Convergent Synthesis and Structural Confirmation of Phellodonin and Sarcodonin ε

Ippei Usui, David W. Lin, Takeshi Masuda, and Phil S. Baran*

Department of Chemistry, The Scripps Research Institute,

10550 N. Torrey Pines Rd, La Jolla, CA 92037

SUPPORTING INFORMATION

Part 1: Experimental Procedures and Characterization Data

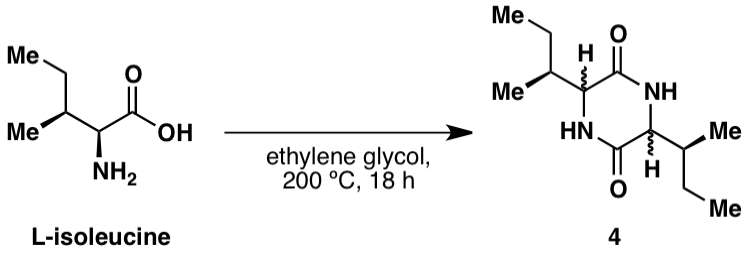
Table of Contents

General Experimental

All reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions unless stated otherwise. Dry acetonitrile (MeCN), dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), toluene (PhMe), benzene (PhH) and triethylamine (Et_3N) were obtained by passing the previously degassed solvents through activated alumina columns. Solvents used for workup and column chromatography such as hexanes and ethyl acetate (EtOAc) were used without purification or removal of water. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous material, unless stated otherwise. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using UV light as the visualizing agent and an acidic solution of *p*-anisaldehyde and heat, ceric ammonium molybdate and heat, or $KMnO_4$ and heat as developing agents. Flash silica gel chromatography was performed using E. Merck silica gel (60, particle size 0.043–0.063 mm). NMR spectra were recorded on Bruker DRX-600, Bruker DRX-500 and AMX-400 instruments and were calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ @ 7.26 ppm ^1H-NMR, 77.16 ppm ^{13}C-NMR). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time-of-flight (ESI-TOF) reflectron experiments. IR experiments were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Optical rotations were obtained on a Perkin-Elmer 341 polarimeter. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected.

Experimental Procedures and Characterization Data

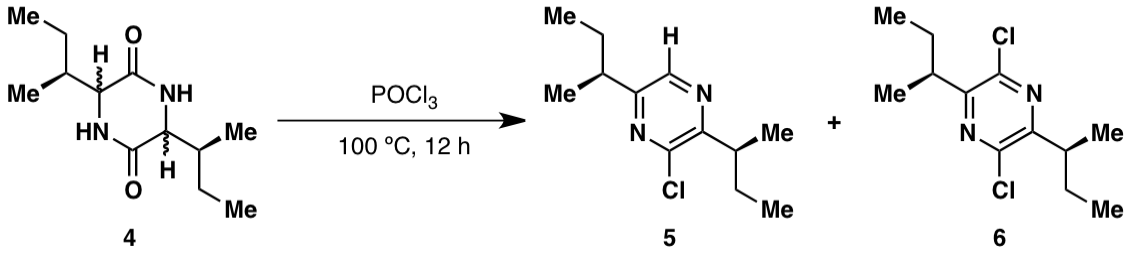
3,6-Di((*S*)-*sec*-butyl)piperazine-2,5-dione (4)



L-isoleucine 4

The procedure that is described previously by Cook *et al.* in *J. Chem. Soc. Perkin Trans. 1* **1992**, 1199–1201 was slightly modified. A suspension of L-isoleucine (10.0 g, 76.2 mmol) in ethylene glycol (20 ml) was heated at 200 ºC. During the heating, the suspension became a brownish solution. After heating for 18 h, the reaction mixture was cooled to room temperature. The resulting solid was filtered off, and washed with ^{i}PrOH. The white solid was dried *in vacuo* to afford 7.49 g (33.1 mmol, 87%) of title compound **4** as an off-white solid. The spectroscopic data for this compound were identical to those reported in Cook's paper.

2,5-Di((*S*)-*sec*-butyl)-3-chloropyrazine (5) and 2,5-di((*S*)-*sec*-butyl)-3,6-dichloropyrazine (6)



4 5 6

A suspension of **4** (1.49 g, 6.6 mmol) in $POCl_3$ (6 ml) was heated at 100 ºC, and after a while the suspension fully dissolved. After stirring for 12 h, the reaction mixture was poured into ice-water carefully, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers was washed first with saturated aqueous $NaHCO_3$ then with brine, dried over $MgSO_4$, and

concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2, a gradient of hexanes to 10:1 hexanes:EtOAc) to provide 1.05 g (4.62 mmol, 70%) of **5** as a yellow oil and 60 mg (0.23 mmol, 3.5%) of **6** as a white solid. The ^{1}H and ^{13}C NMR spectra for **5** completely matched those reported in Dickschat *et al.*, *Eur. J. Org. Chem.* **2005**, 4141–4153.

Data for **6**:

Physical state: Colorless needles, m.p. 59–63 ºC.

TLC: R_f = 0.92 (1:3 EtOAc:hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.26–3.17 (m, 2 H), 1.87–1.76 (m, 2 H), 1.67–1.56 (m, 2 H), 1.25 (d, 6 H), 0.87 (t, 6 H) ppm.

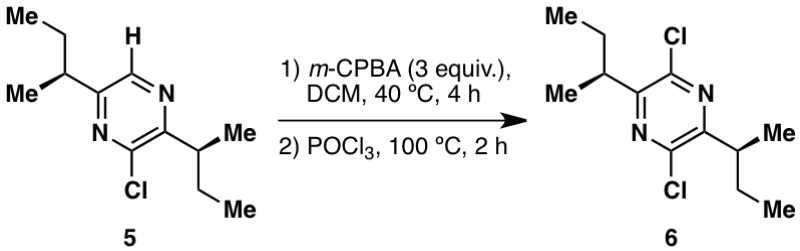
^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6, 145.9, 38.3, 28.7, 18.9, 12.1 ppm.

IR (neat): $\tilde{\nu}$ = 2964, 2926, 2861, 1455, 1407, 1369, 1291, 1246, 1153, 1087, 1003, 707, 518, 495 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{12}H_{18}N_2Cl_2$ [M + H^+] 261.0925, found 261.0928.

Optical rotation: $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$) = +146º.

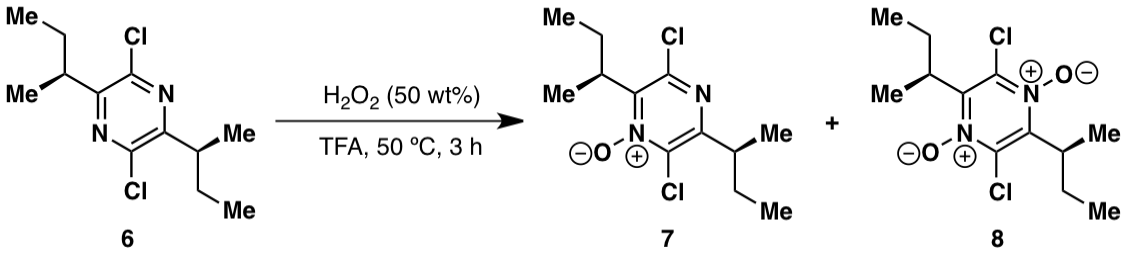
2,5-Di((*S*)-*sec*-butyl)-3,6-dichloropyrazine (6)



A solution of **5** (4.28 g, 18.9 mmol) and *m*-CPBA (~75% purity, 13.0 g, 56.7 mmol) in CH_2Cl_2 (30 ml) was heated at 40 ºC for 4 h, then the reaction mixture was cooled to room temperature. The solution was diluted with 100 ml of EtOAc, and water was added. The organic phase was washed with aqueous $Na_2S_2O_5$ until no more peroxides were detected by starch-iodide paper, and

was further washed with saturated aqueous $NaHCO_3$ then brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude mixture was subjected to the next reaction without purification. This was dissolved in $POCl_3$ and heated at 100 ºC. After stirring for 2 h, the reaction mixture was poured into ice-water. The aqueous phase was extracted twice with CH_2Cl_2. The combined organic phase was washed with saturated aqueous $NaHCO_3$ then with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2, hexanes:CH_2Cl_2 = 9:1) to provide 3.01 g (11.5 mmol, 61%) of the title compound **6** as a white solid. See the previous page for the characterization data of **6**.

2,5-Di((*S*)-*sec*-butyl)-3,6-dichloropyrazine 1-oxide (7) and 2,5-di((*S*)-*sec*-butyl)-3,6-dichloropyrazine 1,4-dioxide (8)



(CAUTION: This reaction can be explosive. It is absolutely necessary to remove all metal deposits from the glassware and stirring bar before starting the reaction. The reaction has to be performed behind a glass shield.)

A solution of 6 (2.90 g, 11.1 mmol) in trifluoroacetic acid (TFA; 29 ml, measured with a graduated cylinder) and H_2O_2 (50 wt%, 5.8 ml, measured with a graduated cylinder) was heated at 50 ºC for 3 h behind a glass shield. After cooling to room temperature, the reaction mixture was slowly poured into an ice-cooled solution of $Na_2S_2O_5$ and diluted with CH_2Cl_2, neutralized with K_2CO_3 slowly at 0 ºC and extracted with CH_2Cl_2 three times. The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected

to column chromatography to afford **7** (2.285 g, 7.79 mmol, 70%) as a white solid, and **8** (40 mg, 0.14 mmol, 1.3%) as a white solid. The ^{1}H spectrum for **7** matches that reported in Inoue *et al.*, *J. Heterocycl. Chem.* **1985**, *22*, 1291–1296.

Data for **8**:

Physical state: White solid, m.p. 72–75 ºC.

TLC: R_f = 0.39 (1:3 EtOAc:hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75–3.25 (m, 2 H), 2.40–2.00 (m, 4 H), 1.81 (dq, J = 7.4, 7.4 Hz, 2 H), 1.42 (d, J = 6.9 Hz, 12 H), 0.85 (t, J = 7.4 Hz, 6 H) ppm.

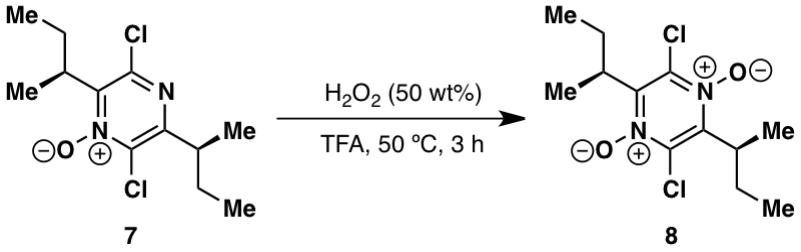
^{13}C NMR (101 MHz, $CDCl_3$): δ 148.3, 140.3, 39.8, 24.3, 14.5, 12.5 ppm.

IR (neat): $\tilde{\nu}$ = 2968, 2933, 2876, 1450, 1366, 1344, 1310, 1274, 1247, 1233, 1216, 1104, 1075, 1017, 950, 853, 754, 666 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{12}H_{18}N_2O_2Cl_2$ [M + H$^+$] 293.0818, found 293.0821.

Optical rotation: $[\alpha]_D^{20}$ (c 0.5, $CHCl_3$) = +12.6º.

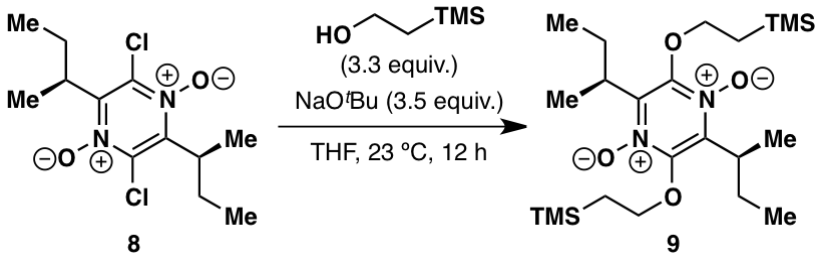
2,5-Di((*S*)-*sec*-butyl)-3,6-dichloropyrazine 1,4-dioxide (8) from 7



(CAUTION: This reaction can be explosive. It is absolutely necessary to remove all metal deposits from the glassware and stirring bar before starting the reaction. The reaction has to be performed behind a glass shield.)

A solution of **7** (455 g, 1.64 mmol) in TFA (16 ml, measured with a graduated cylinder) and H_2O_2 (50 wt%, 1.6 ml, measured with a graduated cylinder) was heated at 50 °C for 3 h behind a glass shield. After cooling to room temperature, the reaction mixture was slowly poured into an ice-cooled $Na_2S_2O_5$ solution and diluted with CH_2Cl_2, neutralized with K_2CO_3 slowly at 0 ºC and extracted with CH_2Cl_2 three times. The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography to afford starting material **7** (218 mg, 0.787 mmol, 48%) as a white solid, and **8** (120 mg, 0.409 mmol, 25%, 52% brsm) as a white solid. See the previous page for the characterization data of **8**.

2,5-Di((*S*)-*sec*-butyl)-3,6-bis(2-(trimethylsilyl)ethoxy)pyrazine 1,4-dioxide (9)



To a suspension of sodium *tert*-butoxide (161 mg, 1.74 mmol) and 2-(trimethylsilyl)ethanol (0.26 ml, 1.82 mmol) in THF (2 ml) was added a solution of **8** (154 mg, 0.525 mmol) in THF (8 ml) at room temperature. After stirring for 12 h, the reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography to give a mixture of product **9** and 2-(trimethylsilyl)ethanol. Further purification resulted in decomposition of the product, therefore the alcohol was removed just by leaving the product vial open for one week under air to afford pure **9** (150 mg, 0.328 mmol, 63%) as a yellow solid.

Physical state: Yellow solid, m.p. 42–44 ºC.

TLC: R_f = 0.73 (1:3 EtOAc:hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.46 (dq, J = 19.3, 9.0 Hz, 4H), 3.65 (s, 2H), 1.80–1.68 (m, 2H), 1.38 (d, J = 7.0 Hz, 6H), 1.28–1.10 (m, 4H), 0.87 (t, J = 7.4 Hz, 6H), 0.06 (s, 18H) ppm.

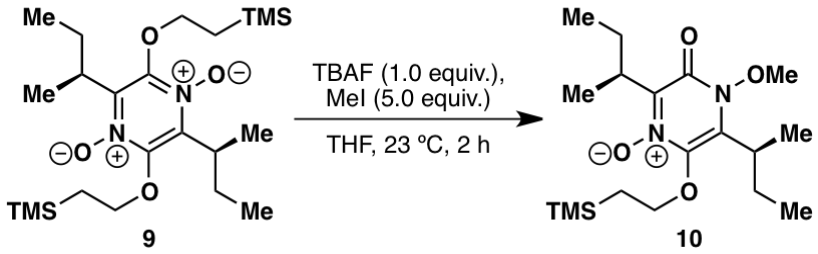
^{13}C NMR (101 MHz, $CDCl_3$): δ 151.3, 142.7, 71.6, 33.4, 25.5, 18.7, 16.0, 12.6, –1.6 ppm.

IR (neat): $\tilde{\nu}$ = 2957, 2932, 2900, 2835, 1659, 1610, 1503, 1339, 1313, 1251, 1146, 858, 836 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{22}H_{44}N_2O_4Si_2$ [M + H^+] 457.2912, found 457.2923.

Optical rotation: $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$) = 0.0º.

2,5-Di((*S*)-*sec*-butyl)-4-methoxy-3-oxo-6-(2-(trimethylsilyl)ethoxy)-3,4-dihydropyrazine 1-oxide (10)



To a solution of **9** (80.0 mg, 0.161 mmol) in THF (10 ml) was added tetrabutylammonium fluoride (TBAF; 0.16 ml, 1 M solution in THF) at room temperature. After stirring for 1 h, iodomethane (60 µl, 0.81 mmol) was added to the reaction mixture. After stirring for 2 h, the solvent was removed under reduced pressure. The residue was subjected to column chromatography to afford pure **10** (59.0 mg, 0.159 mmol, 99%) as a yellow oil.

Physical state: Yellow oil.

TLC: R_f = 0.48 (1:3 EtOAc:hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.28–4.10 (m, 2 H), 4.08 (s, 3H), 3.70 (q, J = 8.0 Hz, 1H), 3.23 (q, J = 8.0 Hz, 1H), 2.05–1.95 (m, 1H), 1.89–1.69 (m, 3H), 1.37 (d, J = 7.2 Hz, 1H), 1.34 (d, J =

7.2 Hz, 1H), 1.24–1.16 (m, 2H), 0.94 (t, J = 7.2 Hz, 1H), 0.86 (t, J = 7.2 Hz, 1H), 3.65 (s, 1H), 1.80–1.68 (m, 1H), 1.38 (d, J = 7.0 Hz, 1H), 0.05 (s, 9H) ppm.

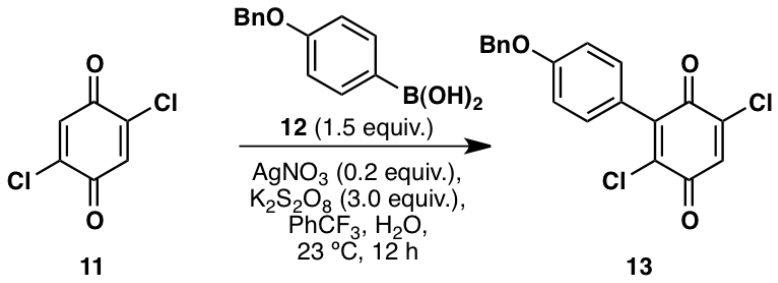
^{13}C NMR (101 MHz, $CDCl_3$): δ 152.6, 144.9, 140.9, 134.6, 72.7, 64.3, 34.1, 33.4, 27.5, 18.6, 18.5 14.7, 12.7, 12.5, 1.5 ppm.

IR (neat): $\tilde{\nu}$ = 2963, 2876, 1658, 1611, 1461, 1405, 1377, 1342, 1317, 1298, 1251, 1198, 1170, 1135, 1111, 1058, 1034, 999, 969, 952, 908, 889, 860, 838, 796, 756, 696, 664 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{18}H_{34}N_2O_4Si$ [M + H$^+$] 371.2375, found 371.2360.

Optical rotation: $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$) = +38.6º.

4'-(Benzyloxy)-3-chloro-6-methoxy-[1,1'-biphenyl]-2,5-dione (13)



To a suspension of 2,5-dichlorobenzoquinone (**11**; 354 mg, 2.0 mmol) and 4-benzyloxyphenylboronic acid (**12**; 684 mg, 3.0 mmol) in $PhCF_3$ (10 ml) and water (6 ml) was added silver nitrate (0.1 M aqueous solution, 4 ml, 0.4 mmol) and potassium persulfate (1.600 g, 6.0 mmol). After stirring for 12 h at room temperature, the reaction mixture was extracted with CH_2Cl_2 and the combined organic phase was washed with water, aqueous $NaHCO_3$ solution then brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography to afford 526 mg (1.47 mmol, 73%) of product **13** as a red solid.

Physical state: Red solid, m.p. 147–155 ºC.

TLC: R_f = 0.75 (1:3 EtOAc:hexanes).

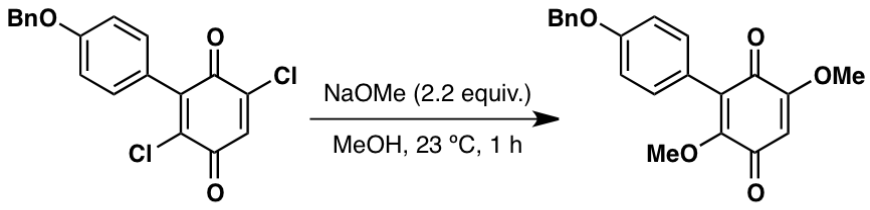
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (t, *J* = 8.1 Hz, 2H), 7.41 (dd, *J* = 8.2, 6.6 Hz, 2H), 7.38–7.33 (m, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.22 (s, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 5.12 (s, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.7, 177.2, 160.0, 144.2, 143.0, 139.9, 136.3, 132.9, 131.6, 128.6, 128.1, 127.5, 122.8, 114.4, 70.0 ppm.

IR (neat): $\tilde{\nu}$ = 3319, 3065, 3035, 2925, 2871, 1676, 1604, 1579, 1507, 1247, 1044 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{19}H_{12}O_3Cl_2$ [M + H^+] 359.0236, found 359.0226.

4'-(Benzyloxy)-3,6-dimethoxy-[1,1'-biphenyl]-2,5-dione (14)



13 **14**

A solution of 4'-(benzyloxy)-3-chloro-6-methoxy-[1,1'-biphenyl]-2,5-dione (**13**; 185 mg, 0.50 mmol) in MeOH (10 ml) was added sodium methoxide (60 mg, 1.10 mmol) at room temperature. After stirring for 1 h at room temperature, solvent was removed and the residue was subjected to column chromatography to afford **14** (85 mg, 0.243 mmol, 47%) as a red solid.

Physical state: Red solid, m.p. 113–118 ºC.

TLC: R_f = 0.29 (1:3 EtOAc:hexanes).

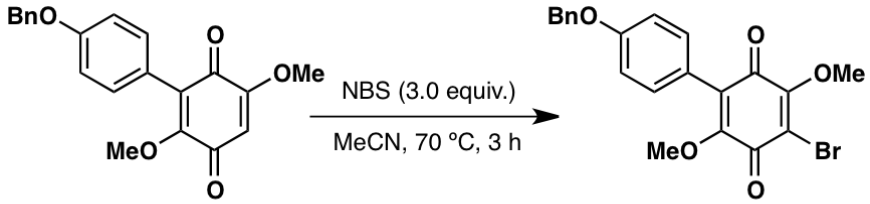
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46–7.43 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.36–7.31 (m, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 5.88 (s, 1H), 5.09 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 183.2, 181.8, 158.8, 158.5, 154.9, 136.6, 131.8, 128.5, 127.9, 127.4, 126.1, 122.1, 114.1, 105.4, 69.8, 61.4, 56.4 ppm.

IR (neat): $\tilde{\nu}$ = 3065, 3009, 1648, 1588, 1508, 1454, 1326, 1283, 1240, 1214, 1177, 1131, 1021, 829, 735 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{21}H_{18}O_5$ [M + H^+] 351.1227, found 351.1216.

4'-(Benzyloxy)-4-bromo-3,6-dimethoxy-[1,1'-biphenyl]-2,5-dione (15)



14 **15**

To a solution of 4'-(benzyloxy)-3,6-dimethoxy-[1,1'-biphenyl]-2,5-dione (**14**; 44.0 mg, 0.126 mmol) in MeCN (6.3 ml) was added *N*-bromosuccinimide (NBS; 67.0 mg, 0.377 mmol). After stirring for 3 h, the reaction mixture was concentrated *in vacuo*, and subjected to column chromatography to afford **15** (32.0 mg, 60%) as a red solid. The yield of this reaction varied between 40 and 60%.

Physical state: Red solid, m.p. 92–94 ºC.

TLC: R_f = 0.66 (1:3 EtOAc:hexanes).

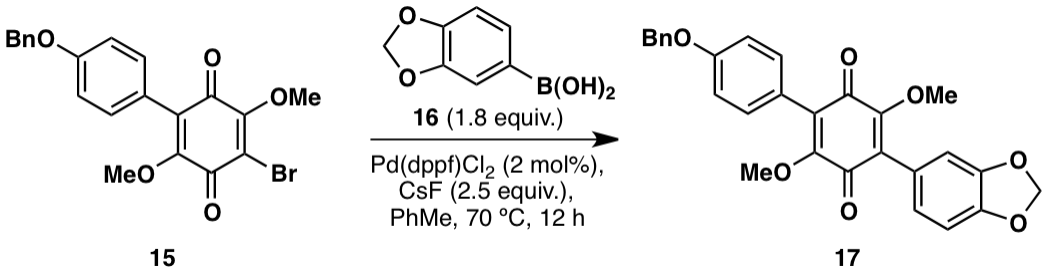
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 5.10 (s, 2H), 4.23 (s, 3H), 3.84 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 181.3, 177.0, 159.1, 156.6, 154.4, 136.6, 131.9, 128.5, 128.0, 127.4, 126.4, 121.8, 115.0, 114.3, 69.9, 61.9, 61.6 ppm.

IR (neat): $\tilde{\nu}$ = 3032, 2951, 2852, 1660, 1604, 1583, 1509, 1454, 1415, 1382, 1321, 1305, 1292, 1247, 1227, 1177, 1127, 1080 1044, 954, 911, 864, 834, 808, 743, 698 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{21}H_{17}O_5Br$ [M + H^+] 429.0332, found 429.0333.

4-(Benzo[*d*][1,3]dioxol-5-yl)-4'-(benzyloxy)-3,6-dimethoxy-[1,1'-biphenyl]-2,5-dione (17)



To a solution of $Pd(dppf)Cl_2$ (13 mg, 0.016 mmol), 4'-(benzyloxy)-4-bromo-3,6-dimethoxy-[1,1'-biphenyl]-2,5-dione (**15**; 324 mg, 0.754 mmol) and cesium fluoride (290 mg, 1.90 mmol) in PhMe (13 ml) was added benzo[*d*][1,3]dioxol-5-ylboronic acid (**17**; 441 mg, 1.39 mmol). After stirring for 12 h at 70 °C, the solvent was removed and the residue was subjected to column chromatography to afford **17** (314 mg, 0.067 mmol, 88%) as a brown solid.

Physical state: Brown solid, m.p. 145–148 ºC.

TLC: R_f = 0.42 (1:3 EtOAc:hexanes).

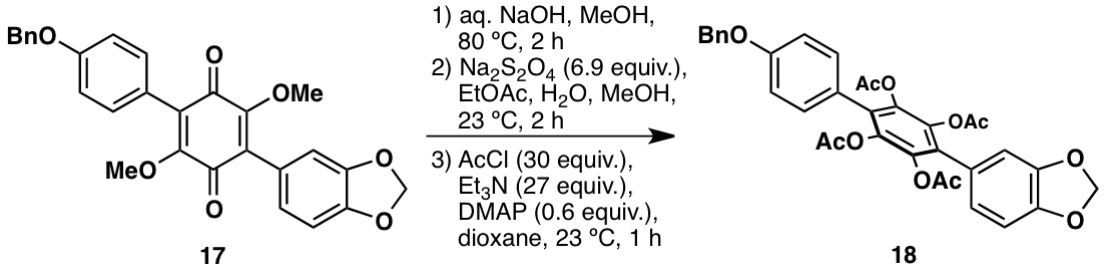
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 7.5 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 7.2 Hz, 1H), 7.23 (d, J = 8.2 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 5.10 (s, 1H), 4.23 (s, 2H), 3.84 (s, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 181.3, 177.0, 159.1, 156.6, 154.4, 136.6, 131.9, 128.5, 128.0, 127.4, 126.4, 121.8, 115.0, 114.3, 69.9, 61.9, 61.6 ppm.

IR (neat): $\tilde{\nu}$ = 3032, 2945, 1653, 1605, 1591, 1507, 1489, 1444, 1382, 1297, 1242, 1178, 1142, 1112, 1082, 1038, 930, 863, 839, 815, 796, 740, 698 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{28}H_{22}O_7$ [M + H^+] 471.1438, found 471.1437.

4-(Benzo[*d*][1,3]dioxol-5-yl)-4'-(benzyloxy)-[1,1'-biphenyl]-2,3,5,6-tetrayl tetraacetate (18)



To a solution of 4-(benzo[*d*][1,3]dioxol-5-yl)-4'-(benzyloxy)-3,6-dimethoxy-[1,1'-biphenyl]-2,5-dione (**17**; 327 mg, 0.695 mmol) in MeOH (18 ml) was added 10% NaOH solution (9 ml). After stirring for 2 h at 80 °C, an HCl solution (2 N) was added until the reaction was more acidic than pH 4; this was subsequently extracted with EtOAc. The combined organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was then dissolved in EtOAc (60 ml), and to this solution was added sodium dithionite (840 mg, 4.82 mmol) in water (30 ml) and MeOH (5 ml). After stirring for 2 h, the red solution became yellow and an HCl solution (2 N) was added until the reaction was more acidic than pH 4. This mixture was extracted with EtOAc, washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. It is note that the crude material should be subjected to the next reaction immediately since it can re-oxidize back to the dihydroxyquinone after exposure to air. The crude product was dissolved in dioxane (20 ml), and to this was added DMAP (50 mg, 0.41 mmol), acetyl chloride (1.50 ml, 21 mmol), and Et_3N (3.0 ml, 19 mmol). After stirring for 1 h at room temperature, the reaction mixture was diluted with EtOAc and quenched with water. The organic phase was washed first with an HCl solution (2 N), then a $NaHCO_3$ solution followed by brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography to afford **18** (295 mg, 69%) as an off-white solid.

Physical state: Off-white solid, m.p. 198–200 ºC.

TLC: R_f = 0.44 (1:1 EtOAc:hexanes).

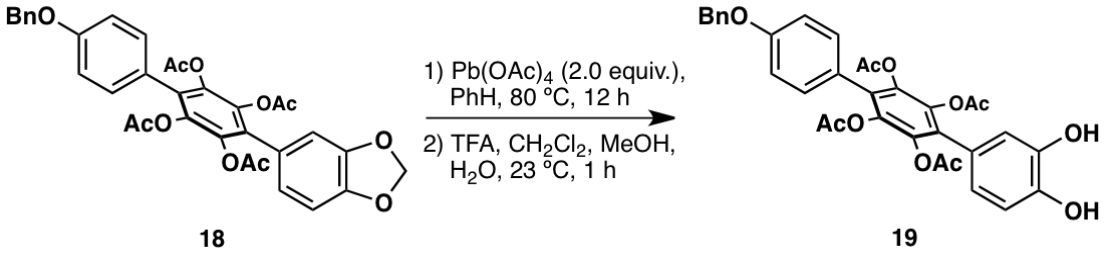
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.34 (t, J = 7.0 Hz, 1H), 7.24 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.6 Hz, 2H), 6.86–6.75 (m, 3H), 6.00 (s, 2H), 5.08 (s, 2H), 2.02 (s, 6H), 1.96 (s, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 158.6, 147.5, 147.4, 139.2, 136.6, 130.8, 130.1, 129.7, 128.6, 128.0, 127.6, 124.7, 123.7, 123.3, 114.6, 110.0, 108.1, 101.2, 69.9, 20.2, 20.1 ppm.

IR (neat): $\tilde{\nu}$ = 1775, 1608, 1518, 1459, 1369, 1240, 1189, 1024, 736, 699 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{34}H_{28}O_{11}$ [M + Na^+] 635.1524, found 635.1539.

4''-(Benzyloxy)-3,4-dihydroxy-[1,1':4',1''-terphenyl]-2',3',5',6'-tetrayl tetraacetate (19)



18 19

A solution of 4-(benzo[*d*][1,3]dioxol-5-yl)-4'-(benzyloxy)-[1,1'-biphenyl]-2,3,5,6-tetrayl tetraacetate (260 mg, 0.424 mmol) and lead acetate (376 mg, 0.849 mmol) in PhH (12 ml) was heated at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with water then brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was then dissolved in CH_2Cl_2 (15 ml), and to it was added TFA (1.0 ml), MeOH (1 ml) and water (1 ml). After stirring for 1 h at room temperature, the reaction mixture was extracted with EtOAc, washed with water then brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography to afford **19** (131 mg, 51%) as a white solid.

Physical state: White solid, m.p. 159–162 ºC.

TLC: R_f = 0.15 (1:1 EtOAc:hexanes).

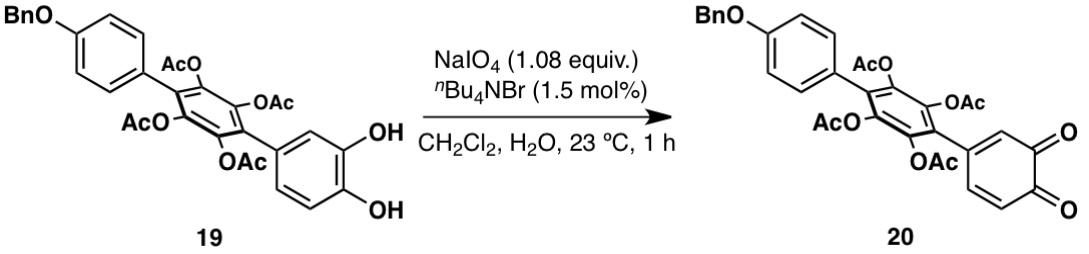
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 7.3 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.34 (t, J = 7.1 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.2 Hz, 1H), 6.78–6.67 (m, 2H), 6.18 (s, 1H), 5.91 (s, 1H), 5.09 (s, 2H), 1.98 (s, 3H), 1.97 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7, 168.5, 158.8, 144.7, 143.9, 139.4, 139.4, 136.8, 131.0, 130.4, 130.0, 128.8, 128.3, 127.8, 123.8, 123.1, 122.1, 116.4, 115.2, 114.9, 70.1, 20.3, 20.3 ppm.

IR (neat): $\tilde{\nu}$ = 3413, 3065, 3035, 2926, 2855, 1772, 1608, 1579, 1523, 1488, 1453, 1430, 1408, 1369, 1275, 1240, 1183, 1101, 1024, 979, 911, 871, 838, 821, 785, 774, 739, 698 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{33}H_{28}O_{11}$ [M + Na^+] 623.1524, found 624.1528.

4''-(Benzyloxy)-3,4-dioxo-3,4-dihydro-[1,1':4',1''-terphenyl]-2',3',5',6'-tetrayl tetraacetate (20)



To a solution of 4''-(benzyloxy)-3,4-dihydroxy-[1,1':4',1''-terphenyl]-2',3',5',6'-tetrayl tetraacetate (**19**; 117 mg, 0.195 mmol) in CH_2Cl_2 (4 ml) was added tetrabutylammonium bromide (1 mg, 0.003 mmol), H_2O (0.8 ml) and $NaIO_4$ (46 mg, 0.21 mmol). After stirring for 1 h at room temperature, the solution was extracted with CH_2Cl_2 and dried over $MgSO_4$, then concentrated *in vacuo*. The residue was subjected to column chromatography to afford **20** (95 mg, 81%) as a black solid. The product was used immediately after purification.

Physical state: Black solid.

TLC: R_f = 0.39 (1:1 EtOAc:hexanes).

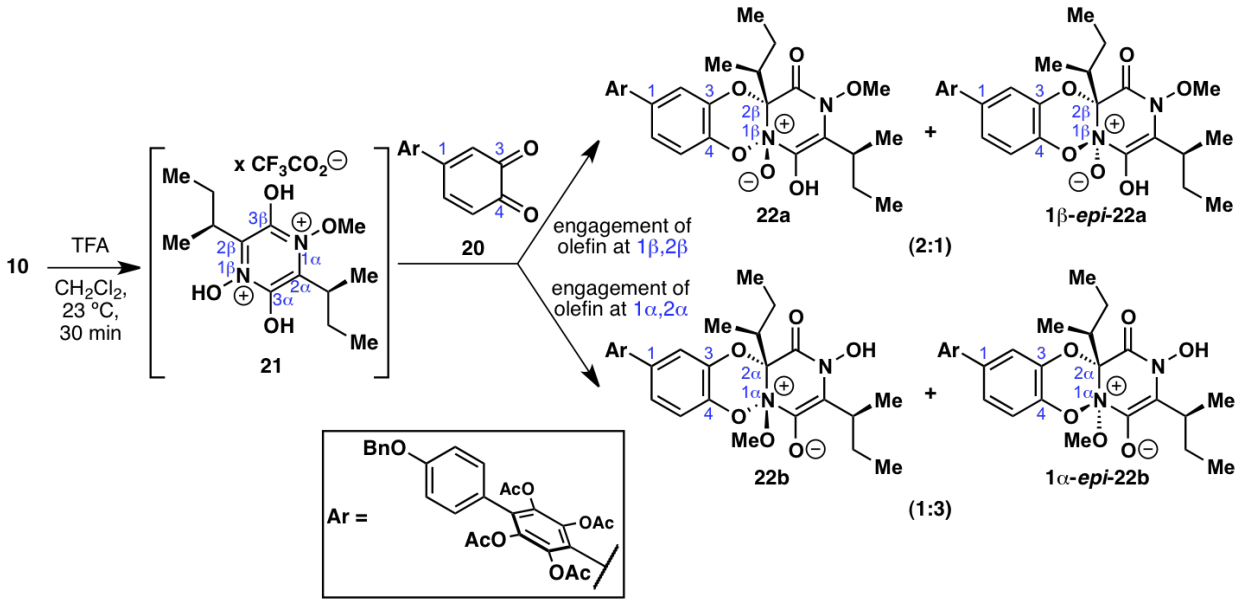
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.31 (m, 5H), 7.19 (d, J = 8.8 Hz, 2H), 7.06 (dd, J = 10.2, 2.1 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 6.44 (d, J = 10.2 Hz, 1H), 6.41 (d, J = 2.1 Hz, 1H), 5.09 (s, 2H), 2.21 (s, 6H), 1.99 (s, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 179.3, 178.8, 167.4, 167.3, 158.9, 144.0, 141.9, 139.5, 138.3, 136.5, 132.8, 130.6, 130.2, 129.7, 128.6, 128.1, 127.5, 125.5, 122.9, 114.7, 70.0, 20.4, 20.0 ppm.

IR (neat): $\tilde{\nu}$ = 3522, 3067, 2937, 1780, 1690, 1668, 1608, 1517, 1454, 1438, 1395, 1371, 1246, 1180, 1101, 1085, 1025, 979, 907, 864, 840, 822, 741, 698 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{33}H_{26}O_{11}$ [M + H^+] 599.1548, found 599.1538.

Formal [4+2] hetero-Diels–Alder reaction between pyrazine dioxide 10 and *ortho*-quinone 20 to give 22a, 1β-*epi*-22a, 22b and 1α-*epi*-22b



To a solution of 2,5-di((*S*)-*sec*-butyl)-4-methoxy-3-oxo-6-(2-(trimethylsilyl)ethoxy)-3,4-dihydropyrazine 1-oxide (**10**; 37 mg, 0.10 mmol) in CH_2Cl_2 (5 ml) was added TFA (0.25 ml) at room temperature. After stirring at room temperature for 30 min, the solvent and TFA were removed *in vacuo*, and to the residue was added 4''-(benzyloxy)-3,4-dioxo-3,4-dihydro-

[1,1':4',1''-terphenyl]-2',3',5',6-tetrayl tetraacetate (**20**; 60 mg, 0.10 mmol) in $CDCl_3$ at room temperature. After stirring for 1 h at room temperature, the consumption of starting materials was verified by ^1H NMR and the solvent was removed *in vacuo*. The residue was purified by preparative TLC to separate the four-compound mixture into two batches: an inseparable mixture of **22a** and **1β-*epi*-22a** (ca. 2:1 mixture) as a off-white solid (29.8 mg, 34%), and another inseparable mixture of **22b** and **1α-*epi*-22b** (ca. 1:3 mixture) as a nearly colorless oil (30.3 mg, 35%).

Data for the 2:1 mixture of **22a** and **1β-*epi*-22a**:

Physical state: Off-white amorphous solid.

TLC: R_f = 0.45 (1:1 EtOAc:hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 0.5H), 8.01 (s, 0.5H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.1 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.10 (s, 1H), 7.05–6.93 (m, 4H), 5.08 (s, 2H), 3.96–3.85 (m, 3H), 3.14–2.95 (m, 1H), 2.58–2.43 (m, 1H), 1.99 (s, 6H), 1.96 (s, 6H), 1.91–1.76 (m, 1H), 1.60 (td, *J* = 14.2, 7.3 Hz, 1H), 1.45–1.17 (m, 4H), 1.03 (ddd, *J* = 21.8, 14.3, 7.2 Hz, 6H), 0.93–0.80 (m, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 167.6, 159.2, 159.0, 158.6, 140.9, 139.3, 139.0, 136.6, 130.7, 130.6, 128.6, 128.1, 127.6, 126.7, 126.4, 123.6, 118.4, 116.9, 114.6, 93.5, 69.9, 66.5, 42.6, 40.6, 36.6, 33.7, 33.2, 29.7, 26.7, 26.1, 24.6, 24.6, 23.8, 20.1, 20.1, 16.1, 15.6, 14.3, 13.3, 12.7, 12.4, 12.1, 11.9 ppm.

IR (neat): $\tilde{\nu}$ = 3439, 2968, 2932, 2879, 2856, 1777, 1670, 1612, 1523, 1458, 1415, 1369, 1271, 1182, 1171, 1099, 1024, 899, 819, 734, 702 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{46}H_{48}N_2O_{15}$ [M + H^+] 869.3127, found 869.3121.

Optical rotation of the mixture: $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$) = –23.4°.

Data for the 1:3 mixture of **22b** and **1α -*epi*-22b**:

Physical state: Nearly colorless oil.

TLC: R_f = 0.55 (1:1 EtOAc:hexanes).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (brs, 1H), 7.45 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.37–7.31 (m, 1H), 7.23 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.4 Hz, 1H), 6.99 (m, 5H), 5.09 (s, 2H), 3.94 (s, 3H), 3.15–2.96 (m, 1H), 2.50–2.42 (m, 1H), 1.98 (s, 6H), 1.96 (s, 6H), 1.95–1.84 (m, 1H), 1.67–1.55 (m, 1H), 1.47–1.16 (m, 7H), 1.10–0.96 (m, 6H), 0.93–0.83 (m, 3H) ppm.

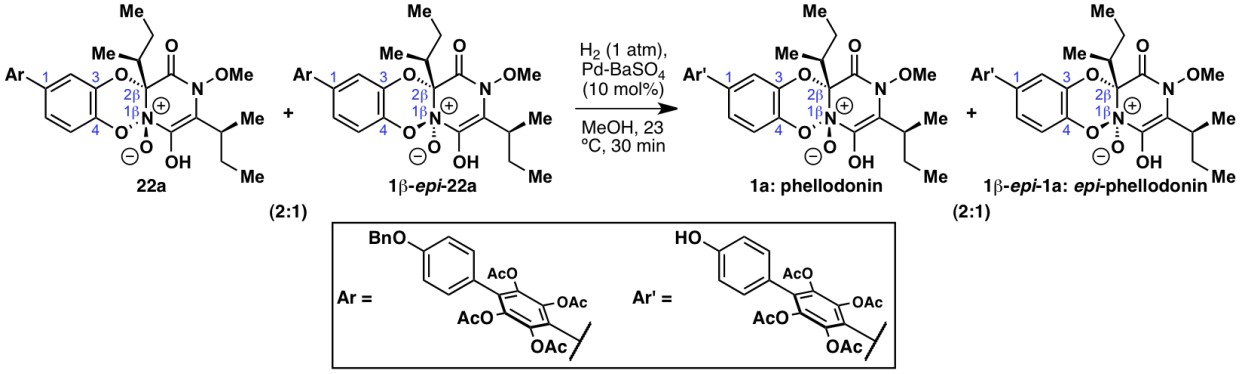
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.8, 167.7, 159.2, 159.1, 159.0, 158.6, 141.0, 140.8, 139.3, 139.0, 136.6, 130.7, 128.8, 128.6, 128.1, 127.6, 124.9, 123.5, 118.4, 116.9, 114.6, 92.4, 77.3, 77.0, 76.7, 69.9, 67.1, 65.8, 45.9, 42.5, 40.7, 37.3, 35.9, 33.8, 29.7, 26.0, 25.4, 23.6, 20.1, 20.1, 16.2, 15.2, 14.2, 13.2, 12.3, 12.1, 11.9, 8.5 ppm.

IR (neat): $\tilde{\nu}$ = 3450, 2970, 2935, 2878, 1780, 1674, 1608, 1519, 1458, 1370, 1274, 1185, 1101, 1025, 737 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{46}H_{48}N_2O_{15}$ [M + H$^+$] 869.3127, found 869.3109.

Optical rotation of the mixture: $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$) = –12.4º.

Debenzylation of the mixture of 22a and 1β-*epi*-22a by hydrogenation to give phellodonin (1a) and *epi*-phellodonin (1β-*epi*-1a)



The flask containing a suspension of the mixture of **22a** and **1β-*epi*-22a** (9.2 mg, 0.011 mmol) and Pd-$BaSO_4$ (5 wt%, 24 mg, 0.0011 mmol) in MeOH (1.5 ml) was purged with hydrogen gas (1 atm) three times. After stirring for 30 min under a balloon filled with hydrogen, the reaction mixture was filtered through Celite® and washed with EtOAc. The filtrate was concentrated *in vacuo*, and the residue was subjected to preparative TLC to afford a ~2:1 mixture of phellodonin (**1a**) and *epi*-phellodonin (**1β-*epi*-1a**) as a white solid (7.0 mg, 82%).

Data for the 2:1 mixture of **1a** and **1β-*epi*-1a**:

Physical state: White amorphous solid.

TLC: R_f = 0.16 (1:1 EtOAc:hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (br, 1 H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.13–7.11 (m, 1H), 7.05–6.93 (m, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 5.25 (br, 1H), 3.93 (s, 1H), 3.90 (s, 2H), 3.08 (q, *J* = 7.0 Hz, 0.4 H), 3.00 (q, *J* = 7.0 Hz, 0.6 H), 2.60–2.45 (m, 1H), 2.00 (s, 6H), 1.97 (s, 6H), 1.91–1.75 (m, 1H), 1.66–1.53 (m, 1H), 1.44–1.31 (m, 1H), 1.31 (d, *J* = 6.5 Hz, 1 H), 1.21 (d, *J* = 7.0 Hz, 2 H), 1.08 (d, *J* = 7.0 Hz, 2 H), 1.04 (d, *J* = 7.5 Hz, 1 H), 1.04–0.97 (m, 4H), 0.92–0.84 (m, 3H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.1, 167.1, 159.3, 159.1, 155.8, 141.1, 141.0, 139.3, 139.0, 130.9, 130.7, 128.8, 128.6, 126.4, 123.2, 118.4, 117.0, 115.2, 93.5, 66.5, 42.6, 42.5, 33.7, 33.2, 26.1, 24.6, 23.8, 22.7, 20.1, 16.1, 15.6, 14.3, 13.3, 12.5, 12.1, 11.9 ppm.

IR (neat): $\tilde{\nu}$ = 3455, 2970, 2938, 2879, 1780, 1675, 1613, 1523, 1458, 1415, 1370, 1275, 1187, 1102, 1026, 978, 913, 869, 832, 733, 670 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{39}H_{42}N_2O_{15}$ [M + H^+] 779.2658, found 779.2641.

Optical rotation of the mixture: $[\alpha]_D^{20}$ (c 0.4, $CHCl_3$) = –25.3°.

Table S1. Comparison of NMR data for synthetic and natural phellodonin (**1a**). Data for the natural sample is reproduced from Fang *et al.*,*Chem. Pharm. Bull.* **2010**, *58*, 1176–1179.

H or C numbering	Synthetic phellodonin (**1a**)		Natural phellodonin (**1a**)	
	δ_H (multiplicity, *J* in Hz)	δ_C	δ_H (multiplicity, *J* in Hz)	δ_C
1	---	128.6	---	128.5
2	7.12 (m)	118.4	7.13 (d, 1.6)	118.4
3	---	141.1	---	141
4	---	141.0	---	140.8
5	6.98 (m)	117.0	7.01 (d, 8.4)	117
6	7.03 (m)	126.4	7.05 (dd, 8.4, 1.6)	126.4
1’	---	123.2	---	122.8
2’	---	139.0	---	138.9
3’	---	139.3	---	139.3
4’	---	123.2	---	122.8
5’	---	139.3	---	139.3
6’	---	139.0	---	138.9
1”	---	128.8	---	128.7
2”,6”	7.17 (d, 8.5)	130.7	7.18 (d, 8.4)	130.8
3”,5”	6.84 (d, 8.5)	115.2	6.85 (d, 8.4)	115.3
4”	---	155.8	---	156.2
2’-$COCH_3$	1.97 (s)	168.1	1.99 (s)	167.9
3’-$COCH_3$	---	20.1	---	20.1
5’-$COCH_3$	2.00 (s)	168.1	2.03 (s)	167.9
6’-$COCH_3$	---	20.1	---	20.1
2α	---	167.1	---	166.6
3α	---	159.1	---	159
4α	3.00 (q, 7.0)	33.7	3.02 (m)	33.7
5α	1.63 (m), 1.39 (m)	26.1	1.63 (m), 1.39 (m)	26
6α	0.88 (m)	12.1	0.90 (t, 7.4)	12.1
7α	1.08 (d, 7.0)	16.1	1.09 (d, 7.2)	16.1
2β	---	93.5	---	93.3
3β	---	159.3	---	159.3
4β	2.55 (m)	42.6	2.55 (m)	42.6
5β	1.88 (m), 1.40 (m)	23.8	1.90 (m), 1.41 (m)	23.7
6β	1.04 (d, 7.5)	12.5	1.05 (t, 7.4)	12.4
7β	1.31 (d, 6.5)	14.3	1.33 (d, 6.8)	14.2
1α-OMe	3.93 (s)	66.5	3.93 (s)	66.6
4”-OH	5.25 (br s)	---	6.37 (br s)	---
3α-OH	7.69 (br s)	---	8.22 (br s)	---

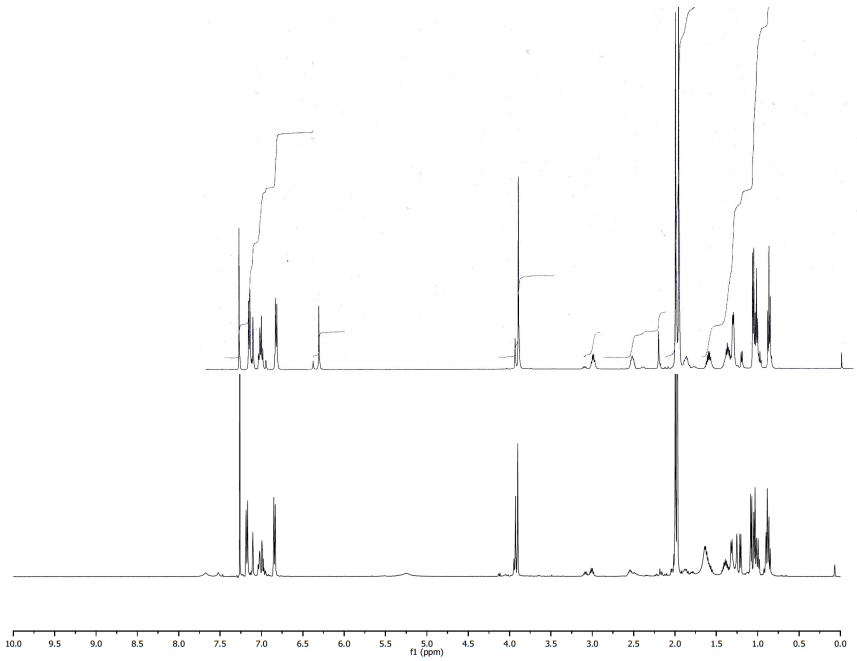


Figure S1. Overlaid ^{1}H NMR spectra of synthetic phellodonin (**1a**, albeit as a mixture of **1a** and **1β-*epi*-1a**) from this manuscript (lower spectrum, $CDCl_3$, 500 MHz) with that of the natural sample isolated by Fang *et al.* (upper spectrum inset, $CDCl_3$, 400 MHz).

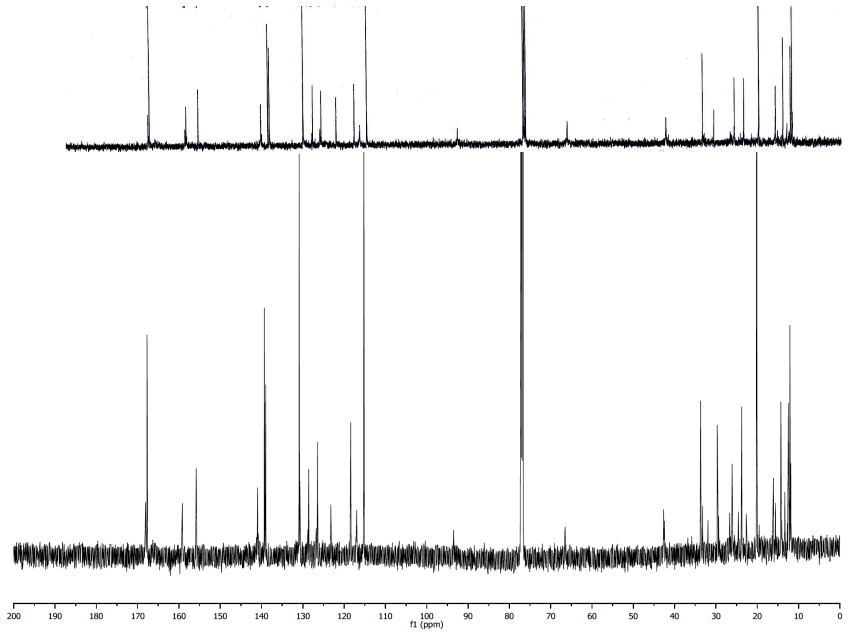
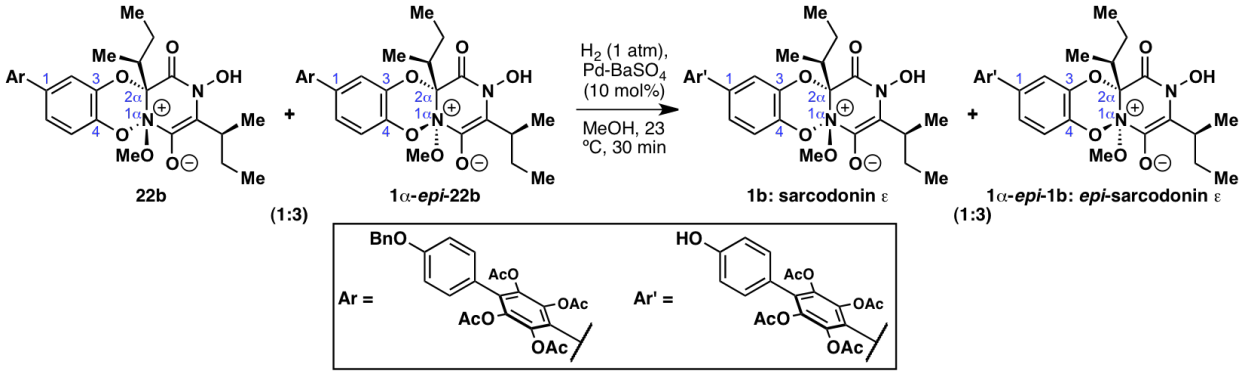


Figure S2. Overlaid ^{13}C NMR spectra of synthetic phellodonin (**1a**, albeit as a mixture of **1a** and **1β-*epi*-1a**) from this manuscript (lower spectrum, $CDCl_3$, 151 MHz) with that of the natural sample isolated by Fang *et al.* (upper spectrum inset, $CDCl_3$, 100 MHz).

Debenzylation of the mixture of 22b and 1α-*epi*-22b by hydrogenation to give sarcodonin ε (1b) and *epi*- sarcodonin ε (1α-*epi*-1b)



The flask containing a suspension of the mixture of **22b** and **1α-*epi*-22b** (20 mg, 0.023 mmol) and Pd-$BaSO_4$ (5 wt%, 48 mg, 0.0023 mmol) in MeOH (3 ml) was purged with hydrogen gas (1 atm) three times. After stirring for 30 min under a balloon filled with hydrogen, the reaction mixture was filtered through Celite® and washed with EtOAc. The filtrate was concentrated *in vacuo*, and the residue was subjected to preparative TLC to afford a ~2:1 mixture of sarcodonin ε (**1b**) and *epi*-sarcodonin ε (**1α-*epi*-1b**) as a white solid (15 mg, 84%).

Data for the 1:3 mixture of **1b** and **1α-*epi*-1b**:

Physical state: White amorphous solid.

TLC: R_f = 0.18 (1:1 EtOAc:hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.32 (br, 1H), 7.15–7.10 (m, 3H), 7.05–6.93 (m, 1H), 6.94 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.48 (br, 1H), 3.94 (s, 3H), 3.10 (q, *J* = 6.6 Hz, 0.3 H), 3.00 (q, *J* = 6.6 Hz, 0.7H), 2.48–2.35 (m, 1H), 2.20–2.09 (m, 1H), 1.99 (s, 6H), 1.96 (s, 6H), 1.91–1.76 (m, 1H), 1.68–1.54 (m, 1H), 1.43–1.31 (m, 1H), 1.29 (d, *J* = 4.2 Hz, 1H), 1.20 (d, *J* = 6.6 Hz, 1H), 1.09–1.05 (m, 3H), 1.02 (t, *J* = 7.2 Hz, 2H), 0.98 (t, *J* = 7.8 Hz, 1H), 0.90 (t, *J* = 7.2 Hz, 2H), 0.85 (t, *J* = 7.2 Hz, 1H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.3, 167.8, 166.4, 159.3, 159.0, 156.1, 141.3, 140.8, 139.3, 139.0, 130.9, 130.8, 128.7, 127.9, 125.1, 122.8, 118.4, 117.0, 115.3, 92.4, 67.2, 42.5, 33.8, 33.2, 26.8, 25.9, 24.5, 23.6, 20.1, 20.0, 16.2, 15.5, 14.1, 13.2, 12.7, 12.3, 12.1, 11.9 ppm.

IR (neat): $\tilde{\nu}$ = 3428, 2968, 2930, 2877, 1781, 1677, 1608, 1520, 1458, 1370, 1187, 1103, 1025, 910, 868, 830 cm^{-1}.

HRMS (ESI-TOF): calc'd for $C_{39}H_{42}N_2O_{15}$ [M + H^+] 779.2658, found 779.2644.

Optical rotation of the mixture: $[\alpha]_D^{20}$ (c 0.4, $CHCl_3$) = +42.0°.

Table S2. Comparison of NMR data for synthetic and natural sarcodonin ε (**1b**). Data for the natural sample is reproduced from Masabuti *et al.*, *Org. Lett.* **2013**, *15*, the manuscript preceding this manuscript in the same issue.

H or C numbering	Synthetic sarcodonin ε (**1b**)		Natural sarcodonin ε (**1b**)	
	δ_H (multiplicity, *J* in Hz)	δ_C	δ_H (multiplicity, *J* in Hz)	δ_C
1	---	127.9	---	128.0
2	6.94 (s)	118.4	6.95 (d, 1.8)	118.5
3	---	140.8	---	140.8
4	---	141.3	---	141.6
5	7.13 (m)	117.0	7.13 (d, 8.3)	117.0
6	7.00 (m)	125.1	7.02 (dd, 8.3, 1.8)	125.1
1'	---	128.7	---	128.8
2', 6'	---	139.0	---	139.1
3', 5'	---	139.3	---	139.4
4'	---	130.8	---	130.9
1"	---	122.8	---	123.1
2",6"	7.14 (m)	130.9	7.16 (d, 8.6)	130.9
3",5"	6.83 (d, 8.4)	115.3	6.84 (d, 8.6)	115.3
4"	---	156.1	---	156.0
2α	---	159.0	---	159.1
3α	---	166.4	---	166.4
4α	3.10 (q, 6.6)	33.2	3.11 (m)	33.3
5α	1.40 (m), 1.60 (m)	26.8	1.42 (m), 1.59 (m)	26.8
6α	0.85 (t, 7.2)	11.9	0.87 (t, 7.5)	11.9
7α	1.07 (m)	15.5	1.07 (d, 7.1)	15.5
2β	---	92.4	---	92.9
3β	---	159.3	---	159.3

4β	2.40 (m)	42.5	2.41 (m)	42.5
5β	1.80 (m), 1.62 (m)	24.5	1.61 (m), 1.79 (m)	24.6
6β	0.98 (t, 7.8)	12.7	0.99 (t, 7.5)	12.7
7β	1.20 (d, 6.6)	13.2	1.21 (d, 6.9)	13.3
2'/6'-OAc	1.99 (s)[a]	20.1	1.99 (s)[a']	20.1
	---	168.3[b]	---	168.2[b']
3'/5'-OAc	1.96 (s)[a]	20.0	1.96 (s)[a']	20.1
	---	167.8[b]	---	167.7[b']
1β-OMe	3.94 (s)	67.2	3.95 (s)	67.0
3α-OH	8.32 (br s)	---	7.92 (br s)	---
4''-OH	6.48 (br s)	---	6.02 (br s)	---

[a b a' b'] denote interchangeable values

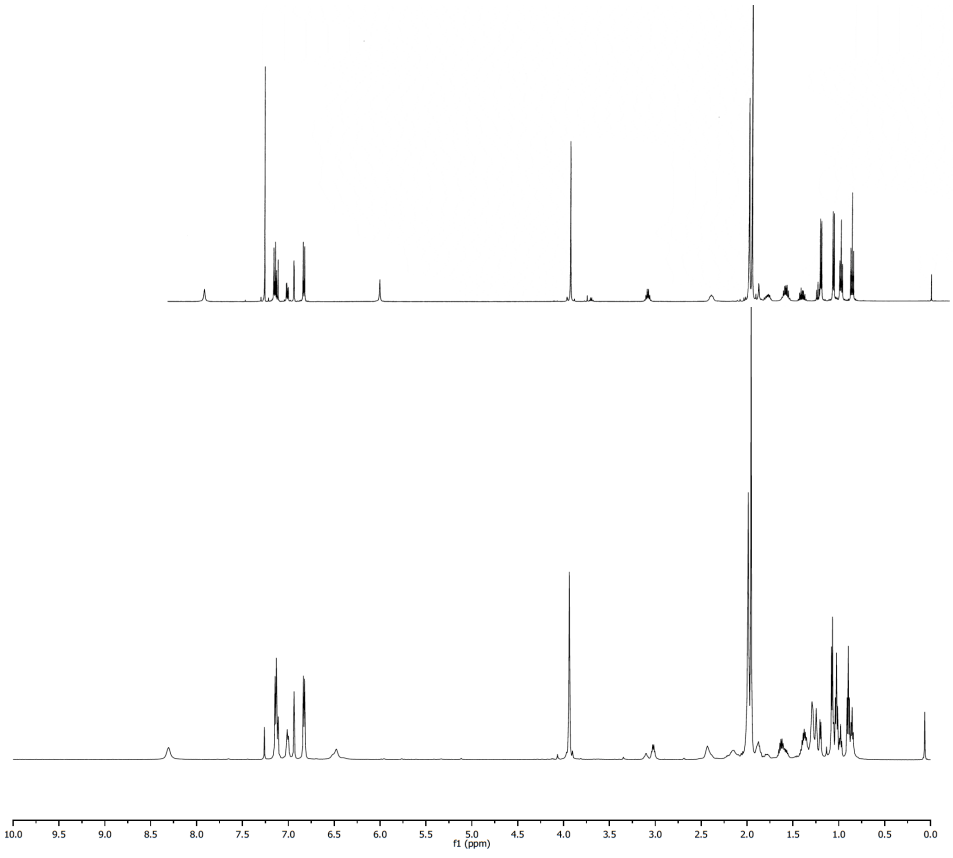


Figure S3. Overlaid ^{1}H NMR spectra of synthetic sarcodonin ε (**1b**, albeit as a mixture of **1b** and **1α-*epi*-1b**) from this manuscript (lower spectrum, $CDCl_3$, 600 MHz) with that of the natural sample isolated by Masabuti *et al.* (upper spectrum inset, $CDCl_3$, 500 MHz).

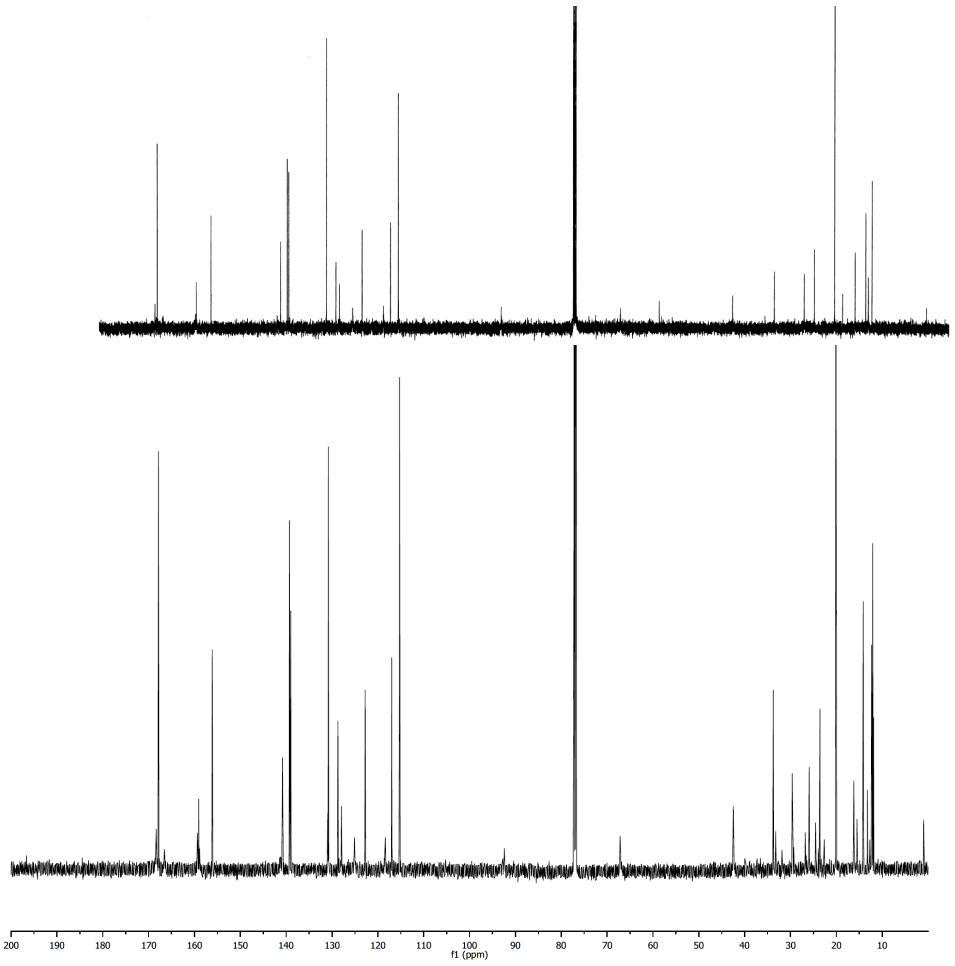


Figure S4. Overlaid ^{13}C NMR spectra of synthetic sarcodonin ε (**1b**, albeit as a mixture of **1b** and **1α-*epi*-1b**) from this manuscript (lower spectrum, $CDCl_3$, 151 MHz) with that of the natural sample isolated by Masabuti *et al.* (upper spectrum inset, $CDCl_3$, 125 MHz).