[Chem. Pharm. Bull. 27(10)2281—2285(1979)]

UDC 547.473.04 : 547.723.04

Heterocyclic Prostaglandins. II.[1] An Effective Synthesis of 3,7-Dioxabicyclo[3.3.0]octane-2,8-dione and Its C_1-Substituted Derivatives

Akihiko Ishida,[2a] Katsuyuki Noguchi, Shigeyoshi Saijo, Jun-ichi Himizu, and Masao Wada

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd.[2b]

(Received February 22, 1979)

New dilactones (**2a**—**j**, **3a**, and **3b**) having a 3,7-dioxabicyclo[3.3.0]octane-2,8-dione system (**1f**) have been prepared starting from diethyl 2-formyl succinate (**5**). Treatment of a 2-ethoxycarbonyl-3-hydroxymethyl-4-butanolide derivative (**9**) with acidic ethanol gave 3,7-dioxabicyclo[3.3.0]octane-2,8-dione (**2a**). Alkylation of **2a** with various alkyl halides gave C_1-substituted-3,7-dioxabicyclo[3.3.0]octane-2,8-diones (**2b**—**g**) in moderate yields. The same compounds (**2b**—**g**) were also prepared from **9** after alkylation followed by acid treatment. 1-(6-Methoxycarbonyl-2-hexynyl)-3,7-dioxabicyclo[3.3.0]octane-2,8-dione (**2h**) and the 1-(6-cyano-2-hexynyl) analog (**2i**) were also prepared from **9**. Partial hydrogenation of the acetylenic derivatives (**2h** and **2i**) gave the corresponding *cis*-olefinic compounds (**3a** and **3b**), which are potential synthetic intermediates for 10-oxa-11-deoxy-prostaglandin E_2 (**4**).

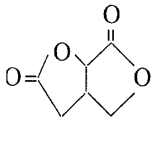
Keywords——3,7-dioxabicyclo[3.3.0]octane-2,8-dione; perhydrofurofuran; *cis*-fused dilactone; alkylation; precursor of 10-oxaprostanoid

Cis-fused dilactones carrying a perhydrofurofuran system have recently attracted considerable attention from both a synthetic and a biological point of view, and many synthetic approaches to their derivatives, such as canadensolide and avenaciolide, have been reported in the literature.[3-7] Of the six possible dilactones with a dioxabicyclo[3.3.0]octane-dione ring system (**1a**—**f**) depicted in Chart 1, no dilactone with the system **1f** has yet been prepared. In connection with our previous work on the heterocyclic prostaglandins,[1] we required a variety of C_1-substituted derivatives with the ring system **1f**. In this report, we describe an efficient general route for the preparation of these hitherto unknown compounds (**2a**—**i**), and also for the transformation of the acetylenic derivatives **2h**, **i** to the corresponding

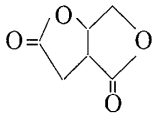
1) Part I: A. Ishida, S. Saijo, K. Noguchi, M. Wada, O. Takaiti, and J. Himizu, *Chem. Pharm. Bull.* (Tokyo), **27**, 625 (1979).
2) *a*) To whom correspondence should be addressed; *b*) Location: *2-2-50, Kawagishi, Toda, Saitama 335, Japan.*
3) *a*) H. Ohrui and S. Emoto, *Tetrahedron Lett.*, **1975**, 3657; *b*) R.C. Anderson and B. Fraser-Reid, *J. Am. Chem. Soc.*, **97**, 3870 (1975); *c*) K. Yamada, M. Kato, M. Iyoda, and Y. Hirata, *J. Chem. Soc. Chem. Commun.*, **1973**, 499; *d*) R.E. Damon and R.H. Schlessinger, *Tetrahedron Lett.*, **1975**, 4551.
4) *a*) T. Mukaiyama, K. Hagio, H. Takei, and K. Saigo, *Bull. Chem. Soc. Jpn.*, **44**, 161 (1971); *b*) M. Kato, M. Kageyama, R. Tanaka, K. Kuwahara, and A. Yoshikoshi, *J. Org. Chem.*, **40**, 1932 (1975); *c*) H. Kosugi, S. Sekiguchi, R. Sekita, and H. Uda, *Bull. Chem. Soc. Jpn.*, **49**, 520 (1976); *d*) W.L. Parker and F. Johnson, *J. Org. Chem.*, **38**, 2489 (1973); *e*) J.L. Herrmann, M.H. Berger, and R.H. Schlessinger, *J. Am. Chem. Soc.*, **95**, 7923 (1973).
5) A. Svendsen and P.M. Boll, *J. Org. Chem.*, **40**, 1927 (1975).
6) *a*) R.B. Woodward, *Pure Appl. Chem.*, **17**, 519 (1968); *b*) K. Hartke, H. Roeber, and R. Matush, *Chem. Ber.*, **108**, 3256 (1975); *c*) H.G. Walraven and U.K. Pandit, *Tetrahedron Lett.*, **1975**, 4507.
7) *a*) S. Tobinaga and E. Kotani, *J. Am. Chem. Soc.*, **94**, 310 (1972); *b*) R. Ahmed, M. Lehrer, and R. Stevenson, *Tetrahedron*, **29**, 3753 (1973); *c*) F. Toda and E. Toda, *Bull. Chem. Soc. Jpn.*, **48**, 583 (1975); *d*) Y. Kumada, H. Naganawa, T. Takeuchi, H. Umezawa, K. Yamashita, and K. Watanabe, *J. Antibiot.* (Tokyo), **31**, 105 (1978); *e*) E.C. Taylor, J.G. Androde, G.J.H. Rall, and A. Mckillop, *Tetrahedron Lett.*, **1978**, 3623.

olefinic compounds **3a**, **b**, which are potentially useful precursors of 10-oxa-11-deoxyprostaglandin E_2 (10-oxa-11-deoxyPGE_2) (**4**).

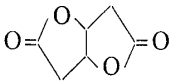
The starting material, 2-formyl succinate (**5**), was prepared according to the procedure of Yosioka.[8] Reduction of **5** with an equimolar amount of sodium borohydride in ethanol gave 3-hydroxymethyl-4-butanolide (**6**) in 70—83% yield as an oil containing a small amount of inorganic substances that could not be removed by repeated distillation. For characterization, it was converted into the acetate (**7**) by treatment with acetic anhydride in pyridine. Distillation gave a pure sample of **7**, and the structure was confirmed by the results of infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy. The hydroxyl group of **6** was protected by reaction with 2,3-dihydropyran in dichloromethane containing a catalytic



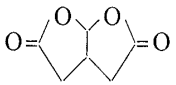
1a



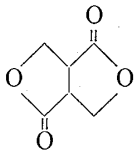
1b



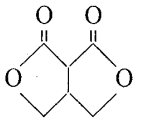
1c



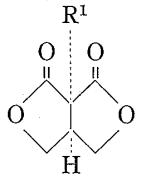
1d



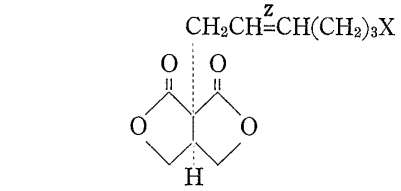
1e



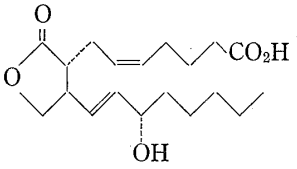
1f



2a : R^1=H
2b : R^1=CH_3
2c : R^1=$CH_2CH{=}CH_2$
2d : R^1=CH_2-C$_6$H$_5$



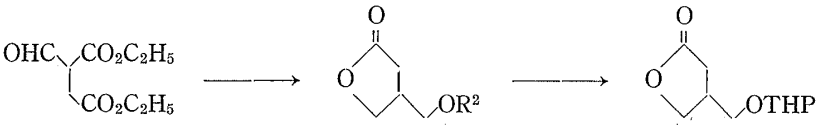
3a : X=CO_2CH_3
3b : X=CN
3c : X=CO_2H



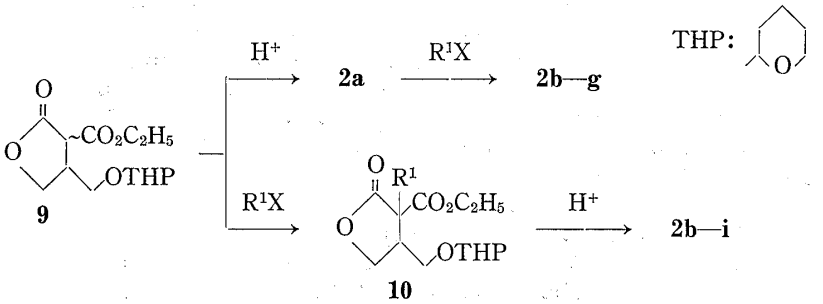
4

2e : R^1=CH_2-C$_6$H$_3$(O)(O)
2f : R^1=$CH_2CO_2C(CH_3)_3$
2g : R^1=$(CH_2)_6CO_2CH_3$
2h : R^1=$CH_2C{\equiv}C(CH_2)_3CO_2CH_3$
2i : R^1=$CH_2C{\equiv}C(CH_2)_3CN$

Chart **1**



5 **6**: R^2=H **7**: R^2=$COCH_3$ **8**



9 **10** **2a** **2b—g** **2b—i** THP:

Chart **2**

8) T. Yosioka, *Yakugaku Zasshi*, **75**, 622 (1955).

amount of *p*-toluenesulfonic acid, giving a tetrahydropyranyl ether (**8**) in 90% yield. Ethoxycarbonylation of **8** with diethyl carbonate and sodium hydride proceeded smoothly in refluxing benzene to give an oily lactone ester (**9**) in 96% yield. Removal of the protecting group was accomplished by refluxing in ethanol containing *p*-toluenesulfonic acid, and spontaneous cyclization afforded the desired dilactone (**2a**) as crystals in 60% yield.

Alkylation of **2a** with various alkyl halides and sodium hydride was carried out in *N*,*N*-dimethylformamide (DMF) at 50° to give the corresponding C_1-alkylated dilactones (**2b**—**g**). The same compounds (**2b**—**g**) were also conveniently prepared by the alternative route outlined in Chart 2, which involved alkylation of **9** followed by treatment with acidic ethanol. The results obtained from both routes are summarized in the table; the latter route is preferable in terms of overall yield from **9**.

The *cis*-olefinic compound (**3a**) was prepared by the route **9**→**2h**→**3a**.[9,10] The reaction of **9** and methyl 7-bromo-5-heptynoate,[13] based on our general procedure, was carried out in 1,2-dimethoxyethane (DME), and subsequent treatment with acidic ethanol afforded 1-(6-methoxycarbonyl-2-hexynyl)-3,7-dioxabicyclo[3.3.0]octane-2,8-dione (**2h**) as an oil in 50% yield from **9**. Hydrogenation of **2h** over 5% Pd-$BaSO_4$ poisoned with quinoline[14] gave the desired dilactone (**3a**) as a single crystalline product in 94% yield. We also prepared 1-(6-cyano-2-hexynyl)-3,7-dioxabicyclo[3.3.0]octane-2,8-dione (**2i**) in 53% yield from **9** and 7-bromo-5-heptynonitrile in a similar manner. Partial hydrogenation of **2i** under the conditions described for the preparation of **3a** gave the nitrile dilactone **3b** in 95% yield as a single product. These compounds, **3a** and **3b**, might also be useful as synthetic intermediates to 10-oxa-11-deoxy PGE_2.

Further studies on the nucleophilic ring-opening of the dilactones (**2**) and on the elaboration of these compounds to 10-oxaprostanoids are in progress.

Table I. 3,7-Dioxabicyclo[3.3.0]octane-2,8-dione and Its C_1-Substituted Derivatives

Compound No.	Yield(%)[a] A	Yield(%)[a] B	Formula	mp (°C)	Recrystn. solvent	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2a	—	—	$C_6H_6O_4$	180—181	EtOH	50.71	4.26		50.74	4.34	
2b	37	43	$C_7H_8O_4$	146—147	AcOEt	53.84	5.16		53.90	5.23	
2c	43	77	$C_9H_{10}O_4$	112—113	AcOEt	59.33	5.53		59.34	5.54	
2d	42	54	$C_{13}H_{12}O_4$	200—201	AcOEt	67.23	5.21		66.93	5.06	
2e	42	50	$C_{14}H_{12}O_6$	175—176	MeOH	60.87	4.38		60.86	4.47	
2f	45	—	$C_{12}H_{16}O_6$	173—174	C_6H_6–hexane	56.24	6.29		56.19	6.38	
2g	39	41	$C_{14}H_{20}O_6$	78— 79	C_6H_6–hexane	59.14	7.09		59.04	7.16	
2h	—	50	$C_{14}H_{16}O_6$	*b*)	—	59.99	5.75		59.76	5.61	
2i	—	53	$C_{13}H_{13}NO_4$	112—113	MeOH	63.15	5.30	5.67	63.33	5.29	5.81

a) A: Yield from **9** *via* **2a**. B: Yield from **9** *via* **10**.
b) Oil.

9) The use of methyl (5Z)-7-bromo-5-heptenoate[11] as an alkylating agent might provide a direct route to **3a**. However, the preparation of this bromide in a stereochemically pure form was tedious and the yield was low in our earlier work.
10) Attempts to react 1-(2-formylmethyl)-3,7-dioxabicyclo[3.3.0]octane-2,8-dione (**2j**) and the Wittig reagent from 5-triphenylphosphoniopentanoic acid[12] under a variety of conditions failed to furnish the *cis*-olefinic acid (**3c**). The dilactone (**2j**) was readily obtained by oxidation of **2c** (see "Experimental").
11) Roussel-UCLAF, Japan Kokai, 46-5626.
12) E.J. Corey, N.M. Weinshenker, T.K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).
13) E.J. Corey and H.S. Sachdev, *J. Am. Chem. Soc.*, **95**, 8483 (1973).
14) *a*) D.J. Cram and N.L. Allinger, *J. Am. Chem. Soc.*, **78**, 2518 (1956); *b*) U. Axen, J.L. Thompson, and J.E. Pike, *J. Chem. Soc. Chem. Commun.*, **1970**, 602.

Experimental[15]

Preparation of 6——Powdered $NaBH_4$ (3.80 g, 100 mmol) was slowly added to a solution of **5** (20.20 g, 100 mmol) in EtOH (200 ml) at 0° over a period of 30 min. The resulting solution was stirred for 4 hr at 70° and then for 15 hr at room temperature. The reaction was quenched at 0° by adding ice-water and conc. HCl (8 ml), and the EtOH was removed under reduced pressure. The residue was extracted with $CHCl_3$. The $CHCl_3$ layer was dried and evaporated down. The oily residue was distilled twice to give **6** (9.68 g, 83%), bp 128—131°/0.7 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 3400, 1760. Acetylation of **6** with acetic anhydride and pyridine gave **7** (90% yield), bp 103—105°/0.6 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1775, 1730. NMR ($CDCl_3$) δ: 4.0—4.7 (4H, m, $2\times OCH_2$), 2.4—3.1 (3H, m), 2.1 (3H, s, CH_3). *Anal.* Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.29; H, 6.31.

Preparation of 8——*p*-Toluenesulfonic acid (2 mg) was added to a mixture of **6** (15.1 g, 130 mmol) and 2,3-dihydropyran (16.8 g, 200 mmol) in CH_2Cl_2 (400 ml) at 0°. After stirring for 1 hr at 0°, the reaction mixture was washed with saturated $NaHCO_3$ and H_2O, then dried and concentrated. The crude product was distilled to give **8** (23.4 g, 90%), bp 111—114°/0.3 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1770. NMR ($CDCl_3$) δ: 4.65 (1H, br.s, $-CH\langle^{O-}_{O-}$), 4.0—4.6 (2H, quasi q, $-CO_2CH_2-$), 3.3—4.0 (4H, m, $2\times OCH_2$), 2.4—3.1 (4H, m), 1.3—2.0 (6H).

Preparation of 9——A mixture of 65% NaH (3.7 g, 100 mmol) and diethyl carbonate (47.2 g, 400 mmol) in dry C_6H_6 (100 ml) was refluxed under a nitrogen atmosphere. A solution of **8** (10.0 g, 50 mmol) in dry C_6H_6 (20 ml) was added over a period of 30 min. After refluxing for 2 hr, the reaction was quenched at 0° by adding AcOH (10 ml) and H_2O (40 ml). The C_6H_6 layer was separated, washed with brine, and dried. Removal of the C_6H_6 gave an oil (**9**) (13.0 g, 96%) which was used in the next step without further purification. IR $\nu_{max}^{liq.}$ cm^{-1}: 1770, 1725. NMR ($CDCl_3$) δ: 4.55 (1H, br.s, $-CH\langle^{O}_{O}$), 4.30 (2H, q, $OC\underline{H}_2CH_3$), 3.3—4.6 (7H, m, $3\times OCH_2$, $-CH\langle^{CO}_{CO}$), 2.5—3.0 (1H, m, CH), 1.3—2.0 (6H), 1.30 (3H, t, $-CH_2C\underline{H}_3$).

Preparation of 2a——A mixture of **9** (5.44 g, 20 mmol) and *p*-toluenesulfonic acid (354 mg, 2 mmol) in EtOH (120 ml) was refluxed for 2 hr. After removal of the solvent, the residue was taken up in AcOEt, washed with saturated $NaHCO_3$ and brine, and dried. Removal of the AcOEt gave crude **2a**, which was washed with ether to give pure **2a** (1.70 g, 60%) as crystals. IR ν_{max}^{Nujol} cm^{-1}: 1800, 1740. NMR (d_6-DMSO) δ: 3.4—4.8 (6H, m). MS *m/e*: 142 (M^+).

General Procedure for the Alkylation of 2a——A solution of **2a** (1.0 equiv.) in dry DMF was added to a suspension of NaH (1.2 equiv.) in dry DMF at room temperature under a nitrogen atmosphere. After stirring for 1 hr, alkyl halide (1.2—2.0 equiv.) was added, and the mixture was stirred for 2 hr at 50°. The DMF was removed at 50°. The residue was taken up in AcOEt, washed with dil. HCl, 5% $NaHCO_3$, and H_2O, then dried. Removal of the AcOEt gave a crude product which was washed with ether to give the pure C_1-substituted dilactone (**2b—g**) as colorless crystals. Each product was characterized by elemental analysis (see Table) and spectral data. IR, NMR, MS data are given below. **2b**: IR ν_{max}^{Nujol} cm^{-1}: 1790, 1745. NMR (d_6-DMSO) δ: 4.55 (2H, dd, $J=10$, 7 Hz, lactone C_α–H), 4.20 (2H, dd, $J=10$, 4 Hz, lactone C_β–H), 3.25—3.5 (1H, m, CH), 1.45 (3H, s, CH_3). MS *m/e*: 157 (M^++1). **2c**: IR ν_{max}^{Nujol} cm^{-1}: 1780, 1740, 1630. NMR (d_6-DMSO) δ: 5.5—5.9 (1H, m, olefinic H), 5.1—5.3 (2H, m, olefinic H), 4.45 (2H, dd, $J=10$, 7 Hz, lactone C_α–H), 4.20 (2H, dd, $J=10$, 4 Hz, lactone C_β–H), 3.2—3.6 (1H, m, CH), 2.65 (2H, d, $J=7$ Hz, $C\underline{H}_2CH=CH_2$). MS *m/e*: 183 (M^++1). **2d**: IR ν_{max}^{Nujol} cm^{-1}: 1780, 1740, 1600. NMR (d_6-DMSO) δ: 7.25 (5H, s, aromatic H), 3.9—4.2 (4H, m, lactone CH_2), 3.4—3.6 (1H, m, CH), 3.20 (2H, s, CH_2). MS *m/e*: 232 (M^+). **2e**: IR ν_{max}^{Nujol} cm^{-1}: 1770, 1740, 1600. NMR (d_6-DMSO) δ: 6.6—6.85 (3H, m, aromatic H), 5.95 (2H, s, $CH_2\langle^{O-}_{O-}$), 3.95—4.15 (4H, m, lactone CH_2), 3.35—3.6 (1H, m, CH), 3.10 (2H, s, CH_2). MS *m/e*: 276 (M^+). **2f**: IR ν_{max}^{Nujol} cm^{-1}: 1790, 1740, 1720. NMR (d_6-DMSO) δ: 4.60 (2H, dd, $J=10$, 7 Hz, lactone C_α–H), 4.30 (2H, dd, $J=10$, 4 Hz, lactone C_β–H), 3.2—3.7 (1H, m, CH), 3.00 (2H, s, CH_2), 1.40 (9H, s, $C(CH_3)_3$). **2g**: IR ν_{max}^{Nujol} cm^{-1}: 1790, 1740. NMR ($CDCl_3$) δ: 4.60 (2H, dd, $J=10$, 7 Hz, lactone C_α–H), 4.20 (2H, dd, $J=10$, 4 Hz, lactone C_β–H), 3.65 (3H, s, OCH_3), 3.1—3.7 (1H, m, CH), 2.3 (2H, br.t, CH_2CO), 1.0—2.5 (10H, m). MS *m/e*: 284 (M^+).

General Procedure for Preparation of the Dilactone (2b—i) from 9 *via* 10——Alkyl halide (1.2—2.0 equiv.) was added to a stirred suspension of the sodio derivative of **9** (prepared from 1.0 equiv. of **9** and 1.2 equiv. of NaH) in an appropriate solvent (C_6H_6, DME, or DMF) at 0—10° under a nitrogen atmosphere. After 48 hr at room temperature, AcOEt (excess) and AcOH (1.2 equiv.) were added to the reaction mixture. The organic layer was washed with H_2O, and dried. Removal of the solvent gave **10** as an oil. This oil,

15) All melting and boiling points are uncorrected. IR spectra were recorded with a Hitachi 215 spectrophotometer. NMR spectra were measured with JEOL JNM-PMX60 and JNM-PS-100 NMR spectrometers using tetramethylsilane as an internal standard. Abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. Mass spectra measurements were performed with a Hitachi RMS-4 mass spectrometer.

without purification, was dissolved in EtOH containing *p*-toluenesulfonic acid (0.1 equiv.) and heated under reflux for 1 hr. The EtOH was evaporated off, and the residue was taken up in AcOEt, washed with 5% $NaHCO_3$ and H_2O, then dried. Removal of the AcOEt gave crude crystals which were washed with ether to give pure C_1-substituted dilactone (**2b—g**) as colorless crystals. The melting points and the spectral data for **2b—g** derived from **9** were identical with those of the samples obtained by alkylation of **2a**. In the case of the preparation of **2h** and **2i**, the crude product obtained by acid treatment of **10**, was chromatographed on silica gel. Elution with hexane–AcOEt (**1**: 2) gave the dilactone in pure form. **2h**: oil: IR $\nu_{max}^{liq.}$ cm^{-1}: 1790, 1740. NMR ($CDCl_3$) δ: 4.65 (2H, dd, $J=10$, 7 Hz, lactone C_α–H), 4.20 (2H, dd, $J=10$, 4 Hz, lactone C_β–H), 3.5—4.0 (1H, m, CH), 3.65 (3H, s, OCH_3), 2.85 (2H, quasi q, $CH_2C{\equiv}C$), 2.1—2.6 (4H, m), 1.80 (2H, quasi q, CH_2). **2i**: IR ν_{max}^{Nujol} cm^{-1}: 2260, 1780, 1740. NMR ($CDCl_3$) δ: 4.65 (2H, dd, $J=10$, 7 Hz, lactone C_α–H), 4.25 (2H, dd, $J=10$, 4 Hz, lactone C_β–H), 3.3—3.85 (1H, m, CH), 2.9 (2H, quasi t, $CH_2C{\equiv}C$), 2.1—2.6 (4H, m), 1.80 (2H, quasi q, CH_2).

Preparation of 3a and 3b——A solution of **2h** (916 mg, 3.25 mmol) in MeOH (40 ml) was hydrogenated in the presence of 5% Pd-$BaSO_4$ (110 mg) and quinoline (110 mg) at room temperature for 1 hr under atmospheric pressure of hydrogen. After removal of the catalyst, the filtrate was concentrated. The residue was taken up in AcOEt, washed with dil. HCl and H_2O, and dried. Removal of the AcOEt gave 865 mg (94%) of **3a**, mp 82—85°. IR ν_{max}^{Nujol} cm^{-1}: 1780, 1730. NMR ($CDCl_3$) δ: 5.5—5.8 (1H, m, olefinic H), 5.15—5.5 (1H, m, olefinic H), 4.55 (2H, dd, $J=10$, 7 Hz, lactone C_α–H), 4.20 (2H, dd, $J=10$, 4 Hz, lactone C_β–H), 3.70 (3H, s, OCH_3), 3.25—3.60 (1H, m, CH), 2.80 (2H, d, $C\underline{H}_2CH{=}CH$), 2.35 (2H, t, CH_2CO_2), 2.15 (2H, quasi q, $CH{=}CHC\underline{H}_2CH_2$), 1.75 (2H, quasi q, CH_2). An analytically pure sample, mp 89—90°, was obtained by recrystallization from AcOEt–ether. *Anal.* Calcd. for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.60; H, 6.38.

Similarly, partial hydrogenation of **2i** (2.20 g, 8.9 mmol) with 5% Pd-$BaSO_4$ (230 mg) and quinoline (230 mg) in MeOH (180 ml) gave 2.10 g (95%) of **3b**, mp 83—86°. IR ν_{max}^{Nujol} cm^{-1}: 2260, 1780, 1740. NMR ($CDCl_3$) δ: 5.5—5.9 (1H, m, olefinic H), 5.2—5.5 (1H, m, olefinic H), 4.55 (2H, dd, $J=10$, 7 Hz, lactone C_α–H), 4.15 (2H, dd, $J=10$, 4 Hz, lactone C_β–H), 3.2—3.6 (1H, m, CH), 2.75 (2H, quasi d, $C\underline{H}_2CH{=}CH$), 2.1—2.6 (4H, m), 1.75 (2H, quasi q, CH_2). An analytically pure sample, mp 88—89°, was obtained by recrystallization from MeOH. *Anal.* Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.45; H, 6.18; N, 5.53.

Preparation of 2j——Osmium tetroxide (143 mg) and sodium metaperiodate (3.21 g, 15 mmol) were added to a solution of **2c** (910 mg, 5 mmol) in dioxane (19 ml) and H_2O (6.3 ml) at 25°. After stirring for 2 hr at 25°, acetone (50 ml) was added to the reaction mixture and insoluble materials were removed by filtration. The filtrate was dried over $MgSO_4$ and concentrated at 25°. Recrystallization of the residue from acetone gave **2j** (616 mg, 67%), mp 180—183°. IR ν_{max}^{Nujol} cm^{-1}: 1780, 1730, 1710. NMR (d_6-DMSO) δ: 9.60 (1H, s, CHO), 4.70 (2H, dd, $J=10$, 7 Hz, lactone C_α–H), 4.25 (2H, dd, $J=10$, 4 Hz, lactone C_β–H), 3.2—3.6 (1H, m, CH), 3.4 (2H, s, $C\underline{H}_2CHO$). An analytically pure sample, mp 184—185°, was obtained by further recrystallization from acetone. *Anal.* Calcd. for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 51.89; H, 4.50.

Acknowledgement The authors are greatly indebted to Professor Emeritus S. Sugasawa (University of Tokyo), Dr. S. Saito (Director of this laboratory), and Dr. T. Oh-ishi for helpful discussions.