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Synthesis of 5,5-Disubstituted 2(3*H*)-Dihydrofuranones Containing Side-Chain Carbonyl Functions, and Some Derivatives.

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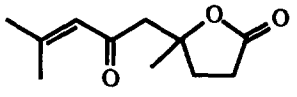
Abstract. *Several title compounds containing aldehyde, ketone or unsaturated ester functions in side-chains at C-5 position have been synthesized for the first time. The ability of some of these compounds as precursors in the preparation of polyfunctional cyclopentadiene or spiro[4.4]nonane derivatives has shown to be feasible.*

INTRODUCTION

Dihydro-2(3*H*)-furanones containing carbonyl functions in side-chains are molecules some of them found among natural products. For instance, pinnatolide, **1**, has been isolated from *Athanasia crithmifolia* and from *Athanasia pinnata*,[1] and (+)-ipomolactone, **2**, is a degradation product obtained from the furano-sesquiterpene ipomeamarone produced by the sweet potato *Ipomea batatas* in response to fungal infection.[2] Otherwise, polyfunctional side-chain butyrolactones can serve as synthetic precursors of more complex mono- or polycyclic structures.



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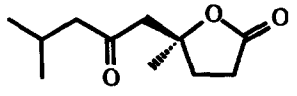

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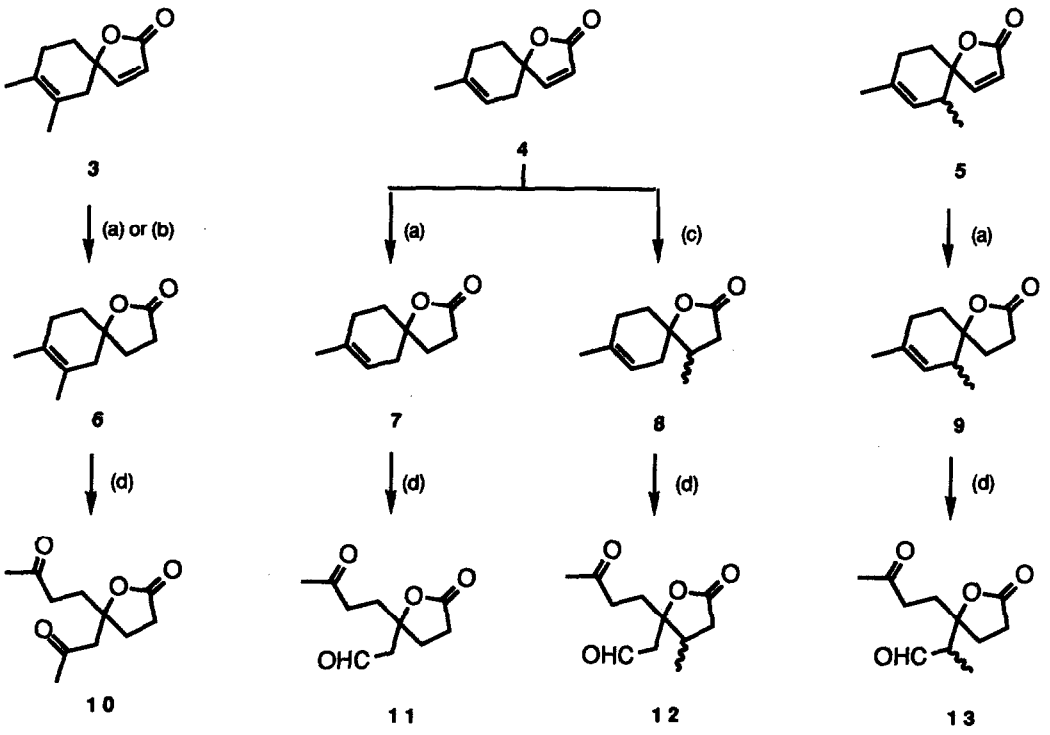
As far as we know, there are no general synthetic methods to prepare these kind of compounds. We reported that bicyclic spirolactones such as **3-5** (Scheme 1) are easily obtained in multigramme scale through Diels-Alder cycloadditions of 5-methylen-2(5*H*)-furanone to convenient dienes.[3] Simple transformations of

these adducts, involving conjugate addition of a dialkylcuprate or selective reduction of the conjugate double bond, allowed the production of derivatives containing only one unsaturation located at the cyclohexene ring.[4]

We describe herein the synthesis of several title compounds which contain a methyl ketone in a branch and an aldehyde, a ketone, or an unsaturated ester in the other side chain. The first results on the obtention of pentagonal rings from these products, via intramolecular cyclizations involving aldolic or conjugate addition reactions, are also reported.

RESULTS AND DISCUSSION

Spirolactones **6-8** had been previously prepared in our laboratory and published.[4] Compound **9** was synthesized for the first time in this work, in 91% yield, by selective reduction of adduct **5** with Vitride in the presence of cuprous bromide and 2-butanol[5] at 0 °C (Scheme 1).



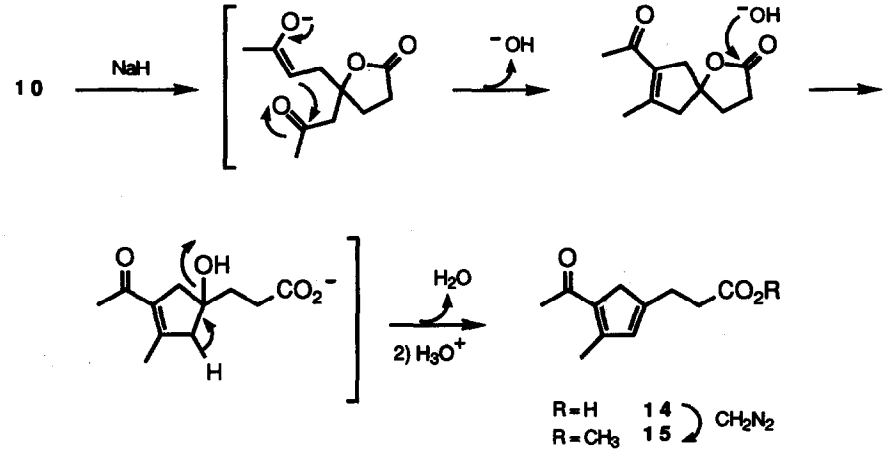
Reagents: (a) 1: Vitride, CuBr. 2: BuOH. (b) H_2, 10%Pd-C. (c) Me_2CuLi. (d) 1: O_3. 2: Me_2S.

Scheme 1

Ozonolysis of the double bond in **6-9** was performed at -78 °C, in dichloromethane as a solvent. In this way compounds **10-13** were obtained in 70-90% yield. Diketone **10** is an oil, b.p. 140 °C (0.01 Torr) which could be fully characterized and gave satisfactory microanalysis. Aldehydes **11-13** were identified by their IR,

^{1}H NMR, and ^{13}C NMR spectral data. However, they hydrated very quickly, as shown by IR, precluding a correct microanalysis. Otherwise, all attempts to characterize them as arylhydrazone derivatives were unsuccessful, since reactions with the chosen arylhydrazines gave very insoluble solids impossible to purify by crystallization or by usual chromatographic techniques.

Several transformations were performed on these polycarbonyl compounds in order to prepare other molecules. Thus, treatment of **10** with NaH (5 mol) in boiling THF for 2 hours afforded the cyclopentadienyl propanoic acid **14**, as a solid, m.p. 108-111 °C (dec), in 75% yield. Formation of this product involves the following one-pot subsequent steps: (a) Regioselective intramolecular aldol condensation. (b) Lactone ring-opening. (c) Dehydration of the resultant tertiary alcohol (Scheme 2). Presumably the preferential enolate attack is directed by the less steric hindered active methylene.



Scheme 2

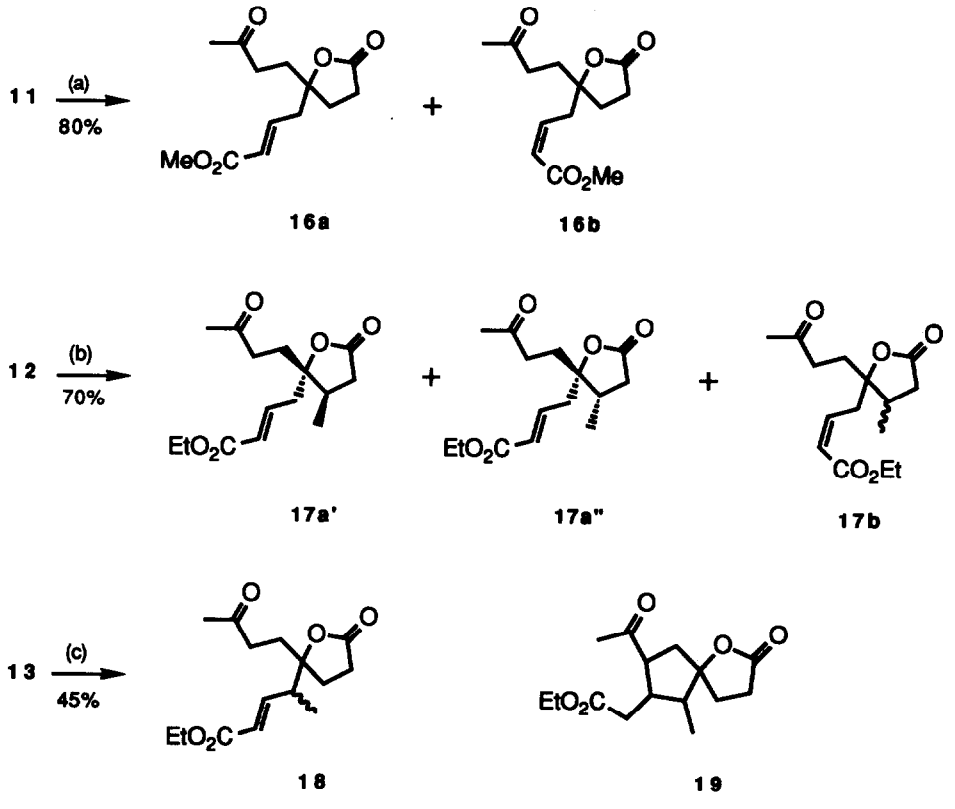
Compound **14** was also obtained but only in 16% yield among other unidentified by-products when n-BuLi was used as a base. However, it was produced in 65% yield when diketone **10** was treated with *p*-toluenesulfonic acid in boiling benzene for 2 hours. This fact evidences that the overall process takes place either in a basic or in an acid medium. Reaction between **3** and diazomethane afforded ester **15** as a liquid b.p. 110 °C (0.04 Torr).

The structures of compounds **14** and **15** were assigned on the basis of their spectral and microanalysis data. For instance, the methyl group attached to the ring in acid **14** appears in the ^{1}H NMR spectrum as a triplet centered at 2.34 ppm with J = 2.3 Hz as a consequence of the allylic coupling to the ring methylene-protons. In contrast, the only olefinic proton gives a singlet at 6.17 ppm. These data exclude any other disposition of the two double bonds in the cyclopentadiene ring. On the other hand, the IR spectrum shows a strong band at 1627 cm^{-1} which agrees with a 2,4-dienone absorption. ^{13}C NMR and UV (ε_{max} 10500 at 308 nm) spectra are also consistent with the structure proposed for **14**. Similar significative signals were observed for the methyl ester **15**.

Cyclopentadiene derivatives are important compounds used as ligands in metal complexes for homogeneous catalysis.[6,7] Therefore, this *a priori* unexpected result prompted us to try this reaction on keto

aldehydes **11-13**, but neither the process described above nor the single aldol reaction was observed to occur and only unidentified substances were obtained in these cases.

However, compounds **11-13** were subjected to Wittig-type condensation under different reaction conditions affording unsaturated esters **16-18**, respectively (Scheme 3). Thus, condensation of **11** with methoxycarbonyltriphenylphosphorane afforded a 1:1.4 mixture of geometric isomers **16a** and **16b** in 80% total yield. On the other hand, compounds **12** and **13** were reacted with the anion derived from triethylphos-



Reagents: (a) $Ph_3P{=}CHCO_2CH_3$. (b) $(EtO)_2POCH_2CO_2Et$, BuLi. (c) $(EtO)_2POCH_2CO_2Et$, NaH.

Scheme 3

phonoacetate by using a slight deffect of NaH to produce (*E*)-unsaturated esters **17a** (35% yield) and **18** (67% yield), respectively. Better total yield was accomplished when the condensation of **12** with the phosphonate was performed by using BuLi as a base, obtaining in this case a 9:7:1 mixture of diastereoisomers.

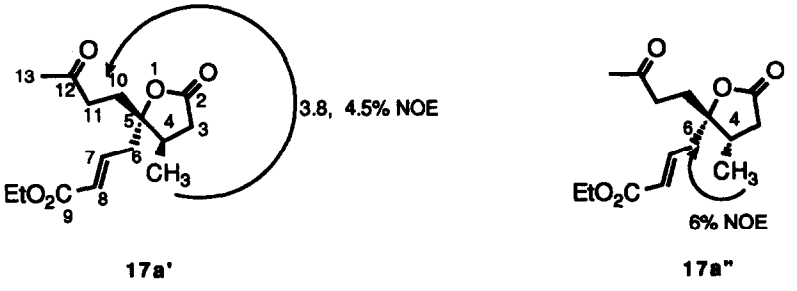
Spirolactone **19**, as a mixture of diastereoisomers,[8] was also obtained from **13** when 1.1 eq of base was used. The ability of **18** to undergo base-induced intramolecular Michael addition was verified in a separate experiment, proving that **18** evolves towards **19** under the Wadsworth-Emmons reaction conditions when

excess base is present. Production of spirocompounds through cyclization of ketoesters **16-18** is actual object of investigation in our laboratory.

Major isomers in the mixtures **16a/b** and **17a/b** could be isolated by column chromatography in each case, and fully characterized. *E/Z* Stereochemistry was easily assigned to **16-18** on the basis of considering coupling constants between the pairs of olefinic protons H_7 and H_8 (Table 1. See Fig 1 for the numeration).

Table 1. Chemical shifts (ppm) and coupling constants (Hz) for H_7 and H_8 protons in compounds **16-18**.

Compound	H_7	H_8	$J_{7,8}$
16a	6.84	5.96	15.9
16b	6.16	6.11	10.3
17a'	6.82	5.91	15.5
17a"	6.83	5.87	15.5
17b	6.13	5.90	11.7
18	6.84	5.92	15.7



17a' **17a"**

Fig 1. NOE enhancements observed on *10*-CH_2 in **17a'** and on *6*-CH_2 in **17a"** when *4*-CH_3 were irradiated.

cis/trans Disposition of the methyl group with respect to the ester containing side-chain in **17a'** and **17a"** was also elucidated by means of ^{1}H NMR techniques. 400 MHz-(2D-COSY) Spectrum allowed the assignment of signals for all protons and differential NOE experiments gave significant results that lead to identify **17a'** and **17a"**. Fig 1 shows that 3.8 and 4.5% NOE was observed, respectively, on the two H_{10} protons while not enhancement on H_6 was appreciated when methyl protons at *C-4* were irradiated in compound **17a'**. Furthermore, when the equivalent methyl in the isomer **17a"** was irradiated, a 6% NOE was observed on the methylene H_6 protons. These results allowed us to assign *cis* stereochemistry for the methyl group with respect to the ketone containing chain and *trans* to the ester branch in isomer **17a'**, being in agreement with the reverse stereochemistry in **17a"**.

CONCLUSION

Efficient synthetic approaches to polyfunctional 5,5-disubstituted 2(3*H*)-dihydrofuranones have been achieved and new polyfunctional cyclopentadiene derivatives have been obtained. Moreover, the use of some

of those molecules in the synthesis of spiro[4.4]nonane derivatives seems feasible and is under study. The results will be published in a next future.

EXPERIMENTAL SECTION

Flash column chromatography was carried out on silica gel (240-400 mesh). Melting points were determined on a hot stage and are uncorrected. Distillation of small amounts of material was effected in a bulb-to-bulb distillation apparatus, with oven temperatures (o.t.) being reported. Electron-impact mass spectra were recorded at 70 eV. Chemical shifts in NMR spectra are given in ppm relative to internal TMS (δ scale).

Selective hydride reduction using bis(2-methoxyethoxy)aluminium sodium hydride (Vitride). General procedure for the preparation of spirolactones 6[4], 7[4] and 9. A typical experiment was run as follows. A 3.59 M solution of Vitride (bis(2-methoxyethoxy)aluminium hydride) (26 mL, 93.9 mmol) was added dropwise to a stirred suspension of CuBr (6.4 g, 44.8 mmol) in 83 mL anhydrous THF kept at 0°C and under inert atmosphere and the resulting mixture was stirred for 30 min. Upon cooling at -78°C, 8.9 mL (97.3 mmol) of 2-butanol were added at once followed by the addition of a solution of adduct 5[3] (1.00 g, 5.61 mmol) in anhydrous THF (13 mL). The mixture was left at -78°C for 15 min and at -20°C for 2 hours. Upon adding 18 mL of water the reaction mixture was poured into a saturated NH_4Cl solution (300 mL). After filtration of the insoluble salts and extraction with ether (3x150 mL), the organic layer was washed with brine (300 mL), and evaporated to give and oil which upon column chromatography (3:1 hexane-ethyl acetate) led to the new spirolactone **9**.

6,8-Dimethyl-1-oxaspiro[4.5]dec-7-en-2-one, 9. 90% Yield. Colorless oil, o.t. 110°C (0.015 Torr). Spectroscopic data for the major diastereoisomer: IR (film): 2966, 2934, 2879, 1773, 1450, 1382, 1287, 1244, 1198, 1175, 1168, 1139, 1090, 1037, 1024, 1012, 944, 909 cm^{-1}; 80-MHz ^1H NMR ($CDCl_3$) 0.96 (d, J=6.7 Hz, 3 H, C*H*$_3$), 1.67 (broad s, 3 H, C*H*$_3$), 1.54-2.77 (complex absorption, 9 H, C*H* and 4xC*H*$_2$), 5.15 (broad s, *olefinic H*); 20-MHz ^{13}C NMR ($CDCl_3$) 15.66, 22.59, 27.48, 28.09, 28.89, 31.60, 38.84, 87.54, 124.37, 132.69, 176.47. Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.31; H, 9.08.

General procedure for the ozonolysis of spirolactones 6-9. A typical experiment was run as follows. To a solution of **8** (408 mg, 2.3 mmol) in dichloromethane (20 mL) was bubbled through ozone (80 L/h (O_2+O_3) flow, 140 mA) at -78°C for 15 minutes and then nitrogen for 20 minutes. Then 0.2 mL of Me_2S (3.0 mmol) was added to the cold solution and the mixture was stirred at room temperature for 3 hours. The organic mixture was washed with water (2x20 mL) and extracted with dicholoromethane (2x20 mL); the combined organic phases were washed (brine, 1x30 mL), dried ($MgSO_4$) and evaporated to yield aldehyde **12**. In the same manner, compounds **10, 11,** and **13** were also obtained

5-(3-Oxobutyl)-5-(2-oxopropyl)-2(3*H*)-dihydrofuranone, 10. 70% Yield. Colorless oil, o.t. 140°C (0.015 Torr); IR (film): 2939, 1771, 1715, 1420, 1361, 1240, 1201, 1166, 1076, 970, 929 cm^{-1}; 80-MHz ^1H NMR ($CDCl_3$): 2.14 (broad s, 6 H, 2xC*H*$_3$), 1.86-2.75 (complex absorption, 8 H, 4xC*H*$_2$), 2.82 (s, 2 H, C*H*$_2$); 20-MHz ^{13}C NMR ($CDCl_3$): 28.4, 29.6, 30.7, 31.0, 32.8, 37.2, 50.3, 84.8, 175.9, 204.7,

206.6; MS, m/e: 194 (M^+-H_2O, 1), 176 (M^+-$2H_2O$, 2), 154 (M^+-C_3H_6O, 7), 141 (M^+-C_4H_7O, 5), 127 (8), 110 (11), 99(16), 81 ($C_4H_5O_2^+$, 4), 43 (CH_3CO^+, 100); Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.22; H, 7.79.

5-(3-Oxobutyl)-5-(2-oxoethyl)-2(3*H*)-dihydrofuranone, 11. 92% Yield. Colorless oil; IR (film): 2928, 2857, 2748, 1772, 1718, 1420, 1358, 1261, 1236, 1167, 1081, 1017, 963, 925; 80-MHz ^1H NMR ($CDCl_3$): 2.19 (s, 3 H, C*H*$_3$), 1.95-2.35 (complex absorption., 4 H, 2xC*H*$_2$), 2.56 (t, J=3.7 Hz, 2 H, C*H*$_2$), 2.59 (t, J=3.7 Hz, 2H, C*H*$_2$), 2.85 (d, J=1.0 Hz, 2H, C*H*$_2$), 9.76 (t, J=1.0 Hz, 1H C*H*O). 20-MHz ^{13}C NMR ($CDCl_3$): 28.26, 29.64, 31.08, 32.78, 37.14, 51.02, 84.59 (84.73), 175.68, 198.50, 206.63.

4-Methyl-5-(3-oxobutyl)-5-(2-oxoethyl)-2(3*H*)-dihydrofuranone, 12. 90% Yield. Colorless oil (mixture of diastereoisomers); IR (film): 2970, 2937, 1775, 1715, 1423, 1376, 1357, 1303, 1264, 1224, 1164, 1071, 958, 925; 400-MHz ^1H NMR ($CDCl_3$): 1.06 (d, J=6.6 Hz) and 1.15 (d, J=6.6 Hz) (3 H, C*H*$_3$), 2.18 (s) and 2.19 (s) (3 H, C*H*$_3$), 1.75-2.37 (complex absoorption, 4 H), 2.56-2.81 (complex absorption, 5 H), 9.79 (m, 1 H, C*H*O). 100-MHz ^{13}C NMR ($CDCl_3$): 13.6/14.9, 26.8, 29.9/31.0, 35.9/36.2, 37.2/37.4, 38.6, 46.9/49.3, 86.7/87.2, 174.6/174.8, 198.9, 206.9.

5-(3-Oxobutyl)-5-(1-methyl-2-oxoethyl)-2(3*H*)-dihydrofuranone, 13. 86% Yield. Colorless oil (mixture of diastereoisomers); IR (film): 2977, 2943, 2856, 2743, 1774, 1719, 1459, 1420, 1379, 1358, 1300, 1183, 1167, 1016, 969, 929; 80-MHz ^1H NMR ($CDCl_3$): 1.16 (d, J=7.2 Hz, 3 H, C*H*$_3$), 2.14 (s, 3 H, *H*$_3$), 1.89-2.33 (complex absorption, 4 H, 2xC*H*$_2$), 2.49 (t, J =9.0 Hz, 2 H, C*H*$_2$), 2.52 (t, J =9.0 Hz, 2 H, 4-C*H*$_2$), 2.76 (m, 1 H), 9.71 (d, J =1.5 Hz, C*H*O); 20-MHz ^{13}C NMR ($CDCl_3$): 8.37, 28.04, 28.58, 29.48, 30.83, 36.74, 52.90, 86.88 (87.10), 175.57, 201.40, 206.47.

3-(4-Acetyl-3-methyl-1,3-cyclopentadienyl)propanoic acid, 14. To a suspension of NaH (236 mg, 50% oily dispersion, 4.9 mmol) in 15 mL anhydrous THF was added a solution of **10** (800 mg, 3.8 mmol) in 10 mL anhydrous THF. The reddish mixture was heated to reflux for 2.5 h, and then MeOH (6 mL) and 10% $NaHCO_3$ solution (50 mL) were subsequently added. The mixture was extracted with AcOEt (3x30 mL). The combined organic phases were washed with brine (60 mL), dried with anhydrous $MgSO_4$, and evaporated to afford a yellow-orange solid (700 mg, 87% crude yield). Flash chromatography (172 mg of crude) (1:1 hexane-ethyl acetate) yielded pure **14** (132 mg) as a white solid. Crystals, m.p. 108-111°C (dec); IR (KBr): 2921, 1730, 1627, 1597, 1527, 1427, 1373, 1287, 1184, 1180, 1047, 946; UV (MeOH): λ_{max} 209 (ε 7500), 308 (ε 10500) nm; 400-MHz ^1H NMR ($CDCl_3$): 2.32 (s, 3 H, C*H*$_3$), 2.34 (t, J =2.4 Hz, 3 H, C*H*$_3$), 2.64 (t, J =7.2 Hz, 2 H, C*H*$_2$), 2.77 (t, J =7.2 Hz, 2 H, C*H*$_2$), 3.31 (m, 2 H, C*H*$_2$), 6.17 (broad s, *olefinic H*); 20-MHz ^{13}C NMR ($CDCl_3$): 16.3, 25.7, 29.2, 33.1, 45.0, 133.8, 136.4, 153.5, 155.4, 177.3, 194.3; MS, m/e: 195 (M^++1, 7), 194 (M^+, 33), 134 (16), 119 (26), 105 (15), 92 (25), 91 (24), 77 (13), 43 (CH_3CO^+, 100). Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.08; H, 7.27.

Methyl 3-(4-acetyl-3-methyl-1,3-ciclopentadienyl)propanoate, 15. A stirred solution of crude **14** (500 mg, 1.9 mmol) in ether at 0°C was treated with excess diazomethane and the stirring was continued at room temperature for 8 h. Removal of the solvent in vacuo yielded an orange oil which was chromatographed on silica gel (hexane-ethyl acetate) to give **15** (322 mg) as a colorless oil, o.t. 110°C (0.04 Torr); IR (film): 2954, 2924, 1738, 1654, 1609, 1535, 1437, 1372, 1362, 1254, 1194, 1169; UV (MeOH): λ_{max} 209 (ε

7000), 307 (ε 10300) nm; 400-MHz ^{1}H NMR ($CDCl_3$): 2.30 (s, 3 H, CH_3), 2.33 (t, J =2.2 Hz, 3 H, CH_3), 2.59 (t, J =7.4 Hz, 2 H, H_2), 2.76 (t, J =7.4 Hz, 2 H, CH_2), 3.30 (m, 2 H, CH_2), 3.69 (s, 3 H, CH_3), 6.14 (s, *olefinic proton*); 20-MHz ^{13}C NMR ($CDCl_3$): 16.06, 25.79, 29.12, 33.10, 44.81, 51.42, 133.42, 136.14, 153.22, 154.53, 172.80, 195.03; MS m/e: 209 (M^++1, 7), 208 (M^+, 37), 161 (5), 149 (20), 134 (28), 119 (36), 91 (23), 43 (CH_3CO^+, 100). Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.15; H, 7.75.

5-(3-(Methoxycarbonyl)allyl)-5-(3-oxobutyl)-2(3*H*)-dihydrofuranone, 16. Methoxycarbonylmethylene(triphenyl)phosphorane (340 mg, 1.0 mmol) was added in small portions to a stirred solution of **11** (200 mg, 1.0 mmol) in anhydrous MeOH (10 mL) kept at 0°C. The reaction mixture was stirred at 0°C for 1 h. Thereafter the solvent was removed and the residue was chromatographed (3:1 hexane-ethyl acetate) to afford 118 mg (0.46 mmol, 46% yield) of the (*E*)-isomer **16a** and 85 mg (0.33 mmols, 33% yield) of the (*Z*)-isomer **16b**.

Compound 16a. Oil, o.t. 170°C (0.1 Torr); IR (film): 2953, 2918, 1773, 1718, 1655, 1438, 1357, 1318, 1277, 1199, 1165, 1126, 1033, 1016, 980, 930; 400-MHz ^{1}H NMR ($CDCl_3$): 1.98 (t, J=7.6 Hz, 2 H), 1.99-2.13 (complex absorption, 2 H), 2.18 (s, 3 H, CH_3), 2.55-2.64 (complex absorption, 6 H, 3xCH_2), 3.76 (s, 3H, OCH_3), 5.96 (d, $J_{8,7}$=15.9 Hz, *H8*), 6.84 (dt, $J_{7,8}$=15.9 Hz, $J_{7,6}$=7.9 Hz, *H7*); 100-MHz ^{13}C NMR ($CDCl_3$): 28.52, 29.90, 30.48, 32.27, 37.24, 41.15, 51.56, 86.02, 125.73, 140.91, 165.89, 175.69, 206.68; MS, m/e: 223 (M^+-CH_3O,1), 222 (M^+-CH_3OH, 1), 183 (M^+-$CH_3COCH_2CH_2$, 3), 155 (M^+-$CH_3O_2CCHCHCH_2$, 52), 127 (100), 109 (13), 99 ($CH_3O_2CCHCHCH_2^+$, 12), 81 (13), 55 (23), 43 (CH_3CO^+, 94). Anal. for the mixture **16a/b**. Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.47; H, 7.16.

Compound 16b. IR (film): 2953, 1773, 1719, 1648, 1358, 1279, 1198, 1176, 1077, 1016, 928, 827; 80-MHz ^{1}H NMR (CDCl3): 1.88-2.07 (complex absorption, 4 H, 2xCH_2), 2.16 (s, 3 H, CH_3), 2.55 (dd, J=8.2 Hz, J'=2.5 Hz, 2 H), 2.47-2.73 (complex absorption, 2 H), 3.07 (d, J =6.6 Hz, 2 H, CH_2), 3.73 (s, 3 H, OCH_3), 6.11 (d, $J_{8,7}$=10.3 Hz, *H8*), 5.90-6.42 (m, *H7*); 20-MHz ^{13}C NMR ($CDCl_3$): 28.55, 29.76, 30.50, 32.23, 36.89, 37.38, 51.07, 88.69, 123.02, 142.13, 166.24, 175.87, 206.71.

5-(3-(Ethoxycarbonyl)allyl)-4-methyl-5-(3-oxobutyl)-2(3*H*)-dihydrofuranone, 17. A solution of triethylphosphonoacetate (0.4 mL, 2.1 mmol) in 13 mL of anhydrous THF was added to a stirred 1.6 M solution of n-BuLi in hexane (1.2 mL, 1.93 mmol) diluted with anhydrous THF (10 mL) at -20°C under inert atmosphere. The system was allowed to reach room temperature, and stirred for one hour under these conditions. Thereafter a solution of **12** (410 mg, 1.9 mmol) in 10 mL of dry THF was added dropwise to the clear solution which changed to a yellow color. The stirring was continued at room temperature for 21 hours. The resulting mixture was poured into 65 mL of water, and separated by extraction with dichloromethane (3x40 mL). The combined extracts were washed with brine (30 mL) and dried with $MgSO_4$. Removal of the solvent in vacuo yielded a pale yellow oil, which was purified over silica gel (1:1, hexane-ethyl acetate) to provide three diferent isomers: 199 mg (37% yield) of isomer **17a'**, 150 mg (28% yield) of isomer **17a"** and 24.1 mg (4% yield) of isomer **17b**. O.t. for the mixture 170°C (0.015 Torr). Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.83; H, 7.80. Found: C, 63.98; H, 8.03.

Compound 17a'. IR(film): 2980, 2033, 1779, 1714, 1656, 1460, 1446, 1423, 1369, 1263, 1216, 1169, 1093, 1041, 982, 929 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$): 1.07 (d, J =6.8 Hz, 3 H, CH_3), 1.28 (t, J =7.1 Hz, 3 H, CH_2CH_3), 1.73 (ddd, $J_{10,10'}$=15.0 Hz, $J_{10,11}$=9.6 Hz, $J_{10,11'}$=5.5 Hz, *H10*), 1.98 (ddd, $J_{10',10}$=15.0 Hz, $J_{10',11}$=9.6 Hz, $J_{10',11'}$=5.5 Hz, *H11'*), 2.17 (s, 3 H, OCH_3), 2.31 (dd, $J_{3,3'}$=17.0 Hz, $J_{3,4}$=10.9 Hz, *H3*), 2.45-2.68 (complex absorption, 6 H), 4.19 (q, J =7.1 Hz, 2 H, CH_2CH_3), 5.91 (dt, $J_{8,7}$=15.5 Hz, $J_{8,6}$=1.4 Hz, *H8*), 6.82 (ddd, $J_{7,8}$=15.5 Hz, $J_{7,6}$=8.3 Hz, $J_{7,6'}$=6.9 Hz, *H7*); 62.5-MHz ^{13}C NMR ($CDCl_3$): 13.7, 14.1, 26.3, 30.0, 36.1, 37.1, 37.3, 39.1, 60.5, 87.8, 125.9, 141.1, 165.5, 174.9, 207.1.

Compound 17a". IR(film): 2981, 2937, 1775, 1712, 1656, 1444, 1427, 1368, 1318, 1268, 1225, 1181, 1122, 1097, 1043, 985, 927; 400-MHz ^1H NMR ($CDCl_3$): 1.05 (d, J =6.9 Hz, 3 H, CH_3), 1.22 (t, J =7.1 Hz, 3 H, CH2CH_3), 1.87 (ddd, $J_{10,10'}$=15.0 Hz, $J_{10,11}$=8.2 Hz, $J_{10,11'}$=6.9 Hz, *H10*), 1.96 (ddd, $J_{10',10}$=15.0 Hz, $J_{10',11}$=8.2 Hz, $J_{10',11'}$=6.9 Hz, *H10'*), 2.10 (s, 3 H, CH_3), 2.21 (dd, $J_{3,3'}$=17.4 Hz, $J_{3,4}$=10.1 Hz, *H3*), 2.37 (complex absorption, 2 H, *H4*, *H6*), 2.48 (complex absorption, 3 H, *H6'*, *H11*, *H11'*), 2.63 (dd, $J_{3',3}$=17.4 Hz, $J_{3',4}$=8.2 Hz, *H3'*), 4.13 (q, J =7.1 Hz, 2 H, CH_2CH_3), 5.87 (dt, $J_{8,7}$=15.5 Hz, $J_{8,6}$=1.5 Hz, *H8*), 6.83 (ddd, $J_{7,8}$=15.5 Hz, $J_{7,6}$=8.2 Hz, $J_{7,6'}$=6.6 Hz, *H7*); 62.5-MHz ^{13}C NMR ($CDCl_3$): 14.2, 29.6, 29.9, 30.0, 36.5, 36.8, 37.2, 37.3, 60.5, 88.1, 125.9, 141.4, 165.6, 174.9, 206.9; MS, m/e: 237 (M^+-C_2H_5O, 4), 236 (M^+-C_2H_5OH, 4), 211 (M^+-C_4H_7O, 5), 169 (M^+-$C_6H_9O_2$, 72), 141 (100), 123 (8), 99 ($C_5H_6O_2H^+$, 24), 43 (CH_3CO^+, 99).

Compound 17b. IR(film): 2969, 2930, 1778, 1718, 1651, 1645, 1446, 1418, 1361, 1261, 1188, 1095, 1032, 976 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$): 1.03 (d, J =6.5 Hz, 3 H, CH_3), 1.24 (t, J =7.2 Hz, 3 H, CH_2CH_3), 1.71 (complex absorption, *H10*), 1.96 (complex absorption, *H10'*), 2.16 (s, 3 H, CH_3), 2.24-2.63 (complex absorption, 5 H), 2.90 (dd, $J_{3,3'}$=15.3 Hz, $J_{3,4}$=6.6 Hz, 1H, *H3*), 3.22 (dd, $J_{3',3}$=15.3 Hz, $J_{3',4}$=8.8 Hz, *H3'*), 4.10 (q, J =7.2 Hz, 2 H, CH_2CH_3), 5.90 (dt, $J_{8,7}$=11.7 Hz, $J_{8,6}$=1.4 Hz, *H8*), 6.13 (ddd, $J_{7,8}$=11.7 Hz, $J_{7,6}$=8.8 Hz, $J_{7,6'}$=5.8 Hz, *H7*); 62.5-MHz ^{13}C NMR ($CDCl_3$): 13.7, 14.1, 26.6, 30.0, 34.3, 36.1, 37.1, 37.3, 60.1, 88.5, 123.4, 142.3, 165.9, 175.3, 207.3.

5-(1-Methyl-3-(ethoxycarbonyl)allyl)-5-(3-oxobutyl)-2(3*H*)-dihydrofuranone, 18. To a suspension of NaH (20.7 mg, 0.4-0.5 mmol, 50-60% oil dispersion) in anhydrous THF (6 mL) was added dropwise a solution of triethylphosphonoacetate (109 mg, 0.5 mmol) in anhydrous THF (3 mL). The mixture was stirred at room temperature for 1 h under inert atmosphere. Then a solution of **13** (120 mg, 0.6 mmol) in dry THF (3 mL) was added dropwise and stirring was continued for 21 hr. The resulting mixture was poured into 20 mL of water and extracted with dicholoromethane (2x20 mL). The combined extracts were washed (brine, 20 mL) and dried with $MgSO_4$. Removal of the solvent in vacuo yielded an oil, which after column chromatography (hexane-ethyl acetate) led to compound **18** (118 mg, 0.4 mmols, 67% yield) as a colorless oil, o.t. 170°C (0.015 Torr); IR (film): 2980, 2940, 1774, 1716, 1654, 1459, 1421, 1368, 1266, 1227, 1182, 1129, 1033, 984, 926; 400-MHz ^1H NMR ($CDCl_3$): 1.11 (d, J =6.8 Hz, 3 H, CH_3), 1.30 (t, J =7.0 Hz, 3 H, CH_2CH_3), 1.96 (t, J=7.7 Hz, 2 H), 1.90-1.98 complex absorption, 2 H), 2.17 (s, 3 H, CH_3), 2.51-2.86 (complex absorption, 5 H), 4.20 (q, J =7.0 Hz, 2H, CH_2CH_3), 5.92 (d, $J_{8,7}$=15.7 Hz, *H8*), 6.84 (dd, $J_{7,8}$= 15.7 Hz, $J'_{7,6}$=8.3 Hz, *H7*); 100-MHz ^{13}C NMR ($CDCl_3$): 13.50, 14.06, 27.67, 28.69, 29.79, 31.29, 37.07 ,43.73, 60.37, 88.02, 123.69, 146.49, 165.75, 175.78, 206.58; MS, m/e: 236 (M^+-C_2H_5OH, 2), 201

(4), 155 (M^+-$C_7H_{11}O_2$, 59), 128 ($C_7H_{11}O_2^+$, 100), 109 (11), 81 (10), 43 (CH_3CO^+, 61); Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.58; H, 7.85.

Cyclization of compound 18: 8-acetyl-7-ethoxycarbonylmethyl-6-methyl-1-oxaspiro[4.4]-nonan-2-one, 19. A solution of **18** (66 mg, 0.23 mmol) in anhydrous THF (3 mL) was added to a suspension of NaH (11.2 mg, 0.23-0.28 mmol, 50-60% oil dispersion) in anhydrous THF (2mL). The mixture was stirred under inert atmosphere for 6 h and then heated to reflux for 1 h. Afterwards, MeOH (1 mL) and water (20 mL) were added. The aqueous layer was extracted with dichloromethane (3x15 mL). The combined organic phases were dried and solvents were removed giving a residue which contains compound **19** as a diastereoisomeric mixture, o.t. 150 °C (0.01 Torr). Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.65; H, 7.94. Column chromatography (hexane-ethyl acetate) of this mixture allowed the isolation of two pure isomers **19a** and **19b** as colorless oils.

Compound 19a. IR(film): 2964, 2933, 2879, 1773, 1726, 1711, 1459, 1420, 1369, 1290, 1260, 1191, 1165, 1133, 1096, 1023, 968, 948, 918, 801 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$): 1.03 (d, J =7.3 Hz, 3 H, CH_3), 1.25 (t, J =7.3 Hz, 3 H, CH_2CH_3), 2.21 (s, 3 H, CH_3), 1.92-3.01 (complex absorption, 11 H), 4.10 (q, J =7.3 Hz, 2 H, CH_2CH_3); 20-MHz ^{13}C NMR ($CDCl_3$): 14.03, 15.36, 27.88, 28.93, 29.70, 39.28, 39.65, 43.70, 47.46, 54.04, 60.33, 95.30, 172.02, 175.75, 208.61; MS, m/e: 282 (M^+, 6), 264 (M^+-H_2O, 5), 236 (M^+-C_2H_5OH, 58), 194 (M^+-$C_4H_8O_2$, 21), 175 (12), 154 (M^+-$C_7H_{12}O_2$, 58), 112 ($C_6H_8O_2^+$, 21), 95 ($C_5H_7O_2^+$, 24), 43 (CH_3CO^+, 100).

Compound 19b. IR(film): 2977, 2938, 1771, 1731, 1717, 1368, 1295, 1253, 1179, 1134, 1030, 946, 919 cm^{-1}; 80-MHz ^1H NMR ($CDCl_3$): 0.80 (d, J=7.0 Hz, 3 H, CH_3), 1.20 (t, J =7.4 Hz, 3 H, CH_2CH_3), 2.16 (s, 3 H, CH_3), 1.90-3.06 (complex absorption, 11 H), 4.04 (q, J =7.4 Hz, 2 H, CH_2CH_3); 20-MHz ^{13}C NMR ($CDCl_3$): 9.94, 14.00, 27.10, 28.50, 29.20, 35.19, 38.87, 40.09, 44.98, 54.29, 60.41, 95.65, 171.77, 175.33, 208.20; MS, m/e: 282 (M^+, 1), 236 (M^+-C_2H_5OH, 15), 194 (M^+-$C_4H_8O_2$, 12), 180 (33), 154 (M^+-$C_7H_{12}O_2$, 21), 149 (26), 135 (28), 93 (34), 83 (15), 43 (CH_3CO^+, 100).

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8. Stereochemical assignments of diastereoisomers **19a** and **19b** (see Experimental Section) will be reported in a future.

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