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Application of Carbonyl Umpolung to Prostaglandin Synthesis, III [1]

Synthesis of 11-Deoxy Prostaglandin Synthons[2]

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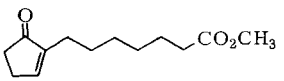
The application of thiazolium salt catalysed addition of aldehydes to α,β-unsaturated esters for the synthesis of the title compounds (**1**, **2** and **3**) is discussed.

Anwendung von Carbonyl Umpolung für Prostaglandin Synthese, III [1]

Synthese von Synthonen der 11-Desoxy-prostaglandine [2]

Der Einsatz der Thiazoliumsalz-katalysierten Addition von Aldehyden an α,β-ungesättigte Ester für die Synthese der Titelverbindungen (**1**, **2** und **3**) wird diskutiert.

New methods of constructing 2-alkylcyclopentenones (**1**, **2** and **3**) are highly desirable since these compounds have served as useful precursors in the synthesis of 11-deoxy analogues of the naturally occurring prostaglandins[3]. Furthermore, the cyclopentenone **1** has also been transformed into its 4-hydroxy-derivative[4], which was successfully elaborated into prostaglandin E_1[3]. Thus, there has been a considerable effort recently in developing new synthetic routes to the cyclopentenone **1**, whereas the intermediates of 11-deoxyprostaglandin E_2 (**2** and **3**) are synthetically much less explored[3,5].



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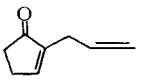

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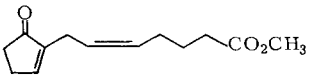

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In a preliminary report we described the application of the conjugate addition of acyl carbanion equivalents to α,β-unsaturated esters for the preparation of the cyclopentenone **1**[2]. In this publication some of our earlier results will be complemented by the application of this method for the synthesis of the cyclopentenone intermediates of both 11-deoxyprostaglandins, E_1 and E_2 (**1**, **2** and **3**).

Our synthetic approach to the title compounds relies on the conjugate addition of appropriately functionalized aldehydes **4** to methyl acrylate (**5**) (Stetter's method), followed by base catalysed cyclization and further simple transformations (Scheme I).

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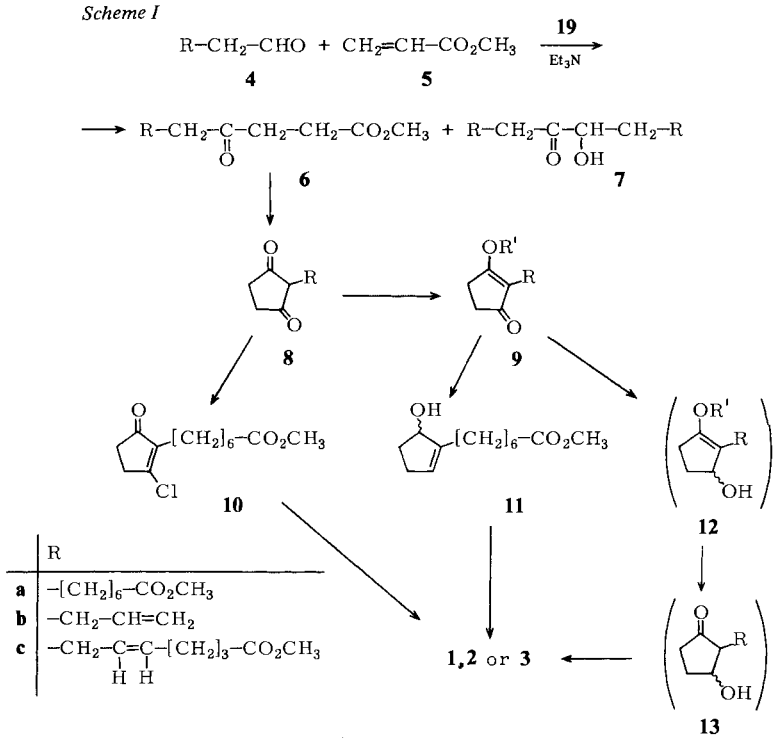
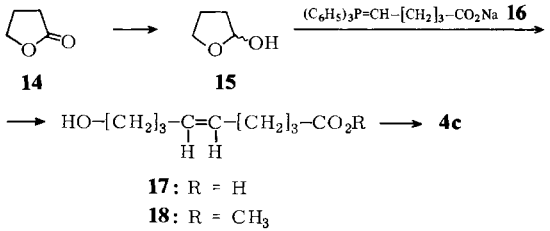
Scheme I



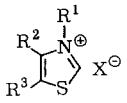
The precursor aldehydes **4** were prepared from commercially available starting materials. Thus, methyl 9-oxononanoate (**4a**) was made in high yield by cleavage of methyl 9,10-dihydroxystearate obtained from oleic acid[6]. 4-Pentenal (**4b**) was prepared by hydride reduction of ethyl 4-pentenoate to 4-penten-1-ol followed by oxidation with pyridinium chlorochromate.

For the preparation of aldehyde **4c**, butyrolactone (**14**) was reduced with diisobutylaluminium hydride to 2-hydroxytetrahydrofuran (**15**) as previously described[7]. Reaction between the latter and the ylide **16** derived from 5-(triphenylphosphonio)pentanoic acid and sodium methylsulfinylmethide yielded the hydroxy acid **17** (isomeric purity 98% by GC), which was transformed into the corresponding hydroxy ester **18** by treatment with ethereal diazomethane. Conversion of the hydroxy ester **18** to the aldehyde **4c** was accomplished by oxidation with pyridinium chlorochromate (Scheme II).

Scheme II



In the course of our study we have thoroughly investigated the reactions of acyl carbanion equivalents with α,β-unsaturated esters. This type of reactions has been the subject of intense study in recent years[8]. For the generation of acyl carbanion equivalents from aldehydes the catalysts most commonly used were thiazolium salts (**19a – d**) in the presence of triethylamine.



	R^1	R^2	R^3	X
19a	benzyl	methyl	2-hydroxyethyl	Cl
b	ethyl	methyl	2-hydroxyethyl	Br
c	2-hydroxyethyl	H	H	Br
d	benzyl	H	H	Cl

The reactions between the aldehydes **4** and methyl acrylate **5** were performed at elevated temperature (up to 100 °C) in the presence of catalytic amounts (0.1 – 0.2 equiv.) of thiazolium salt (**19**) and triethylamine (0.4 equiv.) in dioxane, or without solvent. As anticipated from the previous work of *Stetter* and co-workers[9] the reaction afforded a mixture of the ketoester (**6**) and α-ketol (**7**). The product ratio was most likely controlled by thermodynamic factors since using a longer reaction time it was approximately 1 : 1, in all the cases investigated. The rate of reaction and the yield did not depend significantly on the substituents of the thiazole ring of the catalyst. We have got essentially the same results with catalysts **19a**, **19b** and **19c**[10]. However, the thiazolium salt **19d** was ineffective, probably due to its insolubility in the reaction mixture. At lower temperature or using shorter reaction times the amounts of α-ketol (**7**) increased.

In the cases of **6a** and **6c**, the mixture was separated by simple distillation in vacuo. The ketoester **6b** was isolated by sodium hydroxide extraction, followed by reesterification.

The ketoesters **6a – c** were conveniently transformed into the 1,3-cyclopentanediones **8a – c** by base induced intramolecular cyclization.

To complete the synthesis of enones **1 – 3**, the enol ethers **9** ($R' = CH_3$) were formed by treatment of the diones **8** with ethereal diazomethane, or methanol and sulfuric acid. Reduction of the enol ether **9b** ($R' = CH_3$) with sodium dihydrobis(2-methoxyethoxy)aluminate and hydrolysis of the resulting cyclopentenol derivative **12b** ($R' = CH_3$) followed by acid-promoted elimination afforded the enone **2**[11,12].

The intermediate of 11-deoxyprostaglandin E_2 was prepared in an analogous series of reactions. The enol ether **9c** ($R' = CH_3$) was reduced with sodium dihydrobis(2-methoxyethoxy)aluminate and the resulting alcohol **12c** ($R' = CH_3$) was hydrolyzed and transformed *in situ* with dilute acid to the enone **3**.

The reduction of the enol ether precursor of 11-deoxyprostaglandin E_1 (**9a**; $R' = CH_3$) with sodium dihydrobis(2-methoxyethoxy)aluminate was very slow at low temperature (– 30 °C). At elevated temperature (– 10 °C), however, considerable amounts of the ester group were also reduced. The reduction of the corresponding enol mesitylenesulfonate **9a** (R' = mesitylenesulfonyl group) with sodium borohydride gave a better result. In this reaction only small amounts of side-products were formed and the resulting cyclopentenol **12a** (R' = mesitylenesulfonyl group) smoothly underwent acid catalyzed hydrolysis and elimination to afford the enone **1**, in moderate yield.

Reduction of the enol ether **9a** (R′ = CH_3) with sodium borohydride led directly to the cyclopentenol **11**, probably as a consequence of the instability of the intermediate (**12**; R′ = CH_3) at the elevated temperature (40 °C). Upon oxidation with activated manganese dioxide, **11** gave the enone **1**.

Our inability to accomplish a controlled reduction of the enol ether **9a** prompted us to turn to the alternative approach wherein the dione **8a** was converted to the chloroenone **10**. The chloroenone was dehalogenated by silver-zinc couple in methanol to give the enone **1**, in excellent yield.

The outlined synthesis represents a short and useful alternative route to 11-deoxyprostaglandin synthons (**1**–**3**), since the starting materials are easily accessible, the overall yields are relatively good and it is suitable for large scale preparation.

We thank *Ilona Batta, Pál Kolonits, Lajos Radics, Eszter Baitz-Gács, Sándor Holly* and *Anikó Gergely* for elemental and spectral analyses. Financial assistance from *Chinoin Pharmaceutical and Chemical Works Ltd.*, Budapest, is gratefully acknowledged.

Experimental Part

IR spectra: Perkin Elmer 225 spectrometer. ^{1}H NMR spectra were recorded at 100 MHz with TMS as an internal standard on a Varian S-100 XL Spektrometer. MS measurements: were taken on a JEOL-20K and JMS-0156-2 combined GC/MS system.

Methyl 9-oxononanoate (**4a**): To a rapidly stirred suspension of 66.1 g of *threo*-methyl 9,10-dihydroxystearate (0.2 mol) in 600 ml of dry benzene, under argon atmosphere, was added 90 g of lead tetraacetate (0.2 mol) portionwise. During the addition, the temperature of the solution was maintained at 25–26 °C. The reaction mixture was stirred for a further 10 minutes and then filtered. The filtrate was successively washed with water, 5% sodium hydrogen carbonate solution, water and dried. Removal of the solvent under reduced pressure and distillation gave the aldehyde **4a** (30 g = 80%), b. p. 80–82 °C/0.2 Torr (lit.[6] 94–96 °C/0.75 Torr), n_D^{20} = 1.4370. – IR (film): 2710, 1735, 1710 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 1.2–1.8 (m, 10H, $5CH_2$), 2.32 (t, *J* = 8 Hz, 2H, CH_2–COO), 2.44 (t, *J* = 6 Hz, 2H, CH_2–CHO), 3.66 (s, 3H, OCH_3), 9.79 (t, *J* = 2 Hz, 1H, CHO).

4-Pentenal (**4b**): A solution of 33.5 g of 4-penten-1-ol (0.39 mol) in 200 ml of methylene chloride was added to a suspension of 121 g of pyridinium chlorochromate (0.56 mol) and 9.2 g of sodium acetate (0.11 mol) in 300 ml of methylene chloride. The mixture was heated under reflux for 5 h, cooled to room temperature, and then vigorously shaken with 400 ml of ether followed by decantation. The ethereal extract was concentrated and distilled through a Vigreux-column (30 cm) giving 19.6 g (60%) of the aldehyde **4b**, b. p. 29–32 °C/24 Torr (lit.[13] 101–105 °C). – IR (film): 1720, 1635 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 2.15–2.75 (m, 4H, $2CH_2$), 4.75–5.25 (m, 2H, H_2C=), 5.45–6.15 (m, 1H, HC=), 9.7 (t, *J* = 2 Hz, 1H, CHO).

2-Hydroxytetrahydrofuran (**15**): 94.5 ml of diisobutylaluminium hydride (0.55 mol) were added dropwise to a stirred solution of 43 g of butyrolactone (**14**) (0.5 mol) in 700 ml of dry ether cooled to −78 °C (N_2 atmosphere). The resultant solution was stirred at −78 °C for 3 h, after which the reaction was quenched by the addition of 80 ml of dry methanol. Then the solution was allowed to warm to 0 °C and treated with brine. The precipitate was filtered off and the filtrate was dried with sodium sulfate. The ether was removed on a rotary evaporator, and the residue was

distilled through a small column giving 21.5 g (48.8%) of 2-hydroxytetrahydrofuran (**15**), b. p. 60–65 °C/13 Torr, n_D^{20} = 1.4368 (lit.[7] 51 °C/11 Torr). The spectral data of **15** (IR and NMR) were in agreement with the literature.

Methyl (Z)-9-hydroxy-5-nonenoate (**18**): A suspension of 29.4 g of sodium hydride (1 mol, 80% dispersion in mineral oil) in 250 ml of dimethyl sulfoxide (freshly distilled from CaH_2) was stirred and heated at 75 °C for 1 h, under a nitrogen atmosphere. Then the solution was cooled to room temperature and 177.2 g of 5-(triphenylphosphonio)pentanoic acid (0.4 mol) in 300 ml of dry dimethyl sulfoxide was added. The resultant solution was stirred for 0.5 h and the solution of 20.7 g of 4-hydroxytetrahydrofuran (**15**) (0.23 mol) in 50 ml of dry dimethyl sulfoxide was added dropwise. Stirring at room temperature was continued for 8 h, after which time the solution was acidified to pH 6 with acetic acid, and the dimethyl sulfoxide was removed under reduced pressure. The residue was dissolved in 10% sodium carbonate solution and the solution was extracted with benzene. The aqueous layer was acidified with 10% hydrochloric acid and extracted 3 times with ether. The extract was washed with brine and dried, and the solvent was removed under reduced pressure to leave 36 g of crude (*Z*)-9-hydroxy-5-nonenoic acid (**17**).

The acid **17** was converted into its methyl ester (**18**) with ethereal diazomethane. The crude ester was distilled at 94–96 °C/0.15 Torr to give 22.3 g (51.2%) of pure material, n_D^{20} = 1.4602. – IR (film): 3450, 1740 cm^{-1}. – ^{1}H-NMR (CCl_4): δ = 1.4–2.5 (m, 10H, $5CH_2$), 3.15 (broad, 1H, exchangeable with D_2O, 9-OH), 3.6 (t, *J* = 6 Hz, 2H, CH_2–O), 3.65 (s, 3H, OCH_3), 5.4 (m, 2H, HC=CH).

$C_{10}H_{18}O_3$ (186.3) Calc. C 64.49 H 9.74 Found C 64.15 H 9.79

The corresponding ethyl ester was prepared from the acid **17** by application of the general method (ethanol, *p*-toluenesulfonic acid), b. p. 94–96 °C/0.15 Torr. – IR (film): 3450, 1740 cm^{-1}. – ^{1}H-NMR (CCl_4): δ = 1.1 (t, *J* = 6 Hz, 3H, CH_3), 1.4–2.5 (m, 10H, $5CH_2$), 3.1 (broad, 1H, exchangeable with D_2O, 9-OH), 3.55 (t, *J* = 6 Hz, CH_2–O), 4.1 (q, *J* = 6 Hz, 2H, OCH_2), 5.4 (m, 2H, HC=CH).

$C_{11}H_{20}O_3$ (200.3) Calc. C 65.97 H 10.06 Found C 65.67 H 9.89

Methyl (Z)-9-oxo-5-nonenoate (**4c**): A solution of 22.3 g of the alcohol **18** (0.12 mol) in 120 ml of methylene chloride was added to a vigorously stirred suspension of 38.8 g of pyridinium chlorochromate (0.18 mol) and 2.5 g of sodium acetate in 120 ml of methylene chloride . Stirring at room temperature was continued for 3 h, and then the reaction mixture was diluted with 300 ml of ether. The organic layer was separated and solvents were evaporated under reduced pressure, the residue was dissolved in ether and then filtered through a short column (5 cm) filled with silica gel. The solvent was evaporated and the oily, crude product was distilled through a Vigreux-column to give 14.75 g (66.8%) of pure aldehyde **4c**, b. p. 84–88 °C/0.15 Torr, n_D^{20} = 1.4530. – IR (film): 1730, 1710 cm^{-1}. – ^{1}H-NMR (CCl_4): δ = 1.45–2.5 (m, 10H, $5CH_2$), 3.6 (s, 3H, OCH_3), 5.35 (m, 2H, HC=CH), 9.75 (t, *J* = 2 Hz, 1H, CHO).

$C_{10}H_{16}O_3$ (184.2) Calc. C 65.19 H 8.75 Found C 65.12 H 8.86

The corresponding ethyl ester was prepared from ethyl (*Z*)-9-hydroxy-5-nonenoate by application of the above method and had b. p. 90–92 °C/0.15 Torr. – ^{1}H-NMR (CCl_4): δ = 1.25 (t, *J* = 7 Hz, 3H, CH_3), 1.45–2.5 (m, 10H, $5CH_2$), 4.05 (q, *J* = 7 Hz, CH_2–O), 5.35 (m, 2H, HC=CH), 9.75 (t, *J* = 2 Hz, 1H, CHO).

Dimethyl 4-oxo-dodecanedioate (**6a**): To a stirred, refluxing mixture of 18.6 g of the aldehyde **4a** (0.1 mol), 17.2 g of methyl acrylate (**5**) (0.2 mol) and 2.1 g of 3-(2-hydroxyethyl)thiazolium bromide (**19c**) (0.01 mol) in 150 ml of dry dioxane was added dropwise a solution of 4 g of triethylamine (0.04 mol) during 1 h (under argon). The resulting mixture was stirred and boiled for 24 h. After cooling, the salt of triethylamine precipitated was filtered off and washed with

dioxane. The filtrate was concentrated in vacuo, the residue was treated with 80 ml of N HCl and extracted twice with ether. The combined ethereal extracts were washed successively with N HCl, water, 5% sodium hydrogen carbonate solution, 5% sodium hydrogen sulfite and brine, dried and concentrated. The residue was distilled through a Vigreux-column giving 11.5 g (42%) of pure ketoester (**6a**), b. p. 143–146 °C/0.15 Torr, m. p. 38–40 °C. – IR (KBr): 1740, 1718 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 1.2–1.8 (m, 10H, 5CH_2), 2.31 (t, *J* = 7 Hz, 2H, CH_2-11), 2.45 (t, *J* = 7 Hz, 2H, CH_2-2), 2.63 (t, *J* = 5 Hz, CH_2-5), 2.67 (t, *J* = 5 Hz, 2H, CH_2-3), 3.66 (s, 3H, OCH_3). – MS: M^+ 272, *m/e* 241 (26), 185 (29), 130 (base peak), 115 (52), 98 (77), 87 (19), 59 (33), 55 (52), 41 (33).

$C_{14}H_{24}O_5$ (272.3) Calc. C 61.74 H 8.88 Found C 61.29 H 9.11

The α-ketol **7a** was isolated by distillation of the above residue (10 g, 58%), and had b. p. 190–195 °C/0.15 Torr. – IR (KBr): 3490, 1740, 1712 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 1.2–1.9 (m, 22H, 11CH_2), 2.31 (t, *J* = 7.5 Hz, 2H, CH_2), 2.45 (t, *J* = 7 Hz, 2H, CH_2), 3.66 (s, 6H, OCH_3), 4.15 (m, 1H, CH–O).

Methyl 4-oxo-7-octenoate (**6b**): To a stirred solution of 33.6 g of the aldehyde **4b** (0.4 mol), 107.5 g of methyl acrylate (**5**) (1.25 mol) and 8.6 g of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (**19a**) (0.04 mol) were added 8 g of triethylamine (0.08 mol) at 85 °C, under an argon atmosphere, and the mixture was stirred at 85 °C for 8 h. The reaction mixture was cooled to room temperature, poured onto ice/water, acidified with 20% sulfuric acid and extracted three times with ether. The combined organic extracts were washed with water and dried. The solvent was removed in vacuo and the residue was distilled through a short Vigreux-column giving 29 g of a mixture of ester (**6b**) and hydroxyketone (**7b**) (b. p. 77–79 °C/0.5 Torr). Analysis by GLC showed it to contain **7b** and **6b** in the ratio of ca. 2:3, respectively.

The mixture was separated by base-catalysed hydrolysis of the ester, with an excess of sodium hydroxide to the corresponding acid.

The above mixture was stirred with 150 ml of 10% sodium hydroxide solution at room temperature for 6 h then extracted three times with methylene chloride (50 ml each) to take off the hydroxyketone. The aqueous layer was acidified with 2 N HCl and extracted with ether. The resulting solution was treated with brine, dried and the solvent was distilled off to leave 18 g of crude 4-oxo-7-octenoic acid.

This acid was converted into its methyl ester (**6b**) with ethereal diazomethane and the crude ester was distilled, b. p. 56–58 °C/0.06 Torr, affording 15 g (22%) of oily material, n_D^{25} = 1.4420. – IR (film): 1745, 1720, 1640 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 2.25–2.85 (m, 8H, 4CH_2), 3.7 (s, 3H, OCH_3), 4.9–5.15 (m, 2H, H_2C=), 5.55–6.05 (m, 1H, HC=). – MS: M^+ 170 (3), *m/e* 139 (27), 115 (65), 111 (12), 97 (14), 95 (19), 85 (18), 83 (36), 81 (13), 59 (16), 55 (base peak).

$C_9H_{14}O_3$ (170.2) Calc. C 63.51 H 8.29 Found C 64.0 H 8.27

The α-ketol (**7b**) was isolated from the above methylene chloride extracts and had b. p. 63 °C/0.1 Torr. – ^{1}H-NMR: δ = 4.1 (m, 1H, CH–O), 4.8–6.15 (m, 6H, HC=CH_2).

$C_{10}H_{16}O_2$ (168.2) Calc. C 71.39 H 9.59 Found C 71.20 H 9.62

Dimethyl (Z)-4-oxo-7-dodecenedioate (**6c**): 0.9 g of triethylamine (0.009 mol) was added to a well stirred suspension of 12.3 g of the aldehyde **4c** (0.067 mol), 14 g of methyl acrylate (0.16 mol) and 1.8 g of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (**19a**) (0.007 mol) at 85 °C, under argon atmosphere. The reaction mixture was stirred for 12 h at 85 °C, cooled to room temperature and then dissolved in methylene chloride. The resulting solution was successively washed with 0.1 N HCl, water, 5% sodium hydrogen carbonate solution, water and dried. Removal of solvent under reduced pressure and distillation gave the ester **6c** (3.9 g = 21.5%), b. p. 134–138 °C/0.1 Torr, n_D^{20} = 1.4625. – IR (film): 1725, 1705 cm^{-1}. – ^{1}H-NMR (CCl_4):

δ = 1.5 – 2.7 (m, 14H, 7 CH_2), 3.6 (s, 6H, 2 OCH_3), 5.3 (m, 2H, HC=CH). – MS: M^+ 270 (34), *m/e* 239 (20), 207 (12), 179 (15), 140 (31), 129 (49), 115 (base peak), 109 (11), 98 (58), 81 (42), 71 (45). $C_{14}H_{22}O_5$ (270.3) Calc. C 62.20 H 8.20 Found C 61.96 H 8.07

The corresponding ethyl ester was prepared from ethyl (*Z*)-9-oxo-5-nonenoate and ethyl acrylate using the thiazolium salt **19a** as catalyst, and had b. p. 145 – 148 °C/0.1 Torr. – IR (film): 1720, 1705 cm^{-1}. – ^{1}H-NMR (CCl_4): δ = 1.25 (m, 6H, 2CH_3), 1.5 – 2.7 (m, 14H, 7CH_2), 4.05 (m, 4H, 2CH_2–O), 5.3 (m, 2H, HC=CH).

Methyl 7-(2,5-dioxocyclopentyl)heptanoate (**8a**): To a mechanically stirred, refluxing mixture of sodium ethoxide (obtained from 0.46 g of sodium, 0.02 mol) in 50 ml of dry toluene was added dropwise a solution of 2.72 g of the ester **6a** (0.01 mol) in 20 ml of dry toluene. Refluxing was continued for 0.5 h after the addition was complete, while the alcohol formed was distilled off. The reaction mixture was cooled, diluted with 20 ml of water, acidified with N HCl and the resulting mixture was extracted with ethyl acetate. The organic layer was successively washed with N HCl, water, brine and dried. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel using benzene/acetone (1 : 1). The fractions containing the desired product were pooled and concentrated to dryness yielding 2.2 g of a crystalline residue. Recrystallization from ethyl acetate/hexane afforded pure **8a** (2.0 g, 82%), m. p. 116 – 118 °C (lit.[14] 116 – 118 °C). – IR (KBr): 1740, 1360 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 1.15 – 1.80 (m, 8H, 4CH_2), 2.16 (t, *J* = 7 Hz, 2H, CH_2-7), 2.30 (t, *J* = 7 Hz, 2H, CH_2–COO), 2.51 (s, 4H, CH_2–CH_2-3′, 4′), 3.66 (s, 3H, OCH_3).

$C_{13}H_{20}O_4$ (240.3) Calc. C 64.98 H 8.39 Found C 65.11 H 8.10

2-Allyl-1,3-cyclopentanedione (**8b**): A stirred suspension of sodium ethoxide (obtained from 5.52 g of sodium, 0.24 mol) in 150 ml of dry toluene was boiled gently on an oil bath (160 – 170 °C), under argon, and a solution of 17.84 g of the ester **6b** (0.105 mol) in dry toluene was added dropwise. During the addition a vigorous reaction set on and a mixture of alcohol and toluene distilled off. Stirring and boiling were continued for 1 h after addition. The mixture was cooled to room temperature and acidified with 2 N HCl and then extracted twice with ether (100 ml each). The combined organic layers were washed with brine and dried. The solvent was evaporated in vacuo, and the yellow residue was recrystallized from ethyl acetate to give white crystalline cyclopentanedione **8b** (5.08 g, 35%), m. p. 154 – 155 °C. – IR (KBr): 1640, 1550 cm^{-1}. – ^{1}H-NMR ([D_6]DMSO): δ = 2.15 (s, 4H, 2CH_2), 2.55 (m, 2H, CH_2-1′), 4.50 – 4.95 (m, 2H, H_2C=), 5.1 – 5.8 (m, 1H, –HC=). – MS: M^+ 138 (base peak), *m/e* 123 (29), 109 (20),95 (59), 81 (22), 55 (26).

$C_8H_{10}O_2$ (138.2) Calc. C 69.54 H 7.29 Found C 69.9 H 7.21

Methyl 7-(2,5-dioxocyclopentyl)-(Z)-5-heptenoate (**8c**): A stirred suspension of sodium *tert*-butoxide (prepared from 0.39 g of sodium, 0.017 mol) in 30 ml of dry toluene was heated to boiling point on an oil bath (150 – 160 °C), under argon atmosphere, and then a solution of 1.9 g of the ester **6c** (0.007 mol) in 25 ml of dry toluene was added dropwise. At the beginning of the addition a vigorous reaction set on and a mixture of alcohol and toluene started to distill off. Stirring and boiling were maintained for 1 h after addition. The mixture was then cooled to 0 °C and acidified with N HCl. The organic layer was separated, the aqueous layer was extracted twice with ether and the combined organic layers were dried. The solvents were removed under reduced pressure and the resulting oil was chromatographed on silica gel using chloroform/acetone (10 : 3) as solvent. The eluates were combined, the solvents were eliminated under reduced pressure and the residue was recrystallized from a mixture of hexane and ether to give crystalline cyclopentanedione **8c** (0.9 g, 54.2%), m. p. 65 °C. – IR (film): 1725, 1550 cm^{-1}. – ^{1}H-NMR (CCl_4): δ = 1.6 – 2.7 (m, 10H, 5CH_2), 2.85 (m, 2H, CH_2-7), 3.2 (m, 1H, exchangeable with D_2O, 2′-OH),

3.65 (s, 3H, OCH_3), 5.4 (m, 2H, HC=CH). – MS: M^+ 238 (59), *m/e* 207 (61), 150 (22), 112 (base peak), 111 (72), 96 (47).

$C_{13}H_{18}O_4$ (238.3) Calc. C 65.53 H 7.61 Found C 65.30 H 7.42

The corresponding ethyl ester was prepared from diethyl (*Z*)-4-oxo-7-dodecenedioate by sodium ethoxide catalyzed cyclization and had spectral data as follows; ^{1}H-NMR ($CDCl_3$): δ = 1.2 (t, *J* = 6 Hz, 3H, CH_3), 1.6–2.7 (m, 10H, $5CH_2$), 2.85 (m, 2H, CH_2-7), 4.0 (q, *J* = 6 Hz, 2H, CH_2–O), 5.4 (m, 2H, HC=CH). – MS: M^+ 252 (40), *m/e* 207 (66), 165 (73), 150 (28), 112 (base peak), 111 (67), 96 (51).

Methyl 7-(2-methoxy-5-oxo-1-cyclopentenyl)heptanoate (**9a**, R′ = CH_3): A solution of 2.4 g of the cyclopentanedione **8a** and a catalytic amount of sulfuric acid in 50 ml of dry methanol was heated for 6 h. The solution was cooled to room temperature, treated with solid sodium hydrogen carbonate, filtered and concentrated in vacuo. The residue was taken up in ether and the ethereal solution was successively washed with water, 5% sodium hydrogen carbonate, water, brine and dried. The solvent was evaporated and the residue was distilled to give the enol ether **9a** (R′ = CH_3) (2.2 g, 86%), b. p. 175–180 °C/0.5 Torr (lit.[14] b. p. 170–174 °C/0.08 Torr), n_D^{20} = 1.4870. – IR (film): 1740, 1690, 1625 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 1.15–1.75 (m, 8H, $4CH_2$), 2.12 (t, *J* = 7 Hz, 2H, CH_2-7), 2.29 (t, *J* = 7 Hz, 2H, CH_2–COO), 2.53–2.75 (m, 4H, CH_2–CH_2-3′,4′), 3.65 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3).

$C_{14}H_{22}O_4$ (254.3) Calc. C 66.12 H 7.93 Found C 66.05 H 8.07

2-Allyl-3-methoxy-2-cyclopenten-1-one (**9b**; R′ = CH_3): A solution of the cyclopentanedione **8b** (6.9 g, 0.05 mol) in 60 ml of ether was treated with 0.06 mol of ethereal diazomethane at room temperature for 1 h. Usual work up afforded 7.5 g (98.7%) of crude cyclopentenone, which was used for the next step without further purification. – IR (film): 1700, 1630 cm^{-1}. – ^{1}H-NMR (CCl_4): δ = 2.1–2.7 (m, 4H, $2CH_2$), 2.8 (m, 2H, CH_2-1′), 3.95 (s, 3H, OCH_3), 4.75–5.2 (m, 2H, $=CH_2$), 5.3–6.05 (m, 1H, HC=).

$C_9H_{12}O_2$ (152.2) Calc. C 71.03 H 7.95 Found C 70.70 H 7.95

Methyl 7-(2-methoxy-5-oxo-1-cyclopentenyl)-5-heptenoate (**9c**; R′ = CH_3): A solution of the cyclopentanedione **8c** (1.3 g, 0.005 mol) in 20 ml of ether was treated with 0.01 mol of ethereal diazomethane at room temperature for 1 h. Removal of the solvent afforded a yellow oil, which was purified on silica gel plates (chloroform/acetone 5:1) to give 0.7 g (51%) of **9c** (R′ = CH_3). – IR (film): 1725, 1680, 1620 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 1.6–2.7 (m, 10H, $5CH_2$), 2.85 (m, 2H, CH_2-7), 3.65 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.35 (m, 2H, HC=CH). – MS: M^+ 252 (64), *m/e* 221 (25), 220 (28), 179 (26), 165 (21), 164 (18), 151 (15), 135 (13), 126 (41), 125 (base peak), 111 (8), 96 (11).

$C_{14}H_{20}O_4$ (252.3) Calc. C 66.65 H 7.99 Found C 66.43 H 7.67

Methyl 7-[2-(mesitylenesulfonyloxy)-5-oxo-1-cyclopentenyl]heptanoate (**9a**; R′ = mesitylenesulfonyl group): To a stirred mixture of 2.4 g of the cyclopentanedione **8a** (0.01 mol), 2 g of triethylamine (0.02 mol) and 30 ml of dry tetrahydrofuran was added dropwise a solution of 2.4 g of mesitylenesulfonyl chloride (0.011 mol) at –18 °C, under argon. The resulting solution was stirred at –15 °C for 20 minutes and then at room temperature for 1 h. The reaction mixture was poured into 40 ml of brine and extracted with ether. The ethereal solution was successively washed with water, 5% sodium hydrogen carbonate, water, brine and dried. Evaporation of the solvent afforded an oil, which was chromatographed on silica gel with benzene/acetone (10:1) as eluent furnishing 3.3 g (82%) of enol sulfonate. – IR (film): 1740, 1715, 1660, 1605 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 1.0–1.7 (m, 8H, $4CH_2$), 1.8–2.9 (m, 8H, CH_2-7, CH_2-2 and CH_2–CH_2-3′,4′), 2.35 (s, 3H, CH_3), 2.66 (s, 3H, CH_3O), 7.08 (s, 2H, aromat. protons).

$C_{22}H_{30}O_5S$ (406.6) Calc. C 65.00 H 7.44 S 7.88 Found C 65.12 H 7.36 S 7.70

Methyl 7-(5-hydroxy-1-cyclopentenyl)heptanoate (**11**): To a solution of the enol ether **9a** (R′ = CH_3) (2.54 g, 0.01 mol) in dry methanol was added 1.5 g of sodium borohydride (0.04 mol), and the mixture was stirred at 40 °C for 2 h. The mixture was brought to room temperature, 2 ml of acetone were added and the resulting mixture was stirred for 10 minutes. The solvent was evaporated and the residue was treated with 20 ml of N HCl. The mixture was extracted with ether, the ethereal extract was successively washed with water, 5% sodium hydrogen carbonate solution, water, brine and dried. The solvent was evaporated and the residue was distilled to give 1.5 g of the cyclopentenol **11** (67%), b. p. 147 – 141 °C/0.2 Torr, n_D^{20} = 1.4640. – IR (film): 3380, 1740 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 1.0 – 2.0 (m, 10H, $5CH_2$), 2.0 – 2.4 (m, 6H, CH_2-COO and CH_2-CH_2-3′,4′), 3.64 (s, 3H, CH_3O), 4.64 (m, 1H, CH – O), 5.53 (m, 1H, C = CH).

$C_{13}H_{22}O_3$ (226.3) Calc. C 68.99 H 9.80 Found C 68.77 H 9.51

Methyl 7-(2-chloro-5-oxo-1-cyclopentenyl)heptanoate (**10**): To a solution of 2.4 g of the cyclopentanedione **8a** (0.01 mol) in dry chloroform was added phosphorus trichloride (0.69 g = 0.005 mol) and the mixture was boiled for 5 h. After cooling, the organic layer was separated and then washed successively with 0.5% sodium hydroxide, water, brine and dried. Evaporation of the solvent followed by distillation gave 1.8 g of the chloroenone **10** (70%), b. p. 149 – 151 °C, n_D^{20} = 1.4755. – IR (film): 1745, 1720, 1640 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 1.20 – 1.80 (m, 8H, $4CH_2$), 2.28 (t, *J* = 7 Hz, 2H, CH_2-7), 2.30 (t, *J* = 7 Hz, 2H, CH_2-COO), 2.44 – 2.60 (m, 2H, CH_2-3), 2.72 – 2.88 (m, 2H, CH_2-4), 3.66 (s, 3H, OCH_3).

$C_{13}H_{19}ClO_3$ (258.8) Calc. C 60.34 H 7.40 Cl 13.70 Found C 60.21 H 7.27 Cl 13.10

Methyl 7-(5-oxo-1-cyclopentenyl)heptanoate (**1**): a) To a hot solution of 0.07 g of silver acetate in 10 ml of acetic acid was added 1.95 g (0.03 mol) of zinc dust (previously activated by washing it rapidly with 10% hydrochloric acid). The mixture was shaken for 3 minutes. The acetic acid was decanted and zinc-silver couple was washed with 5 ml of acetic acid, then five times with ether (10 ml each)[15]. To this couple was added a solution of 1.3 g of the chlorocyclopentenone **10** (0.005 mol) in 10 ml of dry methanol and the resulting mixture was stirred at room temperature for 48 h. The reaction mixture was filtered, the filtrate was concentrated and the residue was treated with N HCl. The mixture was extracted with ether, the ethereal solution was washed with water and dried. The solvent was removed in vacuo and the residue was distilled to give 0.70 g of the enone **1** (62%), b. p. 146 – 150 °C/0.2 Torr.

b) To a solution of 0.5 g of the cyclopentenol **11** (0.022 mol) in 15 ml of petroleum ether was added 1.5 g of active manganese dioxide and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was filtered, the filtrate concentrated and the residue was chromatographed on silica gel with benzene/acetone (10 : 1) as eluent to give 0.4 g of pure enone **1** (80%).

c) 0.57 g of sodium borohydride (0.015 mol) was added to a stirred solution of 2.0 g of the enolsulfonate **9a** (R′ = mesitylenesulfonyl group) (0.005 mol) in 30 ml of dry methanol at room temperature. The resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with 2 ml of acetone and then the solvent was evaporated in vacuo. The residue was treated with N HCl and the mixture was extracted with ether. The ethereal extract was successively washed with N HCl, water, 5% sodium hydrogen carbonate solution, brine and dried. Evaporation of the solvent led to the crude cyclopentenol **12a** (R′ = mesitylenesulfonyl group), which was dissolved in 100 ml of chloroform. 3 g of oxalic acid and 3 g of sodium oxalate were then added, and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was filtered, concentrated and the residue was taken up in ether. The ethereal solution was successively washed with 5% sodium hydrogen carbonate, water, brine and dried. Evaporation of the solvent afforded an oil, which was purified by distillation to give 0.58 g (52%) of the enone **1**.

b. p. 146–150 °C/0.2 Torr (lit.[16] 145–150 °C/0.2 Torr), $n_D^{23} = 1.4692$. – IR (film): 1735, 1700, 1630 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ = 1.20–1.80 (m, 8H, $4CH_2$), 2.10–2.40 (m, 6H), 2.47–2.66 (m, 2H, CH_2-4), 3.66 (s, 3H, OCH_3), 7.28 (m, 1H, C=CH).

2-Allyl-2-cyclopenten-1-one (**2**): To a vigorously stirred solution of 4.4 g of the enol ether **9b** (R′ = CH_3) (0.029 mol) in 200 ml of dry tetrahydrofuran below –20 °C was added, dropwise, 10.7 g of sodium dihydrobis(2-methoxyethoxy)aluminate (0.053 mol). The resulting solution was stirred at –20 °C for a further 0.5 h. A mixture of acetic acid and tetrahydrofuran 1:1 (30 ml) was added, dropwise, and the solution was allowed to warm to room temperature. The reaction mixture was poured into brine, the organic layer was separated and then the aqueous layer was extracted with ether. The ethereal extract was washed with water and dried. Evaporation of the solvent gave a yellow oil (5.4 g), which was dissolved in 25% acetic acid solution (80 ml). The resulting solution was stirred at room temperature for 8 h and then water was added (100 ml), and the mixture was extracted with methylene chloride. The extract was successively washed with water, 5% sodium hydrogen carbonate, water and dried. Evaporation of the solvent under reduced pressure afforded 3.5 g of crude enone, which was chromatographed on a silica column (benzene/acetone 10:1) to give 1.75 g of the enone **2** (49.5%)[11]. – IR (film): 1710, 1645 cm^{-1}. – ^{1}H-NMR (CCl_4): δ = 2.15–2.7 (m, 4H, $2CH_2$), 2.85 (m, 2H, 1′-CH_2), 4.8–5.25 (m, 2H, $=CH_2$), 5.35–5.2 (m, 1H, =CH), 7.25 (m, 1H, C=CH). – MS: M^+ 122 (69), *m/e* 109 (18), 107 (18), 95 (19), 94 (28), 81 (17), 79 (base peak), 77 (47).

$C_8H_{10}O$ (122.2) Calc. C 78.65 H 8.25 Found C 77.9 H 8.25

Methyl 7-(5-oxo-1-cyclopentenyl)-5-heptenoate (**3**): 2.0 g of sodium dihydrobis(2-methoxyethoxy)aluminate (0.01 mol) were added to a stirred solution of 0.55 g of the enol ether **9c** (R′ = CH_3) (0.002 mol) in 50 ml of dry tetrahydrofuran cooled to –60 °C. The resultant solution was stirred at –60 °C for 6 h, and then the reaction was quenched by the addition of 20 ml of a mixture of acetic acid/tetrahydrofuran (1:1). After warming to 0 °C, 50 ml of water were added, the organic layer was separated and the aqueous layer was extracted with 100 ml of ether. The combined organic layers were successively washed with brine, 5% sodium hydrogen carbonate, brine and dried. Evaporation of the solvent under reduced pressure afforded an oil, which was dissolved in 40 ml of a mixture of acetic acid/water (3:1) and the resultant solution was stirred at room temperature for 8 h. The reaction mixture was diluted with 100 ml of water and extracted twice with methylene chloride (50 ml each). The combined extracts were successively washed with water, 5% sodium hydrogen carbonate, water and dried. Evaporation of the solvent under reduced pressure afforded an oil (0.45 g), which was purified on silica gel plates (chloroform/acetone 5:1) to give 0.18 g of the pure enone **3** (37.5%)[17]. – IR (film): 1730, 1700, 1625 cm^{-1}. – ^{1}H-NMR (CCl_4): δ = 1.6–2.7 (m, 10H, $5CH_2$), 2.85 (m, 2H, CH_2-7), 3.55 (s, 3H, OCH_3), 5.4 (m, 2H, HC=CH), 7.2 (m, 1H, C=CH). – MS: M^+ 222 (base peak), *m/e* 192 (54), 191 (45), 162 (18), 148 (30), 147 (18), 134 (38), 133 (46), 96 (46), 95 (41).

$C_{13}H_{18}O_3$ (222.3) Calc. C 70.24 H 8.16 Found C 69.95 H 8.02

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