Studies Towards the Synthesis of Oximidines I and II

(Supporting Information)

Torsten Haack,[§] Serdar Kurtkaya,[†] James P. Snyder,^{†*} and Gunda I. Georg^{§*}

[§]Department of Medicinal Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, KS 66045-7582, USA; [†]Department of Chemistry, Emory University, 1515 Pierce Drive, Atlanta, GA 30322, USA

General remarks :

¹H NMR and ¹³C spectra were determined on a 400 MHz NMR. Mass spectra were obtained from a ZAB HS mass spectrometer equipped with an 11/250 data system. Fast atom bombardment mass spectrometry (FABMS) experiments were performed with a Xenon gun operated at 8 KeV energy and 0.8 mA emission. Fast atom bombardment high resolution mass spectra (FAB HRMS) were recorded at 1 : 10,000 resolution using linear voltage scans under data system control and the data were collected in a multichannel analyzer mode. A FT-IR spectrometer was used to record infrared spectra. Optical rotations were obtained at room temperature. Melting points are uncorrected. THF was dried by distillation from sodium/benzophenone. Methylene chloride was dried by distillation from calcium hydride. All other dry solvents and chemicals were obtained commercially. Tetrakis(triphenylphosphine)-palladium(0) was purchased from STREM chemicals. All reactions involving dry solvents were carried out under an argon atmosphere. Extractive workups were carried out using the solvents mentioned in the procedures and water (3 extractions). The combined organic layers were dried over magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure. Column chromatography was performed on silica gel (silica gel 60, 0.040-0.063 mm, 230-400 mesh ASTM) with the solvent systems indicated in the procedures.

4,4-Diethoxybut-2-ynoic Acid Methyl Ester (9).¹

To an ice-cooled solution of propionaldehyde diethylacetal (11.2 mL, 10 g, 78 mmol) in dry THF (30 mL) was added dropwise methylolithium (1.4 M in Et₂O, 61 mL, 86 mmol). When the addition was complete, the resulting mixture was added dropwise to a solution of methyl chloroformate (6.7 mL, 8.2 g, 87 mmol) in dry THF (30 mL) at -78 °C. The resulting mixture was allowed to reach room temperature and was then stirred at this temperature overnight. Extractive workup with ether followed by distillation (52 °C, 0.1 Torr) afforded 9.9 g (68%) of ester **9** as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 5.35 (s, 1H), 3.78 (s, 3H), 3.74 (dq, 2H, ³J = 7.1 Hz, ³J = 2.3 Hz), 3.61 (dq, 2H, ³J = 7.0

Hz, $^3J = 2.2$ Hz), 1.23 (t, 6H, $^3J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 153.3, 90.8, 81.4, 75.8, 61.5, 52.9, 14.9.

2-Diethoxymethyl-6-methoxybenzoic Acid Methyl Ester (11).¹

A mixture of alkyne **9** (573 mg, 3.08 mmol) and 1-methoxy-1,4-cyclohexadiene (6.0 g, 54.4 mmol) was heated at 170 °C under reflux overnight. The resulting mixture was directly subjected to column chromatography (EtOAc/hexanes 2:8) to give 665 mg (80%) of compound **11** as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.35 (t, 1H, $^3J = 8.0$ Hz), 7.22 (d, 1H, $^3J = 7.8$ Hz), 6.90 (d, 1H, $^3J = 7.1$ Hz), 5.65 (s, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.49-3.59 (m, 4H), 1.21 (t, 6H, $^3J = 7.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 168.3, 156.4, 138.0, 130.2, 122.2, 118.8, 111.1, 99.0, 61.2, 56.0, 52.2, 15.0.

3-Hydroxy-7-methoxy-3H-isobenzofuran-1-one (12).¹

Compound **11** (463 mg, 1.73 mmol) was heated in a mixture of AcOH (2 mL) and 2N HCl (2 mL) at reflux temperature overnight. Extractive workup with ethyl acetate and recrystallization from water furnished 188 mg (61%) of **12** as colorless needles.

2-(2-Iodovinyl)-6-methoxybenzoic Acid 4-Methoxybenzyl Ester (13).

A mixture of **12** (970 mg, 5.38 mmol), *p*-methoxybenzyl chloride (1.1 mL, 1.27 g, 8.1 mmol) and diisopropylethylamine (1.4 mL, 1.04 g, 8.1 mmol) in dry DMF (10 mL) was heated at 100 °C overnight. Extractive workup of the resulting mixture with ether gave the crude aldehyde which was dissolved together with iodoform (4.24 g, 10.8 mmol) in dry THF (10 mL). This solution was added dropwise to an ice-cooled suspension of chromium(II)-chloride (3.97 g, 32.3 mmol) in dry THF (30 mL). The resulting red mixture was stirred at 0 °C for 5 h and after this time it was quenched with water. Extractive workup with ether and column chromatography (EtOAc/hexanes 2:8, slower moving spot) yielded 1.24 g (54%) of compound **13** as a slightly yellow oil and 0.31 g

(14%) of its *cis*-isomer (faster moving spot) as a slightly yellow oil: IR (neat) 2957, 2836, 1727, 1515, 1471, 1270, 1247, 1110, 1065, 827, 762 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.40 (d, 2H, $^3J = 8.5$ Hz), 7.28 (d, 1H, $^3J = 14.7$ Hz), 7.28 (t, 1H, $^3J = 6.4$ Hz), 6.95 (d, 1H, $^3J = 7.9$ Hz), 6.93 (d, 2H, $^3J = 8.6$ Hz), 6.84 (d, 1H, $^3J = 8.3$ Hz), 6.80 (d, 1H, $^3J = 14.8$ Hz), 5.32 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.2, 159.6, 156.4, 141.4, 136.2, 130.5, 130.4, 127.5, 121.6, 117.7, 114.0, 110.6, 80.2, 67.1, 55.9, 55.2; HRMS (FAB+) calcd for $\text{C}_{18}\text{H}_{17}\text{O}_4\text{I}+\text{H}$ 425.0259 found 425.0263.

(1*S*,4*S*)-2,2-Dimethylpropionic Acid 1-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3,3-bis-ethylsulfanylpropyl Ester.

A mixture of **15**^{2,3} (12.9 g, 46 mmol), pivaloyl chloride (18 mL, 17.6 g, 146 mmol), triethylamine (20 mL, 14.5 g, 143 mmol) and DMAP (500 mg, 4 mmol) in dry methylene chloride (100 mL) was heated at reflux temperature for 16 h. After cooling to room temperature the mixture was neutralized with sat. K_2CO_3 . Extractive workup with ether and column chromatography (EtOAc/hexanes 2:8) afforded 15.1 g (90%) of the pivaloate as a colorless oil: $[\alpha]_D -10.9$ (c 1.3, CHCl_3); IR (neat) 2972, 2931, 2873, 1730, 1370, 1281, 1156, 1065, 974, 856 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 5.27 (ddd, 1H, $^3J = 8.7$ Hz, $^3J = 3.9$ Hz, $^3J = 3.9$ Hz), 4.20-4.24 (m, 1H), 3.97 (dd, 1H, $^3J = 8.6$ Hz, $^3J = 6.8$ Hz), 3.78 (dd, 1H, $^3J = 9.4$ Hz, $^3J = 5.5$ Hz), 3.70 (dd, 1H, $^3J = 8.6$ Hz, $^3J = 5.9$ Hz), 2.52-2.72 (m, 4H), 2.20 (ddd, 1H, $^2J = 14.5$ Hz, $^3J = 8.8$ Hz, $^3J = 5.5$ Hz), 2.04 (ddd, 1H, $^2J = 14.5$ Hz, $^3J = 9.4$ Hz, $^3J = 4.0$ Hz), 1.42 (s, 3H), 1.31 (s, 3H), 1.24 (t, 3H, $^3J = 7.4$ Hz), 1.24 (t, 3H, $^3J = 7.4$ Hz), 1.21 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 177.9, 109.4, 75.9, 70.4, 65.2, 47.3, 38.9, 36.9, 27.1, 26.2, 25.1, 24.0, 23.9, 14.3, 14.3; HRMS (ES+) calcd for $\text{C}_{17}\text{H}_{32}\text{O}_4\text{S}_2+\text{NH}_4$ 382.2086 found 382.2110.

(1*S*,2*S*)-2,2-Dimethylpropionic Acid 1-(2,2-Bis-ethylsulfanylethyl)-2,3-dihydroxypropyl Ester (16).

(1*S*,4*S*)-2,2-Dimethylpropionic acid 1-(2,2-dimethyl-[1,3]dioxolan-4-yl)-3,3-bis-ethylsulfanylpropyl ester (155 mg, 0.43 mmol) was dissolved in 70% acetic acid (8 mL) and the solution was kept at room temperature overnight. After neutralization with sat. K_2CO_3 the compound was extracted with ether. Column chromatography (EtOAc/hexanes 1:1) gave 122 mg (88%) of the desired diol **16** as a colorless oil: $[\alpha]_D -4.2$ (c 1.4, CHCl_3); IR (neat) 3428, 2969, 2929, 2872, 1731, 1480, 1456, 1283, 1156, 1036, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 5.26 (ddd, 1H, $^3J = 9.0\text{ Hz}$, $^3J = 3.8\text{ Hz}$, $^3J = 3.8\text{ Hz}$), 3.70-3.80 (m, 2H), 3.44-3.55 (m, 2H), 2.70-2.80 (m, 2H), 2.53-2.70 (m, 4H), 2.26 (ddd, 1H, $^2J = 14.4\text{ Hz}$, $^3J = 9.2\text{ Hz}$, $^3J = 5.2\text{ Hz}$), 2.06 (ddd, 1H, $^2J = 14.2\text{ Hz}$, $^3J = 9.7\text{ Hz}$, $^3J = 4.1\text{ Hz}$), 1.23 (t, 3H, $^3J = 7.4\text{ Hz}$), 1.22 (t, 3H, $^3J = 7.4\text{ Hz}$), 1.21 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ 178.9, 72.9, 71.8, 63.2, 47.2, 39.0, 36.8, 27.1, 24.1, 23.7, 14.4, 14.3; HRMS (FAB+) calcd for $\text{C}_{14}\text{H}_{28}\text{O}_4\text{S}_2$ (M^+) 324.1429 found 324.1426.

(1*S*,2*S*)-2,2-Dimethylpropionic Acid 1-(2,2-Bis-ethylsulfanylethyl)-3-*tert*-butyldimethylsilyloxy)-2-hydroxypropyl Ester.

To a solution of **16** (4.69 g, 14.4 mmol) and imidazole (1.46 g, 21.4 mmol) in dry DMF (5 mL) was added *tert*-butyldimethylsilyl chloride (2.45 g, 16.3 mmol) and the mixture was stirred for 1 h after which time water was added. Extractive workup with ether followed by column chromatography (EtOAc/hexanes 1:9) afforded 5.36 g (85%) of the desired TBS-ether as a colorless oil. IR (neat) 3500, 2929, 1731, 1463, 1282, 1257, 1156, 838, 777, 669 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 5.29 (ddd, 1H, $^3J = 8.5\text{ Hz}$, $^3J = 4.4\text{ Hz}$, $^3J = 4.4\text{ Hz}$), 3.80 (dd, 1H, $^3J = 8.9\text{ Hz}$, $^3J = 5.9\text{ Hz}$), 3.69-3.75 (m, 1H), 3.64 (dd, 1H, $^3J = 10.2\text{ Hz}$, $^3J = 4.0\text{ Hz}$), (dd, 1H, $^3J = 10.0\text{ Hz}$, $^3J = 6.9\text{ Hz}$), 2.53-2.72 (m, 4H), 2.45 (d, 1H, $^3J = 4.8\text{ Hz}$), 2.08-2.22 (m, 2H), 1.20-1.25 (m, 6H), 1.20 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 177.9, 72.6, 71.3, 63.8, 47.3, 38.9, 36.7, 27.2, 25.8, 24.0, 23.9, 18.2, 14.3, 14.3, -5.5, -5.5; HRMS (FAB+) calcd for $\text{C}_{20}\text{H}_{42}\text{O}_4\text{S}_2\text{Si} + \text{NH}_4$ 456.2638 found 456.2660.

(1*S*,2*S*)-2,2-Dimethylpropionic Acid 1-(2,2-Bis-ethylsulfanylethyl)-3-hydroxy-2-methoxymethoxypropyl Ester (17).

S5

(1*S*,2*R*)-2,2-Dimethylpropionic Acid 1-(2,2-Bis-ethylsulfanylethyl)-2-methoxymethoxy-3-oxopropyl Ester.

To a solution of alcohol **17** (4.00 g, 10.9 mmol) and pyridine (3 mL) in methylene chloride (100 mL) was added freshly prepared Dess-Martin-periodinane (9.00 g, 21 mmol) in one portion and the resulting solution was stirred at room temperature for 10 min. The reaction was immediately monitored by TLC. When the starting material was consumed (10 min) the mixture was treated with a 1:1 mixture of sat. NaHCO₃/sat. NaS₂O₃ (100 mL) and then neutralized with sat. NaHCO₃. After further 10 min of stirring the mixture was extracted with ether. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude and very unstable aldehyde was directly used in the next step without any purification.

(1*S*,2*S*)-2,2-Dimethylpropionic Acid 1-(2,2-Bis-ethylsulfanylethyl)-4,4-dibromo-2-methoxymethoxybut-3-enyl Ester.

To an ice-cooled solution of carbon tetrabromide (10.0 g, 30 mmol) in dry methylene chloride (100 mL) was added triphenylphosphine (16.0 g, 61 mmol) and the resulting orange solution was stirred in an ice-bath for 30 min. The crude aldehyde prepared in the previous step in dry methylene chloride (20 mL) was added in one portion at the same temperature. The mixture turned deep red. After stirring at 0 °C for 10 min the reaction was quenched with water. Extractive workup with ether and column chromatography (EtOAc/hexanes 5:95) gave 4.3 g (75%) of the desired dibromide as a slightly yellow oil. $[\alpha]_D^{25} +24.2$ (c 0.9, CHCl₃); IR (neat) 2968, 2929, 1733, 1279, 1150, 1101, 1082 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.37 (d, 1H, ³J = 9.0 Hz), 5.30 (ddd, 1H, ³J = 9.2 Hz, ³J = 4.7 Hz, ³J = 4.7 Hz), 4.64 (d, 1H, ²J = 6.7 Hz), 4.57 (d, 1H, ²J = 6.7 Hz), 4.52 (dd, 1H, ³J = 9.0 Hz, 4.7 Hz), 3.79 (dd, 1H, ³J = 8.9 Hz, ³J = 6.1 Hz), 3.38 (s, 3H), 2.51-2.70 (m, 4H), 2.06-2.15 (m, 2H), 1.21-1.28 (m, 6H), 1.21 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 177.4, 134.7, 94.7, 94.1, 75.6, 71.6, 56.0, 47.3, 38.9, 35.8, 27.1, 23.9, 23.7, 14.4, 14.3; HRMS (ES⁺) calcd for C₁₇H₃₀O₄S₂Br₂+NH₄ 538.0296 found 538.0303.

(3Z)-(1S,2S)-2,2-Dimethylpropionic Acid 1-(2,2-Bis-ethylsulfanylethyl)-4-bromo-2-methoxymethoxybut-3-enyl Ester (18).

To a solution of (1S,2S)-2,2-dimethylpropionic acid 1-(2,2-bis-ethylsulfanylethyl)-4,4-dibromo-2-methoxymethoxybut-3-enyl ester (5.05 g, 9.67 mmol) in dry benzene (100 mL) was added palladium-tetrakis(triphenylphosphine) (360 mg, 0.3 mmol) and subsequently dropwise charged with tributyltin hydride (4.4 mL, 4.76 g, 16 mmol). After stirring at room temperature for 2 h the solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc/hexanes 5:95) to give 4.09 g (95%) of the bromide **18** as a colorless oil. $[\alpha]_D^{25} +35.3$ (c 0.8, CHCl_3); IR (neat) 2968, 2929, 1732, 1479, 1280, 1150, 1101, 1030, 920, 734 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 6.46 (d, 1H, $^3J = 7.3$ Hz), 6.06 (dd, 1H, $^3J = 8.9$ Hz, $^3J = 7.4$ Hz), 5.29-5.34 (m, 1H), 4.74 (dd, 1H, $^3J = 8.9$ Hz, $^3J = 4.9$ Hz), 4.62 (d, 1H, $^2J = 6.7$ Hz), 4.56 (d, 1H, $^2J = 6.7$ Hz), 3.78 (t, 1H, $^3J = 7.7$ Hz), 3.37 (s, 3H), 2.53-2.69 (m, 4H), 2.09–2.15 (m, 2H), 1.20-1.25 (m, 6H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 177.5, 131.0, 112.6, 94.7, 73.5, 71.9, 55.9, 47.3, 38.8, 36.2, 27.2, 24.0, 23.7, 14.4, 14.3. HRMS (ES⁺) calcd for $\text{C}_{17}\text{H}_{31}\text{O}_4\text{S}_2\text{Br} + \text{NH}_4$ 460.1191 found 460.1204.

(5Z)-(3S,4S)-6-Bromo-1,1-bis-ethylsulfanyl-4-methoxymethoxyhex-5-en-3-ol.

To a solution of **18** (4.09 g, 9.2 mmol) in dry methylene chloride (50 mL) was added dropwise at room temperature a solution of diisopropylaluminum hydride in THF (1M, 28 mL, 28 mmol). The solution was stirred for 1 h and then quenched with methanol and treated with sat. potassium sodium tartrate solution. Extractive workup with ether and column chromatography (EtOAc/hexanes 2:8) afforded 2.88 g (87%) of the desired alcohol as a colorless oil: $[\alpha]_D^{25} +57.8$ (c 0.8, CHCl_3); IR (neat) 3461, 2963, 2926, 1622, 1449, 1263, 1151, 1100, 1024, 922, 726 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 6.47 (d, 1H, $^3J = 7.3$ Hz), 6.11 (t, 1H, $^3J = 7.6$ Hz), 4.67 (d, 1H, $^2J = 6.6$ Hz), 4.58 (d, 1H, $^2J = 6.7$ Hz), 4.42 (dd, 1H, $^3J = 8.4$ Hz, $^3J = 6.4$ Hz), 4.06 (dd, 1H, $^3J = 10.4$ Hz, $^3J = 4.1$ Hz), 3.97-4.00 (m, 1H), 3.38 (s, 3H), 2.78 (s, br, 1H), 2.49-2.69 (m, 4H), 2.02-2.09 (m, 1H), 1.78-1.85 (m, 1H), 1.21-1.26 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 131.9, 112.5, 94.8, 77.4, 70.7, 55.9, 47.8, 39.1, 24.3, 23.8, 14.5, 14.4. HRMS (ES⁺) calcd for $\text{C}_{12}\text{H}_{23}\text{O}_3\text{S}_2\text{Br} + \text{NH}_4$ 376.0616 found 376.0607.

(5Z)-(3S,4S)-1,1-Bis-ethylsulfanyl-4-methoxymethoxy-8-(trimethylsilanyl)-oct-5-en-7-yn-3-ol.

A solution of (3*S*,4*S*,5*Z*)-6-bromo-1,1-bis-ethylsulfanyl-4-methoxymethoxyhex-5-en-3-ol (480 mg, 1.34 mmol) in degassed diethylamine (2 mL) was charged with palladium-tetrakis(triphenylphosphine) (77 mg, 0.067 mmol) and stirred at room temperature for 30 min. Trimethylsilylacetylene (750 μ L, 0.52 mg, 5.31 mmol) was added followed by copper(I)-iodide (25 mg, 0.13 mmol) and the resulting mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was purified twice by column chromatography (EtOAc/hexanes 2:8) to give 432 mg (84%) of the alkyne as a slightly yellow oil. $[\alpha]_D^{+77.1}$ (c 1.4, CHCl₃); IR (neat) 3473, 2961, 2927, 2149, 1450, 1396, 1250, 1152, 1099, 1027, 845, 760; ¹H NMR (400 MHz, CDCl₃): δ 5.82 (dd, 1H, ³*J* = 11.0 Hz, ³*J* = 9.0 Hz), 5.72 (d, 1H, ³*J* = 11.1 Hz), 4.67 (d, 1H, ²*J* = 6.6 Hz), 4.58 (d, 1H, ²*J* = 6.5 Hz), 4.43 (dd, 1H, ³*J* = 8.9 Hz, ³*J* = 6.8 Hz), 4.07 (dd, 1H, ³*J* = 10.7 Hz, ³*J* = 3.9 Hz), 3.91-3.97 (m, 1H), 3.36 (s, 3H), 2.83 (d, 1H, ³*J* = 2.8 Hz), 2.52-2.69 (m, 4H), 1.99-2.03 (m, 1H), 1.80-1.85 (m, 1H), 1.22 (t, 3H, ³*J* = 7.5 Hz), 1.22 (t, 3H, ³*J* = 7.4 Hz), 0.16 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 140.2, 114.2, 101.2, 100.5, 94.9, 78.0, 70.8, 55.8, 47.8, 39.1, 24.2, 23.7, 14.4, 14.4, -0.3; HRMS (ES⁺) calcd for C₁₇H₃₂O₃S₂Si (M⁺) 376.1562 found 376.1573.

(5Z)-(3S,4S)-1,1-Bis-ethylsulfanyl-4-methoxymethoxyoct-5-en-7-yn-3-ol (19).

To a solution of (3*S*,4*S*,5*Z*)-1,1-bis-ethylsulfanyl-4-methoxymethoxy-8-(trimethylsilyl)-oct-5-en-7-yn-3-ol (423 mg, 1.12 mmol) in methanol (5 mL) was added potassium carbonate (310 mg, 2.2 mmol) and the resulting slurry was stirred at room temperature for 2 h. Extractive workup of the resulting mixture with ether followed by column chromatography (EtOAc/hexanes 2:8) furnished 330 mg (96%) of enyne **19** as a slightly yellow colored oil. $[\alpha]_D^{+76.8}$ (c 0.8, CHCl₃); IR (neat) 3471, 3286, 2963, 2927, 1450, 1264, 1151, 1099, 1027, 921, 637 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.92 (t, 1H, ³*J* = 10.1 Hz), 5.74 (dd, 1H, ³*J* = 11.1 Hz, ⁴*J* = 2.3 Hz), 4.71 (d, 1H, ²*J* = 6.6 Hz),

4.60 (d, 1H, $^2J = 6.6$ Hz), 4.48 (dd, 1H, $^3J = 9.2$ Hz, $^3J = 6.5$ Hz), 4.09 (dd, 1H, $^3J = 10.5$ Hz, $^3J = 4.2$ Hz), 3.97-4.01 (m, 1H), 3.39 (s, 3H), 3.16 (d, 1H, $^4J = 2.3$ Hz), 2.76 (d, 1H, $^3J = 4.0$ Hz), 2.55-2.70 (m, 4H), 2.05 (ddd, 1H, $^2J = 14.4$ Hz, $^3J = 10.1$ Hz, $^3J = 4.2$ Hz), 1.84 (ddd, 1H, $^2J = 13.5$ Hz, $^3J = 10.7$ Hz, $^3J = 2.1$ Hz), 1.25 (t, 3H, $^3J = 7.4$ Hz), 1.25 (t, $^3J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 141.0, 113.2, 94.9, 83.4, 79.1, 77.8, 71.0, 56.0, 47.9, 39.1, 24.4, 23.8, 14.5, 14.5. HRMS (ES+) calcd for $\text{C}_{14}\text{H}_{24}\text{O}_3\text{S}_2 + \text{NH}_4$ 322.1511 found 322.1521.

(1E)-2-(2-Iodovinyl)-6-methoxybenzoic Acid (20).

Ester **13** (100 mg, 0.24 mmol) was dissolved in methylene chloride (1 mL). Trifluoroacetic acid (80 μL , 118 mg, 1 mmol) was added and the solution was stirred at room temperature for 1 h after which time ether was added and the organic phase was three times extracted with sat. NaHCO_3 . The aqueous layer was acidified and extractive workup with ether gave 55 mg (77%) of crude acid **20** as a gum which solidified within a few days: mp 92-95°C; IR (KBr) 3061, 2929, 2620, 1723, 1471, 1272, 1065, 937, 809, 760, 696, 619 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.60 (s, br, 1H), 7.74 (d, 1H, $^3J = 14.6$ Hz), 7.41 (t, 1H, $^3J = 8.0$ Hz), 7.07 (d, 1H, $^3J = 7.7$ Hz), 6.96 (d, 1H, $^3J = 8.2$ Hz), 6.90 (d, 1H, $^3J = 14.7$ Hz), 3.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 170.9, 156.9, 124.1, 138.1, 131.7, 122.7, 118.9, 111.0, 80.3, 56.4; HRMS (ES+) calcd for $\text{C}_{10}\text{H}_9\text{O}_3\text{I} + \text{H}$ 304.9675 found 304.9652.

(1E,3Z)-(1S,2S)-2-(2-Iodovinyl)-6-methoxybenzoic Acid 1-(2,2-Bis-ethylsulfanylethyl)-2-methoxymethoxyhex-3-en-5-ynyl Ester (1).

To a solution of acid **20** (300 mg, 987 μmol) in dry methylene chloride (4 mL) was at room temperature subsequently added triethylamine (138 μL , 100 mg, 988 μmol) and 2,4,6-trichlorobenzoyl chloride (156 μL , 244 mg, 1 mmol). The resulting mixture was stirred for 3 h after which time it was filtered and added to a solution of alkyne **19** (110 mg, 361 μmol) and dimethylaminopyridine (240 mg, 2 mmol) in dry toluene (6 mL) at 90 °C. The resulting mixture was stirred at this temperature overnight. Extractive workup with ether followed by column chromatography (EtOAc/hexanes 1:9) afforded 81 mg (38%) of ester **1** as a yellow oil: $[\alpha]_D +29.6$ (c 1.8, CHCl_3); IR (neat) 3285, 3061, 2964, 2927, 2098, 1732, 1602, 1591, 1571, 1471, 1270, 1151, 1115, 1067, 1028, 947,

763, 625 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.46 (d, 1H, $^3J = 14.9$ Hz), 7.26 (t, 1H, $^3J = 8.1$ Hz), 6.97 (d, 1H, $^3J = 8.1$ Hz), 6.86 (d, 1H, $^3J = 14.8$ Hz), 6.81 (d, 1H, $^3J = 8.3$ Hz), 5.99 (t, 1H, $^3J = 10.0$ Hz), 5.82 (dd, 1H, $^3J = 11.0$ Hz, $^3J = 1.9$ Hz), 5.71 (ddd, 1H, $^3J = 3.6$ Hz, $^3J = 3.6$ Hz, $^3J = 8.5$ Hz), 4.79 (dd, 1H, $^3J = 5.1$ Hz, $^3J = 8.9$ Hz), 4.69 (d, 1H, $^2J = 6.8$ Hz), 4.60 (d, 1H, $^2J = 6.8$ Hz), 4.06 (dd, 1H, $^3J = 10.3$ Hz, $^3J = 4.6$ Hz), 3.79 (s, 3H), 3.33 (s, 3H), 3.18 (d, 1H, $^3J = 1.7$ Hz), 2.58-2.74 (m, 4H), 2.31 (ddd, 1H, $^2J = 14.3$ Hz, $^3J = 8.9$ Hz, $^3J = 4.7$ Hz), 2.10 (ddd, 1H, $^3J = 14.3$ Hz, $^3J = 10.3$ Hz, $^3J = 3.6$ Hz), 1.22-1.26 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 166.8, 156.1, 141.5, 140.5, 136.0, 130.5, 121.9, 117.6, 113.6, 110.6, 94.6, 84.0, 80.5, 78.9, 74.2, 74.0, 55.9, 55.8, 47.5, 37.5, 24.1, 23.7, 14.4, 14.4; HRMS (ES+) calcd for $\text{C}_{24}\text{H}_{31}\text{O}_5\text{S}_2 + \text{NH}_4$ 608.1001 found 608.0998.

(1Z,9Z)-(7S,8S)-7-(2,2-Bis-ethylsulfanylethyl)-4-methoxy-8-methoxymethoxy-8,9-dihydro-6-oxabenzocyclododeca-1,9-dien-11-ynone (3).

A mixture of ester **1** (54 mg, 91 μmol), copper(I)-iodide (2 mg, 11 μmol), triphenylphosphine (6 mg, 23 μmol) and K_2CO_3 (22 mg, 159 μmol) in dry DMF (20 mL) was heated at 110 $^\circ\text{C}$ for 26 h. Extractive workup with ether and column chromatography (EtOAc-hexanes 1:9) furnished 13 mg (31%) of macrocycle **3** as a colorless oil: $[\alpha]_D -156.3$ (c 0.2, CHCl_3); IR (neat) 2962, 2926, 2852, 1727, 1575, 1471, 1455, 1435, 1277, 1244, 1154, 1034, 972, 794 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.34 (t, 1H, $^3J = 8.0$ Hz), 6.87 (d, 1H, $^3J = 8.4$ Hz), 6.84 (d, 1H, $^3J = 12.0$ Hz), 6.78 (d, 1H, $^3J = 7.8$ Hz), 6.03 (dd, 1H, $^3J = 8.4$ Hz, $^3J = 10.5$ Hz), 5.86 (d, 1H, $^3J = 11.9$ Hz), 5.67 (d, 1H, $^3J = 10.6$ Hz), 5.59 (ddd, 1H, $^3J = 10.7$ Hz, $^3J = 4.4$ Hz, $^3J = 1.8$ Hz), 5.29-5.32 (m, 1H), 4.73 (d, 1H, $^2J = 6.5$ Hz), 4.68 (d, 1H, $^2J = 6.5$ Hz), 4.32 (dd, 1H, $^3J = 11.7$ Hz, $^3J = 3.2$ Hz), 3.82 (s, 3H), 3.42 (s, 3H), 2.63-2.77 (m, 4H), 2.11-2.24 (m, 2H), 1.25-1.31 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.0, 158.0, 142.0, 138.7, 137.1, 130.9, 122.8, 121.5, 113.2, 111.1, 111.1, 95.8, 92.1, 91.5, 74.9, 72.8, 56.0, 55.8, 47.8, 34.2, 24.4, 22.7, 14.6, 14.5; HRMS (ES+) calcd for $\text{C}_{24}\text{H}_{30}\text{O}_5\text{S}_2 + \text{NH}_4$ 480.1878 found 480.1897.

³J(H,H) Coupling Constant Calculations

The predicted vicinal coupling constants (³J(H,H)) for structures **21**, **22**, **27** and **28** were obtained by calculating and summing the four individual Ramsey contributions (DSO, PSO, FC and SD; **Table S1**). In each case the MMFF global minimum geometry (see next section) was employed to obtain the vicinal coupling constant using the B3LYP/6-311G(d,p) model as previously described.⁴ Since the predicted ³J(H,H)'s are somewhat higher than the experimental values, we scaled the predictions by employing *cis*- and *trans*-acrylonitrile (geometry optimized with the B3LYP/6-311G(d,p) model) as standards. In this way, the values for **21** and **22** are reduced to 11.8 and 15.9 Hz, respectively, in complete accord with the experiment (**Table S1**).

Table S1. Ramsey contributions and ³J(H,H) total for C8-C9 with the DFT B3LYP/6-311G(d,p) model; Hz.

	DSO	PSO	FC	SD	Total	Exp ^a	Δ ³ J(H,H)
21	-0.002	-0.57	14.78	-0.052	14.2	"11.8"	
22	-2.74	3.02	19.72	0.39	20.4	"15.9"	
<i>cis</i> -CH ₂ =CHCN	-0.76	0.072	14.89	-0.043	14.2	11.8	-2.4
<i>trans</i> CH ₂ =CHCN	-3.30	4.77	20.56	0.33	22.4	17.9	-4.5
27	-2.84	3.05	19.64	0.40	20.2	"15.7"	
28	-2.81	4.39	19.67	0.40	21.7	"17.2"	

^a i) <http://chemistry.utah.edu/faculty/vogler/LectureNotes331/CH331Chapter13.pdf>; ii) Lambert, J. B.; Shurvell, H. F.; Lightner, D. A.; Cooks, R. G. In *Organic Structural Spectroscopy*; Prentice Hall, Englewood Cliffs, N.J., 1998, p 72.

To test whether the methoxy group in the aromatic ring might be responsible for the reduction of ³J(H,H) from 16 to 12 Hz in *trans*-**22**, the vicinal coupling constants for the truncated structures **27** (model for **22**) and **28** (model for **3**) at the same geometries as the full structures were calculated to be 20.2 and 21.7 Hz, respectively. Scaled by the value for *trans*-acrylonitrile, the latter fall to 15.7 and 17.2 Hz, respectively (**Table S1**). The experimental value of 16 Hz for *trans*-oxamidines is not only reproduced by the *J*-calculations; it is also unperturbed by the aromatic OMe substitution. Thus, we conclude that the accurately reproduced value of 12 Hz for the *cis*-structure, along with the

thermodynamic relationships captured by text **Table 2** and **Table S2** below, is fully supportive of *E* to *Z* rearrangement at C8-C9 during formation of **3**.

Energy Calculations

Structures **21-26** cited in **Tables 2** and **S2** were obtained by Monte Carlo conformational searching with the MMFF force field implemented in MacroModel6.5.⁵ Each structure was searched for 3000 steps with an 6.0 kcal/mol energy cap resulting in the number of conformations and number of times the global minima (glomin) were located cited in **Table S2**. That the conformational searches are complete is indicated by the large number of times the glomin were found (**Table S2**). Generally, 5-15 is sufficient to assure completeness.⁶ In each case the lowest energy structure was further subjected to single point energy calculations using the DFT and MP2 methods, B3LYP/6-311G(d,p)//MMFF and MP2/6-311G(d,p)//MMFF, respectively, in Gaussian 03.⁷ The absolute and relative energies are recorded in **Table S2**.

Table S2. Single point DFT and MP2 energies of annelated and unsaturated 12-membered ring lactones optimized with the MMFF force field.

	No. Confs	Glomin Found ^a	DFT, au ^b	$\Delta E(\text{rel})$, kcal ^c	MP2, Au ^d	$\Delta E(\text{rel})$, Kcal ^c
21	2	484	-729.365 592	0.0	-727.254 772	0.0
22	4	351	-729.342 626	14.4	-727.229 779	15.7
23	10	273	-730.589 678	0.0	-728.465 345	0.0
24	4	323	-730.577 734	7.5	-728.450 978	9.0
25	5	390	-730.604 175	2.6	-728.473 487	2.4
26	4	308	-730.608 372	0.0	-728.477 306	0.0

^aNumber of times global minimum located; ^bB3LYP/6-311G(d,p)//MMFF; ^cOnly global minima compared; ^dMP2/6-311G(d,p)//MMFF.

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