Catalytic asymmetric synthesis of butane diacetal-protected (4S,5S)-dihydroxycyclohexen-1-one and use in natural product synthesis

David J. Burns,[a] Shuji Hachisu,[b] Peter O'Brien*[a] and Richard J. K. Taylor[a]

[a] Department of Chemistry, University of York, Heslington, York, U.K.

[b b] Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, U.K.

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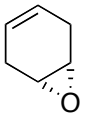
1. Experimental details

1.1 General

Except where specified, all reagents were purchased from commercial sources and were used without further purification. All procedures were carried out in an atmosphere of argon. Where necessary, solvents were dried on an MBraun SPS solvent purification system. Anhydrous tetrahydrofuran (THF) was obtained by distillation over sodium benzophenone. Petroleum ether (petrol) refers to light petroleum ether, bp 40-60 °C. Flash column chromatography was performed using Fluka silica gel 60 at a low positive pressure, unless otherwise stated. Analytical thin layer chromatography was performed on aluminium sheets pre-coated with Merck silica gel 60 F254 and visualised with ultraviolet light (254 nm), aqueous potassium permanganate or anisaldehyde solutions were appropriate. All melting points were taken on a Gallenkamp apparatus. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz on a JEOL ECX 400 spectrometer and are reported as follows: chemical shift δ (ppm) (multiplicity, coupling constant *J* (Hz), number of protons, assignment). The coupling constants are quoted to the nearest 0.5 Hz (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad) and are reported as measured splitting of each individual resonance. The residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) was used as an internal reference. ^{13}C NMR spectra were recorded at 100 MHz on a JEOL ECX 400 spectrometer. The central reference of $CDCl_3$ (δ_C = 77.0 ppm) was used as an internal reference. ^{13}C NMR spectra assignments were verified using DEPT experiments where necessary. Chemical shifts are reported in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H and the nearest 0.1 ppm for ^{13}C. Infrared spectra were carried out on a ThermoNicolet IR100 spectrometer and are recorded as a thin film or nujol© mull between NaCl disks. Absorption maxima are reported in wavenumbers (cm^{-1}) and only selected absorbances are reported. Mass spectra and accurate mass measurements were recorded on a Micromass Autospec spectrometer.

1.2 Experimental Procedures and Characterisation Data

7-Oxa-bicyclo[4.1.0]hept-3-ene 6



6

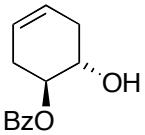
*m*CPBA (43.3 g, 0.25 mol) was added in 1 g portions over 45 min to a stirred solution of 1,4-cyclohexadiene (25 mL, 0.26 mol) and $NaHCO_3$ (33.3 g, 0.40 mol) in CH_2Cl_2 (330 mL) and water (198 mL) at 0 °C under Ar. The resulting suspension was allowed to warm to rt and stirred for 23 h. Saturated $Na_2S_2O_{3(aq)}$ (100 mL) was added and the mixture was stirred at rt for 1 h. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$ (300 mL), dried ($MgSO_4$) and evaporated under reduced pressure (> 400 mbar and < 40 °C) to give crude epoxide **6** as a colourless liquid. Purification by vacuum distillation gave epoxide **6** (16.9 g, 67%) as a colourless liquid, bp 46 °C/469 mbar (lit.,[1] 43-45 °C/14 mmHg); R_F (1:1 petrol-EtOAc) 0.57; ^{1}H NMR (400 MHz; $CDCl_3$) δ: 5.42-5.44 (m, 2H, =CH), 3.25-3.23 (m, 2H, CHO), 2.57 (br d, J = 18.0 Hz, 2H,CH_AH$_B$), 2.44 (br d, J = 18.0 Hz, 2H, CH$_A$$H_B$); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 121.5 (=CH), 60.0 (CHO), 24.9 (CH_2); MS (ESI) 135 (100). Spectroscopic data are consistent with those reported in the literature.[1]

General procedure for the Co-salen desymmetrisation of *meso*-epoxide 6

A solution of (*R*,*R*)-Co-salen (1-5 mol%) and benzoic acid (140 mg, 1.15 mmol, 1.1 eq.) in TBME (1 mL) were stirred under O_2 for 1 h. The solvent was then evaporated under reduced pressure to give the oxidised catalyst as a red slurry. To the catalyst slurry, DiPEA (199 μL, 1.15 mmol, 1.1 eq.), TBME (1 mL) and epoxide **6** (100 mg, 1.05 mmol, 1 eq.) were added. The resulting solution was stirred at rt under O_2 for 53-120 h. Then, Et_2O (10 mL) and 3 M HCl_{aq} (10 mL) were added. The two layers separated and the aqueous layer was extracted with Et_2O (5 × 10 mL). The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

(1*S*,6*S*)-6-Hydroxycyclohex-3-enyl benzoate (*S*,*S*)-5

(Table 1, entry 3)



(*S*,*S*)-**5**

Using the general procedure, (*R*,*R*)-Co-salen (2.1 g, 0.17 mol), benzoic acid (23.3 g, 0.19 mol), TBME (50 mL), DiPEA (33.3 mL, 0.19 mol) and epoxide **6** (16.7 g, 0.17 mol) for 94 h gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave benzoate (*S*,*S*)-**5** (32.4 g, 85%, 85:15 er by CSP-HPLC) as a brown solid. The solid was dissolved in the minimum amount of hot CH_2Cl_2 and heptane was added. The resulting off white crystals were collected by filtration. The same recrystallisation procedure was repeated to give benzoate (*S*,*S*)-**5** (12.07 g, 32%, 98.5:1.5 er by CSP-HPLC), mp 58-59 °C; $[\alpha]_D$ +138.6 (*c* 1.0 in $CHCl_3$); R_F (1:1 petrol-EtOAc) 0.46; IR (NaCl) 3455 (OH), 3033, 1715 (C=O), 1316, 1118, 1069, 1027, 975, 671 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ: 8.03-7.99 (m, 2H, Ph), 7.55-7.49 (m, 1H, Ph), 7.42-7.36 (m, 2H, Ph), 5.65-5.08 (m, 2H, =CH), 5.17-5.08 (m, 1H, CHO), 4.03 (td, *J* = 8.5, 6.0 Hz, 1H, CHO), 2.98 (br s, 1H, OH), 2.72-2.49 (m, 2H, CH), 2.26-2.12 (m, 2H, CH); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 166.5 (C=O), 133.1 (Ph CH), 130.1 (Ph C), 129.6 (Ph CH), 128.3 (Ph CH), 124.3 (=CH), 123.7 (=CH), 74.7 (CHO), 68.9 (CHO), 32.9 (CH_2), 30.1 (CH_2); MS (ESI) 241 [$(M + Na)^+$, 100], 219 [$(M + H)^+$, 17]; HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M + Na)^+$ 241.0835 found 241.0825 (4.1 ppm error); CSP-HPLC:Chiral Pak AS column (95:5 *iso*-Hexane-EtOAc, 0.5 mL min^{-1}) (*S*,*S*)-**5** 3.1 min, (*R*,*R*)-**5** 5.3 min.

(Table 1, entry 1)

Using the general procedure, (*R*,*R*)-Co-salen (31 mg, 0.05 mmol, 5 mol%), benzoic acid (140 mg, 1.15 mmol), TBME (1 mL), DiPEA (199 µL, 1.15 mmol) and epoxide **6** (100 mg, 1.05 mmol) for 53 h gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave benzoate (*S*,*S*)-**5** (167 mg, 74%, 83:17 er by CSP-HPLC) as a brown solid.

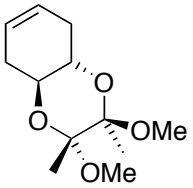
(Table 1, entry 2)

Using the general procedure, (*R*,*R*)-Co-salen (880 mg, 1.46 mmol, 2.5 mol%), benzoic acid (7.83 g, 64.13 mmol), TBME (10 mL), DiPEA (11.1 mL, 64.13 mmol), and epoxide **6** (5.60 g, 58.30 mmol) for 90 h gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave benzoate (*S*,*S*)-**5** (9.99 g, 79%, 85:15 er) as a brown solid.

(Table 1, entry 4)

Using general the procedure, CoSalen (*R*,*R*) catalyst (6 mg, 0.01 mmol, 1 mol%), benzoic acid (140 mg, 1.15 mmol), TBME (1 mL), DiPEA (199 μL, 1.15 mmol) and epoxide **6** (100 mg, 1.05 mmol) for 120 h gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave benzoate (*S*,*S*)-**5** (158 mg, 70%, 79:21 er by CSP-HPLC) as a brown solid.

(2*R*,3*R*,4a*S*,8a*S*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[b][1,4]dioxine 7



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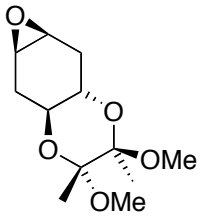
Amberlyst A26 (OH form) resin (10 g) was added to a stirred solution of benzoate (*S*,*S*)-**5** (5.0 g, 22.91 mmol) in MeOH (57 mL) and THF (28 mL) at rt. The reaction mixture was stirred at rt for 5 h. The polymer was removed by filtration and then washed with CH_2Cl_2 (5 × 100 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude diol as a white solid. 2,3-Butanedione (2.20 mL, 25.20 mmol), trimethyl orthoformate (7.57 mL, 68.73 mmol) and $BF_3.OEt_2$ (369 μL, 2.29 mmol) were added to a stirred solution of the crude diol in MeOH (50 mL) at rt under Ar. The reaction mixture was stirred at rt for 16 h. The mixture was evaporated to ~25 mL under reduced pressure. Then, CH_2Cl_2 (100 mL) and $NaHCO_{3(aq)}$ (500 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol-EtOAc (3:2) as eluent gave BDA-protected diol **7** (4.96 g, 95%) as a white solid, mp 78-79 °C; $[\alpha]_D$ –139.9 (*c* 1.0 in $CHCl_3$); R_F (1:1 petrol-EtOAc) 0.71; IR (NaCl) 2931,

1446, 1139, 1079, 977, 899 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.57-5.54 (m, 2H, =CH), 3.82-3.77 (m, 2H, CHO), 3.28 (s, 6H, OMe), 2.37-3.25 (m, 2H, CH), 2.23-2.10 (m, 2H, CH), 1.58 (s, 6H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 124.5 (=CH), 99.2 (OCO), 68.4 (CHO), 47.9 (OMe), 30.5 (CH_2), 17.9 (Me); MS (ESI) 251 [$(M + Na)^+$, 100], 101 (77); HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M + Na)^+$ 251.1254 found 251.1252 (0.7 ppm error).

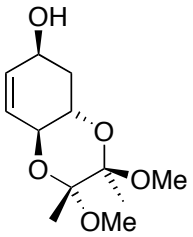
(2a*S*,4*R*,5*R*,6a*S*)-4,5-Dimethoxy-4,5-dimethyl-octahydrooxirino[2.3-g][1,4]benzodioxine 4



4

*m*CPBA (189 mg, 0.657 mmol) was added to a stirred suspension of **7** (100 mg, 0.44 mmol) and $NaHCO_3$ (74 mg, 0.88 mmol) in CH_2Cl_2 (2 mL) at 0 °C under Ar. The reaction mixture was stirred at 0 °C for 1 h and then at rt for 16 h. Saturated $Na_2S_2O_{3(aq)}$ (10 mL) was added and the biphasic mixture was stirred at 0 °C for 1 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave epoxide **4** (94.3 mg, 88%) as a white solid, mp 113 °C; $[\alpha]_D$ –170.5 (*c* 1.0 in $CHCl_3$); R_F (1:1 petrol-EtOAc) 0.43; IR (NaCl) 2991, 1441, 1124, 1037, 911, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.67 (td, *J* = 10.5, 5.5 Hz, 1H, CHO), 3.55 (td, *J* = 10.5, 7.0 Hz, 1H, CHO), 3.25 (s, 3H, OMe), 3.23 (s, 3H, OMe), 3.23-3.19 (m, 1H, CHO), 3.14-3.10 (m, 1H, CHO), 2.42 (dddd, *J* = 14.5, 5.5, 2.0, 1.0 Hz, 1H, CH), 2.25 (ddd, *J* = 15.0, 7.0, 5.5 Hz, 1H, CH), 1.96 (dd, *J* = 14.5, 10.5 Hz, 1H, CH), 1.81 (ddd, *J* = 15.0, 10.5, 2.0 Hz, 1H, CH), 1.27 (s, 6H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 99.2 (OCO), 99.0 (OCO), 67.3 (CHO), 65.3 (CHO), 53.2 (CHO), 50.6 (CHO), 47.94 (OMe), 47.90 (OMe), 29.4 (CH_2), 29.1 (CH_2), 17.77 (Me), 17.75 (Me); MS (ESI) 267 [$(M + Na)^+$, 100], 213 (74); HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_5$ $(M + Na)^+$ 267.1203 found 267.1196 (2.6 ppm error).

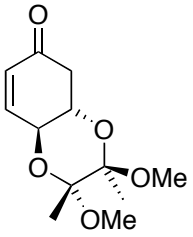
(2*R*,3*R*,4a*S*,6*S*,8a*S*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5,6,8a-hexahydrobenzo[b][1,4]dioxin-6-ol 8



8

*n*BuLi (1.98 mL of a 1.6 M solution in hexanes, 3.17 mmol) was added dropwise over 10 min to a stirred solution of DiPA (560 µL, 3.28 mmol) in THF (5 mL) at 0 °C under Ar. After stirring for 30 min at 0 °C, a solution of epoxide **4** (250 mg, 1.02 mmol) in THF (5 mL) was added dropwise by means of a cannula. After 1 h, the solution was allowed to warm to rt and stirred for 18 h. Then, saturated $NH_4Cl_{(aq)}$ (50 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave allylic alcohol **8** as a white solid (242 mg, 89%), mp 99-100 °C; $[\alpha]_D$ –213.7 (*c* 1.0 in $CHCl_3$); R_F (1:1 petrol-EtOAc) 0.23; IR (NaCl) 3610 (OH), 3016, 2931, 1375, 1237, 1200, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.77 (br s, 2H, =CH), 4.37 (br s, 1H, C*H*OH), 4.13 (d, *J* = 9.0 Hz, 1H, CHO), 3.9 (ddd, *J* = 13.0, 9.0, 3.5 Hz, 1H, CHO), 3.28 (s, 3H, OMe), 3.27 (s, 3H, OMe), 2.01 (br dd, *J* = 13.0, 3.5 Hz, 1H, CH_AH$_B$), 1.84 (td, *J* = 13.0, 5.0 Hz, 1H, CH$_A$$H_B$), 1.34 (s, 3H, Me), 1.33 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 130.2 (=CH), 129.1 (=CH), 100.4 (OCO), 100.0 (OCO), 69.7 (CHO), 65.5 (CHO), 64.9 (CHO), 47.96 (OMe), 47.90 (OMe), 34.6 (CH_2), 17.9 (Me), 17.8 (Me); MS (ESI) 267 [$(M + Na)^+$, 100], 213 (64); HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_5$ $(M + Na)^+$ 267.1203 found 267.1201 (0.9 ppm error).

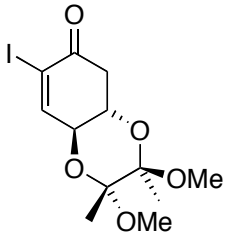
(2*R*,3*R*,4a*S*,8a*S*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5-tetrahydrobenzo[b][1,4]dioxin-6(8aH)-one (*S*,*S*)-1



(*S*,*S*)-**1**

MnO_2 (1.64 g, 18.84 mmol) was added to a stirred solution of allylic alcohol **8** (920 mg, 3.77 mmol) in CH_2Cl_2 (17 mL) at rt under Ar. The resulting suspension was stirred at rt for 12 h. Then, Et_2O (10 mL) was added and the solids were removed by filtration through a celite pad. The celite pad was washed with Et_2O (5 × 100 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an orange solid. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone (*S*,*S*)-**1** as a white solid (898 mg, 98%, 98.5:1.5 er by CSP-HPLC), mp 180-183 °C (lit.,[2] 182-184 °C); $[\alpha]_D$ – 72.0 (*c* 1.0 in $CHCl_3$)(lit.,[2] +64.4 (*c* 0.39 in $CHCl_3$) for (*R*,*R*)-**1**); R_F (1:1 petrol-EtOAc) 0.24; IR (NaCl) 1675 (C=O), 1377, 1248, 1127, 1070, 1033, 883, 848, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.87 (dd, *J* = 10.5, 1.5 Hz, 1H, =CH), 6.01 (dd, *J* = 10.5, 2.5 Hz, 1H, =CH), 4.51 (ddd, *J* = 9.0, 2.5, 1.5 Hz, 1H, CHO), 4.05 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1H, CHO), 3.33 (s, 3H, OMe), 3.27 (s, 3H, OMe), 2.74 (dd, *J* = 16.5, 5.0 Hz, 1H, CH_AH_B), 2.49 (dd, *J* 16.5, 13.5 Hz, 1H, CH_AH_B), 1.37 (s, 3H, Me), 1.34 (s, 3H, Me). ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 196.6 (C=O), 148.4 (=CH), 129.9 (=CH), 100.6 (OCO), 99.5 (OCO), 69.1 (CHO), 67.9 (CHO), 48.0 (OMe), 47.9 (OMe), 41.8 (CH_2), 17.6 (Me), 17.5 (Me); MS (ESI) 265 [$(M + Na)^+$, 100], 211 (61); HRMS (ESI) *m/z* calcd for $C_{12}H_{18}O_5$ $(M + Na)^+$ 265.1046 found 265.1051 (−0.4 ppm error). Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.46; H, 7.40. CSP-HPLC: Chiral Pak AS column (95:5 *iso*-Hexane-EtOAc, 0.5 mL min^{-1}) (*R*,*R*)-**1** 2.4 min, (*S*,*S*)-**1** 4.0 min. Spectroscopic data are consistent with those reported in the literature.[2]

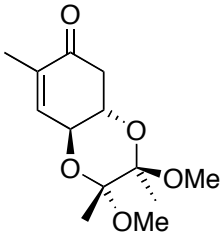
(2*R*,3*R*,4a*S*,8a*S*)-7-Iodo-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5-tetrahydrobenzo[b][1,4]dioxin-6(8aH)-one 9



9

Iodine (419 mg, 1.65 mmol) was added to a stirred solution of enone (*S*,*S*)-**1** (200 mg, 0.83 mmol) in pyridine and CCl_4 (1:1, 5 mL) at rt. The resulting mixture was stirred at rt for 2 h. Then, saturated $Na_2S_2O_{3(aq)}$ (20 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an off-white solid. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave iodo enone **9** (278 mg, 92%) as a white solid, mp 188-190 °C; $[\alpha]_D$ −55.9 (*c* 1.0 in $CHCl_3$); R_F (4:1 petrol-EtOAc) 0.70; IR (NaCl) 1654 (C=O), 1125, 881, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 2.0 Hz, 1H, =CH), 4.48 (dd, *J* = 9.0, 2.0 Hz, 1H, CHO), 4.06 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1H, CHO), 3.31 (s, 3H, OMe), 3.26 (s, 3H, OMe), 2.98 (dd, *J* = 16.5, 5.0 Hz, 1H, C*H*$_A$H$_B$), 2.62 (dd, *J* = 16.5, 13.5 Hz, 1H, CH$_A$*H*$_B$), 1.36 (s, 3H, Me), 1.33 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 189.7 (C=O), 156.6 (=CH), 103.6 (=CI), 100.8 (OCO), 99.6 (OCO), 71.0 (CHO), 67.4 (CHO), 48.14 (OMe), 48.04 (OMe), 39.7 (CH_2), 17.49 (Me), 17.42 (Me); MS (ESI) 390 [(M + Na)$^+$, 22], 369 [(M + H)$^+$, 25], 432 (100); HRMS (ESI) *m/z* calcd for $C_{12}H_{17}IO_5$ (M + H)$^+$ 369.0193, found 369.0202 (−2.4 ppm error).

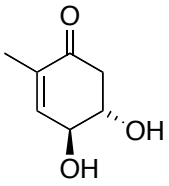
(2*R*,3*R*,4a*S*,8a*S*)-2,3-Dimethoxy-2,3,7-trimethyl-2,3,4a,5-tetrahydrobenzo[*b*][1,4]dioxin-6(8a*H*)-one 11



11

Palladium catalyst **10** (20 mg, 0.03 mmol) was added to a stirred solution of iodo enone **9** (90 mg, 0.25 mmol) and tetramethyltin (136 μL, 0.98 mmol) in THF (5 mL) at rt under Ar in a sealed tube. The reaction mixture was heated at 100 °C for 24 h. After cooling to rt, saturated $Na_2S_2O_{3(aq)}$ (10 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL) and the combined organics were extracted with 10% $KF_{(aq)}$ (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a white solid. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave α-methyl enone **11** (50 mg, 79%) as a white solid, mp 192-193 °C; $[\alpha]_D$ −30.1 (*c* 0.5 in $CHCl_3$); R_F (4:1 petrol-EtOAc) 0.38; IR (NaCl) 1648 (C=O), 1131, 1019, 880 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.61 (q, *J* = 1.5 Hz, 1H, =CH), 4.44 (d, *J* = 9.0, 2.0 Hz, 1H, CHO), 3.98 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1H, CHO), 3.30 (s, 3H, OMe), 3.24 (s, 3H, OMe), 2.74 (dd, *J* = 16.5, 5.0 Hz, 1H, CH_AH$_B$), 2.46 (dd, *J* = 16.5, 13.5 Hz, 1H, CH$_A$$H_B$), 1.77 (dd, *J* = 2.0, 1.5 Hz, 1H, =CMe), 1.35 (s, 3H, Me), 1.32 (s, 3H, Me); ^{13}C NMR (100.6 MHz; CDCl3) δ: 196.9 (C=O), 143.5 (=CH), 136.9 (=*C*Me), 100.7 (OCO), 99.8 (OCO), 69.3 (CHO), 68.3 (CHO), 48.21 (OMe), 48.14 (OMe), 41.9 (CH_2), 17.9 (Me), 17.8 (Me), 15.4 (Me); MS (ESI) 320 (25), 279 [$(M + Na)^+$, 18], 266 (100), 257 (51); HRMS (ESI) *m/z* calcd for $C_{13}H_{20}O_5$ $(M + H)^+$ 257.1384, found 257.1377 (2.4 ppm error), calcd for $C_{13}H_{20}O_5$ $(M + Na)^+$ 279.1203, found 279.1208 (−1.9 ppm error).

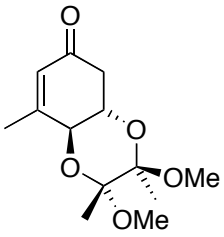
(4*S*,5*S*)-4,5-Dihydroxy-2-methylcyclohex-2-enone (*S*,*S*)-2



(*S*,*S*)-**2**

A solution of α-methyl enone **11** (15 mg, 0.06 mmol) in TFA (1 mL) and water (100 μL) was stirred at rt for 15 min. The solvent was evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with EtOAc as eluent gave diol (*S*,*S*)-**2** (7 mg, 84%) as a colourless oil, $[\alpha]_D$ +141.4 (*c* 0.7 in MeOH)(lit.,[3] +128 (*c* 0.21 in MeOH)); R_F (EtOAc) 0.15; IR (NaCl) 3327 (OH), 1642 (C=O), 1051, 883 cm^{-1}; ^1H NMR (400 MHz, d_4-methanol) δ: 6.62 (dq, *J* = 2.5, 1.5 Hz, 1H, =CH), 4.21-4.17 (m, 1H, CHO), 3.79 (ddd, *J* = 11.5, 7.5, 4.5 Hz, 1H, CHO), 2.69 (dd, *J* = 16.0, 4.5 Hz, 1H, CH_AH$_B$), 2.39 (dd, *J* = 16.0, 11.5 Hz, 1H, CH$_A$$H_B$), 1.73 (dd, *J* = 2.0, 1.5 Hz, 3H, Me); ^{13}C NMR (100.6 MHz; d_4-methanol) δ: 198.5 (C=O), 146.8 (=CH), 135.4 (=*C*Me), 72.3 (CHO), 72.1 (CHO), 44.1 (CH_2), 13.9 (Me); MS (ESI) 296 (34), 200 (63), 143 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_7H_{10}O_3$ $(M + H)^+$ 143.0703, found 143.0698 (3.6 ppm error). Spectroscopic data are consistent with those reported in the literature.[3]

(2*R*,3*R*,4a*S*,8a*S*)-2,3-Dimethoxy-2,3,8-trimethyl-2,3,4a,5-tetrahydrobenzo[*b*][1,4]dioxin-6(8a*H*)-one 12

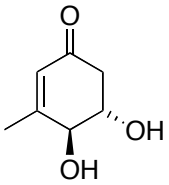


12

MeLi (620 μL of a 1.6 M solution in hexanes, 0.99 mmol) was added dropwise over 15 min to a vigorously stirred suspension of CuCN (44 mg, 0.50 mmol) in THF (2 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, a premixed solution of enone (*S*,*S*)-**1** (100 mg, 0.41 mmol) and Me_3SiCl (63 μL, 0.50 mmol) in THF (5 mL) was added dropwise over 30 min to give a yellow solution. After stirring for 30 min, a mixture of saturated $NaHCO_{3(aq)}$ and Et_3N (30:1, 10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The

combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether. $Pd(OAc)_2$ (9 mg, 0.08 mmol) was added to a stirred solution of the crude silyl enol ether in DMSO (2 mL) and the resulting mixture was stirred at rt under O_2 for 20 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and CH_2Cl_2 (10 ml) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give crude product as a colourless oil. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave β-substituted enone **12** (97 mg, 92%) as a white solid, mp 130-132 °C; $[\alpha]_D$ −121.1 (*c* 1.0 in $CHCl_3$); R_F (4:1 petrol-EtOAc) 0.22; IR (NaCl) 2946, 2846, 2809, 1642 (C=O), 1359, 1108, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.86-5.83 (m, 1H, =CH), 4.39 (ddq, *J* = 9.0, 2.5, 1.0 Hz, 1H, CHO), 4.05 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1H, CHO), 3.31 (s, 3H, OMe), 3.26 (s, 3H, OMe), 2.70 (ddd, *J* = 16.0, 5.0, 1.0 Hz, 1H, CH_AH$_B$), 2.48 (dd, *J* = 16.0, 13.5 Hz, 1H, CH$_A$$H_B$), 2.05 (t, *J* = 1.0 Hz, 3H, Me), 1.37 (s, 3H, Me), 1.33 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 196.0 (C=O), 160.4 (=*C*Me), 127.5 (=CH), 100.7 (OCO), 99.7 (OCO), 71.0 (CHO), 67.8 (CHO), 48.19 (OMe), 48.16 (OMe), 42.2 (CH_2), 18.1 (Me), 17.8 (2 × Me); MS (ESI) 279 [$(M + Na)^+$, 75], 257 [$(M + H)^+$, 100], 225 (71), 193 (55); HRMS (ESI) *m/z* calcd for $C_{13}H_{20}O_5$ $(M + H)^+$ 257.1384, found 257.1383 (0.3 ppm error).

(4*S*,5*S*)-4,5-Dihydroxy-3-methylcyclohex-2-enone (*S*,*S*)-3

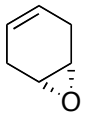


(*S*,*S*)-**3**

A solution of β-methyl enone **12** in TFA (2 mL) and water (200 μL) was stirred at rt for 15 min. The solvent was evaporated under reduced pressure to give the crude product as an orange oil. Purification by flash column chromatography on silica with EtOAc as eluent gave diol (*S*,*S*)-**3** (36 mg, 74%) as a colourless oil, $[\alpha]_D$ +107.0 (*c* 1.0 in MeOH))(lit.,[4] +11.3 (*c* 0.01 in MeOH) for a ~60:40 mixture of (*S*,*S*)-**3** and (*R*,*R*)-**3** isolated from *Lasiodiplodia theobromae*); R_F (EtOAc) 0.19; IR (NaCl) 3324 (OH), 1631 (C=O), 1266, 1053 cm^{-1}; ^1H NMR (400 MHz, d_4-methanol) δ: 5.86-5.83 (m, 1H, =CH), 4.09 (d, *J* = 7.0 Hz, 1H, CHO), 3.90 (ddd, *J* = 10.0, 7.0, 4.5 Hz, 1H, CHO), 2.68 (dd, *J* = 16.5, 4.5 Hz, 1H, CH_AH$_B$), 2.40 (dd, *J* = 16.5, 10.0 Hz, 1H, CH$_A$$H_B$), 2.05 (s,

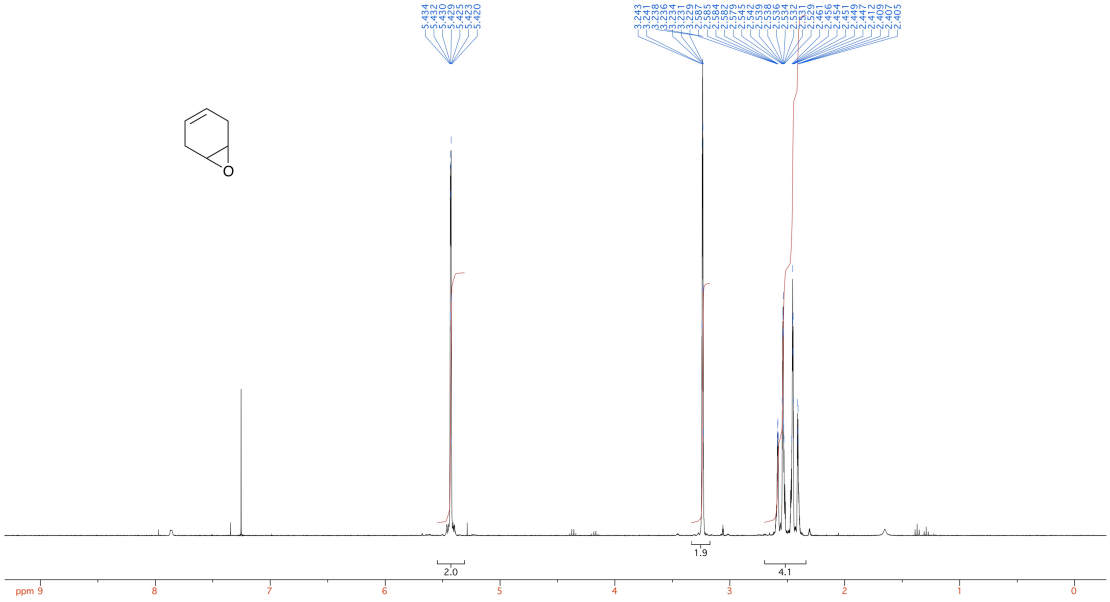
3H, Me). ^{13}C NMR (100.6 MHz; d_4-methanol) δ: 198.4 (C=O), 163.5 (=*C*Me), 126.0 (=CH), 73.5 (CHO), 71.4 (CHO), 43.3 (CH_2), 19.5 (Me); MS (ESI) 279 [$(M + Na)^+$, 75], 257 [$(M + H)^+$, 100], 225 (71), 193 (55); HRMS (ESI) *m/z* calcd for $C_7H_{10}O_3$ $(M + H)^+$ 143.0703, found 143.0703 (−0.3 ppm error), calcd for $C_7H_{10}O_3$ $(M + Na)^+$ 165.0521, found 165.0522 (0.7 ppm error). Spectroscopic data are consistent with those reported in the literature.[4]

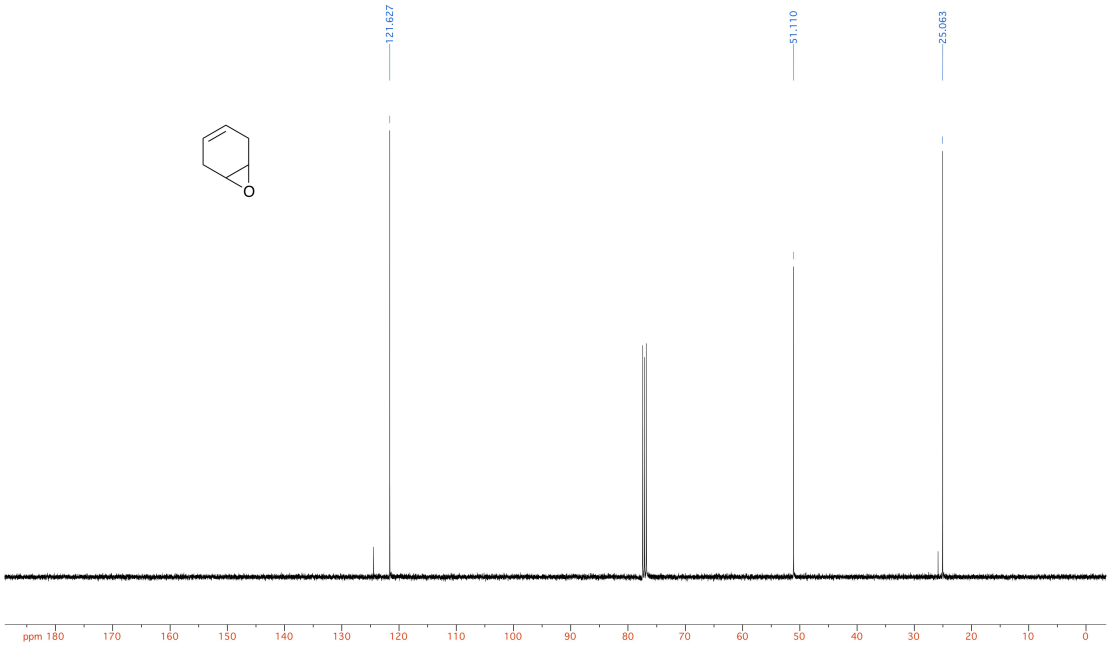
2. $^{1}H/^{13}C$ NMR spectra and CSP-HPLC data



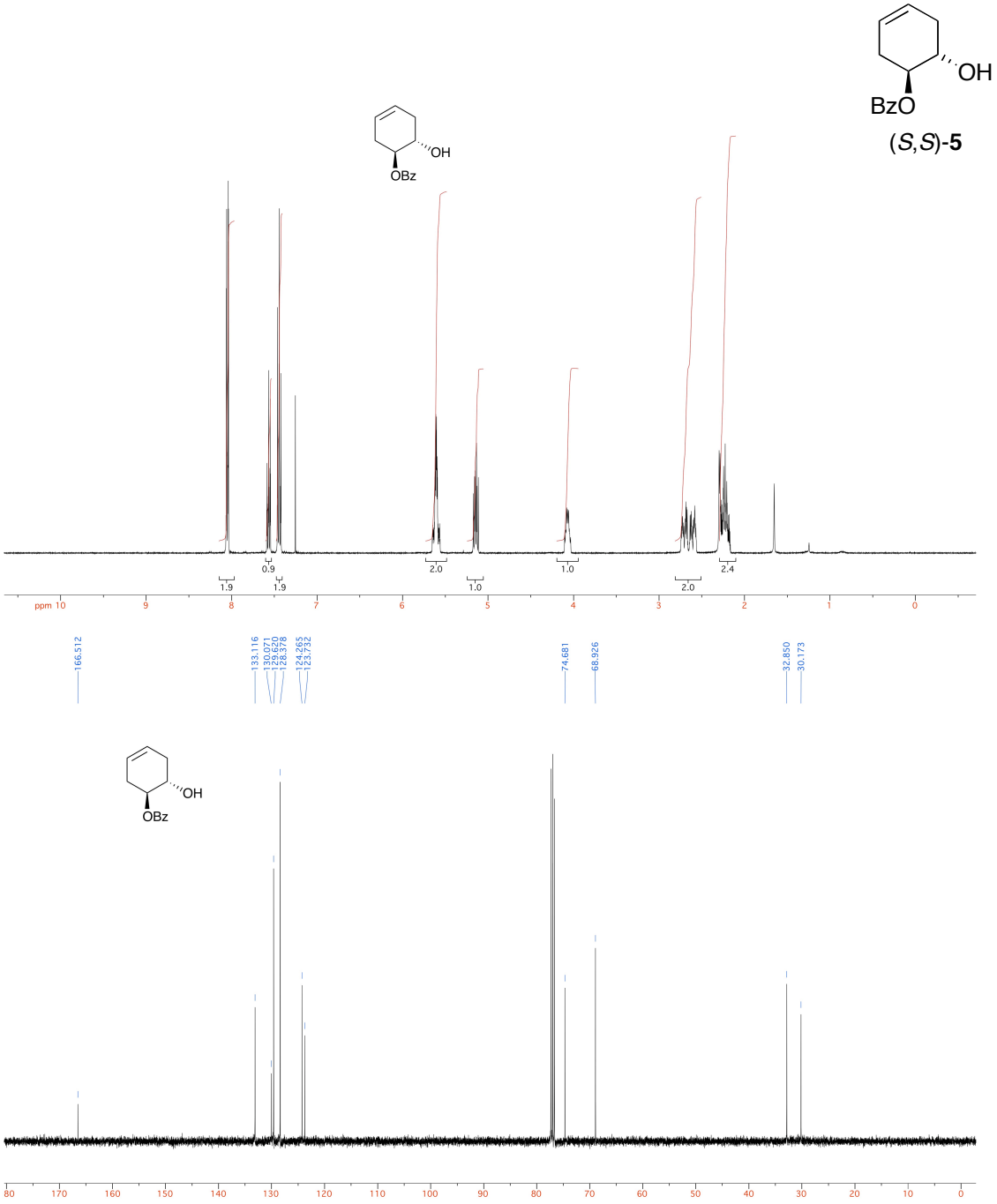
6

400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$

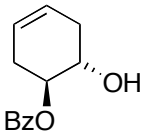




400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



CSP-HPLC for benzoate (*S*,*S*)-**5** of 85:15 er



(*S*,*S*)-**5**

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    Last changed    : 11/5/2010 5:02:11 PM by Graeme
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                      5 mL/min, 17 bar
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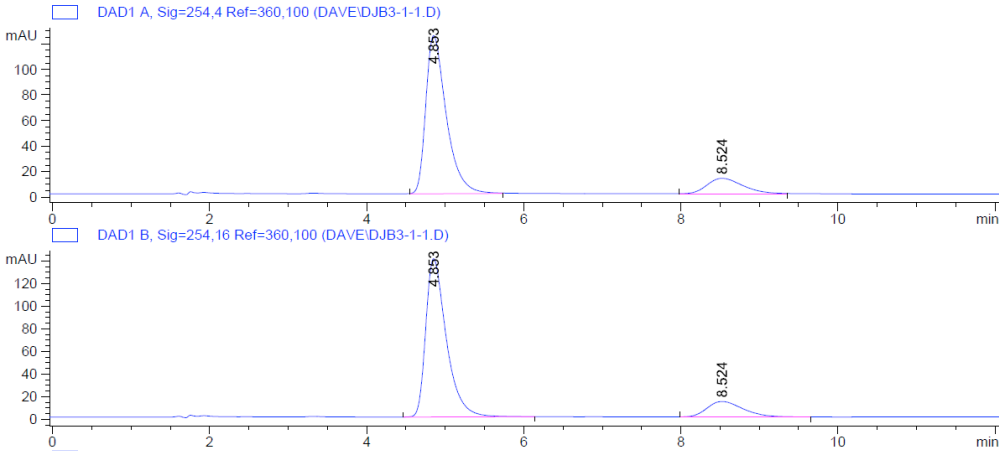


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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
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Totals :                  2629.80969  135.78081


Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
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Totals :                  2997.36462  153.77150
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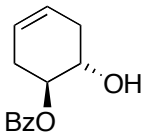
CSP-HPLC for benzoate (*S*,*S*)-**5** of 98.5:1.5 er



(*S*,*S*)-**5**

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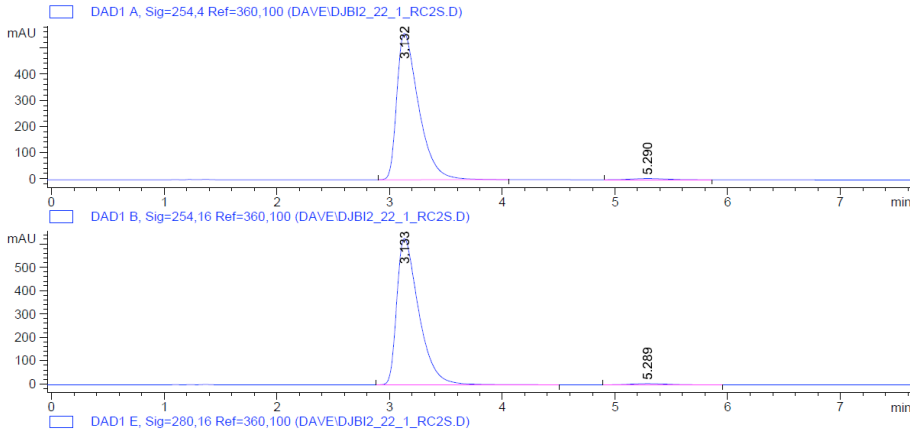


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    Use Multiplier & Dilution Factor with ISTDs


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    Totals :                   7623.56428  563.99025

Instrument 1 2/1/2012 5:16:21 PM Peter                          Page   1 of 2


Data File C:\CHEM32\1\DATA\DAVE\DJBI2_22_1_RC2S.D
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   Totals :                   8623.79642  633.20992
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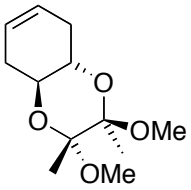
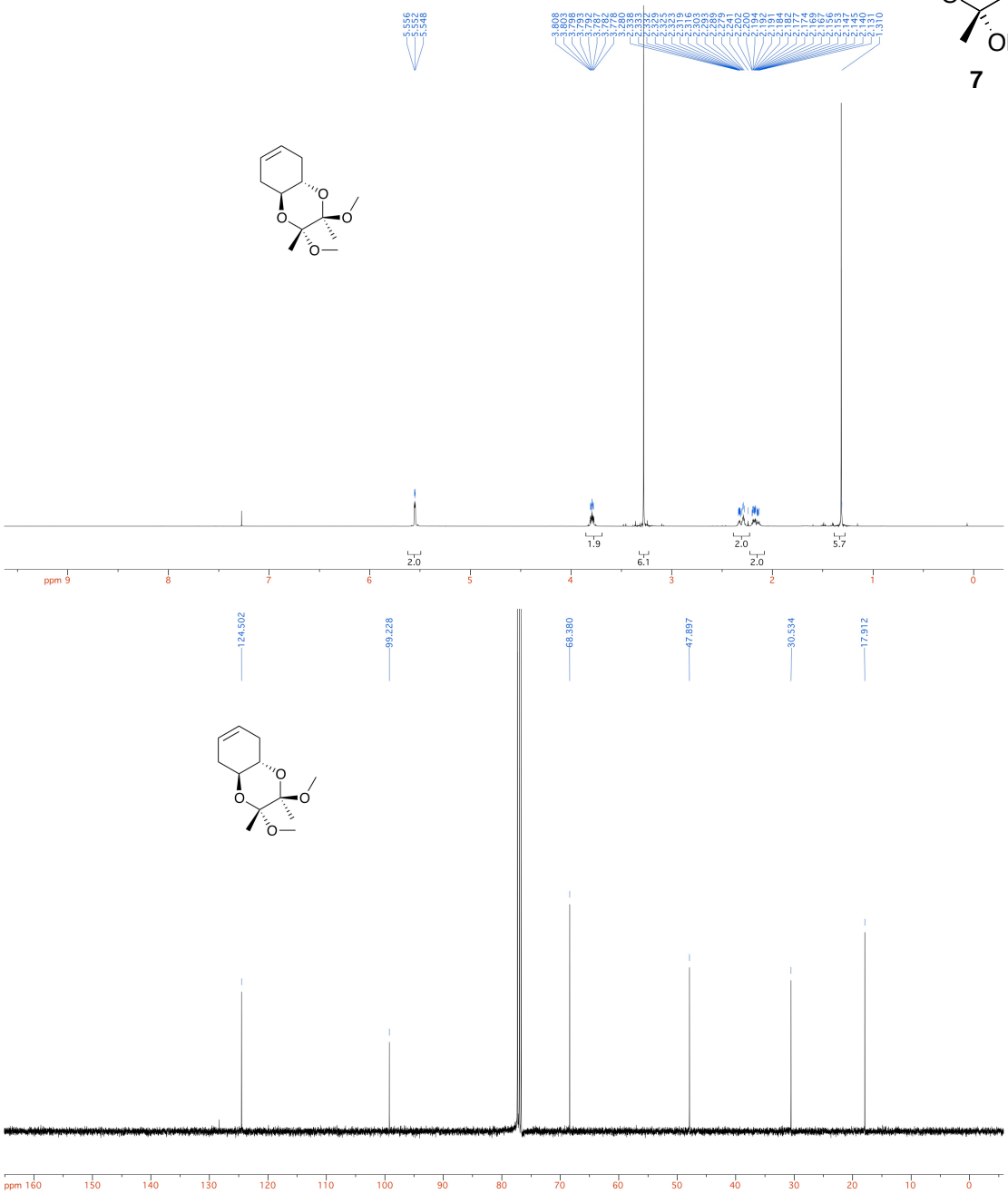
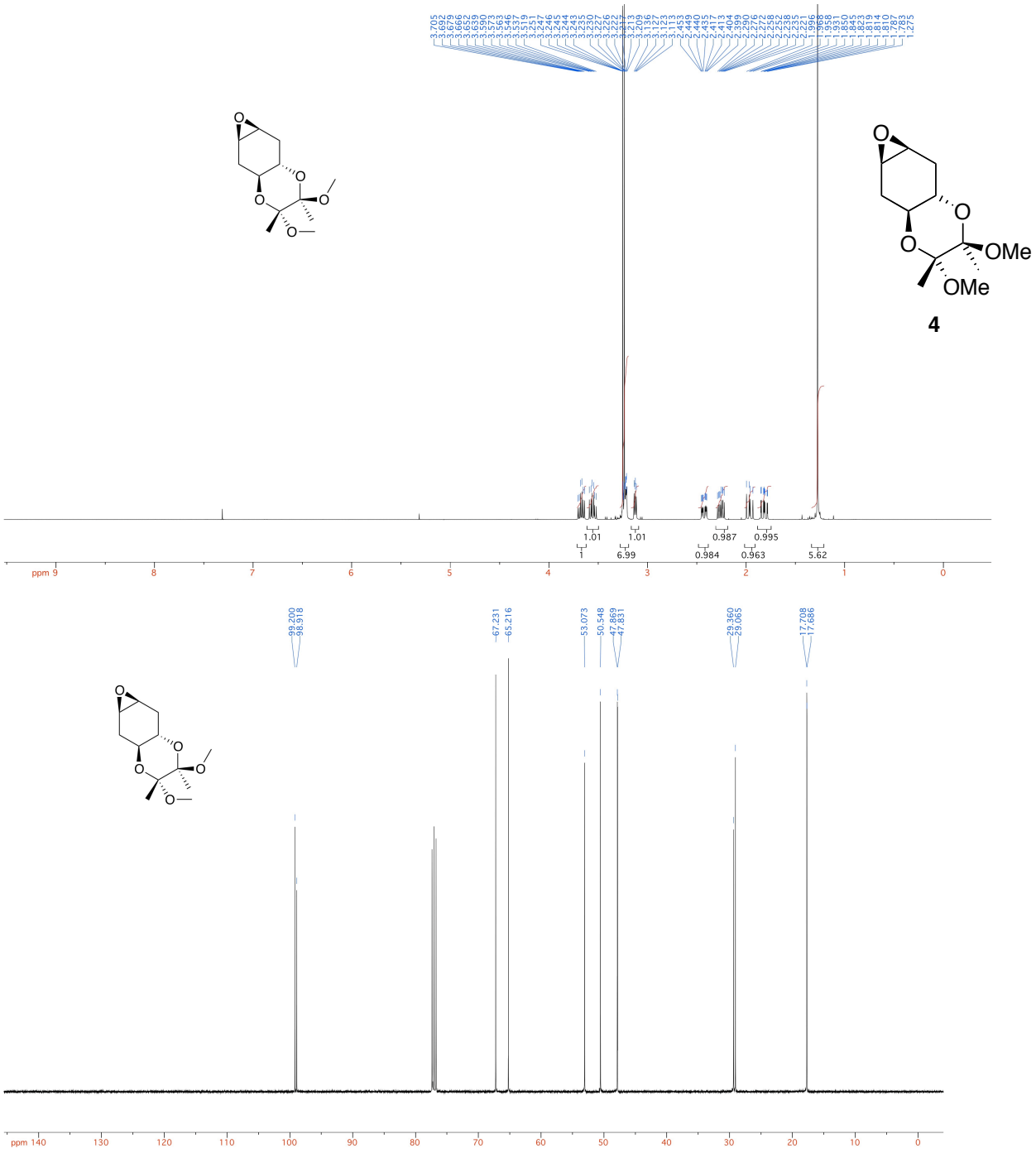
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



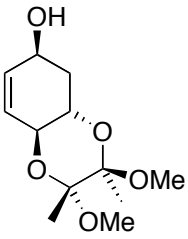
7



400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



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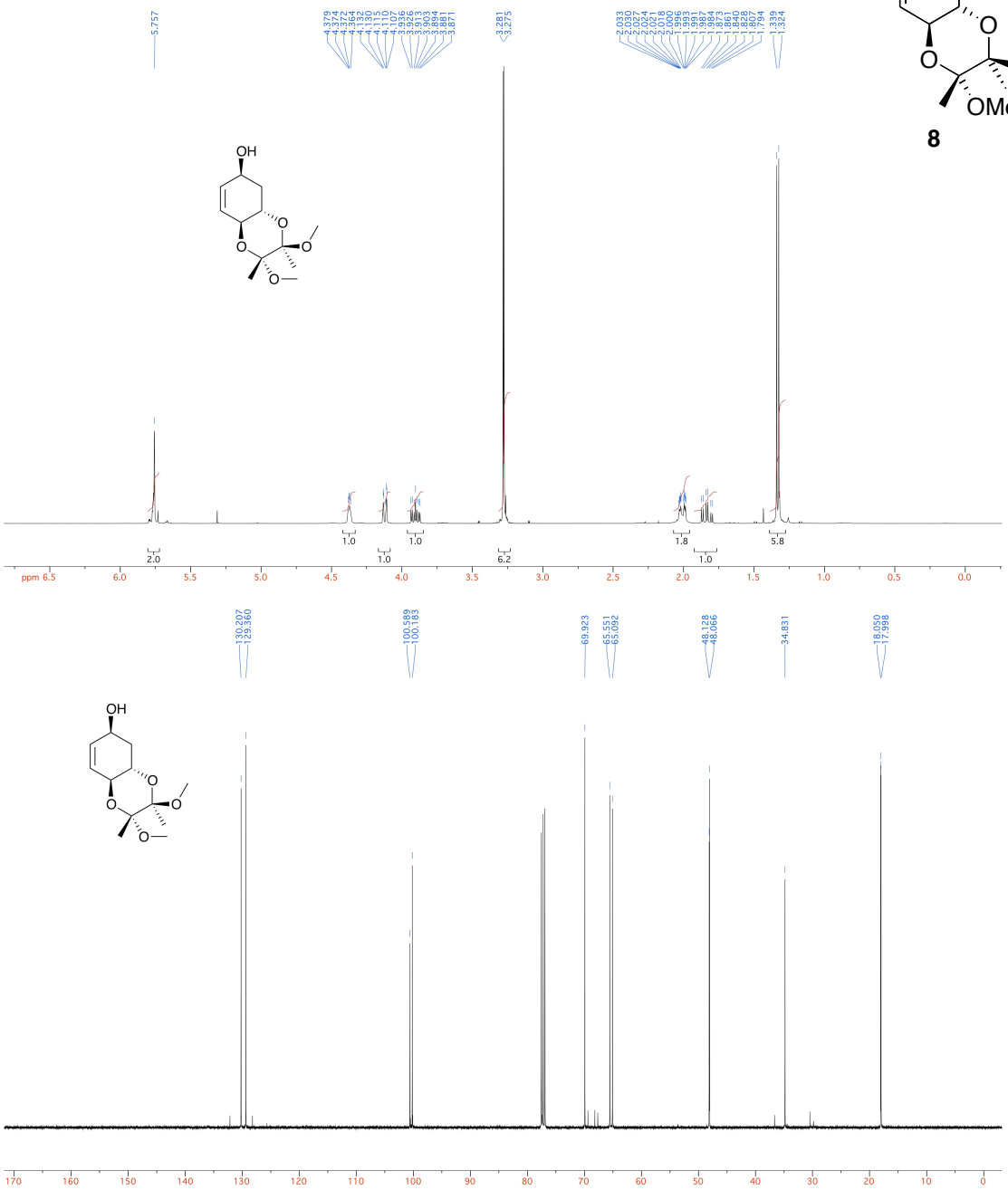
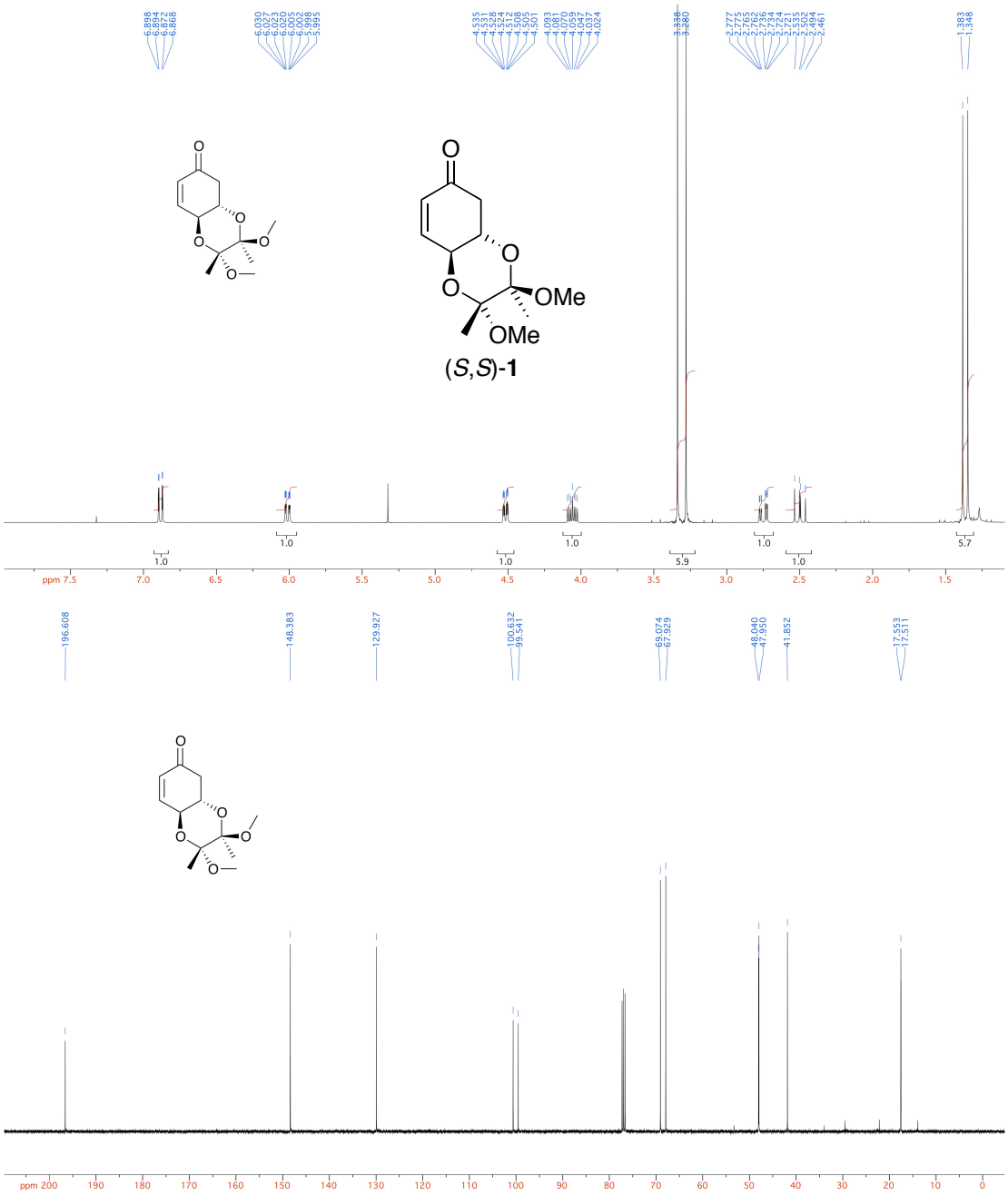
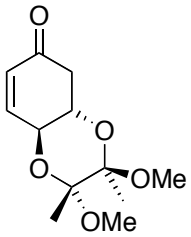


400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



CSP-HPLC for *racemic* enone **1**



rac-**1**

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                      (modified after loading)
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                      mn 19.9 oC
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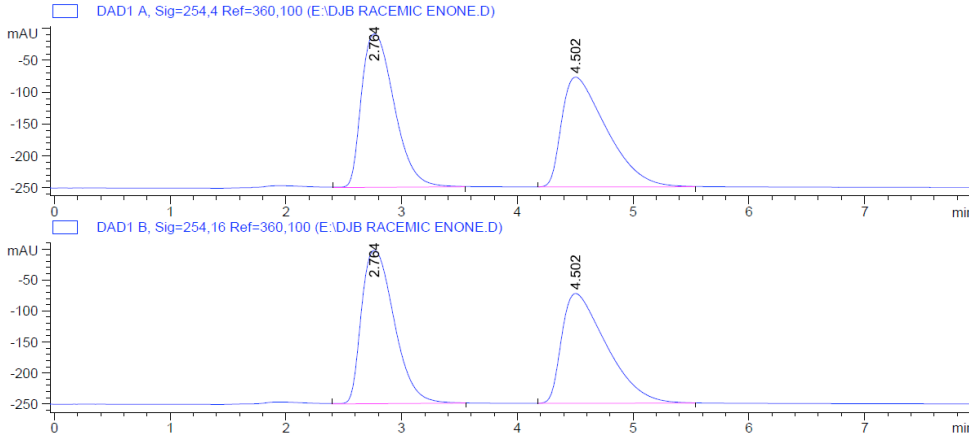


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   Use Multiplier & Dilution Factor with ISTDs


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      2   4.502 BB    0.4016 4626.95264  172.12154  49.5234

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   Signal 2: DAD1 B, Sig=254,16 Ref=360,100

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CSP-HPLC for enone (*S*,*S*)-**1** of 98.5:1.5 er

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                     (modified after loading)
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   Last changed    : 3/7/2012 11:45:02 AM by Peter
                     (modified after loading)
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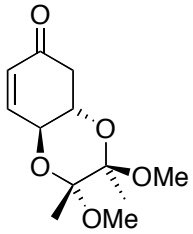
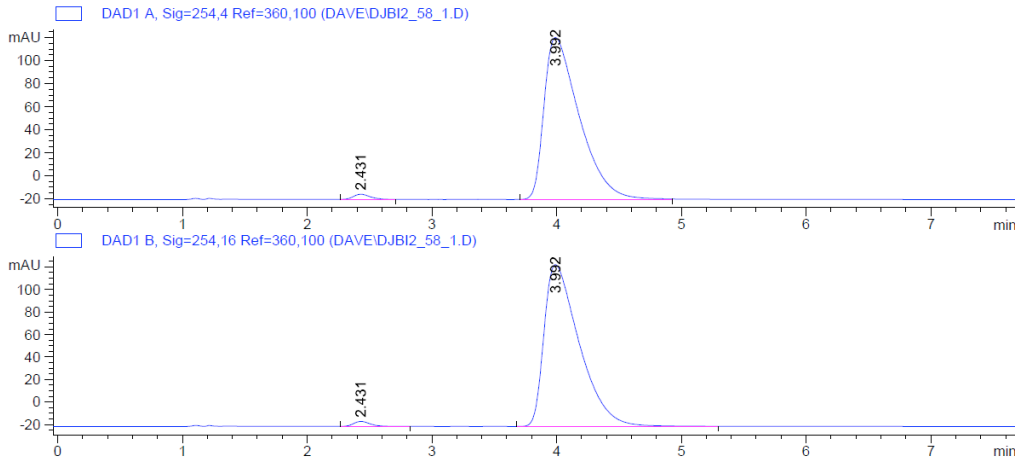


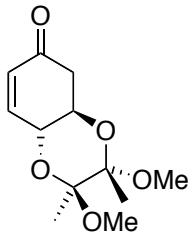
(*S*,*S*)-**1**



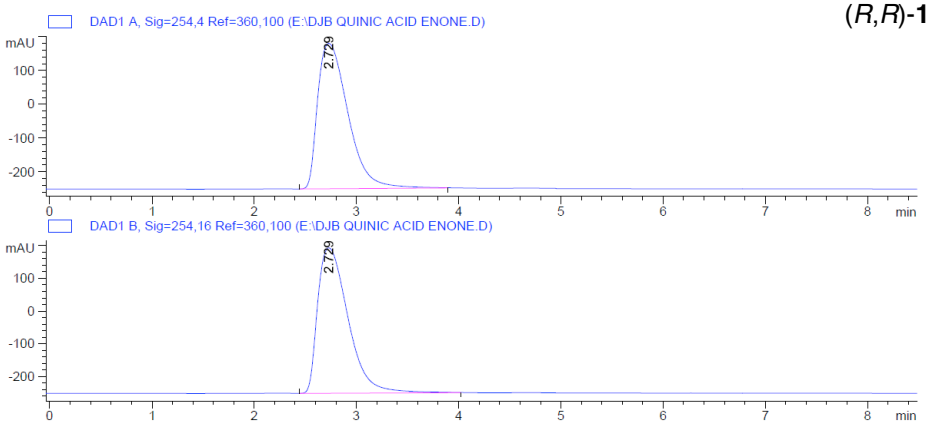

```
Data File C:\CHEM32\1\DATA\DAVE\DJBI2_58_1.D
Sample Name: DJBI2_58_1

   ========================================================================
                          Area Percent Report
   ========================================================================

   Sorted By             :      Signal
   Multiplier            :      1.0000
   Dilution              :      1.0000
   Use Multiplier & Dilution Factor with ISTDs


   Signal 1: DAD1 A, Sig=254,4 Ref=360,100

   Peak RetTime Type  Width     Area      Height     Area
     #   [min]        [min]   [mAU*s]     [mAU]       %
   ----|-------|----|-------|----------|----------|--------|
      1   2.431 BB    0.1458   42.45135    4.50884   1.5193
      2   3.992 BB    0.2963 2751.77686  140.60080  98.4807

   Totals :                   2794.22821  145.10964


   Signal 2: DAD1 B, Sig=254,16 Ref=360,100

   Peak RetTime Type  Width     Area      Height     Area
     #   [min]        [min]   [mAU*s]     [mAU]       %
   ----|-------|----|-------|----------|----------|--------|
      1   2.431 BB    0.1440   44.42133    4.62787   1.5490
      2   3.992 BB    0.2970 2823.24023  143.85551  98.4510

   Totals :                   2867.66156  148.48338
```

CSP-HPLC for enone (*R*,*R*)-**1** of >99:1 er (prepared from (–)-quinic acid[2])

```
Data File E:\DJB QUINIC ACID ENONE.D
Sample Name: DJBQuinicacidEnone

    ======================================================================
    Acq. Operator   : DJB
    Acq. Instrument : Instrument 1                    Location : Vial 1
    Injection Date  : 8/19/2011 2:02:19 PM
    Acq. Method     : C:\CHEM32\1\METHODS\SOS-METHOD A.M
    Last changed    : 8/19/2011 1:31:19 PM by DJB
                      (modified after loading)
    Analysis Method : C:\Chem32\1\METHODS\DEF_LC.M
    Sample Info     : DJBQuinicacidEnone; 95:5 HEX:IPA ; 0.5 ml/min; 36 bar;
                      AS column 19.9 oC
```

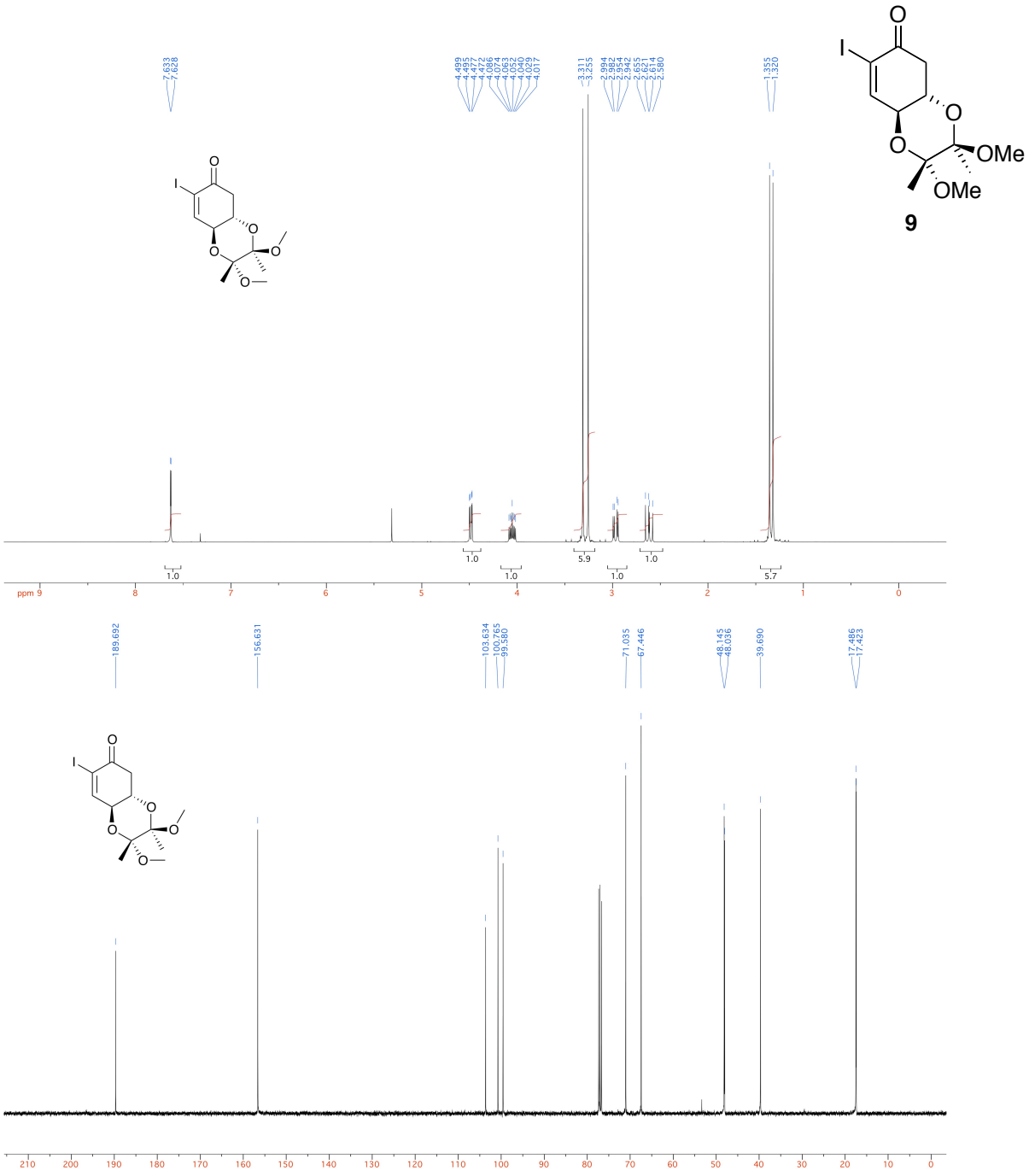


(*R*,*R*)-**1**




```
Data File E:\DJB QUINIC ACID ENONE.D
Sample Name: DJBQuinicacidEnone

   ======================================================================
                            Area Percent Report
   ======================================================================

   Sorted By             :      Signal
   Multiplier            :      1.0000
   Dilution              :      1.0000
   Use Multiplier & Dilution Factor with ISTDs


   Signal 1: DAD1 A, Sig=254,4 Ref=360,100

   Peak RetTime Type  Width     Area      Height     Area
     #   [min]        [min]   [mAU*s]     [mAU]       %
   ----|-------|----|-------|----------|----------|--------|
      1   2.729 BB    0.3259 8865.80371  431.08432 100.0000

   Totals :                   8865.80371  431.08432



   Signal 2: DAD1 B, Sig=254,16 Ref=360,100

   Peak RetTime Type  Width     Area      Height     Area
     #   [min]        [min]   [mAU*s]     [mAU]       %
   ----|-------|----|-------|----------|----------|--------|
      1   2.729 BB    0.3269 9157.22266  443.45895 100.0000

   Totals :                   9157.22266  443.45895
```

400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



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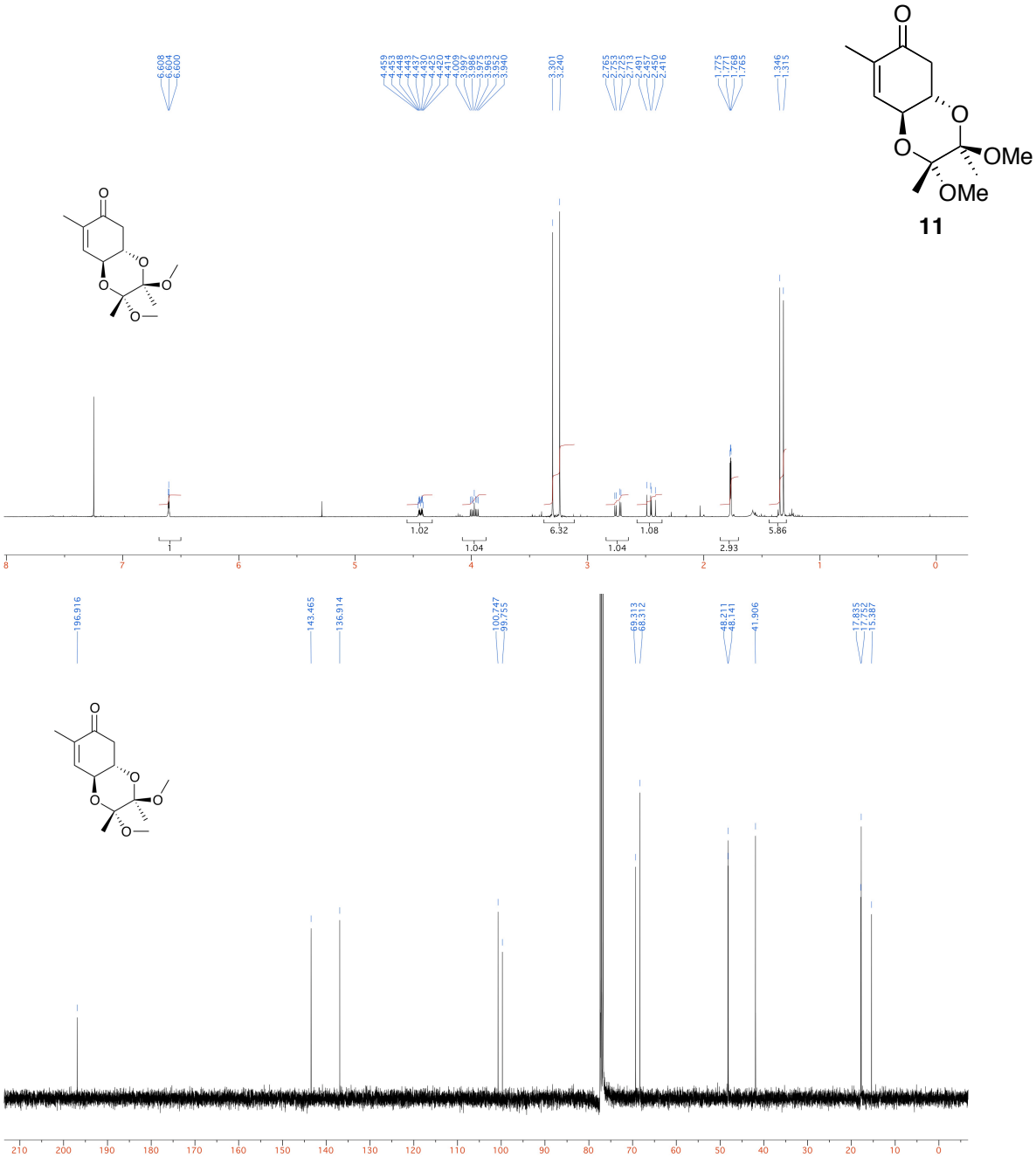
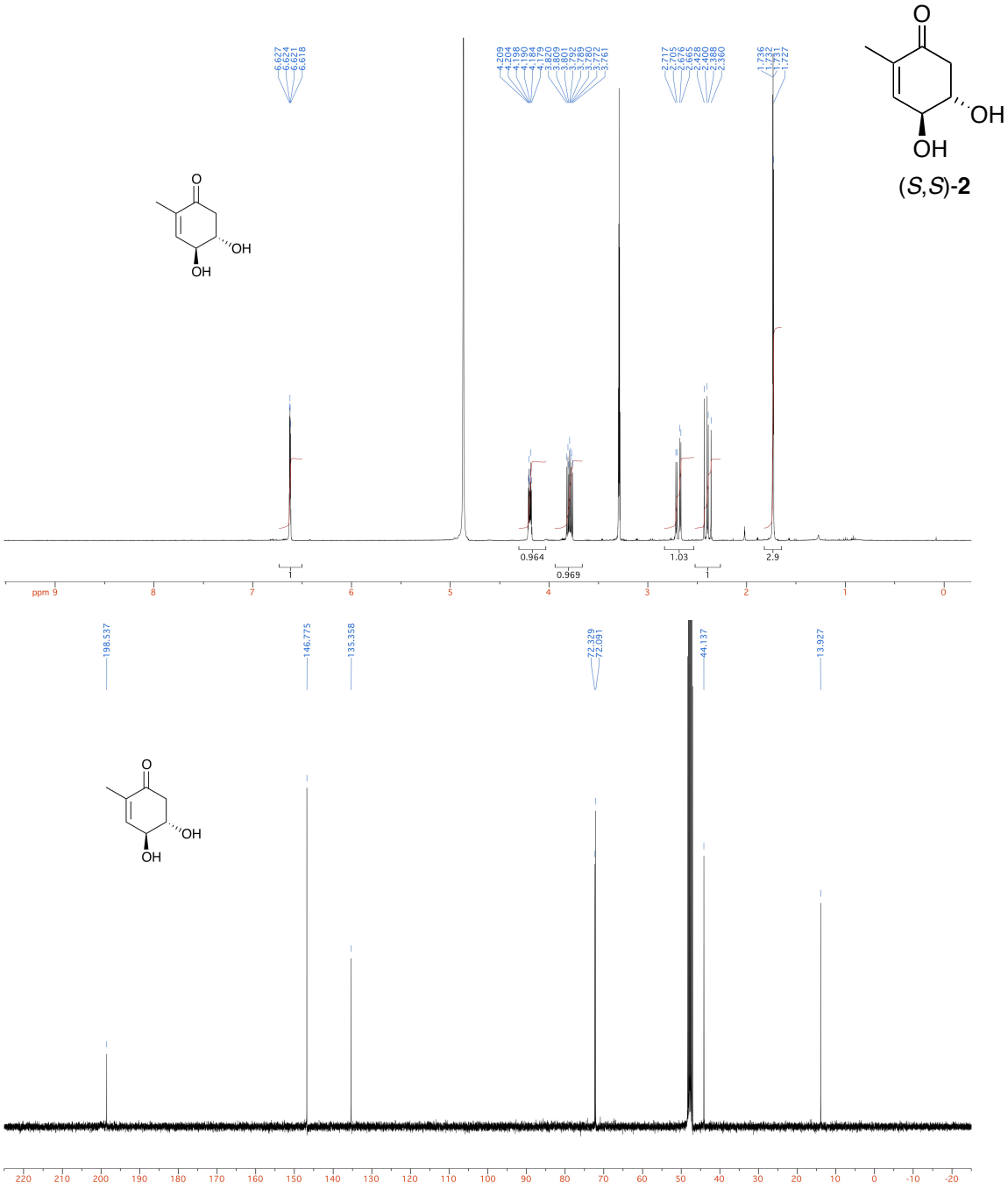
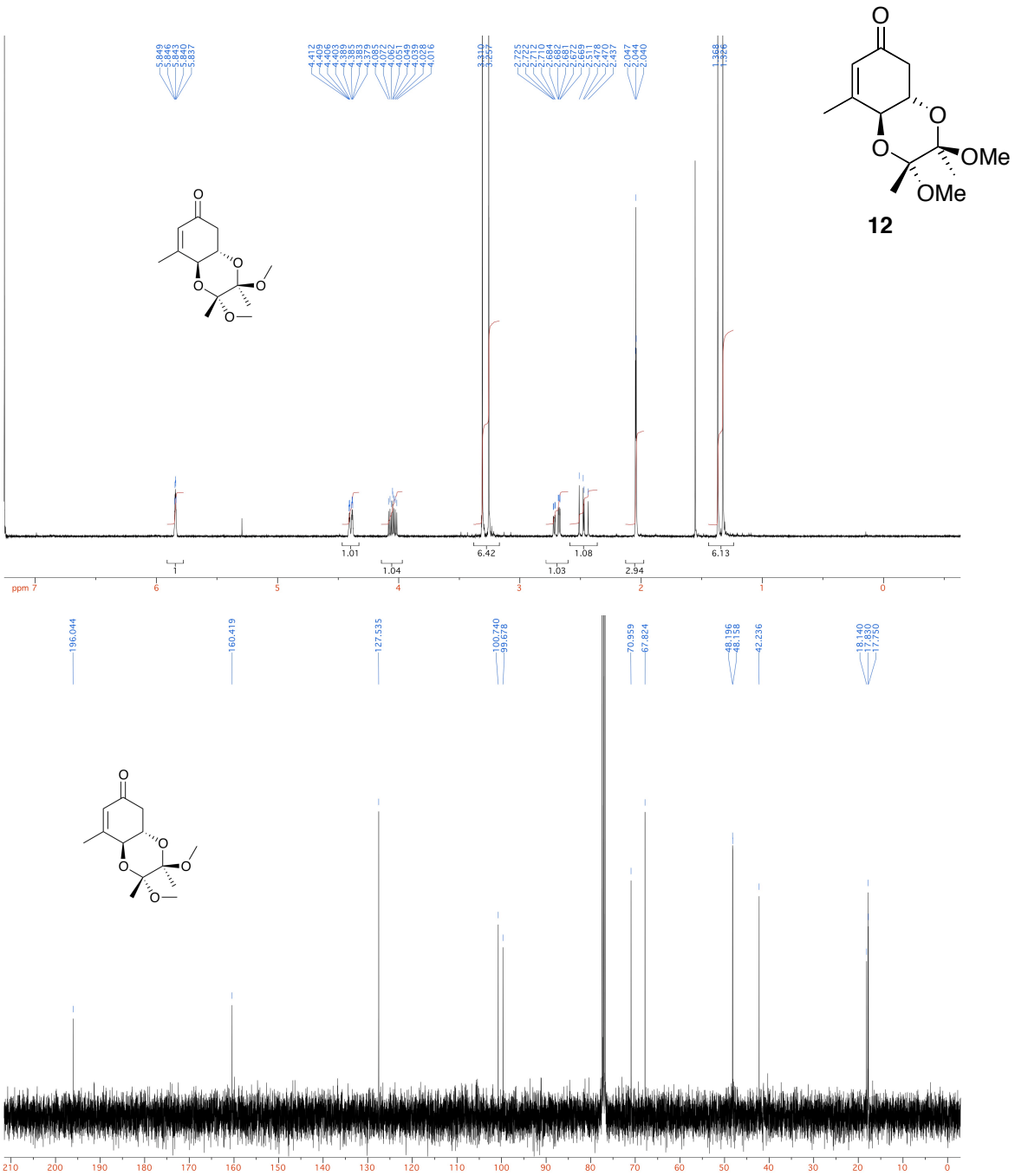
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



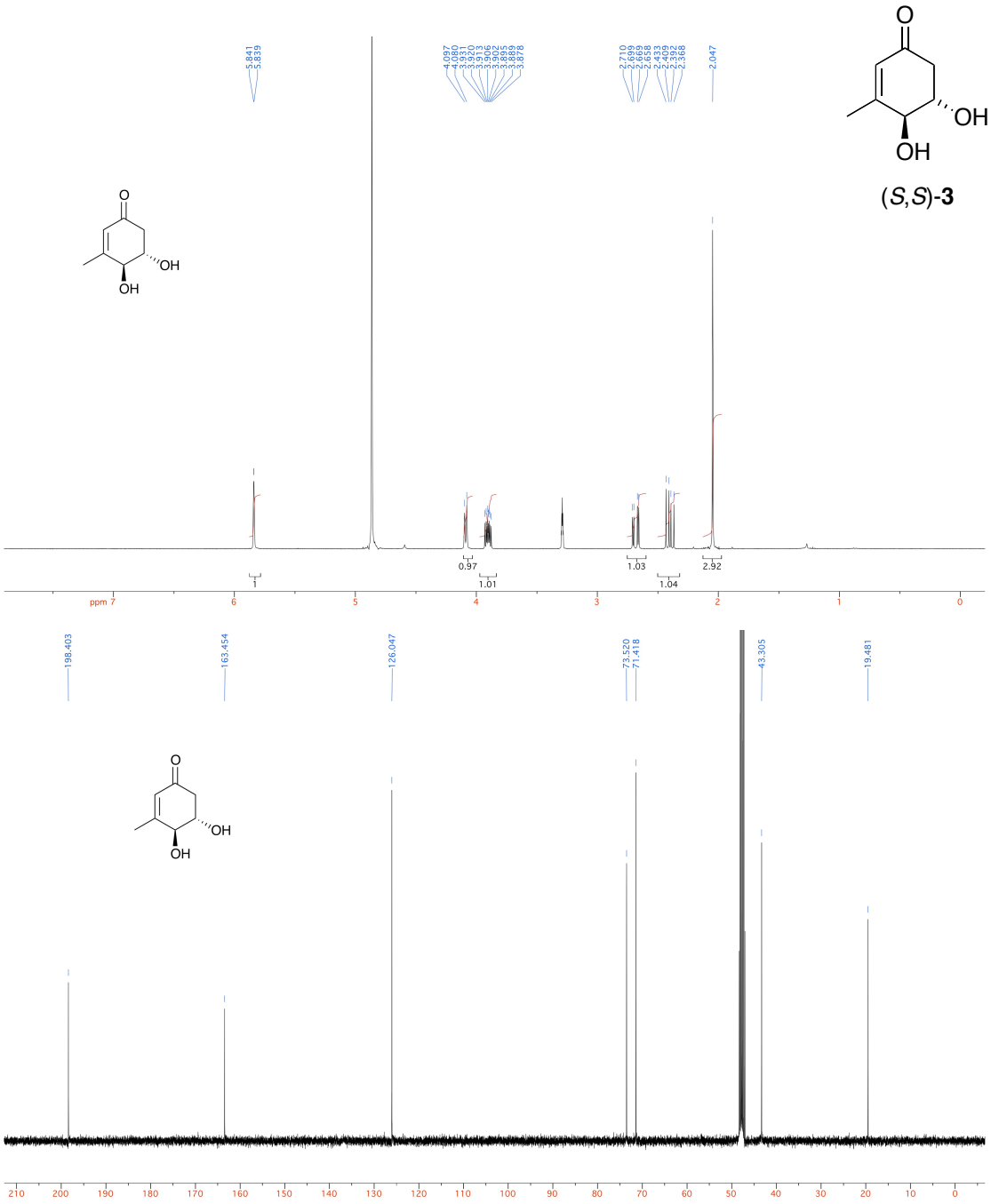
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; d_4-methanol



400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; d_4-methanol



3. References for supporting information:

(1) Q. Tan and M. Hayashi, *Org. Lett.*, 2009, **11**, 3314.

(2) M. T. Barros, C. D. Maycock and M. R. Ventura, *J. Chem. Soc., Perkin Trans. 1*, 2001, 166.

(3) R. Takei, K. Takahashi, H. Matsuura and K. Nabeta, *Biosci. Biotechnol. Biochem.*, 2008, **72**, 2069.

(4) N. Kitaoka, K. Nabeta and H. Matsuura, *Biosci. Biotechnol. Biochem.*, 2009, **73**, 1890.