An unusual reaction of α-alkoxyphosphonium salts with Grignard reagents under an O_2 atmosphere

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General

The ^{1}H and ^{13}C NMR spectra were measured by JEOL JNM-GX 500, JNM-ECS 400 and JNM-AL 300 spectrometers with tetramethylsilane as an internal standard at 25 ºC. The ^{19}F and ^{31}P NMR spectra were measured by JNM-ECS 400 spectrometers at 25 ºC. IR spectra were recorded by SHIMADZU FTIR-8400 or IRAffinity-1 using a diffuse reflectance measurement of samples dispersed in KBr powder. High resolution mass spectra were recorded by JEOL LMS-D 300 spectrometers. Merck silica gel 60 (230-400 mesh) or Kanto Chemical Silicagel 60 (spherical, 63-210 μm) was used for column chromatography.

Materials

Acetals **1a**, **1c**, **1f**, **1g**, **1h**, **1i**, **1j** and **1k** were synthesized from commercially available corresponding aldehydes and alcohols. Acetal **1m** was prepared according to the literature procedure.[1] Grignard reagents **3b**, **3c** and **3d** were prepared from commercially available corresponding aryl bromide and Mg turning with titration using Paquette's method.[2] ^{18}O-methanol and $^{18}O_2$ gas were purchased from Taiyo Nissan Co. Ltd. and used without further purification. Other reagents including **1b**, **1d**, and **1e** were commercially available and used without further purification.

General procedure for the preparation of acetals 1a, 1c, 1f-k, and 1m. [1, 3]

A solution of aldehyde (1 equiv), 10-camphorsulfonic acid (0.15 equiv) and alcohol

(50 equiv) in dry CH_2Cl_2 (0.1 M) was stirred at room temperature. After checking for the disappearance of the aldehyde on TLC, sat. $NaHCO_3$ aq. was added to the reaction mixture and the solution was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and then evaporated under vacuum. The residue was purified by flash column chromatography on SiO_2 to give the acetal **1**.

***n*-Dodecanal dimethyl acetal (1a)**[3]: eluent (hexane-CH_2Cl_2 = 3/2); colorless oil; ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, t, *J* = 7.0 Hz), 1.26-1.33 (18H, brm), 1.56-1.61 (2H, m), 3.31 (6H, s), 4.36 (1H, t, *J* = 5.5 Hz).

***p*-Tolaldehyde dimethyl acetal (1c)**[4]: eluent (hexane-AcOEt = 10/1); colorless oil; ^{1}H NMR ($CDCl_3$): δ 2.35 (3H, s), 3.32 (6H, s), 5.36 (1H, s), 7.17 (2H, d, *J* = 8.5 Hz), 7.33 (2H, d, *J* = 8.5 Hz).

***p*-(Trifluoromethyl)benzaldehyde dimethyl acetal (1f)**[4]: eluent (hexane-CH_2Cl_2 = 3/2); colorless oil; ^{1}H NMR ($CDCl_3$): δ 3.33 (6H, s), 5.44 (1H, s), 7.58 (2H, d, *J* = 8.0 Hz), 7.63 (2H, d, *J* = 8.0 Hz).

Thiophene-2-carbaldehyde dimethyl acetal (1g)[5]: eluent (hexane-AcOEt = 10/1); yellow oil; ^{1}H NMR ($CDCl_3$): δ 3.36 (6H, s), 5.64 (1H, s), 7.01 (1H, dd, *J* = 5.0, 3.7 Hz), 7.08 (1H, dd, *J* = 3.7, 1.4 Hz), 7.30 (1H, dd, *J* = 5.0, 1.4 Hz).

2-Phenyl-1,3-dioxolane (1h)[6]: eluent (hexane-AcOEt = 20/1); colorless oil; ^{1}H NMR ($CDCl_3$): δ 4.02-4.15 (4H, m), 5.82 (1H, s), 7.36-7.41 (3H, m), 7.46-7.50 (2H, m).

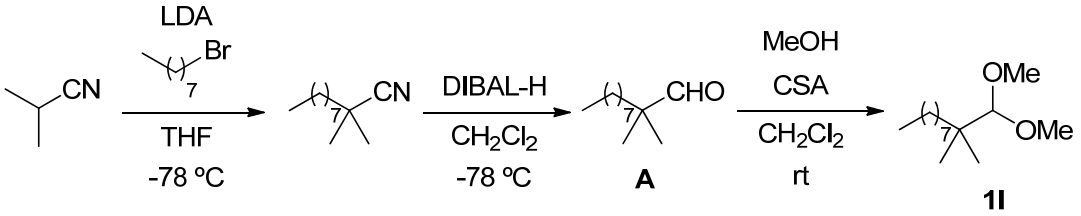
Benzaldehyde diisopropyl acetal (1i)[6]: eluent (hexane-CH_2Cl_2 = 3/2); colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.17 (3H, d, *J* = 6.0 Hz), 1.20 (3H, d, *J* = 6.0 Hz), 3.90 (2H, sep, *J* = 6.0 Hz), 5.55 (1H, s), 7.27-7.37 (3H, m), 7.46-7.49 (2H, m).

3-Phenylpropionaldehyde dimethyl acetal (1j)[3]: eluent (hexane-AcOEt = 10/1); colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.89-1.96 (2H, m), 2.66 (2H, t, *J* = 8.0 Hz), 3.33 (6H, s), 4.36 (1H, t, *J* = 5.7 Hz), 7.16-7.31 (5H, m).

2-Methylundecanal dimethyl acetal (1k)[7]: eluent (hexane-AcOEt = 10/1); colorless oil; ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, t, *J* = 6.8 Hz), 1.07-1.10 (1H, m), 1.26-1.37 (14H, m), 1.46-1.57 (1H, m), 1.69-1.74 (1H, m), 3.35 (6H, s), 4.02 (1H, d, *J* = 6.4 Hz).

5-Bromopentanal dimethyl acetal (1m)[1]: eluent (hexane-AcOEt = 10/1); colorless oil; ^{1}H NMR ($CDCl_3$): δ 1.47-1.54 (2H, m), 1.61-1.65 (2H, m), 1.86-1.93 (2H, m), 3.33 (6H, s), 3.41 (2H, t, *J* = 7.0 Hz), 4.37 (1H, t, *J* = 5.8 Hz).

2,2-Dimethyldecanal dimethyl acetal (1l)[8]:



The aldehyde **A** was synthesized according to the literature procedure.[9] To a solution of diisopropylamine (5.5 ml, 39 mmol) in anhydrous THF (40 mL) was added *n*-butyl lithium (1.66 M solution in hexane, 24 mL, 39 mmol) at -78 °C, and the mixture was stirred for 10 min. Then, isobutyronitrile (4.1 g, 60 mmol) was added to the mixture, which was stirred for 20 min. 1-Bromooctane (5.8 g, 30 mmol) was added and the mixture was stirred for 30 min. Sat. NH_4Cl aq. was added to the reaction mixture, and the resulting solution was extracted with AcOEt. Organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to silica-gel column chromatography using hexane-AcOEt (40/1) as the eluent to give 2,2-dimethyldecanenitrile (4.9 g, 90%) as colorless oil; IR (KBr, cm^{-1}): 2236, 1794, 1470, 1369, 1096; ^{1}H NMR ($CDCl_3$): δ 0.89 (3H, t, *J* = 6.7 Hz), 1.28-1.33 (10H, m), 1.33 (6H, s), 1.45-1.53 (4H, m); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.6, 25.2, 26.7, 29.2, 29.3, 29.6, 31.8, 32.4, 41.1, 125.3; HRFABMS calcd for $C_{14}H_{30}O_2Na$ (M^++H): 182.1909, found: 182.1915. To a solution of 2,2-dimethyldecanenitrile (1.8 g, 10 mmol) in anhydrous CH_2Cl_2 (50 mL) was added DIBAL-H (1.05 M solution in hexane, 14 mL, 15 mmol) at -78 °C, and the reaction mixture was stirred for 2 h at the same temperature. 1 *N* HCl aq. (10 mL) added to the solution at -78 °C, then the mixture was warmed to room temperature, and additional 1 *N* HCl aq. (10 mL) was added. The resulting solution was extracted with CH_2Cl_2, and the organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to silica-gel column chromatography using hexane-AcOEt (40/1) as the eluent to give 2,2-dimethyldecanal[10] (1.4 g, 76%); ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, t, *J* = 6.9 Hz), 1.04 (6H, s), 1.19-1.33 (12H, brm), 1.43-1.47 (2H, m), 9.45 (1H, s). 2,2-Dimethyldecanal

dimethyl acetal (**1l**) was prepared according to the general procedure; eluent (hexane-AcOEt = 20/1); colorless oil; IR (KBr, cm^{-1}): 1794, 1470, 1387, 1186, 1072; ^{1}H NMR ($CDCl_3$): δ 0.86 (6H, s), 0.88 (3H, t, J = 6.4 Hz), 1.24-1.30 (14H, brm), 3.50 (6H, s), 3.82 (1H, s); ^{13}C NMR ($CDCl_3$): δ 14.1, 21.9, 22.7, 23.6, 29.3, 29.7, 30.7, 31.9, 37.8, 39.3, 58.5, 114.1; HRFABMS calcd for $C_{14}H_{30}O_2Na$ (M^++Na): 253.2143, found: 253.2135.

Synthesis and isolation of the α-methoxyphosphonium salt 2a (Scheme 1)

In a flame-dried two-necked Schrenk tube under N_2, TESOTf (1.92 mmol, 0.43 mL) was added slowly to a stirred solution of **1a** (0.96 mmol, 221 mg) and Ph_3P (2.88 mmol, 755 mg) in dry CH_2Cl_2 (5 mL) at 0 ºC and the resulting solution was stirred for 0.5 h at the same temperature. After checking for the disappearance of **1a** and the formation of the α-methoxyphosphonium salt on TLC, sat. $NaHCO_3$ aq. was added to the reaction mixture. The resulting solution was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to neutral silica-gel column chromatography (eluent; CH_2Cl_2-MeOH = 10/1) to give **2a** (395 mg, 67%) as colorless gummy oil.

(1-Methoxydodecyl)triphenylphosphonium trifluoromethanesulfonate (2a): IR (KBr, cm^{-1}): 2926, 2361, 2340, 1439, 1260, 1155, 1030; ^{1}H NMR ($CDCl_3$): δ 0.87 (3H, t, J = 6.9 Hz), 1.21-1.30 (15H, m), 1.61-1.74 (4H, m), 1.85-1.90 (1H, m), 3.51 (3H, s), 5.80 (1H, dt, J = 9.6, 3.0 Hz), 7.68-7.73 (6H, m), 7.79-7.88 (9H, m); ^{13}C NMR ($CDCl_3$): δ 13.8, 22.3, 25.8, 26.0, 29.0, 29.09, 29.14, 29.2, 31.5, 32.0, 32.1, 62.7 (d, $J_{C\text{-}P}$ = 6.7 Hz), 78.1 (d, $J_{C\text{-}P}$ = 59.4 Hz), 116.5 (d, $J_{C\text{-}P}$ = 81.4 Hz), 120.6 (d, $J_{C\text{-}F}$ = 320.2 Hz), 130.1 (d, $J_{C\text{-}P}$ = 11.6 Hz), 134.0 (d, $J_{C\text{-}P}$ = 9.6 Hz), 134.9 (d, $J_{C\text{-}P}$ = 2.9 Hz); ^{19}F NMR ($CDCl_3$): δ -78.1; ^{31}P NMR ($CDCl_3$): δ 22.0; HRFABMS (positive) calcd for $C_{31}H_{42}OP$ (M^+): 461.2973, found: 461.2993; HRFABMS (negative) calcd for CO_3F_3S (M^-): 148.9520, found: 148.9550.

General procedure for the reaction of the α-methoxyphosphonium salt 2b with Grignard reagents (Table 2)

In a flame-dried two-necked Schrenk tube with dry air, TESOTf (2 equiv) was added slowly to a stirred solution of **1b** (1 equiv) and Ph_3P (3 equiv) in dry CH_2Cl_2 (0.2 M) at

0 ºC and the resulting solution was stirred for 0.5 h at the same temperature. After checking for the disappearance of **1b** and the formation of the α-methoxyphosphonium salt on TLC, **3a-d** (5.0 equiv) was added quickly to the mixture, and the solution was then stirred at the same temparature. After checking for the disappearance of the α-methoxyphosphonium salt on TLC, sat. NH_4Cl aq. was added to the reaction mixture. The resulting solution was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to silica-gel column chromatography to give the products **4**. All products **4b-e** are known compounds.

Benzhydrol (4b)[11] **(entry 1)**: eluent (benzene-MeOH = 20/1); white solid; ^{1}H NMR ($CDCl_3$): δ 2.30 (1H, brs), 5.81 (1H, s), 7.23-7.38 (10H, m).

Phenyl(*p*-tolyl)methanol (4c)[11] **(entry 2)**: eluent (benzene-MeOH = 20/1); colorless oil; ^{1}H NMR ($CDCl_3$): δ 2.31 (3H, s), 2.31 (1H, s), 5.75 (1H, s), 7.12 (2H, d, *J* = 7.8 Hz), 7.22-7.25 (3H, m), 7.29 (2H, d, *J* = 7.8 Hz), 7.32-7.36 (2H, m).

(4-Methoxyphenyl)phenylmethanol (4d)[11] **(entry 3)**; eluent (benzene-MeOH = 20/1); colorless oil; ^{1}H NMR ($CDCl_3$): δ 2.22 (1H, d, *J* = 2.8 Hz), 3.78 (3H, s), 5.79 (1H, d, *J* = 2.8 Hz), 6.84-6.87 (2H, m), 7.23-7.38 (7H, m).

(4-Fluorophenyl)phenylmethanol (4e)[11] **(entry 4)**: eluent (benzene-MeOH = 20/1); colorless oil; ^{1}H NMR ($CDCl_3$): δ 2.30 (1H, s), 5.80 (1H, s), 6.98-7.03 (2H, m), 7.24-7.34 (7H, m).

General procedure for the reaction of the α-methoxyphosphonium salt with PhMgBr 3a (Table 3)

In a flame-dried two-necked Schrenk tube with dry air, TESOTf (2 equiv) was added slowly to a stirred solution of acetal **1** (1 equiv) and Ph_3P (3 equiv) in dry CH_2Cl_2 (0.2 M) at 0 ºC and the resulting solution was stirred for 0.5 h at the same temperature. After checking for the disappearance of **1** and the formation of the α-methoxyphosphonium salt on TLC, **3a** (5.0 equiv) was added quickly to the mixture, and the solution was then stirred at the same temparature. After checking for the disappearance of the α-methoxyphosphonium salt on TLC, sat. NH_4Cl aq. was added to the reaction mixture.

The resulting solution was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to silica-gel column chromatography to give the products **4**. Products **4h-k** and **4n** are known compounds.

1-Phenyldodecan-1-ol (4a)[12] **(entry 8)**: eluent (hexane-AcOEt = 7/1); white solid; IR (KBr, cm^{-1}): 3605, 3383, 1815, 1454; ^1H NMR ($CDCl_3$): δ 0.88 (3H, t, *J* = 6.9 Hz), 1.24-1.43 (18H, m), 1.66-1.83 (2H, m), 1.89 (1H, s), 4.64 (1H, t, *J* = 6.6 Hz), 7.24-7.36 (5H, m); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 25.8, 29.3, 29.52, 29.54, 29.58, 29.60, 29.63, 31.9, 39.1, 74.7, 125.9, 127.5, 128.4, 144.9; HRFABMS calcd for $C_{18}H_{30}ONa$ (M^++Na): 285.2194, found: 285.2167.

(4-Bromophenyl)phenylmethanol (4h)[11] **(entry 3)**: eluent (hexane-AcOEt = 5/1); colorless oil; ^1H NMR ($CDCl_3$): δ 2.43 (1H, s), 5.74 (1H, s), 7.19-7.36 (7H, m), 7.42-7.44 (2H, m).

(4-Trifluoromethylphenyl)phenylmethanol (4i)[11] **(entry 4)**: eluent (hexane-AcOEt = 10/1); colorless oil; ^1H NMR ($CDCl_3$): δ 2.40 (1H, s), 5.85 (1H, s), 7.27-7.35 (5H, m), 7.49 (2H, d, *J* = 8.2 Hz), 7.58 (2H, d, *J* = 8.2 Hz).

Phenyl(2-thienyl)methanol (4j)[11] **(entry 5)**: eluent (hexane-AcOEt = 10/1); pale yellow solid; ^1H NMR ($CDCl_3$): δ 2.44 (1H, d, *J* = 3.4 Hz), 6.05 (1H, d, *J* = 3.4 Hz), 6.88 (1H, d, *J* = 3.1 Hz), 6.94 (1H, dd, *J* = 4.9, 3.1 Hz), 7.26 (1H, dd, *J* = 4.9, 1.2 Hz), 7.29-7.32 (1H, m), 7.37 (2H, t, *J* = 7.3 Hz), 7.45 (2H, dd, *J* = 7.3, 1.8 Hz).

1,3-Diphenylpropan-1-ol (4k)[13] **(entry 9)**: eluent (hexane-AcOEt = 7/1); colorless oil; ^1H NMR ($CDCl_3$): δ 1.92 (1H, d, *J* = 3.2 Hz), 2.01-2.13 (2H, m), 2.65-2.74 (2H, m), 4.65-4.68 (1H, m), 7.16-7.38 (10H, m).

2-Methyl-1-phenylundecan-1-ol (diastereo mixture) (4l) (entry 10): eluent (hexane-AcOEt = 10/1); colorless oil; IR (KBr, cm^{-1}): 3605, 3445, 2930, 2249, 1815, 1493, 1454, 1377, 1015; ^1H NMR ($CDCl_3$): δ 0.74 (1.2H, d, *J* = 6.9 Hz), 0.87 (1.8H, dd, *J* = 5.5, 1.4 Hz), 0.90 (3H, t, *J* = 6.6 Hz), 1.04-1.41 (16H, m), 1.75-1.87 (2H, m), 4.42 (0.4H, d, *J* = 6.9 Hz), 4.52 (0.6H, d, *J* = 5.5 Hz), 7.23-7.35 (5H, m); ^{13}C NMR ($CDCl_3$): δ 14.1, 14.3, 15.6, 22.7, 27.0, 27.2, 29.31, 29.33, 29.58, 29.60, 29.7, 29.8, 29.9, 31.88, 31.90, 32.2, 33.1, 40.09, 40.14, 78.2, 79.1, 126.3, 126.7, 127.2, 127.4, 128.12, 128.13,

143.6, 143.9; HRFABMS calcd for $C_{18}H_{30}ONa$ (M^++Na): 285.2194, found: 285.2195.

2,2-Dimethyl-1-phenyldecan-1-ol (4m)[14] **(entry 11)**: eluent (hexane-AcOEt = 10/1); pale yellow oil; IR (KBr, cm^{-1}): 3609, 1794, 1468, 1385, 1096; ^1H NMR ($CDCl_3$): δ 0.81 (3H, s), 0.88 (3H, t, *J* = 6.6 Hz), 0.89 (3H, s), 1.17-1.38 (14H, brm), 1.81 (1H, d, *J* = 2.3 Hz), 4.45 (1H, d, *J* = 2.3 Hz), 7.24-7.33 (5H, m); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.6, 23.1, 23.9, 29.4, 29.7, 30.6, 31.9, 38.1, 38.9, 81.2, 127.2, 127.5, 127.8, 142.2; HRFABMS calcd for $C_{18}H_{30}ONa$ (M^++Na): 285.2194, found: 285.2206.

5-Bromo-1-phenylpentan-1-ol (4n)[15] **(entry 12)**: eluent (hexane-AcOEt = 5/1); colorless oil; ^1H NMR ($CDCl_3$): δ 1.40-1.46 (1H, m), 1.55-1.61 (1H, m), 1.68-1.75 (1H, m), 1.78-1.84 (1H, m), 1.88 (2H, quintet, *J* = 7.0 Hz), 1.94 (1H, s), 3.38 (2H, t, *J* = 6.7 Hz), 4.66 (1H, t, *J* = 6.7 Hz), 7.25-7.37 (5H, m).

Isotopic labelling experiment using the ^{18}O-labelled dimethyl acetal 7 (Scheme 3)

^{18}O-*n*-decanal dimethyl acetal (7): eluent (hexane-CH_2Cl_2 = 1/1); colorless oil; ^1H NMR ($CDCl_3$): δ 0.88 (3H, t, *J* = 6.6 Hz), 1.26-1.30 (14H, brm), 1.56-1.60 (2H, m), 3.31 (6H, s), 4.36 (1H, t, *J* = 5.7 Hz); HRFABMS calcd for $C_{12}H_{27}{}^{18}O_2$ (M^++H): 207.2096, found: 207.2108.

1-Phenyldecan-1-ol (9): eluent (hexane-AcOEt = 10/1); colorless oil; ^1H NMR ($CDCl_3$): δ 0.87 (3H, t, *J* = 6.6 Hz), 1.25-1.44 (14H, brm), 1.69-1.83 (2H, m), 1.86 (1H, s), 4.63-4.68 (1H, m), 7.24-7.37 (5H, m); HRFABMS calcd for $C_{16}H_{26}ONa$ (M^++Na): 257.1881, found: 257.1884.

Isotopic labelling experiment with the α-methoxyphosphonium salt 2b and 3a under an $^{18}O_2$ atmosphere (Scheme 4)

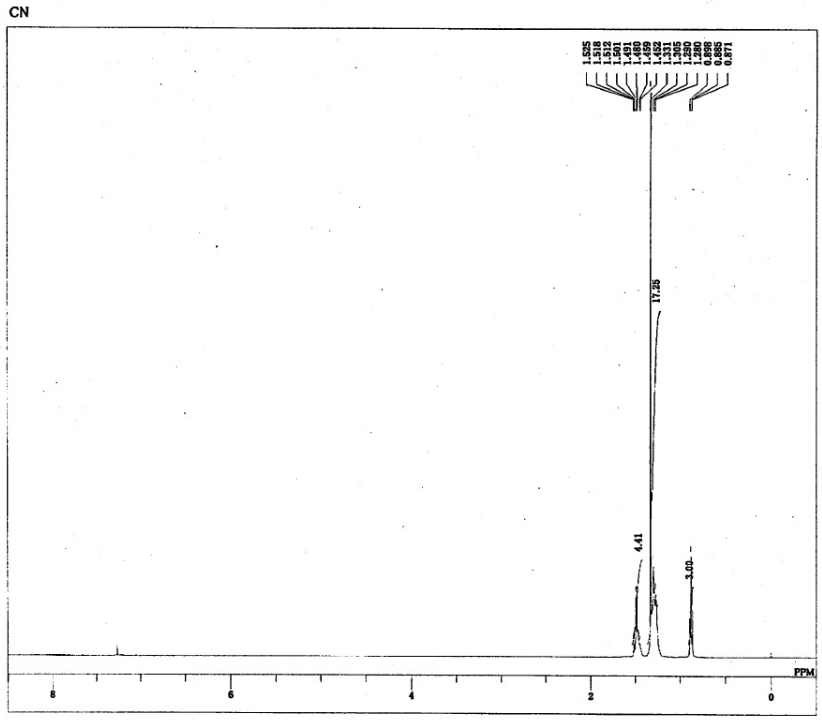
In a flame-dried two-necked Schrenk tube with $^{18}O_2$, TESOTf (77 μL, 2 equiv) was added slowly to a stirred solution of acetal **1b** (26.0 mg, 1 equiv) and Ph_3P (135 mg, 3 equiv) in dry CH_2Cl_2 (0.2 M) at 0 ºC and the resulting solution was stirred for 0.5 h at the same temperature. After checking for the disappearance of **1b** and the formation of the α-methoxyphosphonium salt on TLC, **3a** (5.0 equiv) was added quickly to the mixture, and the solution was then stirred at the same temparature. After checking for the disappearance of the α-methoxyphosphonium salt on TLC, sat. NH_4Cl aq. was added to the reaction mixture. The resulting solution was extracted with CH_2Cl_2 and the

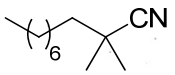
organic layer was dried over anhydrous Na_2SO_4 and filtered. After removal of the solvent, the residue was subjected to silica-gel column chromatography to give ^{18}O-benzhydrol (**10**) (16.6 mg, 52%) and ^{18}O-triphenylphosphine oxide (23.3 mg, 49%).

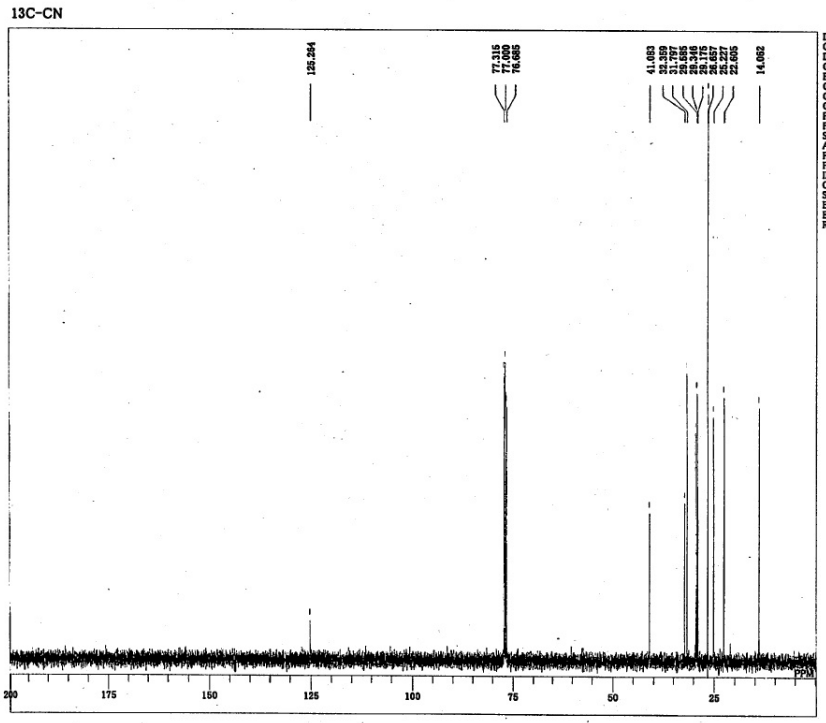
^{18}O-benzhydrol (10): eluent (hexane-AcOEt = 7/1); white solid; ^{1}H NMR ($CDCl_3$): δ 2.23 (1H, s), 5.84 (1H, s), 7.24-7.39 (10H, m); HRFABMS calcd for $C_{13}H_{12}{}^{18}ONa$ (M^++Na): 209.0823, found: 209.0819.

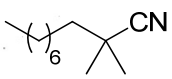
^{18}O-triphenylphosphine oxide: eluent (AcOEt); white solid; ^{1}H NMR ($CDCl_3$): δ 7.44-7.49 (6H, m), 7.53-7.57 (3H, m), 7.65-7.70 (6H, m); ^{31}P NMR ($CDCl_3$): δ 29.7; HRFABMS calcd for $C_{18}H_{16}{}^{18}OP$ (M^++H): 281.0976, found: 281.0960.

^{1}H and ^{13}C NMR of 2,2-dimethyldecanenitrile

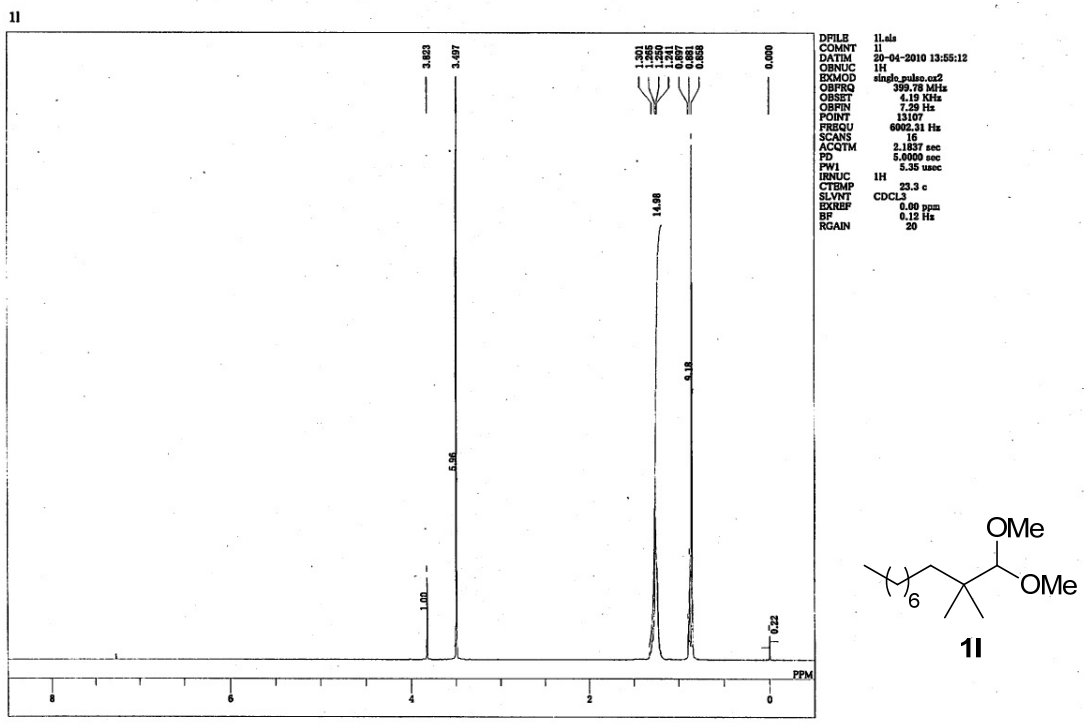








^{1}H and ^{13}C NMR of **1l**



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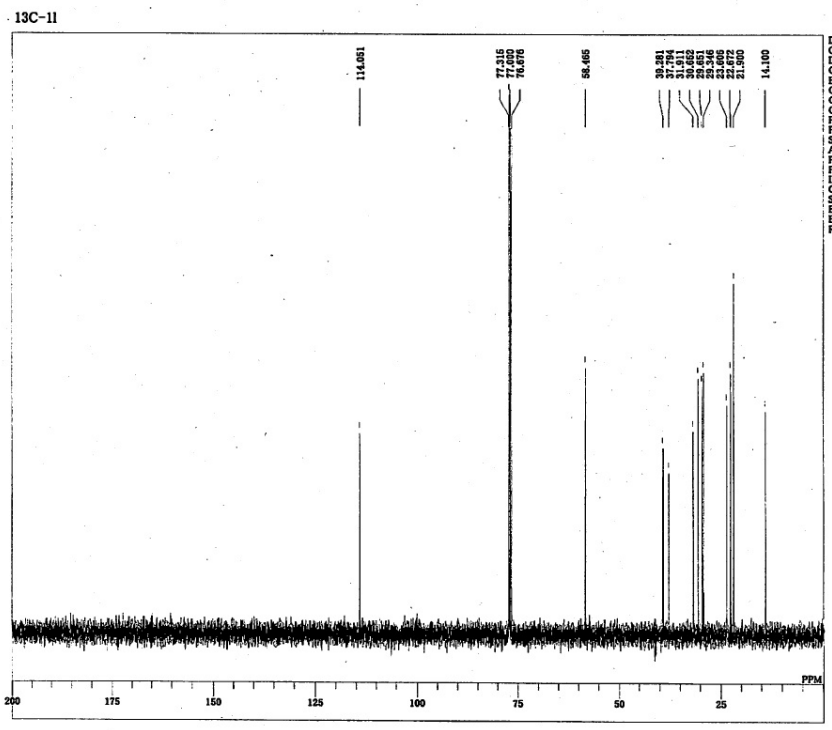
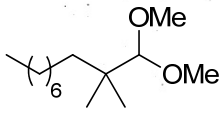
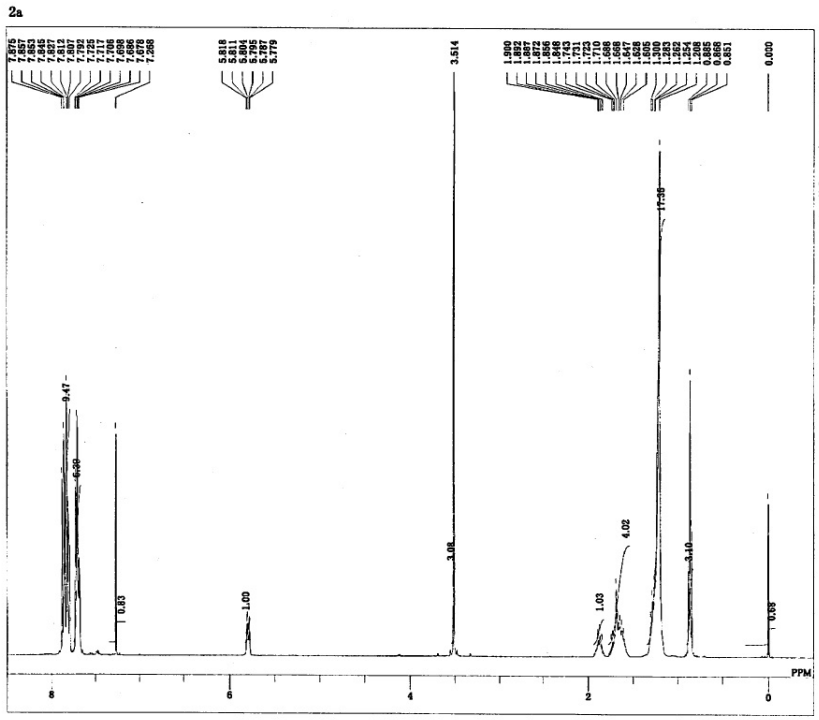
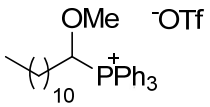




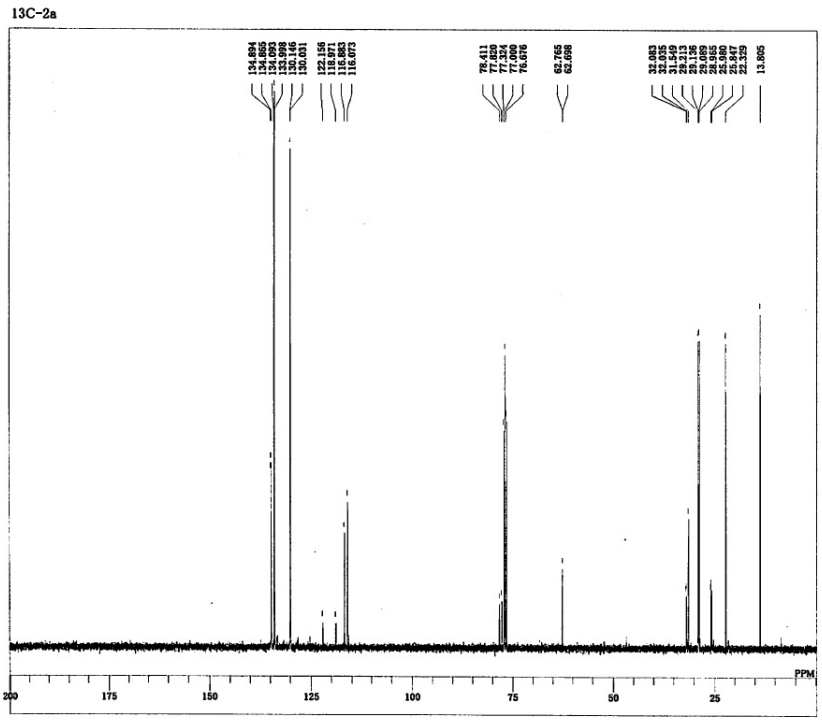
1l

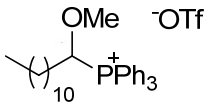
^{1}H and ^{13}C NMR of **2a**





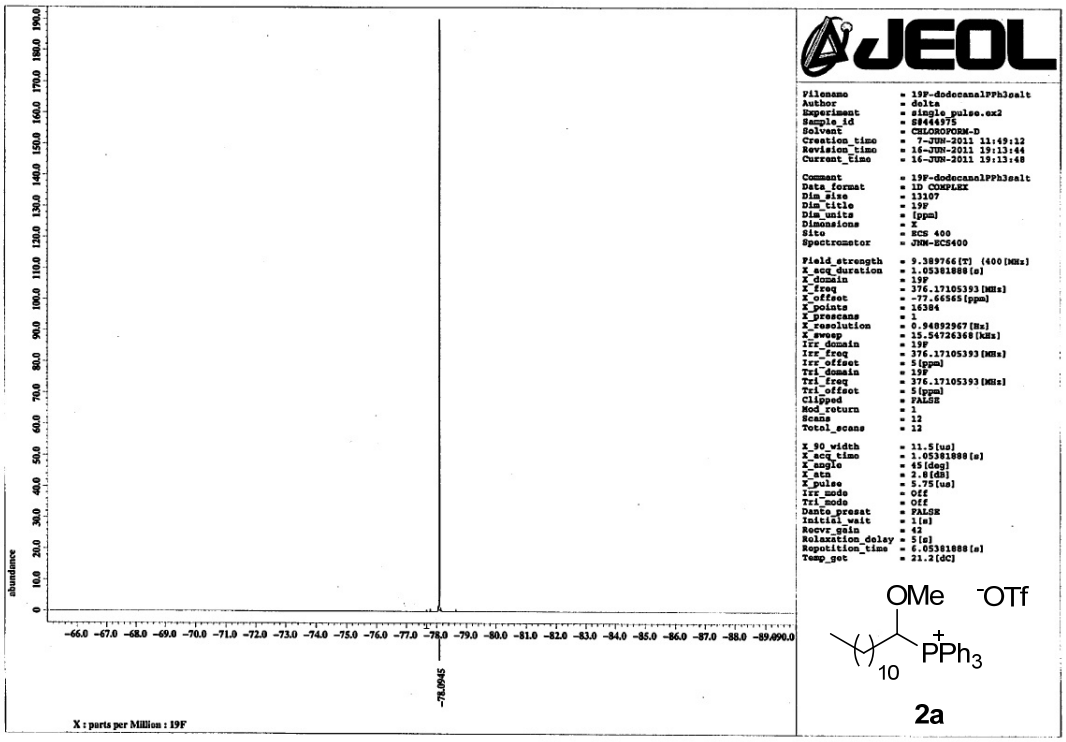
2a

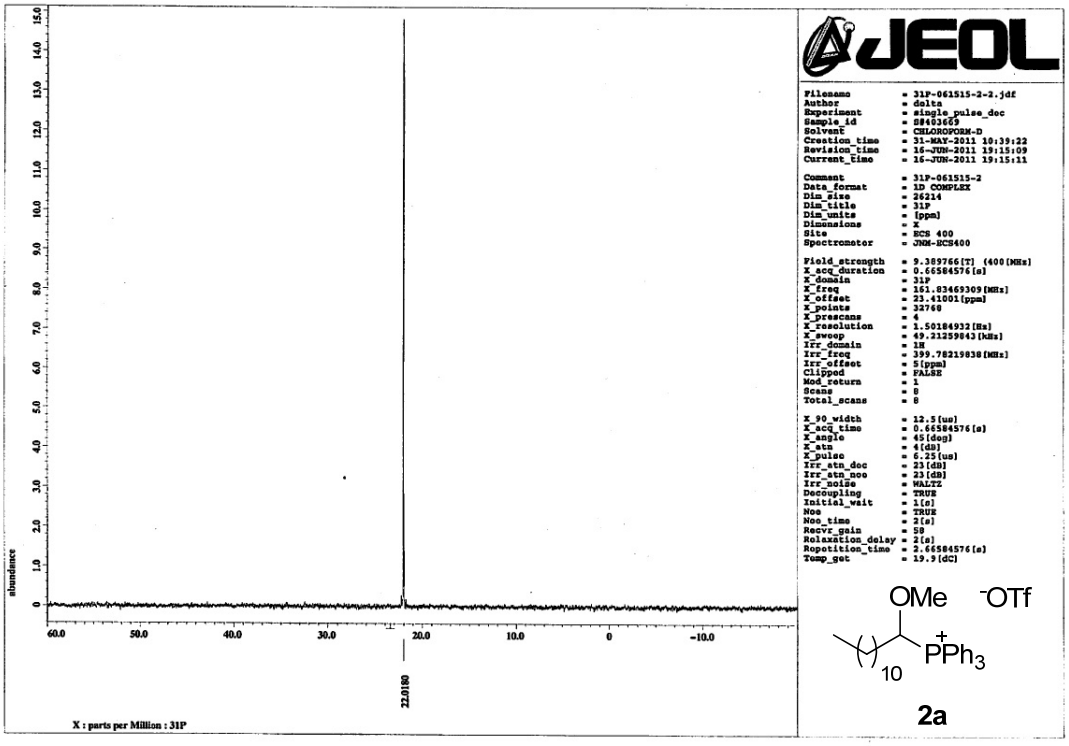




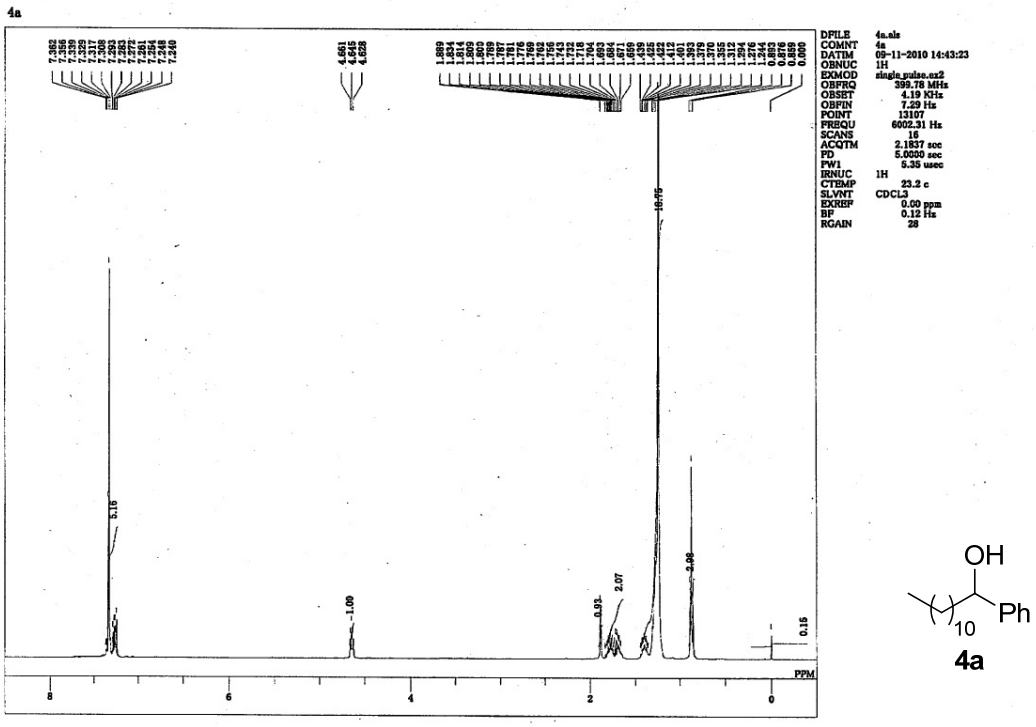
2a

^{19}F and ^{31}P NMR of **2a**

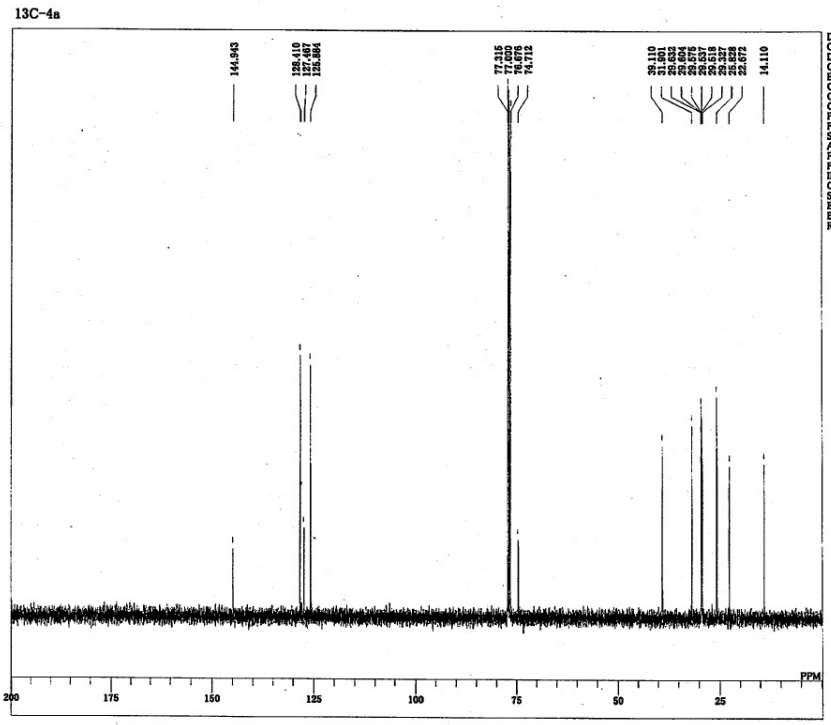


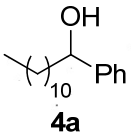


^{1}H and ^{13}C NMR of **4a**



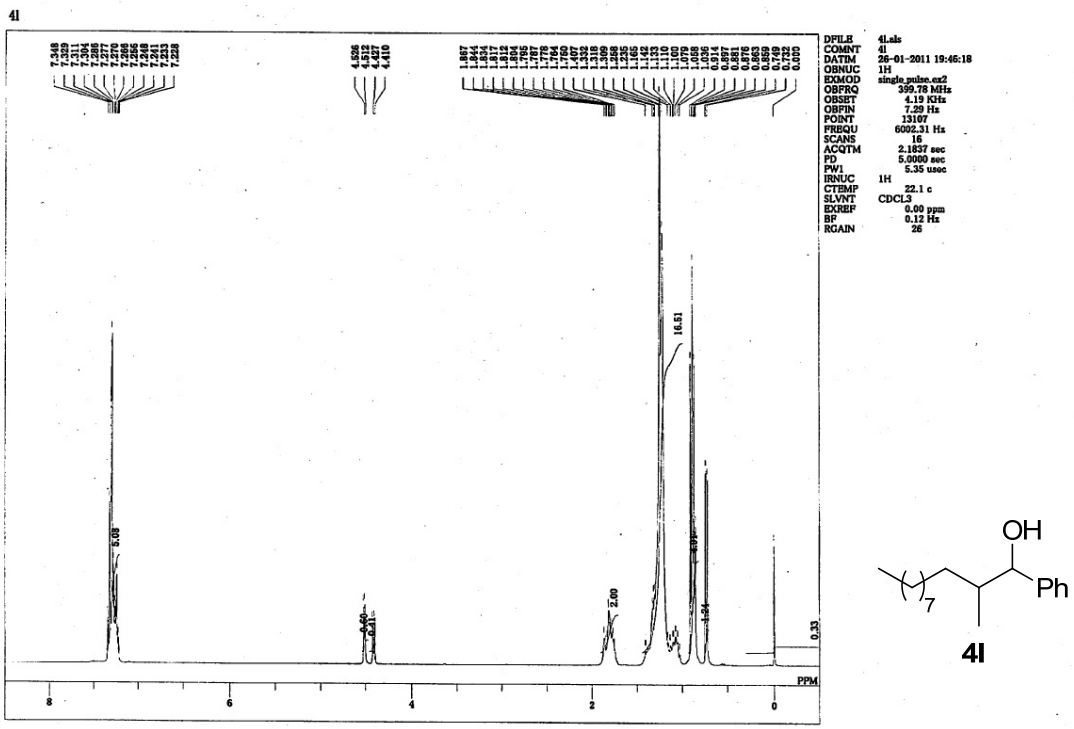
4a

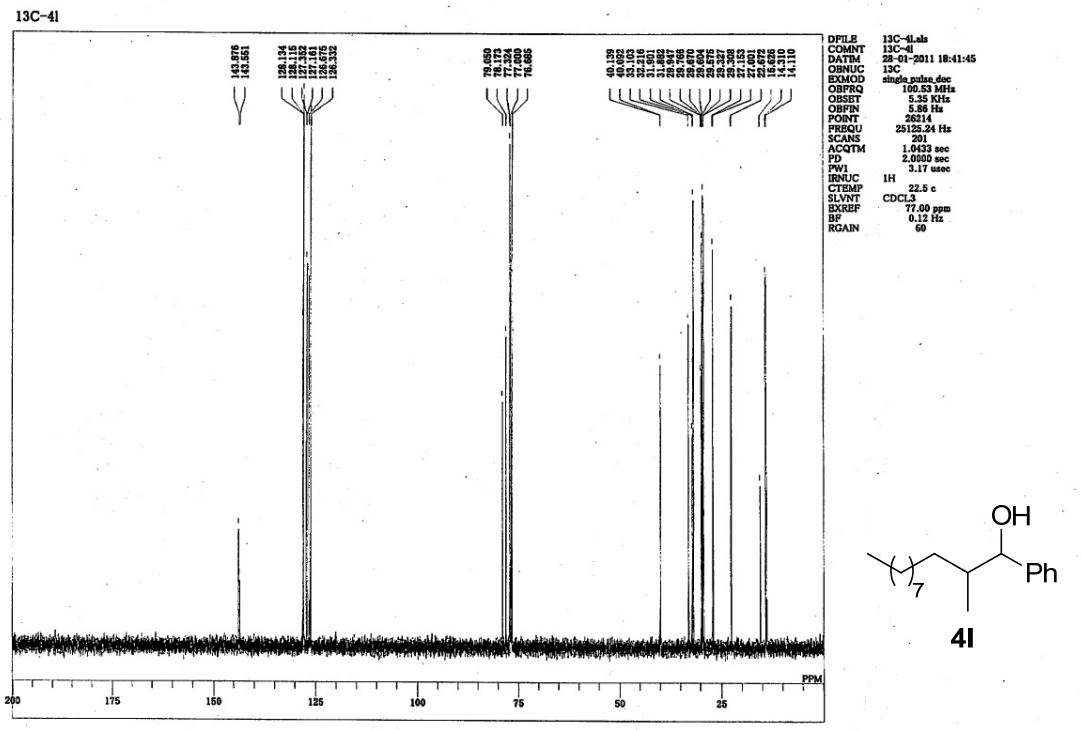




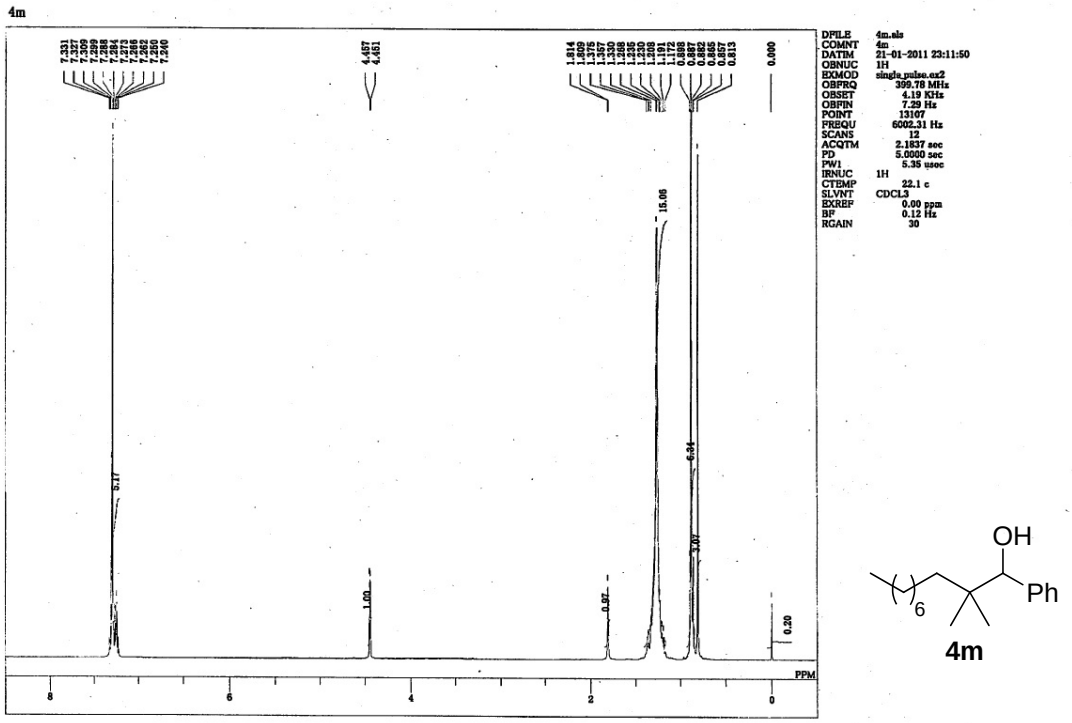
4a

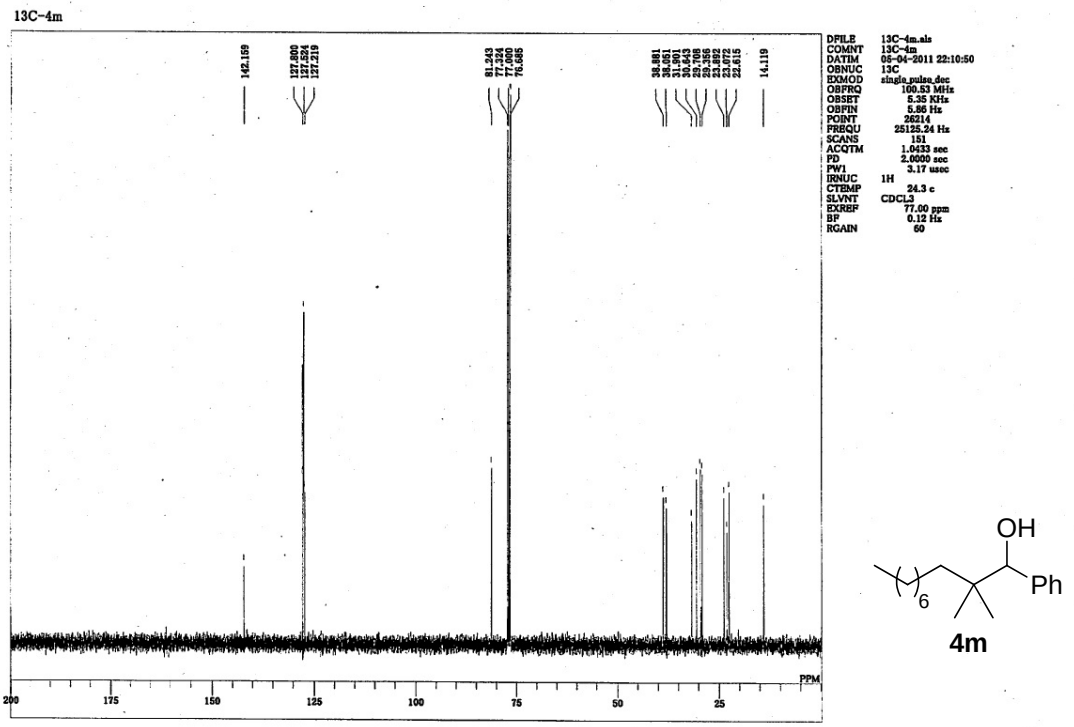
^{1}H and ^{13}C NMR of **4l**





^{1}H and ^{13}C NMR of **4m**





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