[Chem. Pharm. Bull. 27(3) 625—632 (1979)]

UDC 547.475.04 : 547.723.04

Synthesis of 10-Oxa-11-deoxyprostaglandin E_1

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(Received July 26, 1978)

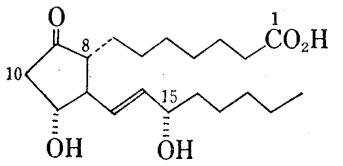
Synthesis of 10-oxa-11-deoxyprostaglandin E_1 (**2b**) and related compounds (**2a**, **17b**, and **20**) was successfully accomplished starting from nonanedioic acid (**3**). Decarboxylation of 3,3-di-*tert*-butoxycarbonyl-2-(6-methoxycarbonyl)hexyl-4-butanolide (**6**) by heating gave predominantly *trans*-3-carboxy-2-(6-methoxycarbonyl)hexyl-4-butanolide (**7a**). Conversion of **7a** into the hydroxymethyl lactone (**13**) and the Pfitzner-Moffatt oxidation of **13** provided *trans*-3-formyl-2-(6-methoxycarbonyl)hexyl-4-butanolide (**14**) which served as a key intermediate. The Wittig reaction of **14** with dimethyl 2-oxoheptylphosphonate gave enone (**15**) which was converted to 10-oxa-11-deoxy PGE_1 methyl ester (**16b**) by $NaBH_4$ reduction. Alkaline hydrolysis of **16b** and relactonization of the resulting diacid (**17b**) gave **2b** as crystals in a good yield.

Keywords——prostaglandin; heterocyclic prostaglandin; 10-oxa-11-deoxyprostaglandin; decarboxylation; *trans*-2,3-disubstituted-4-butanolide

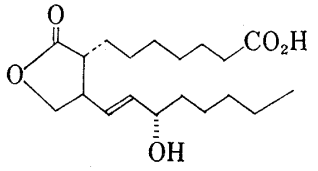
The prostaglandins are a family of C_{20} unsaturated and oxygenated fatty acids with potent pharmacological activities. However, the lack of selectivity, chemical instability and short duration of the action limited their clinical use.[2] Research efforts for excluding these disadvantages of natural materials and for synthesizing their analogs with valuable therapeutic effects have been made since the first prostaglandin structure was published.[3] Particularly, the interest in modified prostaglandins has rapidly developed and led to the synthesis of heterocyclic prostaglandins in which carbon atoms of the five-membered ring are replaced by heteroatoms such as oxygen,[4] nitrogen,[5] and sulfur.[6]

1) Location: *2-2-50, Kawagishi, Toda, Saitama 335, Japan.*
2) T.K. Schaff, *Annu. Rep. Med. Chem.*, **11**, 80 (1976).
3) S. Bergström, R. Ryhage, B. Samuelsson, and J. Sjovall, *Acta Chem. Scand.*, **16**, 969 (1962).
4) *a*) I. Vlattas and L. DellaVecchia, *Tetrahedron Lett.*, **1974**, 4455; *b*) A.E. Greene, J.P. Derprés, H. Nagano, and P. Grabbè, *ibid.*, **1977**, 2365; *c*) J. Himizu, S. Harigaya, A. Ishida, K. Yoshikawa, and M. Sato, *Ger. Offen.*, 2229225 [*Chem. Abstr.*, **78**, 111102*q* (1973)]; *d*) F.M. Hauser and R.C. Huffman, *Tetrahedron Lett.*, **1974**, 905; *e*) F.I. Carroll, F.M. Hauser, R.C. Huffman, and M.C. Coleman, *J. Med. Chem.*, **21**, 321 (1978); *f*) D. Tunemoto, Y. Takahatake, and K. Kondo, *Chem. Lett.*, **1978**, 189; *g*) I.T. Harrison and V.R. Fletcher, *Tetrahedron Lett.*, **1974**, 2729; *h*) I.T. Harrison, V.R. Fletcher, and J.H. Fried, *ibid.*, **1974**, 2733; *i*) I. Vlattas and A.O. Lee, *ibid.*, **1974**, 4451; *j*) S. Hanessian, P. Dextraze, A. Fougerousse, and Y. Guindon, *ibid.*, **1974**, 3983; *k*) G.J. Lourens and J.M. Koekemoer, *ibid.*, **1975**, 3715, 3719.
5) *a*) G. Bolliger and J.M. Muchowski, *Tetrahedron Lett.*, **1975**, 2931; *b*) J.W. Bruin, H. de Koning, and H.O. Huisman, *ibid.*, **1975**, 4599; *c*) R.M. Scribner, *ibid.*, **1976**, 3853; *d*) P.A. Zoretic, N.D. Sinha, and B. Branchaud, *Synth. Commun.*, **7**, 299 (1977); *e*) G.P. Rozing, T.J.H. Moinat, H. de Koning, and H.O. Huisman, *Heterocycles*, **4**, 719 (1976); *f*) K. Kühlein, A. Linkies, and D. Reuschling, *Tetrahedron Lett.*, **1976**, 4463, 4467; *g*) P.A. Zoretic and F. Barcelos, *ibid.*, **1977**, 529; *h*) J.C.L. Armande and U.K. Pandit, *ibid.*, **1977**, 897; *i*) R.L. Smith, T. Lee, N.P. Gould, E.J. Cragoe, Jr., H.G. Oien, and F.A. Kuehl, Jr., *J. Med. Chem.*, **20**, 1292 (1977); *j*) M. Pailer and H. Gutwillinger, *Monatsh. Chem.*, **108**, 653 (1977); *k*) G. Ambrus and I. Barta, *Prostaglandins*, **10**, 661 (1975).
6) *a*) I. Vlattas and L. DellaVecchia, *Tetrahedron Lett.*, **1974**, 4267, 4459; *b*) I. Vlattas, L. DellaVecchia, and A.O. Lee, *J. Am. Chem. Soc.*, **98**, 2008 (1976); *c*) W.J. Vloon, E.R. de Waard, and H.O. Huisman, *Heterocycles*, **6**, 1097 (1977); *d*) I.T. Harrison, R.J.K. Taylor, and J.H. Fried, *Tetrahedron Lett.*, **1975**, 1165.

We have previously reported the synthesis of 10-oxa-11-deoxyprostaglandin E_1 (10-oxa-11-deoxy PGE_1) (**2b**) in the patent.[4c] After our work, an alternative synthetic route to 10-oxaprostanoids was reported by Hauser *et al.*,[4b,e] and the stereospecific synthesis of **2b** was communicated by Kondo *et al.*[4f] In this paper we describe the experimental details of our work and additional new results.

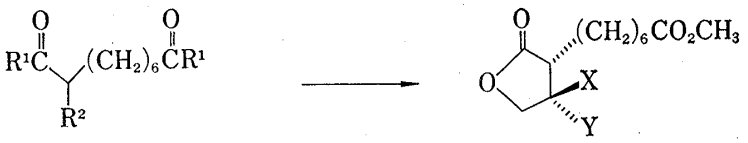


1 prostaglandin E_1(PGE_1)



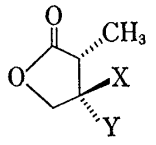
2b 10-oxa-11-deoxy PGE_1

trans-3-Formyl-2-(6-methoxycarbonyl)hexyl-4-butanolide (**14**), which served as a key intermediate in the project, was prepared from commercially available nonanedioic acid (**3**) as illustrated in Chart 1.

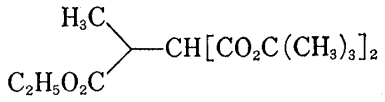


3 : R^1=OH, R^2=H
4 : R^1=OCH_3, R^2=Br
5 : R^1=OCH_3, R^2=$CH[CO_2C(CH_3)_3]_2$

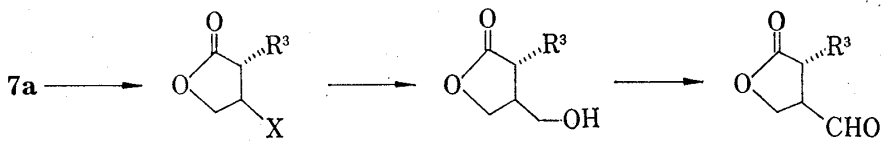
6 : X=Y=$CO_2C(CH_3)_3$
7a : X=CO_2H, Y=H
7b : X=H, Y=CO_2H
8a : X=CO_2CH_3, Y=H
8b : X=H, Y=CO_2CH_3



10a : X=CO_2CH_3, Y=H
10b : X=H, Y=CO_2CH_3



9



11 : X=COCl
12 : X=$COSC_2H_5$, R^3=$(CH_2)_6CO_2CH_3$

13

14

Chart 1

Treatment of the acid (**3**) with thionyl chloride at 50° gave acid chloride, which, without purification, was converted into dimethyl 2-bromononanedioate (**4**) by monobromination with 1.2 equivalents of bromine and subsequent treatment with excess methanol in an overall yield of 53%. The reaction of bromoester (**4**) with sodio derivative of di-*tert*-butyl malonate in N,N-dimethyl formamide (DMF) proceeded smoothly at room temperature to afford 1,1-di-*tert*-butyl 2,8-dimethyl octane-1,1,2,8-tetraester (**5**) in 60% yield. Hydroxymethylation of **5** with paraformaldehyde was carried out at 50° in methanol in the presence of a catalytic amount

of sodium methoxide to give a lactone triester (**6**). This compound (**6**), without purification, was heated at 165—170° to give a crystalline decarboxylation product (**7**) in 57% yield, which consisted of the *trans* (**7a**) and *cis* isomer (**7b**). The major isomer (**7a**) could be isolated by recrystallization from ether in 45% yield based on the compound **5**, but attempts to isolate the minor one (**7b**) in pure form failed. In order to examine the stereochemistry, **7** was converted into the corresponding dimethyl ester (**8**) by treatment with thionyl chloride and then with methanol. After preparative thin-layer chromatography (TLC), the *trans* (**8a**) and *cis* isomer (**8b**) were obtained in 82% and 8% yields, respectively. The configurations of **8a** and **8b** were determined by comparison of the NMR spectra of model compounds, *trans* (**10a**) and *cis*-3-methoxycarbonyl-2-methyl-4-butanolide (**10b**).[7] Two methine protons of *trans* isomers (**8a** and **10a**) showed the signals at δ 2.7—3.4 (2H, m), whereas the corresponding signals of *cis* isomers (**8b** and **10b**) appeared separately at δ 2.6—3.2 (1H, br.m) and δ 3.3—3.8 (1H, br.m).

The *trans* acid (**7a**) was converted into acid chloride (**11**), which on treatment with excess ethyl mercaptan in pyridine afforded thiol ester (**12**) in 86% yield based on **7a**. Treatment of **12** with deactivated Raney-nickel (W_7) in ether according to the procedure of Spero *et al.*[9] gave *trans* hydroxy lactone (**13**)[10] in 75% yield, together with a small amount of aldehyde (**14**) (after purification by column chromatography on silica gel). The hydroxy lactone (**13**)[10] was also prepared directly from **7a** by an alternative procedure, which involved the reaction of **7a** with isobutyl chloroformate followed by reduction with sodium borohydride (according to the method of Yamada *et al.*[11]).

Oxidation of **13** with dicyclohexylcarbodiimide (DCC)–dimethyl sulfoxide (DMSO)[12] gave the desired aldehyde (**14**)[10] as an oil in 75% yield, the structure of which was confirmed by elemental analysis and NMR spectroscopy after leading to crystalline 2,4-dinitrophenylhydrazone.

The synthesis of 10-oxa-11-deoxy PGE_1 (**2b**) from the aldehyde (**14**) is shown in Chart 2. The reaction of **14** with sodio derivative of dimethyl 2-oxoheptylphosphonate[13,14] in dimethoxyethane (DME) proceeded smoothly at room temperature to give enone (**15**)[15] in 71% yield. Reduction of **15** with sodium borohydride in methanol was carried out at −10° to give a mixture of epimeric alcohols, which was purified by column chromatography on silica gel to give 42% yield of 10-oxa-11-deoxy PGE_1 methyl ester (**16b**)[15] and 45% yield of its 15-epimer (**16a**).[15] By analogy to the TLC behavior of natural and 15-epiprostaglandins reported by Anderson,[16] the isomer with lower *Rf* value was assigned to **16b** with natural configuration, and the one with higher *Rf* value to **16a**. Alkaline hydrolysis of **16b** gave diacid

7) The *trans* (**10a**) and *cis* lactone (**10b**) were prepared in 64% overall yield from 1,1-di-*tert*-butyl 2-ethyl propane-1,1,2-tricarboxylate (**9**) according to a similar method as described for the preparation of **8a** and **8b** (see Experimentals). Both isomers (**10a**: **10b**=9: 1) were isolated in pure form by preparative gas chromatography (GL) and characterized by nuclear magnetic resonance (NMR) spectroscopy. The major isomer (**10a**) was assigned to *trans* lactone on the basis of the downfield position of C_3-methyl groups (δ 1.40) compared with that (δ 1.20) of the minor one (**10b**).[8]

8) *a*) D. Savostianoff and M. Pfau, *Bull. Soc. Chim. Fr.*, **1967**, 4162; *b*) T. Matsumoto, T. Okabe, and K. Fukui, *Chem. Lett.*, **1972**, 29; *c*) M. Tokuda, Vo Van Chung, A. Suzuki, and M. Itoh, *ibid.*, **1972**, 405.

9) G.B. Spero, A.V. McIntosh, Jr., and R.H. Levin, *J. Am. Chem. Soc.*, **70**, 1907 (1948).

10) Hauser *et al.*[4d,e] skillfully synthesized the compound **13** by 9 steps sequence of reactions starting with diethyl cyclooct-2-enyl malonate, and converted it to **14** by oxidation with CrO_3–pyridine in 79% yield.

11) K. Ishizumi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 492 (1968).

12) K.E. Pfitzner and J.G. Moffatt, *J. Am. Chem. Soc.*, **88**, 5661, 5670 (1965).

13) E.J. Corey, N.M. Weinshenker, T.K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).

14) W.S. Wadsworth, Jr., "Organic Reactions," Vol. 25, John Wiley and Sons, Inc., New York, 1977, p. 73.

15) Preparation of compounds **15** and **16a**, **b** by a similar sequence of reactions was reported by Hauser *et al.*[4d,e] Although reaction conditions were somewhat different from ours, the results were mostly consistent with ours.

16) N.H. Anderson, *J. Lipid Res.*, **10**, 316 (1969).

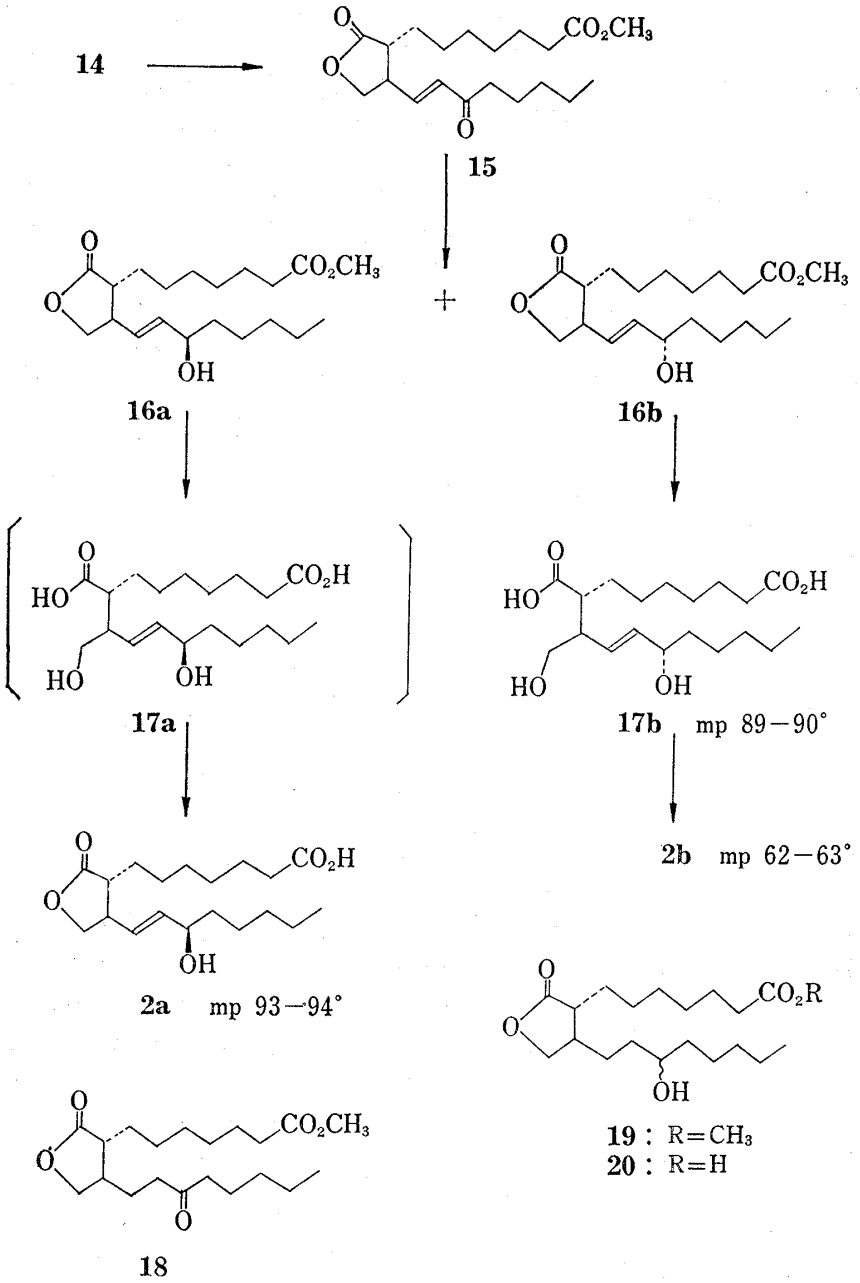


Chart 2

(**17b**) as crystals in quantitative yield. Lactonization to **2b**[17] was performed quantitatively by heating at 90° in a mixed solvent (benzene, dioxane, and ether) containing a catalytic amount of *p*-toluenesulfonic acid. On the other hand, the similar alkaline hydrolysis of **16a** gave diacid (**17a**) as an oil, which partially lactonized to **2a** during work-up. Lactonization was completed by heating the hydrolysis product in benzene and ethyl acetate, giving 15*β*-isomer (**2a**) quantitatively from **16a**.

Preparation of 10-oxa-11-deoxydihydro PGE_1 (**20**) was also attempted. Catalytic hydrogenation of **15** over 5% Pd-$BaSO_4$ gave 13, 14-dihydroketone (**18**) in 83% yield. Reduction of **18** with sodium borohydride in methanol gave an inseparable mixture of C_{15}-epimeric

17) Kondo *et al.*[4f] recently reported a stereoselective synthesis of **16b** by [2,3]sigmatropic rearrangement of allylic sulfoxide and conversion of **16b** to 10-oxa-11-deoxy PGE_1 (**2b**). They described that the physical data of their compounds were coincident with those presented in our earlier work.[4c]

alcohols (**19**) which was converted to **20** (a mixture of C_{15}-epimers) by alkaline hydrolysis followed by relactonization in refluxing benzene-ethyl acetate.

The 10-oxaprostanoic acid derivatives, thus obtained, showed prostaglandin like activities. For example, 10-oxa-11-deoxy PGE_1 (**2b**) showed moderate contractile activity on the isolated uterus of diestrous rat at the concentration of 10^{-7} g/ml. Generally, the toxicity of 10-oxa-11-deoxy PGE_1 and its derivatives examined was considerably low and no detrimental effect was observed on injection intraperitoneally to mice at the dose of 300 mg/kg. The details of pharmacological study will be published elsewhere by the other group of our laboratory.

Experimental[18]

Dimethyl 2-Bromononanedioate (**4**)——A mixture of nonanedioic acid (100 g, 532 mmol) and $SOCl_2$ (200 ml) was stirred at 50° for 18 hr. Evaporation of excess $SOCl_2$ gave a crude acid chloride as an oil (*ca.* 120 g). To this oil was added dropwise bromine (101 g, 638 mmol) at 40° over a period of 6 hr in the presence of a small amount of iodine. After stirring for 36 hr at 40°, MeOH (145 ml) was added to the mixture and refluxed for 1.5 hr. The mixture was poured into ice-cold water, extracted with ether and the extract was washed with saturated $NaHCO_3$, 10% $Na_2S_2O_4$ and H_2O, dried and evaporated. The residual oil was fractionally distilled to give 84 g (53%) of **4**, bp 125—128°/0.8 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1725, 1160. NMR ($CDCl_3$) δ 4.20 (1H, t, J=7 Hz, >CH-Br), 3.65 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 1.30—2.50 (12H).

Reaction of 4 with Di-*tert*-butyl Malonate——To a solution of sodio derivative of di-*tert*-butyl malonate prepared from 63% NaH (15.2 g, 0.4 mol) and di-*tert*-butyl malonate (86.4 g, 0.4 mol) in DMF (500 ml) was added a solution of **4** (115 g, 0.39 mol) in DMF (50 ml) at 0° under a nitrogen atmosphere. After stirring at 25° for 24 hr, the mixture was poured into ice-cold water containing acetic acid and extracted with ether. The extract was washed with water and dried over Na_2SO_4 and evaporated. The resulting oil was distilled to give 100.6 g (60%) of **5**, bp 178—181°/1 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1725, 1160. NMR ($CDCl_3$) δ 3.70 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.55 (1H, d, $-HC\langle^{CO}_{CO}$), 2.10—2.45 (3H, m, $-CH_2CO-$, >CHCO-), 1.45 (9H, s, $-C(CH_3)_3$), 1.40 (9H, s, $-C(CH_3)_3$), 1.1—1.9 (10H). *Anal.* Calcd. for $C_{22}H_{38}O_8$: C, 61.37; H, 8.90. Found: C, 61.28; H, 8.94.

Preparation of 7——To a stirred suspension of **5** (75.5 g, 0.18 mol) and paraformaldehyde (10.6 g, 0.36 mol) in abs. MeOH (150 ml) was added a solution of sodium methoxide prepared from Na (150 mg, 6.5 mg-atom) and abs. MeOH (3 ml) at 50° under a nitrogen atmosphere. The mixture was stirred for 6 hr at 50° and poured into ice water and neutralized with dil. H_2SO_4 and extracted with ether. The extract was washed with H_2O, dried and evaporated to give 64 g of **6** as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1780, 1720, 1160. NMR ($CDCl_3$) δ 4.1—4.7 (2H, m, lactone CH_2), 3.65 (3H, s, OCH_3), 2.9—3.2 (1H, br, lactone CH), 2.15—2.6 (2H, m, $-CH_2-CO-$), 1.1—1.9 (28H). This was heated at 165—170° for 3 hr under reduced pressure (*ca.* 20—30 mmHg). The oily residue was distilled. The distillate was dissolved in ether and extracted with saturated $NaHCO_3$. The aqueous extract was acidified with dil. HCl, saturated with $(NH_4)_2SO_4$ and extracted with ether. The ethereal layer was dried and evaporated to give an oil which was distilled to yield 27.2 g (57%) of **7**, bp 201—202°/0.7 mmHg, mp 56—60°. Recrystallization from ether gave 21.6 g (45%) of almost pure trans acid (**7a**)[19] as colorless needles, mp 69—70°. IR ν_{max}^{Nujol} cm^{-1}: 3000—3400, 2400—2800, 1720, 1690, $\nu_{max}^{dioxane}$ cm^{-1}: 1770, 1720. NMR ($CDCl_3$) δ 9.45 (1H, br.s, CO_2H), 4.25—4.60 (2H, quasi q, lactone CH_2), 3.65 (3H, s, OCH_3), 2.7—3.4 (2H, m, $-COCH\langle$), 2.30 (2H, quasi t, $-CH_2CO$), 1.1—1.9 (10H). *Anal.* Calcd. for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.18; H, 7.60.

Preparation of 8——A mixture of **7** (544 mg, 2 mmol) and $SOCl_2$ (5 ml) was refluxed for 8 hr and excess $SOCl_2$ was removed under reduced pressure to give acid chloride (570 mg). IR $\nu_{max}^{liq.}$ cm^{-1}: 1780, 1770, 1720, 1160. To this was added MeOH (5 ml) at 0°. The mixture was stirred for 30 min at room temperature and refluxed for 1 hr. After removing MeOH, the residue was taken up in ether, washed with saturated $NaHCO_3$ and H_2O and dried. Evaporation of ether gave an oily residue (570 mg) which was subjected to preparative TLC (silica gel, hexane: AcOEt=1: 1) to give two bands. The band of higher *Rf* value consisted

18) All melting and boiling points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 215 spectrophotometer. NMR spectra were measured with a JNM MH-60II NMR spectrometer using tetramethylsilane as an internal standard. Abbreviation used s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. Mass spectra measurements were performed with a Hitachi Mass spectrometer, Model RMS-4. Gas chromatography analysis was performed with Shimadzu GC-4B using a glass column packed with 0.3% EGA on acid washed chromosorb W (60—80 mesh).

19) It was found by GC analysis that dimethyl ester derived from crystalline acid (**7a**) contained a trace of **8b** (*ca.* 1%). Retention time: **8b**/**8a**=1.4.

of 469 mg (82%) of **8a**, bp 150°/0.3 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1770, 1730, 1180. NMR ($CDCl_3$) δ 4.1—4.6 (2H, quasi q, lactone CH_2), 3.70 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 2.7—3.4 (2H, m, 2×-COCH〈), 2.35 (2H, quasi t, -CH_2CO), 1.8—2.1 (10H). *Anal.* Calcd. for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.43; H, 7.71. The band of lower *Rf* value consisted of 46 mg (8%) of **8b**. IR $\nu_{max}^{liq.}$ cm^{-1}: 1770, 1730, 1180. NMR ($CDCl_3$) δ 4.1—4.6 (2H, quasi q, lactone CH_2), 3.75 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.3—3.8 (1H, br.m, -COCH〈), 2.6—3.1 (1H, br.m, -COCH〈), 2.35 (2H, quasi t, -CH_2CO), 1.8—2.1 (10H).

Preparation of 9——To a stirred solution of sodio derivative of di-*tert*-butyl malonate prepared from 63% NaH (1.52 g, 40 mmol) and di-*tert*-butyl malonate (8.65 g, 40 mmol) in DMF (50 ml) was added a solution of ethyl 2-bromopropionate (7.24 g, 40 mmol) in DMF (5 ml) at 0° under a nitrogen atmosphere. After stirring at 25° for 24 hr, the reaction mixture was worked up as described for the preparation of **5**. Distillation of the crude oil gave 8.04 g (65%) of **9**, bp 95—98°/1 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1725, 1160. NMR ($CDCl_3$) δ 4.25 (2H, q, -OCH_2-), 3.50 (1H, d, -$CH\langle^{CO-}_{CO-}$), 2.85—3.05 (1H, m, >CHCO-), 1.45 (9H, s, -$C(CH_3)_3$), 1.40 (9H, s, -$C(CH_3)_3$), 1.25 (3H, t, -CH_3), 1.20 (3H, d, -CH_3).

Preparation of 10——To a stirred solution of **9** (11.0 g, 34.8 mmol) and paraformaldehyde (2.09 g, 69.6 mmol) in abs. EtOH (20 ml) was added a solution of sodium ethoxide prepared from Na (20 mg) and abs. EtOH (3 ml) at 50° under a nitrogen atmosphere. After working up as described for the preparation of **7**, a *cis* and *trans* mixture of 2-methyl-4-butanolide-3-carboxylic acid (**21**) (3.54 g) was obtained in 77% yield, bp 130—135°/0.5 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 2400—3500, 1745. NMR ($CDCl_3$) δ 11.30 (s, CO_2H), 4.20—4.75 (m, lactone CH_2), 2.10—3.70 (br.m, -COCH〈), 2.32 (d, C_3-CH_3), 2.40 (d, C_3-CH_3).

A mixture of the lactonic acid (**21**) (500 mg) and $SOCl_2$ (1 ml) was refluxed for 5 hr and excess $SOCl_2$ was removed. To the residue was added MeOH (2 ml) at 0°. The mixture was worked up as described for the preparation of **8**. The residue was distilled to give a mixture of **10a** and **10b** (453 mg), bp 170°/0.7 mmHg (**10a**: **10b**=9: 1 by GC). Pure samples (**10a, b**) were isolated by Gas chromatography (retention time **10b**/**10a** =1.4). **10a**: IR $\nu_{max}^{liq.}$ cm^{-1}: 1770, 1735. NMR ($CDCl_3$) δ 4.2—4.7 (2H, quasi q, lactone CH_2), 3.75 (3H, s, OCH_3), 2.7—3.4 (2H, br.m, 2×-COCH〈), 1.40 (3H, d, C_3-CH_3). *Anal.* Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.95; H, 6.44. **10b**: IR $\nu_{max}^{liq.}$ cm^{-1}: 1770, 1735. NMR ($CDCl_3$) δ 4.2—4.7 (2H, quasi q, lactone CH_2), 3.70 (3H, s, OCH_3), 3.3—3.8 (1H, br.m, -COCH〈), 2.6—3.2 (1H, br.m, -COCH〈), 1.20 (3H, d, C_3-CH_3).

Conversion of 7a into 12——The acid chloride (**11**) (*ca.* 14 g) was prepared from **7a** (13.3 g, 49 mmol) and $SOCl_2$ (40 ml). To a stirred solution of **11** in pyridine (30 ml) was added a solution of ethyl mercaptan (10.0 g, 161 mmol) in pyridine (30 ml) at 0°. The mixture was allowed to stand overnight and poured into ice water and extracted with ether. The extract was washed with dil. HCl, saturated $NaHCO_3$, and H_2O and dried. After evaporation of the solvent, **12** (13.3 g) was obtained in 86% yield as an oil, which was used in the next step without purification. IR $\nu_{max}^{liq.}$ cm^{-1}: 1780, 1725, 1690, 1160. NMR ($CDCl_3$) δ 4.35 (2H, quasi q, lactone CH_2), 3.60 (3H, s, OCH_3), 3.35 (1H, quasi q, -COCH〈), 2.7—3.1 (1H, br, -COCH〈), 2.9 (2H, q, J=7 Hz, SCH_2), 2.25 (2H, quasi t, CH_2CO), 1.25 (3H, t, $CH_2C\underline{H}_3$), 1.1—1.9 (10H).

Preparation of 13——(i) From Thiol Ester (**12**): To a solution of **12** (10.8 g, 34 mmol) in ether (150 ml) was added 30 g of deactivated Raney-nickel (W_7)[9] in MeOH (50 ml) under ice-cooling. The mixture was stirred at 20° for 1 hr and filtered to remove catalyst. The filtrate was washed with brine, dried and evaporated. The resultant oil (8.2 g) was chromatographed on silica gel. Elution with hexane–AcOEt (1: 1) afforded 720 mg (8%) of **14**. Further elution with hexane–AcOEt (1: 2) afforded 6.60 g (75%) of **13**,[10] bp 188—190°/0.5 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 3420, 1760, 1720, 1170. NMR ($CDCl_3$) δ 4.05—4.55 (2H, m, lactone CH_2), 3.50—3.80 (2H, br, $C\underline{H}_2$OH), 3.65 (3H, s, OCH_3), 3.15 (1H, br, OH), 2.3—2.8 (2H, br.m, 2× >CH-), 2.30 (2H, quasi t, CH_2CO), 1.1—1.9 (10H). *Anal.* Calcd. for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found: C, 60.39; H, 8.51.

(ii) From **7a**: To a solution of **7a** (544 mg, 2 mmol) and triethylamine (202 mg, 2 mmol) in tetrahydrofuran (THF) (3 ml) was added a solution of isobutyl chloroformate (272 mg, 2 mmol) in THF (2 ml) at −10°. After stirring for 1 hr at −10°, the resulting precipitates were filtered and washed with THF. The filtrate was added to a solution of $NaBH_4$ (190 mg, 5 mmol) in H_2O (3 ml) at 10—15°. The reaction mixture was worked up according to the method of Yamada *et al.*[11] The crude product was chromatographed on silica gel to give 345 mg (66%) of **13**,[10] bp 188—190°/0.5 mmHg.

Preparation of 14——To a stirred solution of **13** (11.9 g, 46 mmol) in DMSO (160 ml) and C_6H_6 (160 ml) containing pyridine (3.7 ml, 46 mmol) and trifluoroacetic acid (2.5 ml, 23 mmol) was added DCC (28.5 g, 139 mmol) at 0°.[12] After stirring for 3 days at room temperature, C_6H_6 (1 l) was added followed by addition of a solution of oxalic acid (12.5 g. 139 mmol) in MeOH (20 ml) under ice-cooling. Insoluble materials were removed by filtration and washed with C_6H_6. The filtrate was washed with saturated $NaHCO_3$ and H_2O, dried and evaporated. The residue (13.1 g) was chromatographed on silica gel (hexane: AcOEt=1: 1 as an eluent) to yield 8.9 g (75%) of **14**.[10] IR $\nu_{max}^{liq.}$ cm^{-1}: 1770, 1720, 1170. 2,4-Dinitrophenylhydrazone of **14**: mp 130—131°. IR ν_{max}^{Nujol} cm^{-1}: 3320, 3080, 1760, 1710, 1620, 1580, 1150. NMR ($CDCl_3$) δ 11.20 (1H, s, NH), 9.10 (1H, dd, J=3, 9 Hz, aromatic H), 7.90 (1H, d, J=9 Hz, aromatic H), 7.70 (1H, d, J=6 Hz, CH=N), 4.15—4.80 (2H, m, lactone CH_2), 3.65 (3H, s, OCH_3), 2.6—3.2 (2H, br.m, -COCH〈, >C$\underline{H}$-CH=N), 2.30 (2H, quasi t, -CH_2CO), 1.1—1.9 (10H). *Anal.* Calcd. for $C_{19}H_{24}O_8N_4$: C, 52.29; H, 5.54; N, 12.84. Found: C, 52.15; H, 5.64; N, 12.64.

Preparation of 15——To a stirred suspension of 63% NaH (350 mg, 9.2 mmol) and DME (5 ml) was added a solution of dimethyl 2-oxoheptylphosphonate (1.76 g, 9.2 mmol)[13,14] in DME (5 ml) at room temperature under a nitrogen atmosphere. After 1 hr, to the above mixture was added a solution of **14** (2.37 g, 9.2 mmol) in DME (10 ml) and the mixture was stirred for 3 hr. After adding ether (100 ml), the mixture was washed with H_2O, dried and evaporated. The residue (3.0 g) was chromatographed on silica gel (hexane: AcOEt=3:2 as an eluent) to give 2.30 g (71%) of **15**[15] as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1765, 1720, 1660, 1625, 1170, 990. NMR ($CDCl_3$) δ 6.70 (1H, dd, J=16, 8 Hz, C<u>H</u>=CHCO), 6.25 (1H, d, J=16 Hz, CH=C<u>H</u>CO), 4.4 (1H, quasi t, lactone CH_2), 3.95 (1H, quasi t, lactone CH_2), 3.65 (3H, s, OCH_3), 3.0 (1H, quasi q, -COC<u>H</u><), 2.55 (2H, quasi q, $COCH_2$), 2.3—2.5 (1H, br. m, >C<u>H</u>-CH=CH-), 2.25 (2H, quasi t, $-CH_2CO$), 1.0—1.9 (16H), 0.85 (3H, t, $CH_2C\underline{H}_3$). UV $\lambda_{max}^{ethanol}$ nm (ε): 224.5 (1.56×10^4). MS *m/e*: 352 (M^+), 321, 296, 293, 281. *Anal.* Calcd. for $C_{20}H_{32}O_5$: C, 68.15; H, 9.25. Found: C, 68.41; H, 9.25.

10-Oxa-11-deoxy PGE$_1$ Methyl Ester (16b) and 15β-Isomer (16a)——To a stirred solution of **15** (3.00 g, 8.5 mmol) in MeOH (120 ml) was added powdered $NaBH_4$ (517 mg, 14 mmol) at $-10°$. After stirring for 15 min at $-10°$, the mixture was poured into ice-cold brine containing acetic acid and extracted with ether. The extract was washed with brine and dried and evaporated to give 3.07 g of **16**. This was chromatographed on silica gel. Elution with hexane–AcOEt (3:2) afforded 1.35 g (45%) of **16a**.[15] IR $\nu_{max}^{liq.}$ cm^{-1}: 3440, 1760, 1720, 1170, 980. NMR ($CDCl_3$) δ 5.6—5.75 (2H, br, olefinic H), 3.85—4.55 (3H, m, lactone CH_2, >C<u>H</u>OH), 3.65 (3H, s, OCH_3), 2.65—3.25 (2H, br.m, COC<u>H</u><, >C<u>H</u>-CH=CH), 2.30 (2H, quasi t, CH_2CO), 2.0 (1H, s, OH), 1.0—2.15 (18H), 0.90 (3H, t, $CH_2C\underline{H}_3$). MS *m/e*: 336 (M^+-18), 305, 283. Further elution with hexane–AcOEt (3:2) afforded 1.26 g (42%) of **16b**.[15] IR $\nu_{max}^{liq.}$ cm^{-1}: 3440, 1760, 1720, 1170, 980. NMR ($CDCl_3$) δ 5.6—5.75 (2H, br, olefinic H), 3.8—4.55 (3H, m, lactone CH_2, >C<u>H</u>OH), 3.65 (3H, s, OCH_3), 2.60—3.10 (2H, br.m, COC<u>H</u><, >C<u>H</u>-CH=CH-), 2.30 (2H, quasi t, CH_2CO), 2.0 (1H, s, OH), 1.0—2.1 (18H), 0.9 (3H, t, $CH_2C\underline{H}_3$), MS *m/e*: 336 (M^+-18), 305, 283. *Anal.* Calcd. for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.98; H, 9.53.

Preparation of 17b——To a stirred solution of **16b** (990 mg, 2.8 mmol) in MeOH (45 ml) was added 20% KOH solution (3.6 ml, 12 mmol) at 0° under a nitrogen atmosphere. The mixture was allowed to stand overnight at room temperature and MeOH was removed under reduced pressure. The aqueous layer was acidified with dil. HCl and extracted with AcOEt. The extract was washed with brine and dried. Evaporation of the solvent gave 1.00 g (100%) of **17b**, mp 85—88°. Recrystallization from AcOEt gave an analytically pure sample, mp 89—90°. IR ν_{max}^{Nujol} cm^{-1}: 3440, 2400—3200, 1700. *Anal.* Calcd. for $C_{19}H_{34}O_6$: C, 63.66; H, 9.56. Found: C, 63.89; H, 9.58.

10-Oxa-11-deoxy PGE$_1$ (2b)——Hydroxy acid (**17b**) (806 mg, 2.25 mmol) was dissolved in C_6H_6 (150 ml), dioxane (15 ml), and ether (20 ml) containing *p*-toluenesulfonic acid (3 mg). The mixture was heated at 90° and stirred for 1 hr under a nitrogen atmosphere. After cooling, AcOEt (100 ml) was added to the mixture. The organic layer was washed with brine and dried. Evaporation of the solvent gave 765 mg (100%) of **2b**.[17] An analytically pure sample, mp 62—63°, was obtained by recrystallization from ether–petroleum ether. IR ν_{max}^{Nujol} cm^{-1}: 3480, 2400—3200, 1760, 1730, 980. NMR ($CDCl_3$) δ 5.95 (2H, br.s, CO_2H, OH), 5.70 (2H, br, olefinic H), 3.6—4.55 (3H, m, lactone CH_2, >C<u>H</u>-OH), 2.6—3.1 (2H, br.m, COC<u>H</u><, >C<u>H</u>-CH=CH-), 2.30 (2H, br, $-CH_2CO$), 0.95—2.0 (18H), 0.9 (3H, t, $CH_2C\underline{H}_3$). MS *m/e*: 340 (M^+), 322, 305. *Anal.* Calcd. for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.78; H, 9.38.

Preparation of 15β-Isomer (2a)——To a stirred solution of **16a** (743 mg, 2.1 mmol) in MeOH (40 ml) was added 20% KOH solution (2.8 ml, 10 mmol) at 0° under a nitrogen atmosphere. After stirring for 15 hr at room temperature, the reaction mixture was worked up as described for the preparation of **17b**. The oily residue was dissolved in AcOEt–C_6H_6 (1:1) (40 ml) and refluxed for 2 hr under a nitrogen atmosphere. Evaporation of the solvent gave an oil (710 mg, 100%) which gave colorless crystals (mp 88—92°) standing overnight in a freezer. An analytically pure sample, mp 93—94°, was obtained by recrystallization from AcOEt–hexane. IR ν_{max}^{Nujol} cm^{-1}: 3400, 2400—3200, 1760, 1735, 980. NMR ($CDCl_3$) δ 5.95 (2H, br.s, CO_2H, OH), 5.75 (2H, br, olefinic H), 3.4—4.5 (3H, m, lactone CH_2, >C<u>H</u>OH), 2.4—3.2 (2H, br.m, COC<u>H</u><, >C<u>H</u>-CH=CH), 2.30 (2H, br, $-CH_2CO$-), 0.95—2.0 (18H), 0.90 (3H, t, $-CH_2C\underline{H}_3$). MS *m/e*: 322 (M^+-18), 305. *Anal.* Calcd. for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 67.22; H, 9.38.

Hydrogenation of Enone (15)——A solution of **15** (386 mg, 1.1 mmol) in AcOEt (25 ml) was hydrogenated in the presence of 5% Pd-$BaSO_4$ catalyst (220 mg) at room temperature for 3 hr under atmospheric pressure of hydrogen. After removal of the catalyst, the filtrate was evaporated to dryness, and the residue was chromatographed on silica gel (hexane: AcOEt=1:1 as an eluent) to give 325 mg (83%) of **18**. IR $\nu_{max}^{liq.}$ cm^{-1}: 1770, 1725, 1705, 1170. NMR ($CDCl_3$) δ 4.15—4.55 (1H, m, lactone CH_2), 3.60—4.00 (1H, m, lactone CH_2), 3.70 (3H, s, OCH_3), 2.05—2.70 (8H, m, 2× >CH-, 3×-CH_2CO), 1.0—2.0 (18H), 0.90 (3H, t, $CH_2C\underline{H}_3$). MS *m/e*: 354 (M^+), 323, 298.

2,4-Dinitrophenylhydrazone of **18**: mp 39—41°. *Anal.* Calcd. for $C_{26}H_{38}O_8N_4$: C, 58.41; H, 7.16; N, 10.48. Found: C, 58.71; H, 6.98; N, 10.64.

Reduction of Ketone (18)——To a stirred solution of **18** (240 mg, *ca.* 0.7 mmol) in MeOH (20 ml) was added powdered $NaBH_4$ (44 mg, 1.2 mmol) at 0°. After stirring for 15 min at 0°, the mixture was worked up as described for the reduction of **15** with $NaBH_4$. The oily product was chromatographed on silica gel (hexane: AcOEt=1:1 as an eluent) to give 191 mg (79%) of **19**. IR $\nu_{max}^{liq.}$ cm^{-1}: 3440, 1760, 1725, 1170.

NMR ($CDCl_3$) δ 4.15—4.55 (1H, m, lactone CH_2), 3.35—4.15 (2H, m, lactone CH_2, >C<u>H</u>–OH), 3.65 (3H, s, OCH_3), 2.00—2.75 (4H, m, 2× >CH–, $-CH_2CO$), 1.7 (1H, br, OH), 1.0—2.0 (22H), 0.9 (3H, t, $CH_2C\underline{H}_3$). MS *m/e*: 356 (M^+), 338, 307. *Anal.* Calcd. for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.10; H, 9.92.

10-Oxa-11-deoxydihydro PGE$_1$ (20)——To a stirred solution of **19** (153 mg, 0.43 mmol) in MeOH (10 ml) was added 20% KOH solution (0.6 ml, 2.1 mmol) at 0° under a nitrogen atmosphere. The mixture was worked up as described for the hydrolysis of **16b**. The oily product was dissolved in AcOEt–C_6H_6 (1:1) (10 ml) and refluxed for 1 hr under a nitrogen atmosphere. Evaporation of the solvent gave 108 mg (74%) of **20**. IR $\nu_{max}^{liq.}$ cm^{-1}: 2800—3500, 1760, 1700, 1160. NMR ($CDCl_3$) δ 6.10 (2H, br.s, CO_2H, OH), 4.1—4.55 (1H, m, lactone CH_2), 3.30—4.00 (2H, m, lactone CH_2, >C<u>H</u>–OH), 2.00—2.55 (4H, m, 2× >CH–, $-CH_2CO$), 0.7—2.0 (22H), 0.85 (3H, t, $CH_2C\underline{H}_3$). MS *m/e*: 342 (M^+), 324. *Anal.* Calcd. for $C_{19}H_{34}O_5$: C, 66.63; H, 10.01. Found: C, 66.35; H, 9.83.

Acknowledgement The authors are grateful to Professor Emeritus S. Sugasawa, the University of Tokyo, for his interest in this work. They are also grateful to Drs. K. Abe, M. Yamazaki, S. Saito, A. Kiyomoto, and S. Harigaya for their encouragement.