Electronic Supplementary Information

A Reverse Strategy for Synthesis of Nucleosides

Bert Fraser-Reid,*[a] Parimala Ganney,[a] Changalvala Ramamurty,*[a] Ana M. Gómez,[b] and J. Cristóbal López[b]

[a] *Natural Products and Glycotechnology Research Institute, Inc#. 595 F Weathersfield Road, Pittsboro, NC 27312 USA. #An independent non-profit research facility with laboratories at CiVentiCHEM, P.O. Box 12041, Research Triangle Park, NC 27709.*

[b] *Instituto de Química Orgánica General (IQOG-CSIC) Juan de la Cierva 3, 28006 Madrid, Spain.*

E-mail: dglucose@aol.com (BFR)

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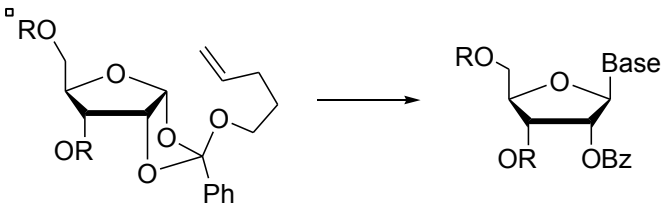
1. General Information

Chemicals were purchased and used without further purification. Dry solvents were obtained by distillation using standard procedures. Unless stated otherwise, reactions were carried out under a dry argon atmosphere in vacuum-flame dried glassware. Detection was by examination under UV light (254 nm) and by charring with 10% sulfuric acid in ethanol. Flash column chromatography was performed using silica gel [Merck, 230−400 mesh (40−63 μm)]. Extracts were concentrated *in vacuo* using both a Büchi rotary evaporator (bath temperatures up to 40 °C) at a pressure of either 15 mmHg (diaphragm pump) or 0.1 mmHg (oil pump), as appropriate, and a high vacuum line at room temperature. ^{1}H NMR and ^{13}C NMR spectra were measured in the solvent stated at 200 and 50 MHz respectively. Chemical shifts are quoted in parts per million from residual solvent peak ($CDCl_3$: ^{1}H - 7.26 ppm and ^{13}C - 77.16 ppm) and coupling constants (*J*) given in Hertz. Multiplicities are abbreviated as: b (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or combinations thereof. The units of the specific rotation, (deg·mL)/(g·dm), are implicit and are not included with the reported value. Concentration *c* is given in g/100 mL. Starting *n*-pentenyl orthoesters **1**, **6** and **25** were prepared following previously described procedures[1] and the exchange of substituents at the different hydroxyl groups was carried out following routine procedures[2].

2. General procedure for N*-glycosidation with* n*-pentenyl orthoesters.*

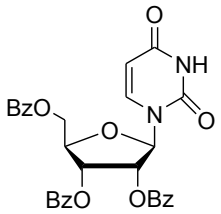


General procedure for silylation of nucleobases. A suspension of the nucleobase (1 mmol), in hexamethyldisilazane (HMDS) (6 mmol) was treated under a N_2 atmosphere with TMSOTf (10% mol), then heated to 85 ºC and kept at that temperature until reaction mixture became clear (~2–3 hr). The reaction mixture was then concentrated *in vacuo* and the crude was azeotroped 2–3 times with anhydrous CH_2Cl_2 under nitrogen. The obtained solids were kept under high vacuum overnight to remove traces of solvent.

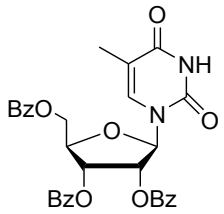
General experimental procedure for *N*-glycosidation. To a stirred solution of the appropriate NPOE (1.0 mmol) in anhydrous acetonitrile (1 mL) was added a solution of silylated base (1.2 mmol) in acetonitrile (2 mL) at 0 ^{o}C and allowed to stir for 10 min at this temperature. To this reaction mixture was

added a solution of NIS (1.1 mmol) and $Yb(OTf)_3$ (30 mol-%) in CH_3CN (2 mL) at 0 ^oC and the mixture was allowed to stir at room temperature for the appropriate time (~3–10 h, analysis by TLC). After which, the reaction mixture was quenched with saturated sodium thiosulphate solution (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuum. The resulting crude mixture was purified by column chromatography on silica gel to afford the pure nucleoside.

3. Synthesis and characterization of perbenzoylated ribo nucleosides.

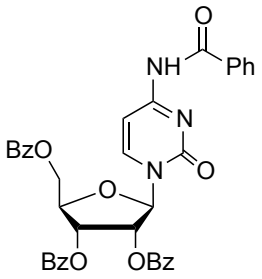


2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl-uracil (11a): The compound was prepared according to general procedure with uracil **7a** (1.2 mmol, 134 mg) and orthoester **6** (1 mmol, 530 mg) over a course of 4 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc (2:3) to give the desired product **11a** (511 mg, 92% yield) as a colorless crystalline solid. ^1H NMR (200 MHz, $CDCl_3$): δ 8.60 (bs, 1H), 8.15–7.90 (m, 6H), 7.65–7.30 (m, 10H), 6.31 (d, J = 4.4 Hz, 1H), 5.74 (dd, J = 5.4 Hz, 6.0 Hz, 1H), 5.60 (d, J = 8.2 Hz, 1H), 4.87–4.62 (m, 3H), ^{13}C NMR (80 MHz, $CDCl_3$): δ 166.3, 165.6, 165.5, 163.4, 150.5, 139.9, 134.0, 134.0, 133.9, 130.2, 130.1, 129.9, 129.5, 129.0, 128.8, 128.6, 103.7, 88.4, 80.4, 74.0, 71.4, 64.0. Proton and carbon NMR were consistent with literature data.[3]

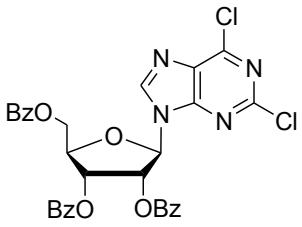


2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl-thymine (11b): The compound was prepared according to general procedure with thymine **7b** (0.6 mmol, 76 mg) and orthoester **6** (0.5 mmol, 265 mg) over a course of 4 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 2:3 to give the desired product **11b** (276 mg, 97% yield). ^1H NMR (200 MHz, $CDCl_3$): δ 8.80 (bs,1H), 8.18–8.14 (m, 2H), 8.0–7.90 (m, 4H), 7.66–7.32 (m, 9H), 6.43 (d, J = 6.2 Hz, 1H), 5.9 (dd, J = 3.2 Hz, J = 3.4 Hz, 1H), 5.75 (t, J = 5.8 Hz, 1H), 4.82–4.94 (m, 1H), 4.72–4.60 (m, 2H), 1.57 (s, 3H), ^{13}C NMR (80 MHz, $CDCl_3$): δ 166.2, 165.6, 165.6, 164.0, 150.8, 135.2, 134.0, 133.9, 130.2, 130.1, 129.9,

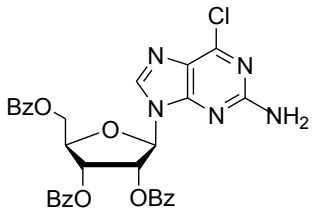
129.5, 129.1, 128.9, 128.8, 128.6, 112.4, 87.3, 80.8, 73.7, 71.7, 64.2, 12.3. Proton and carbon NMR were consistent with literature data.[4]



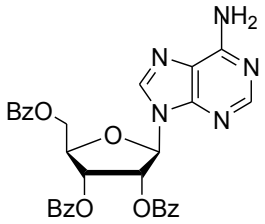
2,3,5-tri-*O*-benzoyl-β-D**-ribofuranosyl-*N*4-benzoyl cytosine (12):** The compound was prepared according to general procedure from *N4*-benzoylcytosine **8** (0.6 mmol, 129 mg) and orthoester **6** (0.5 mmol, 265 mg) over a course of 2 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 3:7 to give the coupling product **12** (287 mg, 82% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.78 (bs, 1H), 8.16–8.03 (m, 2H), 8.0–7.82 (m, 7H), 7.66–7.21 (m, 13H), 6.43 (d, J = 6.2 Hz, 1H), 5.9 (d, J = 4.4 Hz, 1H), 5.88–5.81 (m, 2H), 4.94–4.68 (m, 3H), ^{13}C NMR (80 MHz, $CDCl_3$): δ166.3, 165.4, 144.3, 133.8, 133.4, 130.2, 130.0, 129.8, 129.5, 129.2, 128.9, 128.6, 127.8, 89.7, 80.9, 74.9, 71.2, 63.8, 29.9. Proton and carbon NMR were consistent with literature data.[4,5]



2,3,5-tri-*O*-benzoyl-β-D**-ribofuranosyl-2,6-dichloropurine (13a):** The compound was prepared according to general procedure from 2,6-dichloropurine **9a** (0.6 mmol, 113 mg) and orthoester **6** (0.5 mmol, 265 mg) over a course of 4 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 85:15 to give the coupling product **13a** (269 mg, 85% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.07–7.90 (m, 6H), 7.64–7.33 (m, 9H), 6.48 (d, J = 5.2 Hz, 1H), 6.15 (m, 2H), 4.96–4.70 (m, 3H), ^{13}C NMR (80 MHz, $CDCl_3$): δ 166.2, 165.5, 165.4, 153.5, 152.8, 152.3, 144.5, 134.2, 134.1, 133.8, 131.6, 130.0, 129.8, 129.3, 128.9, 128.8, 128.8, 128.3, 87.4, 81.6, 74.5, 71.8, 63.7. Proton and carbon NMR were consistent with literature data.[6]

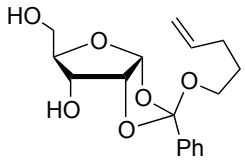


2,3,5-tri-*O*-benzoyl-β-D**-ribofuranosyl-2-amino-6- chloro purine (13b):** The compound was prepared according to general procedure from 2-amino-6-chloropurine **9b** (0.6 mmol, 101 mg) and orthoester **6**(0.5 mmol, 265 mg) over a course of 3 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 4:1 to give the coupling product **13b** (214 mg, 70% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.01–7.80 (m, 6H),7.52–7.05 (m, 10H), 6.48–6.31 (m, 2H), 6.28 (d, J = 4.4 Hz, 1H), 5.20 (bs, 1H), 4.91–4.60 (m, 3H), ^{13}C NMR (80 MHz, $CDCl_3$): δ 166.3, 165.5, 165.3, 159.4, 153.3, 152.0, 141.3, 134.0, 133.9, 133.6, 130.0, 129.9, 129.8, 129.4, 128.9, 128.7, 128.6, 125.9, 87.5, 80.5, 73.7, 71.5, 63.4. Proton and carbon NMR were consistent with literature data.[4]

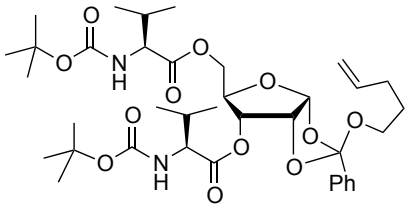


2,3,5-tri-*O*-benzoyl-β-D**-ribofuranosyl-adenine (13c):** The compound was prepared according to general procedure from adenine **9c** (0.6 mmol, 81 mg) and orthoester **6** (0.5 mmol, 265 mg) over a course of 18 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc (100% EtOAc) to give the coupling product **13c** (87 mg, 30% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.12–7.84 (m, 7H), 7.62–7.21 (m, 10H), 6.46–6.32 (m, 2H), 6.30–6.22 (t, J = 4.8 Hz, 1H), 5.72 (bs, 2H), 4.88–4.62 (m, 3H), ^{13}C NMR (80 MHz, $CDCl_3$): δ 166.4, 165.5, 165.3, 156.0, 153.5, 149.9, 139.3,133.9, 133.8, 133.6, 130.0, 129.9, 129.6, 129.0, 128.7, 120.3, 87.1, 80.8, 76.6,74.2, 71.7, 63.9. Proton and carbon NMR were consistent with literature data.[7]

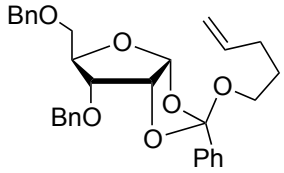
4. Preparation of differentially protected ribo **n-***pentenyl orthoesters* **.**



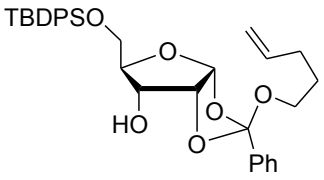
β-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (15a): To a well stirred solution of *n*-pentenyl orthoester **6** (800 mg, 1.54 mmol) in methanol (10 mL) was treated with triethylamine (1.1 mL, 7.72 mmol) and water (0.5 mL). The reaction mixture was heated to 65 °C and then left stirring at this temperature for 48 hours after which it was determined to be complete by TLC. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography using hexane:EtOAc 2:3 to afford the product **15a** (342 mg, 72 %) as a colorless thick syrup. $[\alpha]_D^{25}$: + 31.7 (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 7.60–7.55 (m, 2H), 7.31–45 7.29 (m, 3H), 5.95 (d, *J* = 4.2 Hz, 1H), 5.70 (m, 1H), 4.90 (m, 2H), 4.71 (m, 1H), 3.93 (m, 1H), 3.74 (dd, *J* = 12.5, 3.4 Hz, 1H), 3.53 (dd, *J* = 12.5, *J* = 3.4 Hz, 1H), 3.43 (m, 1H), 3.34 (m, 2H), 2.01 (m, 2H), 1.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 137.2, 129.9, 128.8 (x 2), 126.4 (x 2), 124.0, 115.4, 104.5, 81.4, 80.0, 71.3, 63.1, 60.8, 53.9, 30.7, 29.0. MS (API-ES positive mode): 345.2 $[M+Na]^+$.



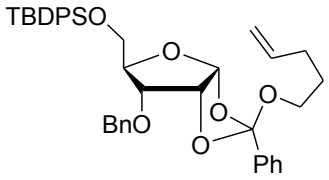
3,5-di-*O*-(*tert*butoxycarbonyl-L-valinoyl)-β-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (15b): A solution of diol **15a** (100 mg, 0.032 mmol), EDCI (124 mg, 0.645 mmol), Fmoc valine (240.4 mg, 0.708 mmol), and DMAP (4.0 mg, 0.032 mmol) in anhydrous DMF (10 mL) was stirred under an N_2 atmosphere at room temperature overnight. The reaction mixture was diluted with water (20 mL) and then extracted with EtOAc (3 x 10 mL) and the organic phase was dried (Na_2SO_4), concentrated in vacuum. The resulting crude mixture was purified on silica gel column using hexane/EtOAc 78:22 to give a colorless syrup **15b** (230 mg, 75%): $[\alpha]_D^{25}$ + 46.0 (*c* 0.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.60 (m, 6H), 7.3 (m, 11H), 6.1 (d, *J* = 3.6 Hz, 1H), 5.75 (m, 1H), 5.3 (t, *J* = 7.6 Hz, 2H), 5.2–4.9 (m, 4H), 4.75 (dd, *J* = 5.2 Hz, *J* = 4.8 Hz, 1H), 4.10–4.0 (m, 10H), 3.42 (m, 2H), 2.1 (m, 4H), 1.6 (pentate, *J* = 7.4 Hz, 2H), 0.95 (d, *J* = 6.6 Hz, 6H), 0.85 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (80 MHz, $CDCl_3$): δ 171.9, 171.3, 144.1, 144.0, 141.6, 138.2, 137.2, 129.6, 128.4, 128.0, 127.3, 126.3, 125.3, 124.3, 120.2, 115.2, 104.4, 77.9, 76.1, 72.9, 67.3, 62.7, 62.6, 59.2, 47.4, 31.5, 30.4, 28.8, 19.2, 17.8.



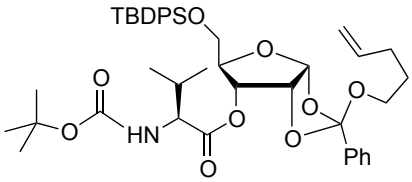
3,5-di-*O*-benzyl–β-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (15c): Sodium hydride (774 mg, 32.25 mmol) was added to a solution of diol **15a** (2.5 g, 8.06 mmol) in dry DMF (30 mL) at 0 °C under N_2 atmosphere. The mixture was stirred at this temperature for 25–30 min, and then benzyl bromide (2.10 mL, 17.74 mmol) was added dropwise for a period of 10 min. The reaction was allowed to warm to room temperature and stirred for an additional 3 h, after which it was quenched with ice cold water (5 mL) and stirred for 30 min. Added more water (30 mL) and extracted with diethyl ether (4 x 40 mL). The organic phase was washed with brine, dried over Na_2SO_4, filtered and evaporated in vacuum. Flash chromatography using hexane/EtOAc 88:12 of the residual syrup afforded less polar compound **15c** (2.8 g, 71 %). $[\alpha]_D^{25}$: +107.4 (*c* 1.0, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.70 (m, 3H), 7.37–7.25 (m, 12H), 6.06 (d, *J* = 3.9 Hz, 1H), 5.80 (tdd, *J* = 16.8, *J* = 10.1, *J* = 6.5 Hz, 1H), 5.05–4.95 (m. 2H), 4.84–4.75 (m, 1H), 4.60–4.44 (m, 4H), 3.94 (dd, *J* = 9.1, *J* = 4.5 Hz, 1H), 3.86 (m, 1H), 3.70 (dd, *J* = 11.4, *J* = 1.9 Hz, 1H), 3.52 (dd, *J* = 11.3, *J* = 3.4 Hz, 1H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.10 (m, 2H), 1.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 138.2, 137.9, 137.3, 129.4, 128.8, 128.7 (x 2), 128.6 (x 2), 128.4 (x 2), 128.3 (x 2), 128.0 (x 2), 127.9, 126.6 (x 2), 123.9, 115.2, 104.8, 78.6, 78.0, 77.0, 73.7, 72.5, 67.7, 62.8, 30.5, 29.0; MS (API-ES positive mode): 525.5 [M+Na].



5-*O*-*tert*butyldiphenylsilyl-β-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (21a): To a stirred solution of diol **15a** (2 g, 6.45 mmol) which had been pre-dried under vacuum in a flame-dried flask for 1 h, was dissolved in anhydrous CH_2Cl_2. The reaction mixture was cooled to 0 °C, after which Et_3N (1.8 mL, 12.9 mmol) and DMAP (78 mg, 0.64 mmol) was added and allowed to stir for 15–20 min. TBDPSCl (1.85 mL, 7.095 mmol) was then slowly added for a period of 20 min after which the resulting solution was allowed to warm to room temperature and stir for a further 3 h. The reaction mixture was washed with water (50 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layer was dried over sodium sulfate, concentrated and the residue was purified by flash chromatography using hexane/EtOAc 4:1 to afford **21a** (2.48 g, 69 %) as a colorless oil. $[\alpha]_D^{25}$: + 17.3 (*c* 0.13, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.72–7.63 (m, 6H), 7.44–7.35 (m, 9H), 6.12 (d, *J* = 4.0 Hz, 1H), 5.92–5.69 (tqt, *J* = 7.0 Hz, *J* = 6.6 Hz, 1H), 5.10–4.94 (m, 2H), 4.89–4.82 (t, *J* = 5.2 Hz, 1H), 4.22–4.08 (m, 1H), 3.95–3.71 (m, 2H), 3.58–3.38 (m, 3H), 2.21–2.01 (m, 3H), 1.80–1.59 (m, 2H),1.2 (s, 9H); ^{13}C NMR (80 MHz, $CDCl_3$): δ 138.2, 135.8, 129.9, 129.6, 128.5, 127.9, 126.2, 115.2, 104.5, 81.9, 79.8, 77.9, 71.4, 62.7, 62.2, 30.4, 28.8, 19.5.

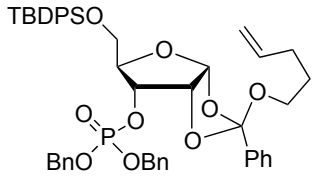


3-*O*-benzyl-5-*O*-*tert*butyldiphenylsilyl-β-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (15d): Sodium hydride (43.8 mg, 1.82 mmol) was added to a solution of compound **21** (500 mg, 0.912 mmol) in dry N,N-dimethyl formamide (20 mL) at 0 °C under N_2 atmosphere. The mixture was stirred at this temperature for 20 min, and then benzyl bromide (0.12 mL, 1.00 mmol) was added. The reaction was allowed to warm to room temperature and stirred for an additional 2 h. The reaction mixture was quenched with cold water (30 mL) and extracted with ether (3 x 30 mL). The organic phase was washed with brine, dried over Na_2SO_4, filtered and evaporated. Flash chromatography of the residual brown syrup afforded **15d** (405 mg, 70%) as colorless liquid. $[\alpha]_D^{25}$: 10.3 (*c 0.25*, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): 7.8–7.6 (m, 7H), 7.4–7.23 (m, 13H), 6.06 (d, *J* = 4.0 Hz, 1H), 5.9–5.7 (tqt, *J* = 6.8 Hz, *J* = 8.0 Hz, 1H), 5.1–4.92 (m, 2H), 4.88–4.82 (t, *J* = 4.0 Hz, 1H), 4.82–4.76 (d, *J* = 10.0 Hz, 1H), 4.64–4.56 (d, *J* = 10.0 Hz, 1H), 4.16–4.04 (dd, *J* = 3.8 Hz, 1H), 3.94–3.66 (m, 3H), 3.48–3.36 (t, *J* = 5.4 Hz, 2H), 2.2–2.0 (m, 2H), 1.78–1.69 (m, 2H), 1.0 (s, 9H).

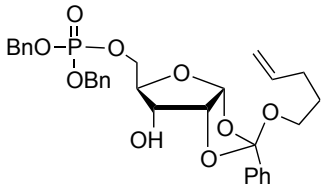


3-*O*-(*tert*butoxycarbonyl-L-valinoyl)-5-*O*-*tert*butyldiphenylsilyl-β-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (15e): A solution of compound **21** (200 mg, 0.364 mmol), Boc-Valine (87.12 mg, 0.4 mmol), DCC (112.6 mg, 0.546 mmol) and DMAP (22.2 mg, 0.182 mmol) in anhydrous CH_2Cl_2 was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (25 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layer was dried over Na_2SO_4, concentrated under vacuum. The obtained crude mixture was purified by silica gel column chromatography using hexane/EtOAc 8:2 to afford **15e** (226 mg, 83%) as colorless syrup. $[\alpha]_D^{25}$: +70.5 (*c* 0.21, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60 (m, 6H), 7.35 (m, 9H), 6.15 (d, *J* = 4.0 Hz, 1H), 5.8 (m, 1H). 5.0 (m, 4H), 4.3 (m, 1H), 3.85 (m, 2H), 3.6 (dd, *J* = 3.2 Hz, *J* = 3.6 Hz, 1H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.1 (m, 3H), 1.7 (m, 2H), 1.46 (s, 9H), 1.05 (s, 9H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.8 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (80 MHz, $CDCl_3$): δ 171.7, 155.7, 138.2, 137.7, 135.8, 135.7, 133.3, 133.1,

130.0, 129.4, 128.3, 128.0, 127.9, 126.4, 124.2, 115.2, 104.7, 80.0, 79.2, 78.0, 72.1, 62.6, 61.7, 58.6, 31.7, 30.4, 29.9, 28.8, 28.6, 27.0, 19.5, 19.1, 17.7.

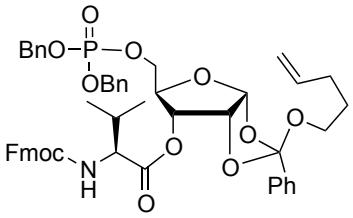


3-*O*-dibenzylphosphoryl-5-*O*-*tert*butyldiphenylsilyl-β-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (15f): To a well stirred solution of dibenzylchlorophosphate (194.0 mg, 0.654 mmol) in anhydrous acetonitrile (2 mL) and under N_2 atmosphere was added at –78 °C a solution of NPOE **15a** (120 mg, 0.22 mmol) and DMAP (133.5 mg, 1.09 mmol) in anhydrous CH_2Cl_2 (10 mL). The mixture was allowed to warm to room temperature and then stirred overnight. The solvents were removed under vacuum and the crude was purified by silica gel column chromatography using hexane/EtOAc 2:3 to give **15f** (90 mg, 51%) as thick syrup. $[\alpha]_D^{25}$: +16.83 (*c* 0.65, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.6 (m, 6H), 7.40–7.24 (m, 19H), 6.05 (d, *J* = 4.0 Hz, 1H), 5.7 (m, 1H), 5.1–4.90 (m, 7H), 4.80 (m, 1H), 3.9–3.6 (m, 3H), 3.4 (dd, *J* = 6.6 Hz, *J* = 5.4 Hz, 2H), 2.1 (m, 2H), 1.7 (m, 2H), 1.05 (s, 9H); ^{31}P NMR (80 MHz, $CDCl_3$): – 0.77; ^{13}C NMR (80 MHz, $CDCl_3$): δ 138.2, 137.6, 135.9, 135.8, 133.5, 133.2, 129.9, 129.4, 128.8, 128.4, 128.1, 127.9, 127.9, 126.3, 124.2, 115.1, 104.3, 79.6, 79.4, 78.8, 74.1, 69.8, 69.7, 62.6, 61.1, 30.5, 28.8, 26.9, 19.5.

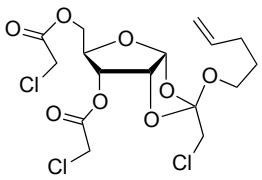


5-*O*-dibenzylphosphoryl-β-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (21b): To a solution of dibenzylphosphoryl chloride (286.6 mg, 0.966 mmol) in anhydrous CH_2Cl_2 (3 mL) was added under a N_2 atmosphere and at –78 ºC a solution of diol **16a** (100 mg, 0.322 mmol) and DMAP (118 mg, 0.966 mmol) in dry CH_2Cl_2 (5 mL). The reaction was allowed to warm to room temperature and then stirred overnight. The solvent was evaporated under vacuum and the mixture was purified by silica gel column chromatography using hexane/EtOAc 1:4 to afford C5'phosphorylated compound **22b** (97 mg, 53%). $[\alpha]_D^{25}$: + 60.0 (*c* 0.1, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.7–7.6 (m, 2H), 7.5–7.2 (m, 13H), 5.97 (d, *J* = 4.0 Hz, 1H), 5.9–5.7 (tqt, *J* = 7.0 Hz, *J* = 6.6 Hz, 1H), 5.1–4.9 (m, 6H), 4.78–4.73 (t, *J* = 4.4 Hz, 1H), 4.3–3.85 (m, 3H), 3.6–3.5 (m, 1H), 3.45–3.3 (m, 2H), 2.5 (d, *J* = 10.0Hz, 1H), 2.2–2.0 (q, *J* = 7.0Hz, 2H), 1.75–1.6 (m, 2H). ^{31}P NMR (80 MHz, $CDCl_3$): δ 0.50; ^{13}C NMR (80 MHz, $CDCl_3$):138.2, 129.6,

129.0, 128.8, 128.6, 128.4, 128.2, 126.3, 126.2, 115.2, 104.2, 79.5, 79.4, 71.4, 69.8, 69.7, 69.6, 65.6, 65.5, 62.9, 30.4, 28.8.



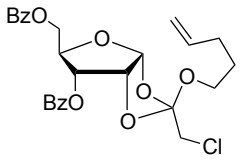
5-*O*-dibenzylphosphoryl-3-O-(9-fluorenylmethoxycarbonyl-L-valinoyl)-β-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (15g): A solution of phosphorylated orthoester **22b** (130 mg, 0.228 mmol) in dry DMF was treated with Fmoc-valine (85.1 mg, 0.250 mmol), EDCI (65.6 mg, 0.342 mmol), and DMAP (14 mg, 0.114 mmol) and the resulting mixture was allowed to react for 12 h. The reaction crude was then washed with water and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was concentrated and purified by silica gel column chromatography using hexane/EtOAc 1:1 to afford compound **11g** (122 mg, 61%). $[\alpha]_D^{25}$: + 60.0 (*c* 0.1, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.4 Hz, 1H), 7.60 (m, 3H), 7.4–7.1 (m, 18H), 6.0 (d, *J* = 4.0 Hz, 1H), 5.73 (m, 1H), 5.2–4.85 (m, 8H), 4.73 (dd, *J* = 5.4 Hz, 5.0 Hz, 1H), 4.5–4.13 (m, 5H), 3.98–3.83 (m, 2H), 3.42–3.25 (m, 2H), 2.1 (m, 3H), 1.6 (m, 2H), 1.0–0.78 (dd, *J* = 6.6 Hz, *J* = 7.0 Hz, 6H), ^{13}C NMR (80 MHz, $CDCl_3$): δ 171.8, 143.95, 141.55, 138.16, 137.27, 129.51, 128.79, 128.39, 128.2, 128.1, 127.95, 127.29, 126.25, 125.23, 120.21, 115.73, 104.5, 77.65, 72.35, 69.66, 67.28, 64.96, 62.71, 59.13, 47.44, 31.54, 30.37, 28.73, 19.1, 17.7; ^{31}P NMR (80 MHz, $CDCl_3$): δ 0.10.



3,5-di-*O*-chloroacetyl-β-D-ribofuranose-1,2-(pent-4-enyl orthochloroacetate (25a) To a cooled (0 ºC) suspension of D- ribose (1 g, 6.66 mmol) in anhydrous methanol (24 ml), was added dropwise acetyl chloride (0.42 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. Pyridine (5 mL) was slowly added, the mixture was concentrated *in vacuo* and the residue co-evaporated with chloroform. The resulting methyl riboside (1.04 g) was dissolved in anhydrous DMF (10 mL), cooled to 0 ºC, treated with sodium bicarbonate (2.52 g, 0.03 mol) and then with chloroacetyl chloride (5.21 g, 0.03 mol) dissolved in dry DMF (2 mL). The mixture was vigorously stirred overnight at rt. Water was added and after stirring for 30 min., it was extracted with diethyl ether (3 x 20 mL). The

combined organic layer was dried over $MgSO_4$, filtered, concentrated and the residue purified by silica gel column chromatography using hexane/EtOAc 4:1 to afford methyl tri-*O*-chloroacetyl D-ribofuranoside (600 mg, 28%). This compound (500 mg, 1.27 mmol) was dissolved in acetic acid (2 mL) and HBr (2.5 mL, 45% in acetic acid) was added. The reaction vessel was tightly stoppered and stirred at rt for 1 hour. The reaction mixture was then diluted with CH_2Cl_2 (25 mL) and ice-cold water was added (20 mL). The organic layer was washed with cold water (20 mL), cold saturated $NaHCO_3$ (2 x 10 mL) and dried. After evaporation of solvent, the corresponding glycosyl bromide was obtained in approximate yield 71 % (400 mg) and used immediately in the next step without any further purification.

The crude glycosyl bromide (400 mg, 1.0 mol) was dissolved in dry CH_2Cl_2 (10 mL), and 4-penten-1-ol (0.208 mL, 2.0 mmol) and 2,6-lutidine (0.257 mL, 2.2 mol) were added followed by Bu_4NI in 3 lots (37.08 mg, 0.1 mol) in 30 min intervals at room temperature. The reaction mixture was stirred for 12 hours and then was washed with cold water (3 x 20 mL), brine (10 mL), dried (Na_2SO_4) and concentrated. The obtained crude was purified by flash column chromatography on silica gel using hexane/EtOAc 4:1 to afford orthoester **25a** (267 mg, 66.4%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.08-6.0 (d, *J*=3.2 Hz, 1H), 5.9-5.7 (m, 1H), 5.1-4.92 (m, 3H), 4.84-4.76 (dddd, *J* =1.6 Hz, *J* =1.4 Hz, *J* =1.4 Hz, *J* =1.4 Hz, 1H), 4.6-4.48 (m, 2H), 4.3-4.23 (m, 1H), 4.19 (d, *J*=1.4 Hz, 2H), 4.12-4.11 (d, *J*=1.6 Hz, 2H), 3.77-3.54 (t, *J*=1.4 Hz, 2H), 3.50-3.44 (t, *J* =5.4 Hz, 2H), 2.17-2.05 (m, 2H), 1.74-1.6 (m, 2H); ^{13}C NMR (80 MHz, $CDCl_3$): δ 167.1, 166.8, 137.9, 122.9, 115.4, 104.9, 78.1, 73.7, 63.7, 62.4, 45.0, 40.7, 40.5, 30.2, 28.6.

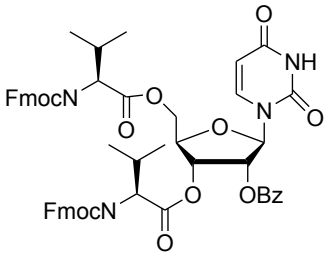


3,5-di-*O*-benzoyl-β-D-ribofuranose-1,2-(pent-4-enyl orthochloroacetate (25b): To a well stirred solution of compound **25a** (250 mg, o.56 mmol) in MeOH (15 mL) was added NaOMe (0.5 ml, 1.0 mmol) at rt. The reaction mixture was then allowed to stir for 45 min and then concentrated under vacuo. The residue was purified by silicagel column chromatography using hexane/EtOAc 2:3 as eluent to give the corresponding diol (139 mg, 84.6%).

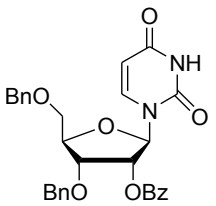
A stirred solution of diol (100 mg, 0.33 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to 0 °C and treated with Et_3N (0.16 mL, 1.209 mmol), DMAP (78 mg, 0.64 mmol) and BzCl (0.10 ml, 0.88 mol). The mixture was allowed to stir for 15-20 min and then was washed with cold water (10 mL), extracted in CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried (Na_2SO_4), concentrated and the residue was purified by flash chromatography hexane/EtOAc 85:15 to afford orthoester **25b** (129 mg, 77%). ^{1}H

NMR (200 MHz, $CDCl_3$): δ 8.15-7.95 (m, 4H), 7.63-7.3 (m, 6H), 6.13-6.11 (d, *J* = 4.0 Hz, 1H), 5.88-5.67 (tqt, *J*=6.6 Hz , *J*=7.0 Hz, *J*=6.6 Hz, 1H), 5.2-5.15 (dd, *J*=4.0 Hz, *J*=4.2 Hz, 1H), 5.08-5.03 (m, 2H), 5.0-4.93 (m, 1H), 4.86-4.65 (m, 2H), 4.53-4.44 (dd, *J*=4.8 Hz, *J*=4.6 Hz, 1H), 3.8 (s, 2H), 3.51-3.44 (t, *J*=6.6 Hz, 2H), 2.15-2.04 (m, 2H), 1.72-1.58 (m, 2H); ^{13}C NMR (80 MHz, $CDCl_3$): δ 166.3, 165.9, 137.9, 133.8, 133.4, 130.2, 129.9, 129.8, 129.1, 128.7, 128.6, 122.8, 115.4, 105.1, 78.8, 77.3, 73.4, 63.2. 62.3, 45.2, 30.2, 28.7.

1. Assembly of nucleobases with C3' and C5' differentiated ribo-NPOEs.

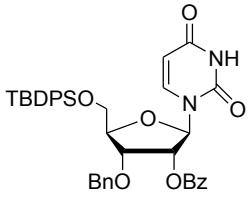


2-*O*-benzoyl-3,5-di-*O*-[9-fluorenylmethoxycarbonyl-L-valinoyl]-β-D-ribofuranosyl-uracil (16): The compound was prepared according to general procedure with uracil **7a** (0.3 mmol, 34 mg) and orthoester **15b** (0.25 mmol, 241 mg) over a course of 3 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 3:1 to give the desired product **16** (205 mg, 83% yield). $[\alpha]_D^{25}$: + 23.7 (*c* 0.65, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 8.83 (bs, 1H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.75 (d, *J* = 7.4 Hz, 4H), 7.6–7.2 (m, 15H), 5.97 (s, 1H), 5.83 (d, *J* = 8.6 Hz, 1H), 5.60 (bs, 2H), 5.4 (d, *J* = 8.8 Hz,1H), 5.23 (d, *J* = 8.8 Hz, 1H), 4.6 (d, *J* = 11.8 Hz, 1H), 4.5–4.0 (m, 10H), 2.1 (m, 2H), 1.0–0.6 (m, 12H); ^{13}C NMR (80 MHz, $CDCl_3$): δ 172.1, 171.2, 165.6, 162.9, 156.6, 156.2, 150.2, 144.0, 143.9, 141.5, 140.8, 134.0, 130.1, 128.8, 128.5, 127.9, 127.3, 125.3, 125.2, 120.2, 103.8, 89.6, 80.4, 73.72, 71.4, 67.3, 63.8, 59.8, 59.2, 52, 47.4, 47.3, 31.4, 31.2, 29.9, 19.3, 19.1, 18.1, 17.8.

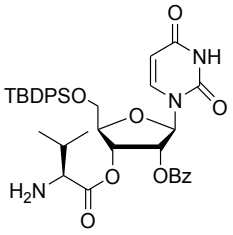


3,5-di-*O*-benzyl-2-*O*-benzoyl-5-O-*tert*-butyldiphenylsilyl-β-D-ribofuranosyl-uracil (17): The compound was prepared according to general procedure with uracil **7a** (0.6 mmol, 34 mg) and orthoester **15c** (0.5 mmol, 301 mg) over a course of 2 h at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 4:1 to give the coupling product **17** (237 mg, 90%

yield): $[\alpha]_D^{25}$: + 60.0 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 8.61 (bs, 1H), 8.1 (m, 2H), 7.8 (d, *J* = 8.0 Hz, 1H), 7.6 (m, 1H), 7.5–7.2 (m, 12H), 6.3 (d, *J* = 4.0 Hz, 1H), 5.5 (dd, *J* = 4.2 Hz, *J* = 4.6 Hz, 1H), 5.35 (dd, *J* = 2.2 Hz, *J* = 1.8 Hz, 1H), 4.65 (d, *J* = 11.8 Hz, 1H), 4.5–4.25 (m, 5H), 3.85 (dd, *J* = 2.2 Hz, *J* = 1.8 Hz, 1H), 3.6 (dd, *J* = 1.8 Hz, *J* = 2.2 Hz, 1H); ^{13}C NMR (80 MHz, $CDCl_3$): δ 165.7, 164.0, 150.7, 140.5, 137.5, 133.8, 130.3, 129.4, 128.9, 128.8, 128.7, 128.5, 128.3, 128.2, 102.7, 88.12, 82.5, 76.1, 75.3, 73.9, 73.4, 68.9.

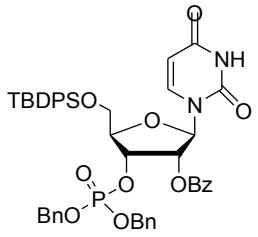


3-*O*-benzyl-2-*O*-benzoyl-5-O-*tert*-butyldiphenylsilyl-β-D-ribofuranosyl-uracil (18a): The compound was prepared according to general procedure with uracil **7a** (0.3 mmol, 33 mg) and orthoester **15d** (0.25 mmol, 162 mg) over a course of 2 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 3:1 to give the desired product **18a** (126 mg, 75% yield) $[\alpha]_D^{25}$: +27.1 (*c* 0.5, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3$): δ 8.9 (bs, 1H), 8.14–8.04 (m, 2H), 7.8 (d, *J* = 8.2 Hz, 1H), 7.71–7.11 (m, 18H), 6.37 (d, *J* = 4.4 Hz, 1H), 5.55 (t, *J* = 4.8 Hz, 1H), 5.4 (dd, *J* = 2.2 Hz, *J* = 2.2 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.48–4.38 (m, 2H), 4.26–4.02 (m, 2H), 3.8 (dd, *J* = 2.0 Hz, *J* = 2.2 Hz, 1H), 1.1 (s, 9H), ^{13}C NMR (80 MHz, $CDCl_3$): δ 165.7, 163.2, 150.3, 139.9, 137.3, 135.9, 135.6, 133.7, 133.0, 132.4, 130.4, 130.4, 130.3, 129.3, 128.7, 128.6, 128.2, 103.0, 87.4, 83.7, 75.8, 75.2, 73.6, 63.0, 27.3, 19.6.

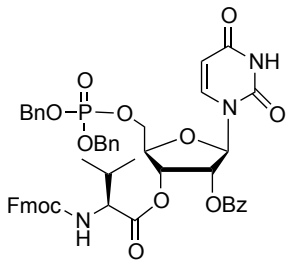


2-*O*-benzoyl-5-O-*tert*-butyldiphenylsilyl-3-*O*-(L-valinoyl)-β-D-ribofuranosyl-uracil (18b): The compound was prepared according to general procedure with uracil **7a** (0.3 mmol, 33 mg) and orthoester **15e** (0.25 mmol, 189 mg) over a course of 18 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 4:1 to give the Boc deprotected product **18b** (151 mg, 88% yield): $[\alpha]_D^{25}$: +5.897 (*c* 0.21, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3$): δ 8.05–8.0 (m, 2H), 7.8–7.4 (m, 14H), 6.48 (d, *J* = 6.4 Hz, 1H), 5.72 (dd, *J* = 3.0 Hz, *J* = 3.2 Hz, 1H), 5.6 (m, 1H), 5.40 (d, *J* = 8.0 Hz,

1H), 4.22 (d, *J* = 3.0 Hz, 1H), 4.1–3.9 (dq, *J* = 11.8 Hz, *J* = 15.8 Hz, *J* = 1.8 Hz, 2H), 3.2 (d, *J* = 5.0 Hz, 1H), 1.9 (m, 1H), 1.5 (s, 9H), 0.85 (dd, *J* = 6.6 Hz, *J* = 6.6 Hz, 6H), ^{13}C NMR (80 MHz, $CDCl_3$): δ 165.4, 163.0, 150.6, 139.5, 135.9, 135.5, 134.0, 132.9, 131.9, 130.5, 130.4, 130.1, 128.9, 128.8, 103.5, 85.8, 83.81, 74.2, 71.3, 63.7, 60.0, 32.1, 27.3, 19.6, 19.5, 17.4, FABMS: 686.3 (M+1).

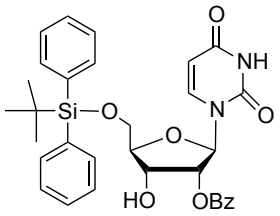


3-*O*-dibenzylphosphoryl-2-*O*-benzoyl-5-O-*tert*-butyldiphenylsilyl-β-D-ribofuranosyl-uracil (18c): The compound was prepared according to general procedure with uracil **7a** (0.3 mmol, 33 mg) and orthoester **15f** (0.25 mmol, 205 mg) over a course of 1 hour at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 88:22 to give the product **18c** (180 mg, 85% yield) $[\alpha]_D^{25}$: –7.6 (*c* 0.21, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (bs, 1H), 8.03 (d, *J* = 7.0 Hz, 1H), 7.70–7.62 (m, 5H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.48–7.36 (m, 8H), 7.30–7.18 (m, 9H), 7.13–7.09 (m, 2H), 6.48 (d, *J* = 7.5 Hz, 1H), 5.52–5.46 (m, 1H), 5.36 (d, *J* = 6.0Hz, *J* = 8.0 Hz, 1H), 5.26–5.22 (m, 1H), 4.94–4.84 (m, 4H), 4.22 (bs, 1H), 3.98–3.76 (dddd, *J* = 1.5Hz, *J* = 12 Hz, *J* = 10 Hz, 2H), 1.12 (s, 9H), ^{31}P NMR (80 MHz, $CDCl_3$): – 0.75, ^{13}C NMR (80 MHz, $CDCl_3$): δ 165.4, 162.5, 150.3, 139.6, 135.9, 135.6, 133.9, 132.9, 131.9, 130.5, 130.5, 130.3, 128.9, 128.8, 128.8, 128.4, 128.3, 128.0, 103.4, 85.1, 84.9, 75.6, 75.5, 74.2, 74.1, 70.0, 69.9, 69.8, 63.9, 27.3, 19.6, HRMS (ESI): calculated for $C_{46}H_{47}N_2O_{10}PSi + Na^+$ 869, found 869.2659.

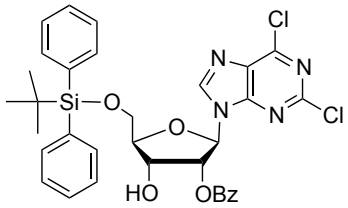


5-*O*-dibenzylphosphoryl-2-*O*-benzoyl-3-*O*-(9-fluorenylmethoxycarbonyl-L-valinoyl)-β-D-ribofuranosyl-uracil (19): The compound was prepared according to general procedure with uracil **7a** (0.3 mmol, 33 mg) and orthoester **15g** (0.25 mmol, 225 mg) over a course of 2 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 2:3 to give the

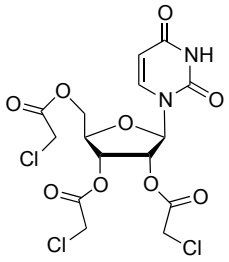
product **19** (139 mg, 60% yield): $[\alpha]_D^{25}$: –16.0 (*c* 0.1, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 8.26 (bs, 1H), 7.95 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.56–7.44 (m, 4H), 7.41–7.25 (m, 16H), 6.24 (d, *J* = 6.5 Hz, 1H), 5.54–5.38 (m, 2H), 5.18–5.03 (m, 5H), 4.42–4.14 (m, 6H), 2.16–2.04 (m, 1H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), ^{13}C NMR (80 MHz, $CDCl_3$): δ 170.8, 165.1, 162.15, 155.9, 149.9, 143.8, 143.6, 141.2, 139.4, 135.3, 133.8, 129.9, 128.8, 128.7, 126.6, 128.1, 127.7, 127.0, 124.9, 119.9, 103.4, 86.6, 77.4, 77.2, 72.9, 71.5, 69.9, 67.0, 66.3, 58.9, 41.1, 31.0, 29.6, 18.9, 17.4, ^{31}P NMR (80 MHz, $CDCl_3$): δ 0.35, HRMS (ESI): calculated for $C_{50}H_{49}N_3O_{13}P + H^+$ 930, found 930.2995.



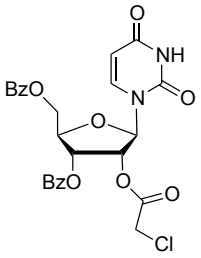
2-*O*-benzoyl-5-*O*-*tert*butyldiphenylsilyl-β-D-ribofuranosyl-uracil (22): The compound was prepared according to general procedure with uracil **7a** (0.3 mmol, 33 mg) and orthoester **21a** (0.25 mmol, 140 mg) over a course of 3 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 3:1 to give the product **22** (65 mg, 60.8% yield): $\alpha]_D^{25}$: 14.5 (*c* 0.16, $CHCl_3$),^1H NMR (200 MHz, $CDCl_3$): δ 8.7 (bs, 1H), 8.04 to 8.08 (d,*J* = 8.0Hz, 2H), 7.8 to 7.85 (d, *J* = 8.0Hz, 1H), 7.3 to 7.76 (m, 13H), 6.36 (d, *J* = 4.8 Hz, 1H),5.4 to 5.49 (m, 2H), 4.68 (bs, 1H), 4.1 to 4.2 (m, 2H), 3.8 to 3.9 (d, *J* = 11.0 Hz, 1H), 2.6 (bs, 1H), 1.1 (s, 9H).^{13}C NMR (80 MHz, $CDCl_3$): δ 166.0, 162.8, 150.2, 139.9, 135.9, 135.6, 134.0, 133.0, 132.3, 130.5, 130.4, 130.2, 128.9, 128.8, 128.3, 103.0, 86.7, 85.0, 76.9, 70.0, 63.4, 27.2, 19.6.



2-*O*-benzoyl-5-*O*-*tert*butyldiphenylsilyl β-D-ribofuranosyl-2,6-dichloropurine (23): The compound was prepared according to general procedure with 2,6-dichloropurine **9a** (0.3 mmol, 57 mg) and orthoester **21a** (0.25 mmol, 140 mg) over a course of 3 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 88:12 to give the product **23** (118 mg, 80.5% yield): ^1H NMR (200 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.1–8.0 (m, 2H), 7.7–7.3 (m, 13H), 6.44 (d, *J* = 5.0 Hz, 1H), 5.8 (t, *J* = 5.0 Hz, 1H), 4.9 (bs, 1H), 4.4–4.3 (m, 1H), 4.16–4.06 (dd, *J* =2.4 Hz, *J* = 9.0 Hz, 1H), 3.96–3.86 (dd, *J* = 2.4 Hz, *J* = 10.0 Hz, 1 H), 2.3 (bs, 1H), 1.1 (s, 9H).

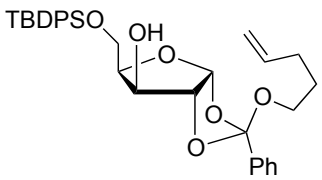


2,3,5-tri-*O*-chloroacetyl-β-D-ribofuranosyl-uracil (24): The compound was prepared according to general procedure with uracil **7a** (0.3 mmol, 33 mg) and orthoester **25a** (0.25 mmol, 112 mg) over a course of 3 hours at -78°C. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 6:4 to give the product **24** (102 mg, 77% yield): ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.0 (bs, 1H), 7.7 (d, *J*=3.4 Hz, 1H), 6.7 (s, 1H), 5.95 (d, *J*=3.4 Hz, 1H), 5.5-5.6 (m, 2H), 4.4-4.6 (m, 2H), 4.24-4.4 (m, 1H), 4.04-4.2 (m, 6H)..



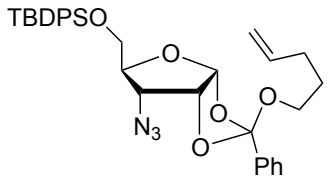
3,5-di-*O*- benzoyl-2-*O*-chloroacetyl-β-D-ribofuranosyl-uracil (26): The compound was prepared according to general procedure with uracil **7a** (0.3 mmol, 33 mg) and orthoester **25b** (0.25 mmol, 125 mg) over a course of 3 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 1:1 to give the product **27** (99 mg, 69% yield): ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.4 (bs. 1H), 7.95-8.1 (m, 4H), 7.3-7.7 (m, 7H), 6.2-6.1 (d, *J*=3.2 Hz, 1H), 5.82-5.5 (m, 3H), 4.84-4.5 (m, 3H), 4.05 (s, 2H).

6. Preparation and N-glycosylation of xylo n*-pentenyl orthoesters.*



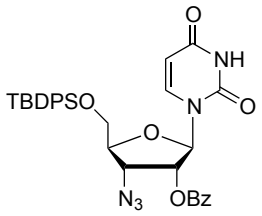
5-*O-tert*butyldiphenylsilyl-β-D-xylofuranose-1,2-(pent-4-enyl orthobenzoate) (27b): A well stirred solution of *n*-pentenyl orthoester **27a** (3 g, 5.79 mmol) in methanol (50 mL) was treated with triethylamine (4.0 mL, 28.9 mmol) and water (0.5 mL). The reaction mixture was allowed to reflux

overnight after which it was determined to be complete by TLC. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography using hexane/EtOAc 7:3 to afford the correspondig diol (1.51 g, 84 %) as a colorless gum. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.5–7.6 (m, 2H), 7.3–7.4 (m, 3H), 6.2 (d, *J* = 4.0 Hz, 1H), 5.64–5.88 (m, 1H), 4.8–5.06 (m, 2H), 4.75 (d, *J* = 4.2 Hz, 1H), 4.20–4.43 (m, 2H), 3.8–3.9 (m, 3H), 3.34–3.55 (m, 3H), 2.0–2.15 (m, 2H), 1.6–1.72 (m, 2H), ^{13}C NMR (80 MHz, $CDCl_3$): 138.2, 137.2, 129.5, 128.5, 126.2, 123.0, 115.2, 105.2, 86.5, 79.9, 76.2, 62.9, 60.7, 30.4, 28.9. This material (1 g, 3.2 mmol) was pre-dried under vacuum in a flame-dried flask for 1 h and then dissolved in anhydrous CH_2Cl_2. The resulting solution was cooled to 0 °C, after which imidazole (435.7 mg, 6.4 mmol), DMAP (10 mol-%) and TBDPSCl (0.92 mL, 3.54 mmol) were added. The reaction mixture was allowed to warm to room temperature (rt) and stirred for another 3 h. The reaction mixture was washed with water (50 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layer was dried over sodium sulfate, concentrated and the residue was purified by flash chromatography using hexane/EtOAc 85:15 to afford **27b** (1.2 g, 68%) as colorless syrup. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.6 to 7.8 (m, 6H), 7.3 to 7.5 (m, 9H), 6.12 to 6.14 (d, *J* = 4.0 Hz, 1H), 5.73 to 5.9 (m, 1H), 5.0 to 5.1 (m, 2H), 4.86 (t, *J* = 4.6 Hz, 1H), 4.11 to 4.22 (m, 1H), 3.74 to 4.0 (m, 2H), 3.4 to 3.56 (m, 3H), 2.1 to 2.2 (m, 3H), 1.65 to 1.8 (pentet, *J* = 6.6 Hz, *J* = 7.0 Hz, 2H), 1.1 (s, 9H), ^{13}C NMR (80 MHz, $CDCl_3$): 138.2, 137.4, 135.9, 135.8, 133.5, 133.4, 130.0, 129.6, 128.6, 128.0, 126.3, 123.8, 115.2, 104.5, 82.0, 79.8, 71.5, 62.8, 62.3, 30.5, 28.9, 27.1, 19.6.



5-*O*-*tert*butyldiphenylsilyl-3-azido-3-deoxy-β-D-ribofuranose-1,2-(pent-4-enyl orthobenzoate) (28) (27): To a stirred solution of **27b** (300 mg, 0.547 mmol) in CH_2Cl_2 was added anhydrous pyridine (0.176 mL, 2.188 mmol) at 0 °C and allowed to stir for 10–20 min and added trifluoromethanesulfonic anhydride (0.110 mL, 0.656 mmol). The mixture was stirred until TLC (hexane/EtOAc 8:2) showed the complete formation of a single faster moving spot. The mixture was washed with water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL), dried over Na_2SO_4, concentrated under vacuum. The obtained crude mixture was co-evaporated with toluene (2x10 mL) and immediately proceeded for next reaction without any purification. Sodium azide (93.45 mg, 1.437 mmol) was added to a solution of compound **27c** (150 mg, 0.239 mmol) in dry DMF (12 mL) and then heated at 70 °C for 2 h. The reaction mixture was cooled to rt and poured into water (50 mL). The aqueous phase was extracted with diethyl ether (3 x 15 mL) and the combined organic layers were dried over sodium sulfate and concentrated under vacuum. Silica gel chromatography

of crude reaction mixture afforded azido compound **28** (108 mg, 79%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.69–7.62 (m, 6H), 7.43–7.34 (m, 9H), 6.11–6.09 (d, *J* = 10.5Hz, 1H), 5.90–5.69 (tqt, *J* = 6.6 Hz, *J* = 6.8 Hz, 1H), 5.07–4.94 (m, 3H), 3.47–3.40 (t, *J* = 6.6 Hz, 2H), 2.18–2.07 (q, *J* = 7.2 Hz, 2H), 1.75–1.61 (pent, *J* = 8.2 Hz, *J* = 6.6 Hz, 2H), ^{13}C NMR (80 MHz, $CDCl_3$): δ 138.2, 136.9, 135.8, 135.7, 133.3, 133.1, 130.0, 129.5, 128.4, 128.0, 127.9, 126.3, 124.1, 115.1, 104.4, 80.7, 79.1, 62.9, 61.7, 60.6, 30.4, 28.9, 27.0, 19.6.



5-*O*-*tert*butyldiphenylsilyl-3-deoxy-3-azido-β-D-ribofuranosyl-uracil (29): The compound was prepared according to general procedure with uracil (0.3 mmol, 33 mg) and orthoester **28** (0.25 mmol, 146 mg) over a course of 2 hours at rt. The crude material was purified by column chromatography on silica gel using hexane/EtOAc 2:3 to give the product **29** (137 mg, 88% yield): $[\alpha]_D^{25}$: +54.0 (*c* 0.15, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.71 (bs, 1H), 8.11–8.07 (m, 2H), 7.76–7.37 (m, 14H), 6.29–6.26 (d, *J* = 5.2 Hz, 1H), 5.68–5.62 (t, *J* = 5.4 Hz, 1H), 5.48–5.44 (d, *J* = 8.2Hz, 1H), 4.51–4.46 (t, *J* = 5.6 Hz, 1H), 4.13–4.07 (m, 2H), 3.87–3.80 (dd, *J* = 2.6 Hz, 1H), 1.17 (s, 9H).^{13}C NMR (80 MHz, $CDCl_3$): δ 165.7, 163.1, 150.3, 139.8, 135.9, 135.6, 134.1, 132.7, 132.2, 130.6, 130.5, 130.4, 128.9, 128.6, 128.4, 128.3, 103.3, 87.2, 83.2, 75.9, 63.4, 60.5, 27.3, 19.6. LCMS: (M+Na) 634.

References

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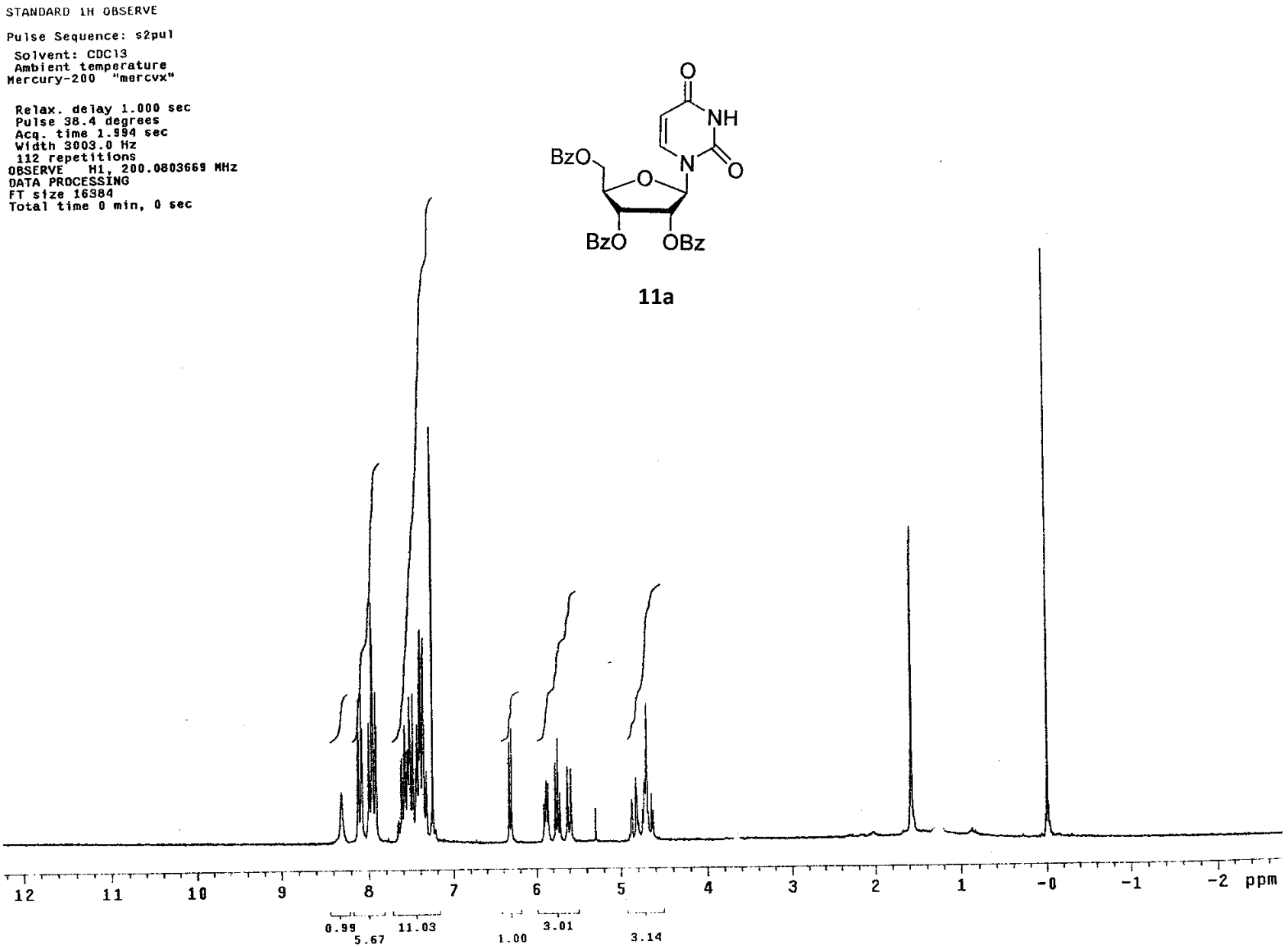

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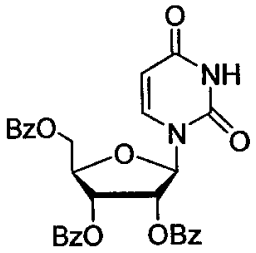

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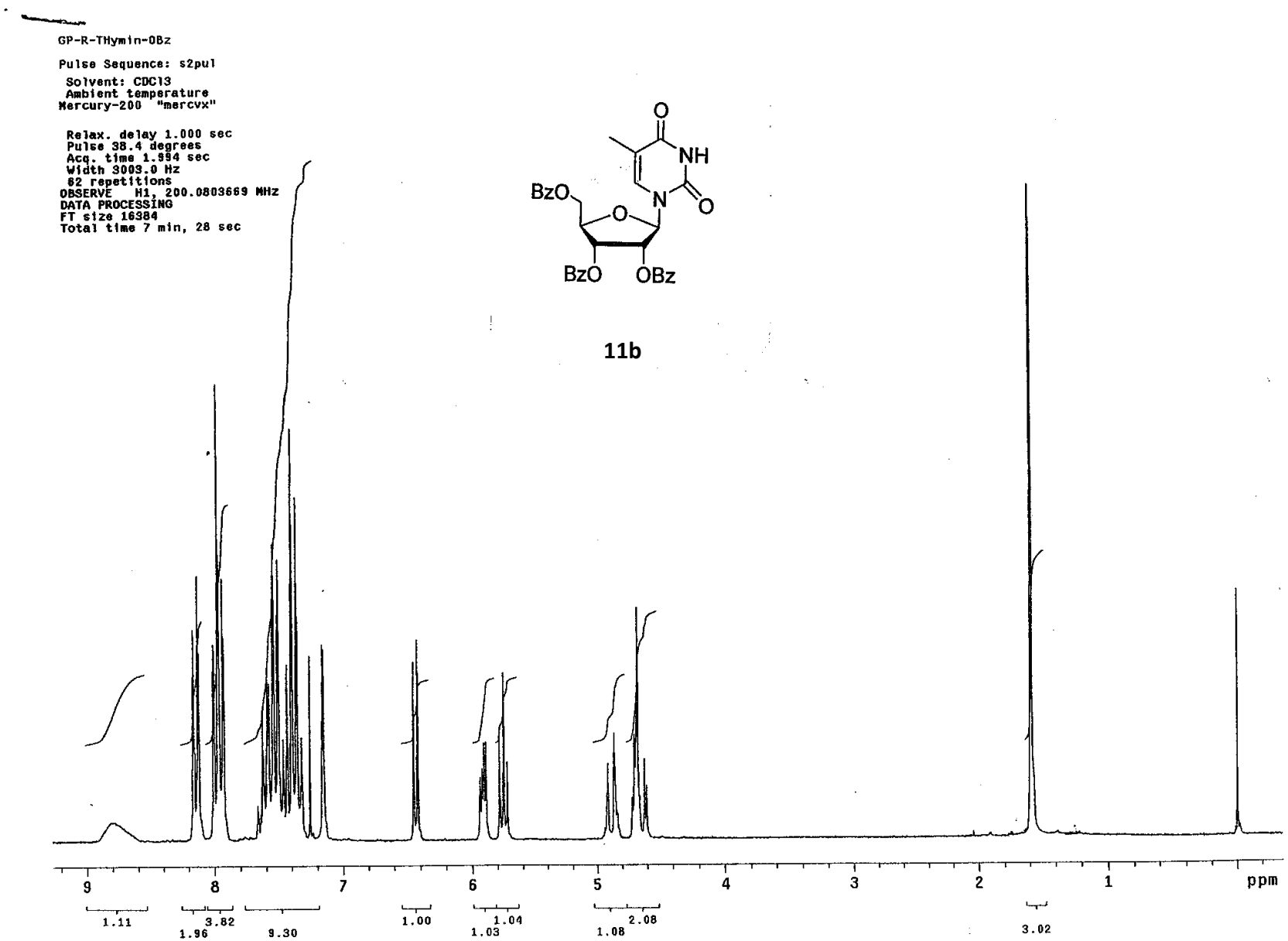

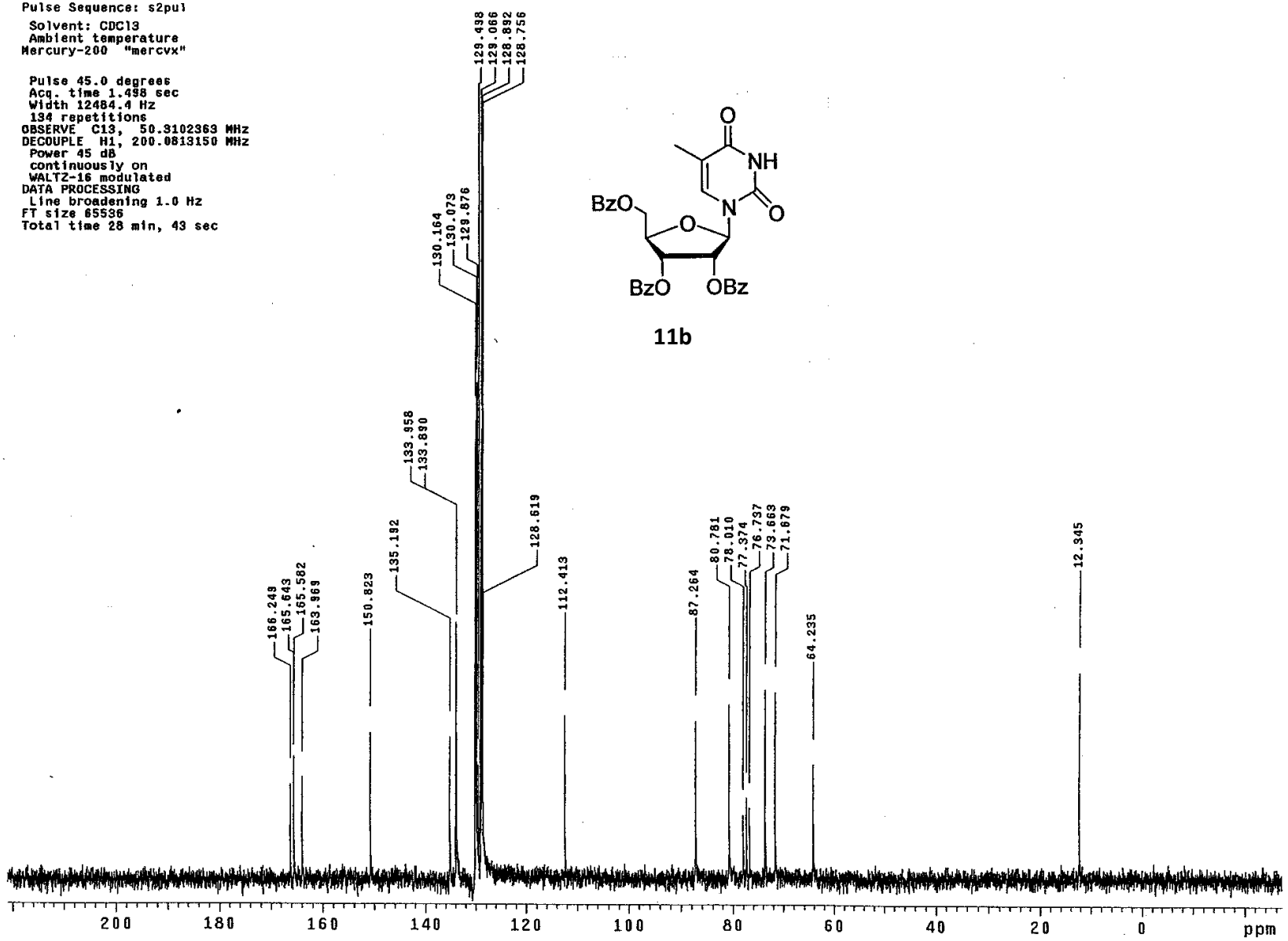

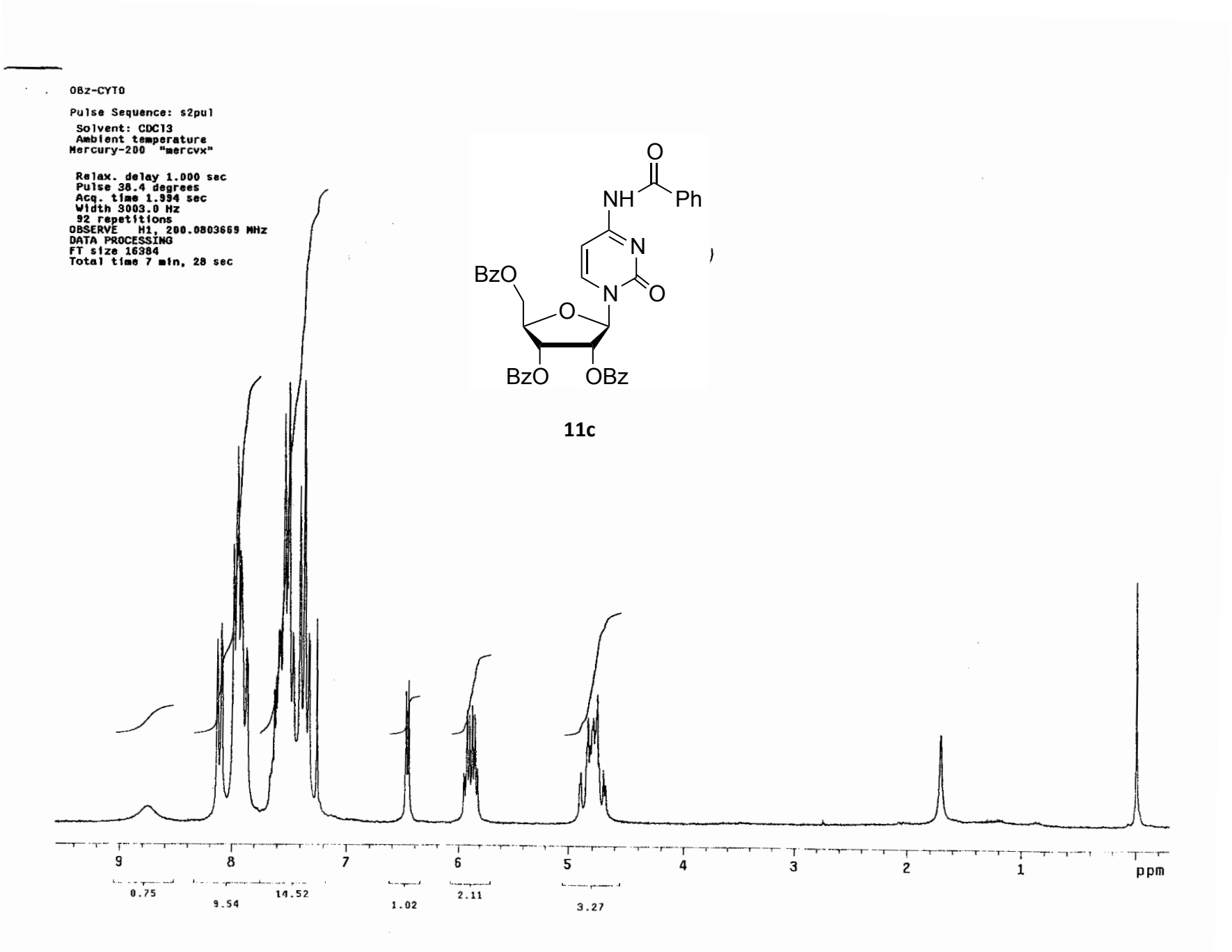

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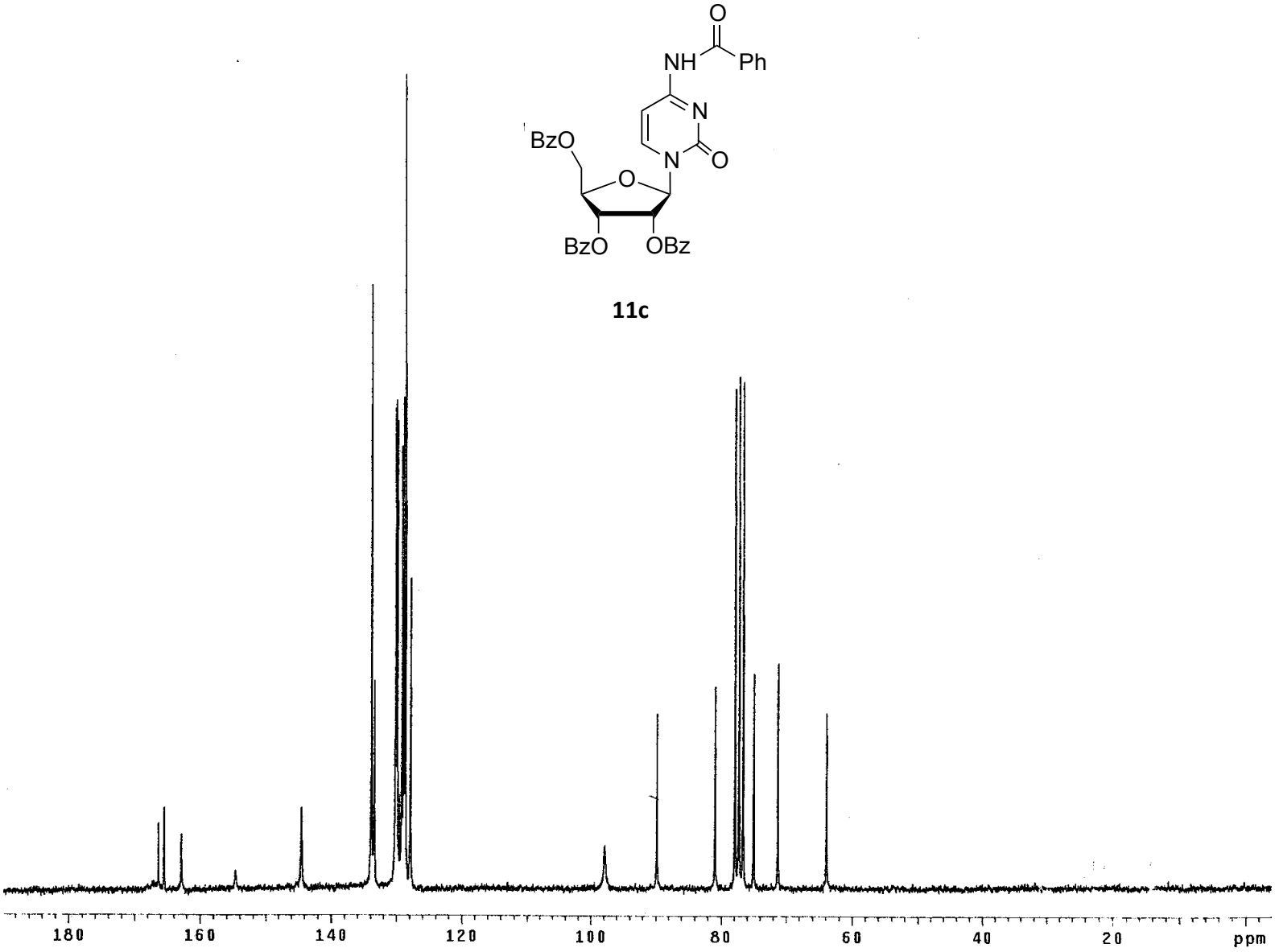

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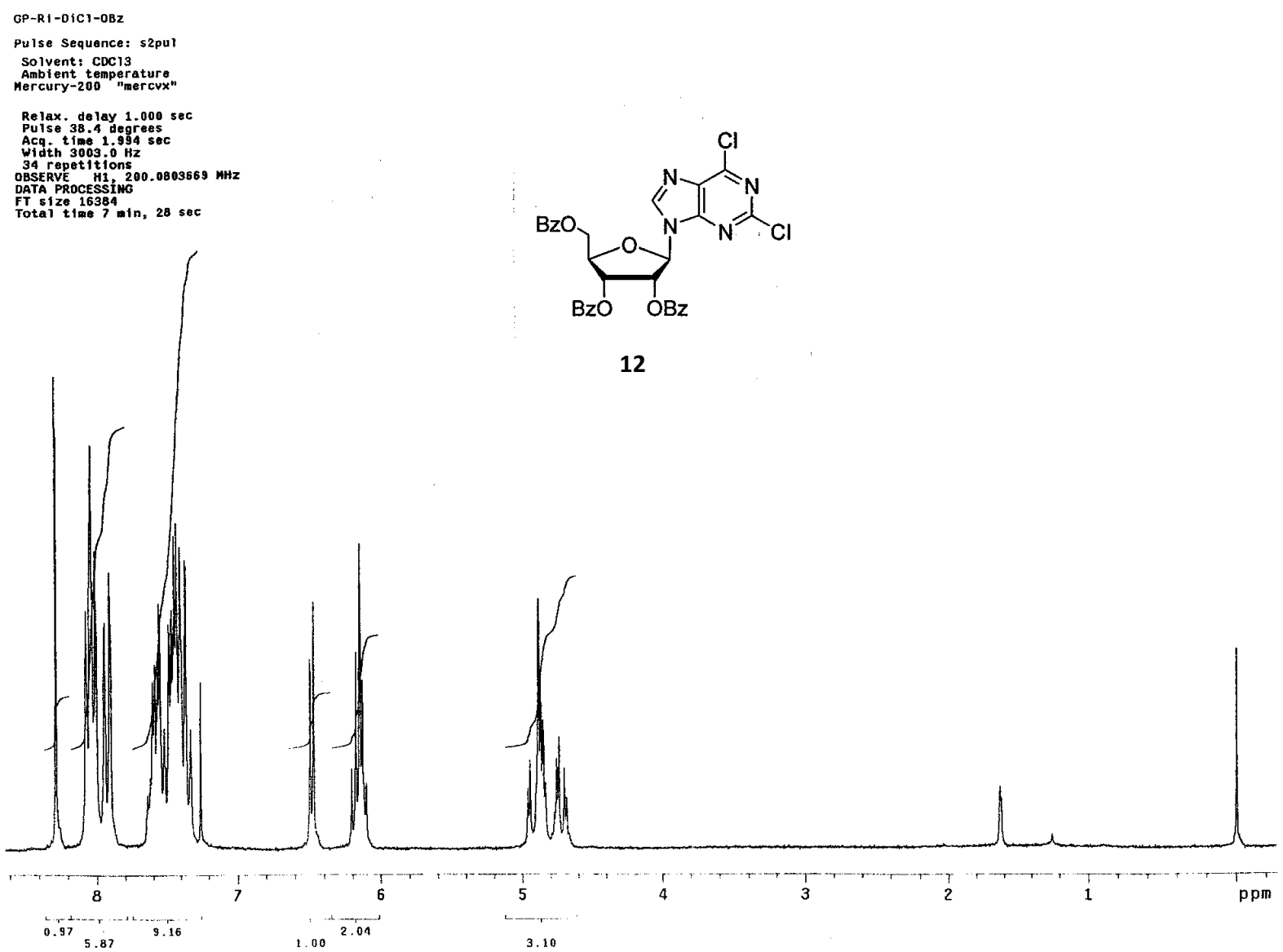
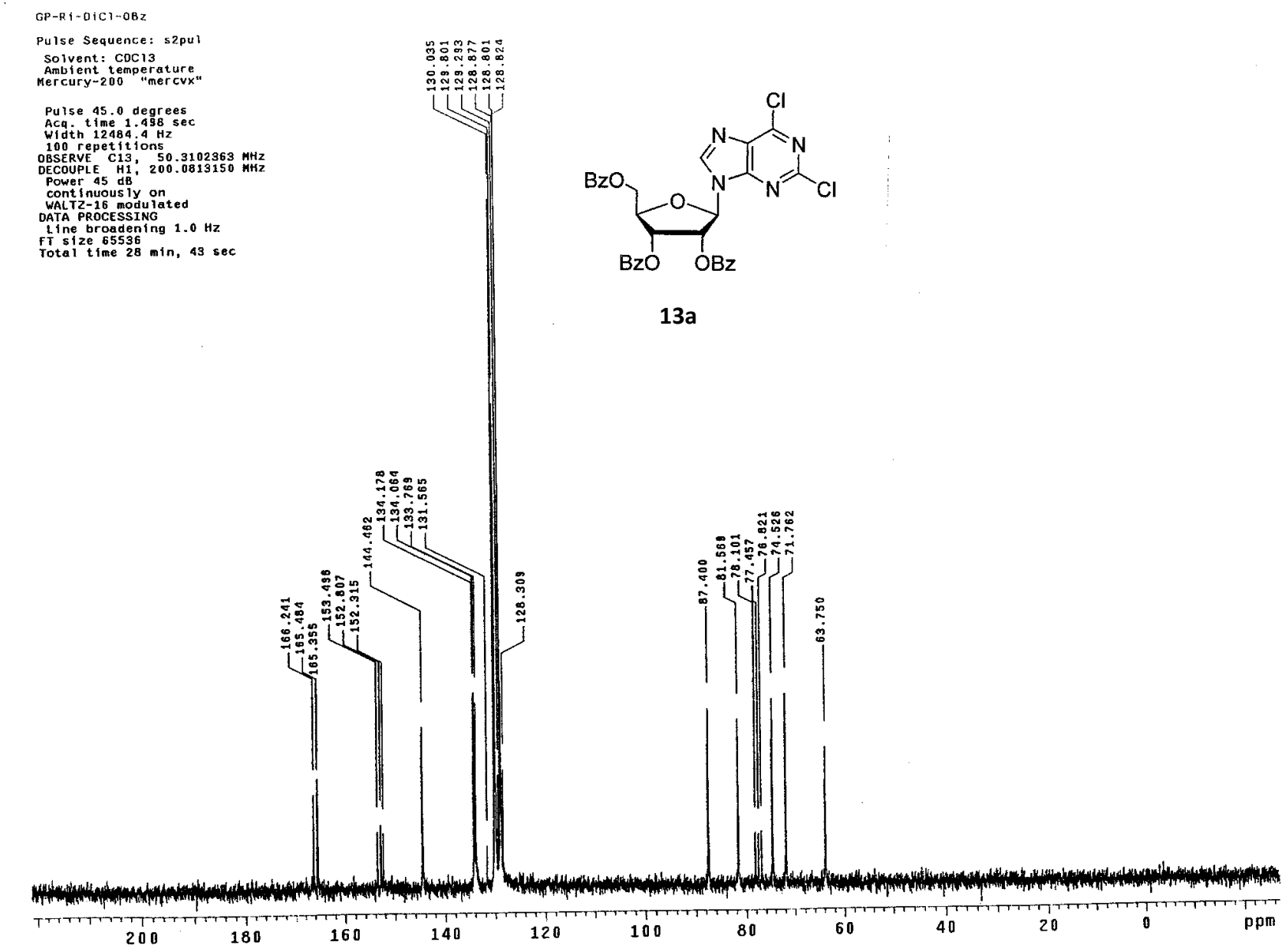
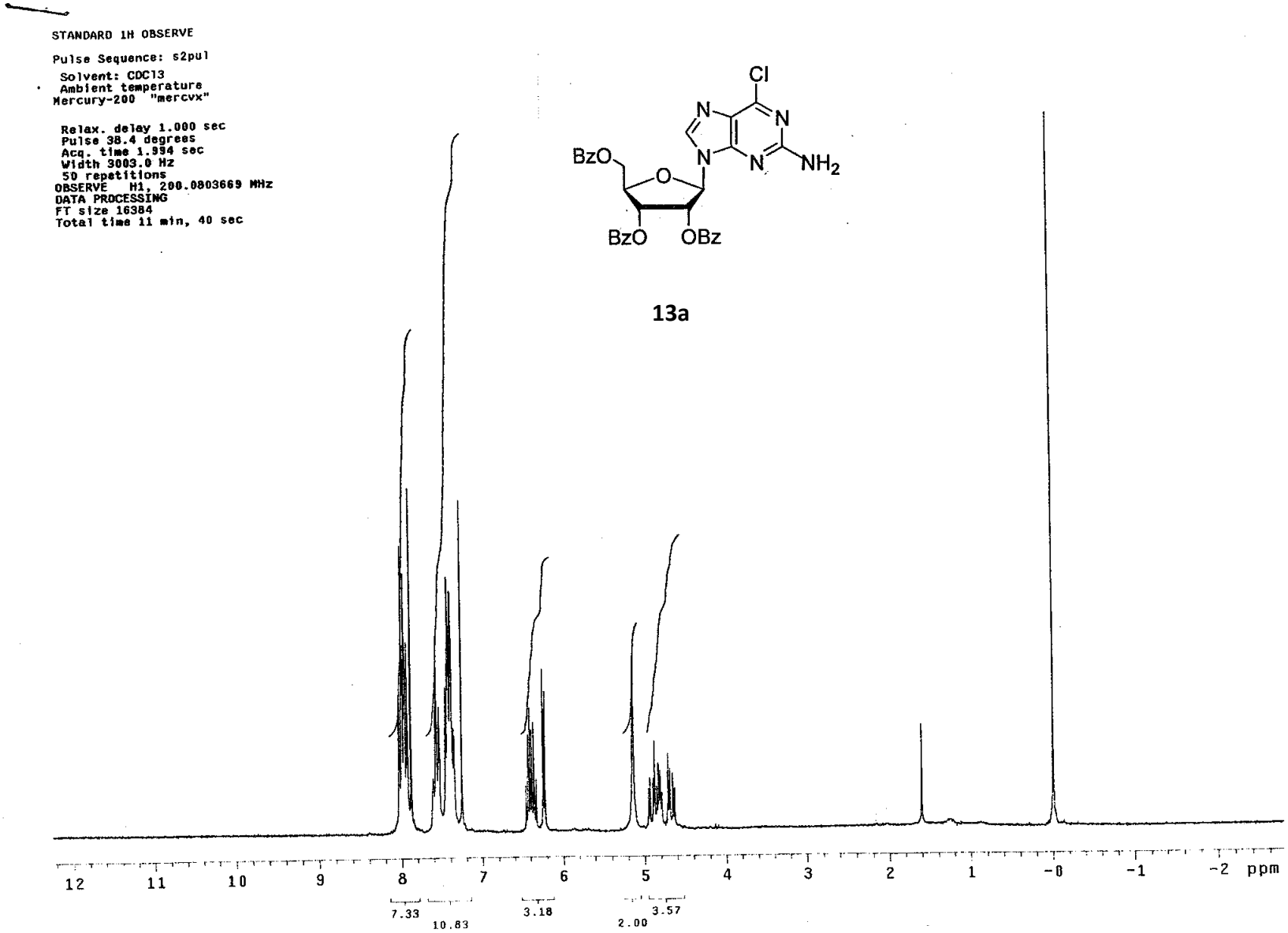
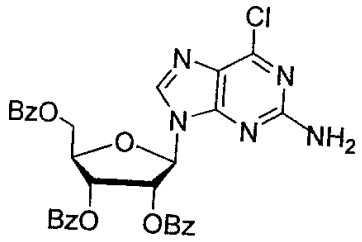


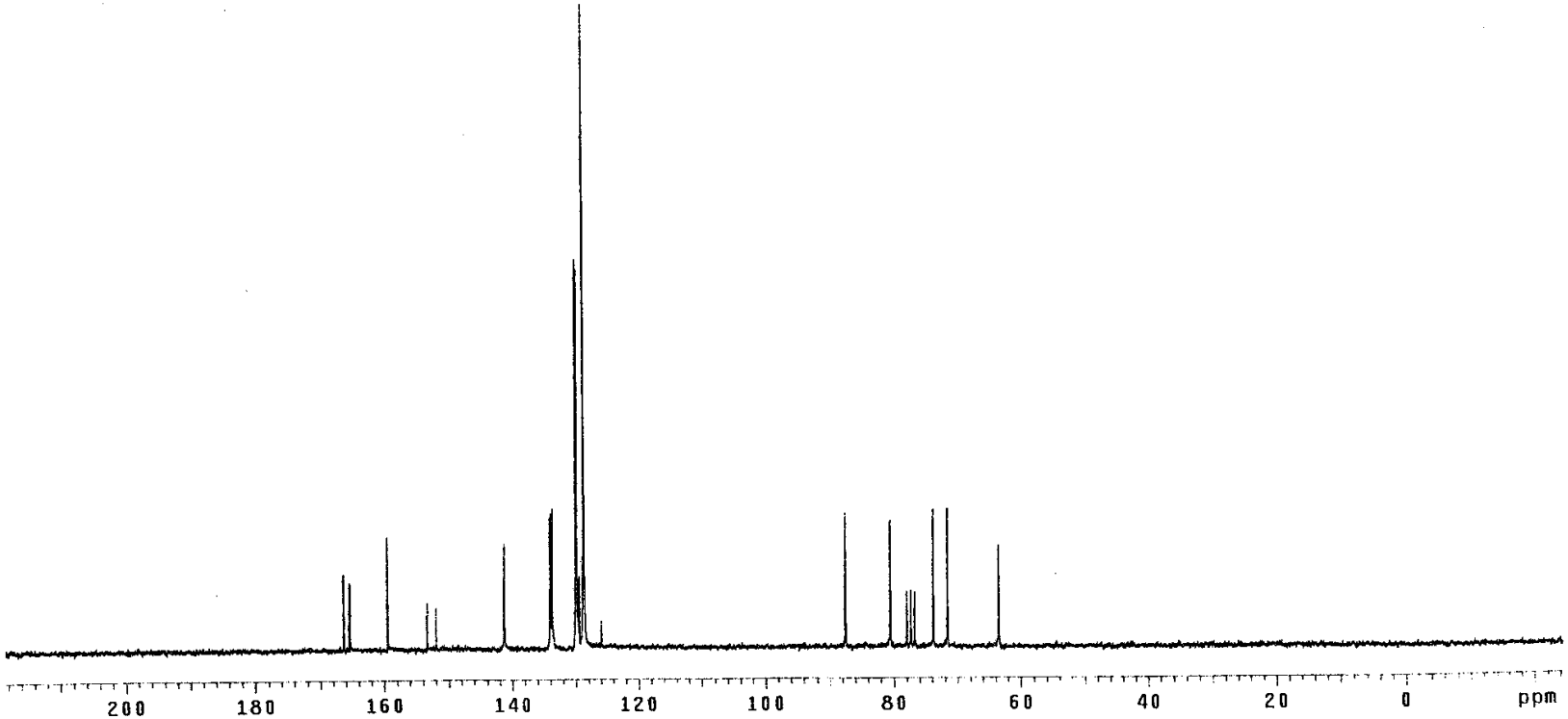
12

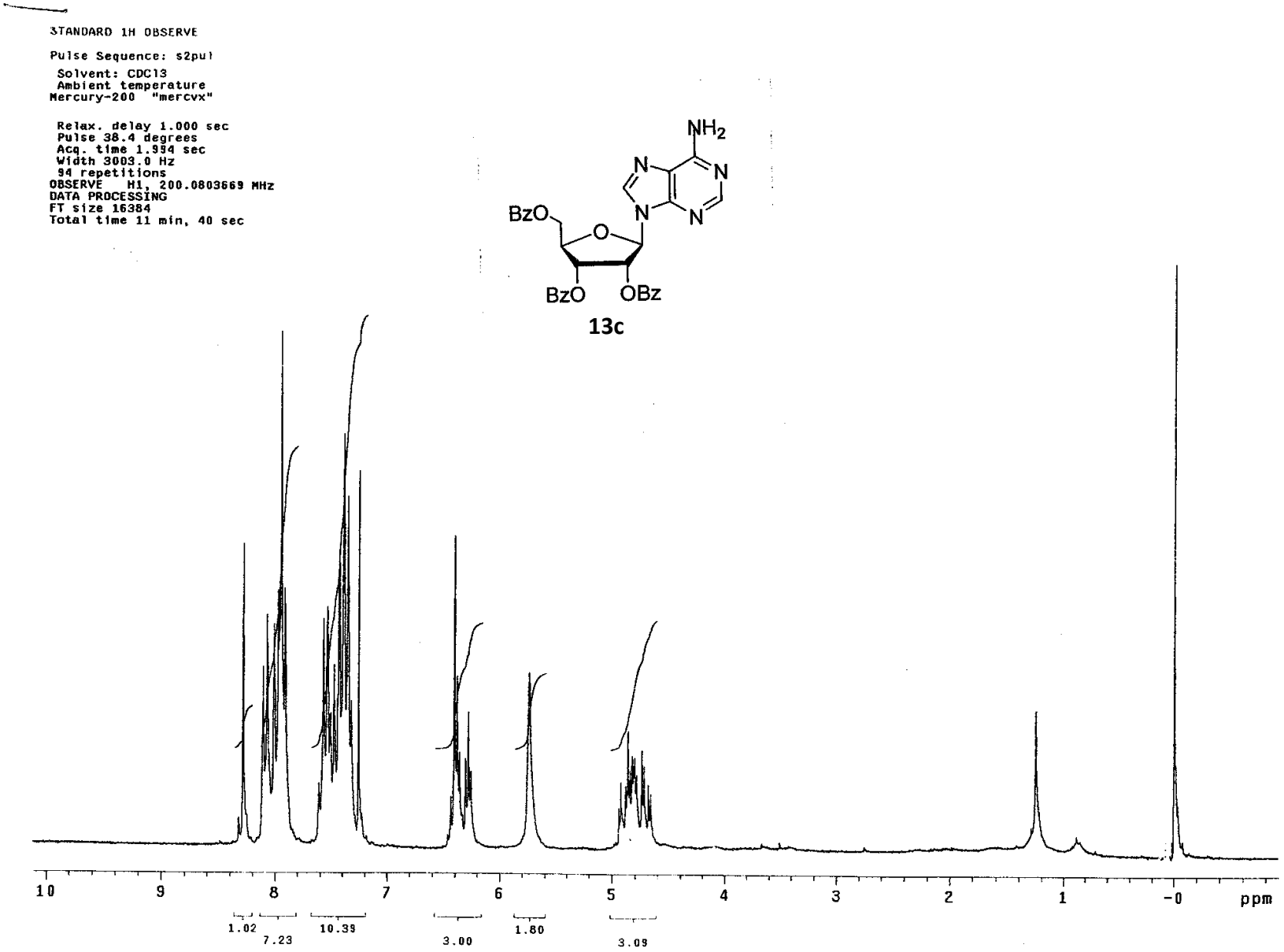


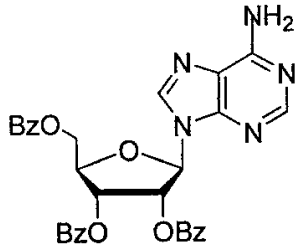




13b







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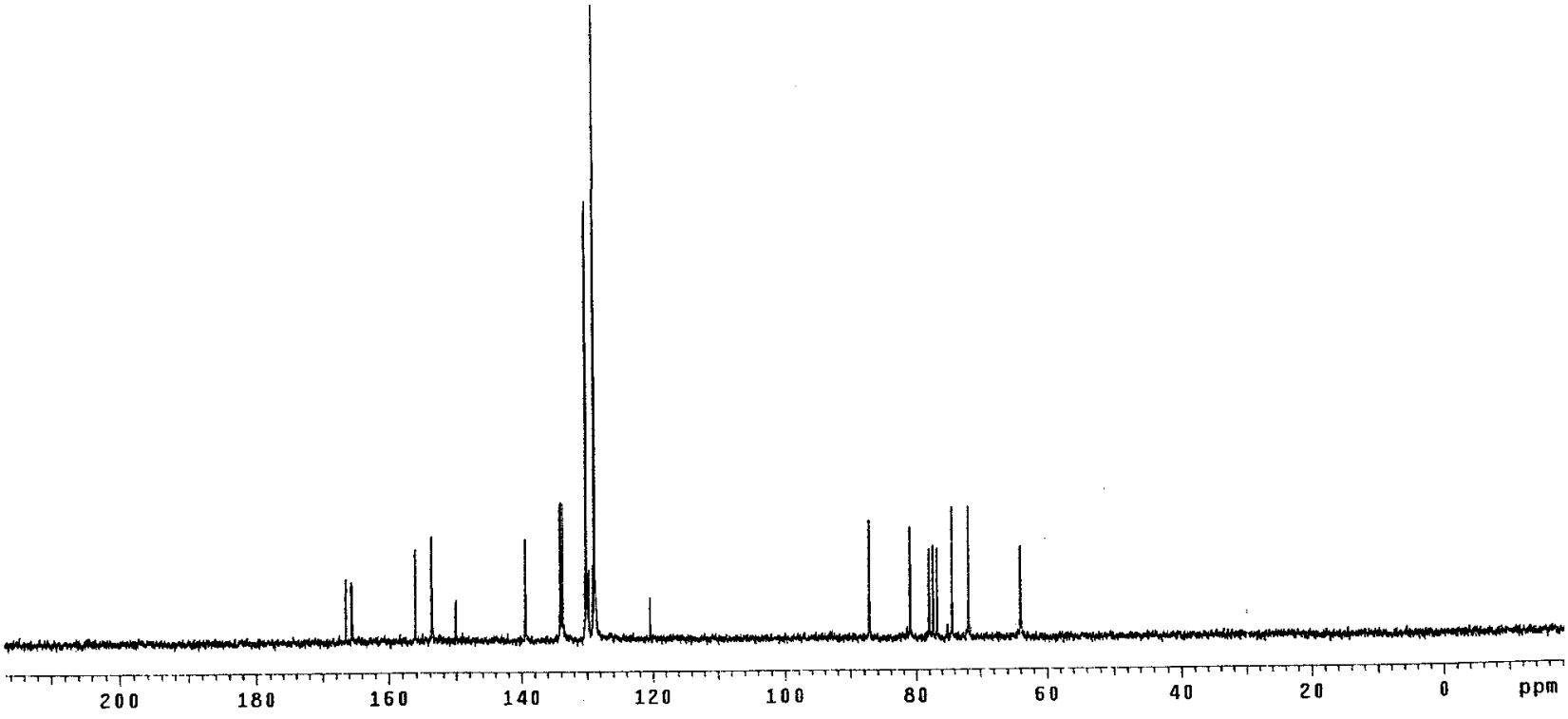
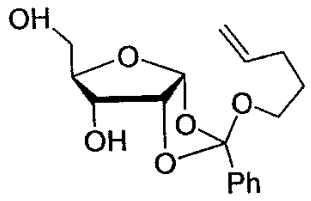


STANDARD 1H OBSERVE

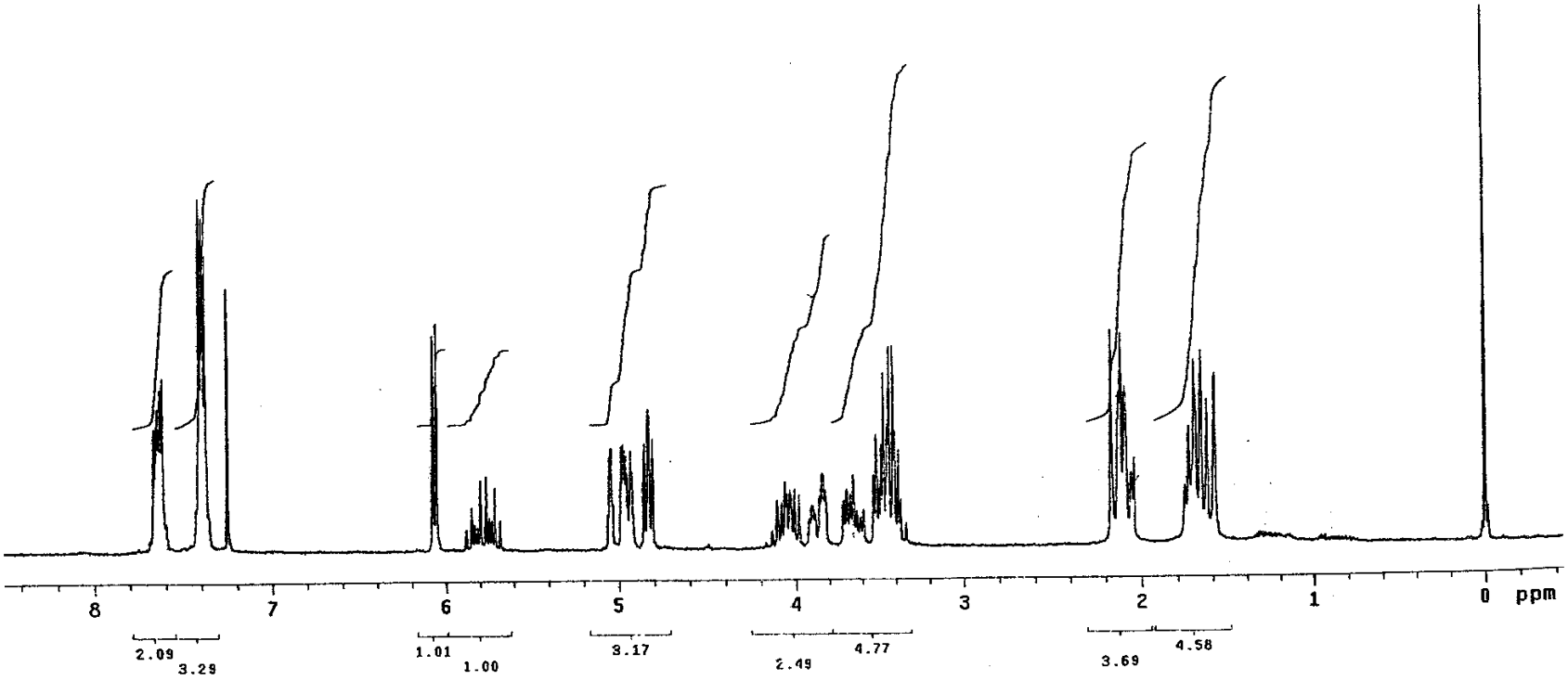
Pulse Sequence: s2pul

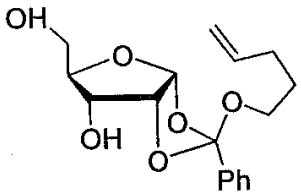
Solvent: CDCl3
Ambient temperature
Mercury-200 "mercvx"

Relax. delay 1.000 sec
Pulse 32.9 degrees
Acq. time 1.994 sec
Width 3003.0 Hz
37 repetitions
OBSERVE H1, 200.0803669 MHz
DATA PROCESSING
FT size 16384
Total time 7 min, 28 sec

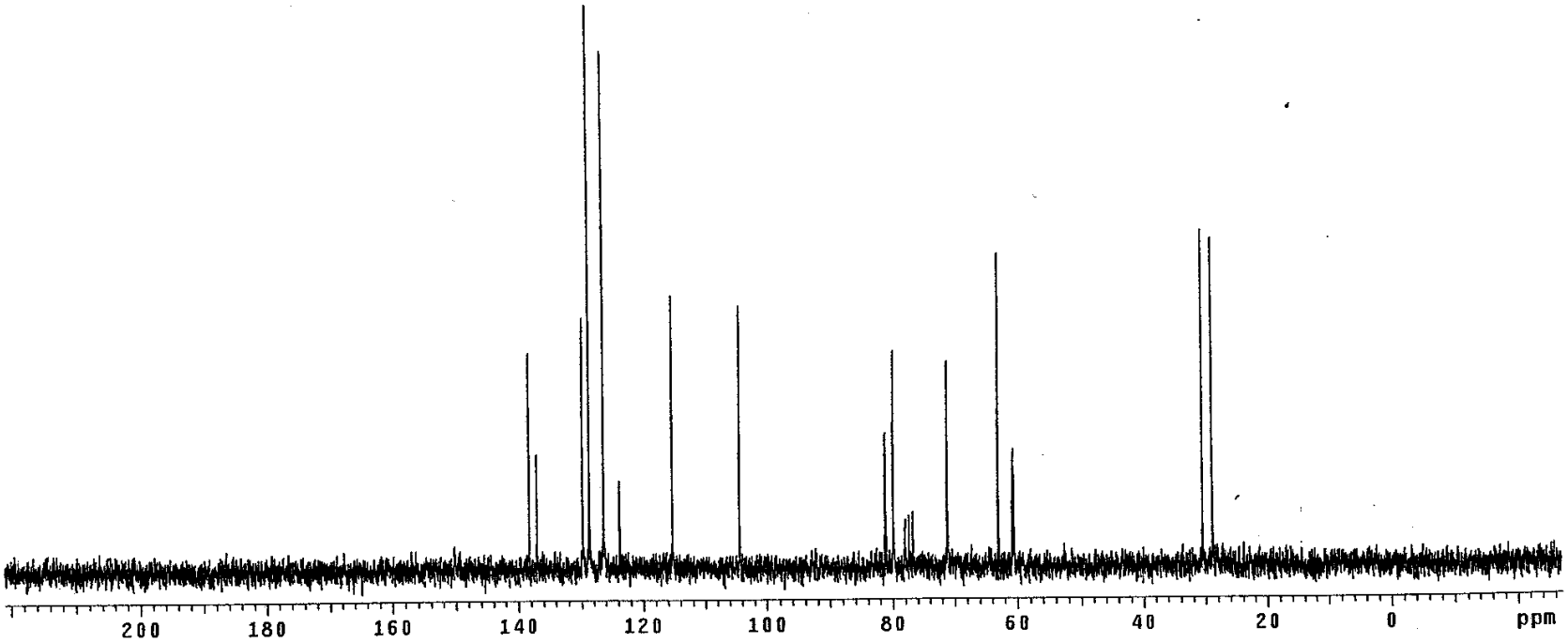


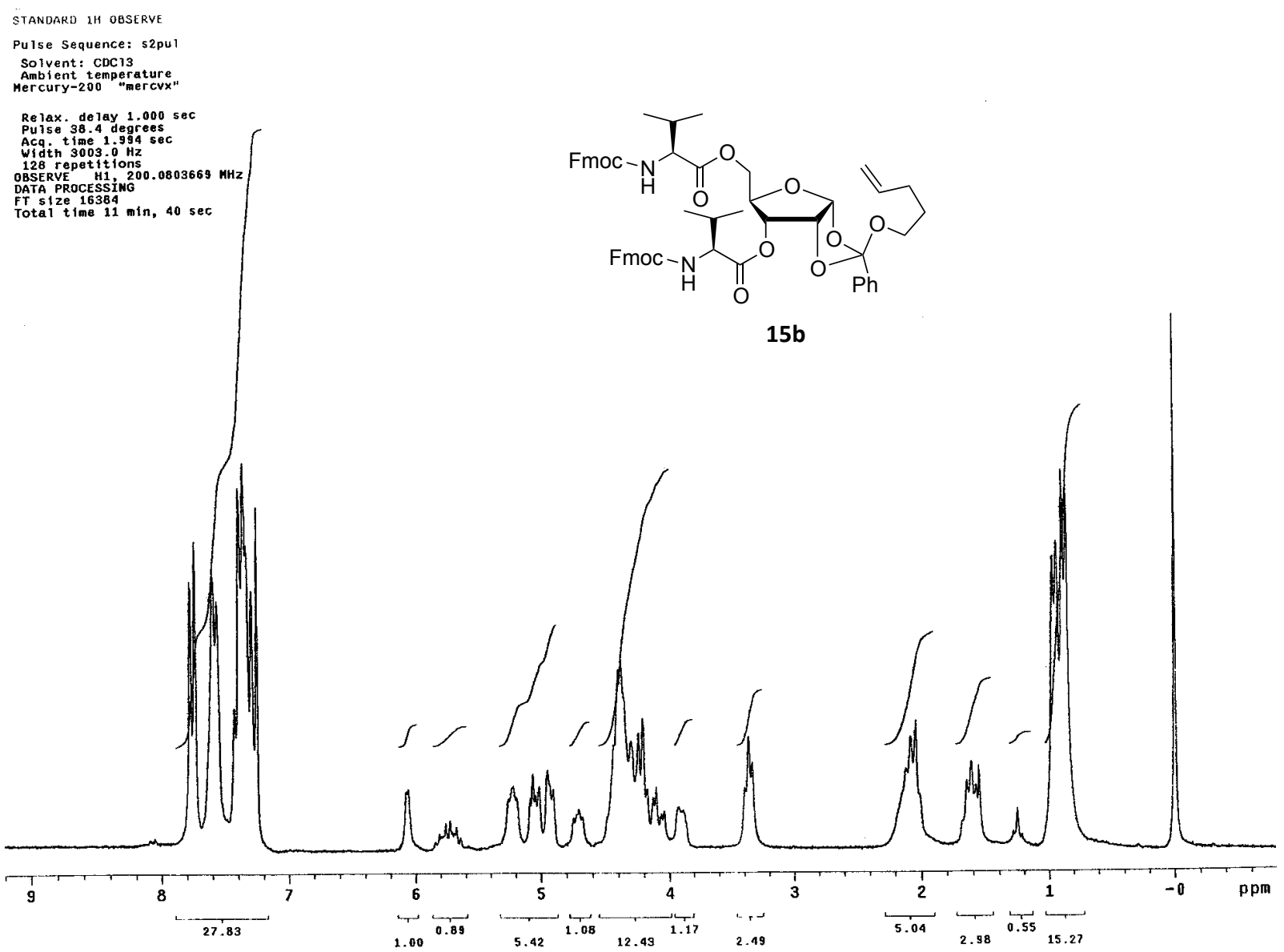
15a

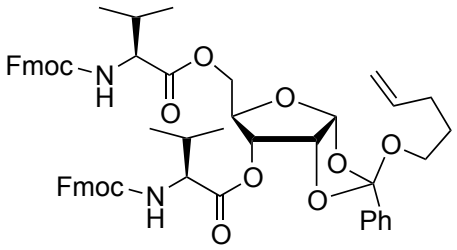




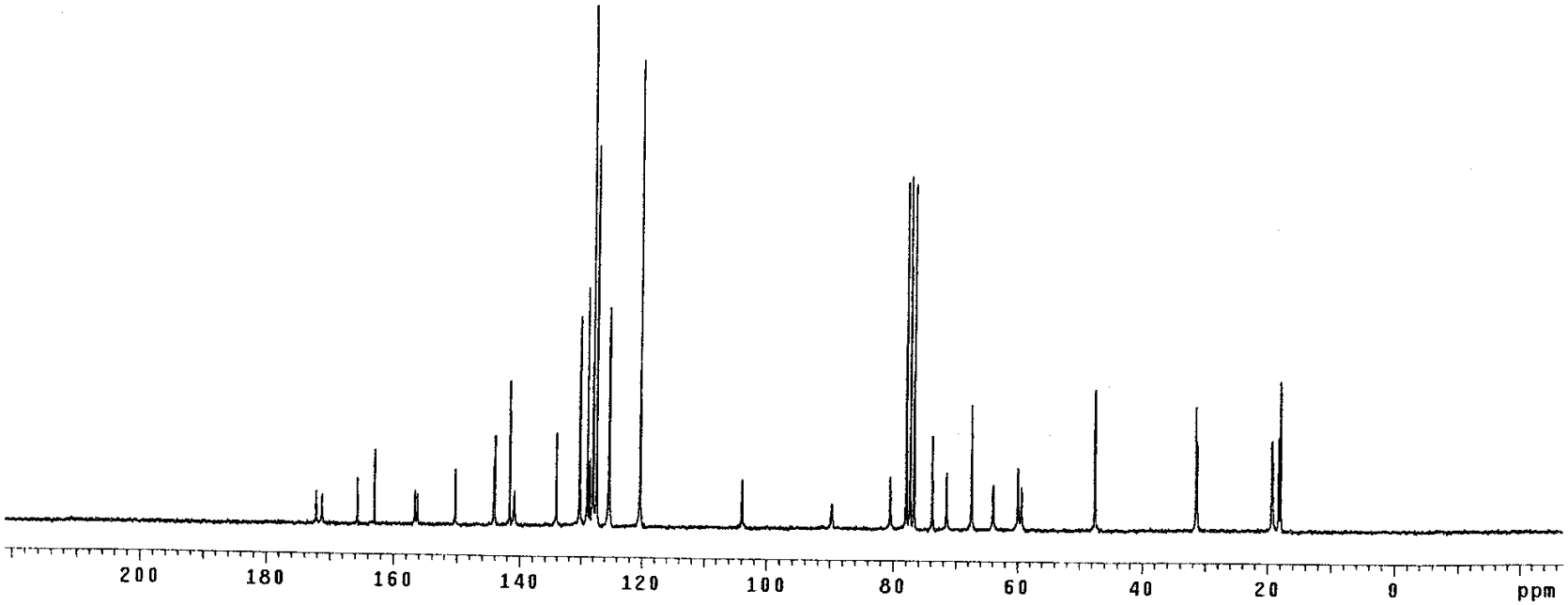
15a

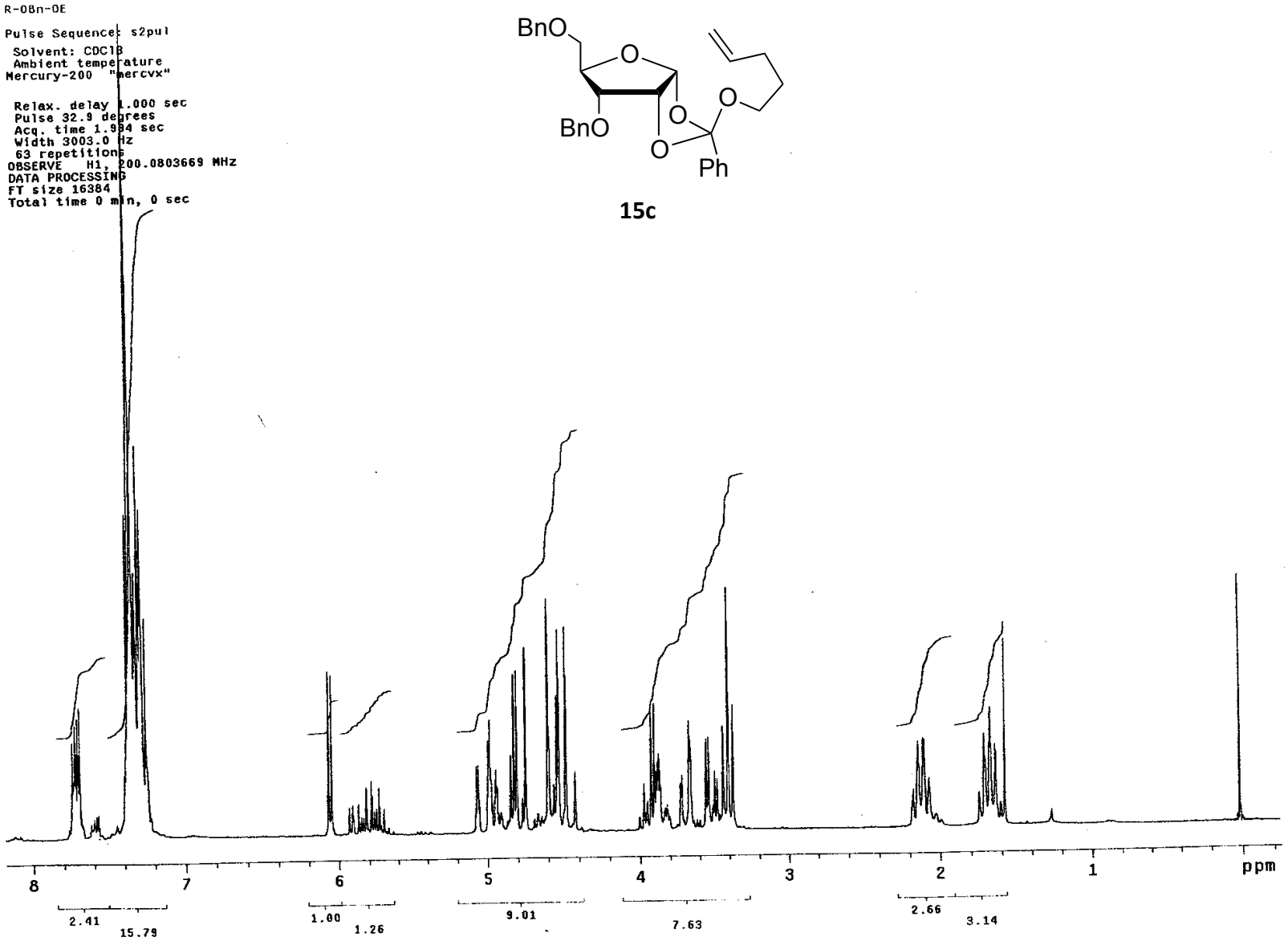


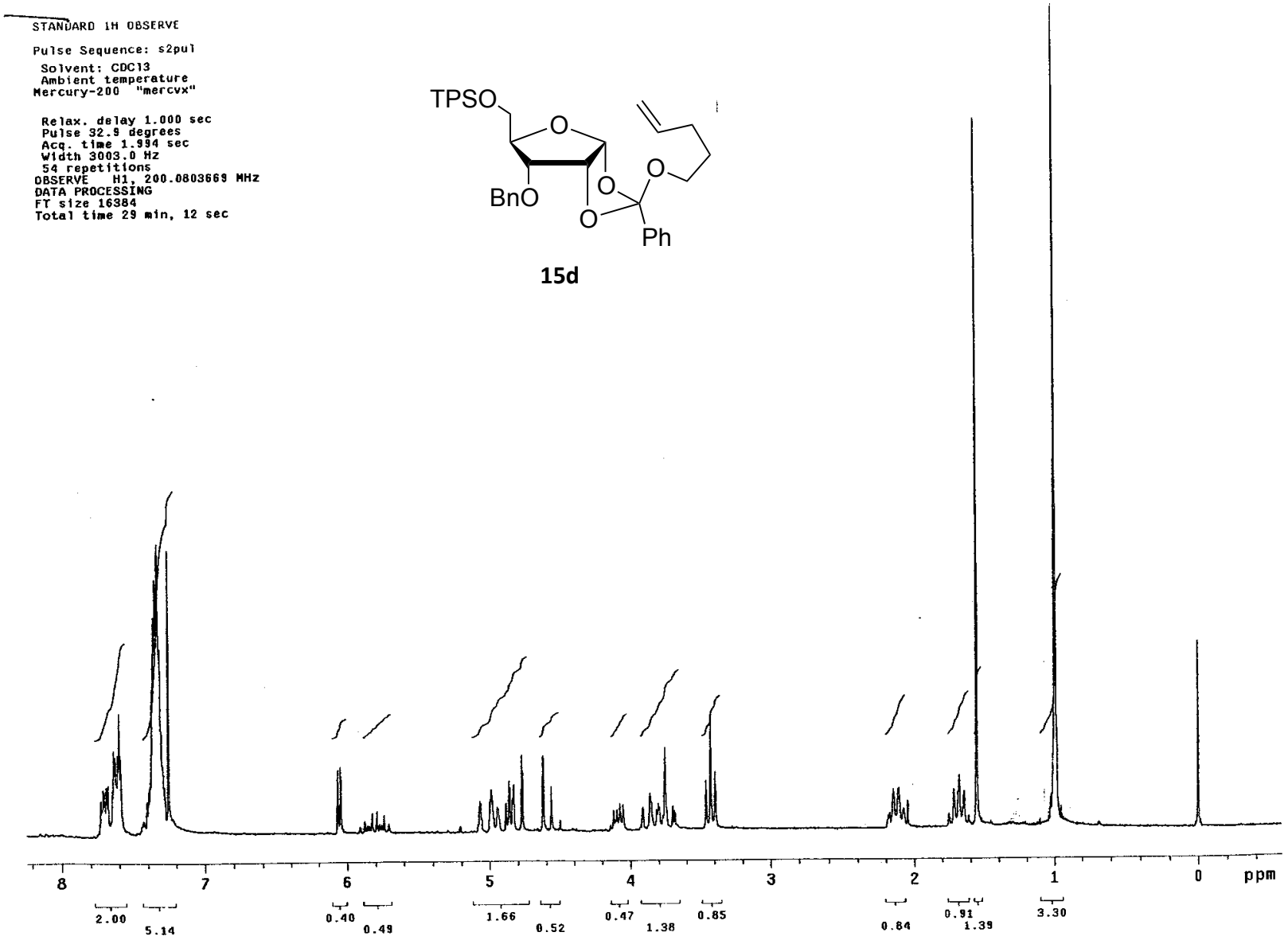


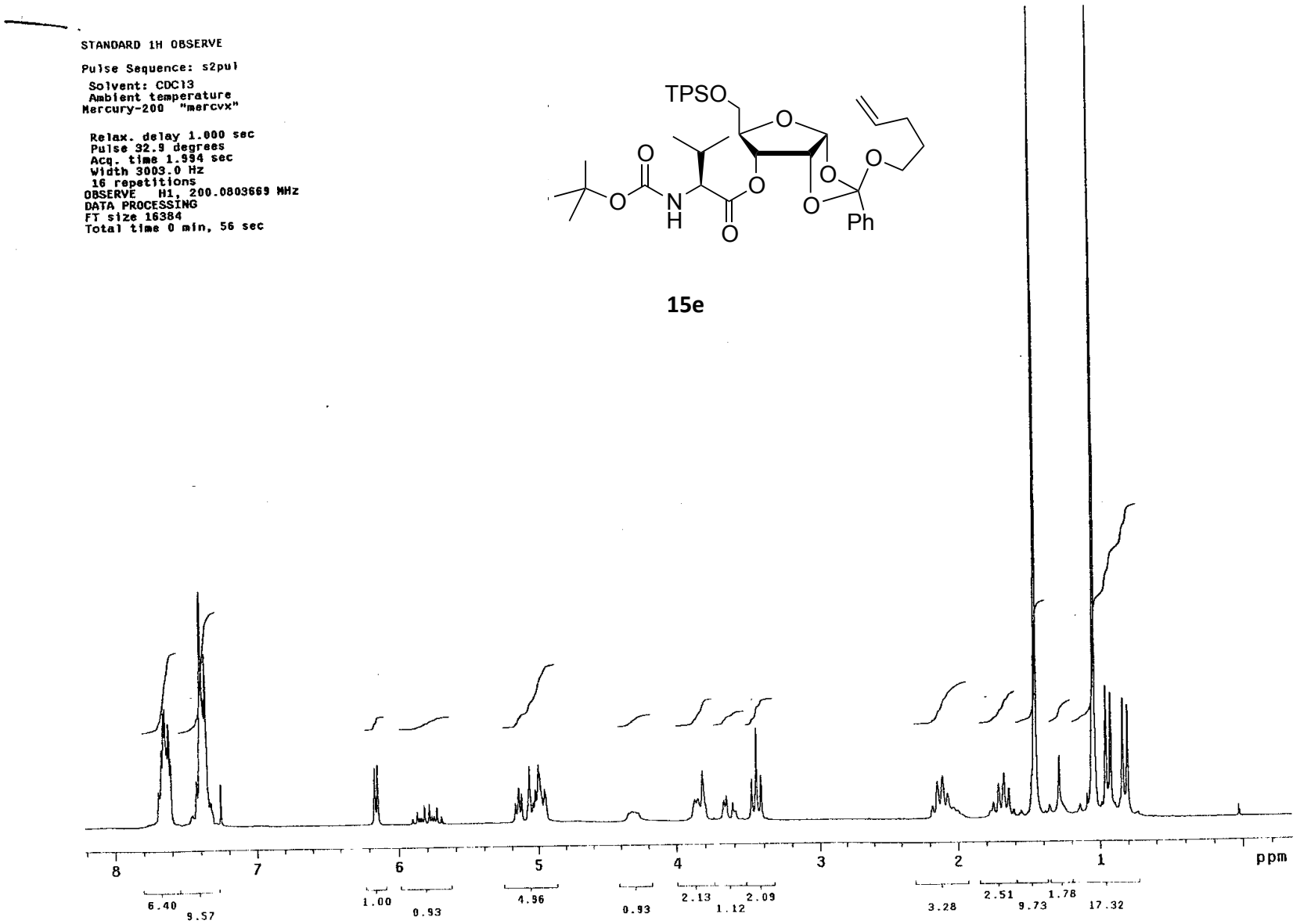


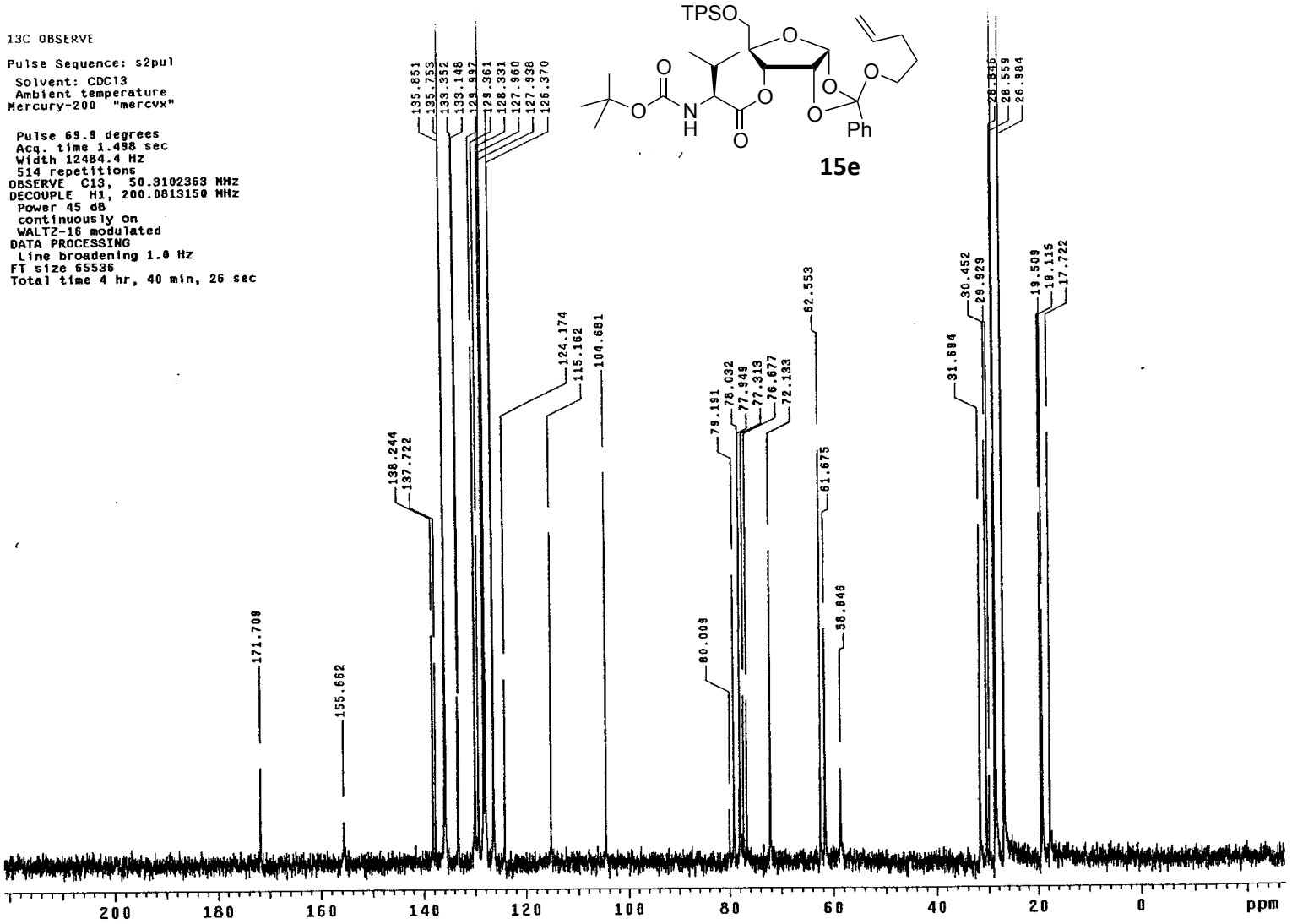
15b

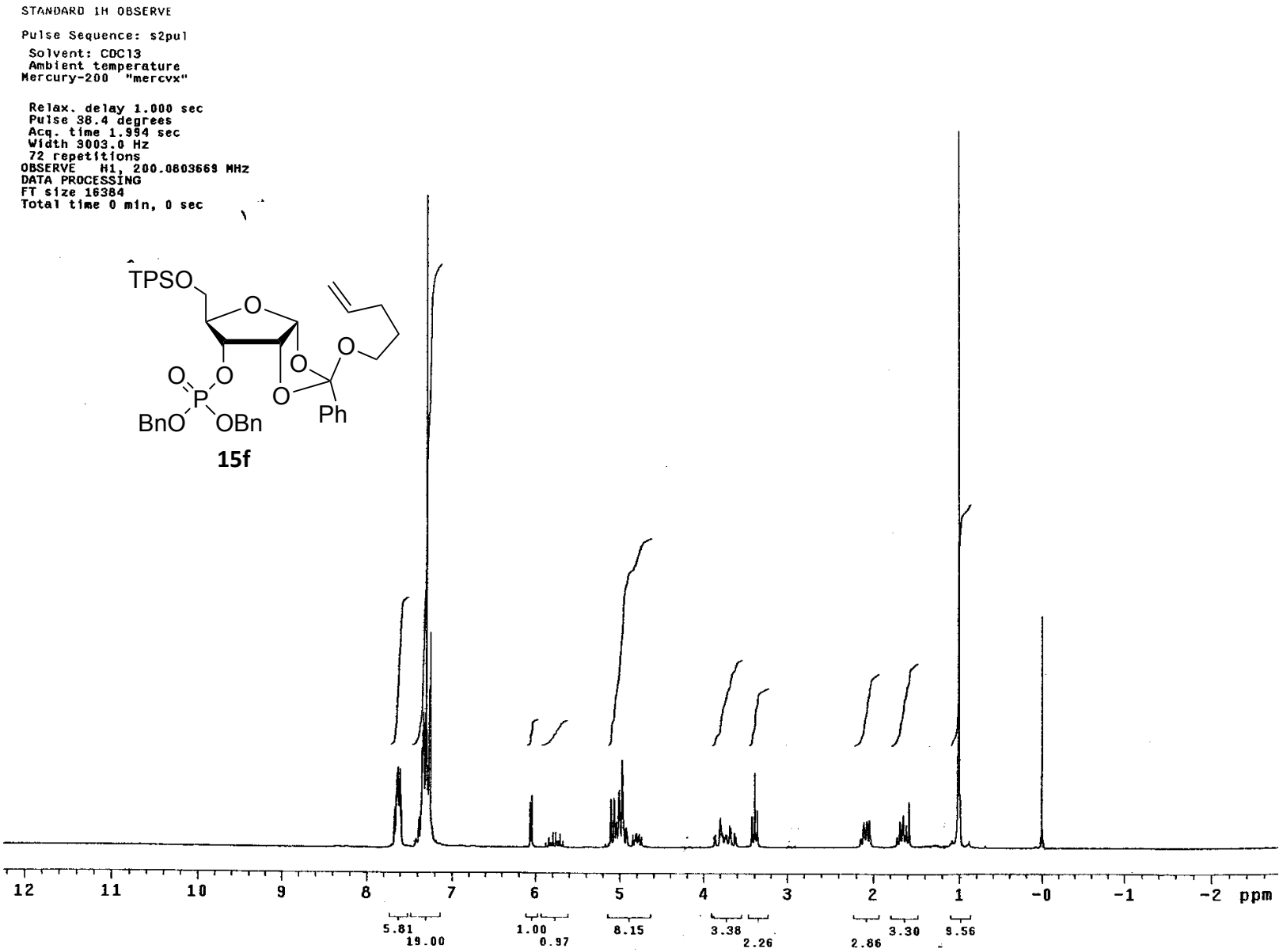


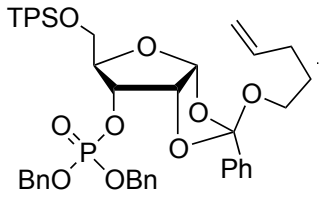

R-OBn-OE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-200 "mercvx"
Relax. delay 1.000 sec
Pulse 32.9 degrees
Acq. time 1.994 sec
Width 3003.0 Hz
63 repetitions
OBSERVE H1, 200.0803669 MHz
DATA PROCESSING
FT size 16384
Total time 0 min, 0 sec
BnO
O
BnO
O
O
O
Ph
15c
8
7
6
5
4
3
2
1
ppm
2.41
15.79
1.00
1.26
9.01
7.63
2.66
3.14



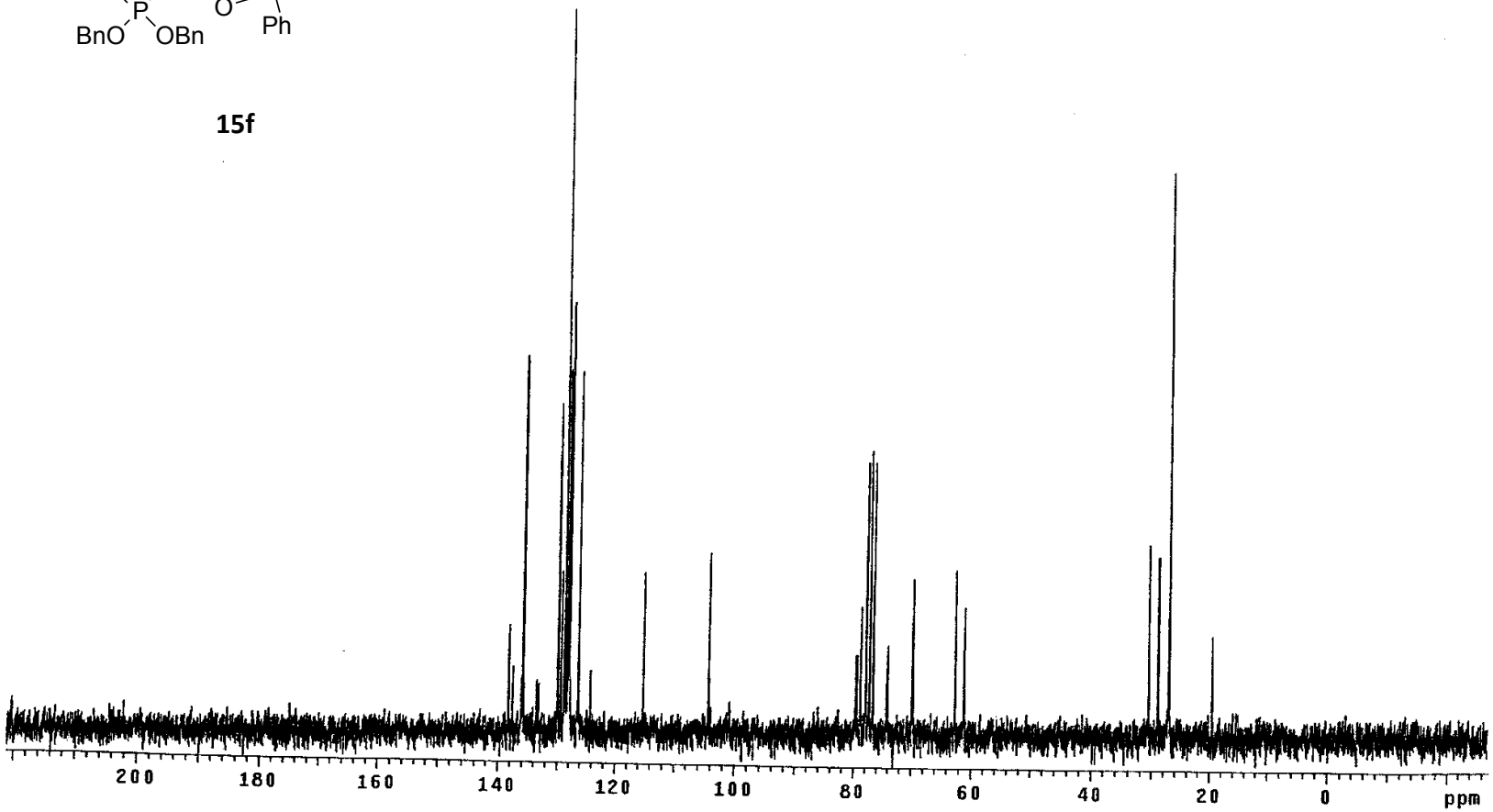



13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-200 "mercvx"
Pulse 69.9 degrees
Acq. time 1.498 sec
Width 12484.4 Hz
514 repetitions
OBSERVE C13, 50.3102363 MHz
DECOUPLE H1, 200.0813150 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 4 hr, 40 min, 26 sec
TPSO
O
N
H
Ph
15e
135.851
135.753
133.352
133.148
129.361
128.331
127.960
127.938
126.370
171.709
155.662
138.244
137.722
124.174
115.162
104.681
80.009
79.191
78.032
77.949
77.313
76.677
72.133
62.553
61.675
58.646
31.694
30.452
29.929
28.816
28.559
26.984
19.509
19.115
17.722
200
180
160
140
120
100
80
60
40
20
0
ppm





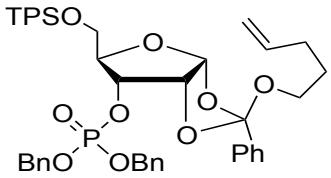
15f



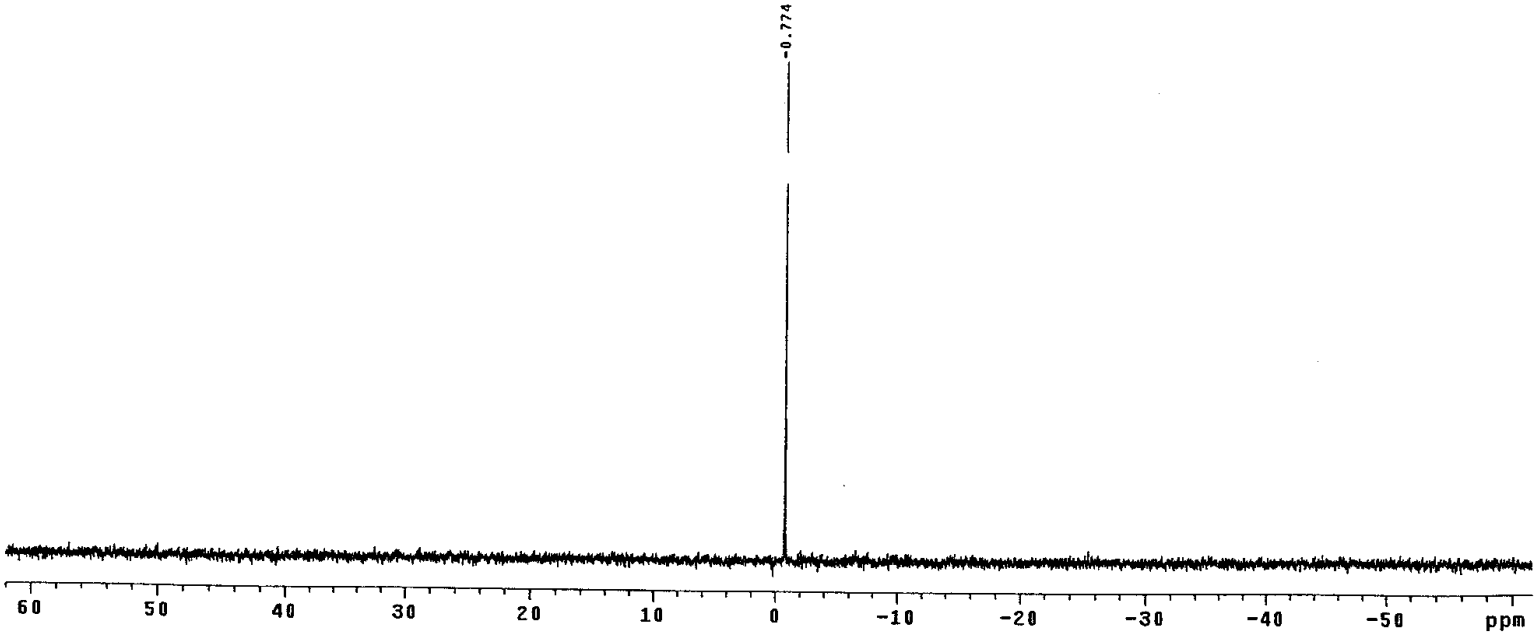
SURVEY PHOSPHORUS PARAMETERS

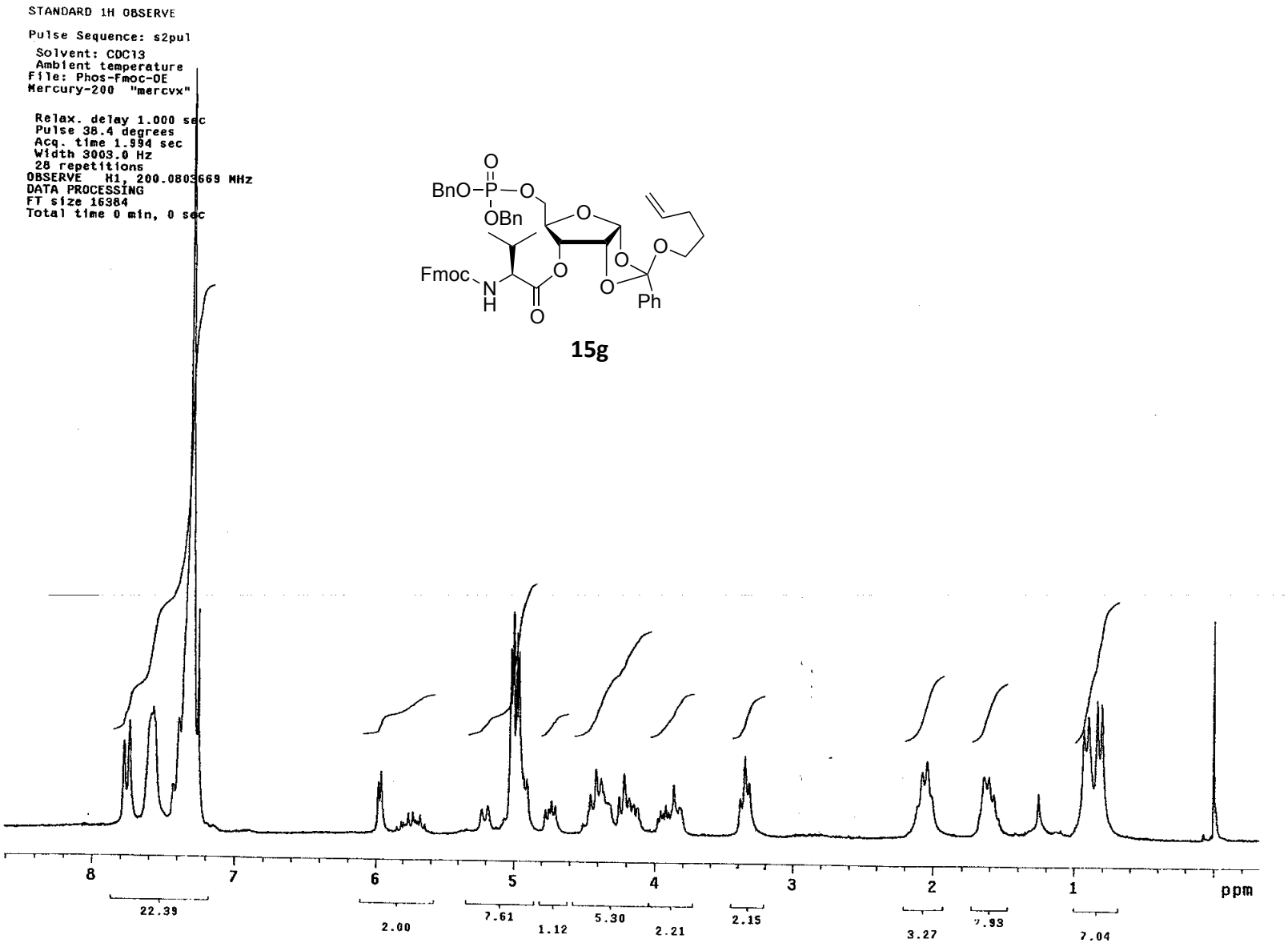
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-200 "mercvx"

Pulse 45.3 degrees
Acq. time 1.600 sec
Width 10010.0 Hz
40 repetitions
OBSERVE P31, 80.9939267
DECOUPLE H1, 200.0813150
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768
Total time 4 min, 36 sec

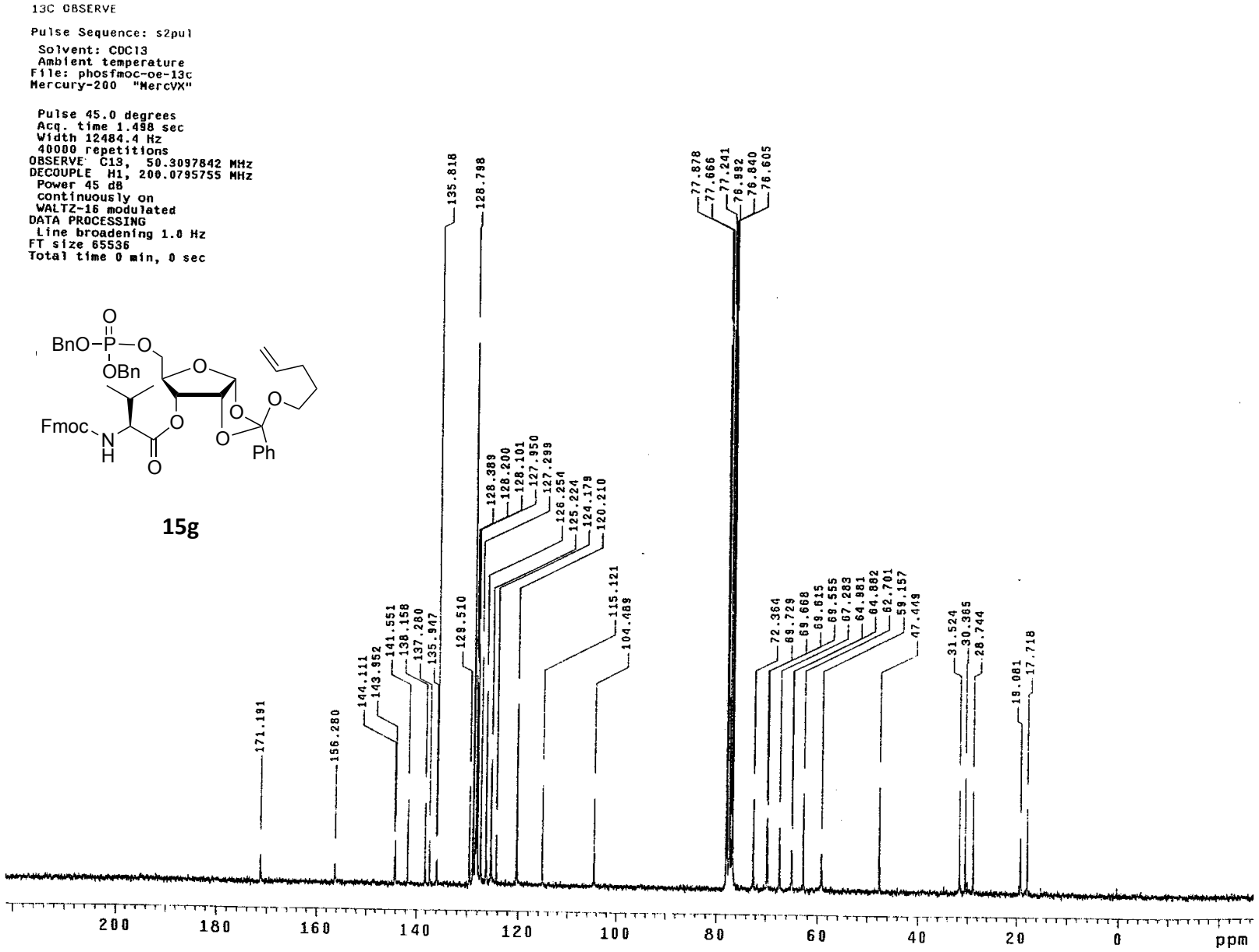


15f

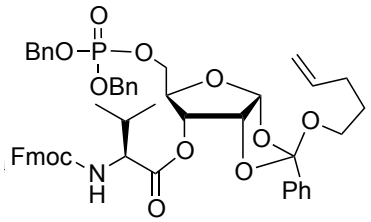




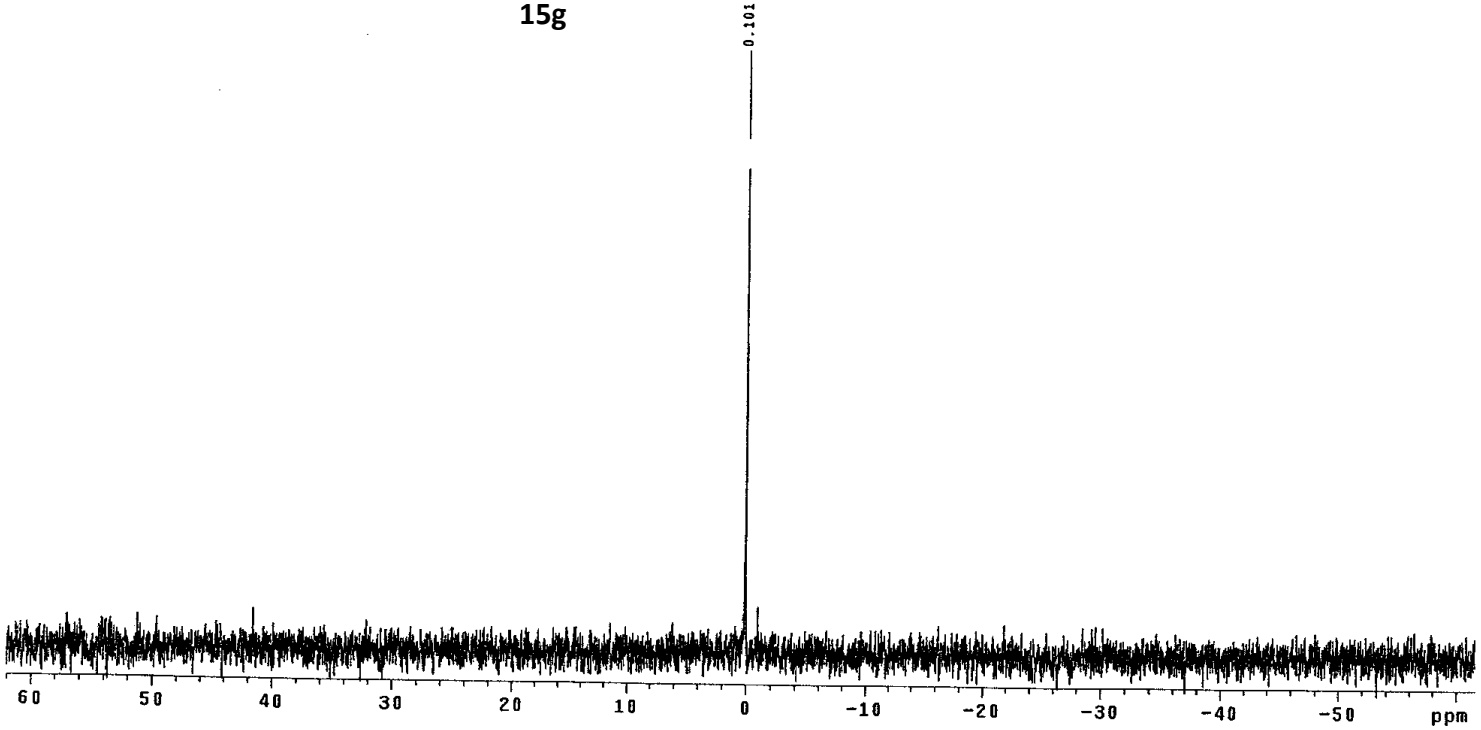
15g

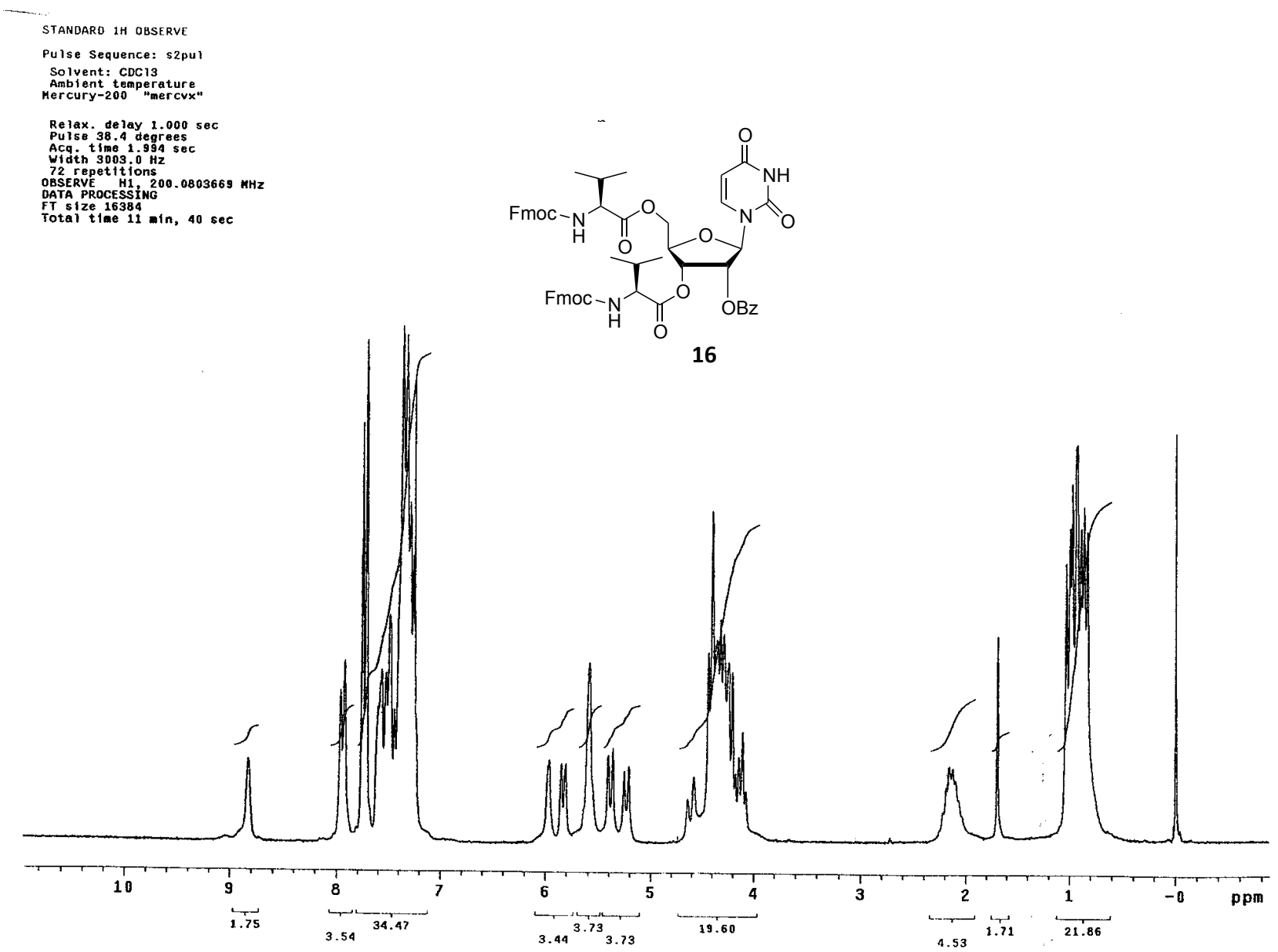


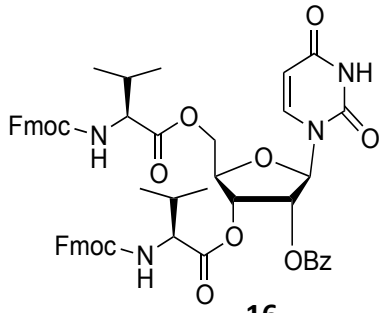
```
SURVEY PHOSPHORUS PARAMETERS

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Mercury-200  "mercvx"

 Pulse 45.3 degrees
 Acq. time 1.600 sec
 Width 10010.0 Hz
 96 repetitions
OBSERVE  P31,  80.9939267 MHz
DECOUPLE  H1, 200.0813150 MHz
 Power 45 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 1.0 Hz
FT size 32768
Total time 7 min, 12 sec
```



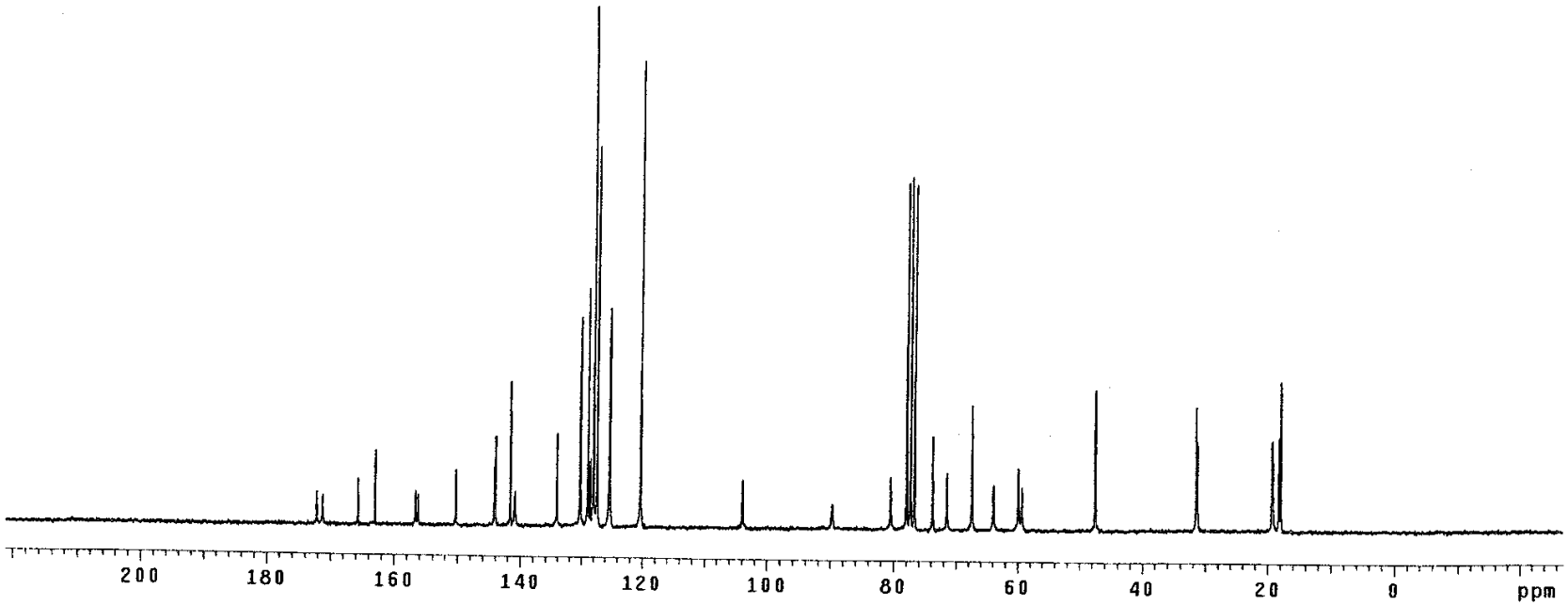
15g

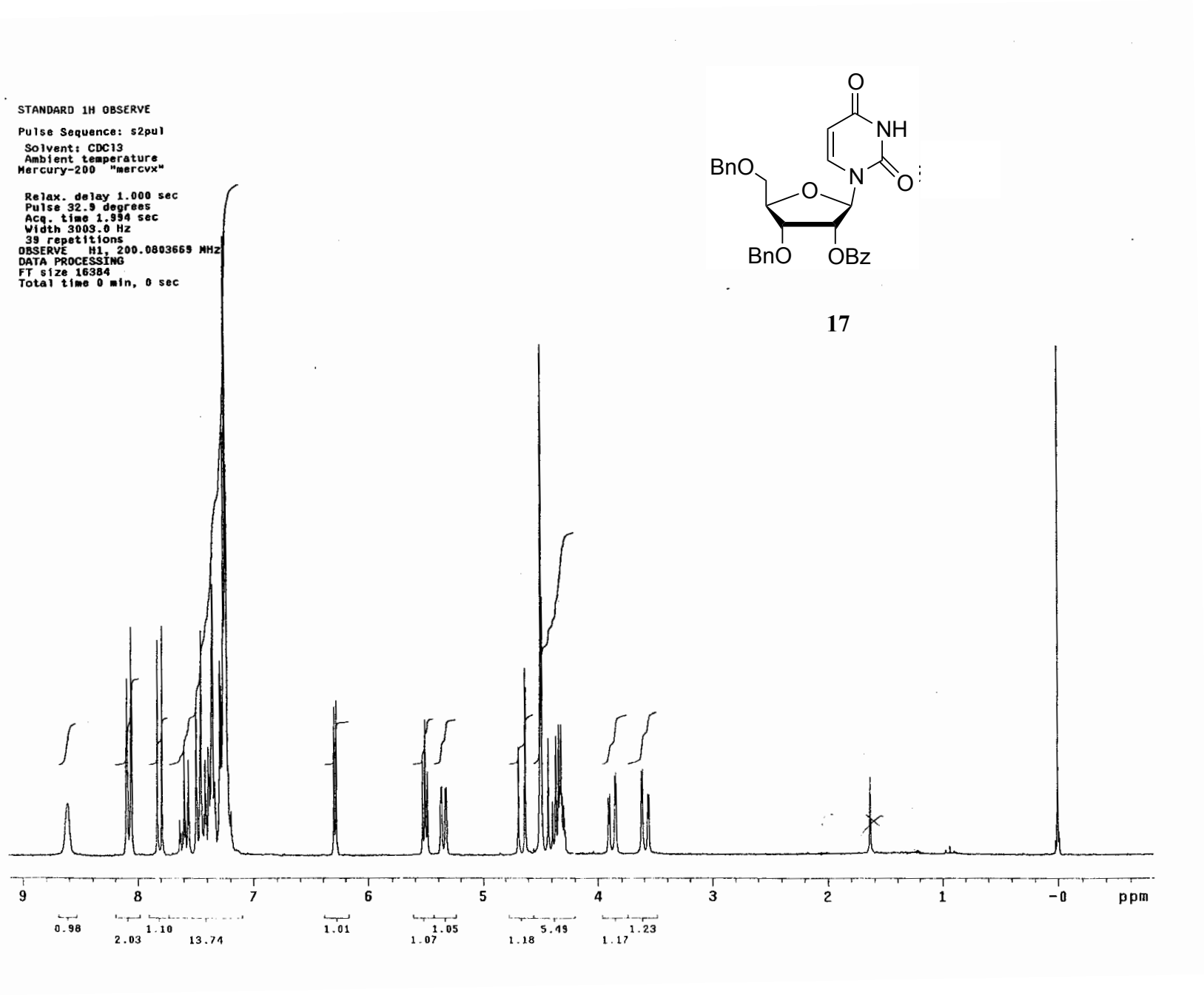




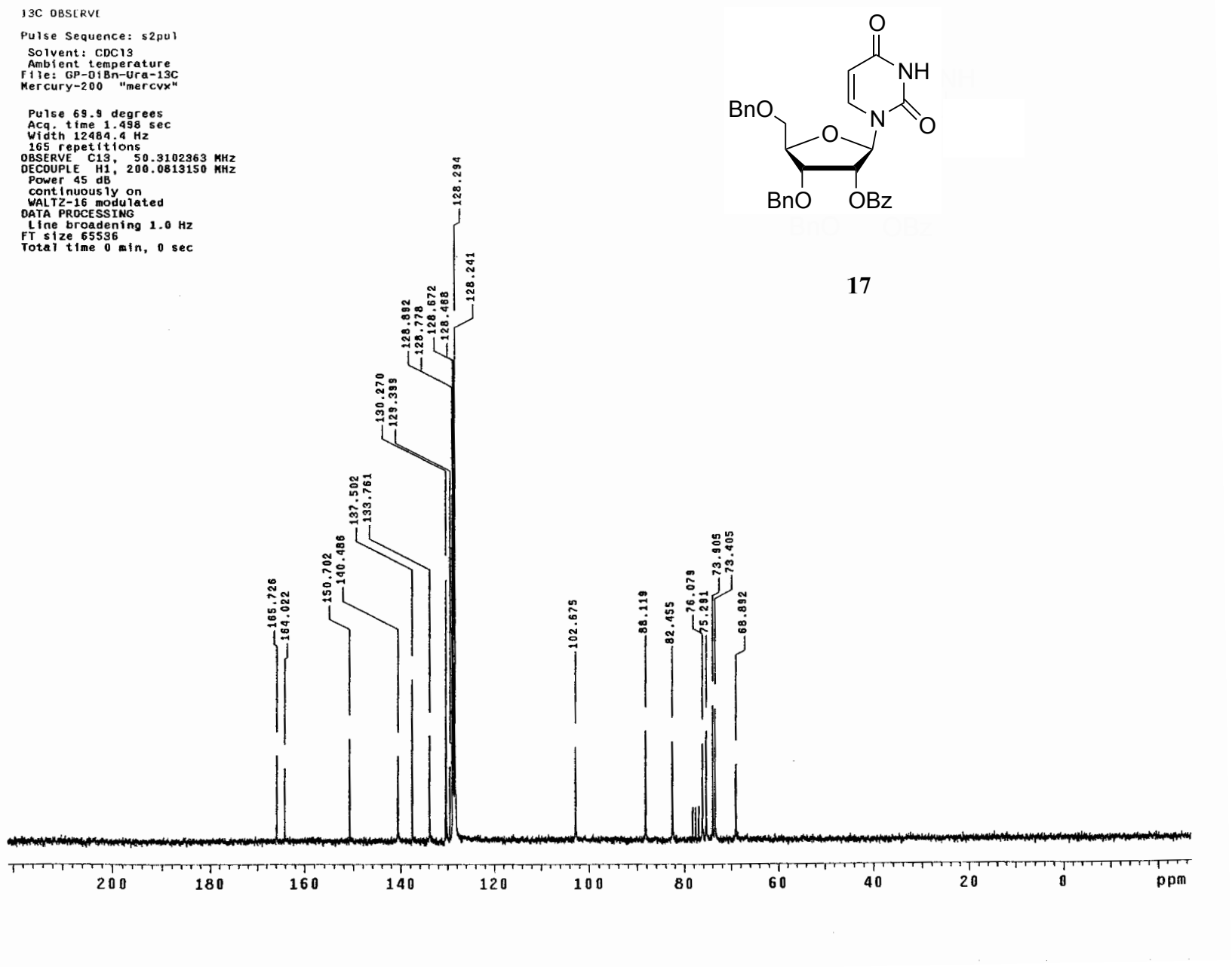


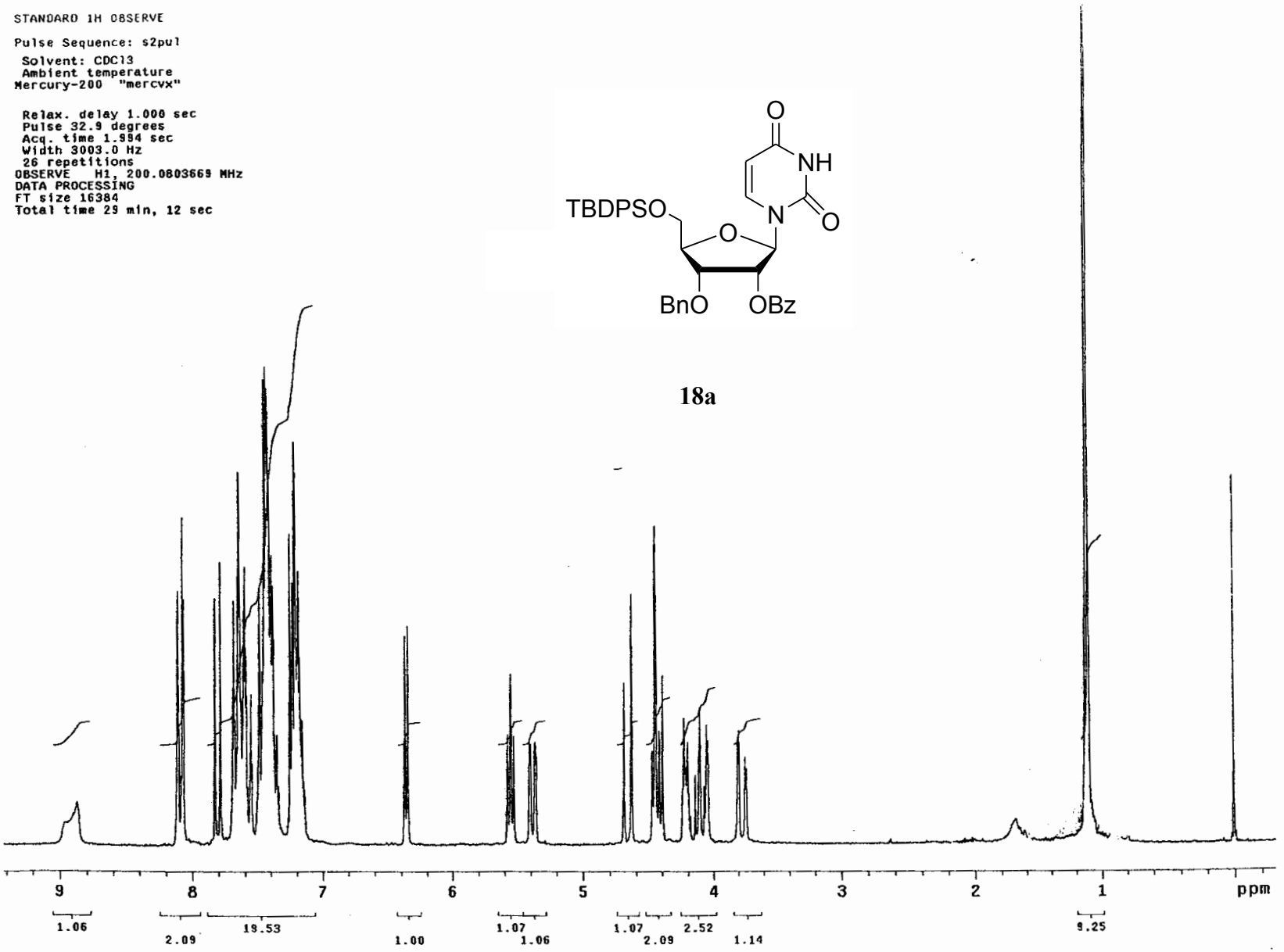
16



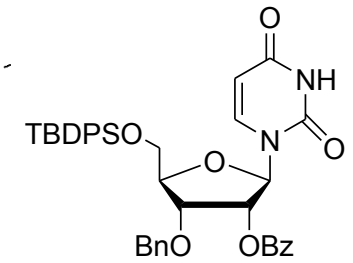


17

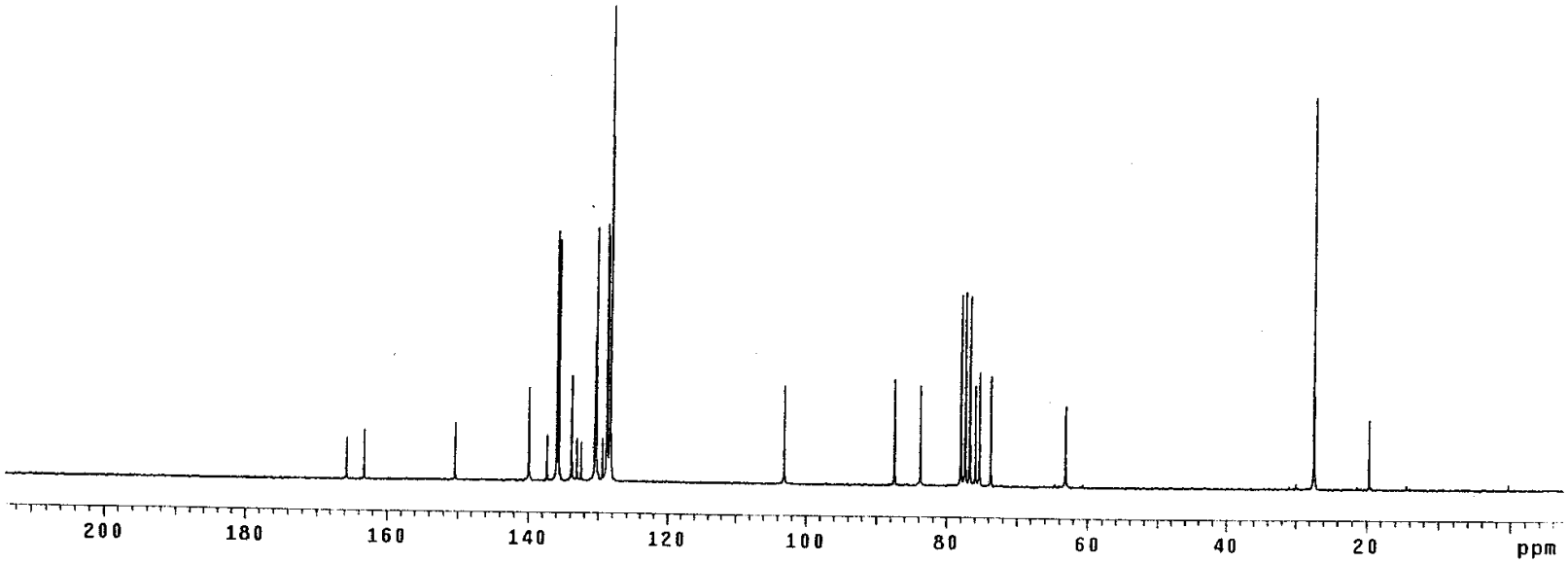


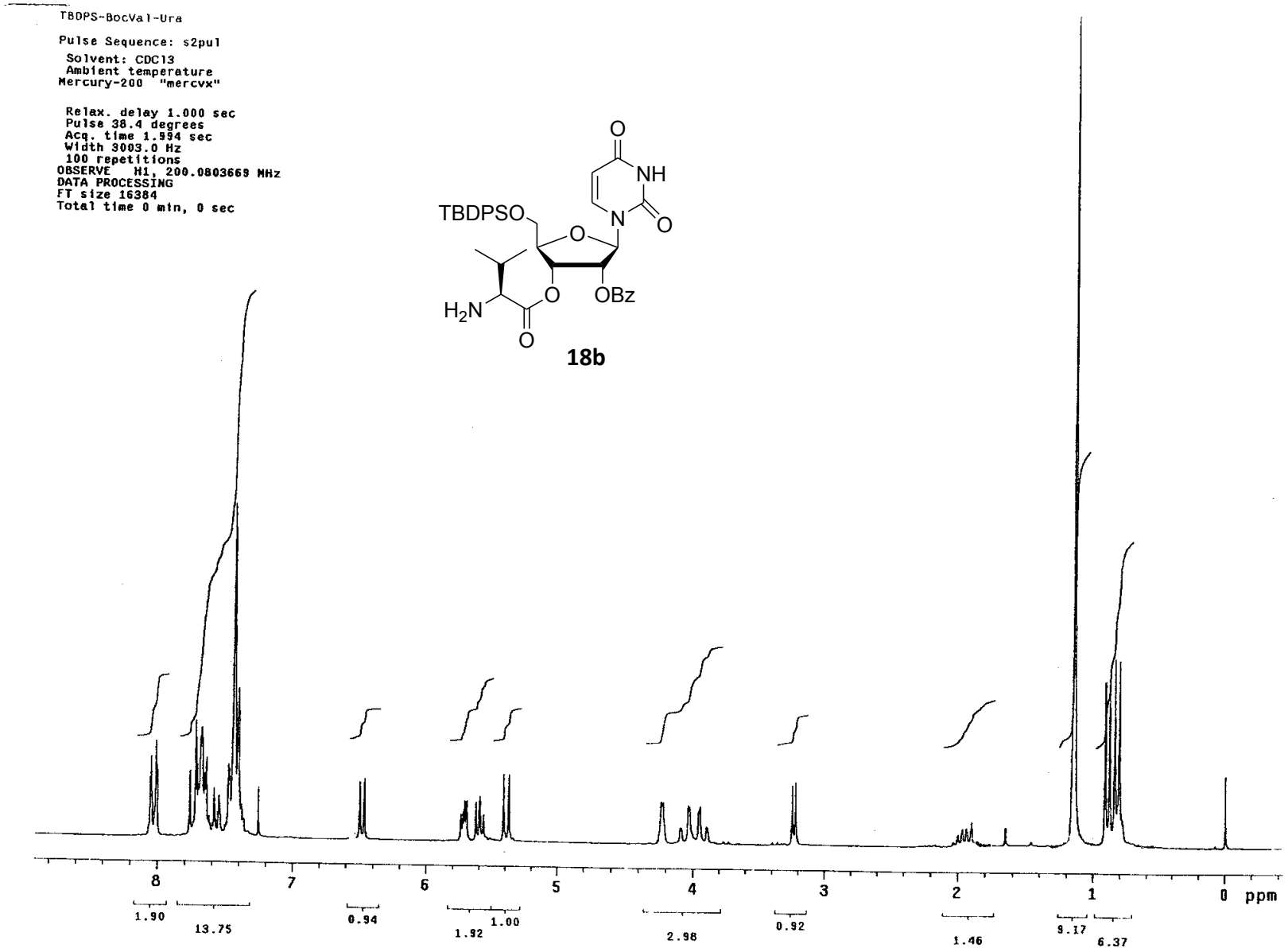


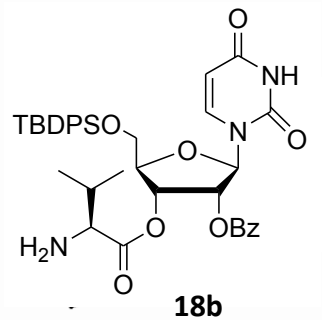
18a



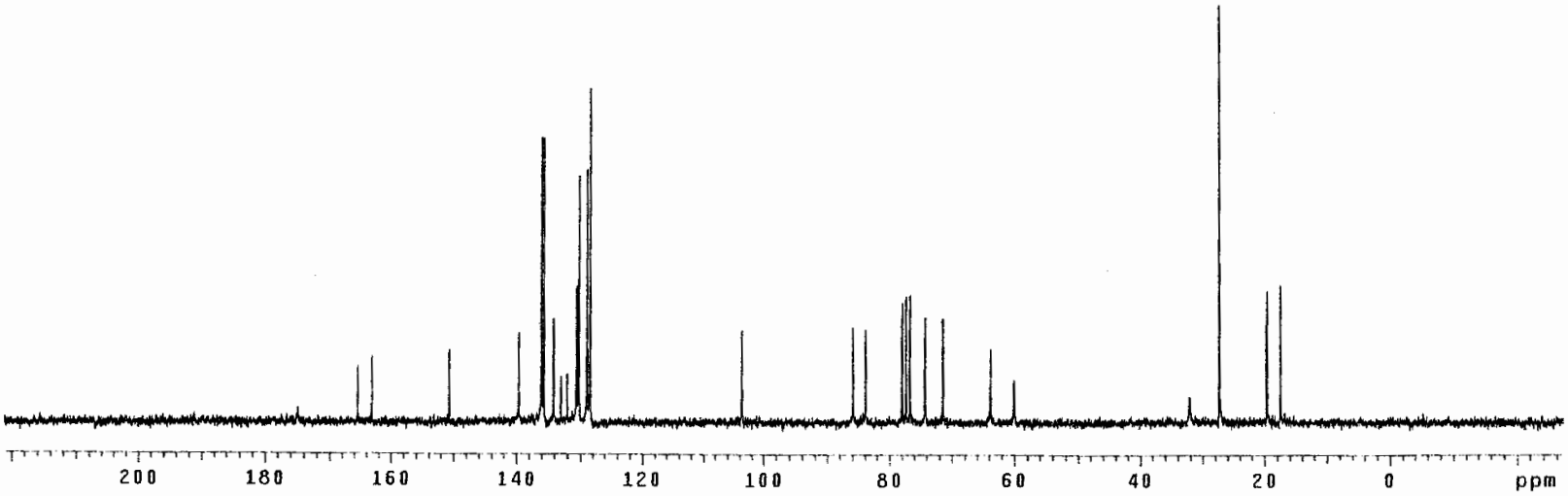
18a







18b

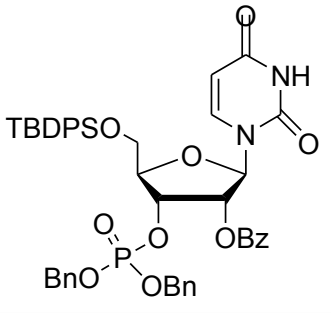


GP-II

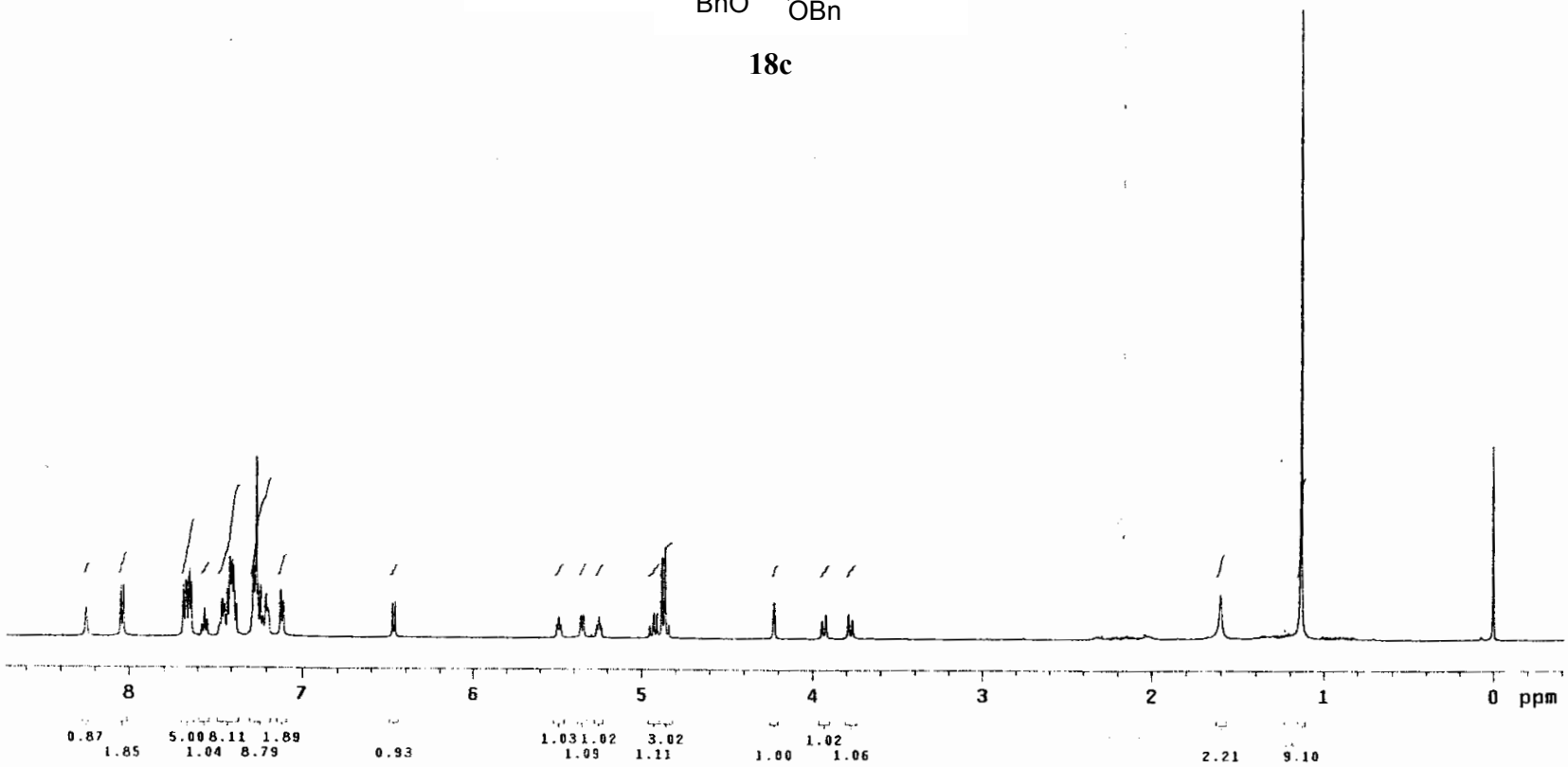
Sample: GP-II
Sample ID: s_20100413_05
File: 0074.fid

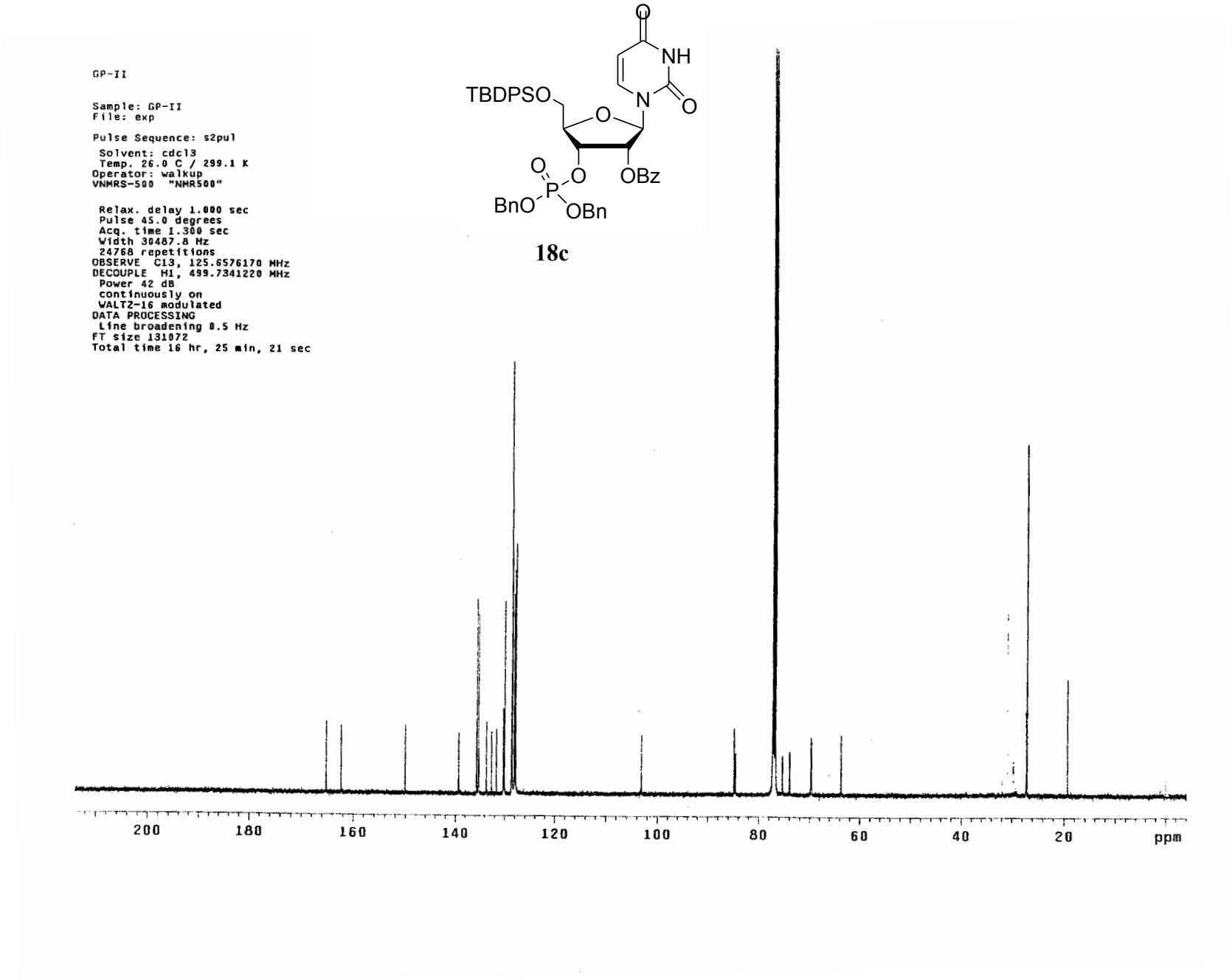
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 26.0 C / 299.1 K
Operator: walkup
File: 0074
VNMRS-500 "NMR500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.049 sec
Width 8012.8 Hz
8 repetitions
OBSERVE H1, 499.7316295 MHz
DATA PROCESSING
Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 31 sec



18c

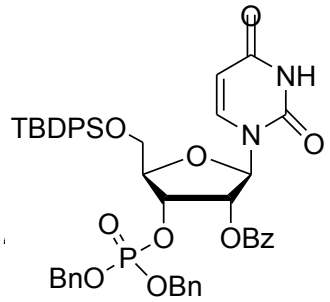




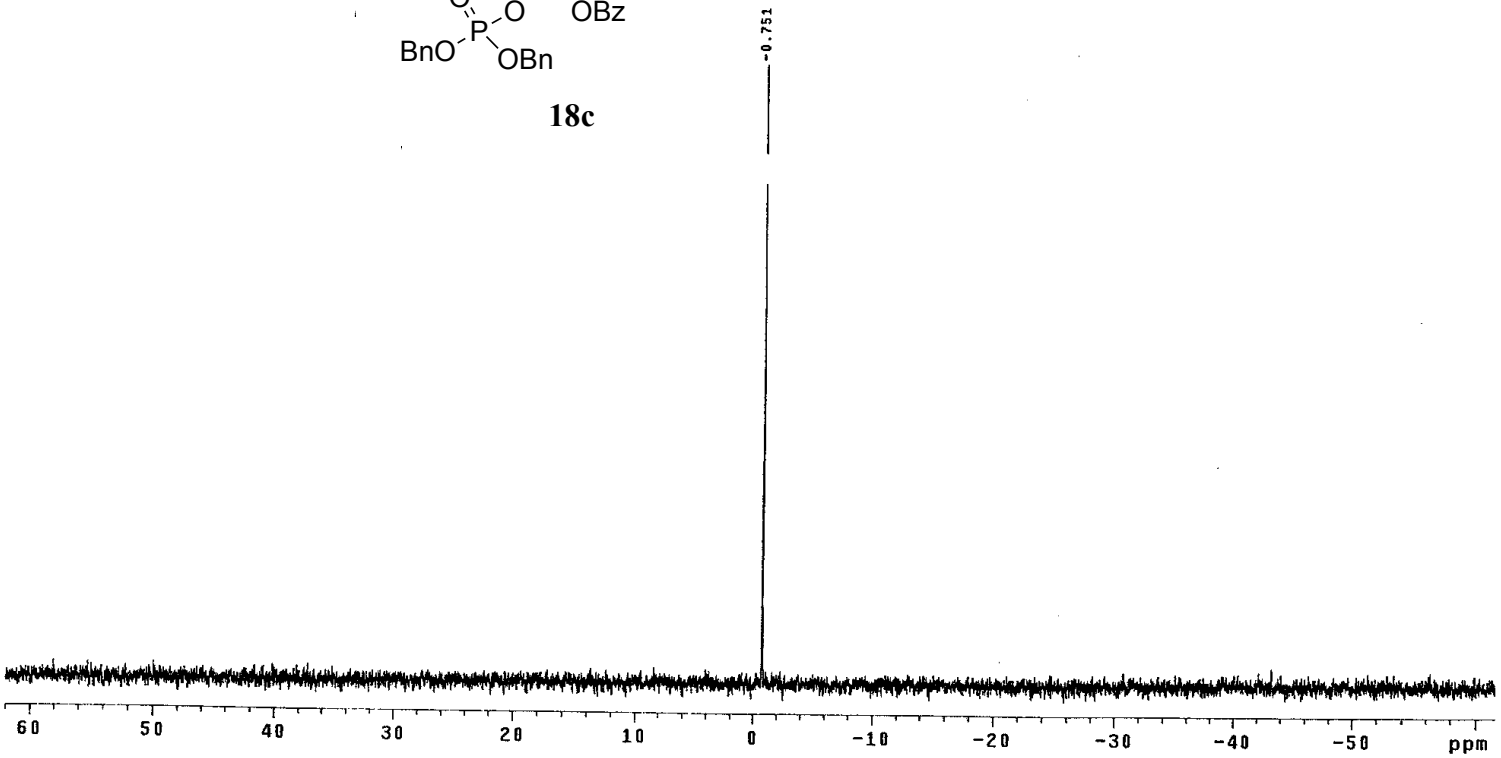
SURVEY PHOSPHORUS PARAMETERS

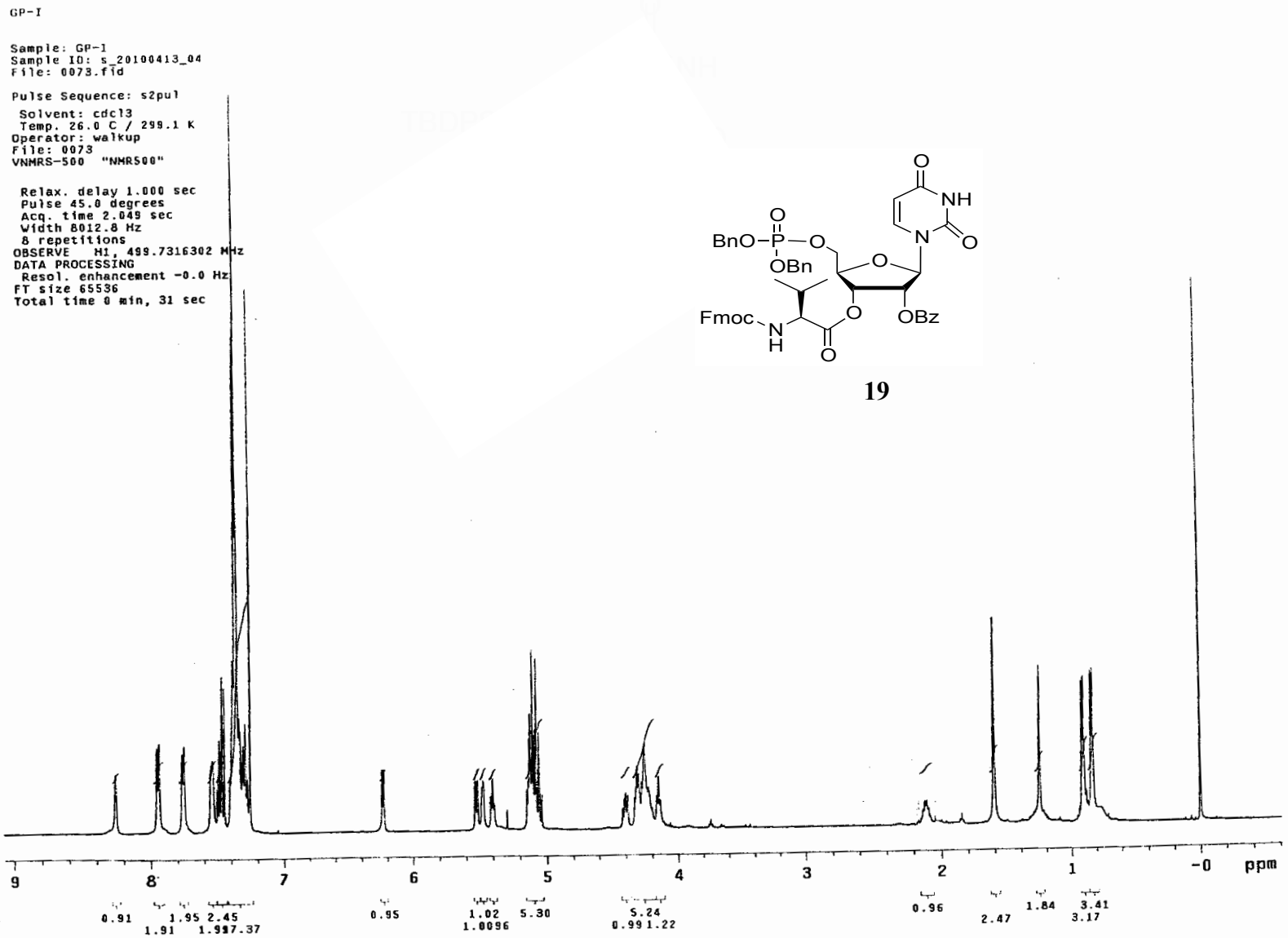
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-200 "mercvx"

Pulse 45.3 degrees
Acq. time 1.600 sec
Width 10010.0 Hz
64 repetitions
OBSERVE P31, 80.9939267 MHz
DECOUPLE H1, 200.0813150 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768
Total time 4 min, 36 sec

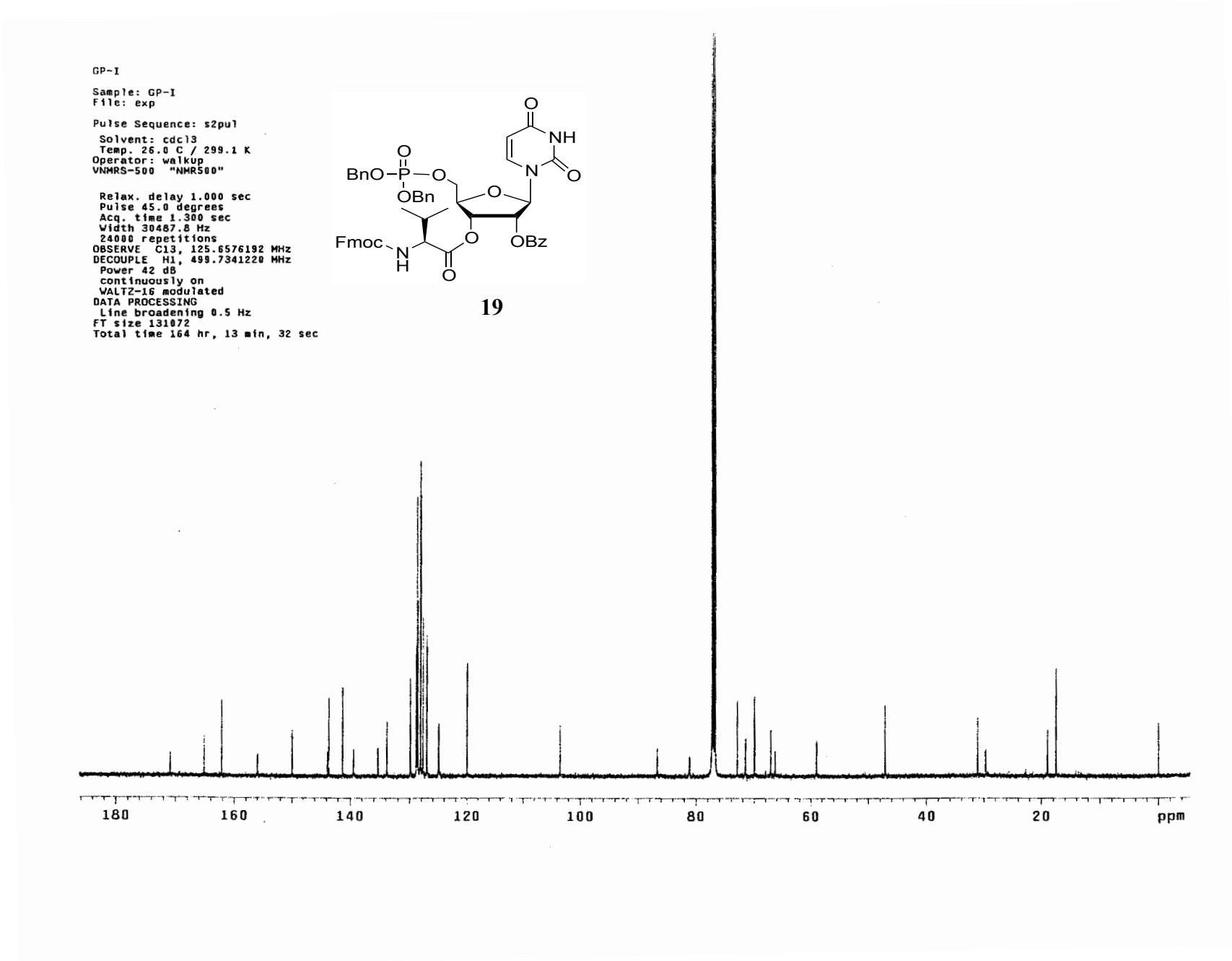


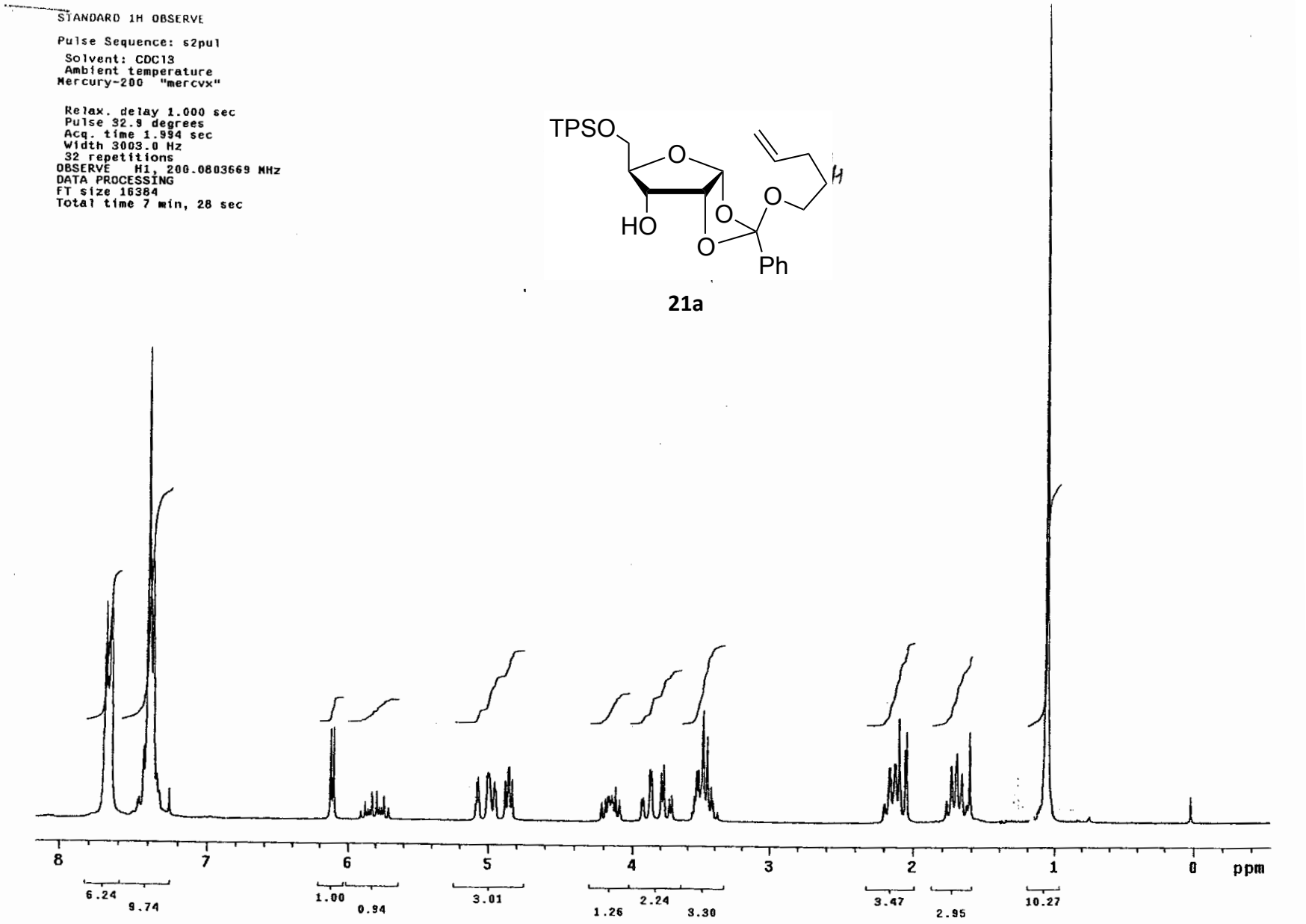
18c



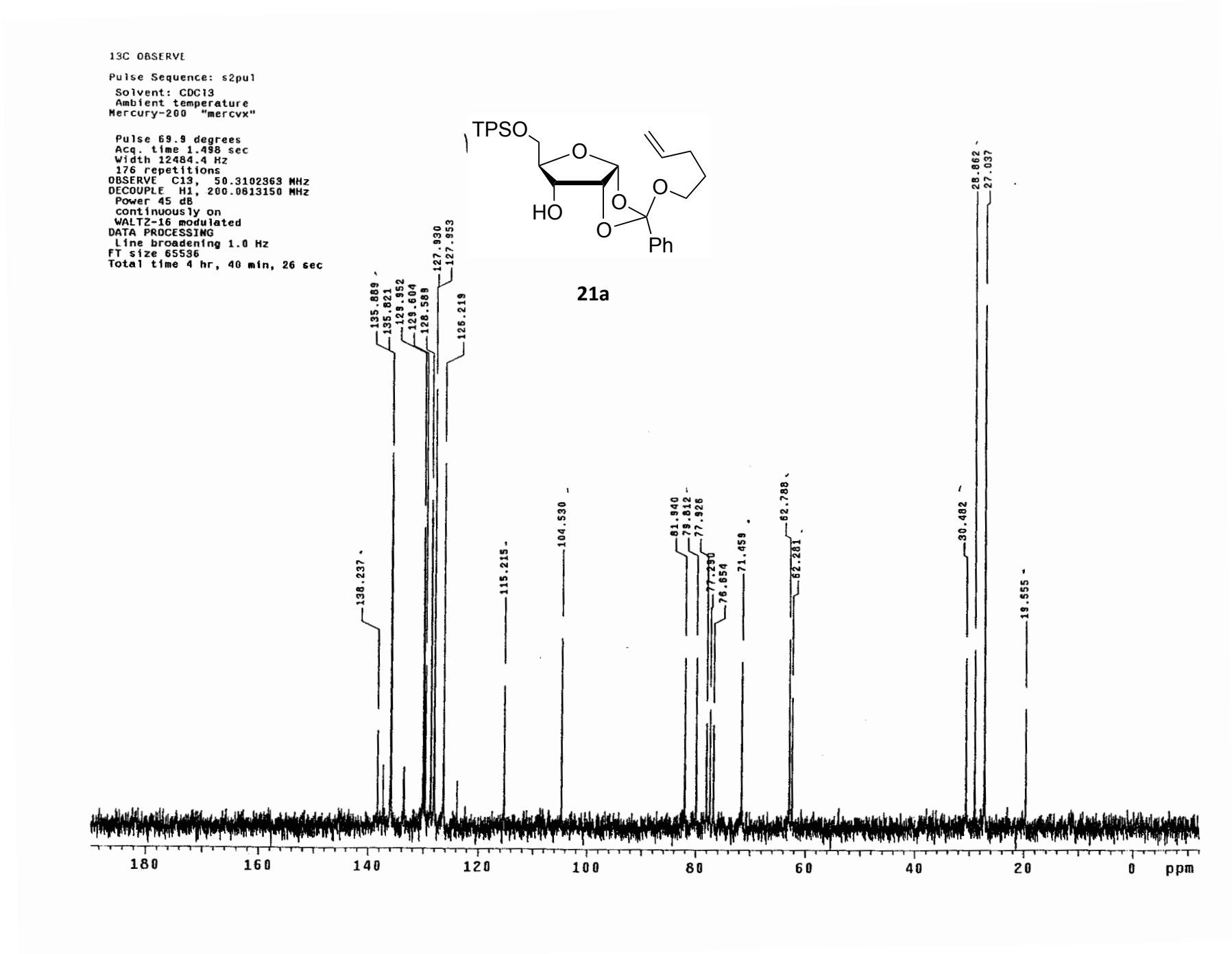


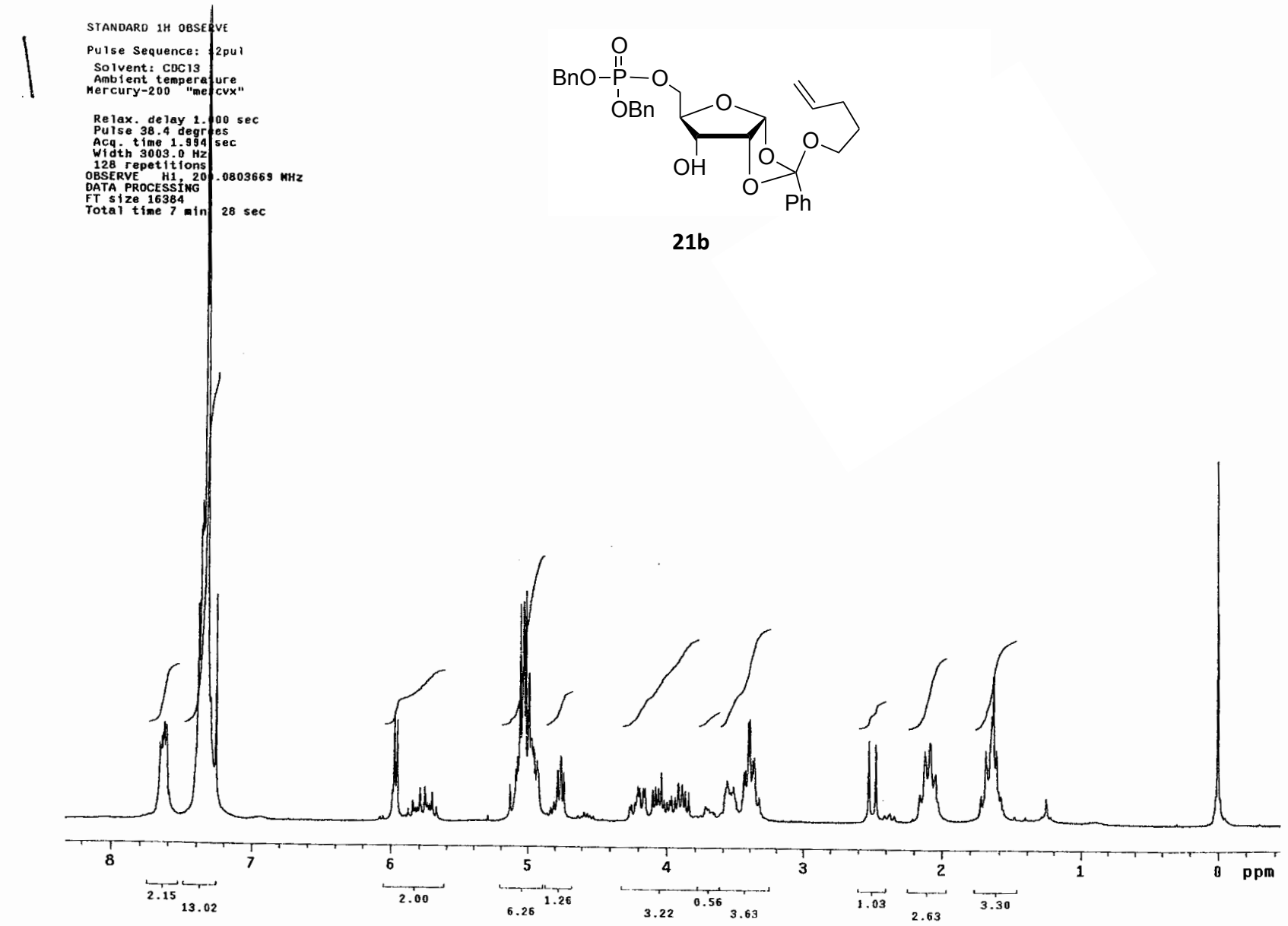
19


GP-I
Sample: GP-I
File: exp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 26.0 C / 299.1 K
Operator: walkup
VNMRS-500 "NMR500"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30487.8 Hz
24000 repetitions
OBSERVE C13, 125.6576192 MHz
DECOUPLE H1, 499.7341220 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 164 hr, 13 min, 32 sec
BnO
OBn
Fmoc
NH
OBz
19
180
160
140
120
100
80
60
40
20
ppm

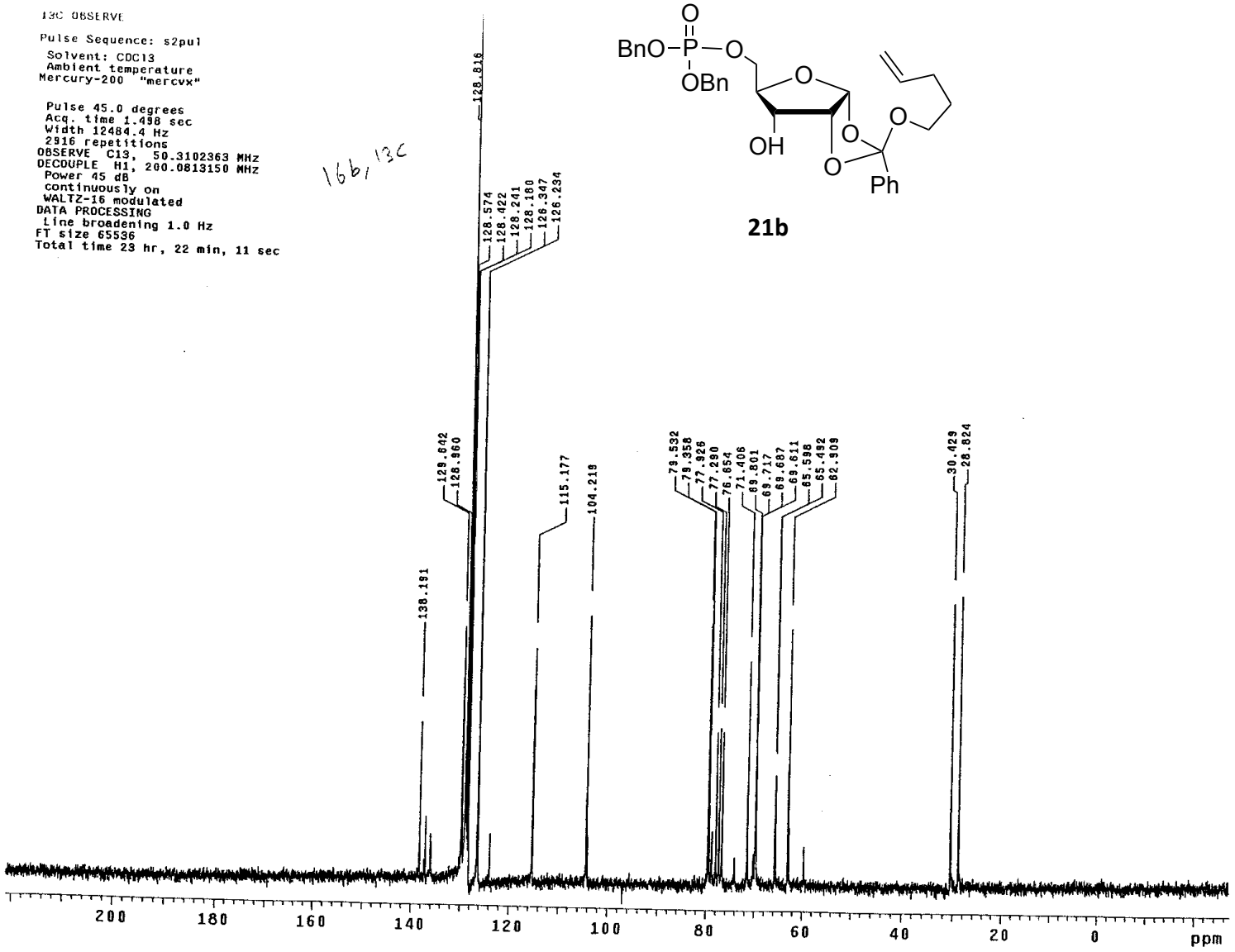


21a


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-200 "mercvx"
Pulse 69.9 degrees
Acq. time 1.498 sec
Width 12484.4 Hz
176 repetitions
OBSERVE C13, 50.3102363 MHz
DECOUPLE H1, 200.0813150 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 4 hr, 40 min, 26 sec
TPSO
HO
O
O
O
O
Ph
21a
135.889
135.821
129.952
129.604
128.589
127.930
127.953
126.219
138.237
115.215
104.530
81.940
79.812
77.926
77.290
76.654
71.459
62.788
62.281
30.482
28.862
27.037
19.555
180
160
140
120
100
80
60
40
20
0
ppm



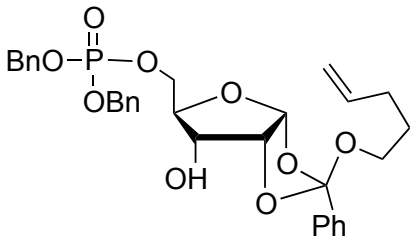
21b



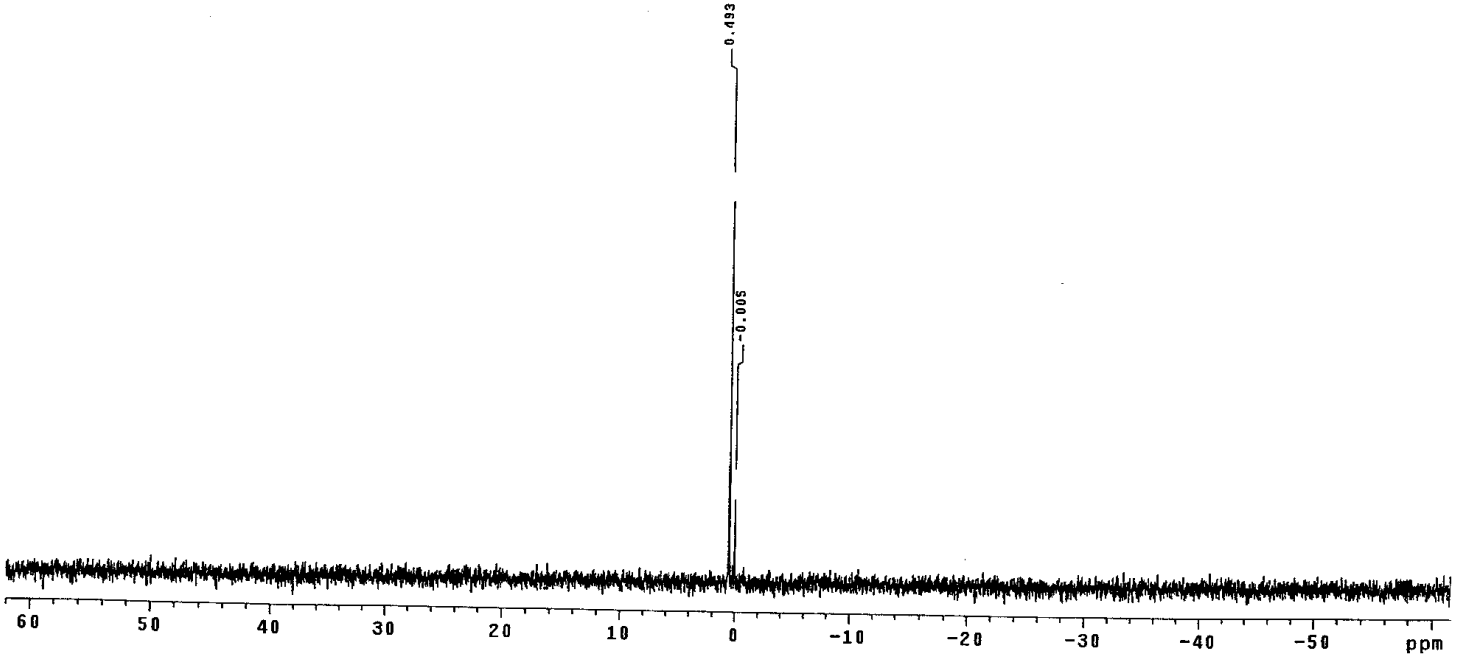
SURVEY PHOSPHORUS PARAMETERS

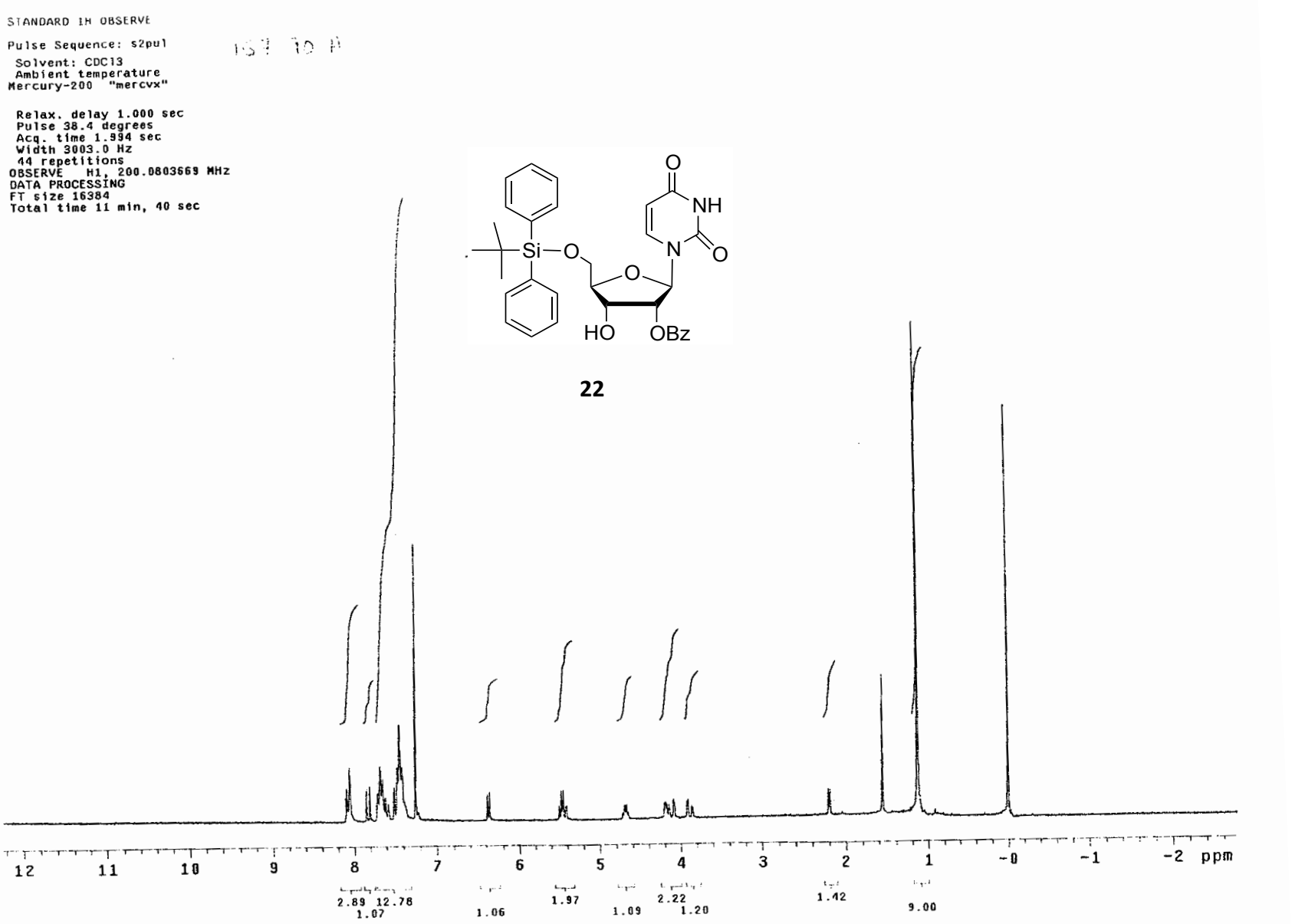
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-200 "mercvx"

Pulse 45.3 degrees
Acq. time 1.600 sec
Width 10010.0 Hz
32 repetitions
OBSERVE P31, 80.9939267 MHz
DECOUPLE H1, 200.0613150 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768
Total time 0 min, 0 sec



21b





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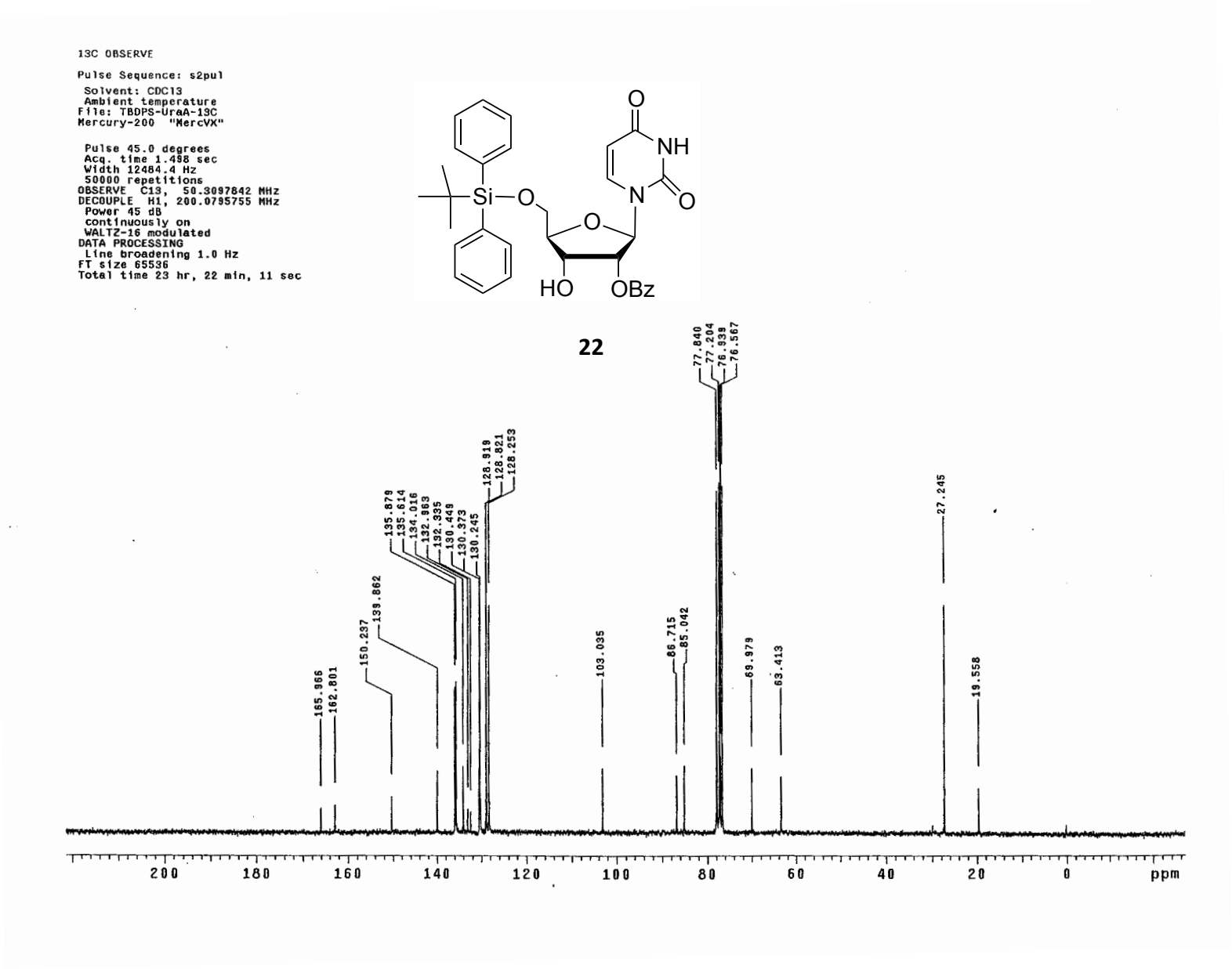
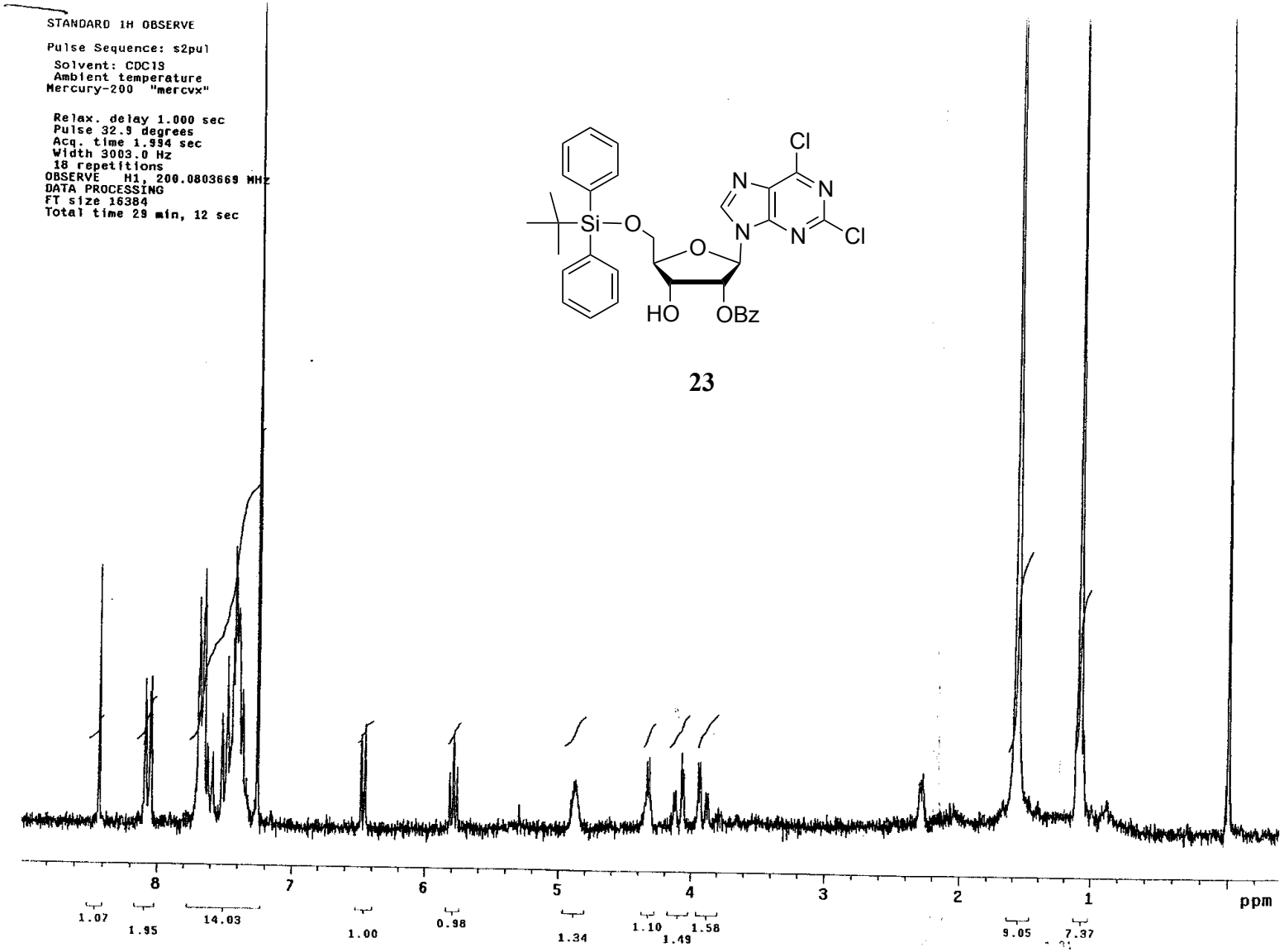


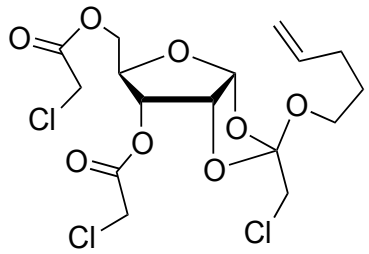


STANDARD 1H OBSERVE

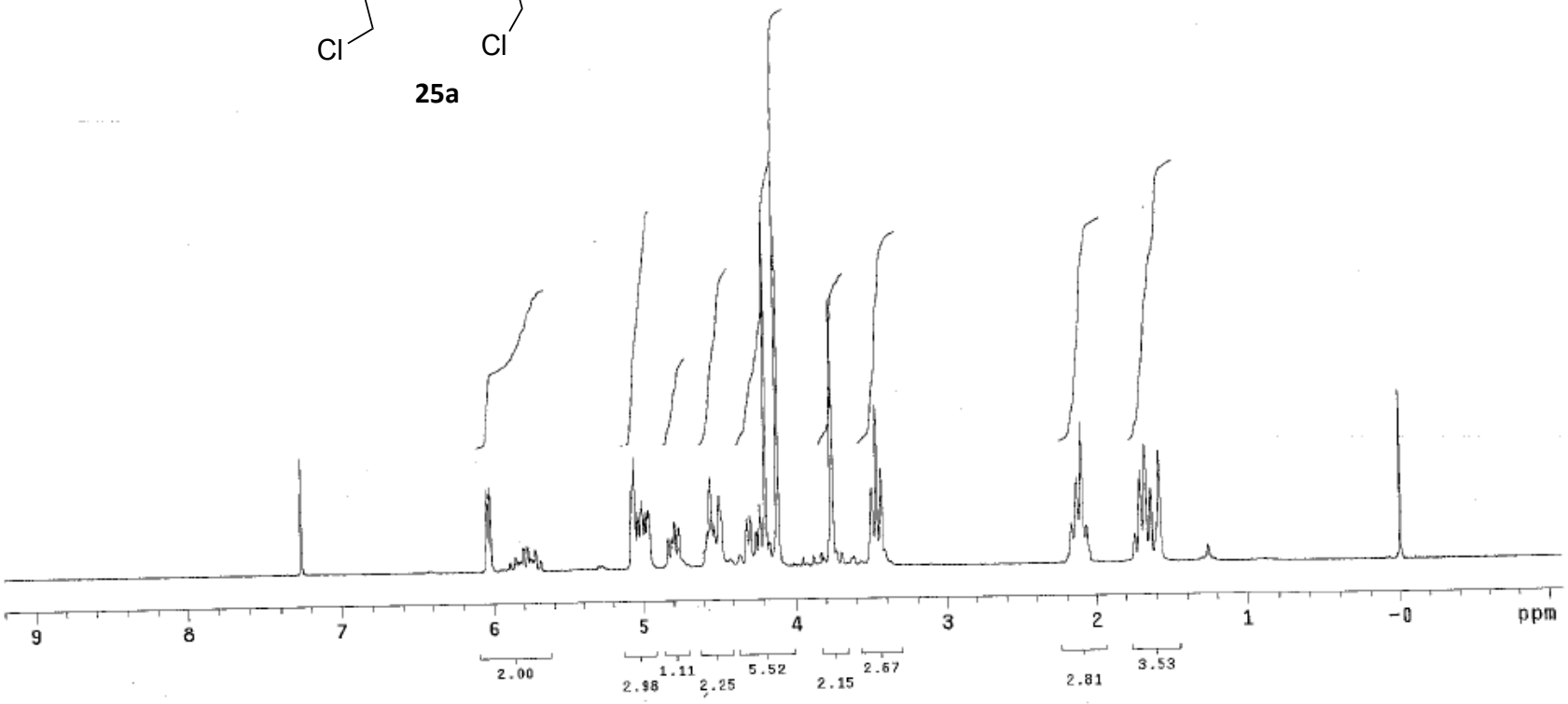
Pulse Sequence: s2pul

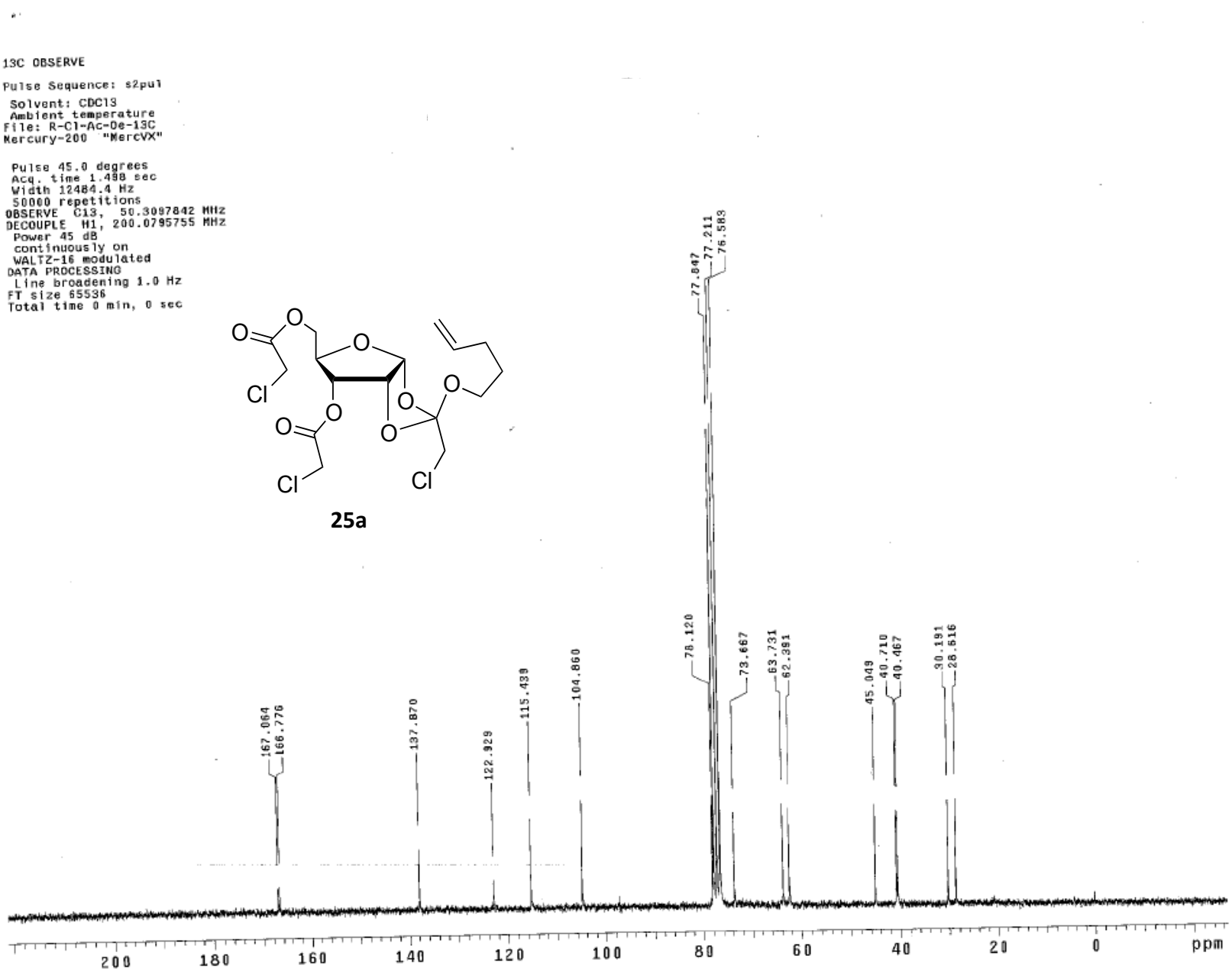
Solvent: CDCl3
Ambient temperature
Mercury-200 "MercVX"

Relax. delay 1.000 sec
Pulse 36.4 degrees
Acq. time 1.994 sec
Width 3003.0 Hz
200 repetitions
OBSERVE H1, 200.0785690 MHz
DATA PROCESSING
FT size 16384
Total time 11 min, 40 sec



25a





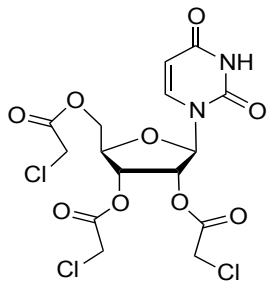
25a

STANDARD 1H OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Mercury-200 "MercVX"

Relax. delay 1.000 sec
Pulse 38.4 degrees
Acq. time 1.994 sec
Width 3003.0 Hz
200 repetitions
OBSERVE H1, 200.0785690 MHz
DATA PROCESSING
FT size 16384
Total time 0 min, 0 sec



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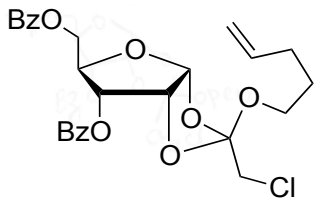
STANDARD 1H OBSERVE

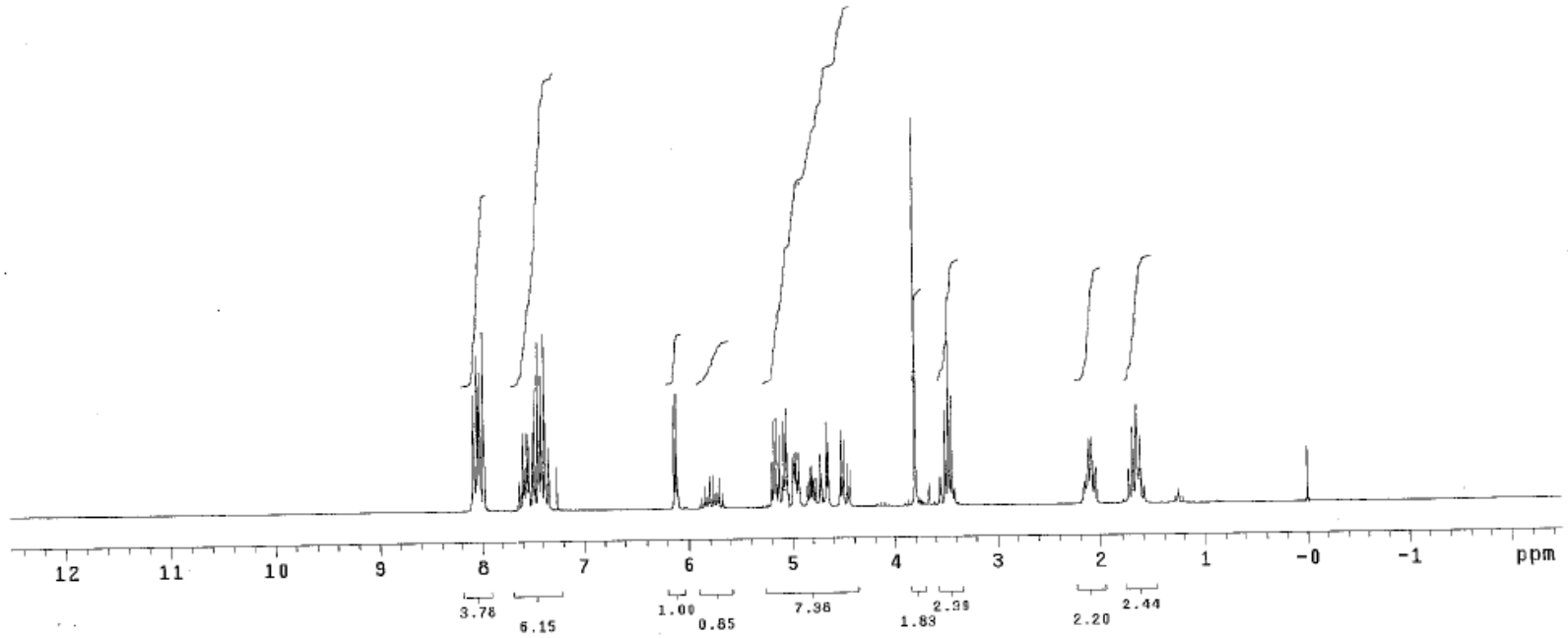
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Mercury-200 "MercVX"

Relax. delay 1.000 sec
Pulse 38.4 degrees
Acq. time 1.984 sec
Width 3003.0 Hz
200 repetitions
OBSERVE H1, 200.0785690 MHz
DATA PROCESSING
FT size 16384
Total time 11 min, 40 sec



25b

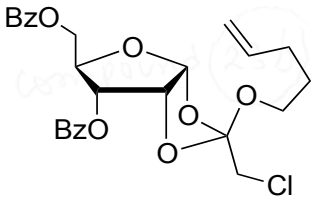


13C OBSERVE

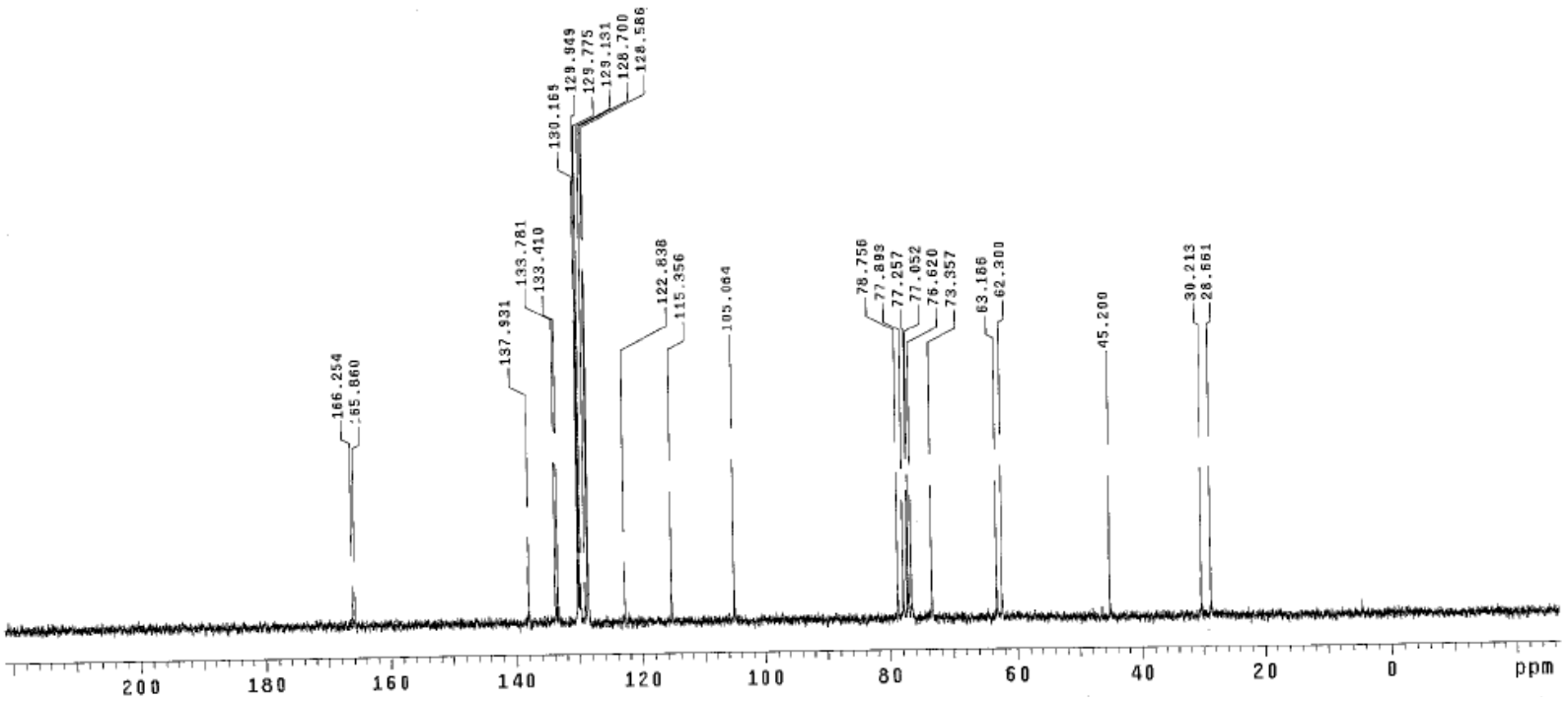
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Mercury-200 "MercVX"

Pulse 45.0 degrees
Acq. time 1.498 sec
Width 12484.4 Hz
10000 repetitions
OBSERVE C13, 50.3097842 MHz
DECOUPLE H1, 200.0795755 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 4 hr, 40 min, 26 sec



25b

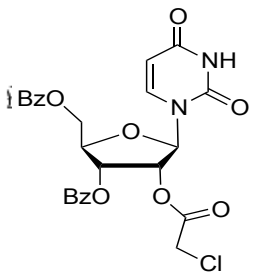


STANDARD 1H OBSERVE

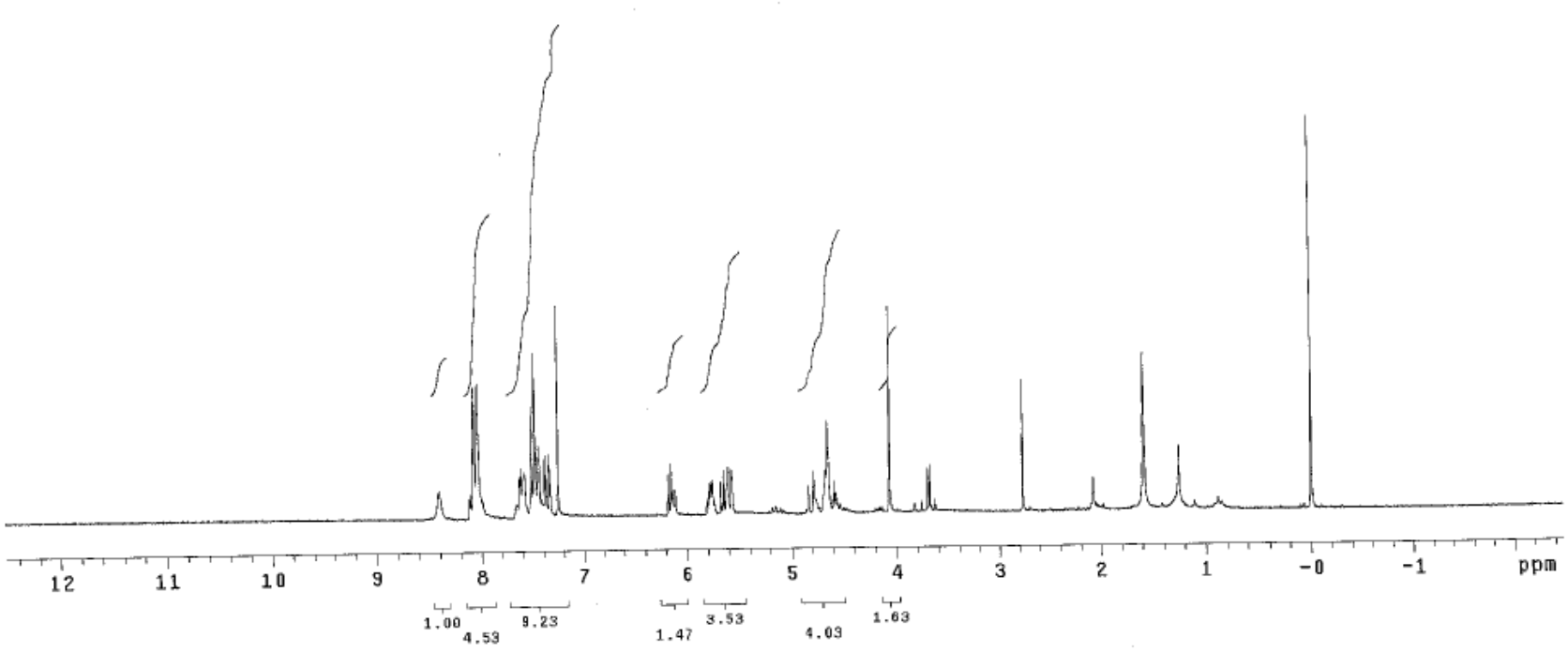
Pulse Sequence: s2pul

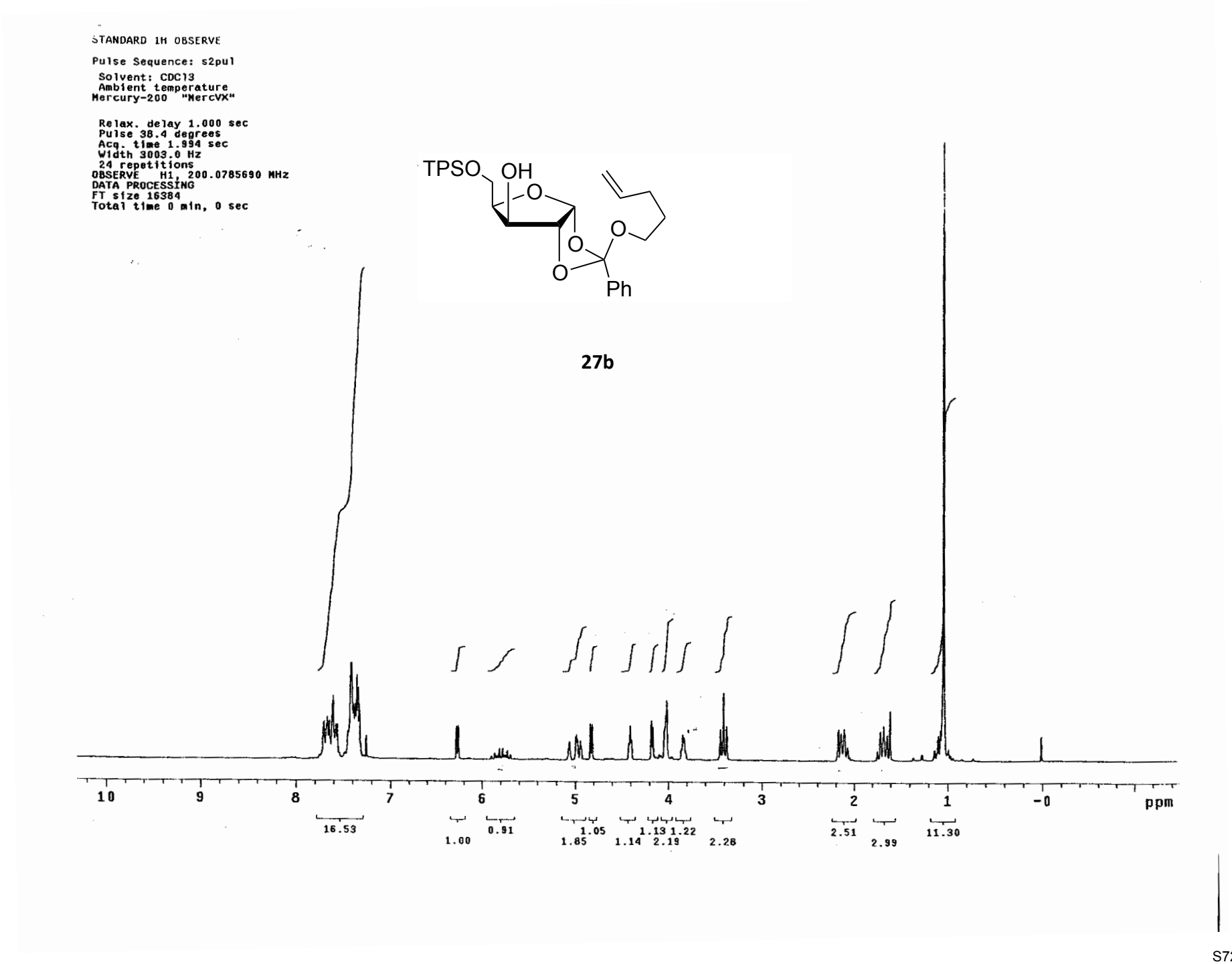
Solvent: CDCl3
Ambient temperature
Mercury-200 "MercVX"

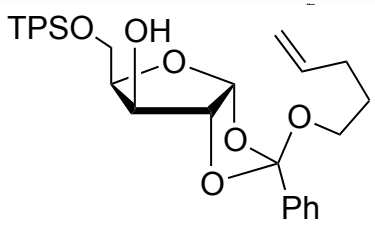
Relax. delay 1.000 sec
Pulse 38.4 degrees
Acq. time 1.994 sec
Width 3003.0 Hz
200 repetitions
OBSERVE H1, 200.0785690 MHz
DATA PROCESSING
FT size 16384
Total time 11 min, 40 sec



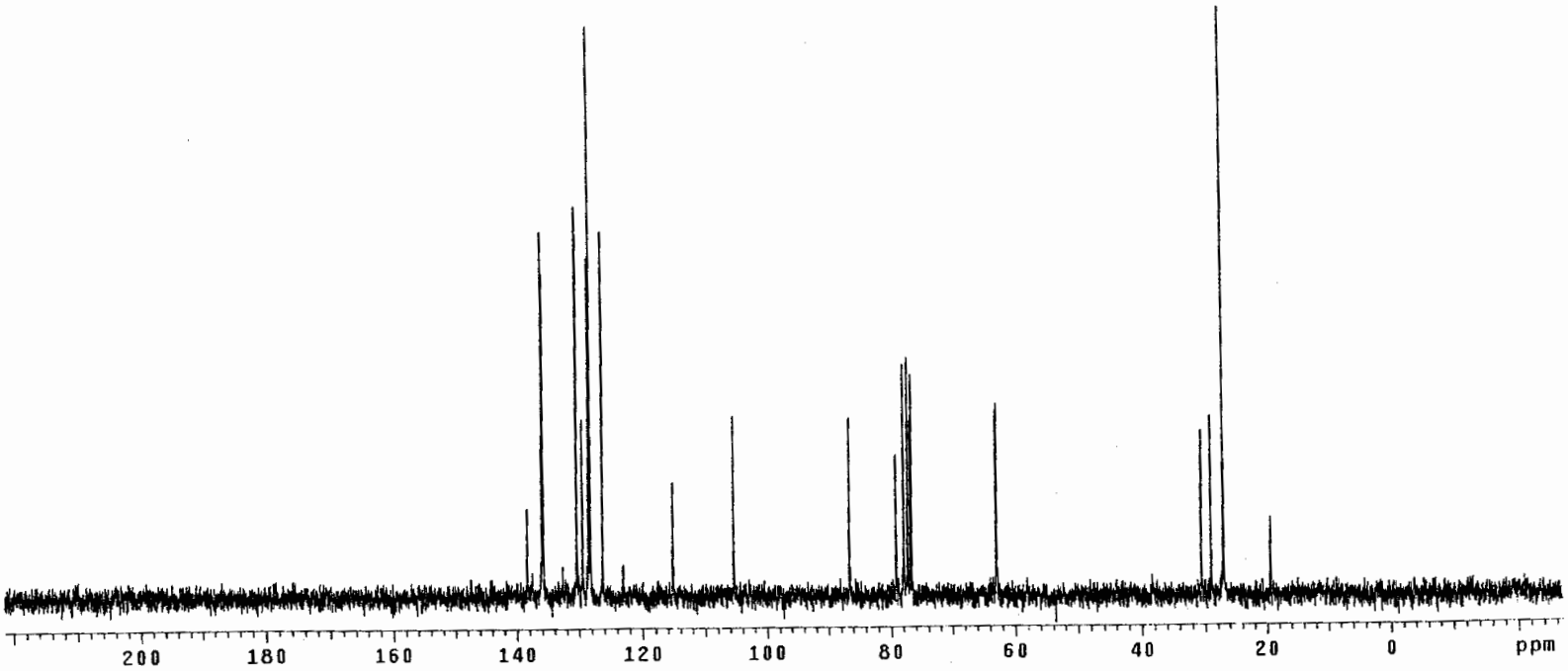
26







27b

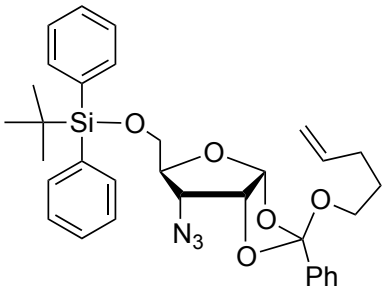


STANDARD 1H OBSERVE

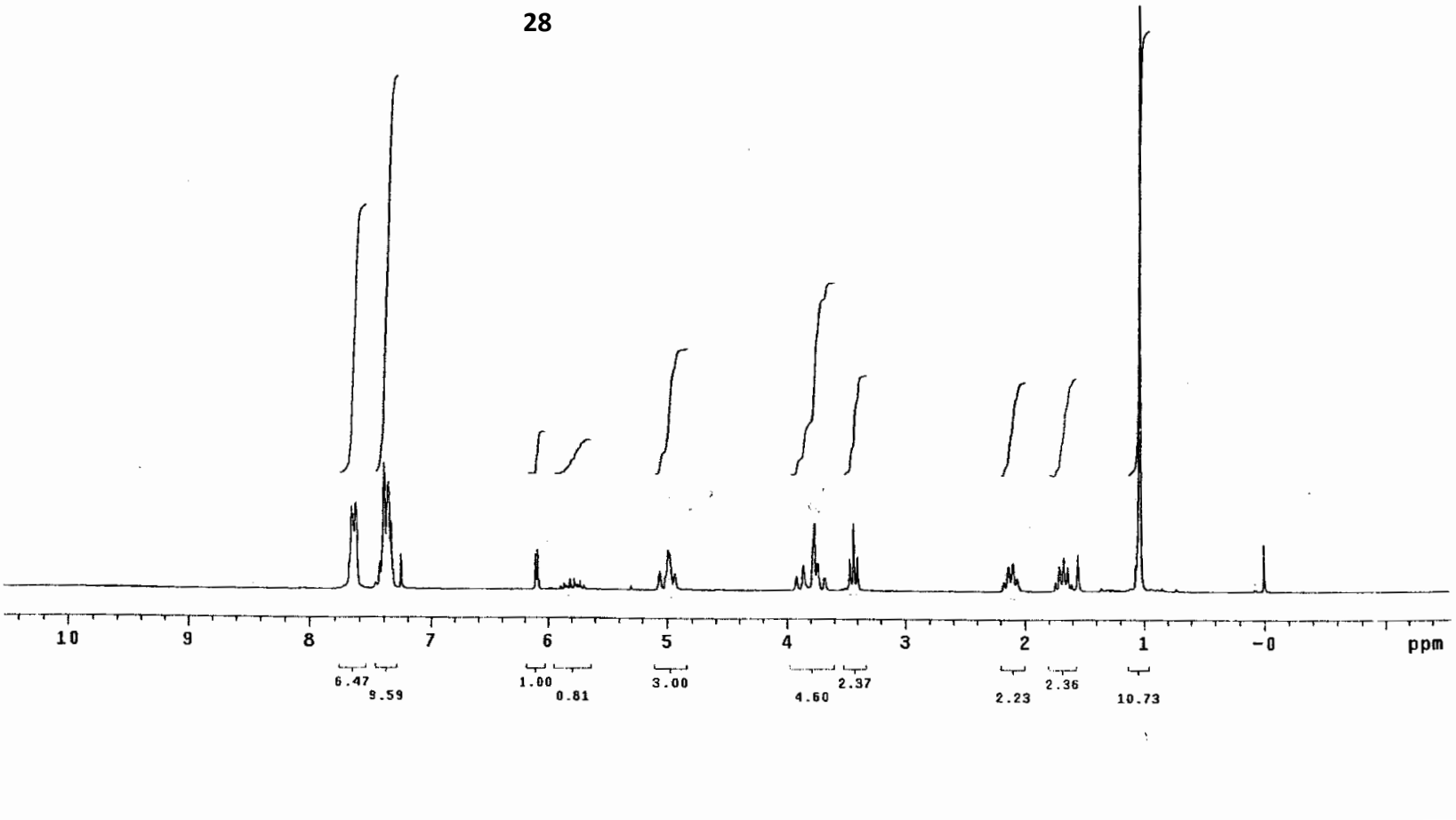
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Mercury-200 "MercVX"

Relax. delay 1.000 sec
Pulse 38.4 degrees
Acq. time 1.994 sec
Width 3003.0 Hz
22 repetitions
OBSERVE H1, 200.0785690 MHz
DATA PROCESSING
FT size 16384
Total time 0 min, 0 sec



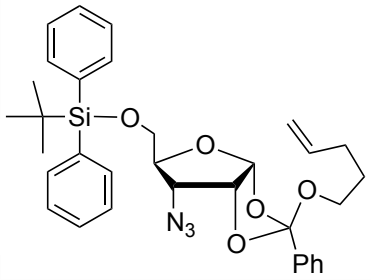
28



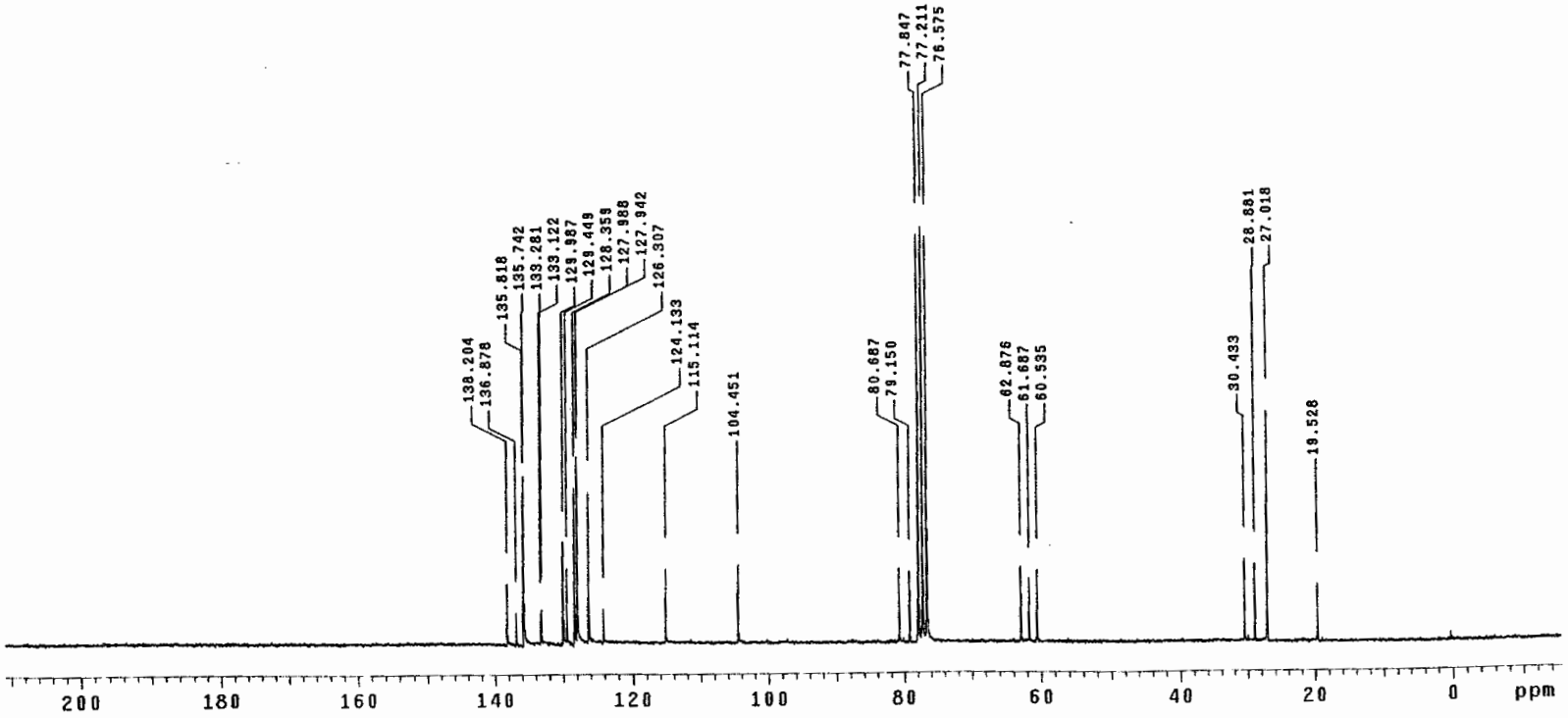
13C OBSERVE

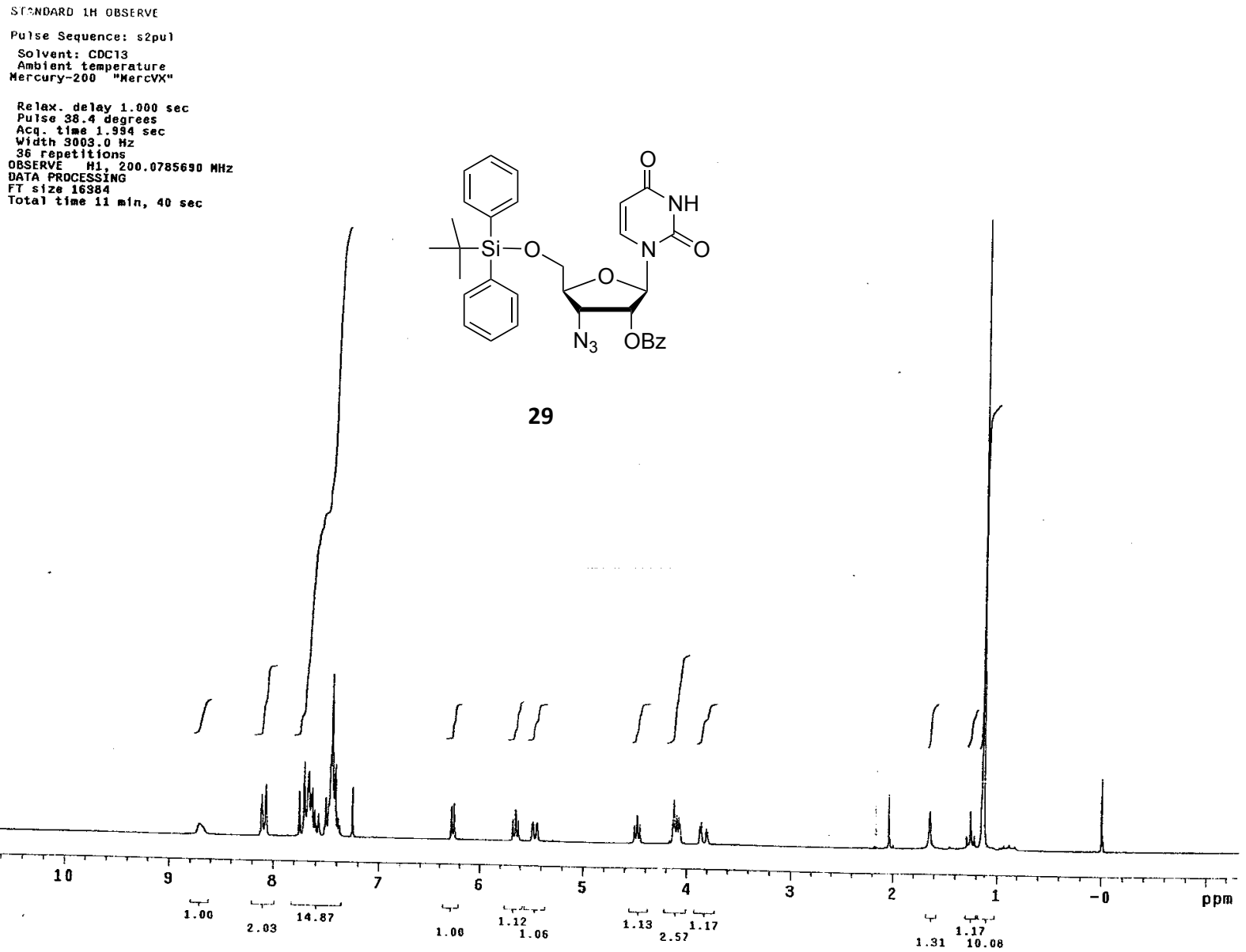
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: xyl-azide
Mercury-200 "MercVX"

Pulse 45.0 degrees
Acq. time 1.498 sec
Width 12484.4 Hz
35992 repetitions
OBSERVE C13, 50.3097842 MHz
DECOUPLE H1, 200.0795755 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 0 min, 0 sec



28

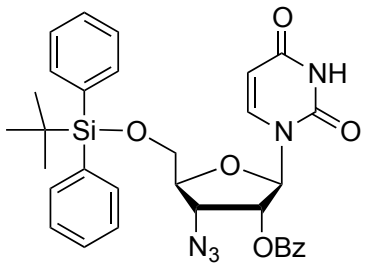




13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-200 "MercVX"

Pulse 45.0 degrees
Acq. time 1.498 sec
Width 12484.4 Hz
2864 repetitions
OBSERVE C13, 50.3097842 MHz
DECOUPLE H1, 200.0795755 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 4 hr, 40 min, 26 sec



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