The Use of Acid Fluorides Increases the Scope of the Reductive Acylation of Esters

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Supporting Information

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Dichloromethane was degassed with argon and passed through two columns of neutral alumina. Pyridine was dried over solid KOH and stored over 4Å molecule sieves. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, aqueous ceric ammonium molybdate, or bromocresol green dips followed by heating.

Benzoyl fluoride was purchased from Aldrich Chemical Co. and used without further purification. Other acyl fluorides were prepared by known literature methods.[1]

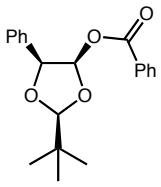
Melting points were measured with a MelTemp II melting point apparatus outfitted with a Fluke 51 thermocouple and are uncorrected. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR and spectra were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard [tetramethylsilane (TMS) or deuterated chloroform ($CDCl_3$)], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR and spectra were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec.

Standard Procedure for the One-Pot DIBAL-H Reduction and Acylation of an Ester with Acyl Fluoride

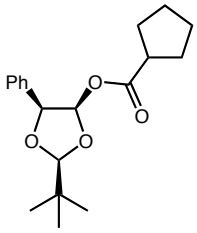
To a solution of starting ester (1 mmol) in CH_2Cl_2 (5 mL) was added DIBAL-H (1.0 M in hexane, 1.1 mL, 1.1 mmol, 1.1 equiv) dropwise at – 78 ºC under an argon atmosphere. After the reaction was stirred for 2 h at –78 ºC, neat pyridine (0.24 mL, 3.0 mmol, 3.0 equiv) was introduced via syringe followed by slow addition of a solution of DMAP (0.13 g, 1.1 mmol, 1.1 equiv) in 1.5 mL of CH_2Cl_2 at –78 ºC. Finally, acyl fluoride (1.5 mmol, 1.5 equiv) was added dropwise. The resulting mixture was allowed to warm to 15 ºC over 12 h. The reaction was quenched with 5 mL of saturated NH_4Cl. Although no emulsion formed in the workup, 5 ml of saturated Rochelle's salt solution was added. After the mixture was stirred for 15 min, the organic layer was separated, and

[1] Chen, C.; Chien, C.-T.; Su, C.-H. *J. Fluorine Chem.* **2002**, *115*, 75.

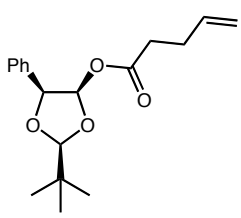
the aqueous layer was extracted with CH_2Cl_2 (4 x 5mL). The combined organic layers were washed with ice-cooled $NaHSO_4$, saturated $NaHCO_3$, brine, and dried over Na_2SO_4. After removal of the volatiles, the product was purified by silica gel chromatography.



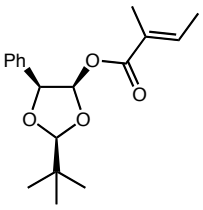
(2S*, 4R*, 5S*)-4-benzoyloxy-2-tert-butyl-5-phenyl-1, 3-dioxolane (3a) According to standard procedure described above, ester **1** (0.22 g, 1 mmol) was treated with DIBAL-H (1.0 M in hexane, 1.1 mL, 1.1 mmol, 1.1 equiv), followed by addition of neat pyridine (0.24 mL, 3.0 mmol, 3.0 equiv), DMAP (0.13 g, 1.1 mmol, 1.1 equiv), and benzoyl fluoride (0.16 mL, 1.5 mmol, 1.5 equiv). The product was purified by column chromatography on silica gel (1% ethyl acetate/hexanes) to afford **3a** (0.30 g, 94 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) 7.77-7.74 (m, 2H), 7.50-7.46 (m, 3H), 7.35-7.25 (m, 5H), 6.63 (d, 1H, *J* = 3.6 Hz), 5.16 (d, 1H, *J* = 3.9 Hz), 4.98 (s, 1H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 165.3, 133.8,133.2, 129.8, 129.7,128.5, 128.4, 128.2, 127.3, 111.8, 94.1, 82.9, 34.7, 24.7; IR (NaCl, neat) 1727, 1266, 1024, 970, 710 cm^{-1}; HRMS $[C_{20}H_{22}O_4\text{-}H]^+$ Calc. 325.1440. Found (EI+) 325.1429.



(2S*, 4R*, 5S*)-4-cyclopentylcarbonyloxy-2-tert-butyl-5-phenyl-1, 3-dioxolane (3b)
According to standard procedure described above, ester **1** (0.22 g, 1 mmol) was treated with DIBAL-H (1.0 M in hexane, 1.1 mL, 1.1 mmol, 1.1 equiv), followed by addition of neat pyridine (0.24 mL, 3.0 mmol, 3.0 equiv), DMAP (0.13 g, 1.1 mmol, 1.1 equiv), and cyclopentanecarbonyl fluoride (0.17 g, 1.5 mmol, 1.5 equiv). The product was purified by column chromatography on silica gel (1% ethyl acetate/hexanes) to afford **3b** (0.31 g, 97 %) ^{1}H NMR (300 MHz, $CDCl_3$) 7.41-7.27 (m, 5H), 6.45 (d, 1H, *J* = 3.6 Hz), 5.04 (d, 1H, *J* = 3.6 Hz), 4.88 (s, 1H), 2.43 (m, 1H), 1.51-1.36 (m, 8H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 175.1, 133.8, 128.2, 128.0, 127.1, 111.3, 93.1, 82.5, 44.0, 34.5, 29.6, 25.8, 24.6; IR (NaCl, neat) 2960, 1739,1125, 1025, 972, 697 cm^{-1}; HRMS $[C_{19}H_{26}O_4]^+$ Calc. 318.1831. Found (EI+) 318.1825.

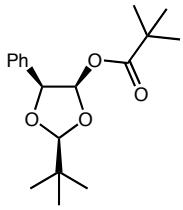


(2S*, 4R*, 5S*)-4-(4-pentenoyloxy)-2-tert-butyl-5-phenyl-1, 3-dioxolane (3c)
According to standard procedure described above, ester **1** (0.22 g, 1 mmol) was treated with DIBAL-H (1.0 M in hexane, 1.1 mL, 1.1 mmol, 1.1 equiv), followed by addition of neat pyridine (0.24 mL, 3.0 mmol, 3.0 equiv), DMAP (0.13 g, 1.1 mmol, 1.1 equiv), and 4-pentenoyl fluoride (0.15 g, 1.5 mmol, 1.5 equiv). The product was purified by column chromatography on silica gel (1% ethyl acetate/hexanes) to afford **3c** (0.28 g, 92 %) ^{1}H NMR (300 MHz, $CDCl_3$) 7.42-7.26 (m, 5H), 6.45 (d, 1H, *J* = 3.9 Hz), 5.55 (m, 1H), 5.03 (d, 1H, *J* = 4.2Hz), 4.88 (s, 1H), 4.88-4.81 (m, 2H), 2.23-2.00 (m, 4H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 171.5, 136.4, 133.7, 128.4, 128.1, 127.3, 115.4, 111.4, 93.4, 82.6, 34.5, 33.7, 28.4, 24.6; IR (NaCl, neat) 2960, 1746, 1129, 1026, 972, 698 cm^{-1}; HRMS $[C_{18}H_{24}O_4]^+$ Calc. 304.1675. Found (EI+) 304.1668.



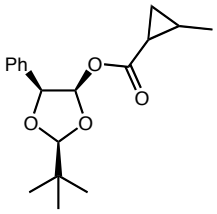
(2S*, 4R*, 5S*)-4-(*E*-2-methyl-2-butenoyloxy)-2-tert-butyl-5-phenyl-1, 3-dioxolane (3d)

According to standard procedure described above, ester **1** (0.22 g, 1 mmol) was treated with DIBAL-H (1.0 M in hexane, 1.1 mL, 1.1 mmol, 1.1 equiv), followed by addition of neat pyridine (0.24 mL, 3.0 mmol, 3.0 equiv), DMAP (0.13 g, 1.1 mmol, 1.1 equiv), and tiglyl fluoride (0.14 g, 1.5 mmol, 1.5 equiv). The product was purified by column chromatography on silica gel (1% ethyl acetate/hexanes) to afford **3d** (0.26 g, 87 %). ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.43-7.26 (m, 5H), 6.59 (qq, 1H, *J* = 6.9, 1.2 Hz), 6.45 (d, 1H, *J* = 3.9 Hz), 5.07 (d, 1H, *J* = 3.6 Hz), 4.92 (s, 1H), 1.66 (d, 3H, *J* = 6.3 Hz), 1.59 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 166.6, 138.2, 133.9, 128.3, 128.1, 128.0, 127.3, 111.5, 93.6, 82.7, 34.6, 24.7, 14.6, 11.9; IR (NaCl, neat) 2960, 1717, 1252, 1120, 1025, 972, 724, 697 cm^{-1}; HRMS $[C_{18}H_{23}O_4\text{-}H]^+$ Calc. 303.1596. Found (EI+) 303.1595.



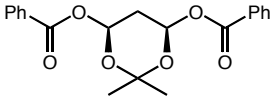
(2S*, 4R*, 5S*)-4-tert-butylcarbonyloxy-2-tert-butyl-5-phenyl-1, 3-dioxolane (3e)

According to standard procedure described above, ester **1** (0.22 g, 1 mmol) was treated with DIBAL-H (1.0 M in hexane, 1.1 mL, 1.1 mmol, 1.1 equiv), followed by addition of neat pyridine (0.24 mL, 3.0 mmol, 3.0 equiv), DMAP (0.13 g, 1.1 mmol, 1.1 equiv), and pivaloyl fluoride (0.15 g, 1.5 mmol, 1.5 equiv). The product was purified by column chromatography on silica gel (1% ethyl acetate/hexanes) to afford **3e** (0.28 g, 92 %). ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.40-7.26 (m, 5H), 6.44 (d, 1H, *J* = 3.9 Hz), 5.07 (d, 1H, *J* = 3.9 Hz), 4.90 (s, 1H), 1.06 (s, 9H), 0.86 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 177.1, 133.9, 128.2, 128.1, 126.9, 111.5, 93.2, 82.5, 33.8, 34.5, 26.8, 24.7; IR (NaCl, neat) 2975, 1736, 1123, 972, 697 cm^{-1}; HRMS $[C_{18}H_{26}O_4\text{-}H]^+$ Calc. 305.1753. Found (EI+) 305.1750



(2S*, 4R*, 5S*)-4-(2-methylcyclopropane)carbonyloxy-2-tert-butyl-5-phenyl-1, 3-dioxolane (3f)

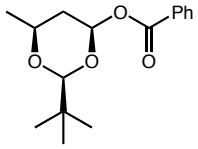
According to standard procedure described above, ester **1** (0.22 g, 1 mmol) was treated with DIBAL-H (1.0 M in hexane, 1.1 mL, 1.1 mmol, 1.1 equiv), followed by addition of neat pyridine (0.24 mL, 3.0 mmol, 3.0 equiv), DMAP (0.13 g, 1.1 mmol, 1.1 equiv), and 2-methylcyclopropanecarbonyl fluoride (0.15 g, 1.5 mmol, 1.5 equiv). The product was purified by column chromatography on silica gel (1% ethyl acetate/hexanes) to afford **3f** (0.20 g, 67 %). The product was isolated as a mixture of diastereomers since the dioxolanone and acid fluoride used were racemates.



cis-4, 6-benzoyloxy-2, 2-dimethyl-1, 3-dioxane (5)

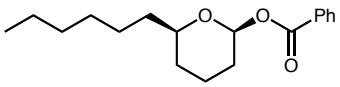
According to standard procedure described above, ester **4** (0.22 g, 1 mmol) was treated with DIBAL-H (1.0 M in hexane, 2.2 mL, 2.2 mmol, 2.2 equiv), followed by addition of neat pyridine (0.48 mL, 6.0 mmol, 6.0 equiv), DMAP (0.26 g, 2.2 mmol, 2.2 equiv), and benzoyl fluoride (0.32 mL, 3.0 mmol, 3.0 equiv). The product was purified by column chromatography on silica gel (1% ethyl

acetate/hexanes) to afford **5** (0.33 g, 93 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-8.07 (m, 4H), 7.62-7.56 (m, 2H), 7.44-7.39 (m, 4H), 6.57 (t, 2H, *J* = 4.2 Hz), 2.54 (1H, ddd, *J* = 14.1, 4.2, 4.2 Hz), 2.23 (1H, ddd, *J* = 14.4, 4.8, 4.8 Hz), 1.73 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 133.5, 130.3, 130.0, 129.7, 128.6, 99.9, 89.1, 32.0, 29.4, 27.6; IR (NaCl, neat) 1728, 1267, 1024, 985, 709 cm^{-1}.



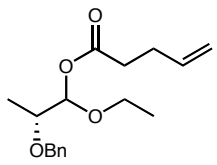
(2S*, 4R*, 6S*)-4-benzoyloxy-6-methyl-2-tert-butyl-1, 3-dioxane (7)

According to standard procedure described above, ester **6** (0.22 g, 1 mmol) was treated with DIBAL-H (1.0 M in hexane, 1.1 mL, 1.1 mmol, 1.1 equiv), followed by addition of neat pyridine (0.24 mL, 3.0 mmol, 3.0 equiv), DMAP (0.13 g, 1.1 mmol, 1.1 equiv), and benzoyl fluoride (0.16 mL, 1.5 mmol, 1.5 equiv). The product was purified by column chromatography on silica gel (1% ethyl acetate/hexanes) to afforded **7** (0.26 g, 94 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11-8.08 (m, 2H), 7.58 (m, 1H), 7.48-7.43 (m, 2H), 6.08 (dd, 1H, *J* = 9.9, 2.4 Hz), 4.31 (s, 1H), 3.83 (qdd, *J* = 2.7, 6.3, 12.6 Hz), 1.87 (ddd, 1H, *J* = 12.6, 2.4, 2.4 Hz), 1.60 (m, 1H), 1.28 (d, 3H, *J* = 6.3 Hz), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 133.4, 130.1, 129.8, 128.5, 105.3, 94.0, 71.2, 37.8, 35.0, 25.0, 21.7; IR (NaCl, neat) 2976, 1731, 1272, 1108, 989, 715 cm^{-1}; HRMS $[C_{16}H_{22}O_4\text{-}H]^+$ Calc. 277.1440. Found (EI+) 277.1444.



cis-2-benzoyloxy-6-hexanylpyran (9) [1]

According to standard procedure described above, lactone **8** (0.22 g, 1 mmol) was treated with DIBAL-H (1.0 M in hexane, 1.1 mL, 1.1 mmol, 1.1 equiv), followed by addition of neat pyridine (0.24 mL, 3.0 mmol, 3.0 equiv), DMAP (0.13 g, 1.1 mmol, 1.1 equiv), and benzoyl fluoride (0.16 mL, 1.5 mmol, 1.5 equiv). The product was purified by column chromatography on silica gel (1% ethyl acetate/hexanes) to afford **9** (0.24 g, 83 %).

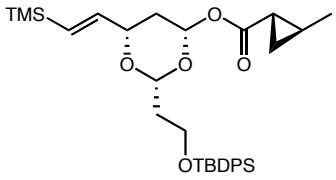


(2R)-1-ethoxy-2-benzyloxypropyl 4-pentenoate (11)

To a solution of ester **10** (100 mg, 0.48 mmol) in CH_2Cl_2 (4 mL) at –78 ºC was added DIBAL-H (1M in hexanes, 1.44 mL, 1.44 mmol) dropwise via syringe. After 45 min, pyridine (175 μl, 2.16 mmol) and DMAP (176 mg, 1.44 mmol, 3.0 equiv) in CH_2Cl_2 were introduced to the solution dropwise followed by slow addition of 4-pentenoyl fluoride (9.0 equiv) via syringe. After the resultant mixture was stirred at -78 ºC for 14h, the acetone-dry ice bath was replaced with an ice-water bath. The mixture was stirred at 0 ºC for an additional 30 min, before the reaction was quenched with aqueous NH_4Cl (7.5 mL) and saturated Rochelle's salt solution (6 mL). After the mixture was stirred for 15 min, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x 5mL). The combined organic layers were washed with ice-cooled $NaHSO_4$, saturated $NaHCO_3$, brine, and dried over Na_2SO_4. After removal of the volatiles, the product was purified by silica gel chromatography to afford **11** (0.12 g, 86 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.25 (m, 5H), 2.92 (d, 1H, *J* = 3.9 Hz, minor isomer), 5.83 (d, 1H, *J* = 5.1 Hz, major isomer), 5.80 (m, 1H), 5.12-4.97 (m, 2H), 4.70-4.57 (m, 2H), 3.81-3.70 (m, 1H), 3.67-

[1] Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2385.

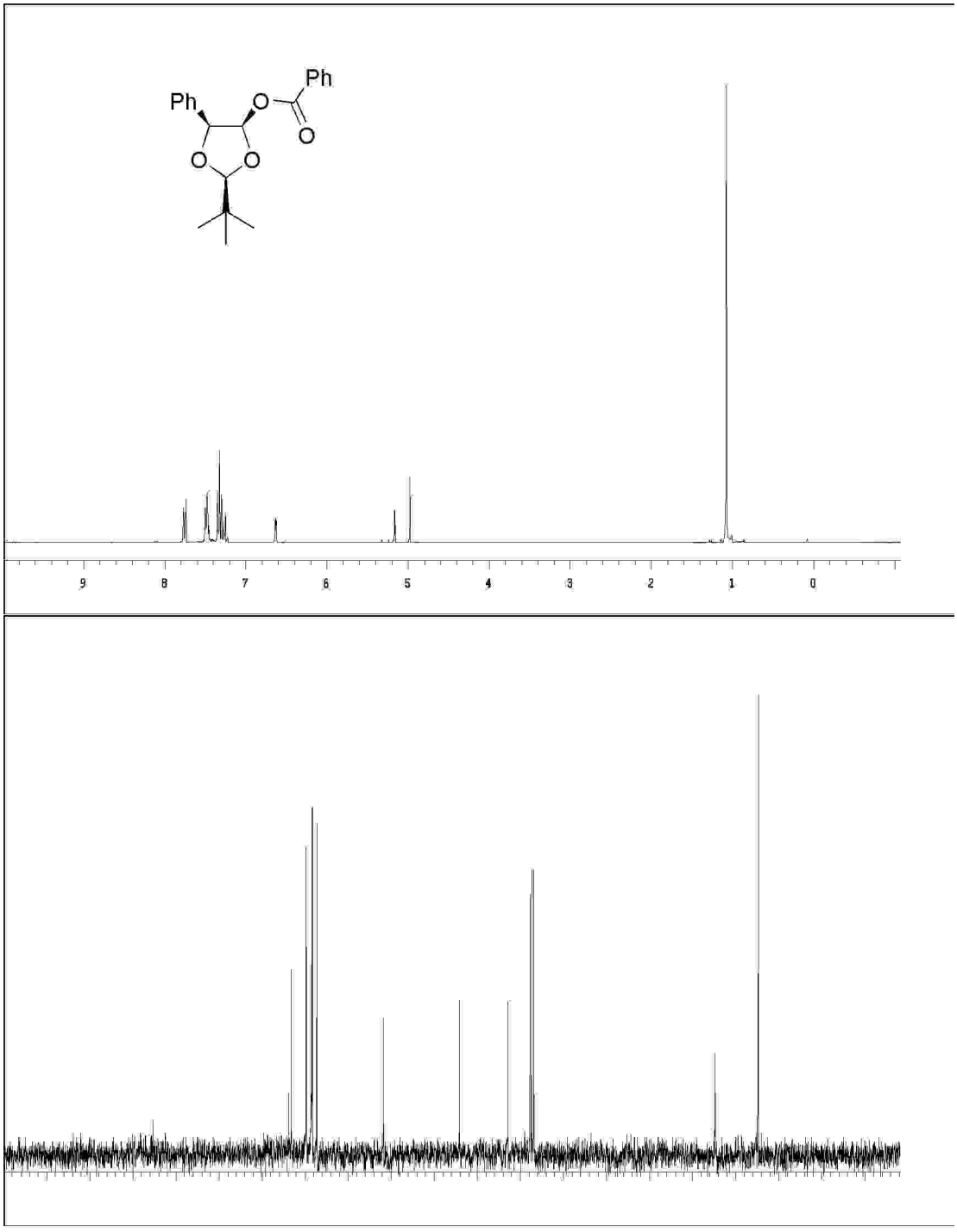
3.53 (m, 2H), 2.51-2.31 (m, 4H), 1.24-1.18 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 172.9, 138.6, 136.6, 128.4, 127.8, 127.7, 115.7, 98.5, 97.7, 75.4, 75.2, 72.0, 71.9, 65.9, 34.0, 29.0, 15.3, 15.1; IR (NaCl, teat) 2960, 1733, 1260, 1104, 800, 701 cm^{-1}; HRMS $[C_{17}H_{24}O_4\text{-}H]^+$ Calc 291.1596. Found (FAB+) 291.1603.



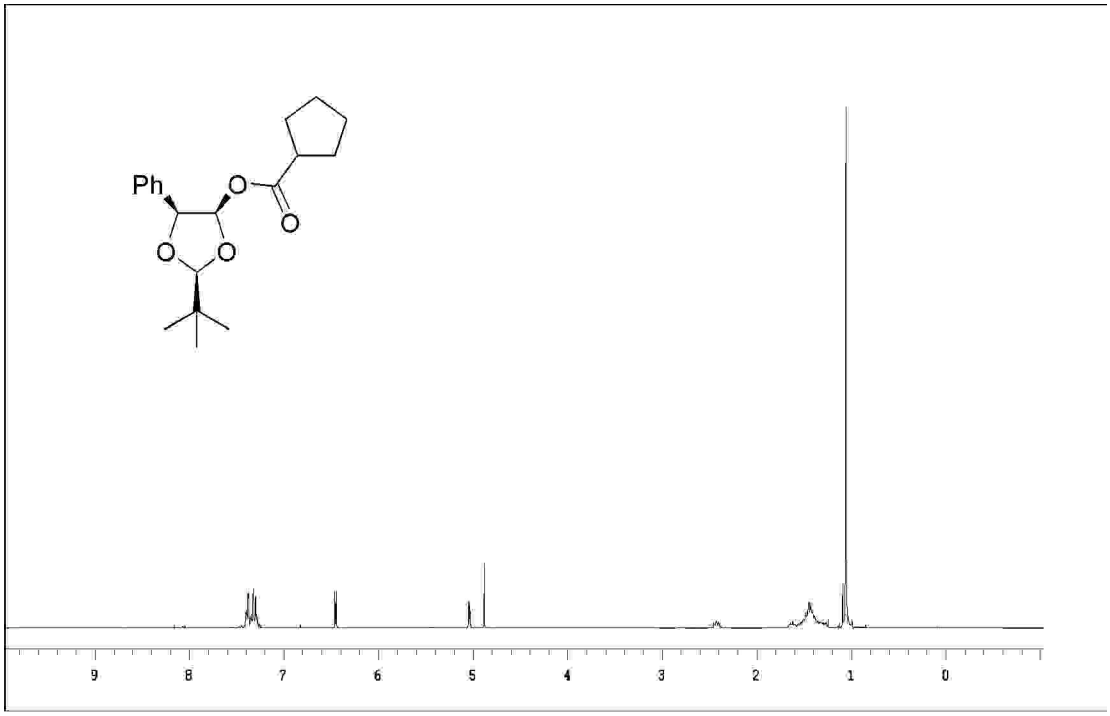
(2R, 4S, 6S)-4-[(2S, 1S)-2-methyl-cyclopropanecarbonyloxy]-2-[2-(tert-butyldiphenyl-silanyloxy)-ethyl]-6-[2-(trimethylsilanylvinyl]-(1, 3-dioxane (16)

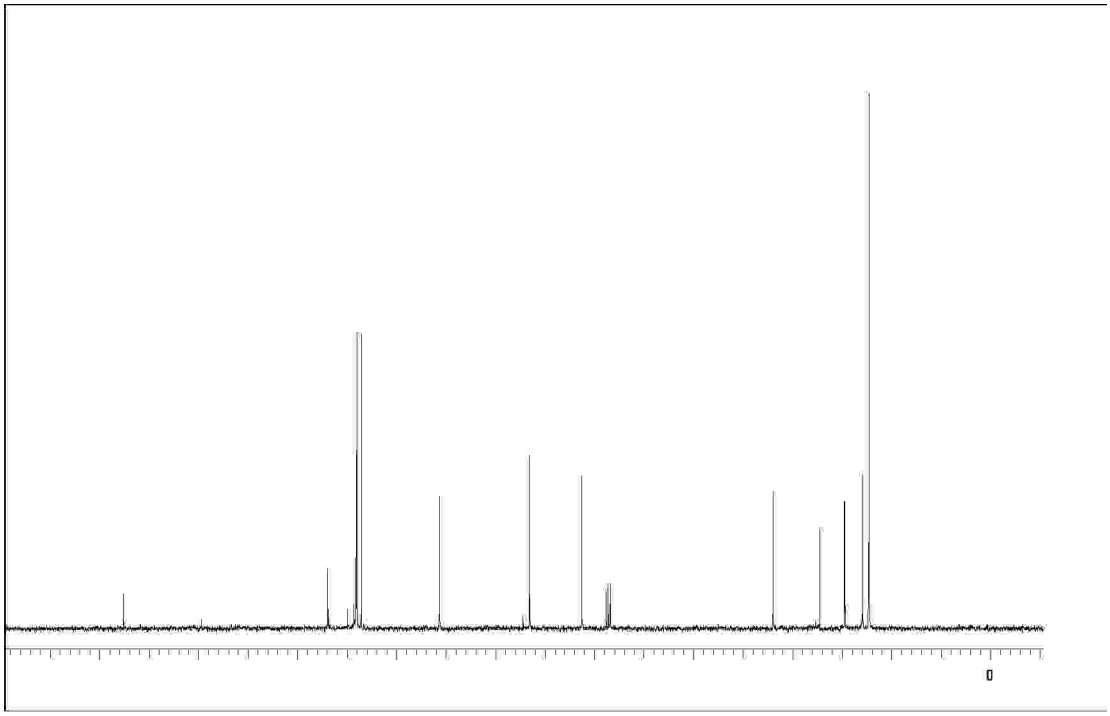
A flame-dried round bottom flask was charged with acid **12** (0.1 g, 0.53 mmol) and HMDS (0.16 mL, 0.8 mmol) in 0.3 mL of CH_2Cl_2, and the solution allowed to stir at room temperature for 13 h. Upon completion, all volatiles including excess HMDS were removed under vacuum. The residue was redissolved in 1 mL of CH_2Cl_2 and cooled down to –78 ºC. The aldehyde (0.18 g, 0.58 mmol) was introduced followed by addition of TMSOTf (3 l, 0.03 equiv). The resultant mixture was stirred at –78 ºC for 19 h and then the reaction was quenched with pyridine (5 l, 0.3 equiv). The mixture was allowed to warm up to room temperature. All volatiles were removed under vacuum. The residue was passed through a short silica gel column using 4:1 hexane-ethyl acetate as eluent. The residue on removal of solvents was treated with DIBAL-H at –78 ºC for 2 h. Then, neat pyridine (0.12 mL, 1.5 mmol, 3.0 equiv) was introduced via syringe followed by slow addition of a solution of DMAP (0.07 g, 0.58 mmol, 1.1 equiv) in 0.5 mL of CH_2Cl_2 at –78 ºC. Finally, 2-methyl cyclopropanecarbonyl fluoride (0.1 g, 0.8 mmol, 1.5 equiv) was added dropwise, and the resulting mixture was allowed to warm up to 10 ºC over 12 h. The reaction was quenched with 3 mL of saturated NH_4Cl. Although no emulsion formed in the workup, 3 ml of saturated Rochelle's salt solution was added. After the mixture was stirred for 15 min, the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 5mL). The combined organic layers were washed with $NaHSO_4$, saturated $NaHCO_3$, brine, and dried over Na_2SO_4. After removal of the volatiles, the product was purified by silica gel chromatography to afford **16** (0.15 g, 50 %). ^{1}H NMR (300 MHz, $CDCl_3$) 7.68-7.66 (m, 4H), 7.43-7.35 (m, 6H), 6.08-5.91 (m, 3H), 5.03 (t, 1H, J = 5.4 Hz), 4.20 (m, 1H), 2.84 (t, 2H, J = 5.4 Hz), 2.07-2.00 (m, 2H), 1.91 (m, 1H), 1.65 (m, 1H), 1.41 (m, 2H), 1.25 (m, 1H), 1.13 (d, 3H, J = 6.0 Hz), 1.06 (s, 9H), 0.76 (m, 1H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 172.6, 143.8, 135.6, 133.8, 133.8, 131.3, 129.6, 127.7, 97.6, 93.2, 77.6, 59.4, 37.3, 36.0, 27.1, 21.5, 19.5, 18.4, 18.0, 17.8, -1.1; IR (NaCl, neat) 2979, 2932, 1739, 1120, 914, 737, 698 cm^{-1}; HRMS $[C_{32}H_{46}O_5Si_2]^+$ Calc 566.2884. Found (EI) 566.2869.

NMR Spectra

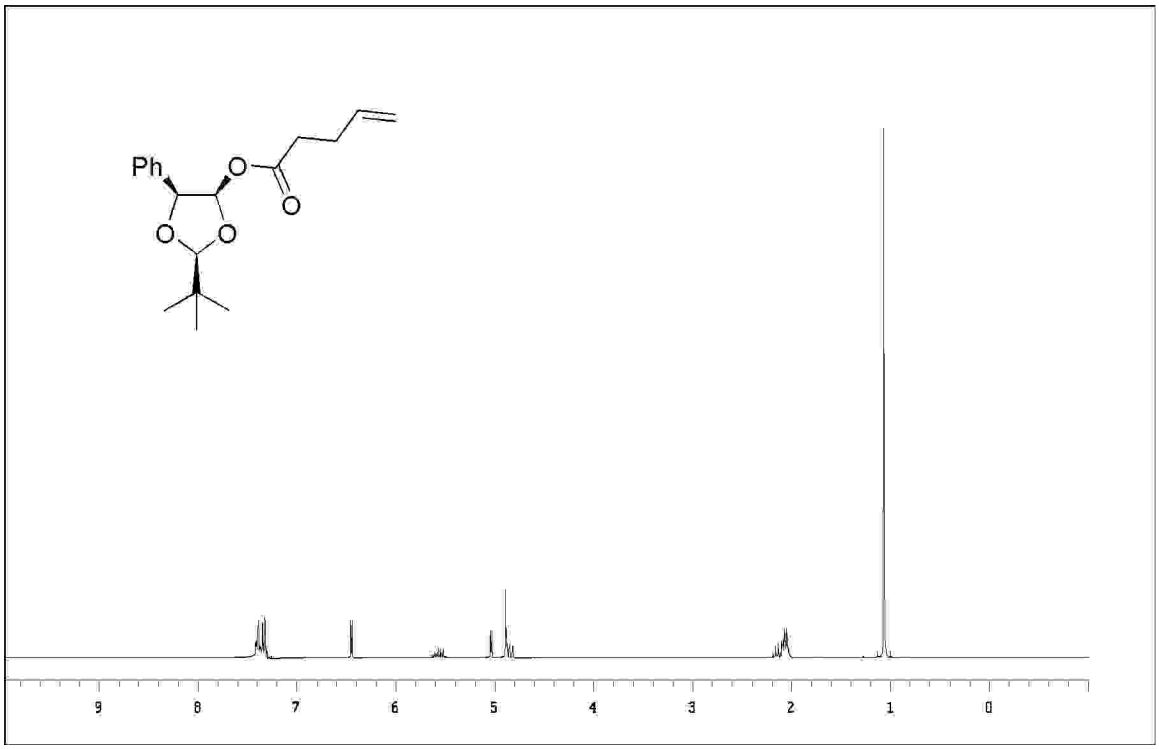


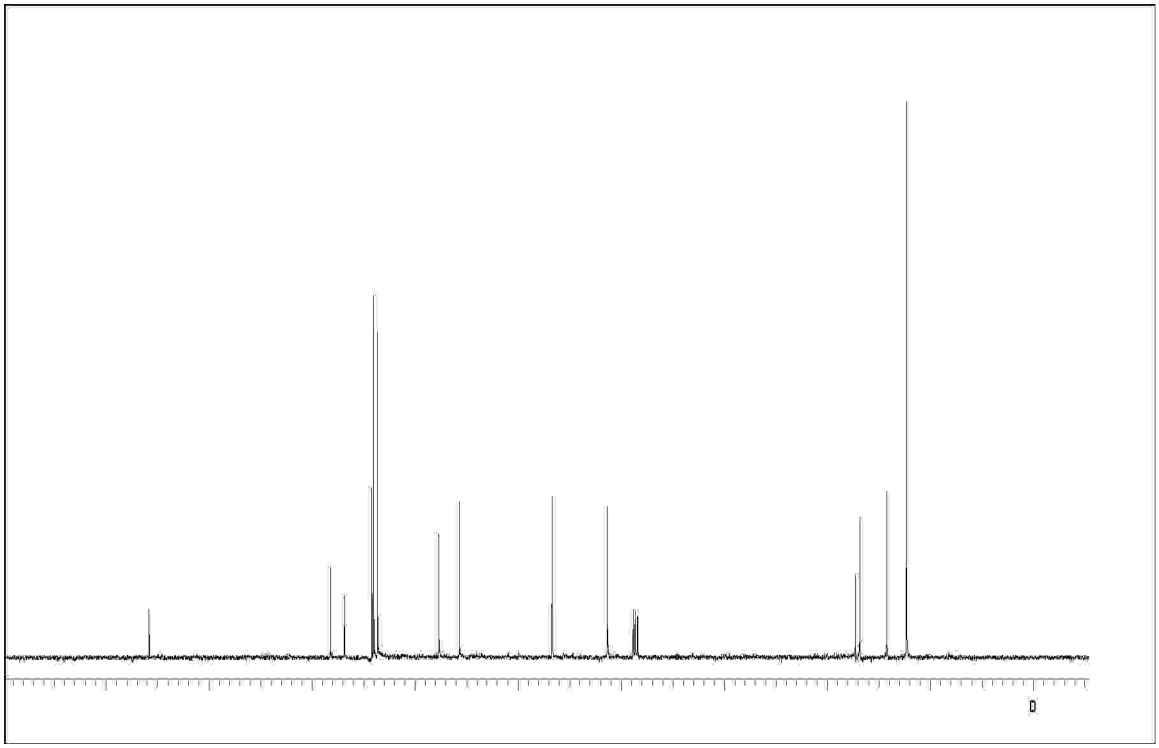
^{1}H NMR and ^{13}C NMR of **3b**



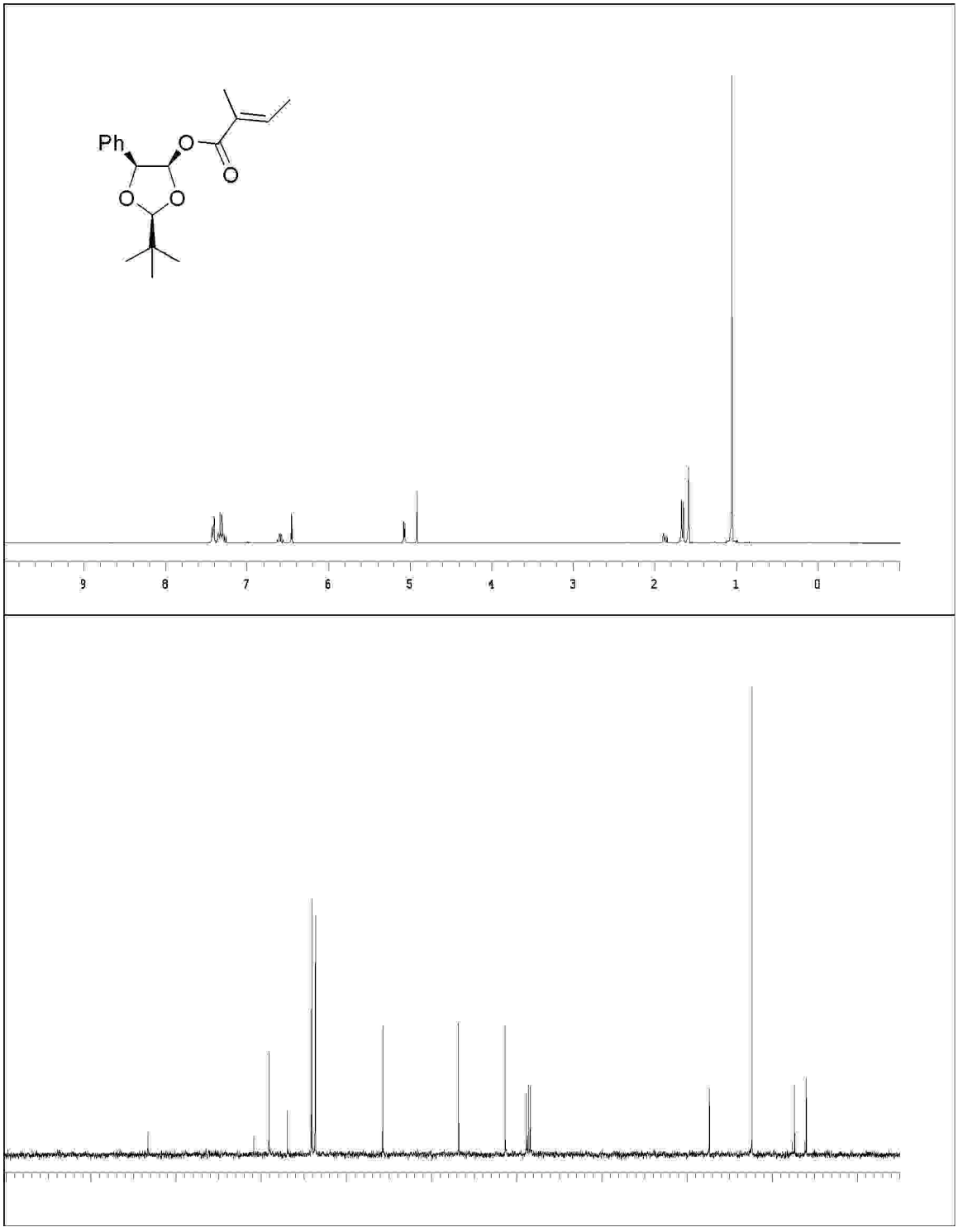


^{1}H NMR and ^{13}C NMR of **3c**

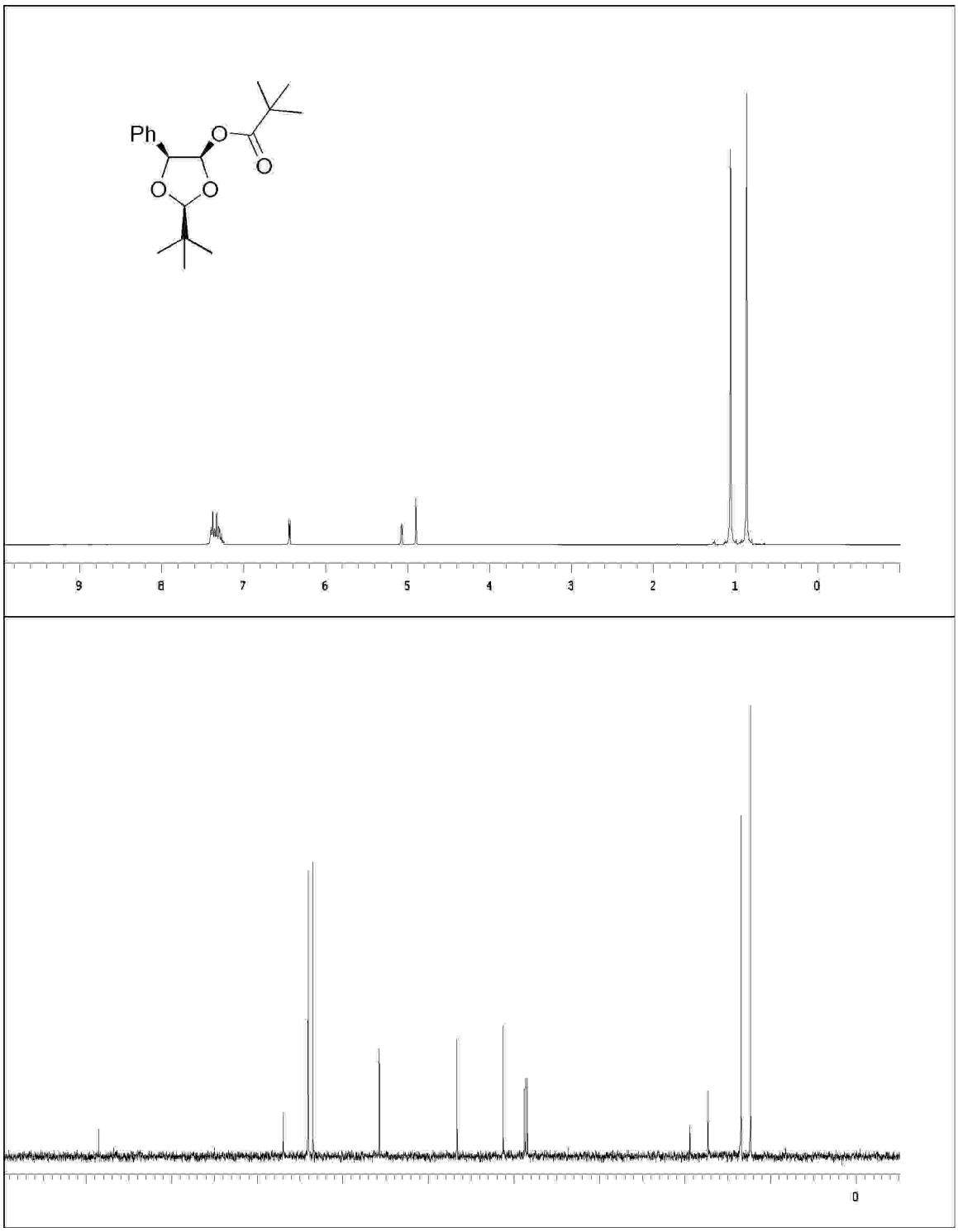




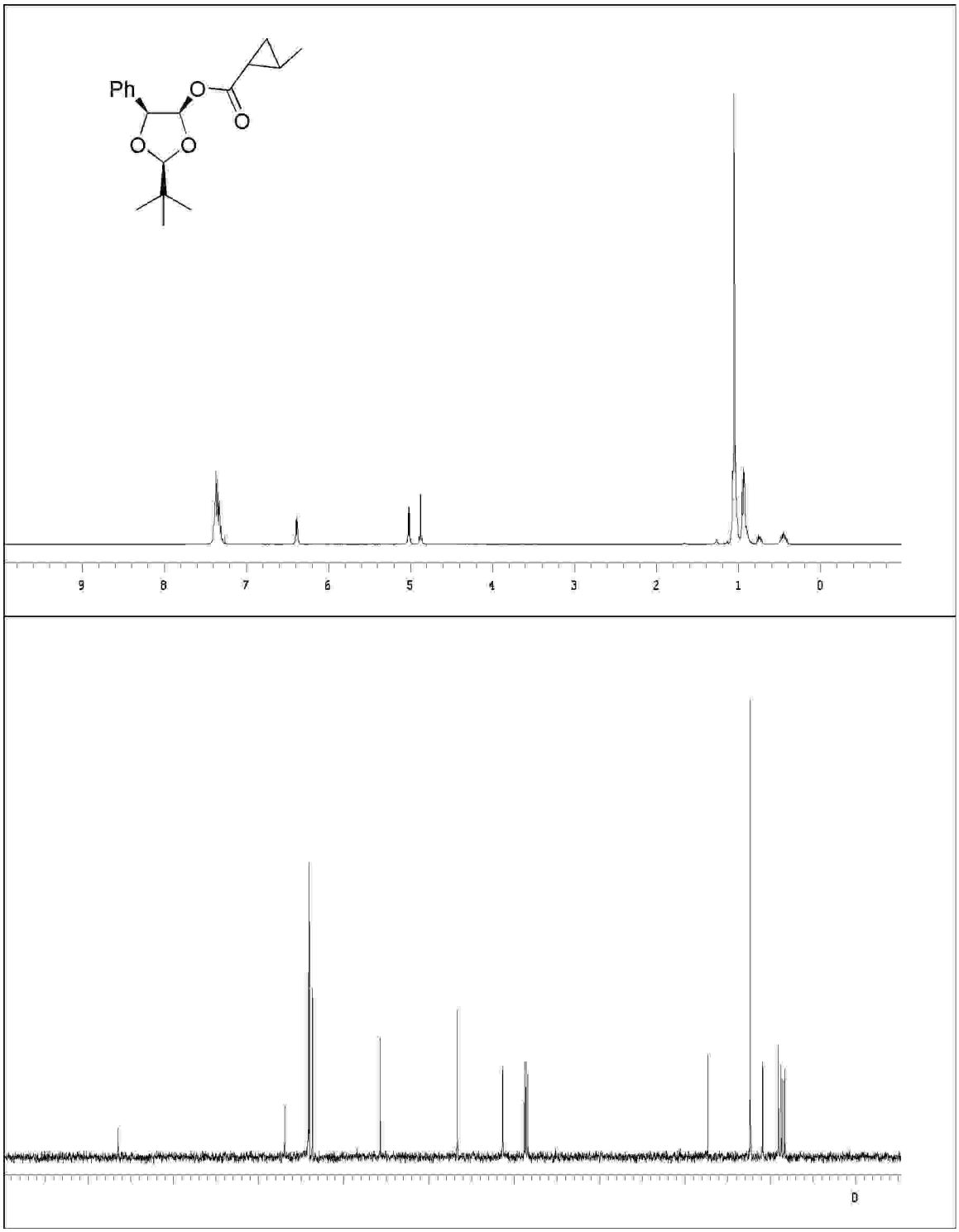
^{1}H NMR and ^{13}C NMR of **3d**



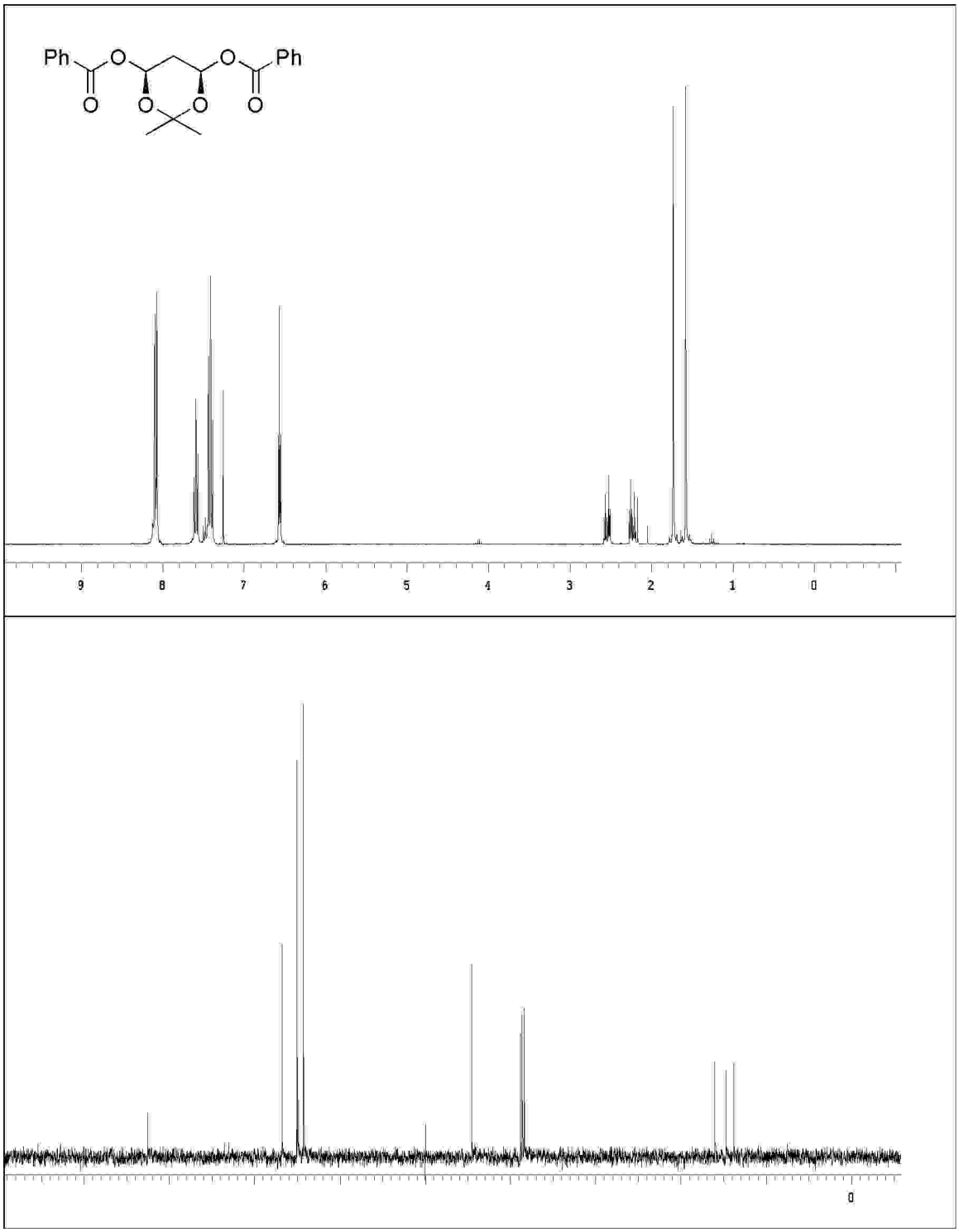
^{1}H NMR and ^{13}C NMR of **3e**



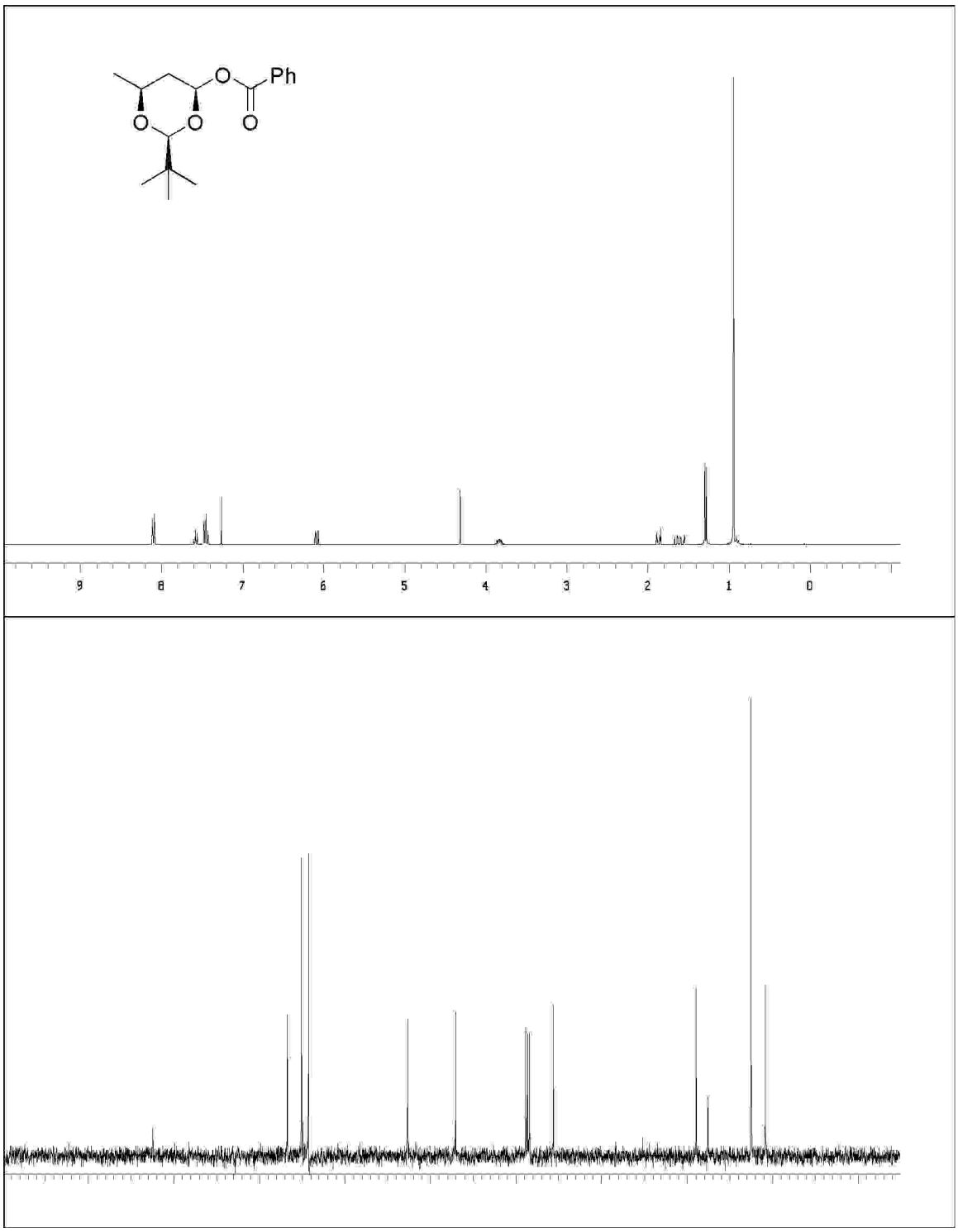
^{1}H NMR and ^{13}C NMR of **3f**



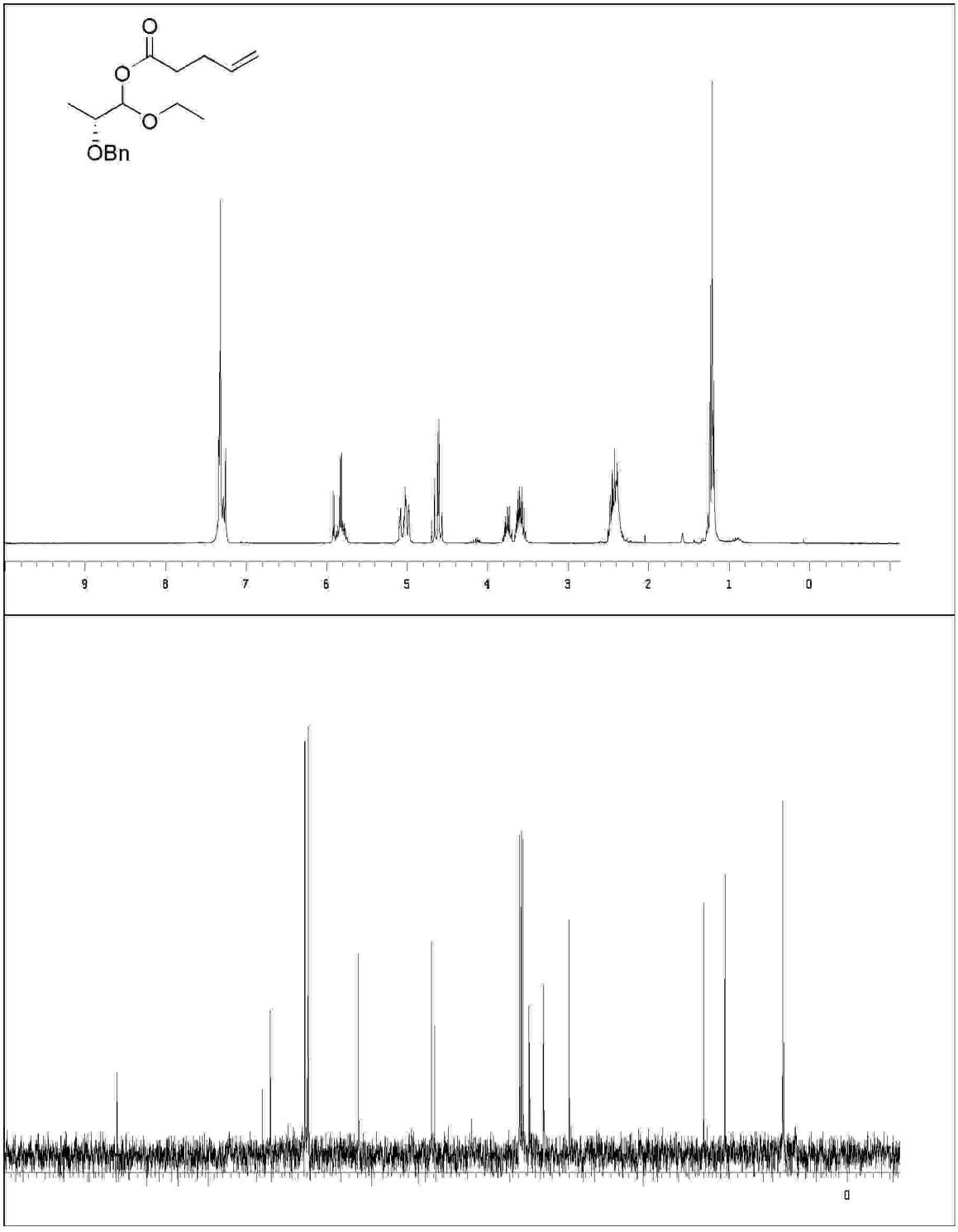
^{1}H NMR and ^{13}C NMR of **5**



^{1}H NMR and ^{13}C NMR of **7**



^{1}H NMR and ^{13}C NMR of **11**



^{1}H NMR and ^{13}C NMR of **16**