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Highly Regioselective Synthesis of Spriocyclic Compounds via Pd-catalyzed Intermolecular Tandem Reaction

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General Remarks:

Column chromatography was carried out on silica gel. ¹H NMR spectra were recorded on 300 MHz or 400 MHz in CDCl₃ and ¹³C NMR spectra were recorded on 75 MHz or 100 MHz in CDCl₃ using TMS as internal standard. IR spectra were recorded on a FT-IR spectrometer and only major peaks are reported in cm⁻¹. Highresolution mass spectra (HRMS) were obtained by the ESI ionization sources. All products were further characterized by HRMS; copies of their ¹H NMR and ¹³C NMR spectra are provided. Commercially available reagents and solvents were used without further purification.

Starting Materials:

2b, ¹ **2c**, ² **2d**, ² **2e**, ² **2f**, ² **2g**, ¹ **2h**, ¹ and **2i** were prepared following the published literature procedures. All other commercially available organic halides were used without further purification.

Diethyl 2-(2-(3-hydroxyprop-1-ynyl)benzyl)malonate was prepared according to the literature.³

Typical procedure for the preparation of propargylic compounds 1a-e. To a solution of propargylic alcohol (2.0 mmol), pyridine (0.63 g, 8.0 mmol), and DMAP (44.8 mg, 0.4 mmol) in CH₂Cl₂ (10 mL) was added at 0 °C ethyl chloroformate (0.87 g, 8.0 mmol). After stirring for 2 h at room temperature, the reaction mixture was diluted with CH₂Cl₂. The CH₂Cl₂ solution was washed with a saturated aqueous copper sulfate solution, water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel to afford the corresponding propargylic compounds.

1a: The **1a** was prepared by the above method, But employing diethyl 2-(2-(3-hydroxyprop-1-ynyl)benzyl)malonate (0.61 g, 2.0 mmol) and ethyl chloroformate (0.87 g, 8.0 mmol) afforded **1a** 0.68 g (90 %) as an oil: 1 H NMR (300 MHz, CDCl₃) δ 7.45-7.42 (d, J = 6.9 Hz, 1H), 7.29-7.18 (m, 3H), 4.99 (s, 2H), 4.28-4.10 (m, 6H), 3.88-3.83 (t, J = 7.5 Hz, 1H), 3.36-3.34 (d, J = 7.8 Hz, 2H), 1.35-1.31 (m, 3H), 1.23-1.18 (t, J = 6.9 Hz, 6H); 13 C NMR (75 MHz, CDCl₃) δ 168.7, 154.5, 140.2, 132.5, 129.7, 128.9, 126.7, 121.6, 87.1, 84.9, 64.3, 61.2, 55.8, 52.1, 33.4, 14.1, 13.9; IR (neat, cm⁻¹) 1750, 1256, 1153, 790, 762.

1b: The **1b** was prepared by the above method, But employing diethyl 2-(2-(3-hydroxyprop-1-ynyl)benzyl)malonate (0.61 g, 2.0 mmol) and methyl chloroformate (0.76 g, 8.0 mmol) afforded **1b** 0.67 g (92 %) as an oil: 1 H NMR (300 MHz, CDCl₃) δ 7.45-7.42 (d, J = 7.8 Hz, 1H), 7.27-7.19 (m, 3H), 4.99 (s, 2H), 4.21-4.10 (m, 4H), 3.87-3.83 (m, 4H), 3.36-3.33 (d, J = 7.8 Hz, 2H), 1.23-1.18 (t, J = 7.8 Hz, 6H); 13 C NMR (75 MHz, CDCl₃) δ 168.8, 155.2, 140.3, 132.6, 129.8, 128.9, 126.7, 121.7, 87.0, 85.1, 61.3, 56.1, 55.1, 52.1, 33.5, 13.9; IR (neat, cm⁻¹) 1754, 1727, 1446, 1372, 1266, 1153, 791, 763.

1c: The **1c** was prepared by the above method, But employing diethyl 2-(2-(3-hydroxyprop-1-ynyl)benzyl)malonate (0.61 g, 2.0 mmol), triethylamine (0.81, 8.0 mmol) and acetic anhydride (0.48 g, 4.0 mmol) afforded **1c** 0.66 g (96 %) as an oil: 1 H NMR (400 MHz, CDCl₃) δ 7.45-7.43 (d, J = 7.2 Hz, 1H), 7.28-7.17 (m, 3H), 4.93 (s, 2H), 4.20-4.12 (m, 4H), 3.87-3.83 (t, J = 8.0 Hz, 1H), 3.36-3.34 (d, J = 8.0 Hz, 2H), 2.13 (s, 3H), 1.23-1.19 (m, 6H); 13 C NMR (100 MHz, CDCl₃) δ 170.2, 168.8, 140.2, 132.5, 129.8, 128.8, 126.8, 121.8, 87.7, 84.3, 61.3, 52.7, 52.1, 33.5, 20.7, 14.0; IR (neat, cm⁻¹) 1748, 1224, 1029, 763.

1d: The 1d was prepared by the above method, But employing diethyl 2-(2-(3-hydroxyprop-1-ynyl)benzyl)malonate (0.61 g, 2.0 mmol), DCC (0.41 g, 2.0 mmol), DMAP (44.8 mg, 0.4 mmol) and benzoic acid (0.49 g, 4.0 mmol) afforded 1e 0.69 g (84 %) as an oil: ¹H NMR (300 MHz, CDCl₃) δ 8.12-8.09 (m, 2H) 7.61-7.55 (m, 1H), 7.48-7.44 (m, 3H), 7.27-7.16 (m, 3H), 5.19 (s, 2H), 4.18-4.07 (m, 4H), 3.93-3.88 (t, J = 7.5 Hz, 1H), 3.40-3.37 (d, J = 8.1 Hz, 2H), 1.20-1.15 (t, J = 7.2 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 168.8, 165.8, 140.2, 133.2, 132.6, 129.8, 129.5, 128.8, 128.4, 126.8, 121.8, 87.8, 84.5, 61.3, 53.3, 52.1, 33.6, 13.9; IR (neat, cm⁻¹) 1728, 1268, 1102, 762, 714. 1e: The 1e was prepared by the above method, But employing diethyl 2-(2-(3-hydroxyprop-1-ynyl)benzyl)malonate (0.61 g, 2.0 mmol) and phosphochloridate (0.69 g, 4.0 mmol) afforded **1e** 0.70 g (82 %) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.43 (d, J = 7.6 Hz, 1H), 7.27-7.19 (m, 3H), 4.95-4.92 (m, 2H), 4.22-4.11 (m, 8H), 3.87-3.83 (t, J = 8.0 Hz, 1H), 3.37-3.35 (d, J = 7.6 Hz, 2H), 1.38-1.35(t, J = 7.2 Hz, 6H), 1.23-1.18 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 168.7, 140.1, 132.6, 129.7, 129.0, 126.8, 121.6, 87.6, 85.1, 64.0, 61.3, 55.6, 52.1, 33.4, 16.1, 13.9; IR (neat, cm⁻¹) 2984, 1733, 1274, 1029, 976, 763.

1f: The **1f** was prepared by the above method, But employing diethyl 2-(2-(3-hydroxyprop-1-ynyl)benzyl)malonate (0.61 g, 2.0 mmol) and 2-iodophenyl chloroformate (2.56 g, 8.0 mmol) afforded **1f** 0.88 g (80 %) as an oil: 1 H NMR (300 MHz, CDCl₃) δ 7.84-7.81 (m, 1H), 7.48-7.45 (d, J = 7.8 Hz, 1H), 7.40-7.35 (m, 1H), 7.26-7.18 (m, 4H), 7.02-6.97 (m, 1H), 5.14 (s, 2H), 4.19-4.08 (m, 4H), 3.91-3.86 (t, J = 8.4 Hz, 1H), 3.39-3.37 (d, J = 8.1 Hz, 2H), 1.20-1.16 (t, J = 7.2 Hz, 6H); 13 C NMR (75 MHz, CDCl₃) δ 168.7, 152.2, 151.0, 140.2, 139.4, 132.6, 129.7, 129.5, 129.0, 127.9, 126.7, 122.4, 121.4, 89.7, 86.3, 85.6, 61.3, 57.1, 52.1, 33.4, 13.9; IR (neat, cm $^{-1}$) 2982, 1771, 1730, 1467, 1371, 1213, 1153, 1035, 764.

1g: The **1g** was prepared by the above method, But employing diethyl 2-(2-(3-hydroxyprop-1-ynyl)benzyl)malonate (0.61 g, 2.0 mmol) and 2-bromophenyl chloroformate (1.87 g, 8.0 mmol) afforded **1g** 0.80 g (80 %) as an oil: 1 H NMR (300 MHz, CDCl₃) δ 7.63-7.60 (m, 1H), 7.47-7.45 (d, J = 6.6 Hz, 1H), 7.35-7.12 (m, 6H), 5.14 (s, 2H), 4.18-4.09 (m, 4H), 3.90-3.85 (t, J = 7.5 Hz, 1H), 3.39-3.36 (d, J = 7.5 Hz, 2H), 1.21-1.16 (t, J = 7.2 Hz, 6H); 13 C NMR (75 MHz, CDCl₃) δ 168.8, 152.2, 148.2, 140.3, 133.4, 132.7, 129.8, 129.1, 128.6, 127.7, 126.8, 123.2, 121.5, 115.9, 86.3, 85.7, 61.3, 57.2, 52.1, 33.5, 13.9; IR (neat, cm⁻¹) 2926, 1772, 1731, 1240, 1219, 1039, 764.

- [1] K. J. Edgar, S. N. Falling, J. Org. Chem. 1990, 55, 5287.
- [2] F. G. Schreiber, R. Stevenson, J. Chem. Soc., Perkin Trans. 1 1977, 90.
- [3] H. -P. Bi, L. -N. Guo, X. -H. Duan, F. -R. Gou, S. -H. Huang, X. -Y. Liu, Y. -M. Liang, *Org. Lett.* **2007**, *9*, 397.

General procedure for the preparation of spriocyclic compounds.

To a solution of Propargylic Compounds 1 (0.20 mmol) in DMF (2.0 mL) was added Cs₂CO₃ (130.4 mg, 0.40 mmol). The mixture was stirred for 5 min and Pd(PPh₃)₄ (11.5 mg, 0.01mmol, 5 mol %), and aryl halides 2 (0.30 mmol) were added. The resulting mixture was then heated under an argon atmosphere at 100°C. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was allowed to cool to room temperature and quenched with a saturated aqueous solution of ammonium chloride, and the mixture was extracted with EtOAc. The combined organic extracts were washed with water and saturated brine. The organic layers were dried over Na₂SO₄,

filtered. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford spriocyclic compounds 3.



3a: The reaction mixture was chromatographed using 40:1 hexanes/EtOAc to afford 51.4 mg (68%) of the indicated compound as an oil: 1 H NMR (400 MHz, CDCl₃) δ 7.43-7.41 (m, 1H), 7.34-7.33 (m, 2H), 7.26-7.22 (m, 2H), 7.11-7.09 (d, J = 7.2 Hz, 1H), 6.97-6.93 (t, J = 6.8 Hz, 1H), 6.85-6.83 (d, J = 8.0 Hz, 1H), 5.58 (s, 1H), 4.78 (s, 1H), 4.06-3.98 (m, 4H), 3.73-3.60 (q, J = 16.8 Hz, 2H), 0.96-0.92 (m, 6H); 13 C NMR (100 MHz, CDCl₃) δ 168.9, 168.7, 160.9, 147.6, 143.4, 140.3, 130.5, 129.4, 127.6, 126.7, 124.5, 123.6, 120.9, 120.4, 110.1, 104.5, 99.4, 71.1, 61.3, 38.6, 13.4; IR (neat, cm $^{-1}$) 1735, 1465, 1284, 1251, 1177, 1096, 1014, 754; HRMS calcd for $C_{23}H_{23}O_{5}$ [M+H] $^{+}$ 379.1540, found 379.1543.

3b: The reaction mixture was chromatographed using 40:1 hexanes/EtOAc to afford 54.4 mg (66%) of the indicated compound as an oil: 1 H NMR (400 MHz, CDCl₃) δ 7.39-7.34 (m, 3H), 7.26-7.24 (m, 1H), 7.20-7.18 (m, 1H), 7.09-7.07 (d, J = 8.0 Hz, 1H), 6.77-6.75 (d, J = 8.4 Hz, 1H), 5.59 (s, 1H), 4.85 (s, 1H), 4.06-3.99 (m, 4H), 3.73-3.57 (q, J = 16.4 Hz, 2H), 1.02-0.97 (m, 6H); 13 C NMR (100 MHz, CDCl₃) δ 168.6, 168.4, 159.3, 146.5, 142.9, 140.5, 130.2, 129.7, 128.5, 127.6, 126.1, 124.6, 123.6, 120.4, 111.1, 106.2, 100.3, 71.1, 61.4, 38.7, 13.5; IR (neat, cm⁻¹) 1737, 1467, 1286, 1251, 1098, 763, 732; HRMS calcd for $C_{23}H_{22}ClO_5$ [M+H]⁺ 413.1150, found 413.1154.

3c: The reaction mixture was chromatographed using 40:1 hexanes/EtOAc to afford 62.6 mg (74%) of the indicated compound as an oil: 1 H NMR (400 MHz, CDCl₃) δ 8.35-8.34 (d, J = 2.4 Hz, 1H), 8.24-8.21 (m, 1H), 7.40-7.38 (m, 2H), 7.28-7.26 (m, 1H), 7.09-7.07 (m, 1H), 6.89-6.87 (d, J = 8.4 Hz, 1H), 5.83-5.82 (d, J = 0.8 Hz, 1H), 5.02-5.02 (d, J = 0.8 Hz, 1H), 4.08-4.00 (m, 4H), 3.78-3.58 (q, J = 16.8 Hz, 2H), 1.05-0.96 (m, 6H); 13 C NMR (100 MHz, CDCl₃) δ 168.2, 165.0, 144.5, 142.4, 141.9, 140.8, 130.2, 128.3, 127.8, 127.1, 124.7, 123.7, 116.7, 110.1, 108.7, 102.0, 71.1, 61.6, 38.7, 13.6; IR (neat, cm⁻¹) 1735, 1522, 1468, 1340, 1273, 1251, 762, 739; HRMS calcd for $C_{23}H_{22}NO_7$ [M+H]⁺ 424.1391, found 424.1389.

3d: The reaction mixture was chromatographed using 40:1 hexanes/EtOAc to afford 72.9 mg (81%) of the indicated compound as an oil: 1 H NMR (300 MHz, CDCl₃) δ 8.14-8.14 (d, J = 1.8 Hz, 1H), 8.02-7.98 (m, 1H), 7.35-7.34 (m, 2H), 7.26-7.23 (m, 1H), 7.08-7.06 (d, J = 7.5 Hz, 1H), 6.86-6.83 (d, J = 8.7 Hz, 1H), 5.72 (s, 1H), 4.88 (s, 1H), 4.41-4.33 (m, 2H), 4.06-3.97 (m, 4H), 3.76-3.58 (q, J = 16.2 Hz, 2H), 1.43-1.35 (m, 3H), 1.00-0.92 (m, 6H); 13 C NMR (75 MHz, CDCl₃) δ 168.5, 168.4, 166.3, 164.1, 145.9, 142.6, 140.5, 132.8, 129.7, 127.6, 127.3, 124.5, 123.6, 123.5, 122.3, 109.8, 106.3, 100.8, 71.0, 61.4, 60.8, 38.6, 14.3, 13.5; IR (neat, cm⁻¹) 1730, 1715, 1609, 1287, 1264, 1109, 1016, 761; HRMS calcd for $C_{26}H_{30}NO_7$ [M+NH₄] $^{+}$ 468.2017, found 468.2012.

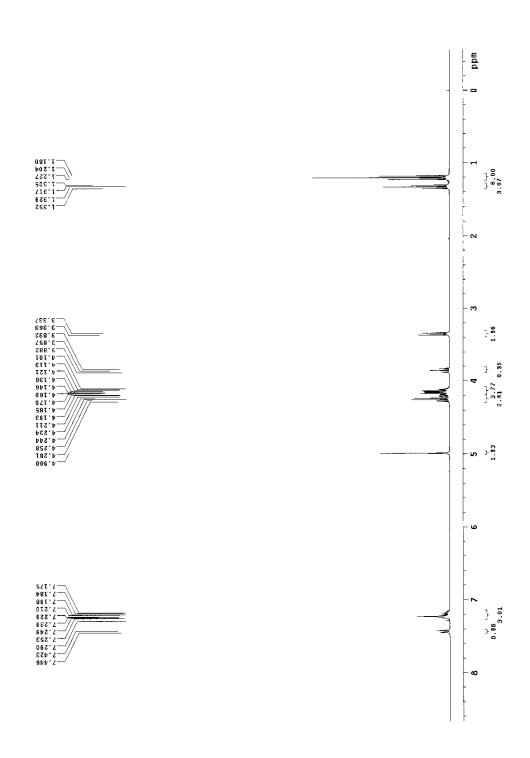
3e: The reaction mixture was chromatographed using 40:1 hexanes/EtOAc to afford 64.5 mg (71%) of the indicated compound as an oil: 1 H NMR (300 MHz, CDCl₃) δ 7.62-7.62 (d, J = 1.5 Hz, 1H), 7.57-7.55 (m, 2H), 7.49-7.40 (m, 3H), 7.34-7.33 (m, 3H), 7.27-7.23 (m, 1H), 7.14-7.11 (d, J = 7.8 Hz, 1H), 6.91-6.88 (d, J = 8.4 Hz, 1H), 5.65-5.65 (d, J = 0.6 Hz, 1H), 4.83 (s, 1H), 4.08-3.98 (m, 4H), 3.76-3.59 (q, J = 16.2 Hz, 2H), 0.99-0.94 (m, 6H); 13 C NMR (75 MHz, CDCl₃) δ 168.8, 168.7, 160.5, 147.4, 143.2, 141.1, 140.4, 134.6, 129.7, 129.5, 128.8, 127.6, 127.3, 126.8, 124.5, 123.7, 119.0, 110.3, 105.0, 100.1, 71.1, 61.4, 61.3, 38.7, 13.5, 13.4; IR (neat, cm⁻¹) 2925, 1735, 1472, 1283, 1255, 761; HRMS calcd for $C_{29}H_{30}NO_{5}$ [M+NH₄] $^{+}$ 472.2118, found 472.2123.

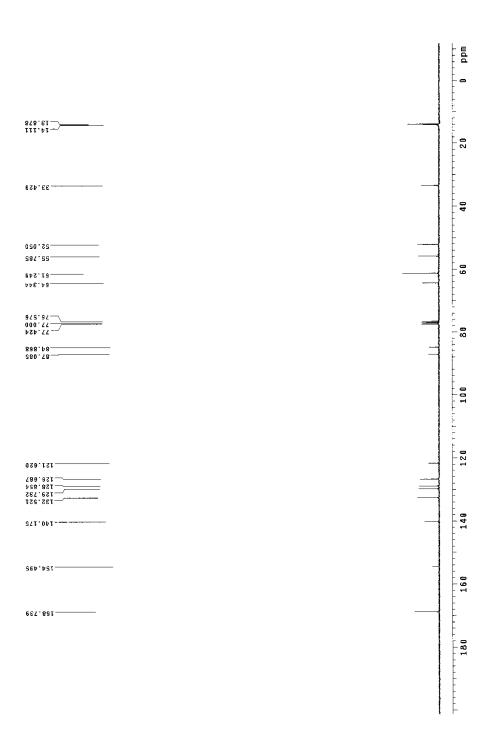
3f: The reaction mixture was chromatographed using 40:1 hexanes/EtOAc to afford 66.4 mg (79%) of the indicated compound as an oil: 1 H NMR (300 MHz, CDCl₃) δ 8.09-8.09 (d, J = 1.8 Hz, 1H), 7.94-7.91 (m, 1H), 7.36-7.23 (m, 3H), 7.08-7.06 (d, J = 7.5 Hz, 1H), 6.88-6.85 (d, J = 8.1 Hz, 1H), 5.74 (s, 1H), 4.90 (s, 1H), 4.06-3.99 (m, 4H), 3.76-3.58 (q, J = 16.5 Hz, 2H), 2.60 (s, 3H), 1.00-0.93 (m, 6H); 13 C NMR (75 MHz, CDCl₃) δ 196.5, 168.4, 168.3, 164.3, 145.8, 142.5, 140.6, 132.1, 131.0, 129.8, 127.6, 127.5, 124.6, 123.6, 121.0, 109.8, 106.6, 100.9, 71.0, 61.4, 38.6, 26.5, 13.5; IR (neat, cm⁻¹) 1735, 1677, 1605, 1261, 763, 730; HRMS calcd for $C_{25}H_{28}NO_{6}$ [M+NH₄]⁺ 438.1911, found 438.1915.

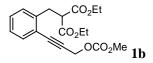
3g: The reaction mixture was chromatographed using 40:1 hexanes/EtOAc to afford 49.4 mg (63%) of the indicated compound as an oil: 1 H NMR (400 MHz, CDCl₃) δ 7.33-7.32 (m, 2H), 7.26-7.20 (m, 2H), 7.10-7.03 (m, 2H), 6.74-6.72 (d, J = 8.4 Hz, 1H), 5.53 (s, 1H), 4.74 (s, 1H), 4.05-3.98 (m, 4H), 3.72-3.59 (q, J = 16.8 Hz, 2H), 0.99-0.94 (m, 6H); 13 C NMR (100 MHz, CDCl₃) δ 168.9, 168.7, 159.1, 147.9, 143.6, 140.4, 131.2, 130.2, 129.3, 127.5, 126.6, 124.5, 123.6, 120.6, 109.7, 104.0, 99.6, 71.1, 61.2, 38.7, 20.8, 13.5; IR (neat, cm⁻¹) 1735, 1484, 1283, 1251, 1095, 810, 762; HRMS calcd for $C_{24}H_{25}O_{5}$ [M+H]⁺ 393.1697, found 393.1702.

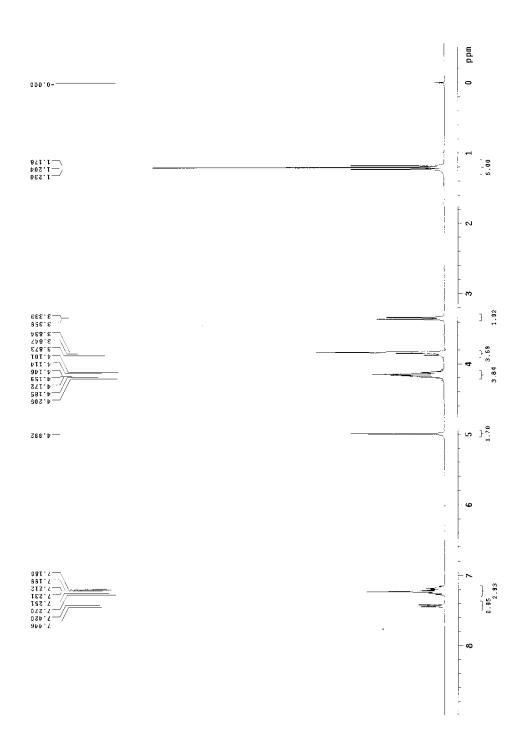
3h: The reaction mixture was chromatographed using 40:1 hexanes/EtOAc to afford 28.4 mg (35%) of the indicated compound as an oil: 1 H NMR (400 MHz, CDCl₃) δ 7.33-7.32 (m, 2H), 7.24-7.21 (m, 1H), 7.09-7.05 (m, 2H), 6.87 (s, 1H), 5.49 (s, 1H), 4.71 (s, 1H), 4.07-3.91 (m, 4H), 3.76-3.55 (q, J = 16.4 Hz, 2H), 2.30 (s, 3H), 2.12 (s, 3H), 0.97-0.94 (m, 6H); 13 C NMR (100 MHz, CDCl₃) δ 169.0, 168.8, 157.7, 148.6, 143.8, 140.7, 132.3, 130.1, 129.2, 127.4, 126.0, 124.3, 123.8, 119.7, 118.0, 103.8, 99.4, 71.4, 61.2, 61.1, 38.7, 20.8, 14.7, 13.5, 13.4; IR (neat, cm⁻¹) 1735, 1480, 1284, 1258, 1224, 762; HRMS calcd for $C_{25}H_{27}O_{5}$ [M+H] $^{+}$ 407.1853, found 407.1856.

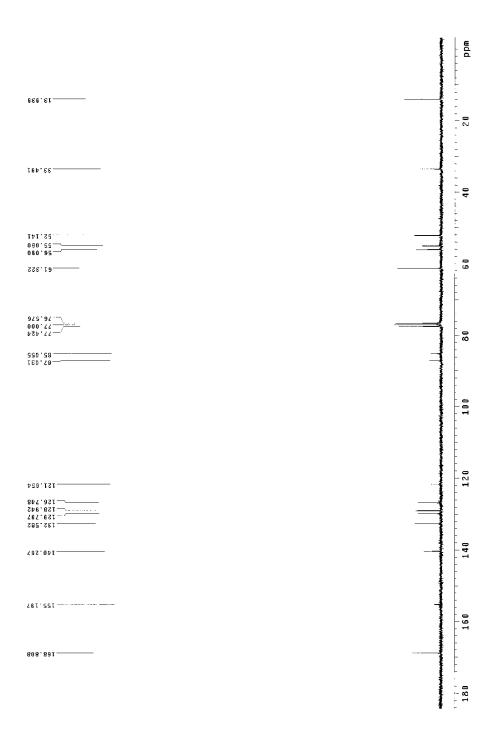
4a: To a solution of 3-(2-(2,2-di(ethoxycarbonyl)ethyl)phenyl)prop-2-ynyl ethyl carbonate **1a** (75.2 mg, 0.20 mmol) in DMF (2.0 mL) was Cs_2CO_3 (130.4 mg, 0.40 mmol). The mixture was stirred for 5 min and Pd(PPh₃)₄ (11.5 mg, 0.01mmol, 5 mol %) was added. The resulting mixture was then heated under an argon atmosphere at 100°C. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was allowed to cool to room temperature and quenched with a saturated aqueous solution of ammonium chloride, and the mixture was extracted with EtOAc. The combined organic extracts were washed with water and saturated brine. The organic layers were dried over Na₂SO₄, filtered. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford **4a** 52.1 mg (91%) as an oil: ¹H NMR (300 MHz, CDCl₃) δ 7.25-7.19 (m, 4H), 5.38 (s, 2H), 4.26-4.20 (q, J = 6.9 Hz, 4H), 3.70 (s, 2H), 1.28-1.24 (t, J = 7.2 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 206.1, 169.9, 139.4, 136.6, 128.1, 127.4, 124.5, 122.4, 82.5, 62.3, 61.9, 39.7, 14.1; IR (neat, cm⁻¹) 1734, 1247, 1179, 1057, 860, 764; HRMS calcd for $C_{17}H_{19}O_4$ [M+H]⁺ 287.1278, found 287.1280.

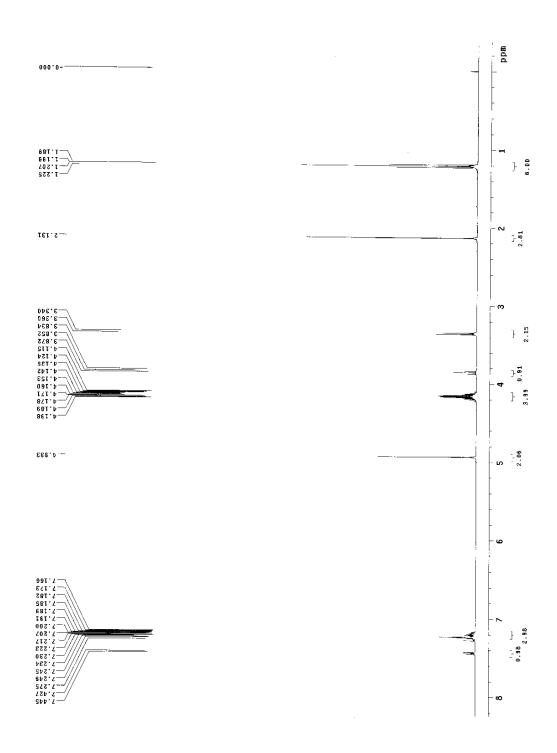


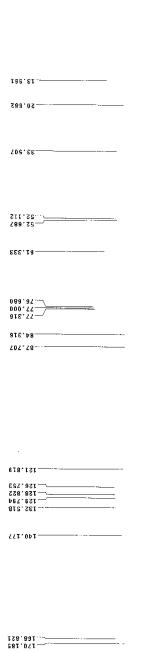




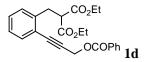


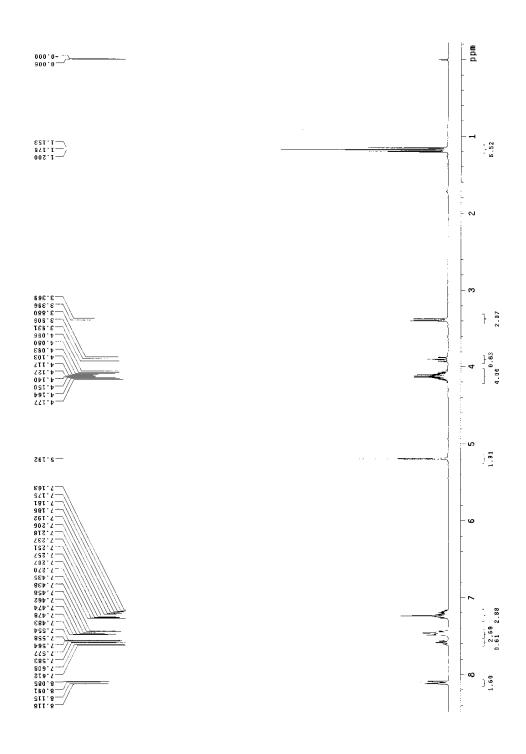


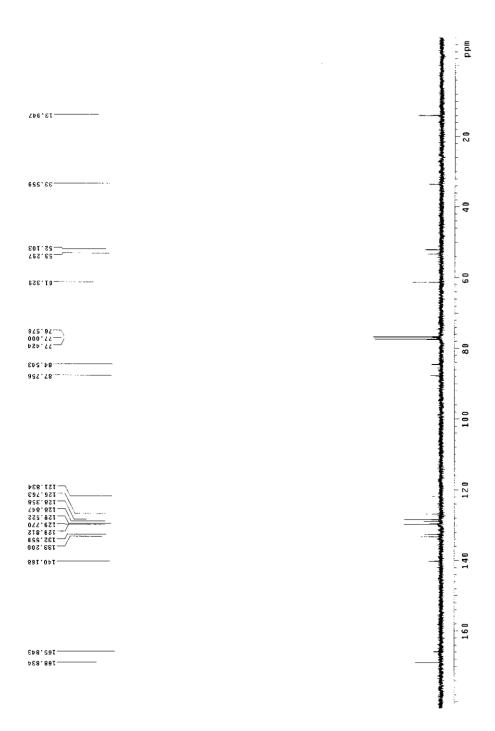


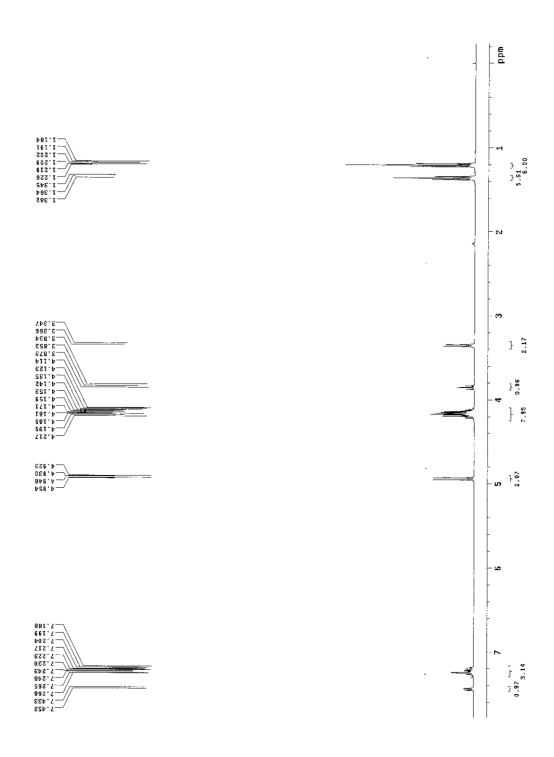


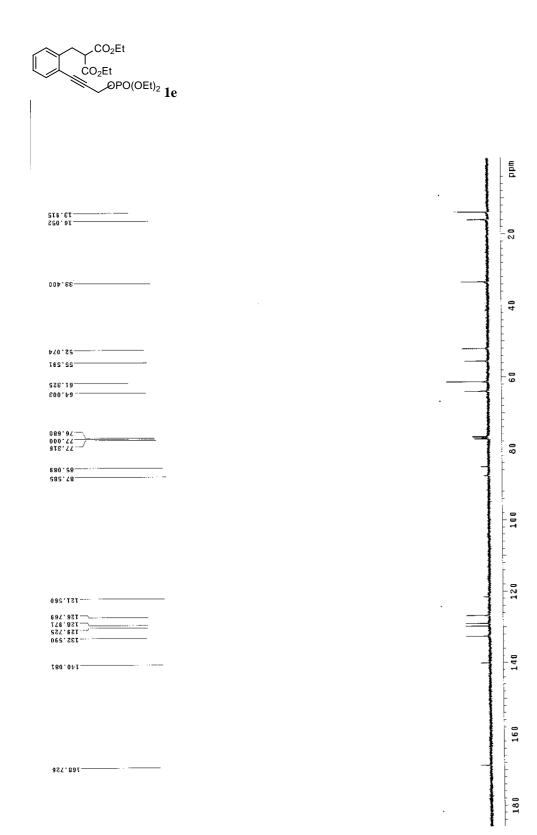


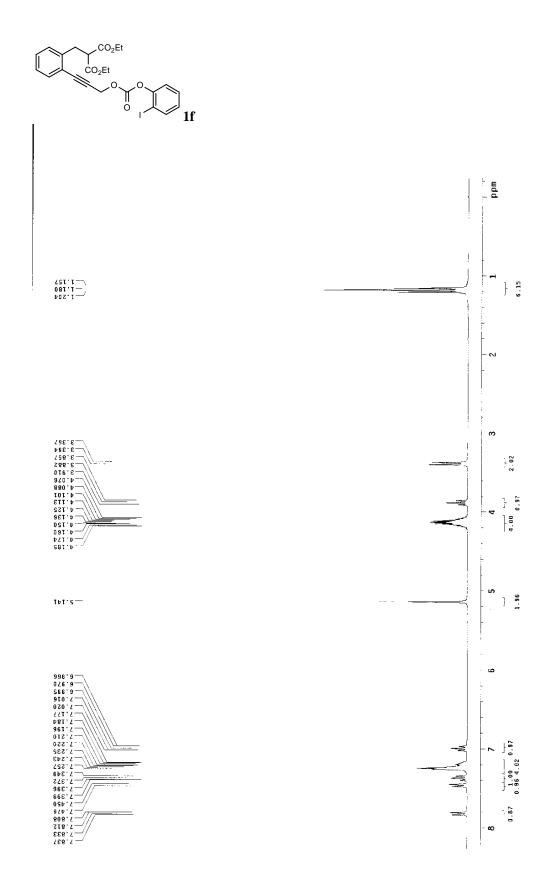




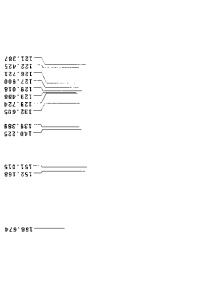


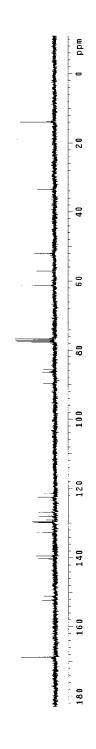


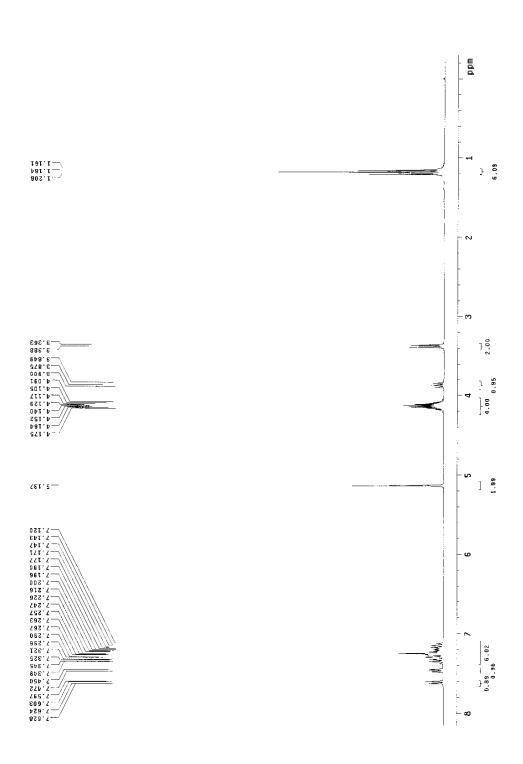












828.81----

884,88----

848.18

\$2\$.57 \$000.57 \$52.85

\$61.521 \$21.891 \$21.891 \$22.621 \$22.621 \$23

697.891 ----

