

Supporting Information

Rapid Access to the Heterocyclic Core of the Calyciphylline A and Daphnicyclidin A-type Daphniphyllum Alkaloids via Tandem Cyclization of a Neutral Aminyl Radical

Ahmad A. Ibrahim, Alexander N. Golonka, Alberto M. Lopez, and Jennifer L. Stockdill*
 Department of Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, MI 48202, United States

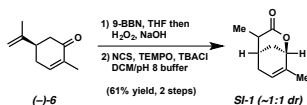
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General Information. Unless otherwise specified, all commercially available reagents were purchased from Aldrich and used without further purification. Anhydrous THF, Et₂O, PhH, PhMe, *n*-hexane, MeCN, DMF, DMSO, CH₂Cl₂ were passed through a commercial solvent purification system (2 columns of alumina) and used without further drying. Triethylamine, diisopropylamine, pyridine, and Hünig's base were distilled over CaH₂ immediately prior to use. Unless otherwise noted, all reactions were performed in flame-dried glassware under 1 atm of pre-purified anhydrous N₂ or argon gas. ¹H NMR spectra and ¹³C NMR spectra were recorded on a Varian Mercury-400 MHz instrument with a multinuclear broadband probe at ambient temperature unless otherwise stated. Chemical shifts are reported in parts per million relative to residual solvent peaks (as established by Stoltz, et. al. in *Organometallics* **2010**, *29*, 2176). All ¹³C spectra are recorded with complete proton decoupling. High-resolution mass spectral analyses were performed by the Lumigen Instrument Center, Wayne State University. All purifications were performed on SiliaFlash® P60 40-63µm (230-400 mesh) 60Å Irregular Silica Gels (cat. # R12030B) or on a Biotage Isolera IV flash purification system using SNAP cartridges (cat. # FSKO-1107-0XXX—depending on the size). Thin layer chromatography was performed using glass-backed SiliaPlate™ TLC Plates (cat. # TLG-R10011B-323) cut to the desired size then visualized with short-wave UV lamps and KMnO₄, CAM, PMA, or Anisaldehyde stains prepared according to standard recipes.¹ All yields refer to chromatographically and spectroscopically pure products. IR data was obtained on a Varian/Digilab Excalibur 3100 High Resolution FT-IR, and optical rotation data was collected on a Perkin-Elmer 341 automated Polarimeter at the concentration noted.

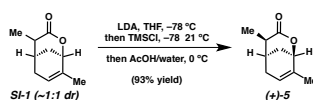
¹ Leonard, J.; Lygo, B.; Procter, G. In *Advanced Practical Organic Chemistry*; CRC Press: Boca Raton, FL, 2013; pp 158. (ISBN: 978-1-4398-6097-7)

Experimental Procedures and Spectroscopic Data



Lactone SI-2. To a cooled (0 °C) solution of 9-BBN (8.93 g, 36.61 mmol, 1.1 equiv) in THF (450 mL, 0.07 M relative to carvone) was added *R*-carvone (–)-6, 5.00 g, 33.29 mmol, 1.0 equiv). The reaction was allowed to warm up to ambient temperature (20 °C) in the melting ice bath and stirred for 20 h, then hydrogen peroxide (110 mL, 30 wt%, 32.5 equiv) was added followed by slow addition (10 min) of sodium hydroxide solution (110 mL, 3M, 9.9 equiv). The reaction flask was equipped with a condenser and heated to reflux. After 20 h, the biphasic reaction mixture was cooled to ambient temperature, and the layers were separated. The aqueous layer was washed with ethyl acetate (2 x 200 mL). The combined organics were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure affording a thick colorless oil.

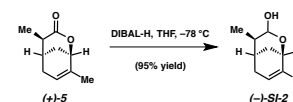
The crude oil was dissolved in methylene chloride (133 mL, 0.25 M), then TBACl (2.31 g, 8.32 mmol, 0.25 equiv), TEMPO (1.30 g, 8.32 mmol, 5.0 equiv), and NCS (40.61 g, 166.41 mmol, 5.0 equiv) were added followed by the addition of 0.05M K₂CO₃/0.5 M NaHCO₃ buffer (133 mL, 0.25 M relative to crude intermediate). The mixture was stirred at ambient temperature (20 °C) for 3 h until TLC showed complete conversion of starting material to SI-1. The reaction was quenched by addition of a saturated sodium thiosulfate solution (400 mL). The layers were separated and the aqueous layer was washed with methylene chloride (3 x 200 mL), the combined organics were dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (23.0 cm X 5.5 cm SiO₂) with a gradient 0–15% ethyl acetate/hexanes. The product was isolated as a yellow oil (3.38 g, 61% yield, ~1:1 mixture of diastereomers): R_f 0.65 (30% EtOAc/hexanes); ¹H NMR and ¹³C NMR spectra matched reported spectra.²



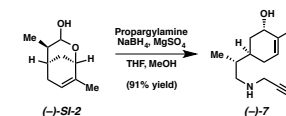
Lactone (+)-5. To a cooled (0 °C) solution of diisopropylamine (3.5 mL, 24.91 mmol, 1.4 equiv) in THF (31 mL, 0.7 M to *n*-BuLi) was added *n*-butyl lithium (9.3 mL, 2.32 M in hexanes, 21.66 mmol, 1.2 equiv) over 5 min. The reaction was stirred for 15 min then was cooled to –78 °C. SI-1 (3.00 g, 18.05 mmol) in THF (11.7 mL, 1.54 M to SI-1) was added slowly over 5 min, and the reaction was stirred for 2 h at –78 °C. TMSCl (3.0 mL, 23.46 mmol) was added and the reaction was warmed to ambient temperature (21 °C). After 2 h, the reaction was cooled to 0 °C and a pre-chilled (0 °C) acetic acid (10.3 mL, 180.48 mmol, 10 equiv), water (3.25 mL, 180.48 mmol, 10.0 equiv) and THF (35 mL, 0.5 M relative to SI-1) mixture was added quickly into the reaction

² Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650–6652.

solution and stirred for 1 h at 0 °C. The reaction was quenched by addition of sat. NaHCO₃ (40 mL), stirred for 10 min, then layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 40 mL). The combined organics were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure and the crude was purified by column chromatography eluted with 15% EtOAc/hexanes to afford (+)-5 a yellow oil (2.80 g, 93% yield): R_f 0.65 (30% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 5.51–5.39 (m, 1H), 4.51–4.35 (m, 1H), 2.82–2.62 (m, 1H), 2.33–2.22 (m, 3H), 2.22–2.11 (m, 1H), 2.00 (ddd, *J* = 14.3, 3.8, 2.3 Hz, 1H), 1.76 (dt, *J* = 2.9, 1.6 Hz, 3H), 1.20 (d, *J* = 7.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 176.6, 135.4, 123.0, 75.3, 39.6, 30.6, 30.3, 26.8, 21.5, 14.9; [α]_D²⁴ 208.9 (c 0.502, CH₂Cl₂); HRMS [M+Na⁺] *m/z* ES calc'd for [C₁₀H₁₄O₂Na]⁺: 189.0886; observed: 189.1388; IR 2937, 2874, 1736, 1450 cm⁻¹.

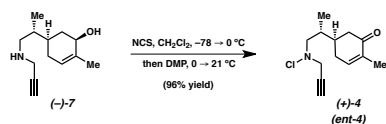


Lactol (–)-SI-2. To a cooled (–78 °C) solution of (+)-5 (1.22 g, 7.33 mmol, 1.0 equiv) in THF (21 mL, 0.35 M) was added a solution of DIBAL-H (1.96 mL, 10.99 mmol, 1.5 equiv) in THF (8 mL). The reaction was stirred for 40 min and was quenched by adding aqueous HCl (30 mL, 1 M) and warmed to ambient temperature. The layers were separated and the aqueous layer was washed with EtOAc (3 x 25 mL). The combined organics were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure to afford (–)-SI-2 as a pale yellow oil (1.17 g, 95% yield, ~9:1 mixture of hemiacetal and aldehyde by ¹H NMR, reported ¹H NMR shifts are for the hemiacetal): R_f 0.31 (30% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 5.63–5.58 (m, 1H), 4.63 (d, *J* = 8.8 Hz, 1H), 4.07–4.02 (m, 1H), 2.75 (br s, 1H), 2.21–1.92 (m, 4H), 1.74 (dd, *J* = 1.8 Hz, 3H), 1.71–1.59 (m, 2H), 0.97 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 131.9, 126.0, 95.8, 71.7, 42.9, 32.8, 31.7, 26.3, 21.9, 15.4; [α]_D²⁵ –120.7 (c 0.484, CH₂Cl₂); HRMS [M+Na⁺] *m/z* ES calc'd for [C₁₀H₁₆O₂Na]⁺: 191.1048 observed: 191.1350; IR 3375, 2915, 1721, 1444 cm⁻¹.

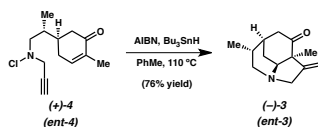


Amino alcohol (–)-7. To a flask containing flame dried MgSO₄ (3.78g, 31.44 mmol, 10 equiv) was added a solution of (–)-SI-2 (0.53 g, 3.14 mmol, 1.0 equiv) in THF (12.5 mL, 0.25 M) followed by propargylamine (211 μL, 3.30 mmol, 1.1 equiv) and stirred at ambient temperature (23 °C). After 20 h, the reaction was filtered under nitrogen into another flask. The filtrate was washed with methanol (12.5 mL, 0.125 M, final concentration) then NaBH₄ (1.19 g, 31.44 mmol, 10 equiv) was added in 4 equal portions every 30 min. The reaction was stirred until the TLC showed complete consumption of starting material (~3-5 h). The solvent was then removed under reduced pressure, and the crude material was suspended in water (20 mL), acidified to

pH \approx 1, and the aqueous layer was washed with EtOAc (2 x 10 mL). The aqueous layer was basified to pH \approx 11 and extracted with methylene chloride (3 x 20 mL). The combined methylene chloride layers were dried over Na_2SO_4 , and the solvent was removed under reduced pressure to afford (**-**)-**7** as a yellow oil (596 mg, 91% yield): R_f 0.29 (EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 5.50–5.44 (m, 1H), 4.20–4.15 (m, 1H), 3.45–3.39 (m, 2H), 2.71 (dd, J = 11.4, 5.5 Hz, 1H), 2.54 (dd, J = 11.4, 7.6 Hz, 1H), 2.22 (t, J = 2.4 Hz, 1H), 2.15–2.02 (m, 1H), 2.01–1.77 (m, 2H), 1.78–1.63 (m, 4H), 1.56 (p, J = 7.0 Hz, 3H), 1.22 (td, J = 12.3, 10.2 Hz, 1H), 0.92 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 136.83, 124.31, 82.55, 71.66, 71.30, 52.68, 38.69, 37.51, 36.59, 36.10, 30.23, 19.16, 15.06; $[\alpha]_D^{23}$ -19.6 (c 0.994, CH_2Cl_2); HRMS $[\text{M}+\text{H}]^+$ m/z ES calc'd for $[\text{C}_{13}\text{H}_{22}\text{NO}]^+$: 208.1696 observed: 208.2151; IR neat 3301, 2914, 2881, 2371, 2323 cm^{-1} .

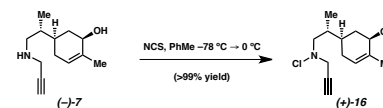


Chloroamine (+)-4. To a cooled ($-78\text{ }^\circ\text{C}$) solution of (**-**)-**7** (81 mg, 0.391 mmol, 1 equiv) in methylene chloride (2 mL) was added NCS (57 mg, 0.430 mmol, 1.1 equiv). The reaction was warmed to $0\text{ }^\circ\text{C}$ over 2 h, and then Dess-Martin periodinane (249 mg, 0.586 mmol, 1.5 equiv) was added, and the reaction was warmed to ambient temperature. After 16 h, the reaction was diluted with hexanes (6 mL) and filtered through a plug of silica gel (10 cm x 1.5 cm) eluted with 10% EtOAc/hexanes to afford (**+**)-**4** as colorless oil (90 mg, 96% yield, *note*: (**+**)-**4** is light sensitive); R_f 0.69 (30% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 6.78–6.72 (m, 1H), 3.81 (d, J = 2.3 Hz, 2H), 2.94 (dd, J = 13.0, 6.9 Hz, 1H), 2.75 (dd, J = 13.0, 7.1 Hz, 1H), 2.42 (t, J = 2.3 Hz, 1H), 2.40–2.11 (m, 5H), 2.01–1.88 (m, 1H), 1.76 (s, 3H), 0.93 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 200.3, 145.4, 135.6, 77.6, 75.3, 65.7, 53.3, 40.3, 37.8, 35.3, 30.7, 15.9, 14.1; $[\alpha]_D^{23}$ 10.4 (c 0.366, CH_2Cl_2); HRMS $[\text{M}+\text{H}]^+$ m/z ES calc'd for $[\text{C}_{13}\text{H}_{19}\text{ClNO}]^+$: 240.1150 observed: 240.1153; IR neat 2892, 1667, 1441, 1372 cm^{-1} .



Compound (-)-3. To a heated ($110\text{ }^\circ\text{C}$) solution of (**+**)-**4** (62 mg, 0.257 mmol, 1 equiv) in toluene (27.3 mL) AIBN (21.1 mg, 0.129 mmol, 0.5 equiv) and tri-*n*-butyltin hydride (139 μL , 0.515 mmol, 2 equiv) in toluene (1.3 mL) were added over 1 h via syringe pump. The reaction was stirred for extra 2 h then was cooled to ambient temperature and concentrated under reduced pressure. The crude was purified by column chromatography on a Biotage SNAP 10 g

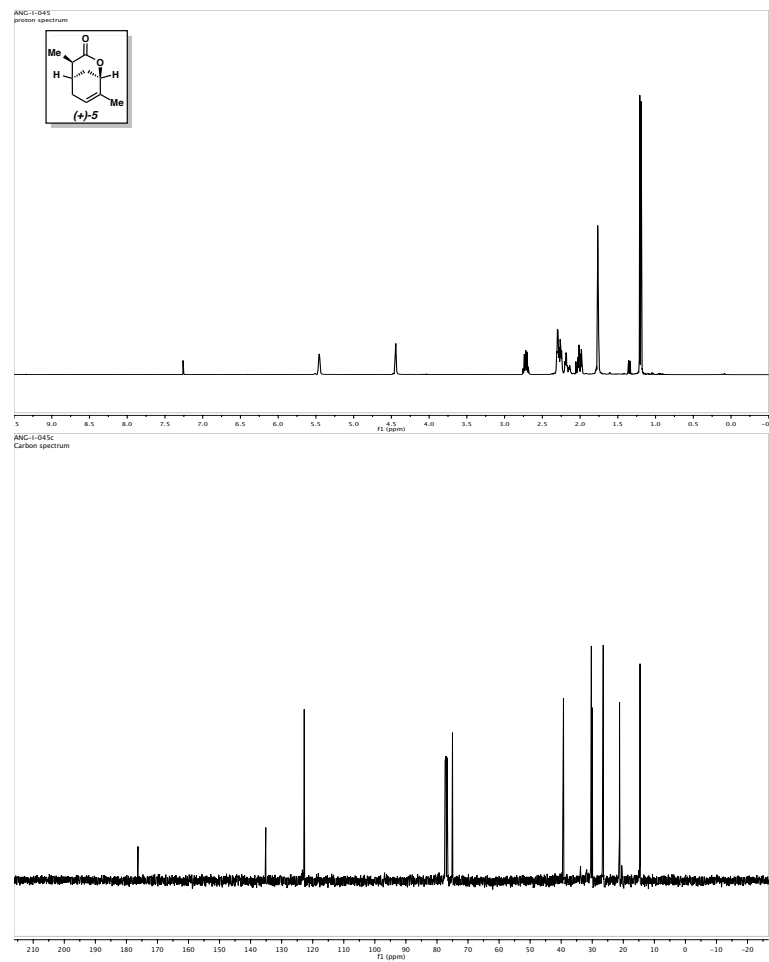
column using 10 wt% K_2CO_3 /silica gel³ eluted with a 0-5% methanol/methylene chloride gradient to afford (**-**)-**3** as a yellow oil (40 mg, 76% yield).⁴ R_f =0.2 (5% methanol/methylene chloride); ^1H NMR (400 MHz, CDCl_3) δ 5.38 (dd, J = 2.9, 1.8 Hz, 1H), 5.19 (dd, J = 2.3, 1.6 Hz, 1H), 3.52 (dt, J = 15.4, 2.7 Hz, 1H), 3.20–3.11 (m, 1H), 3.00 (s, 1H), 2.62 (dd, J = 18.2, 6.0 Hz, 1H), 2.56 (d, J = 13.2 Hz, 1H), 2.46–2.33 (m, 2H), 2.21 (dd, J = 13.2, 4.4 Hz, 1H), 2.08–2.02 (m, 1H), 1.90–1.78 (m, 2H), 1.25 (d, J = 7.2 Hz, 3H), 1.25 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 212.2, 152.4, 110.7, 66.4, 61.0, 55.7, 51.0, 46.2, 33.9, 33.6, 23.6, 21.5, 18.6; $[\alpha]_D^{23}$ -184.5 (c 0.284, CH_2Cl_2); HRMS $[\text{M}+\text{H}]^+$ m/z ES calc'd for $[\text{C}_{13}\text{H}_{20}\text{NO}]^+$: 206.1539 observed: 206.1539; IR neat 2953, 2925, 1701, 1449 cm^{-1} .



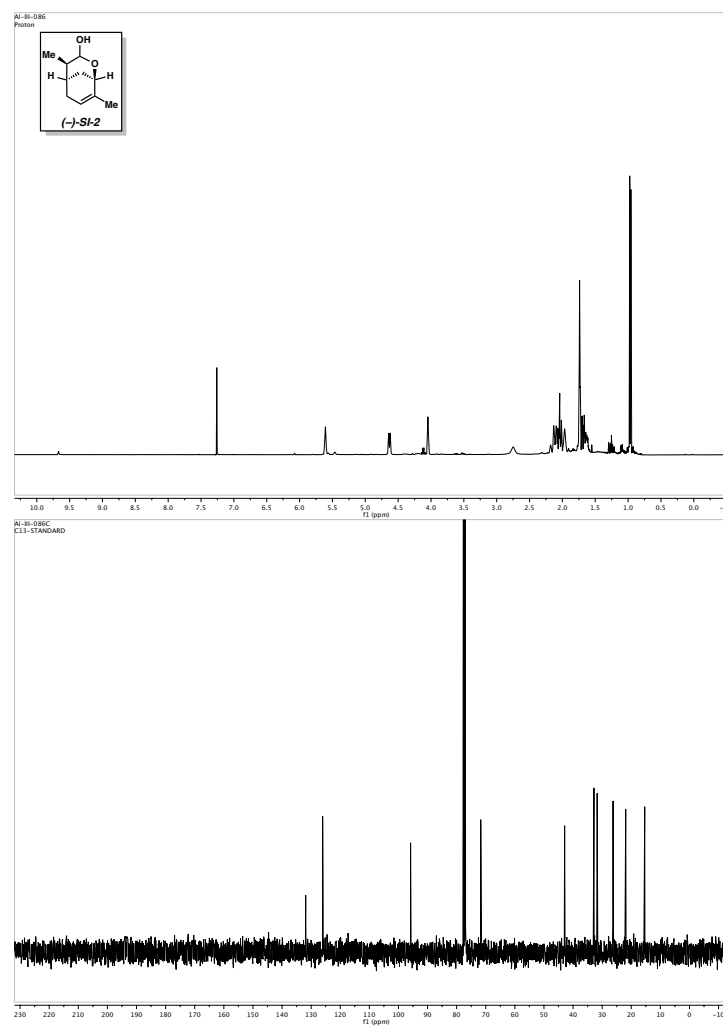
Chloroamine (+)-16. To a cooled ($-78\text{ }^\circ\text{C}$) solution of (**-**)-**7** (59 mg, 0.285 mmol, 1 equiv) in toluene (1.4 mL) was added NCS (42 mg, 0.314 mmol, 1.1 equiv). After 14 h TLC showed incomplete conversion of the starting material, so the mixture was warmed up slowly to ambient temperature over 4 h; then the reaction was loaded on a column of silica gel (16 x 1.5 cm) eluted with a gradient of 10-30 EtOAc/hexanes to afford **16** as a colorless oil (69 mg, >99% yield) R_f 0.53 (30% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 5.46 (s, 1H), 4.16 (s, 1H), 3.81 (t, J = 2.6 Hz, 2H), 3.00 (dd, J = 12.8, 6.2 Hz, 1H), 2.72 (dd, J = 12.8, 7.7 Hz, 1H), 2.41 (t, J = 2.3 Hz, 1H), 2.06 – 1.96 (m, 1H), 1.96 – 1.74 (m, 4H), 1.73 (s, 3H), 1.69 – 1.45 (m, 1H), 1.30 – 1.16 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 136.73, 124.42, 77.90, 75.17, 71.49, 66.13, 53.29, 35.94, 35.66, 35.60, 30.11, 19.14, 14.24; $[\alpha]_D^{25}$ 23.8 (c 2.9, CH_2Cl_2); HRMS $[\text{M}+\text{H}_2\text{O}-\text{Cl}]^-$ for the hydroxyl amine m/z ES calc'd for $[\text{C}_{13}\text{H}_{22}\text{NO}_2]^-$: 224.1645 observed: 224.1644 (No $[\text{M}+\text{H}]^+$ was observed for (**+**)-**16**, the Cl is substituted by OH under the LCMS conditions to form the hydroxylamine, additionally HCl elimination products were observed); IR neat 3300, 2922, 1452, 1383 cm^{-1} .

³ Harrowven, D. C.; Curran, D. P.; Kostiuik, S. L.; Wallis-Guy, I. L.; Whiting, S.; Stenning, K. J.; Tang, B.; Packard, E.; Nanson, L. *Chem. Commun.* **2010**, 46, 6335–6337.

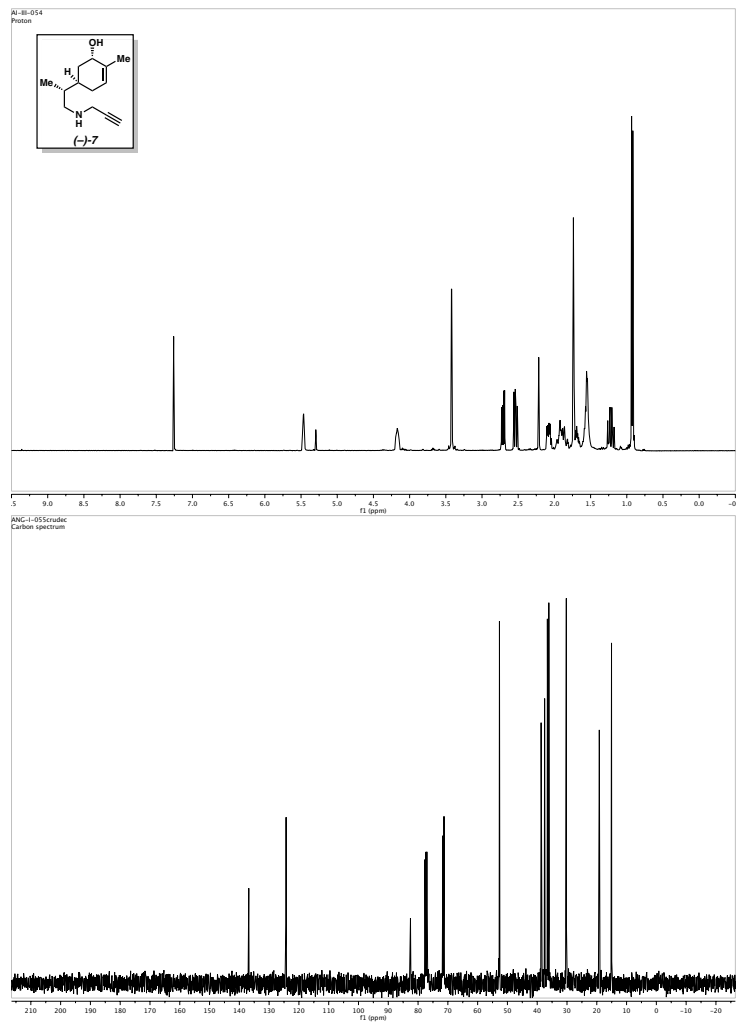
⁴ Best of 5 runs, the average is 74% yield.

^1H , ^{13}C , IR NMR Spectra

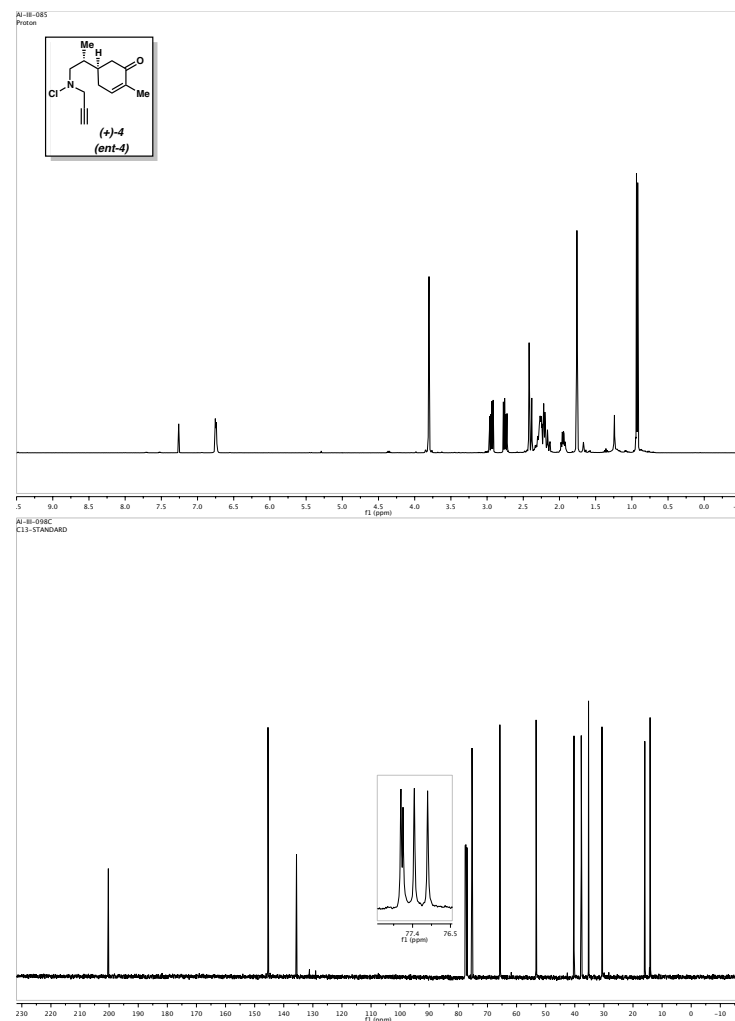
S7



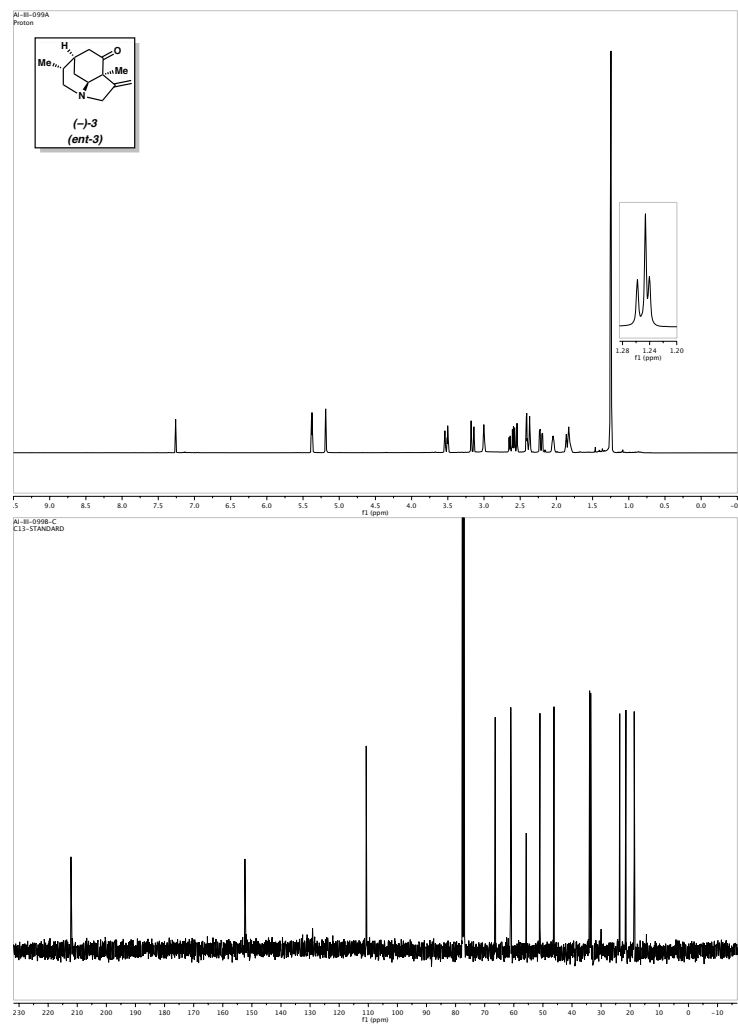
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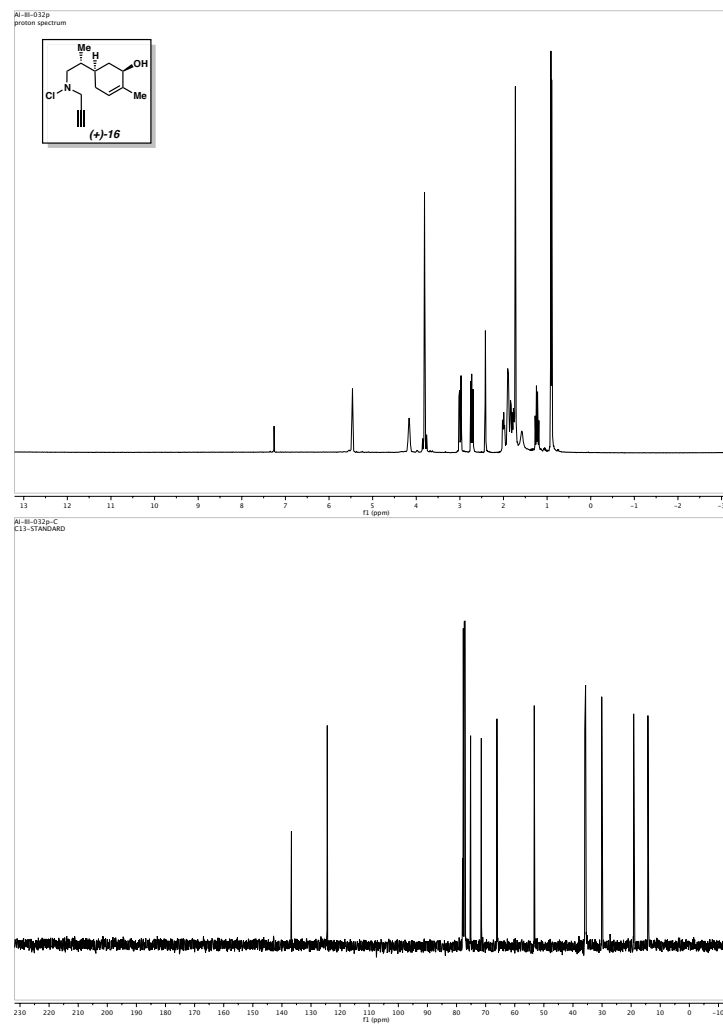
S9



S10



S11



S12