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Supporting Information

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An Alkyne Strategy for the Asymmetric Synthesis of Natural Products: Application to (+)-Spirolaxine Methyl Ether

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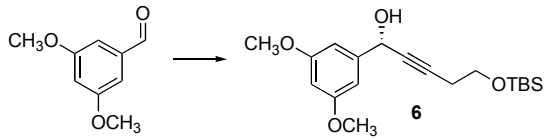
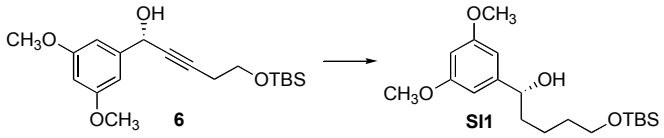
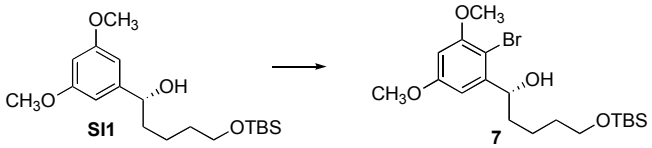


(S)-5-(tert-butyldimethylsilyloxy)-1-(3,5-dimethoxyphenyl)pent-2-yn-1-ol (6):
A flame-dried 100 mL round bottom flask equiped with a T-joint and magnetic stirbar was charged with commercially available (*R,R*)-ProPhenol ligand (416 mg, 0.65 mmol), toluene (40 mL), and finally 4-(*tert*-butyldimethylsilyloxy)-1-butyne (4.02 mL, 19.6 mmol). The clear, yellow solution was degassed (3x freeze/pump/thaw) and flushed with nitrogen. Dimethylzinc (2.0 M in toluene from aldrich, 9.80 mL, 19.6 mmol) was added via syringe rapidly, and the reaction mixture stirred for 90 minutes at ambient temperature and gas slowly evolved. A solution of 3,5-dimethoxybenzaldehyde (1.08 g, 6.5 mmol) in toluene (6 mL, deoxygenated via argon bubbling for 1 hour) was added via cannula over ~10 seconds. This reaction was sealed, and cooled to 4 °C for 48 hours. At this point the reaction mixture was slowly quenched with aqueous sodium bisulfite (1.0 M, 24 mL, *gas evolution*!!!), and the layers were seperated. The aqueous layer was extracted with ethyl acetate (3 x 80 mL), and the combined organic layers were washed with water (20 mL), and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated en vacuo. The crude oil was purified via silica gel chromatography (5:1 PE:EtOAc) yielding the pure product as a clear colorless oil (1.866 gm, 82%, 90% ee). **TLC**: (2:1, PE:EtOAc, R_f= 0.73). **^{1}H NMR** (300MHz): δ 6.69 (2H, d, *J* = 2 Hz), 6.40 (1H, t, *J* = 2 Hz), 5.37 (1H, brs), 3.79 (6H, s), 3.74 (2H, t, *J* = 7 Hz), 2.48 (2H, td, *J* = 7 , 2 Hz), 2.31 (1H, brd, *J* = 4 Hz), 0.88 (9H, s), -0.06 (6H, s). **^{13}C NMR** (75.4 MHz): δ 160.8, 143.4, 104.4, 100.2, 84.2, 80.9, 64.7, 61.7, 55.3, 25.8, 23.2, 18.3. **IR:** 3416, 3000, 2955, 2931, 2857, 1610, 1599, 1464, 1430, 1388, 1316, 1294, 1255, 1205, 1156, 1105, 1060, 1007. **HPLC:** OD column, 90:10 Heptane:Isopropanol, 0.8 mL/min, 220 nm: 9.395 min (major), 11.599 min (minor). **$[\alpha]_D$** = -9.75° (c = 2.55, $CHCl_3$). **HRMS:** calc for M+ $C_{19}H_{30}O_4Si$ = 350.1913, found 350.1907, error = 1.7 ppm.

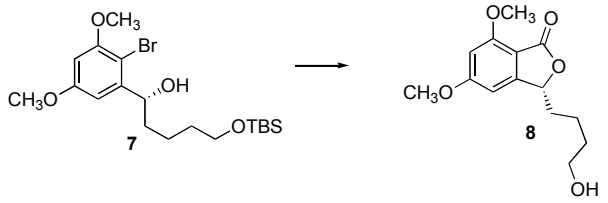


(R)-5-(tert-butyldimethylsilyloxy)-1-(3,5-dimethoxyphenyl)pentan-1-ol (SI1): To propargylic alcohol **6** (1.7794 g, 5.07 mmol) in a 250 mL round bottom flask in EtOAc (51 mL) was added PtO_2•H_2O (62 mg, 0.254 mmol, 5 mol%). The reaction mixture was purged with nitrogen twice then purged with H_2 three times, and turned black as it stirred under an atmosphere of hydrogen (double balloon, 1 atm). After 45 minutes the reaction mixture was filtered through celite, and concentrated en vacuo overnight to yield a clear-colorless oil **SI1** (1.792 g, 100 %). The material was pure and used without purification. **^{1}H NMR** ($CDCl_3$, 400MHz): δ 6.50 (2H, d, *J* = 2 Hz), 6.37 (1H, t, *J* = 2 Hz), 4.61 (1H, dd, *J* = 7, 6 Hz), 3.79 (3H, s), 3.60 (2H, t, *J* = 6 Hz), 1.25-1.85 (6H, m), 0.88 (9H, s), -0.03 (6H, s). **^{13}C NMR** ($CDCl_3$, 100.6MHz): δ 160.8, 147.5, 103.7, 99.3, 74.6, 63.0, 55.3, 38.7, 32.6, 25.9, 22.1, 18.3 -5.3. **IR:** 3416, 2935, 2858, 1609, 1598, 1462, 1430,

1389, 1360, 1313, 1295, 1256, 1205. **[α]$_D$** = 9.80° (c = 1.10, $CHCl_3$) **HRMS:** calc for M+ $C_{19}H_{34}O_4Si$ = 354.2226, found 354.2211, error = 4.2 ppm.

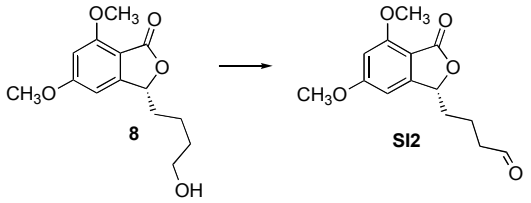


(R)-1-(2-bromo-3,5-dimethoxyphenyl)-5-(tert-butyldimethylsilyloxy)pentan-1-ol (7): To a 50 mL round bottom flask charged with aryl alcohol **SI1** (500 mg, 1.4 mmol), $CHCl_3$ (10 mL), a magnetic stirbar, and a reflux condenser was added NBS (263 mg, 1.48 mmol). The reaction was heated to 60 °C, and stirred for 90 min. A portion was removed and checked via NMR to reveal mostly starting material. The reaction mixture was heated to 75 °C and all starting material had disappeared after an additional 90 minutes. The reaction was cooled to ambient temperature, diluted with diethyl ether (150 mL), and washed with water (3x25 mL) then brine (3x25 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated *en vacuo* to reveal a clear oil purified via silica gel chromatography (5:1 Pet. Ether: EtOAc). The product, aryl bromide **7**, was isolated as a clear oil (580 mg, 95%). **^{1}H NMR** ($CHCl_3$, 400MHz): δ 6.76 (1H, d, *J* = 3 Hz), 6.41 (1H, d, *J* = 3 Hz), 5.13 (1H, dd, *J* = 8, 4 Hz), 3.87 (3H, s), 3.82 (3H, s), 3.63(2H, td, J = 6 ,1Hz), 1.42-1.84 (6H, m), 0.89 (9H, s), -0.04 (6H, s). **^{13}C NMR** ($CDCl_3$, 100.6MHz): δ 159.9, 146.1, 102.9, 98.7, 72.9, 63.1, 56.3, 55.5, 37.2, 32.4, 26.0, 22.1, 0.1, -5.3. **IR (neat):** 3415, 2935, 2857, 1589, 1458, 1431, 1388, 1360, 1323, 1284, 1256, 1201, 1161, 1099, 1078. **[α]$_D$** = 25.2° (c = 2.70, $CHCl_3$). **HRMS:** calc for M+ $C_{19}H_{33}BrO_4Si$: ^{79}Br = 432.1331, ^{81}Br = 434.1311 ; found ^{79}Br = 432.1320, ^{81}Br = 434.1325; errors = 2.6, 3.3 ppm.

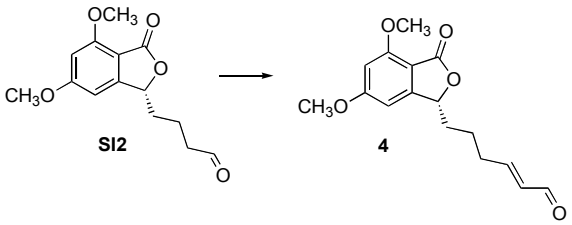


(R)-3-(4-hydroxybutyl)-5,7-dimethoxyisobenzofuran-1(3H)-one (8): To aryl bromide **7** (1.8345 g, 4.232 mmol) stirring vigorously in THF (42 mL), at -78 °C was added *n*-BuLi (2.5 M in hexanes, 3.67 mL, 9.311 mmol, 2.2 equiv) dropwise over 70 seconds. After 60 seconds 4 balloons of CO_2 were bubbled through the yellow solution and the cooling bath was removed. The solution stirred and bubbled as it warmed to ambient temperature over 30 minutes. After stirring for an additional 30 minutes at ambient temperature, 2M aqueous HCl was added (45 mL) and the clear solution stirred for 36 hours. The THF was removed *en vacuo* (stench due to pentanoic acid). The remaining aqueous layer was extracted with CH_2Cl_2 (4x80 mL). The combined organics were washed with brine (30 mL), dried with $MgSO_4$, and the crude solid was purified via silica gel chromatography (1:1-2:1 EtOAc: Pet. Ether) to give phthalide product **8**, 1.020 g (90%) as a white solid. **TLC**: (2:1, EtOAc:PE, R_f= 0.10). **mp** = 96-98 °C. **^{1}H NMR** (400MHz): δ 6.40 (2H, s), 5.30 (1H, dd, *J* = 8, 4 Hz), 3.93 (3H, s), 3.88 (3H, s), 3.63 (2H, t, *J* = 6 Hz), 2.03 (1H,

m), 1.41-1.76 (6H, m). **^{13}C NMR** ($CDCl_3$, 100.6MHz): δ 168.5, 166.7, 159.5, 154.9, 106.7, 98.6, 97.4, 79.8, 62.4, 55.93, 55.89, 34.4, 32.2, 21.0. **IR** (thin film): 2928, 1755 (phthalide), 1605 (phthalide), 1462, 1337, 1218, 1160, 1052 cm^{-1}. **$[\alpha]_D$** = 25.2° (c = 2.70, $CHCl_3$). **HRMS:** calc for M+ $C_{14}H_{18}O_5$ = 266.1154, found 266.1154, error = 0.0 ppm.

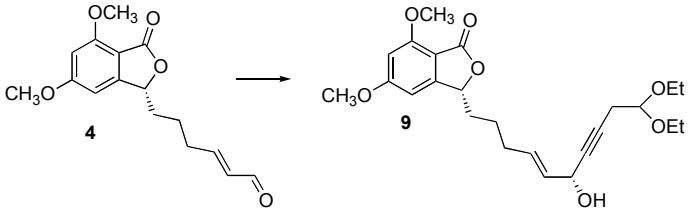


(R)-4-(4,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)butanal (SI2): To a solution alcohol **8** (1.010 g, 3.79 mmol) in DCM (5.5 mL) at ambient temperature were added TEMPO (59.3 mg, 0.380 mmol, 0.1 equiv) and bisacetoxyiodobenzene (1.344 g, 4.17 mmol, 1.1 equiv) neat in one portion. The reaction mixture stirred until the disappearance of starting material (30 hours) was noted. The yellow mixture was diluted with DCM (15 mL), and extracted with saturated aqueous $Na_2S_2O_5$ (2 x 10 mL). The combined aqueous layers were extracted with DCM (4x20 mL). The combined organics were washed with $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated to a crude solid which was purified via silica gel chromatography (2:1 EtOAc: Pet. Ether). Aldehyde **SI2,** 842 mg (84%), was obtained as an off-white solid. **TLC**: (1:1 PE:EtOAc, R_f= 0.20). **mp** = 70-72 °C **^{1}H NMR** ($CHCl_3$, 400MHz): δ 9.76 (1H, t, *J* = 1 Hz), 6.41 (2H, m), 5.31 (1H, dd, *J* = 8, 4 Hz), 3.95 (3H, s), 3.89 (3H, s), 2.54 (2H, t, *J* = 7 Hz), 2.09 (1H, m), 1.66-1.86 (3H, m). **^{13}C NMR** ($CHCl_3$, 100.6 MHz): δ 201.8, 168.2, 166.8, 159.6, 154.5, 106.5, 98.8, 97.3, 79.3, 55.87, 55.85, 43.2, 33.7, 17.2. **$[\alpha]_D$** = 46.4° (c = 0.90, $CHCl_3$). **IR** (thin film): 2926, 2848, 2726, 1749, 1722, 1613, 1495, 1462, 1433, 1337, 1218, 1159. **HRMS:** calc for M+ $C_{14}H_{16}O_5$ = 264.0998, found 266.0992, error = 2.1 ppm.



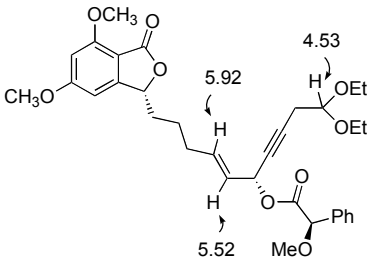
(E)-6-(4,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)hex-2-enal (4): To a solution aldehyde **SI2** (93.8 mg, 0.355 mmol) in benzene (7 mL) was added (Triphenylphosphoranylidene)-acetaldehyde (216 mg, 0.71 mmol, 2.0 equiv). This suspension was heated in a sealed tube under N_2 at 80 ºC. After 19 hours the reaction mixture was added directly to a silica gel column and eluted with 1:1 EtOAc:PE. The product isolated was contaminated with triphenylphosphine oxide and was reflashed under similar conditions to yield a clear oil (57.4 mg, 56%). **TLC**: (2:1, EtOAc:PE, R_f= 0.39). **^{1}H NMR** ($CDCl_3$, 400MHz): δ 9.48 (1H, d, *J* = 8 Hz), 6.79 (1H, dt, *J* = 16, 7 Hz), 6.40 (2H, d, *J* = 8 Hz), 6.09 (1H, ddt, *J* = 16, 8, 2 Hz), 5.31 (1H, m), 3.93 (3H, s), 3.87

(3H, s), 2.38 (2H, m), 2.0-2.2 (1H, m), 1.58-1.76 (3H, m). **^{13}C NMR** ($CHCl_3$, 100.6 MHz): δ 193.8, 168.2, 166.8, 159.5, 157.4, 154.4, 133.2, 106.5, 98.6, 97.3, 79.2, 55.92, 55.88, 33.9, 32.1, 22.8. **IR** (neat): 2943, 1751, 1686, 1611, 1490, 1462, 1438, 1339, 1216, 1159, 1049. **HRMS:** calc for M+ $C_{16}H_{18}O_5$ = 290.1154, found 290.1159, error = 1.8 ppm.

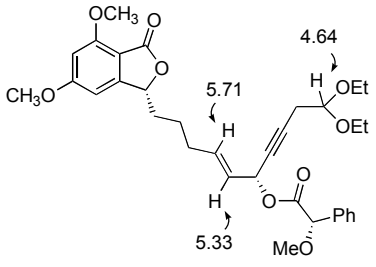


(R,E)-3-(10,10-diethoxy-6-hydroxydec-4-en-7-ynyl)-5,7-dimethoxyisobenzofuran-1(3H)-one (9): To a vial charged with toluene (1.2 mL) was added dimethylzinc (2.0 M in toluene, 289 uL, 0.579 mmol) and 4,4-diethoxybut-1-yne (82 μL, 0.579 mmol). The clear solution remained at ambient temperature under Ar for 90 minutes and was transferred via syringe to another vial containing enal **4** (56 mg, 0.193 mmol) and standard (*S,S*)-ProPhenol ligand (12.3 mg, 0.019 mmol). This solution was sealed and stirred at 4 ºC for 23 hours. The reaction was worked up with $NaHSO_4$ (1.0 M, 0.56 mL) (aqueous layer pH=7). Water (1 mL) and diethyl ether (5 mL) were added and stirred vigoursly for 5 minutes. The layers were separated and the water layer was extracted with EtOAc (4x10 mL), and the combined organics were washed with brine, concentrated to a yellow oil which slowly solidified to an offwhite solid. The crude material was purified via silica gel chromatography (2:1 EtOAc:PE), and was repurified with nuetral alumina column chromatography (500 mL EtOAc then EtOAc:MeOH 97:3) to yield the product as a clear oil (47 mg, 56%). The mass balance remained as starting material and hydrolyzed product. **TLC**: (2:1, EtOAc:PE, R_f= 0.52). **^{1}H NMR** ($CDCl_3$, 400MHz): δ 6.40 (2H, m), 5.81 (1H, dt, *J* = 15, 8Hz), 5.57 (1H, ddt, J = 15, 8 2 Hz), 5.29 (1H, dd, *J* = 8, 4 Hz), 4.80 (1H, d, J= 6 Hz), 4.64 (1H, t, J= 6 Hz), 3.94 (3H, s), 3.88 (3H, s), 3.62-3.71 (2H, m), 3.49-3.59 (2H, m), 2.56 (2H, dd, *J* = 6, 2 Hz), 1.41-2.22 (6H, m), 1.20 (6H, t, *J* = 7 Hz). **^{13}C NMR** ($CDCl_3$, 100.6MHz): δ168.4, 166.7, 159.6, 154.9, 132.4, 132.4, 130.0, 106.8, 100.7, 98.6, 97.4, 81.9, 81.0, 79.6, 79.6, 62.9, 61.8, 56.0 (d), 34.1, 31.4, 25.0, 23.7, 15.2.). **IR** (thin film): 3452 (br, s, OH), 2975, 2927, 1750, 1613, 1495, 1462, 1434, 1339, 1219, 1159, 1117, 1059, 1030. **$[\alpha]_D$** = 20.3° (c = 1.97, $CHCl_3$).

methyl mandelate chemical shifts for determination of dr and absolute configuration:



(R)-methyl mandelate



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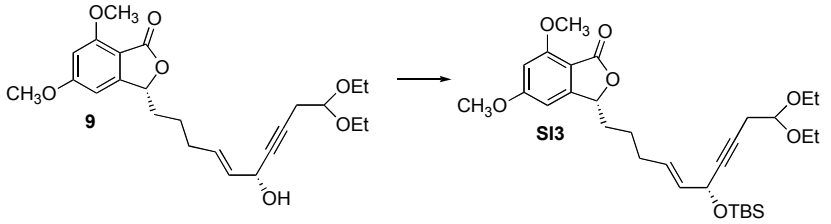
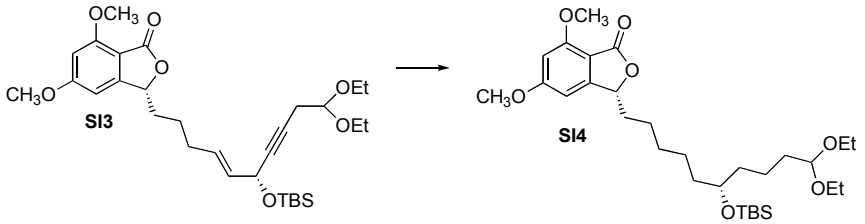
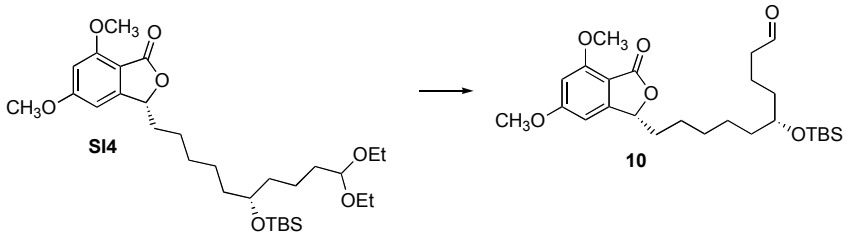


(R)-3-((R,E)-6-(tert-butyldimethylsilyloxy)-10,10-diethoxydec-4-en-7-ynyl)-5,7-dimethoxyisobenzofuran-1(3H)-one* (SI3*): To alcohol **9** (64 mg, 0.148 mmol) in DCM (0.3 mL) was added imidazole (57 mg, 0.83 mmol) and the mixture was cooled to -78 ºC, the septum was removed, and TBSCl (63 mg, 0.416 mmol) was added in one portion. The cooling bath was removed and reaction mixture warmed to ambient temperature over an hour. After disappearance of alcohol (13 hours), the DCM was removed en vacuo and the crude material was purified via silica gel chromatography (2:1 EtOAc, PE). TBS ether **SI3** (57.5 mg, 71%) was obtained as a clear oil. **IR** (thin film): 2930, 2857, 1760, 1613, 1495, 1463, 1433, 1338, 1251, 1218, 1159.). **^{1}H NMR** ($CDCl_3$, 400MHz): δ 6.40 (d, J = 1.5 Hz, 1H), 6.38 (dd, J = 1.5, 0.8 Hz, 1H), 5.72 (dtd, J = 15, 8, 1Hz, 1H), 5.50 (ddt, J = 15, 5, 1 Hz, 1H), 5.28 (dd, J = 8, 3 Hz, 1H), 4.81-4.85 (m, 1H), 4.61 (t, J = 6 Hz, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.60-3.69 (m, 2H), 3.48-3.57 (m, 2H), 2.53 (dd, J = 5, 2 Hz, 2H), 1.94-2.13 (m, 3H), 1.46-1.75 (m, 3H), 1.19 (t, J = 7Hz, 6H), 0.88 (s, 9H), 0.10 (s, 6H). **^{13}C NMR** ($CDCl_3$, 100.6MHz): δ 168.4, 166.6, 159.5, 154.9, 130.8, 130.3, 106.8, 100.8, 98.6, 97.3, 81.6, 80.9, 79.6, 63.4, 61.8, 61.6, 55.92, 55.85, 34.1, 31.4, 25.8, 25.1, 23.9, 18.3, 15.2, -4.6, -4.8. **$[\alpha]_D$** = 23.9° (c = 3.02, $CHCl_3$).

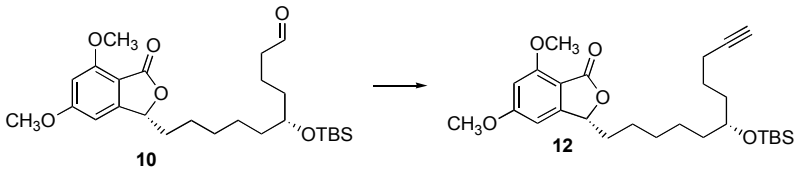


***(R)-3-((R)-6-(tert-butyldimethylsilyloxy)-10,10-diethoxydecyl)-5,7-dimethoxyisobenzofuran-1(3H)-one* (SI4):** A suspension of PtO_2•H_2O (2 mg, 0.08 mmol, 0.08 equiv) and TBS-protected alkynylation adduct **SI3** (56 mg, 0.10 mmol) in EtOAc (2 mL) was vigorously magnetically stirred in an over-sized flask (50 mL) at ambient temperature under an atmosphere of hydrogen (balloon) for 2.5 hours. The suspension was filtered through a pipet of celite to remove the catalyst to yield spectroscopically pure alkane **SI4** (51.8 mg, 91%) as a clear oil. This material was carried on without further purification. **IR** (thin film): 2929, 2857, 1753, 1605, 1494, 1459, 1438, 1359, 1340, 1255, 1217, 1159. **^{1}H NMR** ($CDCl_3$, 400MHz): δ 6.39 (s, 1H), 6.38 (s, 1H), 5.27 (dd, J = 8, 3.8 Hz, 1H), 4.45 (t, J = 5.6 Hz, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.56-3.66 (m, 3H), 3.42-3.51 (m, 3H), 1.91-2.02 (m, 1H), 1.61-1.73 (m, 1H), 1.45-1.61 (m, 2H), 1.21-1.49 (m, 12H), 1.18 (t, J = 7.2 Hz, 6H), 0.85 (s, 9H), 0.01 (d, J = 2Hz, 6H). **^{13}C NMR** ($CDCl_3$, 100.6MHz): δ 168.5, 166.6, 159.5, 155.1, 106.8, 102.9, 98.6, 97.3, 79.8, 72.0, 60.90, 60.87, 55.9, 55.8, 36.9, 36.8, 34.7, 33.8, 29.6, 29.5, 25.8, 25.0,

24.6, 20.6, 18.0, 15.3, -4.46, -4.49. $[\alpha]_D$ = 30.3° (c = 1.10, $CHCl_3$). **HRMS:** calc for (M^+- OEt) $C_{28}H_{47}O_6Si$= 507.3142, found 507.3150, error = 0.8 ppm.

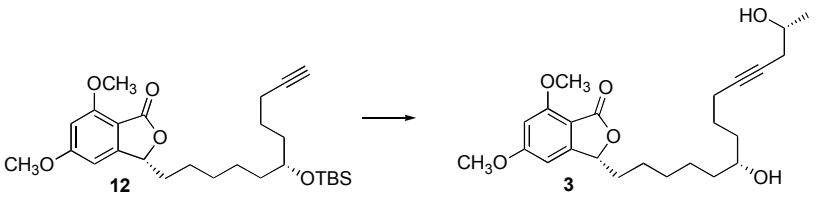


***(R)-5-(tert-butyldimethylsilyloxy)-10-((R)-4,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)decanal* (10):** A 50 mL round-bottomed flask equipped with a reflux condenser was charged with diethyl acetal **SI4** (51.8 mg, 0.094 mmol) dissolved in a mixture of acetone (10 mL) and water (0.25 mL). PPTS (7.0 mg, 0.3 equiv), was added and the reaction mixture was stirred at reflux (oil bath temperature = 60 °C) for 4 hours. The reaction mixture was concentrated to dryness en vacuo, to which water (2 mL) and DCM (10 mL) were added. After separation, the aqueous layer was extracted with DCM (2x 10 mL). The combined organics were dried Na_2SO_4, filtered and concentrated to yield aldehyde **10** as a clear oil (44 mg, 98%). This material was spectroscopically pure and was successfully used without further purification. (Purification via silica gel chromatography resulted in identical material, 91% yield) **IR** (thin film): 2931, 2856, 2715, 1758, 1725, 1612, 1493, 1460, 1436, 1337, 1218, 1159, 1104, 1052. **^{1}H NMR** ($CDCl_3$, 400MHz): δ 9.75 (t, J = 2 Hz, 1H), 6.41 (d, J = 2 Hz, 1H), 6.40 (d, J = 2 Hz, 1H), 5.29 (dd, J = 8, 4 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.63 (quint, J = 6 Hz, 1H), 2.42 (td, J = 8, 2 Hz, 2H), 1.93-2.03 (m, 1H), 1.55-1.74 (m, 2H), 1.18-1.51 (m, 11 H), 0.87 (s, 9H), 0.02 (s, 6H). **^{13}C NMR** ($CDCl_3$, 100.6MHz): δ 202.7, 168.5, 166.7, 159.6, 155.1, 106.9, 98.6, 97.3, 79.9, 71.7, 56.0, 55.9, 44.0, 36.8, 36.2, 34.7, 29.5, 25.9, 25.0, 24.6, 18.1, 17.8, -4.4, -4.5. $[\alpha]_D$ = 32.1° (c = 1.45, $CHCl_3$). **HRMS:** calc for (M^+- H) $C_{26}H_{41}O_6Si$= 477.2672, found 477.2669, error = 0.4 ppm.).

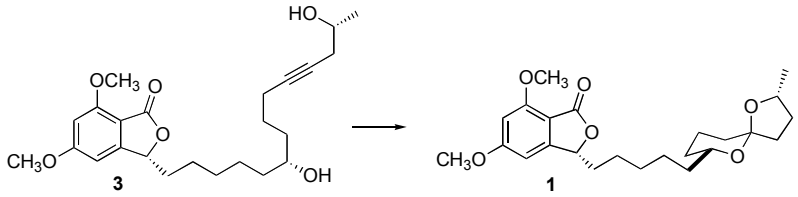


***(R)-3-((R)-6-(tert-butyldimethylsilyloxy)undec-10-ynyl)-5,7-dimethoxyisobenzofuran-1(3H)-one* (12):** A suspension of aldehyde **10** (44 mg, 0.093 mmol) and K_2CO_3 (52 mg, 0.37 mmol, 4 equiv) in dry methanol (1.5 mL) was magnetically stirred at ambient temperature under an atmosphere of nitrogen. A solution of Ohira-Bestmann reagent (36 mg, 0.187 mmol, 2.0 equiv) in dry methanol (1 mL) was added to the reaction suspension via cannula in one portion rapidly at room temperature. The yellow suspension stirred for 18 hours at which point water (2 mL), and saturated aqueous $NaHCO_3$ (2 mL) were added. MeOH was removed en vacuo and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organics were dried Na_2SO_4, filtered and concentrated to a crude, yellow oil. The oil was purified via silica gel chromatography (2:1 Pet. Ether: EtOAc) to yield pure alkyne **12** (32.9 mg, 75%) as a clear oil. **IR** (thin film): 2930, 2856, 1758, 1606, 1492, 1459, 1431, 1359, 1337, 1255, 1218, 1159. **^{1}H NMR** ($CDCl_3$,

400MHz): δ 6.41 (d, J = 2 Hz, 1H), 6.39 (d, J = 2 Hz, 1H), 5.29 (dd, J = 8, 4 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.61-3.67 (m, 1H), 2.14-2.21 (m, 2H), 1.95-2.03 (m, 1H), 1.94 (t, J = 2.6 Hz, 1H), 1.18-1.76 (m, 13H), 0.87 (s, 9H), 0.03 (d, J = 3 Hz, 6H). **^{13}C NMR** ($CHCl_3$, 100.6 MHz): δ 168.5, 166.6, 159.5, 155.1, 106.9, 98.6, 97.3, 84.5, 79.9, 71.7, 68.3, 55.95, 55.86, 36.9, 35.9, 34.8, 29.5, 25.9, 25.0, 24.6, 24.2, 18.5, 18.1, -4.46, -4.49. **$[\alpha]_D$** = 24.5° (c = 1.24, $CHCl_3$). **HRMS:** calc for (M^+- H) $C_{27}H_{41}O_5Si$= 473.2723, found 473.2721, error = 0.2 ppm.



***(R)-3-((6R,13R)-6,13-dihydroxytetradec-10-ynyl)-5,7-dimethoxyisobenzofuran-1(3H)-one* (3):** To a clear solution of alkyne **12** (30.3 mg, 64 μmol) in THF (0.64 mL) stirring at -78 °C under a nitrogen atmosphere was added *n*-BuLi (2.5 M in hexanes, 30.6 μL, 77 μmol, 1.2 equiv). The solution immediately turned yellow, and after 20 minutes, freshly-distilled neat BF_3•Et_2O (10 μL, 77 μmol, 1.2 equiv) was added. After 6 minutes, neat (*R*)-(+)-propylene oxide (13.5 μL, 191 μmol, 3.0 equiv) was added. The yellow solution stirred at -78 °C for 3 hours. The cooling bath was removed and the reaction mixture warmed to ambient temperature. After 5 hours, the solution was quenched with 2.0 N aqueous HCl (0.8 mL). After stirring for 12 hours, the THF was removed en vacuo and the aqueous phase was extracted with EtOAc (3x4 mL). The combined organics were dried with $MgSO_4$, filtered and concentrated. The crude yellow oil was purified via silica gel chromatography (2:1 EtOAc:Pet. Ether). Diol **3** (13.5 mg, 51% yield) was isolated as a clear oil. **$[\alpha]_D$** = 16.8° (c = 0.42, $CHCl_3$). **IR** (thin film): 3391 (br, OH), 2924, 2852, 1740, 1605, 1463, 1432, 1337, 1219, 1159, 1101. **^{1}H NMR** ($CDCl_3$, 500MHz): δ 6.41 (m, 1H), 6.40 (M, 1H), 5.30 (dd, J = Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3 H), 3.87-3.91 (m, obscured, 1H), 3.57-3.68 (m, 1H), 2.27 (ddt, J = 20.5, 6, 3Hz, 1H), 2.27 (ddt, 20.5, 8.5, 3 Hz, 1H), 2.17-2.25 (m, 2H), 1.95-2.05 (m, 2H), 1.25-1.74 (m, 12 H), 1.23 (d, J = 8 Hz, 3H). **^{13}C NMR** (125.7 MHz, $CDCl_3$): δ 168.6, 166.7, 159.6, 155.1, 130.3, 106.9, 98.6, 97.3, 87.3, 82.8, 79.9, 71.3, 66.5, 56.0, 55.9, 37.3, 36.5, 34.7, 29.4, 29.3, 25.4, 25.0, 24.6, 22.2, 18.7.



***(+)-Spirolaxine Methyl Ether* (1):** A mixture of CD_3CN (0.9 mL) and THF-D6 (0.6 mL) was deoxygenated via argon bubbling for 15 minutes and added to $[PdCl_2(PhCN)_2]$(3 mg). 100 μL of this stock solution was added to diol **3** (4.2 mg, mmol) in an NMR tube and heated to 60 °C. At complete conversion (36 hours) the reaction mixture was concentrated en vacuo. Purification by silica column chromatography (1:1 EtOAC:Pet. Ether) yielded (+)-spirolaxine methyl ether as a thin film (3.3 mg, 79%). **$[\alpha]_D$** = 52.3°

(c = 0.33, $CHCl_3$). (lit. $[\alpha]_D$ = 62° (c = 0.22, $CHCl_3$). **IR** (thin film): 2934, 2859, 2342, 1756, 1611, 1495, 1458, 1436, 1337, 1218, 1159, 1052. **HRMS:** calc for (M^+) $C_{24}H_{34}O_6$= 418.2355, found 418.2369, error = 3.3 ppm. **Chiral HPLC**: chiral diacel OB-H column, 220 nm, 0.6 mL/min, 80:20 heptane:i-PrOH, t_R = 20.705 min (one peak observed, no phthalide epimerization). lit[1]: chiral diacel OB, hexane:i-PrOH (80:20), 0.6 mL/min, t_R = 13.36 min, t_R = 14.83 min (phthalide epimer).

^{13}C NMR (125.7 MHz, $CDCl_3$)	Published data[2]	difference
168.6	168.5	0.1
166.6	166.6	0.0
159.6	159.6	0.0
155.2	155.2	0.0
107.0	107.0	0.0
106.0	106.0	0.0
98.6	98.6	0.0
97.3	97.3	0.0
79.9	79.9	0.0
73.6	73.9	0.3
69.9	69.9	0.0
56.0	56.0	0.0
55.9	55.9	0.0
38.0	38.0	0.0
36.1	36.1	0.0
34.8	34.8	0.0
33.5	33.5	0.0
31.3	31.3	0.0
30.9	30.9	0.0
29.4	29.3	0.1
25.4	25.4	0.0
24.6	24.5	0.1
21.3	21.3	0.0
20.4	20.4	0.0

1. R. Nannei, S. Dallavalle, L. Merlini, A. Bava, G. Nasini, *J. Org. Chem.* **2006**, *71*, 6277.
2. J. E. Robinson, M. A. Brimble, *Chem. Commun.* **2005**, 1560

An Alkyne Strategy for the Asymmetric Synthesis of Natural Products: Application to (+)-Spirolaxine Methyl Ether

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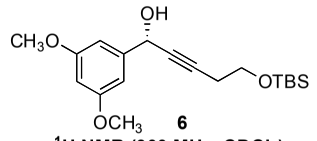
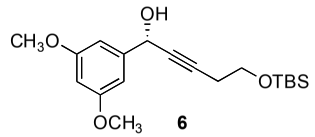
Department of Chemistry, Stanford University, Stanford, California 94305-8080
bmtrost@stanford.edu

Supporting Information 2: NMR Spectra



6

^{1}H NMR (300 MHz, $CDCl_3$)



6

^{13}C NMR (75.4 MHz, $CDCl_3$)

Stanford University Chemistry Department
Trost Lab HPLC Report

Data File: **compound 6**

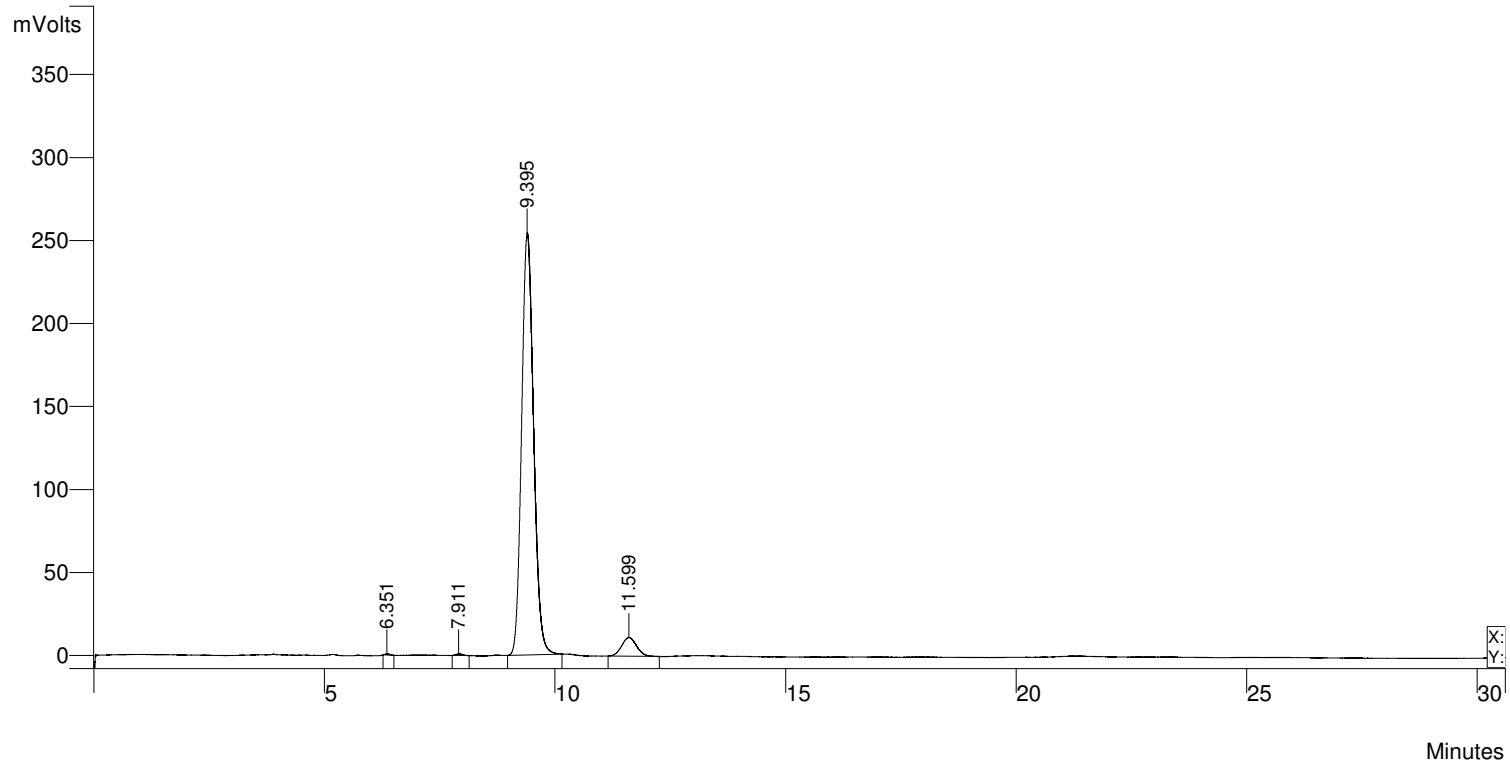
Injection Date: 12/11/2006 11:02:04

Injection Method: c:\star\data\david\chiral right method

Run Time (min): 30.618

Instrument (Inj): Chiral LC Right

Sample Prep Info
Manual injection



Peak No	Ret. Time (min)	Width 1/2 (sec)	Peak Area	Percent Area
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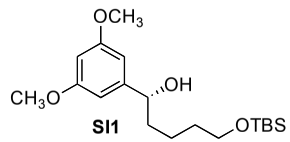
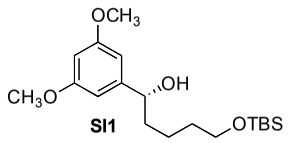
2	7.911	8.8	8961	0.18
3	9.395	16.7	4581864	94.50
4	11.599	20.8	252636	5.21
			4848756	**100.00**

Method Notes
OD column, 90:10 Hept. iPrOH, 0.8 mL/min, 220 nm.



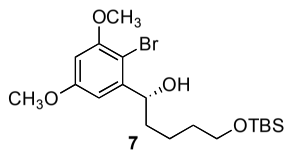
SI1

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



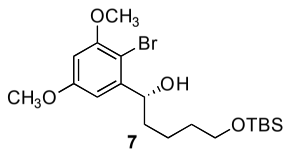
SI1

^{13}C NMR (100.6 MHz, $CDCl_3$)



7

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



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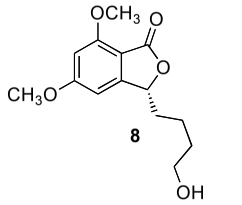
^{13}C NMR (100.6 MHz, $CDCl_3$)



8

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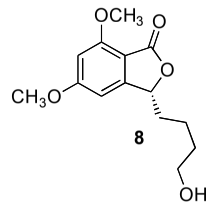

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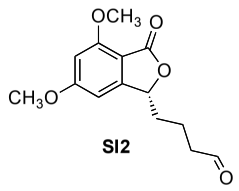
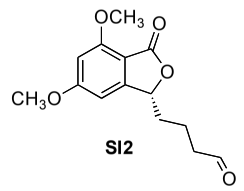
^{13}C NMR (100.6 MHz, $CDCl_3$)



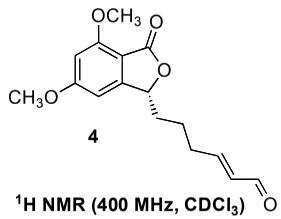
SI2

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



SI2

^{13}C NMR (100.6 MHz, $CDCl_3$)



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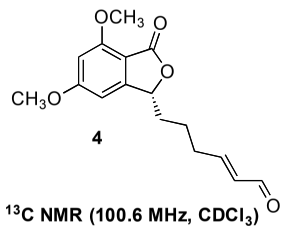

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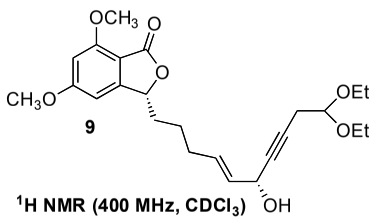
^{13}C NMR (100.6 MHz, $CDCl_3$)



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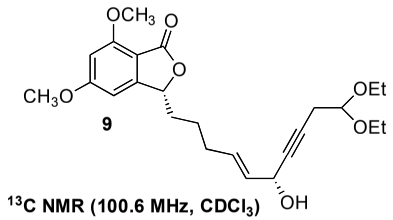
^{1}H NMR (400 MHz, $CDCl_3$)



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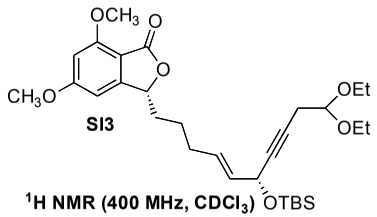
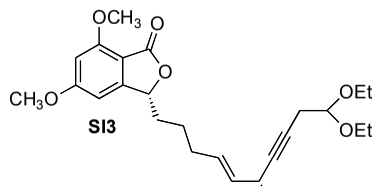
^{13}C NMR (100.6 MHz, $CDCl_3$)



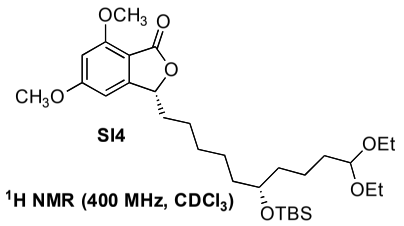
SI3

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



SI3

^{13}C NMR (100.6 MHz, $CDCl_3$)



SI4

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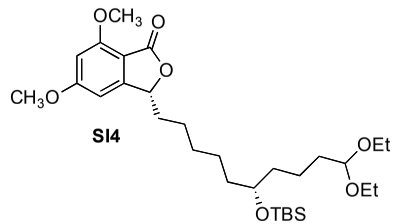

SI4

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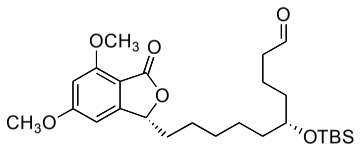

10

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

INDEX	FREQUENCY	PPM	HEIGHT
1	20395.599	202.723	21.8
2	16954.742	168.523	11.8
3	16766.296	166.650	20.0
4	16053.711	159.567	20.8
5	15606.628	155.123	26.7
6	10753.570	106.886	12.7
7	9918.915	98.590	32.3
8	9791.504	97.323	33.2
9	8033.691	79.851	34.7
10	7778.869	77.318	158.2
11	7746.826	77.000	162.0
12	7714.782	76.682	157.3
13	7215.820	71.722	29.2
14	5631.195	55.972	35.9
15	5622.040	55.881	32.0
16	4425.750	43.990	45.4
17	3702.484	36.801	38.2
18	3646.789	36.247	34.8
19	3494.201	34.731	32.6
20	2968.536	29.506	26.2
21	2602.325	25.866	131.4
22	2513.061	24.979	36.0
23	2476.440	24.615	32.4
24	1818.023	18.070	26.5
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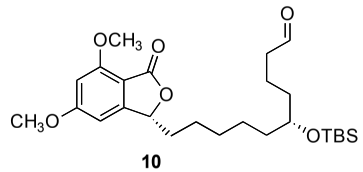
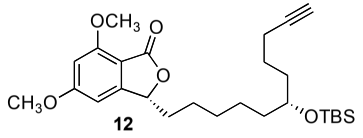
26	-444.855	-4.422	27.1
27	-452.484	-4.497	26.9



10

^{13}C NMR (100.6 MHz, $CDCl_3$)



12

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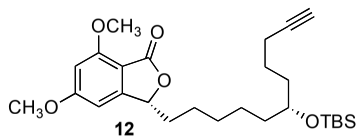
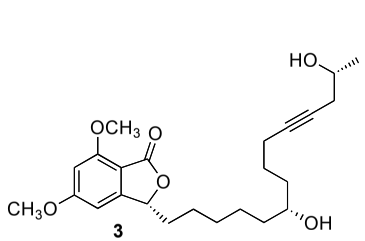


12

^{13}C NMR (100.6 MHz, $CDCl_3$)



3

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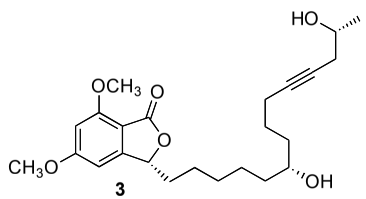

3

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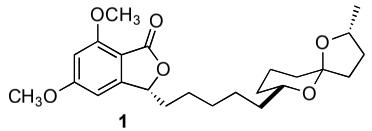
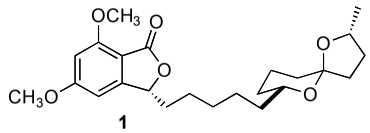


1

^{1}H NMR (500 MHz, $CDCl_3$)



1

^{13}C NMR (125.7 MHz, $CDCl_3$)