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Heterocyclic Prostaglandins. V.[1] Synthesis of (12*R*, 15*S*)-(—)-11-Deoxy-8-azaprostaglandin E_1 and Related Compounds

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The synthesis of (12*R*,15*S*)-(—)-11-deoxy-8-azaprostaglandin E_1 ((*R*)-**1a**) and three diastereomers ((*R*)-**2a**, (*S*)-**1a**, and (*S*)-**2a**) starting from optically active pyroglutamic acid ((*R*)-**3** and (*S*)-**3**) is reported. Esterification of (*R*)-**3** and $NaBH_4$ reduction gave (*R*)-(—)-5-hydroxymethyl-2-pyrrolidinone ((*R*)-**5**). Ethoxyethylation of (*R*)-**5** and N-alkylation with methyl 7-bromoheptanoate, followed by acid treatment, provided (*R*)-hydroxymethyl pyrrolidinone ((*R*)-**8**). The Collins oxidation of (*R*)-**8** gave (*R*)-(—)-methyl 7-(5-formyl-2-oxo-1-pyrrolidine)heptanoate ((*R*)-**9**), which served as a key intermediate. The Wittig reaction of (*R*)-**9** and dimethyl 2-oxoheptylphosphonate gave the (*R*)-enone ((*R*)-**10a**) which was converted to the (12*R*,15*S*)-enol ((*R*)-**11a**) and (12*R*,15*R*)-enol ((*R*)-**12a**) by $NaBH_4$ reduction. Alkaline hydrolysis of (*R*)-**11a** and (*R*)-**12a** gave (*R*)-**1a** and (*R*)-**2a** in high yields.

Similarly, the (*S*)-aldehyde ((*S*)-**9**) was prepared from (*S*)-**3** and converted to the (12*S*,15*S*)-acid ((*S*)-**1a**) and (12*S*,15*R*)-acid ((*S*)-**2a**) by the same sequence of reactions used for the (*R*)-series.

Some (12*R*,15*S*)-acid derivatives ((*R*)-**1b**—**g**) with a modified ω-chain were also synthesized. These analogs ((*R*)-**1b**—**g**) were also prepared from (*R*)-**9** *via* synthetic sequences similar to that described above.

Keywords——heterocyclic prostaglandin; (12*R*,15*S*)-(—)-11-deoxy-8-azaprostaglandin E_1; (12*R*,15*R*)-(—)-11-deoxy-8-azaprostaglandin E_1; (12*S*,15*S*)-(+)-11-deoxy-8-azaprostaglandin E_1; (12*S*,15*R*)-(+)-11-deoxy-8-azaprostaglandin E_1; (*R*)-(—)-methyl 7-(5-formyl-2-oxo-1-pyrrolidine)heptanoate; (*S*)-(+)-methyl 7-(5-formyl-2-oxo-1-pyrrolidine) heptanoate

In recent years, considerable chemical and medicinal interest has been focused on azaprostanoids, in which one or more carbon atoms of the cyclopentane nucleus are replaced by nitrogens.[1,3,4] Among them, 11-deoxy-8-azaprostaglandin E_1 (11-deoxy-8-aza PGE_1) is of special interest because of its biological activities such as inhibition of gastric acid secretion[3a,c] and bronchodilating effect.[1]

The synthesis of racemic 11-deoxy-8-aza PGE_1 (*dl*-**1a**) from *dl*-pyroglutamic acid (*dl*-**3**) *via* *dl*-methyl 7-(5-formyl-2-oxo-1-pyrrolidine)heptanoate (*dl*-**9**) has recently been reported by our[1] and other groups,[3a–c] but the synthesis of optically active-8-aza PGE_1 has not been

1) Part IV: S. Saijo, M. Wada, K. Noguchi, M. Muraki, A. Ishida, and J. Himizu, *Yakugaku Zasshi*, **100**, 489 (1980).
2) Location: *2-2-50, Kawagishi, Toda, Saitama 335, Japan.*
3) *a*) J.W. Bruin, H.de Koning, and H.O. Huisman, *Tetrahedron Lett.*, **1975**, 4599; *b*) G. Bolliger and J.M. Muchowski, *ibid.*, **1975**, 2931; *c*) P.A. Zoretic, B. Branchaud, and N.D. Sinha, *J. Org. Chem.*, **42**, 3201 (1977); *d*) 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); *e*) P.A. Zoretic, N.D. Sinha, T. Shiah, T. Maestrone, and B. Branchaud, *J. Heterocycl. Chem.*, **15**, 1025 (1978); *f*) C.J. Harris, N. Whittaker, G.A. Higgs, J.M. Armstrong, and P.M. Reed, *Prostaglandins*, **16**, 773 (1978); *g*) G.D. Rozing, J. Kip, W. Edam, H.de Koning, and H.O. Huisman, *Heterocycles*, **12**, 29 (1979); *h*) A. Barco, S. Benetti, G.P. Pollini, P.G. Baraldi, D. Simoni, and C.B. Vicentini, *J. Org. Chem.*, **44**, 1734 (1979); *i*) M. Pailer and I. Schlager, *Monatsh. Chem.*, **109**, 313 (1978).
4) *a*) M. Pailer and H. Gutwillinger, *Monatsh. Chem.*, **108**, 1059 (1977); *b*) F. Cassidy and G. Wootton, *Tetrahedron Lett.*, **1979**, 1525; *c*) D.R. Adams, A.F. Barnes, and F. Cassidy, *ibid.*, **1979**, 3335.

accomplished yet. As a part of our continuing studies on the heterocyclic prostaglandins,[1,5] we report herein the synthesis of (12*R*, 15*S*)-(−)-11-deoxy-8-aza PGE_1 ((*R*)-**1a**) having the same configuration as natural prostaglandin at C-12 and C-15, and three diastereomers of (*R*)-**1a**, as well as several significant analogs modified at the ω-chain (C_{13}–C_{20}) of (*R*)-**1a**.

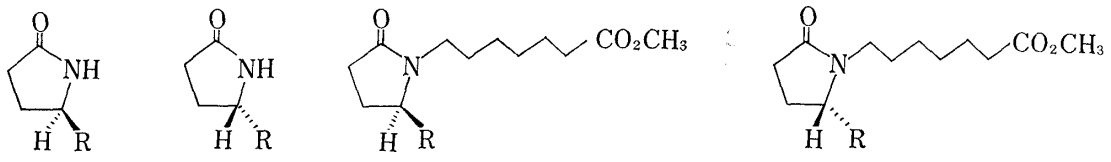
(*R*)-**1a**: X=OH, Y=H
(*R*)-**2a**: X=H, Y=OH

(*S*)-**1a**: X=OH, Y=H
(*S*)-**2a**: X=H, Y=OH

Chart 1

Synthesis of (*R*)-1a and Its Diastereomers ((*R*)-2a, (*S*)-1a, and (*S*)-2a)

(*R*)-(−)-Methyl 7-(5-formyl-2-oxo-1-pyrrolidine)heptanoate ((*R*)-**9**), which served as the precursor to (*R*)-**1a** and (*R*)-**2a**, was prepared from (*R*)-(+)-pyroglutamic acid ((*R*)-**3**) ($[\alpha]_D^{23}$ +10.8°).[6]



(*R*) (*S*) (*R*) (*S*)

3: R=CO_2H
4: R=CO_2CH_3
5: R=CH_2OH
6: R=$CH_2OCH(CH_3)OC_2H_5$
7: R=$CH_2OCH(CH_3)OC_2H_5$
8: R=CH_2OH
9: R=CHO

Chart 2

Esterification of (*R*)-**3** with thionyl chloride in methanol gave the (*R*)-methyl ester ((*R*)-**4**) in 95% yield. Reduction of (*R*)-**4** with sodium borohydride in ethanol gave (*R*)-(−)-5-hydroxymethyl-2-pyrrolidinone ((*R*)-**5**) ($[\alpha]_D^{26}$ −33.3°) in 78% yield (after purification by distillation).[7] The hydroxyl group of (*R*)-**5** was protected by reaction with ethyl vinyl ether in chloroform containing a catalytic amount of trichloroacetic acid, giving the (*R*)-ethoxyethyl ether ((*R*)-**6**) in 97% yield. Alkylation of (*R*)-**6** with methyl 7-bromoheptanoate and sodium hydride in N,N-dimethylformamide (DMF), followed by treatment with acidic methanol gave (*R*)-(−)-methyl 7-(5-hydroxymethyl-2-oxo-1-pyrrolidine)heptanoate ((*R*)-**8**) ($[\alpha]_D^{17}$ −9.6°) in 73% overall yield from (*R*)-**6**. The Collins oxidation[8] of (*R*)-**8** gave the desired (*R*)-aldehyde ((*R*)-**9**) ($[\alpha]_D^{22}$ −2.3°) in 75% yield.

The (*S*)-aldehyde ((*S*)-**9**), a key intermediate for (*S*)-**1a** and (*S*)-**2a**, was also prepared starting from (*S*)-(−)-pyroglutamic acid ((*S*)-**3**)[9] by the same synthetic sequence used for

5) *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. Saijo, and J. Himizu, *ibid.*, **28**, 783 (1980).
6) S. Sugasawa, *Yakugaku Zasshi*, **537**, 934 (1925).
7) The optical purity of (*R*)-**5** was checked by converting it into (*R*)-**3** (see "Experimental").
8) J.C. Collins, W.W. Hess, and F.J. Frank, *Tetrahedron Lett.*, **1968**, 3363.
9) Commercial (*S*)-**3** (Tokyo Kasei Kogyo) was used without purification, $[\alpha]_D^{18}$ −11.1° (*c*=2.0, H_2O). (Lit. $[\alpha]_D^{26}$ −11.9° (*c*=2.0, H_2O),[10a] $[\alpha]_D^{20}$ −11.45° (*c*=4.44, H_2O).[10b])

the (*R*)-series. Conversion of (*S*)-**3** into the (*S*)-methyl ester ((*S*)-**4**) and subsequent sodium borohydride reduction yielded (*S*)-(+)-5-hydroxymethyl-2-pyrrolidinone ((*S*)-**5**) ($[\alpha]_D^{23}$ +32.4°)[11] in 70% yield from (*S*)-**3**. Protection of the alcohol ((*S*)-**5**) as its ethoxyethyl ether, N-alkylation with methyl 7-bromoheptanoate, and removal of the ethoxyethyl protecting group, provided (*S*)-(+)-methyl 7-(5-hydroxymethyl-2-oxo-1-pyrrolidine)heptanoate ((*S*)-**8**) ($[\alpha]_D^{24}$ +9.2°) in 64% overall yield from (*S*)-**5**. The Collins oxidation[8] of (*S*)-**8** gave the (*S*)-aldehyde ((*S*)-**9**) ($[\alpha]_D^{24}$ +2.2°) in 70% yield.

The conversion of the (*R*)-aldehyde ((*R*)-**9**) into (*R*)-**1a** and (*R*)-**2a**, was carried out through the sequence of reactions outlined in Chart 3.

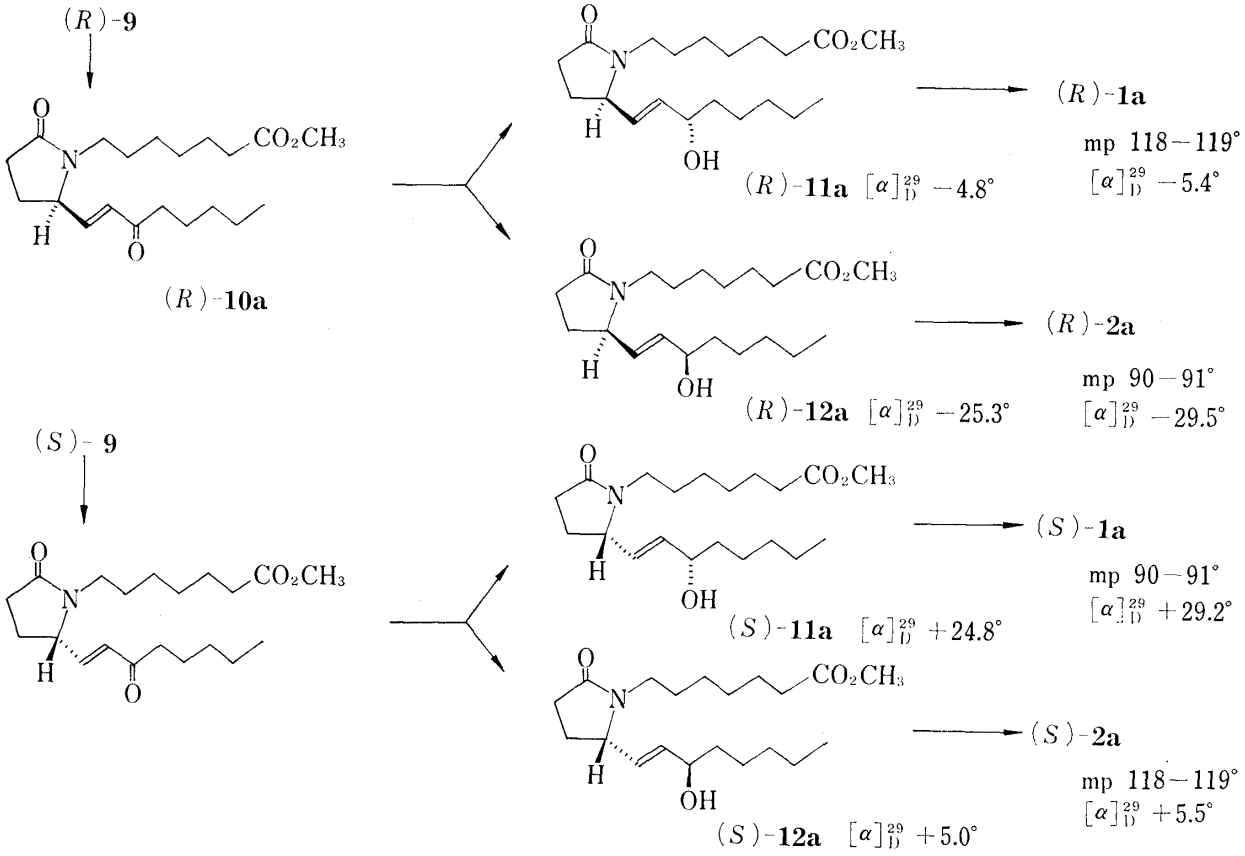


Chart 3

The Wittig reaction of (*R*)-**9** with the sodio derivative of dimethyl 2-oxoheptylphosphonate in 1,2-dimethoxyethane (DME) gave the (*R*)-enone ((*R*)-**10a**) in 72% yield. Reduction of (*R*)-**10a** with sodium borohydride in methanol yielded a mixture of C_{15}-epimeric alcohols ((*R*)-**11a** and (*R*)-**12a**) which was separated into the two isomers in 42% and 40% yields, respectively, by column chromatography. Configurational assignments of (*R*)-**11a** and (*R*)-**12a** were made by comparing the chromatographic behavior as described in the previous paper of this series[1,5a,c] as well as on the basis of the oxidative degradation of an acetate of (*R*)-**11a**. The more polar isomer was assigned as (*R*)-**11a** with the same (12*R*, 15*S*) configuration as naturally occuring prostaglandins, and the less polar one as (*R*)-**12a** with the (12*R*, 15*R*) configuration.

10) *a*) "The Merck Index," 9th ed., Merck and Co., Inc., Rahway, N.J., 1976; *b*) P.M. Hardy, *Synthesis*, **1978**, 290.
11) The optical purity of (*S*)-**5** was checked by converting it into (*S*)-glutamic acid,[12] since the catalytic oxidation of (*S*)-**5** over a Pt catalyst gave a mixture of (*S*)-**3** and (*S*)-glutamic acid (see "Experimental").
12) H.M. Chiles and W.A. Noyes, *J. Am. Chem. Soc.*, **44**, 1798 (1922).

Alkaline hydrolysis of (*R*)-**11a** gave (12*R*, 15*S*)-(−)-11-deoxy-8-aza PGE_1 ((*R*)-**1a**) ($[\alpha]_D^{29}$ −5.4°) in 96% yield. Similarly, (*R*)-**12a** was converted into (12*R*, 15*R*)-(−)-11-deoxy-8-aza PGE_1 ((*R*)-**2a**) ($[\alpha]_D^{29}$ −29.5°) in 94% yield.

Following the synthetic sequence used for the elaboration of (*R*)-**1a** and (*R*)-**2a**, the (*S*)-aldehyde ((*S*)-**9**) was converted into (*S*)-**1a** and (*S*)-**2a**. The Witting reaction gave the (*S*)-enone ((*S*)-**10a**) in 70% yield. Reduction of (*S*)-**10a** with sodium borohydride afforded a mixture of C_{15}-epimeric alcohols ((*S*)-**11a** and (*S*)-**12a**) which were chromatographically separated into each isomer in 40% and 39% yields, respectively. On comparing the specific rotations of (*R*)-**11a** and (*R*)-**12a**, the isomer showing $[\alpha]_D^{29}$ +5.0° was tentatively assigned as (*S*)-**12a** with the (12*S*, 15*R*) configuration (the optical antipode of (*R*)-**11a**). Alkaline hydrolysis of (*S*)-**11a** and (*S*)-**12a** gave (*S*)-**1a** ($[\alpha]_D^{29}$ +29.2°) and (*S*)-**2a** ($[\alpha]_D^{29}$ +5.5°) in 93% and 96% yields, respectively.

To confirm the absolute configuration and the optical purity of (*R*)-**1a**, the acid ((*R*)-**1a**) was converted into the (12*R*, 15*S*)-acteate (**13**) by esterification with ethereal diazomethane followed by acetylation with acetic anhydride in pyridine (95% yield), and subjected to ozonolysis.

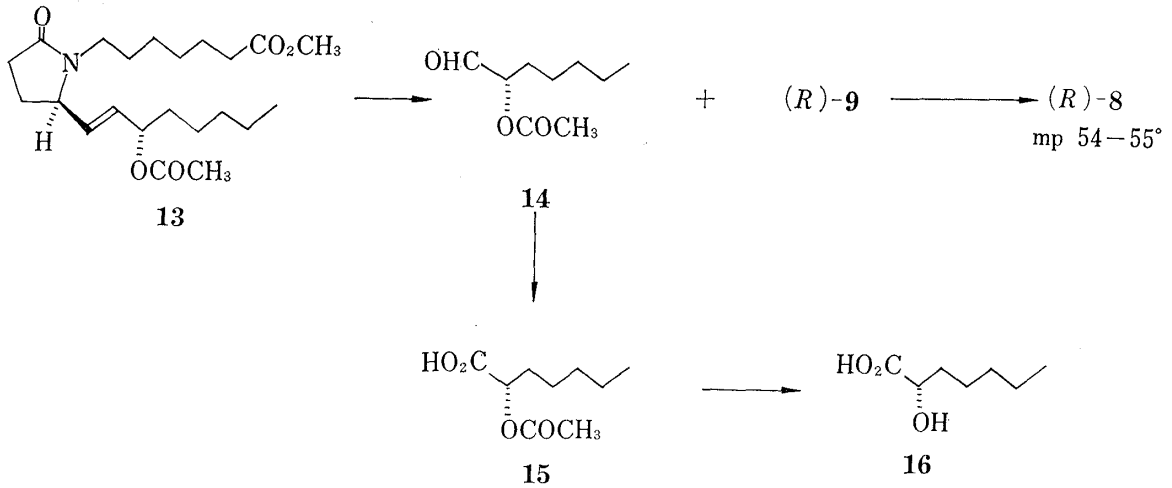


Chart 4

Ozonization of **13** and cleavage of the resulting ozonide with triphenylphosphine[13] gave (*S*)-(−)-2-acetoxyheptanal (**14**) (90% yield) and the (*R*)-aldehyde ((*R*)-**9**) (96% yield). The spectral data and specific rotation of the aldehyde ((*R*)-**9**) thus obtained were identical with those of the synthetic intermediate ((*R*)-**9**) of (*R*)-**1a**. Further, this aldehyde ((*R*)-**9**) was reduced to a crystalline (*R*)-alcohol ((*R*)-**8**), mp and mixed mp 54—55°. Catalytic oxidation of **14** over a platinum catalyst[14] afforded (*S*)-(−)-2-acetoxyheptanoic acid (**15**) in 83% yield. Alkaline hydrolysis of **15** gave the known (*S*)-(+)-2-hydroxyheptanoic acid (**16**) in 95% yield, $[\alpha]_D^{17}$ +6.8° (*c*=5.8, chloroform) (lit.[15] $[\alpha]_D^{25}$ +6.9° (*c*=5.8, chloroform)).

On the basis of the above results, the absolute configuration and optical purity of (*R*)-**1a** were definitely determined.

11-Deoxy-8-azaprostaglandin E_1 Analogs with a Modified ω-Chain

The modification of the ω-chain (C_{13}–C_{20}) of natural prostaglandin is increasingly important from a pharmacological point of view, and a number of these prostglandin analogs have been

13) J.J. Pappas, W.P. Keaveney, M. Berger, and R.V. Rush, *J. Org. Chem.*, 33, 787 (1968).
14) H. Paulsen, W. Koebernick, and E. Autschbach, *Chem. Ber.*, **105**, 1524 (1972).
15) D.H. Nugteren, D.A. van Dorp, S. Bergström, M. Hamberg, and B. Samuelsson, *Nature* (London), **212**, 38 (1966).

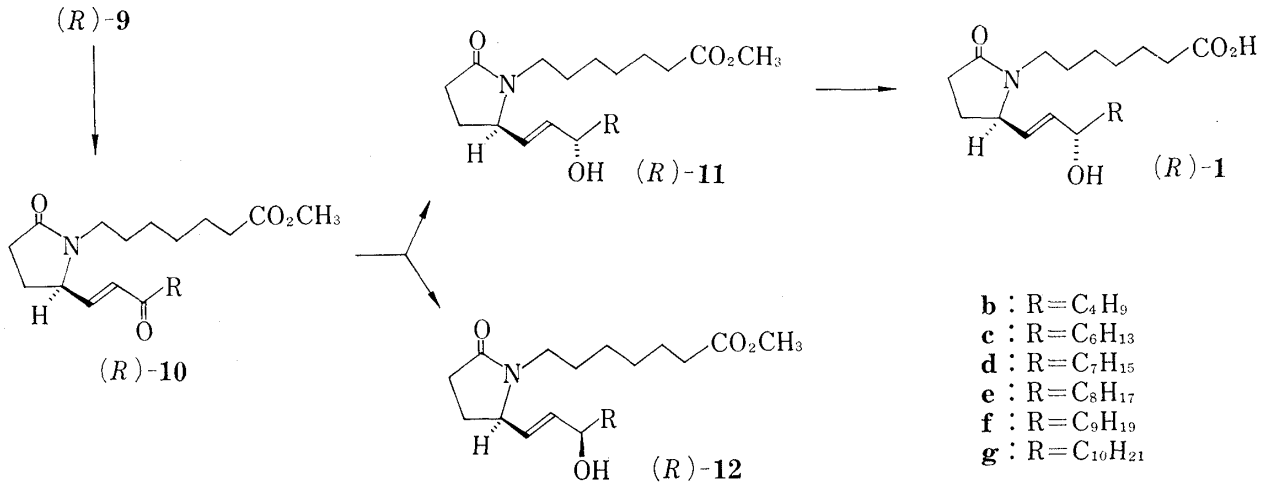


Chart 5

prepared.[16] We planned the synthesis of (12*R*, 15*S*)-11-deoxy-8-aza PGE_1 analogs with a modified ω-chain since (*R*)-**1a**, of the four diastereomers, showed the most potent bronchodilating effect.

The Wittg reaction of the (*R*)-aldehyde ((*R*)-**9**) with various dimethyl 2-oxoalkylphosphonates in the presence of sodium hydride gave the corresponding (*R*)-enone ((*R*)-**10**) which

Table I. Physical Properties of Optically Active 8-Azaprostanoids

Compound No.	Yield (%)	mp (°C)	$[\alpha]_D$ (°) (c=2.0, EtOH)	Formula	*Anal.* (%) Calcd (Found) C	H	N
(*R*)-**1a**	96	118—119[a]	$[\alpha]_D^{29}$ −5.4	$C_{19}H_{33}NO_4$	67.22 (67.13)	9.80 9.79	4.13 4.14)
(*R*)-**2a**	94	90—91[a]	$[\alpha]_D^{29}$ −29.5	$C_{19}H_{33}NO_4$	67.22 (66.97)	9.80 9.78	4.13 4.06)
(*S*)-**1a**	93	90—91[a]	$[\alpha]_D^{29}$ +29.2	$C_{19}H_{33}NO_4$	67.22 (67.44)	9.80 9.79	4.13 4.32)
(*S*)-**2a**	96	118—119[a]	$[\alpha]_D^{29}$ +5.5	$C_{19}H_{33}NO_4$	67.22 (66.99)	9.80 9.75	4.13 4.29)
(*R*)-**1b**	96	56—57[b]	$[\alpha]_D^{29}$ −5.9	$C_{18}H_{31}NO_4$	66.43 (66.56)	9.60 9.51	4.30 4.38)
(*R*)-**1c**	89	115—116[a]	$[\alpha]_D^{25}$ −5.6	$C_{20}H_{35}NO_4$	67.95 (68.16)	9.98 9.71	3.96 4.08)
(*R*)-**1d**	90	76—77[b]	$[\alpha]_D^{32}$ −4.9	$C_{21}H_{37}NO_4$	68.63 (68.49)	10.15 10.10	3.81 3.73)
(*R*)-**1e**	95	Oil	$[\alpha]_D^{28}$ −5.2	$C_{22}H_{39}NO_4$	69.25 (69.04)	10.30 10.16	3.67 3.55)
(*R*)-**1f**	96	Oil	$[\alpha]_D^{28}$ −4.2	$C_{23}H_{41}NO_4$	69.83 (69.60)	10.45 10.39	3.54 3.48)
(*R*)-**1g**	90	Oil	$[\alpha]_D^{28}$ −4.0	$C_{24}H_{43}NO_4$	70.37 (70.19)	10.58 10.51	3.42 3.32)

a) Recrystallized from AcOEt.
b) Recrystallizd from AcOEt–hexane.

16) *a*) N.S. Crossley, *Prostaglandins*, **10**, 5 (1975); *b*) A.P. Labhsetwar, *Nature* (London), **238**, 400 (1972); *c*) E.W. Yankee, U. Axen, and G.L. Bundy, *J. Am. Chem. Soc.*, **96**, 5865 (1974); *d*) D.H. Picker, N.H. Andersen, and E.M.K. Leovey, *Synth. Commun.*, **5**, 451 (1975); *e*) H.C. Arndt, P.J. Gardiner, E. Hong, H.C. Kluender, C. Myers, and W.D. Woessner, *Prostaglandins*, **16**, 67 (1978); *f*) H. Wakatsuka, Y. Konishi, S. Kori, and M. Hayashi, *Chem. Lett.*, **1978**, 141; *g*) H. Miyake, T. Tanouchi, T. Yamato, T. Okada, Y. Konishi, H. Wakatsuka, S. Kori, and M. Hayashi, *ibid.*, **1978**, 145; *h*) W. Bartmann, G. Beck, U. Lerch, and H. Teufel, *Ann. Chem.*, **1978**, 1739.

was reduced with sodium borohydride to a mixture of C_{15}-epimeric alcohols. Both isomers were readily separated by column chromatography on silica gel to afford the (12*R*, 15*S*)-enol ((*R*)-**11**) and (12*R*, 15*R*)-enol ((*R*)-**12**).[17] Alkaline hydrolysis of (*R*)-**11** gave the modified (12*R*, 15*S*)-11-deoxy-8-aza PGE_1 analogs ((*R*)-**1**) in satisfactory yields. Yields and the physical data for (*R*)-**1** are summarized in Table I.

The (12*R*, 15*S*)-acid ((*R*)-**1**) thus obtained showed prostaglandin-like activity. The acid ((*R*)-**1c**) showed a preventive effect against histamine-induced bronchoconstriction (in guinea pig) at a dose of 10^{-6} g/kg. Details of the pharmacological studies will be published elsewhere by another group from our laboratory.

Experimental[18]

Preparation of (*R*)-4——Thionyl chloride (45.2 g, 0.38 mol) was slowly added to a solution of (*R*)-**3** (64.5 g, 0.50 mol) in MeOH (600 ml) at −20° over a period of 30 min. The mixture was stirred for 30 min at 0° and then for 3 hr at room temperature. Removal of the solvent gave an oil which was distilled to afford 67.8 g (95%) of (*R*)-**4**, bp 157—160°/4 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 3225, 1740, 1695. NMR ($CDCl_3$) δ: 7.30 (1H, br, NH), 4.2—4.4 (1H, m, CH), 3.75 (3H, s, OCH_3), 2.1—2.6 (4H, m, $2\times CH_2$). $[\alpha]_D^{26}$ −0.9° (c=2.8, H_2O).

Preparation of (*S*)-4——Thionyl chloride (17.8 g, 0.15 mol) was slowly added to a stirred solution of (*S*)-**3** (25.8 g, 0.2 mol) in MeOH (240 ml) at −20°. After 3 hr at room temperature, the mixture was worked up as described for the preparation of (*R*)-**4**. The oily product was distilled to give 26.5 g (93%) of (*S*)-**4**, bp 136—138°/2 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 3225, 1740, 1695. NMR ($CDCl_3$) δ: 7.30 (1H, br), 4.2—4.4 (1H, m), 3.75 (3H, s), 2.1—2.6 (4H, m). $[\alpha]_D^{26}$ +0.9° (c=2.8, H_2O).

Preparation of (*R*)-5——Powdered $NaBH_4$ (9.46 g, 0.25 mol) was added to a stirred solution of (*R*)-**4** (35.75 g, 0.25 mol) in EtOH (350 ml) at 0°. After stirring for 2 hr at room temperature, the mixture was acidified with conc. HCl under ice-cooling. Removal of the EtOH gave an oil which was chromatographed on silica gel (AcOEt: MeOH=4: 1 as an eluent) to give 22.5 g (78%) of (*R*)-**5**, mp 71—73°. IR ν_{max}^{Nujol} cm^{-1}: 3200, 1660. MS *m/e*: 115 (M^+). NMR ($CDCl_3$) δ: 7.60 (1H, br, NH), 4.90 (1H, quasi t, OH), 3.2—4.1 (3H, m, OCH_2CH), 1.6—2.6 (4H, m, $2\times CH_2$). $[\alpha]_D^{26}$ −33.3° (c=1.76, EtOH). Recrystallization from AcOEt–$CHCl_3$ gave an analytically pure sample, mp 73—74°. *Anal.* Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.02; H, 7.81; N, 12.03.

Preparation of (*S*)-5——Powdered $NaBH_4$ (5.68 g, 0.15 mol) was added to a stirred solution of (*S*)-**4** (21.45 g, 0.15 mol) in EtOH (210 ml) at 0°. After 2 hr at room temperature, the mixture was worked up as described for the preparation of (*R*)-**5**. Distillation of the crude product afforded 12.90 g (75%) of (*S*)-**5**, bp 165—168°/0.2 mmHg, which gave crystals (mp 67—69°) after standing overnight at room temperature. IR ν_{max}^{Nujol} cm^{-1}: 3200, 1660. MS *m/e*: 115 (M^+). NMR ($CDCl_3$) δ: 7.50 (1H, br, NH), 4.60 (1H, br, OH), 3.35—3.95 (3H, m), 1.6—2.5 (4H, m). $[\alpha]_D^{23}$ +32.4° (c=1.76, EtOH). Recrystallization from AcOEt–$CHCl_3$ gave an analytically pure sample, mp 72—73°. *Anal.* Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.05; H, 7.80; N, 12.07.

Oxidation of (*R*)-5 to (*R*)-3——A suspension of (*R*)-**5** (518 mg, 4.5 mmol) in H_2O (30 ml) was oxidized in the presence of $NaHCO_3$ (567 mg, 6.75 mmol) and Pt catalyst (prepared from 1.02 g of PtO_2 according to Paulsen *et al.*[14]) at room temperature under atmospheric pressure of oxygen. After 4 hr, the catalyst was filtered off, the filtrate was neutralized with 1 N HCl and the solution was evaporated to dryness. The residue was extracted with acetone. Removal of the acetone gave 550 mg (95%) of (*R*)-**3**, mp 154—157°. $[\alpha]_D^{24}$ +10.8° (c=2.0, H_2O). (Lit.[6] $[\alpha]_D$ +10.74° (c=0.654, H_2O)).

Conversion of (*S*)-5 into (*S*)-(+)-Glutamic Acid Hydrochloride——Catalytic oxidation of (*S*)-**5** (518 mg, 4.5 mmol) over a Pt catalyst[14] (prepared from 1.02 g of PtO_2) in the presence of $NaHCO_3$ (567 mg, 6.75 6.75 mmol) gave 560 mg of a mixture of (*S*)-**3** and (*S*)-glutamic acid. This mixture was dissolved in 10% HCl (5.6 ml) and then refluxed for 6 hr.[12] Removal of the solvent gave 760 mg (92%) of (*S*)-(+)-glutamic acid hydrochloride (**17**), mp 208—210° (dec.). $[\alpha]_D^{18}$ +23.5° (c=6.0, H_2O). The melting point (with decom-

17) The 15*R*-enol ((*R*)-**12**) could also be utilized in the synthesis of (*R*)-**1**, since it reverts to the precursor ((*R*)-**10**) on treatment with Collins reagent (see "Experimental").

18) 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 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. Optical rotations were measured with JASCO DIP-180 automatic polarimeter.

position) and the specific rotation of **17** were identical with those of the commercial (*S*)-(+)-glutamic acid hydrochloride.

Preparation of (*R*)-6——A mixture of (*R*)-**5** (21.85 g, 190 mmol), ethyl vinyl ether (20.52 g, 285 mmol), and trichloroacetic acid (0.6 g) in $CHCl_3$ (115 ml) was stirred at room temperature. After 4 hr, the reaction mixture was washed with saturated $NaHCO_3$ and brine, and dried. Removal of the $CHCl_3$ gave an oil which was distilled to give 34.5 g (97%) of (*R*)-**6**, bp 145—150°/3 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 3250, 1680. MS *m/e*: 187 (M^+). NMR ($CDCl_3$) δ: 7.40 (1H, m, NH), 4.70 (1H, q, J=5 Hz, $\overset{O}{\underset{O}{>}}$CH), 3.25—4.05 (5H, m, OCH_2CH, OCH_2CH_3), 1.6—2.6 (4H, m, $2\times CH_2$), 1.25 (3H, d, J=5 Hz, $CHCH_3$), 1.15 (3H, t, J=7 Hz, OCH_2CH_3). $[\alpha]_D^{25}$ −20.9° (c=2.0, EtOH).

Preparation of (*S*)-6——A mixture of (*S*)-**5** (9.20 g, 80 mmol), ethyl vinyl ether (8.64 g, 120 mmol), and trichloroacetic acid (0.24 g) in $CHCl_3$ (50 ml) was stirred at room temperature. After 4 hr, the mixture was worked up as described for the preparation of (*R*)-**6**. The oily product was distilled to give 13.76 g (92%) of (*S*)-**6**, bp 119—121°/0.02 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 3250, 1680. MS *m/e*: 187 (M^+). NMR ($CDCl_3$) δ: 7.40 (1H, m), 4.70 (1H, q, J=5 Hz), 3.25—4.05 (5H, m), 1.6—2.6 (4H, m), 1.25 (3H, d, J=5 Hz), 1.15 (3H, t, J=7 Hz). $[\alpha]_D^{24}$ +20.8° (c=2.0, EtOH).

Preparation of (*R*)-8——A solution of (*R*)-**6** (33.66 g, 0.18 mol) in DMF (54 ml) was slowly added to a suspension of 65% NaH (7.02 g, 0.19 mol) and KI (36.52 g, 0.22 mol) in DMF (180 ml) at 0° under an argon atmosphere. After stirring for 1 hr at room temperature, methyl 7-bromoheptanoate (49.06 g, 0.22 mol) in DMF (36 ml) was added to the reaction mixture. The mixture was stirred for 44 hr at 50° and the DMF was removed at 50°. The residue was taken up in AcOEt, washed with brine and dried. Removal of the AcOEt gave a crude (*R*)-**7** (*ca.* 87.5 g) as an oil. This oil, without purification, was dissolved in MeOH (500 ml) containing *p*-toluenesulfonic acid (2.5 g) and the mixture was stirred for 4 hr at room temperature. After removal of the MeOH, AcOEt was added to the residue. The organic layer was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Distillation of the crude oil afforded 33.74 g (73%) of (*R*)-**8**, bp 200—204°/0.04 mmHg, which gave colorless crystals (mp 51—53°) after standing overnight at room temperature. IR $\nu_{max}^{liq.}$ cm^{-1}: 3350, 1730, 1650. MS *m/e*: 257 (M^+). NMR ($CDCl_3$) δ: 4.1—4.4 (1H, m, NCH), 3.65 (3H, s, OCH_3), 2.7—4.0 (5H, m, CH_2OH, NCH_2), 1.90—2.65 (6H, m), 1.1—1.9 (8H). $[\alpha]_D^{17}$ −9.6° (c=2.0, EtOH). Recrystallization from AcOEt–petroleum ether gave an analytically pure sample, mp 54—55°. *Anal.* Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.49; H, 8.92; N, 5.38.

Preparation of (*S*)-8——Alkylation of (*S*)-**6** (11.22 g, 60 mmol) with 65% NaH (2.35 g, 64 mmol), KI (11.95 g, 72 mmol), and methyl 7-bromoheptanoate (16.06 g, 72 mmol) in DMF (90 ml) gave a crude (*R*)-**7** (*ca.* 25.5 g). This oil was dissolved in MeOH (170 ml) containing *p*-toluenesulfonic acid (0.8 g). After stirring for 4 hr, the mixture was worked up as described for the preparation of (*R*)-**8**. Distillation of the crude oil afforded 10.8 g (70%) of (*S*)-**8**, bp 192—194°/0.04 mmHg, which gave colorless crystals, mp 50—51°. IR $\nu_{max}^{liq.}$ cm^{-1}: 3350, 1730, 1650. MS *m/e*: 257 (M^+). NMR ($CDCl_3$) δ: 4.1—4.4 (1H, m), 3.65 (3H, s), 2.7—4.0 (5H, m), 1.90—2.65 (6H, m), 1.1—1.9 (8H). $[\alpha]_D^{24}$ +9.2° (c=2.0, EtOH). Recrystallization from AcOEt–petroleum ether gave an analytically pure sample, mp 51—52°. *Anal.* Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.53; H, 8.96; N, 5.35.

Preparation of (*R*)-9——A mixture of pyridine (10.43 g, 132 mmol) and chromic anhydride (6.60 g, 66 mmol) in CH_2Cl_2 (185 ml) was stirred at room temperature under an argon atmosphere. After 15 min, a solution of (*R*)-**8** (2.83 g, 11 mmol) in CH_2Cl_2 (15 ml) was added and the mixture was stirred for 20 min. The CH_2Cl_2 layer was collected by decantation and the residue was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were concentrated. The resulting oil was chromatographed on silica gel (AcOEt: MeOH= 10: 1 as an eluent) to give 2.10 g (75%) of (*R*)-**9** as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1740, 1690, 1660. MS *m/e*: 255 (M^+). NMR ($CDCl_3$) δ: 9.70 (1H, br, CHO), 4.5—4.8 (1H, m, NCH), 3.65 (3H, s, OCH_3), 2.9—3.9 (2H, m, NCH_2), 2.0—2.5 (6H, m), 1.1—1.8 (8H). $[\alpha]_D^{22}$ −2.3° (c=2.0, EtOH). *Anal.* Calcd for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49. Found: C, 60.85; H, 8.38; N, 5.26.

Preparation of (S)-9——Oxidation of (*S*)-**8** (3.34 g, 13 mmol) with pyridine (12.32 g, 156 mmol) and chromic anhydride (7.8 g, 78 mmol) in CH_2Cl_2 (240 ml) was carried out as described for the preparation of (*R*)-**9**. Chromatography of the crude product on silica gel and elution with AcOEt–MeOH (10: 1) gave 2.32 g (70%) of (*S*)-**9** as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1740, 1690, 1660. MS *m/e*: 255 (M^+). NMR ($CDCl_3$) δ: 9.70 (1H, br), 4.5—4.8 (1H, m), 3.65 (3H, s), 2.9—3.9 (2H, m), 2.0—2.5 (6H), 1.1—1.8 (8H). $[\alpha]_D^{24}$ +2.2° (c=2.0, EtOH). *Anal.* Calcd for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49. Found: C, 60.89; H, 8.23; N, 5.42.

General Procedure for the Preparation of 10——Dimethyl 2-oxoalkylphosphonate (1.1 equiv.) in DME was added to a suspension of 65% NaH (1.0 equiv.) in DME at 0° under an argon atmosphere. After stirring for 20 min, a solution of (*R*)-**9** (1.0 equiv.) in DME was added, and the mixture was stirred for 2.5 hr at room temperature. The mixture was diluted with ether, washed with brine and dried. Removal of the solvent gave an oil which was chromatographed on silica gel (AcOEt: C_6H_6=4: 1 as an eluent) to give the pure enone ((*R*)-**10**) as an oil in a satisfactory yield. Similarly, the reaction of (*S*)-**9** and dimethyl 2-oxoheptylphosphonate afforded the (12*S*)-derivative ((*S*)-**10a**) as an oil. Each product was characterized by elemental analysis and spectroscopy; the data are given below. (*R*)-**10a**: 72% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 1740, 1690, 1635. MS *m/e*: 351 (M^+). NMR ($CDCl_3$) δ: 6.70 (1H, dd, J=16, 8 Hz, CH=CHCO), 6.20 (1H, d, J=16 Hz, CH=

CHCO), 4.1—4.55 (1H, m, NCH), 3.65 (3H, s, OCH_3), 3.35—3.9, 2.8—3.3 (2H, m, NCH_2), 2.1—2.8 (8H, m), 1.15—2.05 (14H), 0.90 (3H, t, $CH_2C\underline{H}_3$). UV λ_{max}^{MeOH} nm (ε): 215 (1.38×10^4). $[\alpha]_D^{29}$ −0.9° (c=2.0, EtOH). *Anal.* Calcd for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46; N, 3.99. Found: C, 68.21; H, 9.39; N, 3.88. (*S*)-**10a**: 70% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 1740, 1690, 1635. MS *m/e*: 351 (M^+). NMR ($CDCl_3$) δ: 6.70 (1H, dd, J=16, 8 Hz), 6.20 (1H, d, J=16 Hz), 4.1—4.55 (1H, m), 3.65 (3H, s), 3.35—3.9, 2.8—3.3 (2H, m), 2.1—2.8 (8H, m), 1.15—2.05 (14H), 0.90 (3H, t). UV λ_{max}^{MeOH} nm (ε): 215 (1.36×10^4). $[\alpha]_D^{28}$ +0.8° (c=2.0, EtOH). *Anal.* Calcd for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46; N, 3.99. Found: C, 68.29; H, 9.41; N, 3.92. (*R*)-**10b**: 68% yield. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1680, 1670, 1630. MS *m/e*: 337 (M^+). NMR ($CDCl_3$) δ: 6.70 (1H, dd, J=16, 8 Hz), 6.20 (1H, d, J=16 Hz), 4.1—4.5 (1H, m), 3.65 (3H, s), 3.35—3.85, 2.8—3.3 (2H, m), 2.1—2.8 (8H, m), 1.1—2.0 (12H), 0.90 (3H, t), UV λ_{max}^{MeOH} nm (ε): 215 (1.4×10^4), $[\alpha]_D^{22}$ −1.4° (c=2.0, EtOH). *Anal.* Calcd for $C_{19}H_{31}NO_4$: C, 67.62; H, 9.26; N, 4.15. Found: C, 67.48; H, 9.20; N, 4.03. (*R*)-**10c**: 72% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 1740, 1690, 1640. MS *m/e*: 365 (M^+). NMR ($CDCl_3$) δ: 6.60 (1H, dd, J=16, 8 Hz), 6.15 (1H, d, J=16 Hz), 4.0—4.4 (1H, m), 3.65 (3H, s), 3.3—3.8, 2.0—3.1 (10H, m), 1.1—1.9 (16H), 0.90 (3H, t). UV λ_{max}^{MeOH} nm (ε): 215 (1.44×10^4). $[\alpha]_D^{25}$ +1.1° (c=2.0, EtOH). *Anal.* Calcd for $C_{21}H_{35}NO_4$: C, 69.00; H, 9.65; N, 3.83. Found: C, 69.22; H, 9.58; N, 3.71. (*R*)-**10d**: 71% yield. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1680, 1670, 1630. MS *m/e*: 379 (M^+). NMR ($CDCl_3$) δ: 6.60 (1H, dd, J=16, 8 Hz), 6.15 (1H, d, J=16 Hz), 4.1—4.3 (1H, m), 3.65 (3H, s), 3.35—3.85, 2.15—2.95 (10H, m), 1.1—1.95 (18H), 0.90 (3H, t). UV λ_{max}^{MeOH} nm (ε): 215 (1.38×10^4). $[\alpha]_D^{27}$ −1.5° (c=2.0, EtOH). *Anal.* Calcd for $C_{22}H_{37}NO_4$: C, 69.62; H, 9.83; N, 3.69. Found: C, 69.53; H, 9.76; N, 3.60. (*R*)-**10e**: 65% yield. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1680, 1670, 1630. MS *m/e*: 393 (M^+). NMR ($CDCl_3$) δ: 6.65 (1H, dd, J=16, 8 Hz), 6.20 (1H, d, J=16 Hz), 4.05—4.45 (1H, m), 3.65 (3H, s), 3.35—3.85, 2.1—3.2 (10H, m), 1.15—1.95 (20H), 0.90 (3H, t). UV λ_{max}^{MeOH} nm (ε): 215 (1.32×10^4). $[\alpha]_D^{27}$ −0.9° (c=2.0, EtOH). *Anal.* Calcd for $C_{23}H_{39}NO_4$: C, 70.19; H, 9.99; N, 3.56. Found: C, 70.07; H, 9.79; N, 3.44. (*R*)-**10f**: 69% yield. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1680, 1670, 1630. MS *m/e*: 407 (M^+). NMR ($CDCl_3$) δ: 6.65 (1H, dd, J=16, 8 Hz), 6.20 (1H, d, J=16 Hz), 4.1—4.4 (1H, m), 3.65 (3H, s), 3.3—3.9, 2.1—3.15 (10H, m), 1.1—1.95 (22H), 0.90 (3H, t). UV λ_{max}^{MeOH} nm (ε): 215 (1.35×10^4). $[\alpha]_D^{30}$ −1.1° (c=2.0, EtOH). *Anal.* Calcd for $C_{24}H_{41}NO_4$: C, 70.72; H, 10.14; N, 3.44. Found: C, 70.53; H, 10.22; N, 3.29. (*R*)-**10g**: 67% yield. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1690, 1675, 1630. MS *m/e*: 421 (M^+). NMR ($CDCl_3$) δ: 6.65 (1H, dd, J=16, 8 Hz), 6.20 (1H, d, J=16 Hz), 4.05—4.4 (1H, m), 3.65 (3H, s), 3.35—3.9, 2.0—3.1 (10H, m), 1.1—1.9 (24H), 0.90 (3H, t). UV λ_{max}^{MeOH} nm (ε): 215 (1.30×10^4). $[\alpha]_D^{27}$ −0.8° (c=2.0, EtOH). *Anal.* Calcd for $C_{25}H_{43}NO_4$: C, 71.22; H, 10.28; N, 3.32. Found: C, 71.01; H, 10.43; N, 3.19.

General Procedure for the Preparation of 11 and 12——Powdered $NaBH_4$ (1.6 equiv.) was slowly added to a solution of **10** (1.0 equiv.) in MeOH at −20°. After stirring for 40 min, the reaction was quenched by adding acetone and the solvent was removed at 25°. The oily residue was taken up in AcOEt, washed with brine and dried. Removal of the AcOEt gave a mixture of C_{15}-epimeric alcohols which was chromatographically separated into the two isomers, **11** and **12**. The compounds, **11** and **12**, were characterized by elemental analysis and spectroscopy; the data are given below.

The mixture of (*R*)-**11a** and (*R*)-**12a** was separated by column chromatography on silica gel, using AcOEt as an eluent, in 42% and 40% yields, respectively. (*R*)-**11a**: oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3400, 1730, 1660. MS *m/e*: 353 (M^+). NMR ($CDCl_3$) δ: 5.75 (1H, dd, J=16, 5 Hz, C_{14}–H), 5.45 (1H, dd, J=16, 8 Hz, C_{13}–H), 3.95—4.3 (2H, m, C_{12}–H, C_{15}–H), 3.60 (3H, s, OCH_3), 3.25—3.9, 2.7—3.2 (2H, m, NCH_2), 3.00 (1H, br, OH), 2.0—2.55 (6H, m), 1.1—1.9 (16H), 0.90 (3H, t, $CH_2C\underline{H}_3$). $[\alpha]_D^{29}$ −4.8° (c=2.0, EtOH). *Anal.* Calcd for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96. Found: C, 67.79; H, 9.88; N, 3.81. (*R*)-**12a**: oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3400, 1730, 1660. MS *m/e*: 353 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, J=16, 5 Hz), 5.50 (1H, dd, J=16, 8 Hz), 3.9—4.3 (2H, m), 3.60 (3H, s), 3.40 (1H, br, OH), 3.25—3.85, 2.7—3.2 (2H, m), 2.0—2.55 (6H, m), 1.1—1.9 (16H), 0.90 (3H, t). $[\alpha]_D^{29}$ −25.3° (c=2.0, EtOH). *Anal.* Calcd for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96. Found: C, 67.68; H, 9.79; N, 3.77.

The mixture of (*S*)-**11a** and (*S*)-**12a** was separated by column chromatography on silica gel, using AcOEt as an eluent, in 40% and 39% yields, respectively. (*S*)-**11a**: oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3400, 1740, 1670. MS *m/e*: 353 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, J=16, 5 Hz), 5.50 (1H, dd, J=16, 8 Hz), 3.9—4.3 (2H, m), 3.65 (3H, s), 2.85 (1H, br, OH), 3.25—3.9, 2.7—3.2 (2H, m), 2.0—2.6 (6H, m), 1.1—1.95 (16H), 0.90 (3H, t). $[\alpha]_D^{29}$ +24.8° (c=2.0, EtOH). *Anal.* Calcd for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96. Found: C, 67.73; H, 9.84; N, 3.86. (*S*)-**12a**: oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3400, 1740, 1670. MS *m/e*: 353 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, J=16, 5 Hz), 5.50 (1H, dd, J=16, 8 Hz), 3.9—4.35 (2H, m), 3.65 (3H, s), 2.90 (1H, br, OH), 3.25—3.9, 2.7—3.2 (2H, m), 2.0—2.6 (6H, m), 1.1—1.95 (16H), 0.90 (3H, t). $[\alpha]_D^{29}$ +5.0° (c=2.0, EtOH). *Anal.* Calcd for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96. Found: C, 67.81; H, 9.73; N, 3.88.

The mixture of (*R*)-**11b** and (*R*)-**12b** was separated by column chromatography on silica gel, using AcOEt–C_6H_6 (2:1) as an eluent, in 38% and 37% yields, respectively. (*R*)-**11b**: oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1730, 1670. MS *m/e*: 339 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, J=16, 5 Hz), 5.50 (1H, dd, J=16, 8 Hz), 3.95—4.35 (2H, m), 3.65 (3H, s), 3.3—3.85, 2.7—3.2 (2H, m), 2.50 (1H, br, OH), 2.0—2.65 (8H, m), 1.15—1.95 (14H), 0.90 (3H, t). $[\alpha]_D^{29}$ −5.5° (c=2.0, EtOH). *Anal.* Calcd for $C_{19}H_{33}NO_4$: C, 67.22; H, 9.80; N, 4.13. Found: C, 67.01; H, 9.67; N, 4.06. (*R*)-**12b**: oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1730, 1670. MS *m/e*: 339 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, J=16, 5 Hz), 5.50 (1H, dd, J=16, 8 Hz), 3.9—4.35 (2H, m), 3.65 (3H, s), 3.3—3.85, 2.65—3.2 (2H, m), 2.80 (1H, br, OH), 2.0—2.6 (8H, m), 1.1—1.95 (14H), 0.90 (3H, t, $CH_2C\underline{H}_3$). $[\alpha]_D^{30}$

$-25.6°$ ($c=2.0$, EtOH).

The mixture of (*R*)-**11c** and (*R*)-**12c** was separated by column chromatography on silica gel, using AcOEt–C_6H_6–MeOH (8: 1: 1) as an eluent, in 41% and 45% yields, respectively. (*R*)-**11c**: oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3375, 1740, 1665. MS *m/e*: 367 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, $J=16$, 5 Hz), 5.50 (1H, dd, $J=16$, 8 Hz), 3.85—4.3 (2H, m), 3.65 (3H, s), 3.25—3.8, 2.6—3.2 (2H, m), 2.30 (1H, br, OH), 2.0—2.55 (6H, m), 1.1—1.95 (18H), 0.90 (3H, t). $[\alpha]_D^{25}$ $-4.5°$ ($c=2.0$, EtOH). *Anal.* Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.49; H, 10.02; N, 3.68. (*R*)-**12c**: oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3375, 1740, 1665. MS *m/e*: 367 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, $J=16$, 5 Hz), 5.45 (1H, dd, $J=16$, 8 Hz), 3.85—4.3 (2H, m), 3.65 (3H, s), 3.25—3.8, 2.6—3.15 (2H, m), 2.35 (1H, br, OH), 2.0—2.6 (6H, m), 1.1—1.95 (18H), 0.90 (3H, t). $[\alpha]_D^{25}$ $-19.5°$ ($c=2.0$, EtOH).

The mixture of (*R*)-**11d** and (*R*)-**12d** was separated by column chromatography on silica gel, using AcOEt–C_6H_6 (2: 1) as an eluent, in 42% and 41% yields, respectively. (*R*)-**11d**: mp 51—52°, (recrystallized from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3325, 1735, 1660. MS *m/e*: 381 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, $J=16$, 5 Hz), 5.50 (1H, dd, $J=16$, 8 Hz), 3.9—4.35 (2H, m), 3.65 (3H, s), 3.25—3.85, 2.7—3.2 (2H, m), 2.35 (1H, br, OH), 2.05—2.6 (6H, m), 1.1—1.95 (20H), 0.90 (3H, t). $[\alpha]_D^{30}$ $-4.9°$ ($c=2.0$, EtOH). *Anal.* Calcd for $C_{22}H_{39}NO_4$: C, 69.25; H, 10.30; N, 3.67. Found: C, 69.09; H, 10.18; N, 3.61. (*R*)-**12d**: mp 40—41°, (recrystallized from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1740, 1650. MS *m/e*: 381 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, $J=16$, 5 Hz), 5.50 (1H, dd, $J=16$, 8 Hz), 3.95—4.35 (2H, m), 3.65 (3H, s), 3.25—3.85, 2.65—3.2 (2H, m), 2.70 (1H, br, OH), 2.05—2.6 (6H, m), 1.1—1.95 (20H), 0.90 (3H, t). $[\alpha]_D^{30}$ $-26.0°$ ($c=2.0$, EtOH).

The mixture of (*R*)-**11e** and (*R*)-**12e** was separated by column chromatography on silica gel, using AcOEt–C_6H_6 (4: 1) as an eluent, in 39% and 37% yields, respectively. (*R*)-**11e**: mp 37—38°, (recrystallized from hexane–AcOEt). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1735, 1640. MS *m/e*: 395 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, $J=16$, 5 Hz), 5.50 (1H, dd, $J=16$, 8 Hz), 3.9—4.35 (2H, m), 3.65 (3H, s), 3.25—3.8, 2.7—3.2 (2H, m), 2.35 (1H, br, OH), 2.0—2.6 (6H, m), 1.1—1.95 (22H), 0.90 (3H, t). $[\alpha]_D^{28}$ $-4.4°$ ($c=2.0$, EtOH). *Anal.* Calcd for $C_{23}H_{41}NO_4$: C, 69.83; H, 10.45; N, 3.54. Found: C, 69.68; H, 10.31; N, 3.49. (*R*)-**12e**: mp 45—46°, (recrystallized from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3400, 1740, 1650. MS *m/e*: 395 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, $J=16$, 5 Hz), 5.50 (1H, dd, $J=16$, 8 Hz), 3.9—4.3 (2H, m), 3.65 (3H, s), 3.2—3.8, 2.7—3.2 (3H, m), 2.40 (1H, br, OH), 2.0—2.6 (6H, m), 1.15—1.95 (22H), 0.90 (3H, t). $[\alpha]_D^{28}$ $-22.6°$ ($c=2.0$, EtOH).

The mixture of (*R*)-**11f** and (*R*)-**12f** was separated by column chromatography on silica gel, using AcOEt–C_6H_6 (2: 1) as an eluent, in 42% and 43% yields, respectively. (*R*)-**11f**: oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1730, 1670. MS *m/e*: 409 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, $J=16$, 5 Hz), 5.45 (1H, dd, $J=16$, 8Hz), 3.95—4.3 (2H, m), 3.65 (3H, s), 3.2—3.85, 2.7—3.1 (2H, m), 2.45 (1H, br, OH), 2.05—2.6 (6H, m), 1.1—1.9 (24H), 0.90 (3H, t). $[\alpha]_D^{29}$ $-3.9°$ ($c=2.0$, EtOH). *Anal.* Calcd for $C_{24}H_{43}NO_4$: C, 70.37; H, 10.58; N, 3.42. Found: C, 70.19; H, 10.48; N, 3.31. (*R*)-**12f**: mp 54—55°, (recrystallized from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3400, 1740, 1650. MS *m/e*: 409 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, $J=16$, 5 Hz), 5.50 (1H, dd, $J=16$, 8 Hz), 3.95—4.35 (2H, m), 3.65 (3H, s), 3.25—3.85, 2.65—3.15 (2H, m), 2.55 (1H, br, OH), 2.05—2.6 (6H, m), 1.1—1.9 (24H), 0.90 (3H, t). $[\alpha]_D^{28}$ $-21.8°$ ($c=2.0$, EtOH).

The mixture of (*R*)-**11g** and (*R*)-**12g** was separated by column chromatography on silica gel, using AcOEt–C_6H_6 (4: 1) as an eluent, in 40% and 39% yields, respectively. (*R*)-**11g**: oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1720, 1660. MS *m/e*: 423 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, $J=16$, 5 Hz), 5.50 (1H, dd, $J=16$, 8 Hz), 3.95—4.3 (2H, m), 3.65 (3H, s), 3.3—3.85, 2.7—3.15 (2H, m), 2.60 (1H, br, OH), 2.05—2.7 (6H, m), 1.1—1.95 (26H), 0.90 (3H, t). $[\alpha]_D^{30}$ $-3.9°$ ($c=2.0$, EtOH). *Anal.* Calcd for $C_{25}H_{45}NO_4$: C, 70.88; H, 10.71; N, 3.31. Found: C, 70.67; H, 10.59; N, 3.14. (*R*)-**12g**: mp 65—66°, (recrystallized from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3400, 1740, 1650. MS *m/e*: 423 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, $J=16$, 5 Hz), 5.50 (1H, dd, $J=16$, 8 Hz), 3.95—4.35 (2H, m), 3.65 (3H, s), 3.3—3.9, 2.7—3.1 (2H, m), 2.55 (1H, br, OH), 2.0—2.7 (6H, m), 1.1—1.95 (26H), 0.90 (3H, t). $[\alpha]_D^{28}$ $-19.6°$ ($c=2.0$, EtOH).

Oxidation of (*R*)-12 to (*R*)-10——A mixture of pyridine (12 equiv.) and chromic anhydride (6 equiv.) in CH_2Cl_2 was stirred for 15 min at room temperature under an argon atmosphere. A solution of (*R*)-**12** (1 equiv.) in CH_2Cl_2 was added to the mixture. After stirring for 20 min, the CH_2Cl_2 layer was collected by decantation and the residue was extracted with CH_2Cl_2. The combined CH_2Cl_2 was washed with 1 N NaOH, 5% HCl, 5% $NaHCO_3$, and brine, and then dried. Removal of the solvent afforded an almost pure (*R*)-**10** which was chromatographed on silica gel (AcOEt: $C_6H_6=4$: 1 as an eluent) to give the pure (*R*)-**10** in 73—90% yield.

General Procedure for the Hydrolysis of 11 and 12——A 20% solution of NaOH (5—10 equiv.) was added to a solution of **11** (1 equiv.) in MeOH at 0° under an argon atmosphere. After 3 hr, the MeOH was removed under reduced pressure. The aqueous layer was washed with ether, acidified with dil. HCl, and extracted with AcOEt. The extract was washed with brine and dried. Removal of the solvent gave **1** in a high yield. Similarly, hydrolysis of **12** (1 equiv.) with 20% NaOH solution (5—10 equiv.) in MeOH gave **2** in a good yield. Each product was characterized by elemental analysis (Table I) and spectroscopy. IR, MS, and NMR data are given below. (*R*)-**1a**: IR ν_{max}^{Nujol} cm^{-1}: 2500—3400, 1720, 1650. MS *m/e*: 339 (M^+). NMR ($CDCl_3$) δ: 6.10 (2H, br, COOH, OH), 5.80 (1H, dd, $J=16$, 5 Hz, C_{14}–H), 5.50 (1H, dd, $J=16$, 8 Hz, C_{13}–H), 3.9—4.4 (2H, m, C_{12}–H, C_{15}–H), 3.3—3.85, 2.85—3.2 (2H, m, NCH_2), 2.05—2.6 (6H, m), 1.15—1.95 (16H),

0.90 (3H, t, $CH_2C\underline{H}_3$). (*R*)-**2a**: IR ν_{max}^{Nujol} cm^{-1}: 2500—3400, 1720, 1640. MS *m/e*: 339 (M^+). NMR ($CDCl_3$) δ: 6.10 (2H, br, COOH, OH), 5.80 (1H, dd, J=16, 5 Hz), 5.50 (1H, dd, J=16, 8 Hz), 3.9—4.4 (2H, m), 3.3—3.85, 2.8—3.2 (2H, m), 2.05—2.6 (6H, m), 1.15—1.95 (16H), 0.90 (3H, t). (*S*)-**1a**: IR ν_{max}^{Nujol} cm^{-1}: 2500—3400, 1720, 1640. MS *m/e*: 339 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, J=16, 5 Hz), 5.50 (1H, dd, J=16, 8 Hz), 5.00 (2H, br, COOH, OH), 3.9—4.35 (2H, m), 3.3—3.85, 2.8—3.25 (2H, m), 2.05—2.6 (6H, m), 1.15—1.95 (16H), 0.90 (3H, t). (*S*)-**2a**: IR ν_{max}^{Nujol} cm^{-1}: 2500—3400, 1720, 1650. MS *m/e*: 339 (M^+). NMR ($CDCl_3$) δ: 6.25 (2H, br, COOH, OH), 5.80 (1H, dd, J=16, 5 Hz), 5.50 (1H, dd, J=16, 8 Hz), 3.9—4.35 (2H, m), 3.3—3.85, 2.75—3.25 (2H, m), 2.05—2.6 (6H, m), 1.15—2.0 (16H), 0.90 (3H, t). (*R*)-**1b**: IR ν_{max}^{Nujol} cm^{-1}: 2400—3400, 1720, 1650. MS *m/e*: 325 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, dd, J=16, 5 Hz), 5.50 (1H, dd, J=16, 8 Hz), 5.45 (2H, br, COOH, OH), 3.9—4.35 (2H, m), 3.25—3.85, 2.7—3.2 (2H, m), 2.05—2.6 (6H, m), 1.1—1.95 (14H), 0.90 (3H, t). (*R*)-**1c**: IR ν_{max}^{Nujol} cm^{-1}: 2500—3200, 1725, 1660. MS *m/e*: 353 (M^+). NMR ($CDCl_3$) δ: 6.50 (2H, br, COOH, OH), 5.75 (1H, dd, J=16, 5 Hz), 5.50 (1H, dd, J=16, 8 Hz), 3.95—4.3 (2H, m), 3.35—3.75, 2.7—3.1 (2H, m), 2.05—2.6 (6H, m), 1.1—1.95 (18H), 0.90 (3H, t). (*R*)-**1d**: IR ν_{max}^{Nujol} cm^{-1}: 2500—3200, 1720, 1650. MS *m/e*: 367 (M^+). NMR ($CDCl_3$) δ: 5.75 (3H, m, COOH, OH, C_{14}–H), 5.45 (1H, dd, J=16, 8 Hz), 3.95—4.3 (2H, m), 3.25—3.8, 2.7—3.15 (2H, m), 2.0—2.6 (6H, m), 1.05—1.95 (20H), 0.90 (3H, t). (*R*)-**1e**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2300—3400, 1700, 1660. MS *m/e*: 381 (M^+). NMR ($CDCl_3$) δ: 5.95 (2H, br, COOH, OH), 5.80 (1H, dd, J=16, 5 Hz), 5.50 (1H, dd, J=16, 8 Hz), 3.9—4.35 (2H, m), 3.3—3.8, 2.65—3.2 (2H, m), 2.05—2.6 (6H, m), 1.05—1.95 (22H), 0.90 (3H, t). (*R*)-**1f**: IR $\nu_{max}^{liq.}$ cm^{-1}: 2300—3500, 1710, 1660. MS *m/e*: 395 (M^+). NMR ($CDCl_3$) δ: 6.40 (2H, br, COOH, OH), 5.75 (1H, dd, J=16, 5 Hz), 5.45 (1H, dd, J=16, 8 Hz), 3.95—4.35 (2H, m), 3.25—3.8, 2.65—3.15 (2H, m), 2.05—2.6 (6H, m), 1.1—1.95 (24H), 0.90 (3H, t). (*R*)-**1g**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1710, 1655. MS *m/e*: 409 (M^+). NMR ($CDCl_3$) δ: 5.80 (1H, m), 5.70 (2H, br, COOH, OH), 5.45 (1H, dd, J=16, 8 Hz), 3.95—4.3 (2H, m), 3.25—3.8, 2.7—3.1 (2H, m), 2.05—2.6 (6H, m), 1.05—1.9 (26H), 0.90 (3H, t).

Preparation of 13——A solution of diazomethane (excess) in ether was added to a solution of (*R*)-**1a** (815 mg, 2.4 mmol) in MeOH (2 ml) and ether (16 ml) at 0°. After stirring for 3 hr, the solvent was removed. The resulting oil (845 mg) was dissolved in pyridine (4 ml) and acetic anhydride (2 ml). The mixture was stirred for 15 hr at room temperature. After usual work-up, the crude product was chromatographed on silica gel (AcOEt: MeOH=30: 1 as an eluent) to give 900 mg (95%) of **13** as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1740, 1695. MS *m/e*: 395 (M^+). NMR ($CDCl_3$) δ: 5.05—5.9 (3H, m, olefinic H, C_{15}–H), 3.85—4.25 (1H, m, C_{12}–H), 3.65 (3H, s, OCH_3), 3.2—3.75, 2.65—3.1 (2H, m, NCH_2), 2.05 (3H, s, $OCOCH_3$), 1.9—2.6 (6H, m), 1.05—1.9 (16H), 0.90 (3H, t, $CH_2C\underline{H}_3$). $[\alpha]_D^{15}$ −26.9° (c=2.1, EtOH). *Anal.* Calcd for $C_{22}H_{37}NO_5$: C, 66.80; H, 9.43; N, 3.54. Found: C, 66.63; H, 9.30; N, 3.39.

Ozonolysis of 13——A stream of ozonized oxygen was passed into a stirred solution of **13** (474 mg, 1.2 mmol) in MeOH–CH_2Cl_2 (1: 1) (24 ml) at −78°. After stirring for 15 min, the system was flushed with nitrogen gas and a solution of triphenylphosphine (629 mg, 2.4 mmol) in CH_2Cl_2 (3 ml) was added. The mixture was further stirred for 30 min at −78° and the solvent was evaporated off. The residue was chromatographed on silica gel. Elution with $CHCl_3$ afforded 185 mg (90%) of **14** as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1740. MS *m/e*: 172 (M^+). NMR ($CDCl_3$) δ: 9.50 (1H, s, CHO), 5.00 (1H, t, J=6 Hz, $C\underline{H}OCOCH_3$), 2.20 (3H, s, $OCOCH_3$), 1.1—2.0 (8H), 0.90 (3H, t, $CH_2C\underline{H}_3$). $[\alpha]_D^{21}$ −33.2° (c=2.0, $CHCl_3$). Further elution with $CHCl_3$–MeOH (30: 1) gave 293 mg (96%) of (*R*)-**9**. $[\alpha]_D^{20}$ −2.2° (c=2.0, EtOH). The spectral data and the specific rotation of this compound ((*R*)-**9**) were identical with those of the synthetic intermediate ((*R*)-**9**).

Reduction of (*R*)-9 to (*R*)-8——Powdered $NaBH_4$ (43 mg, 1.14 mmol) was added to a solution of (*R*)-**9** (290 mg, 1.14 mmol) (obtained by the degradation of **13**) in EtOH (5 ml) at −25°. After stirring for 40 min, the mixture was worked up as described for the preparation of (*R*)-**5**. Distillation of the crude product gave 264 mg (90%) of (*R*)-**8**, bp 206—210°/0.03 mmHg, which gave colorless crystals, mp and mixed mp 54—55°. $[\alpha]_D^{18}$ −9.5° (c=2.0, EtOH).

Conversion of 14 into 16——A suspension of **14** (172 mg, 1 mmol) in iso-PrOH (2 ml) and H_2O (4.5 ml) was oxidized in the presence of $NaHCO_3$ (126 mg, 1.5 mmol) and Pt catalyst[14] (prepared from 227 mg of PtO_2) at room temperature under atmospheric pressure of oxygen. After 6 hr, the catalyst was filtered off. The filtrate was acidified with 4 N H_2SO_4 and extracted with ether. The extract was washed with brine and dried. Removal of the solvent gave **15** (155 mg). IR $\nu_{max}^{liq.}$ cm^{-1}: 2500—3400, 1740, 1720. This oil, without further purification, was dissolved in 0.1 N NaOH (21 ml) and the mixture was stirred at room temperature under an argon atmosphere. After 15 hr, the mixture was acidified with 4 N H_2SO_4 and extracted with ether. The extract was washed with brine, and dried. Removal of the Et_2O gave 115 mg (79% yield from **14**) of **16**. mp 57—59°. IR ν_{max}^{Nujol} cm^{-1}: 3450, 2500—3200, 1735. NMR ($CDCl_3$) δ: 7.30 (2H, br, COOH, OH), 4.30 (1H, t, J=5 Hz, $C\underline{H}OH$), 1.1—2.1 (8H), 0.90 (3H, t, $CH_2C\underline{H}_3$). $[\alpha]_D^{17}$ +6.8° (c=5.8, $CHCl_3$). (Lit.[15] $[\alpha]_D^{25}$ +6.9° (c=5.8, $CHCl_3$)).

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