# Stereoselective Synthesis of Trisubstituted (*E*,*E*)-1,3-Dienes by the Site-Selective Reductive Cross-Coupling of Internal Alkynes with Terminal Alkynes: A Fragment Coupling Reaction for Natural Product Synthesis

**Lark J. Perez, Heidi L. Shimp and Glenn C. Micalizio***

Supporting Information

**Table of Contents:**

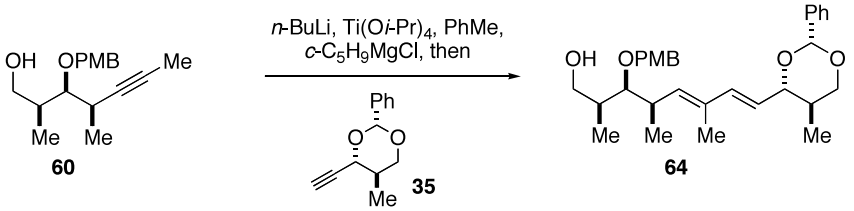
## 1. General Information

All reactions were conducted in flame-dried glassware under nitrogen using anhydrous solvents. Toluene was dried by distillation over $CaH_2$. Methylene chloride, tetrahydrofuran and diethyl ether were used after passing through activated alumina columns. All other commercially available reagents were used as received. All chiral aldehydes were obtained from a Dess-Martin Periodane oxidation of the corresponding primary alcohol and were used without purification except where indicated.

$^1$H-NMR data were recorded at 500 MHz or 400 MHz. $^1$H-NMR chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm). $^{13}$C-NMR data were recorded at 126 MHz or 100 MHz. $^{13}$C chemical shifts are reported relative to the central line of $CDCl_3$ (77.23 ppm). Low resolution mass spectrometry was performed using electrospray ionization (EI) or chemical ionization (CI). High resolution mass spectrometry (HRMS) was performed using EI. Optical rotations were measured using a 1 mL capacity micro cell with a 10 cm path length.

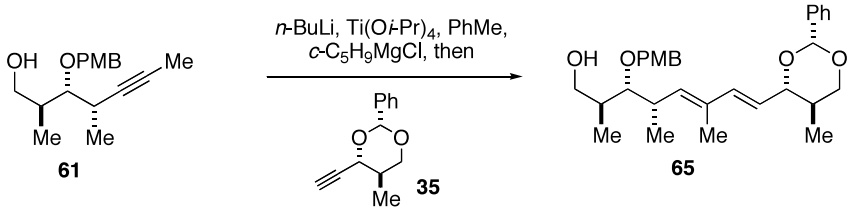
Chromatographic purifications were performed using 60Å, 35-75μm particle size silica gel. All compounds purified by chromatography were sufficiently pure for use in further experiments, unless indicated otherwise.

**2. Synthesis of 1,3-Dienes by the reductive cross-coupling of tris-homopropargylic alcohols.**



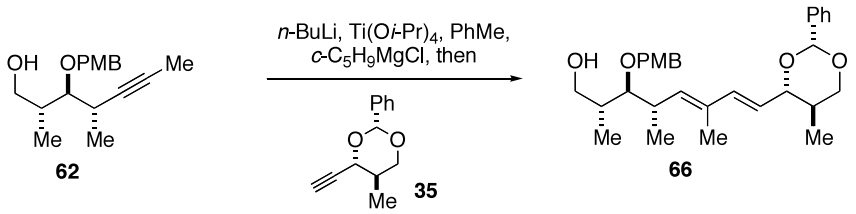

**(2*S*,3*S*,4*R*)-(5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-8-((2'*R*,4'*S*,5'*R*)-5'-methyl-2'-phenyl-1',3'-dioxan-4'-yl)octa-5,7-dien-1-ol, 64**. To a solution of the internal alkyne **60** (20 mg, 0.072 mmol) in $Et_2O$ (725 μL, 0.1 M) at ambient temperature was added *n*-BuLi (30 μL, 0.072 mmol, 2.5 M in hexanes), followed by Ti(O*i*-Pr)$_4$ (32 μL, 0.109 mmol). The resultant pale yellow solution was cooled to –78 °C and treated with *c*-$C_5H_9MgCl$ (110 μL, 0.217 mmol, 2.0 M in $Et_2O$). The mixture was allowed to warm to –30 °C over 1.5 h and was stirred at –30 °C for 30 min. The resulting dark brown solution was cooled to –78 °C and was treated with a solution of terminal alkyne, **35** (102 μL, 0.051 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 °C over 2 h, diluted with $Et_2O$ (2 mL) and quenched by the addition of 1N HCl (1 mL). After stirring at ambient temperature for 45 min, the bi-phasic mixture was transferred to a separatory funnel, extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography on 10 mL $SiO_2$ eluting with 10% EtOAc/hexanes to 50% EtOAc/hexanes provided the coupled product as a 17:1 (A:B, see SI p. 3) mixture of regioisomers (15.8 mg, 64%). Isolation of the major regioisomer was achieved by normal-phase HPLC using a gradient from 20% EtOAc/hexanes to 50% EtOAc/ hexanes over 25 min. $[\alpha]_{589}^{20}$ +32.4° (*c* 0.7, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 6.9 Hz, 2H), 7.38-7.28 (m, 5H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.31 (d, *J* = 15.8

Hz, 1H), 5.61 (dd, *J* = 15.8, 7.3 Hz, 1H), 5.55 (s, 1H), 5.31 (d, *J* = 9.8 Hz, 1H), 4.58 (A of AB, *J* = 10.7 Hz, 1H), 4.53 (B of AB, *J* = 10.7 Hz, 1H), 4.18 (dd, *J* = 11.4, 4.7 Hz, 1H), 3.93 (dd, *J* = 9.8, 8.2 Hz, 1H), 3.80 (s, 3H), 3.59-3.52 (m, 3H), 3.41 (dd, *J* = 8.8, 2.2 Hz, 1H), 2.85-2.77 (m, 1H), 1.99-1.90 (m, 1H), 1.90-1.82 (m, 1H), 1.77 (m, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.2, 138.6, 138.5, 136.7, 132.1, 130.9, 129.4, 128.8, 128.3, 126.3, 124.8, 113.8, 101.4, 84.9, 83.8, 74.7, 73.1, 66.2, 55.3, 38.6, 36.5, 34.5, 31.6, 22.6, 17.9, 14.1, 12.7, 12.6, 10.7; IR (thin film, NaCl) 3481, 2961, 2932, 2872, 2836, 1612, 1514, 1457, 1387, 1364, 1302, 1248, 1174, 1070, 1032, 967, 822, 752, 698; LRMS (EI) calcd for $C_{30}H_{40}O_5Na$ 503.3 *m/z* (M+Na); observed, 503.5 *m/z* (M+Na)$^+$; HRMS (FT-ICR) calcd for $C_{30}H_{40}O_5Na$ 503.2768 *m/z* (M+Na); observed, 503.2778 *m/z* (M+Na)$^+$.



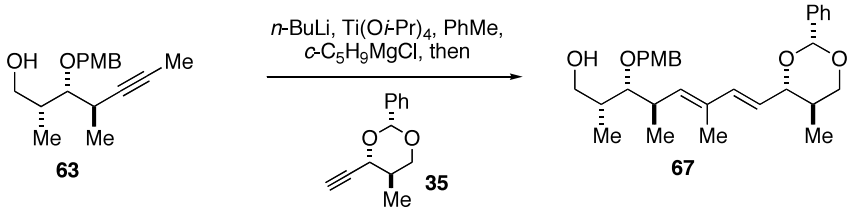

**(2*S*,3*R*,4*S*)-(5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-8-((2'*R*,4'*S*,5'*R*)-5'-methyl-2'-phenyl-1',3'-dioxan-4'-yl)octa-5,7-dien-1-ol, 65**. To a solution of the internal alkyne **61** (20 mg, 0.072 mmol) in $Et_2O$ (725 μL, 0.1 M) at ambient temperature was added *n*-BuLi (30 μL, 0.072 mmol, 2.5 M in hexanes), followed by Ti(O*i*-Pr)$_4$ (32 μL, 0.109 mmol). The resultant pale yellow solution was cooled to –78 °C and treated with *c*-$C_5H_9MgCl$ (110 μL, 0.217 mmol, 2.0 M in $Et_2O$). The mixture was allowed to warm to –30 °C over 1.5 h and was stirred at –30 °C for 30min. The resulting dark brown

solution was cooled to –78 °C and was treated with a solution of terminal alkyne, **35** (102 μL, 0.051 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 °C over 2 h, was diluted with $Et_2O$ (2 mL) and quenched by the addition of 1N HCl (1 mL). After stirring at ambient temperature for 45 min, the bi-phasic mixture was transferred to a separatory funnel, extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography on 10 mL $SiO_2$ eluting with 10% EtOAc/hexanes to 50% EtOAc/hexanes provided the coupled product as a 19:7:1 (A:pyran:C, see SI p. 3) mixture of regioisomers (15.3 mg, 63%). Isolation of the major regioisomer was achieved by normal-phase HPLC using a gradient from 20% EtOAc/hexanes to 50% EtOAc/ hexanes over 25 min. $[\alpha]_{589}^{20}$ –13.7° (*c* 0.5, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.8 Hz, 2H), 7.37-7.29 (m, 3H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.32 (d, *J* = 15.4 Hz, 1H), 5.63 (dd, *J* = 15.4, 7.3 Hz, 1H), 5.55 (s, 1H), 5.39 (d, *J* = 9.8 Hz, 1H), 4.57 (A of AB, *J* = 10.7 Hz, 1H), 4.51 (B of AB, *J* = 10.7 Hz, 1H), 4.19 (dd, *J* = 11.4, 4.7 Hz, 1H), 3.94 (dd, *J* = 9.8, 7.6 Hz, 1H), 3.80 (s, 3H), 3.75-3.70 (m, 1H), 3.59-3.49 (m, 2H), 3.26 (t, *J* = 5.7 Hz, 1H), 2.89-2.81 (m, 1H), 2.70 (t, *J* = 5.7 Hz, 1H), 1.98-1.90 (m, 1H), 1.86-1.80 (m, 1H), 1.77 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 7.2 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.3, 138.5, 138.2, 136.8, 132.3, 130.2, 129.5, 128.8, 128.2, 126.2, 124.9, 113.9, 101.3, 88.8, 84.6, 75.3, 73.0, 65.6, 55.3, 37.5, 36.5, 34.5, 16.3, 15.7, 12.7, 12.6; IR (thin film, NaCl) 3495, 2963, 2931, 2873, 2836, 1612, 1515, 1456, 1387, 1368, 1302, 1249, 1109, 1071, 1032, 968, 918, 823, 758, 699; LRMS (EI) calcd for $C_{30}H_{40}O_5Na$ 503.3 *m/z* (M+Na); observed, 503.4 *m/z* $(M+Na)^+$; HRMS (FT-ICR) calcd for $C_{30}H_{40}O_5Na$ 503.2768 *m/z* (M+Na); observed, 503.2779 *m/z* $(M+Na)^+$.



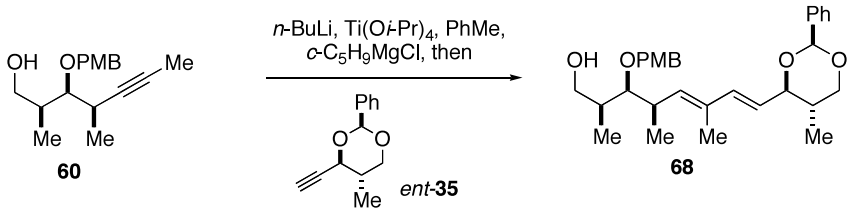

**(2*R*,3*S*,4*S*)-(5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-8-((2'*R*,4'*S*,5'*R*)-5'-methyl-2'-phenyl-1',3'-dioxan-4'-yl)octa-5,7-dien-1-ol, 66**. To a solution of the internal alkyne **62** (20 mg, 0.072 mmol) in $Et_2O$ (725 μL, 0.1 M) at ambient temperature was added *n*-BuLi (30μL, 0.072 mmol, 2.5 M in hexanes), followed by Ti(O*i*-Pr)$_4$ (32 μL, 0.109 mmol). The resultant pale yellow solution was cooled to –78 °C and treated with *c*-$C_5H_9MgCl$ (110 μL, 0.217 mmol, 2.0 M in $Et_2O$). The mixture was allowed to warm to –30 °C over 1.5 h and was stirred at –30 °C for 30 min. The resulting dark brown solution was cooled to –78 °C and was treated with a solution of terminal alkyne, **35** (102 μL, 0.051 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 °C over 2 h, diluted with $Et_2O$ (2 mL) and quenched by the addition of 1N HCl (1 mL). After stirring at ambient temperature for 45 min, the bi-phasic mixture was transferred to a separatory funnel, extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography on 10 mL $SiO_2$ eluting with 10% EtOAc/hexanes to 50% EtOAc/hexanes provided the coupled product as a 17:2:1 (A:pyran:C, see SI p.2) mixture of regioisomers (16.4 mg, 67%). Isolation of the major regioisomer was achieved by normal-phase HPLC using a gradient from 20% EtOAc/hexanes to 50% EtOAc/ hexanes over 25 min. $[\alpha]_{589}^{20}$ –10.6° (*c* 1.0, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.49-7.37 (m, 3H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.37 (d, *J* = 15.5 Hz, 1H), 5.61-5.56 (m, 2H), 5.55 (s, 1H), 4.61 (A of AB, *J* = 10.4 Hz, 1H), 4.49 (B of AB, *J* = 10.4 Hz, 1H), 4.19 (dd, *J* = 11.7, 4.7 Hz,

1H), 3.93 (dd, *J* = 9.5, 7.6 Hz, 1H), 3.80 (s, 3H), 3.72-3.67 (m, 1H), 3.63-3.59 (m, 1H), 3.56 (t, *J* = 11.4 Hz, 1H), 3.28 (dd, *J* = 7.3, 4.4 Hz, 1H), 2.90-2.83 (m, 1H), 2.62 (dd, *J* = 6.6, 5.0 Hz, 1H), 1.99-1.90 (m, 1H), 1.86-1.79 (m, 1H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.4, 138.7, 138.5, 135.4, 132.9, 130.4, 129.6, 128.7, 128.2, 126.2, 124.6, 113.9 101.3, 88.5, 84.9, 75.2, 73.1, 66.2, 55.3, 38.0, 36.2, 34.4, 18.2, 15.3, 12.7, 12.6; IR (thin film, NaCl) 3452, 2959, 2932, 2874, 2838, 1613, 1514, 1456, 1369, 1302, 1249, 1109, 1069, 1032, 968, 919, 823, 766, 699; LRMS (EI) calcd for $C_{30}H_{40}O_5Na$ 503.3 *m/z* (M+Na); observed, 503.5 *m/z* $(M+Na)^+$; HRMS (FT-ICR) calcd for $C_{30}H_{40}O_5Na$ 503.2768 *m/z* (M+Na); observed, 503.2773 *m/z* $(M+Na)^+$.



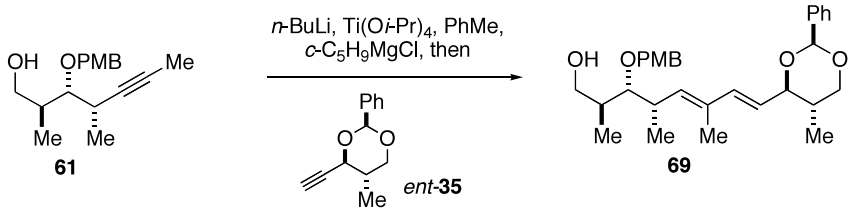

**(2*R*,3*R*,4*R*)-(5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-8-((2'*R*,4'*S*,5'*R*)-5'-methyl-2'-phenyl-1',3'-dioxan-4'-yl)octa-5,7-dien-1-ol, 67.** To a solution of the internal alkyne **63** (20 mg, 0.072 mmol) in $Et_2O$ (725 μL, 0.1 M) at ambient temperature was added *n*-BuLi (30 μL, 0.072 mmol, 2.5 M in hexanes), followed by Ti(O*i*-Pr)$_4$ (32 μL, 0.109 mmol). The resultant pale yellow solution was cooled to –78 °C and treated with *c*-$C_5H_9MgCl$ (110 μL, 0.217 mmol, 2.0 M in $Et_2O$). The mixture was allowed to warm to –30 °C over 1.5 h and was stirred at –30 °C for 30 min. The resulting dark brown solution was cooled to –78 °C and was treated with a solution of terminal alkyne, **35** (102 μL, 0.051 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 °C over

2 h, was diluted with $Et_2O$ (2mL) and quenched by the addition of 1N HCl (1 mL). After stirring at ambient temperature for 45 min, the bi-phasic mixture was transferred to a separatory funnel, extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography on 10 mL $SiO_2$ eluting with 10% EtOAc/hexanes to 50% EtOAc/hexanes provided the coupled product as a 12:1 (A:C, see SI p. 3) mixture of regioisomers (16.6 mg, 68%). Isolation of the major regioisomer was achieved by normal-phase HPLC using a gradient from 20% EtOAc/hexanes to 50% EtOAc/ hexanes over 25 min. $[\alpha]_{589}^{20}$ –14.7° (*c* 0.6, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.6 Hz, 2H), 7.39-7.29 (m, 3H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.35 (d, *J* = 15.8 Hz, 1H), 5.62-5.57 (m, 2H), 5.55 (s, 1H), 4.50 (A of AB, *J* = 10.7 Hz, 1H), 4.45 (B of AB, *J* = 10.7 Hz, 1H), 4.19 (dd, *J* = 11.7, 4.7 Hz, 1H), 3.93 (dd, *J* = 9.4, 7.9 Hz, 1H), 3.77 (s, 3H), 3.60-3.48 (m, 3H), 3.39 (dd, *J* = 5.7, 4.4 Hz, 1H), 2.88-2.81 (m, 1H), 1.98-1.89 (m, 2H), 1.77 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.9 Hz, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.2, 138.5, 136.6, 132.6, 130.8, 129.6, 128.7, 128.2, 126.2, 124.6, 113.7, 101.3, 84.9, 84.4, 73.9, 73.1, 66.2, 55.2, 37.8, 35.6, 34.5, 31.6, 22.6, 18.3, 14.1, 12.8, 12.6, 11.6; IR (thin film, NaCl) 3447, 2962, 2931, 2873, 2837, 1612, 1514, 1456, 1387, 1367, 1302, 1249, 1108, 1070, 1032, 968, 822, 755, 699; LRMS (EI) calcd for $C_{30}H_{40}O_5Na$ 503.3 *m/z* (M+Na); observed, 503.5 *m/z* $(M+Na)^+$; HRMS (FT-ICR) calcd for $C_{30}H_{40}O_5Na$ 503.2768 *m/z* (M+Na); observed, 503.2778 *m/z* $(M+Na)^+$.



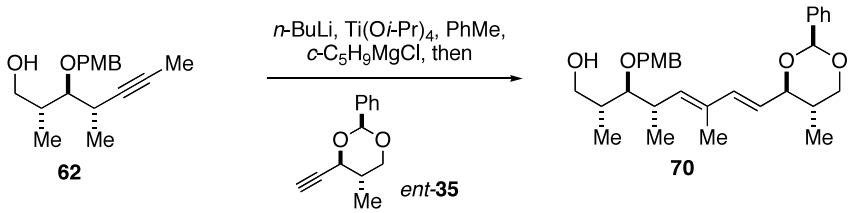

**(2*S*,3*S*,4*R*)-(5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-8-((2'*S*,4'*R*,5'*S*)-5'-methyl-2'-phenyl-1',3'-dioxan-4'-yl)octa-5,7-dien-1-ol, 68**. To a solution of the internal alkyne **60** (20 mg, 0.072 mmol) in $Et_2O$ (725 μL, 0.1 M) at ambient temperature was added *n*-BuLi (30μL, 0.072 mmol, 2.5 M in hexanes), followed by Ti(O*i*-Pr)$_4$ (32 μL, 0.109 mmol). The resultant pale yellow solution was cooled to –78 °C and treated with *c*-$C_5H_9MgCl$ (110 μL, 0.217 mmol, 2.0 M in $Et_2O$). The mixture was allowed to warm to –30 °C over 1.5 h and was stirred at –30 °C for 30 min. The resulting dark brown solution was cooled to –78 °C and was treated with a solution of terminal alkyne, *ent*-**35** (102 μL, 0.051 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 °C over 2 h, was diluted with $Et_2O$ (2 mL) and quenched by the addition of 1N HCl (1 mL). After stirring at ambient temperature for 45 min the bi-phasic mixture was transferred to a separatory funnel, extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography on 10 mL $SiO_2$ eluting with 10% EtOAc/hexanes to 50% EtOAc/hexanes provided the coupled product as a 47:7:1:1 (A:pyran:B:C, see SI p. 3) mixture of regioisomers (14.9 mg, 60%). Isolation of the major regioisomer was achieved by normal-phase HPLC using a gradient from 20% EtOAc/hexanes to 50% EtOAc/ hexanes over 25min. $[\alpha]_{589}^{20}$ –38.7° (*c* 0.3, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.9 Hz, 2H), 7.37-7.30 (m, 3H), 7.28 (d, *J* = 8.5

Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.31 (d, *J* = 15.8 Hz, 1H), 5.59 (dd, *J* = 15.8, 7.6 Hz, 1H), 5.55 (s, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 4.59 (A of AB, *J* = 11.0 Hz, 1H), 4.56 (B of AB, *J* = 11.0 Hz, 1H), 4.19 (dd, *J* = 11.4, 4.7 Hz, 1H), 3.93 (dd, *J* = 9.4, 7.3 Hz, 1H), 3.80 (s, 3H), 3.59-3.51 (m, 2H), 3.40 (dd, *J* = 8.8, 2.2 Hz, 1H), 2.85-2.77 (m, 1H), 1.99-1.91 (m, 1H), 1.87-1.81 (m, 1H), 1.77 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.9 Hz, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.2, 138.6, 138.5, 136.7, 132.1, 130.9, 129.4, 128.8, 128.3, 126.3, 124.8, 113.8, 101.4, 84.9, 83.8, 74.7, 73.1, 66.2, 55.3, 38.6, 36.5, 34.4, 31.6, 22.6, 17.9, 14.1, 12.7, 12.6, 10.7; IR (thin film, NaCl) 3450, 2962, 2932, 2873, 2836, 1613, 1586, 1514, 1457, 1386, 1370, 1301, 1249, 1107, 1070, 1030, 967, 822, 755, 734, 699; LRMS (EI) calcd for $C_{30}H_{40}O_5Na$ 503.3 *m/z* (M+Na); observed, 503.5 *m/z* $(M+Na)^+$; HRMS (FT-ICR) calcd for $C_{30}H_{40}O_5Na$ 503.2768 *m/z* (M+Na); observed, 503.2779 *m/z* $(M+Na)^+$.



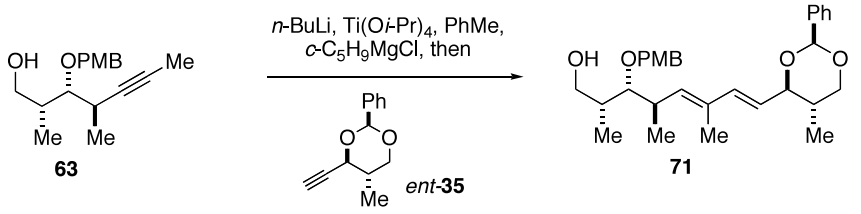

**(2*S*,3*R*,4*S*)-(5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-8-((2'*S*,4'*R*,5'*S*)-5'-methyl-2'-phenyl-1',3'-dioxan-4'-yl)octa-5,7-dien-1-ol, 69**. To a solution of the internal alkyne **61** (20 mg, 0.072 mmol) in $Et_2O$ (725 μL, 0.1 M) at ambient temperature was added *n*-BuLi (30 μL, 0.072 mmol, 2.5 M in hexanes), followed by Ti(O*i*-Pr)$_4$ (32 μL, 0.109 mmol). The resultant pale yellow solution was cooled to –78 °C and treated with *c*-$C_5H_9MgCl$ (110 μL, 0.217 mmol, 2.0 M in $Et_2O$). The mixture was allowed to warm to –30 °C over 1.5 h and was stirred at –30 °C for 30min. The resulting dark brown

solution was cooled to –78 °C and was treated with a solution of terminal alkyne, *ent*-**35** (102 μL, 0.051 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 °C over 2 h, was diluted with $Et_2O$ (2 mL) and quenched by the addition of 1N HCl (1 mL). After stirring at ambient temperature for 45 min the bi-phasic mixture was transferred to a separatory funnel, extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography on 10 mL $SiO_2$ eluting with 10% EtOAc/hexanes to 50% EtOAc/hexanes provided the coupled product as a 14:1 (A:C, see SI p. 3) mixture of regioisomers (14.0 mg, 57%). Isolation of the major regioisomer was achieved by normal-phase HPLC using a gradient from 20% EtOAc/hexanes to 50% EtOAc/ hexanes over 25 min. $[\alpha]_{589}^{20}$ +61.6° (*c* 0.2, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.6 Hz, 2H), 7.40-7.33 (m, 3H), 7.29 (d, *J* = 7.3 Hz, 2H), 6.87 (d, *J* = 7.3 Hz, 2H), 6.31 (d, *J* = 14.8 Hz, 1H), 5.61 (dd, *J* = 15.1, 7.9 Hz, 1H), 5.55 (s, 1H), 5.40 (d, *J* = 10.1 Hz, 1H), 4.57 (A of AB, *J* =10.4 Hz, 1H), 4.49 (B of AB, *J* = 10.4 Hz, 1H), 4.19 (dd, *J* = 12.3, 4.7 Hz, 1H), 3.93 (t, *J* = 8.5 Hz, 1H), 3.80 (s, 3H), 3.70 (d, *J* = 10.1 Hz, 1H), 3.56-3.48 (m, 2H), 3.24 (t, *J* = 6.6 Hz, 1H), 2.88-2.81 (m, 1H), 2.65 (bs, 1H), 1.99-1.91 (m, 1H), 1.86-1.79 (m, 1H), 1.77 (s, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 7.2 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.4, 138.5, 138.4, 136.9, 132.3, 130.3, 129.4, 128.8, 128.2, 126.2, 125.2, 113.9, 101.3, 88.9, 84.9, 75.4, 73.1, 65.7, 55.3, 37.6, 36.5, 34.4, 16.2, 15.6, 12.7, 12.5; IR (thin film, NaCl) 3421, 2960, 2924, 2872, 1636, 1512, 1457, 1394, 1249, 1107, 1071, 1031, 972, 819, 757, 699; LRMS (EI) calcd for $C_{30}H_{40}O_5Na$ 503.3 *m/z* (M+Na); observed, 503.4 *m/z* $(M+Na)^+$; HRMS (FT-ICR) calcd for $C_{30}H_{40}O_5Na$ 503.2768 *m/z* (M+Na); observed, 503.2781 *m/z* $(M+Na)^+$.



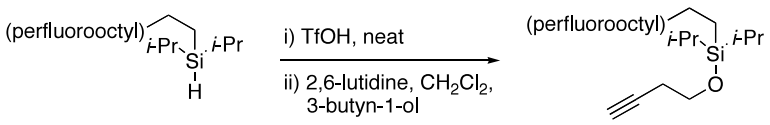

**(2*R*,3*S*,4*S*)-(5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-8-((2'*S*,4'*R*,5'*S*)-5'-methyl-2'-phenyl-1',3'-dioxan-4'-yl)octa-5,7-dien-1-ol, 70**. To a solution of the internal alkyne **62** (20 mg, 0.072 mmol) in $Et_2O$ (725 μL, 0.1 M) at ambient temperature was added *n*-BuLi (30μL, 0.072 mmol, 2.5 M in hexanes), followed by Ti(O*i*-Pr)$_4$ (32 μL, 0.109 mmol). The resultant pale yellow solution was cooled to –78 °C and treated with *c*-$C_5H_9MgCl$ (110 μL, 0.217 mmol, 2.0 M in $Et_2O$). The mixture was allowed to warm to –30 °C over 1.5 h and was stirred at –30 °C for 30 min. The resulting dark brown solution was cooled to –78 °C and was treated with a solution of terminal alkyne, *ent*-**35** (102 μL, 0.051 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 °C over 2 h, was diluted with $Et_2O$ (2 mL) and quenched by the addition of 1N HCl (1 mL). After stirring at ambient temperature for 45 min the bi-phasic mixture was transferred to a separatory funnel, extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography on 10 mL $SiO_2$ eluting with 10% EtOAc/hexanes to 50% EtOAc/hexanes provided the coupled product as a 15:2:1 (A:pyran:C, see SI p. 3) mixture of regioisomers (11.5 mg, 47%). Isolation of the major regioisomer was achieved by normal-phase HPLC using a gradient from 20% EtOAc/hexanes to 50% EtOAc/ hexanes over 25 min. $[\alpha]_{589}^{20}$ +29.8° (*c* 0.9, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 6.9 Hz, 2H), 7.37-7.29 (m, 3H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.36 (d, *J* = 15.8 Hz, 1H), 5.62-5.56 (m, 2H), 5.55 (s, 1H), 4.58 (A of AB, *J* = 10.4 Hz, 1H), 4.50 (B of AB, *J* = 10.4 Hz, 1H), 4.19 (dd, *J* =

11.4, 4.7 Hz, 1H), 3.93 (dd, *J* = 9.8, 7.6 Hz, 1H), 3.78 (s, 3H), 3.66-3.62 (m, 1H), 3.60-3.53 (m, 1H), 3.53 (t, *J* = 11.0 Hz, 1H), 3.28 (dd, *J* = 7.3, 4.1 Hz, 1H), 2.90-2.82 (m, 1H), 2.55 (dd, *J* = 6.6, 4.7 Hz, 1H), 1.99-1.91 (m, 1H), 1.85-1.77 (m, 1H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.3, 138.6, 138.5, 135.3, 133.0, 130.4, 129.6, 128.7, 128.2, 126.2, 124.6, 113.9, 101.3, 88.3, 84.9, 75.1, 73.1, 66.2, 55.2, 37.9, 36.1, 34.5, 18.1, 15.2, 12.7, 12.6; IR (thin film, NaCl) 3464, 2964, 2929, 2874, 1617, 1515, 1457, 1387, 1248, 1107, 1029, 972, 821, 736, 699; LRMS (EI) calcd for $C_{30}H_{40}O_5Na$ 503.3 *m*/*z* (M+Na); observed, 503.4 *m*/*z* $(M+Na)^+$; HRMS (FT-ICR) calcd for $C_{30}H_{40}O_5Na$ 503.2768 *m*/*z* (M+Na); observed, 503.2778 *m*/*z* $(M+Na)^+$.

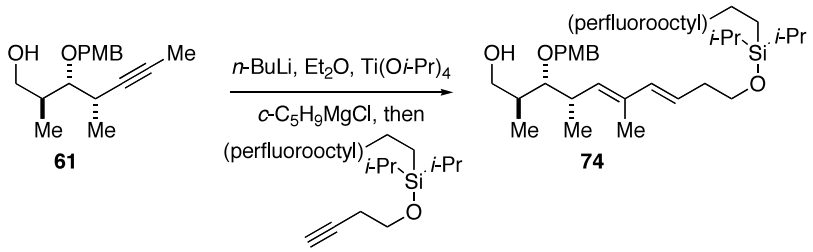



**(2*R*,3*R*,4*R*)-(5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-8-((2'*S*,4'*R*,5'*S*)-5'-methyl-2'-phenyl-1',3'-dioxan-4'-yl)octa-5,7-dien-1-ol, 71**. To a solution of the internal alkyne **63** (20 mg, 0.072 mmol) in $Et_2O$ (725 μL, 0.1 M) at ambient temperature was added *n*-BuLi (30 μL, 0.072 mmol, 2.5 M in hexanes), followed by Ti(O*i*-Pr)$_4$ (32 μL, 0.109 mmol). The resultant pale yellow solution was cooled to –78 °C and treated with *c*-$C_5H_9MgCl$ (110 μL, 0.217 mmol, 2.0 M in $Et_2O$). The mixture was allowed to

warm to –30 °C over 1.5 h and was stirred at –30 °C for 30min. The resulting dark brown solution was cooled to –78 °C and was treated with a solution of terminal alkyne, *ent*-**35** (102 μL, 0.051 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 °C over 2 h, was diluted with $Et_2O$ (2 mL) and quenched by the addition of 1N HCl (1 mL). After stirring at ambient temperature for 45 min the bi-phasic mixture was transferred to a separatory funnel, extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography on 10 mL $SiO_2$ eluting with 10% EtOAc/hexanes to 50% EtOAc/hexanes provided the coupled product as a 22:3:1 (A:pyran:C, see SI p. 3) mixture of regioisomers (12.9 mg, 53%). Isolation of the major regioisomer was achieved by normal-phase HPLC using a gradient from 20% EtOAc/hexanes to 50% EtOAc/ hexanes over 25 min. $[\alpha]_{589}^{20}$ +27.9° (*c* 0.9, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.9 Hz, 2H), 7.38-7.29 (m, 3H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.37 (d, *J* = 15.7 Hz, 1H), 5.63-5.56 (m, 2H), 5.55 (s, 1H), 4.51 (A of AB, *J* = 10.7 Hz, 1H), 4.45 (B of AB, *J* = 10.7 Hz, 1H), 4.19 (dd, *J* = 11.4, 4.7 Hz, 1H), 3.94 (dd, *J* = 9.8, 7.6 Hz, 1H), 3.79 (s, 3H), 3.63-3.42 (m, 3H), 3.38 (m, 1H), 2.89-2.81 (m, 1H), 1.99-1.91 (m, 2H), 1.77 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H) ; $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.2, 138.7, 138.5, 136.8, 132.6, 130.8, 129.6, 128.8, 128.2, 126.2, 124.6, 113.7, 101.3, 84.9, 84.4, 73.9, 73.1, 66.2, 55.3, 37.7, 35.6, 34.4, 18.2, 12.8, 12.6, 11.4; IR (thin film, NaCl) 3447, 2958, 2928, 2876, 1617, 1512, 1457, 1394, 1302, 1248, 1107, 1071, 1029, 972, 821, 698; LRMS (EI) calcd for $C_{30}H_{40}O_5Na$ 503.3 *m*/*z* (M+Na); observed, 503.4 *m*/*z* $(M+Na)^+$; HRMS (FT-ICR) calcd for $C_{30}H_{40}O_5Na$ 503.2768 *m*/*z* (M+Na); observed, 503.2767 *m*/*z* $(M+Na)^+$.

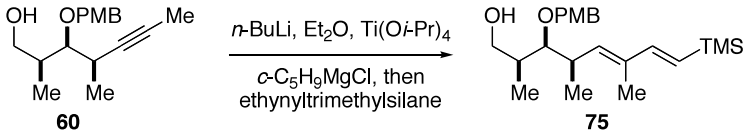



**4-(diisopropyl-(1H,1H,2H,2H-perfluorodecyl)silyloxy)but-1-yn.** To diisopropyl-(1H,1H,2H,2H-perfluorodecyl)silane (1 g, 1.78 mmol, Fluorous Technologies, #F017004) at 0 ºC was added TfOH (140 $\mu$L, 1.58 mmol) and the mixture was stirred for 15 h at ambient temperature. The resulting mixture was cooled to 0 ºC and treated with a solution of 3-butyn-1-ol (104 $\mu$L, 1.37 mmol) and 2,6-lutidine (317 $\mu$L, 2.74 mmol) in $CH_2Cl_2$ (3.4 mL) dropwise via canula. The reaction was allowed to stir for 1 h at 0 ºC and was quenched with pH 7 phosphate buffer (10 mL), extracted with $CH_2Cl_2$ (3 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification was achieved on 25 mL $SiO_2$ eluting with 100% hexanes (50 mL) then 10% EtOAc/hexanes (50 mL) to give the desired product as a clear, colorless oil (622 mg, 72%). $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.79 (t, *J* = 7.0 Hz, 2H), 2.43 (dt, *J* = 7.0, 2.6 Hz, 2H), 2.22-2.07 (m, 2H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.06-1.03 (m, 14H), 0.88-0.84 (m, 2H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 81.2, 69.4, 61.9, 25.6, 25.4, 25.2, 22.8, 17.4, 17.3, 17.1, 17.0, 12.8, 12.4, -0.3; IR (thin film, NaCl) 3319, 2948, 2872, 1465, 1243, 1206, 1152, 1134, 1114, 1062, 887, 705, 643; LRMS (EI) calcd for $C_{20}H_{23}F_{17}OSiNa$ 653.1 *m/z* (M+Na); observed, 653.0 *m/z* $(M+Na)^+$.



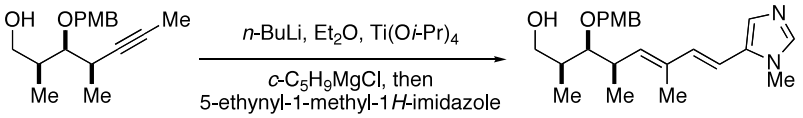

**(2*S*,3*R*,4*S*,5*E*,7*E*)-3-(4-methoxybenzyloxy)-10-(diisopropyl-(1H,1H,2H,2H-perfluorodecyl)silyloxy)-2,4,6-trimethyldeca-5,7-dien-1-ol, 74.** To a solution of internal alkyne **61** (20 mg, 0.0724 mmol) in $Et_2O$ (725 $\mu$L, 0.1 M) at ambient temperature was added *n*-BuLi (30 $\mu$L, 0.0724 mmol, 2.5 M in hexanes) followed by Ti(O*i*-Pr)$_4$ (32 $\mu$L, 0.109 mmol) and the resulting mixture was cooled to –78 ºC. To the cooled mixture was added *c*-$C_5H_9MgCl$ (110 µL, 0.218 mmol) and the reaction was allowed to warm to –30 ºC over 1 h and was stirred at –30 ºC for 1 h before recooling to –78 ºC and addition of 4-(diisopropyl-(1H,1H,2H,2H-perfluorodecyl)silyloxy)but-1-yn (102 $\mu$L, 0.0507 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 ºC while stirring for 2 h The reaction was quenched with sat. $NH_4Cl$, stirred for 2 h at ambient temperature, diluted with $Et_2O$ (10 mL), extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the crude mixture was achieved using a 2 g FluoroFlash® SPE cartridge (Fluorous Technologies, #801-0027S-2), prewashed with 4mL 80:20 MeOH:$H_2O$. The crude reaction mixture was loaded onto the column in 200 $\mu$L of DMF and was allowed to slowly adsorb to the column (5 min.) before eluting with 80:20 MeOH:$H_2O$ (9 mL) then 100% MeOH (9 mL). The 100% MeOH fraction was concentrated to provide the desired product (29.3 mg, 64%). $[\alpha]_{589}^{20}$ +0.7° (*c* 1.4, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.08 (d, *J* = 15.8 Hz, 1H), 5.58 (dt, *J* = 15.8, 6.9 Hz, 1H), 5.26 (d, *J* = 9.8 Hz, 1H), 4.57 (A of AB, *J* = 10.4 Hz, 1H), 4.50 (B of AB, *J* = 10.4 Hz, 1H) 3.80 (s, 3H), 3.75-3.69 (m,

3H), 3.54-3.49 (m, 1H), 3.25 (dd, $J$ = 6.6, 5.4 Hz, 1H), 3.86-2.80 (m, 1H), 2.71 (t, $J$ = 5.7 Hz, 1H), 2.34 (q, $J$ = 6.6 Hz, 2H), 2.18-2.06 (m, 2H), 1.87-1.79 (m, 1H), 1.73 (d, $J$ = 0.9 Hz, 3H), 1.07 (d, $J$ = 6.6 Hz, 3H), 1.05 (d, $J$ = 7.3 Hz, 3H), 1.04 (d, $J$ = 2.5 Hz, 14H), 0.84 (m, 2H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.1, 136.8, 134.3, 132.8, 130.3, 129.5, 124.0, 113.9, 89.2, 75.4, 65.7, 63.4, 55.3, 37.5, 36.5, 36.4, 25.4, 17.5, 17.4, 16.4, 15.6, 12.6, 12.4; IR (thin film, NaCl) 3426, 2959, 2869, 1616, 1516, 1457, 1245, 1039, 887, 822, 704; LRMS (EI) calcd for $C_{37}H_{49}F_{17}O_4SiNa$ 931.3 *m/z* (M+Na); observed, 931.2 *m/z* $(M+Na)^+$; HRMS (FT-ICR) calcd for $C_{37}H_{49}F_{17}O_4SiNa$ 931.3026 *m/z* (M+Na), observed, 931.3089 *m/z* $(M+Na)^+$.



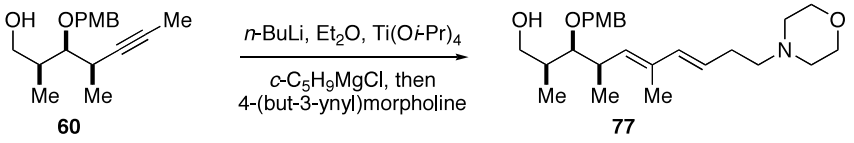

**(2*S*,3*S*,4*R*,5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-8-(trimethylsilyl)octa-5,7-dien-1-ol, 75.** To a solution of internal alkyne **60** (20 mg, 0.0724 mmol) in $Et_2O$ (725 μL, 0.1 M) at ambient temperature was added *n*-BuLi (30 μL, 0.0724 mmol, 2.5 M in hexanes) followed by Ti(O*i*-Pr)$_4$ (32 μL, 0.109 mmol) and the resulting mixture was cooled to –78 ºC. To the cooled mixture was added *c*-$C_5H_9MgCl$ (110 μL, 0.218 mmol) and the reaction was allowed to warm to –30 ºC over 1 h and was stirred at –30 ºC for 1 h before recooling to –78 ºC and addition of ethynyltrimethylsilane (102 μL, 0.0507 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 ºC while stirring for 2 h The reaction was quenched with sat. $NH_4Cl$, stirred for 2 h at ambient temperature, diluted with $Et_2O$ (10 mL), extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification was achieved by column chromatography on 10 mL

$SiO_2$, eluting with 10% EtOAc/hexanes (20 mL), 30% EtOAc/hexanes (20 mL), and 50% EtOAc/hexanes (30 mL) to give a 4:1 mixture of desired product to reduced internal alkyne (11.1 mg, 58% yield of desired product). Separation of the desired product from reduced internal alkyne was achieved by normal-phase HPLC using a gradient from 20% EtOAc/hexanes to 50% EtOAc/hexanes over 25 min. $[\alpha]_{589}^{20}$ +5.8° (*c* 0.6, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.50 (d, *J* = 18.9 Hz, 1H), 5.73 (d, *J* = 18.6 Hz, 1H), 5.33 (d, *J* = 10.1 Hz, 1H), 4.59 (A of AB, *J* = 10.7 Hz, 1H), 4.54 (B of AB, *J* = 11.0 Hz, 1H), 3.81 (s, 3H), 3.59-3.52 (m, 2H), 3.43 (dd, *J* = 9.1, 2.5 Hz, 1H), 2.86-2.78 (m, 1H), 1.90-1.84 (m, 1H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.09 (3, 9H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.2, 148.6, 136.7, 134.4, 130.9, 129.4, 126.3, 113.8, 83.8, 74.7, 66.2, 55.3, 38.6, 36.7, 17.9, 12.1, 10.6, –1.2; IR (thin film, NaCl) 3466, 2956, 2873, 2836, 1613, 1585, 1514, 1460, 1302, 1248, 1082, 1036, 859, 839; LRMS (EI) calcd for $C_{22}H_{36}O_3SiNa$ 399.2 *m/z* (M+Na); observed, 399.4 *m/z* $(M+Na)^+$.



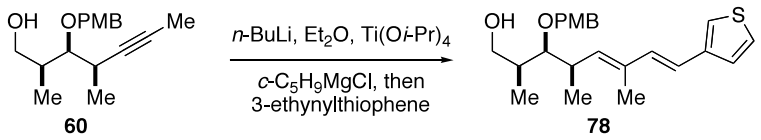

**(2*S*,3*S*,4*R*,5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-8-(1-methyl-1*H*-imidazol-5-yl)octa-5,7-dien-1-ol, 76.** To a solution of internal alkyne **60** (20 mg, 0.0724 mmol) in $Et_2O$ (725 μL, 0.1 M) at ambient temperature was added *n*-BuLi (30 μL, 0.0724 mmol, 2.5 M in hexanes) followed by Ti(O*i*-Pr)$_4$ (32 μL, 0.109 mmol) and the resulting mixture was cooled to –78 ºC. To the cooled mixture was added *c*-$C_5H_9MgCl$ (110 μL, 0.218 mmol) and the reaction was allowed to warm to –30 ºC over 1 h and was stirred at

–30 ºC for 1 h before recooling to –78 ºC and addition of 5-ethynyl-1-methyl (1*H*) imidazole (102 $\mu$L, 0.0507 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 ºC while stirring for 2 h The reaction was quenched with sat. $NH_4Cl$ stirred for 2 h at ambient temperature, diluted with $Et_2O$ (10 mL), extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification was achieved by column chromatography on 10mL $SiO_2$, eluting with 50% EtOAc/hexanes (20 mL), 80% EtOAc/hexanes (20 mL), and 10% MeOH/$CHCl_3$ (40 mL) to give the desired product as a clear, colorless oil (11.4 mg, 58%). $[\alpha]_{589}^{20}$ +12.9° (*c* 0.3, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.41 (bs, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.17 (s, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 15.7 Hz, 1H), 6.18 (d, *J* =16.1 Hz, 1H), 5.40 (d, *J* = 10.4 Hz, 1H), 4.57 (A of AB, *J* = 11.0 Hz, 1H), 4.53 (B of AB, *J* = 10.7 Hz, 1H), 3.81 (s, 3H), 3.63 (s, 3H), 3.59-3.53 (m, 2H), 3.45 (dd, *J* = 8.8, 2.5 Hz, 1H), 2.89-2.82 (m, 1H), 1.92-1.87 (m, 1H), 1.86 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.1, 138.3, 137.2, 134.6, 132.4, 131.6, 130.8, 129.4, 126.5, 113.8, 111.5, 83.7, 74.7, 66.2, 55.3, 38.6, 36.7, 31.7, 17.9, 12.4, 10.8; IR (thin film, NaCl) 3334, 2961, 2928, 1721, 1672, 1613, 1514, 1457, 1249, 1115, 1033, 957, 823; HRMS (FT-ICR) calcd for $C_{23}H_{33}N_2O_3$ 385.2486 *m/z* (M+H); observed, 385.2486 *m/z* $(M+H)^+$.



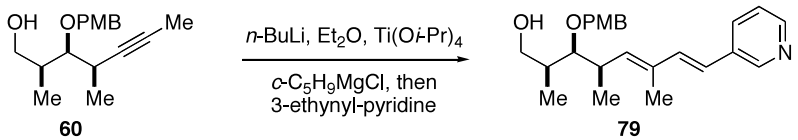

**(2*S*,3*S*,4*R*)-(5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-10-morpholinodeca-5,7-dien-1-ol, 77.** To a solution of internal alkyne **60** (20 mg, 0.0724 mmol) in $Et_2O$ (725 $\mu$L, 0.1 M) at ambient temperature was added *n*-BuLi (30 $\mu$L, 0.0724

mmol, 2.5 M in hexanes) followed by Ti(O*i*-Pr)$_4$ (32 $\mu$L, 0.109 mmol) and the resulting mixture was cooled to –78 ºC. To the cooled mixture was added *c*-$C_5H_9MgCl$ (110 μL, 0.218 mmol) and the reaction was allowed to warm to –30 ºC over 1 h and was stirred at –30 ºC for 1 h before recooling to –78 ºC and addition of 4-(but-3-ynyl)morpholine (102 $\mu$L, 0.0507 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 ºC while stirring for 2 h The reaction was quenched with sat. $NH_4Cl$, stirred for 2 h at ambient temperature, diluted with $Et_2O$ (10 mL), extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification was achieved by column chromatography on 10 mL $SiO_2$, eluting with 50% EtOAc/hexanes (20 mL), 80% EtOAc/hexanes (20 mL), and 10% MeOH/$CHCl_3$ (40 mL) to give the desired product as a clear, colorless oil (11.5 mg, 54%). $[\alpha]_{589}^{20}$ +7.4° (*c* 0.6, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.08 (d, *J* = 15.4 Hz, 1H), 5.51 (dt, *J* = 15.4, 6.6 Hz, 1H), 5.19 (d, *J* = 10.1 Hz, 1H), 4.58 (A of AB, *J* = 10.7 Hz, 1H), 4.53 (B of AB, *J* = 11.0 Hz, 1H), 3.86-3.74 (m, 4H), 3.80 (s, 3H), 3.59-3.50 (m, 2H), 3.39 (dd, *J* = 9.1, 2.5 Hz, 1H), 2.83-2.75 (m, 1H), 2.65-2.47 (m, 6H), 2.46-2.33 (m, 2H), 1.88-1.84 (m, 1H), 1.74 (s, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.2, 136.1, 134.0, 132.5, 130.9, 129.3, 125.1, 113.8, 83.9, 74.6, 66.9, 66.2, 58.9, 55.3, 53.6, 38.5, 36.4, 29.9, 18.1, 12.7, 10.7; IR (thin film, NaCl) 3417, 2959, 2931, 2871, 1613, 1514, 1457, 1248, 1118, 1034, 965, 822; HRMS (FT-ICR) calcd for $C_{25}H_{40}NO_4$ 418.2952 *m/z* (M+H); observed, 418.2948 *m/z* $(M+H)^+$.



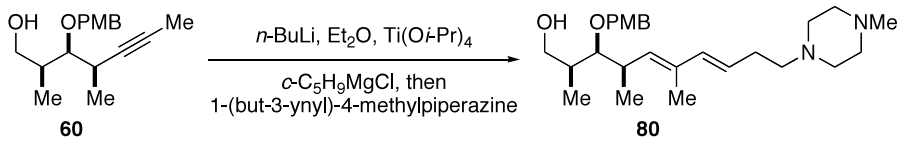

**(2*S*,3*S*,4*R*)-(5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-8-(thiophen-3'-yl)octa-5,7-dien-1-ol, 78.** To a solution of internal alkyne **60** (20 mg, 0.0724 mmol) in $Et_2O$ (725 $\mu$L, 0.1 M) at ambient temperature was added *n*-BuLi (30 $\mu$L, 0.0724 mmol, 2.5 M in hexanes) followed by Ti(O*i*-Pr)$_4$ (32 $\mu$L, 0.109 mmol) and the resulting mixture was cooled to –78 ºC. To the cooled mixture was added *c*-$C_5H_9MgCl$ (110 $\mu$L, 0.218 mmol) and the reaction was allowed to warm to –30 ºC over 1 h and was stirred at –30 ºC for 1 h before recooling to –78 ºC and addition of 3-ethynylthiophene (102 $\mu$L, 0.0507 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 ºC while stirring for 2 h The reaction was quenched with sat. $NH_4Cl$, stirred for 2 h at ambient temperature, diluted with $Et_2O$ (10 mL), extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification was achieved by column chromatography on 10 mL $SiO_2$, eluting with 10% EtOAc/hexanes (20 mL), 30% EtOAc/hexanes (20 mL), and 50% EtOAc/hexanes (30 mL) to give a 1.4:1 mixture of desired product to reduced internal alkyne (20.1 mg, 51% yield of desired product). Seperation of the desired product from reduced internal alkyne was achieved by normal-phase HPLC using a gradient from 20% EtOAc/hexanes to 50% EtOAc/hexanes over 25min. $[\alpha]_{589}^{20}$ +34.0° (*c* 0.6, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 2H), 7.28-7.26 (m, 1H), 7.23 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.13 (dd, *J* = 2.8, 1.3 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.49 (d, *J* = 16.1 Hz, 1H), 5.38 (d, *J* = 10.1 Hz, 1H), 4.58 ( A of AB, *J* = 10.7 Hz, 1H), 4.53 (B of AB, *J* = 10.7 Hz, 1H), 3.81 (s, 3H), 3.61-3.53 (m, 2H), 3.45 (dd, *J* = 8.8,

2.5 Hz, 1H) 2.91-2.83 (m, 1H), 1.93-1.89 (m, 1H), 1.86, d, $J$ = 1.3 Hz, 3H), 1.14 (d, $J$ = 6.6 Hz, 3H), 0.88 (d, $J$ = 6.9 Hz, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.1, 140.5, 136.3, 133.9, 132.8, 130.9, 129.4, 125.9, 124.8, 121.1, 120.6, 113.8, 83.9, 74.7, 66.2, 55.3, 38.6, 36.6, 18.0, 12.6, 10.8; IR (thin film, NaCl) 3474, 2962, 2927, 2875, 1612, 1514, 1458, 1248, 1032, 959, 826, 769, 629; HRMS (FT-ICR) calcd for $C_{23}H_{30}O_3S$ 409.1813 *m/z* (M+Na); observed, 409.1816 *m/z* $(M+Na)^+$.



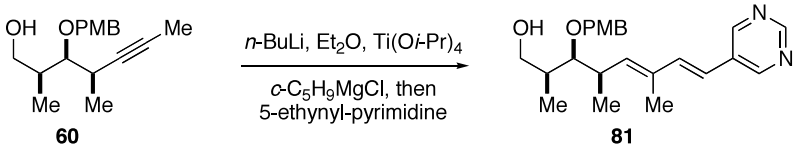

**(2*S*,3*S*,4*R*)-(5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-8-(pyridin-3'-yl)octa-5,7-dien-1-ol, 79.** To a solution of internal alkyne **60** (20 mg, 0.0724 mmol) in $Et_2O$ (725 μL, 0.1 M) at ambient temperature was added *n*-BuLi (30 μL, 0.0724 mmol, 2.5 M in hexanes) followed by Ti(O*i*-Pr)$_4$ (32 μL, 0.109 mmol) and the resulting mixture was cooled to –78 ºC. To the cooled mixture was added *c*-$C_5H_9MgCl$ (110 μL, 0.218 mmol) and the reaction was allowed to warm to –30 ºC over 1 h and was stirred at –30 ºC for 1 h before recooling to –78 ºC and addition of 3-ethynyl-pyridine (102 μL, 0.0507 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 ºC while stirring for 2 h The reaction was quenched with sat. $NH_4Cl$. stirred for 2 h at ambient temperature, diluted with $Et_2O$ (10 mL), extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification was achieved by column chromatography on 10 mL $SiO_2$, eluting with 50% EtOAc/hexanes (20 mL), 80% EtOAc/hexanes (20 mL), and 100% EtOAc, to give the desired product as a clear, colorless oil (10.0 mg, 52%). $[\alpha]_{589}^{20}$ +18.0° (*c* 0.6, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 8.63 (bs, 1H), 8.44 (bs, 1H), 7.74

(d, $J$ = 7.9 Hz, 1H), 7.29 (d, $J$ = 8.8 Hz, 2H), 7.28-7.26 (m, 1H), 6.89 (d, $J$ = 8.5 Hz, 2H), 6.81 (d, $J$ 16.1 Hz, 1H), 6.42 (d, $J$ = 16.1 Hz, 1H), 5.49 (d, $J$ = 10.1 Hz, 1H), 4.58 (A of AB, $J$ = 10.7 Hz, 1H), 4.54 (B of AB, $J$ = 10.7 Hz, 1H), 3.80 (s, 4H), 3.59-3.54 (m, 2H), 3.47 (dd, $J$ = 8.8, 2.5 Hz, 1H), 2.95-2.85 (m, 1H), 1.91-1.86 (m, 1H), 1.90 (s, 3H), 1.15 (d, $J$ = 6.6 Hz, 3H), 0.88 (d, $J$ = 6.9 Hz, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.3, 148.2, 147.8, 138.4, 136.1, 132.6, 132.4, 130.9, 129.4, 129.2, 123.6, 122.4, 113.8, 83.7, 74.7, 66.1, 55.3, 38.7, 36.7, 17.9, 12.6, 10.8; IR (thin film, NaCl) 3378, 2962, 2927, 2871, 1612, 1513, 1457, 1249, 1172, 1032, 962, 822, 707; HRMS (FT-ICR) calcd for $C_{24}H_{32}NO_3$ 382.2377 $m/z$ (M+H); observed, 382.2380 $m/z$ (M+H)$^+$.




**(2*S*,3*S*,4*R*,5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-10-(4'-methylpiperazin-1'-yl)deca-5,7-dien-1-ol, 80**. To a solution of internal alkyne **60** (20 mg, 0.0724 mmol) in $Et_2O$ (725 $\mu$L, 0.1 M) at ambient temperature was added *n*-BuLi (30 $\mu$L, 0.0724 mmol, 2.5 M in hexanes) followed by Ti(O*i*-Pr)$_4$ (32 $\mu$L, 0.109 mmol) and the resulting mixture was cooled to –78 ºC. To the cooled mixture was added *c*-$C_5H_9MgCl$ (110 µL, 0.218 mmol) and the reaction was allowed to warm to –30 ºC over 1 h and was stirred at –30 ºC for 1 h before recooling to –78 ºC and addition of 1-(but-3-ynyl)-4-methylpiperazine (102 $\mu$L, 0.0507 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0ºC while stirring for 2 h The reaction was quenched with sat. $NH_4Cl$, stirred for 2 h at ambient temperature, diluted with $Et_2O$ (10 mL), extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification was achieved by

column chromatography on 10 mL $SiO_2$, eluting with 80% EtOAc/hexanes (40 mL), and 10%MeOH/$CHCl_3$ (80 mL) to give the desired product as a clear, colorless oil (9.4 mg, 43%). $[\alpha]_{589}^{20}$ +9.5° (*c* 0.2, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.07 (d, *J* = 15.4 Hz, 1H), 5.49 (dt, *J* = 15.4, 6.9 Hz, 1H), 5.19 (d, *J* = 9.8 Hz, 1H), 4.58 (A of AB, *J* = 10.7 Hz, 1H), 4.53 (B of AB, *J* = 10.7 Hz, 1H), 3.80 (s, 3H), 3.58-3.51 (m, 2H), 3.39 (dd *J* = 8.8, 2.5 Hz, 1H), 2.93-2.75 (m, 7H), 2.64-2.57 (m, 3H), 2.54-2.41 (m, 1H), 2.49 (s, 3H), 2.41-2.34 (m, 2H), 1.86-1.83 (m, 1H), 1.74 (s, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.1, 136.0, 133.9, 132.5, 130.9, 129.4, 125.3, 113.8, 83.9, 74.6, 66.2, 58.5, 55.3, 55.0, 53.0, 45.9, 38.5, 36.4, 30.4, 18.0, 12.7, 10.7; IR (thin film, NaCl) 3379, 2960, 2931, 2874, 2594, 2457, 1612, 1514, 1457, 1248, 1032, 965, 822; HRMS (FT-ICR) calcd for $C_{26}H_{43}N_2O_3$ 431.3268 *m/z* (M+H); observed, 431.3269 *m/z* $(M+H)^+$.




**(2*S*,3*S*,4*R*)-(5*E*,7*E*)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-8-(pyrimidin-5'-yl)octa-5,7-dien-1-ol, 81.** To a solution of internal alkyne **60** (20 mg, 0.0724 mmol) in $Et_2O$ (725 μL, 0.1 M) at ambient temperature was added *n*-BuLi (30 μL, 0.0724 mmol, 2.5 M in hexanes) followed by Ti(O*i*-Pr)$_4$ (32 μL, 0.109 mmol) and the resulting mixture was cooled to –78 ºC. To the cooled mixture was added *c*-$C_5H_9MgCl$ (110 μL, 0.218 mmol) and the reaction was allowed to warm to –30 ºC over 1 h and was stirred at –30 ºC for 1 h before recooling to –78 ºC and addition of 5-ethynyl-pyrimidine (102 μL, 0.0507 mmol, 0.5 M in $Et_2O$). The mixture was allowed to warm to 0 ºC while stirring for 2 h.

The reaction was quenched with sat. $NH_4Cl$, stirred for 2 h at ambient temperature, diluted with $Et_2O$ (10 mL), extracted with $Et_2O$ (3 x 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification was achieved by column chromatography on 10 mL $SiO_2$, eluting with 50% EtOAc/hexanes (20 mL), 80% EtOAc/hexanes (20 mL), and 100% EtOAc, to give the desired product as a clear, colorless oil (10.1 mg, 52%) that solidifies upon standing to give a waxy glass. $[\alpha]_{589}^{20}$ +2.9° (*c* 0.6, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) δ 9.05 (bs, 1H), 8.77 (bs, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 16.1 Hz, 1H), 6.33 (d, *J* = 16.1 Hz, 1H), 5.55 (d, *J* = 10.1 Hz, 1H), 4.59 (A of AB, *J* = 11.0 Hz, 1H), 4.57 (B of AB, *J* = 11.0 Hz, 1H), 3.80 (s, 3H), 3.60-3.54 (m, 2H), 3.48 (dd, *J* = 8.8, 2.5 Hz, 1H), 2.94-2.86 (m, 1H), 1.91 (d, *J* = 1.3 Hz, 3H), 1.90-1.83 (m, 1H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 159.3, 156.6, 153.9, 139.9, 137.9, 132.4, 130.7, 129.4, 118.7, 113.8, 83.4, 74.7, 66.0, 55.3, 38.7, 36.8, 17.8, 12.4, 10.8; IR (thin film, NaCl) 3411, 2965, 2927, 2878, 1708, 1606, 1513, 1258, 1169, 1100, 1032, 804, 724; HRMS (FT-ICR) calcd for $C_{23}H_{30}N_2O_3Na$ 405.2154 *m/z* (M+Na); observed, 405.2156 *m/z* $(M+Na)^+$.