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Synthesis of Cyclic α-Diones, a Class of Natural Flavor Compounds [1]

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Abstract. A practical and generally applicable synthesis of the important flavor ingredients corylone (**5**) and its alkyl homologues **11**, **13**, **15**, and **16** is described, based on alkylation of methyl 4-methoxyacetoacetate (**6**) with an α-chloro-ketone and subsequent cyclization, hydrolysis, and decarboxylation. The one-pot transformation of methyl 4-chloroacetoacetate to **17** through four consecutive steps is demonstrated. The principle has also been used to prepare the six-membered ring analogues **23** and **24**.

Introduction

Cyclic 1,2-diones are an essential class of flavor ingredients. This is apparent, when one thinks of the high impact of chemicals such as *Furaneol*® (**1**) [3], homofuronol (**2**) [4], maltol (**3**) [5], 3-hydroxy-4,5-dimethyl-2(5*H*)-furanone (**4**; sotolon in the Japanese literature) [6] and 2-hydroxy-3-methylcyclopent-2-en-1-one (**5**, called corylone or cyclotene) [7] to name only the most important representatives (*Scheme 1*).

In this paper, we describe a novel synthetic approach [8][9] to corylone (**5**) and its alkyl and also its cyclohexane homologues. Corylone (**5**) has first been isolated from the dry distillate of beechwood [10] [11], found later in roasted coffee aroma [12] and in maple syrup [13]. The alkyl homologues of **5** have been detected in roasted coffee aroma [14][15], in tobacco smoke [16], and in the spent liquor from kraft pulping of pine wood [17].

The six-membered ring analogue of **5**, 2-hydroxy-3-methylcyclohex-2-en-1-one (**23**) (see *Scheme 5*) has also been found in coffee aroma [13] [14] and together with a number of its alkyl homologues in tobacco smoke [18].

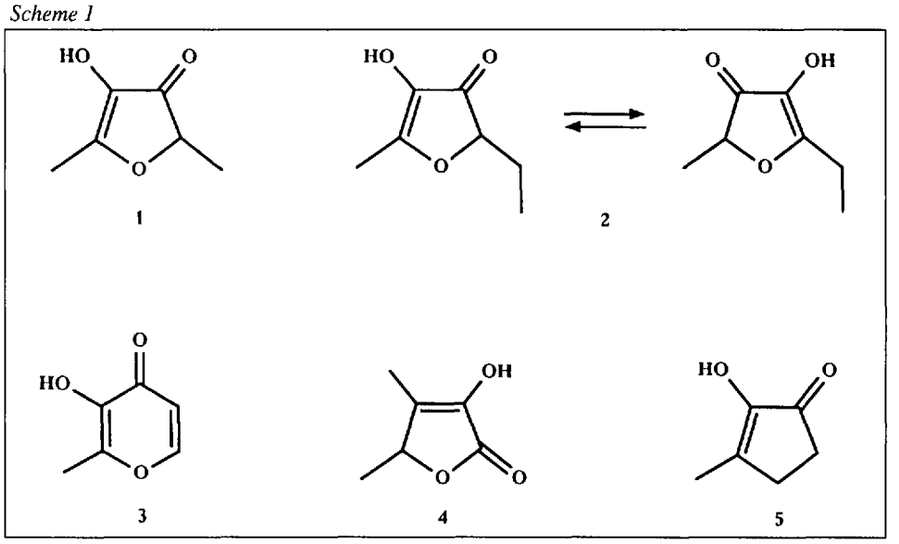
Corylone (**5**) and its homologues appear to be nonenzymatically formed browning reaction products of degradation products of sugars [15][19]. The synthetic routes to **5** and to some higher substituted cyclopentane-diones have been reviewed in [7]. Considering preparative routes to a compound like **5**, it has to be borne in mind, that economical and technical feasibility are the important conditions.

Results

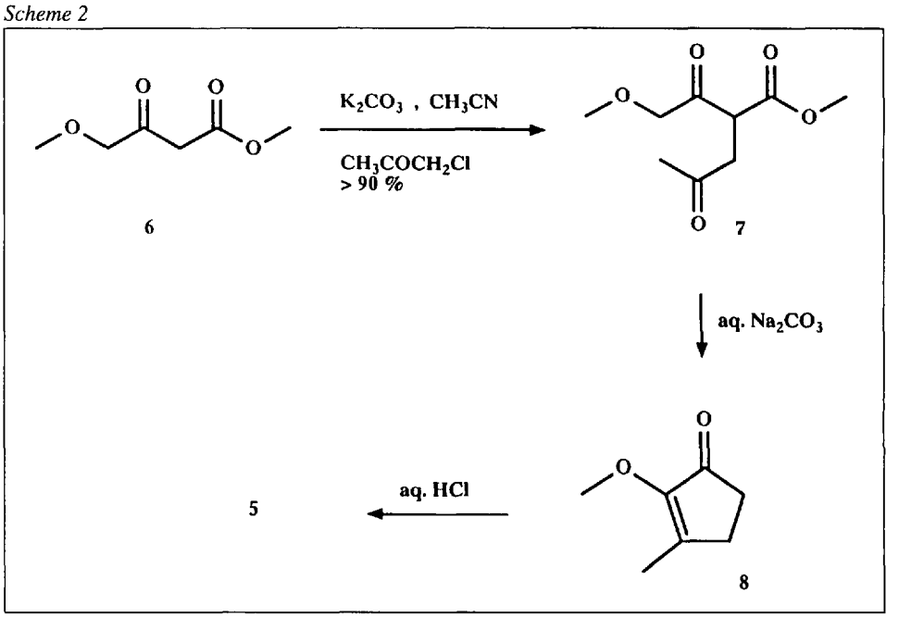
The new synthesis of corylone (**5**) is depicted in *Scheme 2*. Alkylation of methyl 4-methoxyacetoacetate (**6**), a cheap derivative of diketene, with chloroacetone under mild conditions gave a nearly quantitative yield of the required 1,4-dione **7**, which under slightly basic conditions furnished the enol ether **8**. Hydrolysis with aq. HCl led to **5** in >60% overall yield.

This basic concept as shown in *Scheme 2* is ideally suited for the preparation of the homologues of **5**, *e.g.* **11**, **13**, **15**, and **16** (*Schemes 3* and *4*).

Scheme 1



Scheme 2



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Alkylation of the same starting material **6** now with 3-chlorobutan-2-one led to the diastereoisomeric mixture **9**, which upon treatment with aq. Na_2CO_3 at reflux was transformed to the methyl enol ether **10**. Hydrolysis of the latter finally furnished 4-methylcorylone (**11**).

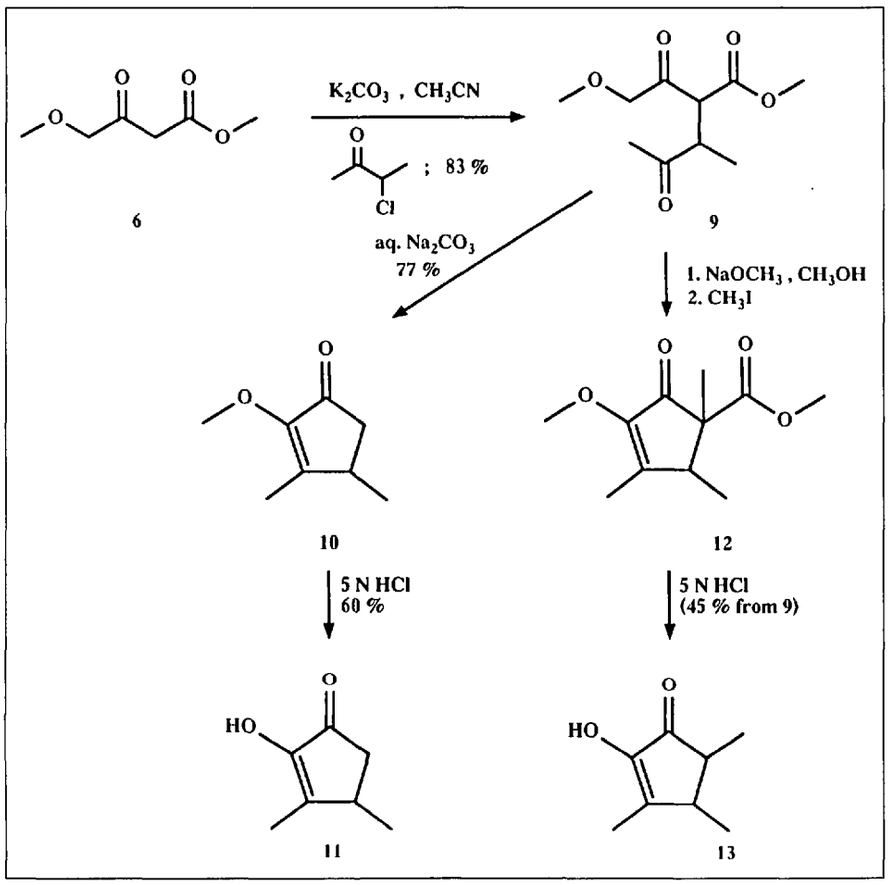
On the other hand, the β-ketoester unit in **9** can be exploited to introduce an other alkyl group under mild conditions. Thus alkylation of **9** with MeI (MeOH, MeONa) furnished directly the methylated and ring-closed product **12**, which was hydrolyzed and decarboxylated to *cis,trans*-4,5-dimethylcorylone **13** in 45% yield from **9** (*Scheme 3*).

The synthesis of a 5-substituted corylone, the 5-ethyl derivative **15** and **16**, is shown in *Scheme 4*. Alkylation of **7** with ethyliodide using sodium methylate as base led directly to the cyclic intermediate **14**, which was hydrolyzed and decarboxylated to a 2:1 mixture of the enols **15** and **16**.

Generally, it is advantageous to carry out the reaction sequence in one pot without isolation of the intermediates. This is demonstrated by the one-pot preparation of the enol ether **17** (*Scheme 4*) from methyl 4-chloroacetoacetate by subsequent addition of the reagents *a*) MeONa, *b*) chloroacetone, *c*) EtI, *d*) H_2O in 61% overall yield (see *Exper. Part*).

Finally, the procedure was applied for the synthesis of the six-membered ring analogues **23** and **24** (*Scheme 5*). The ring enlargement or chain lengthening, respectively, was brought about by *Michael* addition of the acetoacetates **6** and **18** to methyl vinyl ketone to give **19** or **20**, which were cyclized to the corresponding methyl enol ethers **21** [20] [21] and **22**. Hydrolysis of the latter furnished eventually the cyclohexane-α-diones **23** and **24**.

Scheme 3

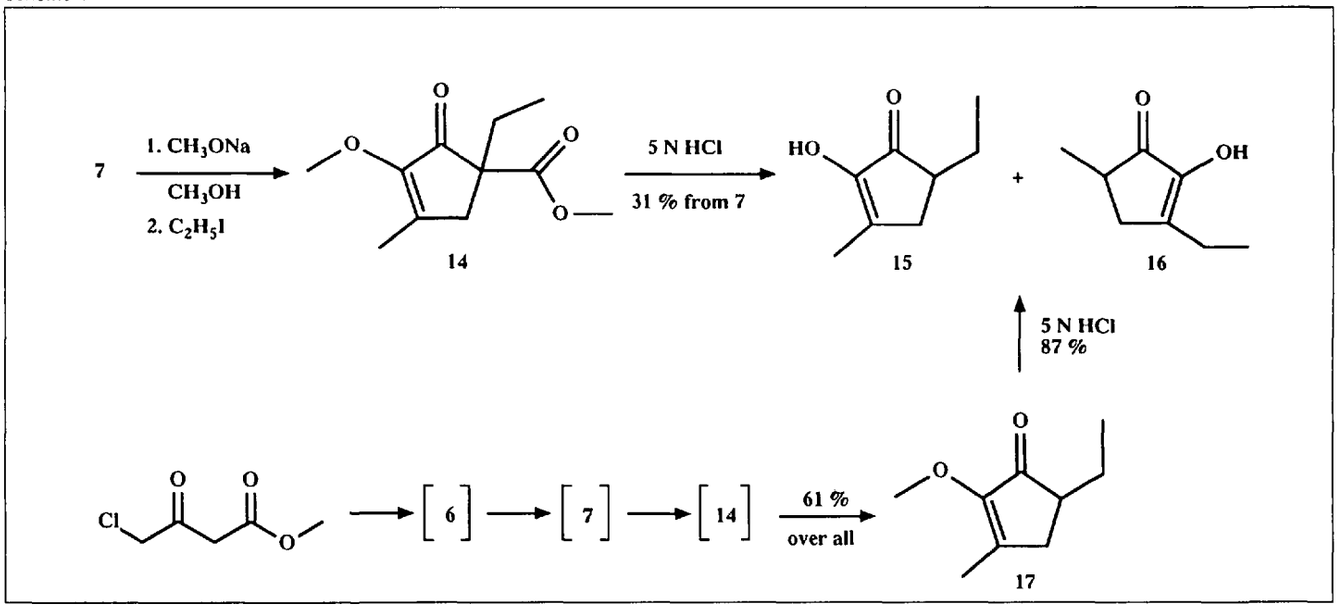


Discussion

Corylone (**5**) and its alkyl homologues **11**, **13**, **15**, and **16** are the more important flavor compounds in comparison with the six-membered ring analogues. Although there are several reasonable syntheses for **5** [7][22][23], they are not easily or not at all applicable for the preparation of the higher homologues like **11**, **13**, **15**, and **16**. As shown in *Schemes 2–4*, the described method is well suited for a general synthesis of all the differently substituted derivatives of **5**.

Sensoric measurements of the described compounds revealed large differences in strength and also in odor and

Scheme 4



taste. The taste threshold values differ by a factor of *ca.* 10^4 (measured in H_2O); **5**: $6.1 \cdot 10^4$ ppb, **11**: 17 ppb, **13**: 570 ppb, **15**, **16**: 5 ppb, **23**: 87 ppb. **5** has a burnt sugar, nutty, maple-like character, whereas **11** shows beside the burnt sugar quality a roasty and spicy tonality; **13** is caramel and maltol-like, and the very powerful mixture of **15** and **16** has a caramel, burnt, and bread-like property. The cyclohexane analogues **23** and **24** are phenolic, salicylaldehyde-like, **23** having an astringent and **24** a slightly medicinal and corylone-like taste.

The skillful experimental work of Miss *A. Tobler* and Mr. *H. Koch* is gratefully acknowledged.

Experimental Part

General. M.p. were measured in open capillary tubes and are uncorrected. IR spectra: *Perkin Elmer 781* spectrophotometer: in cm^{-1}. NMR Spectra: if not otherwise mentioned 60 MHz on a *Varian EM 360*; the 400 MHz on *Brucker AM 400* with TMS as internal standard; chemical shifts (δ) in ppm. MS: *Varian MAT CH-5* instrument, 70 eV, relative peak intensities in % of the base peak (= 100%).

Methyl 2-(Methoxyacetyl)-4-oxopentanoate (**7**). To the soln. (suspension) of 146.1 g (1 mol) of methyl 4-methoxyacetoacetate, 165.8 g (1.2 mol) of K_2CO_3 and 4.6 g (0.02 mol) of (benzyl)-(triethyl)ammonium chloride (TEBA) in 500 ml of MeCN 138.9 g (1.5 mol) of chloroacetone were added slowly at 5–15°. The mixture was stirred at ambient temp. during 7 h, then it was poured in a 10% NaH_2PO_4 soln. and worked up with AcOEt as usual. After evaporation of the solvent on the rotavap and additional drying at 0.1 mm a crude yield of 206.3 g (102%) was isolated. Distillation (120–122°/0.3 Torr) furnished 141.4 g (70%) of **7**. IR (film): 3620 (weak), 3430 (weak), 1750, 1720. NMR: 4.36 (*s*, CH_2O); 4.3–4.1 (*dd*, H–C(2)); 3.82, 3.53 (2*s*, 2 MeO); 3.34–3.03 (*m*, 2 H–C(3)); 2.25 (*s*, CH_3CO).

2-Methoxy-3-methylcyclopent-2-en-1-one (**8**). 140 g (0.69 mol) of **7** were dissolved in 2 l of aq. 2.5% Na_2CO_3 soln. and refluxed during 3 h. The reaction mixture was worked up with CH_2Cl_2 and gave after distillation (82–84°/20 Torr) 55.6 g (64%) of **8**. IR (film): 1705, 1650. NMR: 3.88 (*s*, MeO); 2.4 (*s*, CH_3–C(3)); 2.0 (*s*, 2H–C(4), 2 H–C(5)). MS: 126 (100, M^+), 111 (17), 97 (30), 83 (48), 67 (35), 55 (100).

2-Hydroxy-3-methylcyclopent-2-en-1-one (**5**). 55 g (0.43 mol) of **8** were refluxed in 1.5 l of 5N HCl during 5 h, then it was worked up with CH_2Cl_2. It furnished 50 g of crude yellow-brown crystalls. Recrystallization from aceton/H_2O 1:1 gave 42 g (87%) of slightly beige crystalls. M.p. 101–102°. IR ($CHCl_3$): 3500, 3325, 1715, 1660. NMR: 5.9 (br. OH), 2.48 (*s*, CH_3–C(3)); 2.03 (*s*, $2CH_2$).

Methyl 2-(Methoxyacetyl)-3-methyl-4-oxopentanoate (**9**). The mixture of 146 g (1 mol) of methyl 4-methoxyacetoacetate, 133 g (1.25 mol) of 3-chlorobutan-2-one, 166 g (1.2 mol) of K_2CO_3, 8.5 g (0.05 mol) of KI, 6.4 g (0.02 mol) of Bu_4NBr in 1.5 l of MeCN was stirred at 50° during 7 h, then MeCN was evaporated under reduced pressure, and the residue was taken up in CH_2Cl_2 and worked up as usual. Finally, 180 g (83.3%) of **9** were distilled at 110° and 0.03 Torr. Purity 94% (GLC). In the crude before distillation *ca.* 5% of the α,α-dialkylated product were detected. IR (film): 1750, 1720. NMR: 4.2 (*s*, CH_2O); 3.75 (*s*, MeO); 3.4 (*s*, MeO); 2.2 (*s*, MeCO); 1.15, 1.1 (2*d*, CH_3–C(3)). MS: 216 (1, M^+), 185 (3), 171 (50), 139 (63), 111 (20), 69 (31), 43 (100).

2-Methoxy-3,4-dimethylcyclopent-2-en-1-one (**10**). 43.2 g (0.2 mol) of **9**, 10.6 g (0.1 mol) of Na_2CO_3 in 420 ml of H_2O refluxed during 2.5 h. Normal workup gave 21.6 g (77%) of crude **10**. Purity 97% (GLC). IR (film): 1710, 1645. NMR: 3.9 (*s*, MeO); 2.9–2.4 (*m*, 2 H); 1.95 (*s*, CH_3–C(3)); 2.2–1.8 (*m*, 1 H); 1.2 (*d*, CH_3–C(4)). MS: 140 (95, M^+), 125 (95), 112 (30), 97 (100), 82 (41), 67 (34), 55 (37), 41 (100).

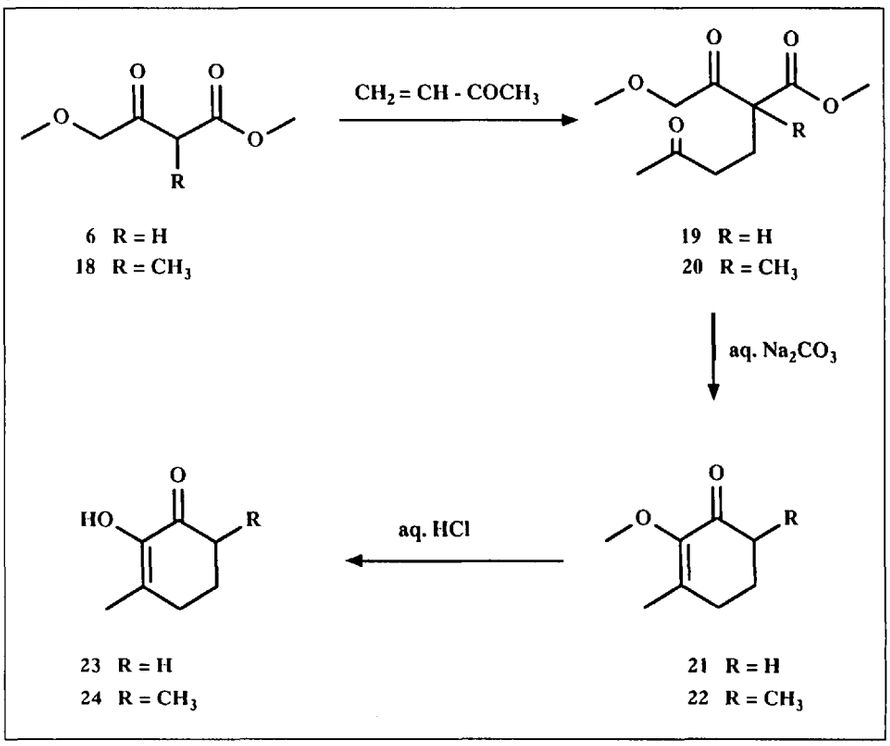
2-Hydroxy-3,4-dimethylcyclopent-2-en-1-one (**11**). 21.6 g of crude **10** were refluxed in 216 g of 5N HCl during 2 h. The resulting dark brown reaction mixture was worked up with Et_2O, and the isolated 14 g (72%) of crude **11** were recrystallized from Et_2O/hexane 1:1 and gave 11 g (56.6%) **11** of slightly beige crystalls. M.p. 65–67°. IR ($CHCl_3$): 3500, 3300, 1715, 1660. ^{1}H-NMR (400 MHz): (br., OH), 2.7 (H–C(4), part of the *ABC multiplett*), 2.66 (*m*, H_{trans}–C(5)); 2.0 (*m*, H_{cis}–C(5)); 1.97 (narrow *m*, CH_3–C(3)); 1.17 (*d*, CH_3–C(4)). Double resonance: ↓ CH_3–C(4) at 1.17 → change at 2.7 (H–C (4)). Diff. NOE: ↓ CH_3–C(4) at 1.17 → NOE observed at 2.7 (H–C(4)), 2.0 (H_{cis}–C(5)) and 1.97 (CH_3–C(3)). Spin simulation (PANIC) of the *ABC* system: $J(5,5') = -19.8$, $J(4,5_{trans}) = 6.4$, $J(4,5_{cis}) = 1.06$ Hz. ^{13}C-NMR: 202.5 (*s*, C=O); 149.37, 148.65 (2*s*, C(2) and C(3)); 40.7 (*t*, C(5)); 33.04 (*d*, C(4)); 19.02 (*q*, CH_3–C(4)); 11.9 (*q*, CH_3–C(3)). MS: 126 (36, M^+), 111 (26), 98 (16), 83 (36), 69 (13), 55 (54), 43 (100).

Methyl 3-Methoxy-1,4,5-trimethyl-2-oxocyclopent-3-ene-1-carboxylate (**12**). 216 g (1 mol) of **9** were dissolved in 1 l of methanolic soln. of 25.3 g (1.1 mol) of Na, warmed to reflux, and treated slowly (1 h) with 213 g (1.5 mol) of MeI. The clear soln. was stirred further at reflux for 4 h, then most of the MeOH was evaporated and the mixture poured on 600 ml of cold 2N HCl and worked up as usual. 214 g (101%) of crude **12** were isolated; purity *ca.* 90% of two diastereoisomers in 1:2 ratio. IR (film): 1740, 1705, 1650. NMR: 3.95 (*s*, MeO); 3.7 (*s*, MeO); 3.2–2.3 (*m*, H–C(5)); 2.05, 1.95 (2*s*, CH_3–C(4)); 1.4 (*s*, CH_3–C(1)); 1.3, 1.1 (2*d*, CH_3–C(5)). MS: 212 (25, M^+), 181 (5), 169 (9), 152 (37), 109 (10), 43 (100).

2-Hydroxy-3,4,5-trimethylcyclopent-2-en-1-one (**13**). 214 g of crude **12** were refluxed in 2.1 l of 5N HCl during 3 h, then the brownish black mixture was cooled to r.t. and extracted with Et_2O. The Et_2O phase was washed twice with a soln. of thiosulfate in H_2O to remove the iodine, formed from excess MeI. After the usual workup, 94.8 g (67%) of crude **13** were isolated; yellowish brown crystalls, which were distilled through a *Widmer* column (67–72°/0.4 Torr). Yield: 62 g (44.3%). M.p. 55–57°. *trans*-**13**/*cis*-**13** 6.5:1. IR ($CHCl_3$): 3500, 3300, 1710, 1660. NMR: 6.9 (*s*, OH); 1.98 (*s*, CH_3–C(3)); 1.15 (*d*, CH_3–C(4), CH_3–C(5)); 2.9–1.7 (*m*, H–C(4), H–C(5)). MS: 140 (83, M^+), 125 (95), 112 (20), 97 (100), 83 (33), 79 (26), 69 (30), 55 (69), 43 (91).

Methyl 1-Ethyl-3-methoxy-4-methyl-2-oxocyclopent-3-ene-1-carboxylate (**14**), *5-ethyl-2-hydroxy-3-methylcyclopent-2-en-1-one* (**15**), *and 3-ethyl-2-hydroxy-5-methylcyclopent-2-en-1-one* (**16**). 70.6 g (0.35 mol) of **7** were dissolved in 385 ml of a 1M methanolic CH_3ONa soln. and treated

Scheme 5



at reflux (65°) slowly (45 min) with 65.5 g (0.42 mol) of EtI. The reddish brown mixture was stirred at reflux during 4 h, then MeOH was distilled off at reduced pressure, and the residue was worked up with cold 4N HCl and AcOEt. The isolated crude product **14** (*ca.* 90 g) was refluxed in 740 g of a 5N HCl soln. during 2.5 h. After workup with CH_2Cl_2, 31.5 g (45.6%) of the crude mixture of **15** and **16** were isolated. Distillation through a *Widmer* column gave 21.47 g (31.1%) of **15** and **16** (65–75°/0.1 Torr). Characterization *vide infra*.

5-Ethyl-2-methoxy-3-methylcyclopent-2-en-1-one (**17**; *the one-pot version from methyl 4-chloroacetoacetate*). To the suspension of 48.6 g (0.9 mol) of MeONa in 450 ml of THF 45.2 g (0.3 mol) of methyl 4-chloroacetoacetate in 50 ml of THF were added. The strongly exothermic reaction is held at 45–50° by means of ice-cooling, and stirring is continued for 90 min. Then, 42 g (0.3 mol) of K_2CO_3, 1.0 g of NaI and 39 g (42 mol) of chloroacetone in 100 ml of THF were added within 10 min at 50–55°, and the mixture was further stirred for 30 min. To the above crude soln. of **7** 66 g (0.42 mol) of EtI were added, and the mixture was refluxed for 24 h, after 12 h a further 42 g (0.3 mol) of K_2CO_3 having been added. At this stage, the GLC shows the presence of 71% of **14**. Now, most of the solvent is distilled off (*ca.* 600 ml), and after addition of 360 ml of H_2O the reddish brown clear soln. is refluxed for 24 h (91–94°). After the usual workup, 37.9 g (82%) of crude **17** were isolated, which after distillation (96–103°/20 Torr) furnished 28.3 g (61% of pure **17**. IR (film): 1705, 1650. NMR: 3.9 (*s*, MeO); 2.0 (*s*, CH_3–C(3)); 3.0–1.1 (*m*, 5 H); 0.92 (*t*, $-CH_2-CH_3$). MS: 154 (60, M^+), 139 (8), 126 (77), 111 (36), 94 (100), 79 (17), 67 (24), 55 (61), 41 (75).

15 *and* **16** *from* **17**: 27 g (0.17 mol) of **17** were refluxed in 135 ml of 5N HCl for 1 h. Usual workup gave 23.7 g (96%) of crude product, which after distillation (87–89°/0.7 Torr) furnished 21.4 g (87.4%) of pure (95%) 2:1 mixture of 15 and **16**. IR ($CHCl_3$): 3500, 3320, 1710, 1660. NMR (400 MHz): 6.35 (br. OH); 2.7 (*dd*, H–C(4) of **16**); 2.6 (*dd*, H–C(4) of **15**); 2.48–2.4 (*m*, CH_3CH_2 and H–C(5) of **16**); 2.4–2.32 (*m*, H–C(5) of **15**); 2.08 (*dd*, H'–C(4) of **15**); 2.01 (*s*, CH_3–C(3)); 1.88–1.76, 1.58–1.36 (*m*, CH_3CH_2 of **15**); 1.2 (*d*, CH_3–C(5)); 1.16 (*t*, CH_3CH_2 of **15**); 0.95 (*t*, CH_3CH_2 of **15**). MS: 140 (80, M^+), 125 (26), 112 (100), 94 (100), 83 (28), 69 (30), 55 (72), 41 (71).

Methyl 2-(Methoxyacetyl)-5-oxohexanoate (**19**). To the soln. of 73 g (0.5 mol) of *methyl 4-methoxyacetoacetate* (**6**), 38 g (0.55 mol) of methyl vinyl ketone in 250 ml of $CHCl_3$, 50.5 g (0.5 mol) of $(i\text{-}Pr)_2NH$ were added at 0–20°. After the addition, the mixture was stirred at 40° for 1 h, evaporated, and distilled. The product **19** was distilled (130–135°/0.15 Torr); 34 g (32%). IR ($CHCl_3$): 1745, 1720. NMR: 4.1 (*s*, 2 H); 3.7, 3.45 (2*s*, 2 MeO); 3.6–3.4 (*t*, H–C(2)); 2.1 (*s*, 3 H–C(6)); 2.7–1.8 (*m*, 2 CH_2). MS: 216 (1, M^+), 184 (18), 171 (95), 139 (100), 113 (19), 45 (90), 43 (60).

2-Methoxy-3-methylcyclohex-2-en-1-one (**21**). 10.8 g (50 mmol) of **19** were refluxed during 90 min in 100 ml (2.5%) of aq. Na_2CO_3 soln. After the usual workup 5.1 g (73%) of crude **21** were isolated, which distilled at 98–101° at 20 Torr; 4.4 g (63%). IR (film): 1680, 1625. NMR: 3.66 (*s*, MeO); 1.93 (*s*, CH_3–C(3)); 2.7–1.7 (*m*, 6 H). MS: 140 (100, M^+), 125 (22), 110 (20), 95 (33), 82 (44), 69 (48), 55 (32), 41 (64).

2-Hydroxy-3-methylcyclohex-2-en-1-one (**23**). 2.8 g (20 mmol) of **21** were refluxed in 20 ml 5N HCl during 9 h. Usual workup gave 1.7 g (67%) of crude **23**, which was purified by bulb-to-bulb distillation (*ca.* 50°/0.05 Torr) to give 1.36 g (54%) of white crystalls. M.p. 55–60°. IR ($CHCl_3$): 3450, 1670, 1640. NMR: 6.12 (*s*, OH); 1.95 (*s*, CH_3); 2.7–1.8 (*m*, 6 H). MS: 126 (100, M^+), 108 (15), 97 (25), 83 (55), 70 (42), 55 (61).

Methyl 2-(Methoxyacetyl)-2-methyl-5-oxohexanoate (**20**). To the mixture of 16 g (0.1 mol) of methyl 4-methoxy-2-methylacetoacetate (**18**), 1.4 g (0.01 mol) of K_2CO_3, 0.4 g (2 mmol) of TEBA in 100 ml of MeCN, 10.5 g (0.15 mol) of methyl vinyl ketone has been added slowly (30 min). The mixture was poured on ice-cold 1N HCl and extracted with AcOEt. The usual workup gave 22.05 g (96%) of crude **20** of high purity, which was used as such. IR (film): 3500 (weak, traces of H_2O); 1740, 1720. NMR: 4.12 (*s*, $-O-CH_2$); 3.75, 3.38 (2*s*, 2 MeO); 2.14 (*s*, 3H–C(6)); 1.37 (*s*, CH_3–C(2)). MS: 230 (2, M^+), 185 (22), 160 (20), 155 (13), 125 (33), 115 (25), 98 (35), 43 (100).

2-Methoxy-3,6-dimethylcyclohex-2-en-1-one (**22**). Analogously to the transformation **19** → **21**, **22** was prepared from **20** in 77% distilled yield. B.p. 131°/20 Torr. IR (film): 1675, 1635. NMR: 3.62 (*s*, MeO); 1.9 (*s*, CH_3–C(3)); 2.7–1.5 (*m*, 5 H); 1.15 (*d*, CH_3–C(6)). MS: 154 (100, M^+), 139 (33), 124 (15), 109 (39), 96 (53), 79 (44), 69 (91), 55 (38).

2-Hydroxy-3,6-dimethylcyclohex-2-en-1-one (**24**). Analogous procedure to **23**. 72% crude was recrystallized from Et_2O/hexane (1:1 to give white crystalls in 62% yield. M.p. 62–63°. Sublimation at 40°/0.05 Torr furnished white crystalls in 97% yield. M.p. 64–65°. IR ($CHCl_3$): 3450, 1680, 1645. NMR: 6.1 (*s*, OH); 2.7–1.5 (*m*, 5 H); 1.92 (br. *s*, CH_3–C(3)); 1.39 (*d*, CH_3–C(6)). MS: 140 (57, M^+), 111 (100), 97 (33), 70 (44), 55 (36).

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