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# Heterocyclic Prostaglandins. VI.[1] Synthesis of 11-Deoxy-8,10-diazaprostaglandin $E_1$ and Its 10-Methyl Derivative

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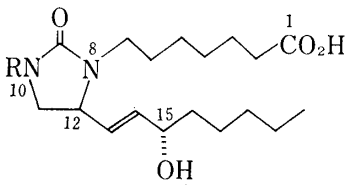
The synthesis of 11-deoxy-8,10-diazaprostaglandin $E_1$ (**1a**) starting from methyl 3-benzyloxycarbonyl-2-oxo-4-imidazolidinecarboxylate (**3a**) is reported. Alkylation of **3a** with methyl 7-bromoheptanoate and NaH gave methyl 1-benzyloxycarbonyl-3-(6-methoxycarbonyl)hexyl-2-oxo-4-imidazolidinecarboxylate (**9**), which was converted into the 4-hydroxymethyl-imidazolidine derivative (**10**). The Moffatt oxidation of **10**, and the Wittig reaction of the resulting aldehyde (**11**) with dimethyl 2-oxoheptylphosphonate provided an enone (**12**). Reduction of **12**, and hydrolysis of a mixture of $C_{15}$-epimeric alcohols (**15**) followed by re-esterification afforded 11-deoxy-8,10-diazaprostaglandin $E_1$ methyl ester (**17a**). Alkaline hydrolysis of **17a** gave **1a** as crystals in a good yield.

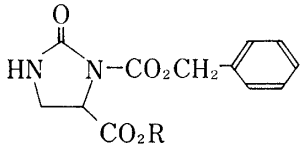
The 10-methyl derivative (**2a**) was also synthesized. Methylation of **3a** with methyl iodide and $K_2CO_3$ gave the 1-methylimidazolidine analog (**7a**), which was converted into methyl 3-(6-methoxycarbonyl)hexyl-1-methyl-2-oxo-4-imidazolidinecarboxylate (**20**) after debenzyloxycarbonylation and alkylation with methyl 7-bromoheptanoate. Conversion of **20** into **2a** was carried out by a synthetic sequence similar to that used for the elaboration of **1a**.

**Keywords**——heterocyclic prostaglandin; 11-deoxy-8,10-diazaprostaglandin $E_1$; 11-deoxy-10-methyl-8,10-diazaprostaglandin $E_1$; benzyloxycarbonyl migration; 1-benzyloxycarbonyl-4-hydroxymethyl-3-(6-methoxycarbonyl)hexyl-2-oxo-imidazolidine

Considerable interest has been shown recently in the synthesis and biological activities of heterocyclic prostaglandins. As a part of our continuing work in this field,[3] we report herein the synthesis of 11-deoxy-8,10-diazaprostaglandins (**1a** and **2a**) starting from methyl 3-benzyloxycarbonyl-2-oxo-4-imidazolidinecarboxylate (**3a**).



**1a**: R=H
**2a**: R=$CH_3$



**3a**: R=$CH_3$
**3b**: R=H

Chart 1

For the synthesis of **1a** and **2a**, we initially studied the methylation of **3a** under various conditions.

The starting compound **3a** was readily prepared by esterification of the known acid (**3b**)[4] with methanol and thionyl chloride (76% yield). When **3a** was treated with sodium hydride

1) Part V: S. Saijo, M. Wada, J. Himizu, and A. Ishida, *Chem. Pharm. Bull.*, **28**, 1449 (1980).
2) Location: *2-2-50, Toda, Saitama 335, Japan.*
3) *a*) A. Ishida, S. Saijo, K. Noguchi, M. Wada, O. Takaiti, and J. Himizu, *Chem. Pharm. Bull.*, **27**, 625 (1979); *b*) A. Ishida, K. Noguchi, S. Saijo, J. Himizu, and M. Wada, *ibid.*, **27**, 2281 (1979); *c*) A. Ishida, S. Saijc, and J. Himizu, *ibid.*, **28**, 783 (1980); *d*) S. Saijo, M. Wada, K. Noguchi, M. Muraki, A. Ishida, and J. Himizu, *Yakugaku Zasshi*, **100**, 489 (1980).
4) F. Schneider, *Ann. Chem.*, **529**, 1 (1937).

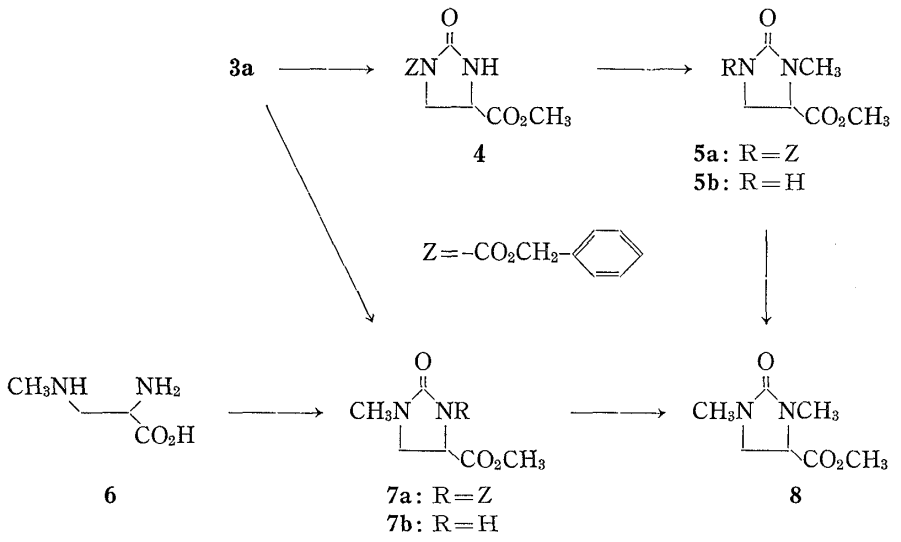



Chart 2

in N,N-dimethylformamide (DMF) at 0°, migration of the benzyloxycarbonyl group occurred readily to give methyl 1-benzyloxycarbonyl-2-oxo-4-imidazolidinecarboxylate (**4**) (85% yield), which scarcely isomerized to **3a** under similar conditions. Consequently, methylation of **3a** with methyl iodide and sodium hydride in DMF gave the 3-methyl-2-oxoimidazolidine derivative (**5a**) (78% yield), together with a small amount of 1-methyl isomer (**7a**). On the other hand, no migration was observed when potassium carbonate was used as a base in the above reaction. Methylation of **3a** with methyl iodide and potassium carbonate in 1,2-dimethoxyethane (DME) proceeded without migration of the benzyloxycarbonyl group to give **7a** (72% yield). For characterization, both products (**5a** and **7a**) were converted into the corresponding 2-oxoimidazolidines (**5b** and **7b**) in high yields. The compound **7b** thus obtained was identical with that prepared by the reaction[5] of 2-amino-3-methylaminopropionic acid (**6**)[6] and phosgene followed by esterification with methanol and thionyl chloride. In addition, methylation of both isomers (**5b** and **7b**) led to the same 1,3-dimethyl-2-oxoimidazolidine derivative (**8**).

The synthesis of 11-deoxy-8,10-diazaprostaglandin $E_1$ (11-deoxy-8,10-diaza $PGE_1$) (**1a**) was achieved by means of the sequence of reactions outlined in Chart 3.

Alkylation of **3a** with methyl 7-bromoheptanoate and sodium hydride was carried out under conditions similar to those used for the preliminary reaction. The reaction proceeded with migration of the benzyloxycarbonyl group, and gave the dimethyl ester (**9**) (46% yield), which was also prepared by alkylation of **4** with the same bromide. The ester function of the 2-oxoimidazolidine ring in **9** was selectively reduced with sodium borohydride in ethanol, affording 1-benzyloxycarbonyl-4-hydroxymethyl-3-(6-methoxycarbonyl)hexyl-2-oxoimidazolidine (**10**) (73% yield). The same alcohol (**10**) was also obtained from **4** through the following sequence. Reduction of **4** with sodium borohydride in ethanol and protection of the hydroxyl group of the resulting alcohol (**13a**) with ethyl vinyl ether provided the ethoxyethyl ether (**13b**) (70% yield from **4**). Alkylation of **13b** with methyl 7-bromoheptanoate gave the 3-(6-methoxycarbonyl)hexyl derivative (**14**) which was converted into **10** by treatment with acidic methanol (51% yield from **13b**). Oxidation of **10** with dicyclohexylcarbodiimide (DCC)-dimethyl sulfoxide (DMSO) gave an aldehyde (**11**).[7] The Witting reaction of **11** with the sodio derivative of dimethyl 2-oxoheptylphosphonate in DME afforded an enone (**12**) (50%

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7) Attempted oxidation of **10** with Collins reagent failed to furnish the aldehyde (**11**).

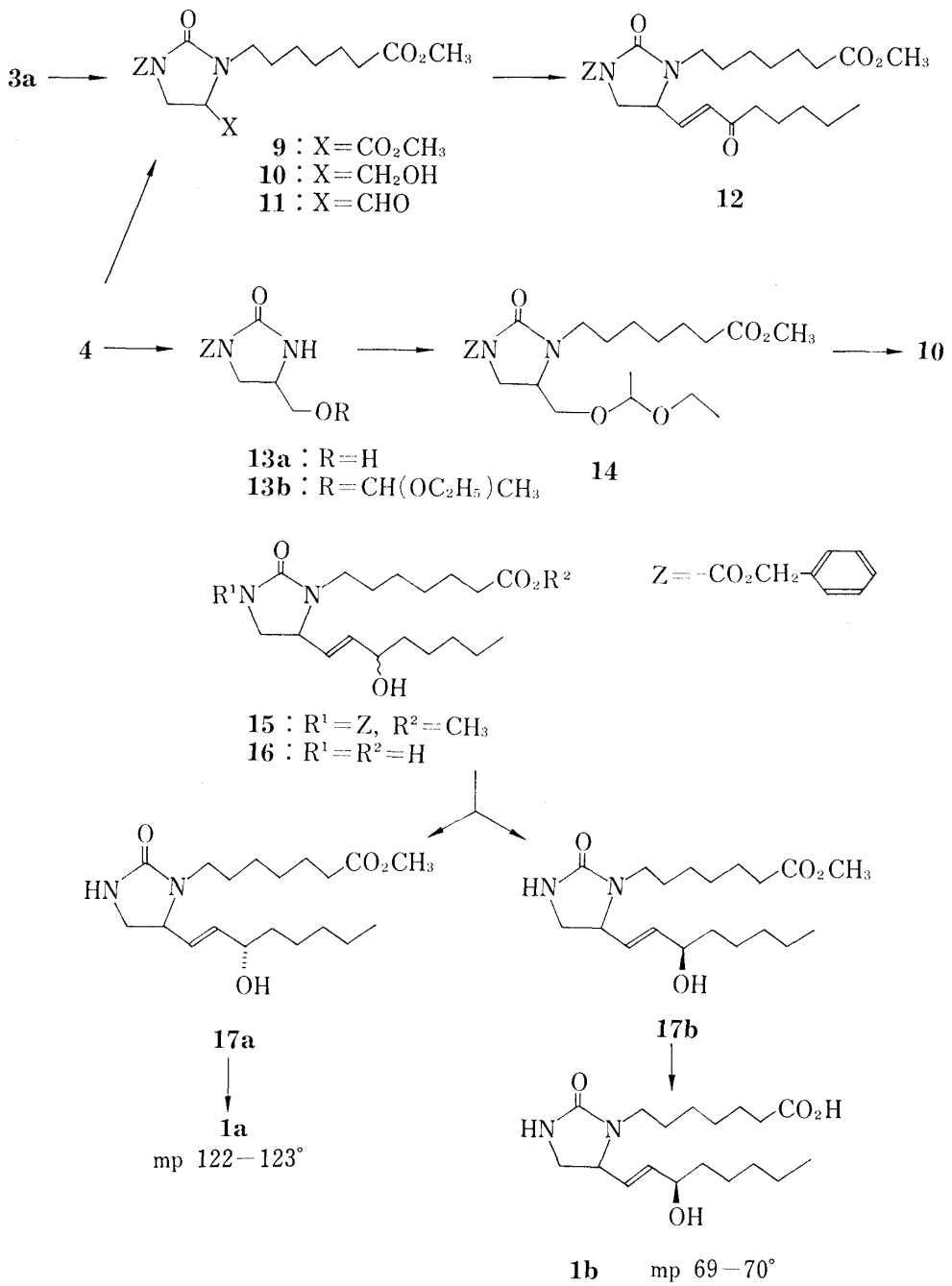


Chart 3

yield from **10**). Reduction of **12** with sodium borohydride in methanol gave an inseparable mixture of $C_{15}$-epimeric alcohols (**15**). To achieve separation, the mixture (**15**) was converted into a mixture of the epimeric enols (**17a, b**) by alkaline hydrolysis and re-esterification with ethereal diazomethane. Chromatographic separation gave 11-deoxy-8,10-diaza $PGE_1$ methyl ester (**17a**) (33% yield from **12**) and its $C_{15}$-epimer (**17b**) (31% yield from **12**). By analogy with the chromatographic behavior of heterocyclic $PGE_1$ derivatives,[1,3] the more polar isomer was tentatively assigned as **17a** with the 15$\alpha$-hydroxy configuration. Hydrolysis of **17a** with sodium hydroxide in aqueous methanol afforded **1a** as crystals in 100% yield. Similarly, alkaline hydrolysis of **17b** gave the 15$\beta$-isomer (**1b**) in 97% yield.

The synthesis of 11-deoxy-10-methyl-8,10-diaza $PGE_1$ (**2a**) was also achived by a synthetic route similar to that used for the elaboration of **1a** (see Chart 4).

Hydrogenation of **14** over 10% palladium on charcoal and subsequent methylation with methyl iodide and sodium hydride gave the 1-methyl-3-(6-methoxycarbonyl)hexyl derivative (**19**). Treatment of **19** with acidic methanol afforded 4-hydroxymethyl-3-(6-methoxycarbonyl) hexyl-1-methyl-2-oxoimidazolidine (**21**) (78% yield from **14**). The same alcohol (**21**) was also conveniently prepared from **7b** through a more attractive and shorter route, which involved alkylation of **7b** with methyl 7-bromoheptanoate and selective reduction of the resulting diester (**20**) with sodium borohydride in ethanol (64% yield from **7b**). The alcohol (**21**) could be converted into the N-methyl enone (**23**) *via* an aldehyde (**22**) using a sequence of reactions similar to that described for the conversion of **10** into **12** (46% yield from **21**). Reduction of **23** with sodium borohydride in ethanol was carried out at −25° to yield a mixture of $C_{15}$-epimeric alcohols (**24a, b**), which was separated into the two isomers in 42% and 40%

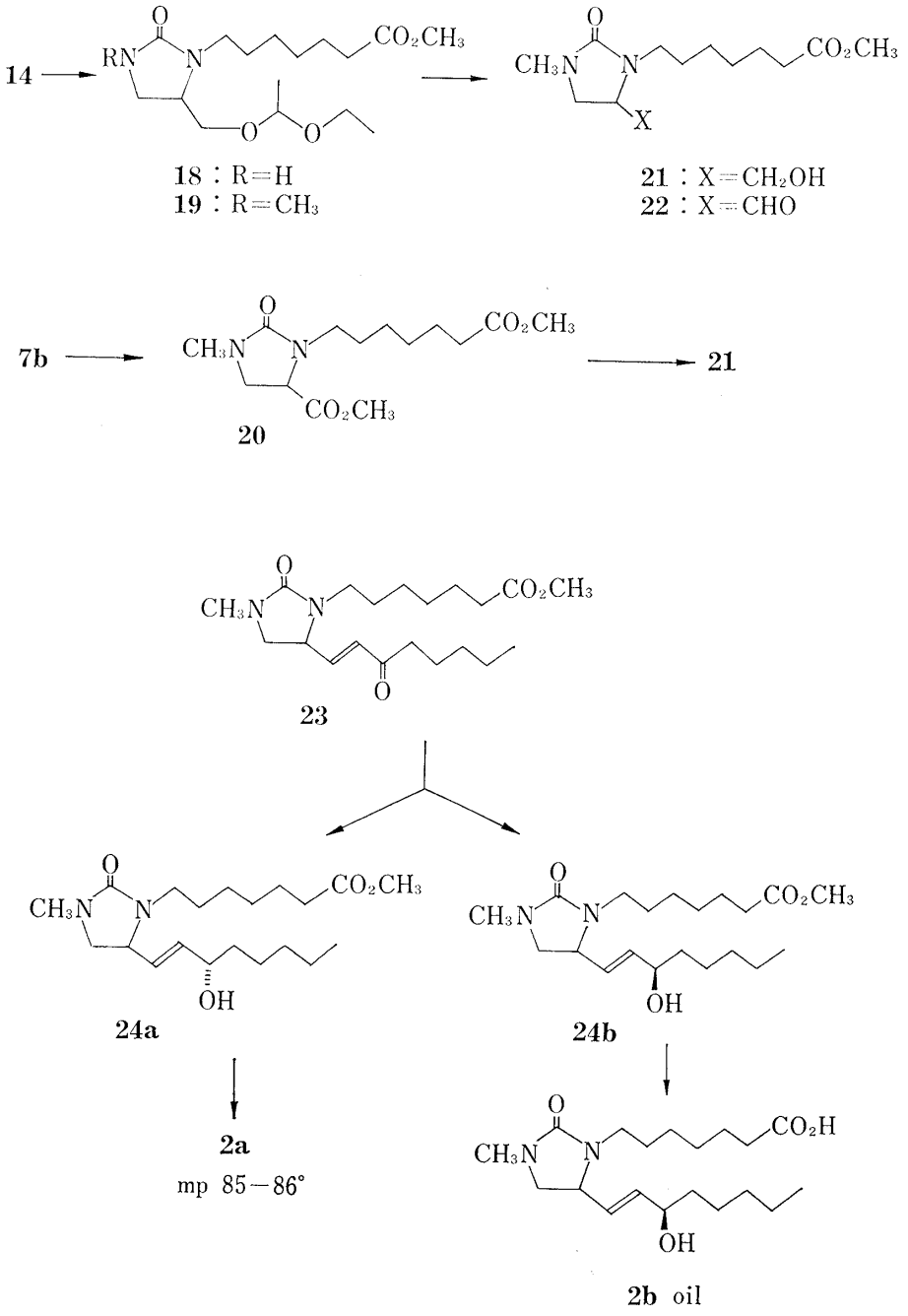


Chart 4

yields, respectively, by preparative thin layer chromatography (TLC). Configurational assignments of **24a** and **24b** were tentatively made on the basis of their chromatographic properties. The more polar isomer was assigned as **24a** with the 15$\alpha$-hydroxy configuration. Hydrolysis of **24a** and **24b** with sodium hydroxide in aqueous methanol furnished 11-deoxy-10-methyl-8,10-diaza $PGE_1$ (**2a**) (93% yield) and the $C_{15}\beta$-isomer (**2b**) (88% yield), respectively.

The diazaprostanoids (**1a** and **2a**) showed moderate bronchodilating activity. Details of the pharmacological studies will be published elsewhere.

## Experimental[8)]

**Methyl 3-Benzyloxycarbonyl-2-oxo-4-imidazolidinecarboxylate** (**3a**)——$SOCl_2$ (9.8 ml) was added to a solution of **3b** (24.5 g, 92.7 mmol) in MeOH (200 ml) at 0°. The mixture was stirred for 4 hr at room temperature then refluxed for 3 hr. After removal of the solvent, the residue was taken up in AcOEt. This solution was washed with 5% $NaHCO_3$ and $H_2O$, and then dried. Removal of the AcOEt followed by recrystallization from AcOEt–hexane gave 19.6 g (76%) of **3a**, mp 139—140°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3300, 1780, 1740, 1700. NMR ($d_6$-DMSO) $\delta$: 7.65 (1H, br.s, NH), 7.40 (5H, s, aromatic H), 5.20 (2H, s, $OCH_2$), 4.7—5.0 (1H, m, CH), 3.60 (3H, s, $OCH_3$), 3.1—3.9 (2H, m, $NCH_2$). *Anal.* Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.10; H, 5.00; N, 10.20.

**Methyl 1-Benzyloxycarbonyl-2-oxo-4-imidazolidinecarboxylate** (**4**)——A solution of **3a** (6.95 g, 25 mmol) in DMF (50 ml) was added to a suspension of 65% NaH (1.05 g, 27.5 mmol) in DMF (50 ml) at 0° under an argon atmosphere. After stirring for 40 min at room temperature, the reaction was quenched at 0° by adding 10% AcOH and the DMF was removed by evaporation at 50°. The residue was taken up in $CHCl_3$, and the solution was washed with brine, and dried. Removal of the $CHCl_3$ followed by recrystallization from AcOEt gave 5.91 g (85%) of **4**, mp 119—121°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3300, 1790, 1740, 1680. NMR ($d_6$-DMSO) $\delta$: 8.05 (1H, br.s, NH), 7.40 (5H, s, aromatic H), 5.20 (2H, s, $OCH_2$), 3.8—4.5 (3H, m), 3.75 (3H, s, $OCH_3$). An analytically pure sample, mp 121—122°, was obtained by further recrystallization from AcOEt. *Anal.* Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.21; H, 5.15; N, 10.13.

**Methylation of 3a with Methyl Iodide and NaH**——A solution of **3a** (556 mg, 2 mmol) in DMF (3 ml) was added to a suspension of 65% NaH (80 mg, 2.1 mmol) in DMF (5 ml) at 0° under an argon atmosphere. After stirring for 30 min at room temperature, methyl iodide (1.42 g, 10 mmol) was added and the mixture was stirred for 15 hr at room temperature. The DMF was removed at 50°. The residue was taken up in AcOEt, and the solution was washed with brine, and dried. Removal of the AcOEt gave the residue, which was subjected to preparative TLC (silica gel, hexane: AcOEt=1: 4) to give two bands. The band of higher *Rf* value yielded 21 mg (4%) of **7a**. The spectral data and the TLC behavior of **7a** were identical with those of the sample prepared by the alkylation of **3a** with methyl iodide and $K_2CO_3$. The band of lower *Rf* value provided 455 mg (78%) of **5a** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1790, 1750, 1720. NMR ($CDCl_3$) $\delta$: 7.35 (5H, s, aromatic H), 5.25 (2H, s, $OCH_2$), 3.7—4.2 (3H, m), 3.80 (3H, s, $OCH_3$), 2.90 (3H, s, $NCH_3$). *Anal.* Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.59; H, 5.67; N, 9.73.

Methylation of **4** (278 mg, 1 mmol) with methyl iodide (710 mg, 5 mmol) and 65% NaH (38 mg, 1 mmol) under conditions similar to those described above gave 248 mg (85%) of **5a**.

**Methylation of 3a with Methyl Iodide and $K_2CO_3$**——Methyl iodide (28.4 g, 200 mmol) was added to a suspension of **3a** (13.9 g, 50 mmol) and anhydrous $K_2CO_3$ (13.8 g, 100 mmol) in DME (250 ml). The mixture was refluxed for 18 hr under an argon atmosphere. After removal of the solvent, the residue was taken up in AcOEt. This solution was washed with brine, and dried. Removal of the AcOEt gave a crude product which was chromatographed on silica gel (hexane: AcOEt=3: 7 as an eluent) to give 10.5 g (72%) of **7a** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1790, 1750, 1710. NMR ($CDCl_3$) $\delta$: 7.35 (5H, s, aromatic H), 5.25 (2H, s, $OCH_2$), 4.55—4.80 (1H, m, CH), 3.65 (3H, s, $OCH_3$), 3.15—3.80 (2H, m, $CH_2N$), 2.80 (3H, s, $NCH_3$). *Anal.* Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.78; H, 5.41; N, 9.88.

**Preparation of 5b**——A solution of **5a** (2.92 g, 10 mmol) in MeOH (150 ml) was hydrogenated in the presence of 10% Pd-C catalyst (300 mg) at room temperature for 3 hr under atmospheric pressure of hydrogen. After removal of the catalyst, the filtrate was concentrated to give 1.52 g (96%) of **5b**, mp 123—126°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3250, 1740, 1690. NMR ($d_6$-DMSO) $\delta$: 6.50 (1H, br.s, NH), 4.2—4.4 (1H, m, CH), 3.75 (3H, s, $OCH_3$), 3.15—3.80 (2H, m, $CH_2$), 2.70 (3H, s, $NCH_3$). An analytically pure sample, mp 126—127°, was obtained by recrystallization from AcOEt. *Anal.* Calcd for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.37; N, 17.71. Found: C, 45.50; H, 6.38; N, 17.51.

8) All melting and boiling points are uncorrected. IR spectra were recorded with a Hitachi 215 spectrophotometer. NMR spectra were measured with JEOL JNM-PM×60 and JEOL 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 mass spectrometer, model RMS-4.

**Preparation of 7b**——i) From **6**: A stream of phosgene was bubbled through a solution of 2-amino-3-methylaminopropionic acid hydrochloride (**6**) (250 mg, 1.3 mmol)[6] and sodium carbonate (458 mg, 4.3 mmol) in $H_2O$ (10 ml) at 0° until the solution became acid to congo red. The mixture was stirred for 1 hr at ambient temperature. After removal of the solvent, the resulting solid was treated with $SOCl_2$ (1 ml) in MeOH (10 ml) under reflux for 2 hr. The solvent was removed and the residue was extracted with hot $CHCl_3$. Removal of the $CHCl_3$ followed by recrystallization from AcOEt gave 155 mg (75%) of **7b**, mp 107—110°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3250, 1730, 1700. NMR ($CDCl_3$) $\delta$: 6.90 (1H, br.s, NH), 4.15—4.35 (1H, m, CH), 3.70 (3H, s, $OCH_3$), 3.25—3.75 (2H, m, $CH_2$), 2.60 (3H, s, $NCH_3$). An analytically pure sample, mp 109—110°, was obtained by further recrystallization from AcOEt. *Anal.* Calcd for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.37; N, 17.71. Found: C, 45.44; H, 6.24; N, 17.86.

ii) From **7a**: A solution of **7a** (2.92 g, 10 mmol) in MeOH (150 ml) was hydrogenated in the presence of 10% Pd-C catalyst (300 mg) at room temperature under atmospheric pressure of hydrogen. After 3 hr, the mixture was worked up as described for the preparation of **5b**. A crude product (1.72 g) was recrystallized from AcOEt to give 1.50 g (95%) of **7b**, mp 108—110°. The melting point and spectral data for **7b** derived from **7a** were identical with those of the sample prepared from **6**.

**Methyl 1,3-Dimethyl-2-oxo-4-imidazolidinecarboxylate (8)**——i) From **5b**: A solution of the sodio derivative of **5b** prepared from 65% NaH (67 mg, 1.5 mmol) and **5b** (237 mg, 1.5 mmol) in DMF (6 ml) was treated with methyl iodide (1.06 g, 7.5 mmol) at 0° under an argon atmosphere. After stirring for 15 hr at room temperature, the reaction was quenched at 0° by adding AcOH (90 mg, 1.5 mmol) and the DMF was removed at 50°. The residue was taken up in AcOEt, and the solution was washed with brine, dried and concentrated. The crude product was chromatographed on silica gel (AcOEt as an eluent) to give 206 mg (80%) of **8**, mp 48—50°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1740, 1700. NMR ($CDCl_3$) $\delta$: 3.9—4.15 (1H, quasi q, CH), 3.75 (3H, s, $OCH_3$), 3.2—3.55 (2H, m, $CH_2$), 2.85 (3H, s, $NCH_3$), 2.75 (3H, s, $NCH_3$). An analytically pure sample, mp 50—51°, was obtained by recrystallization from AcOEt–petroleum ether. *Anal.* Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27. Found: C, 48.89; H, 6.97; N, 16.08.

ii) From **7b**: A solution of the sodio derivative of **7b** prepared from 65% NaH (38 mg, 1 mmol) and **7b** (158 mg, 1 mmol) in DMF (4 ml) was treated with methyl iodide (710 mg, 5 mmol) at 0° under an argon atmosphere. After stirring for 20 hr, the mixture was worked up as described above. The crude product was chromatographed on silica gel (AcOEt as an eluent) to give 134 mg (78%) of **8**, mp 48—51°.

**Preparation of 9**——A solution of **4** (5.56 g, 20 mmol) in DMF (50 ml) was added to a suspension of 65% NaH (810 mg, 22 mmol) in DMF (50 ml) at room temperature under an argon atmosphere. After stirring for 1 hr, potassium iodide (4.32 g, 26 mmol) and methyl 7-bromoheptanoate (5.35 g, 24 mmol) were added and the mixture was stirred for 48 hr at 60°. The DMF was removed at 60°. The residue was taken up in AcOEt, and the solution was washed with $H_2O$, and dried. Removal of the AcOEt gave an oil which was chromatographed on silica gel (hexane: AcOEt=1: 1 as an eluent) to give 4.87 g (58%) of **9** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1790, 1740, 1720. NMR ($CDCl_3$) $\delta$: 7.35 (5H, s, aromatic H), 5.25 (2H, s, $OCH_2$), 3.75 (3H, s, $OCH_3$), 3.65 (3H, s, $OCH_3$), 3.35—4.35 (4H, m, $2\times NCH_2$), 2.75—3.30 (1H, m, CH), 2.30 (2H, t, $COCH_2$), 1.1—2.0 (8H). *Anal.* Calcd for $C_{21}H_{28}N_2O_7$: C, 59.99; H, 6.71; N, 6.66. Found: C, 59.86; H, 6.55; N, 6.82.

Similarly, treatment of **3a** (25 g, 90 mmol) with methyl 7-bromoheptanoate (24.1 g, 108 mmol) and 65% NaH (4.06 g, 99 mmol) in the presence of potassium iodide (19.4 g, 117 mmol) gave 17.48 g (46%) of **9** as an oil.

**Preparation of 10**——i) From **9**: Powdered $NaBH_4$ (1.23 g, 32.5 mmol) was slowly added to a solution of **9** (11.9 g, 28.3 mmol) in EtOH (90 ml) at 0°. After stirring for 1.5 hr at 0°, the reaction was quenched by adding 10% HCl, and the EtOH was removed under reduced pressure. The residue was taken up in AcOEt, and the solution was washed with saturated $(NH_4)_2SO_4$ solution, then dried. Removal of the AcOEt gave an oil which was purified by column chromatography on silica gel (hexane: AcOEt=1: 4 as an eluent) to afford 8.09 g (73%) of **10** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3450, 1780, 1740, 1720. NMR ($CDCl_3$) $\delta$: 7.40 (5H, s, aromatic H), 5.25 (2H, s, $OCH_2C_6H_5$), 3.65 (3H, s, $OCH_3$), 2.75—4.45 (8H), 2.30 (2H, t, $CH_2CO$), 1.1—1.9 (8H). *Anal.* Calcd for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14. Found: C, 61.31; H, 7.07; N, 7.29.

ii) From **14**: A solution of **14** (928 mg, 2 mmol) and *p*-toluenesulfonic acid (90 mg) in MeOH (4 ml) was stirred for 1 hr at room temperature. Triethylamine (50 mg) was added to the solution and the MeOH was removed. The residue was taken up in AcOEt, and the solution was washed with brine and dried. Removal of the AcOEt gave an oil which was chromatographed on silica gel (hexane: AcOEt=1: 4 as an eluent) to give 706 mg (90%) of **10** as an oil.

**Preparation of 11**——DCC (8.07 g, 39.2 mmol) was added to a stirred solution of **10** (5.12 g, 13 mmol) in DMSO (20 ml) and $C_6H_6$ (20 ml) containing pyridine (1.03 g, 13 mmol) and trifluoroacetic acid (0.75 g, 6.5 mmol) at 0°. After stirring for 2 hr at room temperature, $C_6H_6$ (100 ml) was added, followed by addition of oxalic acid (3.53 g, 39.2 mmol) in MeOH (7 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=1: 9 as an eluent) to yield 3.61 g, (71%) of **11** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1780, 1740, 1720, 1690. NMR ($CDCl_3$) $\delta$: 9.55 (1H, br, CHO), 7.35 (5H, s, aromatic H), 5.20 (2H, s, $OCH_2$), 3.65 (3H, s, $OCH_3$), 2.8—4.5 (5H, m), 2.20 (2H, quasi t, $COCH_2$),

1.1—1.95 (8H, m). *Anal.* Calcd for $C_{20}H_{26}N_2O_6$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.38; H, 6.91; N, 7.14.

**Preparation of 12**——Dimethyl 2-oxoheptylphosphonate (1.33 g, 6 mmol) in DME (10 ml) was added to a suspension of 65% NaH (227 mg, 6 mmol) in DME (40 ml) at room temperature under a nitrogen atmosphere. After 1 hr, a solution of **11** (2.34 g, 6 mmol) in DME (20 ml) was added to the above mixture and the whole was stirred for 3 hr. After adding ether (150 ml), the mixture was washed with brine, dried and concentrated. The residue was chromatographed on silica gel (hexane: AcOEt=1: 1 as an eluent) to give 2.07 g (71%) of **12** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1780, 1740, 1720, 1680, 1640. UV $\lambda_{max}^{methanol}$ nm ($\varepsilon$): 211 ($2.9\times10^4$). NMR ($CDCl_3$) $\delta$: 7.35 (5H, s, aromatic H), 6.60 (1H, dd, $J$=16, 8 Hz, C<u>H</u>=CHCO), 6.20 (1H, d, $J$=16 Hz, CH=C<u>H</u>CO), 5.25 (2H, s, $OCH_2$), 3.65 (3H, s, $OCH_3$), 2.8—4.35 (5H, m), 2.0—2.8 (4H, m, $2\times CH_2CO$), 1.1—2.0 (14H), 0.90 (3H, t, $CH_3$). *Anal.* Calcd for $C_{27}H_{38}N_2O_6$: C, 66.64; H, 7.87; N, 5.76. Found: C, 66.71; H, 7.88; N, 5.90.

**Preparation of 13a**——Powdered $NaBH_4$ (520 mg, 14 mmol) was added to a stirred solution of **4** (3.20 g, 11.5 mmol) in EtOH (115 ml) at 0°. After 2 hr, the reaction mixture was worked up as described for the preparation of **10**. The crude product was purified by column chromatography on silica gel ($CHCl_3$: MeOH=9: 1 as an eluent) to give 2.01 g (70%) of **13a**, mp 148—150°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3400, 3300, 1770, 1740, 1680. NMR ($d_6$-DMSO) $\delta$: 7.35 (5H, s, aromatic H), 7.00 (1H, br, NH), 5.20 (2H, s, $OC\underline{H}_2C_6H_5$), 4.60 (1H, br.s, OH), 3.25—3.95 (5H, m). *Anal.* Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.62; H, 5.53; N, 11.22.

**Preparation of 14**——Trichloroacetic acid (850 mg) was added to a solution of **13a** (1.75 g, 7 mmol) and ethyl vinyl ether (7 ml) in DME (70 ml) at 0°. After stirring for 4 hr, AcOEt (100 ml) was added to the reaction mixture. The organic layer was washed with 5% $NaHCO_3$ and brine, and dried. Removal of the AcOEt gave 2.25 g (100%) of **13b** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3300, 1780, 1710. NMR ($CDCl_3$) $\delta$: 7.35 (5H, s, aromatic H), 6.45 (1H, br, NH), 5.25 (2H, s, $OC\underline{H}_2C_6H_5$), 4.65 (1H, q, $\overset{O}{\underset{O}{>}}C\underline{H}CH_3$), 3.1—4.3 (7H, m), 1.25 (3H, d, $CHC\underline{H}_3$), 1.15 (3H, t, $CH_2C\underline{H}_3$). This oil (**13b**) in DMF (12 ml) was added to a suspension of 65% NaH (280 mg, 7.6 mmol) in DMF (6 ml) at 0° under an argon atmosphere and the mixture was stirred for 40 min. Potassium iodide (1.50 g, 9 mmol) and methyl 7-bromoheptanoate (1.87 g, 8.4 mmol) were added at 0°. After stirring for 48 hr at 50°, the reaction mixture was worked up as described for the preparation of **9**. The residual oil was chromatographed on silica gel (hexane: AcOEt=2: 3 as an eluent) to give 1.66 g (51% from **13a**) of **14** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1790, 1740, 1720. NMR ($CDCl_3$) $\delta$: 7.40 (5H, s, aromatic H), 5.30 (2H, s, $OC\underline{H}_2C_6H_5$), 4.70 (1H, q, $\overset{O}{\underset{O}{>}}C\underline{H}CH_3$), 3.65 (3H, s, $OCH_3$), 3.0—4.1 (9H, m), 2.30 (2H, quasi t, $CH_2CO$), 1.30 (3H, d, $CHC\underline{H}_3$), 1.20 (3H, t, $CH_2C\underline{H}_3$), 1.15—2.0 (8H).

**Preparation of 17**——Powdered $NaBH_4$ (91 mg, 2.4 mmol) was added to a stirred solution of **12** (972 mg, 2.0 mmol) at −25°. After 3 hr at −25°, the reaction mixture was worked up as described for the preparation of **10**. The residue was chromatographed on silica gel ($C_6H_6$: AcOEt=1: 2 as an eluent) to give 800 mg (82%) of **15** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3450, 1780, 1740, 1720. NMR ($CDCl_3$) $\delta$: 7.35 (5H, s, aromatic H), 5.3—6.0 (2H, m, olefinic H), 5.25 (2H, s, $OC\underline{H}_2C_6H_5$), 3.65 (3H, s, $OCH_3$), 2.75—4.3 (6H, m), 2.30 (2H, quasi t, $COCH_2$), 2.20 (1H, br, OH), 1.1—1.9 (16H), 0.9 (3H, t). MS *m/e*: 488 ($M^+$). This oil (**13**) was dissolved in MeOH (15 ml), and 20% NaOH solution (4 ml) was added under ice-cooling. After 2 hr, the solvent was removed by evaporation. The aqueous residue was acidified with dil. HCl and extracted with AcOEt. The extract was washed with brine, and dried. Removal of the AcOEt gave 475 mg (70% yield from **12**) of **16**, mp 82—92°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3450, 3200, 2500—3100, 1700, 1680. MS *m/e*: 340 ($M^+$). NMR ($CDCl_3$) $\delta$: 6.30 (2H, br), 5.3—6.0 (2H, m), 2.6—4.4 (6H), 1.0—2.5 (19H), 0.85 (3H, t). This acid (**16**) was dissolved in MeOH (2 ml) and treated with ethereal diazomethane (excess) at 0° for 2 hr. Removal of the solvent gave an oily residue (470 mg) which was subjected to preparative TLC (silica gel, $C_6H_6$: AcOEt: MeOH=4: 16: 1) to give two bands. The band of higher *Rf* value provided 217 mg (31% overall yield from **12**) of **17b**, mp 90—96°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3400, 3250, 1740, 1680. NMR ($CDCl_3$) $\delta$: 5.3—6.0 (2H, m, olefinic H), 4.70 (1H, br, NH), 3.65 (3H, s, $OCH_3$), 2.70—4.35 (6H), 1.0—2.5 (19H), 0.85 (3H, t). An analytically pure sample, mp 97—98°, was obtained by recrystallization from AcOEt–hexane. *Anal.* Calcd for $C_{19}H_{34}N_2O_4$: C, 64.37; H, 9.67; N, 7.90. Found: C, 64.41; H, 9.60; N, 7.90. The band of lower *Rf* value yielded 238 mg (33% overall yield from **12**) of **17a**, mp 112—115°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3450, 3200, 1740, 1680. NMR ($CDCl_3$) $\delta$: 5.35—6.0 (2H, m, olefinic H), 4.75 (1H, m, NH), 3.65 (3H, s, $OCH_3$), 2.65—4.35 (6H), 1.0—2.5 (19H), 0.85 (3H, t). An analytically pure sample, mp 114—115°, was obtained by recrystallization from AcOEt–hexane. *Anal.* Calcd for $C_{19}H_{34}N_2O_4$: C, 64.37; H, 9.67; N, 7.90. Found: C, 64.46; H, 9.63; N, 7.88.

**11-Deoxy-8,10-diaza $PGE_1$ (1a) and 15$\beta$-Isomer (1b)**——A 20% solution of NaOH (0.5 ml) was added to a solution of **17a** (177 mg, 0.5 mmol) in MeOH (2 ml) under ice-cooling. After stirring for 2 hr at room temperature, the MeOH was removed. The aqueous layer was acidified with dil.HCl and extracted with AcOEt. The extract was washed with brine and dried. Removal of the AcOEt gave 169 mg (100%) of **1a**, mp 119—122°. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3400, 2400—3200, 1710, 1680. NMR ($CDCl_3$) $\delta$: 6.30 (2H, br, $CO_2H$, NH), 5.3—6.0 (2H, m, olefinic H), 2.6—4.35 (6H), 1.0—2.5 (19H), 0.85 (3H, t). An analytically pure sample, mp 122—123°, was obtained by recrystallization from AcOEt. *Anal.* Calcd for $C_{18}H_{32}N_2O_4$: C,

63.50; H, 9.48; N, 8.23. Found: C, 63.72; H, 9.32; N, 8.22.

Similarly, hydrolysis of **17b** (177 mg, 0.5 mmol) with 20% NaOH solution (0.5 ml) in MeOH (2 ml) gave 165 mg (97%) of **1b**, mp 66—69°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3300, 2400—3200, 1710, 1680. NMR ($CDCl_3$) $\delta$: 6.30 (2H, br, $CO_2H$, NH), 5.35—6.0 (2H, m, olefinic H), 2.7—4.4 (6H), 1.0—2.5 (19H), 0.85 (3H, t). An analytically pure sample, mp 69—70°, was obtained by recrystallization from AcOEt–hexane. *Anal.* Calcd for $C_{18}H_{32}N_2O_4$: C, 63.50; H, 9.48; N, 8.23. Found: C, 63.69; H, 9.22; N, 7.95.

**Preparation of 21**——i) From **7b**: Potassium iodide (2.80 g, 17 mmol) and methyl 7-bromoheptanoate (2.88 g, 15.6 mmol) in DMF (5 ml) were added to a solution of the sodio derivative of **7b**, prepared from 65% NaH (494 mg, 13 mmol) and **7b** (2.05 g, 13 mmol) in DMF (30 ml), at room temperature under an argon atmosphere. After stirring for 45 hr at 60°, the reaction mixture was worked up as described for the preparation of **9**. The residue was chromatographed on silica gel (hexane: AcOEt=1: 2 as an eluent) to give 2.50 g (64%) of **20** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1740, 1700. NMR ($CDCl_3$) $\delta$: 3.80 (3H, s, $OCH_3$), 3.65 (3H, s, $OCH_3$), 2.95—4.30 (5H), 2.80 (3H, s, $NCH_3$), 2.30 (2H, quasi t, $CH_2CO$), 1.1—1.9 (8H). A solution of this oil (**20**) in EtOH (40 ml) was treated with powdered $NaBH_4$ (380 mg, 10 mmol) at 0°. After 1.5 hr, the reaction mixture was worked up as described for $NaBH_4$ reduction of **9**. The crude product was distilled to give 2.25 g (64% overall yield from **7b**) of **21**, bp 197—199°/0.08 mmHg. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3400, 1740, 1680. NMR ($CDCl_3$) $\delta$: 3.65 (3H, s, $OCH_3$), 2.95—4.0 (8H), 2.75 (3H, s, $NCH_3$), 2.30 (2H, quasi t, $CH_2CO$), 1.0—1.9 (8H). *Anal.* Calcd for $C_{13}H_{24}N_2O_4$: C, 57.33; H, 8.88; N, 10.29. Found: C, 57.57; H, 8.82; N, 10.28.

ii) From **14**: A solution of **14** (730 mg, 1.57 mmol) in AcOEt (55 ml) was hydrogenated in the presence of 10% Pd-C (100 mg) at room temperature as described for the preparation of **5b**. After usual work-up, 517 mg (100%) of **18** was obtained as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3300, 1740, 1700. NMR ($CDCl_3$) $\delta$: 4.90 (1H, br, NH), 4.60 (1H, q, $\overset{O}{O}>C\underline{H}CH_3$), 3.65 (3H, s, $OCH_3$), 2.9—4.0 (9H, m), 2.30 (2H, t, $CH_2CO$), 1.30 (3H, d, $CHC\underline{H}_3$), 1.20 (3H, t, $CH_2C\underline{H}_3$), 1.0—2.0 (8H, m). This oil (**18**) in DMF (5 ml) was added to a suspension of 65% NaH (65 mg, 1.7 mmol) in DMF (5 ml) at 0° under an argon atmosphere. After 30 min at 0°, methyl iodide (0.5 ml) was added and the mixture was stirred for 16 hr at room temperature. After usual work-up, **19** (520 mg) was obtained as an oil. This oil (**19**) was dissolved in MeOH (10 ml) containing *p*-toluenesulfonic acid (50 mg) and the mixture was refluxed for 1 hr. The solvent was removed. The residue was taken up in AcOEt, and the solution was washed with 5% $NaHCO_3$ and brine, and dried. Removal of the AcOEt gave a crude oil which was chromatographed on silica gel (AcOEt: MeOH=20: 1 as an eluent) to give 333 mg (78% overall yield from **14**) of **21** as an oil. The spectral data and the TLC behavior of **21** derived from **14** were identical with those of the sample prepared from **7b**.

**Preparation of 22**——DCC (4.12 g, 20 mmol) was added to a stirred solution of **21** (1.85 g, 6.8 mmol) in DMSO (10 ml) and $C_6H_6$ (10 ml) containing pyridine (537 mg, 6.8 mmol) and trifluoroacetic acid (388 mg, 3.4 mmol) at 0°. After stirring for 2 hr at room temperature, the reaction mixture was worked up as described for the preparation of **11**. The oily residue was chromatographed on silica gel (AcOEt: MeOH=20: 1 as an eluent) to give 1.20 g (65%) of **22** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1740, 1710, 1680. NMR ($CDCl_3$) $\delta$: 9.55 (1H, br, CHO), 3.65 (3H, s, $OCH_3$), 2.9—4.3 (5H), 2.75 (3H, br.s, $NCH_3$), 2.30 (2H, quasi t, $CH_2CO$), 1.1—1.9 (8H). *Anal.* Calcd for $C_{13}H_{22}N_2O_4$: C, 57.76; H, 8.20; N, 10.36. Found: C, 57.86; H, 8.25; N, 10.41.

**Preparation of 23**——Dimethyl 2-oxoheptylphosphonate (222 mg, 1 mmol) in DME (2 ml) was added to a stirred suspension of 65% NaH (38 mg, 1 mmol) in DME (4 ml) at room temperature under an argon atmosphere. After 1 hr, a solution of **22** (270 mg, 1 mmol) was added to the above mixture. The reaction mixture was stirred for 3 hr and worked up as described for the preparation of **12**. The residue was chromatographed on silica gel (AcOEt as an eluent) to give 257 mg (70%) of **23** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1740, 1710, 1680, 1640. NMR ($CDCl_3$) $\delta$: 6.60 (1H, dd, $J$=16, 8 Hz, C$\underline{H}$=CHCO), 6.20 (1H, d, $J$=16 Hz, CH=C$\underline{H}$CO), 3.65 (3H, s, $OCH_3$), 2.75 (3H, s, $NCH_3$), 2.1—4.35 (9H), 1.1—2.0 (14H), 0.9 (3H, t). UV $\lambda_{max}^{methanol}$ nm ($\varepsilon$): 215 ($1.4\times10^4$). *Anal.* Calcd for $C_{20}H_{34}N_2O_4$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.66; H, 9.30; N, 7.74.

**Preparation of 24**——Powdered $NaBH_4$ (26 mg, 0.7 mmol) was added to a stirred solution of **23** (170 mg, 0.46 mmol) in EtOH (3 ml) at −25°. After 1.5 hr, the mixture was poured into ice-cold brine containing acetic acid and extracted with ether. The extract was washed with brine and dried. Removal of the ether gave an oil (170 mg), which was subjected to preparative TLC (silica gel, AcOEt) to give two bands. The band of higher *Rf* value provided 68 mg (40%) of **24b** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3400, 1740, 1680. MS *m/e*: 368 ($M^+$). NMR ($CDCl_3$) $\delta$: 5.3—6.0 (2H, m, olefinic H), 3.65 (3H, s, $OCH_3$), 2.75 (3H, s, $NCH_3$), 2.65—4.25 (6H, m), 2.50 (1H, br.s, OH), 2.30 (2H, t, $CH_2CO$), 1.05—1.90 (16H), 0.9 (3H, t). The band of lower *Rf* value yielded 72 mg (42%) of **24a**, mp 56—59°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3400, 1740, 1680. MS *m/e*: 368 ($M^+$). NMR ($CDCl_3$) $\delta$: 5.30—6.0 (2H, m, olefinic H), 3.65 (3H, s, $OCH_3$), 2.75 (3H, s, $NCH_3$), 2.65—4.25 (6H, m), 2.30 (2H, t, $CH_2CO$), 2.20 (1H, br.s, OH), 1.05—1.9 (16H), 0.9 (3H, t). An analytically pure sample, mp 58—59°, was obtained by recrystallization from AcOEt–petroleum ether. *Anal.* Calcd for $C_{20}H_{36}N_2O_4$: C, 65.18; H, 9.85; N, 7.60. Found: C, 65.32; H, 9.92; N, 7.73.

**11-Deoxy-10-methyl-8,10-diaza PGE$_1$ (2a) and Its 15$\beta$-Isomer (2b)**——A 20% solution of NaOH (0.6 ml) was added to a solution of **24a** (110 mg, 0.3 mmol) in MeOH (1.5 ml) under ice-cooling, and the mixture was stirred for 2 hr at room temperature. After work-up as described for the preparation of **1a**, 99 mg (93%) of **2a**, mp 82—85°, was obtained. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3200, 2400—3100, 1710, 1680. NMR ($CDCl_3$) $\delta$: 6.25

(2H, br, $CO_2H$, OH), 5.25—6.05 (2H, m, olefinic H), 2.65—4.30 (6H), 2.75 (3H, s, $NCH_3$), 2.30 (2H, quasi t, $CH_2CO$), 1.1—1.85 (16H), 0.9 (3H, t). An analytically pure sample, mp 85—86°, was obtained by recrystallization from AcOEt–hexane. *Anal.* Calcd for $C_{19}H_{34}N_2O_4$: C, 64.41; H, 9.61; N, 7.91. Found: C, 64.13; H, 9.70; N, 7.83.

Similarly, hydrolysis of **24b** (110 mg, 0.3 mmol) with 20% NaOH solution (0.6 ml) in MeOH (1.5 ml) gave 93 mg (88%) of **2b** as an oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3400, 2500—3100, 1710, 1680. MS *m/e*: 354 ($M^+$). NMR ($CDCl_3$) $\delta$: 6.15 (2H, br, $CO_2H$, OH), 5.25—6.05 (2H, m, olefinic H), 2.65—4.30 (6H), 2.75 (3H, s, $NCH_3$), 2.30 (2H, quasi t, $CH_2CO$), 1.1—1.85 (16H), 0.9 (3H, t). *Anal.* Calcd for $C_{19}H_{34}N_2O_4$: C, 64.41; H, 9.61; N, 7.91. Found: C, 64.71; H, 9.73; N, 8.09.

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