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Supporting Information

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Supporting Information

A Concise and Flexible Synthesis of the Potent Anti-Influenza Agents – Tamiflu and Tamiphosphor

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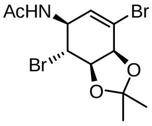
General Part of Experimental Section

All the reagents were commercially available and used without further purification unless indicated otherwise. All solvents were anhydrous grade unless indicated otherwise. Diisopropyl azodicarboxylate (DIAD) was purified by distillation on Na_2SO_4 under reduced pressure. All non-aqueous reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. Reactions were magnetically stirred and monitored by thin-layer chromatography on silica gel. Flash chromatography was performed on silica gel of 60–200 μm particle size. Yields are reported for spectroscopically pure compounds. Melting points were recorded on an Electrothermal MEL-TEMP® 1101D melting point apparatus and are not corrected. NMR spectra were recorded on Bruker AVANCE 600 and 400 spectrometers. Chemical shifts are given in δ values relative to tetramethylsilane (TMS); coupling constants *J* are given in Hz. Internal standards were $CDCl_3$ (δ_H = 7.24), CD_3OD (δ_H = 3.31) or D_2O (δ_H = 4.79) for ^{1}H-NMR spectra, $CDCl_3$ (δ_c = 77.0) or CD_3OD (δ_c = 49.15) for ^{13}C-NMR spectra, and H_3PO_4 in D_2O (δ_P = 0.00) for ^{31}P-NMR spectra. The splitting patterns are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) and dd (double of doublets). IR spectra were recorded on a Thermo Nicolet 380 FT-IR spectrometer. Optical rotations were recorded on a Perkin-Elmer Model 341 polarimeter. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. High resolution ESI mass spectra were recorded on a Bruker Daltonics spectrometer.

Synthetic Procedures and Product Characterization.

***N*-[(1*S*,4*S*,5*R*,6*R*)-3,6-dibromo-4,5-(isopropylidenedioxy)cyclohex-2-en-1-yl]**

acetamide (6).

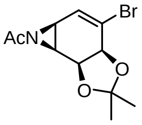


To a cold (0 °C) solution of *cis*-dihydrodiol **5** (8.0 g, 42.1 mmol) in a mixture of acetone (20 mL) and 2,2-dimethoxypropane (40 mL) was treated with *p*-toluenesulfonic acid monohydrate (100 mg, 0.52 mmol). The reaction mixture was stirred at room temperature for 30 min, after which time it was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (60 mL). The organic solvents were removed under reduced pressure, and the residual aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo (do not heat) to provide the crude acetonide as a light yellow oil (8.92 g).

To a solution of *N*-bromoacetamide (NBA, 6.49 g, 47 mmol) in dry acetonitrile (250 mL) was added $SnBr_4$ (4.7 mL of 1 M solution in CH_2Cl_2, 4.7 mmol) and water (0.72 mL, 40 mmol) at 0 °C in the dark. The above-prepared acetamide (8.92 g, 38.8 mmol) in acetonitrile (150 mL) was added dropwise over a period of 1 h to the NBA-$SnBr_4$ mixture at the same temperature. The reaction was vigorously stirred for 8 h at 0 °C and then quenched with saturated aqueous $NaHCO_3$ (100 mL) and Na_2SO_3 (100 mL). The resulting mixture was allowed to warm up to room temperature for 30 min. After separation of organic phase, the aqueous phase was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layers were washed with water (3 × 200 mL) and brine (300 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was recrystallized from Et_2O/CH_2Cl_2 to give bromoacetamide **6** (11.66 g, 75% from *cis*-dihydrodiol **5**) as colorless crystalline solids; m.p. 150–152 °C (dec.); TLC (EtOAc/hexane, 1:1) $R_f = 0.40$; $[\alpha]_D^{20} = +176.6$ ($c = 1.63$, $CHCl_3$); IR (film)

3209, 2988, 1655, 1225 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.19 (1 H, d, *J* = 9.1 Hz), 6.15 (1 H, d, *J* = 5.0 Hz), 4.93–4.90 (1 H, m), 4.66 (1 H, d, *J* = 5.0 Hz), 4.58 (1 H, dd, *J* = 5.2, 2.6 Hz), 4.19 (1 H, dd, *J* = 3.9; 2.0 Hz), 1.95 (3 H, s), 1.49 (3 H, s), 1.40 (3 H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.9, 127.9, 124.7, 112.0, 77.9, 75.8, 50.2, 44.3, 27.8, 26.5, 23.3; HRMS calcd for $C_{11}H_{16}Br_2NO_3$ (M^+ + H): 367.9497, found: *m*/*z* 367.9499.

(1*S*,4*S*,5*S*,6*S*)-7-Acetyl-3-bromo-4,5-isopropylidenedioxy-7-azabicyclo [4.1.0]hept-2-ene (7).

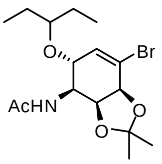


Lithium *bis*(trimethylsilyl)amide (35 mL of 1.0 M solution in THF, 35 mmol) was added dropwise to a stirred solution of bromoacetamide **6** (11.66 g, 31.8 mmol) in THF (150 mL) at −10 °C under an atmosphere of nitrogen. The resulting solution was warmed to 0 °C and stirred for 30 min to give a brown suspension. After addition of buffer solution (100 mL, pH 7), the mixture was extracted with Et_2O (4 × 150 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude aziridine **7** (8.32 g) was used in the next step without further purification.

A pure sample **7** for analysis was prepared by flash column chromatography of the crude product on silica gel (EtOAc/hexane, 2:3). Colorless solid; m.p. 110–112 °C; TLC (EtOAc/hexane, 1:1) R_f = 0.42; $[\alpha]_D^{20}$ = −77.6 (*c* = 0.47, $CHCl_3$); IR (film) 2967, 1980, 1706, 1233, 1072 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.69 (1 H, d, *J* = 4.7 Hz), 4.72 (1 H, dd, *J* = 7.0, 1.1 Hz), 4.45 (1 H, dd, *J* = 7.0, 4.2 Hz), 3.19 (1 H, dd, *J* = 5.9, 5.0 Hz), 3.10 (1 H, dd, *J* = 5.6, 2.8 Hz), 2.16 (3 H, s), 1.55 (3 H, s), 1.41 (3 H, s); ^{13}C

NMR (150 MHz, $CDCl_3$) δ 181.7, 129.9, 122.7, 108.5, 76.5, 71.9, 39.5, 36.7, 27.0, 24.8, 23.2; HRMS calcd for $C_{11}H_{14}BrNNaO_3$ (M^+ + Na): 310.0055, found: *m*/*z* 310.0058.

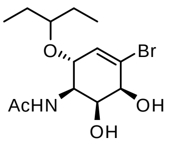
_N_-[(1_S_,2_R_,5_S_,6_S_)-4-bromo-2-(1-ethylpropoxy)-5,6-(isopropylidenedioxy) cyclohex-3-en-1-yl]acetamide (8).



To a solution of crude aziridine **7** (8.32 g, 28.8 mmol) in 3-pentanol (50 mL) was added dropwise boron trifluoride etherate (4.68 mL, 36 mmol) at −10 °C. The reaction mixture was warmed to 0 °C, and stirred for 6 h, and concentrated under reduced pressure. The residue was dissolved in EtOAc (200 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with water (200 mL) and brine (200 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated. The residual oil was purified by flash column chromatography on silica gel (EtOAc/hexane, 3:7) to afford the ether product **8** (8.82 g, 73 % from **6**) as a colorless foam. TLC (EtOAc/hexane, 1:1) $R_f = 0.35$; $[\alpha]_D^{20} = -123$ (c = 1.42, $CHCl_3$); IR (film) 3221, 2988, 1921, 1711, 1199, 1075 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.15 (1 H, d, J = 2.1 Hz), 5.70 (1 H, d, J = 9.0 Hz), 4.59 (1 H, dd, J = 5.2, 1.7 Hz), 4.42 (1 H, dd, J = 5.2, 2.6 Hz), 4.31 (1 H, ddd, J = 11.5, 8.8, 2.6 Hz), 3.90–3.88 (1 H, m), 3.27–3.23 (1 H, m), 2.01 (3 H, s), 1.50–1.45 (4 H, m), 1.40 (3 H, s), 1.36 (3 H, s), 0.89–0.85 (6 H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 132.6, 122.7, 110.0, 82.3, 76.9, 76.1, 73.5, 51.3, 27.3, 26.3, 26.0, 25.6, 23.2, 9.5, 9.2; HRMS calcd for

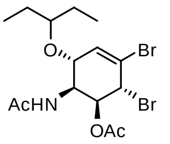
$C_{16}H_{27}BrNO_4$ (M^+ + H): 376.1123, found: *m*/*z* 376.1129.

N-[(1R,2R,5S,6S)-4-bromo-2-(1-ethylpropoxy)-5,6-dihydroxycyclohex-3-en-1-yl] acetamide (9).



To a solution of acetonide **8** (8.82 g, 23.4 mmol) in methanol (100 mL), a conc. HCl solution (2 mL) was added. The reaction mixture was stirred at 50 °C for about 6 h until completion of the deprotection as shown by the TLC analysis. The mixture was cooled to room temperature, the solvent was evaporated under reduced pressure and the residual solid was recrystallized from Et_2O/THF to give dihydroxy acetamide **9** (7.42 g, 94%) as a colorless crystalline solid; m.p. 131−133 °C (dec.); TLC (EtOAc) $R_f = 0.35$; $[\alpha]_D^{20} = -101.2$ ($c = 0.67$, MeOH); IR (film) 3678, 3206, 2972, 1971, 1698, 1208, 1072 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 6.04 (1 H, d, $J = 3.1$ Hz), 4.13 (1 H, dd, $J = 1.7, 0.9$ Hz), 3.95 (1 H, dd, $J = 4.3, 2.2$ Hz), 3.92–3.89 (2 H, m), 3.32–3.29 (1 H, m), 1.86 (3 H, s), 1.44–1.33 (4 H, m), 0.85–0.79 (6 H, m); ^{13}C NMR (150 MHz, CD_3OD) δ 173.3, 132.0, 128.1, 83.4, 75.9, 72.7, 70.8, 55.1, 27.5, 27.3, 23.0, 10.1, 9.9; HRMS calcd for $C_{13}H_{23}BrNO_4$ (M^+ + H): 336.0810, found: *m*/*z* 336.0818

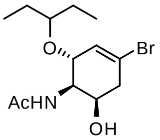
(1S,2R,5R,6S)-6-acetamido-2,3-dibromo-5-(1-ethylpropoxy)-cyclohex-3-en-1-yl acetate (10).



To a stirred solution of diol **9** (7.42 g, 22.1 mmol) in THF (150 mL) at 0 °C under nitrogen atmosphere, α-acetoxyisobutyryl bromide (4.1 mL, 27.8 mmol) was added dropwise over a period of 10 min. The reaction mixture was stirred at same temperature for 30 min, and warmed to room temperature with stirring for 3.5 h. The solvent was evaporated, and the residual oil was partitioned between EtOAc (200 mL) and 5% aqueous $NaHCO_3$ (50 mL). The organic layer was washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated to afford the crude bromoacetate **10** (9.05 g). The crude product was used in the next step without further purification.

A pure sample **10** for analysis was prepared by flash column chromatography of the crude product on silica gel (EtOAc/hexane, 2:1). Light yellow foam; TLC (EtOAc/hexane, 2:1) $R_f = 0.33$; $[\alpha]_D^{20} = -43.2$ ($c = 1.28$, $CHCl_3$); IR (film) 3279, 2981, 1927, 1702, 1687, 1221, 1093 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.17 (1 H, d, $J = 2.3$ Hz), 5.85 (1 H, br s), 5.29 (1 H, s), 4.78–4.75 (1 H, m), 4.54 (1 H, d, $J = 2.8$ Hz), 4.03 (1 H, d, $J = 8.6$ Hz), 3.26 (1 H, dd, $J = 11.3, 5.6$ Hz), 2.09 (3 H, s), 1.96 (3 H, s), 1.49–1.43 (4 H, m), 0.89–0.81 (6 H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 169.9, 133.9, 121.1, 82.4, 75.4, 74.5, 48.8, 47.3, 26.2, 25.8, 23.4, 20.9, 9.4, 9.3; HRMS calcd for $C_{15}H_{24}Br_2NO_4$ ($M^+ + H$): 440.0072, found: *m*/*z* 440.0076.

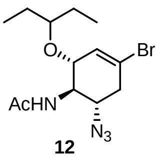
***N*-[(1*R*,2*R*,6*R*)-4-bromo-2-(1-ethylpropoxy)-6-hydroxycyclohex-3-en-1-yl] acetamide (11).**



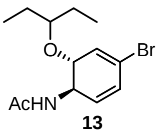
Super-Hydride® ($LiBHEt_3$, 61.5 mL of 1 M solution in THF, 61.5 mmol) was added dropwise to a stirred solution of bromoacetate **10** (9.05 g, 20.5 mmol) in THF (100 mL) at 0 °C under nitrogen atmosphere. The resulting solution was allowed to warmed to room temperature, stirred for 2 h, and treated with saturated aqueous

NH_4Cl (50 mL). The aqueous layer was separated, and extracted with EtOAc (6 × 100 mL). The combined organic layers were washed with water (2 × 200 mL) and brine (200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated to afford a residue of light yellow foam. The crude product was purified by recrystallization from Et_2O to afford hydroxyacetamide **11** (5.78 g, 82% from diol **9**) as white crystalline solids; m.p. 102–104 °C; TLC (EtOAc) $R_f = 0.35$; $[\alpha]_D^{20} = -107.7$ (c = 1.1, $CHCl_3$); IR (film) 3595, 3217, 2923, 1984, 1707, 1286, 1021 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.03 (1 H, d, J = 3.1 Hz), 5.89 (1 H, d, J = 6.7 Hz), 4.23 (1 H, br s), 4.07 (1 H, br s), 3.98 (1 H, br s), 3.93 (1 H, dd, J = 7.5, 2.1 Hz), 3.29–3.26 (1 H, m), 2.82 (1 H, dd, J = 18.2, 4.7 Hz), 2.50 (1 H, dd, J = 18.2, 5.8 Hz), 2.01 (3 H, s), 1.51−1.42 (4 H, m), 0.89–0.85 (6 H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.0, 127.9, 122.5, 81.7, 74.0, 67.7, 54.2, 41.7, 26.3, 26.0, 23.4, 9.7, 9.5; HRMS calcd for $C_{13}H_{22}BrNNaO_3$ (M^+ + Na): 342.0681, found: m/z 342.0688.

***N*-[(1*R*,2*R*,6*S*)-4-bromo-2-(1-ethylpropoxy)-6-azidocyclohex-3-en-1-yl] acetamide (12) and *N*-[(1*R*,6*R*)-4-bromo-6-(1-ethylpropoxy)cyclohexa-2,4-dien-1-yl]acetamide (13).**



12



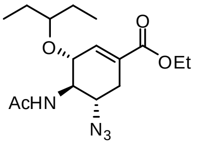
13

A solution of **11** (5.78 g, 18.1 mmol), triphenylphosphine (9.96 g, 38.0 mmol), freshly distilled diisopropyl azodicarboxylate (7.68 g, 38.0 mmol) and diphenylphosphorylazide (10.51 g, 38.0 mmol) in THF (120 mL) was stirred at 40 °C for 24 h. The solvent was removed by rotary evaporation under reduced pressure, and the residue was purified by flash column chromatography (EtOAc/hexane, 1:2) to afford the corresponding azide product **12** with 6*S* configuration (5.23 g, 84% yield), along with 2% of a side product of diene **13** (108 mg, 0.36 mmol).

Azide **12**: White solid, m.p. 138−140 °C; TLC (EtOAc/hexane, 1:1) $R_f = 0.45$; $[\alpha]_D^{20} = -33.4$ ($c = 0.7$, $CHCl_3$); IR (film) 3119, 2927, 2178, 1902, 1698, 1277, 1054 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.33 (1 H, d, $J = 7.8$ Hz), 5.98 (1 H, d, $J = 2.2$ Hz), 4.27 (1 H, d, $J = 8.2$ Hz), 4.22−4.17 (1 H, m), 3.44−3.40 (1 H, m), 3.23−3.20 (1 H, m), 2.77 (1 H, dd, $J = 17.4, 5.8$ Hz), 2.52−2.46 (1 H, m), 1.99 (3 H, s), 1.47−1.42 (4 H, m), 0.86−0.82 (6 H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2, 130.3, 119.0, 82.0, 74.7, 57.5, 56.9, 40.4, 26.2, 25.6, 23.5, 9.6, 9.2; HRMS calcd for $C_{13}H_{22}BrN_4O_2$ ($M^+ + H$): 345.0926, found: *m*/*z* 345.0931.

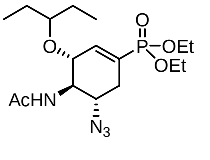
Diene **13**: Colorless solid, m.p. 68−70 °C; TLC (EtOAc/hexane, 2:1) $R_f = 0.60$; $[\alpha]_D^{20} = -215.6$ ($c = 0.98$, $CHCl_3$); IR (film) 3331, 1721, 1607, 1088 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.16 (1 H, d, $J = 5.2$ Hz), 6.09 (1 H, dd, $J = 9.8, 1.3$ Hz), 5.81 (1 H, dd, $J = 9.8, 5.2$ Hz), 5.52 (1 H, d, $J = 7.7$ Hz), 4.60 (1 H, ddd, $J = 8.9, 4.8, 2.4$ Hz), 3.91 (1 H, dd, $J = 4.8, 2.4$ Hz), 3.43−3.39 (1 H, m), 1.94 (3 H, s), 1.49−1.41 (4 H, m), 0.88−0.82 (6 H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 129.9, 128.0, 126.7, 120.0, 80.8, 74.8, 47.0, 26.6, 26.5, 23.3, 9.9, 9.5; HRMS calcd for $C_{13}H_{21}BrNO_2$ ($M^+ + H$): 302.0756, found: *m*/*z* 302.0761.

Ethyl (3*R*,4*R*,5*S*)-4-acetylamino-5-azido-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (14a).[S1,S2]



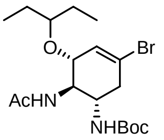
A solution of **12** (349 mg, 1 mmol), *N,N*-diisopropylethylamine (2.5 mL, 15.2 mmol) and bis(triphenylphosphine)dicarbonylnickel(0) (960 mg, 1.5 mmol) in ethanol (3 mL) and THF (15 mL) was stirred for 24 h at 80 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature, and the solvent was evaporated. The residual oil was diluted with EtOAc (20 mL), and the mixture was filtered through a pad of Celite. The filtrate was evaporated to give a light yellow oil, which was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford ester **14a** (274 mg, 81%) as colorless solids; m.p. 115−117 °C; TLC (EtOAc/hexane, 1:1) R_f = 0.4; $[\alpha]_D^{20} = -48.9$ (c = 1.1, $CHCl_3$); IR (film) 3401, 2101, 1712, 1655, 1273 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.75 (1 H, s), 5.98 (1 H, d, J = 7.4 Hz), 4.53 (1 H, d, J = 5.0 Hz), 4.51−4.16 (3 H, m), 3.33−3.28 (2 H, m), 2.82 (1 H, dd, J = 17.6, 5.6 Hz), 2.22−2.16 (1 H, m), 2.00 (3 H, s), 1.49−1.45 (4 H, m), 1.25 (3 H, t, J = 7.1 Hz), 0.95−0.80 (6 H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 165.8, 137.9, 128.1, 82.0, 73.4, 61.0, 58.0, 57.2, 30.5, 26.2, 25.6, 23.5, 14.1, 9.5, 9.3; HRMS calcd for $C_{16}H_{27}N_4O_4$ (M^+ + H): 339.2032, found: *m/z* 339.2039.

Diethyl (3*R*,4*R*,5*S*)-4-acetamido-5-azido-3-(1-ethylpropoxy)-1-cyclohexene phosphonate (14b).[S2]



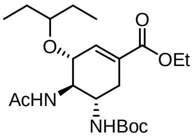
A mixture of **12** (1.72 g, 10 mmol), diethyl phosphite (2.07 g, 15 mmol) and 1,4-diazabicyclo[2.2.2]octane (3.37 g, 30 mmol) in anhydrous toluene (50 mL) was deoxygenated by bubbling with nitrogen for 10 min, and then added to tetrakis(triphenylphosphine)palladium(0) (867 mg, 0.75 mmol) that was placed in a round bottomed flask under nitrogen atmosphere. The resulting solution was gradually heated to 90 °C and maintained at this temperature for 12 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure to give colorless foam (3.91 g), which was purified by flash column chromatography (EtOAc/hexane, 1:1 to 2:1) to afford phosphonate **14b** (3.33 g, 83%) as a colorless oil. TLC (EtOAc/hexane, 1:1) $R_f = 0.2$; $[\alpha]_D^{20} = -62.4$ ($c = 1.2$, $CHCl_3$); IR (film) 3357, 2108, 1754, 1651, 1247 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.56 (1 H, d, $J_{P-2} = 21.6$ Hz), 5.71 (1 H, d, $J = 6.9$ Hz), 4.52 (1 H, d, $J = 7.8$ Hz), 4.34–4.30 (1 H, m), 4.11–4.01 (4 H, m), 3.31–3.23 (2 H, m), 2.69–2.64 (1 H, m), 2.12–2.08 (1 H, m), 2.01 (3 H, s), 1.51–1.43 (4 H, m), 1.39–1.31 (6 H, m), 0.90–0.81 (6 H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 141.7, 126.3 (C-1, d, $J_{P-1} = 182$ Hz), 81.9, 73.7, 62.14, 62.10, 54.3, 57.1, 31.0, 26.2, 25.4, 23.6, 16.4, 16.3, 9.6, 9.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.99; HRMS calcd for $C_{17}H_{32}N_4O_5P$ ($M^+ + H$): 403.2110, found: *m*/*z* 403.2117.

***Tert*-Butyl (1*S*,5*R*,6*R*)-6-acetamido-3-bromo-5-(1-ethylpropoxy)cyclohex-3-en-1-yl carbamate (15).**



To a mixture of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.37 g, 6 mmol) and triphenylphosphine (1.57 g, 6 mmol) in anhydrous acetonitrile (30 mL) at room temperature was added tetrabutylammonium cyanate (1.71 g, 6 mmol) followed by addition of alcohol **11** (1.58 g, 5 mmol). The mixture was stirred for 18 h at room temperature until the reaction was completed. The solvent was evaporated and the black residue was dissolved in *tert*-butanol (20 mL). The resulting solution was heated at reflux for 24 h. The solvent was evaporated under reduced pressure, and the reside was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford carbamate **15** (1.63 g, 78%) as white solids; m.p. 153−155 °C; TLC (EtOAc/hexane, 1:1) $R_f = 0.5$; $[\alpha]_D^{20} = -49.7$ (c = 1.35, $CHCl_3$); IR (film) 3327, 2919, 1708, 1682, 1523, 1244 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.24 (1 H, d, J = 9.1 Hz), 6.00 (1 H, s), 5.48 (1 H, d, J = 9.1 Hz), 4.01 (1 H, dd, J = 17.0, 9.3 Hz), 3.85–3.81 (2 H, m), 3.28−3.24 (1 H, m), 2.71 (1 H, dd, J = 17.6, 4.8 Hz), 2.57 (1 H, dd, J = 17.6, 8.6 Hz), 1.93 (3 H, s), 1.46–1.39 (4 H, m), 1.36 (9 H, s), 0.85–0.80 (6 H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 156.0, 129.5, 121.2, 81.9, 79.6, 76.4, 53.1, 49.8, 40.6, 28.3 (3 ×), 26.0, 25.7, 23.2, 9.5, 9.2; HRMS calcd for $C_{18}H_{31}BrN_2NaO_4$ (M^+ + Na): 441.1365, found: *m*/*z* 441.1368.

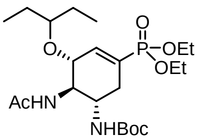
Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-*tert*-butoxycarbonylamino-3-(1-ethylpropoxy)-1-cyclohexene carboxylate (17a).[S3]



A mixture of vinyl bromide **15** (2.11 g, 5 mmol), potassium iodide (1.66 g, 10 mmol) and copper(I) iodide (477 mg, 2.5 mmol) in *n*-butanol (35 mL) was deoxygenated by bubbling with nitrogen for 10 min, and then added to *N*,*N'*-dimethylethyenediamine (54 μL, 0.5 mmol) that was placed in a round bottomed flask under nitrogen atmosphere. The reaction mixture was stirred for 24 h at 120 °C. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc (50 mL) and dilute aqueous ammonia solution (50 mL). The organic phase was washed with water (3 × 30 mL), dried over $MgSO_4$, and concentrated. The residue was filtered through a short column of silica gel (EtOAc/hexane, 1:1) to afford a colorless solid sample of crude vinyl iodide, which **16** (2.29 g) was used in the next step without further purification.

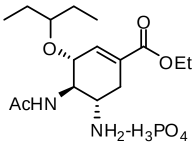
Palladium(II) acetate (90 mg, 0.4 mmol) was added to a solution of the above-prepared vinyl iodide **16** (2.29 g, 4.9 mmol) and sodium acetate (1.64 g, 20 mmol) in anhydrous ethanol (50 mL). The reaction mixture was stirred for 24 h at room temperature under an atmosphere of carbon monoxide. The solvent was evaporated, and the residue was purified by flash column chromatography (EtOAc/hexane, 3:7) to afford **17a** (1.69 g, 82 % from **15**) as white solids; m.p. 142–144 °C [lit.[S3] m.p. 138–139 °C]; TLC (EtOAc/hexane, 1:1) $R_f = 0.35$; $[\alpha]_D^{20} = -76.3$ ($c = 1.67$, $CHCl_3$) [lit.[S3] $[\alpha]_D^{25} = -68.9$ ($c = 1.0$, $CDCl_3$)]; IR (film) 3312, 2951, 1713, 1688, 1651, 1244 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.70 (1 H, s), 6.24 (1 H, d, $J = 9.2$ Hz), 5.26 (1 H, d, $J = 9.3$ Hz), 4.18–4.12 (2 H, m), 4.03–3.98 (1 H, m), 3.95–3.94 (1 H, m), 3.75–3.72 (1 H, m), 3.30 (1 H, t, $J = 5.6$ Hz), 2.67 (1 H, dd, $J = 17.8, 5.1$ Hz), 2.27–2.23 (1 H, m), 1.93 (3 H, s), 1.48–1.42 (4 H, m), 1.37 (9 H, s), 1.24 (3 H, t, $J = 7.2$ Hz), 0.86–0.81 (6 H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 165.9, 156.3, 137.7, 129.2, 82.2, 79.5, 75.8, 60.9, 54.4, 49.2, 30.8, 28.3 (3 ×), 26.1, 25.6, 23.3, 14.1, 9.5, 9.2; HRMS calcd for $C_{21}H_{36}N_2NaO_6$ ($M^+ + Na$): 435.2471, found: *m*/*z* 435.2477.

Diethyl (3*R*,4*R*,5*S*)-4-acetamido-5-*tert*-butoxycarbonylamino-3-(1-ethylpropoxy)-1-cyclohexene phosphonate (17b).



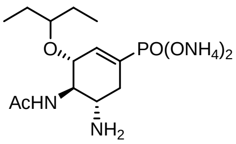
By a procedure similar to that for **14b**, a mixture of vinyl bromide **15** (4.21 g, 10 mmol), diethyl phosphite (2.12 g, 15 mmol), 1,4-diazabicyclo[2.2.2]octane (3.43 g, 30 mmol) in anhydrous toluene (50 mL) and tetrakis(triphenylphosphine)palladium(0) (872 mg, 0.75 mmol) was heated at 90 °C for 12 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was partitioned between EtOAc (50 mL) and water (30 mL). The organic phase was washed again with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated to give a crude product which was purified by recrystallization from Et_2O/CH_2Cl_2 to afford phosphonate **17b** (4.05 g, 85%) as white crystalline solids; m.p. 167−169 °C; TLC (EtOAc) $R_f = 0.31$; $[\alpha]_D^{20} = -88.8$ (c = 1.14, $CHCl_3$); IR (film) 3378, 2901, 1733, 1626, 1262, 1159 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.57 (1 H, d, J_{P-2} = 21.6 Hz), 5.81 (1 H, d, J = 9.0 Hz), 5.06 (1 H, d, J = 8.9 Hz), 4.06–4.01 (5 H, m), 3.88 (1 H, br s), 3.79–3.75 (1 H, m), 3.30 (1 H, t, J = 5.3 Hz), 2.60–2.57 (1 H, m), 2.20–2.16 (1 H, m), 1.95 (3 H, s), 1.48−1.44 (4 H, m), 1.39 (9 H, s), 1.30−1.27 (6 H, m), 0.87−0.82 (6 H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 156.2, 141.5, 126.8 (C-1, d, J_{P-1} = 181 Hz), 82.1, 79.6, 76.0, 62.0, 61.9, 54.2, 49.1, 31.0, 28.3 (3 ×), 26.0, 25.5, 23.3, 16.37, 16.33, 9.5, 9.1; ^{31}P NMR (202 MHz, $CDCl_3$) δ 17.25; HRMS calcd for $C_{22}H_{42}N_2O_7P$ (M^+ + H): 477.2730, found: m/z 477.2732.

Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene carboxylate phosphate (1·H_3PO_4, Tamiflu^{TM}).[S1,S3,S4]



Compound **17a** (1.24 g, 3 mmol) was dissolved in ethanol (20 mL) and added slowly in portions to a hot (50 °C) solution of phosphoric acid (10 mL of 1 M solution in ethanol, 10 mmol). The solution was stirred for 6 h at 50 °C. After cooling to 0 °C, the precipitates were collected by filtration and rinsed with cold acetone (3 × 5 mL) to afford **Tamiflu** (998 mg, 81%) as white crystals; m.p. 187–190 °C [lit.[S4] m.p. 184–186 °C]; $[\alpha]_D^{20} = -36.7$ (c = 1, H_2O) [lit.[S1] $[\alpha]_D = -39.9$ (c = 1, H_2O); or lit.[S4] $[\alpha]_D^{22} = -30.5$ (c = 0.480, H_2O)]; IR (film) 3501, 1734, 1612, 1150 cm^{-1}; ^1H NMR (600 MHz, D_2O) δ 6.91 (1 H, s), 4.39 (1 H, d, J = 8.0 Hz), 4.32–4.30 (2 H, m), 4.11 (1 H, dd, J = 10.5, 5.7 Hz), 3.67–3.59 (2 H, m), 3.01 (1 H, dd, J = 17.4, 5.4 Hz), 2.60–2.56 (1 H, m), 2.14 (3 H, s), 1.61–1.50 (4 H, m), 1.34 (3 H, t, J = 7.1 Hz), 0.94 (3 H, t, J = 7.3 Hz), 0.89 (3 H, t, J = 7.3 Hz); ^{13}C NMR (150 MHz, D_2O) δ 178.1, 170.3, 140.7, 130.4, 87.2, 77.9, 65.2, 55.4, 52.0, 30.9, 28.3, 27.9, 25.2, 16.1, 11.36, 11.30; ^{31}P NMR (162 MHz, D_2O) δ 0.43; HRMS calcd for $C_{16}H_{29}N_2O_4$ ($M^+ - H_3PO_4 + H$): 313.2127, found: m/z 313.2132. Anal. Calcd for $C_{16}H_{31}N_2O_8P$: C, 46.83; H, 7.61; N, 6.83. Found: C, 46.72; H, 7.68; N, 6.75.

Ammonium (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene phosphonate (3, Tamiphosphor).[S2]



Diethy phosphonate **17b** (2.38 g, 5 mmol) was dissolved in CH_2Cl_2 (50 mL) and treated with bromotrimethylsilane (6.67 mL, 50 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 18 h, and concentrated under reduced pressure. The residue was taken up in water (10 mL), stirred for 2 h at room temperature, and subject to lyophilization. The residual pale yellow solid residue was washed with Et_2O (3 × 20 mL) to give white solids, which was dissolved in aqueous NH_4HCO_3 (0.1 M solution, 20 mL), stirred for 1 h at room temperature, and then lyophilization to afford Tamiphosphor **3** (1.56 g, 88% yield) as white solids; m.p. 238–240 °C (dec.); $[\alpha]_D^{20} = -56.7$ (c = 1.2, H_2O); IR (film) 3521, 3212, 2987, 1712, 1686, 1121 cm^{-1}; ^1H NMR (600 MHz, D_2O) δ 6.15 (1 H, d, $J_{P\text{-}2}$ = 18.8 Hz), 4.12 (1 H, d, J = 8.1 Hz), 3.94 (1 H, dd, J = 11.6, 9.2 Hz), 3.45–3.40 (2 H, m), 2.73–2.68 (1 H, m), 2.39–2.34 (1 H, m), 1.97 (3 H, s), 1.46–1.40 (3 H, m), 1.38–1.29 (1 H, m), 0.77 (3 H, t, J = 7.3 Hz), 0.73 (3 H, t, J = 7.3 Hz); ^{13}C NMR (150 MHz, D_2O) δ 175.0, 133.1, 132.9 (C-1, d, $J_{P\text{-}1}$ = 170 Hz), 84.3, 76.0, 52.9, 49.7, 29.3, 25.3, 25.0, 22.2, 8.5, 8.3; ^{31}P NMR (162 MHz, D_2O) δ 10.35; HRMS calcd for $C_{13}H_{24}N_2O_5P$ $[M + H - 2\ NH_4]^+$: 319.1423, found: m/z 319.1429. Anal. Calcd for $C_{13}H_{31}N_4O_5P \cdot H_2O$: C, 41.93; H, 8.93; N, 15.04. Found: C, 41.89; H, 8.99; N, 15.07.

References:

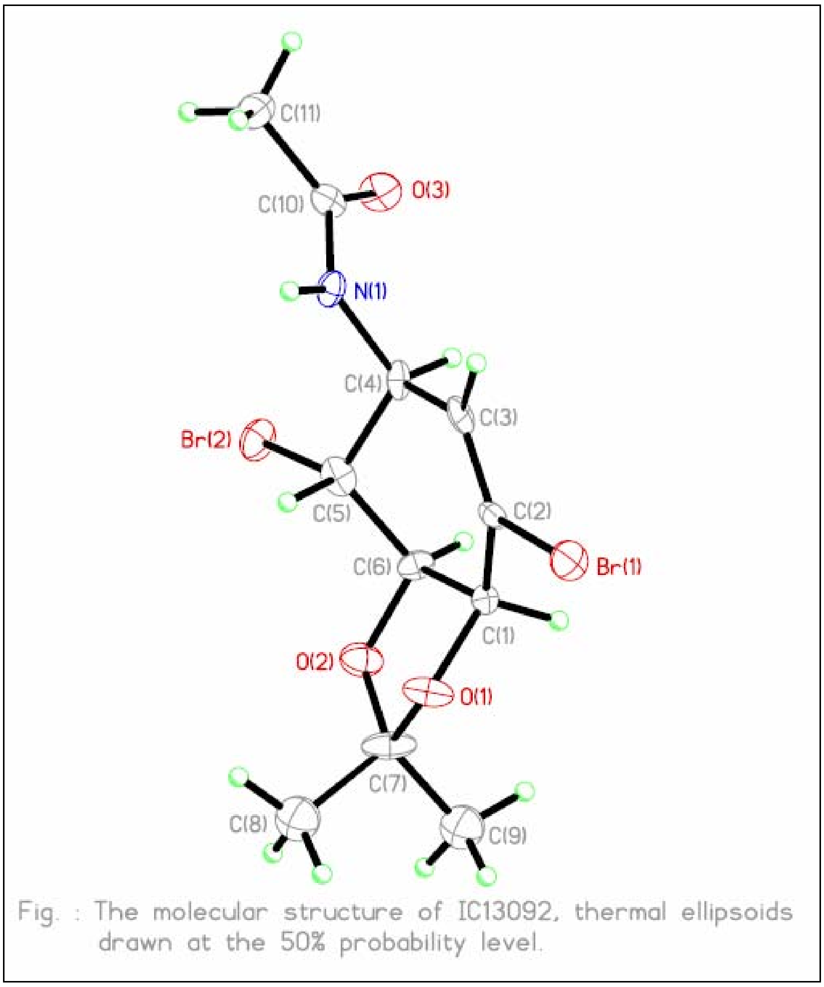
[1] J. C. Rohloff, K. M. Kent, M. J. Postich, M. W. Becker, H. H. Chapman, D. E. Kelly, W. Lew, M. S. Louie, L. R. McGee, E. J. Prisbe, L. M. Schultze, R. H. Yu, L. Zhang, *J. Org. Chem.* **1998**, *63*, 4545–4550.

[2] J.-J. Shie, J.-M. Fang, S.-Y. Wang, K.-L. Tsai, Y.-S. E. Cheng, A.-S. Yang, S.-C. Hsiao, C.-Y. Su, C.-H. Wong, *J. Am. Chem. Soc.* **2007**, *129*, 11892–11893.

[3] Y.-Y. Yeung, S. Hong, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 6310–6311.

[4] Y. Fukuta, T. Mita, N. Fukuda, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6312–6313.

The following crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 684619.



ORTEP drawing of the crystal structure of compound **6** (ic13092).

Table 1. Crystal data and structure refinement for ic13092.

Identification code	ic13092	
Empirical formula	C11 H15 Br2 N O3	
Formula weight	369.06	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 5.0183(3) Å	α= 90°.
	b = 17.7632(12) Å	β= 94.054(1)°.
	c = 7.6826(5) Å	γ = 90°.
Volume	683.12(8) $Å^3$	
Z	2	
Density (calculated)	1.794 Mg/m^3	
Absorption coefficient	5.930 mm^{-1}	
F(000)	364	
Crystal size	0.70 x 0.18 x 0.14 mm^3	
Theta range for data collection	2.29 to 27.50°.	
Index ranges	-6<=h<=6, -23<=k<=23, -9<=l<=9	
Reflections collected	5154	
Independent reflections	3098 [R(int) = 0.0447]	
Completeness to theta = 27.50°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.4907 and 0.1035	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3098 / 5 / 157	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2sigma(I)]	R1 = 0.0551, wR2 = 0.1297	
R indices (all data)	R1 = 0.0619, wR2 = 0.1330	
Absolute structure parameter	0.02(2)	
Largest diff. peak and hole	1.456 and -1.949 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for ic13092. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	-358(1)	10532(1)	12262(1)	23(1)
Br(2)	6146(2)	9468(1)	5573(1)	24(1)
O(1)	992(9)	8967(3)	10496(8)	24(1)
O(2)	4097(10)	8534(3)	8754(8)	24(1)
O(3)	8040(9)	11381(3)	5987(7)	23(1)
N(1)	3728(11)	11102(3)	6414(8)	16(1)
C(1)	3065(12)	9519(4)	10605(9)	15(1)
C(2)	1951(13)	10286(4)	10467(10)	14(2)
C(3)	2581(14)	10793(4)	9336(10)	17(2)
C(4)	4348(12)	10601(5)	7876(9)	16(1)
C(5)	3939(13)	9780(4)	7458(10)	18(2)
C(6)	4705(13)	9305(4)	9051(10)	16(2)
C(7)	2179(13)	8289(4)	9952(10)	25(2)
C(8)	130(30)	7756(10)	9190(30)	32(5)
C(9)	3290(40)	7799(11)	11390(20)	32(5)
C(8')	100(30)	7918(11)	8680(20)	23(4)
C(9')	3930(40)	7993(14)	11490(20)	44(6)
C(10)	5612(13)	11461(4)	5597(10)	17(2)
C(11)	4625(16)	11981(5)	4125(11)	27(2)

Table 3. Bond lengths [Å] and angles [°] for ic13092.

Br(1)-C(2)	1.913(7)
Br(2)-C(5)	1.964(8)
O(1)-C(7)	1.419(9)
O(1)-C(1)	1.428(8)
O(2)-C(6)	1.418(9)
O(2)-C(7)	1.445(9)
O(3)-C(10)	1.242(8)
N(1)-C(10)	1.334(9)
N(1)-C(4)	1.449(9)
C(1)-C(2)	1.474(10)
C(1)-C(6)	1.545(9)
C(2)-C(3)	1.306(10)
C(3)-C(4)	1.517(9)
C(4)-C(5)	1.505(11)
C(5)-C(6)	1.514(10)
C(7)-C(9)	1.485(9)
C(7)-C(8)	1.488(9)
C(7)-C(9')	1.517(9)
C(7)-C(8')	1.529(9)
C(10)-C(11)	1.516(11)

C(7)-O(1)-C(1)	106.3(5)
C(6)-O(2)-C(7)	109.5(5)
C(10)-N(1)-C(4)	122.5(6)
O(1)-C(1)-C(2)	111.1(5)
O(1)-C(1)-C(6)	102.2(6)
C(2)-C(1)-C(6)	113.1(6)
C(3)-C(2)-C(1)	125.3(7)
C(3)-C(2)-Br(1)	120.6(5)
C(1)-C(2)-Br(1)	113.9(5)
C(2)-C(3)-C(4)	121.3(7)
N(1)-C(4)-C(5)	114.3(6)
N(1)-C(4)-C(3)	109.3(6)
C(5)-C(4)-C(3)	107.3(6)
C(4)-C(5)-C(6)	110.1(6)
C(4)-C(5)-Br(2)	110.8(5)

C(6)-C(5)-Br(2)	108.3(4)
O(2)-C(6)-C(5)	111.6(6)
O(2)-C(6)-C(1)	104.0(5)
C(5)-C(6)-C(1)	111.7(5)
O(1)-C(7)-O(2)	104.2(5)
O(1)-C(7)-C(9)	114.9(10)
O(2)-C(7)-C(9)	114.8(10)
O(1)-C(7)-C(8)	111.3(9)
O(2)-C(7)-C(8)	114.4(11)
C(9)-C(7)-C(8)	97.7(14)
O(1)-C(7)-C(9')	107.3(11)
O(2)-C(7)-C(9')	103.0(11)
C(9)-C(7)-C(9')	18.1(12)
C(8)-C(7)-C(9')	115.7(15)
O(1)-C(7)-C(8')	105.8(9)
O(2)-C(7)-C(8')	100.1(9)
C(9)-C(7)-C(8')	115.4(14)
C(8)-C(7)-C(8')	18.5(10)
C(9')-C(7)-C(8')	133.0(15)
O(3)-C(10)-N(1)	123.2(7)
O(3)-C(10)-C(11)	120.9(7)
N(1)-C(10)-C(11)	115.9(6)

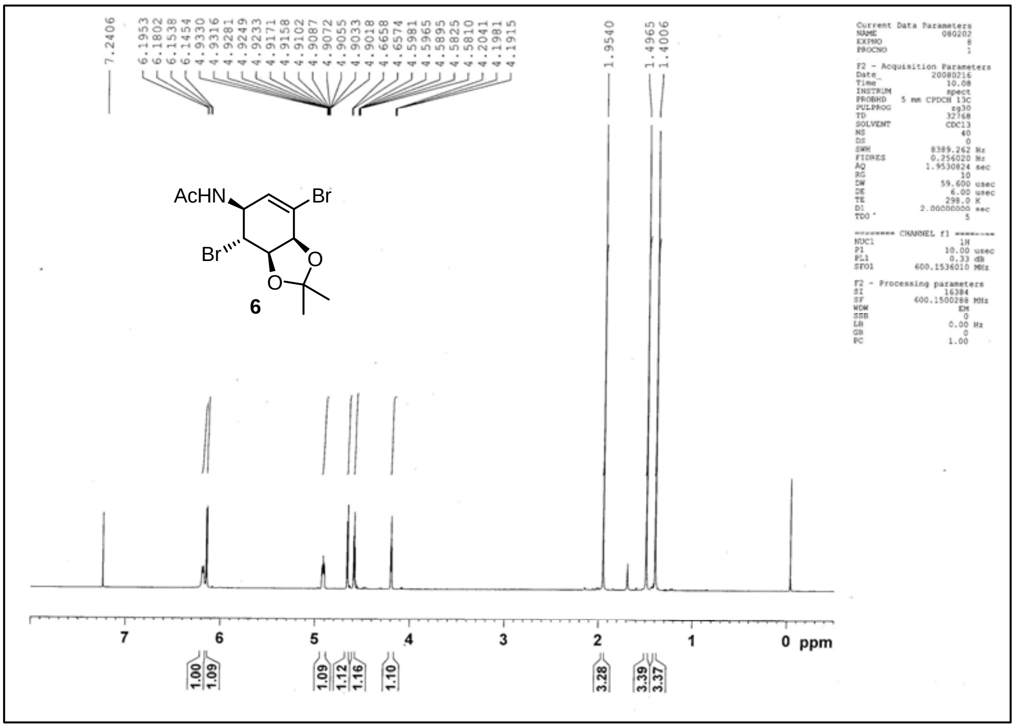
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for ic13092. The anisotropic displacement factor exponent takes the form $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	25(1)	26(1)	20(1)	-5(1)	9(1)	-2(1)
Br(2)	28(1)	28(1)	16(1)	-2(1)	6(1)	4(1)
O(1)	18(3)	14(3)	40(4)	4(2)	9(2)	0(2)
O(2)	26(3)	17(3)	29(3)	-1(2)	8(2)	1(2)
O(3)	13(2)	29(3)	28(3)	3(2)	6(2)	0(2)
N(1)	12(3)	23(3)	13(3)	0(3)	-1(2)	1(2)
C(1)	15(3)	15(3)	13(3)	0(3)	-1(2)	-2(3)
C(2)	15(3)	12(4)	16(4)	-2(3)	0(3)	-5(3)
C(3)	17(3)	17(4)	16(4)	-11(3)	4(3)	-2(3)
C(4)	12(2)	23(4)	13(3)	-5(3)	-2(2)	3(3)
C(5)	8(3)	24(4)	24(4)	-5(3)	4(3)	1(3)
C(6)	15(3)	17(4)	18(4)	4(3)	6(3)	2(3)
C(7)	21(4)	18(4)	39(5)	9(4)	18(3)	3(3)
C(10)	17(3)	15(4)	19(4)	-6(3)	8(3)	-1(3)
C(11)	28(4)	29(5)	24(5)	7(4)	-2(3)	-4(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for ic13092.

	x	y	z	U(eq)
H(1)	2044	11171	6051	20
H(1A)	4184	9462	11727	18
H(3)	1920	11291	9429	20
H(4)	6255	10680	8307	19
H(5)	2014	9691	7085	22
H(6)	6655	9364	9389	20
H(8A)	-1123	7630	10064	49
H(8B)	1007	7297	8813	49
H(8C)	-844	7992	8179	49
H(9A)	4882	8037	11967	48
H(9B)	3781	7310	10918	48
H(9C)	1948	7726	12242	48
H(8'1)	-1405	7742	9312	34
H(8'2)	913	7490	8108	34
H(8'3)	-539	8286	7791	34
H(9'1)	5291	8369	11844	65
H(9'2)	4804	7527	11155	65
H(9'3)	2828	7891	12468	65
H(11A)	5681	12446	4180	41
H(11B)	2740	12102	4240	41
H(11C)	4815	11731	3003	41



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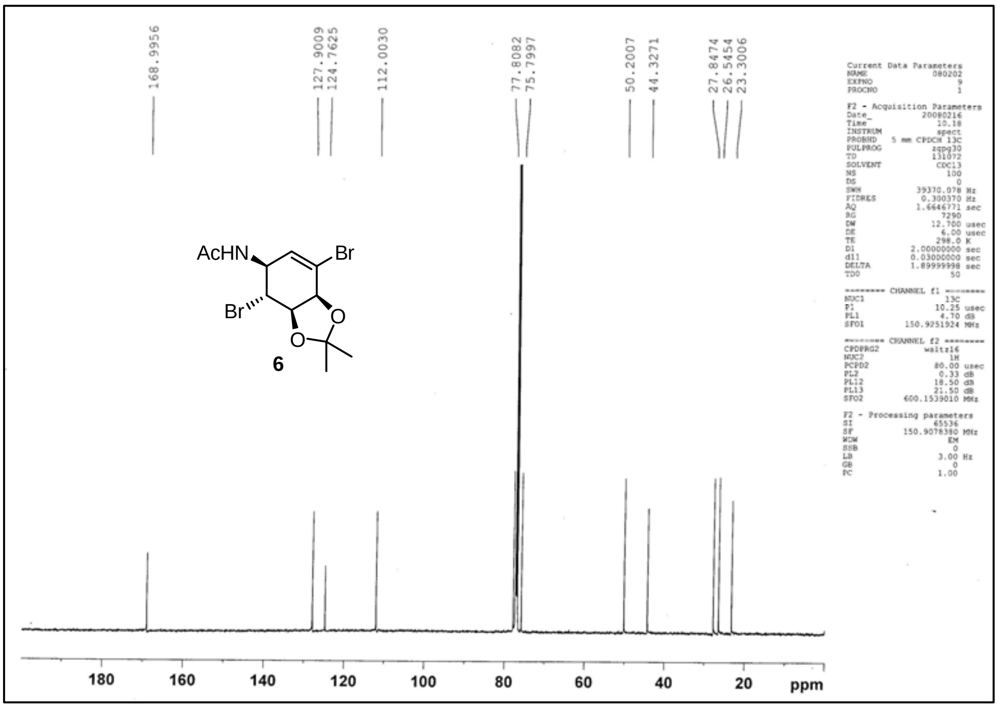
Current Data Parameters
NAME              080202
EXPNO                  8
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080216
Time               10.08
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    40
DS                     0
SWH             8389.262 Hz
FIDRES          0.256020 Hz
AQ             1.9530824 sec
RG                    10
DW                59.600 usec
DE                  6.00 usec
TE                 298.0 K
D1            2.00000000 sec
TD0                    5

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 0.33 dB
SFO1         600.1536010 MHz

F2 - Processing parameters
SI                 16384
SF           600.1500288 MHz
WDW                   EM
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00
```

^{1}H NMR Spectrum (600 MHz, $CDCl_3$) of Compound **6**.



```
Current Data Parameters
NAME              080202
EXPNO                  9
PROCNO                 1

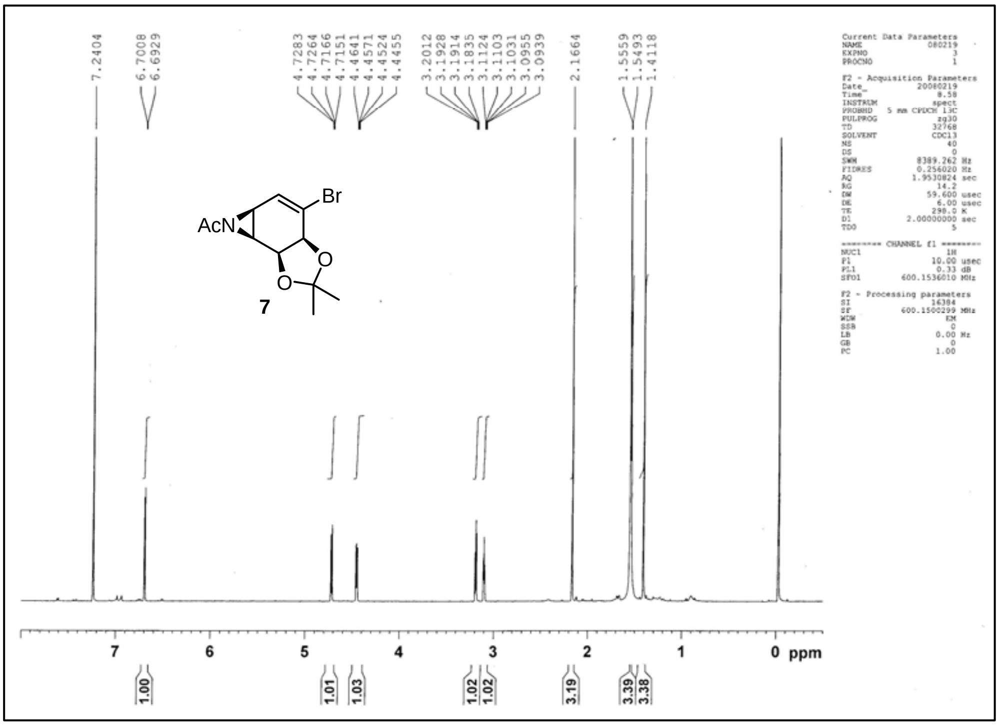
F2 - Acquisition Parameters
Date_           20080216
Time               10.18
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG           zgpg30
TD                131072
SOLVENT            CDCl3
NS                   100
DS                     0
SWH            39370.078 Hz
FIDRES          0.300370 Hz
AQ             1.6646771 sec
RG                  7290
DW                12.700 usec
DE                  6.00 usec
TE                 298.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                   50

======== CHANNEL f1 ========
NUC1                 13C
P1                 10.25 usec
PL1                 4.70 dB
SFO1         150.9251924 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 0.33 dB
PL12               18.50 dB
PL13               21.50 dB
SFO2         600.1539010 MHz

F2 - Processing parameters
SI                 65536
SF           150.9078380 MHz
WDW                   EM
SSB                    0
LB                  3.00 Hz
GB                     0
PC                  1.00
```

^{13}C NMR Spectrum (150 MHz, $CDCl_3$) of Compound **6**.



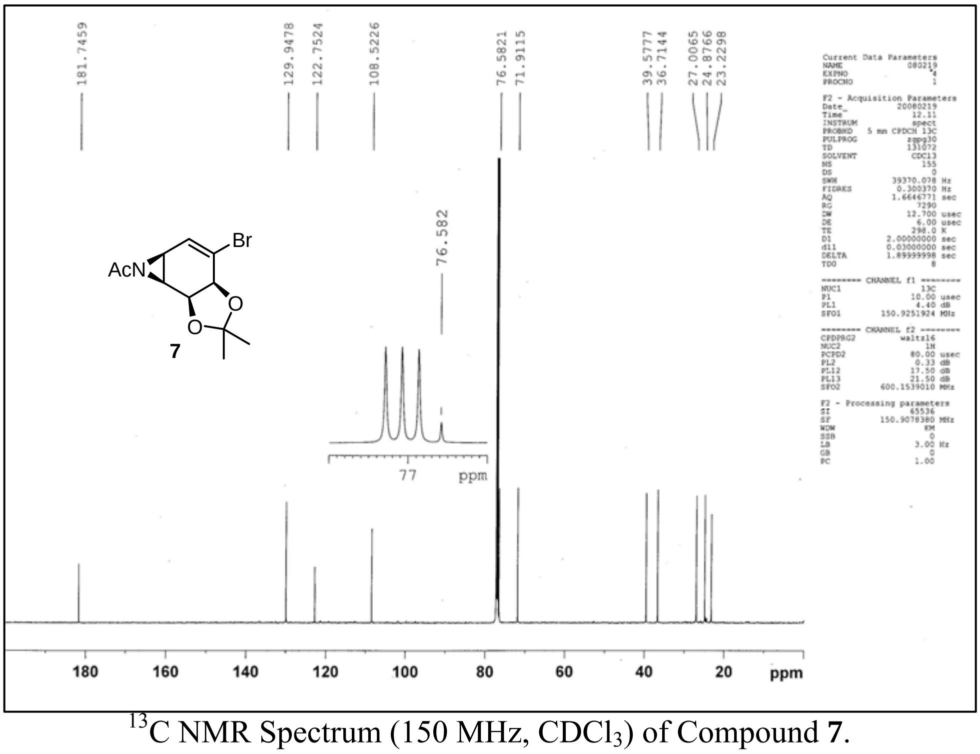
```
Current Data Parameters
NAME              080219
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080219
Time                8.58
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    40
DS                     0
SWH            8389.262 Hz
FIDRES         0.256020 Hz
AQ            1.9530824 sec
RG                  14.2
DW                59.600 usec
DE                  6.00 usec
TE                 298.0 K
D1            2.00000000 sec
TD0                    5

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 0.33 dB
SFO1         600.1536010 MHz

F2 - Processing parameters
SI                 16384
SF           600.1500299 MHz
WDW                   EM
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00
```

^{1}H NMR Spectrum (600 MHz, CDCl$_3$) of Compound **7**.



```
Current Data Parameters
NAME              080219
EXPNO                  4
PROCNO                 1

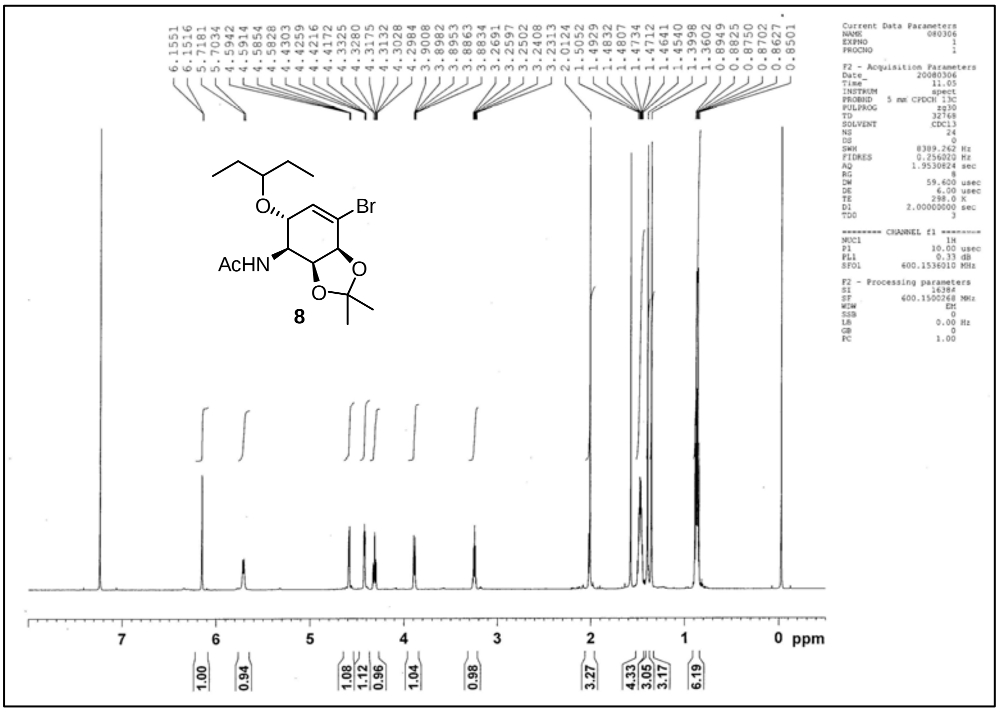
F2 - Acquisition Parameters
Date_           20080219
Time               12.11
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG           zgpg30
TD                131072
SOLVENT            CDCl3
NS                   155
DS                     0
SWH           39370.078 Hz
FIDRES         0.300370 Hz
AQ            1.6646771 sec
RG                  7290
DW                12.700 usec
DE                  6.00 usec
TE                 298.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    8

======== CHANNEL f1 ========
NUC1                 13C
P1                 10.00 usec
PL1                 4.40 dB
SFO1         150.9251924 MHz

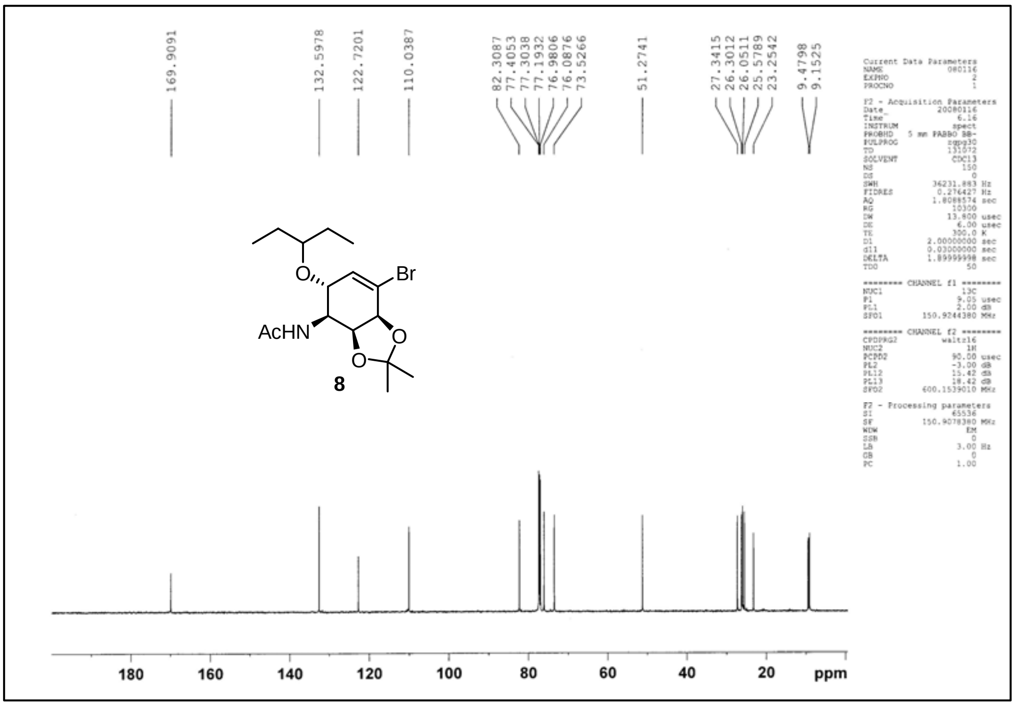
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 0.33 dB
PL12               17.50 dB
PL13               21.50 dB
SFO2         600.1539010 MHz

F2 - Processing parameters
SI                 65536
SF           150.9078380 MHz
WDW                   EM
SSB                    0
LB                  3.00 Hz
GB                     0
PC                  1.00
```

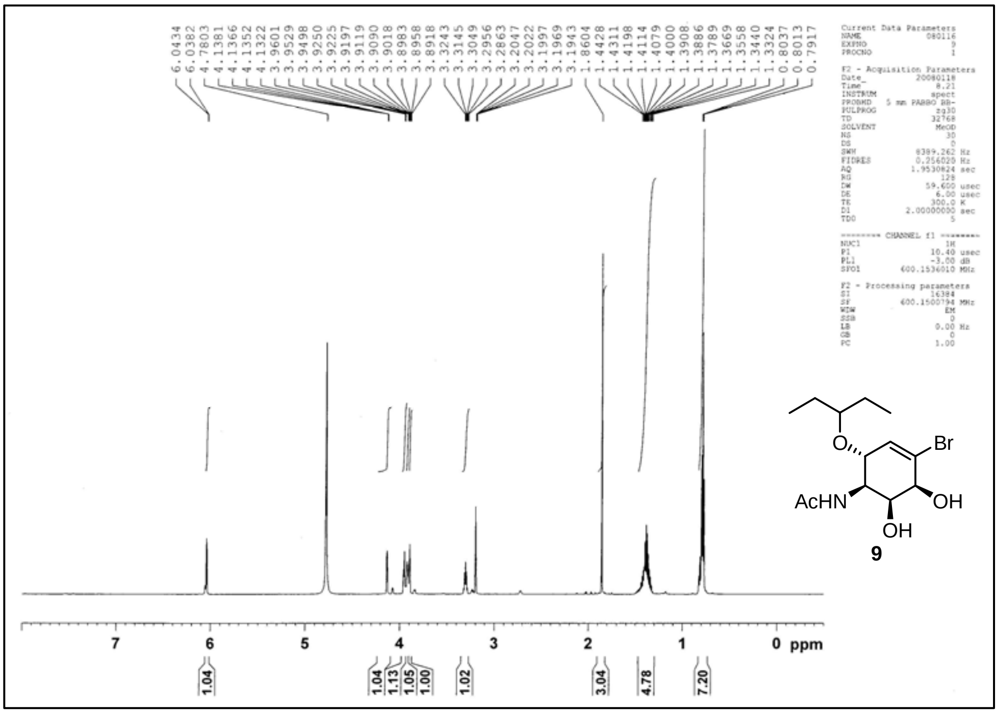
^{13}C NMR Spectrum (150 MHz, CDCl$_3$) of Compound **7**.



^{1}H NMR Spectrum (600 MHz, CDCl$_3$) of Compound **8**.



^{13}C NMR Spectrum (150 MHz, CDCl$_3$) of Compound **8**.



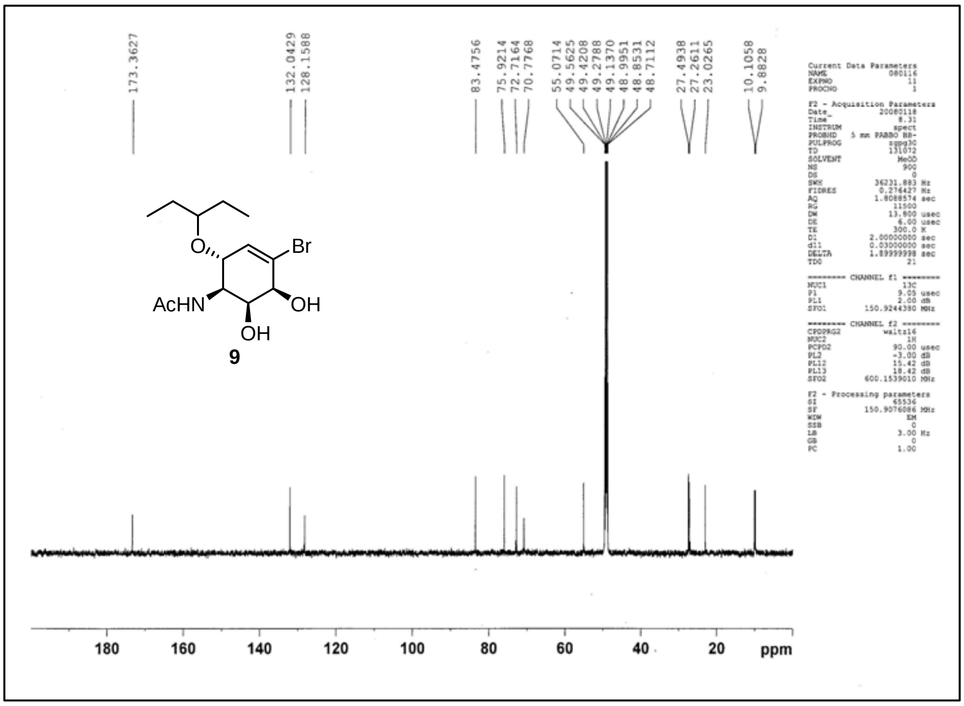
```
Current Data Parameters
NAME              080116
EXPNO                  9
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080118
Time                8.21
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 32768
SOLVENT             MeOD
NS                    30
DS                     0
SWH             8389.262 Hz
FIDRES          0.256020 Hz
AQ             1.9530824 sec
RG                   128
DW                59.600 usec
DE                  6.00 usec
TE                 300.0 K
D1            2.00000000 sec
TD0                    5

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.40 usec
PL1                -3.00 dB
SFO1         600.1536010 MHz

F2 - Processing parameters
SI                 16384
SF           600.1500794 MHz
WDW                   EM
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00
```

^{1}H NMR Spectrum (600 MHz, CD_3OD) of Compound **9**.



```
Current Data Parameters
NAME              080116
EXPNO                 11
PROCNO                 1

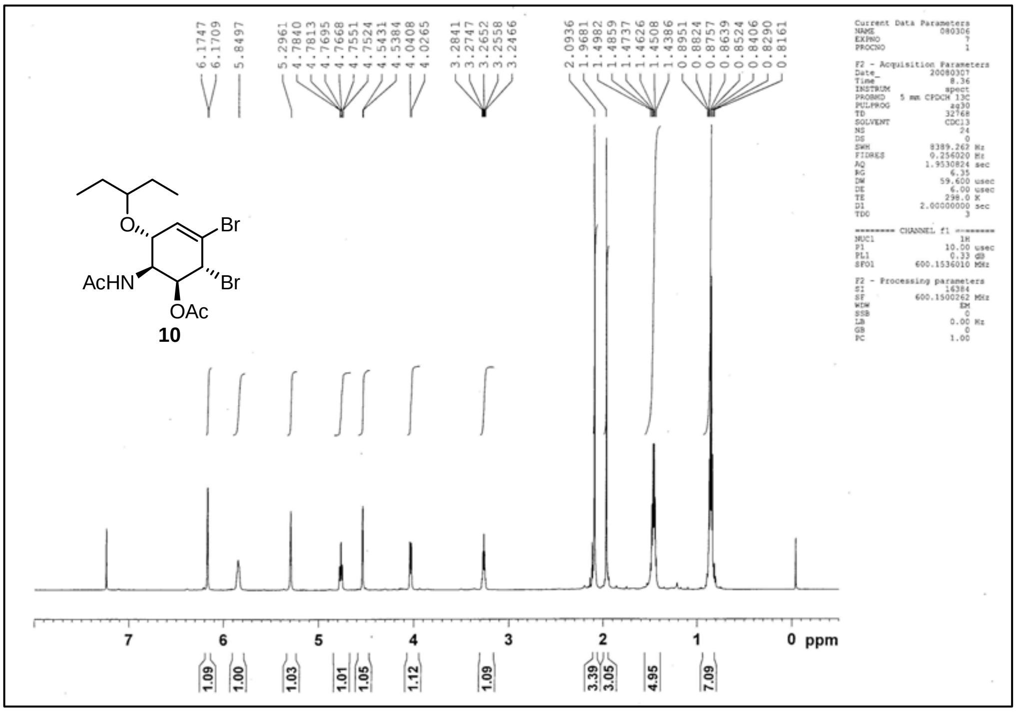
F2 - Acquisition Parameters
Date_           20080118
Time                8.31
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                131072
SOLVENT             MeOD
NS                   900
DS                     0
SWH            36231.883 Hz
FIDRES          0.276427 Hz
AQ             1.8088574 sec
RG                 11500
DW                13.800 usec
DE                  6.00 usec
TE                 300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                   21

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.05 usec
PL1                 2.00 dB
SFO1         150.9244380 MHz

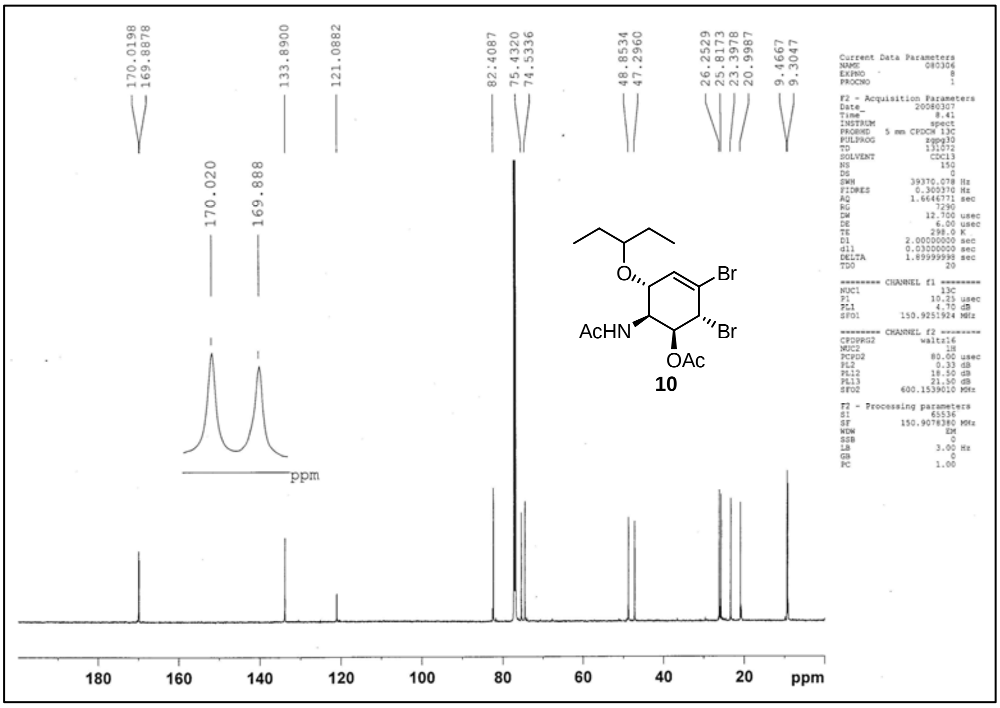
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              90.00 usec
PL2                -3.00 dB
PL12               15.42 dB
PL13               18.42 dB
SFO2         600.1539010 MHz

F2 - Processing parameters
SI                 65536
SF           150.9076086 MHz
WDW                   EM
SSB                    0
LB                  3.00 Hz
GB                     0
PC                  1.00
```

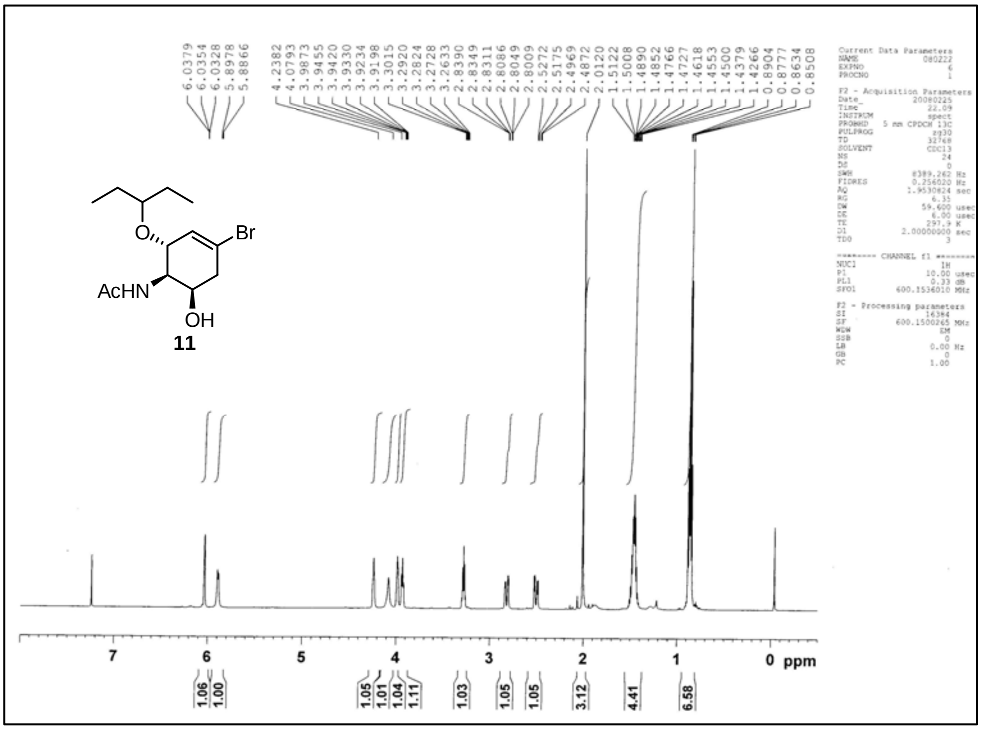
^{13}C NMR Spectrum (150 MHz, CD_3OD) of Compound **9**.



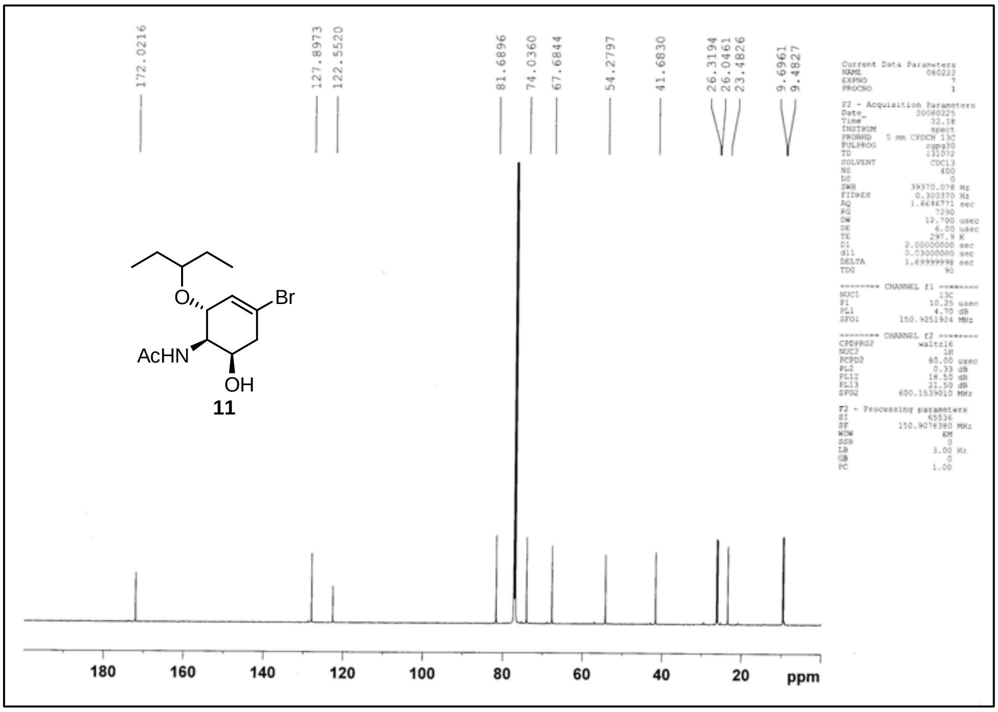
^{1}H NMR Spectrum (600 MHz, CDCl$_3$) of Compound **10**.



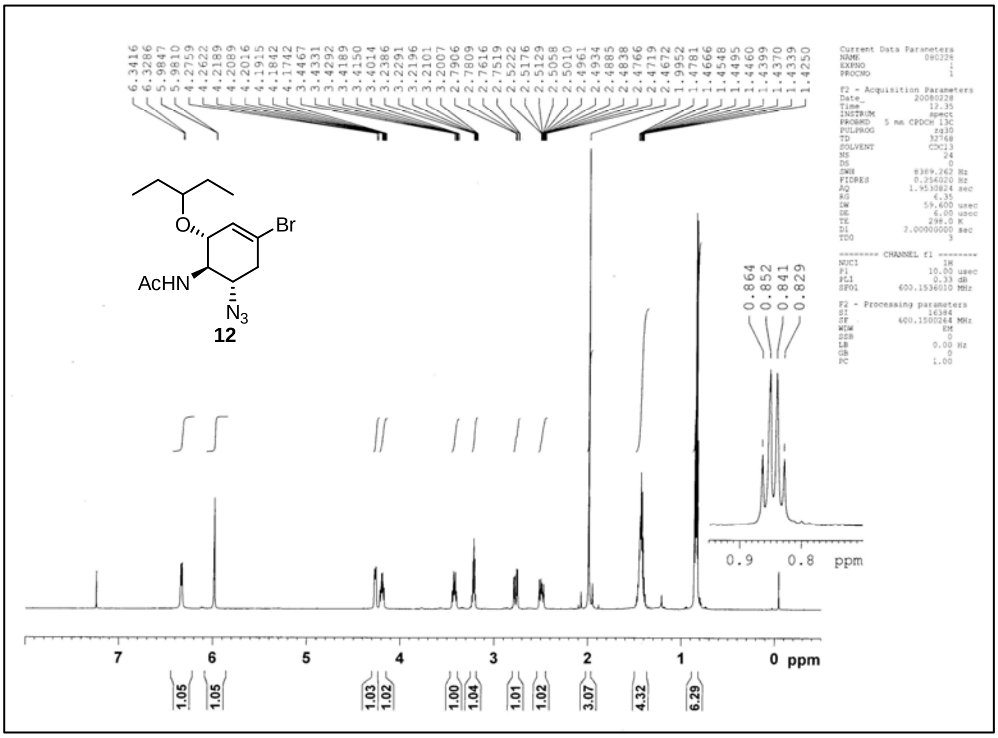
^{13}C NMR Spectrum (150 MHz, CDCl$_3$) of Compound **10**.



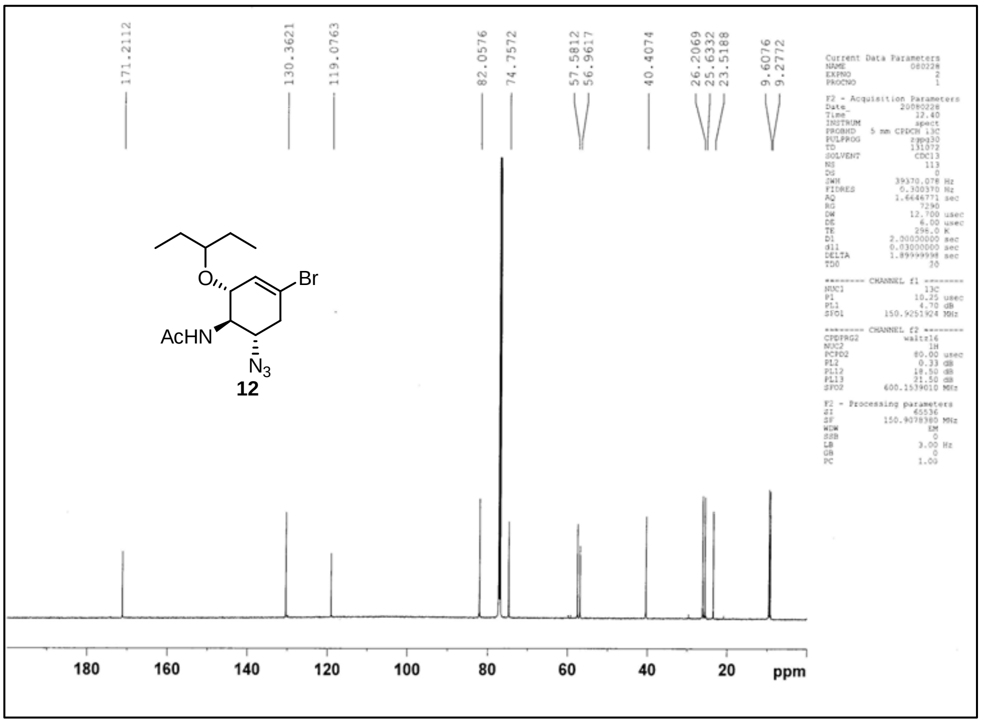
^{1}H NMR Spectrum (600 MHz, CDCl$_3$) of Compound **11**.



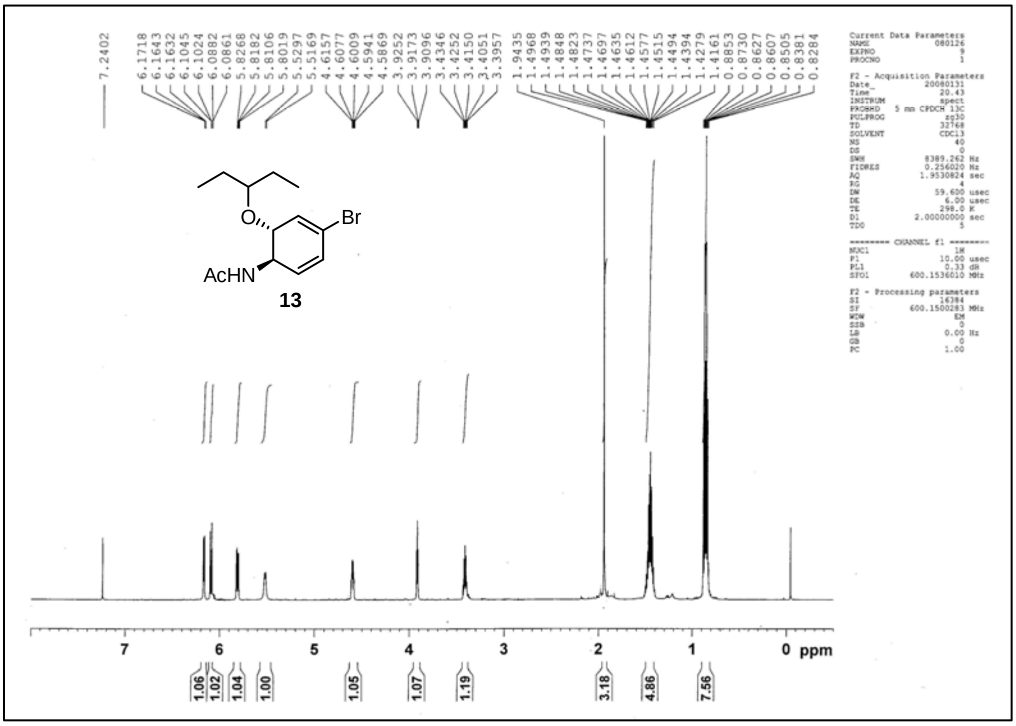
^{13}C NMR Spectrum (150 MHz, CDCl$_3$) of Compound **11**.



^{1}H NMR Spectrum (600 MHz, CDCl$_3$) of Compound **12**.



^{13}C NMR Spectrum (150 MHz, CDCl$_3$) of Compound **12**.



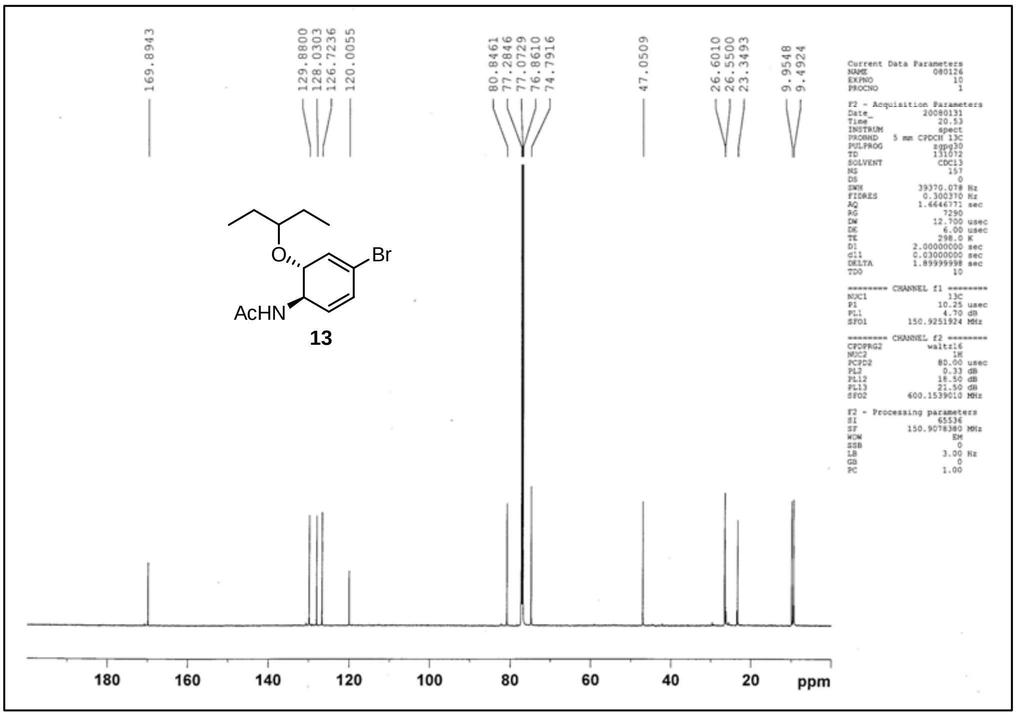
```
Current Data Parameters
NAME             080126
EXPNO                 9
PROCNO                1

F2 - Acquisition Parameters
Date_          20080131
Time              20.43
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG            zg30
TD                32768
SOLVENT           CDCl3
NS                   40
DS                    0
SWH            8389.262 Hz
FIDRES         0.256020 Hz
AQ            1.9530824 sec
RG                    4
DW               59.600 usec
DE                 6.00 usec
TE                298.0 K
D1           2.00000000 sec
TD0                   5

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PL1                0.33 dB
SFO1        600.1536010 MHz

F2 - Processing parameters
SI                16384
SF          600.1500283 MHz
WDW                  EM
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00
```

^{1}H NMR Spectrum (600 MHz, $CDCl_3$) of Compound **13**.



```
Current Data Parameters
NAME             080126
EXPNO                10
PROCNO                1

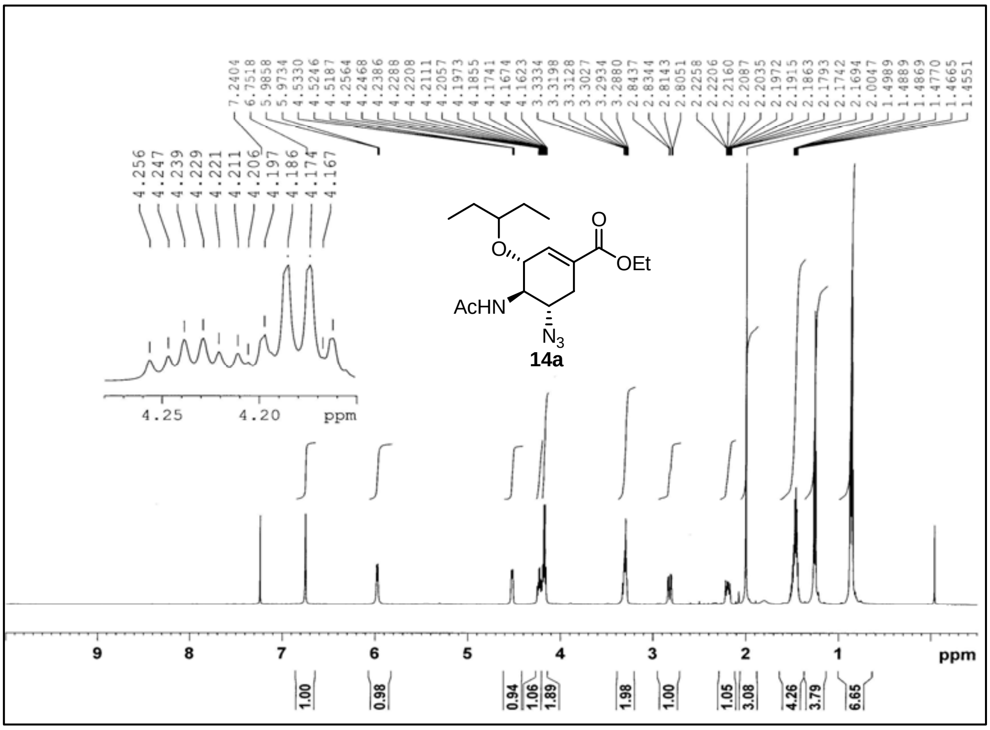
F2 - Acquisition Parameters
Date_          20080131
Time              20.53
INSTRUM           spect
PROBHD   5 mm CPDCH 13C
PULPROG          zgpg30
TD               131072
SOLVENT           CDCl3
NS                  157
DS                    0
SWH           39370.078 Hz
FIDRES         0.300370 Hz
AQ            1.6646771 sec
RG                 7290
DW               12.700 usec
DE                 6.00 usec
TE                298.0 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
TD0                  10

======== CHANNEL f1 ========
NUC1                13C
P1                10.25 usec
PL1                4.70 dB
SFO1        150.9251924 MHz

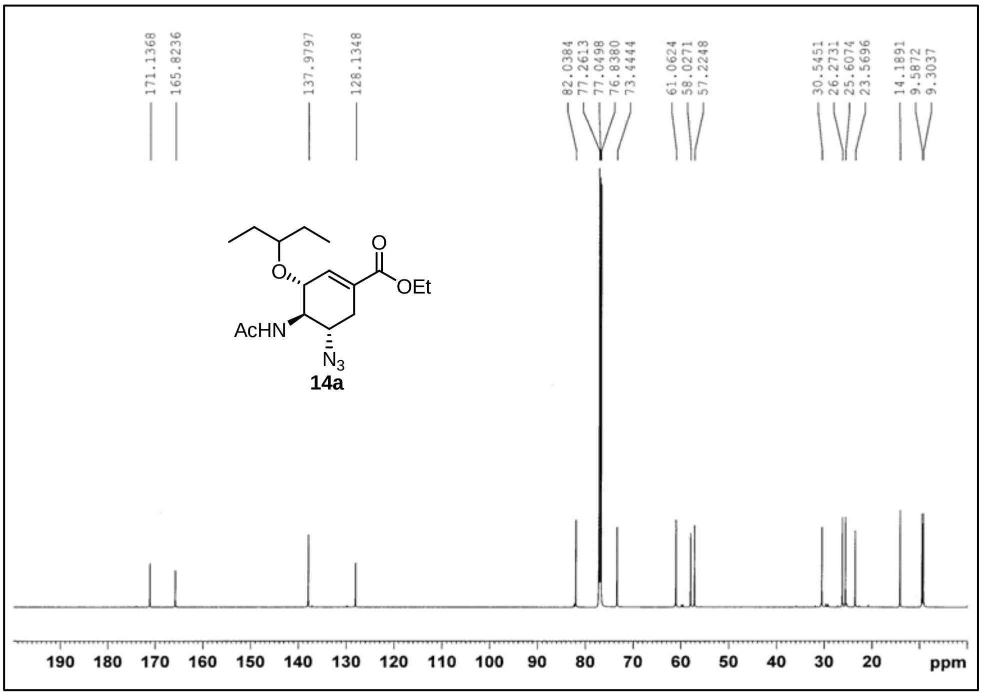
======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                0.33 dB
PL12              18.50 dB
PL13              21.50 dB
SFO2        600.1539010 MHz

F2 - Processing parameters
SI                65536
SF          150.9078380 MHz
WDW                  EM
SSB                   0
LB                 3.00 Hz
GB                    0
PC                 1.00
```

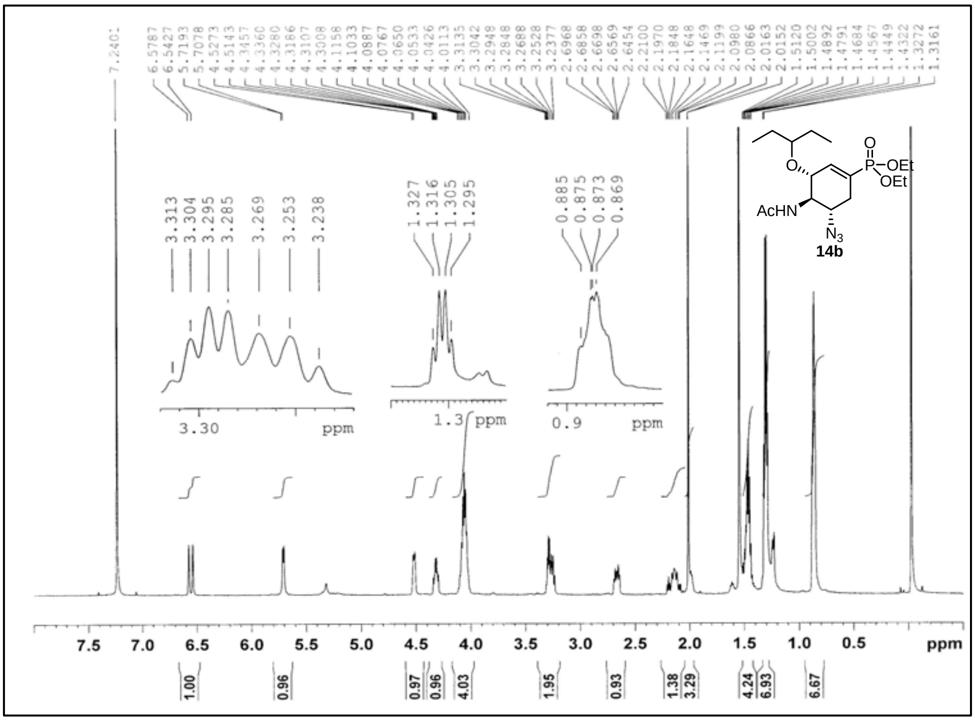
^{13}C NMR Spectrum (150 MHz, $CDCl_3$) of Compound **13**.



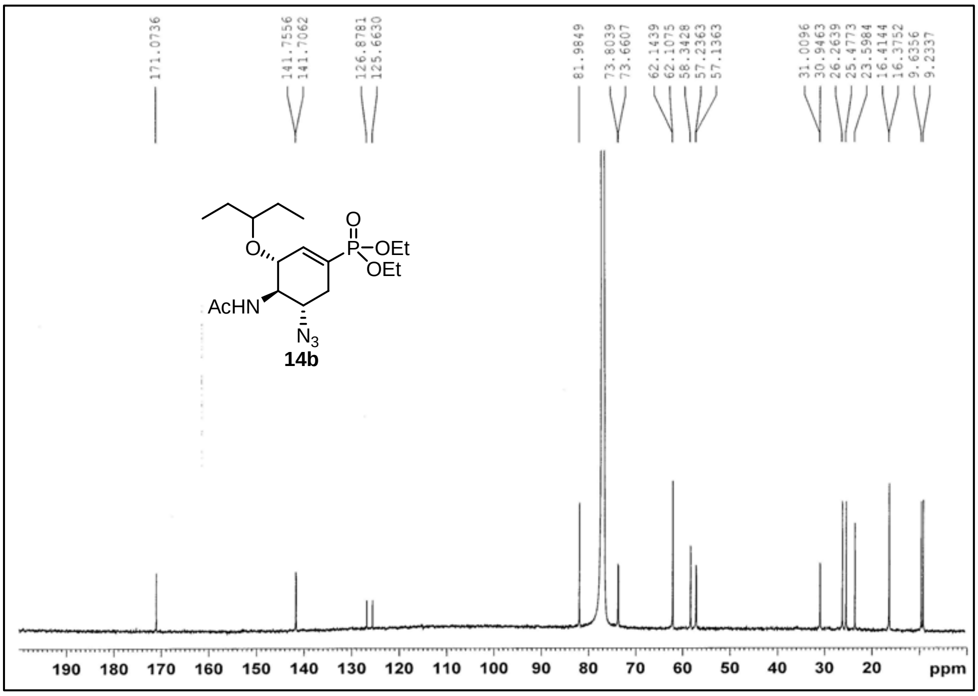
^{1}H NMR Spectrum (600 MHz, CDCl$_3$) of Compound **14a**.



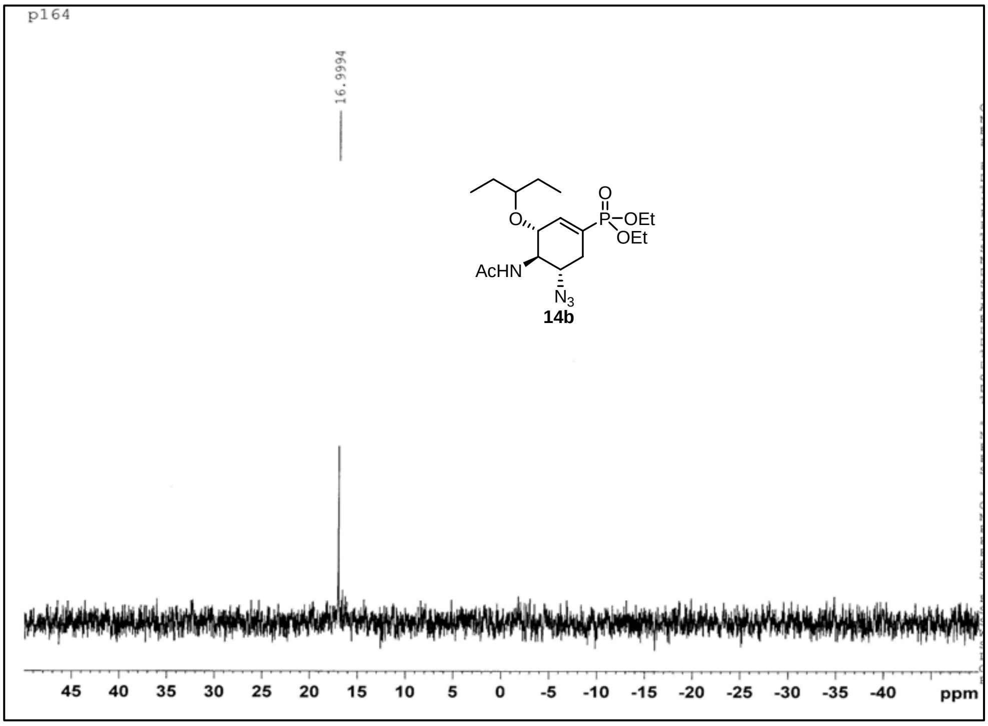
^{13}C NMR Spectrum (150 MHz, CDCl$_3$) of Compound **14a**.



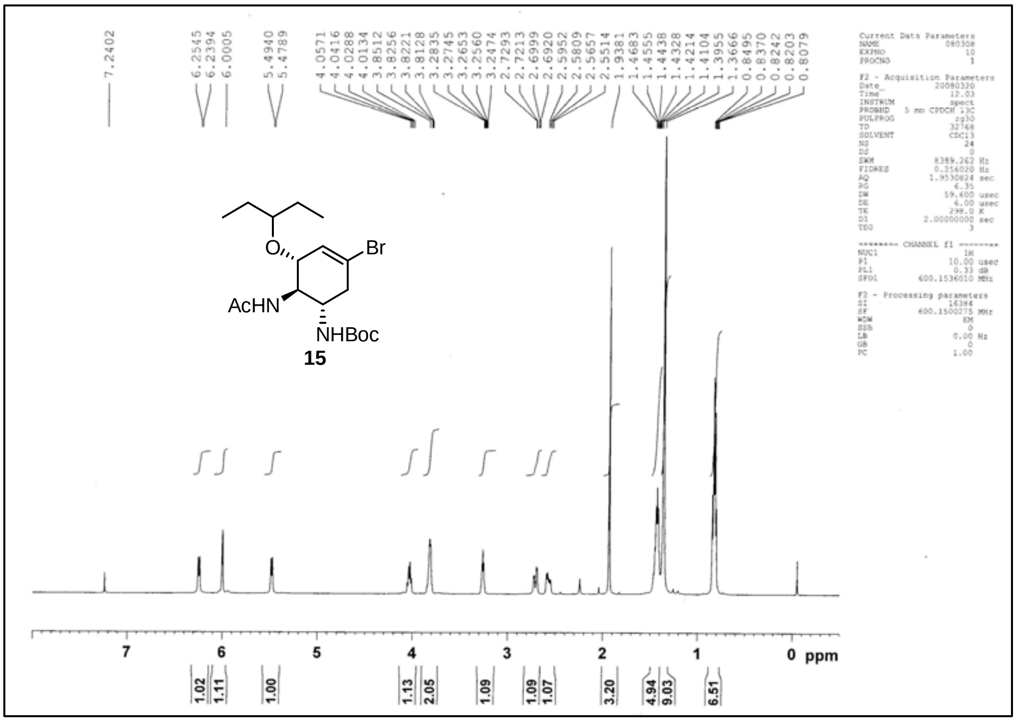
^{1}H NMR Spectrum (600 MHz, CDCl$_3$) of Compound **14b**.



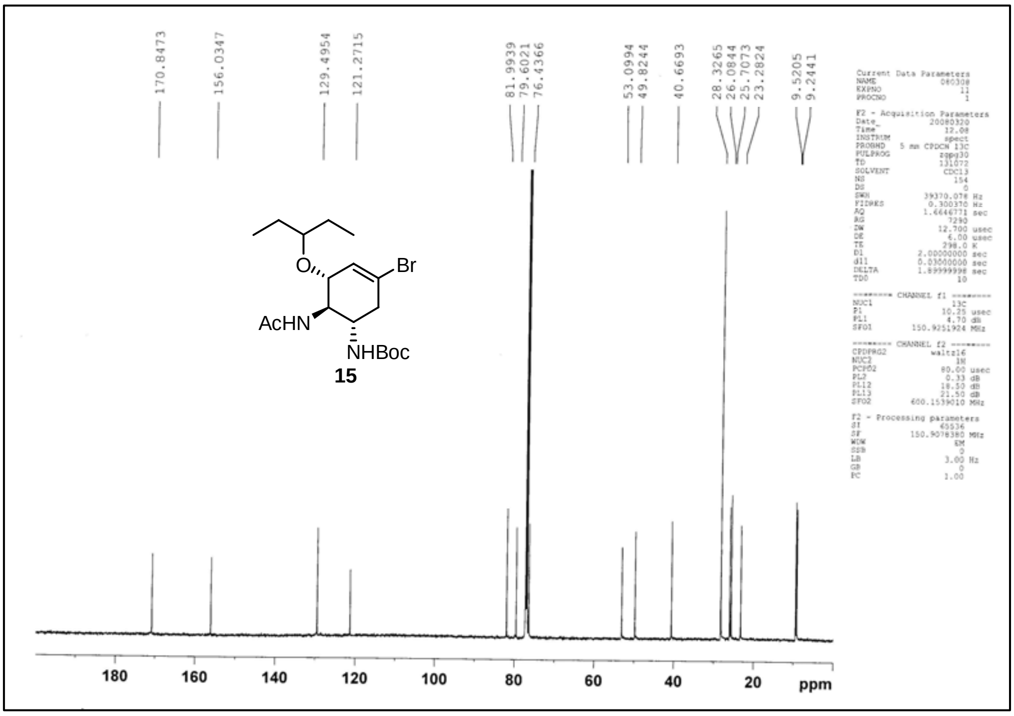
^{13}C NMR Spectrum (150 MHz, CDCl$_3$) of Compound **14b**.



^{31}P NMR Spectrum (162 MHz, CDCl$_3$) of Compound **14b**.



^{1}H NMR Spectrum (600 MHz, CDCl$_3$) of Compound **15**.



```
Current Data Parameters
NAME              080308
EXPNO                 11
PROCNO                 1

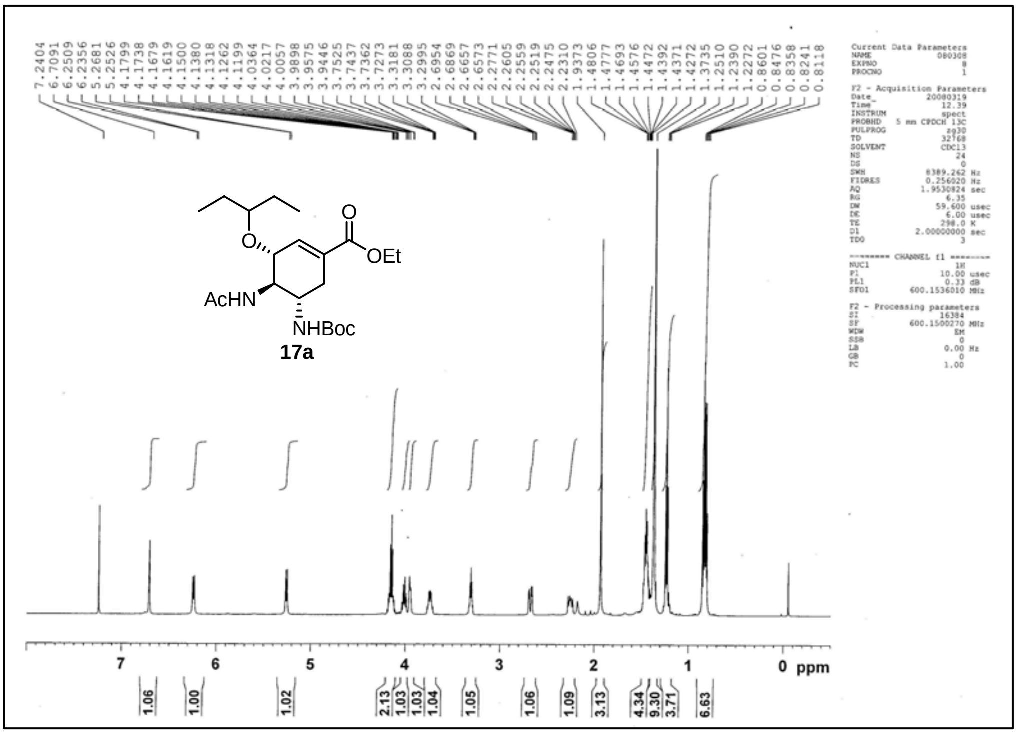
F2 - Acquisition Parameters
Date_           20080320
Time               12.08
INSTRUM            spect
PROBHD   5 mm CPDCN 13C
PULPROG          zgpg30
TD                131072
SOLVENT            CDCl3
NS                   154
DS                     0
SWH            39370.078 Hz
FIDRES          0.300370 Hz
AQ             1.6646771 sec
RG                  7290
DW                12.700 usec
DE                  6.00 usec
TE                 298.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                   10

======== CHANNEL f1 ========
NUC1                 13C
P1                 10.25 usec
PL1                 4.70 dB
SFO1         150.9251924 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 0.33 dB
PL12               18.50 dB
PL13               21.50 dB
SFO2         600.1539010 MHz

F2 - Processing parameters
SI                 65536
SF           150.9078380 MHz
WDW                   EM
SSB                    0
LB                  3.00 Hz
GB                     0
PC                  1.00
```

^{13}C NMR Spectrum (150 MHz, $CDCl_3$) of Compound **15**.



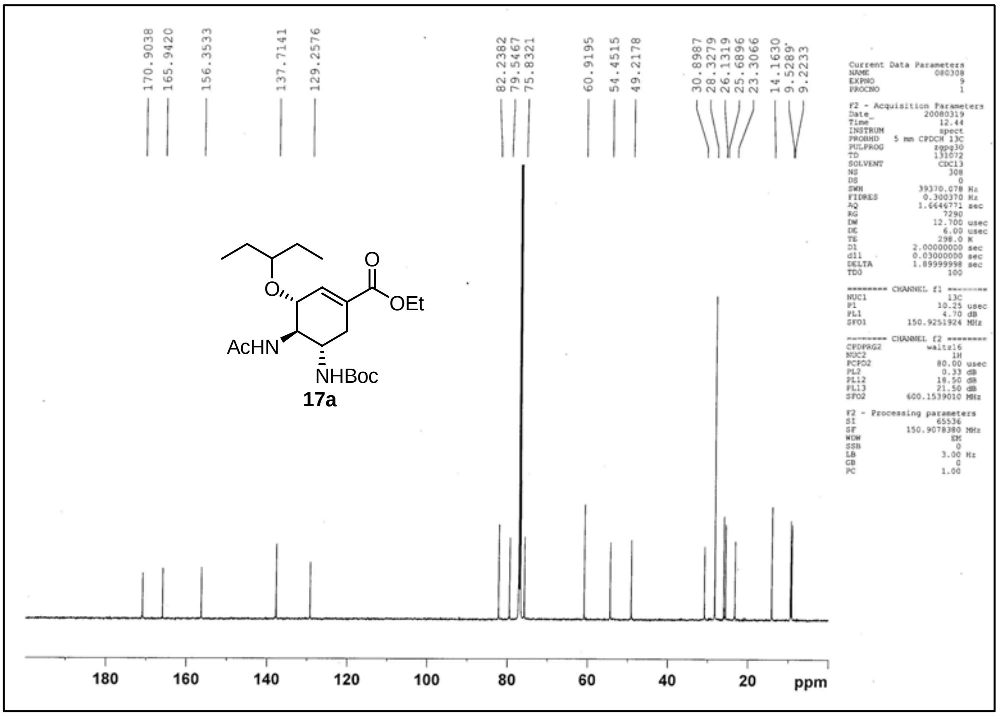
```
Current Data Parameters
NAME              080308
EXPNO                  8
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080319
Time               12.39
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    24
DS                     0
SWH             8389.262 Hz
FIDRES          0.256020 Hz
AQ             1.9530824 sec
RG                  6.35
DW                59.600 usec
DE                  6.00 usec
TE                 298.0 K
D1            2.00000000 sec
TD0                    3

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PL1                 0.33 dB
SFO1         600.1536010 MHz

F2 - Processing parameters
SI                 16384
SF           600.1500270 MHz
WDW                   EM
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00
```

^{1}H NMR Spectrum (600 MHz, $CDCl_3$) of Compound **17a**.



```
Current Data Parameters
NAME              080308
EXPNO                  9
PROCNO                 1

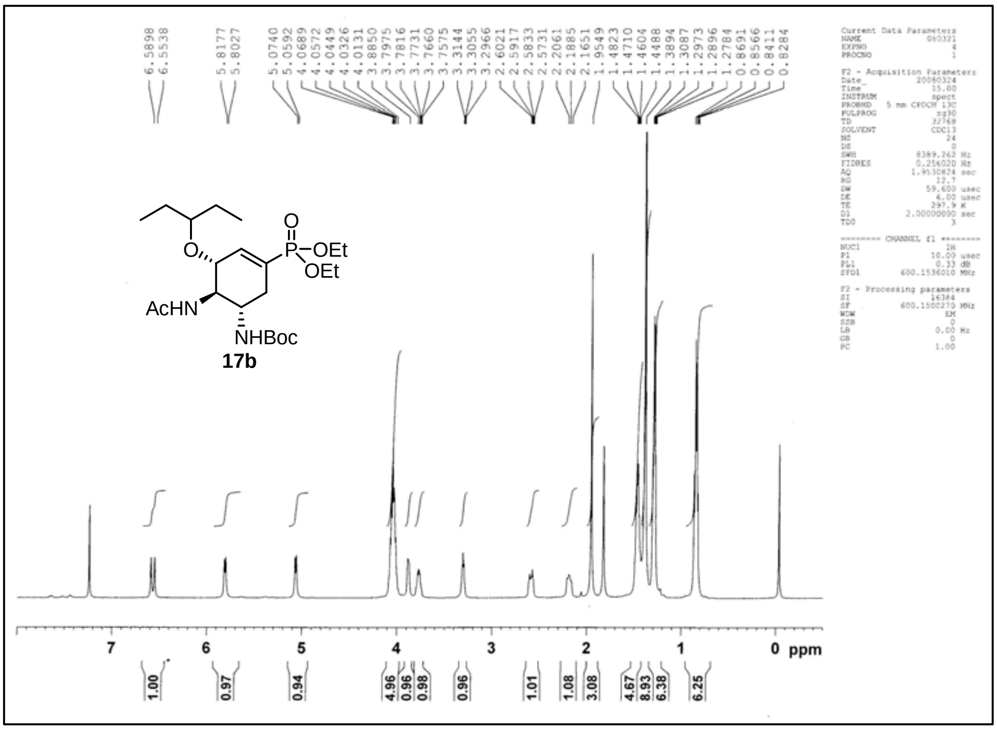
F2 - Acquisition Parameters
Date_           20080319
Time               12.44
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG          zgpg30
TD                131072
SOLVENT            CDCl3
NS                   308
DS                     0
SWH          39370.078 Hz
FIDRES        0.300370 Hz
AQ           1.6646771 sec
RG                  7290
DW             12.700 usec
DE               6.00 usec
TE               298.0 K
D1          2.00000000 sec
d11         0.03000000 sec
DELTA       1.89999998 sec
TD0                  100

======== CHANNEL f1 ========
NUC1                 13C
P1               10.25 usec
PL1               4.70 dB
SFO1      150.9251924 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2            80.00 usec
PL2               0.33 dB
PL12             18.50 dB
PL13             21.50 dB
SFO2      600.1539010 MHz

F2 - Processing parameters
SI                 65536
SF        150.9078380 MHz
WDW                   EM
SSB                    0
LB                3.00 Hz
GB                     0
PC                  1.00
```

^{13}C NMR Spectrum (150 MHz, CDCl$_3$) of Compound **17a**.



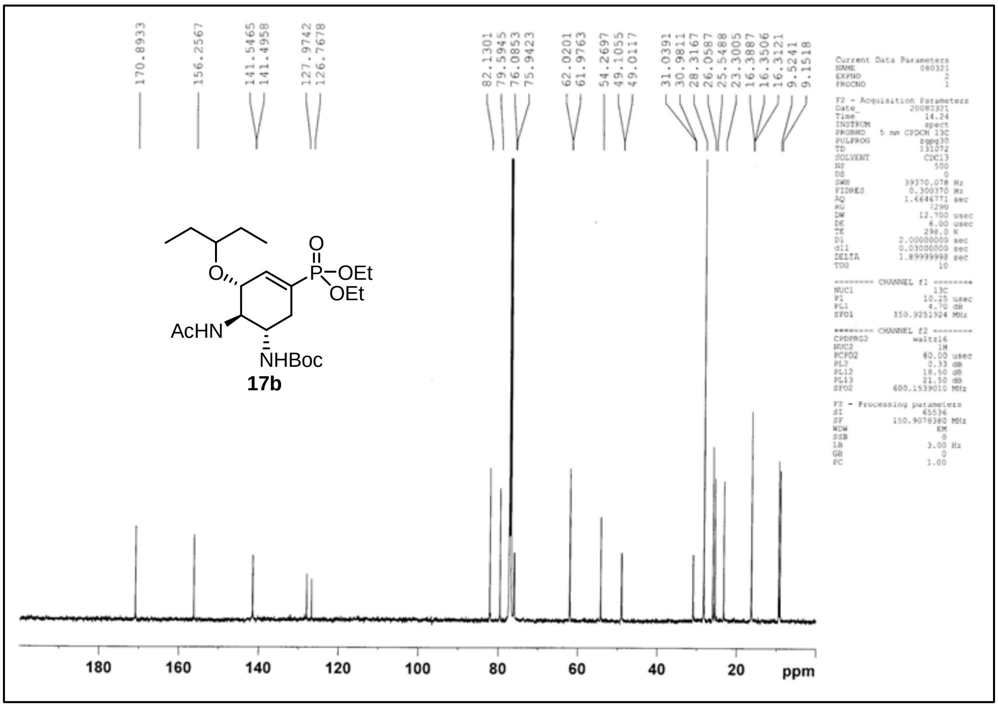
```
Current Data Parameters
NAME              080321
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080324
Time               15.00
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    24
DS                     0
SWH           8389.262 Hz
FIDRES        0.256020 Hz
AQ           1.9530824 sec
RG                  12.7
DW             59.600 usec
DE               6.00 usec
TE               297.9 K
D1          2.00000000 sec
TD0                    3

======== CHANNEL f1 ========
NUC1                  1H
P1               10.00 usec
PL1               0.33 dB
SFO1      600.1536010 MHz

F2 - Processing parameters
SI                 16384
SF        600.1500270 MHz
WDW                   EM
SSB                    0
LB                0.00 Hz
GB                     0
PC                  1.00
```

^{1}H NMR Spectrum (600 MHz, CDCl$_3$) of Compound **17b**.



```
Current Data Parameters
NAME              080321
EXPNO                  2
PROCNO                 1

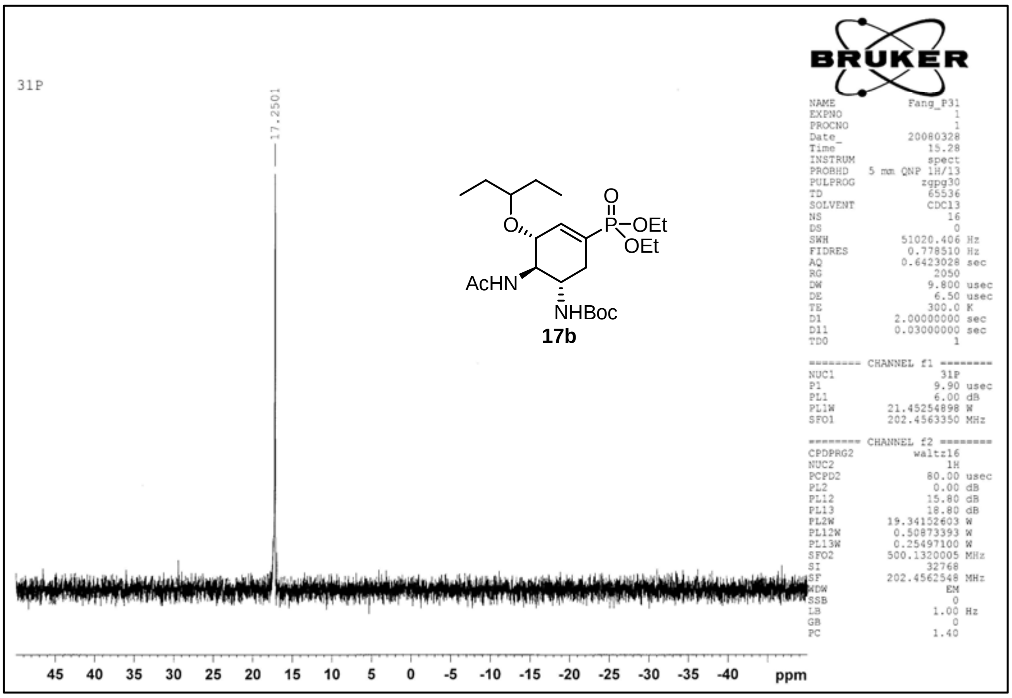
F2 - Acquisition Parameters
Date_           20080321
Time               14.24
INSTRUM            spect
PROBHD   5 mm CPDCH 13C
PULPROG          zgpg30
TD                131072
SOLVENT            CDCl3
NS                   500
DS                     0
SWH            39370.078 Hz
FIDRES          0.300370 Hz
AQ             1.6646771 sec
RG                  7290
DW                12.700 usec
DE                  6.00 usec
TE                 298.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                   10

======== CHANNEL f1 ========
NUC1                 13C
P1                 10.25 usec
PL1                 4.70 dB
SFO1         150.9251924 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 0.33 dB
PL12               18.50 dB
PL13               21.50 dB
SFO2         600.1539010 MHz

F2 - Processing parameters
SI                 65536
SF           150.9078380 MHz
WDW                   EM
SSB                    0
LB                  3.00 Hz
GB                     0
PC                  1.00
```

^{13}C NMR Spectrum (150 MHz, CDCl$_3$) of Compound **17b**.

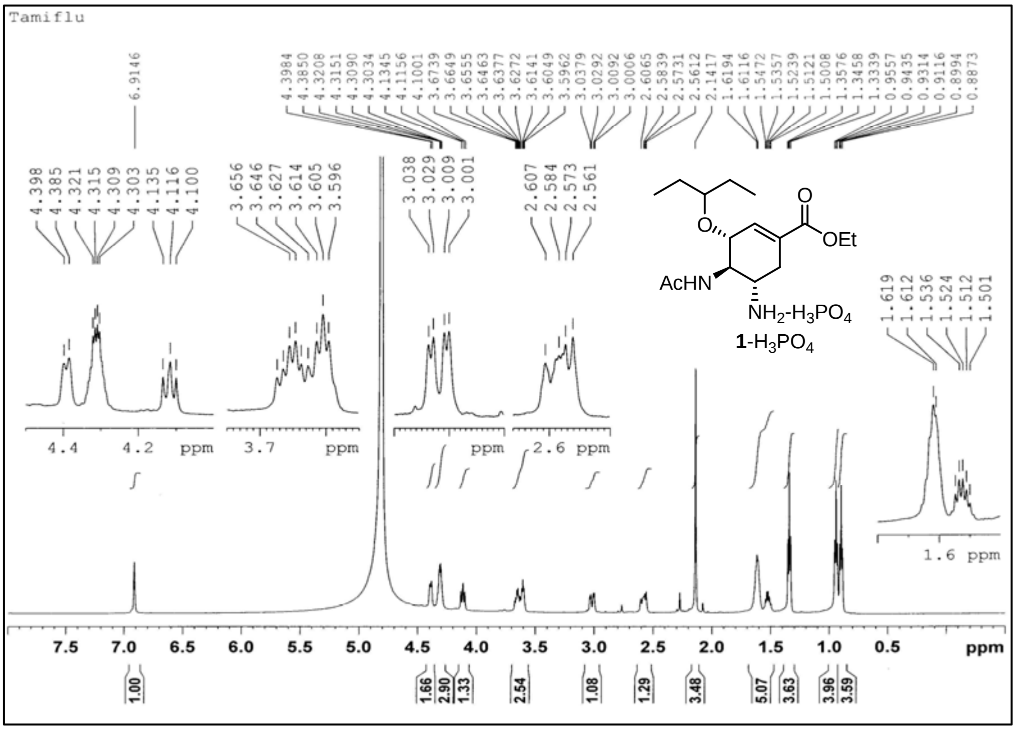


```
NAME           Fang_P31
EXPNO                 1
PROCNO                1
Date_          20080328
Time              15.28
INSTRUM           spect
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    0
SWH           51020.406 Hz
FIDRES         0.778510 Hz
AQ            0.6423028 sec
RG                 2050
DW                9.800 usec
DE                 6.50 usec
TE                300.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

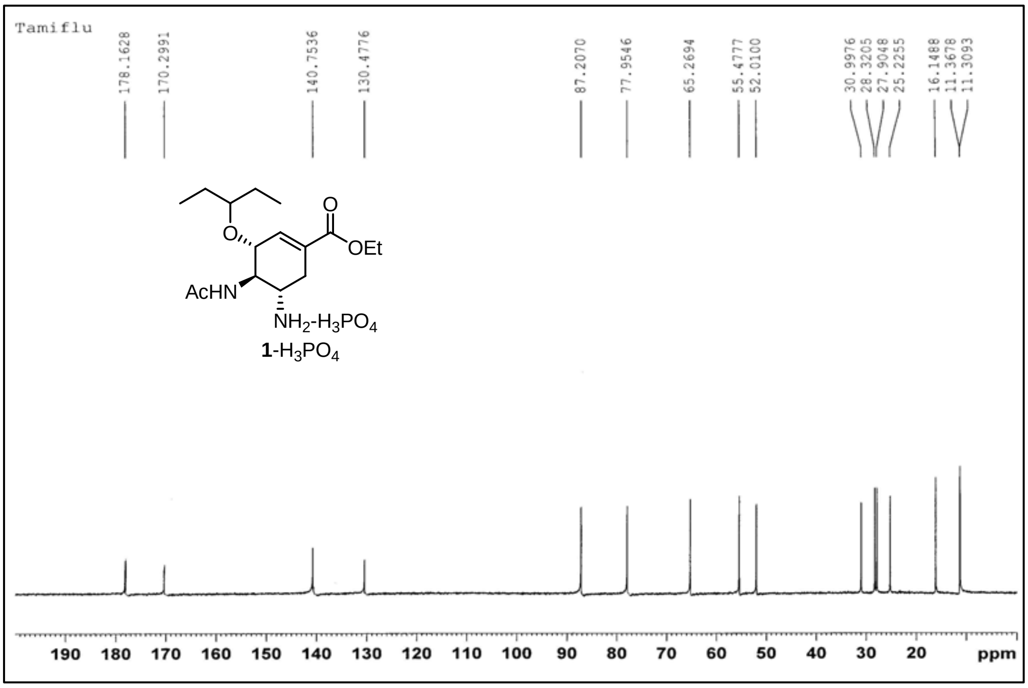
======== CHANNEL f1 ========
NUC1                31P
P1                 9.90 usec
PL1                6.00 dB
PL1W        21.45254898 W
SFO1        202.4563350 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2                0.00 dB
PL12              15.80 dB
PL13              18.80 dB
PL2W        19.34152603 W
PL12W        0.50873393 W
PL13W        0.25497100 W
SFO2        500.1320005 MHz
SI                32768
SF          202.4562548 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

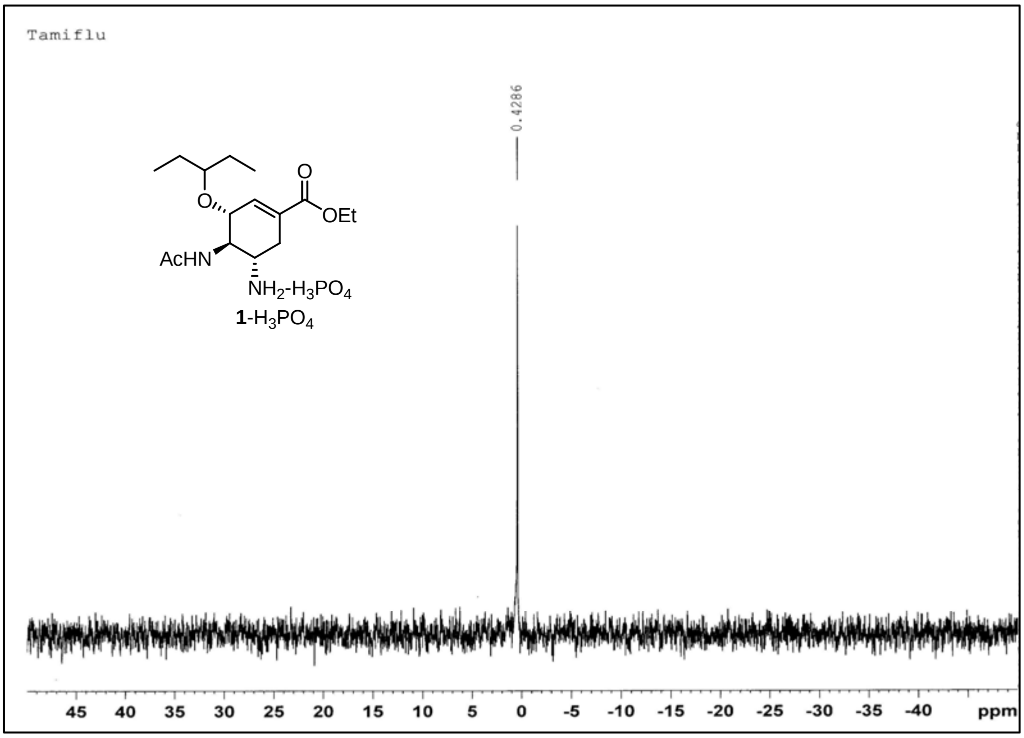
^{31}P NMR Spectrum (202 MHz, CDCl$_3$) of Compound **17b**.



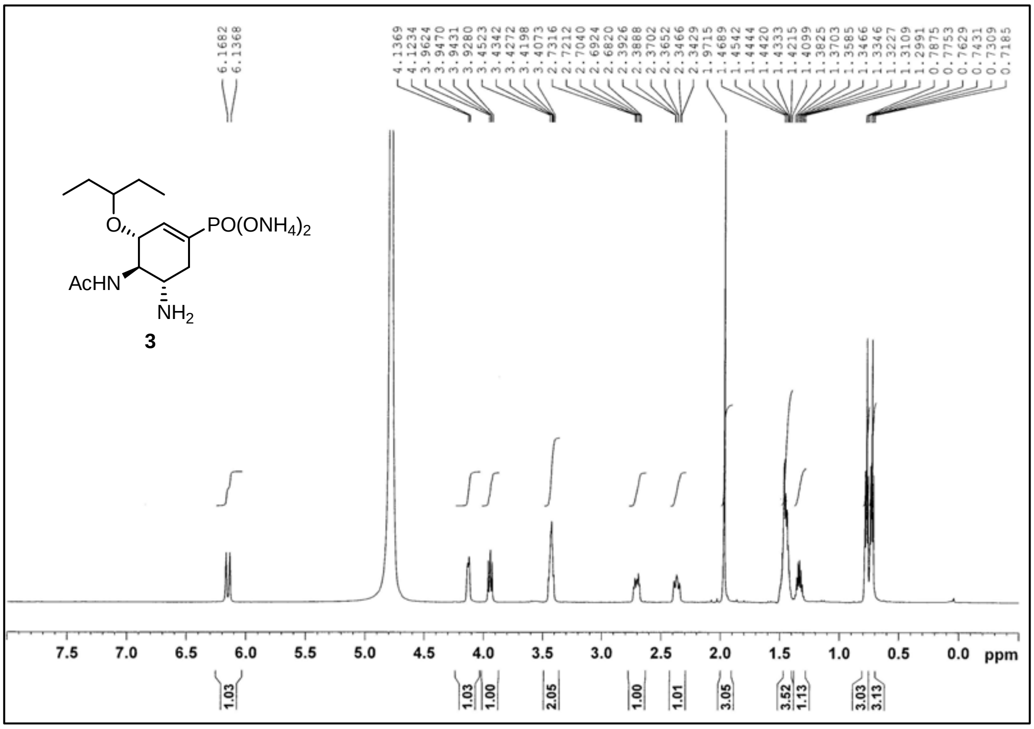
^{1}H NMR Spectrum (600 MHz, D_2O) of Tamiflu (**1**·H_3PO_4).



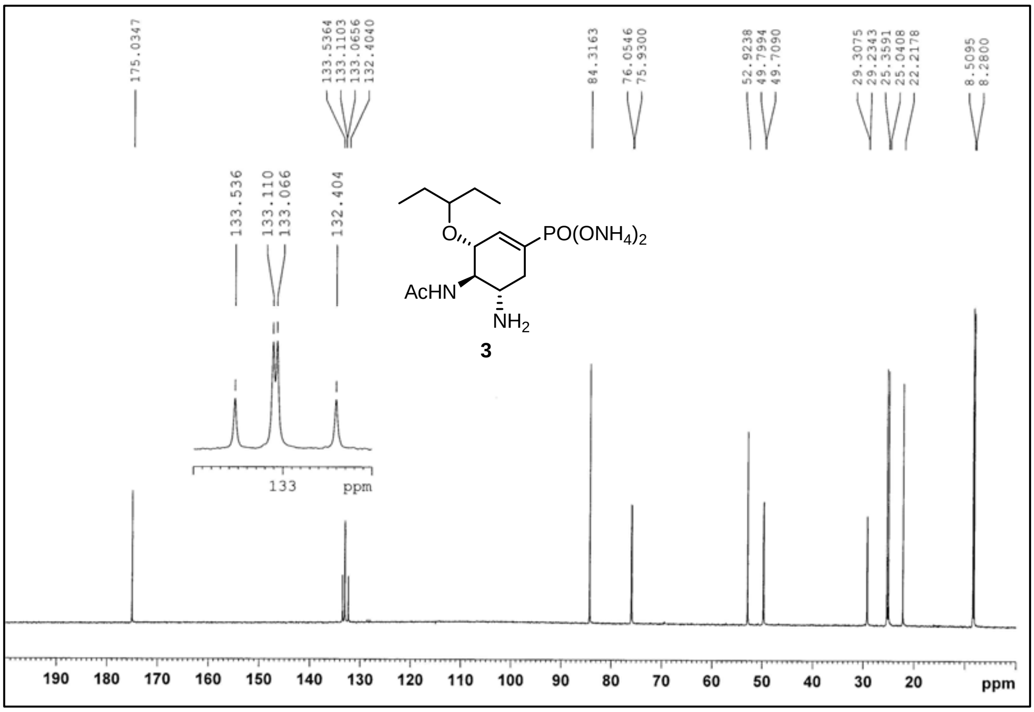
^{13}C NMR Spectrum (150 MHz, D_2O) of Tamiflu (**1**·H_3PO_4).



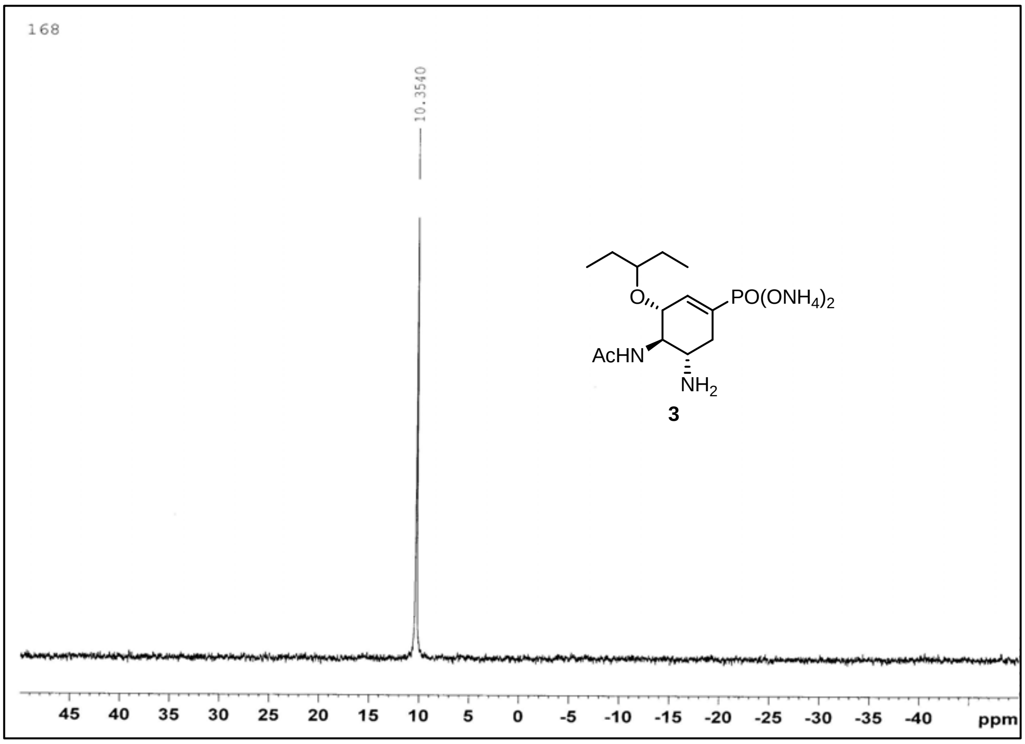
^{31}P NMR Spectrum (162 MHz, D_2O) of Tamiflu (**1**·H_3PO_4).



^{1}H NMR Spectrum (600 MHz, D_2O) of Tamiphosphor (**3**).



^{13}C NMR Spectrum (150 MHz, D_2O) of Tamiphosphor (**3**).



^{31}P NMR Spectrum (162 MHz, D_2O) of Tamiphosphor (**3**).