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Base-Catalyzed Reactions of Dihydromethylenomycin A and Its Derivatives

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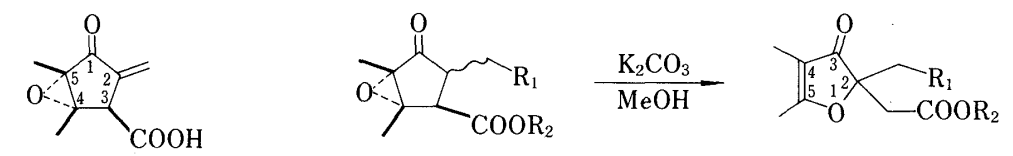
Derivatives of dihydromethylenomycin A undergo a facile cleavage of the five-membered ring ketone and a subsequent reclosure to give 3(2*H*)-furanone derivatives under weakly basic conditions such as in the presence of K_2CO_3. The structure of a typical product was unequivocally determined by synthesis. The reaction mechanism is discussed.

Keywords——cleavage of five-membered ring ketone; 3(2*H*)-furanone; epoxy ketone; methylenomycin A; ring reclosure; antileukemic activity; absolute configuration

Methylenomycin A is an antibiotic which was isolated from a strain of *Streptomyces violaceoruber*.[1] In a previous paper[2] we described the conversion of methylenomycin A into (−)-botryodiplodin, which has antileukemic activity, and also clarified the absolute configuration by correlation with (*S*)-(−)-2-ethyl-3-methyl-1-butanol. Consequently, the absolute configuration of methylenomycin A was found to be favorable for conversion of this compound to prostaglandin analogues. In the course of studies on this conversion, we have found a novel reaction in which derivatives of dihydromethylenomycin A undergo a facile cleavage of the five-membered ring ketone and a subsequent reclosure, affording 3(2*H*)-furanone derivatives under weakly basic conditions.

With the object of isomerization to obtain $C_2\alpha$–Me, dihydromethylenomycin A methyl ester (**1a**) consisting of a mixture of the $C_2\alpha$–Me and the $C_2\beta$–Me compounds was treated with K_2CO_3 in MeOH at room temperature for 0.5 h. Unexpectedly, the spectral data for the product (**2a**) obtained in good yield (89%) were very different from those for **1a**. Though the molecular formula of **2a** was the same ($C_{10}H_{14}O_4$) as that of **1a** (mass spectrum, (MS)), **2a** was optically inactive, and its spectral data suggested the presence of an α,β-unsaturated ketone and two vinyl methyl groups (see Experimental).



methylenomycin A

1a : R_1=H, R_2=Me
1b : R_1=CN, R_2=Me

2a : R_1=H , R_2=Me
2b : R_1=CN, R_2=Me
2c : R_1=H , R_2=H

Chart 1

On the basis of spectroscopic analysis, the structure of **2a** was assigned to be as shown in Chart 1. Unequivocal evidence for this structure was obtained by synthesis starting from pyruvic acid (Chart 2).

Treatment of pyruvic acid (**3**) with trimethylsilyl chloride in the presence of triethylamine followed by Wittig reaction with carbomethoxymethylenetriphenylphosphorane afforded stereospecifically (*E*)-3-methoxycarbonyl-2-methylacrylic acid (**4**)[3] in 16% yield from **3**. The acid chloride (**5**) was obtained from **4** by treatment with $SOCl_2$ in 92.8% yield. The acylation of methyl 2-methylacetoacetate with **5** in a usual manner afforded the diketo ester (**6**) in 32% yield. When **6** was heated at 130—140 °C in AcOH/1,2-dimethoxyethane in the presence of NaI, monodecarboxylation proceeded smoothly to afford the 3(2*H*)-furanone derivative (**2a**) which was identical with **2a** from dihydromethylenomycin A in terms of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum and the infrared (IR) spectrum. The postulated intermediate A was not detected under the conditions employed.

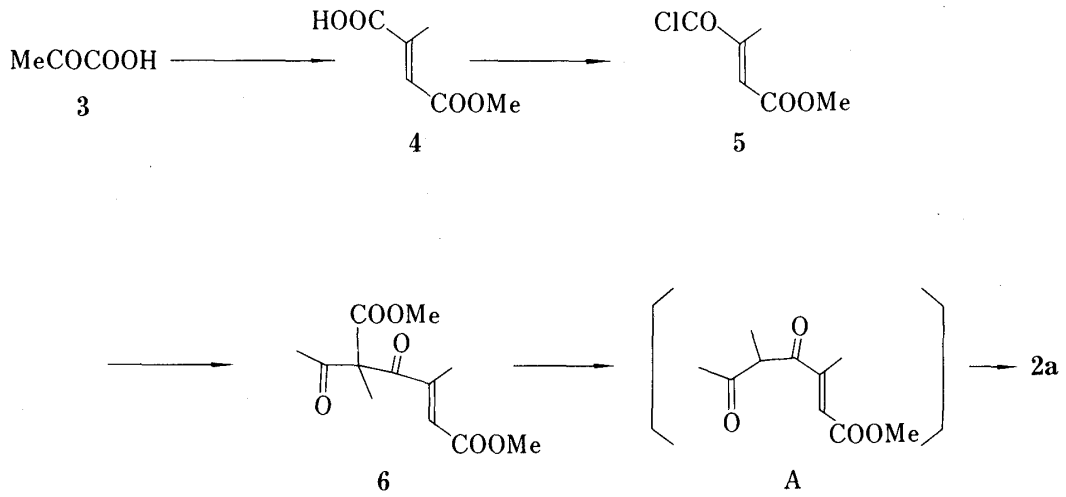
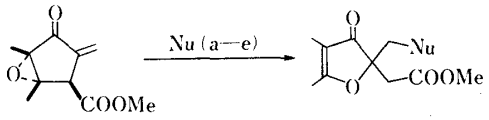
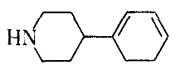
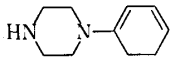
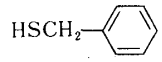


Chart 2

TABLE I



Entry	Nucleophilic reagent (Nu)	II (Yield %)
a		70
b		76
c		46
d		74
e	$HSCH_2(CH_2)_3COOMe$	60

A similar reaction was also observed with the cyanomethyl derivative (**1b**), and the cyanomethyl-3(2*H*)-furanone (**2b**) was obtained in 60% yield.

It was found that, in this reaction, the isolation of the adduct formed initially by 1,4-addition of the nucleophilic reagent (Nu) is not always required. As shown in Table I,

treatment of I with Nu in MeOH and then with K_2CO_3 afforded the same results as in the case of **1a**.

In order to clarify the reaction mechanism the following two reactions (A and B) (Chart 3) were carried out.

A) Similar treatment of the acetate (**7**) with K_2CO_3 in MeOH induced a facile cleavage of the five-membered ring ketone to give the 1,3-diketone (**8**)[4] in 40% yield. However, ring reclosure was not observed at all. On Jones oxidation of **8** followed by treatment with 5% NaOH under ice-water cooling, the ring reclosure product (**2c**) was obtained. The keto acid (**2c**) was identical (in terms of the ^{1}H-NMR spectrum and the IR spectrum) with the corresponding acid obtained by hydrolysis of the ester function in **2a**. These results suggest that a) the reaction from **1a** to **2a** consists of two steps, ring cleavage followed by ring reclosure, b) the carboxyl function is not necessary in ring cleavage, but is required for the ring reclosure. As the 4-oxo-dihydropyran derivative (B) postulated in an alternative ring reclosure was not obtained, the 3(2*H*)-furanone structure seems to be thermodynamically preferable to the 4-oxo-dihydropyran skeleton.

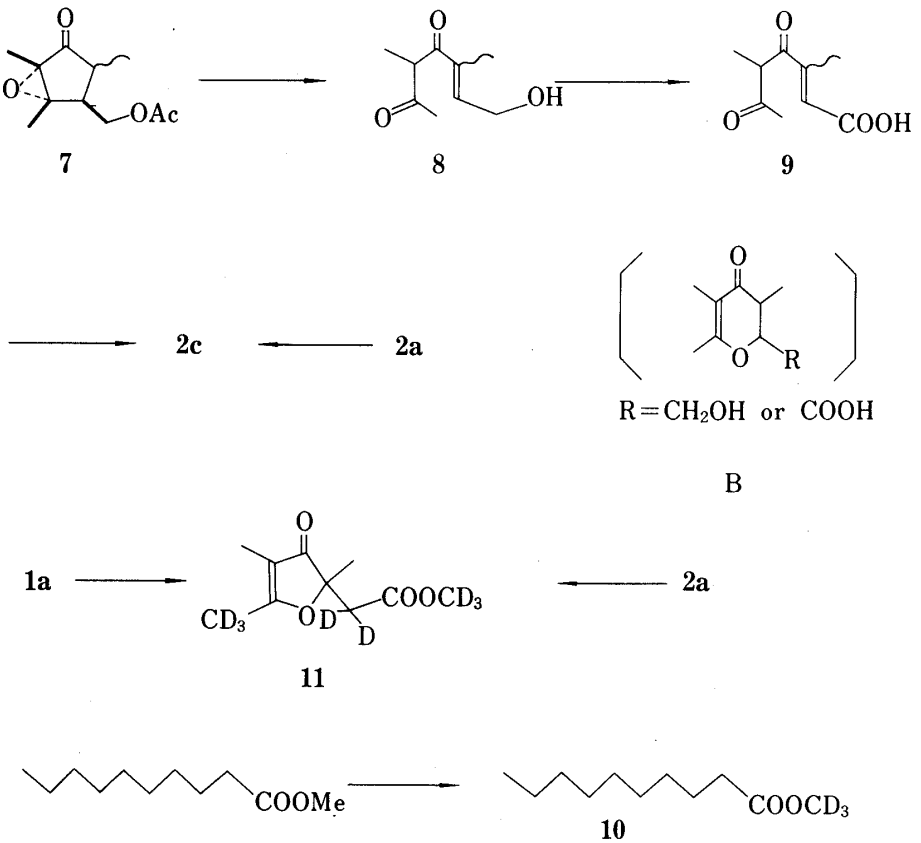


Chart 3

B) Treatment of **1a** with K_2CO_3 in CD_3OD afforded the deuterio-3(2*H*)-furanone (**11**) which was also obtained from **2a** under similar reaction conditions. A similar treatment of methyl decanoate resulted in the formation of the deuteriomethyl ester (**10**) arising from ester exchange, and the methylene function adjacent to COOMe was not replaced by deuterium. These results suggest that the deuterium exchange in **11** arises from a rapid equilibrium between the ring cleavage and the ring reclosure under basic conditions rather than from direct substitution by deuterium.

On the basis of combined data, the reaction mechanism is tentatively proposed to be as shown in Chart 4.

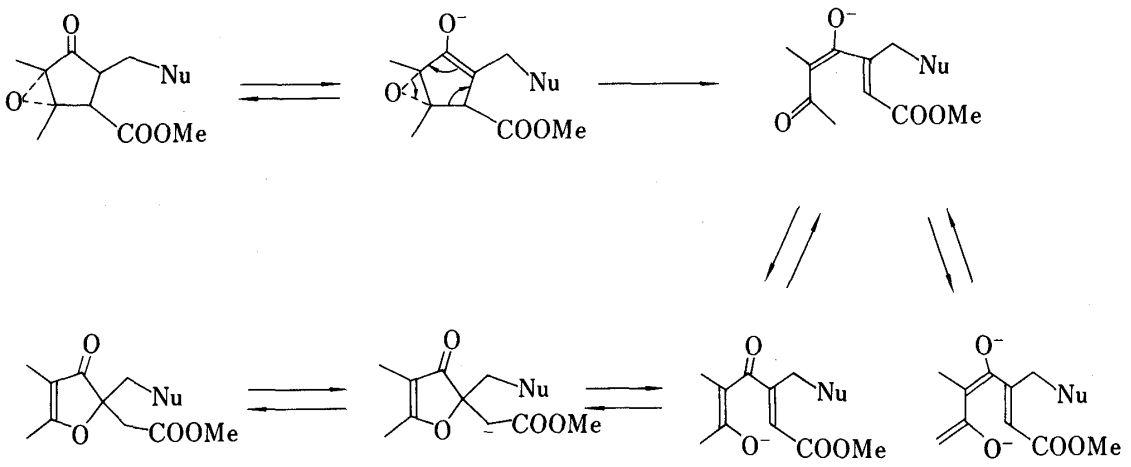


Chart 4

Experimental

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken on a JASCO IRA-2 spectrometer, ^{1}H-NMR spectra on a Varian T-60 (all chemical shifts are given in ppm downfield from tetramethylsilane), and MS on a JEOL OISG. Optical rotations were measured in $CHCl_3$ with a Perkin–Elmer model 141 polarimeter. For column chromatography, Kanto Chemical silica gel (60—100 mesh) was used. Thin layer chromatography (TLC) was performed on Silica gel 60 F_{254} plates (Merck).

Methyl 2,4,5-Trimethyl-3-oxo-2,3-dihydrofuran-2-yl-acetate (2a)——Anhydrous K_2CO_3 (185 mg) was added to a stirred solution of dihydromethylenomycin A methyl ester (**1a**) (1.85 g) in MeOH (56 ml) under ice water cooling. After 0.5 h, the reaction mixture was poured into ice water (200 ml) satd. with NaCl, and extracted with AcOEt (100 ml × 3). The combined extract was washed with H_2O satd. with NaCl (150 ml × 2), and dried (Na_2SO_4). The solvent was evaporated off *in vacuo* to afford an oily residue (1.78 g) which was subjected to column chromatography on silica gel (35 g). The fraction eluted with 10—30% AcOEt in hexane (v/v) was collected. The solvent was evaporated off *in vacuo* to afford optically inactive **2a** (1.64 g, 88.9%) as a colorless oil. IR (neat): 1740, 1695, 1630 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 270 (9000). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, s, C_2–Me), 1.70 (3H, s, C_4–Me), 2.17 (3H, s, C_5–Me), 2.74 (2H, s, C_2–CH_2–COO), 3.65 (3H, s, COOMe). MS *m/e*: 198 (M^+), 167, 125. *Anal.* Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.69; H, 7.06.

Methyl 2-Cyanomethyl-4,5-dimethyl-3-oxo-2,3-dihydrofuran-2-yl-acetate (2b)——Anhydrous K_2CO_3 (100 mg) was added to a stirred solution of β-cyano-dihydromethylenomycin A methyl ester (**1b**) (1.60 g) in MeOH (50 ml) under ice water cooling. Stirring was continued for 0.5 h at the same temperature, and then for 0.5 h at room temperature. The reaction mixture was poured into ice water (250 ml), and extracted with AcOEt (150 ml × 3). The combined extract was washed with H_2O satd. with NaCl, and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave an oily residue (1.60 g), which was chromatographed on Al_2O_3 (GIII, 60 g) using AcOEt–hexane. The fraction eluted with 20—30% AcOEt in hexane (v/v) was collected. Removal of the solvent *in vacuo* afforded optically inactive **2b** (970 mg, 60%) as a colorless oil. IR (neat): 1740, 1710, 1634, 1195 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, s, C_4–Me), 2.26 (3H, s, C_5–Me), 2.68 (1H, d, J = 16 Hz, –CH–CN), 2.82 (2H, s, C_2–CH_2–COO), 3.16 (1H, d, J = 16 Hz, –CH–CN), 3.68 (3H, s, COOMe). MS *m/e*: 233 (M^+), 192, 183, 150. *Anal.* Calcd for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.31; H, 5.71; N, 6.41.

General Procedure for the Synthesis of IIa—e (Table I)——A nucleophilic reagent (6 mmol) was added at room temperature to a stirred solution of methylenomycin A methyl ester (I) (5 mmol) in MeOH (60 ml). The mixture was stirred for 0.5 h, and then anhydrous K_2CO_3 (300 mg) was added. After further stirring for 0.5 h, the reaction mixture was poured into ice water (250 ml) satd. with NaCl, and extracted with AcOEt (150 ml × 3). The combined extract was washed with H_2O satd. with NaCl, and dried (Na_2SO_4). The solvent was evaporated off *in vacuo*. The oily residue was subjected to column chromatography on silica gel (residue (g) × 15). The fraction eluted with 10—40% AcOEt in hexane (v/v) was collected. Removal of the solvent afforded II as a colorless oil.

Methyl 4,5-Dimethyl-3-oxo-2-(4′-phenylpiperidinomethyl)-2,3-dihydrofuran-2-yl-acetate (IIa)——IR (neat): 1743, 1700, 1634, 1200, 990 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, s, C_4–Me), 2.18 (3H, s, C_5–Me), 3.63 (3H, s, COOMe), 7.23 (5H, br, phenyl). MS *m/e*: 357 (M^+), 326, 174. *Anal.* Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.73; H, 7.51; N, 4.15.

Methyl 4,5-Dimethyl-3-oxo-2-(*N*-phenylpiperadinylmethyl)-2,3-dihydrofuran-2-yl-acetate (IIb)——IR (neat): 1743, 1700, 1630, 1600, 1230, 1090 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, s, C_4–Me), 3.63 (3H, s, COOMe). MS *m/e*:

358 (M^+), 327, 175. *Anal.* Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.29; H, 7.19; N, 7.99.

Methyl 4,5-Dimethyl-2-(1′-imidazolylmethyl)-3-oxo-2,3-dihydrofuran-2-yl-acetate (IIc)——IR (neat): 3110, 1740, 1700, 1630, 1435, 1230, 1210, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, s, C_4–Me), 2.07 (3H, s, C_5–Me), 2.85 (2H, s, C_2–CH_2–COO), 3.68 (3H, s, COOMe), 4.20 (1H, d, J=14 Hz, –CH–N), 4.55 (1H, d, J=14 Hz, –CH–N), 6.63 (1H, br), 6.96 (1H, br), 7.38 (1H, br). MS *m/e*: 264 (M^+), 233, 205. *Anal.* Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.33; H, 6.21; N, 10.82.

Methyl 2-(Benzylthiomethyl)-4,5-dimethyl-3-oxo-2,3-dihydrofuran-2-yl-acetate (IId)——IR (neat): 1740, 1700, 1630, 1200, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, s, C_4–Me), 2.20 (3H, s, C_5–Me), 2.83 (4H, m, –S–CH_2–C–CH_2–COO), 3.62 (3H, s, COOMe), 3.72 (2H, s, –S–CH_2-phenyl), 7.30 (5H, s, phenyl). MS *m/e*: 320 (M^+), 289, 197, 91. *Anal.* Calcd for $C_{17}H_{20}O_4S$: C, 63.73; H, 6.29. Found: C, 63.49; H, 6.39.

Methyl 4,5-Dimethyl-2-(6-methoxycarbonyl-2-thia-hexyl)-3-oxo-2,3-dihydrofuran-2-yl-acetate (IIe)——IR (neat): 1740, 1700, 1633, 1200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, s, C_4–Me), 2.20 (3H, s, C_5–Me), 3.63, 3.65 (3H×2, s, COOMe). MS *m/e*: 344 (M^+), 313, 228, 197. *Anal.* Calcd for $C_{16}H_{24}O_6S$: C, 55.80; H, 7.02. Found: C, 56.06; H, 7.12.

(*E*)-3-Methoxycarbonyl-2-methylacrylic Acid (4)——Triethylamine (26 ml) and Me_3SiCl (19 ml) were added successively to a stirred solution of pyruvic acid (**3**) (10 g) in anhydrous tetrahydrofuran (THF, 100 ml) under ice-water cooling. After 1 h, carbomethoxymethylenetriphenylphosphorane (57 g) was added at room temperature, and then the mixture was stirred at 50 °C for 3 h. The reaction mixture was decomposed by adding 7% HCl (120 ml), diluted with ice water (600 ml) satd. with NaCl, and extracted with AcOEt (200 ml×3). The acidic fraction in the extract was extracted with 5% Na_2CO_3 (100 ml×2). The alkaline solution was again made acidic with 5% HCl, and extracted with AcOEt (100 ml×3). The combined extract was washed with H_2O satd. with NaCl (50 ml×2), and dried (Na_2SO_4). The solvent was removed *in vacuo*. The oily residue (5.10 g) was subjected to column chromatography on silica gel (100 g), and the fraction eluted with 10—30% AcOEt in hexane (v/v) afforded **4** (2.62 g, 16%) as crystals, mp 53 °C (ref. 3, mp 52 °C). IR (Nujol): 1730, 1700, 1650, 1290 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s, vinyl Me), 3.80 (3H, s, COOMe), 6.90 (1H, s, olefinic H), 11.20 (1H, s, COOH).

Methyl (*E*)-3-Chloroformyl-3-methylacrylate (5)——The half ester (**4**) (1.3 g) in $SOCl_2$ (3 ml) was refluxed for 1 h. The excess $SOCl_2$ was removed *in vacuo* to afford **5** (1.36 g, 92.8%) as a colorless oil. IR (neat): 1760, 1730, 1640, 1220, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s, vinyl Me), 3.80 (3H, s, COOMe), 7.00 (1H, s, olefinic H).

Dimethyl (*E*)-2,4-Dimethyl-3,5-dioxo-1-hexene-1,4-dicarboxylate (6)——Methyl 2-methyl-acetoacetate (1.43 g) was added dropwise to a stirred solution of Na metal (230 mg, granules) in anhydrous ether (6.4 ml) under ice water cooling. The mixture was stirred for 20 h at room temperature, then **5** (1.36 g) was added dropwise with stirring under ice warer cooling, and the whole was stirred for 2 h at room temperature. The reaction mixture was poured into ice water (30 ml), made acidic with 7% HCl, and then extracted with AcOEt (50 ml×3). The combined extract was washed with H_2O satd. with NaCl, dried (Na_2SO_4), and concentrated *in vacuo* to afford an oily residue (1.97 g), which was subjected to column chromatography on silica gel (30 g). The fraction eluted with 5—20% AcOEt in hexane (v/v) was collected, and the solvent was evaporated off *in vacuo*, yielding **6** (322 mg, 32%) as a colorless oil. IR (neat): 1730 (br), 1640, 1250, 1042 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, s, +Me), 2.30 (3H, d, J=1 Hz, vinyl Me), 2.40 (3H, s, COMe), 3.81 (3H, s, COOMe), 3.85 (3H, s, COOMe), 6.22 (1H, q, J=1 Hz, olefinic H). MS *m/e*: 197 (M^+ −COOMe), 183. *Anal.* Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.49; H, 6.34.

2a from **6**: The diketo ester (**6**) (800 mg) was heated at 130—140 °C in a mixed solvent of diethylene glycol dimethyl ether (7 ml) and AcOH (0.7 ml) in the presence of NaI (740 mg). After 2 h, the reaction mixture was poured into ice water (70 ml), and extracted with AcOEt (100 ml×3). The combined extract was washed with 2% $Na_2S_2O_3$ (20 ml×2), H_2O satd. with NaCl (50 ml×2), and dried (Na_2SO_4). The solvent was evaporated off *in vacuo*. The oily residue (728 mg) was subjected to column chromatography on silica gel (22 g). The fraction eluted with 10—30% AcOEt in hexane (v/v) was collected. The solvent was evaporated off *in vacuo* to yield **2a** (162 mg, 26%).

3,5-Dimethyl-4,6-dioxo-2-hepten-1-ol (8)——3β-Acetoxymethyl-4α,5α-epoxy-2,4β,5β-trimethyl-1-cyclopentanone (**7**) (580 mg) in MeOH (20 ml) was stirred for 1.5 h under ice water cooling in the presence of anhydrous K_2CO_3 (380 mg). The reaction mixture was poured into H_2O (100 ml) satd. with NaCl, and extracted with AcOEt (100 ml×3). The combined extract was washed with H_2O satd. with NaCl (100 ml×2), and dried (Na_2SO_4). The solvent was evaporated off *in vacuo*. The oily residue (305 mg) was purified by preparative TLC (50% AcOEt in hexane, v/v), and **8** (173 mg) was obtained as a colorless oil. IR (neat): 3420, 1720, 1660, 1360, 1200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, d, J=6 Hz, >CH–Me), 1.80 (3H, br, vinyl Me), 2.15 (3H, s, COMe), 4.32 (1H, q, J=6 Hz, –CH–), 4.47 (2H, d, J=7 Hz, –CH_2OH), 6.80 (1H, t, J=7 Hz, olefinic H). MS *m/e*: 170 (M^+), 152, 139, 109, 99. *Anal.* Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.71; H, 8.38.

3,5-Dimethyl-4,6-dioxo-2-heptenoic Acid (9)——Jones reagent (0.5 ml) was added dropwise to a stirred solution of **8** (100 mg) in acetone (10 ml) under ice water cooling. The mixture was stirred for 1 h, and the excess reagent was decomposed by adding isopropanol (0.5 ml). The reaction mixture was poured into ice water (50 ml) satd. with NaCl, then the mixture was extracted with AcOEt (50 ml×3), and the extract was dried (Na_2SO_4). The solvent was removed *in vacuo*. The oily residue (105 mg) was chromatographed on silica gel (5 g), and the fraction eluted with 20—50% AcOEt in hexane (v/v) afforded **9** (73 mg) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.85 (3H, s, vinyl Me), 2.15 (3H, s, COMe), 4.28 (1H, q, J=5 Hz, –CH–), 6.58 (1H, br, olefinic H).

2,4,5-Trimethyl-3-oxo-2,3-dihydrofuran-2-yl-acetic Acid (2c)——The diketo acid (**9**) (50 mg) was dissolved in 5% NaOH (5 ml) and stirred under ice-water cooling. After 1 h, the reaction mixture was made acidic by adding 7% HCl, and extracted with AcOEt (50 ml × 3). The combined extract was washed with H_2O satd. with NaCl, and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the oily residue (50 mg) was subjected to column chromatography on silica gel (5 g). The fraction eluted with 20—40% AcOEt in hexane (v/v) afforded **2c** (25 mg) as a colorless oil. IR (neat): 3100—3200, 1740, 1680, 1610, 1220, 1125 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, s, C_2–Me), 1.70 (3H, s, C_4–Me), 2.20 (3H, s, C_5–Me), 2.80 (2H, s, $-CH_2-COO$), 9.17 (1H, br, COOH). MS *m/e*: 184 (M^+), 139, 125. *Anal.* Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.88; H, 6.71.

2c from 2a by Hydrolysis——A 5% NaOH solution (10 ml) was added to a stirred solution of **2a** (500 mg) in MeOH (25 ml) at room temperature. After 2 h, the reaction mixture was poured into ice water (150 ml), and the whole was made acidic by adding 7% HCl, and extracted with AcOEt (100 ml × 3). The combined extract was washed with H_2O (100 ml × 3) satd. with NaCl, and dried (Na_2SO_4). Chromatography similar to that described for the preparation of **2c** from **9** afforded **2c** (390 mg) as a colorless oil.

Deuteriomethyl 2,4-Dimethyl-5-deuteriomethyl-3-oxo-2,3-dihydrofuran-2-yl-deuterioacetate (11)——a) **11** from **1a**: The reaction was carried out in CD_3OD instead of MeOH in a manner similar to that described for the preparation of **2a** from **1a**, and **11** (281 mg) was obtained from **1a** (300 mg). IR (neat): 1740, 1700, 1630, 1090 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, s, C_2–Me), 1.70 (3H, s, C_4–Me). The signals at 2.17 (C_5–Me), 2.74 (C_2–CH_2–COO) and 3.65 (COOMe) disappeared.

b) **11** from **2a**: In a manner similar to that described in a), **11** (105 mg) was obtained from **2a** (100 mg).

Deuteriomethyl Decanoate (10)——In a manner similar to that described in a), methyl decanoate (150 mg) afforded **10** (210 mg). ^{1}H-NMR ($CDCl_3$) δ: 2.25 (2H, t, J = 3 Hz, $-CH_2COO$), 0.90 (3H, t, J = 3 Hz, Me–). The signal at 3.70 (COOMe) disappeared.

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References and Notes

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