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TETRAHEDRON

A Convenient Synthesis of 3-Functionalized 5-Alkoxymethyl- and 5-Phenoxymethyl-2(5H)-Furanones and Their Transformations into Related Epoxy and Methylene Lactones

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Abstract: A convenient procedure for the preparation of 3-functionalized 5-alkoxymethyl- and 5-phenoxymethyl-2(5H)-furanones is described. The method is based on the condensation of various β-alkoxy- or β-phenoxy-α-hydroxy ketones with β-activated esters in the presence of catalytic amounts of sodium methoxide. Results are reported showing the possible transformations of these 2(5H)-furanones into related epoxy and α-methylene lactones.

INTRODUCTION

3-Functionalized 2(5H)-furanone units are present in a wide range of biologically active compounds, both natural [1] and synthetic.[2] Structurally diverse 2(5H)-furanones, acylated at position 3, have also been successfully incorporated into straightforward syntheses of target molecules of biological and medicinal interest.[3] An increasing interest has been paid in recent years to the chemistry of 3-acylated 2(5H)-furanones bearing the additional heteromethyl moiety at position 5, mostly through the reported ability of 3-acyl-5-(hydroxymethyl)-tetronic acids to inhibit HIV-1 protease,[4] protein tyrosine phosphatase[5] and phospholipase A_2.[6] Due to the wide application of 3-acyl-2(5H)-furanones, their preparation has been the subject of detailed studies [7] starting from appropriate furan derivatives,[3e,8] saturated and unsaturated γ-butyrolactones,[1a,3b,3d,9] but the most convenient and general synthetic method represents the condensation of α-hydroxy ketones with β-activated esters in basic conditions[2b,10] and related approaches.[11]

In an extension of our synthetic studies on chemically and biologically interesting 5-heteromethyl-2(5H)-furanones,[12] we report here a convenient synthesis of the title compounds starting from readily available 3-alkoxy- and 3-phenoxy-2-hydroxy ketones **1**.[13]

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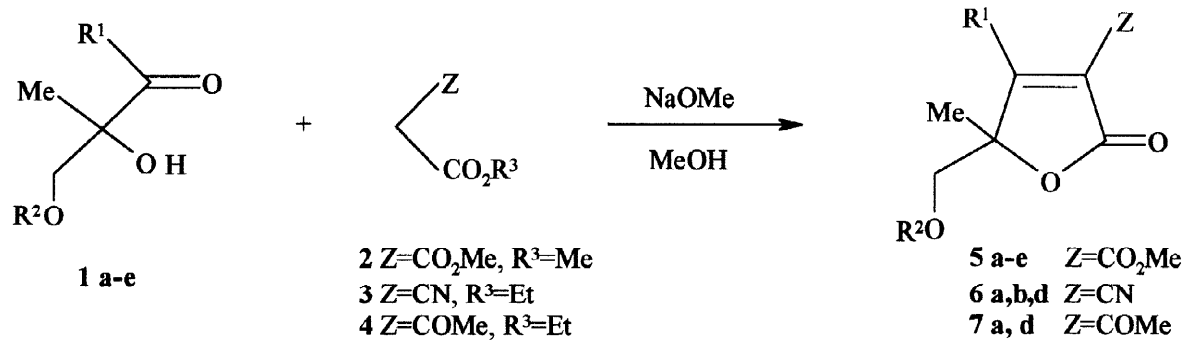
RESULTS AND DISCUSSION

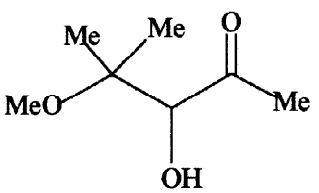
Condensation of hydroxy ketones **1a-e** with a slight excess of dimethyl malonate **2**, ethyl cyanoacetate **3** or ethyl acetoacetate **4** in the presence of sodium methoxide in methanol at room temperature afforded 3-functionalized 5-alkoxymethyl- and 5-phenoxymethyl-2(5H)-furanones **5-7** in 31-85 % yield (Scheme 1).



1 a-e

2 Z=CO_2Me, R^3=Me
3 Z=CN, R^3=Et
4 Z=COMe, R^3=Et

5 a-e Z=CO_2Me
6 a,b,d Z=CN
7 a, d Z=COMe



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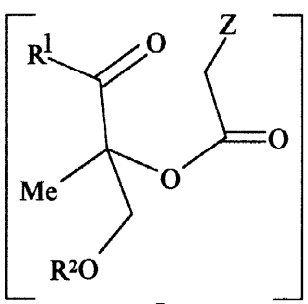

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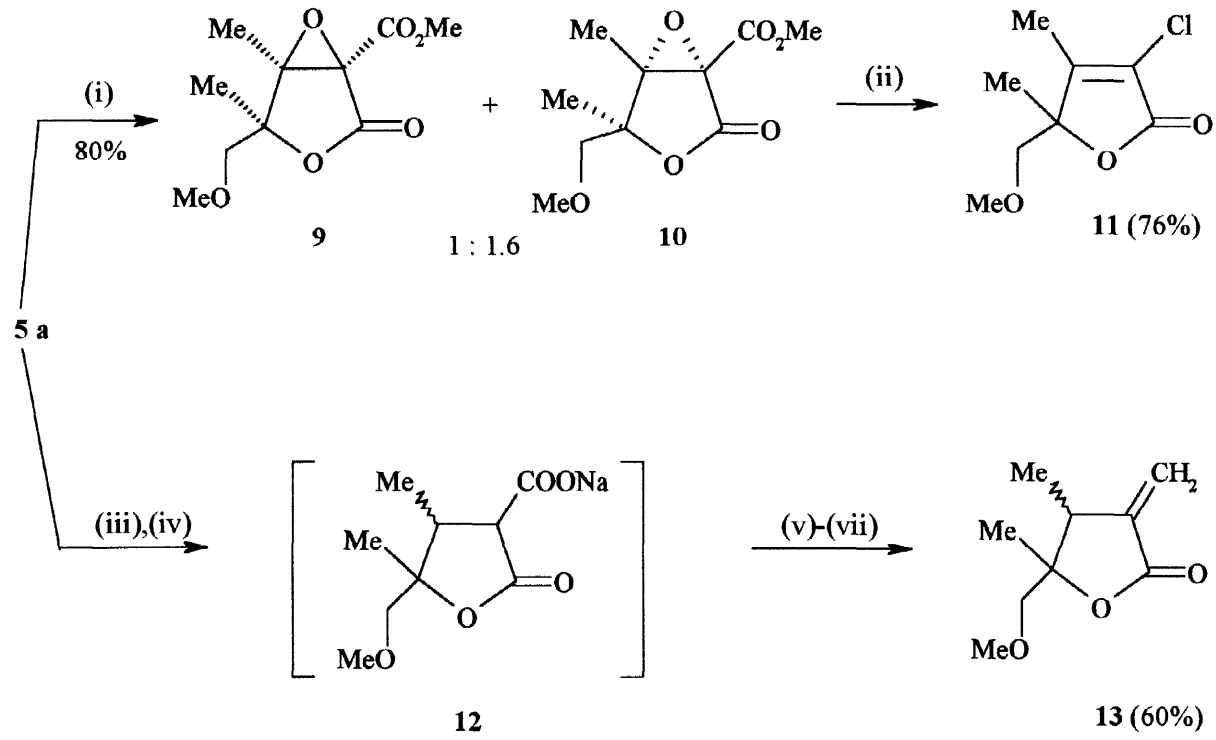
1, 5-7 **a** R^1=Me, R^2=Me
b R^1=Me, R^2=Et
c R^1=Me, R^2=Pr-i
d R^1=Me, R^2=Ph
e R^1=Ph, R^2=Me

Scheme 1

The low yield of furanone **5c** (31 %) in the reaction of ketol **1c** with dimethyl malonate **2** probably is connected with steric hindrance of the isopropoxymethyl group at the stage of formation of the transesterification product **8**, which as was shown before,[10b] takes precedence over lactone ring formation through intramolecular Knoevenagel condensation. Maybe for this reason, the attempt to involve hydroxy ketone **1f** [13] (Scheme 1), having a hindered carbinol moiety, in the reaction with esters **2-4,** failed.

Furanones **5-7** are convenient substrates for the preparation of butyrolactone derivatives on the base of nucleophilic Michael addition reactions to the activated C=C bond.[7,14] Some reactions with nucleophilic reagents (*e.g.* H^- or HOO^-) using lactone **5a** as the model compound have been investigated in this work. Thus, epoxidation of furanone **5a** by treatment with an excess of hydrogen peroxide under phase-transfer catalysis gave a mixture of diastereoisomeric epoxy compounds **9** and **10** in 80 % combined yield. The isomers **9** and **10** have been isolated by column chromatography in the ratio of 1 : 1.6. This result indicates some preference for the addition of hydroperoxide anion from the sterically less hindered face of the furanone π-system, opposite

the more bulky methoxymethyl moiety as compared with the C-5 methyl group. This slight selectivity may reflect a steric rather than an electronic bias of the substituents in these systems.[15]



Reagents: (i) H_2O_2, Bu_4NOH; (ii) HCl, H_2O, dioxane, reflux; (iii) NaOH, H_2O, MeOH; (iv) $NaBH_4$; (v) CH_2O, Et_2NH; (vi) MeI; (vii) NaOH

Scheme 2

Refluxing of the epoxy lactone **10** in 80 % aqueous dioxane, saturated with gaseous hydrogen chloride, afforded 3-chloro-2(5H)-furanone **11** as the major product in good yield. The formation of **11** probably occurs *via* the epoxy ring cleavage by HCl followed by hydrolysis, decarboxylation and dehydration of the intermediate chlorohydrin. The regioselectivity of the oxirane opening was as expected,[12a,c] with the chlorine adding to the α-carbon of the lactone **10**. Under similar conditions, the epoxy compound **9** also formed chlorofuranone **11** in 70% yield.

Finally, furanone **5a** has been also transformed into the methylene lactone **13** by a five-step one-pot procedure in 60% overall yield. The synthesis of compound **13** involved conversion of the ester **5a** to the sodium salt of the corresponding lactonic acid, reduction of the activated double bond with sodium borohydride and reaction of the intermediate tetrahydrofuranone derivative **12** with formaldehyde and diethylamine, resulting in the formation of the Mannich product. Conversion of the latter to its methiodide, followed by treatment with aqueous sodium hydroxide yielded methylene lactone **13** as a colorless oil. In the light of the low stereoselectivity of the nucleophilic epoxidation of furanone **5a**, it was not surprising to find that the same

substrate **5a** underwent sodium borohydride reduction in a nonstereoselective manner. Accordingly, α-methylene lactone **13** was obtained as nearly an equimolecular mixture of two diastereoisomers, as measured by integration of the 3-methylene region in the ^{1}H NMR spectrum, which exhibited two doublets for each isomer.

The structures of all new compounds **5-7, 9-11, 13** were established by ^{1}H NMR spectroscopy and comparison of the data with those obtained for analogous systems.[12] A particular characteristic of the spectra of 2(5H)-furanones **5a-d, 6a,b,d, 7a,d** and **11** is that the methyl protons at C-4 are shifted about 0.6 - 0.9 ppm downfield compared to those at C-5. This value decreases considerably by transition to saturated epoxy compounds **9** and **10**. In order to determine the relative configuration of the latter diastereoisomeric products, a differential NOE experiment was carried out. In contrast with the minor isomer **9**, when both C-4 and C-5 methyl groups at δ 1.37 and 1.57 in ^{1}H NMR spectrum of major isomer **10** were irradiated separately, the two methylene doublets at δ 3.49 and 3.59 showed clear NOE enhancements. This result demonstrated the *cis*-arrangement of the C-4 methylene group and the C-5 methyl group in isomer **10** (Figure 1).

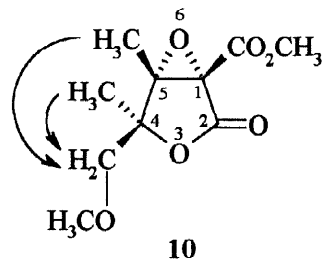


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Figure 1.

In conclusion, readily available 3-alkoxy(phenoxy)-2-hydroxy ketones are convenient substrates for the preparation of 3-functionalized 5-alkoxymethyl- and 5-phenoxymethyl-2(5H)-furanones and related epoxy and methylene lactones.

EXPERIMENTAL

IR spectra were obtained on a Specord 75 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-360 (360 MHz) or a Tesla BS-467A (60 MHz) NMR spectrometer. ^{13}C NMR spectra were recorded on a JEOL JNM-EX 270 (68 MHz). Chemical shifts are expressed in ppm downfield from Me_4Si. Mass spectra were obtained on a Finnigan Matt 112S mass spectrometer (70 eV) using the direct inlet method. Melting points were determined in open capillaries and are uncorrected. For preparative column chromatography, silica gel L Chemapol (40-100 Mesh) was used. All chemicals were reagent grade; solvents were dried and distilled before use. Hydroxy ketones **1a-f** were prepared by literature methods.[13]

General Procedure for the Preparation of 3-Functionalized Furanones 5-7. To a solution of sodium methoxide in methanol, prepared by reaction of sodium metal (0.23 g, 10 mmol) with dry methanol (10 ml), was added in one portion the appropriate α-hydroxy ketone **1a-e** (30 mmol) and ester **2-4**(40 mmol). The mixture

was kept at room temperature for 10 h and acidified with 10 % acetic acid (6 mL). Methanol was evaporated under reduced pressure, the product was extracted with CH_2Cl_2 and dried with anhydrous Na_2SO_4. After removal of the solvent in vacuum, the residue was crystallized to obtain furanones **5a,b,d,e** and **6a,b**, or chromatographed on silica gel using ether-hexane (3 : 1) eluent to isolate compounds **5c, 6d** and **7a,d**.

4,5-Dimethyl-3-(methoxycarbonyl)-5-(methoxymethyl)-2(5H)-furanone (5a): (72 %), m.p. 87 °C (hexane-isopropyl alcohol); IR (CCl_4) 1775, 1715, 1645 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.34 (s, 3H), 2.25 (s, 3H), 3.22(s,3H), 3.48 (br s, 2H), 3.76 (s, 3H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.46 (Me), 19.78 (Me), 52.09 (COOMe), 59.78 (OMe), 74.48 (OCH_2), 87.22 (Me-C-O), 119.55 (=C-C=O), 161.97 and 167.40 (C=O and COOMe), 178.78 (MeC=). MS (70 eV) m/z (%) : 214 (1, M^+), 185(3), 184(23), 169(2), 139(2), 138(19), 137(22), 113(2), 99(1), 67(7), 59(2), 53(1), 46(3), 45(100), 44(1), 43(9), 41(2). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.21; H, 6.76.

4,5-Dimethyl-5-(ethoxymethyl)-3-(methoxycarbonyl)-2(5H)-furanone (5b): (59 %), m.p. 99 °C (hexane-isopropyl alcohol); IR (CCl_4) 1760, 1705, 1645 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.07 (t, J=7 Hz, 3H), 1.38 (s,3H), 2.28 (s, 3H), 3.41 (q, J=7 Hz, 2H), 3.55 (br s, 2H), 3.80 (s, 3H). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 58.03; H, 6.96.

4,5-Dimethyl-5-(isopropoxymethyl)-3-(methoxycarbonyl)-2(5H)-furanone (5c): (31 %), m.p. 39 °C (pentane-Et_2O); IR (CCl_4) 1780, 1720, 1655 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.04 (d, J=7 Hz, 6H), 1.36 (s, 3H), 2.23 (s, 3H), 3.33, 3.57 (AB q, J=10.5 Hz, 2H), 3.43 (sept, J=7 Hz, 1H), 3.75 (s, 3H). Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.33; H, 7.41.

4,5-Dimethyl-3-(methoxycarbonyl)-5-(phenoxymethyl)-2(5H)-furanone (5d): (69%), m.p. 90 °C (hexane-isopropanol); IR (CCl_4) 1775, 1715, 1655 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.43 (s, 3H), 2.25 (s, 3H), 3.70 (s, 3H), 3.99 (s, 2H), 6.55-7.23 (m, 5H). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.31; H, 5.92.

3-(Methoxycarbonyl)-5-(methoxymethyl)-5-methyl-4-phenyl-2(5H)-furanone (5e): (62 %), m.p. 61 °C (hexane-Et_2O); IR (CCl_4) 1780, 1735, 1655 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.40 (s, 3H), 3.33 (s, 3H), 3.50 (s, 2H), 3.58 (s, 3H), 7.05-7.45 (m, 5H). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.08; H, 5.95.

3-Cyano-4,5-dimethyl-5-(methoxymethyl)-2(5H)-furanone (6a): (65 %), m.p. 39 °C (pentane-Et_2O); IR (CCl_4) 2235, 1785, 1645 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.38 (s, 3H), 2.20 (s, 3H), 3.23 (s, 3H), 3.39, 3.59 (AB q, J=11 Hz, 2H). Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.49; H, 6.21; N, 7.87.

3-Cyano-4,5-dimethyl-5-(ethoxymethyl)-2(5H)-furanone (6b): (50 %), m.p. 49 °C (hexane-isopropanol); IR (CCl_4) 2240, 1785, 1655 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.06 (t, J=6.8 Hz, 3H), 1.40 (s, 3H), 2.20 (s, 3H), 3.39 (q, J=6.8 Hz, 2H), 3.53 (s, 2H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.14 (MeC=), 14.84 ($MeCH_2$), 19.75 (Me), 67.71 (OCH_2Me), 72.31 (OCH_2), 89.61 (Me-C-O), 105.96 and 110.58 (=C-CN), 165.53 (C=O); 182.28 (Me-C=). MS (70eV) m/z (%) : no M^+, 165(3), 150(2), 138(2), 137(26), 136(3), 109(2), 94(4), 67(3),

66(25), 65(4), 64(2), 60(4), 59(100), 57(2), 43(20), 42(2), 41(6). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.59; H, 6.90; N, 7.29.

3-Cyano-4,5-dimethyl-5-(phenoxymethyl)-2(5H)-furanone (6d): (85 %), pale yellow oil; IR (CCl_4) 2235, 1780, 1645 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.52 (s, 3H), 2.25 (s, 3H), 4.05 (br s, 2H), 6.60-7.33 (m, 5H). Anal. Calcd for: $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.35; H, 5.61; N, 5.62.

3-Acetyl-4,5-dimethyl-5-(methoxymethyl)-2(5H)-furanone (7a): (59 %), m.p. 28 °C (pentane-Et_2O); IR (CCl_4) 1760, 1685, 1620 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.32 (s, 3H), 2.18 (s, 3H), 2.37 (s, 3H), 3.22 (s, 3H), 3.33, 3.54 (AB q, J=11.2 Hz, 2H). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59, H, 7.12. Found: C, 60.67; H, 7.07.

3-Acetyl-4,5-dimethyl-5-(phenoxymethyl)-2(5H)-furanone (7d): (62 %), m.p. 74 °C (hexane-isopropanol); IR (CCl_4) 1760, 1685, 1625 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.47 (s, 3H), 2.28 (s, 3H), 2.45 (s, 3H), 4.00 (br s, 2H), 6.57-7.23 (m, 5H). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.29; H, 6.35.

Epoxidation of furanone 5a. To a solution of furanone **5a** (2.1 g, 10 mmol) in CH_2Cl_2 (15 mL) was added a solution of the 30 % tetrabutylammonium hydroxide (0.7 g) in 10 % hydrogen peroxide (7 mL, 20 mmol). This mixture was vigorously stirred at room temperature for 4 h, the organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (5 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was chromatographed on silica gel using hexane-chloroform (1:1) eluent. Two isomeric epoxides were subsequently isolated:

(1SR,4SR,5RS)-4,5-Dimethyl-1-(methoxycarbonyl)-4-(methoxymethyl)-3,6-dioxabicyclo[3.1.0]-hexan-2-one (9): (0.7 g, 31 %), m.p. 59 °C (CCl_4-hexane); IR (CCl_4) 1790, 1765, 1750 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.54 (c, 3H), 1.64 (s, 3H), 3.42 (s, 3H), 3.44, 3.65 (AB q, J=9.1 Hz, 2H), 3.91 (s, 3H). Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.03; H, 6.25.

(1RS,4SR,5SR)-4,5-Dimethyl-1-(methoxycarbonyl)-4-(methoxymethyl)-3,6-dioxabicyclo[3.1.0]-hexan-2-one (10): (1.1 g, 49 %), m.p. 100 °C (CCl_4-hexane); IR (CCl_4) 1795, 1765, 1745 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.57 (s, 3H), 3.38 (s, 3H), 3.49, 3.59 (AB q, J=9.8 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 10.24 (Me), 15.54 (Me), 53.26 (COOMe), 59.78 (OMe), 60.86 and 71.75 (epoxide carbons), 74.61 (OCH_2), 85.23 (Me-C-O-C=O), 162.78 and 166.65 (2 x C=O). MS (70 eV) m/z (%) : 230 (2, M^+), 185(4), 171(6), 157(3), 143(7), 141(5), 129(3), 115(7), 113(5), 101(2), 99(2), 98(2), 97(6), 84(15), 83(3), 73(2), 70(2), 69(6), 67(3), 59(7), 57(2), 55(5), 46(3), 45(100), 43(36), 41(4). Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 51.95; H, 6.17.

3-Chloro-4,5-dimethyl-5-(methoxymethyl)-2(5H)-furanone (11). A solution of the epoxy lactone **9** (0.8 g, 3.5 mmol) in 80 % aqueous dioxane (10 mL) was saturated with gaseous HCl and heated at reflux for 10 h repeating saturation twice more during this time. The mixture was diluted with water (10 mL) and extracted with chloroform (5 mL x 5). The organic layer was separated, washed with saturated $NaHCO_3$ and brine, and

then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the solid residue was recrystallized from pentane-Et_2O to afford chlorofuranone **11** (0.5 g, 76 %), m.p. 37.5 °C; IR (CCl_4) 1780, 1655 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.31 (s, 3H), 1.93 (s, 3H), 3.22 (s, 3H), 3.30, 3.48 (AB q, J=10 Hz, 2H). Anal. Calcd for $C_8H_{11}ClO_3$: C, 50.41; H, 5.82; Cl, 18.60. Found: C, 50.57; H, 6.02; Cl, 18.77.

4,5-Dihydro-4,5-dimethyl-5-(methoxymethyl)-3-methylene-2(3H)-furanone (13). To a solution of furanone **5a** (4.2 g, 19.6 mmol) in methanol (80 mL) was added 5 % aqueous NaOH (16 mL, 20 mmol), and the resulting solution was kept at room temperature for 5 h. To the reaction mixture was added $NaBH_4$ (2g, 50 mmol) in a few portions during 30 min, and then were added 34 % formaldehyde (40 mL), diethylamine (20 mL), and acetic acid (25 mL). The mixture was heated at reflux for 15 min and concentrated in vacuum. Then saturated aqueous Na_2CO_3 was added until the mixture became basic. The Mannich base was extracted with Et_2O and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was added to methyl iodide (20 mL) and kept for 28 h at room temperature. An excess of alkyl halogenide was evaporated under reduced pressure, and the residue was treated with 5 % aqueous NaOH (16 mL). The mixture was extracted with Et_2O, and the combined organic layers were washed with brine and dried over Na_2SO_4. Following filtration and concentration under reduced pressure, the crude residue was purified by column chromatography on silica gel using Et_2O-hexane (3:1) eluent to afford methylene lactone **13** (2.0 g, 60 %) as a colorless oil: IR (CCl_4) 1765, 1660 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.06 (d, J=6.8 Hz, 1.5H), 1.08 (s, 1.5H), 1.14 (d, J=6.8 Hz, 1.5H), 1.26 (s, 1.5 H), 2.40-3.05 (m, 1H), 3.00-3.35 (m, 2H), 3.18 (s, 1.5H), 3.28 (s, 1.5H), 5.13 (d, J=3.1 Hz, 0.5H), 5.28 (d, J=3.3 Hz, 0.5H), 5.81 (d, J=3.3 Hz, 0.5H), 5.94 (d, J=3.1 Hz, 0.5H). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.57; H, 8.17.

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