Gold(I)-Catalyzed Cascade Cyclization of Allenyl Epoxides

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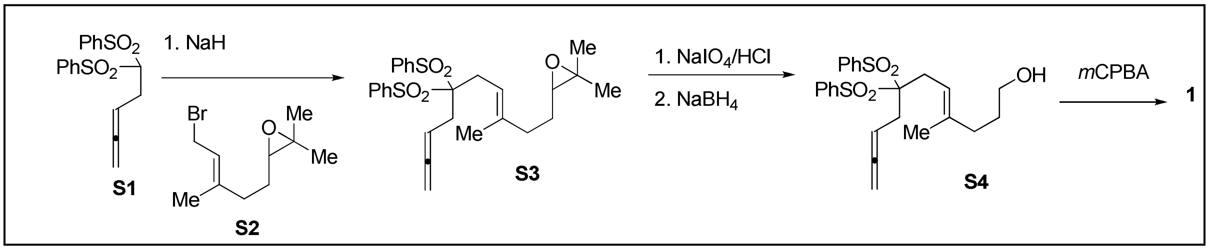
Supporting Information

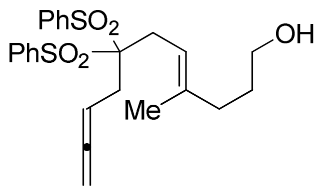
I. General Information: All reactions with air- and water-sensitive compounds were performed in an inert atmosphere drybox or using Schlenk techniques under N_2 with glassware flame-dried under vacuum. Tetrahydrofuran was purified by distillation from sodium benzophenone ketyl. Anhydrous dichloromethane and ether were dried using alumina-packed solvent purification columns under a positive flow of Ar gas. Most commercial organic reagents could be purified by vacuum transfer or distillation prior to use when necessary. Silica flash chromatography was performed with 60Å Silicycle silica gel. All organometallic stocks were titrated[1] prior to use. Spectra are calibrated to residual solvent protons ($CDCl_3$ = 7.24 ppm, C_6D_6 = 7.15 ppm) High resolution mass spectra (HRMS) were obtained from the University of Illinois Mass Spectrometry lab (Dr. Furong Sun), and are reported as sodium (M + 22.989), potassium (M + 39.098) or protonated (M + 1.008) adducts.

[1] Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64*, 3755-3756.

II. Experimental Data

A) Synthesis of Substrate **1** and product **2a, 2b**





Allenyl sulfone **S4**: To a suspension of sodium hydride (60% in mineral oil, 1.2 eq.) in THF was added slowly at room temperature (1,2-Butadienyl)-bis(phenylsulfonyl)methane[2] **S1** (1.0 eq.) The suspension was stirred for 10 minutes, at which point it became a light yellow solution. Geranyl bromide monoepoxide[3] **S2** (1.5 eq.) was added in 10 mL THF, and the resulting suspension was stirred for 12 h at rt. Water was added, and the layers separated. The aqueous residue was extracted 3x with 10 mL diethyl ether. The combined organic layers were washed with water, brine, and dried over $MgSO_4$, and concentrated to crude epoxide **S3.**

Crude epoxide **S3** was taken up in 10:1 THF / H_2O, treated with $NaIO_4$ (1.5 eq.) in one portion, followed by 5 drops of concentrated HCl. The light yellow solution becomes a white suspension formed within 10 minutes. After 1.5 h, the reaction is neutralized with $Na_2S_2O_3$ and $NaHCO_3$, partitioned, the aqueous layer extracted 3x with

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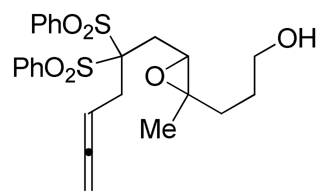
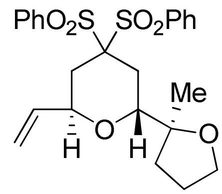
[2] Shu, W.; Jia, G.; Ma, S. *Org. Lett*. **2009**, *11*, 117.
[3] (a) Neighbors, J. D.; Mente, N. R.; Boss, K. D.; Zehnder, D. W. II, Wiemer, D. F. *Tetrahedron Lett.* **2008**, *49,* 516. (b) Zhu, X.; Ganesan, A. *J. Org. Chem.* **2002,** *67,* 2705.

diethyl ether, and the combined organic layers washed with bicarbonate and brine. After drying over $MgSO_4$, filtering, and concentrating, a light yellow oil results.

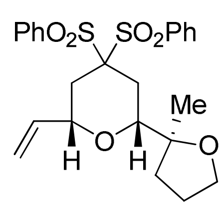
The crude oil from periodate cleavage is dissolved in MeOH, and cooled to -10 ^{o}C in brine / ice bath. $NaBH_4$ is added in portions over 10 minutes, resulting in a bubbling suspension. After 30 minutes, the reaction is warmed slowly to RT, and stirred for an additional 20 minutes. The reaction is diluted with 20 mL Et_2O, 10 mL of NH_4Cl solution is added (slowly!) and the aqueous layer extracted 3x with diethyl ether. Washes of water (10 mL) and brine (10 mL) are followed by drying over $MgSO_4$ and evaporation. Column chromatography on silica gel yields alcohol **S4** as a colorless, viscous oil, 41% (3 steps).



4*E*-7,7'-bis(phenylsulfonyl)-4-epoxy-4-methyl-9,10-dien-1-ol (1): Treatment of alcohol **S4** with *m*CPBA under standard conditions afforded substrate **1** as a hygroscopic white foam: ^{1}H (400 MHz, $CDCl_3$): δ 8.06 (d, 4H), 7.74 (q, 2H), 7.57 (m, 4H), 5.31 (m, 1H), 4.77 (m, 2H), 3.64 (m, 2H), 3.29 (t, 1H), 3.08 (m, 2H), 2.63 (dd, 1H, J_1 = 16 Hz, J_2 = 4.8 Hz), 2.30 (dd, 1H, J_1 = 16 Hz, J_2 = 4.4 Hz), 1.72-1.58 (m, 5H), 1.24 (s, 3H); ^{13}C (100 MHz, $CDCl_3$): 210.4, 136.6, 136.4, 131.5, 131.4, 128.8, 128.7, 89.7, 83.4, 76.0, 62.4, 61.6, 57.9, 34.5, 30.1, 29.8, 27.6, 16.8; HRMS (TOF MS ES+): Calculated for ($C_{24}H_{28}O_6S_2$ + Na) 499.1211, found 499.1225.

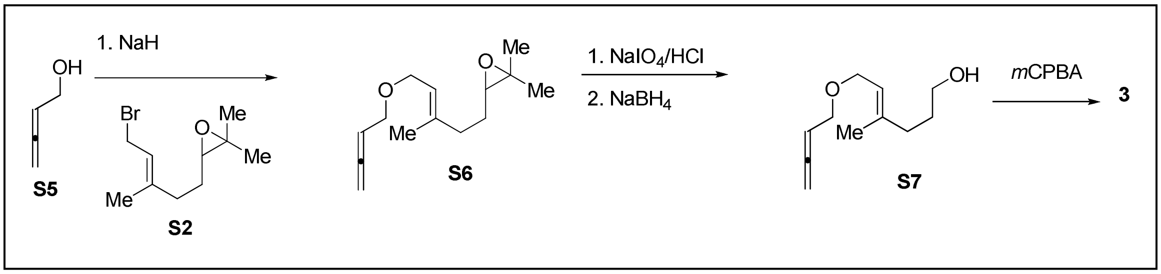


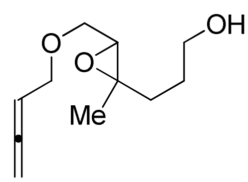
(2*R*,6*S*)-2-((*S*)-2-methyltetrahydrofuran-2-yl)-6-vinyl-4,4'-bis(phenylsulfonyl)-tetrahydropyran (major-2a): Prepared following Representative Procedure for Cyclization : To a 20 mL scintillation vial preloaded with 2.3 mg AgOTf (0.05 equiv.) and 4.6 mg $(PhO)_3PAuCl$ (0.05 equiv.) as white solids is added 1.0 mL of dichloromethane. A white-grey suspension forms within 5 min. 56 mg of **1** is added by pipette, and the pipette tip washed with 0.3 mL fresh DCM into the reaction. Conversion is monitored by TLC. After 15-30 min., the reaction is loaded directly onto a silica column and eluted with EtOAc/hexanes to obtain **2a** as a white foam. ^{1}H (400 MHz, $CDCl_3$): 8.06 (d, 2H), 7.99 (d, 2H), 7.73 (q, 2H), 7.61 (m, 4H), 5.75 (m, 1H), 5.29 (d, 1H), 5.17 (d, 1H), 4.68 (m, 1H), 4.02 (dd, 1H), 3.85 (m, 2H), 2.29 (m, 3H), 2.15 (dd, 1H), 1.94 (m, 2H), 1.66 (m, 1H), 1.14 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 137.9, 134.8, 134.7, 131.6, 131.5, 128.8, 128.7, 128.64, 128.56, 115.9, 83.7, 73.52, 73.48, 70.5, 68.2, 35.5, 31.1, 26.3, 25.8, 20.8; HRMS (ESI) for $C_{24}H_{28}NaO_6S_2$ [M +Na] calc 499.1225, found 499.1207.



(2*R*,6*R*)-2-((*S*)-2-methyltetrahydrofuran-2-yl)-6-vinyl-4,4'-bis(phenylsulfonyl)-tetrahydropyran (minor-2b): White foam. ^{1}H (400 MHz, C_6D_6): 8.30 (m, 2H), 8.09 (d, 2H), 7.12-6.94 (m, 6H), 5.70 (m, 1H), 5.26 (d, 1H), 5.10 (m, 1H), 4.99 (d, 1H), 4.45 (dd, 1H, J_1 = 11.1 Hz, J_2 = 2.4 Hz), 3.68 (m, 2H), 2.90-2.45 (m, 4H), 2.05 (m, 1H), 1.64-1.50 (m, 4H), 1.21 (s, 3H). DEPT135: CH_3 - 21.41. CH - 137.7, 134.8, 134.6, 131.6, 131.4, 128.7, 128.6, 76.79, 73.52. CH_2 - 116.1, 68.52, 35.56, 31.44, 26.13, 25.55.

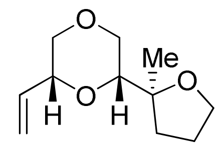
B) Synthesis of Substrate **3** and product **4a, 4b**





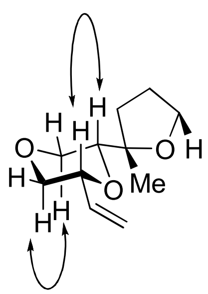
2*E*-epoxy-6-hydroxy-3-methylhexyl 2,3-butadienyl ether (3): Prepared in analogy to **1** (vide supra) by substituting 2,3-butadien-1-ol[4] **S5** for bis-sulfone **S1** (vide supra). Clear oil. ^{1}H (400 MHz, $CDCl_3$): δ 5.19 (p, 1H), 4.76 (m, 2H), 4.03 (m, 2H), 3.59 (m, 3H), 3.52 (dd, 1H), 2.96 (t, 1H), 2.24 (bs, 1H), 1.62 (m, 4H), 1.25 (s, 3H). ^{13}C (166 MHz): 209.4, 87.4, 75.8, 69.0, 68.3, 62.3, 61.2, 60.1, 34.7, 27.8, 16.6 HRMS (TOF MS ES+): Calculated for ($C_{11}H_{18}O_3$ + Na) 221.1157, found 221.1154.

[4] Prepared according to the following procedure: Molander, G. A.; Cormier, E. P. *J. Org. Chem.*, **2005**, *70*, 2622. **IMPORTANT SAFETY NOTE:** 2,3-Butadien-1-ol and its 4-chloro-2-butyn-1-ol precursor were purified by flash chromatography because crude 4-chloro-2-butyn-1-ol was found to decompose uncontrollably and explode upon attempted distillation.

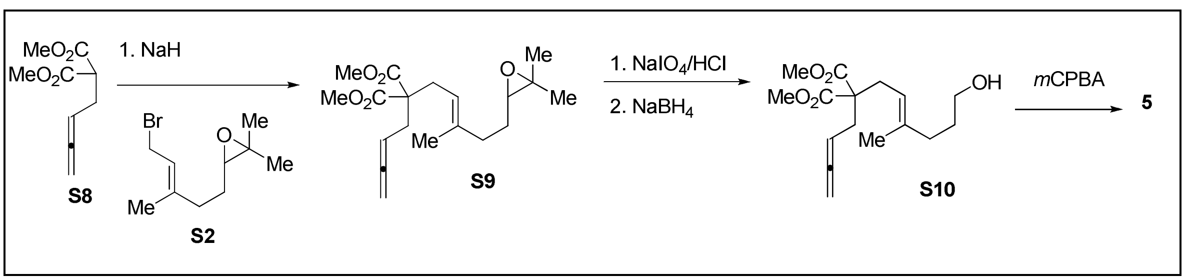


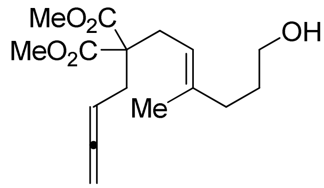
(2*R*,6*S*)-2-((*S*)-2-methyltetrahydrofuran-2-yl)-6-vinyl-1,4-dioxane (4a): Prepared following Representative Procedure. Clear oil. [1]H (300 MHz, $CDCl_3$): 5.69 (m, 1H), 5.31 (dd, 1H, J_1 = 16.8 Hz, J_2 = 1.8 Hz), 5.15 (dt, 1H, J_1 = 10.8 Hz, J_2 = 1.5 Hz), 4.11 (m, 1H), 3.83 (m, 4H), 3.69 (dd, 1H, J_1 = 11.4 Hz, J_2 = 2.7 Hz), 3.51 (dd, 1H, J_1 = 10.2 Hz, J_2 = 2.4 Hz), 3.34 (t, 1H, J = 11.1 Hz), 3.15 (t, 1H, J = 11.1 Hz), 2.06 (m, 1H), 1.87 (m, 2H), 1.59 (m, 1H), 1.16 (s, 3H). [13]C (100 MHz, $CDCl_3$): 134.4, 116.8, 82.54, 79.83, 76.39, 70.42, 68.26, 67.02, 35.30, 25.99, 22.22. MS (ESI) for $C_{11}H_{19}O_3$ [M +H] calc 199.1, found 199.1.

Key NOESY interactions:



C) Synthesis of Substrate **5** and products **6a, 6c**





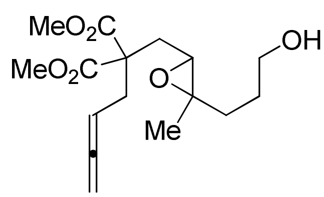
4*E*-7,7'-bis(carbomethoxy)-4-methyl-4,9,10-trien-1-ol (**S10**): To a suspension of sodium hydride (60% in mineral oil, 1.2 eq.) in THF was added slowly at room temperature dimethyl 2-(propa-1,2-dienyl)malonate[5] **S8** (1.0 eq.) The suspension was stirred for 10 minutes, at which point it became a light yellow solution. Geranyl bromide monoepoxide **S2** (1.5 eq.) was added in 10 mL THF, and the resulting suspension was stirred for 12 h at rt. Water was added, and the layers separated. The aqueous residue was extracted 3x with 10 mL diethyl ether. The combined organic layers were washed with water, brine, and dried over $MgSO_4$, and concentrated to crude epoxide **S9** as a dark yellow oil**.**

Crude epoxide **S9** was taken up in 10:1 THF / H_2O, treated with $NaIO_4$ (1.5 eq.) in one portion, followed by 5 drops of concentrated HCl. The light yellow solution becomes a white suspension formed within 10 minutes. After 1.5 h, the reaction is neutralized with $Na_2S_2O_3$ and $NaHCO_3$, partitioned, the aqueous layer extracted 3x with diethyl ether, and the combined organic layers washed with bicarbonate and brine. After drying over $MgSO_4$, filtering, and concentrating, a light yellow oil results. The crude aldehyde is observed by ^1H NMR at 9.74 ppm.

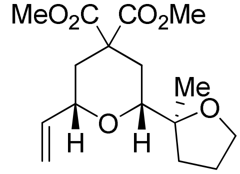
The crude oil from periodate cleavage is dissolved in MeOH, and cooled to -10°C in brine / ice bath. $NaBH_4$ is added in portions over 10 minutes, resulting in a bubbling suspension. After 30 minutes, the reaction is warmed slowly to RT, and stirred for an

[5] Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066

additional 20 minutes. The reaction is diluted with 20 mL Et_2O, 10 mL of NH_4Cl solution is added (slowly!) and the aqueous layer extracted 3x with diethyl ether. Washes of water (10 mL) and brine (10 mL) are followed by drying over $MgSO_4$ and evaporation. Column chromatography on silica gel (1:2 EtOAc / Hex → 1:1) yields alcohol **S10** as a colorless, viscous oil, 41% (3 steps). ^{1}H (400 MHz, $CDCl_3$): δ 4.98 (m, 2H), 4.64 (m, 2H), 3.69 (s, 6H), 3.59 (t, 2H), 2.64 (d, 2H), 2.56 (d, 2H), 2.02 (t, 2H), 1.61 (m, 5H). ^{13}C (166 MHz, $CDCl_3$): 210.0, 171.4, 139.0, 117.9, 84.35, 74.53, 62.41, 57.92, 52.31, 36.18, 32.02, 30.96, 30.69, 16.02.

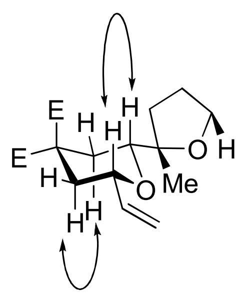


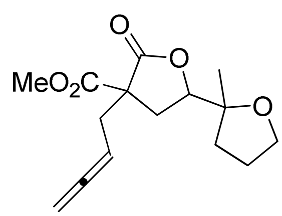
4*E*-7,7'-bis(carbomethoxy)-4-epoxy-4-methyl-9,10-dien-1-ol (5): Treatment of alcohol **S10** with *m*CPBA under standard conditions afforded substrate **5** as a clear oil. ^{1}H (400 MHz, $CDCl_3$): δ 4.91 (m, 1H), 4.59 (m, 2H), 3.67 (s, 3H), 3.66 (s, 3H), 3.53 (t, 2H), 2.71 (dd, 1H), 2.65 (dt, 2H), 2.34 (bs, 1H), 2.23 (dd, 1H), 1.97 (dd, 1H), 1.61-1.48 (m, 4H), 1.18 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 210.1, 171.1, 84.14, 74.77, 62.41, 60.35, 59.31, 56.69, 52.63, 52.51, 34.81, 32.84, 27.81, 16.47. HRMS (ESI) for $C_{16}H_{24}NaO_6$ [M +Na] calc 335.1471, found 335.1463.



(2*R*,6*S*)-2-((*S*)-2-methyltetrahydrofuran-2-yl)-6-vinyl-4,4'-bis(carbomethoxy)-tetrahydropyran (6a): Clear oil upon purification by flash column chromatography, slightly contaminated by triphenylphoshite. ^{1}H (500 MHz, C_6D_6) δ 5.90 (ddd, *J* = 5.0, 10.7, 17.3 Hz, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 4.99 (d, *J* = 10.6 Hz, 1H), 4.21 (m, 1H), 3.69 (m, 2H), 3.56 (dd, *J* = 1.8, 11.8 Hz, 1H), 3.31 (s, 3H), 3.22 (s, 3H), 2.84 (dt, *J* = 2.0, 13.5 Hz, 1H), 2.57 (dt, *J* = 2.2, 13.5 Hz, 1H), 2.00 (dd, *J* = 11.8, 13.4 Hz, 1H), 1.97 (m, 1H), 1.82 (dd, *J* = 11.7, 13.5 Hz, 1H), 1.60-1.50 (m, 2H), 1.45 (m, 1H), 1.24 (s, 3H); ^{13}C NMR (100 MHz) δ 171.7, 171.1, 138.3, 114.8, 83.59, 78.81, 74.38, 68.30, 53.51, 52.83, 52.69, 35.92, 34.65, 30.64, 26.09, 22.26; HRMS (ESI) for $C_{16}H_{24}NaO_6$ [M +Na] calc 335.1471, found 335.1469.

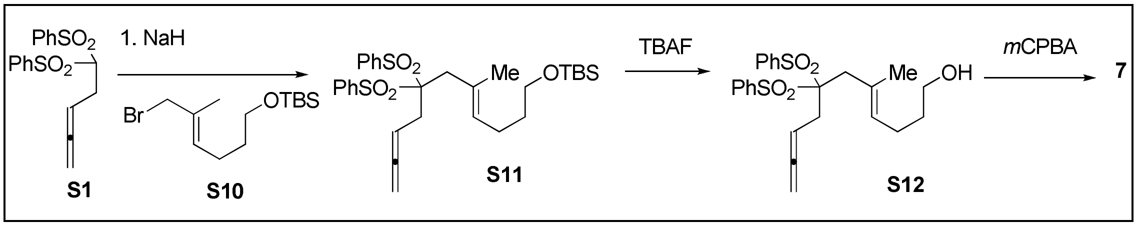
Key NOESY interactions:

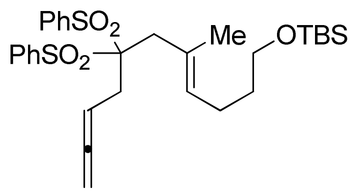




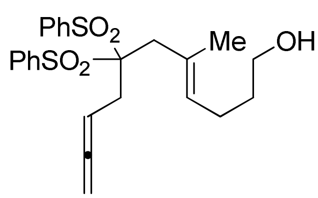
Lactone (6c): Formed under acid or AgOTf catalysis from 5**.** ^{1}H (400 MHz, $CDCl_3$): δ 5.05 (m, 1H), 4.73 (m, 2H), 4.39 (t, 1H), 3.87 (m, 2H), 3.76 (s, 3H), 2.69-2.51 (m, 3H), 2.31 (dd, 1H), 1.94 (m, 3H), 1.72 (m, 1H), 1.21 (s, 3H). GCMS: MW 280.3.

D) Synthesis of substrate **7** and product **8a,b**

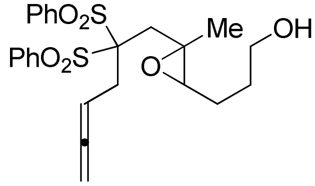




Bis(phenylsulfone) **S11:** Prepared via alkylation of (1,2-butadienyl)bis(phenylsulfonyl) methane **S1** with *(E)-(*6-bromo-5-methylhex-4-enyloxy)(*t*-butyl)dimethylsilane[6] **S10** (NaH, DMF, 50 °C), and used immediately in the subsequent deprotection.

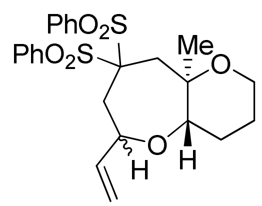


Alcohol **S12**: Deprotection of bis(phenylsulfone) **S11** using TBAF in THF at rt provided the alcohol **S12** as a clear, colorless oil after flash column chromatography (43%, two steps).



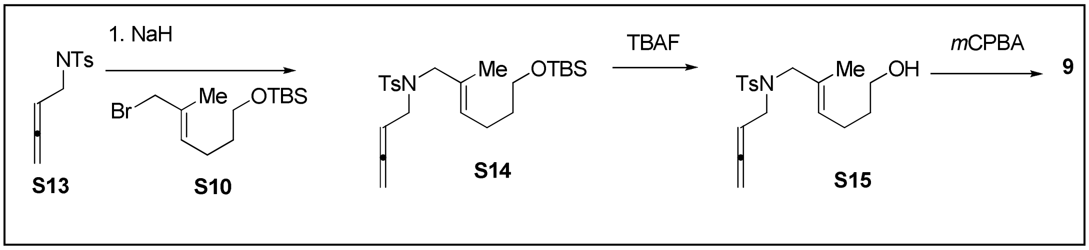
[6] Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962.

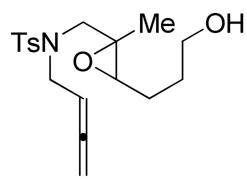
4*E*-7,7'-bis(phenylsulfonyl)-4-epoxy-5-methyl-9,10-dien-1-ol (7): Epoxidation of alcohol **S12** using *m*CPBA under standard conditions provided substrate **7** as an oil: ^{1}H (400 MHz, $CDCl_3$): δ 7.99 (d, 2H), 7.86 (d, 2H), 7.66 (m, 2H), 7.53 (m, 4H), 5.17 (p, 1H), 4.72 (m, 2H), 3.61 (m, 2H), 3.30-3.21 (m, 2H), 3.10 (m, 1H), 2.74 (d, 1H), 2.25 (d, 1H), 1.99 (s, 2H), 1.72 (m, 4H), 1.46 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 210.3, 137.6, 137.0, 134.8, 131.4, 131.35, 128.8. HRMS (TOF MS ES+): Calculated for ($C_{24}H_{28}O_6S_2$ + Na) 499.1211, found 499.1225.



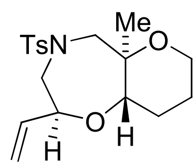
[5.4.0] bis-ether (8a,b): Prepared following Representative Procedure. White foam. ^{1}H (300 MHz, C_6D_6, **8a**): 8.24-8.10 (m, 4H), 7.01 (m, 6H), 5.54 (m, 1H), 4.85 (m, 2H), 3.48 (d, 1H, *J* = 16.8 Hz), 3.31 (t, 2H), 2.72 (d, 1H), 2.57 (d, 1H, *J* = 16.2 Hz), 2.35 (t, 1H), 2.28 (t, 1H), 1.69 (m, 2H), 1.16 (s, 3H); ^{13}C (125 MHz, C_6D_6, **8a**): 137.7, 136.4, 135.8, 134.1, 133.9, 132.0, 131.4, 128.5, 128.4, 117.8, 92.3, 61.6, 58.2, 49.2, 40.6, 37.2, 34.4, 26.8, 19.1; HRMS (ESI) for $C_{24}H_{28}NaO_6S_2$ [M +Na] calc 499.1225, found 499.1236.

E) Synthesis of substrate **9** and product **10a,b**



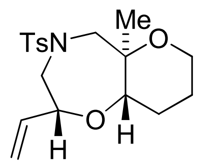


***N*-(1,2-butadienyl)-*N*-(2*E*-epoxy-6-hydroxy-2-methyl)-toluenesulfonamide (9):** Prepared in analogy to substrate **7**, substituting bis(phenylsulfone) **S1** with allenyl tosylamide[7] **S13** (vide supra). ^{1}H (300 MHz, $CDCl_3$): δ 7.57 (d, 2H), 7.20 (d, 2H), 4.72 (m, 1H), 4.56 (m, 2H), 3.87-3.71 (ddd, 2H), 3.57 (t, 2H), 3.15 (dd, 2H), 2.78 (m, 1H), 2.32 (s, 3H), 1.68-1.49 (m, 4H), 1.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 209.5, 143.5, 137.0, 129.7, 127.1, 85.09, 76.15, 62.01, 61.67, 59.70, 53.00, 47.33, 29.39, 24.94, 21.43, 14.85. HRMS (ESI) for $C_{18}H_{25}NNaO_4S$ [M +Na] calc 374.1402, found 374.1401.



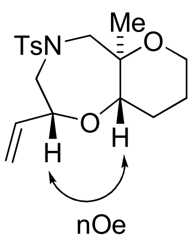
[5.4.0] sulfonamide (major-10a): Prepared following Representative Procedure**.** Light yellow oil. ^{1}H (500 MHz, C_6D_6): 7.57 (d, 2H), 6.69 (d, 2H), 5.48 (m, 1H), 5.10 (d, 1H), 4.90 (d, 1H), 4.19 (b, 1H), 3.98 (dd, 1H, J_1 = 11 Hz, J_2 = 1.5 Hz), 3.77 (d, 1H, J_1 = 11 Hz), 3.55 (q, 1H), 3.51 (t, 1H, J = 7Hz), 3.40 (q, 1H), 2.18 (d, 1H), 1.95 (t, 1H), 1.85 (s, 3H), 1.57 (m, 2H), 1.31 (m, 2H), 1.28 (s, 3H). ^{13}C (125 MHz, C_6D_6): 142.9, 135.8, 133.4, 129.5, 116.3, 83.67, 75.48, 69.65, 68.46, 53.29, 50.58, 26.01, 25.76, 20.88, 14.50. HRMS (ESI) for $C_{18}H_{26}NO_4S$ [M +H] calc 352.1583, found 352.1572.

[7] Ohno, H.; Mizutani, T.; Kadoh, Y.; Aso, A.; Miyamura, K.; Fujii, N.; Tanaka, T. *J. Org. Chem.* **2007**, *72,* 4378.

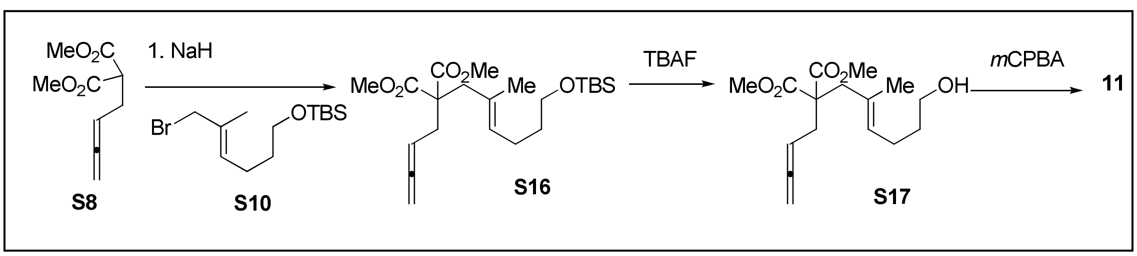


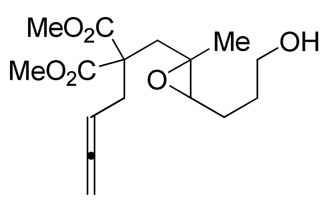
(**10b**): ^{1}H (300 MHz, C_6D_6): 7.58 (d, 2H), 6.73 (d, 2H), 5.48 (m, 1H), 5.12 (d, 1H), 4.90 (d, 1H), 4.56 (t, 1H), 4.20 (dd, 1H, J_1 = 11 Hz, J_2 = 1.5 Hz), 4.02 (m, 1H), 3.78 (dt, 1H), 3.59 (m, 2H), 2.00 (d, 1H), 1.99 (t, 1H), 1.87 (s, 3H), 1.61 (m, 1H), 1.45 (m, 3H), 0.98 (s, 3H).

Key NOESY interaction:



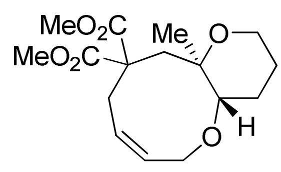
F) Synthesis of substrate **11** and product **12**





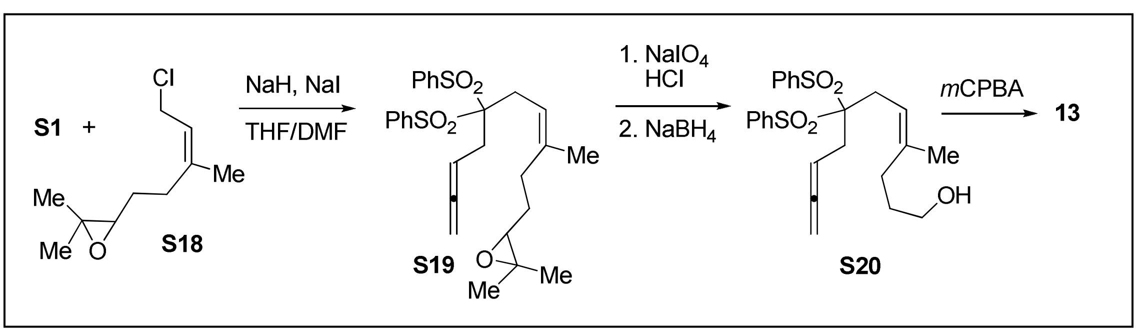
4*E*-7,7'-bis(phenylsulfonyl)-4-epoxy-5-methyl-9,10-dien-1-ol (11): Prepared in analogy to substrate **7**, substituting bis(phenylsulfone) **S1** with dimethyl 2-(propa-1,2-

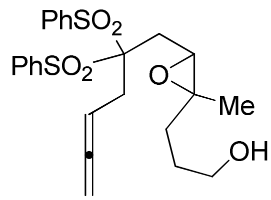
dienyl)malonate **S8** (vide supra). ^{1}H (400 MHz, $CDCl_3$): δ 4.89 (p, 1H), 4.56 (m, 2H), 3.63 (bs, 6H), 3.56 (t, 2H), 2.64 (m, 2H), 2.58-2.49 (m, 2H), 2.27 (d, 1H), 2.02 (d, 1H), 1.62-1.45 (m, 4H), 1.11 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): 209.1, 171.1, 84.47, 74.74, 63.79, 62.07, 58.37, 56.64, 52.20, 41.06, 33.06, 29.42, 24.94, 17.28. HRMS (ESI) for $C_{16}H_{24}NaO_6$ [M +Na] calc 335.1471, found 335.1468.



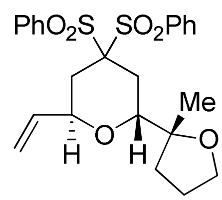
(4aS,11aR,Z)-dimethyl-11a-methyl-4,4a,6,9,11,11a-hexahydro-2H-pyrano[3,2-b] oxonine-10,10(3H)- dicarboxylate (12): Prepared following Representative Procedure**.** Clear oil. ^{1}H (300 MHz, $CDCl_3$): δ 5.62 (m, 2H), 3.90-3.80 (m, 7H), 3.77 (s, 3H), 3.68 (s, 1H), 3.28 (s, 3H), 2.82 (dd, 1H), 2.61 (dd, 1H), 2.42 (d, 1H), 2.25 (d, 1H), 1.93 (m, 4H), 1.38 (s, 3H); ^{13}C (100 MHz, $CDCl_3$): 170.8, 131.7, 127.5, 85.7, 83.3, 72.6, 68.9, 57.9, 56.1, 53.2, 38.2, 36.4, 27.1, 26.1, 23.5; HRMS: Calculated for ($C_{16}H_{24}O_6$ + Na) = 335.1471, found 335.1462.

G) Synthesis of substrate **13** and products **14a,b**





4*Z*-7,7'-bis(phenylsulfonyl)-4-epoxy-4-methyl-9,10-dien-1-ol (13): Prepared in analogy to substrate **1**, but substituting neryl chloride monoepoxide **S18** (prepared from monoepoxidation of neryl chloride[8] with *m*CPBA under standard conditions) for geranyl bromide monoepoxide **S2** (vide supra) and using NaI as a promoter in the alkylation.



(2*R*,6*S*)-2-((*R*)-2-methyltetrahydrofuran-2-yl)-6-vinyl-4,4'-bis(phenylsulfonyl)-tetrahydropyran (major-14a): Prepared following <u>Representative Procedure</u>**.** ^{1}H (300 MHz, C_6D_6) δ 8.23 (dd, 4H, J_1 = 6.3 Hz, J_2 = 1.8 Hz), 7.03 (m, 9H), 5.70 (m, 1H), 5.33 (d, 1H), 5.00 (d, 1H), 4.81 (m, 1H), 4.48 (dd, 1H), 3.73 (t, 2H), 3.28 (dd, 1H), 2.68 (m, 4H), 2.29 (m, 1H), 1.59 (m, 2H), 1.32 (m, 2H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 134.84, 134.79, 131.7, 131.6, 131.4, 128.8, 128.84, 128.75, 128.66, 116.1, 84.3, 74.8, 73.4, 70.4, 68.9, 33.8, 31.5, 26.6, 25.5, 23.9; HRMS (ESI) for $C_{24}H_{29}O_6S_2$ [M +H] calc 477.1406, found 477.1392.

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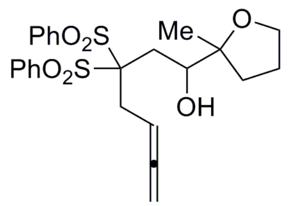
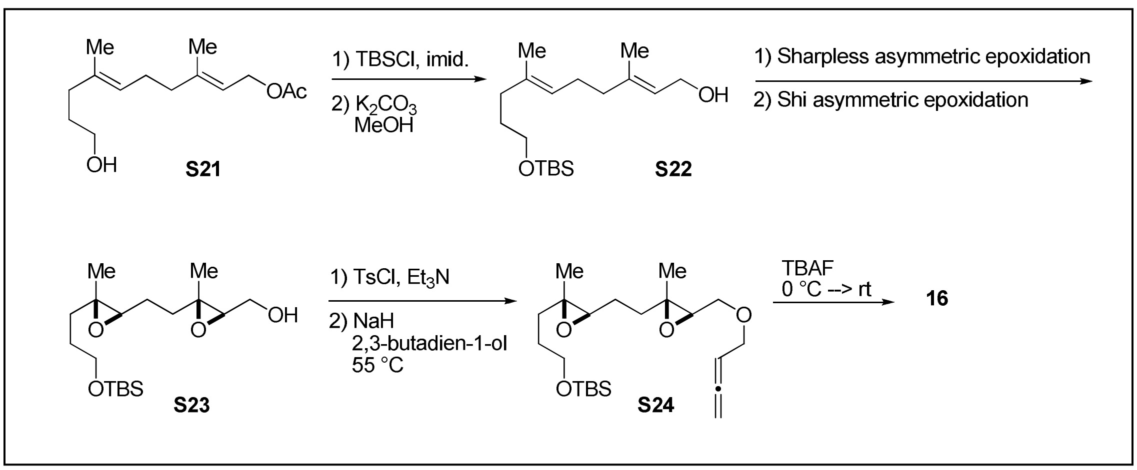
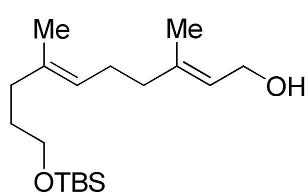
[8] Nowotny, S.; Tucker, C. E.; Jubert, C.; Knochel, P. *J. Org. Chem*. **1995**, *60*, 2762.



Acid-catalyzed product (15): ^{1}H (400 MHz, $CDCl_3$): δ 8.05 (d, H), 7.68 (t, 2H), 7.56 (t, 4H), 5.29 (m, 1H), 4.68 (m, 2H), 4.15 (m, 1H), 3.90-3.75 (m, 2H), 3.47 (d, 1H), 3.14 (m, 2H), 2.82 (d, 1H), 2.24 (dd, 1H), 1.92 (m, 3H), 1.64 (m, 2H), 1.14 (s, 3H).

H) Synthesis of substrate **16** and product **17**

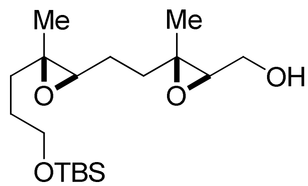




Siloxy alcohol **S22:** To a stirred solution of known alcohol[9] **S21** (1.10 g, 4.58 mmol) in CH_2Cl_2 (46 mL) at 0 °C was added imidazole (470 mg, 6.87 mmol), DMAP (28 mg, 0.23 mmol), and TBSCl (742 mg, 4.92 mmol). The solution was allowed to warm to rt over about 1 h, and after an additional 30 min, water was added. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc in hexanes) provided the silyl ether (1.577 g, 97%) of as a clear, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (t, *J* = 7.1 Hz, 1H), 5.09 (t, *J* = 6.9 Hz, 1H), 4.57 (d, *J* = 7.1 Hz, 2H), 3.57 (t, *J* = 6.6 Hz, 2H), 2.14-1.96 (m, 9H), 1.69 (s, 3H), 1.63-1.55 (m, 2H), 1.58 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 142.3, 135.2, 123.6, 118.2, 62.9, 61.4, 39.5, 35.8, 31.2, 26.2, 26.0, 21.1, 18.4, 16.5, 16.0, -5.3; HRMS (ESI) for $C_{20}H_{38}NaO_3Si$ [M +Na] calc 377.2488, found 377.2480.

To a stirred solution of the silyl ether (1.470 g, 4.146 mmol) in MeOH (30 mL) was added K_2CO_3 (285 mg, 2.06 mmol). After 1.5 h, solid NH_4Cl (250 mg, 4.67 mmol) was added, and the resulting mixture was concentrated in vacuo. Purification by flash column chromatography (40% Et_2O in hexanes) afforded alcohol **S22** (1.269 g, 98%) as a clear, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (t, *J* = 7.0 Hz, 1H), 5.09 (t, *J* = 6.8 Hz, 1H), 4.13 (d, *J* = 6.9 Hz, 2H), 3.56 (t, *J* = 6.6 Hz, 2H), 2.13-1.95 (m, 6H), 1.66 (s, 3H), 1.62-1.55 (m, 2H), 1.58 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 134.9, 123.8, 123.6, 62.7, 59.1, 39.4, 35.7, 31.1, 26.2, 25.9, 18.2, 16.1, 15.8, -5.4; HRMS (ESI) for $C_{18}H_{36}NaO_2Si$ [M +Na] calc 335.2382, found 335.2378.

[9] Uyanik, M.; Ishihara, K.;Yamamoto, H. *Org. Lett.*, **2006**, *8,* 5649.



Bis-epoxy alcohol **S23**: *Sharpless epoxidation.*[10] To a stirred mixture of 4Å molecular sieves (150 mg) and D-(-)-diisopropyl tartrate (70 µL, 0.33 mmol) in CH_2Cl_2 (9.1 mL) at –20 °C was added Ti(O*i*Pr)$_4$ (80 µL, 0.27 mmol) dropwise, followed by the dropwise addition of *t*BuOOH (5.5 M in decanes, 0.28 mL, 1.5 mmol) over 5 min. After 30 min, alcohol **S22** (313 mg, 1.00 mmol) was added dropwise in CH_2Cl_2 (2.5 mL) over 20 min. The reaction was quenched after 2.5 h at –20 °C by pipet transfer into a solution of $FeSO_4$ (1.03 g) and citric acid (0.344 g) in 6.3 mL water at 0 °C. After warming to rt, the aqueous layer was extracted with Et_2O three times, and the combined extracts were poured into 30% NaOH (5 mL) at 0 °C. After 1 h, the aqueous layer was extracted with Et_2O twice, and the combined extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (35% EtOAc in hexanes) furnished the monoepoxy alcohol (293 mg, 89%) as a clear, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (t, *J* = 6.5 Hz, 1H), 3.70 (ddd, *J* = 4.2, 7.0, 11.8 Hz, 1H), 3.57 (ddd, *J* = 4.5, 6.7, 11.4 Hz, 1H), 3.49 (t, *J* = 6.6 Hz, 2H), 3.18 (m, 1H), 2.89 (dd, *J* = 4.2, 6.7 Hz, 1H), 2.00 (t, *J* = 7.7 Hz, 2H), 1.91 (t, *J* = 7.7 Hz, 2H), 1.62-1.48 (m, 3H), 1.52 (s, 3H), 1.39 (m, 1H), 0.81 (s, 9H), -0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.22, 123.1, 63.1, 62.7, 61.1, 61.0, 38.4, 35.6, 30.9, 25.8, 23.4, 18.1, 16.6, 15.8, -5.4; $[\alpha]^{23}_D$ = +4.3 (c 0.023, CH_2Cl_2), HRMS (ESI) for $C_{18}H_{36}NaO_3Si$ [M + Na] calc 351.2331, found 351.2317.

Shi epoxidation.[11] To a stirred solution of the monoepoxy alcohol (292 mg, 0.889 mmol) in CH_3CN (7.2 mL) and dimethoxy methane (14.5 mL) was added $Bu_4N{\bullet}HSO_4$ (29 mg, 0.085 mmol), $Na_2B_4O_7$ (aq) (9.0 mL, [$Na_2B_4O_7$] = 0.05 M, [Na_2EDTA] = 0.4 mM), and

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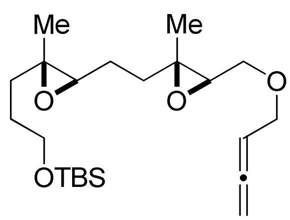
[10] Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
[11] Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119,* 11224.

D-fructose derived (-)-Shi catalyst[12] (228 mg, 0.883 mmol). After cooling the resulting solution to 0 °C, Oxone® (0.766 g, 1.25 mmol) in 0.4 mM Na_2EDTA solution (5 mL) and K_2CO_3 (0.766 g, 5.54 mmol) in 5 mL water were added simultaneously via separate syringes over 1.25 h. The mixture was diluted with water and 2:1 hexanes/Et_2O, and the aqueous layer was extracted with 2:1 hexanes/Et_2O twice. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified twice by flash column chromatography (50% → 60% EtOAc in hexanes) to provide bis-epoxy alcohol **S23** (290 mg, 93%) as a clear, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (dd, J = 4.5, 12.1 Hz, 1H), 3.64 (dd, J = 6.4, 12.1 Hz, 1H), 3.54 (m, 2H), 2.93 (dd, J = 4.6, 6.4 Hz, 1H), 2.67 (t, J = 6.0 Hz, 1H), 2.56 (s (broad), 1H), 1.74 (m, 1H), 1.62-1.39 (m, 7H), 1.27 (s, 3H), 1.20 (s, 3H), 0.82 (s, 9H), -0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.77, 62.75, 62.4, 61.1, 61.0, 60.5, 35.0, 34.9, 28.4, 25.8, 24.2, 18.2, 16.8, 16.4, -5.4; $[\alpha]^{23}_D$ = +12 (c 0.022, CH_2Cl_2), HRMS (ESI) for $C_{18}H_{37}O_4Si$ [M +H] calc 345.2461, found 345.2450.

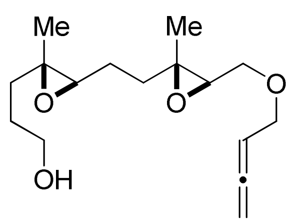


Allene **24**: To a stirred solution of bis-epoxy alcohol **S23** (290 mg, 0.842 mmol) in CH_2Cl_2 (10.5 mL) was added Et_3N (230 μL, 1.65 mmol), DMAP (21 mg, 0.17 mmol), and TsCl (193 mg, 1.01 mmol). After 1.5 h, water was added, and the aqueous layer was extracted with 1:1 hexanes/EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (25% EtOAc in hexanes) afforded the tosylate (394 mg, 94%) as a clear, colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 4.08 (m, 2H), 3.54 (m, 2H), 2.96 (t, J = 5.7 Hz, 1H), 2.63 (t, J = 5.8 Hz, 1H), 2.40 (s, 3H), 1.69 (m, 1H), 1.61-1.39 (m, 7H), 1.19 (s, 6H), 0.83 (s, 9H), -0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 132.5, 129.8, 127.8, 68.3, 62.7, 62.5, 60.7, 60.3, 58.2,

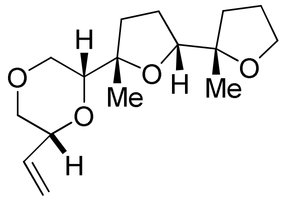
[12] Prepared according to procedure of: Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143.

34.8, 34.4, 28.4, 25.8, 24.0, 21.5, 18.2, 16.6, 16.4, -5.4; $[\alpha]^{23}_{D}$ = +23 (c 0.022, CH_2Cl_2); HRMS (ESI) for $C_{25}H_{43}O_6SSi$ [M +H] calc 499.2550, found 499.2549.

To 2,3-butadien-1-ol[4] (3.1 mL) at 0 °C was added NaH (97 mg, 2.5 mmol) portionwise. The resulting yellow-colored alkoxide solution was added to the tosylate (393 mg, 0.788 mmol) in a separate flask, and after equipping the flask with an air-cooled reflux condenser, the mixture was stirred at 55 °C for 22 h. After cooling to rt, the mixture was diluted with 10% brine (25 mL) and 2:1 hexanes/Et_2O (25 mL), and the aqueous layer was extracted with 2:1 hexanes/Et_2O (25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (25 →30% Et_2O in pentane) furnished allene **S24** (236 mg, 76%) as a clear, colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.22 (p, *J* = 6.7 Hz, 1H), 4.78 (m, 2H), 4.05 (m, 2H), 3.65-3.49 (m, 4H), 2.97 (t, *J* = 5.4 Hz, 1H), 2.69 (t, *J* = 5.9 Hz, 1H), 1.84-1.39 (m, 8H), 1.27 (s, 3H), 1.22 (s, 3H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 87.5, 75.8, 69.0, 68.3, 62.9, 62.8, 60.9, 60.7, 59.7, 35.0, 34.9, 28.5, 25.9, 24.3, 18.3, 16.9, 16.5, -5.3; $[\alpha]^{23}_{D}$ = +24 (c 0.022, CH_2Cl_2), HRMS (ESI) for $C_{22}H_{41}O_4Si$ [M +H] calc 397.2774, found 397.2769.

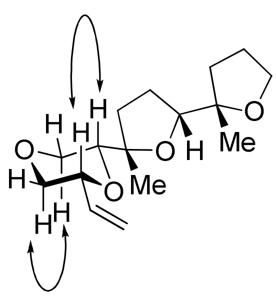


Substrate **16:** To a stirred solution of allene **S24** (236 mg, 0.595 mmol) in THF (7.5 mL) at 0 °C was added TBAF (1.0 M in THF, 1.2 mL, 1.2 mmol). The resulting solution was allowed to warm to rt over about 1 h, and after an additional 2 h, water and EtOAc/hexanes were added. The aqueous layer was extracted with EtOAc/hexanes three times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (85% EtOAc/2% Et_3N/13% hexanes) provided substrate **16**, which was used immediately in the Au(I) cyclization: ^1H NMR (400 MHz, C_6D_6) δ 5.17 (p, *J* = 6.8 Hz, 1H), 4.57 (m, 2H), 3.89 (m, 2H), 3.45-3.37 (m, 4H), 2.94 (t, *J* = 5.4 Hz, 1H), 2.55 (t, *J* = 6.0 Hz, 1H), 1.66 (s (broad), 1H), 1.62-1.33 (m, 8H), 1.05 (s, 3H), 1.03 (s, 3H).

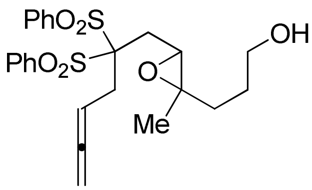


Product **17:** Prepared following Representative Procedure using 76 mg (0.269 mmol) substrate **16**, 9.9 mg $(PhO)_3PAuCl$ (0.018 mmol), and 3.9 mg AgOTf (0.015 mmol) to provide 42 mg (55%) of desired product **17** (dr = 11:1)**:** ^{1}H (500 MHz, C_6D_6) 5.54 (ddd, J = 5.2, 10.8, 17.4 Hz, 1H), 5.22 (dt, J = 1.7, 17.4 Hz, 1H), 4.97 (dt, J = 1.6, 10.8 Hz, 1H), 4.14 (dd, J = 2.4, 11.3 Hz, 1H), 4.03 (m, 1H), 3.85 (dd, J = 7.0, 7.5 Hz, 1H), 3.69 (td, J = 2.5, 6.6 Hz, 2H), 3.63 (dd, J = 2.5, 10.4 Hz, 1H), 3.58 (dd, J = 2.8, 11.4 Hz, 1H), 3.44 (dd, J = 10.6, 11.2 Hz, 1H), 3.09 (dd, J = 10.5, 11.2 Hz), 2.07 (ddd, J = 5.1, 7.6, 17.6 Hz, 1H), 1.81 (ddd, J = 7.8, 12.2, 15.5 Hz, 1H), 1.67-1.60 (m, 2H), 1.60-1.52 (m, 2H), 1.42 (ddd, J = 8.0, 9.0, 12.4 Hz, 1H), 1.34 (ddd, J = 6.4, 7.6, 12.2 Hz, 1H), 1.19 (s, 3H), 1.15 (s, 3H); δ ^{13}C NMR (125 MHz, C_6D_6) δ 134.9, 116.3, 84.7, 83.6, 83.1, 80.3, 76.7, 70.6, 68.2, 67.2, 36.3, 34.6, 27.3, 26.5, 23.1, 21.9; $[\alpha]^{23}_D$ = -35 (c 0.008, CH_2Cl_2), HRMS (ESI) for $C_{16}H_{26}O_4$ [M +H] calc 283.1909, found 283.1898.

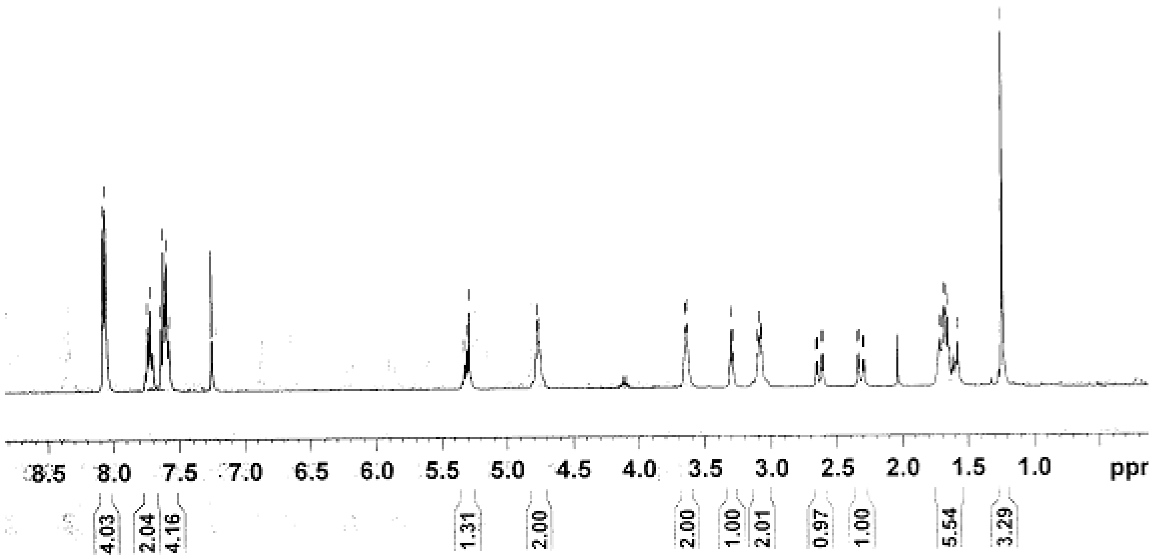
Key NOESY interactions:



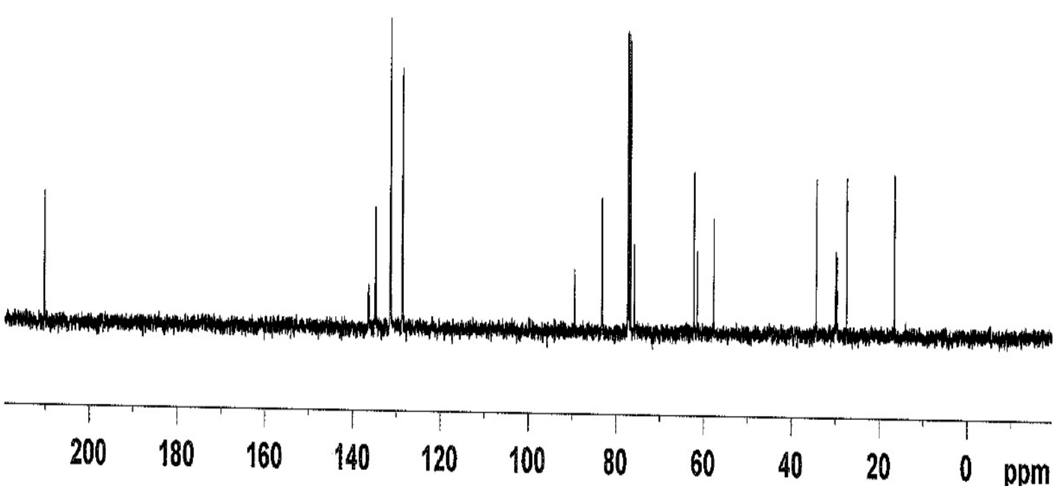
III. NMR Spectra

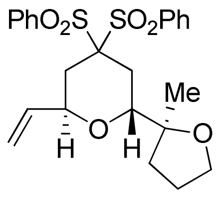


Substrate **1.** ^{1}H (400 MHz, $CDCl_3$)

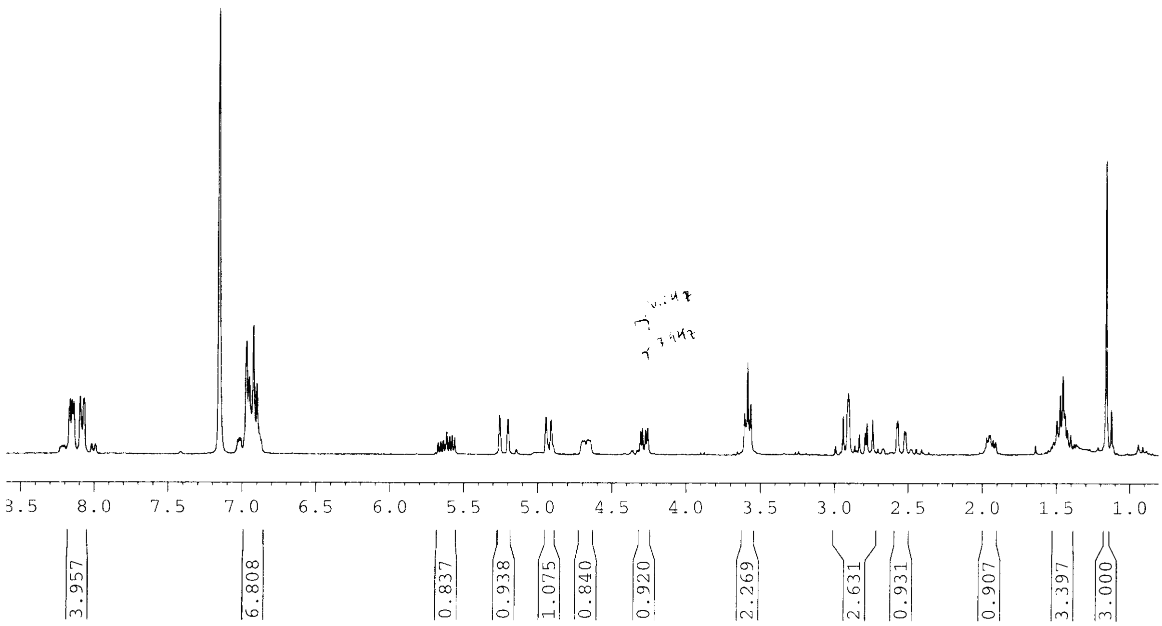


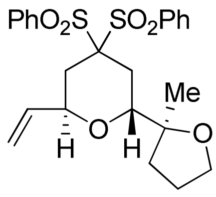
Substrate **1.** ^{13}C (100 MHz, $CDCl_3$)



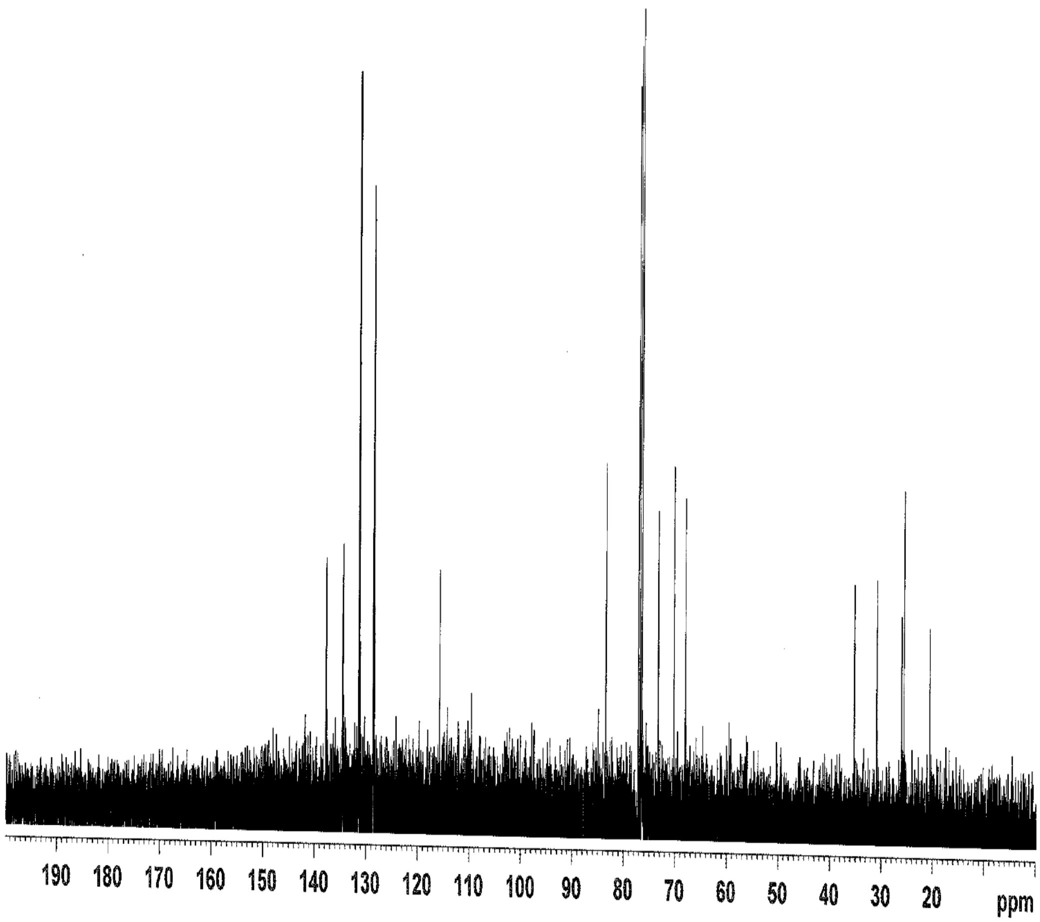


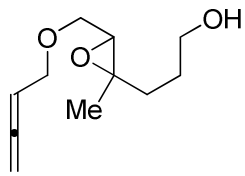
Product **2a.** ^{1}H (400 MHz, $CDCl_3$)



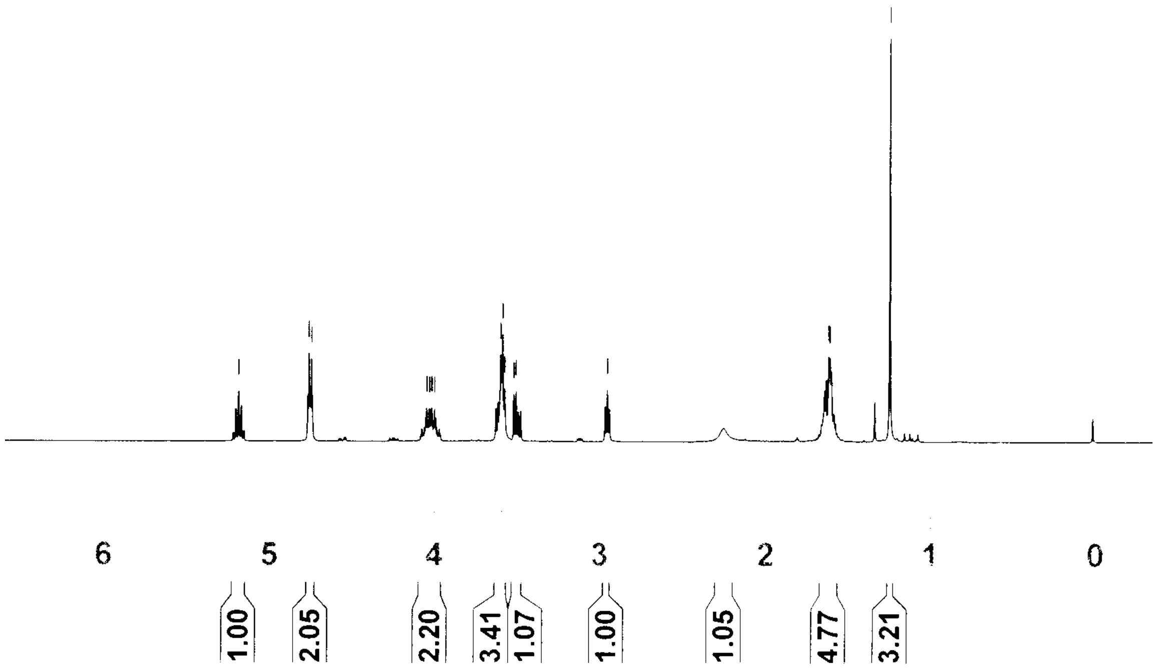


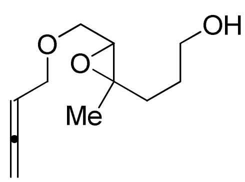
Product **2a.** ^{13}C (100 MHz, $CDCl_3$)



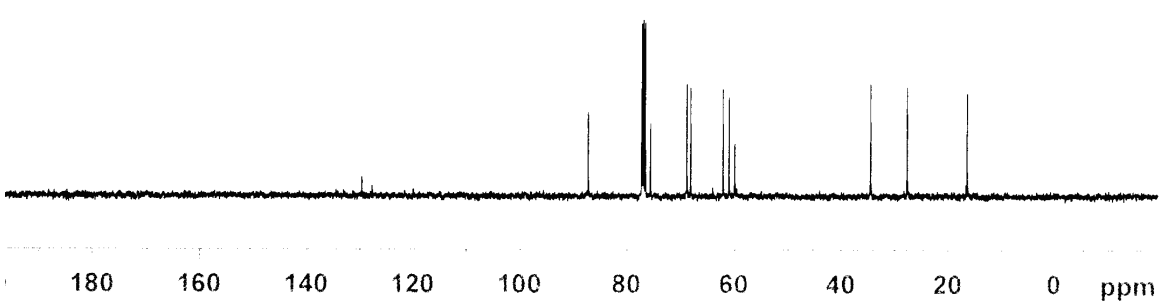


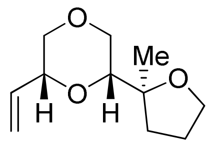
Substrate **3.** ^{1}H (400 MHz, $CDCl_3$)



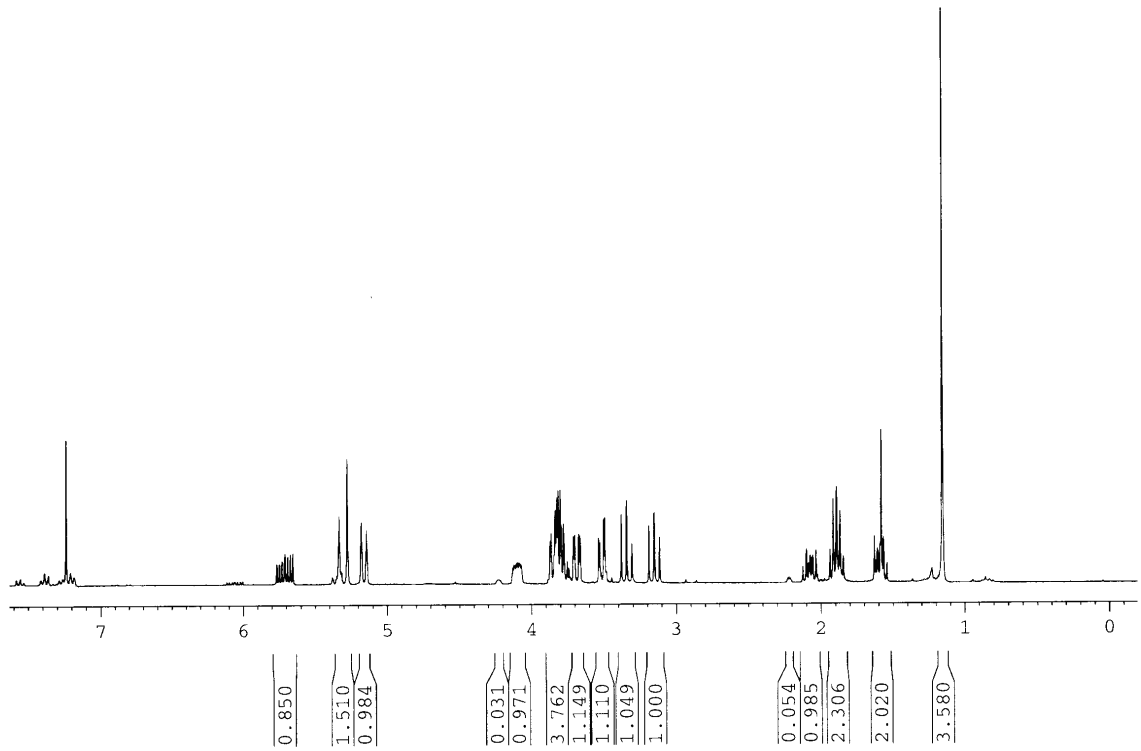


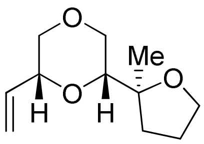
Substrate **3.** ^{13}C (100 MHz, $CDCl_3$)



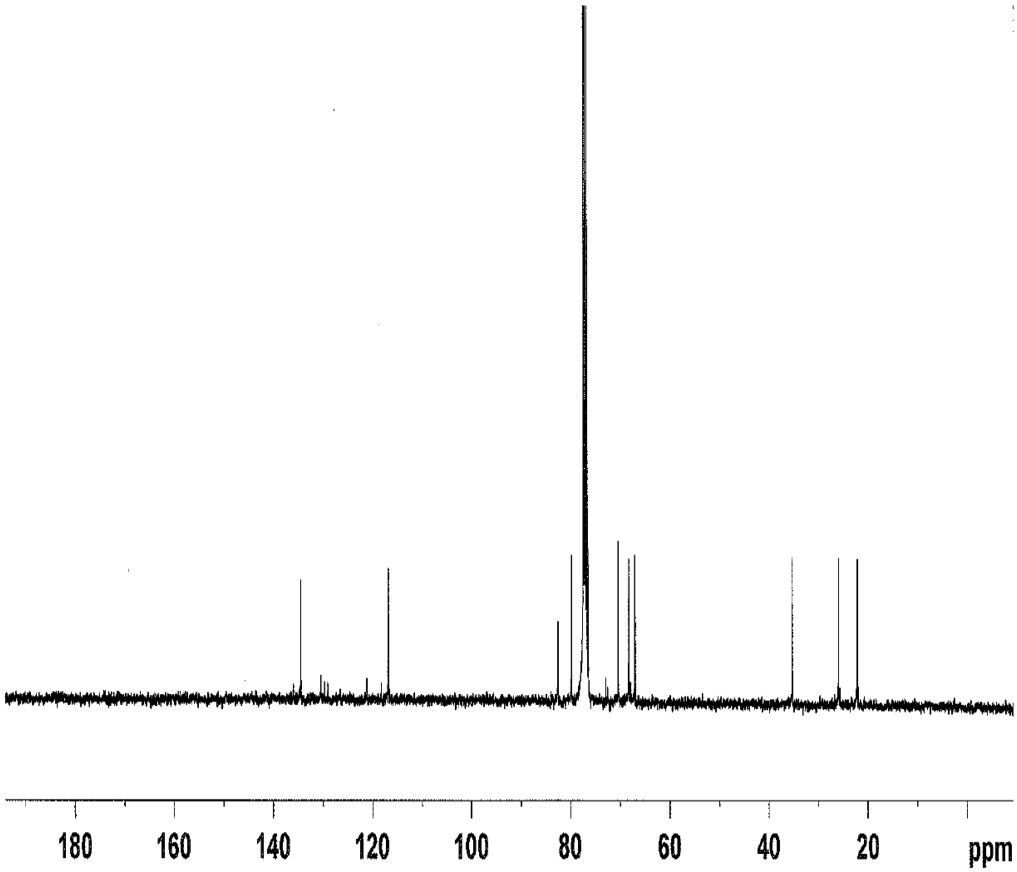


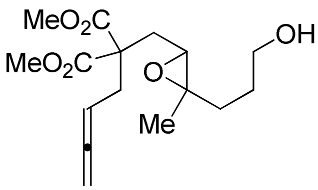
Product **4a.** ^{1}H (300 MHz, $CDCl_3$)



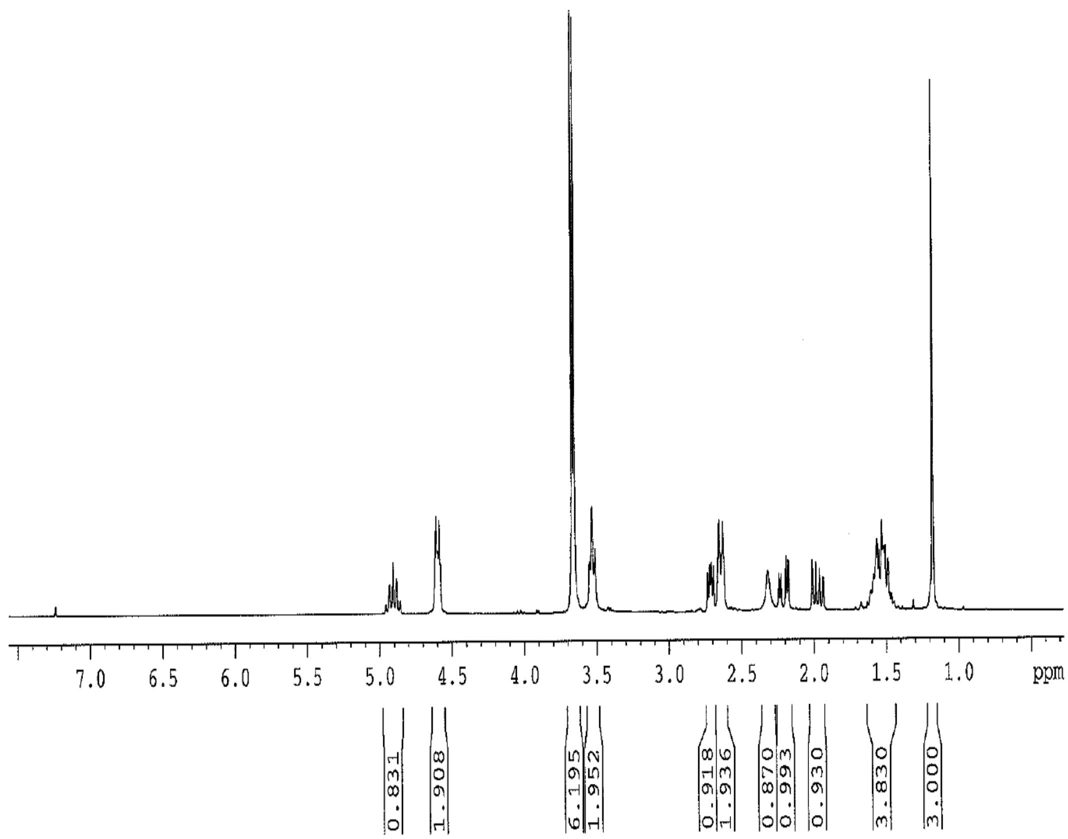


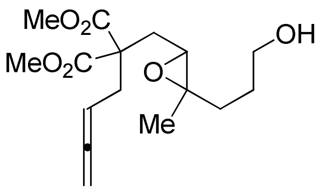
Product **4a.** ^{13}C (100 MHz, $CDCl_3$)



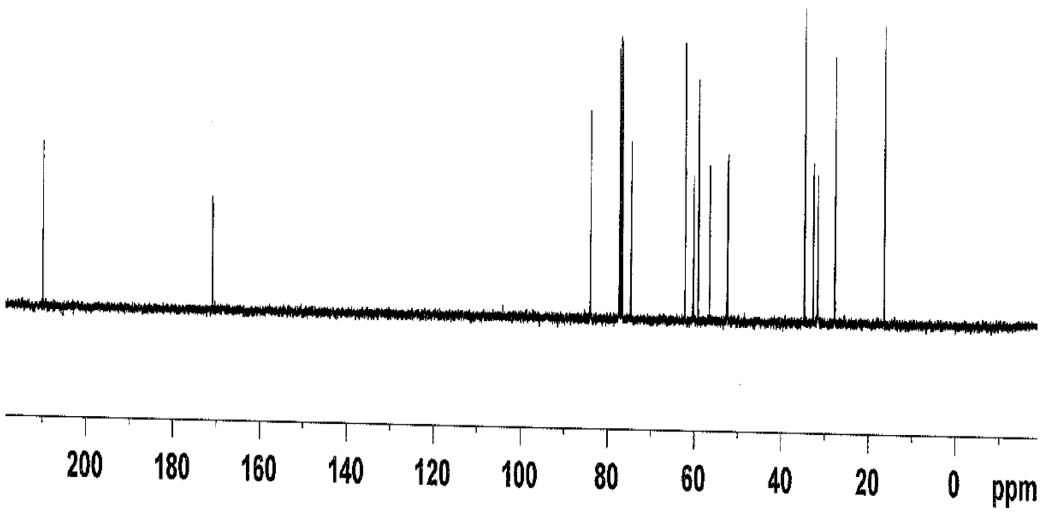


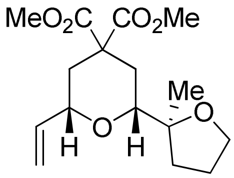
Substrate **5.** ^{1}H (300 MHz, $CDCl_3$)



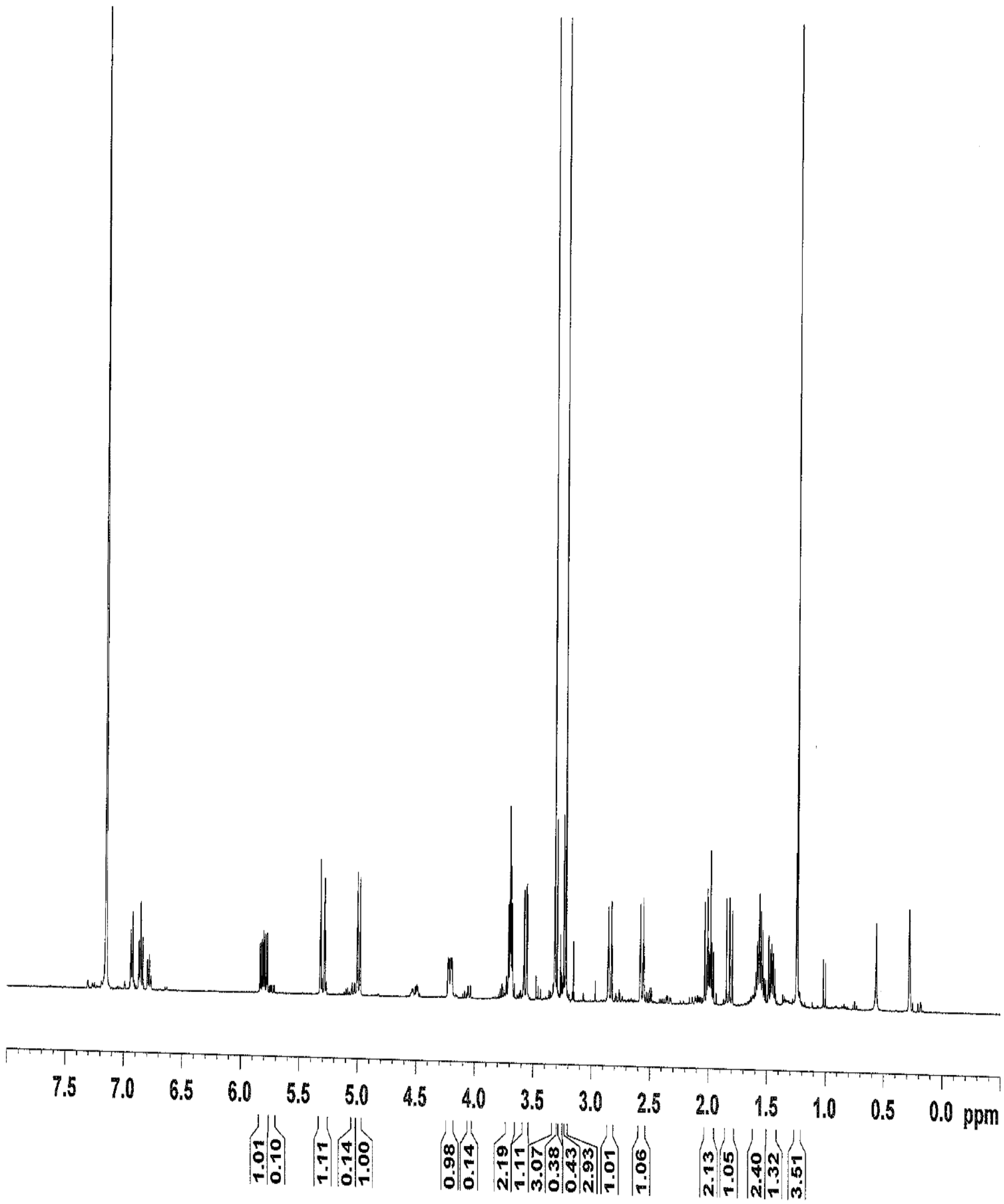


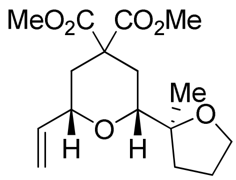
Substrate **5.** ^{13}C (100 MHz, $CDCl_3$)



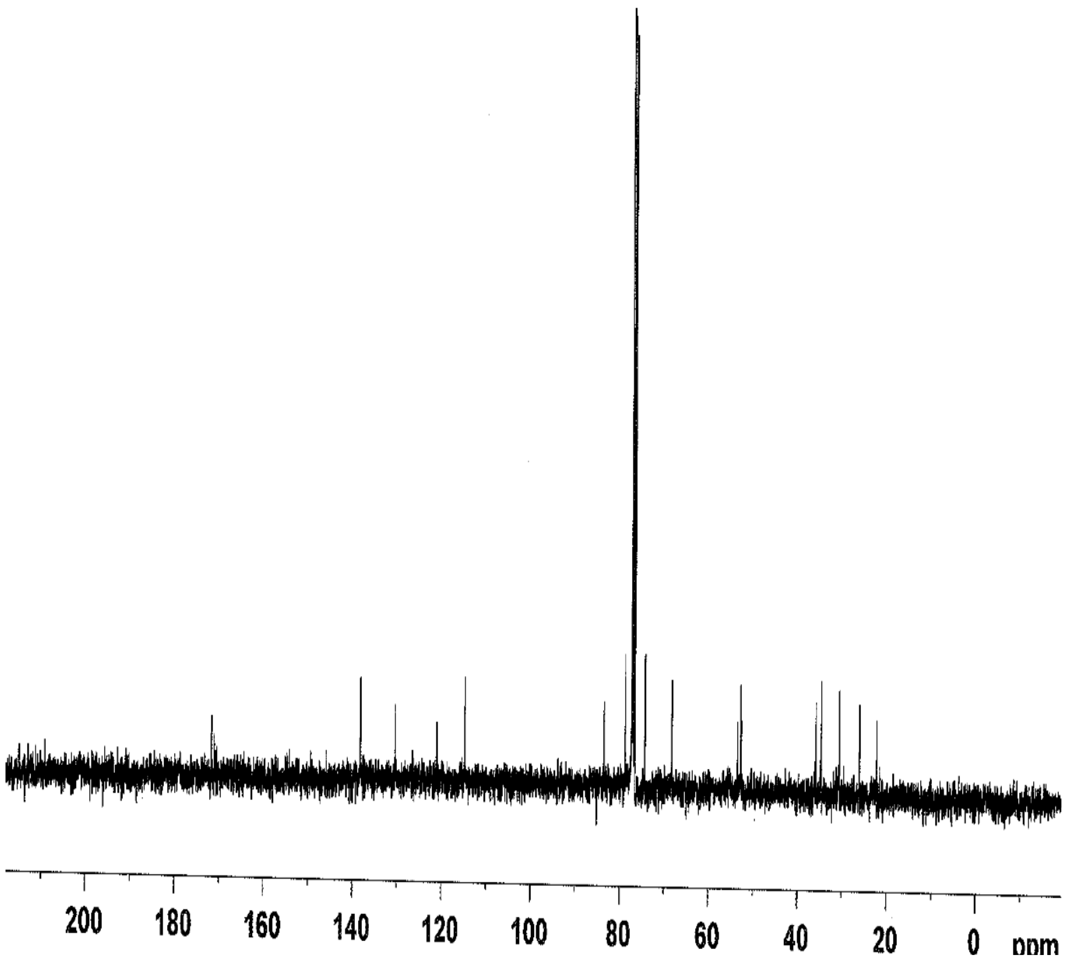


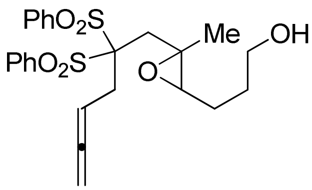
Product **6.** ^{1}H (500 MHz, C_6D_6)



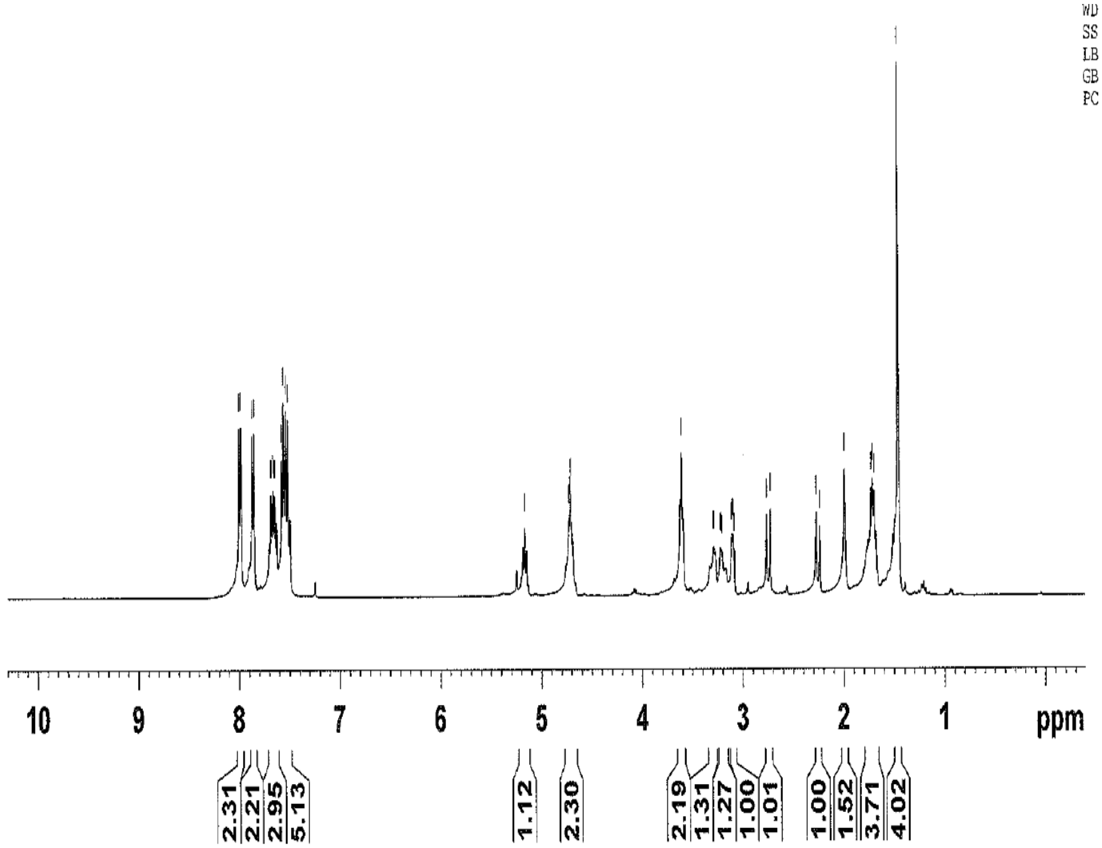


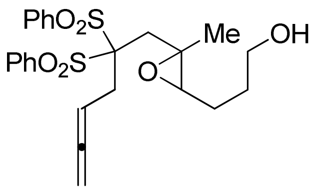
Product **6.** ^{13}C (100 MHz, $CDCl_3$)



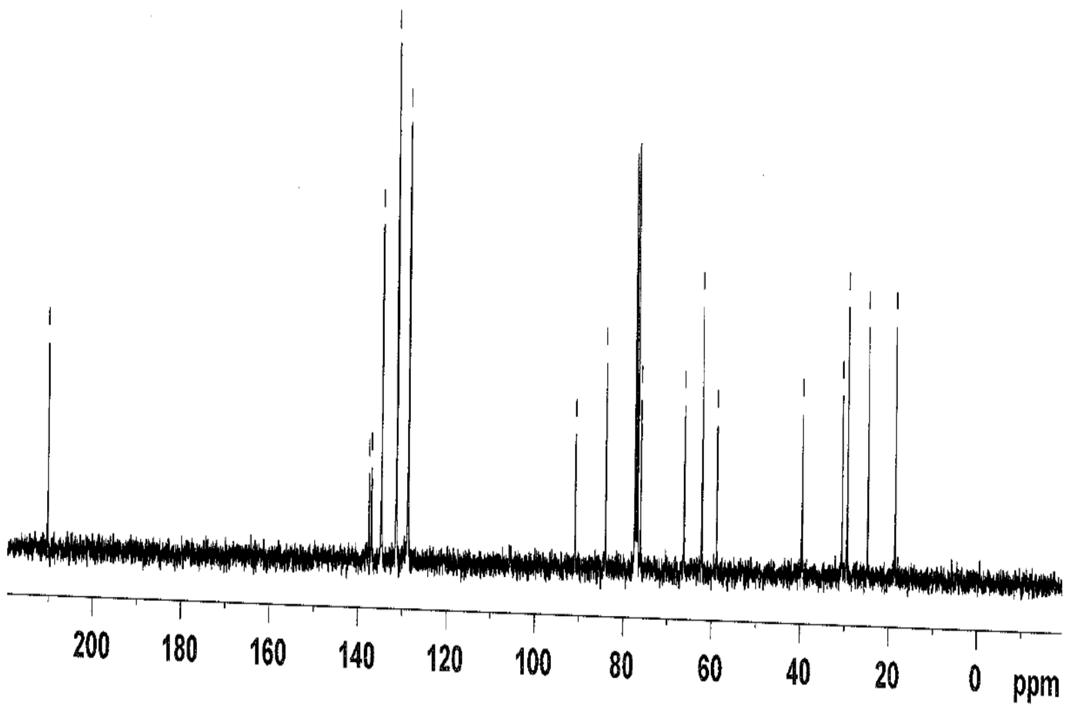


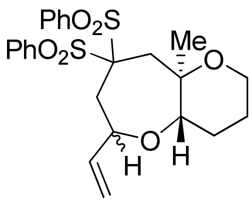
Substrate **7.** ^{1}H (400 MHz, $CDCl_3$)



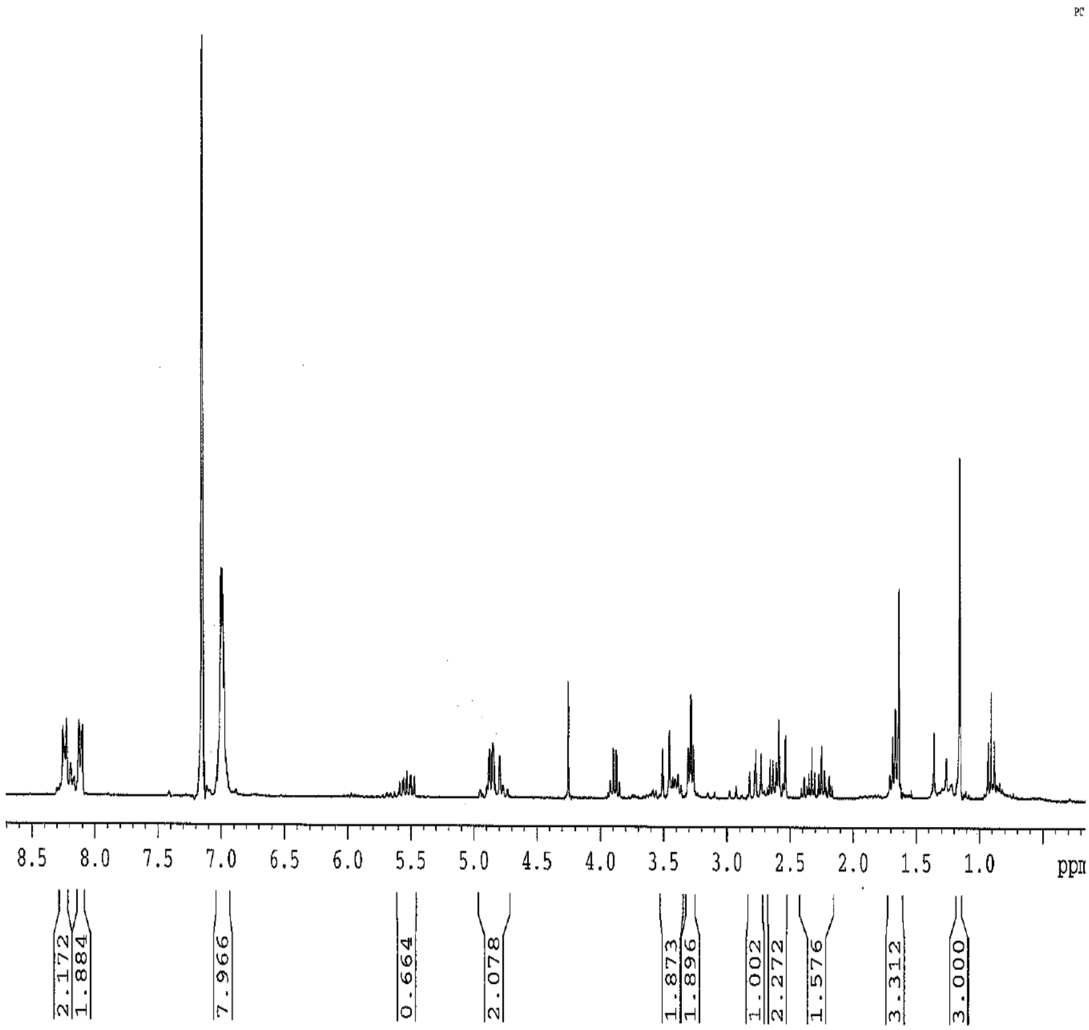


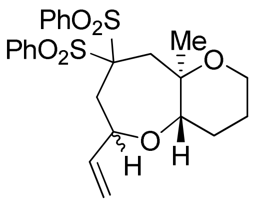
Substrate **7.** ^{13}C (100 MHz, $CDCl_3$)



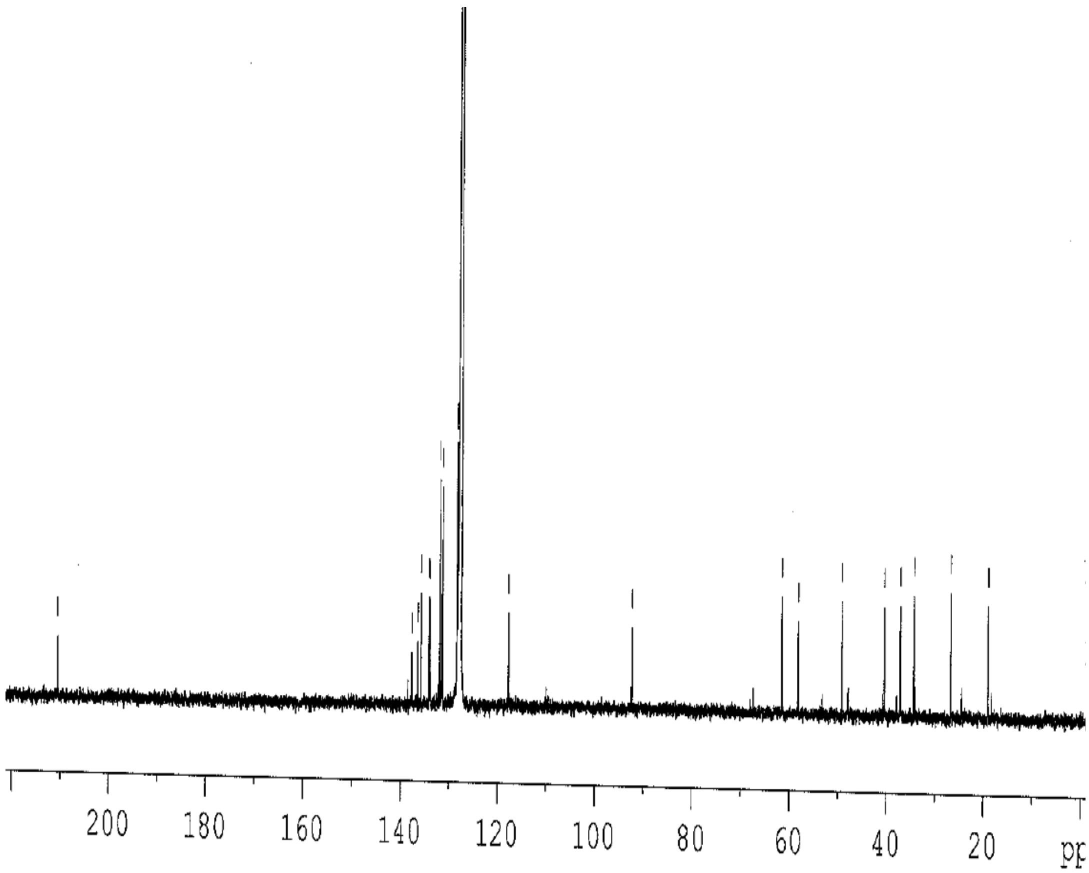


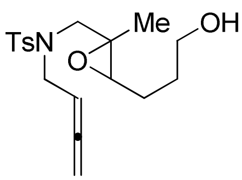
Product **8.** ^{1}H (300 MHz, $CDCl_3$)



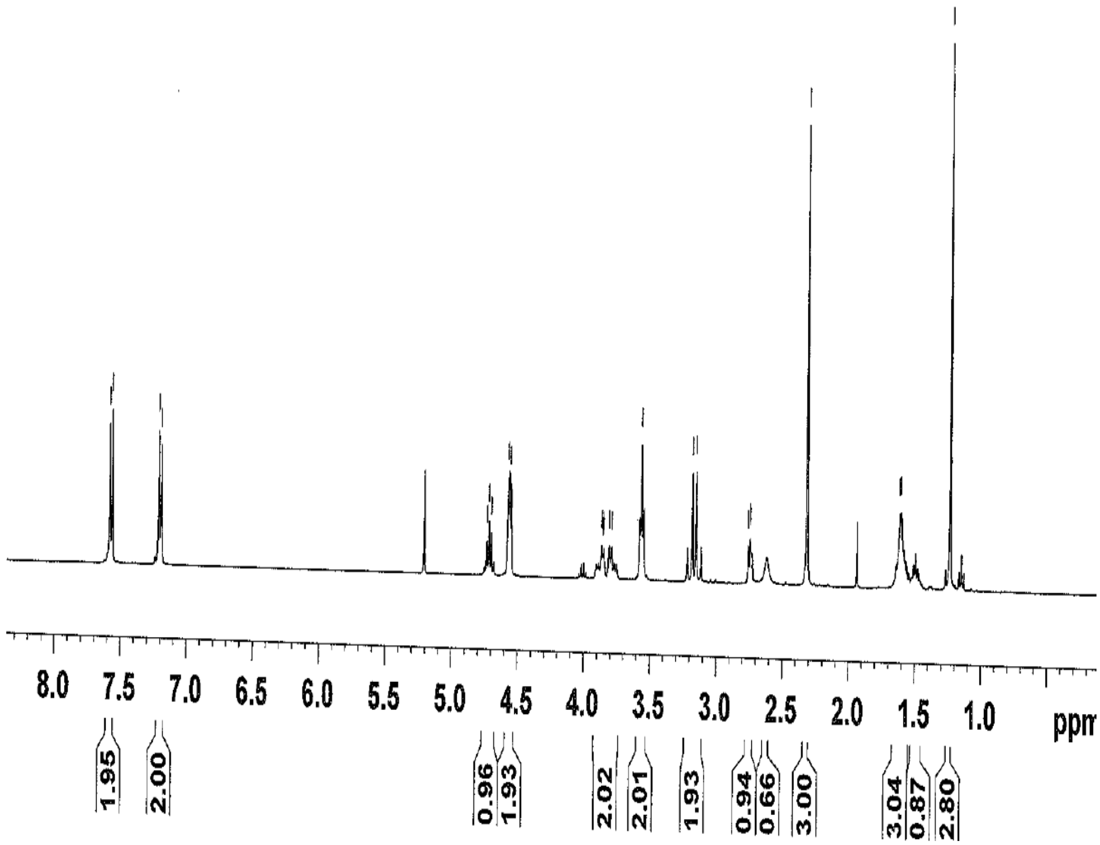


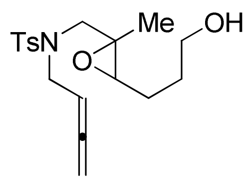
Product **8.** ^{13}C (125 MHz, C_6D_6)



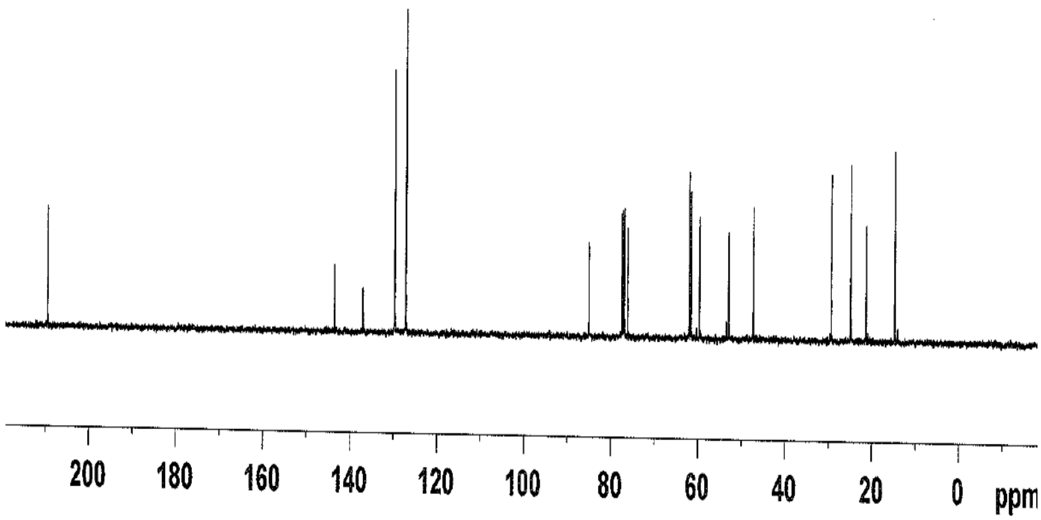


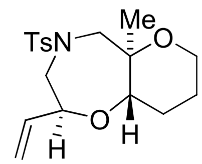
Substrate **9.** ^{1}H (400 MHz, $CDCl_3$)



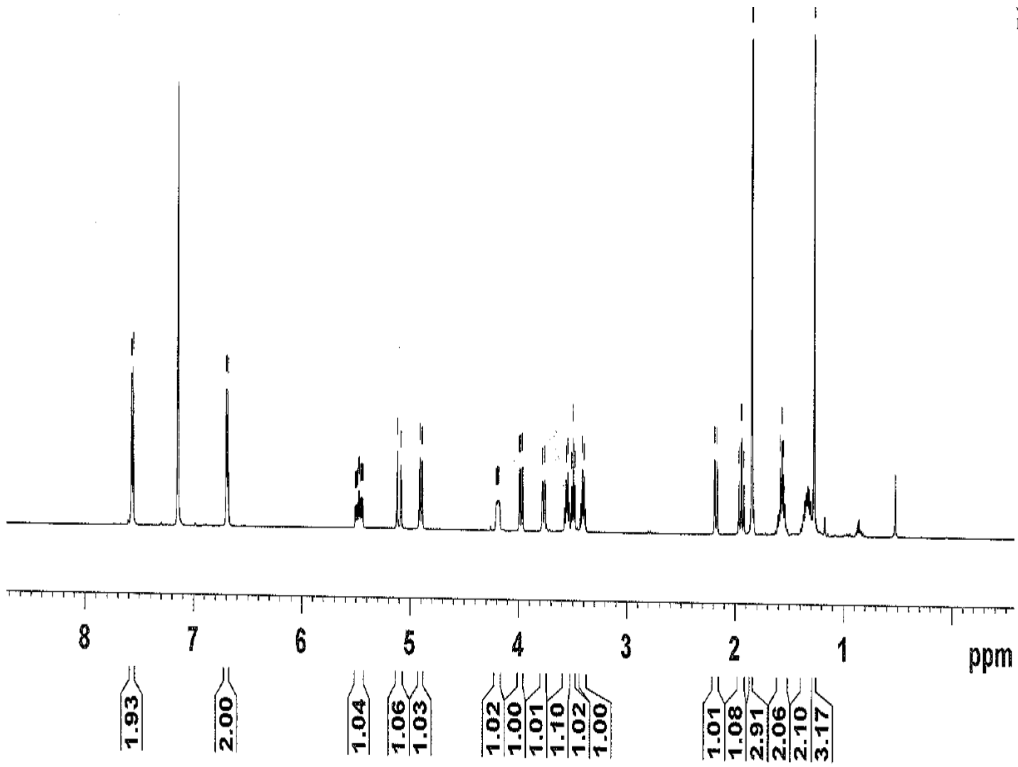


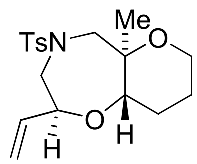
Substrate **9.** ^{13}C (100 MHz, $CDCl_3$)



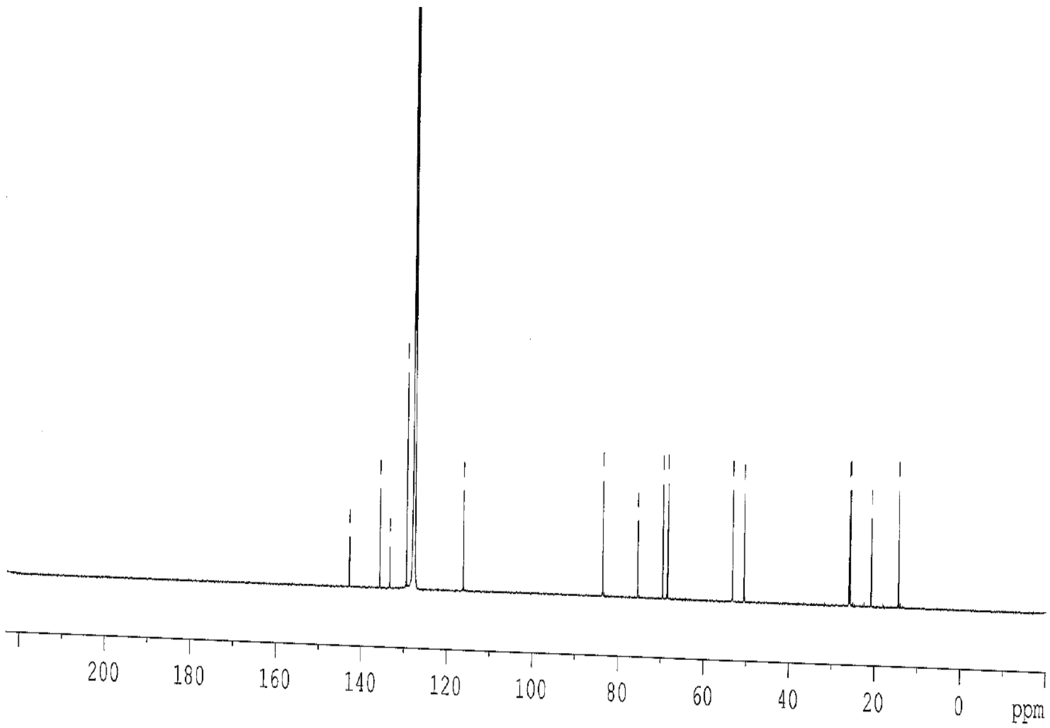


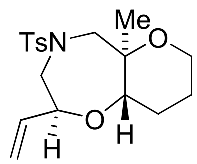
Product **10a.** ^{1}H (500MHz, $CDCl_3$)



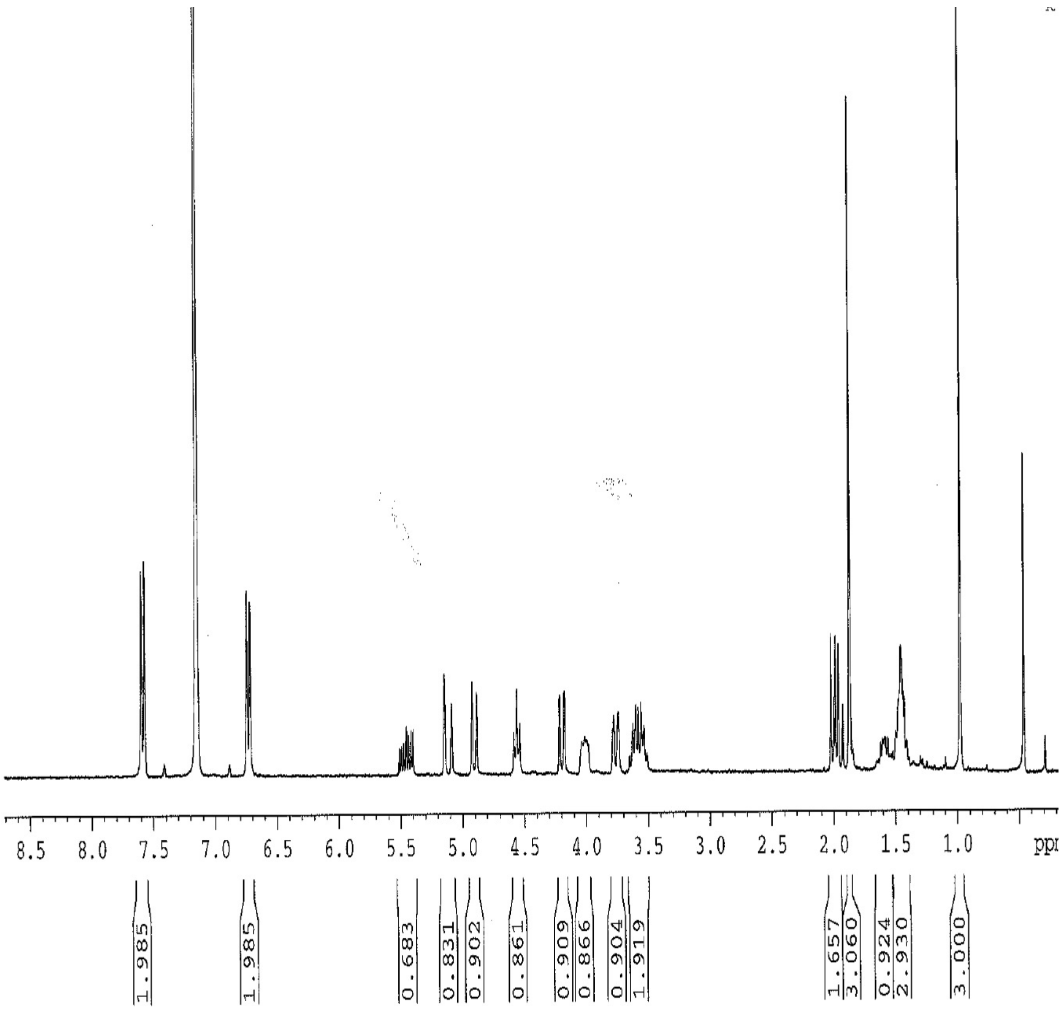


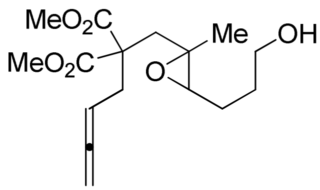
Product **10a.** ^{13}C (125 MHz, C_6D_6)



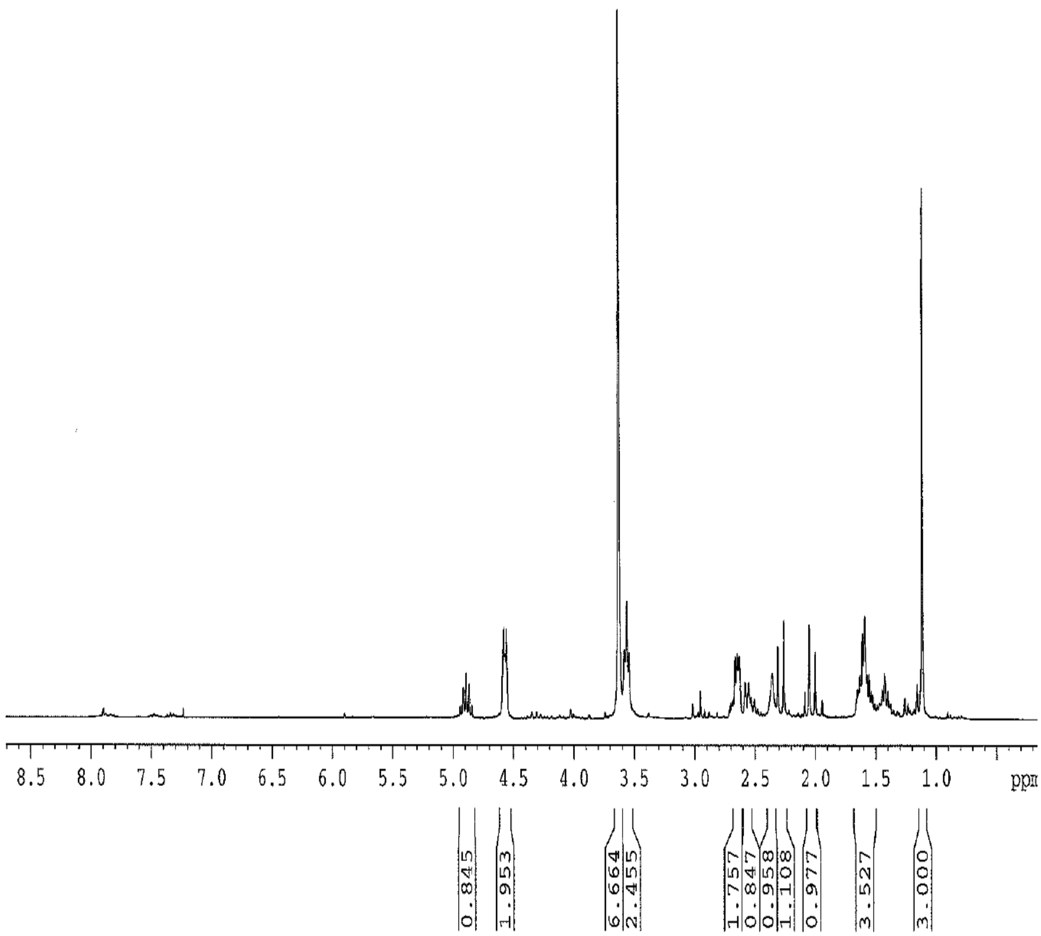


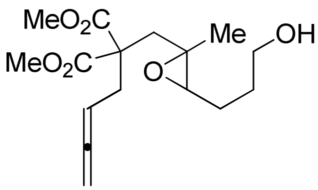
Product **10b.** ^{1}H (300MHz, C_6D_6)



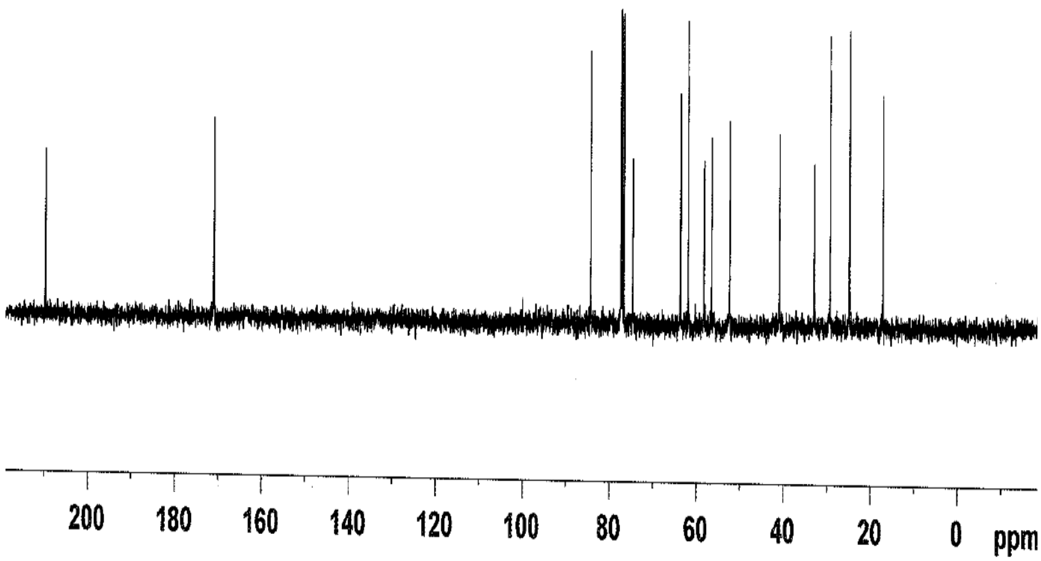


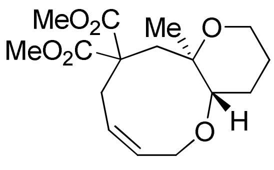
Substrate **11.** ^{1}H (300 MHz, $CDCl_3$)



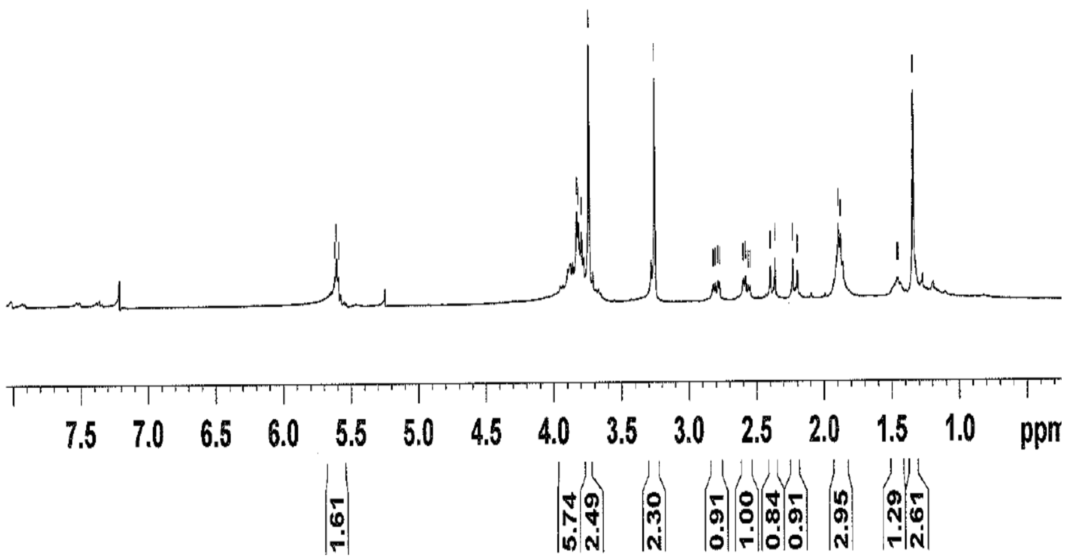


Substrate **11.** ^{13}C (100 MHz, $CDCl_3$)

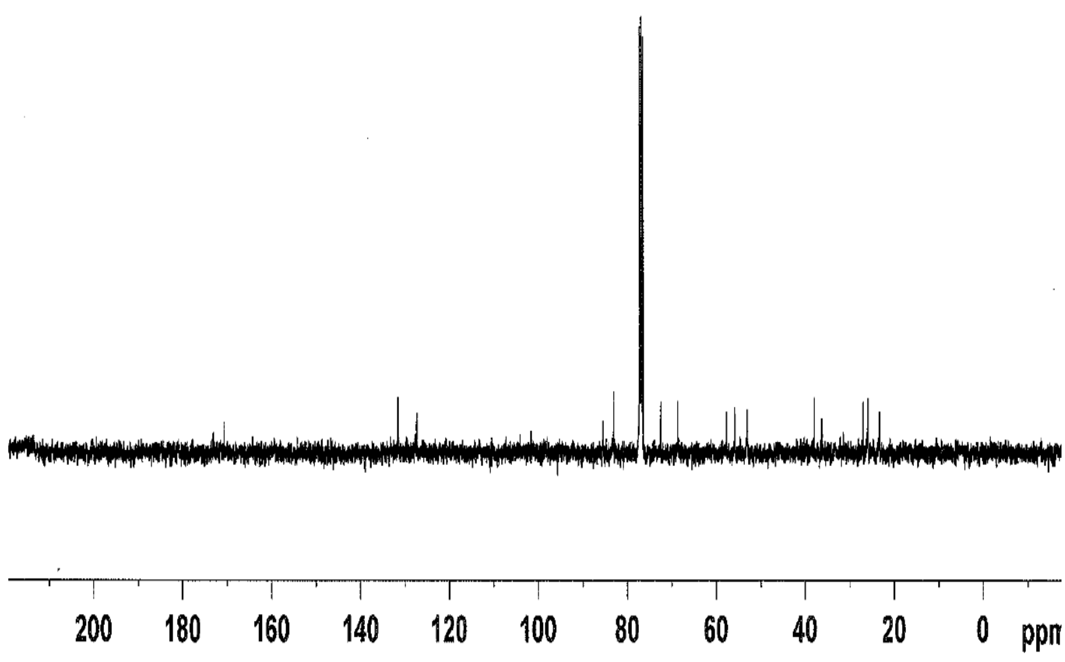


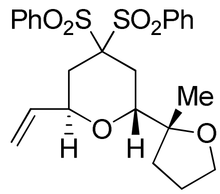


Product **12.** ^{1}H (400 MHz, $CDCl_3$)

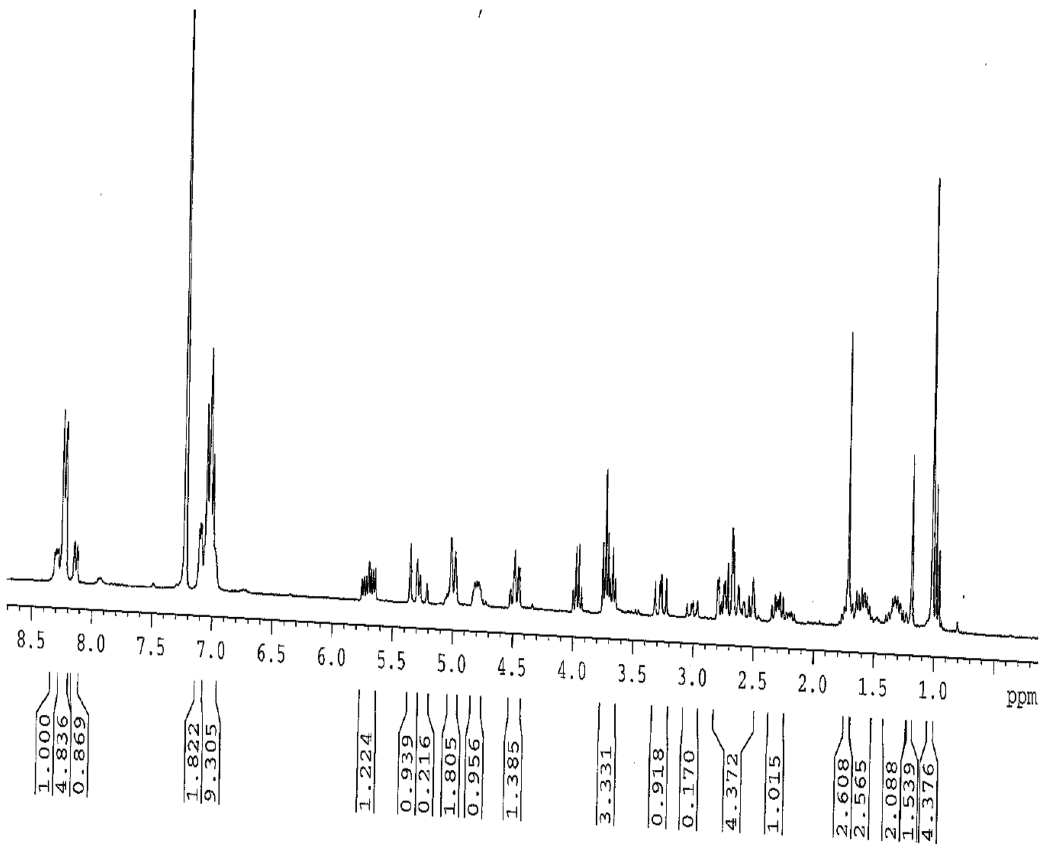


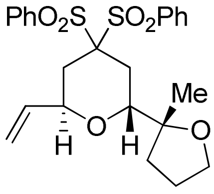
Product **12.** ^{13}C (100 MHz, $CDCl_3$)



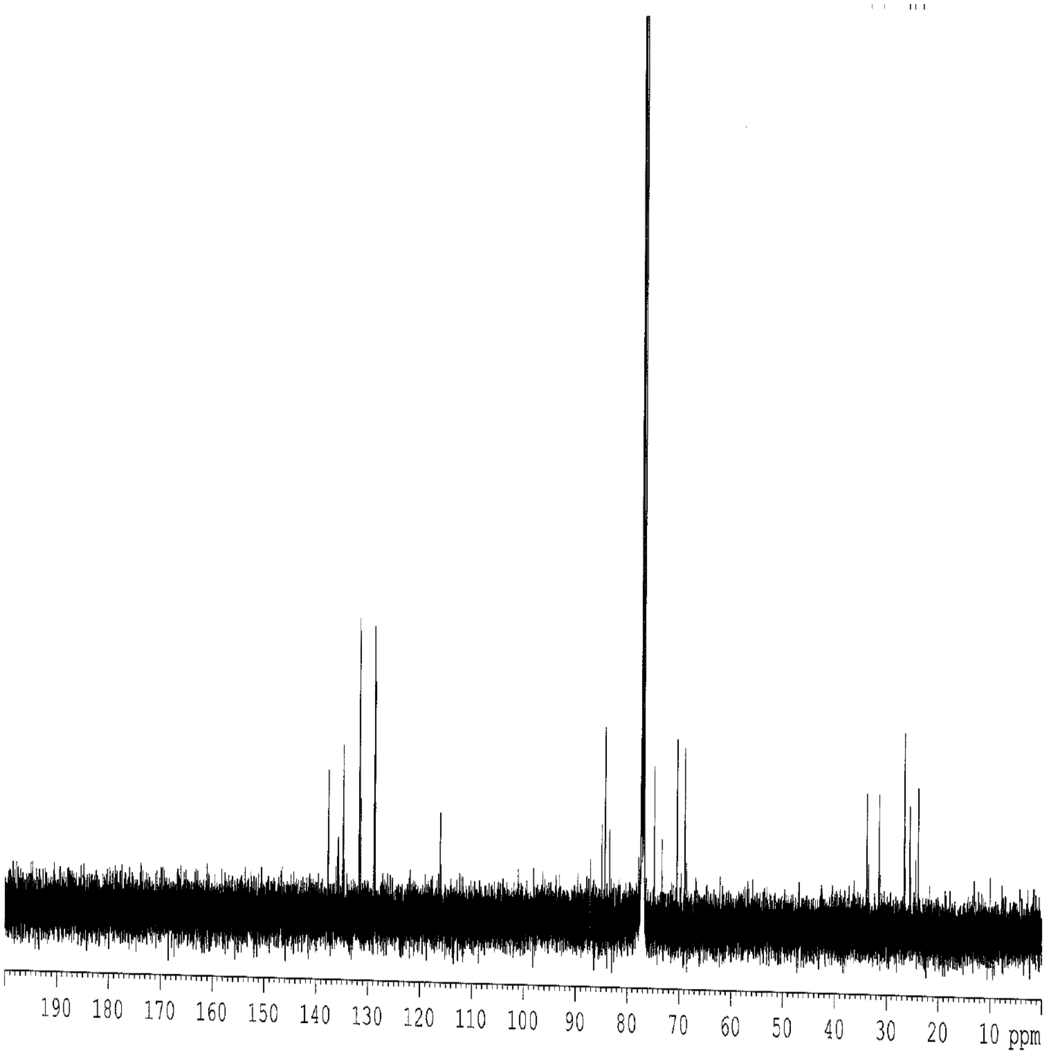


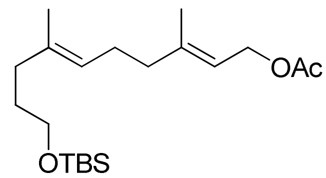
Product **14.** ^{1}H (300 MHz, C_6D_6)



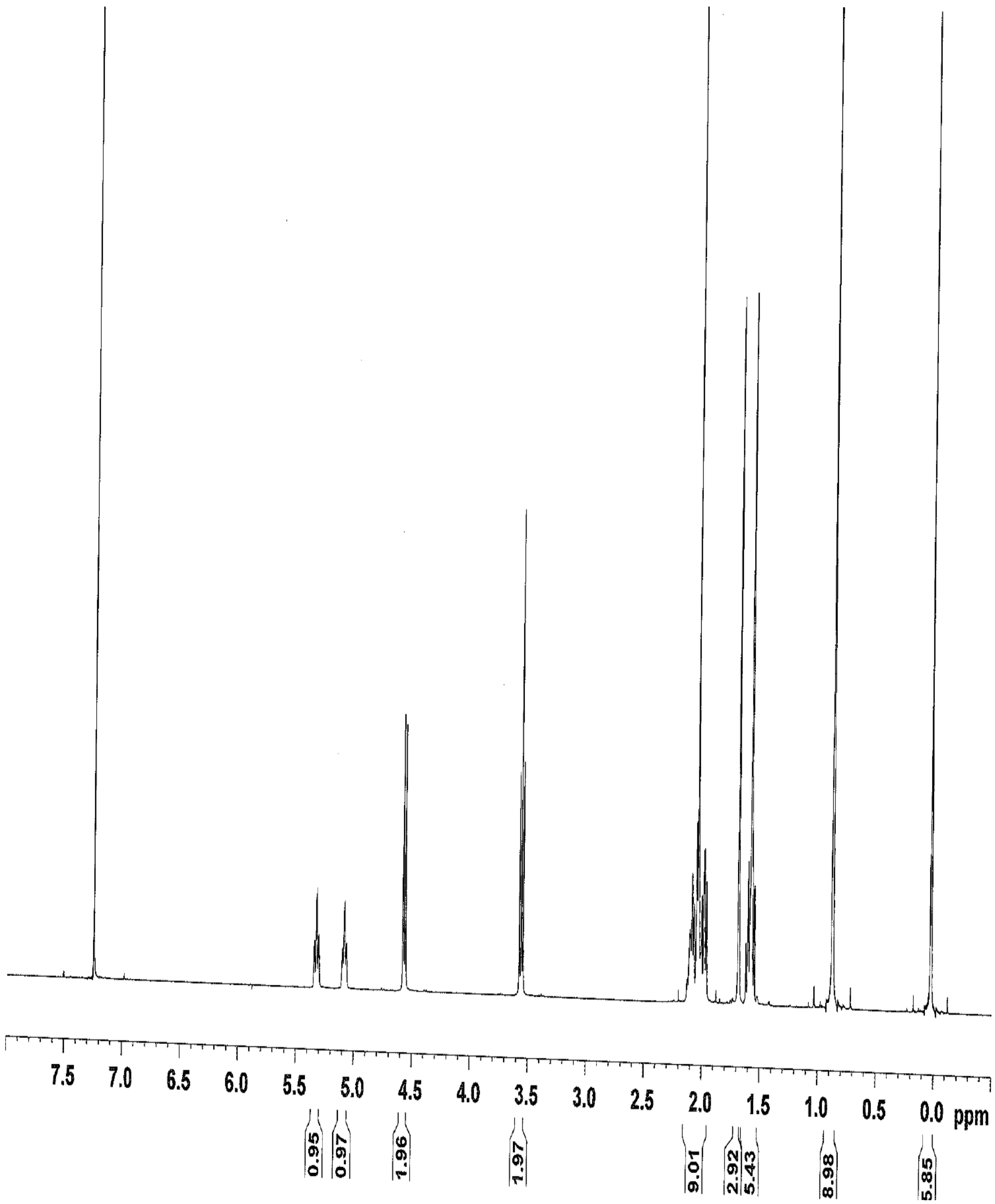


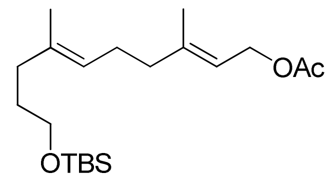
^{13}C (125 MHz, $CDCl_3$)



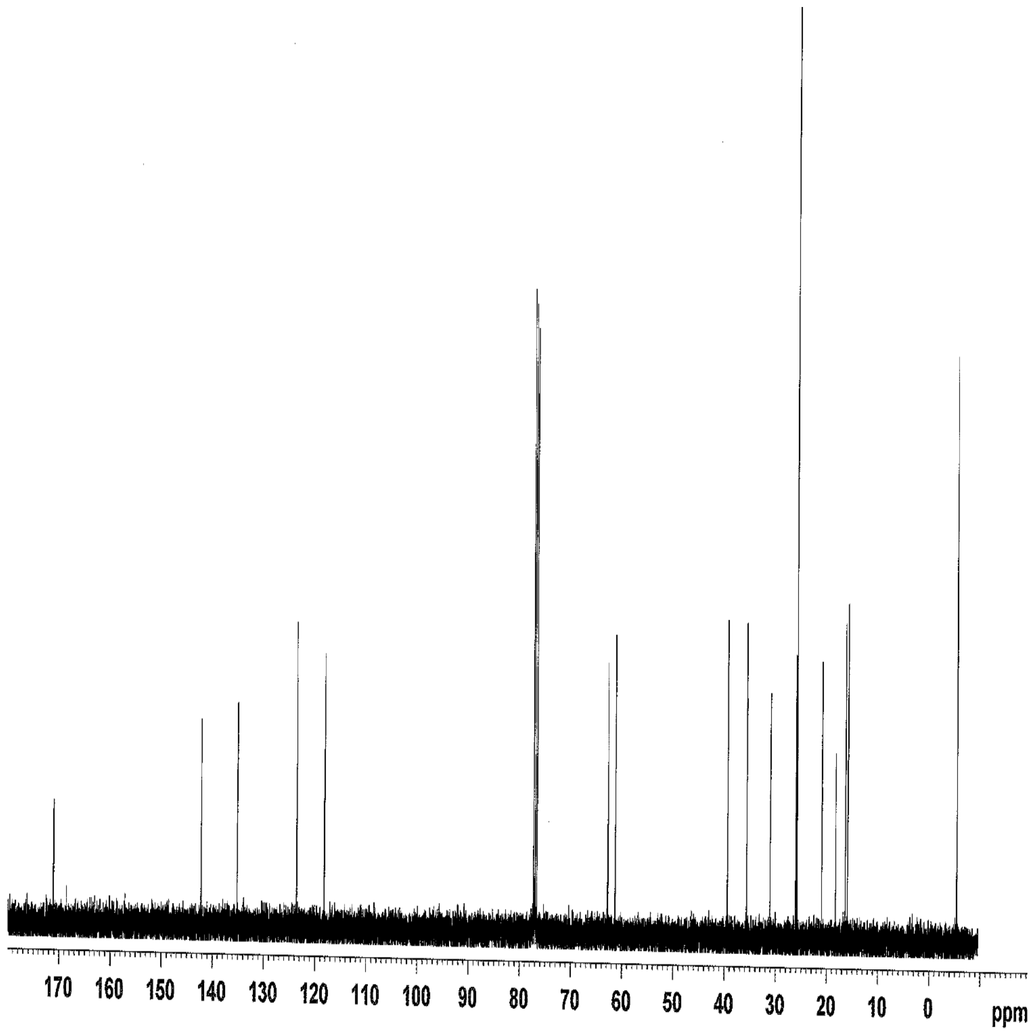


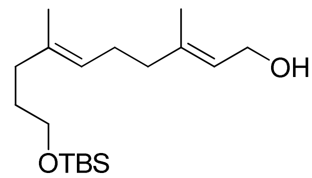
Silyl ether from **S21.** ^{1}H (400 MHz, $CDCl_3$)



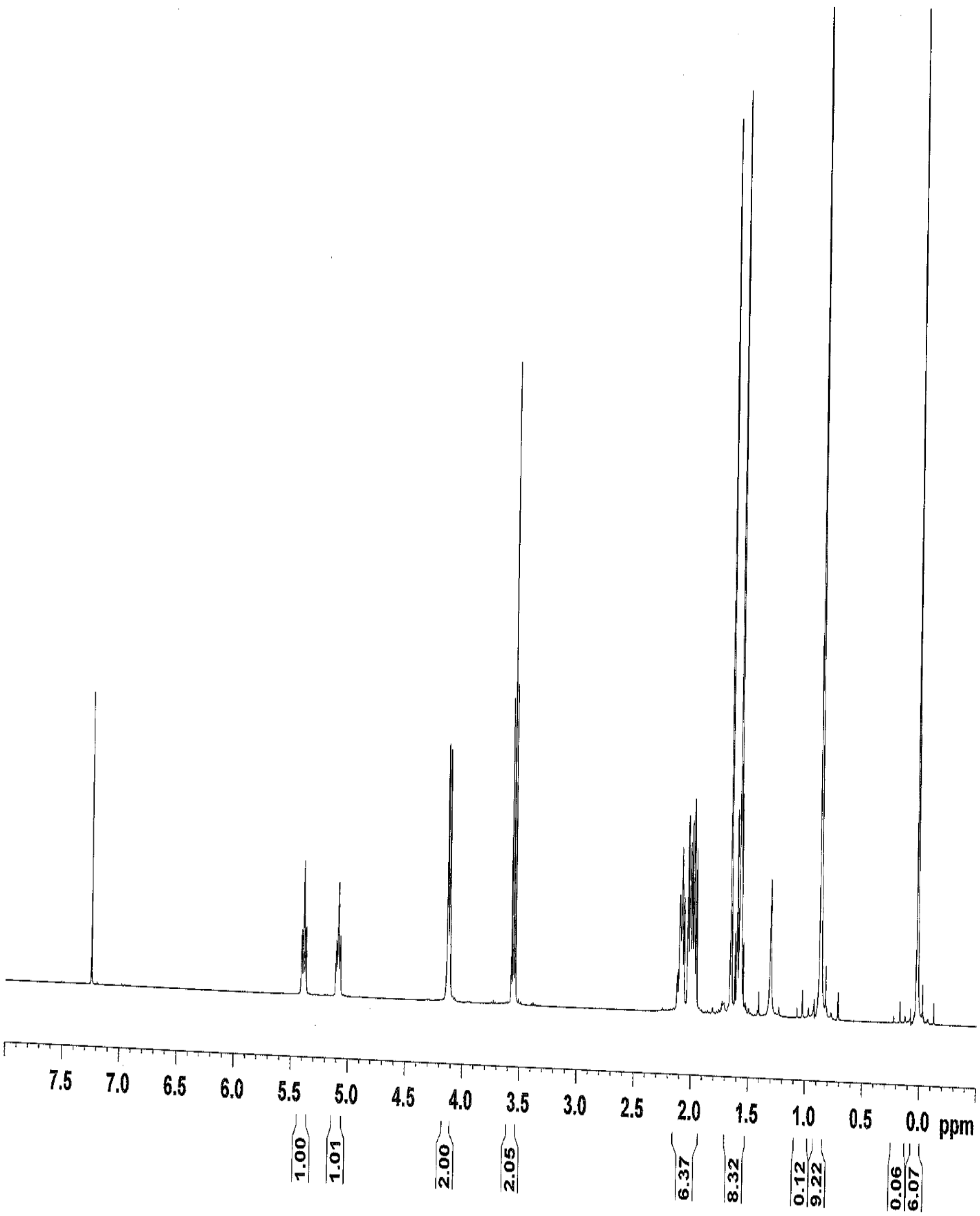


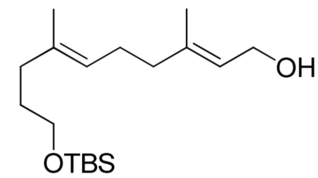
Silyl ether from **S21.** ^{13}C (100 MHz, $CDCl_3$)



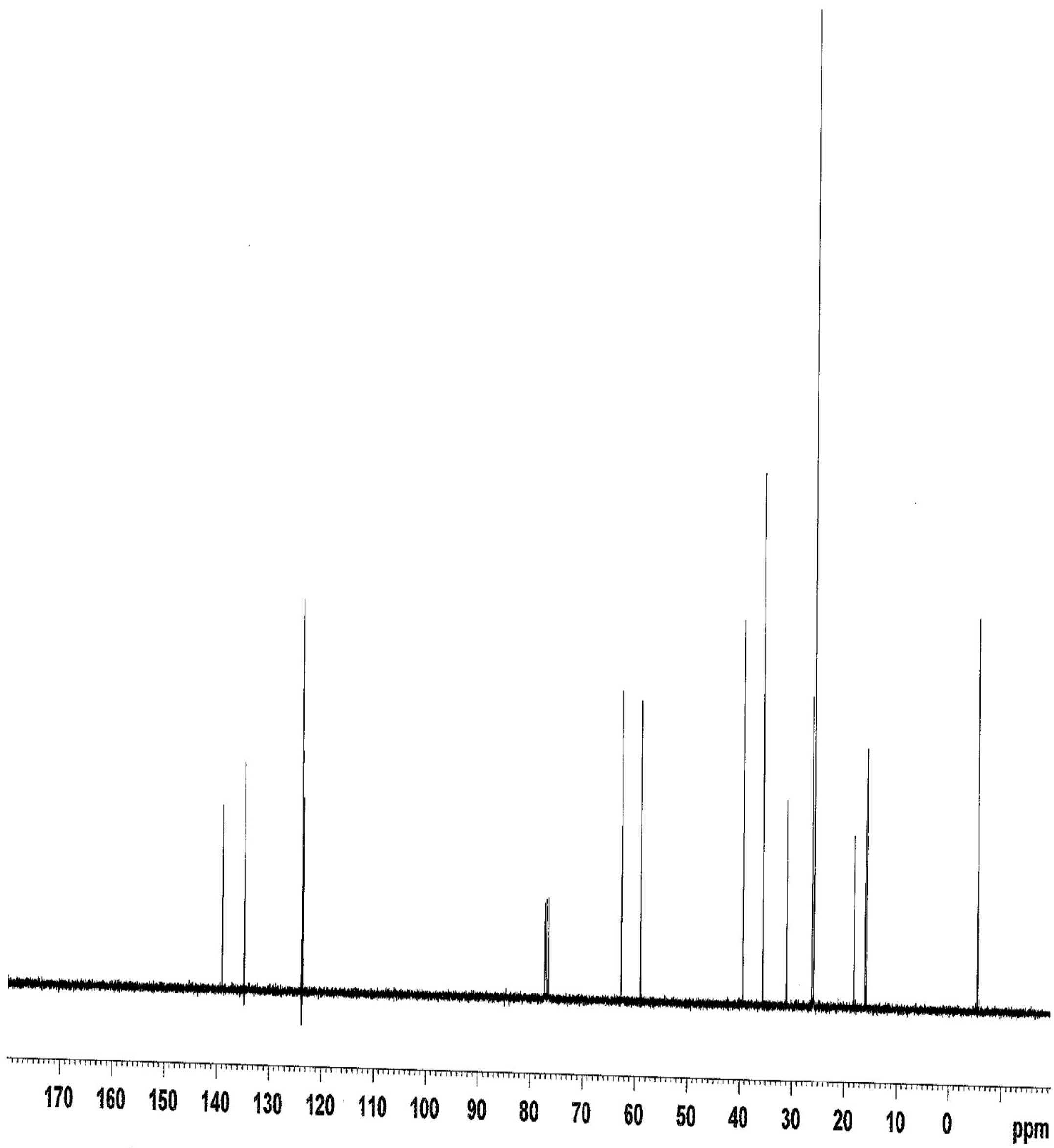


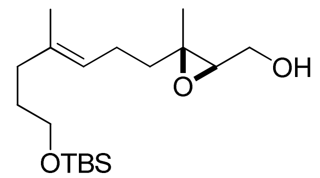
S22. ^{1}H (400 MHz, $CDCl_3$)



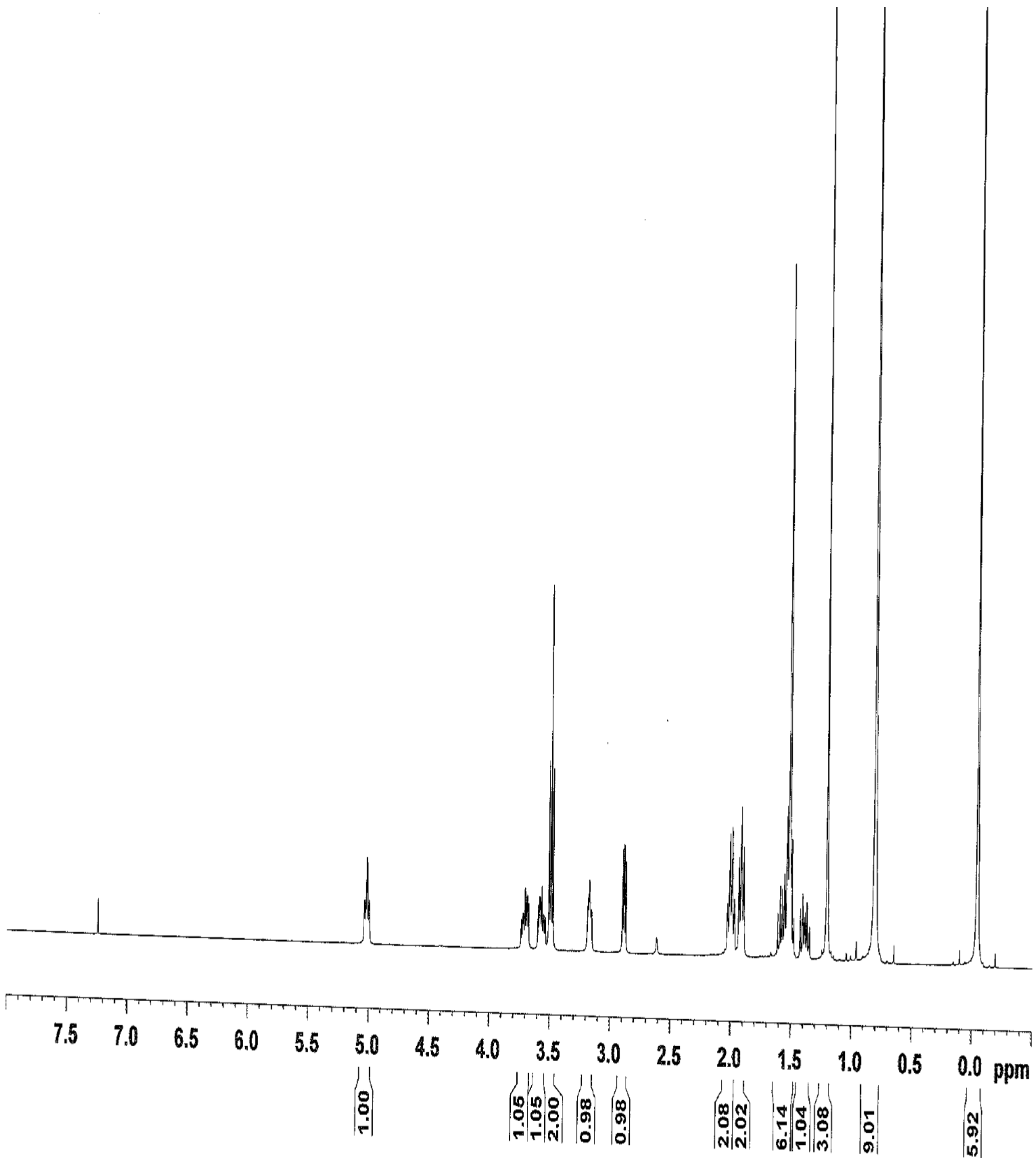


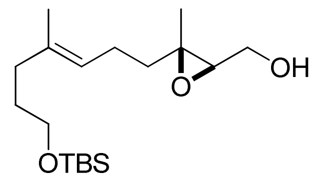
S22. ^{13}C (100 MHz, $CDCl_3$)



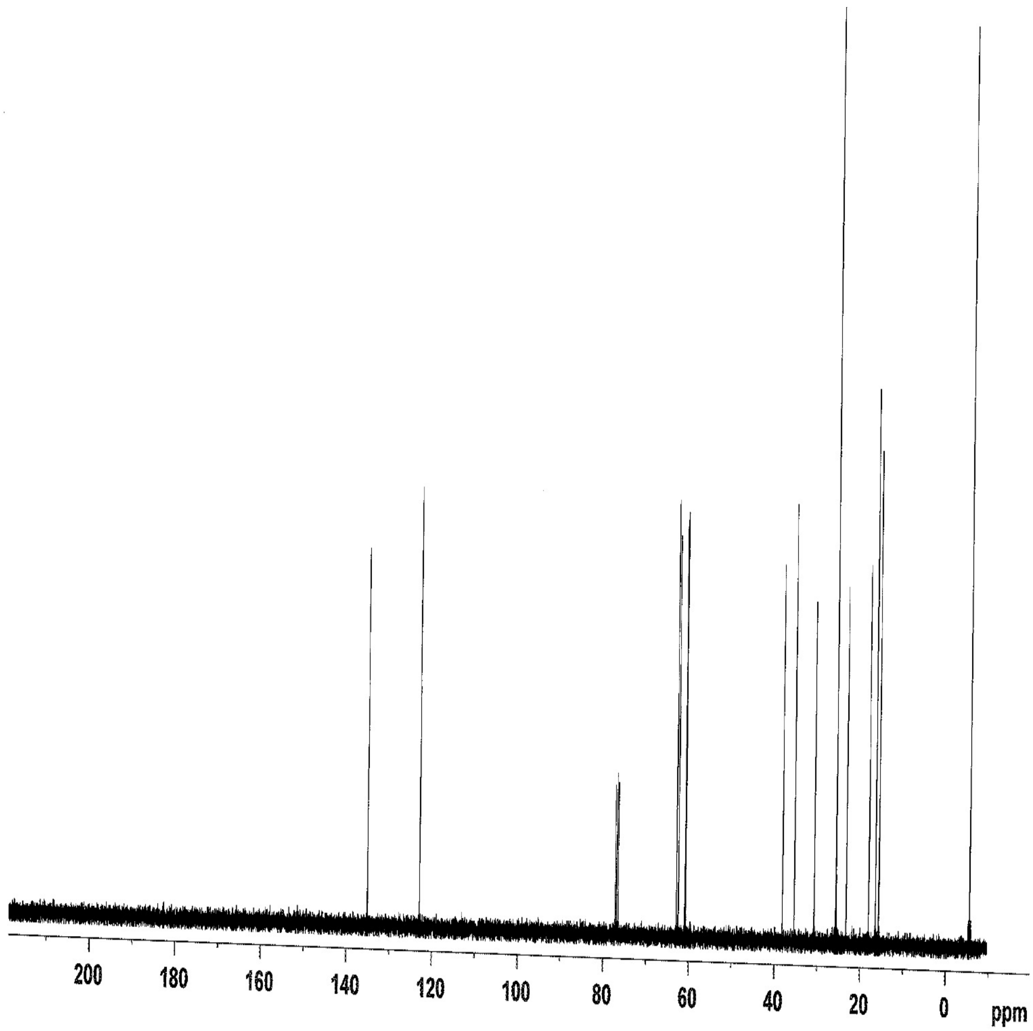


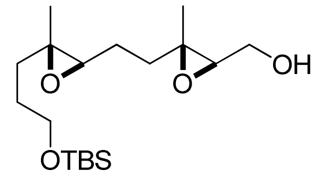
SAE product from **S22.** ${}^{1}H$ (400 MHz, $CDCl_3$)



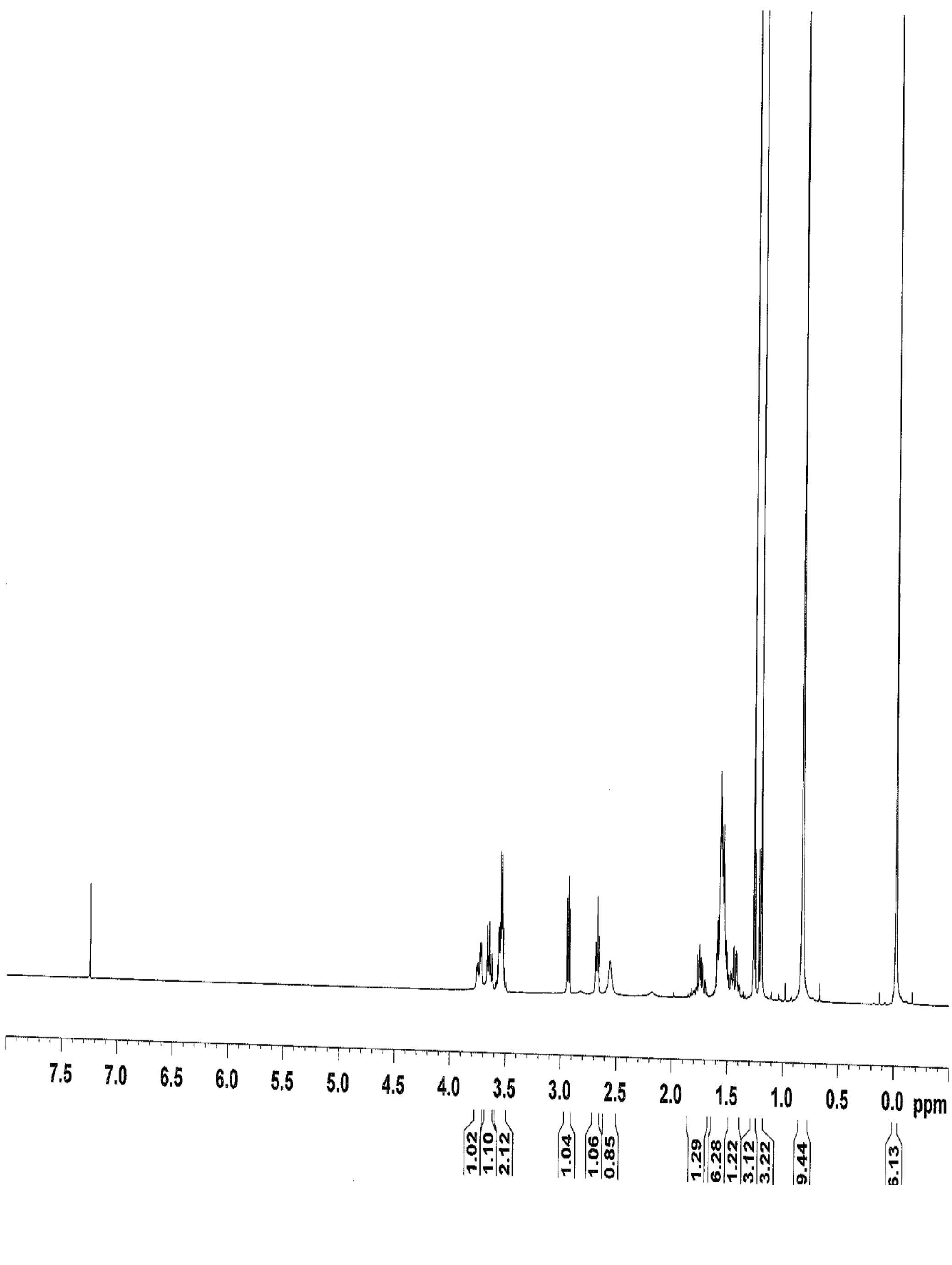


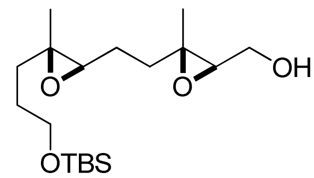
SAE product from **S22.** ^{13}C (100 MHz, $CDCl_3$)



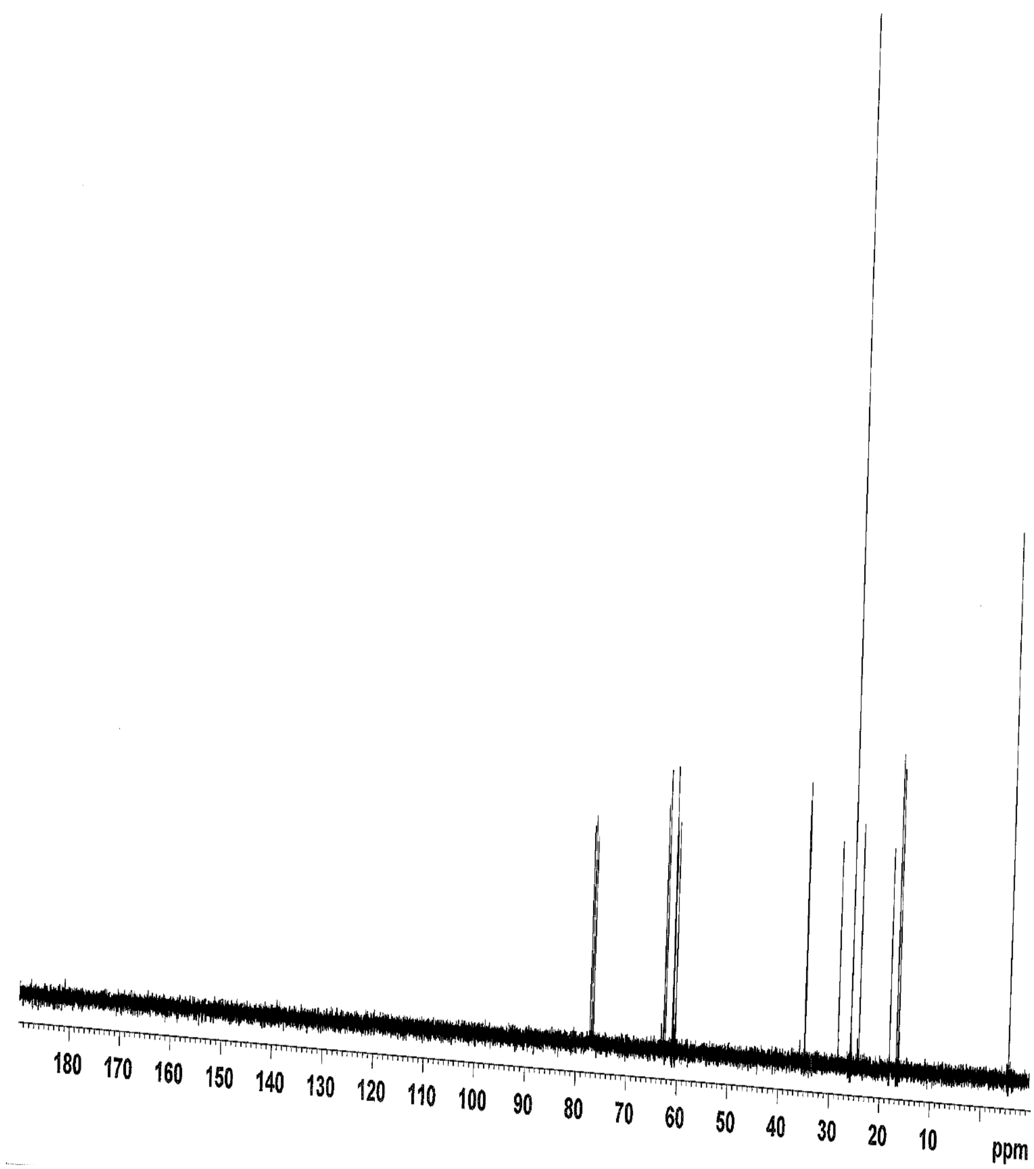


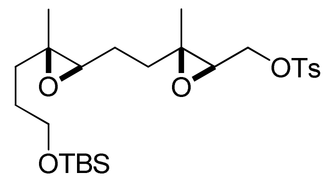
S23. ^{1}H (400 MHz, $CDCl_3$)



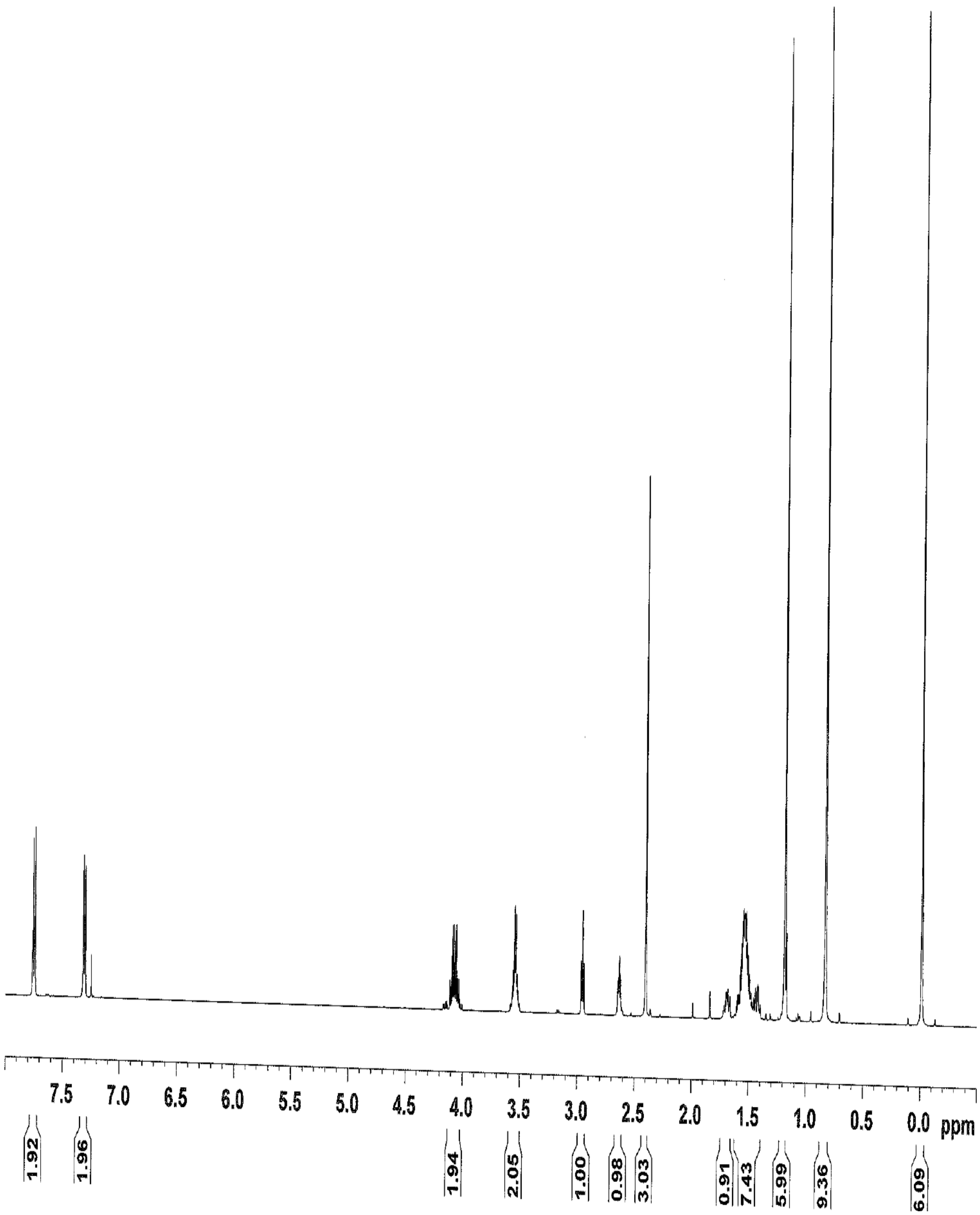


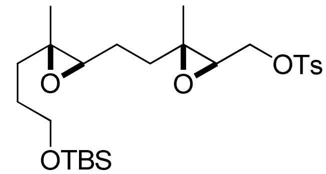
S23. ^{13}C (100 MHz, $CDCl_3$)



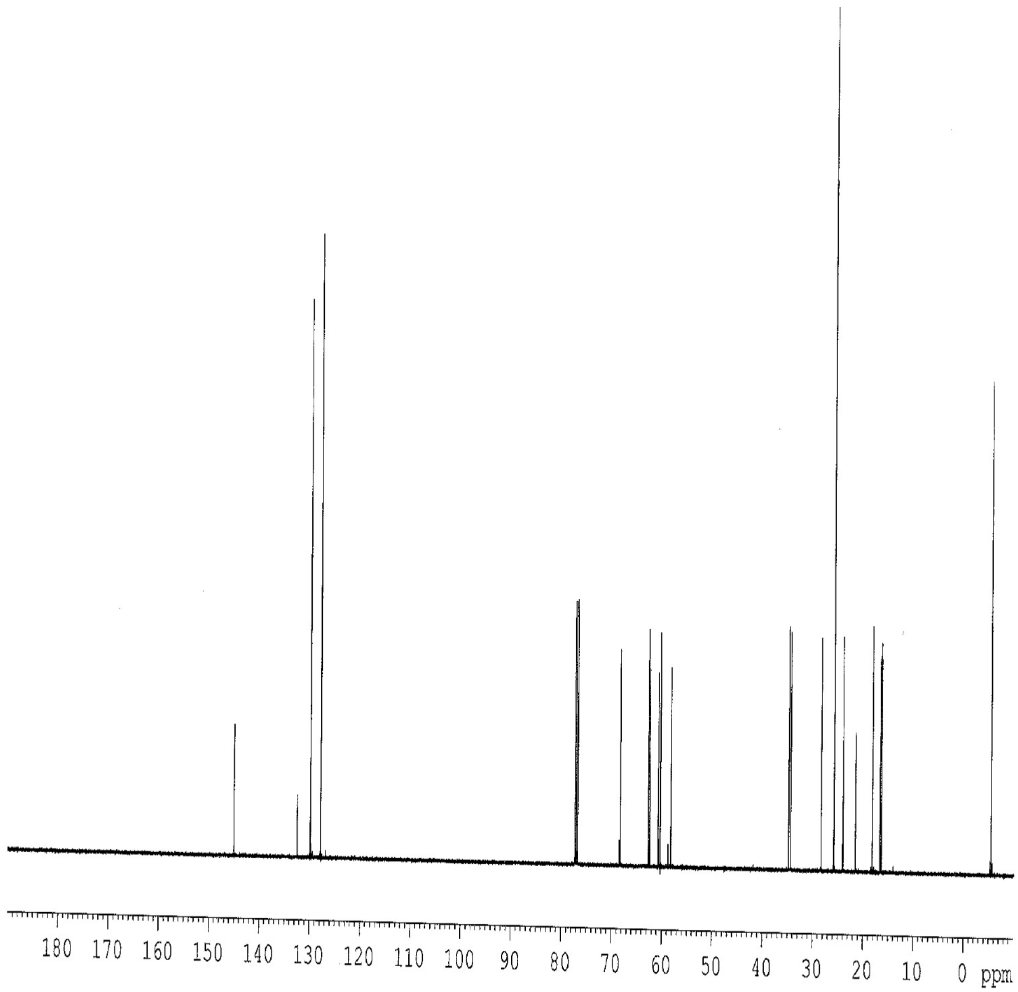


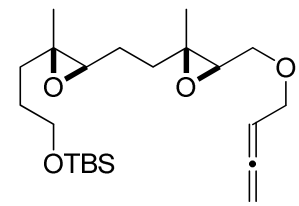
Tosylate from **S23.** ^{1}H (400 MHz, $CDCl_3$)



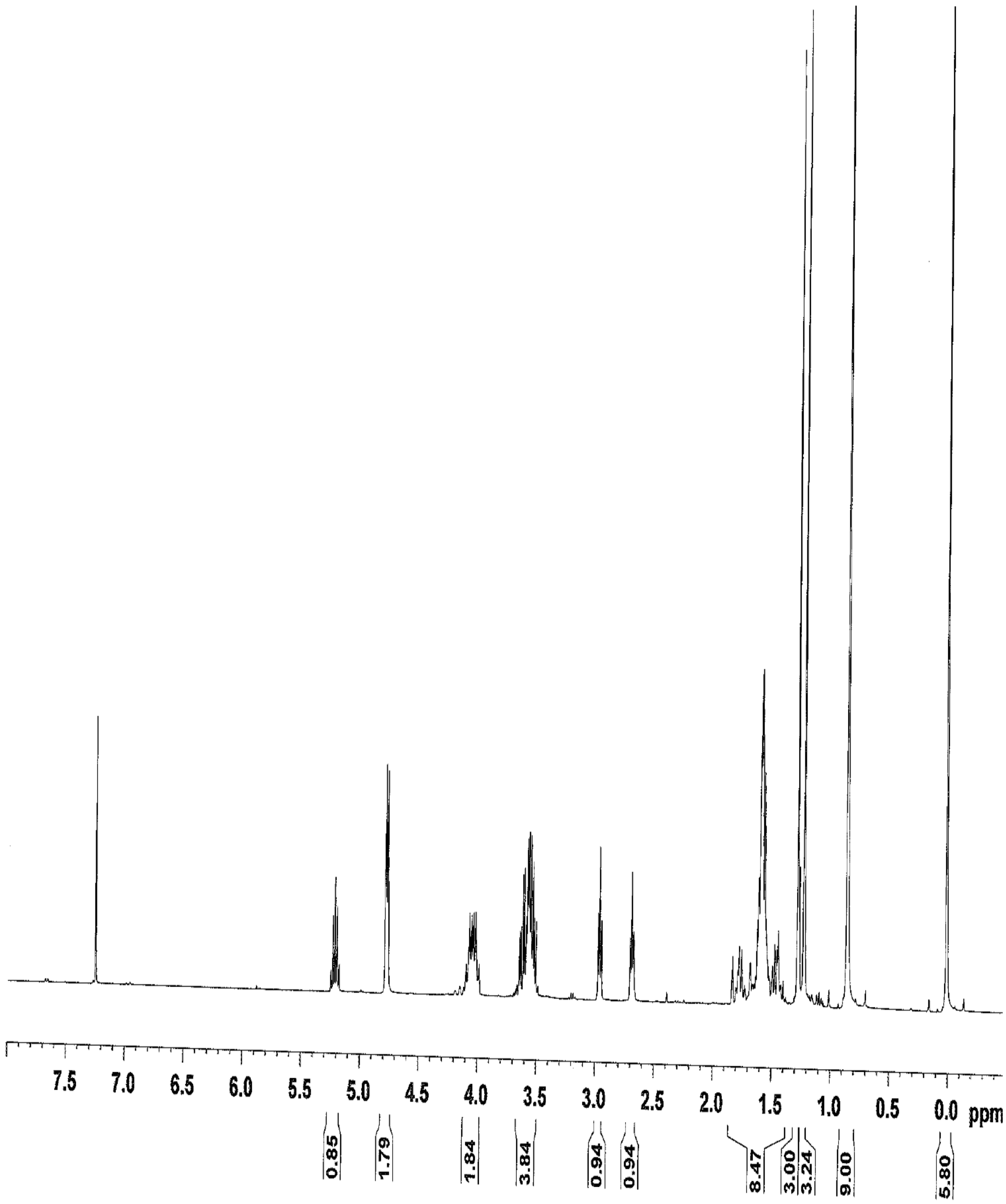


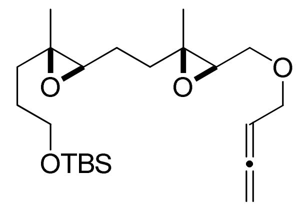
Tosylate from **S23.** ^{13}C (125 MHz, $CDCl_3$)



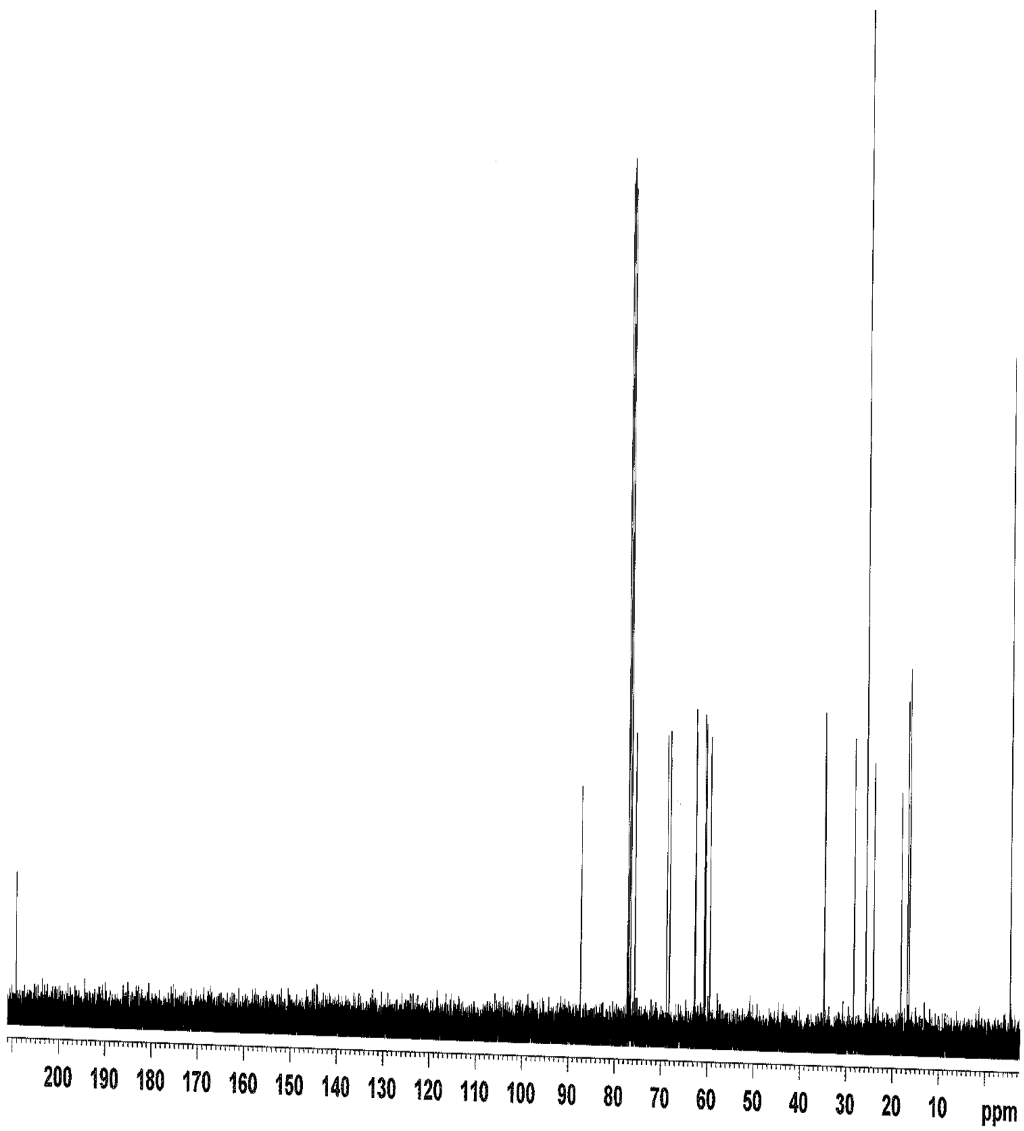


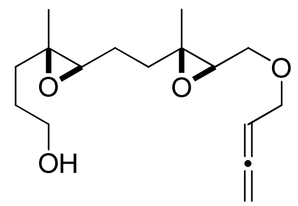
S24. ^{1}H (400 MHz, $CDCl_3$)



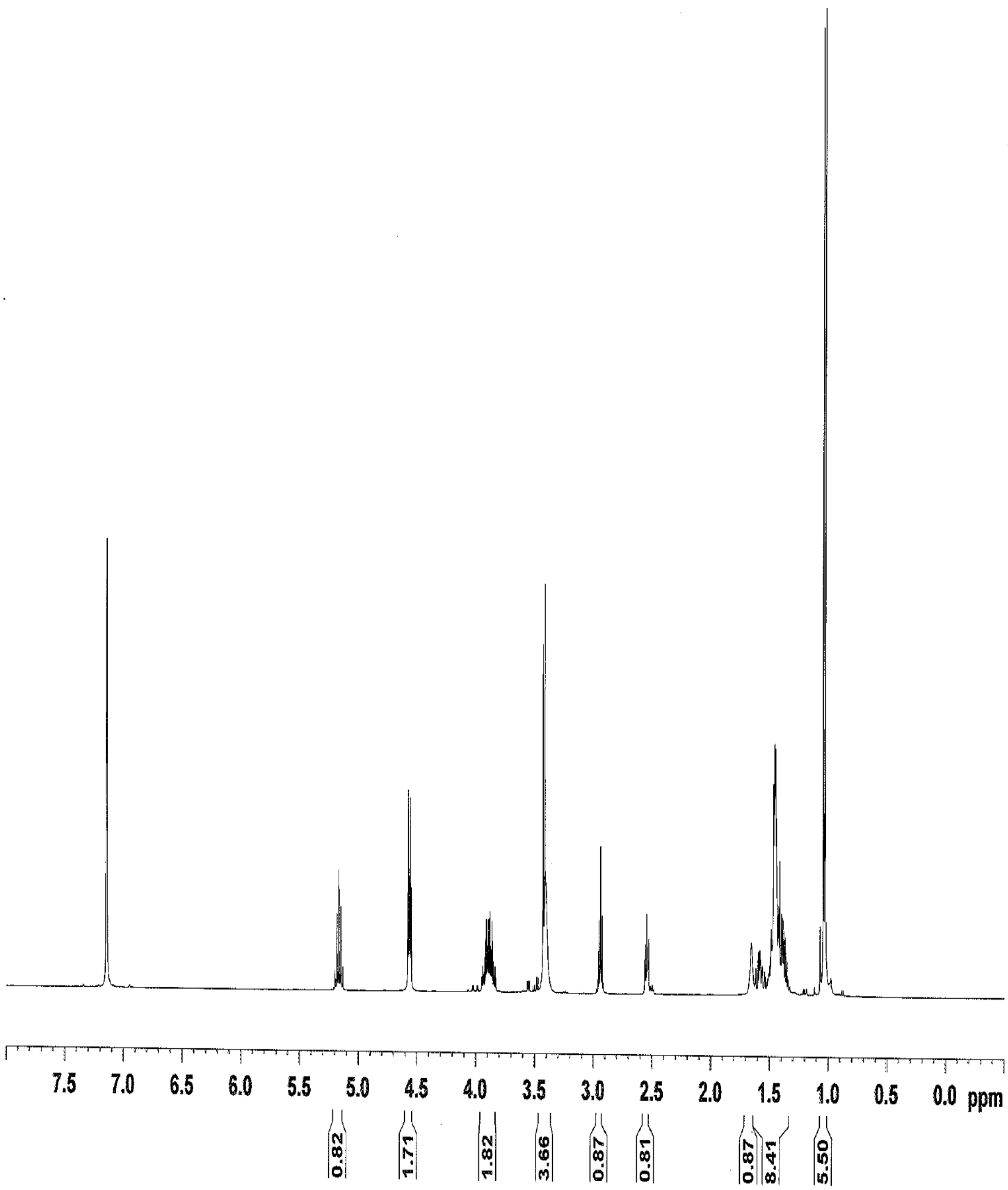


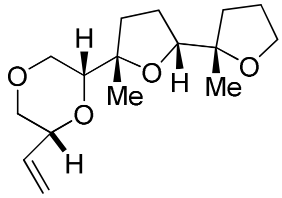
S24. ^{13}C (100 MHz, $CDCl_3$)



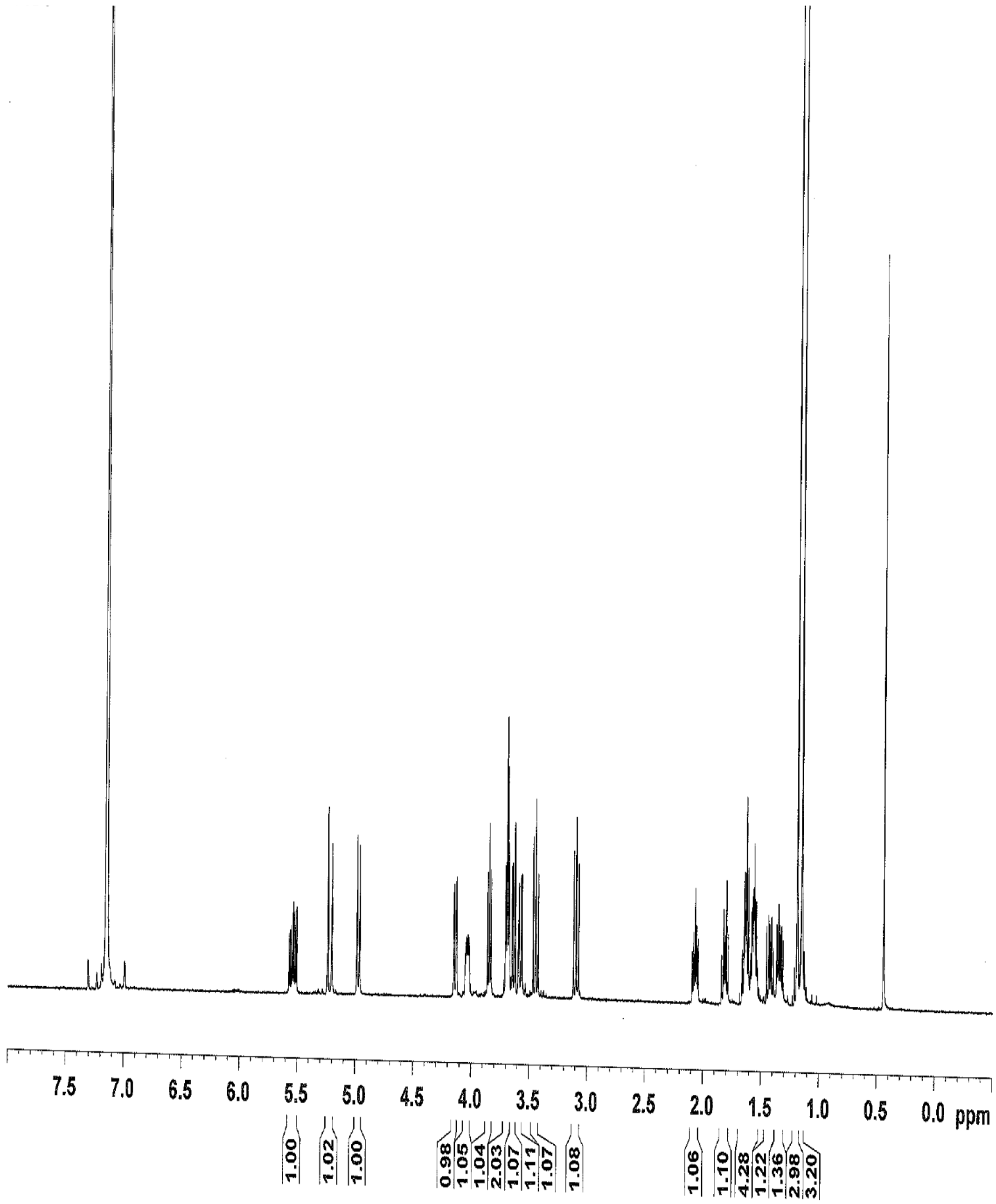


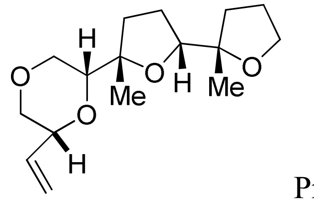
Substrate **16.** ^{1}H (400 MHz, C_6D_6)





Product **17.** ^{1}H (500 MHz, C_6D_6)





Product **17.** ^{13}C (125 MHz, C_6D_6)