Synthesis and Anti-platelet Aggregating Activity of 3-Hetero Analogues of (+)-9(O)-Methano-Δ^{6(9a)}-prostaglandin I₁

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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 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 C₃ position into both prostaglandin E₁ and carbacyclin derivative 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-Δ^{6(9a)}-prostaglandin I₁ (3-oxaisocarbacyclin) in an optically inactive form. It had a quite potent anti-platelet aggregating activity; its IC₅₀ 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. 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 tetrahydropyrany1 ether (3) 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
THP: tetrahydroxyran-2-yl

Chart 1

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 (Et₃N), 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 was alternatively prepared by diisobutylaluminum hydride (DIBAL) reduction of 14. 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) 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 Δ⁶(9α)-isomer (6a) (prostaglandin numbering) on the basis of the relative HPLC retention time, as in the case of the benzoates (9a, b); the Δ⁶(9α)-regioisomer (9a) had shorter retention time than the Δ⁶-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. Deprotonation of the allylic proton in a simple acyclic α,β-unsaturated ester occurs exclusively at the position syn to the ester group through electronic control. 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 Δ⁶(9α)-isomer (16a). On the other hand, the corresponding Z-imer (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 (LiAlH₄) to yield
the alcohol (7\textsubscript{a}, \textsubscript{b}). Benzoylation of 7\textsubscript{a}, \textsubscript{b} with benzoyl chloride in pyridine afforded the benzozate (8\textsubscript{a}, \textsubscript{b}) in 84\% yield from 5\textsubscript{a}, \textsubscript{b}. Deprotection of 8\textsubscript{a}, \textsubscript{b} with aqueous methanolic \textit{p}-TsOH yielded a mixture of 9\textsubscript{a}, \textsubscript{b} in a ratio of 66 to 34 (9\textsubscript{a} to 9\textsubscript{b}) as judged by HPLC analysis. The major isomer (9\textsubscript{a}) had a shorter retention time than 9\textsubscript{b} on HPLC. Several recrystallizations of the above mixture gave the crystalline diol (9\textsubscript{a}), mp 87—89 \textdegree C, as a single isomer in 32\% yield from 8\textsubscript{a}, \textsubscript{b}. Compound 9\textsubscript{a} was confirmed to be the \textit{d\textsubscript{609a1}}-isomer by leading it to 10\textsubscript{a} and 34\textsubscript{a}. The desired alcohol (10\textsubscript{a}) was finally prepared from 9\textsubscript{a} in three steps through a conventional method\textsuperscript{10} in 66\% yield: 1) treatment with one molar equivalent of trichloroacetyl chloride and Et\textsubscript{3}N, 2) protection with dihydropyran and \textit{p}-TsOH, 3) hydrolysis with aqueous sodium bicarbonate. Compound 10\textsubscript{a} showed a signal at \textit{\delta} 3.0 (multiplet) due to the H\textsubscript{a} proton, a characteristic of the \textit{d\textsubscript{609a1}}-double bond isomer, in the proton nuclear magnetic resonance (\textit{1H}-NMR) spectrum.\textsuperscript{41}

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

![Chart 4](chart.png)

Treatment of 1 with \textit{tert}-butyldiphenylchlorosilane and imidazole, followed by deprotection with aqueous acetic acid afforded the ketone (18), mp 103—104 \textdegree C. Protection of the hydroxy group in 18 with dihydropyran and \textit{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 (20\textsubscript{a}) and its regio-isomer (20\textsubscript{b}) in 61 and 29\% yields, respectively, after purification by silica gel column chromatography. Selective formation of 20\textsubscript{a} may be based on the selective deprotonation of the H\textsubscript{b} proton in 19 through the remote steric effect of the \textit{tert}-butyldiphenylsilyloxymethyl moiety. The structure of 20\textsubscript{a} was confirmed by leading 20\textsubscript{a} to 10\textsubscript{a} through the following sequence of reactions. This completed the second route to 10\textsubscript{a}. The Wittig–Horner reaction of 20\textsubscript{a} with trimethyl phosphonoacetate yielded the sulfide (21) in 57\% yield together with recovery of 20\textsubscript{a} (13\%). Deconjugation reaction of an exo-double bond to an \textit{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 \textit{1H}-NMR spectrum. Desulfurization of 21 with Raney nickel, followed by reduction of the product (22) with LiAl\textsubscript{H}\textsubscript{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-
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 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 a-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 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 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 (SO3) complex and Et3N in dimethyl sulfoxide (DMSO) followed by reaction with an ylide, tributyl 2-oxoheptylidene phosphorane, 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 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 C15 in 30a to be S. The hydroxy group in 30a was protected with
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 Ma, mp 62–64 °C, through the sequence of reactions described previously4): 1) n-butyllithium and lithium chloroacetate, 2) camphorsulfonic acid in aqueous acetone. Compound 34a was identical (infrared (IR), 1H-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$_3$N 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 cyanoborohydride17) 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.
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-azaisocarbacyclins (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. 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

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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-50C 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). In general, reactions were carried out under a nitrogen stream.

**(1R,5S,6S,7R)-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), [α]βε0 − 18.6° (c = 1.0, CHCl3), 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 (NH4)2SO4, and extracted with AcOEt. The extract was dried over Na2SO4. 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 afforded 2 (4.03 g) as a colorless oil. Recrystallization from AcOEt gave an analytical sample, mp 95–97 °C. Anal. Calc. for C9H13O3: C, 65.31; H, 8.29. Found: C, 65.25; H, 8.21. IR (Nujol): 3200, 1733 cm−1. 1H-NMR (CDCl3) δ: 4.13 (1H, q, J = 4.5 Hz, −6HOH). MS m/z: 170 (M+), 152, 134. [α]βε0 − 11.9° (c = 1.0, CHCl3).

**[(1S,5S,6S,7R)-3-Methoxycarbonylmethylene-6-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octane (3)](95)** — A catalytic amount of p-TsOH was added to a mixture of 2 (4.03 g) in CH2Cl2 (15 ml) and dihydropyran (DHP) (5.4 ml) at room temperature. The whole was stirred for 30 min, quenched with dilute NaHCO3, and extracted with AcOEt. The extract was washed with brine, and dried over Na2SO4. 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. 1H-NMR (CDCl3) δ: 4.65 (2H, br s, OHO x 2). MS m/z: 338 (M+), 263, 249, 152, 134. [α]βε0 − 19.5° (c = 1.0, MeOH).

**A Mixture of (1S,5S,6S,7R)-3-Methoxycarbonylmethylene-6-(tetrahydropyran-2-yl)oxyethyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octene (5a) and (1S,5R,6S,7R)-3-Methoxycarbonylmethyl-6-(tetrahydropyran-2-yl)oxyethyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octene (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 to −65 °C. After being stirred at the same temperature for 20 min, the reaction mixture was quenched with saturated NH4Cl, diluted with AcOEt, and extracted with water. The extract was washed with brine, and dried over Na2SO4. Removal of the solvent in vacuo gave a residue, which was purified by silica gel column chromatography. Elution with 15—25% AcOEt in hexane (v/v) afforded 5a (30.0 g) and 5b (20.0 g) as colorless oils. After being stirred at the same temperature for 20 min, the reaction mixture was quenched with saturated NH4Cl, diluted with AcOEt, and extracted with water. The extract was washed with brine, and dried over Na2SO4. Removal of the solvent in vacuo gave a residue, which was purified by silica gel column chromatography. Elution with 20—35% AcOEt in hexane (v/v) afforded 5a (21.0 g) and 5b (14.0 g) as colorless oils. The extract was washed with brine, and dried over Na2SO4. 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 5a (6.0 g) and 5b (3.0 g). HPLC analysis showed that the ratio of 5a to 5b (66 to 34) was determined by HPLC analysis of 6a, b derived from 5a, b; solvent, 1% MeOH in a mixture of AcOEt : hexane = 4 : 6; column, ERC-silica-1161 (ERMA); solvent, 1% MeOH in a mixture of AcOEt: hexane = 4 : 6 (v/v); flow rate, 1.0 ml/min; tR 3.89 min (6a), 4.27 min (6b).

**A Mixture of (1S,5S,6S,7R)-3-(2-Hydroxyethyl)-6-(tetrahydropyran-2-yl)oxyethyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octene (7a) and (1S,5R,6S,7R)-3-(2-Hydroxyethyl)-6-(tetrahydropyran-2-yl)oxyethyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octene (7b)** — A solution of 5a, b (50.9 g) in Et2O (150 ml) was added to a suspension of LiAlH4 (9.8 g) in Et2O (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 while 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. 1H-NMR (CDCl3) δ: 4.65 (2H, br s, OCHO x 2), 5.47 (1H, br s, olefinic-H). MS m/z: 366 (M+), 348, 282.

**A Mixture of (1S,5S,6S,7R)-3-(2-Benzoyloxyethyl)-6-(tetrahydropyran-2-yl)oxyethyl-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]octene (8a) and (1S,5R,6S,7R)-3-(2-Benzoyloxyethyl)-6-(tetrahydropyran-2-yl)oxyethyl-
7-(tetrahydrofuran-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 NaHCO3, and then brine, and dried over Na2SO4. 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. 1H-NMR (CDCl3) δ: 4.44 (2H, t, J = 6 Hz, CH2CH2O), 4.64 (2H, brs, OCHO × 2), 5.47 (1H, brs, olefinic-H). MS m/z: 470 (M⁺), 386, 302, 180.

(15,55,65,7R)-3-(2-Benzoxoylethyl)-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 water and dried over Na2SO4. 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; tR 4.60 min (9a), 4.93 min (9b). Four recrystallizations from a mixture of CH2Cl2 and cyclohexane (1:4—5) gave pure 9a (12.6 g), mp 87—88 °C. Anal. Calcéd for C31H31O6: C, 71.45; H, 7.28. Found: C, 71.51; H, 7.32. IR (KBr): 3220, 1715, 1280, 1120, 1080 cm⁻¹. 1H-NMR (CDCl3) δ: 6.9 (3H, s, COOME), 5.80 (1H, brs, olefinic-H), 7.48 (3H, m, arom.-H), 8.05 (2H, m, arom.-H). [α]25° = 28.5° (c = 1.0, MeOH).

(15,55,65,7R)-3-(2-Benzoxoylethyl)-6-(hydroxymethyl)-7-(tetrahydrofuran-2-yl)oxybicyclo[3.3.0]octane (10a) — a) Synthesis from 9a: Et3N (1.75 ml) and then CH3C0C1 (0.78 ml) in benzene (20 ml) were added to a solution of 9a (2.00 g) in benzene (40 ml) at 20—25 °C. After being stirred for 10 min, the reaction mixture was diluted with ice-water, and extracted with Et2O. The extract was washed with water and dried over Na2SO4. 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 CH2Cl2 (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 NaHCO3 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 water and dried over Na2SO4. 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. 1H-NMR (CDCl3) δ: 4.43 (2H, t, J = 6 Hz, CH2CH2O), 4.64 (2H, brs, OHO x 2), 5.47 (1H, brs, olefinic-H). MS m/z: 303 (M⁺), 285, 267, 249. [α]25° = 28.5° (c = 1.0, MeOH).

b) Synthesis from 24: A 1 M solution of Bu4NF 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 water and dried over Na2SO4. 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 (1S,55,65,7R)-3-[(E)-Methoxycarbonylmethylene]-6-hydroxymethyl-7-hydroxybicyclo[3.3.0]octane (11a) and (1S,55,65,7R)-3-[(Z)-Methoxycarbonylmethylene]-6-hydroxymethyl-7-hydroxybicyclo[3.3.0]octane (11b) — p-TsOH (2.9 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 (NH4)2SO4 and extracted with AcOEt. The extract was washed with saturated (NH4)2SO4 and dried over Na2SO4. 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) gave 11a, b as a colorless oil (1.52 g). IR (neat): 3380, 1708, 1658, 1130 cm⁻¹. 1H-NMR (CDCl3) δ: 6.68 (1H, s, COOME), 5.48 (1H, brs, olefinic-H), 7.2—7.6 (3H, m, arom.-H), 7.8—8.1 (2H, m, arom.-H). MS m/z: 303 (M⁺), 285, 267, 249. [α]25° = 28.5° (c = 1.0, MeOH).

HPLC analysis showed that the ratio of 11a to 11b was 50 to 50. HPLC conditions: column, ERC-OFS-1161 (ERMA); solvent, MeOH : H2O = 1:1 (v/v); flow rate, 1.2 ml/min (11a), 3.05 min (11a), 3.50 min (11b).

A Mixture of (1S,55,65,7R)-3-[{(E)-Methoxycarbonylmethylene}-6-trityloxymethyl-7-hydroxybicyclo[3.3.0]octane (12a) and (1S,55,65,7R)-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 Et3N (1.29 g) was heated under reflux for 0.5 h. The reaction mixture was cooled, stirred with dilute NaHCO3 (10 ml), diluted with water and brine, and extracted with AcOEt. The extract was washed with dilute HCl (cooled), and dried over Na2SO4. Removal of the solvent in vacuo gave a residue, which was purified on a Lobar column [Mercer, 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, 3510, 1700, 1660, 1560 cm⁻¹. 1H-NMR (CDCl3) δ: 7.0 (3H, s, COOME), 5.80 (1H, brs, olefinic-H), 4.7—5.7 (15H, m, arom.-H). MS m/z: 468 (M⁺), 450, 381. [α]25° = 90.3° (c = 1.0, CHCl3). 12b: IR (neat): 3550, 3510, 1700, 1660, 1560 cm⁻¹. 1H-NMR (CDCl3) δ: 6.9 (3H, s, COOME), 5.80 (1H, brs, olefinic-H), 7.0—7.7 (15H, m, arom.-H). MS m/z: 468 (M⁺), 450, 391. [α]25° = 36.3° (c = 1.0, CHCl3).
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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 HMFA (0.5 ml)] at -78 °C. The mixture was stirred under the same conditions for 1 h, then a solution of (PhSi₂)₂ (370 mg) in HMFA (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 Et₂O. The extract was washed with water and dried over Na₂SO₄. 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. 1H-NMR (CDCl₃) δ: 1.07 (9H, s, tert-Bu), 4.4-4.7 (1H, m, OHO), 7.1-7.8 (15H, m, arom.-H). MS m/z: 600 (M⁺), 516, 459, 381. [α]D²⁰ +10.9 ° (c=1.0 MeOH). 20b: IR (neat): 3060, 2930, 1735, 1110 cm⁻¹. 1H-NMR (CDCl₃) δ: 1.07 (9H, s, tert-Bu), 4.4-4.7 (1H, m, OHO), 7.1-7.8 (15H, m, arom.-H). MS m/z: 600 (M⁺), 516, 459, 381. [α]D²⁰ -2.1 ° (c=1.0, MeOH).

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 (55 mg) as a colorless oil. Further elution with 6-8% AcOEt in hexane (v/v) gave recovered 21 (75 mg) as a colorless oil. 21: IR (neat): 3070, 2930, 1735, 1110 cm⁻¹. 1H-NMR (CDCl₃) δ: 1.05 (9H, s, tert-Bu), 3.35 (2H, s, CH₂COOMe), 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. [α]D²⁰ -46.6 ° (c=1.0, MeOH).

2-Phenylthio-3-(methoxycarbonylmethyl)-6-(teth-butyldiphenylsilyloxy)methyl)-(7-tetrahydropryan-2-yl)-oxybicyclo[3.3.0]octane (20a) and (1R,5S,6S,7R)-3-Oxo-4-phenylthio-6-(tert-butyldiphenylsilyloxy)methyl)-(7-tetrahydropryan-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 HMFA (0.5 ml)] at -78 °C. The mixture was stirred under the same conditions for 1 h, then a solution of (PhSi₂)₂ (370 mg) in HMFA (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 Et₂O. The extract was washed with water and dried over Na₂SO₄. 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. 1H-NMR (CDCl₃) δ: 1.07 (9H, s, tert-Bu), 4.4-4.7 (1H, m, OHO), 7.1-7.8 (15H, m, arom.-H). MS m/z: 600 (M⁺), 516, 459, 381. [α]D²⁰ +10.9 ° (c=1.0 MeOH). 20b: IR (neat): 3060, 2930, 1735, 1110 cm⁻¹. 1H-NMR (CDCl₃) δ: 1.07 (9H, s, tert-Bu), 4.4-4.7 (1H, m, OHO), 7.1-7.8 (15H, m, arom.-H). MS m/z: 600 (M⁺), 516, 459, 381. [α]D²⁰ -2.1 ° (c=1.0, MeOH).
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 CIP(0)(OPh)2 (9.0 ml) was added, and the whole was stirred at room temperature for 30 min. The reaction mixture was poured into water and extracted with Et2O. The extract was washed with brine and dried over Na2SO4. Removal of the solvent gave an oily residue, which was purified by silica gel chromatography. Elution with 50% Et2O in hexane (v/v) afforded a mixture of 25a, b (14.5 g) as an oil. IR (neat): 2940, 1490, 1190, 965 cm−1. 1H-NMR (CDCl3) δ: 1.08 (9H, s, tert-Bu), 5.42 (1H, brs, olefinic-H), 7.1—8.1 (20H, m, arom.-H). Next, 15% Me3Al in hexane (60 ml) was added to a solution of the phosphate (14.5 g) and Pd(PPh3)4 (2.00 g) in CH2Cl2-CH3Cl (200 ml) at room temperature, and the whole was stirred for 3h. 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, EGC-silica-1161 (ERMA); solvent, 1% AcOEt in hexane (v/v); flow rate, 1.4 ml/min; λ 5.6 min (26a), 6.0 min (26b). 26a: IR (neat): 2920, 1452, 1110 cm−1; 1H-NMR (CDCl3) δ: 1.08 (9H, s, tert-Bu), 1.67 (3H, s, Me), 4.70 (1H, brs, OCHO), 5.28 (1H, brs, 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. 

(1S,2R,3S,5R,6S,7R)-2,3-Epoxy-3-methyl-6-(tert-butyldiphenylsilyloxy)methyl)-7-(tetrahydropryan-2-yl)-oxybicyclo[3.3.0]octane (27a) and (1R,3R,5S,6S,7R)-3,4-Epoxy-3-methyl-6-(tert-butyldiphenylsilyloxy)methyl)-7-(tetrahydropryan-2-yl)-oxybicyclo[3.3.0]octane (27b)—MCPBA (85% purity, 150 mg) was added to a solution of 26a, b (300 mg) in CH2Cl2 (6 ml) under ice-cooling, and the whole was stirred for 1 h. The reaction mixture was diluted with AcOEt, washed with 5% NaHCO3 and brine, and dried over Na2SO4. 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, 1110 cm−1; 1H-NMR (CDCl3) 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. [α]+ 10.6° (c= 1.1, MeOH). 27b: IR (neat): 2940, 1430, 1110 cm−1; 1H-NMR (CDCl3) 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. [α]+ 8.4° (c= 1.1, MeOH). 

(1S,2R,3S,5R,6S,7R)-2-Hydroxy-3-methylen-6-(tert-butyldiphenylsilyloxy)methyl)-7-(tetrahydropryan-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 [prepared8 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 Et2O. The extract was washed with water and dried over Na2SO4. Removal of the solvent in vacuo gave an oily residue, which was chromatographed on a Lobar column [Merck, silica gel, size B, 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 28a, b (4.68 g) as a colorless oil. IR (neat): 3400, 2930, 1110 cm−1. 1H-NMR (CDCl3) 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), 421, 365. [α]+ 10.6° (c= 1.1, MeOH). 

(1S,2R,3S,5R,6S,7R)-2-Hydroxy-3-methylen-6-(tert-butyldiphenylsilyloxy)methyl)-7-(tetrahydropryan-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. 1H-NMR (CDCl3) δ: 1.08 (9H, s, tert-Bu), 4.90 and 5.02 (each 1H, brs, olefinic-H), 7.3—7.5 (6H, m, arom.-H), 7.6—7.8 (4H, m, arom.-H). MS m/z: 449 (M+−57), 437, 347. [α]+ 8.2° (c= 1.1, MeOH).
oxybicyclo[3.3.0]oct-2-ene (30b) —— NaBH₄ (425 mg) was added to a stirred solution of 29 (3.61 g) and CeCl₃·7H₂O (3.40 g) in methanol (60 ml) under ice-cooling. The mixture was stirred for 30 min, then excess reagent was decomposed chromatographically 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) (0.12 g), both as colorless oils.

30a: IR (neat): 3430, 1725, 1270 cm⁻¹. ¹H-NMR (CDCl₃): δ: 4.43 (2H, t, J = 7 Hz, CH₂CH₂O), 4.65 (1H, brs, OCH₂), 5.45 (1H, brs, olefinic-H), 7.3—7.7 (6H, m, arom.-H), 7.9—8.1 (4H, m, arom.-H). MS m/z: 464 (M⁺ - 18), 380, 336. [δ₀⁺ + 4.3] (c = 1.0, MeOH).

30b: IR (neat): 3440, 1725, 1175 cm⁻¹. ¹H-NMR (CDCl₃): δ: 4.43 (2H, t, J = 7 Hz, CH₂CH₂O), 4.67 (1H, brs, OCHO), 5.45 (1H, brs, 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. [δ₀⁺ + 2.0] (c = 1.0, MeOH).

(1S,5S,6S,7R)-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 30a (150 mg) as described for the synthesis of 8a, b, except for the use of 4—10% AcOEt in hexane (ν/v) as the chromatographic eluent, afforded 31 (181 mg) as a colorless oil. IR (neat): 2920, 1720, 1270 cm⁻¹. ¹H-NMR (CDCl₃): δ: 4.45 (2H, t, J = 7 Hz, CH₂CH₂O), 4.72 (2H, brs, OCHO x 2), 5.45 (1H, brs, olefinic-H), 5.5—5.7 (2H, m, 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. [δ₀⁺ - 10.0] (c = 1.0, MeOH).

UV λ_max nm (ε): +12000 (226.5) (positive maximum).

(1S,5S,6S,7R)-3-(2-Hydroxyethyl)-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 methanol (60 ml) under ice-cooling (3.40 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 Na₂SO₄. Removal of the solvent in vacuo afforded 31 (1.81 g) as a colorless oil.

1H-NMR (CDCl₃) δ: 4.47 (2H, t, J = 7 Hz, CH₂CH₂O), 4.72 (2H, brs, OCHO x 2), 5.45 (1H, brs, 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, 336. [δ₀⁺ - 15.1] (c = 1.1, MeOH).

(1S,5S,6S,7R)-3-(2-Benzoyloxyethyl)-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 K₂CO₃ (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 Na₂SO₄. Removal of the solvent in vacuo afforded 33 (2.12 g) as a colorless oil. IR (neat): 2960, 1725, 1275, 1115 cm⁻¹. ¹H-NMR (CDCl₃) δ: 4.43 (2H, t, J = 7 Hz, CH₂CH₂O), 4.65 (1H, br s, OCHO), 5.45 (1H, brs, olefinic-H), 5.5—5.7 (2H, m, olefinic-H), 7.3—7.7 (6H, m, arom.-H), 7.9—8.1 (4H, m, arom.-H). MS m/z: 360 (M⁺ - 102), 280, 258. [δ₀⁺ - 31.0] (c = 1.1, MeOH).

(1S,5S,6S,7R)-3-(2-Mesyloxyethyl)-6-[3(S)-tetrahydropyran-2-yl]oxy-1(E)-octenyl]-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (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.¹ Anal. Calcd for C₂₀H₁₃O₇: C, 68.15; H, 9.15. Found: C, 68.20; H, 9.30. IR (KBr): 3400, 1730, 972 cm⁻¹. ¹H-NMR (CDCl₃): δ: 4.70 (2H, t, J = 7 Hz, CH₂CH₂O), 4.72 (2H, brs, OCHO x 2), 5.40—5.55 (3H, m, olefinic-H). [δ₀⁺ + 6.2] (c = 1.0, MeOH).

Synthesis of 34b —— Through a sequence of reactions similar to that described for the synthesis of 34a, 10a was led to 34b—1 using the corresponding phosphonates. In the case of 34g, the Wittig—Horner reaction (step 2) was done when the THF solution at reflux temperature (1.5 h). Physical data are summarized in Table II.

(1S,5S,6S,7R)-3-(2-Methoxycarbonylmethylethoxy)-6-[3(S)-tetrahydropyran-2-yl]oxy-1(E)-octenyl]-7-(tetrahydropyran-2-yl)oxybicyclo[3.3.0]oct-2-ene (35) —— Mesityl chloride (0.36 ml) was added to a solution of 33 (1.79 g) and Et₂N (0.81 ml) in CH₂Cl₂ (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 Na₂SO₄. Removal of the solvent in vacuo afforded 35 (1.92 g) as a colorless oil. IR (neat): 2950, 1740, 1020 cm⁻¹. ¹H-NMR (CDCl₃): δ: 3.73 (3H, s, COOME), 4.68 (2H, brs, OCHO x 2), 5.32 (1H, brs, olefinic-H), 5.4—5.8 (2H, m, olefinic-H). MS m/z: 448 (M⁺ - 102), 364, 320, 258. [δ₀⁺ - 27.5] (c = 1.1, MeOH).

3-Thioisocarbacyclin 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
extract was washed with brine and dried over Na₂SO₄. 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. 'H-NMR (CDCl₃) (δ): 3.20 (2H, s, SCH₂COOMe), 3.73 (3H, s, COOMe), 5.2-5.6 (3H, m, olefinic-H). MS m/z: 364 (M⁺ - 18), 346, 320, 258, 214. [α]D + 17.2 ° (c = 1.1, MeOH).

3-Thiaisocarbacycin (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 Na₂SO₄. 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) afforded 38 (119 mg) as a colorless oil. IR (neat): 3350, 2950, 1710 cm⁻¹. 'H-NMR (CDCl₃) (δ): 3.20 (2H, s, SCH₂COOH), 5.07 (3H, s, OH x 2 and COOH), 5.2-5.7 (3H, m, olefinic-H). MS m/z: 350 (M⁺ - 18), 340, 258, 214. [α]D + 17.2 ° (c = 0.25, EtOH). HR-MS m/z: Calcd for C₂₀H₂₈O₃S (M⁺ - H₂O): 350.1916. Found: 350.1924. [α]D + 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

<table>
<thead>
<tr>
<th>Compd.</th>
<th>IR (neat)</th>
<th>'H-NMR (CDCl₃)</th>
<th>MS</th>
<th>[α]D (c = 1.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>34b</td>
<td>3350, 1738</td>
<td>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)</td>
<td>348 (M⁺ - 18)</td>
<td>+5.2 (EtOH)</td>
</tr>
<tr>
<td>34c</td>
<td>3380, 1740, 1645</td>
<td>0.89 (3H, m), 3.66 (2H, t), 4.07 (2H, s), 4.7—5.2 (2H, m), 5.3—6.1 (4H, m)</td>
<td>360 (M⁺ - 18)</td>
<td>+7.6 (CHCl₃)</td>
</tr>
<tr>
<td>34d</td>
<td>3380, 1734</td>
<td>1.78 (3H, t, J = 1 Hz), 3.68 (2H, t), 4.09 (2H, s), 5.42 (1H, s), 5.56 (2H, m)</td>
<td>344 (M⁺ - 18)</td>
<td>+20.7 (EtOH)</td>
</tr>
<tr>
<td>34e</td>
<td>3350, 1738</td>
<td>3.68 (2H, t), 4.09 (2H, s), 5.43 (1H, br s), 5.54 (2H, m)</td>
<td>374 (M⁺ - 18)</td>
<td>-0.8 (CHCl₃)</td>
</tr>
<tr>
<td>34f</td>
<td>3400, 1735</td>
<td>0.7—1.1 (6H, m), 4.09 (2H, s), 4.8—5.2 (2H, m), 5.2—6.1 (4H, m)</td>
<td>374 (M⁺ - 18)</td>
<td>+16.4 (c = 0.25, EtOH)</td>
</tr>
<tr>
<td>34g</td>
<td>3350, 1740, 1600, 1590</td>
<td>3.65 (2H, t), 4.07 (2H, s), 5.52 (1H, br s), 5.72 (2H, m), 6.8—7.5 (5H, m)</td>
<td>384 (M⁺ - 18)</td>
<td>-1.7 (EtOH)</td>
</tr>
<tr>
<td>34h</td>
<td>(Nujol)</td>
<td>3.68 (2H, t), 4.08 (2H, s), 5.40 (1H, br s), 5.52 (2H, m)</td>
<td>346 (M⁺ - 18)</td>
<td>+6.5 (CHCl₃)</td>
</tr>
<tr>
<td>34i</td>
<td>3350, 1740</td>
<td>3.67 (2H, t), 4.08 (2H, s), 5.42 (1H, br s), 5.54 (2H, m)</td>
<td>346 (M⁺ - 18)</td>
<td>+11.4 (EtOH)</td>
</tr>
<tr>
<td>34j</td>
<td>3400, 1738</td>
<td>0.7—1.1 (9H, m), 3.77 (2H, t), 4.08 (2H, s), 5.42 (1H, br s), 5.56 (2H, m)</td>
<td>362 (M⁺ - 18)</td>
<td>+17.2 (c = 0.25, EtOH)</td>
</tr>
<tr>
<td>34k</td>
<td>(Nujol)</td>
<td>3.67 (2H, t), 4.07 (2H, s), 5.40 (1H, br s), 5.52 (2H, m)</td>
<td>332 (M⁺ - 18)</td>
<td>+4.2 (CHCl₃)</td>
</tr>
<tr>
<td>34l</td>
<td>3350, 1730</td>
<td>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)</td>
<td>388 (M⁺ - 18)</td>
<td>-1.9 (CHCl₃)</td>
</tr>
</tbody>
</table>

**TABLE II. Physical and Spectral Data for 34b—1**
mixture was diluted with AcOEt, washed with 5% NaHCO₃ and brine, and dried over Na₂SO₄. 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, 1725, 1320 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.72 (2H, s, CH₂COOMe), 3.79 (3H, s, COOMe), 5.2–5.6 (3H, m, olefinic-H). MS m/z: 304 (M⁺ − 80), 292, 274, 248, 214. HR-MS m/z: Calcd for C₁₉H₂₈O₅S (M⁺): 304.1860. Found: 304.1840. [α]D +20.4° (c = 1.0, MeOH).

3-Sulfynilsocarbacyclin (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, 1745, 973 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.86 (3H, br t, Me), 3.37 (2H, s, NCH₂COOMe), 3.69 (3H, s, COOMe), 4.66 (2H, br s, OCHO × 2), 5.2–5.7 (3H, m, olefinic-H). MS m/z: 365 (M⁺ − 102). HR-MS m/z: Calcd for C₂₁H₃₅N₂O₄ (M⁺): 365.5919. Found: 365.5924. [α]D +21.1° (c = 1.0, MeOH).

Methyl Ester of 3-Sulfynilsocarbacyclin (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 still stirred under ice-cooling for 6 h. The reaction mixture was diluted with AcOEt, washed with 5% NaHCO₃ and brine, and dried over Na₂SO₄. 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, 1145 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.85 (3H, br t, Me), 3.37 (2H, s, NCH₂COOMe), 3.69 (3H, s, COOMe), 4.66 (2H, br s, OCHO × 2), 5.2–5.7 (3H, m, olefinic-H). MS m/z: 396 (M⁺ − 18), 352, 325, 258. [α]D +12.7° (c = 1.0, MeOH). Further elution with AcOEt to 10% MeOH in AcOEt (v/v) gave 39 (40 mg).

3-Sulfynilsocarbacyclin (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): 3350, 1725, 1320 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.97 (2H, s, CH₂COOH), 4.47 (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 C₁₉H₂₈O₅S (M⁺ − CH₂O₃): 304.1860. Found: 304.1840. [α]D +20.4° (c = 1.0, MeOH).

3-Aza-isocarbacyclin 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 still stirred under ice-cooling for 10 h, then heated at 35 °C for 1 h, diluted with dilute NaHCO₃ and extracted with AcOEt. The extract was washed with brine and dried over Na₂SO₄. 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. ¹H-NMR (CDCl₃) δ: 0.85 (3H, br t, Me), 3.37 (2H, s, NCH₂COOMe), 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⁺). HR-MS m/z: Calcd for C₂₃H₄₅NO₂ (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 x g for 15 min. Platelet-poor plasma (PPP) was prepared by centrifugation at 10000 x g for 15 min. The number of platelets in the PPP was adjusted to 3.0 x 10⁵/µl (human) or 6.0 x 10⁵/µl (rabbit) by addition of an appropriate volume of PPP. Platelet aggregation was measured with human and rabbit platelets by using the method of Born. 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 IC₅₀ value of each test compound was calculated as the concentration required to reduce the aggregation by 50% of the control value.
References and Notes

9) Final structural proof of 6a was done by leading 6a to 34a.