Supporting Information

Unexpected Alkene Isomerization During Iterative Cross-Coupling to Form Hindered, Electron-Deficient Trienes

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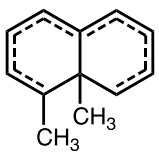
Materials and Methods:

^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 MHz or Bruker 700 MHz spectrometer unless otherwise indicated and were internally referenced to residual protio solvent signal (note: $CDCl_3$ referenced at δ7.26 ppm for ^{1}H NMR and δ77.1 ppm for ^{13}C NMR, respectively. Acetone-D_6 referenced at δ2.05 ppm for ^{1}H NMR and δ29.3 ppm for ^{13}C NMR, respectively). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift and no special nomenclature is used for equivalent carbons. IR spectra were recorded on a Bruker Alpha FT-IR Spectrometer. High-resolution mass spectrometry data were recorded on an Agilent LCTOF instrument using direct injection of samples in dichloromethane into the electrospray source (ESI) with positive ionization.

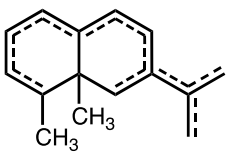
All reactions were carried out under an inert atmosphere of nitrogen in oven dried or flame dried glassware with magnetic stirring, unless otherwise noted. Solvents were dried by passage through columns of activated alumina. All starting materials were prepared according to known literature procedures or used as obtained from commercial sources, unless otherwise indicated. Reactions were monitored by thin-layer chromatography (TLC) and carried out on 0.25 mm coated commercial silica gel plates (Analtech TLC Uniplates, F254 precoated glass plates) using UV light as the visualizing agent and $KMnO_4$ and heat as a developing agent. Flash chromatography was performed on silica gel (Silicycle, SiliaFlash P60, 230-400 mesh).

Structure search:

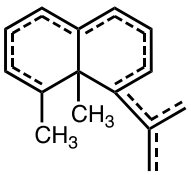
To provide an estimate of the total number of natural products with the specified skeletons, a series of structure searches was performed using Reaxys© (www.reaxys.com) on February 21, 2018. A substructure search "on all atoms" was used with methyl groups explicitly drawn as "CH_3" groups. Other positions were left open and other bonds were available as either single or double bonds. Salts, mixtures and "isotopes" were excluded from the search. Results were filtered using the "Isolated from Natural Product" filter. For the eremophilane skeleton, the molecular weight was arbitrarily limited to < 375 g/mol to filter out higher terpenes such as triterpenes with this substructure. The numbers provided are only estimates given the limitations of this methodology.



cis-dimethyldecalin (**1**)
17,481 natural products



eremophilane skeleton (**2**)
1322 natural products (MW < 375)
(1682 natural products total)



nardosinane skeleton (**3**)
174 natural products

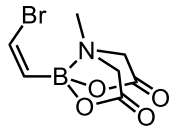
Experimental Procedures:

General Procedure A: Suzuki Cross-Coupling to form Dienes:

To a flask containing 5 mol% $Pd(OAc)_2$ and 10 mol% XPhos was added THF (0.05M). The resulting solution was stirred for 15 minutes and then added to a flask containing bromo MIDA boronate **(14)** (1 equiv), propenyl boronic acid **(15)** (1.2 equiv), and Cs_2CO_3 (3.55 equiv). The reaction was stirred for 24 hours at room temperature. The reactions were tracked by TLC (100% EtOAc). Upon completion, the crude reaction mixture was filtered through celite, concentrated, and then diluted with EtOAc. The organic layer was washed with brine and dried with Na_2SO_4. Volatiles were removed under reduced pressure to afford a crude yellow oil. The crude material was purified using silica gel chromatography with 100% EtOAc.

General Procedure B: Suzuki Cross-Coupling to form Trienes:

To a flask containing vinylbromide (1 equiv)**,** diene MIDA boronate **(13)** (1.2 equiv), 5 mol% $Pd(OAc)_2$ and 10 mol% SPhos was added dioxane (0.08M). The resulting solution was sparged with nitrogen for 30 minutes at room temperature. Aqueous K_3PO_4 (3M) was then added and the reaction was stirred for 24 hours at room temperature. The reactions were tracked by TLC. Upon completion, the crude reaction mixture was filtered through celite, concentrated, and then diluted with EtOAc. The organic layer was washed with brine and dried with Na_2SO_4. Volatiles were removed under reduced pressure to afford a crude yellow oil. The crude material was purified using silica gel chromatography with 1:5 EtOAc/hexanes.

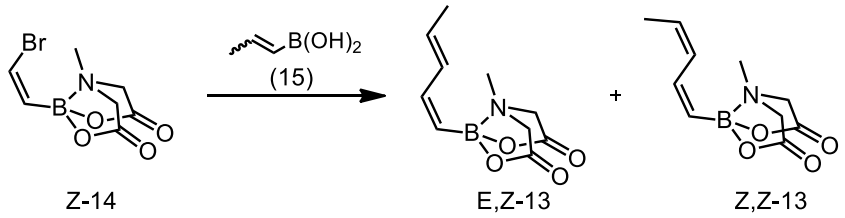


Z-14

Modified procedure for MIDA boronate Z-14

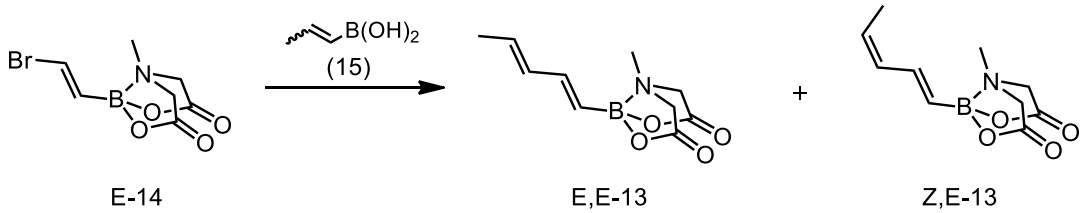
Synthesis conducted according to literature procedure[1] using *E*-diboronate ***E*-17** (1 g, 3.24 mmol), substituting K_3PO_4 with anhydrous Na_2HPO_4 (4.27 g, 30.78 mmol) in the elimination step, to give the desired product **Z-14** (0.685 g, 81%). Spectral data were consistent with literature values.

[1] Woerly, E. M.; Struble, J. R.; Palyam, N.; O'Hara, S. P.; Burke, M. D. *Tetrahedron* **2011**, *67*, 4333-4343.



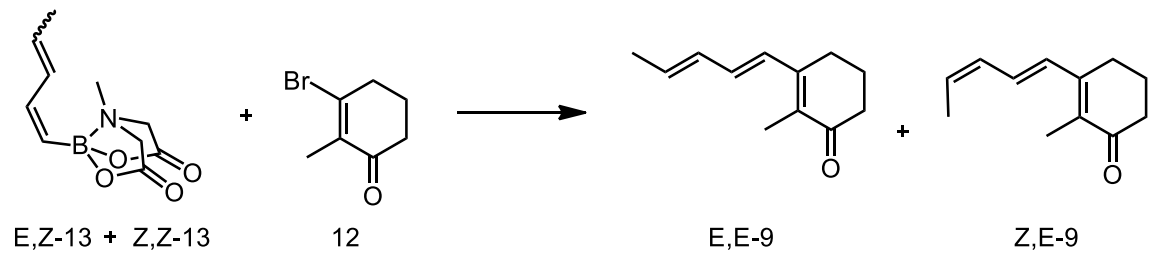
MIDA boronate (E,Z-13 + Z,Z-13)

Prepared according to general procedure A using 5 mol% $Pd(OAc)_2$ (28 mg, 0.127 mmol), 10 mol% XPhos (121 mg, 0.254 mmol), Z-MIDA boronate (**Z-14)** (666 mg, 2.54 mmol, 1 equiv), propenyl boronic acid **(15)** (570 mg, 6.64 mmol, 2.61 equiv), Cs_2CO_3 (2.94 g, 9.02 mmol, 3.55 equiv) in THF (51 mL). Purification afforded the product as a pale yellow solid (524 mg, 2.34 mmol, 92%) in a 1:1 ratio of isomers as determined by ^{1}H NMR. IR (film) 2998, 1758, 1739, 1639, 1450, 983 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, *J* = 13.2 Hz, 1H), 6.73 (t, *J* = 12.8 Hz, 1H), 6.50 (m, 2H), 5.82 (dq, *J* = 13.7, 6.8 Hz, 1H), 5.70 (dtt, *J* = 10.8, 7.2, 1.4 Hz, 1H), 5.27 (d, *J* = 14.4 Hz, 1H), 5.13 (d, *J* = 13.6 Hz, 1H), 3.88 (dd, *J* = 16.4, 2.8 Hz, 2H), 3.71 (dd, *J* = 16.4, 0.8 Hz, 2H), 2.86 (d, *J* = 1.6 Hz, 3H), 1.78 (dt, *J* = 4.8, 1.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 146.3, 140.4, 134.8, 130.6, 130.1, 127.3, 61.7, 46.9, 18.4, 13.0; HRMS (ESI) *m/z* calcd for $C_{10}H_{15}BNO_4$ $(M+H)^+$ 224.1050, found 224.1059.



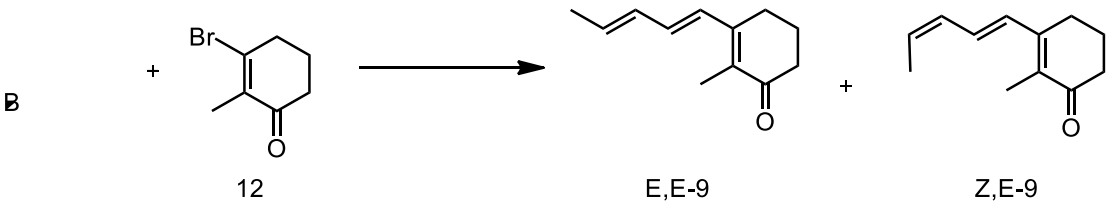
MIDA boronate (E,E-13 + Z,E-13)

Prepared according to general procedure A using 5 mol% $Pd(OAc)_2$ (4 mg, 0.019 mmol), 10 mol% XPhos (18 mg, 0.038 mmol), E-MIDA boronate (**E-14)** (100 mg, 0.382 mmol, 1 equiv), propenyl boronic acid **(15)** (86 mg, 0.996 mmol, 2.61 equiv), Cs_2CO_3 (442 mg, 1.356 mmol, 3.55 equiv) in THF (8 mL). Purification afforded the product as a pale yellow solid (40 mg, 0.015 mmol, 47%) in a 1:1 ratio of isomers as determined by ^{1}H NMR. IR (film) 3058, 2961, 1762, 1641, 1449 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 17.5, 10.5 Hz, 1H), 6.64 (dd, *J* = 17.5, 10.5 Hz, 1H), 6.13 (dd, *J* = 14.7, 10.5 Hz, 1H), 6.08 (dt, *J* = 11.2, 1.4 Hz, 1H), 5.83 (dq, *J* = 14.7, 7 Hz, 1H), 5.61 (dq, *J* = 10.5, 7 Hz, 1H), 5.54 (d, *J* = 16.8 Hz, 1H), 5.42 (d, *J* = 17.5 Hz, 1H), 3.82 (d, *J* = 16.1 Hz, 2H) 3.68 (d, *J* = 16.8 Hz, 2H), 2.85 (s, 3H), 1.79 (dd, *J* = 7, 1.4 Hz). ^{13}C NMR (176 MHz, Acetone-d_6) δ 168.9, 168.9, 144.70, 138.8, 132.75, 131.9, 129.1, 128.6, 62.3, 47.2, 18.23, 12.8.; HRMS (ESI) *m/z* calcd for $C_{10}H_{15}BNO_4$ $(M+H)^+$ 224.1050, found 224.1058.



2-methyl-3-penta-1,3-dien-1-yl)cyclohex-2-enone (E,E-9 + Z,E-9)

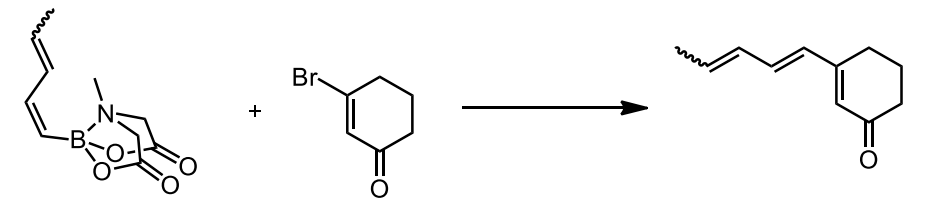
Prepared according to general procedure B using 3-bromo-2-methylcyclohex-2-enone **(12)** (46 mg, 0.244 mmol, 1 equiv)**,** diene MIDA boronate **(E,Z-13 + Z,Z-13)** (66 mg, 0.292 mmol, 1.2 equiv), 5 mol% $Pd(OAc)_2$ (2.7 mg, 0.012 mmol), 10 mol% SPhos (0.024mmol, 10 mg), and 3.05 mL of dioxane. After sparging with nitrogen for 30 minutes at room temperature, aqueous K_3PO_4 (3M, 1.83 mmol, 7.5 equiv) was added. Purification afforded the product as a pale yellow oil (28 mg, 0.159 mmol, 65%) in a 39:61 ratio of isomers as determined by ^{1}H NMR. IR (film) 3053, 2957, 1652, 1596, 1264 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.93 (dd, *J* = 15.4, 11.2 Hz, 1H), 6.71 (d, *J* = 15.4 Hz, 1H), 6.61 – 6.58 (m, 1H), 6.26 – 6.21 (m, 1H), 6.19 (dt, *J* = 10.5, 0.9 Hz, 1H), 5.94 (dq, *J* = 15.4, 7 Hz, 1H), 5.74 (dq, *J* = 10.5, 7.7 Hz), 2.57 – 2.39 (m, 4H), 2.03 – 1.80 (m, 8H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 199.4, 149.9, 149.8, 135.4, 134.2, 132.2, 131.8, 131.3, 130.7, 129.9, 129.8, 129.7, 127.9, 37.8, 26.0, 22.0, 18.5, 13.8, 10.5; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}O$ $(M+H)^+$ 177.1279, found 177.1285.



2-methyl-3-penta-1,3-dien-1-yl)cyclohex-2-enone (E,E-9 + Z,E-9)

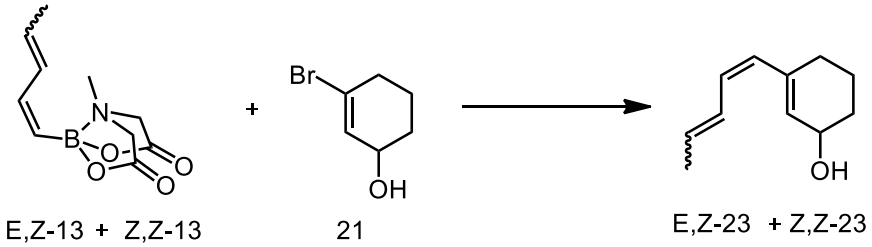
Prepared according to general procedure B using 3-bromo-2-methylcyclohex-2-enone[2] **(12)** (28 mg, 0.148 mmol, 1 equiv)**,** diene MIDA boronate **(E,E-13 + Z,E-13)** (40 mg, 0.179 mmol, 1.2 equiv), 5 mol% $Pd(OAc)_2$ (1/7 mg, 0.008 mmol), 10 mol% SPhos (6 mg, 0.015 mmol), and 1.86 mL of dioxane. After sparging with nitrogen for 30 minutes at room temperature, aqueous K_3PO_4 (3M, 1.12 mmol, 7.5 equiv) was added. Purification afforded the product as a pale yellow oil (15 mg, 0.08 mmol, 56%) as a mixture of triene isomers. The characterization data matches that of the products of the reaction between the same vinyl bromide (**12**) and diene MIDA boronate **(E,Z-13 + Z,Z-13).**

[2] Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210-222.



3-((1E)-penta-1,3-dien-1-yl)cyclohex-2-enone (20)

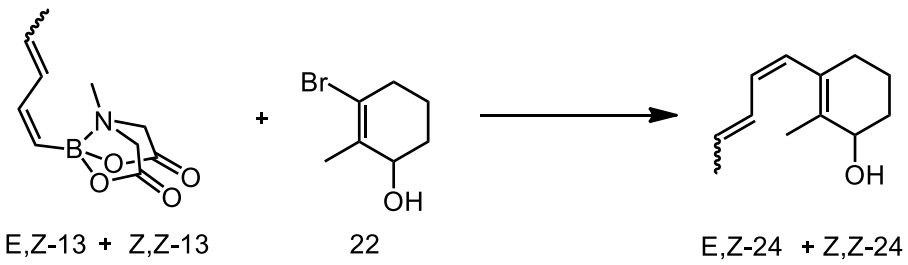
Prepared according to general procedure B using 3-bromocyclohex-2-enone[2] **(19**) (123 mg, 0.703 mmol, 1 equiv), diene MIDA boronate (**E,Z-13 + Z,Z-13)** (189 mg, 0.843 mmol, 1.2 equiv), 5 mol% $Pd(OAc)_2$ (8 mg, 0.035 mmol), 10 mol% SPhos (29 mg, 0.070 mmol) and 9 mL of dioxane. After sparging with nitrogen for 30 minutes at room temperature, aqueous K_3PO_4 (3M, 5.27 mmol, 7.5 equiv) was added. Purification afforded the product as a pale yellow oil (85 mg, 0.521 mmol, 72%). IR (film) 3026, 2931, 2867, 1657, 986 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 6.95 (dd, *J* = 15.6, 11.2 Hz, 1H), 6.62 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.29 (d, *J* = 15.6 Hz, 1H), 6.22 – 6.07 (m, 1H), 6.02-5.85 (m, 1H), 5.75 (dq, *J* = 10.8, 7.2 Hz, 1H) 2.55 – 2.30 (m, 4H), 2.08 – 1.95 (m, 2H), 1.88 – 1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 157.5, 157.4, 136.1, 135.2, 132.7, 131.7, 131.5, 130.6, 130.4, 129.1, 127.5, 127.1, 37.7, 24.9, 22.4, 18.6, 13.9; HRMS (ESI) *m/z* calcd for $C_{11}H_{15}O$ $(M+H)^+$ 163.1117, found 163.1119.



3-((1Z)-penta-1,3-dien-1-yl)cyclohex-2-enol (23)

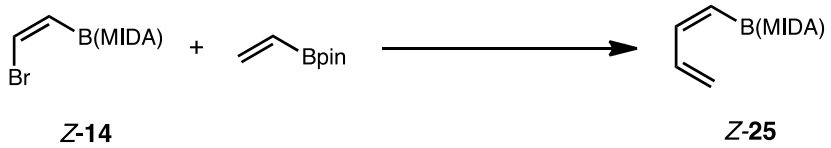
Prepared according to general procedure B using 3-bromocyclohex-2-enol[3] (**21)** (88 mg, 0.288 mmol, 1 equiv), 134 mg diene MIDA Boronate (**E,Z-13 + Z,Z-13)** (0.596 mmol, 1.2 equiv.), 5 mol% $Pd(OAc)_2$ (3 mg, 0.144 mmol), 10 mol% SPhos (12 mg, 0.029 mmol), and 3.60 mL of dioxane After sparging with nitrogen for 30 minutes at room temperature, aqueous K_3PO_4 (3M, 2.16 mmol, 7.5 equiv) was added. Purification afforded the product as a pale yellow oil (47 mg, 0.288 mmol, 58%). IR (film) 3333, 2933, 2861, 1646, 956 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.65 – 6.43 (m, 2H), 6.28 (t, *J* = 11.8 Hz, 1H), 6.17 – 6.12 (m, 1H), 5.95 (t, *J* = 11.6 Hz, 1H), 5.82 – 5.68 (m, 3H), 5.62 (d, *J* = 11.6 Hz, 1H), 5.61 – 5.50 (m, 1H), 4.31 (s, 1H), 2.28 – 2.10 (m, 2H), 1.89 – 1.55 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 131.9, 131.5, 131.0, 130.4, 129.8, 129.6, 129.1, 128.6, 128.1, 126.2, 124.2, 67.2, 66.2, 35.3, 31.7, 30.7, 29.2, 20.6, 19.3, 18.4, 13.1; HRMS (ESI) *m/z* calcd for $C_{11}H_{17}O$ $(M+H)^+$ 164.1201, found 164.1196.

[3] Denmark, S. E.; Habermas, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, *42*, 2821-2829.



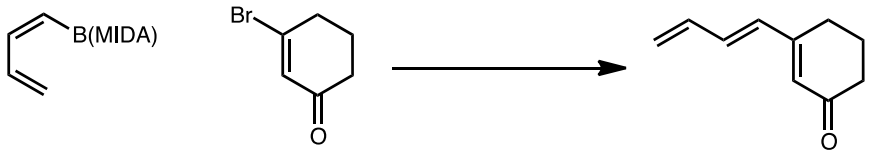
2-methyl-3-((1Z)-penta-1,3-dien-1-yl)cyclohex-2-enol (24)

Prepared according to general procedure B using 3-bromo-2-methylcyclohex-2-enol[3] **(22)** (90 mg, 0.470 mmol, 1 equiv.), 126 mg diene MIDA boronate **(E,Z-13 + Z,Z-13)** (0.564 mmol, 1.2 equiv.), 5 mol% $Pd(OAc)_2$ (5.3 mg, 0.024 mmol), 10 mol% SPhos (19 mg, 0.047 mmol), and 5.89 mL of dioxane. After sparging with nitrogen for 30 minutes at room temperature, aqueous K_3PO_4 (3M, 3.53 mmol, 7.5 equiv) was added. Purification afforded the product as a pale yellow oil (38 mg, 0.213 mmol, 45%). IR (film) 3433, 3054, 2933, 2852, 1659 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 6.30 (t, *J* = 11.2 Hz, 1H), 6.10 (t, *J* = 12.6 Hz, 1H), 6.03 (t, *J* = 11.2 Hz, 1H), 5.96 (t, *J* = 11.2 Hz, 1H), 5.87 (d, *J* = 11.2 Hz, 1H), 5.77 – 5.68 (m, 2H), 5.59 – 5.49 (m, 1H), 4.10 (s, 1H), 2.57 – 2.43 (m, 2H), 2.12 – 1.95 (m, 2H), 1.80 – 1.60 (m, 10H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 134.0, 132.7, 131.3, 130.7, 130.3, 129.4, 128.8, 128.2, 127.1, 126.4, 124.7, 124.0, 70.0, 69.4, 36.7, 32.1, 31.6, 30.3, 20.5, 20.0, 18.4, 17.5; HRMS (ESI) *m/z* calcd for $C_{12}H_{19}O$ $(M+H)^+$ 178.1358, found 178.1353.



MIDA boronate Z-25

To a Schlenk flask containing $Pd(OAc)_2$ (8.6 mg, 10 mol%), XPhos (36.2 mg, 20 mol%), Cs_2CO_3 (436 mg, 3.5 equiv), bromo MIDA boronate **(14)** (100 mg, 1 equiv), was added DMSO (7.6 mL, 0.05M). The resulting solution was stirred for 15 minutes and then added to a flask containing vinyl boronic acid **(15)** (133 µL, 2 equiv), and the reaction was stirred for 24 hours at room temperature. The reactions were tracked by TLC (100% EtOAc). Upon completion, the crude reaction mixture was filtered through celite, concentrated, and then diluted with EtOAc. The organic layer was washed with brine and dried with Na_2SO_4. Volatiles were removed under reduced pressure to afford a crude yellow oil. The crude material was purified using silica gel chromatography with 100% Et_2O, then 1.5% MeOH/Et_2O, then 50% acetone/hexanes to give a light yellow oil (15.2 mg, 0.073 mmol, 19%). Spectral data were consistent with literature values.[1]

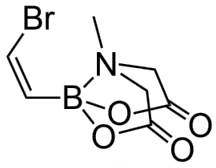


Z-**25** **19** *E*-**26**

(E)-3-(buta-1,3-dien-1-yl)cyclohex-2-enone (26)

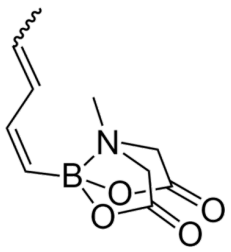
Prepared according to general procedure B using 3-bromocyclohex-2-enone[2] **(19)** (10 mg, 0.058 mmol, 1 equiv), diene MIDA boronate (**Z-25)** (14 mg, 0.069 mmol, 1.2 equiv), 10 mol% $Pd(OAc)_2$ (1.3 mg, 0.006 mmol), 20 mol% SPhos (4.7 mg, 0.070 mmol) and 723 µL of dioxane. After sparging with nitrogen for 30 minutes at room temperature, aqueous K_3PO_4 (3M, 0.4335 mmol, 7.5 equiv) was added. Purification afforded the product as a pale yellow oil (3.8 mg, 44%). IR (film) 2929, 2852, 1667, 1590, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 – 6.55 (m, 1H), 6.44 (dt, *J* = 10.4 Hz, 1H), 6.37 (d, *J* = 15.2 Hz, 1H), 5.97 (s, 1H), 5.47 (d, *J* = 16.8 Hz, 1H), 5.36 (d, *J* = 10.0 Hz, 1H), 2.50 (t, *J* = 6.4 Hz, 2H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.10 – 2.00 (m, 2H); HRMS (ESI) *m/z* calcd for $C_{10}H_{13}O$ $(M+H)^+$ 149.0961, found 149.0959.

^{1}H NMR (500 MHz, acetone-d6)



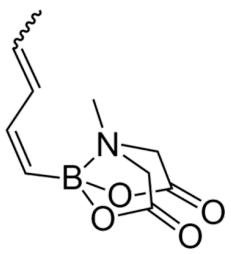
Z-14

^{1}H NMR (400 MHz, $CDCl_3$)



E,Z-13 + Z,Z-13

^{13}C NMR (101 MHz, $CDCl_3$)



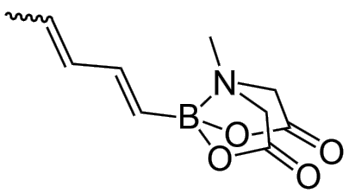
E,Z-13 + Z,Z-13

167.71
146.29
140.39
134.77
130.59
130.13
127.34
61.68
46.85
18.40
13.01

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

^{1}H NMR (700 MHz, $CDCl_3$)



E,E-13 + Z,E-13

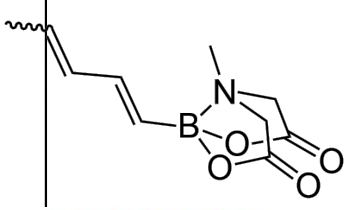
7.01 6.64 6.13 6.08 5.83 5.61 5.54 5.42 3.82 3.68 2.85 1.79

0.83 0.34 0.35 0.78 0.35 0.79 0.78 0.35 2.00 2.19 3.62 3.51

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0

f1 (ppm)

^{13}C NMR (176 MHz, Acetone-d6)



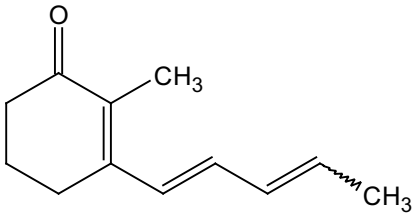
E,E-13 + Z,E-13

168.90
168.87
144.70
138.76
132.75
131.88
129.12
128.64
62.33
47.21
18.29
12.79

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

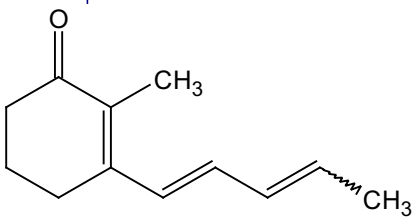
f1 (ppm)

^{1}H NMR (700 MHz, $CDCl_3$)



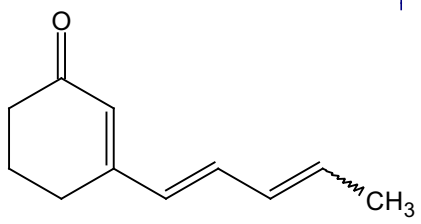
E,E-9 + Z,E-9

^{13}C NMR (176 MHz, $CDCl_3$)



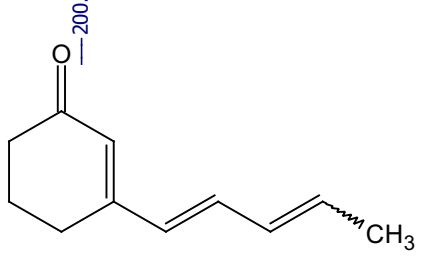
E,E-9 + Z,E-9

^{1}H NMR (400 MHz, $CDCl_3$)



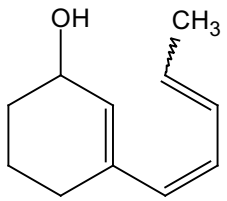
E,E-20 + Z,E-20

^{13}C NMR (101 MHz, $CDCl_3$)



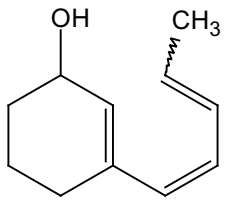
E,E-20 + Z,E-20

^{1}H NMR (400 MHz, $CDCl_3$)



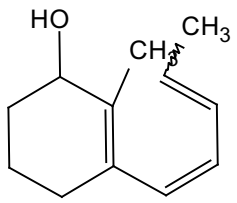
E,Z-23 + Z,Z-23

^{13}C NMR (101 MHz, $CDCl_3$)



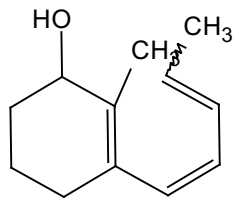
E,Z-23 + Z,Z-23

^{1}H NMR (700 MHz, $CDCl_3$)



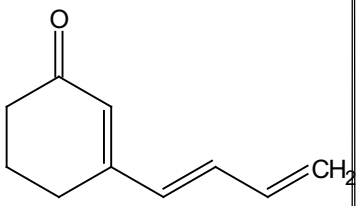
E,Z-24 + Z,Z-24

^{13}C NMR (176 MHz, $CDCl_3$)



E,Z-24 + Z,Z-24

1H NMR (400 MHz, CDCl3)



E,E-**26**