

Programs Towards Tetrahydropyran Containing Small Macrolides of Cyanobacterial Origins: Synthetic Methodology Development and Total Synthesis

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PROGRAMS TOWARDS TETRAHYDROPYRAN CONTAINING
SMALL MACROLIDES OF CYANOBACTERIAL ORIGINS:
SYNTHETIC METHODOLOGY DEVELOPMENT AND TOTAL SYNTHESIS

VOLUME TWO

A Dissertation

Submitted to the Graduate School of
the University of Notre Dame
in Partial Fulfillment of the Requirements
for the Degree of

Doctor of Philosophy

by

Rendy Kartika

Richard E. Taylor, Director

Graduate Program in Chemistry and Biochemistry

Notre Dame, Indiana

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CHAPTER EIGHT

SUPPORTING INFORMATION: EXPERIMENTAL

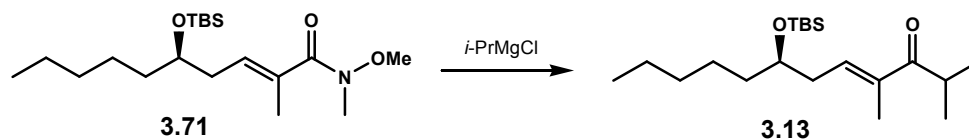
8.1. General Information

Unless otherwise noted, all materials were used as received from a commercial supplier without further purification. All anhydrous reactions were performed using oven-dried or flame-dried glassware, which was then cooled under vacuum and purged with nitrogen gas. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene, and diethyl ether (Et_2O) were filtered through activated alumina under nitrogen. Pentane and triethylamine (TEA) were dried over LiAlH_4 and CaH_2 respectively, and distilled prior to use. 4 Å molecular sieves were oven-dried overnight and then cooled under high vacuum prior to use. All reactions were monitored by Whatman analytical thin layer chromatography (TLC) plates (AL SIL G/UV, aluminum back) and analyzed with 254 nm UV light and / or anisaldehyde – sulfuric acid or potassium permanganate treatment. Silica gel for column chromatography was purchased from E. Merck (Silica Gel 60, 230-400 mesh). Biotage chromatography was performed using Flash 40+M, 25+M, 25+S, or 12+M KP-Sil™ Silica (32-63 μm , 60 Å, nominally 500 m^2/g silica) Cartridges. Unless otherwise noted, all ^1H and ^{13}C NMR spectra were recorded in CDCl_3 using either Varian

Unity Plus 300 spectrometers operating at 299.88 MHz for ^1H and 75.37 MHz for ^{13}C , Varian Inova 500 spectrometers operating at 499.86 MHz for ^1H and 125.69 MHz for ^{13}C , or Varian VNMRs 600 operating at 599.87 MHz for ^1H and 150.84 MHz for ^{13}C . Chemical shifts (δ) were reported in ppm relative to residual CHCl_3 as an internal reference (^1H : 7.26 ppm, ^{13}C : 77.00 ppm). Coupling constants (J) were reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), x (septet), h (heptet), b (broad), and m (multiplet). FT-IR spectra were recorded on Perkin-Elmer Paragon 1000 spectrometer, and absorption frequencies were reported in reciprocal centimeters (cm^{-1}). Mass spectra (FAB) were obtained at the Department of Chemistry and Biochemistry, University of Notre Dame using either a JEOL AX505HA or JEOL JMS-GCmate mass spectrometer.

8.2. Experimental Procedures for Chapter Three

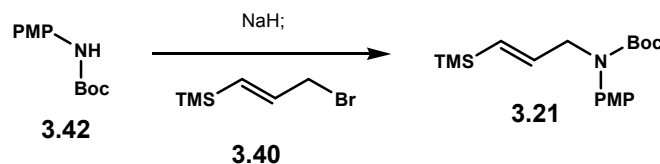
(+)-(R,E)-7-*tert*-butyldimethylsiloxy-2,4-dimethyldodec-4-en-3-one **3.13**



Weinreb amide **3.71** (2.58 g, 7.21 mmol) was dissolved in Et_2O (100 mL) and cooled to 0°C . Isopropylmagnesium chloride (10.8 mL, 21.6 mmol, 2.0 M in Et_2O) was added dropwise via a syringe pump over one hour while maintaining an internal temperature at 0°C . The solution was then stirred for three hours at this temperature.

The reaction was quenched carefully with a half-saturated aqueous solution of NH_4Cl (100 mL). The mixture was poured into a separatory funnel, and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 50 mL). After combining all organic layers, the solution was then dried with MgSO_4 and concentrated. The crude material was purified with silica gel column chromatography with 98:2 pentane : Et_2O to yield ketone **3.13** in 70% yield as a colorless oil (1.73 g, 5.08 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 6.73 (1H, tq, J = 7.0, 1.5 Hz), 3.82 (1H, p, J = 5.5 Hz), 3.32 (1H, h, J = 6.5 Hz), 2.45 – 2.35 (2H, m), 1.78 (3H, d, J = 1.0 Hz), 1.45 – 1.19 (8H, m), 1.09 (3H, d, J = 1.5 Hz), 1.08 (3H, d, J = 2.0 Hz), 0.89 (9H, s), 0.88 (3H, t, J = 5.5 Hz), 0.06 (3H, s), 0.05 (3H, s). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 206.13, 138.43, 136.97, 71.32, 37.34, 36.78, 33.66, 31.88, 25.79, 25.04, 22.61, 19.67, 19.63, 18.03, 14.01, 11.94, -4.84, -4.54. IR (cm^{-1}): ν = 2957, 2951, 2859, 1670, 1470, 1380, 1256, 1086, 836, 775. HRMS-FAB: $(\text{M}-\text{H})^+ = 339.2719$ calculated for $\text{C}_{20}\text{H}_{39}\text{O}_2\text{Si}$, experimental = 339.2730. $[\alpha]_{\text{D}}^{20} = +11.3$ (c = 3.45 in CHCl_3)

tert-butyl 4-methoxyphenyl(*E*)-3-(trimethylsilyl)allylcarbamate **3.21**

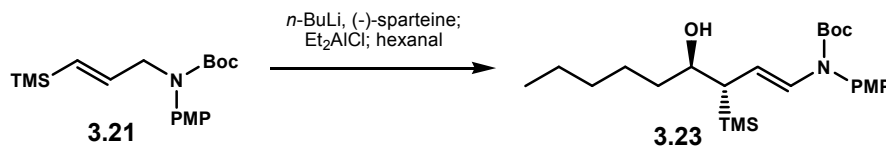


NaH (0.99 g, 41.4 mmol) was suspended in THF (20 mL) and cooled to 0°C . Carbamate **3.42** (4.62 g, 20.7 mmol), as a solution in THF (20 mL), was added dropwise, and yellow solids began to form. After standing for one hour, allylic bromide

3.40 (3.63 g, 18.8 mmol), as a solution in THF (20 mL), was added dropwise which resulted in the solid to slowly dissolve. After stirring the reaction overnight, the mixture was cooled to 0°C, and quenched with slow addition of DI water (50 mL). After separation of layers, the aqueous layer was extracted with Et₂O (3 x 50 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated under vacuum. Purification by silica gel column chromatography with 80:20 hexanes : EtOAc yielded product **3.21** in 74% yield as a yellow oil (4.64 g, 13.8 mmol). ¹H (300 MHz, CDCl₃): δ (ppm) = 7.18 – 7.09 (2H, m, b), 6.80 – 6.85 (2H, m), 6.05 (1H, dt, J = 18.6, 4.8 Hz), 5.76 (1H, d, J = 18.6 Hz), 4.17 (2H, dd, J = 5.1, 1.5 Hz), 3.78 (3H, s), 1.43 (9H, s), 0.05 (9H, s). ¹³C (75 MHz, CDCl₃): δ (ppm) = 157.35, 154.83, 141.72, 136.01, 131.31 (broad), 127.53 (broad), 113.73, 80.01, 55.37, 55.31, 28.26, -1.36. IR (cm⁻¹): ν = 3040, 2955, 1701, 1513, 1248, 1166. HRMS-FAB: M⁺ = 335.1917 calculated for C₁₈H₂₉O₃NSi, experimental 335.1898.

tert-butyl (*E*,3*S*,4*R*)-4-hydroxy-3-(trimethylsilyl)non-1-enyl 4-methoxyphenylcarbamate

3.23

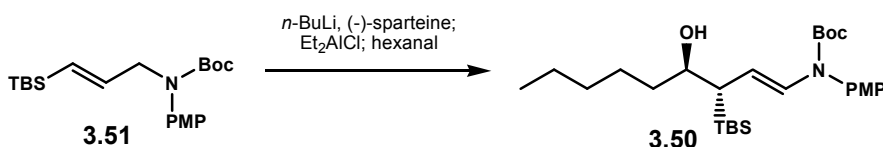


In a flame dried flask, enecarbamate **3.21** (1.78 g, 5.30 mmol) and (-)-sparteine (1.83 mL, 7.95 mmol) was dissolved in toluene (74 mL). This solution was then dried with 2 grams of 4 Å molecular sieves and transferred into a flame-dried round-bottomed

flask via cannula, and then cooled to -78°C . This temperature was maintained throughout the reaction. A solution of *n*-BuLi (3.00 mL, 7.95 mmol, 2.3 M in hexanes) was then added dropwise such that an internal temperature of the solution was maintained below -75°C . After stirring for 40 minutes, a solution of Et_2AlCl (5.9 mL, 10.6 mmol, 1.8M in toluene) was added dropwise over 15 minutes. After stirring the solution for additional 30 minutes, freshly distilled hexanaldehyde (1.27 mL, 10.6 mmol) was added to the mixture dropwise. After stirring for two hours, the reaction completed, and the solution was poured into a separatory funnel containing DI water (50 mL) and 2 M HCl (5 mL). The product was then extracted with Et_2O (3 x 50 mL), and the combined ether layers was washed with a saturated NaHCO_3 aqueous solution (50 mL). The organic layer was dried over MgSO_4 , filtered, and concentrated under vacuum leaving a crude yellow oil. ^1H NMR analysis of the crude material showed only a single diastereomer. The crude product was purified using Biotage purification system. Biotage condition: 40+M column, 95:5 hexanes : EtOAc for 240 mL, then 95:5 \rightarrow 85:25 hexanes : EtOAc linear gradient over 600 mL, then 80:20 hexanes : EtOAc for 240 mL. Removal of solvent afforded homoaldol product **3.23** in 82% yield as a pale yellow oil (1.89 g, 4.35 mmol). The enantiomeric ratio was determined to be 96:4 from a chiral HPLC analysis (ChiralPak AD-H column, 1.0 mL/min, 5% iPrOH in hexanes). The retention time of major enantiomer (*3S*, *4R*) was 4.74 minutes, while the retention time of minor enantiomer (*3R*, *4S*) was 5.85 minutes. ^1H (500 MHz, d_6 -acetone, ref = 2.05): δ (ppm) = 7.08 (2H, m), 6.97 (2H, m), 6.94 (1H, d, J = 16.0 Hz), 4.54 (1H, dd, J = 14.5, 11.5 Hz), 3.81 (3H, s), 3.75 (1H, m), 3.26 (1H, d, J = 5.0 Hz), 1.61 (1H, dd, J = 6.5, 2.0 Hz), 1.38 (9H, s), 1.34 – 1.24 (8H, m), 0.89 (3H, t, J = 7.0 Hz), -0.02 (9H, s). ^{13}C (125 MHz, d_6 -

acetone, ref = 30.83): δ (ppm) = 159.41, 153.18, 133.52, 130.49, 129.84, 115.01, 109.71, 80.71, 71.91, 55.69, 38.29, 37.91, 32.71, 28.45, 26.33, 23.38, 14.42, -1.73. IR (cm⁻¹): ν = 3505, 3063, 2955, 2939, 1706, 1686, 1648, 1513, 1325, 1246, 1168, 1036, 837. HRMS-FAB: (M-H)⁺ = 434.2727 calculated for C₂₄H₄₀O₄NSi, experimental 434.2751.

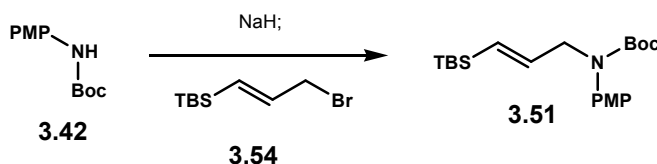
tert-butyl (*E*,3*S*,4*R*)-3-(*tert*-butyldimethylsilyl)-4-hydroxynon-1-enyl-4-methoxyphenyl carbamate **3.50**



In a flame dried flask, enecarbamate **3.51** (2.00 g, 5.30 mmol) and (-)-sparteine (1.83 mL, 7.95 mmol) was dissolved in toluene (74 mL). This solution was then dried using 2 grams of 4 Å molecular sieves and transferred into a flame-dried round-bottomed flask via cannula, and then cooled to -78°C. This temperature was maintained throughout the reaction. A solution of *n*-BuLi (3.00 mL, 7.95 mmol, 2.3 M in hexanes) was then added dropwise such that an internal temperature of the solution was maintained below -75°C. After stirring for 40 minutes, a solution of Et₂AlCl (5.9 mL, 10.6 mmol, 1.8M in toluene) was added dropwise over 15 minutes. After string the solution for additional 30 minutes, freshly distilled hexanaldehyde (1.27 mL, 10.6 mmol) was added to the solution dropwise. After stirring for two hours, the reaction completed, and the solution was poured into a separatory funnel containing DI water (50 mL) and 2 M HCl (5 mL). The product was then extracted with Et₂O (3 x 50 mL), and the combined ether layers was

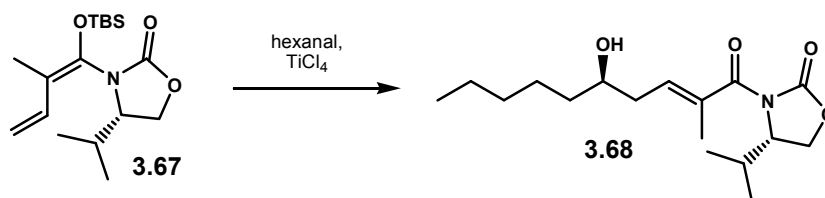
washed with a saturated NaHCO₃ aqueous solution (50 mL). The organic layer was dried over MgSO₄, filtered, and concentrated under vacuum leaving a crude yellow oil. ¹H NMR analysis of the crude material showed only a single diastereomer. The crude product was purified using Biotage purification system. Biotage condition: 40+M column, 95:5 hexanes : EtOAc for 240 mL, then 95:5 → 85:25 hexanes : EtOAc linear gradient over 600 mL, then 80:20 hexanes : EtOAc for 240 mL. Removal of solvent afforded homoaldol product **3.50** in 87% yield as a pale yellow oil (2.21 g, 4.63 mmol). The enantiomeric ratio was determined to be 99:1 from a chiral HPLC analysis (ChiralPak AD-H column, 1.0 mL/min, 5% iPrOH in hexanes). The retention time of major enantiomer (*3S*, *4R*) was 4.98 minutes, while the retention time of minor enantiomer (*3R*, *4S*) was 6.76 minutes. ¹H (300 MHz, d₆-acetone, ref = 2.05): δ (ppm) = 7.07 (2H, m), 6.98 (1H, d, J = 15.0 Hz), 6.96 (2H, m), 4.58 (1H, dd, J = 14.4, 11.4 Hz), 3.81 (3H, s), 3.77 (1H, m, broad), 3.23 (1H, d, J = 4.8 Hz), 1.83 (1H, dd, J = 11.7, 2.4 Hz), 1.38 (9H, s), 1.43 – 1.29 (8H, m, broad), 0.93 (9H, s), 0.93 – 0.88 (3H, m), 0.01 (3H, s), -0.09 (3H, s). ¹³C (75 MHz, d₆-acetone, ref = 30.83): δ (ppm) = 159.43, 153.16, 133.34, 130.52 (2 carbon signals), 114.98, 110.13, 80.71, 72.33, 55.68, 38.16, 34.40, 32.70, 28.44, 27.93, 26.32, 23.35, 18.28, 14.43, -5.39, -5.83. IR (cm⁻¹): *f* = 3513 (broad), 3070, 2955, 2928, 2855, 1708, 1686, 1648, 1513, 1324, 1247, 1161, 1034, 834. HRMS-FAB: (M+H)⁺ = 478.3353 calculated for C₂₇H₄₈O₄NSi, experimental = 478.3347.

tert-butyl (*E*)-3-(*tert*-butyldimethylsilyl)allyl4-methoxyphenylcarbamate **3.51**



NaH (0.85 g, 35.6 mmol) was suspended in DMF (20 mL) and cooled to 0°C. Carbamate **3.42** (7.95 g, 35.6 mmol), as a solution of DMF (20 mL), was added dropwise which resulted in rapid gas evolution. After stirring for one hour, allylic bromide **3.54** (6.44 g, 27.4 mmol), as a solution of DMF (20 mL), was then added dropwise. After stirring the reaction overnight at room temperature, the mixture was cooled to 0°C, and quenched with slow addition of DI water (50 mL). The aqueous layer was extracted with Et₂O (3 x 100 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated under vacuum. Purification by silica gel column chromatography with 80:20 hexanes : EtOAc yielded product **3.21** in 74% yield as a yellow oil (4.64 g, 13.8 mmol). ¹H (300 MHz, CDCl₃): δ (ppm) = 7.12 – 7.09 (2H, b), 6.84 – 6.80 (2H, m), 6.05 (1H, dt, J = 18.6, 5.1 Hz), 5.76 (1H, d, J = 18.6 Hz), 4.20 (2H, dd, J = 4.8, 1.2 Hz), 3.78 (3H, s), 1.43 (9H, s), 0.83 (9H, s), 0.05 (9H, s). ¹³C (75 MHz, CDCl₃): δ (ppm) = 157.38, 154.78, 142.99, 135.86, 128.61 (b), 127.62, 113.74, 80.00, 55.36, 55.34, 28.27, 26.32, 16.42, -6.20. IR (cm⁻¹): ν = 3042, 2953, 2856, 1702, 1513, 1388, 1248, 1166, 1037, 831. HRMS-FAB: M⁺ = 377.2386 calculated for C₂₁H₃₅O₃NSi, experimental 377.2377.

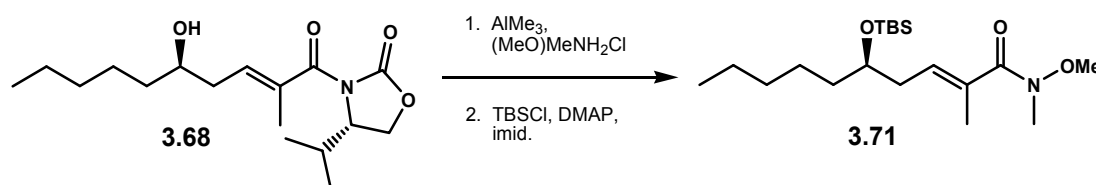
(+)-Vinylogous Mukaiyama Aldol Adduct 3.68



Into a flame dried flask, freshly distilled hexanal (17.8 mL, 144 mmol) was dissolved in CH_2Cl_2 (200 mL) and then cooled to -78°C . A precooled (-78°C) solution of TiCl_4 (8.7 mL, 79.1 mmol) in CH_2Cl_2 (79 mL) was then added rapidly via cannula. After stirring the mixture for 5 minutes, this solution was added via cannula to a precooled (-78°C) solution of *N,O*-silylketene acetal **3.67** in CH_2Cl_2 (400 mL). The reaction mixture was stirred at -78°C for an hour at which all of **3.67** were consumed. The reaction was then quenched with a saturated NaHCO_3 solution (100 mL), warmed up to room temperature, and then a saturated Rochelle's salt solution (200 mL) was added. The mixture was vigorously stirred until separation of layers was achieved. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The organic layers were combined, dried over MgSO_4 , and then concentrated under vacuum. The crude material was purified with silica gel column chromatography with 70:30 hexanes : EtOAc to yield aldol adduct **3.68** as a colorless oil (21.3 g, 68.4 mmol) in 95% yield as a single diastereomer as determined by both ^1H and ^{13}C NMR. ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 6.03 (1H, tq, J = 7.5, 1.5 Hz), 4.53 (1H, ddd, J = 8.5, 5.5, 4.5 Hz), 4.31 (1H, t, J = 9.0 Hz), 4.17 (1H, dd, J = 9.0, 5.5 Hz), 3.69 (1H, m), 2.81 (1H, s, b), 2.37 – 2.30 (2H, m), 2.26 (1H, m), 1.91 (3H, d, J = 1.0 Hz), 1.56 – 1.22 (8H, m), 0.90

(3H, d, $J = 7.0$ Hz), 0.89 (3H, d, $J = 7.0$ Hz), 0.86 (3H, t, $J = 6.5$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 171.48, 154.21, 135.26, 132.87, 70.47, 63.37, 58.04, 36.77, 36.70, 31.75, 28.26, 25.50, 22.56, 17.74, 15.01, 13.98, 13.64. IR (cm^{-1}): $\nu = 3524, 2961, 2938, 2860, 1781, 1686, 1297, 1209, 1056, 773$. HRMS-FAB: $(\text{M}+\text{H})^+ = 312.2175$ calculated for $\text{C}_{17}\text{H}_{30}\text{O}_4\text{N}$, experimental = 312.2157. $[\alpha]_{\text{D}}^{20} = +33.2^\circ$ ($c = 1.24$ in CHCl_3).

(+)-(R,E)-5-tert-butyltrimethylsiloxy-N-methoxy-N,2-dimethyldec-2-enamide **3.71**

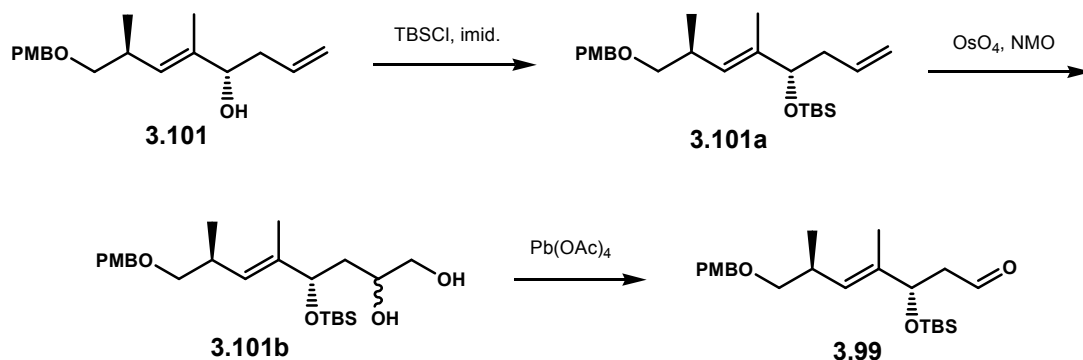


Weinreb's salt (18.6 g, 191 mmol) was suspended in THF (300 mL) and cooled to 0°C . AlMe_3 (95.4 mL, 191 mmol, 2.0 M in hexanes) was then added dropwise which resulted in vigorous gas evolution. The solution was warmed up to room temperature, stirred for an hour, and cooled back to 0°C . In a separate flask, imide **3.68** (19.7 g, 63.1 mmol) was dissolved in THF (400 mL), and this solution was cooled to 0°C . The solution of Weinreb's salt – aluminum complex was then transferred to the solution of imide **3.68** via cannula. The resulting solution was warmed up to room temperature and stirred overnight in which all starting material was completely consumed. After cooling to 0°C , the reaction was quenched very slowly and carefully with DI water (100 mL). A saturated solution of Rochelle's salt (200 mL) was then added. The mixture was

vigorously stirred for an hour until organic and aqueous layers were well separated. Upon separation of the organic layer from the aqueous layer, the aqueous layer was extracted with Et₂O (3 x 100 mL). The organic layers were then combined, dried over MgSO₄, and concentrated under vacuum.

The crude material was then redissolved in CH₂Cl₂ (200 mL) and cooled to 0°C. Imidazole (25.9 g, 382 mmol) and DMAP (1.55 g, 12.7 mmol) was then added, followed by TBSCl (19.2 g, 127 mmol). The mixture was warmed up to room temperature and stirred for an hour at which all starting material was completely consumed. The mixture was diluted with additional CH₂Cl₂ (200 mL), poured into a separatory funnel, and sequentially washed with 2 M HCl (100 mL) and then saturated NaHCO₃ (100 mL) solutions. The organic layers were dried with MgSO₄, filtered, and concentrated under vacuum. The crude material was purified with silica gel column chromatography with 80:20 hexanes : EtOAc to yield title product **3.71** as a yellow oil (12.2 g, 34.1 mmol) in 54% yield over two steps. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 5.91 (1H, tq, J = 7.5, 1.5 Hz), 3.75 (1H, qn, J = 5.5 Hz), 3.62 (3H, s), 3.22 (3H, s), 2.32 – 2.23 (2H, m), 1.85 (3H, d, J = 1.0 Hz), 1.43 – 1.18 (8H, m), 0.87 (9H, s), 0.86 (3H, t, J = 5.0 Hz), 0.04 (3H, s), 0.03 (3H, s). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 172.69, 132.03, 130.32, 71.55, 60.92, 36.84, 35.63, 33.71, 31.92, 25.82, 25.11, 22.61, 18.03, 14.21, 14.00, -4.50, -4.65. IR (cm⁻¹): ν = 2953, 2930, 1655, 1462, 1371, 1257, 1072, 836, 771. HRMS-FAB: (M+H)⁺ = 358.2777 calculated for C₁₉H₄₀O₃NSi, experimental = 358.2763. $[\alpha]_D^{20}$ = +15.2 (c = 1.39 in CHCl₃).

(*E*,3*S*,6*S*)-6-((4-methoxybenzyloxy)methyl)-3-*tert*-butyl-dimethylsiloxy-4-methylhept-4-enal **3.99**



Homoallylic alcohol **3.101** (1.02 g, 3.51 mmol) was dissolved in CH₂Cl₂ (25 mL). Imidazole (1.43 g, 21.1 mmol), DMAP (215 mg, 1.76 mmol), and TBSCl (794 mg, 5.27 mmol) were sequentially added, and the reaction was stirred overnight. After dilution with CH₂Cl₂ (150 mL), the organic phase was washed with 2.0 M HCl (50 mL) followed by saturated NaHCO₃ (50 mL), dried over MgSO₄, and concentrated under vacuum to give TBS ether **3.101a**.

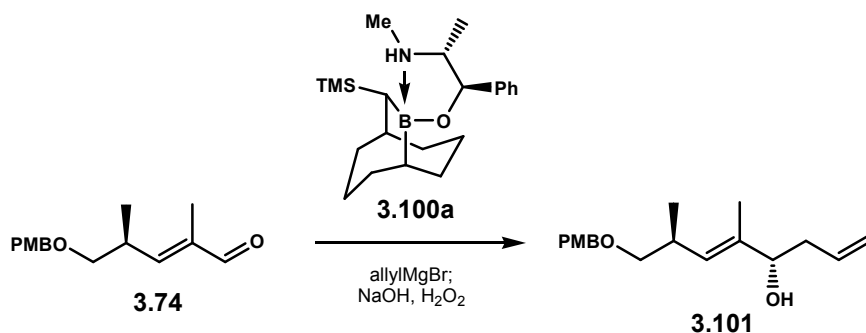
Crude **3.101a** was dissolved in a mixture of 5:5:1 THF : *t*-BuOH : H₂O (66 mL). NMO (2.49 g, 14.0 mmol) and a small crystal of OsO₄ were then added. The reaction was stirred until completion, quenched with a saturated solution of Na₂S₂O₃ (100 mL), and vigorously stirred for 30 minutes. The mixture was then extracted with EtOAc (4 x 50 mL). The organic layers were combined, dried over MgSO₄, filtered, and rotovaped to give diol **3.101b**.

Crude **3.101b** was dissolved in CH₂Cl₂ (100 mL) and cooled to 0°C. NaHCO₃ (882 mg, 10.5 mmol) and Pb(OAc)₄ (2.34 g, 5.27 mmol) were sequentially added. The

suspension was stirred for two hours and carefully quenched with a saturated NaHCO_3 solution (100 mL). After separation of layers, the aqueous phase was extracted with Et_2O (3 x 50 mL). The organic layers were combined, dried over MgSO_4 , filtered, and rotovaped. The crude material was purified in a silica gel column with 90:10 hexanes : EtOAc to give aldehyde **3.99** in 88% yield over 3 steps as a clear oil (1.26 g, 31.0 mmol).

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 9.73 (1H, dd, J = 3.0, 2.5 Hz), 7.26 – 7.23 (2H, m), 6.89 – 6.86 (2H, m), 5.27 (1H, dt, J = 9.5, 1.0 Hz), 4.50 (1H, ddd, J = 8.5, 4.5, 0.5 Hz), 4.47 (1H, d, J = 11.5 Hz), 4.40 (1H, d, J = 11.5 Hz), 3.81 (3H, s), 3.30 (1H, dd, J = 9.0, 6.0 Hz), 3.23 (1H, dd, J = 9.0, 7.0 Hz), 2.69 (1H, m), 2.64 (1H, ddd, J = 15.5, 8.5, 3.0 Hz), 2.40 (1H, ddd, J = 15.5, 4.0, 2.0 Hz), 1.62 (3H, d, J = 1.0 Hz), 0.96 (3H, d, J = 6.5 Hz), 0.85 (9H, s), 0.04 (3H, s), - 0.01 (3H, s). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 202.04 and 202.03 (atropisomer), 158.99, 136.35, 130.61, 129.44 and 129.40 (atropisomer), 129.03, 113.62, 74.67, 73.72, 72.56, 55.19 and 55.16 (atropisomer), 49.93, 32.57, 25.66 and 25.63 (atropisomer), 18.01, 17.45, 11.68, -4.62 and -4.69 (atropisomer), -5.28 and -5.34 (atropisomer). IR (cm^{-1}): ν = 3029, 2951, 2858, 2754, 1725, 1511, 1238, 1098, 820. HRMS-FAB: $(\text{M}-\text{H})^+ = 405.2461$ calculated for $\text{C}_{23}\text{H}_{37}\text{O}_4\text{Si}$, experimental = 405.2462.

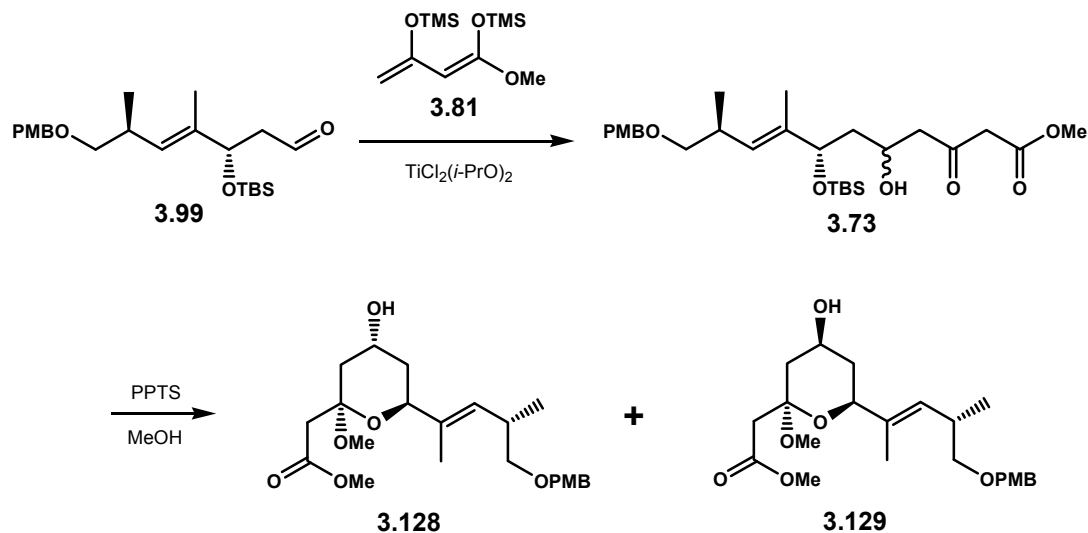
(+)-(E,4S,7S)-8-(4-methoxybenzyloxy)-5,7-dimethylocta-1,5-dien-4-ol **3.101**



(-)-9-(1R, 2R-Pseudoephedrinyl)-(10S)-(trimethylsilyl)-9-borabicyclo[3.3.2]decane **3.100a** (3.77 g, 10.2 mmol) was suspended in Et₂O (200 mL) and cooled to -78°C. Allylmagnesium bromide (10.2 mL, 10.2 mmol, 1.0 M in Et₂O) was added dropwise, and the reaction was brought up to room temperature and stirred for one hour. After recooling to -78°C, aldehyde **3.74** (2.10 g, 8.46 mmol) was introduced dropwise. The mixture was then stirred for three hours, warmed to 0°C, quenched with a premixed solution of H₂O₂ (2.9 mL, 25.4 mmol, 30% in H₂O) and NaOH (12.7 mL, 2.0 M in H₂O), and refluxed for two hours. After cooling to room temperature, DI water (100 mL) was added. After separation of layers, the aqueous phase was extracted with Et₂O (3 x 50 mL). The organic layers were combined, dried over MgSO₄, and rotovaped to give a yellow oil. Purification of the crude material with Biotage purification system gave homoallylic alcohol **3.101** in 95% yield as a colorless oil (2.33 g, 8.02 mmol). Biotage conditions: 40+M column, 90:10 → 60:40 hexanes : Et₂O linear gradient over 960 mL. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.26 – 7.24 (2H, m), 6.89 – 6.86 (2H, m), 5.75 (1H, dddd, J = 17.0, 10.0, 7.0, 7.0 Hz), 5.23 (1H, d, J = 9.0 Hz), 5.11 (1H, m), 5.08 (1H,

m), 4.45 (1H, d, $J = 11.5$ Hz), 4.42 (1H, d, $J = 12.0$ Hz), 4.02 (1H, t, $J = 6.5$ Hz), 3.80 (3H, s), 3.30 (1H, dd, $J = 9.5, 6.5$ Hz), 3.24 (1H, dd, $J = 9.0, 7.0$ Hz), 2.72 (1H, xd, $J = 9.0, 7.0$ Hz), 2.30 (2H, t, $J = 7.0$ Hz), 1.81 (1H, b), 1.65 (3H, d, $J = 1.5$ Hz), 0.97 (3H, d, $J = 7.0$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 159.03, 136.93, 134.79, 130.61, 129.27, 129.10, 117.46, 113.67, 76.33, 74.82, 72.54, 55.22, 39.71, 32.57, 17.55, 11.85. IR (cm^{-1}): $\nu = 3418, 3074, 2957, 2930, 2858, 1612, 1514, 1455, 1248, 1088, 1037, 820$. HRMS-FAB: $M^{++} = 290.1882$ calculated for $\text{C}_{18}\text{H}_{26}\text{O}_3$, experimental = 290.1888. $[\alpha]_D^{20} = +3.35^\circ$ ($c = 2.15$ in CHCl_3).

Methyl 2-((2R,4S,6S)-6-((S,E)-5-(4-methoxybenzyloxy)-4-methylpent-2-en-2-yl)-tetrahydro-4-hydroxy-2-methoxy-2H-pyran-2-yl)acetate **3.129**



Aldehyde **3.99** (1.26 g, 3.10 mmol) was dissolved in CH_2Cl_2 (100 mL), cooled to -78°C , and added a freshly prepared solution of $\text{TiCl}_2(i\text{-PrO})_2$ (4.0 mL, 4.00 mmol, 1.0 M in CH_2Cl_2). After stirring for 5 minutes, Chan's diene **3.81** was introduced dropwise.

The reaction mixture was stirred to completion (15 minutes), quenched with pH 7.00 buffer (50 mL) and then a saturated Rochelle's salt solution (100 mL), and stirred vigorously for two hours while warming up to room temperature. After separation of layers, the aqueous phase was extracted with CH₂Cl₂ (2 x 50 mL). The organic layers were combined, dried over MgSO₄, filtered, and rotovaped. The crude oil was purified with Biotage to give aldol product **3.73** in 92% yield (1.49 g, 2.85 mmol) as a 3:2 mixture of diastereomers. Biotage conditions: 40+M column, 90:10 hexanes : EtOAc over 240 mL, 90:10 → 60:40 hexanes : EtOAc linear gradient over 480 mL, and then 60:40 hexanes : EtOAc over 240 mL.

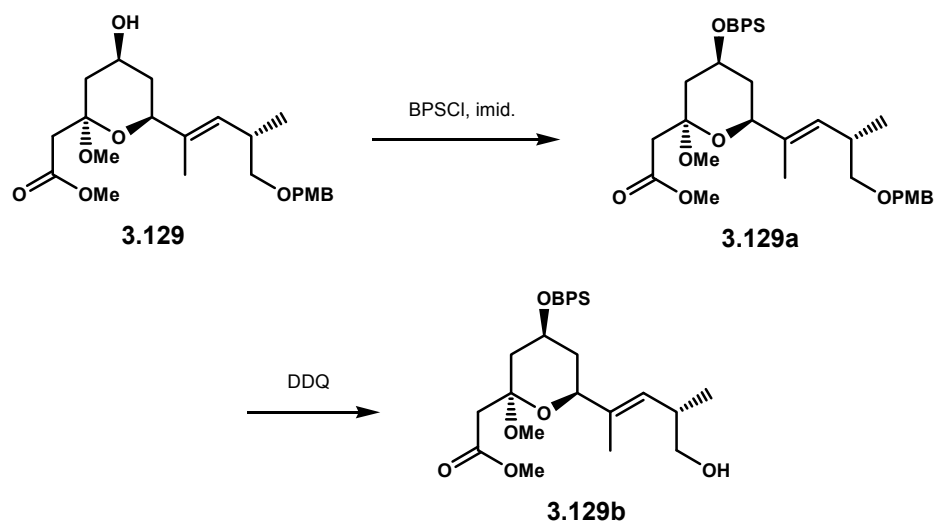
β-ketoester **3.73** (1.26 g, 2.41 mmol) was then dissolved in a 3:1 mixture of MeOH : CH₂Cl₂ (90 mL). TsOH•H₂O (23 mg, 0.121 mmol) was then added. After stirring for 6 hours, the reaction was concentrated under vacuum, and the crude material was purified with Biotage to give pyrans **3.128** in 27% yield (254 mg, 0.601 mmol) and **3.129** in 50% yield (504 mg, 1.19 mmol). Biotage conditions: 40+M column, 80:20 hexanes : EtOAc over 240 mL, then 80:20 → 20:80 hexanes : EtOAc linear gradient over 1185 mL. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.26 – 7.24 (2H, m), 6.88 – 6.85 (2H, m), 5.23 (1H, d, J = 9.0 Hz), 4.45 (1H, d, J = 12.0 Hz), 4.42 (1H, d, J = 11.5 Hz), 4.11 (1H, dddd, J = 11.0, 11.0, 5.0, 5.0 Hz), 3.90 (1H, dd, J = 12.0, 1.5 Hz), 3.80 (3H, s), 3.69 (3H, s), 3.32 (1H, dd, J = 9.5, 6.0 Hz), 3.23 (1H, dd, J = 9.0, 7.5 Hz), 3.22 (3H, s), 2.79 (1H, d, J = 14.0 Hz), 2.72 (1H, m), 2.63 (1H, d, J = 14.0 Hz), 2.29 (1H, ddd, J = 12.5, 4.5, 1.5 Hz), 1.90 (1H, dddd, J = 12.5, 4.0, 2.0, 2.0 Hz), 1.66 (3H, d, J = 1.5 Hz), 1.55 (1H, dd, J = 12.5, 11.0 Hz), 1.37 (1H, q, J = 11.5 Hz), 0.98 (3H, d, J = 6.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 169.91, 159.22, 134.99, 130.84, 129.72, 129.21, 113.75, 99.44,

74.68, 74.42, 72.60, 65.06, 55.63, 52.19, 48.48, 43.15, 42.41, 39.26, 33.43, 18.64, 12.63.

IR (cm⁻¹): ν = 3457, 3071, 2923, 1854, 1742, 1428, 1112, 1041, 700. HRMS-FAB:

(M+H)⁺ = 423.2382 calculated for C₂₃H₃₅O₇, experimental = 423.2312.

(+)-Methyl Pyranoside 3.129b

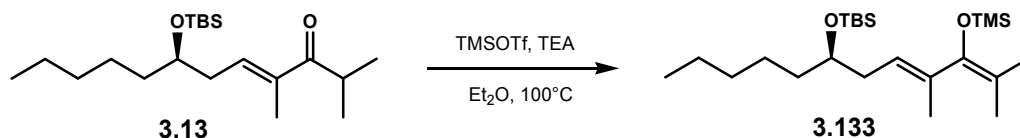


Pyran **3.129** (500 mg, 1.18 mmol) was dissolved in CH₂Cl₂ (25 mL). Imidazole (240 mg, 3.54 mmol), DMAP (72 mg, 0.59 mmol), and BPSCI (0.46 mL, 1.77 mmol) was sequentially added, and the reaction was stirred overnight. After dilution with CH₂Cl₂ (150 mL), the organic phase was washed with 2.0 M HCl (50 mL) followed by saturated NaHCO₃ (50 mL), dried over MgSO₄, and concentrated under vacuum to give BPS ether **3.129a**.

The crude material was redissolved in CH₂Cl₂ (25 mL). After addition of five drops of DI H₂O, DDQ (400 mg, 1.77 mmol) was introduced in one portion. The suspension was stirred for one hour, diluted with CH₂Cl₂ (150 mL), and washed with

saturated NaHCO₃ (50 mL). The organic layer was then dried over MgSO₄, filtered, and rotovaped to give a dark oil. The crude material was loaded into a silica gel column, and product elution was made with 80:20 hexanes : EtOAc to give alcohol **3.129b** in 83% yield over two steps as a yellow oil (528 mg, 0.980 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.68 – 7.65 (4H, m), 7.43 – 7.35 (6H, m), 5.06 (1H, d, J = 10.0 Hz), 4.15 (1H, tt, J = 11.0, 5.0 Hz), 3.68 (1H, dd, J = 11.5, 1.5 Hz), 3.65 (3H, s), 3.46 (1H, dd, J = 11.0, 6.0 Hz), 3.34 (1H, dd, J = 10.5, 7.5 Hz), 3.07 (3H, s), 3.67 (1H, d, J = 13.5 Hz), 2.60 (1H, d, J = 14.0 Hz), 2.60 (1H, m), 2.15 (1H, ddd, J = 13.0, 4.5, 1.5 Hz), 1.70 (1H, dd, J = 12.5, 10.5 Hz), 1.65 (1H, dddd, J = 12.5, 4.5, 2.0, 2.0 Hz), 1.60 (3H, d, J = 1.5 Hz), 1.41 (1H, ddd, J = 12.5, 12.5, 12.5 Hz), 1.05 (9H, s), 0.91 (3H, d, J = 7.0 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 169.72, 137.05, 135.76, 134.54, 134.27, 129.53, 128.44, 127.52, 127.49, 99.53, 74.00, 67.66, 66.34, 51.66, 47.86, 42.41, 41.84, 39.00, 34.97, 26.93, 19.09, 16.77, 12.63. IR (cm⁻¹): ν = 3460, 3072, 2954, 1859, 1742, 1428, 1112, 1042, 703. HRMS-FAB: (M+H)⁺ = 541.2985 calculated for C₃₁H₄₅O₆Si, experimental = 541.2971. $[\alpha]_D^{20}$ = +46.1° (c = 1.70 in CHCl₃).

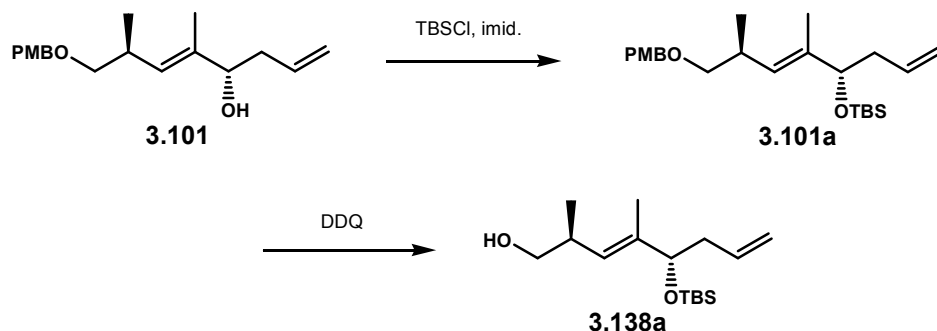
(+)-Silyl Enol Ether 3.133



In a thick-walled reaction tube, ketone **3.13** (1.00 g, 2.94 mmol) was dissolved in Et₂O (50 mL). TEA (2.04 mL, 14.7 mmol) and TMSOTf (1.14 mL, 5.88 mmol) were

sequentially added. The reaction vessel was then sealed and immersed into a sand bath at 100°C for 48 hours. After cooling to room temperature, the reaction was diluted with Et₂O (150 mL) and washed with a saturated NaHCO₃ solution (50 mL). After separation of layers, the organic phase was dried over MgSO₄, filtered, and rotovaped to give a brown oil. The crude material was then flushed over a silica pad with 100% hexanes. After concentration, the title product **3.133** was yielded in 99% as a pale yellow oil (1.20 g, 2.91 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 5.35 (1H, ddq, J = 7.0, 7.0, 1.5 Hz), 3.72 (1H, p, J = 6.0 Hz), 2.23 (2H, t, J = 6.0 Hz), 1.67 (3H, d, J = 1.0 Hz), 1.63 (6H, s), 1.47 – 1.35 (3H, m), 1.31 – 1.20 (5H, m), 0.89 (9H, s), 0.88 (3H, m), 0.12 (9H, s), 0.06 (3H, s), 0.05 (3H, s). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 146.89, 133.53, 126.96, 110.83, 71.95, 36.67, 35.89, 31.96, 25.88, 25.15, 22.62, 19.81, 18.09, 17.73, 15.07, 14.05, 0.29, -4.41, -4.59. IR (cm⁻¹): ν = 2958, 2930, 2858, 1472, 1377, 1252, 1225, 1060, 874, 839, 774. HRMS-FAB: M⁺ = 412.3193 calculated for C₂₃H₄₈O₂Si₂, experimental = 412.3189. $[\alpha]_D^{20}$ = +12.1° (c = 1.50 in CHCl₃).

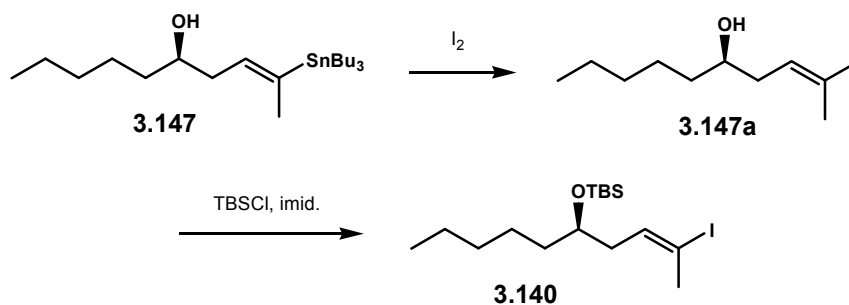
(-)-(E,2S,5S)-5-*tert*-butyldimethylsiloxy-2,4-dimethylocta-3,7-dien-1-ol **3.138a**



Homoallylic alcohol **3.101** (2.33 g, 8.02 mmol) was dissolved in CH₂Cl₂ (50 mL). Imidazole (3.27 g, 48.1 mmol), DMAP (490 mg, 4.01 mmol), and TBSCl (1.81 g, 12.0 mmol) were sequentially added, and the reaction was stirred overnight. After dilution with CH₂Cl₂ (150 mL), the organic phase was washed with 2.0 M HCl (50 mL) followed by saturated NaHCO₃ (50 mL), dried over MgSO₄, and concentrated under vacuum to give TBS ether **3.101a**. The crude material was redissolved in CH₂Cl₂ (50 mL). After addition of ten drops of DI H₂O, DDQ (2.73 g, 12.0 mmol) was introduced in one portion. The suspension was stirred for one hour, and the remaining solid was then filtered under vacuum. The resulting organic filtrate was diluted with CH₂Cl₂ (150 mL) and washed with saturated NaHCO₃ (50 mL). The organic layer was then dried over MgSO₄, filtered, and rotovaped to give a dark oil. Purification of the crude material with Biotage purification system gave alcohol **3.138a** in 99% yield over two steps as a yellow oil (2.25 g, 7.91 mmol). Biotage conditions: 40+M column, 95:5 hexanes : EtOAc over 240 mL, then 95:5 → 90:10 hexanes : EtOAc linear gradient over 720 mL. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 5.74 (1H, dddd, J = 17.5, 10.5, 7.0, 7.0 Hz), 5.10 (1H, ddq,

$J = 10.0, 1.5, 1.5 \text{ Hz}$), $5.00 (1\text{H}, \text{m})$, $5.01 (1\text{H}, \text{m})$, $4.02 (1\text{H}, \text{t}, J = 6.0 \text{ Hz})$, $3.46 (1\text{H}, \text{m})$, $3.32 (1\text{H}, \text{t}, J = 9.0 \text{ Hz})$, $2.62 (1\text{H}, \text{m})$, $2.25 (2\text{H}, \text{ddq}, J = 7.5, 6.0, 1.0 \text{ Hz})$, $1.60 (3\text{H}, \text{d}, J = 1.0 \text{ Hz})$, $1.48 (1\text{H}, \text{b})$, $0.92 (3\text{H}, \text{d}, J = 7.0 \text{ Hz})$, $0.88 (9\text{H}, \text{s})$, $0.03 (3\text{H}, \text{s})$, $-0.01 (3\text{H}, \text{s})$. ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 139.42, 135.48, 127.40, 116.30, 77.39, 67.61, 40.96, 34.96, 25.77, 18.21, 16.81, 12.43, -4.69, -5.00. IR (cm^{-1}): $\nu = 3450, 3077, 2957, 2929, 2857, 1472, 1256, 1073, 1036, 913, 836, 775$. HRMS-FAB: $(\text{M}+\text{H})^+ = 285.2250$ calculated for $\text{C}_{16}\text{H}_{33}\text{O}_2\text{Si}$, experimental = 285.2229. $[\alpha]_{\text{D}}^{20} = -11.6^\circ$ ($c = 2.15$ in CHCl_3).

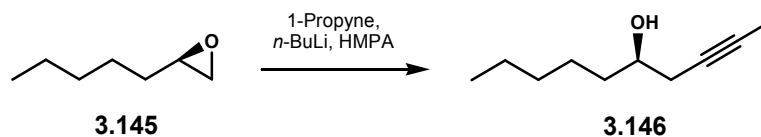
(-)-((S,E)-2-iododec-2-en-5-yloxy)(tert-butyl)dimethylsilane **3.140**



Vinylstannane **3.147** (1.50 g, 3.37 mmol) was dissolved in Et_2O (50 mL). After cooling the reaction to 0°C , I_2 (941 mg, 3.71 mmol) was then added. The reaction was stirred for 15 minutes followed by addition of a KF solution (489 mg, 8.43 mmol, dissolved in 20 mL of DI H_2O) and acetone (50 mL). This mixture was further stirred for 30 minutes, and a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (50 mL) was added. After separation of layers, the aqueous phase was extracted with Et_2O (2 x 50 mL). The organic layers were combined, dried over MgSO_4 , filtered, and rotovaped to give a yellow oil.

The crude material was redissolved in CH₂Cl₂ (50 mL). Imidazole (687 mg, 10.1 mmol), DMAP (82 mg, 0.67 mmol), and TBSCl (1.02 g, 6.74 mmol) were sequentially added, and the mixture was stirred overnight. After dilution with CH₂Cl₂ (250 mL), the organic layer was washed with 2 M HCl (50 mL) and then a saturated NaHCO₃ solution (50 mL). The organic layer was dried over MgSO₄, filtered, and rotovaped. The crude material was loaded into a silica gel column, and product elution with 100:0 → 98:2 hexanes : EtOAc gave vinyl iodide **3.140** in 94% yield over two steps as a yellow oil (1.25 g, 3.15 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 6.18 (1H, ddq, J = 8.0, 8.0, 2.0 Hz), 3.66 (1H, p, J = 5.5 Hz), 2.37 (3H, d, J = 1.0 Hz), 2.15 (2H, t, J = 6.5 Hz), 1.43 – 1.37 (3H, m), 1.35 – 1.23 (5H, m), 0.89 (9H, s), 0.89 (3H, m), 0.05 (3H, s), 0.04 (3H, s). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 138.23, 94.85, 71.44, 38.33, 37.13, 31.94, 27.70, 25.85, 24.98, 22.63, 18.05, 14.03, -4.43, -4.60. IR (cm⁻¹): ν = 2956, 2929, 2857, 1463, 1255, 1058, 836, 774. HRMS-FAB: (M-H)⁺ = 395.1267 calculated for C₁₆H₃₂OSiI, experimental = 395.1248. [α]_D²⁰ = -0.14 (c = 25.0 in CHCl₃).

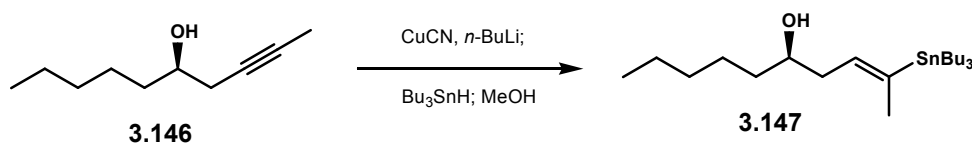
(-)-(S)-dec-2-yn-5-ol **3.146**



Condensed propyne (7.1 mL, 125 mmol) was added into a flask containing THF (200 mL, precooled to -78°C), and *n*-BuLi (36.2 mL, 83.2 mmol, 2.3 M in hexanes) was introduced along the inner wall of the flask. The reaction was allowed to slowly warm up

to 0°C over one hour and then recooled to -78°C. After addition of HMPA (50 mL), epoxide **3.145** (4.75 g, 41.6 mmol) was then added. The reaction mixture was slowly warmed up to room temperature, stirred for 48 hours, and then cooled to 0°C. A half-saturated solution of NH₄Cl (100 mL) and Et₂O (500 mL) was sequentially added. Upon separation of layers, the organic phase was washed with DI H₂O (2 x 100 mL), dried over MgSO₄, filtered, and rotovaped to yield a yellow oil. The crude oil was flushed through a pad of silica gel with 90:10 hexanes : EtOAc to give alcohol **3.146** in 81% yield as a yellow oil (5.19 g, 33.7 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 3.67 (1H, b), 2.36 (1H, ddq, J = 16.5, 5.0, 2.5 Hz), 2.23 (1H, ddq, J = 16.5, 7.5, 2.5 Hz), 1.98 (1H, d, J = 4.0 Hz), 1.80 (3H, t, J = 2.0 Hz), 1.51 – 1.45 (2H, m), 1.42 (1H, m), 1.34 – 1.24 (5H, m), 0.88 (3H, t, J = 6.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 78.29, 75.33, 70.20, 36.18, 31.74, 27.66, 25.31, 22.57, 13.99, 3.49. IR (cm⁻¹): ν = 3369, 2956, 2930, 2859, 1458, 1125, 1080, 1036. HRMS-FAB: (M+H)⁺ = 155.1436 calculated for C₁₀H₁₉O, experimental = 155.1430. [α]_D²⁰ = -5.62° (c = 2.65 in CHCl₃).

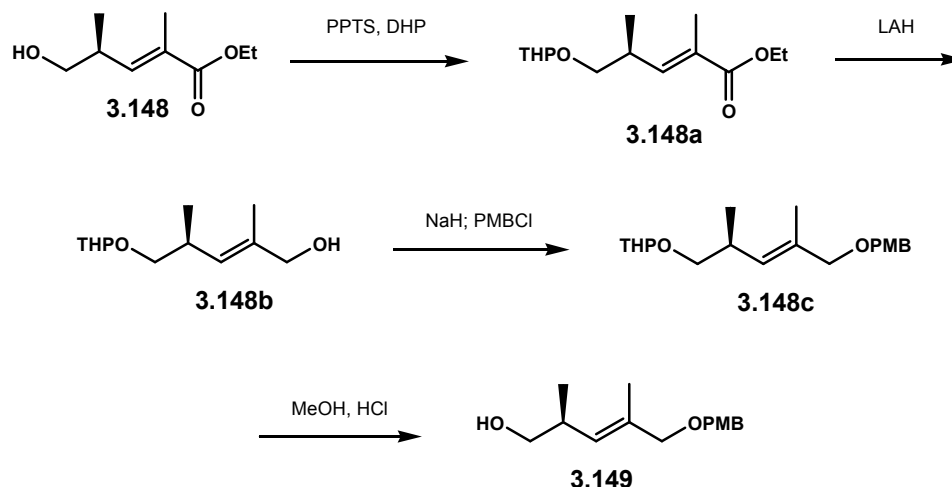
(-)-(S,E)-2-(tributylstannyl)dec-2-en-5-ol **3.147**



A suspension of CuCN (7.31 g, 81.6 mmol) in THF (219 mL) was cooled to -78°C, and *n*-BuLi (70.9 mL, 163.2 mmol, 2.3 M in hexanes) was added dropwise. The mixture was warmed to -40°C, stirred for 10 minutes, and recooled to -78°C. Bu₃SnH

(43.9 mL, 163.2 mmol) was introduced dropwise. Once again, the mixture was warmed to -40°C, stirred for 10 minutes, and recooled to -78°C. The subsequent slow addition of MeOH (121 mL) resulted in significant gas evolution, and then alkyne **3.146** (4.20 g, 27.2 mmol) was introduced. The reaction was warmed up to -10°C, stirred for 24 hours, and then quenched with a saturated solution of NH₄Cl (200 mL). After separation of layers, the aqueous phase was extracted with Et₂O (2 x 100 mL). The organic layers were combined, dried over MgSO₄, filtered, and then rotovaped. The crude material was purified with TEA-neutralized silica gel column chromatography using 90:10 hexanes : EtOAc to give vinylstannate **3.147** in 59% yield as a single olefin isomer (7.10g, 15.9 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 5.57 (1H, m), 3.65 (1H, b), 2.38 – 2.25 (2H, m), 1.91 – 1.82 (3H, m), 1.56 – 1.42 (11H, m), 1.34 – 1.25 (11H, m), 0.94 – 0.84 (16H, m). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 142.34, 136.06, 71.45, 36.72, 36.20, 31.90, 30.30, 29.17, 27.36, 25.43, 22.63, 19.41, 14.04, 13.70, 9.10. IR (cm⁻¹): ν = 3351, 2957, 2927, 2855, 1464, 1376, 1071. HRMS-FAB: (M-C₄H₉)⁺ = 389.1866 calculated for C₁₈H₃₇OSn, experimental = 389.1855. $[\alpha]_D^{20}$ = -7.00° (c = 1.00 in CHCl₃).

(-)-(S,E)-5-(4-methoxybenzyloxy)-2,4-dimethylpent-3-en-1-ol **3.149**



Alcohol **3.148** (24.8 g, 144 mmol) was dissolved in CH₂Cl₂ (500 mL). PPTS (1.81 g, 7.20 mmol) and DHP (39.4 mL, 432 mmol) were sequentially added. After stirring overnight, the reaction mixture was washed with a saturated solution of NaHCO₃ (100 mL). After separation of layers, the organic layer was dried over MgSO₄, filtered, and rotovaped to give crude **3.148a** as a yellow oil.

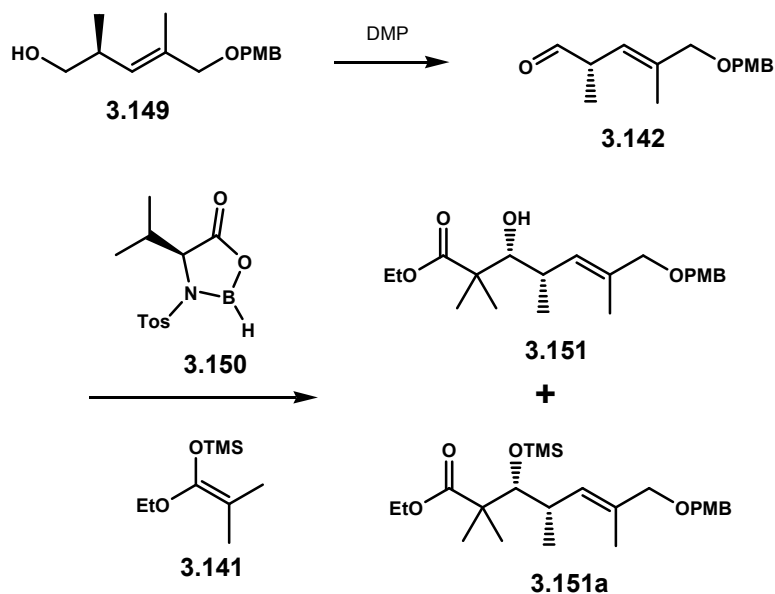
Crude **3.148a** was dissolved in Et₂O (200 mL). This solution was then added dropwise via cannula to a suspension of LAH (6.57 g, 173 mmol) in Et₂O (300 mL, precooled to 0°C) and stirred for one hour. DI water (6.6 mL) was then introduced dropwise very carefully followed by sequential addition of 15% NaOH (6.6 mL) and DI H₂O (19.8 mL) which resulted in the formation of white precipitate. After vigorous stirring for two hours, the white solid was filtered under vacuum and washed with Et₂O. The organic filtrate was then concentrated under vacuum to give crude alcohol **3.148b**.

Crude **3.148b** was dissolved in THF (200 mL). This solution was then added dropwise via cannula to a suspension of NaH (6.57 g, 173 mmol) in THF (300 mL, precooled to 0°C). After stirring for one hour, TBAI (5.30 g, 14.4 mmol) and PMBCl (23.5 mL, 173 mmol) were added. The mixture was then refluxed overnight, cooled to 0°C, and slowly and carefully quenched with a half-saturated solution of NH₄Cl (200 mL). After separation of layers, the aqueous phase was extracted with Et₂O (3 x 100 mL). The organic layers were combined, dried over MgSO₄, filtered, and rotovaped to give crude PMB ether **3.148c**.

Crude **3.148c** was dissolved in MeOH (500 mL), and 37% HCl (2 mL) was added. After stirring the reaction for two hours, a saturated solution of NaHCO₃ (200 mL) was then carefully added. Evaporation of MeOH under vacuum allowed subsequent extraction of the remaining aqueous layer with Et₂O (4 x 100 mL). The organic layers were combined, dried over MgSO₄, filtered, and rotovaped. The crude material was then purified in a silica gel column with 80:20 → 50:50 hexanes : EtOAc. Evaporation of solvent yielded alcohol **3.149** in 87% yield over four steps as a yellow oil (31.2 g, 125 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.31 – 7.28 (2H, m), 6.92 – 6.89 (2H, m), 5.23 (1H, dq, J = 10.0, 1.5 Hz), 4.43 (2H, s), 3.91 (2H, s), 3.83 (3H, s), 3.50 (1H, ddd, J = 11.0, 6.0, 6.0 Hz), 3.40 (1H, dd, J = 10.0, 8.5 Hz), 2.69 (1H, xd, J = 9.5, 6.5 Hz), 1.74 (3H, d, J = 1.0 Hz), 1.67 (1H, b), 0.99 (1H, d, J = 6.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 159.11, 134.28, 130.40, 130.22, 129.35, 113.72, 75.67, 71.41, 67.66, 55.23, 35.21, 16.83, 14.35. IR (cm⁻¹): $\tilde{\nu}$ = 3412, 2956, 2869, 1613, 1514, 1456, 1249, 1073, 1036, 822. HRMS-FAB: M⁺ = 250.1569 calculated for C₁₅H₂₂O₃, experimental = 250.1570. $[\alpha]_D^{20}$ = -10.9° (c = 5.93 in CHCl₃).

(+)-(E,3R,4S)-ethyl 7-(4-methoxybenzyloxy)-3-hydroxy-2,2,4,6-tetramethylhept-5-enoate

3.151



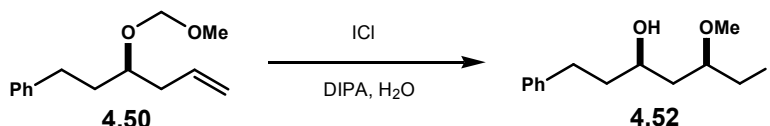
Alcohol **3.149** (1.00 g, 4.00 mmol) was dissolved in CH_2Cl_2 (100 mL) in a round-bottomed flask, and the flask was then placed in a water bath at room temperature. NaHCO_3 (3.36 g, 40.0 mmol) was then added followed by the Dess-Martin reagent (2.04 g, 4.80 mmol). After stirring the suspension was for one hour, the reaction was carefully quenched with slow addition of a saturated aqueous solution of NaHCO_3 until no more gas evolution was observed. After separation of layers, the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The organic layers were then combined, dried over MgSO_4 , filtered, and concentrated under vacuum to give white solids, which were then taken up in hexanes (100 mL). The white residue was filtered over celite, washed with hexanes (2 x 50 mL). Removal of hexanes followed by redissolving the yellow oil in CH_2Cl_2 (50 mL)

provided a solution of aldehyde **3.142** which was immediately subjected to the subsequent aldol reaction.

In a separate flask, *N*-Tos-*L*-valine (2.17 g, 8.00 mmol) was suspended in CH₂Cl₂ (50 mL) and cooled to 0°C. Addition of borane (7.2 mL, 7.2 mmol, 1.0 M in THF) resulted in gas evolution, and the resulting clear solution was warmed to room temperature, stirred overnight, cooled to -78°C, and then transferred via cannula to a precooled (-78°C) solution of aldehyde **3.142**. The reaction mixture was stirred to completion, quenched with pH 7.00 buffer (50 mL), and stirred vigorously while warming to 0°C. After separation of layers, the aqueous phase was extracted with CH₂Cl₂ (2 x 50 mL). The organic layers were combined, dried over MgSO₄, filtered, and rotovaped. The crude oil was purified with Biotage to give aldol product **3.151** in 67% yield (975 mg, 2.67 mmol) and **3.151a** in 9% yield (157 mg, 0.360 mmol). Biotage conditions: 40+M column, 90:10 hexanes : EtOAc over 240 mL, then 90:10 → 70:30 hexanes : EtOAc linear gradient over 720 mL. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.27 – 7.24 (2H, m), 6.89 – 6.86 (2H, m), 5.38 (1H, dq, J = 10.0, 0.5 Hz), 4.38 (1H, d, J = 11.5 Hz), 4.35 (1H, d, J = 11.5 Hz), 4.10 (1H, q, J = 7.0 Hz), 3.83 (1H, d, J = 4.0 Hz), 3.80 (3H, s), 3.53 (1H, dd, J = 7.5, 6.0 Hz), 2.76 (1H, d, J = 7.5 Hz), 2.62 (1H, pd, J = 9.5, 6.5 Hz), 1.66 (3H, d, J = 1.5 Hz), 1.25 (3H, t, J = 7.0 Hz), 1.22 (3H, s), 1.19 (3H, s), 0.97 (3H, d, J = 7.0 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 177.70, 159.04, 131.87, 130.66, 130.56, 129.31, 113.68, 80.07, 75.82, 71.15, 60.65, 55.23, 46.39, 35.16, 22.82, 22.48, 16.45, 14.00, 13.89. IR (cm⁻¹): *f* = 3501, 2980, 1716, 1614, 1515, 1464, 1250, 1035, 821. HRMS-FAB: (M+H)⁺ = 365.2328 calculated for C₂₁H₃₃O₅, experimental = 265.2320. [α]_D²⁰ = +6.38° (c = 4.70 in CHCl₃).

8.3. Experimental Procedures for Chapter Four

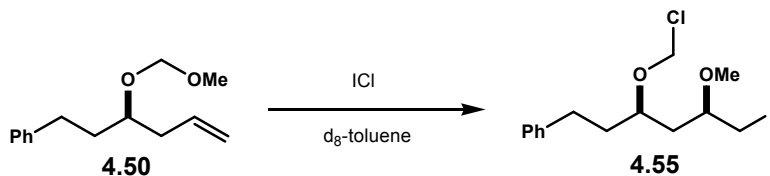
(±)-(3*R*,5*R*)-6-iodo-5-methoxy-1-phenylhexan-3-ol **4.52**



Homoallylic MOM ether **4.50** (204 mg, 0.926 mmol) was dissolved in toluene (25 mL), and the solution was cooled to -78°C. Iodine monochloride (1.02 mL, 1.02 mmol, 1 M in CH₂Cl₂) was then added dropwise. After stirring for 10 minutes, the reaction was quenched with a mixture of diisopropylamine (5 mL) and DI H₂O (0.5 mL), stirred vigorously, and warmed to room temperature. After separating the organic and aqueous layers, the aqueous layer was washed with CH₂Cl₂ (2 x 20 mL). The organic layers were then combined, dried over MgSO₄, filtered, and concentrated to give a dark yellow oil. The ensuing Biotage chromatography of the crude oil gave the title product **4.52** in 87% yield as a yellow oil (270 mg, 0.808 mmol). Biotage condition: 25+M column, 95:5 → 80:20 hexanes : EtOAc linear gradient over 360 mL. ¹H NMR (500 MHz, d₈-toluene, ref = 2.09 ppm): δ (ppm) = 7.18 – 7.01 (5H, m), 3.56 (1H, dddd, J = 8.5, 8.5, 4.0, 2.5 Hz), 2.98 (1H, d, J = 13.0 Hz), 2.87 (1H, dd, J = 17.0, 8.0 Hz), 2.84 (3H, s), 2.82 (1H, dd, J = 16.5, 5.5 Hz), 2.77 – 2.71 (2H, m), 2.64 (1H, ddd, J = 13.5, 9.5, 7.0 Hz), 1.66 (1H, m), 1.59 – 1.50 (2H, m), 1.42 (1H, ddd, J = 14.5, 4.0, 3.0 Hz). ¹³C NMR (125 MHz, d₈-toluene, ref = 20.40 ppm): δ (ppm) = 142.61, 129.00, 128.56, 125.99, 79.48, 69.32,

55.97, 41.99, 39.84, 32.05, 9.01. HRMS-FAB: $(M+H)^+ = 355.0508$ calculated for $C_{13}H_{19}O_2I$, experimental = 355.0536.

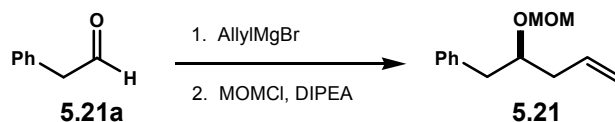
(±)-((3R,5R)-3-(chloromethoxy)-6-iodo-5-methoxyhexyl)benzene 4.55



In an oven-dried NMR tube, homoallylic MOM ether **4.50** (20 mg, 0.091 mmol) was dissolved in anhydrous d_8 -toluene (0.75 mL). The solution was cooled to -78°C . Iodine monochloride (0.14 mL, 0.14 mmol, 1.0 M in CH_2Cl_2) was added dropwise along the inner wall of the tube. The reaction mixture was shaken very rapidly resulting in a brown solution, and the NMR tube was then immediately inserted into a precooled -60°C NMR probe. The NMR probe was then warmed up to -20°C over 10 minutes and equilibrated for 15 minutes. NMR spectra were acquired with the methylene chloride proton signal readily suppressed: δ (ppm) = 4.47, 4.30, 4.11. ^1H NMR (500 MHz, d_8 -toluene, ref = 2.09 ppm): δ (ppm) = 7.14 – 6.97 (5H, m), 5.08 (1H, d, J = 5.5 Hz), 5.01 (1H, d, J = 5.5 Hz), 3.61 (1H, q, J = 6.0 Hz), 2.93 (2H, d, J = 4.0 Hz), 2.84 (3H, s), 2.65 (1H, m), 2.57 – 2.42 (2H, m), 1.68 – 1.63 (1H, m), 1.59 – 1.49 (3H, m). ^{13}C NMR (125 MHz, d_8 -toluene, ref = 20.40 ppm): δ (ppm) = 141.87, 128.57, 126.10, 81.35, 75.62, 75.17, 55.91, 38.52, 35.57, 31.36, 10.46. Note: One aromatic signal missing, presumably buried under the strong d_8 -toluene signals.

8.4. Experimental Procedures for Chapter Five

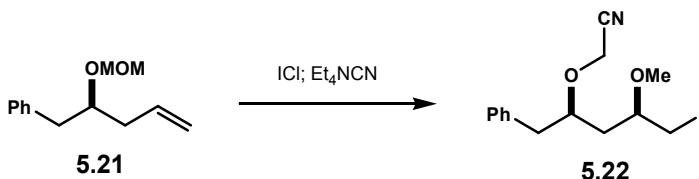
(±)-1-(2-(methoxymethoxy)pent-4-enyl)benzene **5.21**



Phenylacetaldehyde (11.7 mL, 100 mmol) was dissolved in THF (500 mL), and the solution was cooled to -78°C . A solution of allylmagnesium bromide (110 mL, 110 mmol, 1.0 M in Et_2O) was then added dropwise over 15 minutes, and the reaction was stirred for additional 30 minutes at which the aldehyde starting material was completely consumed. The reaction was quenched with a saturated NH_4Cl solution (300 mL) and warmed up to 0°C . After separating the organic and aqueous layers, the aqueous layer was washed with Et_2O (2 x 100 mL). The organic layers were then combined, dried over MgSO_4 , and filtered. The organic solvent was removed under vacuum leaving behind a yellow oil. This yellow oil was redissolved in CH_2Cl_2 (200 mL), and DIPEA (52.2 mL, 300 mmol) was then added. After cooling the mixture to 0°C , MOMCl (9.10 mL, 120 mmol) was added dropwise. The reaction was warmed to room temperature and stirred overnight. The reaction was then diluted with CH_2Cl_2 (300 mL) and washed subsequently with aqueous solutions of 2 M HCl (200 mL) and then saturated NaHCO_3 (200 mL). The organic layer was then dried over MgSO_4 and filtered. A yellow oil was obtained upon removal of CH_2Cl_2 under vacuum. The crude material was purified with column chromatography using 95:5 hexanes : EtOAc to give the title product **5.21** in 72%

yield over two steps as a colorless oil (14.9 g, 72.0 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.30 – 7.27 (2H, m), 7.22 – 7.19 (3H, m), 5.87 (1H, dddd, J = 17.5, 9.5, 7.0, 7.0 Hz), 5.12 (1H, m), 5.09 (1H, m), 4.61 (1H, d, J = 7.0 Hz), 4.50 (1H, d, J = 7.0 Hz), 3.87 (1H, p, J = 6.5 Hz), 3.16 (3H, s), 2.81 (2H, d, J = 6.5 Hz), 2.34 – 2.25 (2H, m). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 138.71, 134.57, 129.47, 128.17, 126.08, 117.40, 95.18, 77.44, 55.21, 40.79, 38.65. IR (cm^{-1}): ν = 3064, 3028, 2930, 1455, 1149, 1100, 1040, 917, 745, 700. HRMS-FAB: $(\text{M}+\text{H})^+ = 207.1385$ calculated for $\text{C}_{13}\text{H}_{19}\text{O}_2$, experimental = 207.1385.

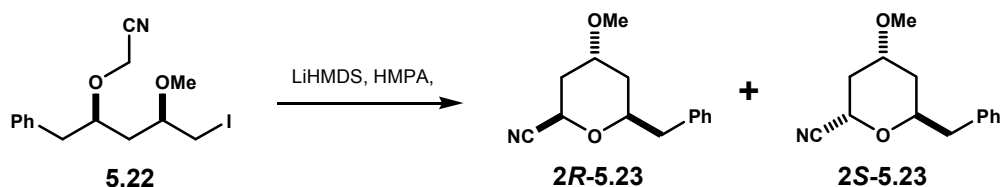
(±)-2-((2R,4R)-5-iodo-4-methoxy-1-phenylpentan-2-yloxy)acetonitrile **5.22**



Homoallylic MOM ether **5.21** (4.39 g, 21.3 mmol) was dissolved in toluene (400 mL), and 4 grams of 4 Å molecular sieves were then added. After cooling this solution to -78°C , an iodide monochloride solution (25.6 mL, 25.6 mmol, 1.0 M in CH_2Cl_2) was added dropwise while maintaining an internal temperature of the reaction below -75°C . The solution became dark red and was stirred for 30 minutes while slowly warming up to -30°C . In a separate flask, tetraethylammonium cyanide (5.00 g, 32.0 mmol) was dissolved in acetonitrile (40 mL), and 2 grams of 4 Å molecular sieves were added. Toluene (20 mL) was then added which caused the solution to become cloudy. This

Et₄NCN solution was introduced via cannula to the reaction vessel, and the mixture was stirred at -30°C for 18 hours. The reaction was warmed to room temperature and quenched with DI water (200 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et₂O (3 x 100 mL). The organic layers were combined, dried over MgSO₄, and filtered. Removal of solvent under vacuum left behind a yellow oil. The crude material was purified with Biotage chromatography to give the title product **5.22** in 78% yield as a yellow oil (5.97 g, 16.6 mmol). Biotage condition: 40+M column, 95:5 hexanes : EtOAc for 120 mL, then 95:5 → 80:20 hexanes : EtOAc linear gradient over 600 mL, then 80:20 hexanes : EtOAc for 240 mL. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.34 – 7.31 (2H, m), 7.27 – 7.21 (3H, m), 4.19 (1H, d, J = 16.5 Hz), 4.06 (1H, d, J = 16.5 Hz), 3.81 (1H, p, J = 6.0 Hz), 3.36 (1H, dd, J = 19.5, 5.5 Hz), 3.33 (3H, s), 3.29 (1H, dd, J = 11.0, 3.5 Hz), 3.10 (1H, m), 2.90 (1H, dd, J = 14.0, 6.5 Hz), 2.84 (1H, dd, J = 13.5, 5.5 Hz), 1.86 – 1.83 (2H, m). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 137.11, 129.35, 128.53, 126.68, 116.32, 79.02, 76.07, 56.64, 54.60, 40.46, 38.63, 9.57. IR (cm⁻¹): ν = 3062, 3028, 2926, 2825, 2191, 1603, 1496, 1454, 1348, 1273, 1182, 1087, 888, 748, 702. HRMS-FAB: (M+H)⁺ = 360.0461 calculated for C₁₄H₁₉O₂, experimental = 360.0466.

(±)-(4*R*,6*R*)-6-benzyl-tetrahydro-4-methoxy-2*H*-pyran-2-carbonitrile **5.23**

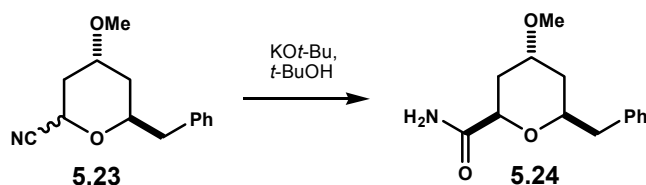


HMDS (4.64 mL, 21.8 mmol) was dissolved in THF (40 mL) and cooled to -78°C. A solution of *n*-BuLi (9.50 mL, 21.8 mmol, 2.3 M in hexanes) was then added dropwise quite rapidly, and the solution was stirred for 10 minutes prior to addition of HMPA (7.60 mL, 43.7 mmol). This LiHMDS solution was further stirred for 10 minutes. In a separate flask, cyanoether **5.22** (5.23 g, 14.6 mmol) was dissolved in THF (300 mL), and the solution was cooled to -78°C. The freshly prepared, cold LiHMDS solution was then added via cannula dropwise over 30 minutes. The reaction was further stirred for 2 hours and then quenched with a half-saturated aqueous NH₄Cl solution (200 mL). After warming up room temperature, the organic and aqueous layers were separated. The aqueous layer was washed with Et₂O (2 x 100 mL). The organic layers were then combined, dried over MgSO₄, filtered, and concentrated under vacuum leaving behind a dark orange oil. The crude material was purified with Biotage chromatography to give title product **2R-5.23** and **2S-5.23** in 82% combined yield as a yellow oil (2.76 g, 11.9 mmol). Crude ¹H NMR indicated 4:1 diastereomeric ratio. Biotage condition: 40+M column, 90:10 hexanes : EtOAc for 240 mL, then 90:10 → 70:30 hexanes : EtOAc linear gradient over 720 mL, then 70:30 hexanes : EtOAc for 120 mL.

Less polar (major) diastereomer 2R-5.23: ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.31 – 7.28 (2H, m), 7.24 – 7.19 (3H, m), 4.60 (1H, dd, J = 12.5, 2.5 Hz), 3.29 (1H, dddd, J = 13.5, 6.5, 6.5, 2.0 Hz), 3.67 (1H, p, J = 3.0 Hz), 3.27 (3H, s), 2.89 (1H, dd, J = 14.0, 7.0 Hz), 2.67 (1H, dd, J = 14.0, 6.0 Hz), 2.09 (1H, dddd, J = 14.0, 5.5, 2.5, 2.5 Hz), 1.91 (1H, ddd, J = 14.0, 12.5, 3.0 Hz), 1.80 (1H, dddd, J = 14.5, 3.0, 2.0, 2.0 Hz), 1.42 (1H, ddd, J = 14.0, 11.5, 2.5 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.39, 129.44, 128.29, 126.44, 118.54, 73.85, 71.56, 61.31, 56.14, 42.04, 33.76, 33.43. IR (cm^{-1}): f = 3021, 2924, 2879, 2826, 1603, 1449, 1342, 1183, 1086, 1070. HRMS-FAB: $(\text{M}+\text{H})^+ = 232.1338$ calculated for $\text{C}_{14}\text{H}_{18}\text{O}_2$, experimental = 232.1325.

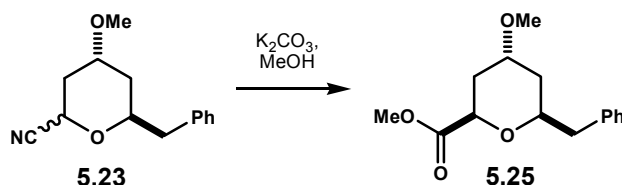
More polar (minor) diastereomer 2S-5.23: ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.31 – 7.28 (2H, m), 7.23 – 7.20 (3H, m), 4.77 (1H, dd, J = 6.0, 0.5 Hz), 4.41 (1H, dddd, J = 13.0, 6.5, 6.5, 2.0 Hz), 3.67 (1H, p, J = 3.0 Hz), 3.36 (3H, s), 2.88 (1H, dd, J = 14.0, 7.0 Hz), 2.74 (1H, dd, J = 14.0, 6.0 Hz), 2.15 (1H, m), 1.89 (1H, m), 1.88 (1H, ddd, J = 15.0, 6.5, 3.0 Hz), 1.47 (1H, ddd, J = 14.5, 12.0, 3.0 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.11, 129.30, 128.35, 126.43, 118.67, 71.00, 69.59, 60.90, 56.01, 41.80, 34.54, 30.03. IR (cm^{-1}): f = 3030, 2924, 2826, 1599, 1449, 1369, 1342, 1187, 1086, 1028. HRMS-FAB: $(\text{M}+\text{H})^+ = 232.1338$ calculated for $\text{C}_{14}\text{H}_{18}\text{O}_2$, experimental = 232.1355.

(±)-(2*R*,4*R*,6*R*)-6-benzyl-tetrahydro-4-methoxy-2*H*-pyran-2-carboxamide **5.24**



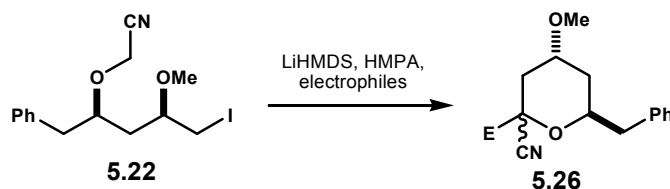
Cyanopyran **5.23** (125 mg, 0.540 mmol) as a 4:1 mixture of diastereomers was charged into a 10 mL round bottomed flask. A solution of KO*t*-Bu (3 mL, 1 M in *t*-BuOH) was then added, and the mixture was stirred for 48 hours. The reaction was quenched with addition of a half-saturated solution of NH₄Cl (10 mL). After extracting the aqueous layer with Et₂O (2 x 10 mL), the organic layers were combined, dried over MgSO₄, filtered, and concentrated under vacuum. The crude material was the loaded into a silica gel column, was eluted with 30:70 hexanes : EtOAc. Upon removal of solvent, title product **5.24** was isolated in 66% yield (89 mg, 0.357 mmol) with a diastereomeric ratio of 18:1 as a yellow oil. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.30 – 7.27 (2H, m), 7.23 – 7.18 (3H, m), 6.45 (1H, b), 5.68 (1H, b), 4.15 (1H, dd, *J* = 12.5, 2.5 Hz), 4.01 (1H, dddd, *J* = 13.5, 7.5, 5.5, 2.0 Hz), 3.69 (1H, p, *J* = 3.0 Hz), 3.32 (3H, s), 2.82 (1H, dd, *J* = 14.0, 7.5 Hz), 2.74 (1H, dd, *J* = 13.5, 5.5 Hz), 2.36 (1H, dddd, *J* = 14.0, 3.0, 2.0, 2.0 Hz), 1.83 (1H, dddd, *J* = 14.0, 3.0, 2.5, 2.5 Hz), 1.44 (1H, ddd, *J* = 14.0, 12.5, 2.5 Hz), 1.42 (1H, ddd, *J* = 14.0, 11.5, 2.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 175.08, 138.11, 129.22, 128.28, 126.30, 73.04, 72.63, 71.90, 56.12, 42.44, 35.45, 31.06. IR (cm⁻¹): *f* = 3469, 3306, 2924, 2873, 1686, 1586, 1454, 1374, 1096, 1076. HRMS-FAB: (M+H)⁺ = 250.1443 calculated for C₁₄H₂₀O₃N, experimental = 250.1461.

(±)-(2R,4R,6R)-methyl 6-benzyl-tetrahydro-4-methoxy-2H-pyran-2-carboxylate **5.25**



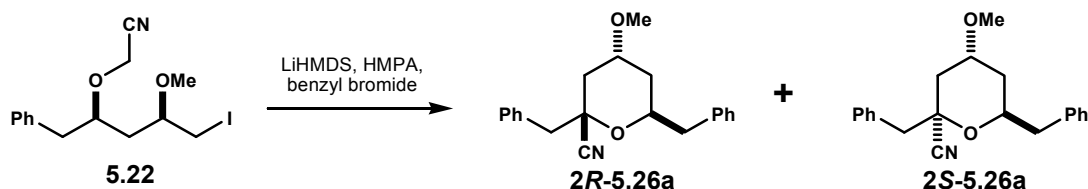
Cyanopyran **5.23** (100 mg, 0.432 mmol) as a 4:1 mixture of diastereomers was dissolved in MeOH (10 mL). K_2CO_3 (597 mg, 4.32 mmol) was then added, and the suspension was stirred overnight at room temperature. The reaction was quenched with addition of a half-saturated solution of NH_4Cl (10 mL). After extracting the aqueous layer with Et_2O (2 x 10 mL), the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was loaded into a silica gel column, was eluted with 80:20 hexanes : EtOAc. Upon removal of solvent, title product **5.25** was isolated in 36% yield (41 mg, 0.155 mmol) with a diastereomeric ratio of 6:1 as a yellow oil. 1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.32- 7.28 (2H, m), 7.25 – 7.22 (3H, m), 4.12 (1H, dd, J = 12.0, 2.0 Hz), 4.03 (1H, dddd, J = 13.5, 7.0, 5.0, 2.0 Hz), 3.77 (3H, s), 3.69 (1H, p, J = 3.0 Hz), 3.33 (3H, s), 2.92 (1H, dd, J = 13.5, 7.0 Hz), 2.76 (1H, dd, J = 13.5, 5.5 Hz), 2.22 (1H, dddd, J = 14.0, 3.0, 3.0, 3.0 Hz), 1.84 (1H, dddd, J = 14.0, 3.0, 3.0, 3.0 Hz), 1.41 (1H, ddd, J = 14.5, 12.0, 3.0 Hz), 1.37 (1H, ddd, J = 14.5, 12.0, 2.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.29, 138.14, 129.46, 128.20, 126.23, 72.87, 72.85, 69.55, 56.05, 52.88, 42.45, 34.85, 32.32. IR (cm^{-1}): ν = 3028, 2925, 2874, 1760, 1667, 1455, 1299, 1190, 1102, 869. HRMS-FAB: $M^{+} = 264.1362$ calculated for $C_{15}H_{20}O_4$, experimental = 264.1353.

GENERAL PROCEDURE A: *One-Pot Cyclization and Alkylation*



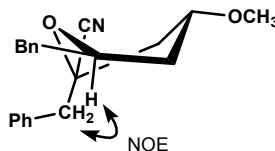
HMDS (1.42 mL, 6.68 mmol) was dissolved in THF (10 mL) and cooled to -78°C. A solution of *n*-BuLi (2.90 mL, 6.68 mmol, 2.3 M in hexanes) was then added dropwise quite rapidly, and the solution was stirred for 15 minutes prior to addition of HMPA (1.45 mL, 8.35 mmol). This LiHMDS solution was further stirred for 30 minutes. In a separate flask, cyanoether **5.22** (300 mg, 0.835 mmol) was dissolved in THF (20 mL), and the solution was cooled to -78°C. The freshly prepared, cold LiHMDS solution was then added via cannula dropwise. The reaction was further stirred for 15 minutes and then alkylating agent (4.18 mmol) was added dropwise. The reaction was then warmed up to -30°C and stirred overnight. A half-saturated solution of NH₄Cl (50 mL) was then added in one portion, and the mixture was warmed up to room temperature. The organic and aqueous layers were separated. The aqueous layer was washed with Et₂O (2 x 20 mL). The organic layers were then combined, dried over MgSO₄, filtered, and concentrated under vacuum leaving behind a yellow oil. The crude material was purified with Biotage chromatography to give title product **5.26** as a mixture of diastereomers. Biotage condition: 25+M column, 95:5 hexanes : EtOAc for 90 mL, then 95:5 → 80:20 hexanes : EtOAc linear gradient over 360 mL, then 80:20 hexanes : EtOAc for 90 mL.

(±)-(4*R*,6*R*)-2,6-dibenzyl-tetrahydro-4-methoxy-2*H*-pyran-2-carbonitrile **5.26a**



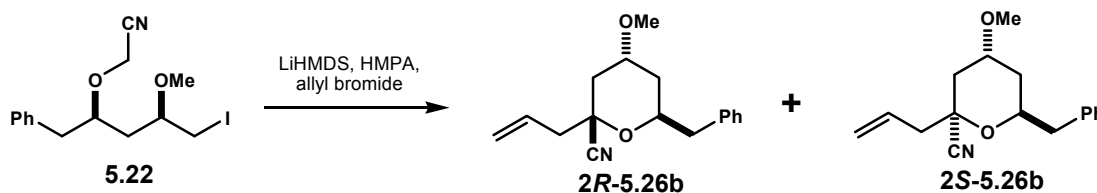
General Procedure A was followed. Benzyl bromide (0.497 mL, 4.18 mmol) was employed as the alkylating agent. Title product **5.26a** was isolated in 82% yield with a diastereomeric ratio of 3:2 as a yellow oil (221 mg, 0.688 mmol).

*Less polar (major) diastereomer 2*R*-5.26a*: ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.32 – 7.28 (2H, m), 7.27 – 7.21 (6H, m), 7.18 – 7.16 (2H, m), 4.26 (1H, m), 3.80 (1H, m), 3.39 (1H, d, J = 14.0 Hz), 3.34 (3H, s), 3.04 (1H, d, J = 14.0 Hz), 3.01 (1H, dd, J = 13.5, 6.5 Hz), 2.83 (1H, dd, J = 13.5, 6.0 Hz), 2.16 (1H, dd, J = 14.0, 4.5 Hz), 1.98 (1H, dd, J = 14.0, 6.0 Hz), 1.78 – 1.75 (2H, m). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.77, 134.36, 130.53, 129.51, 128.37, 128.20, 127.17, 126.43, 121.05, 73.05, 71.66, 70.58, 56.19, 43.45, 41.49, 36.68, 33.05. IR (cm^{-1}): ν = 3030, 2929, 2832, 1497, 1455, 1199, 1077, 1048. HRMS-FAB: $M^{+} = 321.1729$ calculated for $\text{C}_{21}\text{H}_{23}\text{O}_2$, experimental = 321.1730. The relative stereochemistry of the ring was deduced from a ROESY experiment.



More polar (minor) diastereomer 2S-5.26a: ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.29 – 7.27 (7H, m), 7.23 – 7.19 (3H, m), 4.38 (1H, dddd, J = 12.5, 6.5, 6.5, 2.0 Hz), 3.63 (1H, p, J = 3.0 Hz), 3.29 (3H, s), 3.10 (1H, d, J = 13.5 Hz), 3.01 (1H, d, J = 13.5 Hz), 2.90 (1H, dd, J = 14.0, 6.5 Hz), 2.76 (1H, dd, J = 14.0, 6.0 Hz), 2.15 (1H, ddd, J = 14.5, 2.0, 2.0 Hz), 1.86 (1H, dddd, J = 14.0, 3.0, 2.0, 2.0 Hz), 1.55 (1H, dd, J = 14.5, 3.0 Hz), 1.36 (1H, ddd, J = 14.0, 11.5, 3.0 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.32, 133.74, 130.79, 129.48, 128.22, 128.17, 127.37, 126.30, 120.04, 71.73, 71.62, 70.56, 56.02, 47.34, 41.82, 35.56, 34.02. IR (cm^{-1}): ν = 3027, 2925, 1497, 1455, 1100, 1074, 1042. HRMS-FAB: M^{++} = 321.1729 calculated for $\text{C}_{21}\text{H}_{23}\text{O}_2$, experimental = 321.1729.

(±)-(4R,6R)-2-allyl-6-benzyl-tetrahydro-4-methoxy-2H-pyran-2-carbonitrile 5.26b



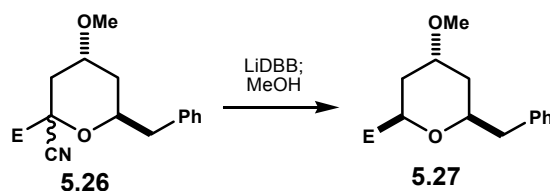
General Procedure A was followed. Allyl bromide (0.364 mL, 4.18 mmol) was employed as the alkylating agent. Title product **5.26b** was isolated in 95% yield with a diastereomeric ratio of 3:2 as a yellow oil (215 mg, 0.792 mmol).

Less polar (major) diastereomer 2R-5.26b: ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.31 – 7.28 (2H, m), 7.24 – 7.20 (3H, m), 5.73 (1H, dddd, J = 17.0, 10.5, 7.0, 7.0 Hz), 5.19 – 5.15 (2H, m), 4.11 (1H, dddd, J = 10.0, 7.0, 7.0, 3.5 Hz), 3.74 (1H, m), 3.30 (3H, s), 2.98 (1H, dd, J = 13.5, 7.0 Hz), 2.93 (1H, dd, J = 14.5, 7.0 Hz), 2.80 (1H, dd, J = 14.0, 6.5

Hz), 2.54 (1H, dd, $J = 14.0, 7.5$ Hz), 2.12 (1H, dd, $J = 14.5, 4.0$ Hz), 1.97 (1H, ddd, $J = 14.0, 5.5, 1.0$ Hz), 1.73 (1H, dddd, $J = 14.0, 5.0, 3.5, 1.0$ Hz), 1.70 (1H, ddd, $J = 13.0, 9.0, 3.5$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.75, 131.03, 129.42, 128.30, 126.39, 121.05, 120.08, 72.29, 71.79, 69.92, 56.18, 41.56, 41.47, 35.88, 33.12. IR (cm^{-1}): $f = 3084, 3029, 2929, 2830, 1644, 1605, 1497, 1455, 1350, 1201, 1079, 1045, 924, 751, 701$. HRMS-FAB: $(\text{M-H})^+ = 270.1494$ calculated for $\text{C}_{17}\text{H}_{20}\text{O}_2$, experimental = 270.1522.

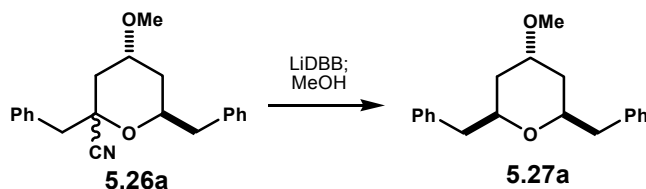
More polar (minor) diastereomer 2S-5.26b: ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.30 – 7.26 (2H, m), 7.23 – 7.20 (3H, m), 5.87 (1H, dddd, $J = 17.0, 10.5, 7.5, 7.0$ Hz), 5.25 – 5.20 (2H, m), 4.37 (1H, dddd, $J = 12.0, 6.0, 6.0, 2.0$ Hz), 3.65 (1H, p, $J = 2.5$ Hz), 3.33 (3H, s), 2.90 (1H, dd, $J = 13.5, 6.0$ Hz), 2.74 (1H, dd, $J = 14.0, 6.0$ Hz), 2.56 (1H, dddd, $J = 14.0, 7.0, 5.5, 5.5$ Hz), 2.48 (1H, dddd, $J = 14.0, 7.5, 1.0, 1.0$ Hz), 2.21 (1H, ddd, $J = 14.5, 3.0, 2.0$ Hz), 1.86 (1H, ddd, $J = 14.0, 3.5, 2.0, 2.0$ Hz), 1.52 (1H, dd, $J = 14.5, 3.0$ Hz), 1.36 (1H, ddd, $J = 14.0, 11.5, 2.5$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.26, 130.46, 129.49, 128.19, 126.31, 120.38, 120.11, 71.66, 70.87, 70.47, 55.98, 45.85, 41.79, 35.52, 34.02. IR (cm^{-1}): $f = 3084, 3028, 2926, 2828, 1644, 1605, 1455, 1348, 1196, 1099, 1083, 924, 744, 701$. HRMS-FAB: $(\text{M-H})^+ = 270.1494$ calculated for $\text{C}_{17}\text{H}_{20}\text{O}_2$, experimental = 270.1499.

GENERAL PROCEDURE B: *Reductive Decyanation Using LiDBB*



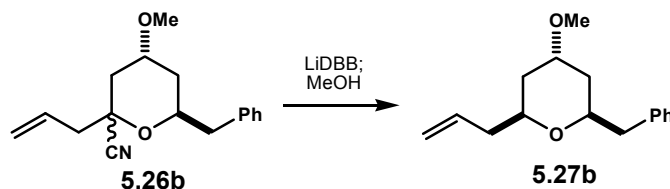
In a flask, cyanopyran **5.26** (1.0 equivalent) as a mixture of diastereomers was dissolved in degassed THF (10 mL). 200 mg of 4 Å molecular sieves were then added. After standing for 10 minutes, this solution was then transferred to a round-bottomed flask via cannula. To ensure cyanopyran **5.26** was completely transferred, the flask was washed with THF (2 x 2.5 mL) and transferred via cannula. This solution was then cooled to -78°C. A freshly prepared solution of LiDBB (2.5 equivalents, 0.4 M in THF) was then added dropwise until reaction mixture turned dark green. After stirring for 30 minutes, MeOH (2 mL) was added dropwise causing the green color to disappear. The mixture was warmed to room temperature and diluted with a half-saturated NH₄Cl solution (20 mL). The organic and aqueous layers were separated. The aqueous layer was washed with Et₂O (2 x 20 mL). The organic layers were then combined, dried over MgSO₄, filtered, and concentrated under vacuum leaving behind a yellow oil. Column chromatography purification with silica gel and 95:5 hexanes : EtOAc provided title product **5.27**.

(±)-(2*S*,4*S*,6*R*)-2,6-dibenzyl-tetrahydro-4-methoxy-2*H*-pyran **5.27a**



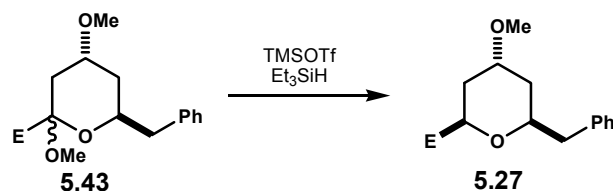
General Procedure B was followed. Cyanopyran **5.26a** (150 mg, 0.467 mmol) and LiDBB (2.93 mL, 1.17 mmol, 0.4 M in THF) were employed, and tetrahydropyran **5.27a** was isolated in 47% yield (65.0 mg, 0.219 mmol) with a diastereomeric ratio of >20:1 as a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.27 – 7.18 (10H, m), 3.48 (2H, m), 3.29 (3H, s), 3.26 (1H, m), 2.97 (2H, dd, J = 14.0, 7.0 Hz), 2.70 (2H, dd, J = 14.0, 6.0 Hz), 1.99 (2H, m), 1.17 (2H, ddd, J = 11.5, 11.5, 11.5 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 138.56, 129.46, 128.14, 126.10, 76.67, 76.56, 55.32, 42.59, 37.15. IR (cm^{-1}): ν = 3027, 2943, 2847, 1495, 1454, 1372, 1152, 1086, 750, 700. HRMS-FAB: $(\text{M}+\text{H})^+$: 297.1855 calculated for $\text{C}_{20}\text{H}_{25}\text{O}_2$, experimental = 297.1842.

(±)-(2*S*,4*S*,6*R*)-2-allyl-6-benzyl-tetrahydro-4-methoxy-2*H*-pyran **5.27b**



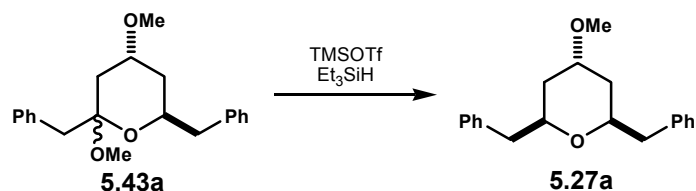
General Procedure B was followed. Cyanopyran **5.26b** (180 mg, 0.663 mmol) and LiDBB (4.15 mL, 1.66 mmol, 0.4 M in THF) were employed, and tetrahydropyran **5.27b** was isolated in 37% yield (60.0 mg, 0.244 mmol) with a diastereomeric ratio of >20:1 as a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.28 – 7.17 (5H, m), 5.82 (1H, dddd, J = 17.0, 10.0, 6.5, 6.5 Hz), 5.07 – 5.00 (2H, m), 3.90 (1H, m), 3.71 (1H, m), 3.61 (1H, p, J = 2.5 Hz), 3.25 (3H, s), 2.89 (1H, dd, J = 14.0, 7.0 Hz), 2.62 (1H, dd, J = 13.5, 6.0 Hz), 2.29 (1H, m), 2.15 (1H, m), 1.82 (1H, ddd, J = 14.0, 4.5, 2.0 Hz), 1.78 (1H, ddd, J = 13.5, 4.5, 2.0 Hz), 1.34 (1H, ddd, J = 11.5, 2.5, 2.5 Hz), 1.32 (1H, ddd, J = 11.5, 6.0, 2.5 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 138.76, 135.02, 129.49, 128.05, 125.98, 116.44, 73.60, 72.77, 71.51, 55.88, 42.66, 40.65, 34.74, 34.70. IR (cm^{-1}): ν = 3064, 3028, 2917, 2865, 1347, 1050, 1032, 912, 699. HRMS-FAB: $(\text{M}+\text{H})^+ = 247.1698$ calculated for $\text{C}_{16}\text{H}_{23}\text{O}_2$, experimental = 247.1687.

GENERAL PROCEDURE C: *Reduction of Methyl Pyranoside 5.43 to 2,6-cis-Tetrahydropyran 5.27*



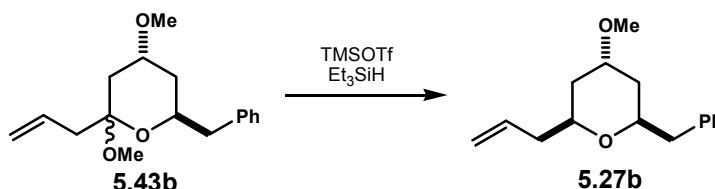
Methyl pyranoside **5.43** as a mixture of diastereomers (1.0 equivalent) was dissolved in CH_2Cl_2 . Several grains of 4 Å molecular sieves were added, and the solution was chilled to -78°C . After addition of Et_3SiH (2.0 equivalents), a freshly prepared solution of TMSOTf (3.0 equivalents, 1.0 M in CH_2Cl_2) was then added dropwise slowly, and the reaction was stirred for one minute. Immediately, the reaction was quenched by one full injection, of a half-saturated NH_4Cl aqueous solution (10 mL) and warmed to 0°C . After separating the organic and aqueous layers, the aqueous layer was washed with CH_2Cl_2 (2 x 20 mL). The organic layers were then combined, dried over MgSO_4 , filtered, and concentrated under vacuum leaving behind a yellow oil. The crude material was loaded into a silica gel column, and product elution was made with 90:10 hexanes : EtOAc. Removal of solvent under vacuum provided the title product **5.27**.

(±)-(2*S*,4*S*,6*R*)-2,6-dibenzyl-tetrahydro-4-methoxy-2*H*-pyran **5.27a**



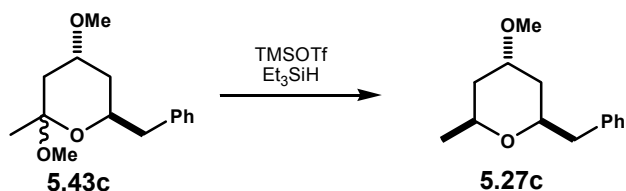
General Procedure C was followed. Methyl pyranoside **5.43a** (280 mg, 0.858 mmol) dissolved in CH₂Cl₂ (25 mL), TMSOTf (2.57 mL, 2.57 mmol, 1.0 M in CH₂Cl₂), and Et₃SiH (0.27 mL, 1.72 mmol) were employed, and tetrahydropyran **5.27a** was obtained in 91% yield with a diastereomeric ratio of >20:1 as a colorless oil (232 mg, 0.783 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.27 – 7.18 (10H, m), 3.48 (2H, m), 3.29 (3H, s), 3.26 (1H, m), 2.97 (2H, dd, J = 14.0, 7.0 Hz), 2.70 (2H, dd, J = 14.0, 6.0 Hz), 1.99 (2H, m), 1.17 (2H, ddd, J = 11.5, 11.5, 11.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 138.56, 129.46, 128.14, 126.10, 76.67, 76.56, 55.32, 42.59, 37.15. IR (cm⁻¹): *f* = 3027, 2943, 2847, 1495, 1454, 1372, 1152, 1086, 750, 700. HRMS-FAB: (M+H)⁺: 297.1855 calculated for C₂₀H₂₅O₂, experimental = 297.1842.

(±)-(2S,4S,6R)-2-allyl-6-benzyl-tetrahydro-4-methoxy-2H-pyran 5.27b



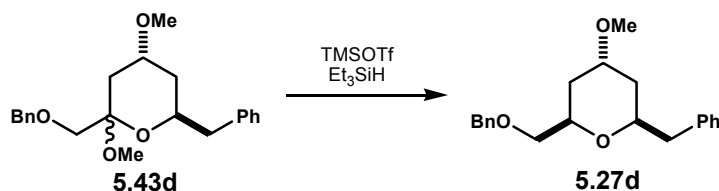
General Procedure C was followed. Methyl pyranoside **5.43b** (150 mg, 0.542 mmol) dissolved in CH₂Cl₂ (15 mL), TMSOTf (1.63 mL, 1.63 mmol, 1.0 M in CH₂Cl₂), and Et₃SiH (0.17 mL, 1.08 mmol) were employed, and tetrahydropyran **5.27b** was obtained in 82% yield with a diastereomeric ratio of >20:1 as a colorless oil (110 mg, 0.447 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.28 – 7.17 (5H, m), 5.82 (1H, dddd, J = 17.0, 10.0, 6.5, 6.5 Hz), 5.07 – 5.00 (2H, m), 3.90 (1H, m), 3.71 (1H, m), 3.61 (1H, p, J = 2.5 Hz), 3.25 (3H, s), 2.89 (1H, dd, J = 14.0, 7.0 Hz), 2.62 (1H, dd, J = 13.5, 6.0 Hz), 2.29 (1H, m), 2.15 (1H, m), 1.82 (1H, ddd, J = 14.0, 4.5, 2.0 Hz), 1.78 (1H, ddd, J = 13.5, 4.5, 2.0 Hz), 1.34 (1H, ddd, J = 11.5, 2.5, 2.5 Hz), 1.32 (1H, ddd, J = 11.5, 6.0, 2.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 138.76, 135.02, 129.49, 128.05, 125.98, 116.44, 73.60, 72.77, 71.51, 55.88, 42.66, 40.65, 34.74, 34.70. IR (cm⁻¹): ν = 3064, 3028, 2917, 2865, 1347, 1050, 1032, 912, 699. HRMS-FAB: (M+H)⁺ = 247.1698 calculated for C₁₆H₂₃O₂, experimental = 247.1687.

(±)-(2*R*,4*S*,6*S*)-2-benzyl-tetrahydro-4-methoxy-6-methyl-2*H*-pyran **5.27c**



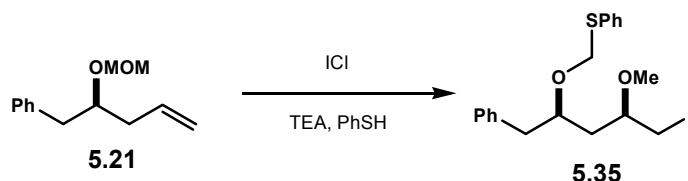
General Procedure C was followed. Methyl pyranoside **5.43c** (140 mg, 0.559 mmol) dissolved in CH₂Cl₂ (20 mL), TMSOTf (1.68 mL, 1.68 mmol, 1.0 M in CH₂Cl₂), and Et₃SiH (0.18 mL, 1.12 mmol) were employed, and tetrahydropyran **5.27c** was obtained in 72% yield with a diastereomeric ratio of >20:1 as a colorless oil (89 mg, 0.404 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.29 – 7.26 (2H, m), 7.23 – 7.18 (3H, m), 3.91 (1H, dddd, J = 13.5, 6.5, 6.5, 1.5 Hz), 3.81 (1H, ddq, J = 12.5, 6.5, 2.0 Hz), 3.59 (1H, p, J = 3.0 Hz), 3.23 (3H, s), 2.89 (1H, dd, J = 6.5, 14.0 Hz), 2.60 (1H, dd, J = 13.5, 7.5 Hz), 1.82 – 1.74 (2H, m), 1.33 (1H, ddd, J = 11.0, 11.0, 3.0 Hz), 1.30 (1H, ddd, J = 11.0, 11.0, 3.0 Hz), 1.16 (3H, d, J = 6.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 138.64, 129.45, 128.18, 126.06, 73.62, 72.75, 68.09, 55.93, 42.82, 36.95, 34.30, 21.95. IR (cm⁻¹): ν = 3028, 2970, 2916, 2867, 1455, 1348, 1104, 1082, 699. HRMS-FAB: (M+H)⁺ = 221.1542 calculated for C₁₄H₂₁O₂, experimental = 221.1561.

(±)-(2*R*,4*R*,6*R*)-2-benzyl-6-((benzyloxy)methyl)-tetrahydro-4-methoxy-2*H*-pyran **5.27d**



General Procedure C was followed. Methyl pyranoside **5.43d** (169 mg, 0.473 mmol) dissolved in CH₂Cl₂ (15 mL), TMSOTf (1.42 mL, 1.42 mmol, 1.0 M in CH₂Cl₂), and Et₃SiH (0.15 mL, 0.946 mmol) were employed, and tetrahydropyran **5.27d** was obtained in 66% yield with a diastereomeric ratio of >20:1 as a colorless oil (102 mg, 0.313 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.39 – 7.35 (4H, m), 7.33 – 7.21 (6H, m), 4.62 (1H, d, J = 12.5 Hz), 4.59 (1H, d, J = 12.5 Hz), 4.03 – 3.96 (2H, m), 3.68 (1H, p, J = 3.0 Hz), 3.53 (1H, dd, J = 10.5, 6.0 Hz), 3.50 (1H, dd, J = 10.5, 4.0 Hz), 3.29 (3H, s), 3.01 (1H, dd, J = 14.0, 7.0 Hz), 2.69 (1H, dd, J = 13.5, 7.0 Hz), 1.84 (1H, m), 1.82 (1H, m), 1.49 (1H, ddd, J = 14.0, 12.0, 2.5 Hz), 1.40 (1H, ddd, J = 14.5, 12.0, 3.0 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 138.54, 138.50, 129.43, 128.25, 128.10, 127.59, 127.41, 126.00, 73.36, 73.19, 73.15, 72.73, 71.54, 55.88, 42.57, 34.57, 31.46. IR (cm⁻¹): ν = 3062, 3028, 2918, 2864, 1496, 1454, 1098, 1080, 736, 698. HRMS-FAB: M⁺ = 326.1882 calculated for C₂₁H₂₆O₃, experimental = 326.1880.

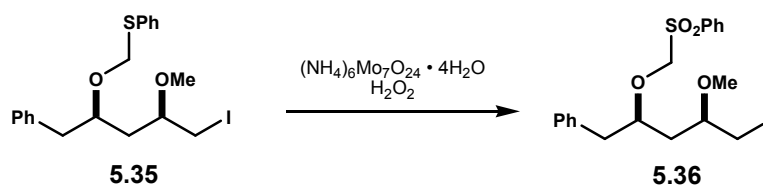
(±)-(((2*R*,4*R*)-5-iodo-4-methoxy-1-phenylpentan-2-yloxy)methyl)(phenyl)sulfane **5.35**



Compound **5.21** (8.00 g, 38.8 mmol) was dissolved in toluene (600 mL), and 8 grams of 4 Å molecular sieves were then added. After cooling this solution to -78°C , iodine monochloride (46.5 mL, 46.5 mmol, 1.0 M in CH_2Cl_2) was added dropwise while maintaining an internal temperature of the reaction below -75°C . The solution became dark red and was stirred for 30 minutes. Then, TEA (16.2 mL, 116 mmol) was added in one injection, followed by PhSH (5.60 mL, 54.3 mmol) in which the solution immediately turned cloudy grey. The reaction was warmed to room temperature over one hour and then quenched with a 1:1 mixture of saturated NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ (300 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et_2O (2 x 100 mL). The organic layers were then combined, dried over MgSO_4 , and filtered. The organic solvent was removed under vacuum leaving behind a yellow oil. The crude material was purified with column chromatography using 95:5 hexanes : EtOAc to give ether transfer product **5.35** in 88% yield with a diastereomeric ratio of >20:1 as a colorless oil (15.0 g, 33.9 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.42 – 7.41 (2H, m), 7.33 – 7.29 (4H, m), 7.26 – 7.20 (4H, m), 5.18 (1H, d, J = 12.0 Hz), 4.84 (1H, d, J = 12.0 Hz), 4.01 (1H, dddd, J = 8.0, 6.5, 6.5, 4.5 Hz), 3.30 (1H, dd, J = 11.0, 4.0 Hz), 3.27 (1H, dd, J = 11.0, 4.0 Hz), 3.22 (3H, s), 2.97 (1H, m), 2.93 (1H, dd, J = 13.5, 6.0

Hz), 2.82 (1H, dd, $J = 13.5, 6.0$ Hz), 1.82 (1H, ddd, $J = 14.5, 8.0, 5.5$ Hz), 1.73 (1H, ddd, $J = 14.0, 7.0, 4.0$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.60, 135.63, 129.50, 129.11, 128.93, 128.37, 126.40, 126.34, 75.71, 74.69, 73.07, 56.42, 40.18, 38.59, 10.58. IR (cm^{-1}): $\nu = 3059, 3026, 2924, 2822, 1584, 1481, 1439, 1088, 1053, 741, 701$. HRMS-FAB: $M^{++} = 442.0464$ calculated for $\text{C}_{19}\text{H}_{23}\text{O}_2\text{SI}$, experimental = 442.0457.

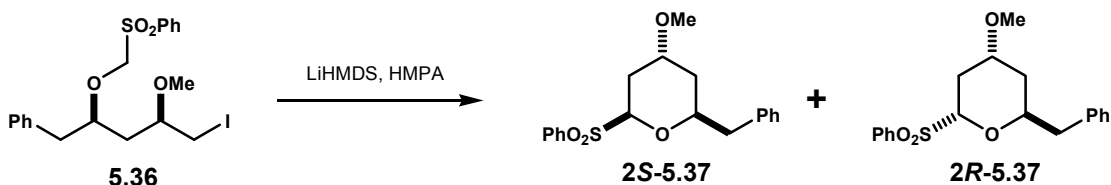
(±)-1-((2R,4R)-2-((phenylsulfonyl)methoxy)-5-iodo-4-methoxypentyl)benzene **5.36**



Compound **5.35** (15.0 g, 33.9 mmol) was dissolved in ethanol (424 mL, 200 proof), and the solution was cooled to 0°C. In a separate flask, ammonium (VI) molybdate tetrahydrate (8.47 g, 6.79 mmol) was dissolved in a cold aqueous hydrogen peroxide solution (30%, 424 mL). This Mo(VI) – H_2O_2 mixture was immediately poured to the solution of **5.35** in one portion causing the reaction to turn yellow and cloudy (the cloudiness eventually dissipated). The reaction was stirred at 0°C for one hour and then at room temperature for two more hours. Addition of DI water (400 mL) quenched the reaction, and the aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL). The pink organic layers were combined, dried over MgSO_4 , filtered, and rotovaped to produce a dark red oily residue. The crude material was then loaded onto silica gel and chromatographed with 80:20 hexanes : EtOAc to afford the corresponding sulfone **5.36** in

83% yield as a yellow oil (13.3 g, 28.1 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.82 – 7.80 (2H, m), 7.67 (1H, m), 7.56 – 7.53 (2H, m), 7.30 – 7.22 (3H, m), 7.15 – 7.14 (2H, m), 4.55 (1H, d, J = 12.5 Hz), 4.39 (1H, d, 12.5 Hz), 4.11 (1H, p, J = 6.0 Hz), 3.29 (1H, dd, J = 10.5, 5.0 Hz), 3.27 (3H, s), 3.23 (1H, dd, J = 11.0, 4.0 Hz), 3.04 (1H, m), 2.86 (1H, dd, J = 14.0, 7.0 Hz), 2.82 (1H, dd, J = 14.0, 6.0 Hz), 1.80 (1H, ddd, J = 17.0, 6.5, 6.5 Hz), 1.78 (1H, ddd, J = 14.5, 5.5, 5.5 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.30, 137.03, 133.94, 129.49, 129.16, 128.70, 128.53, 126.67, 84.38, 80.94, 75.93, 56.55, 40.77, 38.77, 9.73. IR (cm^{-1}): ν = 3062, 3028, 2926, 2825, 1447, 1324, 1298, 1150, 1112, 1080, 746, 702, 688. HRMS-FAB: $(\text{M}+\text{H})^+ = 475.0440$ calculated for $\text{C}_{19}\text{H}_{24}\text{O}_4\text{SI}$, experimental = 475.0447.

(±)-(2*S*,4*S*)-2-benzyl-tetrahydro-4-methoxy-6-(phenylsulfonyl)-2*H*-pyran **5.37**



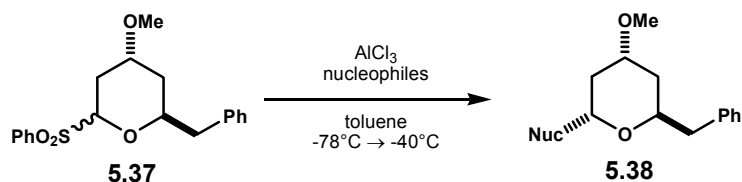
HMDS (7.74 mL, 36.5 mmol) was dissolved in THF (100 mL) and cooled to -78°C. A solution of *n*-BuLi (17.3 mL, 36.5 mmol, 2.1 M in hexanes) was then added dropwise quite rapidly, and the solution was stirred for 10 minutes prior to the addition of HMPA (14.6 mL, 84.1 mmol). This LiHMDS solution was further stirred for 10 minutes. In a separate flask, sulfone **5.36** (13.3 g, 28.0 mmol) was dissolved in THF (500 mL), and the solution was cooled to -78°C. The freshly prepared, cold LiHMDS solution was then

added to this solution via cannula dropwise over 30 minutes. The reaction was further stirred for 2 hours, and then quenched with a half-saturated aqueous NH_4Cl solution (200 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et_2O (2 x 100 mL). The organic layers were then combined, dried over MgSO_4 , filtered, and concentrated under vacuum leaving behind a yellow oil. The crude material was flushed through a thick silica pad with 70:30 hexanes : EtOAc . The solvent was then evaporated to leave the title product **5.37** as a yellow solid (9.31 g, 26.9 mmol) in 96% yield as a 3:2 mixture of diastereomers. Although compound **5.37** was found pure judged by ^1H and ^{13}C NMR, compound **5.37** could be recrystallized by dissolving the solid in hot Et_2O following by cooling to -20°C in freezer overnight at which the product reprecipitated as an amorphous white solid. The solid was then filtered and washed with cold Et_2O . For characterization purposes, the two diastereomers were separated and isolated by column chromatography with 80:20 hexanes : EtOAc .

Less Polar Diastereomer 2S-5.37: ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.84 – 7.82 (2H, m), 7.62 – 7.58 (1H, m), 7.46 – 7.42 (2H, m), 7.15 – 7.13 (3H, m), 7.01 – 6.98 (2H, m), 4.70 (1H, dd, J = 12.0, 2.0 Hz), 3.93 (1H, m), 3.80 (1H, p, J = 3.0 Hz), 3.31 (3H, s), 2.81 (1H, dd, J = 14.0, 8.0 Hz), 2.65 (1H, dd, J = 14.5, 4.5 Hz), 2.41 (1H, ddd, J = 13.5, 5.0, 2.0 Hz), 1.85 – 1.79 (2H, m), 1.49 (1H, ddd, J = 14.0, 11.5, 2.5 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.69, 136.48, 133.57, 129.24, 129.02, 128.66, 128.07, 126.08, 87.54, 74.43, 72.29, 56.21, 41.66, 34.63, 26.44. IR (cm^{-1}): ν = 3063, 3029, 2931, 2880, 2828, 1448, 1321, 1151, 1102, 1071, 1039, 726, 596. HRMS-FAB: $(\text{M}-\text{H})^+ = 345.1161$ calculated for $\text{C}_{19}\text{H}_{21}\text{O}_4\text{S}$, experimental = 345.1169.

More Polar Diastereomer **2R-5.37**: ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.60 – 7.52 (3H, m), 7.40 – 7.37 (2H, m), 7.31 – 7.27 (3H, m), 7.14 – 7.12 (2H, m), 4.75 (1H, dddd, J = 8.5, 7.0, 5.0, 5.0 Hz), 4.70 (1H, dd, J = 7.5, 6.0 Hz), 3.71 (1H, m), 3.43 (3H, s), 2.77 (1H, dd, J = 14.5, 5.0 Hz), 2.71 (1H, dd, J = 14.0, 8.5 Hz), 2.38 – 2.28 (2H, m), 1.87 – 1.79 (2H, m). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.66, 137.17, 133.35, 129.19, 128.96, 128.75, 128.36, 126.30, 87.63, 72.17, 71.09, 55.95, 40.75, 35.11, 25.59. IR (cm^{-1}): ν = 3066, 3022, 2926, 1447, 1321, 1303, 1145, 1119, 1080. HRMS-FAB: $(\text{M}+\text{H})^+ = 347.1317$ calculated for $\text{C}_{19}\text{H}_{23}\text{O}_4\text{S}$, experimental = 347.1318.

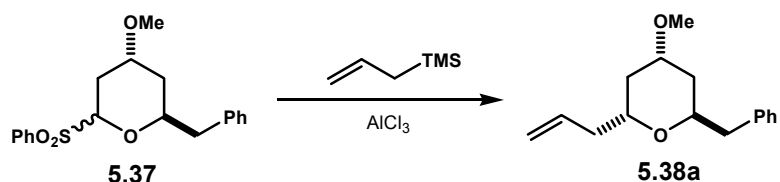
GENERAL PROCEDURE D: *AlCl_3 Mediated Addition of Silyl Nucleophiles to Sulfonylpyran 5.37 To Furnish 2,6-trans-tetrahydropyran 5.38*



A suspension of AlCl_3 (1.5 equivalents) in toluene (10 mL) was cooled to -78°C . In a separate flask, sulfonylpyran **5.37** (1.0 equivalent) as a mixture of diastereomers was dissolved in toluene (5 mL). After cooling to -78°C , this solution was transferred to the AlCl_3 suspension via cannula. To ensure all starting material was completely transferred, the flask was washed with toluene (2 x 2.5 mL) and transferred to the reaction mixture. This mixture was stirred for 5 minutes. Nucleophiles (3.0 equivalents) were then added dropwise, and the reaction was slowly warmed up to -40°C over one hour in which all

pyran **5.37** was consumed. A saturated aqueous solution of Rochelle's salt (20 mL) was then added, and the emulsion was stirred until separation of layers was achieved. After separating the organic and aqueous layers, the aqueous layer was washed with CH₂Cl₂ (2 x 20 mL). The organic layers were then combined, dried over MgSO₄, filtered, and concentrated under vacuum leaving behind a yellow oil. The crude material was purified using Biotage chromatography system which provided 2,6-*trans*-tetrahydropyran **5.38**.

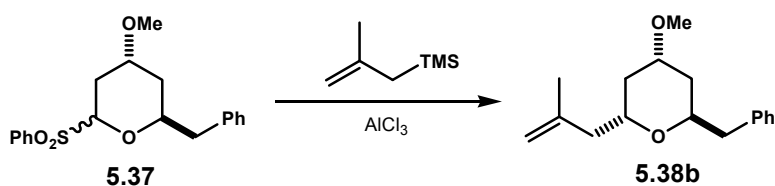
(±)-(2*R*,4*S*,6*R*)-2-allyl-6-benzyl-tetrahydro-4-methoxy-2*H*-pyran **5.38a**



General Procedure D was followed. Sulfonylpyran **5.37** (325 mg, 0.938 mmol), AlCl₃ (188 mg, 1.41 mmol), and allyltrimethylsilane (0.45 mL, 2.81 mmol) were employed, and tetrahydropyran **5.38a** was obtained in 80% with a diastereomeric ratio of >20:1 as a colorless oil (185 mg, 0.447 mmol). Biotage condition: 25+S column, 95:5 hexanes : EtOAc for 90 mL, then 95:5 → 85:15 hexanes : EtOAc linear gradient over 270 mL. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.31 – 7.28 (2H, m), 7.23 – 7.19 (3H, m), 5.76 (1H, dddd, J = 17.0, 10.0, 7.0, 7.0 Hz), 5.07 (1H, ddd, J = 17.0, 3.5, 1.5 Hz), 5.03 (1H, m), 4.26 (1H, m), 3.81 (1H, dddd, J = 10.0, 7.0, 6.0, 3.0 Hz), 3.65 (1H, dddd, J = 9.5, 9.5, 5.0, 4.0 Hz), 3.34 (3H, s), 2.98 (1H, dd, J = 14.0, 7.5 Hz), 2.78 (1H, dd, J = 13.5, 7.5 Hz), 2.40 (1H, m), 2.25 (1H, m), 2.04 (1H, m), 1.86 (1H, m), 1.54 (1H, ddd, J = 13.0,

10.0, 5.5 Hz), 1.30 (1H, ddd, 13.0, 9.5, 9.5 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 138.77, 134.90, 129.09, 128.40, 126.21, 116.78, 73.05, 72.99, 69.28, 55.41, 40.14, 38.74, 36.08, 33.54. IR (cm^{-1}): ν = 3027, 2925, 2858, 1454, 1378, 1089, 913, 700. HRMS-FAB: $(\text{M}+\text{H})^+ = 247.1698$ calculated for $\text{C}_{16}\text{H}_{23}\text{O}_2$, experimental = 247.1680.

(±)-(2*R*,4*S*,6*R*)-2-benzyl-tetrahydro-4-methoxy-6-(2-methylallyl)-2*H*-pyran **5.38b**

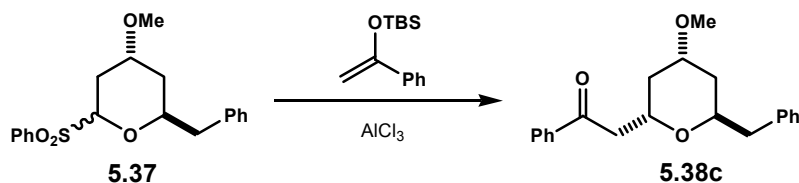


General Procedure D was followed. Sulfonopyran **5.37** (165 mg, 0.476 mmol), AlCl_3 (95 mg, 0.714 mmol), and methallyltrimethylsilane (0.25 mL, 1.43 mmol) were employed, and tetrahydropyran **5.38b** was obtained in 86% with a diastereomeric ratio of >20:1 as a colorless oil (106 mg, 0.407 mmol). Biotage condition: 25+S column, 95:5 hexanes : EtOAc for 90 mL, then 95:5 \rightarrow 85:15 hexanes : EtOAc linear gradient over 270 mL. ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.30 – 7.28 (2H, m), 7.22 – 7.19 (3H, m), 4.77 (1H, m), 4.73 (1H, m), 4.28 (1H, m), 3.93 (1H, m), 3.66 (1H, dddd, J = 9.5, 9.5, 4.0, 4.0 Hz), 3.34 (3H, s), 2.97 (1H, dd, J = 13.5, 7.0 Hz), 2.82 (1H, dd, J = 13.5, 8.0 Hz), 2.37 (1H, dd, J = 13.5, 7.0 Hz), 2.17 (1H, dd, J = 14.0, 5.5 Hz), 2.03 (1H, m), 1.85 (1H, m), 1.71 (3H, s), 1.52 (1H, ddd, J = 15.5, 10.0, 5.5 Hz), 1.28 (1H, ddd, J = 12.5, 9.5, 9.5 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 142.55, 138.70, 129.08, 128.41, 126.21, 112.52, 73.07, 72.96, 68.03, 55.42, 44.08, 38.70, 36.49, 33.27, 22.59. IR (cm^{-1}): ν =

3067, 3027, 2927, 1454, 1376, 1085, 888, 700. HRMS-FAB: $(M-H)^+ = 259.1698$
calculated for $C_{17}H_{23}O_2$, experimental = 259.1715.

(±)-2-((2S,4R,6R)-6-benzyl-tetrahydro-4-methoxy-2H-pyran-2-yl)-1-phenylethanone

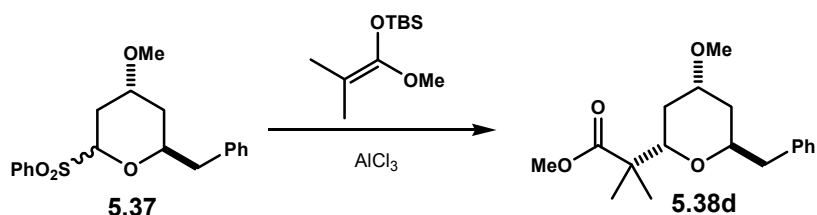
5.38c



General Procedure D was followed. Sulfonfylpyran **5.37** (170 mg, 0.491 mmol), $AlCl_3$ (98 mg, 0.737 mmol), and (1-phenylvinyl)oxy(tert-butyl)dimethylsilane (345 mg, 1.47 mmol) were employed, and tetrahydropyran **5.38c** was obtained in 82% with a diastereomeric ratio of >20:1 as a colorless oil (131 mg, 0.404 mmol). Biotage condition: 25+S column, 95:5 hexanes : EtOAc for 90 mL, then 95:5 \rightarrow 80:20 hexanes : EtOAc linear gradient over 270 mL, then 80:20 hexanes : EtOAc for 90 mL. 1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.95 – 7.93 (2H, m), 7.56 (1H, m), 7.47 – 7.44 (2H, m), 7.27 – 7.25 (2H, m), 7.20 – 7.16 (3H, m), 4.48 (1H, dddd, $J = 9.5, 6.5, 6.5, 3.5$ Hz), 4.23 (1H, m), 3.70 (1H, dddd, $J = 9.0, 9.0, 4.5, 4.5$ Hz), 3.36 (1H, dd, $J = 16.5, 6.5$ Hz), 3.33 (3H, s), 3.16 (1H, dd, $J = 16.0, 6.5$ Hz), 2.98 (1H, dd, $J = 13.5, 7.0$ Hz), 2.79 (1H, dd, $J = 14.0, 6.5$ Hz), 2.17 (1H, m), 1.83 (1H, dddd, $J = 13.0, 4.0, 4.0, 1.5$ Hz), 1.60 (1H, ddd, $J = 13.5, 9.0, 4.5$ Hz), 1.43 (1H, ddd, $J = 13.0, 8.5, 8.5$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 198.43, 138.66, 137.15, 133.11, 129.08, 128.55, 128.38, 128.17, 126.18, 72.86, 72.64,

66.70, 55.58, 44.18, 39.12, 35.88, 33.66. IR (cm⁻¹): ν = 3061, 3026, 2925, 1683, 1449, 1087, 700. HRMS-FAB: (M+H)⁺ = 325.1804 calculated for C₂₁H₂₅O₃, experimental = 325.1812.

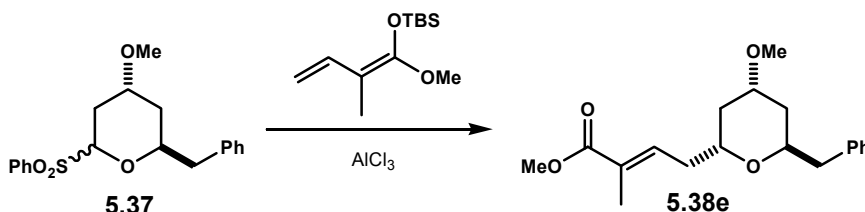
(±)-methyl 2-((2*S*,4*R*,6*R*)-6-benzyl-tetrahydro-4-methoxy-2*H*-pyran-2-yl)-2-methylpropanoate **5.38d**



General Procedure D was followed. Sulfonylpyran **5.37** (190 mg, 0.548 mmol), AlCl₃ (110 mg, 0.822 mmol), and (1-methoxy-2-methylprop-1-enyloxy)(tert-butyl)dimethylsilane (356 mg, 1.64 mmol) were employed, and tetrahydropyran **5.38d** was obtained in 80% with a diastereomeric ratio of >20:1 as a colorless oil (135 mg, 0.441 mmol). Biotage condition: 25+S column, 95:5 hexanes : EtOAc for 90 mL, then 95:5 → 85:15 hexanes : EtOAc linear gradient over 270 mL. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.30 – 7.27 (2H, m), 7.21 – 7.18 (3H, m), 4.34 (1H, qt, J = 7.0 Hz), 3.92 (1H, dd, J = 11.5, 1.5 Hz), 3.67 (1H, dddd, J = 11.5, 11.5, 4.5, 4.5 Hz), 3.60 (3H, s), 3.36 (3H, s), 2.95 (1H, dd, J = 13.5, 7.0 Hz), 2.83 (1H, dd, J = 13.5, 8.0 Hz), 1.96 (1H, m), 1.95 (1H, m), 1.43 (1H, ddd, J = 12.5, 11.5, 6.0 Hz), 1.21 (1H, qt, J = 11.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 177.07, 138.73, 129.01, 128.42, 126.20, 74.52, 73.31, 55.34, 51.80, 46.35, 37.70, 33.24, 32.13, 21.13, 20.02. IR (cm⁻¹): ν = 3027, 2950,

1732, 1455, 1267, 1143, 1089, 1025, 743, 701. HRMS-FAB: $(M+H)^+ = 307.1909$
calculated for $C_{18}H_{27}O_4$, experimental = 307.1908.

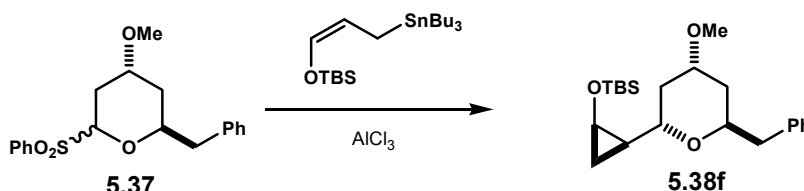
(±)-(E)-methyl 4-((2R,4S,6R)-6-benzyl-tetrahydro-4-methoxy-2H-pyran-2-yl)-2-methylbut-2-enoate **5.38e**



General Procedure D was followed. Sulfonylpyran **5.37** (160 mg, 0.462 mmol), $AlCl_3$ (92 mg, 0.693 mmol), and ((*Z*)-1-methoxy-2-methylbuta-1,3-dienyloxy)(tert-butyl)dimethylsilane (317 mg, 1.39 mmol) were employed, and tetrahydropyran **5.38e** was obtained in 80% with a diastereomeric ratio of >20:1 as a colorless oil (135 mg, 0.441 mmol). Biotage condition: 25+S column, 95:5 hexanes : EtOAc for 90 mL, then 95:5 → 85:15 hexanes : EtOAc linear gradient over 270 mL. 1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.30 – 7.27 (2H, m), 7.22 – 7.18 (3H, m), 6.72 (1H, tq, $J = 7.5, 1.5$ Hz), 4.25 (1H, ddd, $J = 11.5, 7.5, 4.5$ Hz), 3.88 (1H, m), 3.73 (3H, s), 3.65 (1H, dddd, $J = 9.5, 9.0, 5.0, 4.0$ Hz), 3.33 (3H, s), 2.98 (1H, dd, $J = 13.5, 9.0$ Hz), 2.76 (1H, dd, $J = 13.5, 7.0$ Hz), 2.51 (1H, m), 2.37 (1H, m), 2.03 (1H, m), 1.85 (1H, dddd, $J = 13.0, 3.5, 3.5, 1.0$ Hz), 1.82 (3H, d, $J = 1.0$ Hz), 1.59 (1H, ddd, $J = 13.0, 9.5, 5.0$ Hz), 1.34 (1H, ddd, $J = 13.0, 9.0, 9.0$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 168.38, 138.62, 138.37, 129.02, 128.98, 128.39, 126.18, 72.91, 72.57, 68.85, 55.52, 51.66, 38.89, 36.12, 34.82,

33.68, 12.64. IR (cm⁻¹): ν = 3027, 2947, 1713, 1435, 1265, 1090. HRMS-FAB: (M+H)⁺ = 319.1909 calculated for C₁₉H₂₇O₄, experimental = 319.1916.

(±)-((1*R*,2*R*)-2-((2*S*,4*R*,6*R*)-6-benzyl-tetrahydro-4-methoxy-2*H*-pyran-2-yl)cyclopropoxy)(*tert*-butyl)dimethylsilane **5.38f**

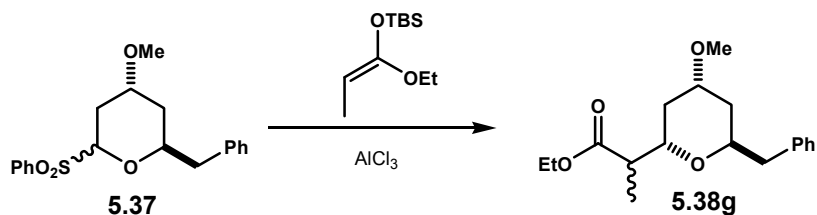


General Procedure D was followed. Sulfonylpyran **5.37** (175 mg, 0.505 mmol), AlCl₃ (101 mg, 0.758 mmol), and ((*Z*)-3-(tributylstannyl)prop-1-enyloxy)(*tert*-butyl)dimethylsilane (699 mg, 1.515 mmol) were employed, and tetrahydropyran **5.38f** (major product) was obtained in 29% as a colorless oil (50 mg, 0.133 mmol). The relative stereochemistry of the cyclopropane group to the tetrahydropyran ring was not determined. Biotage condition: 25+S column, 98:2 hexanes : EtOAc for 180 mL, then 98:2 → 85:15 hexanes : EtOAc linear gradient over 360 mL, then 85:15 hexane : EtOAc for 180 mL. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.28 – 7.31 (2H, m), 7.17 – 7.22 (3H, m), 4.32 (1H, ddd, *J* = 11.5, 7.0, 4.0 Hz), 3.59 (1H, dddd, *J* = 9.0, 9.0, 5.0, 4.0 Hz), 3.34 (3H, s), 3.18 (1H, ddd, *J* = 6.0, 3.0, 3.0 Hz), 3.03 (1H, ddd, *J* = 9.0, 9.0, 3.5 Hz), 2.96 (1H, dd, *J* = 14.0, 8.0 Hz), 2.68 (1H, dd, *J* = 13.5, 7.0 Hz), 1.97 (1H, m), 1.80 (1H, dddd, *J* = 13.0, 4.0, 4.0 1.5 Hz), 1.59 (1H, ddd, *J* = 14.5, 9.0, 5.0 Hz), 1.40 (1H, ddd, *J* = 12.5, 9.0, 9.0 Hz), 1.28 (1H, m), 0.87 (9H, s), 0.68 (1H, ddd, *J* = 10.5, 5.5, 3.5 Hz), 0.37

(1H, ddd, $J = 6.5, 6.0, 6.0$ Hz), 0.05 (6H, s). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 138.66, 129.05, 128.39, 126.19, 73.08, 72.10, 71.78, 55.44, 51.73, 38.96, 34.94, 34.02, 25.84, 24.44, 17.99, 11.51, -4.91, -5.09. IR (cm^{-1}): $\nu = 3025, 2928, 2857, 1455, 1255, 1213, 1156, 1093, 837, 778, 699$. HRMS-FAB: $(\text{M}+\text{H})^+ = 377.2572$ calculated for $\text{C}_{22}\text{H}_{37}\text{O}_3\text{Si}$, experimental = 377.2530.

(±)-methyl 2-((2S,4R,6R)-6-benzyl-tetrahydro-4-methoxy-2H-pyran-2-yl)propanoate

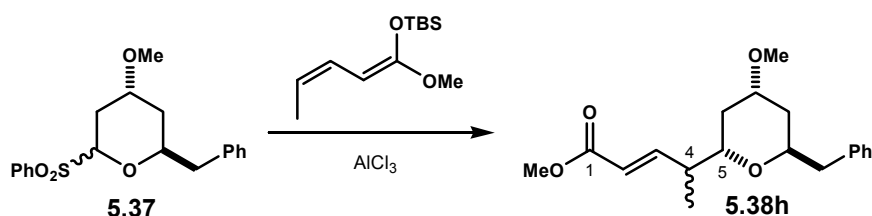
5.38g



General Procedure D was followed. Sulfonylpyran **5.37** (160 mg, 0.505 mmol), AlCl_3 (101 mg, 0.758 mmol), and ((*E*)-1-methoxyprop-1-en-1-yl)tert-butyl)dimethylsilane (281 mg, 1.386 mmol) were employed, and tetrahydropyran **5.38g** was obtained as a 1:1 mixture of diastereomers in 82% combined yield as a colorless oil (115 mg, 0.375 mmol). Biotage condition: 25+S column, 98:2 hexanes : EtOAc for 180 mL, then 98:2 \rightarrow 85:15 hexanes : EtOAc linear gradient over 360 mL, then 85:15 hexane : EtOAc for 180 mL. *The more polar diastereomer*: ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.30 – 7.27 (2H, m), 7.21 – 7.17 (3H, m), 4.26 (1H, m), 4.10 – 3.98 (2H, m), 3.93 (1H, ddd, $J = 9.0, 9.0, 3.0$ Hz), 3.64 (1H, dddd, $J = 9.5, 9.0, 5.0, 4.5$ Hz), 3.33 (3H, s), 2.93 (1H, dd, $J = 13.5, 7.0$ Hz), 2.77 – 2.71 (2H, m), 2.05 (1H, m), 1.18 (1H, dddd, $J =$

14.5, 4.0, 4.0, 1.5 Hz), 1.55 (1H, ddd, $J = 14.5, 9.5, 5.0$ Hz), 1.33 (1H, ddd, $J = 12.5, 9.0, 9.0$ Hz), 1.19 (3H, t, $J = 7.5$ Hz), 1.11 (3H, d, $J = 7.0$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 175.02, 138.65, 129.13, 128.33, 126.14, 72.96, 72.79, 71.78, 60.28, 55.56, 44.68, 38.90, 33.36, 33.03, 14.16, 13.36. IR (cm^{-1}): $\nu = 3027, 2979, 2930, 2825, 1732, 1455, 1376, 1261, 1160, 1095$. HRMS-FAB: $(\text{M}+\text{H})^+$: 307.1909 calculated for $\text{C}_{18}\text{H}_{26}\text{O}_4$, experimental = 307.1932.

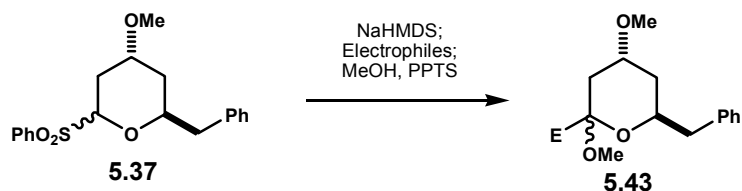
(\pm)-(*E*)-methyl 4-((2*S*,4*R*,6*R*)-6-benzyl-tetrahydro-4-methoxy-2*H*-pyran-2-yl)pent-2-enoate **5.38h**



General Procedure D was followed. Sulfonylpyran **5.37** (150 mg, 0.433 mmol), AlCl_3 (87 mg, 0.650 mmol), and ((*Z*)-1-methoxy-2-methylbuta-1,3-dienyloxy)(tert-butyl)dimethylsilane (297 mg, 1.299 mmol) were employed, and tetrahydropyran **5.38h** was obtained in 62% as the major product as a chromatographically an inseparable 3:2 mixture of diastereomers at C4 stereocenter. **5.38h** was isolated as a colorless oil (89 mg, 0.280 mmol). Biotage condition: 25+S column, 95:5 hexanes : EtOAc for 90 mL, then 95:5 \rightarrow 85:15 hexanes : EtOAc linear gradient over 270 mL. The two diastereomers were labeled A (major) and B (minor) for characterization purposes. Diastereomers A and B were distinguishable by both ^1H and ^{13}C NMR based on their signal intensity. ^1H

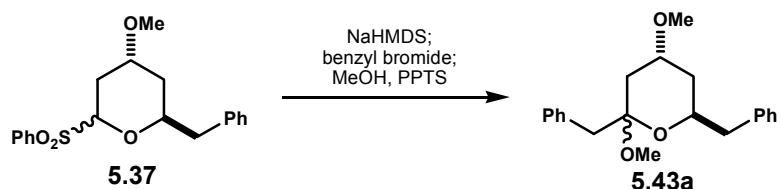
NMR (500 MHz, CDCl₃): δ (ppm) = 7.33 – 7.29 (4H, m, A and B), 7.25 – 7.19 (6H, m, A and B), 6.93 (1H, dd, J = 15.5, 8.0 Hz, A), 6.88 (1H, dd, J = 16.0, 8.5 Hz, B), 5.87 (1H, dd, J = 16.0, 1.0 Hz, B), 5.81 (1H, dd, J = 16.0, 1.0 Hz, A), 4.31 – 4.22 (2H, m, A and B), 3.75 (3H, s, B), 3.74 (3H, s, A), 3.71 – 3.58 (4H, m, A and B), 3.37 (3H, s, A), 3.35 (3H, s, B), 2.98 (1H, dd, J = 13.5, 8.0 Hz, A), 2.96 (1H, dd, J = 14.0, 9.5 Hz, B), 2.77 (2H, dd, J = 14.0, 7.0 Hz, A and B), 2.64 (1H, m, A), 2.55 (1H, m, B), 2.14 – 1.84 (4H, m, A and B), 1.66 – 1.53 (2H, m, A and B), 1.39 – 1.53 (2H, m, A and B), 1.05 (1H, d, J = 7.0 Hz, A), 0.97 (1H, d, J = 6.5 Hz, B). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 166.98 (B), 166.93 (A), 151.32 (A), 151.11 (B), 138.61 (B), 138.58 (A), 129.10 (B), 129.03 (A), 128.38 (A), 128.34 (B), 126.22 (B), 126.17 (A), 121.21 (B), 120.87 (A), 73.28 (A), 73.16 (B), 73.08 (A), 72.52 (B), 72.39 (A), 72.32 (B), 55.65 (B), 55.46 (A), 51.43 (B), 51.34 (A), 41.19 (A), 41.05 (B), 39.08 (B), 38.41 (A), 34.19 (A), 33.89 (B), 33.69 (B), 33.61 (A), 15.72 (A), 15.50 (B). IR (cm⁻¹): ν = 3073, 3015, 2937, 1722, 1655, 1454, 1435, 1273, 1195, 1094, 1013, 741, 700. HRMS-FAB: (M+H)⁺ = 319.1909 calculated for C₁₉H₂₇O₄, experimental = 319.1892.

GENERAL PROCEDURE E: *Alkylation of Sulfonylpyran 5.37*



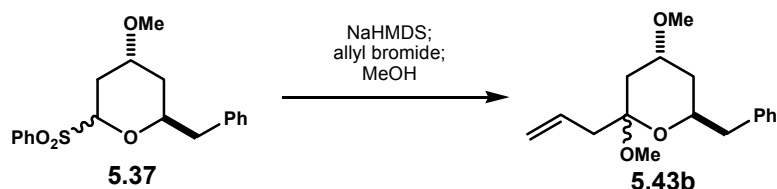
Sulfonylpyran **5.37** (1.0 equivalent) as a mixture of diastereomers was dissolved in toluene (15 mL), and the solution was cooled to -78°C . A solution of NaHMDS (3.0 equivalents, 2.0 M in THF) was then added dropwise. After stirring the mixture for 30 minutes, electrophiles (4.0 equivalents) was added dropwise. The solution was warmed to -50°C and stirred overnight or until starting material was completely consumed. The reaction was diluted with Et_2O (10 mL) and then quenched with half-saturated Na_2CO_3 solution (20 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et_2O (2 x 20 mL). The organic layers were then combined, dried over MgSO_4 , and filtered. The solution was rotovaped in a cold bath *only to remove Et_2O , and toluene must remain* in the flask. MeOH (25 mL) and PPTS (15 mg) was then added to the toluene solution, and the mixture was stirred for one hour. After adding TEA (1 mL), this mixture was then concentrated and eluted through a silica gel column. Removal of solvent under vacuum provided the title product **5.43** as a mixture of diastereomers.

(±)-(4*S*,6*S*)-2,6-dibenzyl-tetrahydro-2,4-dimethoxy-2*H*-pyran **5.43a**



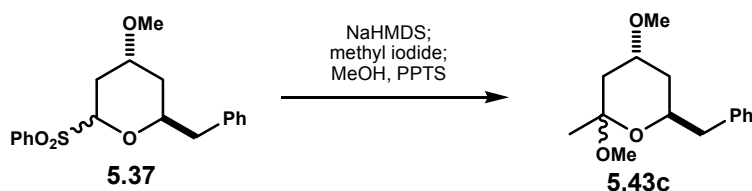
General Procedure E was followed. Sulfonfylpyran **5.37** (200 mg, 0.577 mmol), NaHMDS (0.87 mL, 1.73 mmol, 2.0 M in THF), and benzyl bromide (0.27 mL, 2.31 mmol) were employed, and a diastereomeric mixture of methyl pyranoside **5.43a** was obtained in 79% yield as a colorless oil (148 mg, 0.453 mmol). Product elution was made with 90:10 hexane : EtOAc. *The less polar diastereomer*: ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.33 – 7.21 (10H, m), 3.73 (1H, m), 3.54 (1H, dddd, J = 11.0, 11.0, 4.5, 4.5 Hz), 3.24 (3H, s), 3.11 (3H, s), 2.95 (1H, d, J = 14.0 Hz), 2.91 (1H, dd, J = 13.5, 7.0 Hz), 2.88 (1H, d, J = 14.0 Hz), 2.76 (1H, dd, J = 13.5, 5.5 Hz), 1.99 (1H, m), 1.90 (1H, ddd, J = 13.0, 5.0, 2.0 Hz), 1.16 (1H, dd, J = 12.5, 11.5 Hz), 1.04 (1H, q, J = 11.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 138.53, 136.46, 130.24, 129.55, 128.13, 128.06, 126.37, 126.19, 101.22, 73.60, 70.40, 55.50, 47.42, 42.38, 42.17, 38.35, 36.40. IR (cm⁻¹): ν = 3028, 2939, 2827, 1603, 1496, 1454, 1379, 1149, 1088, 1035, 978, 752, 700. HRMS-FAB: (M-H)⁺ = 325.1804 calculated for C₂₁H₂₅O₃, experimental = 325.1797.

(±)-(4*R*,6*R*)-2-allyl-6-benzyl-tetrahydro-2,4-dimethoxy-2*H*-pyran **5.43b**



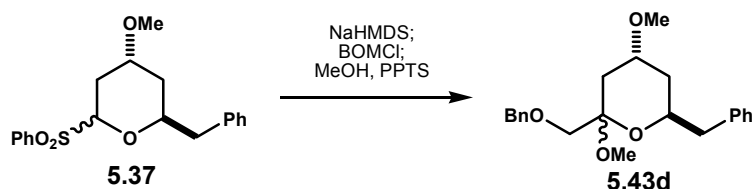
General Procedure E was followed. Sulfonylpyran **5.37** (200 mg, 0.577 mmol), NaHMDS (0.87 mL, 1.73 mmol, 2.0 M in THF), and allyl bromide (0.20 mL, 2.31 mmol) were employed, and a diastereomeric mixture of methyl pyranoside **5.43b** was obtained in 85% yield as a colorless oil (135 mg, 0.488 mmol). *The methanolysis step was run for 24 hours without PPTS and subsequent TEA quench.* Product elution was made with 90:10 hexanes : EtOAc. *The more polar diastereomer:* ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.28 – 7.17 (5H, m), 5.75 (1H, dddd, J = 16.5, 9.5, 7.0, 7.0 Hz), 5.09 – 5.04 (2H, m), 4.08 (1H, dddd, J = 11.0, 7.5, 5.0, 2.0 Hz), 3.56 (1H, m), 3.27 (3H, s), 2.93 (3H, s), 2.79 (1H, dd, J = 13.5, 8.0 Hz), 2.70 (1H, dd, J = 13.5, 5.5 Hz), 2.44 (1H, dddd, J = 14.5, 7.0, 1.5, 1.5 Hz), 2.22 (1H, dddd, J = 14.5, 7.5, 1.0, 1.0 Hz), 1.97 (1H, ddd, J = 15.0, 3.0, 2.0 Hz), 1.82 (1H, dddd, J = 13.5, 3.0, 2.0, 2.0 Hz), 1.54 (1H, dd, J = 14.5, 4.0 Hz), 1.38 (1H, ddd, J = 14.0, 11.5, 3.5 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 138.72, 133.42, 129.64, 127.96, 126.01, 117.67, 99.05, 73.15, 65.84, 56.44, 47.34, 42.28, 41.41, 35.22, 33.73. IR (cm^{-1}): ν = 3080, 3017, 2922, 2820, 1455, 1208, 1110, 1087, 1029. HRMS-FAB: $(\text{M-OMe})^+ = 245.1542$ calculated for $\text{C}_{16}\text{H}_{21}\text{O}_2$, experimental = 245.1559.

(±)-(4*R*,6*R*)-6-benzyl-tetrahydro-2,4-dimethoxy-2-methyl-2*H*-pyran **5.43c**



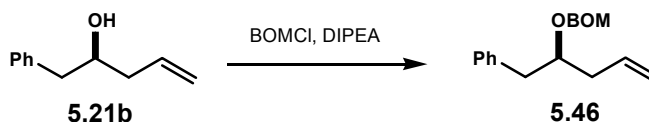
General Procedure E was followed. Sulfonylpyran **5.37** (200 mg, 0.577 mmol), NaHMDS (0.87 mL, 1.73 mmol, 2.0 M in THF), and CH₃I (0.14 mL, 2.31 mmol) were employed, and a diastereomeric mixture of methyl pyranoside **5.43c** was obtained in 97% yield as a colorless oil (140 mg, 0.559 mmol). Product elution was made with 90:10 hexanes : EtOAc. *The more polar diastereomer*: ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.28 – 7.24 (4H, m), 7.19 (1H, m), 4.06 (1H, dddd, J = 11.5, 7.5, 5.5, 2.0 Hz), 3.56 (1H, p, J = 6.0 Hz), 3.28 (3H, s), 2.93 (3H, s), 2.81 (1H, dd, J = 13.5, 7.5 Hz), 2.68 (1H, dd, J = 13.5, 5.5 Hz), 2.06 (1H, ddd, J = 14.5, 2.0, 2.0 Hz), 1.82 (1H, dddd, J = 14.0, 3.0, 2.0, 2.0 Hz), 1.57 (1H, dd, J = 15.0, 4.5 Hz), 1.41 (1H, ddd, J = 14.0, 12.0, 4.0 Hz), 1.26 (3H, s). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 138.74, 129.55, 127.99, 126.00, 98.19, 73.36, 65.91, 56.47, 47.76, 42.31, 37.85, 33.64, 24.18. IR (cm⁻¹): *f* = 3030, 2925, 2826, 1454, 1373, 1201, 1128, 1091, 1034. HRMS-FAB: (M-H)⁺ = 249.1491 calculated for C₁₅H₂₁O₃, experimental = 249.1475.

(±)-(4*R*,6*R*)-6-benzyl-2-((benzyloxy)methyl)-tetrahydro-2,4-dimethoxy-2*H*-pyran **5.43d**



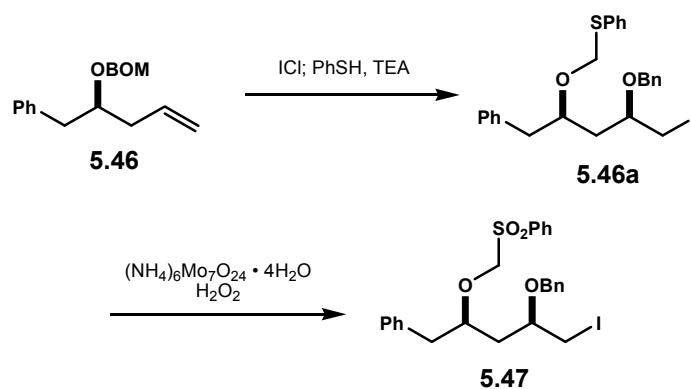
General Procedure E was followed. Sulfonylpyran **5.37** (200 mg, 0.577 mmol), NaHMDS (0.87 mL, 1.73 mmol, 2.0 M in THF), and BOMCl (0.32 mL, 2.31 mmol) were employed. The reaction was warmed to -40°C and stirred overnight. A diastereomeric mixture of methyl pyranoside **5.43d** was obtained in 82% yield as a colorless oil (169 mg, 0.474 mmol). Product elution was made with 95:5 hexanes : *i*-PrOH. *The more polar diastereomer*: ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.37 – 7.33 (4H, m), 7.31 – 7.16 (6H, m), 4.60 (1H, d, *J* = 12.0 Hz), 4.56 (1H, d, *J* = 12.5 Hz), 4.13 (1H, dddd, *J* = 11.5, 8.0, 5.5, 2.5 Hz), 3.59 (1H, p, *J* = 3.5 Hz), 3.47 (1H, d, *J* = 10.5 Hz), 3.30 (3H, s), 3.25 (1H, d, *J* = 10.0 Hz), 2.92 (3H, s), 2.78 (1H, dd, *J* = 13.5, 8.0 Hz), 2.70 (1H, dd, *J* = 13.5, 5.5 Hz), 2.14 (1H, ddd, *J* = 15.0, 3.0, 1.5 Hz), 1.82 (1H, dddd, *J* = 13.5, 3.5, 2.0, 2.0 Hz), 1.72 (1H, dd, *J* = 14.5, 4.0 Hz), 1.48 (1H, ddd, *J* = 14.0, 11.5, 3.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 138.56, 138.21, 129.54, 128.33, 127.98, 127.71, 127.61, 126.04, 98.52, 73.29, 72.78, 71.33, 65.97, 56.36, 47.83, 42.20, 34.39, 33.45. IR (cm⁻¹): *f* = 3028, 2923, 2863, 1454, 1213, 1111, 1100, 1031, 738, 699. HRMS-FAB: (M-OMe)⁺ = 325.1804 calculated for C₂₁H₂₅O₃, experimental = 325.1823.

(±)-1-((S)-2-((benzyloxy)methoxy)pent-4-enyl)benzene **5.46**



Crude 1-phenylpent-4-en-2-ol (5.00 g, 30.8 mmol) was dissolved in CH₂Cl₂ (100 mL), and DIPEA was then added (16.1 mL, 92.5 mmol). After cooling the mixture to 0°C, BOMCl (6.40 mL, 46.2 mmol) was added dropwise. The reaction was warmed to gentle reflux overnight. After recooling to 0°C, the reaction was then diluted with CH₂Cl₂ (100 mL) and washed subsequently with aqueous solutions of 2 M HCl (100 mL) and then saturated NaHCO₃ (100 mL). The organic layer was then dried over MgSO₄ and filtered. A yellow oil was obtained upon removal of CH₂Cl₂ under vacuum. The crude material was purified with Biotage chromatography to give the title product **5.46** in 70% yield as a colorless oil (6.10 g, 21.6 mmol). Biotage condition: 40+M column, 100:0 hexanes : EtOAc for 240 mL, then 100:0 → 98:2 hexanes : EtOAc linear gradient over 240 mL. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.39 – 7.21 (10H, m), 5.91 (1H, m), 5.15 (1H, m), 5.13 (1H, m), 4.78 (1H, d, J = 7.5 Hz), 4.65 (1H, d, J = 7.5 Hz), 4.43 (1H, d, J = 11.5 Hz), 4.30 (1H, d, J = 12.0 Hz), 3.99 (1H, p, J = 6.0 Hz), 2.85 (2H, d, J = 6.5 Hz), 2.37 – 2.34 (2H, m). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 138.80, 137.79, 134.56, 129.56, 128.29, 128.25, 127.85, 127.56, 126.17, 117.57, 92.95, 77.28, 69.22, 40.82, 38.55. IR (cm⁻¹): ν = 3064, 3029, 2939, 2887, 1496, 1454, 1163, 1101, 1042, 916, 744, 699. HRMS-FAB: (M+H)⁺ = 283.1698 calculated for C₁₉H₂₃O₂, experimental = 283.1703.

(±)-1-((2*R*,4*R*)-2-((phenylsulfonyl)methoxy)-4-(benzyloxy)-5-iodopentyl)benzene **5.47**



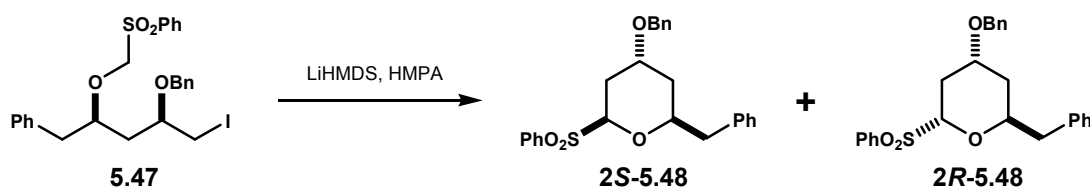
Compound **5.46** (800 mg, 2.83 mmol) was dissolved in toluene (60 mL), and 1 gram of 4 Å molecular sieves was then added. After cooling this solution was cooled to -78°C, an iodine monochloride solution (3.96 mL, 3.96 mmol, 1.0 M in CH_2Cl_2) was added dropwise while maintaining an internal temperature of the reaction below -75°C. The solution became dark red and was stirred for 30 minutes. Then, TEA (1.18 mL, 8.49 mmol) was added in one injection, followed by PhSH (0.41 mL, 3.96 mmol) in which the solution immediately turned cloudy. The reaction was warmed to room temperature over one hour and then quenched with a 1:1 mixture of saturated NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ (100 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et_2O (2 x 50 mL). The organic layers were then combined, dried over MgSO_4 , and filtered. The organic solvent was removed under vacuum leaving behind a yellow oil. The crude material was flushed through a thick silica pad with hexanes which removed the non-polar side product, then with 50:50 hexanes : EtOAc to isolate the product. Upon removal of solvent, the material was then loaded into a silica gel column, and the product was eluted with 95:5 hexanes : EtOAc. The title product **5.46a** was obtained 68% yield

with a diastereomeric ratio of >20:1 as a yellow oil (1.00 g, 1.93 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.40 – 7.15 (15H, m), 5.14 (1H, d, J = 12.0 Hz), 4.83 (1H, d, J = 12.0 Hz), 4.46 (1H, d, J = 11.5 Hz), 4.31 (1H, d, J = 11.5 Hz), 4.02 (1H, m), 3.31 (2H, d, J = 4.5 Hz), 3.25 (1H, m), 2.90 (1H, dd, J = 14.0, 6.5 Hz), 2.78 (1H, dd, J = 13.5, 6.5 Hz), 1.88 (1H, ddd, J = 14.5, 7.5, 5.5 Hz), 1.79 (1H, ddd, J = 14.5, 7.0, 5.0 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.84, 137.65, 135.67, 129.54, 129.25, 128.96, 128.40, 128.38, 127.91, 127.73, 126.42, 126.39, 74.74, 74.03, 73.17, 70.93, 40.22, 38.97, 10.76. IR (cm^{-1}): ν = 3061, 3028, 2921, 1584, 1495, 1454, 1053, 1027, 741, 700. HRMS-FAB: $(\text{M}-\text{H})^+ = 517.0698$ calculated for $\text{C}_{25}\text{H}_{26}\text{O}_2\text{SI}$, experimental = 517.0717.

Compound **5.46a** (5.17 g, 9.97 mmol) was dissolved in ethanol (124 mL, 200 proof), and the solution was cooled to 0°C. In a separate flask, ammonium (VI) molybdate tetrahydrate (2.49 g, 1.99 mmol) was dissolved in a cold aqueous hydrogen peroxide solution (30%, 124 mL). This Mo(VI) – H_2O_2 mixture was immediately poured to the solution of **5.46a** in one portion causing the reaction to turn yellow and cloudy (the cloudiness eventually dissipated). The reaction was stirred at 0°C for one hour and then at room temperature for 48 hours. Addition of DI water (300 mL) quenched the reaction, and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The pink organic layers were combined, dried over MgSO_4 , filtered, and rotovaped to produce a dark red oily residue. The crude material was then loaded onto silica gel and chromatographed with 80:20 hexanes : EtOAc to afford the corresponding sulfone **5.47** in 65% yield as a yellow oil (3.59 g, 6.52 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.77 (2H, d, J = 7.5 Hz), 7.64 (1H, t, J = 7.5 Hz), 7.51 (2H, t, J = 8.0 Hz), 7.39 – 7.31 (5H, m), 7.29 – 7.22 (3H, m), 7.08 (2H, m), 4.56 (1H, d, J = 11.0 Hz), 4.53 (1H, d, J = 12.5 Hz), 4.37 (1H, d, J

= 12.5 Hz), 4.34 (1H, d, J = 11.5 Hz), 4.11 (1H, p, J = 6.0 Hz), 3.34 – 3.26 (3H, m), 2.80 (1H, dd, J = 14.0, 7.0 Hz), 2.76 (1H, dd, J = 14.0, 6.0 Hz), 1.90 – 1.80 (2H, m). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.52, 137.28, 136.99, 133.89, 129.50, 129.14, 128.70, 128.51, 128.47, 128.00, 127.89, 126.65, 84.36, 80.80, 73.81, 70.93, 40.69, 39.04, 9.96. IR (cm^{-1}): ν = 3062, 3029, 2922, 1496, 1447, 1324, 1297, 1150, 1113, 1080, 744, 700. HRMS-FAB: $(\text{M}+\text{H})^+ = 551.0753$ calculated for $\text{C}_{25}\text{H}_{28}\text{O}_4\text{S}$, experimental = 551.0747.

(\pm)-*(2R,4R)*-2-benzyl-4-(benzyloxy)-tetrahydro-6-(phenylsulfonyl)-2H-pyran **5.48**



HMDS (1.75 mL, 8.21 mmol) was dissolved in THF (50 mL) and cooled to -78°C . A solution of *n*-BuLi (3.70 mL, 8.21 mmol, 2.2 M in hexanes) was then added dropwise quite rapidly, and the solution was stirred for 10 minutes prior to the addition of HMPA (2.90 mL, 16.4 mmol). This LiHMDS solution was further stirred for 10 minutes. In a separate flask, sulfone **5.47** (3.01 g, 5.47 mmol) was dissolved in THF (200 mL), and the solution was cooled to -78°C . The freshly prepared, cold LiHMDS solution was then added to this solution via cannula dropwise over 30 minutes. The reaction was further stirred for 2 hours, and then quenched with a half-saturated aqueous NH_4Cl solution (200 mL). After separating the organic and aqueous layers, the aqueous layer was washed

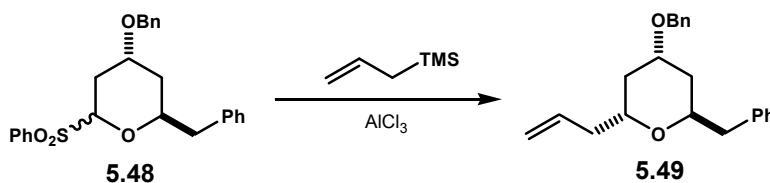
with Et₂O (2 x 100 mL). The organic layers were then combined, dried over MgSO₄, filtered, and concentrated under vacuum leaving behind a yellow oil. The crude material was flushed through a thick silica pad with 70:30 hexanes : EtOAc. The solvent was then evaporated to leave the title product **5.48** as a yellow solid (2.10 g, 4.97 mmol) in 91% yield as a 3:2 mixture of diastereomers. For characterization purposes, the two diastereomers were separated and isolated by column chromatography with 80:20 hexanes : EtOAc.

Less Polar Diastereomer 2S-5.48: ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.85 (2H, d, J = 7.5 Hz), 7.61 (1H, dt, J = 7.5, 0.5 Hz), 7.45 (2H, t, J = 8.0 Hz), 7.37 – 7.30 (5H, m), 7.16 – 7.15 (3H, m), 7.02 – 7.00 (2H, m), 4.79 (1H, dd, J = 12.0, 2.0 Hz), 4.56 (1H, d, J = 12.0 Hz), 4.47 (1H, d, J = 12.0 Hz), 4.05 – 4.00 (2H, m), 2.82 (1H, dd, J = 14.0, 8.0 Hz), 2.67 (1H, dd, J = 14.5, 4.5 Hz), 2.47 (1H, m), 1.91 – 1.85 (2H, m), 1.53 (1H, ddd, J = 14.0, 12.0, 2.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 137.91, 137.74, 136.50, 133.59, 129.29, 129.07, 128.69, 128.42, 128.09, 127.73, 127.45, 126.11, 87.69, 74.53, 70.42, 70.19, 41.69, 34.91, 27.08. IR (cm⁻¹): ν = 3063, 3030, 2920, 2877, 1496, 1448, 1320, 1151, 1090, 1067, 747, 726, 700. HRMS-FAB: (M-H)⁺ = 421.1474 calculated for C₂₅H₂₅O₄S, experimental = 421.1448.

More Polar Diastereomer 2R-5.48: ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.60 – 7.55 (3H, m), 7.42 – 7.38 (6H, m), 7.33 (1H, m), 7.30 – 7.27 (3H, m), 7.11 – 7.10 (2H, m), 4.78 (1H, m), 4.75 (1H, d, J = 12.0 Hz), 4.71 (1H, dd, J = 8.0, 5.5 Hz), 4.55 (1H, d, J = 12.0 Hz), 3.89 (1H, m), 2.75 (1H, dd, J = 14.5, 5.5 Hz), 2.70 (1H, dd, J = 14.0, 9.0 Hz), 2.44 – 2.30 (2H, m), 1.90 – 1.82 (2H, m). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 137.94, 137.61, 137.08, 133.41, 129.20, 129.04, 128.77, 128.42, 128.38, 127.69, 127.67,

126.32, 87.56, 72.48, 70.08, 68.73, 40.59, 35.25, 26.23. IR (cm^{-1}): $\nu = 3063, 3029, 2928, 2868, 1496, 1447, 1329, 1301, 1149, 1083, 742, 699$. HRMS-FAB: $(\text{M}-\text{SO}_2\text{Ph})^+ = 281.1542$ calculated for $\text{C}_{19}\text{H}_{21}\text{O}_2$, experimental = 281.1544.

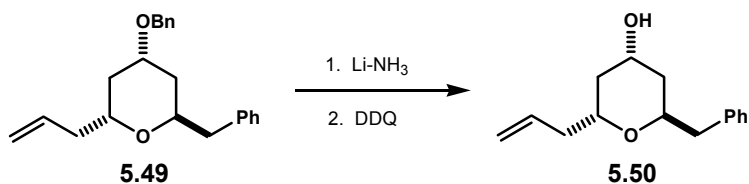
(\pm)-(2*R*,4*S*,6*R*)-2-allyl-6-benzyl-4-(benzyloxy)-tetrahydro-2*H*-pyran **5.49**



A suspension of AlCl_3 (166 mg, 1.24 mmol) in toluene (15 mL) was cooled to -78°C . In a separate flask, sulfonylpyran **5.48** (350 mg, 0.828 mmol) was dissolved in toluene (10 mL). After cooling to -78°C , this solution was transferred to the AlCl_3 suspension via cannula in a rapid stream. To ensure all starting material was completely transferred, the flask was washed with toluene (2 x 2.5 mL) and transferred to the reaction mixture via cannula. This mixture was stirred for 5 minutes. Allyltrimethylsilane (0.39 mL, 2.48 mmol) was then added dropwise, and the reaction was slowly warmed up to -50°C over one hour and stirred at this temperature for additional 30 minutes in which all pyran **5.48** was consumed. A saturated aqueous solution of Rochelle's salt (50 mL) was then added, and the emulsion was stirred until separation of layers was achieved. After separating the organic and aqueous layers, the aqueous layer was washed with CH_2Cl_2 (2 x 20 mL). The organic layers were then combined, dried over MgSO_4 , filtered, and concentrated under vacuum leaving behind a yellow oil. The crude material was loaded into a silica

gel column, and the product was eluted with 95:5 hexanes : EtOAc. Tetrahydropyran **5.49** was obtained as a colorless oil in 88% yield (235 mg, 0.729 mmol) with of >20:1 diastereomeric ratio. ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.39 – 7.35 (4H, m), 7.33 – 7.29 (3H, m), 7.23 (1H, tt, J = 7.5, 2.0 Hz), 7.15 – 7.14 (2H, m), 5.79 (1H, dddd, J = 17.0, 10.0, 7.0, 7.0 Hz), 5.08 (1H, dddd, J = 17.0, 1.5, 1.5, 1.5 Hz), 5.04 (1H, m), 4.58 (1H, d, J = 12.0 Hz), 4.55 (1H, d, J = 12.5 Hz), 4.29 (1H, m), 3.86 (1H, dddd, J = 10.0, 10.0, 4.5, 4.5 Hz), 3.81 (1H, dddd, J = 10.0, 6.5, 6.5, 2.0 Hz), 2.95 (1H, dd, J = 13.5, 7.5 Hz), 2.76 (1H, dd, J = 13.5, 8.0 Hz), 2.42 (1H, m), 2.28 (1H, m), 2.07 (1H, m), 1.89 (1H, m), 1.63 (1H, ddd, J = 15.5, 10.0, 5.5 Hz), 1.42 (1H, ddd, J = 13.5, 10.5, 10.5 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 138.71, 138.57, 134.87, 129.08, 128.39, 128.38, 127.54, 127.50, 126.19, 116.81, 73.15, 70.80, 69.59, 69.33, 40.19, 38.65, 36.67, 33.63. IR (cm^{-1}): ν = 3063, 3027, 2943, 2860, 1496, 1454, 1356, 1090, 913, 738, 699. HRMS-FAB: $(\text{M}+\text{H})^+ = 323.2011$ calculated for $\text{C}_{22}\text{H}_{27}\text{O}_2$, experimental = 323.2002.

(±)-(2*R*,4*S*,6*R*)-2-allyl-6-benzyl-tetrahydro-2*H*-pyran-4-ol **5.50**

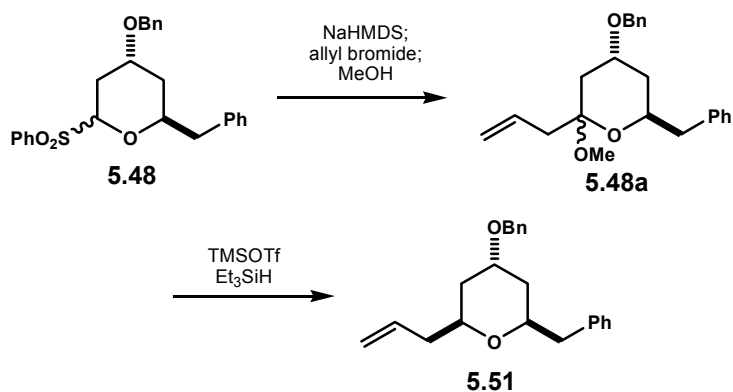


Anhydrous ammonia (30 mL) was condensed into a round-bottomed flask at -78°C, and lithium wire (24 mg, 3.41 mmol) was added in two pieces. The solution immediately turned dark blue and was stirred for 15 minutes. In a separate flask,

tetrahydropyran **5.49** (183 mg, 0.568 mmol) was dissolved in THF (10 mL). After cooling to -78°C , this solution was transferred to the Li-NH₃ mixture rapidly via cannula. To ensure all starting material was completely transferred, the flask was washed with THF (2 x 1 mL), cooled, and then transferred to the reaction mixture. After 5 minutes, solid NH₄Cl was added until the blue color disappeared, and the ammonia was evaporated by warming the reaction to room temperature. The reaction mixture was diluted with Et₂O (20 mL) and then washed with DI water (20 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et₂O (2 x 10 mL). The organic layers were then combined, dried over MgSO₄, filtered, and concentrated under vacuum leaving behind a yellow oil, which was redissolved in CH₂Cl₂ (20 mL). DDQ (387 g, 1.70 mmol) was then added resulting in a red suspension. After stirring overnight, the solid residue was filtered under vacuum, and the filtrate was then washed with a saturated NaHCO₃ solution. After separating the organic and aqueous layers, the aqueous layer was washed with CH₂Cl₂ (20 mL). The organic layers were then combined, dried over MgSO₄, filtered, and concentrated under vacuum leaving behind a red oil. The crude material was purified using silica gel chromatography with 70:30 hexanes : EtOAc. Upon removal of solvent, title product **5.50** was isolated in 92% yield as a clear oil (122 mg, 0.525 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.310 – 7.280 (2H, m), 7.229 – 7.182 (3H, m), 5.771 (1H, dddd, J = 17.0, 10.0, 7.0, 7.0 Hz), 5.077 (1H, ddd, J = 17.0, 3.0, 1.5 Hz), 5.038 (1H, m), 4.283 (1H, m), 4.131 (1H, dddd, J = 10.0, 10.0, 4.5, 4.0 Hz), 3.810 (1H, m), 2.991 (1H, dd, J = 14.0, 7.0 Hz), 2.787 (1H, dd, J = 13.5, 7.5 Hz), 2.372 (1H, m), 2.248 (1H, m), 2.020 (1H, dddd, J = 12.5, 4.5, 2.5, 2.0 Hz), 1.865 (1H, dddd, J = 13.0, 4.5, 2.5, 2.0 Hz), 1.536 (1H, ddd, J = 12.5, 10.0, 5.5 Hz),

1.273 (1H, ddd, $J = 12.5, 10.0, 10.0$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 138.68, 134.71, 129.09, 128.43, 126.25, 116.90, 73.69, 68.92, 64.50, 40.31, 40.26, 38.33, 36.74. IR (cm^{-1}): $\nu = 3391, 3064, 3026, 2923, 2856, 1455, 1373, 1086, 1053, 1086, 1053, 1000, 915, 742, 700$. HRMS-FAB: $(\text{M}-\text{H})^+ = 231.1385$ calculated for $\text{C}_{15}\text{H}_{19}\text{O}_2$, experimental = 231.1388.

(\pm)-(2*S*,4*S*,6*R*)-2-allyl-6-benzyl-4-(benzyloxy)-tetrahydro-2*H*-pyran **5.51**



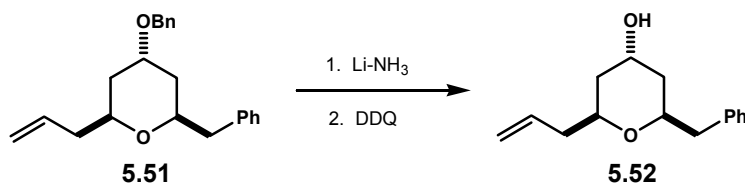
Sulfonylpyran **5.48** (400 mg, 0.945 mmol) was dissolved in toluene (30 mL), and the solution was cooled to -78°C . A solution of NaHMDS (1.42 mL, 2.84 mmol, 2.0 M in THF) was then added dropwise. After stirring the mixture for 45 minutes, allyl bromide (0.33 mL, 3.78 mmol) was added dropwise. The solution was warmed to -50°C and stirred overnight or until starting material was completely consumed. The reaction was diluted with Et_2O (20 mL) and then quenched with a half-saturated Na_2CO_3 solution (20 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et_2O (2 x 20 mL). The organic layers were then combined, dried over MgSO_4 , and filtered. The solution was rotovaped in a cold bath *only to remove Et_2O , and the toluene*

must remain in the flask. MeOH (15 mL) was then added to the toluene solution, and the mixture was stirred for 24 hours. This mixture was concentrated and chromatographed through a silica gel column with 95:5 hexanes : EtOAc. Removal of solvent under vacuum provided product **5.48a** as a 4:1 mixture of diastereomers (233 mg, 0.661 mmol) as a yellow oil. *The more polar diastereomer*: ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.34 – 7.19 (10H, m), 5.79 (1H, dddd, J = 16.5, 9.5, 7.5, 7.5 Hz), 5.10 (1H, m), 5.07 (1H, m), 4.60 (1H, d, J = 12.5 Hz), 4.44 (1H, d, J = 12.0 Hz), 4.18 (1H, dddd, J = 13.0, 7.5, 5.0, 2.0 Hz), 3.77 (1H, p, J = 1.5 Hz), 2.96 (3H, s), 2.79 (1H, dd, J = 14.0, 8.0 Hz), 2.71 (1H, dd, J = 13.5, 5.0 Hz), 2.47 (1H, dd, J = 14.0, 7.0 Hz), 2.25 (1H, dd, J = 14.5, 7.5 Hz), 2.05 (1H, ddd, J = 15.0, 2.5, 2.0 Hz), 1.84 (1H, dddd, J = 13.5, 3.0, 2.0, 2.0 Hz), 1.59 (1H, dd, J = 15.0, 4.5 Hz), 1.42 (1H, ddd, J = 14.5, 12.0, 4.0 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 139.01, 138.74, 133.43, 129.62, 128.22, 127.93, 127.50, 127.25, 125.97, 117.72, 99.06, 69.98, 69.71, 66.03, 47.29, 42.21, 41.40, 35.00, 34.45. IR (cm^{-1}): f = 3064, 3028, 2922, 1496, 1454, 1341, 1206, 1110, 1075, 1030, 736, 698. HRMS-FAB: $(\text{M-OMe})^+ = 321.1855$ calculated for $\text{C}_{15}\text{H}_{21}\text{O}_3$, experimental = 321.1836.

Methyl pyranoside **5.48a** (233 mg, 0.661 mmol) as a mixture of diastereomers was then dissolved in CH_2Cl_2 (20 mL). Several grains of 4 Å molecular sieves were added, and the solution was chilled to -78°C . After addition of Et_3SiH (0.21 mL, 1.32 mmol) to the solution, a freshly prepared solution of TMSOTf (1.98 mL, 1.98 mmol, 1.0 M in CH_2Cl_2) was then added dropwise, and the reaction was stirred for one minute. Immediately, the reaction was quenched by one full injection, of a half-saturated NH_4Cl aqueous solution (10mL) and warmed to 0°C . After separating the organic and aqueous layers, the aqueous layer was washed with CH_2Cl_2 (2 x 20 mL). The organic layers were

then combined, dried over MgSO_4 , filtered, and concentrated under vacuum leaving behind a yellow oil. The crude material was loaded into a silica gel column, and product elution was made with 95:5 hexanes : EtOAc. Tetrahydropyran **5.51** was obtained as a colorless oil in 50% yield (235 mg, 0.729 mmol) over two steps with a 15:1 diastereomeric ratio. ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.339 – 7.190 (10H, m), 5.817 (1H, dddd, J = 17.5, 10.5, 7.0, 7.0 Hz), 5.072 – 5.002 (2H, m), 4.446 (2H, s), 4.000 (1H, m), 3.845 (1H, p, J = 3.0 Hz), 3.814 (1H, m), 2.906 (1H, dd, J = 14.0, 7.0 Hz), 2.631 (1H, dd, J = 14.0, 6.0 Hz), 2.302 (1H, m), 2.157 (1H, m), 1.884 – 1.814 (2H, m), 1.382 (1H, ddd, J = 11.5, 6.5, 2.5 Hz), 1.353 (1H, ddd, J = 11.5, 6.5, 2.5 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 138.81, 138.77, 135.04, 129.50, 128.31, 128.04, 127.41, 127.34, 125.98, 116.46, 72.86, 71.61, 71.46, 70.00, 42.61, 40.66, 35.16, 35.08. IR (cm^{-1}): ν = 3064, 3027, 2915, 2862, 1496, 1454, 1340, 1066, 913, 724, 697. HRMS-FAB: $(\text{M}-\text{H})^+ = 321.1855$ calculated for $\text{C}_{22}\text{H}_{25}\text{O}_2$, experimental = 321.1830.

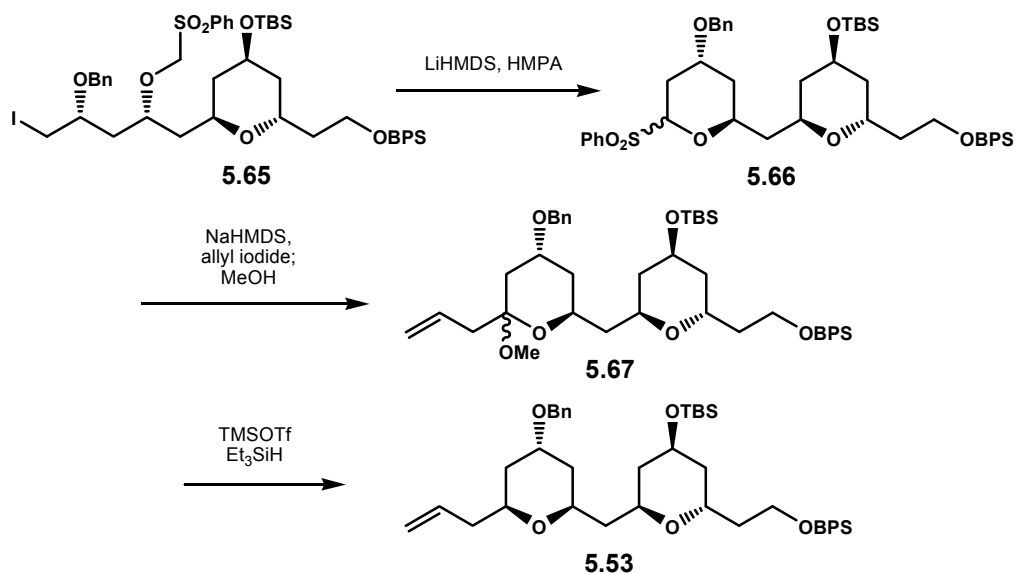
(±)-(2S,4S,6R)-2-allyl-6-benzyl-tetrahydro-2H-pyran-4-ol **5.52**



The preparative procedure for tetrahydropyran **5.50** was followed with the following modifications. Tetrahydropyran **5.51** (134 mg, 0.416 mmol), Li (18 mg, 2.496 mmol), and DDQ (284 mg, 1.248 mmol) were employed, and tetrahydropyran **5.52** was

obtained in 92% yield as a colorless oil (89 mg, 0.383 mmol) over two steps. ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.287 – 7.258 (2H, m), 7.232 – 7.184 (3H, m), 5.822 (1H, dddd, J = 17.0, 10.0, 7.0, 7.0 Hz), 5.081 – 5.013 (2H, m), 4.231 (1H, p, J = 5.013 Hz), 3.975 (1H, dddd, J = 11.5, 6.5, 6.5, 2.0 Hz), 3.809 (1H, dddd, J = 11.0, 6.5, 6.5, 2.0 Hz), 2.930 (1H, dd, J = 13.5, 7.0 Hz), 2.621 (1H, dd, J = 11.0, 6.5, 6.5, 2.0 Hz), 2.309 (1H, m), 2.160 (1H, m), 1.664 (1H, dddd, J = 14.0, 2.0, 2.0, 2.0 Hz), 1.617 (1H, dddd, J = 14.0, 2.5, 2.5, 2.5 Hz), 1.488 (1H, ddd, J = 11.5, 7.0, 3.0 Hz), 1.458 (1H, ddd, J = 12.0, 7.0, 3.0 Hz), 1.340 (1H, b). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 138.57, 134.87, 129.51, 128.11, 126.06, 116.61, 72.51, 71.17, 64.68, 42.61, 40.58, 38.01, 37.96. IR (cm^{-1}): ν = 3392, 3065, 3028, 2916, 2867, 1642, 1496, 1455, 1382, 1338, 1066, 914, 760, 700. HRMS-FAB: $(\text{M}-\text{H})^+ = 231.1385$ calculated for $\text{C}_{15}\text{H}_{19}\text{O}_2$, experimental = 231.1391.

(-)-Bis-Tetrahydropyran 5.53



Sulfone **5.65** was subjected to the procedure as represented in the preparation of compound **5.37** with the following modifications. Sulfone **5.65** (1.60 g, 1.65 mmol), HMDS (0.52 mL, 2.47 mmol), *n*-BuLi (1.18 mL, 2.47 mmol, 2.1 M in hexanes), HMPA (0.86 mL, 4.94 mmol) were employed. LiHMDS was prepared in THF (50 mL), and sulfone **5.65** was dissolved in THF (200 mL). The crude material was then loaded into Biotage chromatography system: 40+M column, 100:0 → 80:20 hexanes : EtOAc linear gradient for 960 mL, then 80:20 → 50:50 hexanes : EtOAc linear gradient over 240 mL to afford the corresponding diastereomeric mixture of sulfonylpyran **5.66** in 86% yield (1.189 g, 1.41 mmol) as a colorless oil.

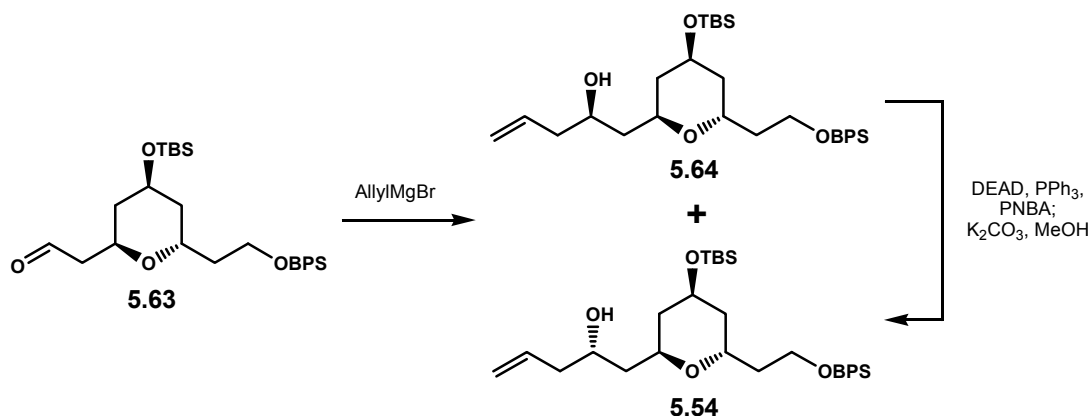
Sulfonylpyran **5.66** (400 mg, 0.474 mmol) as a mixture of diastereomers was dissolved in toluene (47 mL), and the solution was cooled to -78°C. After addition of allyl iodide (1.29 mL, 14.2 mmol), a solution of NaHMDS (2.37 mL, 4.74 mmol, 2.0 M

in THF) was then added dropwise. The mixture was slowly warmed to -50°C . After overnight stirring, the reaction was quenched with a half-saturated Na_2CO_3 solution (50 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et_2O (2 x 30 mL). The organic layers were then combined, dried over MgSO_4 , and filtered. The solution was rotovaped in a cold bath *only to remove Et_2O , and the toluene must remain* in the flask. MeOH (50 mL) was then added to the toluene solution, and the mixture was stirred overnight. This mixture was then concentrated and flushed through a thick silica pad with 90:10 hexanes : EtOAc. Removal of solvent under vacuum provided the title product **5.67** as a mixture of diastereomers in 74% yield (270 mg, 0.349 mmol) as a yellow oil.

Methyl pyranoside **5.67** (270 mg, 0.349 mmol) as a mixture of diastereomers was dissolved in CH_2Cl_2 (35 mL). 270 mg of 4 Å molecular sieves were added, and the solution was chilled to -78°C . After addition of Et_3SiH (0.17 mL, 1.05 mmol) to the solution, a freshly prepared solution of TMSOTf (0.42 mL, 0.419 mmol, 1 M in CH_2Cl_2) was then added very slowly (one drop per 4 seconds) using a glass syringe. After the addition was complete, the reaction was stirred for five minutes. The reaction was quenched by one full injection, of a saturated NaHCO_3 aqueous solution (10 mL) and warmed to 0°C . After separating the organic and aqueous layers, the aqueous layer was washed with CH_2Cl_2 (2 x 50 mL). The organic layers were then combined, dried over MgSO_4 , filtered, and concentrated under vacuum leaving behind a yellow oil. The crude material was loaded into a silica gel column, and product elution was made with 90:10 hexanes : EtOAc. Removal of solvent under vacuum provided *bis*-tetrahydropyran **5.53** as a single diastereomer in 64% yield (165 mg, 0.222 mmol) as a colorless oil. ^1H NMR

(500 MHz, CDCl₃): δ (ppm) = 7.68 – 7.65 (4H, m), 7.42 – 7.24 (11H, m), 5.80 (17.0, 10.0, 7.0, 7.0 Hz), 5.05 – 4.98 (2H, m), 4.51 (1H, d, J = 12.0 Hz), 4.47 (1H, d, J = 12.0 Hz), 4.27 (1H, dddd, J = 9.5, 4.5, 4.5, 4.5 Hz), 3.94 (1H, m), 3.88 – 3.72 (5H, m), 3.68 (1H, ddd, J = 10.5, 5.5, 5.5 Hz), 2.23 (1H, ddd, J = 14.5, 7.5, 7.5 Hz), 2.10 (1H, ddd, J = 13.5, 6.5, 6.5 Hz), 1.91 (1H, m), 1.87 – 1.80 (3H, m), 1.66 – 1.60 (4H, m), 1.40 – 1.26 (4H, m), 1.04 (9H, s), 0.89 (9H, s), 0.050 (6H, s). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 138.90, 135.56, 135.53, 135.19, 133.92, 133.82, 129.51, 129.47, 128.31, 127.60, 127.59, 127.39, 127.31, 116.30, 71.66, 71.32, 69.94, 68.96, 67.63, 66.15, 65.38, 60.78, 41.44, 40.61, 39.49, 38.88, 35.63, 35.48, 35.27, 26.82, 25.88, 19.16, 18.10, -4.60, -4.71. IR (cm⁻¹): ν = 3073, 2927, 2845, 1428, 1250, 1108, 1090, 830, 698. HRMS-FAB: (M+H)⁺ = 743.4527 calculated for C₄₅H₆₇O₅Si₂, experimental = 743.4543. $[\alpha]_D^{20}$ = -20.1° (c = 3.30 in CHCl₃).

(-)-Homoallylic Alcohol 5.54



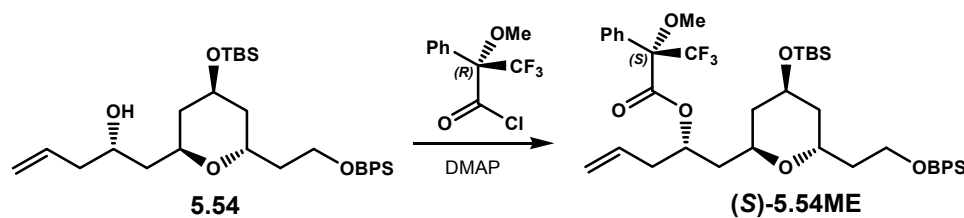
Into a solution of aldehyde **5.63** (2.50 g, 4.62 mmol) in Et₂O (250 mL) precooled to -78°C, a solution of allylmagnesium bromide (9.24 mL, 9.24 mmol, 1.0 M in Et₂O) was added dropwise. The reaction mixture was warmed to room temperature and stirred for two hours at which all starting material was completely consumed. After cooling to 0°C, the reaction was quenched with a saturated ammonium chloride solution (250 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et₂O (100 mL). The organic layers were combined, dried over MgSO₄, filtered, and removed under vacuum. The crude material was then loaded into Biotage chromatography system: 40+M column, 95:5 hexanes : EtOAc for 120 mL, then 95:5 → 85:15 hexanes : EtOAc linear gradient over 840 mL, then 85:15 → 50:50 hexanes : EtOAc linear gradient over 240 mL providing *the more polar* homoallylic alcohol **5.64** in 46% (1.24 g, 2.13 mmol) and *the less polar* homoallylic alcohol **5.54** in 49% (1.32 g, 2.27 mmol), both as a colorless oil.

Homoallylic alcohol **5.64** (1.24 g, 2.27 mmol) was then dissolved in toluene (150 mL). Triphenylphosphine (1.68 g, 6.39 mmol) and *p*-nitrobenzoic acid (1.07 g, 6.39 mmol) were added, and the solution was stirred for 5 minutes. Then, diethylazodicarboxylate (1.02 mL, 6.39 mmol) was then added. After stirring the reaction mixture overnight, toluene was then removed under vacuum leaving a yellow crude material which was redissolved in MeOH (100 mL). K₂CO₃ (1.77 g, 12.8 mmol) was then added, and the suspension was stirred for 2 hours. The reaction was quenched with DI water (100 mL), and the aqueous layer was extracted with Et₂O (3 x 100 mL). The organic layers were combined, dried over Mg₂SO₄, filtered, and removed under vacuum leaving a mixture of a yellow oil and a crystalline solid (methyl *p*-nitrobenzoate). The solid byproduct was filtered off with hexanes (50 mL). The filtrate was then concentrated and loaded into a silica gel column and chromatographed with 90:10 hexanes : EtOAc providing homoallylic alcohol **5.54** in 70% (0.867 g, 1.49 mmol) with a trace amount of methyl *p*-nitrobenzoate contaminant. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.69 – 7.66 (4H, m), 7.44 – 7.36 (6H, m), 5.80 (1H, dddd, J = 17.5, 10.5, 7.0, 7.0 Hz), 5.08 (1H, m), 5.06 (1H, s), 4.30 (1H, dddd, J = 9.0, 4.5, 4.5, 4.5 Hz), 3.90 (1H, m), 3.77 (1H, ddd, J = 10.5, 7.5, 7.5 Hz), 3.71 – 3.66 (3H, m), 3.53 (1H, s), 2.23 (1H, ddd, J = 13.5, 6.5, 6.5 Hz), 2.15 (1H, ddd, J = 14.0, 6.0, 6.0 Hz), 1.95 (1H, dddd, J = 11.5, 9.0, 6.0, 6.0 Hz), 1.76 (1H, ddd, J = 13.0, 3.0, 3.0 Hz), 1.72 – 1.60 (4H, m), 1.52 (1H, ddd, J = 14.5, 2.5, 2.5 Hz), 1.30 (1H, ddd, J = 13.0, 10.0, 10.0 Hz), 1.05 (9H, s), 0.88 (9H, s), 0.04 (6H, s). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 135.58, 135.54, 135.02, 133.83, 133.56, 129.60 (2C), 127.67, 127.64, 117.14, 71.23, 70.38, 68.85, 64.59, 60.67, 41.91, 41.52, 41.40, 38.40, 34.70, 26.83, 25.81, 19.16, 18.08, -4.63, -4.64. IR (cm⁻¹): *f* = 3503,

3075, 2930, 2857, 1428, 1254, 1112, 1081, 836, 702. HRMS-FAB: $(M+H)^+ = 583.3639$ calculated for $C_{34}H_{55}O_4Si_2$, experimental = 583.3654. $[\alpha]_D^{20} = -23.0^\circ$ ($c = 1.87$ in $CHCl_3$).

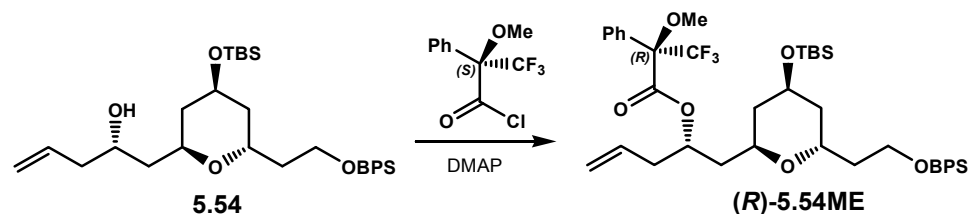
*Absolute Stereochemistry Determination of (-)-Homoallylic Alcohol **5.54** using Mosher's Ester Analysis*

In two separate vials, 5 mg of alcohol **5.54** was dissolved in CH_2Cl_2 (0.5 mL). DMAP (20 mg) and one drop of either (*R*)- or (*S*)-Mosher's acid chloride was then added. The mixture was stirred until completion. After concentrating the reaction mixture under vacuum, the crude material was loaded into a silica gel column and chromatographed with 98:2 hexanes : EtOAc which provided the corresponding the Mosher's ester (*S*)-**5.54ME** or (*R*)-**5.54ME**



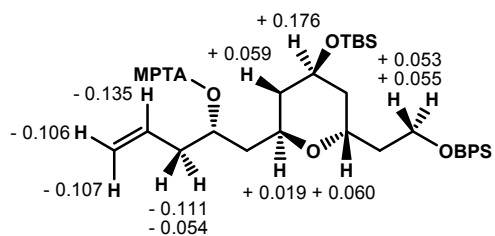
1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.68 – 7.65 (4H, m), 7.52 – 7.51 (2H, m), 7.43 – 7.34 (9H, m), 5.55 (1H, dddd, $J = 14.5, 10.5, 7.5, 7.5$ Hz), 5.23 (1H, dddd, $J = 6.5, 6.5, 6.5, 5.0$ Hz), 4.95 (1H, d, $J = 9.5$ Hz), 4.94 (1H, d, $J = 17.5$ Hz), 4.25 (1H, dddd, $J = 9.5, 5.0, 5.0, 5.0$ Hz), 3.93 (1H, m), 3.74 (1H, ddd, $J = 10.0, 7.5, 6.0$ Hz), 3.66 (1H, ddd, $J = 11.5, 6.0, 6.0$ Hz), 3.64 (1H, m), 3.49 (3H, s), 2.38 (1H, ddd, $J = 15.0, 5.0, 5.0$ Hz),

2.28 (1H, ddd, $J = 14.5, 7.5, 7.5$ Hz), 2.21 (1H, ddd, $J = 14.5, 7.5, 7.5$ Hz), 1.85 – 1.77 (3H, m), 1.64 – 1.58 (3H, m), 1.32 (1H, ddd, $J = 13.0, 8.0, 8.0$ Hz), 1.04 (9H, s), 0.87 (9H, s), 0.037 (3H, s), 0.035 (3H, s).

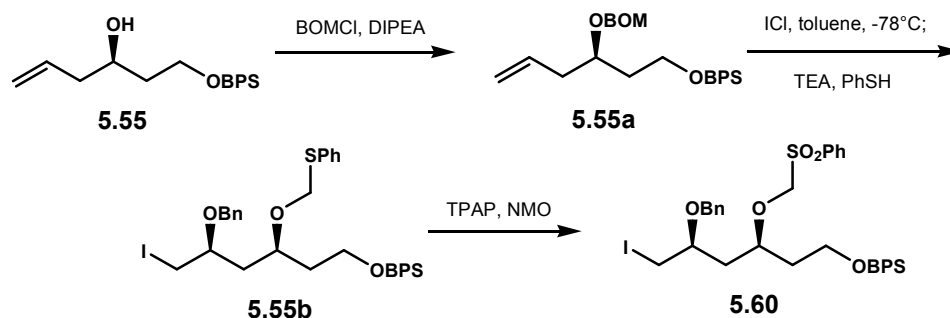


^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.67 – 7.64 (4H, m), 7.52 – 7.51 (2H, m), 7.43 – 7.36 (9H, m), 5.68 (1H, dddd, $J = 17.0, 10.5, 7.5, 6.0$ Hz), 5.23 (1H, p, $J = 5.5$ Hz), 5.05 (1H, d, $J = 10.0$ Hz), 5.05 (1H, d, $J = 17.5$ Hz), 4.23 (1H, dddd, $J = 9.0, 5.0, 5.0, 5.0$ Hz), 3.87 (1H, m), 3.69 (1H, ddd, $J = 10.0, 7.5, 5.0$ Hz), 3.60 (1H, ddd, $J = 11.5, 6.0, 6.0$ Hz), 3.51 (3H, s), 3.46 (1H, m), 2.47 – 2.36 (2H, m), 2.02 (1H, ddd, $J = 14.5, 7.5, 7.5$ Hz), 1.79 – 1.67 (3H, m), 1.60 – 1.49 (3H, m), 1.26 (1H, m), 1.03 (9H, s), 0.88 (9H, s), 0.051 (3H, s), 0.044 (3H, s).

$\Delta\delta$ (*S*)-5.54ME – (*R*)-5.54ME



(+)-Sulfonyl Ether **5.60**



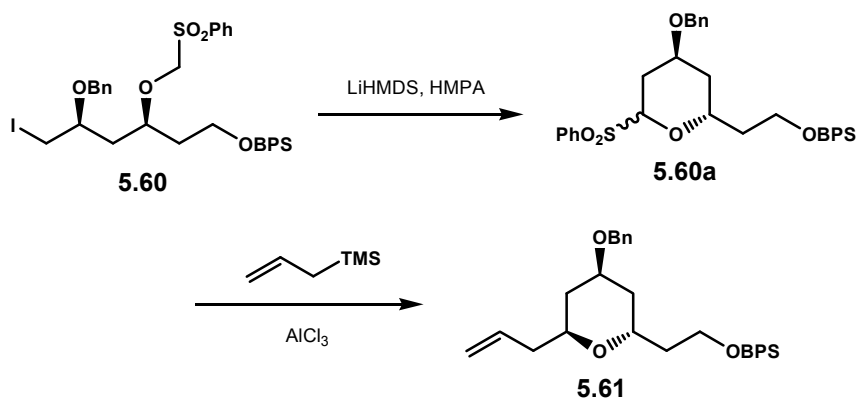
Homoallylic alcohol **5.55** (6.20 g, 17.5 mmol, >95% ee) was dissolved in CH₂Cl₂ (100 mL), and DIPEA (100 mL) was then added. After cooling the mixture to 0°C, BOMCl (7.29 mL, 52.4 mmol) was added dropwise. The reaction was refluxed overnight resulting in dark red color. After cooling to room temperature, the reaction was then diluted with CH₂Cl₂ (300 mL) and washed with 2 M HCl (200 mL). After separating the organic and aqueous layers, the aqueous layer was washed with CH₂Cl₂ (2 x 100 mL). The organic layer was then combined, dried over MgSO₄ and filtered. A red oil was obtained upon removal of CH₂Cl₂ under vacuum. The crude material was flushed through a thick pad of silica with 90:10 hexanes : EtOAc to give a mixture containing the title product **5.55a** and BOMCl residue as a colorless oil (12.0 g). This mixture was carried on the next step without further purification. For characterization purposes, a small aliquot of the mixture was carefully chromatographed with 95:5 hexanes : EtOAc. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.68 – 7.66 (4H, m), 7.44 – 7.27 (11H, m), 5.83 (1H, dddd, J = 17.5, 10.5, 7.0, 7.0 Hz), 5.09 (1H, m), 5.06 (1H, m), 4.79 (1H, d, J = 7.0 Hz), 4.76 (1H, d, J = 7.0 Hz), 4.61 (1H, d, J = 11.5 Hz), 4.54 (1H, d, J = 12.0 Hz), 3.95 (1H, p, J = 6.0 Hz), 3.81 (1H, ddd, J = 10.5, 6.5, 6.5 Hz), 3.77 (1H, ddd, J = 10.0, 6.0, 6.0

Hz), 2.39 – 2.29 (2H, m), 1.81 – 1.77 (2H, m), 1.06 (9H, s). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.88, 135.55 (2C), 135.53, 134.61, 133.80, 129.58, 129.57, 128.37, 127.81, 127.62 (2C), 127.59, 117.28, 93.62, 74.15, 69.44, 60.53, 39.16, 37.07, 26.84, 19.16. IR (cm^{-1}): ν = 3071, 2931, 2858, 1472, 1428, 1169, 1112, 1042, 736, 701. HRMS-FAB: $(\text{M-SiPh}_2t\text{-Bu})^+ = 219.1385$ calculated for $\text{C}_{14}\text{H}_{19}\text{O}_2$, experimental = 219.1375. $[\alpha]_{\text{D}}^{20} = -5.65^\circ$ ($c = 4.23$ in CHCl_3).

A mixture of homoallylic BOM ether **5.55a** and BOMCl residue (12.0 g) was dissolved in toluene (350 mL), and 12 grams of 4 Å molecular sieves were then added. After cooling this solution to -78°C , an iodine monochloride solution (35.0 mL, 35.0 mmol, 1.0 M in CH_2Cl_2) was added dropwise over one hour while maintaining an internal temperature of the reaction below -75°C . The solution became dark red and was stirred for 30 minutes. Then, TEA (9.72 mL, 69.9 mmol) was added in one injection, followed by PhSH (3.59 mL, 35.0 mmol) in which the solution immediately turned cloudy grey. The reaction was warmed to room temperature over one hour and then quenched with a 1:1 mixture of saturated NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ (300 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et_2O (2 x 100 mL). The organic layers were then combined, dried over MgSO_4 , and filtered. The organic solvent was removed under vacuum leaving behind a yellow oil. The crude material was purified with column chromatography: first, using 98:2 hexanes : EtOAc to remove the non-polar byproduct, and then, 90:10 hexanes : EtOAc to elute the inseparable ether transfer product **5.55b** and BOMCl residue. Removal of solvent provided 12.2 g of the mixture, which was carried on the next step without further purification.

A mixture of thioether **5.55b** and BOMCl residue (12.2 g) was divided into 2 separate batches of 6.10 g. For each batch, the material was dissolved in dry CH₃CN (50 mL). 6 grams of 4 Å molecular sieves and NMO (4.95 g, 42.2 mmol) were added, the mixture was stirred until NMO was completely dissolved. TPAP (148 mg, 0.422 mmol) was charged, and the solution was warmed to 40°C and stirred overnight. After cooling to room temperature, the two batches were combined and concentrated under vacuum leaving black crude material. This crude mixture was then loaded into a silica gel column, and sulfone **5.60** was eluted with 80:20 hexanes : EtOAc as a colorless oil in 46% yield over three steps (5.92 g, 7.97 mmol) as a single diastereomer. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.83 (2H, dd, J = 8.0, 0.5 Hz), 7.65 – 7.59 (5H, m), 7.47 – 7.27 (13H, m), 4.54 (1H, d, J = 11.5 Hz), 4.50 (2H, s), 4.36 (1H, d, J = 11.5 Hz), 4.01 (1H, p, = 6.0 Hz), 3.70 – 3.61 (2H, m), 3.35 – 3.25 (3H, m), 1.87 – 1.76 (2H, m), 1.71 (2H, q, J = 6.5 Hz), 1.05 (9H, s). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 137.60, 137.37, 135.54, 135.53, 133.92, 133.48, 133.44, 129.77, 129.74, 129.14, 128.70, 128.44, 127.86, 127.84, 127.75, 127.73, 84.08, 77.27, 73.90, 71.04, 59.86, 39.14, 36.72, 26.87, 19.17, 10.27. IR (cm⁻¹): ν = 3068, 2959, 2928, 2855, 1427, 1324, 1398, 1260, 1150, 1111, 1079, 1027, 799, 741. HRMS-FAB: M⁺ = 742.1645 calculated for C₃₆H₄₃O₅SiSI, experimental = 742.1622. $[\alpha]_D^{20}$ = +0.328° (c = 6.10 in CHCl₃).

(-)-Tetrahydropyran 5.61

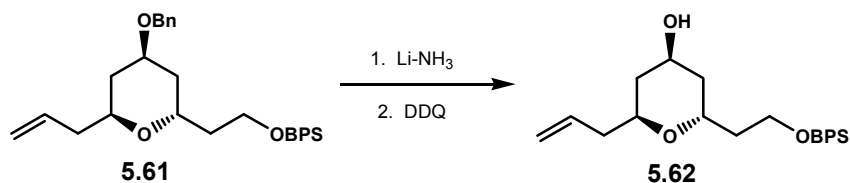


Sulfone **5.60** was subjected to the procedure as represented in the preparation of compound **5.37** with the following modifications. Sulfone **5.60** (9.50 g, 12.8 mmol), HMDS (4.08 mL, 19.2 mmol), *n*-BuLi (8.73 mL, 19.2 mmol, 2.2 M in hexanes), HMPA (6.68 mL, 38.4 mmol) were employed. LiHMDS was prepared in THF (100 mL), and sulfone **5.60** was dissolved in THF (400 mL). The crude mixture was flushed through a thick silica pad with 70:30 hexanes : EtOAc, and the diastereomeric mixture of sulfonylpyran **5.60a** was obtained in 98% (7.68 g, 12.5 mmol) as a yellow oil.

A suspension of AlCl₃ (2.50 g, 18.7 mmol) in toluene (400 mL) was cooled to -78°C. In a separate flask, a diastereomeric mixture of sulfonylpyran **5.60a** (7.68 g, 12.5 mmol) was dissolved in toluene (50 mL). After cooling to -78°C, this solution was transferred to the AlCl₃ suspension via cannula. To ensure all starting material was completely transferred, the flask was washed with toluene (2 x 25 mL), cooled, and transferred to the reaction mixture. This mixture was stirred for 5 minutes. Allyltrimethylsilane (5.96 mL, 37.5 mmol) was then added dropwise, and the reaction was slowly warmed up to -50°C over one hour in which the reaction completed. A

saturated aqueous solution of Rochelle's salt (300 mL) was then added, and the emulsion was stirred until separation of layers was achieved. After separating the organic and aqueous layers, the aqueous layer was washed with CH₂Cl₂ (2 x 100 mL). The organic layers were then combined, dried over MgSO₄, filtered, and concentrated under vacuum leaving behind a yellow oil. The crude material was loaded into a silica gel column and eluted with 92:8 hexanes : EtOAc. Upon removal of solvent, tetrahydropyran **5.61** was isolated as a colorless oil in 98% yield (6.33 g, 12.3 mmol) as a single diastereomer. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.68 – 7.65 (4H, m), 7.43 – 7.27 (11H, m), 5.72 (1H, dddd, J = 17.0, 10.0, 7.0, 7.0 Hz), 5.04 – 4.96 (2H, m), 4.54 (1H, d, J = 12.0 Hz), 4.51 (1H, d, J = 11.5 Hz), 4.29 (1H, m), 3.75 (1H, m), 3.71 – 3.65 (2H, m), 3.46 (1H, m), 2.32 (1H, m), 2.17 (1H, m), 1.97 (1H, m), 1.93 (1H, m), 1.86 (1H, m), 1.71 (1H, ddd, J = 13.0, 10.5, 5.5 Hz), 1.63 (1H, m), 1.31 (1H, ddd, J = 12.5, 10.0, 10.0 Hz), 1.04 (9H, s). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 138.63, 135.57, 135.54, 134.88, 133.87, 133.71, 129.55, 129.54, 128.37, 127.60 (2C), 127.48, 127.46, 116.69, 71.38, 69.63, 68.80, 68.59, 60.82, 40.30, 36.96, 35.18, 34.57, 26.83, 19.16. IR (cm⁻¹): *f* = 3070, 2931, 2857, 1428, 1112, 1089, 701. HRMS-FAB: (M+H)⁺ = 515.2981 calculated for C₃₃H₄₃O₃Si, experimental = 515.2970. [α]_D²⁰ = -29.5° (c = 2.18 in CHCl₃).

(-)-Alcohol 5.62

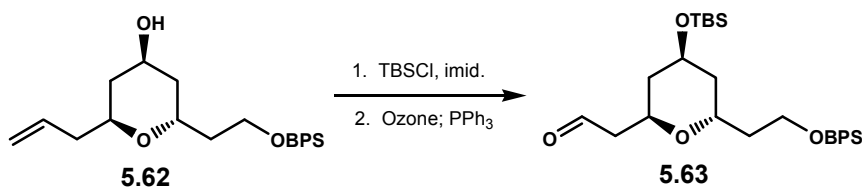


Anhydrous ammonia (300 mL) was condensed into a round-bottomed flask at -78°C, and lithium wire (228 mg, 32.5 mmol) was added in small pieces. The solution immediately turned dark blue and was stirred for 15 minutes. In a separate flask, tetrahydropyran **5.61** (2.79 g, 5.42 mmol) was dissolved in THF (100 mL). After cooling to -78°C, this solution was transferred to the Li-NH₃ mixture rapidly via cannula. To ensure all starting material was completely transferred, the flask was washed with THF (2 x 20 mL), cooled, and then transferred to the reaction mixture. After 5 minutes, solid NH₄Cl was added until the blue color disappeared, and the ammonia was evaporated by warming the reaction to room temperature. The reaction mixture was diluted with Et₂O (100 mL) and then washed with DI water (100 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et₂O (2 x 100 mL). The organic layers were then combined, dried over MgSO₄, filtered, and concentrated under vacuum leaving behind a yellow oil, which was redissolved in CH₂Cl₂ (100 mL).

DDQ (4.92 g, 21.7 mmol) was added resulting in a red suspension. After stirring overnight, the solid residue was filtered under vacuum, and the filtrate was then washed with a saturated NaHCO₃ solution. After separating the organic and aqueous layers, the aqueous layer was washed with CH₂Cl₂ (100 mL). The organic layers were combined,

dried over MgSO_4 , filtered, and concentrated under vacuum leaving behind a red oil. The crude material was purified using Biotage chromatography system: 40+M column, 90:10 \rightarrow 50:50 hexanes : EtOAc linear gradient for 960 mL providing the title product **5.62** in 98% yield (2.25g, 5.30 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.70 – 7.66 (4H, m), 7.44 – 7.37 (6H, m), 5.74 (1H, dddd, J = 17.0, 10.0, 7.0, 7.0 Hz), 5.06 – 4.98 (2H, m), 4.29 (1H, m), 3.92 (1H, dddd, J = 10.5, 10.5, 4.5, 4.5 Hz), 3.76 (1H, ddd, J = 10.5, 7.0, 7.0 Hz), 3.69 (1H, ddd, J = 10.5, 7.0, 5.0 Hz), 3.45 (1H, m), 2.28 (1H, m), 2.16 (1H, m), 2.00 (1H, dddd, J = 14.5, 10.0, 5.5, 5.5 Hz), 1.94 (1H, m), 1.84 (1H, m), 1.68 – 1.59 (2H, m), 1.48 (1H, b), 1.19 (1H, ddd, J = 11.5, 11.0, 11.0 Hz), 1.05 (9H, s). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 135.56, 135.53, 134.67, 133.84, 133.68, 129.56, 129.55, 127.60 (2C), 116.88, 69.33, 68.17, 64.65, 60.76, 40.56, 40.40, 38.12, 34.10, 26.82, 19.14. IR (cm^{-1}): ν = 3369, 3072, 2932, 2857, 1428, 1112, 1088, 1032, 739, 702. HRMS-FAB: $(\text{M}+\text{H})^+ = 425.2512$ calculated for $\text{C}_{26}\text{H}_{37}\text{O}_3\text{Si}$, experimental = 425.2512. $[\alpha]_{\text{D}}^{20} = -32.2^\circ$ (c = 2.44 in CHCl_3).

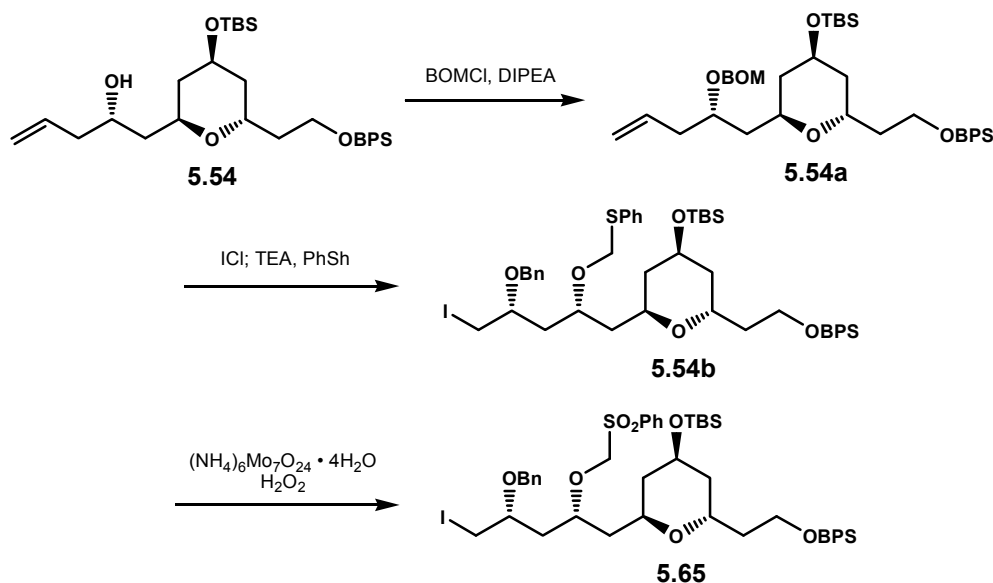
(-)-Aldehyde 5.63



Alcohol **5.62** (2.25 g, 5.30 mmol) was dissolved in CH_2Cl_2 (100 mL). DMAP (130 mg, 1.06 mmol), imidazole (1.08 g, 15.9 mmol), and TBSCl (1.20 g, 7.95 mmol)

were then added. After overnight stirring, the reaction mixture was washed with 2 M HCl (100 mL). After separating the organic and aqueous layers, the aqueous layer was washed with CH₂Cl₂ (2 x 50 mL). The organic layers were combined, dried over MgSO₄, filtered, and then cooled to -78°C. Ozone was bubbled into the solution until a persistent blue color was attained. Addition of PPh₃ (2.78 g, 10.6 mmol) resulted in the disappearance the blue color, and the mixture was stirred overnight. After removing solvent under vacuum, the crude material was loaded into a silica gel column and chromatographed with 90:10 hexanes : EtOAc to yield the title aldehyde **5.63** as a white solid in 81% yield (2.33 g, 4.31 mmol) over two steps. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 9.68 (1H, t, J = 2.0 Hz), 7.68 – 7.66 (4H, m), 7.44 – 7.36 (6H, m), 4.27 (1H, dddd, J = 9.0, 4.5, 4.5, 4.5 Hz), 4.13 (1H, dddd, J = 8.0, 8.0, 4.5, 4.5 Hz), 4.02 (1H, m), 3.77 (1H, ddd, J = 10.5, 8.5, 6.0 Hz), 3.69 (1H, ddd, J = 11.5, 6.5, 5.0 Hz), 2.82 (1H, ddd, J = 17.0, 8.5, 2.5 Hz), 2.58 (1H, ddd, J = 16.5, 5.0, 1.5 Hz), 1.91 – 1.84 (2H, m), 1.68 – 1.60 (3H, m), 1.40 (1H, ddd, J = 13.0, 7.5, 7.5 Hz), 1.05 (9H, s), 0.90 (9H, s), 0.062 (3H, s), 0.056 (3H, s). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 201.41, 135.55 (2C), 133.90, 133.74, 129.59, 129.58, 127.63, 127.62, 129.59, 129.58, 127.63, 127.62, 66.58, 65.38, 64.86, 60.48, 48.82, 39.08, 38.73, 35.86, 26.85, 25.81, 19.18, 18.03, -4.73, -4.74. IR (cm⁻¹): $\tilde{\nu}$ = 3074, 2953, 2857, 2722, 1727, 1472, 1255, 1112, 1084, 836, 702. HRMS-FAB: (M+H)⁺ = 541.3169 calculated for C₃₁H₄₉O₄Si₂, experimental = 541.3189. [α]_D²⁰ = -20.3° (c = 1.20 in CHCl₃). mp = 83°C – 84°C.

(-)-Sulfonyl Ether 5.65



Homoallylic alcohol **5.54** (1.75 g, 3.00 mmol) was dissolved in a mixture of CH_2Cl_2 (20 mL) and DIPEA (20 mL) in a thick-walled tube. BOMCl (2.50 mL, 18.0 mmol) was added dropwise. The tube was then sealed, warmed at 80°C , and stirred for 24 hours. After cooling to room temperature, the reaction was then diluted with CH_2Cl_2 (100 mL) and washed with 2 M HCl (100 mL). After separating the organic and aqueous layers, the aqueous layer was washed with CH_2Cl_2 (2 x 50 mL). The organic layers were then combined, dried over MgSO_4 and filtered. A red oil was obtained upon removal of CH_2Cl_2 under vacuum. The crude material was flushed through a thick pad of silica with 90:10 hexanes : EtOAc to give of a mixture containing the title product **5.54a** and BOMCl residue (3.21 g) as a colorless oil. This mixture was carried on the next step without further purification. For characterization purposes, a small aliquot of the mixture was carefully chromatographed with 95:5 hexanes : EtOAc. ^1H NMR (500 MHz,

CDCl₃): δ (ppm) = 7.69 – 7.66 (4H, m), 7.44 – 7.27 (11H, m), 5.81 (1H, dddd, J = 17.0, 10.5, 7.0, 7.0 Hz), 5.06 (1H, m), 5.03 (1H, s), 4.76 (1H, d, J = 7.0 Hz), 4.74 (1H, d, J = 7.0 Hz), 4.62 (1H, d, J = 11.5 Hz), 4.58 (1H, d, J = 12.0 Hz), 4.26 (1H, dddd, J = 9.5, 4.5, 4.5, 4.5 Hz), 3.94 (1H, m), 3.82 (1H, p, J = 6.0 Hz), 3.80 – 3.67 (3H, m), 2.36 (1H, m), 2.25 (1H, m), 1.98 (1H, ddd, J = 14.0, 7.0, 7.0 Hz), 1.91 (1H, dddd, J = 14.0, 8.5, 5.5, 5.5 Hz), 1.83 (1H, ddd, J = 12.5, 3.5, 3.5 Hz), 1.68 (1H, ddd, J = 14.0, 6.0, 6.0 Hz), 1.66 – 1.59 (3H, m), 1.32 (1H, ddd, J = 13.0, 9.0, 9.0 Hz), 1.05 (9H, s), 0.89 (9H, s), 0.042 (6H, s). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 137.96, 135.53, 135.52, 134.64, 133.88, 133.75, 129.54, 129.53, 128.34, 127.69, 127.62, 127.61, 127.54, 117.26, 93.42, 74.34, 69.43, 67.57, 66.36, 65.14, 60.83, 40.29, 40.00, 38.84, 38.77, 35.33, 26.84, 25.84, 19.16, 18.07, -4.62, -4.65. IR (cm⁻¹): ν = 3071, 2930, 2857, 1428, 1254, 1112, 1042, 836, 701. HRMS-FAB: (M-C₆H₆)⁺ = 625.3745 calculated for C₃₆H₅₇O₅Si₂, experimental = 625.3730. $[\alpha]_D^{20}$ = -18.8° (c = 2.50 in CHCl₃).

A mixture of ether **5.54a** and BOMCl residue (3.21 g) was dissolved in toluene (200 mL), and 3 grams of 4 Å molecular sieves were then added. After cooling this solution to -78°C, an iodine monochloride solution (6.00 mL, 6.00 mmol, 1.0 M in CH₂Cl₂) was added dropwise over one hour while maintaining an internal temperature of the reaction below -75°C. The solution became dark red and was stirred for 30 minutes. Then, TEA (1.67 mL, 12.0 mmol) was added in one injection, followed by PhSH (0.62 mL, 6.00 mmol) in which the solution immediately turned cloudy grey. The reaction was warmed to room temperature over one hour and then quenched with a 1:1 mixture of saturated NaHCO₃ and Na₂S₂O₃ (300 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et₂O (2 x 100 mL). The organic layers were

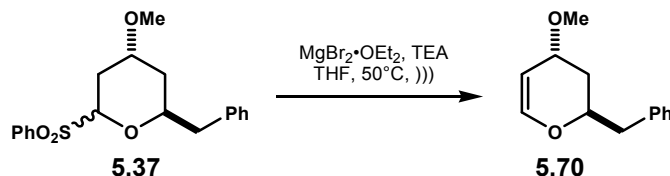
then combined, dried over MgSO_4 , and filtered. The organic solvent was removed under vacuum leaving behind a yellow oil. The crude material was then loaded into Biotage chromatography system: 40+M column, 98:2 hexanes : EtOAc for 240 mL, then 98:2 \rightarrow 90:10 hexanes : EtOAc linear gradient over 720 mL. All fractions containing ether transfer product **5.54b** were combined and rotovaped providing a mixture of title product **5.54b** and BOMCl residue (3.20 g). This mixture was carried on the next step without further purification. For characterization purposes, a small aliquot of the mixture was carefully chromatographed with 98:2 hexanes : EtOAc. ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.69 – 7.66 (4H, m), 7.43 – 7.26 (13H, m), 7.22 (2H, t, J = 7.0 Hz), 7.13 (1H, t, J = 7.0 Hz), 5.01 (1H, d, J = 12.0 Hz), 4.97 (1H, d, J = 12.5 Hz), 4.49 (1H, d, J = 11.0 Hz), 4.33 (1H, d, J = 11.5 Hz), 4.22 (1H, m), 3.84 (1H, p, J = 6.0 Hz), 3.77 (1H, ddd, J = 13.5, 9.0, 3.5 Hz), 3.71 (1H, ddd, J = 10.0, 7.0, 6.5 Hz), 3.65 (1H, ddd, J = 10.5, 6.0, 6.0 Hz), 3.58 (1H, m), 3.30 – 3.21 (3H, m), 1.95 (1H, ddd, J = 13.5, 6.5, 6.5 Hz), 1.85 – 1.76 (4H, m), 1.61 – 1.55 (3H, m), 1.51 (1H, ddd, J = 13.5, 6.5, 6.5 Hz), 1.17 (1H, ddd, J = 12.0, 9.5, 9.5 Hz), 1.05 (9H, s), 0.87 (9H, s), 0.021 (3H, s), 0.011 (3H, s). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.80, 136.27, 135.58, 135.56, 133.84, 133.76, 129.58, 129.57, 128.92, 128.42, 128.36, 127.88, 127.77, 127.65 (2C), 125.99, 73.88, 72.22, 71.02, 69.87, 68.36, 65.88, 64.94, 60.96, 40.89, 39.87, 38.99, 38.57, 34.82, 26.87, 25.85, 19.19, 18.07, 10.98, -4.57, -4.66. IR (cm^{-1}): ν = 3064, 2929, 2856, 1428, 1254, 1112, 1082, 1054, 733, 695. HRMS-FAB: $(\text{M}-\text{C}_4\text{H}_9)^+ = 881.2588$ calculated for $\text{C}_{44}\text{H}_{58}\text{O}_5\text{Si}_2\text{SI}$, experimental = 881.2553. $[\alpha]_D^{20} = -12.8^\circ$ (c = 1.40 in CHCl_3).

A mixture of thioether **5.54b** and BOMCl residue (3.20 g) was dissolved in ethanol (200 mL, 200 proof), and the solution was cooled to 0°C . In a separate flask,

ammonium (VI) molybdate tetrahydrate (11.2 g, 9.00 mmol) was dissolved in a cold aqueous hydrogen peroxide solution (30%, 100 mL). This Mo(VI) – H₂O₂ mixture was immediately poured to the solution of compound **23b** in one portion causing the reaction to turn yellow and cloudy (the cloudiness eventually dissipated). The reaction was stirred vigorously at 0°C for one hour and then at room temperature for two more hours. Addition of DI water (300 mL) quenched the reaction, and the aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL). The yellow organic layers were combined, dried over MgSO₄, filtered, and rotovaped to produce a yellow oily residue. The crude material was then loaded into Biotage chromatography system: 40+M column, 95:5 hexanes : EtOAc for 240 mL, then 95:5 → 80:20 hexanes : EtOAc linear gradient over 720 mL to afford the corresponding sulfone **5.65** in 45% yield over three steps as a yellow oil (1.30 g, 1.34 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.86 (2H, d, J = 7.5 Hz), 7.67 – 7.65 (4H, m), 7.61 (1H, t, J = 7.5 Hz), 7.49 (2H, t, J = 7.5 Hz), 7.44 – 7.28 (11H, m), 4.54 (1H, d, J = 11.0 Hz), 4.53 (1H, d, J = 12.0 Hz), 4.48 (1H, d, J = 12.0 Hz), 4.34 (1H, d, J = 11.5 Hz), 4.20 Hz (1H, m), 3.90 – 3.83 (2H, m), 3.71 (1H, ddd, J = 10.0, 7.0, 7.0 Hz), 3.65 (1H, ddd, J = 10.0, 6.0, 6.0 Hz), 3.59 (1H, dddd, J = 12.5, 9.5, 4.0, 4.0 Hz), 3.32 – 3.27 (2H, m), 3.19 (1H, m), 1.91 – 1.77 (4H, m), 1.72 (1H, m), 1.66 – 1.56 (3H, m), 1.52 (1H, ddd, J = 14.0, 7.0, 4.0 Hz), 1.16 (1H, ddd, J = 13.0, 9.5, 9.5 Hz), 1.05 (9H, s), 0.88 (9H, s), 0.036 (6H, s). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 137.66, 137.58, 135.54 (2C), 133.90, 133.75, 133.68, 129.63, 129.14, 128.69, 128.45, 127.90, 127.86, 127.69, 127.68 (2C), 83.85, 77.56, 73.65, 70.99, 68.39, 65.63, 64.81, 60.96, 40.99, 39.53, 38.68, 38.41, 34.95, 26.86, 25.84, 19.17, 18.06, 10.52, -4.57, -4.63. IR (cm⁻¹): ν = 3064, 2929, 2856, 1428, 1325, 1253, 1112, 1083, 741. HRMS-FAB: (M+H)⁺

= 971.3269 calculated for C₄₈H₆₈O₇Si₂SI, experimental = 971.3301. $[\alpha]_D^{20} = -12.3^\circ$ (c = 2.54 in CHCl₃).

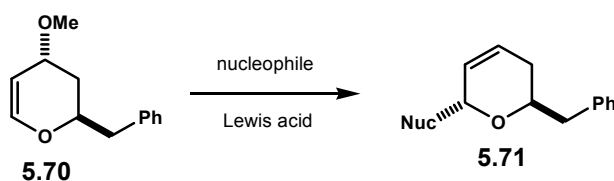
(±)-(2R,4R)-2-benzyl-3,4-dihydro-4-methoxy-2H-pyran 5.70



Sulfonylpyran **5.70** (5.00 g, 14.4 mmol) as a mixture of diastereomers was dissolved in THF (200 mL). Upon addition of TEA (20.0 mL, 144 mmol) and MgBr₂•OEt₂ (11.2 g, 43.2 mmol), the suspension mixture was agitated in an ultrasound bath at 50°C until the starting material was completely consumed. The reaction was cooled to room temperature and quenched with a saturated aqueous NaHCO₃ solution (200 mL). After separation of organic and aqueous layers, the aqueous solution was extracted with Et₂O (2 x 100 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated under vacuum. The crude material was flushed through a thick silica pad with 95:5 hexanes : EtOAc, and dihydropyran **5.70** was produced in 95% yield (2.80 g, 13.7 mmol) as a yellow oil after concentration. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.32 – 7.29 (2H, m), 7.25 – 7.21 (3H, m), 6.51 (1H, d, J = 6.0 Hz), 4.97 (1H, ddd, J = 6.5, 5.5, 2.0 Hz), 4.15 (1H, dddd, J = 12.5, 7.5, 6.0, 2.0 Hz), 3.64 (1H, m), 3.29 (3H, s), 2.97 (1H, dd, J = 14.0, 7.0 Hz), 2.87 (1H, dd, J = 14.0, 5.5 Hz), 1.96 (1H, dddd, J = 14.0, 1.5, 1.5, 1.5 Hz), 1.53 (1H, ddd, J = 14.5, 12.0, 4.0 Hz).

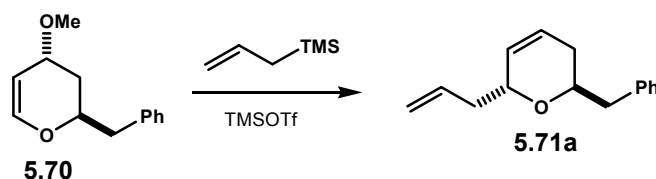
^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 147.22, 137.55, 129.43, 128.26, 126.36, 99.92, 71.93, 68.29, 55.00, 41.41, 33.02. IR (cm^{-1}): ν = 3062, 3029, 2924, 2817, 1639, 1455, 1245, 1081, 700. HRMS-FAB: $(\text{M}-\text{H})^+ = 203.1072$ calculated for $\text{C}_{13}\text{H}_{15}\text{O}_2$, experimental = 203.1068.

GENERAL PROCEDURE F: *Ferrier Rearrangement of Dihydropyran 5.70*

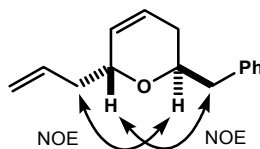


Dihydropyran **5.70** (1.0 equivalent) was dissolved in CH_2Cl_2 (10mL), and the solution was cooled to -78°C . After addition of nucleophile (3.0 equivalents), a freshly prepared 1.0 M solution of Lewis acid (TMSOTf or $\text{BF}_3\cdot\text{OEt}_2$) in CH_2Cl_2 (0.1 – 3.0 equivalents) buffered with oven-dried solid NaHCO_3 was then added dropwise. The reaction mixture was stirred for 5 minutes and then quenched with phosphate buffer (pH 7.00, 20 mL). After separation of layers, the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The organic layers were then combined, dried over MgSO_4 , and concentrated under vacuum. The crude material was purified with a silica gel column using 95:5 hexanes : EtOAc to give the Ferrier rearrangement product **5.71**.

(±)-(2*S*,6*R*)-6-allyl-2-benzyl-3,6-dihydro-2*H*-pyran **5.71a**

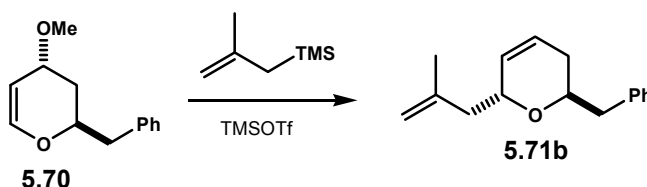


General Procedure F was followed. Dihydropyran **5.70** (100 mg, 0.489 mmol) dissolved in CH₂Cl₂ (10 mL), TMSOTf (0.98 mL, 0.98 mmol, 1.0 M in CH₂Cl₂), and allyltrimethylsilane (0.23 mL, 1.47 mmol) were employed. ¹H NMR of the crude reaction mixture indicated a diastereomeric ratio of >20:1, and after chromatography, dihydropyran **5.71a** was obtained in 91% with as a colorless oil (95.0 mg, 0.443 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.31 – 7.28 (2H, m), 7.25 – 7.20 (3H, m), 5.82 (1H, m), 5.78 – 5.70 (2H, m), 5.01 (1H, m), 4.98 (1H, m), 4.25 (1H, m), 3.95 (1H, dddd, J = 6.5, 6.5, 6.0, 6.0 Hz), 2.92 (1H, dd, J = 13.5, 7.0 Hz), 2.75 (1H, dd, J = 13.5, 6.0 Hz), 2.36 (1H, m), 2.23 (1H, m), 2.02 – 1.98 (2H, m). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 138.70, 134.84, 129.28, 129.16, 128.18, 126.08, 124.09, 116.74, 72.46, 69.08, 41.75, 38.77, 29.99. IR (cm⁻¹): ν = 3064, 3030, 2924, 1496, 1455, 1075, 914, 700. HRMS-FAB: (M-H)⁺ = 213.1279 calculated for C₁₅H₁₇O, experimental = 213.1279. The relative 2,6-*trans* stereochemistry of the ring was deduced from a ROESY experiment.



With catalytic amount of TMSOTf (Table 1, entry 2): Dihydropyran **5.70** (100 mg, 0.489 mmol) dissolved in CH₂Cl₂ (10 mL), TMSOTf (49 μ L, 0.0489 mmol, 1.0 M in CH₂Cl₂), and allyltrimethylsilane (0.23 mL, 1.47 mmol) were employed. ¹H NMR of crude reaction mixture indicated a diastereomeric ratio of >20:1, and after chromatography, dihydropyran **5.71a** was obtained in 90% with as a colorless oil (94.0 mg, 0.439 mmol).

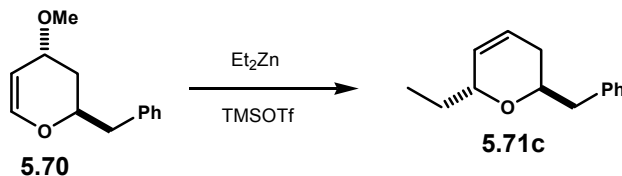
(±)-(2*S*,6*R*)-2-benzyl-3,6-dihydro-6-(2-methylallyl)-2*H*-pyran **5.71b**



General Procedure F was followed. Dihydropyran **5.70** (100 mg, 0.489 mmol) dissolved in CH₂Cl₂ (10 mL), TMSOTf (0.98 mL, 0.98 mmol, 1.0 M in CH₂Cl₂), and trimethyl(2-methylallyl)silane (0.26 mL, 1.47 mmol) were employed. ¹H NMR of the crude reaction mixture indicated a diastereomeric ratio of >20:1, and after chromatography, dihydropyran **5.71b** was obtained in 91% with as a colorless oil (102 mg, 0.447 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.30 – 7.27 (2H, m), 7.24 – 7.19 (3H, m), 5.80 (1H, m), 5.71 (1H, m), 4.73 (1H, s), 4.62 (1H, s), 4.38 (1H, m), 3.94 (1H, dddd, *J* = 7.0, 7.0, 7.0, 5.5 Hz), 2.92 (1H, dd, *J* = 14.0, 7.0 Hz), 2.74 (1H, dd, *J* = 13.5, 6.5 Hz), 2.33 (1H, dd, *J* = 14.0, 8.5 Hz), 2.15 (1H, dd, *J* = 14.0, 5.5 Hz), 2.00 – 1.97 (2H, m), 1.71 (3H, s). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 142.35, 138.65, 129.51, 129.34, 128.17, 126.08, 123.86, 112.52, 71.23, 68.95, 42.27, 41.90, 29.99, 22.42. IR

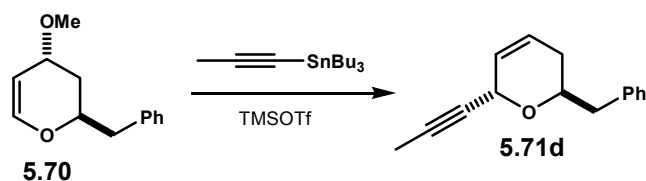
(cm^{-1}): $f = 3071, 3030, 2933, 1648, 1455, 1091, 1043, 887, 741, 699$. HRMS-FAB: (M-H) $^{+} = 227.1436$ calculated for $\text{C}_{16}\text{H}_{19}\text{O}$, experimental = 227.1445.

(\pm)-(2*S*,6*R*)-2-benzyl-6-ethyl-3,6-dihydro-2*H*-pyran **5.71c**



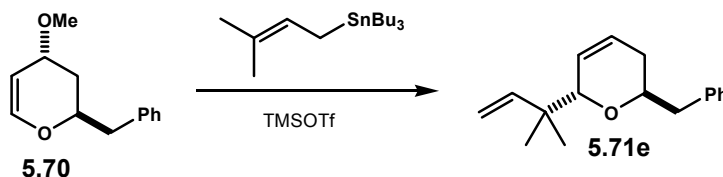
General Procedure F was followed. Dihydropyran **5.70** (100 mg, 0.489 mmol) dissolved in CH_2Cl_2 (10 mL), TMSOTf (0.98 mL, 0.98 mmol, 1.0 M in CH_2Cl_2), and diethylzinc (1.47 mL, 1.47 mmol, 1.0 M in hexanes) were employed. ^1H NMR of the crude reaction mixture indicated a diastereomeric ratio of $>20:1$, and after chromatography, dihydropyran **5.71c** was obtained in 89% with as a colorless oil (88 mg, 0.435 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.30 – 7.27 (2H, m), 7.25 – 7.19 (3H, m), 5.78 (1H, m), 5.72 (1H, m), 4.06 (1H, m), 3.89 (1H, m), 2.90 (1H, dd, $J = 13.5, 7.0$ Hz), 2.74 (1H, dd, $J = 13.5, 6.0$ Hz), 2.04 – 1.93 (2H, m), 1.56 (1H, m), 1.44 (1H, m), 0.83 (3H, t, $J = 7.5$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 138.88, 129.81, 129.29, 128.16, 126.05, 123.59, 123.59, 74.23, 68.79, 41.91, 30.28, 26.93, 10.18. IR (cm^{-1}): $f = 3030, 2962, 2923, 1454, 1186, 1057, 698$. HRMS-FAB: (M-H) $^{+} = 201.1279$ calculated for $\text{C}_{14}\text{H}_{17}\text{O}$, experimental = 201.1292.

(±)-(2*S*,6*S*)-2-benzyl-3,6-dihydro-6-(prop-1-ynyl)-2*H*-pyran **5.71d**



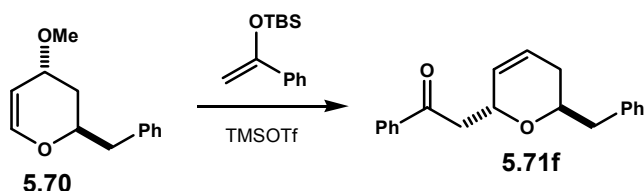
General Procedure F was followed. Dihydropyran **5.70** (100 mg, 0.489 mmol) dissolved in CH₂Cl₂ (10 mL), TMSOTf (0.98 mL, 0.98 mmol, 1.0 M in CH₂Cl₂), and tributyl(prop-1-ynyl)stannane (483 mg, 1.47 mmol) were employed. ¹H NMR of the crude reaction mixture indicated a diastereomeric ratio of >20:1, and after chromatography, dihydropyran **5.71d** was obtained in 96% with as a colorless oil (100 mg, 0.471 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.32 – 7.20 (5H, m), 5.80 (1H, dddd, J = 10.0, 5.5, 2.0, 2.0 Hz), 5.72 (1H, dddd, J = 10.0, 4.0, 3.0, 1.5 Hz), 4.93 (1H, m), 4.23 (1H, dddd, J = 10.5, 7.0, 7.0, 3.5 Hz), 3.03 (1H, dd, J = 14.0, 6.5 Hz), 2.77 (1H, dd, J = 14.0, 7.0 Hz), 2.03 (1H, ddddd, J = 17.5, 10.0, 2.5, 2.5, 2.0 Hz), 1.89 (1H, m), 1.87 (1H, d, J = 2.0 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 138.01, 129.26, 128.19, 126.80, 126.15, 124.56, 81.92, 77.38, 69.50, 64.18, 41.83, 29.92, 3.65. IR (cm⁻¹): $\tilde{\nu}$ = 3030, 2919, 2280, 2216, 1454, 1275, 1183, 1072, 940, 743, 700. HRMS-FAB: (M-H)⁺ = 211.1123 calculated for C₁₅H₁₅O, experimental = 211.1148.

(±)-(2*S*,6*S*)-2-benzyl-3,6-dihydro-6-(2-methylbut-3-en-2-yl)-2*H*-pyran **5.71e**



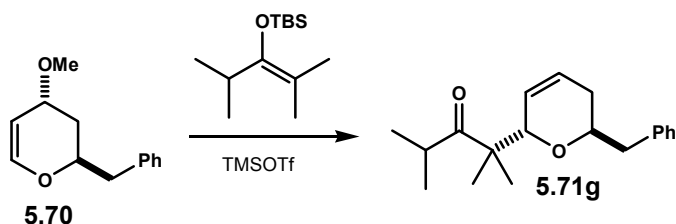
General Procedure F was followed. Dihydropyran **5.70** (100 mg, 0.489 mmol) dissolved in CH₂Cl₂ (10 mL), TMSOTf (0.98 mL, 0.98 mmol, 1.0 M in CH₂Cl₂), and tributyl(3-methylbut-2-enyl)stannane (528 mg, 1.47 mmol) were employed. ¹H NMR of crude reaction mixture indicated a diastereomeric ratio of 10:1, and after chromatography, dihydropyran **5.71e** was obtained in 78% with as a colorless oil (92 mg, 0.380 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.30 – 7.27 (2H, m), 7.23 – 7.19 (3H, m), 5.91 (1H, dddd, *J* = 10.0, 4.0, 3.0, 2.0 Hz), 5.85 (1H, dd, *J* = 17.5, 11.0 Hz), 5.81 (1H, dddd, *J* = 10.5, 2.0, 2.0, 2.0 Hz), 4.96 (1H, dd, *J* = 10.5, 1.5 Hz), 4.91 (1H, dd, *J* = 17.5, 1.5 Hz), 4.10 (1H, dddd, *J* = 6.5, 6.5, 6.5, 4.5 Hz), 3.91 (1H, p, *J* = 2.5 Hz), 2.91 (1H, dd, *J* = 13.0, 7.0 Hz), 2.74 (1H, dd, *J* = 13.5, 6.5 Hz), 2.09 (1H, ddddd, *J* = 17.0, 4.0, 4.0, 2.0, 2.0 Hz), 1.88 (1H, ddddd, *J* = 17.5, 7.0, 3.5, 3.5, 3.5 Hz), 0.97 (3H, s), 0.96 (3H, s). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 145.73 and 145.60 (atropisomer), 139.06, 129.35, 128.14, 126.20 (b), 126.01, 125.08 (b), 111.88, 78.18 and 78.10 (atropisomer), 71.48 and 71.37 (atropisomer), 41.98, 40.77, 29.04, 24.56, 22.44. IR (cm⁻¹): *f* = 3083, 3030, 2963, 2928, 1455, 1190, 1095, 913, 743, 699. HRMS-FAB: (M-H)⁺ = 241.1592 calculated for C₁₇H₂₁O, experimental = 241.1581.

(±)-2-((2*R*,6*S*)-6-benzyl-5,6-dihydro-2*H*-pyran-2-yl)-1-phenylethanone **5.71f**



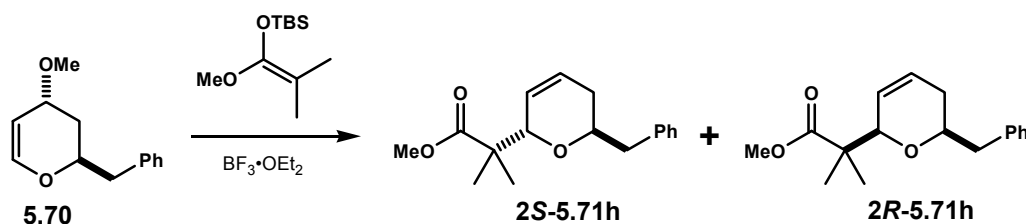
General Procedure F was followed. Dihydropyran **5.70** (100 mg, 0.489 mmol) dissolved in CH₂Cl₂ (10 mL), TMSOTf (1.47 mL, 1.47 mmol, 1.0 M in CH₂Cl₂), and (1-phenylvinyl)oxy(tert-butyl)dimethylsilane (344 mg, 1.47 mmol) were employed. ¹H NMR of the crude reaction mixture indicated a diastereomeric ratio of >20:1, and after chromatography, dihydropyran **5.71f** was obtained in 96% with as a colorless oil (138 mg, 0.471 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.91 – 7.89 (2H, m), 7.56 (1H, m), 7.47 – 7.44 (2H, m), 7.23 – 7.20 (2H, m), 7.17 – 7.13 (3H, m), 5.87- 5.80 (2H, m), 4.94 (1H, m), 3.92 (1H, dddd, J = 11.5, 6.5, 6.5, 4.5 Hz), 3.36 (1H, dd, J= 16.0, 7.5 Hz), 3.03 (1H, dd, J=15.5, 6.0 Hz), 2.87 (1H, dd, J = 14.0, 7.0 Hz), 2.69 (1H, dd, J = 13.5, 6.5 Hz), 2.05 – 1.95 (2H, m). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 198.11, 138.39, 137.15, 133.05, 129.23, 128.81, 128.55, 128.17, 128.15, 126.14, 124.66, 69.70, 69.60, 43.00, 41.63, 29.79. IR (cm⁻¹): ν = 3062, 3030, 2920, 1682, 1598, 1449, 1359, 1275, 1203, 1080, 690. HRMS-FAB: (M+H)⁺ = 293.1542 calculated for C₂₀H₂₁O₂, experimental = 293.1537.

(±)-2-((2*S*,6*S*)-6-benzyl-5,6-dihydro-2*H*-pyran-2-yl)-2,4-dimethylpentan-3-one **5.71g**

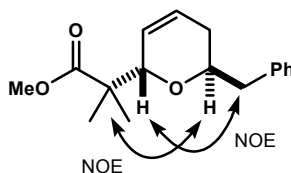


General Procedure F was followed. Dihydropyran **5.70** (100 mg, 0.489 mmol) dissolved in CH₂Cl₂ (10 mL), TMSOTf (1.47 mL, 1.47 mmol, 1.0 M in CH₂Cl₂), and (2,4-dimethylpent-2-en-3-yloxy)(tert-butyl)dimethylsilane (335 mg, 1.47 mmol) were employed. ¹H NMR of crude reaction mixture indicated a diastereomeric ratio of >20:1, and after chromatography, dihydropyran **5.71g** was obtained in 95% with as a colorless oil (133 mg, 0.464 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.29 – 7.26 (2H, m), 7.21 – 7.18 (3H, m), 5.93 (1H, dddd, J = 10.5, 4.0, 4.0, 2.0 Hz), 5.71 (1H, dddd, J = 10.5, 1.5, 1.5, 1.5 Hz), 4.50 (1H, p, J = 2.5 Hz), 4.12 (1H, dddd, J = 7.0, 7.0, 5.0, 5.0 Hz), 3.01 (1H, h, J = 6.5 Hz), 2.94 (1H, dd, J = 14.0, 7.0 Hz), 2.76 (1H, dd, J = 13.5, 7.0 Hz), 2.18 (1H, m), 1.84 (1H, m), 1.11 (3H, s), 1.09 (3H, s), 0.99 (3H, d, J = 6.5 Hz), 0.94 (3H, d, J = 6.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 219.01, 138.73, 129.25, 128.27, 126.13, 125.34, 125.31, 74.61, 71.89, 52.56, 39.70, 34.70, 28.04, 21.12, 20.25, 19.80, 19.52. IR (cm⁻¹): *f* = 3029, 2972, 2934, 2872, 1704, 1470, 1381, 1086, 1032, 700. HRMS-FAB: (M+H)⁺ = 287.2011 calculated for C₁₉H₂₇O₂, experimental = 287.2008.

(±)-methyl 2-((2*S*,6*S*)-6-benzyl-5,6-dihydro-2*H*-pyran-2-yl)-2-methylpropanoate **5.71h**



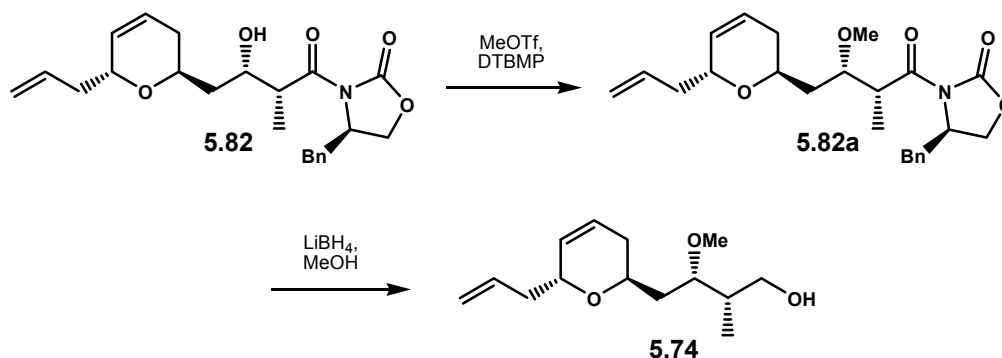
General Procedure F was followed. Dihydropyran **5.70** (100 mg, 0.489 mmol) dissolved in toluene (10 mL), $\text{BF}_3 \cdot \text{OEt}_2$ (1.47 mL, 1.47 mmol, 1.0 M in CH_2Cl_2), and (1-methoxy-2-methylprop-1-enyloxy)(tert-butyl)dimethylsilane (318 mg, 1.47 mmol) were employed. ^1H NMR of crude reaction mixture indicated a diastereomeric ratio of 3.6:1. The two diastereomers were separable by chromatography. The major diastereomer dihydropyran **2S-5.71h** was obtained in 67% with as a colorless oil (90 mg, 0.328 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.30 – 7.27 (2H, m), 7.22 – 7.18 (3H, m), 5.94 (1H, dddd, J = 10.5, 4.0, 4.0, 2.5 Hz), 5.69 (1H, dddd, J = 10.5, 2.0, 2.0, 2.0, 2.0 Hz), 4.41 (1H, p, J = 2.5 Hz), 4.08 (1H, dddd, J = 7.0, 7.0, 5.0, 5.0 Hz), 3.59 (3H, s), 2.95 (1H, dd, J = 13.5, 7.5 Hz), 2.72 (1H, dd, J = 13.5, 6.0 Hz), 2.18 (1H, ddddd, J = 17.0, 4.5, 4.5, 2.0, 2.0 Hz), 1.87 (1H, m), 1.13 (3H, s), 1.12 (3H, s). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 176.92, 138.87, 129.29, 128.17, 126.04, 125.70, 125.08, 75.17, 71.71, 51.77, 47.35, 40.10, 28.61, 21.50, 20.84. IR (cm^{-1}): ν = 3029, 2977, 2947, 1736, 1455, 1263, 1135, 1088, 700. HRMS-FAB: $(\text{M}+\text{H})^+ = 275.1647$ calculated for $\text{C}_{17}\text{H}_{23}\text{O}_3$, experimental = 275.1642. The relative 2,6-*trans* stereochemistry of the ring was deduced from a ROESY experiment.



The minor diastereomer dihydropyran **2R-5.71h** was obtained in 15% yield as a colorless oil (20 mg, 0.0723 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.28 – 7.25 (2H, m), 7.22 – 7.17 (3H, m), 5.88 (1H, dddd, J = 10.5, 6.0, 2.0, 2.0 Hz), 5.58 (1H, dddd, J = 10.5, 1.5, 1.5, 3.0 Hz), 4.30 (1H, m), 3.74 (1H, dddd, J = 10.5, 7.5, 4.5, 3.0 Hz), 3.59 (3H, s), 2.83 (1H, dd, J = 14.0, 8.0 Hz), 2.70 (1H, dd, J = 14.0, 4.5 Hz), 2.01 (1H, m), 1.90 (1H, m), 1.16 (3H, s), 1.13 (3H, s). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 177.05, 138.89, 129.47, 127.96, 126.79, 126.03, 125.94, 79.16, 74.36, 51.69, 46.45, 42.21, 30.79, 20.87, 19.79. IR (cm^{-1}): ν = 3031, 2979, 2948, 2849, 1739, 1469, 1263, 1189, 1135, 1083, 700. HRMS-FAB: $(\text{M}+\text{H})^+ = 275.1647$ calculated for $\text{C}_{17}\text{H}_{23}\text{O}_3$, experimental = 275.1629.

(-)-(2S,3S)-4-((2S,6R)-6-allyl-3,6-dihydro-2H-pyran-2-yl)-3-methoxy-2-methylbutan-1-ol

5.74



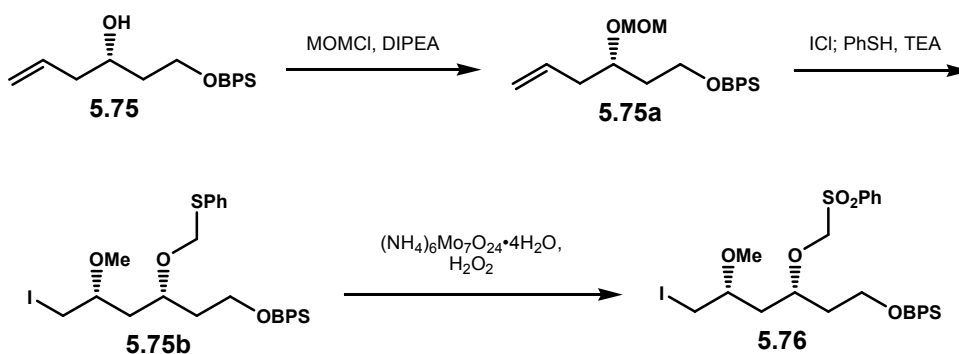
Aldol product **5.82** (847 mg, 2.12 mmol) was dissolved in CH₂Cl₂ (50 mL). 2,6-di-*tert*-butyl-4-methylpyridine (4.35 g, 21.1 mmol) and MeOTf (2.40 mL, 21.2 mmol) were sequentially added, and the reaction mixture was gently refluxed for 36 hours. After cooling to 0°C, the reaction was quenched with careful addition of MeOH (10 mL) followed by a saturated aqueous solution of NaHCO₃ (50 mL). After separation of layers, the aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated under vacuum. The crude oil was chromatographed in a silica gel column with 80:20 hexanes : EtOAc to give title product **5.82a** in 74% yield (649 mg, 1.57 mmol) as a clear oil. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.34 – 7.31 (2H, m), 7.27 (1H, m), 7.22 – 7.20 (2H, m), 5.87 – 5.79 (2H, m), 5.72 (1H, dddd, J = 10.5, 3.0, 3.0, 1.5 Hz), 5.09 (1H, dddd, J = 17.0, 1.5, 1.5, 1.5 Hz), 5.04 (1H, dddd, J = 10.5, 2.5, 1.5, 1.5 Hz), 4.65 (1H, dddd, J = 9.5, 6.5, 3.0, 3.0 Hz), 4.19 – 4.14 (3H, m), 4.07 (1H, dq, J = 7.0, 1.0 Hz), 3.85 (1H, m), 3.56 (1H, ddd, J = 6.5, 6.5, 4.5 Hz), 3.37 (3H, s), 3.27 (1H, dd, J = 13.0, 3.0 Hz), 2.77 (1H, dd, J = 13.0, 9.5 Hz),

2.45 (1H, m), 2.29 (1H, m), 2.04 (1H, m), 1.94 (1H, dddd, $J = 17.0, 9.0, 3.0, 3.0, 3.0$ Hz), 1.82 (1H, ddd, $J = 14.5, 7.0, 7.0$ Hz), 1.72 (1H, ddd, $J = 14.5, 5.5, 4.5$ Hz), 1.27 (1H, d, $J = 7.0$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 175.37, 153.00, 135.28, 135.05, 129.42, 129.12, 128.88, 127.28, 123.95, 116.72, 79.59, 72.44, 66.01, 64.84, 57.58, 55.56, 41.15, 38.81, 37.77, 37.14, 30.59, 13.31. IR (cm^{-1}): $\nu = 3030, 2976, 2928, 2827, 1782, 1695, 1382, 1350, 1211, 1198, 1105, 704$. HRMS-FAB: $(\text{M}+\text{H})^+ = 414.22280$ calculated for $\text{C}_{24}\text{H}_{32}\text{O}_5\text{N}$, experimental = 414.2258. $[\alpha]_{\text{D}}^{20} = -130^\circ$ ($c = 1.93$ in CHCl_3).

Compound **5.82a** (180 mg, 0.435 mmol) was dissolved in Et_2O (10 mL) and cooled to -78°C . In a separate flask, MeOH (0.35 mL, 8.70 mmol) and a solution of LiBH_4 (1.09 mL, 2.18 mmol, 2.0 M in THF) was sequentially added to Et_2O (10 mL) at 0°C , stirred for 5 minutes, and transferred to the solution of **5.82a** via cannula. The reaction mixture was warmed slowly to 0°C . After stirring for one hour, an aqueous solution of 2 M NaOH (20 mL) was cautiously added dropwise, and the resulting mixture was stirred vigorously for 10 minutes. After separation of layers, the aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over MgSO_4 , filtered, and concentrated under vacuum. The crude material was then purified in a silica gel column chromatography with 70:30 hexanes : EtOAc to give alcohol **5.74** in 78% yield (82 mg, 0.341 mmol) as a clear oil. ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 5.89 – 5.81 (2H, m), 5.72 (1H, dddd, $J = 10.0, 2.5, 2.5, 1.0$ Hz), 5.09 (1H, m), 5.07 (1H, m), 4.24 (1H, m), 3.75 (1H, h, $J = 4.5$ Hz), 3.68 – 3.62 (2H, m), 3.52 (1H, ddd, $J = 6.5, 6.5, 3.5$ Hz), 3.36 (3H, s), 2.73 (1H, b), 2.39 (1H, m), 2.26 (1H, m), 2.04 – 1.93 (3H, m), 1.90 (1H, ddd, $J = 14.5, 8.5, 6.0$ Hz), 1.59 (1H, ddd, $J = 14.5, 7.5$ Hz), 0.89 (3H, d, $J = 7.0$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 135.08, 129.11, 124.08, 116.84, 81.30,

72.43, 66.65, 64.92, 57.02, 38.67, 36.32, 35.37, 30.78, 11.14. IR (cm⁻¹): ν = 3437, 3034, 2925, 1462, 1434, 1393, 1184, 1087, 1026, 914, 708. HRMS-FAB: (M+H)⁺ = 241.1804 calculated for C₁₄H₂₅O₃, experimental = 241.1818. $[\alpha]_D^{20}$ = -86.1° (c = 3.80 in CHCl₃).

(-)-((3*S*,5*R*)-3-((phenylsulfonyl)methoxy)-6-iodo-5-methoxyhexyl)(*tert*-butyl)diphenylsilane **5.76**



Homoallylic alcohol **5.75** (11.9 g, 33.5 mmol, >95% ee) was dissolved in CH₂Cl₂ (100 mL), and DIPEA was then added (17.5 mL, 100 mmol). After cooling the mixture to 0°C, MOMCl (25.1 mL, 50.2 mmol, 2.0 M in toluene) was added dropwise. The reaction was warmed to room temperature and stirred overnight. The reaction was then diluted with CH₂Cl₂ (100 mL) and washed subsequently with aqueous solutions of 2 M HCl (100 mL) and then saturated NaHCO₃ (100 mL). The organic layer was then dried over MgSO₄ and filtered. A yellow oil was obtained upon removal of CH₂Cl₂ under vacuum. The crude material was purified with column chromatography using 90:10 hexanes : EtOAc to give the title product **5.75a** in 96% as a colorless oil (12.8 g, 32.1 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.68 – 7.64 (4H, m), 7.45 – 7.36 (6H,

m), 5.81 (1H, m), 5.09 – 5.05 (2H, m), 4.64 (1H, d, $J = 7.0$ Hz), 4.63 (1H, d, $J = 7.0$ Hz), 3.86 (1H, dddd, $J = 7.5, 5.5, 5.5, 5.5$ Hz), 3.78 (1H, ddd, $J = 10.5, 8.0, 6.0$ Hz), 3.74 (1H, ddd, $J = 10.5, 6.5, 5.5$ Hz), 3.32 (3H, s), 2.36 – 2.26 (2H, m), 1.81 – 1.69 (2H, m), 1.05 (9H, s). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 135.54, 134.62, 133.82, 129.56, 127.61, 117.19, 95.68, 74.00, 60.42, 55.46, 39.23, 37.11, 26.82, 19.16. IR (cm^{-1}): $\nu = 3072, 2931, 2987, 2858, 1428, 1112, 1040, 702$. HRMS-FAB: $(\text{M}+\text{H})^+ = 399.2355$ calculated for $\text{C}_{24}\text{H}_{35}\text{O}_3\text{Si}$, experimental = 399.2359. $[\alpha]_{\text{D}}^{20} = +6.87^\circ$ ($c = 7.13$ in CHCl_3).

Compound **5.75a** (12.8 g, 32.1 mmol) was dissolved in toluene (500 mL), and 12.8 grams of 4 Å molecular sieves were then added. After cooling this solution to -78°C , iodine monochloride (38.5 mL, 38.5 mmol, 1.0 M in CH_2Cl_2) was added dropwise while maintaining an internal temperature of the reaction below -75°C . The solution became dark red and was stirred for 30 minutes. Then, TEA (13.4 mL, 96.3 mmol) was added in one injection, followed by PhSH (4.61 mL, 44.9 mmol) in which the solution immediately turned cloudy grey. The reaction was warmed to room temperature over one hour and then quenched with a 1:1 mixture of saturated NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$ (300 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et_2O (2 x 100 mL). The organic layers were then combined, dried over MgSO_4 , and filtered. The organic solvent was removed under vacuum leaving behind a yellow oil. The crude material was purified with column chromatography using 98:2 \rightarrow 80:20 hexanes : EtOAc to give ether transfer product **5.75b** in 84% yield with a diastereomeric ratio of 22:1 as a colorless oil (17.1 g, 27.0 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.67 – 7.64 (4H, m), 7.45 – 7.35 (8H, m), 7.27 – 7.24 (2H, m), 7.18 (1H, tt, $J = 7.5, 1.5$ Hz), 5.10

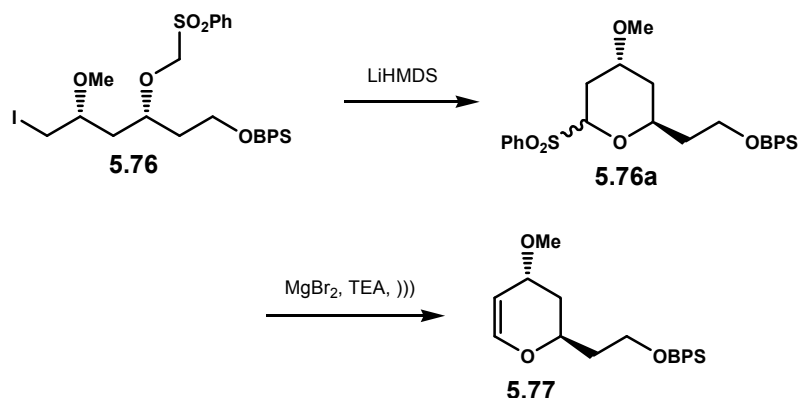
(1H, d, $J = 12.0$ Hz), 4.91 (1H, d, $J = 12.0$ Hz), 3.99 (1H, p, $J = 5.5$ Hz), 3.76 (1H, ddd, $J = 10.5, 6.5, 6.5$ Hz), 3.72 (1H, ddd, $J = 10.5, 6.0, 6.0$ Hz), 3.29 (1H, dd, $J = 10.5, 4.0$ Hz), 3.26 (1H, dd, $J = 10.5, 4.0$ Hz), 3.22 (3H, s), 2.94 (1H, dddd, $J = 6.0, 6.0, 4.0, 4.0$ Hz), 1.82 – 1.68 (4H, m), 1.06 (9H, s). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 136.03, 135.55, 135.54, 133.67, 133.65, 129.65, 129.63, 128.93, 128.86, 127.68, 127.67, 126.20, 75.83, 72.87, 71.11, 60.12, 56.53, 38.86, 36.76, 26.87, 19.15, 10.67. IR (cm^{-1}): $\nu = 3070, 2930, 2857, 1428, 1111, 1088, 1051, 738, 702$. HRMS-FAB: $(\text{M-SPh})^+ = 525.1322$ calculated for $\text{C}_{24}\text{H}_{34}\text{O}_3\text{SiI}$, experimental = 525.1302. $[\alpha]_{\text{D}}^{20} = -35.7^\circ$ ($c = 9.90$ in CHCl_3).

Compound **5.75b** (16.9 g, 26.6 mmol) was dissolved in ethanol (660 mL, 200 proof), and the solution was cooled to 0°C . In a separate flask, ammonium (VI) molybdate tetrahydrate (6.64 g, 5.32 mmol) was dissolved in a cold aqueous hydrogen peroxide solution (30%, 330 mL). This $\text{Mo(VI)} - \text{H}_2\text{O}_2$ mixture was immediately poured to the solution of **5.75b** in one portion causing the reaction to turn yellow and cloudy (the cloudiness eventually dissipated). The reaction was stirred at 0°C for one hour and then at room temperature for two more hours. Addition of DI water (400 mL) quenched the reaction, and the aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL). The pink organic layers were combined, dried over MgSO_4 , filtered, and rotovaped to produce a dark red oily residue. The crude material was then loaded onto silica gel and chromatographed with 90:10 \rightarrow 80:20 hexanes : EtOAc to afford the corresponding sulfone **5.76** in 83% yield as a yellow oil (14.8 g, 22.2 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.88 – 7.86 (2H, m), 7.66 – 7.61 (5H, m), 7.52 – 7.49 (2H, m), 7.46 – 7.37 (6H, m), 4.53 (2H, s), 4.02 (1H, p, $J = 6.0$ Hz), 3.72 – 3.64 (2H, m), 3.29 (1H, dd, J

= 11.0, 5.5 Hz), 3.27 (3H, s), 3.24 (1H, dd, J = 10.5, 3.5 Hz), 3.03 (1H, dddd, J = 6.5, 5.5, 5.5, 4.0 Hz), 1.80 – 1.70 (4H, m), 1.05 (9H, s). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 137.38, 135.51, 135.50, 133.93, 133.47, 133.42, 129.74, 129.72, 129.13, 128.70, 127.72, 127.70, 84.13, 77.25, 75.83, 59.82, 56.56, 38.90, 36.77, 26.84, 19.09, 9.93. IR (cm^{-1}): ν = 3070, 2930, 2857, 1738, 1588, 1428, 1325, 1299, 1151, 1112, 1080, 743, 703. HRMS-FAB: $(\text{M}+\text{H})^+ = 667.1411$ calculated for $\text{C}_{30}\text{H}_{40}\text{O}_5\text{SSiI}$, experimental = 667.1401. $[\alpha]_D^{20} = -2.58^\circ$ ($c = 9.70$ in CHCl_3).

(+)-(2-((2R,4R)-3,4-dihydro-4-methoxy-2H-pyran-2-yl)ethoxy)(tert-butyl)diphenylsilane

5.77



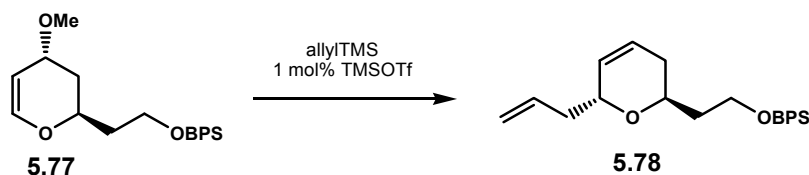
HMDS (7.07 mL, 33.3 mmol) was dissolved in THF (100 mL) and cooled to -78°C . A solution of *n*-BuLi (14.5 mL, 33.3 mmol, 2.3 M in hexanes) was then added dropwise rapidly, and the solution was stirred for 10 minutes prior to the addition of HMPA (11.6 mL, 66.6 mmol). This LiHMDS solution was further stirred for 10 minutes. In a separate flask, sulfone **5.76** (14.8 g, 22.2 mmol) was dissolved in THF (500mL), and

the solution was cooled to -78°C . The freshly prepared, cold LiHMDS solution was then added to this solution via cannula dropwise over 30 minutes. The reaction was further stirred for 2 hours, and then quenched with a half-saturated aqueous NH_4Cl solution (200 mL). After separating the organic and aqueous layers, the aqueous layer was washed with Et_2O (2 x 100 mL). The organic layers were then combined, dried over MgSO_4 , filtered, and concentrated under vacuum leaving behind a yellow oil. The crude material was flushed through a thick silica pad with 70:30 hexanes : EtOAc. The solvent was then evaporated to leave a mixture of diastereomers **5.76a** as a yellow oil (11.7 g).

Sulfonylpyran **5.76a** (11.7 g) as a mixture of diastereomers was dissolved in THF (300 mL). Upon addition of TEA (30.2 mL, 217 mmol) and $\text{MgBr}_2\cdot\text{OEt}_2$ (16.8 g, 65.1 mmol), the suspension mixture was agitated in an ultrasound bath at 50°C until the starting material was completely consumed. The reaction was cooled to room temperature and quenched with a saturated aqueous NaHCO_3 solution (300 mL). After separation of organic and aqueous layers, the aqueous solution was extracted with Et_2O (2 x 100 mL). The organic layers were combined, dried over MgSO_4 , filtered, and concentrated under vacuum. The crude material was flushed through a thick silica pad with 95:5 hexanes : EtOAc, and after concentration, dihydropyran **5.77** was produced in 74% yield (6.52 g, 16.4 mmol) over two steps as a yellow oil. ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.69 – 7.66 (4H, m), 7.44 – 7.36 (6H, m), 6.48 (1H, d, J = 6.5 Hz), 4.96 (1H, ddd, J = 6.0, 5.5, 2.0 Hz), 4.09 (1H, dddd, J = 12.0, 7.0, 5.0, 2.0 Hz), 3.86 – 3.78 (2H, m), 3.63 (1H, m), 3.33 (3H, s), 1.98 (1H, dddd, J = 14.0, 2.0, 2.0, 2.0 Hz), 1.94 – 1.80 (2H, m), 1.55 (1H, ddd, J = 14.0, 12.0, 4.0 Hz), 1.05 (9H, s). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 147.11, 135.57, 135.55, 133.86, 133.76, 129.54 (2C), 127.61, 127.60,

100.07, 68.87, 68.35, 60.23, 55.07, 37.99, 26.82, 19.17. IR (cm⁻¹): ν = 3071, 2930, 2858, 2817, 1639, 1428, 1246, 1094, 702. HRMS-FAB: (M-H)⁺ = 395.2042 calculated for C₂₄H₃₁O₃Si, experimental = 395.2068. $[\alpha]_D^{20}$ = +67.3° (c = 3.13 in CHCl₃).

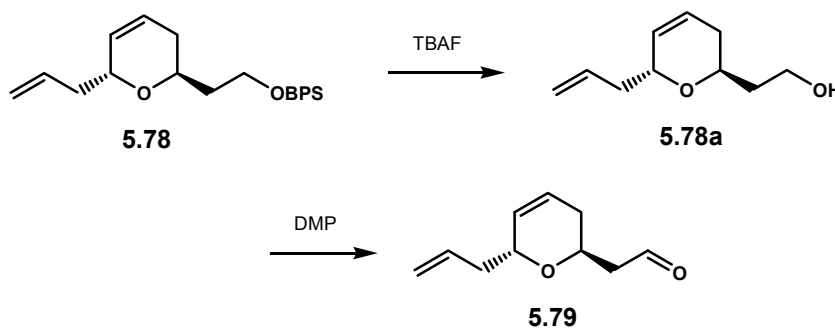
(-)-(2-((2S,6R)-6-allyl-3,6-dihydro-2H-pyran-2-yl)ethoxy)(tert-butyl)diphenylsilane **5.78**



Dihydropyran **5.77** was dissolved in CH₂Cl₂ (300 mL), and the solution was cooled to -78°C. Upon addition of allyltrimethylsilane (7.53 mL, 47.4 mmol), a freshly prepared solution of TMSOTf (0.16 mL, 1.0 M in CH₂Cl₂) was added dropwise. The reaction mixture was stirred for two hours, warmed to 0°C, and then poured into an extraction funnel containing phosphate buffer (pH 7.00, 200 mL). After separation of layers, the aqueous layer was washed with CH₂Cl₂ (2 x 100 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated under vacuum leaving behind a yellow oil. The crude oil was then loaded into a silica gel column and chromatographed using 95:5 hexanes : EtOAc. After concentration, title product **5.78** was obtained in 99% yield (6.39 g, 15.7 mmol) with a diastereomeric ratio of >20:1 as a clear oil. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.69 – 7.65 (4H, m), 7.44 – 7.36 (6H, m), 5.87 – 5.79 (2H, m), 5.71 (1H, m), 5.06 (1H, m), 5.02 (1H, m), 4.15 (1H, m), 3.96 (1H, h, J = 4.0 Hz), 3.85 (1H, ddd, J = 10.0, 7.5, 5.5 Hz), 3.76 (1H, ddd, J = 10.5, 5.5, 5.5

Hz), 2.40 (1H, m), 2.24 (1H, m), 2.01 (1H, m), 1.92 (1H, ddddd, $J = 17.0, 8.0, 3.0, 3.0, 3.0$ Hz), 1.81 (1H, dddd, $J = 13.5, 8.0, 5.5, 5.5$ Hz), 1.72 (1H, dddd, $J = 14.0, 8.0, 6.5, 4.5$ Hz), 1.06 (9H, s). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 135.57, 135.55, 135.13, 134.02, 133.99, 129.53 (2C), 129.21, 127.60 (2C), 124.37, 116.71, 72.11, 64.71, 60.54, 38.85, 38.23, 30.62, 26.87, 19.19. IR (cm^{-1}): $\nu = 3072, 3033, 2931, 2858, 1642, 1472, 1428, 1112, 1084, 702$. HRMS-FAB: $(\text{M}-\text{H})^+ = 405.2250$ calculated for $\text{C}_{26}\text{H}_{33}\text{O}_2\text{Si}$, experimental = 405.2250. $[\alpha]_{\text{D}}^{20} = -43.9^\circ$ ($c = 3.55$ in CHCl_3).

(-)-2-((2S,6R)-6-allyl-3,6-dihydro-2H-pyran-2-yl)acetaldehyde **5.79**



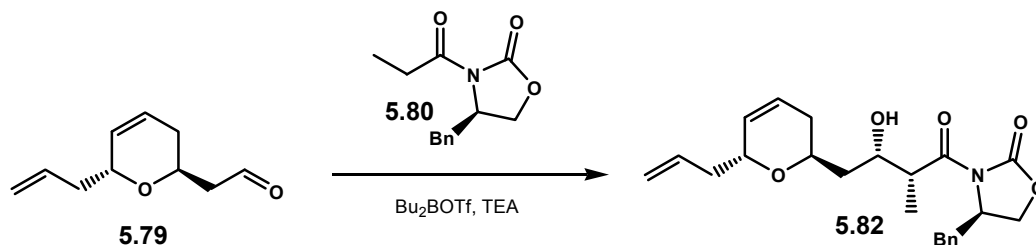
Dihydropyran **5.78** (2.00 g, 4.92 mmol) was dissolved in THF (50 mL), and the solution was cooled to 0°C . A solution of tetrabutylammonium fluoride (9.84 mL, 9.84 mmol, 1.0 M in THF) was then added dropwise. The reaction was warmed to room temperature, stirred until starting material was fully consumed, poured into an extraction funnel, and washed with a half-saturated aqueous solution of NH_4Cl (100 mL). After separation of layers, the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under

vacuum. The residual yellow oil was chromatographed on silica gel using 70:30 hexanes : EtOAc to give alcohol **5.78a** as a clear oil in 97% yield (800 mg, 4.76 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 5.89 – 5.80 (2H, m), 5.70 (1H, dddd, J = 10.5, 3.0, 3.0, 1.5 Hz), 5.13 (1H, dddd, J = 17.0, 1.5, 1.5, 1.5 Hz), 5.10 (1H, m), 4.25 (1H, m), 3.91 (1H, dddd, J = 9.5, 9.5, 3.5, 3.5 Hz), 3.77 (2H, b), 2.73 (1H, b), 2.44 (1H, m), 2.28 (1H, ddddd, J = 14.5, 6.5, 5.5, 1.5, 1.5 Hz), 2.03 (1H, ddddd, J = 17.5, 9.5, 2.5, 2.5, 2.5 Hz), 1.95 (1H, ddddd, J = 17.0, 5.0, 3.5, 1.0, 1.0 Hz), 1.82 – 1.69 (2H, m). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 134.98, 128.78, 124.18, 117.20, 72.38, 67.91, 61.34, 38.66, 37.36, 30.71. IR (cm^{-1}): ν = 3399, 3076, 3033, 2917, 1431, 1077, 1057, 914, 708. HRMS-FAB: $(\text{M}+\text{H})^+ = 169.1229$ calculated for $\text{C}_{10}\text{H}_{17}\text{O}_2$, experimental = 169.1226. $[\alpha]_{\text{D}}^{20} = -181^\circ$ (c = 1.55 in CHCl_3).

Alcohol **5.78a** (780 mg, 4.64 mmol) was dissolved in CH_2Cl_2 (50 mL). Solid sodium bicarbonate (3.90 g, 46.4 mmol) was then added, and the suspension was cooled to 0°C . After dropwise addition of a Dess-Martin periodinane solution (26.2 mL, 9.28 mmol, 15% w/v in CH_2Cl_2), the mixture was allowed to warm up to room temperature and stirred until starting material has been completely oxidized. The reaction was quenched with slow addition of a saturated aqueous NaHCO_3 solution (100 mL) until no more gas was evolved. After separation of layers, the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The organic layers were combined, dried over MgSO_4 , filtered, and concentrated under vacuum. The crude oil was then loaded into a column containing silica gel and eluted using 90:10 hexanes : EtOAc to produce aldehyde **5.79** in 93% yield (721 mg, 4.34 mmol) as a yellow oil. ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 9.80 (1H, dd, J = 3.0, 2.0 Hz), 5.87 – 5.78 (2H, m), 5.73 (1H, dddd, J = 10.5, 3.0, 3.0, 1.5 Hz), 5.09

(1H, m), 5.06 (1H, m), 4.28 (1H, h, $J = 4.0$ Hz), 4.21 (1H, m), 2.65 (1H, ddd, $J = 16.5$, 9.0, 3.0 Hz), 2.50 (1H, ddd, $J = 16.0$, 4.0, 1.5 Hz), 2.42 (1H, ddd, $J = 14.0$, 8.0, 6.5, 1.0, 1.0 Hz), 2.28 (1H, ddd, $J = 13.0$, 7.0, 6.0, 1.0, 1.0 Hz), 2.09 (1H, ddd, $J = 17.0$, 5.0, 3.5, 1.5, 1.5 Hz), 1.99 (1H, ddd, $J = 16.5$, 9.0, 2.5, 2.5, 2.5 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 201.31, 134.72, 129.10, 123.55, 117.10, 72.34, 63.41, 48.77, 38.70, 30.06. IR (cm^{-1}): $\nu = 3076, 3035, 2898, 2833, 2729, 1727, 1392, 1079, 917, 710$. HRMS-FAB: $(\text{M}+\text{H})^+ = 167.1072$ calculated for $\text{C}_{10}\text{H}_{15}\text{O}_2$, experimental = 167.1062. $[\alpha]_{\text{D}}^{20} = -143^\circ$ ($c = 2.27$ in CHCl_3).

(-)-Aldol Product 5.82



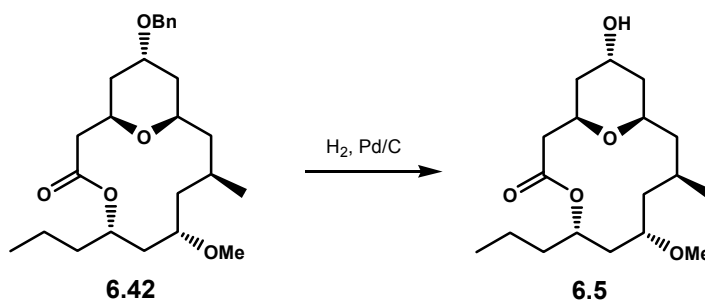
Oxazolidinone **5.80** (1.92 g, 8.22 mmol) was charged into a flask containing 2 grams of 4 Å molecular sieves. CH_2Cl_2 (10 mL) was then added to dissolve the solid, and the resulting solution was then transferred to a reaction flask via cannula. The molecular sieves were rinsed with CH_2Cl_2 (4 x 5 mL) to ensure that oxazolidinone **5.80** was completely transferred to the reaction flask. After cooling the solution to -78°C , a solution of Bu_2BOTf (8.63 mL, 8.63 mmol, 1.0 M in CH_2Cl_2) was added dropwise over 10 minutes followed by TEA (1.43 mL, 10.3 mmol). The mixture was stirred for 45

minutes at -78°C, warmed to 0°C for 15 minutes, and then re-cooled to -78°C. In the meantime, in a separate flask containing aldehyde **5.79** (683 mg, 4.11 mmol) and 1 gram of 4 Å molecular sieves, CH₂Cl₂ (5 mL) was added. The solution was cooled to -78°C and then transferred via cannula to the reaction flask containing a solution of the boron enolate of **5.80**. The flask was rinsed with CH₂Cl₂ (3 x 3 mL) to ensure that aldehyde **5.79** was completely transferred. The reaction mixture was allowed to warm up to -5°C over 2 hours and stirred for 12 hours at this temperature. Phosphate buffer (pH 7.00, 50 mL) was then added in one portion, and the mixture was stirred vigorously. A H₂O₂ solution (30% in H₂O) was added dropwise until no sharp increase in the internal temperature was observed. The internal temperature was crucially maintained around 0°C during this process. The organic layer was then separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). After combining the organic layers, the solvent was removed under vacuum after subsequent drying over MgSO₄ and filtration. The crude material was loaded into a silica gel column, and aldol product **5.82** was eluted with 80:20 → 60:40 hexanes : EtOAc to give a clear thick oil in 82% yield (1.35 g, 3.38 mmol) as a single diastereomer. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.34 – 7.31 (2H, m), 7.27 (1H, m), 7.22 – 7.20 (2H, m), 5.87 – 5.79 (2H, m), 5.70 (1H, dddd, J = 10.0, 2.5, 2.0, 2.0 Hz), 5.12 (1H, dddd, J = 17.0, 1.5, 1.5, 1.5 Hz), 5.08 (1H, dddd, J = 10.0, 2.0, 1.0, 1.0 Hz), 4.69 (1H, dddd, J = 10.0, 7.0, 3.0, 3.0 Hz), 4.25 (1H, m), 4.21 – 4.13 (3H, m), 3.94 (1H, m), 3.85 (1H, dq, J = 7.0, 5.0 Hz), 3.79 (1H, d, J = 0.5 Hz), 3.29 (1H, dd, J = 13.5, 3.5, Hz), 2.77 (1H, dd, J = 13.5, 9.5 Hz), 2.43 (1H, m), 2.29 (1H, m), 2.01 – 1.98 (2H, m), 1.75 (1H, ddd, J = 14.0, 9.5, 9.5 Hz), 1.66 (1H, ddd, J = 14.5, 3.0, 3.0 Hz), 1.27 (3H, d, J = 7.0 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 175.62, 153.10, 135.22,

134.59, 129.36, 128.86, 128.54, 127.26, 123.89, 117.28, 72.51, 71.79, 68.35, 66.03, 55.44, 42.86, 39.22, 38.65, 37.70, 30.77, 11.40. IR (cm⁻¹): ν = 3498, 3066, 3031, 2978, 2918, 1781, 1695, 1386, 1211, 1076, 972, 705. HRMS-FAB: (M+H)⁺ = 400.2124 calculated for C₂₃H₃₀O₅N, experimental = 400.2105. $[\alpha]_D^{20}$ = -117° (c = 3.95 in CHCl₃).

8.5. Experimental Procedures for Chapter Six

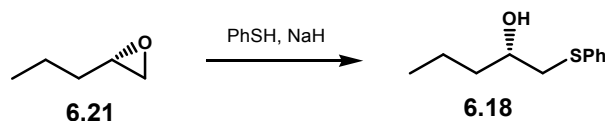
(+)-Neopeltolide Macrolactone **6.5**



Macrolide **6.42** (100 mg, 0.239 mmol) was dissolved in EtOAc (50 mL), and 10% Pd/C (26 mg, 0.024 mmol) was then added. The solution was then bubbled with nitrogen gas for 10 minutes followed by hydrogen gas for 30 minutes at which all starting material was completely consumed. Nitrogen gas was then reintroduced to the system for 5 minutes, and the solution was then filtered over celite. Removal of solvent yielded neopeltolide macrolactone **6.5** in 99% yield as a clear oil (78 mg, 0.238 mmol). ¹H NMR (600 MHz, CDCl₃): δ (ppm) = 5.17 (1H, dddd, J = 9.6, 9.6, 4.8, 0.6 Hz, C13-H), 4.22 (1H, b, C5-H), 4.17 (1H, dddd, J = 11.4, 11.4, 4.8, 2.4 Hz, C3-H), 3.66 (1H, ddd, J = 11.4, 9.0, 2.4 Hz, C7-H), 3.58 (1H, dddd, J = 10.8, 9.6, 2.4, 1.2 Hz, C11-H), 3.29 (3H, s,

C11– OME), 2.56 (1H, dd, $J = 14.4, 4.2$ Hz, C2–**H_a**), 2.32 (1H, dd, $J = 15.0, 11.4$ Hz, C2–**H_b**), 1.86 (1H, b, C5O–**H**), 1.83 (1H, ddd, $J = 15.0, 10.8, 1.8$ Hz, C12–**H_a**), 1.69 – 1.62 (2H, m, C6–**H_{eq}**, C4–**H_{eq}**), 1.55 (1H, ddd, $J = 13.2, 11.4, 2.4$ Hz, C10–**H_a**), 1.55 – 1.44 (5H, m, C4–**H_{ax}**, C6–**H_{ax}**, C9–**H**, C14–**H_a**, C14–**H_b**), 1.39 (1H, ddd, $J = 15.0, 9.0, 5.4$ Hz, C8–**H_a**), 1.37 – 1.29 (3H, m, C12–**H_b**, C15–**H₂**), 1.21 (1H, dd, $J = 15.6, 1.8$ Hz, C8–**H_b**), 1.12 (1H, ddd, $J = 13.2, 10.8, 2.4$ Hz, C10–**H_b**), 0.95 (3H, d, $J = 7.2$ Hz, C9–**CH₃**), 0.89 (3H, t, $J = 7.8$ Hz, C16–**H₃**). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 171.11, 75.59, 74.85, 72.74, 69.09, 64.74, 56.15, 44.12, 42.43, 42.27, 40.09, 39.32, 38.21, 36.89, 31.37, 25.65, 18.87, 13.86. IR (cm^{-1}): $\nu = 3436, 2917, 1732, 1462, 1385, 1277, 1080, 986$. HRMS-FAB: $(\text{M}+\text{H})^+ = 329.2328$ calculated for $\text{C}_{18}\text{H}_{33}\text{O}_5$, experimental = 329.2325. $[\alpha]_{\text{D}}^{20} = +30.0^\circ$ ($c = 1.13$ in CHCl_3).

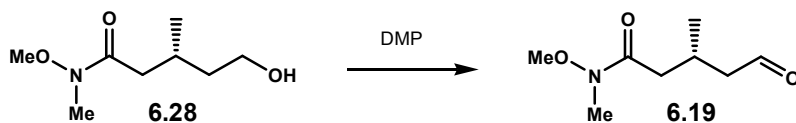
(+)-(S)-1-(phenylthio)pentan-2-ol **6.18**



NaH (2.31 g, 96.4 mmol) was suspended in THF (200 mL) and cooled to 0°C . PhSH (7.62 mL, 74.2 mmol) was then carefully added dropwise and stirred for 30 minutes. After dropwise addition of epoxide **6.21** (10 mL, 96.4 mmol), the reaction mixture was allowed to warm to room temperature and stirred for 4 hours. Upon recooling to 0°C , the reaction was carefully quenched with MeOH until no more gas evolution was observed. The mixture was poured into a separatory funnel containing a

half-saturated NH_4Cl solution (200 mL). The layers were separated, and the aqueous layer was washed with Et_2O (2 x 100 mL). The organic layers were then combined, dried over MgSO_4 , filtered, and concentrated under vacuum to provide β -hydroxysulfide **6.18** in 95% yield as a yellow oil (13.8 g, 70.3 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.40 – 7.37 (2H, m), 7.31 – 7.27 (2H, tt, J = 7.0, 1.5 Hz), 7.21 (1H, tt, J = 7.5, 1.0 Hz), 3.68 (1H, m), 3.15 (1H, dd, J = 13.5, 3.5 Hz), 2.84 (1H, dd, J = 13.5, 9.0 Hz), 2.42 (1H, d, J = 3.5 Hz), 1.56 – 1.43 (3H, m), 1.42 – 1.33 (1H, m), 0.91 (3H, t, J = 7.0). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 135.56, 130.26, 129.31, 126.83, 69.33, 42.50, 38.50, 19.18, 14.31. IR (cm^{-1}): ν = 3401, 3059, 2958, 2930, 2872, 1584, 1480, 1438, 1025, 738, 690. HRMS-FAB: M^+ = 196.0922 calculated for $\text{C}_{19}\text{H}_{30}\text{O}_4\text{N}$, experimental = 196.0931. $[\alpha]_D^{20}$ = +45.8° (c = 4.47 in CHCl_3).

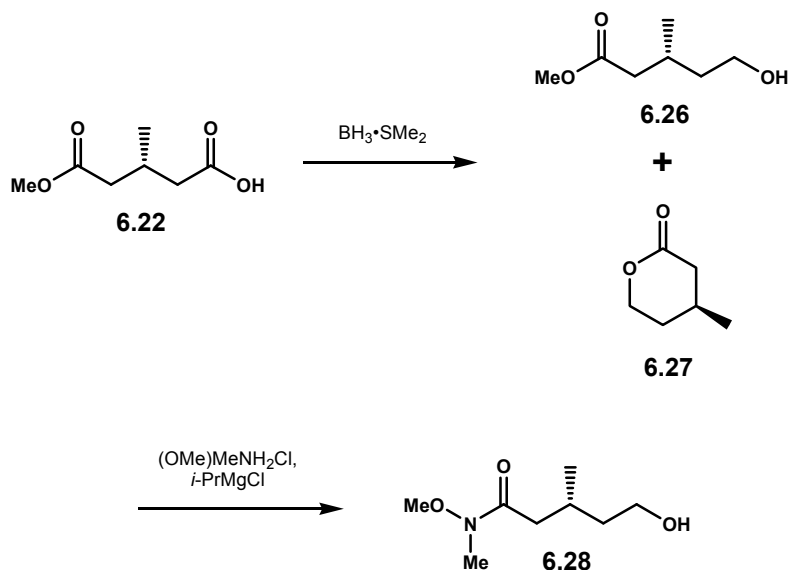
(-)-(R)-3-(formylmethyl)-N-methoxy-N-methylbutanamide **6.19**



Alcohol **6.28** (10.3 g, 58.9 mmol) was dissolved in CH_2Cl_2 (300 mL) in a round-bottomed flask, and the flask was then placed in a water bath at room temperature. NaHCO_3 (24.7 g, 295 mmol) was then added followed by the Dess-Martin reagent (30.0 g, 70.7 mmol) in three 10-gram portions over 15 minutes. After stirring the suspension for one hour, the reaction was very carefully quenched with the slow addition of a saturated aqueous solution of NaHCO_3 until no more gas evolution was observed. After

separation of layers, the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were then combined, dried over MgSO_4 , filtered, and concentrated under vacuum to give a white solid, which was then taken up in hexanes (100 mL). The white residue was filtered over celite and washed with hexanes (2 x 50 mL). Removal of solvent under vacuum then afforded aldehyde **6.19** in 99% yield as a yellow oil (10.1 g, 58.3 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 9.71 (1H, m), 3.64 (3H, s), 3.14 (3H, s), 2.60 (1H, o, $J = 7.0$ Hz), atropisomers 2.51 and 2.50 (1H, ddd, $J = 16.5, 6.0, 1.5$ Hz), 2.38 (2H, d, $J = 6.5$ Hz), atropisomers 2.30 and 2.29 (1H, ddd, $J = 16.5, 7.5, 2.5$ Hz), atropisomers 1.01 and 1.00 (3H, d, $J = 6.5$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 202.11, 172.87, 61.13, 50.34, 38.22, 31.93, 24.79, 20.40. IR (cm^{-1}): $\nu = 3585, 2963, 2826, 2727, 1723, 1652, 1456, 1418, 1386, 1179, 1003$. HRMS-FAB: $(\text{M}+\text{H})^+ = 174.1130$ calculated for $\text{C}_8\text{H}_{16}\text{O}_3\text{N}$, experimental = 174.1138. $[\alpha]_{\text{D}}^{20} = -4.61^\circ$ ($c = 7.13$ in CHCl_3).

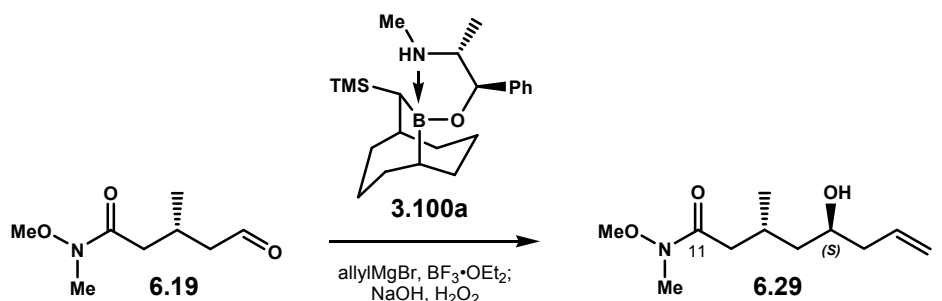
(-)-(R)-5-hydroxy-*N*-methoxy-*N*,3-dimethylpentanamide **6.28**



(*R*)-4-(methoxycarbonyl)-3-methylbutanoic acid **6.22** (13.2 g, 82.4 mmol) was dissolved in THF (300 mL), and the solution was cooled to 0°C. $\text{BH}_3 \cdot \text{SMe}_2$ (8.2 mL, 86.5 mmol) was then added dropwise over three hours via a syringe pump. The reaction was allowed to warm to room temperature and stirred overnight. After recooling the reaction mixture to 0°C, DI H_2O (5 mL) was added very carefully to quench any unreacted borane. Removal of organic solvent under vacuum resulted in white residue. EtOAc (40 mL) was then added, followed by MgSO_4 and then hexanes (60 mL). After stirring the suspension for 15 minutes, the solid was then filtered through a pad of silica and rinsed with 40:60 hexanes : EtOAc. The filtrate was then concentrated under vacuum to yield 11.5 g of a colorless oil. Crude NMR analyses of the oil indicated a 92:8 mixture of alcohol **6.26** and lactone **6.27**.

This oil was dissolved in THF (250 mL) followed by addition of (MeO)MeNH₂Cl (15.2 g, 155.4 mmol). The suspension was then cooled to 0°C. A solution of *i*-PrMgCl (195 mmol, 389 mmol) was added via addition funnel over three hours in which all starting material was completely consumed. The reaction was quenched carefully with a half-saturated solution of NH₄Cl (100 mL) and warmed up to room temperature. After separation of layers, the aqueous layer was extracted with EtOAc (12 x 100 mL). *Note*: the product is readily soluble in water. The organic layers were combined, dried over MgSO₄, filtered, and concentrated under vacuum to give Weinreb amide **6.28** in 87% yield over two steps as a colorless oil (12.5 g, 71.3 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 3.66 (3H, s), 3.64 – 3.56 (2H, m), 3.16 (3H, s), 2.41 (1H, dd, J = 16.0, 8.0 Hz), 2.32 (1H, dd, J = 16.0, 5.0 Hz), 2.22 (1H, o, J = 7.0 Hz), 1.69 (1H, b), 1.56 (1H, m), 1.47 (1H, m), atropisomers 0.98 and 0.97 (1H, d, J = 7.0 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 174.15, 61.03, 60.17, 39.82, 38.59, 31.93, 25.97, 20.59. IR (cm⁻¹): *f* = 3418, 2934, 1660, 1456, 1386, 1180, 1057, 1004. HRMS-FAB: (M+H)⁺ = 176.1287 calculated for C₈H₁₈O₃N, experimental = 176.1267. [α]_D²⁰ = -4.93° (c = 7.00 in MeOH).

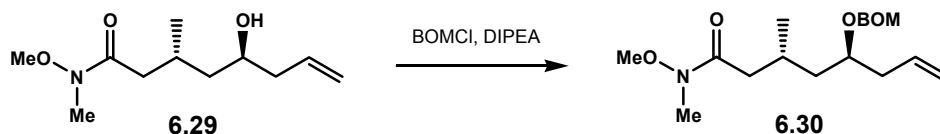
(+)-(3R,5S)-5-hydroxy-N-methoxy-N,3-dimethyloct-7-enamide 6.29



(-)-9-(1R, 2R-Pseudoephedrinyl)-(10S)-(trimethylsilyl)-9-borabicyclo[3.3.2]decane **3.100a** (3.09 g, 8.31 mmol) was suspended in Et₂O (100 mL). The suspension was cooled to -78°C followed by addition of allylmagnesium bromide (8.31 mL, 8.31 mmol, 1.0 M in Et₂O) dropwise. The reaction was stirred for one hour while warming up to room temperature, and then re-cooled to -78°C. In a separate flask, aldehyde **6.19** (960 mg, 5.54 mmol) was dissolved in Et₂O (150 mL) and cooled to -78°C. BF₃•OEt₂ (0.70 mL, 5.54 mmol) was subsequently added, and the solution was stirred for five minutes. The solution of allylborane was then added cold via cannula, and the mixture was stirred for 20 minutes at which aldehyde **6.19** was fully consumed. A premixed solution of NaOH (13.9 mL, 27.8 mmol, 2.0 M in H₂O) and H₂O₂ (3.1 mL, 27.8 mmol, 30% in H₂O) was added to quench the reaction, and the mixture was stirred for two hours while warming up to room temperature. DI water (100 mL) was then added. After separation of layers, the aqueous phase was extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over MgSO₄, and rotovaped to give a yellow oil. Purification of the crude material with Biotage purification system gave homoallylic alcohol **6.29** in 60% yield as a pale yellow oil (720 g, 3.34 mmol) and the minor C7(*R*) diastereomer in

5% yield a clear oil (60 mg, 0.050 mmol). Biotage conditions: 40+M column, 70:30 → 25:75 hexanes : EtOAc linear gradient over 1200 mL, followed by 25:75 → 0:100 hexanes : EtOAc linear gradient over 240 mL, then 90:10 EtOAc : MeOH over 500 mL. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 5.81 (1H, dddd, J = 16.5, 11.0, 7.0, 7.0 Hz), 5.10 – 5.06 (2H, m), 3.71 (1H, dddd, J = 10.0, 7.5, 5.5, 3.5 Hz), 3.65 (3H, s), 3.16 (3H, s), 2.45 (1H, b), 2.42 (1H, dd, J = 16.0, 7.5 Hz), 2.33 (1H, dd, J = 15.0, 7.0 Hz), 2.28 – 2.14 (3H, m), 1.45 (1H, ddd, J = 14.0, 9.5, 4.5 Hz), 1.31 (1H, ddd, J = 14.0, 8.5, 3.0 Hz), 0.97 (3H, d, J = 6.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 174.01, 134.97, 117.57, 68.91, 61.10, 44.09, 42.75, 39.35, 32.00, 26.56, 20.33. IR (cm⁻¹): ν = 3428, 3075, 2962, 2931, 1644, 1463, 1386, 1002, 913. HRMS-FAB: (M+H)⁺ = 216.1600 calculated for C₁₁H₂₂O₃N, experimental = 216.1580. [α]_D²⁰ = +12.6° (c = 3.07 in CHCl₃).

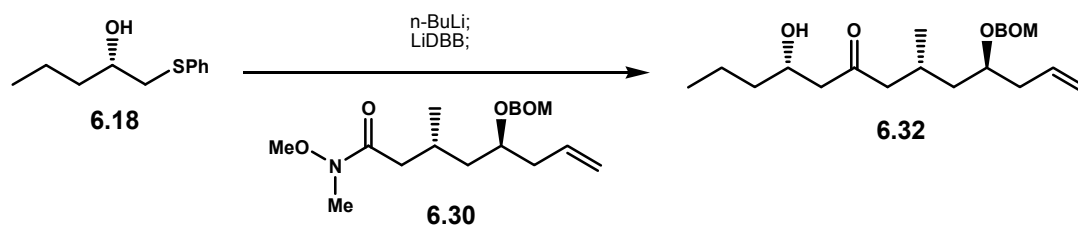
(+)-(3*R*,5*S*)-5-((benzyloxy)methoxy)-*N*-methoxy-*N*,3-dimethyloct-7-enamide **6.30**



In a thick-walled reaction vessel, homoallylic alcohol **6.29** (2.92 g, 13.6 mmol) was dissolved in CH₂Cl₂ (50 mL). DIPEA (50 mL) was then added followed by BOMCl (5.67 mL, 40.8 mmol). The vessel was sealed and heated in a 100°C sand bath for 48 hours. The reaction mixture was then cooled to room temperature, poured into a separatory funnel, and washed with DI H₂O (100 mL). After separation of layers, the aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The organic layers were then

combined, dried over MgSO₄, filtered, and concentrated under vacuum to give a dark red oil. This crude material was chromatographed in a silica gel column, and the elution was made with 95:5 → 90:10 hexanes : *i*-PrOH. Removal of solvent under vacuum gave homoallylic BOM ether **6.30** in 92% yield as a yellow oil (4.20 g, 12.5mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.36 – 7.32 (4H, m), 7.28 (1H, m), 5.82 (1H, dddd, *J* = 17.0, 10.0, 6.5, 6.5 Hz), 5.09 (1H, m), 5.06 (1H, m), 4.84 (1H, d, *J* = 7.5 Hz), 4.77 (1H, d, *J* = 7.0 Hz), 4.66 (1H, d, *J* = 11.5 Hz), 4.62 (1H, d, *J* = 12.0 Hz), 3.80 (1H, m), 3.65 (3H, s), 3.17 (3H, s), 2.41 – 2.25 (5H, m), 1.61 (1H, ddd, *J* = 13.5, 8.5, 4.5 Hz), 1.35 (1H, ddd, *J* = 14.0, 8.5, 4.0 Hz), 0.98 (3H, d, *J* = 6.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 173.71, 137.89, 134.58, 128.35, 127.86, 127.59, 117.30, 93.38, 74.69, 69.66, 61.11, 41.75, 39.54, 39.37, 32.00, 26.33, 19.87. IR (cm⁻¹): *f* = 3067, 2936, 1663, 1455, 1382, 1101, 1041. HRMS-FAB: (M+H)⁺ = 336.2175 calculated for C₁₉H₃₀O₄N, experimental = 336.2176. [α]_D²⁰ = +22.1° (*c* = 4.80 in CHCl₃).

(+)-(4*S*,8*R*,10*S*)-10-((benzyloxy)methoxy)-4-hydroxy-8-methyltridec-12-en-6-one **6.32**

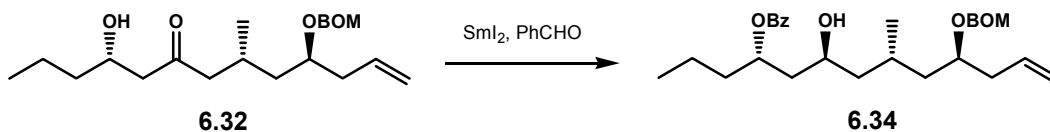


THF used in this reaction was purified via distillation over Na/Ph₂CO. Alcohol **6.18** (5.75 g, 29.3 mmol) was dissolved in THF (150 mL). A few crystals of 1,10-phenanthroline was added, and the solution was cooled to -78°C. *n*-BuLi (~13.5 mL, 2.3

M in hexanes) was then added dropwise until dark red color persisted. Afterward, a freshly prepared solution of LiDBB (~160 mL, 0.4 M in THF) was added dropwise until dark green color persisted. This solution was transferred cold via cannula to a solution of amide **6.30** (3.27 g, 9.75 mmol) which was dissolved in THF (150 mL, distilled over Na/Ph₂CO, and precooled to -78°C) and resulted in a dark red solution. The reaction was stirred at this temperature for 2 hours, slowly warmed to -40°C over 30 minutes, and subsequently quenched with MeOH (50 mL). After allowing the mixture to warm to 0°C, a half-saturated solution of NH₄Cl (200 mL) was then added. The layers were separated. After the ensuing extraction of the aqueous layer with EtOAc (3 x 50 mL), the organic layers were then combined, dried over MgSO₄, filtered, and concentrated under vacuum to give a yellow oil. The crude oil was loaded into a silica gel column, and the product was eluted with 80:20 → 70:30 hexanes : EtOAc. Upon concentration, the title product **6.32** was isolated in 92% yield as a yellow oil (3.25 g, 8.97 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.37 – 7.33 (4H, m), 7.28 (1H, m), 5.79 (1H, dddd, J = 17.0, 10.5, 7.0, 7.0 Hz), 5.09 (1H, m), 5.07 (1H, m), 4.85 (1H, d, J = 7.0 Hz), 4.77 (1H, d, J = 7.0 Hz), 4.66 (1H, d, J = 11.5 Hz), 4.61 (1H, d, J = 11.5 Hz), 4.02 (1H, m), 3.76 (1H, m), 3.09 (1H, b), 2.56 (1H, dd, J = 17.5, 2.5 Hz), 2.45 (1H, dd, J = 17.5, 9.5 Hz), 2.41 (1H, m), 2.36 – 2.25 (4H, m), 1.54 – 1.40 (3H, m), 1.38 – 1.25 (3H, m), 0.91 (3H, d, J = 6.5 Hz), 0.92 (3H, t, J = 6.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 211.93, 137.78, 134.34, 128.42, 127.81, 127.69, 117.51, 93.44, 74.64, 69.77, 67.34, 51.46, 49.42, 41.60, 39.39, 38.51, 25.68, 19.71, 18.63, 13.97. IR (cm⁻¹): ν = 3476, 3067, 2958, 2931, 2874, 1707, 1456, 1379, 1100, 1040. HRMS-FAB: (M+H)⁺ = 363.2535 calculated for C₁₉H₃₀O₄N, experimental = 363.2554. $[\alpha]_D^{20}$ = +51.2° (c = 5.20 in CHCl₃).

(+)-(4*S*,6*S*,8*S*,10*S*)-10-((benzyloxy)methoxy)-6-hydroxy-8-methyltridec-12-en-4-yl

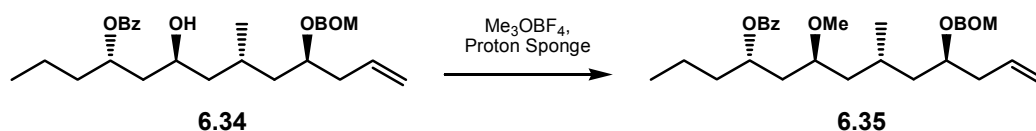
benzoate **6.34**



THF used in this reaction was purified via distillation over Na/Ph₂CO. Into a solution of freshly distilled benzaldehyde (1.01 mL, 9.96 mmol) in THF (20 mL) precooled to -10°C, a freshly prepared solution of SmI₂ (8.30 mL, 0.83 mmol, 0.1 M in THF) was added dropwise over 15 minutes. This solution was then transferred via cannula to a solution of β-hydroxy ketone **6.32** (600 mg, 1.66 mmol) in THF (100 mL, precooled to -10°C). After stirring the reaction mixture at this temperature until starting material was fully consumed (~ 5 hours), a saturated aqueous solution of NaHCO₃ (100 mL) was slowly added. The mixture was then warmed to room temperature and vigorously stirred for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with Et₂O (3 x 50 mL). The organic layers were then combined, dried over MgSO₄, filtered, and concentrated under vacuum. The crude oil was loaded into a silica gel column, and product elution was made with 90:10 → 80:20 hexanes : EtOAc. Removal of solvent under vacuum then provided the title product **6.34** in 80% yield (621 mg, 1.33 mmol) as a yellow oil. ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 8.08 – 8.05 (2H, m), 7.58 (1H, tt, J = 7.5 Hz), 7.46 (2H, tt, J = 8.0, 1.5 Hz), 7.34 – 7.31 (4H, m), 7.28 (1H, m), 5.80 (1H, dddd, J = 17.0, 10.0, 7.0, 7.0 Hz), 5.36 (1H, dddd, J = 11.0, 8.5, 5.0, 3.0 Hz), 5.05 (1H, m), 5.02 (1H, m), 4.81 (1H, d, J = 7.0 Hz), 4.74 (1H, d, J = 7.0 Hz),

4.63 (1H, d, J = 11.5 Hz), 4.60 (1H, d, J = 12.0 Hz), 3.78 (1H, m), 3.63 (1H, m), 3.13 (1H, dd, J = 2.5, 1.0 Hz), 2.31 (1H, ddd, J = 7.0, 1.0, 1.0 Hz), 2.30 (1H, ddd, J = 7.0, 1.0, 1.0 Hz), 1.92 (1H, m), 1.81 – 1.58 (4H, m), 1.56 – 1.49 (2H, m), 1.48 – 1.35 (2H, m), 1.24 (1H, ddd, J = 14.0, 9.0, 4.5 Hz), 1.12 (1H, ddd, J = 13.0, 9.5, 3.0 Hz), 0.93 (3H, t, J = 7.5 Hz), 0.84 (3H, d, J = 6.5 Hz). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 167.72, 137.93, 134.67, 133.16, 129.99, 129.72, 128.43, 128.37, 127.86, 127.60, 117.20, 93.42, 74.86, 72.26, 69.61, 64.83, 44.83, 43.80, 42.40, 39.37, 37.21, 25.82, 19.49, 18.79, 13.88. IR (cm⁻¹): ν = 3516, 3062, 2954, 2926, 1715, 1696, 1274, 1107, 1038. HRMS-FAB: (M+H)⁺ = 469.2954 calculated for C₂₉H₄₁O₅, experimental = 469.2951. $[\alpha]_D^{20}$ = +22.7° (c = 3.60 in CHCl₃).

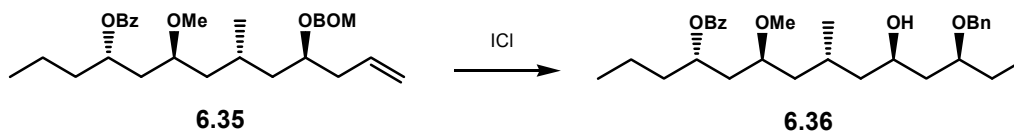
(+)-(4S,6S,8S,10S)-10-((benzyloxy)methoxy)-6-methoxy-8-methyltridec-12-en-4-yl benzoate **6.35**



Alcohol **6.34** (2.00 g, 4.27 mmol) was dissolved in CH₂Cl₂ (100 mL). After cooling the reaction to 0°C, Proton Sponge (5.49 g, 25.6 mmol) and Me₃OBF₄ (3.17 g, 21.4 mmol) were sequentially added. The reaction mixture was warmed to room temperature and stirred for one hour at which starting material was fully consumed. The reaction was diluted with CH₂Cl₂ (200 mL) and washed sequentially with aqueous solutions of NaHCO₃ (50 mL), 2.0 M HCl (2 x 50 mL), and then NaHCO₃ (50 mL). The

organic layer was then dried over MgSO_4 , filtered, and concentrated under vacuum. Filtration of the crude oil through a pad of silica gave the title product **6.35** in 99% as a yellow oil (2.04 g, 4.23 mmol). No chromatography was necessary as the crude NMR indicated only a single compound. ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 8.08 – 8.06 (2H, m), 7.55 (1H, tt, J = 7.5, 1.5, 1.5 Hz), 7.43 (2H, tt, J = 8.0, 1.5, 1.5 Hz), 7.34 – 7.32 (4H, m), 7.29 (1H, m), 5.78 (1H, dddd, J = 17.0, 1.0, 7.0, 7.0 Hz), 5.36 (1H, 9.0, 7.0, 5.0, 3.0 Hz), 5.05 (1H, m), 5.02 (1H, m), 4.82 (1H, d, J = 7.5 Hz), 4.74 (1H, d, J = 7.0 Hz), 4.64 (1H, d, J = 12.0 Hz), 4.60 (1H, d, J = 12.0 Hz), 3.77 (1H, m), 3.32 (1H, m), 3.28 (3H, s), 2.35 – 2.24 (2H, m), 1.84 (1H, dd, J = 9.5, 4.0 Hz), 1.82 (1H, dd, J = 9.0, 3.5 Hz), 1.76 (1H, dd, J = 9.0, 3.5 Hz), 1.70 (1H, m), 1.61 (1H, m), 1.58 (1H, m), 1.53 (1H, ddd, J = 13.5, 8.5, 4.0 Hz), 1.44 – 1.35 (2H, m), 1.26 – 1.16 (2H, m), 0.92 (3H, t, J = 7.5 Hz), 0.91 (3H, d, J = 6.5 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 166.19, 137.89, 134.59, 132.73, 130.69, 129.56, 128.39, 128.31, 127.77, 127.63, 117.25, 93.36, 75.84, 74.63, 72.13, 69.60, 56.98, 42.49, 42.10, 39.83, 39.48, 37.24, 25.91, 19.96, 18.46, 14.03. IR (cm^{-1}): ν = 3063, 2931, 1718, 1452, 1273, 1110, 1042, 1027, 712. HRMS-FAB: $(\text{M}-\text{H})^+ = 481.2954$ calculated for $\text{C}_{30}\text{H}_{41}\text{O}_5$, experimental = 481.2532. $[\alpha]_{\text{D}}^{20} = +65.0^\circ$ (c = 1.80 in CHCl_3).

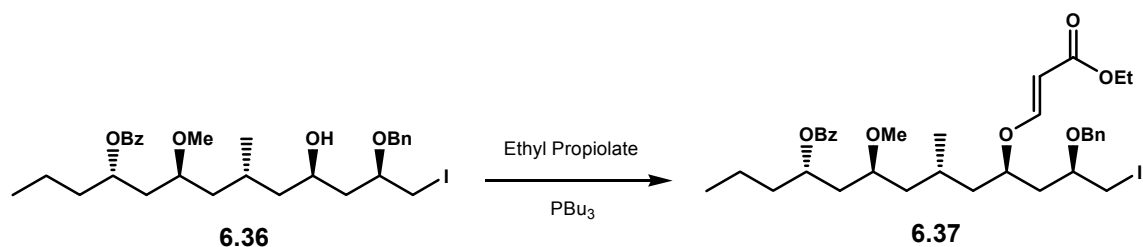
(+)-(4*S*,6*S*,8*R*,10*R*,12*R*)-12-(benzyloxy)-10-hydroxy-13-iodo-6-methoxy-8-methyltridecan-4-yl benzoate **6.36**



Homoallylic BOM ether **6.35** (480 mg, 0.994 mmol) was dissolved in toluene (200 mL), and the solution was cooled to -78°C . Iodine monochloride (1.1 mL, 1.10 mmol, 1.0 M in CH_2Cl_2) was added dropwise over 30 minutes while maintaining an internal temperature below -75°C . Immediately, the reaction mixture was poured into a separatory funnel containing a saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (100 mL) and the mixture was shaken vigorously. After separation of layers, the aqueous layer was extracted with Et_2O (2 x 50 mL). The organic layers were combined, dried over MgSO_4 , filtered, and concentrated under vacuum. The crude material was then loaded into a silica gel column and chromatographed with 80:20 hexanes : EtOAc . Removal of solvent under vacuum gave title product **6.36** in 71% yield with a diastereomeric ratio of $>20:1$ as a yellow oil (420 mg, 0.704 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 8.07 – 8.04 (2H, m), 7.54 (1H, tt, $J = 7.5, 1.5, 1.5$ Hz), 7.43 (2H, tt, $J = 7.5, 1.5, 1.5$ Hz), 7.37 – 7.34 (4H, m), 7.31 (1H, m), 5.34 (1H, dddd, $J = 8.5, 7.5, 5.0, 3.0$ Hz), 4.70 (1H, d, $J = 11.0$ Hz), 4.44 (1H, d, $J = 11.0$ Hz), 3.86 (1H, dddd, $J = 10.0, 8.0, 3.5, 3.5$ Hz), 3.52 (1H, dddd, $J = 9.5, 5.0, 5.0, 5.0$ Hz), 3.33 (2H, d, $J = 4.5$ Hz), 3.29 (1H, m), 3.28 (3H, s), 2.96 (1H, b), 1.85 (1H, ddd, $J = 14.5, 9.5, 3.5$ Hz), 1.81 (1H, m), 1.75 – 1.66 (4H, m), 1.62 (1H, m), 1.56 (1H, ddd, $J = 13.0, 6.5, 6.5$ Hz), 1.46 (1H, ddd, $J = 13.5, 9.5, 4.0$ Hz), 1.43

– 1.35 (2H, m), 1.24 (1H, ddd, J = 13.5, 7.0, 6.0 Hz), 1.06 (1H, ddd, J = 13.5, 3.5, 9.5 Hz), 0.92 (3H, t, J = 7.5 Hz), 0.91 (3H, d, J = 7.0 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 166.22, 137.09, 132.76, 130.63, 129.55, 128.60, 128.36, 128.11, 128.06, 77.45, 76.07, 72.26, 71.13, 67.99, 57.01, 45.02, 42.53, 42.32, 39.69, 37.19, 25.82, 19.90, 18.48, 14.01, 9.32. IR (cm^{-1}): ν = 3512, 3064, 2957, 2939, 2872, 1716, 1452, 1314, 1275, 1112, 713. HRMS-FAB: $(\text{M}+\text{H})^+ = 597.2077$ calculated for $\text{C}_{29}\text{H}_{42}\text{O}_5\text{I}$, experimental = 579.2063. $[\alpha]_D^{20} = +37.9^\circ$ (c = 3.47 in CHCl_3).

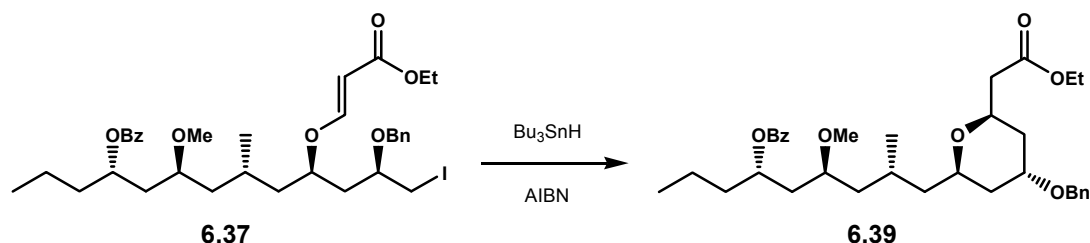
(+)-(4*S*,6*S*,8*S*,10*R*,12*R*)-10-((*E*)-2-(ethoxycarbonyl)vinyl)-12-(benzyloxy)-13-iodo-6-methoxy-8-methyltridecan-4-yl benzoate **6.37**.



Alcohol **6.36** (700 mg, 1.17 mmol) was dissolved in CH_2Cl_2 (150 mL), and one gram of 4 Å molecular sieves was added. Freshly prepared solutions of ethyl propiolate (7.0 mL, 3.51 mmol, 0.5 M in CH_2Cl_2) and tributylphosphine (7.0 mL, 4.21 0.6 mmol, 0.6 M in CH_2Cl_2) were simultaneously added dropwise via syringe pump over 30 minutes at which the color of the solution turned to brown. The reaction was then quenched with H_2O_2 aqueous solution (100 mL, 3% in H_2O) and stirred vigorously for 10 minutes. After separation of layers, the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL).

The organic layers were combined, dried over MgSO_4 , filtered, and concentrated under vacuum to leave a black oil. Purification of the crude material in a silica gel column with 80:20 hexanes : Et_2O gave title product **6.37** in 98% yield as a pale yellow oil (796 mg, 1.15 mmol). ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 8.07 – 8.05 (2H, m), 7.56 (1H, tt, J = 7.0, 1.5 Hz), 7.48 (1H, d, J = 12.5 Hz), 7.46 – 7.42 (2H, m), 7.37 – 7.27 (5H, m), 5.35 (1H, dddd, J = 8.5, 7.5, 5.5, 3.5 Hz), 5.29 (1H, d, J = 12.5 Hz), 4.61 (1H, d, J = 11.0 Hz), 4.36 (1H, d, J = 11.5 Hz), 4.16 (2H, q, J = 7.0 Hz), 4.12 (1H, m), 3.33 – 3.23 (4H, m), 3.27 (3H, s), 1.98 (1H, ddd, J = 14.0, 8.5 Hz), 1.83 – 1.76 (2H, m), 1.74 – 1.66 (3H, m), 1.65 – 1.58 (2H, m), 1.50 (1H, ddd, J = 14.0, 7.0, 7.0 Hz), 1.44 – 1.36 (2H, m), 1.27 (3H, t, J = 7.0 Hz), 1.26 – 1.15 (2H, m), 0.93 (3H, t, J = 7.5 Hz), 0.83 (3H, d, J = 7.0 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 168.03, 166.16, 161.76, 137.37, 132.83, 130.63, 129.56, 128.53, 128.39, 127.99 (2C), 97.58, 78.17, 75.85, 74.18, 72.08, 71.17, 59.72, 57.07, 42.18, 41.50, 39.73, 39.68, 37.25, 25.74, 19.74, 18.48, 14.38, 14.00, 9.10. IR (cm^{-1}): ν = 3028, 2963, 2925, 1710, 1639, 1619, 1273, 1129, 712. HRMS-FAB: $(\text{M}+\text{H})^+$ = 695.2445 calculated for $\text{C}_{34}\text{H}_{48}\text{O}_7\text{I}$, experimental = 695.2452. $[\alpha]_{\text{D}}^{20}$ = +10.0° (c = 0.87 in CHCl_3).

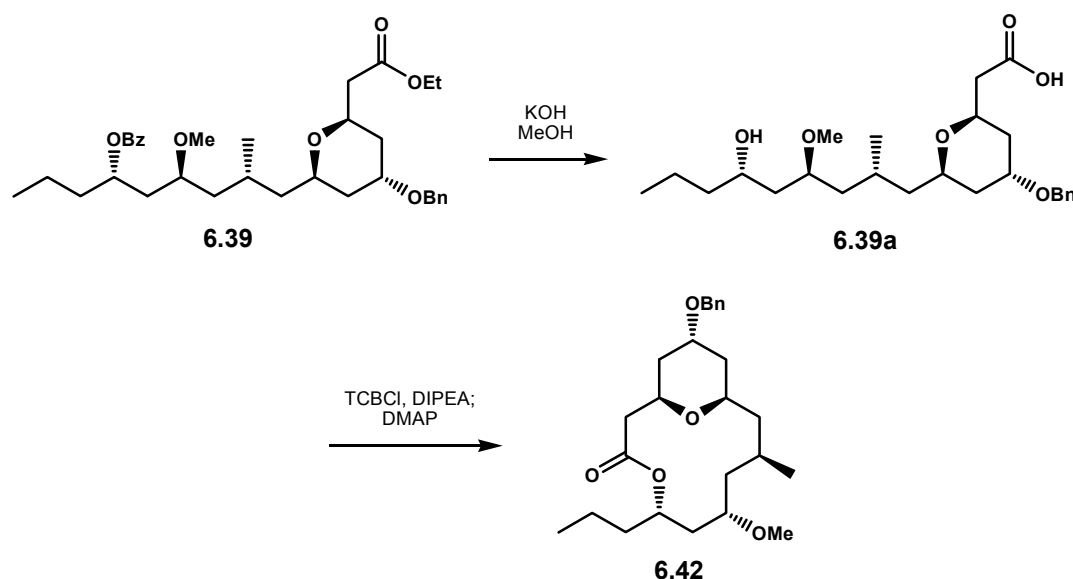
(+)-(4*S*,6*S*,8*S*)-9-((2*R*,4*R*,6*R*)-6-((ethoxycarbonyl)methyl)-4-(benzyloxy)-tetrahydro-2*H*-pyran-2-yl)-6-methoxy-8-methylnonan-4-yl benzoate **6.39**



β -Alkoxyacrylate **6.37** (760 mg, 1.09 mmol) was dissolved in toluene (250 mL). AIBN (18 mg, 0.109 mmol) and Bu_3SnH (0.59 mL, 2.18 mmol) were sequentially added, and the mixture was rapidly brought to reflux, stirred for 5 minutes, and then immediately cooled to room temperature in a water bath. The solvent was removed under vacuum, and the crude oil was loaded into and purified with Biotage chromatography system: 25+M column, 100:0 \rightarrow 60:40 hexanes : EtOAc linear gradient over 720 mL. Removal of solvent under vacuum gave title product **6.39** in 95% yield as a light yellow oil (589 mg, 1.04 mmol) with a diastereomeric ratio of 19:1. ^1H NMR (500 MHz, CDCl_3): δ (ppm) = 8.07 – 8.04 (2H, m), 7.55 (1H, tt, $J = 7.5, 1.5$ Hz), 7.43 (2H, tt, $J = 7.5, 1.5$ Hz), 7.36 – 7.32 (4H, m), 7.28 (1H, m), 5.36 (1H, dddd, $J = 9.5, 6.5, 5.5, 3.5$ Hz), 4.54 (1H, d, $J = 12.0$ Hz), 4.49 (1H, d, $J = 12.0$ Hz), 4.19 (1H, dddd, $J = 11.0, 8.0, 5.0, 2.0$ Hz), 4.11 (2H, dq, $J = 7.0, 2.0$ Hz), 3.84 (1H, m), 3.82 (1H, p, $J = 2.5$ Hz), 3.28 (1H, m), 3.26 (3H, s), 2.48 (1H, dd, $J = 15.0, 8.5$ Hz), 2.35 (1H, dd, $J = 15.0, 5.5$ Hz), 1.92 (1H, dddd, $J = 13.5, 2.5, 2.0, 2.0$ Hz), 1.82 (2H, ddd, $J = 14.5, 9.5, 3.5$ Hz), 1.78 – 1.67 (3H, m), 1.64 – 1.53 (2H, m), 1.48 – 1.33 (3H, m), 1.31 – 1.14 (3H, m), 1.23 (3H, t, $J = 7.0$ Hz), 1.01 (1H, ddd, $J = 13.5, 9.5, 3.0$ Hz), 0.92 (3H, t, $J = 7.5$ Hz), 0.88 (3H, d, $J = 6.5$ Hz). ^{13}C

NMR (125 MHz, CDCl₃): δ (ppm) = 171.28, 166.18, 138.77, 132.69, 130.75, 129.57, 128.35, 128.28, 127.45, 127.37, 75.90, 72.19, 71.30, 70.04, 69.62, 69.07, 60.31, 56.88, 43.27, 42.17, 41.61, 39.81, 37.25, 36.20, 35.15, 25.74, 19.70, 18.49, 14.22, 14.02. IR (cm⁻¹): ν = 3030, 2956, 2922, 1734, 1717, 1452, 1273, 1111, 1068, 1027, 713. HRMS-FAB: (M+H)⁺ = 569.3478 calculated for C₃₄H₄₉O₇, experimental = 569.3497. $[\alpha]_D^{20}$ = +17.4° (c = 2.20 in CHCl₃).

(+)-(1*R*,5*S*,7*S*,9*S*,11*R*,13*R*)-13-(benzyloxy)-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-3-one **6.42**



Tetrahydropyran **6.39** (164 mg, 0.288 mmol) was dissolved in MeOH (30 mL). Upon addition of a solution of KOH (5.8 mL, 5.76 mmol, 1 M in H₂O), the mixture was warmed to 45°C. After stirring overnight, the reaction was sequentially cooled to room temperature, diluted with H₂O (100 mL), and acidified with 2 M HCl until the pH = 2.

The aqueous layer was then extracted with EtOAc (4 x 50 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated under vacuum to leave ~ 2 mL of solvent at which hexanes (4 mL) was then added. This solution was then loaded into and purified with Biotage chromatography system: 25+M column, 80:20 → 50:50 hexanes : EtOAc linear gradient over 270 mL, then 50:50:1 hexanes : EtOAc : AcOH over 450 mL. Removal of solvent gave seco acid **6.39a** in 95% yield as a yellow oil (120 mg, 0.275 mmol). HRMS-FAB: (M+H)⁺ = 437.2903 calculated for C₂₅H₄₁O₆, experimental = 437.2924.

Seco acid **6.39a** (120 mg, 0.275 mmol) was dissolved in 50 mL THF and cooled to 0°C. TEA (0.38 mL, 2.75 mmol) and TCBCl (0.22 mL, 1.38 mmol) were sequentially added. The solution was stirred for one hour, warmed to room temperature, and diluted with toluene (200 mL). This solution was added dropwise via cannula over 24 hours into a solution of DMAP (841 mg, 6.88 mmol) in toluene (500 mL) in which the solution turned cloudy white. Upon completion, the solvent was evaporated under vacuum. The white residues was taken up in hexanes and filtered. The solution was concentrated and purified with Biotage chromatography system: 25+M column, 98:2 → 80:20 hexanes : EtOAc linear gradient over 720 mL to yield macrolactone **6.42** in 87% yield as a clear oil (100 mg, 0.239 mmol). ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.38 – 7.35 (4H, m), 7.29 (1H, m), 5.19 (1H, ddd, J = 9.0, 9.0, 4.5 Hz), 4.55 (1H, d, J = 12.5 Hz), 4.52 (1H, d, J = 12.0 Hz), 4.17 (1H, dddd, J = 11.0, 11.0, 4.0, 2.0 Hz), 3.84 (1H, p, J = 3.0 Hz), 3.66 (1H, t, J = 10.5 Hz), 3.60 (1H, dddd, J = 10.5, 9.5, 2.5, 1.0 Hz), 3.31 (3H, s), 2.59 (1H, dd, J = 14.5, 4.5 Hz), 2.34 (1H, dd, J = 14.5, 11.5 Hz), 1.88 – 1.83 (2H, m), 1.73 (1H, dddd, J = 14.0, 3.0, 2.0, 2.0 Hz), 1.68 (1H, dddd, J = 14.5, 9.0, 9.0, 5.5 Hz), 1.57 (1H,

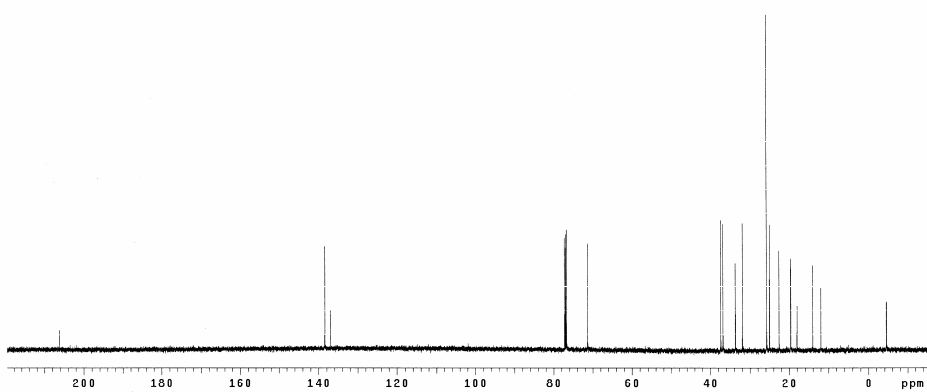
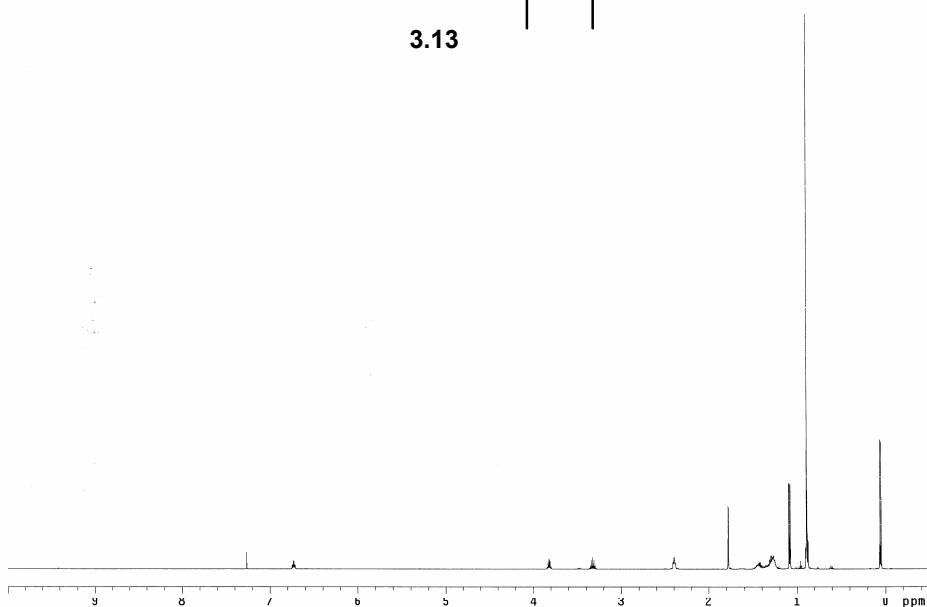
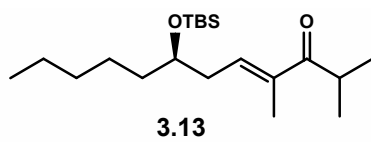
ddd, $J = 13.5, 11.5, 3.0$ Hz), 1.49 (1H, dddd, $J = 14.0, 9.5, 7.0, 4.5$ Hz), 1.48 (1H, b), 1.43 – 1.32 (6H, m), 1.23 (1H, dd, $J = 15.0, 1.5$ Hz), 1.14 (1H, ddd, $J = 13.0, 11.0, 2.5$ Hz), 0.97 (3H, d, $J = 6.5$ Hz), 0.91 (3H, t, $J = 7.5$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 171.13, 138.67, 128.42, 127.59, 127.41, 75.60, 75.28, 72.80, 71.72, 70.31, 69.51, 56.21, 44.26, 42.54, 42.39, 40.17, 36.94, 36.54, 35.27, 31.23, 25.69, 18.94, 13.90. IR (cm^{-1}): $f = 2917, 2870, 1730, 1456, 1341, 1276, 1198, 1087$. HRMS-FAB: $(\text{M}+\text{H})^+ = 419.2797$ calculated for $\text{C}_{25}\text{H}_{39}\text{O}_5$, experimental = 419.2778. $[\alpha]_{\text{D}}^{20} = +32.9^\circ$ ($c = 1.33$ in CHCl_3).

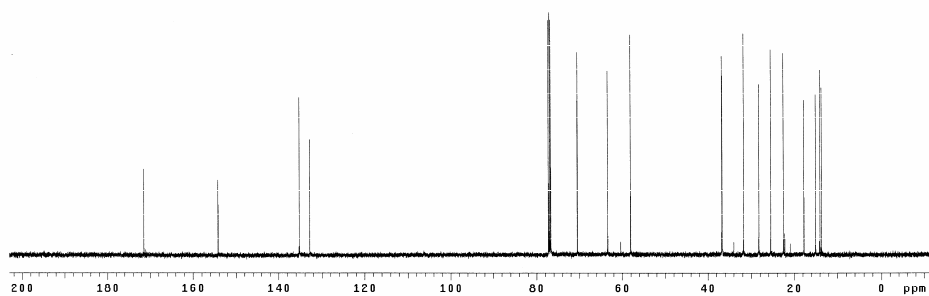
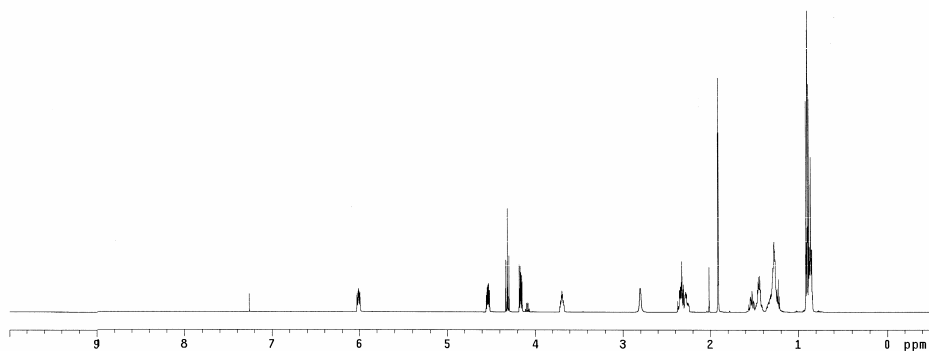
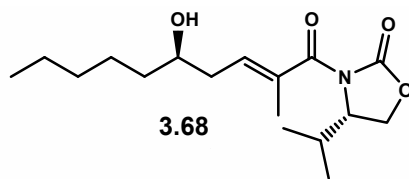
CHAPTER NINE

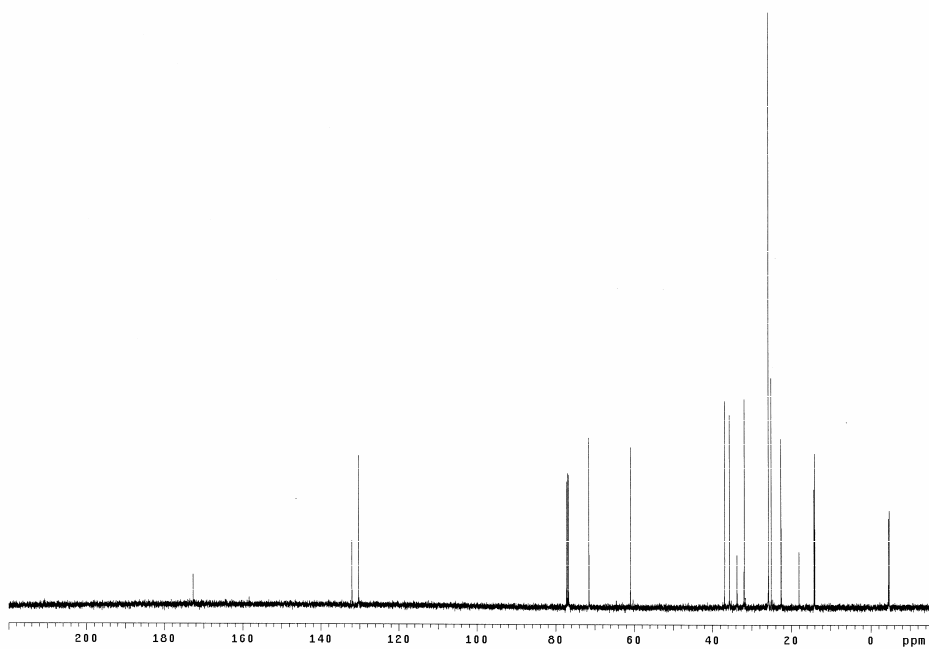
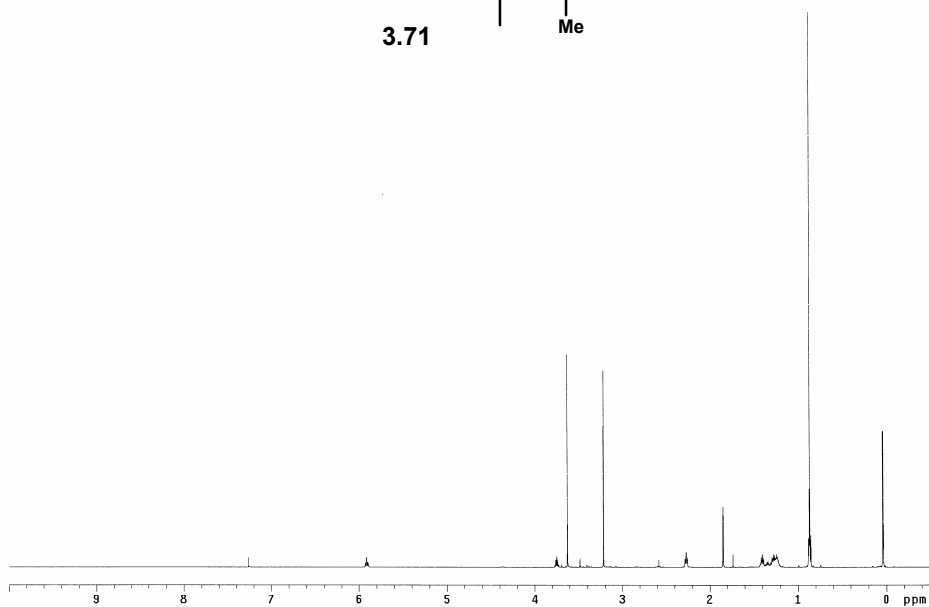
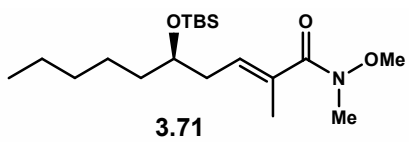
SUPPORTING INFORMATION: NMR SPECTRA

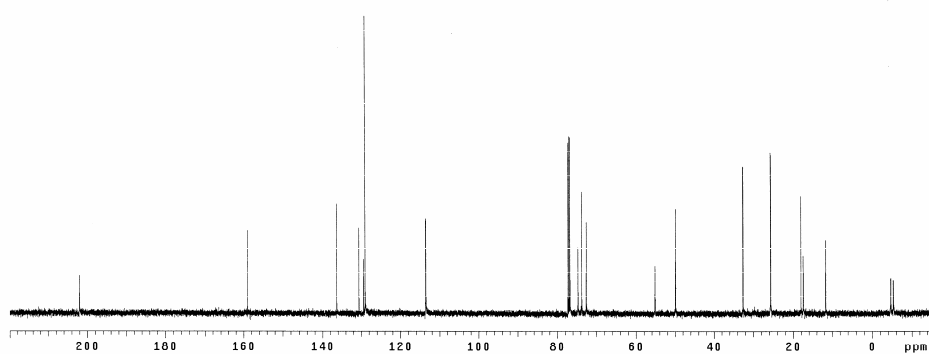
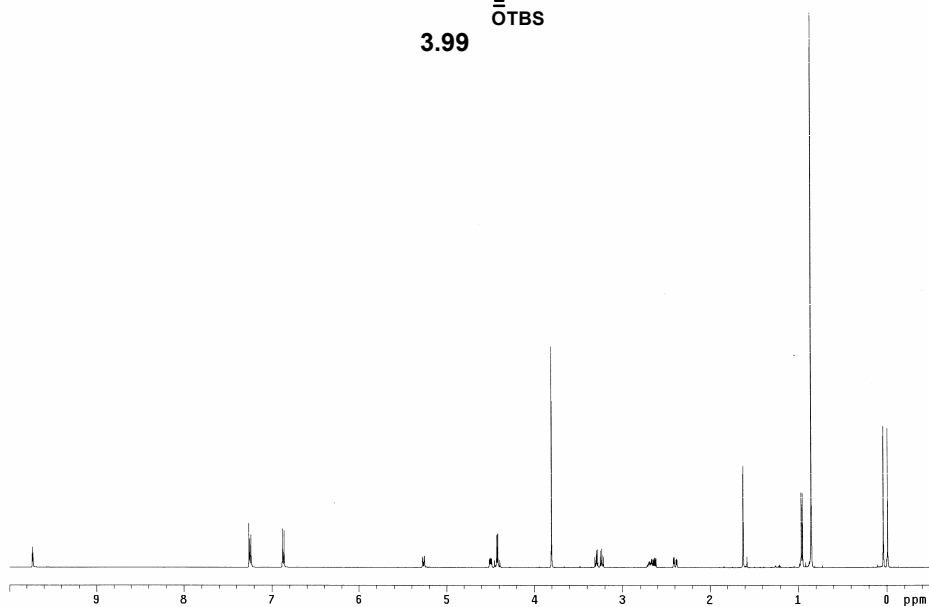
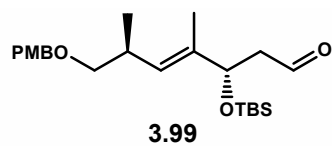
9.1. General Information

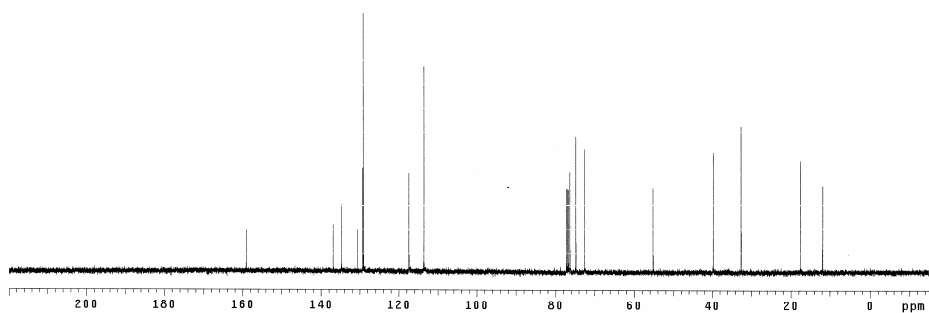
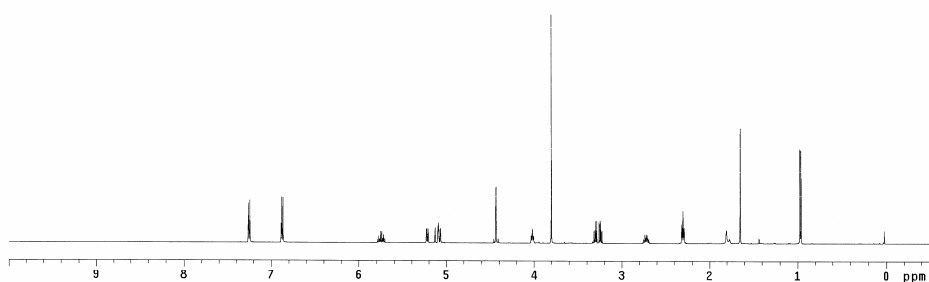
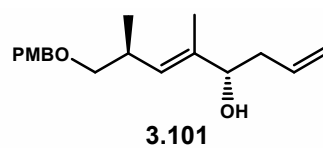
Unless otherwise noted, all ^1H and ^{13}C NMR spectra were recorded in CDCl_3 using either Varian Unity Plus 300 spectrometers operating at 299.88 MHz for ^1H and 75.37 MHz for ^{13}C , Varian Inova 500 spectrometers operating at 499.86 MHz for ^1H and 125.69 MHz for ^{13}C , or Varian VNMRS 600 operating at 599.87 MHz for ^1H and 150.84 MHz for ^{13}C . Chemical shifts (δ) were reported in ppm relative to residual CHCl_3 as an internal reference (^1H : 7.26 ppm, ^{13}C : 77.00 ppm). Coupling constants (J) were reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), x (septet), h (heptet), b (broad), and m (multiplet).

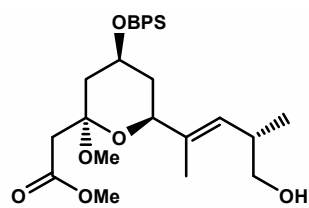




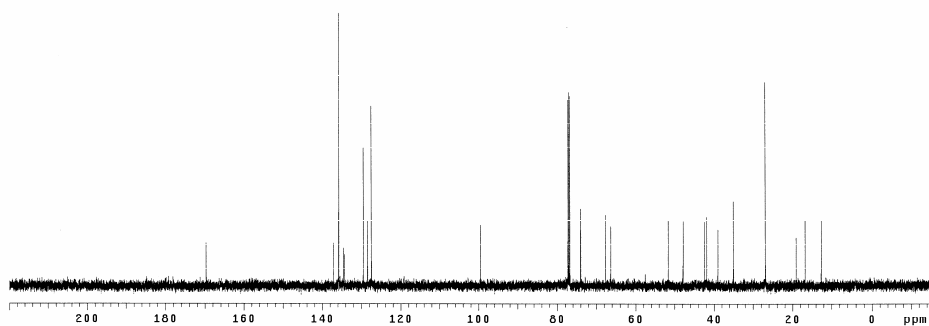
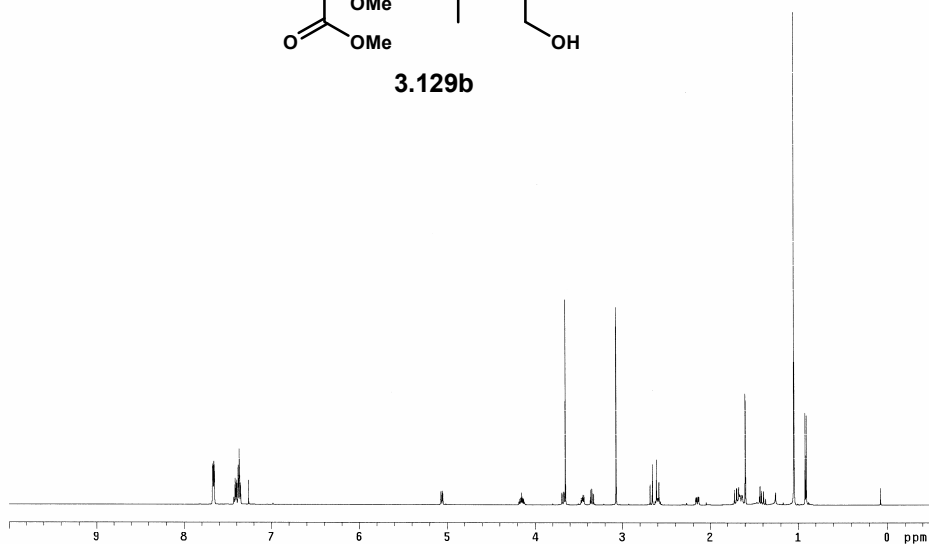


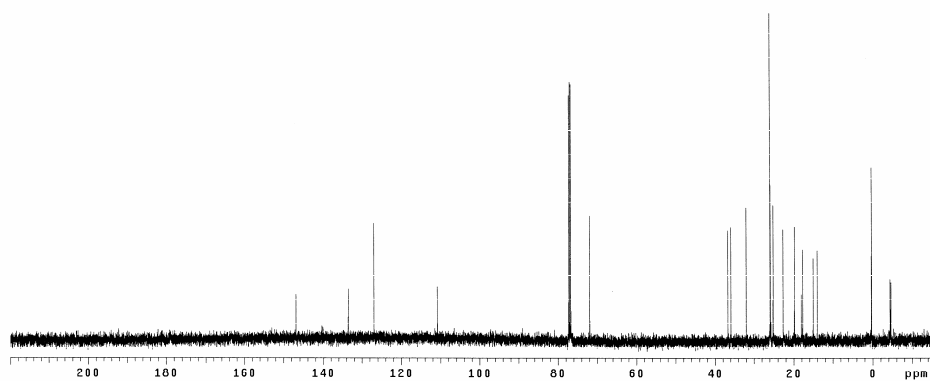
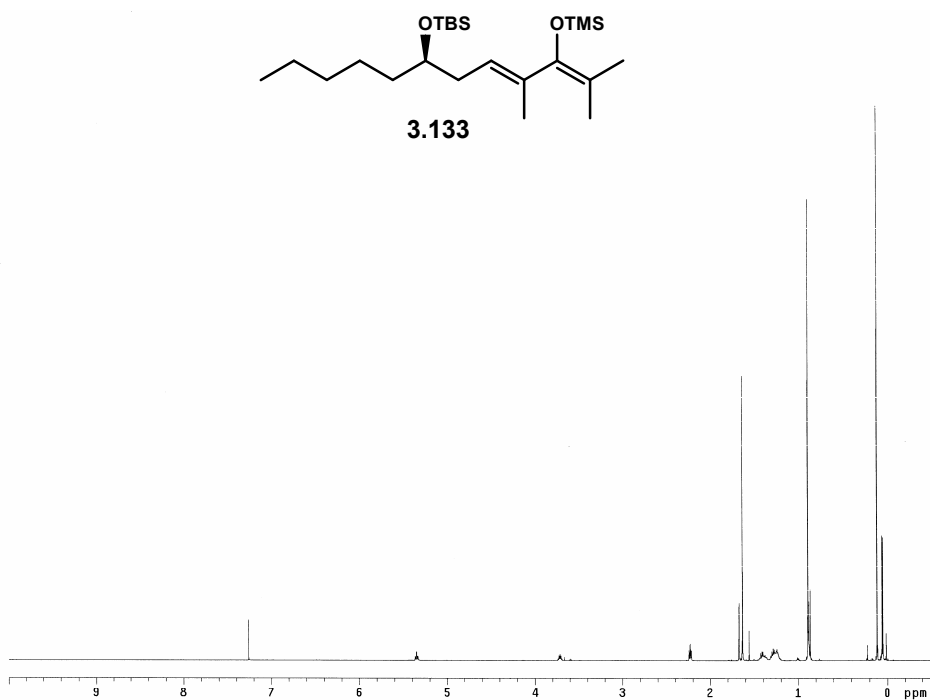


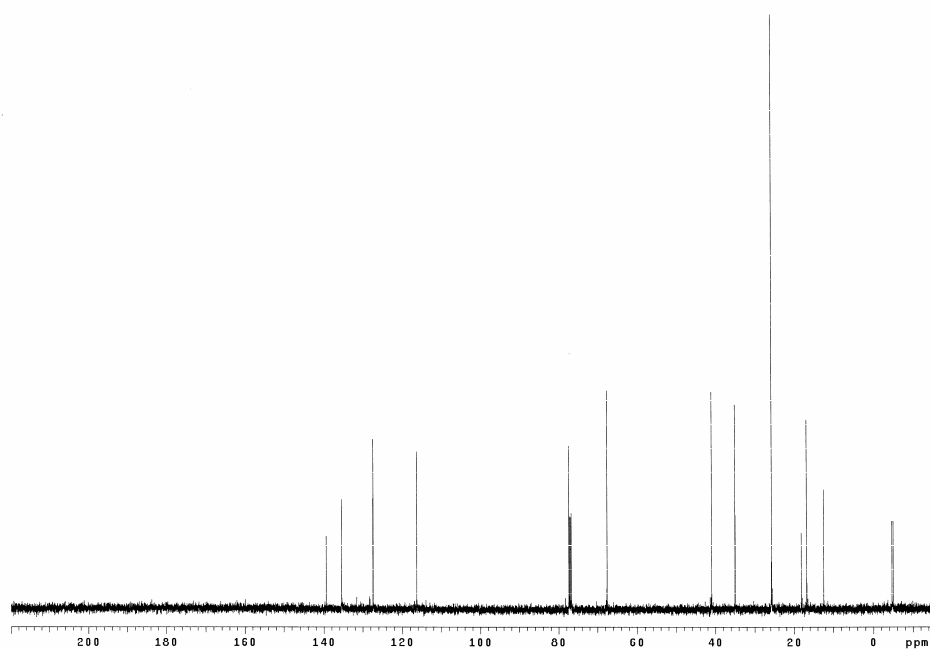
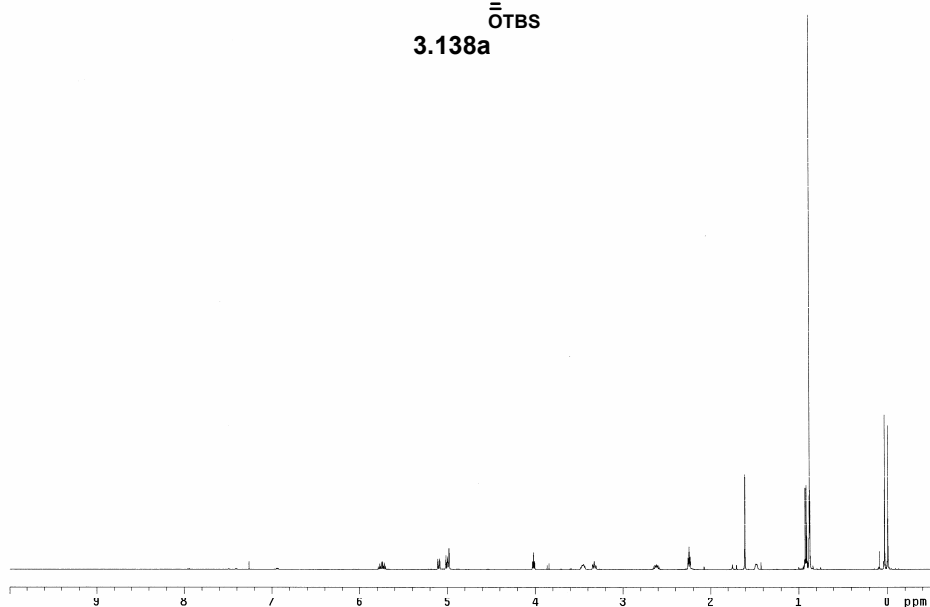
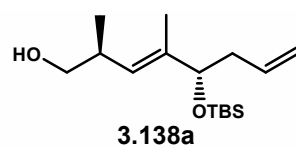


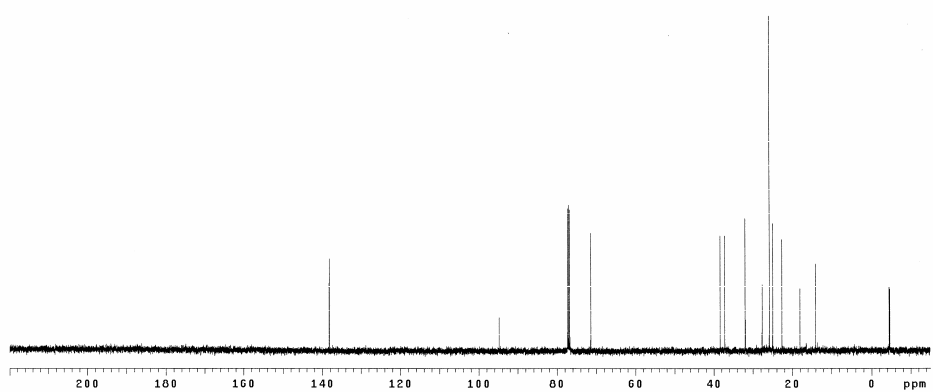
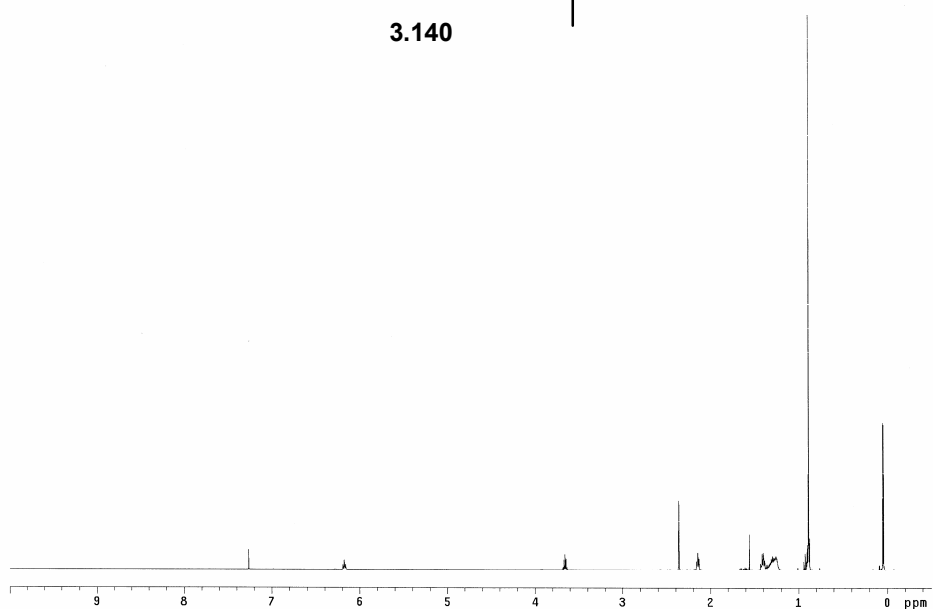


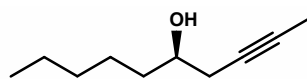
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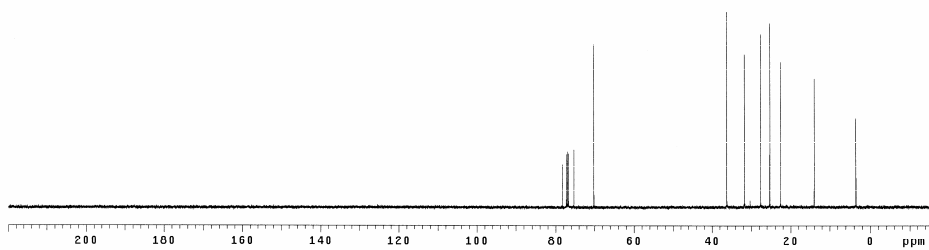
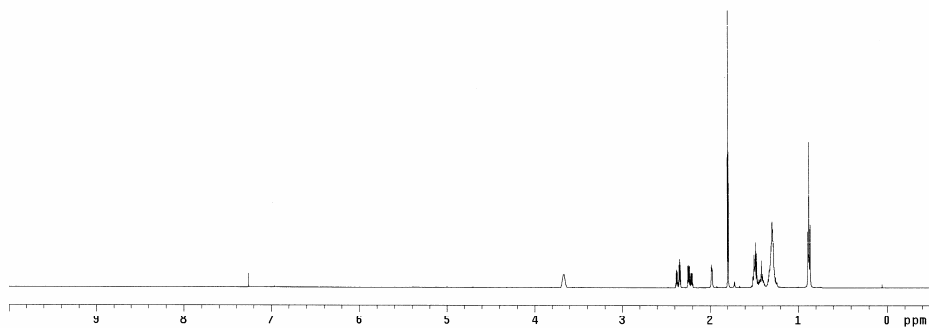


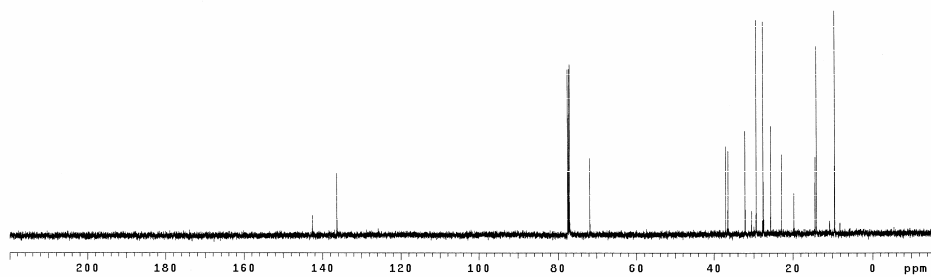
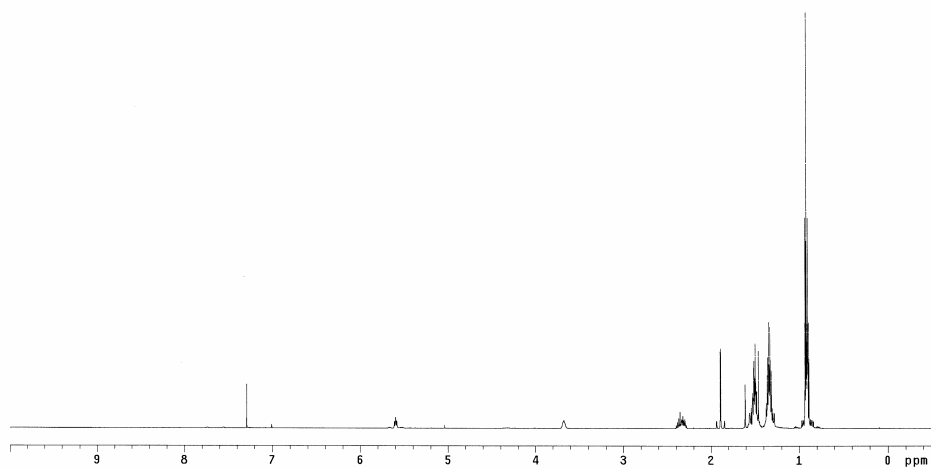
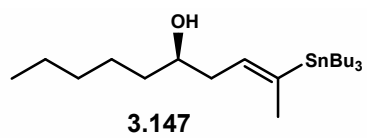


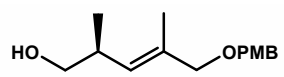




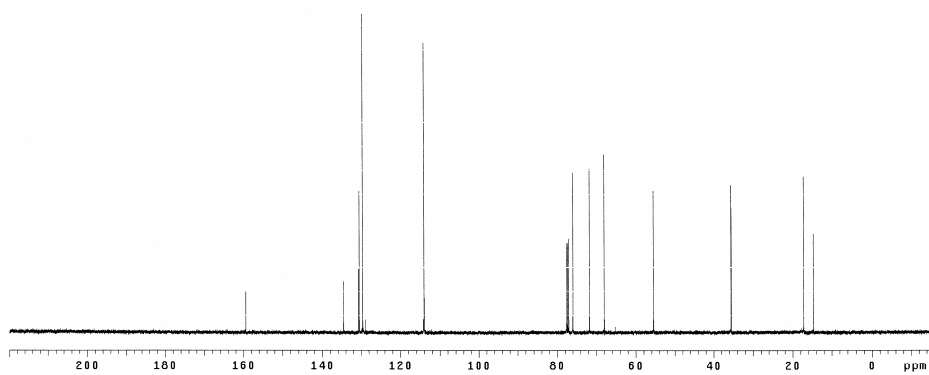
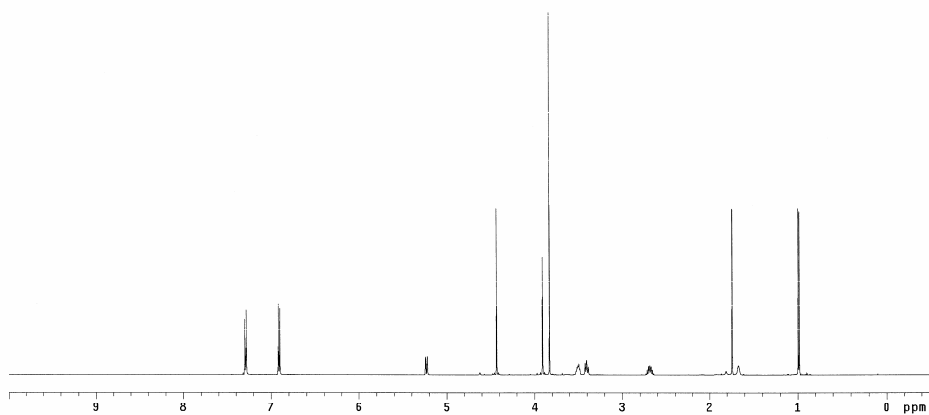
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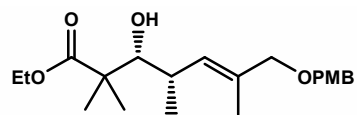




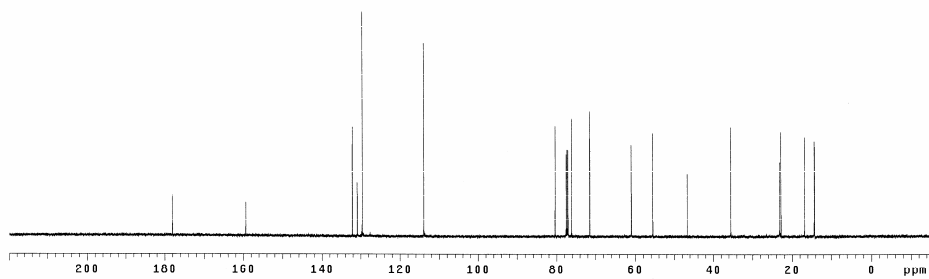
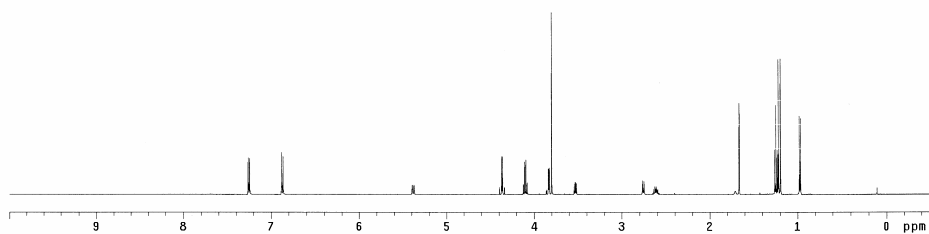


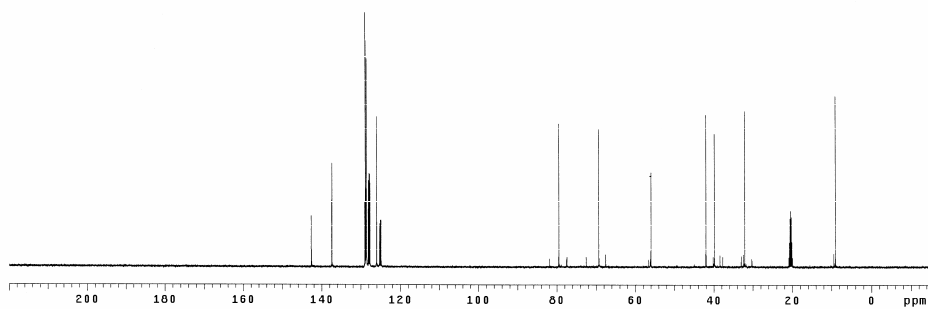
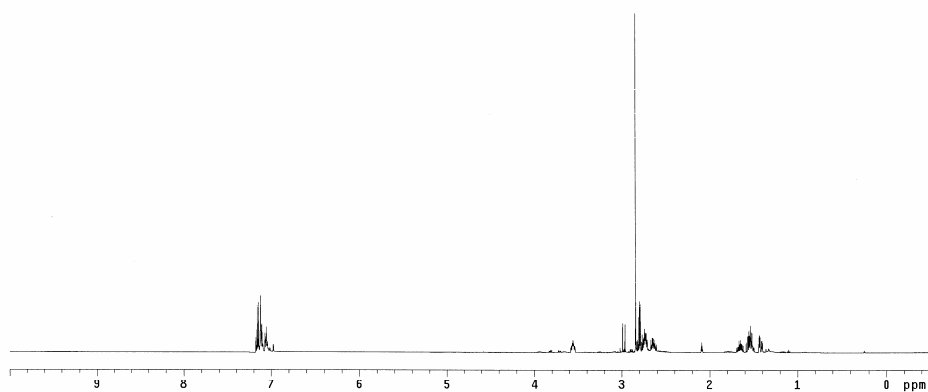
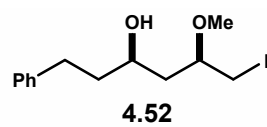
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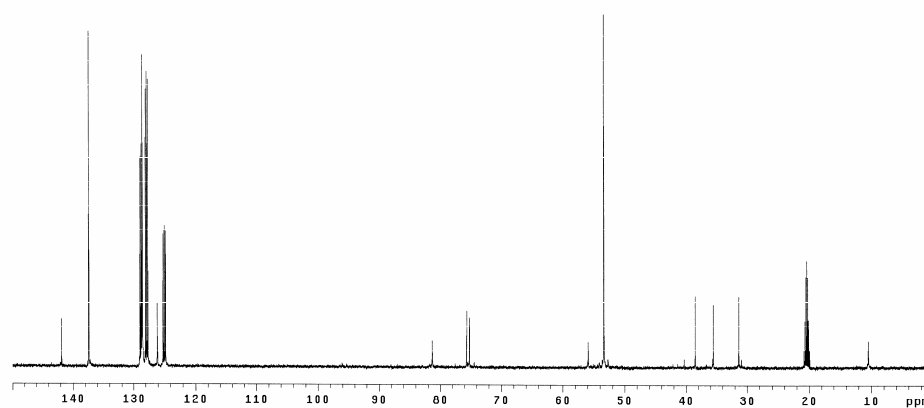
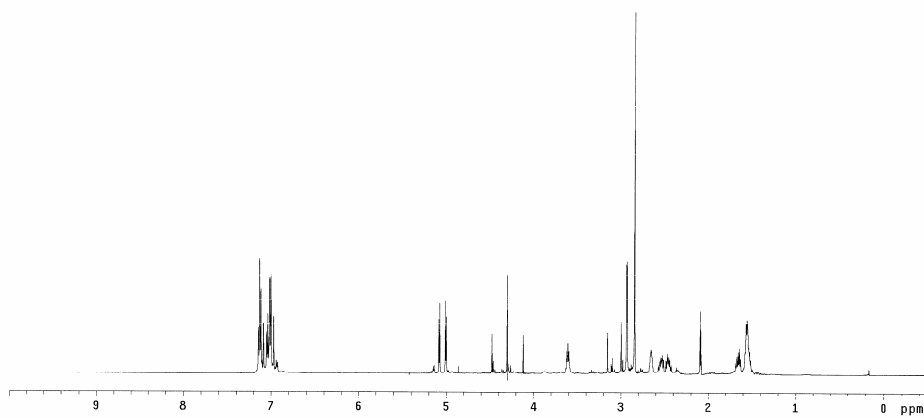
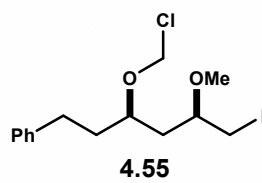


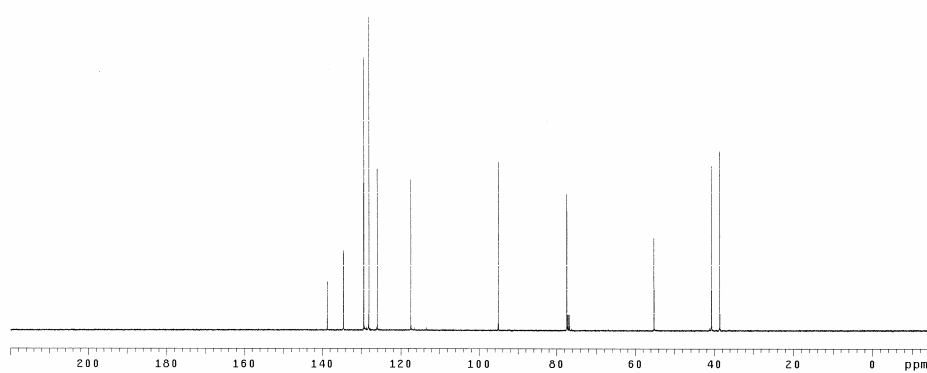
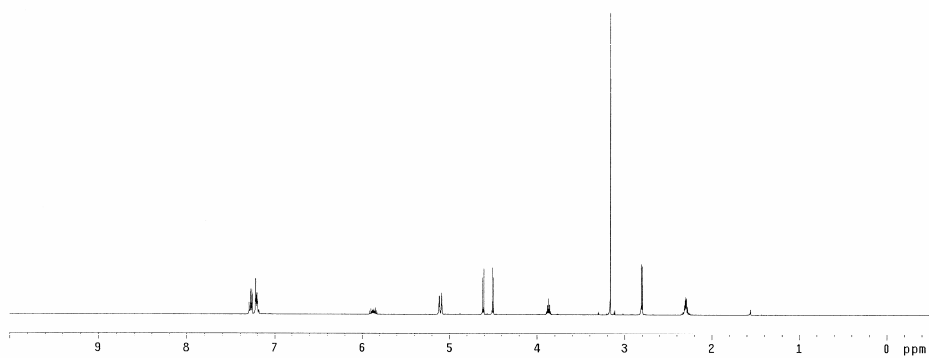
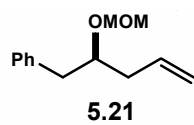


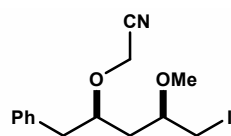
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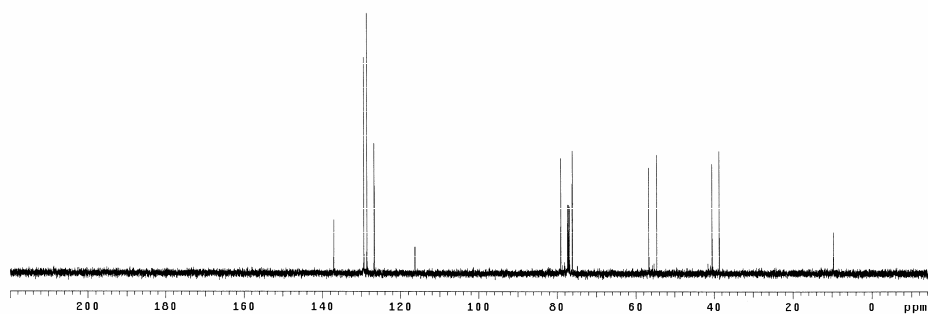
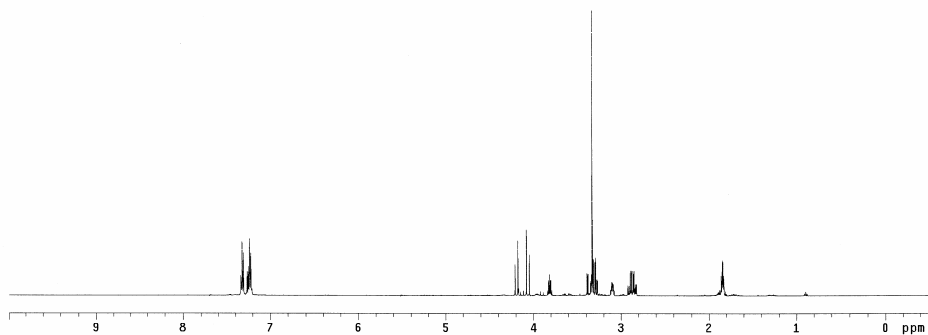


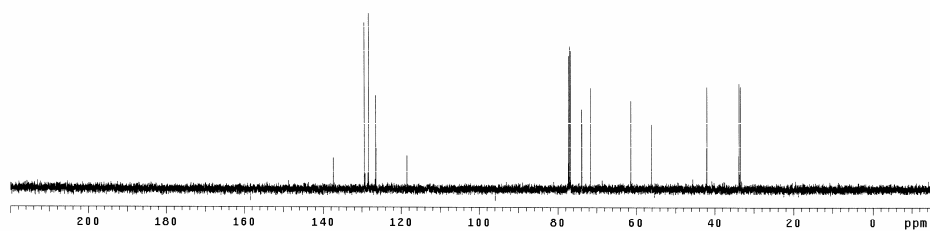
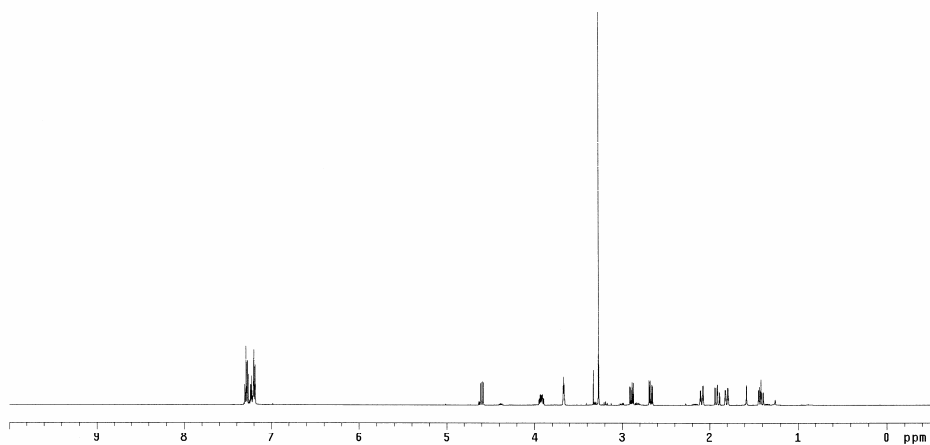
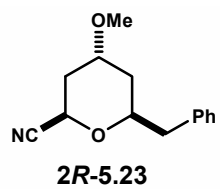


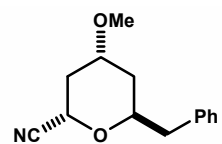




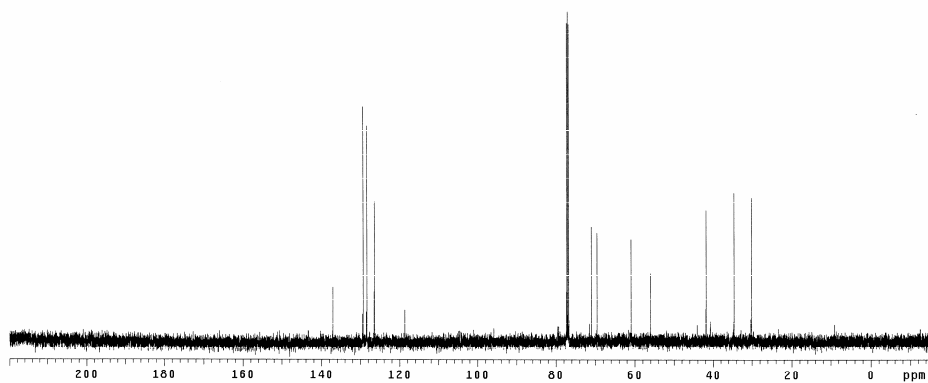
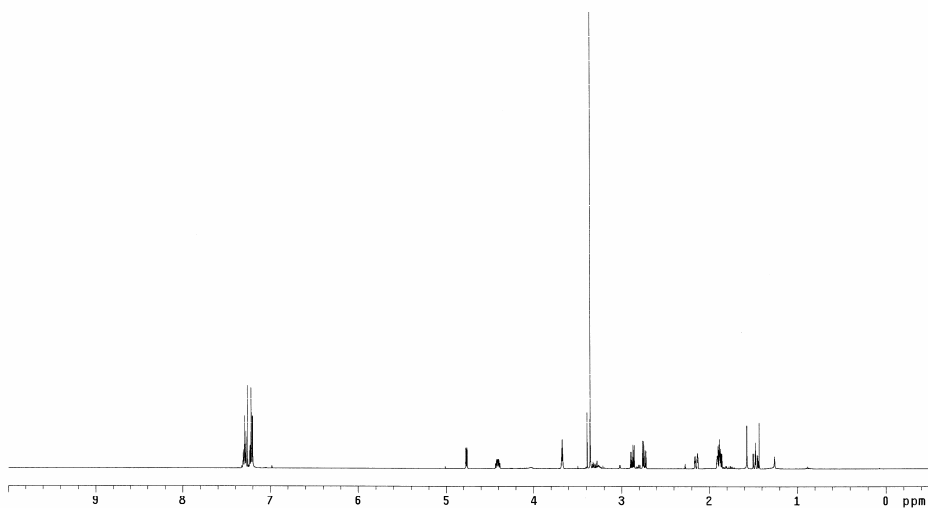
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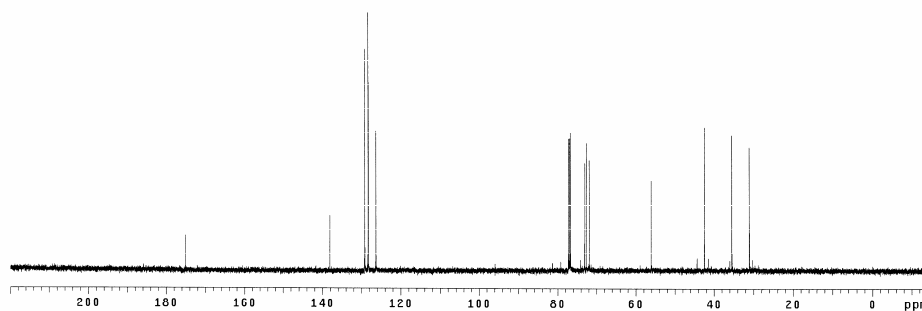
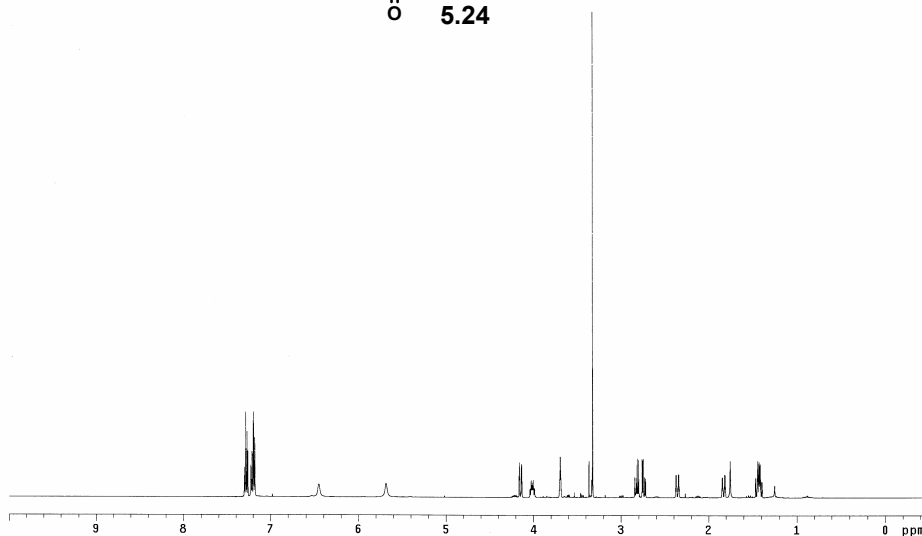
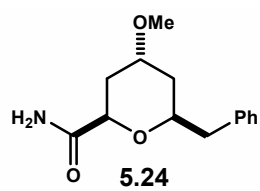


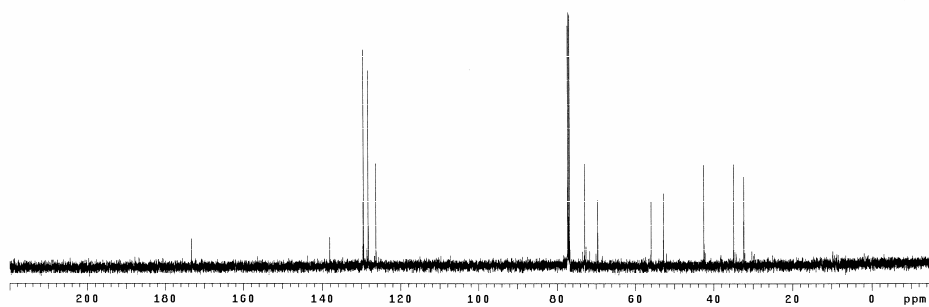
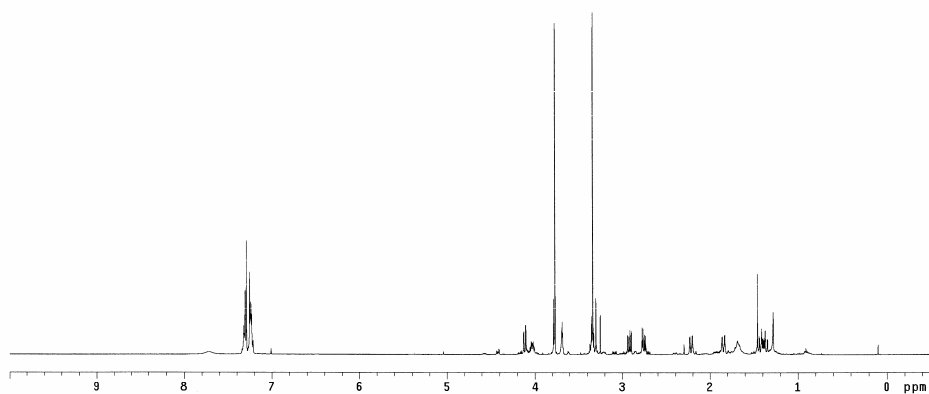
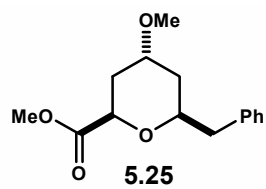


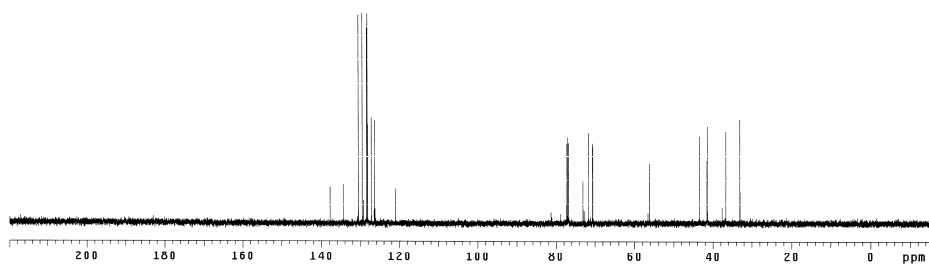
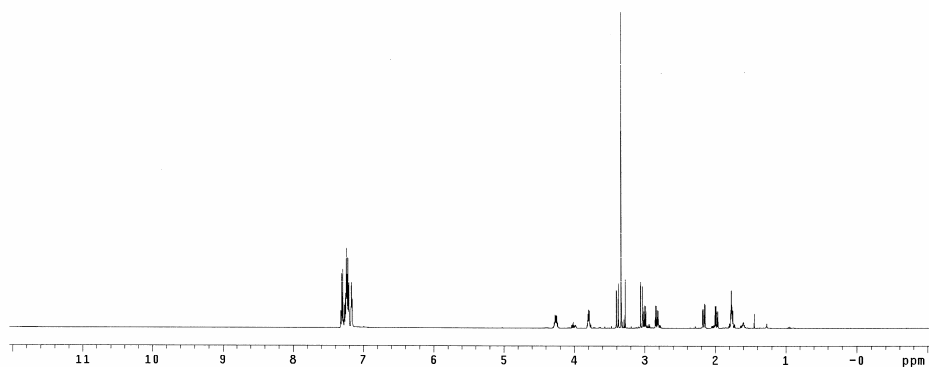
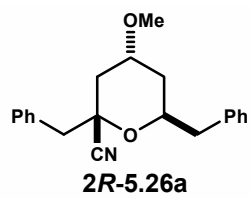


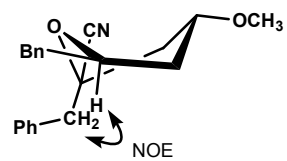
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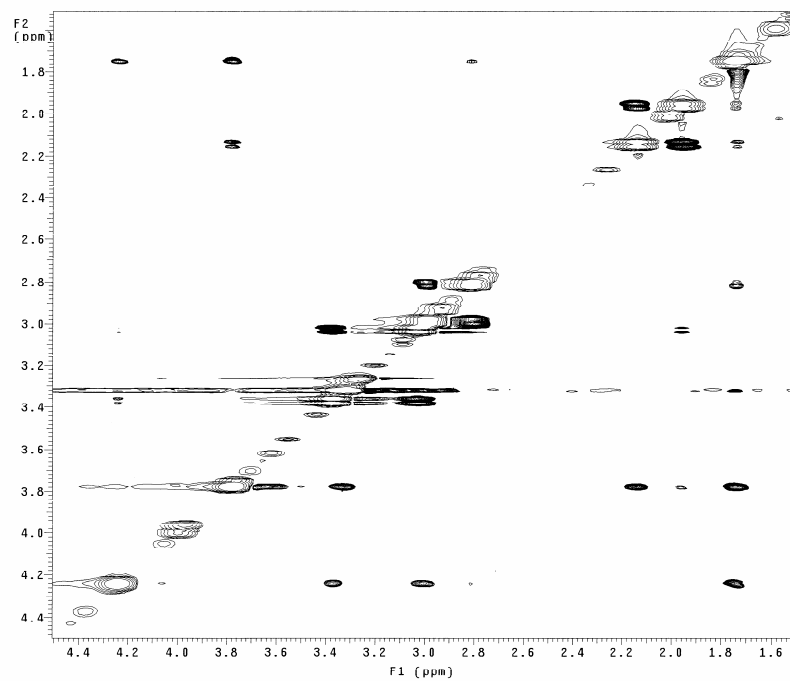


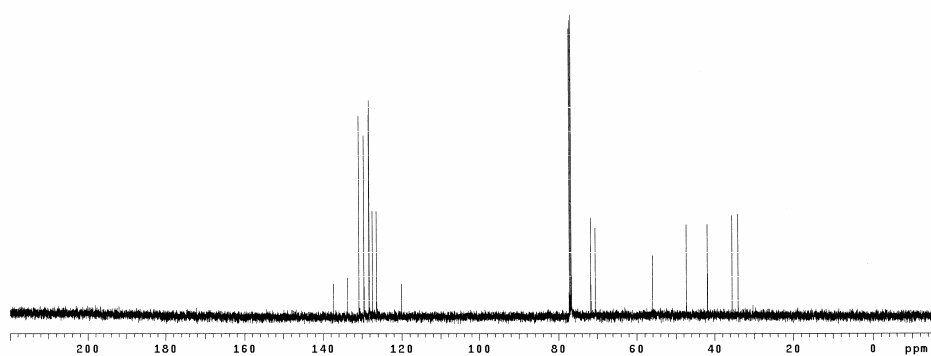
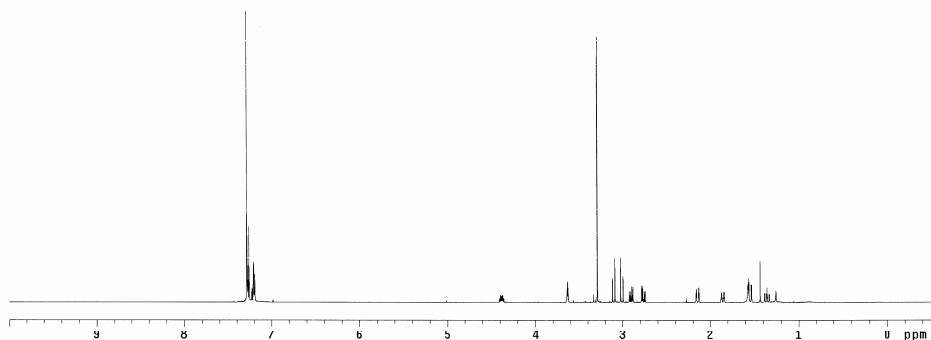
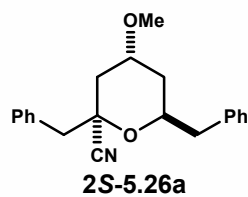


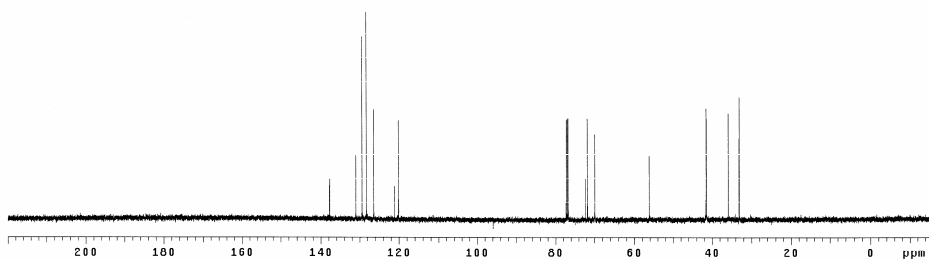
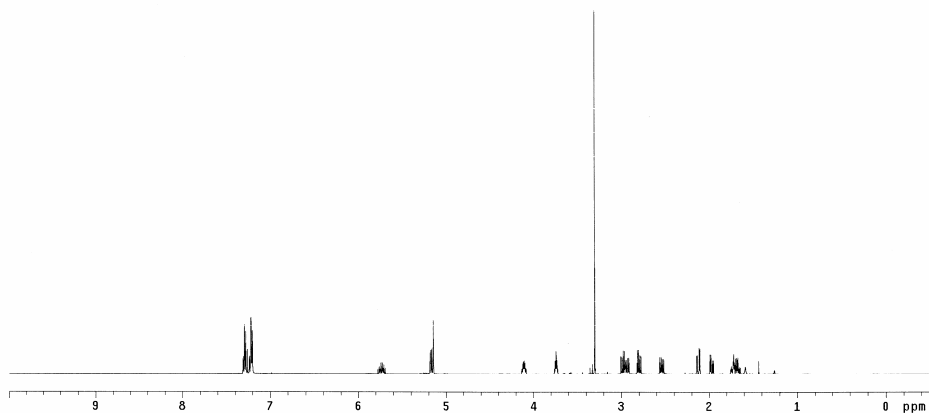
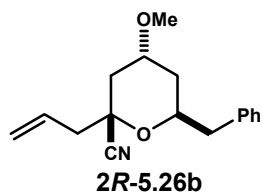


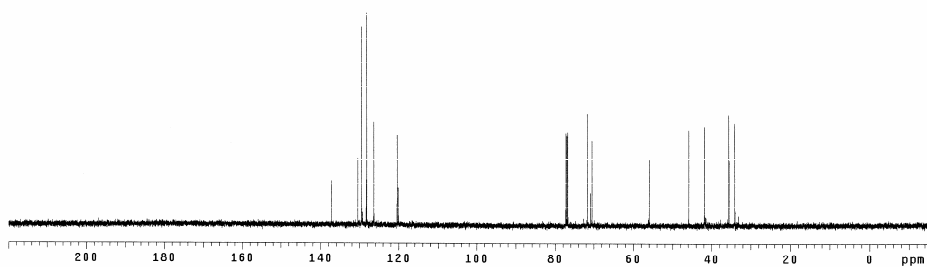
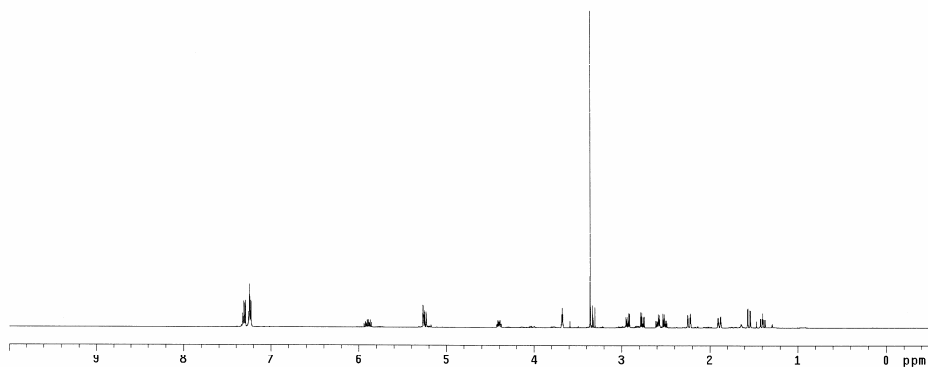
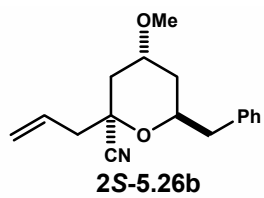


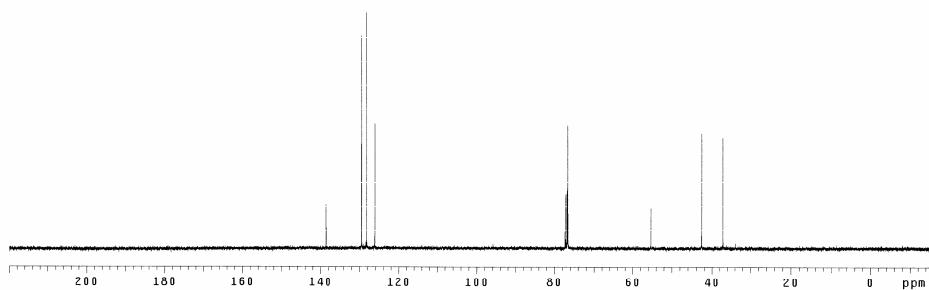
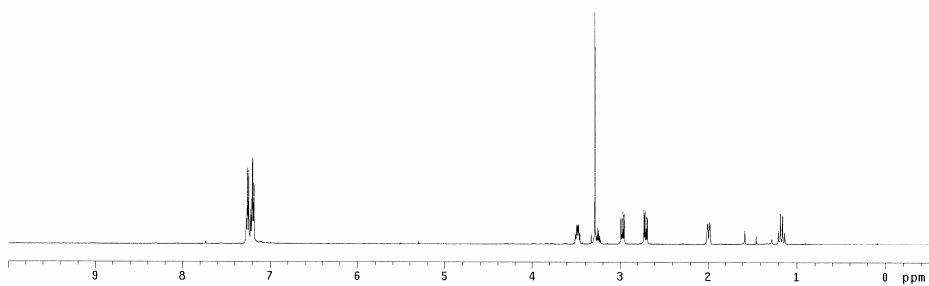
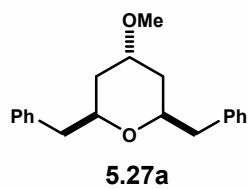
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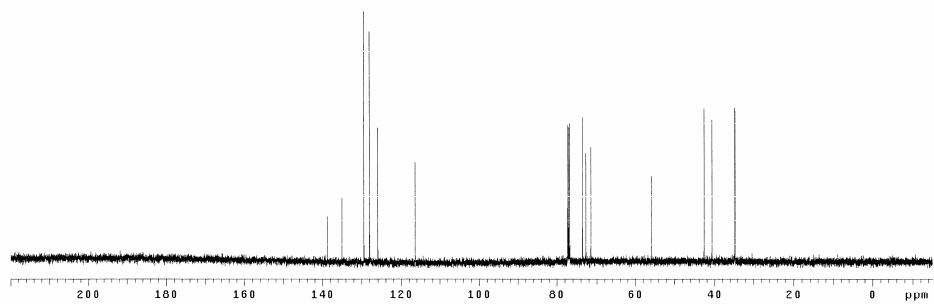
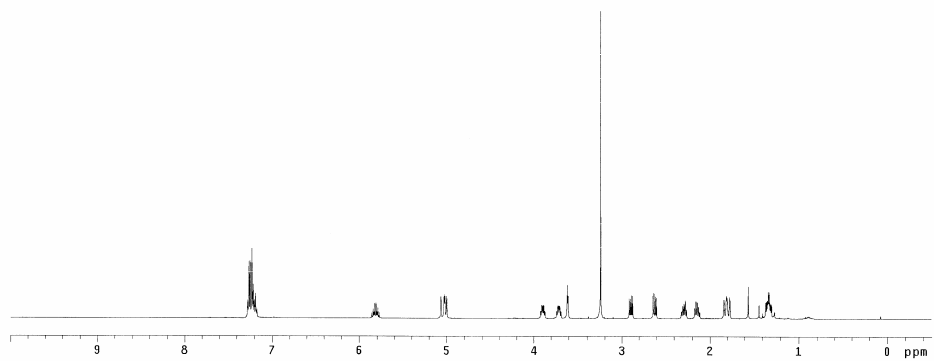
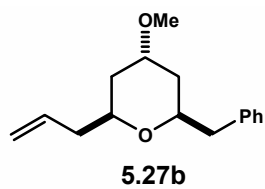


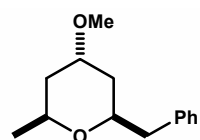




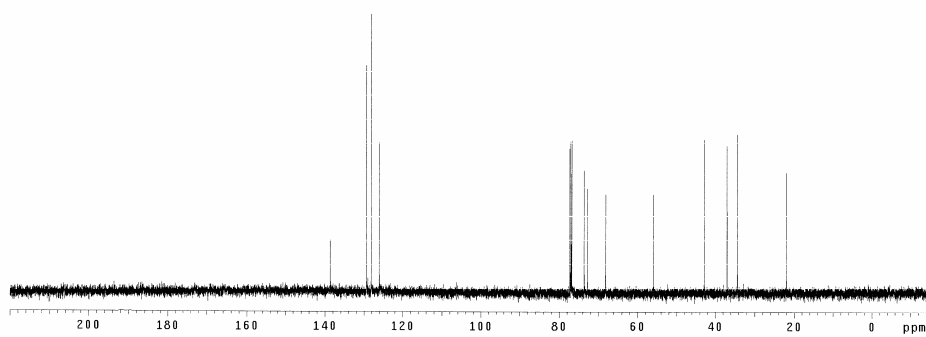
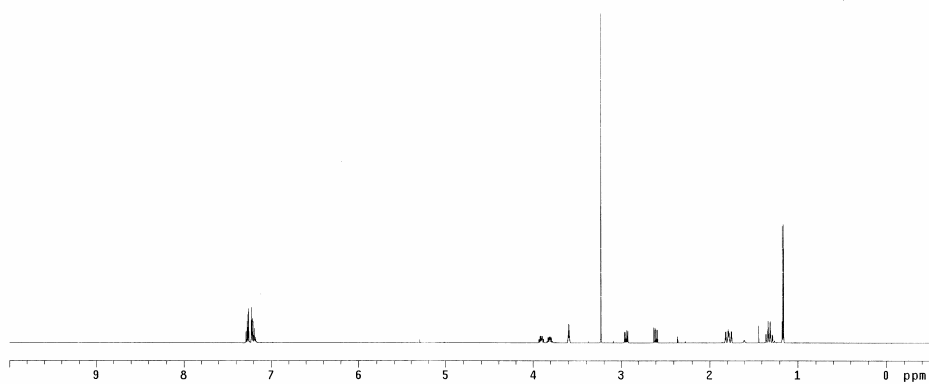


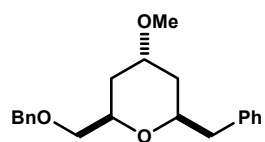




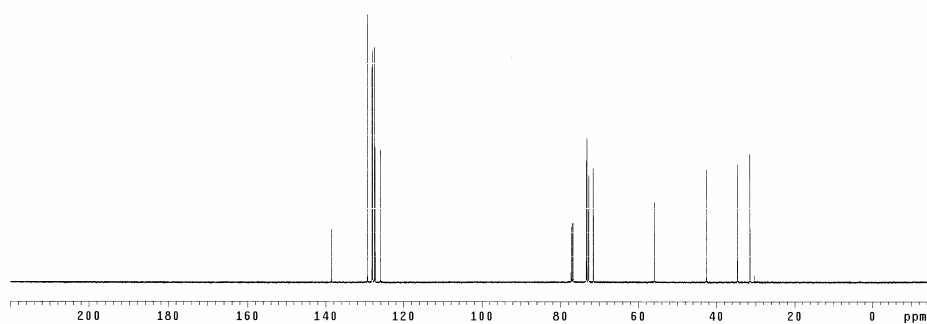
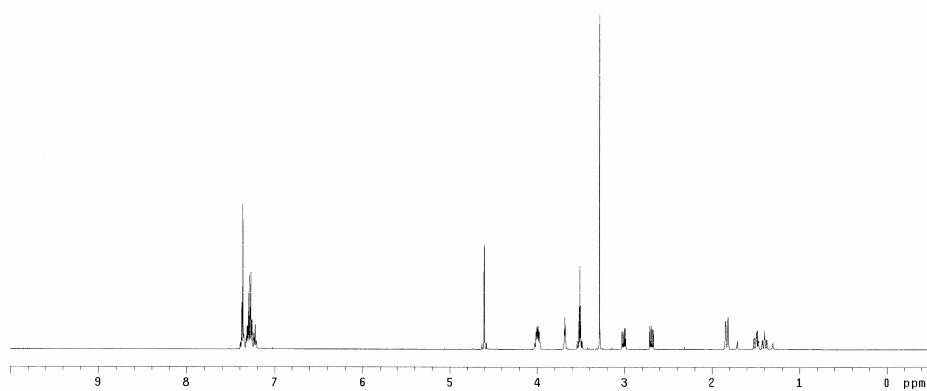


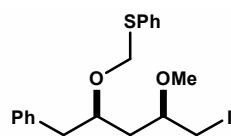
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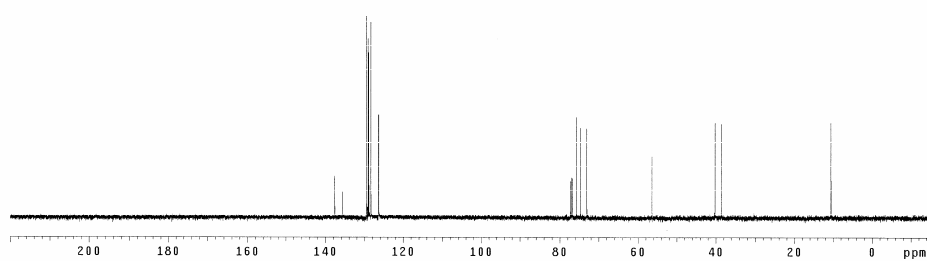
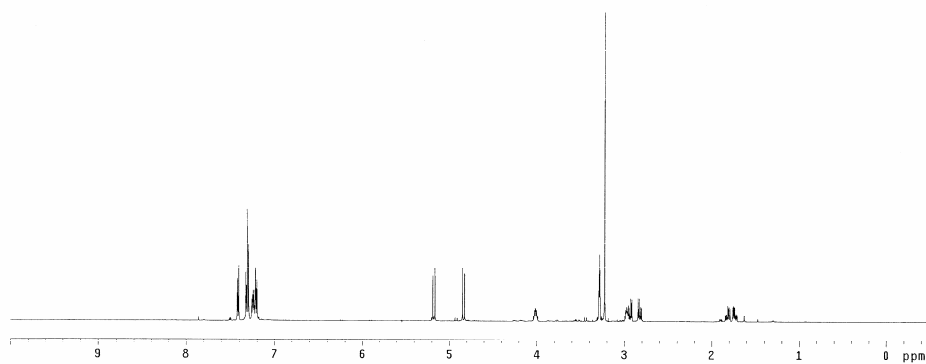


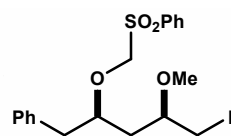
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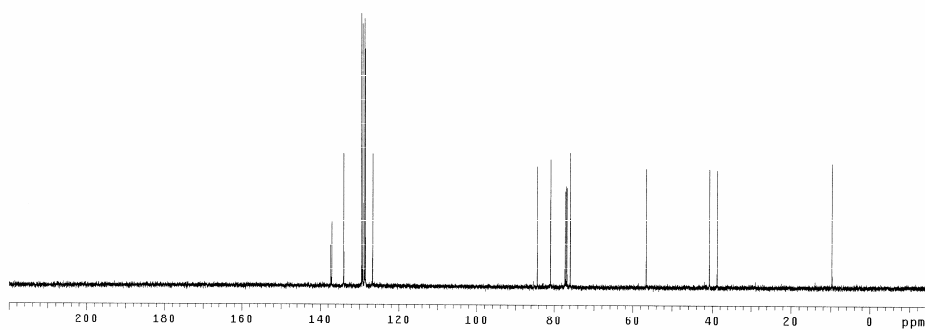
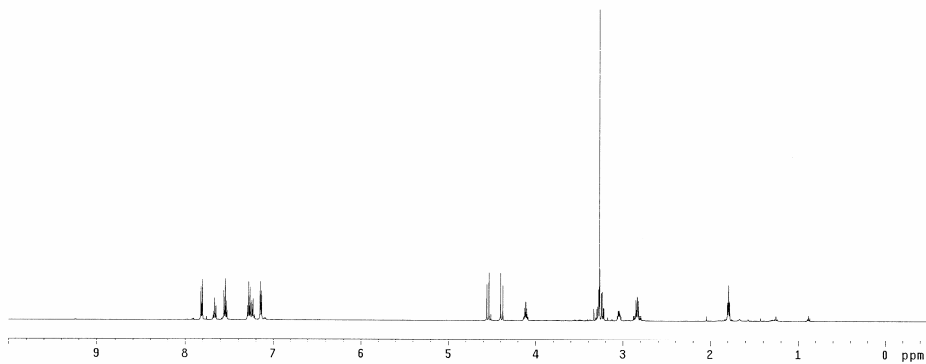


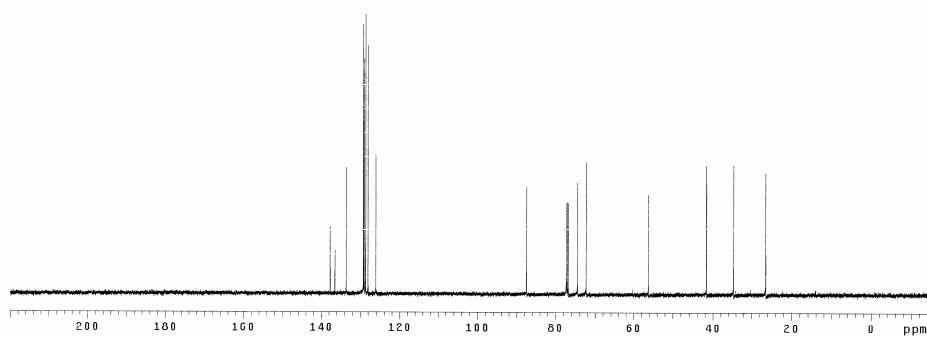
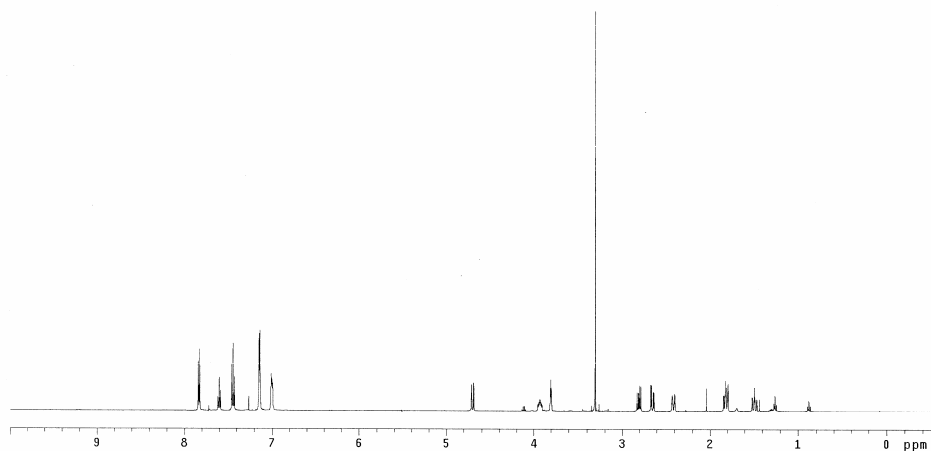
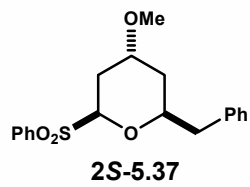
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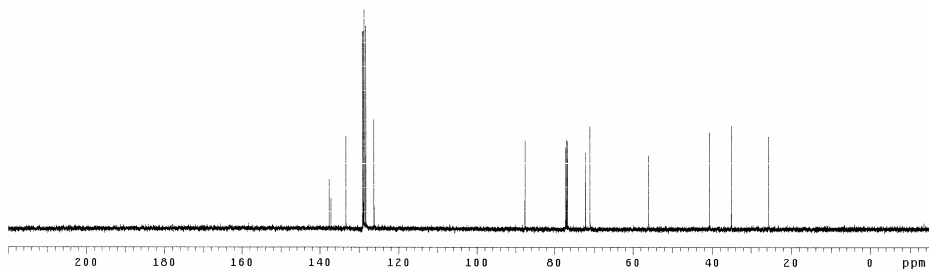
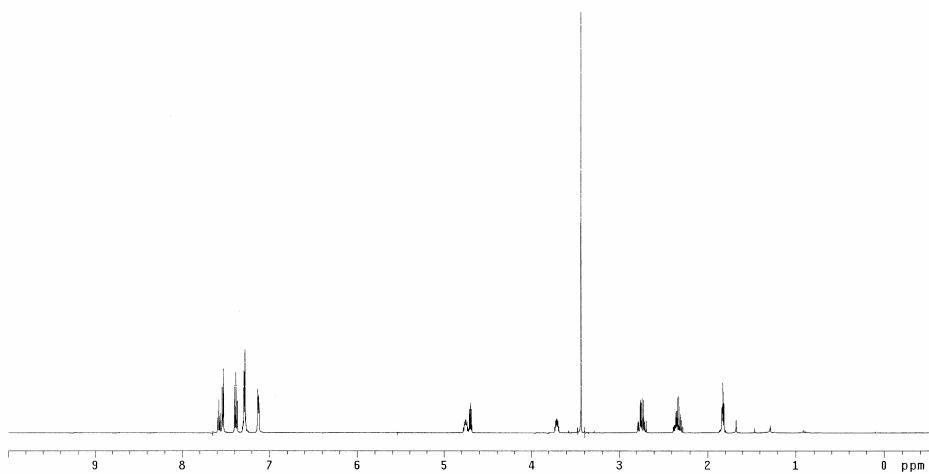
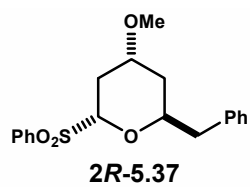


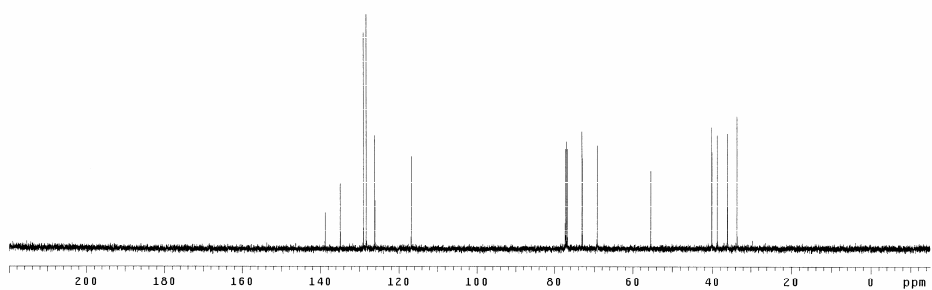
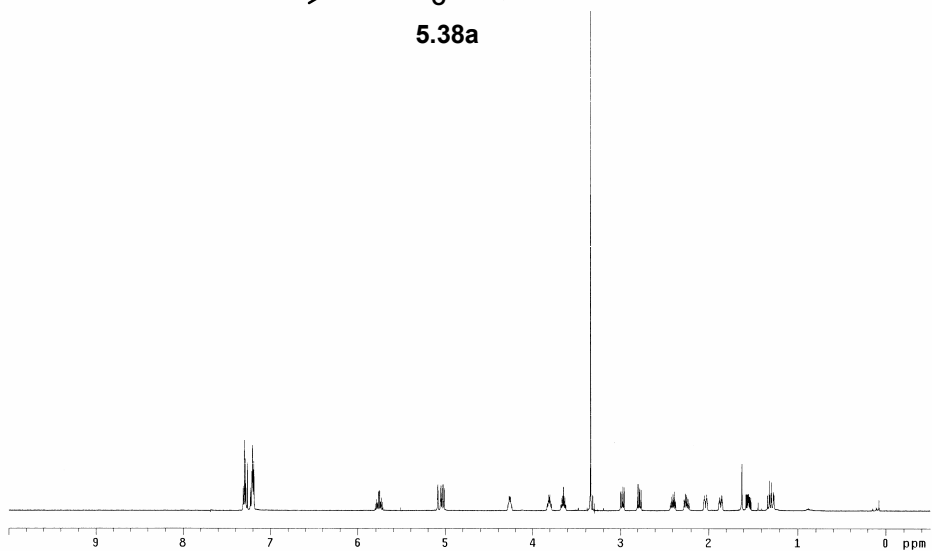
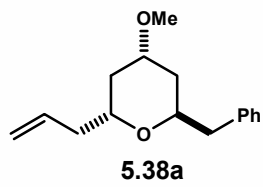


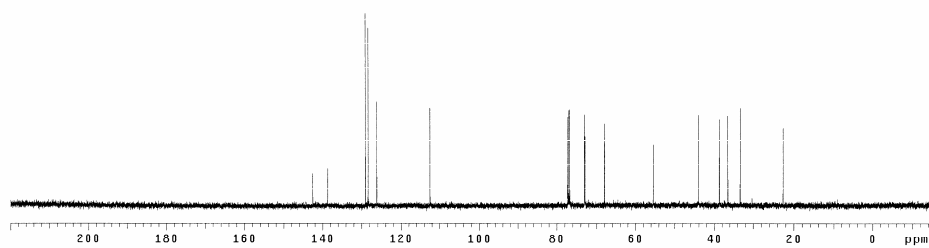
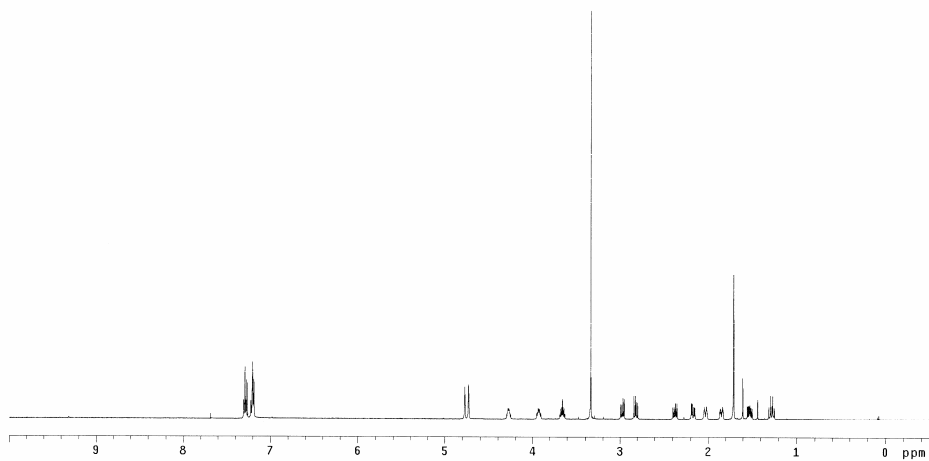
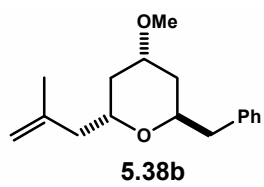
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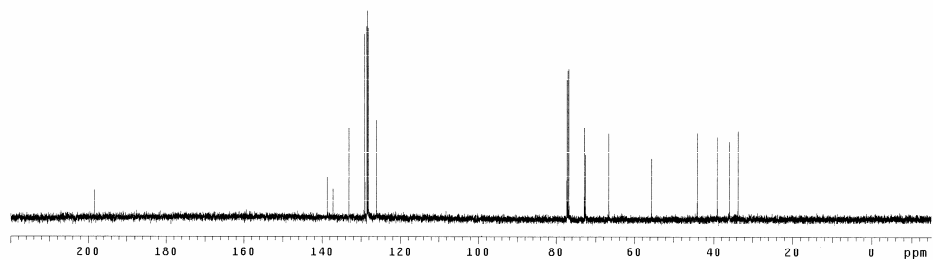
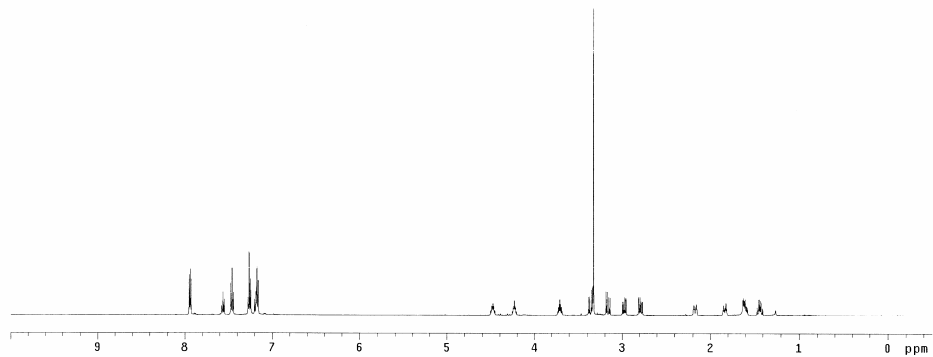
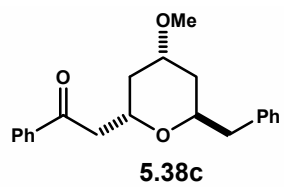


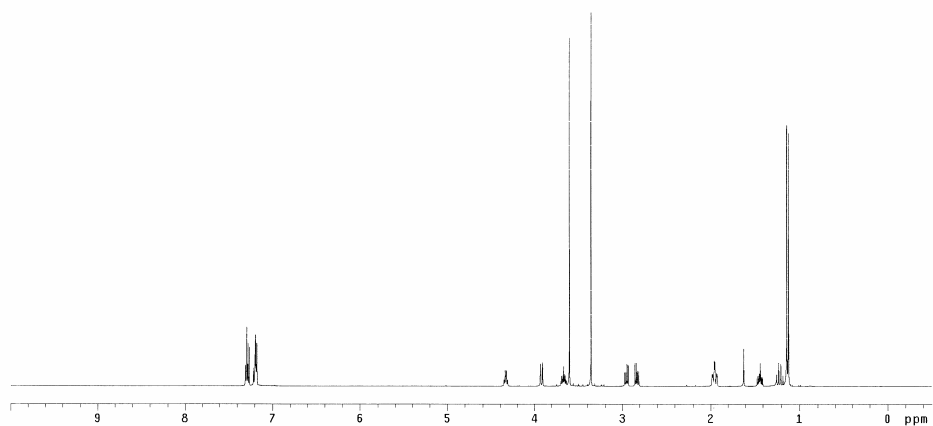


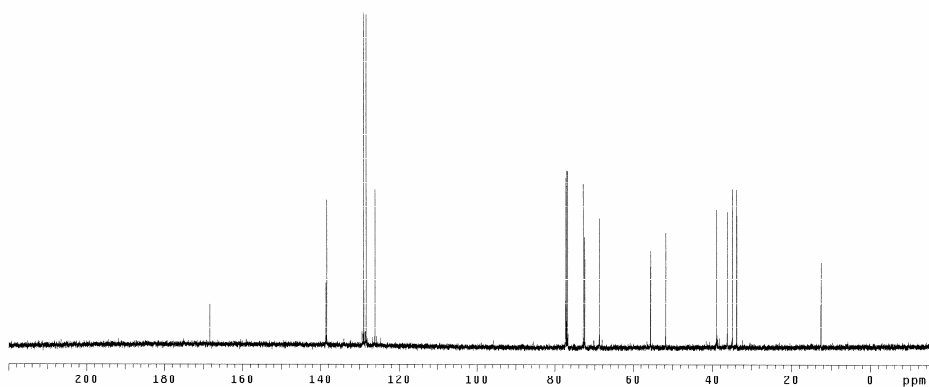
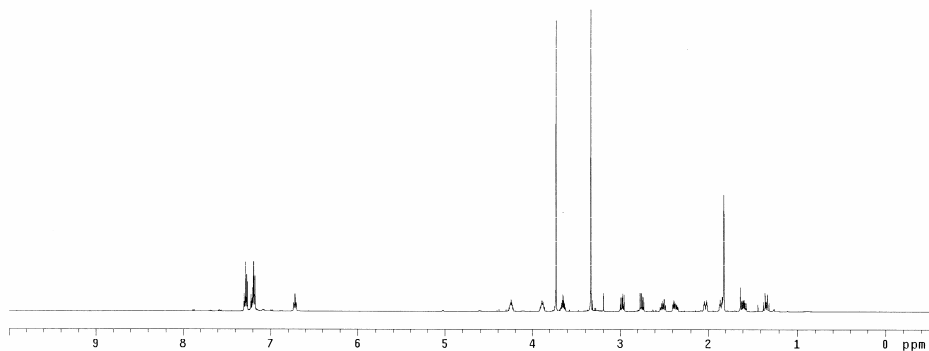
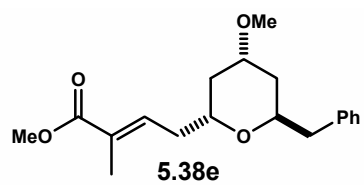


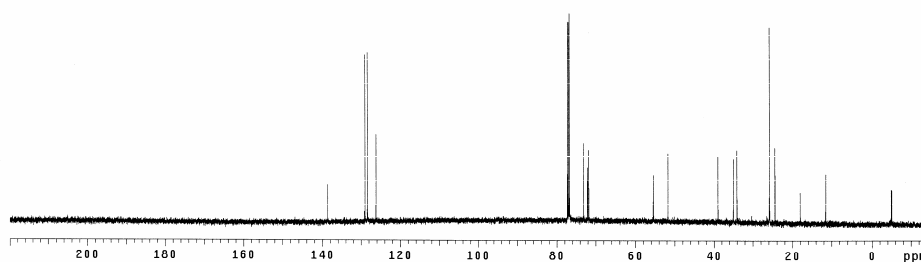
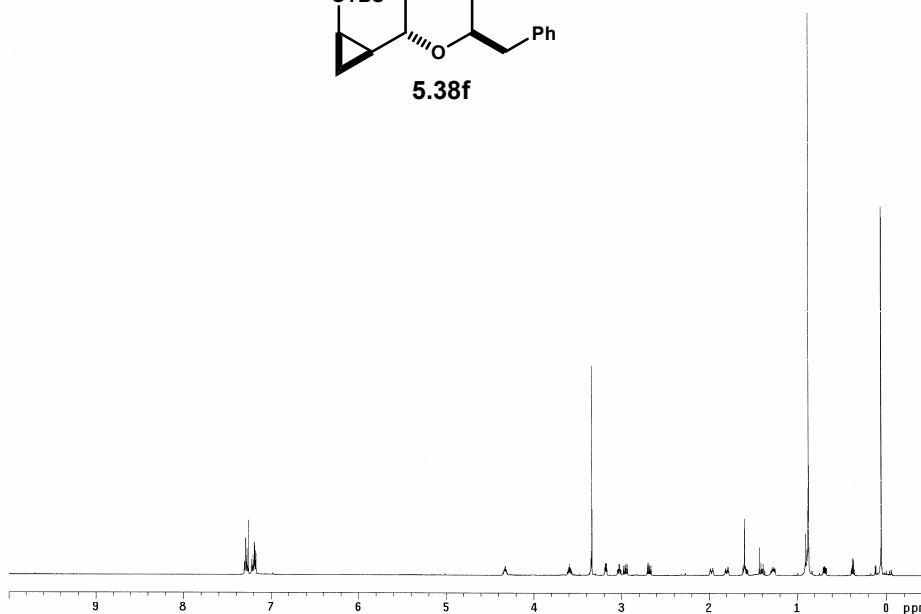
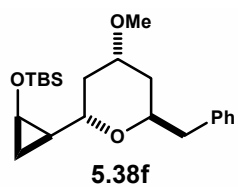


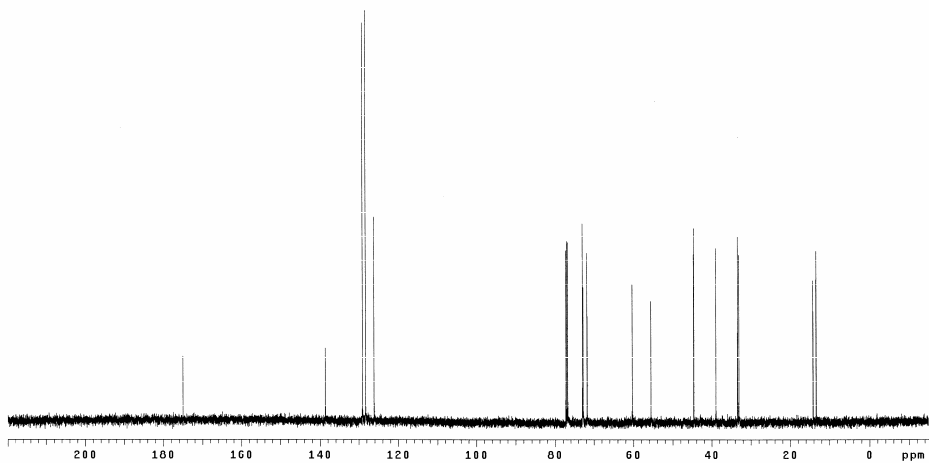
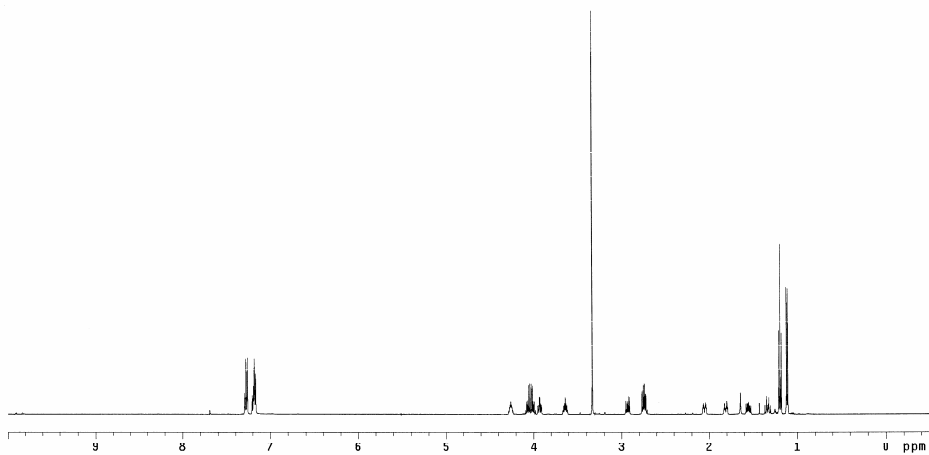
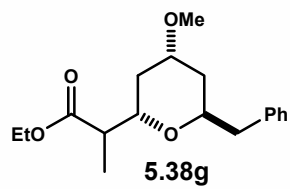


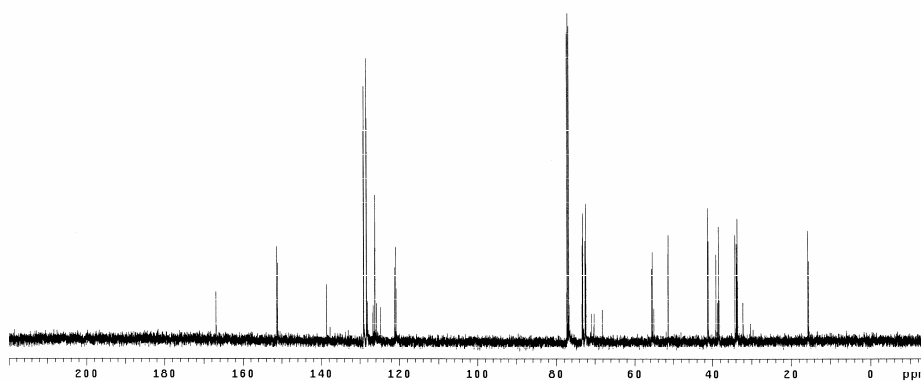
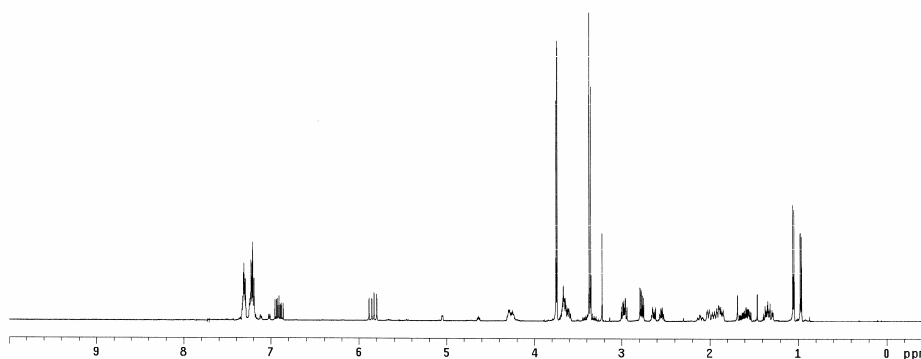


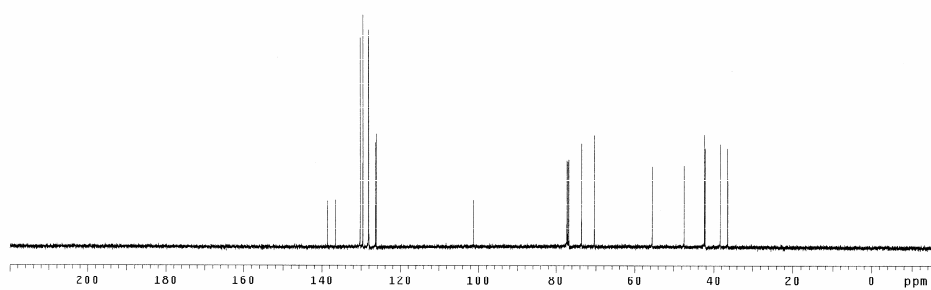
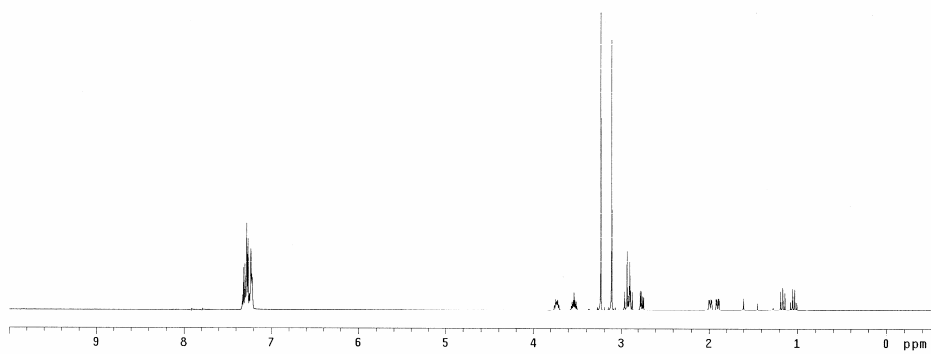
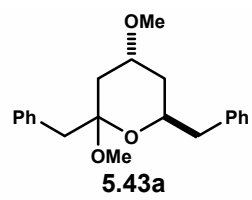


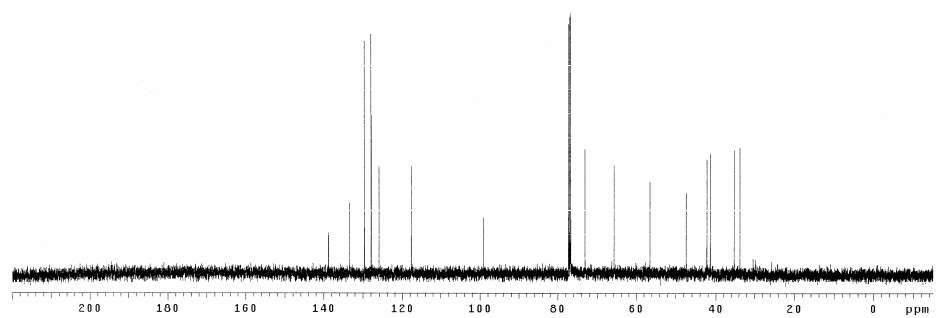
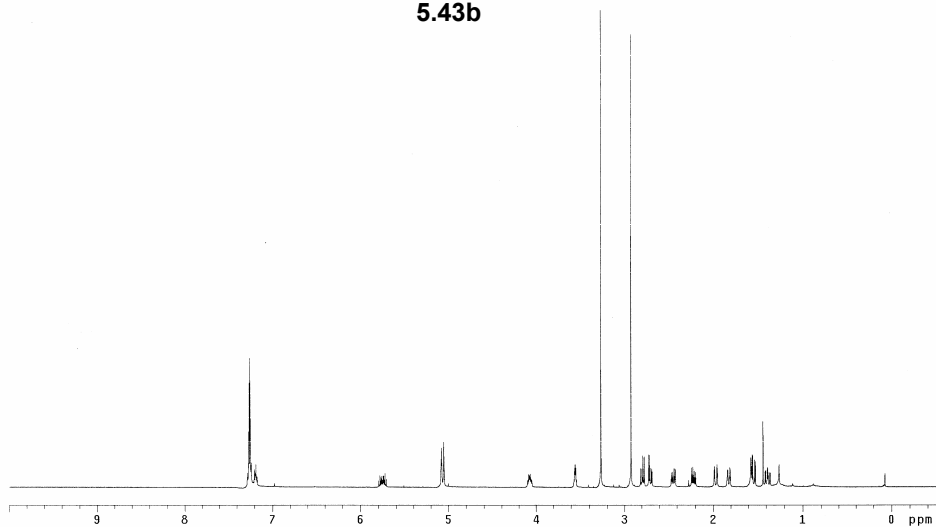
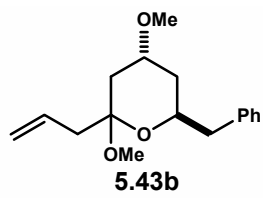


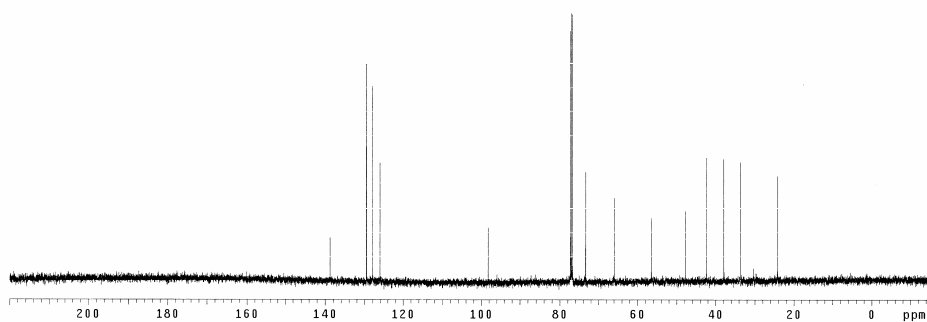
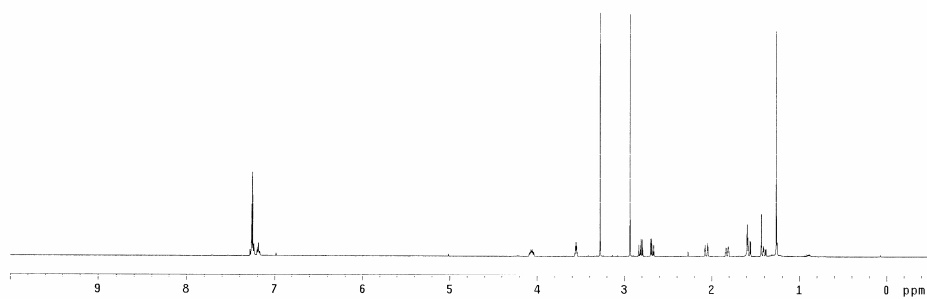
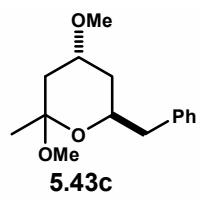


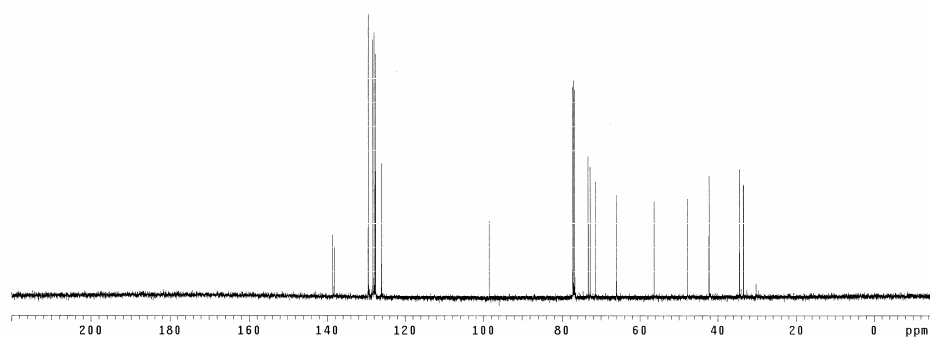
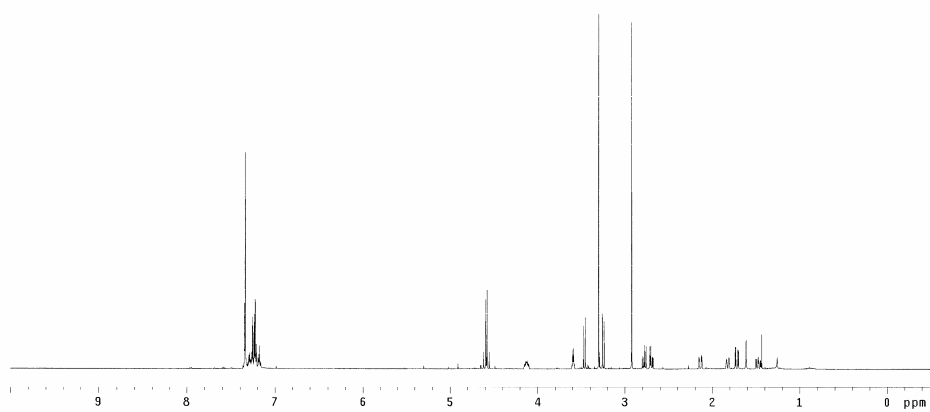
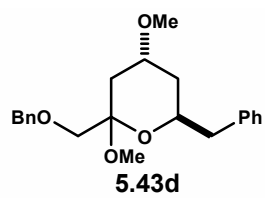


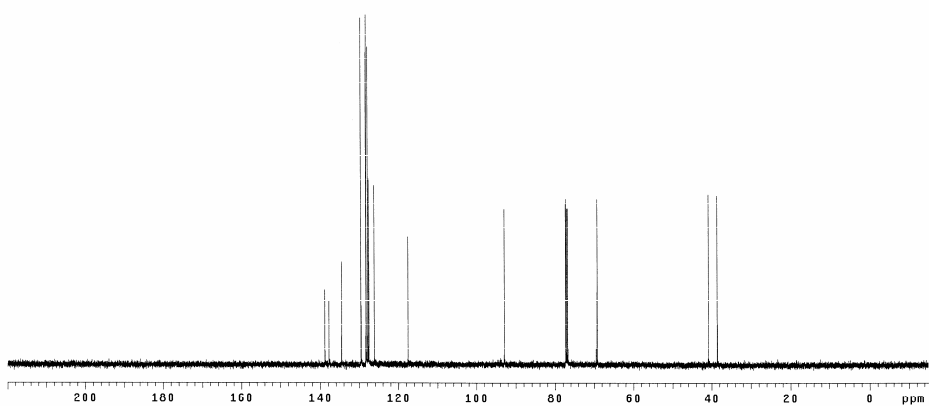
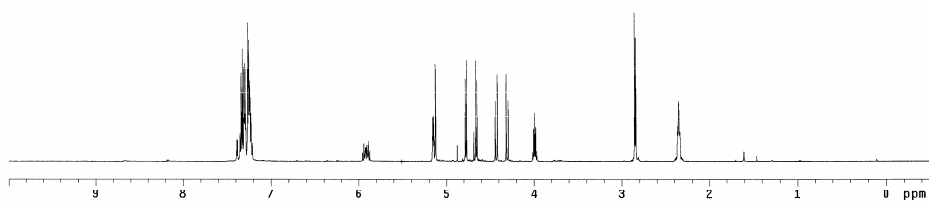
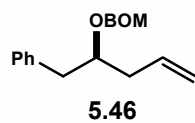


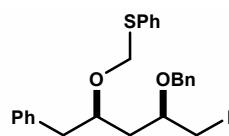




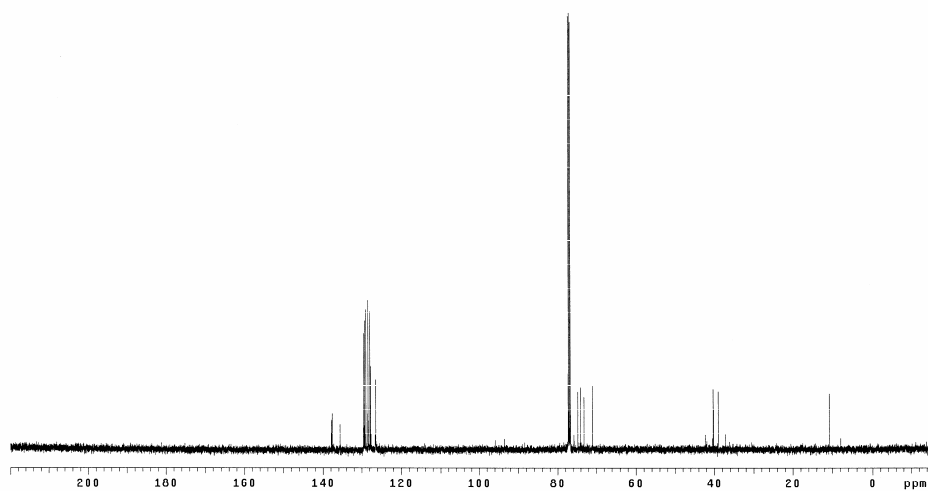
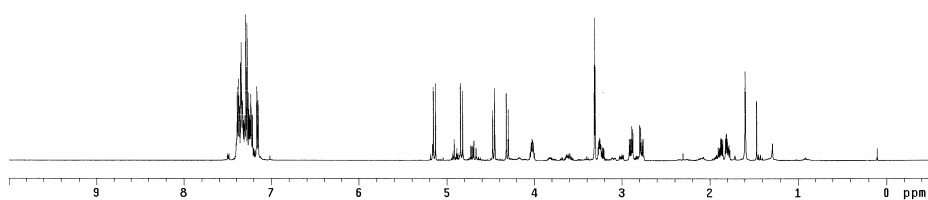


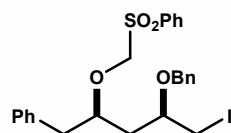




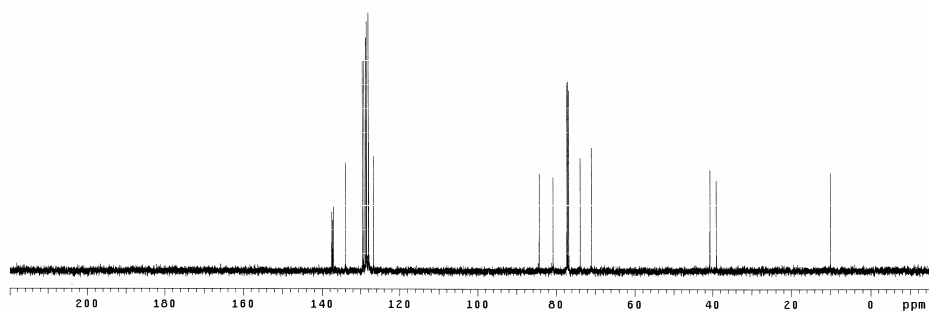
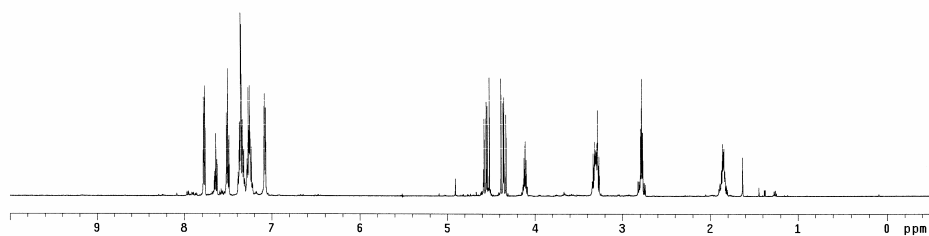


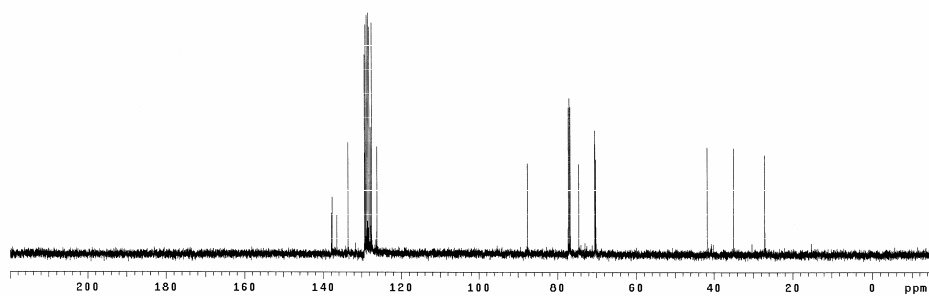
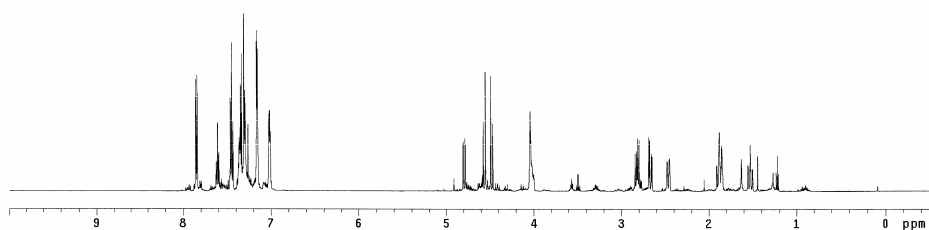
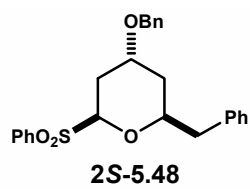
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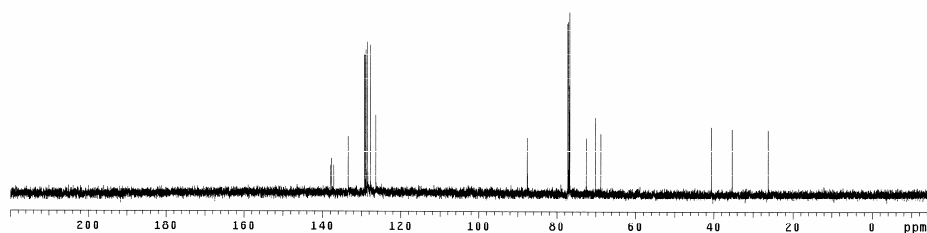
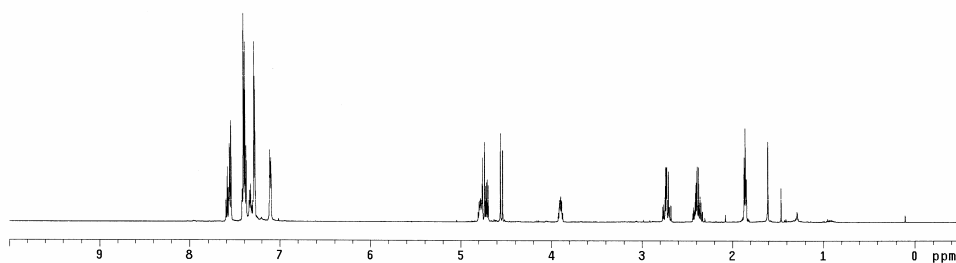
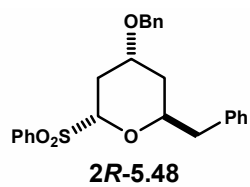


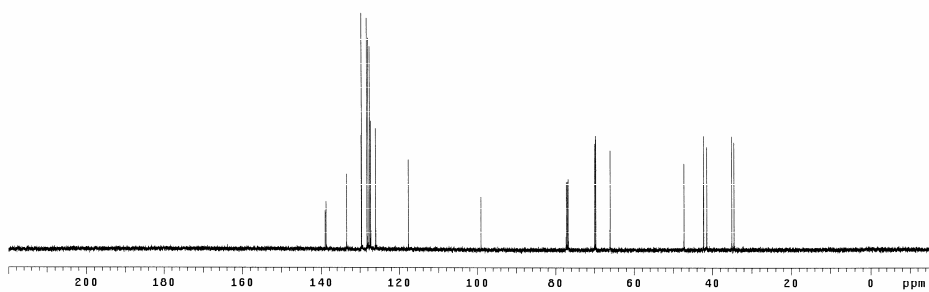
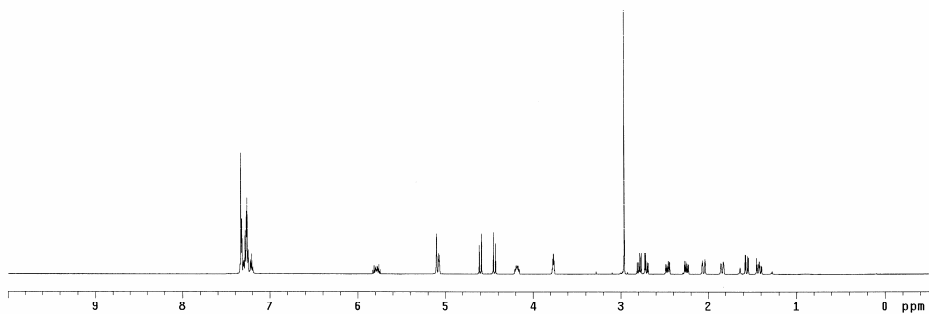
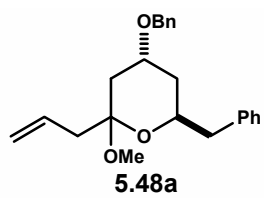


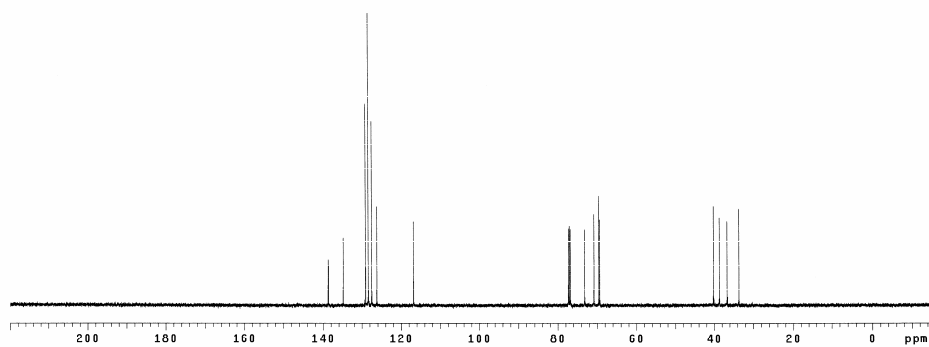
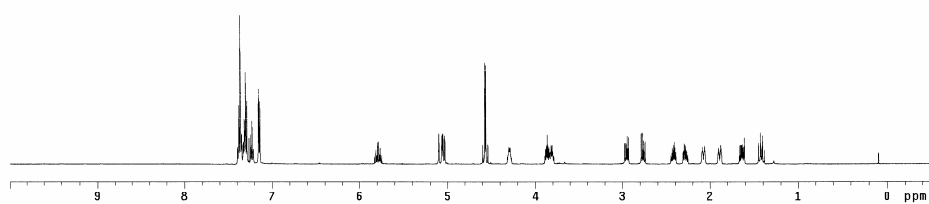
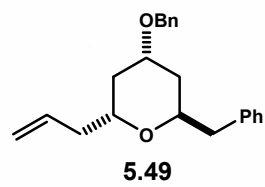
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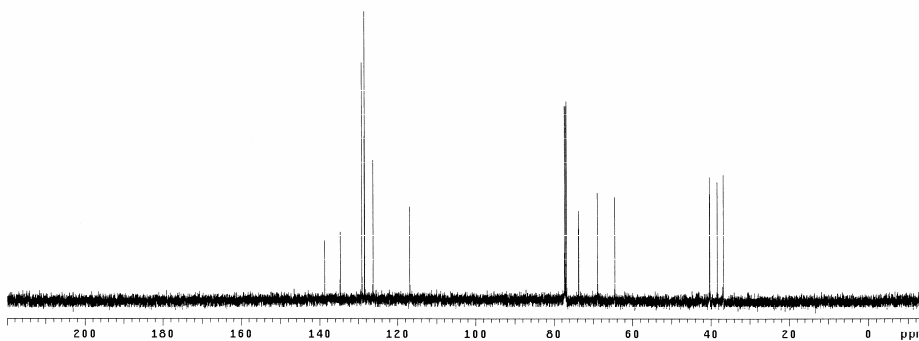
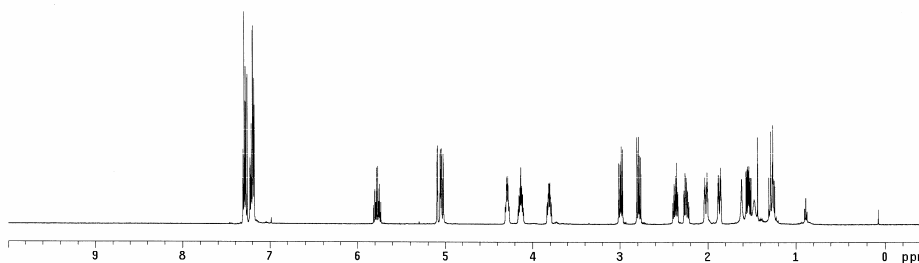
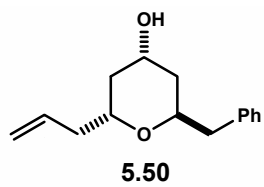


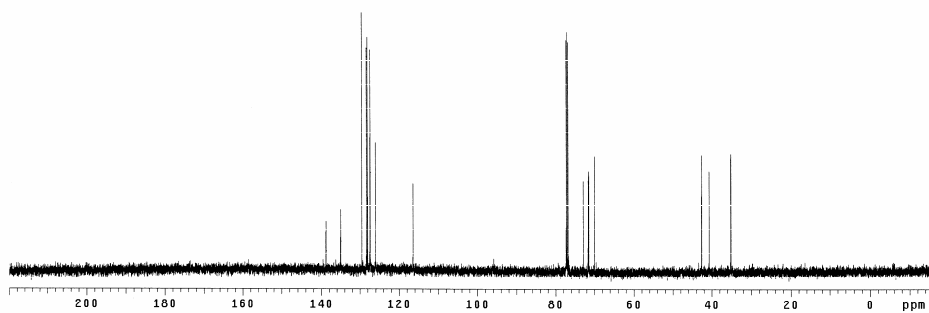
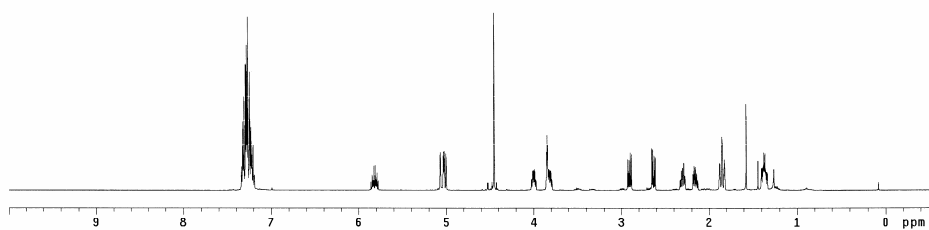
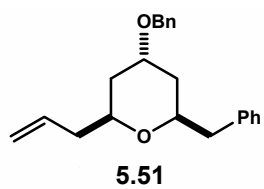


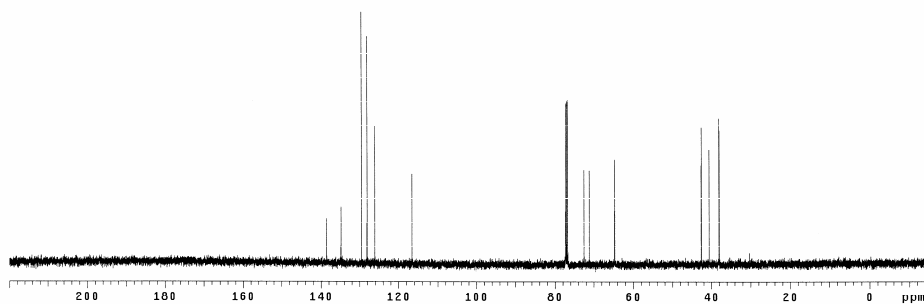
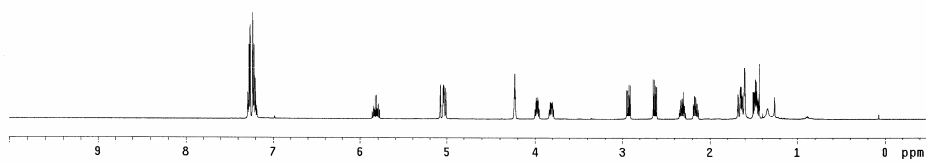
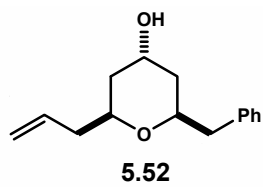


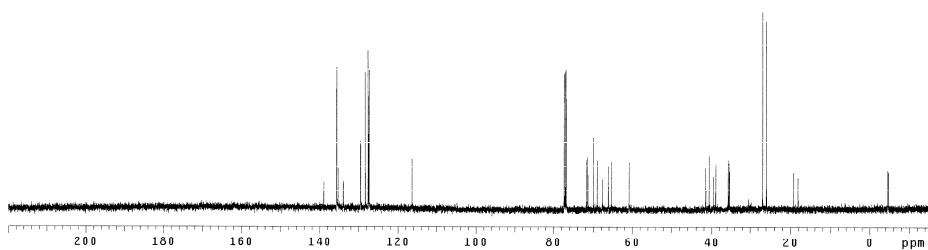
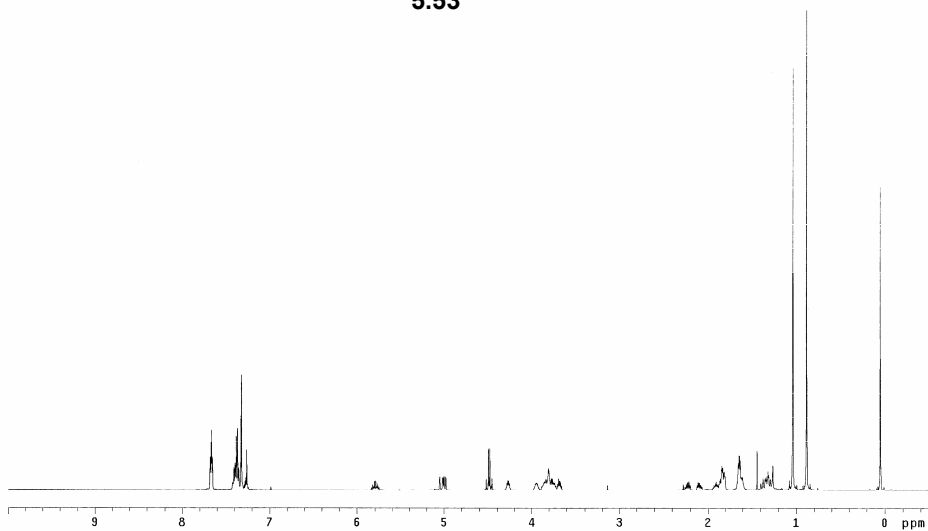
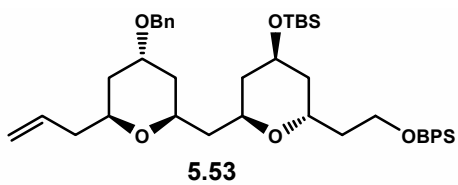


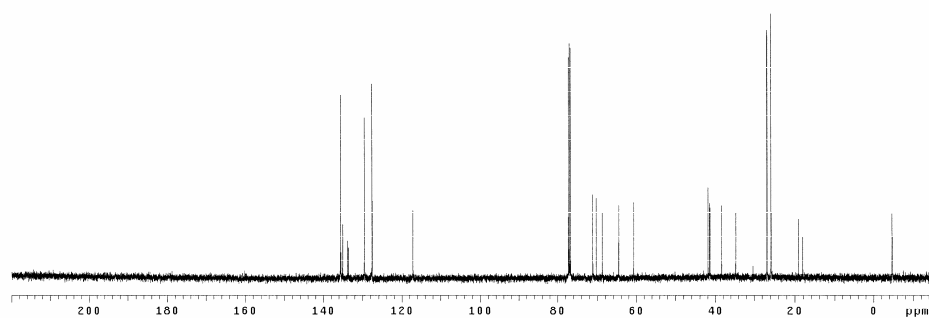
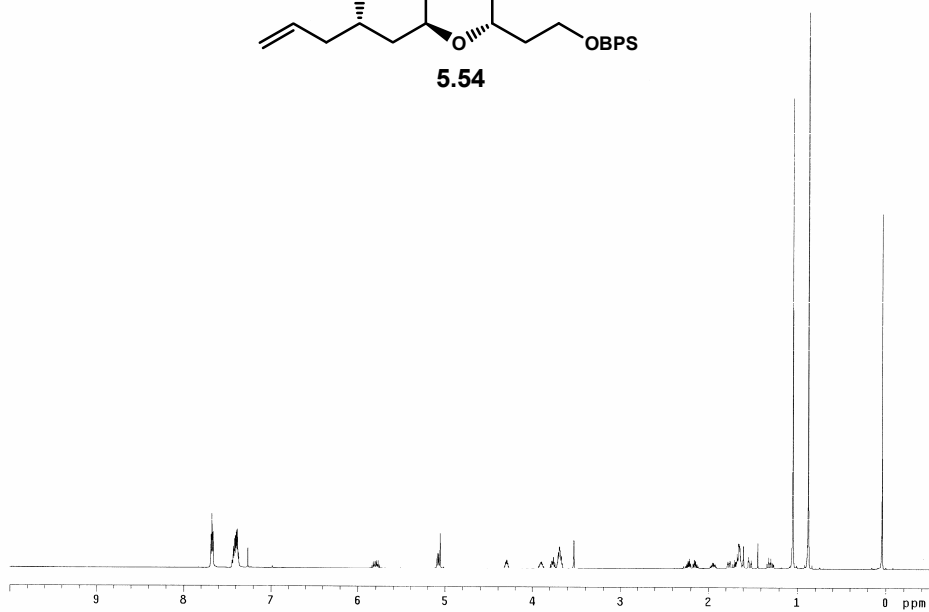
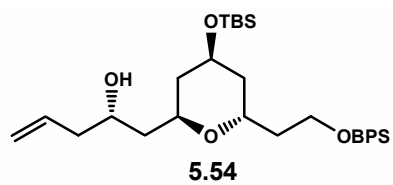


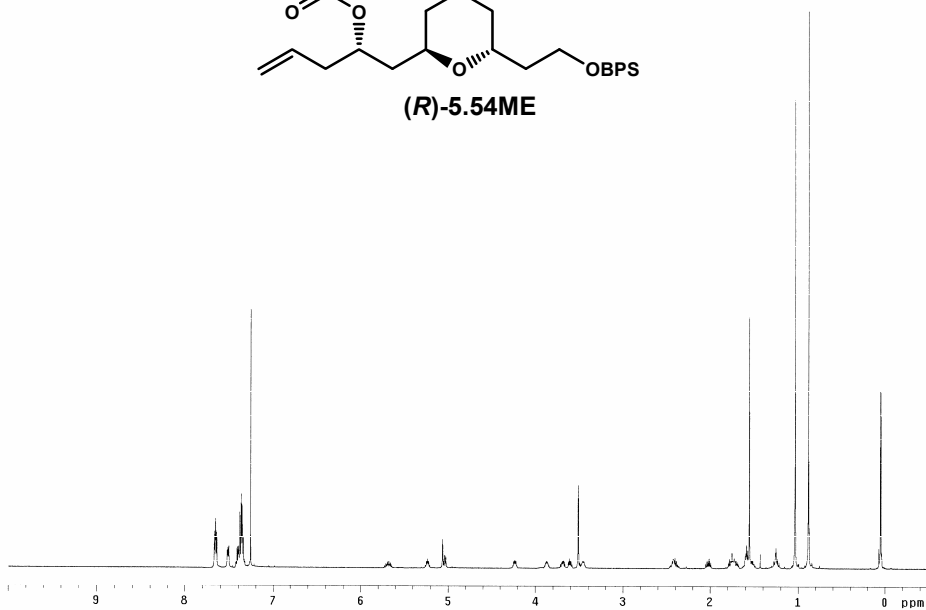
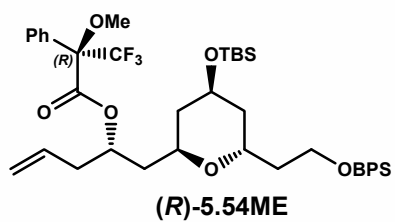
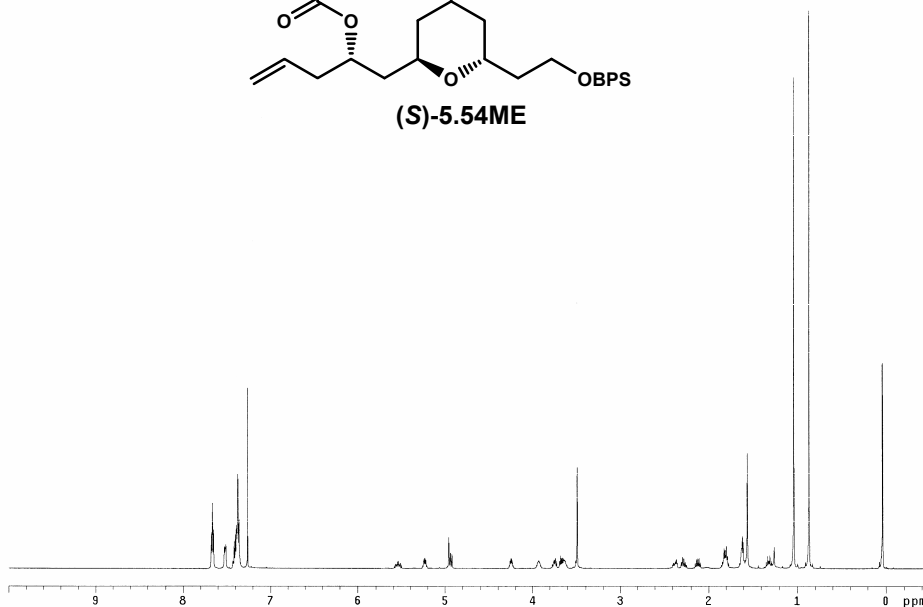
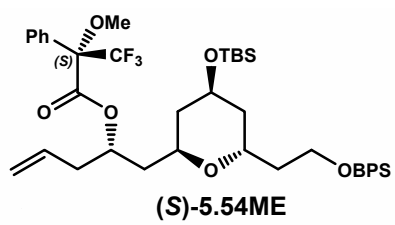


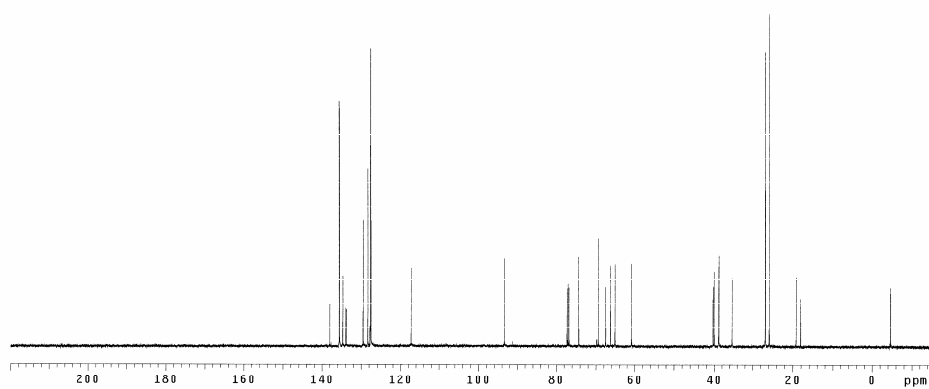
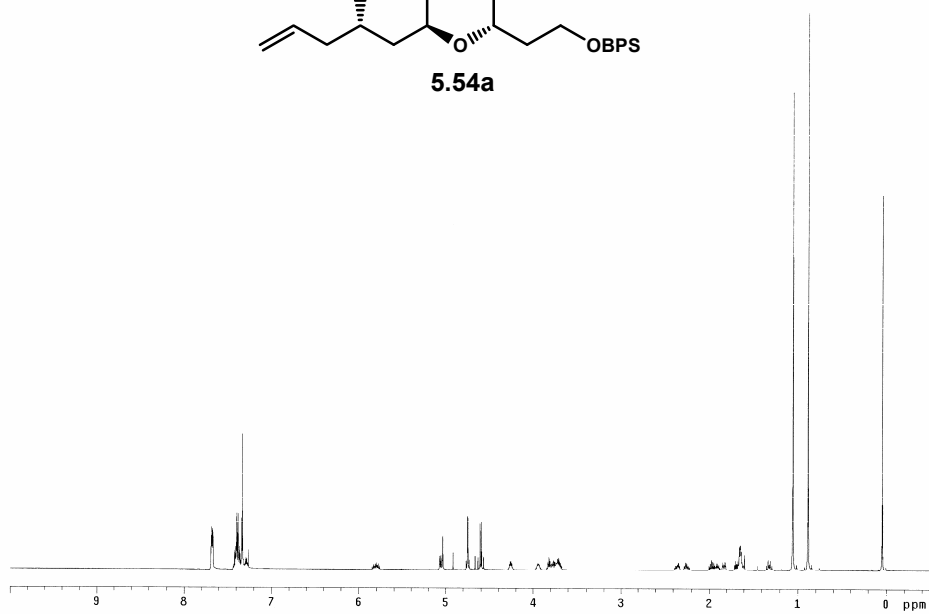
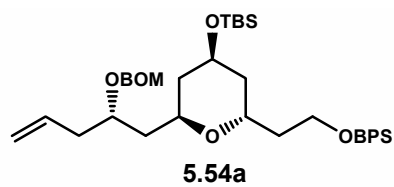


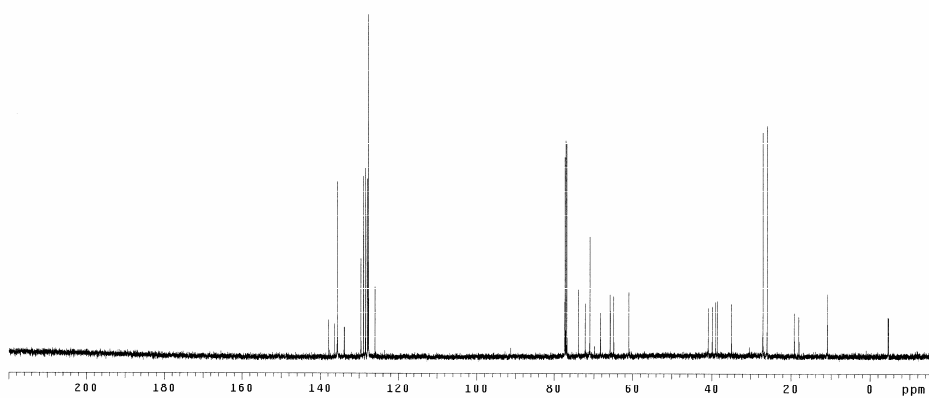
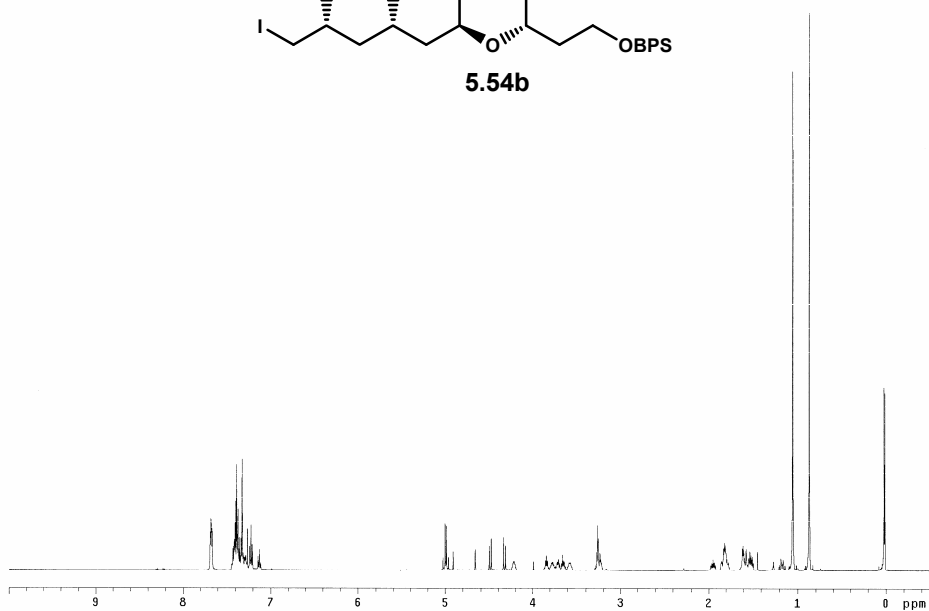
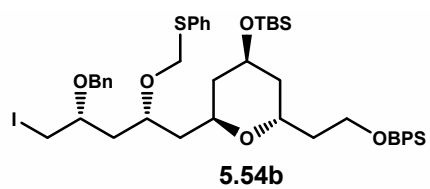


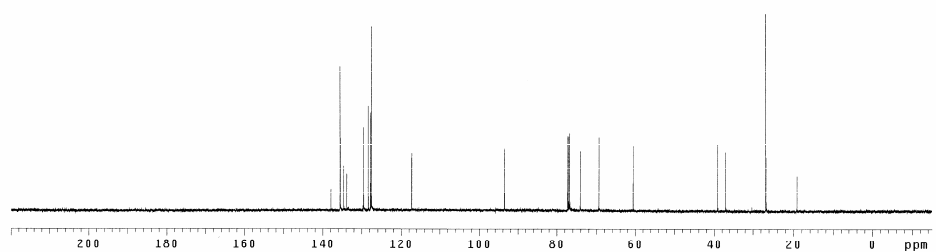
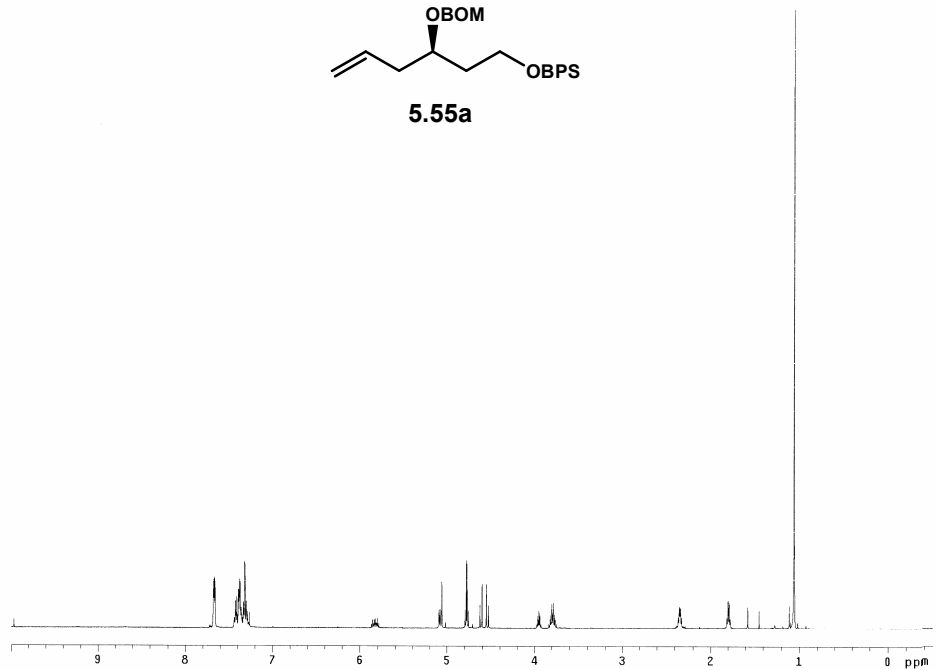
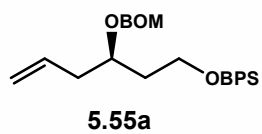


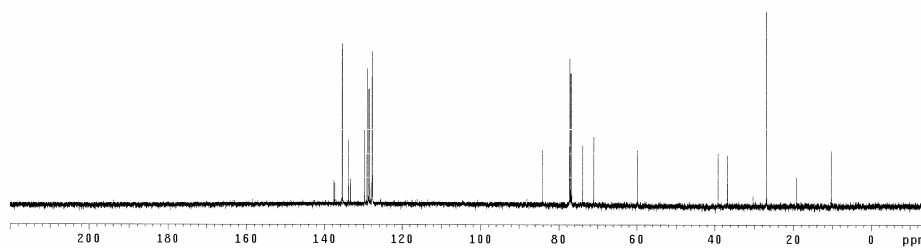
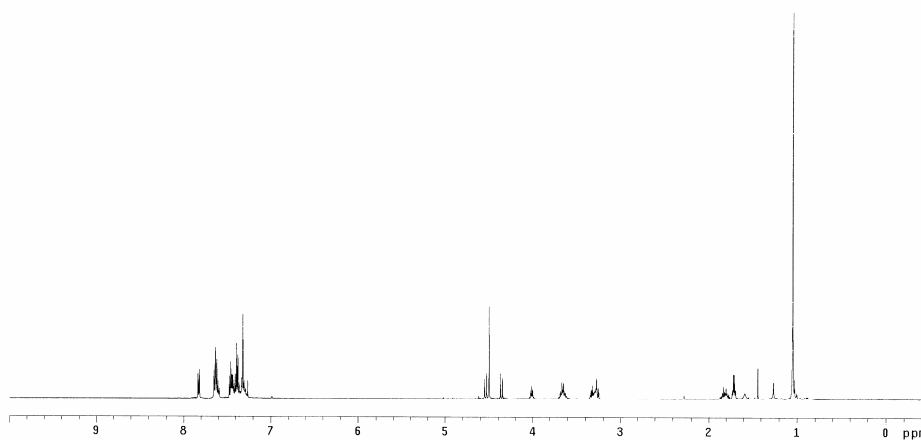
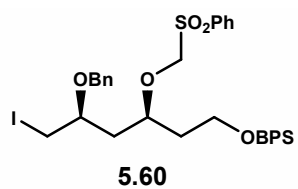


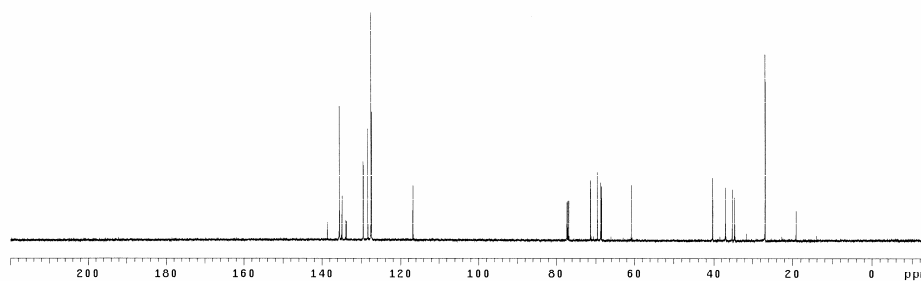
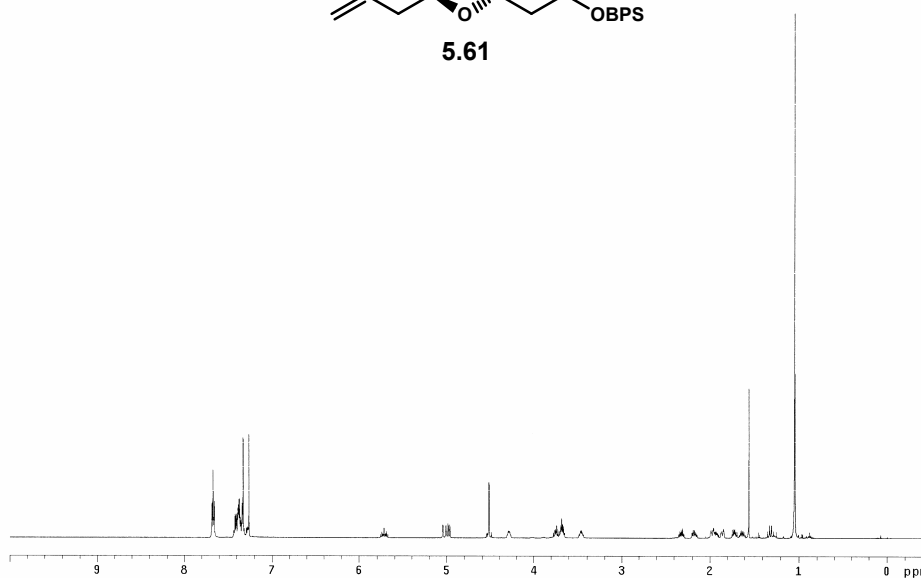
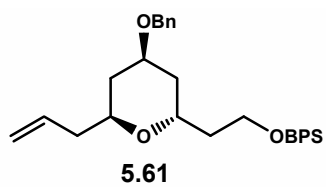


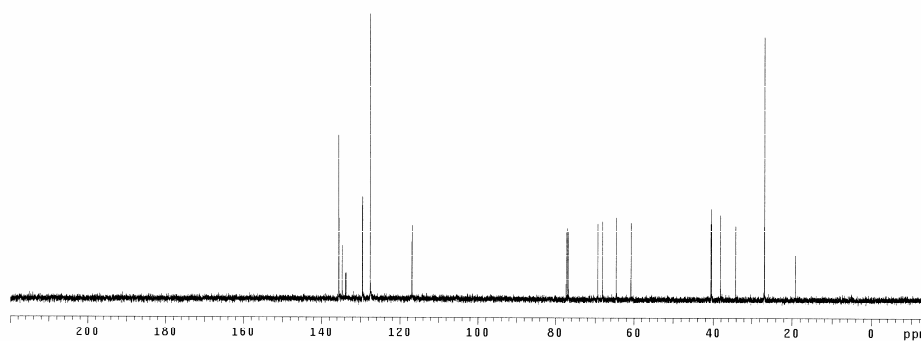
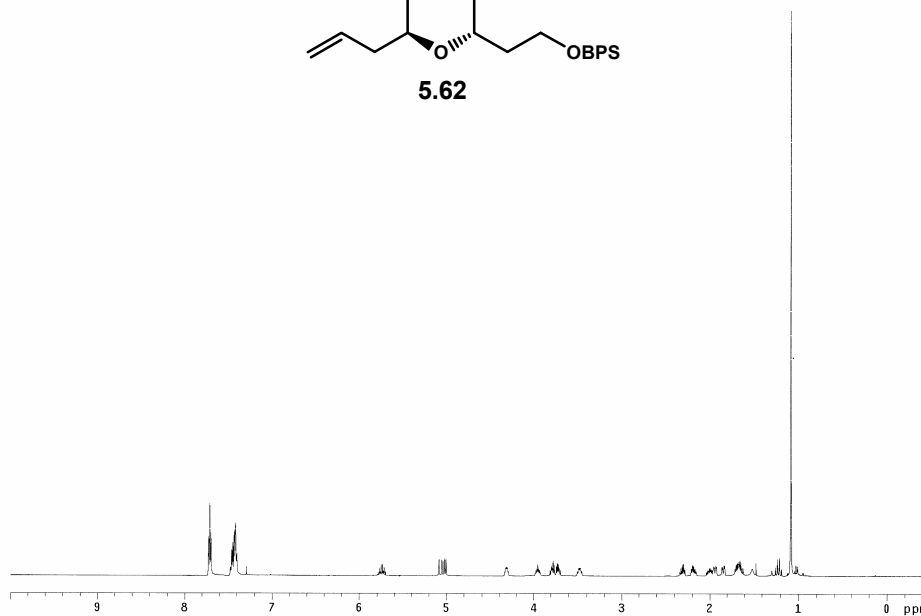
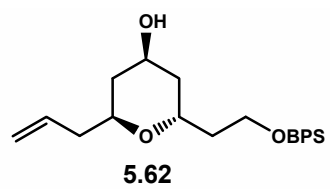


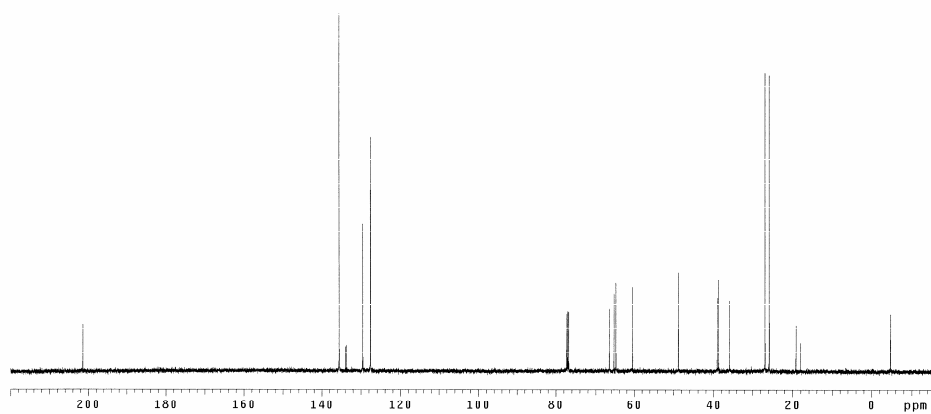
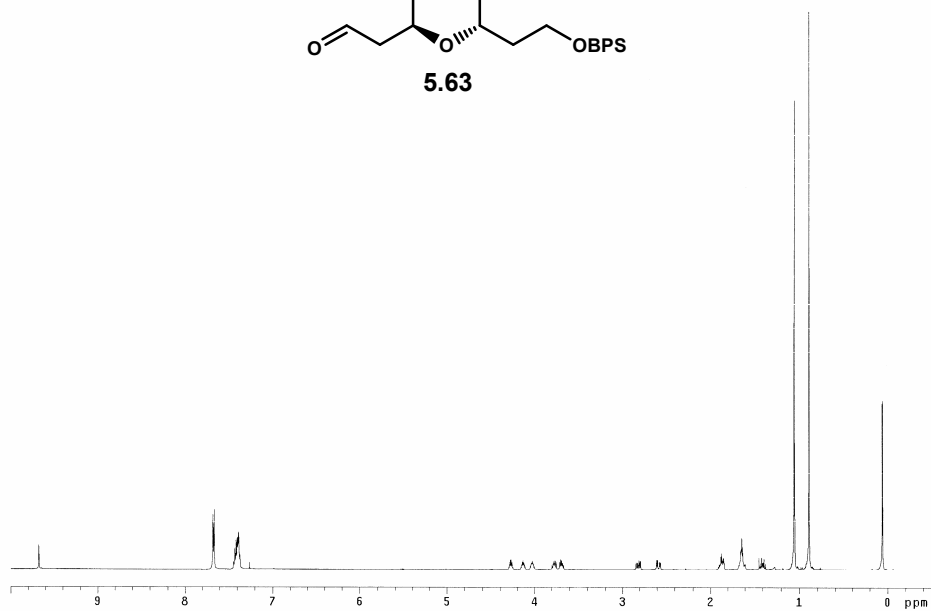
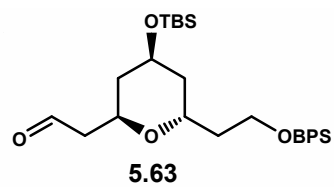


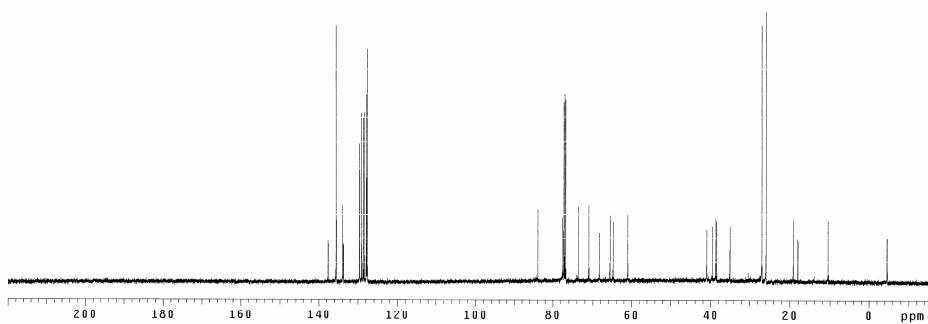
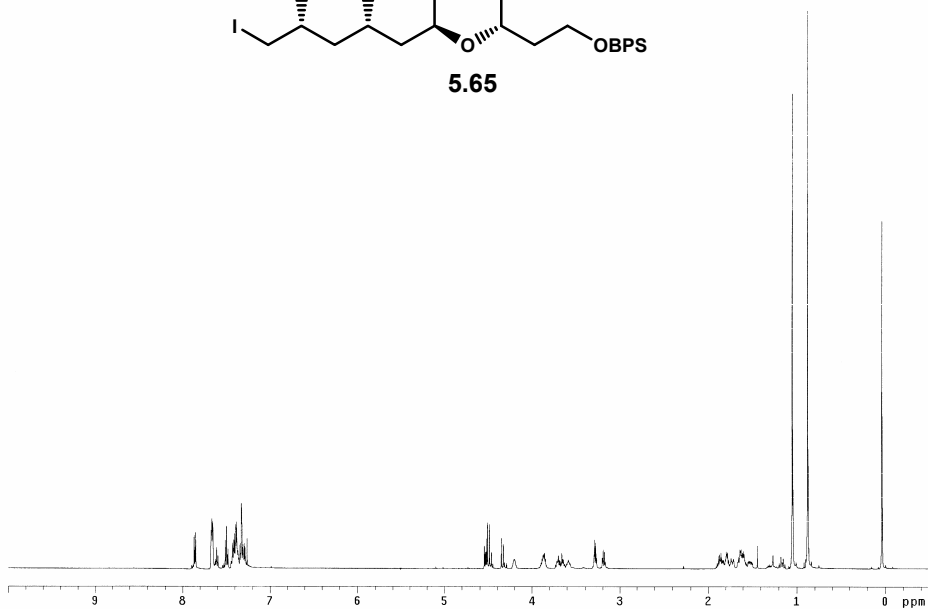
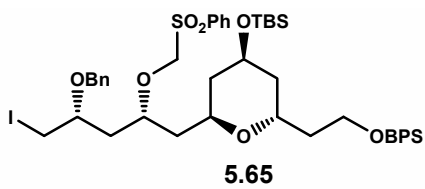


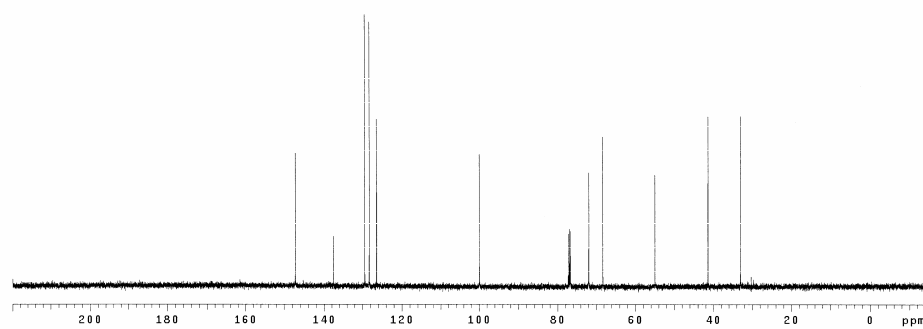
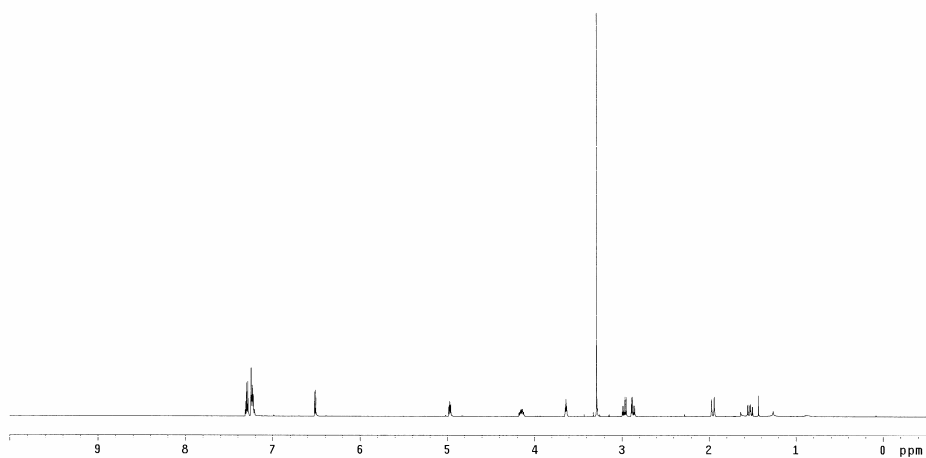


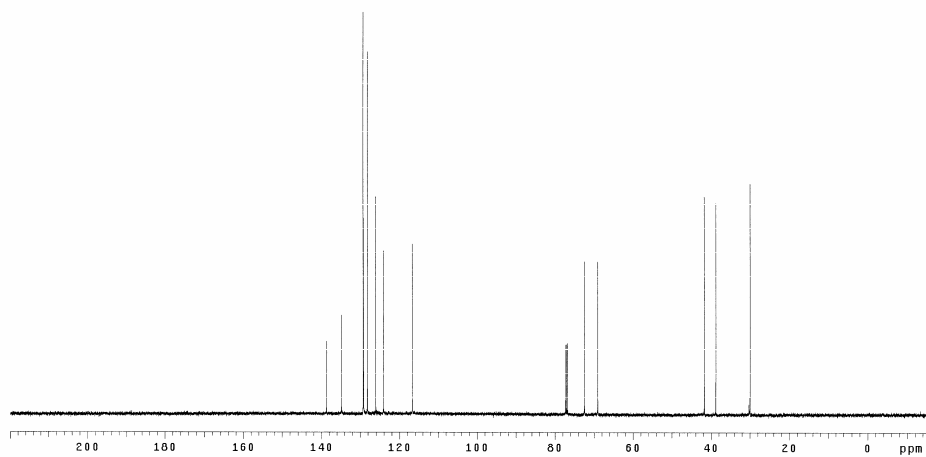
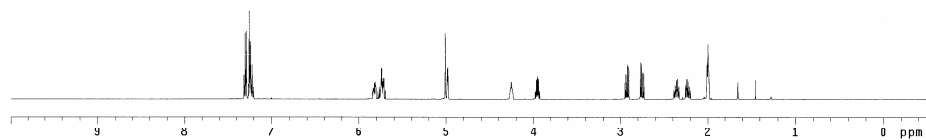
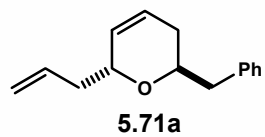


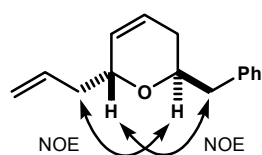




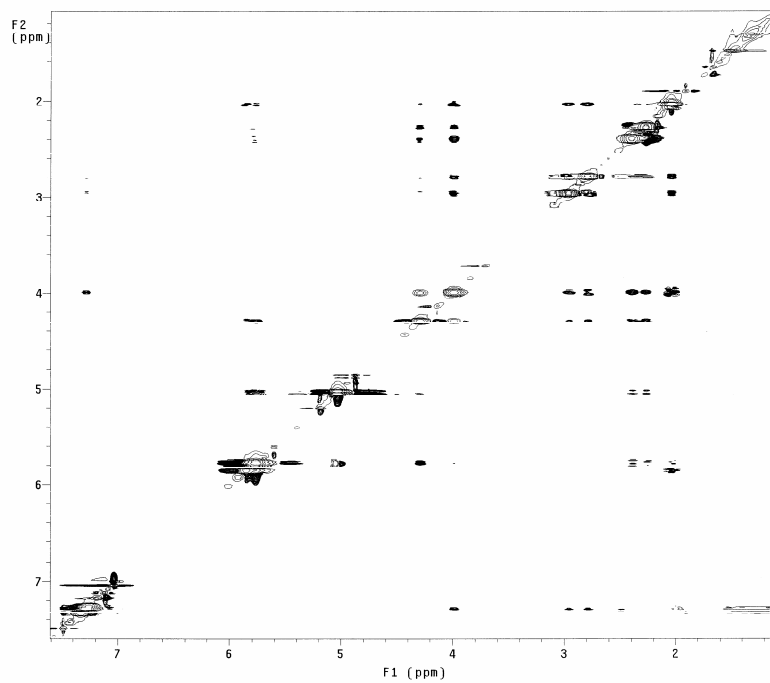


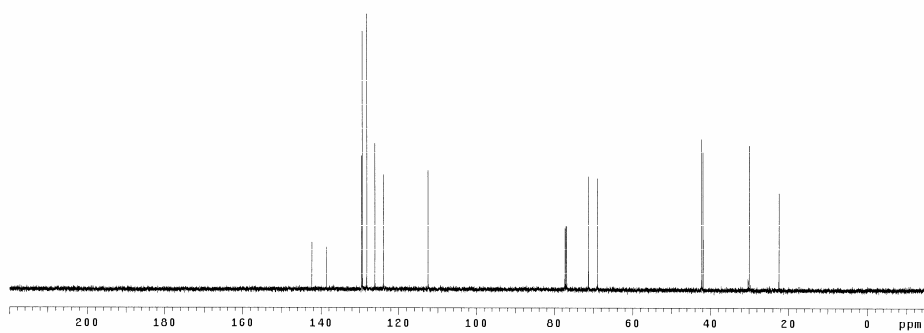
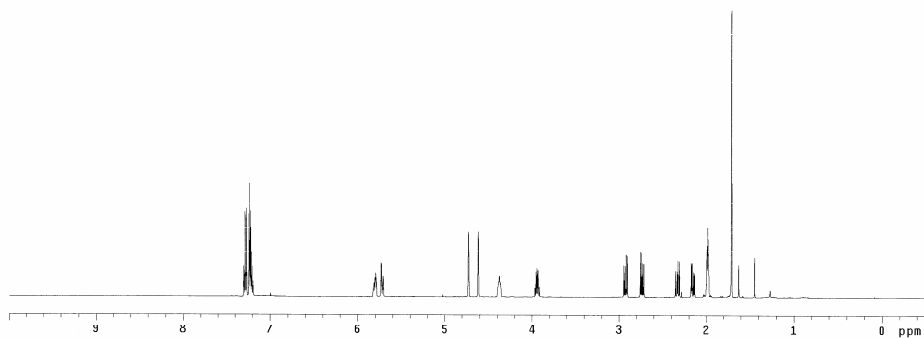
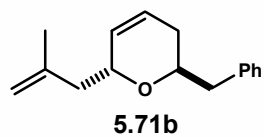


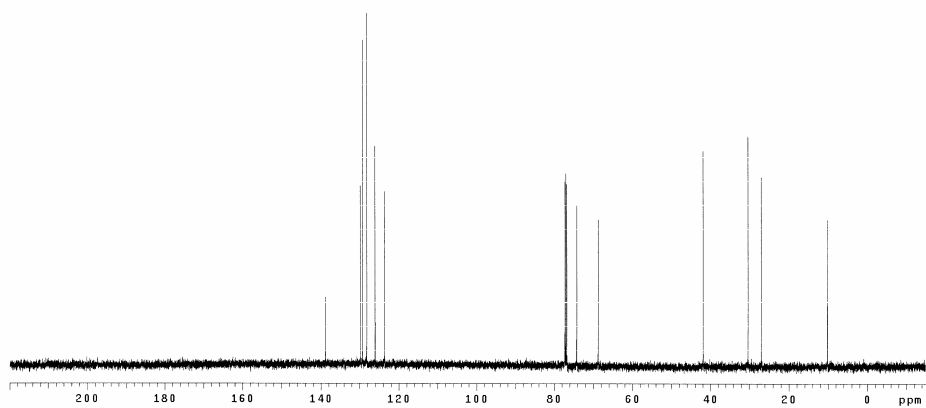
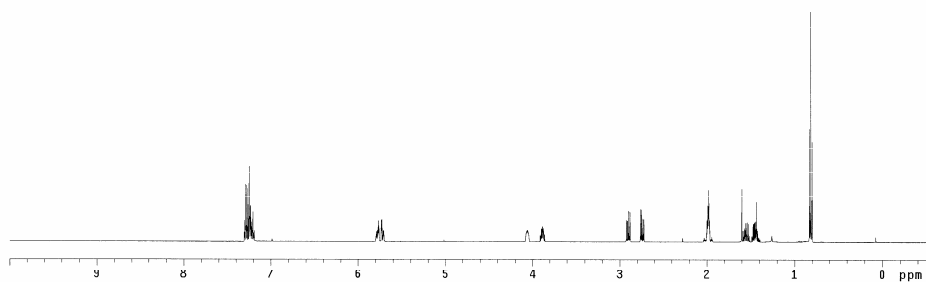
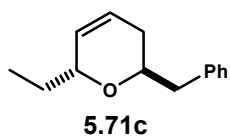


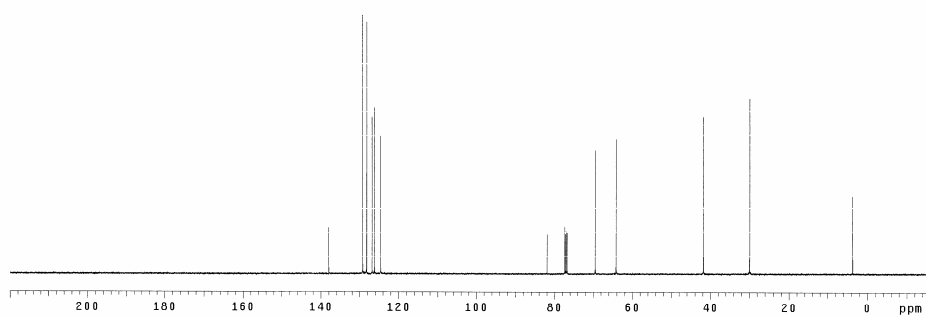
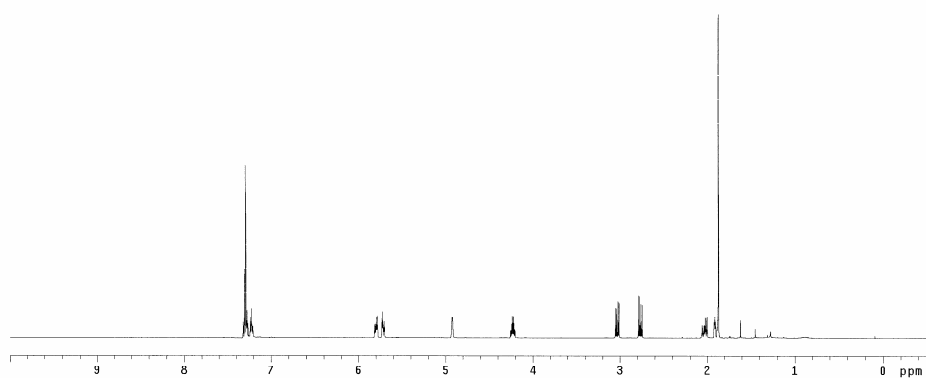
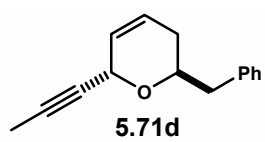


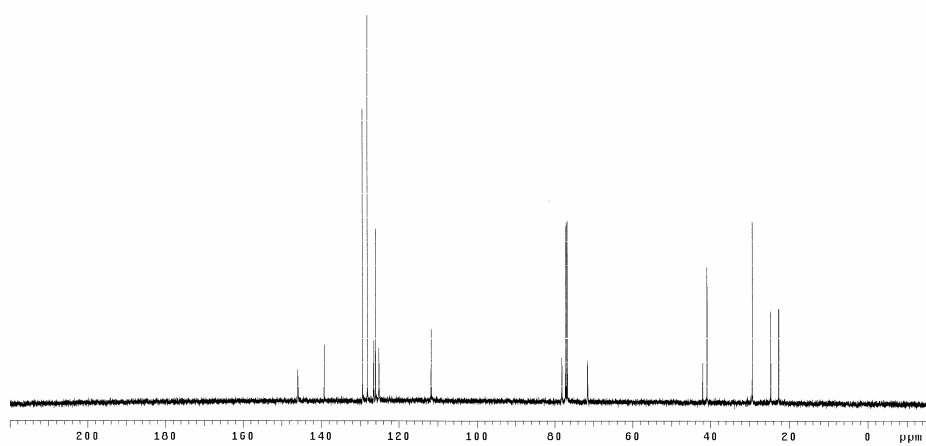
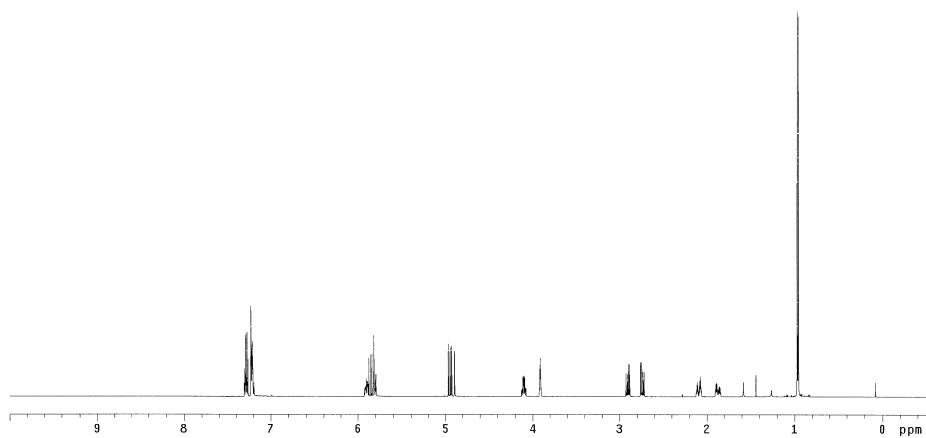
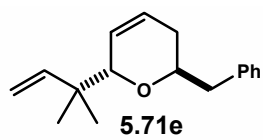
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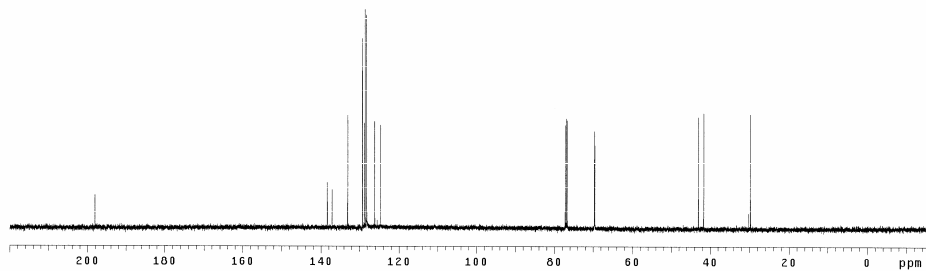
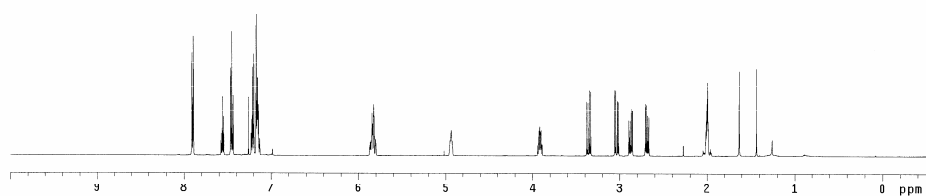
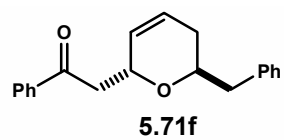


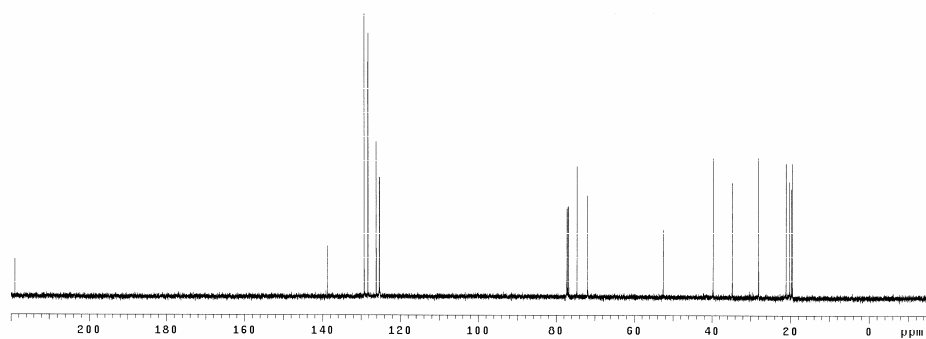
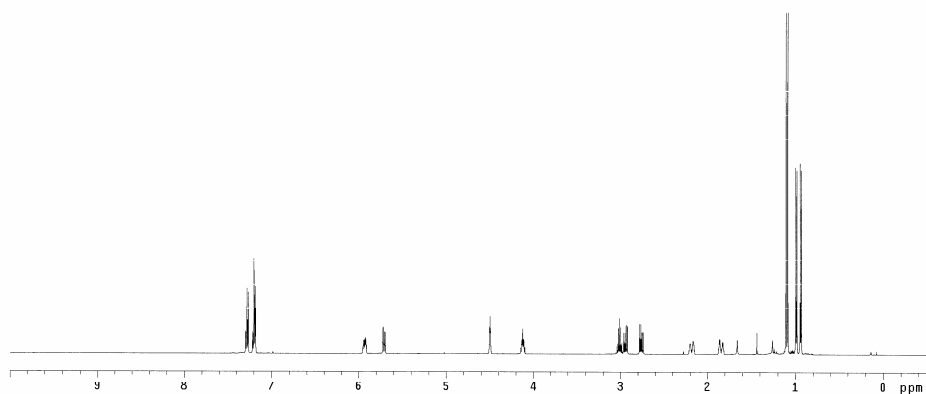
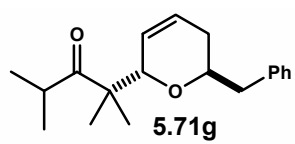


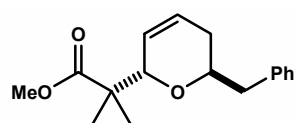




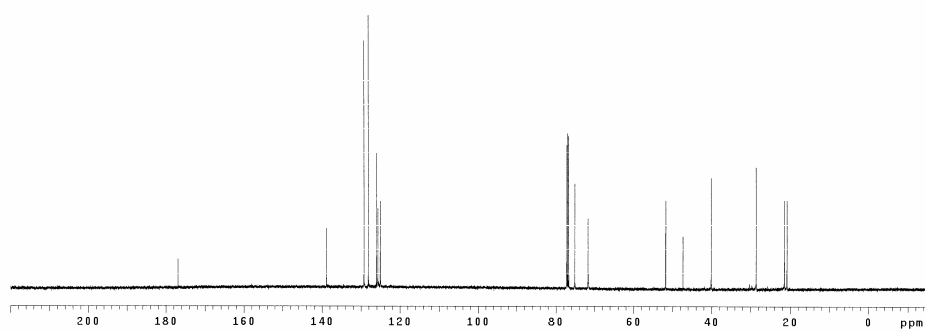
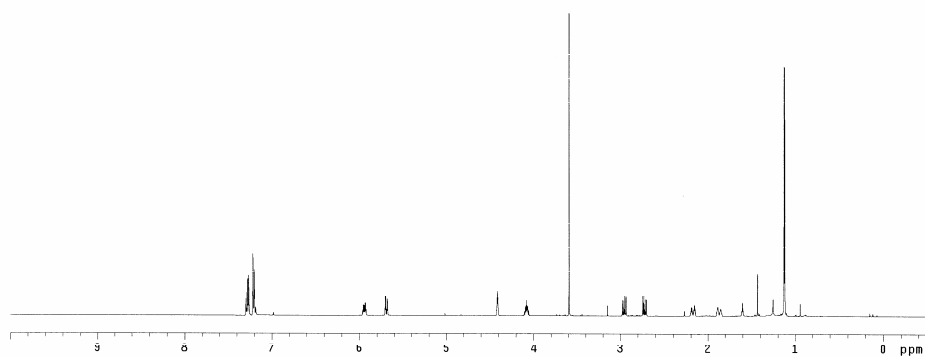


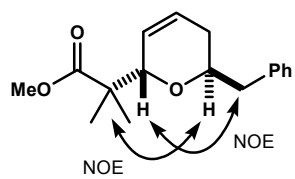




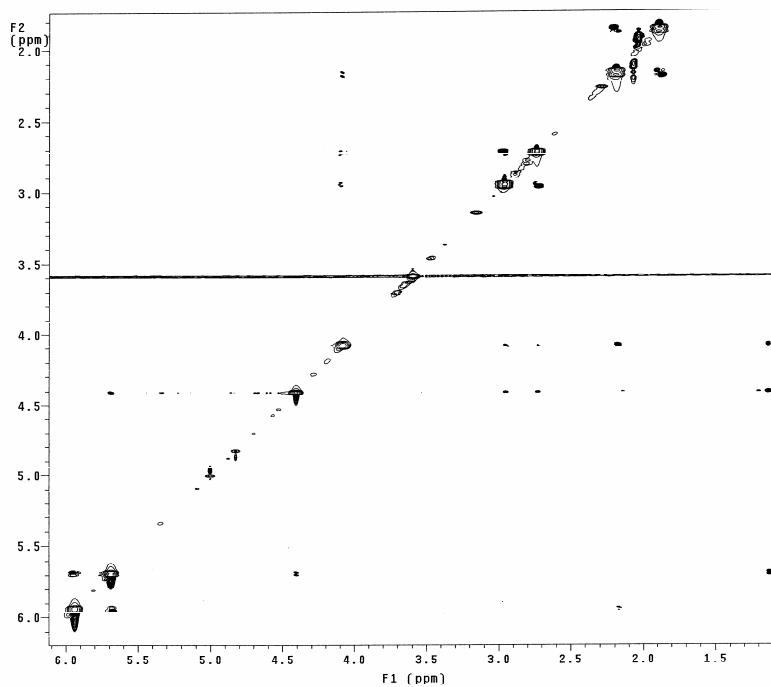


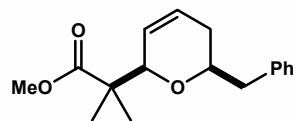
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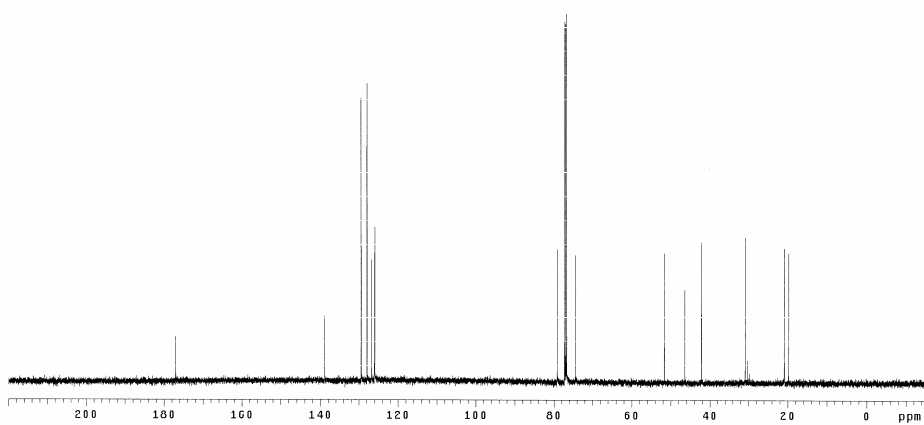
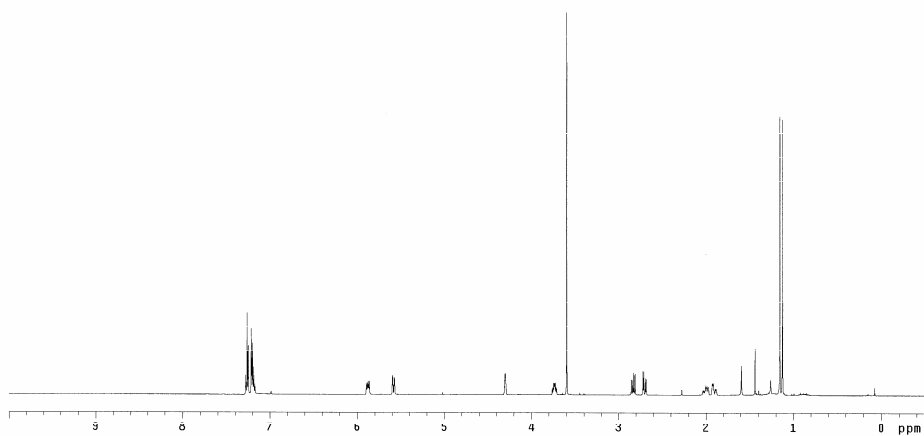


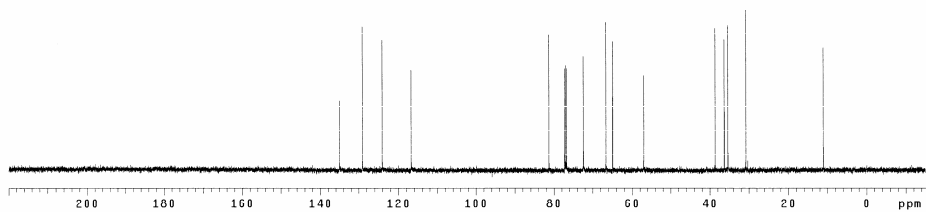
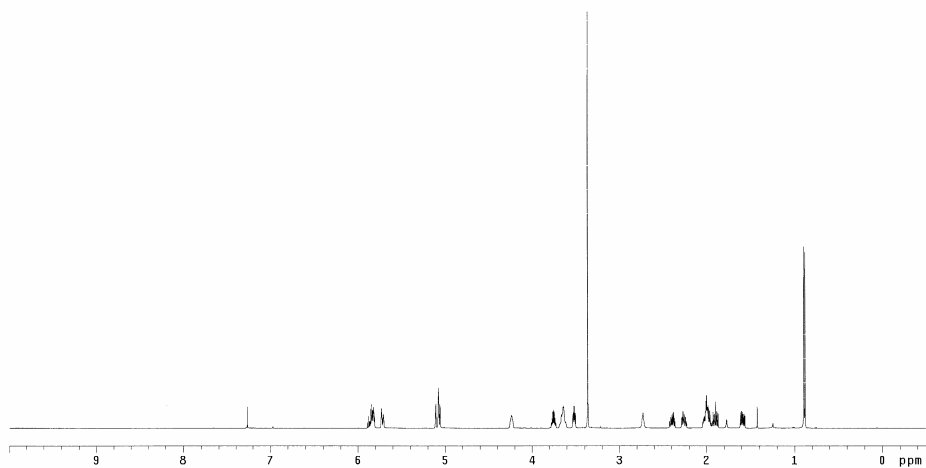
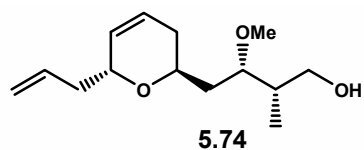
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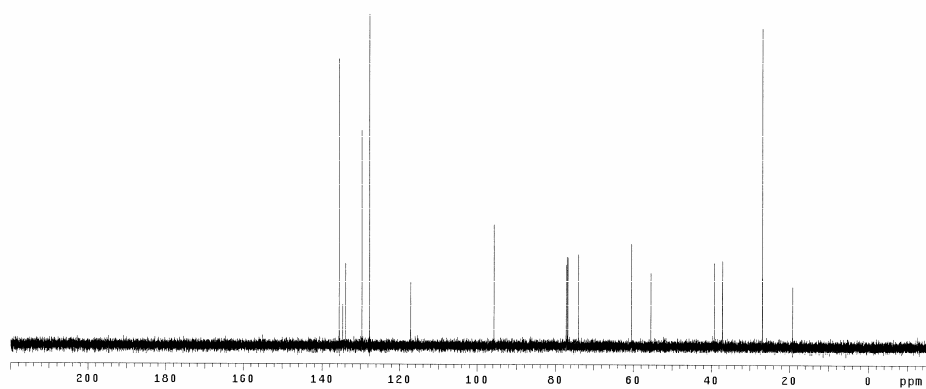
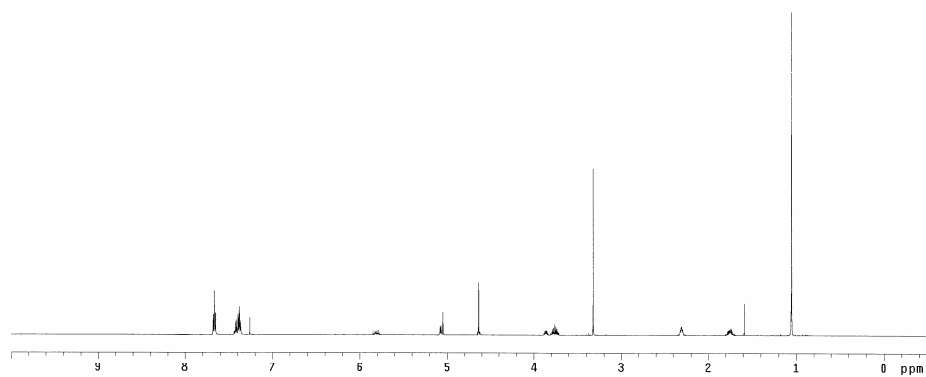
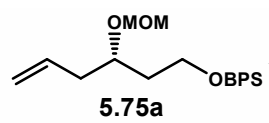


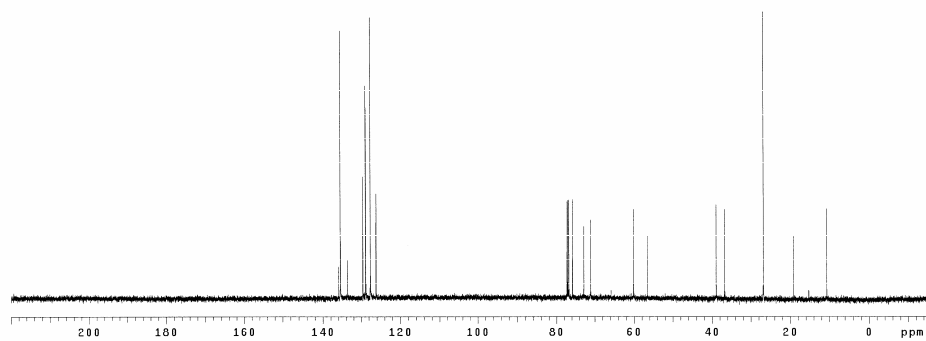
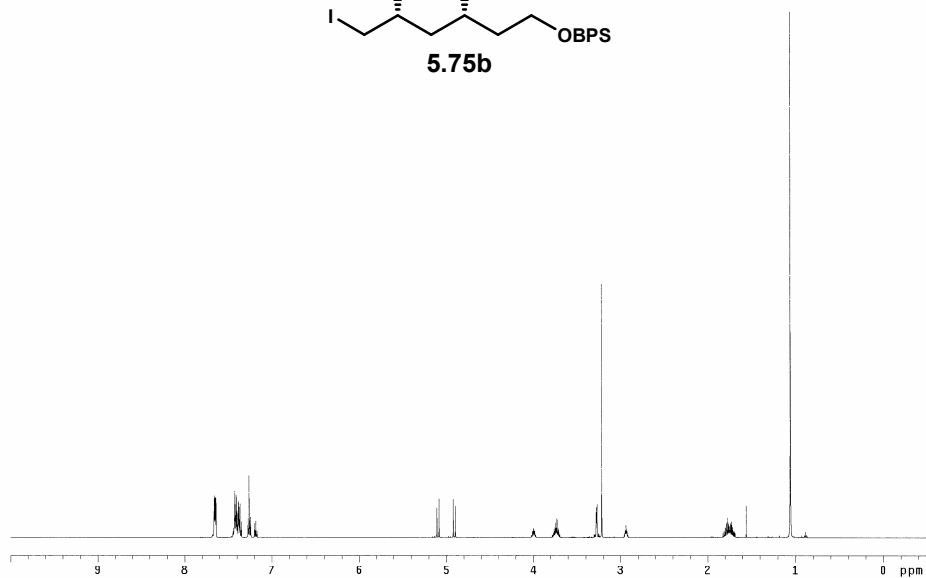
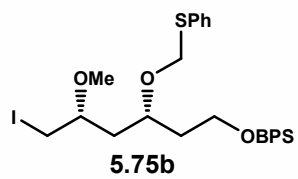


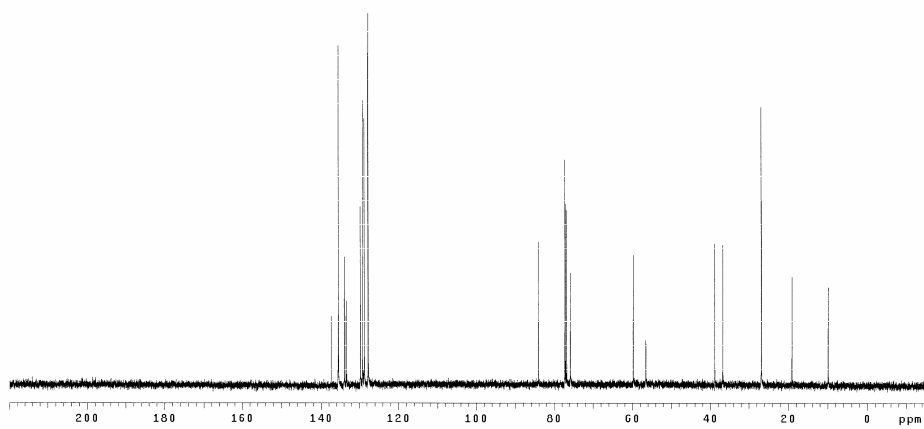
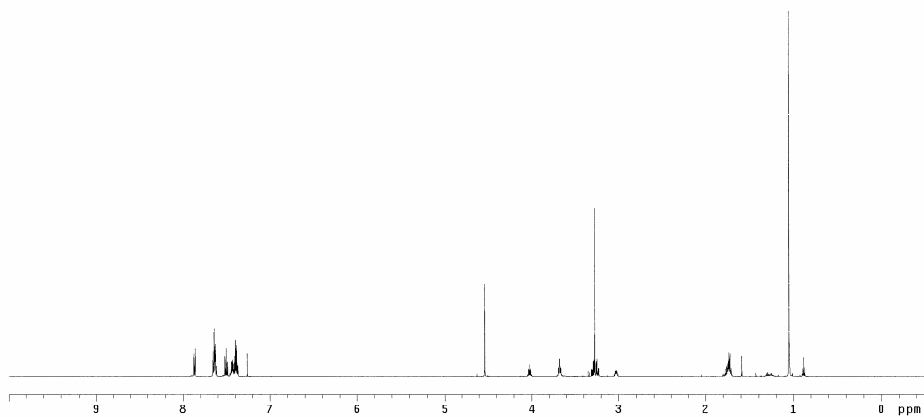
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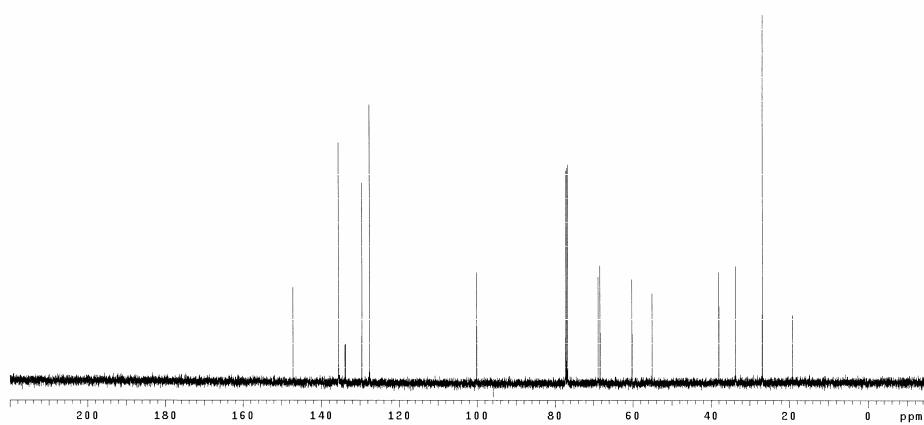
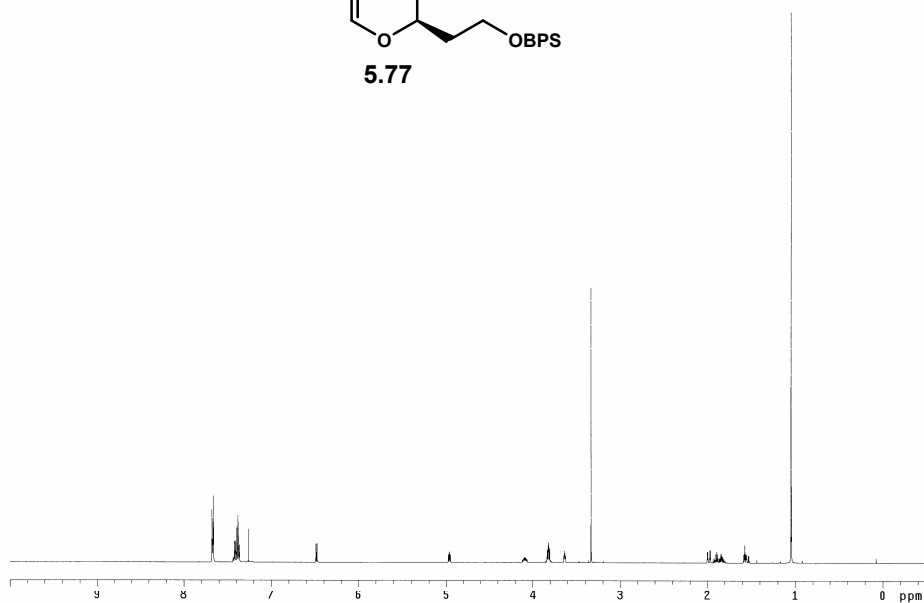
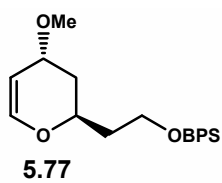


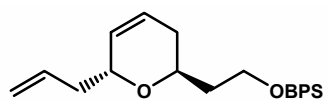




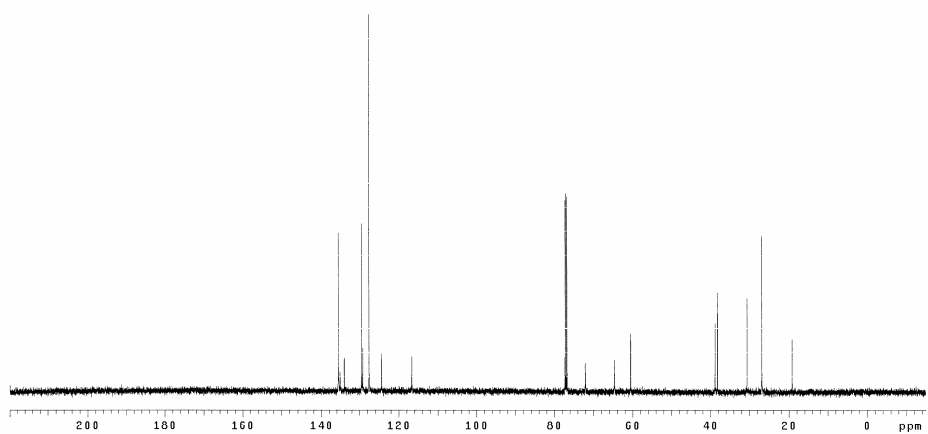
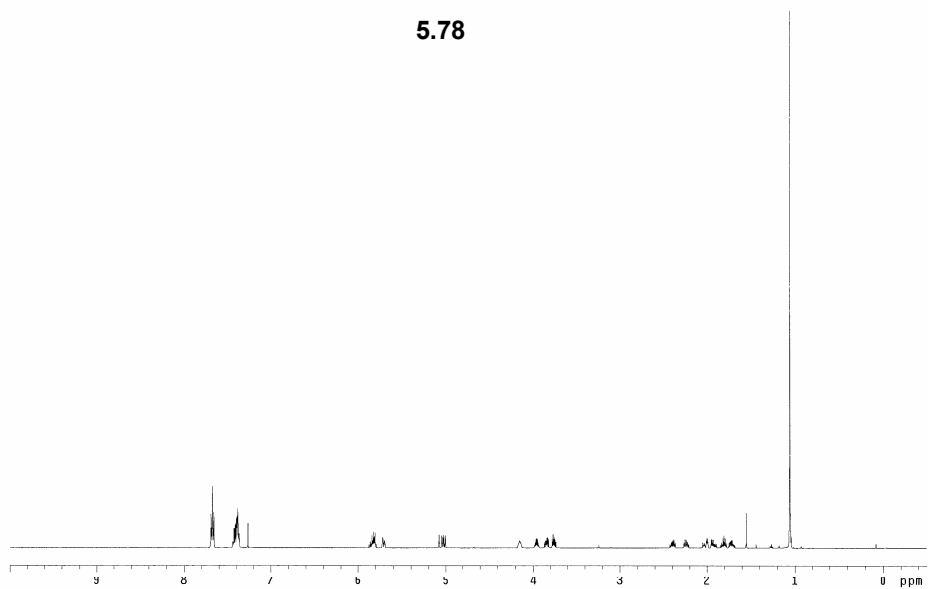


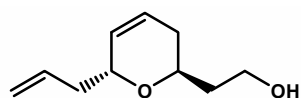




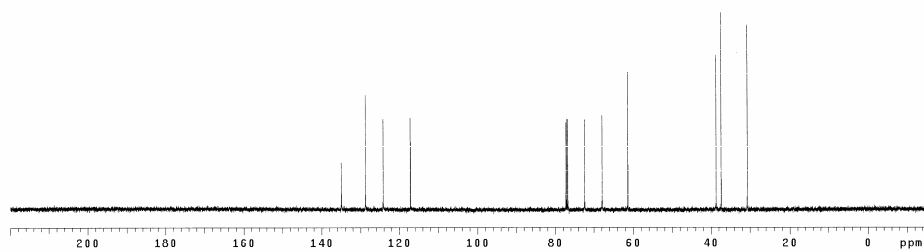
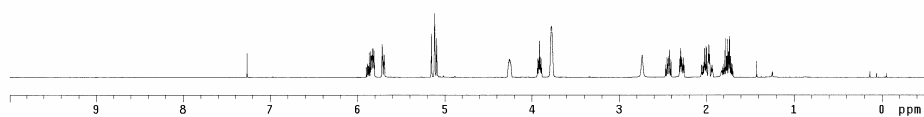


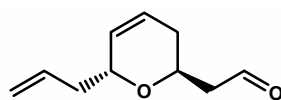
5.78



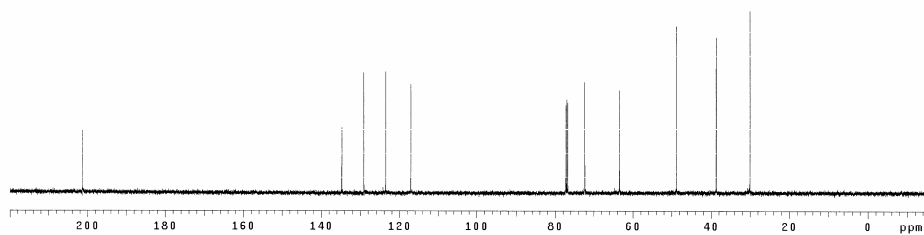
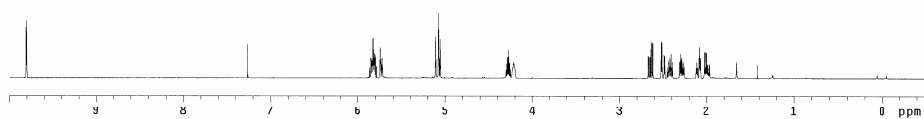


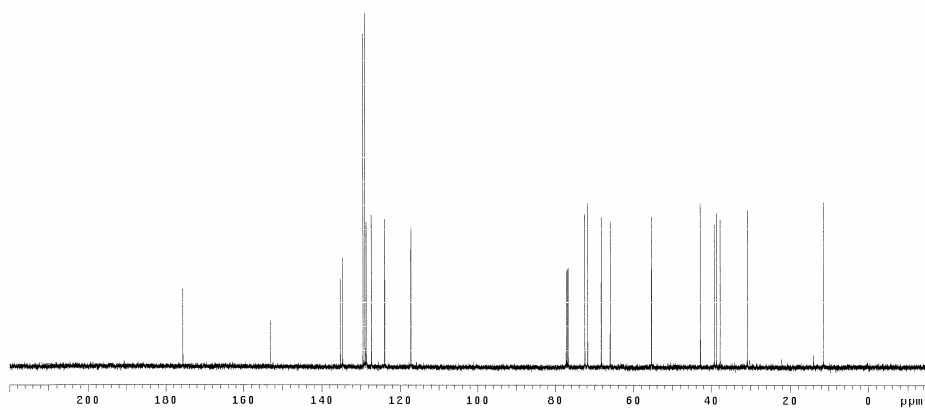
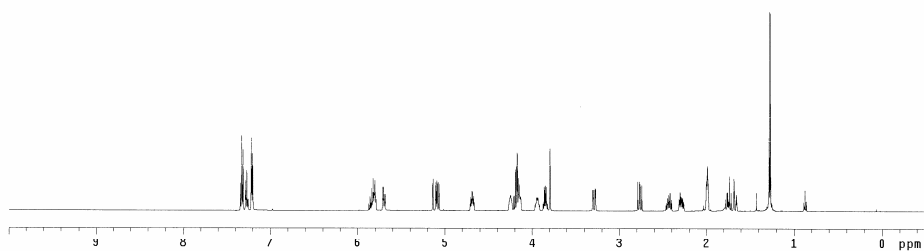
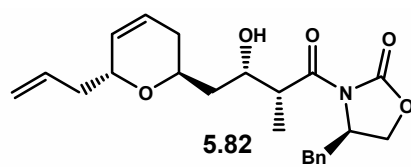
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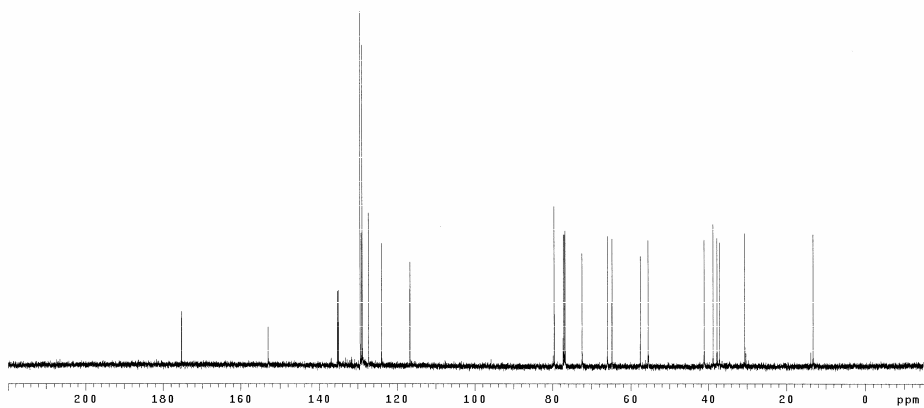
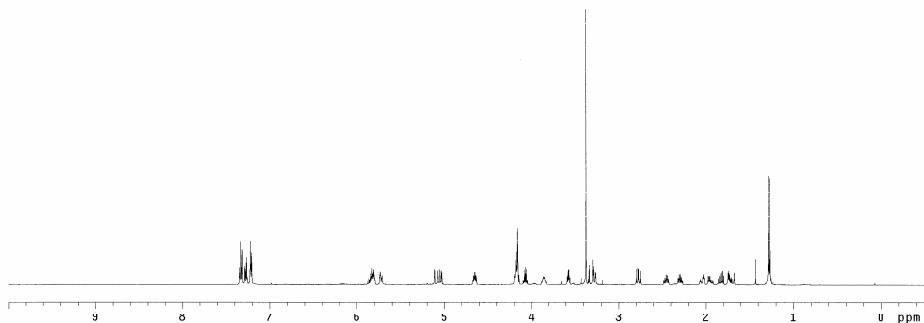
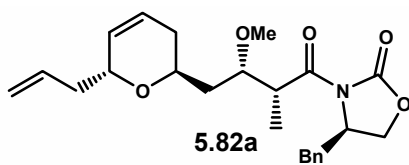


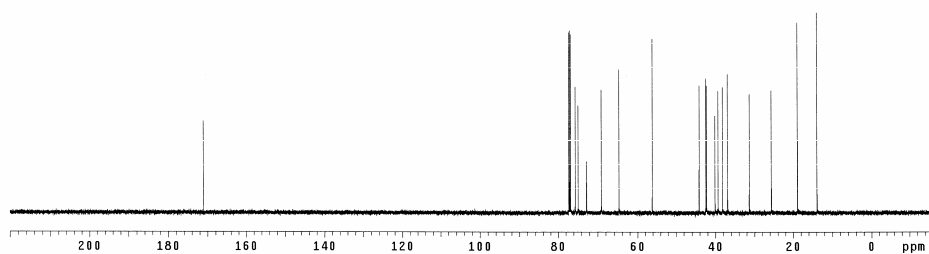
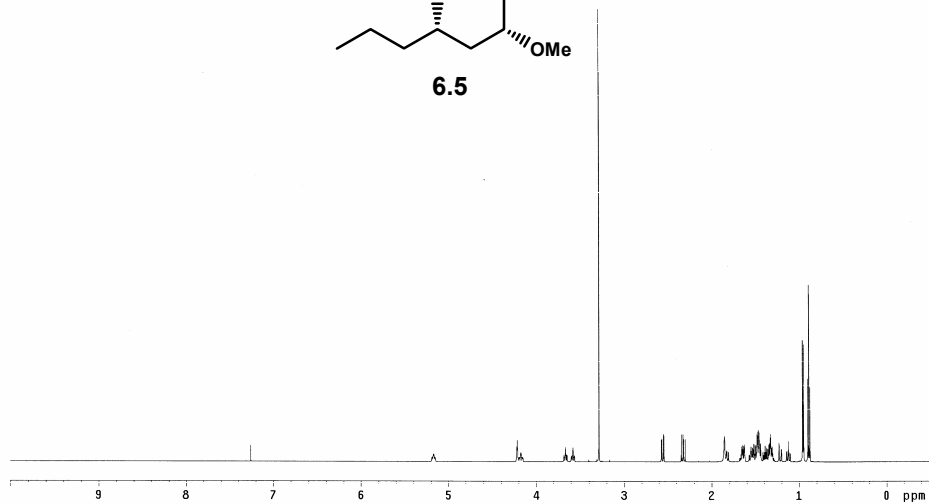
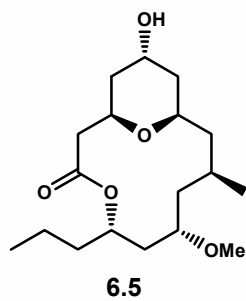


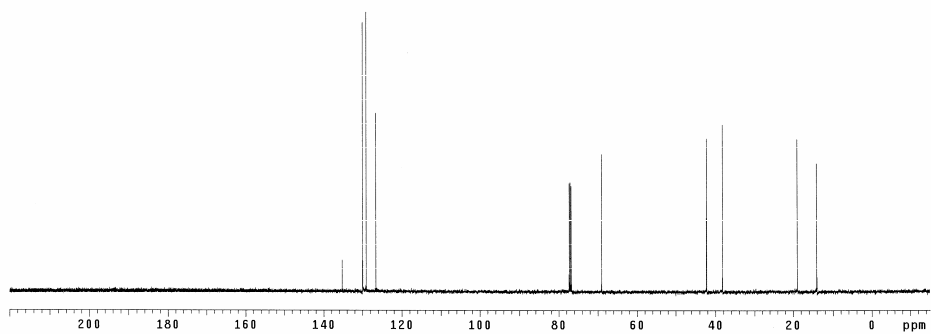
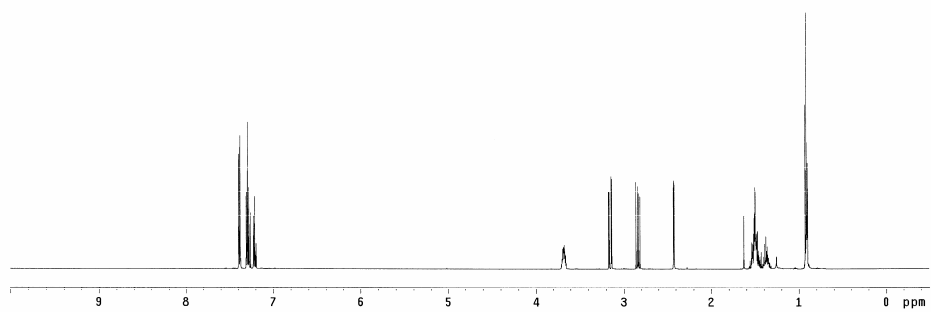
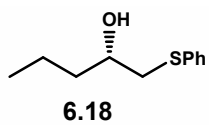
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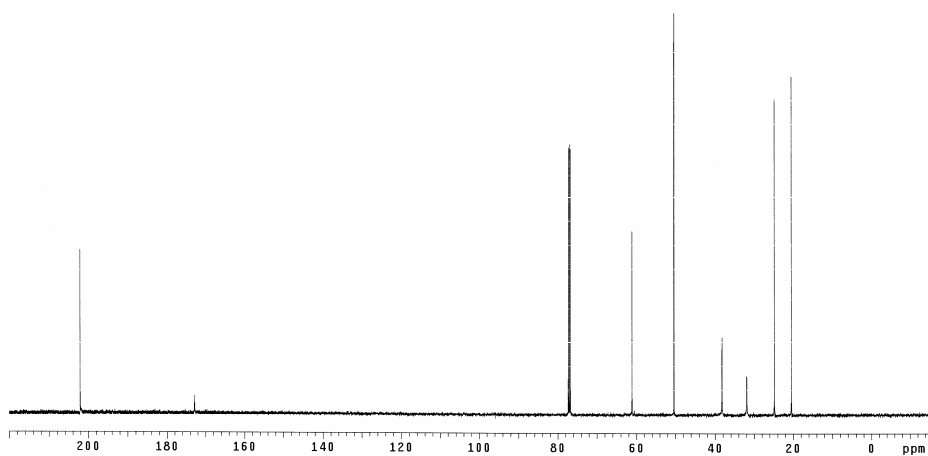
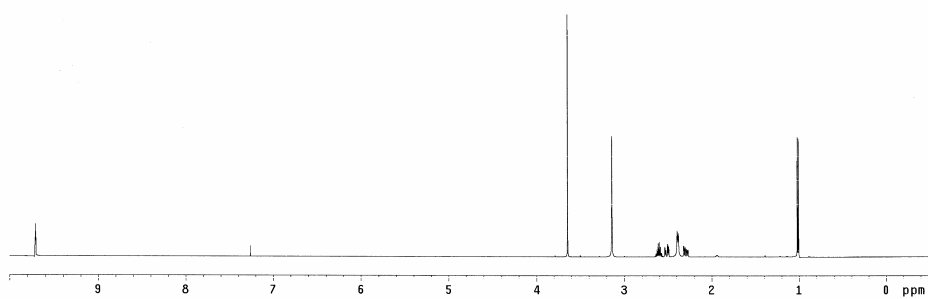
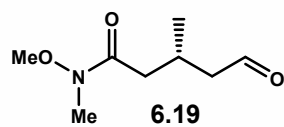


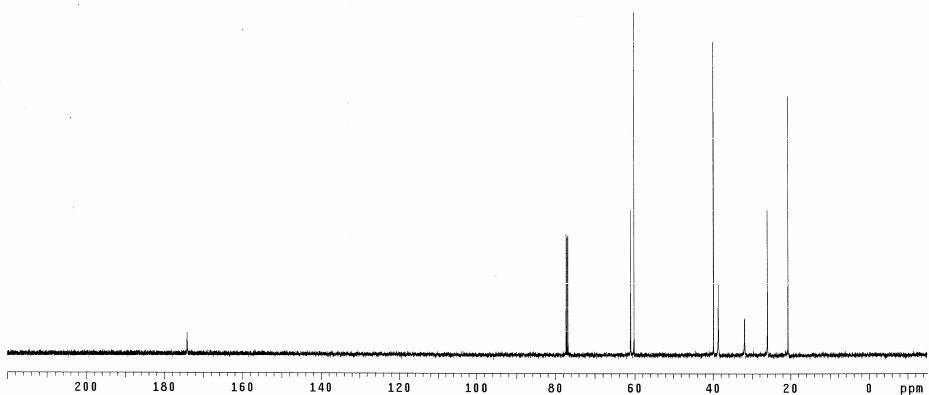
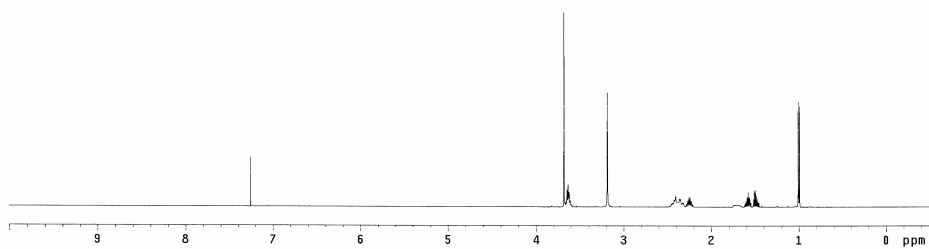
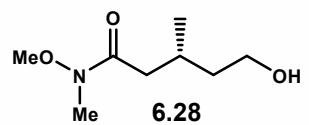


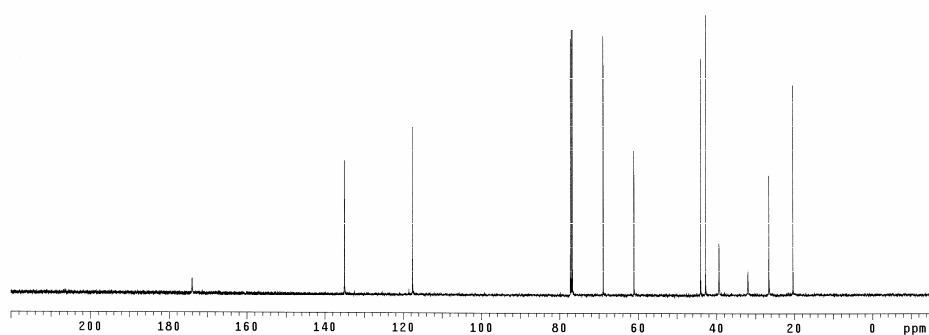
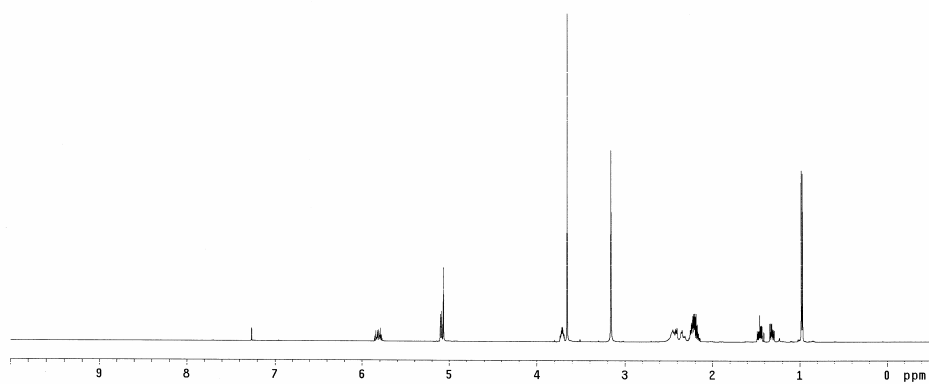
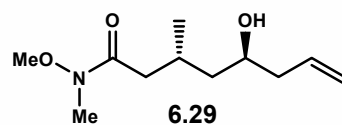


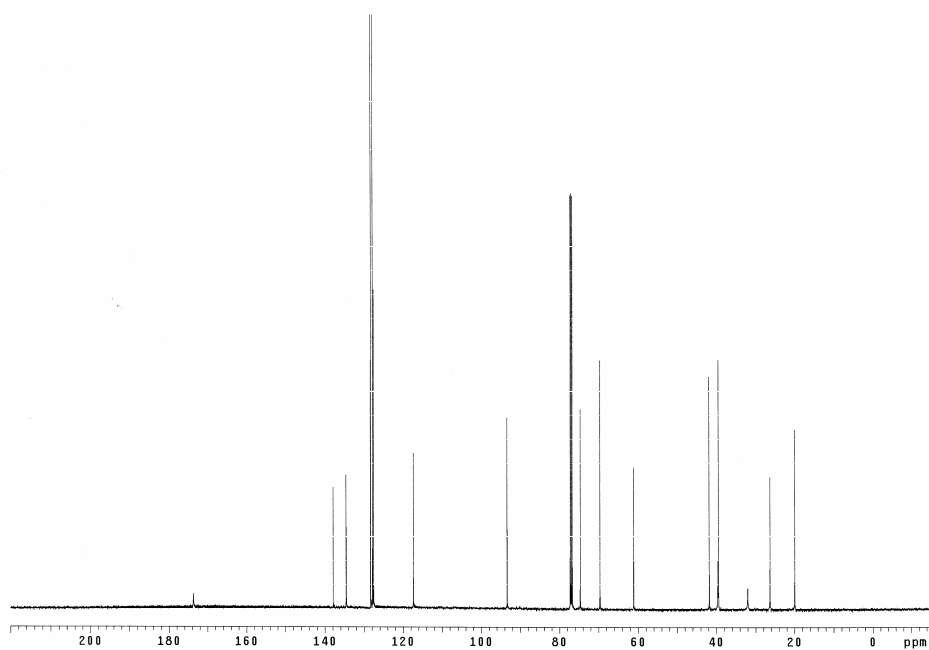
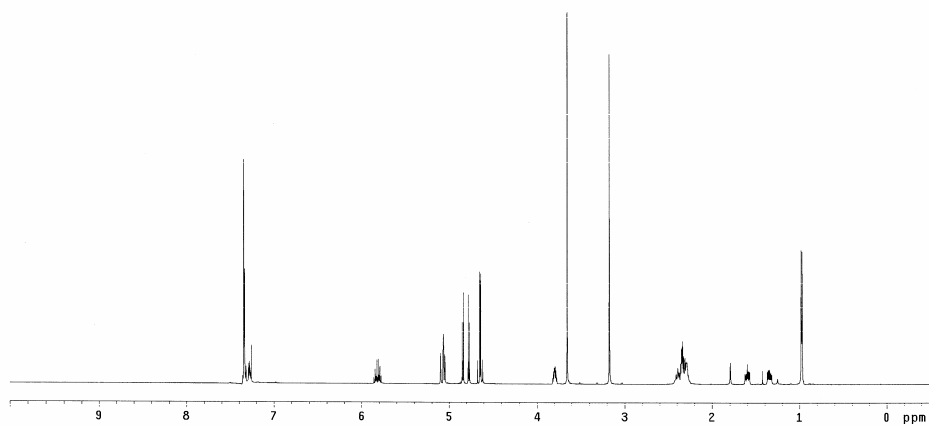
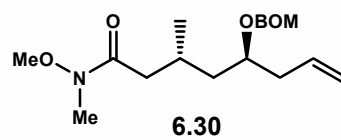


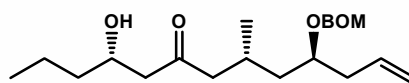




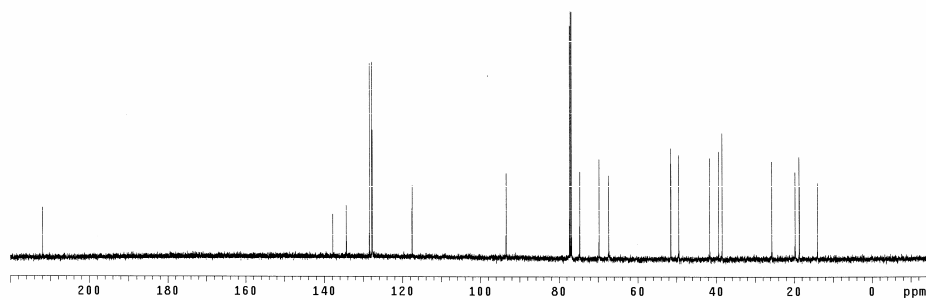
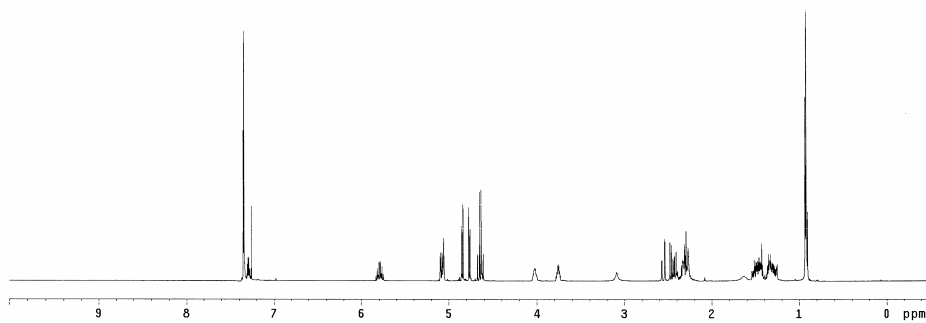


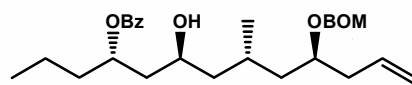




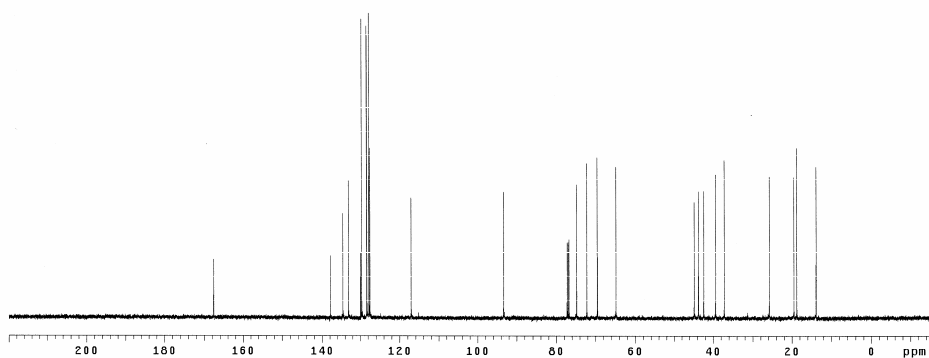
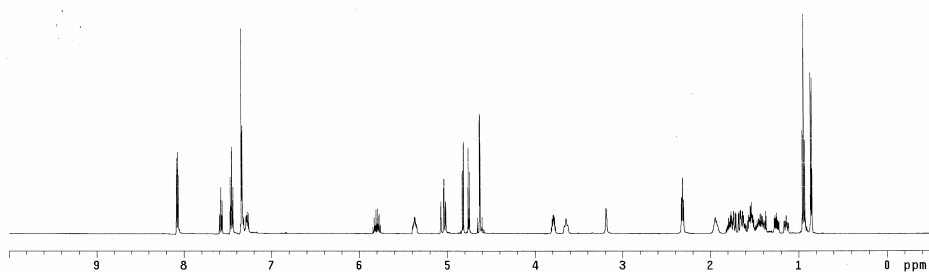


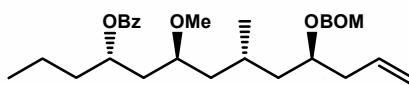
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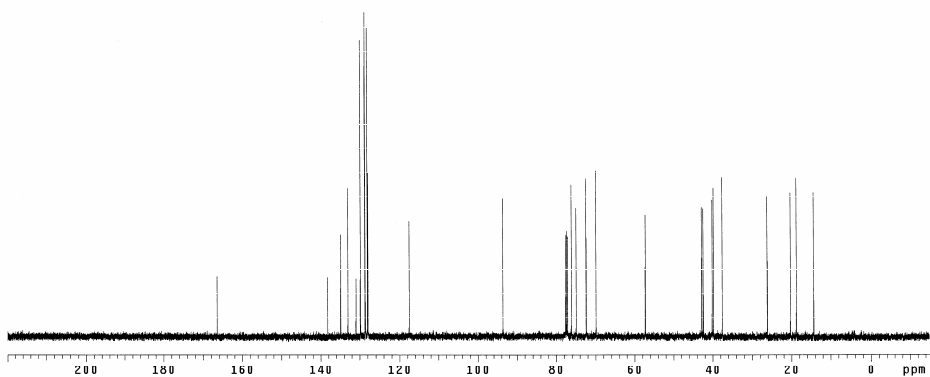
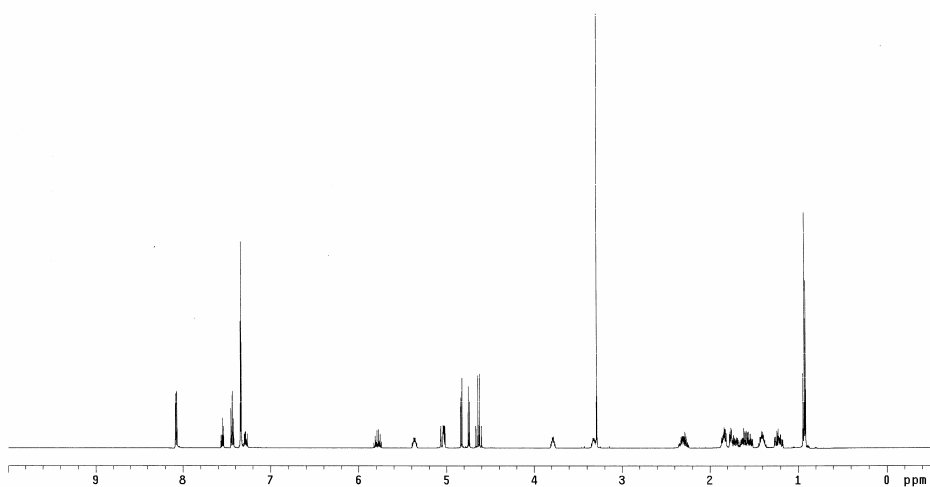


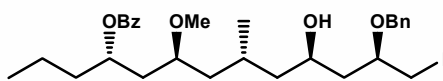
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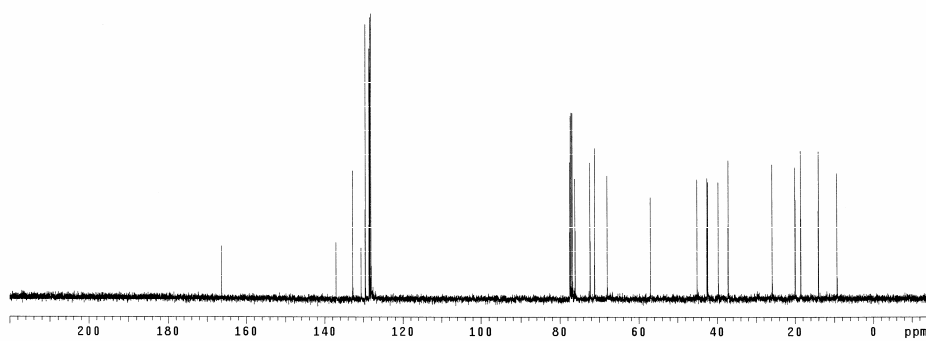
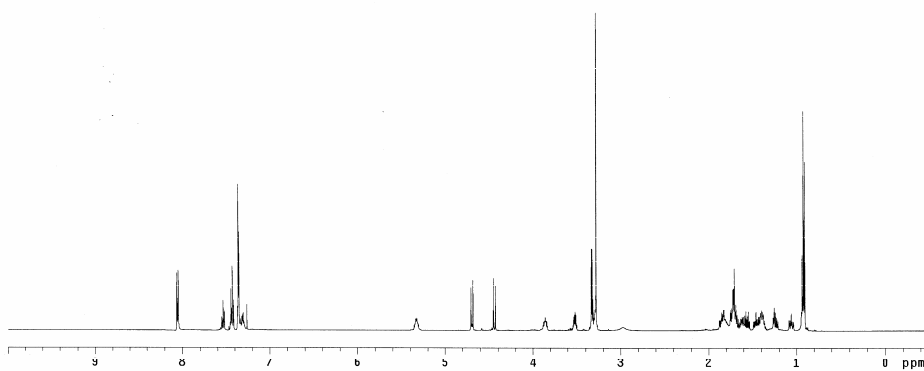


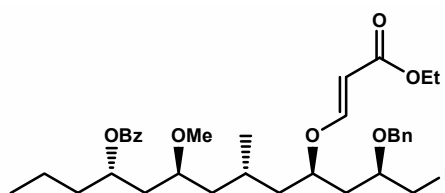
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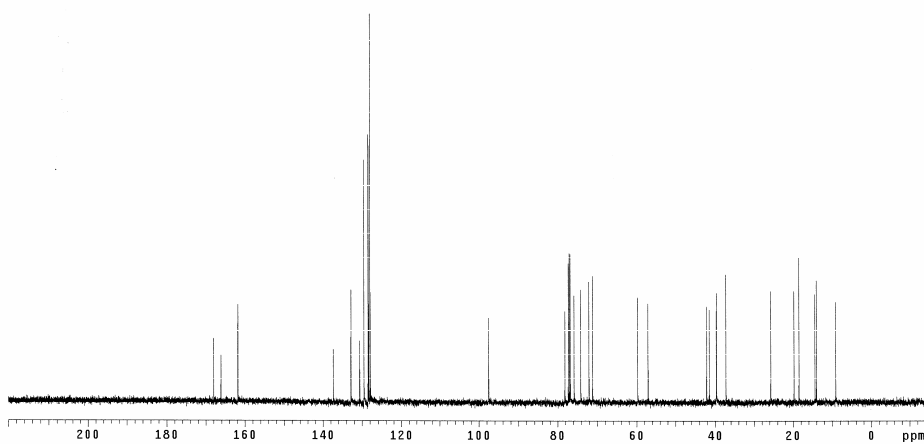
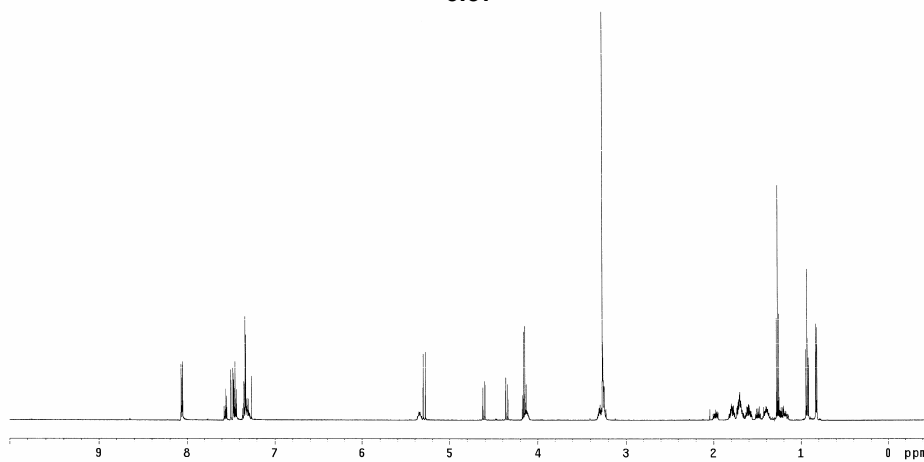


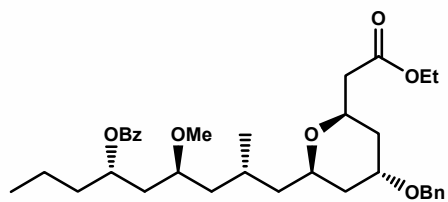
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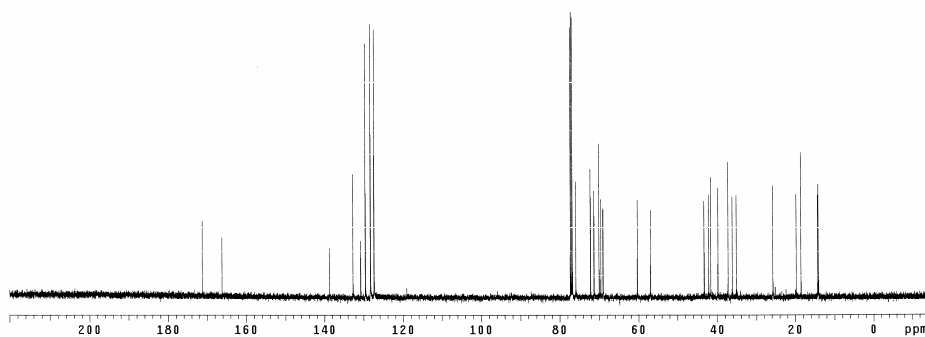
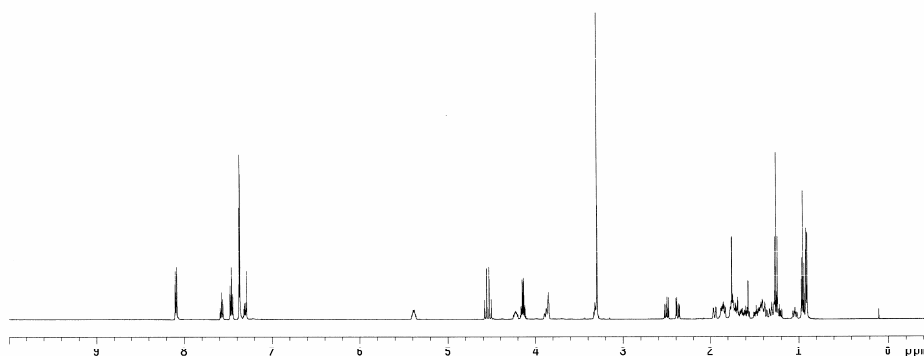


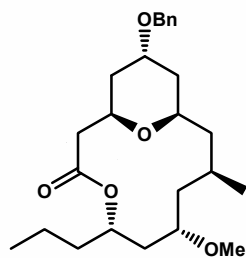
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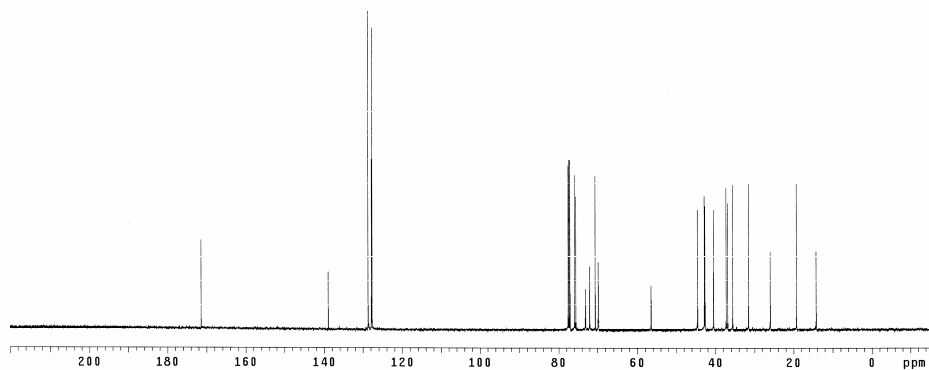
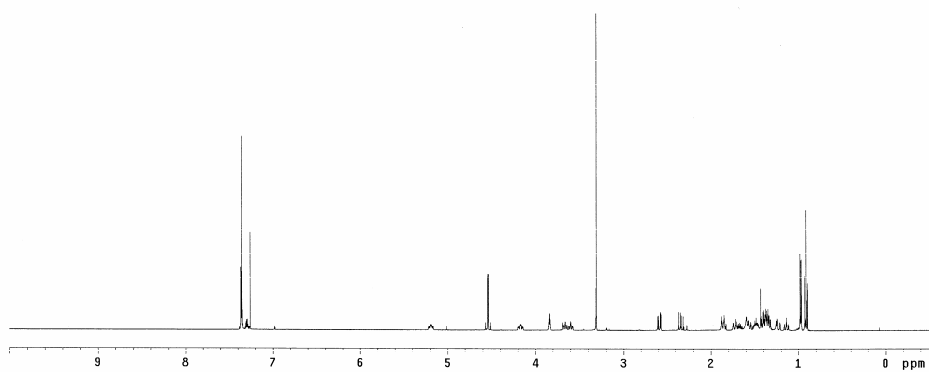


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