A New Synthesis of 2-(6-Methoxycarbonylhexyl)-cyclopent-2-en-1-one

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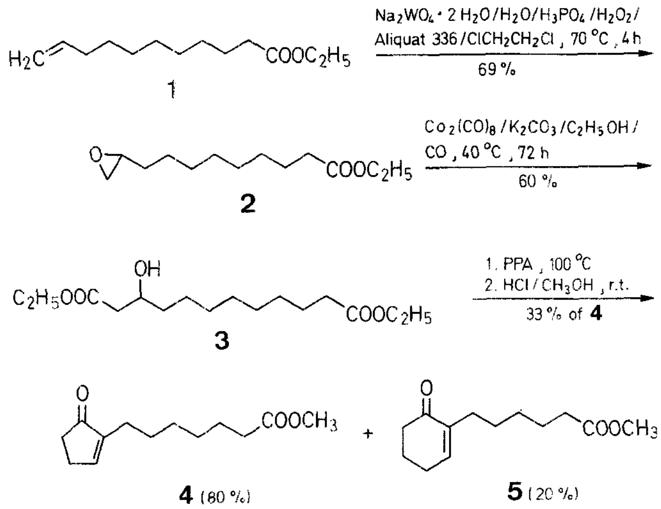
A new, simple and short route to 2-(6-methoxycarbonylhexyl)-cyclopent-2-en-1-one (overall yield: 33 %) starting from ethyl-10-undecenoate is reported. The main feature of this synthesis is a new cobalt-catalyzed carbonylation of the intermediate epoxide, which occurs with satisfactory yield under very mild conditions.

2-Alkylcyclopentenones are useful precursors in the synthesis of various natural products. Many approaches to **4**, a well known intermediate in the synthesis of various prostanoid derivatives[1], have been published[2]. We now report a new synthesis of **4** in only three steps, starting from the inexpensive ethyl-10-undecenoate (**1**), via a new, cobalt catalyzed carbonylation of the epoxide **2**.



PPA = polyphosphoric acid

The first step was the catalyzed oxidation of **1** to **2** by means of hydrogen peroxide under phase transfer conditions, according to a very clean and selective procedure[4]. The carbonylation of **2** to β-hydroxy esters **3** is the key step of the synthesis. This new reaction occurs under very mild conditions in the presence of cobalt tetracarbonyl or its precursor dicobalt octacarbonyl as catalyst and of stoichiometric amount of potassium carbonate (no reaction occurs without the base). Ethanol is the solvent of choice for achieving the highest selectivity.

Mild conditions, selectivity, and wide applicability to epoxides from α-olefins are features of this reaction[5] which then overcomes the limits of the reported methods for cobalt-catalyzed carbonylation of epoxides[6]. In addition to **3** ethyl 10-oxoundecanoate was also formed (4:1 ratio). This byproduct can be formed through a rearrangement of the epoxy ring under the above catalytic conditions[7]. The last step was the cyclization of **3** in polyphosphoric acid which led to the target molecule **4** together with the isomer, 2-(5-methoxycarbonylpentyl)-cyclohex-2-en-1-one (**5**) in a 4:1 ratio. The formation of the latter product cannot be avoided in strong acidic medium, according to the proposed mechanism[8]. No appreciable result was obtained using different acids such as zinc chloride in acetic acid, tin(IV) chloride, phosphorus pentoxide in methanesulfonic acid, trifluoroacetic anhydride, and trifluoromethanesulfonic acid.

^{1}H-N.M.R. spectra were recorded with Bruker WH90 and AM300 instruments; mass spectra with a Varian-MAT 112 S spectrometer; I.R. spectra with a Perkin-Elmer 983 spectrophotometer. Ethyl 10-undecenoate (**1**) was obtained by esterification of the commercially available acid.

Ethyl 10,11-Epoxyundecanoate (2):

To a solution of disodium tungstate dihydrate (0.193 g, 0.58 mmol) in water (3 ml) are added 40% (w/v) orthophosphoric acid (0.3 ml, 1.2 mmol) and 35% (w/v) hydrogen peroxide (11 ml, 112 mmol). The pH of the mixture is adjusted to 1.6 by addition of 30% sulfuric acid. Ethyl 10-undecenoate (**1**; 28.72 g, 134 mmol), 1,2-dichloromethane (5 ml), and Aliquat 336 (0.096 g, 0.24 mmol) are added. The resultant two-phase mixture is heated with vigorous stirring at 70 °C for 4 h until the hydrogen peroxide has been consumed and then saturated solutions of sodium sulfite (10 ml) and sodium hydrogen carbonate (10 ml) are added. The organic phase is separated, dried with sodium sulfate, concentrated, and the residue is fractionally distilled under reduced pressure to give **2**; yield: 21.2 g (69%); b.p. 86–88 °C/0.05 torr. Unreacted starting material **1** is also recovered; yield: 4.6 g; b.p. 68–70 °C/0.05 torr.

$C_{13}H_{24}O_3$ calc. C. 68.38 H 10.59
(228.3) found 68.11 10.69

M.S. (70 eV): $m/e = 200$ ($M^+ - C_2H_4$, 6%); 185 ($M^+ - C_2H_4O$, 19%); 183 ($M^+ - C_2H_5OH$, 12%); 139 ($M^+ - C_2H_4O - C_2H_5OH$, 31%); 88 [$H_2C{=}C(OH)OC_2H_5{}^+$, 100%]; 55 ($C_4H_9^+$, 89%); 29 ($C_2H_5^+$, 80%).

I.R. (film): $\nu = 2925, 1745, 1465, 1372, 1180\ cm^{-1}$.

^{1}H-N.M.R. (CDCl$_3$, 90 MHz): $\delta = 1.27$ (m, 17 H); 2.07–2.48 (m, 3 H); 2.58–2.93 (m, 2 H); 4.02 ppm (g, 2 H).

Diethyl 3-Hydroxydodecanedioate (3):

Dicobalt octacarbonyl (0.366 g, 1.07 mmol) is added to a stirred suspension of potassium carbonate (4.56 g, 33 mmol) in ethanol (15 ml) under a carbon monoxide atmosphere. After 20 min, when the mixture has become pink, **2** (7.53 g, 33 mmol) is added together with ethanol (10 ml) and the suspension is heated at 40 °C. After 72 h. the absorption of carbon monoxide stops (0.72 l absorbed). The solution is acidified with 10% sulfuric acid, filtered, concentrated, and the residue is extracted with diethyl ether (3 × 25 ml). The organic phase is dried with sodium sulfate and concentrated to give a clear oil (7.76 g). Chromatography on silica gel (diethyl ether/hexane, 4/6) gives *ethyl 10-oxoundecanoate* first; yield: 0.99 g.

$C_{13}H_{24}O_3$ calc. C 68.38 H 10.59
(228.3) found 68.21 10.64

M.S. (70 eV): $m/e = 183$ ($M^+ - OC_2H_5$, 7%); 171 ($M^+ - OC_3H_5$, 15%); 125 (56%); 58 [$H_3C{-}C(CO){=}CH_2^+$, 85%]; 43 ($H_3C{-}CO^+$, 100%).

I.R. (film): $\nu = 1735, 1717, 1437, 1360, 1296, 1270\ cm^{-1}$.

^{1}H-N.M.R. (CDCl$_3$, 300 MHz): $\delta = 1.24$ (t, 3 H); 1.30 (br. s, 8 H); 1.58 (m, 4 H); 2.12 (s, 3 H); 2.28 (t, 2 H, $J = 7.6$ Hz); 2.42 (t, 2 H, $J = 7.3$ Hz); 4.11 ppm (q, 2 H).

Product **3** is then eluted; yield: 5.96 g (60%).

$C_{16}H_{30}O_5$ calc. C 63.55 H 10.00
(302.4) found 63.45 9.97

M.S. (70 eV): $m/e = 257$ ($M^+ - OC_2H_5$, 1%); 239 ($M^+ - OC_2H_5 - H_2O$, 6%); 215 ($M^+ - CH_2COOC_2H_5$, 5%); 177 ($C_2H_5OOC{-}CH_2CH_2OH^+$, 100%); 88 [$H_2C{=}C(OH)OC_2H_5^+$, 80%).

M.S. (70 eV) (silyl derivative): $m/e = 359$ ($M^+ - CH_3$, 30%); 313 ($M^+ - CH_3 - C_2H_5OH$, 18%); 287 ($M^+ - CH_2COOC_2H_5$; 20%); 189 [$C_2H_5OOC{-}CH_2{-}CHOSi(CH_3)_3^+$, 79%]; 73 [$Si(CH_3)_3^+$, 100%]

I.R. (film): $\nu = 3490, 2920, 2850, 1705\ cm^{-1}$.

^{1}H-N.M.R. (CDCl$_3$, 90 MHz): $\delta = 1.13$–1.80 (m, 20 H); 2.17–2.52 (m, 4 H); 3.20 (br. s, 1 H, OH); 3.80–4.30 ppm (m, 5 H).

2-(6-Methoxycarbonylhexyl)-cyclopent-2-en-1-one (4):

Compound **3** (2.675 g, 8.84 mmol) is added to freshly prepared polyphosphoric acid [85% orthophosphoric acid (16 ml) + phosphorus pentoxide (32 g)], the resulting mixture is slowly heated to 100 °C with vigorous stirring. After 1 h at 100 °C, the hot, dark red mixture is poured on to crushed ice (200 g), then extracted with diethyl ether (3 × 15 ml) followed by ethyl acetate (3 × 10 ml). The combined organic phases are washed with water (20 ml) and brine (20 ml) to neutrality and then dried with sodium sulfate. Removal of solvent gives a brown syrup (1.58 g) which is esterified by treatment with 3% hydrogen chloride in methanol (15 ml) at room temperature for 1 day. The brown oil (1.57 g) recovered is distilled under vacuum to give a yellow oil (b.p. 110–145 °C/3.10^{-2} torr, 0.897 g) which, as analyzed by G.L.C., is mainly composed of two products. Column chromatography on silica gel (ethyl acetate/benzene 1:10 as eluent) affords first *2-(5-methoxycarbonylpentyl)-cyclohex-2-en-1-one* (**5**); yield: 0.165 g.

$C_{13}H_{20}O_3$ calc. C 69.61 H 8.99
(224.3) found 69.81 9.02

M.S. (70 eV): $m/e = 224$ (M^+, 9%); 192 ($M^+ - CH_3OH$, 14%); 164 ($M^+ - COOCH_3 - H$, 15%); 109 ($C_7H_{10}O^+$, 27%); 41 ($C_3H_7^+$, 100%).

I.R. (neat): $\nu = 1735, 1670, 1435\ cm^{-1}$.

^{1}H-N.M.R. (CDCl$_3$, 300 MHz): $\delta = 1.12$–1.35 (m, 4 H); 1.51 (quin, 2 H, $J = 7.2$ Hz); 1.85 (quin, 2 H, $J = 6.6$ Hz); 2.05 (m, 2 H); 2.18 (t, 2 H, $J = 7.0$ Hz); 2.22–2.32 (m, 4 H); 3.55 (s, 3 H); 6.60 ppm (t, 1 H, $J = 3.5$ Hz). The cylcohexenoic structure of (5) was confirmed by the distinctive chemical shift of the proton on the double bond[9] ($\delta = 6.60$) and by spin decoupling experiments.

Further elution gives *2-(6-methoxycarbonylhexyl)-cyclopent-2-en-1-one* (**4**); yield: 0.665 g (33%); clear, colorless oil.

$C_{13}H_{20}O_3$ calc. C 69.61 H 8.99
(224.3) found 69.74 8.97

M.S. (70 eV): $m/e = 224$ (M^+, 7%); 192 ($M^+ - CH_3OH$, 26%); 150 ($M - COOCH_3 - H$, 42%); 109 ($C_7H_{11}O^+$, 50%); 96 ($C_6H_8O^+$, 100%).

I.R. (film): $\nu = 1735, 1700, 1630\ cm^{-1}$.

^{1}H-N.M.R. (CDCl$_3$, 300 MHz): $\delta = 1.32$ (m, 4 H); 1.47 (m, 2 H); 1.61 (m, 2 H); 2.16 (m, 2 H); 2.30 (t, 2 H, $J = 7.5$ Hz); 2.37–2.42 (m, 2 H); 2.55 (m, 2 H); 3.66 (s, 3 H); 7.26 ppm (m, 1 H).

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[1] Katon, M.P.L., in *New Synthetic Routes to Prostaglandins and Thromboxanes*, Scheinmann, F., Roberts, S.M., Eds., Academic Press, London, 1982, p. 105.

[2] Ellison, R.A. *Synthesis* **1973**, 397.

[3] Gokali, P.D., Dalowoy, U.S., Prakasa Rao, A.S.C., Nayak, U.R., Dev, S. *Synthesis* **1974**, 718.
Prakasa Rao, A.S.C., Nayak, U.R., Dev, S. *Synthesis* **1975**, 608.

[4] Venturello, C., Ricci, M., Alneri, E. *J. Org. Chem.* **1983**, *48*, 3831. The more expensive oxidation by means of *m*-chloroperbenzoic acid afforded **2** in 92% overall yield.

[5] Foà, M., Francalanci, F., unpublished results.

[6] Heck, R.F., in *Organic Syntheses via Metal Carbonyls*, Wender, I., Pino, P., Eds., Interscience Publishers New York, 1968, 384.

[7] Eisenmann, I. L. *J. Org. Chem.* **1962**, *27*, 2706.
Prand, J., Namy, J. L., Menoret, G., Kagan, H. B. *J. Organometal Chem.* **1985**, *285*, 449.
[8] Ansell, M. F., Palmer, M. N. *Quart. Rev.* **1964**, *18*, 211.
[9] Brewner Floyd, M., Weiss, M. G. *J. Org. Chem.* **1979**, *44*, 71.

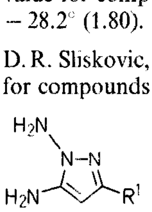
Errata and Addenda 1986

I. Ganboa, C. Palomo *Synthesis* **1986**, 52. The ^{1}H-NMR data for compounds **2d** and **2e** in the Table (p. 53) should be, respectively: 8.13 (d, 2 H_{arom}); 7.46 (d, 2 H_{arom}); 7.3 (s, 5 H_{arom}); 5.73 (m, 1 H, C–H); 5.26 (s, 2 H, $C\underline{H}_2-C_6H_4NO_2$); 4.9 (m, 1 H, C–H); 3.7 (m, 2 H, $C\underline{H}_2$–CO–NH); 3.3 (m, 2 H, S–CH_2); 2.13 (s, 3 H, CH_3). 7.33 (s, 5 H_{arom}); 7.3 (s, 5 H_{arom}); 5.76 (m, 1 H, C–H); 5.2 (s, 2 H, $C_6H_5-C\underline{H}_2$); 4.9 (m, 1 H, C–H); 3.63 (s, 2 H, $C\underline{H}_2$–CO–NH); 3.3 (m, 2 H, S–CH_2); 2.13 (s, 3 H, CH_3).

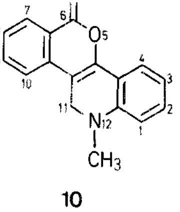
The ^{1}H-NMR data for compound **6** (p. 54) should be:
^{1}H-NMR ($CDCl_3/TMS_{int}$): $\delta = 8.03$ (d, 2 H_{arom}); 7.43 (d, 2 H_{arom}); 5.65 (s, 1 H, CH); 5.23 (s, 2 H, CH_2); 4.5 (s, 1 H, NH); 1.53, 1.35 ppm (2 s, 6 H, 2 CH_3).

K. Tanaka, H. Yoda, K. Inoue, A. Kaji *Synthesis* **1986**, 66. The $[\alpha]_D^{25}$ value for compound **2e** in Table 1 (p. 67) should be:
$-28.2°$ (1.80).

D. R. Sliskovic, M. Siegel, Y. Lin *Synthesis* **1986**, 71. The structures for compounds **6a, b** (p. 73) should be:

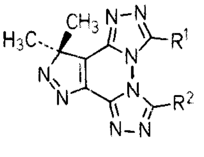


O. Meth-Cohn *Synthesis* **1986**, 76. The correct numbering for compounds **8** and **10** (p. 76) is as illustrated below for compound **10**:



10

B. Furlan, B. Stanovnik, M. Tišler *Synthesis* **1986**, 78. The double-bond arrangement of compounds **3**, **6**, and **7** (pp. 78, 79) should be:

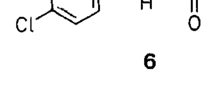


N. Petragnani, H. M. C. Ferraz, G. V. J. Silva *Synthesis* **1986**, 157. The authors wish to include the following pertinent references:
R. M. Adlington, A. G. M. Barret *Tetrahedron* **1981**, *37*, 3935.
R. M. Adlington, A. G. M. Barret *J. Chem. Soc. Perkin Trans. I* **1981**, 2848.
R. M. Adlington, A. G. M. Barret *J. Chem. Soc. Chem. Commun.* **1981**, 65.
R. M. Adlington, A. G. M. Barret *J. Chem. Soc. Chem. Commun.* **1979**, 1122.

A. J. Fatiadi *Synthesis* **1986**, 249. The heading for the first experimental procedure on p. 268 should be:
2,6-Diphenyl-4-(2,3,3-tricyanoallylidene)pyran (201)^{354}:

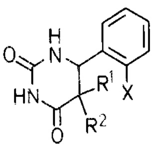
D. P. Matthews, J. P. Whitten, J. R. McCarthy *Synthesis* **1986**, 336. The headings for the first and last experimental procedures should be, respectively:
***N*^{1},*N*^{3}-Bis(2,2-dimethoxyethyl)oxaldiamidine Dihydrochloride (2):**
2-(2-Imidazolyl)-4-methoxy-4,5-dihydroimidazole (5):

T. Schrader, R. Kober, W. Steglich *Synthesis* **1986**, 372. The last equation in the formula scheme (p. 372) should be:

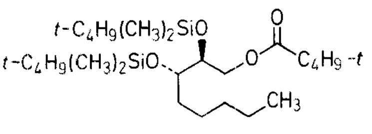


6

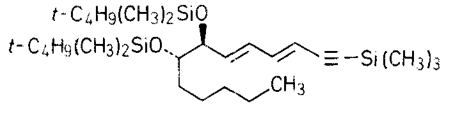
D. N. Dhar, K. S. K. Murthy *Synthesis* **1986**, 437. The heading for Table 2 (p. 440) should be:
4-Aryl-2(1*H*)-quinazolines **(13)** and 4-Aryl-1*H*-2,1,3-benzothiadiazine 2,2-Dioxides **(14)**
The names of compounds **13a** and **14a** in the experimental procedure on the same page should be corrected accordingly.
For compounds **60** and **61** (p. 445) R^3 = H, SO_2Cl.
The product in the lower, left reaction scheme on p. 446 should be:



K. C. Nicolaou, S. E. Webber *Synthesis* **1986**, 453. The structures of compounds **8** (p. 454) and **16** (p. 455) should be:



8

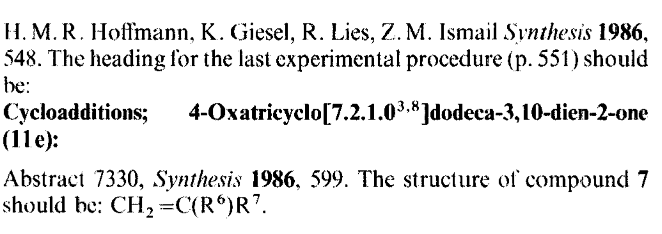


16

E. Dalcanale, M. Foà *Synthesis* **1986**, 492. In the reaction scheme, products **4** and **5** are obtained in 33 and 8%, respectively, a ratio of 80:20.

W. G. Dauben, J. M. Gerdes, G. C. Look *Synthesis* **1986**, 532. In the experimental procedure headings (p. 534), the names of compounds 3, 5, 7, and 9 should read:
(3,3-Ethylenedioxybutyl)triphenylphosphonium Bromide (3)
6-*t*-Butyldimethylsiloxy-3,7-dimethyl-1,6-octadiene (5)
5-[1,1-Bis(ethoxycarbonyl)ethyl]bicyclo[3.3.0]octan-2-one (7)
2,2-Ethylenedioxy-1,3,3-trimethylbicyclo[2.2.1]heptane (9).

S. Cadamuro, I. Degani, R. Fochi, A. Gatti, V. Regondi *Synthesis* **1986**, 544. Formula Scheme **B** should be:



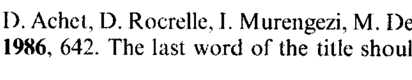
1c **2** **5**

H. M. R. Hoffmann, K. Giesel, R. Lies, Z. M. Ismail *Synthesis* **1986**, 548. The heading for the last experimental procedure (p. 551) should be:
Cycloadditions; 4-Oxatricyclo[7.2.1.0^{3,8}]dodeca-3,10-dien-2-one (11e):

Abstract 7330, *Synthesis* **1986**, 599. The structure of compound **7** should be: $CH_2=C(R^6)R^7$.

Abstract 7333, *Synthesis* **1986**, 600. Line 2 of the text should read: dimenthyl succinate **(1)** with lithium 2,2,6,6-tetramethylpiperidide reacts...

G. Barcelo, J. P. Senet, G. Sennyey, J. Bensoam, A. Loffet *Synthesis* **1986**, 627. The structure of compound **1k** (p. 630) should be:



$$(CH_3)_3Si-CH_2-CH_2-O-\overset{O}{\overset{\|}{C}}-O-\underset{Cl}{\underset{|}{CH}}-CCl_3$$

D. Achet, D. Rocrelle, I. Murengezi, M. Delmas, A. Gaset *Synthesis* **1986**, 642. The last word of the title should be: **Sulfate**