

New Cyclization Strategies to Polyenes Using Palladium(II)-Catalyzed Couplings of Pinacol Vinylboronates

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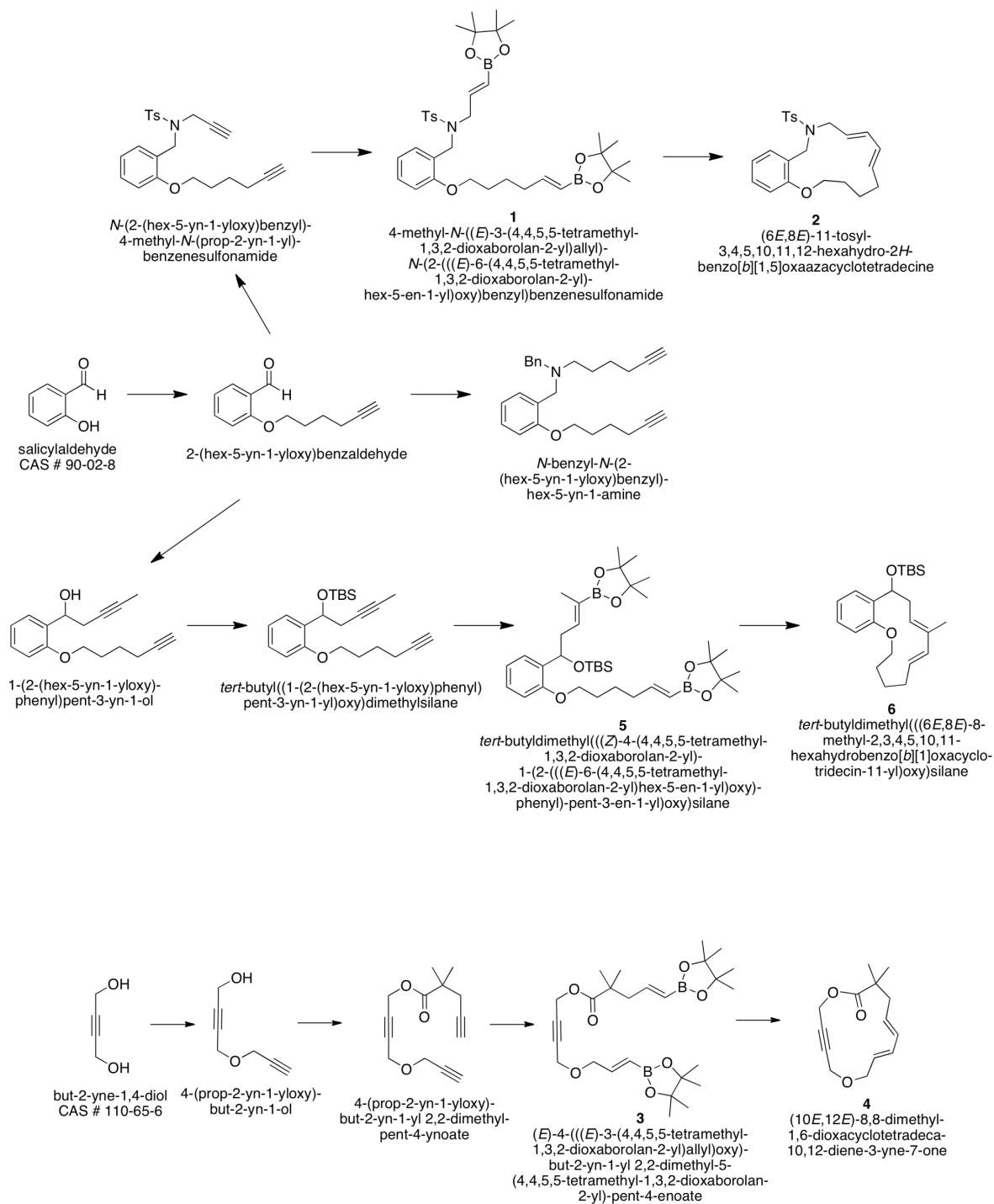
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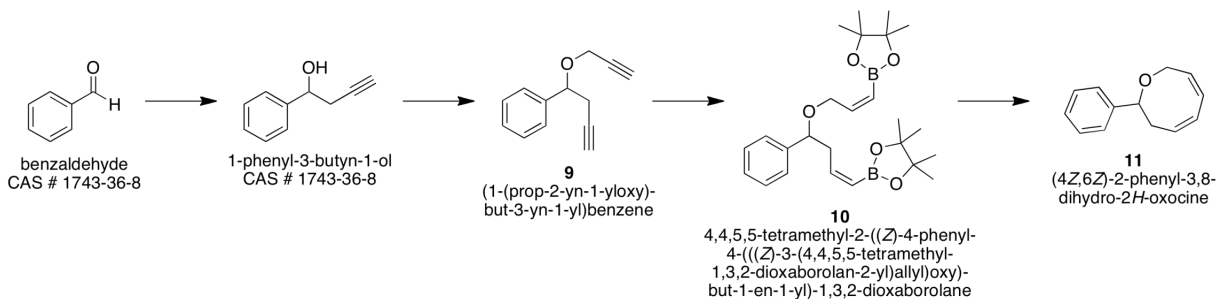
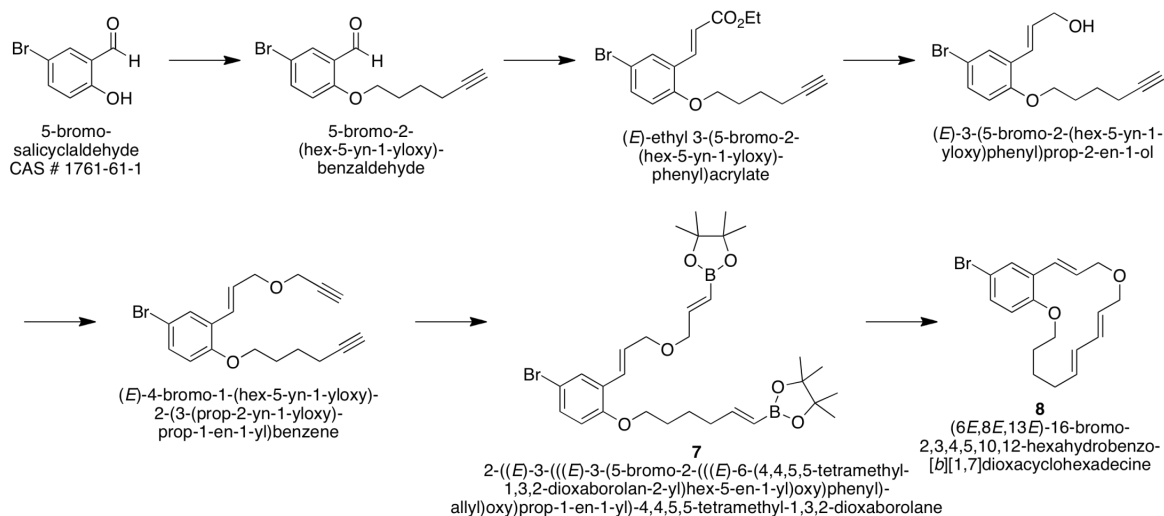
Supporting Information

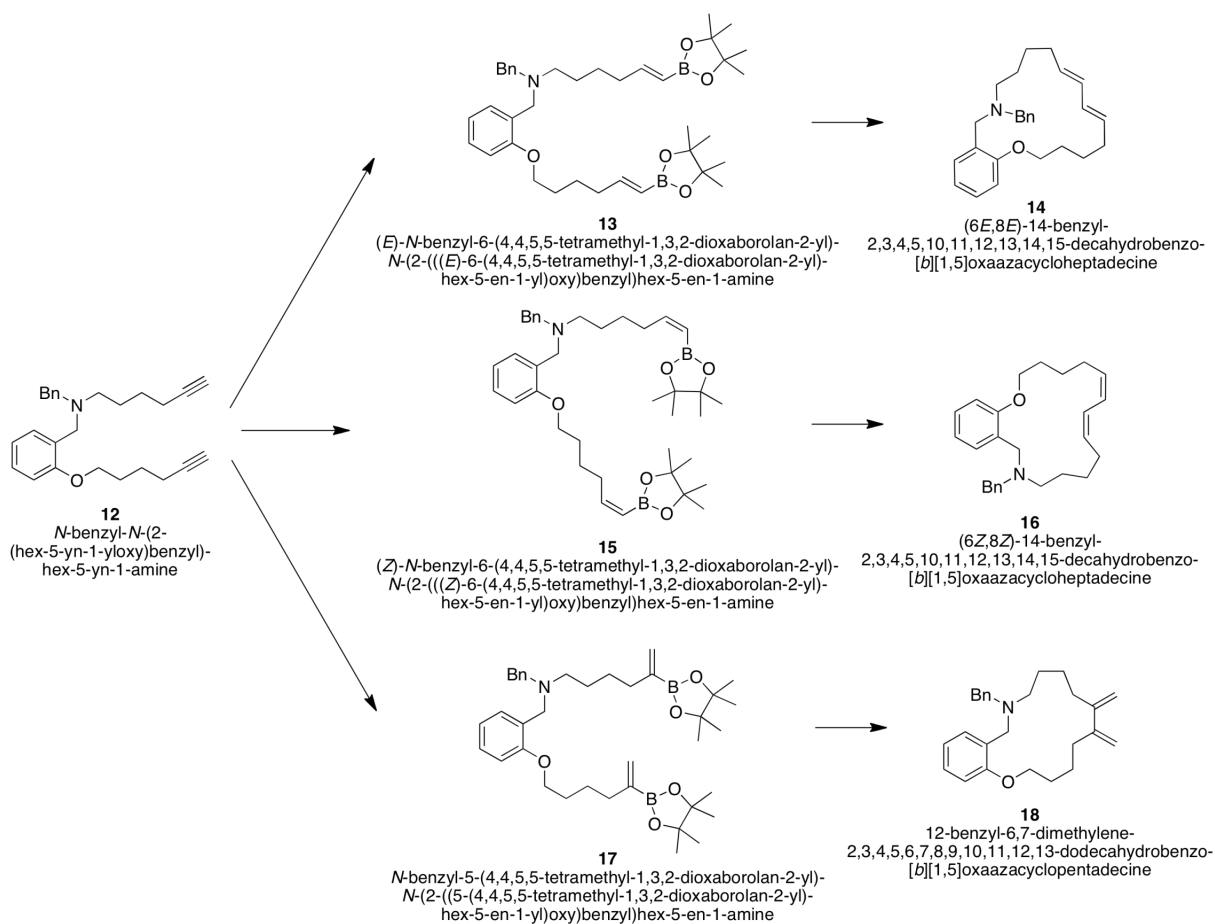
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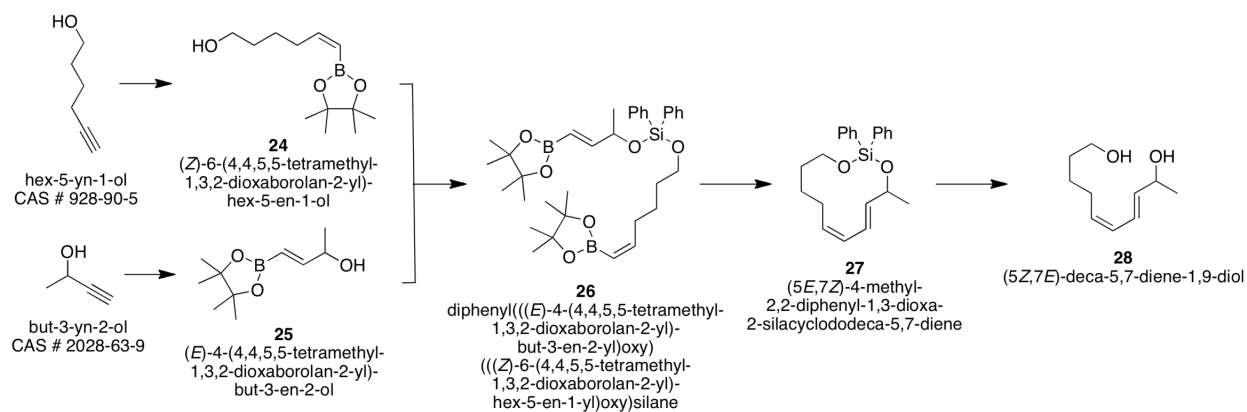
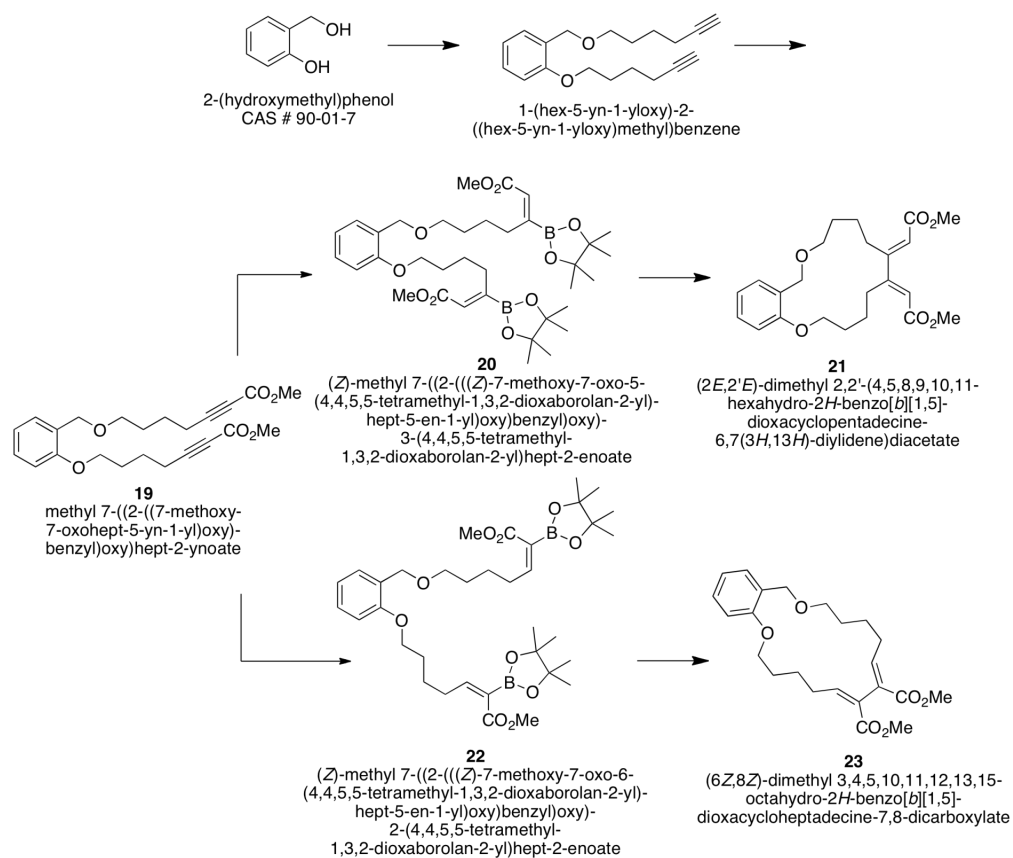
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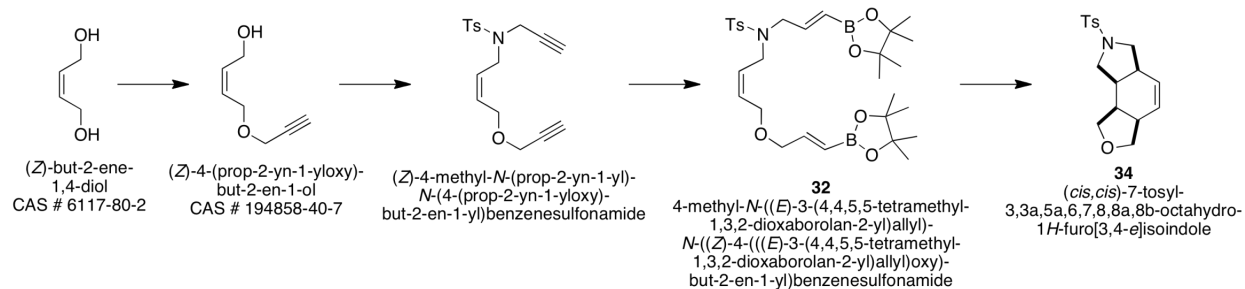
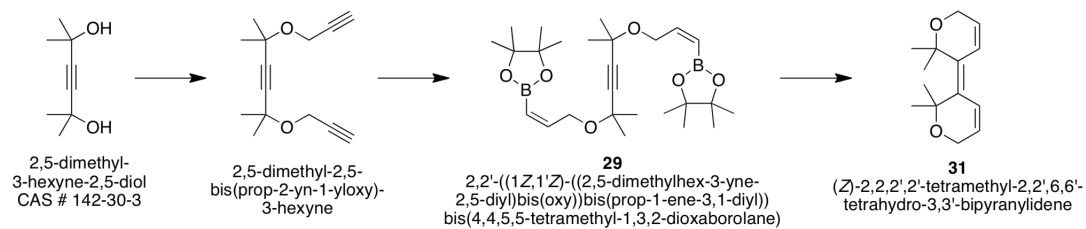
Index of Novel Compounds











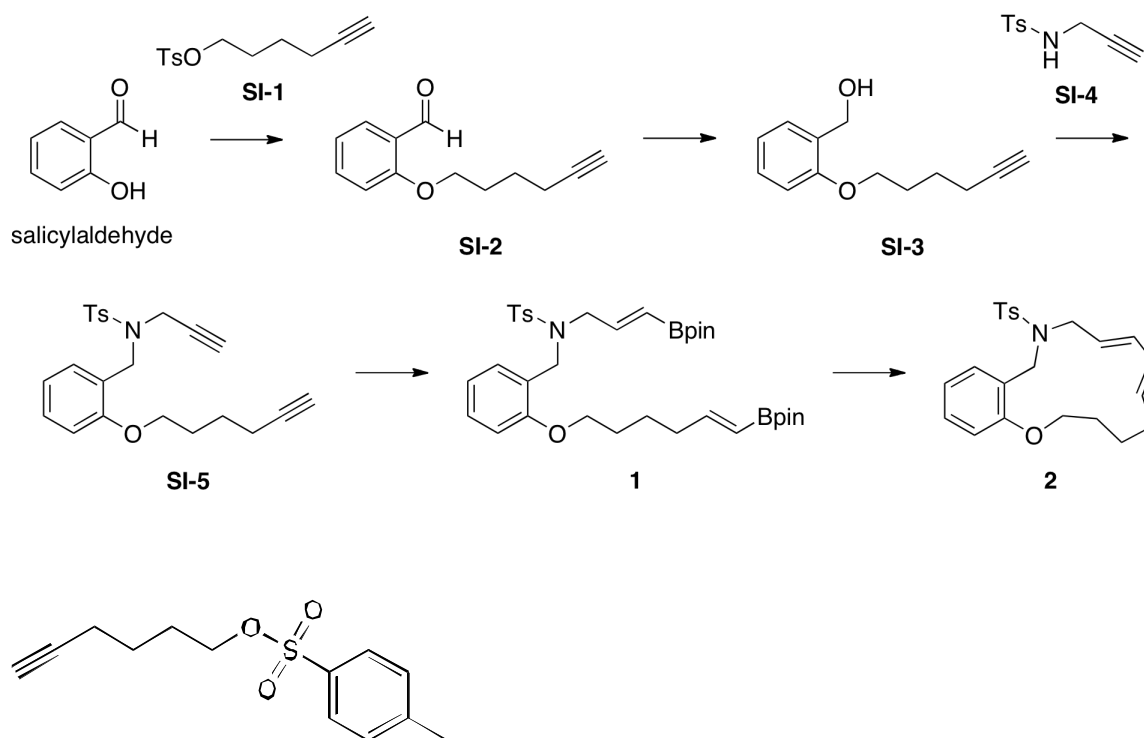
Experimental Procedures

General Procedures:

All commercial compounds were used as received unless otherwise noted. DCM was purified by distillation over CaH_2 . Methanol and ethanol were distilled over Mg. Tetrahydrofuran and ether were distilled prior to use from sodium-benzophenone ketyl. All reactions were carried out in flame-dried glassware under a nitrogen atmosphere, unless otherwise stated. Pinacolborane (Aldrich, 98%) was used as received. Schwartz's catalyst (Strem) was stored in a glovebox and used as received. The reactions were monitored using TLC (Machery-Nagel, 0.2mm layer UV_{254}) and the plates were developed using *p*-anisaldehyde, vanillin, or cerium ammonium molybdate stains. Column chromatography was performed using silica gel (Davisil, 40-63 micron) and HPLC grade solvents without deactivation, unless noted.

NMR spectra were recorded on Bruker ARX-400 instruments and calibrated to the solvent signal (CDCl_3 $\delta = 7.26$ ppm for ^1H NMR, $\delta = 77.0$ ppm for ^{13}C NMR). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), or b (broadened). IR spectra were recorded on a Jasco FTIR-4100 spectrophotometer with an ATR attachment and selected peaks are reported in cm^{-1} .

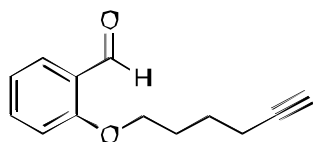
Scheme 1. Preparation of **2**



hex-5-yn-1-yl 4-methylbenzenesulfonate (SI-1)

Tosyl chloride (30.67 g, 160.9 mmol) was added to a flame dried 250 mL round bottom flask. After purging the flask with nitrogen for 10 minutes, DCM (100 mL) was added, and the flask was cooled to 0 °C before 5-hexynol (10 mL, 80.45 mmol), triethylamine (13.5 mL, 96.5 mmol), and DMAP (982 mg, 8.05 mmol) were added. The flask was allowed to stir at 0 °C for 1 hour and at room temperature for 12 hours. After completion, the water was added and the mixture was extracted with ether. The combined organic layers were washed with water, brine, and dried over MgSO₄. Solvent was removed *in vacuo*. Gradient chromatography with 99:1 to 80:20 hexanes:EtOAc afforded 16.94 g (83% yield) of the known¹ clear, yellowish oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.8 (d, *J* = 8.29 Hz, 2H), 7.35 (d, 8.14 Hz, 2H), 4.06 (t, *J* = 6.22 Hz, 2H), 2.46 (s, 3H), 2.17 (dt, *J* = 6.89, 2.62 Hz, 2H), 1.93 (t, *J* = 2.64 Hz, 1H), 1.79 (m, 2H), 1.56 (m, 2H).



2-(hex-5-yn-1-yloxy)benzaldehyde (SI-2)

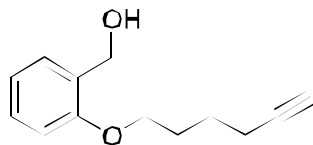
Freshly ground potassium carbonate (1.287 g, 9.31 mmol), DMF (70 mL), salicylaldehyde (813 μ L, 7.76 mmol), and sulfonate **SI-1** (2.35 g, 9.31 mmol) were added to a flame dried 250 mL round bottom flask under inert atmosphere and refluxed for 48 hours. The reaction was quenched with water and extracted with diethyl ether. The combined organic layers were washed with *aq.* 1 M NaOH and brine, and dried over MgSO_4 . The solvent was removed *in vacuo*. Chromatography with 90:10 hexanes/EtOAc afforded 1.554 g (99% yield) of a clear, yellowish oil.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 10.51 (d, J = 0.8 Hz, 1H), 7.83 (dd, J = 7.7, 1.8 Hz, 1H), 7.53 (ddd, J = 8.4, 7.3, 1.8 Hz, 1H), 7.03–6.96 (m, 2H) 4.11 (t, J = 6.2 Hz, 2H), 2.30 (td, J = 7.0, 2.7 Hz, 2H), 2.03–1.96 (m, 2H), 1.98 (t, J = 2.7 Hz, 1H), 1.79–1.71 (m, 2H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 189.8, 161.4, 135.9, 128.3, 124.9, 120.6, 112.4, 83.8, 68.9, 67.8, 28.1, 25.0, 18.1;

IR (neat, ATR): 3296, 3075, 2944, 2867, 2759, 2116, 1684, 1598, 1486, 1457, 1387, 1284, 1239, 1189, 1161, 1103, 1042, 994, 960, 833, 757, 651;

HRMS (ES): calcd $[\text{M}+\text{Na}]^+$ ($\text{C}_{13}\text{H}_{14}\text{O}_2\text{Na}$) 225.0892, found 225.0887.



(2-(hex-5-yn-1-yloxy)phenyl)methanol (SI-3)

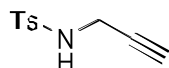
Sodium borohydride (500 mg, 13.1 mmol) was added to a solution of aldehyde **SI-2** (2.123 g, 10.5 mmol) in THF (25 mL). The reaction immediately became hot. After 10 minutes, the reaction was

cooled to 0 °C and quenched with chilled *aq.* 10% HCl. The product generously was extracted with ether, rinsed with brine, and dried over MgSO₄. The solvent was removed *in vacuo*. Chromatography with 85:15 hexanes/EtOAc afforded 2.14 g (100%) of a clear, colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.28 (d, *J* = 7.2 Hz, 1H), 7.26 (td, *J* = 8.0, 1.6 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 4.70 (d, *J* = 6.0 Hz, 2H), 4.05 (t, *J* = 6.4 Hz, 2H), 2.38 (bs, 1H), 2.29 (td, *J* = 7.0, 2.8 Hz, 2H), 1.99 (t, *J* = 2.8 Hz, 1H), 1.98-1.92 (m, 2H), 1.77-1.70 (m, 2H);
¹³C NMR (100 MHz, CDCl₃, ppm) δ: 156.8, 129.2, 128.9, 128.7, 120.6, 111.0, 83.9, 68.9, 67.3, 62.2, 28.3, 25.1, 18.2;

IR (neat): 3564, 3292, 3065, 3040, 2941, 2870, 2116, 1602, 1589, 1493, 1472, 1454, 1433, 1391, 1285, 1237, 1197, 1161, 1115, 1045, 998, 959, 856, 831, 751;

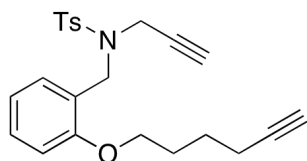
HRMS (ES): calcd [M+Na]⁺ (C₁₃H₁₆O₂Na) 227.1050, found 227.1048.



4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (SI-4)

Prepared according to a modified literature procedure.² A flame dried 250 mL round bottom flask was charged with propargyl amine (1.56 mL, 23.9 mmol), DCM (120 mL), triethylamine (3.33 mL, 23.9 mmol), and DMAP (30 mg, 0.239 mmol) under an inert atmosphere. The solution was cooled to 0 °C and tosyl chloride (4.56 g, 23.9 mmol) was added. The solution was stirred for 30 minutes at 0 °C and 18 hours at room temperature. After completion, the reaction was quenched with water, extracted with ether, and the solvent was evaporated *in vacuo*. Chromatography with 80:20 petroleum ether/EtOAc afforded 4.751 g (95% yield) of the known³ white, crystalline solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.77 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.53 (br, 1H), 3.83 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.44 (s, 3H), 2.11 (t, *J* = 2.5 Hz, 1H).



***N*-(2-(hex-5-yn-1-yloxy)benzyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (SI-5)**

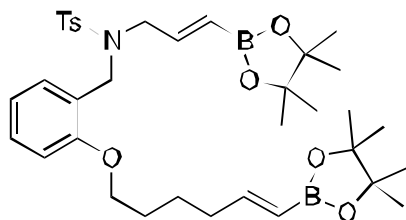
To a solution of alcohol **SI-3** (1.281 g, 6.3 mmol), sulfonamide **SI-4** (1.312 g, 7.4 mmol) and PPh₃ (1.646 g, 6.3 mmol) in THF (12.8 mL) was added diisopropyl azodicarboxylate (DIAD, 1.269 g, 6.3 mmol) at 0 °C. The mixture was allowed to stir for 30 hours at room temperature. Solvent was removed *in vacuo*. Chromatography with 80:20 hexanes/EtOAc afforded 2.001 g (80% yield) of a white solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ : 7.80 (d, J = 8.4 Hz, 2H), 7.40 (dd, J = 7.4, 1.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.25 (td, J = 7.8, 1.6 Hz, 1H), 6.93 (td, J = 8.0, 0.9 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 4.45 (s, 2H), 4.01 (d, J = 2.4 Hz, 2H), 3.98 (t, J = 6.0 Hz, 2H), 2.44 (s, 3H), 2.26 (td, J = 8.4, 2.7 Hz, 2H), 2.00 (t, J = 2.4 Hz, 1H), 1.95-1.88 (m, 2H), 1.93 (t, J = 2.6 Hz, 1H), 1.76-1.71 (m, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : 157.1, 143.4, 136.4, 130.2, 129.4, 129.2, 127.9, 123.5, 120.6, 111.3, 84.2, 77.0, 73.7, 68.7, 67.5, 44.5, 36.3, 28.3, 25.1, 21.6, 18.2;

IR (neat, ATR): 3305, 3018, 2948, 2871, 2115, 1600, 1493, 1455, 1347, 1215, 1159, 1092, 896, 745;

HRMS (ES): calcd [M+Na]⁺ (C₂₃H₂₅NO₃SNa) 418.1453, found 418.1456.



4-methyl-*N*-((*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-*N*-(2-(((*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-yl)oxy)benzyl)benzenesulfonamide (1)

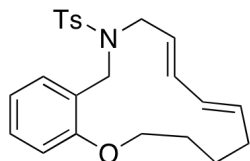
A flame dried 25 mL round bottom flask was charged with sulfonamide **SI-5** (1.322 g, 3.3 mmol), and flushed with nitrogen for 10 minutes. Pinacolborane (1.94 mL, 13.4 mmol), triethylamine (90 μ L, 0.7 mmol), and distilled dichloromethane (10 mL) were added via syringe to the flask and allowed to stir at 0 °C for 5 minutes. The mixture was transferred via a cannula to another round bottom flask containing Cp_2ZrHCl (171 mg, 0.7 mmol). The reaction stirred for 64 hours under reflux. The solvent was removed *in vacuo*. Chromatography with 83:17 petroleum ether/EtOAc afforded 1.226 g (57% yield) of a very viscous colorless oil.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 7.64 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.17 (t, J = 7.8 Hz, 1H), 6.87 (t, J = 7.4 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 6.61 (dt, J = 18.0, 6.4 Hz, 1H), 6.33 (dt, J = 18.0, 5.6 Hz, 1H), 5.44 (d, J = 18.0 Hz, 1H), 5.38 (d, J = 17.6 Hz, 1H), 4.39 (s, 2H), 3.87-3.84 (m, 4H), 2.40 (s, 3H), 2.22-2.17 (m, 2H), 1.76-1.71 (m, 2H), 1.57-1.49 (m, 2H), 1.26 (s, 12H), 1.21 (s, 12H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 156.8, 153.9, 147.3, 142.8, 137.6, 130.2, 129.5, 128.7, 127.3, 124.3, 120.4, 110.9, 83.2, 83.1, 67.6, 51.7, 45.8, 35.3, 28.7, 24.8, 24.7, 24.6, 21.5 (boron substituted carbons, absent);

IR (neat, ATR): 2978, 2929, 2867, 1638, 1494, 1359, 1321, 1241, 1142, 1092, 1142, 1092, 970, 734;

HRMS (ES): calcd $[\text{M}+\text{Na}]^+$ ($\text{C}_{35}\text{H}_{51}\text{B}_2\text{NO}_7\text{SNa}$) 674.3483, found 674.3463.



(6E,8E)-11-tosyl-3,4,5,10,11,12-hexahydro-2H-benzo[b][1,5]oxaazacyclotetradecine (2)

A flame dried 250 mL flask was charged with $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (21 mg, 0.031 mmol). Freshly distilled methanol (160 mL), chloroacetone (0.24 mL, 3.1 mmol), *E,E*-bis(vinylboronate ester) **1** (200 mg,

0.307 mmol), and *aq.* 2 M potassium carbonate (0.77 mL, 1.5 mmol), were subsequently added and the reaction was allowed to stir overnight. Upon completion, methanol was removed *in vacuo*. The product was extracted with ether, washed with water and brine, and dried over MgSO₄. Chromatography with 90:10 hexanes:EtOAc afforded 81 mg (66% yield) of a clear colorless oil.

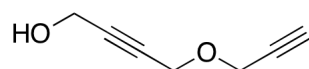
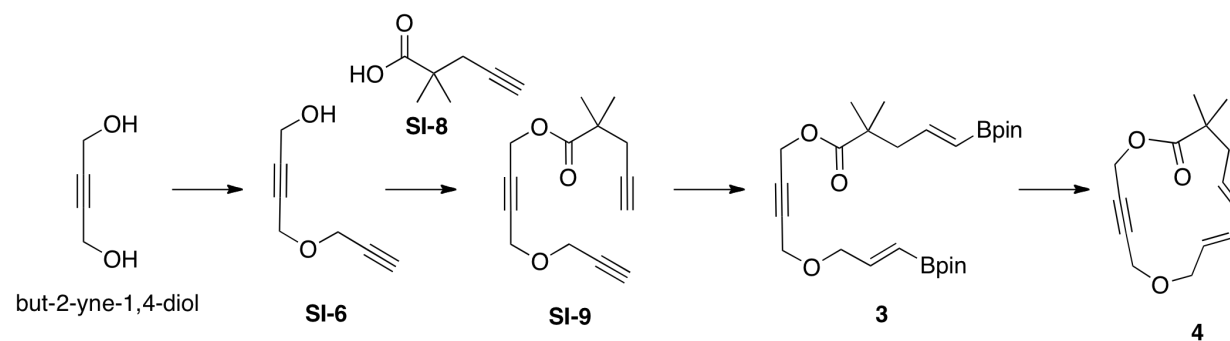
¹H NMR (400 MHz, CDCl₃, ppm) δ : 7.79 (d, *J* = 8.24 Hz, 2H), 7.48 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.20 (td, *J* = 8.6, 1.3 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 8.40 Hz, 1H), 5.92 (dd, *J* = 15.0, 10.6 Hz, 1H), 5.60 (dd, *J* = 15.0, 10.6 Hz, 1H), 5.41 (dt, *J* = 15.2, 7.7 Hz, 1H), 4.89 (dt, *J* = 15.2, 7.5 Hz, 1H), 4.38 (s, 2H), 3.79 (d, *J* = 10.8 Hz, 2H), 3.71 (t, *J* = 7.0 Hz, 2H), 2.47 (s, 3H), 2.16 (dt, *J* = 7.2, 6.9 Hz, 2H), 1.79-1.73 (m, 2H), 1.53-1.49 (m, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ : 156.6, 143.1, 137.7, 136.7, 133.0, 132.0, 129.8, 129.6, 128.2, 127.1, 123.5, 123.3, 121.0, 112.5, 69.8, 48.2, 41.4, 32.7, 25.3, 24.2, 21.6;

IR (neat, ATR): 2925, 2858, 1684, 1600, 1455, 1336, 1240, 1155, 1018, 753, 655;

HRMS (ES): calcd [M+Na]⁺ (C₂₃H₂₇NO₃SNa) 420.1609, found 420.1599.

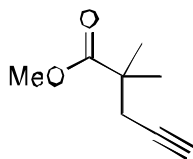
Scheme 2. Preparation of **4**



4-(prop-2-yn-1-yloxy)but-2-yn-1-ol (SI-6)

To a suspension of KOH (12.454 g, 222 mmol) in DMSO (110 mL) were added propargyl bromide (4.94 mL, 44.3 mmol, 80% w/v in toluene) and but-2-yne-1,4-diol (19.303 g, 222 mmol). The mixture was then stirred for 2 hours, poured into water, and extracted with DCM. The aqueous phase was then acidified with aqueous HCl (6 N) and further extracted with DCM. The combined organic phases were reduced in volume, washed with water, dried with MgSO₄, and concentrated in vacuo. Chromatography with 75:25 hexanes/EtOAc afforded 3.04 g (56% yield) of a known⁴ clear, colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ : 4.32 (s, 2H), 4.31 (s, 2H), 4.25 (d, J = 2.4 Hz, 2H), 2.46 (t, J = 2.4 Hz, 1H), 1.77 (bs, 1H).

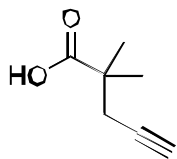


methyl 2,2-dimethylpent-4-ynoate (SI-7)

A solution of *n*-butyllithium (24.5 mL, 39.2 mmol, 1.6 M in hexanes) was added dropwise to a stirred solution of diisopropylamine (5.5 mL, 39.2 mmol) in dry THF (36 mL) at 0 °C. The solution was stirred for 10 minutes and cooled to -78 °C, whereupon a solution of methyl isobutyrate (4.12 mL, 35.6 mmol) in 4 mL of THF was added dropwise. After stirring for 1 hour at -78 °C, propargyl bromide was added dropwise. After completion, the mixture was quenched with saturated ammonium chloride and warmed to room temperature. The THF was removed *in vacuo*. The residue was distilled at reduced pressure to provide 2.49 g (50% yield) of the known⁵ clear, colorless liquid.

Bp 49–51 °C (10 mm Hg);

¹H NMR (400 MHz, CDCl₃, ppm) δ : 3.69 (s, 3H), 2.43 (d, J = 2.8 Hz, 2H), 2.00 (t, J = 2.8 Hz, 1H), 1.27 (s, 6H).



2,2-dimethylpent-4-ynoic acid (SI-8)

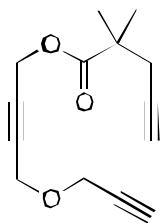
The acid was prepared according to a modified literature procedure.⁶ To a solution of potassium hydroxide (2.2 g, 35.6 mmol) in THF/MeOH/H₂O (50 mL, 3:1:1) was added ynoate **SI-7** (2.49 g, 17.8 mmol) dropwise. The reaction was allowed to stir overnight. The solution was acidified to pH = 3 and extracted with ether. The solvent was removed *in vacuo* resulting in 1.73 g (77% yield) of a clear, colorless liquid.

¹H NMR (400 MHz, CDCl₃, ppm) δ : 2.47 (d, J = 2.8 Hz, 2H), 2.03 (t, J = 2.8 Hz, 1H), 1.32 (s, 6H),
[missing CO₂H];

¹³C NMR (100 MHz, CDCl₃, ppm) δ : 183.4, 80.6, 70.7, 41.9, 29.2, 24.3;

IR (neat, ATR): 3302, 2978, 2938, 2912, 2121, 1698, 1474, 1409, 1388, 1368, 1282, 1261, 1227, 1160,
939, 862, 632;

HRMS (EI): calcd [M]⁺ (C₇H₉O₂) 125.0603, found 125.0608.



4-(prop-2-yn-1-yloxy)but-2-yn-1-yl 2,2-dimethylpent-4-ynoate (SI-9)

A solution of ynoic acid **SI-8** (1.01 g, 8.2 mmol) and alcohol **SI-6** (1.55 g, 12.3 mmol) in DCM (33 mL) was added dropwise to a solution of DCC (1.86 g, 9.0 mmol) and DMAP (100 mg, 0.8 mmol) in

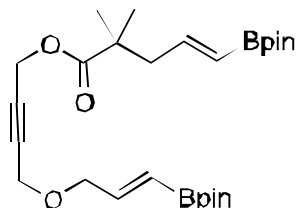
DCM (18 mL) and allowed to stir. After 48 hours the mixture was concentrated *in vacuo*. The residue was diluted with ether and filtered through celite. The sample was concentrated again and chromatographed with 95:5 hexanes:EtOAc to afford 1.12 g (59% yield) of a colorless fragrant oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 4.73 (s, 2H), 4.29 (s, 2H), 4.24 (d, *J* = 2.4 Hz, 2H), 2.45 (d, *J* = 2.5 Hz 2H), 2.45 (t, *J* = 2.4 Hz, 1H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.30 (s, 6H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 175.8, 81.7, 81.1, 80.6, 78.8, 75.1, 70.6, 56.7, 56.5, 52.5, 42.1, 29.5, 24.4;

IR (neat, ATR): 3292, 2977, 2936, 2857, 1734, 1471, 1444, 1389, 1367, 1347, 1316, 1299, 1247, 1192, 1124, 1078, 1022;

HRMS (ES): calcd [M+Na]⁺ (C₁₄H₁₆O₃Na) 255.099, found 255.111.



(*E*)-4-(((*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)but-2-yn-1-yl 2,2-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-enoate (3)

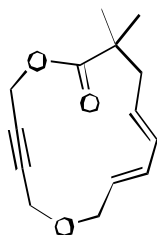
A flame dried round bottom flask was charged with triyne **SI-9** (1.12 g, 4.8 mmol), DCM (4.8 mL) and pinacolborane (3.3 mL, 21.6 mmol) under an inert atmosphere and allowed to stir at 0 °C for 5 minutes. The mixture was transferred via a cannula to another round bottom flask containing a suspension of Cp₂ZrHCl (250 mg, 1.0 mmol) in DCM (4.8 mL). The reaction stirred for 16 hours at room temperature. Water was added slowly, and the crude mixture was extracted with DCM, washed with brine, and dried over MgSO₄. The solvent was removed *in vacuo*, and chromatography with 90:10 hexanes/EtOAc afforded 740 mg (31% yield) of a viscous clear, colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 6.60 (dt, *J* = 18.1, 4.8 Hz, 1H), 6.48 (dt, *J* = 17.8, 7.2 Hz, 1H), 5.70 (dt, *J* = 18.2, 1.7 Hz, 1H), 5.45 (dt, *J* = 17.8, 1.3 Hz, 1H), 4.69 (t, *J* = 1.8 Hz, 2H), 4.19 (t, *J* = 1.8 Hz, 2H), 4.12 (dd, *J* = 4.8, 1.7 Hz, 2H), 2.40 (dd, *J* = 7.2, 1.3 Hz, 2H), 1.25 (s, 12H), 1.24 (s, 12H), 1.18 (s, 6H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 176.6, 149.0, 148.1, 83.3, 83.1, 82.5, 80.6, 71.2, 57.6, 52.3, 46.5, 42.2, 24.9, 24.78, 24.76 (boron substituted vinyl carbons absent);

IR (neat, ATR): 2978, 2933, 1736, 1640, 1358, 1322, 1270, 1244, 1214, 1165, 1142, 1121, 1077;

HRMS (ES): calcd [M+Na]⁺ (C₂₆H₄₂O₇B₂Na) 511.3024, found 511.3017.



(10E,12E)-8,8-dimethyl,1,6-dioxacyclotetradeca-10,12-diene-3-yne-7-one (4)

A flame dried 1.0 L round bottom flask was charged with Pd(PPh₃)₂Cl₂ (29 mg, 0.04 mmol). Freshly distilled methanol (205 mL), chloroacetone (330 μL, 4.1 mmol), *E,E*-bis(vinylboronate ester) **3** (200 mg, 0.40 mmol), and *aq.* 2 M potassium carbonate (610 μL, 1.2 mmol) were subsequently added and the reaction was allowed to stir overnight. Upon completion, methanol was removed *in vacuo*. The product was extracted with ether, washed with water and brine, and dried over MgSO₄. Chromatography using a gradient from 90:10 to 80:20 hexanes/EtOAc afforded 61 mg (64% yield) of a clear, colorless oil.

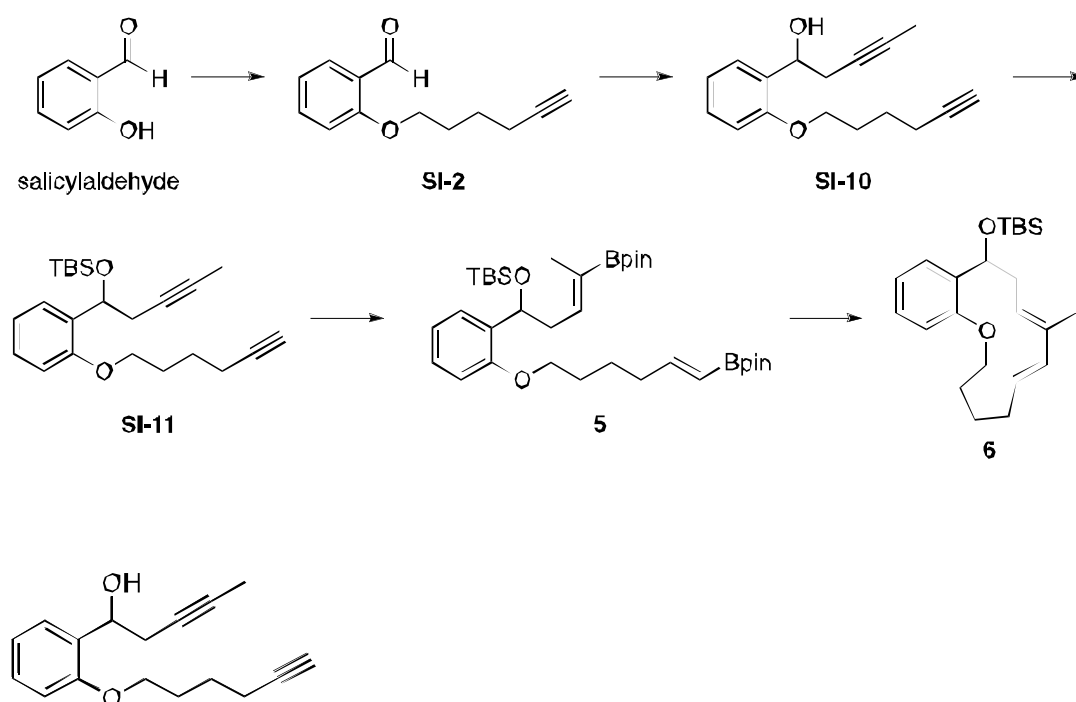
¹H NMR (400 MHz, CDCl₃, ppm) δ: 6.15 (dd, *J* = 15.0, 10.3 Hz, 1H), 6.02 (dd, *J* = 15.0, 10.4 Hz, 1H), 5.79-5.67 (m, 2H), 4.69 (d, *J* = 1.2 Hz, 2H), 4.11 (d, *J* = 1.2 Hz, 2H), 4.07 (d, *J* = 7.4 Hz, 2H), 1.24 (s, 6H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 175.7, 135.3, 134.4, 129.6, 129.1, 85.2, 81.7, 74.1, 58.2, 51.0, 46.2, 45.1, 25.1;

IR (neat, ATR): 3025, 2977, 2934, 2875, 2850, 1729, 1473, 1450, 1434, 1390, 1366, 1297, 1253, 1204, 1135, 1121, 1097, 1060, 1013;

HRMS (ES): calcd $[\text{M}+\text{Na}]^+$ ($\text{C}_{14}\text{H}_{18}\text{NO}_3\text{Na}$) 257.1154, found 257.1153.

Scheme 3. Preparation of **6**



1-(2-(hex-5-yn-1-yloxy)phenyl)pent-3-yn-1-ol (SI-10)

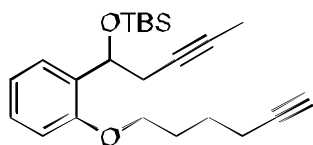
A flame dried 250 mL flask was flushed with nitrogen for 10 minutes. The flask was then charged with zinc metal (2.76 g, 44.2 mmol), iodine (1.12 g, 8.85 mmol), 1-bromo-2-butyne (1.12 mL, 1.24 mmol), and aldehyde **SI-2** (1.79 g, 8.85 mmol), and THF (90 mL) and sonicated for 3 hours. The reaction was then quenched with saturated ammonium chloride and filtered through Celite. The solvent was evaporated and the residue was dissolved in ether, washed with water and brine, and dried over MgSO_4 . The solvent was removed *in vacuo*. Chromatography with 90:10 hexanes/EtOAc afforded 976 mg (43% yield) of a clear, colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.41 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.23 (td, *J* = 7.8, 1.2 Hz, 1H), 6.97 (td, *J* = 7.6, 0.8 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 5.05 (ddd, *J* = 7.7, 5.2, 4.8 Hz, 1H), 4.08–4.01 (m, 2H), 2.82 (d, *J* = 5.6 Hz, 1H), 2.71 (ddq, *J* = 16.5, 4.8, 2.4 Hz, 1H), 5.13 (ddq, *J* = 16.5, 7.7, 2.8 Hz, 1H), 2.29 (td, *J* = 7.0, 2.8 Hz, 2H), 1.98 (t, *J* = 2.8 Hz, 1H), 1.97–1.92 (m, 2H), 1.81 (t, *J* = 2.4 Hz, 3H), 1.76–1.69 (m, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 155.5, 130.8, 128.5, 126.7, 120.6, 111.0, 83.9, 78.2, 75.8, 68.9, 68.8, 67.3, 28.3, 28.0, 25.1, 18.2, 3.6;

IR (neat, ATR): 3553, 3290, 3040, 2918, 2870, 2114, 1602, 1588, 1492, 1472, 1454, 1433, 1390, 1285, 1237, 1161, 1114, 1047, 962, 864, 808, 752;

HRMS (ES): calcd [M+Na]⁺ (C₁₇H₂₀O₂Na) 279.1361, found 279.1363.



***tert*-butyl((1-(2-(hex-5-yn-1-yloxy)phenyl)pent-3-yn-1-yl)oxy)dimethylsilane (SI-11)**

A 25 mL round bottom flask was charged with alcohol **SI-10** (690 mg, 2.69 mmol) and purged with N₂ for 10 minutes. DMF (8 mL), imidazole (458 mg, 6.73 mmol) and *tert*-butyldimethylsilyl chloride (487 mg, 3.23 mmol) were subsequently added and the solution was allowed to stir for 5 hours. The reaction was quenched with water and extracted with diethyl ether. The combined organic layers were washed with water and brine and dried over MgSO₄. The solvent was removed *in vacuo*. Chromatography with 95:5 hexanes/EtOAc afforded 978 mg (98% yield) of a clear, colorless oil.

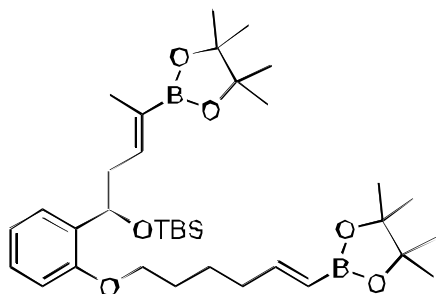
¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.50 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.19 (td, *J* = 7.8, 1.4 Hz, 1H), 6.94 (td, *J* = 7.4, 0.8 Hz, 1H), 6.80 (dd, *J* = 8.0, 0.8 Hz, 1H), 5.22 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.00 (m, 2H), 2.51–2.46 (m, 1H), 2.40–2.33 (m, 1H), 2.30 (td, *J* = 7.0, 2.5 Hz, 2H), 1.98 (t, *J* = 2.6 Hz,

1H), 1.98–1.91 (m, 2H), 1.79–1.73 (m, 2H), 1.78 (t, $J = 2.6$ Hz, 3H), 1.73 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 154.7, 133.0, 127.9, 126.8, 120.4, 110.6, 84.0, 77.4, 76.4, 68.7, 68.1, 67.1, 29.6, 28.3, 25.8, 25.2, 18.4, 18.2, 3.6, -4.8, -5.0;

IR (neat, ATR): 3310, 3040, 2951, 2927, 2856, 2117, 1602, 1590, 1490, 1472, 1454, 1389, 1362, 1281, 1237, 1181, 1160, 1116, 1082, 1006, 939, 876;

HRMS (ES): calcd $[\text{M}+\text{Na}]^+$ ($\text{C}_{23}\text{H}_{34}\text{O}_2\text{SiNa}$) 393.2226, found 393.2227.



tert-butyl dimethyl((*Z*)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2-(((*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-yl)oxy)-phenyl)pent-3-en-1-yl)oxy)silane (5**)**

A flame dried 5 mL round bottom flask was charged with diyne **SI-11** (210 mg, 0.567 mmol) and flushed with nitrogen for 10 minutes. Pinacolborane (346 μL , 2.27 mmol) and triethylamine (16 μL , 0.113 mmol) were added via syringe to the flask and allowed to stir at 0 $^\circ\text{C}$ for 5 minutes. The mixture was transferred via a cannula to another round bottom flask containing Cp_2ZrHCl (29 mg, 0.113 mmol). The reaction stirred for 48 hours at 60 $^\circ\text{C}$. The solvent was removed *in vacuo*. Chromatography with 95:5 petroleum ether/ Et_2O afforded 92 mg (26% yield) of a clear, colorless oil.

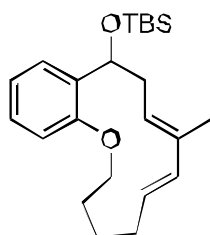
^1H NMR (400 MHz, CDCl_3 , ppm) δ : 7.50 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.16 (td, $J = 7.7, 1.7$ Hz, 1H), 6.92 (t, $J = 7.6$ Hz, 1H), 6.78 (d, $J = 8.1$ Hz, 1H), 6.64 (ddd, $J = 17.9, 6.0, 6.0$ Hz, 1H), 6.51–6.44 (m, 1H), 5.46 (d, $J = 18.0$ Hz, 1H), 5.24–4.15 (m, 1H), 4.00–3.87 (m, 2H), 2.57–2.34 (m, 2H), 2.26–2.21

(m, 2H), 1.84–1.76 (m, 2H), 1.66–1.57 (m, 2H), 1.657 (s, 3H), 1.33 (s, 12H), 1.27 (s, 12H), 0.87 (s, 9H), -0.01 (s, 3H), -0.13 (s, 3H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 154.6, 153.9, 143.9, 143.2, 127.4, 126.7, 120.2, 110.5, 83.01, 82.96, 68.4, 67.4, 38.7, 35.4, 28.8, 25.9, 24.8, 18.3, 13.9, -4.7, -5.0 (boron substituted vinyl carbons absent);

IR (neat, ATR): 2978, 2928, 2856, 1637, 1602, 1589, 1490, 1471, 1454, 1368, 1322, 1303, 1272, 1255, 1236, 1216, 1146, 1127, 1110, 1075;

HRMS (ES): calcd [M+Na]⁺ (C₃₅H₆₀O₆B₂SiNa) 649.4256, found 649.4238.



***tert*-butyldimethyl(((6*E*,8*E*)-8-methyl-2,3,4,5,10,11-hexahydrobenzo-[*b*][1]oxacyclotridecin-11-yl)oxy)silane (6)**

A flame dried 100 mL flask was charged with Pd(PPh₃)₂Cl₂ (10 mg, 0.0146 mmol). Freshly distilled methanol (75 mL), chloroacetone (117 μL, 1.46 mmol), *E,E*-bis(vinylboronate ester) **5** (92 mg, 0.146 mmol), and *aq.* 2 M potassium carbonate (366 μL, 0.732 mmol) were subsequently added and the reaction was allowed to stir overnight at 60 °C. Upon completion, methanol was removed *in vacuo*. The product was extracted with ether, washed with water and brine, and dried over MgSO₄. Chromatography with 92:8 hexanes/EtOAc afforded 36 mg (66% yield) of a clear, colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.53 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.14 (td, *J* = 7.8, 1.8 Hz, 1H), 6.93 (td, *J* = 7.5, 0.6 Hz, 1H), 6.71 (dd, *J* = 8.2, 0.8 Hz, 1H), 5.97 (d, *J* = 15.7 Hz, 1H), 5.35 (ddd, *J* = 15.6, 9.3, 6.0 Hz, 1H), 5.01 (t, *J* = 8.4 Hz, 1H), 4.90 (dd, *J* = 10.5, 3.9 Hz, 1H), 3.99 (dt, *J* = 9.2,

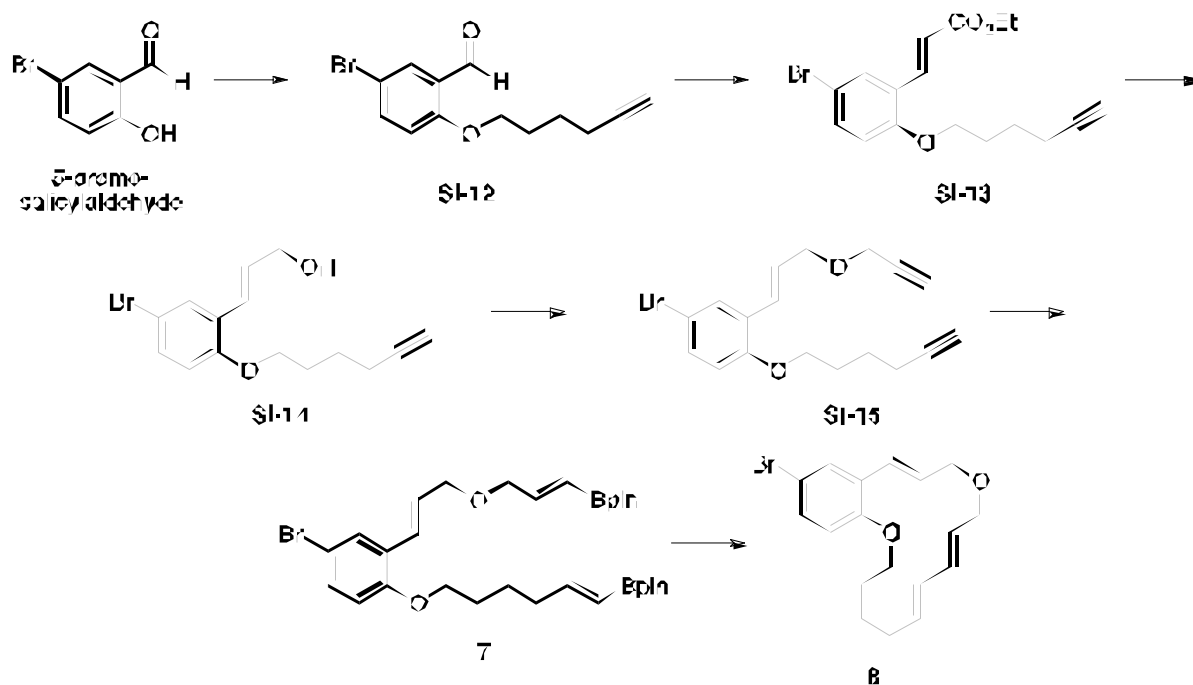
7.2 Hz, 1H), 3.57–3.51 (m, 1H), 2.76–2.70 (m, 1H), 2.34–2.24 (m, 2H), 2.16–2.06 (m, 1H), 1.85–1.69 (m, 2H), 1.65–1.50 (m, 1H), 1.57 (s, 3H), 0.86 (s, 9H), 0.01 (s, 3H), -0.10 (s, 3H);

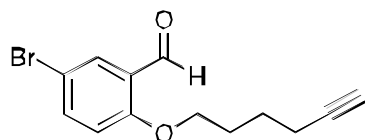
^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 155.6, 139.2, 136.5, 134.3, 127.8, 127.5, 124.5, 123.2, 120.5, 111.7, 68.6, 67.6, 39.9, 31.8, 31.6, 31.4, 25.9, 25.40, 25.36, 18.2, 12.1, -4.9, -5.1;

IR (neat, ATR): 2951, 2928, 2856, 1600, 1489, 1471, 1453, 1286, 1255, 1067, 936;

HRMS (CI): calcd $[\text{M}]^+$ ($\text{C}_{23}\text{H}_{36}\text{O}_2\text{Si}$) 372.2484, found 372.2493.

Scheme 4. Preparation of **8**





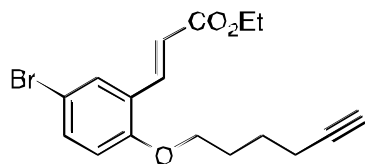
5-bromo-2-(hex-5-yn-1-yloxy)benzaldehyde (SI-12)

To a stirred solution of distilled dimethylformamide (200 mL) and bromosalicylaldehyde (10.0 g, 49.8 mmol) was added slowly a 60% sodium hydride dispersion in paraffin oil (2.19 g, 54.8 mmol). After stirring for 10 minutes, tosylate **SI-1** (1.26 g, 49.8 mmol) was added via syringe. The reaction was taken to 70 °C and stirred for two days. The resulting solution was allowed to cool to room temperature and then quenched with 100 mL of *aq.* 15% NaOH. Diethyl ether (100 mL) was added, the layers separated and the organic layer was washed twice with water. The organic layer was washed once with brine (50 mL) and the organics removed *in vacuo*. The crude product was purified by column chromatography on silica gel using a solvent system of 80:20 hexanes/EtOAc to give 11.8 g of a yellow oil in an 84% yield.

¹H NMR (500 MHz, CDCl₃, ppm) δ: 10.38 (s, 1H), 7.87 (d, *J* = 2.6 Hz, 1H), 7.55 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.86 (t, *J* = 8.9, 1H), 4.08 (t, *J* = 6.2, 2H), 2.27 (td, *J* = 6.9, 2.7 Hz, 2H), 2.02–1.94 (m, 3H), 1.76–1.68 (m, 2H);

¹³C NMR (125 MHz, CDCl₃, ppm) δ: 188.2, 160.1, 138.2, 130.7, 126.0, 114.4, 113.2, 83.6, 68.9, 68.2, 27.8, 24.8, 18.0;

IR (neat, ATR): 3080, 2980, 2362, 1777, 1640, 1490, 1455, 1238, 1163, 1116, 995, 918, 754.



(E)-ethyl 3-(5-bromo-2-(hex-5-yn-1-yloxy)phenyl)acrylate (SI-13)

A solution of ethyl 2-diethoxyphosphoryl acetate (9.16 g, 45.8 mmol) was prepared in THF (200 mL), and cooled to 0 °C. A dispersion of sodium hydride in paraffin oil (1.83 g, 45.8 mmol) was added to

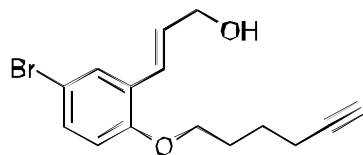
this solution slowly. After stirring for twenty minutes, aldehyde **SI-12** (12.35 g, 41.6 mmol) was added. This was stirred for another hour at 0 °C, and then allowed to warm to room temperature over two hours. Upon completion, aqueous workup constituting a wash with *aq.* sodium bicarbonate (100 mL) and brine (100 mL) was performed followed by removal of the organic solvent *in vacuo*. After column chromatography on silica gel in a solvent system consisting of 80:20 hexanes/EtOAc, 12.3 g of the product was obtained as a yellow oil in 84% yield.

¹H NMR (500 MHz, CDCl₃, ppm) δ: 7.89 (d, *J* = 16.2 Hz, 1H), 7.60 (d, *J* = 2.5 Hz, 1H), 7.38 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 1H), 6.47 (d, *J* = 16.2 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.02 (t, *J* = 6.4, 2H), 2.28 (td, *J* = 6.9, 2.7 Hz, 2H), 2.03–1.94 (m, 3H), 1.76–1.67 (m, 2H), 1.32 (t, *J* = 7.2, 3H);

¹³C NMR (125 MHz, CDCl₃, ppm) δ: 166.9, 156.4, 138.2, 133.6, 130.9, 125.4, 119.8, 113.6, 112.8, 83.7, 68.8, 68.1, 60.4, 27.9, 24.8, 18.0, 14.2;

IR (neat, ATR): 3289, 2933, 2125, 1708, 1627, 1487, 1274, 1165, 1022, 982;

HRMS (EI): calcd [M+Na]⁺ (C₁₇H₁₉BrO₃Na) 373.0415, found 373.0418.



(*E*)-3-(5-bromo-2-(hex-5-yn-1-yloxy)phenyl)prop-2-en-1-ol (SI-14)

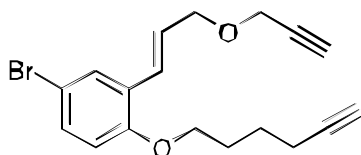
Ester **SI-13** (8.11 g, 23.1 mmol) was stirred in a solution of THF (250 mL) and cooled to 0 °C. A 1.5 M solution of DIBAL-H in toluene (46.2 mL, 69.3 mmol) was added slowly onto the sides of the flask of the stirring solution. After the solution was added, the reaction was stirred for another two hours, and then allowed to warm to room temperature. After dilution with 200 mL ether, the reaction mixture was again cooled to 0 °C. To quench the reaction, 3.2 mL of water was added, followed by 3.2 mL of *aq.* 15% NaOH solution. Another 8.0 mL of water was added, and the reaction was allowed to warm to room

temperature and stirred for another 15 minutes. To the solution was added 3.0 g of magnesium sulfate, and then the reaction mixture was filtered through Celite. Removal of the solvent gave 7.14 g, a quantitative yield, of the desired product.

¹H NMR (500 MHz, CDCl₃, ppm) δ : 7.52 (d, J = 2.4 Hz, 1H), 7.27 (dd, J = 8.4, 2.4 Hz, 1H), 6.84 (dt, J = 16.1, 1.4 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 6.36 (dt, J = 16.0, 5.7 Hz, 1H), 4.32 (dd, J = 5.7, 1.4 Hz, 2H), 3.97 (t, J = 6.3 Hz, 2H), 2.28 (td, J = 7.0, 2.6 Hz, 2H), 1.99 (t, J = 2.6 Hz, 1H) 1.96–1.91 (m, 2H), 1.81–1.73 (br s, 1H), 1.74–1.70 (m, 2H);

¹³C NMR (125 MHz, CDCl₃, ppm) δ : 155.0, 131.0, 130.3, 129.4, 127.8, 124.6, 113.4, 112.9, 83.9, 68.7, 67.9, 63.8, 28.0, 25.0, 18.0;

IR (neat, ATR): 3290, 2925, 2864, 2118, 1588, 1485, 1468, 1242, 1125, 1013, 978, 965, 803.



(E)-4-bromo-1-(hex-5-yn-1-yloxy)-2-(3-(prop-2-yn-1-yloxy)prop-1-en-1-yl)-benzene (SI-15)

To a stirring solution of alcohol **SI-14** (120 mg, 0.36 mmol) in THF (10 mL) was added sodium hydride (14 mg, 0.36 mmol). To this was then added an 80% solution of propargyl bromide in toluene (0.04 mL, 0.36 mmol). This mixture did not react until the addition of 1 mL of DMSO. After stirring overnight at room temperature, the THF was removed *in vacuo* and the resulting mixture diluted with ether (40 mL) and washed with *aq.* sodium bicarbonate solution (5 mL) and twice with water (5 mL). After chromatography on silica gel in a 90:10 hexanes/EtOAc eluent system, 110 mg of the desired product was obtained as a yellow oil in a 87% yield.

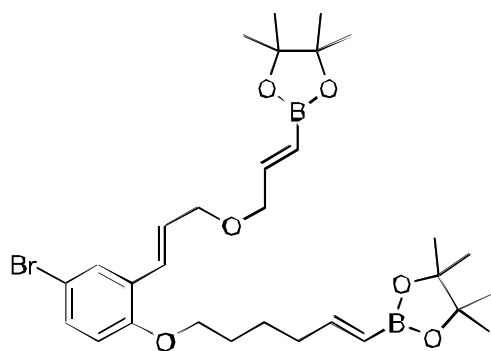
¹H NMR (500 MHz, CDCl₃, ppm) δ : 7.54 (d, J = 2.5 Hz, 1H), 7.29 (dd, J = 8.8, 2.5 Hz, 1H), 6.88 (dt, J = 16.1, 1.0 Hz, 1H), 6.72 (d, J = 8.7 Hz, 1H), 6.27 (dt, J = 16.0, 6.3 Hz, 1H), 4.25 (dd, 6.3, J = 1.0

Hz, 2H), 4.20 (d, $J = 2.4$ Hz, 2H), 3.98 (t, $J = 6.3$ Hz, 2H), 2.46 (t, $J = 2.4$ Hz, 1H), 2.29 (td, $J = 7.0, 2.6$ Hz, 2H), 1.98 (t, $J = 2.6$ Hz, 1H), 1.97–1.92 (m, 2H), 1.76–1.70 (m, 2H);

^{13}C NMR (125 MHz, CDCl_3 , ppm) δ : 155.1, 131.1, 129.5, 127.6, 127.0, 126.8, 113.4, 112.9, 83.9, 79.6, 74.4, 70.3, 68.7, 67.9, 56.9, 28.0, 25.0, 18.0;

IR (neat, ATR): 3297, 2940, 2116, 1589, 1485, 1244, 1105, 973, 880, 805, 626.

HRMS (EI): calcd $[\text{M}+\text{NH}_4]^+$ ($\text{C}_{18}\text{H}_{23}\text{BrNO}_2$) 364.0912, found 364.0916.



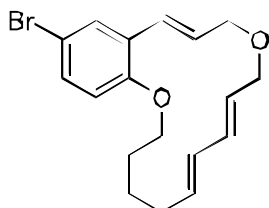
2-(((*E*)-3-(((*E*)-3-(5-bromo-2-(((*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-yl)oxy)phenyl)allyl)oxy)prop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7)

Schwartz's reagent (Cp_2ZrHCl , 51 mg, 0.2 mmol) was weighed out in an inert atmosphere. In a separate flask, to enediyne **SI-15** (360 mg, 1.0 mmol) was added triethylamine (30 μL , 0.2 mmol) and pinacolborane (580 μL , 4.0 mmol). The mixture was transferred into the flask containing Schwartz's reagent via a double-ended needle. The resulting solution was heated to 60 $^\circ\text{C}$ and allowed to stir overnight. The solution was then cooled and subjected to column chromatography on silica gel. In an elution solution of 80:20 hexanes/EtOAc, 0.36 g of the product was found as a yellow oil in 59% yield.

^1H NMR (500 MHz, CDCl_3 , ppm) δ : 7.53 (d, $J = 2.4$ Hz, 1H), 7.26 (dd, $J = 8.7, 2.5$ Hz, 1H), 6.82 (d, $J = 8.7$ Hz, 1H), 6.73–6.57 (m, 3H), 6.28 (dt, $J = 16.0, 6.1$ Hz, 1H), 5.73 (d, $J = 18.1$ Hz, 1H), 5.46 (d, $J = 18.0$ Hz, 1H), 4.16 (dd, $J = 6.0, 1.3$ Hz, 2H), 4.11 (dd, $J = 4.7, 1.7$ Hz, 2H), 3.93 (t, $J = 6.5$ Hz, 2H), 2.25–2.21 (m, 2H) 1.85–1.79 (m, 1H), 1.63–1.57 (m, 2H), 1.26 (s, 12H), 1.26 (s, 12H);

¹³C NMR (125 MHz, CDCl₃, ppm) δ: 155.1, 153.7, 149.1, 130.9, 129.4, 127.9, 127.7, 125.9, 113.4, 112.8, 83.1, 82.9, 71.5, 71.0, 68.2, 35.1, 28.5, 24.6, 24.5 (boron substituted vinyl carbons absent);

IR (neat, ATR): 2977, 2931, 1641, 1469, 1360, 1244, 1144, 971, 880, 805, 643.



(6E,8E,13E)-16-bromo-2,3,4,5,10,12-hexahydrobenzo[*b*][1,7]dioxacyclo-hexadecine (8)

To a solution of *E,E*-bis(vinylboronate ester) **7** (110 mg, 0.22 mmol) in MeOH (65 mL), was added PdCl₂(PPh₃)₂ (15 mg, 0.02 mmol) and chloroacetone (50 μL, 0.66 mmol). The reaction was then activated by adding *aq.* 2 M K₂CO₃ (440 μL, 0.88 mmol). Allowing the solution to stir overnight led to complete consumption of starting material. Diethyl ether (100 mL) was added, and MeOH was removed by two washes with 150 mL water. After isolation of the organics, the solvent was removed *in vacuo*, and the residue was subjected to column chromatography on silica gel. Using a 90:10 hexanes/EtOAc eluent system, 56 mg of the desired macrocycle was found corresponding to a 73% yield.

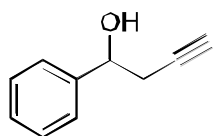
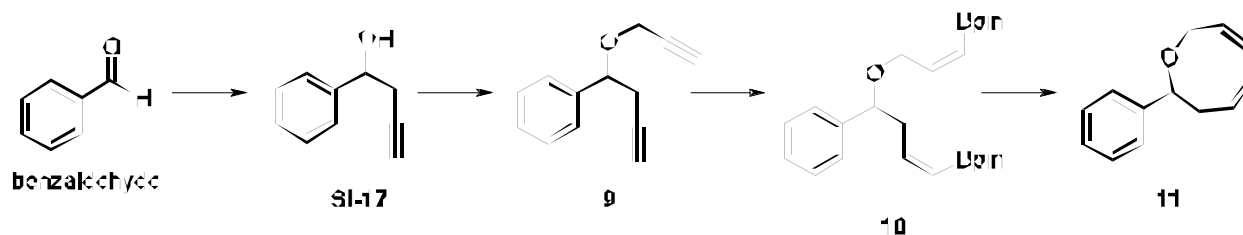
¹H NMR (500 MHz, CDCl₃, ppm) δ: 7.59 (s, 1H), 7.27 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.75 (d, *J* = 8.7 Hz, 1H), 6.61 (d, *J* = 16.1 Hz, 1H), 6.26–6.15 (m, 2H), 6.04 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.72 (dt, *J* = 15.4, 6.9 Hz, 1H), 5.58 (dt, *J* = 15.3, 7.6 Hz, 1H), 4.16 (d, *J* = 7.0 Hz, 2H), 4.12 (d, *J* = 7.0 Hz, 2H), 3.87 (t, *J* = 5.6 Hz, 2H), 2.16–2.14 (m, 2H), 1.87–1.84 (m, 2H), 1.69–1.65 (m, 2H);

¹³C NMR (125 MHz, CDCl₃, ppm) δ: 155.4, 134.3, 133.9, 131.4, 131.0, 128.9, 128.7, 128.6, 128.5, 126.0, 115.6, 113.6, 72.5, 69.6, 69.4, 29.8, 26.6, 25.7;

IR (neat, ATR): 2923, 2851, 1727, 1486, 1464, 1241, 1104, 1024, 971, 801;

HRMS (CI): calcd [M+NH₄]⁺ (C₁₈H₂₅BrNO₂) 366.1069, found 366.1071.

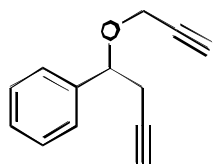
Scheme 5. Preparation of **11**



1-phenyl-3-butyn-1-ol (SI-17)

A flame dried, nitrogen flushed 500 mL round bottom flask was charged with zinc dust (9.24 g, 141.3 mmol), iodine (3.56 g, 28.3 mmol), THF (280 mL), benzaldehyde (3.0 g, 28.3 mmol), and propargyl bromide (3.78 mL, 33.9 mmol) and sonicated for 3 hours. The reaction was quenched with ammonium chloride and filtered through Celite. Chromatography with 90:10 hexanes/EtOAc afforded 3.256 g (79% yield) of the known⁷ clear, colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ : 7.41–7.26 (m, 5H) 4.88 (t, J = 6.4 Hz, 1H), 2.65 (dd, J = 6.2, 2.4 Hz, 2H), 2.50 (bs, 1H), 2.08 (t, J = 2.4 Hz, 1H).



(1-(prop-2-yn-1-yloxy)-3-butyn-1-yl)benzene (9)

To a suspension of NaH (503 mg, 12.6 mmol, 60% w/w dispersion in mineral oil) in THF/DMSO (10:1, 45 mL) was added alcohol **SI-17** (1.60 g, 10.9 mmol) dropwise and stirred for 30 minutes. Propargyl bromide (1.40 mL, 12.6 mmol, 80% w/v in toluene) over was added five minutes and stirred

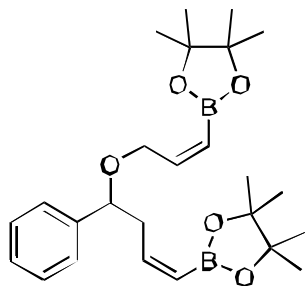
for 48 hours. The reaction was diluted with ether and washed thoroughly with water followed by brine. After drying over MgSO_4 and concentrating *in vacuo*, chromatography with 97:3 hexanes/EtOAc afforded 1.56 g (74% yield) of a clear, yellow oil.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 7.38–7.35 (m, 5H), 4.71 (t, J = 6.8 Hz, 1H), 4.18 (dd, J = 16.0, 2.4 Hz, 1H), 3.92 (dd, J = 16.0, 2.4 Hz, 1H), 2.76 (ddd, J = 16.8, 6.6, 2.4 Hz, 1H), 2.62 (ddd, J = 16.8, 6.8, 2.8 Hz, 1H), 2.43 (t, J = 2.4 Hz, 1H), 1.98 (t, J = 2.8 Hz, 1H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 139.4, 128.5, 128.4, 127.0, 80.4, 79.4, 78.7, 74.6, 70.2, 55.9, 27.7;

IR (neat, ATR): 3290, 3087, 3064, 3032, 2940, 2912, 2858, 2119, 1954, 1885, 1817, 1734, 1603, 1494, 1455, 1430, 1386, 1352, 1307, 1287, 1259, 1201, 1157, 1075, 1019, 935, 916, 850, 756, 700, 632;

HRMS (CI): calcd $[\text{M}+\text{NH}_4]^+$ ($\text{C}_{13}\text{H}_{16}\text{ON}$) 202.1232, found 202.1228.



4,4,5,5-tetramethyl-2-((Z)-4-phenyl-4-(((Z)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)-but-1-en-1-yl)-1,3,2-dioxaborolane (10)

A flame dried 100 mL round bottom flask was charged with diyne **9** (1.035 g, 5.62 mmol) and flushed with nitrogen for 10 minutes. Diethyl ether (50 mL) was added and the flask was cooled to $-78\text{ }^\circ\text{C}$. *n*-Butyl lithium (4.48 mL, 11.2 mmol, 2.5 M in hexanes) was added over 15 minutes and the reaction was allowed to stir for 30 minutes before transferring to a solution of PINBOP (2.29 mL, 11.2 mmol) in diethyl ether (50 mL) in a 250 mL flame-dried flask. After 2 hours, the reaction was allowed to warm to room temperature. After 16 hours, the temperature was lowered to $-50\text{ }^\circ\text{C}$ and HCl (2.80 mL, 11.2 mmol,

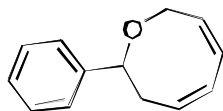
4.0 M in dioxane) was added dropwise. After 2 hours at room temperature, the solution was filtered under nitrogen through Celite, and the solvent was removed *in vacuo*. The crude bis-alkynyl-Bpin was then dissolved in THF (25 mL), delivered to a solution of Cp₂ZrHCl (2.89 g, 11.2 mmol) in THF (25 mL), and stirred for 16 hours. After the reaction pot turned a rusty orange, the zirconocene was hydrolyzed with water (5 mL). The solvent was removed *in vacuo*. Chromatography with 93:7 hexanes/EtOAc afforded 1.42 g (58% yield) of a clear, colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.34–7.22 (m, 5H), 6.53 (ddd, *J* = 13.6, 6.8, 6.8, 1H), 6.46 (ddd, *J* = 14.0, 7.0, 7.0, 1H), 5.47 (ddd, *J* = 14.0, 1.6, 1.6, 1H), 5.40 (ddd, *J* = 13.6, 1.2, 1.2, 1H) 4.37 (dd, *J* = 7.0, 6.4, 1H), 4.20 (m, 2H), 2.93–2.80 (m, 2H), 1.24 (s, 6H), 1.23 (s, 6H), 1.16 (s, 6H), 1.15 (s, 6H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 150.7, 150.6, 142.3, 128.1, 127.2, 126.9, 83.1, 82.9, 81.6, 68.2, 40.4, 24.9, 24.8, 24.7, 24.7 (boron substituted vinyl carbons absent);

IR (neat, ATR): 3062, 2978, 2932, 1629, 1421, 1389, 1371, 1321, 1281, 1258, 1212, 1165, 1143, 1088, 1027, 967, 911, 877, 846, 750, 700;

HRMS (ES): calcd [M+Na]⁺ (C₂₅H₃₈O₅B₂Na) 463.2812, found 463.2809.



(4Z,6Z)-2-phenyl-3,8-dihydro-2H-oxocine (11)

A flame dried 500 mL flask was charged with Pd(PPh₃)₂Cl₂ (20 mg, 0.028 mmol). Freshly distilled methanol (250 mL), chloroacetone (450 μL, 5.68 mmol), Z,Z-bis(vinylboronate ester) **10** (250 mg, 0.568 mmol), and *aq.* 2 M potassium carbonate (852 μL, 1.70 mmol) were subsequently added and the reaction was allowed to stir overnight. Upon completion, methanol was removed *in vacuo*. The

product was extracted with ether, washed with water and brine, and dried over MgSO_4 . Chromatography with 98:2 hexanes/EtOAc afforded 80 mg (76% yield) of a clear, colorless oil.

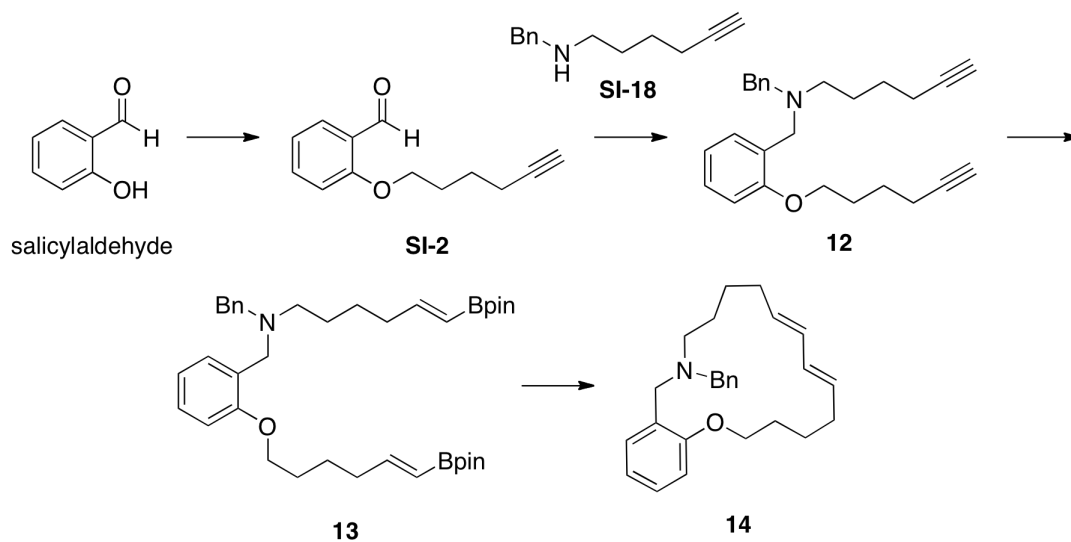
^1H NMR (400 MHz, CDCl_3 , ppm) δ : 7.37–7.31 (m, 4H), 7.28–7.23 (m, 1H), 6.13 (dd, $J = 11.0, 4.6$ Hz, 1H), 5.94 (dd, $J = 11.6, 4.4$ Hz, 1H), 5.72–5.60 (m, 2H), 4.55–4.50 (m, 2H), 4.05 (ddd, $J = 16.1, 5.1, 1.6$ Hz, 1H), 2.89 (ddd, $J = 13.7, 8.3, 3.2$ Hz, 1H), 2.43 (ddd, $J = 13.6, 6.8, 6.8$ Hz, 1H);

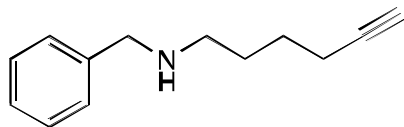
^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 143.0, 129.2, 128.7, 128.2, 128.0, 127.2, 126.3, 126.2, 77.1, 67.6, 35.6;

IR (neat, ATR): 3061, 3022, 2914, 2866, 1949, 1880, 1810, 1727, 1494, 1450, 1360, 1281, 1116, 1093, 1058, 1031, 1010, 729, 706, 697, 656;

HRMS (EI): calcd $[\text{M}]^+$ ($\text{C}_{13}\text{H}_{14}\text{O}$) 186.1045, found 186.1038.

Scheme 6. Preparation of **14**

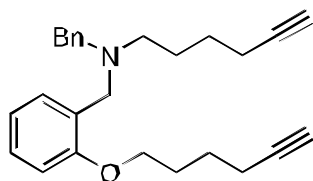




N-benzyl-5-hexyn-1-amine (SI-18)

A solution of benzylamine (4.76 mL, 43.6 mmol) and hex-5-yn-1-yl 4-methylbenzenesulfonate **SI-1** (5.0 g, 19.8 mmol) in DMSO was stirred at 50 °C for 5 hours under nitrogen atmosphere. The reaction mixture was then poured into *aq.* 1% NaOH (100 mL), extracted with ether (3 x 100 mL), washed with brine, and dried over MgSO₄. Solvent was removed *in vacuo*. Chromatography with 60:40 Et₂O/Hex (with 1% Et₃N) afforded 3.26 g (88% yield) of the known⁸ clear, yellowish oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ : 7.36–7.24 (m, 5H), 3.81 (s, 2H), 2.68 (t, J = 6.8 Hz, 2H), 2.23 (td, J = 6.9, 2.6 Hz, 2H), 1.96 (t, J = 2.6 Hz, 1H), 1.70–1.56 (m, 2H), 1.30 (bs, 1H).



N-benzyl-N-(2-(5-hexynyloxy)benzyl)-5-hexyn-1-amine (12)

Prepared according to a modified literature procedure.⁹ Sodium triacetoxyborohydride (NaBH(OAc)₃, 3.14 g, 14.8 mmol) was added to a stirred solution of aldehyde **SI-2** (2.0 g, 9.89 mmol) and amine **SI-18** (2.04 g, 10.9 mmol) in THF (50 mL) and the mixture was allowed to stir for 24 hours at room temperature. The reaction was quenched with *aq.* 3 N NaOH, extracted with diethyl ether, and dried over MgSO₄. Solvent was removed *in vacuo*. Chromatography with 92:8 hexanes/EtOAc afforded 3.152 g (85% yield) of a clear, colorless oil.

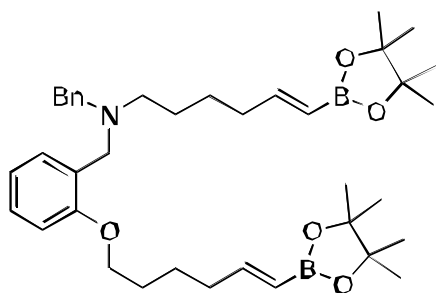
¹H NMR (400 MHz, CDCl₃, ppm) δ : 7.54 (dd, J = 7.5, 1.6 Hz, 1H), 7.39 (d, J = 7.0 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.25–7.18 (m, 2H), 6.96 (td, J = 7.4, 0.9 Hz, 1H), 6.84 (dd, J = 8.1, 0.6 Hz, 1H), 3.99

(t, $J = 6.2$ Hz, 2H), 3.64 (s, 2H), 3.61 (s, 2H), 2.46 (t, $J = 6.9$ Hz, 2H), 2.30 (td, $J = 7.0, 2.6$ Hz, 2H), 2.12 (td, $J = 7.0, 2.6$ Hz, 2H), 2.00 (t, $J = 2.7$ Hz, 1H), 1.96–1.90 (m, 2H), 1.93 (t, $J = 2.6$ Hz, 1H), 1.78–1.71 (m, 2H), 1.69–1.61 (m, 2H), 1.58–1.51 (m, 2H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 157.1, 140.3, 130.0, 128.7, 128.14, 128.11, 127.5, 126.6, 120.4, 111.1, 84.7, 84.2, 68.7, 68.2, 67.3, 58.6, 53.0, 51.6, 28.4, 26.3, 26.2, 25.2, 18.23, 18.24;

IR (neat, ATR): 3296, 3084, 3062, 3028, 2942, 2864, 2797, 2116, 1600, 1588, 1493, 1472, 1453, 1433, 1372, 1324, 1283, 1237, 1160, 1121, 1103, 1050, 964;

HRMS (ES): calcd $[\text{M}+\text{H}]^+$ ($\text{C}_{26}\text{H}_{32}\text{NO}$) 374.2484, found 374.2479.



(*E*)-*N*-benzyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*-(2-(((*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-enyl)oxy)benzyl)hex-5-en-1-amine (13)

A flame dried 50 mL round bottom flask was charged with diyne **12** (500 mg, 1.34 mmol) and flushed with nitrogen for 10 minutes. Pinacolborane (818 μL , 5.35 mmol) and triethylamine (37 μL , 0.268 mmol) were added via syringe to the flask and allowed to stir at 0 $^\circ\text{C}$ for 5 minutes. The mixture was transferred via a cannula to another round bottom flask containing Cp_2ZrHCl (69 mg, 0.268 mmol). The reaction stirred for 16 hours at 60 $^\circ\text{C}$. The solvent was removed *in vacuo*. Chromatography with 90:10 hexanes/EtOAc afforded 460 mg (54% yield) of a very viscous clear, colorless oil.

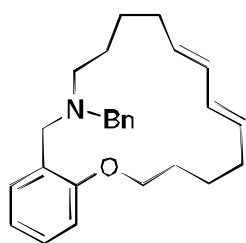
^1H NMR (400 MHz, CDCl_3 , ppm) δ : 7.52 (dd, $J = 7.4, 1.4$ Hz, 1H), 7.37 (d, $J = 7.1$ Hz, 2H), 7.29 (t, $J = 7.4$ Hz, 2H), 7.2 (t, $J = 7.4$ Hz, 1H), 7.16 (td, $J = 7.7, 1.6$ Hz, 1H), 6.93 (t, $J = 7.4$ Hz, 1H), 6.80 (d, $J = 7.8$ Hz, 1H), 6.65 (dt, $J = 17.9, 6.4$ Hz, 1H), 6.59 (dt, $J = 17.9, 6.4$ Hz, 1H), 5.47 (dt, $J =$

17.9, 1.4 Hz, 1H), 5.38 (dt, $J = 18.0, 1.3$ Hz, 1H), 3.93 (t, $J = 6.4$ Hz, 2H), 3.59 (s, 2H), 3.57 (s, 2H), 2.42 (t, $J = 7.0$ Hz, 2H), 2.26–2.20 (m, 2H), 2.10–2.04 (m, 2H), 1.83–1.76 (m, 2H), 1.64–1.57 (m, 2H), 1.57–1.50 (m, 2H), 1.44–1.37 (m, 2H), 1.27 (s, 12H), 1.26 (s, 12H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 157.1, 154.7, 154.0, 140.4, 129.8, 128.7, 128.1, 127.4, 126.6, 120.3, 111.0, 83.0, 82.96, 67.7, 58.6, 53.5, 51.5, 35.7, 35.4, 28.9, 26.8, 25.9, 24.9, 24.8, 24.78 (boron substituted vinyl carbons absent);

IR (neat, ATR): 3062, 2978, 2930, 2859, 2796, 1704, 1637, 1601, 1588, 1493, 1454, 1397, 1360, 1318, 1272, 1238, 1144, 1103, 1048, 998, 971;

HRMS (ES): calcd $[\text{M}+\text{H}]^+$ ($\text{C}_{38}\text{H}_{58}\text{B}_2\text{NO}_5$) 630.4514, found 630.4518.



(6E,8E)-14-benzyl-2,3,4,5,10,11,12,13,14,15-decahydrobenzo[*b*][1,5]oxaaza-cycloheptadecine (14)

A flame dried 250 mL flask was charged with $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (8 mg, 0.012 mmol). Freshly distilled methanol (60 mL), chloroacetone (92 μL , 1.2 mmol), *E,E*-bis(vinylboronate ester) **13** (73 mg, 0.12 mmol), and *aq.* 2 M potassium carbonate (92 μL , 0.58 mmol) were subsequently added and the reaction was allowed to stir overnight. Upon completion, methanol was removed *in vacuo*. The product was extracted with ether, washed with water and brine, and dried over MgSO_4 . Chromatography with 92:8 hexanes/EtOAc afforded 32 mg (74% yield) of a clear, colorless oil that solidified in the freezer.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 7.67 (d, $J = 7.4$ Hz, 1H), 7.43 (d, $J = 7.1$ Hz, 2H), 7.33 (t, $J = 7.4$ Hz, 2H), 7.24 (t, $J = 7.2$ Hz, 1H), 7.16 (t, $J = 7.7$, 1H), 6.95 (t, $J = 7.4$, 1H), 6.82 (d, $J = 8.1$ Hz, 1H), 6.11–6.01 (m, 2H), 5.73 (dt, $J = 14.4, 7.2$ Hz, 1H), 5.40 (dt, $J = 14.3, 7.2$ Hz, 1H), 3.91 (t, $J = 5.8$

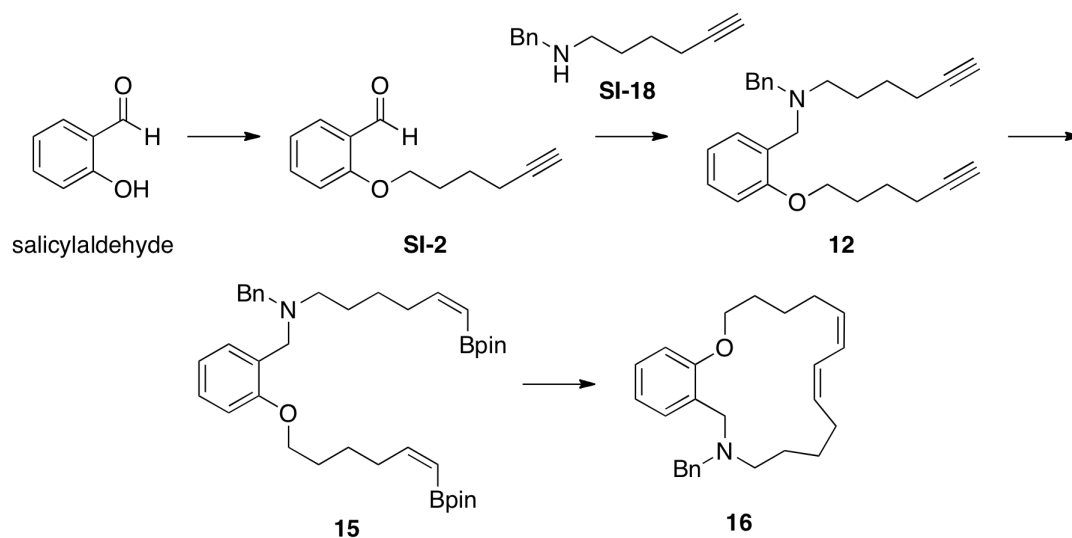
Hz, 2H), 3.64 (s, 2H), 3.56 (s, 2H), 2.45–2.41 (m, 2H), 2.10 (m, 4H), 1.83 (m, 2H), 1.65–1.58 (m, 2H), 1.56–1.49 (m, 2H), 1.39–1.23 (m, 2H);

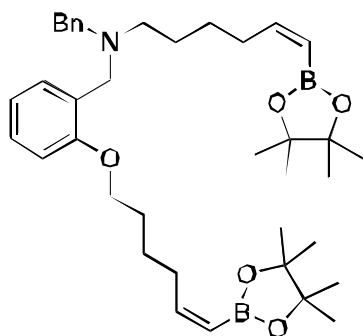
^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 157.2, 140.5, 132.4, 131.8, 131.6, 130.9, 129.2, 128.4, 128.2, 127.9, 126.8, 126.5, 120.6, 111.8, 68.2, 58.6, 52.8, 51.4, 31.2, 31.0, 27.3, 26.5, 24.8, 22.8;

IR (neat, ATR): 3061, 3012, 2926, 2853, 1601, 1587, 1491, 1453, 1372, 1280, 1237, 1101, 1045, 989;

HRMS (ES): calcd $[\text{M}+\text{H}]^+$ ($\text{C}_{26}\text{H}_{34}\text{NO}$) 376.2640, found 376.2640.

Scheme 7. Preparation of **16**





(Z)-N-benzyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(2-(((Z)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-yl)oxy)benzyl)hex-5-en-1-amine (15)

A flame dried 50 mL round bottom flask was charged with diyne **12** (1.00 g, 2.68 mmol) and flushed with nitrogen for 10 minutes. Diethyl ether (25 mL) was added and the flask was cooled to -78 °C. *n*-Butyllithium (2.14 mL, 5.34 mmol, 2.5 M in hexanes) was added over 15 minutes and the reaction was allowed to stir for 30 minutes before transferring to a solution of PINBOP (1.09 mL, 5.34 mmol) in diethyl ether (25 mL) in a 100 mL flame-dried flask. After 2 hours, the reaction was allowed to warm to room temperature. After 16 hours, the temperature was lowered to -50 °C and HCl (1.34 mL, 5.34 mmol, 4.0 M in dioxane) was added dropwise. After 2 hours at room temperature, the solution was filtered under nitrogen through Celite, and the solvent was removed *in vacuo*. The crude bis-alkynyl-Bpin was then dissolved in THF (12 mL), delivered to a solution of Cp₂ZrHCl (1.67 g, 5.34 mmol) in THF (12 mL), and stirred for 16 hours. The zirconocene was then hydrolyzed with water (4 mL) and the solvent was removed *in vacuo*. After extraction with ether, chromatography with 90:10 hexanes/EtOAc afforded 816 mg (49% yield) of a clear, colorless oil.

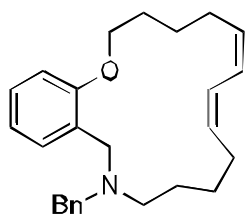
¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.54 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.17 (*J* = 7.8, 1.7 Hz, 1H), 6.93 (td, *J* = 7.4, 0.9 Hz, 1H), 6.82 (dd, *J* = 8.1, 0.6 Hz, 1H), 6.45 (dt, *J* = 13.9, 7.1 Hz, 1H), 6.40 (dt, *J* = 13.9, 7.1 Hz, 1H), 5.39 (dt, *J* = 13.5, 1.2 Hz, 1H), 5.32 (dt, *J* = 13.4, 1.1 Hz, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 3.62 (s, 2H),

3.59 (s, 2H), 2.48 (dq, $J = 7.3, 1.2$ Hz, 2H), 2.45 (t, $J = 7.2$ Hz, 2H), 2.35 (dq, $J = 7.4, 1.0$ Hz, 2H), 1.85–1.78 (m, 2H), 1.62–1.52 (m, 4H), 1.42–1.34 (m, 2H), 1.26 (s, 12H), 1.25 (s, 12H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 157.2, 155.1, 154.6, 140.4, 129.8, 128.7, 128.3, 128.0, 127.3, 126.5, 120.2, 111.0, 82.85, 82.77, 67.7, 58.6, 53.8, 51.5, 32.2, 31.7, 29.7, 28.6, 27.3, 26.8, 25.8, 24.8 (boron substituted vinyl carbons absent);

IR (neat, ATR): 3061, 3027, 2978, 2932, 2859, 2796, 1627, 1601, 1589, 1493, 1453, 1437, 1422, 1389, 1379, 1371, 1321, 1281, 1259, 1144;

HRMS (ES): calcd $[\text{M}+\text{H}]^+$ ($\text{C}_{38}\text{H}_{58}\text{O}_5\text{B}_2\text{N}$) 630.4514, found 630.4523.



(6Z,8Z)-14-benzyl-2,3,4,5,10,11,12,13,14,15-decahydrobenzo[*b*][1,5]oxaaza-cycloheptadecine (16)

A flame dried 250 mL flask was charged with $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (25 mg, 0.036 mmol). Freshly distilled methanol (180 mL), chloroacetone (289 μL , 3.6 mmol), Z,Z-bis(vinylboronate ester) **15** (228 mg, 0.36 mmol), and *aq.* 2 M potassium carbonate (905 μL , 1.8 mmol) were subsequently added and the reaction was allowed to stir overnight. Upon completion, methanol was removed *in vacuo*. The product was extracted with ether, washed with water and brine, and dried over MgSO_4 . Chromatography with 92:8 hexanes/EtOAc afforded 95 mg (70% yield) of a clear, colorless oil that solidified in the freezer.

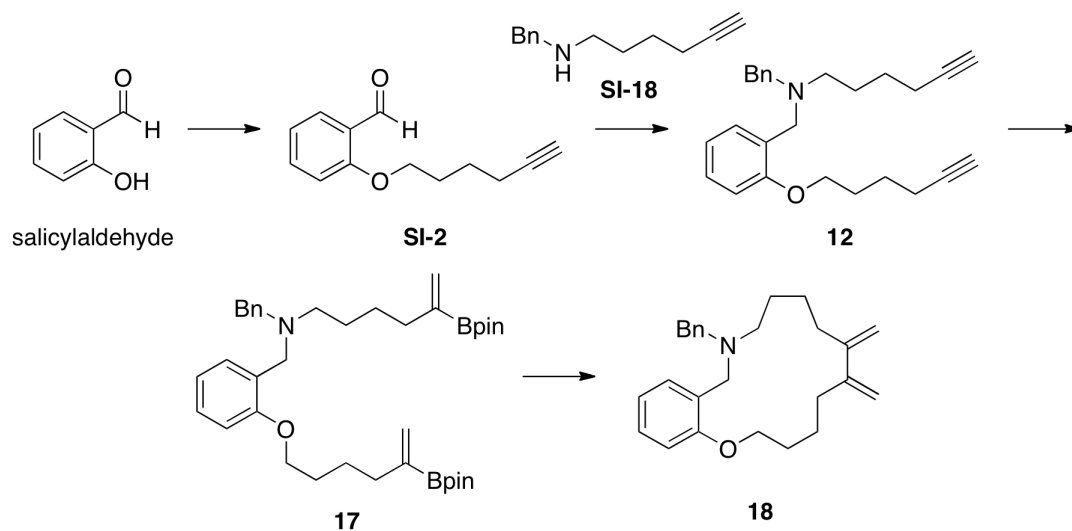
^1H NMR (400 MHz, CDCl_3 , ppm) δ : 7.40–7.16 (m, 7H), 6.88 (td, $J = 7.4, 1.0$ Hz, 1H), 6.82 (dd, $J = 8.2, 0.7$ Hz, 1H), 6.37 (t, $J = 10.5$ Hz, 1H), 6.31 (t, $J = 10.6$ Hz, 1H), 5.64–5.57 (m, 1H), 5.41–5.34 (m, 1H), 3.93 (t, $J = 6.8$ Hz, 2H), 3.63 (s, 2H), 3.53 (s, 2H), 2.40–2.35 (m, 2H), 2.26 (q, $J = 6.8$ Hz, 2H), 2.20 (q, $J = 6.2$ Hz, 2H), 1.85–1.80 (m, 2H), 1.63–1.56 (m, 2H), 1.52–1.44 (m, 2H), 1.34–1.28 (m, 2H);

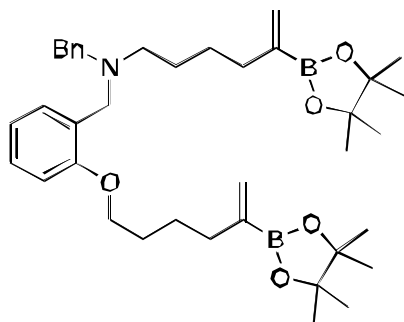
^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 157.5, 140.6, 132.2, 131.2, 130.4, 128.6, 128.1, 128.0, 127.7, 126.4, 125.7, 124.9, 119.9, 111.4, 68.2, 58.1, 54.0, 52.2, 28.2, 27.0, 26.5, 26.4, 26.0, 24.6;

IR (neat, ATR): 3060, 3030, 3003, 2932, 2858, 2791, 1665, 1601, 1587, 1494, 1472, 1453, 1372, 1285, 1248, 1160;

HRMS (ES): calcd $[\text{M}+\text{H}]^+$ ($\text{C}_{26}\text{H}_{34}\text{ON}$) 376.2640, found 376.2631.

Scheme 8. Preparation of **18**





***N*-benzyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*-(2-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-enyl)oxy)benzyl)hex-5-en-1-amine (17)**

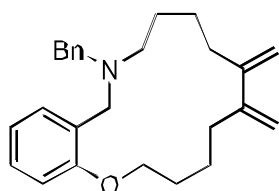
Prepared according to a modified literature procedure.²¹ Commercial grade 1,3-bis(diphenylphosphine)ethane nickel(II) chloride (Ni(dppe)Cl₂, 43 mg, 0.08 mmol) was placed in a flame dried 25 mL round bottom flask and purged with N₂ for 10 minutes. THF (8 mL) was added, followed by dropwise addition of DIBAL-H (620 µL, 3.48 mmol) at room temperature. The resulting black solution was allowed to cool to 0 °C before diyne **12** (500 mg, 1.34 mmol) was added slowly over five minutes. The resulting solution was allowed to warm to room temperature and stirred for an additional two hours. After two hours, 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (PINBOM, 1.316 mL, 8.03 mmol) was added dropwise at 0 °C. The mixture was allowed to stir at room temperature for 16 hours before it was washed with Et₂O (3 x 100 mL). The combined organic layers were dried over MgSO₄ and the solvent was evacuated *in vacuo*. Chromatography with 90:10 hexanes/EtOAc afforded 420 mg (50% yield) of a clear, colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.56 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.38 (d, *J* = 7.1 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.22–7.14 (m, 2H), 6.92 (td, *J* = 7.4, 0.8 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 5.81 (d, *J* = 3.4 Hz, 1H), 5.74 (d, *J* = 3.5 Hz, 1H), 5.64 (d, *J* = 3.2 Hz, 1H), 5.54 (d, *J* = 3.4 Hz, 1H), 3.95 (t, *J* = 6.5 Hz, 2H), 3.61 (s, 2H), 3.58 (s, 2H), 2.43 (t, *J* = 7.1 Hz, 2H), 2.23 (t, *J* = 7.5 Hz, 2H), 2.09 (t, *J* = 7.4 Hz, 2H), 1.83–1.76 (m, 2H), 1.65–1.57 (m, 2H), 1.57–1.50 (m, 2H), 1.45–1.38 (m, 2H), 1.27 (s, 12H), 1.25 (s, 12H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 157.2, 140.5, 129.7, 129.2, 128.9, 128.6, 128.4, 128.0, 127.2, 126.5, 120.2, 111.0, 83.4, 83.2, 67.9, 58.6, 53.7, 51.4, 35.3, 35.0, 29.0, 26.9, 26.0, 24.79, 24.75 (boron substituted vinyl carbons absent);

IR (neat, ATR): 30061, 3028, 2978, 2932, 2861, 2796, 1516, 1601, 1588, 1493, 1453, 1427, 1409, 1369, 1308, 1273, 1238, 1214, 1197, 1165, 1141, 1111, 1049, 1029;

HRMS (ES): calcd [M+H]⁺ (C₂₈H₅₈B₂O₅N) 630.4514, found 630.4520.



12-benzyl-6,7-dimethylene-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydrobenzo-[b][1,5]oxaazacyclopentadecine (18)

A flame dried 250 mL flask was charged with Pd(PPh₃)₂Cl₂ (21 mg, 0.030 mmol). Freshly distilled methanol (150 mL), chloroacetone (240 μL, 3.0 mmol), bis(vinylboronate ester) **17** (190 mg, 0.30 mmol), and *aq.* 2 M potassium carbonate (754 μL, 1.5 mmol) were subsequently added and the reaction was allowed to stir overnight. Upon completion, methanol was removed *in vacuo*. The product was extracted with ether, washed with water and brine, and dried over MgSO₄. Chromatography with 92:8 hexanes/EtOAc afforded 49 mg (43% yield) of a clear, colorless oil.

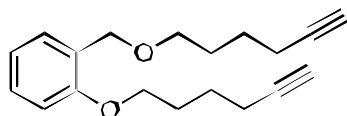
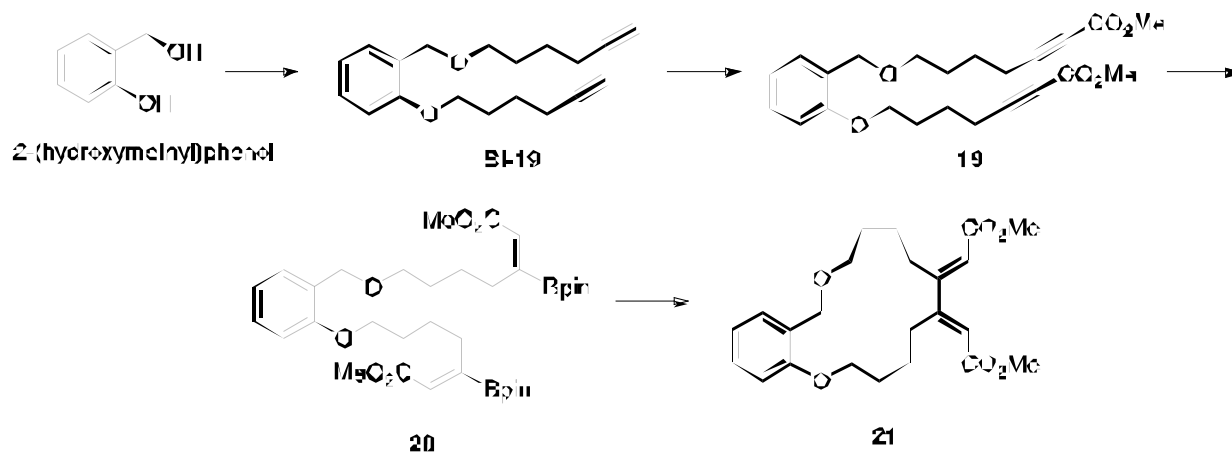
¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.40–7.08 (m, 7H), 6.86–6.82 (m, 2H), 5.10 (d, *J* = 1.5 Hz, 1H), 5.06 (d, *J* = 1.7 Hz, 1H), 4.98 (s, 1H), 4.95 (s, 1H), 3.98–3.92 (m, 2H), 3.69 (s, 2H), 3.57 (s, 2H), 2.43–2.31 (m, 6H), 1.79–1.72 (m, 4H), 1.60–1.49 (m, 2H), 1.40–1.30 (m, 2H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 157.9, 146.8, 146.4, 140.7, 132.4, 128.8, 128.2, 128.0, 126.9, 126.5, 119.6, 112.9, 112.8, 111.0, 67.6, 58.7, 53.1, 50.8, 35.2, 34.7, 29.2, 25.8, 25.3, 24.9;

IR (neat, ATR): 3553, 3083, 3025, 2939, 2861, 2794, 1597, 1494, 1453, 1369, 1287, 1239, 1101, 1054, 966, 911;

HRMS (ES): calcd $[M+H]^+$ ($C_{26}H_{34}ON$) 376.2640, found 376.2646.

Scheme 9. Preparation of **21**



1-(hex-5-yn-1-yloxy)-2-((hex-5-yn-1-yloxy)methyl)benzene (SI-19)

To a stirring solution of 2-(hydroxymethyl)phenol (4.36 g, 35.1 mmol) in 200 mL of THF was added slowly over 5 minutes NaH (1.4 g, 35.1 mmol) as a 60% dispersion in mineral oil. After the reaction mixture cooled to room temperature, hex-5-yn-1-yl 4-methylbenzenesulfonate (8.85 g, 35.1 mmol) was added. The reaction was set to reflux overnight, and then cooled back to room temperature. At that point, more 60% mineral oil dispersion of NaH (1.8 g, 45.7 mmol) and hex-5-yn-1-yl 4-methylbenzenesulfonate (9.74 g, 38.6 mmol) were added in the same method described previously. Again this reaction was heated at reflux overnight. After allowing the reaction to cool, the reaction was quenched with 200 mL of a saturated aqueous solution of ammonium chloride. After separating the organics and extracting the aqueous layer twice with 100 mL of DCM, the organics were concentrated in

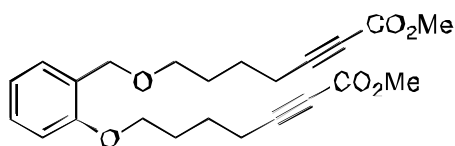
vacuo, then submitted to column chromatography on silica gel. With the eluent being 80% hexanes/ethyl acetate, 9.40 g (94% yield) of the bis-alkyne product was found as a colorless oil.

¹H NMR (CDCl₃, 500 MHz) δ : 7.38 (d, J = 7.5 Hz, 1H), 7.23 (td, J = 7.8, 1.5 Hz, 1H), 6.95 (td, J = 7.4, 0.8 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 4.55 (s, 2H), 4.01 (t, J = 6.3 Hz, 2H), 3.55 (t, J = 6.4 Hz, 2H), 2.29 (td, J = 7.0, 2.7 Hz, 2H), 2.23 (td, J = 7.1, 2.6 Hz, 2H), 1.98 (t, J = 2.6 Hz, 1H), 1.95 (t, J = 2.7 Hz, 1H), 1.89-1.93 (m, 2H), 1.70-1.79 (m, 4H), 1.63-1.69 (m, 2H);

¹³C NMR (CDCl₃, 126 MHz) δ : 156.3, 128.6, 128.3, 127.0, 120.3, 110.9, 84.3, 84.0, 69.9, 68.5, 68.2, 67.5, 67.1, 28.7, 28.2, 25.2, 25.1, 18.1, 18.0;

IR (neat, ATR): 3294, 2940, 2865, 2116, 1603, 1494, 1454, 1238, 1091, 753, 627;

HRMS (ES): calcd [M+Na]⁺ (C₁₉H₂₄O₂Na) 307.1674, found: 307.1670.



methyl 7-((2-((7-methoxy-7-oxohept-5-yn-1-yl)oxy)benzyl)oxy)hept-2-ynoate (19)

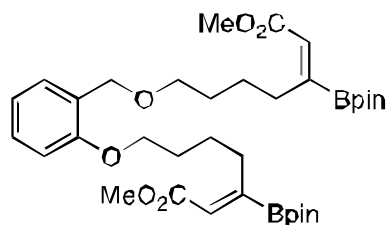
Diyne **SI-19** (2.0 g, 7.0 mmol) was dissolved in 120 mL of THF and cooled to -78 °C. A 1.4 M solution of n-BuLi in hexanes (10 mL, 14 mmol) was added slowly, and the resulting mixture was allowed to stir for 30 minutes. Methyl chloroformate (4.3 mL, 56 mmol) was added to quench the reaction. The mixture was stirred for an hour then allowed to warm to room temperature and stirred for another hour. A saturated aqueous solution of NaCl (100 mL) was added and the organics were extracted three times with 100 mL ether. The organics were concentrated in vacuo, and then submitted to column chromatography on silica gel. With the eluent being 70% hexanes/ethyl acetate, 1.7 g (62% yield) of the bis-ester product was found as a colorless oil.

¹H NMR (CDCl₃, 500 MHz) δ : 7.34 (d, J = 7.3 Hz, 1H), 7.21 (td, J = 7.8, 1.5 Hz, 1H), 6.93 (dt, J = 7.6, 3.7 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 4.51 (s, 2H), 3.98 (t, J = 5.8 Hz, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.52 (t, J = 5.8 Hz, 2H), 2.42 (t, J = 6.8 Hz, 2H), 2.35 (t, J = 6.8 Hz, 2H), 1.85-1.98 (m, 2H), 1.75-1.82 (m, 2H), 1.65-1.74 (m, 4H);

¹³C NMR (CDCl₃, 126 MHz) δ : 156.1, 154.0, 154.0, 128.7, 128.4, 126.8, 120.3, 110.9, 89.5, 89.0, 73.1, 72.9, 69.6, 67.5, 66.9, 52.4, 52.4, 28.7, 28.2, 24.4, 24.2, 18.3, 18.3;

IR (neat, ATR): 2951, 2869, 2235, 1710, 1434, 1251, 1073, 751;

HRMS (ES): calcd [M+Na]⁺ (C₂₃H₂₈O₆Na) 423.1783, found: 423.1785.



(Z)-methyl 7-((2-(((Z)-7-methoxy-7-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-5-en-1-yl)oxy)benzyl)oxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-2-enoate (20)

Copper(I) chloride (3 mg, 0.03 mmol), sodium tert-butoxide (6 mg, 0.06 mmol), xantphos (17 mg, 0.03 mmol), and bis(pinacolato)diboron (280 mg, 1.1 mmol) were weighed into a 10 mL round bottom flask under an inert atmosphere. The starting bis-alkynoate **19** (200 mg, 0.4 mmol) in 2 mL THF were then added through a cannula. Addition of methanol (800 μ L, 2.0 mmol) then initiated the reaction which was allowed to stir for one day. The solvent was removed, and the mixture subjected to column chromatography on silica gel with an elution mixture of 85% hexanes, 13% ethyl acetate and 2% methanol. The product was eluted (0.17 g, 51% yield) as a yellow oil.

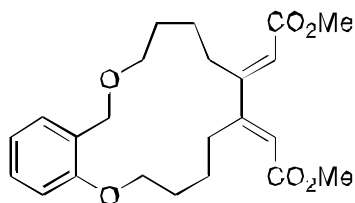
¹H NMR (CDCl₃, 500 MHz) δ : 7.39 (d, J = 6.7 Hz, 1H), 7.19 (t, J = 7.2 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.44 (s, 1H), 6.41 (s, 1H), 4.54 (s, 2H), 3.97 (t, J = 6.6 Hz, 2H),

3.70 (s, 6H), 3.52 (t, $J = 6.6$ Hz, 2H), 2.72 (m, 4H), 1.77-1.88 (m, 2H), 1.46-1.74 (m, 6H), 1.26 (s, 24H);

^{13}C NMR (CDCl_3 , 126 MHz) δ : 166.3, 156.1, 129.7, 129.4, 127.8, 127.5, 120.0, 110.8, 84.0, 83.9, 70.6, 67.7, 67.2, 51.0, 50.9, 29.7, 29.7, 29.5, 29.1, 26.1, 25.9, 24.6 (boron substituted vinyl carbons absent);

IR (neat, ATR): 2978, 2945, 2866, 1721, 1372, 1335, 1143, 752;

HRMS (ES): calcd $[\text{M}+\text{Na}]^+$ ($\text{C}_{35}\text{H}_{54}\text{O}_{10}\text{B}_2\text{Na}$) 679.3813, found: 679.3806.



(2E,2'E)-dimethyl 2,2'-(4,5,8,9,10,11-hexahydro-2H-benzo[b][1,5]dioxacyclopentadecine-6,7-(3H,13H)-diylidene)diacetate (21)

To bis-vinyl pinacol boronate **20** (0.15 g, 0.23 mmol) in 115 mL MeOH was added $\text{PdCl}_2(\text{PPh}_3)_2$ (16 mg, 0.02 mmol), and chloroacetone (0.06 mL, 0.69 mmol). A 2 M solution of aqueous potassium carbonate (0.46 mL, 0.91 mmol) was added, and the mixture was heated to 60 °C overnight. The solution was worked up with 60 mL of DCM along with 80 mL of water, followed by two extractions with 60 mL DCM. The organic solvents were removed, and the crude mixture subjected to column chromatography on silica gel. Using 80% hexanes/ethyl acetate, 70 mg of the macrocyclic product was found in a 76% yield.

^1H NMR (CDCl_3 , 500 MHz) δ : 7.21-7.31 (m, 2H), 6.88 (t, $J = 7.3$ Hz, 1H), 6.84 (d, $J = 7.9$ Hz, 1H), 5.84 (s, 1H), 5.80 (s, 1H), 4.43 (s, 2H), 4.04 (t, $J = 5.0$ Hz, 2H), 3.70 (s, 3H), 3.70 (s, 3H), 3.56 (t, $J = 5.3$ Hz, 2H), 2.85-2.92 (m, 2H), 2.71-2.81 (m, 2H), 1.87-1.95 (m, 2H), 1.78-1.86 (m, 2H), 1.74 (p, $J = 6.0$ Hz, 2H), 1.49-1.57 (m, 2H);

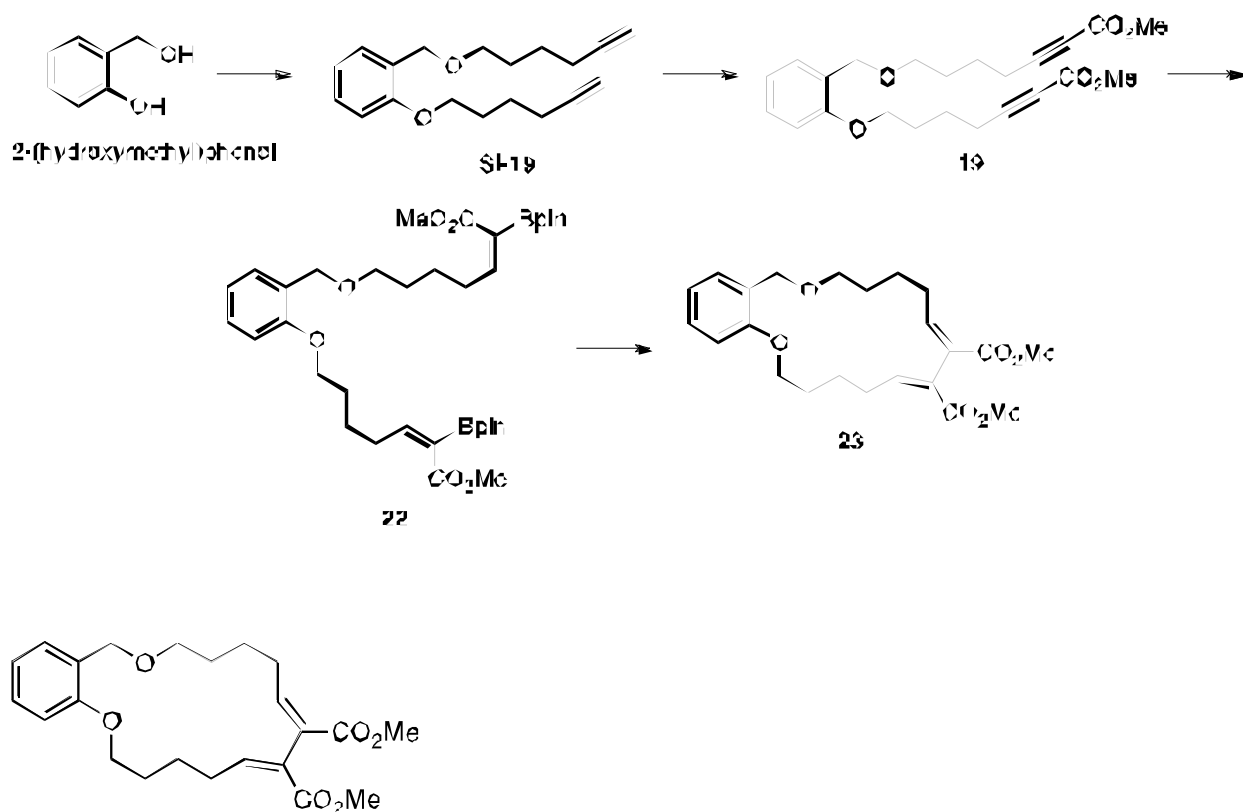
¹³C NMR (CDCl₃, 126 MHz) δ : 166.4, 166.2, 163.6, 162.7, 157.8, 131.9, 129.7, 125.7, 119.9, 117.4,

116.5, 110.8, 69.2, 69.0, 66.8, 51.1, 51.1, 30.1, 29.3, 29.0, 28.0, 26.6, 25.4;

IR (neat, ATR): 2947, 2858, 1714, 1626, 1433, 1249, 1194, 1162, 1101, 869, 753;

HRMS (ES): calcd [M+Na]⁺ (C₂₃H₃₀O₆Na) 425.1940, found: 425.1930.

Scheme 10. Preparation of **23**



(6Z,8Z)-dimethyl 3,4,5,10,11,12,13,15-octahydro-2H-benzo[b][1,5]dioxacycloheptadecine-7,8-dicarboxylate (23)

Under an argon atmosphere, Stryker's reagent [(PPh₃)CuH]₆ (5 mg, 0.0025 mmol) and triphenylphosphine (4 mg, 0.015 mmol) were weighed into a 25 mL round bottom flask. THF (0.5 mL) was added, and the reaction flask was cooled to 0 °C. Pinacol borane (0.15 mL, 1.0 mmol) was added and stirred for 20 min. The starting bis-alkynoate **19** (0.2 g, 0.4 mmol) was added at 0 °C over 2 minutes in 1 mL of THF, and the reaction was allowed to warm to room temperature while stirring overnight. A

separate flask was assembled with PdCl₂(PPh₃)₂ (35 mg, 0.05 mmol), chloroacetone (0.12 mL, 1.5 mmol), and triethylamine (0.21 mL, 1.5 mmol) in 250 mL of THF and 42 mL of H₂O. The crude boronate ester intermediate was then transferred to the flask containing palladium via a cannula. This reaction was left to again stir overnight at room temperature. A saturated aqueous solution of NH₄Cl (100 mL) was added and the organics were extracted three times with 100 mL ether. The organics were concentrated *in vacuo*, then submitted to column chromatography on silica gel. With the eluent being 80% hexanes/ethyl acetate, 80 mg (40% yield) of the macrocycle product was found over two steps as a colorless oil.

¹H NMR (CDCl₃, 500 MHz) δ : 7.39 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.22 (td, *J* = 7.8, 1.5 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.28 (t, *J* = 6.9 Hz, 1H), 6.26 (t, *J* = 6.9 Hz, 1H), 4.53 (s, 2H), 3.92-4.04 (m, 2H), 3.71 (s, 3H), 3.71 (s, 3H), 3.62 (t, *J* = 6.1 Hz, 2H), 2.70 (m, 4H), 1.77 (m, 4H), 1.57-1.70 (m, 4H);

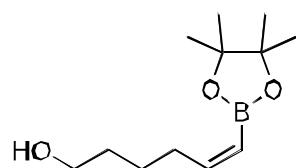
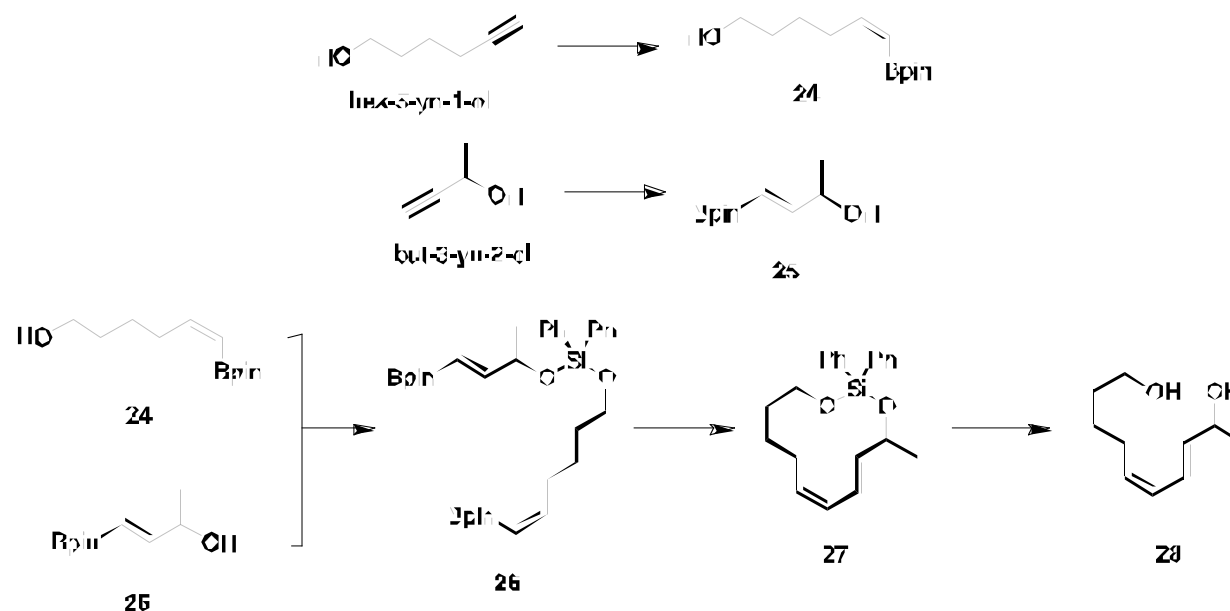
¹H NMR (C₆D₆, 500 MHz) δ : 7.61 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.10 (td, *J* = 7.8, 1.8 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.52 (d, *J* = 7.9 Hz, 1H), 6.22 (t, *J* = 6.8 Hz, 1H), 6.19 (t, *J* = 6.8 Hz, 2H), 4.52 (s, 2H), 3.28-3.58 (m, 10H), 2.60-2.91 (m, 4H), 1.27-1.62 (m, 8H);

¹³C NMR (C₆D₆, 126 MHz) δ : 167.0, 157.2, 148.3, 148.1, 134.7, 134.2, 129.7, 128.8, 128.7, 121.0, 111.6, 70.0, 67.4, 66.0, 51.4, 29.6, 29.1, 29.1, 28.1, 26.0, 24.9;

IR (neat, ATR): 2946, 2865, 2360, 2341, 1721, 1435, 1275, 1204, 752;

HRMS (ES): calcd [M+Na]⁺ (C₂₃H₃₀O₆Na) 425.1940, found: 425.1948.

Scheme 11. Preparation of **28**



(Z)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-ol (24)

To a stirring solution of hex-5-yn-1-ol (7.3 g, 75 mmol) in DMF (160 mL) was added *tert*-butyldimethylsilyl chloride (16.7 g, 112 mmol) and imidazole (12.7 g, 187 mmol). The mixture was stirred for 4 hours at which point 200 mL of water was added, and the mixture was extracted three times with 100 mL ether. The organics were combined, the solvent was removed in vacuo, and the crude mixture was put through a plug of silica gel. Using an eluent system of 90:10 hexanes/ethyl acetate, 12.1 g of the silyl protected alcohol was found in a 76% yield and immediately subjected to the next conditions.

A solution of the silyl protected hex-5-yn-1-ol (12 g, 57 mmol) in diethyl ether (550 mL) was cooled to -78 °C, followed by addition of 1 equiv of 10 M *n*-BuLi (5.7 mL, 57 mmol) in hexanes. After 30 minutes the solution was quenched with isopropyl pinacol borate (11.6 mL, 57 mmol) and allowed to

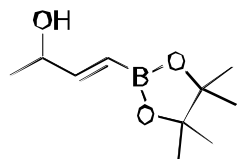
warm to room temperature over 10 hours. The reaction mixture was again cooled to -78 °C, and anhydrous HCl (14.2 mL, 57 mmol, 4 M in dioxane) was added. After two hours, the reaction was allowed to slowly warm to room temperature and the salts were removed by air-free filtration through Celite. The solvent was removed *in vacuo* overnight. The crude mixture was diluted with 50 mL THF, then transferred via double-ended needle to a flask containing 1.1 equiv of Schwartz's catalyst (Cp_2ZrHCl , 16 g, 63 mmol) which was previously weighed in a round bottom flask in an inert atmosphere. After two hours of stirring, the reaction was quenched with an excess of water. Following two extractions with 100 mL diethyl ether, and removal of solvent *in vacuo*, the crude mixture was passed through a plug of silica gel using an eluent system of 80:20 hexanes/EtOAc. The solvent was removed *in vacuo*, and the residue was diluted in 50 mL of THF. To remove the silyl ether, TBAF (85 mL, 85 mmol, 1.5 M in THF) was added to the crude pinacol boronate and the mixture was allowed to stir overnight. The solvent was removed, and the mixture put through a column of silica gel. Utilizing an eluent system of 60% hexanes/ethyl acetate, 6.1 g of the product was found in a 36% yield over the three steps.

^1H NMR (500 MHz, CDCl_3 , ppm) δ : 6.43 (dt, $J = 13.4, 6.4$ Hz, 1H), 5.33 (d, $J = 13.4$ Hz, 1H), 3.64 (t, $J = 6.4$ Hz, 2H), 2.39 (q, $J = 7.3$ Hz, 2H), 1.76 (br s, 1H), 1.61–1.53 (m, 2H), 1.45 (p, $J = 7.3$ Hz, 2H), 1.25 (s, 12H);

^{13}C NMR (125 MHz, CDCl_3 , ppm) δ : 154.5, 82.8, 62.4, 31.6, 31.5, 25.4, 24.7 (boron substituted vinyl carbon absent);

IR (neat, ATR): 3401, 2979, 2932, 2861, 1627, 1422, 1317, 1257, 1143, 758;

HRMS (ES): calcd $[\text{M}+\text{Na}]^+$ ($\text{C}_{12}\text{H}_{23}\text{BO}_3\text{Na}$) 249.1640, found 249.1634.



(*E*)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-2-ol (25)

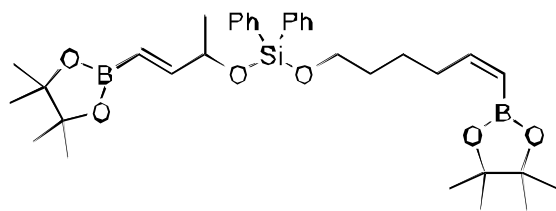
To but-3-yn-2-ol (1.0 mL, 13.6 mmol) was added pinacolborane (3.9 mL, 27.1 mmol) slowly at 0 °C. Triethylamine (190 μ L, 1.4 mmol) was then added, and the resulting mixture was transferred to a flask containing Cp_2ZrHCl (Schwartz's catalyst, 350 mg, 1.4 mmol) via cannula. It was then heated at 60 °C for 15 hours. The crude mixture was cooled to room temperature and subjected immediately to column chromatography on silica gel. With the eluent being 60% hexanes/EtOAc, 2.18 g of the product was found in an 81% yield as a colorless oil.

^1H NMR (500 MHz, CDCl_3 , ppm) δ : 6.65 (dd, J = 18.2, 5.0 Hz, 1H), 5.62 (dd, J = 18.2, 1.4 Hz, 1H), 4.56–4.17 (m, 1H), 1.52 (d, J = 4.9 Hz, 1H), 1.30–1.25 (m, 15H);

^{13}C NMR (125 MHz, CDCl_3 , ppm) δ : 156.0, 83.2, 69.5, 24.6, 22.5 (boron substituted vinyl carbon absent);

IR (neat, ATR): 3451, 2978, 2931, 1642, 1355, 1319, 1142, 969, 849;

HRMS (ES): calcd $[\text{M}+\text{Na}]^+$ ($\text{C}_{10}\text{H}_{19}\text{BO}_3\text{Na}$) 221.1327, found 221.1322.



diphenyl(((*E*)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-2-yl)oxy) (((*Z*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-yl)oxy)silane (26)

To a stirring solution of $\text{Ph}_2\text{Si}(\text{Et}_2\text{N})\text{Cl}$ (560 mg, 1.9 mmol) and triethylamine (360 μ L, 2.6 mmol) in 3 mL DCM was added alcohol **25** (380 mg, 1.9 mmol) in DCM (3 mL) at 0 °C. DMAP (31 mg, 0.26

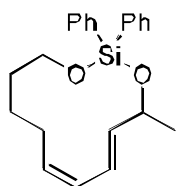
mmol) was then added, and the reaction stirred for 2 hours. Alcohol **24** (290 mg, 1.3 mmol) was then added along with more DMAP (630 mg, 5.1 mmol) in DCM (4 mL). After 1 day, the reaction was quenched with water, and extracted twice with DCM (15 mL). The organic layer was concentrated *in vacuo*, and then subjected to column chromatography on silica gel (elution with 90:10 hexanes/EtOAc) to produce 0.63 g of the product in 80% yield.

¹H NMR (500 MHz, CDCl₃, ppm) δ: 7.67–7.64 (m, 4H), 7.45–7.30 (m, 6H), 6.63 (dd, *J* = 18.0, 4.3 Hz, 1H), 6.40 (dt, *J* = 13.1, 6.3 Hz, 1H), 5.71 (dd, *J* = 17.9, 1.7 Hz, 1H), 5.32 (d, *J* = 13.4 Hz, 1H), 4.57–4.51 (m, 1H), 3.76 (t, *J* = 6.6 Hz, 2H), 2.38 (q, *J* = 7.5 Hz, 2H), 1.63–1.55 (m, 2H), 1.50–1.42 (m, 2H), 1.32–1.19 (m, 27H);

¹³C NMR (125 MHz, CDCl₃, ppm) δ: 155.9, 154.8, 134.9, 134.8, 130.0, 127.6, 83.0, 82.6, 70.0, 62.9, 31.7, 31.7, 25.5, 24.7, 24.7, 23.3 (boron substituted vinyl carbons absent);

IR (neat, ATR): 3071, 2978, 2928, 2868, 1641, 1425, 1369, 1320, 1259, 1143, 1058, 699;

HRMS (ES): calcd [M+Na]⁺ (C₃₄H₅₀B₂O₆SiNa) 627.3473, found 627.3463.



(5*E*,7*Z*)-4-methyl-2,2-diphenyl-1,3-dioxasilacyclododeca-5,7-diene (27)

To *E,Z*-bis(vinylboronate ester) **26** (110 mg, 0.18 mmol) in MeOH (100 mL) was added PdCl₂(PPh₃)₂ (13 mg, 0.02 mmol), and chloroacetone (90 μL, 1.1 mmol). Subsequently, *aq.* 2 M potassium carbonate (360 μL, 0.73 mmol) was added, and the mixture was left to stir at room temperature overnight. The solution was diluted with DCM (60 mL) and water (80 mL), followed by two extractions with DCM (60 mL). The organic solvents were removed, and the crude mixture subjected to column

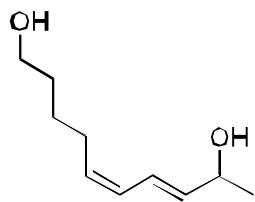
chromatography on silica gel. Using 95:5 hexanes/EtOAc, 0.05 g of the macrocyclic product was found in a 74% yield.

¹H NMR (500 MHz, CDCl₃, ppm) δ: 7.79 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.64 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.51–7.31 (m, 6H), 6.81 (dd, *J* = 15.3, 10.7 Hz, 1H), 6.21 (t, *J* = 10.5 Hz, 1H), 5.74 (dd, *J* = 15.3, 3.7 Hz, 1H), 5.64 (td, *J* = 9.3, 8.5 Hz, 1H), 4.49–4.47 (m, 1H), 4.12–4.04 (m, 1H), 3.84–3.74 (m, 1H), 2.57–2.35 (m, 1H), 2.07–1.89 (m, 1H), 1.80–1.63 (m, 2H), 1.59–1.43 (m, 2H), 1.35 (d, *J* = 6.4 Hz, 3H);

¹³C NMR (125 MHz, CDCl₃, ppm) δ: 135.0, 134.8, 134.7, 133.4, 132.4, 131.0, 130.1, 130.1, 129.2, 127.8, 127.7, 123.9, 69.2, 60.9, 28.3, 24.0, 24.0, 24.0;

IR (neat, ATR): 3069, 3009, 2926, 2872, 1429, 1093, 1065, 988, 717, 699;

HRMS (CI): calcd [M+H]⁺ (C₂₂H₂₇O₂Si) 351.1780, found 351.1777.



(5Z,7E)-deca-5,7-diene-1,9-diol (28)

To diene **27** (70 mg, 0.19 mmol) was added THF (10 mL) and crushed 4 Å molecular sieves (200 mg). TBAF (0.94 mL, 0.94 mmol, 1 M in THF) was then added, and the reaction was allowed to stir overnight. The solvent was then removed *in vacuo* and the crude mixture was subjected to column chromatography with a 90:10 EtOAc/hexanes eluent. The product was found (0.029 g) in an 88% yield.

¹H NMR (500 MHz, CDCl₃, ppm) δ: 6.47 (dd, *J* = 15.3, 11.0 Hz, 1H), 5.98 (t, *J* = 11.0 Hz, 1H), 5.70 (dd, *J* = 15.3, 6.4 Hz, 1H), 5.43 (dt, *J* = 10.6, 7.7 Hz, 1H), 4.36 (p, *J* = 6.3 Hz, 1H), 3.63 (t, *J* = 6.6 Hz,

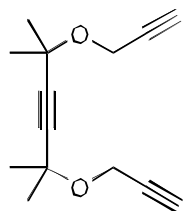
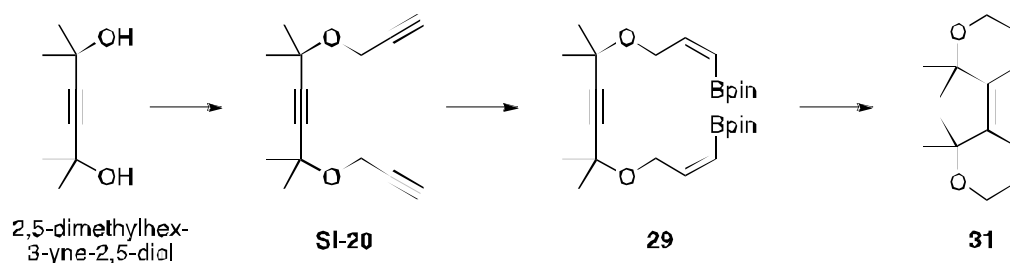
2H), 2.21 (qd, $J = 7.4, 1.2$ Hz, 2H), 1.78 (br s, 2H), 1.65–1.51 (m, 2H), 1.51–1.39 (m, 2H), 1.28 (d, $J = 6.4$ Hz, 3H);

^{13}C NMR (125 MHz, CDCl_3 , ppm) δ : 137.0, 132.2, 128.0, 124.6, 68.5, 62.6, 32.1, 27.3, 25.6, 23.2;

IR (neat, ATR): 3319, 2925, 2856, 1452, 1369, 1057, 984, 946, 741;

HRMS (ES): calcd $[\text{M}+\text{Na}]^+$ ($\text{C}_{10}\text{H}_{18}\text{NaO}_2$) 193.1205, found 193.1199.

Scheme 12. Preparation of **31**



2,5-dimethyl-2,5-bis(prop-2-yn-1-yloxy)hex-3-yne (SI-20)

Prepared according to a modified literature procedure.¹⁰ A solution of 2,5-dimethyl-3-hexyne-2,5-diol (2.0 g, 14.06 mmol) in DMSO (12.5 mL) was added to a stirred solution of KOH (1.93 g, 35.2 mmol) in water (2.5 mL) under nitrogen atmosphere. The mixture was stirred at room temperature for 30 minutes and then cooled to 0 °C. A solution of propargyl bromide (3.92 mL, 35.2 mmol, 80% w/v in toluene) was added dropwise. The solution was allowed to stir for 10 additional minutes at 0 °C, warmed to room temperature, and then stirred at 70 °C for 12 hours. After completion, the mixture was cooled to 0 °C and water (10 mL) was added. The crude mixture was extracted with ether (3 x 150 mL) and washed with

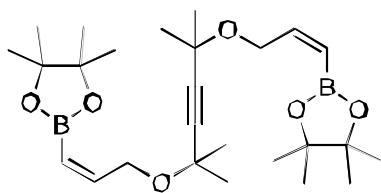
water and brine. Combined organic portions were dried over MgSO_4 and the solvent was evaporated *in vacuo*. Chromatography with 95:5 hexanes/EtOAc afforded 1.28 g (42% yield) of a clear, yellowish oil.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 4.23 (d, $J = 2.5$ Hz, 4H), 2.42 (t, $J = 2.4$ Hz, 2H), 1.49 (s, 12H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 86.2, 80.8, 73.6, 71.3, 52.5, 28.8;

IR (neat, ATR): 3294, 2985, 2935, 2863, 2127, 1465, 1439, 1381, 1362, 1260, 1191, 1152, 1056;

HRMS (ES): calcd $[\text{M}+\text{Na}]^+$ ($\text{C}_{14}\text{H}_{18}\text{O}_2\text{Na}$) 241.1205, found 241.1202.



2,2'-((1Z,1'Z)-((2,5-dimethylhex-3-yne-2,5-diyl)bis(oxy))bis(prop-1-ene-3,1-diyl))bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (29)

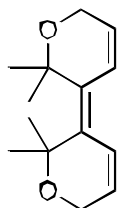
A flame dried 25 mL round bottom flask was charged with triyne **SI-20** (200 mg, 0.914 mmol) and flushed with nitrogen for 10 minutes. Diethyl ether (8 mL) was added and the flask was cooled to -78°C . *n*-Butyl lithium (730 μL , 1.82 mmol, 2.5 M in hexanes) was added over 15 minutes and the reaction was allowed to stir for 30 minutes before transferring to a solution of PINBOP (372 μL , 1.82 mmol) in diethyl ether (8 mL) in a 50 mL flame-dried flask. After 2 hours, the reaction was allowed to warm to room temperature. After 16 hours, the temperature was lowered to -78°C and HCl (456 μL , 1.82 mmol, 4.0 M in dioxane) was added dropwise. After 2 hours at room temperature, the solution was filtered under nitrogen through Celite, and the solvent was removed *in vacuo*. The crude bis-alkynyl-Bpin was then dissolved in THF (4 mL), delivered to a solution of Cp_2ZrHCl (470 mg, 1.83 mmol) in THF (4 mL) at 0°C , and stirred for 16 hours. The zirconocene was then hydrolyzed with water (3 mL) and the solvent was removed *in vacuo*. After extraction with ether, chromatography with 95:5 hexanes/ Et_2O afforded 210 mg (49% yield) of a clear, colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 6.52 (dt, *J* = 13.3, 6.1, 2H), 5.46 (dt; *J* = 13.8, 1.6 Hz, 2H), 4.40 (dd, *J* = 6.1, 1.7, 4H), 1.47 (s, 12H), 1.25 (s, 24H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 151.5, 86.4, 83.1, 70.2, 64.2, 29.0, 24.9 (boron substituted vinyl carbons absent);

IR (neat, ATR): 2980, 2934, 2864, 1633, 1468, 1421, 1371, 1322, 1297, 1260, 1214, 1186, 1144, 1112, 1066;

HRMS (ES): calcd [M+Na]⁺ (C₂₆H₄₄B₂O₆Na) 497.3231, found 497.3222.



(Z)-2,2,2',2'-tetramethyl-2,2',6,6'-tetrahydro-3,3'-bipyranlylidene (31)

A flame dried 500 mL flask was charged with Pd(PPh₃)₂Cl₂ (24 mg, 0.035 mmol). Freshly distilled methanol (175 mL), chloroacetone (278 μL, 3.48 mmol), *Z,Z*-bis(vinylboronate ester) **29** (165 mg, 0.348 mmol), and *aq.* 2 M potassium carbonate (870 μL, 1.74 mmol) were subsequently added, and the reaction was allowed to stir overnight at 60 °C. Upon completion, methanol was removed *in vacuo*. The product was extracted with ether, washed with water and brine, and dried over MgSO₄. Chromatography with 95:5 hexanes/Et₂O afforded 63 mg (82% yield) of a clear, colorless oil.

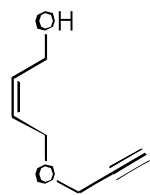
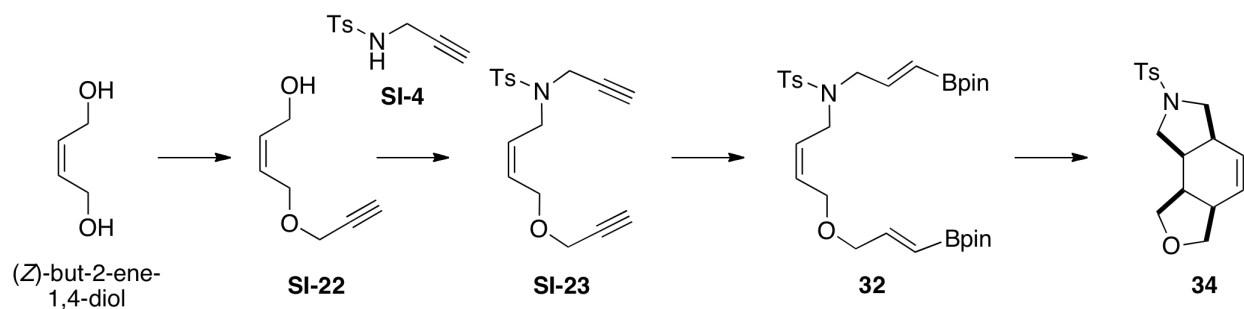
¹H NMR (400 MHz, CDCl₃, ppm) δ: 6.40 (dt, *J* = 10.4, 2.1 Hz, 2H), 5.88 (dt, *J* = 10.4, 2.6 Hz, 2H), 4.25 (t, *J* = 2.3 Hz, 4H), 1.55 (s, 12H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 136.5, 126.0, 125.6, 74.4, 60.3, 26.6;

IR (neat, ATR): 3041, 2976, 2925, 2817, 2745, 2686, 1450, 1386, 1357, 1290, 1254, 1228, 1203, 1184, 1147, 1118, 1091, 1045, 1013, 956, 955, 922, 902, 806;

HRMS (CI): calcd [M+NH₄]⁺ (C₁₄H₂₄O₂N) 238.1807, found 238.1813.

Scheme 13. Preparation of **34**



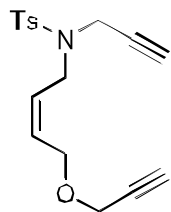
(Z)-4-(prop-2-yn-1-yloxy)but-2-en-1-ol (SI-22)

A solution of *cis*-but-2-ene-1,4-diol (2.67 mL, 30 mmol) in dry THF (10 mL) was added at 0 °C to a suspension of sodium hydride (400 mg, 10 mmol, 60% suspension in mineral oil) in dry THF (5 mL) under nitrogen. The mixture was stirred at room temperature for 30 minutes, then propargyl bromide (1.11 mL, 10 mmol, 80% w/v in toluene) was quickly added and the reaction was refluxed overnight. Upon cooling, the mixture was carefully diluted with water and extracted with ether. Combined organic portions were dried over MgSO₄ and the solvent was evaporated *in vacuo*. Chromatography with 80:20 petroleum ether/EtOAc afforded 1.199 g (95% yield) of the known¹¹ clear, colorless oil.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 5.86–5.80 (m, 1H), 5.70–5.63 (m, 1H), 4.21 (d, *J* = 6.5 Hz, 2H),

4.16–4.14 (m, 4H), 2.45 (t, *J* = 2.4 Hz, 1H), 2.05 (bs, 1H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 133.2, 127.4, 79.4, 74.8, 65.0, 58.8, 57.2.



(Z)-4-methyl-N-(prop-2-yn-1-yl)-N-(4-(prop-2-yn-1-yloxy)but-2-en-1-yl)-benzenesulfonamide (SI-23)

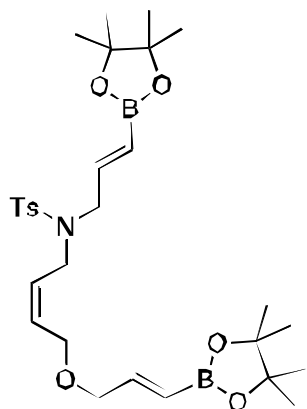
Prepared according to a modified literature procedure.¹² To a solution of alcohol **SI-22** (811 mg, 6.43 mmol), amine **SI-4** (1.346 g, 6.43 mmol), and PPh₃ (1.687 g, 6.43 mmol) in THF (65 mL) was added diisopropyl azodicarboxylate (DIAD, 1.33 mL, 6.43 mmol) at 0 °C. The mixture was allowed to stir for 36 hours at room temperature. Solvent was removed *in vacuo*. Chromatography with 90:10 hexanes/EtOAc afforded 1.696 g (83% yield) of a white solid.

¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.73 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 5.79 (dt, *J* = 11.0, 6.4, 1.4 Hz, 1H), 5.56 (dt, *J* = 11.0, 7.3, 1.4 Hz, 1H), 4.14 (dd, *J* = 6.5, 1.0 Hz, 2H), 4.12, (d, *J* = 2.4 Hz, 2H), 4.09 (d, *J* = 2.4 Hz, 2H), 3.91 (d, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 2.40 (t, *J* = 2.4 Hz, 1H), 2.03 (t, *J* = 2.5 Hz, 1H);

¹³C NMR (100 MHz, CDCl₃, ppm) δ: 143.7, 135.9, 131.2, 129.5, 127.8, 127.3, 79.5, 76.7, 74.7, 73.8, 64.8, 57.4, 43.2, 36.0, 21.6;

IR (neat, ATR): 3285, 3030, 2924, 2855, 2117, 1598, 1494, 1442, 1341, 1306, 1264, 1185, 1158, 1089, 1018, 970;

HRMS (ES): calcd [M+Na]⁺ (C₁₇H₁₉NO₃SNa) 340.0983, found 340.0988.



4-methyl-N-((E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-N-(((Z)-4-(((E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)but-2-en-1-yl)-benzenesulfonamide (32)

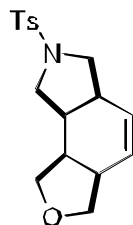
A flame dried 50 mL round bottom flask was charged with enediyne **SI-22** (770 mg, 2.42 mmol) and flushed with nitrogen for 10 minutes. Pinacolborane (1.45 mL, 9.70 mmol) and triethylamine (68 μ L, 0.485 mmol) were added via syringe to the flask and allowed to stir at 0 $^{\circ}$ C for 5 minutes. The mixture was transferred via a cannula to another round bottom flask containing Cp_2ZrHCl (125 mg, 0.485 mmol). The reaction stirred for 16 hours at 60 $^{\circ}$ C. The solvent was removed *in vacuo*. Chromatography with hexanes/EtOAc afforded 885 mg (63% yield) of a very viscous clear, colorless oil.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 7.68 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 7.0 Hz, 2H), 6.60 (dt, J = 18.1, 4.8 Hz, 1H), 6.39 (dt, J = 17.9, 5.6 Hz, 1H), 5.69–5.61 (m, 3H), 5.54 (d, J = 18.0 Hz, 1H), 5.39–5.31 (m, 2H), 3.99 (dd, J = 4.7, 1.6 Hz, 2H), 3.94 (d, J = 6.3 Hz, 2H), 3.85–3.83 (m, 4H), 2.41 (s, 3H), 1.25 (s, 12H), 1.24 (s, 12H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 148.8, 147.0, 143.2, 137.2, 130.4, 129.7, 127.3, 127.0, 83.34, 83.26, 72.0, 65.8, 50.8, 44.2, 24.8, 21.5 (boron substituted vinyl carbons absent);

IR (neat, ATR): 2978, 2930, 1732, 1643, 1599, 1445, 1322, 1268, 1213, 1158, 1142, 1091;

HRMS (ES): calcd $[\text{M}+\text{H}]^+$ ($\text{C}_{29}\text{H}_{46}\text{B}_2\text{NO}_7\text{S}$) 573.3220, found 573.3224.



(cis,syn,cis)-7-tosyl-3,3a,5a,6,7,8,8a,8b-octahydro-1H-furo[3,4-e]-isoindole (34)

A flame dried 250 mL round bottom flask was charged with *E,E*-bis(vinylboronate ester) **32** (196 mg, 0.342 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (24 mg, 0.034 mmol). Subsequently, methanol (170 mL) and chloroacetone (273 μL , 3.42 mmol) were added and allowed to stir for 5 minutes. Rapid addition of *aq.* 2 M K_2CO_3 (855 μL , 1.71 mmol) followed and the reaction mixture was allowed to stir for 5 days at room temperature. The resulting yellow solution was quenched with saturated *aq.* ammonium chloride (5 mL) and the methanol was removed *in vacuo*. The reaction mixture was diluted with Et_2O (20 mL), rinsed with brine (2 x 5 mL), and dried with MgSO_4 . Chromatography with 0.5% MeOH/DCM followed by a second flash column with 65:35 hexanes:EtOAc afforded 79 mg (72% yield) of a clear, colorless oil.

^1H NMR (400 MHz, CDCl_3 , ppm) δ : 7.70 (d, $J = 7.7$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 5.52 (dt, $J = 10.0$, 2.8 Hz, 1H), 5.32 (dt, $J = 10.1$, 2.0 Hz, 1H), 3.73 (dd $J = 8.8$, 6.4 Hz, 1H), 3.59 (dd, $J = 9.0$, 4.4 Hz, 1H), 3.49 (dd, $J = 10.0$, 6.8 Hz, 1H), 3.43 (dd, $J = 8.0$, 7.6 Hz, 1H), 3.40 (t, $J = 7.2$, 1H), 3.17 (dd, $J = 9.8$, 3.2 Hz, 1H), 3.06 (dd, $J = 10.0$, 8.4 Hz, 1H), 2.73–2.70 (m, 1H), 2.67–2.63 (m, 2H), 2.56–2.48 (m, 2H), 2.43 (s, 3H);

^{13}C NMR (100 MHz, CDCl_3 , ppm) δ : 143.4, 133.8, 129.5, 128.0, 127.5, 127.1, 73.2, 71.4, 53.7, 49.4, 37.9, 37.6, 37.27, 37.26, 21.5;

IR (neat, ATR): 3030, 2961, 2938, 2927, 2905, 2883, 2868, 1652, 1596, 1493, 1471, 1451, 1396, 1374, 1363, 1335, 1324, 1304, 1287, 1254, 1218, 1207, 1182, 1153, 1115, 1092, 1066, 1051, 1033, 1013, 996, 965, 947, 913;

HRMS (ES): calcd $[\text{M}+\text{Na}]^+$ ($\text{C}_{17}\text{H}_{21}\text{NO}_3\text{SNa}$) 342.110, found 342.1143.

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