

SUPPORTING INFORMATION

Intramolecular Diels–Alder Reactions of Cycloalkenones: Translation of High *endo* Selectivity to *trans* Junctions

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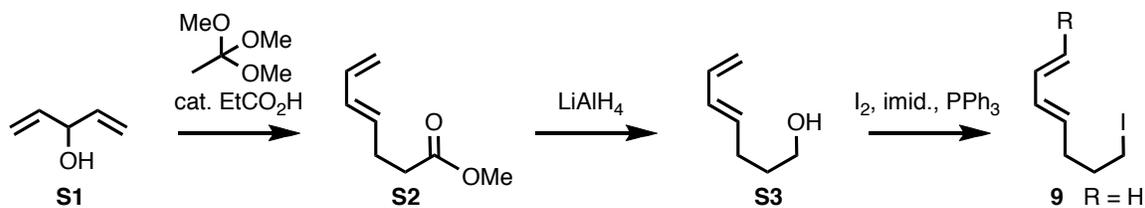
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General Methods

Reactions were performed in oven- or flame-dried glassware, either under positive argon pressure, or in sealed tubes flushed with argon as indicated. Unless otherwise noted, reagents and anhydrous solvents were purchased at the highest commercial quality and used without further purification. CH₂Cl₂ was freshly distilled from CaH₂. Reactions were monitored by thin-layer chromatography on Merck silica gel plates (60-F254), which were visualized with UV light and KMnO₄ stain. Organic solutions were concentrated under reduced pressure using a Büchi rotatory evaporator. Chromatography was performed with Sorbent Technology silica gel 60 (particle size 32–63 µm). Yields are reported for isolated, spectroscopically homogeneous material unless otherwise indicated.

NMR spectra were recorded on Bruker DRX 300, 400, or 500 MHz spectrometers. Abbreviations for ¹H NMR are as follows: br = broad, ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. ¹³C NMR carbon multiplicities were determined by Heteronuclear Single Quantum Coherence (HSQC) spectroscopy. IR spectra were recorded in inverse wavenumbers (cm⁻¹) on a Nicolet AVATAR 370 DTGS spectrometer. High-resolution mass spectra (HRMS) were obtained on a JEOL HX 110 mass spectrometer from the Columbia University Mass Spectral Core Facility.



S2 ester

S2 was prepared based on literature procedure with minor changes.¹

Catalytic propionic acid (0.77 mL, 10 mmol, 0.1 equiv) was added to 1,4-pentadien-3-ol **S1** (10.0 mL, 103 mmol, 1 equiv) in trimethyl orthoacetate (90.0 mL, 704 mmol, 6.8 equiv as solvent) at room temperature, and brought to reflux at 130 °C for 1 h. At this time, the reaction was cooled to 90–100 °C. The reflux condenser was removed to boil off liberated alcohol for 30 min, and then reattached as the reaction was brought back to 130 °C reflux for 2.5 h. Volatiles were distilled out at 140 °C. After cooling to ambient temperature, crude product was purified by flash column chromatography (silica, hexanes to 4:1 hexanes/diethyl ether) to give volatile ester **S2** (13.8 g, 96%) as a clear, colorless liquid that smells of cinnamon.

R_f = 0.63 (4:1 hexanes/diethyl ether).

¹H NMR (300 MHz, CDCl₃) δ 6.29 (dt, *J* = 16.9, 10.2 Hz, 1H), 6.08 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.76 – 5.60 (m, 1H), 5.11 (d, *J* = 16.4 Hz, 1H), 4.99 (d, *J* = 10.1 Hz, 1H), 3.67 (s, 3H), 2.41 (s, 4H).

¹³C NMR (75 MHz, CDCl₃) δ 173.3, 136.8, 132.5, 132.0, 115.7, 51.5, 33.6, 27.7.

IR (thin film, salt plate) 3007, 2944, 1740 cm⁻¹.

APCI-LRMS (M+H)⁺ calculated for C₈H₁₅O 141.09, found 140.89.

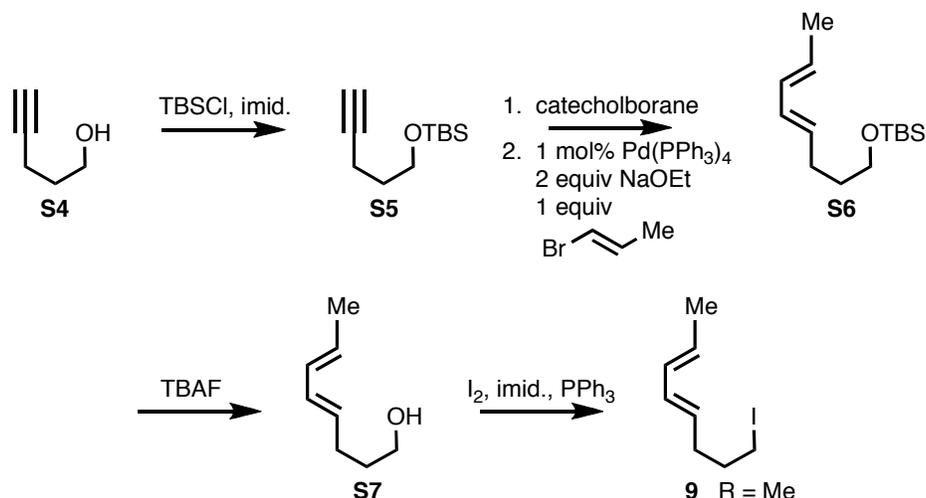
S3 alcohol

LiAlH₄ (49 mL, 98 mmol, 2.0 M in THF) was cooled to 0 °C in an ice bath. To this was added a solution of ester **S2** (13.8 g, 98.5 mmol, 1.0 equiv) in THF (50 mL) over 15 min. Upon completion at 30 min, the reaction was carefully quenched by dropwise addition of water. The mixture was stirred with aqueous 1M HCl, then extracted with diethyl ether. Combined organic layers were washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. Crude product was passed through a plug of celite using methylene chloride, giving **S3** (11.06 g, 94%) as a clear, faint yellow liquid. Samples of **S3** matched literature characterization.²

9 (R = H) iodide

9 was prepared based on literature procedure with minor changes.³

To a solution of alcohol **S3** (4.82 g, 43 mmol, 1.0 equiv) in CH₂Cl₂ (215 mL, 0.2 M) at ambient temperature was added imidazole (8.8 g, 129 mmol, 3.0 equiv), then triphenylphenylphosphine (16.9 g, 64.4 mmol, 1.5 equiv). After complete dissolution of reagents, the reaction was cooled to 0 °C and protected from light. Iodine (16.4 g, 64.6 mmol, 1.5 equiv) was added in portions over 15 min. The reaction was stirred for 1 h at 0 °C, then 1 h at ambient temperature (23 °C). Upon completion, pentane and diethyl ether were added to crash out triphenylphosphine oxide. Remaining liquid was decanted into a saturated aqueous solution of NaHCO₃, which was extracted with CH₂Cl₂. Combined organic layers were washed with water and brine, dried over MgSO₄, and concentrated under reduced pressure. Crude product was purification by flash column chromatography (eluent: pentane) to give **9** (7.0 g, 73%) as a clear, colorless liquid. Samples of **4** matched literature characterization.⁴



S5 silyl ether

S5 was prepared in 96% yield by the standard protection of alcohol **S4**.⁵ Samples of **S5** matched literature characterization.⁶

S6 hydroboration and Suzuki product

S6 was prepared based on literature procedure with minor changes; samples of **S6** matched literature characterization.⁷

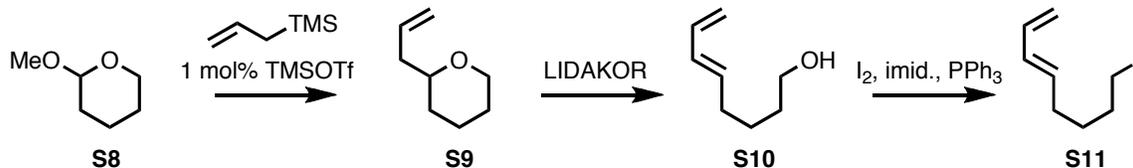
To a THF solution of catecholborane (40.3 mL, 40.3 mmol, 1.0 M in THF, 1 equiv) at ambient temperature was added neat **S5** (8.0 g, 40.3 mmol, 1 equiv). The mixture was refluxed at 70 °C for 14 h, cooled to ambient temperature, and directly concentrated under reduced pressure.

Crude boronate made above (12.83 g theoretical) and *trans*-1-bromo-1-propene (5.0 g, 41.3 mmol, 1 equiv) were dissolved in benzene (80 mL, 0.5 M). The solution was degassed. Catalytic Pd(PPh₃)₄ (312 mg, 0.27 mmol, 0.007 equiv) and a separately degassed solution of NaOMe (17.4 mL, 81 mmol, 25 wt% in methanol, 2 equiv) were added to the reaction, which was then refluxed at 80 °C for 3.5 h. Upon completion, the reaction mixture was cooled to 0 °C and carefully quenched with dropwise addition of H₂O₂ (12 mL, 30 wt% in water) and aqueous NaOH (20 mL, 3 M) over 30 min. The mixture was diluted with diethyl ether after 2 h (200 mL), and extracted with diethyl ether (1 x 200 mL). Combined organic layers were washed with aqueous NaOH (4 x 200 mL, 3 M), dried over MgSO₄, and concentrated under reduced pressure. Crude product was passed through a silica plug (eluent: pentane) and concentrated to give **S6** (7.24 g, 74.6% over two steps) as a clear, pale amber liquid.

9 (R = Me) iodide

Cross coupling product **S6** (7.24 g, 30.1 mmol, 1 equiv) was dissolved in THF (72 mL, 0.4 M) and cooled to 0 °C. Tetrabutylammonium fluoride (TBAF) (39.1 mL, 1.3 equiv, 1.0 M THF) was added over 10 min. The reaction was left to warm to ambient temperature over 2 h, at which time it was quenched by saturated aqueous NH₄Cl, then extracted with diethyl ether. Combined organic layers were dried over MgSO₄, filtered through a silica plug, and concentrated to give alcohol **S7** (3.1 g, 81.6%) as a clear, pale yellow liquid. **S7** R_f = 0.23 (2:1 hexanes/diethyl ether).

Iodide **9 (R = Me)** was prepared from **S7** in the same way as iodide **9 (R = H)**,³ giving **9 (R = Me)** (78.7%) as a clear, colorless liquid. Samples of **9 (R = Me)** matched literature characterization.⁸

**S9**

S9 was prepared based on a literature allylation protocol.⁹

A solution of allyltrimethylsilane (15.8 mL, 1.2 equiv, 99.4 mmol) in CH_2Cl_2 (10.0 mL, ~10M) was cooled to -78°C . Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.18 mL, 0.01 equiv, 0.9 mmol) was added in one portion, followed by dropwise addition of **S8** (10.0 mL, 1 equiv, 82.9 mmol) in CH_2Cl_2 (40 mL, 2 M) over 15 min. The reaction was warmed to -50°C , held at -50°C for 4 h, then placed in a 0°C ice bath for 1 h. Upon completion, the reaction was poured into saturated aqueous NaHCO_3 and extracted with diethyl ether. Combined organic layers were washed with water and brine, dried over MgSO_4 , and carefully concentrated under reduced pressure. The volatile crude product was purified by flash column chromatography (eluent: pentane to 10% diethyl ether in pentane), giving pure **S9** (8.9 g, 85%).

$R_f = 0.65$ (4:1 hexanes/diethyl ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.80 (dq, $J = 17.1, 7.1, 3.5$ Hz, 1H), 5.09 – 4.97 (m, 2H), 3.99 – 3.91 (m, 1H), 3.45 – 3.35 (m, 1H), 3.35 – 3.23 (m, 1H), 2.31 – 2.21 (m, 1H), 2.21 – 2.09 (m, 1H), 1.84 – 1.76 (m, 1H), 1.62 – 1.40 (m, 4H), 1.32 – 1.18 (m, 1H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 135.0, 116.5, 77.3, 68.5, 41.0, 31.4, 26.0, 23.5.

IR (thin film, salt plate) 2930, 2847, 1270 cm^{-1}

APCI-LRMS (M+H)⁺ calculated for $\text{C}_8\text{H}_{14}\text{O}$ 127.11, found 127.16.

S10 alcohol

Superbase LIDAKOR was prepared and used similarly to Schlosser's original procedures.¹⁰ *n*-BuLi (27.7 mL, 2.5 M solution in hexanes, 1.2 equiv, 69.3 mmol) was cooled to -78°C , and diluted with tetrahydrofuran solvent (25 mL). Fresh diisopropylamine (5.9 mL, 1.2 equiv, 68.8 mmol) was added to form lithium diisopropylamine (LDA) over 10 min at ambient temperature, then cooled back to -78°C . No more than 10 mol% of dry potassium *tert*-butoxide (0.65 g, 0.1 equiv, 5.8 mmol) was added to form LIDAKOR. The superbase is formed and ready to use after stirring 10–15 min further at -78°C .

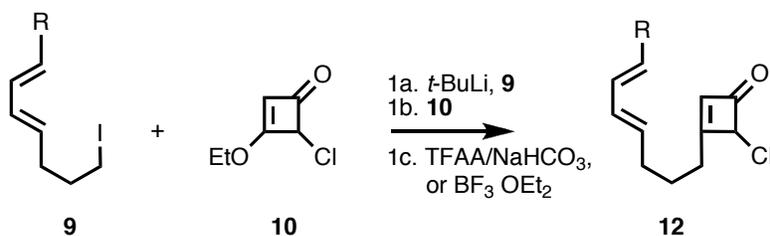
S9 (7.27 g, 1 equiv, 57.6 mmol) was dissolved in THF (12.5 mL), and added to the cold LIDAKOR solution dropwise over 10 min. An intense orange color immediately developed, turning red over time. The mixture was gently warmed from -78°C to -50°C over 1 h. Upon completion as monitored by TLC, the reaction was quenched with water, extracted with ether, and concentrated under reduced pressure to give alcohol **S10** (5.7 g, 78%, 93:7 E/Z mixture) as a clear, pale yellow oil.

Samples of **S10** matched literature characterization.¹¹

S11 iodide

Iodide **S11** was prepared from **S10** in the same way as iodide **9**,³ giving **S11** (7.9 g, 74%) as a clear, colorless liquid.

Samples of **S11** matched literature characterization.¹²



General procedure to prepare substrates of **12**

10 was prepared in 55% yield according to literature procedure.¹³ To facilitate stirring, multiple reactions were run in parallel on a 10 mmol scale.

Iodide **9** (1 equiv, 0.5 M in diethyl ether) was added to a solution of *t*-BuLi (1.7 M in pentane, 2.2 equiv) at -78 °C and protected from light. After exchanging 45–60 min, **10** (0.8 equiv, in equal volume of diethyl ether as iodide) was added. Upon completion at 30 min, the reaction was quenched with trifluoroacetic anhydride (TFAA) (1 equiv) followed by saturated aqueous NaHCO₃.¹³ The mixture was allowed to warm to ambient temperature, then extracted with ether. Combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. Crude halogenated **12** was purified by flash column chromatography (eluent: pentane to 10% diethyl ether in pentane), then concentrated to give **12** (66% for R = H, 56% for R = Me) as clear, pale yellow oils.

If the trienes were not fully unraveled, i.e. if the intermediate 1,2-addition products were isolated, the process could be forced by cooling the material to 0 °C in CDCl₃ or CH₂Cl₂, then treating with trace (<5%) BF₃·OEt₂ for 30 min. Prolonged exposure results in IMDA reaction.

Halogenated trienes were promptly carried forward; spectral characterization is provided:

12 (R = H)

R_f = 0.33 (4:1 hexanes/diethyl ether).

¹H NMR (400 MHz, CDCl₃) δ 6.31 (dt, *J* = 16.9, 10.3 Hz, 1H), 6.17 (s, 1H), 6.14 – 6.02 (m, 1H), 5.67 (dt, *J* = 14.7, 7.0 Hz, 1H), 5.22 (d, *J* = 1.0 Hz, 1H), 5.13 (d, *J* = 16.2 Hz, 1H), 5.02 (d, *J* = 10.1 Hz, 1H), 2.74 – 2.53 (m, 2H), 2.22 (q, *J* = 7.2 Hz, 2H), 1.80 (qt, *J* = 13.6, 6.5 Hz, 2H).

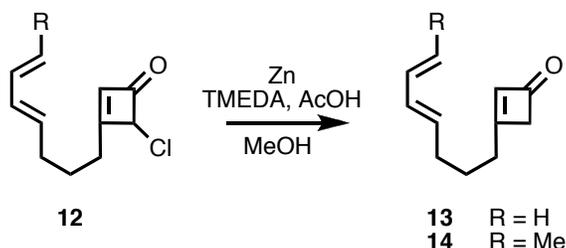
¹³C NMR (125 MHz, CDCl₃) δ 182.3, 182.2, 137.3, 136.7, 132.9, 132.4, 115.9, 69.1, 31.9, 28.3, 25.2.

12 (R = Me)

R_f = 0.37 (4:1 hexanes/diethyl ether).

¹H NMR (400 MHz, CDCl₃) δ 6.15 (dq, *J* = 2.5, 1.4 Hz, 1H), 6.09 – 5.95 (m, 2H), 5.69 – 5.43 (m, 2H), 5.20 (d, *J* = 0.9 Hz, 1H), 2.73 – 2.50 (m, 2H), 2.23 – 2.12 (m, 2H), 1.86 – 1.75 (m, 2H), 1.73 (d, *J* = 6.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 182.4, 182.1, 137.2, 131.8, 131.1, 129.5, 128.0, 69.1, 31.9, 28.3, 25.4, 18.0.



General procedure for reductive dechlorination

Halogenated trienes were reduced according to related literature procedure with some changes.¹⁴ Activated zinc (5 equiv) was suspended in anhydrous methanol (3 M) at ambient temperature. *N,N,N',N'*-tetramethylethane-1,2-diamine (TMEDA) (5 equiv) then glacial acetic acid (5 equiv) were added as the mixture was cooled to 0 °C, followed by addition of a solution of halogenated **12** (1 equiv) in a minimal amount of anhydrous methanol (usually 1 mL). The reaction was stirred at 0 °C for 15 minutes, developing a characteristic green color, then stirred at ambient temperature for 1.5 h to balance conversion with decomposition. The mixtures were diluted with pentane and diethyl ether, filtered, washed with aqueous 1 M HCl, washed twice with saturated aqueous NaHCO₃, then washed with brine. The organic layer was concentrated under reduced pressure, then purified by flash column chromatography (eluent: pentane to 10% diethyl ether in pentane). Final pre-IMDA substrates **13** (69%) and **14** (64%) were obtained as clear, colorless oils.

13

$R_f = 0.33$ (4:1 hexanes/diethyl ether).

¹H NMR (400 MHz, CDCl₃) δ 6.30 (dt, $J = 16.9, 10.3$ Hz, 1H), 6.07 (dd, $J = 15.4, 10.2$ Hz, 1H), 5.90 (s, 1H), 5.67 (dt, $J = 14.6, 7.0$ Hz, 1H), 5.12 (d, $J = 16.9$ Hz, 1H), 4.99 (d, $J = 10.1$ Hz, 1H), 3.15 (s, 2H), 2.57 (t, $J = 7.5$ Hz, 2H), 2.23 – 2.13 (m, 2H), 1.73 (quintet, $J = 7.5$ Hz, 2H).

¹³C NMR (100 MHz, CDCl₃) δ 187.8, 180.7, 136.8, 134.3, 133.4, 132.1, 115.6, 50.7, 31.9, 31.4, 25.6.

IR (thin film, salt plate) 3085, 2932, 1765 cm⁻¹.

APCI-LRMS (M+H)⁺ calculated for C₁₁H₁₅O 163.11, found 163.19.

14

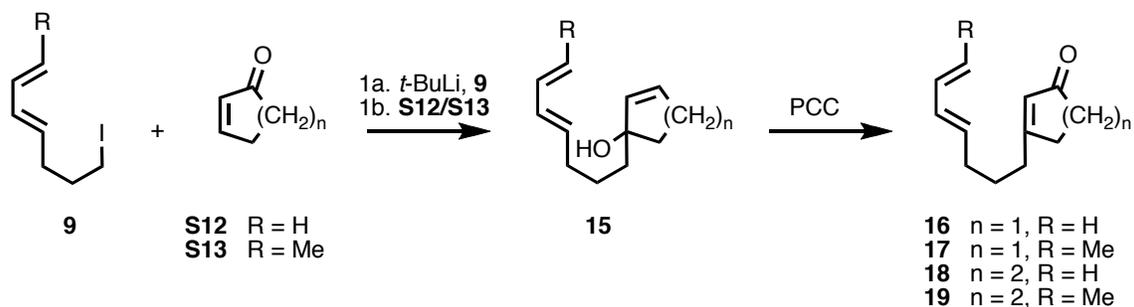
$R_f = 0.38$ (4:1 hexanes/diethyl ether).

¹H NMR (400 MHz, CDCl₃) δ 6.08 – 5.96 (m, 2H), 5.89 (s, 1H), 5.68 – 5.45 (m, 2H), 3.15 (s, 2H), 2.56 (ap t, $J = 7.0$ Hz, 2H), 2.15 (q, $J = 7.1$ Hz, 2H), 1.73 (d, $J = 6.1$ Hz, 3H), 1.72 – 1.65 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ 187.9, 180.9, 134.3, 131.6, 131.2, 130.0, 127.8, 50.7, 32.0, 31.4, 25.8, 18.0.

IR (thin film, salt plate) 3013, 2931, 1766, 1583 cm⁻¹.

APCI-LRMS (M+H)⁺ calculated for C₁₂H₁₇O 177.26, found 177.11



General procedure for preparation of substrates 16–19

Iodide **9** (1 equiv, 0.4 M in diethyl ether) was added to a solution of *t*-BuLi (1.7 M in pentane, 2.2 equiv) at $-78\text{ }^{\circ}\text{C}$ and protected from light. After exchanging 45 – 60 min, **S12** or **S13** (1.5 equiv, in equal volume of diethyl ether as iodide) was added over 10 min. The reaction was allowed to warm to about $0\text{ }^{\circ}\text{C}$ over 2 h, then quenched with water and extracted with diethyl ether. Combined organic layers were washed with brine, dried over MgSO_4 , and concentrated under reduced pressure.

Crude tertiary allylic alcohol **15** was promptly dissolved in CH_2Cl_2 (0.2 M), buffered with sodium acetate (2 equiv), and cooled to $0\text{ }^{\circ}\text{C}$. Pyridinium chlorochromate (PCC) (1.5 equiv) was added in portions over 5 min. The reaction quickly developed a dark color, and was moved to ambient temperature ($23\text{ }^{\circ}\text{C}$) after 15 min. Upon completion at 1.5 h, the crude mixture was filtered through a plug of silica and celite (eluent: diethyl ether), concentrated under reduced pressure, then purified by flash column chromatography (eluent: hexanes to 50% diethyl ether in hexanes). Final substrates **16** (67%), **17** (58%), **18** (62%), and **19** (69%) were obtained as clear, colorless to pale yellow oils.

16

$R_f = 0.27$ (1:1 hexanes/diethyl ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.26 (dt, $J = 16.9, 10.3$ Hz, 1H), 6.02 (dd, $J = 14.9, 10.6$ Hz, 1H), 5.90 (ap quintet, $J = 1.5$ Hz, 1H), 5.63 (dt, $J = 14.7, 7.0$ Hz, 1H), 5.07 (d, $J = 17.0$ Hz, 1H), 4.94 (d, $J = 10.1$ Hz, 1H), 2.57 – 2.50 (m, 2H), 2.42 – 2.31 (m, 3H), 2.11 (q, $J = 7.2$ Hz, 2H), 1.72 – 1.60 (m, 2H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 209.7, 182.4, 136.8, 133.6, 131.8, 129.4, 115.2, 35.1, 32.7, 31.9, 31.4, 26.3.

IR (thin film, salt plate) 2931, 1707, 1615, 1006 cm^{-1} .

FAB-HRMS ($\text{M}+\text{H}$) $^+$ calculated for $\text{C}_{12}\text{H}_{17}\text{O}$ 177.1274, found 177.1286.

17

$R_f = 0.25$ (1:1 hexanes/diethyl ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.05 – 5.94 (m, 2H), 5.92 (s, 1H), 5.66 – 5.41 (m, 2H), 2.58 – 2.51 (m, 2H), 2.38 (t, $J = 7.6$ Hz, 4H), 2.09 (q, $J = 7.2$ Hz, 2H), 1.71 (d, $J = 6.4$ Hz, 3H), 1.68 – 1.59 (m, 2H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 210.0, 182.8, 131.3, 131.2, 130.2, 129.4, 127.5, 35.2, 32.8, 32.0, 31.5, 26.6, 17.9.

IR (thin film, salt plate) 2928, 2360, 2342, 1706 cm^{-1} .

FAB-HRMS ($\text{M}+\text{H}$) $^+$ calculated for $\text{C}_{13}\text{H}_{19}\text{O}$ 191.1436, found 191.1432.

18

$R_f = 0.33$ (1:1 hexanes/diethyl ether).

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 6.27 (dt, $J = 16.9, 10.2$ Hz, 1H), 6.03 (dd, $J = 14.8, 10.7$ Hz, 1H), 5.84 (s, 1H), 5.65 (dq, $J = 14.9, 7.6, 7.0$ Hz, 1H), 5.08 (d, $J = 16.9$ Hz, 1H), 4.95 (d, $J = 10.1$ Hz,

1H), 2.36 – 2.29 (m, 2H), 2.25 (t, $J = 5.9$ Hz, 2H), 2.23 – 2.16 (m, 2H), 2.09 (q, $J = 7.1$ Hz, 2H), 2.00 – 1.92 (m, 2H), 1.59 (quintet, $J = 7.5$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 199.7, 166.0, 1376.9, 133.8, 131.7, 125.7, 115.2, 37.31, 37.26, 31.9, 29.6, 26.3, 22.6.

IR (thin film, salt plate) 2934, 1670, 1006 cm^{-1}

FAB-HRMS ($\text{M}+\text{H}$) $^+$ calculated for $\text{C}_{13}\text{H}_{19}\text{O}$ 191.1436, found 191.1429.

19

$R_f = 0.31$ (4:1 hexanes/diethyl ether).

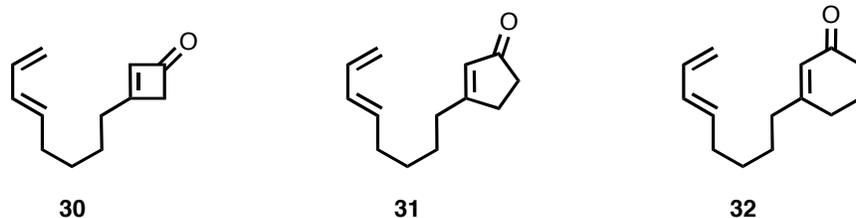
Relative stereochemistry confirmed by NOE.

^1H NMR (500 MHz, CDCl_3) δ 5.99 (d, $J = 13.7$ Hz, 2H), 5.85 (s, 1H), 5.53 (ddq, $J = 40.7, 13.3, 6.6$ Hz, 2H), 2.33 (dd, $J = 9.2, 3.8$ Hz, 2H), 2.26 (t, $J = 5.9$ Hz, 2H), 2.19 (t, $J = 7.7$ Hz, 2H), 2.06 (q, $J = 7.1$ Hz, 2H), 1.96 (p, $J = 6.1$ Hz, 2H), 1.71 (d, $J = 6.6$ Hz, 3H), 1.57 (p, $J = 7.4$ Hz, 2H).

^{13}C NMR (125 MHz, CDCl_3) δ 199.8, 166.2, 131.3, 131.2, 130.5, 127.4, 125.7, 37.4, 37.3, 31.9, 29.6, 26.5, 22.7, 17.9.

IR (thin film, salt plate) 3015, 2931, 2870, 1670, 988 cm^{-1} .

FAB-HRMS ($\text{M}+\text{H}$) $^+$ calculated for $\text{C}_{14}\text{H}_{22}\text{O}$ 205.1592, found 205.1589.



Pre-IMDA substrates **30–32** were prepared from iodide **S11** in the same manner as related compounds **13**, **14**, and **16–19**. The *E/Z* mixture of **S11** is carried through the sequence.

30

$R_f = 0.32$ (4:1 hexanes/diethyl ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.38 – 6.19 (m, 1H), 6.06 – 5.94 (m, 1H), 5.88 (s, 1H), 5.75 – 5.59 (m, 1H), 5.09 (d, $J = 16.5$ Hz, 1H), 4.96 (d, $J = 10.2$ Hz, 1H), 3.13 (s, 2H), 2.59 – 2.51 (m, 2H), 2.12 (q, $J = 6.8$ Hz, 2H), 1.80 – 1.68 (m, 4H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 183.4, 174.9, 137.0, 134.1, 131.6, 130.1, 115.2, 48.1, 32.0, 28.9, 28.8, 25.0.

IR (thin film, salt plate) 3023, 2934, 2851, 1766 cm^{-1} .

APCI-LRMS ($\text{M}+\text{H}^+$) calculated for $\text{C}_{12}\text{H}_{17}\text{O}$ 177.13, found 177.07.

31

$R_f = 0.35$ (1:1 hexanes/diethyl ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.30 (dt, $J = 17.0, 10.3$ Hz, 1H), 6.11 – 5.98 (m, 1H), 5.95 – 5.91 (m, 1H), 5.68 (dt, $J = 14.5, 6.9$ Hz, 1H), 5.10 (d, $J = 16.5$ Hz, 1H), 4.97 (d, $J = 10.2$ Hz, 1H), 2.60 – 2.54 (m, 2H), 2.42 – 2.36 (m, 4H), 2.12 (q, $J = 7.1$ Hz, 2H), 1.63 – 1.54 (m, 2H), 1.52 – 1.40 (m, 2H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 210.1, 182.8, 137.1, 134.4, 131.4, 129.5, 35.3, 33.3, 32.2, 28.8, 26.6.

IR (thin film, salt plate) 3014, 2928, 2854, 1707, 1675, 1615 cm^{-1} .

FAB-HRMS ($\text{M}+\text{H}^+$) calculated for $\text{C}_{13}\text{H}_{19}\text{O}$ 191.1436, found 191.1437.

32

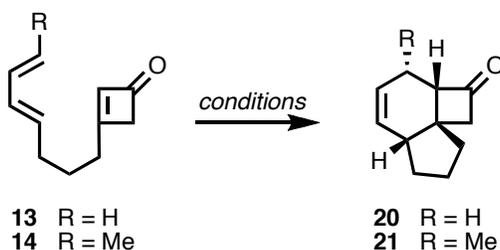
$R_f = 0.37$ (1:1 hexanes/diethyl ether).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.28 (dt, $J = 17.0, 10.3$ Hz, 1H), 6.03 (dd, $J = 15.2, 10.4$ Hz, 1H), 5.85 (s, 1H), 5.65 (dt, $J = 14.6, 6.9$ Hz, 1H), 5.07 (d, $J = 16.8$ Hz, 1H), 4.95 (d, $J = 10.2$ Hz, 1H), 2.36 – 2.31 (m, 2H), 2.26 (t, $J = 5.8$ Hz, 2H), 2.19 (t, $J = 7.3$ Hz, 2H), 2.09 (q, $J = 7.0$ Hz, 2H), 2.00 – 1.94 (m, 2H), 1.52 – 1.45 (m, 2H), 1.45 – 1.33 (m, 2H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 199.8, 166.3, 137.0, 134.5, 131.3, 125.7, 115.0, 37.8, 37.3, 32.2, 29.6, 28.6, 26.3, 22.7.

IR (thin film, salt plate) 2954, 2868, 1708, 1681, 1614 cm^{-1} .

FAB-HRMS ($\text{M}+\text{H}^+$) calculated for $\text{C}_{14}\text{H}_{21}\text{O}$ 205.1592, found 205.1581.



General conditions for Lewis acid catalyzed IMDA of cyclobutenone substrates

13 or **14** was dissolved in toluene (0.05 M) and cooled to 0 °C. To this was added BF₃·OEt₂ (0.2 equiv). The reaction was allowed to warm to ambient temperature over 5.5 h. Direct purification by flash column chromatography (eluent: pentane to 10% diethyl ether in pentane) gave *endo* products **20** (86%) or **21** (92%) as clear yellow oils.

General conditions for thermal IMDA of cyclobutenone substrates

13 or **14** was dissolved in CDCl₃ (0.2 M), then heated at 55 °C for 40 h. After cooling, the material was directly purified by flash column chromatography (eluent: pentane to 10% diethyl ether in pentane) to give *endo* products **20** (35%) or **21** (54%) as clear yellow oils.

20 (endo)

R_f = 0.58 (4:1 hexanes/diethyl ether).

¹H NMR (500 MHz, CDCl₃) δ 6.03 (dt, *J* = 9.3, 2.9 Hz, 1H), 5.67 (dt, *J* = 9.0, 2.6 Hz, 1H), 3.14 (dt, *J* = 7.8, 4.7 Hz, 1H), 2.52 (dd, *J* = 17.8, 3.0 Hz, 1H), 2.39 (dd, *J* = 17.8, 5.0 Hz, 2H), 2.16 (ddd, *J* = 12.0, 6.9, 2.4 Hz, 1H), 2.03 – 1.93 (m, 1H), 1.83 (q, *J* = 9.2, 8.2 Hz, 2H), 1.79 – 1.66 (m, 2H), 1.40 – 1.28 (m, 1H), 1.21 (d, *J* = 7.2 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 210.6, 134.6, 131.1, 65.5, 54.2, 43.9, 41.7, 34.3, 32.4, 25.2, 21.6, 17.3.

IR (thin film, salt plate) 3020, 2957, 2870, 1773 cm⁻¹.

APCI-LRMS (M+H)⁺ calculated for C₁₂H₁₇O 177.13, found 177.11.

21 (endo)

R_f = 0.54 (4:1 hexanes/diethyl ether).

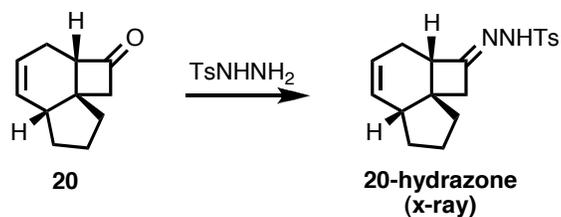
Relative stereochemistry was confirmed through HSQC and NOE spectral analysis.

¹H NMR (400 MHz, CDCl₃) δ 6.08 (ddd, *J* = 9.4, 6.2, 3.1 Hz, 1H), 5.87 (ddd, *J* = 9.5, 6.3, 3.4 Hz, 1H), 3.24 (m, 1H), 2.58 (dd, *J* = 18.0, 3.1 Hz, 1H), 2.48 (d, *J* = 4.9 Hz, 1H), 2.46 – 2.34 (m, 1H), 2.23 – 2.08 (m, 2H), 2.06 – 1.93 (m, 1H), 1.92 – 1.67 (m, 4H), 1.40 – 1.29 (m, 1H).

¹³C NMR (125 MHz, CDCl₃) δ 212.3, 132.1, 127.4, 59.5, 54.2, 43.5, 41.0, 34.7, 25.6, 25.5, 21.2.

IR (thin film, salt plate) 3039, 2957, 1789 cm⁻¹.

APCI-LRMS (M+H)⁺ calculated for C₁₁H₁₅O 163.11, found 163.11.



20-hydrazone

p-toluenesulfonylhydrazide (57 mg, 30.6 mmol, 1 equiv) was added to a solution of **20** (50 mg, 30.6 mmol, 1 equiv) in anhydrous methanol (1.0 mL, 0.3 M) at ambient temperature. After 2 h, the solution was directly concentrated and purified by flash column chromatography (eluent: pentane to 50% diethyl ether in pentane). **20-hydrazone** (94.6 mg, 93%) was obtained as a white solid, which was crystallized and used for X-ray crystallographic analysis.

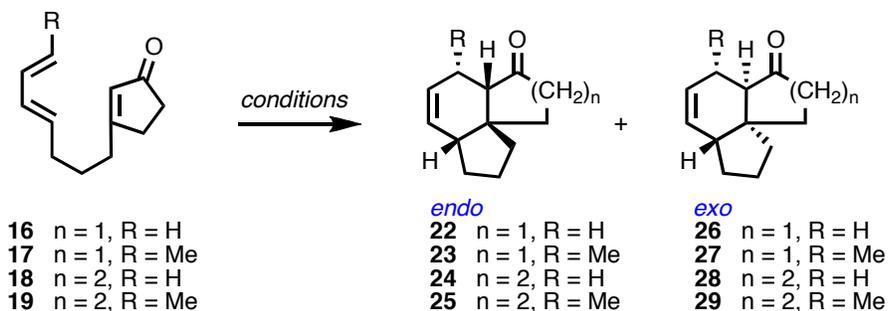
R_f = 0.53 (1:1 hexanes/diethyl ether).

^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, J = 8.3 Hz, 2H), 7.51 (br s, NH), 7.30 (dd, J = 8.2, 3.2 Hz, 2H), 5.88 (dt, J = 9.3, 2.9 Hz, 1H), 5.64 – 5.54 (m, 1H), 3.18 – 3.13 (m, 1H), 2.42 (s, 3H), 2.28 – 2.12 (m, 2H), 2.07 – 2.01 (m, 1H), 2.01 – 1.91 (m, 1H), 1.91 – 1.80 (m, 1H), 1.79 – 1.46 (m, 5H), 1.30 – 1.14 (m, 1H).

^{13}C NMR (100 MHz, CD_3OD) δ 162.4, 143.7, 131.5, 129.1, 127.7, 127.5, 127.4, 46.1, 43.9, 43.3, 39.5, 34.2, 27.4, 24.6, 20.4, 20.1.

IR (thin film, salt plate) 3025, 2950, 2869, 1340, 1164 cm^{-1} .

FAB-HRMS ($\text{M}+\text{H}$) $^+$ calculated for $\text{C}_{18}\text{H}_{23}\text{O}_2\text{N}_2\text{S}$ 331.1480, found 331.1486.



General procedure for Lewis acid catalyzed IMDA of substrates 16–19

Substrate **16–19** (0.3 mmol, 1 equiv) was dissolved in toluene (6 mL, 0.05 M) at ambient temperature. To this solution was added $BF_3 \cdot OEt_2$ (0.06 mmol, 0.2 equiv). Substrates **16** and **18** were refluxed at 110 °C for 24 h; methylated substrates **17** and **19** were heated at 90 °C for 24 h. The reactions were cooled to ambient temperature, then directly purified by flash column chromatography (eluent: pentane to 10% diethyl ether in pentane). Pale yellow oils were obtained without appreciable exo isomer: **22** (88%), **23** (81%), **24** (69%), and **25** (67%).

General procedure for thermal IMDA of substrates 16–19

Substrate **16–19** (0.3 mmol, 1 equiv) was dissolved in mesitylene (1.5 mL, 0.2 M) at ambient temperature, in a microwave tube. 2,6-Bis(1,1-dimethylethyl)-4-methylphenol (BHT, butylated hydroxytoluene) (13 mg, 0.05 mmol, 0.2 equiv) was added. The mixture was sparged with argon gas, then sealed with a crimped aluminum cap. The reaction was heated at 200 °C for 12 h, cooled to ambient temperature, then directly purified by flash column chromatography (eluent: pentane to 20% diethyl ether in pentane). Pale yellow oils were obtained in endo/exo mixtures as follows: **22/26** (67%, 3.7:1), **23/27** (82%, 2.6:1), **24/28** (59%, 2.8:1), **25/29** (62%, 2.4:1). Exo isomers were generally isolated for characterization by several rounds of chromatography; **28** required derivatization.

22 (endo)

$R_f = 0.66$ (1:1 hexanes/diethyl ether).

1H NMR (400 MHz, $CDCl_3$) δ 5.87 (dd, $J = 9.5, 2.5$ Hz, 1H), 5.72 (ddt, $J = 9.6, 5.7, 2.7$ Hz, 1H), 2.39 – 2.22 (m, 4H), 2.18 (ddd, $J = 13.0, 7.2, 2.8$ Hz, 1H), 2.11 – 2.00 (m, 1H), 1.97 – 1.86 (m, 1H), 1.86 – 1.72 (m, 3H), 1.72 – 1.59 (m, 1H), 1.53 – 1.42 (m, 1H), 1.42 – 1.24 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 221.6, 130.2, 126.5, 51.5, 50.4, 43.4, 35.6, 35.5, 25.7, 25.6, 25.6, 20.8.

IR (thin film, salt plate) 3013, 2955, 2873, 1739 cm^{-1} .

EI-HRMS (M)⁺ calculated for $C_{12}H_{16}O$ 176.1201, found 176.1211.

26 (exo)

$R_f = 0.66$ (1:1 hexanes/diethyl ether).

Major compound: 1H NMR (400 MHz, $CDCl_3$) δ 5.58 (dq, $J = 7.2, 2.4$ Hz, 1H), 5.48 (d, $J = 10.7$ Hz, 1H), 2.44 (ddt, $J = 17.6, 4.6, 2.2$ Hz, 1H), 2.37 – 2.29 (m, 1H), 2.24 – 2.10 (m, 4H), 2.05 – 1.94 (m, 2H), 1.84 – 1.76 (m, 1H), 1.75 – 1.60 (m, 4H), 1.46 – 1.37 (m, 1H).

Major compound: ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.4, 131.8, 123.6, 51.7, 47.4, 40.5, 37.6, 36.0, 35.2, 33.0, 23.7, 20.5.

IR (thin film, salt plate) 3023, 2952, 2871, 1740 cm^{-1} .

EI-HRMS (M)⁺ calculated for $C_{12}H_{16}O$ 176.1201, found 176.1193.

23 (endo)

$R_f = 0.71$ (1:1 hexanes/diethyl ether); 0.23 (4:1 hexanes/diethyl ether).

^1H NMR (400 MHz, CDCl_3) δ 5.94 (ddd, $J = 9.4, 6.3, 3.1$ Hz, 1H), 5.64 (ddd, $J = 9.4, 6.2, 2.9$ Hz, 1H), 2.50 (m, 2H), 2.30 (d, $J = 10.8$ Hz, 2H), 2.22 – 2.09 (m, 2H), 2.07 – 1.89 (m, 2H), 1.88 – 1.78 (m, 2H), 1.74 – 1.60 (m, 3H), 1.53 – 1.30 (m, 3H), 1.08 (d, $J = 7.7$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 221.2, 134.4, 131.1, 56.9, 52.2, 44.6, 37.1, 36.8, 31.0, 27.1, 25.4, 21.4, 17.6.

IR (thin film, salt plate) 3023, 2955, 2873, 1763 cm^{-1} .

EI-HRMS (M^+) calculated for $\text{C}_{13}\text{H}_{18}\text{O}$ 190.1358, found 190.1363.

23 (endo)

$R_f = 0.62$ (1:1 hexanes/diethyl ether).

^1H NMR (400 MHz, CDCl_3) δ 5.78 (dd, $J = 13.1, 7.7$ Hz, 1H), 5.62 (dq, $J = 9.9, 3.2$ Hz, 1H), 2.62 (ddd, $J = 15.0, 13.1, 7.7$ Hz, 1H), 2.39 – 2.33 (m, 1H), 2.33 – 2.26 (m, 1H), 2.25 – 2.10 (m, 2H), 2.01 (dd, $J = 8.0, 5.3$ Hz, 1H), 1.96 – 1.86 (m, 1H), 1.84 – 1.54 (m, 6H), 1.40 – 1.26 (m, 1H), 1.19 – 1.10 (m, 1H), 1.02 (qd, $J = 10.9, 2.0$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 214.9, 127.9, 124.9, 56.8, 47.4, 46.5, 35.7, 32.9, 27.6, 25.0, 21.7, 20.4, 20.4.

IR (thin film, salt plate) 3021, 2948, 1709 cm^{-1} .

EI-HRMS (M^+) calculated for $\text{C}_{13}\text{H}_{18}\text{O}$ 190.1358, found 190.1360.

27 (exo)

$R_f = 0.62$ (1:1 hexanes/diethyl ether).

Major compound: ^1H NMR (400 MHz, CDCl_3) δ 5.62 (ap s, 2H), 2.49 (ddd, $J = 14.4, 8.6, 6.4$ Hz, 1H), 2.43 – 2.33 (m, 2H), 2.30 – 2.19 (m, 1H), 2.13 (t, $J = 7.2$ Hz, 1H), 2.10 – 2.02 (m, 1H), 1.89 (m, 4H), 1.72 – 1.62 (m, 2H), 1.62 – 1.56 (m, 1H), 1.50 – 1.44 (m, 1H), 1.37 (dd, $J = 12.5, 6.5$ Hz, 2H).

Major compound: ^{13}C NMR (100 MHz, CDCl_3) δ 213.8, 130.3, 122.8, 51.7, 46.6, 43.4, 38.8, 37.3, 33.6, 32.0, 24.0, 23.5, 22.1.

IR (thin film, salt plate) 3019, 2937, 2871, 1709 cm^{-1} .

FAB-HRMS ($\text{M}+\text{H}^+$) calculated for $\text{C}_{13}\text{H}_{19}\text{O}$ 191.1436, found 191.1431.

25 (endo)

$R_f = 0.62$ (1:1 hexanes/diethyl ether).

Relative stereochemistry was confirmed through HSQC and NOE spectral analysis.

^1H NMR (400 MHz, CDCl_3) δ 5.78 (dt, $J = 9.7, 2.7$ Hz, 1H), 5.57 (dt, $J = 9.7, 2.7$ Hz, 1H), 2.74 – 2.58 (m, 1H), 2.52 (d, $J = 11.1$ Hz, 1H), 2.39 (ddt, $J = 16.1, 3.7, 1.8$ Hz, 1H), 2.15 (ddd, $J = 16.1, 12.2, 7.8$ Hz, 1H), 1.97 (ddt, $J = 10.8, 5.8, 2.9$ Hz, 1H), 1.92 – 1.60 (m, 6H overlapping), 1.55 – 1.31 (m, 2H), 1.21 – 1.12 (m, 1H), 1.03 (d, $J = 7.8$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 215.1, 133.2, 128.4, 59.8, 47.5, 47.3, 41.3, 34.4, 30.2, 25.1, 22.0, 21.1, 20.6, 19.5.

IR (thin film, salt plate) 3024, 2949, 2873, 1701, 1459 cm^{-1} .

EI-HRMS (M^+) calculated for $\text{C}_{14}\text{H}_{20}\text{O}$ 204.1514, found 204.1516.

29 (exo)

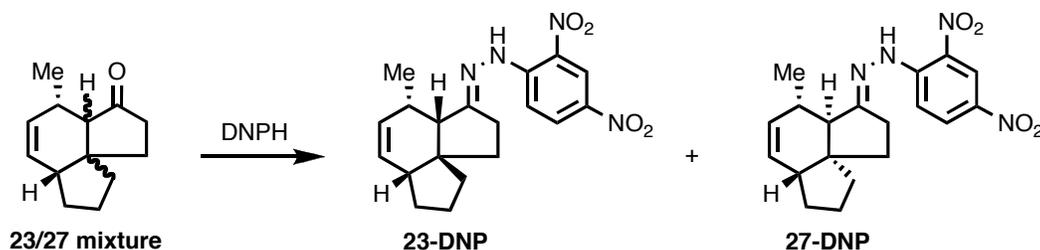
$R_f = 0.62$ (1:1 hexanes/diethyl ether).

^1H NMR (500 MHz, CDCl_3) δ 5.76 (ddd, $J = 9.9, 4.3, 2.7$ Hz, 1H), 5.44 (d, $J = 10.0$ Hz, 1H), 2.55 – 2.46 (m, 2H), 2.20 (dd, $J = 14.3, 3.8$ Hz, 1H), 2.06 – 1.88 (m, 4H), 1.85 (d, $J = 10.6$ Hz, 1H), 1.80 – 1.68 (m, 2H), 1.61 – 1.52 (m, 1H with water peak overlap), 1.50 – 1.43 (m, 1H), 1.34 – 1.17 (m, 2H), 0.93 (d, $J = 7.0$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 215.1, 129.02, 128.96, 60.6, 47.4, 46.7, 37.7, 36.8, 33.2, 32.4, 31.0, 23.9, 23.0, 19.5.

IR (thin film, salt plate) 3014, 1950, 2935, 2869, 1705, 1454 cm^{-1} .

FAB-HRMS ($\text{M}+\text{H}^+$) calculated for $\text{C}_{14}\text{H}_{21}\text{O}$ 205.1592, found 205.1591.



Derivatization protocol

Concentrated sulfuric acid (2.3 mL) was added to a suspension of 2,4-dinitrophenylhydrazine (DNPH) (125 mg, 63.1 mmol, 1.2 equiv) in methanol (2.5 mL, 0.2 M). After the mixture cooled back to ambient temperature, solids were filtered out, and a mixture of **23/27** (100 mg, 52.6 mmol, 1 equiv) was added in methanol (1 mL). At 1 h, the reaction was diluted with diethyl ether, quenched with water, and extracted with diethyl ether. Combined organic layers were washed with saturated aqueous NaHCO_3 to neutral pH, washed with brine, dried over MgSO_4 , and filtered through a silica plug. Crude product was concentrated to a orange solid (174 mg).

The major component, **23-DNP**, was crystallized out of the mixture using diethyl ether and pentane. The minor component, **27-DNP**, was isolated by successive enrichment in the mother liquor, from which it eventually crystallized out from as well.

23-DNP (endo)

$R_f = 0.31$ (4:1 hexanes/diethyl ether)

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 10.84 (s, 1H), 9.12 (d, $J = 2.5$ Hz, 1H), 8.29 (dd, $J = 9.6, 2.5$ Hz, 1H), 7.95 (d, $J = 9.6$ Hz, 1H), 5.90 (dt, $J = 9.4, 2.8$ Hz, 1H), 5.63 (dt, $J = 9.5, 2.8$ Hz, 1H), 2.84 (d, $J = 10.6$ Hz, 1H), 2.70 – 2.59 (m, 1H), 2.50 (dt, $J = 18.3, 9.3$ Hz, 1H), 2.35 – 2.27 (m, 1H), 2.27 – 2.21 (m, 1H), 2.02 – 1.91 (m, 1H), 1.88 – 1.79 (m, 1H), 1.79 – 1.71 (m, 1H), 1.69 – 1.61 (m, 1H), 1.52 – 1.43 (m, 1H), 1.43 – 1.31 (m, 1H), 1.05 (d, $J = 7.7$ Hz, 3H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 169.5, 145.1, 137.5, 134.3, 130.1, 130.0, 128.9, 123.6, 116.4, 53.4, 52.9, 44.1, 36.3, 32.0, 27.9, 26.5, 26.2, 21.3, 18.6.

IR (thin film, salt plate) 3584, 2958, 1619, 1591, 1432, 1337 cm^{-1} .

LRMS ($\text{M}+\text{H}^+$) calculated for $\text{C}_{19}\text{H}_{23}\text{N}_4\text{O}_4$ 371.2, found 370.9.

27-DNP (exo)

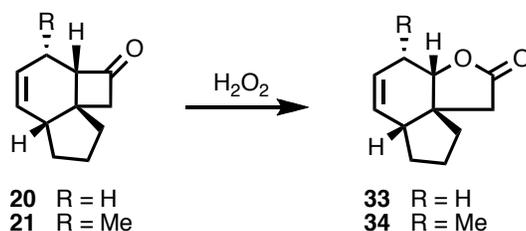
$R_f = 0.31$ (4:1 hexanes/diethyl ether)

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 10.85 (s, 1H), 9.14 (d, $J = 2.5$ Hz, 1H), 8.30 (dd, $J = 9.5, 2.4$ Hz, 1H), 7.96 (dd, $J = 9.6, 4.7$ Hz, 1H), 5.71 (dt, $J = 9.9, 2.8$ Hz, 1H), 5.54 (dt, $J = 9.7, 2.0$ Hz, 1H), 2.51 (t, $J = 7.8$ Hz, 2H), 2.27 – 2.17 (m, 2H), 2.10 – 1.97 (m, 3H), 1.81 (dt, $J = 12.3, 6.1$ Hz, 1H), 1.73 – 1.55 (m, 4H), 1.42 – 1.29 (m, 1H), 1.19 (d, $J = 7.0$ Hz, 3H).

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 169.1, 145.2, 137.6, 130.0, 129.7, 129.6, 129.0, 123.6, 116.4, 54.1, 49.4, 42.0, 39.7, 35.3, 34.2, 30.2, 25.7, 24.1, 19.7.

IR (thin film, salt plate) 3315, 3013, 2954, 2871, 1618, 1336 cm^{-1} .

FAB-HRMS ($\text{M}+\text{H}^+$) calculated for $\text{C}_{19}\text{H}_{23}\text{O}_4\text{N}_4$ 371.1719, found 371.1731.



General procedure for Baeyer-Villiger oxidation of cyclobutanones¹⁵

Cycloadduct **20** or **21** (1 equiv) was dissolved in 2,2,2-trifluoroethanol (0.15 M). The solution was cooled to 0 °C. H₂O₂ (5 equiv, 30 wt% in water) was added over 5 min. The reaction was allowed to warm to ambient temperature over 12–14 h, quenched with water, extracted with diethyl ether, and concentrated under reduced pressure. Crude lactone was purified by flash column chromatography (eluent: pentane to 20% diethyl ether in pentane) to give **33** (84%) or **34** (77%) as clear, colorless oils.

33 lactone

R_f = 0.25 (4:1 hexanes/diethyl ether).

Relative stereochemistry was confirmed through HSQC and NOE spectral analysis.

¹H NMR (400 MHz, CDCl₃) δ 5.97 (s, 1H), 4.78 (ap d, *J* = 6.9 Hz, 1H), 2.54 (ap d, *J* = 17.8 Hz, 1H), 2.44 (dd, *J* = 16.3, 3.7 Hz, 1H), 2.30 (dd, *J* = 18.2, 6.1 Hz, 1H), 2.20 – 2.09 (m, 1H), 2.08 – 1.71 (m, 5H), 1.68 – 1.55 (m, 1H), 1.33 (ddd, *J* = 23.2, 12.4, 7.3 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃) δ 177.0, 131.7, 128.0, 83.3, 50.6, 43.5, 36.0 (2 overlapping signals), 31.6, 25.8, 20.6.

IR (thin film, salt plate) 3039, 2953, 1776 cm⁻¹.

EI-HRMS (M+H)⁺ calculated for C₁₁H₁₅O₂ 179.1072, found 178.0985.

34 lactone

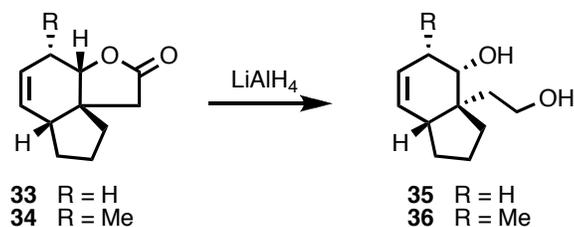
R_f = 0.32 (1:1 hexanes/diethyl ether).

¹H NMR (400 MHz, CDCl₃) δ 5.98 (dt, *J* = 9.0, 3.3 Hz, 1H), 5.76 - 5.67 (m, 1H), 4.64 - 4.57 (m, 1H), 2.43 (d, *J*_{AB} = 18.2 Hz, 1H), 2.39 - 2.29 (m, 1H), 2.17 - 2.07 (m, 1H), 2.00 (overlapping d, *J*_{AB} = 18.2 Hz, 1H), 2.05 - 1.95 (overlapping m, 1H), 1.95 - 1.83 (m, 2H), 1.78 (dddd, *J* = 13.5, 10.8, 8.3, 2.6 Hz, 1H), 1.70 - 1.57 (m, 2H), 1.36 (qd, *J* = 12.2, 6.8 Hz, 1H), 1.23 (d, *J* = 7.4 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 177.0, 134.7, 132.1, 87.3, 51.7, 44.5, 36.9, 36.0, 35.6, 25.3, 21.1, 15.1.

IR (thin film, salt plate) 3026, 2961, 2875, 1771, 1191, 985 cm⁻¹.

EI-HRMS (M)⁺ calculated for C₁₂H₁₆O₂ 192.1150, found 192.1152.



General procedure for use of LiAlH₄

Substrate (1 equiv) was dissolved in anhydrous diethyl ether (0.1 M) at ambient temperature, then cooled to 0 °C. LiAlH₄ (1 equiv, 2.0 M in THF or 1.0 M in diethyl ether) was added over 5 min. After stirring 30 min, the reaction was quenched by dropwise addition of water. The mixture was diluted with water and diethyl ether, extracted with diethyl ether, and concentrated under reduced pressure. Crude products were purified through a short silica column if needed (eluent: 1:1 pentane/ diethyl ether), or crystallized. **35** (96%) and **36** (90%) were isolated as white solids.

35 diol

R_f = 0.56 (diethyl ether).

¹H NMR (400 MHz, CDCl₃) δ 5.61 (dd, *J* = 9.7, 2.2 Hz, 1H), 5.55 (dq, *J* = 9.6, 3.1 Hz, 1H), 3.92 - 3.65 (m, 3H and 2OH), 2.56 - 2.42 (m, 1H), 2.37 - 2.25 (m, 1H), 2.25 - 2.12 (m, 1H), 2.02 (dd, *J* = 12.8, 8.4 Hz, 1H), 1.87 - 1.56 (m, 4H), 1.49 - 1.33 (m, 1H), 1.29 - 1.12 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ 127.3, 126.7, 77.5, 59.1, 49.1, 48.5, 34.8, 31.9, 27.4, 25.2, 20.9.

IR (thin film, salt plate) 3240 (br, OH), 3023, 2952, 2876, 1039 cm⁻¹.

EI-HRMS (M)⁺ calculated for C₁₁H₁₈O₂ 182.1307, found 182.1306.

36 diol

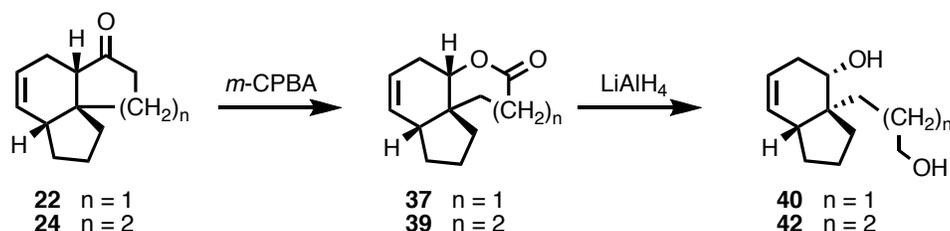
R_f = 0.46 (diethyl ether).

¹H NMR (400 MHz, CDCl₃) δ 5.57 (d, *J* = 4.3 Hz, 2H), 3.87 (d, *J* = 8.5 Hz, 1H), 3.76 (dd, *J* = 9.8, 3.3 Hz, 2H), 3.42 (br s, 2H overlapping), 2.74 (td, *J* = 6.8, 5.9, 2.5 Hz, 1H), 2.34 - 2.24 (m, 1H), 2.07 (dd, *J* = 12.7, 8.3 Hz, 1H), 1.91 - 1.70 (m, 3H), 1.62 (dt, *J* = 21.2, 11.2 Hz, 1H), 1.44 (td, *J* = 11.3, 10.4, 6.1 Hz, 1H), 1.28 - 1.10 (m, 2H), 1.18 (methyl d, *J* = 8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 134.4, 125.4, 79.5, 59.3, 49.4, 48.1, 37.0, 32.5, 28.2, 25.2, 21.2, 15.9.

IR (thin film, salt plate) 3227 (br), 3016, 2954, 2876, 1456, 1115, 1042 cm⁻¹.

EI-HRMS (M)⁺ calculated for C₁₂H₂₀O₂ 196.1463, found 196.1462.



General procedure for Baeyer-Villiger oxidation of **22** and **24**

Cycloadduct **22** or **24** (1 equiv) was dissolved in anhydrous CH_2Cl_2 (0.05 M) at ambient temperature. NaHCO_3 (1.5 equiv) was added, and the mixture was cooled to 0°C . *m*CPBA (1.1eq, 77% activity) was added in one portion. The reaction was warmed to ambient temperature over 2 h, upon which time it was quenched with saturated aqueous NaHCO_3 , then extracted with CH_2Cl_2 . Combined organic layers were washed with brine, dried over MgSO_4 , and then concentrated under reduced pressure. Crude product was purified by flash column chromatography (eluent: hexanes to 50% diethyl ether in hexanes) to give lactones **37** (84%) or **39** (77%) as clear, colorless oils.

These lactones were reductively fragmented by treatment with LiAlH_4 , as described in the general procedure on page S16, giving **40** (94.7%) and **42** (95.0%) respectively.

37 lactone

$R_f = 0.35$ (1:1 hexanes/diethyl ether).

Relative stereochemistry confirmed by NOE.

^1H NMR (400 MHz, CDCl_3) δ 5.68 (dq, $J = 9.6, 2.2$ Hz, 1H), 5.59 (dq, $J = 9.9, 3.3$ Hz, 1H), 4.45 (ddd, $J = 9.5, 7.6, 2.3$ Hz, 1H), 2.90 – 2.76 (m, 1H), 2.71 – 2.61 (m, 2H), 2.28 (ddt, $J = 12.5, 8.2, 3.3$ Hz, 1H), 2.07 (ddq, $J = 18.6, 9.2, 3.1$ Hz, 1H), 1.98 – 1.74 (m, 5H), 1.46 – 1.29 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 171.0, 127.0, 125.2, 83.7, 46.4, 41.8, 34.2, 32.5, 26.5, 25.1, 20.3, 17.6.

IR (thin film, salt plate): 2955, 2875, 1737 cm^{-1} .

FAB-HRMS ($\text{M}+\text{H}$) $^+$ calculated for $\text{C}_{12}\text{H}_{17}\text{O}_2$ 193.1229, found 193.1225.

39 lactone

$R_f = 0.32$ (1:1 hexanes/diethyl ether).

Relative stereochemistry confirmed by NOE.

^1H NMR (400 MHz, CDCl_3) δ 5.69 (dd, $J = 9.7, 2.3$ Hz, 1H), 5.58 (dq, $J = 9.8, 3.3$ Hz, 1H), 4.38 (ddd, $J = 10.9, 7.4, 1.4$ Hz, 1H), 2.88 – 2.77 (m, 1H), 2.72 – 2.60 (m, 1H), 2.60 – 2.47 (m, 2H), 2.34 (m, 1H), 1.99 – 1.92 (m, 1H), 1.88 – 1.59 (m, 6H), 1.50 – 1.25 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 174.8, 127.9, 125.0, 85.6, 50.0, 47.2, 38.0, 31.4, 31.2, 25.1, 24.4, 20.7, 18.9.

IR (thin film, salt plate) 3026, 2949, 2866, 1722, 1199, 1115, 1052 cm^{-1} .

EI-HRMS (M) $^+$ calculated for $\text{C}_{13}\text{H}_{18}\text{O}_2$ 206.1307, found 206.1299.

40 diol

$R_f = 0.33$ (diethyl ether).

^1H NMR (400 MHz, CDCl_3) δ 5.65 – 5.51 (m, 2H overlapping), 3.89 (dd, $J = 9.6, 6.9$ Hz, 1H), 3.62 (t, $J = 6.3$ Hz, 2H), 2.56 – 2.44 (m, 1H), 2.21 – 2.06 (m, 2H), 2.05 – 1.86 (m, 2H), 1.84 – 1.38 (m, 8H), 1.29 – 1.13 (m, 1H), 1.05 (ddd, $J = 17.8, 11.5, 3.5$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 127.6, 126.5, 79.2, 64.2, 49.0, 48.0, 34.5, 32.4, 29.2, 25.6, 21.6, 21.3.

IR (thin film, salt plate) 3342, 3028, 1951, 2872, 1054 cm^{-1} .

EI-HRMS (M) $^+$ calculated for $\text{C}_{12}\text{H}_{20}\text{O}_2$ 196.1463, found 196.1466.

42 diol

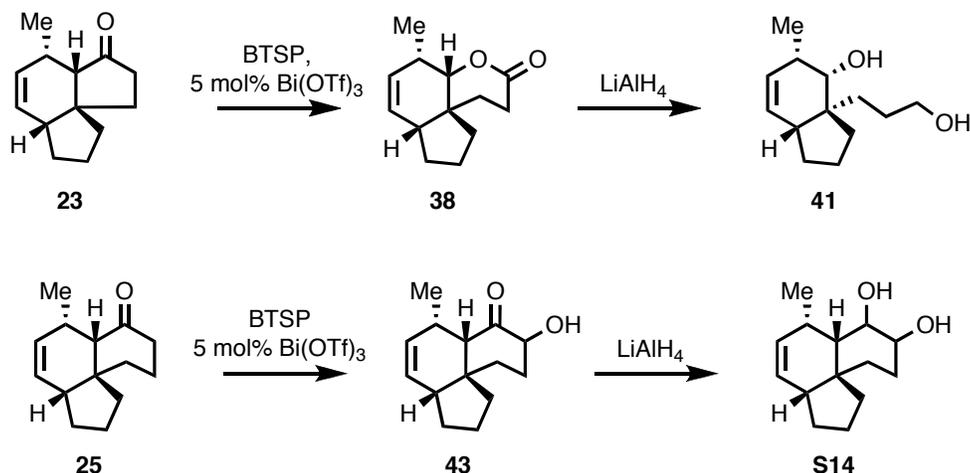
$R_f = 0.30$ (diethyl ether).

^1H NMR (400 MHz, CDCl_3) δ 5.61 (ap d, $J = 10.4$ Hz, 1H), 5.60 – 5.50 (m, 1H), 3.89 (ddd, $J = 10.0, 6.8, 3.9$ Hz, 1H), 3.66 (q, $J = 5.9$ Hz, 2H), 2.60 – 2.41 (m, 1H), 2.22 – 2.04 (m, 2H), 2.01 (dd, $J = 11.3, 7.5$ Hz, 1H), 1.85 – 1.63 (m, 4H), 1.60 – 1.48 (m, 4H), 1.48 – 1.36 (m, 3H), 1.22 – 1.12 (m, 1H), 1.03 – 0.92 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 127.6, 126.5, 79.3, 62.5, 49.0, 48.2, 34.5, 34.0, 32.3, 25.6, 25.1, 22.0, 21.3.

IR (thin film, salt plate) 3333 (br), 3021, 2948, 2871, 1050 cm^{-1} .

FAB-HRMS ($\text{M}+\text{Na}$) $^+$ calculated for $\text{C}_{13}\text{H}_{22}\text{O}_2\text{Na}$ 233.1527, found 233.1527.



Bis(trimethylsilyl) peroxide (BTSP)

Neat BTSP was prepared in an adaptation from literature procedure,¹⁶ using commercial urea-hydrogen peroxide complex instead of preparing diazabicyclooctane-hydrogen peroxide complex.

General procedure for BTSP reactions¹⁷

Methylated cycloadduct **23** or **25** (1 equiv) was dissolved in CH₂Cl₂ (0.1 M). The solution was cooled to 0 °C. Bi(OTf)₃ (5 mol%) was added in one portion (alternate Lewis acids are used in literature), followed by dropwise addition of neat BTSP (2 equiv). The mixture was stirred at 0 °C for 1.5–2 h. Upon consumption of starting material as indicated by TLC, excess solid sodium bisulfite was added to quench the oxidant. The mixture was stirred 5 min at ambient temperature, filtered, and directly concentrated under reduced pressure. Crude oxidized products were purified by flash column chromatography (eluent: pentane to 50% diethyl ether in pentane) to give **38** (77%) or **43** (51%) as clear, colorless oils.

Lactone **38** was reductively fragmented by treatment with LiAlH₄, as described in general procedure on page S16, giving diol **41**, which was recrystallized from diethyl ether (82.7%).

43 was reduced treatment with LiAlH₄, also as described in general procedure on page S16, giving diol **S10** (93.3%).

38 lactone

R_f = 0.31 (1:1 hexanes/diethyl ether).

Relative stereochemistry was confirmed through HSQC and NOE spectral analysis.

¹H NMR (500 MHz, CDCl₃) δ 5.64 (d, *J* = 9.7 Hz, 1H), 5.57 (dt, *J* = 9.6, 2.9 Hz, 1H), 4.55 (dd, *J* = 9.0, 2.5 Hz, 1H), 2.95 (pd, *J* = 7.9, 2.9 Hz, 1H), 2.66 – 2.59 (m, 1H), 2.26 (ddt, *J* = 10.0, 4.7, 2.3 Hz, 1H), 1.95 – 1.87 (m, 2H), 1.87 – 1.79 (m, 2H), 1.46 – 1.27 (m, 3H), 1.08 (d, *J* = 7.8 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 171.4, 132.8, 125.6, 85.9, 46.5, 41.7, 36.2, 33.4, 26.8, 25.2, 20.6, 18.3, 17.1.

IR (thin film, salt plate) 3022, 2958, 2876, 1731, 1176, 1109, 1053 cm⁻¹.

FAB-HRMS (M+H)⁺ calculated for C₁₃H₁₉O₂ 207.1385, found 207.1374.

43 α-hydroxy ketone

R_f = 0.29 (2:1 pentane/diethyl ether).

¹H NMR (400 MHz, CDCl₃) δ 5.64 (dt, *J* = 10.0, 1.9 Hz, 1H), 5.46 (dt, *J* = 9.9, 3.1 Hz, 1H), 4.30 (d, *J* = 6.5 Hz, 1H), 3.61 (s, 1H), 2.72 (ddt, *J* = 10.7, 5.7, 2.9 Hz, 1H), 2.63 – 2.44 (m, 3H), 2.32 –

2.22 (m, 1H), 2.06 – 1.97 (m, 1H), 1.92 – 1.76 (m, 4H), 1.47 – 1.26 (m, 4H), 0.91 (d, $J = 7.7$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 213.0, 133.8, 124.7, 76.7, 50.3, 48.2, 43.8, 34.9, 34.3, 32.4, 25.2, 22.6, 20.9, 18.7.

IR (thin film, salt plate) 3012, 2963, 2869, 1705, 1457 cm^{-1} .

FAB-HRMS ($\text{M}+\text{H}$) $^+$ calculated for $\text{C}_{14}\text{H}_{21}\text{O}_2$ 221.1542, found 221.1530.

41 diol

$R_f = 0.51$ (diethyl ether).

^1H NMR (500 MHz, CDCl_3) δ 5.57 (ap s, 2H), 3.93 (d, $J = 8.0$ Hz, 1H), 3.58 (tt, $J = 10.3, 5.2$ Hz, 2H), 2.77 – 2.70 (m, 1H), 2.19 – 2.12 (m, 1H), 2.04 – 1.91 (m, 2H), 1.84 – 1.67 (m, 4H), 1.67 – 1.51 (m, 3H), 1.49 – 1.37 (m, 2H), 1.22 – 1.10 (m, 1H), 1.13 (d, $J = 7.7$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 133.5, 125.9, 81.3, 64.4, 49.6, 48.2, 36.9, 32.8, 29.0, 25.6, 22.9, 21.4, 15.1.

IR (thin film, salt plate) 3369 (br), 3014, 2917, 2347, 1458, 1050 cm^{-1} .

EI-HRMS (M) $^+$ calculated for $\text{C}_{13}\text{H}_{22}\text{O}_2$ 210.1620, found 210.1614.

S14 diol

$R_f = 0.54$ (diethyl ether).

^1H NMR (500 MHz, CDCl_3) δ 5.92 (dt, $J = 7.2, 3.4$ Hz, 2H), 5.87 – 5.80 (m, 2H), 3.97 (s, 1H), 3.72 (d, $J = 6.9$ Hz, 1H), 2.50 (dt, $J = 7.2, 4.0$ Hz, 2H), 2.07 (td, $J = 13.8, 13.3, 4.9$ Hz, 2H), 1.81 (dtd, $J = 26.2, 10.4, 9.2, 5.4$ Hz, 10H), 1.56 – 1.41 (m, 2H), 1.33 (d, $J = 7.3$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 135.1, 131.6, 72.2, 69.7, 48.4, 48.1, 47.7, 36.0, 32.9, 26.3, 24.0, 22.4, 21.6, 16.1.

IR (thin film, salt plate) 3395 (br), 3025, 2950, 2874, 1062 cm^{-1} .

EI-HRMS (M) $^+$ calculated for $\text{C}_{14}\text{H}_{22}\text{O}_2$ 222.1620, found 222.1612.

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