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A Novel Synthesis of (±)-Carbacyclin

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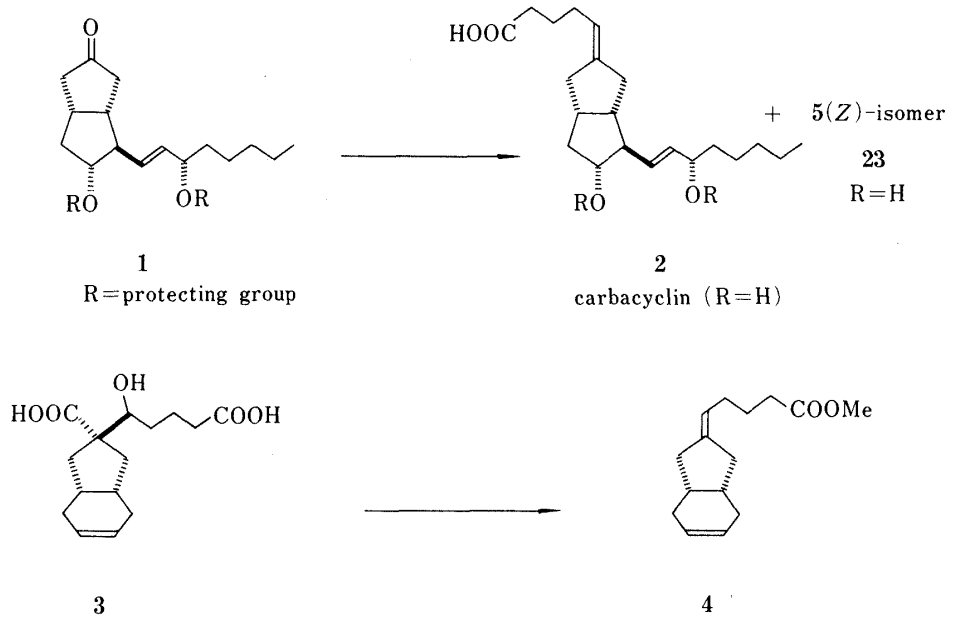
Carbacyclin (**2**, R=H) was synthesized by the application of a new method for introducing the carboxylic acid side chain *via* dehydrative decarboxylation of the β-hydroxy carboxylic acid (**19**).

Keywords——dehydrative decarboxylation; aldol condensation; alkylation; Wittig reaction; ring transformation

Prostacyclin (PGI_2), a metabolite of arachidonic acid, appears to have an important role in preventing stroke, thrombosis, and heart attack. However, because of the labile enol ether linkage, prostacyclin is a very unstable compound. This inherent instability seems to be overcome by replacing the enol ether oxygen atom with a methylene group. Thus, carbacyclin [9(0)methanoprostacyclin, 6a-carbaprostaglandin I_2[1)]] (**2**, R=H) has been synthesized by many groups. It is currently known that the biological profile of carbacyclin is very similar to that of prostacyclin. The synthetic routes have the common feature that the carboxylic acid side chain is introduced by Wittig reaction of the [3.3.0]octan-3-one (**1**) with (4-carboxybutylidene)triphenylphosphorane at the last stage of the synthesis, except for just a few cases[2,3] (Chart 1).



1
R=protecting group

2
carbacyclin (R=H)

3

4

Chart 1

This Wittig reaction requires critical reaction conditions, because of the rapid and ready enolization[3] of the keto group in the bicyclo [3.3.0]octane (**1**). In addition to this problem, the tedious separation of the undesired (*Z*)-form and the desired (*E*)-form is also unavoidable in this synthetic route.

We have investigated the synthesis of carbacyclin involving the use of a new method for introducing the carboxylic acid side chain (Chart 2). In a preliminary experiment, we succeeded in dehydrative decarboxylation of the β-hydroxy carboxylic acid (**3**) by treatment with *N*,*N*-dimethylformamide dimethyl acetal in $CHCl_3$,[4] and the olefin (**4**) was obtained in 53% yield.

This dehydrative decarboxylation reaction seemed to provide a promising route for the synthesis of carbacyclin. The starting material (**5**) was synthesized in 3 steps from *cis*-1,2-dihydroxymethyl-4-cyclohexene according to Krapcho's method.[5] Reaction of the ester (**5**) with methyl 4-chloroformylbutanoate in the presence of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) afforded the keto diester (**6**) as a single stereoisomer in 96.4% yield. The stereochemistry of **6** was assigned as shown in Chart 2 on the assumption that the attack of bulky methyl 4-chloroformylbutanoate from the less hindered side might occur, so that the methyl 5-keto-pentanoate side chain would be introduced in the β-configuration relative to the *cis*-α-fused ring junction. Reduction of **6** with $NaBH_4$ in MeOH afforded the hydroxy ester (**7**) in 77% yield as colorless needles, mp 51 °C. This product was hydrolyzed with 5% aq. NaOH to the hydroxy acid (**3**), mp 119 °C. The acetate (**8**) was obtained in 98% yield from **7** by a usual acetylation procedure.

With the object of transforming the cyclohexene ring to a cyclopentane ring, the olefin linkage in **8** was subjected to oxidative cleavage with O_3 to give the dialdehyde (**9**) in 97% yield. The intramolecular aldol condensation of **9**, which was catalyzed by organic bases such as piperidine, resulted in the formation of the undesired α,β-unsaturated aldehyde (**11**) accompanied with a small amount of the desired hydroxy aldehyde (**10**). However, we found that the aldol condensation in the presence[6] of Zn^{++} showed a remarkably reduced formation of **11**, affording **10** in excellent yield. In this aldol condensation, other possible isomers such as the 11β-hydroxy-12α-formyl compound (PG numbering) were not detected. The hydroxy aldehyde (**10**), which gave a single spot on thin layer chromatography (TLC), should theoretically consist of a mixture (**10A** and **10B**) of the C_5-epimers, but attempts to separate these components were not successful.

Horner–Wittig reaction of **10** with 2-oxo-heptylidene-tributylphosphorane gave the enone (**12**) in 66% yield. Prior to reduction of the C_{15}-ketone, the C_{11}–OH in **12** was protected as the tetrahydro pyranyl ether with dihydropyran (97% yield) because, in a preliminary reduction of the C_{11}-tetrahydropyranyl ether with $NaBH_4$ in MeOH, the yield of the desired 15(*S**)-OH was improved in comparison with that obtained from the C_{11}–OH compound.

The tetrahydropyranyl acetate (**13**) was reduced with $NaBH_4$ in MeOH to yield a mixture (**14**) of the 15(*S**)-OH and 15(*R**)-OH products in 90% yield, and then the tetrahydropyranyl function in **14** was deprotected in aq. AcOH to facilitate the separation of the C_{15}-epimeric alcohols. Thus, the diols (**15**) were separated into the less polar fraction [(**15b**, 15(*R**)-OH] in 25% yield and the polar fraction [**15a**, 15(*S**)-OH] in 35% yield by column chromatography on silica gel. In order to differentiate the C_5-alcohols the 11, 15-diol in **15a** was again protected as the bistetrahydropyranyl ether (**16**, 86% yield) in a usual manner.

By treatment with K_2CO_3 in MeOH at room temperature, **16** was hydrolyzed to a mixture (**17** and **18**) of the C_5-epimeric alcohols which were observed as two adjacent spots on TLC (**17**, *Rf* 0.63 and **18**, *Rf* 0.70 in AcOEt–hexane 1 : 1) and were separated by column chromatography on silica gel. In this way, the C_5-epimeric alcohols [**17**, 5(*S**)-OH] and [**18**, 5(*R**)-OH] were obtained in 39% and 25% yields, respectively. The alcohol (**17**) having *Rf* 0.63 was hydrolyzed with 5% aq. KOH to afford the diacid (**19**) in 92% yield, and this was

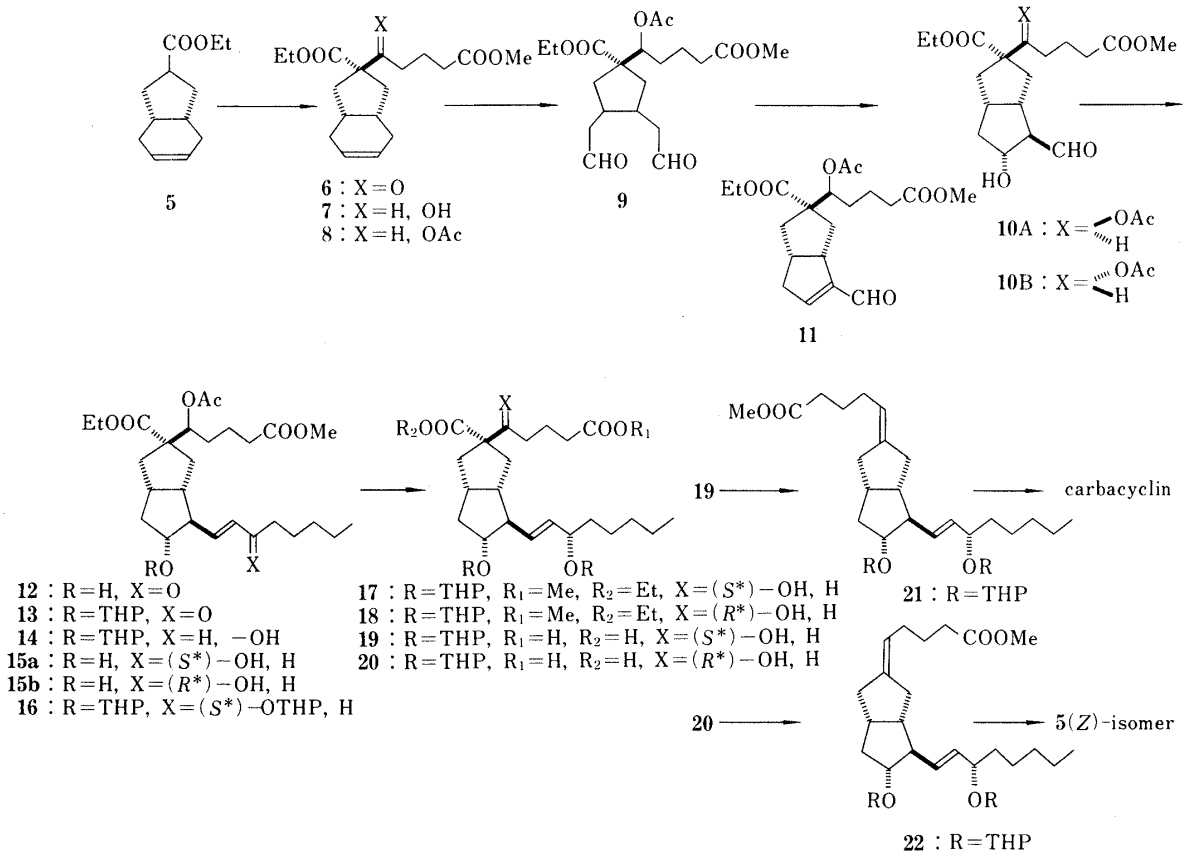


Chart 2

subjected to dehydrative decarboxylation by treatment with *N,N*-dimethylformamide dimethyl acetal in a manner similar to that used in the preliminary experiment. The dehydrative decarboxylation reaction of **19** proceeded stereospecifically to afford only the 5(*E*)-olefin ester (**21**) in 47.2% yield. Deprotection of the tetrahydropyranyl function in **21** by treatment with aq. AcOH followed by hydrolysis of the ester function with 5% aq. KOH afforded (±)-carbacyclin (**2**, R=H) in 50% yield as colorless crystals, mp 70 °C, recrystallized from AcOEt–hexane. The product was identical with an authentic sample[7] on the basis of mixed mp determination and proton nuclear magnetic resonance (^{1}H-NMR) and infrared (IR) spectral comparisons.

Similarly, the alcohol (**18**) having *Rf* 0.70 was converted to the 5 (*Z*)-isomer (**23**)[7] of (±)-carbacyclin *via* the diacid (**20**) and then the 5(*Z*)-olefin ester (**22**). The stereospecific formation of carbacyclin from **17** and of the 5(*Z*)-isomer from **18** suggests that the configuration of the C_5-alcohol in **17** is *S** and that of **18** is *R**.

Experimental

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken on a JASCO IRA-2 spectrometer, and ^{1}H-NMR spectra on a Varian T-60; all chemical shifts are given in ppm downfield from tetramethylsilane. For column chromatography, Kanto chemical silica gel (60—100 mesh) was used. TLC was performed on Silica gel 60 F_{254} plates (Merck). An Ishii ozone generator was used for O_3 oxidation.

5-Hydroxy-5-(8α-carboxy-1β*H*,6β*H*-bicyclo[4.3.0]non-3-en-8β-yl)pentanoic Acid (3)——A mixture of **7** (500 mg), MeOH (10 ml) and 5% NaOH (5 ml) was heated at 60 °C with stirring for 5 h. The reaction mixture was diluted with H_2O (100 ml), made acidic with 5% HCl at 0 °C and extracted with AcOEt (100 ml × 3). The combined

extracts were washed with H_2O (100 ml) and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded a crystalline mass, which was recrystallized from AcOEt–hexane to give **3** (280 mg, 64%) as colorless crystals, mp 119 °C. IR (Nujol): 3400, 1720, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.47 (1H, m, CHOH), 5.60 (2H, s, olefinic H), 6.90 (3H, br, COOH × 2, OH). *Anal.* Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.88; H, 7.77.

8-(4-Methoxycarbonylbutylidene)-1*βH*,6*βH*-bicyclo[4.3.0]non-3-ene (4)——*N*,*N*-Dimethylformamide dimethyl acetal (0.56 ml) was added to a stirred solution of **3** (199 mg) in $CHCl_3$ (10 ml) at room temperature. The mixture was stirred for 1 h and then refluxed for 6 h. The reaction mixture was diluted with H_2O (30 ml) and extracted with AcOEt (50 ml × 3). The combined extracts were washed with H_2O (50 ml × 2) and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded an oily residue which was purified by column chromatography on silica gel (2 g). The fraction eluted with 1—2% AcOEt in hexane (v/v) was collected, and removal of the solvent afforded **4** (87 mg, 53%) as a colorless oil. IR (neat): 1740, 1685, 1175, 1055 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.67 (3H, s, COOMe), 5.20 (1H, t, J=6 Hz, olefinic H), 5.57 (2H, s, olefinic H). *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.01; H, 9.61.

Methyl 5-Oxo-5-(8α-ethoxycarbonyl-1*βH*,6*βH*-bicyclo[4.3.0]non-3-en-8*β*-yl)pentanoate (6)——A solution of **5** (15.72 g) in THF (10 ml) was added dropwise over 0.5 h to a stirred solution of LDA [prepared from BuLi (15% in hexane w/v) (50 ml) and diisopropylamine (17.2 ml)] in THF (400 ml) under an Ar atmosphere at −78 °C and the whole was stirred for 1 h. Methyl 4-chloroformylbutanoate (14.66 g) in THF (10 ml) was added dropwise to the resulting carbanion with stirring at −78 °C, and then the reaction temperature was kept for 1 h at −15 to −30 °C. The reaction mixture was poured into ice water (300 ml), and extracted with AcOEt (200 ml × 3). The combined extracts were washed with H_2O (300 ml × 2) satd. with NaCl, and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded an oily residue which was subjected to column chromatography on silica gel (500 g). The fraction eluted with 5—30% AcOEt in hexane (v/v) was collected. Removal of the solvent afforded **6** (25.11 g, 96%) as a colorless oil. IR (neat): 1730, 1710, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=5 Hz, CH_2CH_3), 3.66 (3H, s, COOMe), 4.17 (2H, q, J=5 Hz, OCH_2CH_3), 5.58 (2H, s, olefinic H). *Anal.* Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.23; H, 8.01.

Methyl 5-Hydroxy-5-(8α-ethoxycarbonyl-1*βH*,6*βH*-bicyclo[4.3.0]non-3-en-8*β*-yl)pentanoate (7)——$NaBH_4$ (1.22 g) was added portionwise to a stirred solution of **6** (9.92 g) in MeOH (200 ml) at 0—3 °C. The reaction mixture was stirred for 1.5 h, poured into ice water (500 ml) and extracted with AcOEt (400 ml × 3). The combined extracts were washed with H_2O (500 ml × 2) satd. with NaCl, and dried (Na_2SO_4). The solvent was removed *in vacuo* to afford a crystalline residue which was recrystallized from hexane to yield colorless needles **7** (7.65 g, 77%), mp 51 °C. IR (Nujol): 3500, 1730, 1245, 1190 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=5 Hz, CH_2CH_3), 3.67 (3H, s, COOMe), 4.15 (2H, q, J=5 Hz, OCH_2CH_3), 5.63 (2H, s, olefinic H). *Anal.* Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.49; H, 8.59.

Methyl 5-Acetoxy-5-(8α-ethoxycarbonyl-1*βH*,6*βH*-bicyclo[4.3.0]non-3-en-8*β*-yl)pentanoate (8)——Ac_2O (20 ml) was added dropwise to a stirred solution of **7** (4.34 g) in pyridine (20 ml) at 5 to10 °C. The reaction mixture was stirred for 10 h at room temperature, poured into ice water (200 ml) and extracted with AcOEt (200 ml × 3). The combined extracts were successively washed with 7% HCl (100 ml × 2), 5% $NaHCO_3$ (100 ml), and H_2O (200 ml × 2) satd. with NaCl, then dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded **8** (4.89 g, 98%) as a colorless oil. IR (neat): 1740, 1225, 1190, 1165 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, COMe), 3.65 (3H, s, COOMe), 5.30 (1H, t, J=6 Hz, CHOAc), 5.62 (2H, s, olefinic H). *Anal.* Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.71; H, 8.31.

Methyl 5-Acetoxy-5-[1α-ethoxycarbonyl-3α,4α-bis(formylmethyl)-1*β*-yl]pentanoate (9)——Ozone gas was bubbled into a solution of **8** (3.01 g) in CH_2Cl_2 (70 ml) at −78 °C and the reaction was monitored by TLC. The resulting ozonide was gradually decomposed with Zn powder (6 g) in the presence of AcOH (2 ml) at 20 to 25 °C. The Zn powder was filtered off, and the filtrate was concentrated *in vacuo* to afford a colorless oil (3.19 g, 97%). IR (neat): 2720, 1725, 1230, 1020 cm^{-1}. 1H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=5 Hz, CH_2CH_3), 2.10 (3H, s, COMe), 3.65 (3H, s, COOMe), 4.16 (2H, q, J=5 Hz, OCH_2CH_3), 5.37 (1H, t, J=6 Hz, CHOAc), 10.5 (2H, m, CHO).

Methyl 5-Acetoxy-5-(3α-ethoxycarbonyl-6*β*-formyl-7α-hydroxy-1*βH*,5*βH*-bicyclo[3.3.0]oct-3*β*-yl)pentanoate (10)——Piperidine HCl salt (200 mg) and $Zn(OAc)_2$ (20 mg) were added successively to a stirred solution of **9** (3.31 g) in CH_3CN (60 ml) at 0 to 3 °C. The mixture was stirred for 0.5 h at 5 to 10 °C, and directly subjected to column chromatography on silica gel (25 g) without work-up. The fraction eluted with 15—40% AcOEt in hexane (v/v) was collected, and removal of the solvent *in vacuo* yielded the unstable **10** (3.18 g, 96%) as a colorless oil. IR (neat): 3480, 2720, 1730, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=5 Hz, CH_2CH_3), 2.10 (3H, s, COMe), 3.70 (3H, s, COOMe), 4.20 (2H, q, J=5 Hz, OCH_2CH_3), 9.70 (1H, s, CHO).

Methyl 5-Acetoxy-5-{3α-ethoxycarbonyl-6*β*-[(*E*)-3-oxo-oct-1-enyl]-7α-hydroxy-1*βH*,5*βH*-bicyclo[3.3.0]oct-3*β*-yl}pentanoate (12)——2-Oxo-heptylidene-tributylphosphorane (3.44 g) in ether (20 ml) was added dropwise to a stirred solution of **10** (3.29 g) in ether (30 ml) at room temperature. The mixture was stirred for 15 h, and the solvent was removed *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel (70 g). The fraction eluted with 35—40% AcOEt in hexane (v/v) was collected. Removal of the solvent afforded **12** (2.72 g, 67%) as a colorless oil. IR (neat): 3470, 1740, 1670, 1620, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6 Hz, CH_2CH_3), 1.29 (3H, t, 5 Hz, CH_2CH_3), 2.07 (3H, s, COMe), 3.66 (3H, s, COOMe), 4.22 (2H, q, J=5 Hz, OCH_2CH_3), 5.17 (1H, t, J=6 Hz, CHOAc), 6.00 (1H, d, J=16 Hz, C_{14}–H), 6.63 (1H, dd, J=16, 7 Hz, C_{13}–H). *Anal.* Calcd for

$C_{27}H_{42}O_8$: C, 65.56; H, 8.56. Found: C, 65.42; H, 8.49.

Methyl 5-Acetoxy-5-(3α-ethoxycarbonyl-6-formyl-1βH,5βH-bicyclo[3.3.0]oct-6-en-3β-yl)pentanoate (11)——Piperidine (100 mg) was added to a stirred solution of **9** (401 mg) in CH_2Cl_2 (10 ml) at 5 °C. The reaction mixture was stirred for 0.5 h at 5 to 10 °C, diluted with H_2O (20 ml) and extracted with AcOEt (50 ml × 3). The combined extracts were washed with H_2O (100 ml × 2) and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (4 g). The fraction eluted with 20% AcOEt in hexane (v/v) was collected, and the solvent was removed *in vacuo* to afford **11** (220 mg, 57%) as a colorless oil. The fraction eluted with 40% AcOEt in hexane (v/v) gave **12** (90 mg, 23%) as a colorless oil. **11**: IR (neat): 2720, 1725, 1680, 1620, 1260, 1200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=5 Hz, CH_2CH_3), 2.00 (3H, s, COMe), 3.70 (3H, s, COOMe), 4.20 (2H, q, J=5 Hz, OCH_2CH_3), 5.20 (1H, t, J=6 Hz, CHOAc), 6.68 (1H, d, J=4 Hz, olefinic H), 8.20 (1H, s, CHO). *Anal.* Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C, 63.33; H, 7.39.

Methyl 5-Acetoxy-5-{3α-ethoxycarbonyl-6β-[(*E*)-3-oxo-oct-1-enyl]-7α-(tetrahydropyran-2-yl)oxy-1βH,5βH-bicyclo[3.3.0]oct-3β-yl}pentanoate (13)——2,3-Dihydropyran (1.5 ml) in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of **13** (1.60 g) in CH_2Cl_2 (25 ml) in the presence of *p*-toluenesulfonic acid (30 mg) at 0 to 5 °C. The reaction mixture was stirred for 1 h at room temperature then diluted with AcOEt (150 ml). The organic layer was washed with 5% aq. $NaHCO_3$ (50 ml), H_2O (100 ml × 2) satd. with NaCl, then dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded an oily residue which was subjected to column chromatography on silica gel (40 g). The fraction eluted with 20—40% AcOEt in hexane (v/v) was collected, and the solvent was removed *in vacuo* to afford **13** (1.82 g, 97%) as a colorless oil. IR (neat): 1740, 1695, 1670, 1630, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.65 (1H, m), 5.17 (1H, t, J=6 Hz, CHOAc), 6.15 (1H, d, J=16 Hz, C_{14}–H), 6.67 (1H, dd, J=16, 7 Hz, C_{13}–H). *Anal.* Calcd for $C_{32}H_{50}O_9$: C, 66.41; H, 8.71. Found: C, 66.69; H, 8.88.

Methyl 5-Acetoxy-5-{3α-ethoxycarbonyl-6β-[(*E*)-3-hydroxy-oct-1-enyl]-7α-(tetrahydropyran-2-yl)oxy-1βH,5βH-bicyclo[3.3.0]oct-3β-yl}pentanoate (14)——$NaBH_4$ (200 mg) was added portionwise to a stirred solution of **13** (1.73 g) in MeOH (30 ml) at 0 to 5 °C. The reaction mixture was stirred for 0.5 h, diluted with H_2O (100 ml) satd. with NaCl, and extracted with AcOEt (50 ml × 3). The combined extracts were washed with H_2O (100 ml) satd. with NaCl, and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel (25 g). The fraction eluted with 30—40% AcOEt in hexane (v/v) was collected, and removal of the solvent afforded **14** (1.58 g) as a colorless oil. IR (neat): 3450, 1740, 1240, 1200 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.05 (3H, s, COMe), 3.68 (3H, s, COOMe), 4.60 (1H, m), 5.10 (1H, t, J=6 Hz, CHOAc), 5.30—5.50 (2H, m, olefinic H). *Anal.* Calcd for $C_{32}H_{52}O_9$: C, 66.18; H, 9.03. Found: C, 66.29; H, 9.18.

5-Acetoxy-6α-ethoxycarbonyl-6a-carbaprostaglandin I_1 Methyl Ester (15a) and Its 15-Epimer (15b)——The tetrahydropyranyl ether (**14**) (1.50 g) dissolved in a mixture of AcOH (16 ml) and H_2O (30 ml) was stirred for 2 h at 50 °C, poured into H_2O (100 ml) satd. with NaCl, and extracted with AcOEt (100 ml × 3). The combined extracts were washed with H_2O (100 ml × 3) satd. with NaCl, and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded an oily residue which was subjected to column chromatography on silica gel (45 g). The fraction eluted with 50—55% AcOEt in hexane (v/v) was collected, and the solvent was removed *in vacuo* to afford the 15(*R**)-OH compound (**15b**) (323 mg, 25%). The fraction eluted with 55—60% AcOEt in hexane afforded a mixture (310 mg, 24%) of **15a** and its 15 epimer (**15b**), and the fraction eluted with 70—100% AcOEt in hexane (v/v) yielded the 15(*S**)-OH compound (**15a**) (451 mg, 35%) as a colorless oil. **15a**: [IR (neat): 3400, 1730, 1260, 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s, COMe), 3.65 (3H, s, COOMe), 4.17 (2H, q, J=6 Hz, OCH_2CH_3), 5.40 (2H, m, olefinic H). *Anal.* Calcd for $C_{27}H_{44}O_8$: C, 65.30; H, 8.93. Found: C, 65.55; H, 8.88]. **15b**: [IR (neat): 3400, 1730, 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, COMe), 3.77 (3H, s, COOMe), 5.40 (2H, m, olefinic H). *Anal.* Calcd for $C_{27}H_{44}O_8$: C, 65.30; H, 8.93. Found: C, 65.40; H, 8.83].

5-Acetoxy-6α-ethoxycarbonyl-6a-carbaprostaglandin I_1 Methyl Ester 11,15-Bis(tetrahydropyran-2-yl)ether (16)——In a manner similar to that described for **13**, the 11,15-diol of **15a** (725 mg) was protected with dihydropyran (0.4 ml) in the presence of *p*-toluenesulfonic acid (trace). The resultant crude oil (1.02 g) was purified by column chromatography on silica gel (20 g). The fraction eluted with 15—25% AcOEt in hexane was collected, and removal of the solvent *in vacuo* afforded **16** (834 mg, 86%) as a colorless oil. IR (neat): 1740, 1240, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, COMe), 3.75 (3H, s, COOMe), 5.10 (1H, t, J=6 Hz, CHOAc), 5.40 (2H, m, olefinic H). *Anal.* Calcd for $C_{37}H_{60}O_{10}$: C, 66.84; H, 9.10. Found: C, 66.72; H, 9.00.

5(*S)-Hydroxy-6α-ethoxycarbonyl-6a-carbaprostaglandin I_1 Methyl Ester 11,15-Bis(tetrahydropyran-2-yl)ether (17) and Its 5(*R**)-Epimer (18)**——K_2CO_3 (175 mg) was added to a stirred solution of **16** (810 mg) in MeOH (30 ml) at room temperature. The mixture was stirred for 18 h, diluted with H_2O (150 ml) and extracted with AcOEt (100 ml × 3). The combined extracts were washed with H_2O (100 ml × 2) satd. with NaCl and dried (Na_2SO_4). The solvent was removed *in vacuo*, yielding an oily residue which was chromatographed on silica gel (30 g). The less polar fraction eluted with 12.5—15% AcOEt in hexane (v/v) afforded the 5(*R**)-OH compound (**18**) (181 mg, 25%, *Rf* 0.70 in AcOEt–hexane 1 : 1) as a colorless oil. The polar fraction eluted with 17.5—25% AcOEt in hexane (v/v) afforded the 5(*S**)-OH compound (**17**) (294 mg, 38.7%, *Rf* 0.63 in AcOEt–hexane 1 : 1) as a colorless oil. **17**: [IR (neat): 3450, 1740, 1200, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.62 (3H, s, COOMe), 4.15 (2H, q, J=5 Hz, OCH_2CH_3), 4.63 (2H, br), 5.30—5.50 (2H, m, olefinic H). *Anal.* Calcd for $C_{35}H_{58}O_9$: C, 67.49; H, 9.39. Found: C, 67.70; H, 9.30]. **18**: [IR (neat):

3450, 1735, 1200, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.55 (3H, s, COOMe), 4.20 (2H, q, J=5 Hz, OCH_2CH_3), 4.63 (2H, br), 5.30—5.50 (2H, m, olefinic H). *Anal.* Calcd for $C_{35}H_{58}O_9$: C, 67.49; H, 9.39. Found: C, 67.68; H, 9.31].

5(*S)-Hydroxy-6α-carboxy-6a-carbaprostaglandin I_1 11,15-Bis(tetrahydropyran-2-yl)ether (19) and the 5(*R**)-Epimer (20)**——A stirred solution of **17** (250 mg) in MeOH (5 ml) was treated dropwise with 10% NaOH (5 ml) at room temperature. The mixture was stirred at 50 °C for 3 h, diluted with ice water (50 ml), made acidic with 7% HCl at 0 to 2 °C, and extracted with AcOEt (50 ml × 3). The combined extracts were washed with H_2O (50 ml × 2) satd. with NaCl, and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded **19** (215 mg, 92%) as a colorless oil, which was subjected to dehydrative decarboxylation without being purified. IR (neat): 3450, 1730, 1700, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.68 (2H, br), 5.50 (2H, m, olefinic H).

In a manner similar to that described for **19**, **18** (151 mg) afforded **20** (125 mg, 86%) as a colorless oil, which was subjected to dehydrative decarboxylation without being purified. IR (neat): 3450, 1710, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.72 (2H, br), 5.45 (2H, m, olefinic H).

Carbacyclin Methyl Ester 11,15-Bis(tetrahydropyran-2-yl)ether (21)——A solution of the 5(*S**)-alcohol **19** (540 mg) in a mixture of $CHCl_3$ (15 ml) and *N*,*N*-dimethylformamide dimethyl acetal (0.8 ml) was stirred at room temperature for 1 h, and then refluxed for 3 h. The reaction mixture was diluted with H_2O (50 ml) and extracted with AcOEt (50 ml × 3). The combined extracts were washed with H_2O (50 ml × 2) and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded on oily residue which was purified by column chromatography on silica gel (5 g). The fraction eluted with 10—15% AcOEt in hexane (v/v) was collected. The solvent was removed *in vacuo* to afford **21** (234 mg, 47%) as a colorless oil. IR (neat): 1740, 1200, 1130, 1070, 1035 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 3.65 (3H, s, COOMe), 4.60 (2H, br), 5.00—5.40 (3H, m, olefinic H). *Anal.* Calcd for $C_{32}H_{52}O_6$: C, 72.14; H, 9.84. Found: C, 72.33; H, 9.79.

5(*Z*)-Carbacyclin Methyl Ester 11,15-Bis(tetrahydropyran-2-yl)ether (22)——In a similar manner to that described for **21**, **20** (93 mg) yielded **22** (55 mg, 64.5%) as a colorless oil. IR (neat): 1745, 1200, 1130, 1075, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.65 (3H, s, COOMe), 4.68 (2H, br), 5.00—5.50 (3H, m, olefinic H). *Anal.* Calcd for $C_{32}H_{52}O_6$: C, 72.14; H, 9.84. Found: C, 72.29; H, 9.71.

Carbacyclin(2, R = H) and Its 5(*Z*)-Isomer (23)——A stirred solution of **21** (211 mg) in acetone (10 ml) was treated with 3.5% HCl (5 ml). The mixture was stirred at room temperature for 1 h, then diluted with H_2O (100 ml), and extracted with AcOEt (50 ml × 3). The combined extracts were washed with H_2O (50 ml × 2) satd. with NaCl and dried (Na_2SO_4). The solvent was removed *in vacuo* to afford an oily residue (138 mg), which was hydrolyzed with 5% aq. KOH (2 ml) in MeOH (3 ml) at room temperature. The solution was made acidic with 7% HCl, and extracted with AcOEt (50 ml × 3). The combined extracts were washed with H_2O satd. with NaCl, and dried (Na_2SO_4). Removal of the solvent *in vacuo* yielded **2** (R = H) (70 mg, 50%) as colorless needles, mp 70 °C, recrystallized from AcOEt–hexane. The product was identical with an authentic sample on the basis of mixed mp determination and ^{1}H-NMR and IR spectral comparisons.[7]

In a similar manner, **22** (50 mg) afforded **23** (19 mg) as colorless needles, mp 90 °C, recrystallized from AcOEt–hexane. This product was also identical with an authentic sample on the basis of mixed mp determination and ^{1}H-NMR and IR spectral comparisons.[7]

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References and Notes

1) W. Bartmann and G. Beck, *Angew. Chem. Int. Ed. Engl.*, **21**, 751 (1982).
2) Y. Konishi, M. Kawamura, Y. Iguchi, Y. Arai, and M. Hayashi, *Tetrahedron*, **37**, 4391 (1981).
3) D. R. Morton, Jr. and F. C. Brokaw, *J. Org. Chem.*, **44**, 2880 (1979). The introduction of the carboxylic acid side chain was accomplished by Johnson's method using sulfoximine at the last stage of the synthesis.
4) S. Hara, H. Taguchi, H. Yamamoto, and H. Nozaki, *Tetrahedron Lett.*, **1975**, 1545.
5) A. P. Krapcho and B. P. Mundy, *Tetrahedron*, **26**, 5437 (1970).
6) The role of Zn^{++} in the aldol condensation is not clear.
7) K. Kojima and K. Sakai, *Tetrahedron Lett.*, **1978**, 3743.