Chem. Pharm. Bull.
28(3) 783—788 (1980)

Heterocyclic Prostaglandins. III.[1] Synthesis of 10-Oxa-11-deoxyprostaglandin E_2

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(Received August 11, 1979)

The decarboxylation of various 1-substituted-3,7-dioxabicyclo[3.3.0]octane-2,8-diones (**2b**—**j**) was investigated. On treatment with potassium acetate in aqueous pyridine under reflux, all the compounds (**2b**—**j**) examined were decarboxylated in high yields to give the corresponding *trans*-3-hydroxymethyl-4-butanolides (**3b**—**j**).

The synthesis of 10-oxa-11-deoxyprostaglandin E_2 (**1a**) from the compounds **3i** and **3j** is also described. The Moffatt oxidation of **3i** and the Wittig reaction of the resulting aldehyde (**6a**) with dimethyl 2-oxoheptylphosphonate gave an enone (**7a**), which was converted into 10-oxa-11-deoxyprostaglandin E_2 methyl ester (**8a**) and the C_{15}-epimer (**9a**) by $NaBH_4$ reduction. Hydrolysis and subsequent relactonization of **8a** gave **1a** in 88% yield. A similar treatment of **9a** gave **1b** in 87% yield. Using a similar sequence of reactions, **1a** and **1b** were also prepared from the nitrile analog **3j** *via* **8b** and **9b**.

Keywords——decarboxylation; *trans*-2-substituted-3-hydroxymethyl-4-butanolide; prostaglandin; heterocyclic prostaglandin; 10-oxa-11-deoxyprostaglandin E_2

In the previous paper of this series,[1b] we reported an effective route for the synthesis of 3,7-dioxabicyclo[3.3.0]octane-2,8-dione (**2a**) and its C_1-substituted derivatives (**2b**—**j**) starting from diethyl 2-formyl succinate. In this paper, we describe the conversion of these dilactones (**2b**—**j**) into *trans*-2-substituted-3-hydroxymethyl-4-butanolide (**3b**—**j**), and also the synthesis of 10-oxa-11-deoxyprostaglandin E_2 (10-oxa-11-deoxy PGE_2) (**1a**) from **3i** and **3j**.

The Conversion of 2 into 3

The decarbalkoxylation of esters by heating them in the presence of alkali halides, sodium cyanide, or other reagents has been widely employed as a versatile synthetic method.[3] The use of sodium cyanide in dimethyl sulfoxide (DMSO) is particularly favored for the decarbalkoxylation of malonic esters. In a recent communication by Sakai *et al.*,[4] dibasic sodium phosphate in aqueous dioxane was reported to be useful for the hydrolysis and spontaneous decarboxylation of a lactone moiety of 1-substituted 3-oxabicyclo[3.3.0]octane-2,8-diones.

We examined the conversion of the dilactones (**2b**—**j**) into *trans*-hydroxymethyl lactones (**3b**—**j**) by a similar method. After experiments under various conditions, it was found that the decarboxylation proceeded smoothly on refluxing the dilactones in acetic acid in the presence of potassium acetate. The products were, however, a mixture of *trans* (**4**) and *cis*-3-acetoxymethyl-4-butanolide (**5**). For example, the 1-allyl derivative (**2c**) afforded a mixture of *trans*-3-acetoxymethyl-2-(2-propenyl)-4-butanolide (**4c**) and the *cis* isomer (**5c**), which were isolated by column chromatography in 67% and 6% yields, respectively. For the characterization of both isomers, the *cis* acetate (**5c**) was converted into the *trans* acetate (**4c**). Alkaline hydrolysis of **5c** afforded 4-hydroxy-3-hydroxymethyl-2-(2-propenyl)

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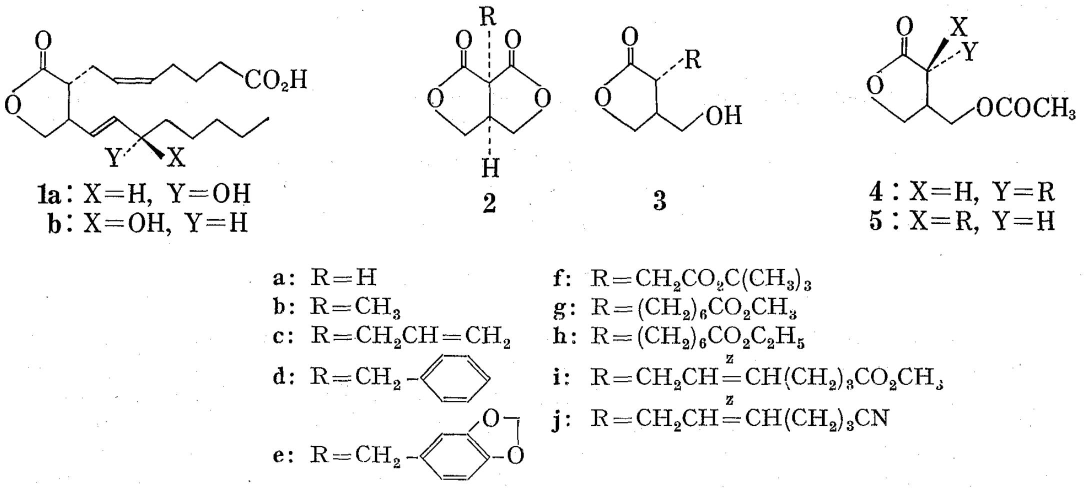

1a: $X=H$, $Y=OH$
b: $X=OH$, $Y=H$

2

3

4 : $X=H$, $Y=R$
5 : $X=R$, $Y=H$

a: $R=H$
b: $R=CH_3$
c: $R=CH_2CH=CH_2$
d: $R=CH_2-$
e: $R=CH_2-$
f: $R=CH_2CO_2C(CH_3)_3$
g: $R=(CH_2)_6CO_2CH_3$
h: $R=(CH_2)_6CO_2C_2H_5$
i: $R=CH_2CH\overset{Z}{=}CH(CH_2)_3CO_2CH_3$
j: $R=CH_2CH\overset{Z}{=}CH(CH_2)_3CN$

Chart 1

butanoic acid, which was readily lactonized to yield the *trans* alcohol (**3c**) during work-up.[5] Acetylation of **3c** gave **4c** in 83% overall yield from **5c**. 1-Benzyl dilactone (**2d**) gave an inseparable mixture of **4d** and **5d** in 86% yield on decarboxylation under the same conditions.

Expecting the exclusive formation of the *trans*-3-hydroxymethyl lactones (**3**), we further examined the reaction in other solvent systems. Better results were achieved when aqueous pyridine was used. Decarboxylation proceeded similarly in the presence of potassium acetate, and the desired *trans* isomer (**3**) was obtained as a sole product under these conditions. The reaction conditions and yields are summarized in the table. The results with **2f**—**j** were of special significance. Functional groups in the side chain, such as esters and nitriles, remained intact and the corresponding *trans*-hydroxymethyl lactones (**3f**—**j**) could be obtained in high yields. We have previously reported an alternative synthetic route to **3g** as an intermediate for 10-oxa-11-deoxy PGE_1.[1a] The present method is more convenient for the preparation of **3g** than the previous one, and consequently the total yield of 10-oxa-11-deoxy PGE_1 was considerably improved.

The Synthesis of 10-Oxa-11-deoxy PGE_2 (1a)

The success in the facile synthesis of **3i** and **3j** prompted us to attempt their conversion into 10-oxa-11-deoxy PGE_2 (**1a**). Chart 2 illustrates the five-step sequence of reactions to **1a**.

Oxidation of **3i** with dicyclohexylcarbodiimide (DCC)-DMSO[7] gave an aldehyde (**6a**) (73% yield), which was converted to an enone (**7a**) (77% yield) by the Wittig reaction with the sodio derivative of dimethyl 2-oxoheptylphosphonate[8] in 1,2-dimethoxyethane (DME). Reduction of **7a** with sodium borohydride in methanol gave a mixture of C_{15}-epimeric alcohols (**8a** and **9a**) which was separated into each isomer in 44% and 43% yields, respectively, by column chromatography. Configurational assignments of **8a** and **9a** were tentatively made by comparing their chromatographic properties as described for the 10-oxa-11-deoxy PGE_1 series.[1a] The more polar isomer was assigned as **8a** with the desired 15α-hydroxy configuration. Hydrolysis of **8a** with potassium hydroxide in aqueous methanol, followed by relactonization in refluxing benzene–ethyl acetate (1:1) gave 10-oxa-11-deoxy PGE_2 (**1a**) in 88% yield. Analogous treatments of **9a** afforded the 15β-isomer (**1b**) in 86% yield.

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5) Hauser *et al.*[6] reported that *cis*-3-hydroxymethyl-2-(5-methoxycarbonyl)pentyl-4-butanolide was easily isomerized to the *trans*-butanolide under acidic conditions, and applied this strategy to the synthesis of 10-oxa-11-deoxy PGE_1.

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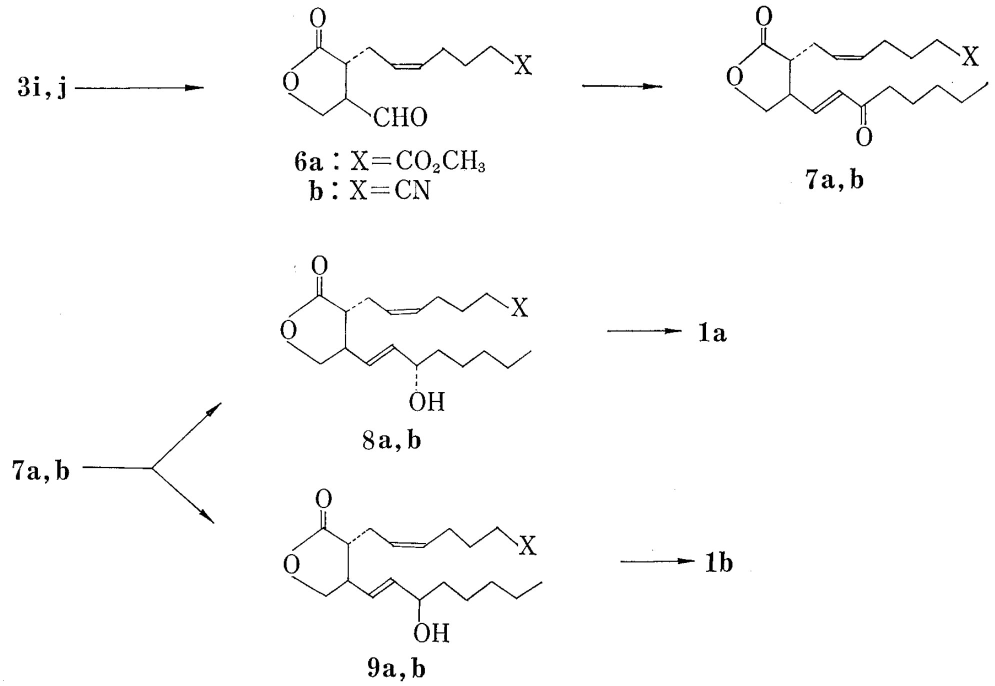

Chart 2

Starting from the nitrile derivative (**3j**), **1a** and **1b** were also prepared by similar sequences of reactions, as shown in Chart 2. The Moffatt oxidation and the Wittig reaction gave an enone (**7b**) in satisfactory yield. Reduction of **7b** with sodium borohydride gave a mixture of the 15α-alcohol (**8b**) (45% yield) and 15β-alcohol (**9b**) (44% yield). After separation by column chromatography, both isomers were hydrolyzed to the corresponding carboxylic acids and relactonization in refluxing benzene–ethyl acetate (1:1) afforded **1a** (87% yield) and **1b** (76% yield), respectively.

10-Oxa-11-deoxy PGE$_2$ derivatives, thus obtained, showed prostaglandin-like activities, as observed with the 10-oxa-11-deoxy PGE$_1$ series.[1a)] The details of pharmacological studies will be published elsewhere by another group in our laboratory.

Table. *trans*-2-Substituted-3-hydroxymethyl-4-butanolide (3)

Compound No.	Conditions refl. time (hr)	Yield of 3 (%)	Formula	*Anal.* (%) Calcd (Found) C	H	N
3b	24	87	$C_6H_{10}O_3$	55.37 (55.17	7.75 7.57)	
3c	12	92	$C_8H_{12}O_3$	61.52 (61.78	7.75 7.64)	
3d	6	93	$C_{12}H_{14}O_3$	69.88 (69.73	6.84 6.72)	
3e	6	94	$C_{13}H_{14}O_5$	62.39 (62.17	5.64 5.59)	
3f	24	95	$C_{11}H_{18}O_5$	57.38 (57.12	7.88 7.70)	
3g	24	92	$C_{13}H_{22}O_5$	60.44 (60.30	8.59 8.33)	
3h	15	88	$C_{14}H_{24}O_5$	61.74 (62.02	8.88 8.99)	
3i	15	89	$C_{13}H_{20}O_5$	60.92 (61.18	7.87 7.93)	
3j	15	95	$C_{12}H_{17}NO_3$	64.55 (64.79	7.68 7.73	6.27 6.27)

Experimental[9)]

General Procedure for Conversion of 2 into 3——A mixture of **2** (1.0 eq) and AcOK (2.0 eq) in pyridine (25- to 30-fold excess over **2**) containing H_2O (10—15 eq) was refluxed for 6—24 hr. The solvent was removed under reduced pressure. The residue was extracted with AcOEt, washed with brine and dried. Removal of the AcOEt gave a crude product which was purified by distillation to give *trans*-2-substituted-3-hydroxymethyl-4-butanolide (**3b**—**j**). Each product was characterized on the basis of spectral data and analytical data (see the table). Boiling points, IR and NMR data are given below. **3b**: bp 102—105°/0.05 mmHg. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3450, 1750. NMR ($CDCl_3$) δ: 3.95—4.60 (2H, m, lactone CH_2), 3.75 (2H, d, $C\underline{H}_2OH$), 2.1—3.2 (3H, m), 1.30 (3H, d, $J=7$ Hz, CH_3). **3c**: bp 120—123°/0.3 mmHg. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3450, 1760, 1640. NMR ($CDCl_3$) δ: 5.5—6.2 (1H, m, olefinic H), 4.9—5.35 (2H, m, olefinic H), 4.0—4.55 (2H, m, lactone CH_2), 3.5—3.85 (2H, m, $C\underline{H}_2OH$), 2.2—2.8 (5H, m). **3d**: bp 160—162°/0.1 mmHg. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3450, 1760, 1600. NMR ($CDCl_3$) δ: 7.25 (5H, s, aromatic H), 3.85—4.35 (2H, m, lactone CH_2), 3.40 (2H, d, $C\underline{H}_2OH$), 2.20—3.25 (5H, m). **3e**: bp 237—239°/0.04 mmHg. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3450, 1770, 1610. NMR ($CDCl_3$) δ: 6.70 (3H, s, aromatic H), 5.90 (2H, s, $\begin{smallmatrix}-O\diagdown\\ -O\diagup\end{smallmatrix}CH_2$), 3.9—4.4 (2H, m, lactone CH_2), 3.50 (2H, m, $C\underline{H}_2OH$), 2.1—3.2 (5H, m). **3f**: bp 140—141°/0.04 mmHg. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3450, 1770, 1730. NMR ($CDCl_3$) δ: 3.95—4.60 (2H, m, lactone CH_2), 3.75 (2H, d, $C\underline{H}_2OH$), 3.3—2.4 (5H, m), 1.45 (9H, s, $3\times CH_3$). **3g**: The spectral data and the TLC behavior of **3g** were identical with those of an authentic sample.[1a)] bp 188—190°/0.5 mmHg. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3420, 1760, 1720. NMR ($CDCl_3$) δ: 4.05—4.55 (2H, m, lactone CH_2), 3.50—3.80 (2H, br, $C\underline{H}_2OH$), 3.65 (3H, s, OCH_3), 3.15 (1H, br, OH), 2.3—2.8 (2H, br.m, $2\times CH$), 2.30 (2H, quasi t, CH_2CO), 1.1—1.9 (10H, m). **3h**: bp 210—213°/0.6 mmHg. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3420, 1770, 1720. NMR ($CDCl_3$) δ: 4.1—4.6 (2H, m, lactone CH_2), 4.10 (2H, q, $OC\underline{H}_2CH_3$), 3.70 (2H, br.d, $C\underline{H}_2OH$), 2.0—2.8 (3H, m, $2\times CH$, OH), 2.30 (2H, quasi t, CH_2CO), 1.2—2.0 (10H, m), 1.25 (3H, t, $OCH_2C\underline{H}_3$).

Decarboxylation of 2c in AcOH——A mixture of **2c** (1.82 g, 10 mmol) and AcOK (1.47 g, 15 mmol) in AcOH (15 ml) was refluxed for 48 hr. The AcOH was removed under reduced pressure. The residue was taken up in AcOEt, washed with 5% $NaHCO_3$ and H_2O, and then dried. Removal of the AcOEt gave a mixture of **4c** and **5c** (1.62 g). This was chromatographed on silica gel. Elution with hexane–AcOEt (1:2) gave 1.33 g (67%) of **4c**, bp 103—105°/0.3 mmHg. The spectral data and the TLC and GC behavior of **4c** were identical with those of the sample prepared by acetylation of **3c**. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 1770, 1730, 1630. NMR ($CDCl_3$) δ: 5.4—6.1 (1H, m, olefinic H), 4.9—5.4 (2H, m, olefinic H), 3.8—4.45 (4H, m, $2\times CH_2O$), 2.3—2.9 (4H, m), 2.05 (3H, s, $COCH_3$). *Anal.* Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.71; H, 7.04. Further elution with hexane–AcOEt (1:2) gave 120 mg (6%) of **5c**. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 1770, 1730, 1630. NMR ($CDCl_3$) δ: 5.5—6.2 (1H, m), 4.9—5.4 (2H, m), 3.8—4.5 (4H, m), 2.2—3.0 (4H, m), 2.00 (3H, s).

Similarly, a mixture of **4d** and **5d** was obtained from **2d**. Yield: 86%, bp 148—151°/0.04 mmHg. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 1775, 1740, 1600. NMR ($CDCl_3$) δ: 7.20 (5H, s), 3.8—4.35 (4H, m), 2.35—3.4 (4H, m), 2.00 (3H, s). *Anal.* Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.93; H, 6.38.

Conversion of 5c into 4c——A 20% KOH solution (0.3 ml) was added to a stirred solution of **5c** (35 mg) in MeOH (3 ml) at room temperature under a nitrogen atmosphere. After 15 hr, the reaction was quenched by addition of 10% HCl and the solvent was removed. The residue was taken up in AcOEt, washed with saturated $(NH_4)_2SO_4$ solution, and dried. Removal of the AcOEt gave 24 mg (87%) of **3c** as an oil. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3450, 1760, 1640. A solution of **3c** and Ac_2O (0.1 ml) in pyridine (0.5 ml) was stirred for 15 hr at room temperature. After usual work-up, the *trans* isomer **4c** (29 mg) was obtained in 83% overall yield from **5c**. The spectral data and the TLC and GC behavior of **4c** derived from **5c** were identical with those of the *trans* isomer (**4c**) (retention time: **5c**/**4c**$=1.14$).

Preparation of 3i and 3j——A mixture of **2i** (1.072 g, 3.8 mmol) and AcOK (745 mg, 7.6 mmol) in pyridine (30 ml) containing H_2O (0.8 ml) was refluxed for 15 hr. After usual work-up, the crude product was distilled to yield 866 mg (89%) of **3i**, bp 185—188°/0.03 mmHg. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3100—3600, 1780, 1740. NMR ($CDCl_3$) δ: 5.3—5.7 (2H, m, olefinic H), 4.3—4.5 (1H, m, lactone CH_2), 4.0—4.2 (1H, m, lactone CH_2), 3.6—3.8 (2H, br, $C\underline{H}_2OH$), 3.65 (3H, s, OCH_3), 2.4—2.8 (5H, m), 2.35 (2H, t, $C\underline{H}_2CO_2CH_3$), 1.95—2.30 (2H, quasi q, $CH{=}CH{-}C\underline{H}_2{-}CH_2$), 1.6—1.9 (2H, quasi q).

Similarly, treatment of **2j** (1.743 g, 7 mmol) with AcOK (1.37 g, 14 mmol) in pyridine (45 ml) and H_2O (1.4 ml) gave 1.484 g (95%) of **3j**, bp 220—222°/0.6 mmHg. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3100—3600, 2260, 1765. NMR ($CDCl_3$) δ: 5.5 (2H, quasi t, olefinic H), 3.9—4.5 (2H, m, lactone CH_2), 3.70 (2H, quasi d, $C\underline{H}_2OH$), 3.0 (1H, s, OH), 2.0—2.8 (8H, m), 1.4—2.0 (2H, quasi q).

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9) 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. Gas chromatographic (GC) analysis was performed with a Shimadzu GC-4B machine using a glass column packed with 10% NGS.

Preparation of 6a——DCC (2.472 g, 12 mmol) was added to a stirred solution of **3i** (1.024 g, 4 mmol) in DMSO (8 ml) and C_6H_6 (8 ml) containing pyridine (316 mg, 4 mmol) and trifluoroacetic acid (228 mg, 2 mmol) at 0°.[7] After stirring for 2 hr at room temperature, C_6H_6 (20 ml) was added followed by addition of a solution of oxalic acid (1.08 g, 12 mmol) in MeOH (3 ml) under ice-cooling. Insoluble materials were removed by filtration and washed with C_6H_6. The filtrate was washed with 5% $NaHCO_3$ and H_2O, dried and concentrated. The residue was chromatographed on silica gel (hexane: AcOEt=2: 3 as an eluent) to yield 742 mg (73%) of **6a**. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 1780, 1740, 1730. NMR ($CDCl_3$) δ: 9.65 (1H, d, CHO), 5.1—5.7 (2H, m, olefinic H), 4.1—4.55 (2H, m, lactone CH_2), 3.65 (3H, s, OCH_3), 2.8—3.4 (2H, m, CH), 2.4—2.8 (2H, m), 2.35 (2H, t, $C\underline{H}_2CO_2CH_3$), 2.1 (2H, quasi q, $CH{=}CHC\underline{H}_2$), 1.75 (2H, quasi q, CH_2). 2,4-Dinitrophenylhydrazone of **6a**: mp 137—138° (recrystallized from EtOH). *Anal.* Calcd for $C_{19}H_{22}N_4O_8$: C, 52.53; H, 5.10; N, 12.90. Found: C, 52.29; H, 5.11; N, 12.84.

Preparation of 6b——DCC (7.27 g, 35.1 mmol) was added to a stirred solution of **3j** (2.60 g, 11.7 mmol) in DMSO (18 ml) and C_6H_6 (18 ml) containing pyridine (0.94 ml) and trifluoroacetic acid (0.47 ml) at 0°. After stirring for 2 hr at room temperature, the mixture was worked up as described for the preparation of **6a**. The oily product was chromatographed on silica gel (hexane: AcOEt=1: 4 as an eluent) to give 1.91 g (74%) of **6b**. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 2260, 1770, 1720. NMR ($CDCl_3$) δ: 9.60 (1H, d, CHO), 5.3—5.6 (2H, m, olefinic H), 4.0—4.6 (2H, m), 2.75—3.5 (2H, m, CH), 2.0—2.7 (6H, m), 1.4—2.0 (2H, m). 2,4-Dinitrophenylhydrazone of **6b**: mp 120—121° (recrystallized from EtOH). *Anal.* Calcd for $C_{18}H_{19}N_5O_6$: C, 53.86; H, 4.77; N, 17.46. Found: C, 53.76; H, 4.73; N, 17.59.

Preparation of 7a——A solution of dimethyl 2-oxoheptylphosphonate[8] (666 mg, 3 mmol) in DME (5 ml) was added to a stirred suspension of 65% NaH (111 mg, 3 mmol) in DME (5 ml) at room temperature under a nitrogen atmosphere. After 1 hr, a solution of **6a** (762 mg, 3 mmol) in DME (5 ml) was added and the mixture was stirred for 2 hr. After adding AcOEt (50 ml), the mixture was washed with H_2O, and then dried. Removal of the solvent gave an oil which was chromatographed on silica gel (hexane: AcOEt=2: 1 as an eluent) to give 809 mg (77%) of **7a**. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 1780, 1740, 1680, 1640. NMR ($CDCl_3$) δ: 6.65 (1H, d,d, J=16, 8 Hz, $C\underline{H}{=}CHCO$), 6.20 (1H, d, J=16 Hz, $CH{=}C\underline{H}CO$), 5.1—5.7 (2H, m, olefinic H), 4.40 (1H, t, lactone CH_2), 4.00 (1H, t, lactone CH_2), 3.65 (3H, s, OCH_3), 3.10 (1H, quasi t, COCH), 2.4—2.7 (3H, m), 2.35 (2H, t, $C\underline{H}_2CO_2$), 2.10 (2H, quasi q, $CH{=}CHC\underline{H}_2$), 1.2—1.9 (10H, m), 0.9 (3H, t, $CH_2C\underline{H}_3$). UV $\lambda_{\max}^{\text{EtOH}}$ nm (ε): 224 (1.6×10^4). *Anal.* Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.84; H, 8.69.

Preparation of 7b——A solution of **6b** (531 mg, 2.4 mmol) in DME (5 ml) was added at room temperature under a nitrogen atmosphere to a stirred solution of the sodio derivative of dimethyl 2-oxoheptylphosphonate prepared from 65% NaH (99 mg, 2.6 mmol) and dimethyl 2-oxoheptylphosphonate (578 mg, 2.6 mmol) in DME (10 ml). After 2 hr, the reaction mixture was worked up as described for the preparation of **7a**. The oily residue was chromatographed on silica gel (hexane: AcOEt=1: 1 as an eluent) to give 548 mg (72%) of **7b**. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 2260, 1770, 1660, 1620. NMR ($CDCl_3$) δ: 6.65 (1H, d,d, J=16, 8 Hz, $C\underline{H}{=}CHCO$), 6.10 (1H, d, J=16 Hz, $CH{=}C\underline{H}CO$), 5.40 (2H, quasi t, olefinic H), 4.35 (1H, t, lactone CH_2), 3.90 (1H, t, lactone CH_2), 2.8—3.5 (2H, m, CH), 2.0—2.8 (8H, m), 1.05—2.0 (8H, m), 0.85 (3H, t, $CH_2C\underline{H}_3$), UV $\lambda_{\max}^{\text{EtOH}}$ nm (ε): 224 (1.39×10^4). *Anal.* Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.03; H, 8.79; N, 4.43.

Preparation of 8a and 9a——Powdered $NaBH_4$ (76 mg, 2 mmol) was added to a stirred solution of **7a** (701 mg, 2 mmol) in MeOH (20 ml) at −10°. After 15 min, the mixture was poured into ice-cold brine containing AcOH and extracted with AcOEt. The extract was washed with brine, dried and concentrated to give a mixture of **8a** and **9a**. This mixture was chromatographed on silica gel. Elution with hexane–AcOEt (1: 1) afforded 303 mg (43%) of **9a**. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3200—3600, 1780, 1740. NMR ($CDCl_3$) δ: 5.3—5.7 (4H, m, olefinic H), 4.35 (1H, t, lactone CH_2), 3.85 (1H, t, lactone CH_2), 3.9—4.3 (1H, br. $CHO\underline{H}$), 3.65 (3H, s, OCH_3), 2.6—3.3 (2H, br), 1.8—2.6 (7H, m), 1.1—1.8 (10H, m), 0.9 (3H, t, $CH_2C\underline{H}_3$). Further elution with hexane–AcOEt (1: 1) afforded 310 mg (44%) of **8a**. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3200—3600, 1780, 1740. NMR ($CDCl_3$) δ: 5.3—5.7 (4H, m, olefinic H), 4.35 (1H, t, lactone CH_2), 3.85 (1H, t, lactone CH_2), 3.9—4.3 (1H, br, $C\underline{H}OH$), 3.65 (3H, s, OCH_3), 2.6—3.3 (2H, br), 1.85—2.55 (7H, m), 1.1—1.8 (10H, m), 0.9 (3H, t). *Anal.* Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.40; H, 9.12.

Preparation of 8b and 9b——Powdered $NaBH_4$ (95 mg, 2.5 mmol) was added to a solution of **7b** (785 mg, 2.5 mmol) in MeOH (20 ml) at −10°. After 15 min, the reaction mixture was worked up as described for the preparation of **8a** and **9a**. The epimeric mixture was chromatographed on silica gel. Elution with hexane–AcOEt (1: 1) afforded 355 mg (44%) of **9b**. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3200—3600, 2250, 1770. NMR ($CDCl_3$) δ: 5.3—5.7 (4H, m, olefinic H), 4.30 (1H, t, lactone CH_2), 3.9—4.2 (1H, br, $C\underline{H}OH$), 3.85 (1H, t, lactone CH_2), 2.6—3.2 (2H, m), 2.0—2.6 (7H, m), 1.1—2.0 (10H, m), 0.85 (3H, t, $CHC\underline{H}_3$). Further elution with hexane–AcOEt (1: 1) afforded 362 mg (45%) of **8b**. IR $\nu_{\max}^{\text{Liq.}}$ cm^{-1}: 3200—3600, 2250, 1770. NMR ($CDCl_3$) δ: 5.3—5.7 (4H, m, olefinic H), 4.30 (1H, t, lactone CH_2), 3.9—4.2 (1H, br, $C\underline{H}OH$), 3.80 (1H, t, lactone CH_2), 2.6—3.2 (2H, m), 2.0—2.6 (7H, m), 1.1—2.0 (10H, m), 0.85 (3H, t). *Anal.* Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.39. Found: C, 71.24; H, 9.00; N, 4.45.

Preparation of 1a——i) From **8a**: A 20% KOH solution (1.2 ml) was added to a stirred solution of **8a** (282 mg, 0.8 mmol) in MeOH (12 ml) at 0° under a nitrogen atmosphere. The mixture was allowed to stand overnight at room temperature and the MeOH was removed under reduced pressure. The aqueous layer was acidified with dil. HCl and extracted with AcOEt. The extract was washed with brine, dried and concentrated. The oily residue was dissolved in AcOEt–C_6H_6 (1: 1) (20 ml), and refluxed for 1 hr under a nitrogen atmosphere. Removal of the solvent gave 237 mg (88%) of **1a**. IR $\nu_{max}^{Liq.}$ cm^{-1}: 3200—3600, 2400—2800, 1760, 1700. NMR ($CDCl_3$) δ: 6.35 (2H, br.s, CO_2H, OH), 5.3—5.8 (4H, m, olefinic H), 4.35 (1H, t, lactone CH_2), 3.85 (1H, t, lactone CH_2), 3.95—4.3 (1H, br, C$\underline{H}$OH), 2.7—3.3 (2H, m), 2.0—2.7 (6H, m), 1.1—2.0 (10H, m), 0.9 (3H, t). *Anal.* Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.14; H, 9.11.

ii) From **8b**: A solution of **8b** (638 mg, 2 mmol) and KOH (560 mg, 10 mmol) in EtOH–H_2O (3: 1) (30 ml) was heated at 80° for 72 hr under a nitrogen atmosphere. After usual work-up, the hydrolysis product was obtained as an oil. Relactonization of this oil by refluxing in AcOEt–C_6H_6 (1: 1) (60 ml) gave 590 mg (87%) of **1a**.

Preparation of 1b——i) From **9a**: A 20% KOH solution (0.9 ml) was added to a stirred solution of **9a** (211 mg, 0.6 mmol) in MeOH (10 ml) at 0° under a nitrogen atmosphere. After reaction for 15 hr followed by work-up as described for the preparation of **1a**, 174 mg (86%) of **1b** was obtained. IR $\nu_{max}^{Liq.}$ cm^{-1}: 3200—3600, 2400—2800, 1760, 1700. NMR ($CDCl_3$) δ: 6.35 (2H, br.s, CO_2H, OH), 5.3—5.8 (4H, m, olefinic H), 4.35 (1H, t, lactone CH_2), 3.85 (1H, t, lactone CH_2), 3.9—4.3 (1H, br, C$\underline{H}$OH), 1.9—2.6 (6H, m), 1.1—1.9 (10H, m), 0.9 (3H, t). *Anal.* Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.29; H, 8.77.

ii) From **9b**: A solution of **9b** (287 mg, 0.9 mmol) and KOH (254 mg) in EtOH–H_2O (3: 1) (20 ml) was heated at 80° for 72 hr under a nitrogen atmosphere. After work-up as described for the preparation of **1a**, 231 mg (76%) of **1b** was obtained.

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.