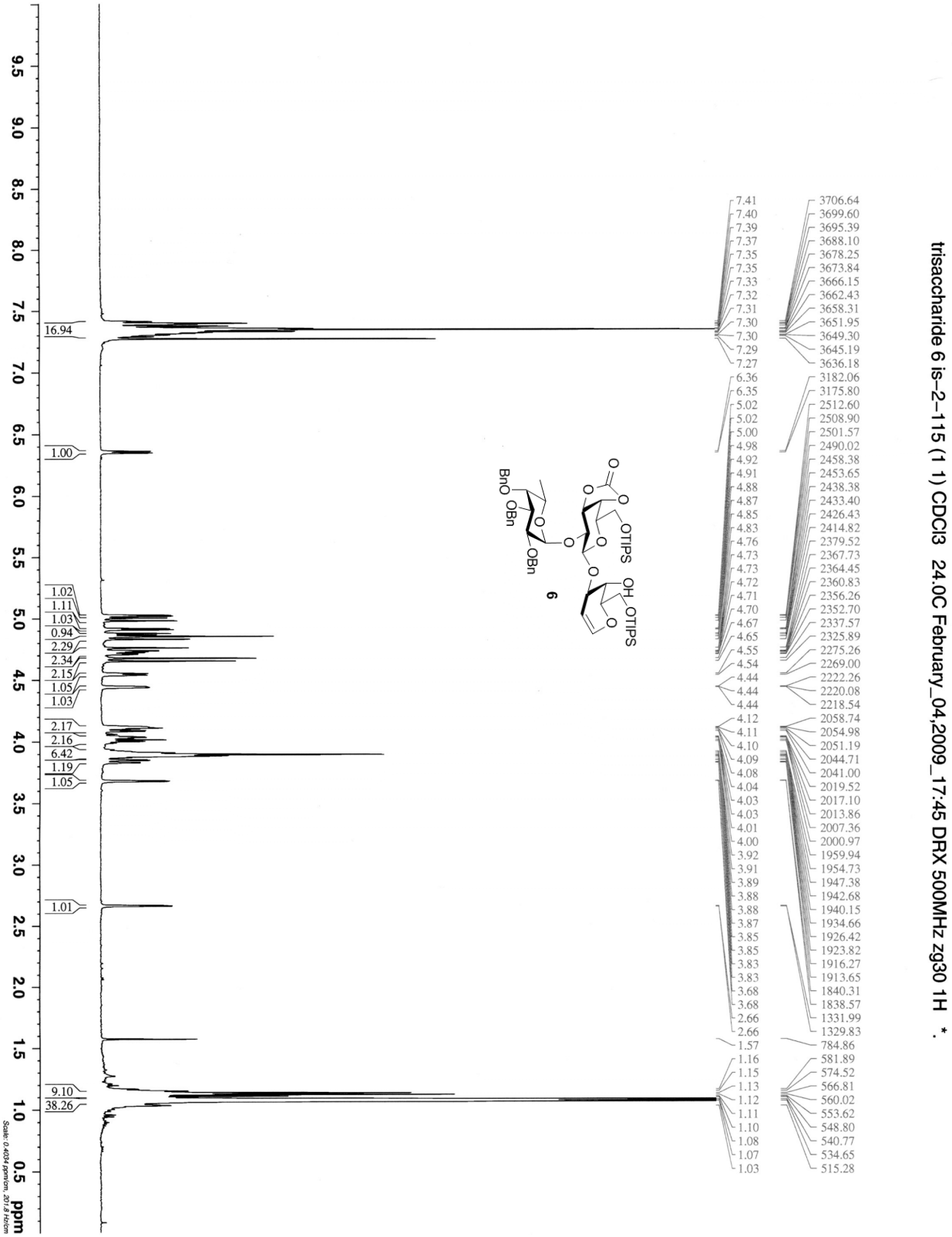
2. Allen, J. R.; Allen, J. G.; Zhang, X.-F.; Williams, L. J.; Zatorski, A.; Ragupathi, G.; Livingston, P. O.; Danishefsky, S. J. *Chem. Eur. J.*, **2000**, *6*, 1366-1375.

500 MHz ^{1}H NMR spectrum of trisaccharide **6** in $CDCl_3$



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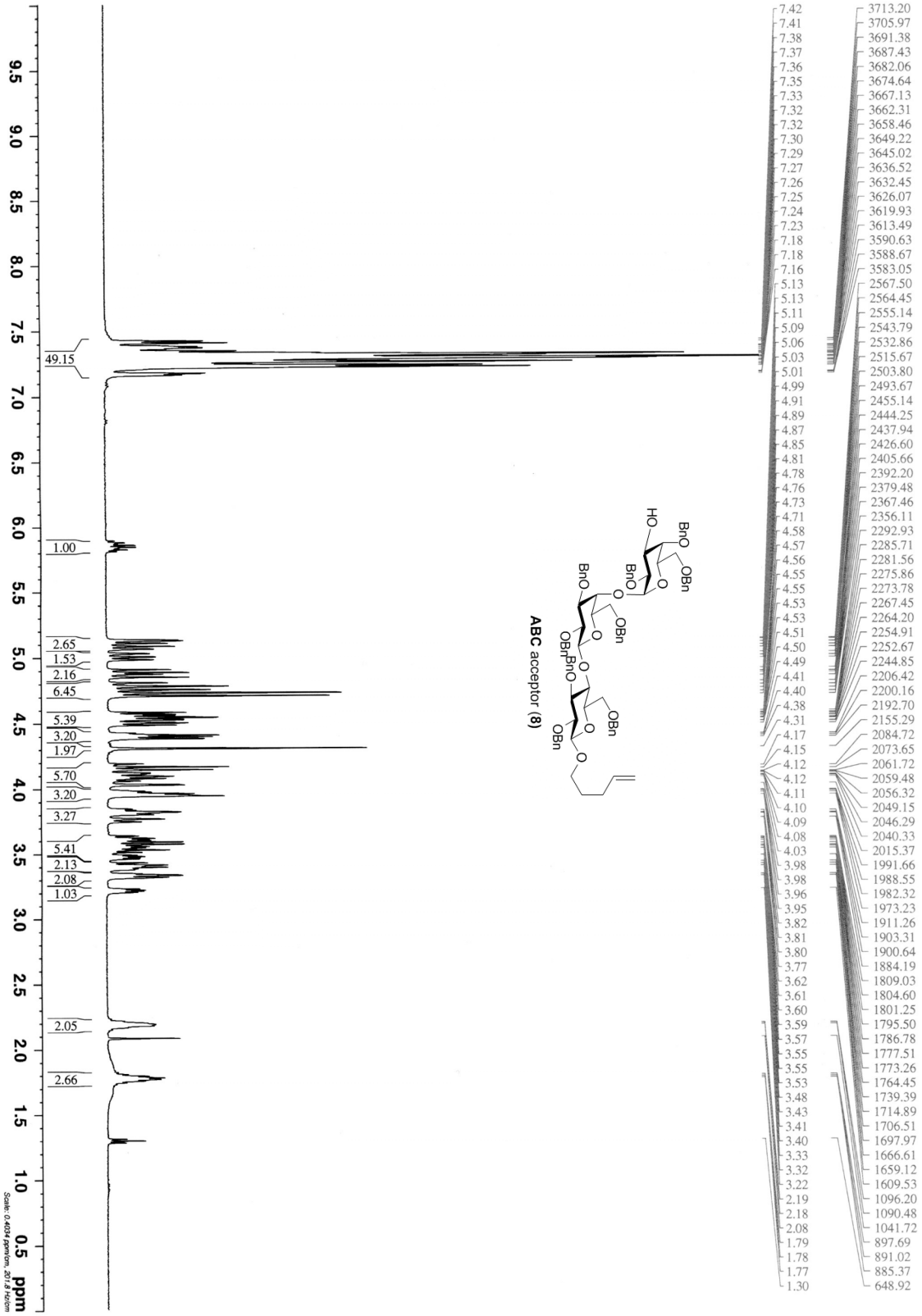

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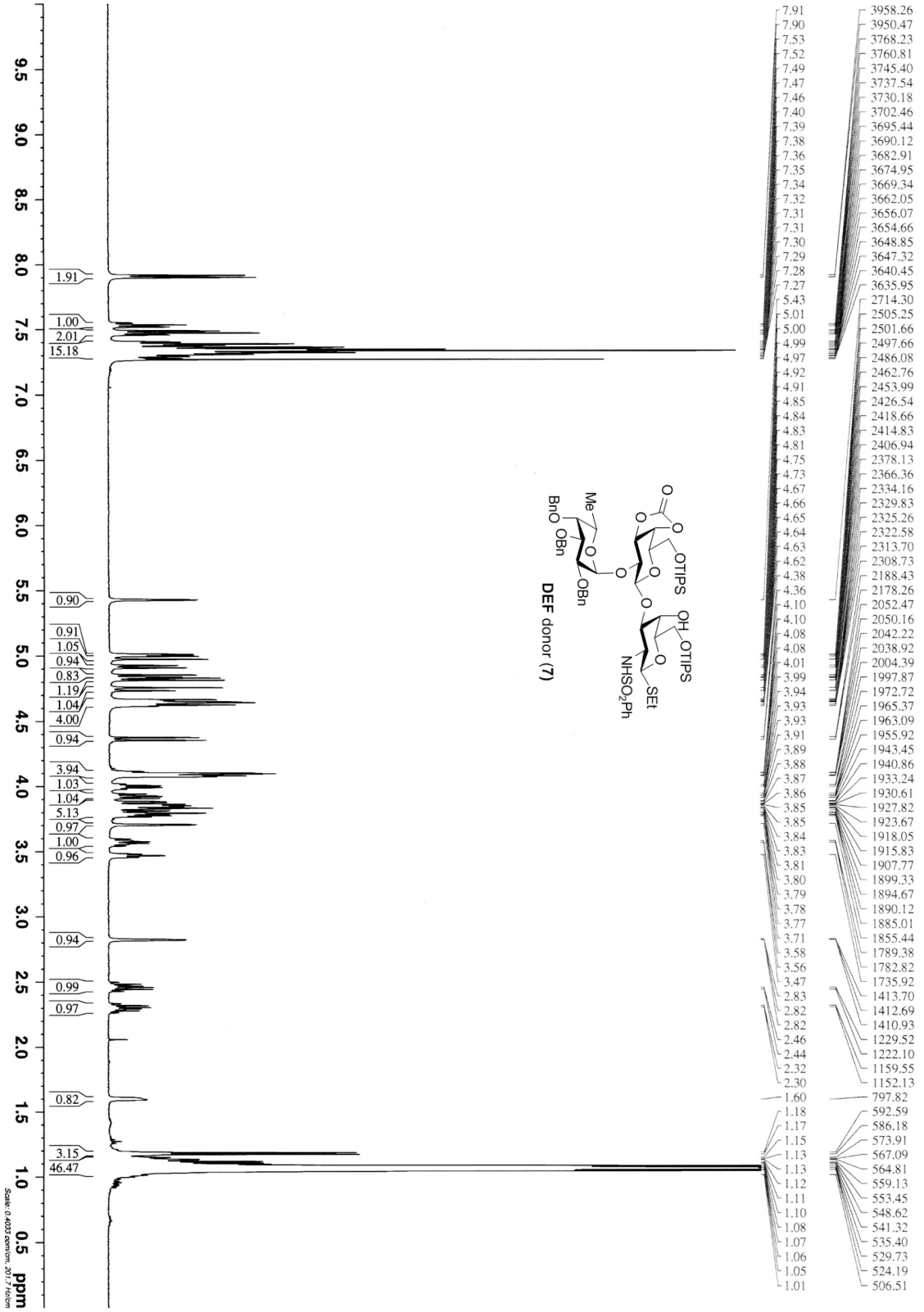

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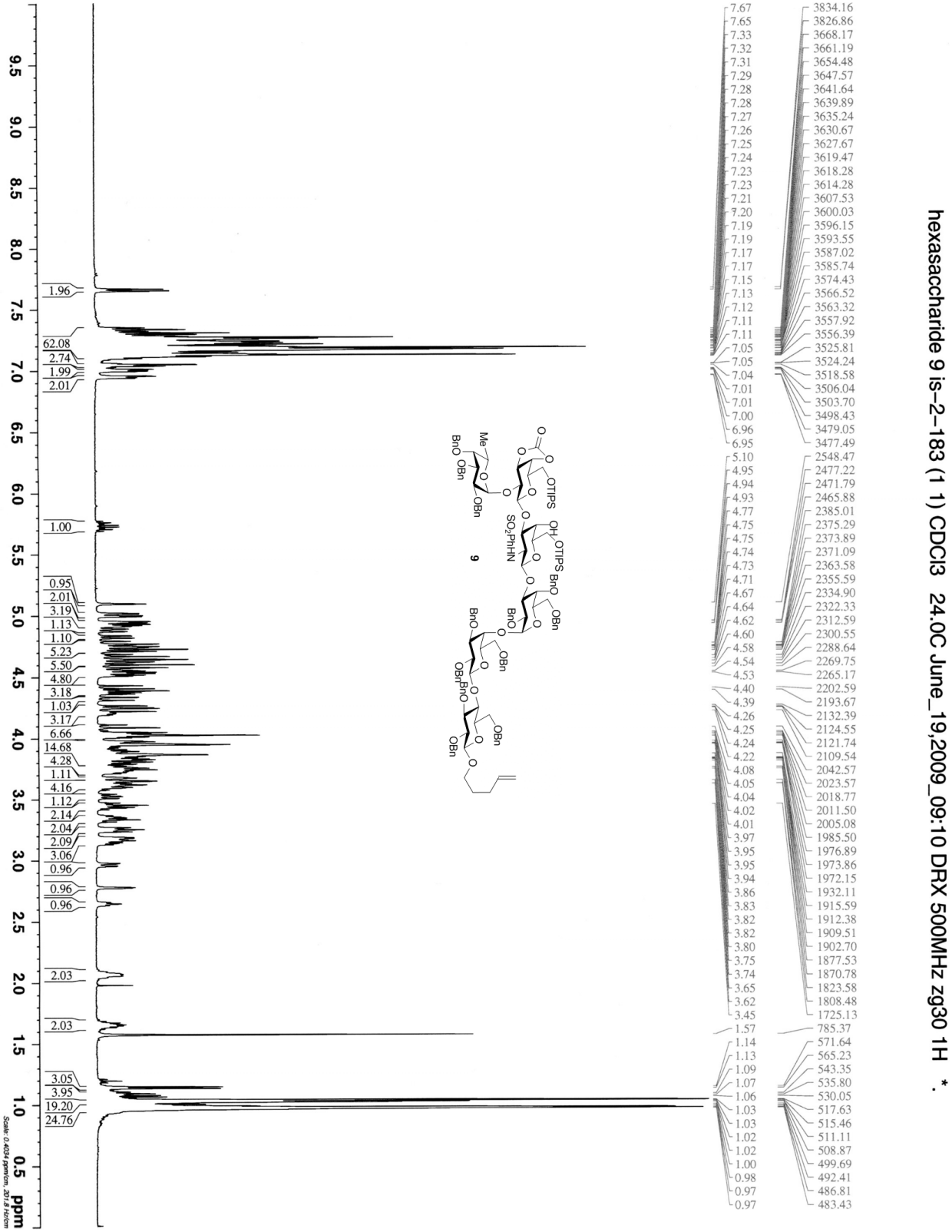

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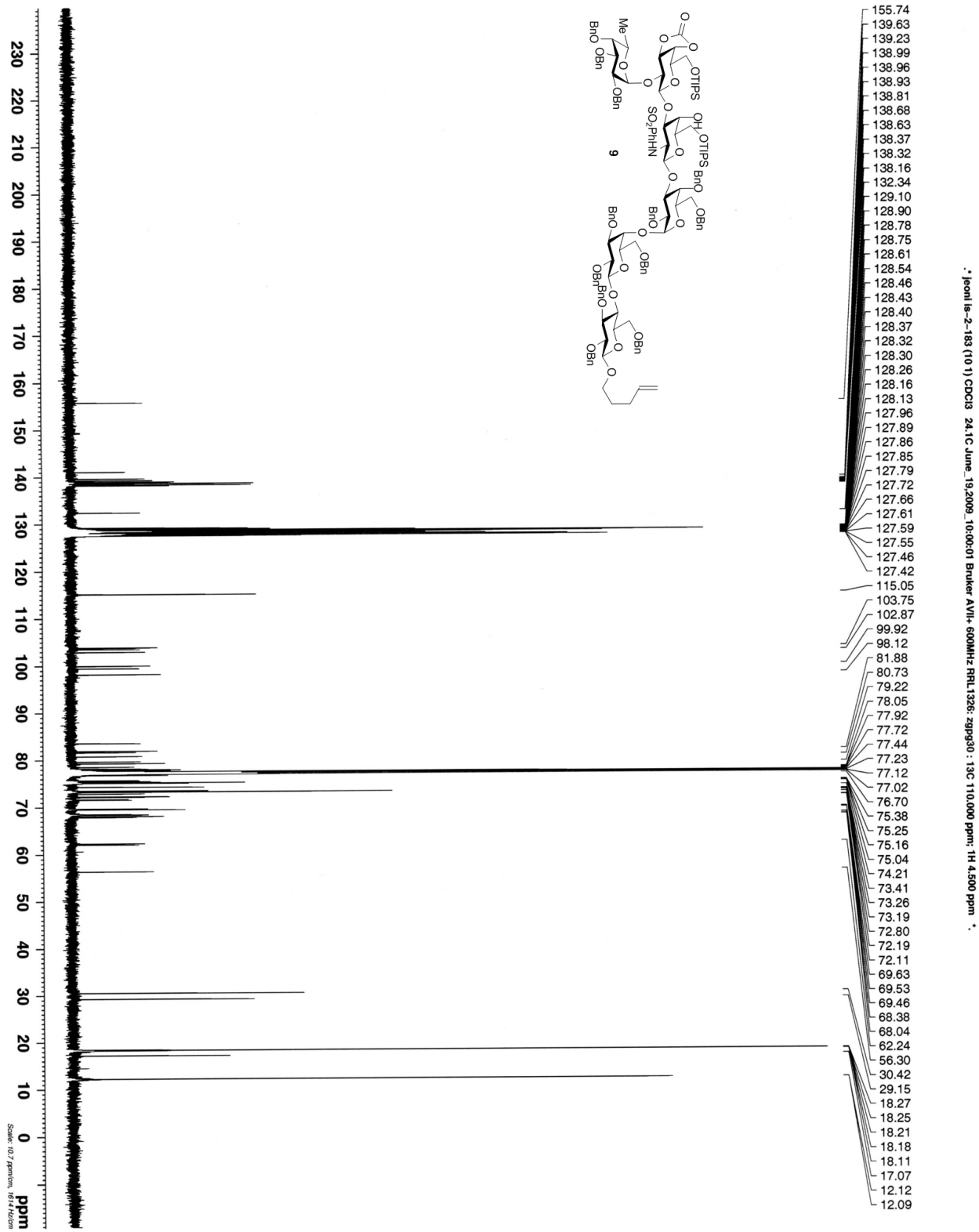

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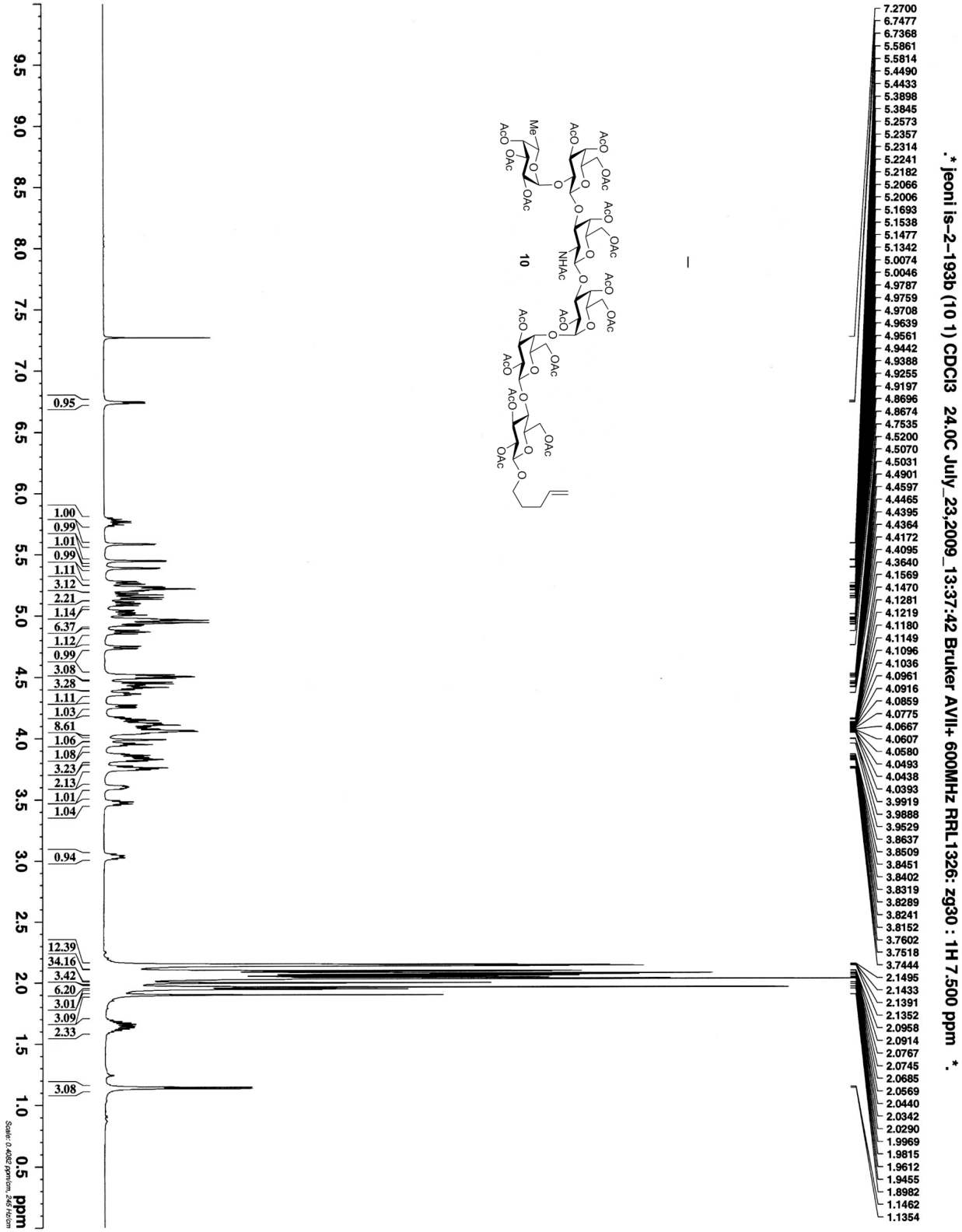

150 MHz ^{13}C NMR spectrum of hexasaccharide **10** in $CDCl_3$