Supporting Information

**A New, Iterative Strategy for the Synthesis of Unsymmetrical
Polyynes: Application to the Total Synthesis of 15,16-
Dihydrominquartynoic Acid**

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Full experimental procedures and analytical data of compounds; copies of ^1H NMR and ^{13}C NMR spectra of compounds **12**, **14**, and **15**.

1-((3-Bromoprop-2-ynoxy)methyl)benzene (7).¹¹ To a solution of **6** (2.69 g, 18.4 mmol) in acetone (50 mL) was added *N*-bromosuccinimide (3.61 g, 20.3 mmol) and AgNO₃ (312 mg, 1.84 mmol). The reaction mixture was stirred at room temperature for 2 h and then it was poured into cold water. The white suspension was filtered. The filtrate was diluted with ether, washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexane/EtOAc, 70:1) to give the known bromoalkyne **7** (3.40 g, 82%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 4.23 (s, 2H), 4.63 (s, 2H), 7.34-7.40 (m, 5H).

(5-(Benzyloxy)penta-1,3-diynyl)triisopropylsilane (8). To a degassed solution of **7** (1.02 g, 4.53 mmol), (triisopropylsilyl)acetylene (1.20 mL, 5.40 mmol), Pd(PPh₃)₂Cl₂ (32 mg, 0.046 mmol) and CuI (8.5 mg, 0.045 mmol) in THF (15 mL) was added diisopropylamine (1.30 mL, 9.28 mmol). The reaction mixture was stirred for 2 h at room temperature and then quenched with saturated NH₄Cl solution. It was diluted with ether, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting residue was purified by flash silica gel column chromatography (hexane/EtOAc, 50:1) to give TIPS-diyne **8** (1.30 g, 88%) as a yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 1.10-1.13 (m, 21H), 4.25 (s, 2H), 4.62 (s, 2H), 7.31-7.38 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 11.2, 18.5, 57.6, 71.7, 71.8, 72.9, 84.4, 88.9, 127.9, 128.1, 128.4, 137.1; IR (CHCl₃) ν_{max} 2943.6, 2891.6, 2866.5, 2104.5, 1458.3, 883.5, 796.7 (cm⁻¹); UV (MeOH) λ_{max} (log ε) 242 (0.40), 255 (0.44), 264 (0.24), 269 (0.27) nm; MS (EI) *m/z* (rel int) 326 (M⁺, 1); HRMS (EI) calcd for C₂₁H₃₀OSi (M⁺) 326.2066, found 326.2066.

1-((5-Bromopenta-2,4-diynyl)oxy)methylbenzene (9). To a solution of TIPS-diyne **8** (425 mg, 1.30 mmol) in acetonitrile (13 mL) was added *N*-bromosuccinimide (278 mg, 1.56 mmol) and AgF (198 mg, 1.56 mmol) in the dark. The reaction mixture was stirred at room temperature for 2 h and then filtered through a pad of celite. The filtrate was diluted with ether, washed with water, dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting residue was purified by flash silica gel column chromatography (hexane/EtOAc, 50:1) to give bromo-diyne **9** (280 mg, 86%) as a yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 4.22 (s, 2H), 4.60 (s, 2H), 7.32-7.37 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 41.3, 57.4, 64.9, 71.39, 71.44, 71.8, 128.0, 128.1, 128.5, 136.9; IR (CHCl₃) ν_{max} 2943.6, 2864.6, 2239.6, 1699.4, 1456.4, 1072.5 (cm⁻¹); UV (MeOH) λ_{max} (log ε) 218 (4.73), 223 (4.53), 234 (4.53), 288 (2.52), 302 (3.01), 329 (2.06), 355 (1.81) nm; MS (EI) *m/z* (rel int) 248 (M⁺, 2); HRMS (EI) calcd for C₁₂H₉BrO (M⁺) 247.9837, found 247.9839.

(7-(Benzyloxy)hepta-1,3,5-triynyl)triisopropylsilane (10). Following the same procedure as for **8**, from bromo-diyne **9** (280 mg, 1.12 mmol) in THF (10 mL), (triisopropylsilyl)acetylene (0.32 mL, 1.44 mmol), Pd(PPh₃)₂Cl₂ (8.5 mg, 0.012 mmol), CuI (2.5 mg, 0.013 mmol), and diisopropylamine (0.33 mL, 2.35 mmol), after a reaction time of 3 h, TIPS-triyn **10** (294 mg, 75%) was obtained as a brown oil: ¹H NMR (300 MHz, CDCl₃) δ 1.09-1.15 (m, 21H), 4.25 (s, 2H), 4.61 (s, 2H), 7.34-7.37 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 11.2, 18.5, 57.5, 60.1, 63.7, 71.5, 71.8, 74.3, 85.3, 89.5, 128.1, 128.2, 128.5, 136.9; IR (CHCl₃) ν_{max} 2945.6, 2891.6, 2866.5, 2160.5, 2075.6, 1458.3, 1074.5, 883.5 (cm⁻¹)

¹); UV (MeOH) $\lambda_{\max}$ (log ϵ) 226 (4.57), 240 (4.46), 249 (4.35), 276 (2.39), 285 (2.36), 292 (2.70), 303 (2.41), 311 (2.47), 324 (1.89), 348 (1.23) nm; MS (EI) m/z (rel int) 350 (M^+ , 2); HRMS (EI) calcd for $C_{23}H_{30}OSi$ (M^+) 350.2066, found 350.2063.

1-((7-Bromohepta-2,4,6-triynyloxy)methyl)benzene (11). Following the same procedure as for **9**, from TIPS-triyn **10** (213 mg, 0.608 mmol) in acetonitrile (6 mL), *N*-bromosuccinimide (161 mg, 0.905 mmol), and AgF (91 mg, 0.717 mmol), after a reaction time of 3 h, bromo-triyn **11** (128 mg, 77%) was obtained as a brown oil: ¹H NMR (300 MHz, CDCl₃) δ 4.25 (s, 2H), 4.61 (s, 2H), 7.32-7.40 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 41.6, 57.5, 58.5, 63.6, 65.8, 71.2, 72.0, 73.7, 128.08, 128.13, 128.5, 136.8; IR (CHCl₃) $\nu_{\max}$ 2359.2, 2326.4, 1699.4, 1541.3, 1456.4, 1074.5 (cm⁻¹); UV (Hexane) $\lambda_{\max}$ (log ϵ) 234 (4.36), 239 (4.37), 273 (1.76), 289 (2.06), 305 (1.94), 355 (0.77) nm; MS (EI) m/z (rel int) 272 (M^+ , 3); HRMS (EI) calcd for $C_{14}H_9BrO$ (M^+) 271.9837, found 271.9838.

(9-(Benzyloxy)nona-1,3,5,7-tetraynyl)triisopropylsilane (12). Following the same procedure as for **8**, from bromo-triyn **11** (86 mg, 0.31 mmol) in THF (3 mL), (triisopropylsilyl)acetylene (0.10 mL, 0.45 mmol), Pd(PPh₃)₂Cl₂ (6.5 mg, 9 μ mol), CuI (2 mg, 10 μ mol), and diisopropylamine (0.09 mL, 0.64 mmol), after a reaction time of 1 h, TIPS-tetrayne **12** (63 mg, 53%) was obtained as a brown oil: ¹H NMR (300 MHz, CDCl₃) δ 1.09-1.13 (m, 21H), 4.25 (s, 2H), 4.60 (s, 2H), 7.34-7.37 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 11.3, 18.5, 57.6, 61.0, 61.1, 62.9, 63.8, 71.5, 72.0, 74.7, 86.1, 89.5, 128.1, 128.2, 128.5, 136.8; IR (CHCl₃) $\nu_{\max}$ 2945.6, 2887.7, 2866.5, 2374.6, 2347.6, 2320.6, 2060.2,

1699.4, 1458.3, 1099.5, 1072.5, 881.6, 738.8 (cm^{-1}); UV (MeOH) λ_{max} (log ϵ) 225 (4.86), 233 (4.27), 239 (4.31), 252 (4.35), 263 (4.13), 304 (1.38), 323 (1.08), 331 (1.06), 355 (0.84), 362 (0.82) nm; MS (EI) m/z (rel int) 374 ($[\text{M}]^+$, 3); HRMS (CI) calcd for $\text{C}_{25}\text{H}_{30}\text{OSi}$ (M^+) 374.2066, found 374.2063.

(E)-12-(benzyloxy)dodeca-2-en-4,6,8,10-tetrayn-1-ol (14). Following the same procedure as for **8**, from bromo-triyn **11** (46 mg, 0.17 mmol) in THF (2 mL), commercially available 2-penten-4-yn-1-ol (**13**) (21 mg, 0.26 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (3.5 mg, 5 μmol), CuI (1 mg, 5 μmol), and diisopropylamine (0.05 mL, 0.36 mmol), after a reaction time of 3 h, enetetrayne **14** (23.5 mg, 50%) was obtained as a brown oil: ^1H NMR (300 MHz, CDCl_3) δ 4.26 (s, 2H), 4.28 (dd, $J = 2.1, 4.5$ Hz, 2H), 4.60 (s, 2H), 5.84 (td, $J = 2.1, 15.9$ Hz, 1H), 6.54 (td, $J = 4.5, 15.9$ Hz, 1H), 7.29-7.40 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ 57.6, 62.2, 62.6, 63.1, 63.7, 66.7, 71.5, 72.0, 74.8, 75.5, 75.7, 107.6, 128.1, 128.2, 128.5, 136.8, 148.6; IR (CHCl_3) ν_{max} 3314.0, 2870.3, 2218.3, 2143.1, 1346.4, 1095.7, 738.8 (cm^{-1}); UV (MeCN) λ_{max} (log ϵ) 223 (4.52), 227 (4.40), 242 (4.56), 253 (4.35), 258 (4.29), 266 (4.23), 276 (4.22), 305 (1.83), 325 (2.32), 349 (2.47), 376 (1.62) nm; MS (EI) m/z (rel int) 274 (M^+ , 2); HRMS (EI) calcd for $\text{C}_{19}\text{H}_{14}\text{O}_2$ (M^+) 274.0994, found 274.0997.

10-(Trimethylsilyl)dec-9-ynoic acid (17).¹⁷ To a solution (trimethylsilyl)acetylene (3.4 mL, 24 mmol) in THF (20 mL) was added $n\text{BuLi}$ (16.5 mL, 26.4 mmol, 1.6M soln in hexanes) at -78 $^\circ\text{C}$. After the mixture was stirred for 20 min, a solution of 8-bromooctanoic acid (**16**) (2.9 g, 13.4 mmol) in THF (60 mL) and HMPA (40 mL) was added via syringe

over 10 min at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for 2 h and then quenched with saturated NH_4Cl solution. It was diluted with ether, washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The resulting residue was purified by flash silica gel column chromatography (hexane/EtOAc, 1:1) to give **17** (3.40 g, 82%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 0.11 (s, 9H), 1.32-1.41 (m, 6H), 1.44-1.51 (m, 2H), 1.58-1.64 (m, 2H), 2.18 (t, $J = 6.9\text{ Hz}$, 2H), 2.32 (t, $J = 7.5\text{ Hz}$, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 0.1, 19.7, 24.5, 28.4, 28.5, 28.6, 28.8, 34.0, 84.3, 107.5, 180.5; IR (CHCl_3) ν_{max} 3036.2, 2935.9, 2858.8, 2675.5, 2175.9, 1711.0, 1458.3, 1415.9, 1250.0, 843.0, 760.0 (cm^{-1}); MS (CI) m/z (rel int) 241 ($[\text{M}+1]^+$, 12); HRMS (CI) calcd for $\text{C}_{13}\text{H}_{25}\text{O}_2\text{Si}$ ($[\text{M}+\text{H}]^+$) 241.1624, found 241.1624.

Methyl 10-(trimethylsilyl)dec-9-ynoate (18). A solution of **17** (2.16 g, 8.98 mmol) in ether (30 mL) was treated with an ethereal solution of diazomethane. The reaction mixture was stirred for 10 min, and then the solvent was removed under reduced pressure to afford **18** (2.28 g, 99%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 0.10 (s, 9H), 1.28-1.37 (m, 6H), 1.42-1.50 (m, 2H), 1.54-1.61 (m, 2H), 2.17 (t, $J = 7.2\text{ Hz}$, 2H), 2.27 (t, $J = 7.5\text{ Hz}$, 2H), 3.62 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 0.1, 19.7, 24.8, 28.4, 28.5, 28.6, 28.9, 34.0, 51.3, 84.2, 107.5, 174.1; IR (CHCl_3) ν_{max} 2935.9, 2858.8, 2359.16, 2326.67, 2174.0, 1741.9, 1437.1, 1250.0, 843.0 (cm^{-1}); MS (CI) m/z (rel int) 255 ($[\text{M}+1]^+$, 48); HRMS (CI) calcd for $\text{C}_{14}\text{H}_{27}\text{O}_2\text{Si}$ ($[\text{M}+\text{H}]^+$) 255.1780, found 255.1776.

Methyl 10-bromodec-9-ynoate (19).^{8a} Following the same procedure as for **7**, from **18**

(495 mg, 1.95 mmol) in acetone (20 mL), *N*-bromosuccinimide (406 mg, 2.28 mmol), and AgNO₃ (34 mg, 0.20 mmol), after a reaction time of 2 h, bromo-acetylene **19** (458 mg, 90%) was obtained as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 1.26-1.40 (m, 6H), 1.43-1.52 (m, 2H), 1.54-1.64 (m, 2H), 2.16 (t, *J* = 7.1 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 3.63 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 19.5, 24.8, 28.1, 28.5, 28.6, 28.9, 33.9, 37.5, 51.3, 80.2, 174.1; IR (CHCl₃) ν_{max} 2934.0, 2858.8, 1738.0, 1458.3, 1435.2, 1197.7, 1170.1 (cm⁻¹); MS (CI) *m/z* (rel int) 261 ([M+H]⁺, 21); HRMS (CI) calcd for C₁₁H₁₈O₂Br ([M+H]⁺) 261.0490, found 261.0485.

Methyl 14-bromotetradeca-9,11,13-triynoate (20). Following the iterative procedure as for **8** and **9**, from **19** (418 mg, 1.60 mmol), bromo-triynes **20** (271 mg, 47% from **19** (four steps)) was obtained as a dark brown oil: ¹H NMR (300 MHz, CDCl₃) δ 1.25-1.45 (m, 6H), 1.49-1.64 (m, 4H), 2.28 (t, *J* = 6.9 Hz, 2H), 2.30 (t, *J* = 7.2 Hz, 2H), 3.67 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 19.3, 24.8, 27.8, 28.58, 28.63, 28.9, 34.0, 39.2, 51.4, 59.8, 60.2, 65.4, 66.2, 79.9, 174.2; IR (CHCl₃) ν_{max} 2934.0, 2858.8, 2216.4, 2102.6, 1738.0, 1437.1, 1172.8 (cm⁻¹); UV (MeOH) λ_{max} (log ε) 214 (4.03), 287 (0.55), 301 (0.65), 355 (0.37) nm; MS (FAB) *m/z* (rel int) 309 ([M+1]⁺, 24); HRMS (FAB) calcd for C₁₅H₁₈BrO₂ (M⁺) 309.0490, found 309.0498.

(S)-(E)-Methyl 17-hydroxyoctadeca-15-en-9,11,13-triynoate (22). To a solution of (S)-(E)-4-(tributylstannyl)but-3-en-2-ol¹⁸ (**21**, >99% ee) (57 mg, 0.15 mmol), Pd(PPh₃)₄ (17 mg, 0.01 mmol) and CuI (3 mg, 0.01 mmol) in DMF (1 mL) was slowly added the bromotriyne

20 (44.5 mg, 0.14 mmol) in DMF (1 mL). The mixture was stirred at room temperature for 2 h and then quenched with saturated NH_4Cl . It was diluted with ether, washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The resulting residue was purified by flash silica gel column chromatography (hexane/EtOAc, 3:1) to give **22** (30 mg, 69%) as a dark brown oil: $[\alpha]_{\text{D}} -34.8$ (c 0.4, MeOH); ^1H NMR (300 MHz, CDCl_3) δ 1.27 (d, J = 6.6 Hz, 3H), 1.28-1.41 (m, 6H), 1.47-1.65 (m, 4H), 1.92 (br s, 1H), 2.29 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 6.8 Hz, 2H), 3.65 (s, 3H), 4.36 (ddq, J = 1.5, 5.4, 6.6 Hz, 1H), 5.73 (dd, J = 1.5, 15.9 Hz, 1H), 6.37 (dd, J = 5.4, 15.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 19.5, 22.8, 24.8, 27.9, 28.56, 28.59, 28.9, 34.0, 51.4, 59.5, 65.6, 66.9, 67.9, 73.8, 75.1, 82.4, 107.3, 151.5, 174.3; IR (CHCl_3) ν_{max} 3420.1, 2932.1, 2858.8, 2366.9, 2322.5, 2214.5, 1736.1, 1437.1, 1363.8 (cm^{-1}); UV (MeOH) λ_{max} (log ϵ) 203 (1.98), 212 (1.97), 231 (3.20), 242 (3.44), 258 (0.28), 273 (0.40), 290 (0.68), 309 (0.89), 330 (0.65) nm; MS (EI) m/z (rel int) 300 ($[\text{M}]^+$, 15); HRMS (EI) calcd for $\text{C}_{19}\text{H}_{24}\text{O}_3$ (M^+) 300.1725, found 300.1731.

(S)-(E)-15,16-Dihydrominquartynoic acid (15).¹⁶ To a solution of methyl ester **22** (22 mg, 0.07 mmol) in THF (1 mL) and distilled water (0.1 mL) was added 1 N LiOH (0.35 mL, 0.35 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 7 h and then quenched with 1 N HCl. It was diluted with EtOAc, washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The resulting residue was purified by flash silica gel column chromatography (hexane/EtOAc, 1:1) to give **15** (18 mg, 90%) as a white solid: mp 70-75 °C (lit.⁹ mp 49-52 °C); $[\alpha]_{\text{D}} -32.2$ (c 1.0, MeOH) { lit.⁹ $[\alpha]_{\text{D}} -10.7$ (c 0.1, MeOH) and lit.¹⁶ $[\alpha]_{\text{D}} -12.8$ (c 0.05, MeOH)}; ^1H NMR (300 MHz, CDCl_3) δ 1.25-1.44 (m, 6H),

1.29 (d, $J = 6.6$ Hz, 3H), 1.50-1.58 (m, 2H), 1.59-1.68 (m, 2H), 2.31 (t, $J = 7.1$ Hz, 2H), 2.34 (t, $J = 7.5$ Hz, 2H), 4.39 (ddq, $J = 1.5, 5.4, 6.6$ Hz, 1H), 5.75 (dd, $J = 1.5, 16.2$ Hz, 1H), 6.38 (dd, $J = 5.4, 16.2$ Hz 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 19.5, 22.9, 24.6, 27.9, 28.59, 28.64, 28.8, 33.9, 59.6, 65.7, 67.0, 68.0, 73.8, 75.2, 82.4, 107.5, 151.3, 179.5; IR (CHCl_3) ν_{max} 3337.2, 2937.9, 2854.9, 2361.1, 2341.8, 2212.6, 1712.9, 1464.1, 1417.8, 1296.3, 1261.6 (cm^{-1}); UV (MeOH) λ_{max} (log ϵ) 205 (0.84), 212 (0.87), 231 (1.54), 243 (2.40), 258 (0.12), 273 (0.18), 290 (0.30), 309 (0.39), 330 (0.27) nm; MS (CI) m/z (rel int) 287 ($[\text{M}+1]^+$, 18); HRMS (CI) calcd for $\text{C}_{18}\text{H}_{23}\text{O}_3$ ($[\text{M}+\text{H}]^+$) 287.1647, found 287.1648.