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Kinetic Control in Direct α-Silyloxy Ketone Synthesis: A New Regiospecific Catalyzed Cross Silyl Benzoin Reaction

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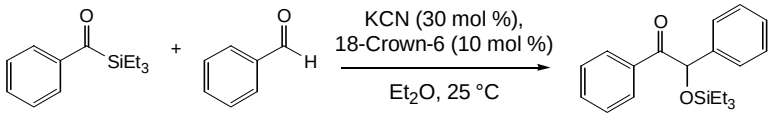
Experimental Section

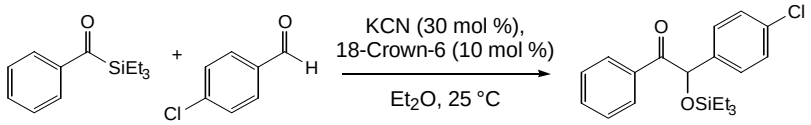
Materials and Methods: General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C{^{1}H} NMR) were recorded on the following instruments: Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{13}C{^{1}H} NMR at 100 MHz) and Varian Gemini 300 (^{1}H NMR at 300 MHz and ^{13}C{^{1}H} at 75 MHz) spectrometers with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; C_6D_6 at 7.15 ppm, and ^{13}C{^{1}H} NMR: $CDCl_3$ at 77.0 ppm; C_6D_6 at 128.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet), coupling constants (Hz), and integration. Combustion analyses were performed by Atlantic Microlab Inc., Norcross, GA. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and aqueous ceric ammonium nitrate molybdate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Sorbent Technologies silica gel 60 (32-63 μm). All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material. Diethyl ether and toluene were dried by passage through a column of neutral alumina under nitrogen prior to use. Acylsilanes were prepared in three steps from the corresponding aldehydes. Unless otherwise noted, reagents were obtained from commercial sources and used without further purification. 18-crown-6 was recrystallized from acetonitrile and dried at 25 °C under vacuum overnight. Potassium cyanide was dried at 100 °C under vacuum. **CAUTION:** Potassium cyanide is toxic and releases HCN upon exposure to acid. While we have encountered no problems in the chemistry described herein, we regularly employ an HCN detector (BW Technologies, Ltd.) in manipulations involving cyanide reagents as a precautionary measure. Reactions should be conducted in a well-ventilated fume hood.

General procedure (A) for the reaction of acylsilanes with aldehydes. A dry round-bottom flask with a magnetic stir bar was charged with 0.5 mmol of acylsilane, KCN (0.3 equiv), 18-crown-6 (0.1 equiv) and 10 mL of Et_2O. To the resulting mixture, aldehyde (1.1 equiv) was added neat *via* syringe or as an Et_2O solution (6 mL) *via* cannula. The reaction was stirred at 25 °C under N_2 until the starting material was consumed (TLC analysis). To the reaction mixture was added 15 mL of H_2O. The mixture was stirred for 5 min before the organic layer was separated and the aqueous

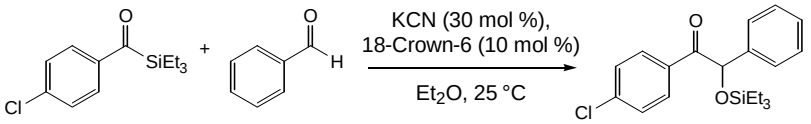
layer was extracted with three 15 mL portions of Et_2O. The organic extracts were combined, dried ($MgSO_4$), and the solvent was removed with a rotary evaporator. The product was purified by flash chromatography, eluting with the indicated solvent system to afford the pure silyl-protected benzoin product.



1,2-diphenyl-2-triethylsilyloxy-ethanone (3a). The title compound was prepared according to General Procedure **A** using 104 mg (0.47 mmol) of acylsilane, 53 µL (0.52 mmol) of benzaldehyde, 8.0 mg (0.12 mmol) of KCN, 13 mg (0.047 mmol) of 18-crown-6, and 8 mL of Et_2O. After 2.5 h at 25 °C, the crude product was purified by flash chromatography with 33:1 hexanes/EtOAc to afford 140 mg (90%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3087, 3062, 3029, 2957, 2913, 2877, 1700, 1680, 1598, 1579, 1493, 1448, 1413, 1277, 1238, 1190, 1119, 1071, 1004, 980, 850, 764, 745, 606; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02-8.00 (m, 2H), 7.53-7.51 (m, 2H), 7.46-7.42 (m, 1H), 7.35-7.30 (m, 4H), 7.25-7.21 (m, 1H), 5.77 (s, 1H), 0.88 (t, *J* = 8.0 Hz, 9H), 0.64-0.57 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.8, 139.0, 134.5, 132.8, 129.8, 128.5, 128.1, 127.7, 125.8, 80.0, 6.6, 4.7; TLC (33:1 hexanes/EtOAc) R_f 0.17; **Anal.** Calcd. for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.22; H, 8.05.

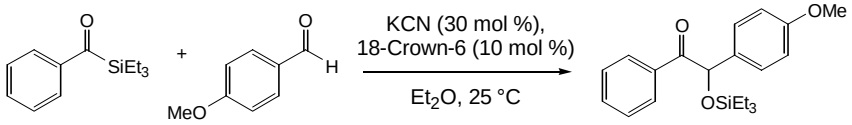


1-phenyl-2-(4-chlorophenyl)-2-triethylsilyloxy-ethanone (3b). The title compound was prepared according to General Procedure **A** using 117 mg (0.53 mmol) of acylsilane, 83 mg (0.59 mmol) of *p*-chlorobenzaldehyde, 10.5 mg (0.16 mmol) of KCN, 15 mg (0.053 mmol) of 18-crown-6, and 10 mL of Et_2O. After 2 h at 25 °C, the crude product was purified by flash chromatography with 33:1 hexanes/EtOAc to afford 156 mg (82%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3066, 3028, 2958, 2913, 2877, 1698, 1681, 1598, 1579, 1490, 1448, 1409, 1281, 1238, 1189, 1122, 1092, 1014, 979, 850, 777, 745, 688; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01-7.98 (m, 2H), 7.48-7.45 (m, 3H), 7.38-7.34 (m, 2H), 7.33-7.29 (m, 2H), 5.72 (s, 1H), 0.89 (t, *J* = 8.0 Hz, 9H), 0.64-0.56 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.5, 137.6, 134.3, 133.7, 133.0, 129.8, 128.8, 128.2, 127.2, 79.5, 6.6, 4.6; TLC (33:1 hexanes/EtOAc) R_f 0.21; **Anal.** Calcd. for $C_{20}H_{25}ClO_2Si$: C, 66.55; H, 6.98. Found: C, 66.58; H, 6.79.

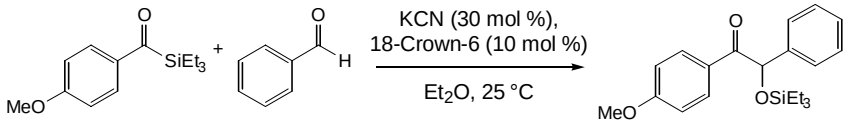


1-(4-chlorophenyl)-2-phenyl-2-triethylsilyloxy-ethanone (3c). The title compound was prepared according to General Procedure **A** using 109 mg (0.43 mmol) of acylsilane, 48 µL (0.47 mmol) of benzaldehyde, 8.7 mg (0.13 mmol) of KCN, 12 mg (0.043 mmol) of 18-crown-6, and 8 mL of Et_2O. After 2 h at 25 °C, the crude product was purified by flash chromatography with 38:1 hexanes/EtOAc to afford 132 mg (86%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3088,

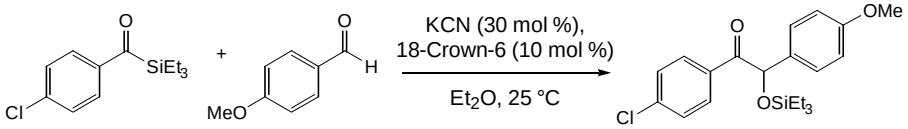
3063, 3030, 2956, 2912, 2877, 1682, 1588, 1570, 1488, 1450, 1414, 1400, 1278, 1239, 1189, 1176, 1093, 1009, 983, 857, 817, 776, 743, 701, 624; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.01-7.97 (m, 2H), 7.52-7.49 (m, 2H), 7.37-7.24 (m, 5H), 5.70 (s, 1H), 0.89 (t, *J* = 8.1 Hz, 9H), 0.65-0.60 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.7, 139.3, 138.7, 132.6, 131.4, 128.7, 128.4, 127.9, 125.5, 80.4, 6.6, 4.7; TLC (35:1 hexanes/EtOAc) R_f 0.27; **Anal.** Calcd. for $C_{20}H_{25}ClO_2Si$: C, 66.55; H, 6.98. Found: C, 66.30; H, 7.03.



1-phenyl-2-(4-methoxyphenyl)-2-triethylsilyloxy-ethanone (3d). The title compound was prepared according to General Procedure **A** using 103 mg (0.47 mmol) of acylsilane, 63 µL (0.52 mmol) of *p*-anisaldehyde, 8.0 mg (0.12 mmol) of KCN, 13 mg (0.047 mmol) of 18-crown-6, and 8 mL of Et_2O. After 1.5 h at 25 °C, the crude product was purified by flash chromatography with 28:1 hexanes/EtOAc to afford 132 mg (79%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3059, 3002, 2957, 2934, 2913, 2877, 1698, 1680, 1610, 1562, 1511, 1464, 1448, 1415, 1304, 1277, 1250, 1172, 1120, 1101, 1034, 984, 853, 798, 750, 689; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02-8.00 (m, 2H), 7.48-7.40 (m, 3H), 7.38-7.33 (m, 2H), 6.88-6.84 (m, 2H), 5.76 (s, 1H), 3.76 (s, 3H), 0.90 (t, *J* = 8.0 Hz, 9H), 0.64-0.58 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.8, 159.2, 134.6, 132.7, 131.0, 129.7, 128.1, 127.3, 114.0, 79.3, 55.2, 6.7, 4.7; TLC (20:1 hexanes/EtOAc) R_f 0.22. Combustion analysis was not successful. For ^{1}H NMR and ^{13}C{^{1}H} NMR spectra, see the Appendix.

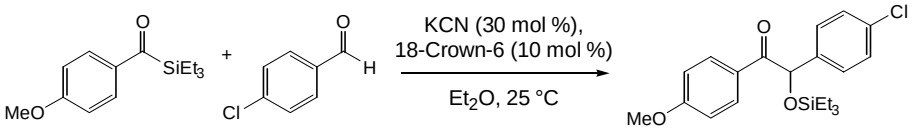


1-(4-methoxyphenyl)-2-phenyl-2-triethylsilyloxy-ethanone (3e). The title compound was prepared according to General Procedure **A** using 108 mg (0.43 mmol) of acylsilane, 49 µL (0.48 mmol) of benzaldehyde, 9.4 mg (0.14 mmol) of KCN, 12 mg (0.043 mmol) of 18-crown-6, and 8 mL of Et_2O. After 2.5 h at 25 °C, the crude product was purified by flash chromatography with 13:1 hexanes/EtOAc to afford 131 mg (85%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3086, 3063, 3029, 3007, 2955, 2911, 2876, 1689, 1671, 1602, 1574, 1511, 1494, 1456, 1419, 1309, 1258, 1172, 1117, 1070, 980, 857, 826, 808, 744, 703, 593; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08-8.04 (m, 2H), 7.54-7.52 (m, 2H), 7.34-7.30 (m, 2H), 7.26-7.22 (m, 1H), 6.84-6.81 (m, 2H), 5.72 (s, 1H), 3.81 (s, 3H), 0.90 (t, *J* = 8.0 Hz, 9H), 0.65-0.56 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.3, 163.2, 139.4, 132.3, 128.5, 127.6, 127.3, 125.6, 113.3, 80.2, 55.3, 6.7, 4.7; TLC (12:1 hexanes/EtOAc) R_f 0.26; **Anal.** Calcd. for $C_{21}H_{28}O_3Si$: C, 70.74; H, 7.92. Found: C, 70.53; H, 8.00.

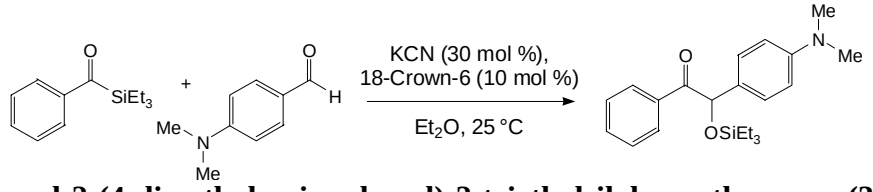


1-(4-chlorophenyl)-2-(4-methoxyphenyl)-2-triethylsilyloxy-ethanone (3f). The title compound was prepared according to General Procedure **A** using 116 mg (0.46 mmol) of acylsilane, 61 µL (0.50 mmol) of *p*-anisaldehyde, 9.0 mg (0.14 mmol) of KCN,

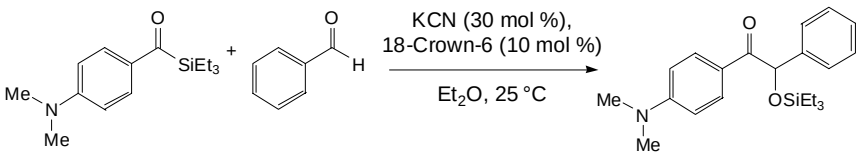
13 mg (0.046 mmol) of 18-crown-6, and 9 mL of Et_2O. After 3.0 h at 25 °C, the crude product was purified by flash chromatography with 30:1 hexanes/EtOAc to afford 143 mg (80%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3074, 3036, 3002, 2957, 2914, 2876, 1681, 1610, 1587, 1570, 1511, 1487, 1464, 1414, 1304, 1251, 1172, 1121, 1092, 1037, 1014, 987, 859, 831, 786, 765, 745, 730, 624; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98-7.95 (m, 2H), 7.40-7.36 (m, 2H), 7.31-7.28 (m, 2H), 6.86-6.83 (m, 2H), 5.66 (s, 1H), 3.75 (s, 3H), 0.87 (t, *J* = 8.0 Hz, 9H), 0.64-0.56 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.7, 159.3, 139.2, 132.7, 131.3, 130.6, 128.4, 127.0, 114.0, 80.0, 55.2, 6.6, 4.6; TLC (30:1 hexanes/EtOAc) R_f 0.16; **Anal.** Calcd. for $C_{21}H_{27}ClO_3Si$: C, 64.51; H, 6.96. Found: C, 64.28; H, 7.07.



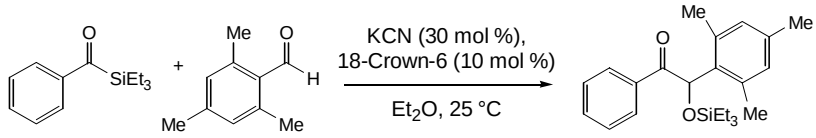
1-(4-methoxyphenyl)-2-(4-chlorophenyl)-2-triethylsilyloxy-ethanone (3g). The title compound was prepared according to General Procedure **A** using 126.5 mg (0.51 mmol) of acylsilane, 74.7 mg (0.53 mmol) of *p*-chlorobenzaldehyde, 10 mg (0.15 mmol) of KCN, 14 mg (0.051 mmol) of 18-crown-6, and 11 mL of Et_2O. After 5 h at 25 °C, the crude product was purified by flash chromatography with 20:1 hexanes/EtOAc to afford 158 mg (80%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3005, 2956, 2911, 2876, 1671, 1600, 1574, 1510, 1485, 1460, 1420, 1312, 1286, 1261, 1170, 1120, 1092, 1014, 981, 856, 830, 802, 746, 728; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06-8.02 (m, 2H), 7.48-7.46 (m, 2H), 7.31-7.28 (m, 2H), 6.86-6.82 (m, 2H), 5.67 (s, 1H), 3.82 (s, 3H), 0.89 (t, *J* = 7.5 Hz, 9H), 0.65-0.57 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.0, 163.4, 137.9, 133.5, 132.3, 128.7, 127.0, 113.4, 79.7, 55.3, 6.7, 4.6 (two coincident resonances in the aromatic region); TLC (10:1 hexanes/EtOAc) R_f 0.32; **Anal.** Calcd. for $C_{21}H_{27}ClO_3Si$: C, 64.51; H, 6.96. Found: C, 64.23; H, 6.99.



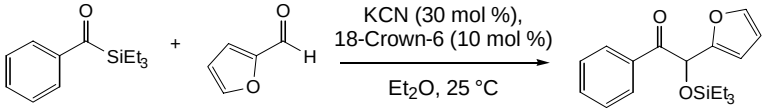
1-phenyl-2-(4-dimethylaminophenyl)-2-triethylsilyloxy-ethanone (3h). The title compound was prepared according to General Procedure **A** using 103 mg (0.47 mmol) of acylsilane, 77 mg (0.52 mmol) of *p*-dimethylaminobenzaldehyde, 9.3 mg (0.14 mmol) of KCN, 13.5 mg (0.047 mmol) of 18-crown-6, and 10 mL of Et_2O. After 10 h at 25 °C, the crude product was purified by flash chromatography with 12:1 hexanes/EtOAc to afford 115 mg (66%) of the product as a yellow oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3070, 3057, 3027, 2950, 2934, 2911, 2879, 2803, 1696, 1677, 1615, 1579, 1521, 1457, 1447, 1413, 1352, 1278, 1234, 1180, 1133, 1002, 984, 947, 853, 783, 735, 688; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.6 Hz, 2H), 7.45-7.33 (m, 5H), 6.68 (d, *J* = 7.6 Hz, 2H), 5.79 (s, 1H), 2.91 (s, 6H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.69-0.59 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.8, 150.0, 134.9, 132.5, 129.6, 128.0, 127.2, 126.3, 112.3, 79.2, 40.3, 6.7, 4.7; TLC (9:1 hexanes/EtOAc) R_f 0.31. For ^{1}H NMR and $^{13}C\{^1H\}$ NMR spectra, see the Appendix.



1-(4-dimethylaminophenyl)-2-phenyl-2-triethylsilyloxy-ethanone (3i). The title compound was prepared according to General Procedure **A** using 54.5 mg (0.21 mmol) of acylsilane, 23 µL (0.23 mmol) of benzaldehyde, 4.2 mg (0.062 mmol) of KCN, 6.0 mg (0.021 mmol) of 18-crown-6, and 5 mL of Et_2O. After 10 h at 25 °C, the crude product was purified by flash chromatography with 10:1 hexanes/EtOAc to afford 73 mg (95%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3086, 3061, 3028, 2954, 2912, 2873, 2823, 1668, 1593, 1548, 1529, 1493, 1450, 1416, 1373, 1313, 1238, 1190, 1120, 1072, 1005, 977, 947, 885, 856, 816, 735, 703, 665; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 9.2 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.33-7.18 (m, 3H), 6.55 (d, *J* = 9.2 Hz, 2H), 5.74 (s, 1H), 2.99 (s, 6H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.69-0.58 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.6, 153.1, 140.1, 132.1, 128.3, 127.3, 125.7, 122.1, 110.2, 79.9, 39.8, 6.7, 4.7; TLC (10:1 hexanes/EtOAc) R_f 0.20. For ^{1}H NMR and $^{13}C\{^1H\}$ NMR spectra, see the Appendix.

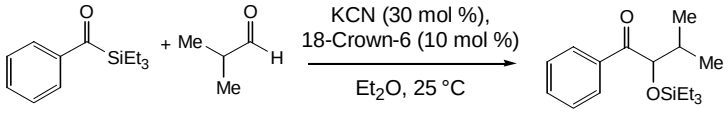


1-phenyl-2-(2,4,6-trimethylphenyl)-2-triethylsilyloxy-ethanone (3j). The title compound was prepared according to General Procedure **A** using 111 mg (0.51 mmol) of acylsilane, 81 µL (0.56 mmol) of mesitaldehyde, 10 mg (0.16 mmol) of KCN, 14.5 mg (0.051 mmol) of 18-crown-6, and 9 mL of Et_2O. After 2 h at 25 °C, the crude product was purified by flash chromatography with 28:1 hexanes/EtOAc to afford 159 mg (85%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3062, 2955, 2913, 2876, 1700, 1611, 1597, 1579, 1458, 1414, 1379, 1239, 1223, 1199, 1146, 1114, 1001, 986, 866, 853, 818, 732, 690, 661; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72-7.70 (m, 2H), 7.46-7.41 (m, 1H), 7.35-7.30 (m, 2H), 6.80 (s, 2H), 6.06 (s, 1H), 2.34 (s, 6H), 2.22 (s, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.72-0.58 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.7, 137.6, 136.8, 136.6, 134.0, 132.2, 130.0, 128.2, 128.1, 75.9, 20.9, 20.3, 6.8, 5.1; TLC (26:1 hexanes/EtOAc) R_f 0.27; **Anal.** Calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75. Found: C, 74.58; H, 8.85.

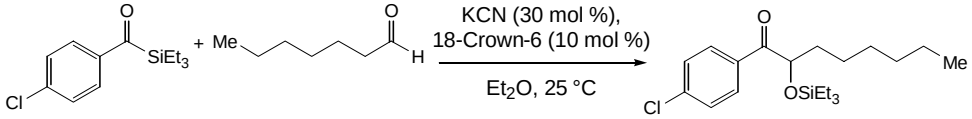


1-phenyl-2-(2-furyl)-2-triethylsilyloxy-ethanone (3k). The title compound was prepared according to General Procedure **A** using 105 mg (0.48 mmol) of acylsilane, 44 µL (0.53 mmol) of 2-furaldehyde, 9.4 mg (0.15 mmol) of KCN, 13.5 mg (0.048 mmol) of 18-crown-6, and 9 mL of Et_2O. After 2.5 h at 25 °C, the crude product was purified by flash chromatography with 35:1 hexanes/EtOAc to afford 114 mg (75%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 2956, 2912, 2877, 1706, 1683, 1598, 1579, 1497, 1448, 1413, 1287, 1230, 1149, 1112, 1012, 980, 851, 740, 688; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08-8.05 (m, 2H), 7.54-7.49 (m, 1H), 7.43-7.37 (m,

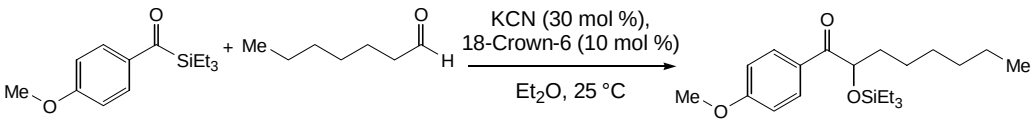
3H), 6.34-6.31 (m, 2H), 5.89 (s, 1H), 0.91 (t, *J* = 7.8 Hz, 9H), 0.65-0.57 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.9, 152.0, 142.8, 134.6, 133.1, 129.4, 128.2, 110.7, 108.8, 73.3, 6.6, 4.6; TLC (30:1 hexanes/EtOAc) R_f 0.20; **Anal.** Calcd. for $C_{18}H_{24}O_3Si$: C, 68.31; H, 7.64. Found: C, 68.10; H, 7.77.



1-phenyl-2-triethylsilyloxy-3-methyl-butanone (3l). The title compound was prepared according to General Procedure **A** using 106 mg (0.48 mmol) of acylsilane, 9.5 mg (0.15 mmol) of KCN, 14 mg (0.048 mmol) of 18-crown-6, and 4 mL of Et_2O. 48 µL (0.53 mmol) of isobutyraldehyde was added as an Et_2O solution (6 mL) *via* cannula over 2 h, and the reaction was kept for another 1 h at 25 °C. The crude product was purified by flash chromatography with 45:1 hexanes/EtOAc to afford 93 mg (66%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3063, 3029, 2960, 2912, 2876, 1700, 1678, 1598, 1579, 1468, 1435, 1414, 1388, 1365, 1278, 1242, 1188, 1150, 1093, 1072, 1003, 951, 842, 773, 742, 693; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07-8.05 (m, 2H), 7.56-7.52 (m, 1H), 7.45-7.41 (m, 2H), 4.46 (d, *J* = 6.4 Hz, 1H), 2.13 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 8.0 Hz, 9H), 0.57 (q, *J* = 8.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.3, 135.6, 132.8, 129.2, 128.3, 82.9, 33.1, 19.2, 17.8, 6.7, 4.8; TLC (40:1 hexanes/EtOAc) R_f 0.22; **Anal.** Calcd. for $C_{17}H_{28}O_2Si$: C, 69.81; H, 9.65. Found: C, 69.73; H, 9.70.

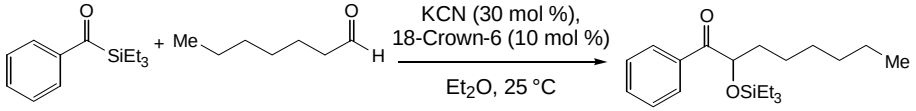


1-(4-chlorophenyl)-2-triethylsilyloxy-octanone (3m). The title compound was prepared according to General Procedure **A** using 115 mg (0.45 mmol) of acylsilane, 8.9 mg (0.14 mmol) of KCN, 13 mg (0.045 mmol) of 18-crown-6, and 4 mL of Et_2O. 70 µL (0.50 mmol) of heptanal was added as an Et_2O solution (6 mL) *via* cannula over 1.5 h, and the reaction was kept for another 0.5 h at 25 °C. The crude product was purified by flash chromatography with 40:1 hexanes/EtOAc to afford 124 mg (75%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 2960, 2932, 2876, 1699, 1683, 1588, 1569, 1487, 1458, 1414, 1400, 1379, 1280, 1240, 1175, 1146, 1093, 1015, 978, 894, 822, 744, 675; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08-8.03 (m, 2H), 7.43-7.39 (m, 2H), 4.65 (t, *J*=6.6 Hz, 1H), 1.80-1.73 (m, 2H), 1.38-1.22 (m, 8H), 0.89 (t, *J* = 7.5 Hz, 9H), 0.86 (t, *J* = 6.9 Hz, 3H), 0.60-0.50 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.4, 139.4, 133.1, 130.8, 128.6, 78.3, 36.1, 31.6, 29.0, 25.6, 22.5, 14.0, 6.7, 4.7; TLC (35:1 hexanes/EtOAc) R_f 0.24; **Anal.** Calcd. for $C_{20}H_{33}ClO_2Si$: C, 65.10; H, 9.01. Found: C, 64.84; H, 9.00.

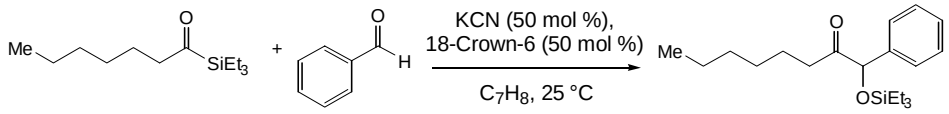


1-(4-methoxyphenyl)-2-triethylsilyloxy-octanone (3n). The title compound was prepared according to General Procedure **A** using 110 mg (0.44 mmol) of acylsilane, 68 µL (0.48 mmol) of heptanal, 9.0 mg (0.14 mmol) of KCN, 13 mg (0.045 mmol) of 18-crown-6, and 10 mL of Et_2O. After 2 h at 25 °C, the crude product was purified by flash

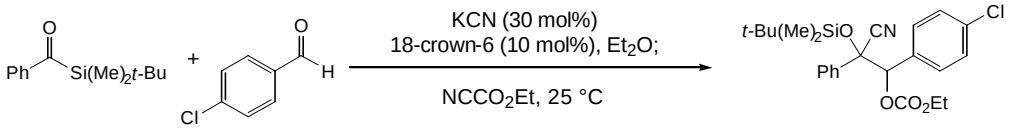
chromatography with 25:1 hexanes/EtOAc to afford 81 mg (51%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 2937, 2875, 2858, 1690, 1673, 1601, 1575, 1510, 1460, 1419, 1311, 1257, 1172, 1144, 1116, 1100, 1032, 1014, 979, 895, 831, 743, 728, 678; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.12-8.07 (m, 2H), 6.94-6.89 (m, 2H), 4.69 (t, *J*=6.9 Hz, 1H), 3.87 (s, 3H), 1.80-1.73 (m, 2H), 1.38-1.22 (m, 8H), 0.90 (t, *J* = 8.1 Hz, 9H), 0.86 (t, *J* = 6.9 Hz, 3H), 0.62-0.52 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.0, 163.3, 131.6, 127.8, 113.5, 77.8, 55.4, 36.3, 31.7, 29.1, 25.7, 22.6, 14.1, 6.7, 4.7; TLC (20:1 hexanes/EtOAc) R_f 0.17; **Anal.** Calcd. for $C_{21}H_{36}O_3Si$: C, 69.19; H, 9.95. Found: C, 69.29; H, 10.10.



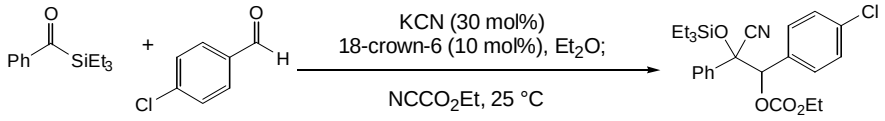
1-phenyl-2-triethylsilyloxy-octanone (3o). The title compound was prepared according to General Procedure **A** using 109 mg (0.50 mmol) of acylsilane, 9.8 mg (0.15 mmol) of KCN, 14 mg (0.050 mmol) of 18-crown-6, and 4 mL of Et_2O. 76 µL (0.55 mmol) of heptanal was added as an Et_2O solution (6 mL) *via* cannula over 1.5 h, and the reaction was kept for another 0.5 h at 25 °C. The crude product was purified by flash chromatography with 55:1 hexanes/EtOAc to afford 115 mg (70%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3060, 2957, 2934, 2876, 1700, 1680, 1597, 1579, 1458, 1448, 1414, 1277, 1240, 1180, 1146, 1101, 1003, 978, 894, 840, 772, 743, 697; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08-8.04 (m, 2H), 7.57-7.52 (m, 1H), 7.46-7.41 (m, 2H), 4.78 (t, *J* = 6.3 Hz, 1H), 1.81-1.74 (m, 2H), 1.38-1.22 (m, 8H), 0.91 (t, *J* = 7.8 Hz, 9H), 0.86 (t, *J* = 6.9 Hz, 3H), 0.64-0.53 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.5, 135.0, 132.9, 129.1, 128.3, 77.5, 36.0, 31.6, 29.0, 25.6, 22.5, 14.0, 6.7, 4.7; TLC (30:1 hexanes/EtOAc) R_f 0.25; **Anal.** Calcd. for $C_{20}H_{34}O_2Si$: C, 71.80; H, 10.24. Found: C, 71.80; H, 10.51.



(1-triethylsilyloxy)-benzyl-hexyl-ketone (3p). A dry round-bottom flask with a magnetic stir bar was charged with 113 mg (0.50 mmol, 1.0 equiv) of acylsilane, 200 µL (1.98 mmol, 4 equiv) of benzaldehyde, 16 mg (0.25 mmol, 0.5 equiv) of KCN, 43 mg (0.15 mmol, 0.3 equiv) of 18-crown-6, and 10 mL of EtO_2. After 3 h at 25 °C, the crude product was purified by flash chromatography with 3.5:1 petroleum ether/CH_2Cl_2 to afford 84 mg (51%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3088, 3065, 3030, 2957, 2934, 2876, 1719, 1494, 1452, 1414, 1379, 1349, 1240, 1190, 1149, 1113, 1094, 1069, 1007, 974, 853, 743, 699; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.36-7.24 (m, 3H), 5.07 (s, 1H), 2.65-2.36 (ABXY, J_{AX} = 6.6 Hz, J_{AY} = 8.1 Hz, J_{AB} = 17.1 Hz, 2H), 1.49-1.38 (m, 2H), 1.25-1.04 (m, 6H), 0.92 (t, *J* = 7.8 Hz, 9H), 0.82 (t, *J* = 7.2 Hz, 3H), 0.60 (q, *J* = 7.8 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.9, 138.9, 128.4, 127.9, 125.9, 80.9, 35.8, 31.5, 28.7, 23.2, 22.4, 14.0, 6.7, 4.7; TLC (3:1 petroleum ether/CH_2Cl_2) R_f 0.2; **Anal.** Calcd. for $C_{20}H_{34}O_2Si$: C, 71.80; H, 10.24. Found: C, 71.90; H, 10.36.



Ethyl (2-*tert*-butyldimethylsilyloxy-1-(4-chlorophenyl)-2-cyano-2-phenylethyl) carbonate (7). A dry round-bottom flask with a magnetic stir bar was charged with 102 mg (0.46 mmol) of acylsilane, 68 mg (0.49 mmol) of *p*-chlorobenzaldehyde, 9 mg (0.14 mmol) of KCN, 13 mg (0.046 mmol) of 18-crown-6 and 9 mL of Et_2O. After 2 h at 25 °C under N_2, acylsilane was consumed (monitored by TLC). To the resulting mixture was added 92 µL (0.926 mmol) of ethyl cyanoformate *via* syringe. The reaction was stirred for another 30 min until the intermediate was consumed (TLC analysis). To the reaction solution was added 15 mL of H_2O. The mixture was stirred for 5 min before the organic layer was separated and the aqueous layer was extracted with three 15 mL portions of Et_2O. The organic extracts were combined, dried ($MgSO_4$), and the solvent was removed with a rotary evaporator. The product was purified by the flash chromatography with 25:1 hexanes/EtOAc to afford 194 mg (91%) of the product as a single regioisomer (d.r. = 77:23 (determined by ^{1}H NMR), relative stereochemistry unassigned) as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3066, 3034, 2957, 2929, 2886, 2857, 2361, 2338, 1768, 1599, 1493, 1472, 1452, 1409, 1391, 1370, 1296, 1252, 1124, 1092, 1012, 978, 855, 849, 781, 740, 698; NMR data for major and minor diastereomers: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53-7.51 (m, 2H, minor diastereomer), 7.42-7.10 (m, 7H, major and minor diastereomers), 6.88-6.86 (m, 2H, major diastereomer), 5.06 (s, 1H, major diastereomer), 4.92 (s, 1H, minor diastereomer), 4.26-4.12 (ABX, J_{AB} = 10.8 Hz, J_{AX} = 7.2 Hz, 2H, major diastereomer), 4.13-4.07 (m, 2H, minor diastereomer), 1.27 (t, J = 7.2 Hz, 3H, major diastereomer), 1.21 (t, J = 7.2 Hz, 3H, minor diastereomer), 0.90 (s, 9H, major diastereomer), 0.75 (s, 9H, minor diastereomer), 0.19 (s, 3H, major diastereomer), 0.09 (s, 3H, major diastereomer), -0.36 (s, 3H, minor diastereomer), -0.41 (s, 3H, minor diastereomer); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.1, 151.7, 136.2, 135.0, 134.9, 134.8, 134.5, 133.3, 129.8, 129.5, 129.4, 128.5, 128.2, 128.0, 127.7, 126.2, 126.0, 115.9, 115.5, 83.2, 82.2, 79.2, 79.1, 65.1 (two coincident resonances), 25.6, 25.5, 18.2, 17.9, 14.1, 14.0, -5.0, -5.2 (two peaks overlapped), -6.1 (two coincident resonances in the aromatic region); TLC (33:1 hexanes/EtOAc) R_f 0.21. Calcd. for $C_{24}H_{30}ClNO_4Si$: C, 62.66; H, 6.57; N, 3.04. Found: C, 62.71; H, 6.55; N, 2.98.

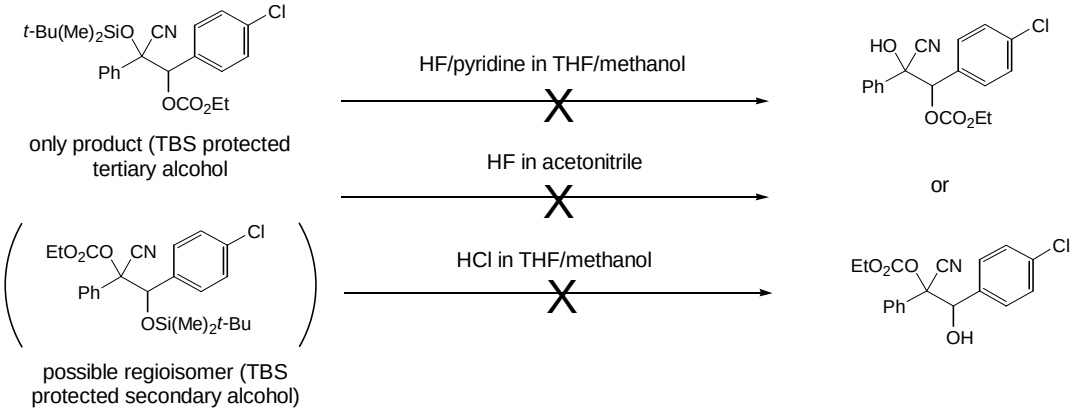


8

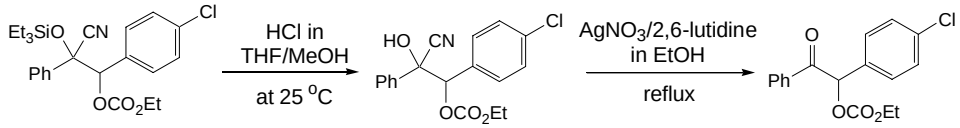
Ethyl (1-(4-chlorophenyl)-2-cyano-2-phenyl-2-triethylsilyloxyethyl) carbonate (8) A dry round-bottom flask with a magnetic stir bar was charged with 148 mg (0.67 mmol) of acylsilane, 99 mg (0.71 mmol) of *p*-chlorobenzaldehyde, 13 mg (0.20 mmol) of KCN, 19 mg (0.067 mmol) of 18-crown-6 and 12 mL of Et_2O. After 2 h at 25 °C under N_2, acylsilane was consumed (monitored by TLC). To the resulting mixture was added 130 µL (1.35 mmol) of ethyl cyanoformate *via* syringe. The reaction was stirred for another 10 min until the intermediate was consumed (TLC analysis). To the reaction solution was added 15 mL of H_2O. The mixture was stirred for 5 min before the organic layer was separated and the aqueous layer was extracted with three 15 mL portions of

Et_2O. The organic extracts were combined, dried ($MgSO_4$), and the solvent was removed with a rotary evaporator. The product was purified by flash chromatography with 25:1 hexanes/EtOAc to afford 228 mg (74%) of the product as a single regioisomer (d.r. = 70:30 (determined by ^1H NMR), relative stereochemistry unassigned) as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3066, 3034, 2958, 2939, 2912, 2877, 2356, 2335, 1766, 1599, 1493, 1452, 1410, 1371, 1296, 1254, 1128, 1093, 1014, 978, 885, 829, 785, 733, 698; NMR data for major and minor diastereomers: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H, minor diastereomer), 7.43-7.09 (m, 7H, major and minor diastereomers), 6.91-6.88 (m, 2H, major diastereomer), 5.09 (s, 1H, major diastereomer), 4.97 (s, 1H, minor diastereomer), 4.26-4.08 (m, 2H, major and minor diastereomers), 1.26 (t, *J* = 6.8 Hz, 3H, major diastereomer), 1.20 (t, *J* = 7.2 Hz, 3H, minor diastereomer), 0.92 (t, *J* = 8.0 Hz, 9H, major diastereomer), 0.71 (t, *J* = 8.0 Hz, 9H, minor diastereomer), 0.68-0.56 (m, 6H, major diastereomer), 0.33-0.22 (m, 6H, minor diastereomer); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.1, 151.6, 136.2, 135.0, 134.6, 134.3, 133.3, 129.6, 129.3 129.2, 128.3, 128.1, 127.9, 127.5, 125.9, 125.7, 115.8, 115.5, 83.2, 82.1, 78.8 (two coincident resonances), 64.9 (two coincident resonances), 13.9, 13.8, 6.4, 6.3, 4.5, 4.1 (two coincident resonances in the aromatic region); TLC (25:1 hexanes/EtOAc) R_f 0.2. For ^{1}H NMR and $^{13}C\{^1H\}$ NMR spectra, see the Appendix.

Regiochemical proof for (7).



(1) Three normal procedures to deprotect dimethyl-*t*-butyl-silyl protected secondary alcohols under acidic conditions failed. This suggested that the silyl ether was hindered and/or electronically deactivated.



8 **9** **10**

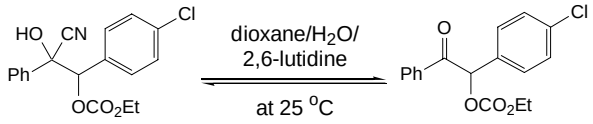
(2) Since the dimethyl-*t*-butyl-silyloxy group was too robust to be deprotected under conditions in which the carbonate group was kept intact, the triethylsilyl adduct was chosen for further experiments to prove the regiochemistry of the product.

Cyanohydrin (9) A 25 mL round-bottom flask with a magnetic stir bar was charged with 88 mg (0.19 mmol) of the triethylsilyl adduct (**8**), 4 mL

of THF, 2 mL of MeOH, and 6 drops of conc. HCl. After 12 h at 25 °C, the solvent was removed in vacuo, and the product was purified by the flash chromatography with 4.5:1 hexanes/EtOAc to afford 58 mg (88%) of cyanohydrin product (**9**) as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3419 (broad), 3064, 3037, 2985, 2939, 2389, 2279, 1754, 1741, 1598, 1495, 1450, 1373, 1255, 1201, 1100, 1062, 1009, 920, 880, 854, 835, 811, 786, 756, 700; NMR data for major diastereomer: **^{1}H NMR** (400 MHz, C_6D_6) δ 7.15-7.13 (m, 2H), 6.89-6.86 (m, 1H), 6.82-6.78 (m, 6H), 5.91 (s, 1H), 3.86-3.78 (m 2H), 3.23 (s, 1H), 0.86 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, C_6D_6) δ 154.3, 135.5, 135.4, 132.2, 129.7, 129.6, 128.5, 128.4, 126.8, 118.4, 83.0, 77.3, 64.9, 13.9; TLC (3:1 hexanes/EtOAc) R_f 0.35. For ^{1}H NMR and ^{13}C{^{1}H} NMR spectra, see Appendix.

Keto carbonate (10) A 25 mL round-bottom flask with a magnetic stir bar was charged with 20 mg (0.058 mmol) of cyanohydrin (**9**), 11 mg (0.064 mmol, 1.1 equiv) of $AgNO_3$, 0.2 mL of 2,6-lutidine, and 3 mL of EtOH. After refluxing for 1 h, the resulting white solid was filtered and the solvent was then removed in vacuo. The product was purified by flash chromatography with 10:1 hexanes/EtOAc to afford 18 mg (98%) of keto carbonate (**10**) as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3379, 3062, 2984, 2935, 1743, 1700, 1597, 1581, 1493, 1448, 1373, 1259, 1180, 1093, 1036, 1014, 958, 899, 823, 786, 723, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93-7.90 (m, 2H), 7.56-7.52 (m, 1H), 7.44-7.40 (m, 4H), 7.36-7.33 (m, 2H), 6.72 (s, 1H), 4.27-4.21 (ABX, J_{AB} = 10.0 Hz, J_{AX} = 6.8 Hz, 2H), 1.32 (t, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.3, 154.4, 135.6, 134.3, 133.7, 131.6, 129.9, 129.4, 128.8, 128.7, 79.2, 77.3, 64.8, 14.2; TLC (8:1 hexanes/EtOAc) R_f 0.21. For ^{1}H NMR and ^{13}C{^{1}H} NMR spectra, see Appendix.

Obtention of **10** gives direct evidence that silyloxy and cyano groups are on the same carbon in **8** (and hence **7**).



9 **10**

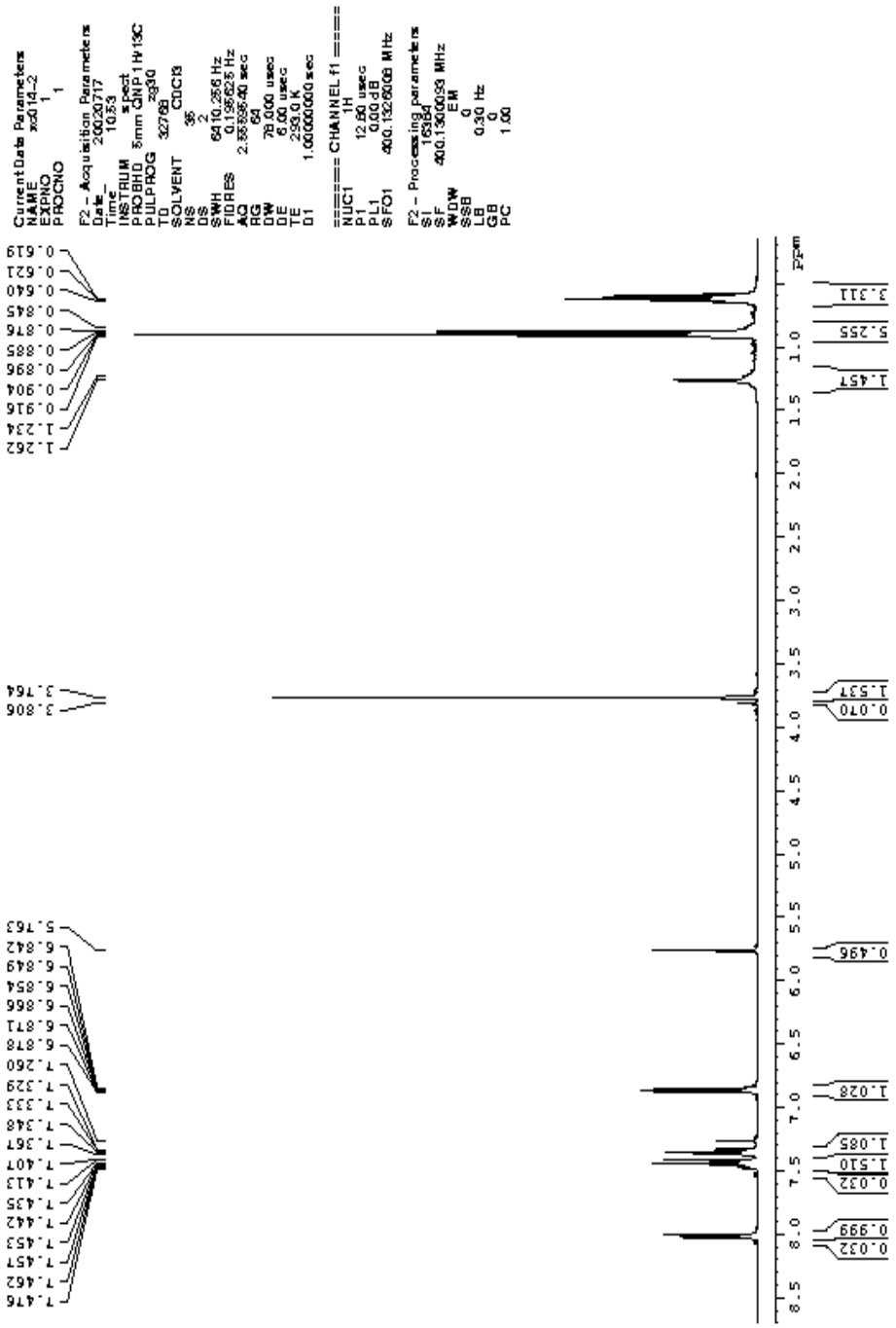
(3) Under mild conditions (dioxane/H_2O/2,6-lutidine solution), cyanohydrin (**9**) is in equilibrium with keto carbonate (**10**). A 25 mL round-bottom flask with a magnetic stir bar was charged with 20 mg (0.058 mmol) of cyanohydrin (**9**), three drops of 2,6-lutidine, three drops of H_2O and 5 mL of dioxane. After 12 h at 25 °C, the solvent was removed in vacuo. ^{1}H NMR showed a 3:5 mixture of cyanohydrin (**9**)/keto carbonate (**10**). See Appendix.

(4) In the ^{1}H NMR of cyanohydrin (**9**), the protons on both the oxygen of hydroxyl group and the carbon of methine group appeared as singlets both in dry $CDCl_3$ and dry C_6D_6, which means there is no three-bond coupling between those two protons. (In contrast, the methine proton and hydroxyl

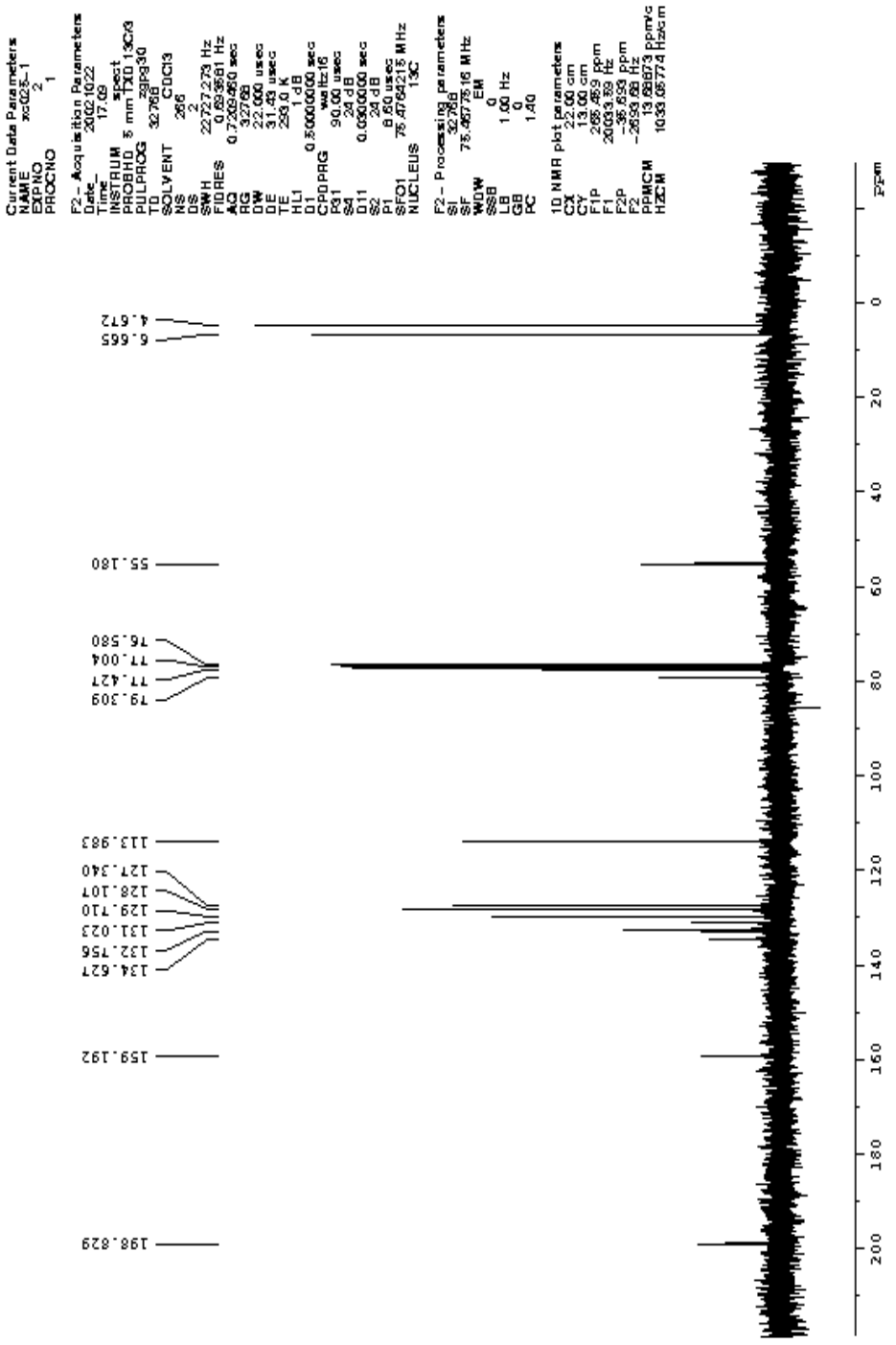
proton of benzoin, PhC(O)CH(OH)Ph, both appear as doublets in $CDCl_3$.) Additionally, 2D-NMR (COSY) showed no cross peaks between those two protons (see Appendix).

Appendix

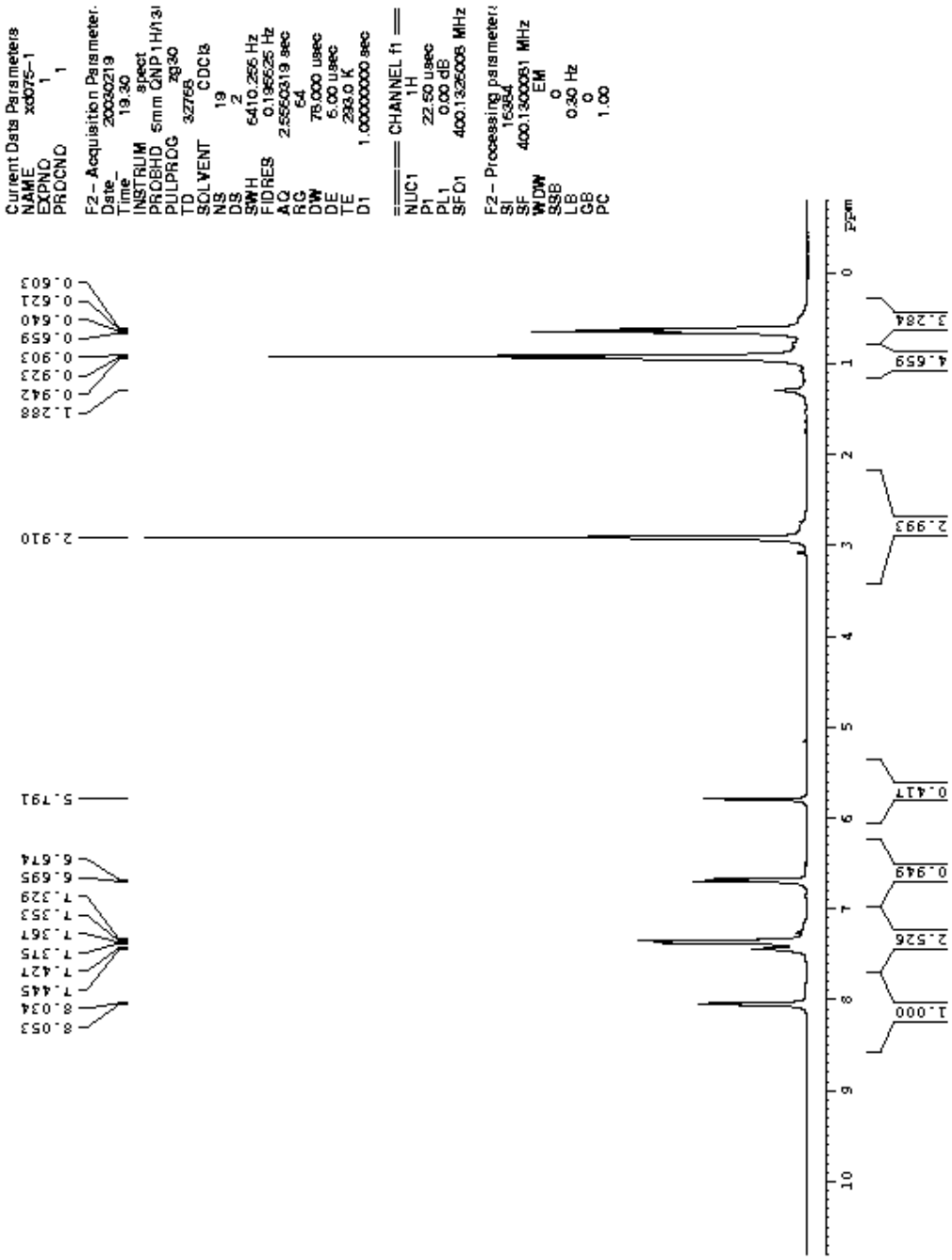
^{1}H NMR in $CDCl_3$ for (**3d**)



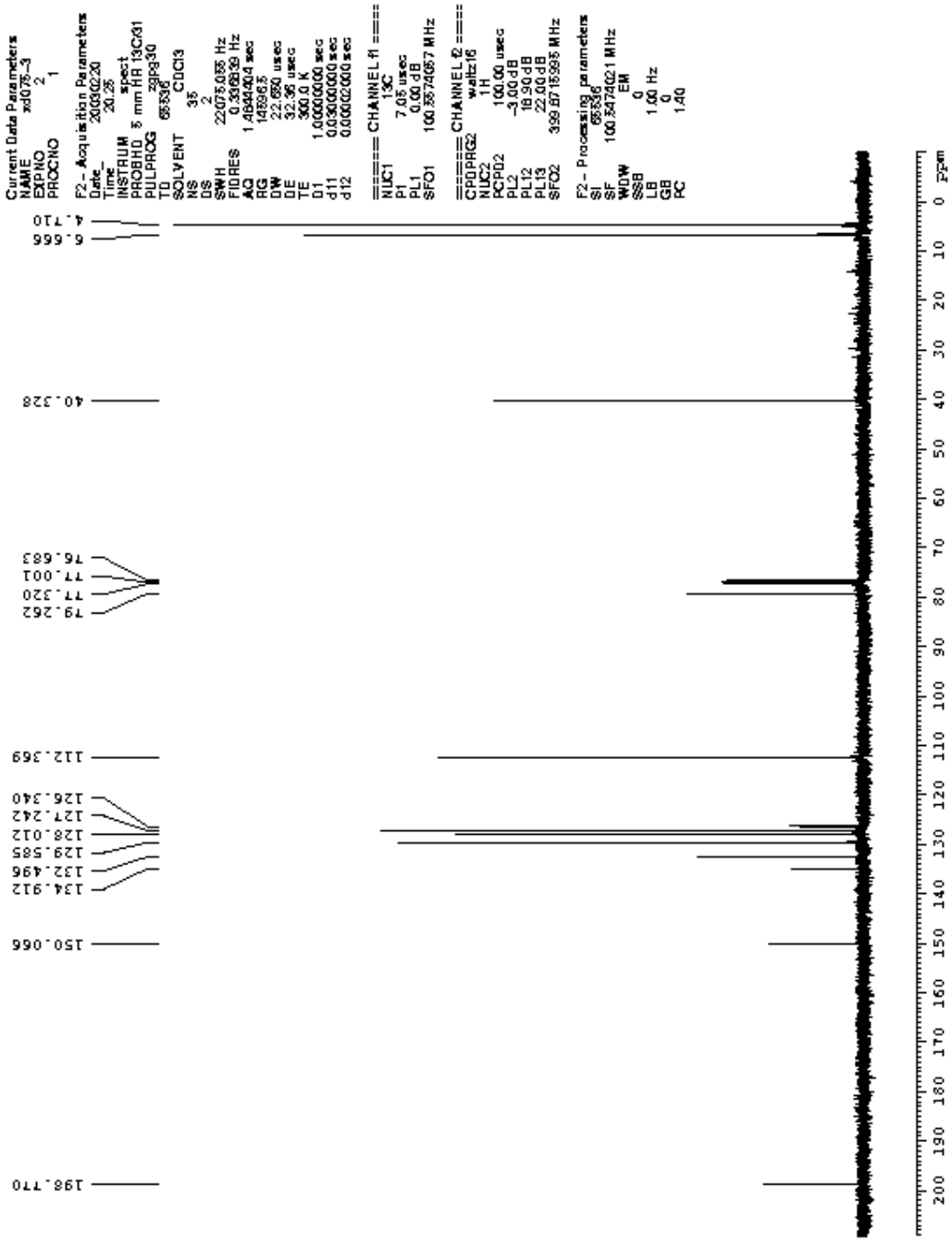
^{13}C NMR in $CDCl_3$ for (**3d**)



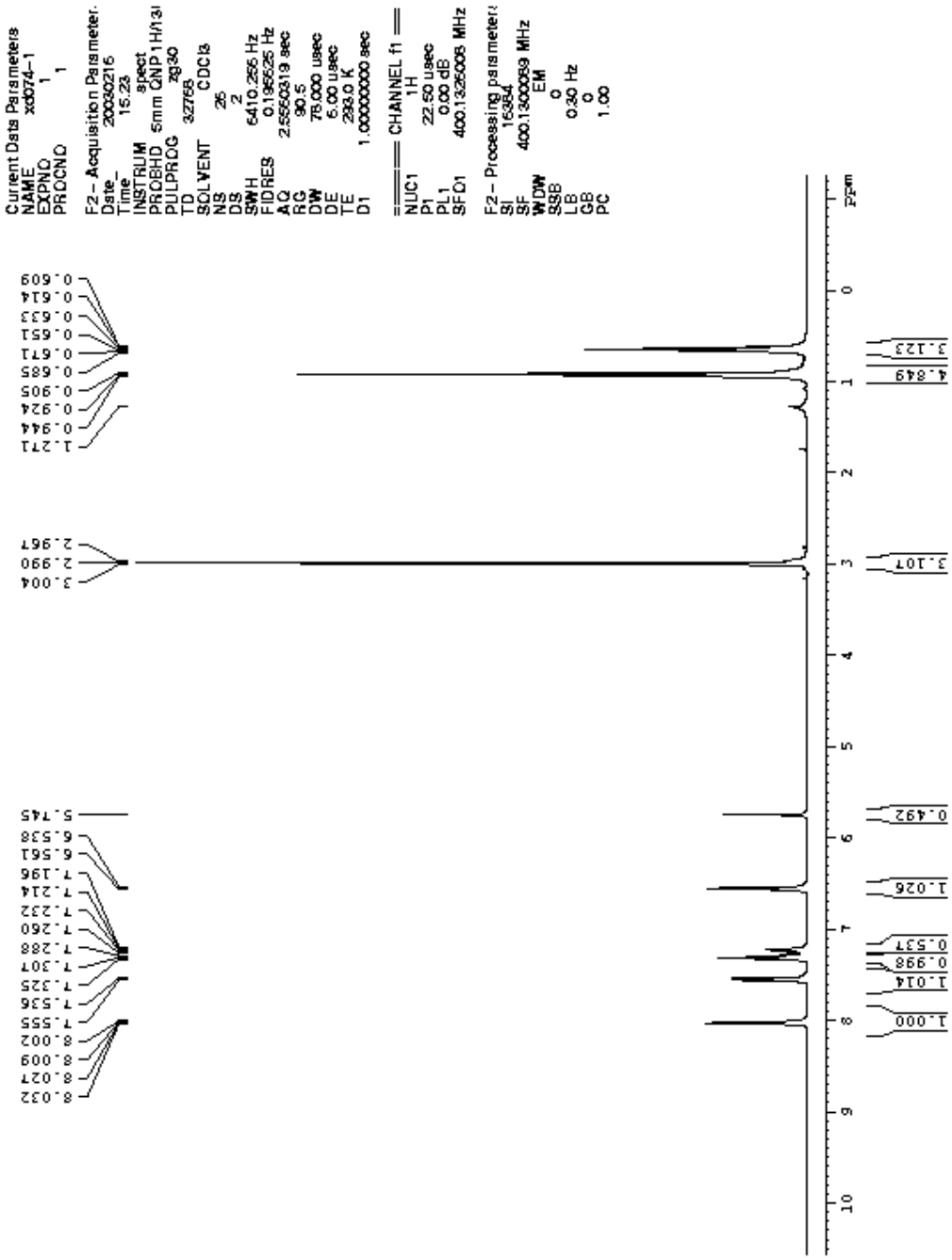
^{1}H NMR in $CDCl_3$ for (**3h**)



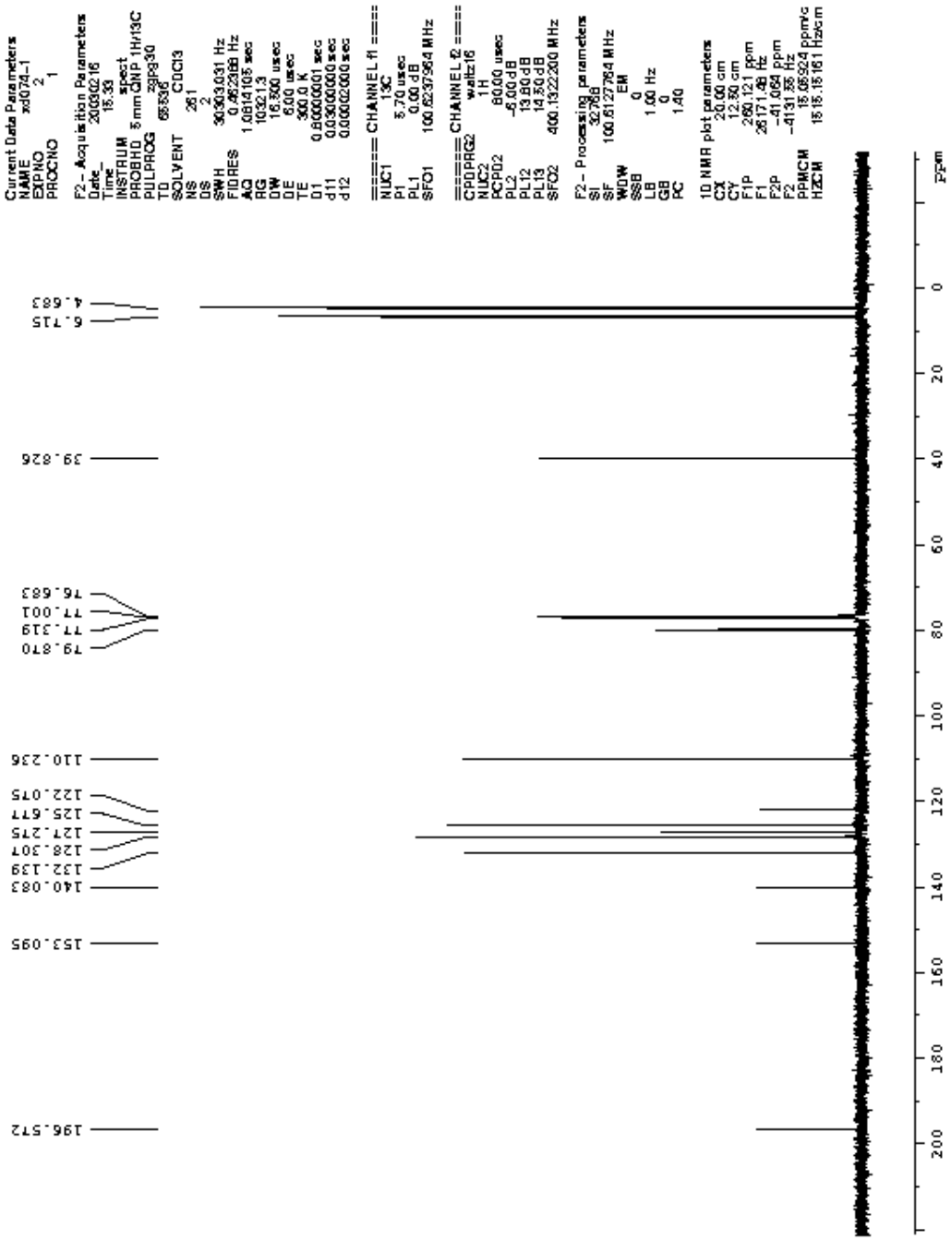
^{13}C NMR in $CDCl_3$ for (**3h**)



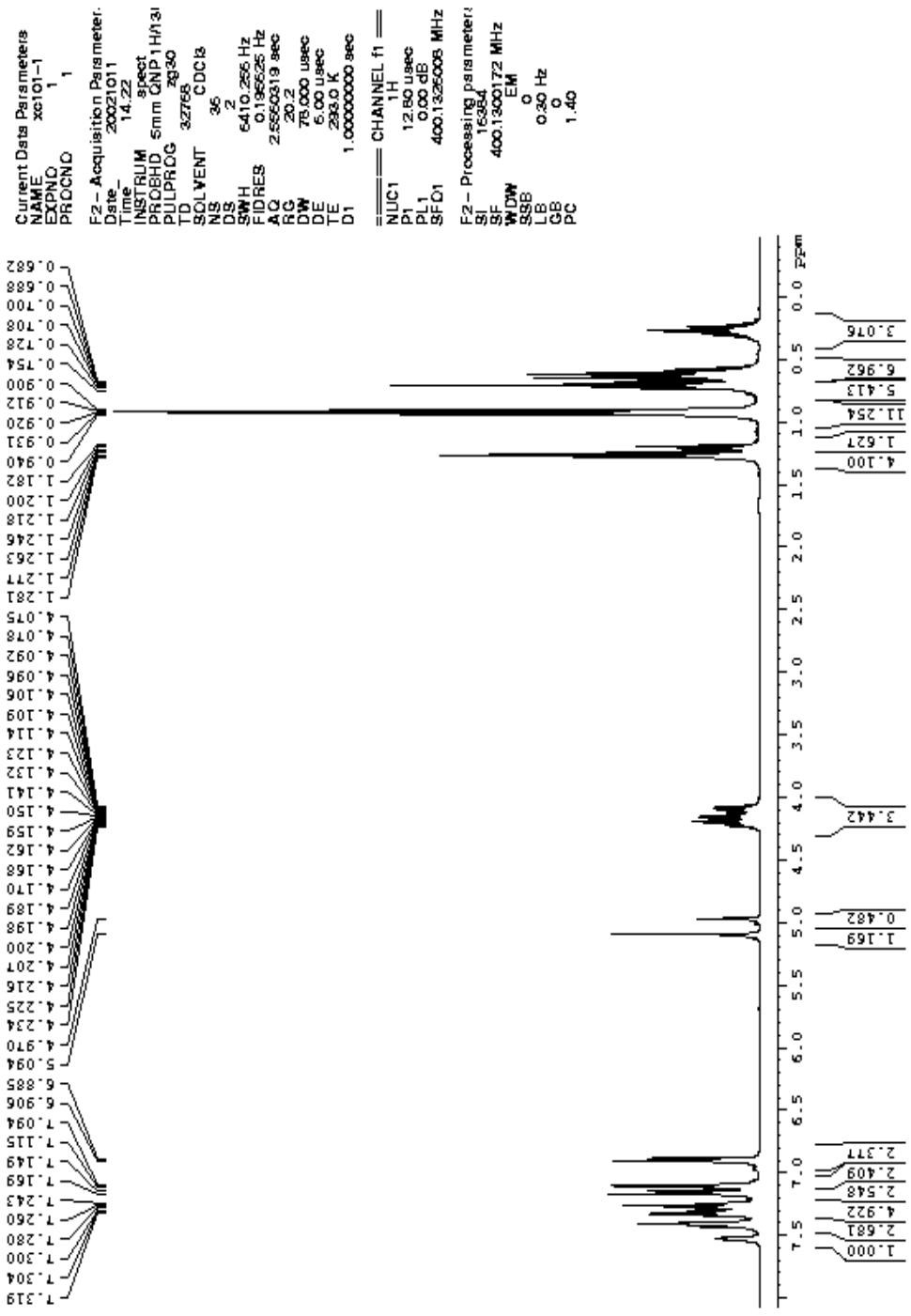
^{1}H NMR in $CDCl_3$ for (**3i**)



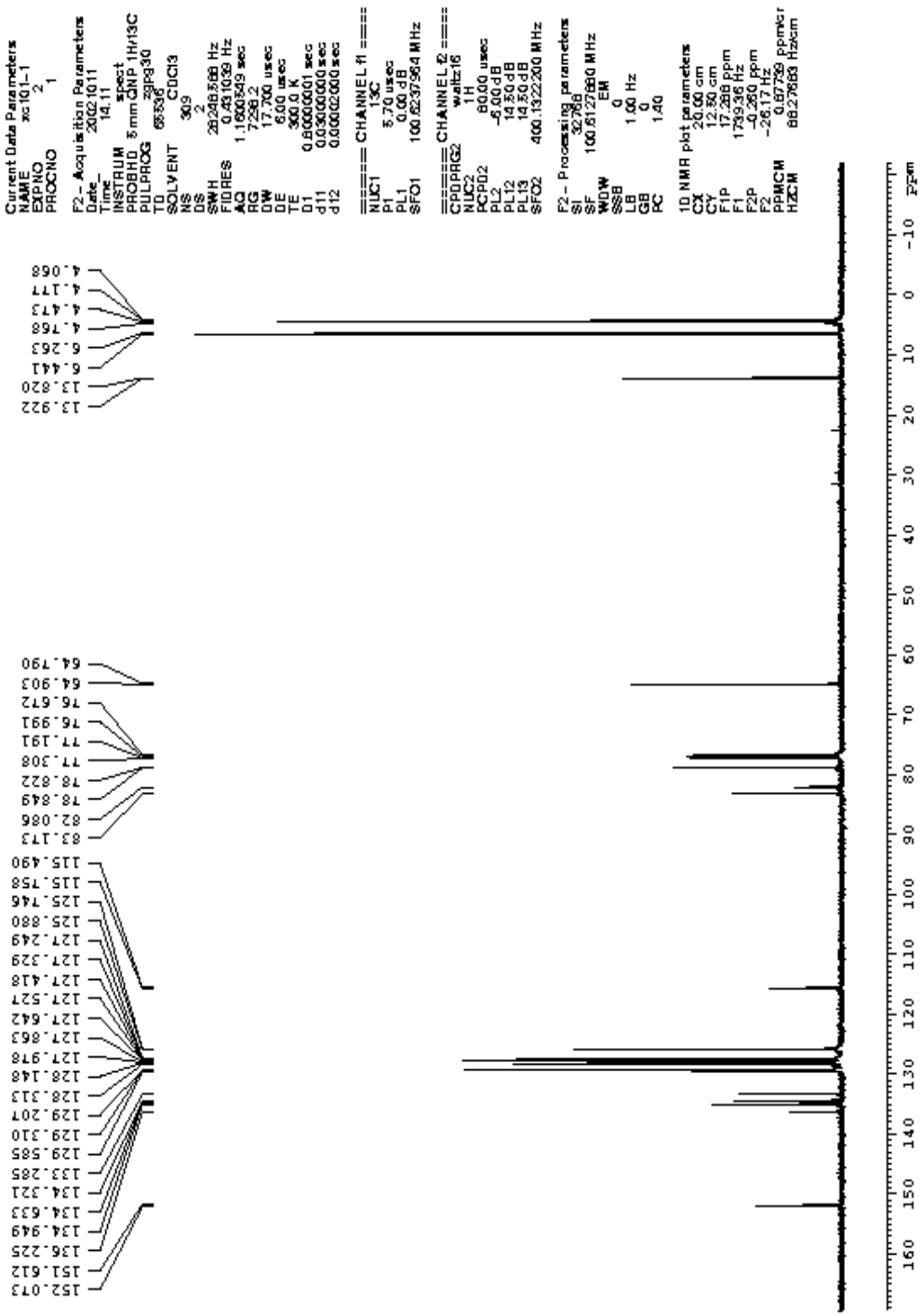
^{13}C NMR in $CDCl_3$ for (**3i**)



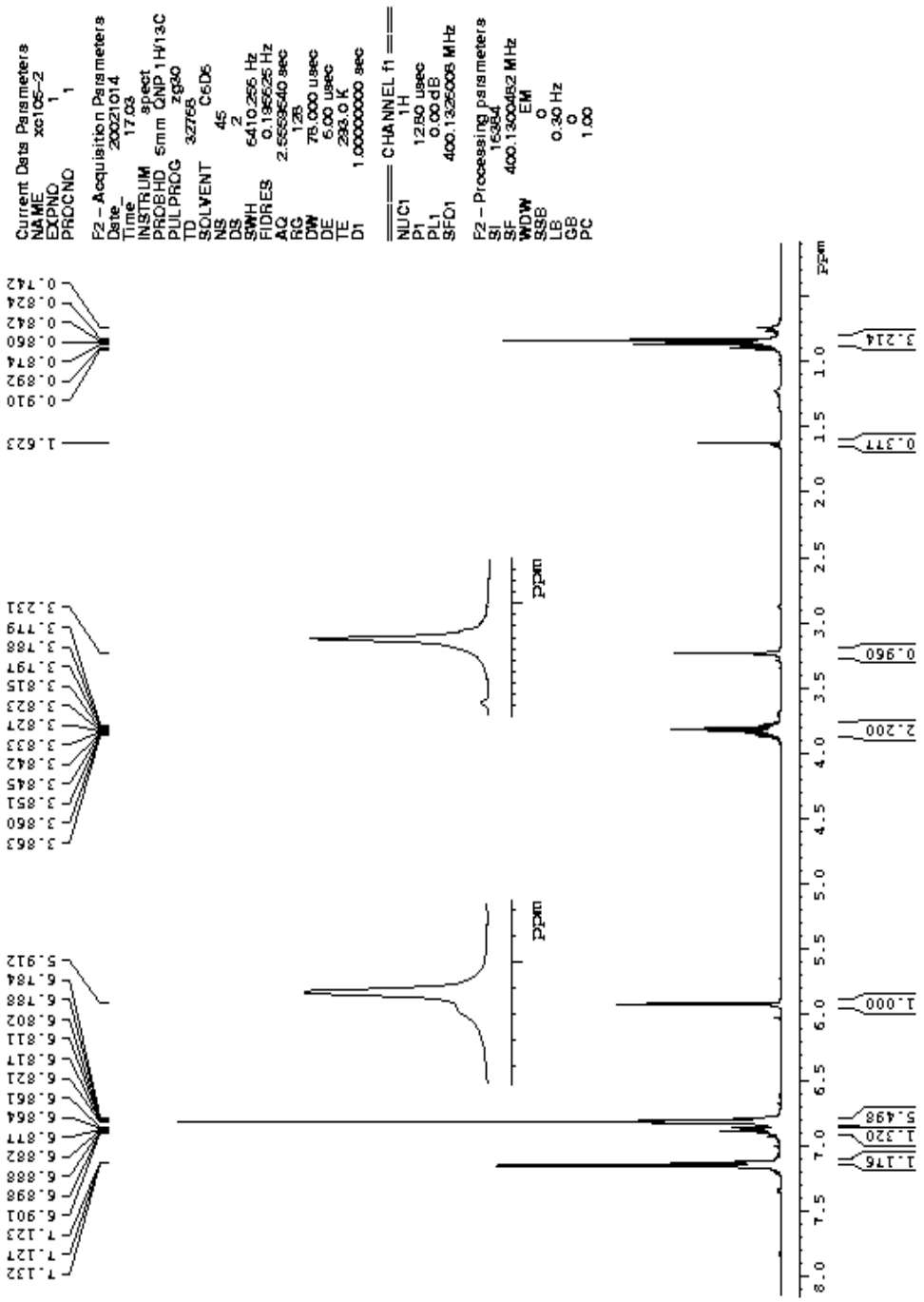
^{1}H NMR in $CDCl_3$ for (**8**)



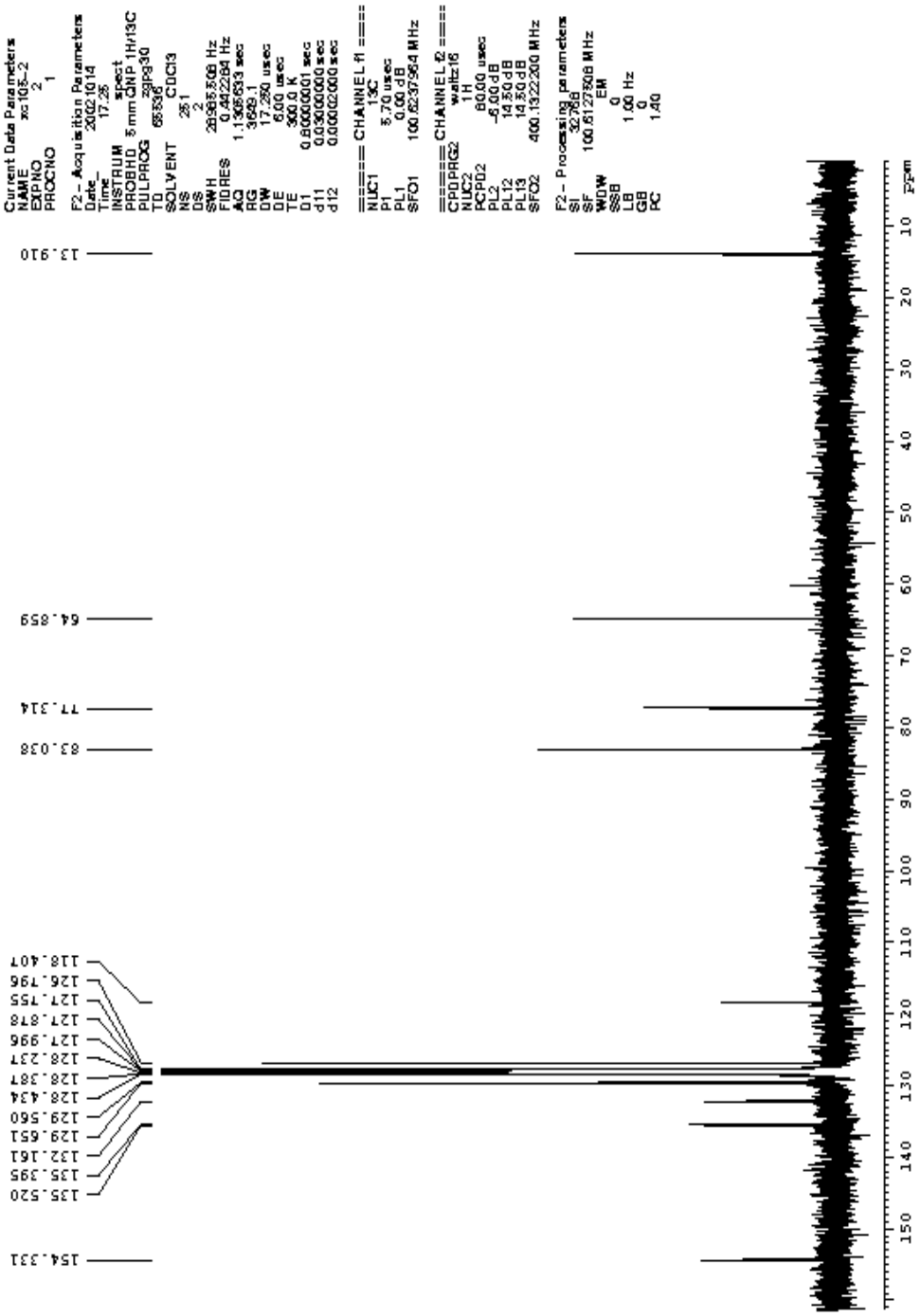
^{13}C NMR in $CDCl_3$ for (**8**)



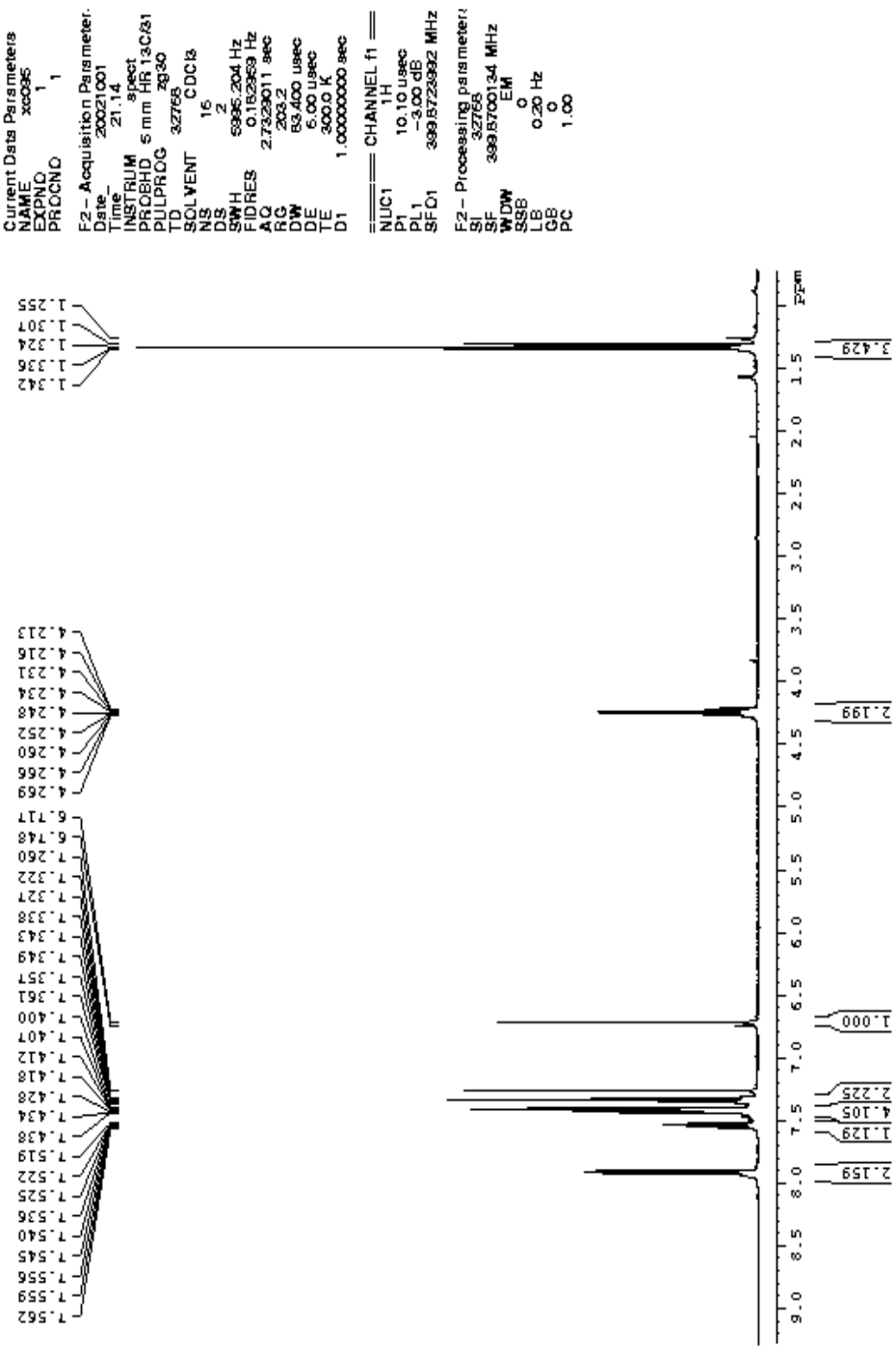
^{1}H NMR in C_6D_6 for (**9**) (major diastereomer)



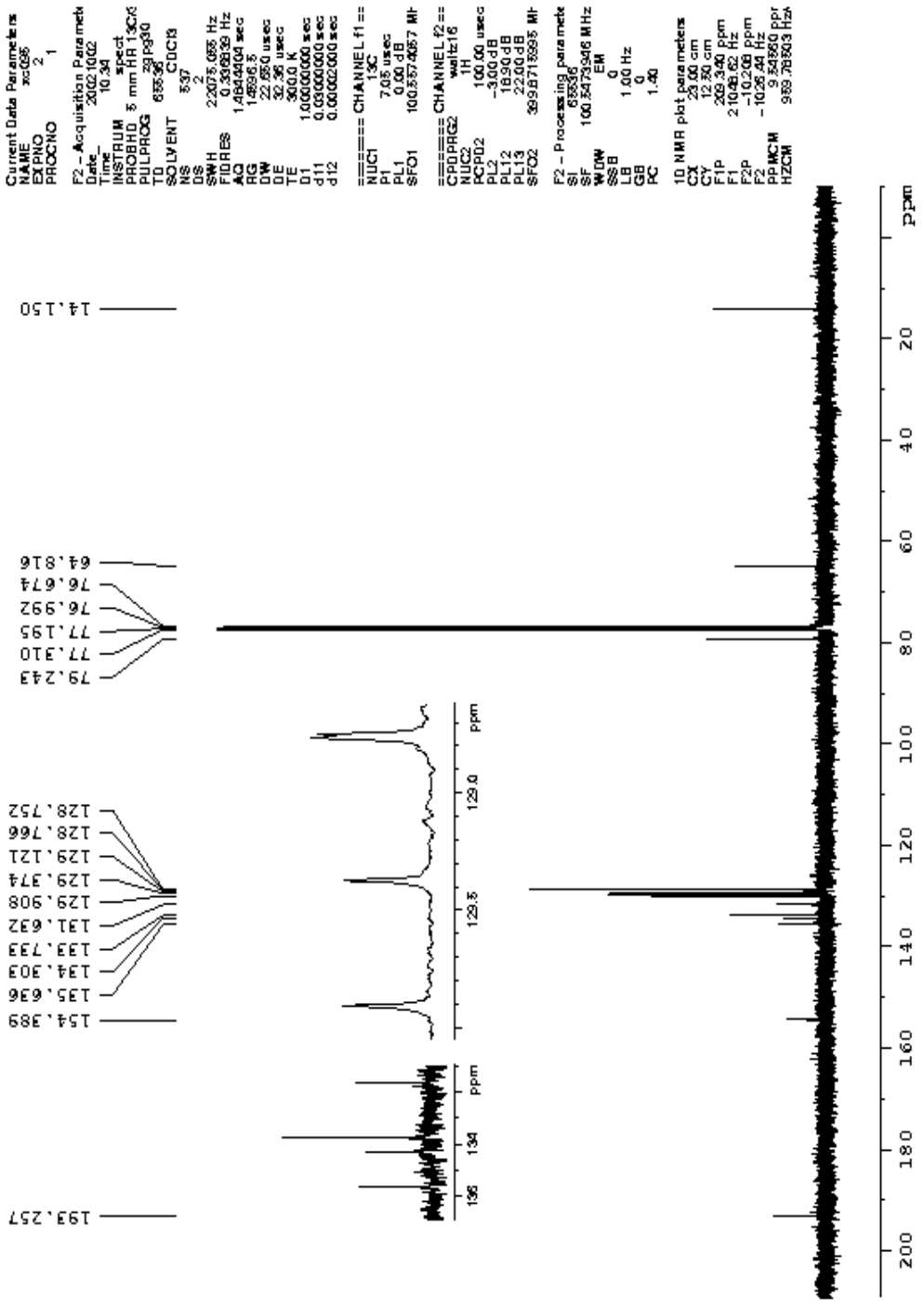
^{13}C NMR in C_6D_6 for (**9**) (major diastereomer)



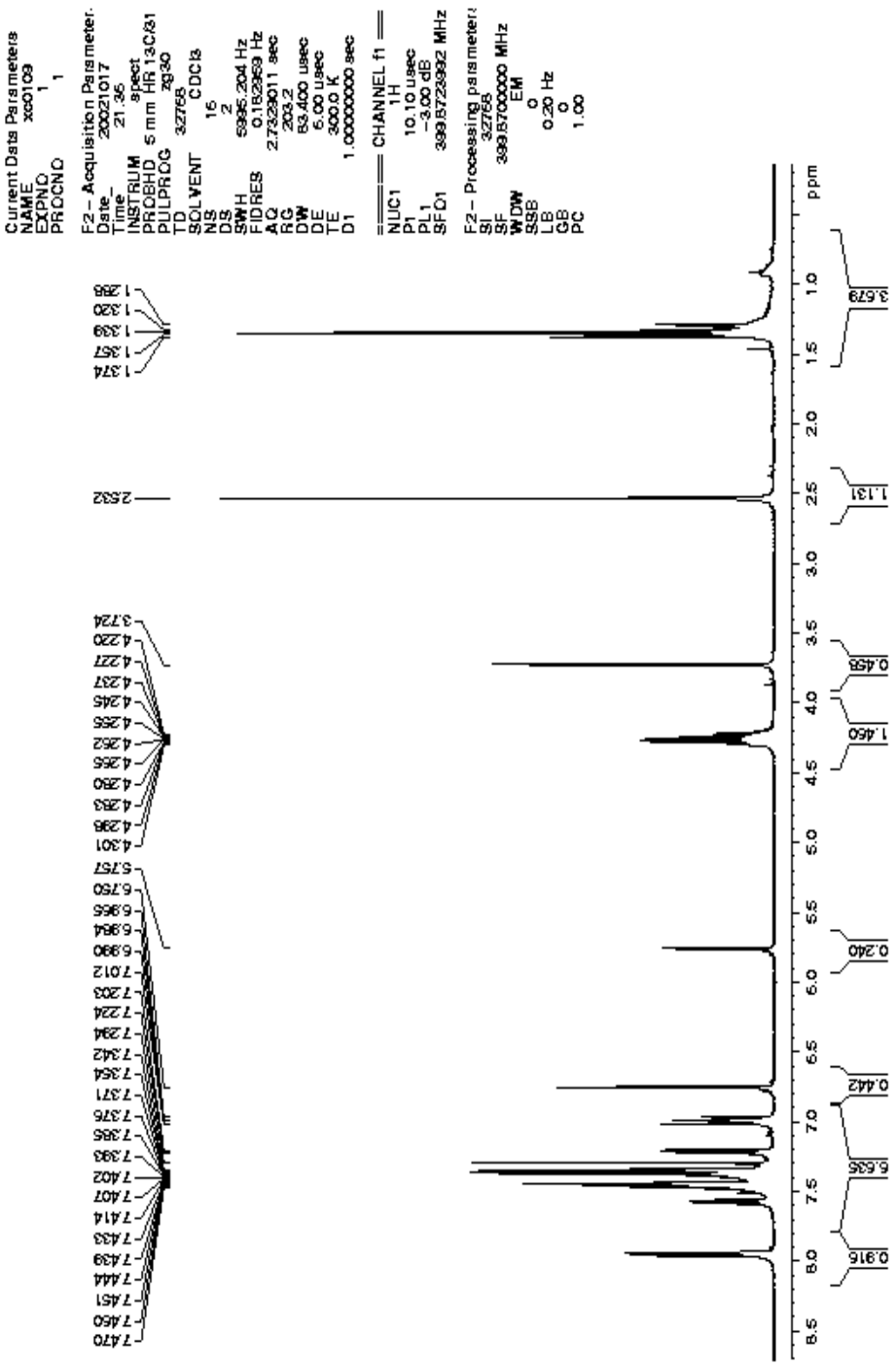
^{1}H NMR in $CDCl_3$ for (**10**)



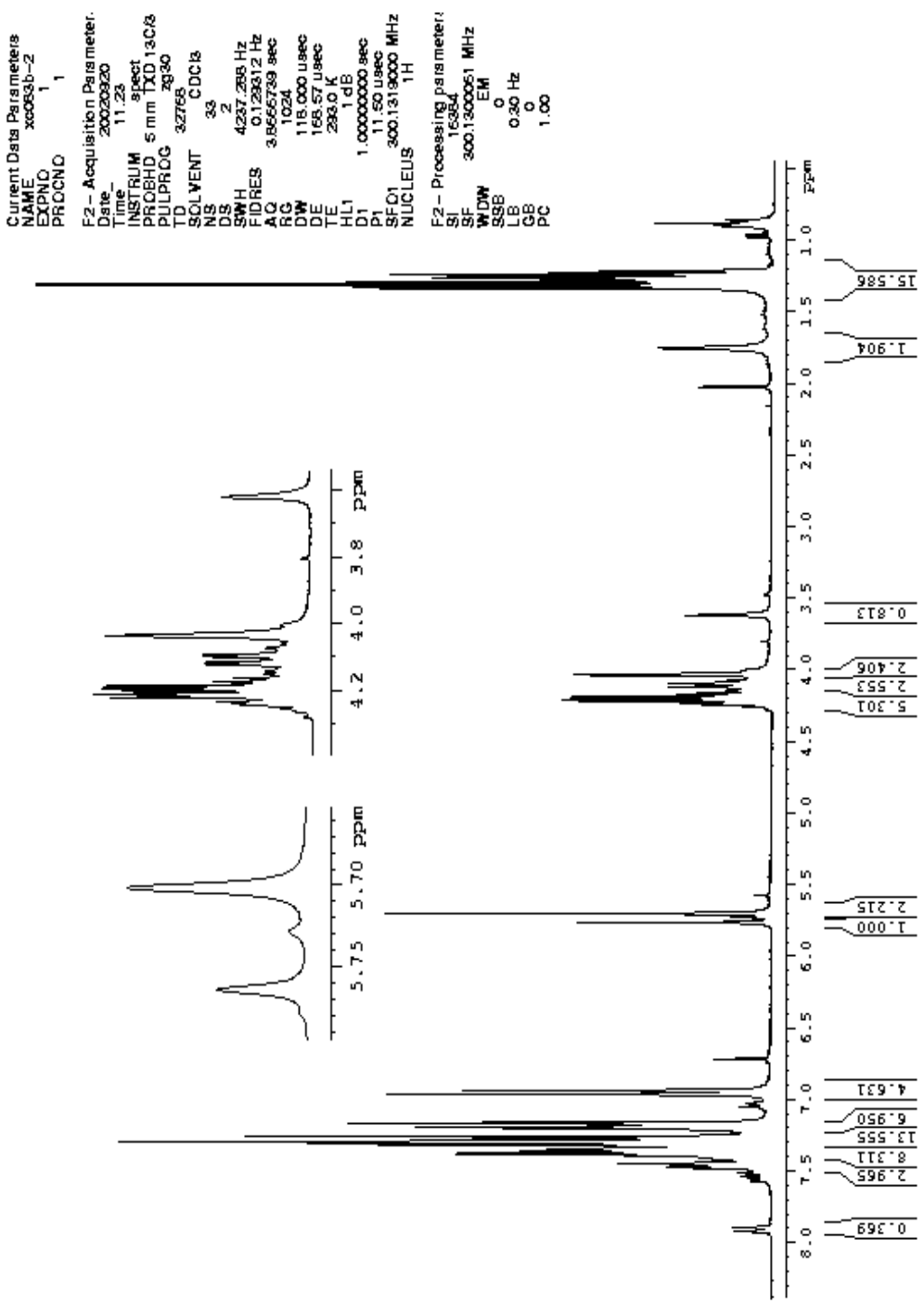
^{13}C NMR in $CDCl_3$ for (**10**)



Equilibrium between cyanohydrin (**9**) and keto carbonate (**10**)



^{1}H NMR in $CDCl_3$ for (**9**) (both diastereomers)



2D NMR (COSY) in $CDCl_3$ for (**9**) (both diastereomers)