Asymmetric Synthesis of the Chlorocyclopropane-Containing Callipeltoside A Side Chain

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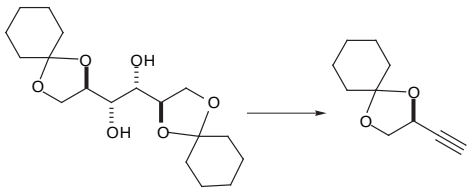
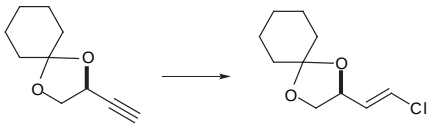
Supporting Information

General Information. All reactions were carried out under an atmosphere of argon or nitrogen in flame-dried glassware with magnetic stirring. THF, CH_2Cl_2 and toluene were purified by passage through a bed of activated alumina.[1] MeOH was distilled from $Mg(OMe)_2$. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and anisaldehyde or ceric ammonium nitrate stain followed by heating. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_\lambda^{T\ °C}$ (c = g/100 mL, solvent). Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Varian Inova-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration). Ambiguous assignments were resolved on the basis of two dimensional gCOSY experiments. Proton-decoupled ^{13}C-NMR spectra were recorded on a Varian Mercury 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). High resolution mass spectra were obtained on Jeol AX-505 or SX-102 spectrometers in the Harvard University Mass Spectrometry Laboratory. Gas chromatography was performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a split-mode capillary injection system and flame ionization detector using a DB 1701 capillary column (30 m x 0.25 mm). Gas chromatography with mass spectral detection was carried out on a Hewlett-Packard 5890 Series II Gas chromatograph equipped with a Hewlett-Packard 5971 Mass Selective Detector using a DB-1701 capillary column (30 m x 0.25 mm) employing chemical ionization with methane/helium gases.

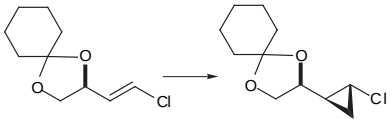


(2*S*)-2-ethynyl-1,4-dioxaspiro[4.5]decane (11). A solution of 590 mg of **9** (1.72 mmol) in 1 mL THF was added dropwise via syringe to a mixture of 590 mg of KIO_4 (1.90 mmol) and 17 mg of $KHCO_3$ (0.17 mmol) in 3 mL H_2O. The resulting slurry was stirred vigorously for 3 h at 25 °C. The mixture was then filtered, and the filter cake was rinsed with 8 mL EtOAc and 3 mL H_2O. The aqueous layer was saturated with NaCl, and the biphasic mixture refiltered. The layers were separated, and the aqueous layer was extracted with 10 mL EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The unpurified aldehyde **10** was then diluted with 35 mL MeOH, and 1.0 g K_2CO_3 (7.24 mmol) was added. A solution of 793 mg of **12**[2] (4.13 mmol) in 4 mL MeOH was prepared, and this solution was added to the reaction mixture via cannula (1 mL MeOH rinse). The mixture became homogeneous upon stirring vigorously at 25 °C overnight. The alkyne was extracted from the MeOH with 3×40 mL hexanes, followed by washing the combined hexanes extracts with 80 mL H_2O. These extracts were then dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound as a clear, colorless

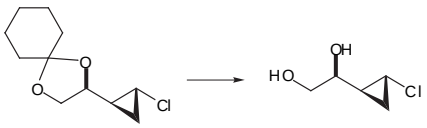
oil in 83% yield (475 mg, 2.85 mmol). Analytical data for **11**: $[\alpha]_D^{25}$ = +35.5 (*c* 0.40, CH_2Cl_2); IR (neat) 3290, 2937, 2120, 1450, 1162, 1103, 1042 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.74 (td, *J* = 6.3, 2.0 Hz, 1H), 4.19 (dd, *J* = 7.8, 6.3 Hz, 1H), 3.97 (dd, *J* = 7.8, 6.3 Hz, 1H), 2.51 (d, *J* = 2.0 Hz, 1H), 1.72-1.37 (m, 10H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 111.1, 81.5, 73.7, 69.4, 64.8, 35.6, 35.3, 24.9, 23.8.



2-((1*E*)-2-chlorovinyl(2*S*)-1,4-dioxaspiro[4.5]decane ((+)-8). A solution of 1.74 mL of 2-methyl-2-butene (16.4 mmol) in 7.0 mL THF was chilled to –15 °C, followed by addition of 8.19 mL of BH_3•THF (1.0 M, 8.19 mmol). The resulting colorless solution was stirred for 30 min at –15 °C and then 1.5 hours at 0 °C, followed by recooling to –15 °C. A solution of 1.36 g of **11** (8.18 mmol) in 5.0 mL THF was then added via cannula (2.0 mL THF rinse), and the mixture was stirred at –15 °C for 30 min and 0 °C for 3 h. Hexamethylphosphoramide (8.0 mL), 2.64 g $CuCl_2$ (19.6 mmol), 176 μL H_2O (9.77 mmol) and 7.0 mL THF were then added sequentially. The resulting orange-brown solution was then stirred for 1 h at 0 °C, 8 h at 25 °C, and 4 h at 70 °C. 4.08 g of $NaBO_3$•$4H_2O$ (26.5 mmol), 7.0 mL H_2O and 7.0 mL THF were then added, and the resulting heterogenous mixture was stirred for 5 h at 25 °C. The mixture was diluted with 100 mL Et_2O and washed with 50 mL sat. NH_4Cl (aq) and 70 mL brine. The aqueous layers were extracted with an additional 20 mL Et_2O, and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (linear gradient, 1 to 4% Et_2O in hexanes) yielded the title compound as a clear, colorless oil in 70% yield (1.16 g, 5.7 mmol). Analytical data for (+)-**8**: $[\alpha]_D^{25}$ = +23.5 (*c* 0.32, CH_2Cl_2); IR (neat) 2937, 2863, 1621, 1448, 1162, 1102, 933; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.33 (dd, *J* = 13.2, 1.0 Hz, 1H), 5.96 (dd, *J* = 13.2, 7.3 Hz, 1H), 4.56 (dddd, *J* = 7.3, 7.3, 6.3, 1.0 Hz, 1 H), 4.13 (dd, *J* = 7.3, 6.3 Hz, 1H), 3.66 (dd, *J* = 8.3, 6.3 Hz, 1H), 1.75-1.30 (m, 10 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 131.8, 122.1, 110.6, 74.6, 68.9, 36.4, 35.5, 25.3, 24.1, 24.1.

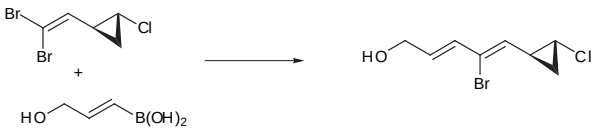


(2*S*)-2-((1*S*,2*R*)-2-chlorocyclopropyl)-1,4-dioxaspiro[4.5]decane (13). A solution of 5.31 mL of Et_2Zn (51.8 mmol) in 300 mL CH_2Cl_2 was prepared in a 3-necked flask fitted with an Ar inlet, and chilled to 0 °C. A solution of 3.99 mL CF_3COOH (51.8 mmol) in 20 mL CH_2Cl_2 was added dropwise over 20 min via syringe, followed by stirring for 20 min at 0 °C. To the resulting slurry, a solution of 4.17 mL CH_2I_2 (51.8 mmol) in 10 mL CH_2Cl_2 was added via cannula. The resulting mixture became homogeneous upon stirring for 20 min at 0°C. A solution of 2.00 g of (+)-**8** (9.87 mmol) in 10 mL CH_2Cl_2 was then added via cannula, followed by removal of the ice bath and stirring for 4 h at 25 °C. The reaction was quenched by the addition of 100 mL sat. NH_4Cl (aq) and stirring for 30 min. The biphasic mixture was poured into an additional 200 mL sat. NH_4Cl (aq), and the organic layer removed. The aqueous layer was extracted with an additional 2×200 mL CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. Flash column chromatography (linear gradient, 1 to 6% Et_2O in hexanes) afforded the title compound as a clear, colorless oil in 82% yield (1.75 g, 8.07 mmol). Analytical data for **13**: $[\alpha]_D^{25}$ = -42.8 (*c* 0.64, CH_2Cl_2); IR (neat) 2936, 2863, 1716, 1449, 1366, 1164, 1102, 1041, 927 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.13(dd, *J* = 8.3, 6.3 Hz, 1H), 3.96 (ddd, *J* = 6.8, 6.3, 5.9 Hz, 1H), 3.70 (dd, *J* = 8.3, 6.8 Hz, 1H), 3.00 (ddd, *J* = 7.3, 3.9, 3.4 Hz, 1H), 1.64-1.34 (m, 11H), 1.11 (ddd, *J* = 7.3, 6.3, 6.3 Hz, 1H) 1.04 (ddd, *J* = 9.8, 6.3, 3.9 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 109.6, 74.7, 68.6, 36.1, 35.0, 29.7, 25.0, 24.5, 23.9, 23.7, 12.6; GC (DB-1701, 125-135 °C, 0.5 °C/min, 10 psi); t_r = 15.5.



(1*S*)-1-((1*S*,2*R*)-2-chlorocyclopropyl)ethane-1,2-diol (14). To a solution of 430 mg of **13** (1.98 mmol) in 70 mL MeOH was added 4.0 g Dowex 50WX8-100 resin, and the resulting slurry was stirred vigorously for 3 h at 25 °C. The resin was removed by filtration, and rinsed with 3×10 mL MeOH. Cyclohexanone dimethyl ketal was then removed by washing the MeOH solution with 3×100 mL hexanes. Concentration of the MeOH layer *in vacuo*, followed by purification by flash column (linear gradient, 60 to 100% EtOAc in hexanes) afforded the title compound as a clear, colorless oil in 84% yield (228 mg, 1.67 mmol). Analytical data for **14**: $[\alpha]_D^{25}$ = -67.4 (*c* 0.37, CH_2Cl_2); IR (neat) 3378, 2925, 1094, 1036 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.81 (ddd, *J* = 6.3, 5.9, 3.4 Hz, 1H), 3.62 (ddd, *J* = 7.3, 6.3, 5.9 Hz, 1H), 3.49 (dddd, *J* = 7.3, 6.8, 3.9, 3.4 Hz, 1H), 3.00 (ddd, *J* = 7.3, 3.9, 3.4 Hz, 1H), 2.14 (d, *J* = 3.9 HZ, 1H), 1.94 (t, *J* = 5.9 Hz, 1H), 1.35 (dddd, *J* = 9.8, 6.8, 6.3, 3.4 Hz, 1H), 1.10 (ddd, *J* = 7.3, 6.3, 6.3 Hz, 1H), 1.04 (ddd, *J* = 9.8, 6.3, 3.9 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 72.0, 66.2, 29.7, 24.5, 12.7; HRMS (CI, NH_3): Exact mass calcd for $C_5H_9ClO_2$ $[M + NH_4]^+$, 154.0635. Found 154.0635.

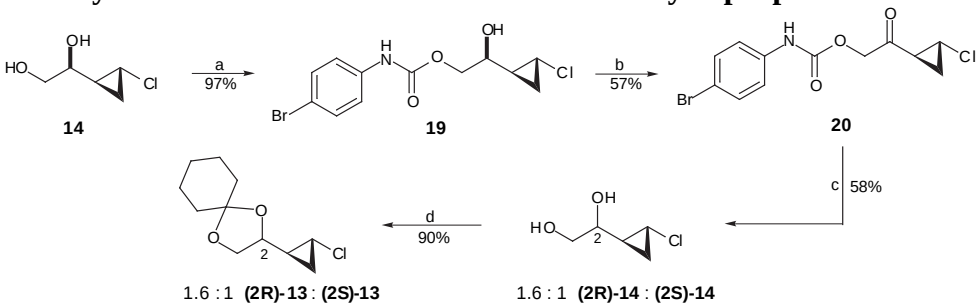
2-((1*S*,2*R*)-2-chlorocyclopropyl)-1,1-dibromoethene ((–)-5). To a solution of 520 mg of **14** (3.81 mmol) in 30 mL CH_2Cl_2 was added 2.63 g of K_2CO_3 (19.0 mmol), and the resulting slurry was chilled to 0 °C. 1.94 g of $Pb(OAc)_4$ (4.38 mmol) was added in one portion, and the mixture was stirred vigorously for 30 min at 0 °C (flask A). Meanwhile, 6.31 g of CBr_4 (19.0 mmol) was added to 30 mL CH_2Cl_2 in a separate flask (flask B) and chilled to 0 °C. 9.99 g of PPh_3 (38.1 mmol) was added in 5 equal portions to flask B, producing a bright red solution, which was stirred for 20 min at 0 °C. The contents of flask A were then filtered through Celite 545 directly into flask B with a 2×5 mL CH_2Cl_2 rinse. The resulting red solution was stirred for 2 hours at 0 °C to 25 °C. The solution was poured into 100 mL ice-cold pentane, and filtered through a silica plug with 300 mL Et_2O. Removal of the solvent *in vacuo* and flash column chromatography (pentane) afforded the title compound as a clear, colorless oil in 94% yield (930 mg, 3.57 mmol). Analytical data for (–)-**5**: $[\alpha]_D^{25}$ = -80.5 (*c* 0.71, CH_2Cl_2); IR (neat) 3006, 2924, 1432, 1360, 1279, 936, 781 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.83 (d, *J* = 9.3 Hz, 1H), 3.06 (ddd, *J* = 6.8, 3.9, 3.4 Hz, 1H), 2.02 (dddd, *J* = 9.8, 9.3, 6.8, 3.4 Hz, 1H), 1.36 (ddd, *J* = 9.8, 6.3, 3.9 Hz, 1H), 1.14 (ddd, *J* = 6.8, 6.8, 6.3 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.1, 89.6, 33.0, 26.0, 17.5.



5-((1*S*,2*R*)-2-chlorocyclopropyl)(4*Z*,2*E*)-4-bromopenta-2,4-diene-1-ol (18). A solution of 587 mg of **7**[3] (5.76 mmol) and 300 mg of (–)-**5** (1.15 mmol) in 18 mL THF and 6 mL H_2O was prepared. After three freeze-pump-thaw cycles, 179 mg of $Pd(PPh_3)_4$ (0.115 mmol) was added, and the mixture was stirred for 5 min at 25 °C. To the yellow solution was added 147 μL of TlOEt (2.08 mmol) dropwise, resulting in the immediate formation of a yellow precipitate. After stirring for 30 min at 25 °C, the reaction mixture was poured into 50 mL Et_2O and 10 mL 1 N $NaHSO_4$ (aq), and the biphasic mixture was filtered through celite with a 2×10 mL Et_2O rinse. An additional 20 mL 1 N $NaHSO_4$ (aq) was added, the layers were separated, and the aqueous layer was extracted with 10 mL Et_2O. The combined organic fractions were washed with 30 mL brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash column chromatography (linear gradient, 20 to 40% EtOAc in hexanes) afforded the title compound as a light yellow oil in 85% yield (231 mg, 0.973 mmol). Analytical data for **18**: $[\alpha]_D^{25}$ = -96.7 (*c* 0.135, CH_2Cl_2); IR (neat) 3346, 3052, 2863, 1729, 1648, 1616, 1373, 1265, 1094, 949, 739 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.26 (d, *J* = 14.6 Hz, 1H), 6.21 (dt, *J* = 14.6, 4.4 Hz, 1H), 5.39 (d, *J* = 9.3, 1H), 4.32 (d, *J* = 4.4, 2H), 3.09 (ddd, *J* = 7.3, 4.4, 3.4 Hz, 1H), 3.34 (dddd, *J* = 9.8, 9.3, 6.3, 3.4 Hz, 1H), 1.51 (s, 1H), 1.43 (ddd, *J* = 9.8, 6.3, 4.8 Hz, 1H), 1.16 (ddd, *J* = 7.3, 6.3, 6.3 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.0, 129.0, 124.9, 62.5, 34.2, 25.1, 18.3; HRMS (EI): Exact mass calcd for $C_8H_{10}BrClO$ $[M]^+$, 235.9604. Found 235.9602.

(2*E*)-5-((1*S*,2*R*)-2-chlorocylcopropyl)pent-2-en-4-yn-1-ol (17). A solution of 38.5 mg of **18** (0.162 mmol) and 170 μL of DBU (1.14 mmol) in 1.5 mL toluene was prepared in a 10 mL flask fitted with a reflux condenser. The resulting solution was heated to 110 °C for 24 h during which time a brown oil separated from the solution. The mixture was cooled to rt and diluted with 20 mL EtOAc. This solution was washed with 2×10 mL H_2O and 10 mL sat. $CuSO_4$ (aq), and the aqueous layers were then extracted with an additional 10 mL EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography (linear gradient, 10 to 25% EtOAc in hexanes) afforded the title compound as a clear, colorless oil in 91% yield (23.0 mg, 0.147 mmol). Analytical data for **17**: $[\alpha]_D^{25}$ = -78.9 (*c* 0.705, CH_2Cl_2); IR (neat) 3354, 3015, 2925, 2857, 2220, 1718, 1636, 1432, 1258, 1095, 954, 688 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.18 (dt, *J* = 15.6, 5.4 Hz, 1 H), 5.68 (dq, *J* = 15.6, 2.0, 1H), 4.19 (dd, *J* = 5.4, 2.0 Hz, 2H), 3.17 (m, 1H) 1.78 (m, 1H), 1.39 (b, 1H), 1.30-1.24 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.5, 110.2, 89.5, 76.3, 62.9, 34.2, 19.1, 11.8; HRMS (EI): Exact mass calcd for C_8H_9ClO $[M]^+$, 156.0342. Found 156.0330.

Synthesis of a diastereomeric mixture of cyclopropane 13.



Reaction conditions: a) *p*-BrPhNCO, DMAP, pyr, rt; b) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C to rt; c) $LiAlH_4$, THF, 0 °C to rt; d) cyclohexananone dimethyl ketal, *p*-TsOH, MePh, rt

To verify the selectivity of the cyclopropanation of (+)-**8**, a diastereomeric mixture of **13** was synthesised. The *para*-bromoisocyanate **19** was prepared with the intention of growing an X-ray quality crystal for verification of the cyclopropanation stereochemistry. Attempts to grow adequate crystals failed, so this compound was used to prepare a diastereomeric mixture of **13**. Swern oxidation to ketone **20** followed by $LiAlH_4$ reduction provided diol **14** as a 1.6:1 mixture of C-2 isomers, favoring the 2R isomer. Protection as the cyclohexylidene ketal then provided a 1.6:1 mixture of **(2R)-13** and **(2S)-13**, which were distinguishable by ^{1}H-NMR and GC.

^{1}H-NMR (500 MHz, $CDCl_3$) CCl*H* – **(2R)-13**: δ 3.08 (m, 1H); **(2S)-13** δ 3.00 (m, 1H)

GC (DB-1701, 125-135 °C, 0.5 °C/min, 10 psi); t_r (**(2R)-13**) = 15.1, t_r (**(2S)-13**) = 15.5

X-ray Crystallographic Data for 15.

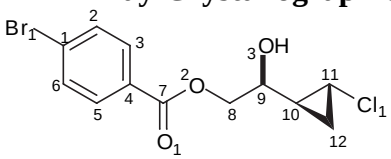


Table 1 – Bond Lengths (Å) – see figure above for atom labeling

Br(1) – C(1)	1.885(5)		Cl(1) – C(12)	1.757(5)
O(3) – C(9)	1.439(4)		C(5) – C(4)	1.373(6)
C(5) – C(6)	1.376(7)		O(2) – C(7)	1.356(5)
O(2) – C(8)	1.447(5)		C(9) – C(10)	1.506(6)
C(9) – C(8)	1.506(6)		C(4) – C(3)	1.397(6)
C(4) – C(7)	1.456(7)		C(10) – C(12)	1.484(6)
C(10) – C(11)	1.510(5)		C(3) – C(2)	1.375(7)
C(7) – O(1)	1.214(5)		C(1) – C(6)	1.372(7)
C(1) – C(2)	1.377(7)		C(11) – C(12)	1.476(6)

Table 2 – Bond Angles (°) – see figure above for atom labeling

C(4) – C(5) – C(6)	121.7(5)		C(7) – O(2) – C(8)	116.2(3)
O(3) – C(9) – C(10)	109.9(3)		O(3) – C(9) – C(8)	110.4(3)
C(10) – C(9) – C(8)	109.8(3)		C(5) – C(4) – C(7)	119.1(4)
C(3) – C(4) – C(7)	122.8(4)		C(12) – C(10) – C(9)	120.0(4)
C(1) – C(6) – C(5)	119.0(5)		C(9) – C(10) – C(11)	121.8(4)
C(2) – C(3) – C(4)	121.0(4)		O(1) – C(7) – O(2)	120.4(4)
O(1) – C(7) – C(4)	125.2(4)		O(2) – C(7) – C(4)	114.4(4)
C(6) – C(1) – C(2)	121.2(5)		C(6) – C(1) – Br(1)	118.8(4)
C(2) – C(1) – Br(1)	120.0(4)		C(3) – C(2) – C(1)	119.0(5)
C(5) – C(4) – C(3)	118.1(4)		O(2) – C(8) – C(9)	107.6(3)
C(10) – C(12) – Cl(1)	119.3(3)		C(11) – C(12) – Cl(1)	119.6(3)
C(11) – C(12) – C(10)	61.4(3)		C(12) – C(11) – C(10)	59.6(3)
C(12) – C(10) – C(11)	59.1(3)			

(1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organomettalics* **1996**, *15*, 1518-1520.
(2) Callant, P.; D'Haenens, L.; Vandewalle, M. *Synth. Commun.* **1984**, *14*, 155-161.
(3) Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989-8992.