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Synthesis and Anti-platelet Aggregating Activity of 3-Hetero Analogues of (+)-9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1

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Optically active 3-hetero analogues of isocarbacyclin (**34a**, **38**, **39**, **40** and **42**) as well as ω-chain analogues have been synthesized from the bicyclic alcohol (**1**). Compound **34d** had more potent anti-platelet aggregating activity than prostacyclin in human platelet-rich plasma.

Keywords——isocarbacyclin; 3-oxaisocarbacyclin; 3-thiaisocarbacyclin; 3-azaisocarbacyclin; 3-heteroisocarbacyclin; platelet aggregation inhibitor; regioselective deprotonation

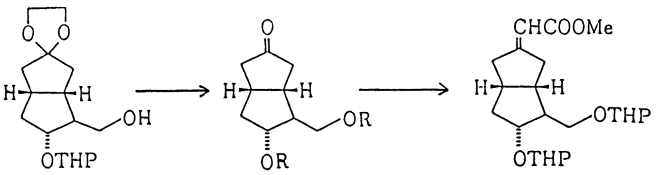
Prostaglandins are metabolized very quickly in the body. One of their main metabolic pathways is the β-oxidation reaction[1] of the α-carboxylic side chain, which results in the loss of biological activity. It is, therefore, of interest to block the β-oxidation reaction from the medicinal point of view. In order to block the β-oxidation reaction, the introductions of an oxygen atom at the C_3 position into both prostaglandin E_1[2] and carbacyclin derivative[3] have been reported.

As one of our synthetic programs on stable prostacyclin analogues, we have already reported the synthesis of 3-oxa-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (3-oxaisocarbacyclin) in an optically inactive form.[4] It had a quite potent anti-platelet aggregating activity; its IC_{50} value was 23 ng/ml against adenosine-5′-diphosphate (ADP)-induced platelet aggregation in rabbit platelet-rich plasma (*in vitro*). This finding prompted us to prepare an optically active 3-oxaisocarbacyclin, its ω-chain analogues, and other 3-hetero analogues of isocarbacyclin such as 3-thia-, 3-sulfinyl-, 3-sulfonyl- and 3-azaisocarbacyclins. In this paper, we describe the synthesis and anti-platelet aggregating activity of optically active 3-heteroisocarbacyclins (**34a**, **38**, **39**, **40** and **42**) and some ω-chain analogues.

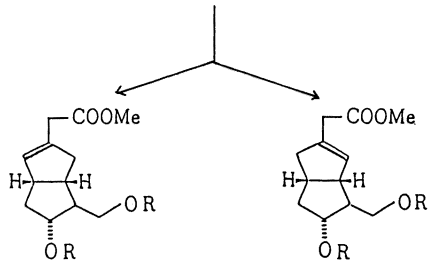
Synthesis of (+)-3-Oxaisocarbacyclin and Its ω-Chain Analogues

In order to synthesize (+)-3-oxaisocarbacyclin (**34a**), we selected the alcohol (**10a**) as a key intermediate. This compound was synthesized from the optically active alcohol (**1**) *via* three routes as shown in Charts 1, 4 and 5. The alcohol (**1**) is readily available from *cis*-bicyclo[3.3.0]octane-3,7-dione.[5]

The first route utilized the crystalline diol (**9a**) as a key intermediate. Compound **9a** was prepared through the following sequence of reactions (Chart 1). Deprotection of **1** with *p*-toluenesulfonic acid (*p*-TsOH) in aqueous acetone, followed by protection of the resulting diol (**2**), mp 95—99 °C, with dihydropyran and *p*-TsOH afforded the known tetrahydropyranyl ether (**3**)[6] in 80% yield from **1**. The Wittig–Horner reaction of **3** with trimethyl phosphonoacetate gave the ester (**4**) as an inseparable mixture of *E*- and *Z*-isomers in 90% yield. The ratio of *E*- to *Z*-isomer was determined to be 51 to 49 by reverse-phase high-performance liquid chromatographic (HPLC) analysis of the diol (**11a**, **b**) derived from **4** by

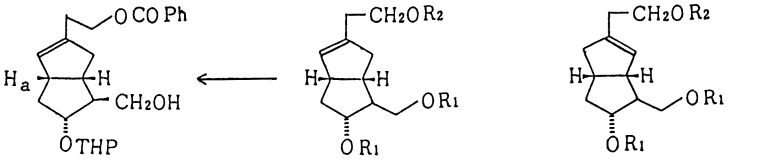


1 **2** : R=H
3 : R=THP **4**



5a : R=THP
6a : R=H

5b : R=THP
6b : R=H



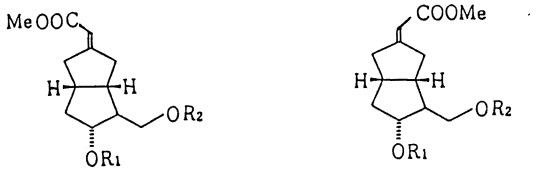
10a

7a : R_1=THP, R_2=H
8a : R_1=THP, R_2=COPh
9a : R_1=H, R_2=COPh

7b : R_1=THP, R_2=H
8b : R_1=THP, R_2=COPh
9b : R_1=H, R_2=COPh

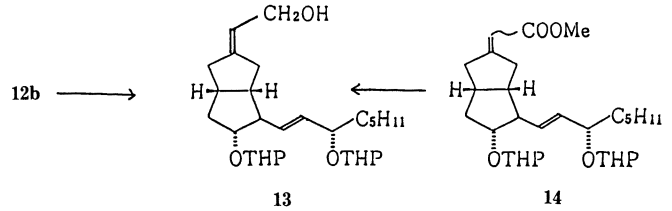
THP: tetrahydropyran-2-yl

Chart 1



11a : R_1=R_2=H
12a : R_1=H, R_2=CPh_3

11b : R_1=R_2=H
12b : R_1=H, R_2=CPh_3



13 **14**

Chart 2

acid treatment (Chart 2). The *E*- and *Z*-configurations of **11a** and **11b** were assigned on the basis of the following data; treatment of a mixture of the diol (**11a, b**) with trityl chloride and triethylamine (Et_3N), followed by careful chromatographic separation afforded the less polar alcohol (**12b**) and the more polar alcohol (**12a**). The structures of **12a** and **12b** were assigned on the basis of the fact that the alcohol (**12b**) was led, by a conventional method, to **13**. Authentic **13** having *Z*-configuration[3] was alternatively prepared by diisobutylaluminum hydride (DIBAL) reduction of **14**.[7] The product (**13**) was identical with the authentic sample. Deprotection of **12a** yielded the diol (**11a**), which corresponded to the peak having shorter retention time on reverse-phase HPLC. From these data, the *E*- and *Z*-configurations of **11a** and **11b** were determined.

Next, we investigated the deconjugation reaction of the α,β-unsaturated ester moiety in 4. Thus, treatment of **4** with lithium dicyclohexylamide in tetrahydrofuran (THF) in the presence of hexamethylphosphoric triamide (HMPA)[8a] quantitatively afforded the β,γ-unsaturated methyl ester (**5a, b**) as an inseparable mixture of the double bond isomers. The isomeric ratio (**5a** : **5b** = 66 : 34) was determined by HPLC analysis of the diol (**6a, b**) derived from **5a, b** by treatment with aqueous methanolic *p*-TsOH. The major isomer having shorter retention time was assigned as the $\Delta^{6(9\alpha)}$-isomer (**6a**) (prostaglandin numbering)[9] on the basis of the relative HPLC retention time, as in the case of the benzoates (**9a, b**); the $\Delta^{6(9\alpha)}$-regioisomer (**9a**) had shorter retention time than the Δ^{6}-regioisomer (**9b**). Preferential formation of **5a** may be due to regioselective deprotonation of the allylic proton on the bicyclo[3.3.0]octane ring through electronic and remote steric control.[8b-d] Deprotonation of the allylic proton in a simple acyclic α,β-unsaturated ester occurs exclusively at the position

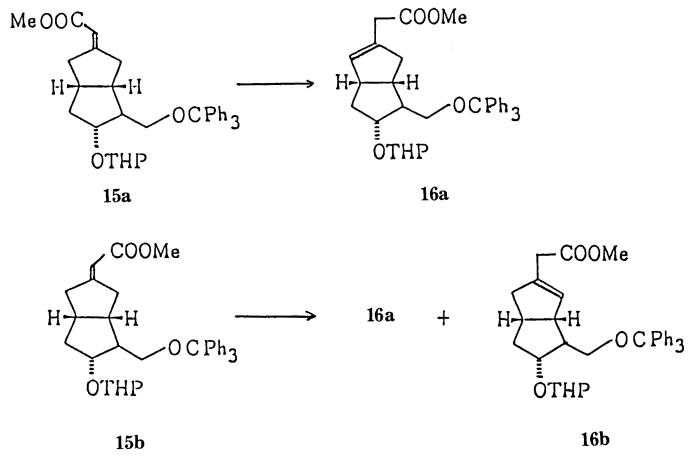


Chart 3

syn to the ester group through electronic control.[8b] The electronic and remote steric control in the case of *cis*-bicyclo[3.3.0]octane derivatives was more clearly demonstrated by the following results (Chart 3): treatment of the *E*-ester (**15a**) having a bulky trityl protecting group as described for **4** gave exclusively the $\Delta^{6(9\alpha)}$-isomer (**16a**). On the other hand, the corresponding *Z*-iomer (**15b**) afforded a mixture of **16a, b** in a ratio of 53 to 47 (**16a** to **16b**). It seemed to be better, from the viewpoint of stereoselectivity, to use **16a** for further elaboration of the synthesis. In practice, however, we used the ester mixture (**5a, b**) because these double bond isomers could be easily separated, in a later step, by recrystallization. Accordingly, a mixture of **5a, b** was led to **10a** through the following sequence of reactions (Chart 1).

Firstly, a mixture of **5a, b** was treated with lithium aluminum hydride ($LiAlH_4$) to yield

the alcohol (**7a, b**). Benzoylation of **7a, b** with benzoyl chloride in pyridine afforded the benzoate (**8a, b**) in 84% yield from **5a, b**. Deprotection of **8a, b** with aqueous methanolic *p*-TsOH yielded a mixture of **9a, b** in a ratio of 66 to 34 (**9a** to **9b**) as judged by HPLC analysis. The major isomer (**9a**) had a shorter retention time than **9b** on HPLC. Several recrystallizations of the above mixture gave the crystalline diol (**9a**), mp 87—89 °C, as a single isomer in 32% yield from **8a, b**. Compound **9a** was confirmed to be the $\Delta^{6(9\alpha)}$-isomer by leading it to **10a** and **34a**. The desired alcohol (**10a**) was finally prepared from **9a** in three steps through a conventional method[10] in 66% yield: 1) treatment with one molar equivalent of trichloroacetyl chloride and Et_3N, 2) protection with dihydropyran and *p*-TsOH, 3) hydrolysis with aqueous sodium bicarbonate. Compound **10a** showed a signal at δ 3.0 (multiplet) due to the H_a proton, a characteristic of the $\Delta^{6(9\alpha)}$-double bond isomer, in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum.[4]

The second route used the sulfide (**21**) as a key intermediate, whose synthesis was achieved in several steps from **1** (Chart 4).

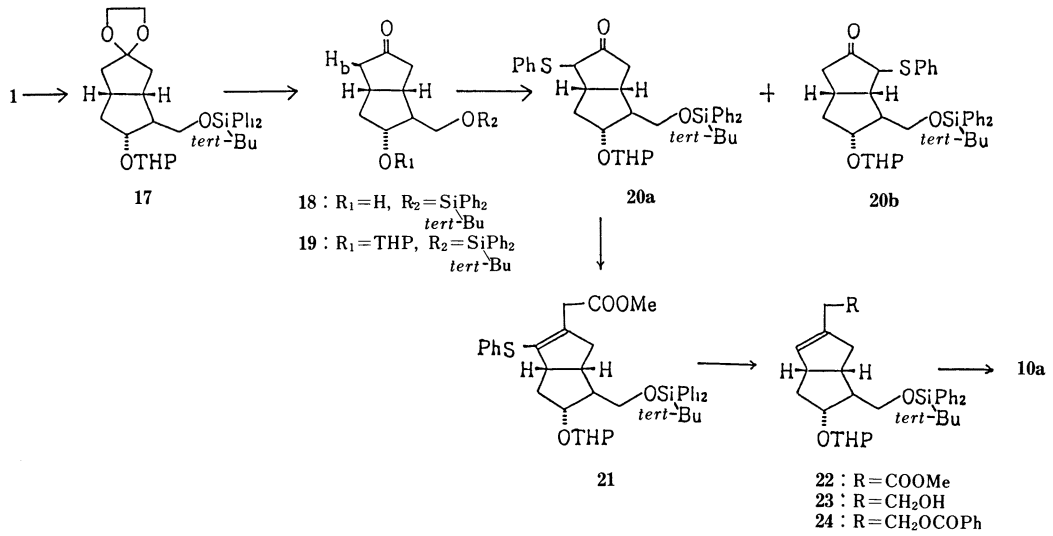


Chart 4

Treatment of **1** with *tert*-butyldiphenylchlorosilane and imidazole, followed by deprotection with aqueous acetic acid afforded the ketone (**18**), mp 103—104 °C. Protection of the hydroxy group in **18** with dihydropyran and *p*-TsOH gave **19** in 83% yield from **1**. Reaction of **19** with lithium dicyclohexylamide and HMPA in THF, followed by addition of diphenyl disulfide afforded the sulfide (**20a**) and its regio-isomer (**20b**) in 61 and 29% yields, respectively, after purification by silica gel column chromatography. Selective formation of **20a** may be based on the selective deprotonation of the H_b proton in **19** through the remote steric effect of the *tert*-butyldiphenylsilyloxymethyl moiety. The structure of **20a** was confirmed by leading **20a** to **10a** through the following sequence of reactions. This completed the second route to **10a**. The Wittig–Horner reaction of **20a** with trimethyl phosphonoacetate yielded the sulfide (**21**) in 57% yield together with recovery of **20a** (13%). Deconjugation reaction of an *exo*-double bond to an *endo*-double bond occurred during this reaction. This was easily determined from the fact that the compound (**21**) showed no olefinic proton signal in the ^{1}H-NMR spectrum. Desulfurization of **21** with Raney nickel, followed by reduction of the product (**22**) with $LiAlH_4$ afforded the alcohol (**23**) in 90% yield from **21**. Benzoylation of **23** with benzoyl chloride in pyridine gave **24**, which was deprotected with tetrabutylam-

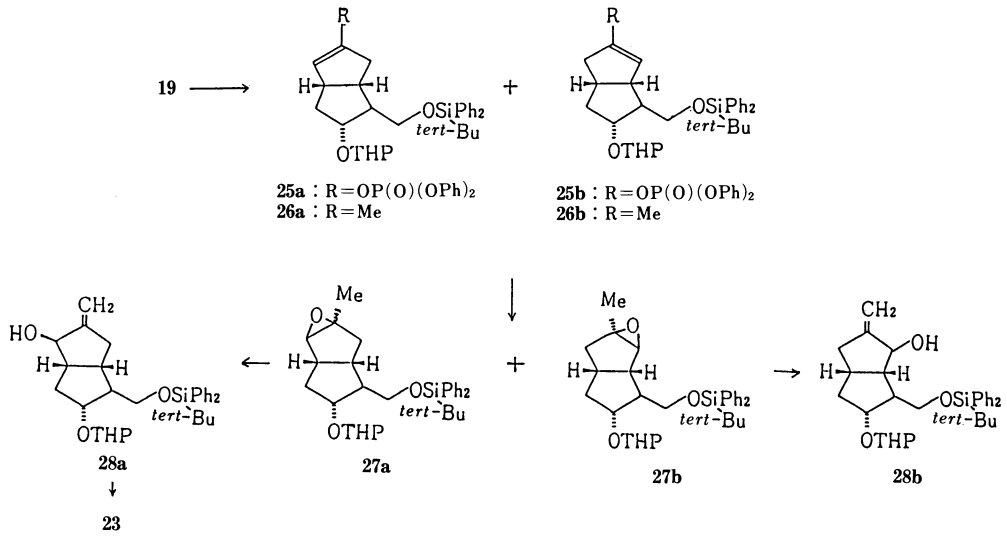


Chart 5

monium fluoride to afford the alcohol (**10a**) in 80% yield from **23**.

The third route started with the ketone (**19**) (Chart 5). Deprotonation of **19** with lithium dicyclohexylamide in THF, followed by the addition of diphenyl phosphorochloridate afforded the enol phosphate (**25a, b**) as an inseparable mixture of double bond isomers (*vide infra*). The reaction of **25a, b** with trimethylaluminum in the presence of tetrakis(triphenylphosphine)palladium[11] gave the olefin (**26a, b**) in 47% yield. This product showed two close peaks on HPLC, due probably to double bond isomers. Epoxidation of **26a, b** with *m*-chloroperbenzoic acid (MCPBA) in methylene chloride, followed by careful chromatographic purification yielded the epoxide (**27a** and **27b**, in 42 and 32% yields, respectively). The β-configurations of the epoxide ring in **27a** and **27b** were assigned on the basis of the steric effects due to the *cis*-bicyclo[3.3.0]octane structure including the α-tetrahydropyranyloxy group. The structure of **27a** was further confirmed by leading **27a** to the alcohol (**23**) as described below.

Isomerization of **27a** with diethylaluminum 2,2,6,6-tetramethylpiperidinylamide[12] afforded the allyl alcohol (**28a**) as a single isomer in 72% yield. Similarly, treatment of **27b** afforded exclusively the isomeric allyl alcohol (**28b**). Sequential treatment of **28a** with potassium hydride, tributyltiniodomethane and 15% *n*-butyllithium in THF in the presence of 18-crown-6[13] afforded the alcohol (**23**) in 24% yield along with recovery of **28a** (18%). The alcohol (**23**) was led to **10a** as described in route 2 (Chart 4).

Among the three routes described above, the first route was considered to be the most practical.

With the required intermediate in hand, we then converted the alcohol (**10a**) to 3-oxaisocarbacyclin (**34a**) through the following sequence of reactions. Oxidation of **10a** with pyridine sulfur trioxide (SO_3) complex and Et_3N in dimethyl sulfoxide (DMSO),[14] followed by reaction with an ylide, tributyl 2-oxoheptylidenephosphorane, gave the enone (**29**) in 97% yield from **10a**. Sodium borohydride reduction of **29** yielded the alcohol (**30a**) and its 15(*R*)-epimer (**30b**) in a ratio of 2 to 1. The 15(*S*)-configuration of **30a** was assigned on the basis of the circular dichroism (CD) spectrum[15] of the benzoate (**31**) derived from **30a**; the benzoate (**31**) exhibited a positive Cotton effect showing a positive chirality. This result showed the configuration at C_{15} in **30a** to be *S*. The hydroxy group in **30a** was protected with

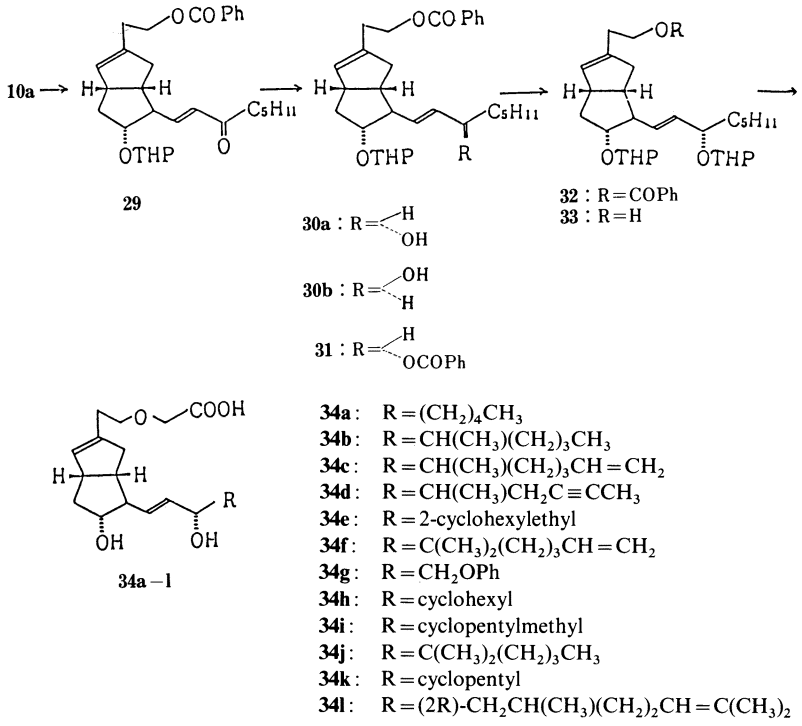


Chart 6

dihydropyran and *p*-TsOH to give **32**. Methanolysis of **32** with potassium carbonate in methanol afforded the alcohol (**33**) in 96% yield from **30a**. The alcohol (**33**) was led to **34a**, mp 62—64 °C, through the sequence of reactions described previously[4]: 1) *n*-butyllithium and lithium chloroacetate, 2) camphorsulfonic acid in aqueous acetone. Compound **34a** was identical (infrared (IR), ^{1}H-NMR and mass (MS) spectra) with *dl*-**34a** synthesized previously.[4]

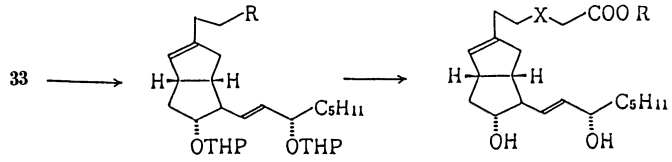
By using the same sequence of reactions as described for the synthesis of **34a**, the alcohol (**10a**) was led to various 3-oxaisocarbacyclins (**34b**—**l**) with a modified ω-side chain.

Synthesis of 3-Thia-, 3-Sulfinyl-, 3-Sulfonyl- and 3-Azaisocarbacyclins

The alcohol (**33**) was also converted to 3-heteroisocarbacyclins (**38**, **39**, **40** and **42**) through the following sequence of reactions (Chart 7).

Mesylation of **33** with mesyl chloride and Et_3N gave the mesylate (**35**) in 97% yield. Treatment of **35** with thioglycolic acid in DMSO in the presence of NaH, followed by esterification with diazomethane, afforded the ester (**36**). Deprotection of **36** with aqueous acetic acid yielded the diol (**37**) in 43% yield from **35**. The ester group in **37** was hydrolyzed with sodium hydroxide (NaOH) in aqueous methanol to give 3-thiaisocarbacyclin (**38**) in 95% yield. Oxidation of **37** with one molar equivalent of MCPBA, followed by hydrolysis of the ester group gave 3-sulfinylisocarbacyclin (**39**) in 93% yield from **37**. On the other hand, oxidation of **37** with two molar equivalents of MCPBA, followed by hydrolysis of the ester group afforded 3-sulfonylisocarbacyclin (**40**) in 84% yield from **37**.

Oxidation of **33** with trifluoroacetic anhydride and MDSO in dichloromethane,[16] followed by sequential treatment with methyl glycinate and sodium cyanoborohydride[17] afforded the amine (**41**). Hydroxy protecting groups in **41** were removed by treatment with aqueous acetic acid to give the methyl ester of 3-azaisocarbacyclin (**42**) in 29% yield from **33**.



35: R=OMs
36: R=SCH_2COOMe
41: R=$NHCH_2COOMe$
37: R=Me, X=S
38: R=H, X=S
39: R=H, X=SO
40: R=H, $X=SO_2$
42: R=Me, X=NH

Chart 7

TABLE I. Anti-platelet Aggregating Activity of 3-Hetero Analogues of Isocarbacyclin (IC_{50}: ng/ml)

Compd.	Rabbit	Human
34a	11	4.6
34b	2.4	6.1
34c	1.9	2.9
34d	2.4	0.42
34e	347	770
34f	56	128
34g	103	>1000
34h	3.7	1.4
34i	9.5	5.5
34j	87	697
34k	3.5	1.4
34l	6.3	6.2
38	132	52
39	>1000	>1000
40	>1000	>1000
42	>1000	>1000
Prostacyclin	5.2	0.9

Anti-platelet Aggregating Activity

Anti-platelet aggregating activities of the 3-heteroisocarbacyclins are shown in Table I. The introduction of an oxygen atom in place of the 3-methylene group slightly decreased the activity. Accordingly, 3-oxaisocarbacyclin (**34a**) was still quite a potent inhibitor of platelet aggregation. This decrease was fully compensated by a modification of the ω-side chain, and **34d** was found to be more potent than prostacyclin in human platelet-rich plasma (*in vitro*). On the other hand, 3-thiaisocarbacyclin (**38**) was a weak inhibitor and 3-sulfinyl-, 3-sulfonyl- and 3-azaisocarbacylins (**39**, **40**, **42**) were inactive.

Some of these compounds were tested for oral activity. An *ex vivo* experiment showed that **34b—d** were orally active in the rabbit. Furthermore the anti-platelet aggregating activity of **34d** lasted for more than five hours after oral administration of 0.3 mg/kg in the rabbit.[18] Further pharmacological investigation of **34d** is in progress. Details will be published elsewhere.

Experimental

Melting points are uncorrected. IR spectra were recorded with a JASCO A-102 spectrophotometer. ^{1}H-NMR spectra were recorded with a Varian T-60A (60 MHz) or EM-390 (90 MHz) spectrometer in deuteriochloroform, with tetramethylsilane as an internal reference. MS spectra were obtained with a JEOL JMS-01SG or JMS-G300 mass

spectrometer. Optical rotation was measured with a Perkin Elmer model 141 polarimeter. Ultraviolet (UV) spectra were taken with a Cary 118C spectrophotometer and CD spectra with a JASCO J-500C spectrophotometer. Removal of solvents *in vacuo* was accomplished with a rotating flash evaporator at 20—30 mmHg and usually at 35—50 °C. Plates for thin layer chromatography (TLC) were Silica gel 60 F-254 (E. Merck AG) and spots were visualized by spraying a solution of 0.5% vanillin in 20% ethanol in sulfuric acid (v/v), followed by heating. Columns for ordinary chromatography were prepared with Silica gel 60 (70—230 mesh or 230—400 mesh, E. Merck AG). In general, reactions were carried out under a nitrogen stream.

(1*R*,5*S*,6*S*,7*R*)-3-Oxo-6-hydroxymethyl-7-hydroxybicyclo[3.3.0]octane (2)——*p*-TsOH (1.0 g) was added to a solution of **1** (8.00 g), $[\alpha]_D^{24}$ −18.6° (c=1.0, $CHCl_3$), in a mixture of acetone (80 ml) and water (30 ml). The whole was heated at 40 °C for 2 h, then diluted with saturated $(NH_4)_2SO_4$, and extracted with AcOEt. The extract was dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a residue, which was purified by silica gel column chromatography. Elution with AcOEt to 2% MeOH in AcOEt (v/v) afforded **2** (4.03 g) as crystals. Recrystallization from AcOEt gave an analytical sample, mp 95—97 °C. *Anal.* Calcd for $C_9H_{14}O_3$: C, 65.31; H, 8.29. Found: C, 65.25; H, 8.21. IR (Nujol): 3200, 1733 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.13 (1H, q, J=4.5 Hz, –CHOH). MS m/z: 170 (M^+), 152, 134. $[\alpha]_D^{26}$ −11.9° (c=1.0, $CHCl_3$).

(1*R*,5*S*,6*S*,7*R*)-3-Oxo-6-(tetrahydropyran-2-yl)oxymethyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (3)——A catalytic amount of *p*-TsOH was added to a mixture of **2** (4.03 g) in CH_2Cl_2 (15 ml) and dihydropyran (DHP) (5.4 ml) at room temperature. The whole was stirred for 30 min, quenched with dilute $NaHCO_3$, and extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a residue, which was purified by silica gel column chromatography. Elution with 10—15% AcOEt in hexane (v/v) afforded **3** (7.25 g) as a colorless oil. IR (neat): 1743, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.65 (2H, br s, OCHO × 2). MS m/z: 338 (M^+), 254. $[\alpha]_D^{26}$ −19.5° (c=1.0, MeOH).

(1*S*,5*S*,6*S*,7*R*)-3-Methoxycarbonylmethylene-6-(tetrahydropyran-2-yl)oxymethyl-7-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]octane (4)——A solution of **3** (82.1 g) in THF (145 ml) was added at 20—30 °C to a solution of the sodium salt of trimethyl phosphonoacetate [prepared from 55% NaH in oil (14.3 g) and trimethylphosphonoacetate (66.3 g) in THF (675 ml) and dimethylformamide (DMF) (490 ml)]. After being stirred at 20—30 °C for 4 h, the reaction mixture was diluted with ice-water and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a residue, which was purified by silica gel column chromatography. Elution with 10—15% AcOEt in hexane (v/v) afforded **4** (86.2 g) as a colorless oil. IR (neat): 1715, 1656, 1430, 1130, 1032 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s, COOMe), 4.65 (2H, br s, OCHO × 2), 5.80 (1H, br s, olefinic-H). MS m/z: 263 (M^+ − 31), 310, 226.

A Mixture of (1*S*,5*S*,6*S*,7*R*)-3-Methoxycarbonylmethyl-6-(tetrahydropyran-2-yl)oxymethyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (5a) and (1*S*,5*R*,6*S*,7*R*)-3-Methoxycarbonylmethyl-6-(tetrahydropyran-2-yl)-oxymethyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-3-ene (5b)——HMPA (38.9 ml) was added to a solution of lithium dicyclohexylamide [prepared from 15% *n*-butyllithium in hexane (118 ml) and dicyclohexylamine (40.2 ml) in THF (650 ml)]. A solution of **4** (50.0 g) in THF (150 ml) was added to the above solution at −73—−65 °C. After being stirred at the same temperature for 20 min, the reaction mixture was quenched with saturated NH_4Cl, diluted with water and extracted with AcOEt. The extract was washed with brine, 3% HCl (filtration of the precipitate), and water, and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography. Elution with 15—25% AcOEt in hexane (v/v) gave **5a, b** (50.0 g) as a colorless oil. IR (neat): 1742, 1038 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.68 (3H, s, COOMe), 4.67 (2H, m, OCHO × 2), 5.53 (1H, br s, olefinic-H). MS m/z: 263 (M^+ − 31), 310, 226. The ratio of **5a** to **5b** (66 to 34) was determined by HPLC analysis of **6a, b** derived from **5a, b**; *p*-TsOH (100 mg) was added to a solution of **5a, b** (520 mg) in a mixture of MeOH (10 ml) and water (4 ml). The whole was stirred at 35 °C for 2 h, then diluted with saturated $(NH_4)_2SO_4$, and extracted with AcOEt. The extract was washed with saturated $(NH_4)_2SO_4$, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a residue, which was purified by silica gel column chromatography. Elution with 30—90% AcOEt in hexane gave **6a, b** (371 mg). HPLC analysis showed that the ratio of **6a** to **6b** (**5a** to **5b**) was 66 to 34. HPLC conditions: column, ERC-silica-1161 (ERMA); solvent, 1% MeOH in a mixture of AcOEt : hexane = 4 : 6 (v/v); flow rate, 2.5 ml/min; t_R 3.89 min (**6a**), 4.27 min (**6b**).

A Mixture of (1*S*,5*S*,6*S*,7*R*)-3-(2-Hydroxyethyl)-6-(tetrahydropyran-2-yl)oxymethyl-7-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]oct-2-ene (7a) and (1*S*,5*R*,6*S*,7*R*)-3-(2-Hydroxyethyl)-6-(tetrahydropyran-2-yl)oxymethyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-3-ene (7b)——A solution of **5a, b** (50.9 g) in Et_2O (150 ml) was added to a suspension of $LiAlH_4$ (9.8 g) in Et_2O (870 ml) at 5—10 °C. The mixture was stirred at 5—10 °C for 0.5 h, then 4% NaOH solution (39.2 ml) was added dropwise under stirring. Stirring was continued for 2 h, then the precipitate was filtered off and the filtrate was evaporated to dryness. The residue obtained was purified by silica gel column chromatography. Elution with 20—35% AcOEt in hexane (v/v) afforded **7a, b** (41.1 g) as a colorless oil. IR (neat): 3450, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.65 (2H, br s, OCHO × 2), 5.47 (1H, br s, olefinic-H). MS m/z: 366 (M^+), 348, 282.

A Mixture of (1*S*,5*S*,6*S*,7*R*)-3-(2-Benzoyloxyethyl)-6-(tetrahydropyran-2-yl)oxymethyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (8a) and (1*S*,5*R*,6*S*,7*R*)-3-(2-Benzoyloxyethyl)-6-(tetrahydropyran-2-yl)oxymethyl-

7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-3-ene (8b)——Benzoyl chloride (19.1 ml) was added to a solution of **7a**, **b** (46.3 g) in pyridine (140 ml) at 20—30 °C, and the reaction mixture was allowed to stand for 15 min. The reaction mixture was quenched with ice-water, diluted with brine and extracted with AcOEt. The extract was washed with brine, 3% HCl, brine, dilute $NaHCO_3$ and then brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a residue, which was purified by silica gel column chromatography. Elution with 5—15% AcOEt in hexane (v/v) gave **8a**, **b** (57.0 g) as a colorless oil. IR (neat): 1720, 1590, 1280, 1030, 1005 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.44 (2H, t, J= 6 Hz, CH_2CH_2O), 4.64 (2H, br s, OCHO × 2), 5.47 (1H, br s, olefinic-H). MS *m/z*: 470 (M^+), 386, 302, 180.

(1*S*,5*S*,6*S*,7*R*)-3-(2-Benzoyloxyethyl)-6-hydroxymethyl-7-hydroxybicyclo[3.3.0]oct-2-ene (9a)——Water (100 ml) and *p*-TsOH (15.8 g) were added to a solution of **8a**, **b** (59.0 g) in MeOH (630 ml). The whole was stirred for 1.5 h, then diluted with water, and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a crystalline residue (36.0 g). HPLC analysis showed that the ratio of **9a** to **9b** was 66 to 34. HPLC conditions: column, ERC-silica-1161 (ERMA); solvent, 1% MeOH in a mixture of AcOEt : hexane = 4 : 6 (v/v); flow rate, 2.4 ml/min; t_R 4.60 min (**9a**), 4.93 min (**9b**). Four recrystallizations from a mixture of CH_2Cl_2 and cyclohexane (1 : 4—5) gave pure **9a** (12.6 g), mp 87—88 °C. *Anal.* Calcd for $C_{18}H_{22}O_4$: C, 71.45; H, 7.28. Found: C, 71.51; H, 7.32. IR (KBr): 3220, 1715, 1280, 1120, 1080 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.43 (2H, t, J = 6 Hz, CH_2CH_2O), 5.46 (1H, br s, olefinic-H), 7.48 (3H, m, arom.-H), 8.05 (2H, m, arom.-H). $[\alpha]_D^{24}$ −2.8° (c = 1.0, $CHCl_3$).

(1*S*,5*S*,6*S*,7*R*)-3-(2-Benzoyloxyethyl)-6-(hydroxymethyl)-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (10a)——a) Synthesis from **9a**: Et_3N (1.75 ml) and then CCl_3COCl (0.78 ml) in benzene (20 ml) were added to a solution of **9a** (2.00 g) in benzene (40 ml) at 10—20 °C. After being stirred for 10 min, the reaction mixture was diluted with ice-water, and extracted with Et_2O. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent gave a residue, which was purified by silica gel column chromatography. Elution with 20—35% AcOEt in hexane (v/v) gave the trichloroacetate (2.36 g) as a colorless oil. Dihydropyran (0.72 ml) and a catalytic amount of *p*-TsOH were added to a solution of the trichloroacetate (2.36 g) in CH_2Cl_2 (7.4 ml). Treatment as described for the synthesis of **19** afforded 2.72 g of product as an oil. A mixture of the crude product (2.72 g) in MeOH (55 ml) and saturated $NaHCO_3$ solution (3.8 ml) was stirred at 40—45 °C for 2 h. The reaction mixture was diluted with water, and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a residue, which was purified by silica gel column chromatography. Elution with 20—40% AcOEt in hexane (v/v) gave **10a** (1.69 g) as a colorless oil. IR (neat): 3420, 2940, 1715, 1270 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.02 (1H, m, C_1-H), 4.45 (2H, t, J = 6 Hz, CH_2CH_2O), 4.68 (1H, br s, OCHO), 5.46 (1H, br s, olefinic-H), 7.2—7.6 (3H, m, arom.-H), 7.8—8.1 (2H, m, arom.-H). MS *m/z*: 303 ($M^+ - 57$), 180, 162. $[\alpha]_D^{26}$ −28.5° (c = 1.0, MeOH).

b) Synthesis from **24**: A 1 M solution of Bu_4NF in THF (0.5 ml) was added to a solution of **24** (30 mg) in THF (1.0 ml), and the whole was stirred at room temperature for 7 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 18—25% AcOEt in hexane (v/v) afforded **10a** (18 mg) as a colorless oil.

A Mixture of (1*S*,5*S*,6*S*,7*R*)-3-[(*E*)-Methoxycarbonylmethylene]-6-hydroxymethyl-7-hydroxybicyclo[3.3.0]-octane (11a) and (1*S*,5*S*,6*S*,7*R*)-3-[(*Z*)-Methoxycarbonylmethylene]-6-hydroxymethyl-7-hydroxybicyclo[3.3.0]-octane (11b)——*p*-TsOH (2.0 g) was added to a solution of **4** (3.00 g) in a mixture of MeOH (50 ml) and water (8 ml). After being stirred at room temperature for 1 h, the reaction mixture was diluted with saturated $(NH_4)_2SO_4$, and extracted with AcOEt. The extract was washed with saturated $(NH_4)_2SO_4$ and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 50—90% AcOEt in hexane (v/v) afforded **11a**, **b** as a colorless oil (1.52 g). IR (neat): 3380, 1708, 1658, 1130 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, s, COOMe), 5.84 (1H, br s, olefinic-H). MS *m/z*: 226 (M^+), 208. HPLC analysis showed that the ratio of **11a** to **11b** was 51 to 49. HPLC conditions: column, ERC-ODS-1161 (ERMA); solvent, MeOH : H_2O = 1 : 1 (v/v); flow rate, 1.2 ml/min; t_R 3.05 min (**11a**), 3.50 min (**11b**).

A Mixture of (1*S*,5*S*,6*S*,7*R*)-3-[(*E*)-Methoxycarbonylmethylene]-6-trityloxymethyl-7-hydroxybicyclo[3.3.0] octane (12a) and (1*S*,5*S*,6*S*,7*R*)-3-[(*Z*)-Methoxycarbonylmethylene]-6-trityloxymethyl-7-hydroxybicyclo[3.3.0]-octane (12b)——A mixture of **11a**, **b** (1.81 g) in toluene (50 ml), trityl chloride (2.45 g) and Et_3N (1.29 ml) was heated under reflux for 0.5 h. The reaction mixture was cooled, stirred with dilute $NaHCO_3$ (10 ml), diluted with brine, and extracted with AcOEt. The extract was washed with dilute HCl (cooled), and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a residue, which was purified on a Lobar column [Merck, silica gel, size A, hexane : AcOEt = 2 : 1 (v/v)] to afford less polar **12b** (1.01 g) and more polar **12a** (0.82 g), both as oils. **12a**: IR (neat): 3550, 1710, 1660, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.68 (3H, s, COOMe), 5.80 (1H, br s, olefinic-H), 7.0—7.7 (15H, m, arom.-H). MS *m/z*: 468 (M^+), 450, 391. $[\alpha]_D^{24}$ +90.3° (c = 1.0, $CHCl_3$). **12b**: IR (neat): 3550, 1710, 1660, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.69 (3H, s, COOMe), 5.80 (1H, br s, olefinic-H), 7.0—7.7 (15H, m, arom.-H). MS *m/z*: 468 (M^+), 450, 391. $[\alpha]_D^{24}$ +36.3° (c = 1.0, $CHCl_3$).

(1*S*,5*S*,6*S*,7*R*)-3[(*Z*)-2-Hydroxyethylene]-6-[3(*S*)-(tetrahydropyran-2-yl)oxy-1(*E*)-octenyl]-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (13)——a) Synthesis from **14**[5]: A solution of DIBAL in toluene (25.9 ml) was added at 0—5 °C to a solution of **14** (2.47 g) in toluene (62 ml) at 0—5 °C. After being stirred for 1.5 h, the reaction mixture was

quenched by addition of aqueous THF and stirred for 30 min. The precipitate was filtered off and the filtrate was evaporated to dryness. The residue was purified on a Lobar column [Merck, silica gel, size C, 35% AcOEt in hexane (v/v)] to give less polar **13** (940 mg) and the more polar *E*-isomer (930 mg), both as oils. TLC *Rf* 0.40 (**13**), 0.36 (*E*-isomer of **13**) [AcOEt : hexane = 1 : 2 (v/v)]. **13**: IR (neat): 3440, 1024 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, br t, Me), 4.71 (2H, br s, OCHO × 2), 5.2—5.8 (3H, m, olefinic-H). MS *m/z*: 360 ($M^+ - 102$), 342. $[\alpha]_D^{26}$ −13.4° (*c* = 1.2, MeOH). *E*-Isomer of **13**: IR (neat): 3440, 1024 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, br t, Me), 4.71 (2H, br s, OCHO × 2), 5.2—5.8 (3H, m, olefinic-H). MS *m/z*: 360 ($M^+ - 102$), 342. $[\alpha]_D^{26}$ −10.6° (*c* = 1.1, MeOH).

b) Synthesis from **12b**: Treatment of **12b** (490 mg) as described in the following procedures 1, 2 and 3 gave **13** (78 mg) as an oil; 1) deprotection with *p*-TsOH in aqueous methanol as described for the synthesis of **11a, b**, 2) conversion reaction as described for the synthesis of **32** from **9a**, and 3) DIBAL reduction as described for the synthesis of **13** from **14**.

(1*S*,5*S*,6*S*,7*R*)-3-[(*E*)-Methoxycarbonylmethylene]-6-trityloxymethyl-7-(tetrahydropyran-2-yl)oxybicyclo-[3.3.0]octane (15a)——DHP (0.22 ml) and a catalytic amount of *p*-TsOH were added to a solution of **12a** (733 mg) in CH_2Cl_2 (1.5 ml). Treatment as described for the synthesis of **3**, except for the use of 10—15% AcOEt in hexane (v/v) as the chromatographic eluent, afforded **15a** (895 mg) as a colorless oil. IR (neat): 1719, 1660, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.68 (3H, s, COOMe), 5.80 (1H, br s, olefinic-H), 7.0—7.7 (15H, m, arom.-H). MS *m/z*: 552 (M^+), 475, 309. $[\alpha]_D^{24}$ +25.3° (*c* = 1.0, $CHCl_3$).

(1*S*,5*S*,6*S*,7*R*)-3-[(*Z*)-Methoxycarbonylmethylene]-6-trityloxymethyl-7-(tetrahydropyran-2-yl)-oxybicyclo-[3.3.0]octane (15b)——Reaction and treatment of **12b** (723 mg) as described for the synthesis of **15a** yielded **15b** (770 mg) as a colorless oil. IR (neat): 1720, 1660, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.68 (3H, s, COOMe), 5.77 (1H, br s, olefinic-H), 7.0—7.7 (15H, m, arom.-H). MS *m/z*: 552 (M^+), 475, 309. $[\alpha]_D^{24}$ −20.4° (*c* = 1.0, $CHCl_3$).

(1*S*,5*S*,6*S*,7*R*)-3-Methoxycarbonylmethyl-6-trityloxymethyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (16a) and (1*S*,5*S*,6*S*,7*R*)-3-Methoxycarbonylmethyl-6-hydroxymethyl-7-hydroxybicyclo[3.3.0]oct-2-ene (6a)——Reaction and treatment of **15a** (200 mg) as described for the synthesis of **5a, b** afforded pure **16a** (190 mg) as a colorless oil. IR (neat): 1741, 1600, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.65 (3H, s, COOMe), 5.40 (1H, br s, olefinic-H), 7.0—7.6 (15H, m, arom.-H). MS *m/z*: 552 (M^+), 475, 309. *p*-TsOH (100 mg) was added to a solution of **16a** (190 mg) in MeOH (5 ml). The whole was stirred for 1 h, then diluted with saturated $(NH_4)_2SO_4$, and extracted with AcOEt. The extract was washed with saturated $(NH_4)_2SO_4$, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a residue, which was purified by silica gel column chromatography. Elution with 30—90% AcOEt in hexane (v/v) afforded 57 mg of a crystalline solid. HPLC analysis showed that it was 99% homogeneous (**6a** : **6b** = 99 : 1). HPLC conditions: column, ERC-silica-1161 (ERMA); solvent, 1% MeOH in a mixture of AcOEt : hexane = 4 : 6 (v/v); flow rate, 2.5 ml/min; t_R 3.87 min (**6a**). Recrystallization from AcOEt–hexane mixture gave **6a** (32 mg), mp 96—99 °C. *Anal.* Calcd for $C_{12}H_{18}O_4$: C, 63.66; H, 7.95. Found: C, 63.53; H, 8.04. IR (KBr): 3300, 1740, 1215, 1080 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.69 (3H, s, COOMe), 5.54 (1H, br s, olefinic-H). MS *m/z*: 226 (M^+), 208, 190. $[\alpha]_D^{24}$ −22.1° (*c* = 1.0, MeOH).

Deconjugation and Deprotection Reaction of 15b——Reaction and treatment of **15b** (237 mg) as described for the synthesis of **5a, b** afforded a mixture of **16a, b** (225 mg) as a colorless oil. IR (neat): 1741, 1600, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.65 (3H, s, COOMe), 5.60 (1H, br s, olefinic-H), 7.0—7.6 (15H, m, arom.-H). MS *m/z*: 552 (M^+), 475, 309. Acid treatment of **16a, b** as described in the synthesis of **6a** gave the diol products (**6a, b**). HPLC analysis showed that the ratio of **6a** to **6b** (**16a** to **16b**) was 53 : 47. The same HPLC conditions as described for the analysis of **6a** were used.

(1*R*,5*S*,6*S*,7*R*)-3,3-Ethylenedioxy-6-(tert-butyldiphenylsilyloxymethyl)-7-tetrahydropyran-2-yl)oxybicyclo[3.3.0]-octane (17)——A mixture of **1** (10.0 g), *tert*-butyldiphenylchlorosilane (13.8 g) and imidazole (3.42 g) in DMF (100 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 6—10% AcOEt in hexane (v/v) afforded **17** (17.8 g) as a colorless oil. IR (neat): 2940, 2860, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (9H, s, *tert*-Bu), 3.88 (4H, s, OCH_2CH_2O), 7.3—7.5 (6H, m, arom.-H), 7.6—7.8 (4H, m, arom.-H). MS *m/z*: 479 ($M^+ - 57$), 395, 283, 199. $[\alpha]_D^{26}$ −7.5° (*c* = 1.1, MeOH).

(1*R*,5*S*,6*S*,7*R*)-3-Oxo-6-(*tert*-butyldiphenylsilyloxymethyl)-7-hydroxybicyclo[3.3.0]octane (18)——A mixture of **17** (1.53 g), AcOH (6 ml), THF (4 ml) and water (6 ml) was stirred at 45—50 °C for 7 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with 5% $NaHCO_3$ and brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave **18** (0.982 g) as crystals. Recrystallization from AcOEt–hexane gave an analytical sample, mp 103—104 °C. *Anal.* Calcd for $C_{25}H_{32}O_3Si$: C, 73.44; H, 7.83. Found: C, 73.33; H, 7.93. IR (KBr): 3520, 1730, 1105 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (9H, s, *tert*-Bu), 4.0—4.4 (1H, m, -CHOH), 7.3—7.5 (6H, m, arom.-H), 7.6—7.9 (4H, m, arom.-H). MS *m/z*: 351 ($M^+ - 57$), 333. $[\alpha]_D^{26}$ −14.6° (*c* = 1.0, MeOH).

(1*R*,5*S*,6*S*,7*R*)-3-Oxo-6-(*tert*-butyldiphenylsilyloxymethyl)-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (19)——A mixture of **18** (800 mg), DHP (0.27 ml) and a catalytic amount of *p*-TsOH in CH_2Cl_2 (16 ml) was stirred under ice-cooling for 30 min. The reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ and brine, and then dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 6—10% AcOEt in hexane (v/v) afforded **19** as a colorless oil (960 mg). IR (neat): 2940,

2860, 1740, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (9H, s, *tert*-Bu), 4.50 (1H, m, OCHO), 7.3—7.5 (6H, m, arom.-H), 7.6—7.8 (4H, m, arom.-H). MS *m/z*: 435 ($M^+ - 57$), 351, 333. $[\alpha]_D^{26}$ $-10.9°$ ($c=1.1$, MeOH).

(1*S*,5*R*,6*S*,7*R*)-2-Phenylthio-3-oxo-6-(*tert*-butyldiphenylsilyloxymethyl)-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (20a) and (1*R*,5*S*,6*S*,7*R*)-3-Oxo-4-phenylthio-6-(*tert*-butyldiphenylsilyloxymethyl)-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (20b)——A solution of **19** (340 mg) in THF (4 ml) was added to lithium dicyclohexylamide solution [prepared from dicyclohexylamine (0.34 ml) and 15% *n*-BuLi in hexane (1.0 ml) in THF (3 ml) and HMPA (0.5 ml)] at -78 °C. The mixture was stirred under the same conditions for 1 h, then a solution of $(PhS)_2$ (370 mg) in HMPA (4 ml) was added under ice-cooling, and the whole was stirred for 45 min. The reaction mixture was poured into water, and extracted with Et_2O. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on a Lobar column [Merck, silica gel, size B, hexane : AcOEt = 7 : 2 (v/v)] to give the less polar sulfide (**20a**) (253 mg), and the more polar sulfide (**20b**) (120 mg), both as colorless oils. **20a**: IR (neat): 3080, 2940, 1740, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (9H, s, *tert*-Bu), 4.4—4.7 (1H, m, OCHO), 7.1—7.8 (15H, m, arom.-H). MS *m/z*: 600 (M^+), 516, 459, 381. $[\alpha]_D^{26}$ $+10.9°$ ($c=1.0$ MeOH). **20b**: IR (neat): 3060, 2930, 1735, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (9H, s, *tert*-Bu), 4.4—4.7 (1H, m OCHO), 7.1—7.8 (15H, m, arom.-H). MS *m/z*: 600 (M^+), 516, 459, 381. $[\alpha]_D^{26}$ $-2.1°$ ($c=1.0$, MeOH).

(1*S*,5*R*,6*S*,7*R*)-2-Phenylthio-3-(methoxycarbonylmethyl)-6-(*tert*-butyldiphenylsilyloxymethyl)-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (21)——Trimethyl phosphonoacetate (0.15 ml) was added to NaH [prepared from 55% NaH in oil (42 mg) by hexane washing] in a mixed solvent of THF (3 ml), DMF (3 ml) and HMPA (0.6 ml). The mixture was stirred for 30 min, then a solution of **20a** (120 mg) in THF (1 ml) was added, and the whole was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 4—5% AcOEt in hexane (v/v) afforded **21** (75 mg) as a colorless oil. Further elution with 6—8% AcOEt in hexane (v/v) gave recovered **20a** (15 mg). **21**: IR (neat): 2940, 1740, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (9H, s, *tert*-Bu), 3.35 (2H, s, CH_2COOMe), 3.67 (3H, s, COOMe), 4.62 (1H, br s, OCHO), 7.2—7.8 (15H, m, arom.-H). MS *m/z*: 656 (M^+), 571, 515. $[\alpha]_D^{26}$ $-46.6°$ ($c=1.0$, MeOH).

(1*S*,5*S*,6*S*,7*R*)-3-(Methoxycarbonylmethyl)-6-(*tert*-butyldiphenylsilyloxymethyl)-7-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]oct-2-ene (22)——A mixture of **21** (64 mg) and Raney Ni [Kawaken Fine Chemical, suspended in EtOH] (0.2 ml) in EtOH (2 ml) was refluxed for 1 h, and then the Raney Ni was filtered off. Removal of the solvent of the filtrate *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 3—5% AcOEt in hexane (v/v) afforded **22** (52 mg) as a colorless oil. IR (neat): 2950, 1740, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (9H, s, *tert*-Bu), 3.05 (2H, s, CH_2COOMe), 3.67 (3H, s, COOMe), 5.50 (1H, br s, olefinic-H), 7.2—7.9 (10H, m, arom.-H). MS *m/z*: 491 (M^+), 407, 283. $[\alpha]_D^{26}$ $-13.6°$ ($c=0.8$, MeOH).

(1*S*,5*S*,6*S*,7*R*)-3-(2-Hydroxyethyl)-6-(*tert*-butyldiphenylsilyloxymethyl)-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (23)——a) Synthesis from **22**: A solution of **22** (51 mg) in THF (2 ml) was added to a stirred suspension of $LiAlH_4$ (5 mg) in THF (2 ml) under ice-cooling, and the whole was stirred for 30 min. The mixture was poured into water and extracted with Et_2O. The extracts were washed with water and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was purified by silica gel column chromatography. Elution with 10—15% AcOEt in hexane (v/v) afforded **23** (45 mg) as a colorless oil. IR (neat): 3420, 2920, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (9H, s, *tert*-Bu), 4.62 (1H, br s, OCHO), 5.40 (1H, br s, olefinic-H), 7.3—7.5 (6H, m, arom.-H), 7.6—7.8 (4H, m, arom.-H). MS *m/z*: 463 ($M^+ - 57$), 379, 361. $[\alpha]_D^{26}$ $-15.9°$ ($c=1.1$, MeOH).

b) Synthesis from **28a**: A solution of **28a** (202 mg) in THF (4 ml) was added to KH [prepared from 35% KH dispersion in oil (82 mg) by hexane washing] in THF (6 ml) at room temperature. The mixture was stirred for 15 min, then 18-crown-6 (190 mg) followed by ICH_2SnBu_3 (0.2 ml) were added, and the whole was stirred for a further 3 h. The reaction mixture was cooled to -78 °C, and 15% *n*-BuLi in hexane (0.6 ml) was added. The whole was stirred at the same temperature for 20 min, and then allowed to stand at ambient temperature. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 7—8% AcOEt in hexane (v/v) afforded **23** (50 mg). Further elution with 12—15% AcOEt in hexane (v/v) gave recovered **28a** (36 mg).

(1*S*,5*S*,6*S*,7*R*)-3-(2-Benzoyloxyethyl)-6-(*tert*-butyldiphenylsilyloxymethyl)-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (24)——A mixture of **23** (32 mg) in pyridine (0.5 ml) and benzoyl chloride (0.05 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with 3% HCl and brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 4—6% AcOEt in hexane (v/v) afforded **24** (32 mg) as a colorless oil. IR (neat): 2920, 1720, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (9H, s, *tert*-Bu), 4.38 (2H, t, $J=7$ Hz, CH_2CH_2O), 4.65 (1H, br s, OCHO), 5.42 (1H, br s, olefinic-H), 7.2—8.2 (15H, m, arom.-H). MS *m/z*: 567 ($M^+ - 57$), 483, 405. $[\alpha]_D^{26}$ $+22.4°$ ($c=0.7$, MeOH).

A Mixture of (1*S*,5*S*,6*S*,7*R*)-3-Methyl-6-(*tert*-butyldiphenylsilyloxymethyl)-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (26a) and (1*S*,5*R*,6*S*,7*R*)-3-Methyl-6-(*tert*-butyldiphenylsilyloxymethyl)-7-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]oct-3-ene (26b)——A solution of **19** (10.0 g) in THF (100 ml) was added to lithium dicyclohexyl-

amide solution [prepared from dicyclohexylamine (9.5 ml) in THF (300 ml) and 15% *n*-BuLi in hexane (25 ml)] under ice-cooling. The mixture was stirred at the same temperature for 10 min, the $ClP(O)(OPh)_2$ (9.0 ml) was added, and the whole was stirred at room temperature for 20 min. The reaction mixture was poured into water and extracted with Et_2O. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was purified by silica gel chromatography. Elution with 50% Et_2O in hexane (v/v) afforded a mixture of **25a**, **b** (14.5 g) as an oil. IR (neat): 2940, 1490, 1190, 1160, 965 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (9H, s, *tert*-Bu), 5.42 (1H, br s, olefinic-H), 7.1—8.1 (20H, m, arom.-H). Next, 15% Me_3Al in hexane (60 ml) was added to a solution of the phosphate (14.5 g) and $Pd(PPh_3)_4$ (2.00 g) in $ClCH_2CH_2Cl$ (200 ml) at room temperature, and the whole was stirred for 3 h. The reaction was quenched by addition of water–saturated ether, and the precipitate was filtered off. Removal of the solvent of the filtrate *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 3—4% AcOEt in hexane (v/v) afforded a mixture of **26a**, **b** (4.68 g) as a colorless oil. HPLC analysis showed that this was a 63 : 37 mixture of **26a**, **b**. HPLC conditions: column, ERC-silica-1161 (ERMA); solvent, 1% AcOEt in hexane (v/v); flow rate, 1.4 ml/min; t_R 5.6 min (**26a**), 6.0 min (**26b**). **26a**, **b**: IR (neat): 2920, 1425, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (9H, s, *tert*-Bu), 1.67 (3H, s, Me), 4.70 (1H, br s, OCHO), 5.28 (1H, br s, olefinic-H), 7.3—7.5 (6H, m, arom.-H), 7.6—7.8 (4H, m, arom.-H). MS *m/z*: 433 ($M^+ - 57$), 404, 348.

(1*S*,2*R*,3*S*,5*R*,6*S*,7*R*)-2,3-Epoxy-3-methyl-6-(*tert*-butyldiphenylsilyloxymethyl)-7-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]octane (27a) and (1*R*,3*R*,4*S*,5*S*,6*S*,7*R*)-3,4-Epoxy-3-methyl-6-(*tert*-butyldiphenylsilyloxymethyl)-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (27b)——MCPBA (85% purity, 150 mg) was added to a solution of a 3 : 2 mixture of **26a**, **b** (300 mg) in CH_2Cl_2 (6 ml) under ice-cooling, and the whole was stirred for 1 h. The reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ and brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on a Lobar column [Merck, silica gel, size B, hexane : AcOEt = 4 : 1 (v/v)] to give the less polar epoxide (**27b**) (100 mg), and the more polar epoxide (**27a**) (130 mg), both as colorless oils. **27a**: IR (neat): 2940, 1430, 1115 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (9H, s, *tert*-Bu), 1.41 (3H, s, Me), 7.3—7.5 (6H, m, arom.-H), 7.6—7.8 (4H, m, arom. H). MS *m/z*: 449 ($M^+ - 57$), 421, 365. $[\alpha]_D^{26}$ −7.1° (*c* = 1.1, MeOH). **27b**: IR (neat): 2940, 1430, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (9H, s, *tert*-Bu), 1.42 (3H, s, Me), 7.3—7.5 (6H, m, arom.-H), 7.6—7.8 (4H, m, arom.-H). MS *m/z*: 449 ($M^+ - 57$), 421, 365. $[\alpha]_D^{26}$ −4.8° (*c* = 1.1, MeOH).

(1*S*,2*R*,5*R*,6*S*,7*R*)-2-Hydroxy-3-methylene-6-(*tert*-butyldiphenylsilyloxymethyl)-7-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]octane (28a)——A solution of **27a** (50 mg) in benzene (0.5 ml) was added to diethylaluminum 2,2,6,6-tetramethylpiperidinylamide [prepared[12] from 2,2,6,6-tetramethylpiperidine (0.11 ml) in benzene (3 ml), 15% *n*-BuLi in hexane (0.37 ml) and 15% diethylaluminum chloride in hexane (0.73 ml)] under ice-cooling, and the whole was stirred for 30 min. The reaction mixture was poured into water and extracted with Et_2O. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 12—14% AcOEt in hexane (v/v) afforded **28a** (36 mg) as a colorless oil. IR (neat): 3400, 2930, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (9H, s, *tert*-Bu), 4.94 and 5.06 (each 1H, br s, olefinic-H), 7.3—7.5 (6H, m, arom.-H), 7.6—7.8 (4H, m, arom.-H). MS *m/z*: 449 ($M^+ - 57$), 365, 347. $[\alpha]_D^{26}$ −22.6° (*c* = 1.1, MeOH). For the large scale experiment, a 3 : 2 mixture of **26a**, **b** (3.60 g) was epoxidized with MCPBA to afford a mixture of **27a**, **b** (3.72 g), which was treated with diethylaluminum 2,2,6,6-tetramethylpiperidinylamide. The obtained product was purified by silica gel column chromatography. Elution with 10—14% AcOEt in hexane (v/v) afforded **28b** (1.25 g), and further elution with 16—20% AcOEt in hexane (v/v) afforded **28a** (1.56 g).

(1*S*,4*S*,5*S*,6*S*,7*R*)-4-Hydroxy-3-methylene-6-(*tert*-butyldiphenylsilyloxymethyl)-7-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]octane (28b)——Compound **27b** (48 mg) was converted into oily **28b** (32 mg) by the same procedure as used for the synthesis of **28a**. IR (neat): 3400, 2930, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (9H, s, *tert*-Bu), 4.90 and 5.02 (each 1H, br s, olefinic-H), 7.3—7.5 (6H, m, arom.-H), 7.6—7.8 (4H, m, arom.-H). MS *m/z*: 449 ($M^+ - 57$), 365, 347. $[\alpha]_D^{26}$ +10.6° (*c* = 1.1, MeOH).

(1*S*,5*S*,6*S*,7*R*)-3-(2-Benzoyloxyethyl)-6-[3-oxo-1(*E*)-octenyl]-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (29)——A solution of pyridine–SO_3 complex (6.00 g) in DMSO (20 ml) was added to a stirred mixture of **10a** (3.00 g) and Et_3N (16.2 ml) in DMSO (30 ml) at room temperature. After being stirred for 1 h, the reaction mixture was poured into ice-water and extracted with AcOEt. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a practically pure aldehyde (3.10 g) as a pale yellow oil. The crude material was used for the subsequent step without purification. IR (neat): 2720, 1720, 1280 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.44 (2H, t, *J* = 7 Hz, CH_2CH_2O), 4.64 (1H, br s, OCHO), 5.46 (1H, br s, olefinic-H), 7.3—7.7 (3H, m, arom.-H), 8.0—8.2 (2H, m, arom.-H), 9.80 (1H, d, *J* = 3 Hz, CHO). Tributyl 2-oxoheptylidenephosphorane (3.00 g) in ether (30 ml) was added to a solution of the aldehyde (3.00 g) obtained above in ether (60 ml), and the whole was stirred at room temperature for 3 h, then evaporated to dryness. The residue was purified by silica gel column chromatography. Elution with 8—9% AcOEt in hexane (v/v) afforded **29** (3.61 g) as a colorless oil. IR (neat): 1725, 1675, 1630, 1275 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.43 (2H, t, *J* = 7 Hz, CH_2CH_2O), 4.63 (1H, br s, OCHO), 5.47 (1H, br s olefinic-H), 6.18 (1H, dd, *J* = 15, 3 Hz, olefinic-H), 6.7—7.1 (1H, m, olefinic-H), 7.3—7.7 (3H, m, arom.-H), 8.0—8.2 (2H, m, arom.-H). MS *m/z*: 398 ($M^+ - 84$), 378, 352, 232. $[\alpha]_D^{26}$ +16.8° (*c* = 1.1, MeOH).

(1*S*,5*S*,6*S*,7*R*)-3-(2-Benzoyloxyethyl)-6-[3(*S*)-hydroxy-1(*E*)-octenyl]-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]-oct-2-ene (30a) and (1*S*,5*S*,6*S*,7*R*)-3-(2-Benzoyloxyethyl)-6-[3(*R*)-hydroxy-1(*E*)-octenyl]-7-(tetrahydropyran-2-yl)-

oxybicyclo[3.3.0]oct-2-ene (30b)——$NaBH_4$ (425 mg) was added to a stirred solution of **29** (3.61 g) and $CeCl_3 \cdot 7H_2O$ (3.40 g) in methanol (60 ml) under ice-cooling. The mixture was stirred for 30 min, then excess reagent was decomposed by addition of AcOH, and the reaction mixture was diluted with brine and extracted with AcOEt. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on a Lobar column [Merck, silica gel, size C, toluene : AcOEt = 3 : 2 (v/v)] to give the less polar 15(*R*)-alcohol (**30b**) (1.10 g) and the more polar 15(*S*)-alcohol (**30a**) (2.12 g), both as colorless oils. **30a**: IR (neat): 3430, 1725, 1275 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.43 (2H, t, J = 7 Hz, CH_2CH_2O), 4.65 (1H, br s, OCHO), 5.45 (1H, br s, olefinic-H), 5.5—5.8 (2H, m, olefinic-H), 7.3—7.7 (3H, m, arom.-H), 8.0—8.2 (2H, m, arom.-H). MS *m/z*: 464 ($M^+ - 18$), 380, 336. $[\alpha]_D^{25}$ +4.3° (*c* = 1.0, MeOH). **30b**: IR (neat): 3440, 1725, 1275, 1115 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.43 (2H, t, J = 7 Hz, CH_2CH_2O), 4.67 (1H, br s, OCHO), 5.45 (1H, br s, olefinic-H), 5.5—5.7 (2H, m, olefinic-H), 7.3—7.7 (3H, m, arom.-H), 8.0—8.2 (2H, m, arom.-H). MS *m/z*: 464 ($M^+ - 18$), 380, 336. $[\alpha]_D^{25}$ +2.0° (*c* = 1.0, MeOH).

(1*S*,5*S*,6*S*,7*R*)-3-(2-Benzoyloxyethyl)-6-[3(*S*)-benzoyloxy-1(*E*)-octenyl]-7-(tetrahydropyran-2-yl)oxybicyclo-[3.3.0]oct-2-ene (31)——Reaction and treatment of of **30a** (150 mg) as described for the synthesis of **8a**, **b**, except for the use of 4—10% AcOEt in hexane (v/v) as the chromatographic eluent, afforded **31** (181 mg) as a colorless oil. IR (neat): 2920, 1720, 1270 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.45 (2H, t, J = 7 Hz, CH_2CH_2O), 5.3—5.9 (3H, br s, olefinic-H), 7.3—7.7 (6H, m, arom.-H), 7.9—8.1 (4H, m, arom.-H). MS *m/z*: 484 ($M^+ - 102$), 464, 380, 362. $[\alpha]_D^{26}$ −10.0° (*c* = 1.0, MeOH). UV λ_{max}^{MeOH} nm (ε): 228.3 (26600), 271.5 (1800). CD (*c* = 0.0039, MeOH) $[\theta]^{25}$ (nm): +14900 (226.5) (positive maximum).

(1*S*,5*S*,6*S*,7*R*)-3-(2-Benzoyloxyethyl)-6-[3(*S*)-(tetrahydropyran-2-yl)oxy-1(*E*)-octenyl]-7-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]oct-2-ene (32)——A mixture of **30a** (1.97 g), DHP (0.57 ml) and a catalytic amount of *p*-TsOH in CH_2Cl_2 (20 ml) was stirred under ice-cooling for 30 min. The reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ and brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 6—9% AcOEt in hexane (v/v) afforded **32** (2.30 g) as a colorless oil. IR (neat): 2960, 1725, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.47 (2H, t, J = 7 Hz, CH_2CH_2O), 4.72 (2H, br s, OCHO × 2), 5.45 (1H, br s, olefinic-H), 5.5—5.7 (2H, m, olefinic-H), 7.3—7.7 (3H, m, arom.-H), 8.0—8.2 (2H, m, arom.-H). MS *m/z*: 464 ($M^+ - 102$), 380, 338. $[\alpha]_D^{25}$ −15.1° (*c* = 1.1, MeOH).

(1*S*,5*S*,6*S*,7*R*)-3-(2-Hydroxyethyl)-6-[3(*S*)-(tetrahydropyran-2-yl)oxy-1(*E*)-octenyl]-7-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]oct-2-ene (33)——A mixture of **32** (2.29 g) and anhydrous K_2CO_3 (1.18 g) in methanol (50 ml) was stirred at 40—45 °C for 1 h. The reaction mixture was poured into water, and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 14—18% AcOEt in hexane (v/v) afforded **33** (1.81 g) as a colorless oil. IR (neat): 3470, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.70 (2H, br s, OCHO × 2), 5.42 (1H, br s, olefinic-H), 5.5—5.7 (2H, m, olefinic-H). MS *m/z*: 360 ($M^+ - 102$), 316, 276. $[\alpha]_D^{25}$ −31.0° (*c* = 1.1, MeOH).

(+)-3-Oxaisocarbacyclin (34a)——The alcohol (**33**) (603 mg) was led to **34a** (260 mg), mp 62—64 °C, through the sequence of reactions described in the previous report.[4] *Anal.* Calcd for $C_{20}H_{35}O_5$: C, 68.15; H, 9.15. Found: C, 68.20; H, 9.30. IR (KBr): 3400, 1730, 972 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, br t, Me), 3.00 (1H, m, C_9-H), 3.67 (2H, t, J = 6 Hz, CH_2CH_2O), 4.07 (2H, s, OCH_2COOH), 5.40—5.55 (3H, m, olefinic-H). $[\alpha]_D^{25}$ +6.2° (*c* = 1.0, MeOH).

Synthesis of 34b—l——Through a sequence of reactions similar to that described for the synthesis of **34a**, **10a** was led to **34b—l** using the corresponding phosphonates. In the case of **34g**, the Wittig–Horner reaction (step 2) was done by heating the THF solution at reflux for 1.5 h. Physical data are summarized in Table II.

(1*S*,5*S*,6*S*,7*R*)-3-(2-Mesyloxyethyl)-6-[3(*S*)-(tetrahydropyran-2-yl)oxy-1(*E*)-octenyl]-7-(tetrahydropyran-2-yl)-oxybicyclo[3.3.0]oct-2-ene (35)——Mesyl chloride (0.36 ml) was added to a solution of **33** (1.79 g) and Et_3N (0.81 ml) in CH_2Cl_2 (35 ml) under ice-cooling, and the whole was stirred for 30 min. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave **35** (2.03 g) as a colorless oil. IR (neat): 2950, 1360, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.98 (3H, s, $MeSO_3$), 4.70 (2H, br s, OCHO × 2), 5.40 (1H, br s, olefinic-H), 5.5—5.7 (2H, m, olefinic-H). MS *m/z*: 354 ($M^+ - 102 - 84$), 336, 310, 283, 258. $[\alpha]_D^{25}$ −27.5° (*c* = 1.1, MeOH).

(1*S*,5*S*,6*S*,7*R*)-3-(2-Methoxycarbonylmethylthioethyl)-6-[3-(*S*)-(tetrahydropyran-2-yl)oxy-1(*E*)-octenyl]-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (36)——Thioglycolic acid (0.6 ml) was added dropwise to a mixture of NaH [55% NaH in oil (600 mg) was washed with hexane] in DMSO (20 ml) at 18—20 °C, and the whole was stirred for 30 min. A solution of **35** (1.92 g) in DMSO (20 ml) was added, and the whole was stirred at room temperature for 2 h. The reaction mixture was poured into ice-water, acidified with 10% HCl and then extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was treated with excess CH_2N_2 in ether, and purified by silica gel column chromatography. Elution with 6—10% AcOEt in hexane (v/v) afforded **36** (1.03 g) as a colorless oil. IR (neat): 2950, 1740, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.73 (3H, s, COOMe), 4.68 (2H, br s, OCHO × 2), 5.32 (1H, br s, olefinic-H), 5.4—5.8 (2H, m, olefinic-H). MS *m/z*: 448 ($M^+ - 102$), 364, 320, 258. $[\alpha]_D^{25}$ −15.1° (*c* = 1.1, MeOH).

3-Thiaisocarbacyclin Methyl Ester (37)——A mixture of **36** (503 mg) in AcOH (5 ml) and water (2.5 ml) was stirred at room temperature overnight. The reaction mixture was poured into water and extracted with AcOEt. The

TABLE II. Physical and Spectral Data for **34b**—**1**

Compd.	IR (neat)	^{1}H-NMR ($CDCl_3$)	MS	$[\alpha]_D^{24}$ ($c=1.0$)
34b	3350, 1738	0.7—1.1 (6H, m), 3.68 (2H, t, $J=6$ Hz), 4.07 (2H, s), 5.42 (1H, br s), 5.55 (2H, m)	348 (M^+-18)	+5.2 (EtOH)
34c	3380, 1740, 1645	0.89 (3H, m), 3.66 (2H, t), 4.07 (2H, s), 4.7—5.2 (2H, m), 5.3—6.1 (4H, m)	360 (M^+-18)	+7.6 ($CHCl_3$)
34d	3380, 1734	1.78 (3H, t, $J=1$ Hz) 3.68 (2H, t), 4.09 (2H, s), 5.42 (1H, s), 5.56 (2H, m)	344 (M^+-18)	+20.7 (EtOH)
34e	3350, 1738	3.68 (2H, t), 4.09 (2H, s), 5.43 (1H, br s), 5.54 (2H, m)	374 (M^+-18)	−0.8 ($CHCl_3$)
34f	3400, 1735	0.7—1.1 (6H, m), 4.09 (2H, s), 4.8—5.2 (2H, m), 5.2—6.1 (4H, m)	374 (M^+-18)	+16.4 ($c=0.25$, EtOH)
34g	3350, 1740, 1600, 1590	3.65 (2H, t), 4.07 (2H, s), 5.52 (1H, br s), 5.72 (2H, m), 6.8—7.5 (5H, m)	384 (M^+-18)	−1.7 (EtOH)
34h[a]	(Nujol) 3550, 3450, 1741	3.68 (2H, t), 4.08 (2H, s), 5.40 (1H, br s), 5.52 (2H, m)	346 (M^+-18)	+6.5 ($CHCl_3$)
34i	3350, 1740	3.67 (2H, t), 4.08 (2H, s), 5.42 (1H, br s), 5.54 (2H, m)	346 (M^+-18)	+11.4 (EtOH)
34j	3400, 1738	0.7—1.1 (9H, m), 3.77 (2H, t), 4.08 (2H, s), 5.42 (1H, br s), 5.56 (2H, m)	362 (M^+-18)	+17.2 ($c=0.25$, EtOH)
34k[b]	(Nujol) 3410, 3350, 1705, 1660	3.67 (2H, t), 4.07 (2H, s), 5.40 (1H, br s), 5.52 (2H, m)	332 (M^+-18)	+4.2 ($CHCl_3$)
34l	3350, 1730	0.94 (2H, t), 4.07 (2H, s), 1.06 (3H, s), 1.69 (3H, s), 3.68 (2H, t), 4.08 (2H, s), 5.11 (1H, br t), 5.41 (1H, br s), 5.54 (2H, m)	388 (M^+-18)	−1.9 ($CHCl_3$)

a) mp 92—94 °C. *Anal.* Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.38; H, 8.78. *b*) mp 98—101 °C. *Anal.* Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.43; H, 8.59.

extract was washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel column chromatography. Elution with 40—70% AcOEt in hexane (v/v) afforded **37** (287 mg) as a colorless oil. IR (neat): 3360, 2940, 1735, 1280 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.20 (2H, s, SCH_2COOMe), 3.73 (3H, s, COOMe), 5.2—5.6 (3H, m, olefinic-H). MS *m/z*: 364 (M^+-18), 346, 320, 258, 214. $[\alpha]_D^{25}$ +17.2° ($c=1.1$, MeOH).

3-Thiaisocarbacyclin (38)——A mixture of **37** (130 mg) and 5% NaOH (1.0 ml) in methanol (2 ml) was stirred under ice-cooling for 1 h. The reaction mixture was poured into water, acidified with 10% HCl, and then extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by acid-washed silica gel column chromatography. Elution with 70% AcOEt in hexane (v/v) to AcOEt afforded **38** (119 mg) as a colorless oil. IR (neat): 3350, 2950, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.20 (2H, s, SCH_2COOH), 5.07 (3H, s, OH×2 and COOH), 5.2—5.7 (3H, m, olefinic-H). MS *m/z*: 350 (M^+-18), 332, 306, 291, 258. HR-MS *m/z*: Calcd for $C_{20}H_{30}O_3S$ (M^+-H_2O): 350.1916. Found: 350.1924. $[\alpha]_D^{25}$ +17.0° ($c=1.1$, MeOH).

Methyl Ester of 3-Sulfinylisocarbacyclin (39)——MCPBA (85% purity, 85 mg) was added to a solution of **37** (151 mg) in methanol (10 ml) at −50 °C, and the whole was stirred under the same conditions for 1.5 h. The reaction

mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ and brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by acid-washed silica gel column chromatography. Elution with AcOEt to 10% methanol in AcOEt (v/v) afforded the methyl ester of **39** (149 mg) as a colorless oil. IR (neat): 3400, 2940, 1740, 1145 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.72 (2H, s, CH_2COOMe), 3.79 (3H, s, COOMe), 5.2—5.6 (3H, m, olefinic-H). MS *m/z*: 380 (M^+-18), 362, 345, 289, 214. $[\alpha]_D^{27}$ +21.1° ($c=1.0$, MeOH).

3-Sulfinylisocarbacyclin (39)——The methyl ester of **39** (127 mg) was hydrolyzed to **39** (120 mg) by the same procedure as used for the synthesis of **38**. IR (neat): 3350, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.74 (2H, s, CH_2COOH), 4.75 (3H, s, OH × 2 and COOH), 5.2—5.6 (3H, m, olefinic-H). MS *m/z*: 304 (M^+-80), 292, 274, 248, 214. HR-MS *m/z*: Calcd for $C_{19}H_{28}OS$ ($M^+-CH_4O_4$): 304.1860. Found: 304.1840. $[\alpha]_D^{27}$ +20.4° ($c=1.0$, MeOH).

Methyl Ester of 3-Sulfonylisocarbacyclin (40)——MCPBA (85% purity, 115 mg) was added to a solution of **37** (102 mg) in methanol (10 ml) at −50 °C, and the whole was stirred under ice-cooling for 6 h. The reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ and brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by acid-washed silica gel column chromatography. Elution with 50—70% AcOEt in hexane (v/v) afforded the methyl ester of **40** (59 mg) as a colorless oil. IR (neat): 3400, 2940, 1740, 1320 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.82 (3H, s, COOMe), 3.98 (2H, s, CH_2COOMe), 5.3—5.6 (3H, m, olefinic-H). MS *m/z*: 396 (M^+-18), 352, 325, 258. $[\alpha]_D^{27}$ +12.7° ($c=1.0$, MeOH). Further elution with AcOEt to 10% MeOH in AcOEt (v/v) gave **39** (40 mg).

3-Sulfonylisocarbacyclin (40)——The methyl ester of **40** (84 mg) was hydrolyzed to **40** (80 mg) by the same procedure as used for the synthesis of **38**. IR (neat): 3400, 1725, 1320 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.97 (2H, s, CH_2COOH), 4.47 (3H, s, OH × 2 and COOH), 5.3—5.6 (3H, m, olefinic-H). MS *m/z*: : 338 (M^+-62), 320, 267. HR-MS *m/z*: Calcd for $C_{19}H_{30}O_3S$ ($M^+-CH_2O_3$): 338.1916. Found: 338.1904. $[\alpha]_D^{27}$ +13.2° ($c=1.0$, MeOH).

(1*S*,5*S*,6*S*,7*R*)-3-(2-Methoxycarbonylmethylazaethyl)-6-[3(*S*)-(tetrahydropyran-2-yl)oxy-1(*E*)-octenyl]-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (41)——A solution of trifluoroacetic anhydride (0.35 ml) in CH_2Cl_2 (1 ml) was added to a solution of DMSO (0.27 ml) in CH_2Cl_2 (2 ml) at −78 °C. The mixture was stirred for 5 min, then a solution of **33** (580 mg) in CH_2Cl_2 (5 ml) was added at −78 °C, and the whole was stirred for 10 min. Et_3N (0.75 ml) was added and the reaction mixture was stirred at −70——30 °C for 30 min, then diluted with ice-water, and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a residue, which was purified by silica gel column chromatography. Elution with 10—15% AcOEt in hexane (v/v) gave the aldehyde (336 mg) as a colorless oil. IR (neat): 2720, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, br t, Me), 4.67 (2H, br s, OCHO × 2), 5.2—5.6 (3H, br s, olefinic-H), 9.66 (1H, t, $J=2$ Hz, CHO). MS *m/z*: 358 (M^+-102). A solution of the aldehyde (330 mg) obtained above in MeOH (1 ml) was added to a solution of methyl glycinate hydrogen chloride salt (540 mg) in MeOH (5 ml) at room temperature. The mixture was stirred for 10 min, then $NaBH_3(CN)$ (58 mg) was added. The whole was further stirred at room temperature for 30 min and stored at −20 °C for 48 h, then diluted with dilute $NaHCO_3$ and brine, and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave a residue, which was purified by silica gel column chromatography. Elution with 25—45% AcOEt in hexane (v/v) gave **41** (262 mg) as a colorless oil. IR (neat): 1748, 1025 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, br t, Me), 3.37 (2H, s, NCH_2COOMe), 3.69 (3H, s, COOMe), 4.66 (2H, br s, OCHO × 2), 5.2—5.7 (3H, m, olefinic-H). MS *m/z*: 533 (M^+).

3-Azaisocarbacyclin Methyl Ester (42)——Camphorsulfonic acid (326 mg) was added to a solution of **41** (232 mg) in a mixture of acetone (23 ml) and water (10 ml). The whole was stirred at room temperature for 10 h, then heated at 35 °C for 1 h, diluted with dilute $NaHCO_3$, and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent gave a residue, which was purified by silica gel column chromatography. Elution with AcOEt gave **42** (117 mg) as a colorless oil. IR (neat): 3350, 1745, 973 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, br t, Me), 3.41 (2H, s, NCH_2COOMe), 3.73 (3H, s, COOMe), 5.42 (1H, br s, olefinic-H), 5.56 (2H, m, olefinic-H). MS *m/z*: 365 (M^+). HR-MS *m/z*: Calcd for $C_{21}H_{35}NO_4$ (M^+): 365.5919. Found: 365.5924.

Biological Test Method——All manipulations were carried out at room temperature. For the isolation of platelet-rich plasma (PRP) from human blood or rabbit blood, the following procedure was used. Blood was obtained from human volunteers and Japanese white rabbits, and was anticoagulated with 1/10 volume of 3.8% trisodium citrate. PRP was prepared by centrifugation of whole blood at 95 × *g* for 15 min. Platelet-poor plasma (PPP) was prepared by centrifugation at 1000 × *g* for 15 min. The number of platelets in the PRP was adjusted to $3.0\times10^5/\mu l$ (human) or $6.0\times10^5/\mu l$ (rabbit) by addition of an appropriate volume of PPP. Platelet aggregation was measured with human and rabbit platelets by using the method of Born.[19] Twenty-five microliters of a test compound was added to 250 μl of stirred PRP in the aggregometer. After 2 min, 25 μl of ADP, at a final concentration of 2—5 μM, was added and the platelet aggregation response was recorded. To evaluate control platelet aggregation, 25 μl of saline without any test compound was added to the PRP, and an identical procedure was performed. The IC_{50} value of each test compound was calculated as the concentration required to reduce the aggregation by 50% of the control value.

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