Electronic Supplementary Information

Synthesis of *N*-Dialkylphosphoryl Iminosugar Derivatives and Their Immunosuppressive Activities

Xuemei Yang,[+a,b] De-Cai Xiong,[+a] Chengcheng Song,[a,c] Guihua Tai[c] and Xin-Shan Ye[*a]

[a]State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Xue Yuan Road No. 38, Beijing 100191, China. E-mail: xinshan@bjmu.edu.cn; Fax: +86-10-82802724; Tel: +86-10-82805736.

[b]School of Pharmacy, Guangdong Medical College, Dongguan 523808, China.

[c]School of Life Sciences, Northeast Normal University, Changchun 130024, China.

[+]These authors contributed equally to this work.

Table of contents

Chemistry Section

General. All chemicals were purchased as reagent grade and used without further purification except otherwise noted. Dichloromethane (CH_2Cl_2) and acetonitrile (CH_3CN) were distilled over calcium hydride (CaH_2). Tetrahydrofuran (THF) was distilled over sodium potassium alloy. Methanol was distilled from magnesium. Pulverized molecular sieves 3Å MS for reductive amination were activated by heating at 400 ^oC for 6 hours. Reactions were monitored by thin-layer chromatography (TLC) analysis, which was visualized by UV light (254 nm) and acidic ceric ammonium molybdate. Solvents were evaporated under reduced pressure and below 40 ^oC (water bath). Column chromatography was performed on silica gel. ^1H NMR spectra were recorded on the Avance III 400 instruments from Bruker at room temperature. Chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0 ppm) in deuterated chloroform. ^{13}C NMR spectra were obtained by using the same NMR spectrometers and were calibrated with $CDCl_3$ (δ = 77.16 ppm). HRMS (ESI) data were obtained by Thermo Scientific LTQ Orbitrap Discovery mass spectrometer or Waters Xevo G2 QT of mass spectrometer.

***N*-Benzyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (13)**

According to the method reported in the literature,[1] 2,3-*O*-isopropylidene-D-ribose (**11**) was prepared from D-ribose (15.0 g, 0.10 mol), dry acetone (180 mL), anhydrous $CuSO_4$ (47.88 g, 0.30 mol) and sulfuric acid (0.45 mL). Yield: 12.41 g (65%).

To a solution of $NaIO_4$ (10.95 g in 50 mL of H_2O, 51.2 mmol) at 0 ^oC, a solution of compound **11** (4.674 g in 10 mL of H_2O, 24.6 mmol) was added dropwise. The reaction mixture was stirred at 0 ^oC for 30 min and then kept at room temperature for another 4 h. After the disappearence of the starting material derected by TLC (petroleum ether/EtOAc = 1:2), the reaction mixture was directly concentrated under reduced pressure. The residue was diluted with EtOAc (150 mL) and then filtered through a celite pad. The filtrate was evaporated under vacuum to give a colorless oil **12**, which was used directly in the next step without further purification.

To a solution of activated 3Å molecular sieves, $NaBH_3CN$ (6.18 g, 98.4 mmol) and anhydrous $ZnCl_2$ (4.02 g, 29.5 mmol) containing 90 mL of anhydrous MeOH at 0 ^oC, a solution of **12** containing 10 mL of anhydrous MeOH was added dropwise, which was followed by the addition of a solution of $BnNH_2$ (3.5 mL in 20 mL of anhydrous MeOH, 32.0 mmol). The reaction mixture was stirred at 0 ^oC for 30 min and then stirred at room temperature overnight. After the disappearence of the starting material derected by TLC (petroleum ether/EtOAc = 2:1), the reaction mixture was filtered through a celite pad, and then the solvent was evaporated under reduced pressure. The residue was diluted with 100 mL of ammonia water (1 M), and then extracted with EtOAc (50 mL×4). The combined rganic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with petroleum ether/acetone (12:1) to give compound **13** (4.88 g, 85% yield, R_f = 0.57, petroleum ether/acetone, 2:1, v/v) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.21-7.35 (m, 5H, ph), 4.63-4.66 (m, 2H, 2OC*H*), 3.62 (s, 2H, ph-CH_2), 3.04 (d, *J* = 11.6 Hz, 2H, 2C*H*H), 2.14 (ddd, *J* = 11.4 Hz, *J* = 3.0 Hz, *J* = 1.3 Hz, 2H, 2C*H*H), 1.57 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). The ^1H NMR data coincide with the previous report.[2]

2,3-*O*-Isopropylidene-1,4-dideoxy-1,4-iminoerythritol (9)

A mixture of compound **13** (238.8 mg, 1.0 mmol) and $Pd(OH)_2/C$ (20% Pd, 450.0 mg) in dry THF (3.0 mL) was stirred under an atmosphere of 0.4 MPa H_2 at room temperature for 2 days. After TLC (CH_2Cl_2/MeOH 20:1) showed the complete consumption of **13** (R_f = 0.72), the reaction mixture was filtered through a celite pad, then the filtrate was concentrated under reduced pressure to afford the compound **9** as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.63-4.66 (m, 2H, 2OC*H*), 3.10 (d, *J* = 14 Hz, 2H, 2C*H*HN), 2.52 (dd, *J* = 13.6 Hz, *J* = 1.2 Hz, 2H, 2C*H*HN), 2.19 (br s, 1H, N*H*), 1.45 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). The ^1H NMR data coincide with the

previous report.[2]

General procedure A for the synthesis of compounds 15j-15l:

To a solution of alcohol (1.0 equiv.) in dry pyridine (8 mL) at 0 ^{o}C, diphenyl phosphite (3.0 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 1 h, which was followed by the addition of methanol (5.0 equiv.). After stirring for an additional 1 h, 2 N hydrochloric acid (60 mL) was added. The resulting solution was extracted with ethyl acetate (50 mL×3). The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by column chromatography on silica gel eluted with petroleum ether/EtOAc to give the compounds **15j-15l**.

Methyl octyl phosphite (15j)

The reaction of *n*-octanol (0.50 mL, 3.17 mmol) with diphenyl phosphite (1.83 mL, 9.51 mmol) and methanol (0.64 mL, 15.85 mmol) was performed as described in the general procedure A, affording **15j** (0.61 g, 93% yield, R_f = 0.25, petroleum ether/EtOAc, 1:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 0.5H, P*H*), 5.92 (s, 0.5H, P*H*), 4.05-4.11 (m, 2H, 2OCH_2), 3.78 (d, *J* = 12 Hz, 3H, 2OCH_3), 1.66-1.73 (m, 2H, 2OCH$_2$CH_2), 1.28-1.40 (m, 10H, 5CH_2), 0.88 (t, *J* = 6.8 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 66.02, 65.96, 51.95, 51.90, 31.76, 30.46, 30.40, 29.16, 29.08, 25.49, 22.64, 14.09; ^{31}P NMR (162 MHz, $CDCl_3$): δ 11.25, 6.96. HRMS (ESI) calcd. for $C_9H_{21}O_3P$ $[M+Na]^+$: 231.1121, found: 231.1117.

Methyl nonyl phosphite (15k)

The reaction of *n*-nonanol (0.50 mL, 2.87 mmol) with diphenyl phosphite (1.65 mL, 8.60 mmol) and methanol (0.58 mL, 14.35 mmol) was performed as described in the general procedure A, affording **15k** (0.57 g, 90% yield, R_f = 0.27, petroleum ether/EtOAc, 1:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.66 (s, 0.5H, P*H*), 5.92 (s, 0.5H, P*H*), 4.05-4.11 (m, 2H, 2OCH_2), 3.77 (d, *J* = 12 Hz, 3H, 2OCH_3), 1.66-1.73 (m, 2H, 2OCH$_2$CH_2), 1.27-1.39 (m, 12H, 6CH_2), 0.88 (t, *J* = 6.8 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 66.12, 66.06, 52.01, 51.96, 31.93, 30.56, 30.50, 29.54, 29.29, 29.20, 25.58, 22.75, 14.17; ^{31}P NMR (162 MHz, $CDCl_3$) δ 11.29, 7.00. HRMS (ESI) calcd for $C_{10}H_{23}O_3P$ $[M+Na]^+$: 245.1277, found: 245.1274.

Methyl decyl phosphite (15l)

The reaction of *n*-decanol (0.50 mL, 2.87 mmol) with diphenyl phosphite (1.65 mL, 8.60 mmol) and methanol (0.64 mL, 15.85 mmol) was performed as described in the general procedure A, affording **15l** (0.55 g, 87% yield, R_f = 0.27, petroleum ether/EtOAc, 1:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 0.5H, P*H*), 5.92 (s, 0.5H, P*H*), 4.05-4.11 (m, 2H, 2OCH_2), 3.77 (d, *J* = 11.6 Hz, 3H, 2OCH_3), 1.66-1.73 (m, 2H, 2OCH$_2$CH_2), 1.27-1.39 (m, 14H, 7CH_2), 0.88 (t, *J* = 6.8 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 66.14, 66.08, 52.06, 52.00, 31.99, 30.57, 30.51, 29.61, 29.60, 29.40, 29.22, 25.59, 22.79, 14.22; ^{31}P NMR (162 MHz, $CDCl_3$) δ 11.28, 6.99. HRMS (ESI) calcd for $C_{11}H_{25}O_3P$ $[M+Na]^+$: 259.1434, found: 259.1429.

General procedure B for the preparation of compounds 14b-h: To a stirred solution of alcohol (3.0 equiv.) in dry CH_2Cl_2 (5 mL) at 0 ^{o}C under N_2, a solution of phosphorus trichloride (3.0 equiv.) in dry CH_2Cl_2 (2 mL) was added dropwise over a period of 30 min. Blowing air constantly, the reaction mixture was stirred at this temperature for 30 min, then allowed to warm up to room temperature for an additional 3 h. After a solution of trichloroisocyanuric acid (0.45 equiv. in 10 mL of dry CH_3CN) was added dropwise at 0 ^{o}C, the resulting solution was allowed to warm up to room temperature and stirred overnight. The reaction mixture was filtered through a celite pad to remove cyanuric acid. The filtrate was concentrated under vacuum to afford the crude product **14b-l**.

General procedure B for the preparation of compounds 14j-l: To a solution of compound **15j-l** (1.0 equiv.) in dry CH_3CN (0.5 mL) at 0 ^oC, a solution of trichloroisocyanuric acid (1.0 equiv. in 0.5 mL of dry CH_3CN) was added dropwise. The resulting solution was allowed to warm up to room temperature and stirred overnight. The reaction mixture was filtered through a celite pad to remove cyanuric acid. The filtrate was concentrated under vacuum to afford the crude product **14j-l**.

General procedure C for the synthesis of compounds 16a-16l: To a mixture of compound **9** (1.0 equiv.) and DIPEA (5.0 equiv.) in THF (10 mL) at 0 ^oC, the compound **14a-l** (3.0 equiv.) in dry THF (2 mL) was added dropwise. After stirred at 0 ^oC for 30 min, the reaction mixture was stirred for an additional 4 h at room temperature. The resulting solution was filtered through a celite pad and then evaporated. The syrup was diluted with saturated $NaHCO_3$ (40 mL), and extracted with EtOAc (50 mL×4). The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by column chromatography on silica gel eluted with petroleum ether/EtOAc to give the compound **16a-l**.

***N*-Diethylphosphoryl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (16a)**

Compound **16a** was prepared from compound **9** starting from compound **13** (200.6 mg, 0.86 mmol), and **14a** (445.3 mg 2.58 mmol) as described in the general procedure C, affording **16a** (112.8 mg, 47% yield, two steps from compound **13**, R_f = 0.19, petroleum ether/acetone, 2:1, v/v) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.68-4.70 (br m, 2H, 2OC*H*), 4.05-4.12 (m, 4H, 2OC$H_2$$CH_3$), 3.49 (dd, *J* = 12 Hz, *J* = 2 Hz, 2H, 2NC*H*HCH), 3.03 (d, *J* = 12 Hz, 2H, 2NC*H*HCH), 1.47 (s, 3H, CCH_3), 1.31-1.34 (m, 9H, 2CH_2CH_3, CCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.64, 80.26, 80.15, 62.53, 62.48, 52.98, 52.94, 26.31, 24.53, 16.35, 16.29; ^{31}P NMR (162 MHz, $CDCl_3$): δ 6.38. HRMS (ESI) calcd for $C_{11}H_{22}NO_5P$ $[M+H]^+$: 302.1128; found: 302.1123.

***N*-Dibutylphosphoryl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (16b)**

Compound **16b** was prepared from compound **9** starting from compound **13** (233.2 mg 1.0 mmol), and the crude product **14b** (686 mg, 3.0 mmol) as described in the general procedure B and C, affording **16b** (173.0 mg, 52% yield, two steps from compound **13**, R_f = 0.20, petroleum ether/acetone, 2:1, v/v) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.68-4.70 (br m, 2H, 2OC*H*), 3.95-4.06 (m, 4H, 2OC$H_2$$CH_2$), 3.46-3.50 (dd, *J* = 12 Hz, *J* = 2 Hz, 2H, 2NC*H*HCH), 3.01-3.04 (dd, *J* = 12 Hz, *J* = 2.4 Hz, 2H, 2NC*H*HCH), 1.62-1.69 (m, 4H, 2OCH_2CH_2), 1.47 (s, 3H, CCH_3), 1.35-1.44 (m, 4H, 2C$H_2$$CH_3$), 1.31 (s, 3H, CC$H_3$), 0.93 (t, *J* = 7.2 Hz, 6H, 2CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.73, 80.31, 80.04, 66.33, 66.28, 53.04, 53.00, 32.56, 32.49, 26.42, 24.61, 18.93, 13.79; ^{31}P NMR (162 MHz, $CDCl_3$): δ 6.47. HRMS (ESI) calcd for $C_{15}H_{30}NO_5P$ $[M+Na]^+$: 358.1754; found: 358.1748.

***N*-Dihexylphosphoryl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (16c)**

Compound **16c** was prepared from compound **9** starting from compound **13** (137.2 mg, 0.59 mmol), and the crude product **14c** (513.2 mg, 1.80 mmol) as described in the general procedure B and C, affording **16c** (101.0 mg, 44% yield, two steps from compound **13**, R_f = 0.23, petroleum ether/acetone, 3:1, v/v) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.69 (br s, 2H, 2OC*H*), 3.96-4.02 (m, 4H, 2OC$H_2$$CH_2$), 3.48 (dd, *J* = 12.4 Hz, *J* = 2 Hz, 2H, 2NC*H*HCH), 3.02 (d, *J* = 11.6 Hz, 2H, 2NC*H*HCH), 1.63-1.70 (m, 4H, 2OCH_2CH_2), 1.47 (s, 3H, CCH_3), 1.25-1.39 (m, 15H, 6CH_2, CCH_3), 0.89 (t, *J* = 6.8 Hz, 6H, 2CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.65, 80.26, 80.15, 66.60, 66.54, 52.99, 52.95, 31.48, 30.44, 30.37, 26.38, 25.32, 24.55, 22.65, 14.11; ^{31}P NMR (162 MHz, $CDCl_3$): δ 6.46. HRMS (ESI) calcd for $C_{19}H_{38}NO_5P$ $[M+Na]^+$: 414.2380; found: 414.2381.

***N*-Diheptylphosphoryl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (16d)**

Compound **16d** was prepared from compound **9** starting from compound **13** (149.3 mg, 0.64 mmol), and the crude

product **14d** (600.5 mg, 1.92 mmol) as described in the general procedure B and C, affording **16d** (153.3 mg, 58% yield, two steps from compound **13**, R_f = 0.20, petroleum ether/ EtOAc, 1:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.68-4.69 (br m, 2H, 2OC*H*), 3.93-4.04 (m, 4H, 2OCH_2CH_2), 3.47 (d, *J* =12 Hz, *J* = 2 Hz, 2H, 2NC*H*HCH), 3.02 (d, *J* = 11.2 Hz, 2H, 2NC*H*HCH), 1.63-1.70 (m, 4H, 2OCH$_2$CH_2), 1.47 (s, 3H, CCH_3), 1.28-1.32 (m, 19H, 8CH_2, CCH_3), 0.88 (t, *J* = 7.2 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.72, 80.30, 80.20, 66.65, 66.59, 53.03, 52.99, 31.87, 30.53, 30.46, 29.01, 26.44, 25.66, 24.62, 22.71, 14.19; ^{31}P NMR (162 MHz, $CDCl_3$): δ 6.46. HRMS (ESI) calcd for $C_{21}H_{43}NO_5P$ $[M+H]^+$: 420.2879; found: 420.2874.

***N*-Dioctylphosphoryl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (16e)**

Compound **16e** was prepared from compound **9** starting from compound **13** (126.0 mg, 0.54 mmol), and the crude product **14e** (552.3 mg, 1.62 mmol) as described in the general procedure B and C, affording **16e** (89.5 mg, 40% yield, two steps from compound **13**, R_f = 0.20, petroleum ether/ EtOAc, 1:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.66-4.69 (br m, 2H, 2OC*H*), 3.93-4.05 (m, 4H, 2OCH_2CH_2), 3.47 (dd, *J* = 12.4 Hz, *J* = 2 Hz, 2H, 2NC*H*HCH), 3.03 (d, *J* = 11.2 Hz, 2H, 2NC*H*HCH), 1.63-1.69 (m, 4H, 2OCH$_2$CH_2), 1.47 (s, 3H, CCH_3), 1.27-1.37 (m, 23H, 10CH_2, CCH_3), 0.88 (t, *J* = 6.8 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.74, 80.32, 80.21, 66.66, 66.61, 53.05, 53.01, 31.93, 30.55, 30.48, 29.34, 29.32, 26.46, 25.71, 24.64, 22.78, 14.23; ^{31}P NMR (162 MHz, $CDCl_3$): δ 6.46. HRMS (ESI) calcd for $C_{23}H_{46}NO_5P$ $[M+Na]^+$: 470.3006; found: 470.3007.

***N*-Dinonylphosphoryl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (16f)**

Compound **16f** was prepared from compound **9** starting from compound **13** (149.3 mg, 0.64 mmol), and the crude product **14f** (708.3 mg, 1.92 mmol) as described in the general procedure B and C, affording **16f** (150.3 mg, 50% yield, two steps from compound **13**, R_f = 0.30, petroleum ether/ EtOAc, 1:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.67-4.69 (br m, 2H, 2OC*H*), 3.93-4.04 (m, 4H, 2OCH_2CH_2), 3.47 (dd, *J* = 12 Hz, *J* = 2 Hz, 2H, 2NC*H*HCH), 3.03 (d, *J* = 11.2 Hz, 2H, 2NC*H*HCH), 1.62-1.69 (m, 4H, 2OCH$_2$CH_2), 1.47 (s, 3H, CCH_3), 1.27-1.33 (m, 23H, 10CH_2, CCH_3), 0.88 (t, *J* = 7.2 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.74, 80.32, 80.21, 66.66, 66.60, 53.05, 53.01, 32.00, 30.55, 30.48, 29.64, 29.37, 29.36, 26.47, 25.71, 24.64, 22.80, 14.23; ^{31}P NMR (162 MHz, $CDCl_3$): δ 6.46. HRMS (ESI) calcd for $C_{25}H_{50}NO_5P$ $[M+H]^+$: 476.3499; found: 476.3512.

***N*-Didecylphosphoryl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (16g)**

Compound **16g** was prepared from compound **9** starting from compound **13** (168.0 mg, 0.72 mmol), and the crude product **14g** (857.5 mg, 2.16 mmol) as described in the general procedure B and C, affording **16g** (176.7 mg, 49% yield, two steps from compound **13**, R_f = 0.30, petroleum ether/ EtOAc, 1:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.69 (br s, 2H, 2OC*H*), 3.95-4.03 (m, 4H, 2OCH_2CH_2), 3.47 (dd, *J* = 12 Hz, *J* = 2 Hz, 2H, 2NC*H*HCH), 3.03 (d, *J* = 11.6 Hz, 2H, 2NC*H*HCH), 1.62-1.69 (m, 4H, 2OCH$_2$CH_2), 1.47 (s, 3H, CCH_3), 1.26-1.34 (m, 31H, 14CH_2, CCH_3), 0.88 (t, *J* = 6.8 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.74, 80.32, 80.21, 66.65, 66.59, 53.04, 53.01, 32.03, 30.55, 30.48, 29.68, 29.44, 29.35, 26.46, 25.71, 24.63, 22.82, 14.24; ^{31}P NMR (162 MHz, $CDCl_3$): δ 6.45. HRMS (ESI) calcd for $C_{27}H_{54}NO_5P$ $[M+Na]^+$: 526.3632; found: 526.3611.

***N*-Didodecylphosphoryl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (16h)**

Compound **16h** was prepared from compound **9** starting from compound **13** (149.3 mg, 0.64 mmol), and the crude product **14h** (870.0 mg, 1.92 mmol) as described in the general procedure B and C, affording **16h** (125.8 mg, 35% yield, two steps, two steps from compound **13**, R_f = 0.25, petroleum ether/ EtOAc, 1:1, v/v) as a colorless oil. ^{1}H

NMR (400 MHz, $CDCl_3$): δ 4.67-4.69 (br m, 2H, 2OC*H*), 3.95-4.03 (m, 4H, 2OCH_2CH_2), 3.48 (dd, *J* = 12 Hz, *J* = 2 Hz, 2H, 2NC*H*HCH), 3.02 (d, *J* = 11.2 Hz, 2H, 2NC*H*HCH), 1.62-1.69 (m, 4H, 2OCH$_2$CH_2), 1.47 (s, 3H, CCH_3), 1.26-1.31 (m, 39H, 18CH_2, CCH_3), 0.88 (t, *J* = 6.8 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.71, 80.30, 80.19, 66.63, 66.57, 52.03, 52.99, 32.05, 30.53, 30.46, 29.77, 29.71, 29.68, 29.48, 29.34, 26.44, 25.70, 24.61, 22.82, 14.24; ^{31}P NMR (162 MHz, $CDCl_3$): δ 6.45. HRMS (ESI) calcd for $C_{31}H_{63}NO_5P$ $[M+H]^+$: 560.4444; found: 560.4438.

***N*-Diphenylphosphoryl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (16i)**

Compound **16i** was prepared from compound **9** starting from compound **13** (153.2 mg, 0.66 mmol), and **14i** (531.8 mg, 1.98 mmol) as described in the general procedure C, affording **16i** (156.9 mg, 64% yield, two steps, two steps from compound **13**, R_f = 0.23, petroleum ether/acetone, 1:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13-7.34 (m, 10H, 2ph), 4.69-4.71 (br m, 2H, 2OC*H*), 3.71 (dd, *J* = 12.4 Hz, *J* = 2.8 Hz, 2H, 2NC*H*HCH), 3.17 (m, 2H, 2NC*H*HCH), 1.30 (s, 3H, CCH_3), 1.28 (s, 3H, CCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.01, 150.94, 129.81, 125.04, 120.37, 120.32, 111.99, 80.17, 80.06, 53.41, 53.37, 26.13, 24.58; ^{31}P NMR (162 MHz, $CDCl_3$): δ -3.39. HRMS (ESI) calcd for $C_{19}H_{22}NO_5P$ $[M+Na]^+$: 398.1128; found: 398.1122.

***N*-(Methyl-octyl-phosphoryl)-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (16j)**

Compound **16i** was prepared from compound **9** starting from compound **13** (59.4 mg, 0.24 mmol), and **15j** (79.1 mg, 0.38 mmol) as described in the general procedure B and C, affording **16j** (42.9 mg, 51% yield, two steps from compound **13**, R_f = 0.18, petroleum ether/ EtOAc, 1:3, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.68-4.70 (br m, 2H, 2OC*H*), 3.96-4.04 (m, 2H, OCH_2CH_2), 3.72 (d, *J* = 10.8 Hz, 3H, OCH_3), 3.46-3.51 (m, 2H, 2NC*H*HCH), 3.03 (d, *J* = 12 Hz, 2H, 2NC*H*HCH), 1.62-1.69 (m, 2H, 2OCH$_2$CH_2), 1.48 (s, 3H, CCH_3), 1.27-1.37 (m, 13H, 5CH_2, CCH_3), 0.88 (t, *J* = 6.8 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.75, 80.30, 80.20, 66.82, 66.76, 53.04, 53.01, 31.91, 30.52, 30.46, 29.32, 29.29, 26.42, 25.67, 24.58, 22.77, 14.22; ^{31}P NMR (162 MHz, $CDCl_3$): δ 7.65. HRMS (ESI) calcd for $C_{16}H_{32}NO_5P$ $[M+H]^+$: 350.2091; found: 350.2096.

***N*-(Methyl-nonyl-phosphoryl)-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (16k)**

Compound **16k** was prepared from compound **9** starting from compound **13** (32.7 mg, 0.14 mmol), and **15k** (46.7 mg, 0.21 mmol) as described in the general procedure B and C, affording **16k** (25.2 mg, 50% yield, two steps from compound **13**, R_f = 0.22, petroleum ether/EtOAc, 1:3, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.69-4.70 (br m, 2H, 2OC*H*), 3.97-4.03 (m, 2H, OCH_2CH_2), 3.72 (d, *J* = 11.2 Hz, 3H, OCH_3), 3.46-3.51 (m, 2H, 2NC*H*HCH), 3.03 (d, *J* = 11.6 Hz, 2H, 2NC*H*HCH), 1.63-1.70 (m, 2H, 2OCH$_2$CH_2), 1.48 (s, 3H, CCH_3), 1.27-1.33 (m, 15H, 6CH_2, CCH_3), 0.88 (t, *J* = 6.8 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.74, 80.30, 80.19, 66.82, 66.76, 53.24, 53.18, 53.04, 53.01, 52.97, 31.99, 30.53, 30.46, 29.62, 29.36, 29.34, 26.42, 25.67, 24.58, 22.84, 14.24; ^{31}P NMR (162 MHz, $CDCl_3$): δ 8.42. HRMS (ESI) calcd for $C_{17}H_{34}NO_5P$ $[M+H]^+$: 364.2247; found: 364.2257.

***N*-(Methyl-decyl-phosphoryl)-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-iminoerythritol (16l)**

Compound **16l** was prepared from compound **9** starting from compound **13** (151.6 mg, 0.65 mmol), and **15l** (231.6 mg, 0.98 mmol) as described in the general procedure B and C, affording **16l** (97.9 mg, 40% yield, two steps from compound **13**, R_f = 0.29, petroleum ether/EtOAc, 1:3, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.68-4.70 (br m, 2H, 2OC*H*), 3.96-4.03 (m, 2H, OCH_2CH_2), 3.72 (d, *J* = 11.2 Hz, 3H, OCH_3), 3.46-3.51 (m, 2H, 2NC*H*HCH), 3.03 (d, *J* = 12 Hz, 2H, 2NC*H*HCH), 1.62-1.70 (m, 2H, 2OCH$_2$CH_2), 1.47 (s, 3H, CCH_3), 1.26-1.35 (m, 15H, 6CH_2, CCH_3), 0.88 (t, *J* = 6.8 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.75, 80.31, 80.20,

66.81, 66.76, 53.23, 53.17, 53.05, 53.01, 52.98, 32.03, 30.53, 30.46, 29.68, 29.44, 29.34, 26.43, 25.68, 24.59, 22.82, 14.25; ^{31}P NMR (162 MHz, $CDCl_3$): δ 8.43. HRMS (ESI) calcd for $C_{18}H_{36}NO_5P$ $[M+H]^+$: 378.2404; found: 378.2413.

General procedure D for the preparation of compounds 8a-8l:

The compound **16a-l** was dissolved in 85% AcOH (2.0 mL) under N_2. The resulting solution was stirred at 80 ^oC for 2-4 h until the reaction was complete. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with CH_2Cl_2/MeOH to give the compound **8a-l**.

Diethyl ((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)phosphonate (8a)

Compound **8a** was prepared from compound **16a** (82.0 mg, 0.29 mmol) as described in the general procedure D, affording **8a** (24.3 mg, 35% yield, R_f = 0.18, CH_2Cl_2/MeOH, 10:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23-4.24 (br m, 2H, 2OC*H*), 4.01-4.11 (m, 4H, 2OCH_2CH$_2$), 3.40-3.45 (m, 2H, 2NC*H*HCH), 3.17-3.23 (m, 4H, 2NC*H*HCH, 2O*H*), 1.32 (t, *J* = 6.8 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.83, 71.74, 62.67, 62.61, 51.53, 51.50, 16.38, 16.31; ^{31}P NMR (162 MHz, $CDCl_3$): δ 7.09. HRMS (ESI) calcd for $C_8H_{18}NO_5P$ $[M+H]^+$: 240.0995; found: 240.0992.

Dibutyl ((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)phosphonate (8b)

Compound **8b** was prepared from compound **16b** (27.2 mg, 0.08 mmol) as described in the general procedure D, affording **8b** (10.6 mg, 45% yield, R_f = 0.18, CH_2Cl_2/MeOH, 10:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21-4.22 (br m, 2H, 2OC*H*), 3.93-4.01 (m, 4H, 2OCH_2CH$_2$), 3.65-3.66 (br m, 2H, 2O*H*), 3.38-3.43 (m, 2H, 2NC*H*HCH), 3.16-3.21 (m, 2H, 2NC*H*HCH), 1.61-1.68 (m, 4H, 2OCH$_2$CH_2), 1.35-1.45 (m, 4H, 2CH_2CH$_3$), 0.93 (t, *J* = 7.2 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.77, 71.68, 66.44, 66.38, 51.52, 51.49, 32.51, 32.44, 18.93, 13.79; ^{31}P NMR (162 MHz, $CDCl_3$): δ 7.24. HRMS (ESI) calcd for $C_{12}H_{26}NO_5P$ $[M+Na]^+$: 318.1441; found: 318.1446.

Dihexyl ((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)phosphonate (8c)

Compound **8c** was prepared from compound **16c** (65.1 mg, 0.17 mmol) as described in the general procedure D, affording **8c** (29.5 mg, 51% yield, R_f = 0.33, CH_2Cl_2/MeOH, 15:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.24 (br s, 2H, 2OC*H*), 3.93-4.02 (m, 4H, 2OCH_2CH$_2$), 3.42-3.47 (m, 2H, 2NC*H*HCH), 3.17-3.22 (m, 2H, 2NC*H*HCH), 2.57 (br s, 2H, 2O*H*), 1.62-1.69 (m, 4H, 2OCH$_2$CH_2), 1.25-1.40 (m, 12H, 6CH_2), 0.89 (t, *J* = 6.8 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.74, 71.65, 66.75, 66.70, 51.50, 51.47, 31.49, 30.46, 30.39, 25.36, 22.67, 14.14; ^{31}P NMR (162 MHz, $CDCl_3$): δ 7.22. HRMS (ESI) calcd for $C_{16}H_{34}NO_5P$ $[M+H]^+$: 352.2247; found: 352.2249.

Diheptyl ((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)phosphonate (8d)

Compound **8d** was prepared from compound **16d** (98.7 mg, 0.24 mmol) as described in the general procedure D, affording **8d** (35.4 mg, 40% yield, R_f = 0.19, petroleum ether/acetone, 1:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.22 (br s, 2H, 2OC*H*), 3.90-4.02 (m, 4H, 2OCH_2CH$_2$), 3.39-3.44 (m, 2H, 2NC*H*HCH), 3.32 (br s, 2H, 2O*H*), 3.17-3.22 (m, 2H, 2NC*H*HCH), 1.62-1.69 (m, 4H, 2OCH$_2$CH_2), 1.28-1.32 (m, 16H, 8CH_2), 0.88 (t, *J* = 6.8 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.82, 71.73, 66.78, 66.72, 51.62, 51.58, 31.87, 30.54, 30.48, 29.01, 25.68, 22.72, 14.20; ^{31}P NMR (162 MHz, $CDCl_3$): δ 7.27. HRMS (ESI) calcd for $C_{18}H_{38}NO_5P$ $[M+H]^+$: 380.2566; found: 380.2566.

Dioctyl ((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)phosphonate (8e)

Compound **8e** was prepared from compound **16e** (46.0 mg, 0.10 mmol) as described in the general procedure D, affording **8e** (13.0 mg, 31% yield, R_f = 0.23, CH_2Cl_2/MeOH, 15:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21 (br s, 2H, 2OC*H*), 3.90-4.01 (m, 4H, 2OCH_2CH$_2$), 3.57 (br s, 2H, 2O*H*), 3.38-3.43 (m, 2H, 2NC*H*HCH), 3.17-3.21 (m, 2H, 2NC*H*HCH), 1.62-1.69 (m, 4H, 2OCH$_2$CH_2), 1.27-1.32 (m, 20H, 10CH_2), 0.88 (t, *J* = 6.8 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.83, 71.74, 66.76, 66.71, 51.58, 51.55, 31.93, 30.53, 30.46, 29.34, 29.31, 25.72, 22.78, 14.24; ^{31}P NMR (162 MHz, $CDCl_3$): δ 7.30. HRMS (ESI) calcd for $C_{20}H_{42}NO_5P$ $[M+H]^+$: 408.2873; found: 408.2884.

Dinonyl ((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)phosphonate (8f)

Compound **8f** was prepared from compound **16f** (45.8 mg, 0.08 mmol) as described in the general procedure D, affording **8f** (16.1 mg, 49% yield, R_f = 0.33, CH_2Cl_2/MeOH, 15:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.22-4.23 (br m, 2H, 2OC*H*), 3.91-4.02 (m, 4H, 2OCH_2CH$_2$), 3.40-3.45 (m, 2H, 2NC*H*HCH), 3.17-3.22 (m, 2H, 2NC*H*HCH), 2.90 (br s, 2H, 2O*H*), 1.62-1.67 (m, 4H, 2OCH$_2$CH_2), 1.27-1.37 (m, 20H, 12CH_2), 0.88 (t, *J* = 6.8 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.88, 71.80, 66.79, 66.73, 51.65, 51.61, 32.00, 30.56, 30.49, 29.65, 29.39, 29.36, 25.73, 22.81, 14.25; ^{31}P NMR (162 MHz, $CDCl_3$): δ 7.35. HRMS (ESI) calcd for $C_{22}H_{46}NO_5P$ $[M+H]^+$: 436.3186; found: 436.3201.

Didecyl ((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)phosphonate (8g)

Compound **8g** was prepared from compound **16g** (31.2 mg, 0.06 mmol) as described in the general procedure D, affording **8g** (15.4 mg, 54% yield, R_f = 0.20, CH_2Cl_2/MeOH, 20:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.25 (m, 2H, 2OC*H*), 3.92-4.02 (m, 4H, 2OCH_2CH$_2$), 3.67 (br s, 2H, 2O*H*), 3.38-3.43 (m, 2H, 2NC*H*HCH), 3.19-3.24 (m, 2H, 2NC*H*HCH), 1.62-1.69 (m, 4H, 2OCH$_2$CH_2), 1.26-1.34 (m, 28H, 14CH_2), 0.88 (t, *J* = 6.8 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.85, 71.76, 66.91, 66.85, 51.66, 51.63, 32.04, 30.55, 30.48, 29.71, 29.46, 29.38, 25.74, 22.83, 14.26; ^{31}P NMR (162 MHz, $CDCl_3$): δ 7.28. HRMS (ESI) calcd for $C_{24}H_{50}NO_5P$ $[M+H]^+$: 464.3499, found: 464.3502.

Didodecyl ((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)phosphonate (8h)

Compound **8h** was prepared from compound **16h** (87.7 mg, 0.16 mmol) as described in the general procedure D, affording **8h** (32.4 mg, 40% yield, R_f = 0.18, CH_2Cl_2/MeOH, 20:1, v/v) as a pale yellow solid. M.p. 42-43 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21 (br s, 2H, 2OC*H*), 3.91-4.01 (m, 4H, 2OCH_2CH$_2$), 3.56 (br s, 2H, 2O*H*), 3.38-3.43 (m, 4H, 2NC*H*HCH), 3.17-3.21 (m, 2H, 2NC*H*HCH), 1.63-1.67 (m, 4H, 2OCH$_2$CH_2), 1.26-1.34 (m, 36H, 18CH_2), 0.88 (t, *J* = 6.8 Hz, 6H, 2CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.74, 71.65, 66.78, 66.72, 51.53, 51.50, 32.05, 30.55, 30.48, 29.79, 29.77, 29.74, 29.69, 29.48, 29.37, 25.73, 22.81, 14.22; ^{31}P NMR (162 MHz, $CDCl_3$): δ 7.28. HRMS (ESI) calcd for $C_{28}H_{58}NO_5P$ $[M+H]^+$: 520.4131, found: 520.4123.

Diphenyl ((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)phosphonate (8i)

Compound **8i** was prepared from compound **16i** (35.4 mg, 0.09 mmol) as described in the general procedure D, affording **8i** (24.2 mg, 77% yield, R_f = 0.35, CH_2Cl_2/MeOH, 15:1, v/v) as a white solid. M.p. 113-114 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.15-7.36 (m, 10H, 2ph), 4.15-4.16 (br s, 2H, 2OC*H*), 3.53-3.58 (m, 2H, 2NC*H*HCH), 3.29-3.33 (m, 2H, 2NC*H*HCH), 2.61 (br s, 2H, 2O*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.73, 150.66, 129.92, 125.27, 120.26, 120.21, 71.41, 71.30, 51.61, 51.57; ^{31}P NMR (162 MHz, $CDCl_3$): δ -3.04. HRMS (ESI) calcd for $C_{16}H_{18}NO_5P$ $[M+H]^+$: 336.0995, found: 336.1001.

Methyl-octyl-((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)phosphonate (8j)

Compound **8j** was prepared from compound **16j** (20.2 mg, 0.058 mmol) as described in the general procedure D, affording **8j** (9.8 mg, 55% yield, R_f = 0.39, CH_2Cl_2/MeOH, 7:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (br s, 2H, 2OC*H*), 3.93-4.01 (m, 2H, 2OCH_2CH$_2$), 3.70 (d, *J* = 10.8 Hz, 3H, OCH_3), 3.39-3.45 (m, 2H, 2NC*H*HCH), 3.17-3.23 (m, 4H, 2NC*H*HCH, 2O*H*), 1.62-1.69 (m, 2H, OCH$_2$CH_2), 1.28-1.35 (m, 10H, 5CH_2), 0.88 (t, *J* = 6.8 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.85, 71.83, 71.76, 71.74, 66.92, 66.86, 53.25, 53.19, 51.62, 51.58, 51.54, 51.51, 31.92, 30.54, 30.47, 29.32, 29.29, 25.70, 22.77, 14.21; ^{31}P NMR (162 MHz, $CDCl_3$): δ 9.19. HRMS (ESI) calcd for $C_{13}H_{28}NO_5P$ $[M+H]^+$: 310.1783, found: 310.1788.

Methyl-nonyl-((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)phosphonate (8k)

Compound **8k** was prepared from compound **16k** (26.3 mg, 0.072 mmol) as described in the general procedure D, affording **8k** (10.1 mg, 43% yield, R_f = 0.44, CH_2Cl_2/MeOH, 7:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (br s, 2H, 2OC*H*), 3.93-4.01 (m, 2H, 2OCH_2CH$_2$), 3.70 (d, *J* = 11.2 Hz, 3H, OCH_3), 3.39-3.45 (m, 2H, 2NC*H*HCH), 3.17-3.23 (m, 4H, 2NC*H*HCH, 2O*H*), 1.62-1.69 (m, 2H, OCH$_2$CH_2), 1.27-1.33 (m, 12H, 6CH_2), 0.88 (t, *J* = 6.8 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.83, 71.81, 71.74, 71.72, 66.92, 66.86, 53.26, 53.20, 51.59, 51.56, 51.52, 51.48, 31.99, 30.53, 30.46, 29.62, 29.37, 29.34, 25.69, 22.80, 14.24; ^{31}P NMR (162 MHz, $CDCl_3$): δ 8.43. HRMS (ESI) calcd for $C_{14}H_{30}NO_5P$ $[M+Na]^+$: 346.1754, found: 346.1761.

Methyl-decyl-((3S,4R)-3,4-dihydroxypyrrolidin-1-yl)phosphonate (8l)

Compound **8l** was prepared from compound **16l** (15.0 mg, 0.040 mmol) as described in the general procedure D, affording **8l** (7.2 mg, 53% yield, R_f = 0.29, CH_2Cl_2/MeOH, 10:1, v/v) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.24 (br s, 2H, 2OC*H*), 3.93-4.02 (m, 2H, 2OCH_2CH$_2$), 3.70 (d, *J* = 10.8 Hz, 3H, OCH_3), 3.39-3.42 (m, 2H, 2NC*H*HCH), 3.18-3.22 (m, 2H, 2NC*H*HCH), 2.84 (m, 2H, 2O*H*), 1.61-1.68 (m, 2H, OCH$_2$CH_2), 1.26 (br m, 14H, 7CH_2), 0.88 (t, *J* = 6.4 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.85, 71.83, 71.76, 71.74, 66.91, 66.85, 53.25, 53.20, 51.61, 51.57, 51.54, 51.50, 32.03, 30.54, 30.47, 29.67, 29.44, 29.34, 25.70, 22.82, 14.25; ^{31}P NMR (162 MHz, $CDCl_3$): δ 9.19. HRMS (ESI) calcd for $C_{15}H_{32}NO_5P$ $[M+H]^+$: 338.2091, found: 338.2014.

Biology Section

All experiments were performed in compliance with the relevant laws and institutional guidelines, and were approved by the Ethics Committee of Peking University Health Science Center.

Mouse-Splenocyte-Proliferation-Inhibition Assay

Male BALB/c mouse splenocytes (5×10^5 cells per well), which had been pretreated with Con A (Sigma) (5 μg/mL) and each compound (30 μM), were incubated at 37 °C for 48 h under 5% CO_2 in a RPMI-1640 medium (Hyclone) that contained 10% fetal bovine serum (Hyclone). CCK-8 (10 μL, Dojindo) was added to each well and the plates were further incubated for 3 h at 37 ℃. The optical density was measured by using a Microplate Reader (Tecan) at 450 nm. The IC_{50} values were determined from the results of three independent experiments and calculated from the inhibition curves.

Mouse-Cytokine-Secretion-Inhibition Assay

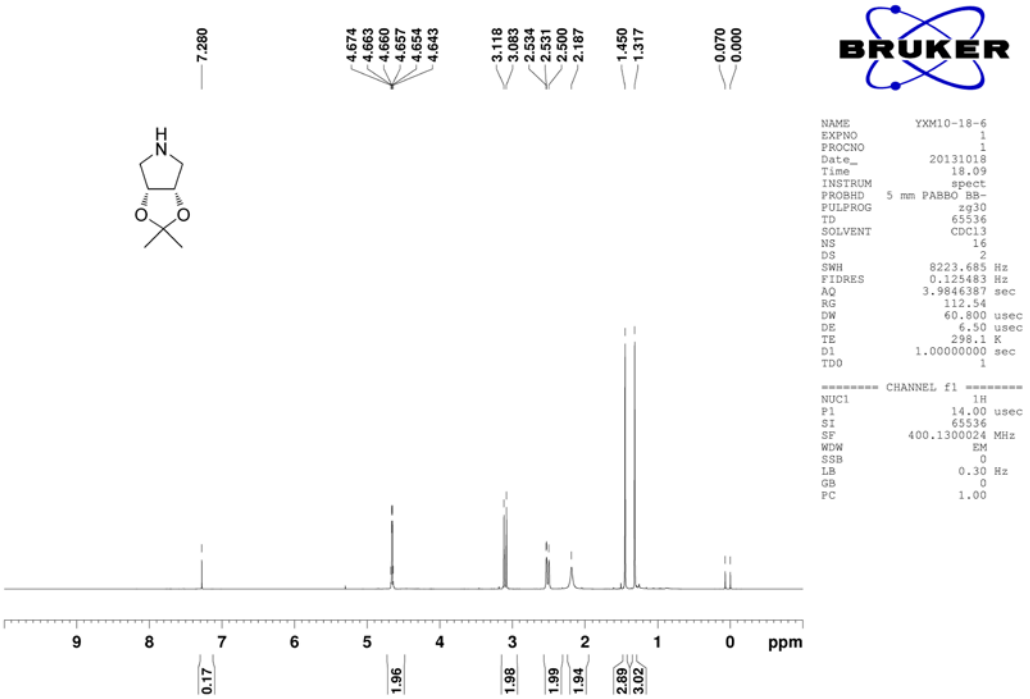
Male BALB/c mouse splenocytes were pretreated with Con A (5 μg/mL) and each compound (30 μM) in 5% CO_2 at 37 °C. After 48 h, the supernatant was collected and stored at -20 °C. The concentration of IL-4 or IFN-γ was

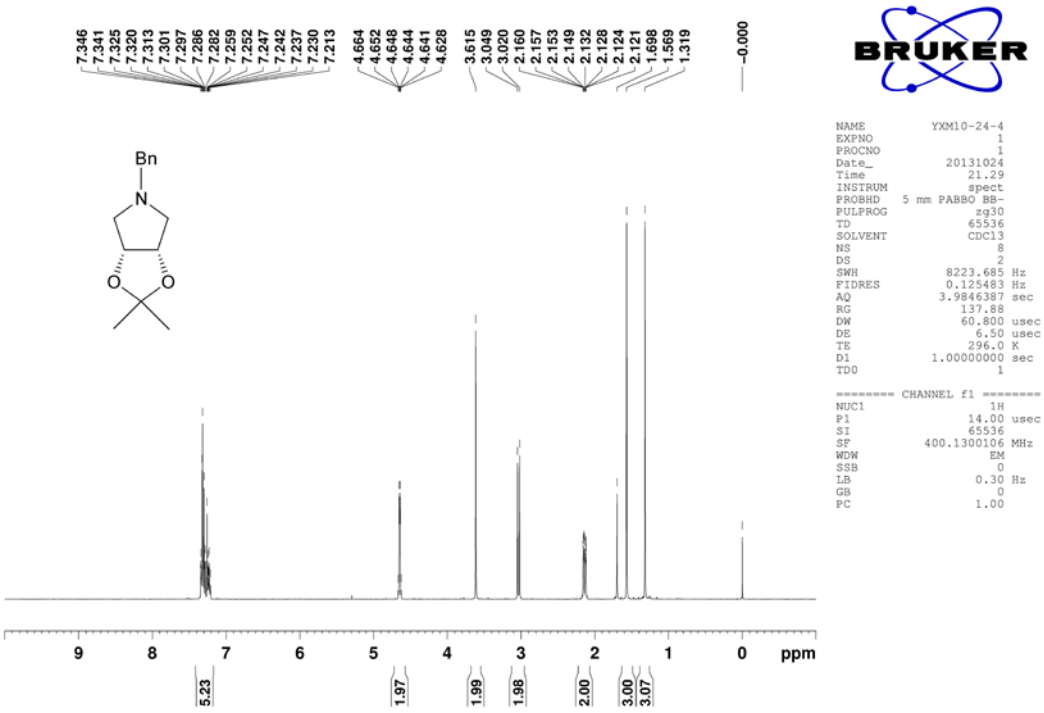
detected with instant ELISA kits (eBioscience). The 96-well plates were precoated with the capture antibody of IFN-γ or IL-4 and blotted. Then, the standards and the detecting samples were added to the appropriate wells. The plates were covered and incubated at room temperature for 2 h until the addition of detection antibody and Avilin-HRP. The wells were washed with PBST after each step above. Finally, the substrate solution was added to each well for 15 min. The reaction was stopped and read at 450 nm. The density of IFN-γ or IL-4 in the samples was determined according to the standard curve.

References:

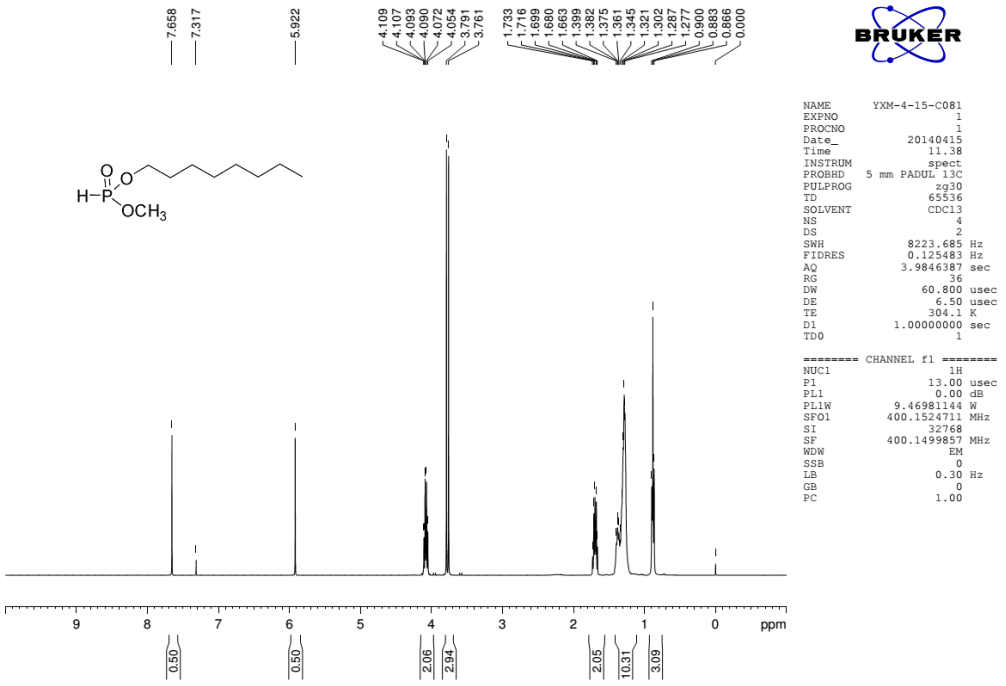
1 P. Srihari, B. Kumaraswamy and J. S. Yadav, *Tetrahedron*, 2009, **65**, 6304-6309.

2 T. M. Chapman, S. Courtney, P. Hay and B. G. Davis, *Chem. Eur. J.*, 2003, **9**, 3397-3414.

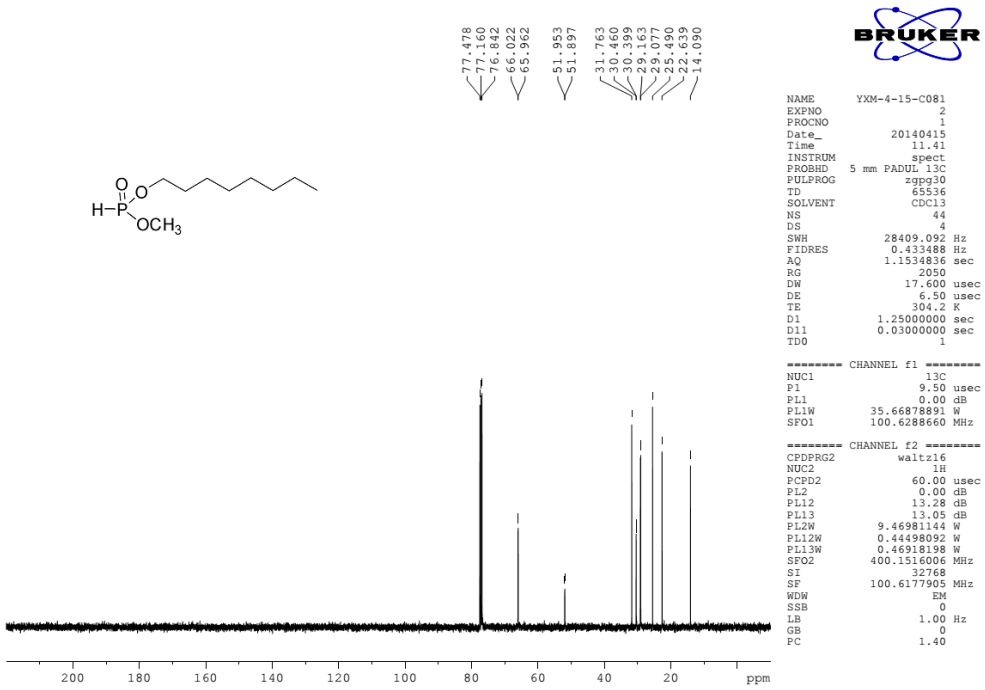




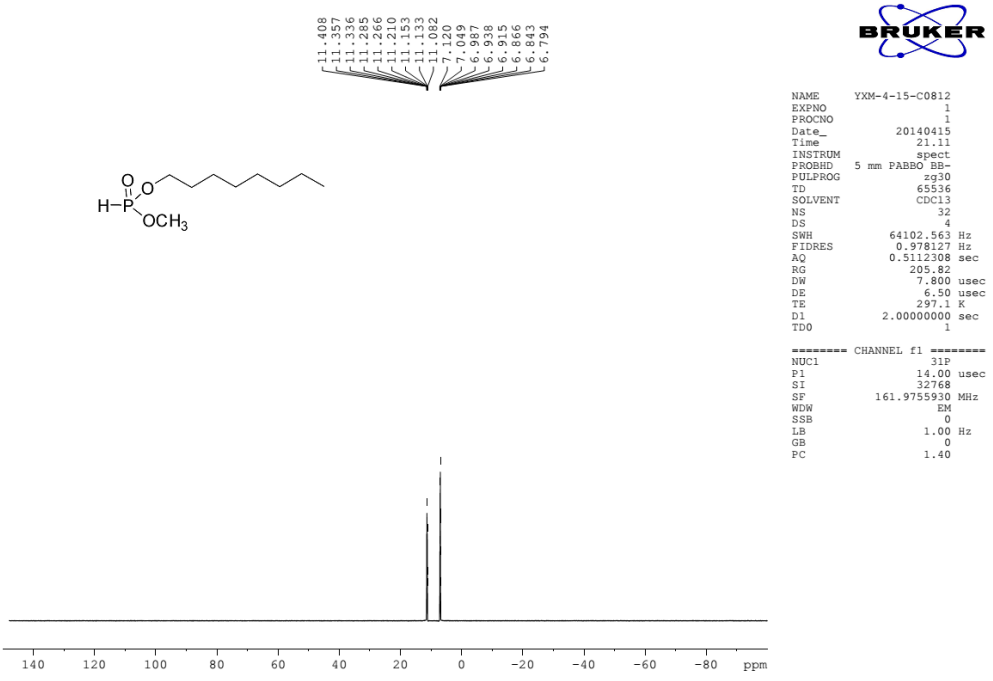
^{1}H NMR Spectrum of Compound **13**



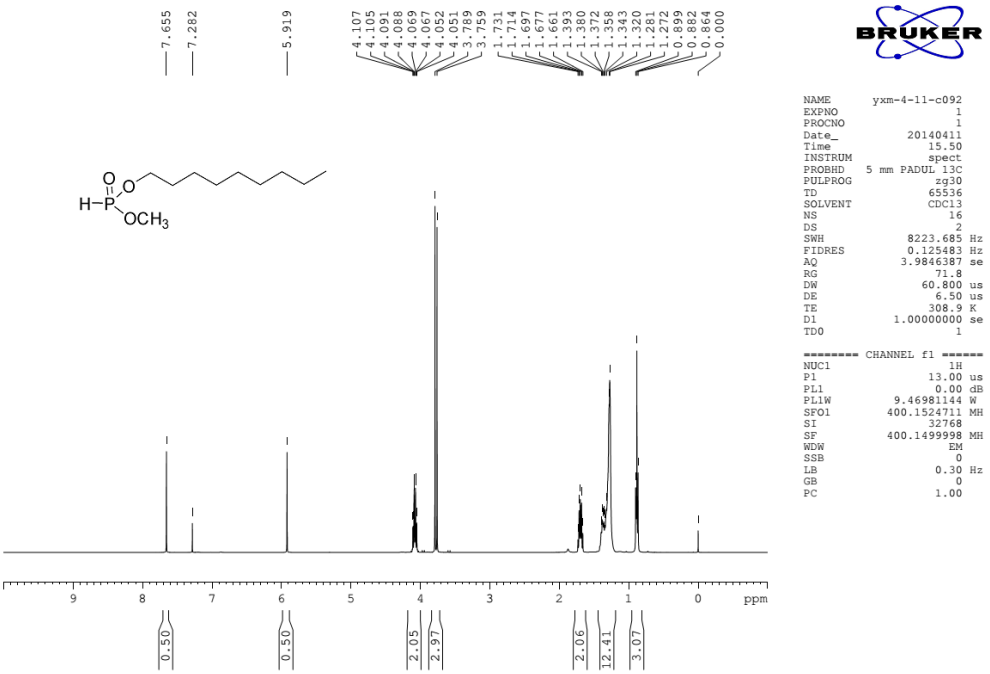
^{1}H NMR Spectrum of Compound **15j**



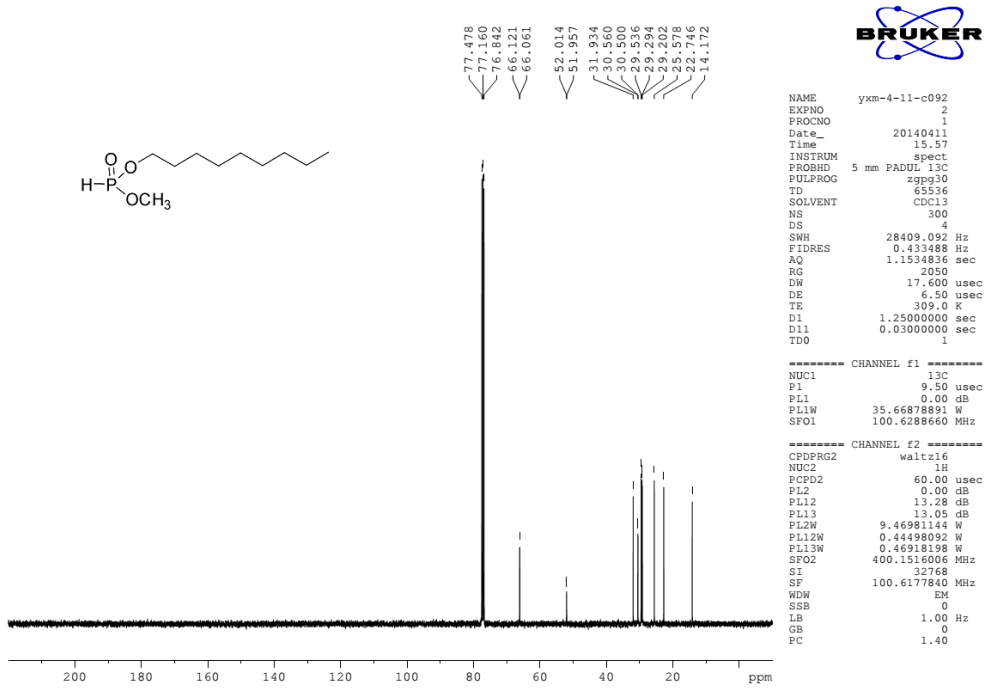
^{13}C NMR Spectrum of Compound **15j**



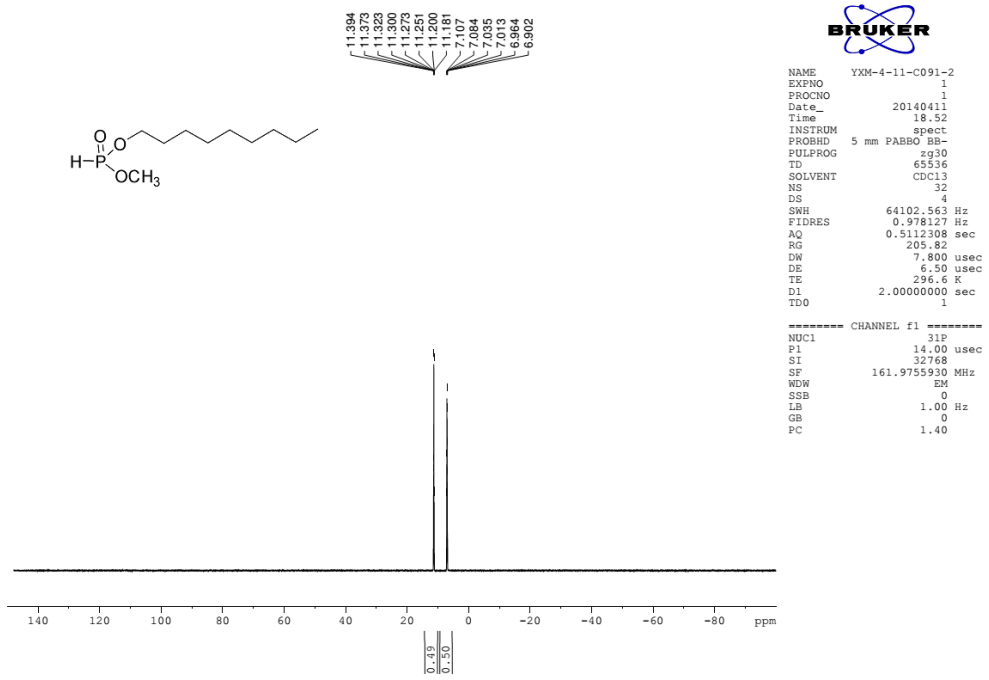
^{31}P NMR Spectrum of Compound **15j**



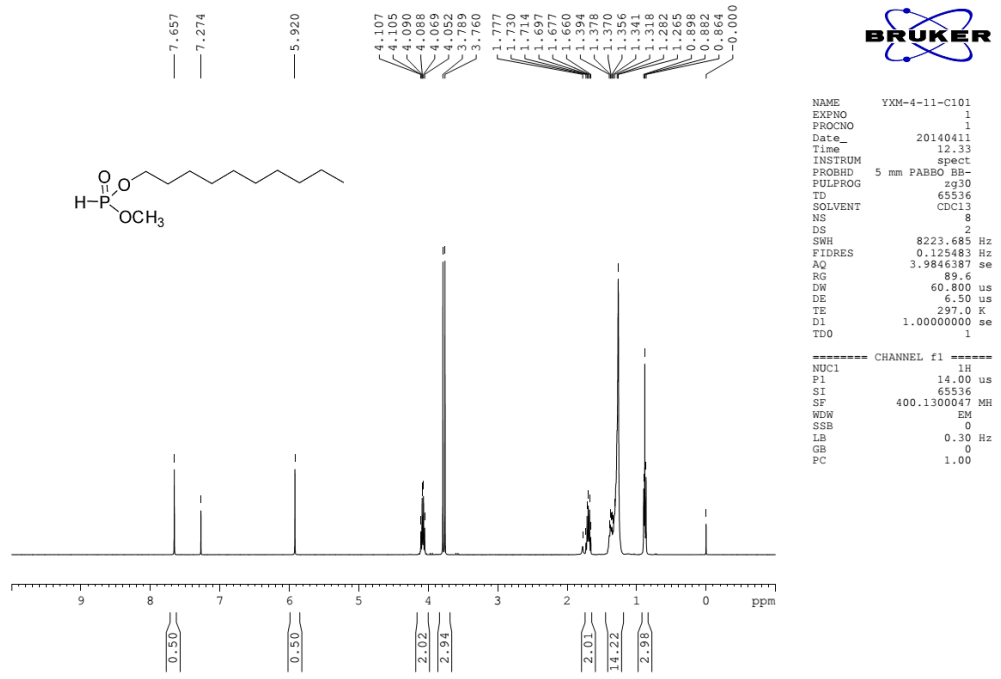
^{1}H NMR Spectrum of Compound **15k**



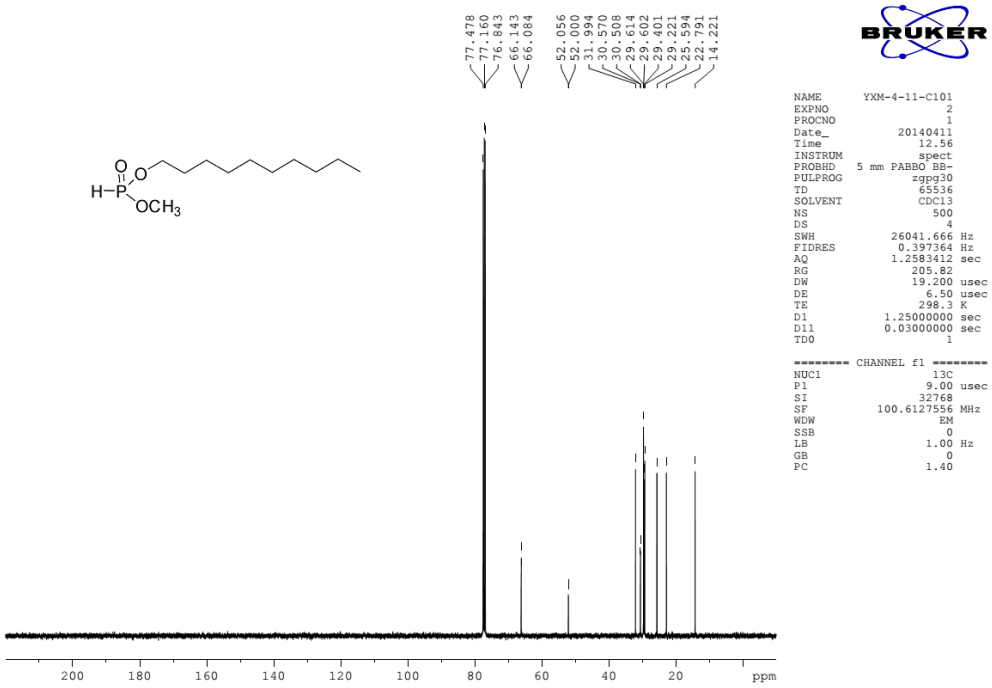
^{13}C NMR Spectrum of Compound **15k**



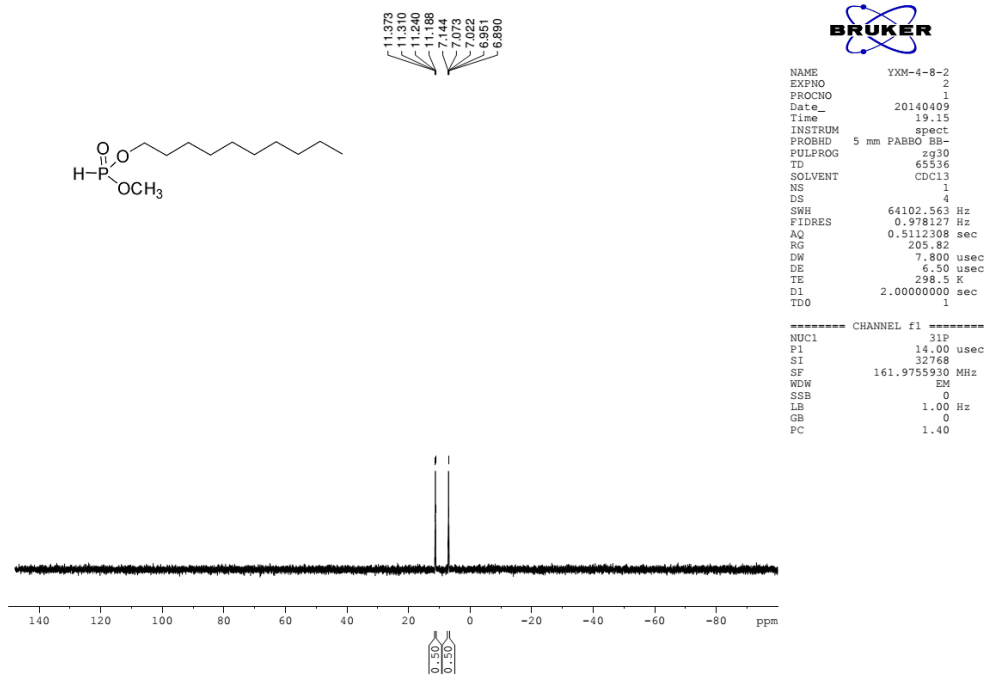
^{31}P NMR Spectrum of Compound **15k**



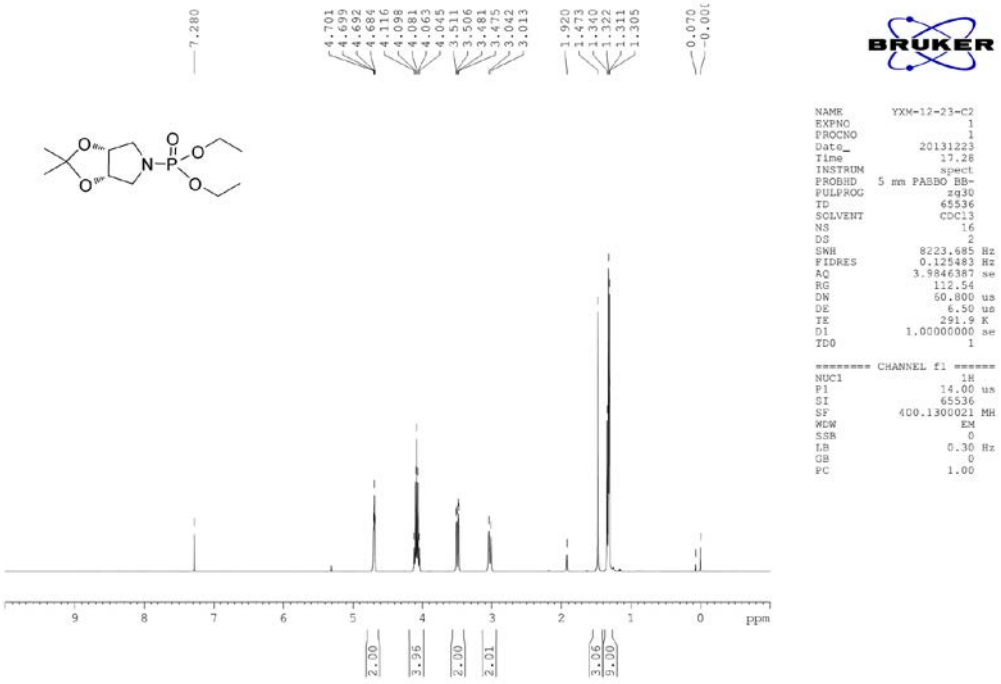
^{1}H NMR Spectrum of Compound **15l**



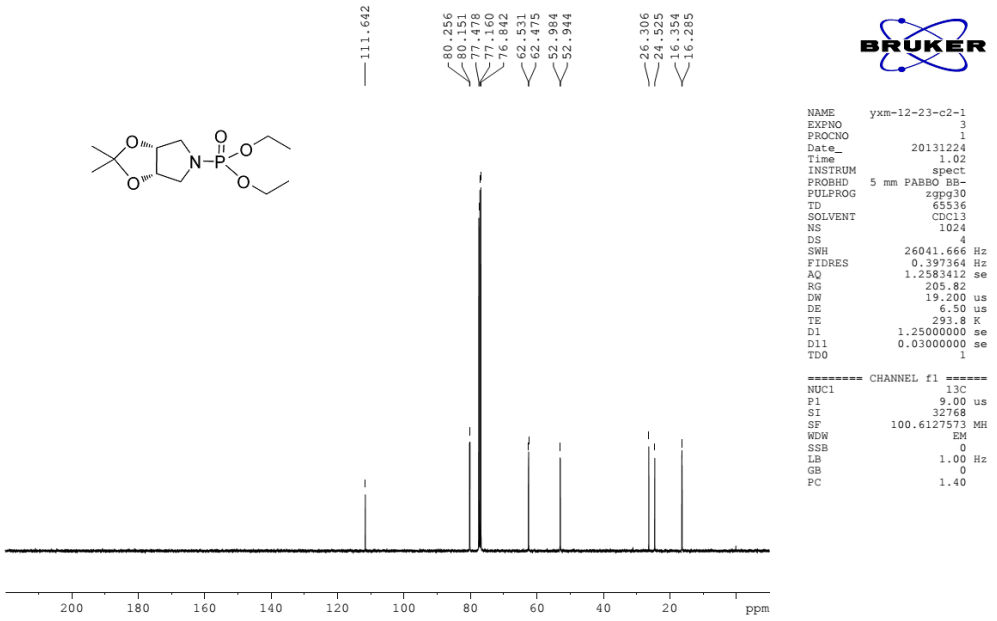
^{13}C NMR Spectrum of Compound **15l**



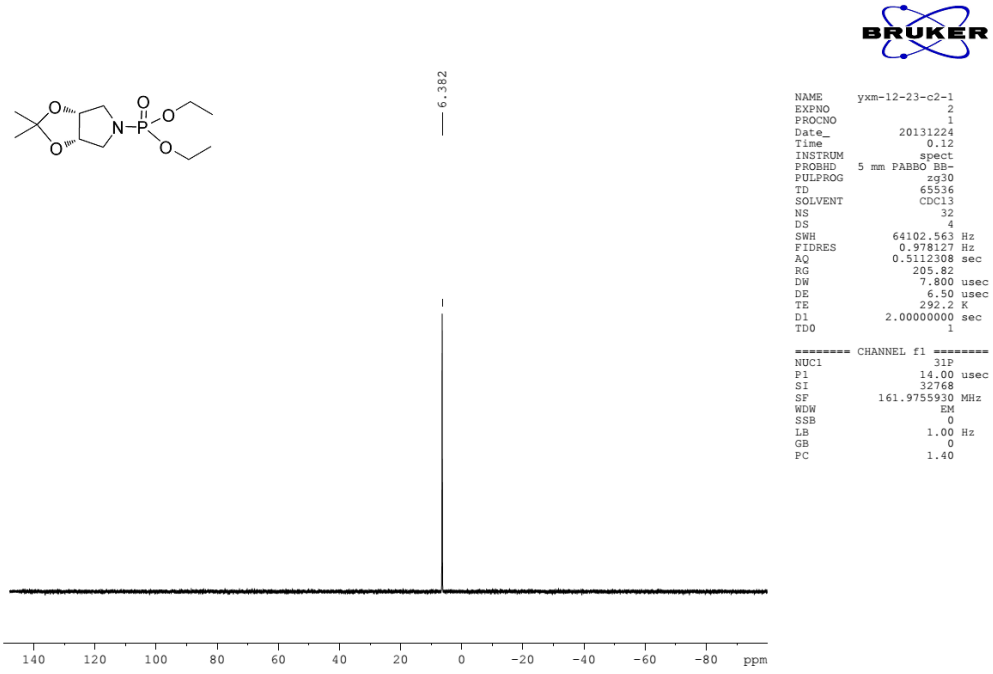
^{31}P NMR Spectrum of Compound **15l**



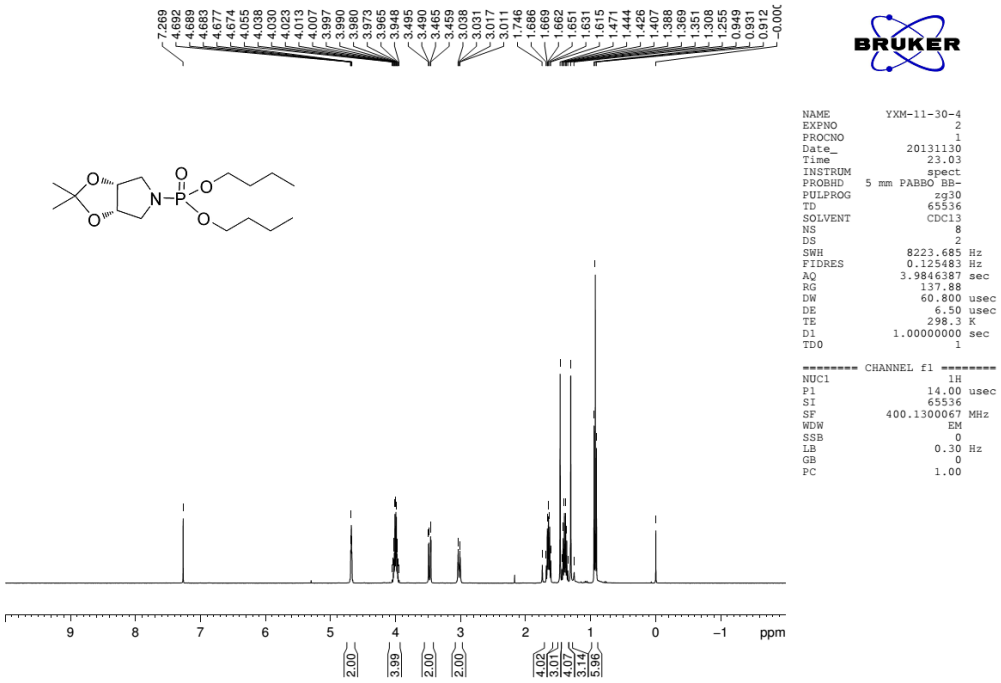
^{1}H NMR Spectrum of Compound **16a**



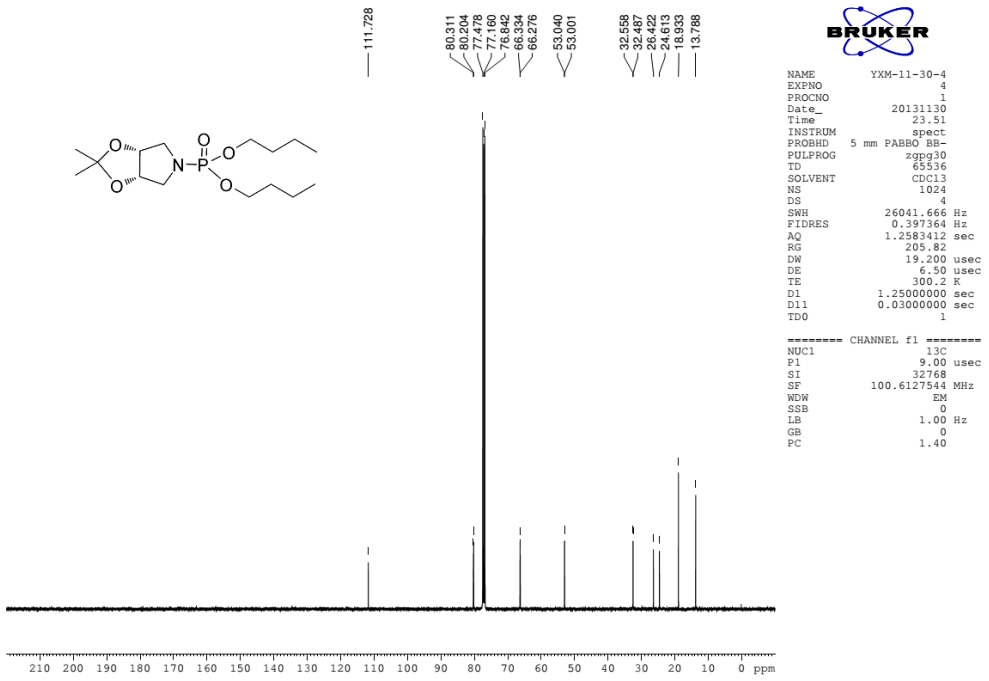
^{13}C NMR Spectrum of Compound **16a**



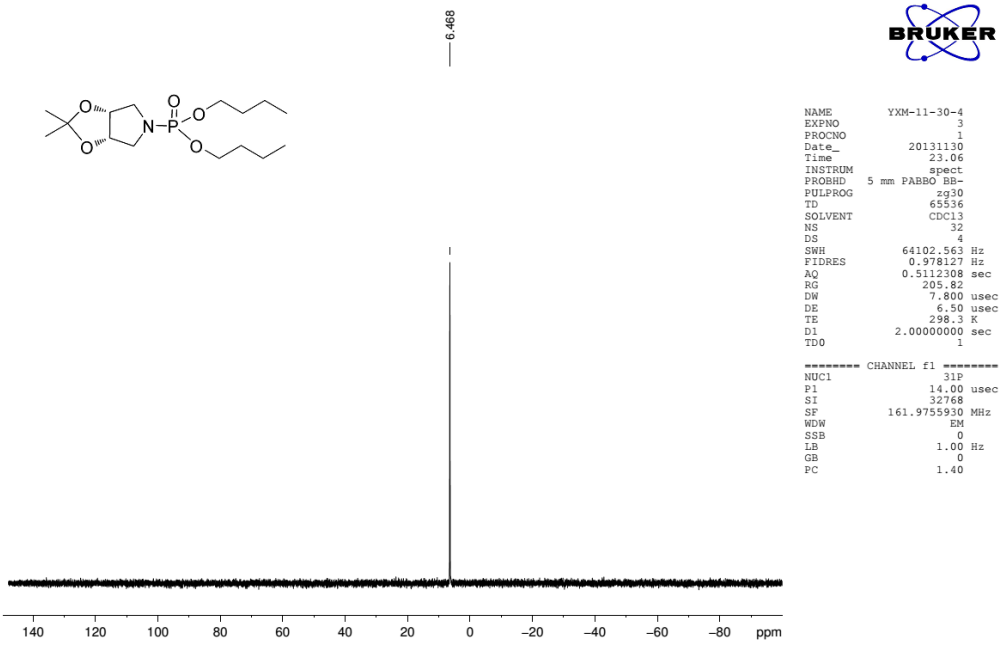
^{31}P NMR Spectrum of Compound **16a**



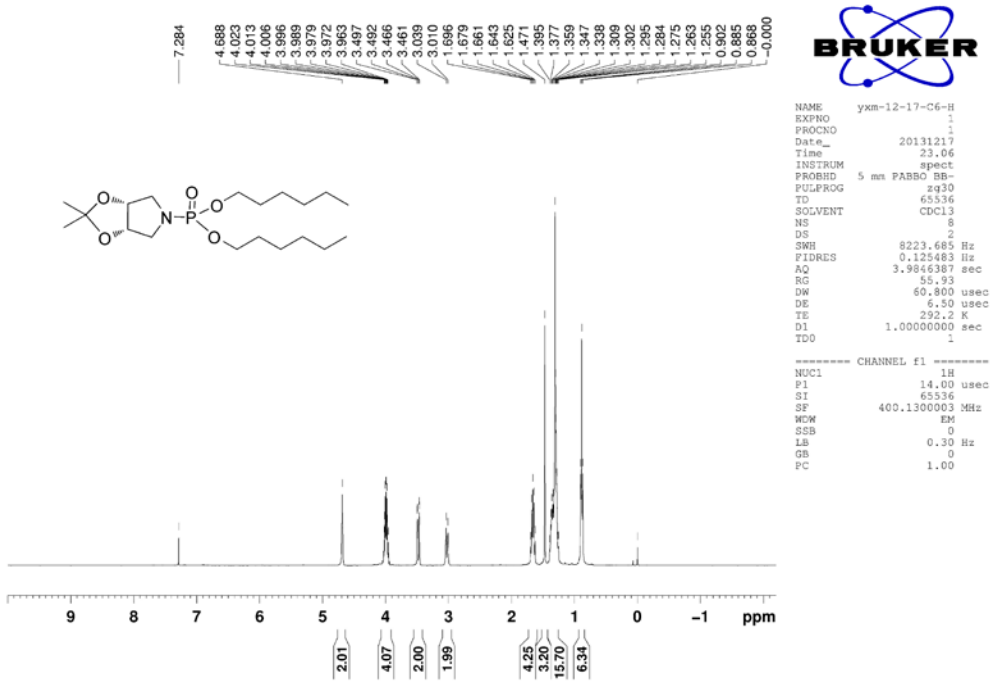
^{1}H NMR Spectrum of Compound **16b**



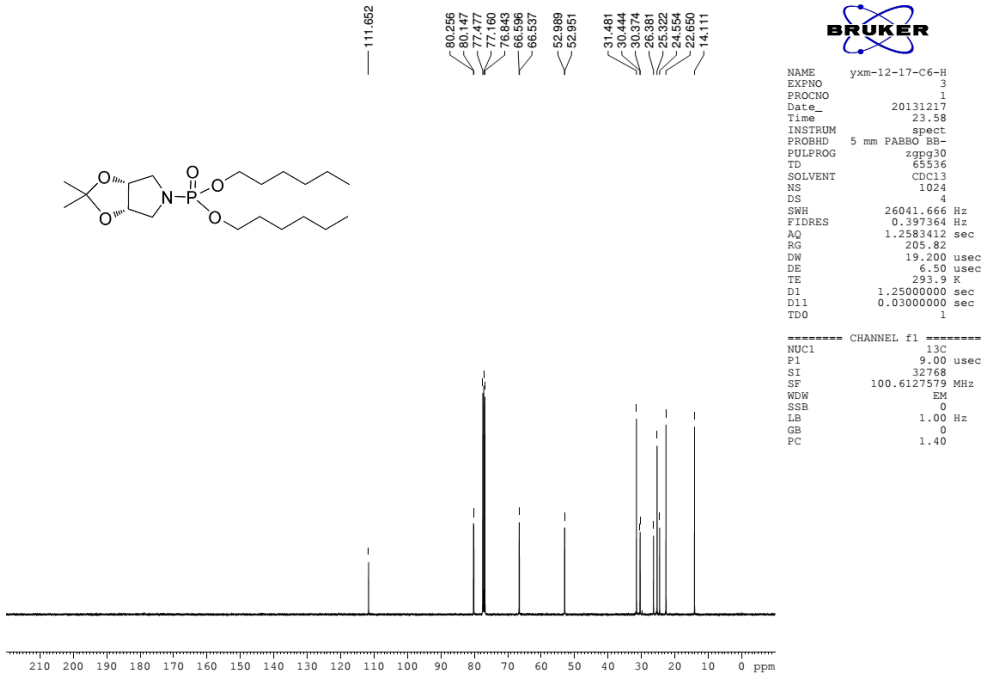
^{13}C NMR Spectrum of Compound **16b**



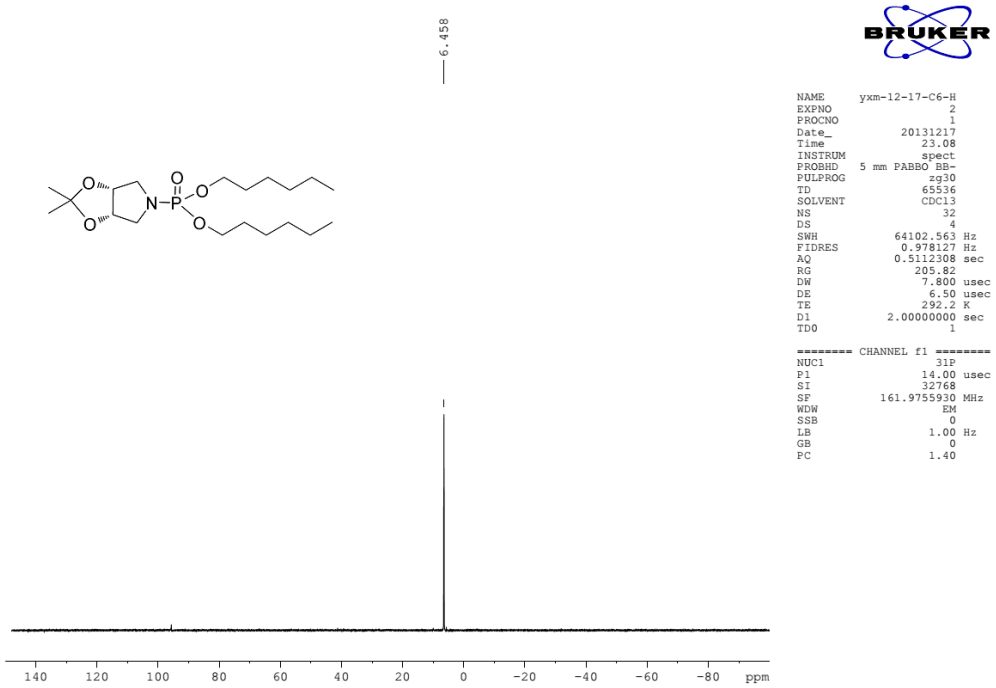
^{31}P NMR Spectrum of Compound **16b**



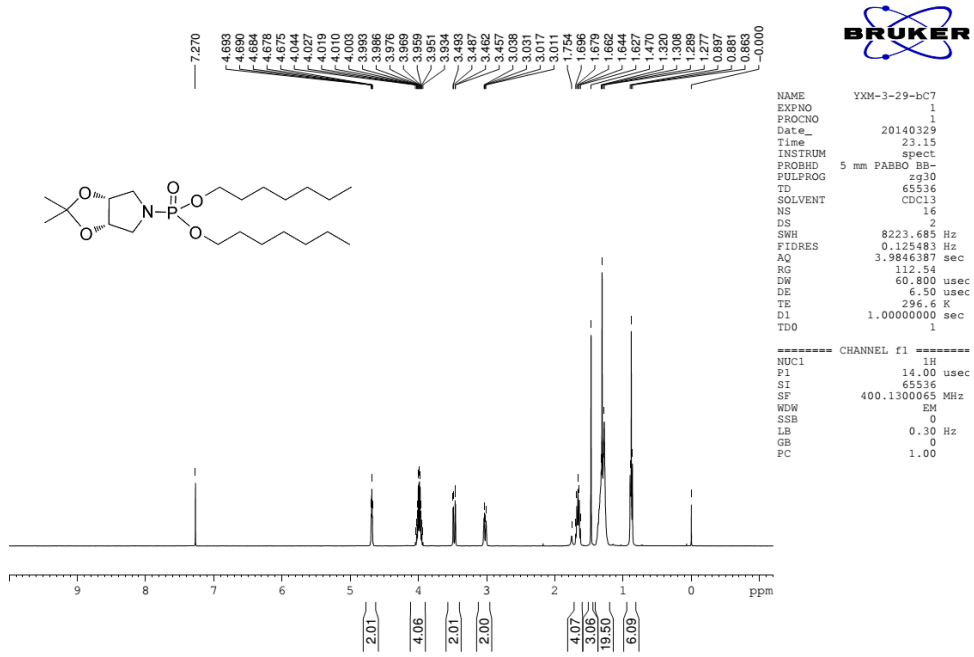
^{1}H NMR Spectrum of Compound **16c**



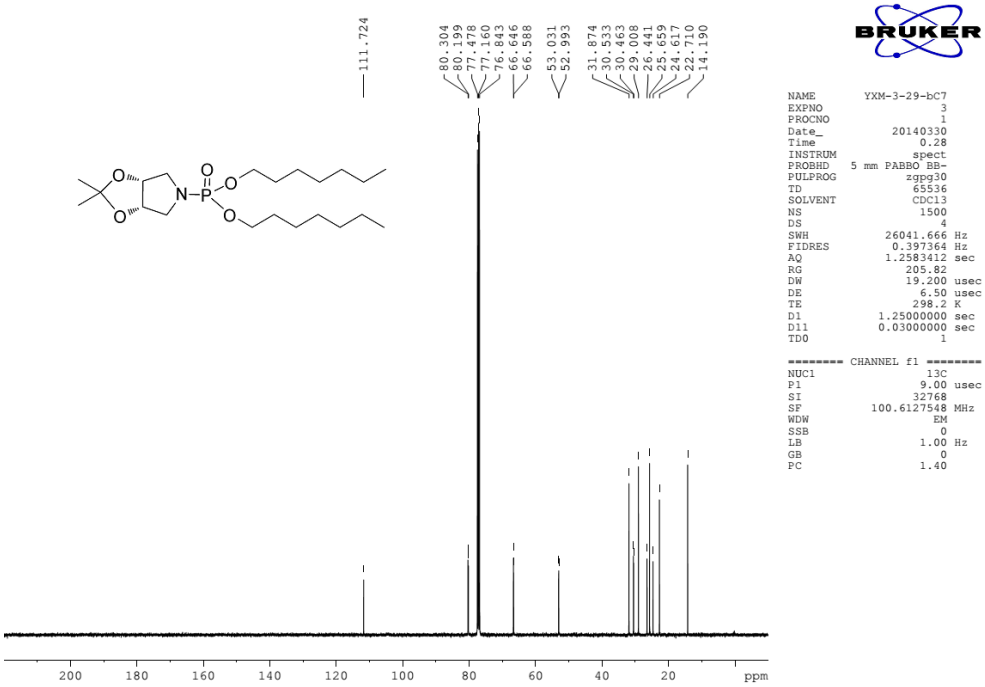
^{13}C NMR Spectrum of Compound **16c**



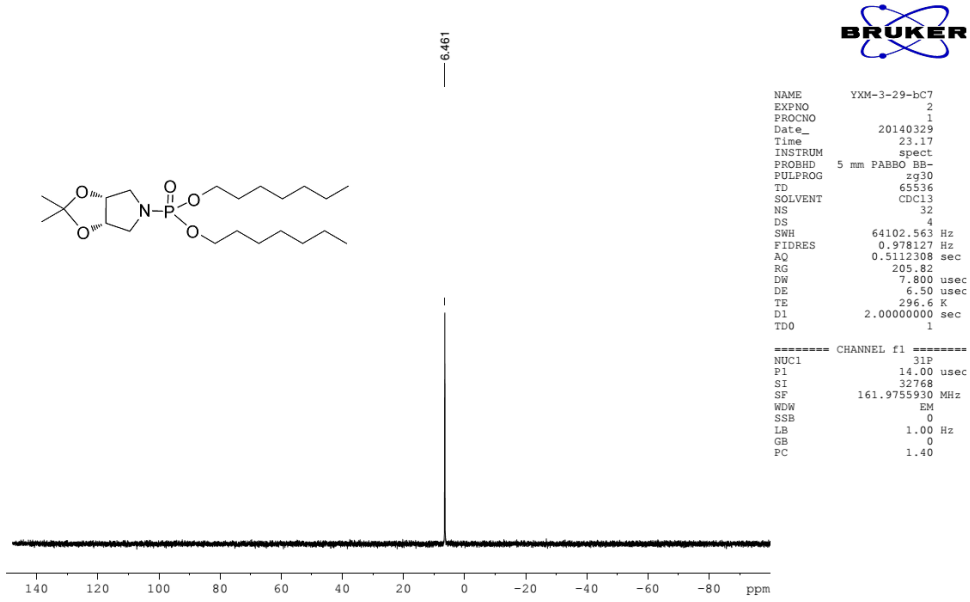
^{31}P NMR Spectrum of Compound **16c**



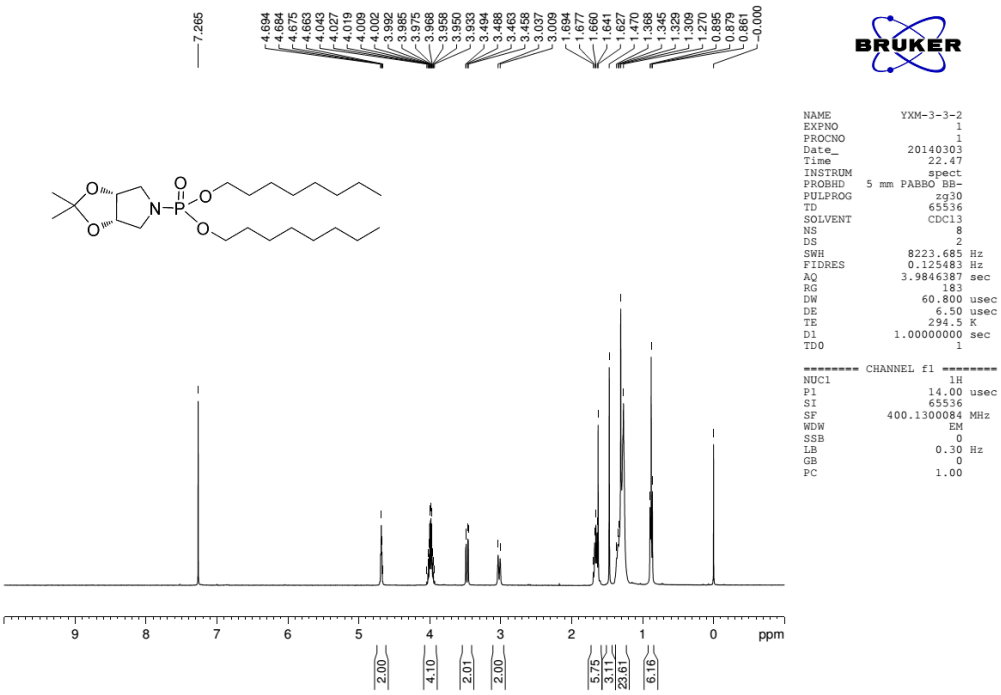
^{1}H NMR Spectrum of Compound **16d**



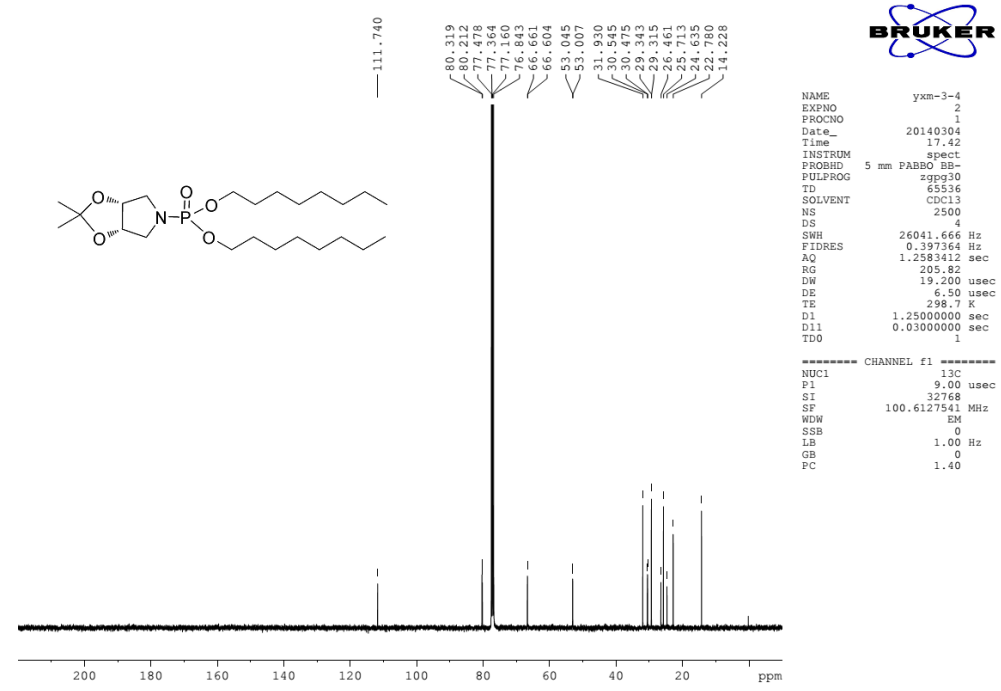
^{13}C NMR Spectrum of Compound **16d**



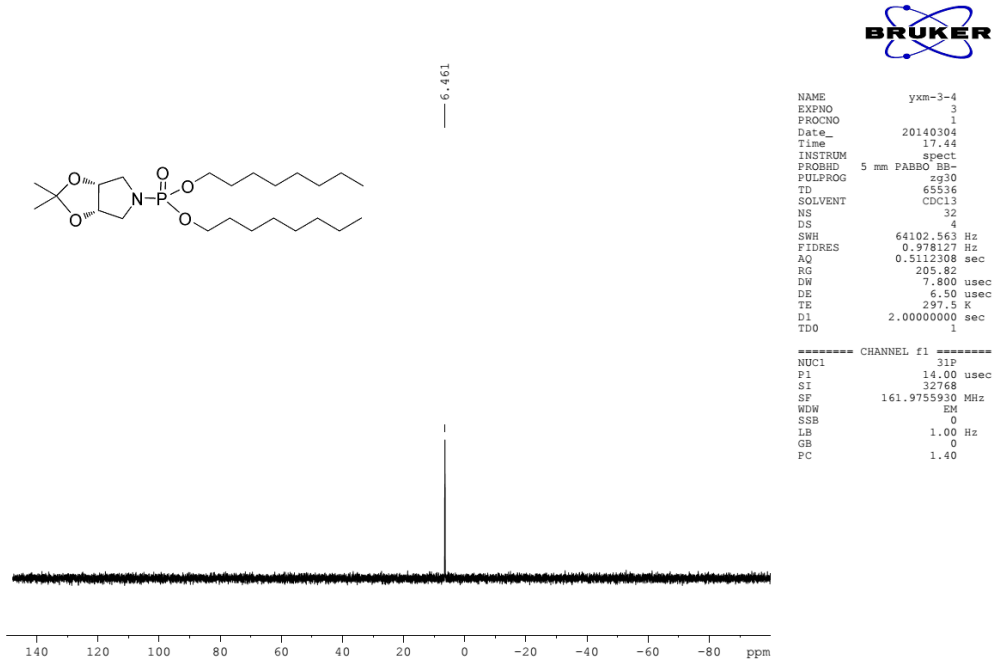
^{31}P NMR Spectrum of Compound **16d**



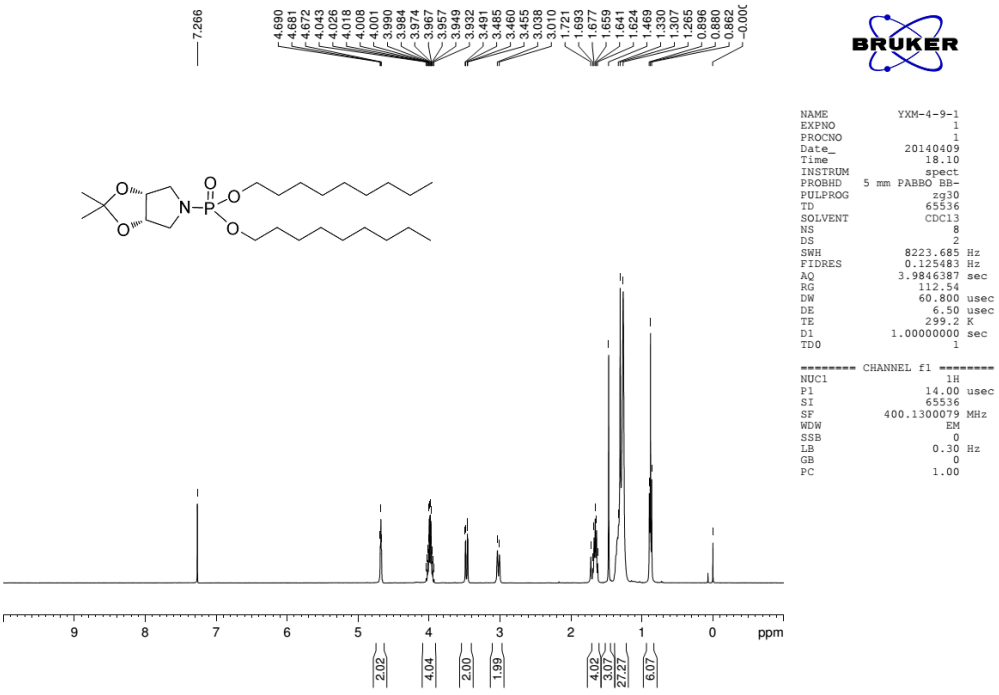
^{1}H NMR Spectrum of Compound **16e**



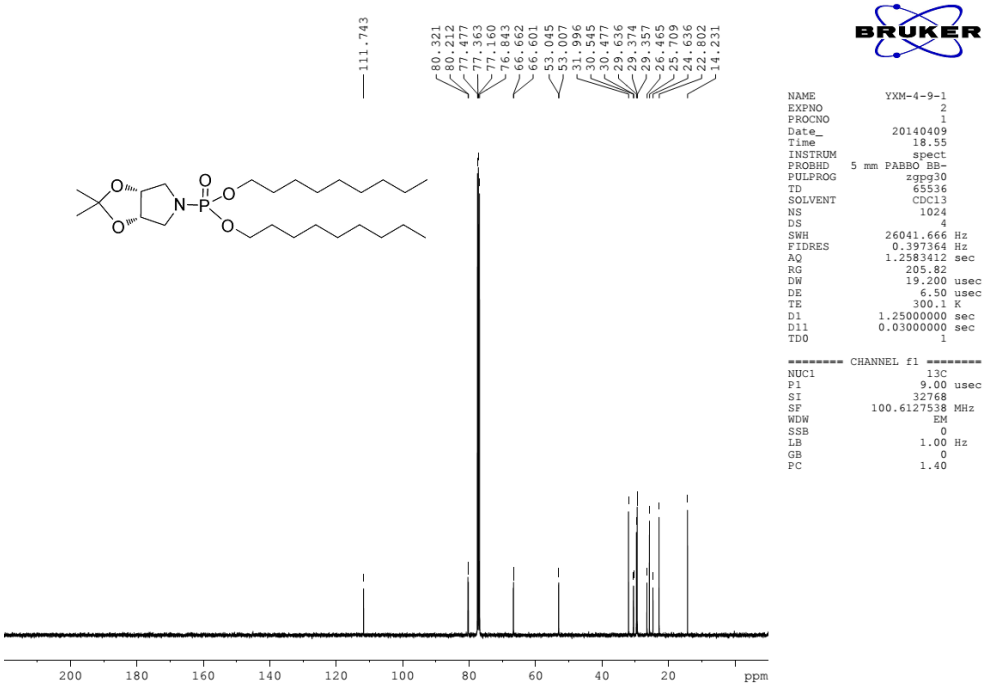
^{13}C NMR Spectrum of Compound **16e**



^{31}P NMR Spectrum of Compound **16e**



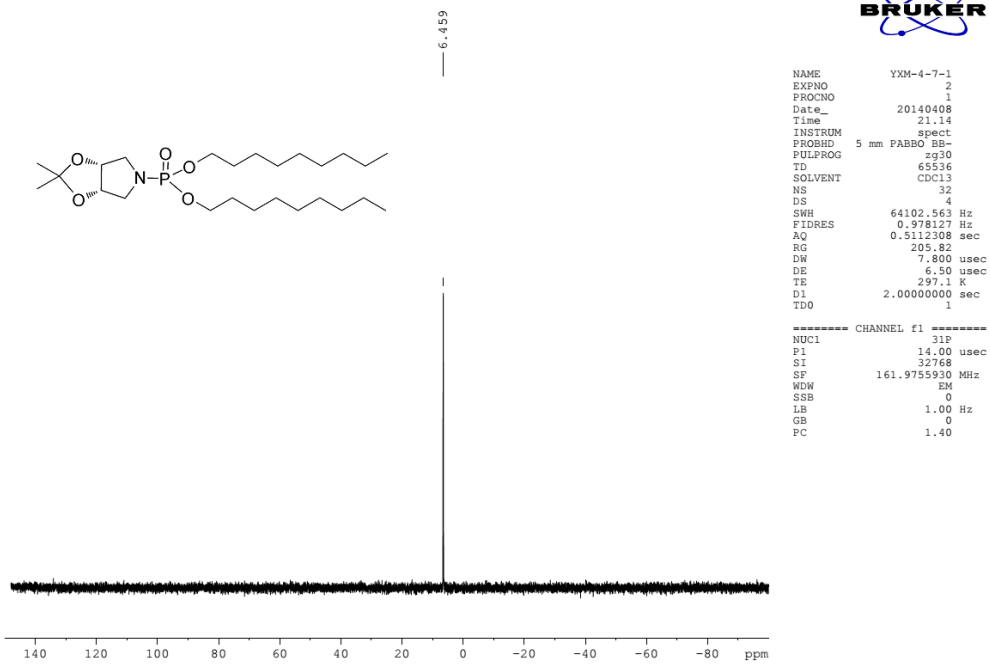
^{1}H NMR Spectrum of Compound **16f**




```
NAME            YXM-4-9-1
EXPNO                   2
PROCNO                  1
Date_            20140409
Time                18.55
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    1024
DS                       4
SWH             26041.666 Hz
FIDRES          0.397364 Hz
AQ              1.2583412 sec
RG                  205.82
DW                19.200 usec
DE                 6.50 usec
TE                 300.1 K
D1             1.25000000 sec
D11            0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                  9.00 usec
SI                     32768
SF            100.6127538 MHz
WDW                    EM
SSB                     0
LB                  1.00 Hz
GB                      0
PC                   1.40
```

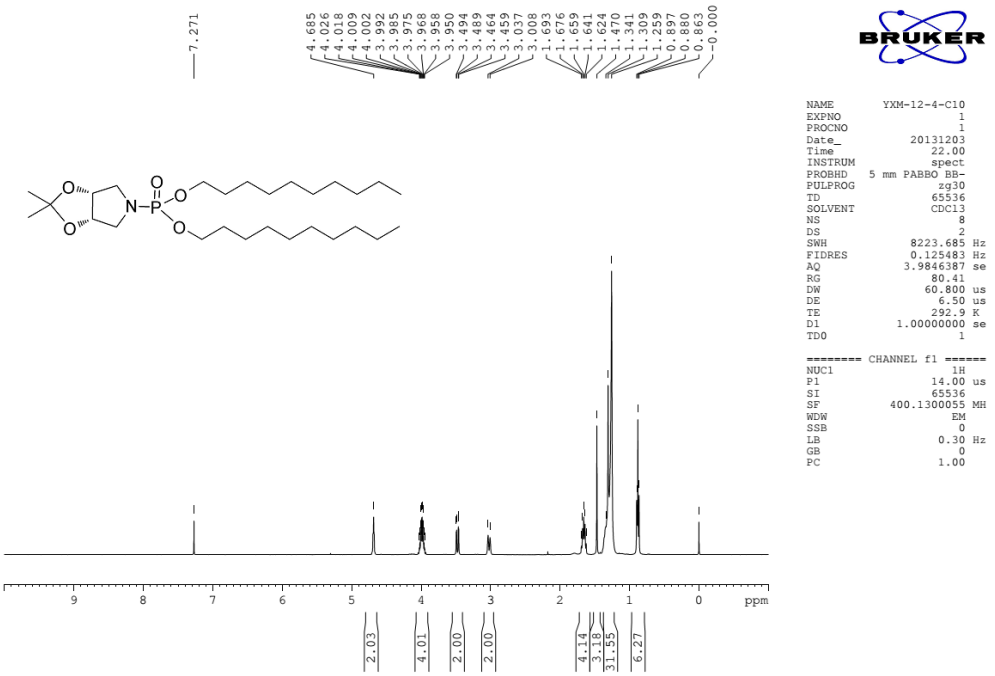
^{13}C NMR Spectrum of Compound **16f**



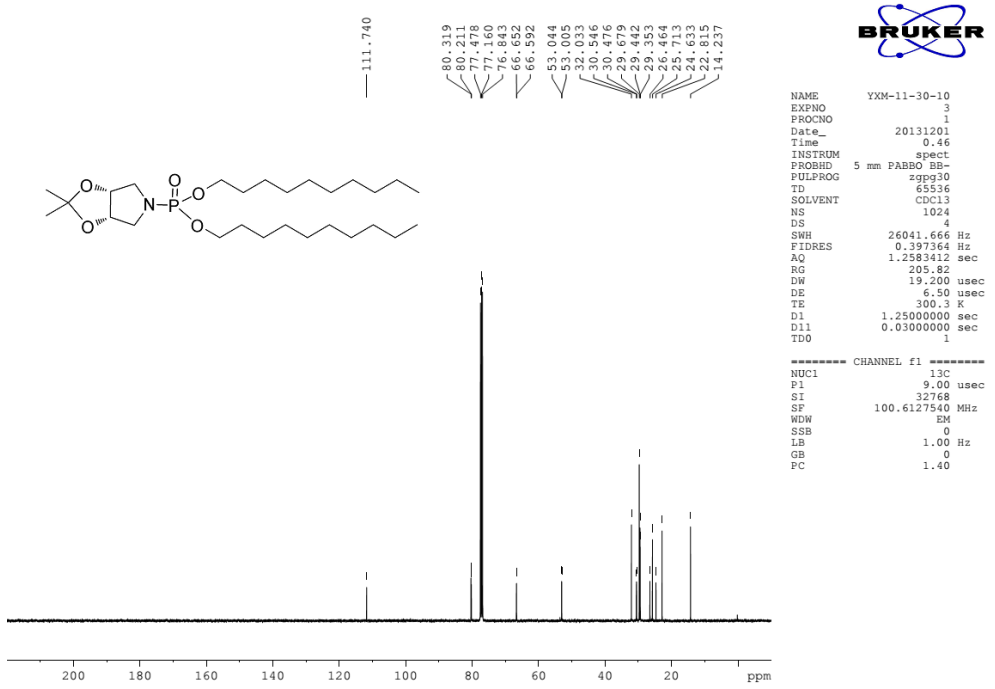

```
NAME            YXM-4-7-1
EXPNO                   2
PROCNO                  1
Date_            20140408
Time                21.14
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      32
DS                       4
SWH             64102.563 Hz
FIDRES          0.978127 Hz
AQ              0.5112308 sec
RG                  205.82
DW                 7.800 usec
DE                 6.50 usec
TE                 297.1 K
D1             2.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   31P
P1                 14.00 usec
SI                     32768
SF            161.9755930 MHz
WDW                    EM
SSB                     0
LB                  1.00 Hz
GB                      0
PC                   1.40
```

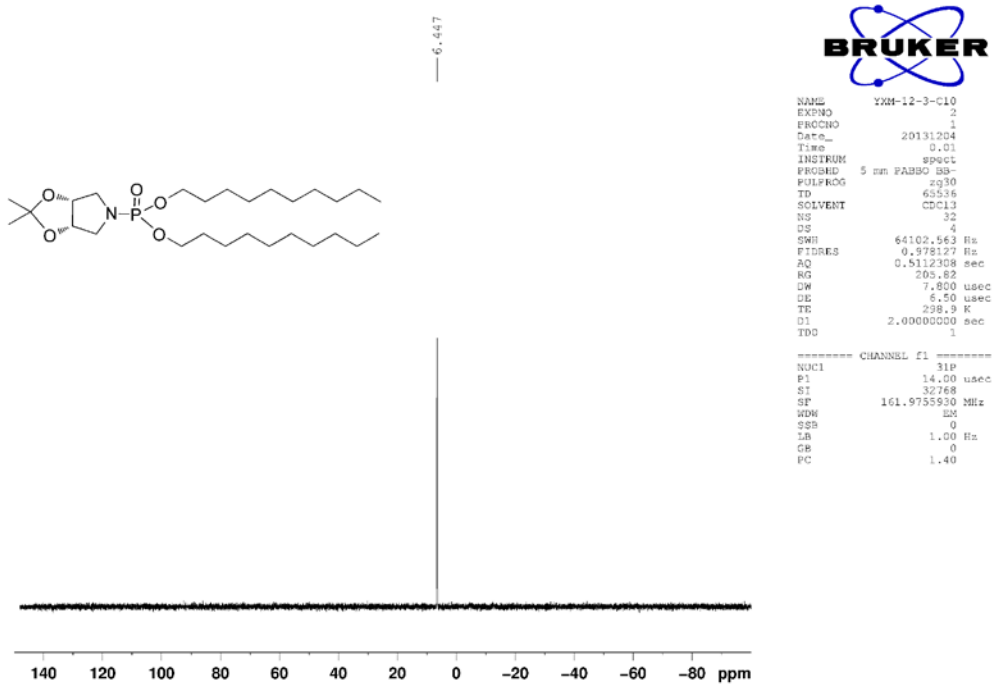
^{31}P NMR Spectrum of Compound **16f**



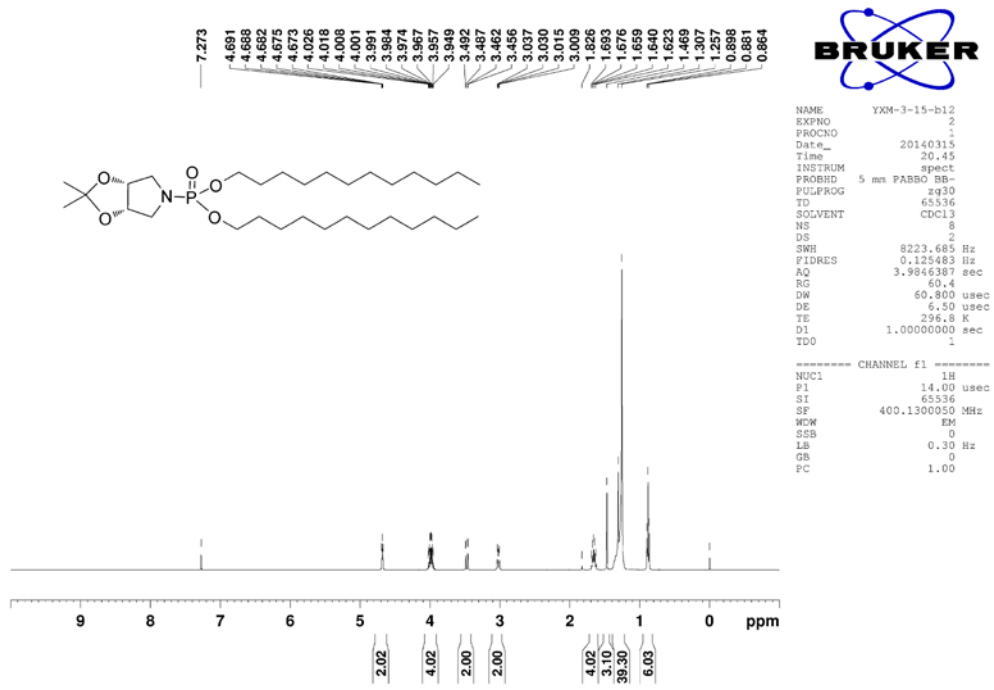
^{1}H NMR Spectrum of Compound **16g**



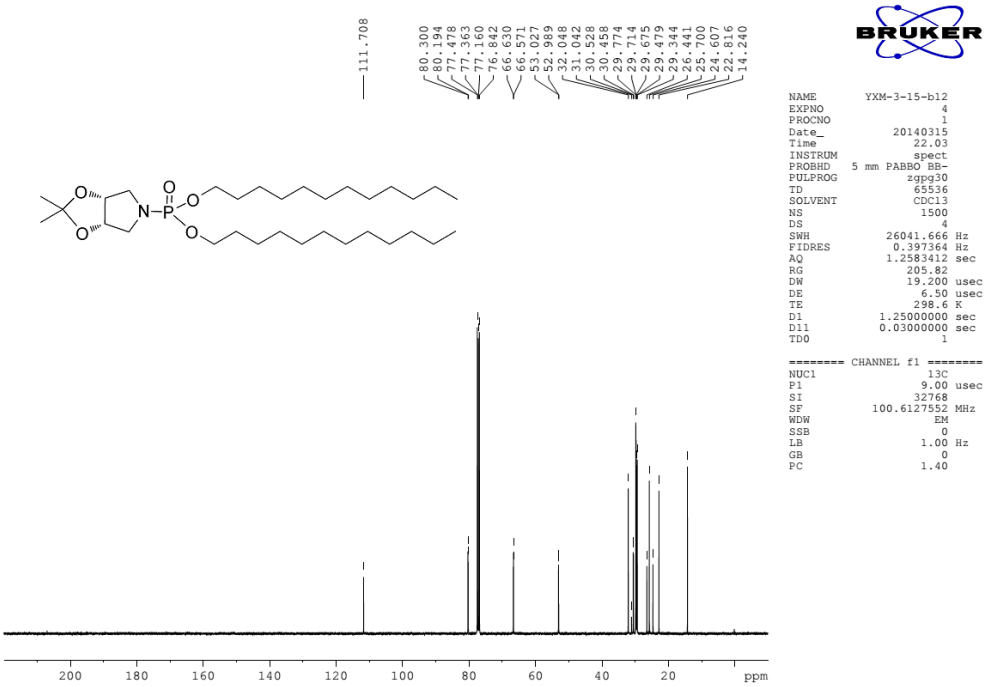
^{13}C NMR Spectrum of Compound **16g**



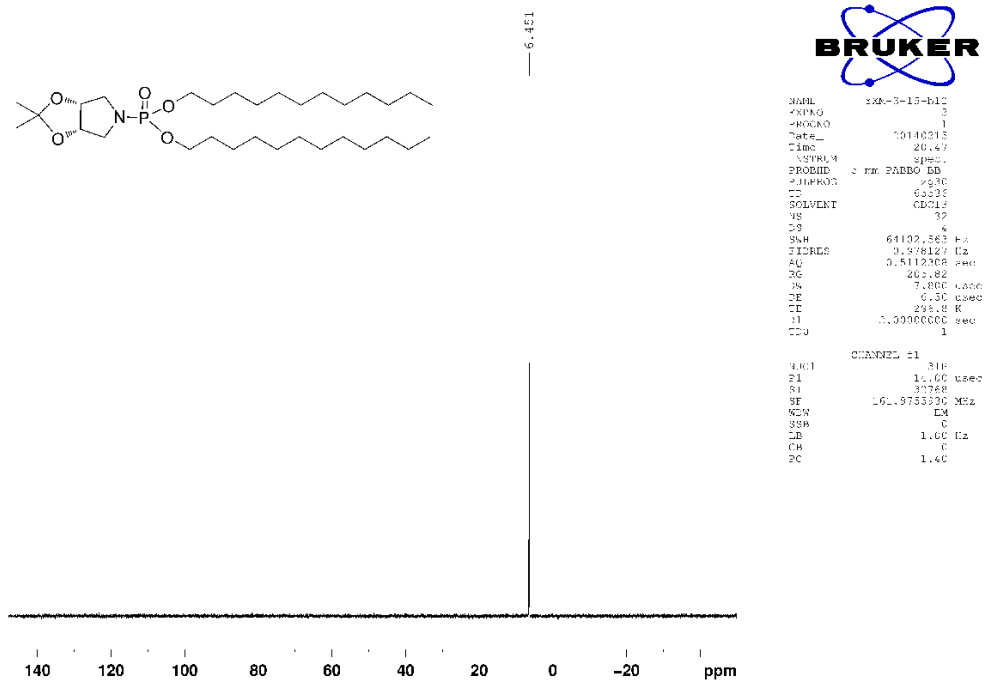
^{31}P NMR Spectrum of Compound **16g**



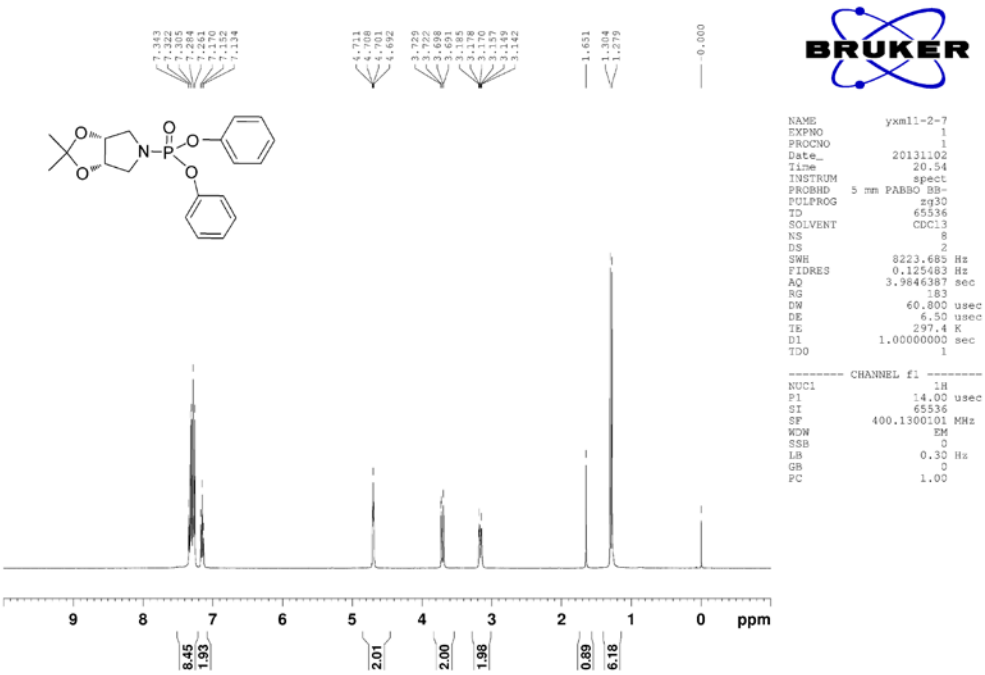
^{1}H NMR Spectrum of Compound **16h**



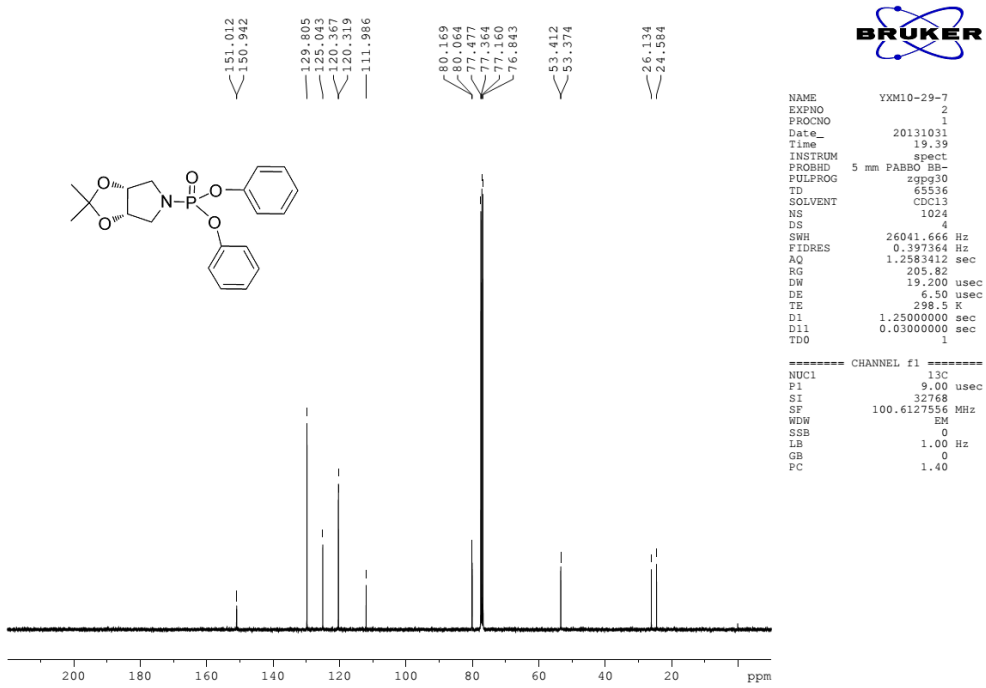
^{13}C NMR Spectrum of Compound **16h**



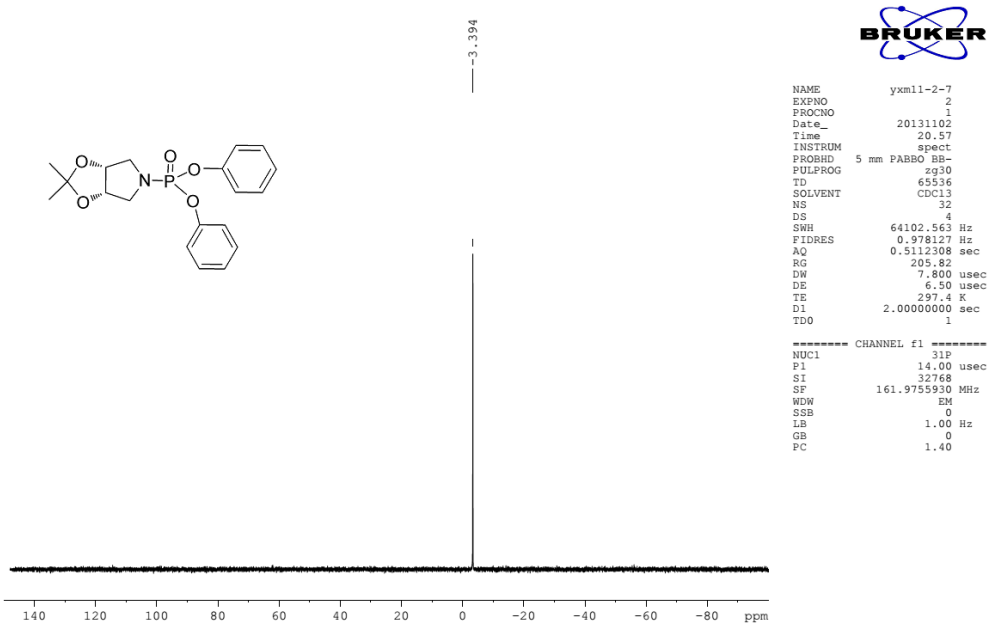
^{31}P NMR Spectrum of Compound **16h**



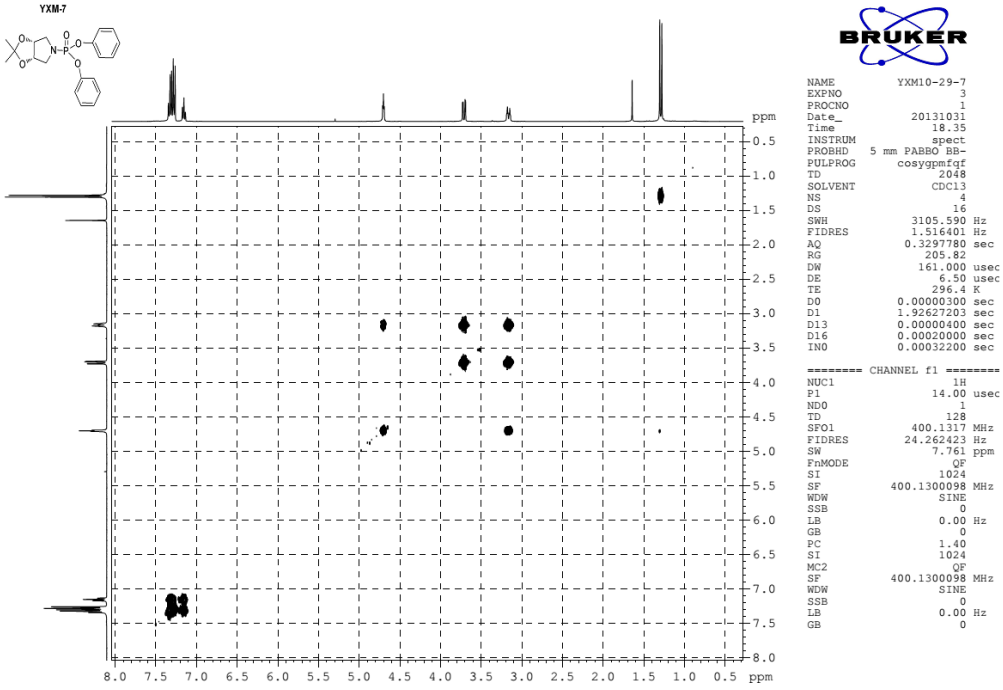
^{1}H NMR Spectrum of Compound **16i**



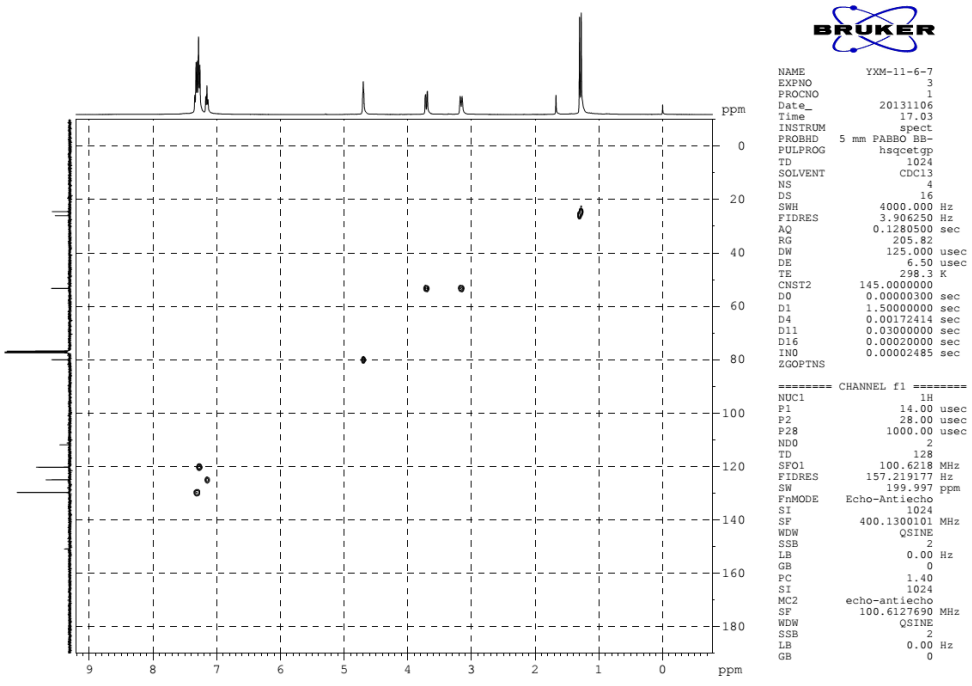
^{13}C NMR Spectrum of Compound **16i**



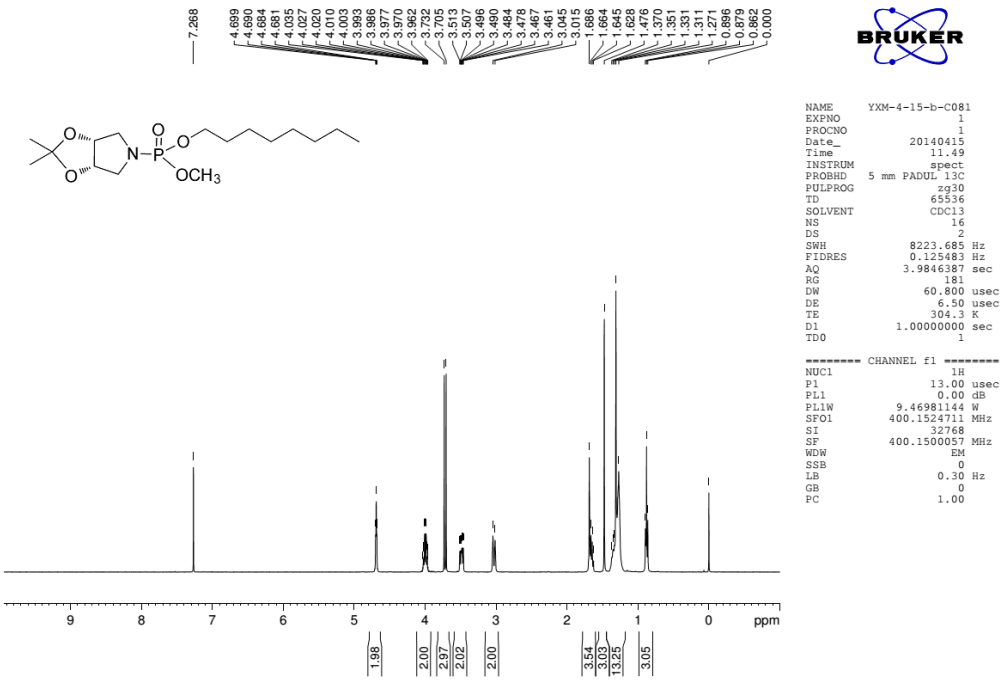
^{31}P NMR Spectrum of Compound **16i**



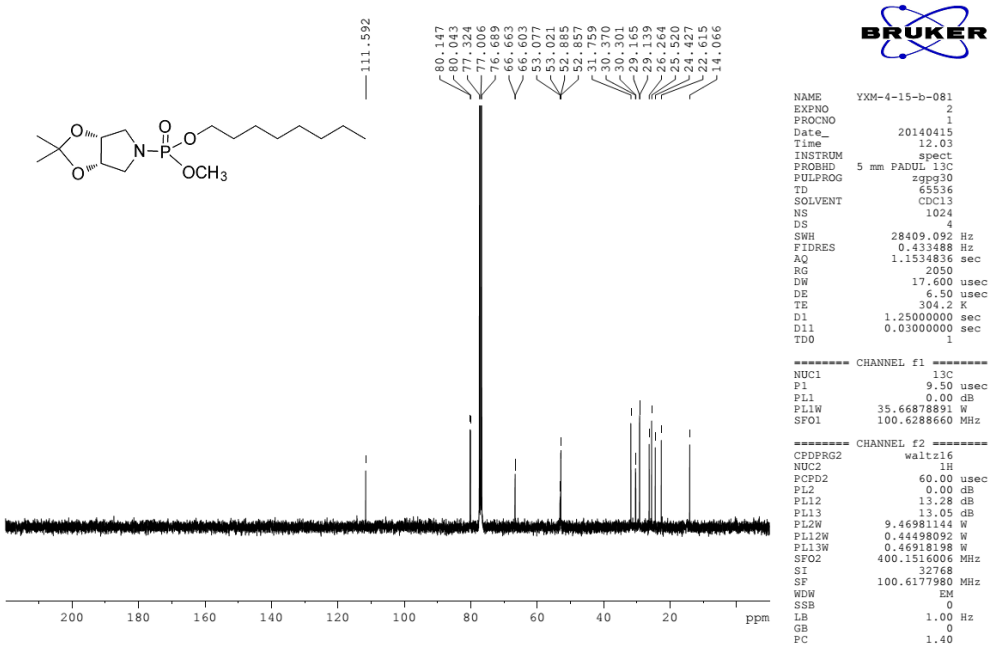
H-H COSY Spectrum of Compound **16i**



HSQC Spectrum of Compound **16i**



^{1}H NMR Spectrum of Compound **16j**

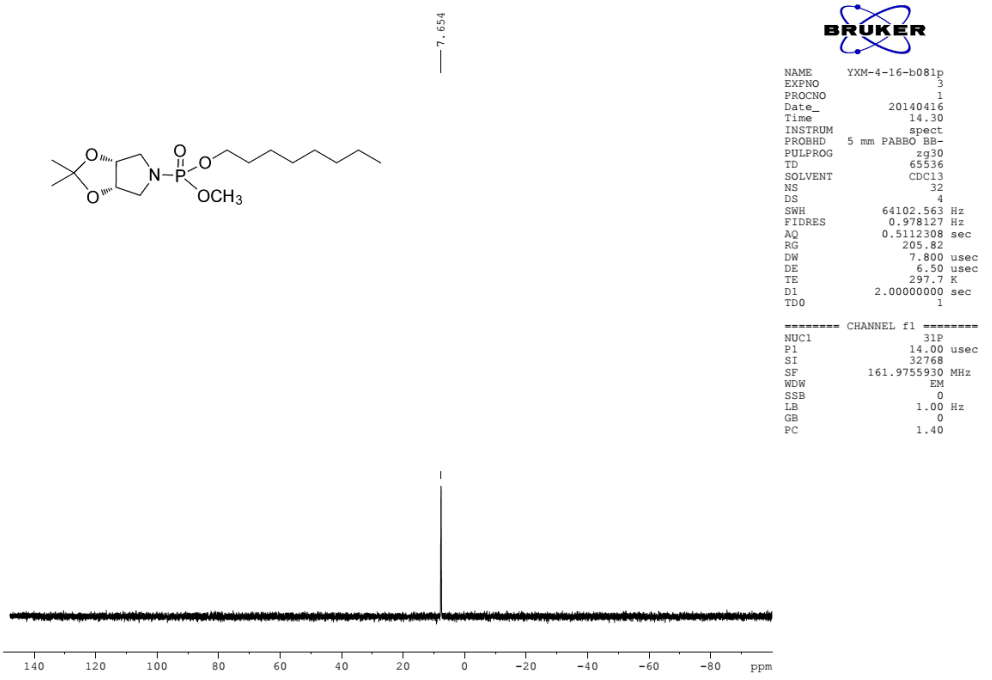



```
NAME        YXM-4-15-b-081
EXPNO                   2
PROCNO                  1
Date_            20140415
Time                12.03
INSTRUM             spect
PROBHD    5 mm PADUL 13C
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  1024
DS                     4
SWH            28409.092 Hz
FIDRES          0.433488 Hz
AQ             1.1534836 sec
RG                  2050
DW                17.600 usec
DE                 6.50 usec
TE                304.2 K
D1             1.25000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.50 usec
PL1                 0.00 dB
PL1W         35.66878891 W
SFO1         100.6288660 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                  1H
PCPD2              60.00 usec
PL2                 0.00 dB
PL12               13.28 dB
PL13               13.05 dB
PL2W          9.46981144 W
PL12W         0.44498092 W
PL13W         0.46918198 W
SFO2         400.1516006 MHz
SI                 32768
SF           100.6177980 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

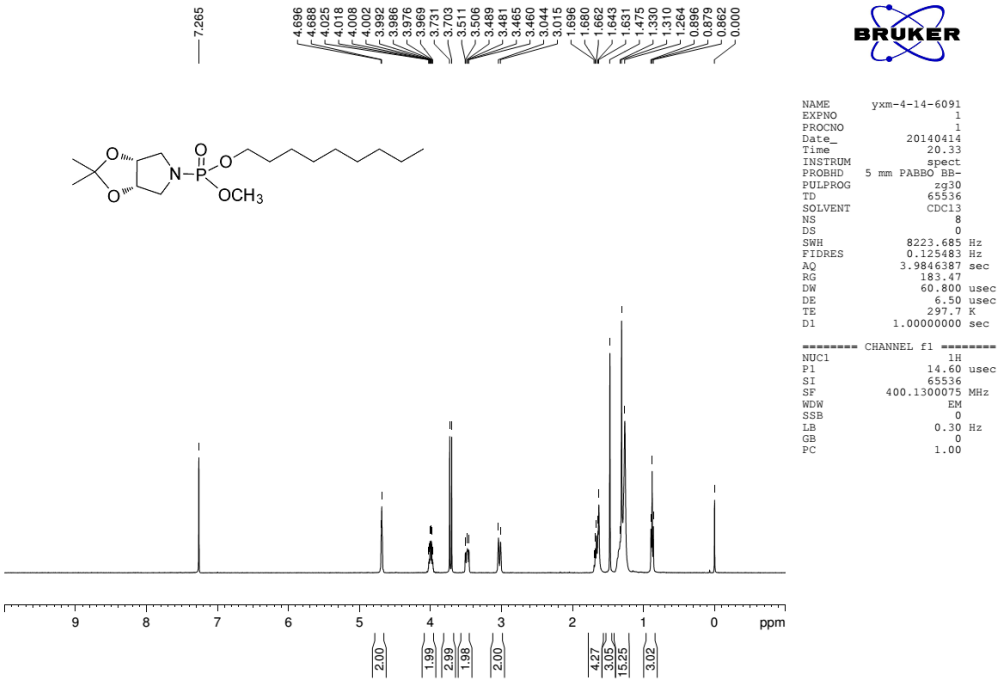
^{13}C NMR Spectrum of Compound **16j**



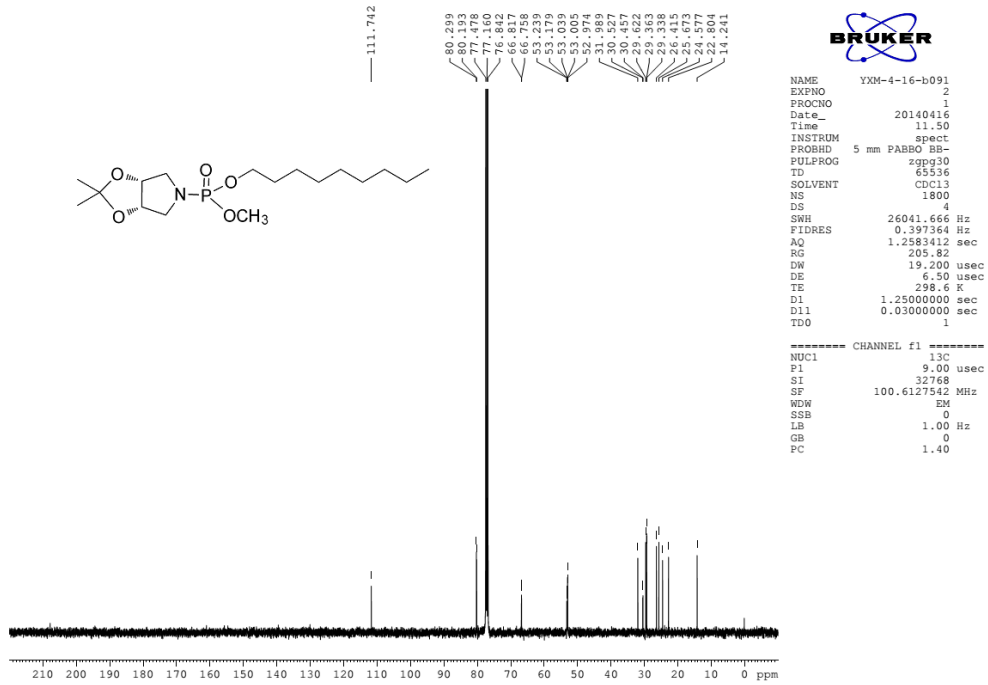

```
NAME        YXM-4-16-b081p
EXPNO                   3
PROCNO                  1
Date_            20140416
Time                14.30
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    32
DS                     4
SWH            64102.563 Hz
FIDRES          0.978127 Hz
AQ             0.5112308 sec
RG                205.82
DW                 7.800 usec
DE                 6.50 usec
TE                297.7 K
D1             2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  31P
P1                 14.00 usec
SI                 32768
SF           161.9755930 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

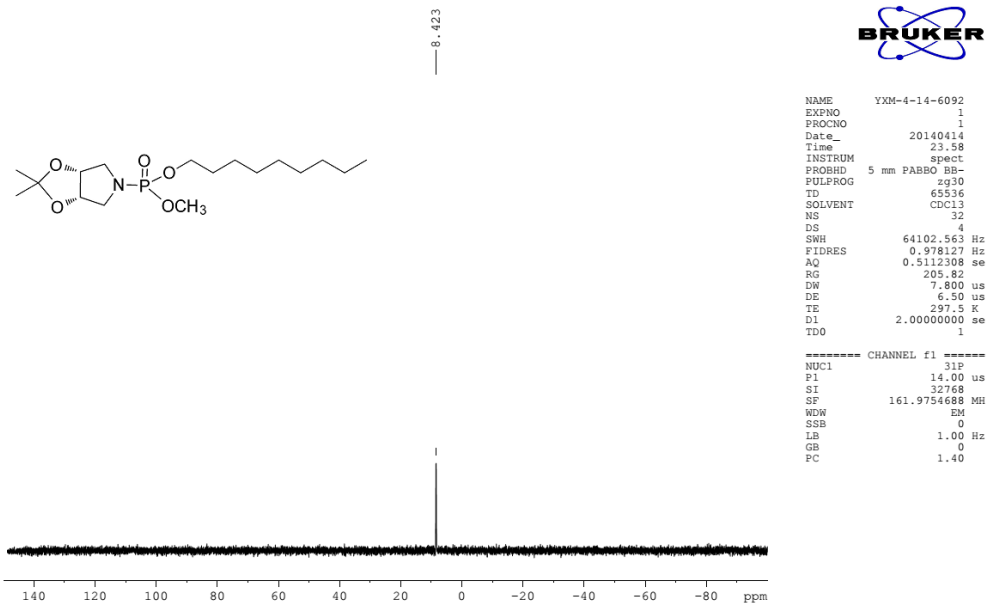
^{31}P NMR Spectrum of Compound **16j**



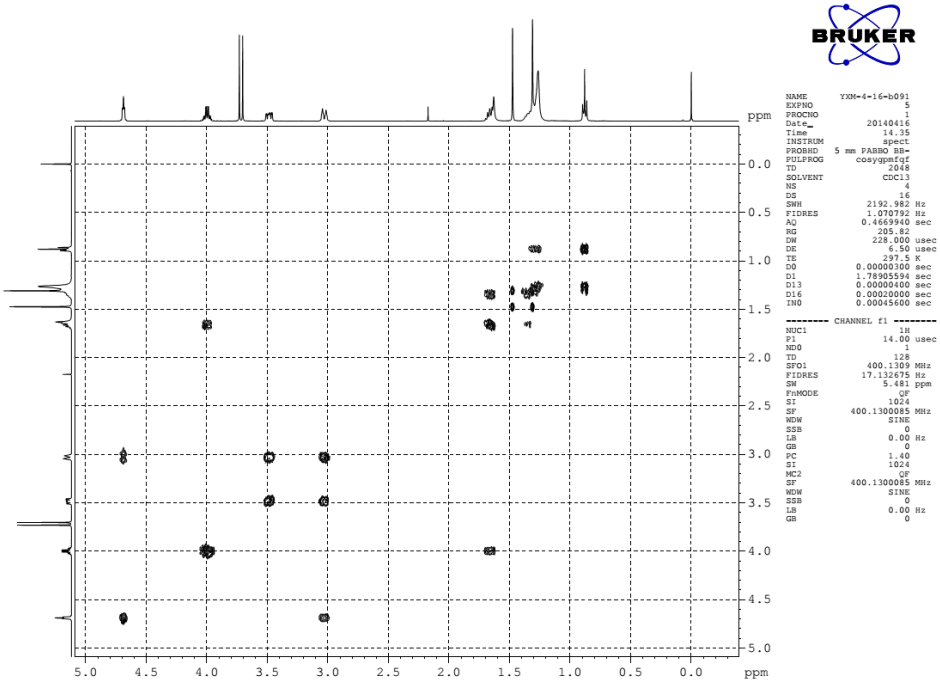
^{1}H NMR Spectrum of Compound **16k**



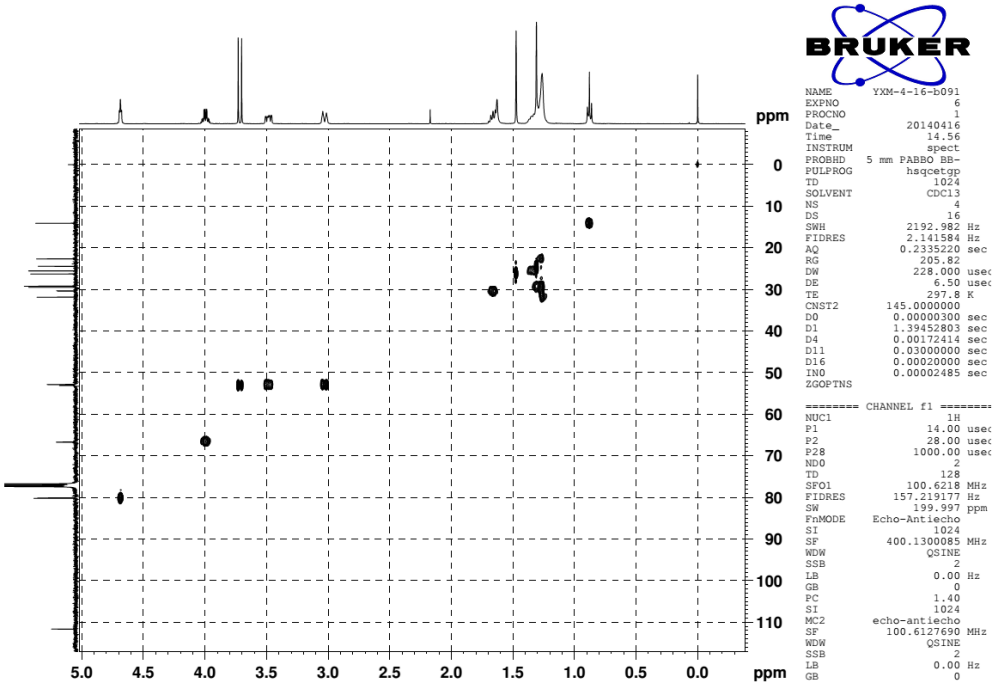
^{13}C NMR Spectrum of Compound **16k**



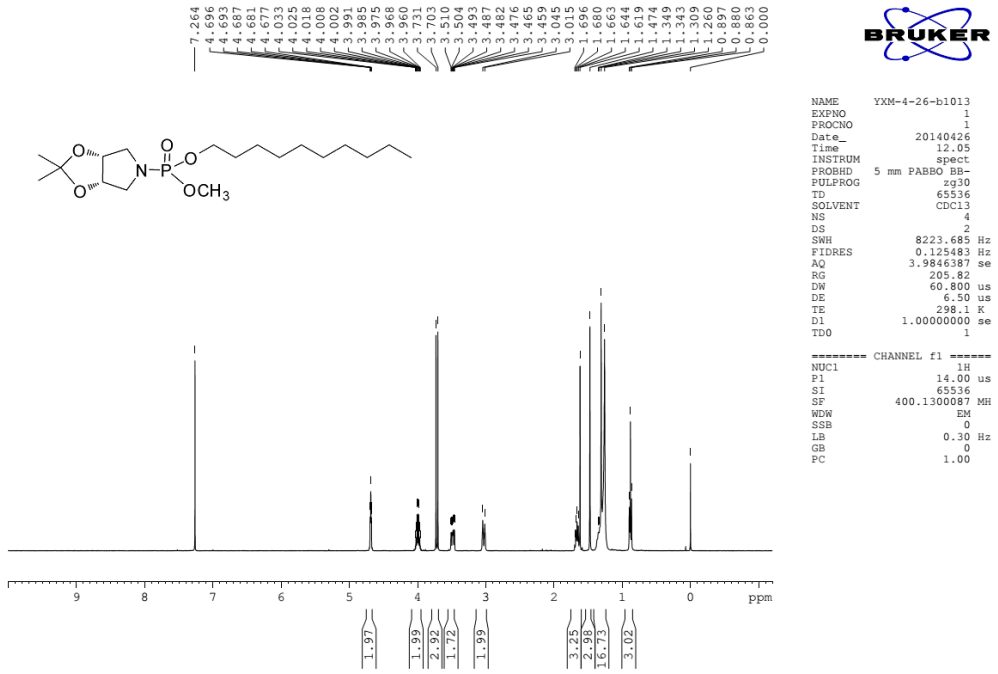
^{31}P NMR Spectrum of Compound **16k**



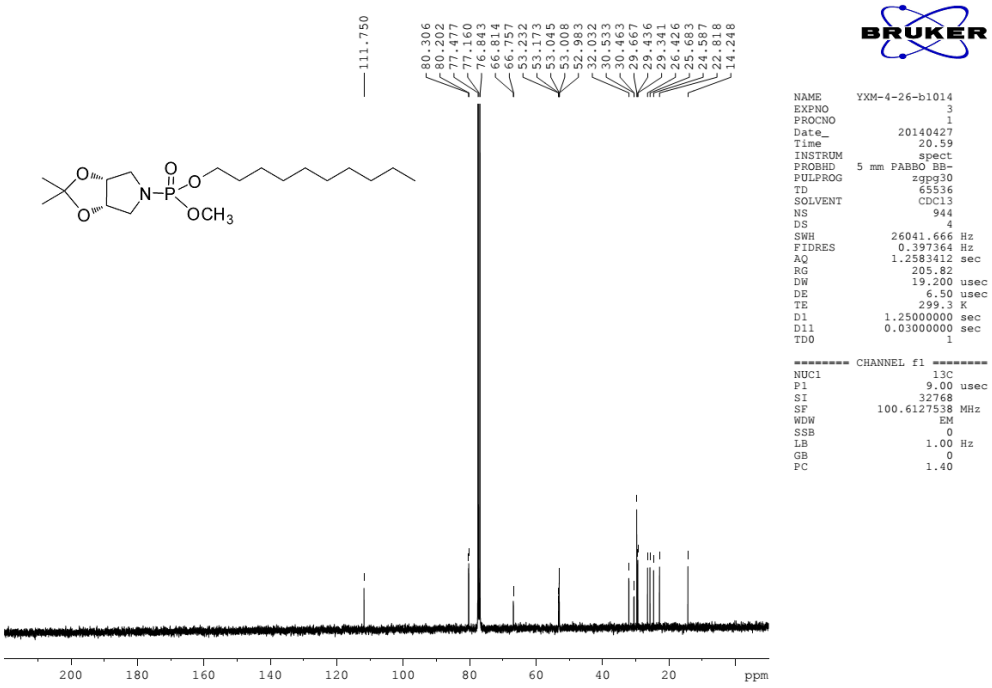
H-H COSY Spectrum of Compound **16k**



HSQC Spectrum of Compound **16k**



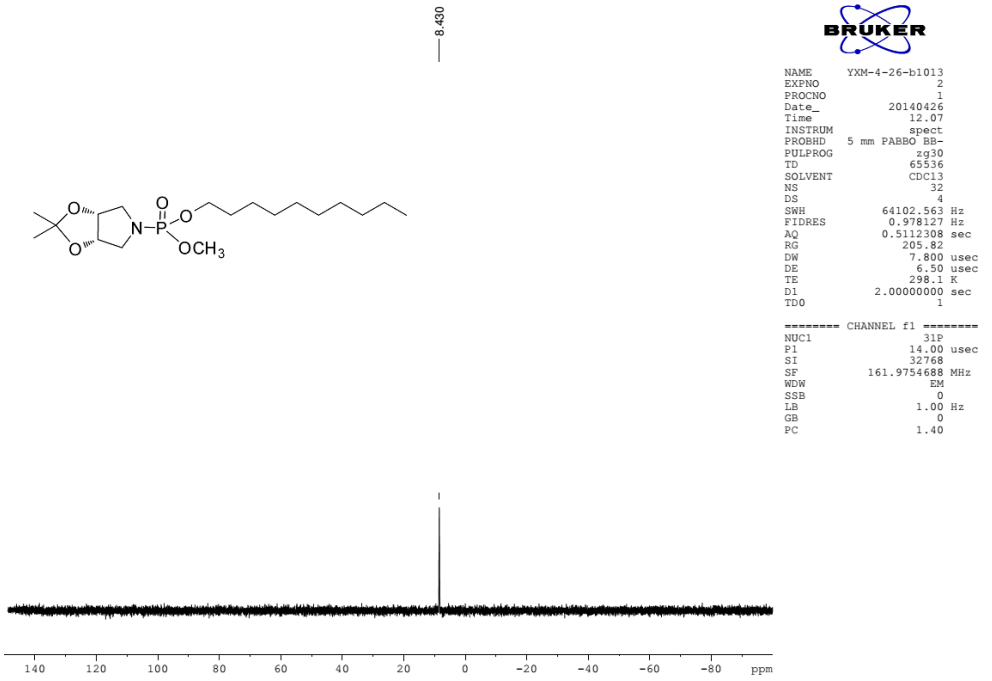
[1]H NMR Spectrum of Compound **16l**




```
NAME        YXM-4-26-b1014
EXPNO                    3
PROCNO                   1
Date_             20140427
Time                 20.59
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   944
DS                     4
SWH            26041.666 Hz
FIDRES          0.397364 Hz
AQ              1.2583412 sec
RG                 205.82
DW                 19.200 usec
DE                  6.50 usec
TE                 299.3 K
D1            1.25000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.00 usec
SI                 32768
SF           100.6127538 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

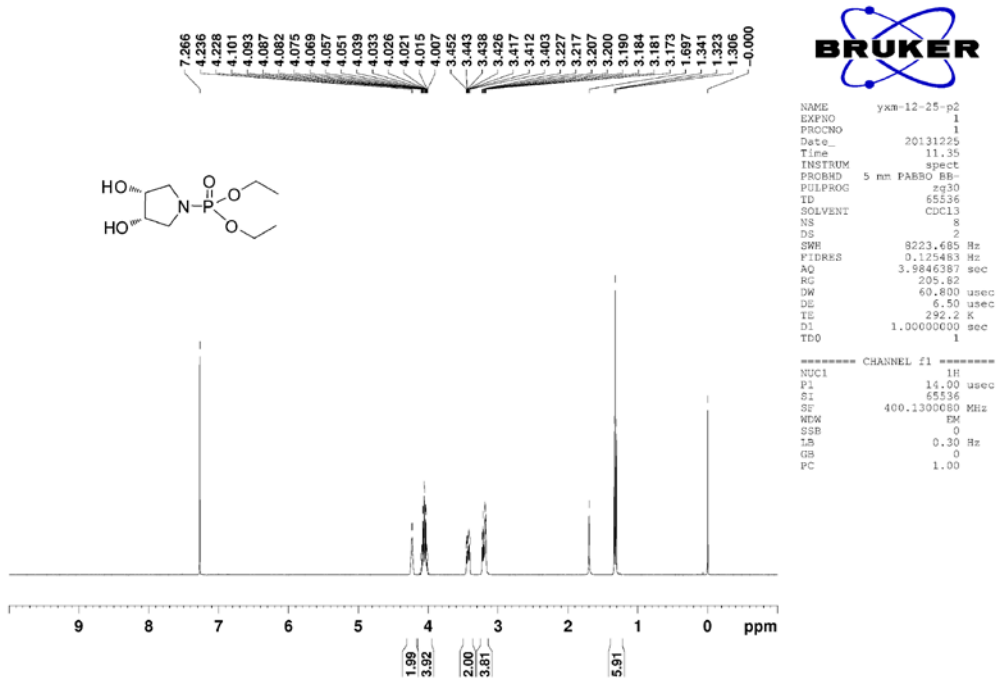
^{13}C NMR Spectrum of Compound **16l**



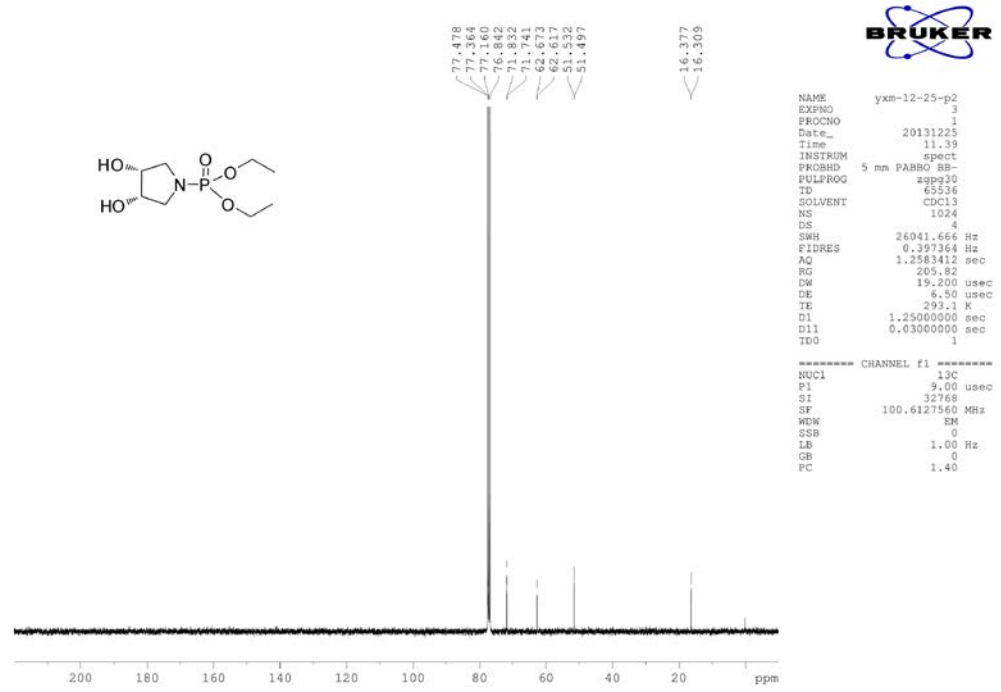

```
NAME        YXM-4-26-b1013
EXPNO                    2
PROCNO                   1
Date_             20140426
Time                 12.07
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                   32
DS                     4
SWH            64102.563 Hz
FIDRES          0.978127 Hz
AQ              0.5112308 sec
RG                 205.82
DW                 7.800 usec
DE                  6.50 usec
TE                 298.1 K
D1            2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 31P
P1                 14.00 usec
SI                 32768
SF           161.9754688 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

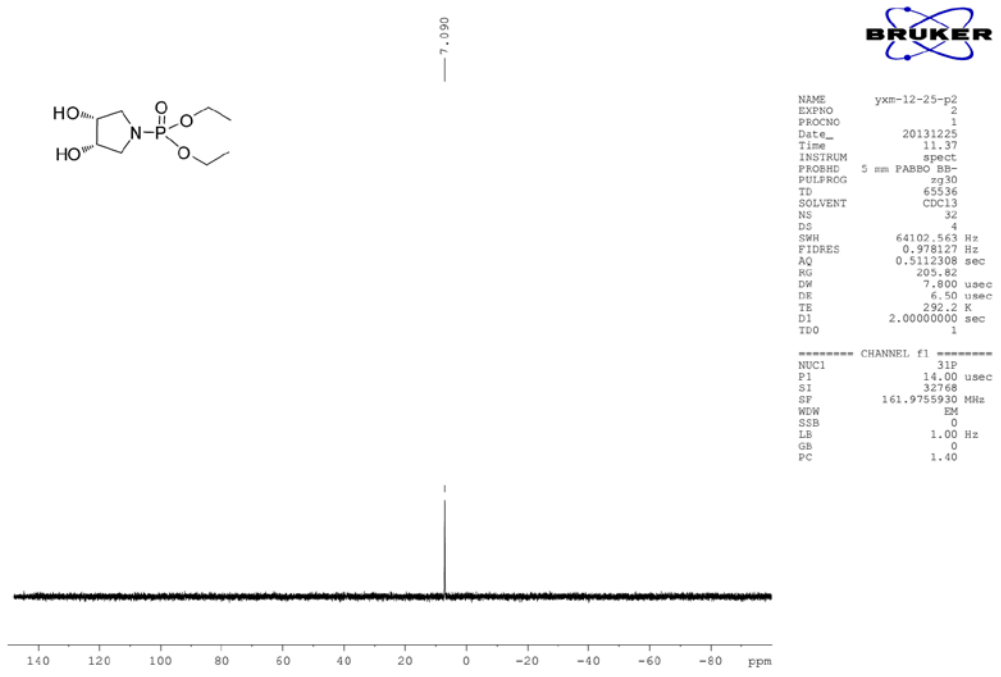
^{31}P NMR Spectrum of Compound **16l**



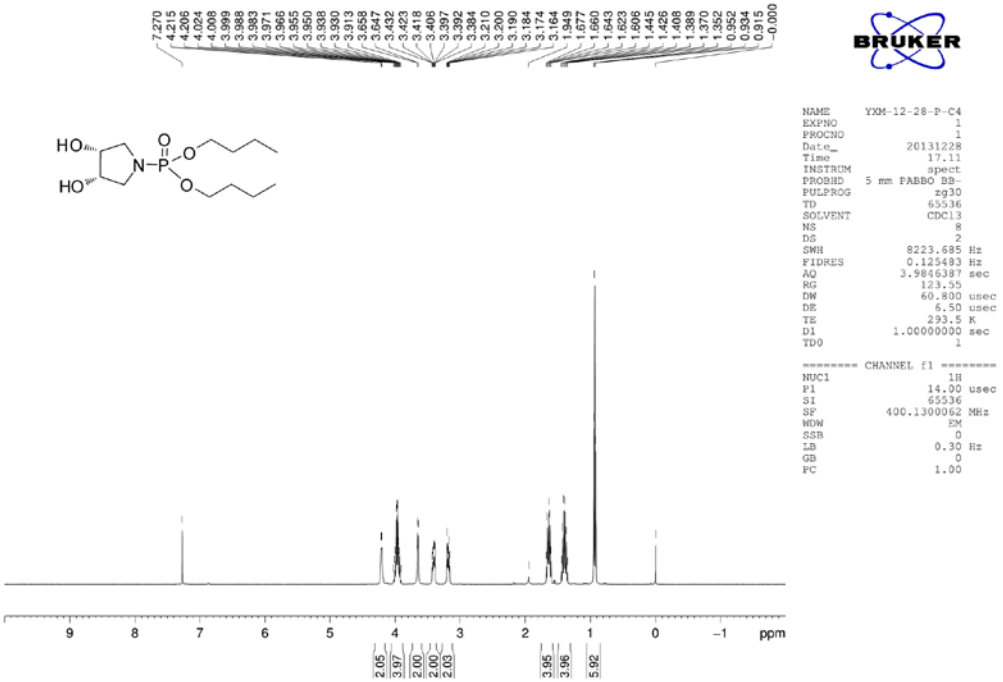
^{1}H NMR Spectrum of Compound **8a**



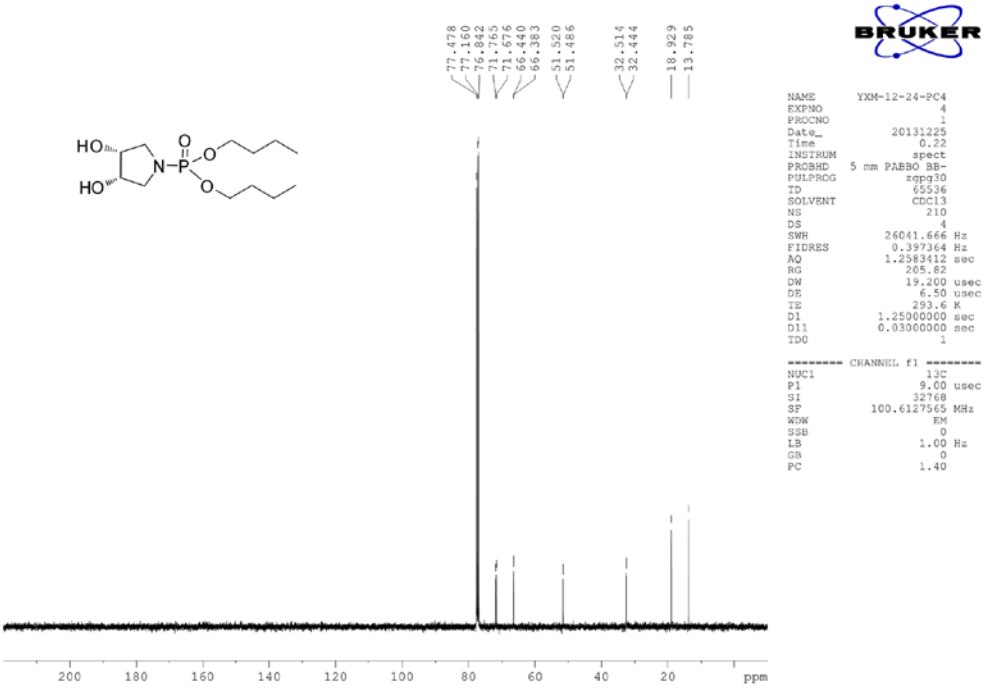
^{13}C NMR Spectrum of Compound **8a**



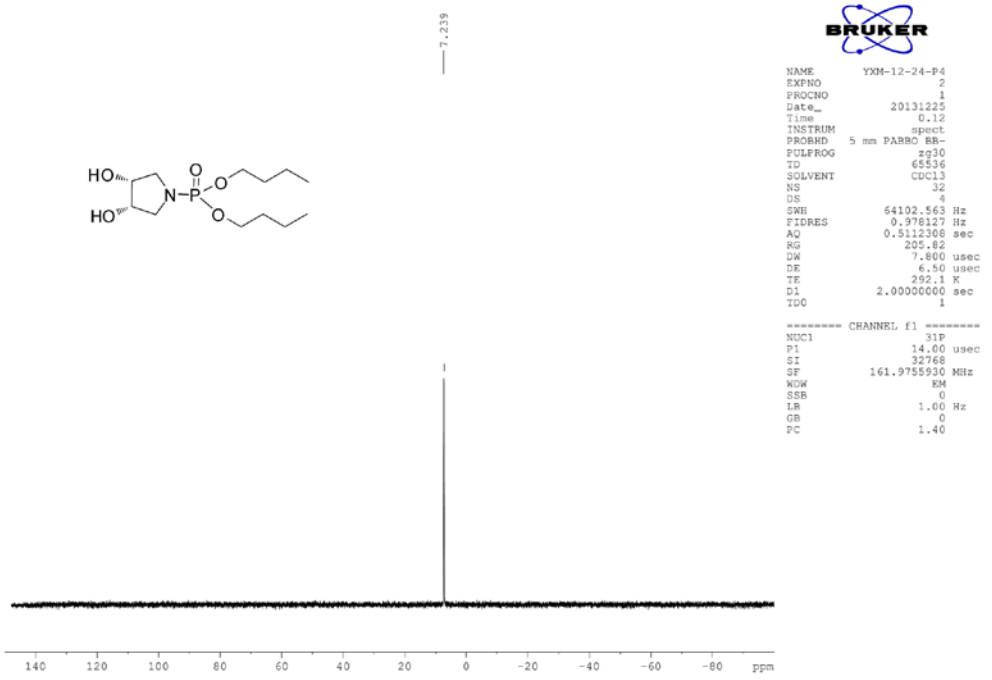
^{31}P NMR Spectrum of Compound **8a**



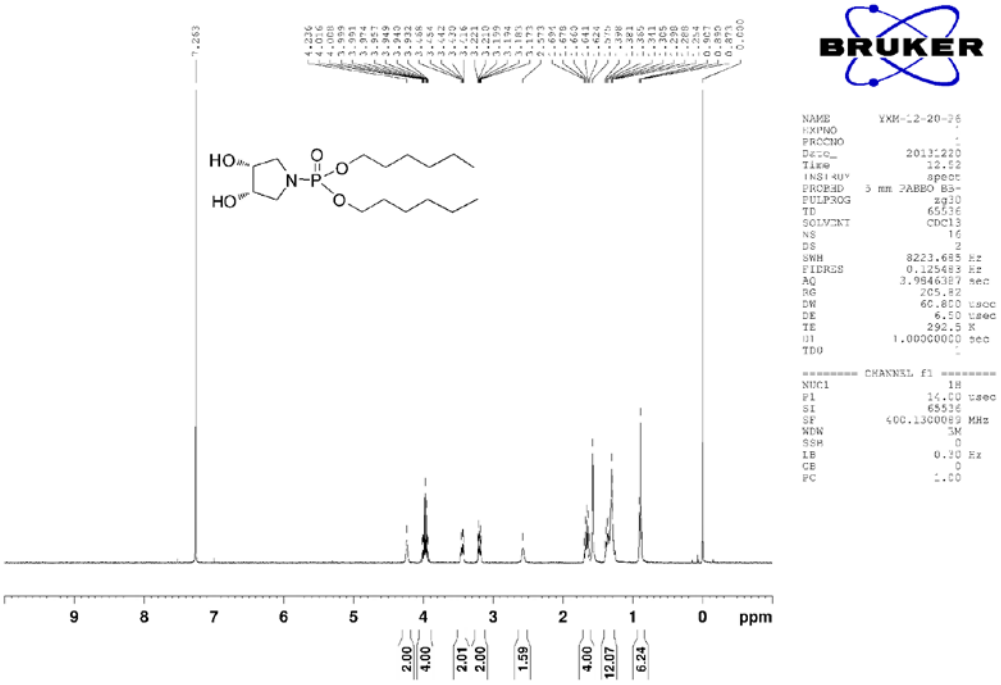
^{1}H NMR Spectrum of Compound **8b**



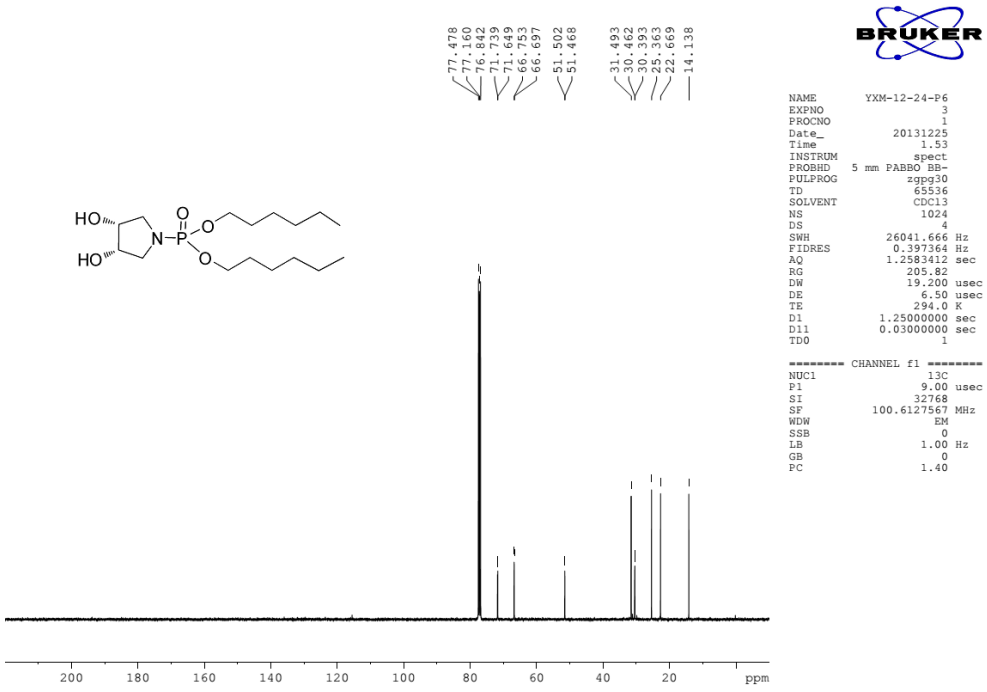
^{13}C NMR Spectrum of Compound **8b**



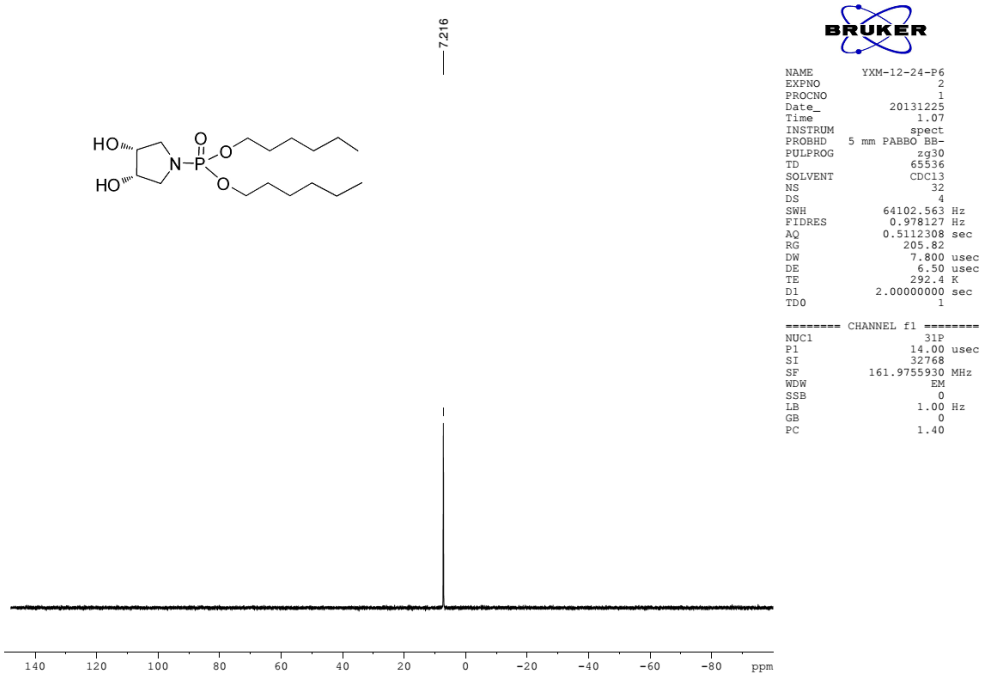
^{31}P NMR Spectrum of Compound **8b**



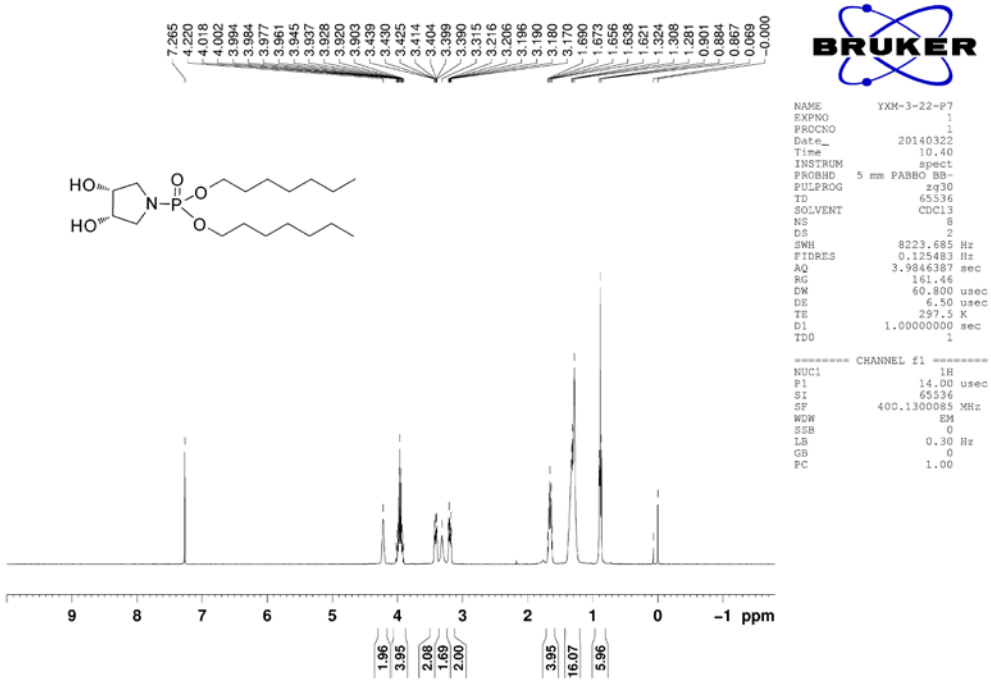
^{1}H NMR Spectrum of Compound **8c**



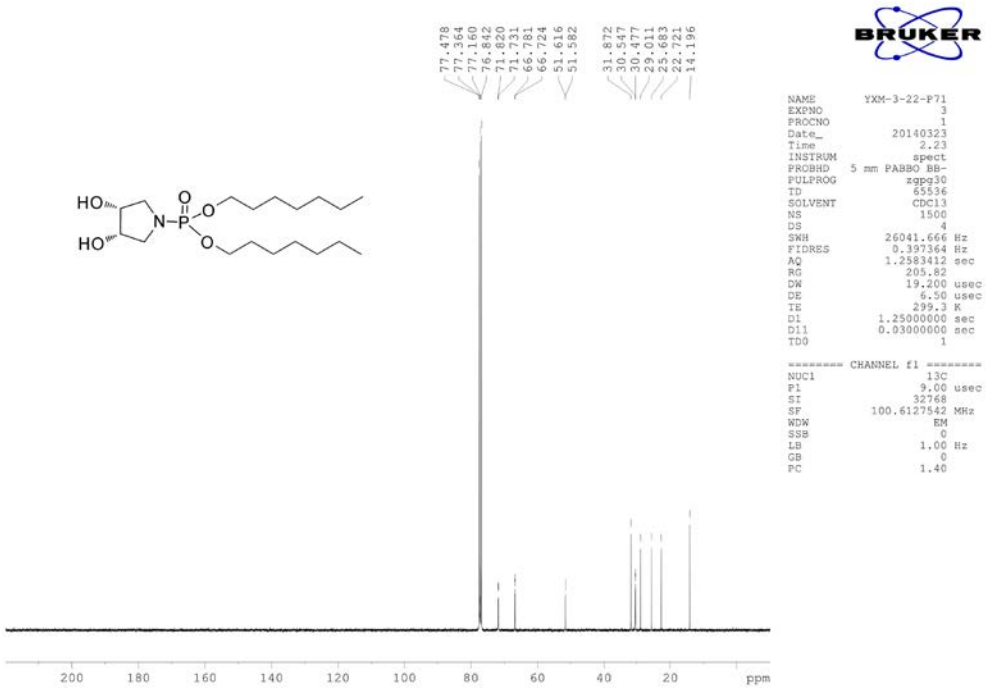
^{13}C NMR Spectrum of Compound **8c**



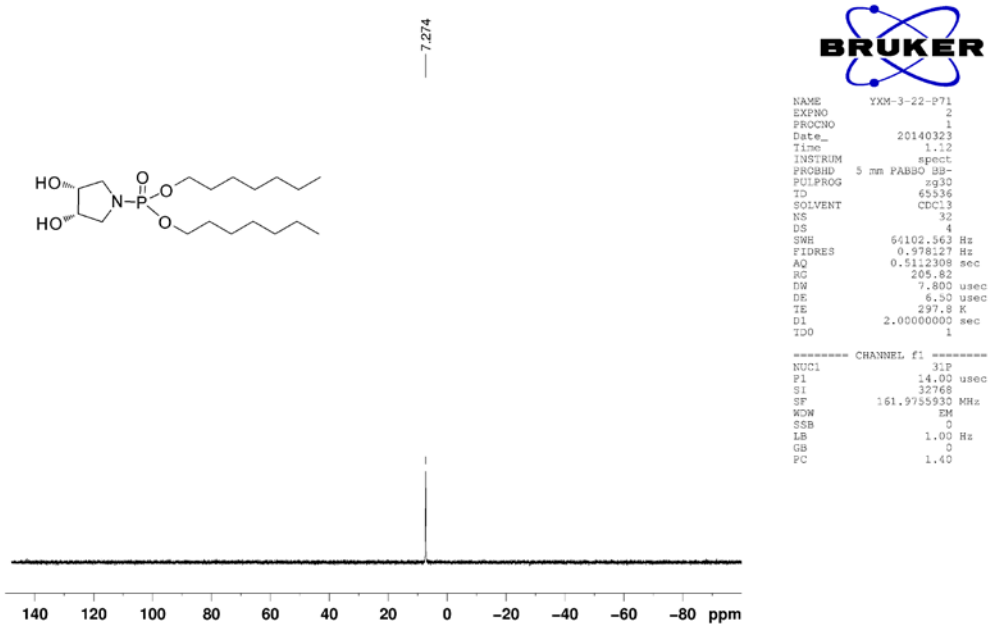
^{31}P NMR Spectrum of Compound **8c**



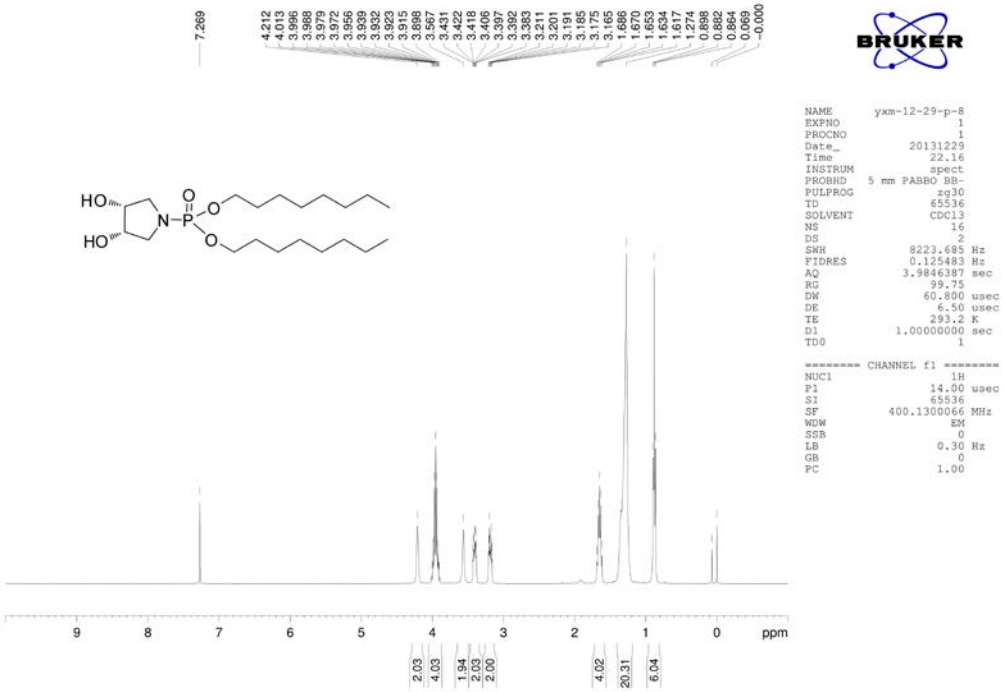
^{1}H NMR Spectrum of Compound **8d**



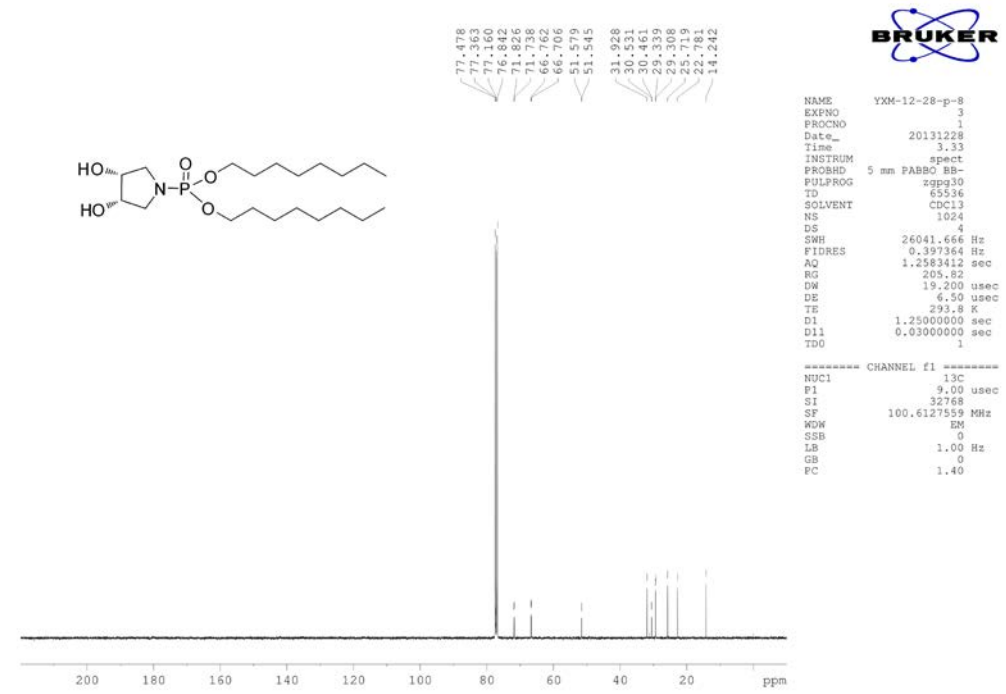
^{13}C NMR Spectrum of Compound **8d**



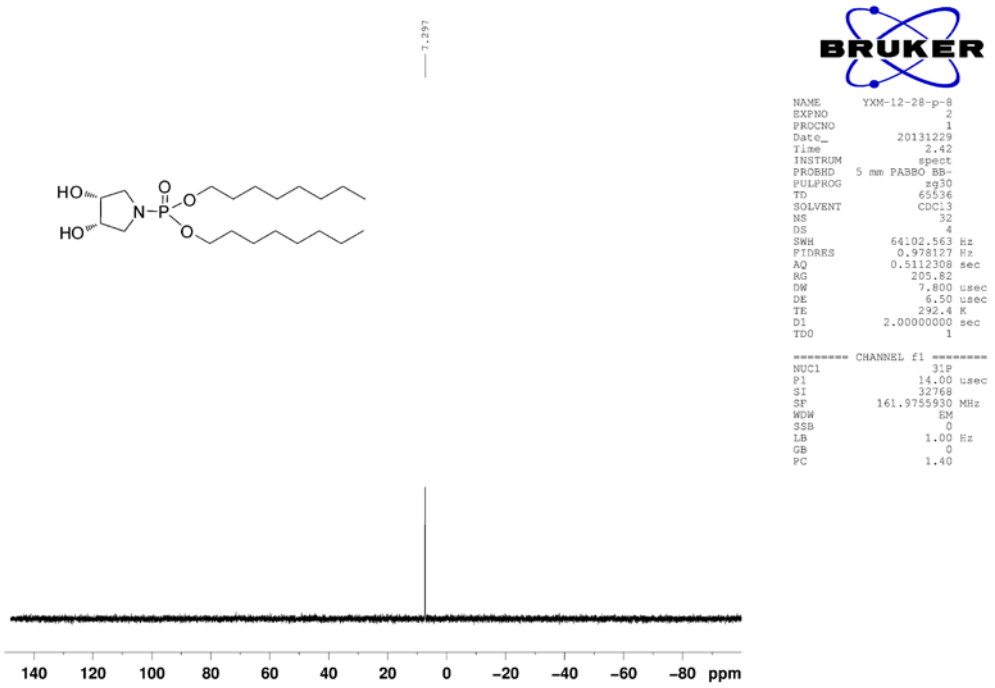
^{31}P NMR Spectrum of Compound **8d**



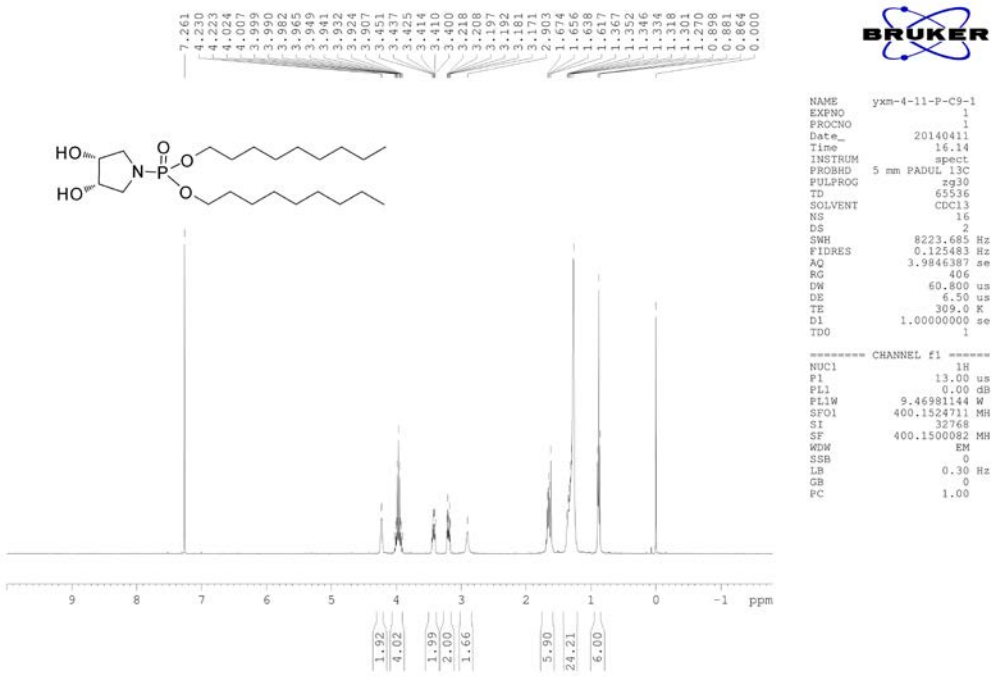
^{1}H NMR Spectrum of Compound **8e**



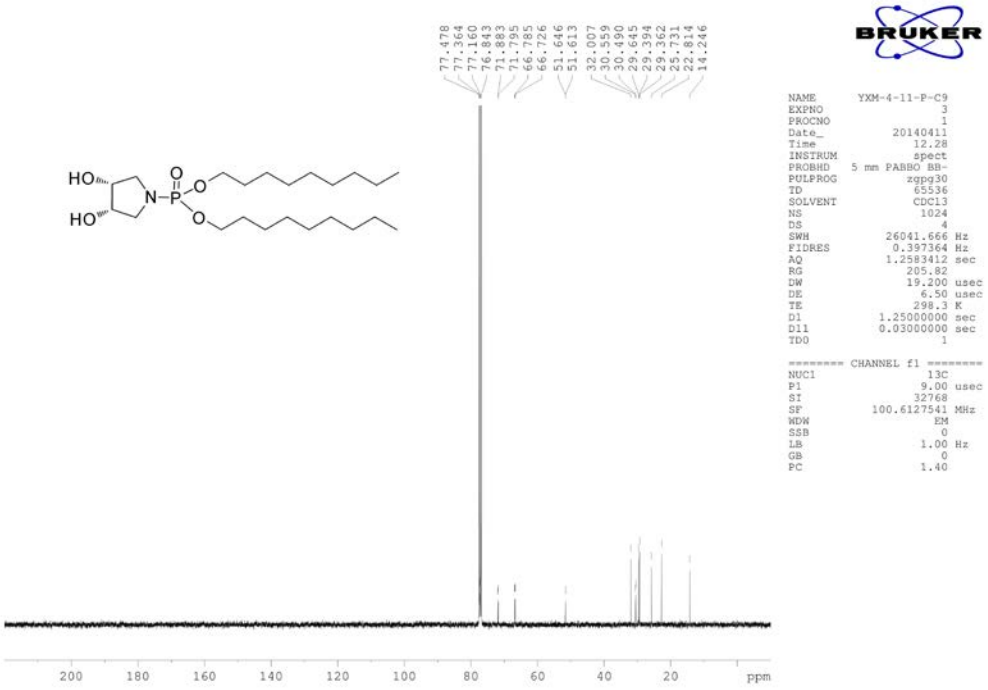
^{13}C NMR Spectrum of Compound **8e**



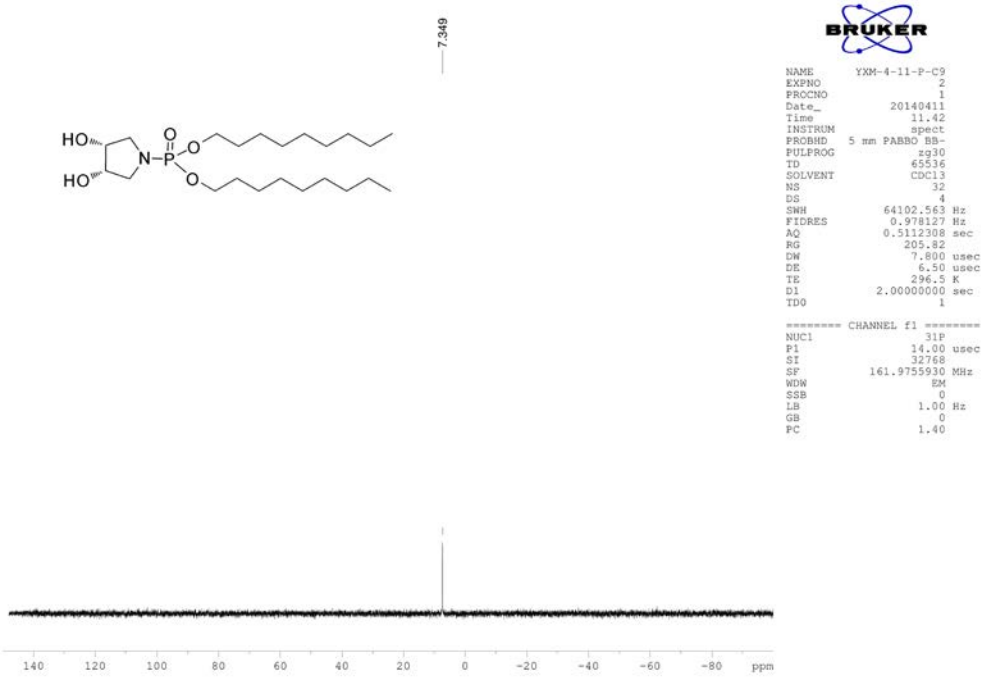
^{31}P NMR Spectrum of Compound **8e**



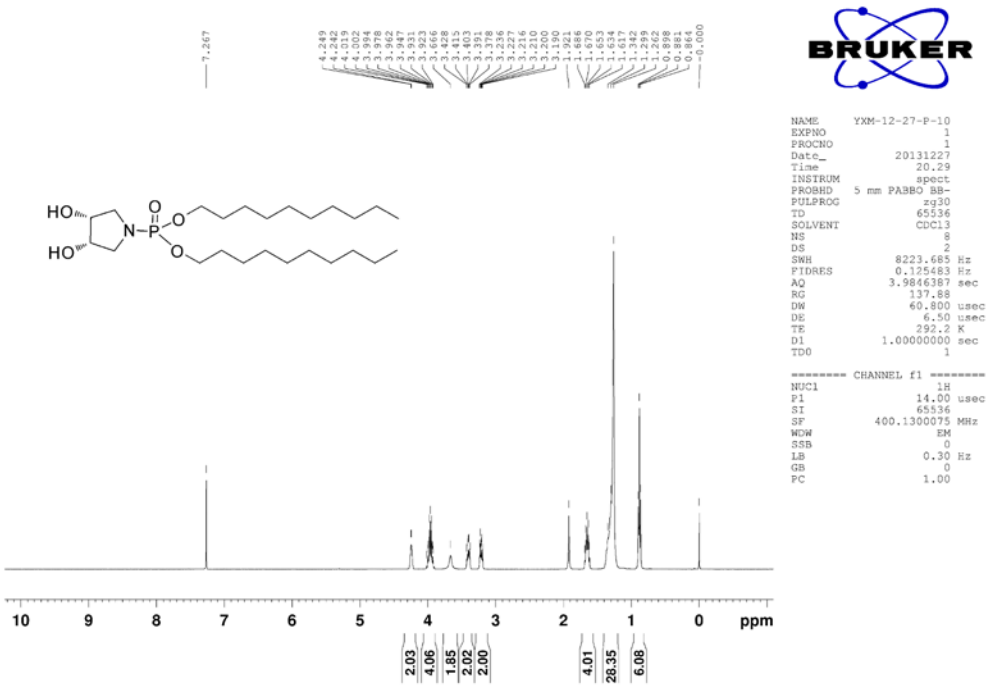
^{1}H NMR Spectrum of Compound **8f**



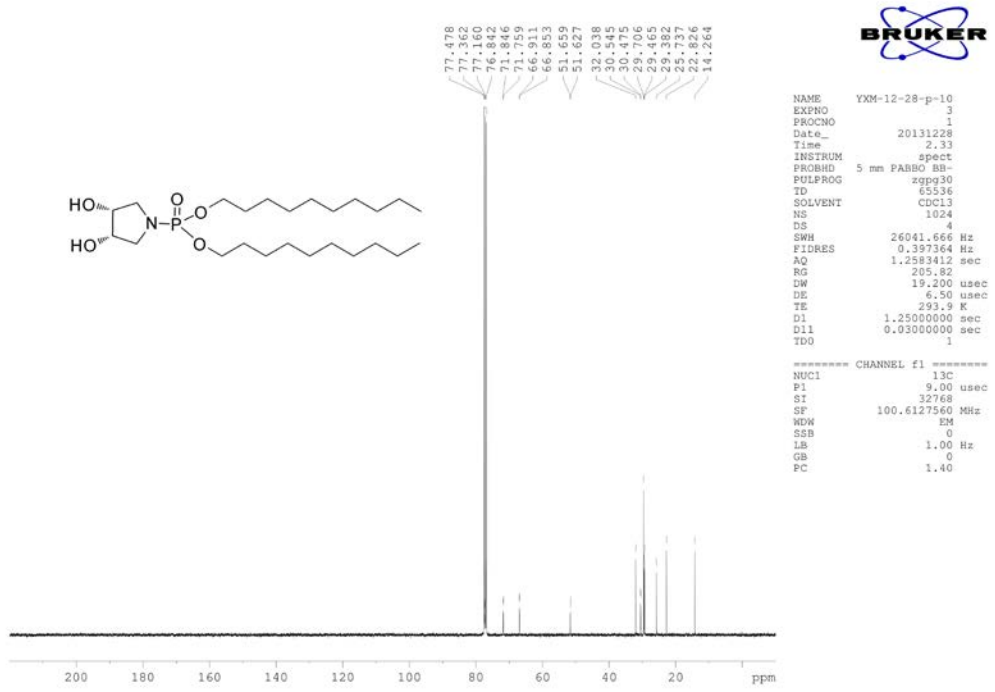
^{13}C NMR Spectrum of Compound **8f**



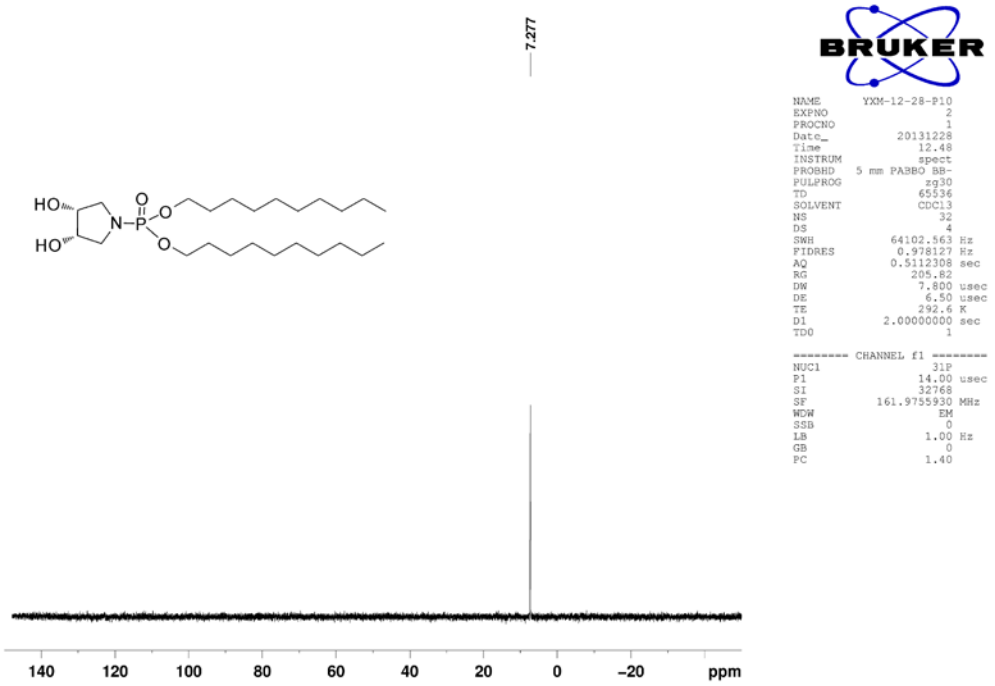
^{31}P NMR Spectrum of Compound **8f**



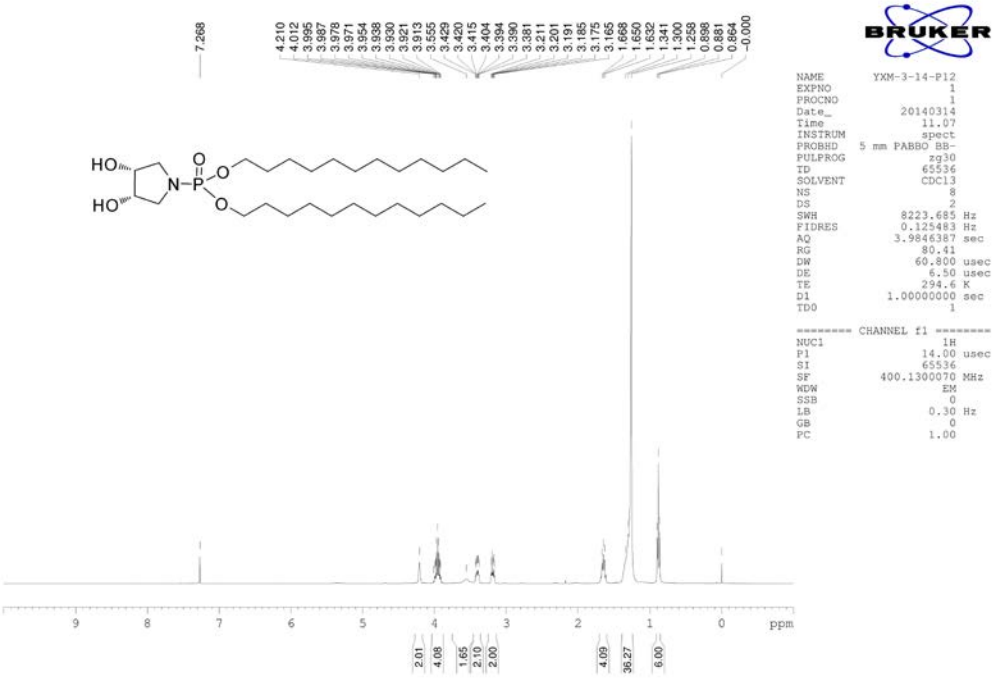
^{1}H NMR Spectrum of Compound **8g**



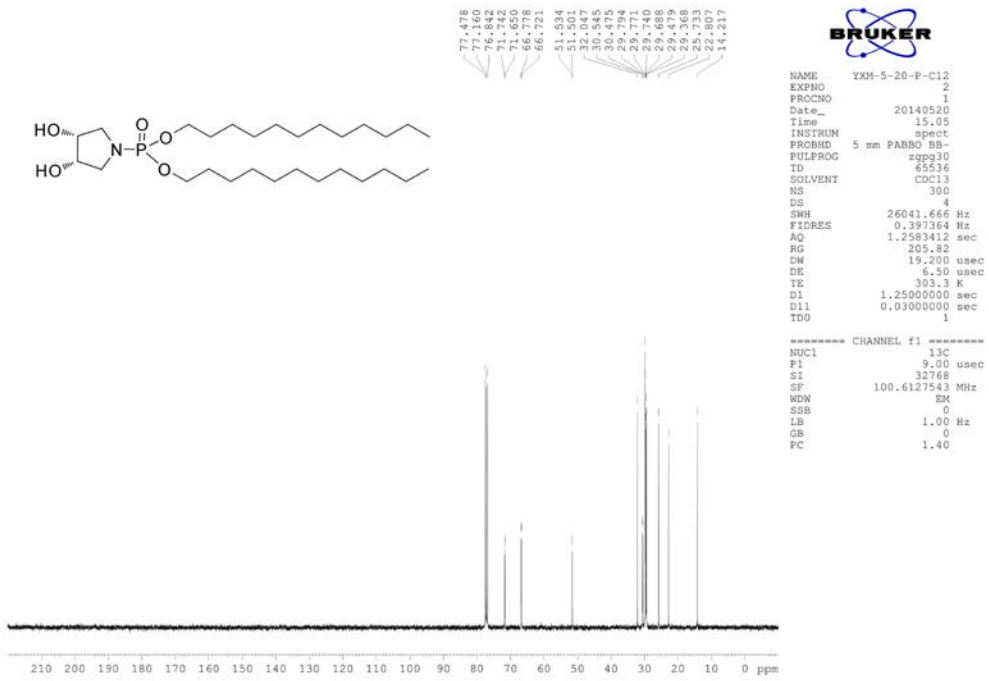
^{13}C NMR Spectrum of Compound **8g**



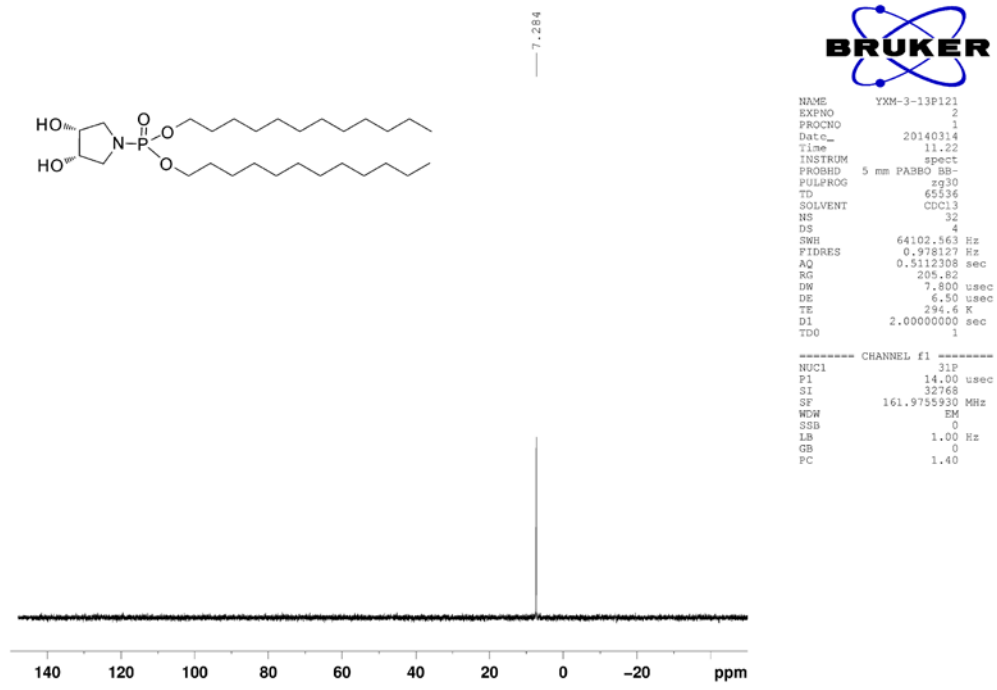
^{31}P NMR Spectrum of Compound **8g**



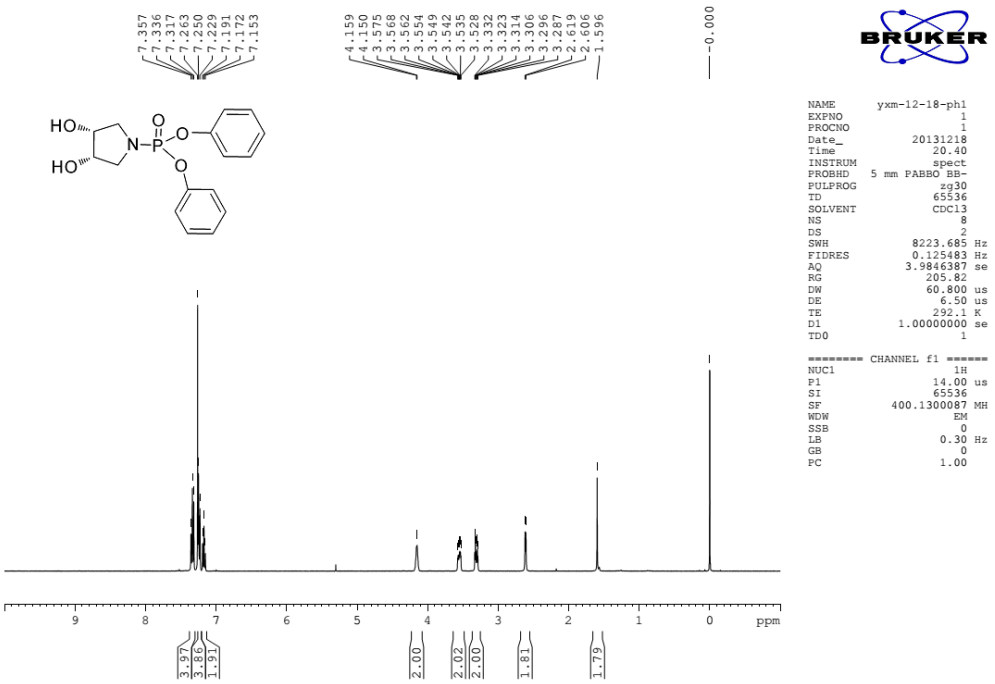
^{1}H NMR Spectrum of Compound **8h**



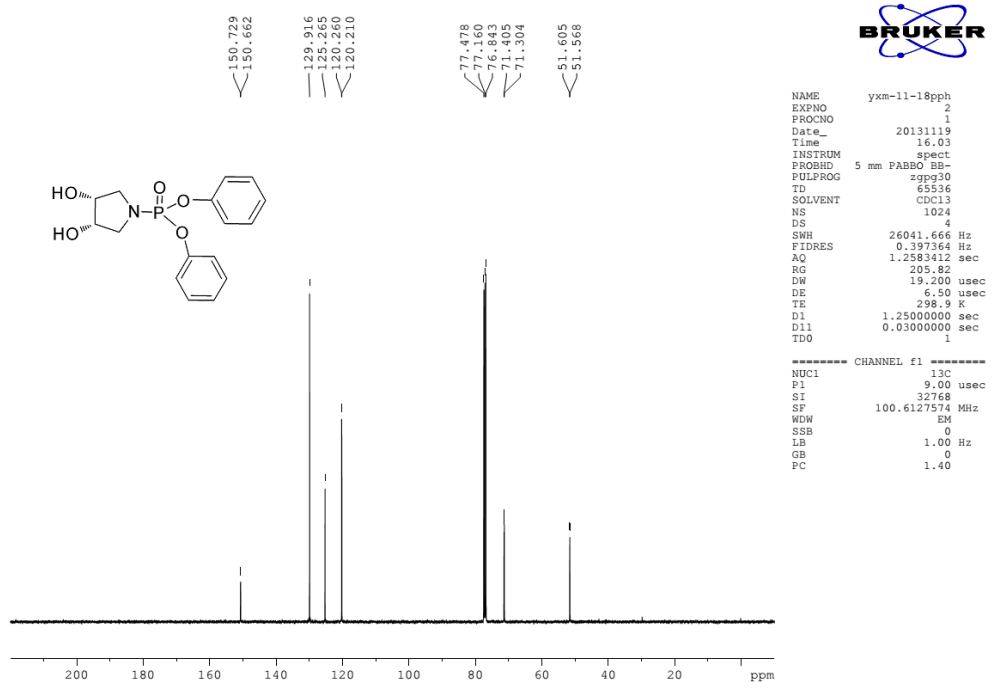
^{13}C NMR Spectrum of Compound **8h**



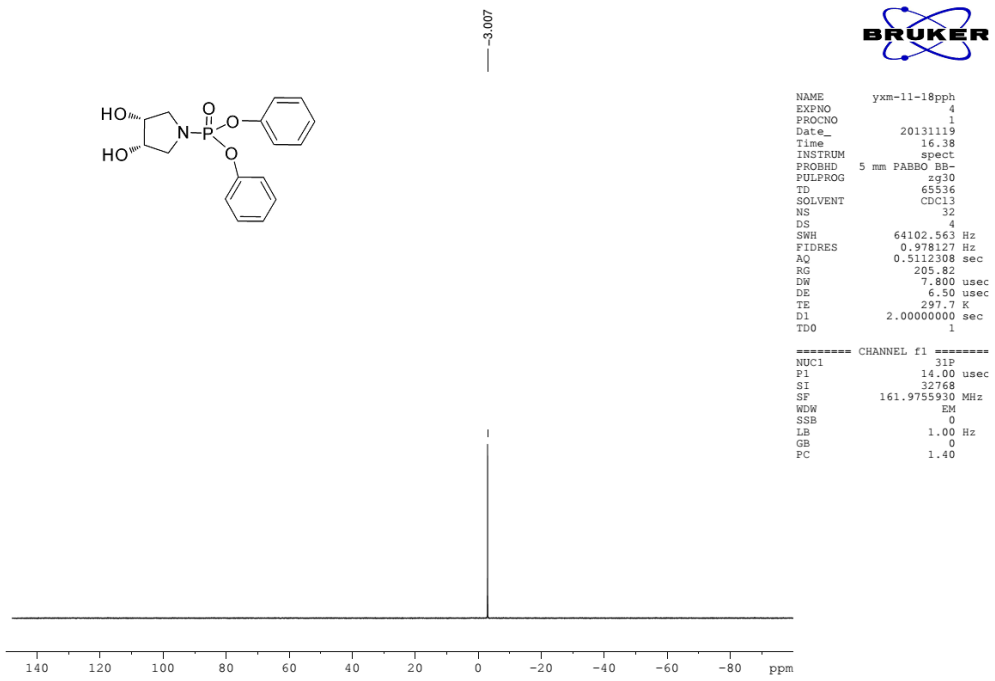
^{31}P NMR Spectrum of Compound **8h**



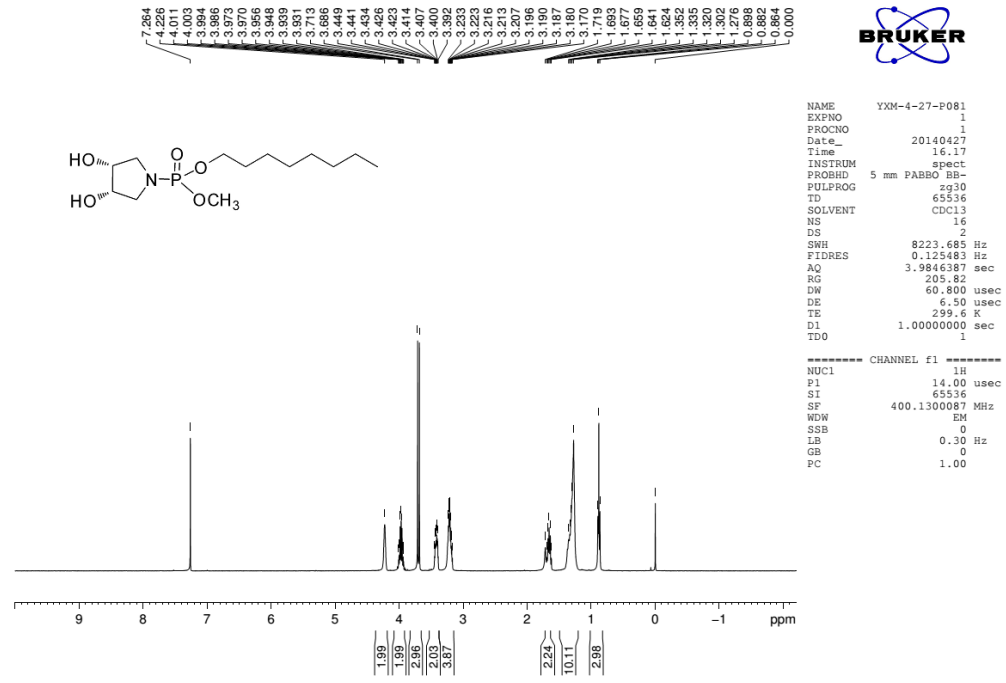
^{1}H NMR Spectrum of Compound **8i**



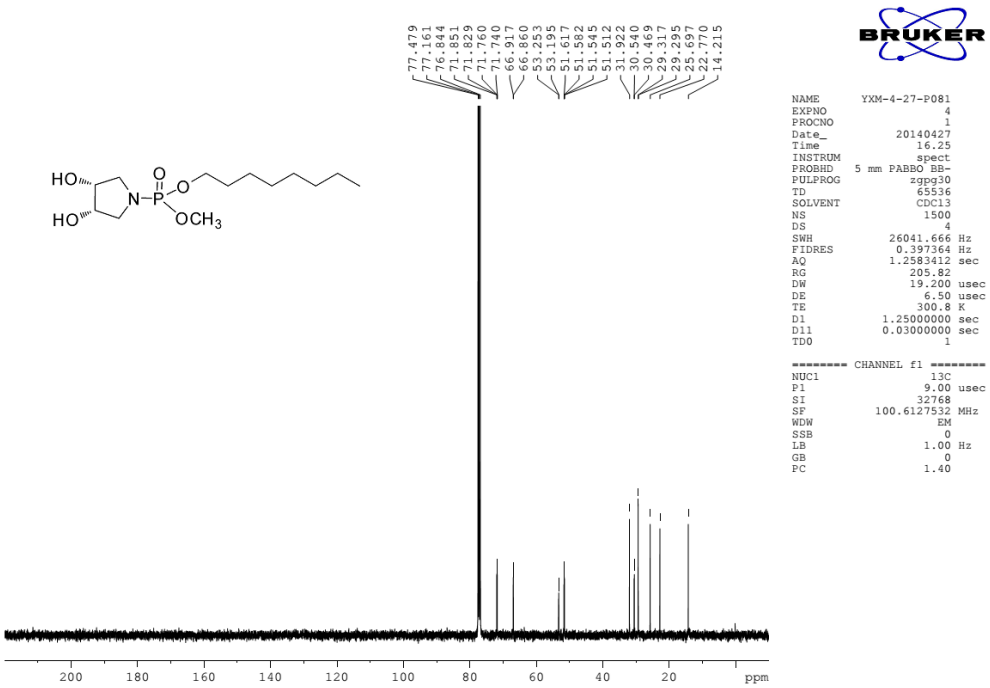
^{13}C NMR Spectrum of Compound **8i**



^{31}P NMR Spectrum of Compound **8i**



^{1}H NMR Spectrum of Compound **8j**

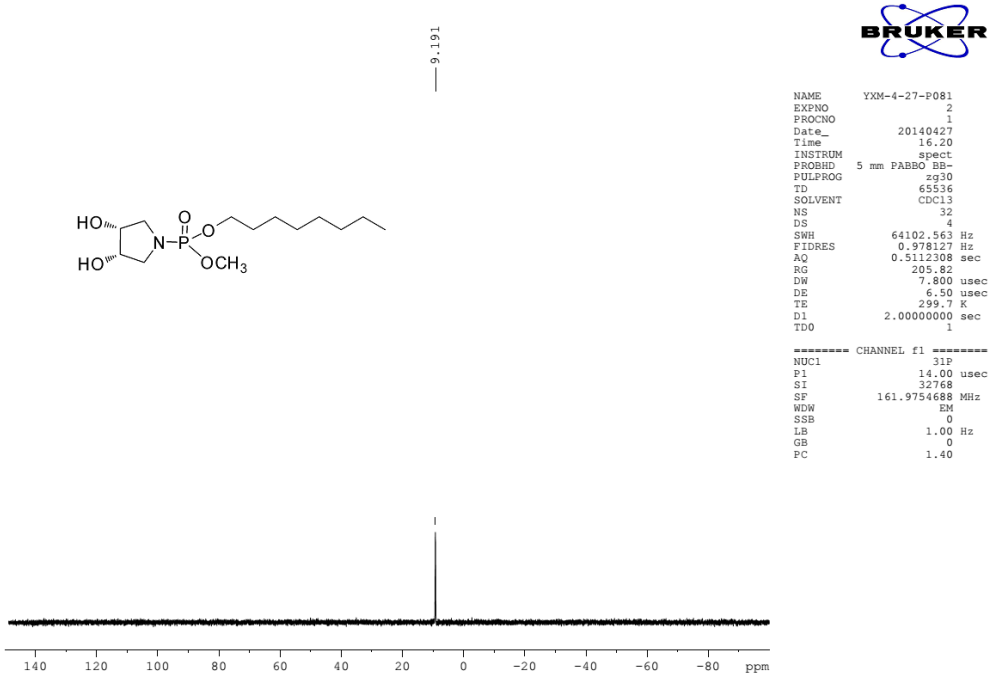


BRUKER

```
NAME          YXM-4-27-P081
EXPNO                    4
PROCNO                   1
Date_             20140427
Time                 16.25
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     1500
DS                        4
SWH              26041.666 Hz
FIDRES            0.397364 Hz
AQ                1.2583412 sec
RG                   205.82
DW                19.200 usec
DE                 6.50 usec
TE                   300.8 K
D1             1.25000000 sec
D11            0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                   9.00 usec
SI                      32768
SF             100.6127532 MHz
WDW                       EM
SSB                        0
LB                   1.00 Hz
GB                         0
PC                      1.40
```

^{13}C NMR Spectrum of Compound **8j**

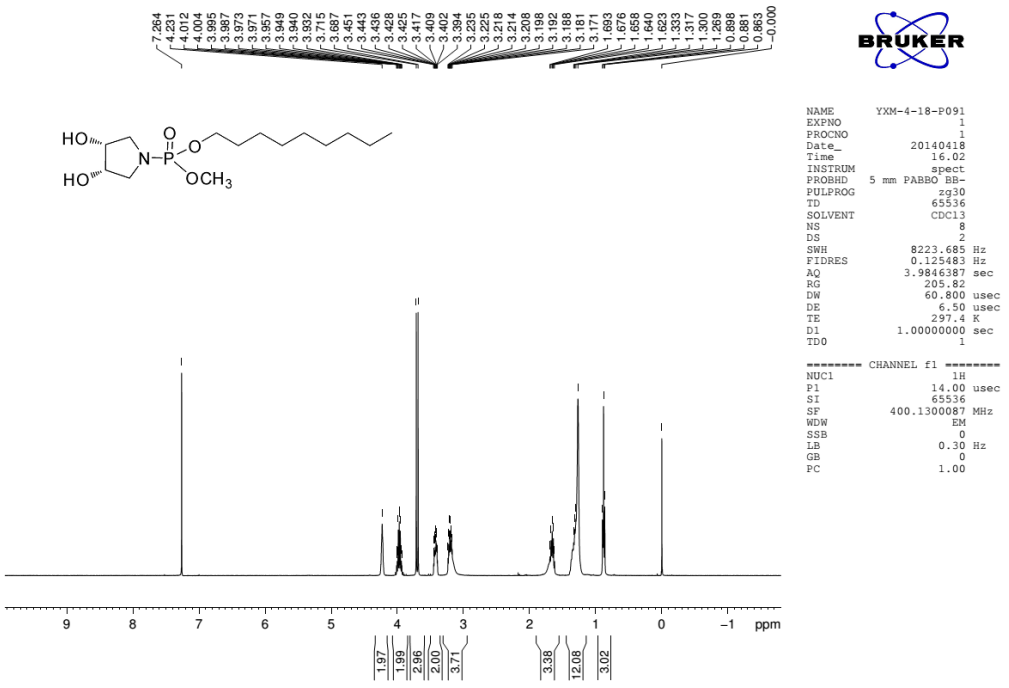


BRUKER

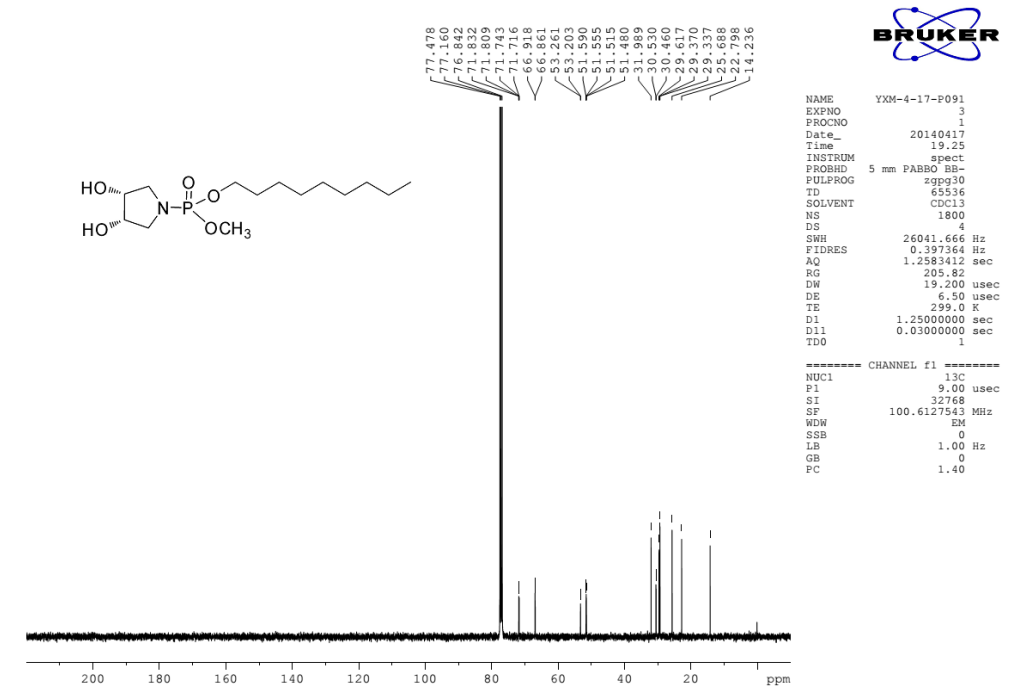
```
NAME          YXM-4-27-P081
EXPNO                    2
PROCNO                   1
Date_             20140427
Time                 16.20
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                    65536
SOLVENT               CDCl3
NS                       32
DS                        4
SWH              64102.563 Hz
FIDRES            0.978127 Hz
AQ                0.5112308 sec
RG                   205.82
DW                 7.800 usec
DE                 6.50 usec
TE                   299.7 K
D1             2.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    31P
P1                  14.00 usec
SI                      32768
SF             161.9754688 MHz
WDW                       EM
SSB                        0
LB                   1.00 Hz
GB                         0
PC                      1.40
```

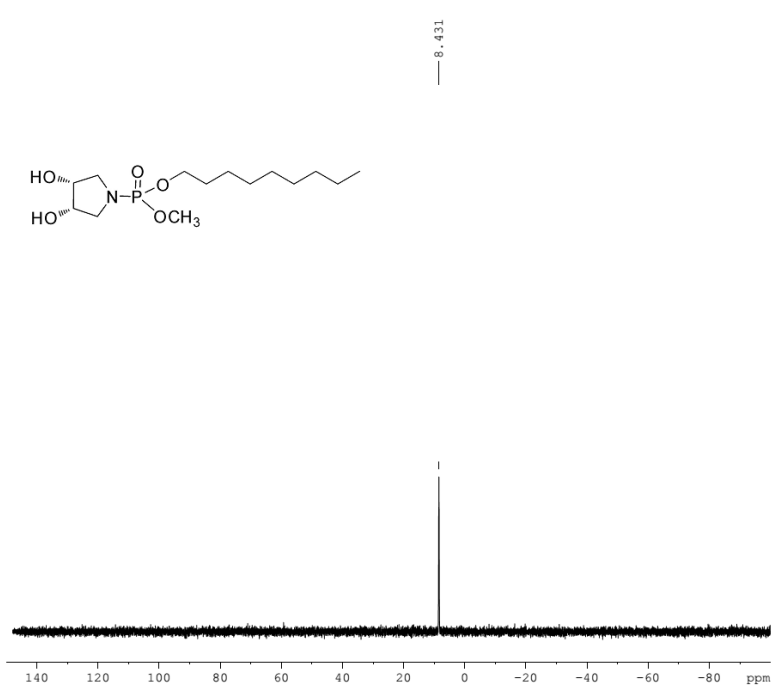
^{31}P NMR Spectrum of Compound **8j**



^{1}H NMR Spectrum of Compound **8k**



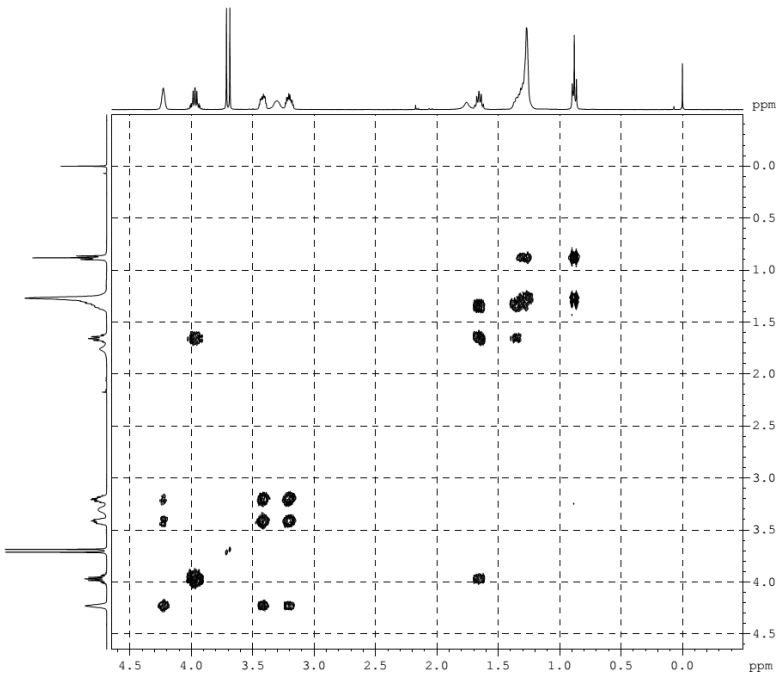
^{13}C NMR Spectrum of Compound **8k**




```
NAME       YXM-4-17-P091
EXPNO                 2
PROCNO                1
Date_          20140417
Time              18.06
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   32
DS                    4
SWH           64102.563 Hz
FIDRES        0.978127 Hz
AQ            0.5112308 sec
RG               205.82
DW                7.800 usec
DE                6.50 usec
TE               297.4 K
D1            2.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 31P
P1                14.00 usec
SI                32768
SF          161.9755930 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

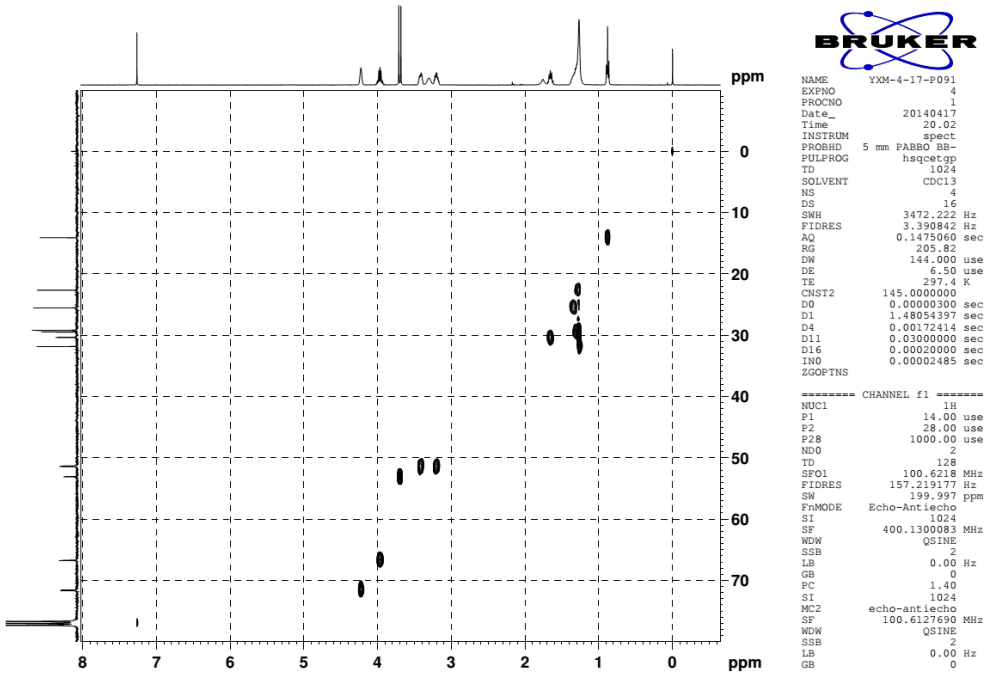
^{31}P NMR Spectrum of Compound **8k**




```
NAME       YXM-4-17-P0914
EXPNO                 5
PROCNO                1
Date_          20140417
Time              20.22
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG       cosygpmfqf
TD                 2048
SOLVENT           CDCl3
NS                    4
DS                   16
SWH           2057.613 Hz
FIDRES        1.004694 Hz
AQ            0.4977140 sec
RG               205.82
DW              243.000 usec
DE                6.50 usec
TE               297.2 K
D0            0.00000300 sec
D1            1.75833595 sec
D13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00048600 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                14.00 usec
ND0                   1
TD                  128
SFO1          400.1308 MHz
FIDRES        16.075104 Hz
SW                5.142 ppm
FnMODE                QF
SI                 1024
SF          400.1300082 MHz
WDW                SINE
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.40
SI                 1024
MC2                   QF
SF          400.1300082 MHz
WDW                SINE
SSB                   0
LB                 0.00 Hz
GB                    0
```

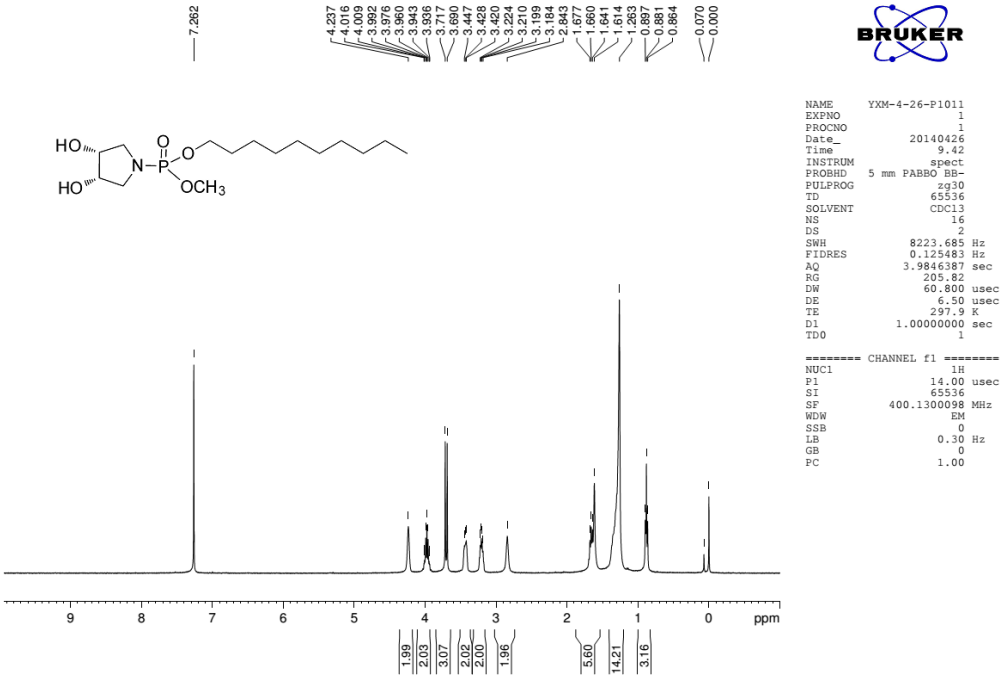
H-H COSY Spectrum of Compound **8k**




```
NAME          YXM-4-17-P091
EXPNO                    4
PROCNO                   1
Date_             20140417
Time                 20.02
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG          hsqcetgp
TD                    1024
SOLVENT            CDCl3
NS                       4
DS                      16
SWH               3472.222 Hz
FIDRES            3.390842 Hz
AQ               0.1475060 sec
RG                  205.82
DW                  144.000 use
DE                    6.50 use
TE                  297.4 K
CNST2          145.0000000
D0              0.00000300 sec
D1              1.48054397 sec
D4              0.00172414 sec
D11             0.03000000 sec
D16             0.00020000 sec
IN0             0.00002485 sec
ZGOPTNS

======== CHANNEL f1 =======
NUC1                    1H
P1                   14.00 use
P2                   28.00 use
P28                1000.00 use
ND0                      2
TD                     128
SFO1             100.6218 MHz
FIDRES           157.219177 Hz
SW                199.997 ppm
FnMODE     Echo-Antiecho
SI                    1024
SF             400.1300083 MHz
WDW                  QSINE
SSB                      2
LB                    0.00 Hz
GB                       0
PC                    1.40
SI                    1024
MC2          echo-antiecho
SF              100.6127690 MHz
WDW                  QSINE
SSB                      2
LB                    0.00 Hz
GB                       0
```

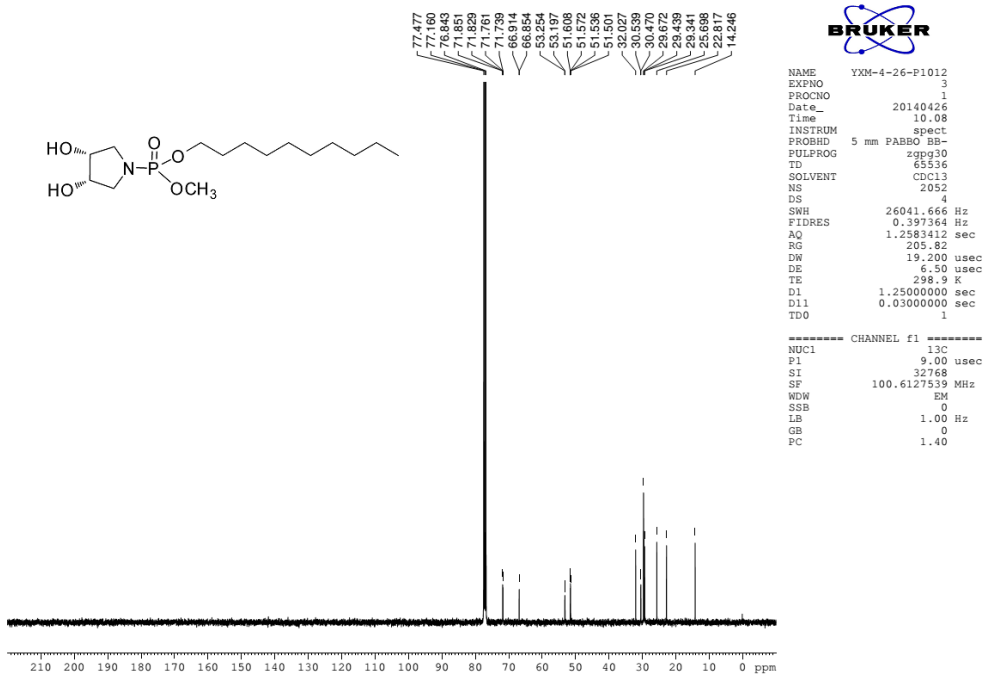
HSQC Spectrum of Compound **8k**




```
NAME          YXM-4-26-P1011
EXPNO                    1
PROCNO                   1
Date_             20140426
Time                 9.42
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT            CDCl3
NS                      16
DS                       2
SWH               8223.685 Hz
FIDRES            0.125483 Hz
AQ                3.9846387 sec
RG                  205.82
DW                  60.800 usec
DE                    6.50 usec
TE                  297.9 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   14.00 usec
SI                  65536
SF             400.1300098 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

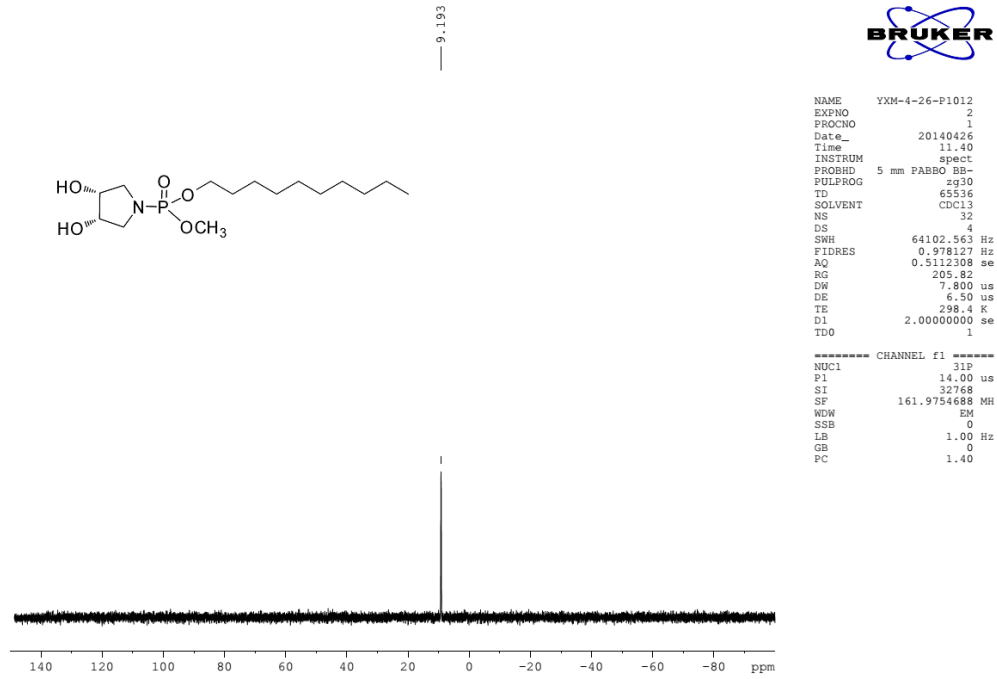
^{1}H NMR Spectrum of Compound **8l**



NAME YXM-4-26-P1012
EXPNO 3
PROCNO 1
Date_ 20140426
Time 10.08
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 2052
DS 4
SWH 26041.666 Hz
FIDRES 0.397364 Hz
AQ 1.2583412 sec
RG 205.82
DW 19.200 usec
DE 6.50 usec
TE 298.9 K
D1 1.25000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
SI 32768
SF 100.6127539 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

^{13}C NMR Spectrum of Compound **8l**



NAME YXM-4-26-P1012
EXPNO 2
PROCNO 1
Date_ 20140426
Time 11.40
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDC13
NS 32
DS 4
SWH 64102.563 Hz
FIDRES 0.978127 Hz
AQ 0.5112308 se
RG 205.82
DW 7.800 us
DE 6.50 us
TE 298.4 K
D1 2.00000000 se
TD0 1

======== CHANNEL f1 ======
NUC1 31P
P1 14.00 us
SI 32768
SF 161.9754688 MH
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

^{31}P NMR Spectrum of Compound **8l**