Supplementary Material (9 pages)

**The First Conjugate Addition Reaction of Terminal Alkynes
Catalytic in Metal: Copper(I)-Catalyzed Conjugate Addition
of Alkynes in Water**

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General Information:

For the reactions nanopure water was used. For flash chromatography and extractions technical grade solvents were used, which were distilled prior to use. All chemicals were purchased from Aldrich or Fluka and used as received unless noted otherwise. Phenylacetylene was distilled prior to use. Copper(II)acetate monohydrate (98+%, ACS) was purchased from Aldrich. 2-Ethynylfuran¹ and Meldrum's alkylidenes (**1a-g**²; **1h**³) were prepared according to a literature procedures.

Chromatographic purification was performed as flash chromatography using Merck silica 60 or Brunschwig Silica 60, with 0.4 bar pressure.

TLC was performed on Merck silica gel 60 F254 TLC glass plates and visualized with UV light and/or permanganate stain.

¹H-NMR spectra were recorded on a VARIAN Mercury 300 MHz spectrometer in chloroform-d, acetonitrile-d₃ or benzene-d₆. All signals are reported in ppm relative to TMS with the internal solvent signal (CDCl₃: 7.26 ppm, CD₃CN: 1.95 ppm, C₆D₆: 7.16 ppm) as standard. The data is reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration).

¹³C-NMR spectra were recorded with ¹H-decoupling on a VARIAN Mercury 75 MHz spectrometer in chloroform-d, acetonitrile-d₃ or benzene-d₆, all signals are reported in ppm relative to TMS with the internal solvent signal (CDCl₃: 77.0 ppm, CD₃CN: 1.24 ppm, C₆D₆: 128.02 ppm) as standard, the attached protons were assigned by recording DEPT spectra.

Infrared spectra were recorded on a Perkin-Elmer Spectrum RX-I FT-IR spectrophotometer as thin films. The data is being reported as absorption maxima (ν, cm⁻¹) with corresponding characteristic intensity (w=weak, m=medium, s=strong, br=broad).

Melting points were measured on a Buechi 510 melting point apparatus using open glass capillaries and are uncorrected.

Mass spectrometric measurements were performed by the mass spectrometry service of the LOC at the ETHZ.

Combustion analyses were performed by the Mikroelementarisches Laboratorium of the LOC at the ETHZ.

References:

- (1) Carpita, A.; Rossi, R.; Veracini, C. A. *Tetrahedron* **1985**, *41*, 1919-1929.
- (2) Bigi, F.; Carloni, S.; Ferrari, L.; Maggi, R.; Mazzacani, A.; Sartori, G. *Tetrahedron Lett.* **2001**, *42*, 5203-5205.
- (3) Ziegler, F. E.; Guenther, T.; Nelson, R. V. *Synth. Commun.* **1980**, *10*, 661-665.

General Procedures:

General procedure for the conjugate addition of alkynes to Meldrum's alkylidenes (GP 1).

A solution of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (20 mg; 0.1 mmol) in $\text{H}_2\text{O}/t\text{-BuOH}$ (2.2ml; 10:1) was treated with the indicated amount of alkyne (Table 2), Meldrum's alkylidene (0.5 mmol) and Sodium ascorbate (40 mg; 0.2 mmol). The reaction was stirred vigorously for the indicated time, treated with CH_2Cl_2 and sat aq. NH_4Cl soln. The organic layer was separated and the water phase was extracted twice with CH_2Cl_2 . The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC (SiO_2 , hexanes:EtOAc) to yield the pure product as a solid.

General procedure for the conversion of the Meldrum's adducts to the carboxylic acids (GP 2).

A solution of 0.25 mmol Meldrum's adduct (0.25 mmol) in $\text{DMF}/\text{H}_2\text{O}$ (2.2 ml; 10:1) was stirred at 100°C for 1h. After cooling to 23°C the reaction mixture was treated with $\text{H}_2\text{O}/\text{sat. aq. NH}_4\text{Cl}$ soln. (1:1) and extracted three times with Et_2O . The combined org. layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC (SiO_2 , hexanes/EtOAc (3:1), 0.1% AcOH). The acetic acid was removed by coevaporation with toluene. Since the obtained product contained a small amount of an unidentified byproduct it was dissolved in Et_2O , extracted three times with 1N NaOH. The combined water phases were acidified with 1N HCl and extracted three times with Et_2O . The org. layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield the pure product.

5-(1-Isopropyl-3-phenyl-prop-2-ynyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (2a).

Prepared according to GP 1 using 100 mg (0.50 mmol) of **1a**. Purification by column chromatography gave 118 mg (78%) of the title compound as a light yellow solid. mp: 113-116 °C (decomp.). ¹H NMR (300 MHz, CDCl₃) δ 1.05 (d, *J* = 6.5, 3H), 1.21 (d, *J* = 6.5, 3H), 1.77 (s, 3H), 1.78 (s, 3H), 2.43-2.60 (m, 1H), 3.27 (dd, *J* = 2.5, 10.6, 1H), 3.73 (d, *J* = 2.5, 1H), 7.24-7.30 (m, 3H), 7.33-7.40 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 20.5, 22.0, 28.1, 28.6 (CH₃), 30.5, 40.8, 47.6 (CH), 84.3, 87.7, 105.2, 122.8 (C), 128.0 (2xCH), 131.6 (CH), 163.6, 165.5 (C). FTIR (thin film, cm⁻¹): 2968 (m), 2872 (w), 1784 (m), 1751 (s), 1490 (w), 1296 (s), 1206 (m), 1072 (w), 995 (m), 758 (m), 693 (m). MS (ESI, neg.) calcd for C₁₈H₁₉O₄ (M-H)⁻ 299.1 found 299.0. Anal. Calcd for C₁₈H₂₀O₄: C, 71.98; H, 6.71. Found: C, 71.96; H, 6.77.

5-(1,3-Diphenyl-prop-2-ynyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (2b).

Prepared according to GP 1 using 116 mg (0.50 mmol) of **1b**. Purification by column chromatography gave 142 mg (85%) of the title compound as a white solid. mp: 159-161 °C (decomp.). ¹H NMR (300 MHz, CDCl₃) δ 1.63 (s, 3H), 1.74 (s, 3H), 4.00 (d, *J* = 2.5, 1H), 5.16 (d, *J* = 2.5, 1H), 7.27-7.41 (m, 6H), 7.46-7.51 (m, 2H), 7.60-7.65 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 27.9, 28.4 (CH₃), 37.1, 52.9 (CH), 88.5, 86.1, 105.2, 122.6 (C), 127.7, 128.1, 128.3, 128.4, 128.6, 131.7 (CH), 137.0, 162.9, 163.7 (C). FTIR (thin film, cm⁻¹): 3002 (w), 2896 (w), 1792 (m), 1750 (s), 1490 (m), 1296 (s), 1202 (m), 1057 (w), 1014 (w), 894 (m), 751(m), 710 (m), 693 (m). MS (ESI, neg.) calcd for C₂₁H₁₇O₄ (M-H)⁻ 333.1 found 333.0. Anal. Calcd for C₂₁H₁₈O₄: C, 75.43; H, 5.43. Found: C, 75.58; H, 5.66.

5-(3-Furan-2-yl-1-phenyl-prop-2-ynyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (2c).

Prepared according to GP 1 using 116 mg (0.50 mmol) of **1b**. Purification by column chromatography gave 114 mg (70%) of the title compound as an off-white solid. mp: 155-156 °C (decomp.). ¹H NMR (300 MHz, CD₃CN) δ 1.66 (s, 3H), 1.78 (s, 3H), 4.84 (d, *J* = 2.5, 1H), 5.13 (d, *J* = 2.5, 1H), 6.45-6.47 (m, 1H), 6.66 (d, *J* = 3.7, 1H), 7.26-7.41 (m, 3H), 7.47-7.50 (m, 1H), 7.60 (d, *J* = 8.1, 2H). ¹³C NMR (75 MHz, CD₃CN) δ 27.0, 28.4 (CH₃), 36.6, 53.1 (CH), 75.5, 92.3, 106.4 (C), 111.7, 116.1, 128.2, 129.0, 129.2 (CH), 137.0, 137.6 (C), 144.9 (CH), 163.7, 164.7 (C). FTIR (thin film, cm⁻¹): 3004 (w), 2902 (w), 1793 (m), 1751 (s), 1384 (w), 1298 (s), 1203 (m), 1011 (m), 1001 (m), 894 (m), 746 (m), 712 (m). MS (ESI, neg.) calcd for C₁₉H₁₅O₅ (M-H)⁻ 323.1 found 323.1. Anal. Calcd for C₁₉H₁₆O₅: C, 70.36; H, 4.97. Found: C, 70.28; H, 5.10

5-[3-(4-Bromo-phenyl)-1-phenyl-prop-2-ynyl]-2,2-dimethyl-[1,3]dioxane-4,6-dione (2d).

Prepared according to GP 1 using 116 mg (0.50 mmol) of **1b**. Purification by column chromatography gave 149 mg (72%) of the title compound as a white solid. mp: 138-139 °C (decomp.). ¹H NMR (300 MHz, C₆D₆) δ 0.83 (s, 3H), 0.96 (s, 3H), 3.63 (d, *J* = 2.5, 1H), 5.26 (d, *J* = 2.5, 1H), 7.01-7.10 (m, 5H), 7.12-7.18 (m, 2H), 7.70 (d, *J* = 6.8, 2H). ¹³C NMR (75 MHz, C₆D₆) δ 26.7, 28.0 (CH₃), 37.4, 53.3 (CH), 84.5, 88.9, 104.7, 122.2, 122.8 (C), 128.1, 128.7, 129.4, 131.8, 133.6 (CH), 137.6, 162.9, 163.4 (C). FTIR (thin film, cm⁻¹): 3003 (w), 2883 (w), 1787 (m), 1750 (s), 1487 (m), 1296 (s), 1204 (m), 1070 (m), 1012 (m), 894 (w), 826 (m), 756 (m), 712 (m). MS (ESI, neg.) calcd for C₂₁H₁₆BrO₄ (M-H)⁻ 411.0 found 410.9. Anal. Calcd for C₂₁H₁₇BrO₄: C, 61.03; H, 4.15. Found: C, 60.82; H, 4.33.

5-[1-(4-Methoxy-phenyl)-3-phenyl-prop-2-ynyl]-2,2-dimethyl-[1,3]dioxane-4,6-dione (2e).

Prepared according to GP 1 using 131 mg (0.50 mmol) of **1c**. Purification by column chromatography gave 175 mg (96%) of the title compound as a white solid. mp: 88-91 °C (decomp.). ¹H NMR (300 MHz, CDCl₃) δ 1.61 (s, 3H), 1.73 (s, 3H), 3.80 (s, 3H), 3.99 (d, *J* = 2.5, 1H), 5.11 (d, *J* = 2.5, 1H), 6.88 (d, *J* = 8.7, 2H), 7.28-7.33 (m, 3H), 7.45-7.50 (m, 2H), 7.54 (d, *J* = 8.7, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 27.8, 28.3 (CH₃), 36.4, 52.9 (CH), 55.3 (CH₃), 85.1, 86.1, 105.1 (C), 113.7 (CH), 122.6 (C), 128.1, 128.2 (CH), 128.9 (C), 129.8, 131.7 (CH), 158.9, 163.1, 163.6 (C). FTIR (thin film, cm⁻¹): 3002 (w), 2937 (w), 1787 (m), 1750 (s), 1610 (w), 1513 (s), 1297 (s), 1253 (s), 1203 (m), 1179 (m), 1031 (m), 758 (m), 692 (w). MS (ESI, neg.) calcd for C₂₂H₁₉O₅ (M-H)⁻ 363.1 found 363.0. Anal. Calcd for C₂₂H₂₀O₅: C, 72.51; H, 5.53. Found: C, 72.31; H, 5.78.

2,2-Dimethyl-5-[1-(4-nitro-phenyl)-3-phenyl-prop-2-ynyl]-[1,3]dioxane-4,6-dione (2f).

Prepared according to GP 1 using 139 mg (0.50 mmol) of **1d**. Purification by column chromatography gave 105 mg (55%) of the title compound as an off-white solid. mp: 142-145 °C (decomp.). ¹H NMR (300 MHz, CDCl₃) δ 1.74 (s, 3H), 1.79 (s, 3H), 4.03 (d, *J* = 2.5, 1H), 5.26 (d, *J* = 2.5, 1H), 7.31-7.37 (m, 3H), 7.46-7.50 (m, 2H), 7.83 (d, *J* = 8.7, 2H), 8.23 (d, *J* = 8.7, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 27.6, 28.4 (CH₃), 36.4, 52.6 (CH), 84.6, 86.4, 105.5, 121.9 (C), 123.5, 128.3, 128.7, 129.8, 131.8 (CH), 144.3, 147.2, 162.6, 163.1 (C). FTIR (thin film, cm⁻¹): 3004 (w), 2897 (w), 1791 (m), 1749 (s), 1520 (s), 1348 (s), 1296 (s), 1202 (m), 1016 (w), 758 (m), 668 (m). HRMS (ESI, neg.) calcd for C₂₁H₁₆NO₆ (M-H)⁻ 378.0983 found 378.0980.

5-[1-(4-Chloro-phenyl)-3-phenyl-prop-2-ynyl]-2,2-dimethyl-[1,3]dioxane-4,6-dione (2g).

Prepared according to GP 1 using 133 mg (0.50 mmol) of **1e**. Purification by column chromatography gave 162 mg (88%) of the title compound as an off-white solid. mp: 124-127 °C (decomp.) ¹H NMR (300 MHz, CDCl₃) δ 1.67 (s, 3H), 1.74 (s, 3H) 4.01 (d, *J* = 2.5, 1H), 5.12 (d, *J* = 2.5, 1H), 7.28-7.35 (m, 5H), 7.43-7.50 (m, 2H), 7.57 (d, *J* = 8.7, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 27.6, 28.3 (CH₃), 36.2, 52.7 (CH), 85.6, 85.7, 105.2, 122.3 (C), 128.1, 128.4, 128.4, 130.1, 131.7 (CH), 133.5, 135.4, 162.8, 163.3 (C). FTIR (thin film, cm⁻¹): 3003 (w), 2887 (w), 1788 (m), 1750 (s), 1491 (m), 1297 (s), 1203 (m), 1092 (m), 1016 (m), 907 (w), 830 (w), 757 (m), 692 (w). MS (ESI, neg.) calcd for C₂₁H₁₈ClO₄ (M-H)⁻ 367.1 found 367.0. Anal. Calcd for C₂₁H₁₇ClO₄: C, 68.39; H, 4.65. Found: C, 68.20; H, 4.86.

5-(1-Furan-2-yl-3-phenyl-prop-2-ynyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (2h).

Prepared according to GP 1 using 111 mg (0.50 mmol) of **1f**. Purification by column chromatography gave 138 mg (85%) of the title compound as an off-white solid. mp: 129-131 °C (decomp.). ¹H NMR (300 MHz, CDCl₃) δ 1.76 (s, 3H), 1.80 (s, 3H), 4.20 (d, *J* = 2.5, 1H), 5.16 (d, *J* = 2.5, 1), 6.38 (dd, *J* = 1.9, 3.1, 1H), 6.52-6.55 (m, 1H), 7.28-7.36 (m, 4H), 7.43-7.49 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 27.6, 28.2 (CH₃), 31.5, 49.7 (CH), 83.8, 84.4, 105.3 (C), 108.4, 111.0 (CH), 122.3 (C), 128.2, 128.5, 131.9, 141.8 (CH), 150.0, 162.4, 163.3 (C). FTIR (thin film, cm⁻¹): 3001 (w), 2895 (w), 1787 (m), 1751 (s), 1490 (w), 1337 (m), 1298 (s), 1204 (m), 1070 (m), 1004 (m), 895 (w), 758 (m), 692 (m). HRMS (ESI, neg.) calcd for C₁₉H₁₅O₅ (M-H)⁻ 323.0925 found 323.0925.

2,2-Dimethyl-5-(3-phenyl-1-phenylethynyl-allyl)-[1,3]dioxane-4,6-dione (2i).

Prepared according to GP 1 using 130 mg (0.50 mmol) of **1g**. Purification by column chromatography gave 178 mg (98%) of the title compound as an off-white solid. mp: 129-132 °C (decomp.). ¹H NMR (300 MHz, CDCl₃) δ 1.76 (s, 3H), 1.78 (s, 3H), 3.90 (d, *J* = 3.1, 1H), 4.58-4.63 (m, 1H), 6.51 (dd, *J* = 7.5, 15.6, 1H), 6.81 (d, *J* = 15.6, 1H), 7.22-7.37 (m, 6H), 7.40-7.49 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 27.3, 28.4 (CH₃), 34.7, 51.6 (CH), 84.4, 86.2, 105.2, 122.6 (C), 124.9, 126.5, 127.8, 128.0, 128.2, 128.4, 131.7, 133.7 (CH), 136.1, 163.0, 163.2 (C). FTIR (thin film, cm⁻¹): 3003 (w), 2882 (w), 1786 (m), 1750 (s), 1491 (m), 1295 (s), 1205 (m), 1069 (m), 1007 (m), 757 (s), 692 (m). MS (ESI, neg.) calcd for C₂₃H₁₉O₄ (M-H)⁻ 359.1 found 359.0. Anal. Calcd for C₂₃H₂₀O₄: C, 76.65; H, 5.59. Found: C, 76.63; H, 5.79.

5-(1-Ethyl-3-phenyl-prop-2-ynyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione (2j).

Prepared according to GP 1 using 92 mg (0.50 mmol) of **1h**. Purification by column chromatography gave 93 mg (65%) of the title compound as a light yellow solid. mp: 139-140 °C (decomp.). ¹H NMR (300 MHz, CDCl₃) δ. 1.13 (t, *J* = 7.5, 3H), 1.69-1.84 (m, 1H), 1.77 (s, 6H), 2.08-2.22 (m, 1H), 3.52-3.59 (m, 1H), 3.68 (d, *J* = 2.5, 1H), 7.25-7.30 (m, 3H), 7.35-7.42 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ. 12.7 (CH₃), 26.2 (CH₂), 27.6, 28.5 (CH₃), 34.1, 49.8 (CH), 83.7, 87.7, 105.1, 122.8 (C), 127.9, 128.0, 131.6 (CH), 163.5, 164.3 (C). FTIR (thin film, cm⁻¹): 2972 (w), 2877 (w), 1786 (m), 1750 (s), 1490 (w), 1384 (m), 1297 (s), 1204 (m), 1070 (m), 992 (m), 899 (w), 864 (w), 759 (m), 693 (m). MS (ESI, neg.) calcd for C₁₇H₁₇O₅ (M-H)⁻ 285.1132 found 285.1132.

3-Isopropyl-5-phenyl-pent-4-ynoic acid (3a).

Prepared according to GP 2 using 75 mg (0.25 mmol) of **2a**. Purification gave 49 mg (91%) of the title compound as a pale yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 1.05 (d, $J = 6.8$, 3H), 1.09 (d, $J = 6.8$, 3H), 1.79-1.95 (m, 1 H), 2.59 (dd, $J = 6.8$, 15.6, 1H), 2.67 (dd, $J = 8.1$, 15.6, 1H), 2.99-3.08 (m, 1H), 7.25-7.32 (m, 3H), 7.36-7.44 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 18.2, 21.2 (CH_3), 31.5, 35.5 (CH), 38.0 (CH_2), 83.3, 89.3, 123.5 (C), 127.7, 128.1, 131.6 (CH), 178.1 (C). FTIR (thin film, cm^{-1}): 3034 (br m), 2963 (m), 1711 (s), 1490 (w), 1442 (w), 1413 (w), 1280 (br w), 756 (m), 691 (m). MS (ESI, neg.) calcd for $\text{C}_{14}\text{H}_{15}\text{O}_2$ (M-H) $^-$ 215.1 found 215.3. Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_2$: C, 77.75; H, 7.46. Found: C, 77.91; H, 7.61.

3-(4-Methoxy-phenyl)-5-phenyl-pent-4-ynoic acid (3e).

Prepared according to GP 2 using 88 mg (0.24 mmol) of **2e**. Purification gave 61 mg (90%) of the title compound as a light brown solid. mp: 118-120 $^\circ\text{C}$ (decomp.). ^1H NMR (300 MHz, CDCl_3) δ 2.85 (dd, $J = 6.8$, 15.6, 1H), 2.97 (dd, $J = 8.1$, 15.6, 1H), 3.81 (s, 3H), 4.31-4.39 (m, 1H), 6.90 (d, $J = 8.1$, 2H), 7.27-7.32 (m, 3H), 7.37-7.46 (m, 4H). ^{13}C NMR (75 MHz, CDCl_3) δ 33.6 (CH), 43.2 (CH_2), 55.2 (CH_3), 83.5, 89.8 (C), 114.1 (CH), 123.2 (C), 128.0, 128.2, 128.4, 131.7 (CH), 132.2, 158.8, 177.1 (C). FTIR (thin film, cm^{-1}): 3034 (br w), 2956 (w), 1710 (s), 1610 (w), 1512 (s), 1251 (s), 1178 (m), 1035 (m), 831 (m), 757 (m), 692 (m). MS (ESI, neg.) calcd for $\text{C}_{18}\text{H}_{15}\text{O}_3$ (M-H) $^-$ 279.1 found 279.3. Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{O}_3$: C, 77.12; H, 5.75. Found: C, 76.97; H, 5.90.