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# An Efficient Synthesis of Acetylenic γ- and δ-Hydroxy Ketones, γ- and δ-Keto Acids, and γ- Diketones via Addition of 1-Alkinyllithium Compounds to γ- and δ-Lactones [1]

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*Dedicated to Prof. Dr. Sigfrid Schwarz on the occasion of his 60th birthday*

**Abstract.** 2-Hydroxy-6-alkyn-5-ones **3**, 1-hydroxy-5-alkyn-4-ones **4**, and 1-hydroxy-6-alkyn-5-ones **5** are conveniently obtained in exellent yields through a highly selective monoaddition of an 1-alkynyllithium compound **2** to γ-valerolactone (**1a**), γ-butyrolactone (**1b**) or δ-valerolactone (**1c**). They are oxidized by pyridinium dichromate or Jones reagent to the corresponding acetylenic 1,4-diketones **6**, 4-oxo carboxylic acids **7**, and 5-oxo carboxylic acids **8**, respectively.

1,4-Diketones are versatile intermediates for the preparation of various carbo- [2] and heterocyclic compounds [3 – 5]. This is the reason for a permanent interest in the development of new syntheses for this class of bifunctionalized compounds.

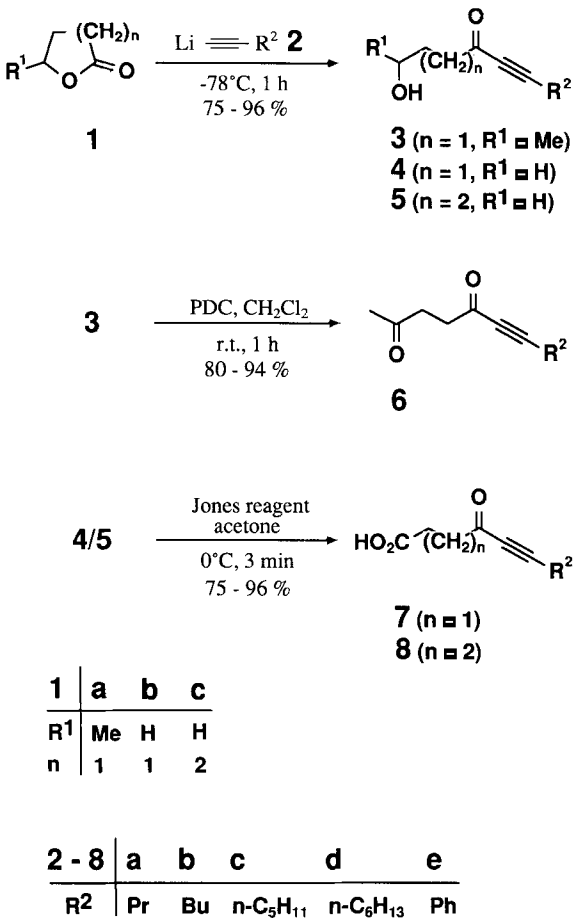
4-Oxoalkanoic acid derivatives have been proven to be especially suited starting materials, since they already exhibit an essential part of the desired final structure and formally only require the nucleophilic addition of an organic residue to the carboxylic group. This is generally achieved by the reaction with a suitable organometallic reagent.

The main problem in this conversion consists in the insufficient selectivity of the commonly used organolithium and organomagnesium compounds. They have the tendency to add more than one organic residue to the 4-oxoalkanoic acid derivative, thus forming tertiary alcohols. A highly selective monoaddition requires a fine tuning of the reactivity of the 4-oxoalkanoic acid derivative and the organometallic reagent. Several methods are known to influence the reactivity of the 4-oxoalkanoic acid derivative [6 – 13]. The modification of the organometallic reagent, however, has received less consideration. In order to achieve the desired selectivity by the last mentioned possibility the reactivity of the metal organyl should be reduced either by selecting an appropriate metal or by lowering the nucleophilicity of the organic part of the reagent. The latter should be realized by using a less nucleophilic alkenyllithium or alkynyllithium instead of the corresponding alkyllithium. The multiple bond automatically introduced by this procedure can be removed by hydrogenation, should it not be desired for further transformations of the expected α,β-unsaturated carbonyl system.

A thorough search of the literature revealed that this conception has already been used for the selective monoaddition of the 1-lithiated 1-alkynes **2b** and **2e** to saturated lactones, such as γ-butyrolactone (**1b**) and δ-valerolactone (**1c**). Thus the hydroxy ketones **4b** [14, 15], **4e** [15], **5b** [15 – 17], and **5e** [15] were prepared in high yields.

According to this protocol, 3-penten-4-olide (α-angelica lactone), the enol lactone of the simplest 4-oxoalkanoic acid, was treated at −20 °C with 1-hexynyllithium (**2b**) in diethyl ether. Disappointingly, no reaction took place. Obviously, the enol lactone was deprotonated at the α-methylene group as already described for the reaction with alkylmagnesium halides [18].

This failure caused us to turn our interest to 4-pentanolide (**1a**; γ-valerolactone), the saturated analogue of α-angelica lactone. The enolization tendency of this lactone should be reduced and a reactivity similar to that of **1b** and **1c** could be expected. Indeed, the reaction of 1-pentynyllithium (**2a**) with **1a** at −78 °C in




| 1 | a | b | c |
|---|---|---|---|
| $R^1$ | Me | H | H |
| n | 1 | 1 | 2 |

| 2 - 8 | a | b | c | d | e |
|---|---|---|---|---|---|
| $R^2$ | Pr | Bu | n-$C_5H_{11}$ | n-$C_6H_{13}$ | Ph |

tetrahydrofuran afforded the hydroxy ketone rac-**3a** in 90 % isolated yield. When the temperature was kept below − 60 °C no double addition resulting in the formation of a tertiary alcohol could be detected, even when **2a** was applied in excess. This very clean monoaddition also could be realized with the alkynyllithium compounds **2b–e**. The corresponding hydroxy ketones rac-**3b–e** were obtained in 85–96 % yield.

In order to obtain the desired 1,4-diketones **6**, the secondary hydroxy group of rac-**3a–e** had to be oxidized. This was most conveniently achieved by oxidation with pyridinium dichromate (PDC) [19, 20] in dichloromethane. Jones reagent [21] produced less satisfying results.

The smooth addition of the lithiated 1-alkynes **2a–e** to the lactone **1a** caused us to prepare also the hydroxy ketones **4a–e** and **5a–e** from the lactones **1b** and **1c**, respectively. The yields were in the order of 75–95 %. The oxidation of these compounds with Jones reagent [21] afforded the 4-oxo- and 5-oxoalkynoic acids **7a–e** and **8a–e** in good yields.

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## Experimental

The lactones **1a** and **1b**, the alkynes for the preparation of **2a–e**, and butyllithium were purchased from E. Merck, the lactone **1c** from Aldrich. THF was dried with sodium wire and stored over molecular sieves 4 Å. The reactions with organometallics were performed under dry argon. Melting points were determined on a Boëtius micro melting point apparatus and are corrected. Microanalyses were obtained by using a Carlo Erba autoanalyzer 1106. IR spectra were measured on a Bruker spectrometer IFS 66. $^{13}$C-NMR spectra were recorded at 75 MHz on a Varian Gemini 300 spectrometer. Mass spectra were obtained on a GC/MS Datensystem HP 5985 B. Flash chromatography was performed with silica gel 60 (0.040-0.063 mm, E. Merck).

*Acetylenic Hydroxy Ketones rac-***3a–e**, **4a–e**, *and* **5a–e**

*General Procedure.* A solution of the alkynyllithium compounds **2a–e** was prepared by addition of butyllithium (6 mmol, 1N in hexane) at −20 °C to the corresponding alkyne (6 mmol) in THF (6 ml). The mixture was allowed to warm up to room temperature, stirred for a further 30 min, and then cooled to −78 °C. At this temperature a solution of the lactone **1a** (300 mg, 3 mmol), **1b** (430 mg, 5 mmol), or **1c** (501 mg, 5 mmol) in THF (2 ml) was added dropwise. The mixture was kept at −78 °C for 1 h, then warmed up to −20 °C, and poured into an ice-cold aqueous $NH_4Cl$ solution (20 ml, 20 %). After stirring for 1 h, THF was distilled off at reduced pressure. The mixture was extracted with $Et_2O$ (3 × 20 ml). The combined extracts were dried ($Na_2SO_4$). The crude hydroxy ketones rac-**3**, **4**, and **5**, obtained after removal of the solvent at reduced pressure, were purified by flash chromatography on silica gel (30 g) by using hexane/EtOAc (2 : 1) for *rac*-**3a–e** and hexane/EtOAc (1 : 1) for **4a–e** and **5a–e**. All the hydroxy ketones were colorless oils (Table 1).

*6-Alkyne-2,5-diones* (**6a–e**)

*General Procedure.* Pyridinium dichromate (1.13 g, 3 mmol) was added to a mixture of a hydroxy ketone *rac*-**3** (2 mmol), dichloromethane (6 ml), $MgSO_4$ (1.20 g, 10 mmol), and powdered molecular sieves 4 Å (2.0 g) and stirred at ambient temperature for 1 h. Then the mixture was diluted with diethyl ether (20 ml) and filtered over Celite (2.0 g). Evaporation of the solvent under reduced pressure afforded the corresponding diketone **6** as a light yellow oil. Flash chromatography on silica gel (15 g) with hexane/EtOAc (2 : 1) resulted in a pure, colorless product (Table 2).

*4-Oxo-5-alkynoic Acids* **7a–e** *and 5-Oxo-6-alkynoic Acids* **8a–e**

**General Procedure.** Jones reagent [21] (1.5 ml, containing 4 mmol of $CrO_3$) was added dropwise to a solution of a hydroxy ketone **4** or **5** (2 mmol) in acetone (6 ml) while stirring at 0 °C. After complete addition the mixture was stirred at this temperature for a further 3 min. The excess of the oxidant was destroyed by isopropanol (2 ml). The precipitated chromium salts were dissolved by addition of water (3 ml), and the organic solvents were removed under reduced pressure. Then water (5 ml) was added and the mixture extracted with diethyl ether (3 × 15 ml). The combined extracts were dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude keto acids **7** and **8** were purified by flash chroma-

**Table 1** Yields and analytical data of the hydroxyketones *rac*-**3a–e**, **4a–e**, and **5a–e**

| Product | Yield (%) | Elemental Analyses Molecular Formula | C (calcd.) C (found) | H (calcd.) H (found) | IR ν (cm$^{-1}$) | $^{13}$C-NMR ($CDCl_3$/TMS) δ | MS (70 eV) m/z (%) |
|---|---|---|---|---|---|---|---|
| *rac*-**3a** | 90 | $C_{10}H_{16}O_2$ (168.2) | 71.39 71.45 | 9.59 9.84 | 1660, 2200 | 13.46, 20.89, 21.15, 23.59, 32.94, 41.96, 67.14, 81.02, 94.58, 188.24 | 167 [(M − 1)$^+$, 5], 95 (100) |
| *rac*-**3b** | 87 | $C_{11}H_{18}O_2$ (182.3) | 72.49 72.40 | 9.95 10.25 | 1670, 2200 | 13.45, 18.63, 21.95, 23.57, 29.73, 32.96, 41.95, 67.10, 80.90, 94.77, 188.26 | 182 (M$^+$, < 1), 109 (100) |
| *rac*-**3c** | 96 | $C_{12}H_{20}O_2$ (196.3) | 73.43 73.19 | 10.27 10.69 | 1675, 2205 | 13.88, 18.91, 21.95, 23.49, 27.42, 31.02, 32.97, 41.99 66.89, 80.90, 94.83, 188.44 | 195 [(M − 1)$^+$, 0.5], 123 (100) |
| *rac*-**3d** | 96 | $C_{13}H_{22}O_2$ (210.3) | 74.24 74.34 | 10.54 10.98 | 1658, 2210 | 13.98, 18.95, 22.45, 23.58, 27.67, 28.52, 31.19, 32.95, 41.95, 67.12, 80.88, 94.86, 188.26 | 210 (M +, < 1), 137 (100) |
| *rac*-**3e** | 85 | $C_{13}H_{14}O_2$ (202.3) | 77.20 77.18 | 6.98 6.88 | 1680, 2200 | 23.62, 32.97, 42.00, 67.15, 87.96, 91.21, 120.09, 128.84, 130.95, 133.26, 188.39 | 201 [(M − 1)$^+$, 1], 129 (100) |
| **4a** | 94 | $C_9H_{14}O_2$ (154.2) | 70.10 69.77 | 9.15 9.38 | 1680, 2205 | 13.44, 20.90, 21.31, 27.03, 42.27, 61.64, 81.17, 94.81, 188.53 | 153 [(M − 1)$^+$, < 1], 95 (100) |
| **4b** | 82 | $C_{10}H_{16}O_2$ (168.2) | 71.39 71.23 | 9.59 9.98 | 1675, 2200 | 13.48, 18.66, 21.99, 26.91, 29.77, 42.25, 61.76, 80.98, 94.13, 188.61 | 167 [(M − 1)$^+$, 0.5], 150 (20) 109 (100) |
| **4c** | 76 | $C_{11}H_{18}O_2$ (182.3) | 72.49 72.20 | 9.95 10.35 | 1675, 2205 | 13.85, 18.91, 22.11, 27.00, 27.46, 31.04, 42.19, 61.42 80.92, 94.96, 188.25 | 187 [(M − 1)$^+$, 1], 123 (100) |
| **4d** | 81 | $C_{12}H_{20}O_2$ (196.3) | 73.43 73.49 | 10.27 10.83 | 1675, 2200 | 13.00, 18.00, 22.49, 26.94, 27.73, 28.58, 31.25, 42.27, 61.93, 81.02, 95.12, 188.43 | 195 [(M − 1)$^+$, 2], 137 (100) |
| **4e** | 75 | $C_{12}H_{12}O_2$ (188.2) | 76.57 76.66 | 6.43 6.59 | 1670, 2200 | 26.89, 42.21, 61.76, 87.90, 91.29, 120.05, 128.85, 130.98, 133.27, 188.25 | 187 [(M − 1)$^+$, < 1], 129 (100) |
| **5a** | 95 | $C_{10}H_{16}O_2$ (168.2) | 71.39 71.12 | 9.59 9.93 | 1670, 1730, 2210 | 13.44, 20.28, 20.90, 21.28, 31.91, 45.12, 62.27, 81.03, 94.40, 188.12 | 150 [(M − 18)$^+$ 10], 95 (100) |
| **5b** | 90 | $C_{11}H_{18}O_2$ (182.3) | 72.49 72.43 | 9.95 10.20 | 1670, 1730, 2200 | 13.44, 18.64, 20.27, 21.96, 29.77, 31.93, 45.11, 62.30, 80.91, 94.58, 188.11 | 182 (M$^+$, < 1), 109 (100) |
| **5c** | 86 | $C_{12}H_{20}O_2$ (196.3) | 73.43 73.13 | 10.27 10.56 | 1670, 1730, 2205 | 13.88, 18.95, 20.31, 22.12, 27.47, 31.07, 31.94, 45.20, 62.33, 81.04, 94.89, 188.57 | 196 (M$^+$, < 1), 178 (10), 123 (100) |
| **5d** | 87 | $C_{13}H_{20}O_2$ (208.3) | 74.24 74.10 | 10.54 10.86 | 1670, 1730, 2205 | 13.95, 18.95, 20.38, 22.45, 27.70, 28.53, 31.19, 31.91, 45.11, 62.25, 80.90, 94.66 188.12 | 211 [(M + 1)$^+$, < 1), 192 (10), 137 (100) |
| **5e** | 82 | $C_{13}H_{14}O_2$ (202.3) | 77.20 77.28 | 6.98 7.07 | 1670, 2200 | 20.30, 31.88, 45.15, 62.30, 87.91, 91.09, 120.10, 128.84, 130.95, 133.27, 188.32 | 201 [(M − 1)$^+$, < 1), 129 (100) |

**Table 2** Yields and analytical data of the 1,4-diketones **6a–e**, 4-oxo-5-alkynoic acids **7a–e**, and 5-oxo-6-alkynoic acids **8a–e**

| Product | Yield (%) | Elemental Analyses Molecular Formula | C (calcd.) C (found) | H (calcd.) H (found) | IR ν (cm$^{-1}$) | $^{13}$C-NMR ($CDCl_3$/TMS) δ | MS [12 or 70 eV[a]] m/z (%) |
|---|---|---|---|---|---|---|---|
| **6a** | 80 | $C_{10}H_{14}O_2$ (166.2) | 72.26 72.20 | 8.49 8.73 | 1680, 1720, 2210 | 13.46, 20.91, 21.24, 29.87, 36.83, 39.10, 80.77, 94.65, 186.03, 206.26 | 166 ($M^+$, <1), 95 (100) |
| **6b** | 85 | $C_{11}H_{16}O_2$ (180.2) | 73.30 73.12 | 8.95 9.33 | 1670, 1710, 2200 | 13.48, 18.59, 21.97, 29.73, 29.78, 36.80, 39.16, 80.66, 94.49, 185.88, 206.08 | 188 ($M^+$, <1), 109 (100) |
| **6c** | 84 | $C_{12}H_{18}O_2$ (194.3) | 74.19 74.10 | 9.34 9.54 | 1680, 1720, 2210 | 13.18, 18.88, 22.03, 27.31, 29.81, 30.95, 36.76, 39.03, 80.57, 94.85, 185.98, 206.20 | 193 [$(M-1)^+$, < 1], 123 (100) |
| **6d** | 94 | $C_{13}H_{20}O_2$ (208.3) | 74.96 74.93 | 9.68 9.93 | 1685, 1730, 2220 | 13.99, 18.96, 22.46, 27.66, 28.53, 29.85, 31.21, 36.82, 39.10, 80.63, 94.88, 186.01, 206.22 | 207 [$(M-1)^+$, <1], 137 (100) |
| **6e** | 84 | $C_{13}H_{12}O_2$ (200.2) | 77.98 77.66 | 6.04 5.90 | 1670, 1715, 2200 | 29.92, 36.85, 39.12, 87.67, 91.20, 120.07, 128.84, 130.96, 133.25, 186.14, 206.56 | 200 ($M^+$, 10), 129 (100) |
| **7a** | 85 | $C_9H_{12}O_3$ (168.2) | 64.27 63.63 | 7.19 7.19 | 1670, 1710, 2200 | 13.41, 20.87, 21.21, 27.91, 39.78, 80.62, 95.66, 178.66, 185.91 | 151 {[$(M-18)+1]^+$, <1}, 95 (100) |
| **7b** | 75 | $C_{10}H_{14}O_3$ (182.2) | 65.91 66.25 | 7.74 7.77 | 1670, 1700, 2200 | 13.49, 18.69, 22.01, 27.96, 29.73, 39.80, 80.53, 95.81, 178.74, 185.83 | 182 ($M^+$, <1), 109 (100) |
| **7c** | 82 | $C_{11}H_{16}O_3$ (196.2) | 67.32 67.08 | 8.22 8.20 | 1670, 1710, 2200 | 13.90, 18.97, 22.17, 27.42, 27.97, 31.09, 39.82, 80.55, 95.88, 178.77, 185.90 | 179 {[$(M-18)+1]^+$, <1}, 123 (100) |
| **7d** | 88 | $C_{12}H_{18}O_3$ (210.3) | 68.54 68.53 | 8.63 8.83 | 1670, 1710, 2205 | 14.01, 19.01, 22.49, 27.65, 27.89, 28.58, 31.25, 39.78, 80.53, 95.78, 178.51, 185.66 | 193 {[$(M-18)+1]^+$, <1}, 137 (100) |
| **7e** | 90 | $C_{12}H_{10}O_3$ (202.2) | 71.28 71.23 | 4.98 4.97 | 1660, 1700, 2200 | 27.91, 39.77, 87.48, 91.87, 119.88, 128.93, 131.18, 133.33, 178.47, 185.69 | 202 ($M^+$, 20), 129 (100) |
| **8a** | 75 | $C_{10}H_{14}O_3$ (182.2) | 65.91 65.71 | 7.74 7.95 | 1670, 1700, 2205 | 13.46, 18.94, 20.90, 21.29, 32.90, 44.33, 81.01, 95.14, 179.53, 187.64 | 183 [$(M+1)^+$, <1), 95 (100) |
| **8b** | 96 | $C_{11}H_{16}O_3$ (196.2) | 67.32 67.51 | 8.22 8.32 | 1670, 1700, 2200 | 13.49, 18.66, 18.85, 21.99, 29.72, 32.86, 44.27, 80.84, 95.19, 179.60, 187.47 | 179 {[$(M-18)+1]^+$, <1}, 109 (100) |
| **8c** | 85 | $C_{12}H_{18}O_3$ (210.3) | 68.54 68.35 | 8.63 8.74 | 1670, 1700, 2200 | 13.87, 18.87, 18.94, 22.11, 27.40, 31.05, 32.86, 44.27, 80.85, 95.21, 179.48, 187.39 | 211 [$(M+1)^+$, <1], 123 (100) |
| **8d** | 83 | $C_{13}H_{20}O_3$ (224.3) | 69.61 69.38 | 8.99 9.02 | 1670, 1710, 2200 | 14.02, 18.92, 18.98, 22.51, 27.70, 28.59, 31.26, 32.90, 44.31, 80.88, 95.28, 179.58 187.51 | 167 [$(M-57)^+$, 1], 109 (100) |
| **8e** | 84 | $C_{13}H_{12}O_3$ (216.2) | 72.21 72.02 | 5.59 5.59 | 1660, 1700, 2200 | 18.90, 32.80, 44.28, 87.80, 91.32, 120.05, 128.87, 131.02, 133.32, 179.02, 187.06 | 216 ($M^+$, 3), 129 (100) |

[a] 12eV were applied for **7a–e** and **8a–e**, 70eV for **6a–e**.

tography on silica gel (10 g) with hexane/ethyl acetate/acetic acid (66 : 33 : 1) as eluent. **7e** (m.p. 84 – 85 °C) and **8e** (m.p. 106 – 108 °C) were obtained as colorless crystals (diethyl ether/hexane), all other alkynoic acids as colorless oils (Table 2).

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