Supplemental Materials for:

Progress Toward the Synthesis of Garsubellin A and Related Phloroglucins: The Direct Diastereoselective Synthesis of the Bicyclo[3.3.1]nonane Core[‡]

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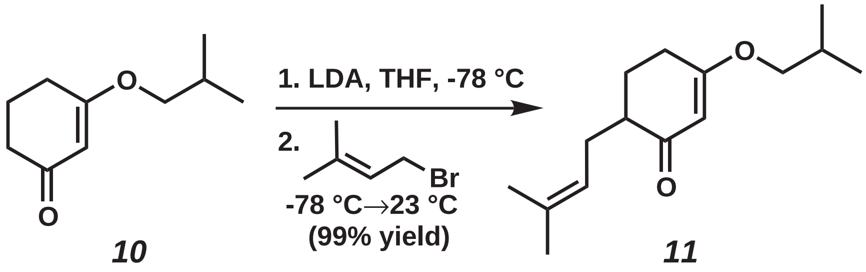
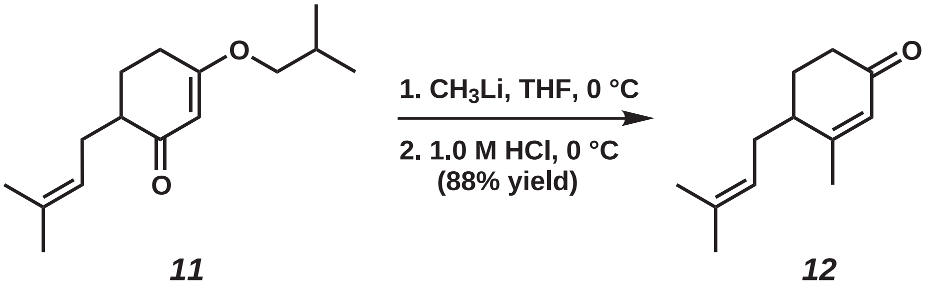
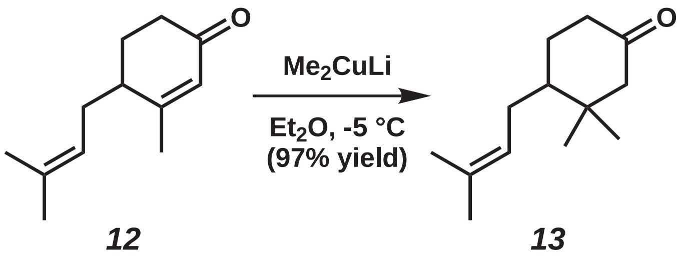
Material and Methods. Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen or an argon atmosphere, using freshly distilled solvents. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV or anisaldehyde staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) and are referenced to the chloroform-d peak (7.27 ppm and 77.00 ppm, respectively) relative to Me_4Si. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the UC Irvine Mass Spectral Facility.



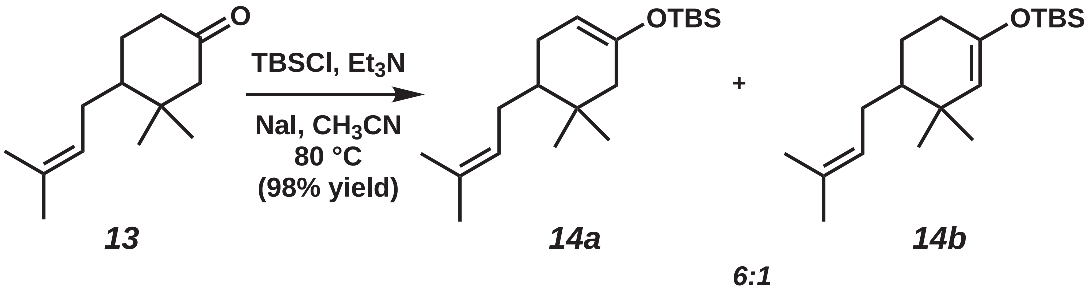
Cyclohexenone 11: To a –78 °C solution of LDA (31.21 mmol, 1.05 equiv) in dry THF (125 mL) was added a solution of 3-isobutoxy-2-cyclohexenone (**10**, 5.0 g, 29.73 mmol, 1.0 equiv) in dry THF (20 mL). The reaction mixture was warmed to 0 °C for 1 h, cooled to -78 °C and treated with prenyl bromide (3.60 mL, 30.32 mmol, 1.02 equiv) in a dropwise fashion to afford an orange solution. After stirring for 4 h at 23 °C, the reaction was quenched with saturated ammonium chloride solution (100 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to provide **11** as a brown oil (6.95 g, 99% yield) that was used without further purification. R_F = 0.5 (30% ethyl acetate in hexanes eluent); FTIR (thin film) 1657, 1609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (s, 1H), 5.10 (app.t, *J* = 6.6 Hz, 1H), 3.57 (d, *J* = 6.6 Hz, 2H), 2.55 (m, 1H), 2.41 (d, *J* = 5.0 Hz, 1H), 2.38 (d, *J* = 5.0 Hz, 1H), 1.97-2.15 (m, 4H), 1.70 (s, 3H), 1.64-1.76 (m, 1H), 1.61 (s, 3H), 0.96 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 177.0, 160.9, 133.2, 121.9, 102.3, 74.7, 45.6, 28.2, 28.1, 27.8, 25.9, 19.1, 17.9; HRMS (EI) m/z calcd for 236.1775, found 236.1776.



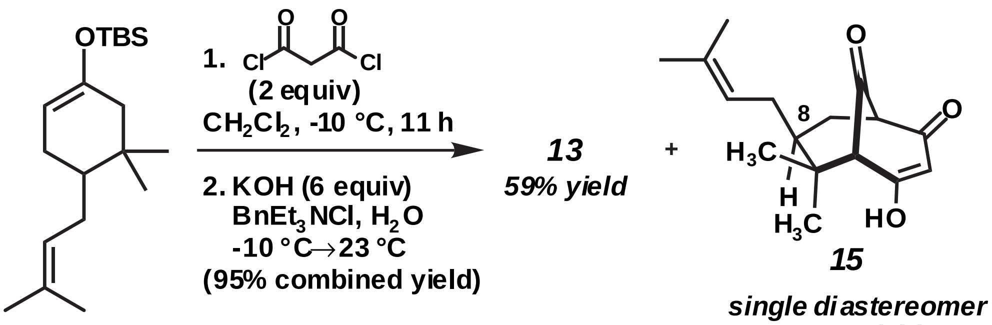
Enone 12: To a –5 °C solution of **11** (6.89 g, 29.18 mmol, 1.0 equiv) in dry THF (100 mL) was added methyl lithium (34 mL, 1.3 M in Et_2O, 43.77 mmol, 1.50 equiv). After stirring for 30 min at 23 °C, no starting material remained, as judged by TLC. The reaction mixture was cooled to 0 °C and treated slowly with 1.0 M HCl (73 mL, 73.0 mmol, 2.5 equiv). After stirring for another 30 min at 23 °C, the layers were separated and the aqueous layer extracted with Et_2O (2 x 100 mL). The combined organic layers were dried and concentrated to a yellow oil, which was purified by silica gel chromatography (10% ethyl acetate in hexanes eluent) to afford enone **12** as a yellow oil (4.67 g, 88% yield). R_F = 0.44 (30% ethyl acetate in hexanes eluent); FTIR (thin film) 1716, 1668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (s, 1H), 5.10 (m, 1H), 2.36-2.48 (m, 1H), 2.08-2.32 (m, 4H), 1.94-2.06 (m, 1H), 1.97 (s, 3H), 1.80-1.91 (m, 1H), 1.71 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 165.5, 133.8, 126.8, 121.7, 40.0, 34.1, 29.8, 26.5, 25.9, 23.1, 17.9; HRMS (EI) m/z calcd for 178.1436, found 178.1432.

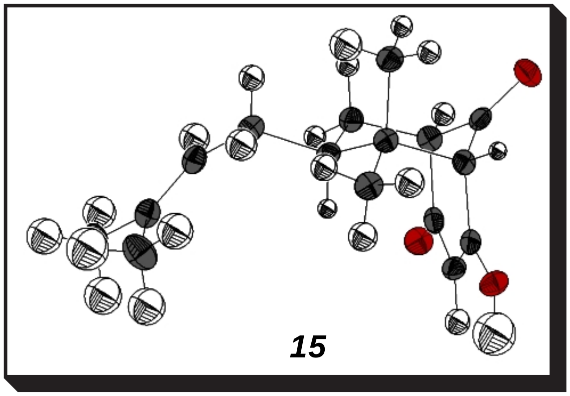


Dimethylcyclohexanone 13. To a -5 °C slurry of copper (I) iodide (9.83 g, 50.56 mmol, 2.0 equiv) in Et_2O (250 mL) was added dropwise methyl lithium (72.2 mL, 1.4 M solution in Et_2O, 101.12 mmol, 4.0 equiv). The resulting light tan solution stirred for 60 min at -5 °C before a solution of enone **12** (4.5 g, 25.28 mmol, 1.0 equiv) in Et_2O (100 mL) was added over 10 min via addition funnel. The bright yellow reaction mixture was stirred for an additional 10 min at -5 °C until all starting material appeared to be consumed by TLC. After quenching with saturated aqueous NH_4Cl/NH_4OH solution (250 mL), the layers were separated and the aqueous layer was extracted with Et_2O (2 x 250 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to a yellow oil, which was purified by passing through a silica gel plug (10% ethyl acetate in hexanes eluent) to afford ketone **13** (4.76 g, 97% yield) as a pale yellow oil. R_F = 0.56 (30% ethyl acetate in hexanes); FTIR (thin film) 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (app.t, *J* = 7.1 Hz, 1H), 2.20-2.40 (m, 4H), 1.97-2.17 (m, 2H), 1.79-1.65 (m, 1H), 1.72 (s, 3H), 1.62 (s, 3H), 1.56-1.39 (m, 2H), 1.06 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 132.5, 123.4, 56.0, 46.1, 41.0, 38.7, 29.9, 27.9, 27.7, 25.9, 20.8, 17.9; HRMS (EI) *m/z* calcd for 194.1665, found 194.1671.



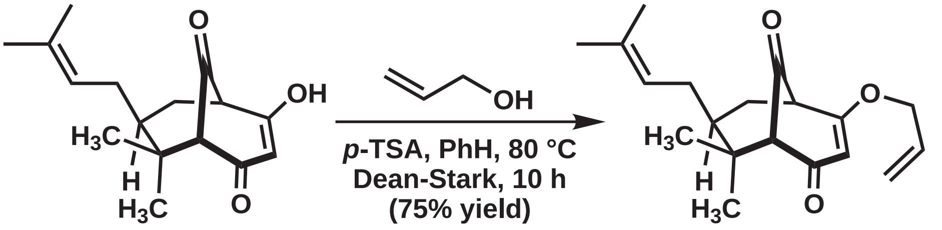
Silyl enol ethers 14a and 14b: A round bottomed flask (200 mL) was charged with ketone **13** (4.75 g, 24.48 mmol, 1.0 equiv) in dry acetonitrile (50 mL). Freshly distilled triethylamine (4.30 mL, 30.61 mmol, 1.25 equiv) was added, followed by *tert*-butyldimethylsilyl chloride (4.61 g, 30.61 mmol, 1.25 equiv) and sodium iodide (4.59 g, 30.61 mmol, 1.25 equiv). The reaction flask was topped with a condenser and heated to 80 °C for 1 h, then cooled to room temperature and concentrated to a brown solid. After trituration of the solid with pentane (100 mL) and concentration, a pale yellow oil was obtained. Purification by silica gel chromatography (1% ethyl acetate and 1% triethylamine in hexanes eluent) yielded **14a** and **14b** (7.40 g, 98% yield) as a mixture of two silyl enol ether isomers in a 6:1 ratio of **14a** to **14b**, as determined by ^1H NMR. Major isomer (**14a**): R_F = 0.71 (10% ethyl acetate in hexanes); FTIR 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.11 (m, 1H), 4.77 (s, 1H), 2.06-2.18 (m, 2H), 1.64-1.92 (m, 4H), 1.70 (s, 3H), 1.60 (s, 3H), 1.22 (m, 1H), 0.96 (s, 3H), 0.92 (s, 9H), 0.87 (s, 3H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 131.6, 124.2, 102.6, 44.5, 42.9, 33.1, 28.9, 27.8, 26.8, 25.9, 25.8, 22.3, 18.1, 17.9, –4.2, –4.2; HRMS (EI) *m/z* calcd for 308.2536, found 308.2535. The minor isomer (**14b**) was identified by a ^1H NMR vinyl stretch at 4.63 ppm (d, *J* = 1.6 Hz, 1H).





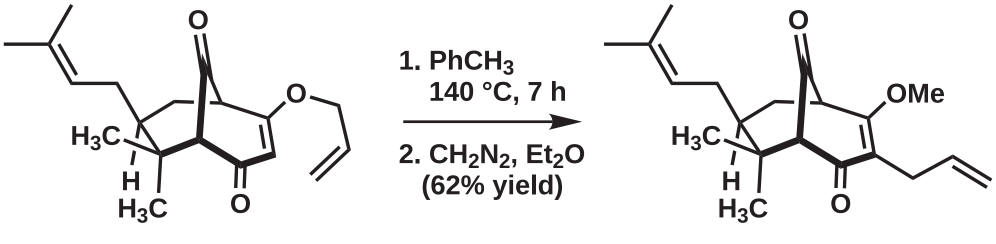
Bicycle 15: To a solution of silyl enol ethers **14a** and **14b** (1.0 g, 3.24 mmol, 1.0 equiv) in dry methylene chloride (0.80 mL) at -10 °C (dry ice/ethylene glycol cold bath) was added dropwise a solution of malonyl dichloride (0.63 mL, 6.49 mmol, 2.0 equiv) in 0.80 mL methylene chloride. The reaction mixture was stirred at -10 °C for 11 h, then treated with a solution of potassium hydroxide (1.46 g, 25.95 mmol, 8.0 equiv) and benzyltriethylammonium chloride (0.037 g, 0.16 mmol, 0.05 equiv) in H_2O (1.60 mL). The reaction mixture was stirred at -10 °C for an additional 1 h, and then was allowed to warm to 23 °C over 10 h. After dilution with water (50 mL) and methylene chloride (50 mL), the phases were separated and the aqueous phase was extracted with methylene chloride (3 x 50 mL). These organic extracts were combined and dried over $MgSO_4$. Concentration and purification by silica gel chromatography (0% to 5% ethyl acetate in hexanes eluent) provided recovered ketone **13 (**0.370 g, 1.91 mmol, 59% yield). The aqueous layer was acidified to pH 1 with 1 M HCl and extracted with methylene chloride (5 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to provide bicycle **15** as an orange-yellow solid (0.306 g, 36% yield, 87% yield based on recovered ketone, 95% yield of total mass recovery), which was used without further purification. Crystals suitable for X-ray analysis were obtained by crystallization from methylene chloride at 23 °C: mp 166-168 °C; R_F = 0.46 (20% methanol in methylene chloride eluent); FTIR (thin film) 1740, 1577 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.67 (broad s, 1H), 5.87

(s, 1H), 5.01 (m, 1H), 3.18 (s, 1H), 2.82 (s, 1H), 2.13 (m, 2H), 1.60-1.80 (m, 3H), 1.67 (s, 3H), 1.57 (s, 3H), 1.15 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 189.9, 185.8, 133.4, 107.7, 68.9, 57.5, 42.2, 39.2, 32.7, 27.8, 27.2, 25.9, 20.6, 20.6, 18.0; HRMS (EI) *m/z* calcd for 262.1565, found 262.1569.



15 ***16***

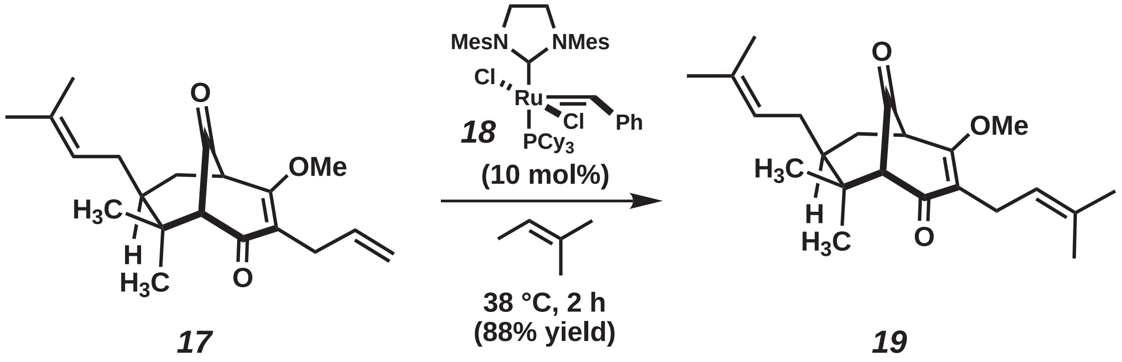
Allyl ether 16: To a solution of bicycle **15** (0.200 g, 0.762 mmol, 1.0 equiv) in benzene (5 mL) was added allyl alcohol (0.259 mL, 3.81 mmol, 5.0 equiv) and *p*-toluenesulfonic acid (3 mg, 0.015 mmol, 0.02 equiv). The reaction flask was fitted with a Dean-Stark apparatus and a condenser and the reaction mixture was heated to reflux for 10 h (oil bath temperature: 90-95 °C). Upon cooling, the reaction mixture was concentrated and purified by silica gel chromatography (25% ethyl acetate in hexanes to 100% ethyl acetate eluent) to afford **16** (172 mg, 75% yield) as a pale yellow oil. $R_F = 0.40$ (30% ethyl acetate in hexanes eluent); FTIR (thin film) 1737, 1656, 1601 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (m, 1H), 5.67 (s, 1H), 5.42-5.32 (m, 2H), 5.00 (m, 1H), 4.49 (d, *J* = 1.1 Hz, 1H), 4.47 (d, *J* = 1.1 Hz, 1H), 3.18 (s, 1H), 2.78 (d, *J* = 1.7 Hz, 1H), 2.08-2.18 (m, 2H), 1.64-1.80 (m, 3H), 1.69 (s, 3H), 1.57 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 193.9, 174.3, 133.2, 130.5, 122.2, 119.2, 106.2, 74.0, 70.1, 53.4, 42.8, 39.6, 32.1, 27.5, 26.9, 25.9, 20.6, 17.9; HRMS (EI) *m/z* calcd for 302.1882, found 302.1882.



16 ***17***

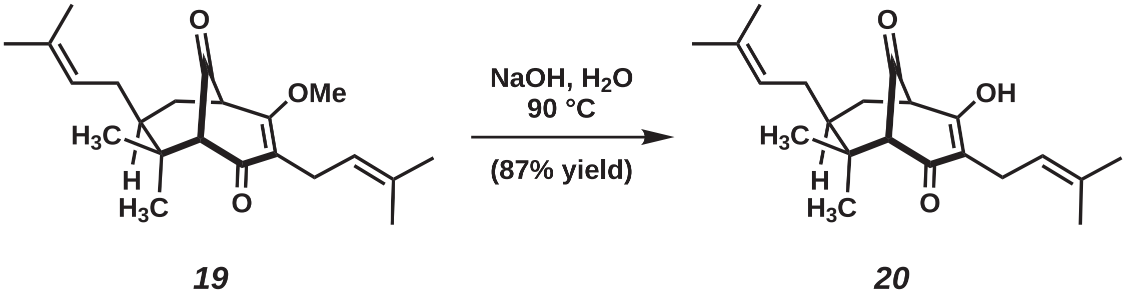
Methyl ether 17: Allyl ether **16** (36 mg, 0.119 mmol) in dry toluene (1.3 mL) was placed in a sealed tube and heated to 140-145 °C (oil bath temperature) for 7 h. The reaction mixture was concentrated, then dissolved in THF (1 mL) and treated with diazomethane (10 mL of a 0.2 M solution in Et_2O) at 0 °C. After

1 h, the reaction mixture was warmed to 23 °C and then concentrated to give a clear oil, which was purified by preparative TLC (CH_2Cl_2 eluent) to yield **17** as separable isomers (**17a** and **17b**) in a 1:1 ratio (23.2 mg, 62% yield) along with recovered ether **16** (10.5 mg, 30% yield). Bicycle **17a** (faster eluting isomer): R_F = 0.44 (30% ethyl acetate in hexanes eluent), FTIR (thin film) 1735, 1657, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (m, 1H), 4.97 (m, 3H), 3.83 (s, 3H), 3.23 (s, 1H), 3.20 (m, 1H), 3.14 (s, 1H), 3.12 (s, 1H), 1.90-2.50 (m, 3H), 1.56-1.70 (m, 2H), 1.66 (s, 3H), 1.55 (s, 3H), 1.13 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 195.0, 169.7, 135.4, 133.4, 124.0, 121.9, 114.8, 61.03, 60.5, 56.9, 42.1, 38.4, 33.5, 27.9, 27.1, 26.1, 25.9, 20.9, 17.9. Bicycle **17b** (slower eluting isomer): R_F = 0.43 (30% ethyl acetate in hexanes eluent); FTIR (thin film) 1734, 1648, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 1H), 4.99 (m, 3H), 3.85 (s, 3H), 3.57 (broad s, 1H), 3.10 (d, J = 1.7 Hz, 1H), 3.08 (d, J = 1.1 Hz, 1H), 2.83 (d, J = 1.7 Hz, 1H), 2.13 (m, 2H), 1.60-1.80 (m, 3H), 1.70 (s, 3H), 1.58 (s, 3H), 1.10 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 192.4, 169.2, 135.4, 133.5, 122.1, 121.3, 114.6, 73.6, 55.8, 48.7, 43.1, 39.0, 31.6, 27.4, 26.9, 26.8, 25.9, 20.6, 18.0; HRMS (EI) *m/z* calcd for 316.2037, found 316.2038.

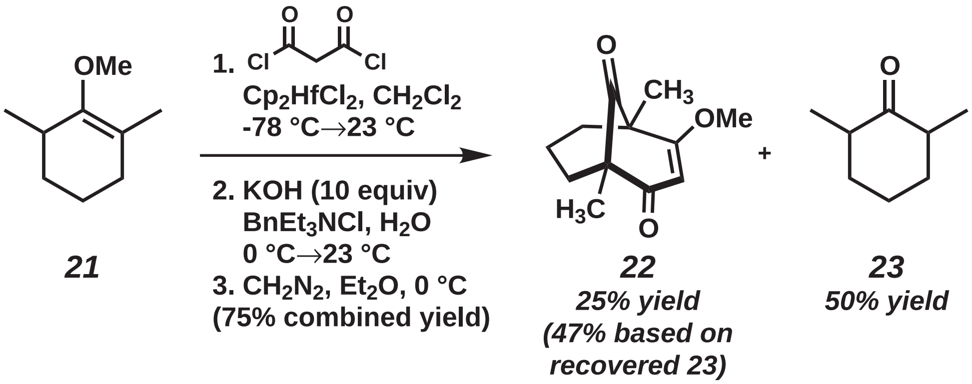


Prenyl bicycle 19: To a solution of allyl bicycle **17a** and **17b** (6.5 mg, 0.020 mmol, 1 equiv) in 2-methyl-2-butene (5 mL) was added ruthenium catalyst **18** (1.7 mg, 0.002 mmol, 0.1 equiv). The reaction flask was fitted with a dry ice-acetone condenser and the mixture was heated to reflux for 2 h. The reaction mixture was cooled, filtered through a small silica gel plug (ethyl acetate eluent), and concentrated to give a brown oil. Purification by preparative TLC (CH_2Cl_2 eluent) provided a mixture of enol ether isomers of **19a** and **19b** (6.1 mg, 88% yield) as an off-white solid. Alternatively, the reaction could be performed on a single enol ether (**17a**) to obtain a comparable yield of an analytically pure enol ether (**19a**). R_F = 0.47 (30% ethyl acetate in hexanes eluent); FTIR (thin film) 1737, 1655, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ

4.92-5.02 (m, 2H), 3.81 (s, 3H), 3.21 (s, 1H), 3.19 (d, *J* = 3.8 Hz, 1H), 3.08 (s, 1H), 3.06 (s, 1H), 2.13 (m, 3H), 1.60-1.80 (m, 2H), 1.71 (s, 3H), 1.67 (s, 3H), 1.57 (s, 3H), 1.55 (s, 3H), 1.12 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 195.2, 168.8, 133.3, 132.0, 126.0, 122.0, 121.6, 61.2, 60.4, 56.8, 42.0, 38.3, 33.6, 29.8, 27.9, 26.1, 25.9, 25.8, 22.1, 20.9, 17.9; HRMS (EI) *m/z* calcd for 344.2349, found 344.2351.



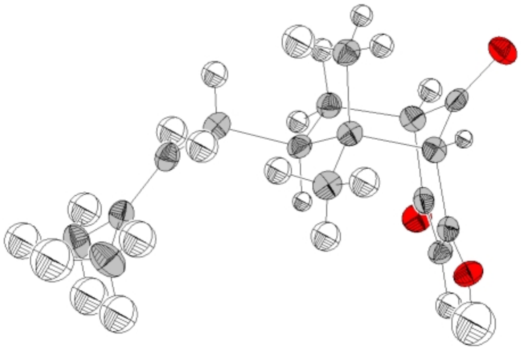
Trione 20: Bicycle **19** (3 mg, 0.009 mmol) was dissolved in 10% aqueous NaOH (1 mL, plus 100 μL of THF for solubility) and heated to 90 °C for 8 h in a sealed vial. Upon cooling, the solution was acidified with 1 M HCl, then concentrated under reduced pressure. Trituration with THF gave a yellow solid that was further purified by preparative TLC (50% ethyl acetate in hexanes eluent) to afford trione **20** (2.5 mg, 87% yield) as a pale yellow solid. R_F = 0.43 (50% ethyl acetate in hexanes eluent); FTIR (thin film) 1728, 1606 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.24 (m, 1H), 4.99 (m, 1H), 3.24-3.12 (m, 3H), 2.81 (d, *J* = 1.6 Hz, 1H), 2.46-1.90 (m, 3H), 1.84-1.52 (m, 2H), 1.80 (s, 3H), 1.68 (s, 3H), 1.57 (s, 6H), 1.13 (s, 3H), 0.94 (s, 3H).



Dimethyl Methyl Bicycle (22): To a solution of 2,6-dimethyl-1-methoxy-1-cyclohexene (**21**, 0.30 g, 2.14 mmol, 1.0 equiv) in CH_2Cl_2 (0.50 mL) was added a solution of malonyl dichloride (0.208 mL, 2.14 mmol, 1.0 equiv) in CH_2Cl_2 (0.50 mL) at -78 °C. Bis(cyclopentadienyl)hafnium dichloride (0.812 g, 2.14

mmol, 1.0 equiv) was added in one portion. The reaction mixture was warmed to 0 °C for 1 hour, then to 23 °C for 72 h. After cooling to 0 °C, a solution of KOH (1.20 g, 21.4 mmol, 10.0 equiv) and benzyltriethylammonium chloride (0.025 g, 0.011 mmol, 0.05 equiv) in H_2O (1 mL) and CH_2Cl_2 (1 mL) was added dropwise. The resulting dark red reaction mixture was allowed to warm to 23 °C over 3 h. It was then acidified with 1 M HCl (to ~pH 1) and filtered through a pad of celite, washing thoroughly with H_2O and CH_2Cl_2. The filtrate was poured into a separatory funnel, extracted with CH_2Cl_2 (5 x 50 mL), and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was dissolved in THF (5 mL) and treated with diazomethane (30 mL of a 0.2 M solution in ether) at 0 °C. Warming to 23 °C after 1 h and removal of solvent afforded a brown residue that was further purified by silica gel chromatography (5% to 30% ethyl acetate in hexanes eluent) to furnish bicycle **22** (0.111 g, 25% yield, 47% yield based on recovery of 0.125 g ketone **23**). $R_F = 0.27$ (30% ethyl acetate in hexanes eluent); FTIR (thin film) 1728, 1656, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (s, 1H), 3.77 (s, 3H), 1.94-2.04 (m, 2H), 1.50-1.80 (m, 4H), 1.29 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8, 197.1, 176.4, 105.3, 60.3, 56.9, 53.0, 40.8, 38.6, 19.4, 16.6, 16.2; HRMS (EI) *m/z* calcd for 208.1097, found 208.1099.

X-Ray Crystallographic analysis of bicycle **15**.



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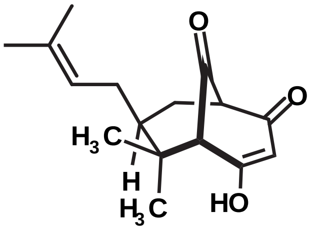

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Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 173065.

Table 1. Crystal data and structure refinement for SJS21 (CCDC 173065).

Empirical formula	$C_{16}H_{22}O_3$
Formula weight	262.34
Crystallization Solvent	Dichloromethane/acetone/hexane
Crystal Habit	Fragment
Crystal size	0.30 x 0.22 x 0.07 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation	
Type of diffractometer	CCD area detector	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	98(2) K	
θ range for 1416 reflections used in lattice determination	2.88 to 27.67°	
Unit cell dimensions	a = 13.226(3) Å b = 8.3873(16) Å c = 13.282(3) Å	β= 104.962(4)°
Volume	1423.5(5) Å^3	

Z	4
Crystal system	Monoclinic
Space group	$P2_1/n$
Density (calculated)	1.224 Mg/m^3
F(000)	568
Data collection program	Bruker SMART
θ range for data collection	1.94 to 28.47°
Completeness to $\theta = 28.47°$	81.6 %
Index ranges	$-14 \leq h \leq 16$, $-7 \leq k \leq 11$, $-16 \leq l \leq 7$
Data collection scan type	ω scans at 2 ϕ settings
Data reduction program	Bruker SAINT v6.2
Reflections collected	5304
Independent reflections	2929 [R_{int}= 0.0533]
Absorption coefficient	0.083 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9939 and 0.9759

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2929 / 0 / 260
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	0.986
Final R indices [$I>2\sigma(I)$, 1729 reflections]	R1 = 0.0467, *w*R2 = 0.0723
R indices (all data)	R1 = 0.0886, *w*R2 = 0.0809
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.000
Average shift/error	0.000
Largest diff. peak and hole	0.313 and -0.220 e.Å^{-3}