The Catalyst-free Tandem Ring-opening/Click Reaction of Acetylene-Bearing Donor Acceptor Cyclopropanes

Supporting Information

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General Information. All solvents for routine isolation of products and chromatography were reagent grade. Reagents used were purchased from Sigma Aldrich, Alfa Aesar, Caledon or VWR. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (60F-254) visualizing under UV light and developed using acidic anisaldehyde stain. All flash column chromatography was performed using silica gel (230-400 mesh) with indicated solvents. $^1$H and $^{13}$C NMR spectra were recorded on either a 400 MHz or on a 600 MHz NMR spectrometer. Chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constants in hertz (Hz), and number of protons. HRMS were measured with electron impact (EI) ionization and quadrupolar mass analyzer.

Dimethyl 2-(2-formylphenyl)cyclopropane-1,1-dicarboxylate (13) (1 equivalent) was dissolved in methanol and slightly heated for 10 minutes until the starting material was fully dissolved. Once removed from heat, potassium carbonate was added (2.5 equivalent) and the reaction mixture was stirred at room temperature. Dimethyl (1-diazo-2-oxopropyl)phosphonate (Ohira-Bestmann reagent) (2.5 equivalent) was dissolved in methanol and slowly added dropwise over 5 minutes. Reaction mixture was left to stir at room temperature, and was quenched with brine once deemed complete by TLC analysis (approx. 18 h). Brine was added to the reaction mixture and the aqueous layer was extracted with EtOAc 3 times. The organic phases were combined and dried with MgSO$_4$, filtered and the solvent was removed. The residue was purified by flash column chromatography (gradient elution, EtOAc/Hexanes) to yield the desired compound (14a).

Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (14a): Reagents employed: dimethyl 2-(2-formylphenyl)cyclopropane-1,1-dicarboxylate (13) (1.00 g, 3.81 mmol), potassium carbonate (1.32 g, 9.50 mmol), dimethyl (1-diazo-2-oxopropyl)phosphonate (3) (1.83 g, 9.50 mmol), methanol: yield 88% (0.857 g, 3.32 mmol) as a light red solid; MP: 70$^\circ$C, R$_f$ = 0.50, 30% EtOAc in hexanes; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 7.48 (dd, J = 7.8, 7.4 Hz, 1H), 7.28-7.19 (m, 2H), 7.04 (d, J = 7.8 Hz, 1H), 3.80 (s, 3H), 3.53 (dd, J = 8.8, 8.6 Hz, 1H), 3.35 (s, 3H), 3.32 (s, 1H), 2.26 (dd, J = 8.2, 5.1 Hz, 1H), 1.79 (dd, J = 9.0, 5.1 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 170.0, 167.1, 137.3, 132.5, 128.4, 127.2, 126.7, 124.1, 82.3, 81.5, 52.7, 52.2, 36.9, 31.8, 19.1; IR (thin film, cm$^{-1}$) 3286, 3027, 2953, 1727, 1437, 1334, 1132; HRMS (EI) calc’d for C$_{15}$H$_{14}$O$_4$ 258.0892, found 258.0901.

General Experimental Procedure for the Synthesis of Substrates 14b-g.
Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (14a) (1 equivalent) was dissolved in triethylamine (C = 0.890 mM), followed by the addition of the aryl halide (1.2 equivalent), copper iodide (CuI) (5 mol %) and tetrakis(triphenylphosphine)palladium(0) (Pd(PPh$_3$)$_4$)(2.5 mol %). The reaction mixture was heated to reflux under argon atmosphere, for 8 to 18 hours depending on the substrate. Upon completion deemed by TLC analysis, the reaction was cooled to room temperature and the solvent was removed. The crude product was dissolved in dichloromethane and washed with water 3 times. The organic phase was dried with MgSO$_4$, filtered, and the solvent was removed. The residue was purified by flash column chromatography (EtOAc/Hexanes) to yield the desired compounds (14b-g).
Dimethyl 2-(2-(phenylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (14b): Reagents employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (14a) (0.100 g, 0.387 mmol), iodobenzene (0.052 mL, 0.465 mmol), Pd(PPh₃)₄ (0.010 g, 0.009 mmol), CuI (0.003 g, 0.018 mmol), triethylamine (0.500 mL, C = 0.890 mM): yield 61% (0.079 g, 0.236 mmol) as a clear oil; R₇ = 0.51, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 7.57-7.52 (m, 3H), 7.38-7.34 (m, 3H), 7.27-7.25 (m, 2H), 7.11-7.09 (m, 1H), 3.71 (s, 3H), 3.64 (t, J = 8.8 Hz, 1H), 3.37 (s, 3H), 2.30 (dd, J = 8.2, 5.3 Hz, 1H), 1.80 (dd, J = 9.4, 5.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.2, 167.1, 136.6, 131.7, 131.6, 128.3, 127.9, 127.3, 127.0, 125.3, 123.3, 110.0, 94.6, 87.3, 52.6, 52.2, 36.8, 32.4, 19.2; IR (thin film, cm⁻¹) 3061, 2951, 1728, 1495, 1436, 1332, 1284, 1215, 1130, 757, 692; HRMS (EI) calc’d for C₂₁H₁₈O₄ 334.1205, found 334.1209.

Dimethyl 2-(2-(naphthalen-1-ylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (14c): Reagents employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (14a) (0.150 g, 0.581 mmol), 1-iodonaphthalene (0.102 mL, 0.699 mmol), Pd(PPh₃)₄ (0.015 g, 0.013 mmol), CuI (0.006 g, 0.030 mmol), triethylamine (0.700 mL, C = 0.890 mM): yield 78% (0.175 g, 0.455 mmol) as a clear oil; R₇ = 0.46, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 8.46 (d, J = 8.2 Hz, 1H), 7.87 (dd, J = 10.6, 8.8 Hz, 2H), 7.78 (d, J = 7.6 Hz, 1H), 7.66-7.65 (m, 1H), 7.62 (t, J = 7.0 Hz, 1H), 7.54 (t, J = 7.0 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.30-7.29 (m, 2H), 7.13-7.12 (m, 1H), 3.72 (dd, J = 8.8, 8.2 Hz, 1H), 3.54 (s, 1H), 3.40 (s, 1H), 2.35 (dd, J = 8.2, 5.3 Hz, 1H), 1.85 (dd, J = 9.4, 5.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.0, 167.1, 136.4, 133.1, 132.0, 128.7, 128.1, 128.0, 127.3, 126.9, 126.7, 125.4, 125.2, 120.9, 92.6, 92.1, 52.5, 52.2, 37.0, 32.2, 19.1; IR (thin film, cm⁻¹) 3057, 2951, 1728, 1608, 1509, 1331, 132.0, 136.4, 133.1, 132.0, 128.7, 128.1, 128.0, 127.3, 126.9, 126.7, 125.4, 125.2, 120.9, 92.6, 92.1, 52.5, 52.2, 37.0, 32.2, 19.1; IR (thin film, cm⁻¹) 3057, 2951, 1728, 1436, 1283, 1130, 802; HRMS (EI) calc’d for C₂₅H₂₀O₄ 384.1362, found 384.1363.

Dimethyl 2-(2-(2,4-dimethoxyphenyl)ethynyl)phenyl)cyclopropane-1,1-dicarboxylate (14d): Reagents employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (14a) (0.125 g, 0.484 mmol), 1-iodo-2,4-dimethoxybenzene (0.153 g, 0.581 mmol), Pd(PPh₃)₄ (0.014 g, 0.012 mmol), CuI (0.005 g, 0.024 mmol), triethylamine (0.600 mL, C = 0.890 mM): yield 57% (0.108 g, 0.274 mmol) as a clear oil; R₇ = 0.29, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) δ = 7.53-7.51 (m, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.21-7.19 (m, 2H), 7.05-7.02 (m, 1H), 6.50-6.45 (m, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H), 3.64 (dd, J = 9.0, 8.6 Hz, 1H), 3.36 (s, 3H), 2.32 (dd, J = 8.6, 5.1 Hz, 1H), 1.84 (dd, J = 9.4, 5.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 176.1, 161.1, 136.2, 134.4, 131.7, 127.3, 127.1, 126.7, 125.9, 110.0, 105.3, 104.8, 98.4, 91.1, 90.1, 55.8, 55.4, 52.5, 52.1, 36.9, 32.3, 19.4; IR (thin film, cm⁻¹) 2951, 2210, 1727, 1608, 1509, 1300, 1211, 1124, 1030, 758; HRMS (EI) calc’d for C₂₃H₂₂O₆ 394.1416, found 394.1412.
Dimethyl 2-(2-((2-nitrophenyl)ethynyl)phenyl)cyclopropane-1,1-dicarboxylate (14e): Reagents employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (14a) (0.050 g, 0.190 mmol), 1-iodo-2-nitrobenzene (0.057 g, 0.230 mmol), Pd(PPh3)4 (0.006 g, 0.005 mmol), Cul (0.002 g, 0.009 mmol), triethylamine (0.300 mL, C = 0.890 mM): yield 85% (0.061 g, 0.161 mmol) as a clear oil; Rf = 0.29, 30% EtOAc in hexanes; 1H NMR (400 MHz, CDCl3) δ = 8.10 (dd, J = 8.2, 1.2 Hz, 1H), 7.77 (dd, J = 7.8, 1.2 Hz, 1H), 7.61 (dt, J = 7.4, 1.6 Hz, 2H), 7.49-7.45 (m, 1H), 7.33-7.27 (m, 2H), 7.09 (br d, J = 8.2, 5.1 Hz, 1H) 1.84 (dd, J = 9.4, 5.5 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ = 170.0, 167.0, 149.2, 137.0, 134.9, 132.8, 132.6, 128.9, 128.6, 127.4, 127.0, 124.6, 124.4, 118.8, 95.1, 89.6, 52.6, 52.2, 37.1, 31.8, 19.1; IR (thin film, cm⁻¹) 2952, 2853, 2217, 1727, 1525, 1342, 1286, 1216, 1130, 746; HRMS (EI) calc’d for C21H17NO6 379.1056, found 380.1136.

Dimethyl 2-(2-(quinolin-3-ylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (14f): Reagents employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (14a) (0.100 g, 0.390 mmol), 3-iodoquinoline (0.128 g, 0.500 mmol), Pd(PPh3)4 (0.012 g, 0.010 mmol), CuI (0.004 g, 0.020 mmol), triethylamine (0.500 mL, C = 0.890 mM): (0.025 g product, 0.062 g of dimer isolated), as a clear oil; Rf = 0.24, 30% EtOAc in hexanes; 1H NMR (400 MHz, CDCl3) (mixture of products) δ = 8.98 (br s, 1H), 8.32 (br s, 1H), 7.81 (dd, J = 8.2, 7.0 Hz, 1H), 7.49-7.56 (m, 2H), 7.09 (br d, J = 8.2, 5.1 Hz, 1H), 7.06 (d, J = 8.2, 5.1 Hz, 1H), 3.82 (br s, 2H), 3.71 (s, 3H), 3.65 (dd, J = 8.8, 8.2 Hz, 1H), 3.48 (br t, 1H), 3.39 (br s, 2H), 3.35 (s, 3H), 2.36 (dd, J = 9.4, 5.5 Hz, 1H), 2.33 (dd, J = 7.6, 5.3 Hz, 1H), 1.89-1.82 (br m, 2H).

Dimethyl 2-(2-(thiophen-2-ylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (14g): Reagents employed: Dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (14a) (0.075 g, 0.290 mmol), 2-bromothiophene (0.042 mL, 0.430 mmol), Pd(PPh3)4 (0.006 g, 0.006 mmol), Cul (0.003 g, 0.002 mmol), triethylamine (0.350 mL, C = 0.890 mM): yield 72% (0.071 g, 0.209 mmol) as a clear oil; Rf = 0.42, 30% EtOAc in hexanes; 1H NMR (600 MHz, CDCl3) (mixture of products) δ = 7.48 (br dd, J = 7.0, 2.4 Hz, 1H), 7.29 (d, J = 4.1 Hz, 2H), 7.25-7.22 (m, 2H), 7.09 (br d, J = 7.0, 1.8 Hz, 1H), 7.02 (t, J = 4.7 Hz, 1H), 3.74 (s, 3H), 3.57 (t, J = 8.8 Hz, 1H), 3.36 (s, 3H), 2.29 (dd, J = 8.2, 5.3 Hz, 1H), 1.80 (dd, J = 9.4, 5.3 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ = 170.0, 167.1, 136.5, 132.0, 131.4, 128.0, 127.3, 127.2, 127.1, 127.0, 124.9, 123.2, 91.0, 87.8, 52.6, 52.1, 36.7, 32.1, 19.1; IR (thin film, cm⁻¹) 2950, 2925, 1725, 1434, 1383, 1127; HRMS (EI) calc’d for C19H16O4S 340.0769, found 340.0770.

General Experimental Procedure for the Synthesis of Substrate 16
2-bromobenzaldehyde (15) (1 equivalent) was dissolved in triethylamine (3.0 mL) under Argon atmosphere. To this solution, 1-hexyne (1.2 equivalent), tetrakis(triphenylphosphine)palladium(0) (Pd(PPh3)4) (2 mol %) and copper iodide (Cul) (1 mol %) were added. The solution was stirred at 50 °C for 4 hours, than cooled to room temperature. The reaction mixture was filtered and the solid remaining was rinsed with ether. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired compound (16).
2-(hex-1-yn-1-yl)benzaldehyde (16): Reagents employed: 2-bromobenzaldehyde (15) (0.095 mL, 0.811 mmol), 1-hexyne (0.112 mL, 0.975 mmol), Pd(PPh₃)₄ (0.018 g, 0.016 mmol), CuI (0.002 g, 0.008 mmol), triethylamine (3.0 mL): yield 80 % (0.121 g, 0.649 mmol) as a yellow oil: data matched that previously reported¹

General Experimental Procedure for the Synthesis of Substrate 17.
2-(hex-1-yn-1-yl)benzaldehyde (16) (1 equivalent) was dissolved in benzene (5 mL) and dimethyl malonate (1.3 equivalent) was added. In a separate flask, the piperidine (0.1 equivalent) and acetic acid (0.1 equivalent) were added together, this was added to the reaction flask and the reaction mixture was heated to reflux overnight using a Dean-Stark apparatus. After 16-18 hours, upon completion by TLC analysis, the reaction was cooled and water was added and the aqueous was extracted with EtOAc 3 times. The organic layers were combined and washed with 1M NaOH solution 4 times, followed by a water wash. From there the organic layers were dried with MgSO₄, filtered and the solvent was removed. This yielded the desired compound 17.

Dimethyl 2-(2-(hex-1-yn-1-yl)benzylidene)malonate (17): Reagents employed: 2-(hex-1-yn-1-yl)benzaldehyde (16) (0.075 g, 0.403 mmol), dimethyl malonate (0.068 g, 0.515 mmol), piperidine (0.003 g, 0.040 mmol), acetic acid (0.002 g, 0.040 mmol), benzene: yield 65% (0.078 g, 0.262 mmol) as a yellow oil: data matched that previously reported²

General Experimental Procedure for the Synthesis of Substrate 14h.
Dimethyl 2-(2-(hex-1-yn-1-yl)benzylidene)malonate (17) (1 equivalent) was dissolved in DMSO (2 mL). In a separate reaction flask, the Corey-Chaykovsky ylide (1.7 equivalent) was dissolved in DMSO (5 mL) and sodium hydride (1.7 equivalent, in 60% mineral oil) was added portionwise and stirred until the evolution of H₂ ceased. The starting material solution was slowly added dropwise over 5 minutes, the reaction mixture was stirred at room temperature for 6 hours and as the reaction was complete by TLC analysis. Water was added to the reaction and the aqueous was extracted 4 times with ether. The organic phases were combines and washed 4 times with brine, and 3 times with water. The organic phases were dried with MgSO₄, filtered, and the solvent was removed. The residue needed no further purification to yield the desired compound 14h.

Dimethyl 2-(2-(hex-1-yn-1-yl)phenyl)cyclopropane-1,1-dicarboxylate (14h): Reagents employed: dimethyl 2-(2-(hex-1-yn-1-yl)benzylidene)malonate (17) (0.075 g, 0.250 mmol), trimethyl sulfoxonium iodide (Corey-Chaykovsky Reagent) (0.092 g, 0.420 mmol), sodium hydride (in 60% mineral oil, 0.016 g, 0.420 mmol), DMSO: yield 38 % (0.030 mg, 0.095 mmol) as a clear oil; Rᵓ = 0.53, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) δ = 7.37-7.35 (m,1H), 7.18-7.14 (m, 2H), 7.01-6.99 (m, 1H), 3.78 (s, 3H), 3.51 (t, J = 8.8 Hz, 1H), 3.34 (s, 3H), 2.42 (t, J = 7.0 Hz, 2H), 2.26 (dd, J = 8.8, 5.3 Hz, 1H) 1.77 (dd, J = 9.4, 5.3 Hz, 1H), 1.60-1.56 (m, 2H), 1.50-1.45 (m, 2H), 0.95 (t, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.1, 167.2, 136.4, 131.7, 127.1, 126.6, 126.1, 95.9, 78.4, 52.6, 52.1, 36.7, 32.3, 30.7, 22.0, 19.3, 13.6; IR (thin film, cm⁻¹) 2954, 2932, 2872, 1730, 1436, 1332, 1282, 1212, 1130, 756; HRMS (EI) calc’d for C₁₉H₂₂O₄ 314.1518, found 314.1517.
General Experimental Procedure for the Synthesis of Substrates 18a-h.
Subjecting the alkyne-bearing cyclopropane diesters 14a-h, the starting material (1 equivalent) was dissolved in methanol and 1.7 M NaOH was added (1.7 equivalent). The reaction mixture was stirred at room temperature until completion determined by TLC analysis. Once reaction was done, water was added and the reaction was extracted with ethyl acetate. The aqueous layer was acidified and extracted 3 times with ethyl acetate. The combined organic layer was washed with water and dried with MgSO₄, filtered and the solvent was removed. No further purification was needed, yielding the desired cyclopropane hemimalonates 18a-h.

2-(2-ethynylphenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (18a): Reagents employed: dimethyl 2-(2-ethynylphenyl)cyclopropane-1,1-dicarboxylate (14a) (0.120 g, 0.465 mmol), 1.7 M NaOH (0.465 mL, 0.790 mmol), methanol: yield 88 % (0.100 mg, 0.409 mmol) to give a white solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.44 (br d, J = 7.8 Hz, 1H), 7.34-7.30 (m, 1H), 7.26-7.22 (m, 2H), 3.51 (dd, J = 9.4, 9.0 Hz, 1H), 3.37 (s, 1H), 3.25 (s, 3H), 2.41-2.33 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 173.9, 170.9, 137.5, 132.2, 128.7, 128.5, 127.7, 83.6, 80.7, 52.6, 40.3, 33.1, 22.2; IR (thin film, cm⁻¹) 3283, 3028, 2955, 1754, 1675, 1447, 1352, 1146, 759; HRMS (EI) calc’d for C₁₄H₁₃O₄ 245.0814, found 245.0807 (M+H).

1-(methoxycarbonyl)-2-(2-(phenylethynyl)phenyl)cyclopropanecarboxylic acid (18b): Reagents employed: dimethyl 2-(2-(phenylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (14b) (0.075 g, 0.224 mmol), 1.7 M NaOH (0.230 mL, 0.381 mmol), methanol: yield 95 % (0.068 g, 0.212 mmol) to give a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ = 7.52-7.48 (m, 3H), 7.34-7.30 (m, 3H), 7.28-7.22 (m, 3H), 3.60 (t, J = 9.0 Hz, 1H), 3.23 (s, 3H), 2.43-2.35 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 173.9, 170.6, 136.2, 131.9, 131.8, 131.6, 128.8, 128.6, 128.4, 128.0, 127.8, 122.5, 110.0, 95.7, 86.3, 52.6, 40.5, 33.2, 22.4; IR (thin film, cm⁻¹) 3060, 2922, 1757, 1675, 1443, 1216, 1146, 756, 691; HRMS (EI) calc’d for C₂₀H₁₆O₄ 320.1049, found 320.1046.

1-(methoxycarbonyl)-2-(2-(naphthalen-1-ylethynyl)phenyl)cyclopropanecarboxylic acid (18c): Reagents employed: dimethyl 2-(2-(naphthalen-1-ylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (14c) (0.175 g, 0.460 mmol), 1.7 M NaOH (0.460 mL, 0.770 mmol), methanol: yield 80 % (0.137 g, 0.370 mmol) to give a yellow oil; ¹H NMR (600 MHz, CDCl₃) δ = 8.37 (d, J = 8.8 Hz, 1H), 7.86 (t, J = 7.0 Hz, 2H), 7.80 (d, J = 7.0 Hz, 1H), 7.68 (br t, 1H), 7.61 (dd, J = 8.2, 7.0 Hz, 1H), 7.52 (dt, J = 22.3, 8.2, 7.0 Hz, 2H), 7.30-7.35 (m, 3H), 3.73 (t, J = 8.8 Hz, 1H), 3.30 (s, 3H), 2.50-2.48 (m, 1H), 2.45-2.43 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 173.4, 171.0, 136.1, 133.1, 132.2, 131.0, 129.1, 128.6, 128.4, 128.0, 127.8, 122.5, 110.0, 95.7, 86.3, 52.6, 40.5, 33.6, 22.2; IR (thin film, cm⁻¹) 3058, 2953, 2853, 1755, 1675, 1443, 1216, 1146, 756, 691; HRMS (EI) calc’d for C₂₄H₁₈O₄ 370.1205, found 370.1203.

2-(2-(2,4-dimethoxyphenyl)ethynyl)phenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (18d): Reagents employed: dimethyl 2-(2-(2,4-dimethoxyphenyl)ethynyl)phenyl)cyclopropane-1,1-dicarboxylate (14d) (0.100 g, 0.250 mmol), 1.7 M NaOH (0.250 mL, 0.430 mmol), methanol: yield 86 % (0.082 g, 0.216 mmol) to give a clear oil; ¹H NMR (600 MHz, CDCl₃) δ = 7.54-7.52 (m, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.25-7.21 (m, 3H), 6.52 (dd, J = 8.2, 2.4 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.64 (t, J = 9.4 Hz, 1H), 3.27 (s, 3H), 2.47-2.40 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 174.0, 170.3, 161.5, 135.9, 134.4, 131.8, 128.8, 127.6, 127.2, 125.6, 104.9, 104.5, 98.3, 89.1, 55.7, 55.4,
72.5, 40.5, 33.2, 22.3; IR (thin film, cm\(^{-1}\)) 2925, 2853, 1735, 1509, 1439, 1211, 1030; HRMS (EI) calc’d for C\(_{22}\)H\(_{20}\)O\(_{6}\) 380.1260, found 380.1265.

1-(methoxycarbonyl)-2-(2-(2-nitrophenyl)ethynyl)phenyl)cyclopropanecarboxylic acid (18e): Reagents employed: dimethyl 2-(2-(2-nitrophenyl)ethynyl)phenyl)cyclopropane-1,1-dicarboxylate (14e) (0.060 g, 0.160 mmol), 1.7 M NaOH (0.160 mL, 0.270 mmol), methanol: yield 68 % (0.040 mg, 0.109 mmol) to give a yellow oil; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 8.08\) (d, \(J = 8.2\) Hz, 1H), 7.73 (d, \(J = 8.2\) Hz, 1H), 7.65-7.60 (m, 2H), 7.47 (dd, \(J = 8.2, 7.6\) Hz, 1H), 7.37-7.27 (m, 3H), 3.65 (dd, \(J = 9.4, 8.8\) Hz, 1H), 3.28 (s, 3H), 2.46 (dd, \(J = 8.8, 4.7\) Hz, 1H), 2.39 (dd, \(J = 9.4, 4.7\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 173.9, 170.3, 136.7, 134.8, 133.2, 132.7, 129.0, 128.8, 128.0, 124.7, 93.7, 90.5, 52.7, 40.3, 29.7, 22.3; IR (thin film, cm\(^{-1}\)) 3025, 2925, 2854, 2217, 1737, 1525, 1342, 1217, 1145, 746; HRMS (EI) calc’d for C\(_{22}\)H\(_{20}\)O\(_{6}\) 380.1260, found 380.1265.

1-(methoxycarbonyl)-2-(2-(quinolin-3-ylethynyl)phenyl)cyclopropanecarboxylic acid (18f): Reagents employed: dimethyl 2-(2-(quinolin-3-ylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (14f) (0.025 g, 0.065 mmol), 1.7 M NaOH (0.065 mL, 0.111 mmol), methanol: yield 58% (0.014 g, 0.038 mmol) to give a yellow oil; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta = 9.00\) (br s, 1H), 8.37 (br s, 1H), 8.07 (br d, \(J = 8.2\) Hz, 1H), 7.86 (br d, \(J = 8.2\) Hz, 1H), 7.71 (br t, \(J = 7.6\) Hz, 1H), 7.56 (dd, \(J = 8.6\) Hz, 1H), 7.37 (t, \(J = 7.0\) Hz, 1H), 7.31 (t, \(J = 7.6\) Hz, 2H), 3.69 (t, \(J = 9.0\) Hz, 1H), 3.30 (s, 3H), 2.48 (dd, \(J = 8.2, 4.7\) Hz, 1H), 2.41-2.38 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 172.7, 171.3, 138.2, 136.9, 133.2, 132.0, 129.0, 128.7, 128.4, 127.9, 127.8, 123.4, 123.2, 113.9, 80.4, 80.2, 52.7, 39.1, 33.5, 21.9; IR (thin film, cm\(^{-1}\)) 2923, 1958, 1731, 1445, 1333, 1342, 1145, 755; HRMS (EI) calc’d for C\(_{23}\)H\(_{17}\)NO\(_4\) 371.1158, found 371.1169.

1-(methoxycarbonyl)-2-(2-(thiophen-2-ylethynyl)phenyl)cyclopropanecarboxylic acid (18g): Reagents employed: dimethyl 2-(2-(thiophen-2-ylethynyl)phenyl)cyclopropane-1,1-dicarboxylate (14g) (0.071 g, 0.210 mmol), 1.7 M NaOH (0.210 mL, 0.360 mmol), methanol: yield 75 % (0.051 mg, 0.157 mmol) to give a clear oil; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.50\) (d, \(J = 5.5\) Hz, 1H), 7.37 (d, \(J = 3.5\) Hz, 1H), 7.32-7.28 (m, 3H), 7.13 (br d, 1H), 6.80 (br d, 1H), 3.59 (t, \(J = 9.0\) Hz, 1H), 3.27 (s, 3H), 2.46-2.40 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 172.7, 171.3, 138.2, 136.9, 133.2, 129.0, 128.7, 128.4, 127.9, 127.8, 123.4, 123.2, 113.9, 80.4, 80.2, 52.7, 39.1, 33.5, 21.9; IR (thin film, cm\(^{-1}\)) 3105, 2953, 2201, 1753, 1445, 1333, 1217, 1141, 755; HRMS (EI) calc’d for C\(_{18}\)H\(_{14}\)O\(_4\)S 326.0613, found 326.0210.

2-(2-(hex-1-yn-1-yl)phenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (18h): Reagents employed: dimethyl 2-(2-(hex-1-yn-1-yl)phenyl)cyclopropane-1,1-dicarboxylate (14h) (0.030 g, 0.100 mmol), 1.7 M NaOH (0.100 mL, 0.160 mmol), methanol: yield 90 % (0.027 g, 0.090 mmol) to give a yellow oil; \(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta = 7.36\) (br d, \(J = 7.6\) Hz, 1H), 7.24-7.19 (m, 3H), 3.48 (dd, \(J = 9.4, 8.8\) Hz, 1H), 3.24 (s, 3H), 2.43 (dd, \(J = 7.6, 7.0\) Hz, 2H), 2.40-2.35 (m, 2H), 1.61-1.56 (m, 2H), 1.48-1.43 (m, 2H), 0.94 (dd, \(J = 7.6, 7.0\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 174.1, 170.8, 136.4, 131.5, 128.6, 127.6, 127.1, 125.7, 97.4, 77.7, 52.5, 40.9, 33.1, 30.6, 29.7, 22.3, 22.1, 19.3, 13.6; IR (thin film, cm\(^{-1}\)) 2924, 2853, 1735, 1449, 1248, 755; HRMS (EI) calc’d for C\(_{18}\)H\(_{20}\)O\(_4\) 300.1362, found 300.1350.
General Experimental Procedure for the synthesis of Triazoles 8a-h
Cyclopropane hemimalonate (18a-h) (1 equivalent) was dissolved in a solution of 2-methoxyethanol:water (10:1) and then sodium azide (NaN₃) (1.2 equivalent) and ammonium chloride (NH₄Cl) (1.4 equivalent) were added. The mixture was heated to reflux and monitored until completion by TLC analysis (1.5 – 2 h). The reaction mixture was cooled to room temperature, and water was added. The reaction was extracted 3 times with ether. The organic layers were combined and dried with MgSO₄, filtered and the solvent was removed. The residue was purified by flash column chromatography (EtOAc/hexanes) to yield the desired triazole (8a-h).

Methyl 3-(8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (8a): Reagents employed: 2-(2-ethynylphenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (18a) (0.080 g, 0.328 mmol), NaN₃ (0.026 g, 0.394 mmol), NH₄Cl (0.025 g, 0.459 mmol), 2-methoxyethanol/water: yield 80% (0.064 g, 0.263 mmol) as a clear oil; Rᵣ = 0.12, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 7.82 (s, 1H), 7.63 (d, J = 7.0 Hz, 1H), 7.50-7.40 (m, 3H), 5.54 (dd, J = 7.8, 3.9 Hz, 1H), 3.64 (s, 3H), 2.81-2.73 (m, 1H), 2.60-2.52 (m, 1H), 2.47-2.40 (m, 1H), 2.29-2.20 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.8, 144.8, 129.1, 128.6, 127.1, 124.3, 123.8, 121.7, 61.9, 51.8, 28.8, 28.5; IR (thin film, cm⁻¹) 3136, 3057, 2998, 2951, 2850, 1734, 1624, 1471, 1437, 1416, 1379, 1245, 1205, 1094; HRMS (EI) calc’d for C₁₃H₁₃N₃O₂ 243.1008, found 243.1006.

Methyl 3-(3-phenyl-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (8b): Reagents employed: 1-(methoxycarbonyl)-2-(2-(phenylethynyl)phenyl)cyclopropanecarboxylic acid (18b) (0.046 g, 0.143 mmol), NaN₃ (0.011 g, 0.172 mmol), NH₄Cl (0.013 g, 0.242 mmol), 2-methoxyethanol/water: yield 77% (0.035 g, 0.110 mmol) as a white solid; Rᵣ = 0.17, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 7.96 (d, J = 7.04 Hz, 2H), 7.91 (d, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.0 Hz, 1H), 7.45-7.40 (m, 2H), 5.58 (dd, J = 7.0, 4.1 Hz, 1H), 3.65 (s, 3H), 2.84-2.78 (m, 1H), 2.63-2.58 (m, 1H), 2.50-2.45 (m, 1H), 2.34-2.28 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.9, 145.0, 133.9, 131.0, 129.1, 128.6, 127.1, 124.3, 123.8, 121.7, 61.9, 51.8, 28.8, 28.5; IR (thin film, cm⁻¹) 3853, 3058, 2950, 2852, 1735, 1609, 1446, 1358, 1174; HRMS (EI) calc’d for C₁₉H₁₇N₃O₂ 319.1321, found 319.1324.

Methyl 3-(3-(naphthalen-1-yl)-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (8c): Reagents employed: 1-(methoxycarbonyl)-2-(2-(naphthalen-1-ylethynyl)phenyl)cyclopropanecarboxylic acid (18c) (0.021 g, 0.060 mmol), NaN₃ (0.005 g, 0.070 mmol), NH₄Cl (0.005 g, 0.042 mmol), 2-methoxyethanol/water: yield 77% (0.016 g, 0.043 mmol) as a clear oil; Rᵣ = 0.17, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 8.18 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.88 (br s, 1H), 7.64 (br s, 1H), 7.54 (dt, J = 7.8, 7.0 Hz, 3H), 7.40 (t, J = 7.4 Hz, 1H), 7.32 (t, J = 7.4 Hz, 1H), 5.64 (br s, 1H), 3.68 (s, 3H), 2.92-2.83 (br m, 1H), 2.76-2.68 (m, 1H), 2.62-2.54 (m, 1H), 2.42-2.33 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.9, 145.0, 133.9, 131.0, 129.1, 128.9, 128.5, 127.7, 127.6, 126.6, 126.2, 125.8, 125.4, 123.6, 122.1, 62.0, 51.9, 29.0, 28.8; IR (thin film, cm⁻¹) 3853, 3058, 2850, 2852, 1735, 1609, 1446, 1358, 1174; HRMS (EI) calc’d for C₁₉H₁₇N₃O₂ 369.1477, found 369.1473.

Methyl 3-(3-(2,4-dimethoxyphenyl)-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (8d): Reagents employed: 2-(2-((2,4-dimethoxyphenyl)ethynyl)phenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (18d) (0.021 g, 0.055 mmol), NaN₃ (0.005 g,
0.070 mmol), NH₄Cl (0.005 g, 0.080 mmol), 2-methoxyethanol/water: yield 73% (0.015 g, 0.040 mmol) as a clear oil; Rᵣ = 0.10, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 7.78 (d, J = 8.2 Hz, 1H), 7.48 (t, J = 8.2 Hz, 2H), 7.42 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 6.67 (dd, J = 8.2, 2.4 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 5.55 (dd, J = 7.6, 4.1 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.65 (s, 3H), 2.87-2.77 (br m, 1H), 2.65-2.59 (m, 1H), 2.52-2.47 (m, 1H), 2.34-2.28 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 173.0, 161.4, 157.4, 144.8, 139.1, 135.1, 131.2, 128.7, 127.7, 123.2, 113.3, 105.0, 98.6, 61.5, 55.5, 55.2, 51.8, 28.9, 28.7; IR (thin film, cm⁻¹): 3445, 3001, 2924, 2850, 1735, 1617, 1580, 1509, 1454, 1308, 1210, 1161, 1117, 1032; HRMS (EI) calc’d for C₂₁H₂₁N₃O₄ 379.1532, found 379.1527.

Methyl 3-(3-(2-nitrophenyl)-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (8e): Reagents employed: 1-(methoxycarbonyl)-2-(2-(2-nitrophenyl)ethynyl)phenyl)cyclopropanecarboxylic acid (18e) (0.068 g, 0.190 mmol), NaN₃ (0.015 g, 0.220 mmol), NH₄Cl (0.014 g, 0.260 mmol), 2-methoxyethanol/water: yield 61% (0.042 g, 0.115 mmol) as a clear oil; Rᵣ = 0.12, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 8.08 (d, J = 8.2 Hz, 1H), 7.83 (d, J = 7.0 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 7.0 Hz, 1H), 7.44-7.38 (m, 3H), 5.60 (q, J = 7.0, 3.5 Hz, 1H), 3.65 (s, 3H), 2.84-2.78 (br m, 1H), 2.64-2.59 (m, 1H), 2.51-2.46 (m, 1H), 2.34-2.28 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.9, 144.9, 133.0, 132.2, 129.4, 129.1, 128.9, 127.1, 124.9, 121.5, 120.7, 119.6, 112.5, 62.1, 58.5, 29.7, 28.8, 28.6; IR (thin film, cm⁻¹) 2922, 2851, 1735, 1529, 1438, 1361, 754; HRMS (EI) calc’d for C₁₉H₁₆N₄O₄ 364.1172, found 364.1166.

Methyl 3-(3-(quinolin-3-yl)-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (8f): Reagents used: 1-(methoxycarbonyl)-2-(2-(quinolin-3-ylethynyl)phenyl)cyclopropanecarboxylic acid (18f) (0.027 g, 0.073 mmol), NaN₃ (0.006 g, 0.087 mmol), NH₄Cl (0.006 g, 0.100 mmol), 2-methoxyethanol/water: yield 30% (0.008 g, 0.022 mmol) as a clear oil; Rᵣ = 0.07, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) δ = 9.52 (br s, 1H), 8.76 (br s, 1H), 8.20 (br d, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.0 Hz, 1H), 7.44-7.38 (m, 3H), 5.60 (q, J = 7.0, 3.5 Hz, 1H), 3.65 (s, 3H), 2.89-2.81 (br m, 1H), 2.70-2.62 (m, 1H), 2.56-2.48 (m, 1H), 2.38-2.31 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.8, 149.2, 147.7, 145.1, 138.8, 136.3, 133.3, 129.8, 129.4, 129.3, 129.0, 128.1, 128.0, 127.3, 127.2, 124.6, 124.1, 121.3, 62.0, 51.9, 28.9, 28.6; IR (thin film, cm⁻¹) 3361, 2924, 2853, 2362, 1734, 1594, 1419, 1375, 1123, 1043; HRMS (EI) calc’d for C₁₉H₁₆N₄O₂ 370.1430, found 370.1443.

Methyl 3-(3-(thiophen-2-yl)-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (8g): Reagents employed: 1-(methoxycarbonyl)-2-(2-(thiophen-2-ylethynyl)phenyl)cyclopropanecarboxylic acid (18g) (0.035 g, 0.110 mmol), NaN₃ (0.009 g, 0.130 mmol), NH₄Cl (0.008 g, 0.150 mmol), 2-methoxyethanol/water: yield 39% (0.014 g, 0.043 mmol) as a clear oil; Rᵣ = 0.10, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) δ = 8.03 (d, J = 7.6 Hz, 1H), 7.63 (t, J = 2.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.47-7.43 (m, 1H), 7.41 (d, J = 4.1 Hz, 1H), 7.20-7.18 (m, 1H), 5.58 (dd, J = 5.3, 3.5 Hz, 1H), 3.65 (s, 3H), 2.83-2.78 (br m, 1H), 2.62-2.56 (m, 1H), 2.48-2.43 (m, 1H), 2.33-2.29 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.8, 144.8, 137.2, 133.9, 133.2, 129.1, 128.6, 127.8, 127.2, 125.1, 123.8, 121.6, 61.9, 51.8, 28.9, 28.5; IR (thin film, cm⁻¹) 3421, 2918, 2849, 2361, 2336, 1735, 1458, 1084; HRMS (EI) calc’d for C₁₇H₁₅N₃O₂S 325.0885 found 325.0877.
Methyl 3-(3-butyl-8H-[1,2,3]triazolo[5,1-a]isoindol-8-yl)propanoate (8h): Reagents employed: 2-(2-(hex-1-yn-1-yl)phenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (18h) (0.027 g, 0.089 mmol), NaN₃ (0.007 g, 0.108 mmol), NH₄Cl (0.008 g, 0.151 mmol), 2-methoxyethanol/water: yield 53% (0.014 g, 0.047 mmol) as a clear oil; Rᵢ = 0.17, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) δ = 7.60 (d, J = 7.4 Hz, 1H), 7.46 (dd, J = 7.8, 7.4 Hz, 2H), 7.38 (dd, J = 7.8, 7.0 Hz, 1H), 5.48 (dd, J = 7.4, 4.3 Hz, 1H), 3.64 (s, 3H), 2.94 (t, J = 7.0 Hz, 1H), 2.80-2.71 (m, 1H), 2.58-2.50 (m, 1H), 2.46-2.38 (m, 1H), 2.29-2.20 (m, 1H), 1.83-1.76 (m, 1H), 1.49-1.40 (m, 1H), 0.97 (t, J = 6.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ = 163.3, 154.7, 129.0, 123.8, 120.8, 93.2, 61.7, 51.8, 31.7, 28.9, 28.5, 25.6, 22.4, 13.9; IR (thin film, cm⁻¹) 2954, 2925, 2854, 1737, 1457, 1437, 1378, 1170, 767; HRMS (EI) calcd for C₁₇H₂₁N₃O₂ was 299.1634, found 299.1632.

References:

1. Dopico, P. G.; Finn, M. G. Tetrahedron 1999, 55, 29
Sample Name: Michele

Data collected on: 

/note/441.444/24/20_Michelle

Archive directory:
/home/data/kerry/Michelle

Sample directory:

NP-4-MO2-PHETIONCH-244.24_52

File: CARBON

Pulse Sequence: CARBON (z2pol)
Solvent: cdcl3
Data collected on: Apr 24 2014

Temp. 25.8 C / 298.1 K
Sample H27, Operator: Kerry

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.304 sec
Mist 25.25.3 Hz
1000 repetitions

Crossp. C13, 100.603253 MHz
Decoupled H1, 400.603224 MHz
Power 41 dB
continuously on
DART-16 modulated
DATA PROCESSING
line broadening 0.5 Hz
FF size 65534
Total time 56 min
\[ \text{Chemical Structure:} \quad \text{NO}_2 \quad \text{CO}_2\text{CH}_3 \]