Efficient Synthesis of Isocarbacyclins

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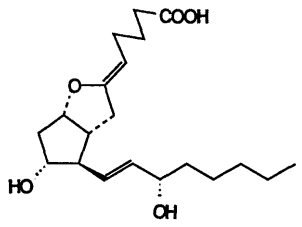
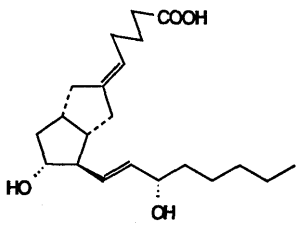
An efficient and useful synthesis of isocarbacyclins, potent carbon analogs of Prostacyclin (PGI_2), has been accomplished. Three synthetic routes to isocarbacyclins using intramolecular thermal ene reaction or intramolecular aldol condensation as a key step are described.

Keywords isocarbacyclin; thermal ene reaction; intramolecular aldol condensation; regioselective hydrogenation; bicyclo-[3.3.0]octene

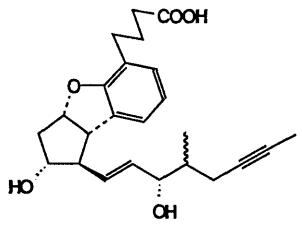
Prostacyclin (PGI_2, **1**), a naturally occurring bioregulator, has remarkable platelet aggregation-inhibiting activity.[2] However, its instability limits its clinical application as a therapeutic agent for the treatment of heart attack and stroke. To overcome this disadvantage, various analogs have been synthesized. Among them, carbacyclin (**2**), the carbon analog of PGI_2, was firstly noted as a substance which possessed sufficient activity and chemical stability,[3] and some ω-chain derivatives[4] and TRK-100 (**3**)[5] are now being studied in clinical trials. On the other hand, to develop a better analog of PGI_2, the Teikyo group synthesized isocarbacyclin (**4**),[6] and found that it showed better activity than carbacyclin in a preliminary biological test. They prepared **4** using either intramolecular pinacol coupling reaction or protodesilylation reaction as a key step. Both of them, however, appeared rather unsatisfactory in terms of efficiency and versatility to synthesize this promising new PGI_2 analog **4** and its ω-chain derivatives in sufficient amounts for pharmacological testing. Therefore, we started our research for developing a practical synthetic route which would yield large amounts of isocarbacyclin (**4**) and its ω-chain analogs.[7,8] The regioisomer of isocarbacyclin (**5**), which was also synthesized by the Teikyo group,[9] was found to be much less active than **4**. Thus the position of the double bond was crucial for potent biological activity, indicating that regiocontrolled construction of the bicyclo[3.3.0]octene framework is a key point for the synthesis of isocarbacyclin, one of the most promising compounds as a chemically stable therapeutic agent for cardiovascular and circulatory diseases.



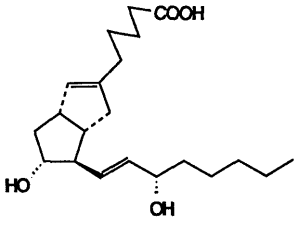
prostacyclin (PGI_2) **1**



carbacyclin **2**



TRK-100 **3**



isocarbacyclin **4**

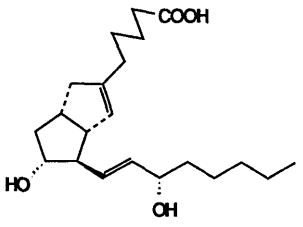


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Fig. 1

Our three basic strategies for the construction of the bicyclo[3.3.0]octene framework are shown in Chart 1. The first one uses the intramolecular ene reaction of the olefin-aldehyde **6**. The second one consists of Dieckmann condensation and successive alkylation and dehydroxylative decarboxylation. The third one utilizes the intramolecular aldol condensation of the dialdehyde **12** to give the α,β-unsaturated aldehyde having the required skeleton **13**. The α-chain would be introduced into **13** in a regiocontrolled manner using the selective hydrogenation of the diene **14** or the alkylation of the allyl halide **15**. Among them, the synthetic route using the intramolecular ene reaction and the route using the aldol reaction realized efficient, industrial-scale syntheses of isocarbacyclin **4**. This account describes these efficient synthetic routes to **4**.

Synthesis from Corey Lactone; The Intramolecular Ene Reaction Route An efficient synthesis of **29** was first investigated for the introduction of various ω-chains. Toward this end, first of all, the use of the intramolecular ene reaction was planned. Lewis acid-mediated and thermal ene reactions of aldehyde-olefins are known.[10] In this case, however, the former was found not to be appropriate as a result of model studies. Namely treatment of *cis*-2-(6-methoxycarbonyl-*Z*-2-hexenyl)cyclopentylaldehyde with dimethylaluminum chloride ($-25\,^\circ C$, CH_2Cl_2) gave none of the desired ene-products but yielded structurally unidentified products[11] and a small amount of 3-(4-methoxycarbonyl-1-chlorobutyl)bicyclo[3.3.0]octan-2-ol. No other Lewis acids examined ($SnCl_4$, $TiCl_4$, $SbCl_5$, $ZnCl_2$, trimethylsilyl triflate (TMSOTf) gave a better result. Therefore, we focused our attention on the thermal ene reaction.

At the outset, we tried the thermal ene reaction of **22** ($180\,^\circ C$, 5% toluene solution, 24 h). Although the desired ene reaction was found to proceed smoothly, concomitant

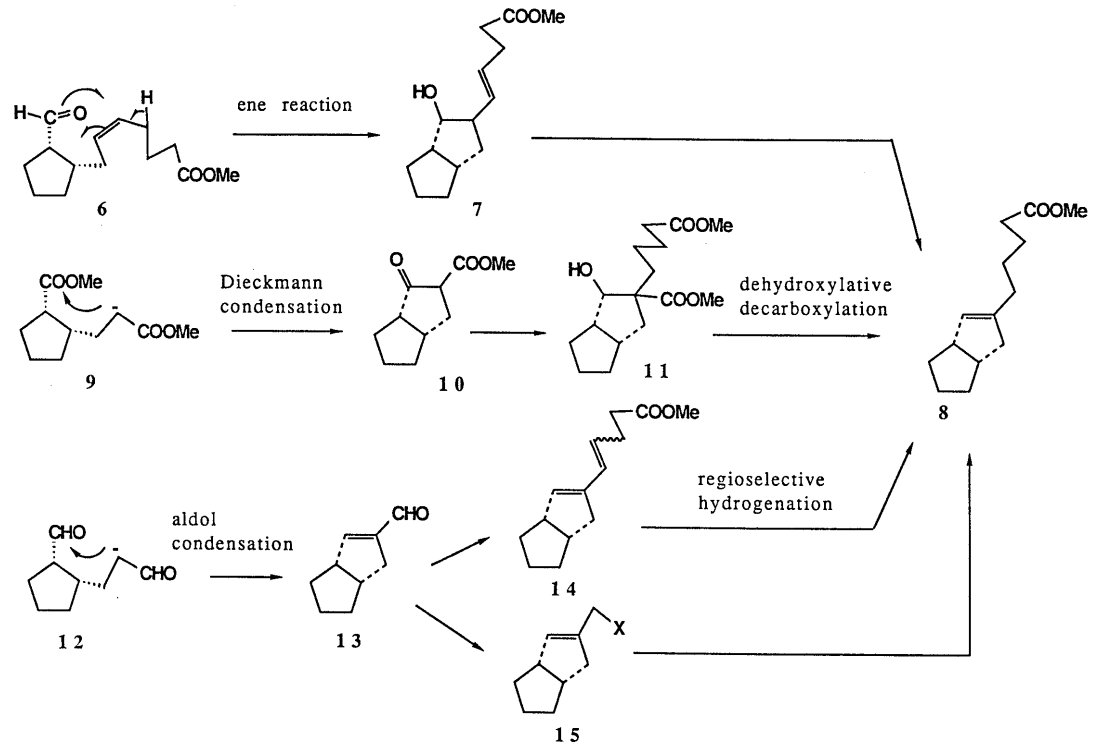

Chart 1

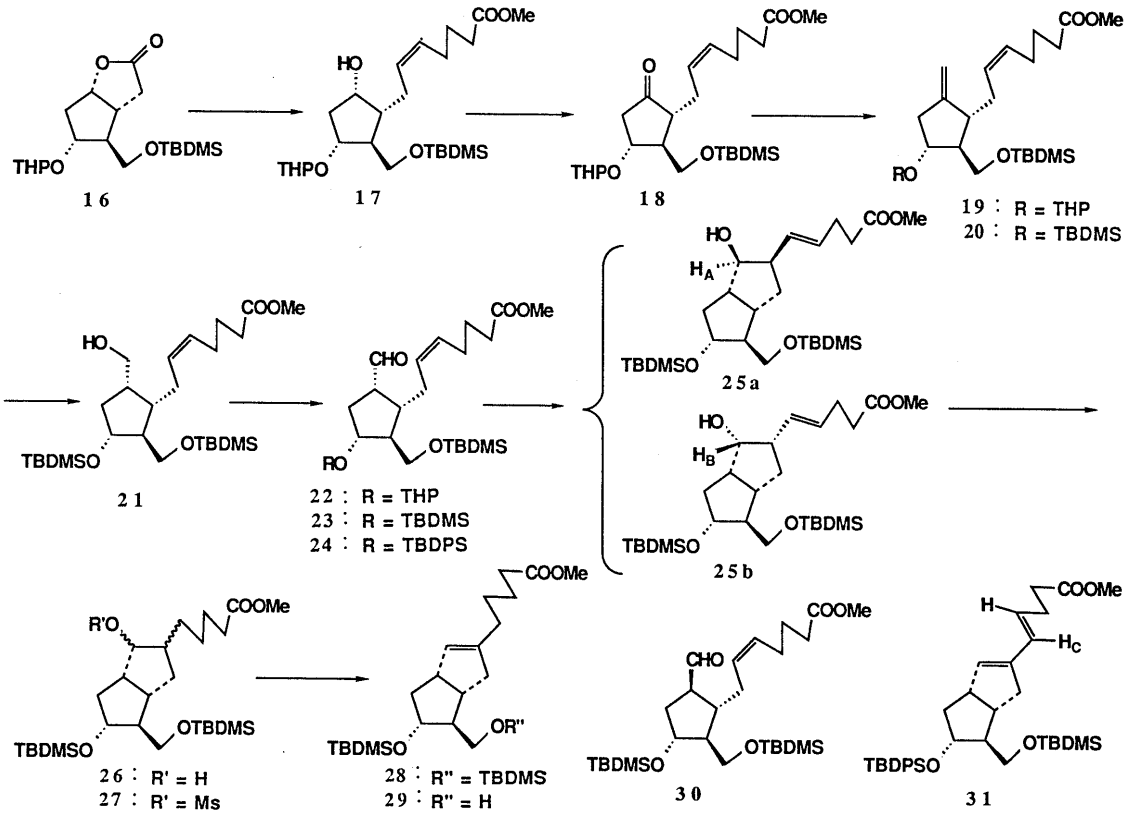

Chart 2

deprotection of the tetrahydropyranyl (THP) group occurred. Therefore, the more appropriate aldehyde **23**, protected by the two thermally stable *tert*-butyldimethylsilyl groups, was prepared from Corey lactone (**16**) as described below. Compound **16** was converted to the hydroxy-ester **17** in the usual manner (i. diisobutylalminum hydride (DIBAH) in toluene, ii. 4-carboxybutyltriphenylphosphonium bromide, potassium *tert*-butoxide in tetrahydrofuran (THF), iii. CH_2N_2, 98% overall yield), which was followed by oxidation with pyridinium chlorochromate (PCC) in the presence of sodium acetate to afford the keto-ester **18** (92%). Methylenation of **18** was effectively carried

out by the action of $Zn–CH_2Br_2–TiCl_4$,[12] giving the diene **19** (81%). The THP ether of **19** was selectively deprotected by our method (Me_2AlCl in CH_2Cl_2),[13] and then converted to the *tert*-butyldimethylsilyl (TBDMS) ether (*tert*-butyldimethylsilyl chloride, imidazole in dimethylformamide (DMF), 89% from **19**).[14] Hydroboration of **20** with 9-borabicyclo[3.3.1]nonane (9-BBN) in THF (2.5 eq, 0 °C) followed by treatment with alkaline hydrogen peroxide provided the primary alcohol **21** in a stereocontrolled manner (72%), and this was subsequently treated with Collins reagent to provide the aldehyde **23** in 92% yield. The epimeric aldehyde **30** was not formed in the above transformation.

Thermal ene reaction of **23** in toluene at 180 °C proceeded quite smoothly to provide a mixture of the two desired ene products **25a** and **25b** (87%) in a ratio of 5:3 along with **30** produced by thermal epimerization (13%).[15] The ene products were converted to the diene **31** (i. mesyl chloride, triethylamine, ii. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), toluene, reflux, 50% from **23**). The coupling constant of H_C (δ 6.25 ppm, 16.5 Hz) indicated that the stereochemistry of the newly formed double bond in **25a** and **25b** was *E*. The stereochemistry of **25a** and **25b** was tentatively assigned on the basis of mechanistic consideration of the thermal ene reaction[10b] coupled with nuclear magnetic resonance (NMR) analysis.[16] Relative stereochemistry of the alcohol group and the α-chain of both products was further supported by the fact that both of the ene-products could be readily converted to the bicyclo[3.3.0]octene derivative **28** by a series of reactions involving *E*2 elimination.

A mixture of **25a** and **25b** underwent hydrogenation to give **26** in quantitative yield. Reaction of **26** with methanesulfonyl chloride and triethylamine in toluene at 23 °C afforded the mesylates **27**, which, after addition of DBU, were heated at 120 °C to provide **28** in 70% overall yield from **26**. The bicyclo[3.3.0]octene derivative **28** was converted to the key intermediate **29** by treatment of **28** with a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in aqueous ethanol[17] at 23 °C for 15 h (71% yield based on the recovery of **28**). The overall yield of **29** from **16** was about 19%.

The alcohol **29** was then transformed to (+)-isocarbacyclin (**4**) in the usual manner. Oxidation of **29** with SO_3–pyridine complex and triethylamine in dimethyl sulfoxide (DMSO) gave the aldehyde **32**, which was directly treated with dimethyl (2-oxoheptyl)phosphonate and sodium hydride in THF to provide the enone **33** in 71% overall yield. Reduction of **33** with sodium borohydride in methanol at −20 °C afforded a mixture of the C_{15}-epimeric alcohols (**34**) (prostaglandin (PG) numbering), which, after deprotection of *tert*-butyldimethylsily ether, gave the more polar diol **35a** in 55% overall yield together with less polar **35b** (22%). Finally, hydrolysis of **35a** with sodium hydroxide in aqueous methanol followed by acidic work-up provided (+)-**4** as a colorless solid (quantitative yield).

In this way, a new synthetic route to (+)-isocarbacyclin (**4**) utilizing the intramolecular thermal ene reaction as a key step has been realized. (+)-Isocarbacyclin (**4**) was synthesized in a completely regiocontrolled manner in 7% overall yield from Corey lactone.

Synthesis from Corey Lactone; The Intramolecular Aldol Reaction Route To improve the efficiency of the synthetic route to (+)-isocarbacyclin (**4**), next, we planned to use the intramolecular Dieckmann condensation as a key step. Toward this end, the diol **37** was prepared in a regio- and stereocontrolled manner. Namely, **16** was first transformed to the diene **36** in four steps (86% overall yield) (i. DIBAH, ii, methyltriphenylphosphonium bromide, potassium *tert*-butoxide in THF, iii. PCC, sodium acetate in CH_2Cl_2, iv. $Zn–CH_2Br_2–TiCl_4$). Hydroboration of **36** with disiamylborane in THF at 0 °C followed by treatment with alkaline hydrogen peroxide led to the diol **37** in a stereocontrolled manner (quantitative yield).[18] Although hydroboration using 9-BBN also proceeded smoothly, it was found to be unsuited to large-scale synthesis owing to the formation of 1,5-cyclooctanediol, which had to be separated from **37** by careful silica gel chromatography. The hydroboration with thexylborane was unsatisfactory, producing the regio isomer **38** (mixture of the two stereoisomers, 6% and 24%

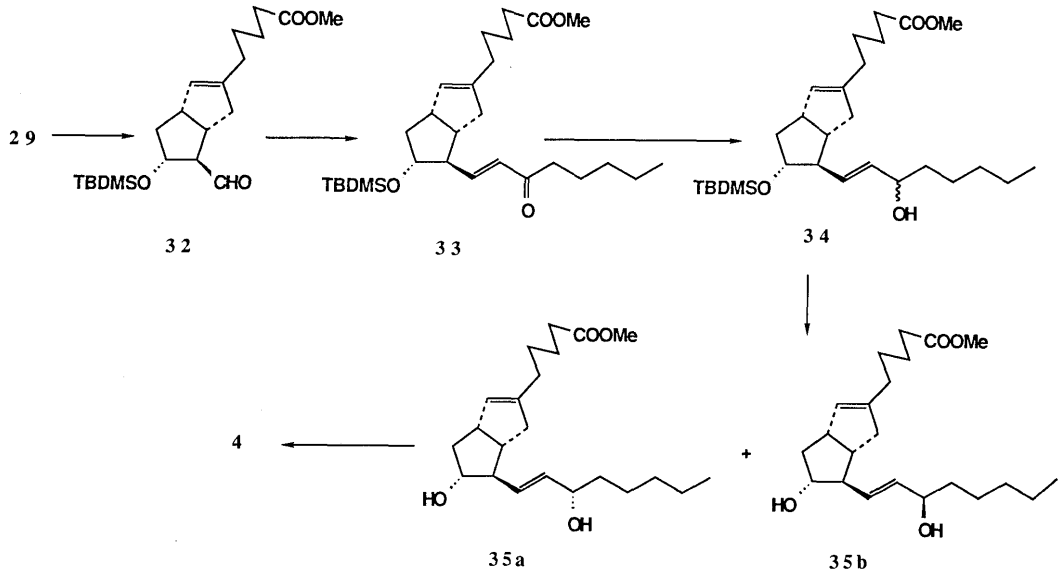

Chart 3

yields, respectively) along with the desired diol **37** (58%).

The oxidation of the diol **37** to the dicarboxylic acid **39** for the Dieckmann condensation reaction by several oxidation methods such as pyridinium dichromate (PDC) in DMF was unsuccessful, and we turned our attention to the aldol reaction of the dialdehyde **42** (Chart 4). The oxidation of the diol **37** with reagents such as PCC, PDC and CrO_3–Py_2 gave the seven-membered lactone **41** exclusively th-

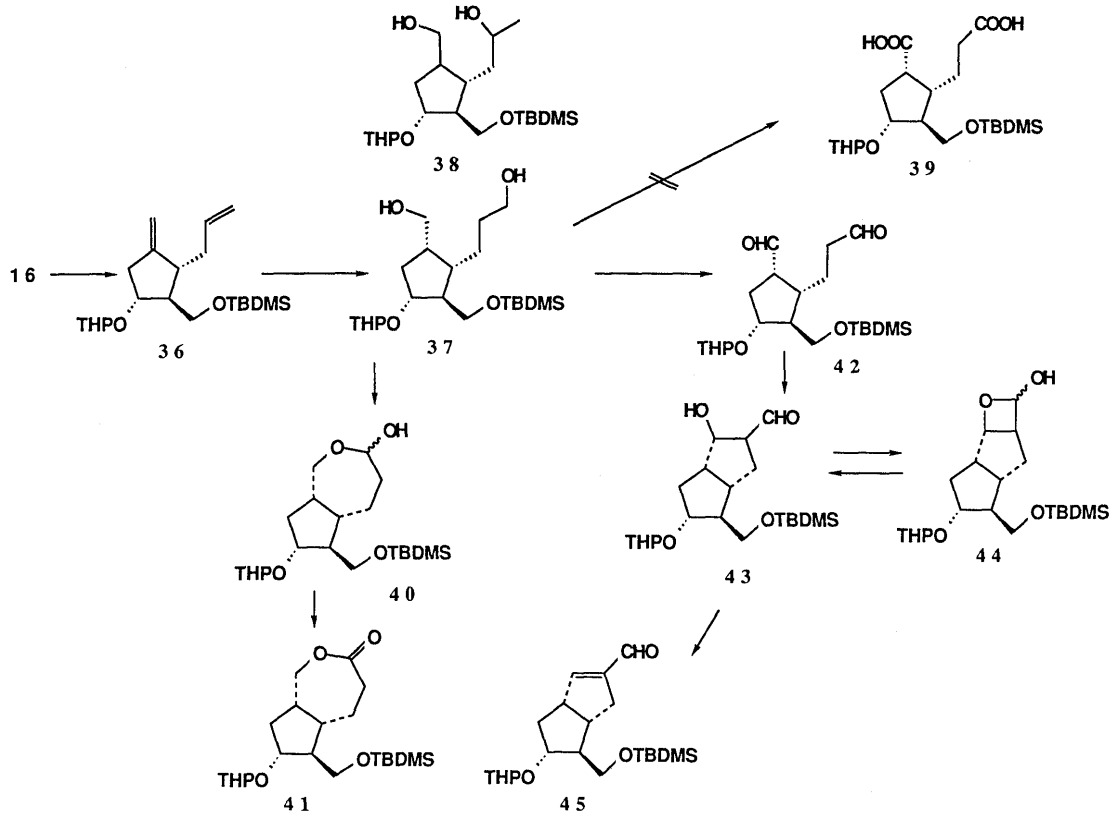

Chart 4

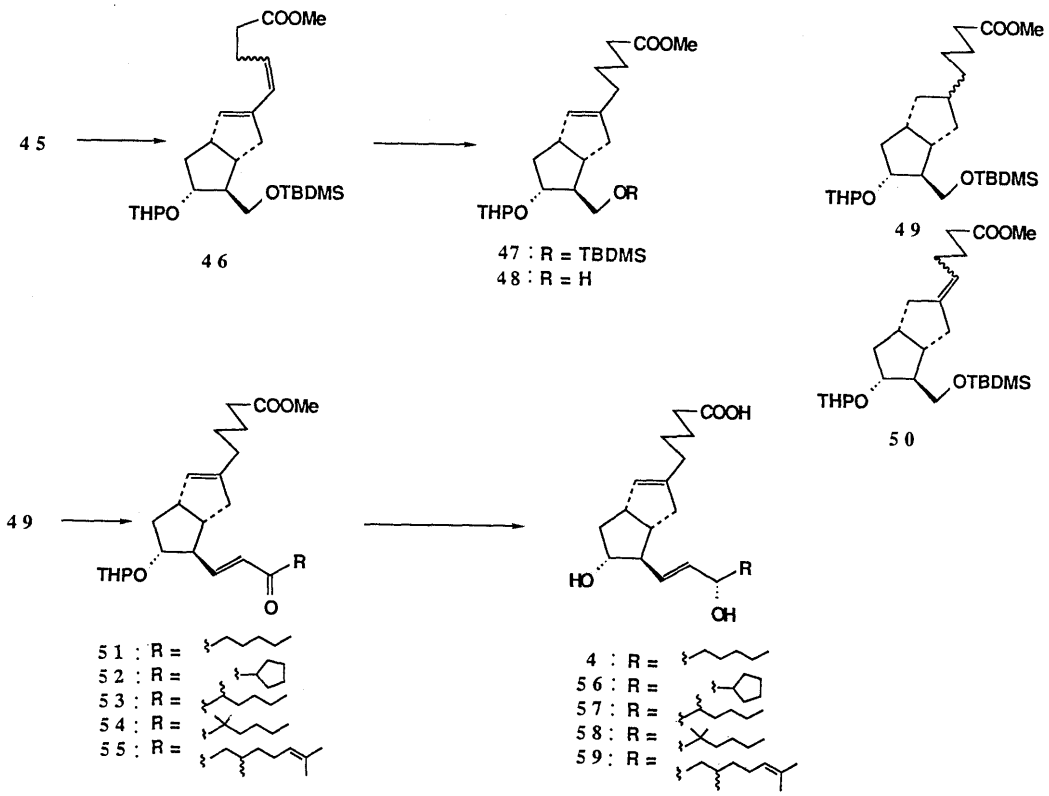

Chart 5

rough the lactol **40**. On the other hand, the oxidation of **37** with SO_3–pyridine complex and triethylamine in DMSO at 23 °C afforded the aldol products in a state of equilibrium between **43** and **44** (8%) together with **45** (21%) and **40** (25%). Finally, Swern oxidation of **37** followed by aldol condensation reaction was found to give a satisfactory result. Namely, treatment of **37** with oxalyl chloride and DMSO in CH_2Cl_2 (−60 °C) followed by addition of triethylamine (−60—23 °C) led to the dialdehyde **42** together with the aldol **43** in a ratio of *ca.* 1:1, to which dibenzylammonium trifluoroacetate was added.[19] After changing the solvent to benzene, the reaction mixture was maintained at 70 °C for 6 h, providing the α,β-unsaturated aldehyde **45** in "one-pot" from the diol (84% overall yield from **37**).

Wittig reaction of **45** with the ylide derived from 3-carboxypropyltriphenylphosphonium bromide and potassium *tert*-butoxide in THF gave the diene, which was subsequently converted to **46** by treatment with ethereal diazomethane in 94% yield from **45** (*cis*: *trans* = 2.2:1). The regioselective hydrogenation of **46** to **47** was effected by treating **46** with a catalytic amount of 10% Pd on C in methanol under a hydrogen atmosphere (1 atm) at 23 °C for 1 h. The desired 1,2-reduction product **47** was obtained in 85% yield together with the over-reduction product **49** (13%) and the 1,4-reduction product **50** (2%). Compound **49** could be removed at this stage by silica gel chromatography, and the 1,4-reduction product **50** could also be separated at the stage of the enone **51**. Removal of a *tert*-butyldimethylsilyl group in **47** by reaction with tetrabutylammonium fluoride in THF led to the versatile intermediate **48** in 100% yield. The overall yield of **48** from Corey lactone in this 9-step sequence is about 58%.

The alcohol **48** was then transformed to (+)-**4** in the usual manner in 42% overall yield. The overall yield of (+)-isocarbacyclin (**4**) from Corey lactone (**16**) goes up to *ca.* 24%. Using this route, sufficient amounts of various ω-chain analogs (**56**—**59**) to investigate biological activities could also be synthesized for the first time.

Synthesis from the ω-Chain Intermediate As mentioned above, very efficient and versatile synthetic routes to (+)-**4** and its analogs from Corey lactone were achieved. Furthermore, we envisioned that a more efficient synthetic route to isocarbacyclin **4** and its analogs would be realized by the combination of the aldol reaction route with the recently developed cuprate coupling method in PG synthesis. Fortunately, two efficient ways to the allyl ketone **60** having the ω-chain were reported by the Teijin group.[20] One uses furfural as a very cheap starting material producing racemic **60**, and the other includes the three-component coupling process to afford optically pure **60**. We planned to apply our intramolecular aldol method to this allyl ketone **60**.

First of all, the racemic allyl ketone **60** (epimeric mixture at the C-15 position) was used, which was synthesized in five steps from furfural. The α,β-unsaturated aldehyde **63** was prepared in the same manner as mentioned above. Thus, the allyl ketone **60** was converted to the diene **61** (Zn–CH_2Br_2–$TiCl_4$) (90%). Hydroboration of **61** with 9-BBN followed by treatment with hydrogen peroxide gave the diol **62** (85%) in a stereo- and regiocontrolled manner.[18] Swern oxidation of **62** gave a mixture of the dialdehyde and the corresponding aldol, which was subsequently treated with dibenzylammonium trifluoroacetate in benzene at 70 °C to afford the conjugated aldehyde **63** in 85% yield from **62**.

With an efficient construction of **63**, regiocontrolled transformation of **63** to **65** *via* the 1,3-diene intermediate **64** was first examined. The diene **64** (*E*:*Z* = *ca.* 1:2) was prepared from **63** (88%) by treatment with the ylide generated from 3-carboxypropyltriphenylphosphonium bromide and potassium *tert*-butoxide in THF followed by esterification with diazomethane and separation of the 15α-isomer. In an attempt toward the regioselective hydrogenation of the 4–5 double bond (PG numbering) in the presence of two other olefinic double bonds, various hydrogenation conditions were examined. For example, the hydrogenation of **64** in benzene with the Wilkinson catalyst (10 mol%) under 1 atm of hydrogen (45 °C, 1.5 h) afforded the desired product **65** (45%) together with the 1,4-reduction product **66** (5%) and the over-reduction product **67** (50%). The modified Wilkinson catalyst[21] obtainable from chlorodicyclooctenerhodium(I) and phenyldipiperidylphosphine (24 mol% catalyst, 1 atm of H_2, 25 °C, 4 h in benzene : ethanol = 3:1) provided a slightly better result (**65**, 60%; **66**, 24%; **67**, 16%). In all cases, although the ω-chain double bond was not hydrogenated, the selectivity of diene reduction was unsatisfactory.

In order to develop a more practical route to **4**, we turned our attention to the synthetic approach involving the organocopper coupling reaction with the allylic electrophile. Thus, the allylic alcohol **68** (88%) was obtained from **63** by treatment with DIBAH in toluene at −78 °C.

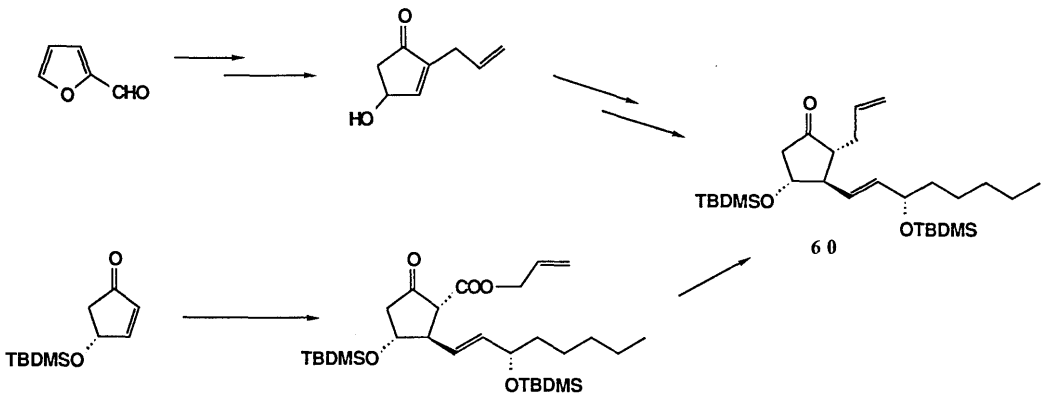

Chart 6

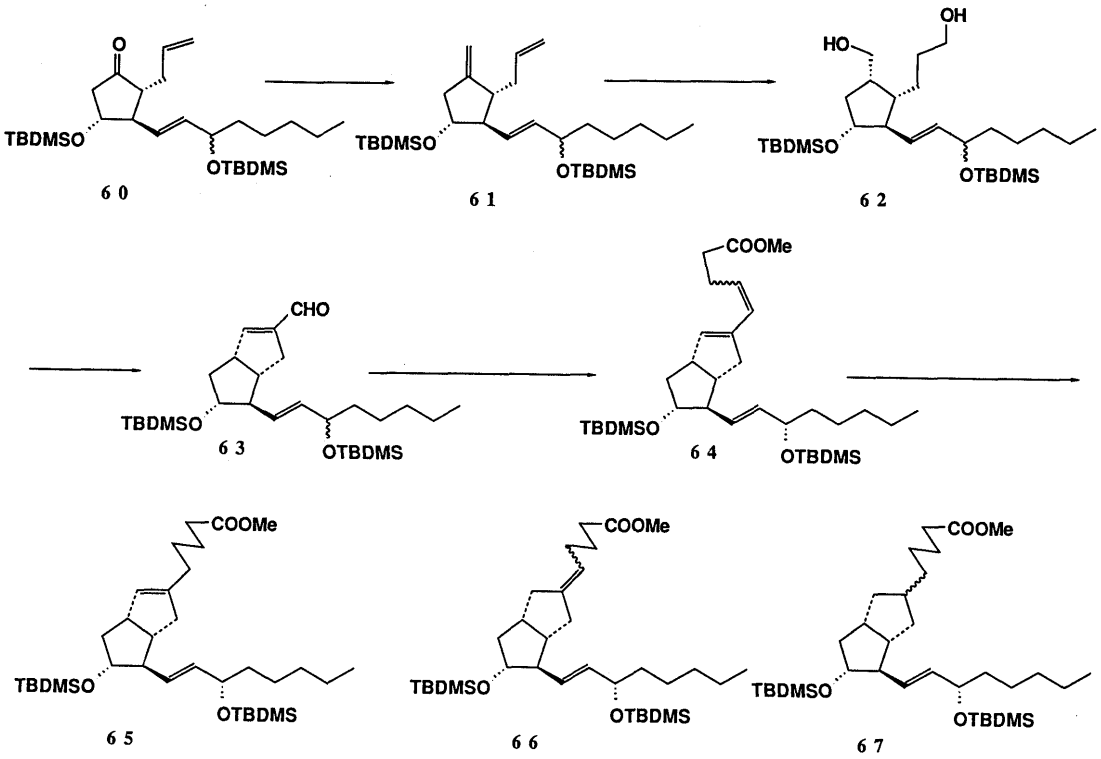

Chart 7

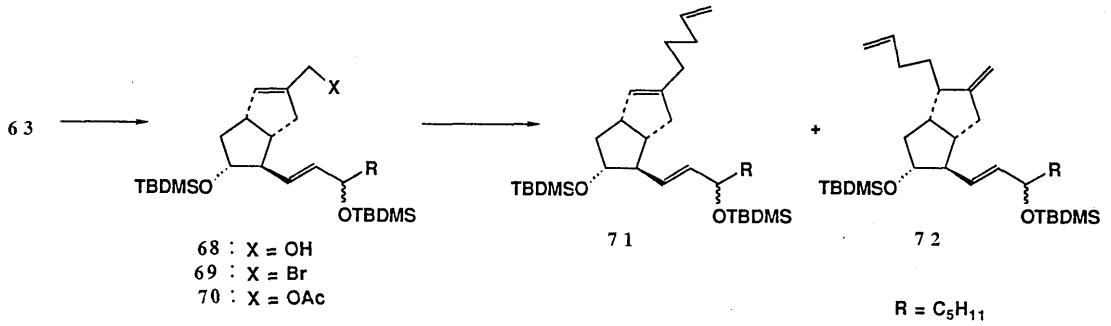

Chart 8

TABLE I. Coupling Reaction of Allylic Electrophiles with Butenylmetal Reagents

Run	Reagent R′=CH_2CH_2-CH=CH_2	Substrate	Solvent	Temp. (°C)	Product ratio **71**:**72**	Yield (%)
1	R′MgBr	**69**	THF	r.t.	—	40
2	Li_2CuCl_4–R′MgBr	**69**	THF	−10—r.t.	1:10	82
3	R'_2CuLi	**69**	Et_2O	−78—r.t.	3:2	89
4	R′Li	**69**	Et_2O	−78—r.t.	3:1	93
5	R′Li	**69**	THF–HMPA	−30—r.t.	3:1	85
6	$CeCl_3$–R′Li	**69**	THF	−78	3.6:1	90
7	R'_2CuLi	**70**	Et_2O	−78—r.t.	27:1	93

Then the alcohol **68** was converted to the allylic bromide **69** (triphenylphosphine-CBr_4 in CH_2Cl_2, 98%) and also the allylic acetate **70** (Ac_2O, 4-(dimethylamino)pyridine (DMAP), pyridine, 97%). The results of the coupling reaction of these allylic electrophiles with butenyl-metal reagents are summarized in Table I. First, the coupling reaction of the allylic bromide **69** was investigated. Although the reaction with 3-butenylmagnesium bromide was very slow, the addition of a catalytic amount of dilithium tetrachlorocuprate accelerated the reaction, producing the γ-attacked product **72** as a major product (run 1 and 2). On the other hand, the reaction with the Gilman reagent derived from 3-butenyllithium[22] and cuprous iodide showed slight α-selectivity (run 3), and in the case of 3-butenyllithium itself, the α-attacked product **71** was obtained as a major product (3:1) (run 4). Some attempts to increase the α-selectivity (run 5 and 6) were carried out, giving the nearly same results as already mentioned (runs 3 and 4). However, it was found that this selectivity problem was fully overcome by the procedure using the allylic acetate **70**. Thus, the reaction of the allylic acetate **70** with the Gilman reagent (2.5 eq) generated from 3-butenyllithium and cuprous iodide, afforded the α-attacked product **71** (*ca.* 90%) in a highly selective manner together with small amounts of the γ-attacked product **72** (*ca.* 3%) and the allylic alcohol **68** (7%). A mixture of **71** and **72**, easily separable from **68** by silica gel column chromatography,

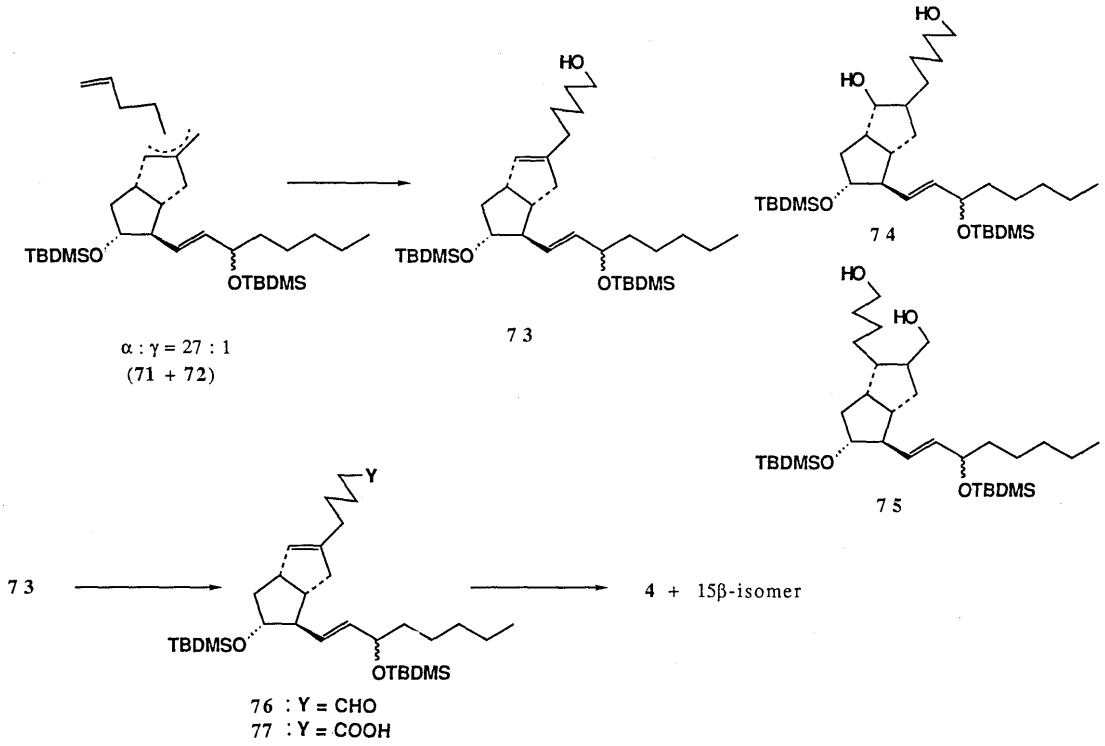

Chart 9

was subjected to hydroboration (1.2 eq of 9-BBN, THF solvent, 0—23 °C) followed by alkaline hydrogen peroxide oxidation, giving the alcohol **73** in 89% yield. The highly polar diol **75** (3%) which was produced from the γ-attacked product and also **74** (2%) were easily removed from the desired product. The alcohol **73** was then oxidized to the carboxylic acid **77** by a two-step sequence (67%) (i. PCC, AcONa in CH_2Cl_2, ii. silver oxide). Finally, treatment of **77** with tetra-*n*-butylammonium fluoride afforded racemic isocarbacyclin (**4**) and its 15β-isomer in 90% yield. This result means that (+)-isocarbacyclin (**4**) can be synthesized in only 10 steps and 29% overall yield starting from the optically pure ketone **60**.[23]

As described above, we have established three efficient synthetic routes to isocarbacyclins. Although the best selectivity concerning the regio-control at the C-6 double bond was obtained by the first route, the overall yield was rather unsatisfactory because of the protective group problem. The second route, by which the highest overall yield was achieved, played an important role in the synthesis of various ω-chain analogs of isocarbacyclin. The key intermediate of the second route, **45**, is now commercially available, and is being produced on a kilogramscale. It should be emphasized that **45** is being used not only for the synthesis of isocarbacyclins but also for that of ohter PGI_2 analogs.[24] The third route has enabled the industrial-scale production of isocarbacyclins for the first time because of the easy separation of by-products at every stage as well as its high overall yield. We hope that our chemistry will contribute to the development of potent new medicines.

Experimental

General Methods Infrared (IR) spectra were measured on a JASCO A-202 diffraction grating infrared spectrophotometer. ^{1}H-NMR spectra were recorded with a Varian EM 390 NMR spectrometer or a Hitachi R-90H Fourier-transform NMR spectrometer or a Brucker AN-400 spectrometer with tetramethylsilane as an internal standard. Low-resolution mass spectra (MS) were obtained with a Hitachi RUM-6MG mass spectrometer. Optical rotation was measured on a Horiba SEPA-200 high-sensitivity polarimeter. In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned.

(1*S*,5*R*,6*S*,7*R*)-6-*tert*-Butyldimethylsilyloxymethyl-3-hydroxy-2-oxa-7-tetrahydropyranyloxybicyclo[3.3.0]octane A solution of diisobutylaluminum hydride in hexane (1.76 M, 14.1 ml, 24.8 mmol) was added to a stirred solution of Corey lactone (**16**) (5.70 g, 15.4 mmol) in toluene (25 ml) at −75 °C. Stirring was continued at the same temperature for 40 min, and the reaction was quenched by the addition of methanol (0.9 ml). After dilution with ethyl acetate, saturated aqueous NaCl was added. Stirring was continued at 23 °C until the organic layer become clear. The aqueous layer was extracted with ethyl acetate, and the organic layers were combined and dried over $MgSO_4$. Removal of the solvent afforded the lactol as a colorless oil in quantitative yield. IR (neat): 3430 (OH), 2950, 2860, 835 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.40—2.75 (12H, m), 3.25—4.40 (5H, m), 4.45—4.85 (2H, m), 5.30—5.70 (1H, m). MS *m/z*: 355 ($M^+ - OH$), 287 ($M^+ - THP$), 213, 159, 85, 75, 73. HR-MS *m/z*: 355.2269 (Calcd for $C_{19}H_{35}O_4Si$, 355.2302, $M^+ - OH$). $[\alpha]_D^{20}$: −28° (*c* = 1.98, MeOH).

Methyl (*Z*)-7-[(1*R*,2*S*,3*R*,5*S*)-2-*tert*-Butyldimethylsilyloxymethyl-5-hydroxy-3-tetrahydropyranyloxycyclopentyl]hept-5-enoate (17) A solution of the lactol (5.0 g, 13.4 mmol) in THF (30 ml) was added to a stirred solution of 4-carboxybutyltriphenylphosphonium bromide (25.5 g, 57 mmol) and potassium *tert*-butoxide (12.7 g, 114 mmol) in THF (30 ml) at room temperature. After stirring for 30 min, saturated aqueous NH_4Cl (150 ml) and ether (50 ml) were added. The reaction mixture was then acidified (pH 4—5) with 10% aqueous HCl and extracted with ethyl acetate. The organic layers were combined, washed with saturated aqueous NaCl and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was treated with ethereal diazomethane. After evaporation, the residue was purified by silica gel column chromatography (ether–hexane, 1 : 1) to afford the methyl ester **17** as a colorless oil (6.2 g, 98%). IR (neat): 3580 (OH), 1738 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.90 (9H, s), 3.20—3.80 (7H, m), 3.65 (3H, s), 4.65 (1H, br s), 5.40 (2H, m). HR-MS *m/z*: 470.3092 (Calcd for $C_{25}H_{46}O_6Si$, 470.3062, M^+). $[\alpha]_D^{20}$: +22° (*c* = 1.84, MeOH).

Methyl (*Z*)-7-[(1*R*,2*S*,3*R*)-2-*tert*-Butyldimethylsilyloxymethyl-5-oxo-3-tetrahydropyranyloxycyclopentyl]hept-5-enoate (18) AcONa (90 mg), celite (1.16 g) and pyridinium chlorochromate (PCC, 1.16 g, 5.4 mmol)

were added to a stirred solution of the alcohol (**17**) (1.29 g, 2.7 mmol) in methylene chloride (15 ml) at 0 °C. The reaction mixture was stirred overnight at 0 °C and for an additional 3 h at 23 °C. After dilution with ether, the suspension was filtered through a Florisil column. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (ether–hexane, 1 : 1) to give the ketone (**18**) (92%) as a colorless oil. IR (neat): 1742 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.90 (9H, s), 3.40—4.00 (5H, m), 3.65 (3H, s), 4.70 (1H, br s), 5.45 (2H, m). HR-MS *m/z*: 411.2219 (Calcd for $C_{21}H_{35}O_6Si$, 411.2201, M^+ – *tert*-Bu). $[\alpha]_D^{20}$: −30° (*c* = 1.80, MeOH).

Methyl (*Z*)-7-[(1*R*,2*S*,3*R*)-2-*tert*-Butyldimethylsilyloxymethyl-5-methylene-3-tetrahydropyranyloxycyclopentyl]hept-5-enoate (19) The methylenation reagent prepared by Lombardo's method[12] (Zn–CH_2Br_2–$TiCl_4$) (1.2 ml) was added to a solution of the ketone (**18**) (100 mg, 0.21 mmol) in methylene chloride (1 ml), and the mixture was stirred at 23 °C for 30 min. The reaction mixture was poured into a mixture of saturated $NaHCO_3$ (20 ml), ether (20 ml) and a small amount of celite, and stirred vigorously. After filtration of the pale green suspension through a celite pad, the ether layer was separated and the water layer was further extracted with ether. The combined ether extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent and purification of the residue by silica gel column chromatography (ether–hexane, 1 : 4) afforded **19** as a colorless oil (81 mg, 81%). IR (neat): 1745 (C=O), 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.90 (9H, s), 3.50—4.20 (5H, m), 3.65 (3H, s), 4.60 (1H, br s), 4.85 (2H, m), 5.40 (2H, m). MS *m/z*: 381 (M^+ – THP), 233, 201, 159, 91, 75. HR-MS *m/z*: 381.2459 (Calcd for $C_{21}H_{37}O_4Si$, 381.2459, M^+ – THP). $[\alpha]_D^{20}$: −35° (*c* = 1.36, MeOH).

Methyl (*Z*)-7-[(1*R*,2*S*,3*R*)-2-*tert*-Butyldimethylsilyloxymethyl-3-hydroxy-5-methylenecyclopentyl]hept-5-enoate Dimethylaluminum chloride (9.9 ml, 9.9 mmol, 1 M solution in hexane) was added to a solution of the diene (**19**) (925 mg, 1.98 mmol) in methylene chloride (30 ml) at −25 °C, and the solution was stirred at the same temperature for 2 h. The reaction was quenched by the dropwise addition of saturated aqueous $KHCO_3$, followed by extraction with ether. The combined ether extracts were washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent afforded the alcohol as a colorless oil in quantitative yield. IR (neat): 3480 (OH), 1742 (C=O), 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.90 (9H, s), 3.30—4.15 (4H, m), 3.65 (3H, s), 4.85 (2H, m), 5.35 (2H, m). MS *m/z*: 325 (M^+ – *tert*-Bu), 233, 201, 183, 154, 75. HR-MS *m/z*: 325.1832 (Calcd for $C_{17}H_{29}O_4Si$, 325.1833, M^+ – *tert*-Bu).

Methyl (*Z*)-7-[(1*R*,2*S*,3*R*)-3-*tert*-Butyldimethylsilyloxy-2-*tert*-butyldimethylsilyloxymethyl-5-methylenecyclopentyl]hept-5-enoate (20) A mixture of the alcohol (264 mg, 0.62 mmol), *tert*-butyldimethylsilyl chloride (279 mg, 1.86 mmol) and imidazole (140 mg, 2.1 mmol) in DMF (1 ml) was stirred overnight at 23 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by extraction with ether. The combined ether extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was purified by silica gel column chromatography to afford the disilylether (**20**) (89%) as a colorless oil. IR (neat): 1745 (C=O), 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (12H, s), 0.90 (18H, s), 3.30—3.70 (2H, m), 3.65 (3H, s), 4.00 (1H, m), 4.85 (2H, m), 5.45 (2H, m). MS *m/z*: 439 (M^+ – *tert*-Bu), 233, 201, 189, 183, 173, 159, 147, 73. HR-MS *m/z*: 439.2704 (Calcd for $C_{23}H_{43}O_4Si_2$, 439.2698, M^+ – *tert*-Bu). $[\alpha]_D^{20}$: −38° (*c* = 1.36, MeOH).

Methyl (*Z*)-7-[(1*S*,2*S*,3*R*,5*S*)-3-*tert*-Butyldimethylsilyloxy-2-*tert*-butyldimethylsilyloxymethyl-5-hydroxymethylcyclopentyl]hept-5-enoate (21) A solution of **20** (2.7 g, 5.4 mmol) in THF (10 ml) was added to a stirred solution of 9-BBN (1.65 g, 13.6 mmol) in THF (24 ml) at 0 °C, and the mixture was stirred at the same temperature for 2 h. Then, aqueous 3 N NaOH (5 ml) and 30% H_2O_2 (5 ml) were added, and the whole reaction mixture was stirred at 60 °C for 1 h and 20 min. After cooling to room temperature and evaporation of THF, the reaction mixture was neutralized with 10% aqueous HCl at 0 °C and extracted with ethyl acetate. The organic layer was washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (ether–hexane, 1 : 1) to give the alcohol (**21**) (2.0 g, 72%) as a colorless oil. IR (neat): 3450 (OH), 1742 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.10 (6H, s), 0.90 (18H, s), 3.20—3.80 (5H, m), 3.65 (3H, s), 4.15 (1H, m), 5.40 (2H, m). MS *m/z*: 514 (M^+), 233, 221, 219, 201, 189, 73. HR-MS *m/z*: 457.2814 (Calcd for $C_{23}H_{45}O_5Si_2$, 457.2803, M^+ – *tert*-Bu). $[\alpha]_D^{20}$: +4° (*c* = 1.36, MeOH).

Methyl (*Z*)-7-[(1*S*,2*S*,3*R*,5*S*)-3-*tert*-Butyldimethylsilyloxy-2-*tert*-butyldimethylsilyloxymethyl-5-formylcyclopentyl]hept-5-enoate (23) Collins reagent (8.8 g, 34 mmol) was added to a stirred solution of the alcohol (**21**) (1.77 g, 3.4 mmol) in methylene chloride (70 ml) at 0 °C, and the mixture was stirred at the same temperature for 30 min. After addition of $NaHSO_4 \cdot H_2O$ (17.6 g) and dilution with methylene chloride, ether and anhydrous $MgSO_4$ were added to the reaction mixture. The obtained suspension was filtered through a Florisil column. Removal of the solvent gave the aldehyde (**23**) (1.60 g, 92%) as a colorless oil. IR (neat): 1730 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (12H, s), 0.90 (18H, s), 2.80 (1H, m), 3.40—3.70 (2H, m), 3.65 (3H, s), 4.20 (1H, q, *J* = 6 Hz), 5.35 (2H, m), 9.85 (1H, d, *J* = 3.6 Hz). HR-MS *m/z*: 512.3359 (Calcd for $C_{27}H_{52}O_5Si_2$, 512.3351, M^+). $[\alpha]_D^{20}$: +1° (*c* = 1.63, MeOH).

Methyl (1*R*,5*S*,6*S*,7*R*)-7-*tert*-Butyldimethylsilyloxy-6-*tert*-butyldimethylsilyloxymethylbicyclo[3.3.0]oct-2-ene-3-pentanoate (28) A degassed 5% solution of the aldehyde (**23**) in toluene was heated in a sealed glass tube at 180 °C for 18 h. After cooling to room temperature and removal of the solvent, the reaction mixture was purified by silica gel column chromatography (ether–hexane, 1 : 2) to afford a mixture of the alcohols **25a** and **25b** (87%) in a ratio of 5 : 3 and the epimerized aldehyde (**30**) (13%). Spectral data of **25a**: IR (neat): 3420 (OH), 1740 (C=O), 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (12H, s). 0.90 (18H, s), 1.20—2.95 (12H, m), 2.55—2.95 (1H, m), 3.65 (3H, s), 3.60—4.00 (4H, m), 5.55 (2H, m). MS *m/z*: 455 (M^+ – *tert*-Bu), 437, 324, 323, 249, 231, 217, 199, 189, 171, 157, 147. HR-MS *m/z*: 455.2670 (Calcd for $C_{23}H_{43}O_5Si_2$, 455.2646, M^+ – *tert*-Bu). $[\alpha]_D^{20}$: −23° (*c* = 1.40, MeOH). Spectral data of **25b**: IR (neat): 3450 (OH), 1742 (C=O), 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.10 (6H, s), 0.90 (18H, s), 1.20—2.95 (12H, m), 2.55—2.95 (1H, m), 3.65 (3H, s), 3.10—4.00 (3H, m), 4.30 (1H, m), 5.20—5.90 (2H, m). MS *m/z*: 455 (M^+ – *tert*-Bu), 437, 363, 249, 232, 231, 217, 205, 199, 189, 171, 157. HR-MS *m/z*: 455.2641 (Calcd for $C_{23}H_{43}O_5Si_2$, 455.2646, M^+ – *tert*-Bu). $[\alpha]_D^{20}$: +19° (*c* = 1.36, MeOH). **30**: ^{1}H-NMR ($CDCl_3$) δ: 0.05 (12H, s), 0.90 (18H, s), 1.60—2.55 (12H, m), 3.40—3.70 (2H, m), 3.65 (3H, s), 4.10 (1H, m), 5.35 (2H, m), 9.60 (1H, m). As a catalyst, 10% Pd on C (431 mg) was added to a solution of the alcohol (mixture of **25a** and **25b**, 4.31 g) in methanol (108 ml). The mixture was stirred under a hydrogen atmosphere (1 atm) at 23 °C. After filtration through celite, removal of the solvent gave the hydrogenated alcohol (**26**). Triethylamine (2.43 ml, 17.4 mmol) and mesyl chloride (1.34 ml, 17.4 mmol) were added to a solution of **26**, and the reaction mixture was stirred at 23 °C until the starting materials disappeared. Then, DBU (7.94 ml, 87 mmol) was added, and the reaction mixture was refluxed for 15 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by extraction with ether. The combined ether extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent and the purification by silica gel column chromatography (ether–hexane, 1 : 10) afforded the desired compound (**28**) (70% from **25a** and **25b**). IR (neat): 1745 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (12H, s), 0.85 (9H, s), 0.90 (9H, s), 2.90 (1H, m), 3.60 (2H, m), 3.85 (1H, m), 3.65 (3H, s), 5.30 (1H, br s). MS *m/z*: 439 (M^+ – *tert*-Bu), 234, 233, 201, 189, 183, 175, 173, 159, 147, 73. HR-MS *m/z*: 439.2697 (Calcd for $C_{23}H_{43}O_4Si$, 439.2697, M^+ – *tert*-Bu). $[\alpha]_D^{20}$: −22° (*c* = 1.76, MeOH).

Methyl (1*R*,5*S*,6*S*,7*R*)-7-*tert*-Butyldimethylsilyloxy-6-hydroxymethylbicyclo[3.3.0]oct-2-ene-3-pentanoate (29) A catalytic amount of PPTS was added to a solution of **28** (210 mg, 0.42 mmol) in 95% ethanol (45 ml), and the mixture was stirred at 23 °C for 17 h. The reaction was quenched by the addition of saturated $NaHCO_3$, followed by evaporation of ethanol and extraction with ethyl acetate. The combined organic layers were washed with brine, and dried over $MgSO_4$. The residue obtained by evaporation of the solvent was purified by silica gel column chromatography to give the desired alcohol (**29**) (46%) and the diol (18%) accompanied with recovery of the starting material (35%). IR (neat): 3500 (OH), 1745 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.90 (9H, s), 2.90 (1H, m), 3.30—4.10 (3H, m), 3.65 (3H, s), 5.27 (1H, br s). MS *m/z*: 325 (M^+ – *tert*-Bu), 307, 233, 229, 201, 183, 175, 173, 159, 157, 75. HR-MS *m/z*: 325.1833 (Calcd for $C_{17}H_{29}O_4Si$, 325.1834, M^+ – *tert*-Bu). $[\alpha]_D^{20}$: −35° (*c* = 1.63, MeOH).

Methyl (1*R*,5*S*,6*R*,7*R*)-7-*tert*-Butyldimethylsilyloxy-6-(3-oxo-(*E*)-1-octenyl)bicyclo[3.3.0]oct-2-ene-3-pentanoate (33) A solution of sulfur trioxide pyridine complex (168 mg) in DMSO (2.4 ml) was added to a stirred solution of the alcohol (**29**) (105 mg, 0.27 mmol) and triethylamine (0.31 ml) in DMSO (3 ml), and the mixture was stirred at 23 °C for 20 min. The reaction mixture was poured into ice-water (15 ml), and extracted with ether. The ether extracts were washed with water and brine, and dried over $MgSO_4$. Removal of the solvent gave the crude aldehyde (**32**). On the other hand, sodium hydride (60% in oil, 15 mg) was washed with pentane, and suspended in THF (2.5 ml). A solution of dimethyl (2-oxoheptyl)phosphonate (90 mg) in THF (2 ml) was added to the suspension, and the mixture was stirred at 23 °C for 20 min. Then, the aldehyde in THF (1.5 ml) was added dropwise into the solution of the ketophosphonate, and the whole mixture was stirred for 50 min. The reaction was quenched by

the addition of saturated aqueous NH_4Cl, followed by extraction with ether. The combined ether extracts were washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography afforded the enone (**33**) (93 mg, 71%) as a colorless oil. IR (neat): 1745 (C=O), 1702, 1680, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.00 (6H, s), 0.93 (9H, s), 3.00 (1H, m), 3.65 (3H, s), 3.85 (1H, m), 5.25 (1H, br s), 6.15 (1H, d, J=16 Hz), 6.70 (1H, dd, J=16, 8 Hz). MS m/z: 476 (M^+), 461 (M^+−Me), 445 (M^+−MeO), 420, 419, 319, 293, 199. HR-MS m/z: 476.3312 (Calcd for $C_{28}H_{48}O_4Si$, 476.3319, M^+). $[\alpha]_D^{20}$: −9° (c=1.82, MeOH).

Methyl (1*R*,5*S*,6*R*,7*R*)-7-*tert*-Butyldimethylsilyloxy-6-(3-hydroxy-(*E*)-1-octenyl)bicyclo[3.3.0]oct-2-ene-3-pentanoate (34) Excess sodium borohydride was added to a stirred solution of the enone (**33**) (89 mg) in methanol (2.5 ml) at −20 °C, and the mixture was stirred at the same temperature for 1 h. The reaction was quenched by the addition of acetone, and then saturated aqueous NH_4Cl was added to the reaction mixture. After evaporation of the organic solvents, the water layer was extracted with ethyl acetate. The combined ethyl acetate extracts were dried over $MgSO_4$, and concentrated to give the alcohol (**34**) as a epimeric mixture. All of this crude alcohol was used for the next reaction. IR (neat): 3500 (OH), 1740 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.00 (6H, s), 0.90 (12H, m), 3.65 (3H, s), 3.60—3.85 (1H, m), 5.30 (1H, br s), 5.50—5.70 (2H, m). MS m/z: 422, 421 (M^+−*tert*-Bu), 330, 329, 323, 304, 303, 297, 271, 253, 227, 201, 199, 187, 183, 173, 171, 161, 157. HR-MS m/z: 421.2778 (Calcd for $C_{24}H_{41}O_4Si$, 421.2772, M^+−*tert*-Bu).

Methyl (1*R*,5*S*,6*R*,7*R*)-7-Hydroxy-6-[3(*S*)-hydroxy-(*E*)-1-octenyl]-bicyclo[3.3.0]oct-2-ene-3-pentanoate (35a) Tetra-*n*-butylammonium fluoride (1 M solution in THF, 0.28 ml) was added to a solution of the alcohol (**34**) (88 mg, 0.18 mmol) in THF (2.5 ml), and the mixture was stirred overnight at 23 °C. The reaction mixture was quenched by the addition of brine, followed by extraction with ethyl acetate. The combined organic layer was dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (ether–hexane, 5 : 1—ether–methanol, 40 : 1) to give the desired 15α-diol (**35a**) (37 mg, 55%) as a more polar fraction and the 15β-diol (**35b**) (15 mg, 22%) as a less polar fraction. Spectral data of **35a**: IR (neat): 3400 (OH), 2940, 1740 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=6 Hz), 3.00 (1H, m), 3.68 (3H, s), 3.80 (1H, m), 4.12 (1H, m), 5.32 (1H, br s), 5.60 (2H, m). MS m/z: 346 (M^+-H_2O), 328, 315, 302, 232, 180, 179, 148, 145, 133, 131, 129, 119, 117, 107, 106, 105, 99, 95, 93, 91, 81, 79, 71, 67, 55, 43, 41. HR-MS m/z: 346.2516 (Calcd for $C_{22}H_{34}O_3$, 346.2499, M^+-H_2O). $[\alpha]_D^{20}$: +10° (c=0.546, MeOH). The spectral data of **35b** were nearly identical with those of **35a** except the optical rotation.

(1*R*,5*S*,6*R*,7*R*)-7-Hydroxy-6-[3(*S*)-hydroxy-(*E*)-1-octenyl]bicyclo-[3.3.0]oct-2-ene-3-pentanoic Acid, Isocarbacyclin (4) A 10% NaOH aqueous solution (0.2 ml) was added to a stirred solution of the diol **35a** (10 mg, 0.027 mmol) in methanol (0.3 ml) at 0 °C, and the mixture was stirred at the same temperature for 9 h. The reaction mixture was neutralized by adding 10% aqueous HCl, followed by evaporation of methanol. Then, the reaction mixture was acidified to pH 3—4 with 10% aqueous HCl, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded isocarbacyclin (**4**) in quantitative yield as a colorless solid. The spectral data of **4** thus obtained were identical with those of an authentic sample.[6] ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=6 Hz), 1.10—1.80 (m), 1.85—2.60 (m), 3.00 (1H, m), 3.80 (1H, m), 4.11 (1H, m), 5.33 (1H, br s), 5.60 (2H, m). $[\alpha]_D^{20}$: +8° (c=0.54, MeOH).

(1*S*,2*R*,3*S*,4*R*)-2-Allyl-3-*tert*-butyldimethylsilyloxymethyl-4-tetrahydropyranyloxy-1-cyclopentanol A solution of the lactol (7.74 g, 20.8 mmol) in THF (70 ml) was added to a stirred solution of methyltriphenylphosphonium bromide (22.8 g, 61.8 mmol) and potassium *tert*-butoxide (97%, 7.15 g, 61.8 mmol) in THF (180 ml) at 23 °C. After stirring for 40 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by extraction with ether. The combined ether extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (ether–hexane, 2 : 3) to afford the alcohol as a colorless oil (7.40 g, 96%). IR (neat): 3500 (OH), 2950, 2870, 1640, 835 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.15—2.60 (13H, m), 3.00—4.30 (6H, m), 4.65 (1H, br s), 5.00 (2H, m), 5.80 (1H, m). MS m/z: 285 (M^+−THP), 229, 211, 159, 85, 75, 73. HR-MS m/z: 285.1875 (Calcd for $C_{15}H_{29}O_3Si$, 281.1883, M^+−THP). $[\alpha]_D^{20}$: +21° (c=2.44, MeOH).

(2*R*,3*S*,4*R*)-2-Allyl-3-*tert*-butyldimethylsilyloxymethyl-4-tetrahydropyranyloxy-1-cyclopentanone AcONa (640 mg, 7.8 mmol), celite (8.45 g) and PCC (8.45 g) was added to a stirred solution of the alcohol (7.27 g, 19.6 mmol) in methylene chloride (90 ml) at 0 °C. The reaction mixture was stirred for 13 h at 0 °C. After dilution with ether, the reaction mixture was purified by Florisil column chromatography (ether–hexane, 1 : 3—1 : 1) to give the ketone (7.23 g, 100%) as a colorless oil. IR (neat): 2950, 2880, 1748 (C=O) 1642, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.50 (6H, s), 0.90 (9H, s), 1.60 (1H, m), 2.00—3.00 (6H, m), 3.30—4.00 (4H, m), 4.30 (1H, m), 4.65 (1H, br s), 5.00 (1H, d, J=11 Hz), 5.03 (1H, d, J=17 Hz), 5.70 (1H, m). MS m/z: 311 (M^+−*tert*-Bu), 267 (M^+−THPO), 227, 209, 159, 85, 75, 73, 41. HR-MS m/z: 311.1658 (Calcd for $C_{16}H_{27}O_4Si$, 311.1677, M^+−*tert*-Bu). $[\alpha]_D^{20}$: −55° (c=2.19, MeOH).

(2*R*,3*S*,4*R*)-2-Allyl-3-*tert*-butyldimethylsilyloxymethyl-1-methyelene-4-tetrahydropyranyloxycyclopentane (36) The methylenation reagent prepared by Lombardo's method[12] ($Zn-CH_2Br_2-TiCl_4$) (46 ml) was added to a solution of the ketone (2.79 g, 7.57 mmol) in methylene chloride (26 ml), and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into a mixture of saturated $NaHCO_3$ (500 ml), ether (500 ml) and a small amount of celite, and stirred vigorously. After filtration of the pale green suspension through a celite pad, the ether layer was separated and the water layer was further extracted with ether. The combined ether extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent and purification of the residue by silica gel column chromatography (ether–hexane, 1 : 10) afforded **36** as a colorless oil (2.48 g, 90%). IR (neat): 2950, 2870, 1660, 1640, 835 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.20—3.00 (12H, m), 3.30—4.30 (5H, m), 4.63 (1H, br s), 4.75—5.20 (4H, m), 5.60 (1H, m). MS m/z: 225, 207, 159, 133, 91, 85, 75, 73, 41. HR-MS m/z: 309.1858 (Calcd for $C_{17}H_{29}O_3Si$, 309.1884, M^+−*tert*-Bu). $[\alpha]_D^{20}$: −43° (c=2.84, MeOH).

(1*S*,2*S*,3*S*,4*R*)-3-*tert*-Butyldimethylsilyloxymethyl-1-hydroxymethyl-2-(3-hydroxypropyl)-4-tetrahydropyranyloxycyclopentane (37) A solution of disiamylborane in THF (1.2 M, 37.5 ml, 45 mmol) was added to a stirred solution of **36** (5.50 g, 15 mmol) in THF (30 ml) at 0 °C, and the mixture was stirred at the same temperature for 5 h. Then, aqueous 6 N NaOH (30 ml, 180 mmol) and 31% H_2O_2 (25.6 ml, 225 mmol) were added, and the whole reaction mixture was stirred at 23 °C for 1 h. After separation of THF, the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with aqueous $Na_2S_2O_3$ and brine, and dried over $MgSO_4$. Removal of the solvent afforded the diol (**37**) in quantitative yield as a colorless oil. IR (neat): 3400 (OH), 2940, 2860, 835 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.10—2.40 (17H, m), 3.15—3.95 (8H, m), 4.10 (1H, m), 4.65 (1H, br s). MS m/z: 317 (M^+−THP), 261, 243, 159, 149, 133, 105, 85, 75, 73, 67, 57,55, 43, 41. HR-MS m/z: 317.2150 (Calcd for $C_{16}H_{33}O_4Si$, 317.2147, M^+THP). $[\alpha]_D^{20}$: +2° (c=1.65, MeOH). The NMR data of **38** obtained by thexylborane treatment are as follows. Less polar isomer (yield 6%): ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.17 (3H, d, J=6 Hz), 1.30—3.20 (15H, m), 3.20—4.20 (8H, m), 4.57 (1H, m). More polar isomer (yield 24%): ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.20 (3H, d, J=6 Hz), 1.30—3.30 (15H, m), 3.30—4.15 (8H, m), 4.63 (1H, m).

(1*R*,5*S*,6*S*,7*R*)-6-*tert*-Butyldimethylsilyloxymethyl-7-tetrahydropyranyloxybicyclo[3.3.0]oct-2-ene-3-carbaldehyde (45) DMSO (7.45 ml, 104.9 mmol) in methylene chloride (20 ml) was added to a solution of oxalyl chloride (4.13 ml, 48.4 mmol) in methylene chloride (100 ml) at −80 °C, and the mixture was stirred for 15 min at the same temperature. Then, a solution of the diol (**37**) (3.25 g, 8.07 mmol) in methylene chloride (50 ml) was added dropwise at −80 °C, and the whole reaction mixture was stirred at the same temperature for 20 min. After addition of triethylamine (33.7 ml, 242 mmol), the reaction mixture was warmed to room temperature, and dibenzylammonium trifluoroacetate (2.51 g, 8.07 mmol) was added. The solvent was exchanged to benzene by evaporation of methylene chloride and addition of benzene (50 ml). The mixture was stirred at 70 °C for 2.75 h and then cooled to room temperature. The reaction was quenched by the addition of water, followed by extraction with ether. The combined extracts were washed with saturated aqueous NH_4Cl, brine and water, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (ether–hexane, 1 : 1) to give the aldehyde (**45**) (2.58 g, 84%) as a pale yellow oil. IR (neat): 2950, 2870, 1680, 1620, 835 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.30—2.00 (8H, m), 2.00—3.00 (4H, m), 3.00—4.20 (6H, m), 4.60 (1H, br s), 6.71 (1H, d, J=2 Hz), 9.78 (1H, s). MS m/z: 295 (M^+−THP), 279 (M^+−THPO), 239, 221, 159, 85, 75, 73, 67, 57, 43. HR-MS m/z: 295.1742 (Calcd for $C_{16}H_{27}O_3Si$, 295.1728, M^+−THP). $[\alpha]_D^{20}$: −77° (c=2.77, MeOH).

Oxidation of 37 with SO_3–Pyridine Complex A solution of SO_3–pyridine complex (310 mg, 2 mmol) in DMSO (5 ml) was added to a stirred solution of the diol (**37**) (160 mg, 0.4 mmol) and triethylamine (1.1 ml) in

DMSO (3 ml) at 23 °C, and the mixture was stirred at the same temperature for 1 h and then at 65 °C for 3.5 h. After dilution with ether, the reaction mixture was quenched with brine, followed by neutralization with 10% aqueous HCl and extraction with ether. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (ether–hexane, 1 : 1) to afford the aldehyde (**45**) (32 mg, 21%), the seven-membered lactol (**40**) (40 mg, 25%) and the four-membered lactol (**44**) (13 mg, 8%). Spectral data of **40**: IR (neat): 3450, 2950, 1730 (very weak), 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.00—2.60 (16H, m), 2.90—4.20 (7H, m), 4.62 (1H, br s), 4.75—5.25 (about 1H, m), 9.80 (trace, br s). MS *m/z*: 315 (M^+ − THP), 299 (M^+ − THPO), 259, 241, 167, 159, 149, 131, 121, 119, 105, 85, 75, 57, 43, 41. Spectral data of **44** (**43**): IR (neat): 3450, 2950, 1730 (weak), 835 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.05 (6H, s), 0.90 (9H, s), 1.00—2.50 (15H, m), 3.00—4.50 (6.6H, m), 4.65 (1H, m), 9.75 (0.4H, d, J = 1 Hz). MS *m/z*: 313 (M^+ − THP), 297 (M^+ − THPO), 239, 159, 85, 75, 73, 57, 41. The structures of **40** and **44** (**43**) were also confirmed by the conversion [i) $BrPh_3P(CH_2)_3COOH$, CH_3SOCH_2Na, ii) CH_2N_2, iii) H_2, Pd/C, iv) MsCl, NEt_3, v) DBU] of **40** to the exomethylene compound [(2*R*,3*S*,4*R*)-3-*tert*-butyldimethylsilyloxymethyl-2-(6-methoxycarbonylhexyl)-4-tetrahydropyranyloxy-1-cyclopentyridene)], and of **44** (**43**) to **47**.

Methyl (1*R*,5*S*,6*S*,7*R*)-6-*tert*-Butyldimethylsilyloxymethyl-7-tetrahydropyranyloxybicyclo[3.3.0]oct-2-ene-3-γ-pentenoate (46) A solution of potassium *tert*-butoxide (97%, 2.43 g, 21.0 mmol) in THF (40 ml) was added to a stirred suspension of 4-carboxybutyltriphenylphosphonium bromide (4.51 g, 10.5 mmol) in THF (25 ml), and the mixture was stirred at 23 °C for 10 min. Then, a solution of the aldehyde (**45**) (5.0 g, 13.4 mmol) in THF (10 ml) was added to the ylide solution at 23 °C. After stirring for 30 min, saturated aqueous NaCl was added. After separation of THF layer, the reaction mixture was acidified (pH 4—5) with 10% aqueous HCl and extracted with ethyl acetate. The organic layers were combined, washed with saturated aqueous NaCl and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was treated with ethereal diazomethane. After evaporation, the residue was purified by silica gel column chromatography (ether–hexane, 1 : 3) to afford the diene **46** (1.15 g, 94%, *cis* : *trans* = 2.2 : 1) as a colorless oil. IR (neat): 2950, 2870, 1745, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.10—1.95 (8H, m), 2.10—2.75 (8H, m), 2.95 (1H, m), 3.20—4.25 (5H, m), 3.65 (3H, s), 4.60 (1H, br s), 5.30 (1H, m), 5.57 (1H, br s), 5.98 (2.2/3.2H, d, J = 11 Hz), 6.24 (1/3.2H, d, J = 16 Hz). MS *m/z*: 464 (M^+), 363 (M^+ − THPO), 323, 231, 159, 157, 117, 91, 85, 75, 73, 67, 57, 43, 41. HR-MS *m/z*: 363.2327 (Calcd for $C_{21}H_{35}O_3Si$, 363.2353, M^+ − THPO). $[\alpha]_D^{20}$: −50° (*c* = 1.36, MeOH).

Methyl (1*R*,5*S*,6*S*,7*R*)-6-*tert*-Butyldimethylsilyloxymethyl-7-tetrahydropyranyloxybicyclo[3.3.0]oct-2-ene-3-pentanonate (47) As a catalyst, 10% Pd on C (120 mg) was added to a solution of the diene (**46**) (500 mg, 1.08 mmol) in methanol (10 ml), and the mixture was stirred under a hydrogen atmosphere (1 atm) at 23 °C for 1 h. The reaction could be monitored by thin layer chromatographic (TLC) analysis (silica gel impregnated with $AgNO_3$, ether–hexane, 1 : 2, *Rf*: *cis*-**46** = 0.16, *trans*-**46** = 0.23, **47** = 0.29, **49** = 0.35). After filtration to remove the catalyst, the filtrate was concentrated and purified by silica gel column chromatography (Lobar column, Merck, ether–hexane, 1 : 5) to afford the semi-hydrogenated product (435 mg, **47** : 85% and **50** : 2%) as more polar fractions and the over-reduction product (**49**) (65 mg, 13%) as a less polar fraction. Spectral data of **47**: IR (neat): 2950, 2880, 1745, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.05—2.65 (20H, m), 2.90 (1H, m), 3.25—4.10 (5H, m), 3.65 (3H, s), 4.60 (1H, br s), 5.25 (1H, d, J = 1 Hz). MS *m/z*: 435 (M^+ − MeO), 409 (M^+ − *tert*-Bu), 325, 307, 233, 159, 85, 75, 73. HR-MS *m/z*: 325.1834 (Calcd for $C_{17}H_{29}O_4Si$, 325.1834, M^+ − DHP, *tert*-Bu). $[\alpha]_D^{20}$; −12° (*c* = 1.68, MeOH). Spectral data of **49**: ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H, s), 0.89 (9H, s), 1.05—2.40 (24H, m), 3.40—4.20 (5H, m), 3.69 (3H, s), 4.68 (1H, br s). MS *m/z*: 437 (M^+ − MeO), 411 (M^+ − *tert*-Bu), 159, 85, 75. The spectral data of **50** were identical with those of an authentic sample.[24]

Methyl (1*R*,5*S*,6*S*,7*R*)-6-Hydroxymethyl-7-tetrahydropyranyloxybicyclo[3.3.0]oct-2-ene-3-pentanoate (48) Tetra-*n*-butylammonium fluoride (1 M solution in THF, 0.7 ml) was added to a solution of **47** (154 mg, 0.33 mmol), and the mixture was stirred for 5 h at 23 °C. The reaction mixture was quenched by the addition of brine, followed by extraction with ether. The combined organic layer was dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (ether–hexane, 3 : 2) to give the alcohol (**48**) (109 mg, 94%) and the starting material (**47**) (9 mg, 6%). IR (neat): 3480, 2950, 2880, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00—2.65 (21H, m), 3.00 (1H, m), 3.30—4.10 (5H, m), 3.66 (3H, s), 4.60 (1H, m), 5.25 (1H, d, J = 1 Hz). MS *m/z*: 352 (M^+), 334 ($M^+ - H_2O$), 268 (M^+ − DHP), 250, 85, 67, 57, 41. HR-MS *m/z*: 268.1688 (Calcd for $C_{15}H_{24}O_4$, 268.1673, M^+ − DHP). $[\alpha]_D^{20}$: −19° (*c* = 2.09, MeOH).

Methyl (1*R*,5*S*,6*R*,7*R*)-6-(3-Oxo-(*E*)-1-octenyl)-7-tetrahydropyranyloxybicyclo[3.3.0]oct-2-ene-3-pentanoate (51) A solution of SO_3–pyridine complex (148 mg, 0.93 mmol) in DMSO (2.5 ml) was added to a stirred solution of the alcohol (**48**) (109 mg, 0.31 mmol) and triethylamine (0.26 ml) in DMSO (3.5 ml), and the mixture was stirred at 23 °C for 20 min. The reaction mixture was poured on ice-water (20 ml), and extracted with ether. The ether extracts were washed with water and brine, and dried over $MgSO_4$. Removal of the solvent gave the crude aldehyde. On the other hand, sodium hydride (60% in oil, 17 mg, 0.43 mmol) was washed with pentane, and suspended in THF (3 ml). A solution of dimethyl (2-oxoheptyl)phosphonate (103 mg, 0.47 mmol) in THF (2 ml) was added to the suspension, and the mixture was stirred at 23 °C for 30 min. Then, the aldehyde in THF (1.5 ml) was dropped into the solution of the sodium ketophosphonate, and the whole mixture was stirred for 40 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by extraction with ether. The combined ether extracts were washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and the purification by silica gel column chromatography (ether–hexane, 2 : 5) afforded the enone (**51**) (101 mg, 73%) as a colorless oil. IR (neat): 2950, 1740 (C=O), 1698, 1675, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, d, J = 6 Hz), 1.00—2.60 (28H, m), 3.00 (1H, m), 3.20—4.10 (3H, m), 3.68 (3H, s), 4.65, 4.55 (total 1H, each br s), 5.30 (1H, d, J = 1 Hz), 6.17 (1H, dd, J = 16, 4 Hz), 6.80 (1H, m). MS *m/z*: 415 (M^+ − MeO), 362 (M^+ − DHP), 344 (M^+ − THPOH), 318, 99, 85. HR-MS *m/z*: 362.2473 (Calcd for $C_{22}H_{34}O_4$, 362.2455, M^+ − DHP).

In a similar manner, **52**—**55** were synthesized from **48** and the corresponding ketophosphonates. The spectral data were as follows.

Methyl (1*R*,5*S*,6*R*,7*R*)-6-(3-Cyclopentyl-3-oxo-(*E*)-1-propenyl)-7-tetrahydropyranyloxybicyclo[3.3.0]oct-2-ene-3-pentanoate (52) Yield 83%. IR (neat): 2950, 2880, 1742 (C=O), 1698, 1675, 1628 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10—2.60 (28H, m), 3.05 (2H, m), 3.50 (1H, m), 3.68 (3H, s), 4.63, 4.50 (total 1H, each br s), 5.28 (1H, d, J = 1 Hz), 6.20 (1H, dd, J = 15, 4 Hz), 6.80 (1H, m). MS *m/z*: 413 (M^+ − MeO), 360 (M^+ − DHP), 342 (M^+ − THPOH), 316, 273, 97, 91, 85, 69, 67, 57, 55, 43, 41. HR-MS *m/z*: 360.2318 (Calcd for $C_{22}H_{32}O_4$, 360.2299, M^+ − DHP).

Methyl (1*R*,5*S*,6*R*,7*R*)-6-(4-Methyl-3-oxo-(*E*)-1-octenyl)-7-tetrahydropyranyloxybicyclo[3.3.0]oct-2-ene-3-pentanoate (53) Yield 65%. IR (neat): 2950, 2880, 1742 (C=O), 1698, 1672, 1628 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 6 Hz), 1.10 (3H, d, J = 7 Hz), 1.20—2.80 (27H, m), 3.00 (1H, m), 3.25—4.15 (3H, m), 3.66 (3H, s), 4.65, 4.50 (total 1H, each br s), 5.28 (1H, br s), 6.25 (1H, dd, J = 15, 4 Hz), 6.80 (1H, m). MS *m/z*: 429 (M^+ − MeO), 376 (M^+ − DHP), 358 (M^+ − THPOH), 332, 273, 149, 91, 85, 57, 55, 43, 41. HR-MS *m/z*: 376.2601 (Calcd for $C_{23}H_{36}O_4$, 376.2611, M^+ − DHP).

Methyl (1*R*,5*S*,6*R*,7*R*)-6-(4,4-Dimethyl-3-oxo-(*E*)-1-octenyl)-7-tetrahydropyranyloxybicyclo[3.3.0]oct-2-ene-3-pentanoate (54) Yield 45%. IR (neat): 2950, 2880, 1742 (C=O), 1698, 1672, 1628 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J = 6 Hz), 1.00—2.70 (33H, m), 3.00 (1H, m), 3.50 (1H, m), 3.68 (3H, s), 3.80 (2H, m), 4.65, 4.50 (total 1H, each br s), 5.10 (1H, t, J = 7 Hz), 5.28 (1H, br s), 6.20 (1H, dd, J = 15, 4 Hz), 6.75 (1H, m). MS *m/z*: 469 (M^+ − MeO), 416 (M^+ − DHP), 398 (M^+ − THPOH), 372, 167, 149, 109, 85, 71, 69, 57, 55, 43, 41. HR-MS *m/z*: 416.2920 (Calcd for $C_{26}H_{40}O_4$, 416.2923, M^+ − DHP).

Methyl (1*R*,5*S*,6*R*,7*R*)-6-(5,9-Dimethyl-3-oxo-(*E*)-1,8-decadienyl)-7-tetrahydropyranyloxybicyclo[3.3.0]oct-2-ene-3-pentanoate (55) Yield 76%. IR (neat): 2950, 2880, 1742 (C=O), 1692, 1622 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 6 Hz), 1.00—2.70 (32H, m), 3.00 (1H, m), 3.48 (1H, m), 3.65 (3H, s), 3.80 (2H, m), 4.66, 4.50 (total 1H, each br s), 5.28 (1H, br s), 6.35—7.15 (2H, m). MS *m/z*: 443 (M^+ − MeO), 390 (M^+ − DHP), 372 (M^+ − THPOH), 346, 273, 99, 85, 57, 55, 43, 41. HR-MS *m/z*: 390.2784 (Calcd for $C_{24}H_{38}O_4Si$, 390.2758, M^+ − DHP).

Methyl (1*R*,5*S*,6*R*,7*R*)-7-Hydroxy-6-[3(*S*)-hydroxy-(*E*)-1-octenyl]bicyclo[3.3.0]oct-2-ene-3-pentanoate (35a) An excess amount of sodium borohydride was added to a stirred solution of the enone (**51**) (32 mg, 0.072 mmol) in methanol (5 ml) at −20 °C, and the mixture was stirred at the same temperature for 20 min. The reaction was quenched by the addition of acetone, and then saturated aqueous NH_4Cl was added to the reaction mixture. After evaporation of the organic solvents, the water layer was extracted with ether. The combined ether extracts were dried over $MgSO_4$, and concentrated to give the alcohol as an epimeric mixture.

Then, these alcohols were dissolved in a mixture of acetic acid, water and THF (3:1:1, 0.5 ml), and the mixture was stirred at 45—50 °C for 5 h. After dilution with ether, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ at 0 °C. Removal of THF gave the water layer, which was extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (ether–hexane, 5:1—ether–methanol, 40:1) to afford the desired 15α-diol (**35a**) (13 mg, 48%) as a more polar fraction and the 15β-diol (**35b**) (7 mg, 26%) as a less polar fraction. The spectral data were identical with those of **35a** obtained in the ene reaction route.

In a similar manner, **52**—**55** were converted to the corresponding diols. Furthermore, the diols were hydrolyzed to carboxylic acids **56**—**59** by the method described in the case of **4**. The C15 stereochemistry of each compound was tentatively assigned according to the general rule in other PGI_2 analogs[3-6] that the more polar isomer is 15α and the less polar isomer is 15β, and it was confirmed by the biological tests of both isomers of final products (all of the more polar isomers were 100 times as active as the corresponding less polar isomers with regard to the platelet aggregation-inhibitory activity). The spectral data were as follows.

Methyl (1*R*,5*S*,6*R*,7*R*)-6-[3-Cyclopentyl-3(*R*)-hydroxy-(*E*)-1-propenyl]-7-hydroxybicyclo[3.3.0]oct-2-ene-3-pentanoate Yield 15α-diol, 39%; 15β-diol, 20%. Spectral data of 15α-diol: IR (neat): 3400 (OH), 2940, 1740 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10—2.60 (m), 3.00 (1H, m), 3.67 (3H, s), 3.85 (2H, m), 5.32 (1H, br s), 5.60 (2H, m). MS *m/z*: 344 ($M^+ - H_2O$), 326, 300, 275, 243, 232, 225, 199, 193, 183, 181, 179, 141, 119, 117, 105, 93, 91, 81, 79, 69, 67, 55, 41. HR-MS *m/z*: 344.2326 (Calcd for $C_{22}H_{32}O_3$, 344.2349, $M^+ - H_2O$). $[\alpha]_D^{20}$: +33° (*c*=1.33, MeOH).

(1*R*,5*S*,6*R*,7*R*)-6-[3-Cyclopentyl-3(*R*)-hydroxy-(*E*)-1-propenyl]-7-hydroxybicyclo[3.3.0]oct-2-ene-3-pentanoic Acid (56) Yield 96%. IR (KBr): 3440, 2960, 1702, 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10—2.70 (m), 3.00 (1H, m), 3.90 (2H, m), 5.32 (1H, br s), 5.60 (2H, m). $[\alpha]_D^{20}$: +28.6° (*c*=0.37, MeOH). mp 115—116 °C (recryst. from ethyl acetate–hexane).

Methyl (1*R*,5*S*,6*R*,7*R*)-7-Hydroxy-6-[3(*R*)-hydroxy-4-methyl-(*E*)-1-octenyl]bicyclo[3.3.0]oct-2-ene-3-pentanoate Yield 15α-diol, 46%; 15β-diol, 31%. Spectral data of 15α-diol: IR (neat): 3400 (OH), 2950, 2880, 1740 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, m), 1.10—2.60 (23H, m), 3.00 (1H, m), 3.69 (3H, s), 3.75 (1H, m), 3.99 (1H, m), 5.33 (1H, br s), 5.60 (2H, m). MS *m/z*: 360 ($M^+ - H_2O$), 342, 316, 275, 167, 149,57, 43, 41. HR-MS *m/z*: 360.2662 (Calcd for $C_{23}H_{36}O_3$, 360.2662, $M^+ - H_2O$).

(1*R*,5*S*,6*R*,7*R*)-7-Hydroxy-6-[3(*R*)-hydroxy-4-methyl-(*E*)-1-octenyl]bicyclo[3.3.0]oct-2-ene-3-pentanoic Acid (57) Yield 97%. IR (neat): 3400 (OH), 2940, 2880, 1710 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, m), 1.10—1.80 (m), 1.85—2.80 (m), 3.00 (1H, m), 3.80 (1H, m), 3.95 (1H, m), 5.33 (1H, br s), 5.58 (2H, m).

Methyl (1*R*,5*S*,6*R*,7*R*)-7-Hydroxy-6-[3(*R*)-hydroxy-4,4-dimethyl-(*E*)-1-octenyl]bicyclo[3.3.0]oct-2-ene-3-pentanoate Yield 15α-diol, 45%; 15β-diol, 22%. Spectral data of 15α-diol: IR (neat): 3420 (OH), 2950, 2880, 1740 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, m), 1.00—2.70 (m), 3.00 (1H, m), 3.69 (3H, s), 3.85 (2H, m), 5.33 (1H, br s), 5.55 (2H, m). MS *m/z*: 374 ($M^+ - H_2O$), 356, 330, 276, 275, 243, 179, 121, 105, 95, 91, 79, 57, 55, 43, 41. HR-MS *m/z*: 374.2816 (Calcd for $C_{24}H_{38}O_3$, 374.2816, $M^+ - H_2O$).

(1*R*,5*S*,6*R*,7*R*)-7-Hydroxy-6-[3(*R*)-hydroxy-4,4-dimethyl-(*E*)-1-octenyl]bicyclo[3.3.0]oct-2-ene-3-pentanoic Acid (58) Yield 100%. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (9H, m), 1.10—2.60 (m), 3.00 (1H, m), 3.82 (2H, m), 5.32 (1H, br s), 5.62 (2H, m).

Methyl (1*R*,5*S*,6*R*,7*R*)-7-Hydroxy-6-[3(*S*)-hydroxy-5,9-dimethyl-(*E*)-1,8-decadienyl]bicyclo[3.3.0]oct-2-ene-3-pentanoate Yield 15α-diol, 41%; 15β-diol, 16%. Spectral data of 15α-diol: IR (neat): 3400 (OH), 2940, 1740 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, *J*=6 Hz), 1.10—2.60 (m), 3.00 (1H, m), 3.69 (3H, s), 3.80 (1H, m), 4.22 (1H, m), 5.12 (1H, t, *J*=6 Hz), 5.33 (1H, br s), 5.60 (2H, m). MS *m/z*: 400 ($M^+ - H_2O$), 382, 109, 107, 105, 95, 93, 91, 81, 79, 69, 67, 55, 43, 41. HR-MS *m/z*: 400.2951 (Calcd for $C_{26}H_{40}O_3$, 400.2974, $M^+ - H_2O$).

(1*R*,5*S*,6*R*,7*R*)-7-Hydroxy-6-[3(*S*)-hydroxy-5,9-dimethyl-(*E*)-1,8-decadienyl]bicyclo[3.3.0]oct-2-ene-3-pentanoic Acid (59) Yield 95%, ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, *J*=7 Hz), 1.10—2.60 (m), 3.00 (1H, m), 3.80 (1H, m), 4.20 (1H, m), 5.12 (1H, t, *J*=7 Hz), 5.33 (1H, br s), 5.60 (2H, m).

The allyl ketone (**60**) was converted to the diene (**64**) in the same manner as described for the allyl ketone without the ω-chain to **46**. The spectral data were as follows.

(2*R,3*S**,4*R**)-2-Allyl-4-*tert*-butyldimethylsilyloxy-3-(3-*tert*-butyldimethylsilyloxy-(*E*)-1-octenyl)-1-methylenecyclopentane (61)** Yield 88%. IR (neat): 3080, 2930, 2850, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.02 (12H, s), 0.88 (21H, s), 1.40 (8H, m), 2.00—2.70 (6H, m), 3.76 (1H, m), 4.02 (1H, m), 4.87—5.03 (4H, m), 5.41 (2H, m), 5.70 (1H, m). MS *m/z*: 435 ($M^+ - tert$-Bu), 421, 393, 323, 303, 289, 229, 147, 75, 73. HR-MS *m/z*: 435.3125 (Calcd for $C_{25}H_{47}O_2Si_2$, 435.3113, $M^+ - tert$-Bu).

(1*S,2*S**,3*S**,4*R**)-4-*tert*-Butyldimethylsilyloxy-3-(3-*tert*-butyldimethylsilyloxy-(*E*)-1-octenyl)-1-hydroxymethyl-2-(3-hydroxypropyl)-cyclopentane (62)** Yield 85%. IR (neat): 3350, 2930, 2850 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (12H, s), 0.87 (21H, s), 2.16 (3H, m), 2.83 (1H, m), 3.59 (4H, m), 3.96 (2H, m), 5.38 (2H, m). MS *m/z*: 471 ($M^+ - tert$-Bu), 453, 396, 379, 339, 325, 321, 247, 229, 75, 73. HR-MS *m/z*: 471.3404 (Calcd for $C_{25}H_{51}O_4Si_2$, 471.3399, $M^+ - tert$-Bu).

(1*R,5*S**,6*R**,7*R**)-7-*tert*-Butyldimethylsilyloxy-6-(3-*tert*-butyldimethylsilyloxy-(*E*)-1-octenyl)bicyclo[3.3.0]oct-2-ene-3-carbaldehyde (63)** Yield 97%. IR (neat): 2950, 2850, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (12H, s), 0.87—0.90 (21H, 2s, 1t), 3.24 (1H, m), 3.76 (1H, m), 4.08 (1H, m), 5.48 (2H, m), 6.73 (1H, br s), 9.82 (1H, s). MS *m/z*: 449 ($M^+ - tert$-Bu), 435, 202, 91. HR-MS *m/z*: 449.2905 (Calcd for $C_{25}H_{45}O_3Si_2$, 449.2921, $M^+ - tert$-Bu).

Methyl (1*R,5*S**,6*R**,7*R**)-7-*tert*-Butyldimethylsilyloxy-6-(3-*tert*-butyldimethylsilyloxy-(*E*)-1-octenyl)bicyclo[3.3.0]oct-2-ene-3-γ-pentenoate (64)** Yield 88%. Spectral data of α-isomer of **64** (after separation by silica gel column chromatography): IR (neat): 2950, 2850, 1750, 1460, 1360, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (12H, s), 0.87 (8H, t, *J*=6 Hz), 0.90 (18H, s), 2.97 (1H, m), 3.69 (3H, s), 3.70 (1H, m), 4.07 (1H, m), 5.51 (4H, m), 6.02 (1/3H, d, *J*=12 Hz), 6.27 (2/3H, d, *J*=16 Hz). MS *m/z*: 590 (M^+), 533 ($M^+ - tert$-Bu), 519, 458, 427, 401, 301, 75, 73. HR-MS *m/z*: 533.3484 (Calcd for $C_{30}H_{53}O_4Si_2$, 533.3484, M^+).

Hydrogenation of 64 A solution of phenyldipiperidylphosphine (31 mg, 0.113 mmol) and chlorodicyclooctenerhodium(I) (20 mg, 0.056 mmol) in benzene (0.25 ml) and ethanol (0.25 ml) was stirred at 23 °C for 10 min under a hydrogen atmosphere. Then, a solution of the diene (**64**) (137 mg, 0.23 mmol) in benzene (0.5 ml) was added to the mixture, and the whole reaction mixture was stirred at 23 °C for 4 h under a hydrogen atmosphere (1 atm). Removal of the solvent and purification by silica gel (inpreganted with $AgNO_3$) chromatography afforded the desired product **65** (60%), the 1,4-reduction product **66** (24%) and the over-reduction product **67** (16%). Their spectral data were identical with those of authentic samples.[24,25]

(1*R,5*S**,6*R**,7*R**)-7-*tert*-Butyldimethylsilyloxy-6-(3-*tert*-butyldimethylsilyloxy-(*E*)-1-octenyl)-3-hydroxymethylbicyclo[3.3.0]oct-2-ene (68)** Diisobutylaluminum hydride (1.76 M solution in hexane, 0.71 ml, 1.25 mmol) was added to a stirred solution of the aldehyde (**63**) (420 mg, 0.83 mmol) in toluene (3.5 ml) at −78 °C, and the mixture was stirred at the same temperature for 90 min. The reaction was quenched by the addition of methanol. After dilution with ether, saturated aqueous NaCl was added. The mixture was stirred at room temperature until the organic layer became clear. The aqueous layer was extracted with ether. The combined ether extracts were dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography to afford the alcohol (**68**) (373 mg, 88%) as a colorless oil. IR (neat): 3350,(OH), 2930, 2850 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.01 (12H, s), 0.83—0.87 (21H, 2s, 1t), 1.10—1.63 (10H, m), 1.77—2.57 (5H, m), 2.97 (1H, m), 3.73 (1H, m), 4.13 (3H, m), 5.47 (3H, m). MS *m/z*: 451 ($M^+ - tert$-Bu), 437, 376, 369, 299, 227, 171, 131, 73. HR-MS *m/z*: 451.3076 (Calcd for $C_{25}H_{47}O_3Si_2$, 451.3062, $M^+ - tert$-Bu).

(1*R,5*S**,6*R**,7*R**)-3-Bromomethyl-7-*tert*-butyldimethylsilyloxy-6-(3-*tert*-butyldimethylsilyloxy-(*E*)-1-octenyl)bicyclo[3.3.0]oct-2-ene (69)** Triphenylphosphine (231 mg, 0.88 mmol) and carbon tetrabromide (292 mg, 0.88 mmol) were added to a stirred solution of the alcohol (**68**) (373 mg, 0.734 mmol) in methylene chloride (7 ml) at 0 °C, and the mixture was stirred at the same temperature for 30 min. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$, followed by extraction with ether. The combined ether extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded the bromide (**69**) (407 mg, 97%) as a colorless oil. IR (neat): 2950, 2880 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.01 (12H, s), 0.85—0.89 (21H, 2s, 1t), 1.00—1.60 (10H, m), 1.80—2.80 (4H, m), 3.00 (1H, m), 3.70 (1H, m), 4.00 (2H, br s), 4.06 (1H, m), 5.46 (2H, m), 5.70 (1H, br s). MS *m/z*: 515 ($M^+ - tert$-Bu), 513 ($M^+ - tert$-Bu), 227, 171, 147, 131, 117, 93, 91, 79, 75, 73. HR-MS *m/z*: 515.2185, 513.2189 (Calcd for $C_{25}H_{46}BrO_2Si_2$, 515.2197, 513.2217, $M^+ - tert$-Bu).

(1*R,5*S**,6*R**,7*R**)-3-Acetoxymethyl-7-*tert*-butyldimethylsilyloxy-6-(3-*tert*-butyldimethylsilyloxy-(*E*)-1-octenyl)bicyclo[3.3.0]oct-2-ene (70)** Acetic anhydride (27 μl, 0.29 mmol) and a catalytic amount of 4-dimethylaminopyridine were added to a stirred solution of the alcohol (**68**) (97 mg, 0.19 mmol) in pyridine (1.5 ml), and the mixture was stirred at 23 °C for 30 min. Saturated aqueous $CuSO_4$ was added to the reaction mixture, followed by extraction with ether. The combined ether extracts

were washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and purification of the residue by silica gel chromatography afforded the acetate (**70**) (104 mg, 99%) as a colorless oil. IR (neat): 2950, 2855, 1755 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.02 (12H, s), 0.83—0.87 (21H, 2s, 1t), 1.00—1.60 (10H, m), 1.70—2.65 (4H, m), 2.05 (3H, s), 2.93 (1H, m), 3.68 (1H, m), 4.01 (1H, m), 4.55 (2H, br s), 5.47 (3H, m). MS *m/z*: 493 ($M^+ - tert$-Bu), 433 ($M^+ - tert$-Bu − AcOH), 359, 319, 227, 171, 159, 147, 131, 117, 93, 91, 79, 75, 73. HR-MS *m/z*: 493.3147 (Calcd for $C_{27}H_{49}O_4Si_2$, 493.3166, $M^+ - tert$-Bu).

(1*R,5*S**,6*R**,7*R**)-7-*tert*-Butyldimethylsilyloxy-6-(3-*tert*-butyldimethylsilyloxy-(*E*)-1-octenyl)-3-(4-pentenyl)bicyclo[3.3.0]oct-2-ene (71)** 3-Butenyllithium (1.62 M in hexane, 1.11 ml, 1.80 mmol) was added to a stirred suspension of cuprous iodide (175 mg, 0.92 mmol) in ether (2 ml) at −30 °C, and the mixture was stirred for 30 min at the same temperature and then for 5 min at 23 °C. A solution of the acetate (**70**) (202 mg, 0.367 mmol) in ether (1 ml) was added to the dibutenylcuprate solution at −78 °C, and the whole was stirred for 1 h at the same temperature and then for 20 min at 23 °C. After dilution with ether, the reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by the extraction with ether. The combined ether extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography afforded the desired α-attacked product (**71**) (90%)[26] together with **72** (3%), and **68** (7%). Spectral data of **71**: IR (neat): 2950, 2870, 1640 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.00 (12H, s), 0.88 (21H, 2s, 1t), 1.00—2.50 (20H, m), 2.90 (1H, m), 3.73 (1H, m), 4.08 (1H, m), 4.80—5.20 (2H, m), 5.25 (1H, br s), 5.45 (2H, m), 5.75 (1H, m). MS *m/z*: 489 ($M^+ - tert$-Bu), 473, 341, 73. HR-MS *m/z*: 489.3584 (Calcd for $C_{29}H_{53}O_2Si_2$, 489.3581, $M^+ - tert$-Bu). Spectral data of **72**: IR (neat): 2950, 2870, 1640 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.02 (12H, s), 0.85—0.89 (21H, 2s, 1t), 1.00—2.80 (20H, m), 3.70 (1H, m), 4.05 (1H, m), 4.60—5.20 (4H, m), 5.45 (2H, m), 5.80 (1H, m). MS *m/z*: 489 ($M^+ - tert$-Bu), 473, 341, 73. HR-MS *m/z*: 489.3579 (Calcd for $C_{29}H_{53}O_2Si_2$, 489.3581, $M^+ - tert$-Bu).

(1*R,5*S**,6*R**,7*R**)-7-*tert*-Butyldimethylsilyloxy-6-(3-*tert*-butyldimethylsilyloxy-(*E*)-1-octenyl)-3-(5-hydroxyphenyl)bicyclo[3.3.0]oct-2-ene (73)** 9-BBN (0.5 M in THF solution, 0.74 ml, 0.37 mmol) was added to a stirred solution of the mixture of **71** and **72** (27 : 1, 168 mg, 0.31 mmol) in THF (2.5 ml) at 0 °C, and the mixture was stirred for 3 h at 0 °C, and then for 1 h at 23 °C. Aqueous 6 N NaOH (0.21 ml) and 30% H_2O_2 (0.18 ml) were added to the reaction mixture, and the whole was stirred at 50 °C for 1 h. After cooling to room temperature, the reaction mixture was extracted with ether. The combined ether extracts were washed with saturated aqueous $Na_2S_2O_3$ and brine, and dried over $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography afforded the desired alcohol (**73**) (155 mg, 89%) together with the diol **74** (2%) and **75** (3%). Spectral data of **73**: IR (neat): 3350, 2950, 2850 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.01 (12H, s), 0.83—0.87 (21H, 2s, 1t), 1.00—2.60 (21H, m), 2.91 (1H, m), 3.64 (3H, m), 4.05 (1H, m), 5.24 (1H, m), 5.47 (2H, m). MS *m/z*: 507 ($M^+ - tert$-Bu), 375, 301, 275, 75, 73. HR-MS *m/z*: 507.3693 (Calcd for $C_{29}H_{55}O_3Si_2$, 507.3687, $M^+ - tert$-Bu). Spectral data of **74**: IR (neat): 3350, 2960, 2890, 1260, 840, 778 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.02 (12H, s), 0.87 (21H, 2s, 1t), 1.00—2.40 (26H, m), 3.40—4.12 (5H, m), 5.38 (2H, m). MS *m/z*: 525 ($M^+ - tert$-Bu), 393, 379, 301, 187, 171, 147, 131, 117, 105, 75, 73, 55, 43. HR-MS *m/z*: 525.3809 (Calcd for $C_{29}H_{57}O_4Si_2$, 525.3795, $M^+ - tert$-Bu). Spectral data of **75**: IR (neat): 3380, 2970, 2900, 1260, 845, 780 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.01 (12H, s), 0.87 (21H, 2s, 1t), 1.00—2.40 (25H, m), 3.30—3.90 (5H, m), 4.02 (1H, m), 5.40 (2H, m). MS *m/z*: 525 ($M^+ - tert$-Bu), 393, 379, 301, 283, 215, 187, 171, 147, 131, 117, 105, 75, 73, 55, 43. HR-MS *m/z*: 525.3812 (Calcd for $C_{29}H_{57}O_4Si_2$, 525.3795, $M^+ - tert$-Bu).

(1*R,5*S**,6*R**,7*R**)-7-*tert*-Butyldimethylsilyloxy-6-(3-*tert*-butyldimethylsilyloxy-(*E*)-1-octenyl)bicyclo[3.3.0]oct-2-ene-3-pentanal (76)** AcONa (3 mg) and PCC (19 mg) were added to a stirred solution of the alcohol (21 mg, 0.037 mmol) in methylene chloride (0.4 ml) at 23 °C, and the mixture was stirred for 2 h. After dilution with ether, the reaction mixture was filtered through a Florisil column. The filtrate was concentrated to give the aldehyde (18 mg, 87%) as a colorless oil. IR (neat): 2950, 2850, 1730 (C=O) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.00 (12H, s), 0.89 (9H, s), 0.86 (9H, s), 1.00—2.60 (24H, m), 2.90 (1H, m), 3.66 (1H, m), 4.08 (1H, m), 5.24 (1H, m), 5.45 (2H, m), 9.77 (1H, t, J=2 Hz). MS *m/z*: 505 ($M^+ - tert$-Bu), 373, 281, 215, 185, 171, 147, 145, 117, 105, 91, 79, 75, 73. HR-MS *m/z*: 505.3555 (Calcd for $C_{29}H_{53}O_3Si_2$, 505.3530, $M^+ - tert$-Bu).

(1*R,5*S**,6*R**,7*R**)-7-*tert*-Butyldimethylsilyloxy-6-(3-*tert*-butyldimethylsilyloxy-(*E*)-1-octenyl)bicyclo[3.3.0]oct-2-ene-3-pentanoic Acid (77)** Aqueous 5 N NaOH (0.28 ml) was added to an aqueous solution of $AgNO_3$ (125 mg in 0.34 ml) to give a silver oxide solution. Methanol (0.86 ml) and a solution of the aldehyde (**76**) (154 mg, 0.274 mmol) in methanol–THF (1 : 1, 1.3 ml) were added to the silver oxide solution at 23 °C, and the mixture was stirred at 45 °C for 25 min. After dilution with ether, the reaction mixture was acidified to pH 5 by adding 10% aqueous HCl, followed by evaporation of the organic solvents, and extraction with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and purified by silica gel chromatography to afford the carboxylic acid (**77**) (122 mg, 77%). IR (neat): 2950, 2850, 1715 (C=O) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.00 (12H, s), 0.89 (9H, s), 0.86 (9H, s), 1.00—2.60 (24H, m), 2.92 (1H, m), 3.70 (1H, m), 4.05 (1H, m), 5.25 (1H, m), 5.46 (2H, m). MS *m/z*: 521 ($M^+ - tert$-Bu), 389, 289, 171, 117, 105, 91, 79, 75, 73. HR-MS *m/z*: 521.3504 (Calcd for $C_{29}H_{53}O_4Si_2$, 521.3480, $M^+ - tert$-Bu).

Deprotection of 77 Tetra-*n*-butylammonium fluoride (1 M solution in THF, 0.44 ml) was added to a solution of **77** (122 mg, 0.22 mmol), and the mixture was stirred for 2 d at 23 °C. The reaction mixture was quenched by the addition of water, followed by extraction with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography to give *dl*-isocarbacyclin (31 mg) and its 15β-isomer (38 mg) in 90% yield. The spectral data of *dl*-isocarbacyclin were identical with those of an authentic sample except the optical rotation.

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15) Also in the case of the aldehyde-olelfin **24** protected by the *tert*-butyldiphenylsilyl (TBDPS) group, the thermal ene reaction proceeded smoothly. The TBDMS group was deprotected by treatment with PPTS in ethanol in a much more selective manner.
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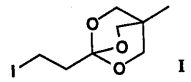

Fig. 2

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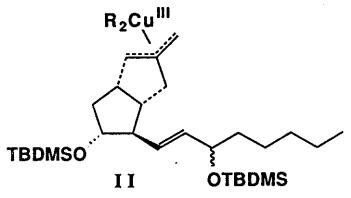

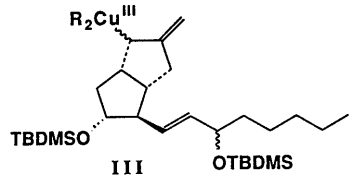

R = $CH_2CH_2CH{=}CH_2$

Fig. 3