Asymmetric [4 + 3] Cyloadditions between Vinylcarbenoids and Dienes: Application to the Total Synthesis of the Natural Product (–)-5-*epi*-Vibsanin E.

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Supporting Information

General Methods

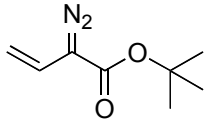
^{1}H and ^{13}C NMR spectra were recorded at 400.13 MHz (and 100.62 MHz), 300.13 MHz (and 75.47 MHz), or 500.13 MHz (and 125.76 MHz) in the solvents specified. Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. High resolution electrospray ionisation (HRESIMS) accurate mass measurements were recorded in positive mode. Low and high resolution electron impact ionisation mass measurements were recorded (EI 70 eV) using perfluorokerosene-H as reference calibrant. Column chromatography was undertaken on silica gel. Optical rotations were measured on Jasco polarimeters. Microwave irradiation was conducted with a CEM Discover microwave in 40 mL pressurized vials. Preparative and analytical enantioselective chromatography associated with compounds **7** and **2** were performed using a Diacel AD-H column (isopropanol/hexane gradient) and a PDR-chiral Inc. detector.

Methyl 2-diazobut-3-enoate (11a): 11a was prepared by a modified procedure of Davies.[1] Triethylamine (108 mL, 0.77 mol) was added to a stirred solution of methyl 3-oxobutanoate (28 mL, 0.26 mol) and *p*-(acetamido)benzenesulfonyl azide (*p*-ABSA) (68 g, 0.28 mol) in acetonitrile (1.2 L) at 0 °C. The reaction was gradually warmed to room temperature overnight and then placed in a freezer for 3 h. The mixture was then filtered, washed with pentane/ether (4:1 v/v, 500 mL), and the filtrate was then concentrated *in vacuo*. Pentane/Et_2O (2:1 v/v, 300 mL) was then added and the mixture was placed in the freezer for another 3 h. The mixture was then filtered through Florisil/Celite® (1:1 wt/wt, 50 g) and washed with pentane/ether (3:2 v/v, 1L). The filtrate was then concentrated *in vacuo* to give methyl 2-diazo-3-oxobutanoate (35.6 g, 97% yield) as a yellow oil. The physical and spectral data were identical to those previously reported for this compound:[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (s, 3H), 2.54 (s, 3H).

Sodium borohydride (9.52 g, 0.25 mol) was added in four portions to a stirred solution of methyl 2-diazo-3-oxobutanoate (29.8 g, 0.21 mol) in DCM/MeOH (1:1 v/v, 200 mL) at 0 °C. The

reaction was then aged 2 h at 0 °C and 1 h at room temperature. The reaction was then quenched with ice/water (10 g / 10 mL) and stirred for 30 min at 0 °C. Water (200 mL) was then added followed by DCM (100 mL). The layers were then separated and the *aq*. layer was extracted with DCM (5 X 100 mL). The organic extracts were combined, washed with brine (250 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The yellow oil was predominantly methyl 2-diazo-3-hydroxybutanoate (23.0 g, 76% yield) and was used immediately in the following reaction.

$POCl_3$ (21.9 mL, 0.24 mol) in DCM (50 mL) was added dropwise to a stirred solution of methyl 2-diazo-3-hydroxybutanoate (23.0 g, 0.16 mol) and triethylamine (90 mL, 0.65 mol) in DCM (500 mL) at 0 °C. The reaction was then left overnight, gradually warming to room temperature. The red solution was then washed with water (3 X 400 mL), sat. NH_4Cl (2 X 500 mL), water (2 X 500 mL), and brine (500 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo* at 0 °C. The crude residue was then purified by flash chromatography (SiO_2, pentane/ether = 100:0 ⇒ 9:1) to give **11a** (11.0 g, 55% yield) as a red oil. The physical and spectral data were identical to those previously reported for this compound:[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (dd, J = 17.4, 11.0 Hz, 1H), 5.01 (d, J = 11.0 Hz, 1H), 4.94 (d, J = 17.4 Hz, 1H), 3.79 (s, 3H).

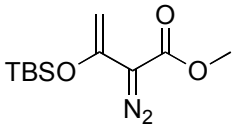


***t*-Butyl 2-diazobut-3-enoate (11b): 11b** was prepared by a modified procedure of Davies.[1] Triethylamine (0.97 mL, 0.063 mol) was added to a stirred solution of *t*-butyl 3-oxobutanoate (5.00 g, 0.032 mol) and *p*-ABSA (7.97 g, 0.033 mol) in acetonitrile (200 mL) at 0 °C. The reaction was gradually warmed to room temperature overnight and then placed in a freezer for 3

h. The mixture was then filtered, washed with pentane/ether (4:1 v/v, 200 mL), and the filtrate was then concentrated *in vacuo*. The residue was purified by flask chromatography (SiO_2, pentane/Et_2O = 20:1) to give *t*-butyl 2-diazo-3-oxobutanoate (5.24 g, 90% yield) as a yellow oil. The physical and spectral data were identical to those previously reported for this compound:[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 1.53 (s, 9H).

Sodium borohydride (3.78 g, 0.10 mol) was added in four portions to a stirred solution of *t*-butyl 2-diazo-3-oxobutanoate (3.13 g, 0.017 mol) in MeOH (150 mL) at 0 °C. The reaction was then stirred for 2 h at 0 °C and 1 h at room temperature. The reaction was then diluted with Et_2O and washed with sat. $NaHCO_3$ (3 X 250 mL), and brine (250 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The yellow oil was predominantly *t*-butyl 2-diazo-3-hydroxybutanoate, which was subjected directly into the next reaction.

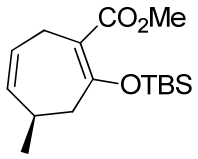
$POCl_3$ (2.30 mL, 0.025 mol) in DCM (20 mL) was added dropwise to a stirred solution of the crude *t*-butyl 2-diazo-3-hydroxybutanoate and triethylamine (9.5 mL, 0.068 mol) in DCM (200 mL) at 0 °C. The reaction was then aged overnight gradually warming to room temperature. The red solution was then diluted with Et_2O (600 mL) and washed with water (3 X 250 mL), and brine (250 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was then purified by flash chromatography (SiO_2, pentane/ether = 100:0 ⇒ 9:1) to give **11b** (1.90 g, 66% yield) as a red oil. The physical and spectral data were identical to those previously reported for this compound:[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.08 (d, *J* = 11.0 Hz, 1H), 4.81 (d, *J* = 17.0 Hz, 1H), 1.50 (s, 9H).



Methyl 3-(*tert*-butyldimethylsilyloxy)-2-diazobut-3-enoate (11c): The diazo compound was prepared by a modified procedure of Davies.[2] TBSOTf (19.5 mL, 0.085 mol) was added drop-wise to a stirred solution of methyl 2-diazo-3-oxobutanoate (10.0 g, 0.070 mol) and triethylamine

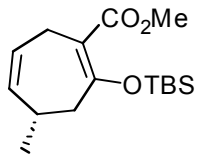
(12.3 mL, 0.088 mol) in DCM (200 mL) at 0 °C. The reaction was then aged overnight gradually warming to room temperature. The red solution was then diluted with hexanes (800 mL), washed with dilute $NaHCO_3$ (2X 500 mL), brine (500 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. This gave the desired compound **11c** (17.8 g) in >98% yield. The physical and spectral data were identical to those previously reported for this compound:[2] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98 (d, *J* = 2.0 Hz, 1H), 4.23 (d, *J* = 2.0 Hz, 1H), 3.78 (s, 3H), 0.90 (s, 9H), 0.21 (s, 6H).

General procedure for Rh_2(*S*-PTAD)$_4$-Catalyzed [4 + 3] Cycloadditions Between 11c and Dienes (Table 2): To a flame-dried 25 mL flask containing Rh_2(*S*-PTAD)$_4$ (4.7 mg, 0.01 equiv) and the corresponding dienes (1.50 mmol, 5.0 equiv) in hexane (6 mL) and trifluorotoluene (0.2 mL) under argon atmosphere was added a solution of diazoacetate **11c** (77 mg, 0.30 mmol, 1.0 equiv) in hexane (6 mL) by syringe pump over 2 h at -26 °C. The solution was stirred at -26 °C overnight and the heated under reflux for an additional 1 h. The mixture was concentrated under vacuum and purified by flash chromatography in silica gel to provide pure products.

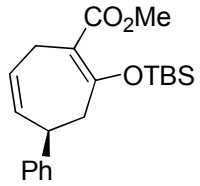


(*R*)-methyl 2-(*tert*-butyldimethylsilyloxy)-4-methylcyclohepta-1,5-diene carboxylate (12): Derived from *trans*-piperylene (103 mg, 1.50 mmol, 5.0 equiv) and purified by flash chromatography (25/1 pentane/Et_2O, R_f: 0.40) in silica gel to provide **12** as a colorless oil (78.3 mg, 88 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.64-5.69 (m, 1H), 5.38 (dd, *J* = 11.3, 1.2 Hz, 1H), 3.68 (s, 3H), 2.98-3.09 (m, 2H), 2.64 (dd, *J* = 11.0, 13.7 Hz, 1H), 2.44-2.53 (br, 1H), 2.29 (dd, *J* = 2.7, 13.7 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 161.9, 135.1, 126.0, 112.2, 51.1, 41.9, 30.2, 25.7, 25.4, 22.3,

18.3, -3.77, -3.84; IR (neat): 2956, 2930, 2858, 1717, 1692, 1625, 1435, 1372, 1301, 1254, 1219, 1192, 1143, 842, 807, 781 cm^{-1}; HRMS (ESI) calc for $C_{16}H_{28}O_3SiNa$ $(M+Na)^+$ 319.1700 found 319.1704; HPLC: (AD-H, hexane, 0.3 mL/min) retention times of 25.9 min (major) and 29.3 min (minor), 95 % ee; $[\alpha]^{25}_D$ -20.5 (*c* = 1.36, $CHCl_3$).

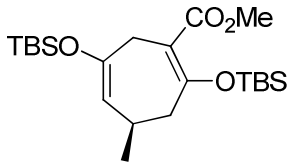


(*S*)-methyl 2-(*tert*-butyldimethylsilyloxy)-4-methylcyclohepta-1,5-diene carboxylate (13): Derived from *cis*-piperylene (103 mg, 1.50 mmol, 5.0 equiv) and purified by flash chromatography (25/1 pentane/Et_2O, R_f: 0.40) in silica gel to provide **13** as a colorless oil (71.2 mg, 80 % yield). HPLC: (AD-H, hexane, 0.5 mL/min) retention times of 16.5 min (minor) and 17.7 min (major), 87 % ee.

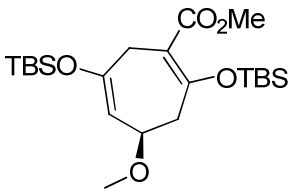


(*R*)-methyl 2-(*tert*-butyldimethylsilyloxy)-4-phenylcyclohepta-1,5-diene carboxylate (14): Derived from (*E*)-buta-1,3-dienylbenzene (195 mg, 1.50 mmol, 5.0 equiv) and purified by flash chromatography (25/1 pentane/Et_2O, R_f: 0.43) in silica gel to provide **14** as a colorless oil (88.2 mg, 82 % yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.31-7.34 (m, 2H), 7.22-7.26 (m, 3H), 5.89-5.94 (m, 1H), 5.54 (dm, *J* = 11.3 Hz, 1H), 3.72 (s, 3H), 3.68 (dm, *J* = 11.3 Hz, 1H), 3.15-3.25 (m, 2H), 3.10 (dd, *J* = 11.6, 13.7 Hz, 1H), 2.47 (dd, *J* = 3.1, 13.7 Hz, 1H), 0.92 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 167.9, 161.4, 144.9, 132.2, 128.6, 127.54, 127.46, 126.6, 112.7, 51.1, 42.8, 41.8, 25.6, 25.3, 18.2, -3.77, -3.82; IR (neat): 2951, 2930, 2858,

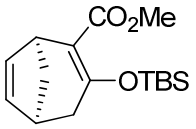
1716, 1689, 1624, 1435, 1371, 1252, 1212, 1142, 839, 806, 781, 700 cm^{-1}; HRMS (ESI) calc for $C_{21}H_{30}O_3SiNa$ $(M+Na)^+$ 381.1856 found 381.1863; HPLC: ((S,S)-Whelk-O 1, 0.1 % isopropanol in hexane, 0.7 mL/min) retention times of 61.1 min (major) and 79.2 min (minor), 95 % ee; $[\alpha]^{25}_D$ -26.3 (*c* = 5.15, $CHCl_3$).



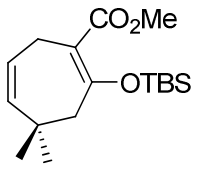
(*R*)-methyl 2,6-bis(*tert*-butyldimethylsilyloxy)-4-methylcyclohepta-1,5-diene carboxylate (15): Derived from (*E*)-*tert*-butyldimethyl(penta-1,3-dien-2-yloxy)silane (298 mg, 1.50 mmol, 5.0 equiv) and purified by flash chromatography (30/1 pentane/Et_2O, R_f: 0.45) in silica gel to provide **15** as a colorless oil (89.8 mg, 70 % yield). ^1H NMR (500MHz, C_6D_6): δ 4.78 (d, *J* = 3.1 Hz, 1H), 3.42 (s, 3H), 3.29-3.44 (m, 2H), 2.45 (br, 1H), 2.31 (dd, *J* = 10.4, 13.7 Hz, 1H), 2.17 (dd, *J* = 3.1, 13.7 Hz, 1H), 0.99 (s, 18H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.20 (s, 3H), 0.174 (s, 3H), 0.166 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75MHz, C_6D_6): δ 167.0, 162.3, 150.5, 112.7, 110.0, 50.6, 42.4, 32.5, 29.8, 26.0, 25.9, 23.1, 18.6, 18.2, -3.7, -3.8, -4.3, -4.4; IR (neat): 2956, 2930, 2858, 1719, 1693, 1627, 1332, 1254, 1221, 1142, 913, 839, 780 cm^{-1}; HRMS (APCI) calc for $C_{22}H_{43}O_4Si_2$ $(M+H)^+$ 427.2694 found 427.2683; HPLC: ((S,S)-DACH DNB 5/100, hexane, 0.7 mL/min) retention times of 21.3 min (minor) and 26.7 min (major), 99 % ee; $[\alpha]^{25}_D$ -36.1 (*c* = 1.49, $CHCl_3$).



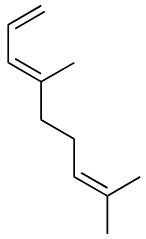
(*R*)-methyl 2,6-bis(*tert*-butyldimethylsilyloxy)-4-methoxycyclohepta-1,5-diene carboxylate (16): Derived from (*E*)-3-(*tert*-butyldimethylsiloxy)-1- methoxy-1,3-butadiene (322 mg, 1.50 mmol, 5.0 equiv) and purified by flash chromatography (10/1 pentane/Et_2O containing 0.5 % Et_3N, R_f: 0.57) in silica gel to provide **16** as a colorless oil (83.4 mg, 63 % yield). ^1H NMR (500 MHz, $CDCl_3$): δ 4.92 (d, *J* = 3.4 Hz, 1H), 4.02-4.04 (m, 1H), 3.68 (s, 3H), 3.33 (s, 3H), 3.24 (d, *J* = 18.0 Hz, 1H), 3.13 (d, *J* = 18.0 Hz, 1H), 2.78 (dd, *J* = 10.1, 13.7 Hz, 1H), 2.54 (dd, *J* = 3.1, 13.7 Hz, 1H), 0.96 (s, 9H), 0.92 (s, 9H), 0.199 (s, 3H), 0.193 (s, 3H), 0.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 159.9, 153.6, 110.4, 107.4, 73.8, 55.2, 51.2, 39.9, 32.7, 25.66, 25.61, 18.3, 18.0, -3.8, -4.5, -4.6; IR (neat): 2953, 2930, 2858, 1720, 1693, 1666, 1628, 1329, 1255, 1220, 1142, 1086, 840, 781 cm^{-1}; HRMS (ESI) calc for $C_{21}H_{39}O_4Si_2$ $(M\text{-}CH_3)^+$ 411.2381 found 411.2389; HPLC: (OD-H, hexane, 0.3 mL/min) retention times of 25.9 min (major) and 29.7 min (minor), 95.4 % ee; $[\alpha]^{25}_D$ -34.0 (*c* = 1.70, $CHCl_3$).



(*1S,5S*)-methyl 3-(*tert*-butyldimethylsilyloxy)bicyclo[3.2.1]octa-2,6-diene-2 -carboxylate (17): Derived from cyclopentadiene (99 mg, 1.50 mmol, 5.0 equiv) and purified by flash chromatography (30/1 pentane/Et_2O, R_f: 0.46) in silica gel to provide **17** as a colorless oil (76.3 mg, 86 % yield). The NMR data were consistent with published data.[3] HRMS (APCI) calc for $C_{16}H_{27}O_3Si_1$ $(M+H)^+$ 295.1724 found 295.1720; HPLC: ((S,S)-Whelk-O 1, 0.4 % isopropanol in hexane, 0.3 mL/min) retention times of 27.6 min (minor) and 29.1 min (major), 92 % ee; $[\alpha]^{25}_D$ -62.7 (*c* = 1.35, $CHCl_3$).



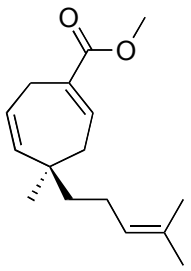
methyl 2-(*tert*-butyldimethylsilyloxy)-4,4-dimethylcyclohepta-1,5-diene carboxylate (18): Derived from 4-methylpenta-1,3-diene (123 mg, 1.50 mmol, 5.0 equiv) and purified by flash chromatography (25/1 pentane/Et_2O, R_f: 0.52) in silica gel to provide **18** as a colorless oil (52.8 mg, 57 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.56 (dt, *J* = 5.9, 11.3 Hz, 1H), 5.22 (dm, *J* = 11.3 Hz, 1H), 3.68 (s, 3H), 3.01 (dd, *J* = 1.6, 5.9 Hz, 2H), 2.46 (s, 2H), 1.04 (s, 6H), 0.95 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 162.1, 139.5, 123.7, 112.6, 51.0, 47.4, 34.0, 29.9, 25.7, 25.4, 18.3, -3.6; IR (neat): 2954, 1716, 1690, 1363, 1218, 1194, 1143, 1050, 822, 779 cm^{-1}; HRMS (APCI) calc for $C_{17}H_{31}O_3Si$ $(M+H)^+$ 311.2037 found 311.2037.



(*E*)-4,8-Dimethylnona-1,3,7-triene (10): Geraniol (100 mL, 0.57 mol) in DCM (250 mL) was added dropwise to a mechanically stirred solution of Dess-Martin periodinane (254 g, 0.60 mol) in DCM (2.0 L) at 0 °C. The reaction was then stirred for 6 h gradually warming to room temperature. The reaction was then cooled to 0 °C and sat. $NaHCO_3/Na_2S_2O_3$ (1:1 v/v, 2.0 L) was added slowly. The layers were then separated and the organic layer was washed with sat. $NaHCO_3/Na_2S_2O_3$ (1:1 v/v, 2.0 L), sat. $NaHCO_3$ (1.0 L), sat. $Na_2S_2O_3$ (1.0 L), and then brine (1.0 L). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the aldehyde, which was immediately used in the next reaction.

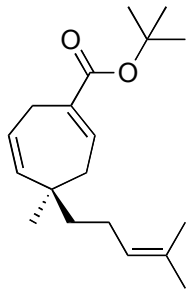
This reaction was preformed as described by Leopold.[4] Phenyl lithium (1.6 M in hexane, 374 mL) was added dropwise to a stirred solution of methytriphenylphosphonium iodide (265 g,

0.66 mol) in THF (2.0 L) at 0 °C. The ice bath was then removed and the yellow slurry was stirred for 30 min at room temperature. The orange solution was then cooled to 0 °C and the aldehyde (~0.57 mol) in THF (200 mL) was added dropwise over 20 min. The ice bath was then removed and the reaction was stirred for 2 h at room temperature. MeOH (10 mL) was then added and the slurry was concentrated *in vacuo*. Pentane/Et_2O (9:1 v/v, 1.0 L) was then added and the slurry was put in the freezer overnight. The resulting mixture was then filtered through Celite® and washed with pentane/Et_2O (9:1 v/v, 1.0 L). The filtrate was then concentrated *in vacuo*. The dark yellow oil was then filtered through Florisil®, washed with 1% EtOAc in hexanes (1.0 L) and concentrated *in vacuo*. The yellow oil was then purified by flash chromatography (SiO_2, hexanes/EtOAc = 99:1) to give the desired triene **10** (60.0 g, 70% yield) as a colorless oil. The physical and spectral data were identical to those previously reported for this compound:[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (dt, *J* = 16.4, 10.4 Hz, 1H), 5.84 (d, *J* = 10.4 Hz, 1H), 5.10-5.06 (m, 2H), 4.96 (d, *J* = 10.4 Hz, 1H), 2.10-2.04 (m, 4H), 1.74 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H).



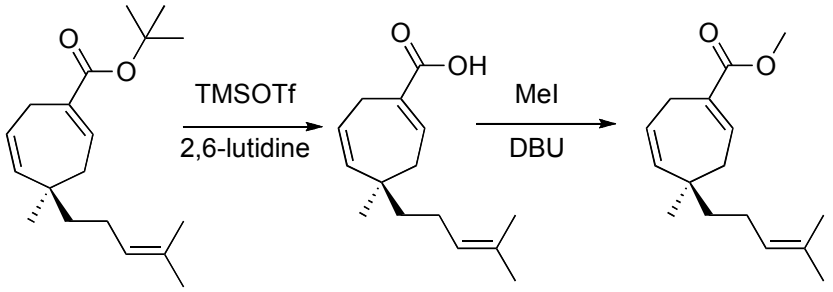
(*R*)-Methyl 4-methyl-4-(4-methylpent-3-enyl)cyclohepta-1,5-dienecarboxylate (22a): A solution of methyl 2-diazobut-3-enoate (0.063 g, 0.50 mmol) in hexanes (5 mL) was added dropwise to a stirred solution of triene **10** (0.225 g, 1.50 mmol) and Rh_2(*S*-PTAD)$_4$ (8.0 mg, 1 mol %) in toluene (10 mL) at room temperature over 3 h by syringe pump. The contents were stirred for 1 h and then heated under reflux for 3 h. The solution was then cooled to room temperature and concentrated *in vacuo*. The excess of **10** was removed by Kügelrohr distillation

and the residue was then purified by flash chromatography (SiO_2, hexanes/Et_2O = 20:1) to give **22a** (0.084 g, 67% yield) as a colorless oil. The physical and spectral data were identical to those previously reported for this compound:[5] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 7.4, 7.4 Hz, 1H), 5.50 (dt, *J* = 11.6, 5.2 Hz, 1H), 5.29 (d, *J* = 11.6 Hz, 1H), 5.06 (t, *J* = 6.6 Hz, 1H), 3.71 (s, 3H), 3.11 (d, *J* = 5.2 Hz, 2H), 2.50 (dd, *J* = 13.2, 7.4 Hz, 1H), 2.24 (dd, *J* = 13.2, 7.4 Hz, 1H), 1.95 (ddd, *J* = 11.2, 6.6, 6.4 Hz, 2H), 1.65 (s, 3H), 1.58 (s, 3H), 1.30 (dd, *J* = 11.2, 6.4 Hz, 2H), 0.98 (s, 3H). The enantiomeric excess was determined by chiral HPLC (Chiralpak AS-H, 0.0% *i*-PrOH in hexanes, flowrate = 0.7 mL/min, 230 nm) t_r = 10.5 min (major), t_r = 12.7 min (minor); 40% ee.



(*R*)-*t*-Butyl 4-methyl-4-(4-methylpent-3-enyl)cyclohepta-1,5-dienecarboxylate (22b): A solution of *t*-butyl 2-diazobut-3-enoate (0.100 g, 0.59 mmol) in toluene (10 mL) was added dropwise to a stirred solution of triene **10** (0.270 g, 1.80 mmol) and Rh_2(*S*-PTAD)$_4$ (10.0 mg, 1 mol %) in toluene (10 mL) at room temperature over 3 h by syringe pump. The contents were stirred for 1 h and then heated under reflux for 3 h. The solution was then cooled to room temperature and concentrated *in vacuo*. The excess triene was removed by Kügelrohr distillation and the residue was then purified by flash chromatography (SiO_2, hexanes/Et_2O = 20:1) to give **22b** (0.138 g, 80% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (t, *J* = 7.5 Hz, 1H), 5.54-5.49 (m, 1H), 5.30 (d, *J* = 11.5 Hz, 1H), 5.11 (t, *J* = 7.0 Hz, 1H), 3.09-3.08 (m, 2H), 2.49 (dd, *J* = 13.5, 7.5 Hz, 1H) 2.24 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.00-1.95 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.48 (s, 9H), 1.34-1.30 (m, 2H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3,

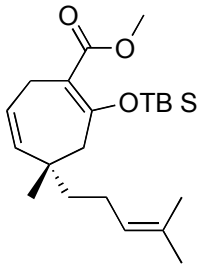
140.1, 139.4, 136.7, 131.2, 124.7, 123.5, 79.9, 43.2, 37.7, 37.1, 28.1, 28.0, 25.6, 23.1, 17.5; IR (neat) 2969, 2928, 1704 (C=O), 1367, 1166 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{30}O_2Na$ $[M]^+$, required *m/z* : 313.2138, found *m/z* : 313.2137. The enantiomeric excess could not be directly determined due to lack of separation of the enantiomers by chiral HPLC or chiral GC. In order to generate resolvable compounds, the following synthetic sequence was conducted.



(*R*)-Methyl 4-methyl-4-(4-methylpent-3-enyl)cyclohepta-1,5-dienecarboxylate (22a): TMSOTf (0.10 mL, 0.553 mmol) was added dropwise to a stirred solution of (*R*)-*t*-butyl 4-methyl-4-(4-methylpent-3-enyl)cyclohepta-1,5-dienecarboxylate (0.129 g, 0.444 mmol) and 2,6-lutidine (0.08 mL, 0.687 mmol) in DCM (5 mL) at 0 °C. The reaction was stirred overnight while gradually warming to room temperature. HCl (2M, 10 mL) was added and the layers were separated. The *aq*. layer was then extracted with DCM (2 X 10 mL) and the organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was the desired acid with >95% conversion and was used in the following reaction without further purification.

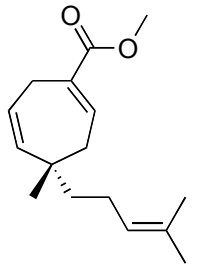
Methyl iodide (0.09 mL, 1.45 mmol) was added dropwise to a stirred solution of the crude acid (0.444 mmol) and DBU (0.20 mL, 1.34 mmol) in DCM (10 mL) at 0 °C. The reaction was stirred overnight and concentrated *in vacuo*. The residue was then purified by flash chromatography (SiO_2, hexanes/Et_2O = 20:1) to give **22a** (0.086 g, 79% yield over the two steps) as a colorless oil. The physical and spectral data of **22a** were identical to those previously reported for this compound:[5] ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 7.4, 7.4 Hz, 1H0, 5.50 (dt, *J* = 11.6, 5.2

Hz, 1H), 5.29 (d, J = 11.6 Hz, 1H), 5.06 (t, J = 6.6 Hz, 1H), 3.71 (s, 3H), 3.11 (d, J = 5.2 Hz, 2H), 2.50 (dd, J = 13.2, 7.4 Hz, 1H), 2.24 (dd, J = 13.2, 7.4 Hz, 1H), 1.95 (ddd, J = 11.2, 6.6, 6.4 Hz, 2H), 1.65 (s, 3H), 1.58 (s, 3H), 1.30 (dd, J = 11.2, 6.4 Hz, 2H), 0.98 (s, 3H). The enantiomeric excess was determined by chiral HPLC (Chiralpak AS-H, 0.0% *i*-PrOH in hexanes, flowrate = 0.7 mL/min, 230 nm) t_r = 10.5 min (major), t_r = 12.7 min (minor).



(*S*)-Methyl 2-(*tert*-butyldimethylsilyloxy)-4-methyl-4-(4-methylpent-3-enyl)cyclohepta-1,5-dienecarboxylate (23): A solution of methyl 3-(*tert*-butyldimethylsilyloxy)-2-diazobut-3-enoate (10.0 g, 0.039 mol) in toluene (200 mL) was added dropwise to a stirred solution of triene **10** (17.8 g, 0.118 mol) and Rh_2(*R*-PTAD)$_4$ (0.320 g, 0.5 mol %) in toluene (600 mL) at ~ -10 ^oC over 3 h by an addition funnel. The contents were aged 4 h between -15 to -5 °C and then warmed to room temperature overnight. The green solution was then refluxed for 4 h. After which time, the solution was cooled to room temperature and concentrated *in vacuo*. The excess of **10** was removed by Kügelrohr distillation and the residue was then purified by flash chromatography (SiO_2, hexanes/Et_2O = 20:1) to give **23** (9.59 g, 65% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70-5.62 (m, 1H), 5.21 (d, J = 11.5 Hz, 1H), 5.08 (t, J = 7.0 Hz, 1H), 3.68 (s, 3H), 3.03-2.99 (m, 2H), 2.83 (d, J = 13.5 Hz, 1H), 2.11 (d, J = 13.5 Hz, 1H), 1.99-1.95 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.33 (t, J = 8.5 Hz, 2H), 1.03 (s, 3H), 0.95 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 162.1, 138.2, 131.2, 124.9, 124.7, 112.6, 50.9, 45.3, 43.7, 36.9, 27.4, 25.7, 25.6, 25.5, 23.0, 18.3, 17.6, -3.7; IR (neat) 2929, 2858, 1720 (C=O), 1693, 1368, 1212, 841 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{35}O_3Si$ $[M]^+$, required *m/z* : 363.2350,

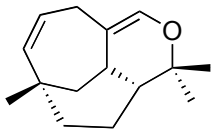
found *m/z* : 363.2359. $[\alpha]^{25}_{D} = {}^{+}29.3$ (*c* = 1.37, $CHCl_3$). The enantiomeric excess was determined by chiral HPLC ((*R*,*R*)-Whelk-O 1, 0.0% *i*-PrOH in hexanes, flowrate = 0.7 mL/min, 245 nm) t_r = 17.8 min (major), t_r = 21.0 min (minor); 90% ee.



(*S*)-Methyl 4-methyl-4-(4-methylpent-3-enyl)cyclohepta-1,5-dienecarboxylate (24): TBAF (50.7 mL, 0.051 mol) was added dropwise to a stirred solution of (*S*)-methyl 2-(*tert*-butyldimethylsilyloxy)-4-methyl-4-(4-methylpent-3-enyl)cyclohepta-1,5-dienecarboxylate (9.59 g, 0.025 mol) in acetonitrile (250 mL) at 0 °C. The ice bath was then removed and the reaction was aged at room temperature for 12 h. Water (400 mL) was then added and the solution was extracted with Et_2O (3 X 250 mL). The organic extracts were combined and washed with 3M HCl (2 X 250 mL), water (250 mL), sat. $NaHCO_3$ (2 X 250 mL), and brine (250 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was a mixture of keto/enol tautomers and was further dried for 12 h before use in the next reaction.

The mixture of tautomers (0.025 mol) in THF (75 mL) was added dropwise to a stirred slurry of NaH (3.04 g, 0.127 mol) in THF (125 mL) at 0 °C and aged 1 h. After which time, Comin's reagent (19.9 g, 0.051 mol) in THF (75 mL) was added dropwise over 15 min at 0 °C. The reaction was aged for 1 h and then diluted with pentane/Et_2O (1:1 v/v, 200 mL). The slurry was then filtered through a pad of SiO_2/Celite® (1:1 wt/wt, 10 g) to remove unreacted NaH and the pad was further rinsed with pentane/Et_2O (1:1 v/v, 2 X 100 mL). The filtrate was kept cold and washed with cold 1 M KOH (3 X 300 mL), brine (300 mL). The crude triflate was then dried over $MgSO_4$, filtered, concentrated *in vacuo*, and kept at 0 °C until used in the following reaction.

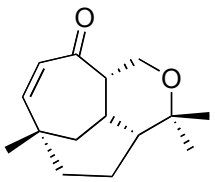
n-Bu_3SnH (33.5 mL, 0.124 mol) was added dropwise over 30 min to a degassed solution of crude triflate (0.0025 mol), lithium chloride (3.17 g, 0.075 mol), and $Pd(PPh_3)_4$ (1.44 g, 5 mol %) in THF (250 mL) at room temperature. The reaction was then stirred overnight at room temperature. A solution of sat. KF (250 mL) was then added and the layers were separated. The *aq*. layer was then extracted with Et_2O (2 X 250 mL) and the organic extracts were combined. The extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was then purified by flash chromatography (SiO_2, hexanes/Et_2O = 100: 0 $\Rightarrow$ 50:1 $\Rightarrow$20:1) to give **24** (4.41 g, 70% yield) as a colorless oil. The physical and spectral data were identical to those previously reported for this compound:[5] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 7.4, 7.4 Hz, 1H), 5.50 (dt, *J* = 11.6, 5.2 Hz, 1H), 5.29 (d, *J* = 11.6 Hz, 1H), 5.06 (t, *J* = 6.6 Hz, 1H), 3.71 (s, 3H), 3.11 (d, *J* = 5.2 Hz, 2H), 2.50 (dd, *J* = 13.2, 7.4 Hz, 1H), 2.24 (dd, *J* = 13.2, 7.4 Hz, 1H), 1.95 (ddd, *J* = 11.2, 6.6, 6.4 Hz, 2H), 1.65 (s, 3H), 1.58 (s, 3H), 1.30 (dd, *J* = 11.2, 6.4 Hz, 2H), 0.98 (s, 3H).



Hetero Diels-Alder Adduct (25): The diene was prepared by the described procedures of Davies and Loe.[5] DIBAL-H (53.3 mL, 1M in hexanes) was added dropwise to a stirred solution of (*S*)-methyl 4-methyl-4-(4-methylpent-3-enyl)cyclohepta-1,5-dienecarboxylate (**24**) (4.41 g, 0.018 mol) in THF (125 mL) at 0 °C. The reaction was stirred overnight while gradually warming to room temperature. The crude mixture was quenched with ice/water and diluted with 1 M HCl (100 mL). The solution was extracted with Et_2O (2 X 100 mL) and the organic extracts were then washed with 1 M HCl (2 X 100 mL), water (100 mL), and brine (250 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting alcohol was used without further purification.

DMSO (4.04 mL, 0.057 mol) was added dropwise to a stirred solution of oxalyl chloride (3.05 mL, 0.036 mol) in DCM (200 mL) at -78 °C and stirred for15 min. The crude alcohol in DCM (100 mL) was then added dropwise over 15 min and stirred for 45 min at -78 °C. After which time, TEA (27.7 mL, 0.199 mol) was added over 15 min and the cooling bath was removed. The mixture was allowed to gradually warm to room temperature. The organics were then washed with water (3 X 100 mL), then brine (100 mL), and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexanes/Et_2O = 19:1) to give the desired aldehyde (3.47 g, 90% yield) as a yellow oil. The physical and spectral data were identical to those previously reported for this compound:[5] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (s, 1H), 6.84 (t, *J* = 6.7 Hz, 1H), 5.52 (dt, *J* = 17.1, 11.6 Hz, 1H), 5.38 (d, *J* = 11.6 Hz, 1H), 5.09 (t, *J* = 7.0 Hz, 1H), 3.08 (dd, *J* = 19.5, 5.2 Hz, 1H), 3.03 (dd, *J* = 19.5, 5.2 Hz, 1H), 2.68 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.45 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.02-1.97 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.40-1.33 (m, 2H), 1.05 (s, 3H).

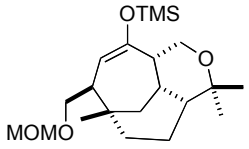
Boron trifluoride etherate (6.87 mL, 0.056 mol) was added dropwise to a stirred solution of (*S*)-4-methyl-4-(4-methylpent-3-enyl)cyclohepta-1,5-dienecarbaldehyde (3.47 g, 0.016 mol) in DCM (125 mL) at -78 °C. The reaction was stirred for 25 min and then water (125 mL) was added. The cooling bath was then removed and the mixture was gradually warmed to room temperature. The solvent layers were separated and the *aq*. layer was extracted with DCM (3 X 50 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexanes/Et_2O = 24:1) to give **25** (2.95 g, 85% yield, 77% yield over the three steps) as a clear oil. The physical and spectral data were identical to those previously reported for this compound:[5] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (d, *J* = 2.1 Hz, 1H), 5.74 (ddd, *J* = 11.1, 11.1, 1.8 Hz, 1H), 4.99 (d, *J* = 11.1 Hz, 1H), 2.97 (d, *J* = 15.6 Hz, 1H), 2.79 (bs, 1H), 2.32 (m, 2H), 1.55-1.47 (m, 2H), 1.39 (dd, *J* = 12.8, 4.0 Hz, 1H), 1.31-1.21 (m, 2H), 1.25 (s, 3H), 1.24 (s, 3H), 1.14 (dt, *J* = 12.8, 4.0 Hz, 1H), 0.96 (s, 3H).



Tricyclic enone (7): The enone was prepared by the described procedures of Davies and Loe.[5] Sodium cyanoborohydride (5 X 0.76 g, 0.061 mol) was added in five equal portions to a stirred solution of diene **25** (2.95 g, 0.014 mol) in acetic acid (100 mL) at room temperature and then stirred for 20 min. The same quantity of sodium cyanoborohydride (5 X 0.76 g, 0.061 mol) was added again and the mixture was stirred for a further 20 min. The reaction was then quenched with water (250 mL) and diluted with hexanes (100 mL). The layers were separated and the *aq* layer was extracted with hexanes (2 X 100 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The yellow residue was purified by flash chromatography (SiO_2, hexanes/Et_2O = 19:1) to give the desired alkene (2.53 g, 85% yield) as a clear oil. The physical and spectral data were identical to those previously reported for this compound:[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (ddd, *J* = 12.2, 7.3, 2.4 Hz, 1H), 5.42 (ddd, *J* = 12.2, 2.7, 1.5 Hz, 1H), 3.83 (dd, *J* = 10.6, 2.6 Hz, 1H), 3.35 (d, *J* = 10.6 Hz, 1H), 2.85 (ddd, *J* = 14.4, 7.0, 3.3 Hz, 1H), 2.39 (br d, *J* = 4.4 Hz, 1H), 2.23 (ddd, *J* = 14.4, 11.7, 7.0 Hz, 1H), 1.77-1.68 (m, 3H), 1.57-1.47 (m, 3H), 1.31 (s, 3H), 1.30-1.21 (m, 2H), 1.20 (s, 3H), 1.02 (s, 3H).

Selenium dioxide (1.53 g, 0.014 mol) was added in one portion to a stirred solution of alkene (2.53 g, 0.011 mol) in 1,4-dioxane (100 mL) at room temperature. The mixture was then heated under reflux for 2 h. The reaction was thencooled to room temperature and water (250 mL) was added. The solution was then extracted with Et_2O (3 X 100 mL), and the organic extracts were combined. The extracts were then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was then dried for an additional 12 h before the next step was performed.

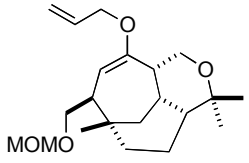
Pyridinium chlorochromate (5.94 g, 0.28 mol) was added to a stirred mixture of crude allylic alcohol (0.011 mol) and 4 Å molecular sieves (4.60 g) in DCM (100 mL) at room temperature. The reaction was stirred at room temperature for 8 h and was then diluted with Et_2O (150 mL). The black mixture was filtered through a pad of Celite® and the pad was washed with Et_2O (3 X 150 mL). The filtrate was then washed with water (2 X 250 mL), and then with brine (250 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexanes/acetone = 9:1) to give **7** (1.88 g, 70% yield, 60% overall yield over the three steps) as a white solid. The physical and spectral data were identical to those previously reported for this compound:[5] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (s, 2H), 4.57 (d, *J* = 11.7 Hz, 1H), 3.60 (dd, *J* = 11.7, 3.1 Hz, 1H), 2.62 (d, *J* = 4.4 Hz, 1H), 2.16 (t, *J* = 4.4 Hz, 1H), 2.08 (d, *J* = 13.7 Hz, 1H), 1.73 (dd, *J* = 13.7, 5.8 Hz, 1H), 1.56 (m, 2H), 1.30 (s, 3H), 1.27 (m, 2H), 1.17 (s, 3H), 1.15 (m, 1H), 1.12 (s, 3H). The enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H, 5.0% *i*-PrOH in hexanes, flowrate = 0.7 mL/min, 245 nm) t_r = 12.0 min (major), t_r = 14.9 min (minor); 88% ee. The material could then be enriched to >98% ee by a single recrystallization from hexanes (200 mg in 5 mL) to give **7** (recovery yield of ~75%) as clear crystals. $[\alpha]^{25}_D$ = +5.1 (*c* = 0.45, $CHCl_3$, >98% ee).



26

Conjugate addition of $LiCH_2OMOM$ to 7. To a stirred solution of *n*-Bu_3SnCH_2OMOM[6] (1.56 g, 4.28 mmol) in anhydrous THF (10 mL) was added a solution of *n*-BuLi (2.90 mL, 4.28 mmol, 1.48 M in hexanes) at −78 °C under an argon atmosphere. After 5 min the reaction mixture was transferred via a cannula to a solution of TMEDA (0.97 mL, 6.42 mmol) and CuI (410 mg, 2.14 mmol) in THF (8 mL) at −78 °C. The reaction was stirred for 30 min after which time TMSCl (810 μL, 6.42 mmol) was added dropwise followed by a solution of **7** (500 mg, 2.14 mmol) in

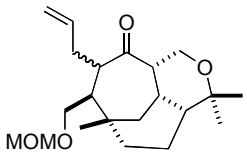
THF (5 mL). The reaction was stirred at −78 °C for 1 h then warmed slowly to −20 °C and stirred for a further 45 min. The mixture was then poured into ice cold saturated sodium bicarbonate solution (25 mL) and extracted with ether (3 × 25 mL). The combined organic layer was then washed with a 10% aqueous ammonia solution (2 × 20 mL) followed by brine (15 mL) then dried (Na_2SO_4) and concentrated *in vacuo* to provide an oil which was purified by flash chromatography (1:20 ether:petroleum ether) which gave **26** as a colorless oil (745 mg, 91%). $[\alpha]^{22}_D$ + 63.5 (*c* 0.7, C_6H_6). ^{1}H NMR (400 MHz, C_6D_6) δ 5.24 (ddd, *J* = 7.64, 2.59, 0.75 Hz, 1H), 4.51 (AB, *J* = 6.7 Hz, 2H), 4.46 (dd, *J* = 11.4, 1.5 Hz, 1H), 3.57 (dd, *J* = 9.4, 4.4 Hz, 1H), 3.53 (dd, *J* = 9.4, 6.2 Hz, 1H), 3.40 (ddd, *J* 11.4, 2.8, 0.7 Hz, 1H), 3.23 (s, 3H), 2.38 (qd, *J* = 13.4, 4.5 Hz, 1H), 1.99–2.12 (m, 4H), 1.63–1.69 (m, 1H), 1.33–1.41 (m, 1H), 1.21–1.28 (m, 2H), 1.17 (s, 3H), 1.14 (s, 3H), 0.98 (s, 3H), 0.96–1.02 (m, 1H), 0.26 (s, 9H). ^{13}C NMR (100 MHz, C_6D_6) δ 152.9, 111.7, 96.9, 73.2, 71.5, 63.5, 55.0, 48.1, 44.6, 43.8, 43.3, 40.7, 32.8, 32.6, 31.9, 28.1, 24.3, 23.8, 0.5 (3C). GC/MS EI m/z (%) 382 (M^+, 17) 367 (2), 320 (3), 307 (10), 279 (17), 249 (44), 167 (7), 73 (100), 45 (64). HRMS Calculated for $[C_{21}H_{38}O_4Si]^+$: 382.2539, Found: 382.2538.



27

Allylation of 26. A solution of methyl lithium (0.73 mL, 0.94 mmol, 1.3 M in diethyl ether) was added dropwise to a solution of **26** (200 mg, 0.524 mmol) in anhydrous THF (5 mL) at –20 °C under an argon atmosphere. The reaction was stirred for 45 min, cooled to −78 °C then anhydrous HMPA (0.45 mL, 2.02 mmol) and allyl bromide (560 mg, 4.62 mmol) were added sequentially by dropwise addition. The reaction was stirred for 45 min and then warmed to –40 °C and stirred for a further 45 min. The reaction was quenched by pouring into ice cold saturated sodium bicarbonate solution (25 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic layer was then washed with an aqueous 10% lithium chloride solution (20 mL)

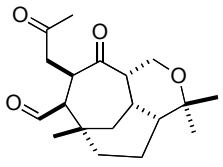
and brine (15 mL), then dried (Na_2SO_4). The solution was concentrated *in vacuo*, which afforded an oil that was purified by flash chromatography (1:20 diethyl ether:petroleum ether) to give **27** (137 mg, 74%) as a colorless oil. $[\alpha]^{22}_D$ + 53.2 (*c* 0.5, C_6H_6). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (ddt, *J* = 17.3, 10.4, 5.1 Hz, 1H), 5.29 (app. qd, *J* = 17.3, 1.7 Hz, 1H), 5.13 (app. qd, *J* = 10.5, 1.5 Hz, 1H), 4.84 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.55 (s, 2H), 0.96 (s, 3H), 4.45 (dd, *J* = 11.6, 1.8 Hz, 1H), 4.12–4.30 (m, 2H), 3.59 (dd, *J* = 9.3, 4.3 Hz, 1H), 3.51 (ddd, *J* = 11.5, 2.9, 0.7 Hz, 1H), 3.44 (dd, *J* = 9.3, 7.0 Hz, 1H), 3.30 (s, 3H), 2.28–2.40 (m, 2H), 2.04–2.22 (m, 3H), 1.64–1.73 (m, 1H), 1.37–1.44 (m, 2H), 1.27 (s, 3H), 1.17–1.33 (m, 2H), 1.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 134.3, 116.1, 103.2, 96.6, 73.5, 71.5, 68.4, 62.7, 55.1, 47.2, 44.3, 42.9, 42.1, 40.5, 32.4, 32.3, 31.8, 27.7, 24.4, 23.5. HRMS Calculated for $[C_{21}H_{34}O_4]^+$: 350.2452, Found: 350.2452.



28 (*Syn*, 41%)
29 (*Anti*, 11%)

Microwave promoted Claisen rearrangement of 27. A solution of *O*-allylated material **27** (180 mg, 0.51 mmol) in anhydrous toluene (60 mL) was divided into three separate 20 mL batches and were heated sequentially under microwave irradiation with a silicon carbide passive heating element[7] for 2 h (maximum temperature 185 °C, 300 W). The batches were combined and solvent was removed *in vacuo* which afforded an oil that was purified by flash chromatography (1:10 ether:pet. spirit) to give *C*-allylated isomers **28** (73 mg, 41%) and **29** (20 mg, 11%) as colorless oils. *Syn Isomer* **28** $[\alpha]^{21}_D$ - 109.7 (*c* 0.8, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (dddd, *J* = 16.7, 10.1, 8.6, 5.4 Hz, 1H), 4.98–5.07 (m, 2H), 4.46 (d, *J* = 6.6 Hz, 1H), 4.42 (d, *J* = 6.6 Hz, 1H), 4.21 (dd, *J* = 12.1, 1.1 Hz, 1H), 3.78 (dd, *J* = 12.1, 4.7 Hz, 1H), 3.55 (dd, *J* = 10.7, 2.2 Hz, 1H), 3.45 (dd, *J* = 10.7, 4.8 Hz, 1H), 3.29 (s, 3H), 3.28–3.32 (m, 1H), 2.79–2.87 (m, 1H), 2.43–2.48 (m, 1H), 2.36–2.40 (m, 1H), 2.20 (td, *J* = 14.4, 2.8 Hz, 1H), 2.06

(dt, J = 15.2, 8.3 Hz, 1H), 1.66–1.81 (m, 4H), 1.42–1.52 (m, 1H), 1.39 (ddd, J = 14.1, 4.9, 1.4 Hz, 1H), 1.23–1.33 (m, 1H), 1.28 (s, 3H), 1.09 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.3, 137.5, 116.3, 96.6, 73.8, 65.4, 64.6, 55.7, 52.2, 51.8, 48.7, 41.1, 39.7, 39.4, 33.9, 33.7, 33.0, 23.8, 30.1, 27.1, 24.3. HRMS Calcd for $[C_{21}H_{34}O_4]^+$: 350.2452, Found: 350.2461 *Anti Isomer* **29** $[\alpha]^{22}_D$ - 49.5 (*c* 0.5, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 4.85–4.99 (m, 2H), 4.55 (AB, J = 6.6 Hz, 2H), 4.16 (d, J = 11.9 Hz, 1H), 3.63 (dd, J = 10.5, 2.1 Hz, 1H), 3.49–3.56 (m, 2H), 3.36 (s, 3H), 2.94 (td, J = 11.1, 3.2 Hz, 1H), 2.52–2.61 (m, 2H), 2.38 (dt, J = 14.9, 2.1 Hz, 1H), 2.10–2.20 (m, 2H), 1.44–1.52 (m, 2H), 1.32–1.41 (m, 3H), 1.23 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 1.03–1.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9, 137.1, 116.2, 97.0, 72.9, 67.3, 59.0, 56.1, 50.9, 50.9, 45.3, 43.5, 42.7, 42.1, 34.1, 33.1, 30.3, 29.5, 27.9, 23.3, 18.9. GC/MS EI m/z (%) ($M^{+\cdot}$-15, 1), 320 (0.3), 288 (1), 275 (10), 247 (0.3), 189 (1), 135 (6), 79 (14), 45 (100). HRMS Calcd for $[C_{21}H_{34}O_4]^+$: 350.2452, Found: 350.2466.



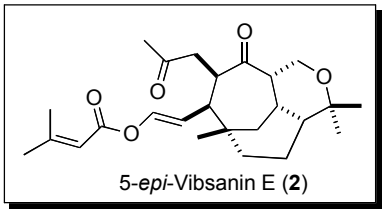
30

Diketoaldehyde 30. A mixture of **28** (73 mg, 0.21 mmol) in MeOH (13 mL), water (1.5 mL) and aqueous hydrochloric acid (1 mL, 10M) was stirred at 55 °C for 2 h. The mixture was quenched with saturated sodium bicarbonate solution (10 mL) and then the methanol was removed *in vacuo* followed by extraction with dichloromethane (3 × 15 mL). The combined organic layer was washed with brine (10 mL), dried (Na_2SO_4), then filtered through a plug of silica and concentrated *in vacuo* affording 42 mg of an oil that was used without further purification. To a stirred solution of oxalyl chloride (34 μL, 0.39 mmol) in anhydrous dichloromethane (5 mL) under an argon atmosphere at –78 °C was added dimethyl sulfoxide (35 μL, 0.49 mmol) dropwise. After 10 min a solution of the alcohol in anhydrous dichloromethane

(1.5 mL) was added dropwise. After 1 h at –78 °C excess anhydrous triethylamine (165 μL, 1.18 mmol) was added, and stirring continued at that temperature for a further 15 min. The solution was warmed to 0°C and stirred for 20 min, then diluted with dichloromethane (30 mL), washed with brine (10 mL) and dried ($MgSO_4$). Evaporation *in vacuo* gave a residue, which was subjected to column chromatography (1:5 ethyl acetate:petroleum ether) affording ketoaldehyde (25 mg, 39%, 2 steps) as a colorless paste. $[\alpha]^{23}_D$ -40.2 (*c* 0.5, $CDCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, *J* = 2.9 Hz, 1H), 5.65 (dddd, *J* = 17.0, 10.2, 8.7, 5.6 Hz, 1H), 4.99–5.02 (m, 1H), 4.96 (ddt, *J* = 17.0, 1.9, 1.2 Hz, 1H), 4.21 (dd, *J* = 12.2, 1.4 Hz, 1H), 3.77 (dd, *J* = 12.2, 4.8 Hz, 1H), 3.24 (ddd, *J* = 8.1, 5.5, 3.8 Hz, 1H), 2.76 (ttd, *J* = 14.5, 5.5, 1.6 Hz, 1H), 2.67 (td, *J* = 3.6, 1.5 Hz, 1H), 2.50–2.55 (m, 1H), 2.43 (ddd, *J* = 6.3, 4.8, 1.4 Hz, 1H), 1.84–1.94 (m, 3H), 1.64–1.72 (m, 2H), 1.37–1.52 (m, 2H), 1.29–1.34 (m, 1H), 1.27 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 204.2, 136.7, 117.3, 73.7, 63.7, 60.8, 51.9, 50.1, 40.7, 40.2, 39.9, 34.6, 34.0, 32.2, 29.9, 27.0, 23.9, 23.7. HRMS Calculated for $[C_{19}H_{28}O_3]^+$: 304.2033, Found: 304.2031.

The above ketoaldehyde (25 mg, 82 μmol) was dissolved in a mixture of *N*,*N*-dimethylformamide and water (7:1, 1 mL), and to this was added palladium dichloride (2 mg, 11 μmol) and copper (II) chloride dihydrate (19 mg, 110 μmol). The reaction mixture was then stirred under a balloon of oxygen for 1 h at room temperature. The mixture was diluted with diethyl ether, filtered through celite and concentrated *in vacuo*. The residue was then subjected to column chromatography (1:1 ethyl acetate:petroleum ether), which afforded diketoaldehyde **30** (12 mg, 47%) as a colorless foam. $[\alpha]^{21}_D$ -53.7 (*c* 0.6, C_6D_6), ^{1}H NMR (100 MHz, C_6D_6) δ 9.41 (d, *J* = 2.4 Hz, 1H), 4.64 (dd, *J* = 11.9, 2.0 Hz, 1H), 3.88 (td, *J* = 6.1, 3.6 Hz, 1H), 3.47 (dd, *J* = 11.8, 4.5 Hz, 1H), 3.19 (dd, *J* = 18.0, 6.3 Hz, 1H), 2.24–2.27 (m, 1H), 2.14 (ddd, *J* = 6.2, 4.6, 1.9 Hz, 1H), 1.90–1.95 (m, 1H), 1.75–1.87 (m, 2H), 1.70 (s, 3H), 1.65–1.75 (m, 1H), 1.51 (dt, *J* = 14.4, 2.9 Hz, 1H), 1.28–1.37 (m, 1H), 0.99 (s, 3H), 0.98 (s, 3H), 0.91–1.02 (m, 1H), 0.84 (s,

3H), 0.79–0.86 (m, 1H), 0.74 (dt, J = 13.0, 5.0, Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6) δ 210.7, 205.6, 203.6, 73.2, 64.1, 63.0, 52.0, 46.1, 45.2, 40.5, 41.2, 39.4, 34.0, 32.3, 30.6, 29.6, 27.0, 24.1, 24.0. HRESIMS Calculated for $[C_{19}H_{28}NaO_4]^+$: 343.1880, Found: 343.1883.



5-*epi*-Vibsanin E (**2**)

5-epi-Vibsanin E (2). A suspension of [(3-methylbut-2-enoyloxy)-methyl]triphenylphosphonium chloride (45 mg, 0.11 mmol) in anhydrous tetrahydrofuran (2 mL) under an argon atmosphere was sonicated for 10 min until a uniform milky dispersion had formed. The mixture was then cooled to –78 °C and a solution of sodium bis(trimethylsilyl)amide solution (110 μL , 0.11 mmol, 1M solution in THF) was added strictly dropwise. The brightly orange coloured reaction mixture was stirred for 10 mins, then a solution of aldehyde **30** (12 mg, 37 μmol) in anhydrous tetrahydrofuran (2 mL) was added dropwise. After complete addition the solution turned colorless within 60 sec. The mixture was then poured onto saturated ice-cold sodium bicarbonate (5 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography (1:5 ethyl acetate: petroleum ether), which gave 5-*epi*-vibsanin E (4 mg, 26%, >99.5% ee) as a colorless paste. $[\alpha]^{22}_D$ -49.7 (*c* 0.1, $CDCl_3$), {lit. $[\alpha]^{22}_D$ -34.7 (*c* 0.21, $CHCl_3$)}, ^{1}H NMR (600 MHz, C_6D_6) δ 7.31 (d, J = 12.3 Hz, 1H), 5.66–5.68 (m, 1H), 5.26 (dd, J = 12.4, 11.8 Hz, 1H), 4.36 (dd, J = 12.1, 2.9 Hz, 1H), 4.14–4.17 (m, 1H), 3.70 (dd, J = 12.2, 5.9 1H), 2.98 (dd, J = 17.9, 7.4 Hz, 1H), 2.19–2.22 (m, 1H), 2.05 (d, J = 1.1, 3H), 2.00–2.08 (m, 1H), 1.90–1.97 (m, 2H), 1.76–1.83 (m, 2H), 1.70 (s, 3H), 1.55 (dt, J = 14.6, 2.5 Hz, 1H), 1.51–1.45 (m, 1H), 1.37 (d, J = 1.1 Hz, 3H), 1.28 (dt, J = 14.2, 6.6 Hz, 1H), 1.06 (s, 3H), 1.03 (s, 3H), 0.96–1.02 (m, 1H), 0.87–0.94 (m, 1H), 0.80 (s, 3H). ^{13}C NMR (150 MHz, C_6D_6) δ 212.6, 205.6, 163.3, 160.0, 137.8, 115.1, 111.8, 73.6, 64.0, 53.6, 50.7,

48.5, 45.3, 40.8, 38.9, 38.3, 34.0, 33.9, 29.7, 29.1, 27.0, 26.6, 25.2, 24.8, 20.3. HRESIMS Calculated for $[C_{25}H_{36}NaO_5]^+$: 439.2455, Found: 439.2445.

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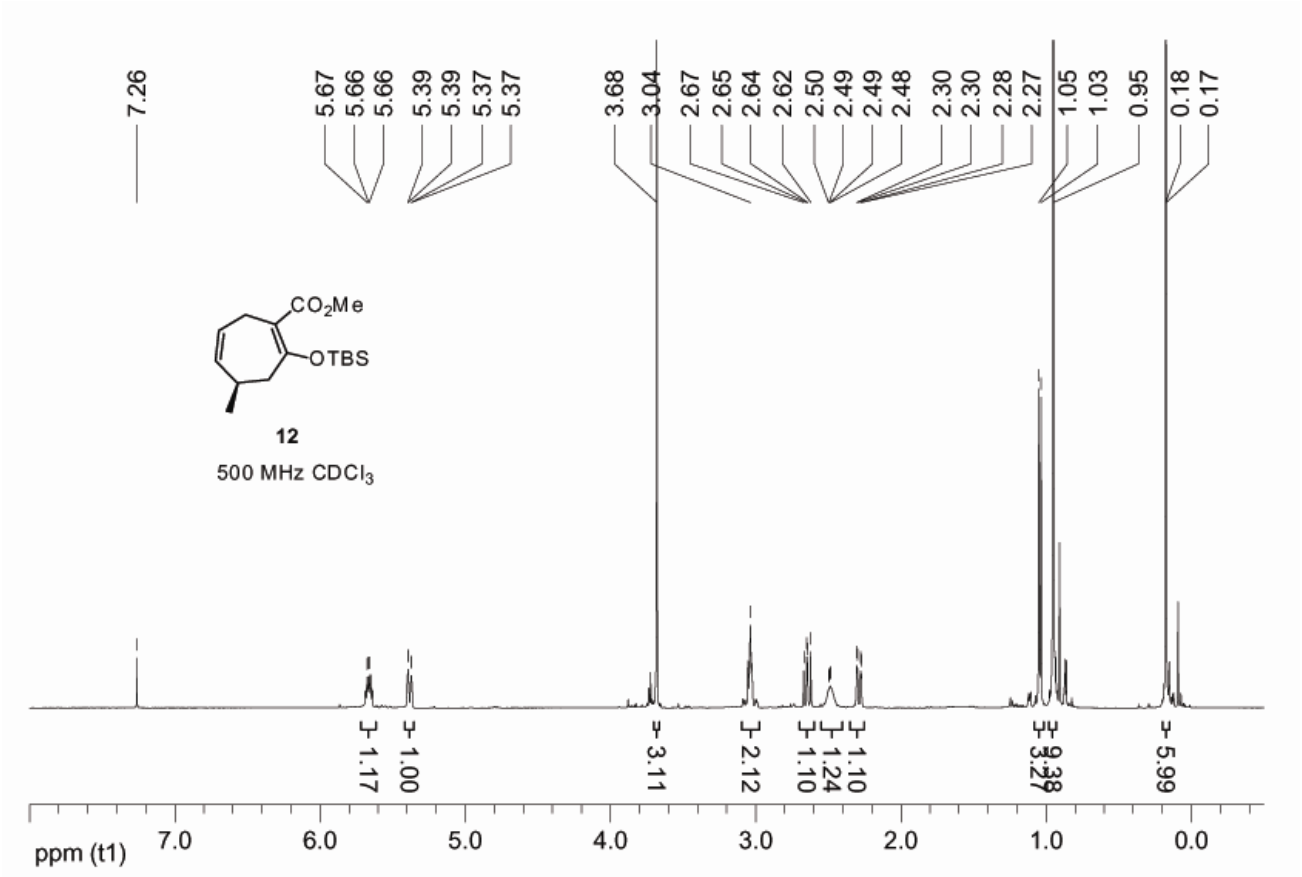
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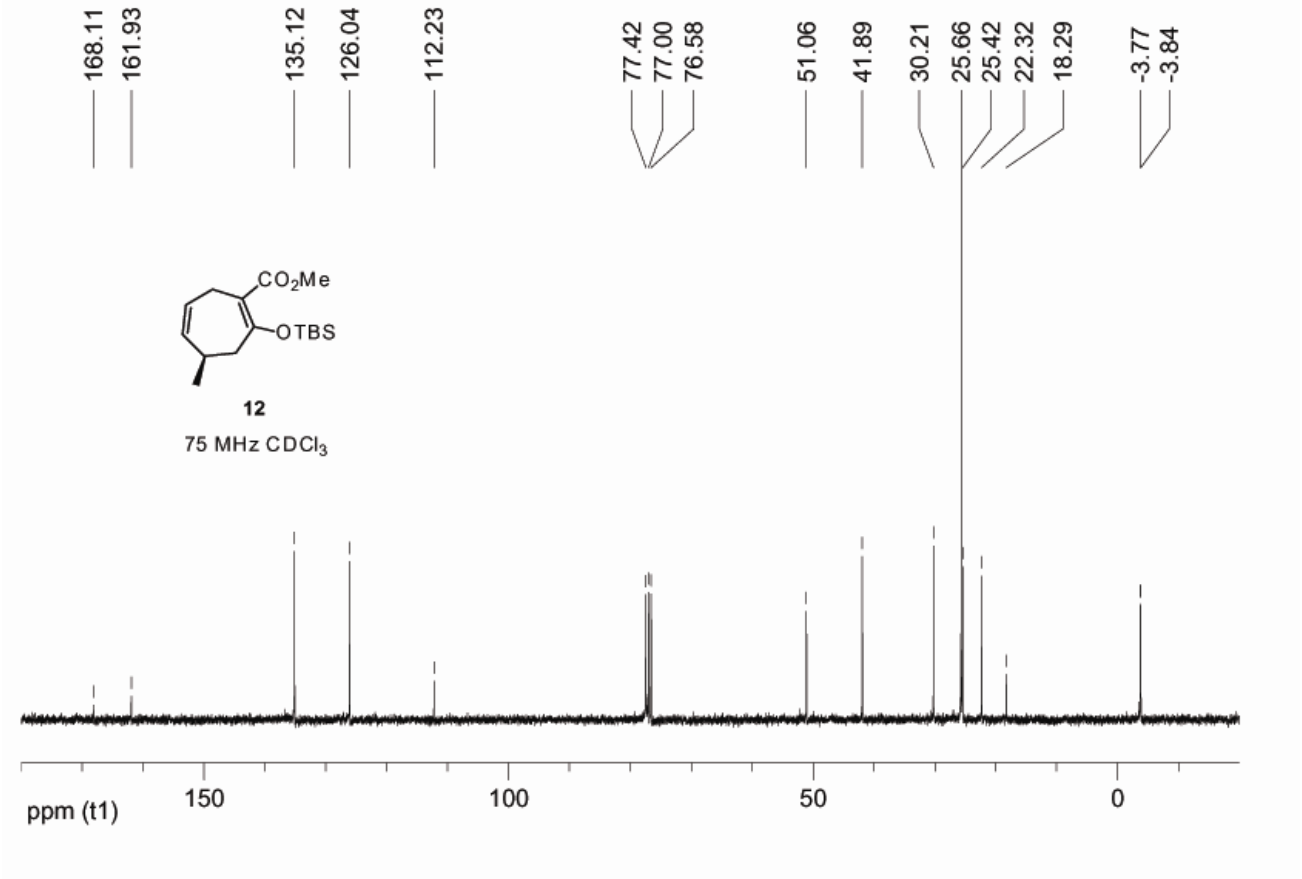
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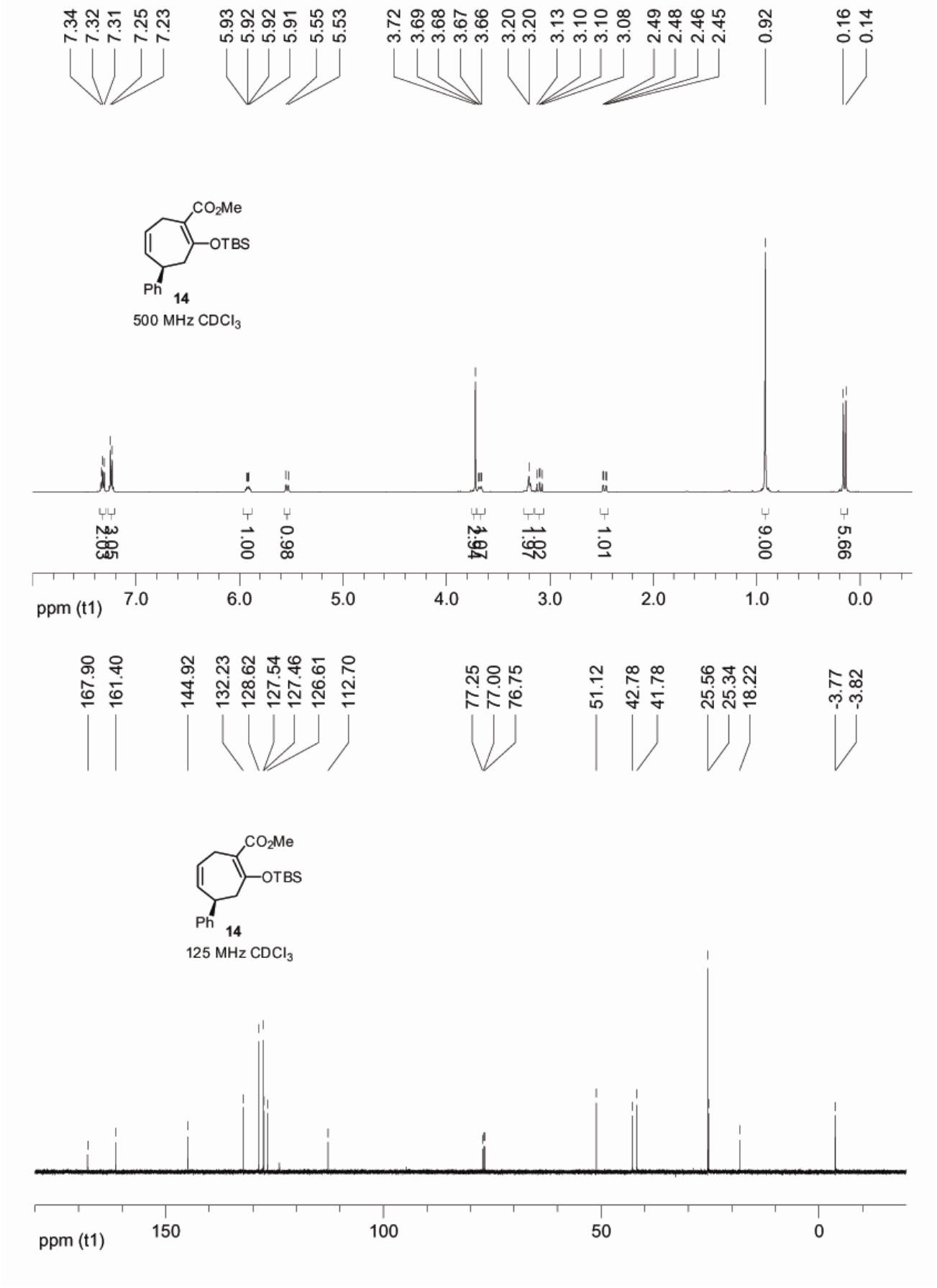
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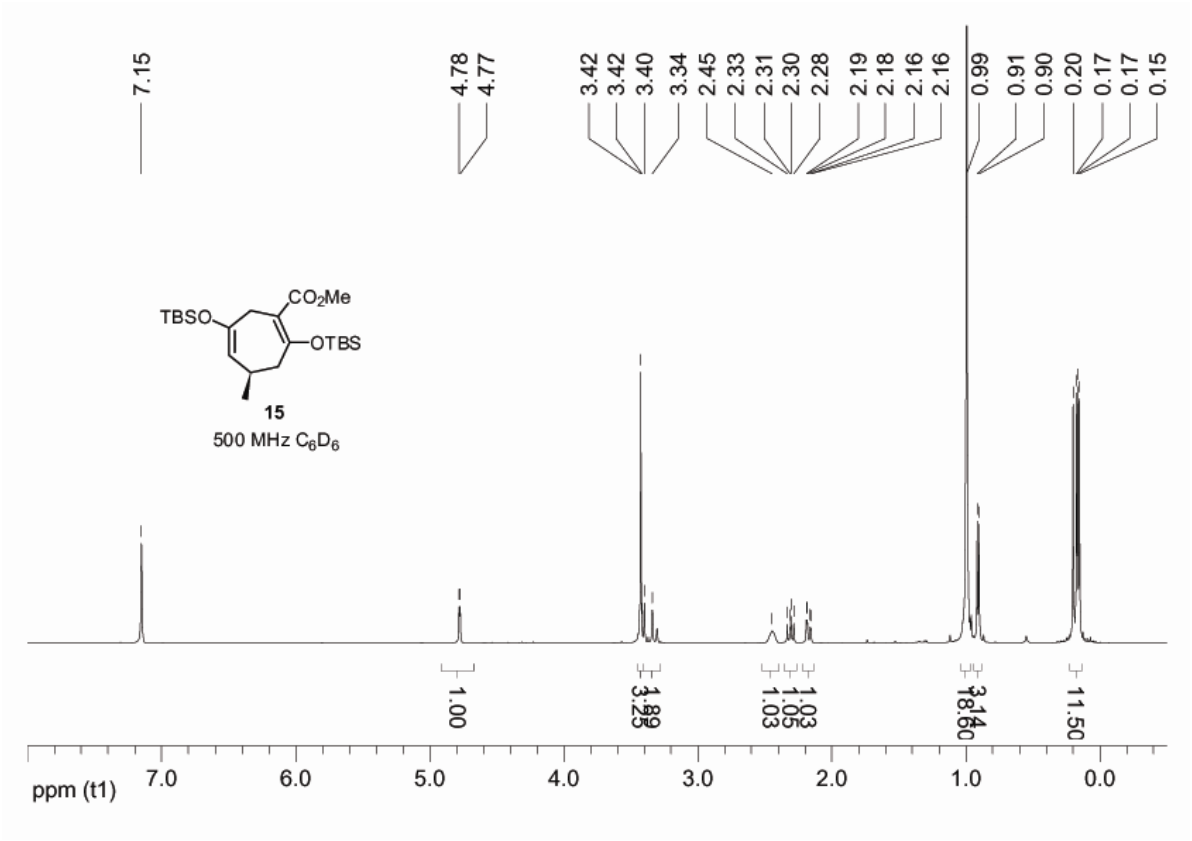
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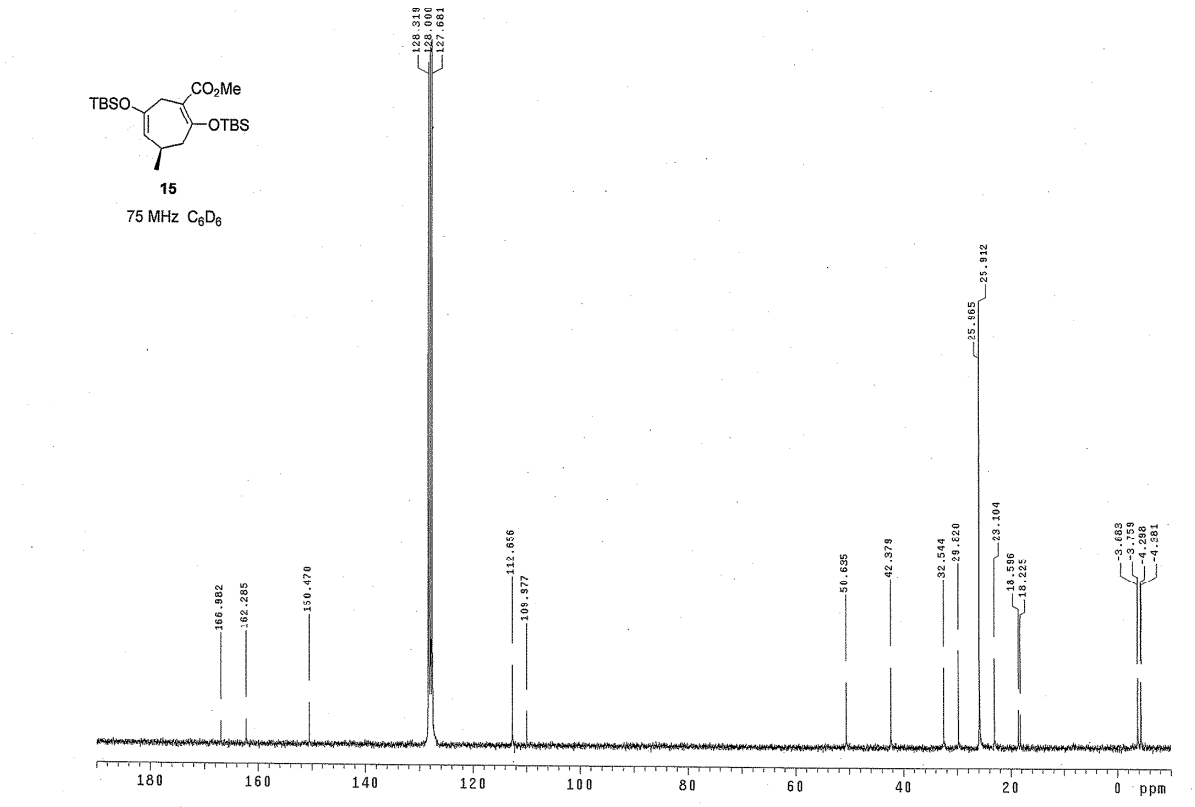
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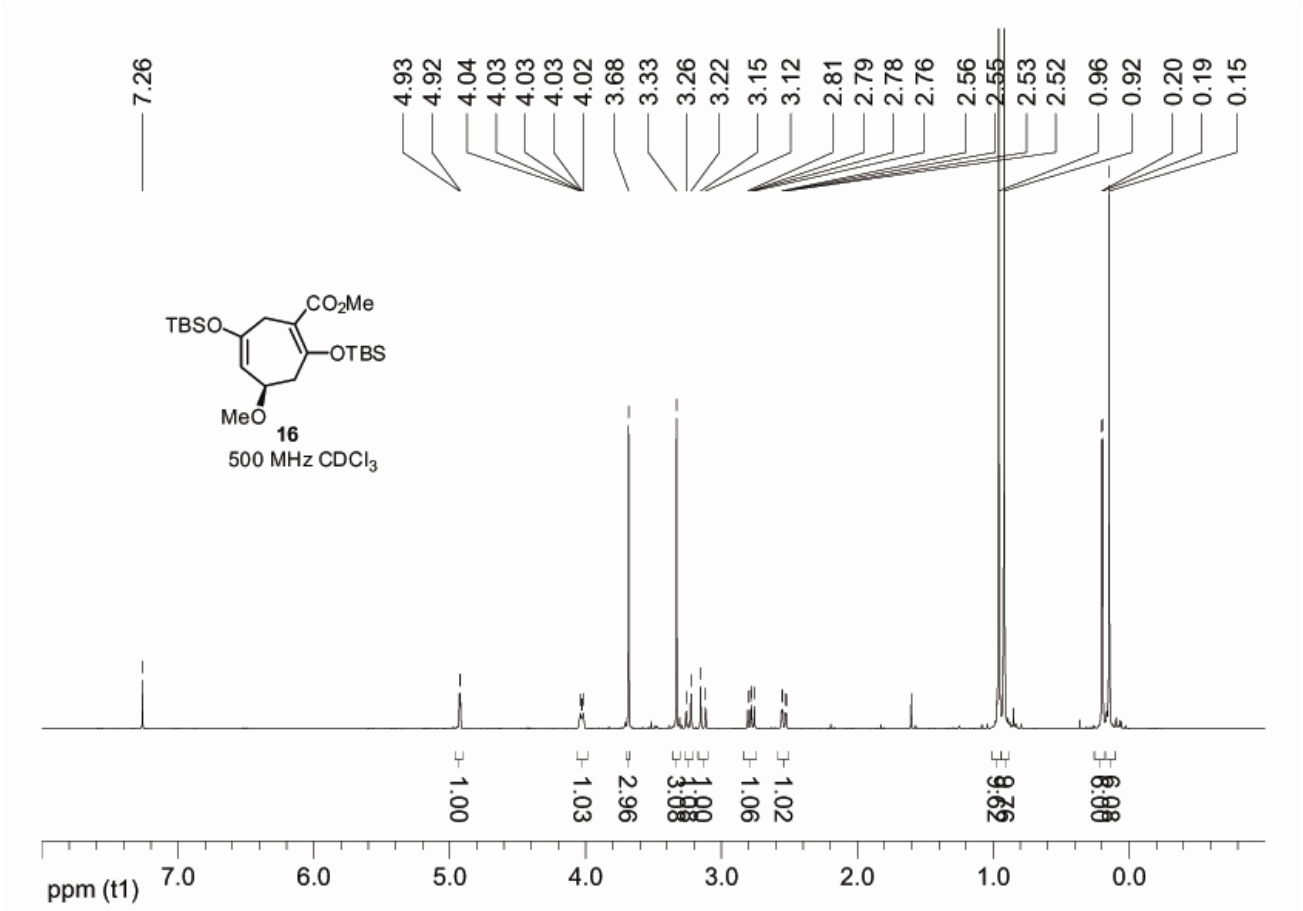
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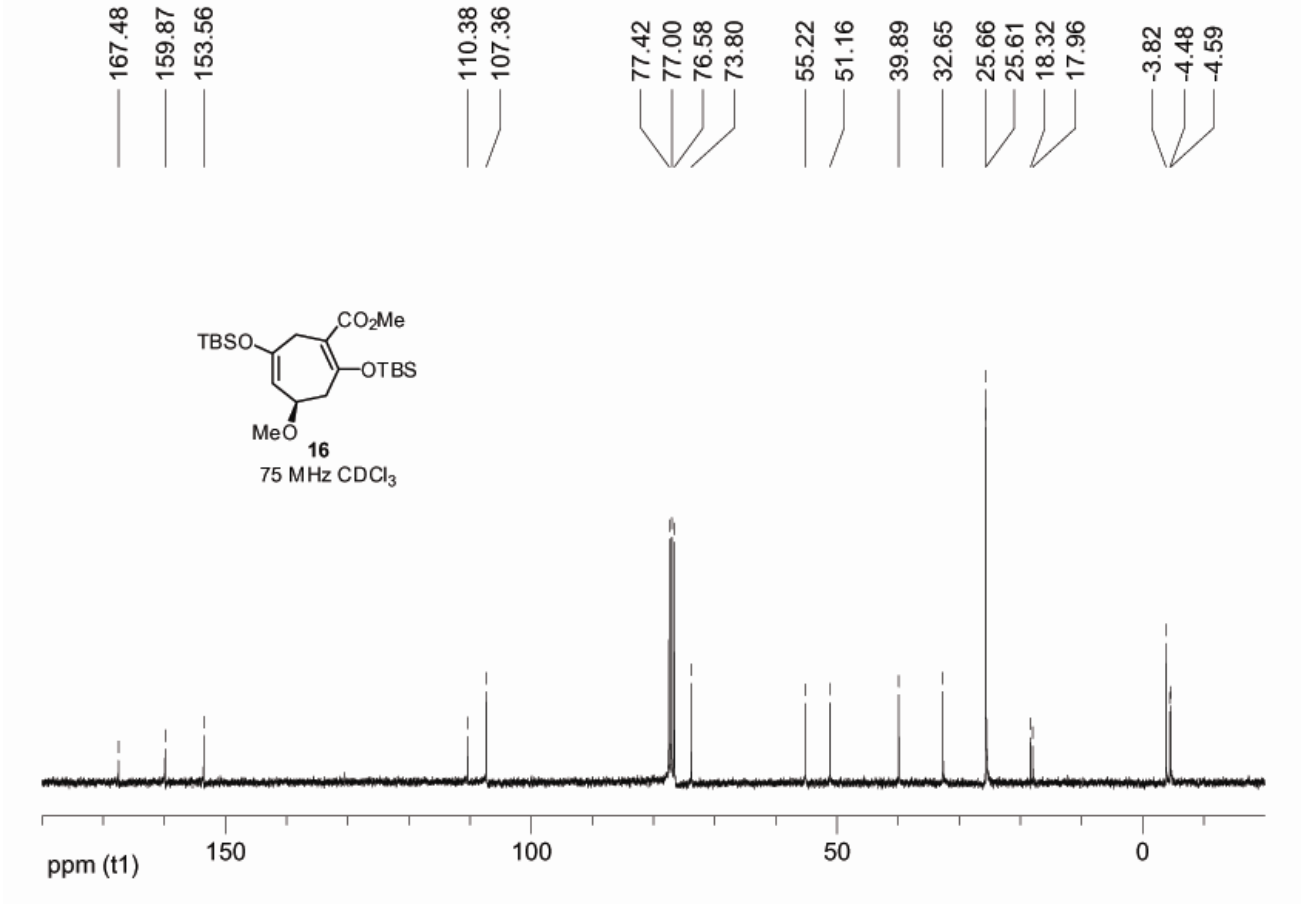
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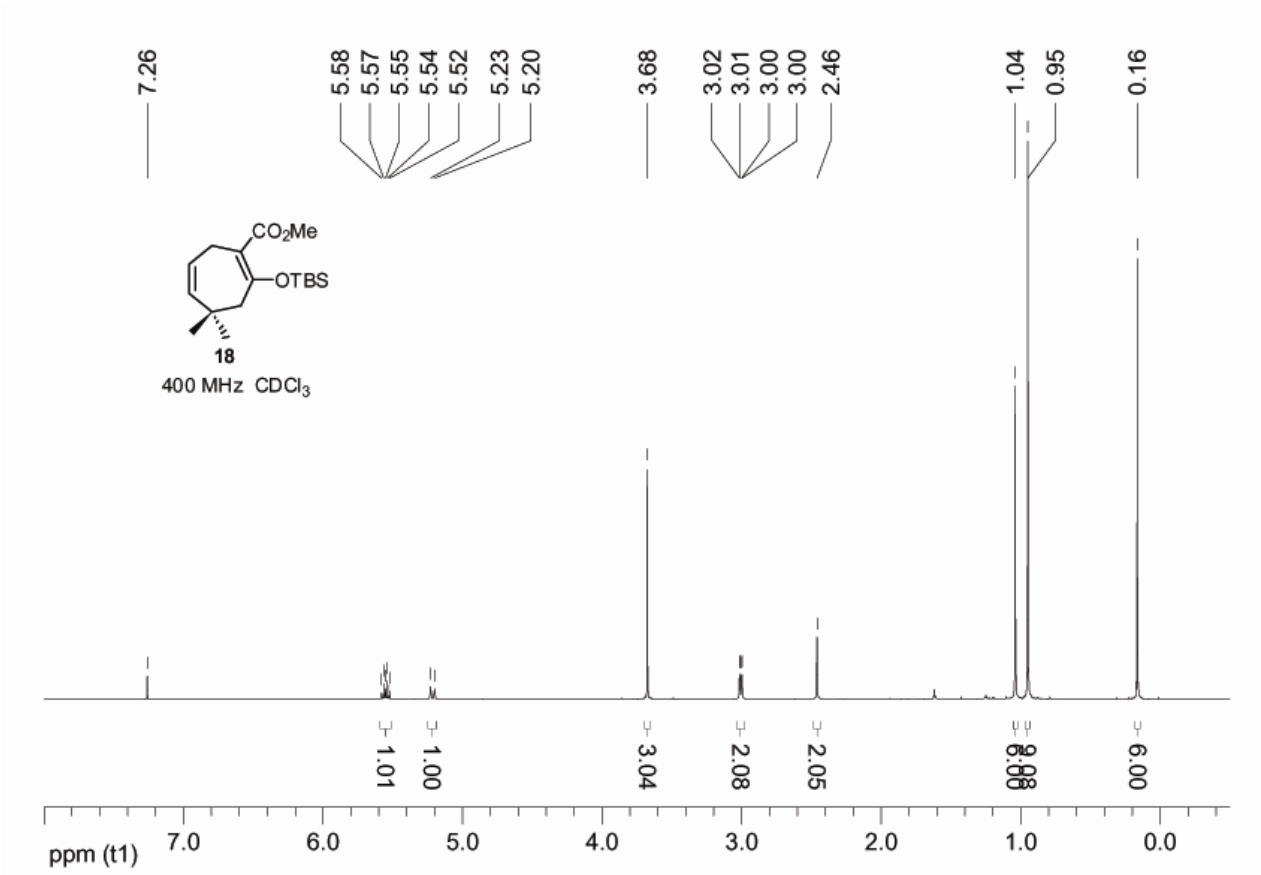
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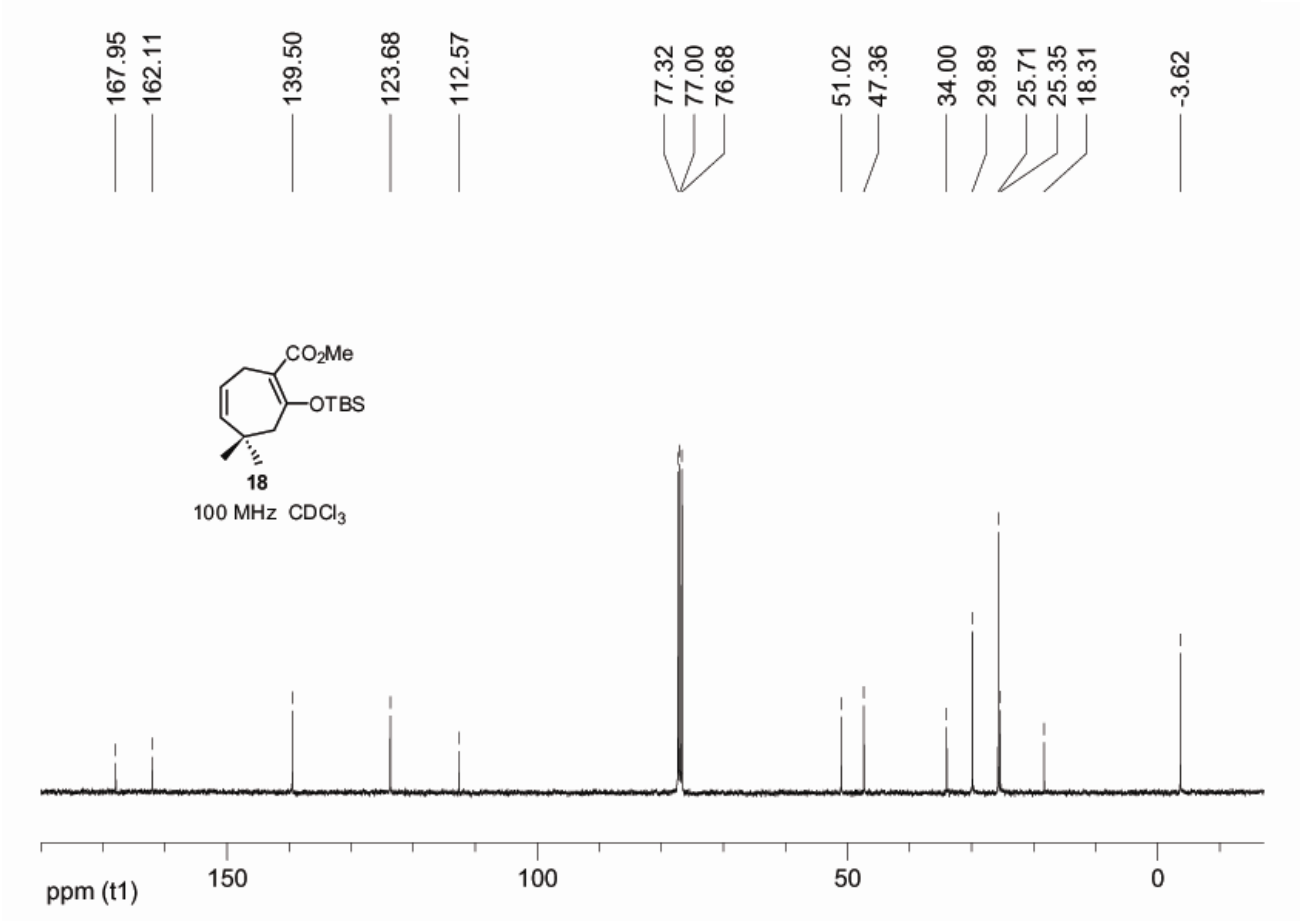
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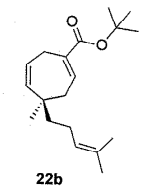
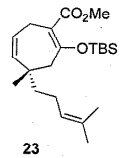


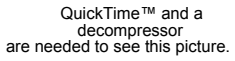
22b

500 MHz $CDCl_3$



23

500 MHz $CDCl_3$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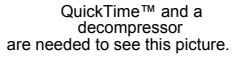
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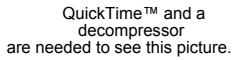
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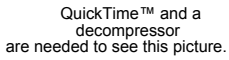
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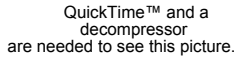
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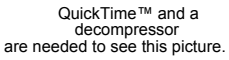
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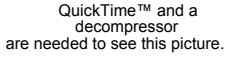
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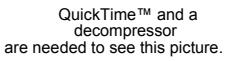
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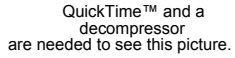
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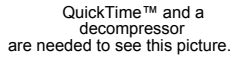
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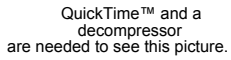
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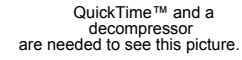
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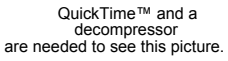
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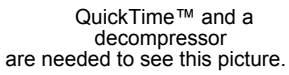
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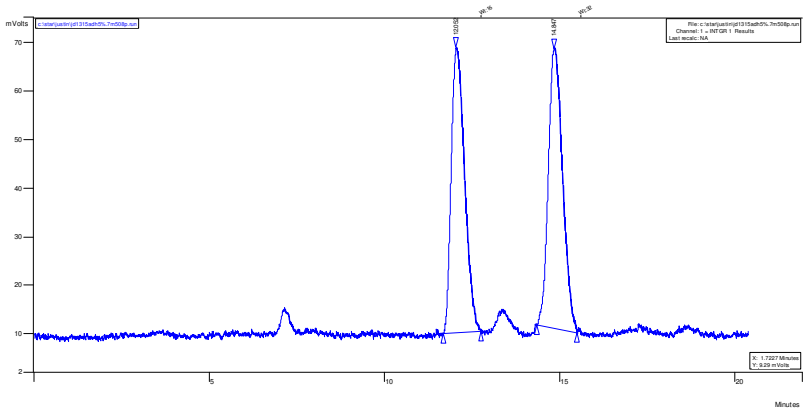
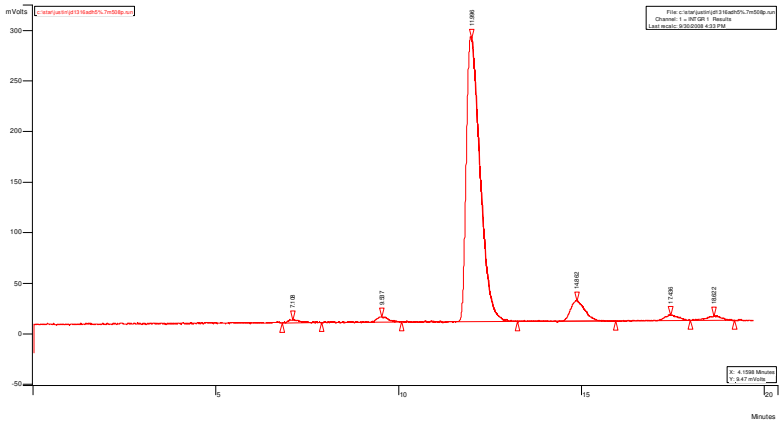
HPLC trace for racemic sample of tricycle **7.**



HPLC trace for enriched sample of tricycle **7** (88% ee)**.**



HPLC trace for the enantiomerically pure sample of tricycle **7** (>98% ee)**.**