Supplementary Material

A Highly Chemo-, Regio-, and Stereoselective Metallacycle-Mediated Annulation Between a Conjugated Enyne and an Ene-Diyne

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1. Materials and Methods

A. Compound Names

Compound names were generated using Cambridgesoft ChemDraw Professional 17.0 software. For more complex molecules, a synecdochic descriptor has been used.

B. Reagents and Solvents

All reagents and starting materials were purchased from commercial sources and used as received, unless otherwise indicated. Anhydrous tetrahydrofuran (THF) and toluene (PhMe) were obtained by passing HPLC grade solvents through a column of activated alumina using a Glass Contour Solvent Purification System by Pure Process Technology, LLC. For flash column chromatography, HPLC grade solvents were used without further purification.

Solutions of *n*-BuLi were purchased from Sigma-Aldrich and titrated against *N*-benzylbenzamide in accordance with the procedure reported by Chong.[1]

C. Reaction Set-Up and Purification

All reactions were conducted in flame-dried glassware under an atmosphere of dry nitrogen unless otherwise indicated. Reaction mixtures were magnetically stirred and their progress was monitored by thin layer chromatography (TLC) on EMD TLC silica gel 60 F_{254} glass-backed plates. Compounds were visualized by initial exposure of TLC plates to UV-light (254 nm), followed by staining with *p*-anisaldehyde.

Purification of crude isolates was achieved by flash column chromatography on a Biotage® Isolera One™ Automated Liquid Chromatography System using Biotage® SNAP Ultra 25 μm HP-Sphere 10–25 g or Biotage® SNAP KP-Sil 10 g silica gel cartridges, or performed using a forced flow of the indicated solvent system on Sorbent Technologies™ silica gel 60 Å (40–63 μm particle size). Concentration of reaction product solutions and chromatography fractions was accomplished by rotary evaporation at 30–35 °C under the appropriate pressure, followed by concentration at room temperature on a vacuum pump (approx. 0–1 mbar). Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise indicated.

D. Characterization Data for New Compounds

i. Nuclear Magnetic Resonance Spectroscopy

^{1}H-NMR data were recorded on a Bruker Avance III 500 MHz NMR spectrometer (TBI probe) and a Bruker Avance III 600 MHz spectrometer (BBFO probe). ^{1}H chemical shifts are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the residual $CHCl_3$ in the deuterated solvent ($CDCl_3$: δ 7.26). NMR coupling constants are measured in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. ^{13}C{^{1}H decoupled} NMR data were recorded at 125 MHz on a Bruker Avance III 500 MHz spectrometer (TBI probe) and at 150 MHz on a Bruker Avance III 600

[1] Burchat, A. F.; Chong, J. M.; Nielsen, N., *J. Organomet. Chem.* **1997**, *542*, 281–283.

MHz spectrometer (BBFO probe). ^{13}C chemical shifts are reported in parts per million (ppm, δ scale) and are referenced to the central line of the carbon resonances of the solvent ($CDCl_3$: δ 77.16).

Structural assignments for new compounds were supported by two-dimensional NMR experiments (COSY, HSQC, and HMBC) recorded on a Bruker Avance III 600 MHz spectrometer (BBFO probe), while the relative stereochemical assignments were determined by analysis of the data obtained from 1D- or 2D-NOESY experiments, recorded on a Bruker Avance III 500 MHz NMR spectrometer (TBI probe) or a Bruker Avance III 600 MHz spectrometer (BBFO probe), respectively.

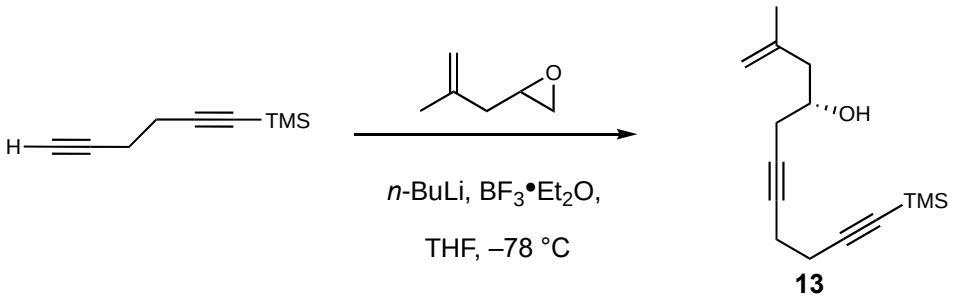
ii. Infrared Spectroscopy

Infrared spectra were collected on a JASCO FT/IR-4100 Fourier Transform Infrared Spectrometer. IR absorptions are reported as very strong (vs), strong (s), medium (m), weak (w), or broad (br).

iii. Accurate Mass Determination

HRMS (EI-TOF) analyses were performed at the Mass Spectrometry Laboratory of the University of Illinois at Urbana-Champaign.

2. Experimental Procedures



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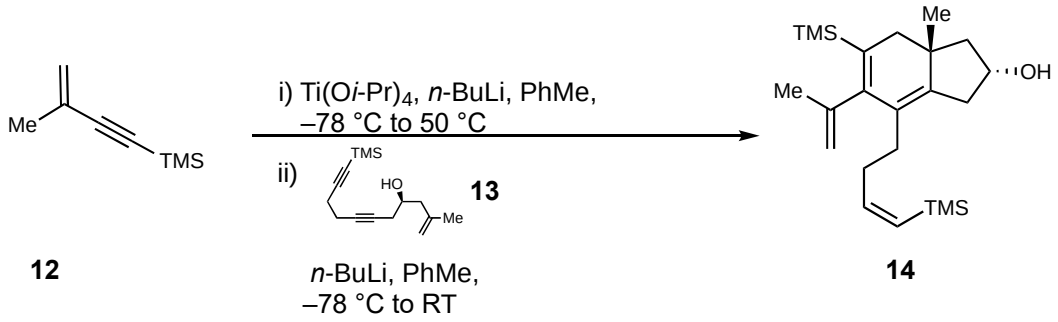
Synthesis of 2-methyl-10-(trimethylsilyl)deca-1-en-5,9-diyn-4-ol (13)

To a solution of hexa-1,5-diyn-1-yltrimethylsilane (6.00 g, 39.9 mmol) in anhydrous THF (120 mL) was added *n*-BuLi (2.33 M in hexanes, 15.4 mL, 35.9 mmol) drop-wise via syringe at –78 °C. After 30 min, BF_3•Et_2O (4.19 mL, 33.93 mmol) was added and the resulting solution was stirred at –78 °C for 15 min. Next, 2-(2-methylallyl)oxirane (1.96 g, 19.96 mmol) was added via syringe and progress of the reaction was monitored by TLC. After 30 min, the reaction was quenched at –78 °C with a saturated aqueous solution of $NaHCO_3$ (50 mL) and then warmed to room temperature. The organic and aqueous phases were separated, and the aqueous layer was extracted with EtOAc (× 3). The combined organic phases were dried over anhydrous $MgSO_4$, the solids removed by vacuum filtration through a glass-fritted funnel, and the solvents were removed *in vacuo*. The crude product was was purified by flash column chromatography on silica gel with 85:15 hexanes–EtOAc to afford **13** (3.26 g, 66%) as a clear, colorless oil.

Analytical Data for 13:

TLC (SiO_2) R_f = 0.31 (hexanes–ethyl acetate, 85:15); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.85 (s, 1H), 4.79 (s, 1H), 3.93 – 3.80 (m, 1H), 2.44 – 2.33 (m, 5H), 2.33 – 2.28 (m, 1H), 2.21 (ddq, *J* = 13.9, 8.1, 1.2 Hz, 1H), 2.13 – 2.09 (m, 1H), 1.75 (s, 3H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 113.5, 105.5, 85.6, 81.4, 77.4, 67.9, 44.8, 27.2, 22.6, 19.1, 0.18; **IR** (neat) 3419, 2960, 2931, 2914, 2176, 1646, 1249, 1061, 1043, 842, 760 cm^{-1}; **HRMS** (ES-TOF) *m*/*z* [M + H]: calcd for $C_{15}H_{25}OSi$ 249.1675; found 249.1683.



Synthesis of (3*R*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-4-(furan-2-yl-3-methylbutan-1-ol (14):
To a solution of 2-methyl-4-trimethylsilyl-1-butene (**12**, 1.288 mL, 7.24 mmol) in anhydrous toluene (45 mL) was added Ti(O-*i*-Pr)$_4$ (2.145 mL, 7.24 mmol) at room temperature. The mixture was cooled to –78 °C and *n*-BuLi (2.46 M in hexanes, 5.87 mL, 14.46 mmol) was added drop-wise via syringe. The reaction flask was removed from the cooling bath and the mixture was warmed to room temperature before heating to 50 °C (without a reflux condenser) for 1 h. After this period, the reaction solution was cooled to room temperature and then placed in a –78 °C cooling bath.

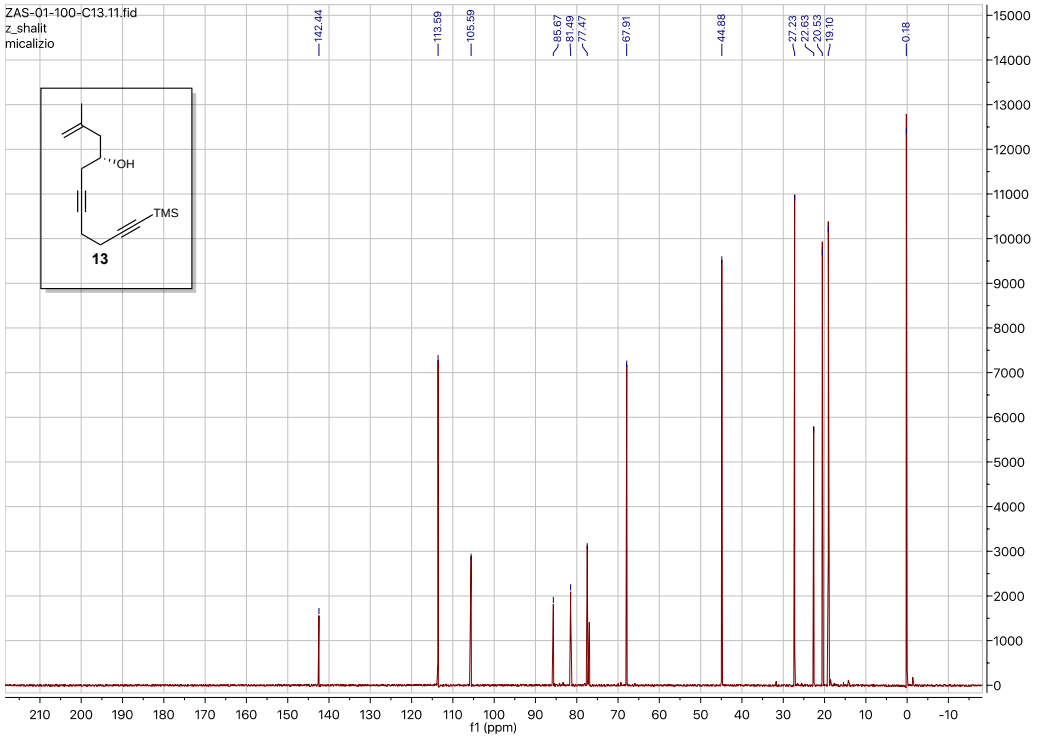
Simultaneously, ene-diyne **13** (0.600 g, 2.41 mmol) was dissolved in anhydrous toluene (15 mL) and treated with *n*-BuLi (2.46 M in hexanes, 0.981 mL, 2.41 mmol) at –78 °C. The reaction mixture was stirred at –78 °C for 15 minutes, and then warmed to room temperature over 5 minutes. The alkoxide solution was added dropwise, via cannula, to the Ti–alkyne complex and then gradually warmed to room temperature overnight (13 h). The reaction was quenched with saturated aqueous $NaHCO_3$ (40 mL), and the organic and aqueous phases were separated. The aqueous layer was extracted with EtOAc (× 3), and the combined organic phases were dried over anhydrous $MgSO_4$. The supernatant was removed from the drying agent by vacuum filtration through a glass fritted funnel, and the solvents were removed *in vacuo* to afford the crude product, which was purified by flash column chromatography with 89:11 hexanes–EtOAc to afford **14** (475 mg, 51%) as a clear, colorless, amorphous solid.

Analytical Data for 14:

TLC (SiO_2) R_f = 0.30 (hexanes–ethyl acetate, 87:13); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.26 (dt, *J* = 14.0, 7.0 Hz, 1H), 5.46 (d, *J* = 14.2 Hz, 1H), 4.99 (app s, 1H), 4.80 (br s, 1H), 4.48 (app quintet, *J* = 6.9 Hz, 1H), 2.83 (dd, *J* = 17.7, 7.4 Hz, 1H), 2.36 (dd, *J* = 17.7, 6.3 Hz, 1H), 2.22 (d, *J* = 15.4 Hz, 1H), 2.17–2.02 (m, 5H), 2.01 (d, *J* = 15.4 Hz, 1H), 1.77 (br s, 3H), 1.50 (dd, *J* = 12.3, 7.8 Hz, 1H), 0.84 (s, 3H), 0.10 (s, 9H), 0.09 (s, 9H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.7, 128.6, 115.3, 71.7, 50.6, 40.3, 39.1, 38.3, 33.2, 29.3, 20.5, 0.0; **IR** (neat) 3315, 2953, 2924, 1606, 1246, 850, 836 cm^{-1}; **HRMS** (ES-TOF) *m*/*z* [M + H]: calcd for $C_{23}H_{41}OSi_2$ 389.2696; found 389.2701.

3. NMR Spectra

Figure S1: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) of S13.



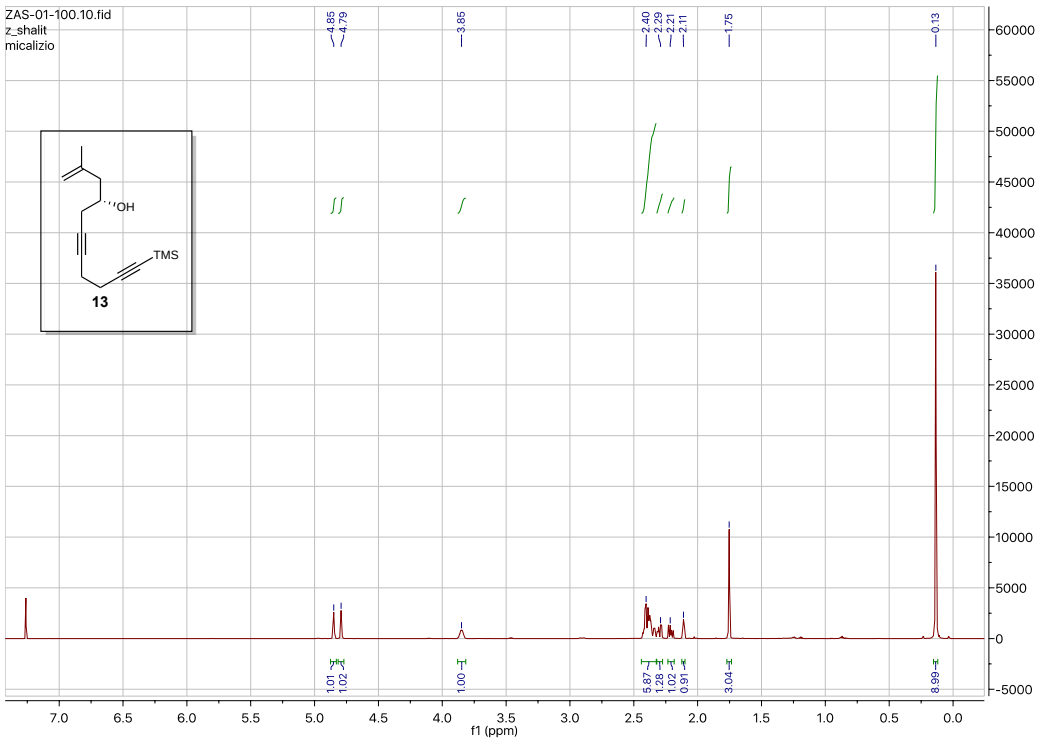


Figure S2: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of S14.