Highly Diastereoselective Preparation of Aldol Products Using New Functionalized Allylic Aluminum Reagents

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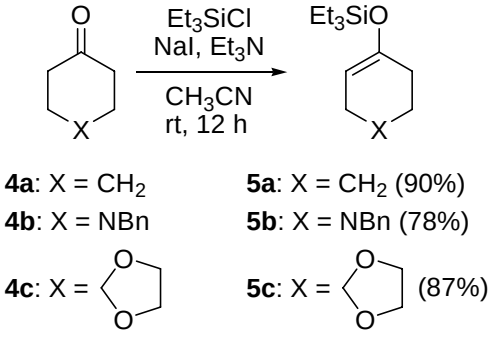
General Information

All reactions were carried out under nitrogen atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves. Aluminum powder (99%, ~200 mesh) was purchased from Aldrich. Indium(III) chloride (anhydrous, 99.99%) was purchased from Chempur. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC. Column chromatography was performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck. All reagents were obtained from commercial sources.

Experimental Procedure

1. Preparation of silyl enol ethers **5a-c**.[1]

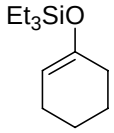


4a: X = CH_2 **5a**: X = CH_2 (90%)
4b: X = NBn **5b**: X = NBn (78%)
4c: X = **5c**: X = (87%)

To a 250 mL round-bottomed flask was sequentially added ketone **4** (50 mmol), CH_3CN (80 mL), Et_3N (6.07 g, 8.4 mL, 60 mmol), TESCl (9.04 g, 60 mmol, 10 mL), and NaI (9 g, 60 mmol, pre-dried at 90 ^{o}C for 12 h under high vacuum). The reaction mixture was stirred at room temperature for 12 h. After the reaction conversion was completed as monitored by GC analysis, the resulting mixture was extracted by isohexane (100 mL x 3) through vigorous stirring of the reaction mixture with isohexane. The combined extracts were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), and dried over Na_2SO_4. After filtration and removal of the solvent under vacuum, the residue obtained was directly purified by silica gel column chromatography using isohexane and ethyl acetate as eluant to afford the corresponding silyl enol ether **5** as colorless oil.

[1] (a) Saraber, F. C. E.; Dratch, S.; Bosselaar, G.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2006**, *62*, 1717–1725. (b) Hong, A. Y.; Krout, M. R.; Jensen, T.; Bennett, N. B.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2756–2760. (c) Cui, L.-Q.; Liu, K.; Zhang, C. *Org. Biomol. Chem.* **2011**, *9*, 2258-2265. (d) Huang, L.; Zhang, X.; Zhang, Y. *Org. Lett.* **2009**, *11*, 3730-3733.

Cyclohexenyloxytriethylsilane (**5a**)[1a]



The reaction was performed according to the above procedure using cyclohexanone **4a** (4.91 g, 50 mmol), leading to the corresponding silyl enol ether **5a** in 90% yield (9.6 g) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 4.88-4.85 (m, 1H), 2.04-1.96 (m, 4H), 1.69-1.61 (m, 2H), 1.54-1.47 (m, 2H), 1.00-0.95 (m, 9H), 0.69-0.61 (m, 6H).

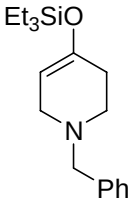
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 150.4, 103.9, 29.9, 23.8, 23.2, 22.4, 6.7, 5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2934, 2876, 1667, 1458, 1366, 1266, 1237, 1186, 1170, 1004, 986, 885, 827, 741, 726, 682.

MS (EI, 70 eV): m/z (%) = 212 (M^+, 17), 184 (15), 183 (100), 169 (22), 156 (15), 155 (13), 103 (12).

HRMS ($C_{12}H_{24}OSi$, EI): calc.: 212.1596; found: 212.1593 (M^+).

1-Benzyl-4-(triethylsilyloxy)-1,2,3,6-tetrahydropyridine (**5b**)



The reaction was performed according to the above procedure using 1-benzylpiperidin-4-one **4b** (9.47 g, 50 mmol), leading to the corresponding silyl enol ether **5b** in 78% yield (11.78 g).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.39-7.23 (m, 5H), 4.80 (tt, *J* = 3.5, 1.3 Hz, 1H), 3.61 (s, 2H), 3.01 (dt, *J* = 3.5, 2.5 Hz, 2H), 2.63 (t, *J* = 5.8 Hz, 2H), 2.18 (ttd, *J* = 5.8, 2.5, 1.3 Hz, 2H), 1.03-0.97 (m, 9H), 0.74-0.60 (m, 6H).

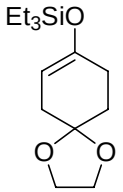
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.0, 138.5, 129.0, 128.1, 126.9, 101.0, 62.0, 51.4, 49.9, 30.3, 6.6, 5.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2910, 2874, 2798, 1677, 1454, 1371, 1360, 1238, 1215, 1185, 1125, 1004, 966, 873, 813, 771, 729, 697.

MS (EI, 70 eV): m/z (%) = 304 (17), 303 (M^+, 60), 302 (100), 274 (13), 266 (15), 211 (13), 187 (11), 172 (14), 161 (26), 149 (10), 91 (16).

HRMS ($C_{18}H_{28}NOSi$, EI): calc.: 302.1940; found: 302.1941 (M^+-H).

8-((Triethylsilyl)oxy)-1,4-dioxaspiro[4.5]dec-7-ene (**5c**)



The reaction was performed according to the above procedure using 1,4-dioxaspiro[4.5]decan-8-one **4c** (7.81 g, 50 mmol), leading to the corresponding silyl enol ether **5c** in 87% yield (11.8 g).

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 4.73 (tt, *J* = 3.9, 1.1 Hz, 1H), 3.99-3.95 (m, 4H), 2.26-2.23 (m, 4H), 1.81 (t, *J* = 6.5 Hz, 2H), 1.01-0.95 (m, 9H), 0.70-0.62 (m, 6H).

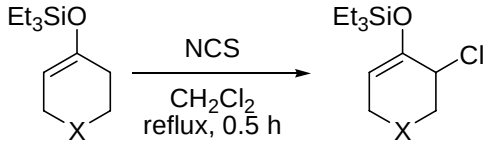
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.9, 107.7, 100.4, 64.4, 34.0, 31.2, 28.5, 6.7, 5.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2875, 1670, 1373, 1238, 1204, 1184, 1117, 1061, 1018, 986, 948, 857, 758, 742, 727, 669.

MS (EI, 70 eV): m/z (%) = 271 (19), 270 (M^+, 100), 240 (14), 227 (12), 197 (24), 171 (26), 157 (15), 143 (13), 141 (20), 138 (18), 127 (54), 115 (22), 103 (77), 101 (21), 99 (15), 92 (16), 87 (48), 75 (44), 67 (14), 59 (63), 57 (12), 55 (19), 47 (16), 42 (13), 41 (11).

HRMS ($C_{14}H_{26}O_3Si$, EI): calc.: 270.1651; found: 270.1638 (M^+).

2. Chlorination of silyl enol ethers **5a-c** by NCS.[2]



5a: X = CH_2 **2a**: X = CH_2 (40%)

5b: X = NBn **2b**: X = NBn (58%)

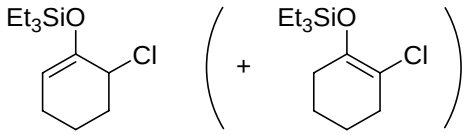
5c: X =  **2c**: X =  (69%)

To a solution of silyl enol ether **5** (20 mmol) in CH_2Cl_2 (100 mL) was added NCS (2.67 g, 20 mmol, pre-dissolved in CH_2Cl_2 (100 mL)) in one portion, and the mixture was stirred at 40 °C for 30 min. After reaction the solvent was removed under vacuum and the resulting residue was diluted by isohexane (300 mL). The white precipitate of succinimide was filtered off and the filtrate was evaporated under vacuum. Further

[2] Hambly, G. F.; Chan, T. H. *Tetrahedron Lett.* **1986**, *27*, 2563-2566.

purification by silica gel column chromatography using isohexane and ethyl acetate as eluant provided the product **2** as colorless oil.

(6-Chlorocyclohex-1-enyloxy)triethylsilane (**2a**)



A

The reaction was performed according to the above procedure using silyl enol ether **5a** (4.25 g, 20 mmol), leading to the corresponding allylic chloride **2a** in 40% yield (1.98 g, contaminated with 20% regioisomer **A**) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 4.99 (dd, *J* = 5.0, 2.8 Hz, 1H), 4.37 (t, *J* = 2.9 Hz, 1H), 2.35-1.56 (m, 6H), 1.04-0.98 (m, 9H), 0.75-0.67 (m, 6H).

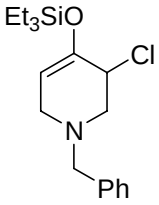
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 148.7, 107.5, 58.3, 32.9, 23.8, 17.1, 6.7, 5.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2876, 1659, 1457, 1366, 1334, 1231, 1196, 1010, 982, 896, 877, 830, 766, 728, 705, 677.

MS (EI, 70 eV): m/z (%) = 219 (35), 218 (17), 217 (100), 210 (14), 181 (17), 179 (14), 151 (15), 149 (11), 123 (48), 121 (87), 111 (12), 108 (12), 103 (19), 97 (23), 95 (16), 95 (22), 87 (31), 85 (15), 83 (22), 82 (10), 81 (17), 79 (24), 77 (20), 75 (20), 71 (22), 70 (12), 69 (29), 68 (15), 67 (20), 65 (11), 59 (26), 57 (44), 56 (14), 55 (34), 44 (21), 43 (30), 43 (53), 41 (30).

HRMS ($C_{12}H_{23}ClOSi$, EI): calc.: 246.1207; found: 246.1202 (M^+).

1-Benzyl-3-chloro-4-(triethylsilyloxy)-1,2,3,6-tetrahydropyridine (**2b**)



The reaction was performed according to the above procedure using silyl enol ether **5b** (6.07 g, 20 mmol), leading to the corresponding allylic chloride **2b** in 58% yield (3.91 g) as colorless oil.

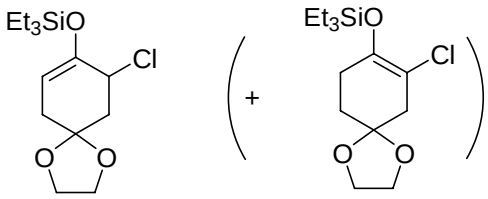
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.42-7.24 (m, 5H), 4.97 (dd, *J* = 4.2, 3.0 Hz, 1H), 4.33 (tt, *J* = 3.9, 1.3 Hz, 1H), 3.78 (d, *J* = 13.3 Hz, 1H), 3.59 (d, *J* = 13.3 Hz, 1H), 3.26 (ddt, *J* = 15.5, 4.2, 1.1 Hz, 1H), 3.02-2.92 (m, 2H), 2.82 (ddd, *J* = 12.4, 3.9, 1.1 Hz, 1H), 1.06-1.00 (m, 9H), 0.78-0.70 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 147.3, 137.6, 128.8, 128.2, 127.1, 105.0, 61.3, 57.6, 56.6, 51.3, 6.6, 4.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2875, 2800, 1668, 1454, 1356, 1238, 1210, 1137, 1058, 1005, 976, 869, 802, 729, 696.

MS (EI, 70 eV): m/z (%) =338 (12), 337 (M^+, 14), 336 (27), 303 (20), 302 (84), 301 (21), 300 (22), 289 (22), 288 (100), 115 (5), 91 (42), 87 (6).

HRMS ($C_{18}H_{27}ClNOSi$, EI): calc.: 336.1550; found: 336.1544 (M^+-H).

9-Chloro-8-((triethylsilyl)oxy)-1,4-dioxaspiro[4.5]dec-7-ene (**2c**)



B

The reaction was performed according to the above procedure using silyl enol ether **5c** (5.41 g, 20 mmol), leading to the corresponding allylic chloride **2c** in 69% yield (4.22 g, contaminated with 5% regioisomer **B**) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 4.90-4.87 (m, 1H), 4.56-4.50 (m, 1H), 4.02-3.91 (m, 4H), 2.54-2.19 (m, 4H), 1.02-0.96 (m, 9H), 0.74-0.66 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 147.5, 106.7, 103.5, 64.5, 64.3, 56.3, 41.4, 34.3, 6.6, 4.9.

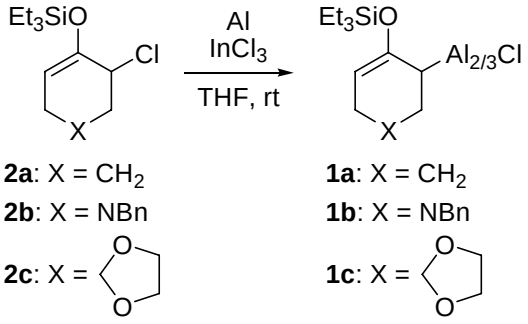
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2876, 1658, 1363, 1238, 1216, 1202, 1141, 1123, 1085, 1047, 1016, 1002, 946, 864, 828, 801, 727, 703, 676.

MS (EI, 70 eV): m/z (%) = 304 (M^+, 6), 277 (28), 276 (14), 275 (88), 270 (18), 269 (100), 262 (29), 216 (10), 190 (21), 188 (65), 123 (15), 121 (41), 115 (22), 87 (31), 86 (80), 73 (11), 59 (22).

HRMS ($C_{14}H_{24}ClO_3Si$, EI): calc.: 304.1261; found: 304.1247 (M^+).

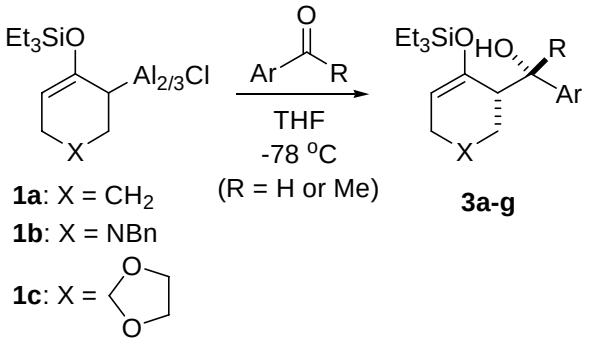
3. Preparation of allylic aluminium reagents **1a-c**.[3]

[3] Peng, Z.; Blümke, T. D.; Mayer, P.; Knochel, P. *Angew. Chem.*, *Int. Ed.* **2010**, *49*, 8516-8519.



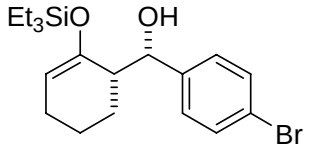
Aluminum powder (0.162 g, 6 mmol) and $InCl_3$ (22 mg, 0.1 mmol) were placed in a nitrogen-flushed flask and flame-dried for 5 min by heat gun (380 ^{o}C) under high vacuum. The flask was evacuated and backfilled with nitrogen 3 times and THF (2 mL) was added. A solution of allylic chloride **2** (2 mmol) in THF (2 mL) was added at room temperature, and the resulting solution was stirred at room temperature for 1-3 days (1 day for substrates **2a**-**b**, 3 days for substrate **2c**). The resulting allylic aluminum reagent **1** (ca. 70% yields for **1a**-**b**, ca. 50% yield for **1c**) was directly used in the following reactions with various aromatic aldehydes and methyl ketones.

4. General procedure for the reaction of allylic aluminum reagents **1a-c** with various carbonyl compounds.



The above preformed allylic aluminum reagents **1a-c** were slowly added to a solution of an aromatic aldehyde or methyl ketone (1 mmol) in THF (3 mL) at -78 °C and the mixture was stirred at this temperature for 2 h. After warming to room temperature, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Further purification by silica gel column chromatography using ethyl acetate and isohexane as eluant provided the homoallylic alcohols **3a-g** as colorless oil. The diastereoselectivities of the products were determined by ^{1}H NMR analysis of crude reaction mixture (after workup) by integration of the ratio of the two peaks arising from the alkene proton which mostly have typical doublet of doublet of doublets pattern (within 4.5-5.5 ppm area).

(4-Bromophenyl)(2-(triethylsilyloxy)cyclohex-2-enyl)methanol (**3a**)



The reaction was performed according to the above procedure using 4-bromobenzaldehyde (0.185 g, 1 mmol), leading to the corresponding homoallylic alcohol **3a** in 85% yield (0.337 g) with 95:5 dr as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.48-7.43 (m, 2H), 7.25-7.21 (m, 2H), 5.20 (d, *J* = 2.8 Hz, 1H), 5.09 (td, *J* = 4.1, 1.6 Hz, 1H), 2.52-2.46 (m, 1H), 2.39 (br, s, 1H), 2.01-1.95 (m, 2H), 1.65-1.41 (m, 2H), 1.37-1.22 (m, 2H), 1.06-1.01 (m, 9H), 0.78-0.70 (m, 6H).

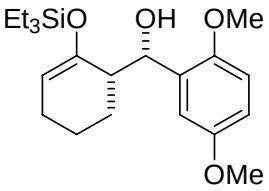
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.6, 141.6, 131.0, 127.8, 120.4, 107.5, 72.4, 46.3, 24.0, 22.7, 21.3, 6.8, 5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3461, 2952, 2874, 1700, 1662, 1486, 1457, 1237, 1212, 1172, 1070, 1009, 969, 911, 841, 815, 740, 724, 675.

MS (EI, 70 eV): m/z (%) = 396 (M^+, 0.08), 213 (16), 212 (100), 187 (12), 185 (18), 183 (42), 169 (14), 156 (12), 115 (67), 103 (27), 87 (39), 78 (11), 77 (21), 75 (25), 59 (21).

HRMS ($C_{19}H_{29}BrO_2Si$, EI): calc.: 396.1120; found: 396.1123 (M^+).

(2,5-Dimethoxyphenyl)(2-(triethylsilyloxy)cyclohex-2-enyl)methanol (**3b**)



The reaction was performed according to the above procedure using 2,5-dimethoxybenzaldehyde (0.166 g, 1 mmol), leading to the corresponding homoallylic alcohol **3b** in 90% yield (0.34 g) with 92:8 dr as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.13-7.12 (m, 1H), 6.76-6.75 (m, 2H), 5.58 (d, *J* = 2.8 Hz, 1H), 5.10 (ddd, *J* = 4.9, 3.2, 1.7 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 2.70-2.61 (m, 1H), 2.17 (br, s, 1H), 1.71-1.52 (m, 2H), 1.38-1.19 (m, 2H), 1.07-1.02 (m, 9H), 0.78-0.70 (m, 6H).

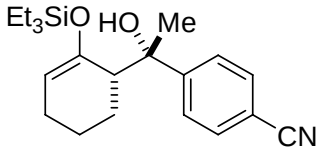
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 153.5, 150.3, 150.0, 132.1, 113.4, 112.0, 110.9, 107.6, 67.7, 55.7, 55.6, 43.6, 24.1, 22.8, 21.6, 6.8, 5.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3477, 2949, 2874, 1697, 1661, 1495, 1463, 1276, 1212, 1177, 1155, 1047, 1007, 902, 802, 729, 715.

MS (EI, 70 eV): m/z (%) = 281 (12), 212 (26), 183 (19), 167 (100), 139 (19), 103 (10), 87 (14), 75 (13), 59 (10).

HRMS ($C_{21}H_{34}O_4Si$, EI): calc.: 378.2226; found: 378.2236 (M^+).

4-(1-Hydroxy-1-(2-(triethylsilyloxy)cyclohex-2-enyl)ethyl)benzonitrile (**3c**)



The reaction was performed according to the above procedure using 4-acetylbenzonitrile (0.145 g, 1 mmol), leading to the corresponding homoallylic alcohol **3c** in 76% yield (0.272 g) with 95:5 dr as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.57 (s, 4H), 4.94 (s, 1H), 4.91 (ddd, *J* = 5.6, 3.0, 1.4 Hz, 1H), 2.67-2.61 (m, 1H), 1.93-1.64 (m, 3H), 1.59 (s, 3H), 1.50-1.18 (m, 3H), 1.00-0.94 (m, 9H), 0.74-0.65 (m, 6H).

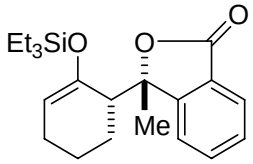
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 151.7, 150.3, 131.2, 127.0, 119.0, 110.1, 107.3, 77.0, 49.3, 28.5, 26.4, 23.7, 21.0, 6.6, 4.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3484, 2954, 2876, 2228, 1660, 1166, 1018, 907, 826, 729.

MS (EI, 70 eV): m/z (%) = 260 (16), 213 (18), 212 (100), 211 (10), 184 (10), 183 (53), 169 (16), 156 (13), 146 (37), 130 (21), 116 (11), 115 (95), 103 (37), 102 (13), 87 (59), 79 (12), 75 (34), 59 (31), 47 (100), 43 (42).

HRMS ($C_{21}H_{32}NO_2Si$, EI): calc.: 358.2202; found: 358.2208 (M^++H).

3-Methyl-3-(2-(triethylsilyloxy)cyclohex-2-enyl)isobenzofuran-1(3*H*)-one (**3d**)



The reaction was performed according to the above procedure using ethyl 2-acetylbenzoate (0.192 g, 1 mmol), leading to the corresponding lactone **3d** in 79% yield (0.282 g) with 98:2 dr as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.77 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.57 (td, *J* = 7.6, 1.2 Hz, 1H), 7.43-7.38 (m, 2H), 4.85 (ddd, *J* = 4.7, 3.5, 1.2 Hz, 1H), 2.70-2.67 (m, 1H), 2.00-1.84 (m, 2H), 1.67 (s, 3H), 1.64-1.51 (m, 2H), 1.33-1.20 (m, 2H), 0.90-0.86 (m, 9H), 0.63-0.57 (m, 6H).

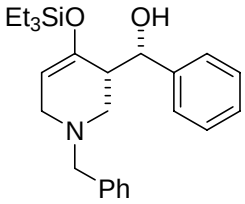
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 170.0, 154.0, 148.9, 133.4, 128.4, 126.3, 125.1, 121.2, 106.4, 89.5, 45.2, 26.4, 26.1, 23.5, 20.3, 6.5, 4.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2934, 2253, 1759, 1466, 1223, 904.

MS (EI, 70 eV): m/z (%) = 358 (M^+, 4), 329 (33), 212 (18), 211 (100), 183 (11), 148 (16), 147 (93), 115 (31), 87 (26).

HRMS ($C_{21}H_{30}O_3Si$, EI): calc.: 358.1964; found: 358.1968 (M^+).

(1-Benzyl-4-(triethylsilyloxy)-1,2,3,6-tetrahydropyridin-3-yl)(phenyl)methanol (**3e**)



The reaction was performed according to the above procedure using benzaldehyde (0.106 g, 1 mmol), leading to the corresponding homoallylic alcohol **3e** in 69% yield (0.283 g) with 95:5 dr as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.48-7.35 (m, 5H), 7.23-7.14 (m, 3H), 7.03-7.00 (m, 2H), 5.16 (s, 1H), 5.05 (dd, *J* = 5.0, 1.8 Hz, 1H), 3.70 (d, *J* = 12.4 Hz, 1H), 3.43-3.33 (m, 2H), 2.92 (d, *J* = 11.1 Hz, 1H), 2.82 (dt, *J* = 14.9, 1.8 Hz, 1H), 2.18-2.12 (m, 2H), 1.13-1.08 (m, 9H), 0.86-0.78 (m, 6H).

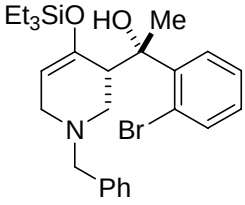
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.4, 144.7, 137.0, 129.8, 128.5, 127.8, 127.5, 126.0, 125.5, 101.9, 73.4, 62.2, 52.1, 49.2, 46.8, 6.7, 5.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3251, 2954, 2875, 1673, 1454, 1369, 1358, 1261, 1238, 1199, 1188, 1126, 1049, 1023, 988, 908, 893, 849, 726, 698.

MS (EI, 70 eV): m/z (%) = 409 (M^+, 3.5), 304 (14), 303 (40), 302 (100), 300 (15), 261 (14), 221 (13), 115 (12), 91 (41), 87 (14).

HRMS ($C_{25}H_{35}NO_2Si$, EI): calc.: 409.2437; found: 409.2445 (M^+).

(1-Benzyl-4-(triethylsilyloxy)-1,2,3,6-tetrahydropyridin-3-yl)-1-(2-bromophenyl)ethanol (**3f**)



The reaction was performed according to the above procedure using 1-(2-bromophenyl)ethanone (0.199 g, 1 mmol), leading to the corresponding homoallylic alcohol **3f** in 72% yield (0.364 g) with 96:4 dr as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.65 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.50-7.47 (m, 1H), 7.33-7.29 (m, 2H), 7.26-7.21 (m, 2H), 7.06-6.94 (m, 2H), 4.96 (ddd, *J* = 3.3, 2.1, 1.0 Hz, 1H), 3.46 (d, *J* = 12.4 Hz, 1H), 3.40-3.39 (m, 1H), 3.32 (dd, *J* = 15.2, 4.4 Hz, 1H), 3.25 (d, *J* = 12.4 Hz, 1H), 2.71 (d, *J* = 15.2 Hz, 1H), 2.49 (d, *J* = 11.6 Hz, 1H), 2.23 (dd, *J* = 11.6, 3.7 Hz, 1H), 1.77 (s, 3H), 1.06-1.00 (m, 9H), 0.79-0.70 (m, 6H).

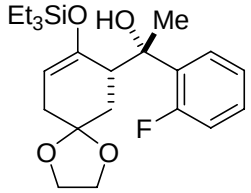
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.5, 147.3, 136.8, 134.8, 129.5, 128.9, 128.4, 127.8, 127.5, 127.2, 119.6, 102.7, 78.3, 62.0, 52.8, 51.5, 43.8, 26.4, 6.8, 5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2875, 2817, 1671, 1455, 1349, 1240, 1190, 1146, 1125, 1014, 1004, 882, 830, 762, 742, 725, 702.

MS (EI, 70 eV): m/z (%) = 501 (M^+, 1.0), 304 (15), 303 (55), 302 (100), 300 (18), 261 (10), 212 (27), 187 (11), 186 (14), 185 (11), 115 (15), 92 (10), 91 (90), 87 (20), 75 (13), 43 (19).

HRMS ($C_{26}H_{36}BrNO_2Si$, EI): calc.: 501.1699; found: 501.1703 (M^+).

1-(8-((Triethylsilyl)oxy)-1,4-dioxaspiro-[4.5]dec-7-ene-9-yl)-1-(2-fluorophenyl)ethanol (**3g**)



The reaction was performed according to the above procedure using 1-(2-fluorophenyl)ethanone (0.138 g, 1 mmol), leading to the corresponding homoallylic alcohol **3g** in 64% yield (0.262 g) with 95:5 dr as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.65 (td, *J* = 8.0, 2.1 Hz, 1H), 7.23-7.09 (m, 2H), 6.97 (ddd, *J* = 11.9, 7.7, 1.4 Hz, 1H), 4.91 (br, s, 1H), 4.88 (t, *J* = 3.7 Hz, 1H), 3.87-3.78 (m, 2H), 3.66-3.57 (m, 2H), 3.16 (dd, *J* = 4.4, 1.9 Hz, 1H), 2.39-2.20 (m, 2H), 1.79-1.72 (m, 4H), 1.54 (dddd, *J* = 14.1, 3.2, 1.5, 1.4 Hz, 1H), 1.05-1.00 (m, 9H), 0.79-0.70 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.9 (d, *J* = 244.3 Hz), 150.0, 135.9 (d, *J* = 14.3 Hz), 128.1 (d, *J* = 8.1 Hz), 127.2 (d, *J* = 5.3 Hz), 123.8 (d, *J* = 3.1 Hz), 115.5 (d, *J* = 24.1 Hz), 107.3, 102.7, 75.5 (d, *J* = 5.3 Hz), 64.3, 64.1, 46.6 (d, *J* = 4.8 Hz), 34.8, 34.1, 29.1 (d, *J* = 2.8 Hz), 6.7, 5.0.

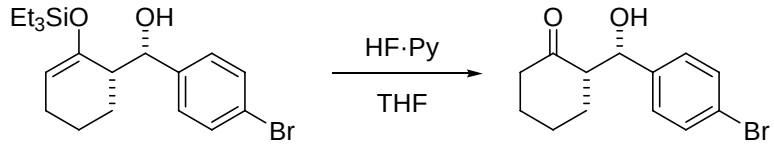
^{19}F NMR (282 MHz, $CDCl_3$): -111.92 ~ -112.01 (m, 1F).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3432, 2956, 2876, 1661, 1448, 1375, 1210, 1190, 1125, 1071, 1040, 1014, 1003, 948, 906, 831, 758, 728.

MS (EI, 70 eV): m/z (%) = 408 (M^+, 0.2), 271 (22), 270 (100), 269 (19), 241 (15), 226 (10), 225 (12), 211 (14), 210 (54), 209 (17), 208 (29), 197 (12), 179 (24), 156 (11), 155 (15), 140 (12), 139 (67), 138 (15), 123 (26), 115 (44), 103 (32), 95 (13), 94 (12), 87 (50), 86 (30), 75 (28), 59 (30), 43 (50).

HRMS ($C_{22}H_{33}FO_4Si$, EI): calc.: 408.2132; found: 408.2120 (M^+).

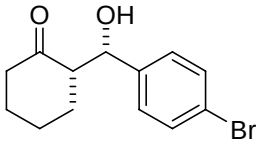
5. Synthesis of β-hydroxy ketone **7** by the de-silylation of homoallylic alcohol **3a**[4]



3a **7** : 72%

A solution of hydrogen fluoride pyridine (~70% hydrogen fluoride, 0.2 mL) was added into a solution of homoallylic alcohol **3a** (0.199 g, 0.5 mmol) in THF (4 mL) at -20 °C. The mixture was stirred for 1 h at -20 °C then warmed up to 0 °C with stirring for another 1 h. The mixture was quenched by saturated $NaHCO_3$ (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to provide the β-hydroxyl ketone **7** in 72% yield (0.102 g) as a white solid.

(4-Bromophenyl)(hydroxy)methyl)cyclohexanone (**7**)



^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 7.49-7.46 (m, 2H), 7.34-7.30 (m, 2H), 5.28 (t, *J* = 3.8 Hz, 1H), 4.09 (d, *J* = 4.1 Hz, 1H), 2.69 (dddd, *J* = 11.5, 6.0, 3.7, 1.1 Hz, 1H), 2.42-2.26 (m, 2H), 2.08-1.96 (m, 1H), 1.86 - 1.52 (m, 5H).

^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 212.3, 144.7, 132.1, 129.5, 121.1, 70.7, 58.2, 43.2, 28.6, 27.3, 25.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3431, 2944, 2861, 1696, 1483, 1396, 1364, 1311, 1258, 1130, 1116, 1089, 1063, 1010, 985, 895, 827, 794, 752, 715, 667.

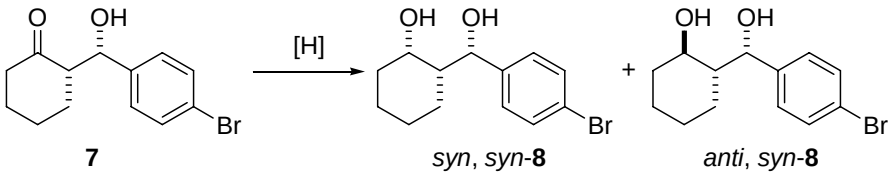
[4] (a) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921–5942. (b) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453-461. (c) Wipf, P.; Kim, H. *J. Org. Chem.* **1993**, *58*, 5592–5594.

MS (EI, 70 eV): m/z (%) = 284 (12), 282 (M^+, 10), 266 (28), 265 (10), 264 (29), 187 (38), 186 (17), 186 (19), 185 (100), 185 (79), 184 (18), 159 (13), 157 (29), 155 (19), 129 (16), 128 (12), 116 (15), 115 (18), 98 (91), 97 (19), 83 (25), 78 (29), 77 (57), 76 (15), 74 (10), 70 (29), 55 (22), 50 (14), 42 (16), 42 (14), 41 (28).

HRMS ($C_{13}H_{15}BrO_2$, EI): calc.: 282.0255; found: 282.0241 (M^+).

M.P. (^oC): 120-122.

6. Diastereoselective reduction of *β*-hydroxy ketone **7** by using various reducing agents.



7 *syn*, *syn*-**8** *anti*, *syn*-**8**

1) L-selectride, THF, -78 ^oC, 90% yield, 98:2 dr;
2) DIBAL-H,CH_2Cl_2, -78 ^oC, 3 h, 89% yield, 95:5 dr;
3) $Zn(BH_4)_2$, CH_2Cl_2, -78 ^oC, 2 h, 99% yield, 94:6 dr;
4) $Me_4NBH(OAc)_3$, HOAc, -40 ^oC, 18 h, 92%, 25:75 dr.

(1) L-Selectride reduction[5]

To a solution of *β*-hydroxyl ketone **7** (0.142 g, 0.5 mmol) in dry THF (5 mL) was added L-Selectride (1 mmol, 1 mL, 1.0 M in THF) dropwise at -78 °C under nitrogen atmosphere. The reaction mixture was stirred for 3 h at -78 °C and then allowed to warm to room temperature for another 1 h. The mixture was then diluted with ethyl acetate (100 mL) and filtered through a pad of silica gel, which was rinsed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give 1,3-diol **8** as white solid (0.128 g, 90% yield, 98:2 dr). The diastereoselectivity of the product was determined by ^1H NMR analysis of crude reaction mixture (after workup) by integration of the ratio of the two peaks located at 4.20 ppm (d, *J* = 2.2 Hz, 1H, for *syn* isomer) and 3.47 ppm (td, *J* = 10.5, 4.5 Hz, 1H, for *anti* isomer) which belong to the aliphatic (not benzylic) CH attaching to a hydroxyl group.

(2) DIBAL-H reduction[6]

[5] (a) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159-7161. (b) Krishnamurthy, S.; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 3383–3384. (c) Chun, J.; Byun, H.-S.; Arthur, G.; Bittman, R. *J. Org. Chem.* **2003**, *68*, 355–359.
[6] (a) Kiyooka, S.-i.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009-3012. (b) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531-13540.

To a solution of *β*-hydroxyl ketone **7** (0.23 g, 0.8 mmol) in anhydrous THF (10 mL) at –78 °C under nitrogen was added DIBAL-H (0.285 g, 0.36 mL, 2 mmol) dropwise. After 2 h, the reaction was quenched by the addition of EtOAc (0.2 mL) and saturated aqueous sodium potassium tartrate (10 mL) and the slurry was warmed to room temperature with vigorous stirring for 12 h. The resulting clear biphase was extracted with ethyl acetate (30 mL x 3) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography using ethyl acetate and isohexane as eluant to provide 1,3-diol **8** as white solid (0.203 g, 89% yield, 95:5 dr).

(3) $Zn(BH_4)_2$ reduction[7]

To a stirred solution of *β*-hydroxyl ketone **7** (0.142 g, 0.5 mmol) in anhydrous CH_2Cl_2 (6 mL) at -78 ^oC was dropwise added a freshly prepared THF solution of $Zn(BH_4)_2$ (1.5 mmol, 3 mL, 0.5 M) and the solution was stirred at the same temperature for 2 h. Then the reaction mixture was quenched by a saturated aqueous NH_4Cl (10 mL). The resulting solution was allowed to warm to room temperature with stirring for 12 h. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under vacuum. The crude oil was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the 1,3-diol **8** as white solid (0.141 g, 99% yield, 94:6 dr).

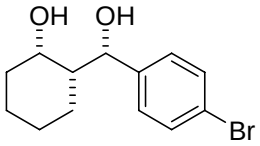
(4) Tetramethylammonium triacetoxyborohydride [$Me_4NHB(OAc)_3$] reduction[8]

To a solution of tetramethylammonium triacetoxyborohydride (1.053 g, 4 mmol) in anhydrous CH_3CN (2.2 mL) was added anhydrous CH_3COOH (2.2 mL) and the mixture was stirred at ambient temperature for 30 min. The mixture was cooled to -40 ^oC, and a solution of *β*-hydroxyl ketone **7** (0.142 g, 0.5 mmol) in anhydrous CH_3CN (1 mL) was added dropwise via syringe. The mixture was stirred at -40 ^oC for 18 h. The reaction mixture was quenched with aqueous sodium potassium tartrate (6 mL, 0.5 M) and the mixture was allowed to warm slowly to room temperature. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 for 4 times, and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried with Na_2SO_4 and concentrated *in vacuo*. After concentration under vacuum, the residue obtained was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give 1,3-diol **8** as white solid (0.132 g, 92% yield; 25:75 dr).

[7] (a) Narasimhan, S.; Balakumar, R. *Aldrichimica Acta* **1998**, *31*, 19-27. (b) Hoyveda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev*. **1993**, *93*, 1307-1370. (c) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc*. **1998**, *120*, 5921-5942. (d) Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 3995–3998.

[8] (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578. (b) Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; O'Brien, M.; Scott, J. P.; Sereinig, N. *J. Org. Chem.* **2005**, *70*, 150-160.

(4-Bromophenyl)(hydroxy)methyl)cyclohexanol (*syn*,*syn*-**8**)



syn, *syn*-**8**

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.47-7.45 (m, 2H), 7.23-7.21 (m, 2H), 4.95 (d, *J* = 3.0 Hz, 1H), 4.20 (d, *J* = 2.2 Hz, 1H), 2.61 (br, s, 2H), 1.81-1.72 (m, 2H), 1.68-1.46 (m, 5H), 1.29 (dq, *J* = 13.1, 3.2 Hz, 1H), 1.09 (qt, *J* = 13.1, 3.7 Hz, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 142.2, 131.1, 127.6, 120.7, 77.3, 71.6, 47.7, 34.0, 25.5, 19.6, 18.2.

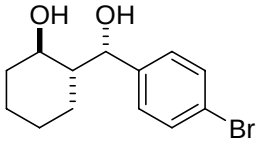
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3254, 2929, 2852, 1485, 1445, 1401, 1329, 1290, 1181, 1087, 1069, 1009, 967, 806, 723.

MS (EI, 70 eV): m/z (%) = 284 (M^+, 0.07), 187 (90), 185 (100), 157 (10), 82 (62), 81 (11), 78 (18), 77 (35), 67 (47), 54 (13), 41 (9).

HRMS ($C_{13}H_{16}BrO_2$, EI): calc.: 283.0334; found: 283.0339 (M^+-H).

M.P. (^{o}C): 155-157.

(4-Bromophenyl)(hydroxy)methyl)cyclohexanol (*anti*,*syn*-**8**)



anti, *syn*-**8**

^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 7.49-7.46 (m, 2H), 7.33-7.29 (m, 2H), 5.16 (dd, *J* = 5.2, 2.4 Hz, 1H), 4.60 (d, *J* = 5.5 Hz, 1H), 4.11 (br, s, 1H), 3.55 (t, *J* = 10.1 Hz, 1H), 2.08-1.93 (m, 2H), 1.65-0.99 (m, 7H).

^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 145.5, 131.8, 129.6, 120.7, 73.1, 71.3, 53.0, 37.2, 26.6, 25.9, 24.9.

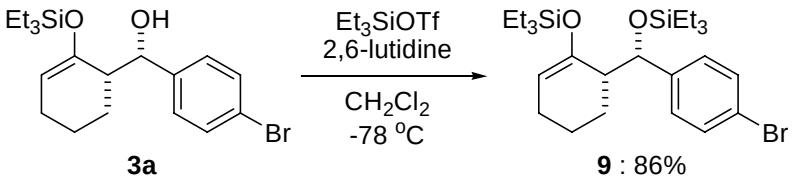
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3414, 3351, 2935, 2922, 2850, 1486, 1446, 1405, 1333, 1226, 1141, 1121, 1081, 1031, 1010, 984, 912, 827, 795, 778, 724, 680, 653.

MS (EI, 70 eV): m/z (%) = 284 (M^+, 0.13), 187 (87), 185 (100), 157 (10), 82 (64), 81 (14), 78 (20), 77 (38), 67 (53), 54 (16), 43 (10), 41 (13).

HRMS ($C_{13}H_{17}BrO_2$, EI): calc.: 284.0412; found: 284.0420 (M^+).

M.P. (^{o}C): 144-146.

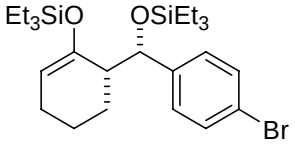
7. Synthesis of disilyl protected compound **9**.[9]



3a **9** : 86%

To a solution of the homoallylic alcohol **3a** (1.192 g, 3 mmol) in CH_2Cl_2 (30 mL) at -78 °C was added 2,6-lutidine (0.643 g, 0.7 mL, 6 mmol) followed by TESOTf (1.19 g, 1.03 mL, 4.5 mmol). The resulting mixture was stirred at -78 °C for 1 h and warmed up to room temperature for 1 h. The mixture was quenched by saturated aqueous NH_4Cl (20 mL) and extracted with diethyl ether (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Further purification by silica gel column chromatography using isohexane as eluent provided the product **9** as colorless oil (1.32 g, 86% yield).

1-Bromo-4-((triethylsilyloxy)(2-(triethylsilyloxy)cyclohex-2-enyl)methyl)benzene (**9**)



^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.45-7.40 (m, 2H), 7.21-7.17 (m, 2H), 5.31 (d, *J* = 2.5 Hz, 1H), 4.98 (ddd, *J* = 4.8, 3.5, 1.4 Hz, 1H), 2.15-2.10 (m, 1H), 2.04-1.95 (m, 2H), 1.83-1.66 (m, 2H), 1.36-1.17 (m, 2H), 1.06-1.00 (m, 9H), 0.92-0.87 (m, 9H), 0.75-0.67 (m, 6H), 0.59-0.51 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 149.9, 144.5, 130.7, 127.7, 120.0, 106.5, 72.3, 48.1, 24.3, 21.6, 21.3, 6.9, 6.8, 5.2, 4.8.

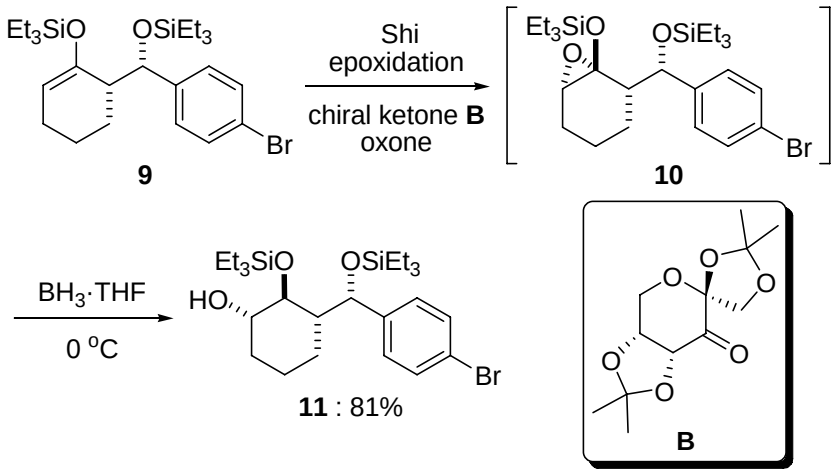
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2874, 1665, 1486, 1457, 1412, 1238, 1213, 1171, 1112, 1085, 1071, 1004, 976, 916, 903, 844, 810, 738, 723, 681.

MS (EI, 70 eV): m/z (%) = 302 (16), 301 (100), 300 (17), 299 (98), 115 (42), 87 (37), 59 (16).

HRMS ($C_{25}H_{43}BrO_2Si_2$, EI): calc.: 510.1985; found: 510.1977 (M^+).

8. Conversion of compound **9** to **11** via Shi-epoxidation followed by ring-opening with BH_3·THF according to Myers' procedure.[10]

[9] (a) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455-2458. (b) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287–11314. (c) Lister, T.; Perkins, M. V. *Org. Lett.* **2006**, *8*, 1827–1830.



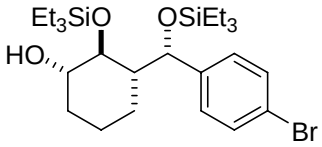
Disilyl protected compound **9** (0.266 g, 0.52 mmol, 1.0 equiv) was added to a 100 mL round-bottomed flask and the flask was cooled to 0 °C. CH_3CN (2.5 mL), dimethoxymethane (5.0 mL), and an aqueous stock solution of sodium borate-ethylenediaminetetraacetic acid disodium salt (5.0 mL) were added to the cooled flask. D-Fructose-derived Shi catalyst (40 mg, 0.16 mmol, 0.30 equiv) and tetrabutylammonium bisulfate (7.1 mg, 0.021 mmol, 0.04 equiv) were added in sequence to the stirring mixture at 0 °C. Separately, Oxone (443 mg, 0.72 mmol, 1.38 equiv) was added to an aqueous stock solution of ethylenediaminetetraacetic acid disodium salt (3.2 mL) and the resulting solution was drawn into a 5 mL disposable plastic syringe. A solution of potassium carbonate (418 mg, 3.03 mmol, 5.8 equiv) in water (3.2 mL) was drawn into a second 5 mL disposable plastic syringe. The contents of both syringes were added simultaneously over 90 min using a syringe drive to the ice-cooled, stirring reaction mixture. After the addition was complete, the reaction mixture was stirred for 30 min at 0 °C, then was diluted with ice-cooled pentane (30 mL) and ice-cooled water (30 mL), producing a biphasic mixture. The layers were separated. The aqueous layer was extracted with ice-cooled pentane (70 mL x 2). The organic extracts were combined, washed with brine (100 mL), and dried over Na_2SO_4. After filtration, the filtrate was concentrated to a volume of ca. 5 mL by rotary evaporation.

A solution of borane−tetrahydrofuran complex in THF (1.05 mmol, 1.0 M, 2.0 equiv) was added dropwise by syringe to an ice-cooled, stirring solution of the crude product in pentane (5 mL) in a 100 mL round-bottomed flask. The reaction mixture was stirred for 1 h at 0 °C, followed by the addition of pentane (15 mL). An aqueous solution of tris(hydroxymethyl)aminomethane hydrochloride (10 mL, 1.0 M) was then added carefully, causing vigorous evolution of gas. The biphasic mixture was allowed to warm to 25 °C. After stirring for 30 min at 25 °C, the reaction mixture was partially concentrated by rotary evaporation. Water (25 mL) was added, and the mixture was extracted by ethyl acetate (70 mL x 2). The combined organic extracts

[10] Lim, S. M.; Hill, N.; Myers, A. G. *J. Am. Chem. Soc.* **2009**, *131*, 5763–5765.

were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to provide the desired product **11** as colorless oil in 81% yield (0.222 g).

3-((4-Bromophenyl)(triethylsilyloxy)methyl)-2-(triethylsilyloxy)cyclohexanol (**11**)



^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.45-7.40 (m, 2H), 7.19-7.14 (m, 2H), 5.24 (s, 3 H), 3.50 (t, *J* = 8.5 Hz, 1H), 3.38 (ddd, *J* = 10.5, 8.3, 4.4 Hz, 1H), 1.94-1.88 (m, 1H), 1.71 (br, s, 1H), 1.62 (dt, *J* = 13.0, 3.5 Hz, 1H), 1.44-1.15 (m, 5H), 1.06-1.01 (m, 9H), 0.93-0.87 (m, 9H), 0.78-0.69 (m, 6H), 0.59-0.51 (m, 6H).

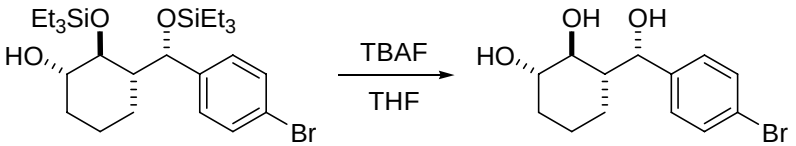
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 144.6, 130.8, 127.8, 120.1, 77.5, 75.7, 71.3, 52.5, 33.4, 22.2, 21.2, 7.3, 6.9, 6.4, 5.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3472, 2951, 2874, 1485, 1458, 1404, 1237, 1110, 1093, 1070, 1003, 973, 928, 838, 800, 781, 724, 676.

MS (EI, 70 eV): m/z (%) = 381 (11), 379 (11), 369 (21), 367 (20), 302 (20), 301 (100), 300 (20), 299 (97), 289 (12), 287 (11), 263 (32), 217 (10), 171 (11), 169 (11), 168 (14), 115 (49), 103 (32), 87 (41), 75 (32), 59 (12).

HRMS ($C_{23}H_{40}BrO_3Si_2$, EI): calc.: 499.1699; found: 499.1710 (M^+-C_2H_5).

9. Preparation of triol **12** via the desilylation of compound **11**.[11]



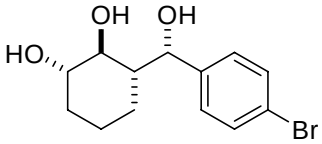
11 **12** : 90%

A solution of TBAF in THF (2.0 mmol, 2 mL, 1.0 M) was slowly added into a solution of compound **11** (0.265 g, 0.5 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min then warmed up to room temperature with stirring for another 4 h. The mixture was quenched by saturated aqueous NH_4Cl (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel

[11] (a) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191. (b) For example, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.

column chromatography using ethyl acetate as eluant to provide triol **12** as a white solid (0.136 g, 90% yield).

3-((4-Bromophenyl)(hydroxy)methyl)cyclohexane-1,2-diol (**12**)



^{1}H-NMR (400 MHz, CD_3COCD_3): δ / ppm = 7.50-7.46 (m, 2H), 7.33-7.30 (m, 2H), 5.19 (dd, *J* = 5.3, 2.2 Hz, 1H), 4.49 (d, *J* = 5.3 Hz, 1H), 4.07 (br, s, 1H), 3.76 (br, s, 1H), 3.40-3.30 (m, 2H), 1.86-1.81 (m, 1H), 1.59-1.55 (m, 2H), 1.30-1.11 (m, 4H).

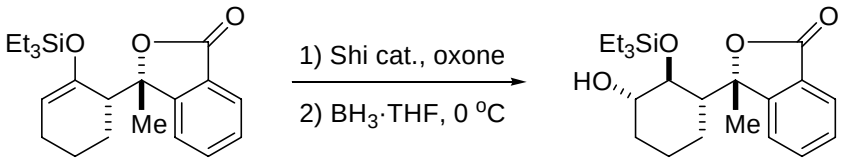
^{13}C-NMR (100 MHz, CD_3COCD_3): δ / ppm = 145.9, 132.0, 129.6, 120.8, 77.0, 76.7, 72.2, 51.0, 34.4, 24.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3343, 2945, 2922, 2862, 1486, 1403, 1348, 1242, 1232, 1108, 1071, 1049, 1026, 1010, 992, 879, 845, 830, 793, 725, 675.

MS (EI, 70 eV): m/z (%) = 187 (76), 185 (82), 183 (21), 159 (16), 157 (27), 155 (13), 115 (12), 106 (14), 105 (16), 98 (85), 97 (45), 83 (34), 80 (12), 79 (28), 78 (64), 77 (100), 76 (11), 75 (11), 70 (36), 69 (10), 67 (22), 57 (29), 55 (14), 44 (10), 43 (16), 41 (39).

HRMS ($C_{13}H_{17}BrO_3$, EI): calc.: 300.0361; found: 300.0356 (M^+).

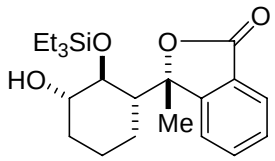
10. Preparation of lactone **13** with four contiguous chiral centers starting from lactone **3d**.[10]



3d **13** : 68%

The reaction was performed according to the above procedure using substrate **3d** (0.186 g, 0.52 mmol), leading to the corresponding product **13** in 68% yield (0.133 g) as colorless oil.

3-(3-Hydroxy-2-(triethylsilyloxy)cyclohexyl)-3-methylisobenzofuran-1(3*H*)-one (**13**)



^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.85 (d, *J* = 7.5 Hz, 1H), 7.68-7.63 (m, 1H), 7.48 (td, *J* = 7.5, 0.8 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 3.89 (t, *J* = 8.0 Hz, 1H), 3.50-3.43 (m, 1H), 2.09-1.98 (m, 2H), 1.94-1.88 (m, 1H), 1.82 (s, 3H), 1.54-1.12 (m, 4H), 1.03 (t, *J* = 7.7 Hz, 9H), 0.91-0.86 (m, 1H), 0.81-0.73 (m, 6H).

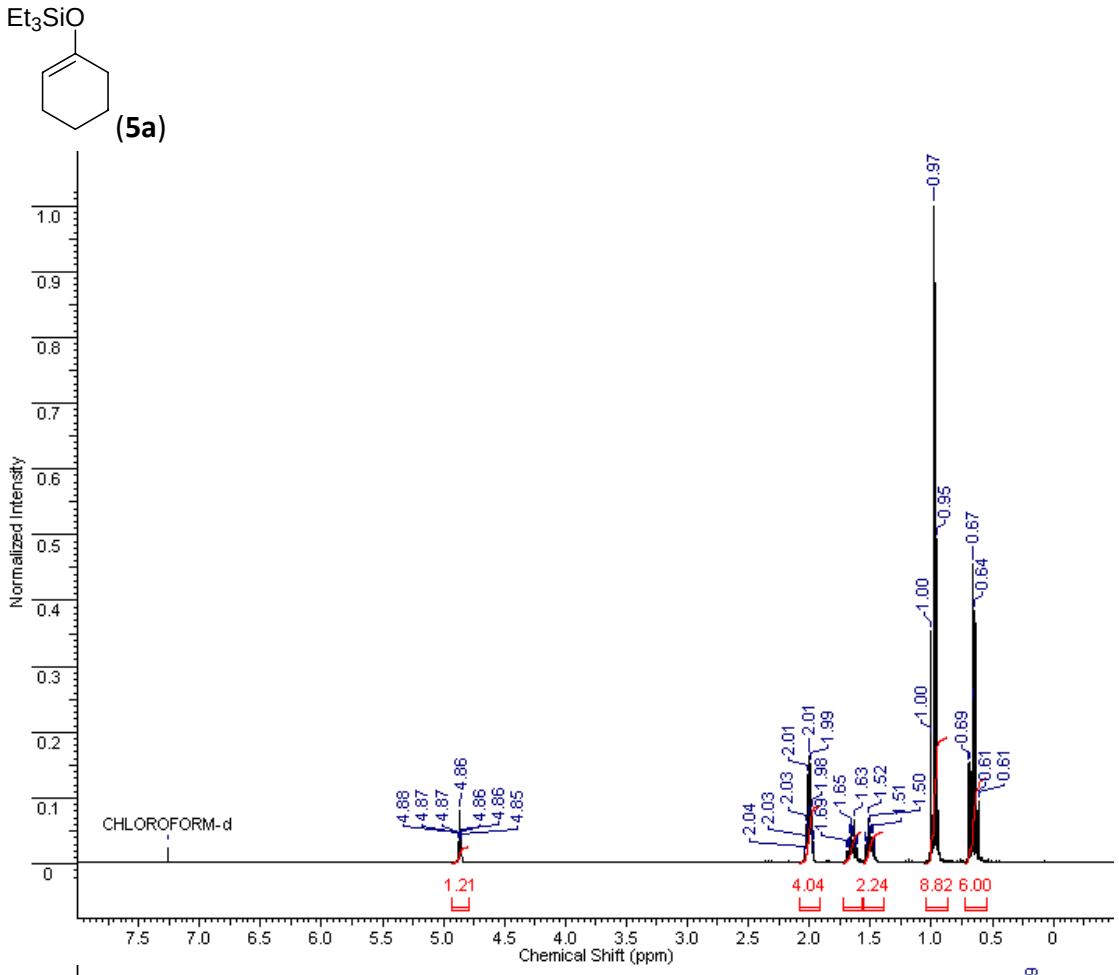
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 170.1, 155.4, 134.2, 128.7, 125.7, 125.4, 121.0, 89.6, 77.2, 75.2, 48.9, 32.2, 27.2, 25.5, 21.6, 7.1, 5.6.

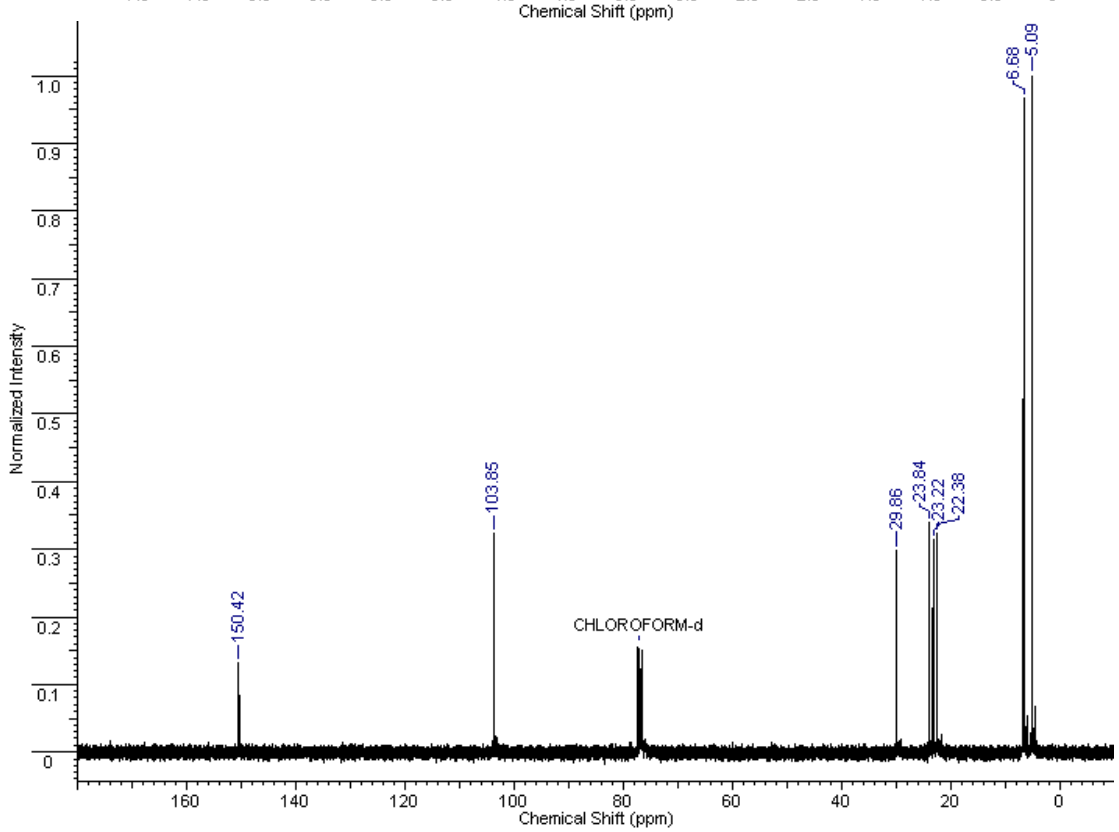
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3391, 2953, 2929, 2874, 1738, 1465, 1286, 1235, 1127, 1056, 1038, 906, 847, 767, 728, 698.

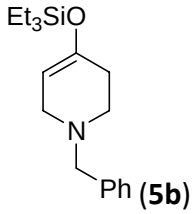
MS (EI, 70 eV): m/z (%) = 376 (M^+, 2), 347 (35), 229 (19), 147 (100), 115 (28), 103 (24), 75 (37), 59 (10).

HRMS ($C_{21}H_{32}O_4Si$, EI): calc.: 376.2070; found: 376.2083 (M^+).

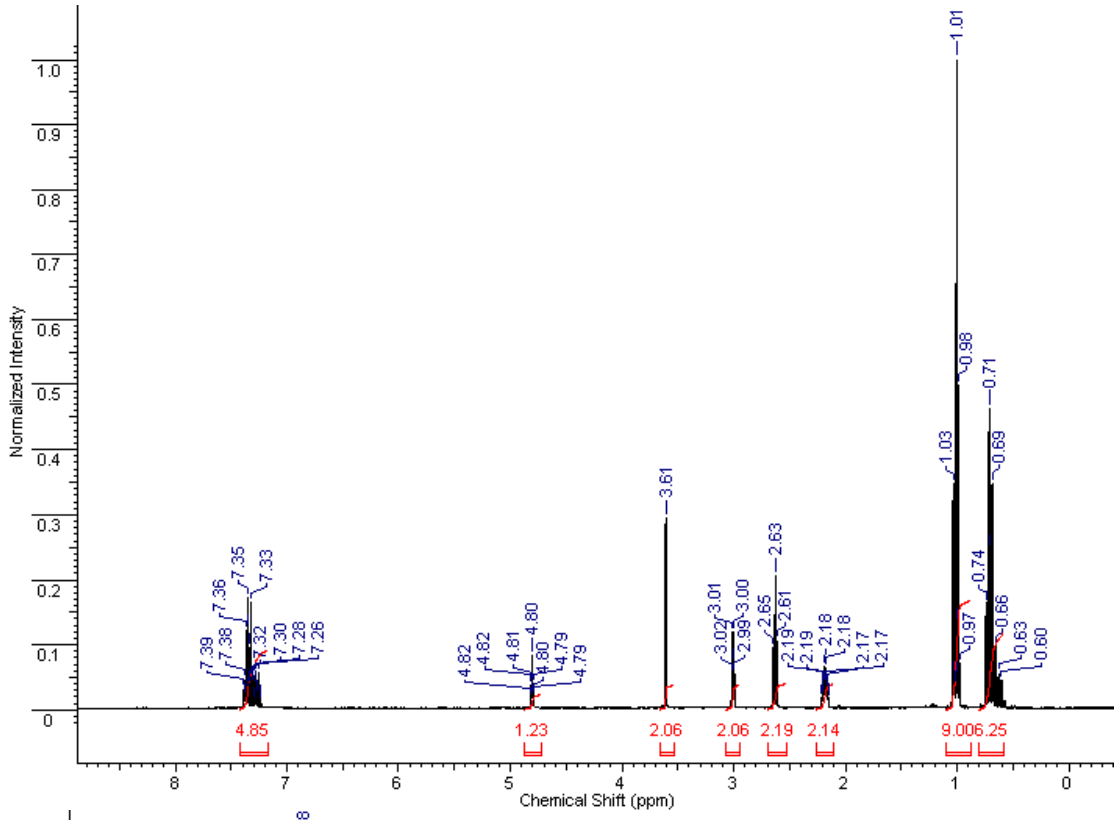
Copies of ^{1}H and ^{13}C NMR Spectral of Products

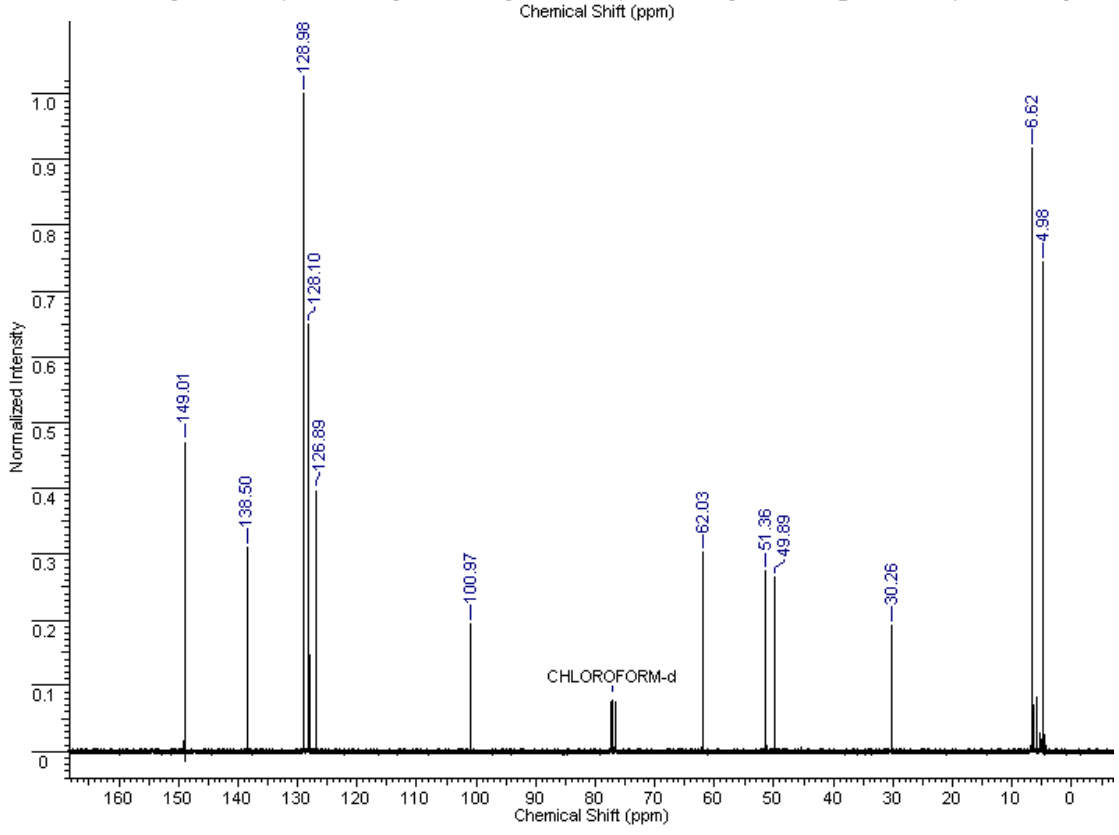





Et3SiO
N
Ph

(5b)


Normalized Intensity
Chemical Shift (ppm)
7.39
7.38
7.36
7.35
7.33
7.32
7.30
7.28
7.26
4.82
4.82
4.81
4.80
4.80
4.79
4.79
3.61
3.02
3.01
2.99
3.00
2.65
2.63
2.61
2.19
2.19
2.18
2.18
2.17
2.17
1.03
1.01
0.98
0.97
0.74
0.71
0.69
0.66
0.63
0.60
4.85
1.23
2.06
2.06
2.19
2.14
9.00
6.25


Normalized Intensity
Chemical Shift (ppm)
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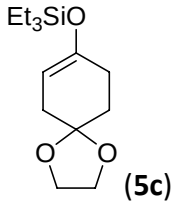
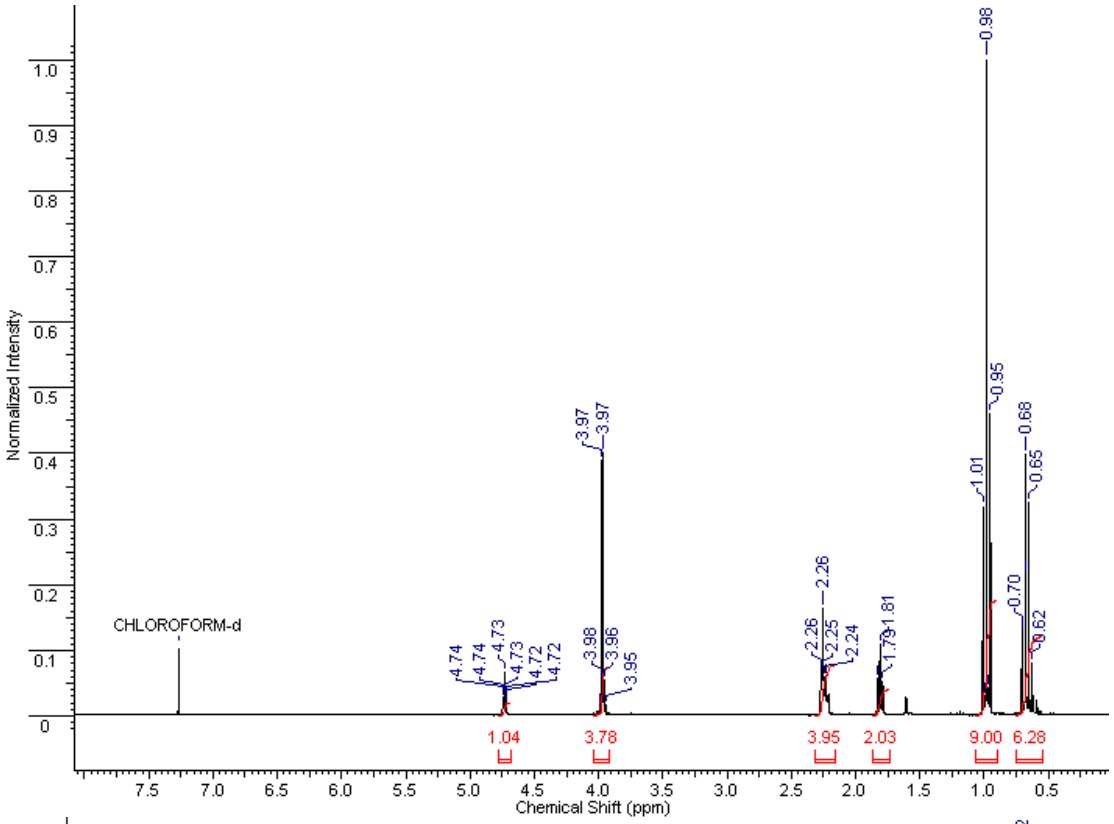
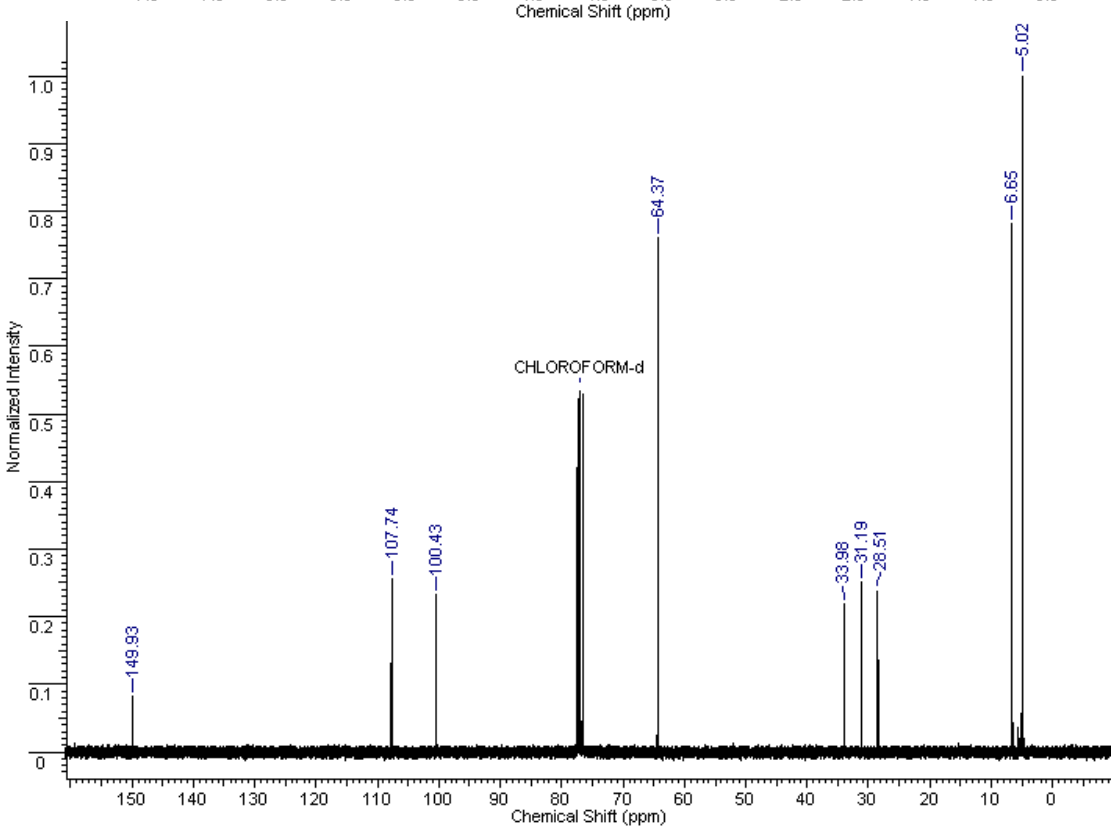
138.50
128.96
128.10
126.89
100.97
CHLOROFORM-d
62.03
51.36
49.89
30.26
6.62
4.98


Et3SiO
O
O

(5c)


Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
4.74
4.74
4.73
4.73
4.72
4.72
3.98
3.97
3.97
3.96
3.95
2.26
2.26
2.25
2.24
1.81
1.79
1.01
0.98
0.95
0.70
0.68
0.65
0.62
1.04
3.78
3.95
2.03
9.00
6.28


Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
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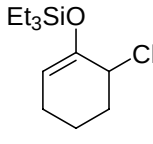
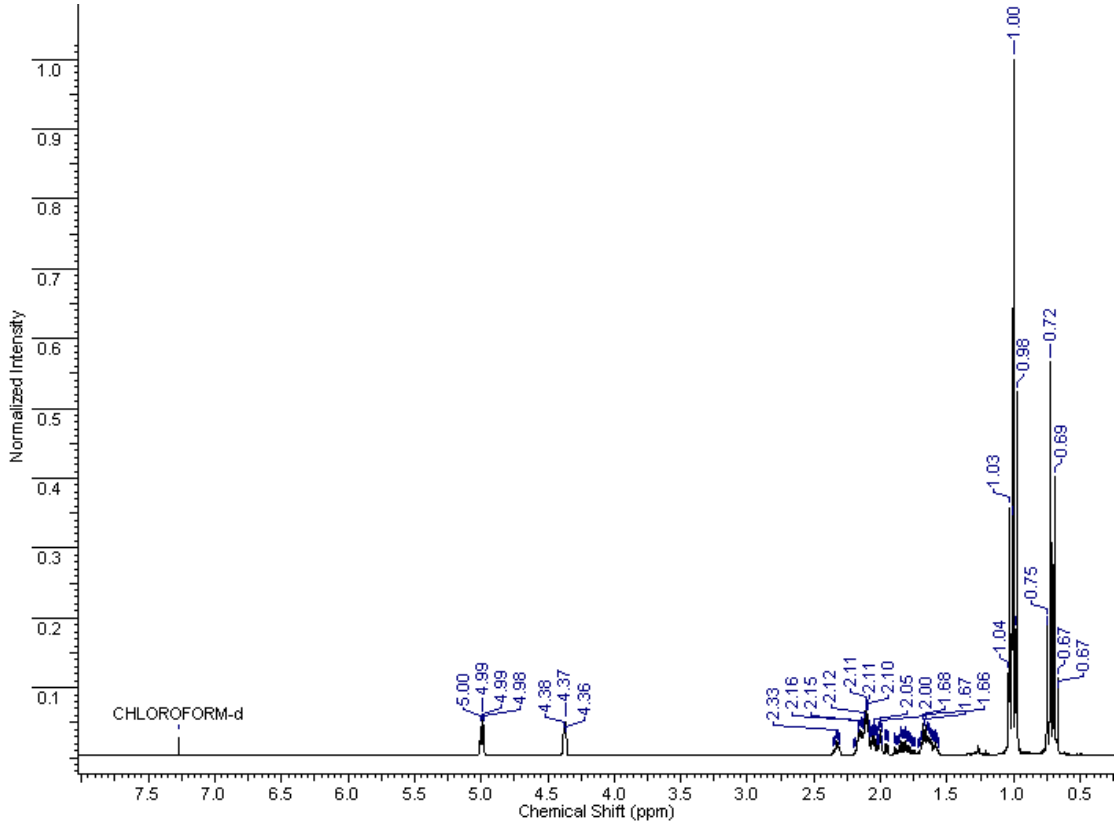
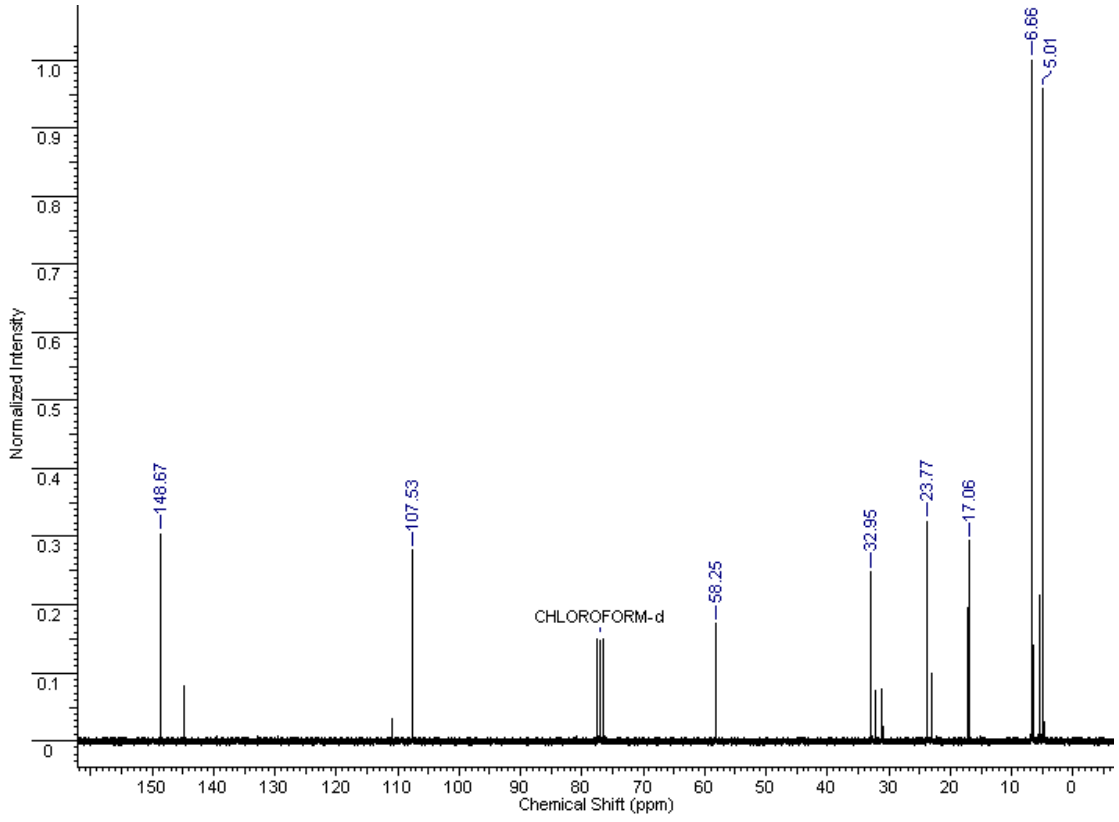
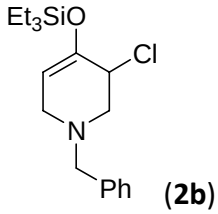
100.43
64.37
33.98
31.19
28.51
6.65
5.02


Et3SiO
Cl

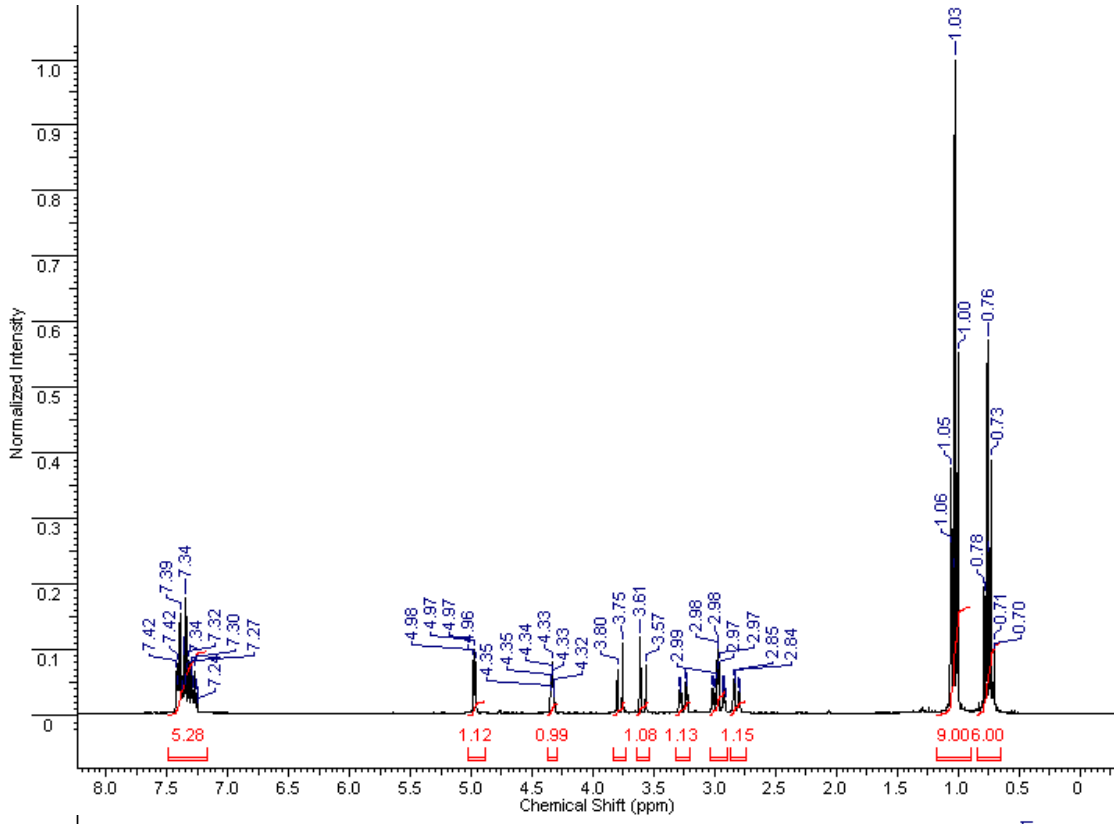
(**2a**)

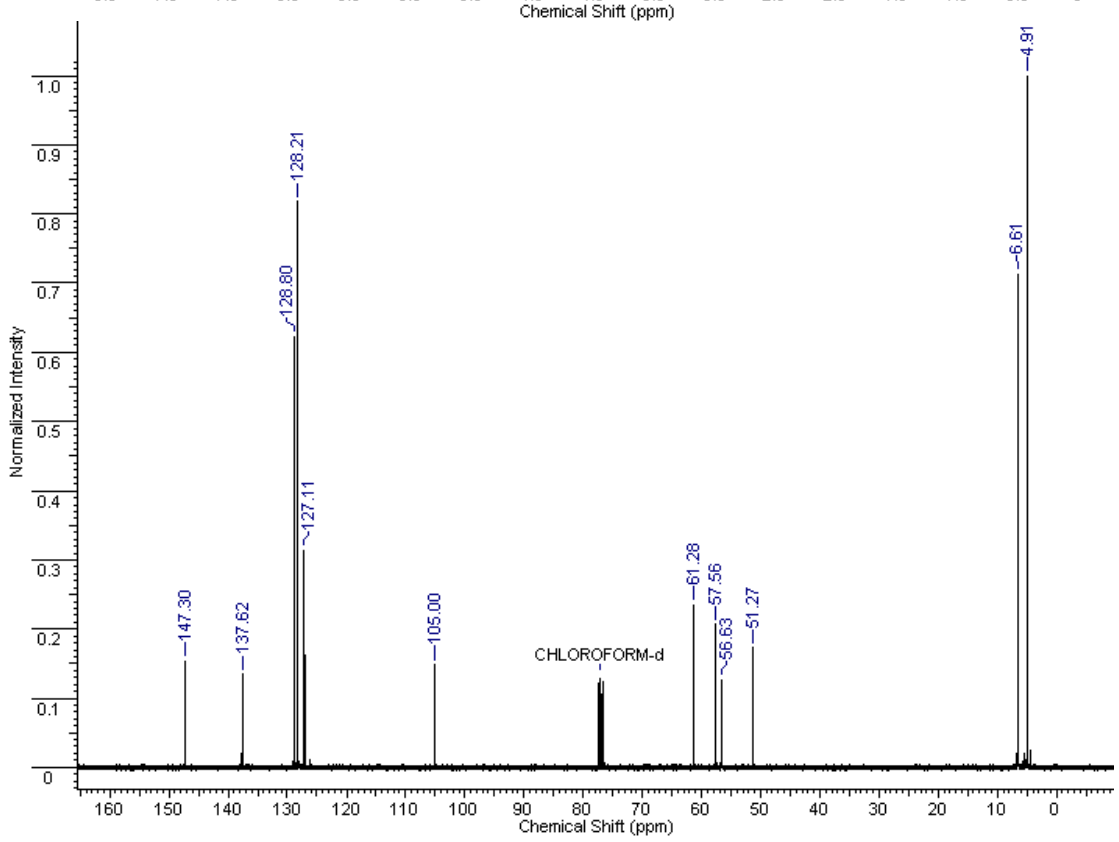

Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
1.00
0.98
0.72
0.69
1.03
0.75
1.04
0.67
0.67
5.00
4.99
4.99
4.98
4.38
4.37
4.36
2.33
2.16
2.15
2.12
2.11
2.11
2.10
2.05
2.00
1.68
1.67
1.66

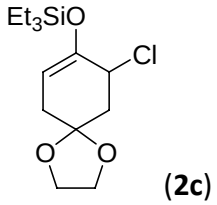

Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
148.67
107.53
58.25
32.95
23.77
17.06
6.66
5.01


Et3SiO
Cl
N
Ph

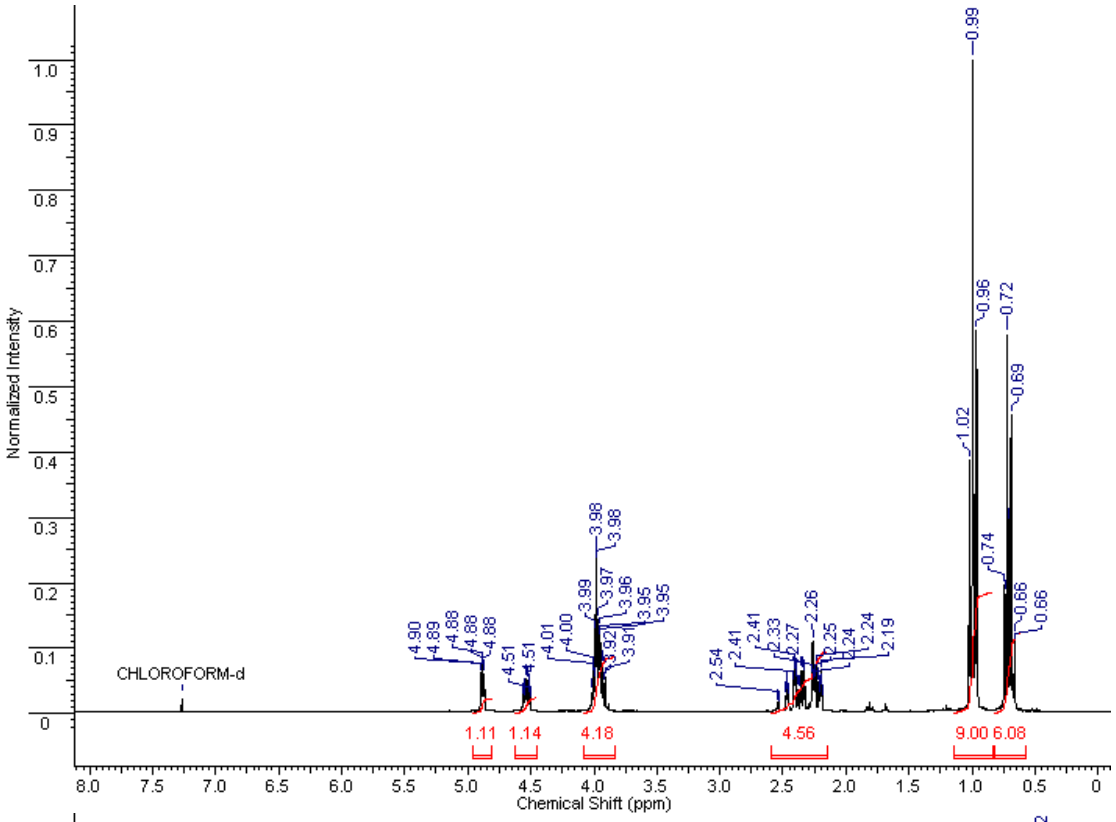
(**2b**)

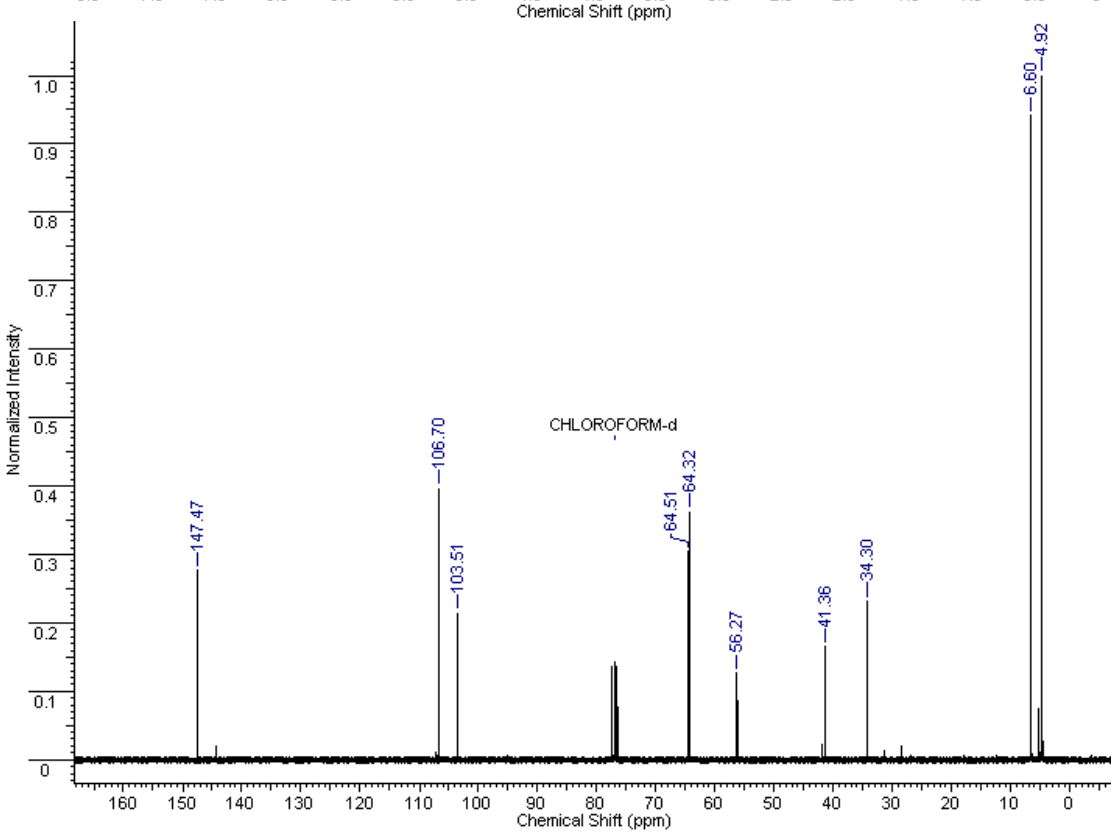

Normalized Intensity
Chemical Shift (ppm)
5.28
1.12
0.99
1.08
1.13
1.15
9.00
6.00


Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d


Et3SiO
Cl
O
O

(**2c**)


Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
0.99
1.02
0.96
0.72
0.69
0.74
0.68
0.66
1.11
1.14
4.18
4.56
9.00
6.08


Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
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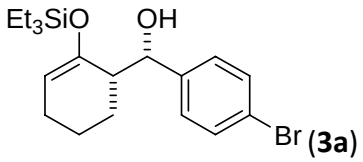
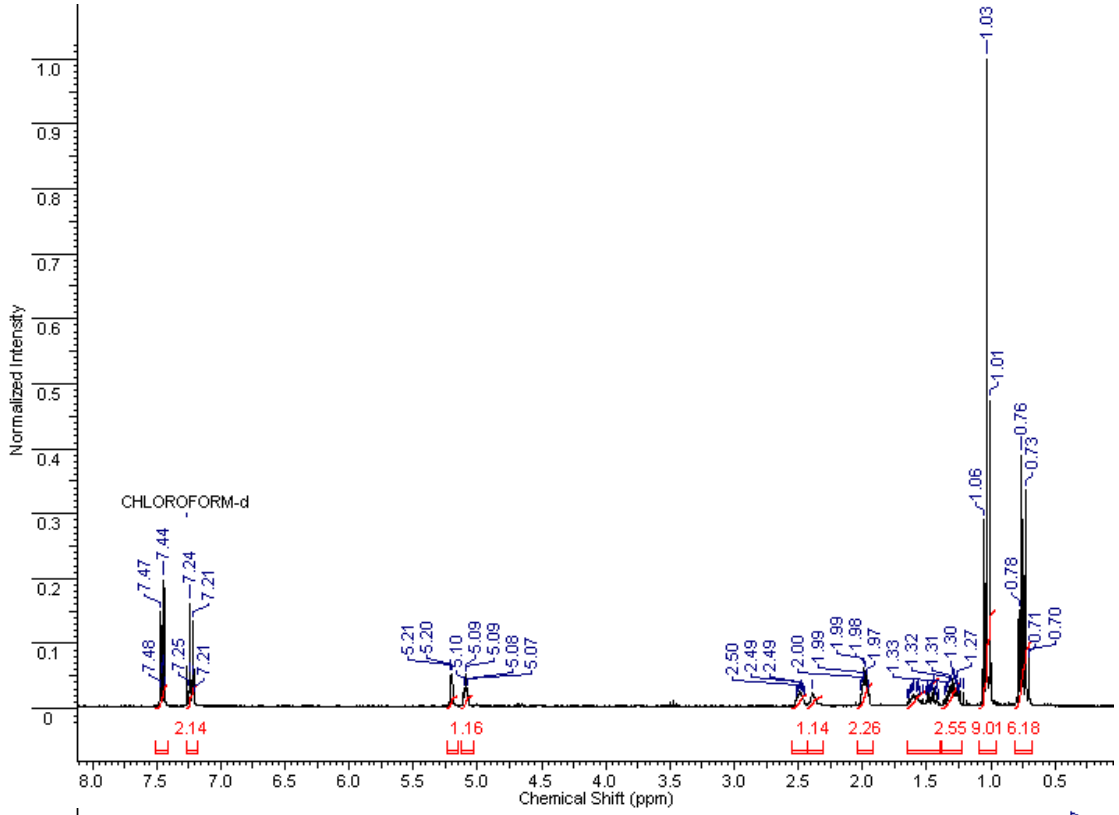
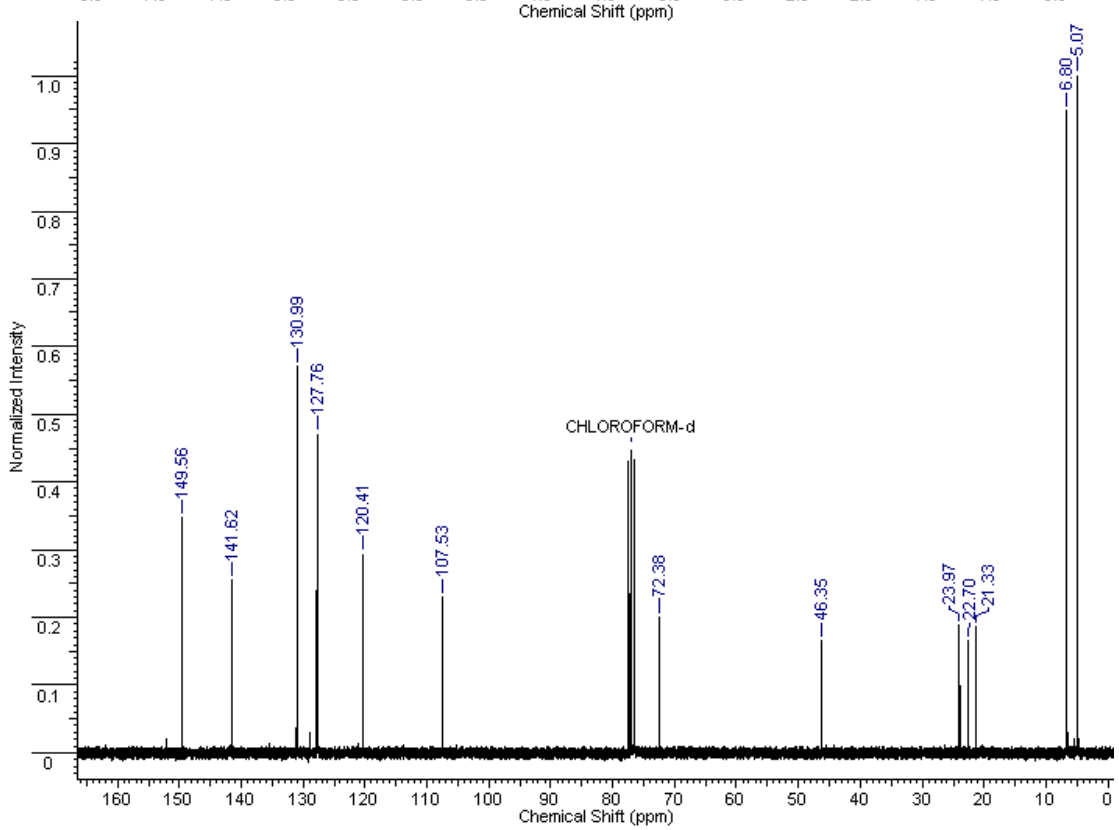
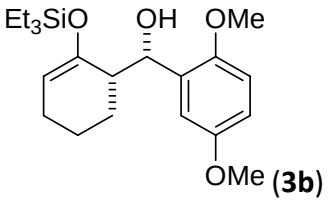
103.51
64.51
64.32
56.27
41.36
34.30
6.60
4.92


Et3SiO
OH
Br

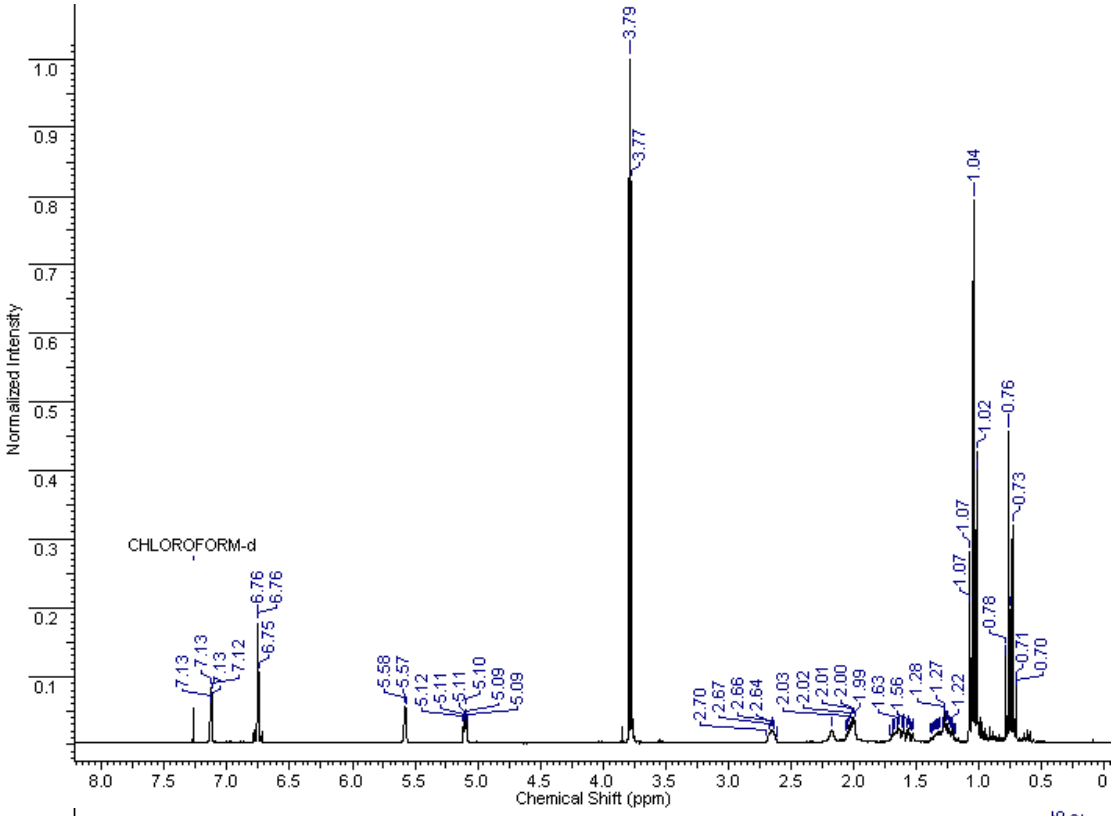
(**3a**)

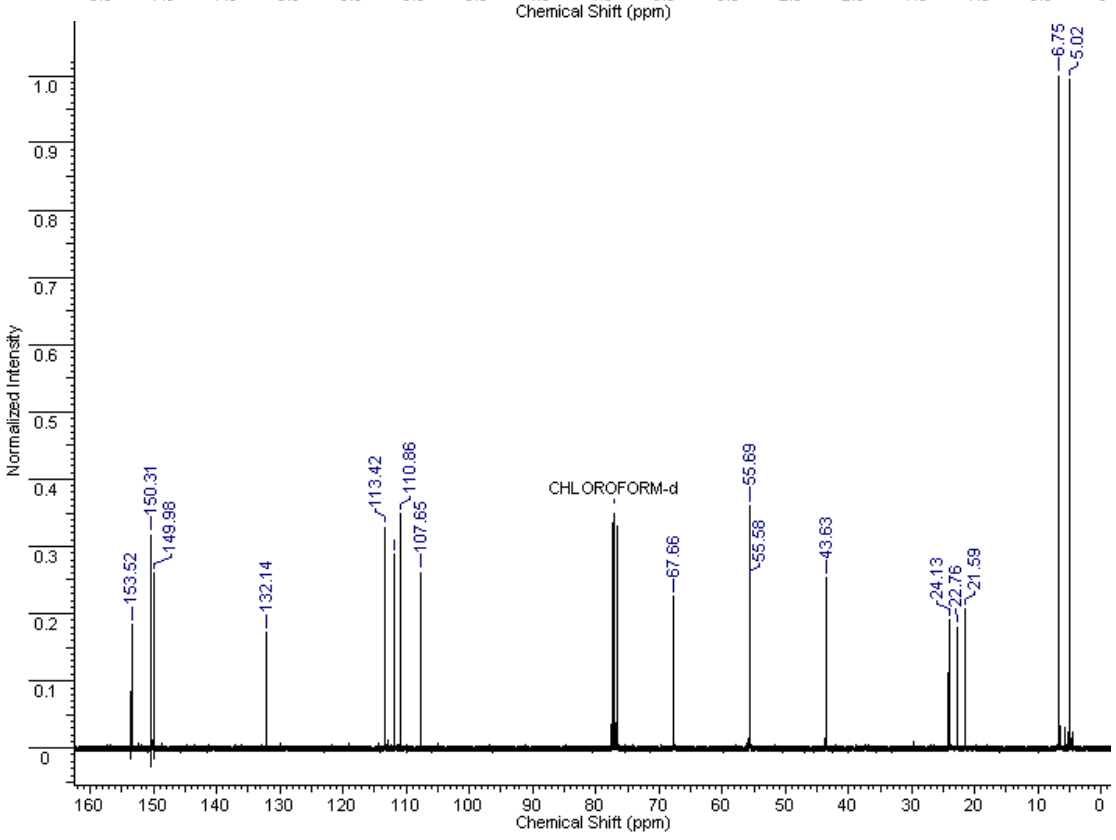

Normalized Intensity
CHLOROFORM-d
7.47
7.44
7.24
7.21
7.48
7.25
7.21
5.21
5.20
5.10
5.09
5.09
5.08
5.07
2.50
2.49
2.49
2.00
1.99
1.99
1.98
1.97
1.33
1.32
1.31
1.30
1.27
1.03
1.01
1.06
0.76
0.73
0.78
0.71
0.70
2.14
1.16
1.14
2.26
2.55
9.01
6.18
Chemical Shift (ppm)

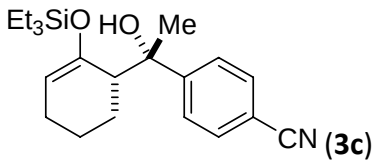

Normalized Intensity
6.80
5.07
149.56
141.62
130.99
127.76
120.41
107.53
CHLOROFORM-d
72.38
46.35
23.97
22.70
21.33
Chemical Shift (ppm)


Et3SiO
OH
OMe
OMe

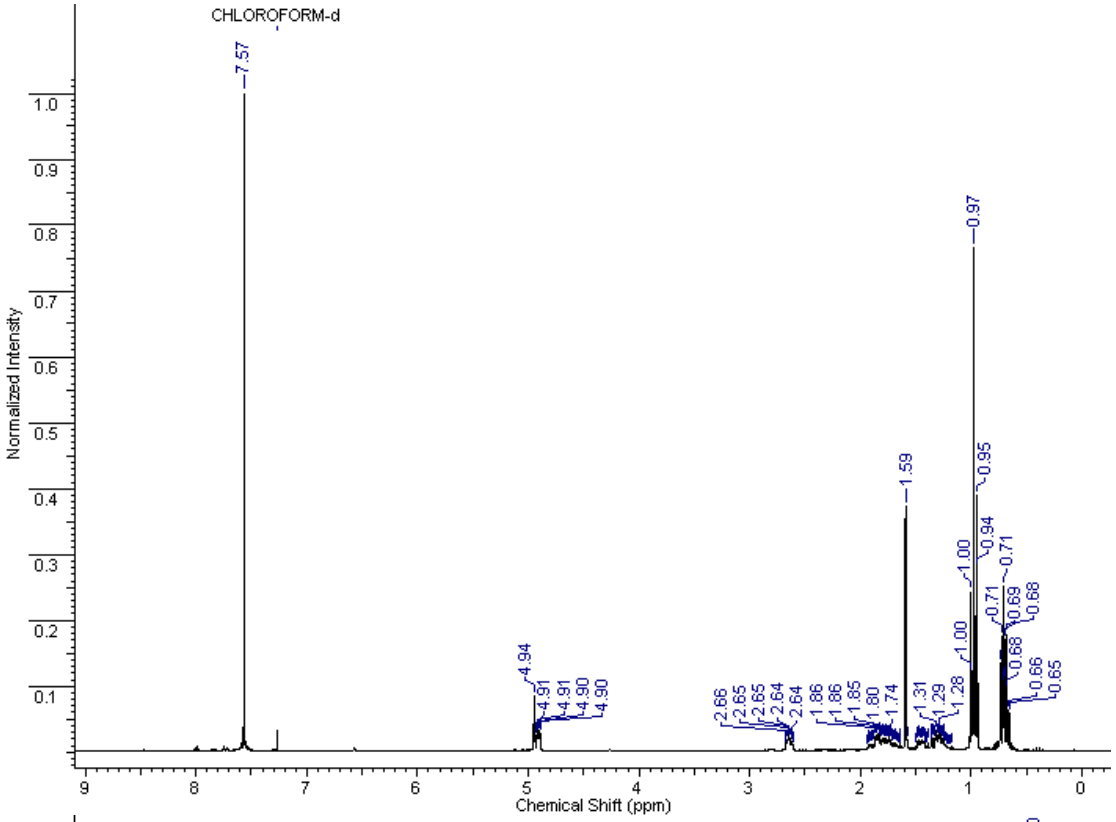
(**3b**)

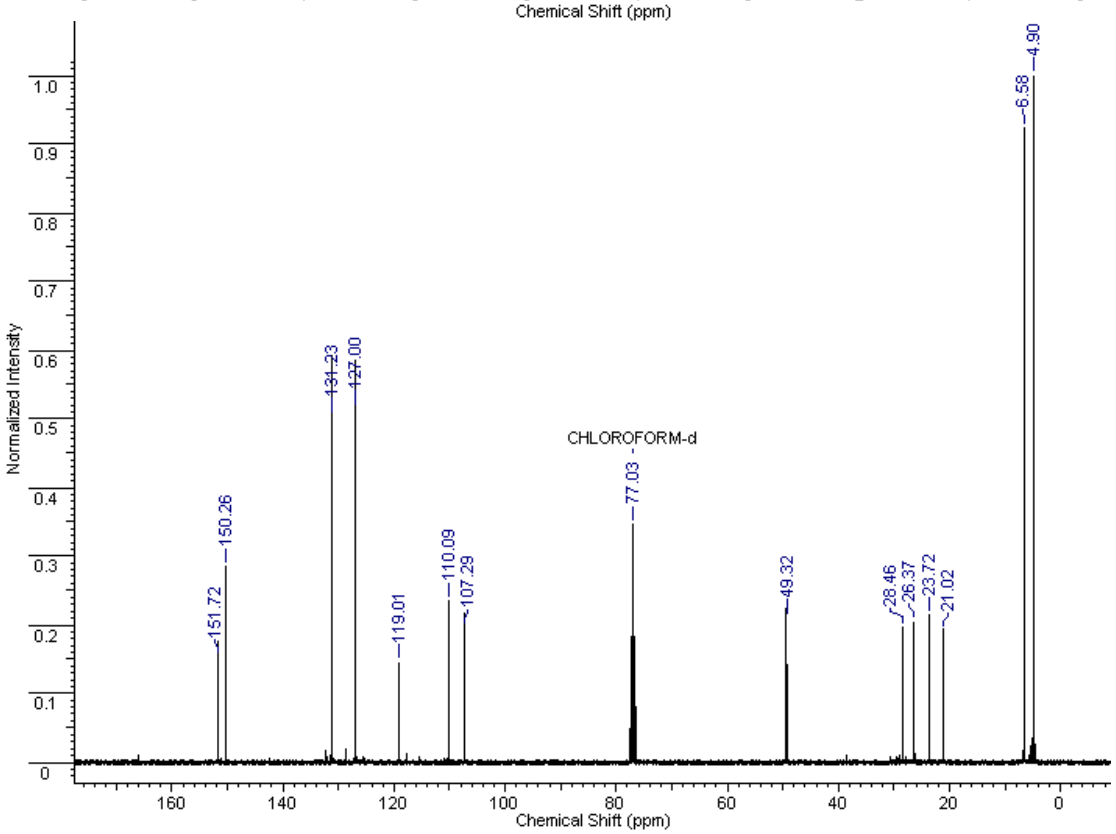

Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
3.79
3.77
1.04
1.02
0.76
0.73
1.07
1.07
0.78
0.71
0.70
6.76
6.76
6.75
7.13
7.13
7.13
7.12
5.58
5.57
5.12
5.11
5.11
5.10
5.09
5.09
2.70
2.67
2.66
2.64
2.03
2.02
2.01
2.00
1.99
1.63
1.56
1.28
1.27
1.22

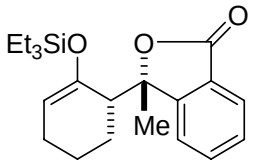

Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
153.52
150.31
149.98
132.14
113.42
110.86
107.65
67.66
55.69
55.58
43.63
24.13
22.76
21.59
6.75
5.02


Et3SiO
HO
Me
CN

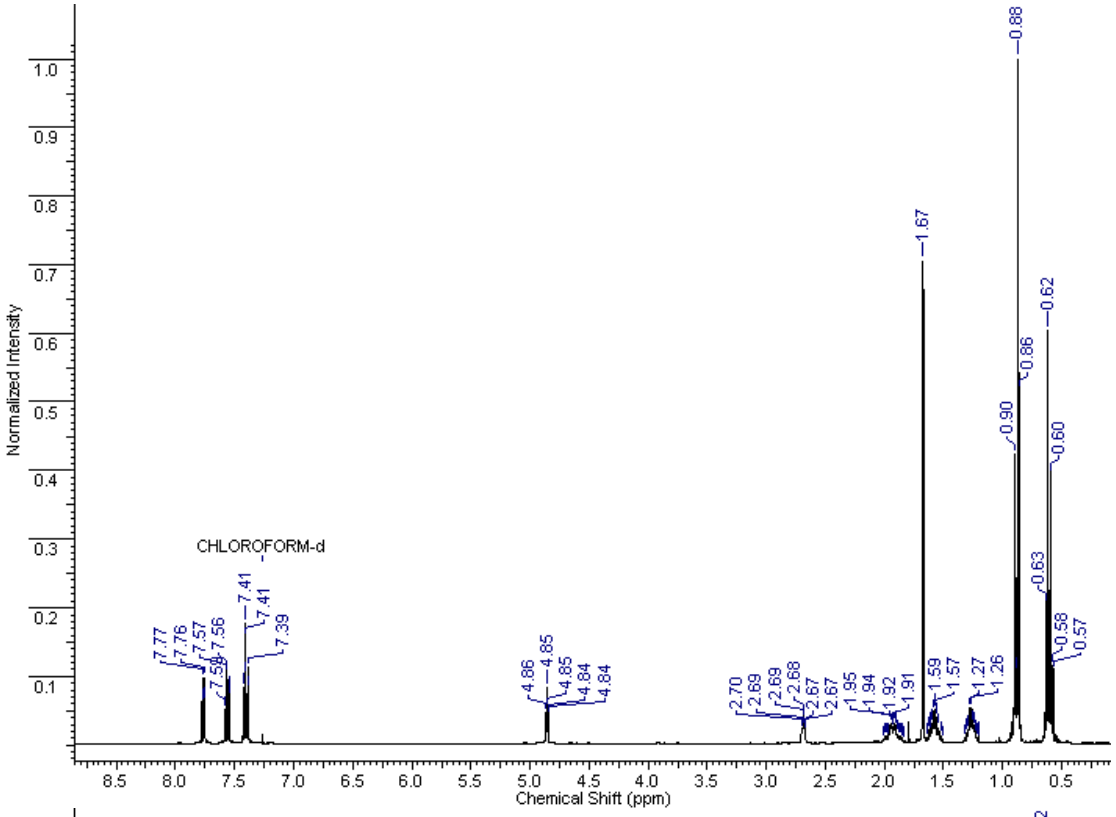
(3c)

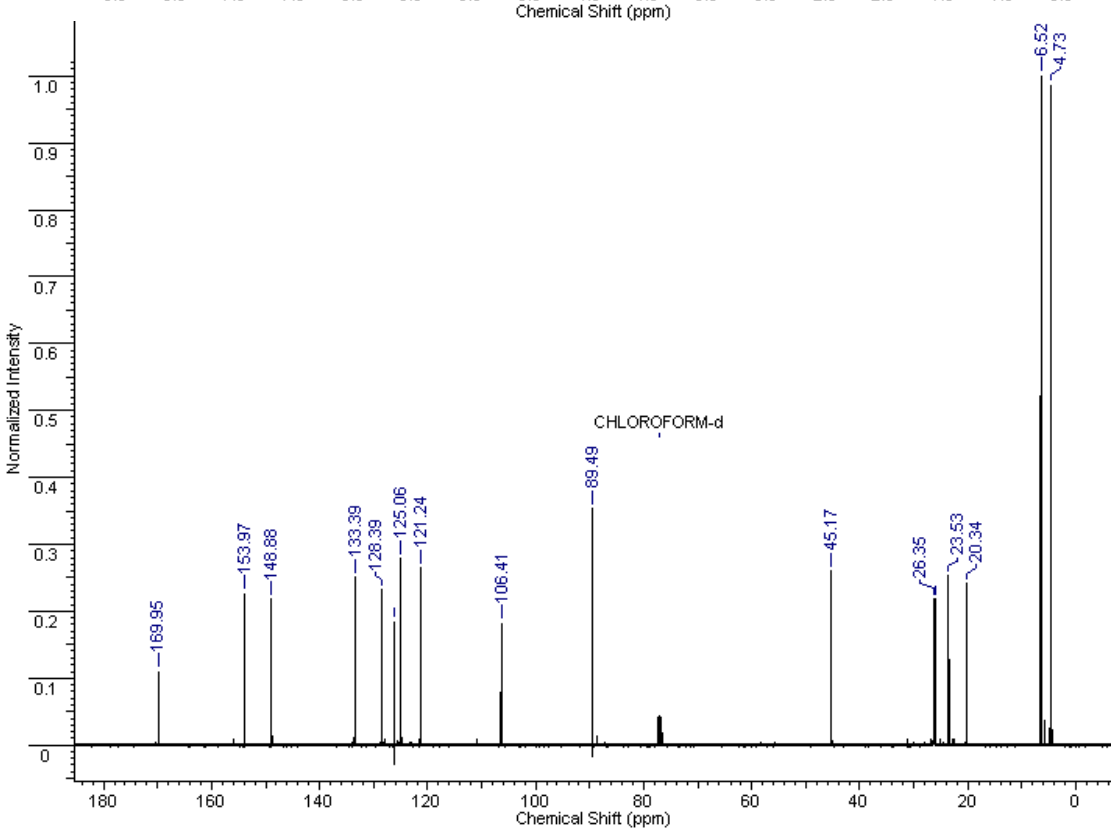

CHLOROFORM-d
7.57
Normalized Intensity
Chemical Shift (ppm)
4.94
4.91
4.91
4.90
4.90
2.66
2.65
2.65
2.64
2.64
1.86
1.86
1.85
1.80
1.74
1.59
1.31
1.29
1.28
0.97
0.95
0.94
1.00
0.71
0.71
0.69
0.68
1.00
0.68
0.66
0.65

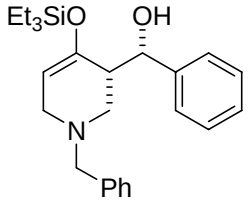

Normalized Intensity
Chemical Shift (ppm)
6.58
4.90
134.23
127.00
CHLOROFORM-d
77.03
150.26
151.72
119.01
110.09
107.29
49.32
28.46
26.37
23.72
21.02


Et3SiO
O
O
Me

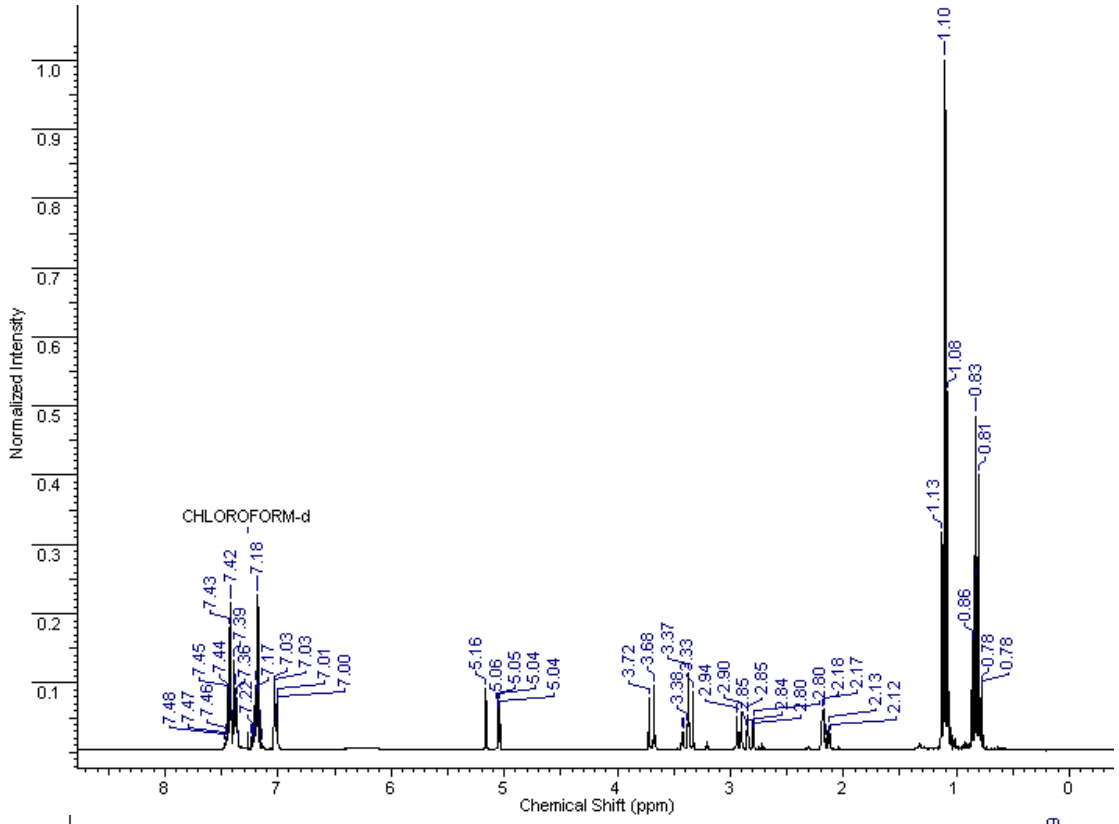
(**3d**)

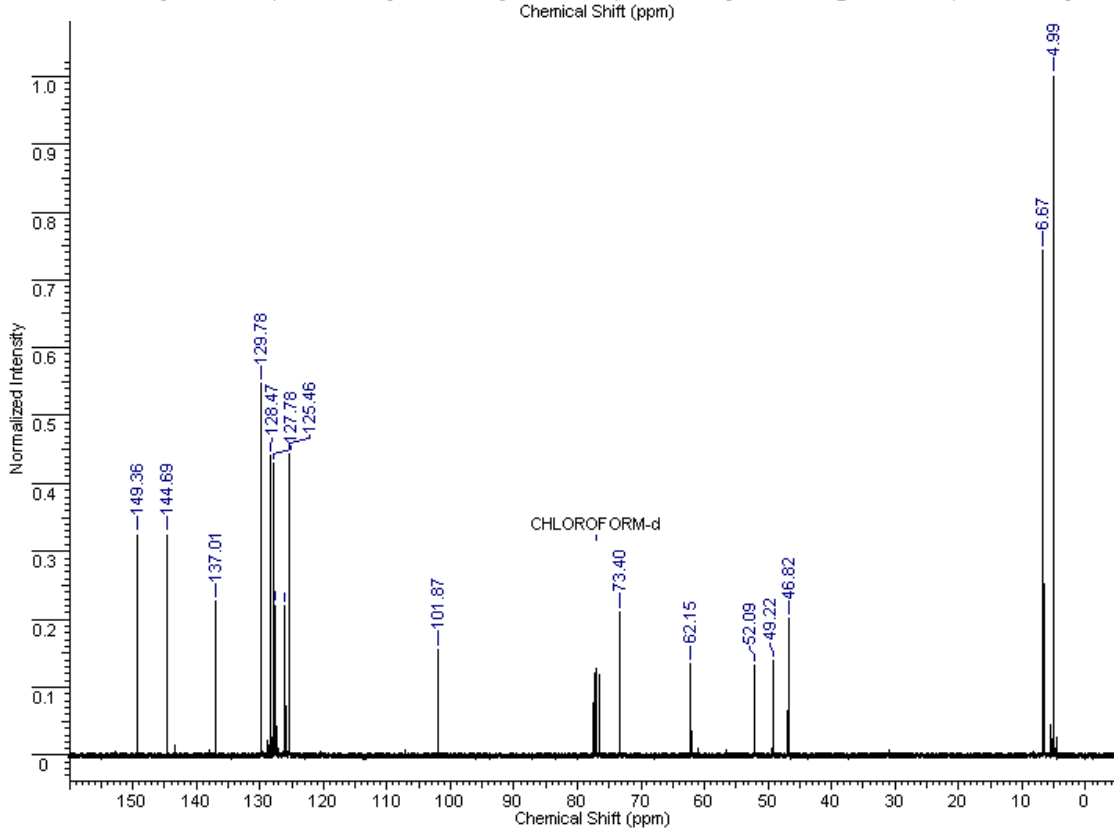

Normalized Intensity
CHLOROFORM-d
7.77
7.76
7.57
7.56
7.41
7.41
7.39
4.86
4.85
4.84
4.84
2.70
2.69
2.69
2.68
2.67
2.67
1.95
1.94
1.92
1.91
1.67
1.59
1.57
1.27
1.26
0.88
0.90
0.86
0.62
0.60
0.63
0.58
0.57
Chemical Shift (ppm)

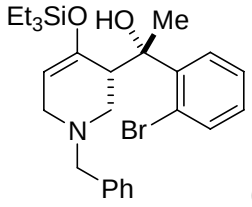

Normalized Intensity
CHLOROFORM-d
169.95
153.97
148.88
133.39
128.39
125.06
121.24
106.41
89.49
45.17
26.35
23.53
20.34
6.52
4.73
Chemical Shift (ppm)


Et3SiO
OH
N
Ph

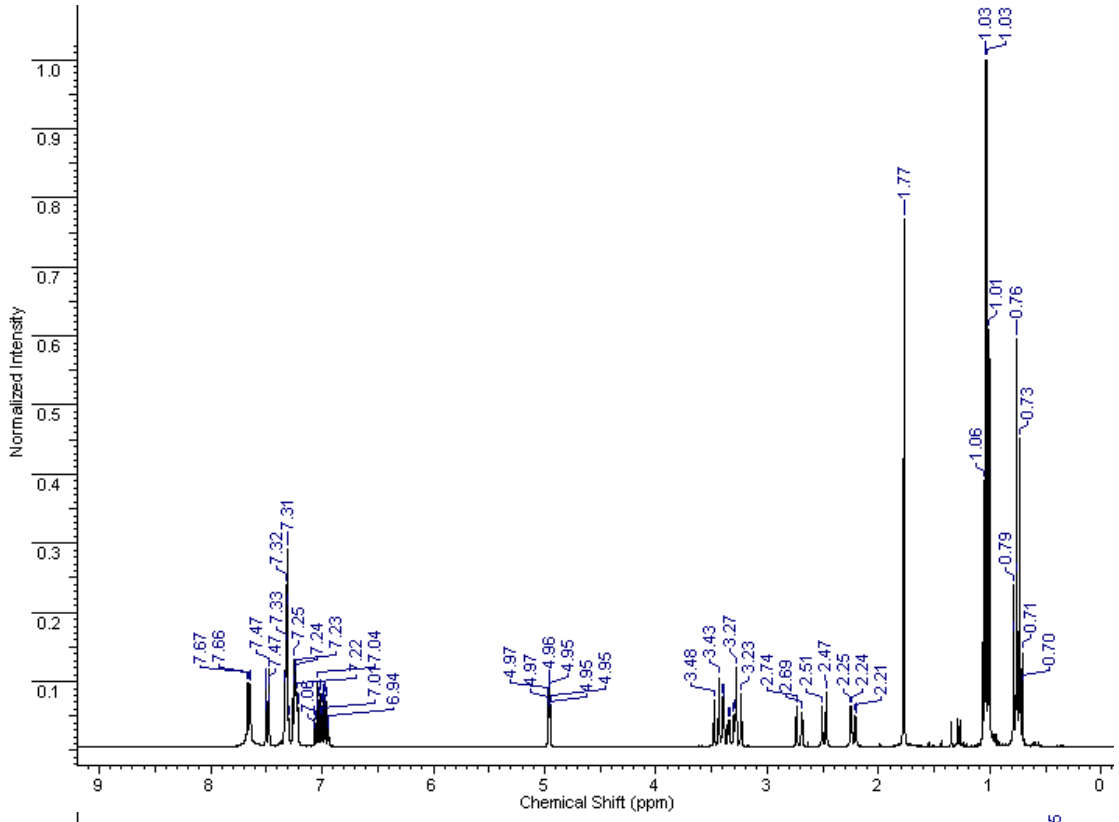
(**3e**)

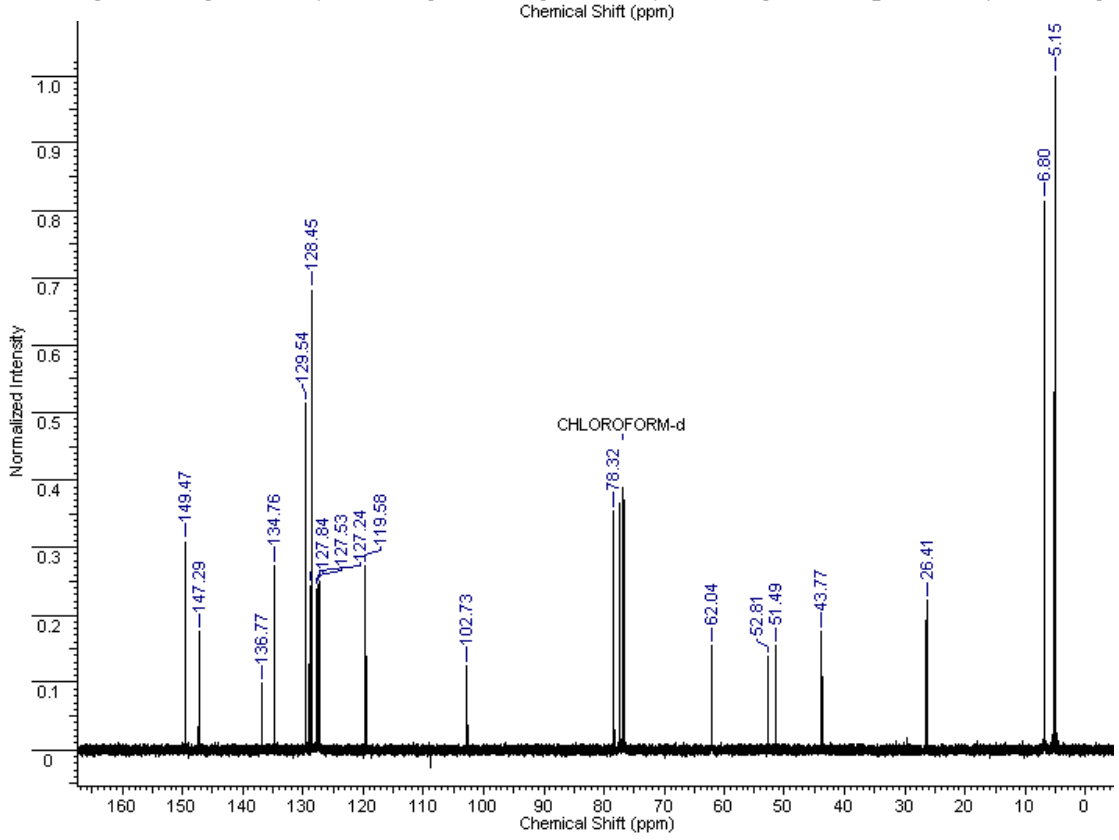

Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
7.48
7.47
7.46
7.45
7.44
7.43
7.42
7.39
7.36
7.27
7.18
7.17
7.03
7.03
7.01
7.00
5.16
5.06
5.05
5.04
5.04
3.72
3.68
3.37
3.33
3.33
2.94
2.90
2.85
2.85
2.84
2.80
2.80
2.18
2.17
2.13
2.12
1.13
1.10
1.08
0.86
0.83
0.81
0.78
0.78

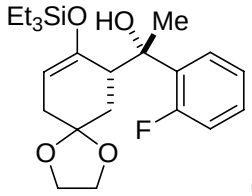

Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
149.36
144.69
137.01
129.78
128.47
127.78
125.46
101.87
73.40
62.15
52.09
49.22
46.82
6.67
4.99


Et3SiO
HO
Me
N
Br
Ph

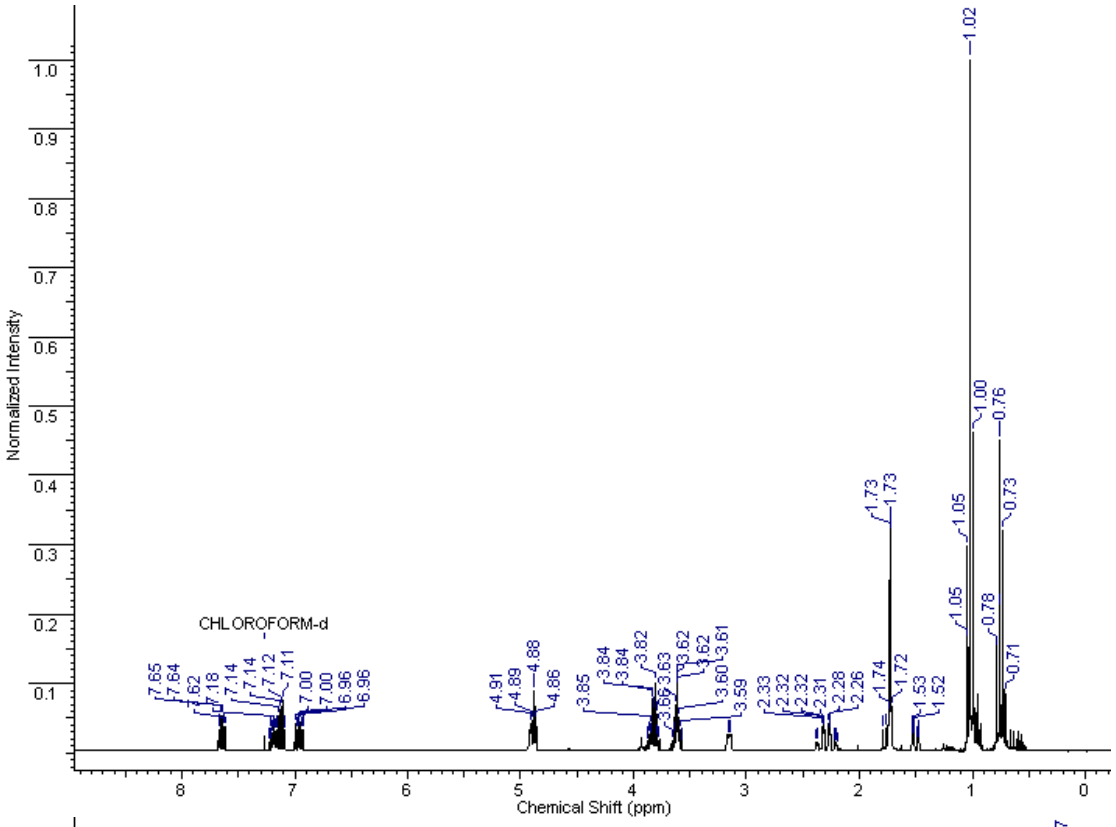
(**3f**)

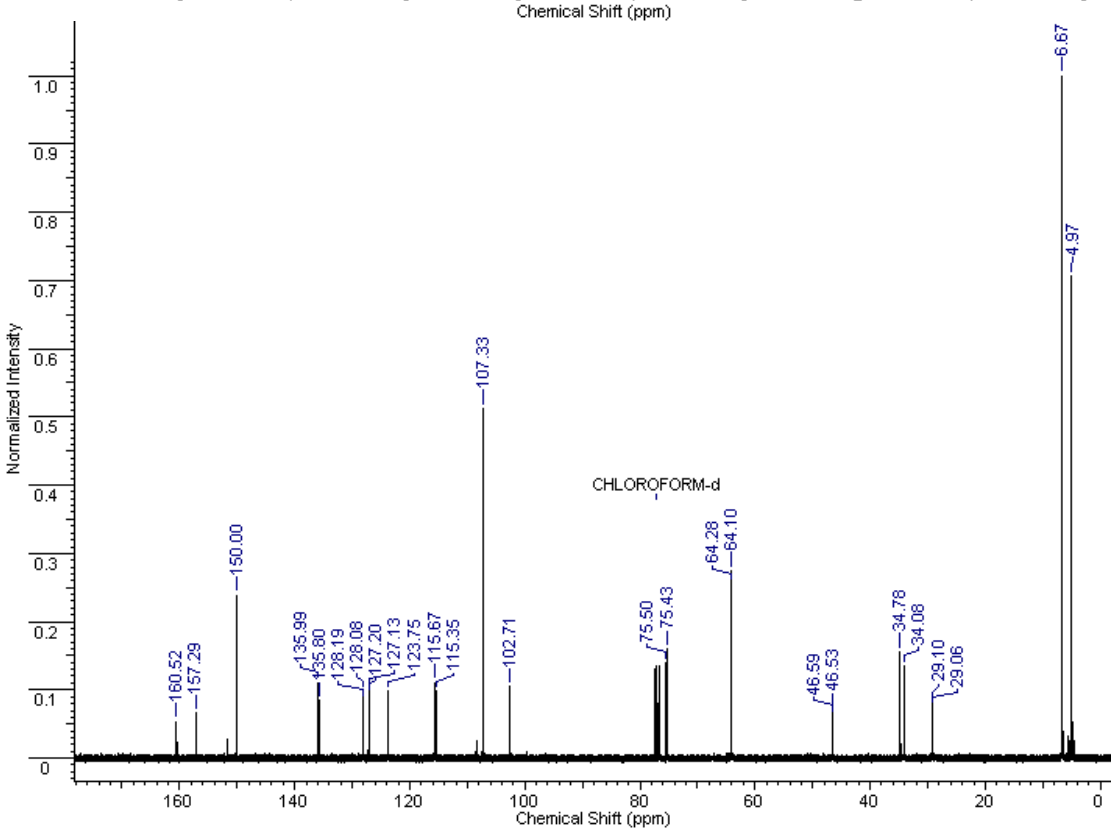

Normalized Intensity
Chemical Shift (ppm)
7.67
7.66
7.47
7.47
7.33
7.32
7.31
7.25
7.24
7.23
7.22
7.04
7.04
6.94
4.97
4.97
4.96
4.95
4.95
4.95
3.48
3.43
3.27
3.23
2.74
2.69
2.51
2.47
2.25
2.24
2.21
1.77
1.03
1.03
1.06
1.01
0.79
0.76
0.73
0.71
0.70

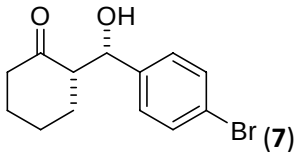

Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
149.47
147.29
136.77
134.76
129.54
128.45
127.84
127.53
127.24
119.58
102.73
78.32
62.04
52.81
51.49
43.77
26.41
6.80
5.15


Et3SiO
HO
Me
F
O
O

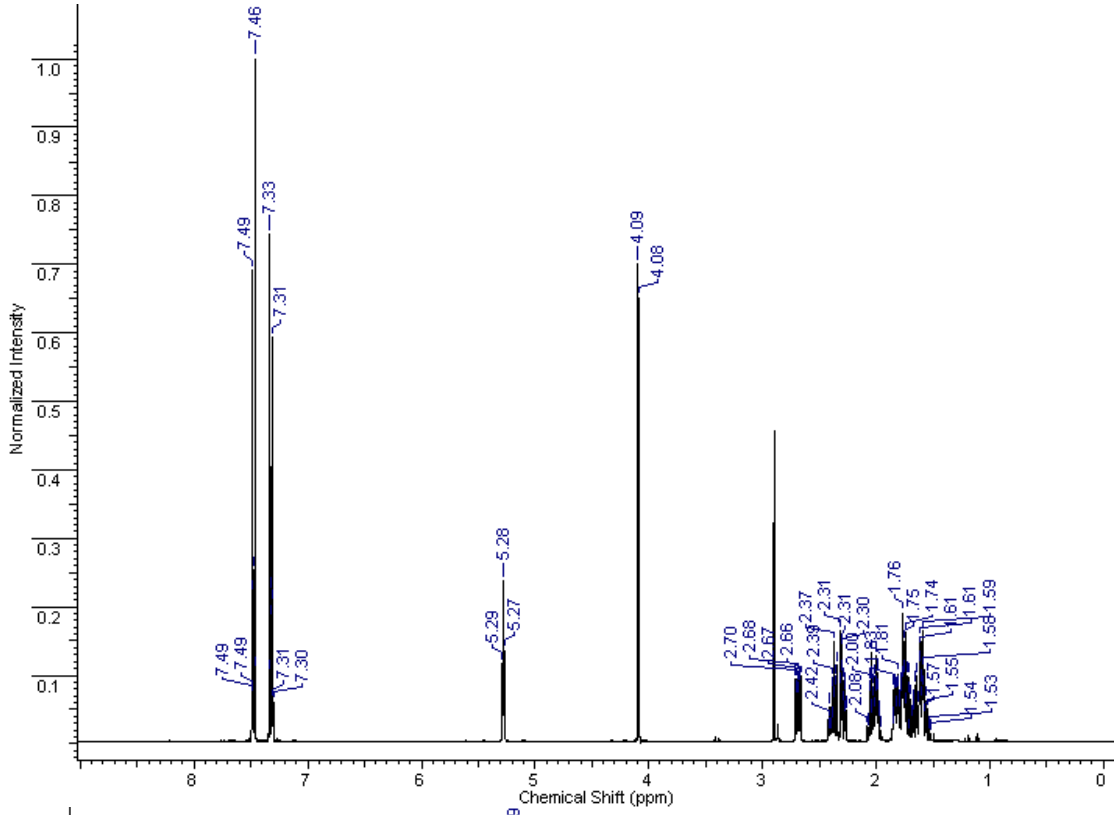
(**3g**)

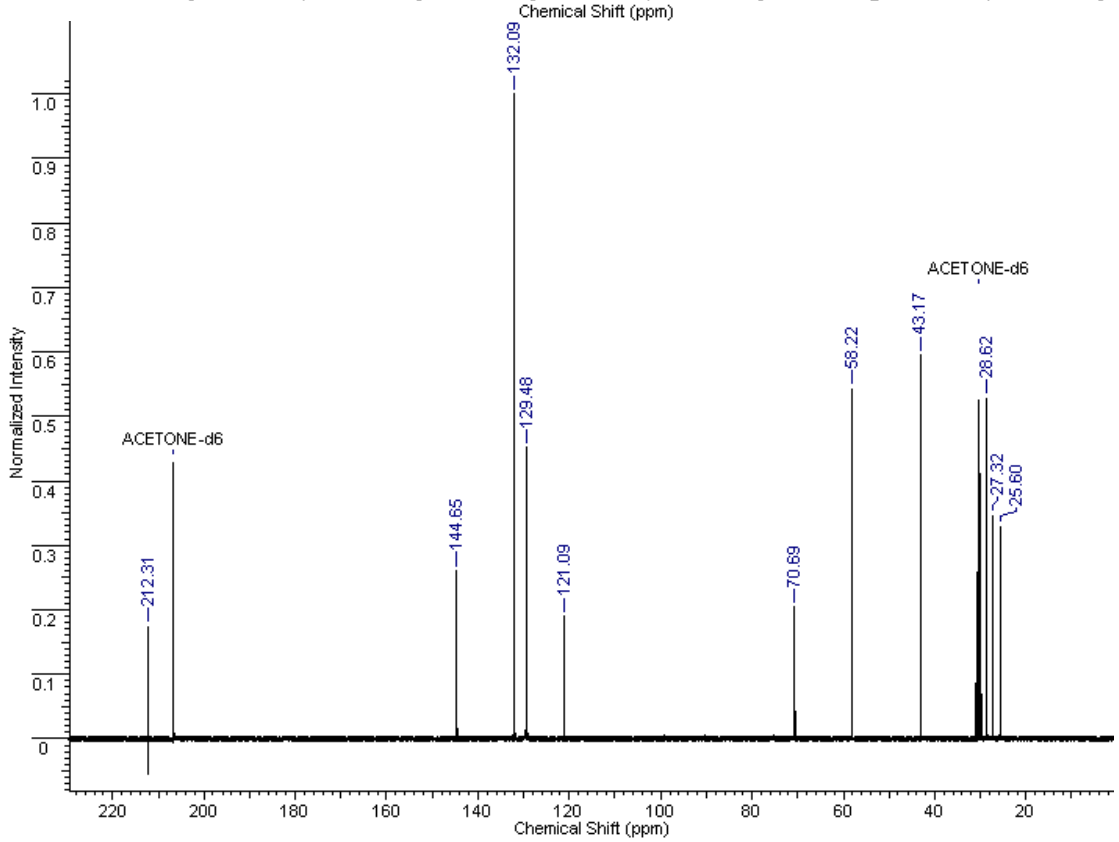

Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
7.65
7.64
7.62
7.18
7.14
7.14
7.12
7.11
7.00
7.00
6.96
6.96
4.91
4.89
4.88
4.86
3.85
3.84
3.84
3.82
3.63
3.62
3.62
3.61
3.60
3.59
2.33
2.32
2.32
2.31
2.28
2.26
1.74
1.73
1.73
1.72
1.53
1.52
1.05
1.05
1.02
1.00
0.78
0.76
0.73
0.71

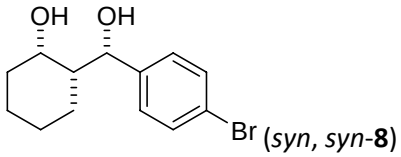

Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
160.52
157.29
150.00
135.99
135.80
128.19
128.08
127.20
127.13
123.75
115.67
115.35
107.33
102.71
77.50
77.43
75.50
75.43
64.28
64.10
46.59
46.53
34.78
34.08
29.10
29.06
6.67
4.97


O
OH
Br

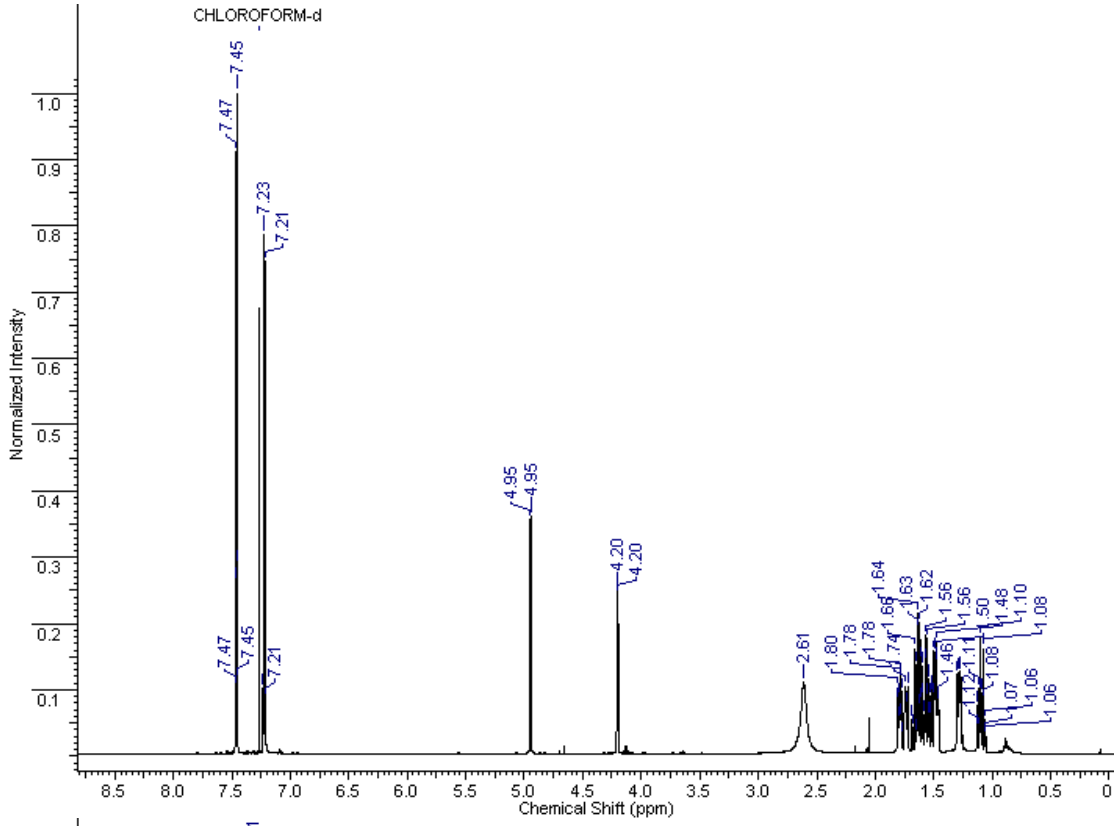
(**7**)

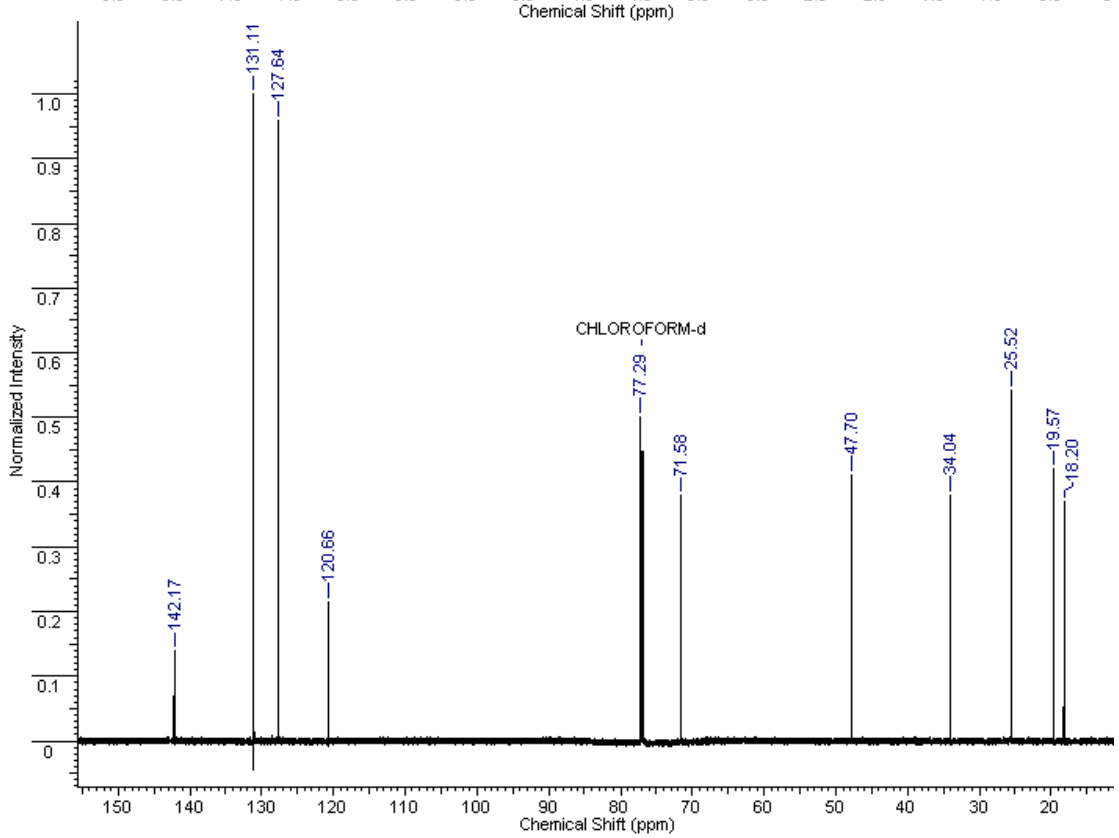

Normalized Intensity
Chemical Shift (ppm)
7.46
7.49
7.33
7.31
4.09
4.08
5.28
5.29
5.27
7.49
7.49
7.31
7.30
2.70
2.68
2.67
2.66
2.42
2.39
2.37
2.31
2.31
2.30
2.08
2.06
1.81
1.76
1.75
1.74
1.61
1.61
1.59
1.58
1.57
1.55
1.54
1.53

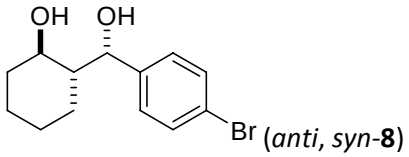

Normalized Intensity
Chemical Shift (ppm)
ACETONE-d6
ACETONE-d6
132.09
129.48
144.65
121.09
212.31
70.69
58.22
43.17
28.62
27.32
25.60


OH
OH
Br

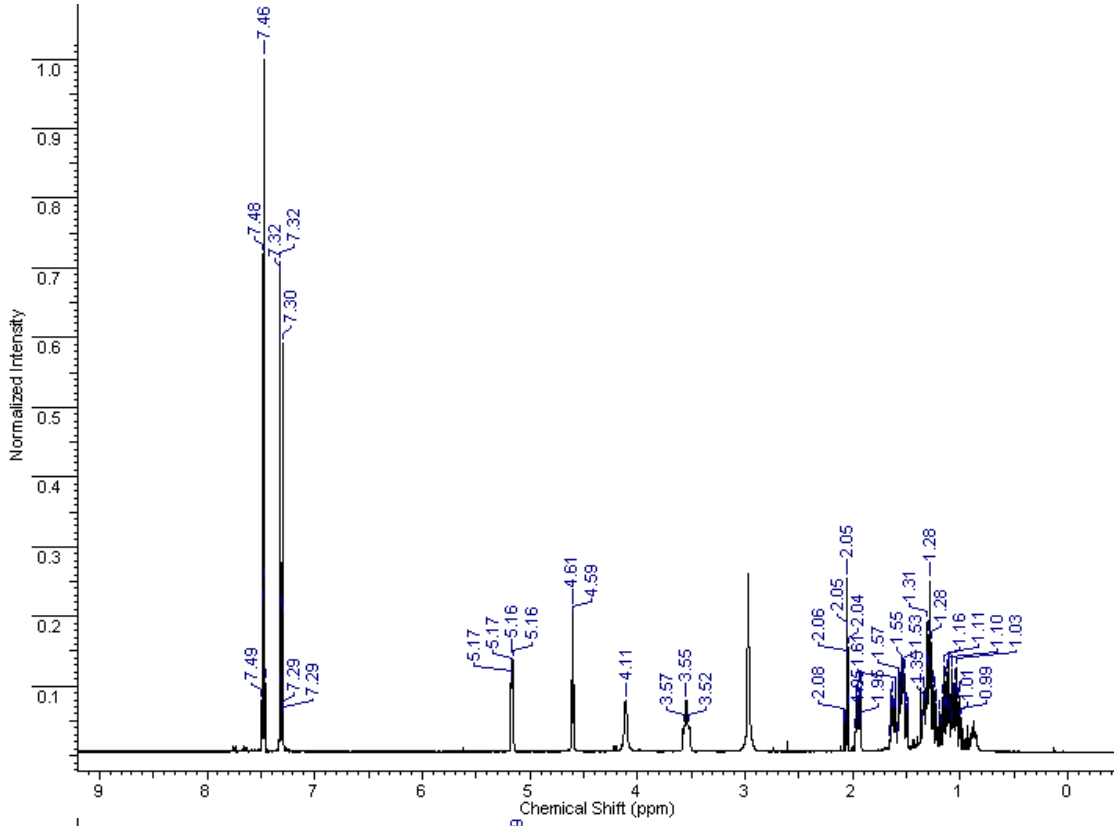
(*syn*, *syn*-**8**)

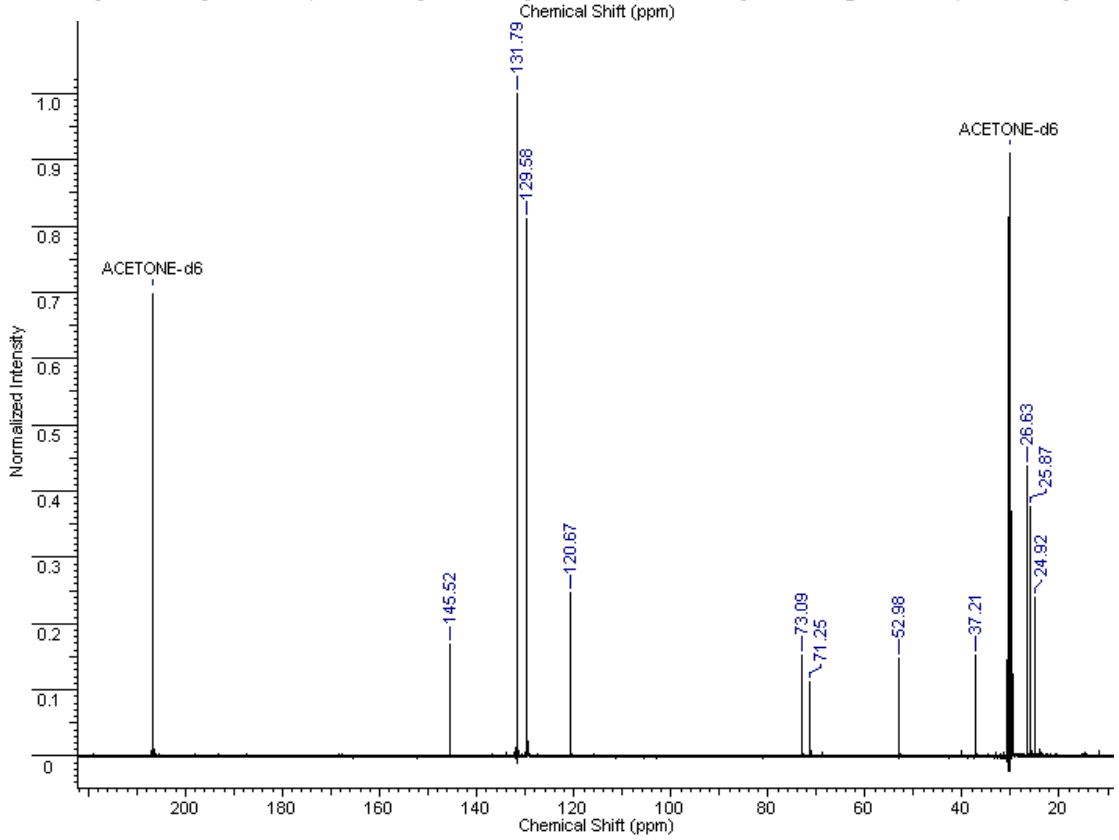

CHLOROFORM-d
7.47
7.45
7.23
7.21
4.95
4.20
2.61
Normalized Intensity
Chemical Shift (ppm)

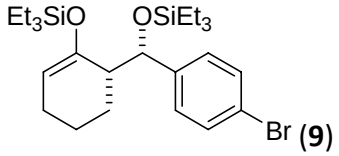

131.11
127.64
120.66
142.17
CHLOROFORM-d
77.29
71.58
47.70
34.04
25.52
19.57
18.20
Normalized Intensity
Chemical Shift (ppm)


OH
OH
Br

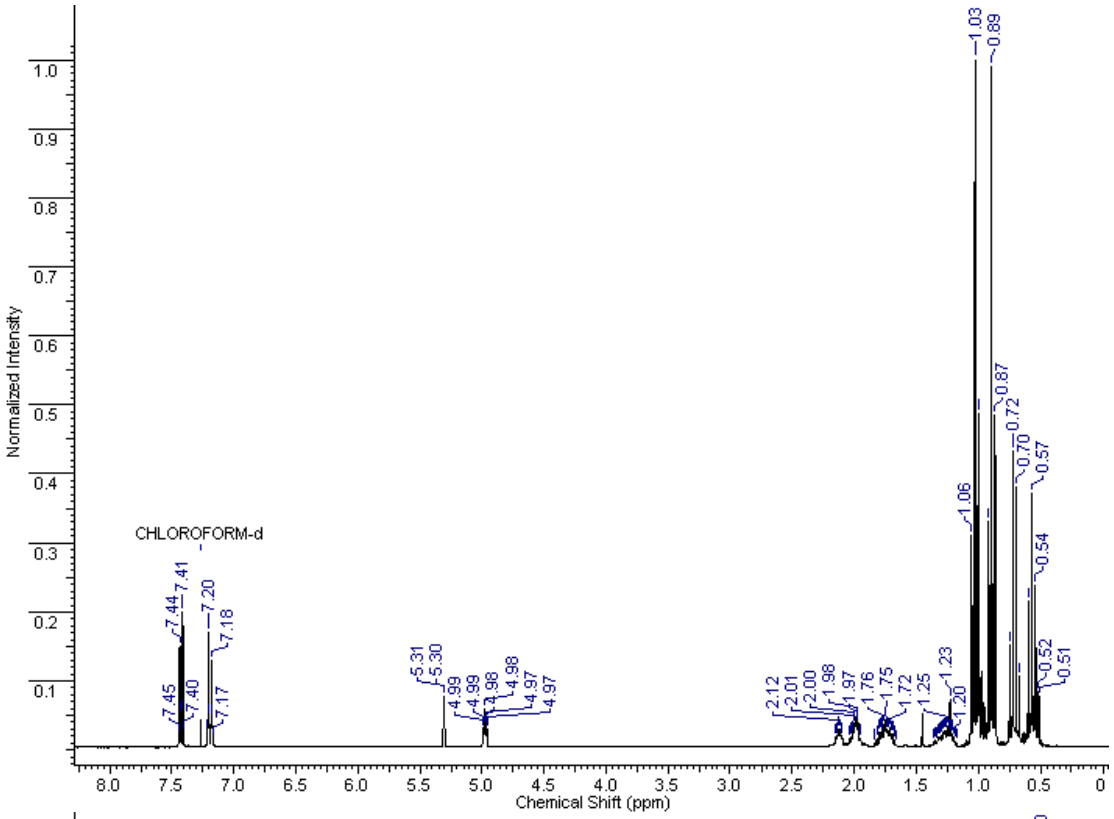
(*anti*, *syn*-**8**)

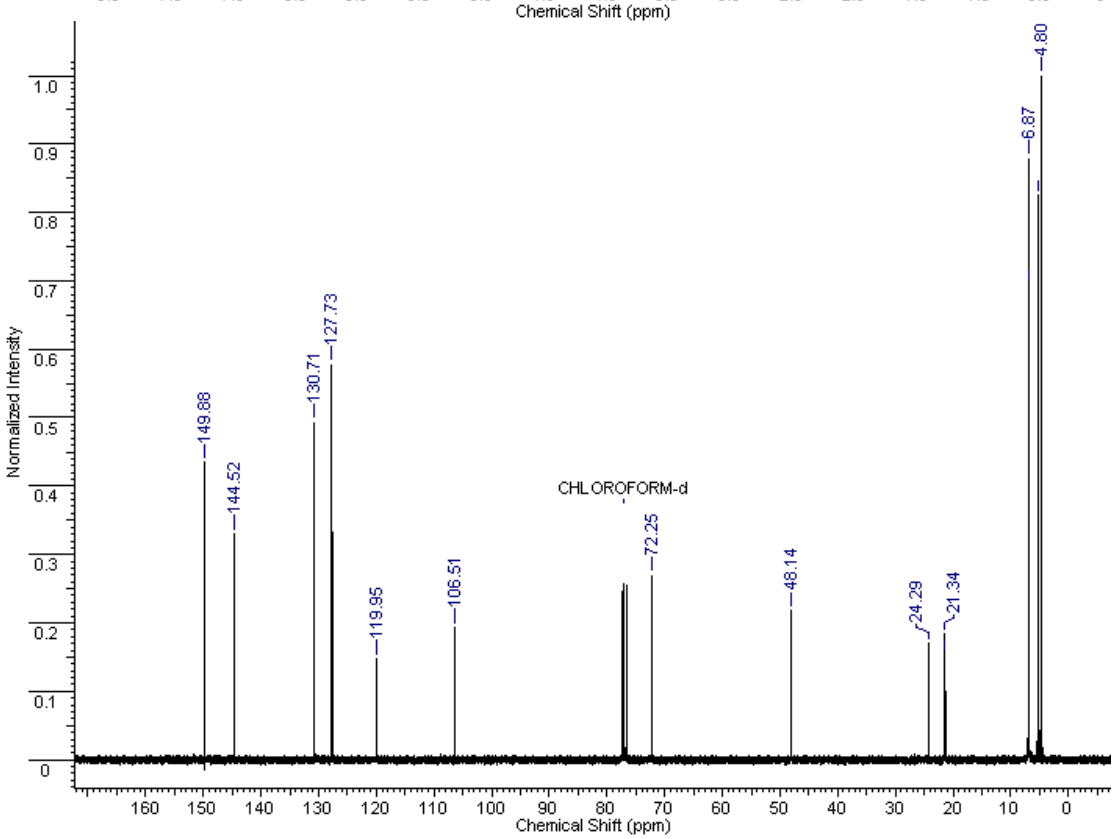

Normalized Intensity
Chemical Shift (ppm)
7.46
7.48
7.32
7.32
7.30
7.49
7.29
7.29
5.17
5.17
5.16
5.16
4.61
4.59
4.11
3.57
3.55
3.52
2.08
2.06
2.05
2.05
2.04
1.96
1.57
1.55
1.53
1.31
1.28
1.28
1.16
1.11
1.10
1.03
1.01
0.99

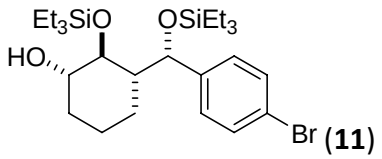

Normalized Intensity
Chemical Shift (ppm)
ACETONE-d6
ACETONE-d6
131.79
129.58
120.67
145.52
73.09
71.25
52.98
37.21
26.63
25.87
24.92


Et3SiO
OSiEt3
Br

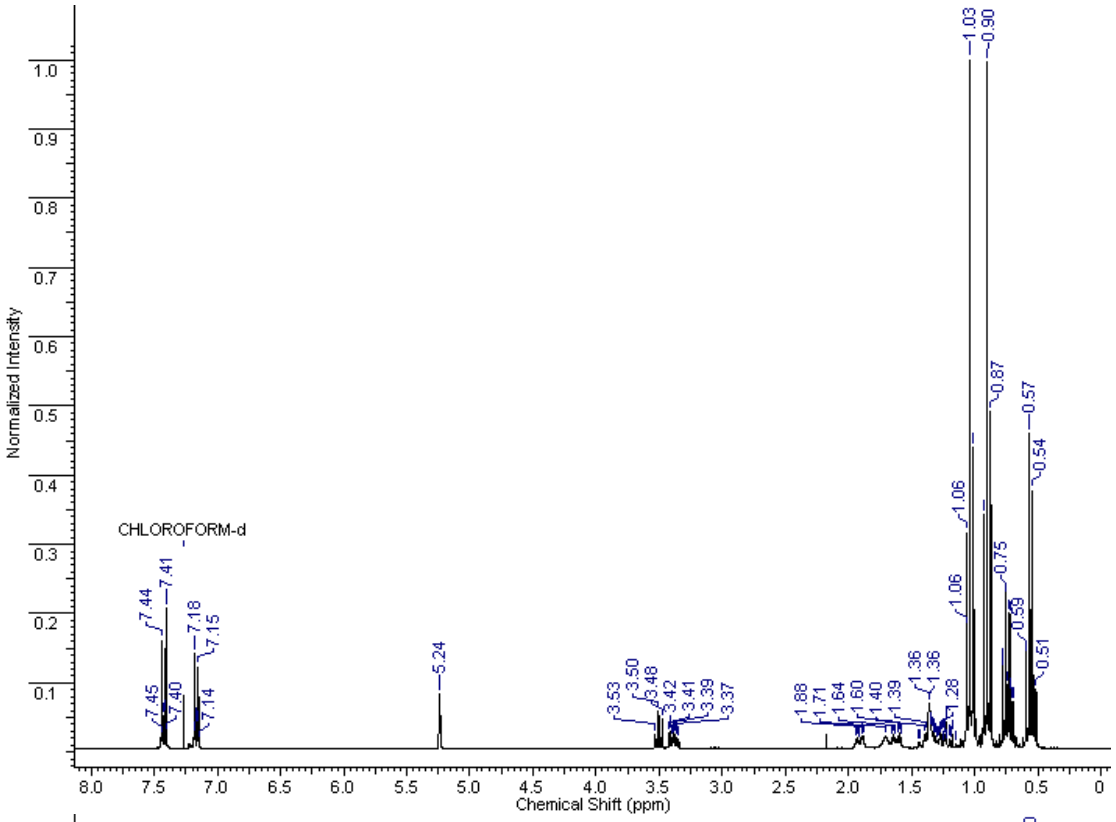
(**9**)

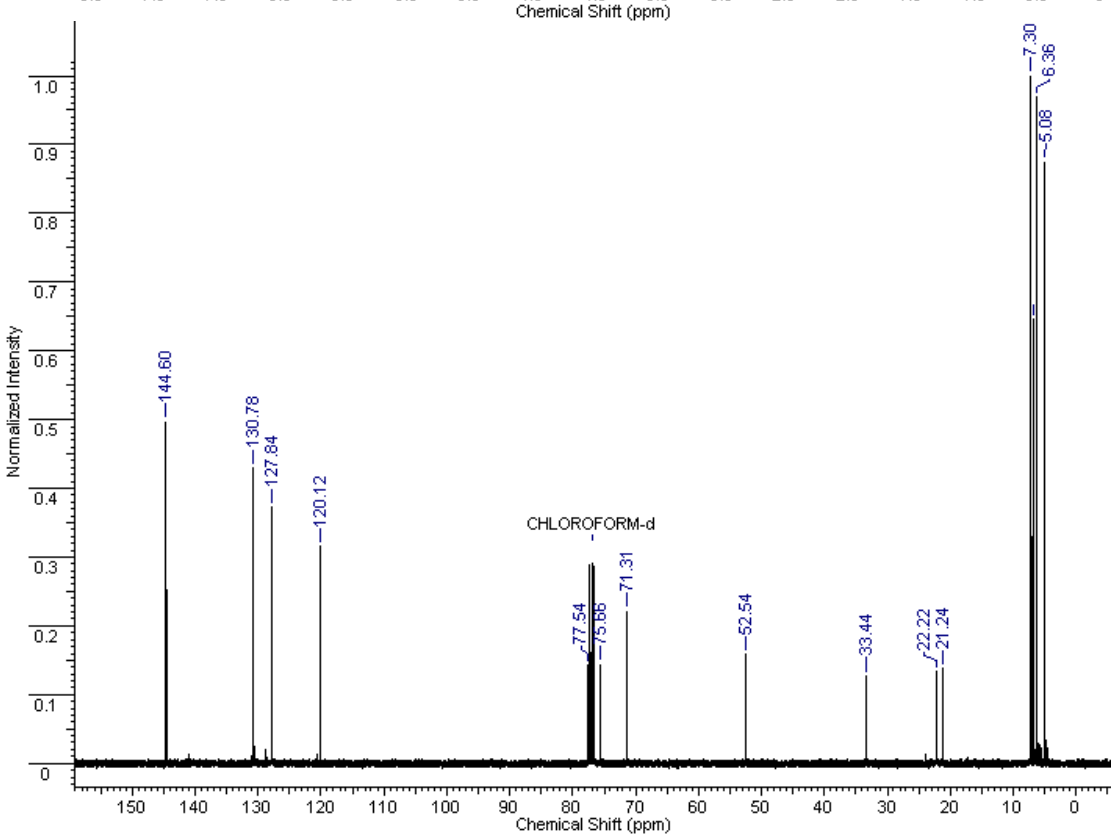

Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
7.45
7.44
7.41
7.40
7.20
7.18
7.17
5.31
5.30
4.99
4.99
4.98
4.98
4.97
4.97
2.12
2.01
2.00
1.98
1.97
1.76
1.75
1.72
1.25
1.23
1.20
1.06
1.03
0.89
0.87
0.72
0.70
0.57
0.54
0.52
0.51

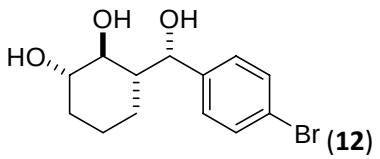

Normalized Intensity
Chemical Shift (ppm)
149.88
144.52
130.71
127.73
119.95
106.51
CHLOROFORM-d
72.25
48.14
24.29
21.34
6.87
4.80


Et3SiO
OSiEt3
HO
Br

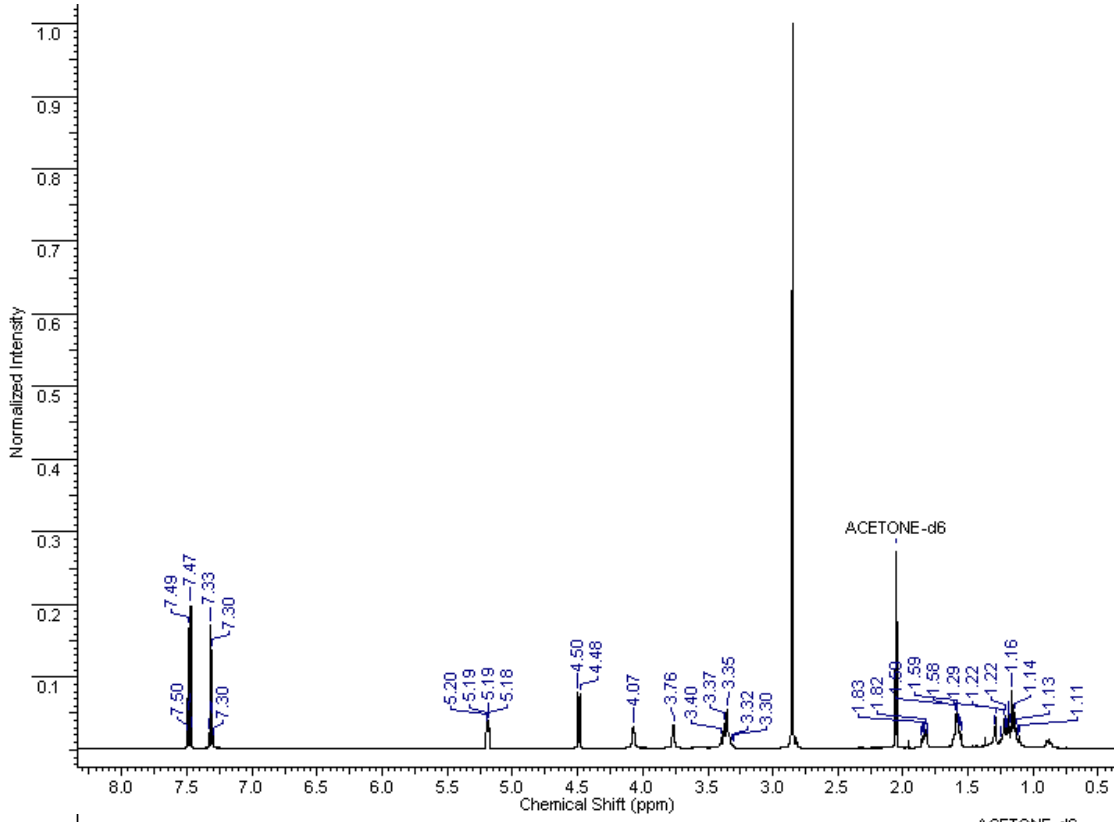
(**11**)

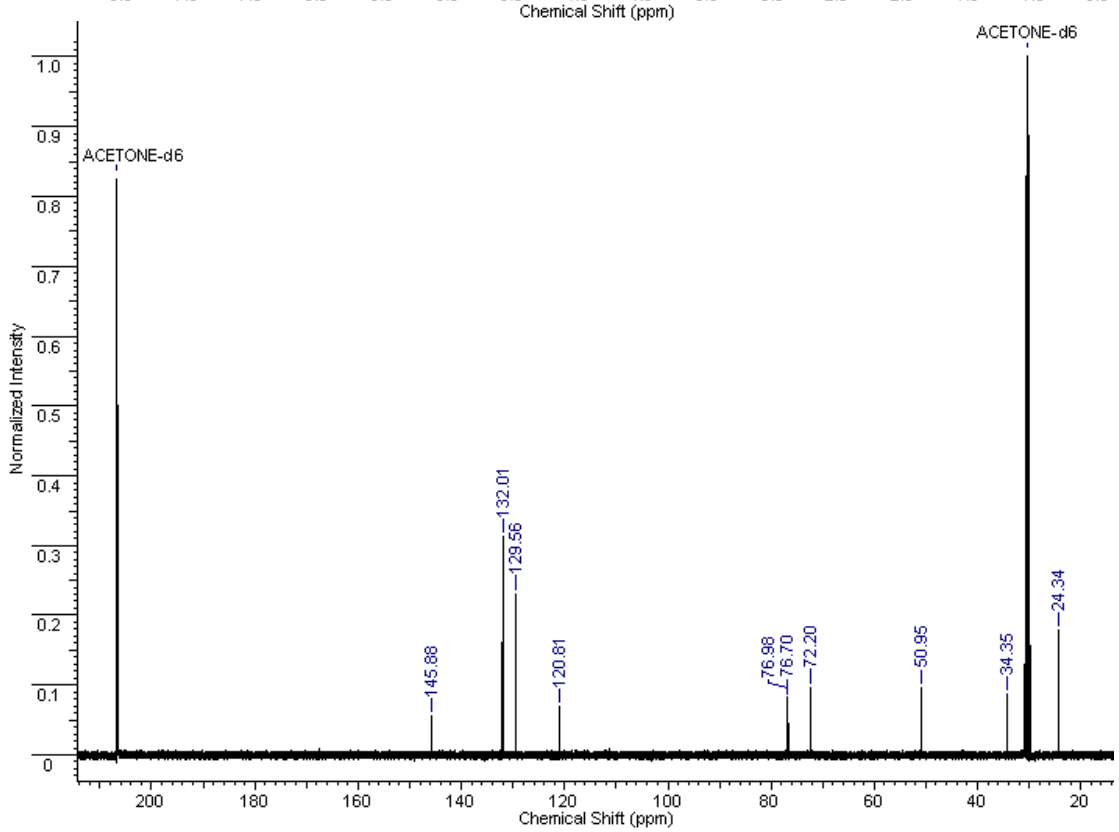

Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
7.45
7.44
7.41
7.40
7.18
7.15
7.14
5.24
3.53
3.50
3.48
3.42
3.41
3.39
3.37
1.88
1.71
1.64
1.60
1.40
1.39
1.36
1.36
1.28
1.06
1.06
1.03
0.90
0.87
0.75
0.59
0.57
0.54
0.51

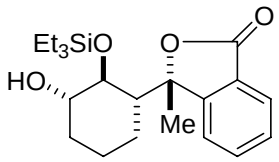

Normalized Intensity
Chemical Shift (ppm)
144.60
130.78
127.84
120.12
CHLOROFORM-d
77.54
75.86
71.31
52.54
33.44
22.22
21.24
7.30
6.36
5.08


OH
OH
HO
Br

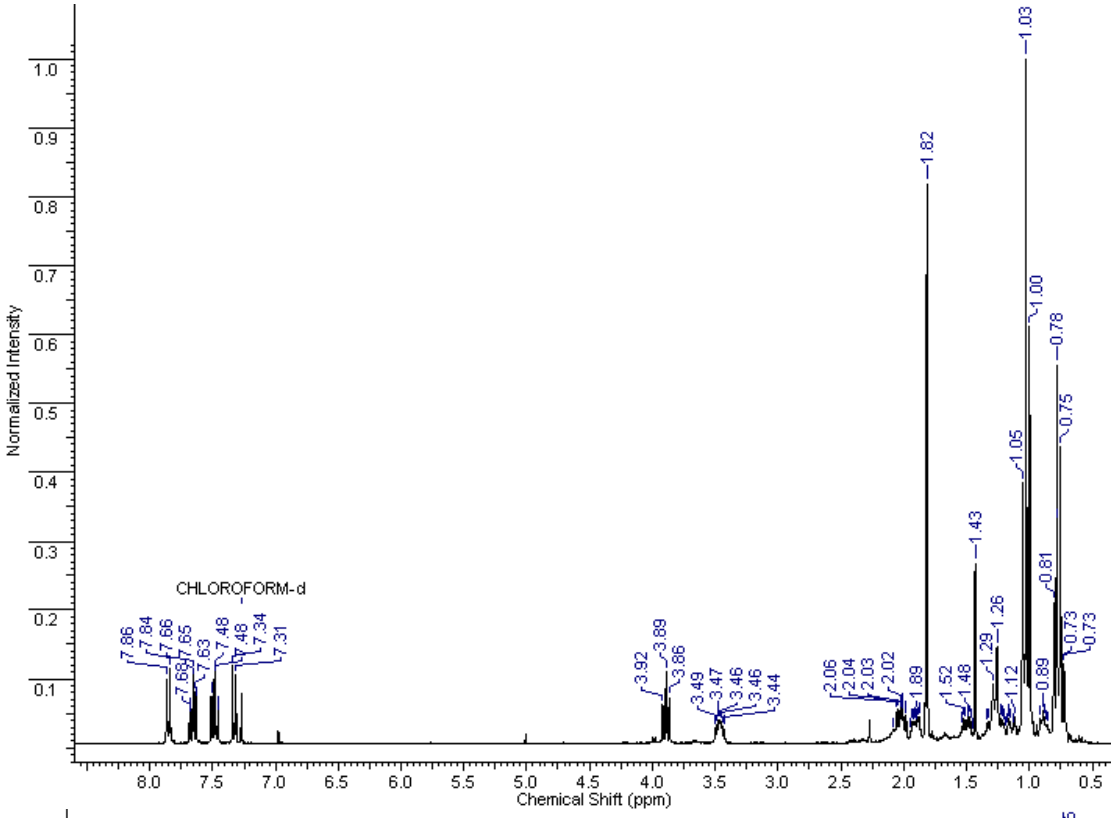
(**12**)

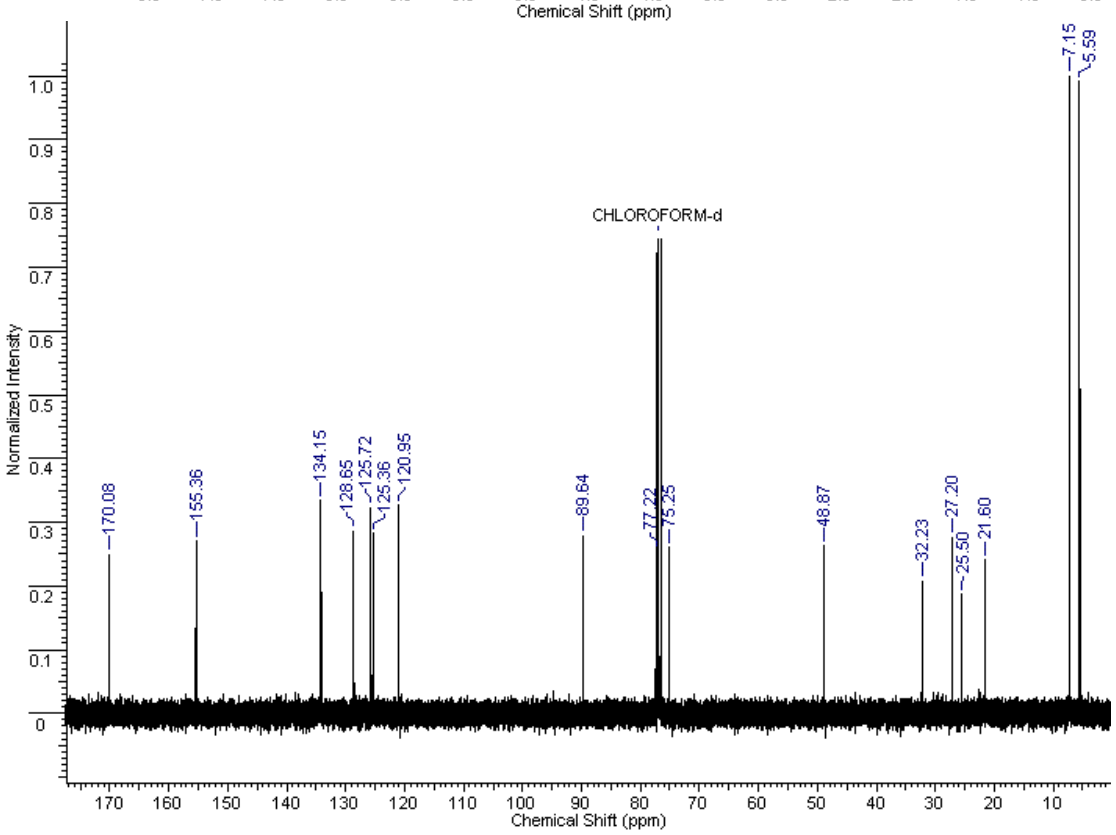

Normalized Intensity
Chemical Shift (ppm)
ACETONE-d6
7.49
7.47
7.33
7.30
7.50
7.30
5.20
5.19
5.19
5.18
4.50
4.48
4.07
3.76
3.40
3.37
3.35
3.32
3.30
1.83
1.82
1.59
1.58
1.29
1.22
1.22
1.16
1.14
1.13
1.11


Normalized Intensity
Chemical Shift (ppm)
ACETONE-d6
ACETONE-d6
145.88
132.01
129.56
120.81
76.98
76.70
72.20
50.95
34.35
24.34


Et3SiO
HO
O
O
Me

(**13**)


Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
7.86
7.84
7.66
7.65
7.63
7.48
7.48
7.34
7.31
3.92
3.89
3.86
3.49
3.47
3.46
3.46
3.44
2.06
2.04
2.03
2.02
1.89
1.52
1.48
1.29
1.26
1.12
1.03
1.82
1.00
0.78
0.75
1.05
1.43
0.81
0.89
0.73
0.73


Normalized Intensity
Chemical Shift (ppm)
CHLOROFORM-d
7.15
5.59
170.08
155.36
134.15
128.65
125.72
125.36
120.95
89.64
77.22
75.25
48.87
32.23
27.20
25.50
21.60