Synthesis of 3-Oxa-5-alkylideneisocarbacyclins

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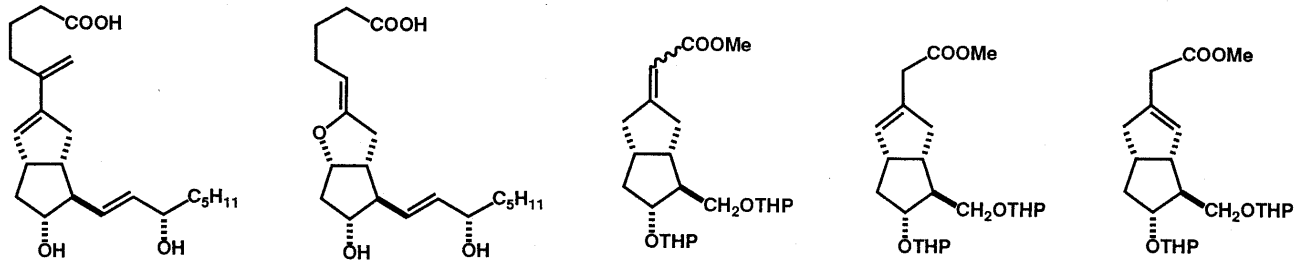
3-Oxa-5-methyleneisocarbacyclin (14a) and 3-oxa-5-ethylideneisocarbacyclin (19a) were synthesized. Compound 14a showed a potent antiplatelet aggregating activity, whereas 19a was inactive.

Keywords carbacyclin; isocarbacyclin; synthesis; methyleneisocarbacyclin; platelet aggregation; β-oxidation

Introduction of a substituent at the C-5 position of prostacyclin was intensively investigated in order to obtain an analogue in which the enol ether linkage in prostacyclin would be stabilized.[1] Suitable substituents are electron withdrawing moieties such as cyano, chloro, carboxy, and formyl groups. Prostacyclin analogues having such a substituent at the C-5 position were quite stable compared to prostacyclin itself. However, antiplatelet aggregating activity was markedly decreased. In the course of our study to synthesize a stable prostacyclin analogue, we found that the introduction of methylene moiety at the C-5 position of isocarbacyclin generated a highly potent analogue of isocarbacyclin, namely 5-methyleneisocarbacyclin.[2] This high potency is attributed to electronic and conformational similarity to prostacyclin. On the other hand, β-oxidation reaction is one of the main metabolic pathways of prostaglandins. In order to obtain a biologically more stable analogue, we planned to synthesize the 3-oxa-analogue of 5-methyleneisocarbacyclin (**1**). Here we describe the synthesis and biological activity of 3-oxa-5-methyleneisocarbacyclin and some ω-chain analogues. Because of the observed high potency of 3-oxa-5-methylneisocarbacyclin we were further interested in 3-oxa-5-ethylideneisocarbacyclin, whose synthesis and biological activity are also described.

Synthesis of 3-Oxa-5-methyleneisocarbacyclin and Its Analogues We started the synthesis with **5a**, a key intermediate for carbacyclin synthesis.[3] Horner–Emmons reaction of the ketone (**5a**) with trimethyl phosphonoacetate and NaH gave the ester (**6a**) in 97% yield as a mixture of *E*,*Z*-stereoisomers (1 : 1). In order to introduce the 3-oxa and 5-alkylidene moieties, the first step is a deconjugative alkylation of the ester (**6a**) leading to the ester (**7a**). In this step, another ester (**7b**) is expected to be formed as well. Therefore, as a model reaction, a deconjugation reaction of the α,β-unsaturated ester (**3**) was examined to obtain the β,γ-unsaturated ester (**4a**) regioselectively: the deconjugation of the ester (**3**) with lithium dicyclohexylamide alone in tetrahydrofuran (THF) resulted in incomplete conversion. Addition of hexamethylphosphoramide caused the complete conversion in the isomer ratio of 66 to 34 for the ester (**4a**) to the ester (**4b**). In this deconjugation reaction hexamethylphosphoramide seems to play a significant role. Therefore, we investigated the deconjugation reaction using other additive such as hexaethylphosphoramide, tripiperidinophosphoramide, *N*,*N*-tetraethylethylenediamine, and *N*,*N*-tetramethylpropylenediamine in place of hexamethylphosphoramide. However, these additives did not improve an isomer ratio of the ester (**4a**) to the ester (**4b**), resulting in a ratio of approximately 50 to 50.[4] Therefore, the deconjugative alkylation reaction of the ester (**6a**) was carried out using the most favorable deconjugation reaction condition using lithium dicyclohexylamide and hexamethylphosphoramide: treatment of the ester (**6a**) with lithium dicyclohexylamide and hexamethylphosphoramide in tetrahydrofuran yielded an ester-enolate which was alkylated with benzylchloromethylether to give a mixture of benzyl ethers (**7a** and **7b**) in 67% yield (**7a** : **7b** = 56 : 34).[5]

In order to introduce the 3-oxa-carboxylic side chain, the mixture of the benzyl ethers (**7a** and **7b**) was reduced with lithium aluminum hydride to afford the mixture of the alcohols (**8a** and **8b**) in 97% yield. Alkylation reaction of a mixture of the alcohols (**8a** and **8b**) with *n*-butyllithium and then lithium chloroacetate yielded a mixture of the acids (**9a** and **9b**) in 87% yield. Thus, we have introduced the 3-oxa-carboxylic side chain. Next, we constructed a 5-methylene moiety from the benzyloxymethyl function at the C-5 position. Debenzylation of the acids (**9a** and **9b**) with sodium in liquid ammonia, followed by esterification with diazomethane afforded a mixture of the alcohols (**10a** and **10b**) in 66% yield. Mesylation of a mixture of the alcohols (**10a** and **10b**) with methanesulfonyl chloride



1 2 3 4a 4b

Chart 1

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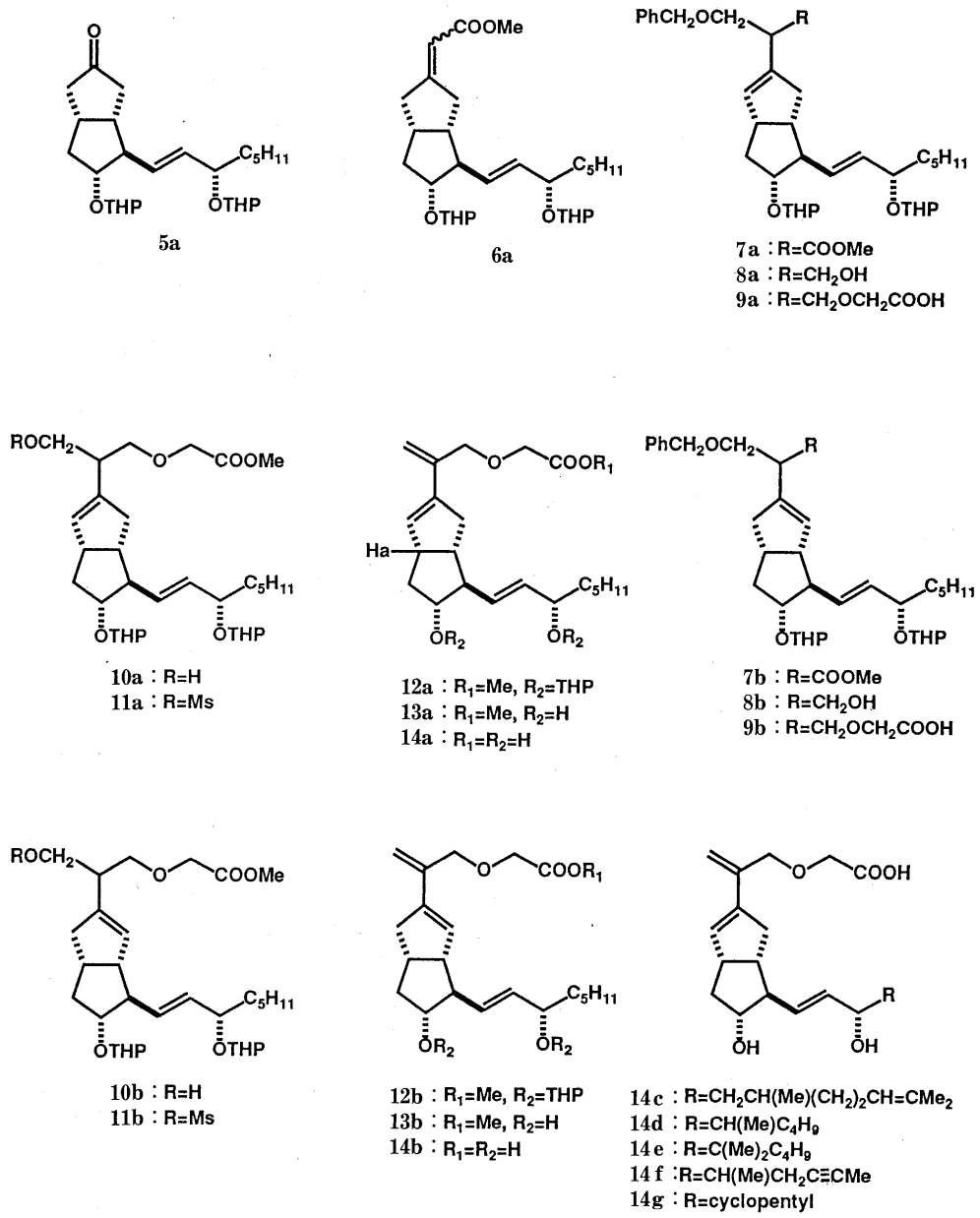

Chart 2

yielded a mixture of the mesylates (**11a** and **11b**) in 98% yield. Treatment of a mixture of the mesylates (**11a** and **11b**) with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) gave the more polar, desired diene (**12a**) and the less polar diene (**12b**) having an isomeric double bond in 56% and 34% yields, respectively. The position of the double bond in the diene (**12a**) was determined on the basis of the ^{1}H-NMR absorption at δ 3.12 ppm due to the H_a proton typical of isocarbacyclin. Hence, the other isomer (**12b**) has a new double bond at the C-3 position on the bicyclooctane ring.

Finally, two protective groups were cleaved by the following reaction: treatment of the diene (**12a**) with aqueous acetic acid yielded the ester (**13a**) in 72% yield. Hydrolysis of the ester (**13a**) with 5% sodium hydroxide solution gave 3-oxa-5-methyleneisocarbacyclin (**14a**), mp 45—47 °C, in 89% yield. By using the same sequence of reactions as described for the synthesis of **14a**, the corresponding ω-chain analogues of the ketone (**5a**) were led to the ω-chain analogues **14c**, **14d**, **14e**, **14f**, and **14g**.

By using the same sequence of reactions as described for the synthesis of **14a**, the diene (**12b**) was also led to 3-oxa-5-methylene-6,9α-methylene-Δ^6-prostaglandin I_1 (**14b**), mp 82—84 °C, in 58% total yield.

Synthesis of 3-Oxa-5-(*Z*)-ethylideneisocarbacyclin In order to introduce a methyl group onto the methylene moiety at the C-5 position of 3-oxa-5-methyleneisocarbacyclin, we investigated the aldol-type alkylation of the ester enolate generated *in situ* from the ester (**6a**) and lithium dicyclohexylamide in the presence of hexamethylphosphoramide: treatment of the ester (**6a**) with lithium dicyclohexylamide in the presence of hexamethylphosphoramide in THF afforded an ester enolate which was alkylated with acetaldehyde to give a mixture of alcohols (**15a** and **15b**) containing γ-alkylated products (**15c**) in 98% yield. These isomers were separated in a later stage of the synthesis. Next, the 5-ethylidene moiety was constructed using the mixture of the alcohols (**15a** and **15b**). Mesylation of the mixture of the alcohols (**15a** and **15b**) with mesyl

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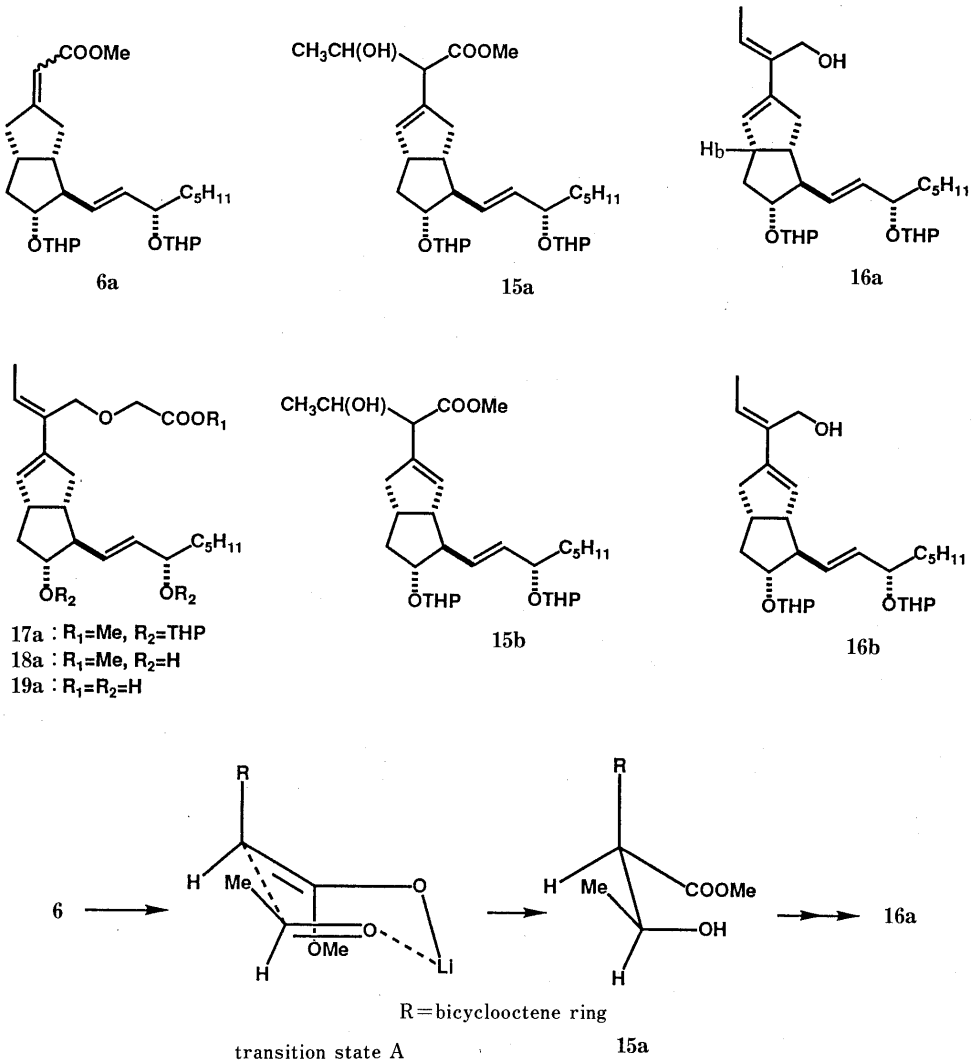

Chart 3

chloride in pyridine, followed by treatment with NaI and DBU, and then lithium aluminum hydride afforded the desired (*Z*)-alconol (**16a**) in 30% overall yield from the ester (**6a**) together with the (*E*)-alcohol (**16b**) containing γ-alkylated products (52% yield). At this stage the isomeric products were easily separated by silica gel column chromatography. The position of the double bond on the bicyclooctane ring in the dienol (**16a**) was determined on the basis of the ^{1}H-NMR absorption at δ 3.12 ppm due to the H_b proton typical of isocarbacyclin. The stereochemistry of the newly formed double bond in **16a** was assigned as *Z* on the basis of the result on a nuclear Overhauser effect (NOE) experiment on the final product (**19a**) derived from **16a**.

The origin of the stereoselective formation of the *Z*-double bond in **16a** is probably the aldol-type reaction of the first step: the ester enolate formed probably has *E* configuration[6] and the reaction of the ester enolate with acetaldehyde proceeds through the most probable transition state A to form the alcohol (**15a**) having the stereostructure shown. Based on *S*N substitution and *E*2 elimination mechanism the compound (**15a**) gives the *Z*-olefin (**16a**).[7]

The 3-oxa-carboxylic side chain was then introduced by means of the following reactions. Treatment of the alcohol (**16a**) with *n*-butyl lithium, followed by the addition of lithium chloroacetate gave the acid, which was esterified with diazomethane to give the ester (**17a**) in 63% yield. The stereochemistry of the double bond at the C-5 position was assigned as *Z* on the basis of the result of a NOE experiment; NOEs were observed between methylene protons at the C-4 position and the methyl protons on the ethylidene moiety.

Finally, the two protective groups were cleaved by the following reactions: treatment of the ester (**17a**) with aqueous acetic acid yielded the ester (**18a**), mp 69—70 °C, in

Table I. Antiplatelet Aggregating Activity of 3-Oxa-5-alkylideneisocarbacyclins (IC_{50} ng/ml) Using Rabbit and Human Platelet Rich Plasma

Compound	Rabbit	Human
14a	8.8	2.3
14b	1560	—
14c	12.3	23
14d	6.6	9.0
14e	258	—
14f	5.1	0.4
14g	4.7	0.8
19a	5520	—
1	1.1	1.0

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62% yield. Hydrolysis of the ester (**18a**) with 5% sodium hydroxide solution gave 3-oxa-5-ethylideneisocarbacyclin (**19a**), mp 100—106 °C, in 77% yield.

Biological Activity Antiplatelet aggregating activity of the compounds synthesized was tested by using rabbit and human platelets.[8] Results are summarized in Table I.[9] In general, introduction of the oxygen function in place of the carbon function at the C-3 position very slightly decreased the activity. Among the 3-oxa-5-methyleneisocarbacyclins, some analogues (**14d**, **14f**, and **14g**) exhibited potent antiaggregating activity for rabbit platelets. In particular, the cyclopentyl analogues (**14g**) and the acetylene analogue (**14f**) showed highly potent activity for human platelets, being more active than 5-methyleneisocarbacyclin (**1**). On the other hand, introduction of a methyl group as in **19a** onto the methylene group at the C-5 position of **14a** markedly decreased the activity.[10] The stereochemical features of **19a** seem to be similar to those of **14a**, because the methyl group on the ethylidene moiety has *cis* configuration to the carboxylic side chain. The compounds (**14a** and **19a**) take the similar three-dimensional shape to that of **1**,[2] in relation to prostacyclin receptor. However, the methyl group of **19a**, oriented outwards, probably hinders a good fit to the receptor,[11] causing the marked decrease of the antiaggregating activity.

In conclusion we have synthesized **14a** and its ω-chain analogues (**14c**, **14d**, **14e**, **14f**, and **14g**). We have also synthesized an analogue (**19a**) having an extra methyl group on the methylene group at the C-5 position of **14a**. Some of the 3-oxa-5-methyleneisocarbacyclins (**14f** and **14g**) have highly potent antiaggregating activity. However, 3-oxa-5-ethylideneisocarbacyclin (**19a**) was only very weakly active.

Experimental

All melting points are uncorrected. ^{1}H-NMR spectra were recorded with a Varian EM-390 (90 MHz) spectrometer in $CDCl_3$, with tetramethylsilane as an internal reference. Infrared (IR) spectra were recorded with a JASCO A-102 spectrometer. Mass spectra (MS) were obtained with a JEOL JMS-G300 spectrometer. Optical rotations were measured with a Perkin Elmer model 141 polarimeter at 24 °C. Removal of the solvent was accomplished with a rotating flash evaporator at 30 mmHg and at 40 °C. Plates for TLC were Silica gel 60-F 254 (E. Merck AG). Columns for ordinary chromatography are prepared with Silica gel 60 (70—230 mesh). In general, reactions were carried out under a nitrogen stream.

(1*S*,2*R*,3*R*,5*R*)-7-Methoxycarbonylmethylene-3-(tetrahydropyran-2-yl)oxy-2-[3(*S*)-(tetrahydropyran-2-yl)oxy-*E*-1-octenyl]bicyclo[3.3.0]octane (6a) NaH in oil (55%, 0.52 g) (washed with hexane) was suspended in dry THF (25 ml) and dry *N*,*N*-dimethylformamide (DMF) (25 ml). Trimethyl phosphonoacetate (2.38 g) was added under ice-cooling and the whole was stirred at room temperature for 40 min. A solution of (1*S*,2*R*,3*R*,5*R*)-7-oxo-3-(tetrahydropyran-2-yl)oxy-2-[3(*S*)-(tetrahydropyran-2-yl)oxy-*E*-1-octenyl]bicyclo[3.3.0]octane (**5a**, 3.0 g) in dry THF (15 ml) was then added under ice-cooling and the whole was further stirred for 3 h. The reaction mixture was poured into brine (150 ml) and the product was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with hexane containing 10—25% EtOAc afforded **6a** (3.29 g, 97%) as an oil. IR (neat): 985, 1030, 1625, 1691 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, br s, CH_3), 3.68 (3H, s, CH_3), 4.70 (2H, br s, OCHO), 5.0—5.75 (2H, m, –CH=CH–), 5.80 (1H, br s, =CH–). MS *m/z*: 490 (M^+), 388, 304.

A Mixture of (5*S*,6*R*,7*R*,1*S*)-3-(2-Benzyloxy-1-methoxycarbonylethyl)-7-(tetrahydropyran-2-yl)oxy-6-[3(*S*)-(tetrahydropyran-2-yl)oxy-*E*-1-octenyl]bicyclo[3.3.0]oct-2-ene (7a) and (5*S*,6*R*,7*R*,1*S*)-3-(2-Benzyloxy-1-methoxycarbonylethyl)-7-(tetrahydropyran-2-yl)oxy-8-[3(*S*)-(tetrahydropyran-2-yl)oxy-*E*-1-octenyl]bicyclo[3.3.0]oct-2-ene (7b) A solution of 15% *n*-butyl lithium in hexane (9.24 ml) was added to a solution of dicyclohexylamine (3.02 ml) in dry THF (70 ml) at −78 °C. The mixture was stirred for 10 min, then hexamethylphosphoramide (2.9 ml) was added and the whole was stirred for a further 10 min. Next, a solution of the ester (**6a**, 3.72 g) in dry THF (10 ml) was added. The reaction mixture was stirred for 10 min, then chloromethyl benzyl ether (2.11 ml) was added at −78 °C and the whole was warmed to −30 °C and stirred for 2.5 h. The reaction mixture was diluted with saturated NH_4Cl (15 ml) and then brine, and extracted with EtOAc. The extract was washed with dilute HCl, dilute $NaHCO_3$ solution and then brine, and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with hexane containing 15—25% EtOAc afforded a mixture of **7a** and **7b** (3.11 g, 67%) as an oil. IR (neat): 980, 1025, 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, br t, CH_3), 3.70 (3H, s, CH_3), 4.55 (2H, s, CH_2), 4.72 (2H, br s, OCHO), 5.1—5.8 (3H, m, =CH–), 7.32 (5H, s, arom-H). MS *m/z*: 610 (M^+), 508, 420.

A Mixture of (5*S*,6*R*,7*R*,1*S*)-3-(1-Benzyloxymethyl-2-hydroxyethyl)-7-(tetrahydropyran-2-yl)oxy-6-[3(*S*)-(tetrahydropyran-2-yl)oxy-*E*-1-octenyl]bicyclo[3.3.0]oct-2-ene (8a) and (5*S*,6*R*,7*R*,1*S*)-3-(1-Benzyloxymethyl-2-hydroxyethyl)-7-(tetrahydropyran-2-yl)oxy-8-[3(*S*)-(tetrahydropyran-2-yl)oxy-*E*-1-octenyl]bicyclo[3.3.0]oct-2-ene (8b) A solution of the mixture of the esters (**7a** and **7b**, 3.09 g) in dry THF (10 ml) was added to a suspension of $LiAlH_4$ (300 mg) in dry THF (50 ml) under ice-cooling. After stirring for 20 min, 4% NaOH solution (1.2 ml) was added and the whole was stirred for 1 h at room temperature. The white precipitate was filtered off. Evaporation of the filtrate gave an oily residue, which was purified by silica gel column chromatography. Elution with hexane containing 30—50% EtOAc afforded a mixture **8a** and **8b** (2.86 g, 97%) as an oil. IR (neat): 980, 1025, 3470 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, br t, CH_3), 4.53 (2H, s, CH_2), 4.70 (2H, br s, OCHO), 5.1—5.8 (3H, m, =CH–), 7.35 (5H, s, arom-H). MS *m/z*: 564 (M^+-18), 480, 396.

A Mixture of 5-Benzyloxymethyl-3-oxaisocarbacyclin 11,15-Di(tetrahydropyran-2-yl) Ether (9a) and 5-Benzyloxymethyl-6(9α)-methylene-3-oxa-Δ^6-prostaglandin I_1 11,15-Di(tetrahydropyran-2-yl) Ether (9b) *n*-Butyl lithium in hexane (15%, 4 ml) was added to a solution of a mixture of the alcohols (**8a** and **8b**, 2.84 g) in dry THF (12 ml) under ice-cooling until the reaction mixture became reddish-yellow. Next, dry DMF (6 ml), dry lithium chloroacetate (734 mg), dry dimethyl sulfoxide (DMSO) (6 ml), and then dry NaI (2.2 g) were added to the reaction mixture. The whole was heated at 40 °C for 1 h, diluted with ice-water mixture, acidified with dilute HCl and extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with hexane containing 30% EtOAc to EtOAc afforded a mixture of **9a** and **9b** (2.7 g, 87%) as an oil. IR (neat): 980, 1025, 1735, 1760 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, m, CH_3), 4.05 (2H, s, CH_2), 4.53 (2H, s, CH_2), 5.1—5.8 (3H, m, =CH–), 7.35 (5H, m, arom-H). MS *m/z*: 640 (M^+), 538, 454.

A Mixture of 5-Hydroxymethyl-3-oxaisocarbacyclin 11,15-Di(tetrahydropyran-2-yl) Ether Methyl Ester (10a) and 5-Hydroxymethyl-6(9α)-methylene-3-oxa-Δ^6-prostaglandin I_1 11,15-Di(tetrahydropyran-2-yl) Ether Methyl Ester (10b) A solution of the mixture of **9a** and **9b** (2.7 g) in dry THF (40 ml) was added to liquid NH_3 (*ca.* 60 ml) below −50 °C. Sodium metal (0.6 g) was added in small pieces and gradually the reaction mixture turned blue. Stirring was continued for 20 min, then excess NH_4Cl was added and the whole was allowed to stand at ambient temperature, while excess NH_3 was stripped off with a stream of nitrogen. The reaction mixture was diluted with ice-water mixture, acidified with dilute HCl and extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was esterified with diazomethane in Et_2O. Evaporation of ether gave an oil, which was purified by silica gel column chromatography. Elution with hexane containing 30—50% EtOAc afforded a mixture of **10a** and **10b** (1.58 g, 66%) as an oil. IR (neat): 975, 1025, 1740, 1758, 3500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, br t, CH_3), 3.78 (3H, s, CH_3), 4.10 (2H, s, CH_2), 4.70 (2H, br s, OCHO), 5.1—5.8 (3H, m, =CH–). MS *m/z*: 462 (M^+-102), 378.

A Mixture of 5-(Methanesulfonyloxy)methyl-3-oxaisocarbacyclin 11,15-Di(tetrahydropyran-2-yl) Ether Methyl Ester (11a) and 5-(Methanesulfonyloxy)methyl-6(9α)-methylene-3-oxa-Δ^6-prostaglandin I_1 11,15-Di(tetrahydropyran-2-yl) Ether Methyl Ester (11b) Methanesulfonyl chloride (878 mg) was added to a solution of the mixture of **10a** and **10b** (1.54 g) in dry pyridine (20 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 1.5 h, diluted with water and extracted with EtOAc. The exract was washed with dilute HCl, brine, dilute $NaHCO_3$ solution, and then brine. The organic phase was dried over Na_2SO_4.

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Evaporation of the solvent gave an oily residue, which was esterified with diazomethane in Et_2O. Evaporation of the Et_2O gave an oil, which was purified by silica gel column chromatography. Elution with hexane containing 30—50% EtOAc afforded a mixture of **11a** and **11b** (1.72 g, 98%) as an oil. IR (neat): 980, 1025, 1758 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, br t, CH_3), 3.01 (3H, s, CH_3), 3.86 (3H, s, CH_3), 4.08 (2H, s, CH_2), 4.70 (2H, br s, OCHO), 5.1—5.8 (3H, m, =CH–). MS *m/z*: 456 ($M^+ - 102 - 84$).

5-Methylene-3-oxaisocarbacyclin 11,15-Di(tetrahydropyran-2-yl) Ether Methyl Ester (12a) and 5(5),6(9α)-Dimethylene-3-oxa-Δ^6-prostaglandin I_1 11,15-Di(tetrahydropyran-2-yl) Ether Methyl Ester (12b) The mixture of the mesylates (**11a** and **11b**, 1.7 g) in dry hexamethylphosphoramide (25 ml), DBU (2.5 ml) and dry NaI (0.8 g) was heated at 100 °C under stirring for 1 h. The reaction mixture was diluted with brine and extracted with EtOAc. The extract was washed with water, dilute HCl, water, dilute $NaHCO_3$ solution, and then brine. The orgaic phase was dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with hexane containing 10—20% EtOAc afforded **12b** (470 mg, 34%) as an oil and further elution with hexane containing 20—25% EtOAc afforded **12a** (783 mg, 56%) as an oil. **12a**: IR (neat): 975, 1025, 1740 (sh), 1758 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, br t, CH_3), 3.78 (3H, s, CH_3), 4.10 (2H, s, CH_2), 4.30 (2H, s, CH_2), 4.72 (2H, br s, OCHO), 5.0—5.8 (4H, m, =CH–), 5.88 (1H, br s, =CH–). MS *m/z*: 540 (M^+), 444, 360. **12b**: IR (neat): 980, 1025, 1740 (sh), 1758 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, br t, CH_3), 3.77 (3H, s, CH_3), 4.09 (2H, s, CH_2), 4.30 (2H, s, CH_2), 4.72 (2H, br s, OCHO), 5.0—5.8 (4H, m, =CH–), 5.88 (1H, br s, =CH–). MS *m/z*: 540 (M^+), 444, 360.

5-Methylene-3-oxaisocarbacyclin Methyl Ester (13a) A solution of **12a** (760 mg) in THF (12 ml) and AcOH (25 ml) was stirred at 50°C for 1.2 h, while water (50 ml) was added to the reaction mixture in several portions so as to keept the solution clear. The reaction mixture was diluted with brine and extracted with EtOAc. The extract was washed with brine, cold 3% NaOH solution, and then brine. The organic phase was dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with hexane containing 60—90% EtOAc afforded the desired compound (527 mg, 99%) as crystals. Recrystallization from a mixture of hexane and EtOAc (5 : 1) afforded the pure compound (**13a**, 372 mg, 72%), mp 64—65 °C. IR (KBr): 970, 1125, 1625, 1720, 1750, 1765, 3430 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, br t, CH_3), 3.13 (1H, m, –CH–), 3.75 (3H, s, CH_3), 4.10 (2H, s, CH_2), 4.30 (2H, s, CH_2), 5.10 (1H, s, –CH=), 5.22 (1H, s, –CH=), 5.57 (2H, m, –CH=CH–), 5.90 (1H, br s, –CH=). *Anal.* Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.84; H, 8.82. MS *m/z*: 378 (M^+), 360. $[\alpha]_D = -28.3°$ ($c = 1.0$, $CHCl_3$).

5(5),6(9α)-Dimethylene-3-oxa-Δ^6-prostaglandin I_1 Methyl Ester (13b) A solution of **12b** (450 mg) in THF (7.5 ml) and AcOH (15 ml) was stirred at 50 °C for 1.0 h, while water (30 ml) was added to the reaction mixture in several portions so as to keep the solution clear. The reaction mixture was diluted with brine and extracted with EtOAc. The extract was washed with brine, cold 3% NaOH solution, and then brine. The organic phase was dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with hexane containing 50—90% EtOAc afforded **13b** (272 mg, 86%) as an oil. IR (neat): 970, 1130, 1630, 1755, 3350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, br t, CH_3), 3.76 (3H, s, CH_3), 4.09 (2H, s, CH_2), 4.31 (2H, s, CH_2), 5.12 (1H, s, –CH=), 5.22 (1H, s, –CH=), 5.58 (2H, m, –CH=CH–), 5.91 (1H, br s, –CH=). MS *m/z*: 378 (M^+), 360. $[\alpha]_D = +120.7°$ ($c = 1.0$, $CHCl_3$).

5-Methylene-3-oxaisocarbacyclin (14a) A 5% NaOH solution (8 ml) was added to a solution of **13a** (325 mg) in MeOH (20 ml) under ice-cooling and the whole was stirred for 30 min. The reaction mixture was diluted with brine, acidified with dilute HCl, and extracted with EtOAc. The extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was crystallized from wet acetone to give **14a** (280 mg, 89%), mp 45—47 °C. IR (KBr): 970, 1125, 1630, 1730, 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, br t, CH_3), 3.10 (1H, m, –CH–), 4.07 (2H, s, CH_2), 4.31 (2H, s, CH_2), 5.12 (1H, s, –CH=), 5.20 (1H, s, –CH=), 5.55 (2H, m, –CH=CH–), 5.90 (1H, br s, –CH=). MS *m/z*: 346 ($M^+ - 18$). $[\alpha]_D = -32.5°$ ($c = 1.0$, $CHCl_3$).

5(5),6(9α)-Dimethylene-3-oxa-Δ^6-prostaglandin I_1 (14b) A 5% NaOH solution (6 ml) was added to a solution of **13b** (250 mg) in MeOH (15 ml) under ice-cooling and the whole was stirred for 30 min. The reaction mixture was diluted with brine, acidified with dilute HCl, and extracted with EtOAc. The extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue (225 mg), which was crystallized from a mixture of hexane and EtOAc (1 : 1) to give **14b** (161 mg, 67%), mp 82—84 °C. IR (KBr): 965, 1140, 1630, 1703, 1770, 3430 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, br t, CH_3), 4.08 (2H, s, CH_2), 4.30 (2H, s, CH_2), 5.11 (1H, s, –CH=), 5.20 (1H, s, –CH=), 5.58 (2H, m, –CH=CH–), 5.90 (1H, br s, –CH=). *Anal.* Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.18; H, 8.76. MS *m/z*: 346 ($M^+ - 18$). $[\alpha]_D = +136°$ ($c = 1.0$, $CHCl_3$).

20-Isopropylidene-17(*R*)-methyl-5-methylene-3-oxaisocarbacyclin (14c) Through a sequence of reactions similar to that described for the synthesis of **14a** from **5a**, (1*S*,2*R*,3*R*,5*R*)-7-oxo-3-(tetrahydropyran-2-yl)oxy-2-[3(*S*)-(tetrahydropyran-2-yl)oxy-5(*R*),9-dimethyl-1(*E*),8-decadienyl]-bicyclo[3.3.0]octane[12] was led to **14c** as an oil. IR (neat): 970, 1120, 1630, 1735, 3350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, $J = 6$ Hz, CH_3), 1.60 (3H, s, CH_3), 1.68 (3H, s, CH_3), 3.1 (1H, m, –CH–), 4.08 (2H, s, CH_2), 4.32 (2H, s, CH_2), 5.13 (1H, s, =CH–), 5.26 (1H, s, =CH–), 5.5 (2H, m, =CH–). MS *m/z*: 418 (M^+), 406. $[\alpha]_D = -23.9°$ ($c = 1.0$, $CHCl_3$).

16-Methyl-5-methylene-3-oxaisocarbacyclin (14d) Through a sequence of reactions similar to that described for the synthesis of **14a** from **5a**, (1*S*,2*R*,3*R*,5*R*)-7-oxo-3-(tetrahydropyran-2-yl)oxy-2-[3(*S*)-(tetrahydropyran-2-yl)oxy-4-methyl-*E*-1-octenyl]bicyclo[3.3.0]octane[13] was led to **14d** as an oil. IR (neat): 970, 1600, 1630, 1733, 3350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.0 (6H, m, CH_3), (3H, s, CH_3), 3.21 (1H, m, –CH–), 4.10 (2H, s, CH_2), 4.31 (2H, s, CH_2), 5.12 (1H, s, =CH–), 5.22 (1H, s, =CH–), 5.55 (2H, m, =CH–). MS *m/z*: 360 ($M^+ - 18$). $[\alpha]_D = -17.0°$ ($c = 1.0$, $CHCl_3$).

16,16-Dimethyl-5-methylene-3-oxaisocarbacyclin (14e) Through a sequence of reactions similar to that described for the synthesis of **14a** from **5a**, (1*S*,2*R*,3*R*,5*R*)-7-oxo-3-(tetrahydropyran-2-yl)oxy-2-[3(*R*)-(tetrahydropyran-2-yl)oxy-4,4-dimethyl-*E*-1-octenyl]bicyclo[3.3.0]-octane[13] was led to **14e** as an oil. IR (neat): 970, 1595, 1630, 1735, 3350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9 (9H, m, CH_3), 3.1 (1H, m, –CH–), 4.08 (2H, s, CH_2), 4.30 (2H, s, CH_2), 5.12 (1H, s, =CH–), 5.21 (1H, s, =CH–), 5.55 (2H, m, =CH–), 5.91 (1H, s, =CH–). MS *m/z*: 374 ($M^+ - 18$). $[\alpha]_D = -9.8°$ ($c = 1.0$, $CHCl_3$).

16-Methyl-5-methylene-3-oxa-18,19-tetradehydroisocarbacyclin (14f) Through a sequence of reactions similar to that described for the synthesis of **14a** from **5a**, (1*S*,2*R*,3*R*,5*R*)-7-oxo-3-(tetrahydropyran-2-yl)oxy-2-[3(*S*)-(tetrahydropyran-2-yl)oxy-4-methyl-6,7-tetradehydro-*E*-1-octenyl]bicyclo[3.3.0]octane[14] was led to **14f** as an oil. IR (neat): 975, 1590, 1630, 1735, 3350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.78 (3H, t, $J = 1.5$ Hz, CH_3), 3.1 (1H, m, –CH–), 4.08 (2H, s, CH_2), 4.29 (2H, s, CH_2), 5.11 (1H, s, =CH–), 5.21 (1H, s, =CH–), 5.56 (2H, m, =CH–), 5.90 (1H, s, =CH–). MS *m/z*: 374 (M^+). $[\alpha]_D = -12.6°$ ($c = 1.0$, $CHCl_3$).

15-Cyclopentyl-5-methylene-3-oxa-16,17,18,19,20-pentanorisocarbacyclin (14g) Through a sequence of reactions similar to that described for the synthesis of **14a** from **5a**, (1*S*,2*R*,3*R*,5*R*)-7-oxo-3-(tetrahydropyran-2-yl)oxy-2-[3(*S*)-(tetrahydropyran-2-yl)oxy-3-cyclopentyl-*E*-1-propenyl]-bicyclo[3.3.0]octane[13] was led to **14g** as crystals. mp 140 °C (dec.). IR (KBr): 970, 1590, 1630, 1746, 3440 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.1 (1H, m, –CH–), 4.05 (2H, s, CH_2), 4.30 (2H, s, CH_2), 5.12 (1H, s, =CH–), 5.24 (1H, s, =CH–), 5.6 (2H, m, =CH–), 5.92 (1H, s, =CH–). *Anal.* Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.28; H, 8.30. $[\alpha]_D = -11.8°$ ($c = 1.0$, CH_3OH).

Synthesis of 5-Ethylidene-3-oxaisocarbacyclin. (5*S*,6*R*,7*R*,1*S*)-3-[1(*Z*)-Hydroxymethylpropenyl]-7-(tetrahydropyran-2-yl)oxy-6-[3(*S*)-(tetrahydropyran-2-yl)oxy-*E*-1-octenyl]bicyclo[3.3.0]oct-2-ene (16a) and (5*S*,6*R*,7*R*,1*S*)-3-[1(*Z*)-Hydroxymethylpropenyl]-7-(tetrahydropyran-2-yl)oxy-8-[3(*S*)-(tetrahydropyran-2-yl)oxy-*E*-1-octenyl]bicyclo[3.3.0]oct-2-ene (16b) *n*-Butyl lithium in hexane (15%, 2.48 ml) was added to a solution of dicyclohexylamine (0.81 ml) in dry THF (18 ml) at −78 °C. After 10 min stirring, hexamethylphosphoramide (0.78 ml) was added and the whole was stirred for a further 10 min. Next, a solution of the ester (**6a**, 1.0 g) in dry THF (5 ml) was added. The reaction mixture was stirred for 10 min, then acetaldehyde (0.23 ml) was added at −78 °C and the whole was stirred for 30 min. The reaction mixture was diluted with saturated NH_4Cl solution (15 ml) and then brine, and extracted with EtOAc. The extract was washed with dilute HCl, dilute $NaHCO_3$ solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with hexane containing 15—30% EtOAc afforded a mixture of oily compounds (**15a** and **15b**, 1.05 g, 98%) containing γ-alkylated products. IR (neat); 3470, 1740, 1025 cm^{-1}.

Methanesulfonyl chloride (0.29 ml) was added to a solution of the

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mixture of **15a** and **15b** (1.0 g) in dry pyridine (15 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 2.5 h, diluted with water and extracted with EtOAc. The extract was washed with dilute HCl, brine, dilute $NaHCO_3$ solution, and then brine. The organic phase was dried over Na_2SO_4. Evaporation of the solvent gave an oily compound (1.13 g). IR (neat); 1740, 1025 cm^{-1}.

A mixture of the mesylate (1.1 g) in dry hexamethylphosphoramide (22 ml), DBU (2.2 ml) and dry NaI (0.54 g) was heated at 100 °C under stirring for 20 min. The reaction mixture was diluted with brine and extracted with EtOAc. The extract was washed with water, dilute HCl, water, dilute $NaHCO_3$ solution, and then brine. The organic phase was dried over Na_2SO_4.

Evaporation of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with hexane containing 10—15% EtOAc afforded the compound (896 mg) as an oil. IR (neat): 1725, 1625, 1025 cm^{-1}.

A solution of the ester (870 mg) in dry ether (5 ml) was added to a mixture of $LiAlH_4$ (190 mg) in dry Et_2O (10 ml) and aluminum chloride (220 mg) in dry Et_2O (5 ml) under ice-cooling. After stirring for 20 min, 4% NaOH solution (0.78 ml) was added and the whole was stirred for 1 h at room temperature. The white precipitate was filtered off. Evaporation of the solvent from the filtrate gave an oily residue, which was purified by silica gel column chromatography. Elution with hexane containing 15—20% EtOAc afforded **16b** (510 mg, 52%) containing γ-alkylated products as an oil and elution with hexane containing 20—25% EtOAc afforded the desired compound (**16a**, 289 mg, 30%) as an oil. IR (neat): 870, 1020, 1665, 3450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, br t, CH_3), 1.83 (3H, d, J=4 Hz, CH_3), 4.4, 4.7, (2H, br s × 2, OCHO), 5.2—5.8 (4H, m, =CH–). MS m/z: 302 ($M^+ - 102 - 84$), 285.

5-Ethylidene-3-oxaisocarbacyclin 11,15-Di(tetrahydropyran-2-yl) Ether Methyl Ester (17a) *n*-Butyl lithium in hexane (15%, 0.50 ml) was added to a solution of the alcohol (**16a**, 0.27 g) in dry THF (2 ml) under ice-cooling until the reaction mixture become reddish-yellow. Next, dry DMF (0.5 ml), dry lithium chloroacetate (83 mg), dry DMSO (0.5 ml), and then dry NaI (0.25 g) were added to the reaction mixture. The whole was heated to 40 °C and then allowed to stand at room temperature for 17 h. The reaction mixture was diluted with ice-water mixture, acidified with dilute HCl and extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which, after esterification with diazomethane, was purified by silica gel column chromatography. Elution with hexane containing 10—15% EtOAc afforded **17a** (196 mg, 63%) as an oil. IR (neat): 980, 1030, 1755 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, m, CH_3), 1.82 (3H, d, J=4 Hz, CH_3), 3.76 (3H, s, CH_3), 4.32 (2H, s, CH_2), 4.70 (2H, br s, OCHO), 5.2—6.0 (4H, m, =CH–). MS m/z: 560 (M^+), 458, 374.

5-Ethylidene-3-oxaisocarbacyclin Methyl Ester (18a) A solution of **17a** (180 mg) in THF (3.5 ml) and AcOH (7 ml) was stirred at 50 °C for 2 h, while water (15 ml) was added in several portions so as to keep the solution clear. The reaction mixture was diluted with brine and extracted with EtOAc. The extract was washed with brine, cold 3% NaOH solution, and then brine. The organic phase was dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with hexane containing 60—90% EtOAc afforded **18a** (113 mg, 62%) as crystal. Recrystallization from a mixture of hexane and EtOAc (4:1) afforded the pure compound (78 mg, 62%), mp 69—70 °C. IR (neat): 970, 1130, 1725, 1765, 3450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, br t, CH_3), 1.81 (3H, d, J=4 Hz, CH_3), 3.1 (1H, m, –CH–), 3.78 (3H, s, CH_3), 4.01 (2H, s, CH_2), 4.4 (2H, s, CH_2), 5.4—5.9 (4H, m, =CH–). *Anal.* Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.39; H, 9.35. $[\alpha]_D = -21.0°$ (c=1.0, $CHCl_3$).

5-Ethylidene-3-oxaisocarbacyclin (19a) A 5% NaOH solution (2 ml) was added to a solution of **18a** (68 mg) in MeOH (5 ml) under ice-cooling and the whole was stirred for 30 min at room temperature. The reaction mixture was diluted with brine, acidified with dilute HCl, and extracted with EtOAc. The extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave an residue, which was crystallized from a mixture of EtOAc and hexane (6:5) to give **19a** (50 mg, 77%), mp 100—106 °C. IR (KBr): 970, 1125, 1630, 1740, 3430 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.9 (3H, br t, CH_3), 1.82 (3H, d, J=4 Hz, CH_3), 3.1 (1H, m, –CH–), 4.03 (2H, s, CH_2), 4.4 (2H, s, CH_2), 5.4—5.9 (4H, m, =CH–). *Anal.* Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.92; H, 9.02. MS m/z: 378 (M^+), 360. $[\alpha]_D = -18.9°$ (c=1.0, $CHCl_3$).

References and Notes

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5) The ratio of **7a** to **7b** is 56 to 34.
6) S. R. Wilson and R. S. Myers, *J. Org. Chem.*, **40**, 3309 (1975).
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9) We thank Dr. T. Oshima for testing biological activity.
10) 5-*Z*-Ethylidene-6(9α)-methylene-3-oxa-Δ^6-prostaglandin I_1, synthesized from **16b**, was also very weakly active in the same test.
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14) This ketone was synthesized by a similar method to that described for the synthesis of **5a** in reference 3 or 12 using dimethyl 3-methyl-2-oxo-5,6-tetradehydroheptylphosphonate. See also: W. Skuballa and H. Vorbrüggen, *Angew. Chem. Int. Ed. Engl.*, **20**, 1046 (1981).

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