Synthesis of a Dimer of β–(1,4)-L-Arabinosyl-(2*S*,4*R*)-4-hydroxy-proline Inspired by Art v 1, the Major Allergen of Mugwort

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SUPPORTING INFORMATION

Experimental procedures for the preparation of compounds and their ^{1}H and ^{13}C NMR spectra. Compounds are listed in the order that they appear in the manuscript, with page references:

Scheme	Compound	Procedure	^{1}H NMR	^{13}C NMR
Scheme 2	**3**	S3	S12	S13
	4	S4	S14	S15
	5	S5	S16	S17
	6	S5	**6A**: S18	S19
			6B: S20	S21
Scheme 3	**7**	S6	S22	S23
	8β	S7	S24	S25
Scheme 4	**9**	S7	S26	S27
	10	S8	S28	S29
Scheme 5	**11β**	S9	S30	S31
	1	S10	S32	S33

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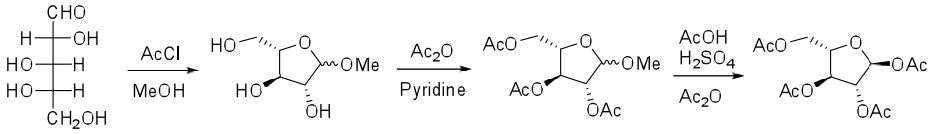
General Experimental Methods:

All reactions were performed under a dry nitrogen atmosphere unless otherwise noted. Reagents were obtained from commercial sources and used directly, with the following exceptions. Pyridine, 2,6-lutidine, morpholine and diisopropylethylamine were dried and distilled from CaH_2 and stored over KOH pellets. Methanol was distilled from magnesium turnings and stored over 3 Å molecular sieves. Powdered 4 Å molecular sieves were flame-dried immediately prior to use.

Reactions were followed by TLC on pre-coated silica plates (200 μm, F-254). Flash chromatography was performed using flash silica gel (32-63 μ). The compounds were visualized by UV fluorescence or by staining with a 10% solution of sulfuric acid in ethanol or an acidic, ethanolic solution of ninhydrin.

NMR spectra were recorded at either 400 or 700 MHz. Proton NMR data is reported in ppm downfield from TMS as an internal standard. High resolution mass spectra were recorded using either time-of-flight MS, or LC-ion trap MS with electrospray ionization. Optical rotations were recorded under the specified conditions.

Peracetylated-α-*L*-Arabinofuranoside



L-Arabinose (5.0 g, 33.3 mmol, 1 equiv.) was dissolved in methanol (100 mL) and treated with a solution of acetyl chloride (2.5 mL) in methanol (30 mL) at rt under N_2. The mixture was stirred for 3 h, during which time the solid completely dissolved. The reaction was quenched dropwise with pyridine. The solvent was evaporated, followed by azeotroping with CH_2Cl_2 to give the methyl arabinoside as a mixture of anomers. The crude product was dissolved in pyridine (40 mL) and cooled to 0 °C, after which acetic anhydride (20 mL) was added and the reaction was stirred overnight at rt. The solvent was evaporated and the mixture was diluted with CH_2Cl_2 (250 mL), washed with water (250 mL), 1 M HCl (250 mL), sat. $NaHCO_3$ (250 mL), and brine (250 mL). The organic phase was filtered through $MgSO_4$ and concentrated to give the triacetate. The crude product was dissolved in acetic anhydride (80 mL) and cooled to 0 °C. Acetic acid (20 mL) was added dropwise. After 15 min, sulfuric acid (5 mL) was added dropwise. The

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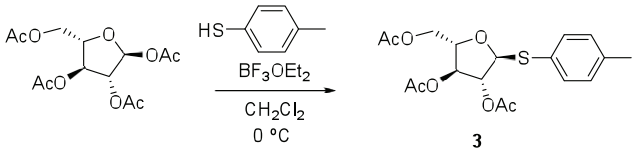
mixture was warmed to rt while stirring for approximately 2 h. The solution was poured over a mixture of ice (50 g), CH_2Cl_2 (250 mL) and sat'd aq. $NaHCO_3$ (200 mL). The organic layer was separated and washed again with several volumes of sat'd aq. $NaHCO_3$, filtered through $MgSO_4$, and concentrated to give the crude peracylated furanoside as a light oil (9.071 g, 85%; 3 steps).

_p_-Cresyl 2,3,5-_O_-acetyl-1-thio-α-_L_-arabinofuranoside (3)*



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A solution of peracetylated arabinofuranoside (4.47 g, 14 mmol, 1.0 equiv.) and *p*-thiocresol (2.64 g, 21 mmol, 1.5 equiv.) in dry CH_2Cl_2 (60 mL) was cooled to 0 °C under N_2. Boron trifluoride diethyl etherate (1.0 mL, 1.17 g, 8.1 mmol, 0.5 equiv.) was added dropwise and the mixture stirred for 5 h under N_2 at 0 °C. The reaction was quenched with Et_3N (4 mL) and concentrated. The mixture was diluted with EtOAc (150 mL) and washed with H_2O (150 mL) and brine (150 mL). The organic layer was filtered through $MgSO_4$ and concentrated. The residue was purified by flash chromatography eluting with 4:1 Hex/EtOAc to give **3** as a light colored oil (3.54 g, 66 %). R_f 0.25 (3:1 Hexanes/EtOAc). $[\alpha]_D^{25}$ -170.2 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.11 (s 3H), 2.13 (s, 3H), 2.34 (s, 3H), 4.28 (dd, *J* = 12.1, 5.5 Hz, 1H), 4.39 (dd, *J* = 12.1, 3.6 Hz, 1H), 4.48 (app. q, *J* = 4.7 Hz, 1H), 5.07 (d, *J* = 5.5 Hz, 1H), 5.27 (s, 1H), 5.47 (s, 1H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (3C), 21.1, 62.8, 77.2, 79.9, 81.4, 91.2, 129.6, 129.8, 132.7, 138.1, 169.6, 170, 170.5. HRMS (ESI) calcd for $C_{18}H_{21}O_7SNa$ $(M+Na)^+$: 405.0978; obsd: 405.0985.

The synthesis of ent-3** has been previously reported by Crich and co-workers, however, without purification and characterization of this intermediate.*

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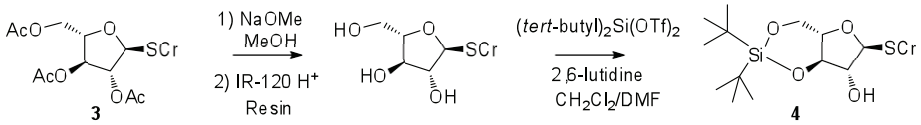
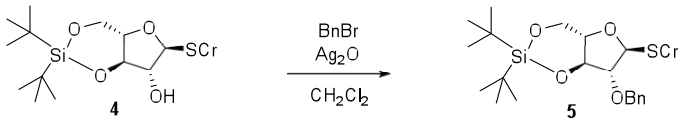
***p*-Cresyl 3,5-*O*-(Di-*tert*-butylsilylene)-1-thio-α-*L*-arabinofuranoside (4)**



Thioglycoside triacetate (**3**) (694 mg, 1.8 mmol) was dissolved in MeOH (15 mL). Sodium methoxide (200 μL, 25% in MeOH) was added and stirred under N_2 overnight. Amberlite® IR-120 acid resin was added portionwise while stirring until solution was neutralized, after which it was filtered and rinsed with MeOH, and concentrated. A portion of the crude triol (363 mg, 1.4 mmol, 1.0 equiv.) was suspended in a mixture of dry CH_2Cl_2 (13 mL) and DMF (2.5 mL) and cooled to 0 °C under N_2. 2,6-Lutidine (762 μL, 705 mg, 6.6 mmol, 4.7 equiv.) and di-*tert*-butylsilyl *bis*-(trifluoromethanesulfonate) (545 μL, 741 mg, 1.7 mmol, 1.2 equiv.) were then added sequentially. The mixture was stirred overnight under N_2 at rt. The mixture was concentrated and the residue diluted with EtOAc (30 mL) and washed with H_2O (30 mL) and brine (30 mL). The organic layer was filtered through $MgSO_4$ and concentrated. The residue was purified by flash chromatography eluting with 15:1 Hex/EtOAc to give **4** as an amorphous colorless solid (297 mg, 54%, 2 steps). R_f 0.49 (3:1 Hexanes/EtOAc). $[\alpha]_D^{25}$ -181.0 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.08 (s, 9H), 2.33 (s, 3H), 3.58 (d, *J* = 4.2 Hz, 1H), 3.87-3.98 (m, 2H), 4.02 (app. t, *J* = 8.3 Hz, 1H), 4.14 (app. q, *J* ~ 5 Hz, 1H), 4.35 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.27 (d, *J* = 5.9 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 21.1, 22.7, 27.1, 27.5, 67.4, 73.7, 80.6, 77.4, 91.5, 129.8, 130.3, 132.3, 137.9. HRMS (ESI) calcd for $C_{20}H_{33}O_4SSi$ $(M+H)^+$: 397.1863; obsd: 397.1856.

***p*-Cresyl 2-*O*-Benzyl-3,5-*O*-(di-*tert*-butylsilylene)-1-thio-α-*L*-arabinofuranoside (5)**



Compound **4** (400 mg, 1.1 mmol, 1 equiv.) was dissolved in dry CH_2Cl_2 (11 mL) and stirred under N_2. Benzyl bromide (240 μL, 345 mg, 2.0 mmol, 2 equiv.) was added, followed by Ag_2O (714 mg, 3.1 mmol, 3 equiv.). The mixture was stirred for 3 d, filtered through an inch of silica and washed with $CHCl_2$, and concentrated. The residue was purified by flash chromatography eluting with 120:1 Hex/Ether → 60:1 Hex/EtOAc to give **5** as a colorless solid (336 mg, 64%). R_f 0.62 (3:1 Hexanes/EtOAc). $[\alpha]_D^{25}$ -129.93 (*c* 1,

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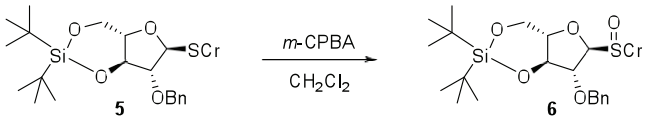
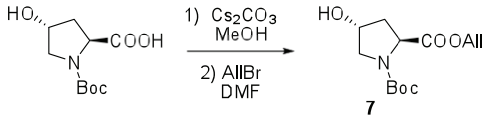
CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.06 (s, 9H), 2.28 (s, 3H), 3.84-3.98 (m, 3H), 4.12 (app. t, *J* = 8.4 Hz, 1H), 4.31 (dd, *J* = 8.2, 4.1 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 5.34 (d, *J* = 5.2 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 2H), 7.26-7.40 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 21.2, 22.7, 27.2, 27.6, 67.4, 72.2, 73.8, 81.4, 86.8, 90.3, 127.9, 128.1, 128.5, 129.8, 130.6, 132.3, 137.71, 137.74. HRMS (ESI) calcd for $C_{27}H_{39}O_4SSi$ $(M+H)^+$: 487.2333; obsd: 487.2324.

_p_-Cresyl 2-_O_-Benzyl-3,5-_O_-(di-_tert_-butylsilylene)-1-thio-α-_L_-arabinofuranoside _S_-Oxide (6)



A solution of 3-chloroperoxybenzoic acid (63.5 mg, 77 wt %, 0.28 mmol, ~1.2 equiv.) in dry CH_2Cl_2 (1 mL) was added dropwise to a solution of compound **5** (116 mg, 0.24 mmol, 1 equiv.) in dry CH_2Cl_2 (4 mL) at -80 °C under Argon and stirred. The reaction mixture was gradually warmed to rt over 2 h. The solution was diluted with CH_2Cl_2 (30 mL), washed with sat'd aq. $NaHCO_3$ (30 mL), filtered through $MgSO_4$, and concentrated. The residue was purified by column chromatography, eluting with 10:1 Hex/EtOAc to afford **6** as a colorless gel (68 mg, 57%) and a mixture of diastereomers. Diastereomer **6A**: R_f 0.42 (3:1 Hexanes/EtOAc). $[\alpha]_D^{25}$ 101.4 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.05 (s, 9H), 2.40 (s, 3H), 3.89 (app. t, *J* = ~10 Hz, 1H), 3.99-4.05 (td, J = 10, 5.0 Hz, 1H), 4.22 (dd, *J* = ~10, 7.2 Hz, 1H), 4.30 (d, *J* = 11.4 Hz, 1H), 4.35 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.57-4.59 (m, 1H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.65 (d, *J* = 5.1 Hz, 1H), 6.98 (app. t, *J* = 3.6 Hz, 2H), 7.25-7.27 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 21.4, 22.6, 27.1, 27.4, 67.4, 72.0, 77.0, 78.5, 82.0, 99.3, 124.4, 127.7, 127.9, 128.2, 129.9, 136.2, 137.3, 141.7. HRMS (ESI) calcd for $C_{27}H_{39}O_5SSi$ $(M+H)^+$: 503.2282; obsd: 503.2298. Diastereomer **6B**: R_f 0.33 (3:1 Hexanes/EtOAc). $[\alpha]_D^{25}$ -178.6 (*c* 1.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.05 (s, 9H), 2.40 (s, 3H), 3.78-3.84 (m, 1H), 3.86 (app. t = ~9.4 Hz, 1H), 4.20 (app. t, *J* = 8.2 Hz, 1H), 4.30 (dd, *J* = 8.6, 4.5 Hz, 1H), 4.35 (app. t, *J* = 6.4 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 5.6 Hz, 1H), 4.76 (d, *J* = 11.7 Hz, 1H), 7.23-7.36 (app. m, 7H), 7.52 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 21.5, 22.6, 27.0, 27.4, 67.3, 72.3, 76.9, 81.1, 81.5, 98.2, 125.6, 128.0, 128.1, 128.4, 129.9, 136.4, 137.3, 142.3. HRMS (ESI) calcd for $C_{27}H_{39}O_5SSi$ $(M+H)^+$: 503.2282; obsd: 503.2294.

***N-tert*-butoxycarbonyl-*trans*-4-hydroxy-L-proline allyl ester (7)**

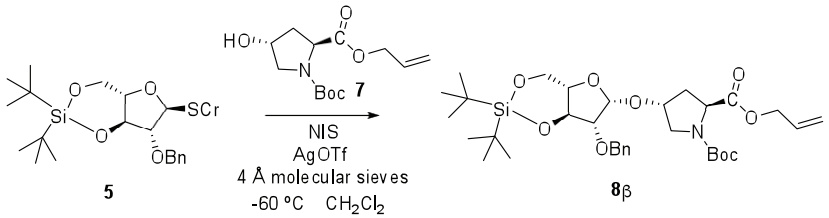


7

To a suspension of Boc-Hyp-OH (1.77 g, 7.7 mmol, 1.0 equiv.) in dry MeOH (16 mL) was added cesium carbonate (1.37 g, 4.2 mmol, 0.55 equiv.). The mixture was stirred under N_2 for 1.5 h during which time the reaction mixture became a homogeneous solution. The solvent was evaporated, and the residue dissolved in dry DMF (10 mL) and treated immediately with allyl bromide (0.86 mL, 1.2 g, 9.9 mmol, 1.3 equiv.). The mixture was stirred overnight at RT under N_2. The mixture was diluted with EtOAc (150 mL) and washed with H_2O (150 mL) and brine (150 mL). The organic layer was filtered through $MgSO_4$ and concentrated. The residue was purified by flash column chromatography, eluting with 2:1 EtOAc/Hex to give the title compound as a light oil (1.86 g, 89%). R_f 0.34 (2:1 EtOAc/Hex). $[\alpha]_D^{25}$ -65.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (1.46)* (s, 9H), 2.03-2.10 (m, 1H), 2.25-2.35 (m, 1H), 2.96 (s, 1H), 3.44-3.65 (m, 2H), 4.40-4.48 (m, 2H), 4.56-4.71 (m, 2H), 5.25 (app. t, *J* = ~11.3 Hz, 1H), 5.35 (dt, *J* = 17.1, 3.8, 1.2 Hz, 1H), 5.87-5.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 (28.3), 39.1 (38.3), 54.6, 58.0 (57.7), 65.6, 69.1 (69.8), 80.5 (80.2), 118.8 (118.3), 131.6 (131.8), 154.1 (154.6), 172.9 (172.6). HRMS (ESI) calcd for $C_{13}H_{21}NO_5Na$ $(M+Na)^+$: 294.1312, obs'd: 294.1320.

* values in parentheses signifiy a second signal due to a minor rotamer

***Nα-tert*-butyloxycarbonyl-*trans*-4-hydroxy-4-*O*-[2-*O*-Benzyl-3,5-*O*-(di-*tert*-butylsilylene)-*L*-arabinofuranosyl]-*L*-proline Allyl Ester (8β)**



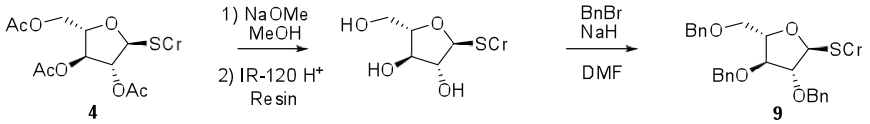
5 **8β**

A solution of compound **5** (219 mg, 0.45 mmol, 1.0 equiv.) and **7** (250 mg, 0.92 mmol, 2.0 equiv.) in dry CH_2Cl_2 (30 mL) was added to a flask containing activated 4 Å crushed molecular sieves under N_2. The

suspension was stirred for ~20 min at RT, then cooled in a bath of ethylene glycol and dry ice. The temperature lowered to -30 °C and NIS (173 mg, 0.68 mmol, 1.5 equiv.) was added, followed by a solution of AgOTf (57 mg, 0.22 mmol, 0.5 equiv) in toluene (0.6 mL) as the temperature continued to drop to -60 °C. The suspension was stirred for 1 h during which it was allowed to gradually warm to rt. Solution continued to stir until room temperature was reached. After ~20 mins at rt, the reaction was quenched with a few drops of Et_3N, filtered, and concentrated. The residue was diluted with EtOAc (50 mL) and washed with sat'd aq. $Na_2S_2O_3$ (50 mL) and brine (50 mL), filtered through $MgSO_4$, and concentrated. The residue was purified by column chromatography, eluting with 10:1 Hex/EtOAc to afford crude **8β** as a colorless oil (147 mg, 51%) as a mixture of anomers and rotamers. Crude **8β** was subjected to HPLC, eluting with 20% EtOAc, 80% hexanes at 13.0 mL min^{-1} on an Econosil 10μ silica column (21 x 250 mm). R_T (**8β**) = 23 min; β-anomer: R_f 0.30 (3:1 Hexanes/EtOAc). $[\alpha]_D^{25}$ +57.3 (*c* 1, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.07 (s, 9H), 1.38 (1.45) (1 s, 9H), 2.08-2.15 (m, 1H), 2.35-2.42 (2.43-2.49)* (m, 1H), 3.58-3.69 (m, 3H), 3.86-3.91 (m, 2H), 4.26-4.32 (m, 3H), 4.36-4.44 (m, 1H), 4.56-4.73 (m, 3H), 4.79 (d, *J* = 12.2 Hz, 1H), 4.97 (4.93) (d, *J* = ~5.3 Hz, 1H), 5.24 (app. t, *J* = 11.6 Hz, 1H), 5.32 (ddd, *J* = 17.2, 5.9, 1.3 Hz, 1H), 5.85-5.96 (m, 1H), 7.29-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 22.6, 27.1, 27.5, 28.2 (28.4)*, 37.6 (36.8), 51.1 (51.6), 58.1 (57.7), 65.5 (65.6), 68.4, 71.8 (71.9), 73.6 (73.4), 75.2, 78.4, 80.2 (80.1), 80.7, 99.2 (100.0), 118.7 (118.3), 127.7, 127.8, 127.9, 128.0, 128.4, 131.7 (131.9), 137.7, 153.7 (154.2), 172.7 (172.4). HRMS (ESI) calcd for $C_{33}H_{52}NO_9Si$ $(M+H)^+$: 634.3406; obsd: 634.3408.

* values in parentheses signify a second signal due to a minor rotamer

_p_-Cresyl 2,3,5-_O_-Benzyl-1-thio-α-_L_-arabinofuranoside (9)



Thioglycoside triacetate **4** (2.86 g, 7.5 mmol, 1.0 equiv.) was dissolved in MeOH (35 mL). Sodium methoxide (0.5 mL, 25% in MeOH, 4.1 mmol, 0.55 equiv.) was added and stirred under N_2 overnight. Amberlite® IR-120 acid resin was added in portions, stirring until the solution was neutralized. The resin

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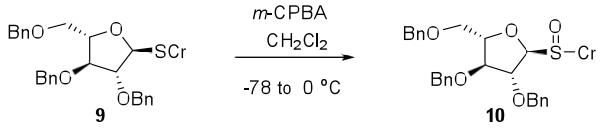
was filtered, rinsed with MeOH, and the filtrate concentrated. The crude triol (1.91 g, 7.5 mmol, 1.0 equiv.) was dissolved in dry DMF (15 mL) and cooled to 0 °C under N_2. Benzyl bromide (5.3 mL, 7.61 g, 44.5 mmol, 6.0 equiv.) and NaH (1.78 g, 60% dispersion, 44.5 mmol, 6.0 equiv.) were added sequentially. The reaction mixture was allowed to warm to RT while it stirred under N_2 for 3 h. The reaction was quenched with sat'd aq. $NaHCO_3$ (150 mL) and extracted with CH_2Cl_2 (150 mL). The organic layer was washed with H_2O (150 mL) and brine (150 mL), filtered through $MgSO_4$, and concentrated. The residue was purified by flash chromatography eluting with 20:1 → 10:1 → 1:2 Hex/EtOAc to give **9** as a clear gel (3.26 g, 84%; 2 steps). R_f 0.46 (3:1 Hexanes/EtOAc). $[\alpha]_D^{25}$ -107.9 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.63 (dd, *J* = 10.8, 4.7 Hz, 1H), 3.68 (dd, *J* = 10.8, 3.9 Hz, 1H), 4.03 (app. q, *J* = 3.3 Hz, 1H), 4.11 (t, *J* = 2.9 Hz, 1H), 4.36-4.38 (m, 1H), 4.48-4.65 (m, 6H), 5.53 (d, *J* = 2.0 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 2H), 7.26-7.35 (m, 15H), 7.41 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 69.1, 72.7, 72.3, 73.4, 80.5, 83.5, 88.4, 90.6, 127.6, 127.7, 127.8, 127.9, 127.9, 128.0, 128.3, 128.4, 128.5, 129.7, 131.0, 132.0, 137.4, 137.8, 138.2. HRMS (ESI) calcd for $C_{33}H_{34}NaO_4S$ $(M+Na)^+$: 549.2070; obsd: 549.2067.

_p_-Cresyl 2,3,5-_O_-Benzyl-1-thio-α-_L_-arabinofuranoside _S_-Oxide (10)



A solution of 3-chloroperoxybenzoic acid (283 mg, 77 wt %, 1.3 mmol, 1.2 equiv.) in dry CH_2Cl_2 (4 mL) was added dropwise to a solution of compound **9** (555 mg, 1.1 mmol, 1.0 equiv.) in dry CH_2Cl_2 (16 mL) at -78 °C under N_2 and stirred. The reaction mixture was gradually warmed to RT over 1.5 h. The solution was diluted with CH_2Cl_2 (70 mL), washed with sat'd aq. $NaHCO_3$ (70 mL), filtered through $MgSO_4$, and concentrated. The residue was purified by column chromatography, eluting with 3:1 Hex/EtOAc to afford **10** as a colorless gel (429mg, 75%), essentially a single diastereomer. Major diastereomer: R_f 0.19 (3:1 Hexanes/EtOAc). $[\alpha]_D^{25}$ +30.1 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.53 (dd, *J* = 10.6, 5.5 Hz, 1H), 3.60 (dd, *J* = 10.6, 4.8 Hz, 1H), 4.15 (dd, *J* = 5.5, 2.8 Hz, 1H), 4.37-4.51 (m, 6H), 4.59 (d, *J* = 11.8 Hz, 1H), 4.63 (d, *J* = 1.8 Hz, 1H), 4.74 (app. t, *J* = ~2.4 Hz, 1H), 7.20-7.32 (m, 17H), 7.57 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 69.1, 71.9, 72.2, 73.3, 83.3, 83.9, 84.4, 102.0, 124.8,

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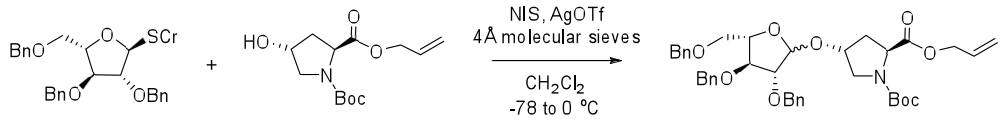
127.7, 127.9, 128.0 (2 signals), 128.4 (2 signals), 128.5, 129.9, 137.3, 137.4, 137.9, 138.7, 141.8. HRMS (ESI) calcd for $C_{33}H_{35}O_5S$ $(M+H)^+$: 543.2160; obsd: 543.2206.

Nα-*tert*-Butyloxycarbonyl-*trans*-4-hydroxy-4-*O*-[2,3,5-*O*-Benzyl-*L*-arabinofuranosyl]-*L*-proline Allyl Ester (11)



9 **7** **11β**

A solution of compound **9** (1.17 g, 2.2 mmol, 1.0 equiv.) and **7** (0.688 g, 2.5 mmol, 1.1 equiv.) in dry CH_2Cl_2 (40 mL) was stirred with activated 4 Å molecular sieves (3.5 g) under N_2 for ~30 min at RT. The suspension was cooled to -78 °C (acetone/dry ice) and then NIS (0.747 g, 3.2 mmol, 1.5 equiv.) and AgOTf (0.285 g, 0.55 mmol, 0.5 equiv.) were added. The reaction was allowed to gradually reach 0 °C over 3 h, at which time it was quenched with Et_3N (3 mL) and filtered. The filtrate was diluted with EtOAc (150 mL) and washed with 10% aqueous $Na_2S_2O_3$ (2 x 200 mL) and brine (200 mL). The organic layer was filtered through $MgSO_4$ and concentrated. The residue, determined to be a 4:1 β:α ratio by NMR, was purified by column chromatography, eluting with 3:1 Hex/EtOAc to afford **11β** (0.732 g, 50%, 2:1 ratio of conformations) as an orange oil. R_f 0.56 (1:1 Hexanes/EtOAc). $[\alpha]_D^{25}$ +17.9 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (1.44)* (s, 9H), 1.96-2.07 (m, 1H), 2.27-2.37 (m, 1H), 3.44-3.67 (m, 4H), 4.03-4.12 (m, 3H), 4.25-4.71 (m, 10H), 4.96 (4.92) (d, *J* = 3.2 Hz, 1H), 5.20-5.34 (m, 2H), 5.86-5.91 (m, 1H), 7.28-7.33 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3 (28.4), 37.4 (36.5), 50.7 (51.4), 58.1 (57.8), 65.6 (65.7), 72.0, 72.4, 73.3, 75.5, 80.1, 80.3, 82.7, 83.8, 83.9, 99.0 (99.9), 118.8 (118.4), 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5; 131.7 (131.9), 137.4, 137.9, 138.1, 153.7 (155.4), 172.7 (172.4). HRMS (ESI) calcd for $C_{39}H_{48}NO_9$ $(M+H)^+$: 674.3324, obs'd: 674.3343.

* values in parentheses signifiy a second signal due to a minor rotamer

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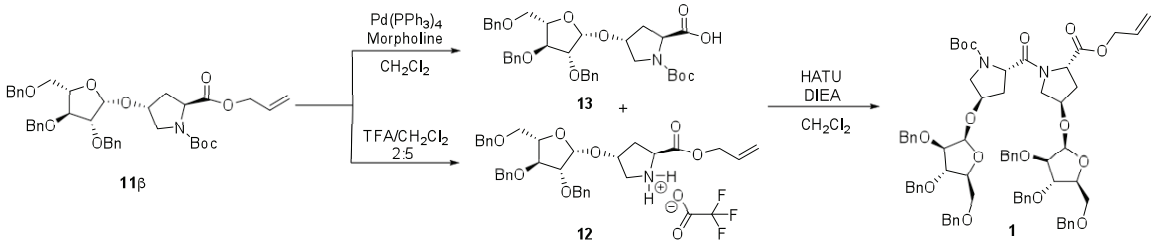
Diglycopeptide (1)



***N*α-*tert*-Butyloxycarbonyl-*trans*-4-hydroxy-4-*O*-[2,3,5-*O*-Benzyl-β-*L*-arabinofuranosyl]-*L*-proline (13).** A solution of compound **11β** (383 mg, 0.57 mmol, 1.0 equiv.) and $Pd(PPh_3)_4$ (66.0 mg, 0.05 mmol, 0.1 equiv.) in dry THF (10 mL) was treated with morpholine (345 µL, 347 mg, 4.0 mmol, 7.0 equiv.) and stirred at RT under N_2 for 1 h. The solvent was evaporated and the residue dissolved in CH_2Cl_2 (60 mL), washed with 1M HCl (3 x 50 mL), filtered through $MgSO_4$, and concentrated. The crude acid **13** (350 mg, 97%) was used in the next reaction without further purification.

***trans*-4-hydroxy-4-*O*-[2,3,5-*O*-Benzyl-β-*L*-arabinofuranosyl]-*L*-proline Allyl Ester (12).** Compound **11β** (144 mg, 0.21 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (2.5 mL) and stirred under N_2. The mixture was cooled to 0 °C and treated with TFA (1 mL) and thioanisole (25 µL, 27 mg, 0.21 mmol, 1.0 equiv.). The mixture was stirred at 0 °C for 30 min, warmed to RT over the next 2.5 h, and concentrated. The residue was purified by flash column chromatography, starting with 2:1 EtOAc/Hex and flushing with 4:1 CH_2Cl_2/MeOH to give **12** as a light brown oil (107 mg, 73%).

Compound **12** (53 mg, 0.08 mmol, 1.0 equiv.) and compound **13** (68 mg, 0.11 mmol, 1.4 equiv.) were suspended in dry CH_2Cl_2 (3 mL). The mixture was cooled to 0 °C and DIEA (40 µL, 30 mg, 0.23 mmol, 3.0 equiv.) and HATU (35 mg, 0.10 mmol, 1.2 equiv.) were added successively. The reaction was allowed to gradually warm to rt overnight while stirring under N_2. The mixture was diluted with CH_2Cl_2 to 25 mL total volume, washed with 1M HCl (2 x 20 mL), sat'd $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was filtered through $MgSO_4$ and concentrated. The residue was purified by flash column chromatography, eluting with 1.5:1 Hex/EtOAc → 1.5:1 EtOAc/Hex to give **1** as a light oil (45 mg, 49%). R_f 0.56 (2:1 EtOAc/Hex). $[\alpha]_D^{25}$ +30.1 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (1.30)* (s, 9H), 1.96-2.13 (m, 2H), 2.17-2.37 (m, 2H), 3.40-3.75 (m, 8H), 3.90-4.27 (m, 7H), 4.38-4.72 (m, 19H), 4.88 (5.08) (s {d, *J* = 4.0 Hz}, 1H), 4.99 (app. t, *J* = ~4.3 Hz, 1H), 5.20 (app. d, *J* = 10.4 Hz, 1H), 5.29 (app. d, *J* = 16.9 Hz, 1H), 5.82-5.91 (m, 1H), 7.25-7.33 (m, 30H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *t*-Boc (28.4, 28.5)*,

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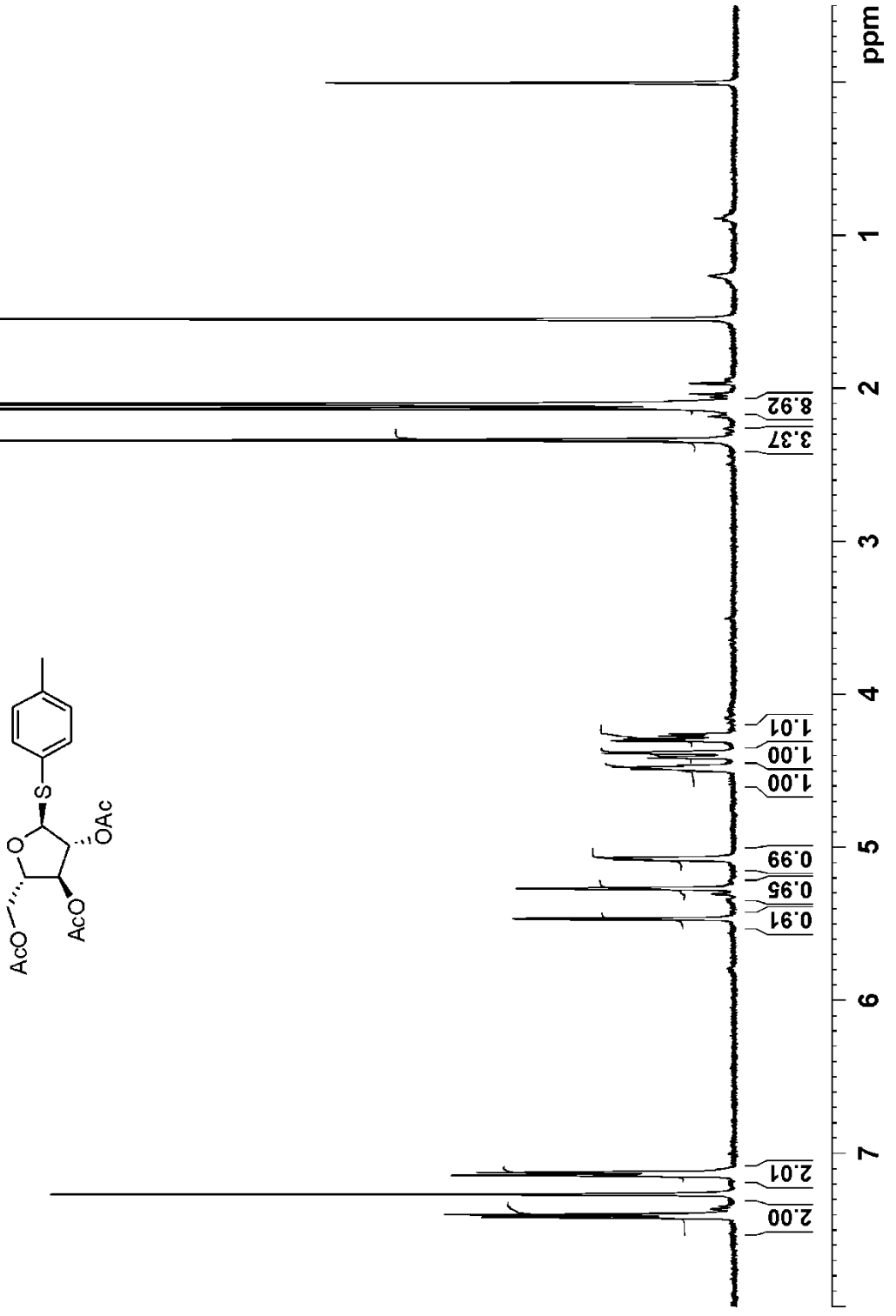
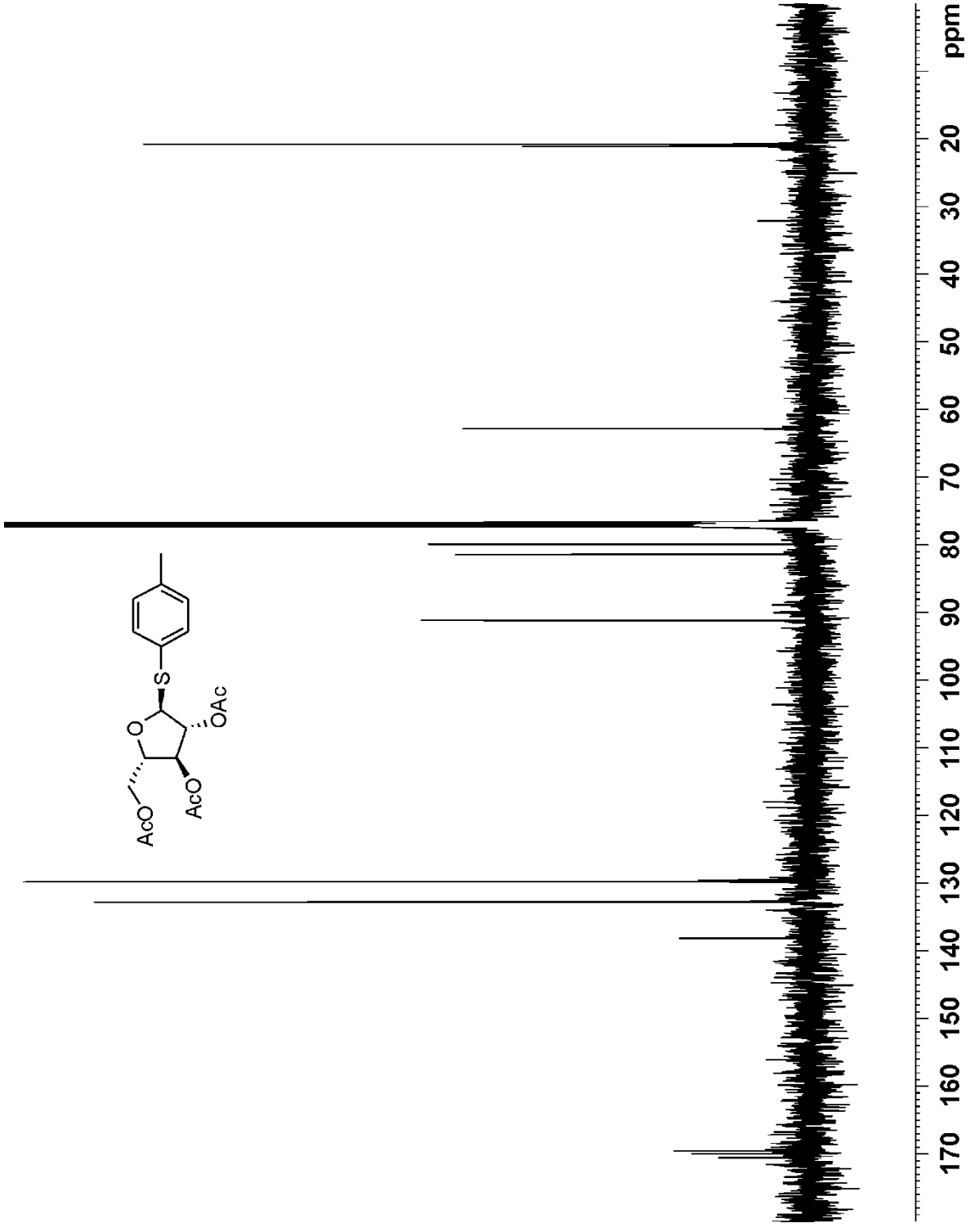
C-β (35.3, 35.5, 36.0, 36.6), C-δ (50.3, 51.0, 51.6, 51.7), C-α (56.6, 56.8, 57.8, 58.0), **C**H_2CH=CH_2 (65.7, 65.9), O**C**H_2Ph (72.0-72.8, 73.4, 73.5), furanose C5 73.3, C-γ (73.8, 74.3), $(CH_3)_3$**C**- (75.5, 76.8), furanose C2,3,4 (79.8-84.2), furanose C1 (98.5, 99.3, 98.9, 101.3), CH_2CH=**C**H_2 (118.4, 118.7), aromatic CH (127.7-128.6), CH_2**C**H=CH_2 (131.8, 131.9), aromatic -C- (137.4-138.2), N**C**OOR (153.7, 154.2), **C**OR (171.4, 171.6, 171.4, 171.5); HRMS (ESI) calcd $C_{70}H_{80}N_2O_{15}Na$ for $(M+Na)^+$: 1211.5456; obsd: 1211.5412.

*signals in parentheses signify pairs of rotamers.

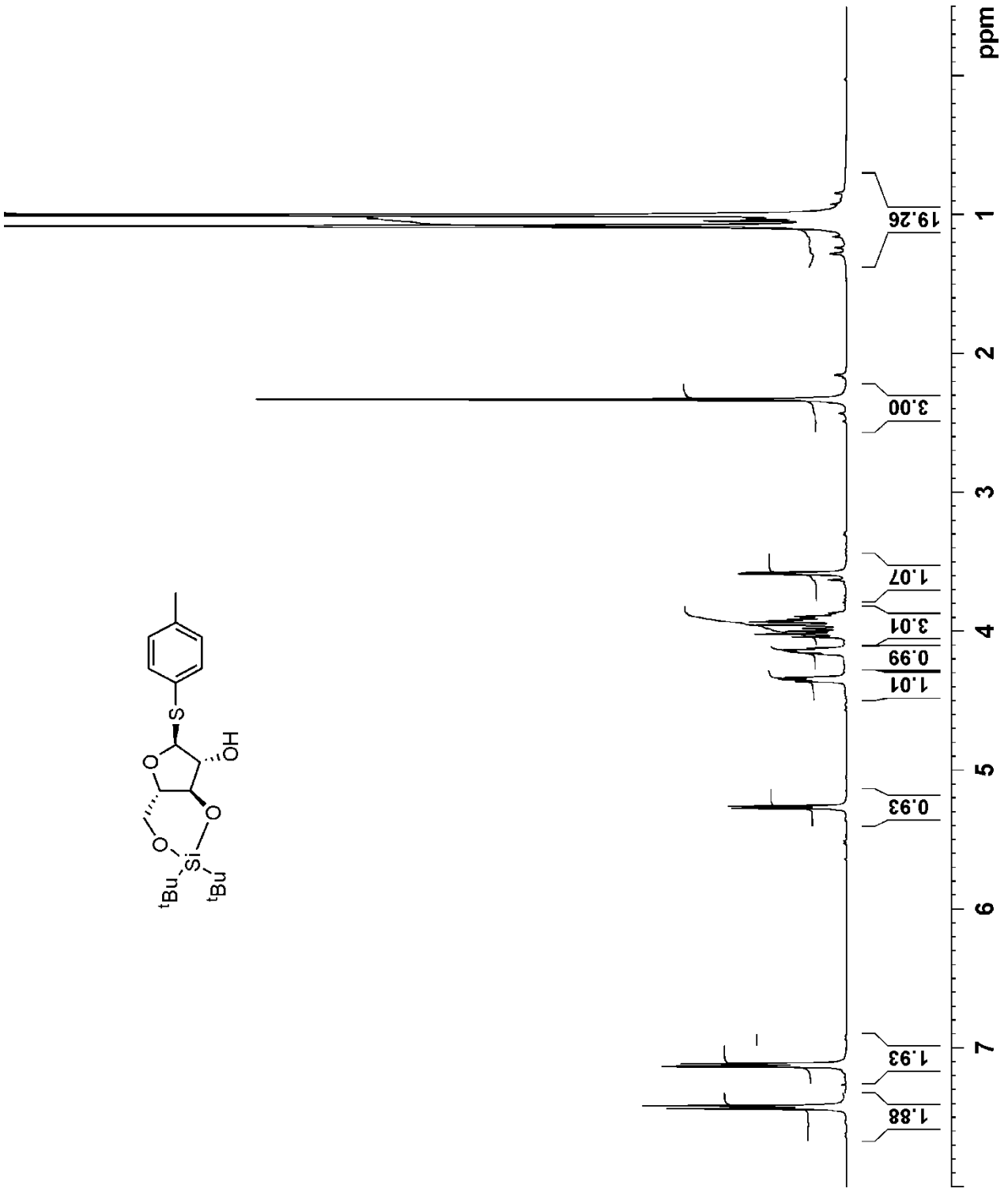
Compound **3** – thioglycoside triacetate – ^{1}H NMR spectrum - $CDCl_3$, 400 MHz



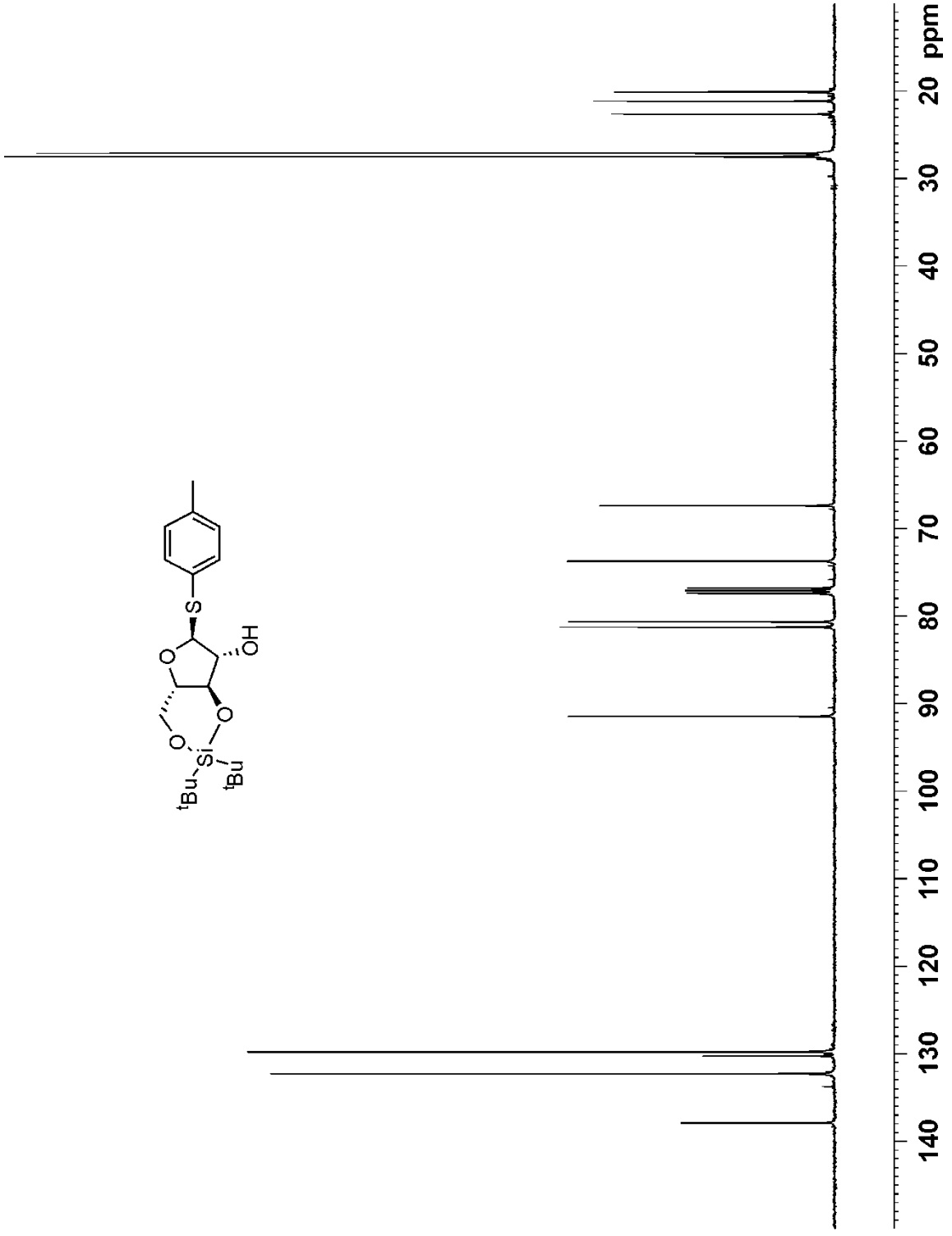
Compound **3** – thioglycoside triacetate – ^{13}C NMR spectrum - $CDCl_3$, 100 MHz



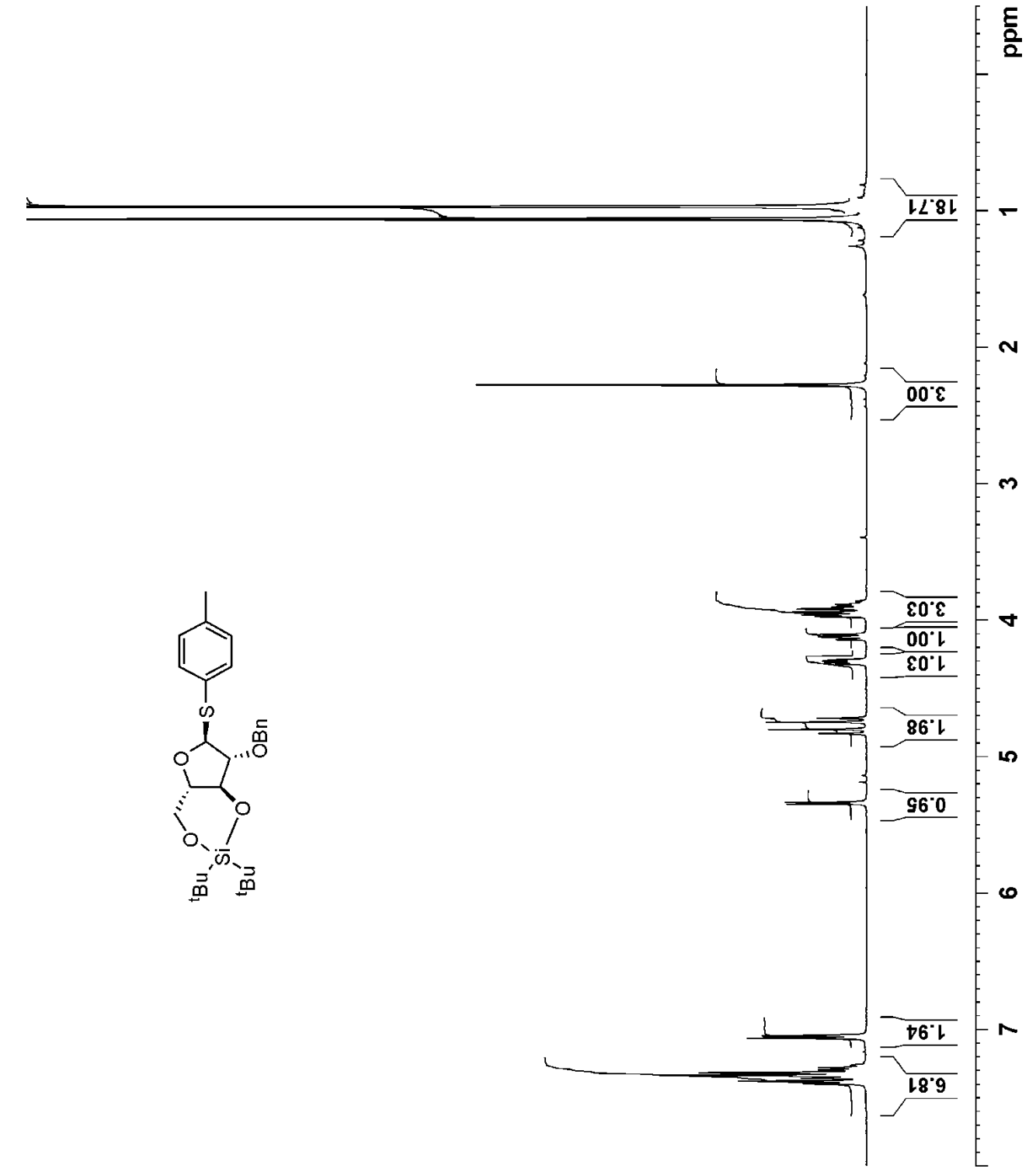
Compound **4** – silyl acetal – ^{1}H NMR spectrum - $CDCl_3$, 400 MHz



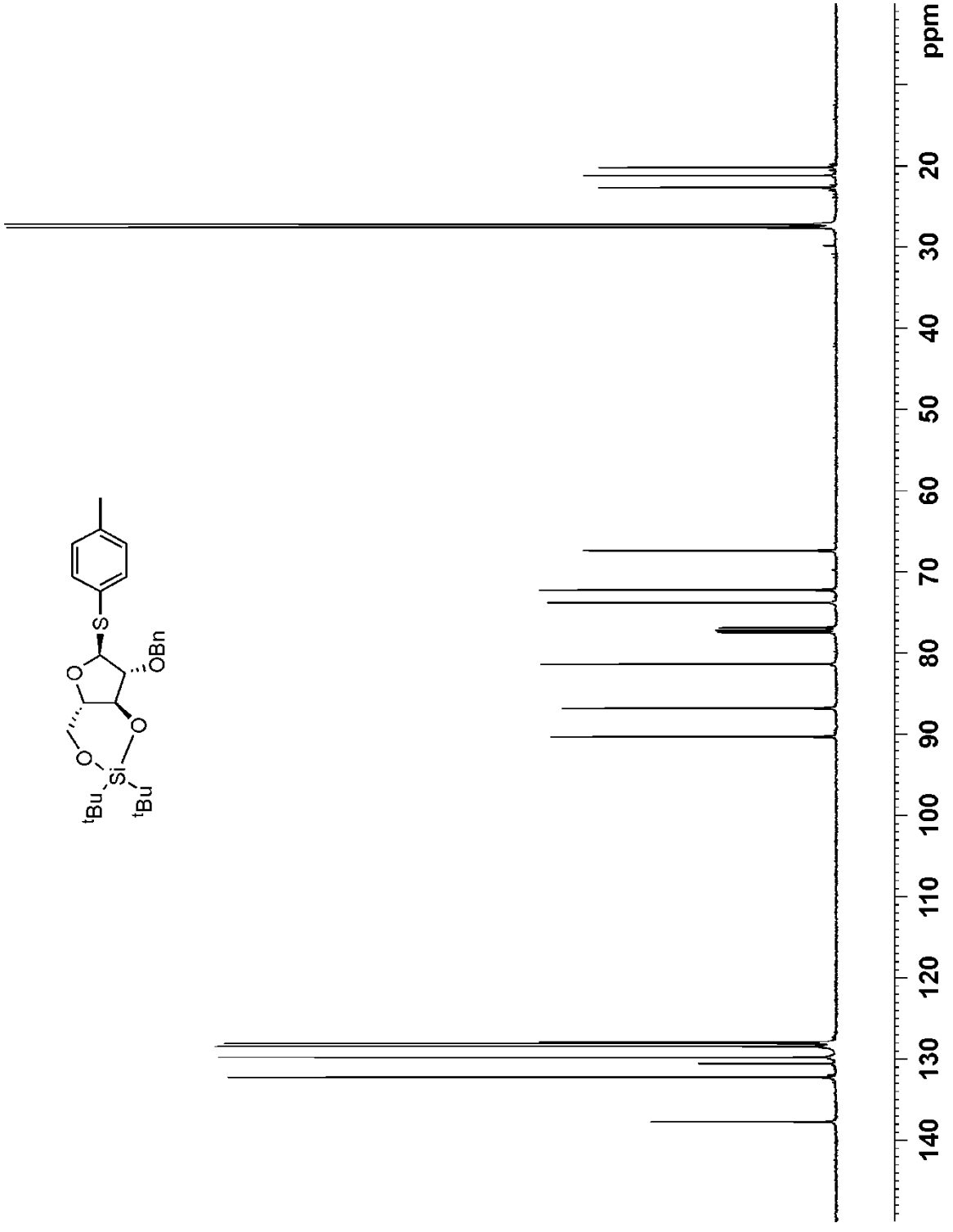
Compound **4** – silyl acetal – ^{13}C NMR spectrum - $CDCl_3$, 100 MHz



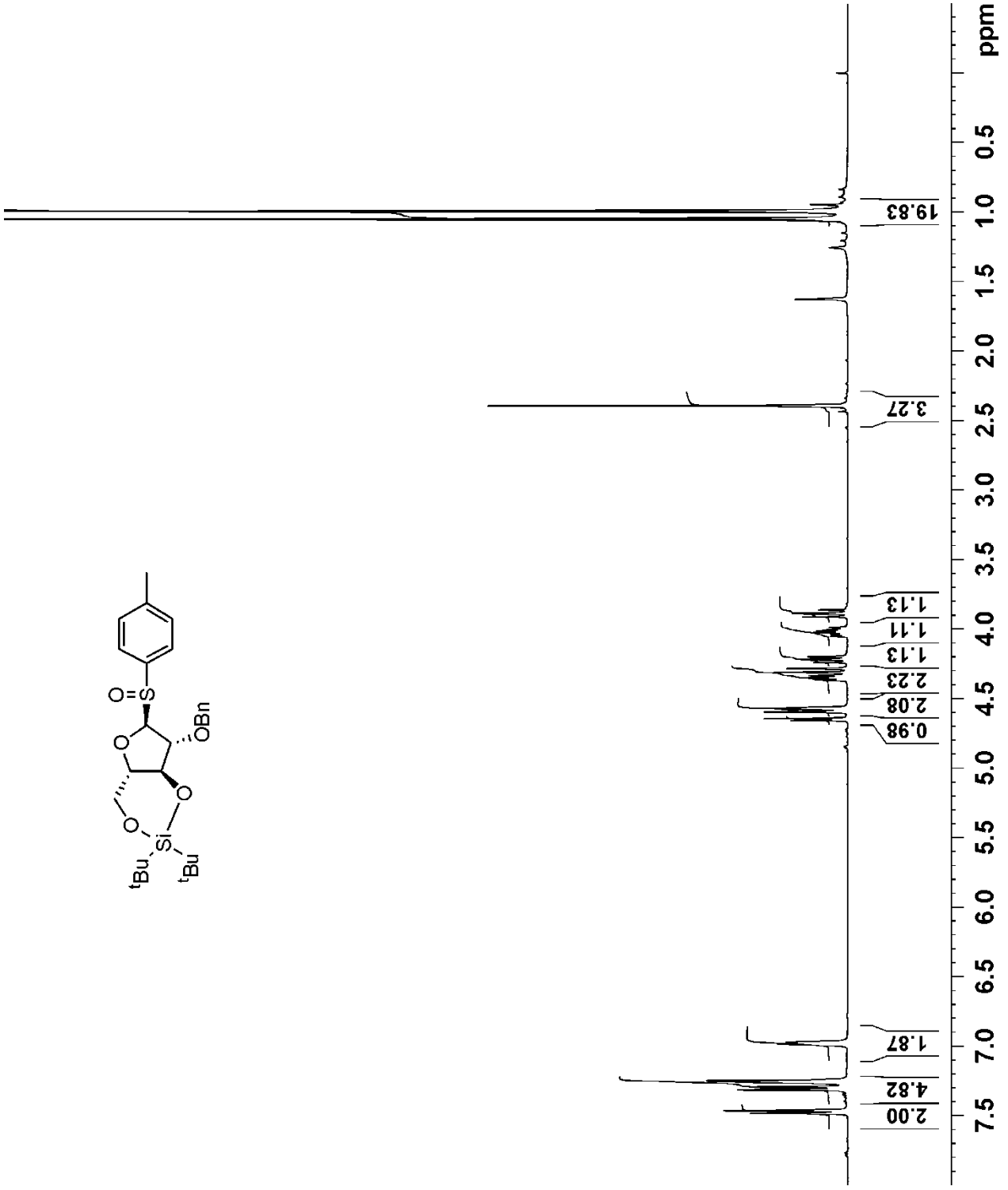
Compound **5** – silyl acetal, benzyl ether – ^{1}H NMR spectrum - $CDCl_3$, 400 MHz



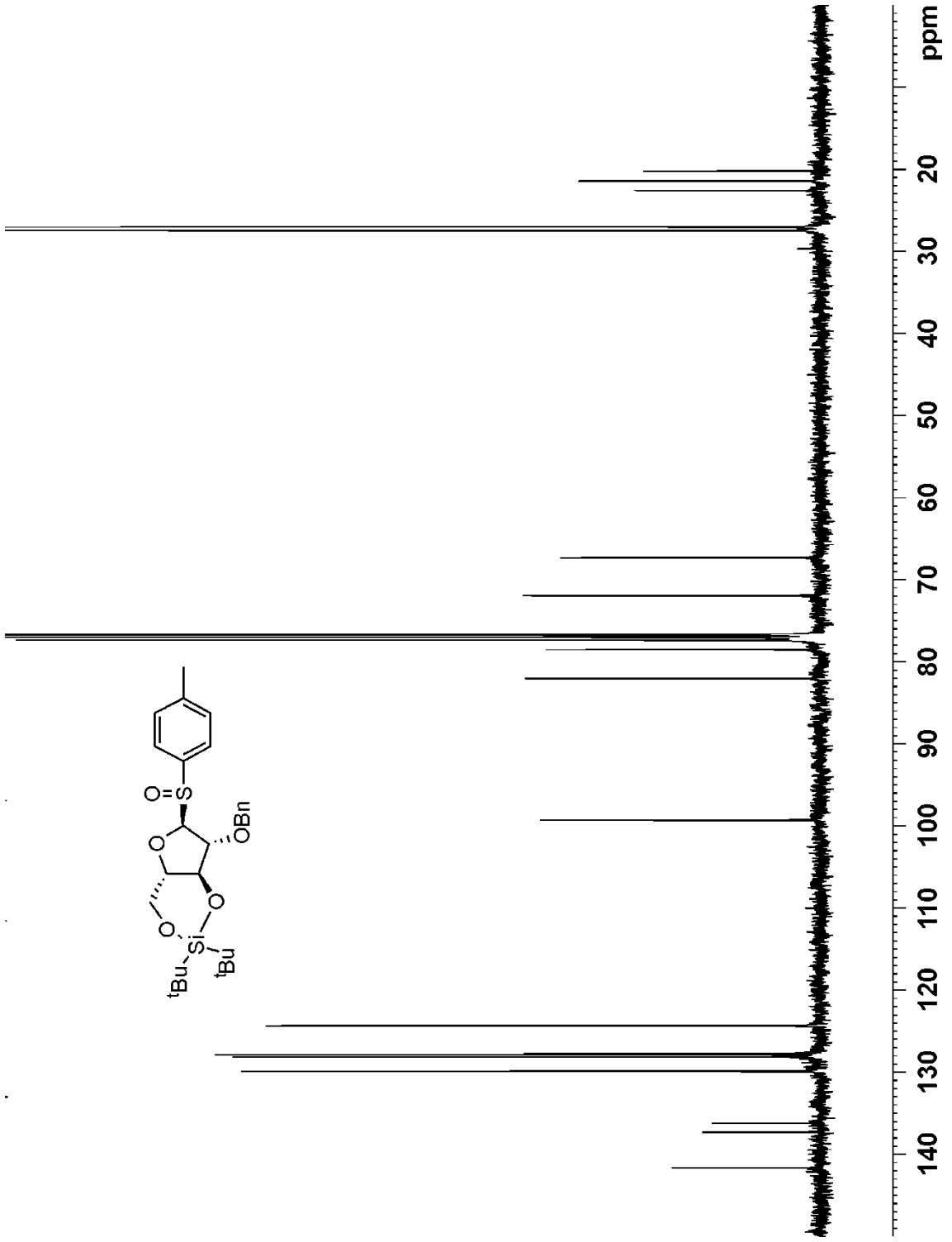
Compound **5** – silyl acetal, benzyl ether – ^{13}C NMR spectrum - $CDCl_3$, 100 MHz



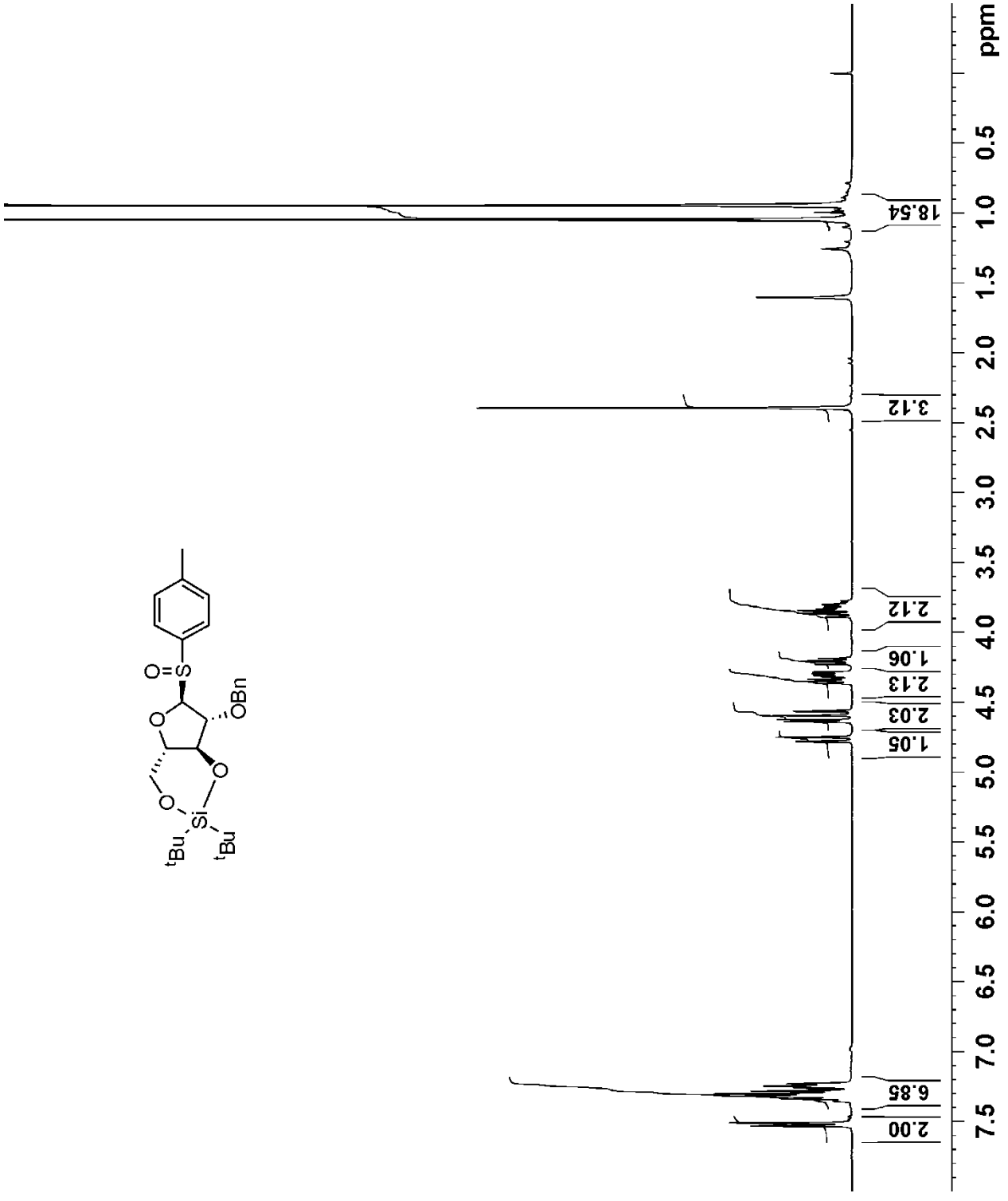
Compound **6A** – sulfoxide, first-eluting diastereomer – ^{1}H NMR spectrum - $CDCl_3$, 400 MHz



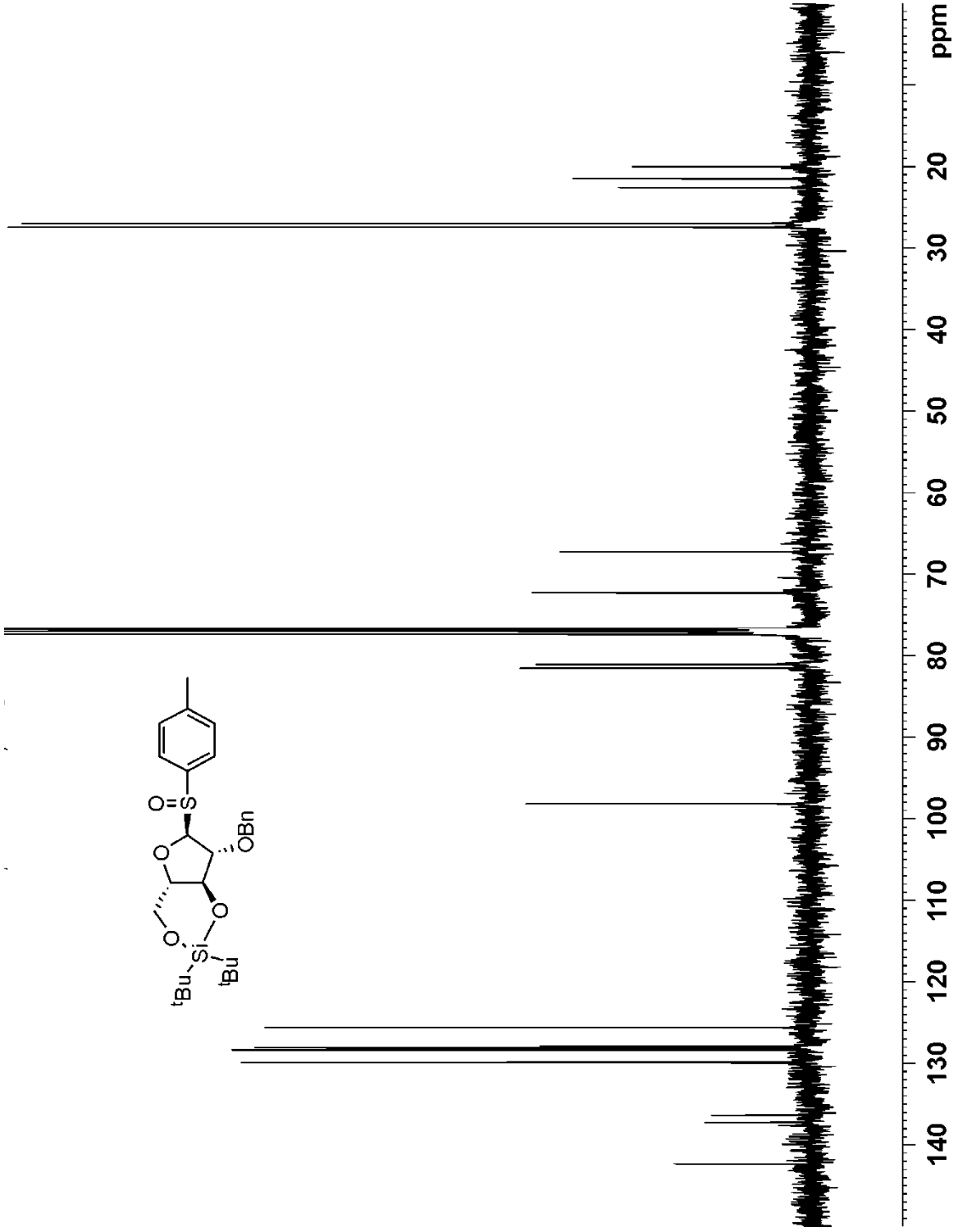
Compound **6A** – sulfoxide, first-eluting diastereomer – ^{13}C NMR spectrum - $CDCl_3$, 100 MHz



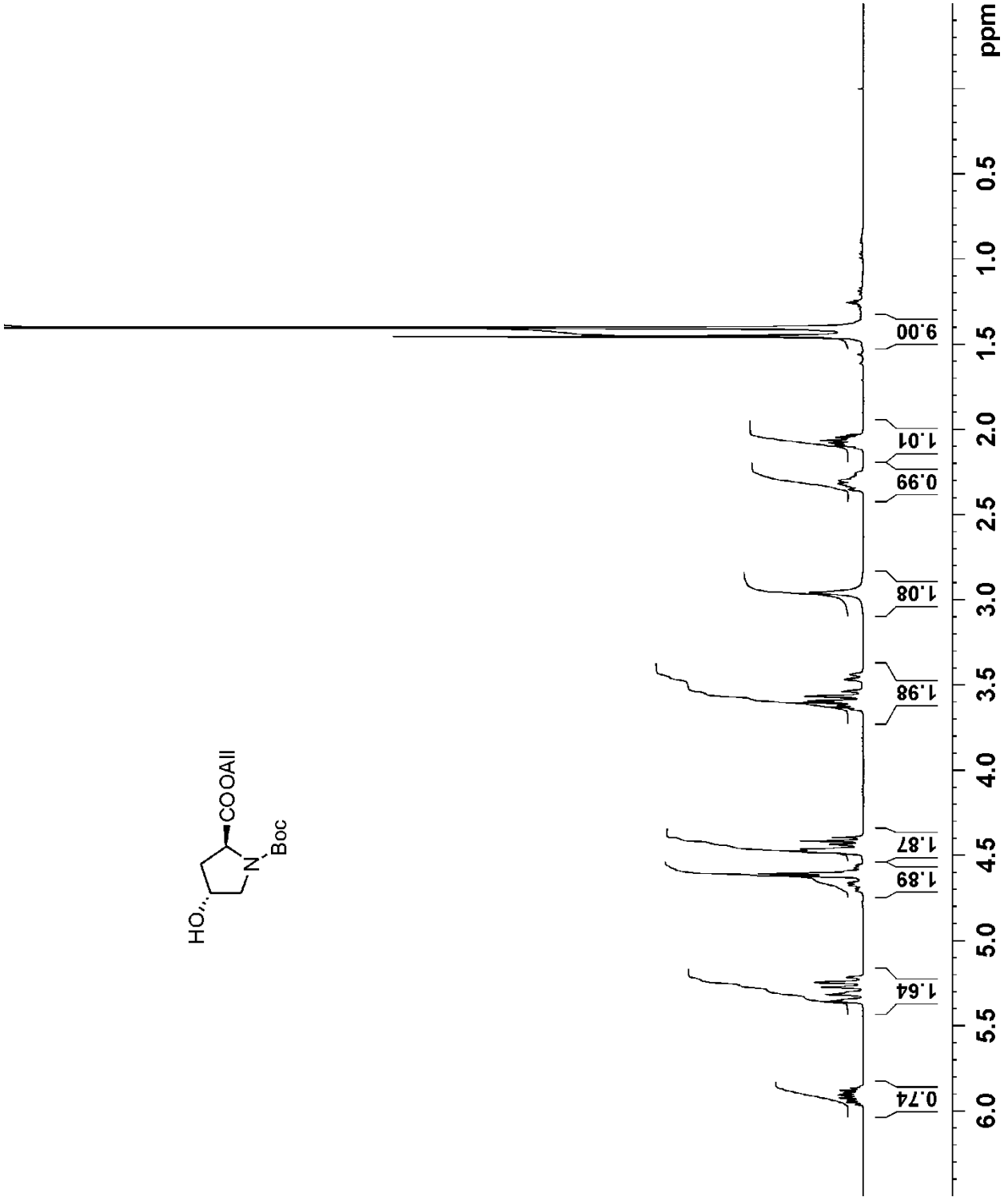
Compound **6B** – sulfoxide, second-eluting diastereomer – ^{1}H NMR spectrum - $CDCl_3$, 400 MHz



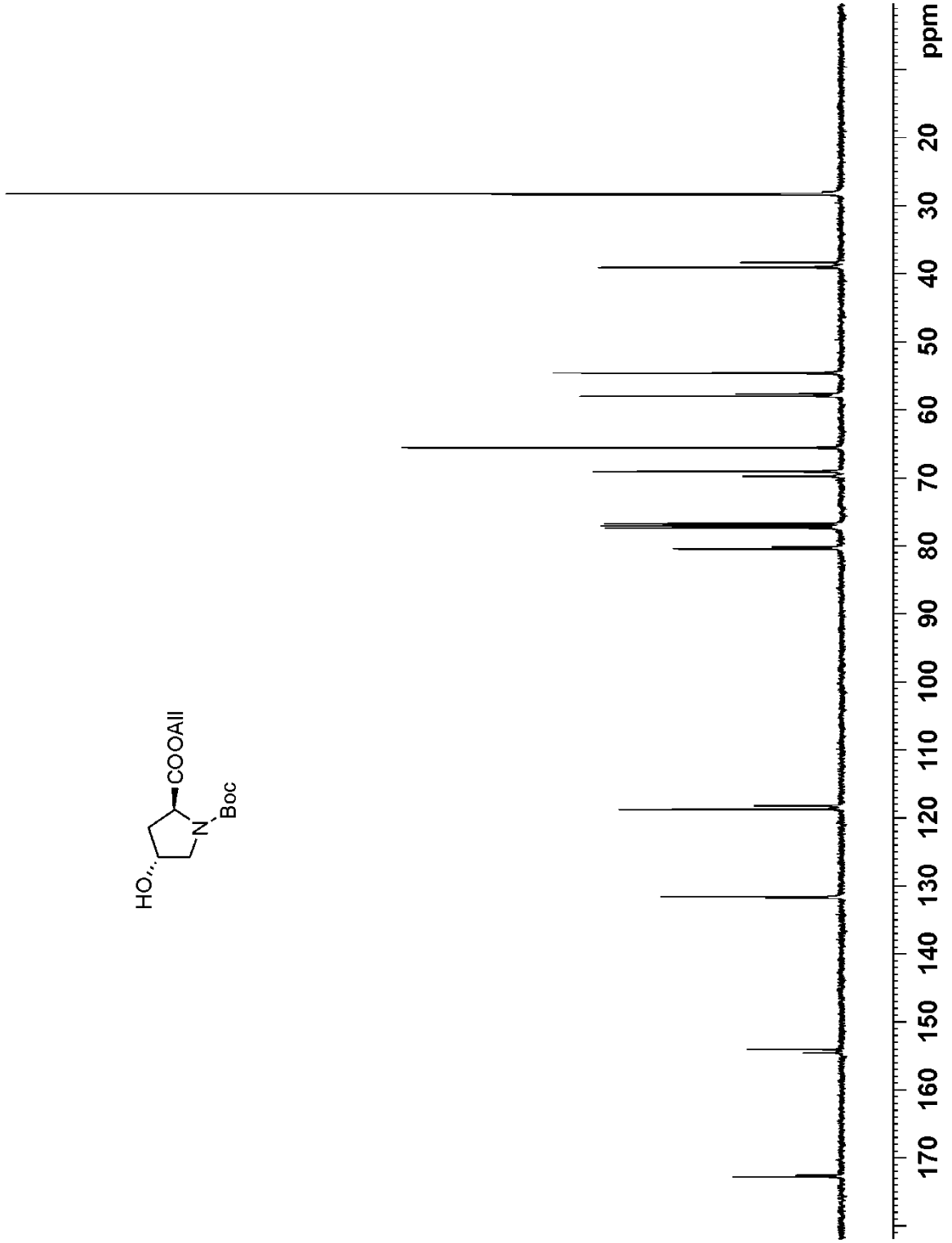
Compound **6B** – sulfoxide, second-eluting diastereomer – ^{13}C NMR spectrum - $CDCl_3$, 100 MHz



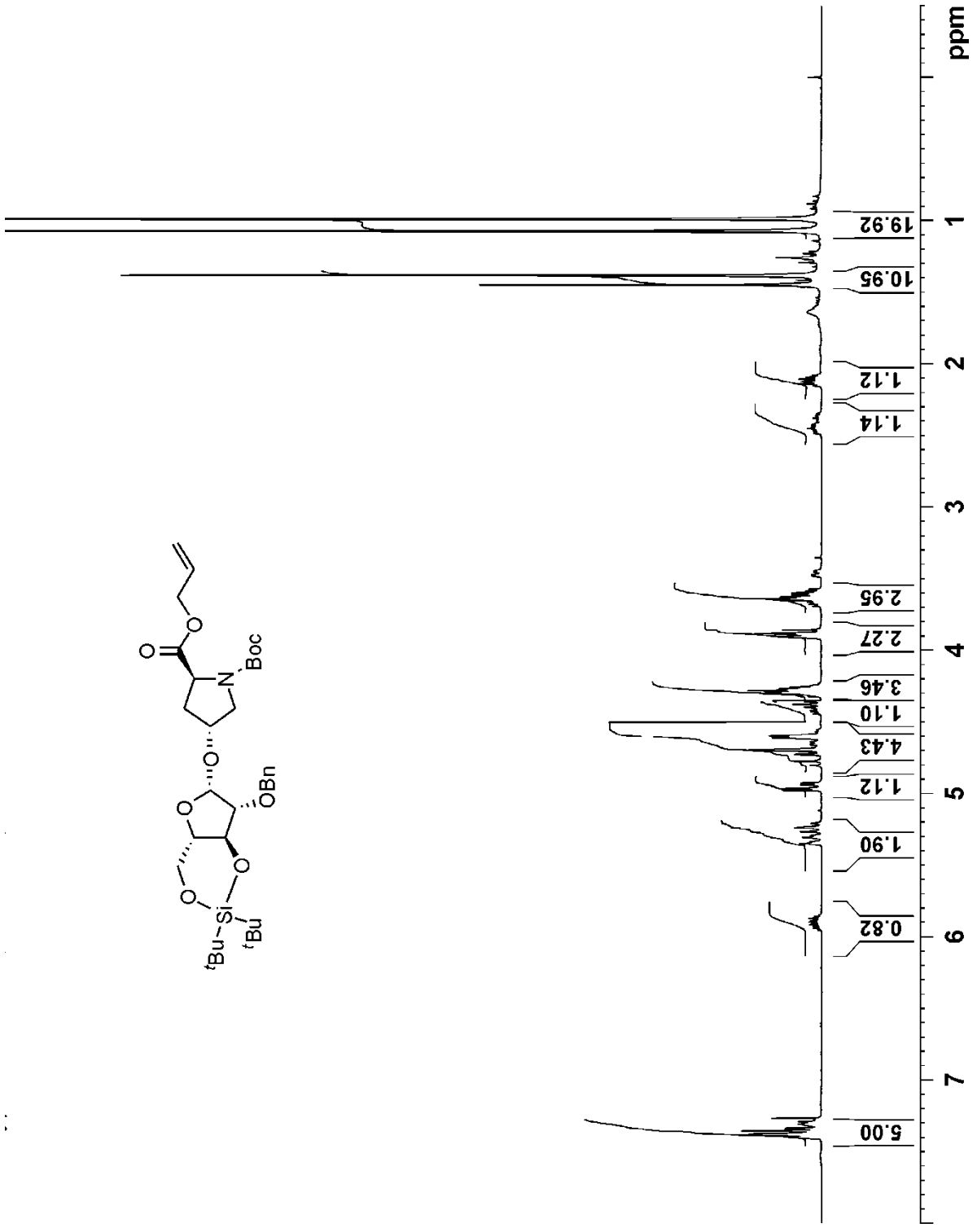
Compound **7** – Boc-Hyp-OAll – ^{1}H NMR spectrum - $CDCl_3$, 400 MHz



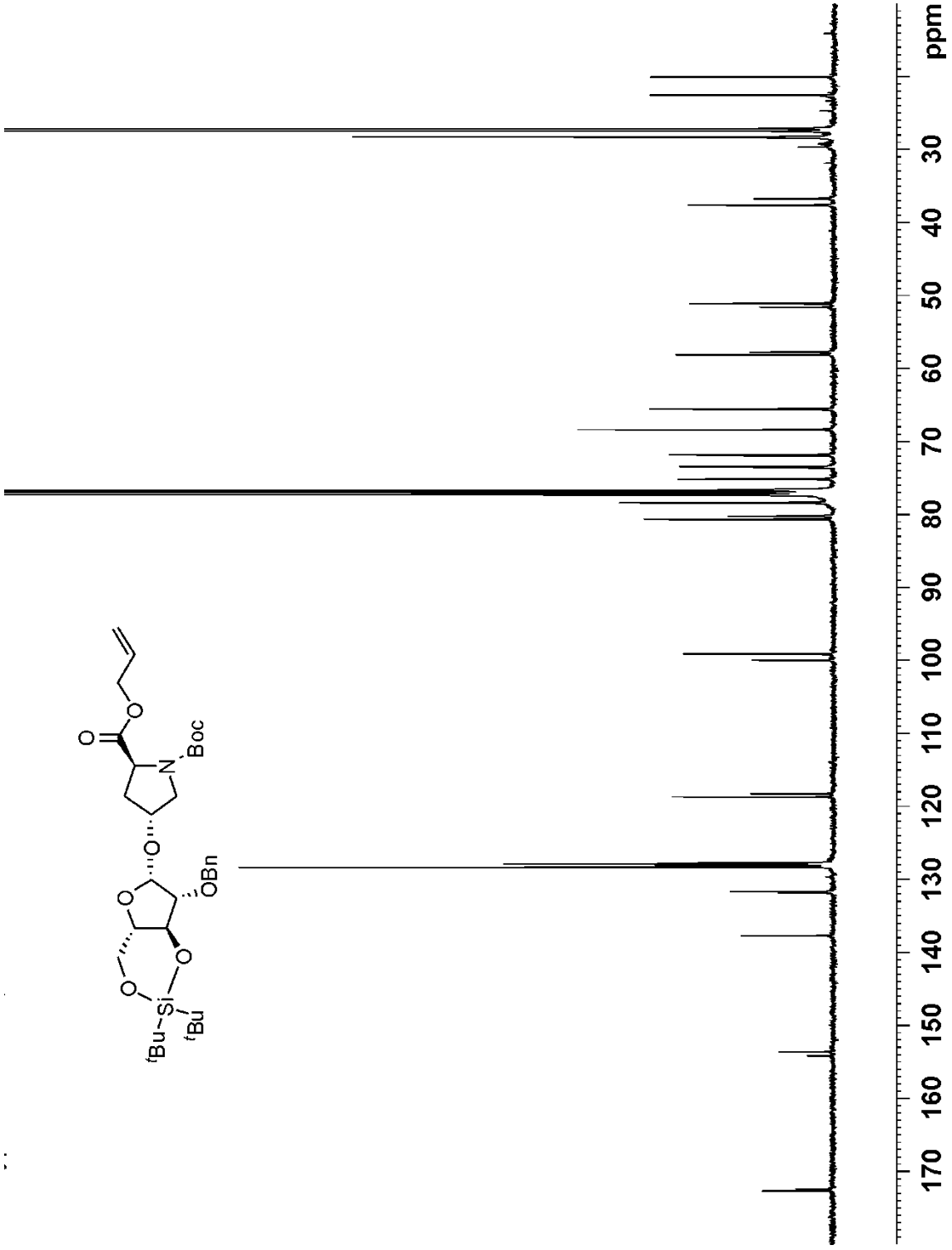
Compound **7** – Boc-Hyp-OAll – ^{13}C NMR spectrum - $CDCl_3$, 100 MHz



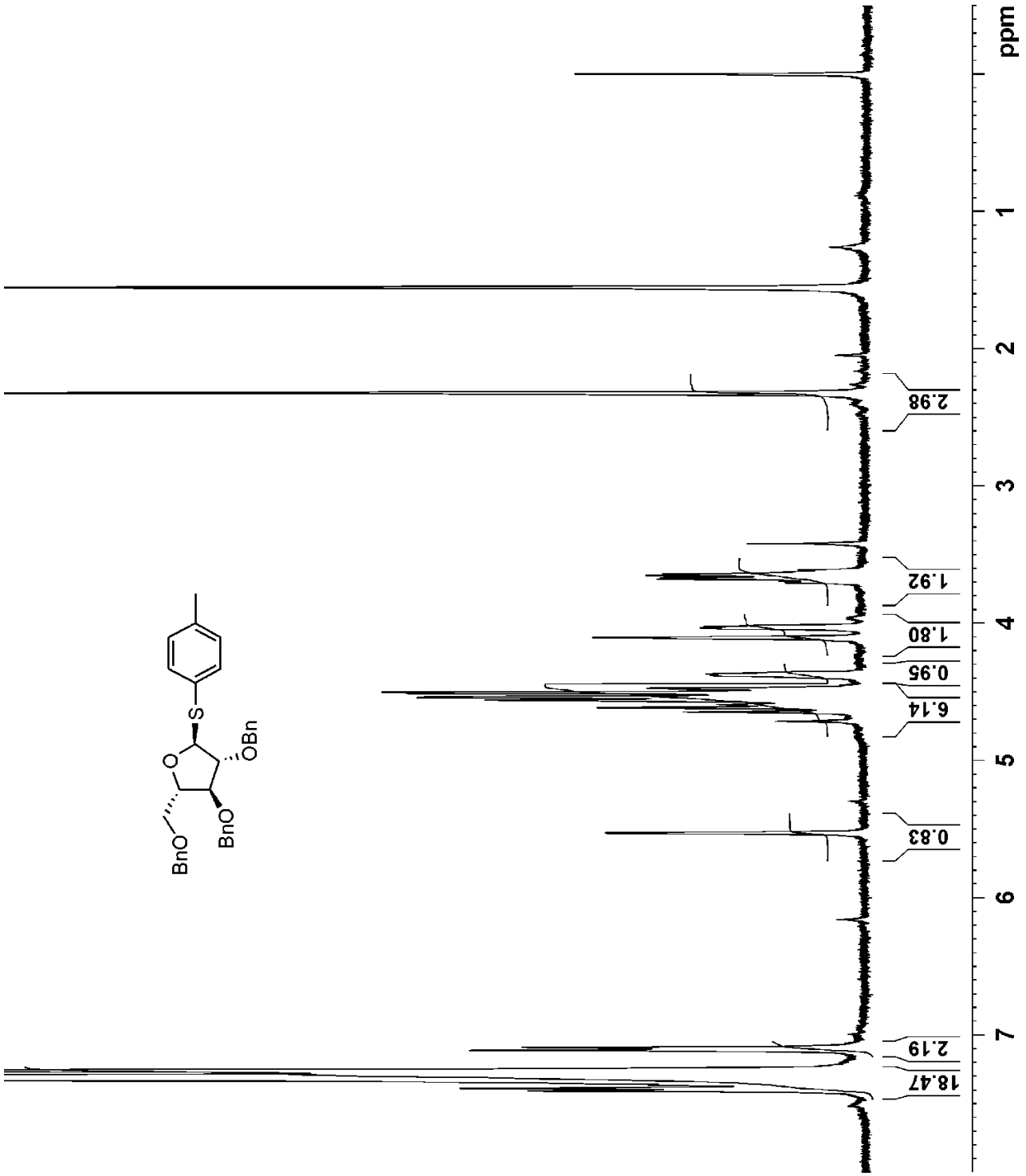
Compound **8β** – beta-glycoside – ^{1}H NMR spectrum - $CDCl_3$, 400 MHz



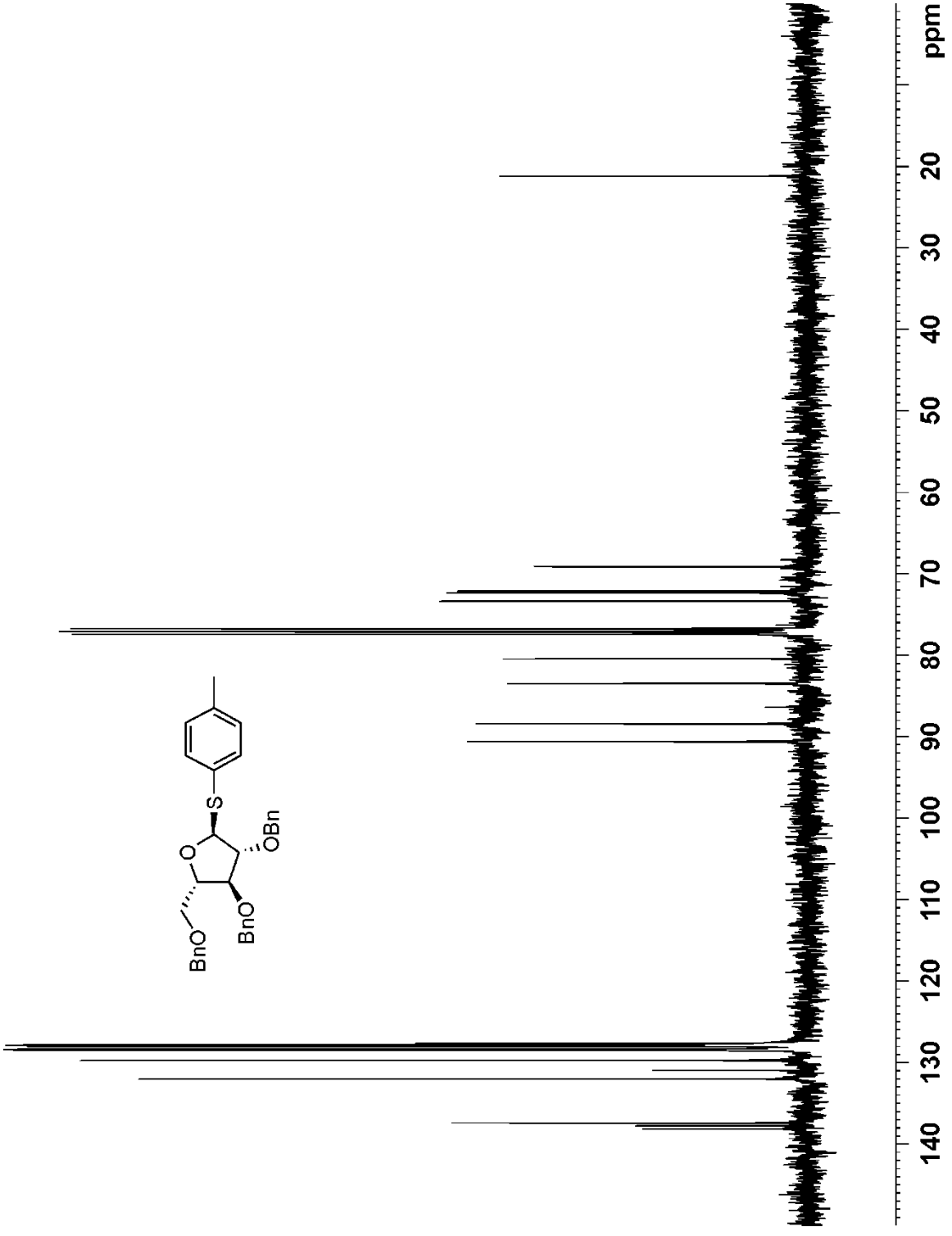
Compound **8β** – beta-glycoside – ^{13}C NMR spectrum - $CDCl_3$, 100 MHz



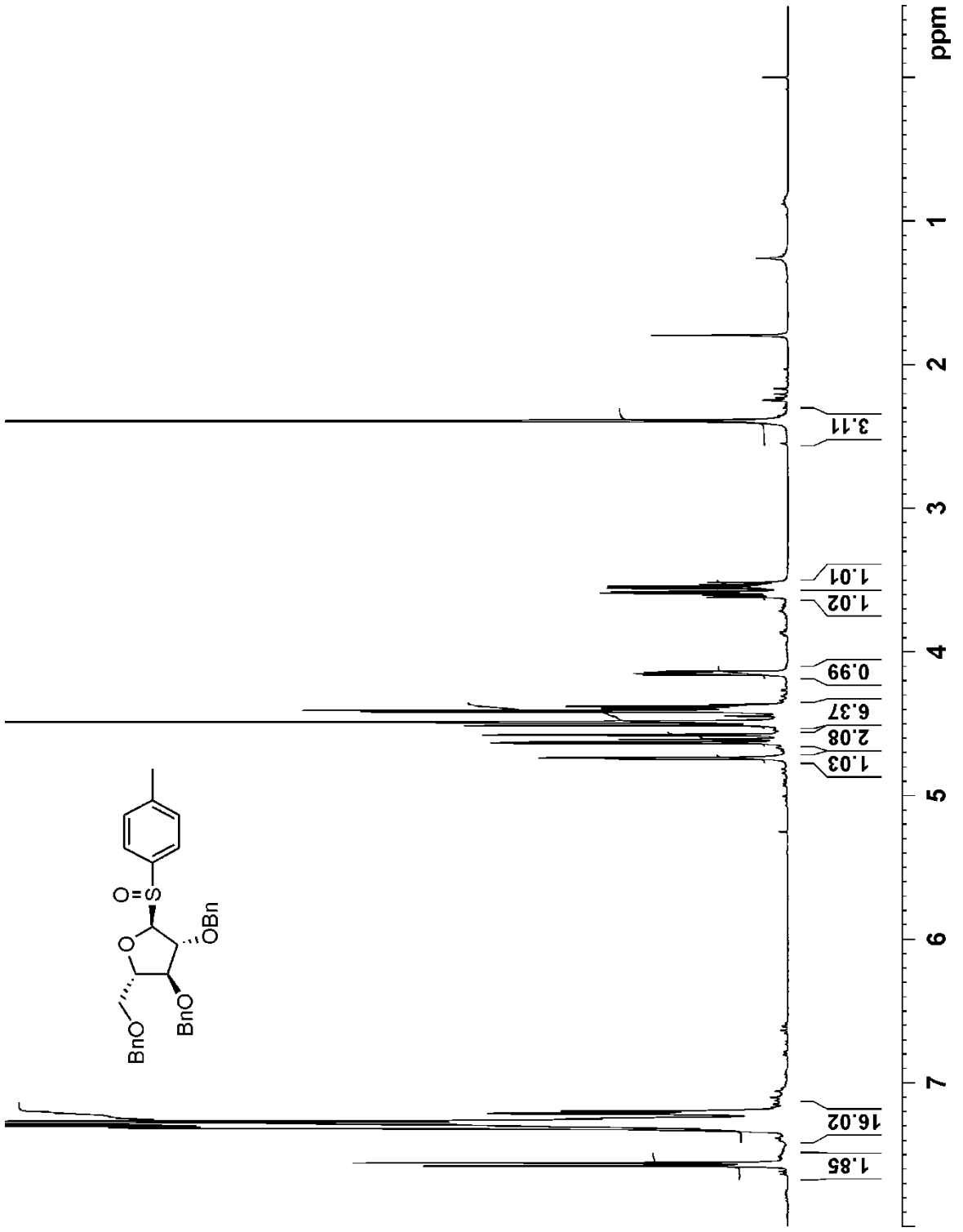
Compound **9** – perbenzylated thioglycoside – ^{1}H NMR spectrum - $CDCl_3$, 400 MHz



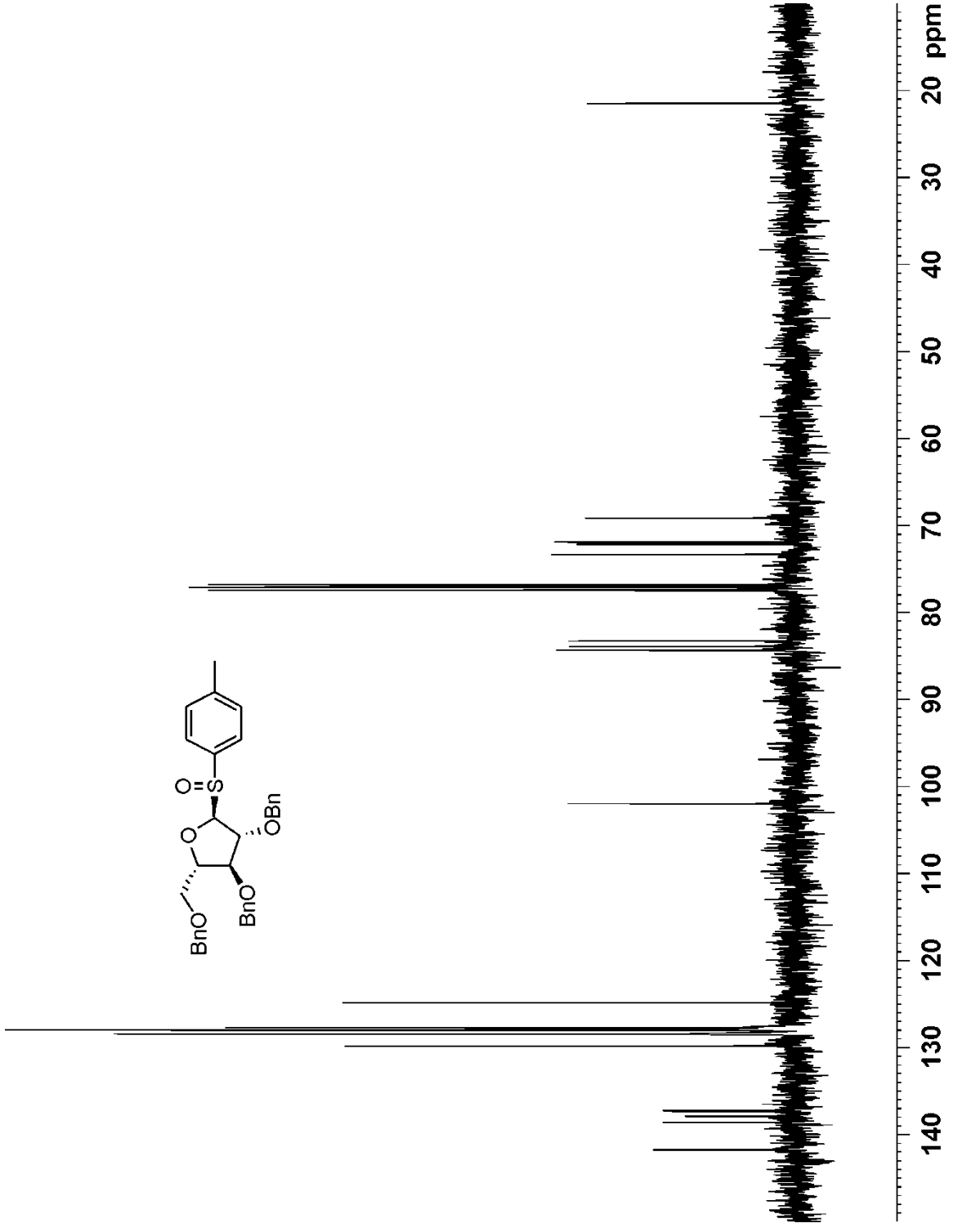
Compound **9** – perbenzylated thioglycoside – ^{13}C NMR spectrum - $CDCl_3$, 100 MHz



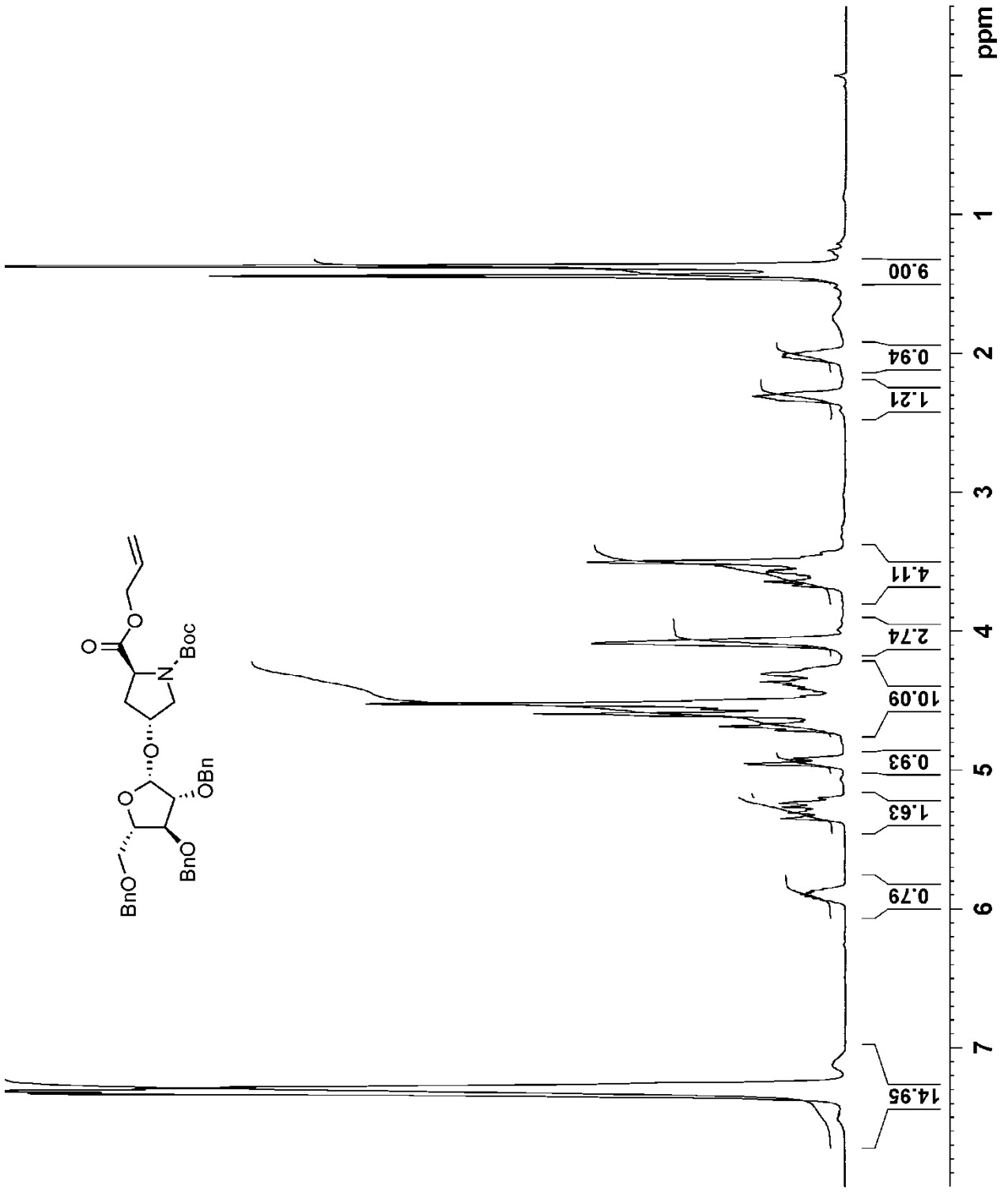
Compound **10** – perbenzylated sulfoxide – ^{1}H NMR spectrum - $CDCl_3$, 400 MHz



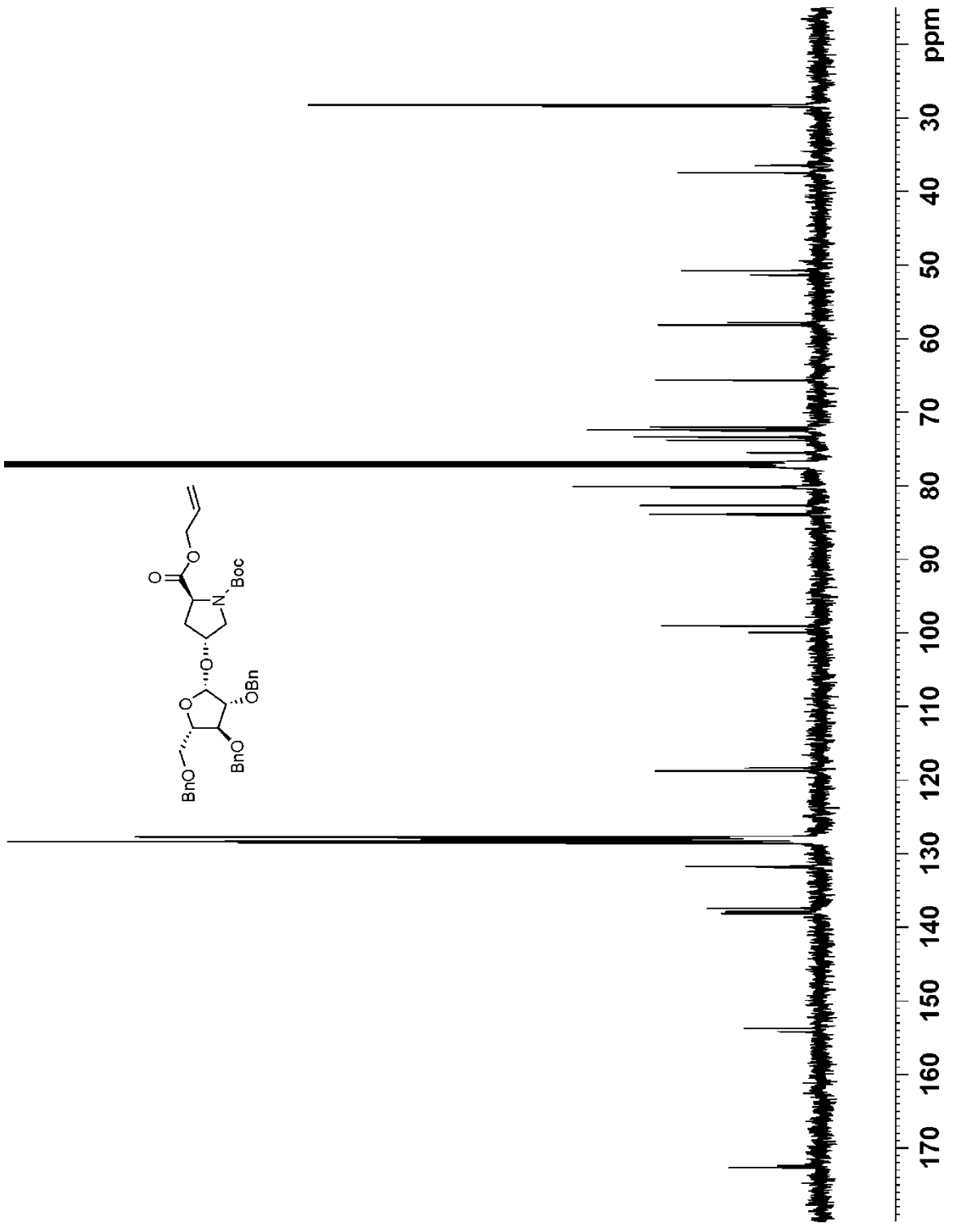
Compound **10** – perbenzylated sulfoxide – ^{13}C NMR spectrum - $CDCl_3$, 100 MHz



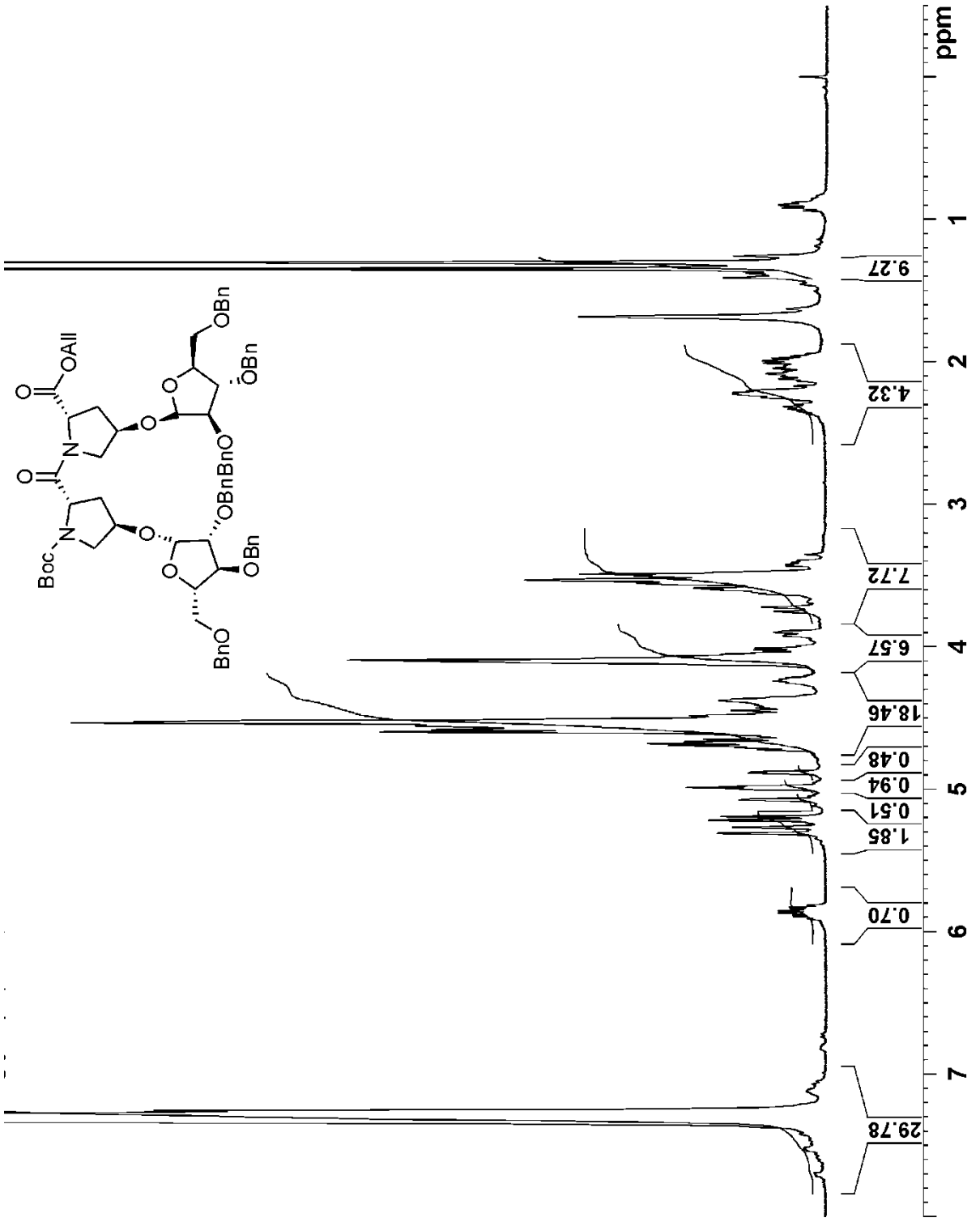
Compound **11β** – beta-glycoside – ^{1}H NMR spectrum - $CDCl_3$, 400 MHz



Compound **11β** – beta-glycoside – ^{13}C NMR spectrum - $CDCl_3$, 100 MHz



Compound **1** – Boc-[(β-*L*-Ara*f*)Hyp]$_2$-OAll – ^{1}H NMR spectrum - $CDCl_3$, 400 MHz



Compound **1** – Boc-[(β-*L*-Ara*f*)Hyp]$_2$-OAll – ^{13}C NMR spectrum - $CDCl_3$, 100 MHz