Concise Synthesis of (+)-[$^{13}C_4$]-Anatoxin-a by a Dynamic Kinetic Resolution of a Cyclic Iminium Ion

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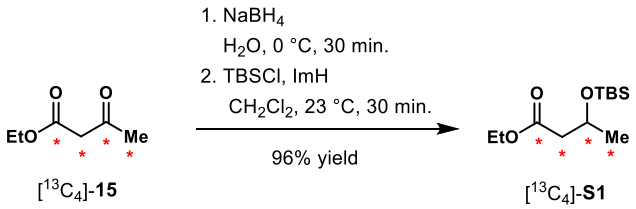
Supplementary Information

General Information.

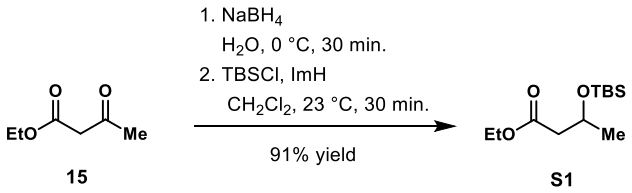
All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware, unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane (CH_2Cl_2), diisopropylamine (*i*-Pr_2NH), *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt), and acetonitrile (MeCN) were distilled from calcium hydride in a continuous still under an atmosphere of argon. Reaction temperatures were controlled by IKA ETS-D4 fuzzy thermo couples. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F_{254} (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate and iodine staining. Flash column chromatography was preformed using 40–63 µm silica gel (Merck, Geduran, no. 11567-1) as the stationary phase. Proton nuclear magnetic resonance spectra were recorded at 400, 500, and 600 MHz on Varian Unity Inova spectrometers. Carbon nuclear magnetic resonance spectra were recorded at 100 MHz, 125 MHz, and 150 MHz on Varian Unity Inova spectrometers. All Chemical shifts were reported in δ units relative to tetramethylsilane. High Resolution mass spectral data were obtained using Waters Xevo G2-XS Tof mass spectrometer at the University of California, Santa Barbara. Ethyl [$^{13}C_4$]-acetoacetate ([$^{13}C_4$]-**15**, ^{13}C, 99.1% isotope purity) was purchased from Cambridge Isotope Laboratories. Sulfide **23** was purchased from TCI America. * denotes the ^{13}C isotope.



Ethyl ester [$^{13}C_4$]-S1. A solution of sodium borohydride (93 mg, 2.50 mmol, 0.33 equiv.) in water (1.0 mL) was added in three portions over 5 min to a heterogeneous mixture of commercially available ethyl [$^{13}C_4$]-acetoacetate ([$^{13}C_4$]-**15**, 1.00 g, 7.5 mmol) and water (2.0 mL) at 0 °C, and

the reaction mixture was stirred at 0 ˚C for 30 min. Then the mixture was carefully quenched by slow addition of 1 M HCl (2 mL) followed by the addition of solid NaCl (1.35 g). The product was extracted with CH_2Cl_2 (6×15 mL), the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure at 0 °C. The crude product was submitted to the next step without further purification.

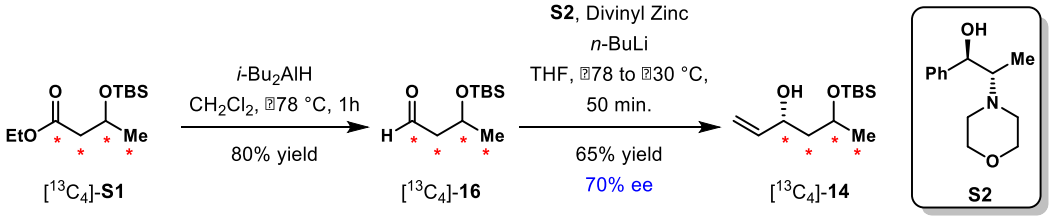
The crude β-hydroxyester was dissolved in CH_2Cl_2 (15 mL) and the solution was cooled to 0 ˚C. Imidazole (1.23 g, 17.6 mmol, 2.4 equiv.) and TBSCl (1.36 g, 9.02 mmol, 1.2 equiv.) were added sequentially. The reaction mixture was stirred at 0 °C for 30 min, then warmed to 23 ˚C and left to stir for another 12 h. The resulting solution was quenched with water (50 mL) and the product was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel (5% EtOAc in hexanes) to give ethyl ester ([$^{13}C_4$]-**S1** (1.80 g, 7.2 mmol, 96% yield) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.25 (dm, *J* = 151.7 Hz, 1H), 4.16 – 4.04 (m, 2H), 2.44 (dm, *J* = 134.0 Hz, 1H), 2.34 (dm, *J* = 126.4 Hz, 1H), 1.24 (t, *J* = 10 Hz, 6H), 1.17 (ddd, *J* = 125.9, 10.5, 4.6 Hz, 1H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.8 (dd, *J* = 57.6, 3.5 Hz), 66.0 (td, *J* = 39.2, 1.3 Hz), 60.4 (d, *J* = 2.4 Hz), 45.1 (ddd, *J* = 57.7, 38.9, 1.8Hz), 25.9, 24.1 (ddd, *J* = 39.4, 3.5, 1.7 Hz), 18.1, 14.3, -4.4, -4.9. HRMS-ESI (m/z): $[M+H]^+$ calcd for $^{13}C_4C_8H_{26}O_3SiNa$, 273.1683; found, 273.1683.



Ethyl ester S1. The title compound was obtained using the procedure described above, starting from 9.05 g (69.6 mmol) of ethyl acetoacetate **15** (natural isotope), 0.87 g (23.0 mmol, 0.33 equiv.) of sodium borohydride and 27.0 mL of water for the first step. The second step was performed using 12.6 g (83.5 mmol, 1.2 equiv.) of TBSCl, 11.4 g (167.0 mmol, 2.4 equiv.) of imidazole in CH_2Cl_2 (135 mL). Ethyl ester **S1** was obtained in 91% yield (15.6 g, 63.3 mmol) ^{1}H NMR (500MHz, $CDCl_3$): δ 4.30 – 4.24 (m, 1H), 4.16 – 4.07 (m, 2H), 2.45 (dd, *J* = 14.5, 7.6 Hz, 1H),

2.35 (dd, *J* = 14.5, 5.3 Hz, 1H), 1.26 (t, *J* = 7.15 Hz, 3H), 1.19 (d *J* = 6.15 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.8, 66.0, 60.4, 45.1, 25.8, 24.1, 18.1, 14.3, -3.4, -4.9. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{12}H_{26}O_3SiNa$, 269.1549; found, 269.1553.

Allylic alcohol [$^{13}C_4$]-14. Method 1:

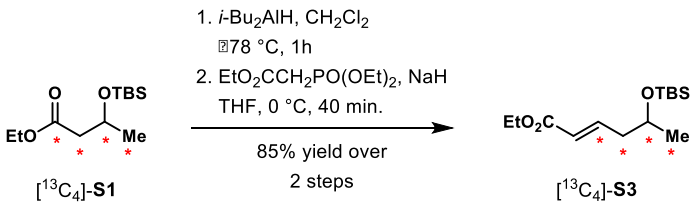


Aldehyde [$^{13}C_4$]-16. *i*-Bu_2AlH (1.27 mL, 7.10 mmol, 1.05 equiv.) was added dropwise to a solution of ethyl ester [$^{13}C_4$]-**S1** (1.68 g, 6.80 mmol) in CH_2Cl_2 (40 mL) over 30 min at -78 ˚C. The resulting solution was stirred for 1 h at –78 ˚C before 2 mL of MeOH was added dropwise over 2 min. After 5 min the reaction mixture was warmed to 23 ˚C and a saturated solution of potassium sodium tartrate (20 mL) was added. The heterogeneous mixture was stirred vigorously for 1 h, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure on a rotary evaporator (bath temp 7 ˚C). The crude material was purified by column chromatography on silica gel (5% EtOAc in hexanes) to give [$^{13}C_4$]-**16** (1.05 g, 5.19 mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 4.45 – 4.30 (m, 1H), 2.63 – 2.38 (m, 2H), 1.24 (d, *J* = 6.12 Hz, 3H), 0.98 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 202.3, 64.7, 53.1, 25.9, 24.3, 18.1, -4.2, -4.8. HRMS-ESI (m/z): $[M+Na+CH_3OH]^+$ calcd for $^{13}C_4C_7H_{26}O_3SiNa$, 261.1683; found, 261.1675.

Allyl alcohol [$^{13}C_4$]-14. A solution of *n*-butyllithium in hexanes (2.50 M, 0.350 mL, 0.872 mmol, 2.0 equiv.) was added dropwise over 3 min to a solution of (1*S*,2*R*)-2-morpholin-4-yl-1-phenylpropanol **S2** (0.193 g, 0.872 mmol, 2.0 equiv.) in toluene (1 mL) at 0 ˚C. The solution was stirred for 30 min at 0 ˚C before a divinyl zinc solution[1] (0.289 M, 3.02 mL, 0.872 mmol, 2.0 equiv.) was added dropwise over 5 min at 0 ˚C. The resulting solution was stirred for an

additional 1 h at 0 ˚C before it was cooled to –78 ˚C. A solution of aldehyde [$^{13}C_4$]-**16** (88 mg, 0.436 mmol) in toluene (0.55 mL) was added to the reaction mixture. After the reaction mixture was stirred at –78 ˚C for 40 min, the temperature was raised to –30 ˚C and stirred for another 10 min. An aqueous citric acid solution (30% by weight, 5 mL) was then added slowly, and the reaction was diluted with EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), washed with aqueous 1M NaOH (4 × 5 mL), and brine (5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude material was purified by column chromatography on silica gel (1% EtOAc in hexanes to 5% EtOAc in hexanes) to give [$^{13}C_4$]-**14** (65 mg, 0.282 mmol, 65% yield). The enantiopurity of the material (70% ee) was measured by HPLC trace analysis after derivatization (see below). ^{1}H NMR (600 MHz, $CDCl_3$, mixture of diastereomers): δ (ppm) 5.90 – 5.80 (m, 2H), 5.29 – 5.22 (m, 2H), 5.10 – 5.03 (m, 2H), 4.58 – 3.9 (m, 4H), 3.31 (br. s, 2H), 1.81 – 1.65 (m, 2H), 1.58 – 1.46 (m, 2H), 1.22 (ddd, *J* = 125.6, 6.2, 4.3 Hz, 3H), 1.18 (ddd, *J* = 125.7, 6.9, 4.5 Hz), 0.89 (s, 9H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, mixture of diastereomers) δ (ppm): 141.3 (dd, *J* = 47.0, 3.7 Hz), 140.86 (dd, *J* = 47.6, 4.1 Hz), 114.0 (dd, *J* = 31.5, 2.9 Hz), 72.3 (ddd, *J* = 37.0, 3.7, 1.2 Hz), 69.7 (ddd, *J* = 37.2, 2.7, 2.0 Hz), 69.6 (td, *J* = 39.3, 1.1 Hz), 67.2 (td, *J* = 39.1, 1.9 Hz), 46.1 (dd, *J* = 38.9, 37.4 Hz), 44.6 (dd, *J* = 38.4, 37.3 Hz), 25.95, 25.94, 24.6 (ddd, *J* = 38.8, 3.7, 0.9 Hz), 23.21 (ddd, *J* = 39.0, 2.7, 0.8 Hz), 18.06 (d, *J* = 0.8 Hz), 18.03 (d, *J* = 0.9 Hz), -3.7, -4.3, -4.7, -4.8. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $^{13}C_4C_8H_{26}O_2SiNa$, 257.1734; found, 257.1727.

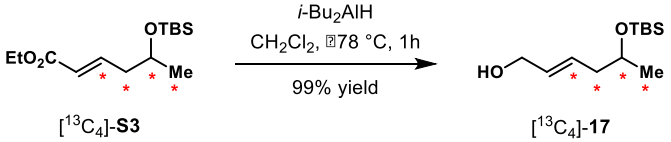
Allylic alcohol [$^{13}C_4$]-14. Method 2:



[$^{13}C_4$]-**S1** [$^{13}C_4$]-**S3**

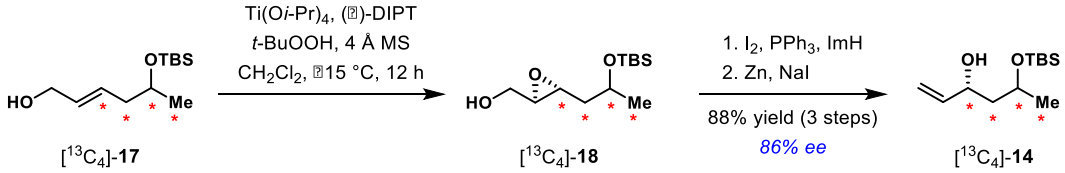
Ethyl ester [$^{13}C_4$]-S3. *i*-Bu_2AlH (1.27 mL, 7.10 mmol, 1.05 equiv.) was added dropwise over 30 min to a solution of ethyl ester [$^{13}C_4$]-**S1** (1.68 g, 6.80 mmol) in CH_2Cl_2 (40 mL) at –78 °C. The resulting solution was stirred for 1 h at –78 °C before 2 mL of MeOH was added dropwise over 2 minutes. After 5 min the reaction mixture was warmed to 23 °C and a saturated solution of potassium sodium tartrate (20 mL) was added. The heterogeneous mixture was stirred for 1 h, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure on a rotary evaporator (bath temp 7 °C). The crude aldehyde was submitted to the next step without further purification.

Triethyl phosphonoacetate (1.98 g, 8.83 mmol, 1.3 equiv.) was added dropwise over 10 min to a suspension of sodium hydride (0.33 g, 8.15 mmol, 1.2 equiv., 60% sodium hydride suspension in mineral oil was used) in THF (20 mL) at 0 °C. The mixture was stirred until homogeneity was observed (~30 min). A solution of the crude aldehyde from the previous step in THF (3 mL) was then added, and the reaction was stirred for 30 min at 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and the aqueous layer was extracted with EtOAc (4 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude material was purified by column chromatography on silica gel (1% EtOAc in hexanes to 5% EtOAc in hexanes) to give [$^{13}C_4$]-**S3** (1.60 g, 5.77 mmol, 85% yield) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (dddd, *J* = 155.6, 15.3, 7.5, 2.7 Hz, 1H), 5.78 (dd, *J* = 15.6, 5.5 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.87 (dm, *J* = 140.5 Hz, 1H), 2.27 (d, *J* = 127.7, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.11 (ddd, *J* = 125.3, 5.9, 4.5 Hz, 3H), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.5 (d, *J* = 6.4 Hz), 146.13 (d, J = 42.3 Hz), 123.3 (dd, *J* = 70.4, 2.2 Hz), 67.8 (d, *J* = 39.9, 38.1, 2.0 Hz), 60.2, 42.55 (ddd, *J* = 42.3, 38.1, 1.3 Hz), 25.9, 23.9 (ddd, *J* = 39.7, 2.6, 1.2 Hz), 18.2, 14.4, -4.4, -4.7. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $^{13}C_4C_{10}H_{28}O_3SiNa$, 299.1840; found, 299.1843.



[$^{13}C_4$]-**S3** [$^{13}C_4$]-**17**

Allylic alcohol [$^{13}C_4$]-17. *i*-Bu_2AlH (2.40 mL, 13.3 mmol, 2.3 equiv.) was added dropwise over 5 min to a solution of [$^{13}C_4$]-**S3** (1.60 g, 5.80 mmol) in CH_2Cl_2 (115 mL) at -78 °C. After the reaction was stirred at this temperature for 1 h, a saturated aqueous solution of potassium sodium tartrate (60 mL) was added. The mixture was vigorously stirred at 23 °C for 3 h, then the organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude material was purified by column chromatography on silica gel (30% EtOAc in hexanes) to afford the product [$^{13}C_4$]-**17** (1.35 g, 5.76 mmol, 99% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.71 – 5.61 (m, 1H), 5.68 (dm, *J* = 153.4, 1H), 4.12 – 4.07 (m, 2H), 3.84 (dm, *J* = 139.9, 1H), 2.17 (dm, *J* = 125.9 Hz, 2H), 1.43 (br. s, 1H), 1.12 (ddd, *J* = 125.5, 6.0, 4.4 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 131.3 (dd, *J* = 71.8, 2.9 Hz), 129.93 (d, *J* =43.4 Hz), 68.5 (ddd, *J* = 40.1, 38.5, 2.0 Hz), 63.9 (d, *J* = 5.6 Hz), 42.7 (ddd, *J* = 43.4, 38.5, 1.1 Hz), 26.01, 23.6 (ddd, *J* = 39.8, 2.4, 1.2 Hz), 18.3, -4.4, -4.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $^{13}C_4C_8H_{26}O_2SiNa$, 257.1734; found, 257.1739.

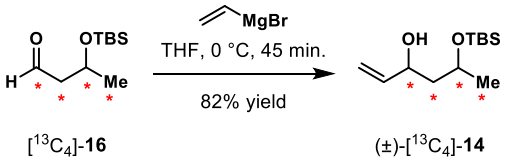


Chiral alcohol [$^{13}C_4$]-14. Crushed 4 Å molecular sieves (0.27 g) and Ti(O*i*-Pr)$_4$ (0.24 mL, 0.81 mmol, 0.14 equiv.) were added sequentially to a solution of (–)-diisopropyl D-tartrate (0.24 g, 1.03 mmol, 0.18 equiv.) in CH_2Cl_2 (9 mL) at –5 °C and the mixture was stirred at this temperature for 15 min. The mixture was then cooled to –20 °C and *t*-BuOOH (2.1 mL of 5.5 M solution, 11.4 mmol, 2 equiv.) was added. After 15 min of stirring, a solution of allylic alcohol [$^{13}C_4$]-**17** (1.34 g, 5.72 mmol) in CH_2Cl_2 (2.5 mL) was added and the mixture was stirred at –15 °C for 24 h. The reaction was then diluted with Et_2O (25 mL) and quenched by the addition of a saturated solution of Na_2SO_4 (15 mL). After stirring for 1 h, the aqueous layer was extracted with EtOAc (4 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated

to dryness under reduced pressure. The crude product was submitted to the next step without further purification.

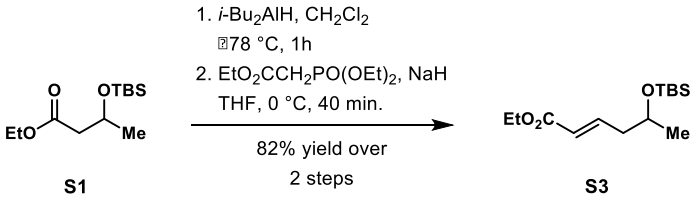
Triphenylphosphine (4.50 g, 17.16 mmol, 3 equiv.) and imidazole (2.92 g, 42.9 mmol, 7.5 equiv.) were added sequentially to a solution of crude epoxide [$^{13}C_4$]-**18** in CH_2Cl_2 (57 mL). The mixture was cooled to 0 °C and crushed iodine (4.36 g, 17.16 mmol, 3 equiv.) was added. After stirring for 10 min, the cooling bath was removed and the reaction was warmed to 23 °C. Stirring was continued for 1 h, at which point the mixture was diluted with CH_2Cl_2 (80 mL) and washed with a 1:1 mixture of saturated aqueous solutions of $NaHCO_3$ and $Na_2S_2O_3$ (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. Et_2O (30 mL) was added to the dry, solid residue. The precipitate was crushed with a spatula and filtered, washing with an additional portion of Et_2O (20 mL). The filtrate was concentrated under reduced pressure and purified by column chromatography (3% EtOAc in hexanes to 8% EtOAc in hexanes) to produce the unstable iodide that was immediately submitted to the next step.

Zinc (1.86 g, 28.6 mmol, 5 equiv.) and sodium iodide (2.15 g, 14.3 mmol, 2.5 equiv.) were added sequentially to a solution of the the iodide from the previous step in MeOH (29 mL) and the mixture was heated to reflux with vigorous stirring for 1 h. The reaction mixture was cooled to room temperature, then concentrated to dryness under reduced pressure. Water (20 mL) and CH_2Cl_2 (30 mL) were added to the residue, and the white precipitate formed was filtered and washed with CH_2Cl_2 (2 × 20 mL). The filtrate was transferred into separatory funnel and organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (5% EtOAc in hexanes to 15% EtOAc in hexanes) to afford [$^{13}C_4$]-**14** (1.18 g, 5.03 mmol, 88% yield over 3 steps) as a pale yellow oil. The enantiopurity of the material (86% ee) was measured by HPLC trace analysis after derivatization to compound [$^{13}C_4$]-**S5** (see below). The ^{1}HNMR, ^{13}C NMR and mass spectral data are in full agreement with ones for the compound obtained by method 1 (see above).



[$^{13}C_4$]-**16** (±)-[$^{13}C_4$]-**14**

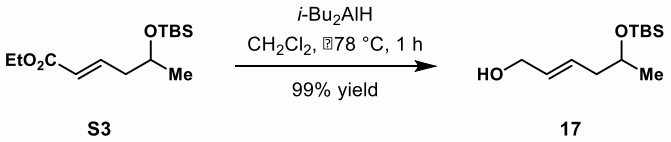
(±)-Alcohol-[$^{13}C_4$]-14:[2] A solution of vinylmagnesium bromide (0.97 M in THF, 1.55 mL, 1.50 mmol, 1.5 equiv.) was added dropwise to a solution of aldehyde [$^{13}C_4$]-**16** (0.206 g, 1.00 mmol) in THF (3 mL) at –78 ˚C. The solution was warmed to 0 ˚C and stirred for 45 min. before being quenched with a solution of saturated aqueous ammonium chloride. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude material was purified by column chromatography on silica gel (1% EtOAc in hexanes to 5% EtOAc in hexanes) to give (±)-[$^{13}C_4$]-**14** (0.193 g, 0.823 mmol, 82% yield). The ^{1}H NMR, ^{13}C NMR and mass spectral data are in full agreement with ones for the compound obtained by method 1 (see above).



S1 **S3**

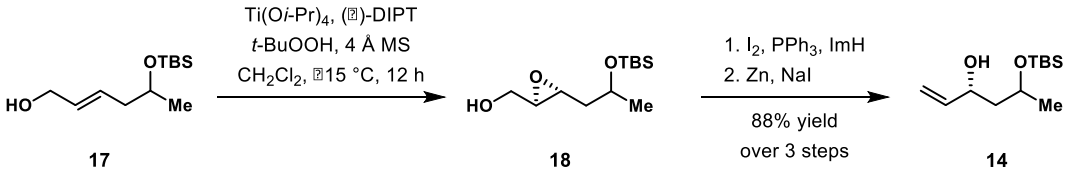
Ethyl ester S3. The title compound was prepared according to the procedure described above for its $^{13}C_4$ analog starting from 4.88 g (19.8 mmol) of ethyl ester **S1**, 3.71 mL (20.8 mmol, 1.05 equiv.) of *i*-Bu_2AlH in CH_2Cl_2 (115 mL) for the first step. The second step was conducted using 0.95 g (23.8 mmol. 1.2 equiv.) of 60% sodium hydride suspension in mineral oil and 5.8 g (25.7 mmol, 1.3 equiv.) of triethyl phosphonoacetate in THF (66 mL). Ethyl ester **S3** was obtained in 82% yield over 2 steps (4.42 g, 16.2 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 – 6.87 (m, 1H), 5.84 (d, *J* = 15.65 Hz, 1H), 4.17 (q, *J* = 7.15 Hz, 2H), 3.96 – 3.89 (m, 1H), 2.38 – 2.24 (m, 2H), 1.28 (t, *J* = 16.1 Hz, 3H), 1.15 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125.7

MHz, $CDCl_3$): δ 166.6, 146.2, 123.4, 67.8, 60.3, 42.6, 26.0, 23.9, 18.2, 14.4, -4.4, -4.7. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{28}O_3SiNa$, 295.1705; found, 295.1711.



S3 **17**

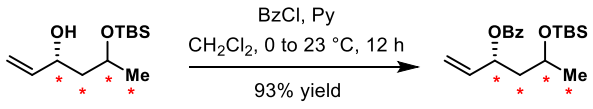
Allylic alcohol 17. The title compound was prepared using the procedure described above for its $^{13}C_4$ analog starting from 5.7 g (20.9 mmol) of ethyl ester **S3** and 8.6 mL (48.1 mmol, 2.3 equiv.) of *i*-Bu_2AlH in CH_2Cl_2 (420 mL). Allylic alcohol **17** was obtained in 99% yield (4.8 g, 20.83 mmol). ^1H NMR (500 MHz, $CDCl_3$): δ 5.75 – 5.60 (m, 2H), 4.11 – 4.08 (m, 2H), 3.86 – 3.80 (m, 1H), 2.25 – 2.09 (m, 2H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 131.3, 130.0, 68.6, 64.0, 42.7, 26.0, 23.6, 18.3, -4.4, -4.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{12}H_{26}O_2SiNa$, 253.1600; found, 253.1605.



17 **18** **14**

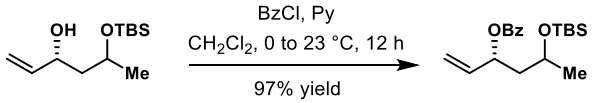
Alcohol 14. The title compound was prepared using the procedure described above for its $^{13}C_4$ analog starting from 1.53 g (6.64 mmol) of allylic alcohol **17**. The following reagents were used with the indicated quantities: $Ti(Oi\text{-}Pr)_4$ (0.14 mL, 0.46 mmol); D-DIPT (0.13 mL, 0.60 mmol); *t*-BuO_2H (2.6 mL of 5.14 M solution, 13.28 mmol); iodine (5.0 g, 19.92 mmol); PPh_3 (5.2 g, 19.92 mmol); imidazole (3.4 g, 49.8 mmol); zinc (2.16 g, 33.2 mmol); NaI (2.5 g, 16.6 mmol). After the final purification, **14** (1.30 g, 5.64 mmol, 85% yield) was obtained as a clear oil. The enantiopurity of the material (86% ee) was measured by HPLC trace analysis after derivatization to **S5** (see below). ^1H NMR (500 MHz, $CDCl_3$, mixture of diastereomers): δ 5.91 – 5.78 (m, 2H), 5.32 – 5.22 (m, 2H), 5.11 – 5.05 (m, 2H), 4.48 – 4.42 (m, 1H), 4.32 – 4.24 (m, 1H), 4.22 – 4.14 (m, 1H), 4.13 – 4.05 (m, 1H), 3.38 (s, 1H), 3.27 (s, 1H), 1.69 – 1.58 (m, 4H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.19 (d, *J* = 6.1 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.09 (s,

3H). ^{13}C NMR (151 MHz, $CDCl_3$, mixture of diastereomers) δ 141.3, 140.9, 114.1, 113.9, 72.3, 69.7, 69.6, 67.3, 46.1 44.6, 25.95, 25.94, 24.7, 23.2, 18.6, 18.0, -3.74, -4.3, -4.7 -4.8. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{12}H_{26}O_2SiNa$, 253.1600; found, 253.1604.



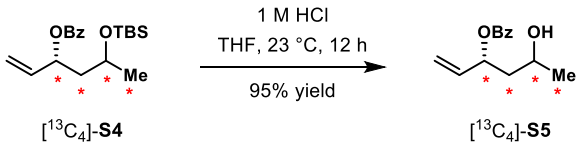
[$^{13}C_4$]-**14** [$^{13}C_4$]-**S4**

Allylic benzoate [$^{13}C_4$]-S4. Benzoyl chloride (0.050 mL, 0.43 mmol, 5 equiv.) was added to a mixture of allylic alcohol [$^{13}C_4$]-**14** (20 mg, 0.085 mmol) and pyridine (0.14 mL, 1.71 mmol, 20 equiv.) in CH_2Cl_2 (0.17 mL) at 0 °C. The mixture was allowed to warm to 23 °C and stirred for 12 h. The resulting solution was diluted with CH_2Cl_2 (5 mL) and sequentially washed with aqueous 1 M HCl solution (5 mL), saturated $NaHCO_3$ solution (5 mL), and brine (5 mL). The organic phase was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The resulting crude material was purified by column chromatography on silica gel (3% EtOAc in hexanes) to afford [$^{13}C_4$]-**14** (27 mg, 0.0807 mmol, 93% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers): δ (ppm): 8.10 (d, *J* = 7.5 Hz, 4H), 7.60 (t, *J* = 7.4 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 4H), 6.01 – 5.89 (m, 2H), 5.61 (dd, *J* = 149.5, 25.5 Hz, 2H), 5.37 (ddd, *J* = 24.2, 17.3, 6.9 Hz, 2H), 5.29 – 5.19 (m, 2H), 4.00 (dm, *J* = 140.0 Hz, 2H), 2.28 – 1.67 (m, 4H), 1.25 (dm, *J* = 125.6 Hz, 6H), 0.94 (s, 9H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, mixture of diastereomers) δ (ppm): 165.8, 165.9, 137.1 (dd, *J* = 47.4, 3.1 Hz), 136.7 (dd, *J* = 47.6, 2.3 Hz), 133.0, 132.9, 130.8, 130.7, 129.71, 129.65, 128.48, 128.47, 117.0, 116.2, 73.0 (dd, *J* = 39.0, 2.2 Hz), 72.9 (dd, *J* = 39.8, 2.8 Hz), 65.3 (m), 44.7 (m), 26.03, 26.01, 24.5 (ddd, *J* = 39.2, 3.0, 1.5 Hz), 23.9 (dd, *J* = 39.2, 0.9 Hz), 18.3, 18.1, -4.08, -4.11, -4.6, -4.8. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $^{13}C_4C_{15}H_{30}O_3SiNa$, 361.1996; found, 361.1992.



14 **S4**

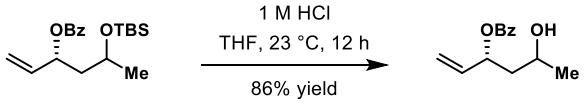
Allylic benzoate S4. This title compound was prepared using the procedure described above from 50.0 mg (0.22 mmol) of allyl alcohol **14** to give 70.4 mg, 0.21 mmol, 97% yield of **S4** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ (ppm) 8.05 (d, *J* = 7.6 Hz, 4H), 7.56 (t, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 4H), 5.97 – 5.85 (m, 2H), 5.64 – 5.51 (m, 2H), 5.39 – 5.14 (m, 4H), 4.03 – 3.89 (m, 2H), 2.10 – 2.01 (m, 2H), 1.95 – 1.73 (m, 2H), 1.21 (d, *J* = 2.56 Hz, 3H), 1.19 (d, *J* = 2.56 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.00 (s, 3H), -0.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 165.9, 165.8, 137.1, 136.7, 133.0, 132.9, 130.8, 130.7, 129.7, 129.7, 128.5, 128.5, 117.0, 116.2, 73.0, 72.9, 65.6, 65.1, 44.8, 44.6, 26.0, 26.0, 24.6, 23.9, 18.3, 18.1, -4.08, -4.09, -4.12, -4.6, -4.8. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{30}O_3SiNa$, 357.1862; found, 357.1865.



[$^{13}C_4$]-**S4** [$^{13}C_4$]-**S5**

Alcohol [$^{13}C_4$]-S5. HCl (1 M, 0.2 mL) was added to a solution of allylic benzoate [$^{13}C_4$]-**S4** (27 mg, 0.0807 mmol) in THF (2 mL) at 23 °C. The reaction was left to stir overnight, then it was diluted with EtOAc (8 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL). The organic phase was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude product was purified by column chromatography (10% EtOAc in hexanes to 35% EtOAc in hexanes) to produce alcohol [$^{13}C_4$]-**S5** (17 mg, 0.0772 mmol, 95% yield) as a colorless oil. ee: 86% [Chiralpak ® AD-H; 1% *i*-PrOH- hexanes; flow rate = 1 mL/ min; 10 µL injection of a 1 mg/ mL solution; detection at 254 nm; t_1 = 17.68 min. (major), t_2 = 21.94 min. (minor), t_3 = 27.47 min. (major), t_4 = 29.84 min. (minor)]. ^{1}H NMR (600 MHz, $CDCl_3$, mixture of diastereomers) δ 8.06 (ddt, *J* = 10.9, 6.9, 1.4 Hz, 2H), 7.61 – 7.54 (m, 1H), 7.45 (q, *J* = 8.0 Hz, 2H), 6.01 – 5.91 (m, 1H), 5.91 – 5.49 (m, 1H), 5.43 – 5.33 (m, 1H), 5.29 – 5.18 (m, 1H), 4.16 – 3.63 (m, 1H), 2.21 – 1.59 (m, 3H), 1.34 (ddt, *J* = 23.5, 6.2, 4.5 Hz, 1.5H), 1.13 (ddt, *J* = 23.6, 6.2, 4.5 Hz, 1.5H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ 157.0, 165.9, 136.6 (dd, *J* = 48.3,

3.0 Hz), 136.4 (dd, *J* = 48.3, 2.5 Hz), 133.4, 133.2, 130.4, 130.1, 130.0, 129.7, 128.59, 138.55, 117.2 (d, *J* = 3.0 Hz), 116.6 (d, *J* = 3.0 Hz), 73.7 (dd, *J* = 38.9, 3.2 Hz), 72.7 (ddd, *J* = 39.1, 3.7, 1.5 Hz), 65.4 (t, *J* = 38.2 Hz), 63.7 (ddd, *J* = 39.3, 37.8, 1.4 Hz), 44.6 (ddd, *J* = 39.3, 37.7, 1.5 Hz), 43.6 (ddd, *J* = 39.0, 37.7, 1.1 Hz), 23.9 (ddd, *J* = 38.6, 3.2, 1.1 Hz), 23.2 (ddd, *J* = 39.4, 3.8, 1.5 Hz).



S4 **S5**

Alcohol S5. The title compound was prepared using the procedure described above from 65.0 mg (0.19 mmol) of allylic benzoate **S4** to give alcohol **S5** (37.0 mg, 0.17 mmol, 86% yield). The enantiopurity of the product was determined to be 86% ee using the same HPLC conditions as those described for its $^{13}C_4$ analog with identical retention times. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers): δ 8.06 (t, *J* = 7.48 Hz, 4H), 7.56 (q, *J* = 7.48 Hz, 2H), 7.44 (q, *J* = 7.48 Hz, 4H), 6.03 – 5.88 (M, 2H), 5.81 – 5.60 (m, 2H), 5.39 (dd, *J* = 5.04, 17.2 Hz, 2H), 5.23 (t, *J* = 10.28 Hz, 2H), 4.05 – 3.75 (m, 2H), 2.10 – 1.72 (m, 6H), 1.25 (d, *J* = 6.16 Hz, 3H), 1.21 (d, *J* = 6.16 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, mixture of diastereomers): δ 166.9, 165.8, 136.6, 133.4, 130.4, 129.7, 128.5, 117.2, 116.5, 73.7, 72.7, 65.4, 63.7, 44.6, 43.7, 23.9, 23.2.

==== Shimadzu LCsolution Analysis Report ====

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Acquired by	: Artur Mailyan
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Sample ID	: kyc1-167a_AD-H
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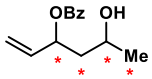

(±)-[$^{13}C_4$]-**S5**

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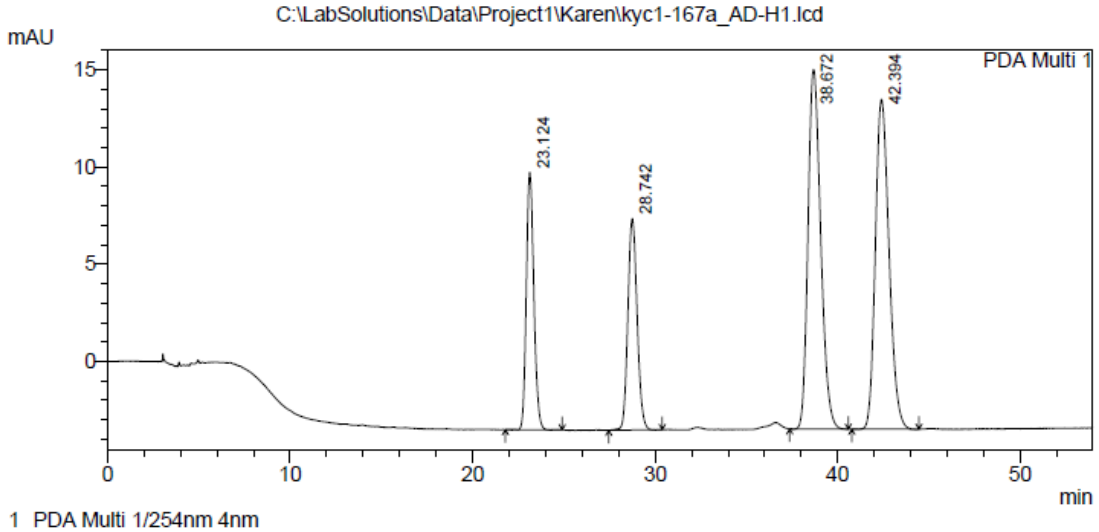

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PeakTable

PDA Ch1 254nm 4nm

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2	28.742	383514	10881	15.105	18.253
3	38.672	893630	18509	35.197	31.047
4	42.394	884093	16978	34.821	28.479
Total		2538939	59616	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

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Sample ID	: kyc2-8a
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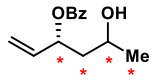

[$^{13}C_4$]-**S5**

70% ee

<Chromatogram>

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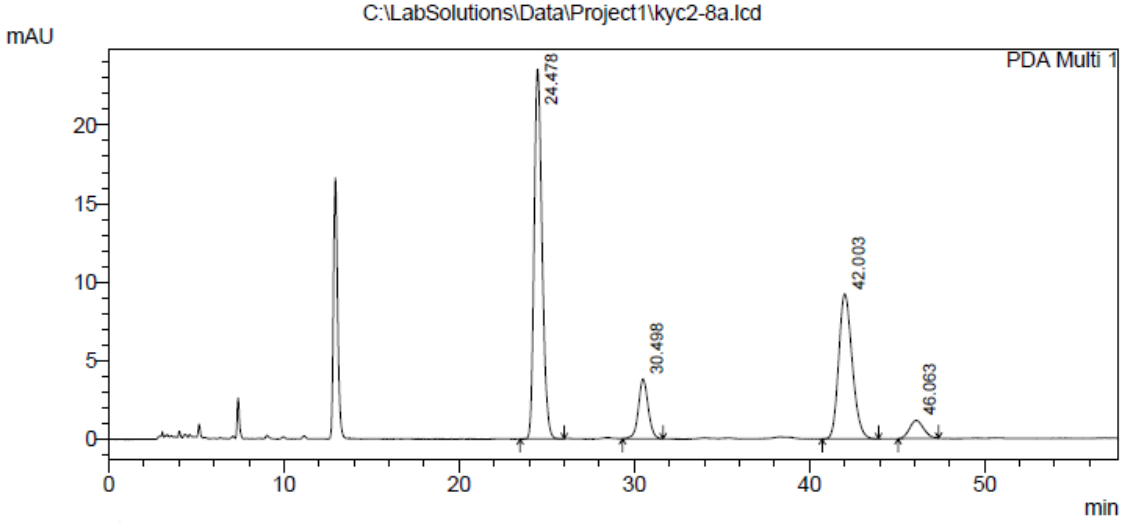

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PeakTable

PDA Ch1 254nm 4nm

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3	42.003	493881	9238	34.198	24.483
4	46.063	64405	1157	4.460	3.068
Total		1444172	37730	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

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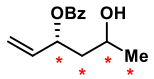

[$^{13}C_4$]-**S5**

86% ee

<Chromatogram>

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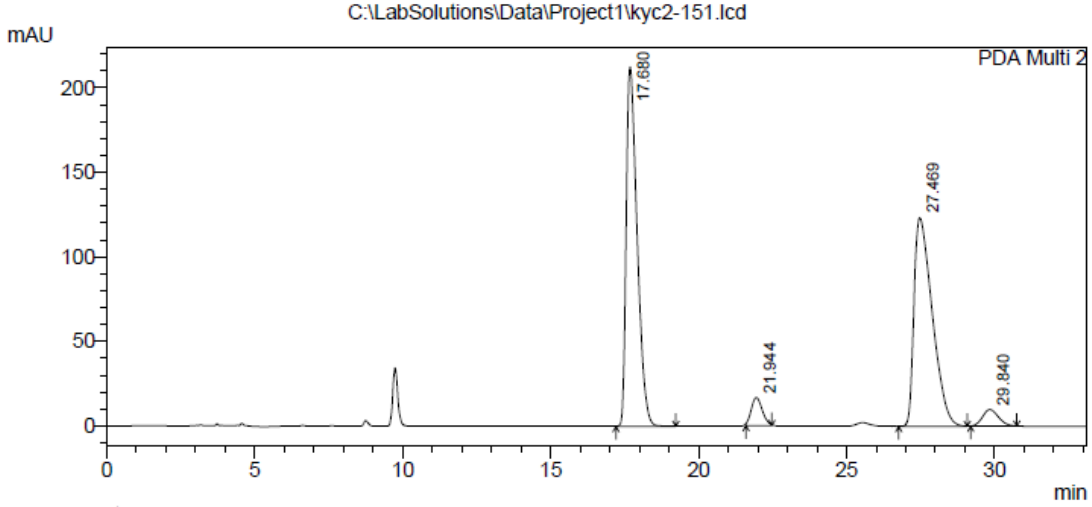

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3	27.469	5312796	123514	45.955	34.070
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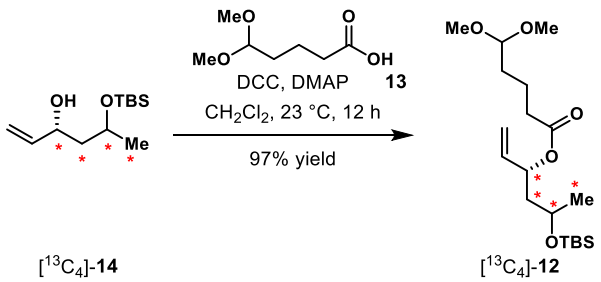
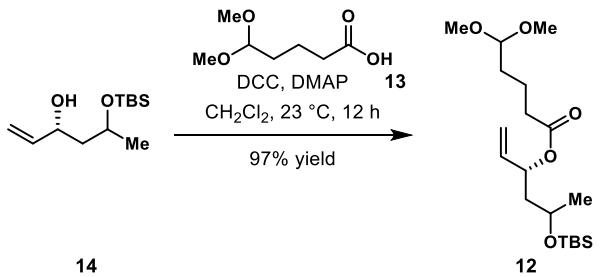
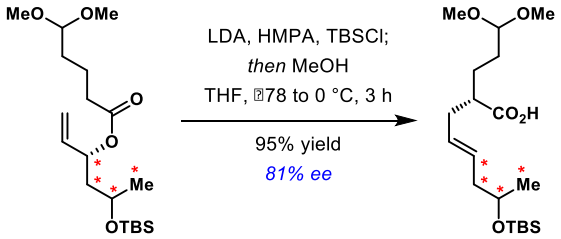
Total		11560813	362535	100.000	100.000



Ester [$^{13}C_4$]-12. 4-(Dimethylamino)pyridine (0.68 g, 5.55 mmol, 2 equiv.) and N,N'-dicyclohexylcarbodiimide (1.14 g, 5.55 mmol, 2.0 equiv.) were added sequentially to a solution of allylic alcohol [$^{13}C_4$]-**14** (0.650 g, 2.77 mmol) and 5,5-dimethoxypentanoic acid[3] (0.900 g, 5.55 mmol, 2.0 equiv.) in CH_2Cl_2 (14 mL), at 23 ˚C and the reaction mixture was left to stir at the same temperature for 12 h. The N,N'-dicyclohexylurea precipitate was removed by filtration and the filtrate was concentrated to dryness under reduced pressure. The crude residue was purified by column chromatography on silica gel (10% EtOAc in hexanes) to produce the desired product [$^{13}C_4$]-**12** (1.02 g, 2.69 mmol, 97% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$, mixture of diastereomers): δ 5.81 – 5.71 (m, 2H), 5.49 – 5.38 (m, 1H), 5.26 – 5.07 (m, 5H), 4.35 (t, *J* = 5.5, 2H), 3.84 (dm, *J* = 141.8 Hz, 2H), 3.30 (s, 12H), 2.32 (t, *J* = 7.2 Hz, 4H), 2.02 – 1.48 (m, 12H), 1.14 (dm, *J* = 125.6 Hz, 6H), 0.87 (s, 9H), 0.86 (s, 9H), 0.03 (s, 6H), 0.02 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, mixture of diastereomers): δ 172.5, 172.4, 137.2 (dd, J = 47.4 Hz, 3.0 Hz), 136.7 (dd, *J* = 47.5, 2.3 Hz), 117.0 (d, *J* = 2.6 Hz), 116.2 (d, *J* = 2.6 Hz), 104.28, 104.26, 72.3 (dd, *J* = 39.0, 2.3 Hz), 72.2 (dd, *J* = 39.8, 2.9 Hz), 65.4 (t, *J* = 39.4 Hz), 64.9 (t, *J* = 39.4), 52.86 (d, *J* = 1.1 Hz), 52.80 (*J* = 2.2 Hz), 44.6 (td, *J* = 39.7, 1.2 Hz), 44.4 (td, *J* = 39.2, 0.8 Hz), 34.29, 34.24, 31.99, 31.96, 25.99, 25.98, 24.4 (ddd, *J* = 39.2, 3.0, 1.4 Hz), 23.8 (ddd, *J* = 39.2, 3.2, 1.1 Hz), 20.24, 20.20, 18.2, 18.1, -4.07, -4.10, -4.6, -4.8. HRMS-ESI (m/z): [M+Na]$^+$ calcd for $^{13}C_4C_{15}H_{38}O_5SiNa$, 401.2520; found, 401.2520.



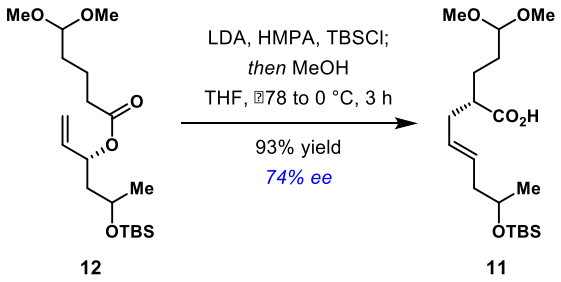
Ester 12. The title compound was prepared according to the procedure described above using allylic alcohol **14** (0.95 g, 4.12 mmol), 5,5-dimethoxypentanoic acid (1.00 g, 6.18 mmol, 1.5 equiv.), N,N'-dicyclohexylcarbodiimide (1.27 g, 6.18 mmol, 1.5 equiv.), and 4-(dimethylamino)pyridine (0.75 g, 6.18 mmol, 1.5 equiv.) in CH_2Cl_2 (21 mL). Ester **12** was isolated in 97% yield (1.50 g, 4.0 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 5.83 – 5.73 (m, 2H), 5.40 – 5.09 (m, 6H), 4.36 (t, *J* = 5.1 Hz, 2H), 3.92 – 3.79 (m, 2H), 3.31 (s, 12H), 2.33 (t, *J* = 7.2 Hz, 6H), 1.92 – 1.83 (m, 1H), 1.73 – 1.59 (m, 11H), 1.16 (d, *J* = 2.6 Hz, 3H), 1.14 (d, *J* = 2.6 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, mixture of diastereomers): δ 172.56, 172.49, 137.1, 136.7, 117.0, 116.2, 104.28, 104.26, 72.28, 72.21, 65.5, 64.9, 52.86, 52.81, 44.6, 44.4, 34.28, 34.24, 31.99, 31.96, 25.99, 25.97, 24.4, 23.9, 20.23, 20.20, 18.2, 18.1, -4.07, -4.11, -4.6, -4.8. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{38}O_5SiNa$, 397.2386; found, 397.2393.



[$^{13}C_4$]-**12** [$^{13}C_4$]-**11**

Acid [$^{13}C_4$]-11. A solution of ester [$^{13}C_4$]-**12** (0.500 g, 1.32 mmol) in THF (2 mL) was added dropwise over 5 min to a solution of freshly prepared lithium diisopropylamide (2.64 mmol, 2 equiv.) in THF (14 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min, then TBSCl (0.46 g, 3.04 mmol, 2.3 equiv.) and HMPA (2.1 mL) were added sequentially and the reaction mixture was stirred for an additional 30 min at –78 °C. Methanol (0.53 mL, 13.2 mmol, 10.0 equiv.) was added dropwise over 1 min to quench excess LDA, then the mixture was warmed to 0 °C and stirred at the same temperature until complete disappearance of the starting material was observed by TLC (approx. 2 h). A solution of lithium hydroxide (63 mg, 2.64 mmol, 2 equiv.) in water (1 mL) was added and the mixture was stirred at 0 °C until a complete hydrolysis of the silyl ester was observed by TLC. The reaction mixture was diluted with EtOAc (30 mL) and water (20 ml), cooled to 0 °C and acidified to pH = 5 with 1 M

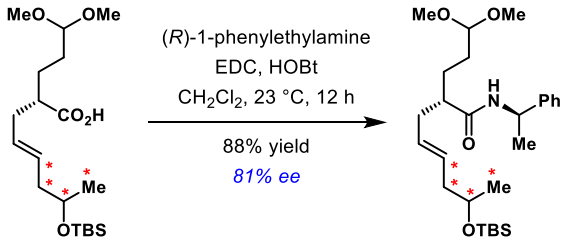
hydrochloric acid. The product was immediately extracted with EtOAc (3 × 20 ml). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel (15% EtOAc in hexanes to 50% EtOAc, 1% AcOH in hexanes) to give [$^{13}C_4$]-**12** (0.49 g, 1.31 mmol, 99% yield) as a pale yellow oil. The enantiopurity of the material (81% ee) was measured by HPLC trace analysis after derivatization to [$^{13}C_4$]-**S6** (see below). ^{1}H NMR (600 MHz, $CDCl_3$, mixture of diastereomers): δ 5.50 (dm, *J* = 137.3 Hz, 1H), 5.37 (m, 1H), 4.35 (t, *J* = 4.92 Hz, 1H), 3.77 (dm, *J* = 140.7 Hz), 3.31 (s, 3H), 3.30 (s, 3H), 2.45 – 2.15 (m, 4H), 2.10 – 1.92 (m, 1H), 1.70 – 1.52 (m, 4H), 1.09 (ddd, *J* = 125.4, 9.2, 4.4 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) mixture of diastereomers: δ 181.32, 181.34, 130.1 (dd, *J* = 43.4, 1.9 Hz), 128.7 (d, *J* = 2.1 Hz), 104.3, 68.8 (t, *J* = 39.1Hz), 53.0 (d, *J* = 2.2 Hz), 52.6 (d, *J* = 0.8 Hz), 45.3 (d, *J* = 2.6 Hz), 43.0 (ddd, *J* = 43.4, 38.7, 4.2 Hz), 35.3, 30.2, 26.4, 26.3, 26.02, 23.5 (dd, *J* = 39.8, 1.0 Hz), 18.3, -4.6, -4.4. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $^{13}C_4C_{15}H_{38}O_5SiNa$, 401.2520; found, 401.2523.



12 11

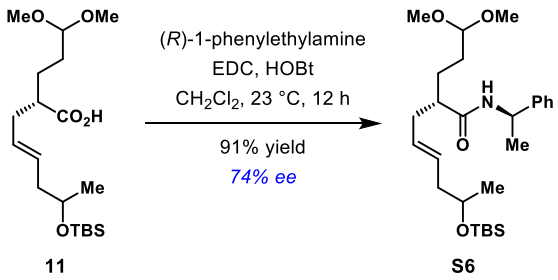
Acid 11. The title compound was prepared according to the procedure described above with ester **12** (2.0 g, 5.34 mmol), lithium diisopropylamide (10.68 mmol, 2 equiv.), TBSCl (1.85 g, 12.28 mmol, 2.3 equiv.), and HMPA (8.0 mL) in THF (54 mL). Acid **11** was isolated in 93% yield (1.86 g, 4.97 mmol). The enantiopurity of the material was measured by HPLC trace analysis after derivatization to **S6** (see below). ^{1}H NMR (400 MHz, $CDCl_3$), mixture of diastereomers: δ 5.52 – 5.44 (m, 1H), 5.42 – 5.34 (m, 1H), 4.35 (t, *J* = 5.2 Hz, 1H), 3.81 – 3.74 (m, 1H), 3.30 (s, 3H), 3.29 (s, 3H), 2.44 – 2.30 (m, 2H), 2.24 – 2.03 (m, 3H), 1.71 – 1.52 (m, 4H), 1.08 (d, *J* = 6.1 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$, mixture of diastereomers): δ

181.48, 181.46, 130.1, 128.6, 104.2, 68.8, 52.6, 52.6, 45.3, 43.00, 35.3, 30.2, 26.4, 26.3, 26.0, 23.4, 18.3, -4.4, -4.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{38}O_5SiNa$, 397.2386; found, 397.2389.



[$^{13}C_4$]-**11** [$^{13}C_4$]-**S6**

Amide [$^{13}C_4$]-S6. EDC hydrochloride (15.3 mg (0.08 mmol, 3 equiv.) was added to a solution of acid [$^{13}C_4$]-**11** (10 mg, 0.026 mmol), (*R*)-1-phenylethylamine (10.2 µL, 0.08 mmol, 3 equiv.), and 1-hydroxybenzotriazole hydrate (11 mg, 0.08 mmol, 3 equiv.) in CH_2Cl_2 (0.5 mL) at 23 °C. The reaction mixture was stirred overnight, then it was diluted with CH_2Cl_2 (7 mL) and sequentially washed with water (5 mL) and brine (5 mL). The organic phase was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel (30% EtOAc in hexanes) to give [$^{13}C_4$]-**S6** (11.2 mg, 0.023 mmol, 88% yield) as a pale yellow oil. ee: 81% [Chiralpak ® AD-H; 5% *i*-PrOH- hexanes; flow rate = 1 mL/ min; 10 µL injection of a 1 mg/ mL solution; detection at 210 nm; t_1 = 5.84 min. (major), t_2 = 6.55 min. (major), t_3 = 7.39 min., t_4 = 9.44 min.]. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.37 – 7.22 (m, 5H), 5.78 (d, *J* = 6.3 Hz, 1H), 5.42 (dm, *J* = 134.0 Hz, 1H), 5.33 – 5.23 (m, 1H), 5.20 – 5.10 (m, 1H), 4.33 (t, *J* = 5.3 Hz, 1H), 3.71 (dm, *J* = 141.8 Hz, 1H), 3.32 (s, 3H), 3.30 (s, 3H), 2.34 – 1.82 (m, 5H), 1.72 – 1.51 (m, 3H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.05 (ddd, *J* = 125.4, 10.2, 4.3 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers): δ 174.0, 143.4, 129.7 (dd, *J* = 43.4, 5.3), 129.4, 128.8 (d, *J* = 0.8 Hz), 127.4 (d, *J* = 2.6 Hz), 126.4, 104.8, 68.8 (m), 53.5 (d, *J* = 2.2 Hz), 52.7, 48.6 (d, *J* = 1.8 Hz), 47.7, 43.1 (m), 36.3, 30.5, 27.5, 26.0, 23.5 (ddd, *J* = 39.8, 9.2, 1.0 Hz), 21.9 (d, *J* = 6.5 Hz), 18.3, -4.4, -4.5. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $^{13}C_4C_{23}H_{47}NO_4SiNa$, 504.3306; found, 504.3310.



Amide S6. The title compound was prepared according to the procedure described above for its $^{13}C_4$ analog with acid **11 (**20 mg, 0.053 mmol), (*R*)-1-phenylethylamine (20.4 µL, 0.16 mmol, 3 equiv.), EDC hydrochloride (30.7 mg, 0.16 mmol, 3 equiv.), and 1-hydroxybenzotriazole hydrate (22 mg, 0.16 mmol, 3 equiv.) in CH_2Cl_2 (1 mL). **S6** was isolated in 91% yield (23.2 mg, 0.048 mmol, 91% yield). The enantiopurity of the product was determined to be 74% ee using the same HPLC conditions as those described for its $^{13}C_4$ analog with identical retention times. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.37 – 7.20 (m, 5H), 5.82 (d, *J* = 4.7 Hz, 1H), 5.47 – 5.36 (m, 1H), 5.33 – 5.23 (m, 1H), 5.20 – 5.07 (m, 1H), 4.33 (t, *J* = 5.3 Hz, 1H), 3.78 – 3.67 (m, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 2.35 – 2.23 (m, 1H), 2.15 – 2.03 (m, 3H), 2.03 – 1.93 (m, 1H), 1.72 – 1.49 (m, 3H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.1 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers): δ 174.0, 143.4, 129.6, 129.4, 128.7, 127.4, 126.3, 104.8, 68.8, 53.4, 52.6, 48.6, 47.7, 43.1, 36.3, 30.4, 27.5, 26.0, 23.5, 21.9, 18.3, -4.4, -4.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{27}H_{47}NO_4SiNa$, 500.3172; found, 500.3174.

==== Shimadzu LCsolution Analysis Report ====

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Vail #	:
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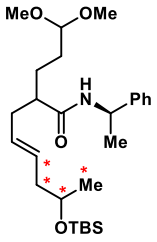

(±)-[$^{13}C_4$]-**S6**

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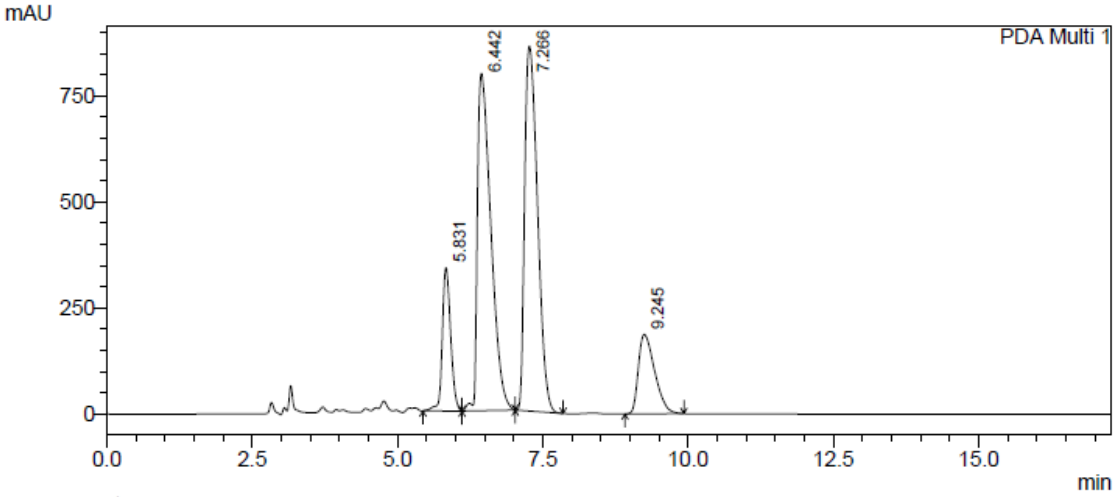

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PDA Ch1 210nm 4nm

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4	9.245	3661508	187404	11.046	8.590
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==== Shimadzu LCsolution Analysis Report ====

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Sample ID	: AKM-09-133.2
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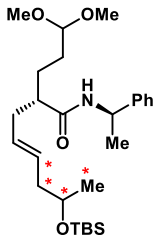

[$^{13}C_4$]-**S6**

81% ee

<Chromatogram>

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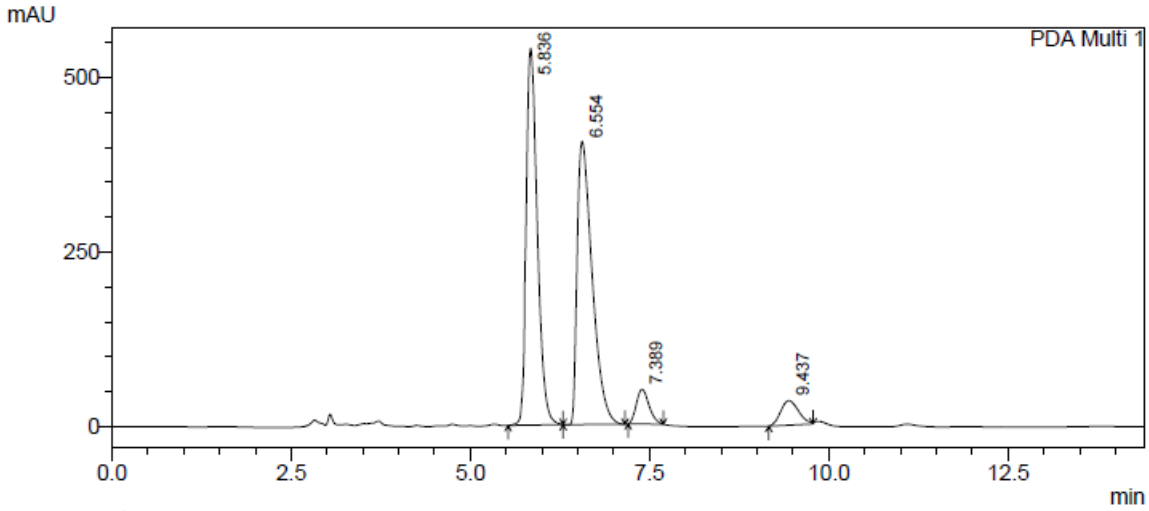

1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch1 210nm 4nm

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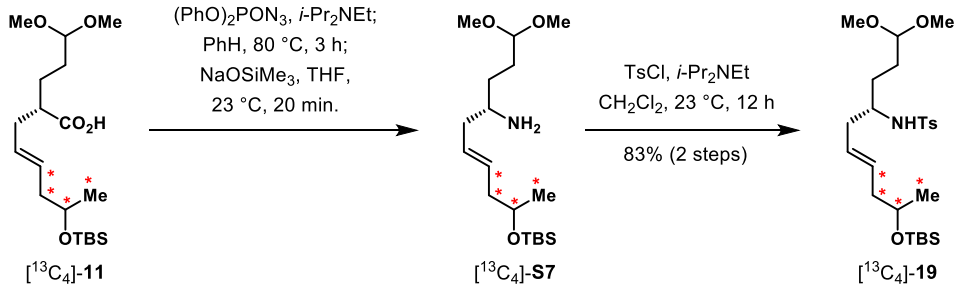
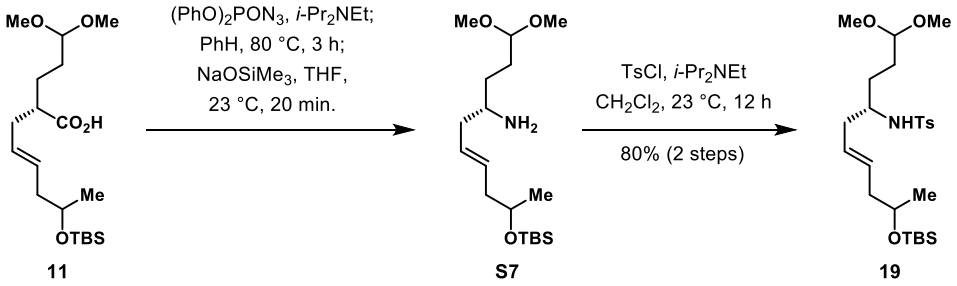
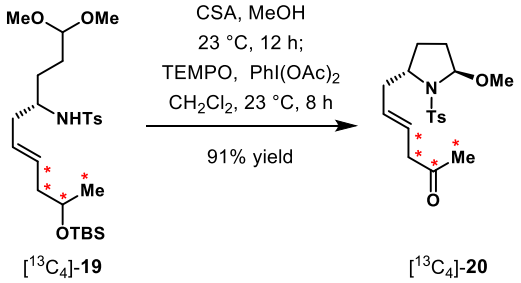


Tosyl amine [$^{13}C_4$]-19. A solution of acid [$^{13}C_4$]-**11** (0.48 g, 1.27 mmol) diphenyl phosphoryl azide (0.41 mL, 1.9 mmol, 1.5 equiv.), and *i*-Pr_2NEt (0.44 mL, 2.54 mmol, 2 equiv.) in benzene (12.7 mL) was heated at reflux for 3 h with a drying tube attached. Then the reaction mixture was cooled to 23 °C and a solution of Me_3SiONa (0.64 g, 5.7 mmol, 4.5 equiv.) in THF (6.4 mL) was added in one portion. The mixture was stirred for 20 min, then diluted with EtOAc (20 mL) and quenched with water (20 mL). The product was extracted with EtOAc (3 × 20 ml), the combined organic layers were washed with 3M aqueous NaOH (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude amine [$^{13}C_4$]-**S7** was dissolved in CH_2Cl_2 (12.7 mL), then *i*-Pr_2NEt (0.44 mL, 2.54 mmol, 2 equiv.) and *p*-toluenesulfonyl chloride (0.31 g, 1.65 mmol, 1.3 equiv.) were added sequentially to the mixture. After complete disappearance of [$^{13}C_4$]-**S7** was observed by TLC (1 h), the mixture was concentrated under reduced pressure, and the residue directly subjected to column chromatography on silica gel (15% EtOAc in hexanes to 35% EtOAc in hexanes) to produce [$^{13}C_4$]-**19** (0.53 g, 1.05 mmol, 83% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers): δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 4H), 5.33 (dm, *J* = 151.8 Hz, 1H), 5.20 – 5.07 (m, 1H), 4.66 – 4.56 (m, 1H), 4.23 (t, *J* = 5.1 Hz, 1H), 3.74 (dm, *J* = 139.9 Hz, 1H), 3.25 (s, 6H), 3.24 – 3.17 (m, 1H), 2.41 (s, 3H), 2.01 (dm, *J* = 125.9 Hz, 2H), 2.08 – 1.06 (m, 2H), 1.58 – 1.46 (m, 3H), 1.43 – 1.34 (m, 2H), 1.06 (dm, *J* = 125.4 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, mixture of diastereomers): δ 143.3, 131.8 (dd, *J* = 43.4, 10.9 Hz), 129.7 (d, *J* = 1.0 Hz), 127.2, 104.4, 68.6 (td, *J* = 39.1, 1.8 Hz), 68.4 (td, J = 39.1, 1.8 Hz), 53.6, 53.1, 53.0, 43.0 (ddd, *J* = 43.4, 38.5, 9.6 Hz), 38.17, 29.4, 28.6, 26.0, 23.5 (ddd, *J* = 39.8, 9.4, 1.1 Hz), 21.6, 18.3, -4.4, -4.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{21}{}^{13}C_4H_{45}NO_5SSiNa$, 526.2820; found, 526.2827.

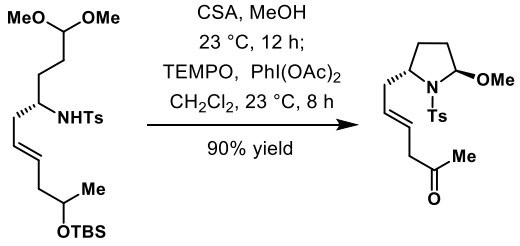


Tosyl amine 19. The title compound was prepared according to the procedure described above for its $^{13}C_4$ analog, using acid **11** (1.5 g, 4.0 mmol) with the following reagents in the indicated quantities: diphenyl phosphoryl azide (1.3 mL, 6.0 mmol, 1.5 equiv.), *i*-Pr_2NEt (1.4 mL, 8.0 mmol, 2 equiv.) in benzene (40 mL), then Me_3SiONa (2.0 g, 18 mmol, 4.5 equiv.) in THF (20 mL) for the first step; crude amine **S7** was treated with *i*-Pr_2NEt (1.4 mL, 8.0 mmol, 2 equiv.) and *p*-toluenesulfonyl chloride (1.0 g, 5.2 mmol, 1.3 equiv.) in 40 mL of CH_2Cl_2 (40 mL). **19** was isolated in 80% yield (1.6 g, 3.20 mmol). ^{1}H NMR (500 MHz, $CDCl_3$), mixture of diastereomers: δ 7.74 (d, *J* = 8.3 Hz, 4H), 7.29 (d, *J* = 8.1 Hz, 4H), 5.41 – 5.30 (m, 2H), 5.20 – 5.08 (m, 2H), 4.49 (d, *J* = 8.0 Hz, 1H), 4.45 (d, J = 7.8 Hz, 1H), 4.27 – 4.23 (m, 2H), 3.80 – 3.72 (m, 2H), 3.28 – 3.26 (s, 12H), 3.25 – 3.18 (m, 2H), 2.42 (s, 6H), 2.11 – 1.96 (m, 8H), 1.56 – 1.45 (m, 6H), 1.45 – 1.35 (m, 2H), 1.09 (d, *J* = 2.4 Hz, 3H), 1.07 (d, *J* = 2.4 Hz, 3H), 0.87 (s, 18H), 0.03 (s, 6H), 0.02 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers): δ 143.34, 131.92, 129.74, 127.27, 126.69, 104.42, 68.44, 53.58, 53.14, 53.10, 43.07, 38.18, 29.48, 28.67, 26.02, 23.56, 21.65, 18.30, -4.37, -4.57. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{25}H_{45}NO_5SSiNa$, 522.2685; found, 522.2682.



***N*-Tosylpyrrolidine [$^{13}C_4$]-20.** (±)-10-Camphorsulfonic acid (10 mg, 0.04 mmol, 0.05 equiv.) was added to a solution of tosyl amine [$^{13}C_4$]-**19** (0.450 g, 0.89 mmol) in MeOH (8.9 mL) at 23 ˚C and

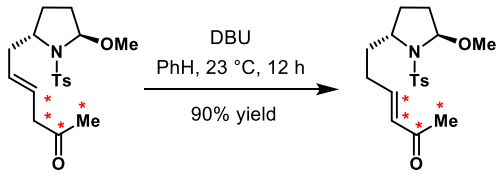
the reaction was left to stir overnight. The solvent was evaporated under reduced pressure and the dry residue was dissolved in CH_2Cl_2 (8.9 mL). TEMPO (42 mg, 0.27 mmol, 0.3 equiv.) and $PhI(OAc)_2$ (0.58 g, 1.79 mmol, 2 equiv.) were then added and the mixture was stirred at 23 °C for 8 h. The solvent was removed under reduced pressure and the residue was directly purified by column chromatography on silica gel (25% EtOAc in hexanes to 35% EtOAc in hexanes) to give [$^{13}C_4$]-**19** (0.290 g, 0.81 mmol, 91% yield) as a pale yellow oil. $[\alpha]_D^{21}$ –79.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 5.63 (dm, *J* = 126.5 Hz, 1H), 5.55 – 5.41 (m, 1H), 5.02 (d, *J* = 5.0 Hz, 1H), 3.56 – 3.46 (m, 1H), 3.41 (s, 3H), 3.12 (ddd, *J* = 126.4, 12.8, 6.4 Hz, 2H), 2.69 – 2.61 (m, 1H), 2.41 (s, 3H), 2.40 – 2.33 (m, 1H), 2.14 (ddd, *J* = 127.3, 5.8, 0.9 Hz, 3H), 1.82 – 1.69 (m, 3H), 1.15 – 1.02 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 207.2 (t, *J* = 39.8 Hz), 143.7, 135.8, 130.3, 129.8, 127.4, 125.0 (dd, *J* = 43.3, 2.9 Hz), 92.8, 60.5, 54.8, 47.7 (ddd, *J* = 43.3, 38.8, 14.4 Hz), 40.1 (d, *J* = 39.8 Hz), 32.1, 29.4 (dd, *J* = 14.4, 40.8 Hz), 29.0, 21.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $^{13}C_4C_{14}H_{25}NO_4SNa$, 378.1536; found, 378.1548.



19 **20**

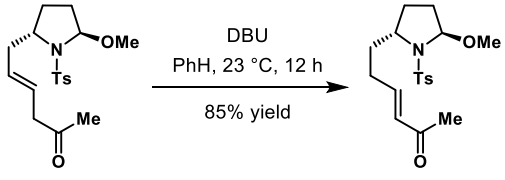
***N*-Tosylpyrrolidine 20.** The title compound was prepared according to the procedure described above for its $^{13}C_4$ analog using tosyl amine **19** (1.10 g, 2.20 mmol) and (±)-10-camphorsulfonic acid (25.6 mg, 0.11 mmol, 0.05 equiv.) in methanol (4.4 mL), followed by treatment with TEMPO (103 mg, 0.66 mmol, 0.3 equiv.) and $PhI(OAc)_2$ (1.42 g, 4.40 mmol, 2 equiv.) CH_2Cl_2 (22 mL). *N*-tosylpyrrolidine **20** was isolated in 90% yield (0.70 g, 1.98 mmol). $[\alpha]_D^{21}$ –81.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 1H), 5.66 – 5.58 (m, 1H), 5.55 – 5.48 (m, 1H), 5.03 (d, *J* = 5.0 Hz, 1H), 3.56 – 3.48 (m, 1H), 3.41 (s, 3H), 3.12 (d, *J* = 6.8 Hz, 2H), 2.69 – 2.62 (m, 1H), 2.43 (s, 3H), 2.42 – 2.35 (m, 1H), 2.15 (s, 3H), 1.82 – 1.72 (m, 3H), 1.15 – 1.04 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 207.2, 143.7, 135.7, 130.5, 129.8, 127.3,

125.1, 92.8, 60.5, 54.8, 47.7, 40.0, 32.1, 29.5, 29.0, 21.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{25}NO_4SNa$, 374.1402; found, 374.1402.



$[^{13}C_4]$-**20** $[^{13}C_4]$-**10**

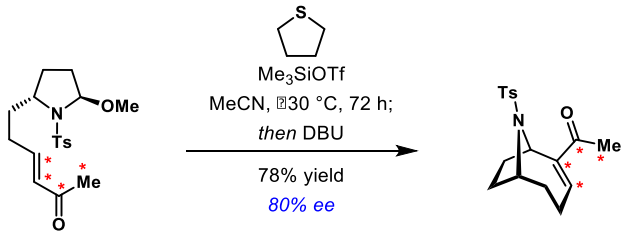
Vinyl ketone $[^{13}C_4]$-10. DBU (0.63 mL, 4.2 mmol, 5.0 equiv.) was added to a solution of *N*-tosylpyrrolidine $[^{13}C_4]$-**20** (0.300 g, 0.84 mmol) in benzene (8.4 mL) at 23 °C. The resulting solution was stirred at 23 ˚C for 12 h, then it was diluted with EtOAc (35 mL) and washed with saturated aqueous NH_4Cl (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (35% EtOAc in hexanes to 50% EtOAc in hexanes) to give $[^{13}C_4]$-**10** (0.270 g, 0.76 mmol, 90% yield) as a pale yellow oil. $[\alpha]_D^{21}$ –93.2 (*c* 1.0, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.82 (ddt, *J* = 152.6, 15.9, 6.5 Hz, 1H), 6.09 (dd, *J* = 157.4, 16.0 Hz, 1H), 5.04 (d, *J* = 5.1 Hz, 1H), 3.54 – 3.46 (m, 1H), 3.42 (s, 3H), 2.43 (s, 3H), 2.26 (dd, *J* = 127.3, 5.8, 3H), 2.35 – 2.20 (m, 2H), 2.11 – 2.03 (m, 1H), 1.85 – 1.68 (m, 4H), 1.18 – 1.06 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 198.7 (dd, *J* = 53.2, 42.1 Hz), 147.6 (dd, *J* = 67.9, 1.2 Hz), 143.8, 135.7, 131.6 (ddd, *J* = 67.9, 53.1, 14.7), 129.9, 127.4, 92.9, 60.4, 55.0, 35.3, 32.2, 28.5 (dd, *J* = 41.4, 5.7 Hz), 26.9 (dd, *J* = 42.1, 14.7), 27.0 (dd, *J* = 14.7, 42.1 Hz), 21.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $^{13}C_4C_{14}H_{25}NO_4SNa$, 378.1536; found, 378.1529.



20 **10**

Vinyl ketone 10. The title compound was prepared according to the procedure described above for its $^{13}C_4$ analog with *N*-tosylpyrrolidine **10** (0.400 g, 1.14 mmol) and DBU (0.85 mL, 5.69 mmol, 5 equiv.) in benzene (11.4 mL). Vinyl ketone **10** was isolated in 85% yield (0.340 g, 0.97

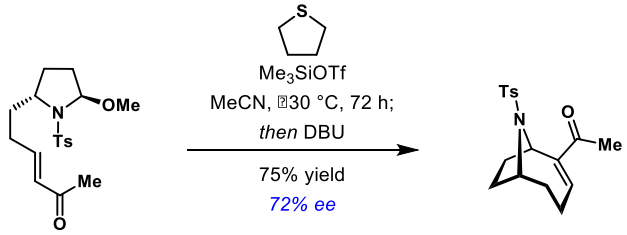
mmol). $[\alpha]_D^{21}$ –95.1 (*c* 1.0, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (d, *J* = 9.1 Hz, 2H), 7.29 (d, *J* = 9.4 Hz, 2H), 6.82 (dt, *J* = 16.0, 6.8 Hz, 1H), 6.08 (d, *J* = 16.0 Hz, 1H), 5.02 (d, *J* = 5.1 Hz, 1H), 3.54 – 3.44 (m, 1H), 3.41 (s, 3H), 2.41 (s, 3H), 2.37 – 2.27 (m, 1H), 2.27 – 2.18 (m, 4H), 2.12 – 2.03 (m, 1H), 1.84 – 1.67 (m, 4H), 1.16 – 1.05 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 198.7, 147.7, 143.9, 135.7, 131.7, 129.9, 127.4, 92.9, 60.4, 55.0, 35.3, 32.2, 29.4, 28.6, 27.0, 21.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{25}NO_4SNa$, 374.1402; found, 374.1398.



[$^{13}C_4$]-**10** [$^{13}C_4$]-**21**

***N*-Tosylanatoxin-a [$^{13}C_4$]-21.** Me_3SiOTf (0.65 mL, 3.58 mmol, 2.5 equiv.) was added to a solution of vinyl ketone [$^{13}C_4$]-**10** (0.510 g, 1.43 mmol) and tetrahydrothiophene (0.19 mL, 2.15 mmol, 1.5 equiv.) in MeCN (14.3 mL) at –30 °C. The resulting mixture was stirred at –30°C for 72 h, then quenched with DBU (0.43 mL, 2.87 mmol, 2 equiv.) and stirred at 23°C for 30 min. The solution was diluted with EtOAc (40 mL), washed with saturated aqueous NH_4Cl (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel (35% EtOAc in hexanes) to give [$^{13}C_4$]-**10** (0.360 g, 1.11 mmol, 78% yield) as a white solid. ee: 80% [Chiralpak ® AD-H; 10% i-PrOH- Hexanes; flow rate = 1 mL/ min; detection at 254 nm; t_1 = 16.6 min. (minor), t_2 = 23.4 min. (major)]. This material can be recrystallized from *i*-PrOH/Hexanes mixture to produce material with ee = 98% (0.240 g, 67% yield, 52% overall yield). $[\alpha]_D^{18}$ –14.6 (*c* 0.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 6.86 (ddd, *J* = 152.6, 12.5, 6.4 Hz, 1H), 5.24 – 5.16 (m, 1H), 4.46 – 4.40 (m, 1H), 2.70 – 2.59 (m, 1H), 2.39 (s, 3H), 2.25 (dd, *J* = 127.7, 5.8 Hz, 3H), 2.39 – 2.31 (m, 1H), 2.20 – 2.13 (m, 1H), 1.77 – 1.58 (m, 3H), 1.55 – 1.43 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 197.36 (ddd, *J* = 50.4, 43.3, 4.1 Hz), 147.3 (ddd, *J* = 69.6, 50.5, 12.2 Hz), 143.5 (dd, *J* = 69.6, 3.7 Hz), 143.4, 137.2, 129.7, 126.8, 58.9,

56.1, 33.3, 31.9, 29.6, 25.3 (dd, *J* = 43.3, 12.2 Hz), 24.3 (dd, *J* = 40.0, 5.6 Hz), 21.5. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $^{13}C_4C_{13}H_{21}NO_3SNa$, 346.1274; found, 346.1276.



10 **21**

***N*-Tosylanatoxin-a 21.** The title compound was prepared according to the procedure described above for its $^{13}C_4$ with vinyl ketone **21** (0.260 g, 0.74 mmol), Me_3SiOTf (0.34 mL, 1.85 mmol, 2.5 equiv.), tetrahydrothiophene (98 µL, 1.11 mmol, 1.5 equiv.), DBU (0.22 Ml (1.48 mmol, 2 equiv.) in MeCN (7.4mL). *N*-Tosylanatoxin-a **21** was isolated in 75% yield (0.177 g, 0.55 mmol).). The enantiopurity of the product was determined to be 72% ee using the same HPLC conditions as those described for its $^{13}C_4$ analog with identical retention times. $[\alpha]_D^{20}$ –13.9 (*c* 0.8, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 6.86 (t, *J* = 5.8 Hz, 1H), 5.21 (d, *J* = 8.7 Hz, 1H), 4.46 – 4.40 (m, 1H), 2.71 – 2.61 (m, 1H), 2.44 – 2.32 (m, 4H), 2.26 (s, 3H), 2.22 – 2.12 (m, 1H), 1.80 – 1.60 (m, 3H), 1.57 – 1.44 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 197.6, 147.5, 143.4, 143.3, 137.4, 129.8, 127.1, 59.0, 56.5, 33.7, 32.1, 29.9, 25.5, 24.5, 21.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{21}NO_3SNa$, 342.1140; found, 342.1136.

==== Shimadzu LCsolution Analysis Report ====

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Sample Name	: AKM-09-234
Sample ID	: AKM-09-234
Vail #	:
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Method File Name	: brad.lcm
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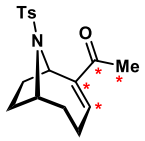

(±)-[$^{13}C_4$]-**21**

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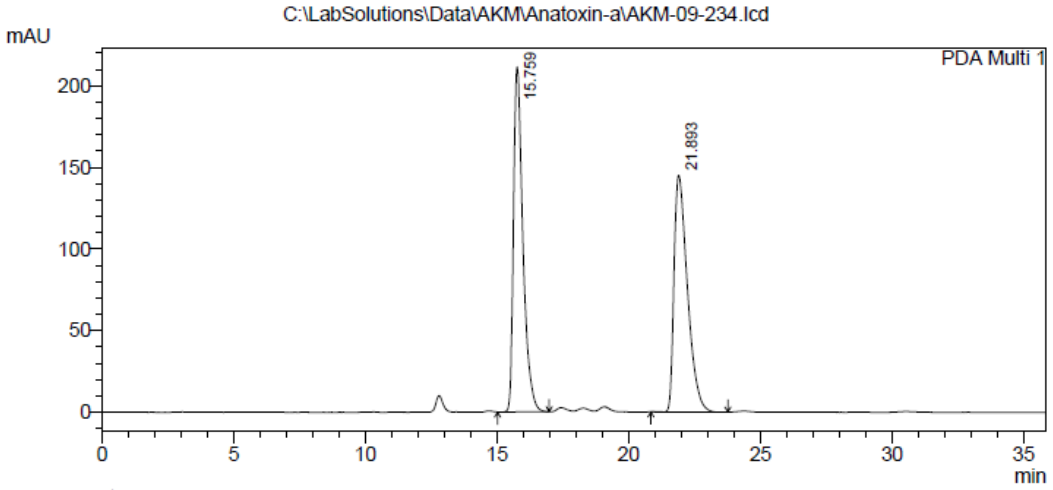

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

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2	21.893	5128905	144968	49.399	40.679
Total		10382640	356373	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

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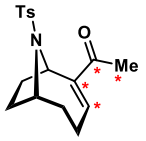

[$^{13}C_4$]-**21**

80% ee

<Chromatogram>

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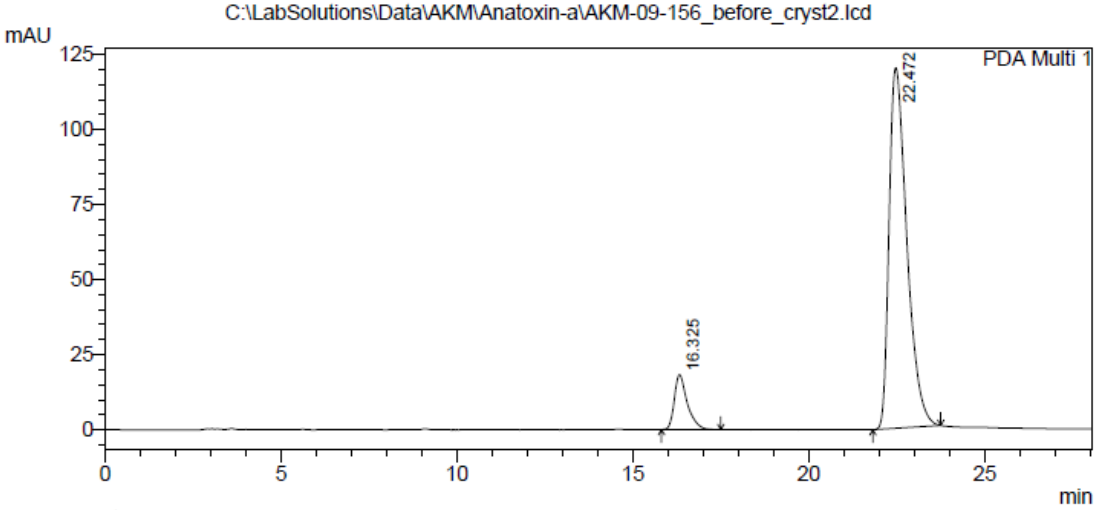

1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

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2	22.472	4214128	120103	89.969	86.772
Total		4683991	138412	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

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Sample Name	: AKM-09-156_after_cryst2
Sample ID	: AKM-09-156_after_cryst2
Vail #	:
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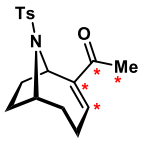
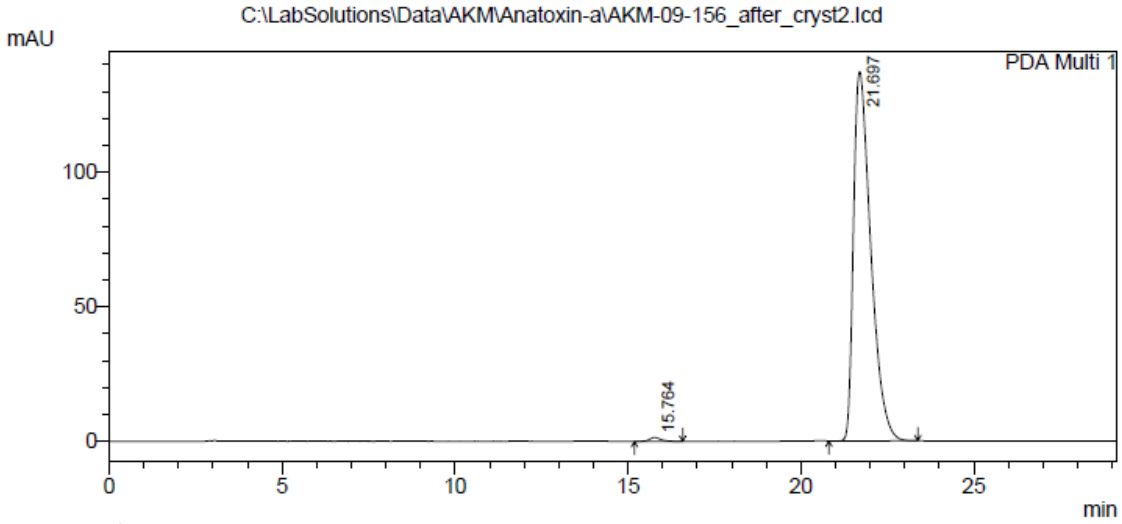


[$^{13}C_4$]-**21**

98% ee

<Chromatogram>



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

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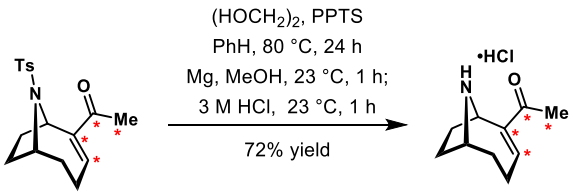
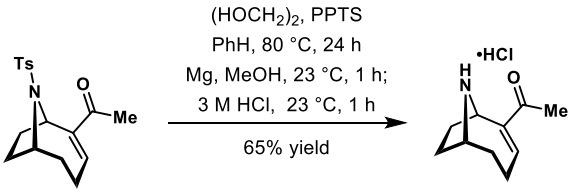


[$^{13}C_4$]-**21** [$^{13}C_4$]-**1•HCl**

(–)-[$^{13}C_4$]-Anatoxin-a [$^{13}C_4$]-1•HCl. A mixture of *N*-tosylanatoxin-a [$^{13}C_4$]-**21** (0.240 g, 0.74 mmol), ethylene glycol (0.42 mL, 7.42 mmol, 10 equiv.) and pyridinium *p*-toluenesulfonate (19 mg, 0.074 mmol) in benzene (10 mL) was heated to reflux with a Dean-Stark apparatus for 24 h. The reaction mixture was cooled to 23 °C and the solvent was evaporated under reduced pressure. The crude acetal was taken up in MeOH (15 mL), magnesium (0.530 g, 22.2 mmol, 30 equiv.) was added, and the resulting suspension was sonicated at 23 °C for 1 h. The reaction was quenched with 3 M hydrochloric acid (20 mL) and stirred for 1 h at 23 °C. Solid K_2CO_3 was carefully added to the reaction mixture until pH ~12 and the mixture was filtered through celite to remove the inorganic precipitate. The product was extracted with CH_2Cl_2 (4 × 20 ml), the combined organic phase was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude product was purified by reversed-phase column chromatography on C18 reversed-phase silica gel (1% MeOH, 0.1% TFA in water to 3% MeOH, 0.3% TFA in water) followed by the treatment with a 1 M HCl solution in MeOH to produce the title compound (0.110 g, 0.53 mmol, 72% yield) as a white solid upon precipitation from dry diethyl ether. $[\alpha]_D^{21}$ +41.3 (*c* 1.0, MeOH). ^{1}H NMR (600 MHz, CD_3OD): δ 7.40 (dm, *J* = 157.4 Hz, 1H), 5.16 – 5.06 (m, 1H), 4.32 – 4.23 (m, 1H), 2.79 – 2.68 (m, 1H), 2.67 – 2.58 (m, 1H), 2.48 – 2.39 (m, 1H), 2.35 (dd, *J* = 128.0, 6.0 Hz, 3H), 2.30 – 2.20 (m, 1H), 2.19 – 2.11 (m, 1H), 2.05 – 1.89 (m, 3H). ^{13}C NMR (151 MHz, CD_3OD): δ 198.4 (ddd, *J* = 51.2, 44.0, 3.8), 149.5 (d, *J* = 68.2 Hz), 144.7 (ddd, *J* = 68.1, 51.3, 13.0), 60.6 (d, *J* = 11.8 Hz), 53.7 (dd, *J* = 46.6, 15.8 Hz), 31.2, 29.0, 28.3, 25.42 (ddd, *J* = 44.0, 13.0, 5.4 Hz), 24.5 (dd, *J* = 39.0, 5.6 Hz). HRMS-ESI (m/z): $[M+H]^+$ calcd for $^{13}C_4C_6H_{16}NO$, 170.1366; found, 170.1365.

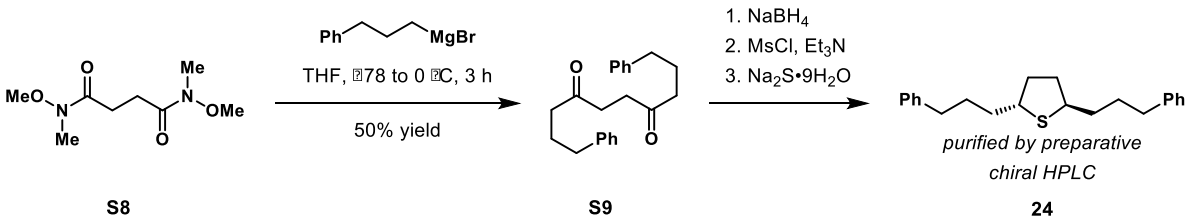


21 **1•HCl**

Anatoxin-a 1•HCl. The title compound was prepared according to the procedure described above for its $^{13}C_4$ analog with *N*-tosylanatoxin-a **21** (130 mg, 0.41 mmol), ethylene glycol (0.23 mL, 4.1 mmol, 10 equiv.), and pyridinium *p*-toluenesulfonate (10.3 mg, 0.041 mmol) in benzene (4.1 mL). The crude acetal was then treated with magnesium (0.295 g, 12.3 mmol, 30 equiv.) and sonicated in methanol (7 mL). Anatoxin-a **1•HCl** was obtained in 65% yield (54 mg, 0.27 mmol). $[\alpha]_D^{21}$ +39.1 (*c* 1.0, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ 7.39 (dd, *J* = 8.6, 2.7 Hz, 1H), 5.10 (d, *J* = 9.3 Hz, 1H), 4.30 – 4.24 (m, 1H), 2.78 – 2.68 (m, 1H), 2.68 – 2.58 (m, 1H), 2.49 – 2.39 (m, 1H), 2.35 (s, 3H), 2.30 – 2.20 (m, 1H), 2.19 – 2.09 (m, 1H), 2.06 – 1.91 (m, 3H). ^{13}C NMR (125.6 MHz, CD_3OD): δ 198.5, 149.5, 144.7, 60.6, 53.7, 31.2, 29.0, 28.3, 25.5, 24.6. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{10}H_{16}NO$, 166.1232; found, 166.1228.

Preparation of Chiral Sulfides for enantioselective MBH Cyclization:

Chiral sulfide **22** is commercially available and was purchased from TCI America. Sulfides **23**[4] and **25**[5] have been prepared previously. All other sulfides were synthesized according to the procedures outlined below. The absolute stereochemistry of thiolanes **24**, **26**, **27**, **28**, and **29** was not determined. In all cases, the enantiomer which eluted first during preparative chiral HPLC purification was used in the enantioselective MBH cyclization. Chiral sulfide **25** is known to have a positive optical rotation and gave the non-natural enantiomer of *N*-tosyl anatoxin-a (*ent*-**21**). Sulfides **24** and **26** also had positive optical rotations and favored the formation of *ent*-**21**, so their structures were tentatively drawn with a (2*S*,5*S*) configuration based on correlation to **25**. Thiolanes **27**, **28**, and **29** all had negative optical rotations and favored the formation of **21** over *ent*-**21**, so their structures were tentatively drawn with a (2*R*,5*R*) configuration.



S8 **S9** **24**

Thiolane 24. A solution of 3-phenylpropylmagnesium bromide (0.91 M in THF, 8.1 mL, 7.35 mmol, 3.0 equiv.) was added dropwise to a solution of **S8**[6] (0.500 g, 2.45 mmol) in THF (12.3 mL) at –30 °C. The solution was warmed to 0 °C and stirred at this temperature for 3 h. The mixture was then quenched with saturated aqueous NH_4Cl (25 mL), the layers separated, and the aqueous layer extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (60 mL), dried over $NaSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10% EtOAc in hexanes) to deliver **S9** (0.396 g, 1.23 mmol, 50% yield). Spectral data matched that reported in the literature.[7]

Sodium borohydride (93 mg, 2.46 mmol, 2.0 equiv.) was added portion-wise to a solution of **S9** in MeOH (8.2 mL) and THF (4.1 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 30 min., at which point it was concentrated under reduced pressure. The residue was taken up in EtOAc (50 mL), washed with 1 M HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), dried over $NaSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (50% EtOAc in hexanes). The resulting diol (0.391 g, 1.20 mmol, 97% yield) was submitted to the next step.

Methanesulfonyl chloride (0.28 mL, 3.58 mmol, 3.0 equiv.) was added dropwise to a solution of the diol from the previous step (0.391 g, 1.20 mmol) and trimethylamine (0.67 mL, 3.58 mmol, 4 equiv.) in CH_2Cl_2 (2.5 mL) at –10 °C. The mixture was warmed to room temperature and stirred for 2 h. The mixture was diluted with additional CH_2Cl_2 (30 mL) and washed sequentially with 1 M HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), dried over $NaSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20% EtOAc in hexanes to 25% EtOAc in hexanes to 30%

EtOAc in hexanes to 40% EtOAc in hexanes). The corresponding bismesylate was isolated in 84% yield (0.480 g, 0.994 mmol) as a clear oil and submitted to the next step.

A solution of the bismesylate from the previous step (0.467 g, 0.969 mmol) was dissolved in DMF (49 mL). $Na_2S \bullet 9H_2O$ (1.16 g, 4.84 mmol, 5.0 equiv.) was then added and the mixture was stirred at room temperature for 15 h. The mixture was then diluted with water (300 mL) and extracted with EtOAc (4 x 75 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over $NaSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2% EtOAc in hexanes) to give an impure 1:1 mixture of *cis*- to *trans*-(±)-**24** (~0.234 g, 0.722 mmol, 75% yield). A portion of this mixture (95 mg, 0.294 mmol) was purified through preparative chiral HPLC [Chiralpak ® AD-H; 250 x 20 mm i.d.; 0.25% *i*-PrOH- Hexanes; flow rate = 6 mL/ min; 3 mL injections of a 10 mg/ mL solution; detection at 210 nm; t_1 = 9.95 min. (*cis*-**24**), t_2 = 12.49 min. (**24**), t_3 = 15.85 min. (*ent*-**24**)]. Following preparative HPLC, **24** was isolated in 21% yield (20 mg, 0.0620 mmol, 99% ee) along with *ent*-**24** in 22% yield (21 mg, 0.0650 mmol, 98% ee), both as colorless oils.

Thiolane 24: $[\alpha]_D^{24}$ +100.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (t, *J* = 7.8 Hz, 4H), 7.21 – 7.15 (m, 6H), 3.41 (tt, *J* = 8.4, 4.9 Hz, 2H), 2.63 (t, *J* = 6.7Hz, 4H), 2.17 (qd, *J* = 6.4, 3.7 Hz, 2H), 1.77 – 1.64 (m, 6H), 1.57 (tt, *J* =10.6, 4.9 Hz, 2H), 1.51 (t, *J* = 8.3 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 142.4, 128.5, 128.4, 125.8, 49.6, 37.4, 37.4, 35.9, 31.0. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{22}H_{29}S$, 325.1990; found, 325.1987.

==== Shimadzu LCsolution Analysis Report ====

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Vail #	:
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Method File Name	: JakeADHPrep.lcm
Batch File Name	:
Report File Name	: Default.lcr
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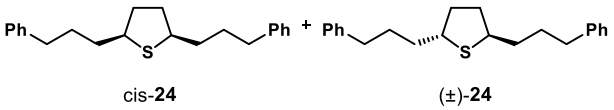
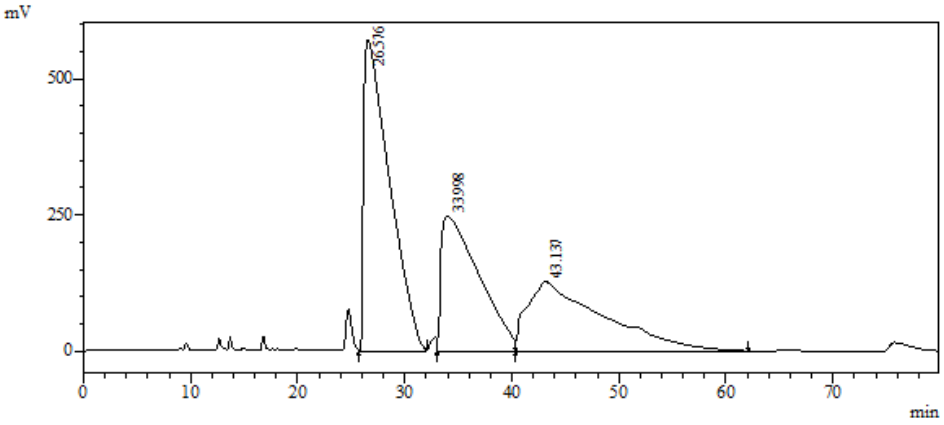


cis-**24** (±)-**24**

<Chromatogram>



1 Det.A Ch1 / 254nm
2 Det.A Ch2 / 210nm

PeakTable

Detector A Ch2 210nm

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Total		220329544	947282	100.000	100.000

*Thiolanes **24** and *ent*-**24** overlap slightly during preparative HPLC separation, so they were collected in fractions. The fraction containing thiolane **24** was analyzed to determine its enantiopurity, as shown below.

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Project1\kyc3-113a.lcd

Acquired by	: Karen Chen
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Sample ID	: kyc3-113a
Vail #	:
Injection Volume	: 10 uL
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Method File Name	: brad.lcm
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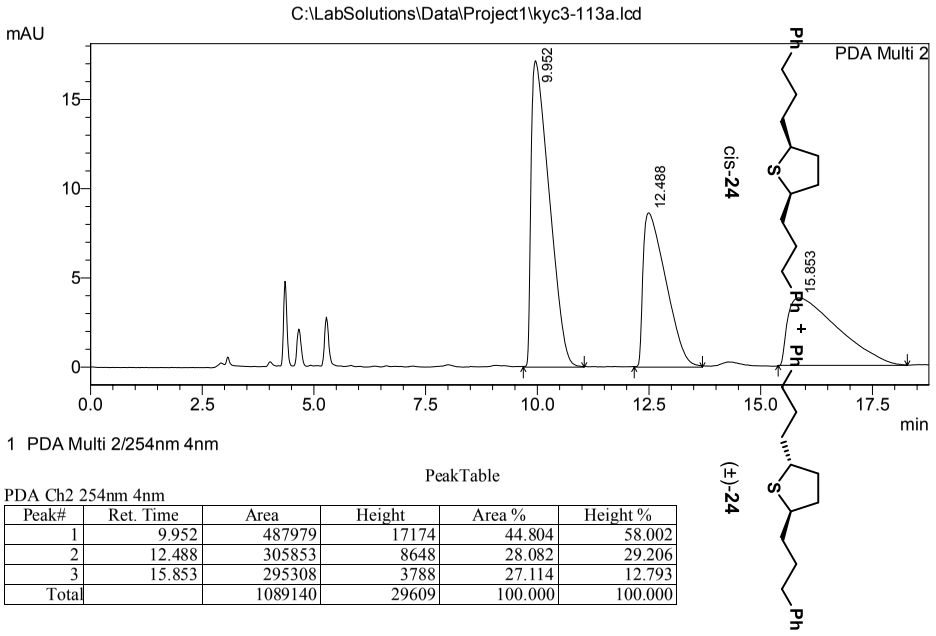

1 PDA Multi 2/254nm 4nm

PeakTable

PDA Ch2 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.952	487979	17174	44.804	58.002
2	12.488	305853	8648	28.082	29.206
3	15.853	295308	3788	27.114	12.793
Total		1089140	29609	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

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Acquired by	: Karen Chen
Sample Name	: kyc3-113a-fB
Sample ID	: kyc3-113a-fB
Vail #	:
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Method File Name	: brad.lcm
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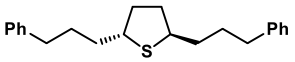
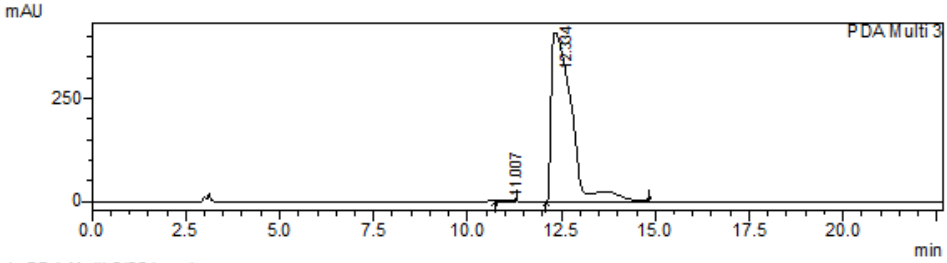


24

<Chromatogram>



1 PDA Multi 2/254nm 4nm
2 PDA Multi 3/210nm 4nm

PeakTable

PDA Ch3 210nm 4nm

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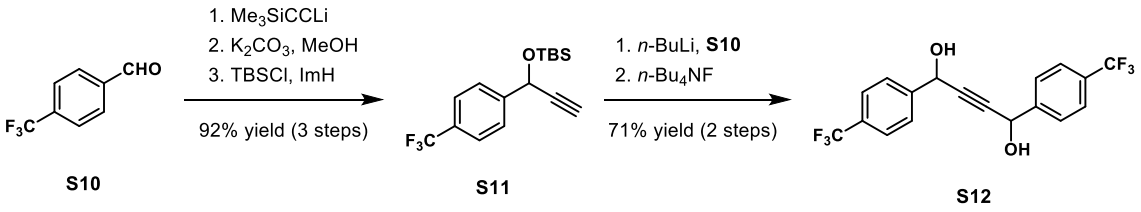
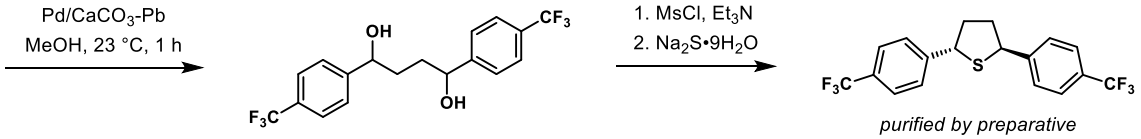


S10 **S11** **S12**



S13 *purified by preparative chiral HPLC* **26**

Thiolane 26. *n*-Butyllithium (2.55 M in hexanes, 7.8 mL, 20.0 mmol, 2.00 equiv.) was added dropwise to a solution of trimethylsilyl acetylene (2.16 g, 22.0 mmol, 2.20 equiv.) in THF (40 mL) at –78 °C. After 30 min, a solution of 4-(trifluoromethyl)benzaldehyde **S10** (1.74 g, 10.0 mmol)

in THF (10 mL) was added dropwise. The solution was warmed to 0 °C and stirred at this temperature for 30 min. The mixture was then quenched with saturated aqueous NH_4Cl (75 mL), the layers separated, and the aqueous layer extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (200 mL), dried over $NaSO_4$, and concentrated under reduced pressure, and the crude residue submitted to the next step without further purification.

The crude product from the previous reaction was taken up in MeOH (100 mL) and potassium carbonate was added (1.66 g, 12.0 mmol, 1.20 equiv.) The mixture was stirred for 45 min. and then concentrated under reduce pressure. The residue was diluted with EtOAc (75 mL) and water (100 mL) and the layers separated. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (200 mL), dried over $NaSO_4$, and concentrated under reduced pressure, and the crude residue submitted to the next step without further purification.

The crude product from the previous reaction was taken up in CH_2Cl_2 (100 mL). Imidazole (1.63 g, 24.0 mmol, 2.40 equiv.) and TBSCl (1.81 g, 12.0 mmol, 1.2 equiv.) were added sequentially and the mixture was stirred at room temperature overnight. The reaction was quenched with water (100 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL), the combined organic extracts were dried over $NaSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20% EtOAc in hexanes) to give **S11** (2.91 g, 9.25 mmol, 92% yield) which was used in the next step.

n-Butyllithium (2.55 M in hexanes, 2.16 mL, 5.50 mmol, 1.10 equiv.) was added dropwise to a solution of **S11** (1.57 g, 5.00 mmol) in THF (25 mL) at −78 °C. After 30 min, a solution of 4-(trifluoromethyl)benzaldehyde **S10** (1.31 g, 7.50 mmol, 1.50 equiv.) in THF (10 mL) was added dropwise. The solution was warmed to 0 °C and stirred at this temperature for 30 min. The mixture was then quenched with saturated aqueous NH_4Cl (75 mL), the layers separated, and the aqueous layer extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (200 mL), dried over $NaSO_4$, and concentrated under reduced pressure, and the crude residue submitted to the next step without further purification.

A solution of *n*-$Bu_4NF \bullet xH_2O$ (1.57 g, 6.00 mmol, 1.20 equiv.) in THF (5 mL) was added to a solution of the crude product from the previous step and acetic acid (0.43 mL, 7.50 mmol, 1.50 equiv.) in THF (20 mL) and the mixture was stirred at room temperature for 6 h. The mixture was then quenched with saturated aqueous $NaHCO_3$ (50 mL), diluted with EtOAc (30 mL), and the layers separated. The aqueous layer extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (200 mL) and dried over $NaSO_4$. Silica (~5.0 g) was added to the filtrate which was then carefully concentrated under reduced pressure and dry-loaded onto a silica gel column. The product was purified by column chromatography on silica gel (25% EtOAc in hexanes to 50% EtOAc in hexanes) to give diol **S12** (1.33 g, 3.56 mmol) which was submitted to the next step.

A solution of diol **S12** (1.24 g, 3.40 mmol) and palladium on calcium carbonate, poisoned with lead (5 wt % Pd, 0.793 g, 0.340 mmol, 10 mol %) in MeOH (34 mL) was stirred under an atmosphere of hydrogen gas for 24 h. The mixture was filtered through celite, concentrated under reduced pressure, and submitted to the next step without further purification.

Methanesulfonyl chloride (0.80 mL, 10.2 mmol, 3.0 equiv.) was added dropwise to a solution of the diol from the previous step and trimethylamine (1.90 mL, 13.6 mmol, 4.0 equiv.) in CH_2Cl_2 (34 mL) at 0 °C and stirred at this temperature for 1 h. The mixture was diluted with additional CH_2Cl_2 (50 mL) and washed sequentially with 1 M HCl (75 mL), saturated aqueous $NaHCO_3$ (75 mL), and brine (75 mL), dried over $NaSO_4$, and concentrated under reduced pressure. The crude bismesylate was submitted to the next step without further purification.

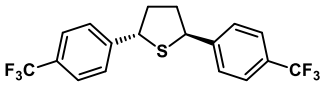
A solution of the bismesylate from the previous step was dissolved in DMF (68 mL) and sparged with argon for 10 min. $Na_2S \bullet 9H_2O$ (4.08 g, 17.0 mmol, 5.0 equiv.) was then added and the reaction was stirred at room temperature for 2 h. The mixture was then diluted with water (500 mL) and extracted with EtOAc (4 x 100 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over $NaSO_4$, and concentrated under reduced pressure. The crude residue (1.4:1 (±)-*trans*- to *cis*-**26**) was purified by column chromatography on silica gel (8% PhMe in hexanes to 10 % PhMe in hexanes to 12 % PhMe in hexanes) to give (±)-*trans*-**26** (0.548 g, 1.46 mmol, 42% yield) which eluted first, followed by a 10:1 mixture of *cis*-**26** (0.439 g, 1.17 mmol, 34% yield) and (±)-*trans*-**26** (44 mg, 0.117 mmol, 3.4% yield). A portion of (±)-*trans*-

26 (0.300 g, 0.797 mmol) collected after chromatography was purified through preparative chiral HPLC [Chiralpak ® AD-H; 250 x 20 mm i.d.; 0.5% *i*-PrOH- Hexanes; flow rate = 6 mL/ min; 3 mL injections of a 10 mg/ mL solution; detection at 210 nm; t_1 = 20.33 min. (**26**), t_2 = 24.96 min. (*ent*-**26**)]. Following preparative HPLC, 0.130 g (0.345 mmol, 43% yield) of both **26** and *ent*-**26** were isolated as enantiopure, crystalline, white solids.

Thiolane 26: $[\alpha]_D^{22}$ +8.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (s, 8H), 4.90 (t, *J* = 7.3 Hz, 2H), 2.64 (qd, *J* = 9.1, 5.6 Hz, 2H), 2.13 (p, *J* = 11.6 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 146.4, 129.7 (q, *J* = 32.5 Hz), 128.2, 125.7 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 272.0 Hz), 54.0, 41.2. HRMS-ESI (m/z): $[M+C_2H_5]^+$ calcd for $C_{20}H_{19}F_6S$, 405.1112; found, 405.1107.

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>



(±)-**26**

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Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 1500 uL		
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Date Processed	: 11/16/2019 2:24:28 PM	Processed by	: Jacob Lacharity

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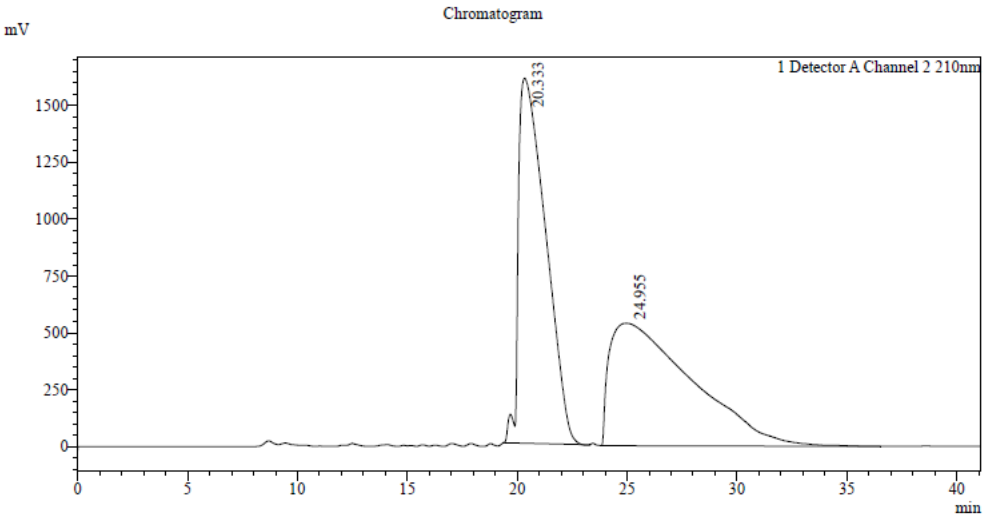

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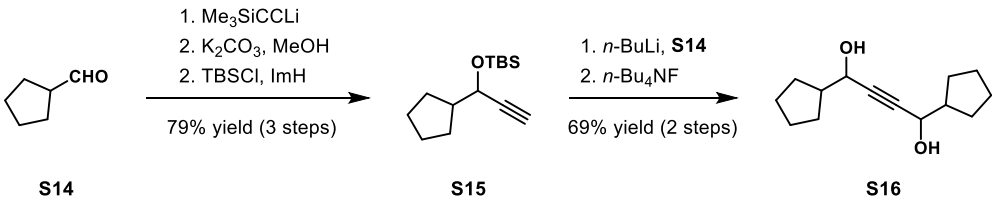
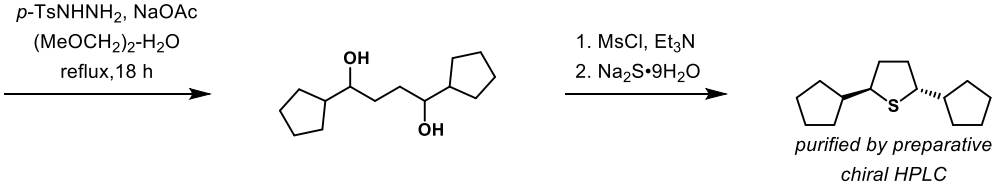


S14 **S15** **S16**



S17 **27**

Thiolane 27. The title compound was prepared from **S14** according to the procedures described above for **26** on the same scale for the first step. The obtained alcohol **S15** (1.88 g, 7.88 mmol, 79% yield) was used in the next step with *n*-butyllithium (2.55 M in hexanes, 3.71 mL, 9.46 mmol, 1.20 equiv.) in THF (30 mL), followed by addition of **S14** (1.16 g, 11.8 mmol, 1.50 equiv.) in THF (9 mL). The crude residue obtained after work up was dissolved in THF (30 mL) with acetic acid (0.65 mL, 11.3 mmol, 1.50 equiv.) and treated with a solution of *n*-$Bu_4NF \bullet xH_2O$ (2.37 g, 9.06 mmol, 1.20 equiv.) in THF (8 mL). The reaction was stirred at 50 °C for 6 h. The product was purified by column chromatography on silica gel (40% EtOAc in hexanes to 60% EtOAc in hexanes) to give diol **S16** (1.22 g, 5.47 mmol, 72% yield) which was submitted to the next step.

A solution of diol **S16** (0.966 g, 4.51 mmol) and *p*-toluenesulfonyl hydrazide (10.1 g, 54.1 mmol, 12.0 equiv.) in 1,2-dimethoxyethane (45 mL) and water (45 mL) was heated to reflux. A solution of sodium acetate (9.20 g, 67.7 mmol, 15.0 equiv.) was added over 5 h using a syringe pump. The mixture was then stirred overnight, cooled to room temperature, diluted with EtOAc (100 mL), and washed with water (3 x 100 mL). The organic phase was dried over $NaSO_4$, and concentrated under reduced pressure. The crude residue **S17** was submitted directly to the next step.

Conversion of crude diol **S17** to thiolane **28** follows the procedures outlined above for **26**, using methanesulfonyl chloride (1.05 mL, 13.5 mmol, 3.0 equiv.) and trimethylamine (2.51 mL, 18.0 mmol, 4.0 equiv.) in CH_2Cl_2 (45 mL). The crude bismesylate was submitted to the next step without further purification. The crude was dissolved in DMF (225 mL) and treated with $Na_2S \bullet 9H_2O$ (5.42 g, 22.6 mmol, 5.0 equiv.), and stirred at 50 °C for 15 h. The crude residue was purified by column chromatography on silica gel (hexanes) to give an impure 1.6:1 mixture of (±)-*trans*- to *cis*-**27** (~0.603 g, 2.69 mmol, 60% yield over 3 steps). A portion this material (0.300 g, 1.33 mmol) was purified through preparative chiral HPLC [Chiralpak ® AD-H; 250 x 20 mm i.d.; 0.05% *i*-PrOH- Hexanes; flow rate = 6 mL/ min; 3 mL injections of a 10 mg/ mL solution; detection at 210 nm; t_1 = 17.38 min. (*cis*-**27**), t_2 = 22.12 min. (**27**), t_3 = 26.0 min. (*ent*-**27**)]. Following preparative HPLC, **27** was isolated in 14% yield (42 mg, 0.187 mmol, >99% ee) along with *ent*-**27** in 13% yield (40 mg, 0.178 mmol, 96% ee), both as white crystalline solids.

Thiolane 27: $[\alpha]_D^{22}$ −150.0 (*c* 1.0, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ 3.28 (td, *J* = 9.1, 6.1 Hz, 2H), 2.17 (dp, *J* = 10.9, 5.5 Hz, 2H), 1.88 (h, *J* = 8.4 Hz, 2H), 1.78 (dp, *J* = 14.3, 5.6, 4.1 Hz, 4H), 1.66 – 1.55 (m, 4H), 1.51 (dtd, *J* = 9.8, 7.5, 3.2 Hz, 6H), 1.25 (dq, *J* = 12.1, 8.1 Hz, 2H), 1,16 (dq, 12.0, 8.3 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 55.8, 47.6, 37.1, 32.5, 31.9, 25.6, 25.5. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{25}S$, 225.1677; found, 225.1674.

SHIMADZU LabSolutions **Analysis Report**

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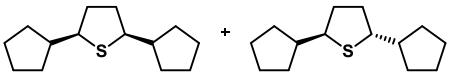
Date Acquired	: 12/17/2019 9:34:37 AM
Date Processed	: 12/17/2019 10:15:14 AM



cis-**27** (±)-**27**

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Acquired by	: Jacob Lacharity
Processed by	: Jacob Lacharity

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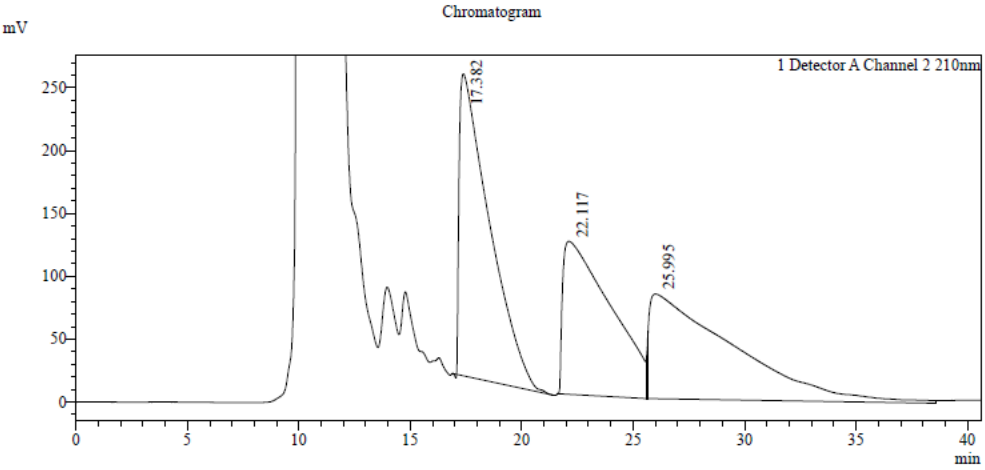

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Peak Table

Detector A Channel 2 210nm

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3	25.995	21740084	83255	34.692	18.700
Total		62665563	445217	100.000	100.000

*Thiolanes **27** and *ent*-**27** overlap slightly during preparative HPLC separation, so they were collected in fractions. The fractions were analyzed to determine their enantiopurity, as shown below.

SHIMADZU LabSolutions

Analysis Report

<Sample Information>

Chiralpak AD-H, 0.15% i-PrOH/hex, 1 mL/min, 2 mg/mL, 10 uL

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Sample ID	: JJL-7-020-a
Data Filename	: JJL-7-020-a.lcd
Method Filename	: JakeAnalytical.lcm
Batch Filename	:
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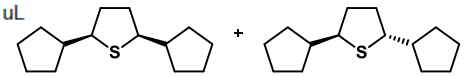

cis-**27** (±)-**27**

Sample Type	: Unknown
Acquired by	: Jacob Lacharity
Processed by	: Jacob Lacharity

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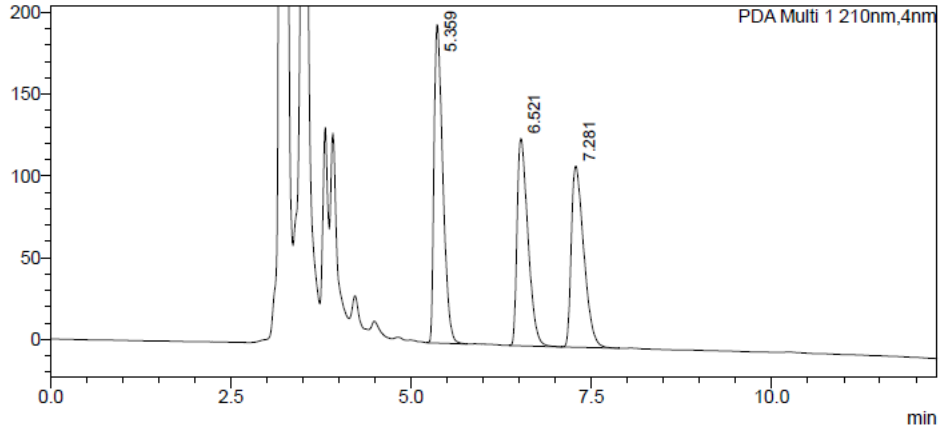

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Peak Table

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3	7.281	1335929	110928	30.937	25.636
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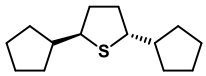
SHIMADZU LabSolutions

Analysis Report



27

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Sample Name	: JJL-7-020-prepHPLC-b		
Sample ID	: JJL-7-020-prepHPLC-b		
Data Filename	: JJL-7-020-prepHPLC-b.lcd		
Method Filename	: JakeAnalytical.lcm		
Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 12/18/2019 9:08:13 AM	Acquired by	: Jacob Lacharity
Date Processed	: 12/18/2019 9:23:21 AM	Processed by	: Jacob Lacharity

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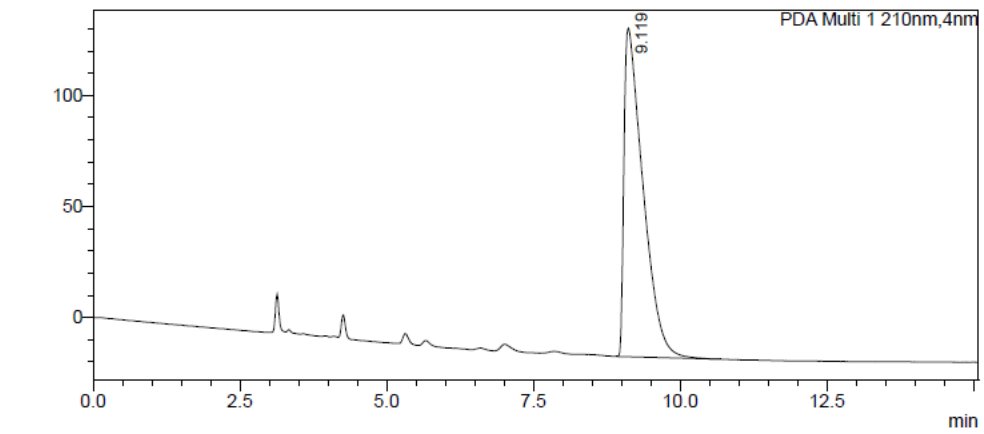

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Peak Table

PDA Ch1 210nm

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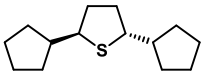
SHIMADZU LabSolutions **Analysis Report**



ent-**27**

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Sample ID	: JJL-7-020-prepHPLC-c		
Data Filename	: JJL-7-020-prepHPLC-c.lcd		
Method Filename	: JakeAnalytical.lcm		
Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 12/18/2019 9:25:16 AM	Acquired by	: Jacob Lacharity
Date Processed	: 12/18/2019 9:37:38 AM	Processed by	: Jacob Lacharity

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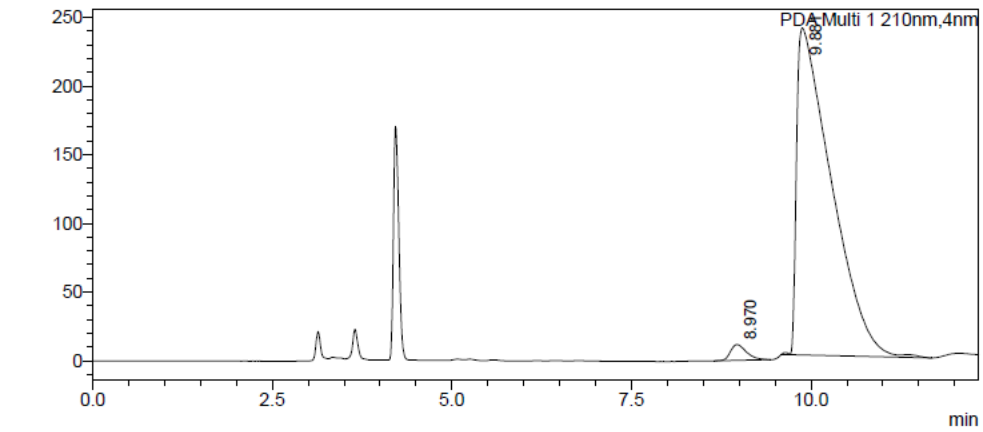

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Peak Table

PDA Ch1 210nm

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2	9.881	8010177	237836	97.812	95.370
Total		8189350	249383	100.000	100.000

S18 **28**

Thiolane 28. Sodium borohydride (0.263 g, 6.94 mmol, 2.0 equiv.) was added portion-wise to a solution of **S18**[8] (0.869 g, 3.47 mmol) in MeOH (18 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 30 min., at which point it was concentrated under reduced pressure. The residue was taken up in EtOAc (75 mL), washed with 1 M HCl (50 mL), saturated

aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried over $NaSO_4$, and concentrated under reduced pressure. The residue was submitted to the next step without further purification.

Methanesulfonyl chloride (0.81 mL, 10.4 mmol, 3.0 equiv.) was added dropwise to a solution of the crude diol from the previous step and trimethylamine (1.93 mL, 13.9 mmol, 4 equiv.) in CH_2Cl_2 (17 mL) at 0 °C. The mixture was stirred 1 h at this temperature, then diluted with additional CH_2Cl_2 (50 mL) and washed sequentially with 1 M HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), dried over $NaSO_4$, and concentrated under reduced pressure. The corresponding bismesylate was submitted to the next step without further purification.

A solution of the crude bismesylate from the previous step was dissolved in DMF (170 mL) and sparged with argon for 10 min. $Na_2S \bullet 9H_2O$ (4.17 g, 17.4 mmol, 5.0 equiv.) was then added and the mixture was stirred at 50 °C for 15 h. The mixture was then diluted with water (1000 mL) and extracted with EtOAc (4 x 200 mL). The combined organic layers were washed with brine (3 x 300 mL), dried over $NaSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes) to give an impure 3.8:1 mixture of (±)-*trans*- to *cis*-**28** (~0.294 g, 1.16 mmol, 33% yield over 3 steps). The mixture was purified through preparative chiral HPLC [Chiralpak ® AD-H; 250 x 20 mm i.d.; 0.15% *i*-PrOH-Hexanes; flow rate = 6 mL/ min; 3 mL injections of a 10 mg/ mL solution; detection at 210 nm; t_1 = 12.65 min. (*cis*-**28**), t_2 = 16.48 min. (**28**), t_3 = 20.68 min. (*ent*-**28**)]. Following preparative HPLC, 75.1 mg (0.297 mmol, 26% yield) of both **28** and *ent*-**28** were isolated as enantiopure, crystalline, white solids.

Thiolane 28: $[\alpha]_D^{20}$ −168.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.10 (td, *J* = 8.5, 4.7 Hz, 2H), 2.21 (ddd, *J* = 7.5, 4.4, 2.0 Hz, 2H), 1.81 (ddd, *J* = 11.1, 6.6, 3.2 Hz, 4H), 1.69 (dd, *J* = 8.4, 4.7 Hz, 4H), 1.63 (dddd, *J* = 12.5, 5.1, 3.3, 1.5 Hz, 2H), 1.45 (t, *J* = 9.3 Hz, 2H), 1.31 (tdt, *J* = 11.9, 8.7, 3.5 Hz, 2H), 1.22 (ddt, *J* =16.4, 12.5, 3.3 Hz, 4H), 1.14 (qt, *J* = 12.7, 3.3 Hz, 2H), 1.01 (qd, *J* = 12.7, 3.5 Hz, 2H), 0.93 (qd, *J* = 12.4, 3.6 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) 55.9, 45.3, 35.7, 33.4, 31.7, 26.5, 26.3, 26.3. HRMS-ESI (m/z): $[M+C_2H_5]^+$ calcd for $C_{18}H_{33}S$, 281.2303; found, 281.2305.

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Project1\JJL-6-062-a-prep.lcd

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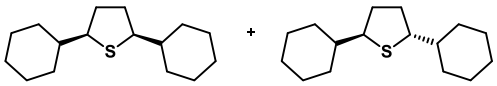
Sample ID	: JJL-6-062-a-prep
Vail #	:
Injection Volume	: 1 uL
Data File Name	: JJL-6-062-a-prep.lcd
Method File Name	: JakeADHPrep.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 5/2/2019 4:06:42 PM
Data Processed	: 5/2/2019 4:42:15 PM



cis-**28** (±)-**28**

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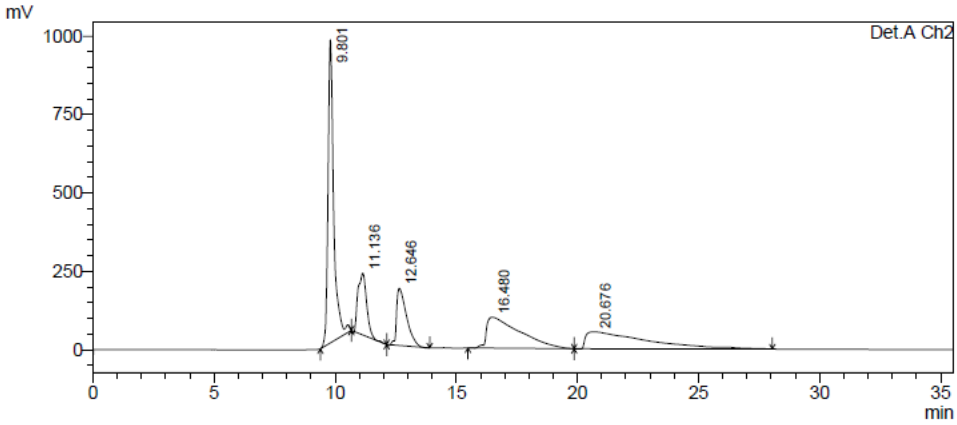

==== Shimadzu LCsolution Analysis Report ====

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Injection Volume	: 10 uL
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Method File Name	: brad.lcm
Batch File Name	:
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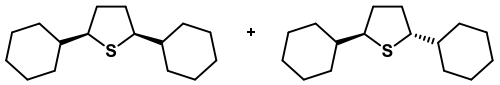

cis-**28** (±)-**28**

<Chromatogram>

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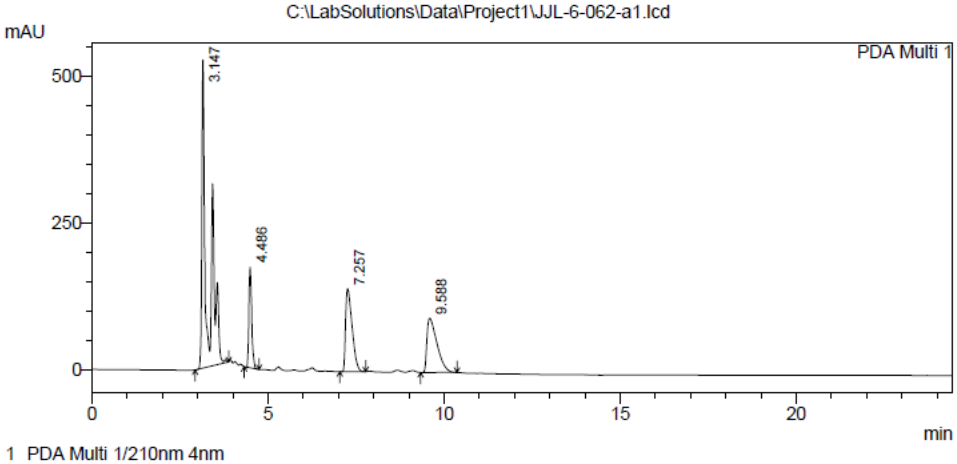

1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch1 210nm 4nm

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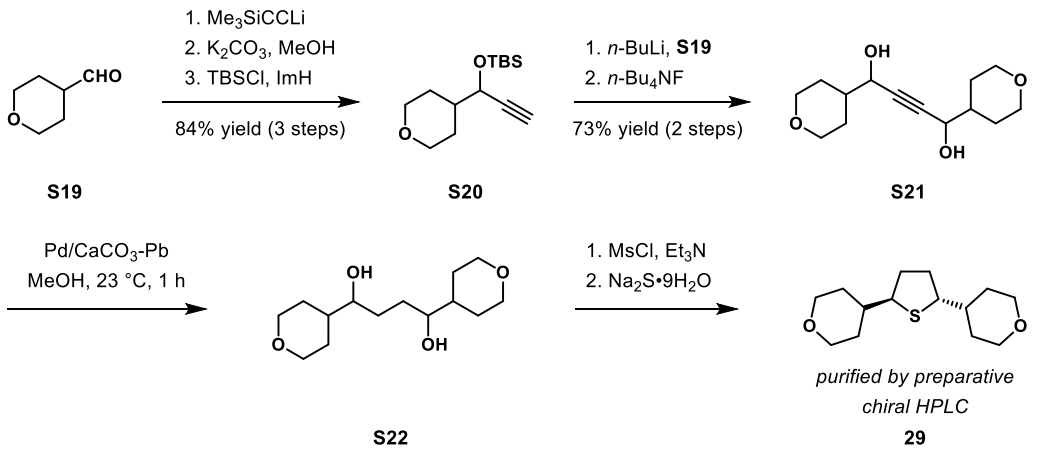
2	4.486	966510	171243	9.900	18.433
3	7.257	1813006	141526	18.570	15.234
4	9.588	1834699	92602	18.792	9.968
Total		9763165	929020	100.000	100.000



Thiolane 29. The title compound was prepared according to the procedures described above for thiolane **26**. The first step used aldehyde **S19**[9] (1.00 g, 8.76 mmol) in THF (14mL), with trimethylsilyl acetylene (1.81 g, 18.4 mmol, 2.10 equiv.) and *n*-butyllithium (2.55 M in hexanes, 6.9 mL, 17.5 mmol, 2.00 equiv.) in THF (40 mL). The second step used potassium carbonate (1.45 g, 10.5 mmol, 1.20 equiv.) in MeOH. The crude product from this step was then treated with imidazole (1.43 g, 21.0 mmol, 2.40 equiv.) and TBSCl (1.58 g, 10.5 mmol, 1.2 equiv.) in CH_2Cl_2 (88 mL). After purification by column chromatography on silica gel (5% EtOAc in hexanes), alkyne **S20** was obtained in 84% yield over 3 steps (1.86 g, 7.33 mmol) and used directly in the next step.

Following the same procedure as that used for thiolane **26**, alkyne **S20** was treated with *n*-butyllithium (2.55 M in hexanes, 3.15 mL, 8.04 mmol, 1.10 equiv.) in THF (12 mL) followed by addition of a solution of **S19** (1.03 g, 9.00 mmol, 1.23 equiv.) in THF (5 mL) The crude residue obtained after work up was treated with a solution of *n*-Bu_4NF (1 M in THF, 8.30 mL, 8.30 mmol, 1.20 equiv.) in THF (35 mL) and the mixture was stirred at room temperature for 6 h. After work up, the product was purified by column chromatography on silica gel (5% MeOH in EtOAc) to give diol **S21** (1.37 g, 5.38 mmol, 77% yield).

A solution of diol **S21** (0.782 g, 3.08 mmol) and palladium on calcium carbonate, poisoned with lead (5 wt % Pd, 0.656 g, 0.308 mmol, 10 mol %) in MeOH (30 mL) was stirred under an atmosphere of hydrogen gas for 15 h. The mixture was filtered through celite,

concentrated under reduced pressure, and submitted to the next step without further purification.

Methanesulfonyl chloride (0.72 mL, 9.24 mmol, 3.0 equiv.) was added dropwise to a solution of the diol from the previous step and trimethylamine (1.70 mL, 12.3 mmol, 4.0 equiv.) in CH_2Cl_2 (30 mL) at 0 °C and stirred at this temperature for 1 h. The mixture was diluted with additional CH_2Cl_2 (50 mL) and washed sequentially with 1 M HCl (75 mL), saturated aqueous $NaHCO_3$ (75 mL), and brine (75 mL), dried over $NaSO_4$, and concentrated under reduced pressure. The crude bismesylate was submitted to the next step without further purification.

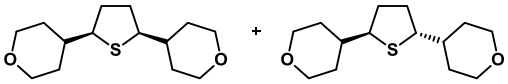
A solution of the bismesylate from the previous step was dissolved in DMF (154 mL) and sparged with argon for 10 min. $Na_2S \bullet 9H_2O$ (3.70 g, 15.4 mmol, 5.0 equiv.) was then added and the reaction was stirred at 50 °C for 15 h. The mixture was then diluted with water (1000 mL) and extracted with EtOAc (4 x 200 mL). The combined organic layers were washed with brine (3 x 300 mL), dried over $NaSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30% EtOAc in hexanes) to give an impure 3:1 mixture of (±)-*trans*- to *cis*-**29** (~0.400 g, 1.56 mmol, 51% yield over 3 steps). The mixture was purified through preparative chiral HPLC [Chiralpak ® AD-H; 250 x 20 mm i.d.; 5% *i*-PrOH-Hexanes; flow rate = 6 mL/ min; 3 mL injections of a 10 mg/ mL solution; detection at 210 nm; t_1 = 27.69 min. (*cis*-**29**), t_2 = 43.39 min. (**29**), t_3 = 57.15 min. (*ent*-**29**)]. Following preparative HPLC, 0.112 g (0.437 mmol, 14% yield) of both **29** and *ent*-**29** were isolated as enantiopure, crystalline, white solids.

Thiolane 29: $[\alpha]_D^{25}$ −158.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.94 (dt, *J* = 11.3, 5.4 Hz, 4H), 3.34 (q, *J* = 11.5 Hz, 4H), 3.14 (td, *J* = 8.9, 5.1 Hz, 2H), 2.25 (tq, 11.1, 5.6 Hz, 2H), 1.75 – 1.62 (m, 4H), 1.60 – 1.44 (m, 4H), 1.35 (qd, *J* = 12.2, 4.5 Hz, 4H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 68.0, 67.8, 55.1, 42.4, 34.9, 33.1, 31.6. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{25}O_2S$, 257.1575; found, 257.1575.

SHIMADZU LabSolutions

Analysis Report

<Sample Information>



cis-**29** (±)-**29**

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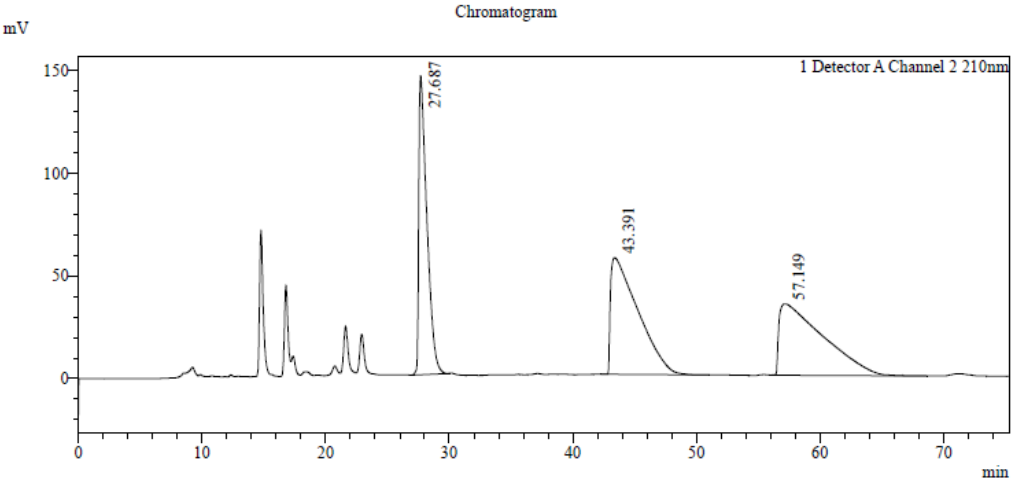

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Peak Table

Detector A Channel 2 210nm

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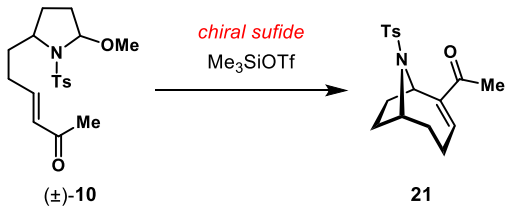
Total		24047681	236899	100.000	100.000

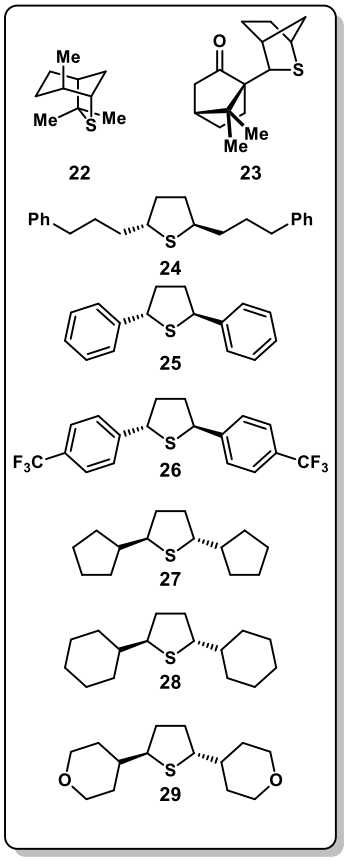
General Procedure for Enantioselective aza-MBH Cyclization:



(±)-**10** **21**

entry	solvent	sulfide	temp.	time	yield	ee
1	MeCN	**22**	0 °C	2 h	85%	4%
2	MeCN	**23**	0 °C	3 h	85%	0%
3	MeCN	**24**	0 °C	2 h	68%	6%
4[a]	MeCN	**25**	20 °C	22 h	53%	22%
5[b]	MeCN-CH_2Cl_2 (1:1)	**26**	15 °C	24 h	19%	
6	MeCN-CH_2Cl_2 (1:1)	**27**	0 °C	3 h	59%	44%
7	MeCN-PhMe (1:1)[c]	**28**	0 °C	3 h	40%	62%
8	MeCN-CH_2Cl_2 (1:1)	**29**	0 °C	3 h	29%	82%
9[d]	MeCN-CH_2Cl_2 (1:1)	**29**	0 °C	2 h	50%	78%
10	MeCN-PhMe (1:1)	**28**	40 °C	24 h	42%	70%
11	MeCN-CH_2Cl_2 (1:1)	**29**	78 °C	4 h	28%	93%

[a]Epimerization of the sulfide was observed. [b]TBSOTf was used instead of Me_3SiOTf. [c]Concentration was 0.03 M with respect to (±)-10. [d]Me_3SiOTf was added at 78 °C, stirred for 1 h, then warmed to 0 °C and stirred 1 h.



A solution of (±)-**10** (20 mg, 0.0569 mmol) and chiral sulfide (0.0854 mmol, 1.50 equiv.) in the solvent (0.60 mL, except for entry 7) was cooled to the indicated temperature. Me_3SiOTf (26 µL, 0.142 mmol, 2.50 equiv.) was added carefully and the solution was stirred for the indicated amount of time. The mixture was then quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The residue was dissolved in CH_2Cl_2 (0.60 mL), treated with DBU (17 µL, 0.114 mmol, 2.0 equiv.), and stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure and purified directly by column chromatography on silica (30% EtOAc in hexanes to 40% EtOAc in hexanes to 50% EtOAc in hexanes) to deliver **21**.

==== Shimadzu LCsolution Analysis Report ====

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Sample ID	: AKM-09-36a
Vail #	:
Injection Volume	: 10 uL
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Method File Name	: brad.lcm
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Report File Name	: Default.lcr
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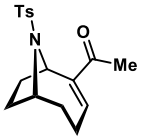

(±)-**21**

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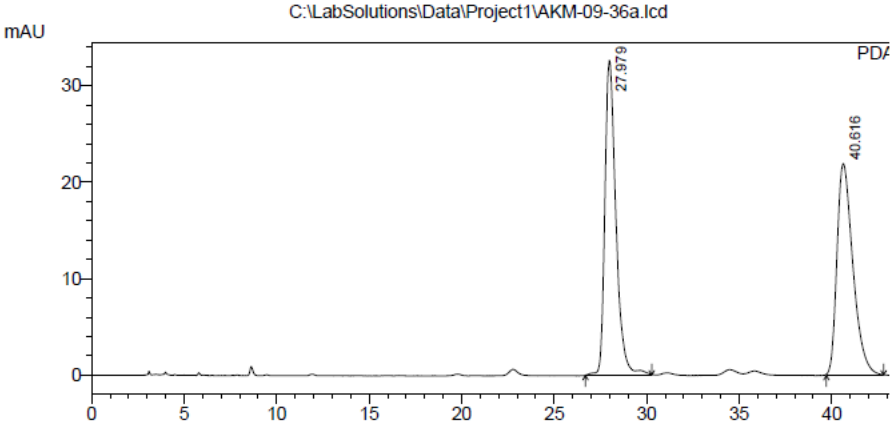

1 PDA Multi 2/254nm 4nm

PeakTable

PDA Ch2 254nm 4nm

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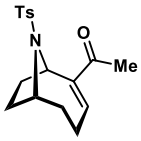
Total		2674576	54582	100.000	100.000

SHIMADZU LabSolutions

Analysis Report

<Sample Information>



21

78% ee

Sample Name	: kyc3-242b		
Sample ID	: kyc3-242b		
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Method Filename	: JakeAnalytical.lcm		
Batch Filename	:		
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Injection Volume	: 10 uL		
Date Acquired	: 12/12/2019 10:18:15 AM	Acquired by	: Karen Chen
Date Processed	: 12/12/2019 11:06:45 AM	Processed by	: Karen Chen

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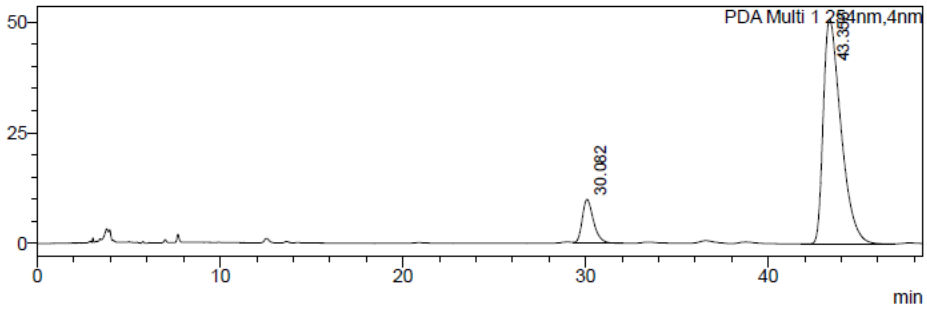

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PDA Ch1 254nm

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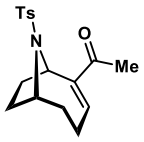
SHIMADZU LabSolutions **Analysis Report**



21

93% ee

<Sample Information>

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Sample ID	: kyc3-244ba		
Data Filename	: kyc3-244ba.lcd		
Method Filename	: JakeAnalytical.lcm		
Batch Filename	:		
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Date Processed	: 1/10/2020 11:55:56 AM	Processed by	: Karen Chen

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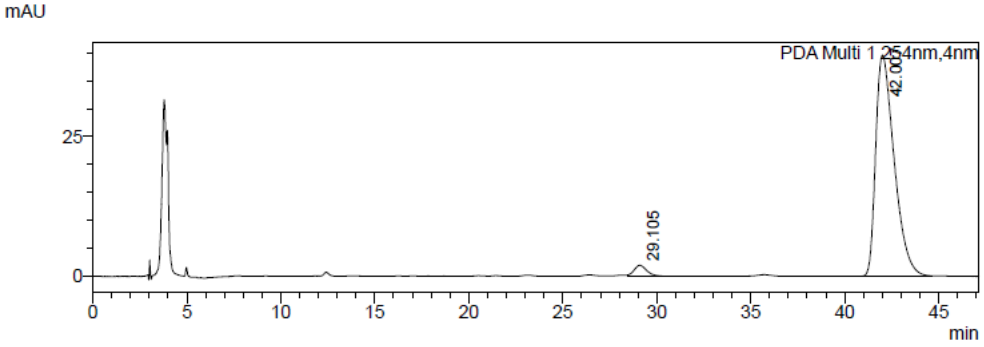

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PDA Ch1 254nm

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Total		2804278	41520	100.000	100.000

[1] J.D. Brubaker, A.G. Myers, *Org. Lett.* **2007**, *18*, 3523.
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