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Syntheses and Biological Activities of Chemically Stable Prostacyclin Mimics with *cis*-Bicyclo[4.3.0]nonene Ring System: The Novel Homoisocarbacyclin Analogues

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Abstract—The synthetic studies concerning a series of homoisocarbacyclin analogues, which are homologous compounds of isocarbacyclin, with *cis*-bicyclo[4.3.0]non-2-ene or *cis*-bicyclo[4.3.0]non-3-ene as a nucleus have been carried out. The general synthetic methods of homoisocarbacyclin analogues have been accomplished starting with the versatile Corey lactone. Among the analogues synthesized in the present studies, a promising compound (TY-11223) exhibiting a good selectivity in biological actions was found to be studied further.

Introduction

Since the identification of biologically potent prostacyclin (PGI_2; **1**), which plays an important role in the biological homeostasis as an endogenous autacoid locating widely in various tissues,[1] it has attracted notice as a target for development of a novel therapeutic agent mainly in the cardiovascular and gastrointestinal fields. Due to the inherent instability of PGI_2 with the labile enol ether moiety, the therapeutic use of PGI_2 itself is limited. Therefore, great efforts have been focused on the synthesis of chemically stable PGI_2 mimics.[2] One of the synthetic studies on PGI_2 mimics was directed toward a stabilization of the enol ether moiety by the introduction of an electron withdrawing group such as a cyano group, fluorine atom, etc. into a neighboring carbon atom of the enol ether, or by the constructional inclusion of it into the more stable conjugated system connected to the aromatic ring. In these trials nileprost (**2**),[3] beraprost sodium (**3**)[4] and CG-4203 (**4**)[5] have been found and verified to improve the instability of enol ether. Another important aspect in structural modifications is the replacement of an oxygen atom at the enol ether moiety with a methylene group, leading to the carboanalogues such as carbacyclin (**5**)[6] and isocarbacyclin (**6**).[7] Both analogues **5** and **6** were characterized to have a similar pharmacological profile to that of PGI_2, which is recognized as a powerful stimulator of blood platelet adenylate cyclase. Isocarbacyclin (**6**) is an especially interesting compound due to its chemically and metabolically stable properties. In the subsequent synthetic studies to improve bioavailability and pharmacokinetic properties responsible for various therapeutic uses, **5** and **6** have shared important positions as leading compounds. Among the numerous synthesized analogues of **5** and **6**, iloprost (**7**),[8] cicaprost (**8**),[9] OP-41483 (**9**)[10] and others[2c-e] have been reported as quite interesting compounds in the last decade (Fig. 1).

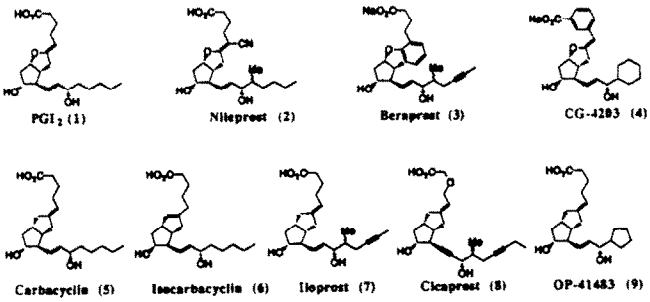


Figure 1.

In the course of our synthetic studies on chemically stable and biologically potent PGI_2 analogues, we were interested in the homologous compound of **6** with *cis*-bicyclo-[4.3.0]non-2-ene nucleus (named as "homoisocarbacyclin": **10**), because the carboxyl and hydroxyl groups involved in homoisocarbacyclin (**10**) at C_1, C_{11} and C_{15} (PG numbering) positions might be stereochemically oriented to spatial positions similar to those of isocarbacyclin (**6**), on the basis of the statistical calculation by the MM2 program.[11] Furthermore, Upjohn's researchers had already reported that a homologous compound of PGI_2 with an enlarged ring system (**11**), which retained a platelet anti-aggregatory activity equipotent to the parent compound (Fig. 2).[12]

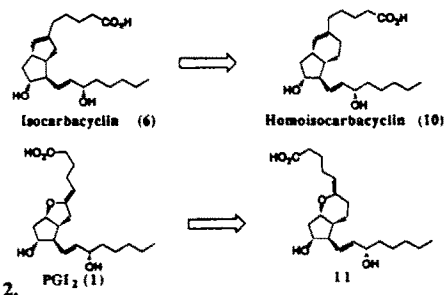


Figure 2.

We were intrigued by these facts and carried out a synthetic study on the homologues of compound **6**. As a result, homoisocarbacyclin (**10**) was verified as possessing a

satisfactory stability and pharmacological profile close to that of **6**. Remarkably, some analogues of **10** with modified upper and lower side chains showed interesting properties in the selectivity of biological actions as compared to that of PGI_2 (**1**). In this paper, we wish to report the syntheses and preliminary pharmacological activities of homoisocarbacyclin (**10**) and its analogues.

Synthesis of Homoisocarbacyclin

In the synthesis of homoisocarbacyclin (**10**), we planned a versatile route to introduce a variety of upper and lower side chains into *cis*-bicyclo[4.3.0]non-2-ene skeleton, so that we settled on the enal (**21**) as a key intermediate. The construction of the compound **21** was achieved from a nine step procedure starting with Corey lactone (**12**) as described below.[13,14] Corey lactone (**12**) was converted into the conjugated ester (**14**) in the usual manner ((i) diisobutylaluminum hydride (DIBAH) in toluene, (ii) methyl (triphenylphosphoranylidene)acetate in toluene), which was followed by hydrogenation and Swern oxidation to afford the keto-ester (**16**). Methylenation of **16** was effectively carried out by Nozaki–Lombardo's reagent ($Zn–CH_2Br_2–TiCl_4$),[15] giving the *exo*-methylene compound (**17**). Hydroboration of **17** with disiamylborane followed by oxidative workup gave the alcohol (**18**) in a stereocontrolled manner,[16] which was then reduced with lithium aluminum hydride to furnish the diol (**19**). Swern oxidation of **19** led to the dialdehyde (**20**), followed by intramolecular cyclization in the presence of dibenzylammonium trifluoroacetate[17] at 80°C, which afforded the versatile key intermediate (**21**) in a fully regiocontrolled manner in 46% overall yield from Corey lactone (**12**) (Scheme I).

The absence of the *trans* isomer (**22**) at the ring junction was evidenced by 400 MHz ^{1}H-NMR and 100.6 MHz ^{13}C-NMR spectra of the alcohol (**25**)[18] derived from enal (**21**) in three steps (Scheme II).

Thus, the key intermediate (**21**) was efficiently obtained, and we proceeded with subsequent attempts to introduce the upper and lower side chains into the *cis*-bicyclo[4.3.0]non-2-ene nucleus in a similar manner to isocarbacyclin synthesis.[16] Wittig reaction of the enal (**21**) with the ylide derived from 3-carboxypropyltriphenylphosphonium bromide and potassium *tert*-butoxide in THF and subsequent reaction with ethereal diazomethane provided the conjugated diene (**26**) (*E*:*Z* = *ca.* 1:2). The regioselective hydrogenation of **26** with a catalytic amount of 10% palladium on carbon under hydrogen atmosphere gave the desired compound (**27**) in 84% yield. Deprotection of a *tert*-butyldimethylsilyl moiety in **27** by treating with tetrabutylammonium fluoride (TBAF) afforded the alcohol (**28**).

Oxidation of **28** with sulfur trioxide pyridine complex and triethylamine in dimethyl sulfoxide (DMSO) gave the aldehyde (**29**) which was directly treated with dimethyl (2-oxoheptyl)phosphonate anion to provide the enone (**30**). Reduction of the enone (**30**) with sodium borohydride afforded the alcohol (**31**) as an epimeric mixture at C_{15}, which was deprotected to give the chromatographically separable epimers **32** and **33** in a ratio of 3:2.[19] Finally, the desired diol (**32**) was hydrolyzed with sodium hydroxide in aqueous methanol to afford homoisocarbacyclin (**10**) as a colorless powder in 29% overall yield from the alcohol (**28**) (Scheme III).

Preliminary biological examinations indicated that this compound (**10**) was a less potent inhibitor of platelet aggregation than PGI_2 (**1**) and isocarbacyclin (**6**). However, **10** was found to have a further property compared to them, hypotensive activity being separable from platelet anti-aggregatory activity (Table 1). Consequently, it was expected that chemical modifications on the upper and lower side chains of **10** would be worthwhile for the purpose of increasing the potency and duration of activity.

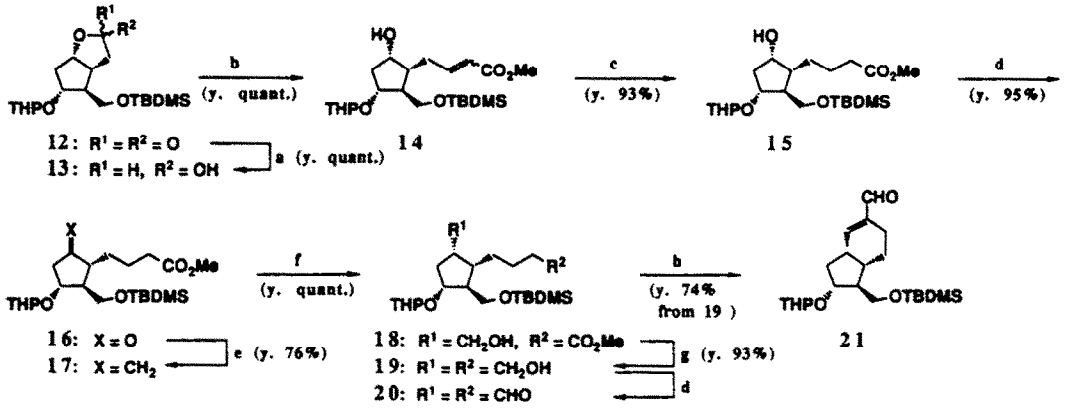
Table 1. Biological data of homoisocarbacyclin (**10**)

compound	anti-aggregatory activity [a] IC_{50} (M) [b]		hypotensive activity in dogs [a] ED_{50mmHg} (μg/kg, i.v.) [c]
10	ADP [d]	2.9×10^{-7} (1/100)	17.9mmHg lowering at 10 μg/kg (1/213)
	Collagen [e]	2.8×10^{-7} (1/82)	
PGI_2	ADP [d]	2.9×10^{-9} (1)	0.24 (1)
	Collagen [e]	3.4×10^{-9} (1)	
Isocarbacyclin	ADP [d]	9.4×10^{-9} (1/3.2)	1.10 (1/2.4)
	Collagen [e]	6.1×10^{-9} (1/1.8)	

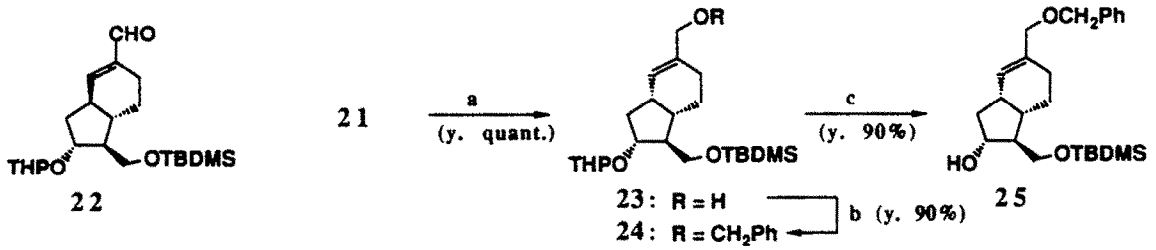
a) The values in parentheses are activity ratio.
b) IC_{50} represents the concentration that inhibits induced aggregation by 50%.
c) The dose that lowers the diastolic blood pressure by 50mmHg (peak effect). ED_{50mmHg} was calculated by linear regression from three dose groups of four to five animals each.
d) Inhibition of platelet aggregation induced by adenosine diphosphate (ADP) in rabbit washed platelets.
e) Inhibition of platelet aggregation induced by collagen in rabbit washed platetets.

Synthesis of 3-Oxahomoisocarbacyclins

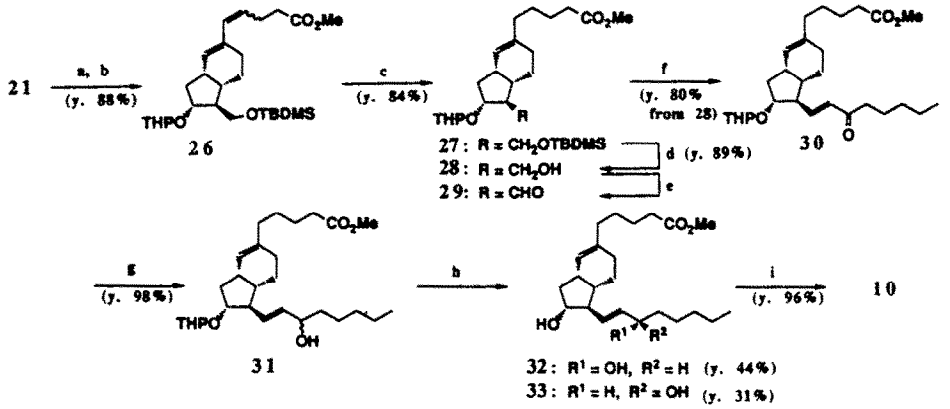
Many efforts have been made to prepare metabolically stable mimics of the natural prostaglandin series. One of the strategies concerning the upper side chain is the replacement of the C_3-methylene group with an oxygen atom in order to prevent metabolic β-oxidation.[20] Then, 3-oxahomoisocarbacyclins (**43**)[14] with various lower side chains were synthesized as follows. Wittig reaction of the versatile enal (**21**) and subsequent hydroboration with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by oxidative workup furnished the homoallylalcohol (**35**). The alcohol (**35**) was converted to the *tert*-butylester (**36**) by treatment with *tert*-butyl bromoacetate in 50% aqueous sodium hydroxide and methylene chloride containing the phase-transfer catalyst and then **36** was desilylated with TBAF to provide the versatile alcohol (**37**) in 65% overall yield from **21**. Horner–Emmons reaction using the various β-ketophosphonate anions and the aldehyde (**38**) derived by treatment with sulfur trioxide pyridine complex from **37** afforded the enones (**39**), which were deprotected to give the alcohols (**40**). In most cases, reduction of **40** with diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide in toluene (Yamamoto–Ono reagent)[21] efficiently gave the desired alcohols (**41**) with a small amount of epimers (**42**). The desired diols (**41**) were hydrolyzed with potassium hydroxide in aqueous methanol to afford 3-oxahomoisocarbacyclins (**43**) having various lower side chains (Scheme IV). Biological data of these compounds are summarized in Table 2.



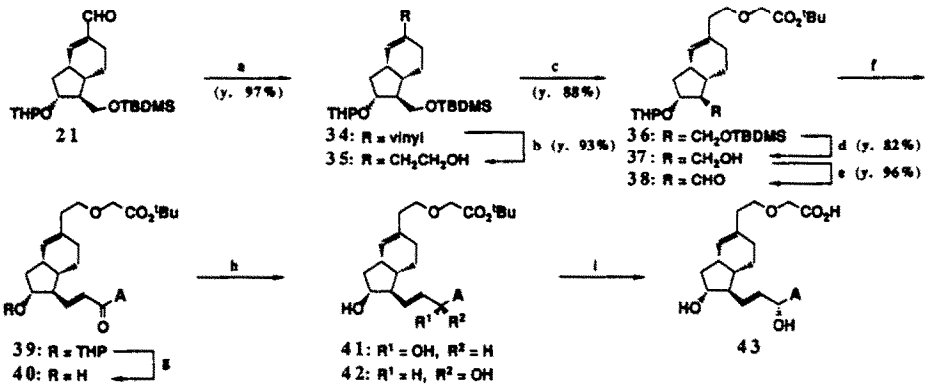
Scheme I. a) DIBAH, toluene, -78°C; b) $Ph_3P{=}CHCO_2Me$, toluene, 60°C; c) H_2, 10%Pd-C, MeOH; d) $(COCl)_2$, DMSO, Et_3N, -78°C; e) Zn-CH_2Br_2-$TiCl_4$, CH_2Cl_2, r.t.; f) Sia_2BH, THF, 0°C then 6NNaOH, 30%H_2O_2, 0°C; g) $LiAlH_4$, THF, 0°C; h) Bn_2NH•TFA, benzene, 80°C.



Scheme II. a) DIBAH, toluene, -78°C; b) BnCl, NaH, THF-HMPA, 60°C; c) Et_2AlCl, CH_2Cl_2, -25°C.



Scheme III. a) $Br^-Ph_3P^+CH_2(CH_2)_2CO_2H$, *tert*-BuOK, THF, r.t.; b) CH_2N_2 in Et_2O, 0°C; c) H_2, 10%Pd-C, MeOH, r.t.; d) TBAF, THF, r.t.; e) SO_3•Py., DMSO, Et_3N, r.t.; f) $(MeO)_2P(O)CH_2C(O)CH_2(CH_2)_3CH_3$, NaH, THF, r.t.; g) $NaBH_4$, MeOH, -25°C; h) 65%AcOH, THF, 50°C; i) 10%NaOH, MeOH, 0°C.



Scheme IV. a) $Br^-Ph_3P^+CH_3$, *tert*-BuOK, THF, r.t.; b) 9-BBN, THF, 0°C then 6NNaOH, 30%H_2O_2, r.t; c) $BrCH_2CO_2{}^tBu$, $Bu_4N^+HSO_4^-$, 50%NaOH, CH_2Cl_2, r.t.; d) TBAF, THF, r.t.; e) SO_3•Py., DMSO, Et_3N, r.t.; f) $(MeO)_2P(O)CH_2C(O)$-A, NaH, THF, r.t.; g) *p*-TsOH, MeOH, r.t.; h) DIBAH, 2,6-di-*tert*-butyl-4-methylphenol, toluene, -78°C ~ -10°C; i) 7%KOH, MeOH, r.t..

Table 2. Biological data of 3-oxahomoisocarbacyclins (**43**)

compound	A	anti-aggregatory activity IC_{50} (M)[a]		cytoprotective activity ED_{50} (μg/kg, *p.o.*)[d]	
		ADP[b]	collagen[c]	after 30 min[e]	after 4 hr[f]
43a		6.8×10^{-7}	4.2×10^{-7}	>30.0	—
43b		3.8×10^{-8}	2.9×10^{-8}	5.4	>300
43c		6.4×10^{-8}	7.8×10^{-8}	6.9	160
43d		2.5×10^{-8}	1.2×10^{-8}	>30.0	—
43e		>1.0×10^{-7}	>1.0×10^{-7}	0.44	25
43f		5.9×10^{-8}	1.0×10^{-7}[g]	>30.0	—
43g		6.0×10^{-8}	8.1×10^{-8}	>30.0	—
43h		1.8×10^{-8}	1.5×10^{-8}	>30.0	—
43i		3.2×10^{-10}	5.9×10^{-10}	2.2	—
43j		2.2×10^{-9}	3.3×10^{-9}	>30.0	—
43k		7.0×10^{-10}	2.0×10^{-9}	>30.0	—
43l		>3.0×10^{-6}	>3.0×10^{-6}	>30.0	—
43m		2.0×10^{-8}	1.5×10^{-8}	>30.0	—
43n		2.0×10^{-8}	1.5×10^{-8}	>30.0	—
43o		>3.0×10^{-6}	>3.0×10^{-6}	>30.0	—
43p		>3.0×10^{-6}	>3.0×10^{-6}	8.9	98
43q		aggregation	aggregation	8.2	83
43r		aggregation	aggregation	>30.0	—
43s		5.2×10^{-7}	4.6×10^{-7}	19.4	130
43t		>3.0×10^{-6}	>3.0×10^{-6}	>30.0	—
43u		6.2×10^{-7}	3.6×10^{-7}	4.7	56
43v		>3.0×10^{-6}	>3.0×10^{-6}	>30.0	—
43w		>3.0×10^{-6}	>3.0×10^{-6}	1.5	25
43x		8.5×10^{-7}	6.7×10^{-7}	>30.0	—
43y		aggregation	aggregation	>30.0	—
PGE_2		—	—	9.0	>300

a) IC_{50} represents the concentration that inhibits induced aggregation by 50%.
b) Inhibition of platelet aggregation induced by ADP in rabbit washed platelets.
c) Inhibition of platelet aggregation induced by collagen in rabbit washed platelets.
d) The dose that inhibits ethanol-induced gastric lesions by 50%.
e) Ethanol was given 30 min after administration of each test compound.
f) Ethanol was given 4 h after administration of each test compound.
g) **43f** produced 14.3% inhibition at this concentration.

Synthesis of (*Z*)-4-Dehydrohomoisocarbacyclins

Iseki and co-workers had introduced a conjugated diene system (*Z*, *E* geometry) between an upper side chain and the bicyclo[3.3.0]oct-2-ene nucleus,[22] obtaining more potent isocarbacyclin analogues. Therefore, the synthesis of (*Z*)-4-dehydrohomoisocarbacyclins (**51**) was next carried out according to their method. Wittig reaction of the enal (**21**) with the ylide derived from 3-ethoxycarbonylpropyltriphenylphosphonium bromide and potassium *tert*-butoxide in THF at -78°C provided the conjugated diene (**44**). A ratio of stereoisomers (*E*:*Z* = 1:24) at a double bond of **44** was defined by 200 MHz ^{1}H-NMR spectrum of the alcohol (**52**) derived from **44** by deprotection of a tetrahydropyranyl moiety with diethylaluminum chloride.[23] The conjugated diene (**44**) was desilylated with TBAF to provide the versatile alcohol (**45**) in 86 % overall yield from the aldehyde (**21**). The alcohol (**45**) was converted into (*Z*)-4-dehydrohomoisocarbacyclins (**51**) with various lower side chains in the same manner as mentioned in the synthesis of 3-oxahomoisocarbacyclins (**43**) (Scheme V). The results of preliminary biological examinations are summarized in Table 3.

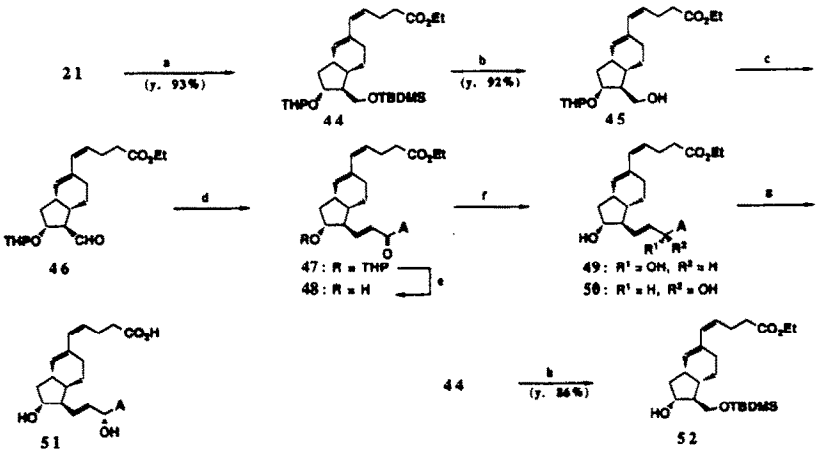
Table 3. Biological data of (*Z*)-4-dehydrohomoisocarbacyclins (**51**)

compound	A	anti-aggregatory activity IC_{50} (M)[a]		cytoprotective activity ED_{50} (μg/kg, *p.o.*)[d]	
		ADP[b]	collagen[c]	after 30 min[e]	after 4 hr[f]
51a		5.0×10^{-8}	7.3×10^{-8}	>30.0	—
51b		8.9×10^{-9}	4.9×10^{-9}	2.6	240
51c		5.2×10^{-9}	6.7×10^{-9}	6.3	47
51d		1.1×10^{-8}	7.2×10^{-9}	>30.0	—
51e		2.8×10^{-8}	4.8×10^{-8}	>30.0	—
51f		1.3×10^{-8}	5.6×10^{-9}	>30.0	—
51g		5.4×10^{-9}	2.6×10^{-9}	>30.0	—
51h		2.3×10^{-9}	1.1×10^{-9}	1.9	—
51i		3.8×10^{-10}	2.9×10^{-10}	8.0	—
51j		1.5×10^{-10}	2.1×10^{-10}	1.5	—
51k		5.2×10^{-9}	8.0×10^{-9}	3.9	127
51l		5.4×10^{-9}	3.4×10^{-9}	5.7	—

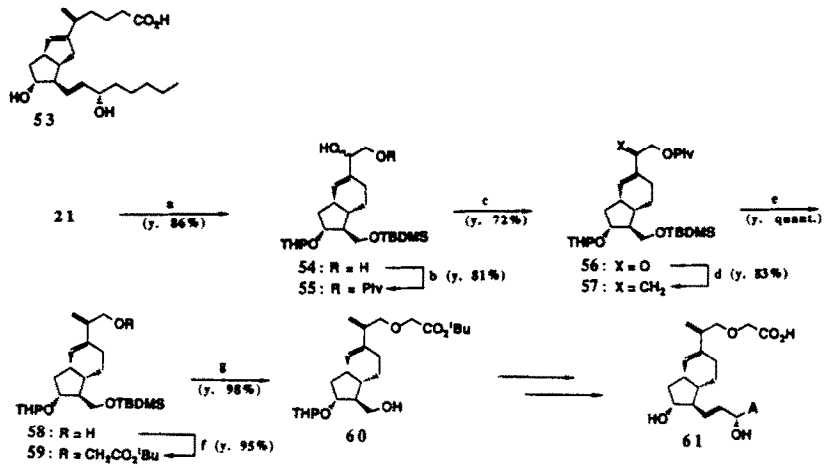
a) IC_{50} represents the concentration that inhibits induced aggregation by 50%.
b) Inhibition of platelet aggregation induced by ADP in rabbit washed platelets.
c) Inhibition of platelet aggregation induced by collagen in rabbit washed platelets.
d) The dose that inhibits ethanol-induced gastric lesions by 50%.
e) Ethanol was given 30 min after administration of each test compound.
f) Ethanol was given 4 h after administration of each test compound.

Synthesis of 5-Methylene-3-oxahomoisocarbacyclins

Subsequently, we planned to introduce a new type of upper side chain including both conjugated diene and 3-oxa system, which would increase biological activities and metabolic stability, because 5-methyleneisocarbacyclin (**53**) with a conjugated diene system, whose platelet anti-aggregatory activity in human platelet rich plasma is as potent as that of PGI_2, had been reported by Kojima and co-workers.[24] The versatile enal (**21**) was efficiently converted into the diol (**54**) by use of (isopropoxydimethylsilyl)methyl Grignard reagent[25] and subsequent oxidative workup. After selective protection of the primary alcohol moiety in the diol (**54**) with a pivaloyl group, the secondary alcohol moiety was oxidized with Collins reagent to the ketone (**56**). Construction of the conjugated diene (**57**) was achieved by Wittig reaction of **56** with the ylide derived from methyltriphenylphosphonium bromide and potassium *tert*-butoxide in THF. Reductive deprotection of a pivaloyl moiety in **57** afforded the alcohol (**58**), which was converted into the versatile alcohol (**60**) in 36% overall yield from the aldehyde (**21**) by the same reactions as described in the synthesis of 3-oxahomoisocarbacyclins (**43**). Then, the introduction of typical lower side chains was carried out in a usual manner to give 5-methylene-3-oxahomoisocarbacyclins (**61**) (Scheme VI). The results of preliminary biological examinations concerning these analogues are given in Table 4.



Scheme V. a) $Br^-Ph_3P^+CH_2(CH_2)_2CO_2Et$, *tert*-BuOK, THF, -78°C ~ r.t.; b) TBAF, THF, r.t.; c) SO_3·Py., DMSO, Et_3N, r.t.; d) $(MeO)_2P(O)CH_2C(O)$-A, NaH, THF, r.t.; e) *p*-TsOH, MeOH, r.t.; f) DIBAH, 2,6-di-*tert*-butyl-4-methylphenol, toluene, -78°C ~ -10°C; g) 10%NaOH, EtOH, 0°C; h)Et_2AlCl, CH_2Cl_2, 0°C.



Scheme VI. a) *iso*-$PrO(CH_3)_2SiCH_2MgCl$, THF, -10°C then $NaHCO_3$, 30%H_2O_2, MeOH–THF, reflux; b) $(CH_3)_3CCOCl$, Et_3N, 4-DMAP, CH_2Cl_2, r.t.; c) CrO_3·2Py., CH_2Cl_2, r.t.; d) $Br^-PPh_3P^+CH_3$, *tert*-BuOK, THF, r.t.; e) $LiAlH_4$, Et_2O, r.t.; f) $BrCH_2CO_2{}^tBu$, $Bu_4N{\cdot}HSO_4$, 50%NaOH, CH_2Cl_2, r.t. ~ 30°C; g) TBAF, THF, r.t.

Table 4. Biological data of 5-methylene-3-oxahomoisocarbacyclins (**61**)

compound	A	ano-aggregatory activity IC_{50} (M)[a]		cytoprotective activity ED_{50} (μg/kg, *p.o.*)[d]	
		ADP[b]	collagen[c]	after 30 min[e]	after 4 hr[f]
61a	~~	2.9×10^{-7}	1.3×10^{-7}	>30.0	—
61b	><~	1.3×10^{-8}	1.3×10^{-8}	9.5	—
61c	>O⬡	$>1.0\times10^{-7}$	$>1.0\times10^{-7}$	>30.0	—

a) IC_{50} represents the concentration that inhibits induced aggregation by 50%.
b) Inhibition of platelet aggregation induced by ADP in rabbit washed platelets.
c) Inhibition of platelet aggregation induced by collagen in rabbit washed platelets.
d) The dose that inhibits ethanol-induced gastric lesions by 50%.
e) Ethanol was given 30 min after administration of each test compound.
f) Ethanol was given 4 h after administration of each test compound.

Synthesis of 13-Dehydrohomoisocarbacyclins

In order to impede a metabolic inactivation by PG Δ^{13}-reductase,[26] a conversion of the C_{13} double bond of homoisocarbacyclin analogues (**I**) into a triple bond, namely synthesis of 13-dehydro one (**II**), was carried out (Figure 3).

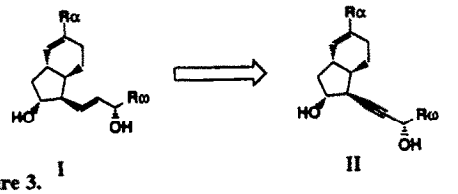


Figure 3.

Several methods for synthesis of 13-dehydroprostaglandin analogues have been reported to date.[9a, 22, 27, 28] We have also previously reported a novel and general method for the introduction of a carbon–carbon triple bond at C_{13} in PG synthesis through an aldol reaction of the aldehyde (**64**) with the α-bromoenolate anion (**63**) generated from the 1,1-dibromoketone (**62**) and subsequent dehydration as a key step (Figure 4)[2,9] So, an attempt to synthesize 13-dehydrohomoisocarbacyclins was made according to our method.

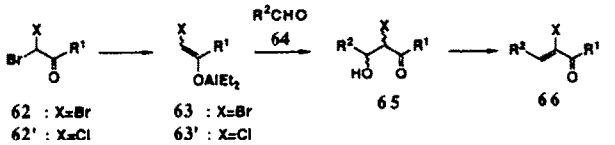


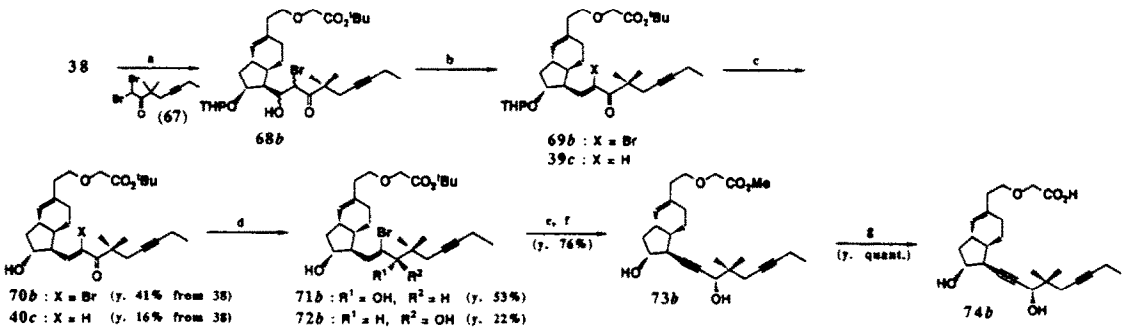
Figure 4.

An aldol reaction of the aldehyde (**38**) with the α-bromoenolate anion derived from the 1,1-dibromoketone (**67**), zinc powder and diethylaluminum chloride containing a catalytic amount of copper (I) bromide in THF at -20°C for *ca.* 30 min provided the α-bromo-β-hydroxyketone (**68b**). Dehydration of **68b** via the mesylate followed by acidic cleavage of a tetrahydropyranyl moiety furnished the α-bromoenone (**70b**) in 41 % overall yield from **38** as a single stereoisomer together with the undesired enone (**40c**, y. 16%).[30] Reduction of **70b** with diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide in toluene at -78°C to -10°C to give the diol (**71b**) in 53% yield together with the undesired diol (**72b**, y. 22 %). Dehydrobromination of **71b** in 50 % aqueous sodium hydroxide and toluene–ether (2:1) in the presence of tetrabutylammonium hydrogen sulfate provided **74b**, which was followed by esterification with diazomethane in ether for subsequent purification to give the methylester (**73b**). Hydrolysis of **73b** with sodium hydroxide in aqueous methanol afforded 13-dehydrohomoisocarbacyclin analogue (**74b**) in a nearly quantitative yield (Scheme VII).

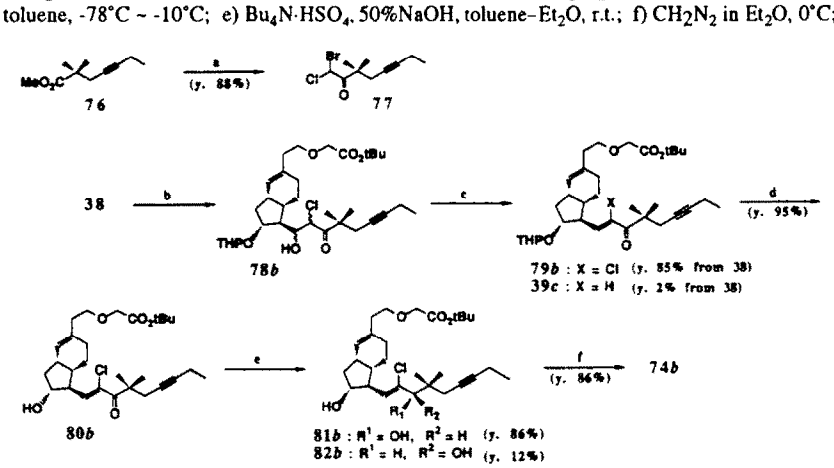
By using the same sequence of reactions as described in the synthesis of **74b**, the aldehydes (**38**, **46**) were led to various 13-dehydrohomoisocarbacyclins (**74**, **75**) with a variety of lower side chains (Table 5).

Most of analogues (**74** and **75**) including 13-dehydro moiety, especially the analogue **74b**,[31] were found to have predominant properties compared to PGI_2 and other PGI_2 analogues, showing extremely potent activities and excellent duration in the present assay system. However, the synthetic method described above was not satisfactory in regard to the yield at the stage of the aldol reaction and subsequent dehydration because of concomitant formation of the undesired enone (**40c**). The enone (**40c**) was produced through debromination of the α-bromo-β-hydroxyketone (**68b**) with zinc, so we have continued to study an improved synthetic method for 13-dehydro-homoisocarbacyclin analogues. An aldol reaction was conducted with the α-chloroenolate anion (**63'**) derived from the 1-bromo-1-chloroketone (**62'**), instead of **63**, because the chloro derivative may be preventable from being reduced with zinc. At the outset, the 1-bromo-1-chloroketone (**77**) was efficiently synthesized from the ester (**76**) by utilizing (bromochloromethyl)lithium.[32]

Although our previous method using the α-bromoenolate anion afforded the α-bromoenone (**70b**) (y. 41 %) and the enone (**40c**) (y. 16 %), the aldol reaction of **38** with the 1-bromo-1-chloroketone (**77**) and subsequent dehydration under the same conditions described above, as expected, gave the desired α-chloroenone (**79b**) in excellent yield (85 %) together with a small amount of the undesired enone (**39c**) (y. 2 %). We presumed that the stereochemistry of **79b** would be a desired *Z* form, which was confirmed at the dehydrochlorination step.[33] Conversion of the α-chloroenone (**79b**) into 13-dehydro-homoisocarbacyclin analogue (**74b**) was accomplished in the same way as described above (Scheme VIII).[34]

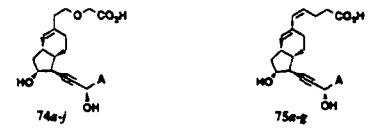


Scheme VII. a) 67, Zn–Et_2AlCl–CuBr, THF, -20°C ~ 0°C; b)MsCl, Et_3N, DBU, CH_2Cl_2, 0°C; c) 65%AcOH, THF, 65°C; d) DIBAH, 2,6-di-*tert*-butyl-4-methylphenol, toluene, -78°C ~ -10°C; e) $Bu_4N{\cdot}HSO_4$, 50%NaOH, toluene–Et_2O, r.t.; f) CH_2N_2 in Et_2O, 0°C; g) 10%NaOH, MeOH, 0°C.



Scheme VIII. a) $BrCH_2Cl$, LDA, THF-Et_2O, -100°C ~ -78°C; b) 77, Zn-Et_2AlCl-CuBr, THF, -20°C; c) MsCl, Et_3N, DBU, CH_2Cl_2, 0°C; d) *p*-TsOH, MeOH, r.t.; e) DIBAH, 2,6-di-*tert*-butyl-4-methylphenol, toluene, -78°C ~ -60°C; f) $Bu_4N{\cdot}HSO_4$, 50%NaOH, toluene, 65°C.

Table 5. Biological data of 13-dehydrohomoisocarbacyclins (**74** and **75**)



74a-j 75a-g

compound	A	anti-aggregatory activity IC_{50} (M) [a]		cytoprotective activity ED_{50} (μg/kg, *p.o.*) [d]	
		ADP [b]	collagen [c]	after 30 min [e]	after 4 hr [f]
74a	~~	1.8×10^{-7}	6.7×10^{-8}	>30.0	—
74b	×~~	2.7×10^{-9}	8.6×10^{-9}	15.3	—
74c	Y~~	5.4×10^{-9}	3.4×10^{-9}	>30.0	—
74d	-○	2.1×10^{-8}	1.9×10^{-8}	31.3	67
74e	-○○	2.9×10^{-10}	2.4×10^{-10}	3.6	—
74f	-○~	2.1×10^{-9}	1.6×10^{-9}	4.7	—
74g	-○Y	3.6×10^{-10}	2.4×10^{-10}	—	—
74h	-○□	4.2×10^{-9}	9.5×10^{-9}	2.5	—
74i	~○	3.1×10^{-8}	2.6×10^{-8}	>30.0	—
74j	×○□	$>1.0 \times 10^{-7}$	$>1.0 \times 10^{-7}$	>30.0	—
75a	~~	2.5×10^{-8}	2.6×10^{-8}	>30.0	—
75b	×~~	1.3×10^{-9}	5.8×10^{-10}	0.97	3.2
75c	Y~~	1.7×10^{-8}	1.8×10^{-8}	>30.0	—
75d	-○	4.9×10^{-9}	4.4×10^{-9}	1.7	—
75e	-○○	2.6×10^{-10}	1.7×10^{-10}	3.3	—
75f	-○~	1.2×10^{-9}	1.1×10^{-9}	2.6	—
75g	-○□	1.3×10^{-9}	2.3×10^{-9}	2.2	—
PGI_2		2.9×10^{-9}	3.4×10^{-9}	>30.0	—

a) IC_{50} represents the concentration that inhibits induced aggregation by 50%.
b) Inhibition of platelet aggregation induced by ADP in rabbit washed platelets.
c) Inhibition of platelet aggregation induced by collagen in rabbit washed platelets.
d) The dose that inhibits ethanol-induced gastric lesions by 50%.
e) Ethanol was given 30 min after administration of each test compound.
f) Ethanol was given 4 h after administration of each test compound.

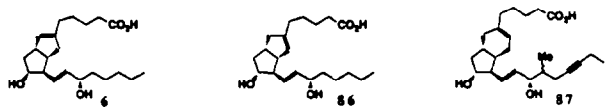
Synthesis of 13,14-Dihydrohomoisocarbacyclins

Next we turned our attention to the synthesis of 13,14-dihydrohomoisocarbacyclins, which would show the higher chemical and metabolic stabilities.[35] At the outset, the 13,14-dihydroanalogue (**85a**) was synthesized according to the following sequence. Deprotection of the tetrahydropyranyl group in **47j** followed by 1,4-reduction of the enone (**48j**) with sodium bis(2-methoxyethoxy)-aluminum hydride (Vitride®: 70 % in benzene) and copper (I) bromide[36] in the presence of 2-butanol in THF at -78 °C afforded the saturated ketone (**83a**) in 86% overall yield. Reduction of **83a** with diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide in toluene at -78 °C to -20 °C for 2 h gave the diol (**84a**) as a single spot on TLC. Finally, **84a** was hydrolyzed with sodium hydroxide in aqueous methanol to afford the desired compound (**85a**) (Scheme IX), which was identified as an epimeric mixture of a hydroxyl group at C_{15} by HPLC analysis [16:1 (**85a**α: **85a**β)]. On the other hand, the ratio of the epimers (**85a**α:**85a**β) was determined to be *ca.* 1:1 when sodium borohydride in methanol instead of diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide in toluene was used.[37]

By using a sequence of reactions similar to that described in the synthesis of **85a**, the enones (**47i, 47c, 39k, 39j**) were led to the 13,14-dihydrohomoisocarbacyclins (**85b–85e**) (Scheme X). These biological results are shown in Table 6.

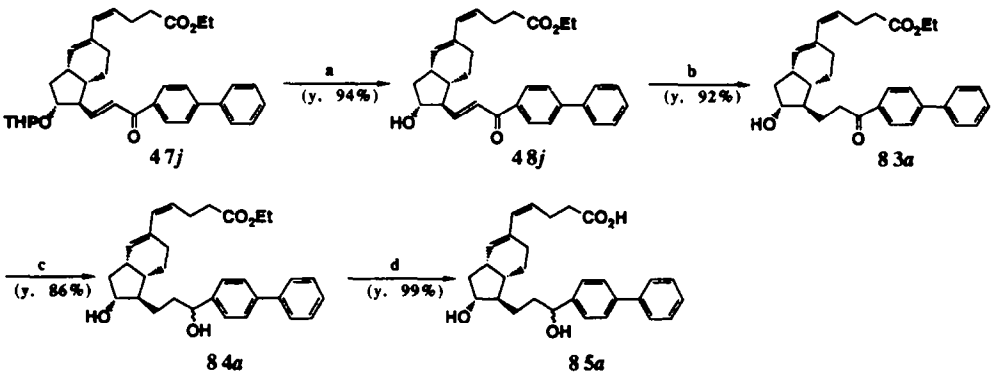
Synthesis of *cis*-Bicyclo[4.3.0]non-3-ene Analogues of Homoisocarbacyclin

During the study of homoisocarbacyclin analogue synthesis, we had a plan to synthesize a regioisomeric analogue of homoisocarbacyclin (**87**)[13] with *cis*-bicyclo[4.3.0]non-3-ene nucleus in view of the structure–activity relationship. The regioisomer of isocarbacyclin (**86**), which was synthesized by the Teikyo group, was reported to be less potent than isocarbacyclin (**6**).[38]



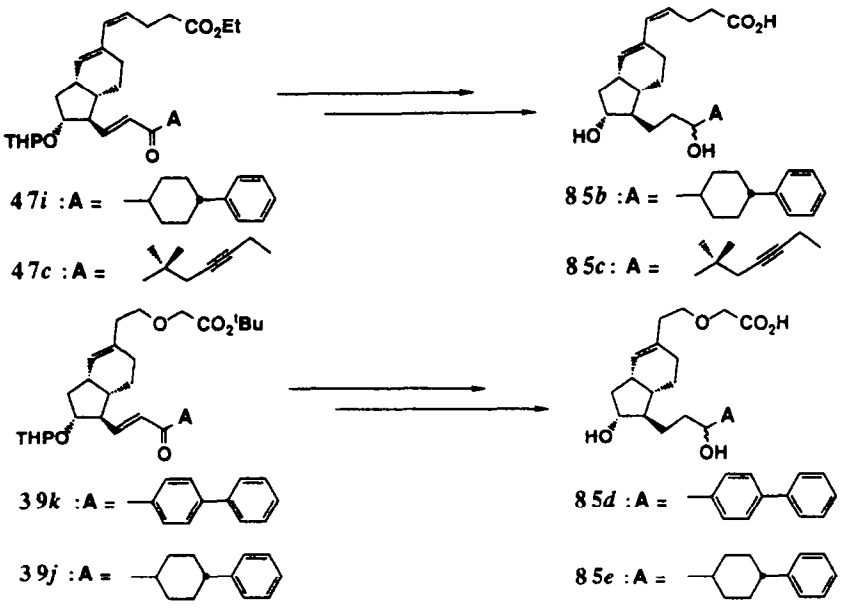
6 86 87

Figure 5.



47j 48j 83a 84a 85a

Scheme IX. a) *p*-TsOH, MeOH-THF, r.t.; b) Vitride®, CuBr, *sec*-BuOH, THF, -78°C; c) DIBAH, 2,6-di-*tert*-butyl-4-methylphenol, toluene, -78°C ~ -20°C; d) 10%NaOH, EtOH, r.t.



Scheme X.

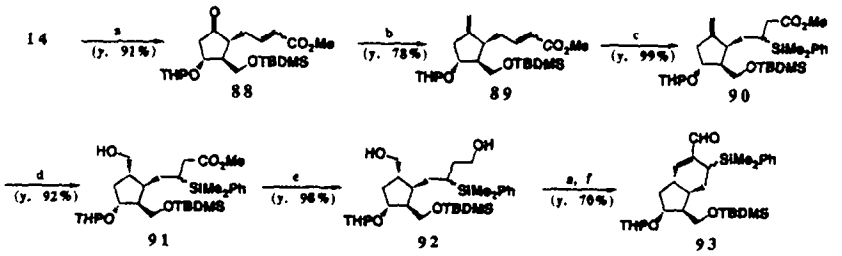
Table 6. Biological data of 13,14-dihydrohomoisocarbacyclins (**85**)

compound	A	anti-aggregatory activity IC_{50} (M)[a] ADP[b]	collagen[c]	cytoprotective activity ED_{50} (μg/kg, p.o.)[d] after 30 min[e]	after 4 hr[f]
(Z) 4-dehydro analogues					
85a[g]		4.2×10^{-10}	2.8×10^{-10}	>30.0	—
85b[g]		2.8×10^{-8}	3.0×10^{-8}	2.8	—
85c[h]		2.5×10^{-8}	3.4×10^{-8}	>30.0	—
3-oxa analogues					
85d[g]		3.1×10^{-8}	2.4×10^{-8}	2.4	—
85e[g]		1.4×10^{-8}	2.0×10^{-8}	>30.0	—

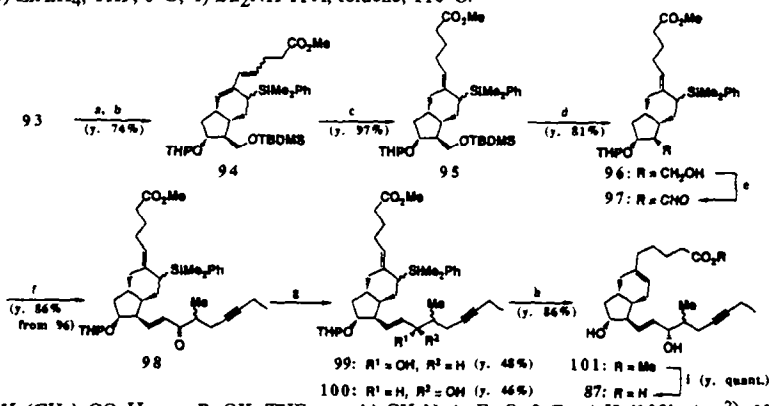
a) IC_{50} represents the concentration that inhibits induced aggregation by 50%.
b) Inhibition of platelet aggregation induced by ADP in rabbit washed platelets.
c) Inhibition of platelet aggregation induced by collagen in rabbit washed platelets.
d) The dose that inhibits ethanol-induced gastric lesions by 50%
e) Ethanol was given 30 min after administration of each test compound.
f) Ethanol was given 4 h after adminstration of each test compound.
g) The ratio of epimers (**85**α:**85**β) was determined by HPLC analysis as follows, **85a** (16:1), **85b** (4:1), **85d** (1:1), **85e** (1:1).
h) The α-epimer was isolated by silica gel column chromatography and used for biological evaluation.

For a stereo- and regiocontrolled synthesis of the *cis*-bicyclo[4.3.0]non-3-ene analogue (**87**), we utilized 1,4-hydrogenation of the conjugated diene (**94**) having a dimethylphenylsilyl moiety by use of Ar·$Cr(CO)_3$ catalyst[39] and subsequent protodesilylation of the resulting allylic silane derivative (**99**) as key steps. Toward this end, the versatile enal (**93**) was prepared in a regio- and stereocontrolled manner. The hydroxy-ester (**14**) was converted into the α,β-unsaturated ester (**89**) in two steps ((i) Swern oxidation, (ii) Zn–CH_2Br_2–$TiCl_4$ in THF). Treatment of **89** with dimethylphenylsilyllithium and copper (I) cyanide[40] in THF at 0°C afforded the β-dimethylphenylsilyl-ester (**90**) as an epimeric mixture. Hydroboration of **90** with disiamylborane followed by oxidative workup gave the alcohol (**91**) in a stereocontrolled manner, which was then reduced with lithium aluminum hydride in THF to furnish the diol (**92**). Swern oxidation of the diol (**92**) provided the dialdehyde, which, after workup, was treated with dibenzylammonium trifluoroacetate in toluene at 110 °C to afford the versatile enal (**93**)[41] in 70% yield (Scheme XI).

With the versatile key intermediate in hand, the subsequent study was carried out to construct the upper side chain. Wittig reaction of **93** with the ylide derived from 3-carboxypropyltriphenylphosphonium bromide and potassium *tert*-butoxide in THF gave the diene, which was subsequently converted into **94** by treatment with ethereal diazomethane (*E*:*Z* = *ca.* 1:2). 1,4-Hydrogenation of the conjugated diene (**94**) with a catalytic amount of naphthalene·$Cr(CO)_3$ in degassed THF at 50°C for 12 h (100 atm of H_2 pressure) afforded the *E*-allylic silane (**95**). The stereochemistry of **95** was tentatively determined to be *E* on the basis of the mechanism of the 1,4-hydrogenation reaction.[39] Removal of a *tert*-butyldimethylsilyl group in **95** by reaction with TBAF led to the versatile alcohol (**96**). Oxidation of **96** with sulfur trioxide pyridine complex and triethylamine in DMSO afforded the aldehyde (**97**), which was directly condensed with the β-ketophosphonate anion derived from racemic dimethyl (3-methyl-2-oxo-5-octynyl)phosphonate and sodium hydride in THF to furnish the enone (**98**). The enone (**98**) was then reduced with sodium borohydride in methanol, giving the desired alcohol (**99**) together with an epimer (**100**). Treatment of **99** with *p*-toluenesulfonic acid in wet acetonitrile[42] provided the diol (**101**) in 86 % yield. The 400 MHz ^{1}H-NMR spectrum of **101** strongly indicated the absence of the regioisomers **102** and **103** (Figure 6),[43,44] hereby giving the unequivocal proof for the regiochemistry of the present synthetic technology. Hydrolysis of **101** with sodium hydroxide in aqueous methanol afforded the *cis*-bicyclo[4.3.0]non-3-ene analogue of homoisocarbacyclin (**87**) (Scheme XII). By the same procedure, the analogue (**104**) was also synthesized.



Scheme XI. a) $(COCl)_2$, DMSO, Et_3N, -78°C; b) Zn-CH_2Br_2-$TiCl_4$, CH_2Cl_2, r.t.; c) $(Me_2PhSi)_2Cu(CN)Li_2$, THF, 0°C; d) Sia_2BH, THF, 0°C then 6NNaOH, 30%H_2O_2, r.t.; e) $LiAlH_4$, THF, 0°C; f) Bn_2NH·TFA, toluene, 110°C.



Scheme XII. a) $Br^-Ph_3P^+CH_2(CH_2)_2CO_2H$, *tert*-BuOK, THF, r.t.; b) CH_2N_2 in Et_2O, 0°C; c) H_2(100kg/cm^2), Np·$Cr(CO)_3$, THF, 50°C; d) TBAF, THF, r.t.; e) SO_3·Py., DMSO, Et_3N, r.t.; f) $(MeO)_2P(O)CH_2C(O)CH(Me)CH_2CCEt$, NaH, r.t.; g) $NaBH_4$, MeOH, -25°C; h) *p*-TsOH, CH_3CN-H_2O(98:2), r.t.; i) 10%NaOH, MeOH, 0°C.

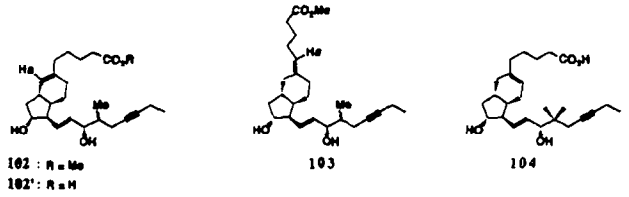


Figure 6.

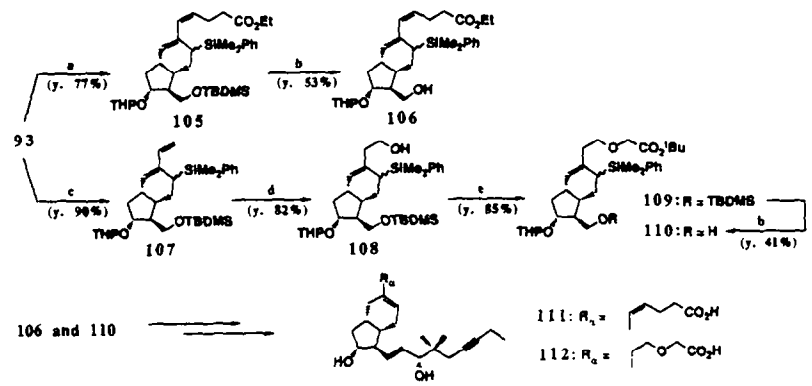
Furthermore, analogues (**111** and **112**) including two types of the upper side chain were synthesized in the same manner (Scheme XIII).

Preliminary biological results of the *cis*-bicyclo[4.3.0]non-3-ene analogues of homoisocarbacyclin are shown in Table 7.

Table 7. Biological data of *cis*-bicyclo[4.3.0]non-3-ene analogues of homoisocarbacyclin

compound	anti-aggregatory activity IC_{50} (M) [a]		cytoprotective activity ED_{50} (μg/kg, *p.o.*) [d]	
	ADP [b]	collagen [c]	after 30 min [e]	after 4 hr [f]
87	2.2×10^{-9}	2.4×10^{-8}	30.0 [g]	—
104	9.1×10^{-8}	6.2×10^{-8}	>30.0	—
111	5.3×10^{-8}	4.5×10^{-8}	>30.0	—
112	5.2×10^{-8}	5.8×10^{-8}	17.0	—
102'	2.3×10^{-8}	2.7×10^{-8}	30.0 [h]	—

a) IC_{50} represents the concentration that inhibits induced aggregation by 50%.
b) Inhibition of platelet aggregation induced by ADP in rabbit washed platelets.
c) Inhibition of platelet aggregation induced by collagen in rabbit washed platelets.
d) The dose that inhibits ethanol-induced gastric lesions by 50%.
e) Ethanol was given 30 min after administration of each test compound.
f) Ethanol was given 4 h after administration of each test compound.
g) **87** produced 61.4% inhibition at this dose.
h) **102'** produced 79.1% inhibition at this dose.



Scheme XIII. a) $Br^-Ph_3P^+CH_2(CH_2)_2CO_2Et$, *tert*-BuOK, THF, -78°C ~ 0°C; b) TBAF, THF, r.t.; c) $Br^-Ph_3P^+CH_3$, *tert*-BuOK, THF, r.t.; d) Sia_2BH, THF, 0°C then 6NNaOH, 30%H_2O_2, r.t.; e) $BrCH_2CO_2{}^tBu$, Bu_4N·HSO_4, 50%NaOH, CH_2Cl_2, r.t.

Biological Results and Discussion

The many compounds synthesized were evaluated as inhibitors of adenosine diphosphate (ADP)- or collagen-induced aggregation in rabbit washed platelets prepared according to the previously reported experimental protocol[45] and the results are presented in Tables 1–7. With respect to cytoprotective effect of the various analogues, the experimental gastric lesions caused by orally administrated ethanol in rats were employed for evaluation according to the method reported by Robert and co-workers.[46]

In these assays, prostacyclin (**1**), isocarbacyclin (**6**) and iloprost (**7**) inhibit ADP-induced platelets aggregation with IC_{50} values of 2.9, 9.4 and 1.5 x 10^{-9}M, respectively.[47] The novel homoisocarbacyclin (**10**) synthesized in the present study exhibits an IC_{50} value of 2.9 x 10^{-7}M, which is less effective than isocarbacyclin (**6**), and similar results are obtained in the test of collagen-induced platelet aggregation (Table 1). However, **10** is demonstrated to have a similar pharmacological profile to that of **6**. Namely, both compounds were observed to increase the coronary arterial blood flow in experimental animal models, and time-course changes of diastolic blood pressure in the same species exhibited almost the same pattern after the intravenous administration of **6** and **10** (data not shown). Among other known analogues with the enlarged ring system, the analogue (**11**) was reported to have an activity as equipotent as that of the parent compound, prostacyclin (**1**).[12] On the other hand, a homologous compound of carbacyclin (**5**) was reported to lose completely the inhibiting effect on ADP-induced platelet aggregation.[44] In the present case, homoisocarbacyclin was found to retain the weaker biological activities. Furthermore, from the standpoint of the separation of platelet anti-aggregatory activity from hypotensive effect, it seems that **10** might have a better property than those of the other PGI_2 analogues which have already been reported, because the drop in blood pressure is considered to be an unfavorable effect for clinical use. Thus, homoisocarbacyclin (**10**) was considered to be fairly suitable as a leading compound for a new drug.

We, therefore, attempted to compensate the decreased activities of the compound (**10**) by chemical modifications of the upper and lower side chains. The series of naturally occurring prostaglandins and those analogues, as already reported,[48] are metabolically inactivated in a body through enzymatic β- and ω-oxidations, reduction by PG Δ^{13}-reductase and oxidation by 15-hydroxy-PG-dehydrogenase. In order to avoid these metabolic dispositions, many chemical modifications have been investigated in various manners. On the basis of findings concerning the upper and lower side chains reported, we planned to make the following structural changes in homoisocarbacyclin (**10**) with the *cis*-bicyclo[4.3.0]non-2-ene nucleus. (1) A replacement of the methylene carbon at C_3 position with an oxygen atom in the upper side chain. (2) An introduction of a double bond in the upper side chain conjugated with the inner double bond in the six-membered ring, of which usefulness have been previously reported by Iseki and co-workers in the bicyclo[3.3.0]oct-2-ene nucleus system.[2e,22] (3) Modifications of the straight alkyl moiety in the lower side chain. (4) Changes of the C_{13} double bond to a single bond or a triple bond in the lower side chain.

As a result of these studies, an increase of platelet anti-aggregatory activities are found in some 3-oxa analogues (**43**) with *trans*-4-substituted cyclohexyl (**43i,j**) and biphenyl moieties (**43k**) in the lower side chain, of which methylene carbon at C_3 is changed to an oxygen atom in the upper side chain (Table 2). Apart from them, cyclopentylmethyl analogue (**43e**) and phenoxymethyl analogues (**43p, q, u** and **43w**) are found to be potent and lasting inhibitors to ethanol-induced gastric lesions. In particular, **43w** exhibits a good selective action, excluding any platelet anti-aggregatory activities. Pharmacological profile of **43w** was previously evaluated by Okabe and co-workers in several experimental animal models.[49]

(*Z*)-4-Dehydrohomoisocarbacyclin (**51a**), modified with the conjugated diene system in the upper side chain, is demonstrated to be about five to ten times as active as the 3-oxa analogue (**43a**) in the platelet anti-aggregatory activities, as shown in Table 3. In general, (*Z*)-4-dehydro-homoisocarbacyclins (**51**) tend to show higher anti-aggregatory activities compared to 3-oxa analogues (**43**) with the similar substituent in the lower side chain, and 3-oxa analogues bearing a phenoxy moiety tend to have a selective property in biological activities.

With a view to improving the biological activities and metabolic stabilities of the analogue further, we were attracted to constructing the upper side chain with both 3-oxa and conjugated diene systems. The results of pharmacological examinations indicate that the analogue (**61a**) with "5-methylene-3-oxa" system in the upper side chain shows approximately twice the potency of the 3-oxa analogue (**43a**) (Table 4).

In order to impede a metabolic inactivation by PG Δ^{13}-reductase, some synthetic studies on the 13-dehydro derivatives of PGI_2 mimics were reported, showing that the dehydrogenated analogues with a triple bond at C_{13} in the lower side chain enhanced the intrinsic potencies and metabolic stabilities.[2e,9a] Therefore, we have tried a conversion of the C_{13} double bond into a triple bond in the lower side chain of homoisocarbacyclin analogues (**I**), namely synthesis of 13-dehydro one (**II**) which have 3-oxa or (*Z*)-4-dehydro type upper side chain and various lower side chains (Figure 3). The results of examinations on platelet anti-aggregatory activities and cytoprotective activities of 13-dehydrohomoisocarbacyclins (**74** and **75**) are presented in Table 5. Among them, the analogues **74e, g** and **75e** are verified to be extremely potent inhibitors of platelet aggregation in rabbit washed platelets with IC_{50} values of the order 10^{-10} M. In addition, the analogue **75b** is shown to possess a potent and long-lasting cyto-protective activity, of which inhibitory activities (ED_{50}) in ethanol-induced gastric lesions at 1.5 and 5 h after oral administration are 0.97 μg/kg and 3.2 μg/kg, respectively.

Another trial to prevent the lower side chain from being metabolized by PG Δ^{13}-reductase was directed to synthesize 13,14-dihydroanalogues (**85**) in which the double bond at the C_{13} position was saturated. One of the dihydro-analogues (**85a**) is observed to have very strong inhibiting activities (IC_{50} = 4.2 x 10^{-10} M) against ADP-induced platelet aggregation in rabbit washed platelets (Table 6).

Considering another aspect of the chemical modification of *cis*-bicyclo[4.3.0]nonene ring system, we attempted to prepare a regioisomeric ring system with a *cis*-bicyclo[4.3.0]non-3-ene nucleus. As shown in Table 7, the inhibitory potency of **87** is an eighth as active as that of PGI_2 in platelet aggregation induced by ADP in rabbit washed platelets. It is noteworthy that the regioisomeric analogue of homoisocarbacyclin with the *cis*-bicyclo-[4.3.0]non-3-ene ring system retains the PGI_2-like activities, because a remarkable reduction of the activities was caused in the case of the regioisomeric analogue of isocarbacyclin (**6**) with bicyclo[3.3.0]oct-3-ene ring system.[38]

Thus, among many homoisocarbacyclin analogues synthesized in the present studies, the analogues including 1,1-dimethyl-3-hexynyl, 4-biphenyl or 4-substituted cyclohexyl moieties in the lower side chain are shown to have superior properties to PGI_2 in our pharmacological evaluation system. In consideration of the results of preliminary biological studies, several analogues **43k, 51j, 74b, 74e, 74g, 75b, 75e** and **85a** were selected for the next step of pharmacological evaluation and were examined on *ex vivo* platelet anti-aggregatory activities under intravenous infusion and by oral administration in rabbits. At the same time, the hypotensive effects on blood pressure in the same species were also evaluated. It was found that the biphenyl moiety included in analogues (**43k, 51j**) exhibited a tendency to accelerate decomposition of themselves in acidic medium. Especially, **51j** was decomposed gradually even in neutral solution in spite of exhibiting very potent activities. The pharmacological results examined are given in Tables 8 and 9. In view of separation of platelet anti-aggregatory activities from hypotensive effect, the analogues **74b, 75e** and **85a** are shown to have excellent pharmacological properties.

Meanwhile, the natural prostaglandins and their analogues contingently exhibit unfavorable effects, such as diarrhea based on an entero-pooling activity. In fact, pharmacological profiles of both analogues (**75e**) and (**85a**) are considered to be unsatisfactory in comparison with that of **74b** because of insufficient separation of the undesired effect.[50] Furthermore, as shown in Table 9, the analogue (**74b**) is demonstrated to have a lasting activity of anti-aggregation *ex vivo* after oral administration of 0.3 and 1.0 mg/kg presumably owing to its chemical and metabolic stabilities. While, a duration of activity for the analogue (**74g**) is shorter than that of **74b** under the same conditions, although **74g** shows extremely potent activity. Thus, in consequence of these pharmacological examinations, the analogue (**74b**) is characterized to have a potent and long-lasting activity in inhibiting platelet aggregation and a good selectivity in pharmacological actions, which suggests possibility to be used for the oral route.

Table 8. *Ex vivo* inhibitory activity of homoisocarbacyclins on platelet aggregation and hypotensive effect in rabbits[a]

compound	intravenous infusion (μg/kg/min)[b]	inhibition of platelet aggregation (%)[c]	hypotensive effect (mmHg)[d]
43k	10.0	100 ± 0	-56.8 ± 5.4
	3.0	81.5 ± 5.6	-30.1 ± 3.3
	1.0	9.9 ± 5.2	-9.1 ± 1.8
74b	10.0	100 ± 0	-57.9 ± 6.9
	3.0	91.3 ± 8.7	-36.1 ± 2.9
	1.0	80.5 ± 19.5	-8.8 ± 3.0
74e	0.3	22.0 ± 17.4	-21.6 ± 2.1
75b	10.0	100 ± 0	-56.8 ± 5.4
	3.0	84.0 ± 14.4	-30.1 ± 3.3
	1.0	32.6 ± 19.6	-9.1 ± 1.8
75e	0.3	97.4[e]	-36.5[e]
	0.1	83.1[e]	-8.4[e]
85a	1.0	93.0 ± 7.0	-16.3 ± 4.7
	0.1	45.9 ± 29.2	-6.0 ± 8.8
PGI_2	10.0	81.5 ± 11.4	-74.1 ± 3.2
	3.0	56.1 ± 27.7	-54.7 ± 2.7
	1.0	25.3 ± 9.5	-48.6 ± 7.2

a) The values of anti-aggegatory activity and hypotensive effect represents mean ± S.E. that was calculated by experimental results from three to four animals.
b) Intravenous infusion was performed to each animal in a period of 20 min.
c) Blood was collected from the carotid artery vein 15 min after initiating infusion, and aggregation was induced by 5μg/ml of collagen.
d) The maximum reduction of mean blood pressure during infusion for 20 min was compared to the initial value.
e) The average value of two cases is given.

Table 9. Inhibitory activity by oral administration of **74b** and **74g** on *ex vivo* platelet aggregation in rabbits

compound	dose (mg/kg, p.o.)	time-course changes of inhibition rate on platelet aggregation (%)[a]					
		30	60	120	180	300	360 min
74b	1.0	56.2 ± 14.5	60.1 ± 11.2	54.4 ± 23.3	65.9 ± 2.3	79.4 ± 12.3	66.4 ± 11.0
	0.3	30.2 ± 9.2	42.9 ± 2.1	59.1 ± 16.1	48.2 ± 17.7	49.6 ± 23.7	49.5 ± 22.8
	0.1	8.7 ± 8.2	9.0 ± 7.5	7.4 ± 6.1	0.8 ± 0.8	—	—
74g	0.1	56.9 ± 11.7	53.0 ± 14.4	49.7 ± 16.5	39.2 ± 19.7	—	—
	0.03	51.4 ± 10.8	47.7 ± 11.3	39.2 ± 7.5	37.6 ± 13.4	10.7 ± 9.0	5.8 ± 5.4
	0.01	7.3[b]	0.8[b]	9.7[b]	0[b]	—	—

a) Platelet aggregation was induced by 10μM of ADP, and inhibition rate was compared to the initial value. The values represents mean ± S.E. that was calculated by experimental results from three to four animals.
b) The average value of two cases is given.

On the other hand, the analogues (**43w**) and (**75b**) were selected as the most potent compounds from the examination on cytoprotective activity, and were further evaluated by comparative examinations of inhibitory activities against gastric lesions in some experimental animal models. Both analogues **43w** (TY-10957) and **75b** were found to possess very potent anti-ulcer activities in these assay systems (Table 10), and the pharmacological results of **43w** obtained in the present experiments were evaluated to be substantially similar to the previously reported data.[49]

Table 10. Anti-ulcer and anti-secretory effects of **43w** and **75b** in several gastrointestinal animals

compound	0.6N HCl-induced gastric lesions ED_{50} (μg/kg, p.o.)[a]	indomethacin-induced gastric lesions ED_{50} (μg/kg, p.o.)[a]	water-immersion stress-induced gastric lesions ED_{50} (μg/kg, p.o.)[a]	cysteamine-induced duodenal ulcers ED_{50} (μg/kg, p.o.)[a]	suppression of acid secretion stimulated by pentagastrin
43w	17.3 (35.0 ~ 2.2)	36.8 (53.2 ~ 19.8)	>100	76.7 x 2 (127.8 ~ 36.3) x 2	duration time: 20 min[b] at 30μg/kg, i.v.
75b	6.3 (12.4 ~ 1.4)	—	65.5 (89.2 ~ 45.2)	>100	duration time: 100 min[b] at 30μg/kg, i.v.

a) ED_{50} represents mean value and was calculated by probit method based on linear reggression from three or four dose groups of five to ten animals. The values in parentheses are 95% confidence limits.
b) The secretion was suppressed by more than 50% compared to the initial level in five to eight animals, and the duration time is expressed in mean value.

In conclusion, a variety of homoisocarbacyclin analogues with many kinds of upper and lower side chains were prepared by versatile synthetic routes, which allow large scale preparation. Among the homoisocarbacyclin analogues synthesized, some analogues showed superior properties to PGI_2 and its stable analogues, in terms of potent activities and chemical stability. Remarkably, analogue **74b** (TY-11223) was found to be a promising candidate responsible for a novel medicine in the cardiovascular field. Further experimental evaluations are now in progress on pharmacological properties.

Experimental

General methods

All melting points were obtained with Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a JASCO A-202 diffraction grating infrared spectrophotometer, a JASCO A-300 diffraction grating infrared spectrophotometer or a HITACHI 270-30 infrared spectrophotometer. ^{1}H-NMR spectra were recorded with a HITACHI R-90H spectrometer, a JEOL JNM-FX 100 spectrometer, a Varian Gemini-200 spectrometer, a JEOL JNM-GX 270 spectrometer or a Bruker AM-400 spectrometer with tetramethylsilane as an internal standard and ^{13}C-NMR spectra were measured on a HITACHI R-90H spectrometer at 22.3 MHz, a Varian Gemini-200 spectrometer at 50 MHz or a Bruker AM-400 spectrometer at 100.6 MHz with $CDCl_3$ as an internal standard. Low-resolution mass spectra (MS) or high-resolution mass spectra (HR-MS) were obtained with a HITACHI RUM-6MG mass spectrometer, a HITACHI M-80A mass spectrometer, a JEOL JMS-D 300 mass spectrometer or a JXL-LX 1000 mass spectrometer. The electron impact mass spectra (EIMS) were determined using an ionization potential of 70 eV. The fast atom bombardment mass spectra (FABMS) were obtained by using glycerol as the matrix. Optical rotations were measured on a HORIBA SEPA-200 high-sensitivity polarimeter or a JASCO DIP-360 digital polarimeter. Thin-layer chromatography was performed on precoated TLC plates (silica gel 60 F-254, layer thickness 0.25 mm) manufactured by E. Merck. Silica gel column chromatography was performed on Wakogel C-300 manufactured by Wako Pure Chemical Industries, Ltd. HPLC was carried out on a Shimadzu HPLC system (pump; waters model 510, detector; waters M-490 measured at 214 nm, column; YMC-pack A-304, 4.6 mm i.d. x 30 cm, mobile phase; 30% (w/w) acetonitrile in 50 mM phosphate buffer (pH 7.2), flow rate; 1.2 ml/min). In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned.

*(1S,5R,6S,7R)-6-*tert*-Butyldimethylsilyloxymethyl-7-tetrahydropyranyloxy-3-hydroxy-2-oxabicyclo[3.3.0]octane(13)*

Diisobutylaluminum hydride (1.0M in toluene, 40.5ml, 40.5mmol) was added to a stirred solution of Corey lactone (**12**) (10.0g, 27.0mmol) in toluene (80ml) at -78 °C. Stirring was continued at the same temperature for 1 h, and the reaction was quenched by the addition of methanol at -78 °C. After dilution with ethyl acetate, brine was added. Vigorous stirring was continued at room temperature until the organic layer had 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 (**13**) (10.1g, quantitative yield) as a colorless oil. IR (neat): 3430, 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 (EI) m/z: 355 (M^+- OH), 287 (M^+-DHP-H). HR-MS (EI) m/z: 355.2269 (Calc'd for $C_{19}H_{35}O_4Si$, 355.2302, M^+-OH).

*Methyl 4-[(1R,2S,3R,5S)-2-*tert*-butyldimethylsilyloxymethyl-3-tetrahydropyranyloxy-5-hydroxycyclopentyl]-2-butenoate(14)*

To a solution of the lactol (**13**) (22.0g, 54.0mmol) in toluene (200ml) was added methyl (triphenylphosphoranylidene)acetate (23.4g, 30.0mmol) at room temperature. The mixture was stirred at 60 °C for 18 h. After cooling, the solvent was distilled off, and the residue was purified by silica gel column chromatography (ether–hexane, 1:2) to obtain the α,β-unsaturated ester (**14**) (24.1g, quantitative yield) as a colorless oil. IR (neat): 3530, 2960, 1730, 1660, 1440, 1260 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.85 (9H, s), 1.32–2.06 (10H, m), 2.29–2.56 (3H, m), 3.25–3.90 (4H, m), 3.70 (3H, s), 3.95–4.26 (2H, m), 4.53–4.76 (1H, m), 5.95 (1H, d. J=15.0 Hz), 7.06 (1H, dt, J=7.5, 15.0Hz). MS (EI) m/z: 371 (M^+- *tert*-Bu), 344 (M^+-DHP). HR-MS (EI) m/z: 344.2018 (Calc'd for $C_{17}H_{32}O_5Si$, 344.2018, M^+-DHP).

*Methyl 4-[(1R,2S,3R,5S)-2-*tert*-butyldimethylsilyloxymethyl-3-tetrahydropyranyloxy-5-hydroxycyclopentyl]-butanoate(15)*

The unsaturated ester (**14**) (7.0g, 16.4mmol) was hydrogenated on 0.7g of 10% Pd–C in methanol (50ml) under the atmospheric pressure of hydrogen at room temperature for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated to give the ester (**15**) (6.5g, 93%) as a colorless oil. IR (neat): 3520, 2940, 2850, 1740, 1430, 1250, 830 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (6H, s), 0.90 (9H, s), 2.20–2.63 (3H, m), 3.23–4.00 (4H, m), 3.66 (3H, s), 4.05–4.26 (2H, m), 4.60–4.80 (1H, m). MS (EI) m/z: 373 (M^+- *tert*-Bu), 345 (M^+- DHP- H). HR-MS (EI) m/z: 345.2117 (Calc'd for $C_{17}H_{33}O_5Si$, 345.2096, M^+- DHP- H).

*Methyl 4-[(1R,2S,3R)-2-*tert*-butyldimethylsilyloxymethyl-3-tetrahydropyranyloxy-5-oxocyclopentyl]-butanoate(16)*

Dimethyl sulfoxide (DMSO) (6.5ml, 90.6mmol) in methylene chloride (30ml) was added to a solution of oxalyl chloride (3.8ml, 44.3mmol) in methylene chloride (30ml) at -78 °C, and the mixture was stirred at the same temperature for 30 min. Then, a solution of the alcohol (**15**) (6.5g, 15.1mmol) in methylene chloride (50ml) was added dropwise to the mixture at -78 °C, and the whole

reaction mixture was stirred at the same temperature for 30 min. After dropwise addition of triethylamine (31.3ml, 227mmol) at -78 °C, the reaction mixture was stirred at room temperature for 15 min. The reaction mixture was quenched by the addition of water, followed by extraction with methylene chloride. 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, 1:2) to give the ketone (**16**) (6.2g, 95%) as a colorless oil. IR (neat): 2900, 2810, 1750, 1730, 1420, 820 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.87 (9H, s), 1.10–1.90 (10H, m), 1.93–2.43 (7H, m), 2.48–2.66 (1H, m), 3.26–4.00 (2H, m), 3.66 (3H, s), 4.00–4.43 (1H, m), 4.50–4.73 (1H, m). MS (EI) m/z: 371 (M^+- *tert*-Bu), 343 (M^+- DHP- H). HR-MS (EI) m/z: 343.1922 (Calc'd for $C_{17}H_{31}O_5Si$, 343.1938, M^+- DHP- H).

*Methyl 4-[(1S,2S,3R)-2-*tert*-butyldimethylsilyloxymethyl-3-tetrahydropyranyloxy-5-methylenecyclopentyl]-butanoate(**17**)*

The methylenation reagent prepared by Lombardo's method ($Zn–CH_2Br_2–TiCl_4$) was added to a solution of the ketone (**16**) (10.0g, 23.0mmol) in methylene chloride (100ml) until the starting material had disappeared on TLC, and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into a mixture of saturated aqueous $NaHCO_3$ (500ml), ether (500ml) 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 aqueous 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, 1:6) afforded **17** (7.6g, 76%) as a colorless oil. IR (neat): 2900, 2800, 1730, 1420, 1240, 820 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.86 (9H, s), 1.10–2.06 (11H, m), 2.10–2.83 (5H, m), 3.30–4.16 (5H, m), 3.66 (3H, s), 4.52–4.65 (1H, m), 4.76, 4.86 (each 1H, s). MS (EI) m/z: 369 (M^+- *tert*-Bu), 342 (M^+- DHP). HR-MS (EI) m/z: 342.2330 (Calc'd for $C_{18}H_{34}O_4Si$, 342.2335, M^+-DHP).

*Methyl 4-[(1S,2S,3S,4R)-3-*tert*-butyldimethylsilyloxymethyl-3-tetrahydropyranyloxy-5-hydroxymethylcyclopentyl]butanoate(**18**)*

A solution of disiamylborane in THF (0.9M, 43.0ml, 38.7mmol) was added to a stirred solution of **17** (7.5g, 17.6mmol) in THF (70ml) at 0°C, and the mixture was stirred at the same temperature for 1 h. Then, 6N aqueous NaOH (25.5ml, 153mmol) and 30% H_2O_2 (22.0ml, 194mmol) were added at 0°C, and the whole reaction mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with ethyl acetate, and the combined organic layer was washed with saturated aqueous $Na_2S_2O_3$ and brine, and dried over $MgSO_4$. Removal of the solvent afforded the alcohol (**18**) (7.8g, quantitative yield) as a colorless oil. IR (neat): 3450, 2930, 2850, 1740, 1430, 1250, 1020, 830 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.03–2.00 (15H, m), 2.16–2.45 (3H, m), 3.16–4.06 (5H, m), 3.63 (3H, s), 4.13 (2H, brd, J=6.0Hz), 4.56–4.70 (1H, m). MS (EI) m/z: 387 (M^+- *tert*-Bu), 359 (M^+- DHP- H). HR-MS (EI) m/z: 359.2237 (Calc'd for $C_{18}H_{35}O_5Si$, 359.2251, M^+-DHP-H).

*(1S,2S,3S,4R)-3-*tert*-Butyldimethylsilyloxymethyl-4-tetrahydropyranyloxy-1-hydroxymethyl-2-(4-hydroxybutyl)-cyclopentane(**19**)*

A solution of the alcohol (**18**) (7.8g, 17.6mmol) in THF (100ml) was added to a suspension of $LiAlH_4$ (3.34g, 88.0mmol) in THF (70ml) at 0°C. The mixture was stirred at 0°C for 30 min, then the $Na_2SO_4·10H_2O$ was added at 0°C. The precipitate was filtered off and the filtrate was evaporated to dryness. The obtained residue was purified by silica gel column chromatography (ether) to afford the diol (**19**) (6.8g, 93%) as a colorless oil. IR (neat): 3450, 2950, 2850, 1430, 835 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.26–2.30 (18H, m), 3.33–3.86 (8H, m), 3.90–4.10 (2H, m), 4.43–4.70 (1H, m). MS (EI) m/z: 331 (M^+-DHP-H). HR-MS (EI) m/z: 331.2296 (Calc'd for $C_{17}H_{35}O_4Si$, 331.2302, M^+- DHP- H).

*(1R,6S,7S,8R)-7-*tert*-Butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-*cis*-bicyclo[4.3.0]non-2-ene-3-carbaldehyde(**21**)*

A solution of DMSO (12.3ml, 173.7mmol) in methylene chloride (40ml) was added dropwise to a solution of oxalyl chloride (6.6ml, 77.2mmol) in methylene chloride (80ml) at -78 °C, and the mixture was stirred at the same temperature for 30 min. Then, a solution of the diol (**19**) (8.0g, 19.3mmol) in methylene chloride (40ml) was added dropwise to the mixture at -78 °C, and the whole reaction mixture was stirred at the same temperature for 30 min. After dropwise addition of triethylamine (53.4ml, 386mmol) at -78 °C, the reaction mixture was stirred at room temperature for 15 min. The reaction mixture was quenched by the addition of water, followed by extraction with methylene chloride. The combined organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was dissolved with benzene (100ml), and dibenzylammonium trifluoroacetate (6.1g, 19.3mmol) was added to the mixture. The mixture was stirred at 80 °C for 40 min and then cooled to room temperature. The reaction mixture was quenched by the addition of water, followed by extraction with ether. The combined organic layer was washed with saturated aqueous NH_4Cl, brine and water, and dried over $MgSO_4$. Removal of the solvent afforded the oily residue, which was purified by silica gel column chromatography (ether–hexane, 1:4) to give the enal (**21**) (5.6g, 74%) as a pale yellow oil. IR (neat): 2950, 2870, 1690, 1640, 1260, 840 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.90 (9H, s), 1.13–2.52 (14H, m), 2.53–2.86 (1H, m), 3.30–4.26 (5H, m), 4.54–4.73 (1H, m), 6.73 (1H, brs), 9.42 (1H, s). MS (EI) m/z: 310 (M^+-DHP), 309 (M^+- DHP- H). HR-MS (EI) m/z: 310.1948 (Calc'd for $C_{17}H_{30}O_3Si$, 310.1961, M^+-DHP).

*(1R,6S,7S,8R)-3-Benzyloxymethyl-7-*tert*-butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-*cis*-bicyclo[4.3.0]non-2-ene(**24**)*

Diisobutylaluminum hydride (1.0M in toluene, 0.77ml, 0.77mmol) was added to a stirred solution of the enal (**21**) (200mg, 0.51mmol) in toluene (1ml) at -78 °C. Stirring was continued at the same temperature for 30 min, and the reaction was quenched by the addition of methanol at -78°C. After dilution with ethyl acetate, brine was added. Vigorous stirring was continued at room temperature until the organic layer had become clear. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded the alcohol (**23**) (202mg, quantitative yield) as a colorless oil.

Sodium hydride (60% in oil, 37mg, 0.92mmol) was washed with pentane, and suspended in THF (1ml). A solution of the alcohol (**23**) (202mg, 0.92mmol) in THF (2ml) was added to the suspension. and the mixture was stirred at room temperature for 40 min. Then, benzyl chloride (174mg, 1.02mmol) in THF–HMPA (9:1, 1ml) was added dropwise to the reaction mixture, and the whole mixture was stirred at room temperature for 2 h, and then stirred at 60 °C for 12 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl at 0 °C, and extracted with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and purification by the silica gel column chromatography (ether–hexane, 1:10) afforded **24** (223mg, 90%) as a colorless oil. IR (neat): 2950, 1460, 1260, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.96 (9H, s), 1.20–2.50 (11H, m), 3.28–4.21 (5H, m), 3.53 (2H, s), 4.43 (2H, s), 4.50–4.72 (1H, m), 5.63 (1H, brs), 7.15–7.45 (5H, m). MS (EI) m/z: 402 (M^+- DHP), 401 (M^+- DHP-H). HR-MS (EI) m/z: 402.2118 (Calc'd for $C_{24}H_{36}O_3Si$, 402.2133, M^+- DHP).

*(1R,6S,7S,8R)-3-Benzyloxymethyl-7-*tert*-butyldimethylsilyloxymethyl-8-hydroxy-*cis*-bicyclo[4.3.0]non-2-ene(**25**)*

Diethylaluminum chloride (1.15M in hexane, 1.14ml, 1.32mmol) was added to a stirred solution of **24** (161mg, 0.33mmol) in methylene chloride (1ml) at -25 °C, and the reaction mixture was stirred at the same temperature for 90 min. The reaction was quenched by the addition of saturated aqueous $KHCO_3$ at -25 °C. After dilution with ether, brine was added. Vigorous stirring was continued at room temperature until the organic layer had become clear. The aqueous layer was extracted with ether, and the combined 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 (**25**) (119mg, 90%) as a colorless oil. IR (neat): 3450, 2950, 2900, 1460, 1260, 840 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.07 (6H, s), 0.09 (9H, s), 1.42 (1H, ddd, J=9.00, 9.01, 12.35Hz), 1.48–1.58 (1H, m), 1.68–1.80 (3H, m), 1.97–2.02 (2H, m), 2.21 (1H, ddd, J=7.03, 7.10, 12.35Hz), 2.45–2.53 (1H, m), 2.58 (1H, brs), 3.57 (1H, dd, J=8.40, 9.50Hz), 3.85 (1H, dd, J=4.50, 9.50Hz), 3.90 (2H, s), 4.01 (1H, ddd, J=7.10, 8.40, 9.00Hz), 4.46 (1H, s), 5.67 (1H, t, J=1.70Hz), 7.25–7.36 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: -5.47 (q), -5.41 (q), 18.27 (s), 23.70 (t), 25.83 (t), 25.97 (q), 35.85 (d), 37.20 (d), 39.99 (t), 52.97 (d), 66.23 (t), 71.76 (t), 74.68 (t), 77.45 (d), 127.53 (d), 127.79 (d), 128.35 (d), 128.38 (d), 134.27 (s), 138.62 (s). MS (EI) m/z: 402 (M^+), 384 (M^+- H_2O). HR-MS (EI) m/z: 402.2567 (Calc'd for $C_{28}H_{38}O_3Si$, 402.2590, M^+).

*Methyl 5-[(1R,6S,7S,8R)-7-*tert*-butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-4-pentenoate(**26**)*

Potassium *tert*-butoxide (0.65g, 5.0mmol) in THF (10ml) was added to a stirred suspension of 4-carboxybutyltriphenylphosphonium bromide (1.10g, 2.5mmol) in THF (10ml), and the mixture was stirred at room temperature for 20 min. Then, a solution of the enal (**21**) (200mg, 0.5mmol) in THF (5ml) was added to the ylide solution at room temperature. After stirring for 30 min, saturated aqueous NH_4Cl was added, followed by separation of THF layer. The aqueous layer was acidified to pH 4–5 with 10% aqueous HCl and extracted with ethyl acetate. The organic layers were combined, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was treated with ethereal diazomethane at 0° C until the carboxylic acid had disappeared on TLC. After evaporation, the residue was purified by silica gel column chromatography (ether–hexane, 1:4) to afford the conjugated diene (**26**) (210mg, 88%, *E:Z* =*ca.* 1:2) as a colorless oil. IR (neat): 2950, 2860, 1740, 1430, 1255, 1030, 835 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (6H, s), 0.90 (9H, s), 1.06–2.25 (14H, m), 2.25–2.80 (5H, m), 3.23–3.76 (4H, m), 3.70 (3H, s), 3.80–4.13 (1H, m), 4.60–4.73 (1H, m) 5.10–5.42 (1H, m), 5.63 (1H, brs), 5.96 (2/3H, d, J=12.0Hz), 6.12 (1/3H, d, J=15.0Hz). MS (EI) m/z: 394 (M^+- DHP). HR-MS (EI) m/z: 394.2542 (Calc'd for $C_{22}H_{38}O_4Si$, 394.2537, M^+- DHP).

*Methyl 5-[(1R,6S,7S,8R)-7-*tert*-butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl]pentanoate(**27**)*

A suspension of the conjugated diene (**26**) (190mg, 0.4mmol) and 60mg of 10% Pd–C in methanol (10ml) was stirred under atmospheric pressure of hydrogen at room temperature until the starting material had disappeared on TLC. After filtration of the catalyst, the filtrate was concentrated under reduced pressure. The resulting colorless oil was chromatographed on silica gel (ether–hexane, 1:8) to give **27** (162mg, 84%) as a colorless oil. IR (neat): 2930, 2850, 1740, 1250, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.86 (9H, s), 1.06–2.10 (20H, m), 2.10–2.46 (3H, m), 3.30–4.31 (5H, m), 3.66 (3H, s), 4.53–4.83 (1H, m), 5.35 (1H, brs). MS (EI) m/z: 396 (M^+- DHP), 395 (M^+- DHP- H). HR-MS (EI) m/z: 395.2617 (Calc'd for $C_{22}H_{39}O_4Si$, 395.2616, M^+- DHP-H).

*Methyl 5-[(1R,6S,7S,8R)-8-Tetrahydropyranyloxy-7-hydroxymethyl-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-pentanoate(**28**)*

Tetrabutylammonium fluoride (TBAF) (1.0M in THF, 0.48ml, 0.48mmol) was added to a solution of **27** (93mg,

0.19mmol) in THF (3ml), and the mixture was stirred at room temperature for 13 h. 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 the silica gel column chromatography (ether–hexane, 3:1) to give the alcohol (**28**) (62mg, 89%) as a colorless oil. IR (neat): 3450, 2930, 2850, 1740, 1430, 1200, 1020, 860 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.00–2.60 (24H, m), 3.22–4.12 (5H, m), 3.66 (3H, s), 4.50–4.85 (lH, m), 5.35 (1H, brs). MS (EI) m/z: 282 (M^+- DHP), 264 (M^+- DHP- H_2O). HR-MS (EI) m/z: 282.1822 (Calc'd for $C_{16}H_{26}O_4$, 282.1829, M^+- DHP).

Methyl 5-[(1R,6S,7R,8R)-8-tetrahydropyranyloxy-7-[(E)-3-oxo-1-octenyl]-cis-*bicyclo[4.3.0]non-2-en-3-yl]-pentanoate(30)*

A solution of sulfur trioxide pyridine complex (133.0mg, 0.84mmol) in DMSO (2ml) was added to a stirred mixture of the alcohol (**28**) (51mg, 0.14mmol) and triethylamine (0.12ml, 0.84mmol) in DMSO (3ml) at room temperature. After stirring for 1 h, the reaction mixture was poured into ice water and extracted with ethyl acetate. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent gave almost pure aldehyde (**29**) (53mg) as a pale yellow oil. The crude aldehyde was used for the subsequent step without purification.

Sodium hydride (60% in oil, 6.2mg, 0.23mmol) was washed with pentane, and suspended in THF (2ml). A solution of dimethyl (2-oxoheptyl)phosphonate (62mg, 0.28mmol) in THF (3ml) was added to the suspension, and the mixture was stirred at room temperature for 1 h. Then, the aldehyde (**29**) (53mg) in THF (3ml) was dropped into the solution of the sodium β-ketophosphonate, and the whole mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by extraction with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography (ether–hexane, 1:3) afforded the enone (**30**) (51.0mg, 80%) as a colorless oil. IR (neat): 2930, 2880, 1740, 1700, 1675, 1625, 1440, 1030 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=6.0Hz), 1.10–2.15 (24H, m), 2.20–2.76 (7H, m), 3.20–4.22 (3H, m), 3.70 (3H, s), 4.55–4.75 (1H, m), 5.33 (1H, brs), 6.16, 6.20 (total 1H, each d, J=15.0Hz), 6.82, 6.85 (total 1H, each dd, J=9.2, 15.0Hz). MS (EI) m/z: 376 (M^+-DHP). HR-MS (EI) m/z: 376.2619 (Calc'd for $C_{23}H_{36}O_4$, 376.2627, M^+-DHP).

Methyl 5-[(1R,6S,7R,8R)-8-tetrahydropyranyloxy-7-[(E)-3-hydroxy-1-octenyl]-cis-*bicyclo[4.3.0]non-2-en-3-yl]-pentanoate(31)*

An excess amount of sodium borohydride was added to a stirred solution of the enone (**30**) (120mg, 0.26mmol) in methanol (5ml) at -25 °C. The mixture was stirred at the same temperature for 30 min, then the excess of reagent was decomposed by the addition of acetone at -25 °C, and finally saturated aqueous NH_4Cl was added to the reaction mixture. After removal of the organic solvent, the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, and dried over $MgSO_4$. Removal of the solvent gave the alcohol (**31**) (118mg, 98%) as an epimeric mixture. IR (neat): 3450, 2930, 2850, 1740, 1430, 1020, 840 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J=6.0Hz), 1.10–2.15 (28H, m), 2.20–2.65 (5H, m), 3.26–3.63 (1H, m), 3.66 (3H, s), 3.73–4.23 (3H, m), 4.53–4.76 (1H, m), 5.31 (1H, brs), 5.46–5.66 (2H, m). MS (EI) m/z: 360 (M^+- DHP- H_2O). HR-MS (EI) m/z: 360.2646 (Calc'd for $C_{23}H_{36}O_3$, 360.2661, M^+- DHP- H_2O).

Methyl 5-[(1R,6S,7R,8R)-8-hydroxy-7-[(E)-(3S)-3-hydroxy-1-octenyl]-cis-*bicyclo[4.3.0]non-2-en-3-yl]-pentanoate(32)*

The crude alcohol (**31**) (epimeric mixture, 115mg, 0.25mmol) was dissolved in a mixture of 65% aqueous acetic acid (1.5ml) and THF (1ml), and the mixture was stirred at 50–55 °C for 4 h. After dilution with ethyl acetate, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ at 0 °C, and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$. Removal of the solvent afforded a pale yellow oily residue, which was purified by silica gel column chromatography (ether) gave the desired 15α-diol (**32**) (42mg, 44%) as a more polar fraction and the 15β-diol (**33**) (29mg, 31%) as a less polar fraction. Spectral data of the 15α-diol (**32**): IR (neat): 3400, 2940, 1740, 1430, 1110, 960 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J=5.8Hz), 1.06–2.70 (27H, m), 3.68 (3H, s), 3.73–4.23 (2H, m), 5.33 (lH, brs), 5.45–5.65 (2H, m). MS (EI) m/z: 360 (M^+- H_2O), 342 (M^+- $2H_2O$). HR-MS (EI) m/z: 360.3970 (Calc'd for $C_{23}H_{36}O_3$, 360.3988, M^+- H_2O). The spectral data of **33** were nearly identical with those of **32**.

5-[(1R,6S,7R,8R)-8-Hydroxy-7-[(E)-(3S)-3-hydroxy-1-octenyl]-cis-*bicyclo[4.3.0]non-2-en-3-yl]pentanoic acid; homoisocarbacyclin(10)*

To a solution of the diol (**32**) (38mg, 0.10mmol) in methanol (1ml) was added 10% aqueous NaOH (1ml) at 0 °C. After stirring at the same temperature for 12 h, the reaction mixture was washed with pentane (2ml), and then acidified to pH 3–4 with 2N aqueous HCl, and extracted with ethyl acetate. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent afforded homoisocarbacyclin (**10**) (35mg, 96%) as a colorless powder. IR (KBr): 3400, 2950, 2850, 1710, 1460, 960 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J=6.0Hz), 1.03–2.63 (27H, m), 3.75–3.93 (1H, m), 4.00–4.23 (1H, m), 5.30 (1H, brs), 5.50–5.65 (2H, m). ^{13}C-NMR ($CDCl_3$) δ ; 178.1, 135.5, 135.3, 133.8, 125.6, 77.3, 73.4, 53.5, 40.3, 39.8, 37.5, 36.9, 34.9, 33.9, 31.7, 26.9, 25.2, 24.4, 24.3, 23.6, 22.6, 14.0. MS (EI) m/z: 346 (M^+-H_2O), 328 (M^+-$2H_2O$). HR-MS (EI) m/z: 346.2150 (Calc'd for $C_{22}H_{34}O_3$, 346.2138, M^+- H_2O). $[\alpha]^{22}_D$: +32.91° (c=1.58, $CHCl_3$). m.p. 64–66 °C.

*(1R,6S,7S,8R)-7-*tert*-Butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-3-vinyl-*cis*-bicyclo[4.3.0]non-2-ene(**34**)*

A solution of potassium *tert*-butoxide (25.6g, 228mmol) in THF (150ml) was added dropwise to a suspension of methyltriphenylphosphonium bromide (81.5g, 228mmol) in THF (350ml) at room temperature. After stirring for 40 min, a solution of the enal (**21**) (31.5g, 79.9mmol) in THF (150ml) was added to the stirring mixture at the same temperature. Stirring was continued for 30 min to complete the reaction, followed by quenching the reaction by the addition of saturated aqueous NH_4Cl, and the mixture was extracted with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent afforded a pale yellow oily residue, which was purified by silica gel column chromatography (ether–hexane, 1:20) to give the diene (**34**) (30.4g, 97%) as a pale yellow oil. IR (neat): 2950, 2875, 1640, 1610, 1470, 1260, 840 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 1.06–2.66 (15H, m), 3.20–4.33 (5H, m), 4.48–4.68 (1H. m), 4.83 (1H, d, J=10.5Hz), 4.98 (1H, d, J=18.0Hz), 5.66 (1H, brs), 6.22 (1H, dd, J=10.5, 18.0Hz). MS (EI) m/z: 392 (M^+), 308 (M^+-DHP). HR-MS (EI) m/z: 392.2741 (Calc'd for $C_{23}H_{40}O_3Si$, 392.2744, M^+).

*(1R,6S,7S,8R)-7-*tert*-Butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-3-(2-hydroxyethyl)-*cis*-bicyclo[4.3.0]non-2-ene(**35**)*

A solution of 9-BBN dimer (19.0g, 76.3mmol) in THF (300ml) was added dropwise to a solution of the diene (**34**) (30.4g, 77.5mmol) in THF (200ml) at 0 °C. After stirring at the same temperature for 2 h, a solution of 9-BBN dimer (9.5g, 38.2mmol) in THF (150ml) was added again at 0 °C, and stirred at the same temperature for 1.5 h. Then, 6N aqueous NaOH (185ml) and 30% H_2O_2 (160ml) was added dropwise to the reaction mixture at 0 °C, and stirred at room temperature for 1 h. After addition of ice water, the reaction mixture was extracted with ether. The combined organic layer was washed with saturated aqueous $Na_2S_2O_3$, water and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel (ether–hexane, 1:1) to give the homoallylalcohol (**35**) (29.6g, 93%) as a pale yellow oil. IR (neat): 3450, 2930, 2860, 1475, 1255, 830 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.06 (6H, s), 0.90 (9H, s), 1.13–2.66 (18H, m), 3.23–4.30 (7H, m), 4.45–4.66 (1H, m), 5.40 (1H, brs). MS (EI) m/z: 326 (M^+- DHP), 269 (M^+-DHP-*tert*-Bu). HR-MS (EI) m/z: 326.2285 (Calc'd for $C_{18}H_{34}O_3Si$, 326.2275, M^+-DHP).

tert-*Butyl 5-[(1R,6S,7S,8R)-7-*tert*-butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoate(**36**)*

To a mixture of the homoallylalcohol (**35**) (29.6g, 72.0mmol), *tert*-butyl bromoacetate (116ml, 720mmol) and tetrabutylammonium hydrogen sulfate (0.90g, 2.57mmol) in methylene chloride (270ml) was added 50% aqueous NaOH (270ml) at room temperature. The reaction mixture was stirred at the same temperature for 2.5 days. After dilution with ether (1000ml), the organic layer was washed with water and brine, and dried over $MgSO_4$. The solution was concentrated, and the residue was chromatographed on silica gel (ether–hexane, 1:10) to give the *tert*-butylester (**36**) (33.4g, 88%, containing a small amount of *tert*-butyl bromoacetate) as a pale yellow oil. IR (neat): 2950, 1750, 1255, 1215, 1130, 1080, 1030, 940, 840, 780 cm^{-1}. ^1H-NMR ($CDCl_3$) δ : 0.05 (6H, s). 0.90 (9H, s), 1.30–2.06 (13H, m), 1.50 (9H, s), 2.15–2.45 (4H, m), 3.40–3.78 (7H, m), 4.12 (2H, s), 4.52–4.74 (1H, m), 5.47 (1H, brs). MS (EI) m/z: 440 (M^+- DHP). HR-MS (EI) m/z: 440.2952 (Calc'd for $C_{24}H_{44}O_5Si$, 440.2958. M^+- DHP).

tert-*Butyl 5-[(1R,6S,7S,8R)-8-tetrahydropyranyloxy-7-hydroxymethyl-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoate(**37**)*

TBAF (1.0M in THF, 127ml, 127mmol) was added to a solution of **36** (33.4g, 63.7mmol) in THF (100ml), and the mixture was stirred at room temperature for 6 h. 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, 2:1) to give the alcohol (**37**) (21.4g, 82%) as a pale yellow oil. IR (neat): 3500, 2950, 1750, 1370, 1200, 1130, 1080, 1020, 865, 845 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.10–2.60 (16H, m), 1.50 (9H, s), 2.31 (2H, t, J=6.0Hz), 3.35–4.20 (5H, m), 3.61 (2H, t, J=6.0Hz), 3.96 (2H. s), 4.55–4.83 (1H, m), 5.45 (1H, brs). MS (EI) m/z: 326 (M^+- DHP). HR-MS (EI) m/z: 326.2079 (Calc'd for $C_{18}H_{30}O_5$, 326.2094, M^+-DHP).

Ethyl (Z)-*5-[(1R,6S,7S,8R)-7-*tert*-butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-4-pentenoate(**44**)*

A solution of potassium *tert*-butoxide (356mg, 3.17mmol) in THF (12ml) was added to a suspension of 4-ethoxycarbonylpropyltriphenylphosphonium bromide (1.45g, 3.17mmol) in THF (8ml) at -78 °C, and the mixture was stirred at the same temperature for 1 h. Then a solution of the enal (**21**) (566mg, 1.44mmol) in THF (5ml) was added to the ylide solution at -78 °C, and the reaction mixture was stirred at the same temperature for 3 h. After removal of a cooling bath, stirring was continued for 1 h to complete the reaction, and then the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl. After extraction with ethyl acetate, the combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (ether–hexane, 1:5) to give the conjugated diene (**44**) (659mg, 93%) as a colorless oil. IR (neat): 2950, 2930, 2860, 1730, 1030, 835 cm^{-1}. ^1H-NMR ($CDCl_3$) δ : 0.04 (6H, s), 0.88 (9H, s), 1.10–1.95 (12H, m), 1.24 (3H, t, J=7.0Hz), 1.96–2.75 (7H, m), 3.30–4.30 (5H, m), 4.10 (2H, q, J=7.0Hz), 4.50–4.72 (1H, m), 5.00–5.40 (1H, m), 5.53 (1H, brs), 5.74 (1H, d, J=12.0Hz). MS (EI) m/z: 492 (M^+), 447 (M^+- OEt), 408 (M^+- DHP). HR-

MS (EI) m/z: 492.3273 (Calc'd for $C_{28}H_{48}O_5Si$, 492.3271, M^+).

Ethyl (Z)-*5*-[(*1*R,*6*S,*7*S,*8*R)-*8-tetrahydropyranyloxy-7-hydroxymethyl*-cis-*bicyclo[4.3.0]non-2-en-3-yl]-4-pentenoate(45)*

TBAF (1.0M in THF, 2.7ml, 2.7mmol) was added to a solution of **44** (659mg, 1.34mmol) in THF (6ml), and the mixture was stirred at room temperature for 13 h. 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, 2:1) to give the alcohol (**45**) (464mg, 92%) as a pale yellow oil. IR (neat): 3450, 2950, 2870, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 1.03–2.73 (20H, m), 1.25 (3H, t, J=7.0Hz), 3.30–4.33 (5H, m), 4.10 (2H, q, J=7.0Hz), 4.50–4.76 (1H, m). 5.06–5.40 (1H, m), 5.54 (1H, brs), 5.75 (1H, d, J=12.0Hz). MS (EI) m/z: 378 (M^+), 360 (M^+- H_2O), 333 (M^+- OEt), 315 (M^+- OEt - H_2O), 294 (M^+- OEt - DHP). HR-MS (EI) m/z: 378.2433 (Calc'd for $C_{22}H_{34}O_5$, 378.2406, M^+).

Ethyl (Z)-*5*-[(*1*R,*6*S,*7*S,*8*R)-7-tert-*butyldimethylsilyloxymethyl-8-hydroxy*-cis-*bicyclo[4.3.0]non-2-en-3-yl]-4-pentenoate(52)*

To a solution of the conjugated diene (**44**) (51mg, 0.103mmol) in methylene chloride (1ml) was added dropwise diethylaluminum chloride (0.97M in hexane, 0.50ml, 0.517mmol) at -78 °C. Then, the reaction mixture was warmed to 0 °C and stirred for 1.5 h. The reaction mixture was quenched by the addition of saturated aqueous $KHCO_3$ (5 drops) at -78 °C, and diluted with ether. After warming to room temperature, the reaction mixture was extracted with ether. The combined organic layer was washed with brine, and dried over $MgSO_4$. The solvent was concentrated and the residue was chromatographed on silica gel (ether–hexane, 1:1) to give the alcohol (**52**) (36.4mg, 86%) as a pale yellow oil. IR (neat): 3452, 2928, 2856, 1736, 1470, 1372, 1252, 1156, 1098, 836, 774 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ : 0.08 (6H, s), 0.89 (9H, s), 1.25 (3H, t, J=7.0Hz), 1.36–1.82 (6H, m), 2.46–2.64 (4H, m), 2.15–2.42 (3H, m), 2.03–2.15 (2H, m), 3.58 (1H, dd, J=8.0, 10.0Hz), 3.85 (1H, dd, J=4.8, 10.0Hz), 4.02 (1H, dt, J=7.5, 7.5Hz), 4.16 (2H, q, J=7.0Hz), 5.25 (1H, dt, J=7.0, 12.0Hz), 5.60 (1H, d, J=2.5Hz), 5.81 (24/25H, d, J=12.0Hz), 6.06 (1/25H, d, J=16.0Hz). MS (FAB) m/z: 409 (M^+ + H), 391 (M^+ + H - H_2O). HR-MS (FAB) m/z: 391.2694 (Calc'd for $C_{23}H_{39}O_3Si$, 391.2669, M^+ + H - H_2O).

(*1*R,*6*S,*7*S,*8*R)-7-tert-*Butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-3-(1,2-dihydroxyethyl)*-cis-*bicyclo-[4.3.0]non-2-ene(54)*

To a solution of the enal (**21**) (1.25g, 3.17mmol) in THF (5ml) was added dropwise a solution of (isopropoxydimethylsilyl)methylmagnesium chloride in THF (1.2M, 5.0ml, 6.0mmol) at -10 °C, and the mixture was stirred at the same temperature for 20 min. Then, saturated aqueous NH_4Cl was added to the reaction mixture, and the mixture was extracted with ether. The combined organic layer was washed with cold water and brine, and dried over Na_2SO_4. After removal of the solvent at 30 °C, the residue was dissolved with methanol–THF (1:1, 15ml), followed by addition of $NaHCO_3$ (277mg, 3.18mmol) and 30% H_2O_2 (2.75ml), and the mixture was refluxed for 14 h. After dilution with ether (50ml), powdered $Na_2S_2O_3$ was added to the reaction mixture, followed by filtration with celite. After concentration, the residue was dissolved with ether (100ml), and dried over Na_2SO_4. Removal of the solvent afforded a white oily residue, which was purified by silica gel column chromatography (ether–hexane, 3:1) to give the diol (**54**) (1.16g, 86%) as a pale yellow oil. IR (neat): 3400, 2950, 2860, 1470, 1440, 1380, 1360, 1320, 1260, 1200, 1180, 1030, 910, 840, 780, 660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.20–2.70 (17H, m), 3.27–4.27 (8H, m), 4.45–4.65 (1H, m), 5.65 (1H, brs). MS (EI) m/z: 342 (M^+- DHP), 324 (M^+- DHP-H_2O). HR-MS (EI) m/z: 342.2220 (Calc'd for $C_{18}H_{34}O_4Si$, 342.2226, M^+-DHP).

(*1*R,*6*S,*7*S,*8*R)-*7*-tert-*Butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-3-(1-hydroxy-2-pivaloyloxyethyl)*-cis-*bicyclo[4.3.0]non-2-ene(55)*

Pivaloyl chloride (0.18ml, 1.45mmol) was added to a mixture of the diol (**54**) (422mg, 0.989mmol), triethylamine (0.41ml, 2.94mmol) and a catalytic amount of 4-dimethylaminopyridine in methylene chloride (5ml) at 0 °C. After stirring the mixture at room temperature for 13 h, triethylamine (0.41ml, 2.94mmol) and pivaloyl chloride (0.18ml, 1.45mmol) were added again at 0 °C, and the mixture was stirred at room temperature for 30 min. Then, ice water was added to the reaction mixture, and the mixture was extracted with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography (ether–hexane, 1:2) afforded the pivaloate (**55**) (411mg, 81%) as a pale yellow oil. IR (neat): 2932, 2856, 1732, 1462, 1282, 1254, 1198, 1156, 1078, 1032, 978, 834, 774 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H, s), 0.86 (9H, s), 1.00–2.60 (16H, m), 1.17 (9H, s), 3.30–4.35 (8H, m), 4.50–4.72 (lH, m), 5.70 (lH, brs). MS (EI) m/z: 426 (M^+-DHP), 408 (M^+- DHP - H_2O). HR-MS (EI) m/z: 426.2782 (Calc'd for $C_{23}H_{42}O_5Si$, 426.2802, M^+-DHP).

(*1*R,*6*S,*7*S,*8*R)-*7*-tert-*Butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-3-pivaloyloxyacetyl*-cis-*bicyclo-[4.3.0]non-2-ene(56)*

Pyridine (1.28ml, 15.8mmol) was added to a suspension of CrO_3 (789mg, 7.89mmol) in methylene chloride (8ml) at room temperature, and then the mixture was supersonically irradiated for 5 min. After stirring at room temperature for 5 min, a solution of the pivaloate (**55**) (403mg, 0.789mmol) in methylene chloride (5ml) was added in one portion to the mixture of CrO_3 and pyridine at the same temperature. After stirring for 1 h, the reaction mixture

was diluted with ether, and then this suspension was filtered through florisil column with ether. The filtrate was concentrated and the residue was chromatographed on silica gel (ether–hexane, 1:8) to give the ketone (**56**) (289mg, 72%) as a colorless oil. IR (neat): 2932, 2856, 1740, 1690, 1284, 1254, 1148, 1078, 1032, 836, 776 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.87 (9H, s), 1.25 (9H, s), 1.30–2.70 (15H, m), 3.28–4.25 (5H, m), 4.51–4.72 (1H, m), 6.74 (1H, brs). MS (EI) m/z: 424 (M^+- DHP), 367 (M^+- DHP - *tert*-Bu). HR-MS (EI) m/z: 424.2614 (Calc'd for $C_{23}H_{40}O_5Si$, 424.2645, M^+-DHP).

(*1R,6S,7S,8R*)-7-tert-*Butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-3-(1-pivaloyloxymethylvinyl)*-cis-*bicyclo[4.3.0]non-2-ene(57)*

A solution of potassium *tert*-butoxide (298mg, 2.66mmol) in THF (5ml) was added to a suspension of methyltriphenylphosphonium bromide (949mg, 2.66mmol) in THF (5ml) at room temperature. After stirring for 15 min, a solution of the ketone (**56**) (285mg, 0.560mmol) in THF (4ml) was added to the stirring mixture at the same temperature. After stirring for 30 min, the reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with ether. The combined organic layer was dried over $MgSO_4$, and concentrated to give a yellow oily residue. The residue was purified by silica gel column chromatography (ether–hexane, 1:8) to give the exomethylene compound (**57**) (234mg, 83%) as a colorless oil. IR (neat): 2932, 2856, 1730, 1282, 1254, 1152, 1078, 1032, 1004, 976, 836, 774 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.19 (9H, s), 1.33–2.68 (15H, m), 3.30–4.32 (5H, m), 4.51–4.73 (1H, m), 4.74 (2H, s), 5.09, 5.15 (each 1H, s), 5.75 (1H, brs). MS (EI) m/z: 422 (M^+- DHP), 404 (M^+- THPOH), 365 (M^+- DHP - *tert*-Bu). HR-MS (EI) m/z: 404.2765 (Calc'd for $C_{24}H_{40}O_3Si$, 404.2747, M^+- THPOH).

(*1R,6S,7S,8R*)-7-tert-*Butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-3-(1-hydroxymethylvinyl)*-cis-*bicyclo[4.3.0]non-2-ene(58)*

$LiAlH_4$ (18mg, 0.456mmol) was added to a solution of the exomethylene compound (**57**) (231mg, 0.456mmol) in ether (10ml) at 0 °C. After stirring at room temperature for 30 min, the reaction mixture was cooled to 0 °C, and then quenched by the addition of $Na_2SO_4 \cdot 10H_2O$ and a small portion of water. After dilution with ether, the mixture was filtered with celite and the filtrate was dried over Na_2SO_4. Removal of the solvent afforded the allylalcohol (**58**) (193mg, quantitative yield) as a colorless oil. IR (neat): 3456, 2928, 2856, 1252, 1116, 1076, 1052, 1030, 834, 774 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 1.20–2.80 (16H, m), 3.30–4.20 (5H, m), 4.30 (2H, s), 4.50–4.70 (1H, m), 5.07 (2H, s), 5.82 (1H, brs). MS (EI) m/z : 422 (M^+), 338 (M^+- DHP). HR-MS (EI) m/z:: 338.2264 (Calc'd for $C_{19}H_{34}O_3Si$, 338.2277, M^+- DHP).

tert-*Butyl 5-*[(*1R,6S,7S,8R*)-7-tert-*butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy*-cis-*bicyclo[4.3.0]non-2-en-3-yl]-3-oxa-5-hexenoate(59)*

To a mixture of the allylalcohol (**58**) (190mg, 0.450mmol), *tert*-butyl bromoacetate (0.72ml, 4.50mmol) and a catalytic amount of tetrabutylammonium hydrogen sulfate in methylene chloride (3ml) was added 50% aqueous NaOH (1.5ml) at room temperature. The reaction mixture was stirred at the same temperature for 2 days, and stirred at 30 °C for 1 day, and then water was added to the reaction mixture. After extraction with methylene chloride, the combined organic layer was washed with water and brine, and dried over $MgSO_4$. The solution was concentrated, and the residue was chromatographed on silica gel (ether–hexane, 1:10) to give the *tert*-butylester (**59**) (219mg, 91%) as a colorless oil. IR (neat): 2932, 2856, 1750, 1254, 1160, 1132, 1078, 1030, 836, 776 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.88 (9H, s), 1.10–2.70 (15H, m), 1.47 (9H, s), 3.30–4.20 (5H, m), 3.92 (2H, s), 4.25 (2H, s), 4.50–4.70 (1H, m), 5.08, 5.13 (each 1H, s), 5.80–5.98 (1H, m). MS (EI) m/z: 536 (M^+), 452 (M^+-DHP). HR-MS (EI) m/z: 536.3563 (Calc'd for $C_{30}H_{52}O_6Si$, 536.3533, M^+).

tert-*Butyl 5-*[(*1R,6S,7S,8R*)-*8-tetrahydropyranyloxy-7-hydroxymethyl*-cis-*bicyclo[4.3.0]non-2-en-3-yl]-3-oxa-5-hexenoate(60)*

TBAF (1.0M in THF, 0.80ml, 0.80mmol) was added to a solution of **59** (216mg, 0.402mmol) in THF (3ml), and the mixture was stirred at room temperature for 15 h. 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, 2:1) to give the alcohol (**60**) (162mg, 95%) as a colorless oil. IR (neat): 3460, 2928, 2868, 1746, 1366, 1160, 1130, 1076, 1028 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.30–2.70 (15H, m), 1.47 (9H, s), 3.00 (1H, brs), 3.25–4.40 (5H, m), 3.91 (2H, s), 4.25 (2H, s), 4.45–4.80 (1H, m), 5.10, 5.14 (each 1H, s), 5.80–6.00 (1H, m). MS (EI) m/z: 422 (M^+), 338 (M^+- DHP), 320 (M^+- DHP - H_2O). HR-MS (EI) m/z: 338.2081 (Calc'd for $C_{19}H_{30}O_5$, 338.2093, M^+- DHP).

The typical procedure for the introduction of lower side chains; the synthesis of 5-[(*1R,6S,7S,8R*)-*8-hydroxy-7-[(E)-(3S)-3-hydroxy-1-octenyl*-cis-*bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoic acid(43a)*

tert-*Butyl 5-*[(*1R,6S,7S,8R*)-*7-formyl-8-tetrahydropyranyloxy*-cis-*bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoate(38)*

A solution of sulfur trioxide pyridine complex (2.33g, 14.6mmol) in DMSO (12ml) was added to a solution of the alcohol (**37**) (1.0g, 2.44mmol) and triethylamine (2.04ml, 14.6mmol) in DMSO (12ml), and the mixture was stirred at room temperature for 20 min. The reaction mixture was poured into ice water, and extracted with ethyl acetate. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography (ether–hexane, 1:2) afforded the aldehyde (**38**) (957mg, 96%) as a pale yellow oil. IR (neat): 2932, 1749, 1725,

1368, 1224, 1131, 1032 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10–2.80 (16H, m), 1.46 (9H, s), 3.30–4.10 (3H, m), 3.56 (2H, t, J=6.0Hz), 3.92 (2H, s), 4.20–4.45 (1H, m), 4.45–4.68 (1H, m), 5.39 (1H, brs), 9.72 (1H, brs). MS (FAB) m/z: 409 (M^+ + H), 381 (M^+ + H - CHO), 325 (M^+ + H - DHP). HR-MS (FAB) m/z: 325.2051 (Calc'd for $C_{18}H_{29}O_5$ 325.2015, M^+ + H - DHP).

tert-*Butyl 5-{(1*R,6S,7S,8R)-8-*tetrahydropyranyloxy-7-[(*E)-3-*oxo-1-octenyl]*-cis-*bicyclo[4.3.0]non-2-en-3-yl}-3-oxapentanoate(39a)*

To a suspension of sodium hydride (60% in oil, 22mg, 0.558mmol) in THF (1ml) was added a solution of dimethyl (2-oxoheptyl)phosphonate (186mg, 0.836mmol) in THF (2ml) at 0 °C, and the mixture was stirred at room temperature for 1 h. Then, a solution of the aldehyde (**38**) (114mg, 0.279mmol) in THF (3ml) was added dropwise to the solution of the sodium β-ketophosphonate, and the mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl, and extracted with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography (ether–hexane, 1:4) afforded the enone (**39a**) (125mg, 89%) as a pale yellow oil. IR (neat): 2932, 1750, 1673, 1134, 1034 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=6.0Hz), 1.00–2.09 (18H, m), 1.46 (9H, s), 2.09–2.66 (7H, m), 3.20–4.13 (3H, m), 3.58 (2H, t, J=6.5Hz), 3.93 (2H, s), 4.45–4.68 (1H, m), 5.35 (1H, brs), 6.13, 6.17 (total 1H, each d, J=17.0Hz), 6.75, 6.78 (total 1H, each dd, J=9.2, 17.0Hz). MS (FAB) m/z: 505 (M^+ + H), 421 (M^+ + H - DHP). HR-MS (FAB) m/z: 505.3500 (Calc'd for $C_{30}H_{49}O_6$, 505.3529, M^+ + H).

tert-*Butyl 5-{(1*R,6S,7S,8R)-*8-hydroxy-7-*[(E)-*3-oxo-1-octenyl]*-cis-*bicyclo[4.3.0]non-2-en-3-yl}-3-oxapentanoate (40a)*

A solution of the enone (**39a**) (125mg, 0.247mmol) in methanol (3.5ml) was stirred at room temperature for 30 min in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The combined 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) which afforded the alcohol (**40a**) (93mg, 90%) as a pale yellow oil. IR (neat): 3450, 2928, 2872, 1748, 1675, 1630, 1368, 1226, 1162, 1132 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.0Hz), 1.13–2.80 (20H, m), 1.46 (9H, s), 3.60 (2H, t, J=6.5Hz), 3.80–4.20 (1H, m), 3.94 (2H, s), 5.42 (1H, brs), 6.17 (1H, d, J=17.0Hz), 6.73 (1H, dd, J=9.2, 17.0Hz). MS (FAB) m/z: 421 (M^+ + H), 403 (M^+ + H - H_2O), 365 (M^+ + H - C_4H_8), 347 (M^+ + H - H_2O - C_4H_8). HR-MS (FAB) m/z: 421.2957 (Calc'd for $C_{25}H_{41}O_5$, 421.2954, M^+ + H).

tert-*Butyl 5-{(1*R,6S,7S,8R)-*8-hydroxy-7-[(E)-(3*S*)-*3-hydroxy-1-octenyl]*-cis-*bicyclo[4.3.0]non-2-en-3-yl}-3-oxapentanoate(41a)*

Diisobutylaluminum hydride (1.5M in toluene, 1.48ml, 2.22mmol) was added to a solution of 2,6-di-*tert*-butyl-4-methylphenol (977mg, 4.43mmol) in toluene (4.5ml) at -10 °C. After stirring at the same temperature for 1 h, a solution of the alcohol (**40a**) (93mg, 0.222mmol) in toluene (4.5ml) was added to the reaction mixture at -78 °C, which was allowed to warm to -10 °C for 6 h. The reaction mixture was quenched by the addition of methanol (2 drops), and after removal of the cooling bath, brine (1ml) and ethyl acetate (6ml) were added to the reaction mixture, and vigorous stirring was continued for 2 h. After decantation of organic layer, the residue was extracted with ethyl acetate. The combined organic layer was concentrated, and the residue was chromatographed on silica gel (ether–hexane, 3:1) to give the desired 15α-diol (**41a**) (57mg, 61%) as a more polar fraction and 15β-diol (**42a**) (27mg, 29%) as a less polar fraction. Spectral data of 15α-diol (**41a**): IR (neat): 3384, 2928, 2860, 1748, 1368, 1226, 1162, 1134 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.0Hz), 1.06–2.70 (21H, m), 1.46 (9H, s), 3.58 (2H, t, J=6.5Hz), 3.69–4.20 (2H, m), 3.93 (2H, s), 5.42–5.60 (3H, m). MS (FAB) m/z: 423 (M^+ + H), 405 (M^+ + H-H_2O). HR-MS (FAB) m/z: 423.3082 (Calc'd for $C_{25}H_{43}O_5$, 423.3110, M^+ + H). The spectral data of **42a** were nearly identical with those of **41a**.

*5-{(1*R,6S,7S,8R)-*8-Hydroxy-7-[(E)-(3*S*)-*3-hydroxy-1-octenyl]*-cis-*bicyclo[4.3.0]non-2-en-3-yl}-3-oxapentanoic acid(43a)*

To a solution of the diol (**41a**) (57mg, 0.135mmol) in methanol (2ml) was added 7% aqueous KOH (1.5ml) at 0 °C. After stirring at room temperature for 1 hr, the reaction mixture was washed with pentane (2ml), and then acidified to pH 3–4 with 2N aqueous HCl, and extracted with ethyl acetate. The combined ethyl acetate layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent afforded **43a** (46mg, 93%) as a pale yellow oil. IR (neat): 3370, 2926, 1737, 1131 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.0Hz), 1.05–2.80 (21H, m), 3.63 (2H, t, J=6.5Hz), 3.70–4.20 (2H, m), 4.05 (2H, s), 5.30–5.70 (3H, m). ^{13}C-NMR ($CDCl_3$) δ: 172.8, 135.2, 133.8, 132.7, 127.6, 77.6, 73.5, 70.1, 67.7, 53.0, 40.1, 40.0, 38.0, 36.8, 35.5, 31.7, 25.2, 24.4, 23.1, 22.6, 14.0. MS (FAB) m/z: 367 (M^+ + H), 349 (M^+ + H - H_2O), 331 (M^+ + H - $2H_2O$). HR-MS (FAB) m/z: 331.2240 (Calc'd for $C_{21}H_{31}O_3$, 331.2273, M^+ + H - $2H_2O$). $[\alpha]^{25}_D$: +22.5° (c = 0.68, $CHCl_3$).

Other 3-oxahomoisocarbacyclins (**43**), (*Z*)-4-dehydro-homoisocarbacyclins (**51**) and 5-methylene-3-oxahomo-isocarbacyclins (**61**) were also synthesized from the corresponding versatile alcohols (**37**, **45** and **60**) in the same sequence of reactions for the synthesis of **43a** using the corresponding β-ketophosphonates. In the case of (*Z*)-4-

dehydrohomoisocarbacyclins (**51**), the hydrolysis was achieved by using 10% aqueous NaOH in ethanol. These spectral data are summarized in Tables 11, 12 and 13.

*The typical procedure for the synthesis of 13-dehydro-homoisocarbacyclins; the synthesis of 5-[(1R,6S,7S,8R)-8-hydroxy-7-[(3S)-3-hydroxy-4,4-dimethyl-1,6-nonadiynyl]-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoic acid(**74b**)*

tert-*Butyl 5-[(1R,6S,7S,8R)-7-[(Z)-2-bromo-4,4-dimethyl-3-oxo-1-nonen-6-ynyl]-8-hydroxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoate(**70**)*

Diethylaluminum chloride (1.0M in hexane, 0.81ml, 0.81mmol) was added to a slurry of zinc dust (53mg, 0.81mmol) and a catalytic amount of copper (I) bromide in THF (3ml) and the resulting mixture was activated with supersonic irradiation at room temperature for 1 h. To this suspension was added slowly a mixture of 1,1-dibromoketone (**67**) (683mg, 2.22mmol) and the aldehyde (**38**) (300mg, 0.74mmol) in THF (7ml) at -40 °C. The reaction mixture was stirred at -40 °C for 30 min, and then allowed to warm to 0 °C for 1 h. The reaction was quenched with saturated aqueous $KHCO_3$, and the product was extracted with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent afforded the α-bromo-β-hydroxyketone (**68b**). A solution of **68b** in methylene chloride (5ml) was treated with methanesulfonyl chloride (2.0ml, 26.0mmol) in the presence of triethylamine (7ml, 50.5mmol) at -70 °C. After stirring at -70 °C for 15 min, the resulting suspension was allowed to warm to 0 °C and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.0ml, 15.4mmol) was added to this suspension at 0 °C. The whole reaction mixture was stirred at 0 °C for 12 h. The reaction mixture was poured into ice water and extracted with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and purification of the residue by silica gel column chromatography (ether–hexane, 1:4) gave the inseparable mixture (226mg) of the α-bromoenone (**69b**) and the enone (**39c**) as a pale yellow oil. To a solution of this mixture in THF (6ml) was added 65% aqueous acetic acid (7ml), and the reaction mixture was stirred at 65 °C for 5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the residue was extracted with ether. The combined organic layer was washed with water and 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 (**70b**) (163mg, 41%) as a pale yellow oil together with the undesired enone (**40c**) (54mg, 16%). Spectral data of **70b**: IR (neat): 3500, 2950, 2880, 1740, 1690, 1620, 1460, 1365 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7.2Hz), 1.35 (6H, s), 1.50 (9H, s), 1.56–2.70 (15H, m), 2.80–3.08 (1H, m), 3.60 (2H, t, J=7.2Hz), 3.95 (2H, s), 3.98–4.16 (1H, m), 5.42 (1H, brs), 6.20 (1H, d, J=8.8Hz). MS (FAB) m/z: 537 (M^+ + H), 481 (M^+ + H - C_4H_8). HR-MS (FAB) m/z: 481.1577 (Calc'd for $C_{24}H_{34}O_5Br$, 481.1590, M^+ + H - C_4H_8).

tert-*Butyl 5-[(1R,6S,7S,8R)-7-[(Z)-(3S)-2-bromo-3-hydroxy-4,4-dimethyl-1-nonen-6-ynyl]-8-hydroxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoate(**71b**)*

Diisobutylaluminum hydride (1.0M in toluene, 1.8ml, 1.8mmol) was added dropwise to a solution of 2,6-di-*tert*-butyl-4-methylphenol (475mg, 2.16mmol) in toluene (4ml) at -20 °C. After stirring at -20 °C for 1 h, a solution of the α-bromoenone (**70b**) (88mg, 0.16mmol) in toluene (6ml) was added to the reaction mixture at -78 °C, which was stirred at -78 °C for 40 min and then allowed to warm to -10 °C for 3.5 h. The reaction mixture was quenched by the addition of methanol (2 drops), and after removal of the cooling bath, brine (1ml) and ethyl acetate (6ml) were added to the reaction mixture, and vigorous stirring was continued for 2 h. After decantation of organic layer, the residue was extracted with ethyl acetate. The combined organic layer was washed with brine, and dried over $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography (ethyl acetate–hexane, 2:3) afforded the desired 15α-diol (**71b**) (45.8mg, 53 %) as a more polar fraction and the 15β-diol (**72b**) (18.5mg, 22%) as a less polar fraction. Spectral data of the 15α-diol (**71b**): IR (neat): 3450, 2950, 2930, 1750, 1450, 1370, 1140 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.06, 1.10 (each 3H, s), 1.16 (3H, t, J=7.2Hz), 1.50 (9H, s), 1.55–2.65 (16H, m), 2.73–3.04 (1H, m), 3.62 (2H, t, J=7.2Hz), 3.82–4.00 (1H, m), 3.90 (2H, s), 5.40 (1H, brs), 5.84 (1H, d, J=8.8Hz). MS (FAB) m/z: 539 (M^+ + H), 483 (M^+ + H - C_4H_8). HR-MS (FAB) m/z: 483.1773 (Calc'd for $C_{24}H_{36}O_5Br$, 483.1746, M^+ + H - C_4H_8). The spectral data of **72b** were nearly identical with those of **71b**.

*Methyl 5-[(1R,6S,7S,8R)-8-hydroxy-7-[(3S)-3-hydroxy-4,4-dimethyl-1,6-nonadiynyl]-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoate(**73b**)*

A solution of the diol (**71b**) (45.8mg, 0.09mmol) in toluene–ether (6ml, 2:1) was added to tetrabutylammonium hydrogen sulfate (152mg, 0.45mmol) containing water (2 drops). After adding 50% aqueous NaOH (0.50ml), the whole reaction mixture was stirred at room temperature for 2.5 days. The reaction was acidified to pH 3–4 with 5% aqueous HCl and extracted with ethyl acetate. The combined organic layer was washed with 5% aqueous HCl, water, and brine, and then dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was treated with ethereal diazomethane at 0 °C until the carboxylic acid had disappeared on TLC. After evaporation, the residue was purified by silica gel column chromatography (ether–hexane, 5:1) which afforded the methylester (**73b**) (28.3mg, 76%) as a pale yellow oil. IR (neat): 3400, 2950, 2900, 2250, 1760, 1440, 1210, 1140 cm^{-1}. ^1H-NMR ($CDCl_3$) δ : 1.08, 1.10 (each 3H, s), 1.16 (3H, t, J=7.2Hz), 1.30–2.70 (17H, m), 3.60 (2H, t, J=7.2Hz), 3.80 (3H, s), 4.00–4.16 (1H, m), 4.08 (2H, s), 4.26 (1H, d, J=2.0Hz), 5.36 (1H, brs). MS (FAB) m/z: 417 (M^+ + H), 399 (M^+ + H - H_2O), 381 (M^+ + H - $2H_2O$). HR-MS (FAB) m/z: 417.2623 (Calc'd for $C_{25}H_{37}O_5$, 417.2641, M^+ + H).

*5-[(1R,6S,7S,8R)-8-Hydroxy-7-[(3S)-3-hydroxy-4,4-dimethyl-1,6-nonadiynyl]-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoic acid(**74b**)*

To a solution of the methyl ester (**73b**) (28mg, 0.067mmol) in methanol (2ml) was added 10% aqueous NaOH (5ml) at 0 °C. After stirring at 0 °C for 12 h, the reaction mixture was washed with pentane (2ml), and then acidified to pH 3–4 with 2N aqueous HCl, and extracted with ethyl acetate. The combined ethyl acetate layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent afforded **74b** (27mg, quantitative yield) as a pale yellow oil. IR (neat): 3406, 2968, 2920, 2230, 1734, 1434, 1320 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04, 1.08 (each 3H, s), 1.12 (3H, t, J=7.2Hz), 1.60–2.68 (17H, m), 3.60 (2H, t, J=7.2Hz), 4.00–4.15 (1H, m), 4.04 (2H, s), 4.26 (1H, d, J=2.0Hz), 5.38 (1H, brs). ^{13}C-NMR ($CDCl_3$) δ: 173.4, 132.7, 126.8, 87.7, 83.7, 80.5, 78.1, 76.8, 69.9, 69.3, 67.5, 41.7, 41.2, 39.6, 38.6, 37.6, 35.3, 28.2, 24.1, 23.3, 22.8, 22.1, 14.2, 12.3. MS (FAB) m/z: 403 (M^+ + H), 385 (M^+ + H - H_2O), 367 (M^+ + H-$2H_2O$). HR-MS (FAB) m/z: 385.2372 (Calc'd for $C_{24}H_{33}O_4$, 385.2379, M^+ + H - H_2O). $[\alpha]^{27}_D$: +61.58° (c=1.01, CH_3OH).

In a similar manner, **38** and **46** were converted into various 13-dehydrohomoisocarbacyclins (**74** and **75**) using the corresponding 1,1-dibromoketones. These spectral data are summarized in Table 14.

*1-Bromo-1-chloro-3,3-dimethyl-5-octyn-2-one(**77**)*

To a solution of diisopropylamine (6.9ml, 49.6ml) in THF–ether (60ml, 1:2) was added a solution of *n*-butyllithium (1.54M in hexane, 31.4ml, 48.4mmol) at -78 °C. After stirring at -78 °C for 1 h, the mixture was cooled to -100 °C and a solution of bromochloromethane (3.4ml, 51.9mmol) in THF (14ml) was added dropwise to lithium diisopropylamide solution over 25 min. After stirring at -100 °C for 25 min, a solution of the ester (**76**) (4.30g, 23.6mmol) in THF (20ml) was added to the solution of bromochloromethyllithium, and the whole reaction mixture was stirred at -100 to -78 °C for 45 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl at -70 °C, and extracted with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography (ether–hexane, 1:40) gave the 1-bromo-1-chloroketone (**77**) (5.49g, 88%) as a pale yellow oil. IR (neat): 2976, 2936, 1728, 1468 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7.5Hz), 1.35 (6H, s), 1.93–2.23 (2H, m), 2.30–2.43 (2H, m), 6.45 (1H, s). MS (FAB) m/z: 265 (M^+ + H). HR-MS (FAB) m/z : 265.0025 (Calc'd for $C_{10}H_{15}OClBr$, 264.9995, M^+ + H).

tert-*Butyl 5-[(1R,6S,7S,8R)-7-[(Z)-2-chloro-4,4-dimethyl-3-oxo-1-nonen-6-ynyl]-8-tetrahydropyranyloxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoate(**79b**)*

Diethylaluminum chloride (1.0M in hexane, 4.2ml, 4.20mmol) was added to a slurry of zinc dust (287mg, 4.24mmol) and copper(I) bromide (63mg, 0.44mmol) in THF (20ml) and the resulting mixture was activated with supersonic irradiation for 45 min at room temperature. To this suspension was added slowly over 20 min a mixture of 1-bromo-1-chloroketone (**77**) (2.43g, 9.20mmol) and the aldehyde (**38**) (1.50g, 3.68mmol) in THF (25ml) at -20 °C. After stirring at the same temperature for 45 min, the reaction was quenched with saturated aqueous $KHCO_3$, and the product was extracted with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent afforded the α-chloro-β-hydroxyketone (**78b**). A solution of **78b** in methylene chloride (46ml) was treated with methanesulfonyl chloride (5.1ml. 66.5mmol) in the presence of triethylamine (30ml, 219mmol) at -40 °C. The resulting suspension was allowed to warm to 0 °C and stirred for 30 min. To this suspension was added 1,8-diazabicyclo[5.4.0]undec-7-ene (9.9ml, 60.5mmol) at 0 °C and the whole reaction mixture was stirred at 0 °C for 13.5 h. The reaction mixture was poured into ice water and extracted with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and purification of the residue by silica gel column chromatography (ether–hexane, 1:4) gave the α-chloroenone (**79b**) (1.85g, 85% as a pale yellow oil together with the enone (**39c**) (35.8mg, 2%). Spectral data of the α-chloroenone (**79b**): IR (neat): 2926, 1749, 1689, 1610, 1458, 1368, 1254 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 1.06 (3H, t, J=7.2Hz), 1.33 (6H, s), 1.40–2.63 (20H, m), 1.45 (9H, s), 2.85–3.10 (1H, m), 3.30–3.80 (2H, m), 3.54 (2H, t, J=7.2Hz), 3.85–4.13 (1H, m), 3.90 (2H, s), 4.40–4.65 (1H, m), 5.33 (1H, brs), 6.33, 6.36 (total 1H, each d, J=10.2Hz). MS (FAB) m/z: 493 (M^+ + H - DHP). HR-MS (FAB) m/z: 493.2749 (Calc'd for $C_{28}H_{42}O_5Cl$, 493.2721, M^+ + H - DHP).

tert-*Butyl 5-[(1R,6S,7S,8R)-7-[(Z)-2-chloro-4,4-dimethyl-3-oxo-1-nonen-6-ynyl]-8-hydroxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoate(**80b**)*

A solution of **79b** (5.70g, 9.89mmol) in methanol (35ml) was stirred at room temperature for 75 min in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$, and the organic solvent was evaporated. The residue was extracted with ether, and the ether layer was washed with water and 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 give the alcohol (**80b**) (4.62g, 95%) as a pale yellow oil. IR (neat): 3480, 2976, 2932, 1748, 1686, 1600, 1458, 1392, 1226, 1132 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 1.07 (3H, t, J=7.2Hz), 1.35 (6H, s), 1.45 (9H, s), 1.52–2.70 (15H, m), 2.75–3.10 (1H, m), 3.66 (2H, t, J=7.2Hz), 3.85–4.10 (1H, m), 3.90 (2H, s), 5.38 (1H, brs), 6.30 (1H, d, J=10.2Hz). MS (FAB) m/z: 493 (M^+ + H). HR-MS (FAB) m/z: 493.2712 (Calc'd for $C_{28}H_{42}O_5Cl$, 493.2721, M^+ + H).

tert-*Butyl 5-[(1R,6S,7S,8R)-7-[(Z)-(3S)-2-chloro-3-hydroxy-4,4-dimethyl-1-nonen-6-ynyl]-8-hydroxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoate(**81b**)*

Diisobutylaluminum hydride (1.5M in toluene, 18.5ml, 27.8mmol) was added to a solution of 2,6-di-*tert*-butyl-4-

methylphenol (9.78g, 44.5mmol) in toluene (84ml) at 0 °C over 30 min. After stirring at 0 °C for 90 min, a solution of the alcohol (**80b**) (1.37g, 2.78mmol) in toluene (30ml) was added to the reaction mixture at -78°C, which was allowed to warm to -60°C for 2 h. The reaction mixture was quenched by the addition of methanol (0.8ml). After removal of the cooling bath, brine (15ml) and ethyl acetate (30ml) were added to the reaction mixture, and vigorous stirring was continued for 2 h. After decantation of organic layer, the residue was extracted with ethyl acetate. The combined organic layer was washed with brine, and dried over $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography (ether–hexane, 1:1) gave the desired 15α-diol (**81b**) (1.18g, 86%) as a more polar fraction and the 15β-diol (**82b**) (0.16g, 12%) as a less polar fraction. Spectral data of the 15α-diol (**81b**): IR (neat): 3432, 2976, 2928, 1746, 1368, 1240, 1134, 1044 cm^{-1}. ^1H-NMR ($CDCl_3$) δ : 1.01 (6H, s), 1.10 (3H, t, J=7.2Hz), 1.35–2.65 (16H, m), 1.45 (9H, s), 2.68–3.00 (1H, m), 3.56 (2H, t, J=7.2Hz), 3.90 (2H, s), 3.95–4.20 (2H, m), 5.35 (1H, brs), 5.58 (1H, d, J=10.2Hz). MS (FAB) m/z: 495 (M^++ H). HR-MS (FAB) m/z : 495.2861 (Calc'd for $C_{28}H_{44}O_5Cl$, 495.2878, M^+ + H). The spectral data of **82b** were nearly identical with those of **81b**.

*5-[(1*R,6S,7S,8R*)-8-Hydroxy-7-[(3*S*)-3-hydroxy-4,4-dimethyl-1,6-nonadiynyl]-8-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoic acid(**74b**)*

A solution of the diol (**81b**) (500mg, 1.01mmol) in toluene (20ml) was added to tetrabutylammonium hydrogen sulfate (3.46g, 10.2mmol) containing water (20 drops). After adding 50% aqueous NaOH (16.3ml, 204mmol), the whole reaction mixture was stirred at 65 °C for 11 h. After cooling, the reaction was acidified to pH 3–4 with 5% aqueous HCl, and extracted with ethyl acetate. The combined organic layer was washed with 5% aqueous HCl, water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (chloroform–methanol–acetic acid, 50:2:1), followed by treating with active carbon in ether. Removal of the solvent afforded **74b** (351mg, 86%) as a pale yellow oil, whose spectral data were identical with those of an authentic material.

The typical procedure for the synthesis of 13,14-dihydrohomoisocarbacyclins; the synthesis of (Z)*-5-[(1*R,6S,7S,8R*)-7-[3-(4-biphenyl)-3-hydroxypropyl]-8-hydroxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-4-pentenoic acid(**85a**)*

Ethyl (Z)*-5-[(1*R,6S,7S,8R*)-7-[(*E*)-3-(4-biphenyl)-3-oxo-1-propenyl]-8-hydroxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-4-pentenoate(**48j**)*

A solution of the tetrahydropyranyloxy ether (**47j**) (473mg, 0.853mmol) in methanol–THF (4ml, 1:1) was stirred at room temperature for 2 h in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The combined organic layer was washed with water and 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 (**48j**) (376mg, 94%) as a yellow oil. IR (neat): 3436, 2924, 1732, 1666, 1616, 1556, 1192 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.5Hz), 1.36–2.90 (14H, m), 3.26–3.53 (1H, m), 4.12 (2H, q, J=7.5Hz), 5.08–5.43 (1H, m), 5.54 (1H, brs), 5.79 (1H, d, J=12.0Hz), 6.86–7.10 (1H, m), 7.26–8.09 (10H, m). MS (FAB) m/z: 471 (M^+ + H), 453 (M^+ + H - H_2O). HR-MS (FAB) m/z: 471.2522 (Calc'd for $C_{31}H_{35}O_4$, 471.2535, M^+ + H).

Ethyl (Z)*-5-[(1*R,6S,7S,8R*)-7-[3-(4-biphenyl)-3-oxopropyl]-8-hydroxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-4-pentenoate(**83a**)*

Sodium bis(2-methoxyethoxy)aluminum hydride (Vitride®, 70% in benzene, 1.09ml, 7.99mmol) was added dropwise to a suspension of copper(I) bromide (604mg, 4.00mmol) in THF (5ml) at -20 °C, and the mixture was stirred at -20 °C for 30 min. To this solution was added slowly a mixture of the enone (**48j**) (376mg, 0.799mmol) and 2-butanol (0.74ml, 8.07mmol) in THF (10ml) at -78 °C, and the whole reaction mixture was stirred at -78 °C for 40 min. The reaction mixture was quenched by the addition of water and saturated aqueous NH_4Cl, and vigorous stirring was continued until the aqueous layer had become blue, and extracted with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography (ether–hexane, 1:1) afforded the saturated ketone (**83a**) (346mg, 92%) as a yellow oil. IR (neat): 3452, 2924, 1730, 1680, 1604, 1448, 1404, 1372, 1190 cm^{-1}. ^1H-NMR ($CDCl_3$) δ : 1.25 (3H, t, J=7.0Hz), 1.30–2.76 (16H, m), 3.15 (2H, t, J=6.0Hz), 3.70–4.00 (1H, m), 4.10 (2H, q, J=7.0Hz), 5.08–5.40 (1H, m), 5.55 (1H, brs), 5.78 (1H, d, J=12.0Hz), 7.27–7.78 (7H, m), 7.85–8.16 (2H, m). MS (FAB) m/z: 473 (M^+ + H), 455 (M^+ + H - H_2O). HR-MS (FAB) m/z: 455.2614 (Calc'd for $C_{31}H_{35}O_3$, 455.2586, M^+ + H - H_2O).

Ethyl (Z)*-5-[(1*R,6S,7S,8R*)-7-[3-(4-biphenyl)-3-hydroxypropyl]-8-hydroxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl]-4-pentenoate(**84a**)*

Diisobutylaluminum hydride (1.5M in toluene, 4.9ml, 7.32ml) was added to a solution of 2,6-di-*tert*-butyl-4-methylphenol (3.23g, 14.6mmol) in toluene (15ml) at -10 °C. After stirring at -10 °C for 1 h, a solution of the saturated ketone (**83a**) (346mg, 0.732mmol) in toluene (15ml) was added dropwise to the solution at -78 °C, and the reaction mixture was stirred at -78 to -20 °C for 7 h. The reaction mixture was quenched by the addition of methanol (5 drops), after removal of the cooling bath, brine (3ml) and ethyl acetate (20ml) were added to the reaction mixture, and vigorous stirring was continued for 2 h. After decantation of organic layer, the residue was extracted with ethyl acetate. The combined organic layer was washed with brine, and dried over $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography (ether–hexane, 1:1) gave the diol (**84a**)

(299mg, 86%) as a pale yellow oil. IR (neat): 3384, 2924, 1728, 1486, 1414, 1372, 1158, 1038 cm^{-1}. ^1H-NMR ($CDCl_3$) δ : 1.23 (3H, t, J=7.0Hz), 1.35–2.83 (19H, m), 3.33–3.90 (1H, m), 4.10 (2H, q, J=7.0Hz), 4.83 (1H, t, J=6.0Hz), 5.10–5.40 (1H, m), 5.53 (1H, brs), 5.78 (1H, d, J=12.0Hz), 7.28–7.68 (9H, m). MS (FAB) m/z: 475 (M^+ + H), 457 (M^+ + H - H_2O), 439 (M^+ + H - $2H_2O$). HR-MS (FAB) m/z: 457.2737 (Calc'd for $C_{31}H_{37}O_3$, 457.2743, M^+ + H - H_2O).

*(Z)-5-{(1R,6S,7S,8R)-7-[3-(4-Biphenyl)-3-hydroxypropyl]-8-hydroxy-*cis*-bicyclo[4.3.0]non-2-en-3-yl}-4-pentenoic acid(85a)*

To a solution of the diol (**84a**) (299mg, 0.630mmol) in ethanol (10ml) was added 10% aqueous NaOH (5ml) at 0 °C. After stirring at room temperature for 2.5 h, the reaction mixture was washed with pentane (10ml) and acidified to pH 3–4 with 2N aqueous HCl, and then extracted with ethyl acetate. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent afforded **85a** (278mg, 99%) as a colorless amorphous solid. **85a** was separated into two peaks at t_R (min) = 51.0 (15α-diol) and t_R (min) = 58.5 (15β-diol) in a ratio of 16:1 by HPLC. IR (KBr): 3384, 2924, 1712, 1486, 1410, 1374 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.06–2.86 (19H, m), 3.65–3.93 (lH, m), 4.76 (1H, t, J=6.0Hz), 5.03–5.35 (1H, m), 5.50 (1H, brs), 5.77 (1H, d, J=12.0Hz), 7.23–7.65 (9H, m). ^{13}C-NMR ($CDCl_3$) δ: 176.7, 143.5, 140.6, 140.0, 134.3, 132.6, 130.4, 128.6, 128.6, 127.1, 127.0, 126.9, 126.9, 126.8, 126.8, 126.2, 126.2, 78.7, 74.4, 50.9, 41.0, 40.8, 37.0, 36.4, 34.6, 29.7, 26.7, 26.1, 24.3. MS (FAB) m/z : 429 (M^+ + H - H_2O), 411 (M^+ + H - $2H_2O$). HR-MS (FAB) m/z: 429.2448 (Calc'd for $C_{29}H_{33}O_3$, 429. 2429, M^+ + H - H_2O).

The enones (**47i**, **47c**, **39k** and **39j**) were converted into 13, 14-dihydrohomoisocarbacyclins (**85b**, **85c**, **85d** and **85e**) in the same manner as described for the synthesis of **85a**. Spectral data are summarized in Table 15.

*Methyl 4-[(1R,2S,3R)-2-*tert*-butyldimethylsilyloxymethyl-3-tetrahydropyranyloxy-5-oxocyclopentyl]-2-butenoate(88)*

DMSO (3.3ml, 43.2mmol) in methylene chloride (10ml) was added to a solution of oxalyl chloride (1.85ml, 21.6mmol) in methylene chloride (10ml) at -78 °C, and the mixture was stirred at the same temperature for 30 min. Then, a solution of the alcohol (**14**) (3.08g, 7.2mmol) in methylene chloride (15ml) was added dropwise at -78 °C, and the whole reaction mixture was stirred at the same temperature for 30 min. After dropwise addition of triethylamine (15.0ml, 108mmol) at -78 °C, the reaction mixture was stirred at room temperature for 10 min, and quenched by the addition of water, followed by extraction with methylene chloride. The combined 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, 1:2) to give the ketone (**88**) (2.78g, 91%) as a colorless oil. IR (neat): 2950, 2860, 1740, 1720, 1660, 1480, 1440, 1030, 840 cm^{-1}. ^1H-NMR ($CDCl_3$) δ : 0.04 (6H, s), 0.86 (9H, s), 1.13–1.90 (6H, m), 1.93–3.00 (6H, m), 3.30–4.03 (4H, m), 3.66 (3H, s), 4.05–4.52 (1H, m), 4.56–4.80 (1H, m), 5.86 (1H, d, J=15.0Hz), 6.90 (1H, dt, J=7.5, 15.0Hz). MS (EI) m/z: 369 (M^+- *tert*-Bu), 285 (M^+ - DHP - *tert*-Bu). HR-MS (EI) m/z: 369.1710 (Calc'd for $C_{18}H_{29}O_6Si$, 369.1731, M^+- *tert*-Bu).

*Methyl 4-[(1S,2S,3R)-2-*tert*-butyldimethylsilyloxymethyl-3-tetrahydropyranyloxy-5-methylenecyclopentyl]-2-butenoate(89)*

The methylenation reagent prepared by Lombardo's method ($Zn–CH_2Br_2–TiCl_4$) was added to a solution of the ketone (**88**) (1.60g, 3.7mmol) in methylene chloride (20ml) at room temperature until the starting material had disappeared on TLC. The reaction mixture was poured into a mixture of saturated aqueous $NaHCO_3$ (150ml), ether (150ml) and a small amount of celite, following this it was stirred vigorously. After filtration of the pale green suspension through celite pad, the ether layer was separated and the aqueous layer was further extracted with ether. The combined organic layer was washed with brine, and dried over $MgSO_4$. Removal of the solvent and purification of the residue by silica gel column chromatography (ether–hexane, 1:6) afforded **89** (1.23g, 78%) as a colorless oil. IR (neat): 2950, 2860, 1730, 1660, 1480, 1440, 1260, 1200, 840 cm^{-1}. ^1H-NMR ($CDCl_3$) δ : 0.05 (6H, s), 0.90 (9H, s), 1.10–1.96 (6H, m), 2.00–2.86 (6H, m), 3.10–4.26 (5H, m), 3.70 (3H, s), 4.50–4.65 (1H, m), 4.80, 4.90 (each 1H, s), 5.85 (1H, d, J=15.0Hz), 6.96 (1H, dt, J=7.5, 15.0Hz). MS (EI) m/z: 367 (M^+- *tert*-Bu), 340 (M^+-DHP). HR-MS (EI) m/z: 367.1968 (Calc'd for $C_{19}H_{31}O_5Si$, 367.1939, M^+- *tert*-Bu).

*Methyl 4-[(1S,2S,3S)-2-*tert*-butyldimethylsilyloxymethyl-3-tetrahydropyranyloxy-5-methylenecyclopentyl]-3-dimethylphenylsilylbutanoate(90)*

Dimethylphenylsilyllithium (1.83M in THF, 6.1ml, 11.3mmol) was added to a stirred suspension of copper (I) cyanide (500mg, 5.66mmol) in THF (5ml) at 0 °C, and the mixture was stirred at the same temperature for 25 min. A solution of the α,β-unsaturated ester (**89**) (1.20g, 2.83mmol) in THF (5ml) was added to the reaction mixture at 0 °C, and the whole reaction mixture was stirred at the same temperature for 30 min. After dilution with ether, the reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by extraction with ether. The combined organic layer was washed with brine, and dried over $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography (ether–hexane, 1:8) afforded the β-dimethylphenylsilyl ester (**90**) (1.56g, 99%) as a pale yellow oil. IR (neat): 3000, 2950, 2860, 1740, 1660, 1470, 1430, 1250, 840 cm^{-1}. ^1H-NMR ($CDCl_3$) δ : 0.05 (6H, s), 0.30 (6H, s), 0.90 (9H, s), 1.03–2.00 (10H, m), 2.00–2.80 (5H, m), 3.20–3.60 (3H, m), 3.53 (3H, s), 3.70–4.16 (2H, m), 4.53–4.70 (1H, m), 4.86 (2H, d, J=9.0Hz), 7.23–7.66 (5H, m). MS (EI) m/z: 560 (M^+), 503 (M^+- *tert*-Bu), 476 (M^+- DHP). HR-MS (EI) m/z: 560.3341 (Calc'd for $C_{31}H_{52}O_5Si_2$, 560.3350, M^+).

Methyl 4-[(*1S,2S,3R,5S*)-2-tert-*butyldimethylsilyloxymethyl-3-tetrahydropyranyloxy-5-hydroxymethylcyclopentyl]-3-dimethylphenylsilylbutanoate(**91**)*

A solution of disiamylborane in THF (0.73M, 14.2ml, 10.4mmol) was added to a stirred solution of **90** (2.32g, 4.14mmol) in THF (10ml) at 0 °C, and the mixture was stirred at the same temperature for 1 h. Then, 6N aqueous NaOH (7.1ml, 42.6mmol) and 30% H_2O_2 (5.9ml, 52.0mmol) were added at 0 °C, and the whole reaction mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with ethyl acetate, and the combined organic layer was washed with saturated aqueous $Na_2S_2O_3$ and brine, and dried over $MgSO_4$. Removal of the solvent and purification of the residue by silica gel column chromatography (ether) afforded the alcohol (**91**) (2.2g, 92%) as a colorless oil. IR (neat): 3500, 3100, 2970, 2860, 1740, 1480, 1440, 1260, 1200, 850 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.03, 0.05 (total 6H, each s), 0.36 (6H, s), 0.93 (9H, s), 1.10–2.06 (14H, m), 2.10–2.50 (3H, m), 3.20–4.32 (7H, m), 3.62,3.68 (total 3H, each s), 4.63–4.85 (lH, m), 7.26–7.70 (5H, m). MS (EI) m/z: 521 (M^+-*tert*-Bu), 494 (M^+- DHP). HR-MS (EI) m/z: 494.2853 (Calc'd for $C_{26}H_{46}O_5Si$, 494.2880, M^+- DHP).

(*1S,2S,3S,4R*)-*3*-tert-*Butyldimethylsilyloxymethyl-4-tetrahydropyranyloxy-1-hydroxymethyl-2-(2-dimethylphenylsilyl-4-hydroxybutyl)cyclopentane(**92**)*

A solution of the alcohol (**91**) (2.2g, 3.8mmol) in THF (10ml) was added to a suspension of $LiAlH_4$ (0.7g, 19.0mmol) in THF (20ml) at 0 °C. The mixture was stirred at 0 °C for 40 min, then Na_2SO_4•$10H_2O$ was added at 0 °C. The precipitate was filtered off and the filtrate was evaporated. The obtained residue was purified by silica gel column chromatography (ether) to afford the diol (**92**) (2.06g, 98%) as a colorless oil. IR (neat): 3400, 3050, 2950, 2870, 1480, 1430, 1260, 1200, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.03, 0.05 (total 6H, each s), 0.30 (6H, s), 0.90, 0.92 (total 9H, each s), 1.20–2.35 (16H, m), 3.63–4.26 (11H, m), 4.55–4.70 (1H, m), 7.23–7.70 (5H, m). MS (EI) m/z: 391 (M^+- DHP - H_2O -*tert*-Bu). HR-MS (EI) m/z : 391.2154 (Calc'd for $C_{21}H_{35}O_3Si_2$, 391.2123, M^+- DHP - H_2O -*tert*-Bu).

(*1R,6S,7S,8R*)-*7*-tert-*Butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-4-dimethylphenylsilyl*-cis-*bicyclo[4.3.0]non-2-ene-3-carbaldehyde(**93**)*

A solution of DMSO (0.64ml, 9.0mmol) in methylene chloride (3ml) was added dropwise to a solution of oxalyl chloride (0.34ml, 4.0mmol) in methylene chloride (5ml) at -78 °C, and the mixture was stirred at the same temperature for 30 min. Then, a solution of the diol (**92**) (550mg, 1.0mmol) in methylene chloride (5ml) was added dropwise to the mixture at -78 °C, and the whole reaction mixture was stirred at the same temperature for 30 min. After dropwise addition of triethylamine (2.8ml, 20.1mmol) at -78 °C, the reaction mixture was stirred at room temperature for 15 min. The reaction mixture was quenched by the addition of water, followed by extraction with methylene chloride. The combined organic layer was washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was dissolved with toluene (10ml), and dibenzylammonium trifluoroacetate (318mg, 1.0mmol) was added to the mixture. The mixture was stirred at 110 °C for 70 min, and then cooled to room temperature. The reaction mixture was quenched by the addition of water, followed by extraction with ether. The combined organic layer was washed with saturated aqueous NH_4Cl, brine and water, and dried over $MgSO_4$. Removal of the solvent afforded the oily residue, which was purified by silica gel column chromatography (ether–hexane, 1:6) to give the enal (**93**) (370mg, 70%) as a pale yellow oil. IR (neat): 3100, 2980, 2880, 1690, 1620, 1470, 1260, 1200, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.03, 0.05 (total 6H, each s), 0.26, 0.30, 0.36 (total 6H, each s), 0.80, 0.86 (total 9H, each s), 1.10–2.46 (14H, m), 3.16–3.60 (3H, m), 3.63–4.36 (2H, m), 4.43–4.70 (1H, m), 6.50–6.80 (1H, m), 7.13–7.65 (5H, m), 9.30, 9.36 (total 1H, each s). MS (EI) m/z: 444 (M^+- DHP), 443 (M^+-DHP - H). HR-MS (EI) m/z: 444.2492 (Calc'd for $C_{25}H_{40}O_3Si_2$, 444.2513, M^+- DHP).

Methyl [(*1R,6S,7S,8R*)-*7*-tert-*butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-4-dimethylphenylsilyl*-cis-*bicyclo[4.3.0]non-2-ene-3yl]-4-pentenoate(**94**)*

Potassium *tert*-butoxide (3.66g, 32.7mmol) was added to a stirred suspension of 4-carboxybutyltriphenylphosphonium bromide (6.74g, 13.5mmol) in THF (60ml), and the mixture was stirred at room temperature for 20 min. Then, a solution of the enal (**93**) (1.73g, 3.27mmol) in THF (20ml) was added to the ylide solution at room temperature. After stirring for 30 min, saturated aqueous NH_4Cl was added, followed by separation of THF layer. The aqueous layer was acidified (pH 4–5) with 10% aqueous HCl and extracted with ethyl acetate. The organic layers were combined, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was treated with ethereal diazomethane at 0 °C until the carboxylic acid had disappeared on TLC. After evaporation, the residue was purified by silica gel chromatography (ether–hexane, 1:6) to afford the conjugated diene (**94**) (1.46g, 74%, *E:Z* = *ca.* 1:2) as a colorless oil. IR (neat): 3050, 2910, 2830, 1740, 1460, 1430, 1240, 1200, 820 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.05 (6H, s), 0.30 (6H, s), 0.90 (9H, s), 1.10–2.00 (12H, m), 2.03–2.73 (6H, m), 3.30–3.62 (4H, m), 3.70 (3H, s), 3.75–4.06 (1H, m), 4.50–4.70 (1H, m), 5.05–5.40 (1H, m), 5.52 (1H, brs), 5.64 (2/3H, d, J=12.0Hz), 6.00(1/3H, d, J=15 0Hz), 7.15–7.66 (5H, m). MS (EI) m/z: 612 (M^+), 528 (M^+- DHP), 527 (M^+- DHP - H). HR-MS (EI) m/z: 612.3633 (Calc'd for $C_{35}H_{56}O_5Si_2$, 612.3662, M^+).

Methyl (E)-[(*1S,6S,7S,8R*)-*7*-tert-*butyl-dimethylsilyloxymethyl-8-tetrahydropyranyloxy-4-dimethylphenylsilyl*-cis-*bicyclo[4.3.0]nonan-3-ylidene]-pentanoate(**95**)*

The conjugated diene (**94**) (100mg, 0.16mmol) and naphthalene·$Cr(CO)_3$ (13mg, 0.05mmol) were dissolved in THF (10ml). The solution was degassed by three freeze–pump–thaw cycles, and then transferred into an autoclave with glass insert (100ml) under an argon atmosphere. The autoclave was purged repeatedly with hydrogen. The

solution was stirred at 50 °C under 100 kg/cm^2 of hydrogen pressure for 12 h. After cooling to room temperature, the reaction mixture was exposed to air and light to decompose the catalyst. Removal of the solvent gave a dark green residue, which was purified by silica gel column chromatography (ether–hexane, 1:6) to afford the *E*-allylic silane (**95**) (97mg, 97%) as a colorless oil. IR (neat): 3100, 2960, 2880, 1740, 1470, 1430, 1260, 1030, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.05 (6H, s), 0.30 (6H, s), 0.90 (9H, s), 1.02–2.43 (22H, m), 3.26–4.00 (5H, m), 3.66 (3H, s), 4.40–4.60 (1H, m), 4.96 (1H, brt, J=6.0Hz), 7.15–7.65 (5H, m). MS (EI) m/z: 614 (M^+), 530 (M^+- DHP), 529 (M^+- DHP -H). HR-MS (EI) m/z: 614.3821 (Calc'd for $C_{35}H_{58}O_5Si_2$, 614.3822, M^+).

Methyl (E)-[(*1S,6S,7S,8R*)-*8-tetrahydropyranyloxy-7-hydroxymethyl-4-dimethylphenylsilyl*-cis-*bicyclo[4.3.0]-nonan-3-ylidene]pentanoate(**96**)*

TBAF (1.0M in THF, 0.3ml, 0.3mmol) was added to a solution of **95** (61mg, 0.1mmol) in THF (1.5ml), and the mixture was stirred at room temperature for 3 h. 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, 2:1) to give the alcohol (**96**) (40mg, 81%) as a colorless oil. IR (neat): 3450, 3050, 2950, 2850, 1740, 1440, 1240, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.30 (6H, s), 1.10–2.46 (23H, m), 3.30–4.10 (5H, s), 3.70 (3H, s), 4.50–4.80 (1H, m), 5.02 (1H, brt, J=6.0Hz), 7.20–7.60 (5H, m). MS (EI) m/z: 500 (M^+), 416 (M^+- DHP), 415 (M^+-DHP-H). HR-MS (EI) m/z: 500.2979 (Calc'd for $C_{29}H_{44}O_5Si$, 500.2955, M^+).

Ethyl (Z)-*5*-[(*1R,6S,7S,8R*)-*7*-tert-*butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-4-dimethylphenylsilyl*-cis-*bicyclo[4.3.0]non-2-en-3-yl]-4-pentenoate(**105**)*

A solution of potassium *tert*-butoxide (182mg, 1.63mmol) in THF (5ml) was added to a suspension of 4-ethoxycarbonylpropyltriphenylphosphonium bromide (950mg, 2.08mmol) in THF (10ml) at -78 °C, and the mixture was stirred at the same temperature for 30 min. Then a solution of the enal (**93**) (409mg, 0.77mmol) in THF (8ml) was added to the ylide solution at -78 °C and the mixture was stirred at the same temperature, for 1 h then stirred at 0 °C for 1 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl. After extraction with ethyl acetate, the combined organic layer was washed with water and brine, and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (ether–hexane, 1:6) to give the conjugated diene (**105**) (369mg, 77%, *E:Z= ca.* 1:9) as a colorless oil. IR (neat): 2950, 2880, 1740, 1660, 1460, 1250, 1030, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.06 (6H, s), 0.29 (6H, s), 0.91 (9H, s), 1.26 (3H, t, J=7.1Hz), 1.38–2.00 (12H, m), 2.00–2.76 (6H, m), 3.56 (2H, dd, J=4.0, 10.0Hz), 3.18–3.96 (3H, m), 4.14 (2H, q, J=7.1Hz), 4.45–4.70 (1H, m), 5.00–5.30 (1H, m), 5.50 (1H, brs), 5.57 (1H, d, J=13.0Hz), 7.15–7.60 (5H, m). MS (EI) m/z: 626 (M^+), 541 (M^+- DHP - H). HR-MS (EI) m/z: 626.3843 (Calc'd for $C_{36}H_{58}O_5Si_2$, 626.3823, M^+).

Ethyl (Z)-*5*-[(*1R,6S,7S,8R*)-*8-tetrahydropyranyloxy-7-hydroxymethvl-4-dimethylphenylsilyl*-cis-*bicyclo[4.3.0]-non-2-en-3-yl]-4-pentenoate(**106**)*

TBAF (1.0M in THF, 0.6ml, 0.6mmol) was added to a solution of **105** (250mg, 0.4mmol) in THF (5ml) and the mixture was stirred at room temperature for 3 h. The reaction mixture was quenched by the addition of brine, followed by extraction with ethyl acetate. The combined organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (ether–hexane, 2:1) to give the alcohol (**106**) (108mg, 53%) as a pale yellow oil. IR (neat): 3450, 2950, 2870, 1740, 1430, 1350, 1250, 1030, 820 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.28, 0.30 (each 3H, s), 1.27 (3H, t, J=7.1Hz), 1.36–1.98 (13H, m), 2.00–2.72 (6H, m), 3.30–3.98 (5H, m), 4.14 (2H, q, J=7.1Hz), 4.40–4.70 (1H, m), 5.10–5.36 (1H, m), 5.45 (1H, brs), 5.63 (1H, d, J=13.0Hz), 7.20–7.55 (5H, m). MS (EI) m/z: 512 (M^+), 427 (M^+- DHP-H). HR-MS (EI) m/z: 512.2963 (Calc'd for $C_{30}H_{44}O_5Si$, 512.2958, M^+).

(*1R,6S,7S,8R*)-*7*-tert-*Butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-4-dimethylphenylsilyl-3-vinyl*-cis-*bicyclo[4.3.0]non-2-ene(**107**)*

A solution of potassium *tert*-butoxide (365mg, 3.26mmol) in THF (5ml) was added dropwise to a suspension of methyltriphenylphosphonium bromide (1.32g, 3.70mmol) in THF (15ml) at room temperature, and stirred for 15 min. Then a solution of the enal (**93**) (639mg, 1.21mmol) in THF (10ml) was added to the ylide solution at the same temperature. After stirring for 30 min, saturated aqueous NH_4Cl was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. Removal of the solvent afforded a yellow oily residue, which was purified by silica gel column chromatography (ether–hexane, 1:10) to give the diene (**107**) (574mg, 90%) as a pale yellow oil. IR (neat): 2960, 2880, 1630, 1470, 1255, 1120, 1030, 840 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.07 (6H, s), 0.31 (6H, s), 0.93 (9H, s), 1.14–2.48 (15H, m), 3.56 (2H, dd, J=4.0, 10.5Hz), 3.67–4.16 (2H, m), 4.50–4.70 (1H, m), 4.80 (1H, d, J=11.OHz), 5.04 (1H, d, J=17.0Hz), 5.60 (1H, brs), 6.23 (1H, dd, J=11.0, 17.0Hz). 7.15–7.55 (5H, m). MS (EI) m/z: 526 (M^+), 469 (M^+- *tert*-Bu), 441 (M^+- DHP - H). HR-MS (EI) m/z: 526.3303 (Calc'd for $C_{31}H_{50}O_3Si$, 526.3329, M^+).

(*1R,6S,7S,8R*)-*7*-tert-*Butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-4-dimethylphenylsilyl-3-(2-hydroxyethyl)*-cis-*bicyclo[4.3.0]non-2-ene(**108**)*

A solution of disiamylborane in THF (1.1M, 2.4ml, 2.64mmol) was added to a stirred solution of the diene (**107**) (556mg, 1.06mmol) in THF (15ml) at 0 °C. After stirring at the same temperature for 40 min, 6N aqueous NaOH (1.8ml) and 30% H_2O_2 (1.45ml) were added to the

reaction mixture at 0 °C, and stirred at room temperature for 1 h. After addition of water, the reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous $Na_2S_2O_3$, water and brine, and then dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel (ether–hexane, 1:3) to give the homoallylalcohol (**108**) (474mg, 82%) as a pale yellow oil. IR (neat): 3450. 2950, 2880, 1460, 1250, 1115, 830 cm^{-1}. ^1H-NMR ($CDCl_3$) δ : 0.05 (6H, s), 0.30, 0.33 (each 3H, s), 0.91 (9H, s), 1.12–2.48 (17H, m), 3.12–3.68 (5H, m), 3.68–4.16 (2H, m), 4.50–4.60 (1H, m), 5.36 (1H, brs), 7.20–7.60 (5H, m). MS (EI) m/z: 544 (M^+), 526 (M^+- H_2O), 487 (M^+- *tert*-Bu). HR-MS (EI) m/z: 544.3430 (Calc'd for $C_{31}H_{52}O_4Si_2$, 544.3404, M^+)

tert-*Butyl 5-[(1R,6S,7S,8R)-7-tert-butyldimethylsilyloxymethyl-8-tetrahydropyranyloxy-4-dimethylphenylsilyl*-cis-*bicyclo[4.3.0]non-2-en-3-yl]-3-oxapentanoate(**109**)*

To a mixture of the homoallylalcohol (**108**) (474mg, 0.87mmol), *tert*-butyl bromoacetate (2.8ml, 17.3mmol) and tetrabutylammonium hydrogen sulfate (295mg, 0.87mmol) in methylene chloride (1ml) was added 50% aqueous NaOH (5ml) at room temperature. The reaction mixture was stirred at the same temperature for 2.5 days. After dilution with ether (30ml), the reaction mixture was washed with water and brine, and dried over Na_2SO_4. The solution was concentrated, the residue was purified by silica gel column chromatography (ether–hexane, 1:8) to give the *tert*-butylester (**109**) (476mg, 83%) as a pale yellow oil. IR (neat): 2950, 2860, 1750, 1460, 1370, 1220, 1130, 1030, 840 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.30, 0.32 (each 3H, s), 0.90 (9H, s), 1.28–2.38 (16H, m), 1.48 (9H, s), 3.28–4.00 (5H, m), 3.50 (2H, t, J=6.5Hz), 4.09 (2H, s), 4.50–4.65 (1H, m), 5.30 (lH, brs), 7.15–7.55 (5H, m). MS (EI) m/z: 658 (M^+), 601 (M^+- *tert*-Bu), 573 (M^+- DHP - H). HR-MS (EI) m/z: 658.4098 (Calc'd for $C_{37}H_{62}O_6Si_2$, 658.4085, M^+).

tert-*Butyl 5-[(1R,6S,7S,8R)-8-tetrahydropyranyloxy-7-hydroxymethyl-4-dimethylphenylsilyl*-cis-*bicyclo[4.3.0]-non-2-en-3-yl]-3-oxapentanoate(**110**)*

TBAF (1.0M in THF, 0.48ml. 0.48mmol) was added to a solution of **109** (210mg, 0.32mmol) in THF (5ml) and the mixture was stirred at 0 °C for 22 h. The reaction mixture was quenched by the addition of brine, followed by extraction with ethyl acetate. The combined organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (ether–hexane, 2:1) to give the alcohol (**110**) (72.9mg, 41%) as a pale yellow oil. IR (neat): 3450, 2950, 2860, 1750, 1365, 1250, 1130, 1020, 830 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.29, 0.30 (each 3H, s), 1.30–1.96 (13H, s), 1.48 (9H, s), 1.96–2.40 (4H, m), 3.28–4.05 (5H, m), 3.50 (2H, t, J=6.5Hz), 3.90 (2H, s), 4.45–4.70 (1H, m), 5.30 (1H, brs), 7.20–7.55 (5H, m). MS (EI) m/z: 544 (M^+), 487 (M^+- *tert*-Bu), 459 (M^+- DHP - H). HR-MS (EI) m/z: 544.3212 (Calc'd for $C_{31}H_{48}O_6Si$, 544.3220, M^+).

The typical procedure for the synthesis of cis-*bicyclo-[4.3.0]non-3-ene analogues of homoisocarbacyclin; the synthesis of 5-[(1S,6S,7R,8R)-8-hydroxy-7-[(E)-(3S)-3-hydroxy-4-methyl-1-nonen-6-ynyl]-*cis-*bicyclo[4.3.0]non-3-en-3-yl]pentanoic acid(**87**)*

Methyl (E)-*[(1R,6S,7R,8R)-8-tetrahydropyranyloxy-4-dimethylphenylsilyl-7-[(E)-4-methyl-3-oxo-1-nonen-6-ynyl]-*cis-*bicyclo[4.3.0]nonan-3-ylidene]pentanoate(**98**)*

A solution of sulfur trioxide pyridine complex (57mg, 0.36mmol) in DMSO (1ml) was added to a stirred mixture of the alcohol (**96**) (30mg, 0.06mmol) and triethylamine (0.05ml, 0.36mmol) in DMSO (1.0ml) at room temperature. After stirring for 30 min, the reaction mixture was poured into ice water and extracted with ethyl acetate. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent gave almost pure aldehyde (**97**) (29mg) as a pale yellow oil. The crude aldehyde was used for the subsequent step without purification.

Sodium hydride (60% in oil, 7mg, 0.18mmol) was washed with pentane, and suspended in THF (0.5ml). A solution of dimethyl (3-methyl-2-oxo-5-octynyl)phosphonate (59mg, 0.24mmol) in THF (1ml) was added to the suspension, and the mixture was stirred at room temperature for 70 min. Then, the aldehyde (**97**) (29mg) in THF (1.5ml) was dropped into the solution of sodium β-ketophosphonate, and the whole mixture was stirred at room temperature for 40 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by extraction with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent and the purification by the silica gel column chromatography (ether–hexane, 1:3) afforded the enone (**98**) (32mg, 86%) as a colorless oil. IR (neat): 3050, 2950, 2890, 1740, 1690, 1670, 1620, 1450, 1440, 1250, 1030, 830 cm^{-1}. ^1H-NMR ($CDCl_3$) δ : 0.30 (6H, s), 1.10 (3H, t, J=6.6Hz), 1.16 (3H, d. J=7.5Hz), 1.33–2.65 (26H, m), 2.70–3.00 (1H, m), 3.25–4.00 (3H, m), 3.70 (3H, s), 4.46–4.75 (1H, m), 5.06 (1H, brt, J=6.0Hz), 6.18, 6.22 (total 1H, each d. J=15.0Hz), 6.84, 6.87 (total 1H, each dd, J=9.0. 15.0Hz), 7.15–7.60 (5H, m). MS (EI) m/z: 534 (M^+- DHP), 533 (M^+- DHP - H). HR-MS (EI) m/z: 534.3168 (Calc'd for $C_{33}H_{46}O_4Si$, 534.3162, M^+- DHP).

Methyl (E)-*[(1R,6S,7R,8R)-8-tetrahydropyranyloxy-7-[(E)-(3S)-3-hydroxy-4-methyl-1-nonen-6-ynyl]-4-dimethylphenylsilyl*-cis-*bicyclo[4.3.0]nonan-3-ylidene]-pentanoate(**99**)*

An excess amount of sodium borohydride was added to a stirred solution of the enone (**98**) (32mg, 0.05mmol) in methanol (1ml) at -25 °C. The mixture was stirred at the same temperature for 20 min, and the excess of reagent was decomposed by the addition of acetone at -25 °C, and then saturated aqueous NH_4Cl was added to the reaction mixture. After removal of the organic solvent, the aqueous layer was extracted with ethyl acetate. The combined organic layer

was washed with brine and dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (ether–hexane, 1:1) to give the desired 15α-alcohol (**99**) (15.4mg, 48%) as a more polar fraction and the 15β-alcohol (**100**) (14.7mg, 46%) as a less polar fraction. Spectral data of the 15α-alcohol (**99**): IR (neat): 3470, 3020, 2950, 2880, 1740, 1450, 1240, 1020, 830 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.30 (6H, s), 0.83–1.30 (6H, m), 1.30–2.45 (28H, m), 3.30–4.20 (4H, m), 3.70 (3H, s), 4.60–4.75 (1H, m), 5.06 (1H, brt, J=6.0Hz), 5.40–5.63 (2H, m), 7.20–7.60 (5H, m). MS (EI) m/z : 602 (M^+- H_2O), 518 (M^+- DHP - H_2O), 517 (M^+- DHP - H - H_2O). HR-MS (EI) m/z: 602.3777 (Calc'd for $C_{38}H_{54}O_4Si$, 602.3787, M^+- H_2O). The spectral data of **100** were nearly identical with those of **99**.

Methyl 5-[(1S,6S,7R,8R)-8-hydroxy-7-[(E)-(*3S*)-*3-hydroxy-4-methyl-1-nonen-6-ynyl]*-cis-*bicyclo[4.3.0]non-3-en-3-yl]pentanoate(101)*

To a solution of **99** (22.0mg, 0.035mmol) in acetonitrile–water (98:2, 1ml) was added *p*-toluenesulfonic acid monohydrate (7.0mg, 0.035mmol) at room temperature, and the mixture was stirred at the same temperature for 12 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, followed by extraction with ethyl acetate. The combined 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, 5:1) to afford the diol (**101**) (12.2mg, 86%) as a colorless oil. IR (neat): 3400, 2930, 2850, 1740, 1450, 1430, 1010, 810 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 0.96, 1.01 (total 3H, each d, J=6.83Hz), 1.12, 1.13 (total 3H, each t, J=7.43Hz), 1.25–1.46 (6H, m), 1.55–1.86 (6H, m), 1.96–2.36 (12H, m), 3.67 (3H, s), 3.89 (1H, q, J=7.5Hz), 3.97–4.13 (1H, m), 5.43–5.48 (1H, m), 5.51–5.57 (2H, m). MS (EI) m/z: 384 (M^+- H_2O), 366 (M^+- $2H_2O$). HR-MS (EI) m/z: 384.2633 (Calc'd for $C_{25}H_{36}O_3$, 384.2661, M^+- H_2O).

5-[(1S,6S,7R,8R)-8-Hydroxy-7-[(E)-(*3S*)-*3-hydroxy-4-methyl-1-nonen-6-ynyl]*-cis-*bicyclo[4.3.0]non-3-en-3-yl]-pentanoic acid(87)*

To a solution of the diol (**101**) (30.1mg, 0.05mmol) in methanol (0.7ml) was added 10% aqueous NaOH (0.7ml) at 0 °C. After stirring at the same temperature for 12 h, the reaction mixture was neutralized by adding 10% aqueous HCl, followed by evaporation of the organic solvent. Then the remaining aqueous layer was acidified to pH 4–5 by adding 10% aqueous HCl, and extracted with ethyl acetate. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent afforded **87** (19.4mg, quantitative yield) as a colorless oil. IR (neat): 3400, 2980, 2930, 1710, 1450, 1320, 1100, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.98 (3H, d, J=6.6Hz), 1.12 (3H, t, J=7.5Hz), 1.51–2.83 (24H, m), 3.63–4.60 (2H, m), 5.36–5.53 (1H, m), 5.53–5.70 (2H. m). ^{13}C-NMR ($CDCl_3$, the data of diastereomers at C_{16}, PG numbering) δ : 178.2, 138.0, 135.0, 134.5, 133.3, 133.2, 120.4, 83.2, 77.9, 77.7, 77.2, 76.6, 76.2, 56.3, 41.1, 40.5, 38.5, 38.3, 37.4, 33.9, 33.4, 32.2, 26.7, 25.6, 24.3, 22.6. 22.4, 15.7, 14.9, 14.4, 12.5. MS (EI) m/z: 370 (M^+- H_2O). HR-MS (EI) m/z: 370.2508 (Calc'd for $C_{24}H_{34}O_3$, 370.2506, M^+- H_2O).

Other *cis*-bicyclo[4.3.0]non-3-ene analogues of homoisocarbacyclin (**104**, **111** and **112**) were synthesized from the corresponding versatile alcohols (**96**, **106** and **110**) in the same sequence of reactions for the synthesis of **87** using the corresponding β-ketophosphonates. In the case of **112**, the hydrolysis was achieved by using 7% aqueous KOH in methanol. Those spectral data are summarized in Table 16.

Biological Experiments

Preparation of washed rabbit platelets

Male Japanese white rabbits (2.0–2.5kg) under sodium pentobarbital anesthesia were used. Blood sample was collected from the carotid artery into a siliconized glass syringe filled with a 1/7 volume of citric acid–dextrose solution containing 65 mM citric acid, 85 mM sodium citrate and 111 mM glucose. The mixture was subjected to centrifugal separation at 140 x *g* for 15 min, whereupon the supernatant platelet rich plasma (PRP) was obtained. PRP was subjected again to centrifugal separation at 1300 x *g* for 7 min. The blood platelet pellets thus obtained were washed with the first wash solution and subjected to centrifugation at 1300 x *g* for 7 min. The platelet pellets washed twice under such conditions were resuspended in the first wash solution which contained 0.1% of human fibrinogen, 2.0 mM of $CaCl_2$ and 1.2 mM of $MgCl_2$, at a concentration of 5 to 8 x 10^8 platelets/ml.

Platelet aggregation in rabbits (in vitro)

The platelet aggregation was measured by an aggregometer (NKK HEMA TRACER 1). To a 380 μl of washed rabbit platelet suspension, 10 μl of a test compound (5% ethanol 0.5 mM Tris-buffer) or the vehicle alone as a control, was added at 37 °C under stirring. After stirring for 3 min, aggregation was initiated by adding an inducing substance (final concentration; 10 μM of ADP, 1 mg/ml of collagen). The inhibitory activities of each test compound were expressed by IC_{50} values, which were calculated by linear regression from three or four dose groups of three to five animals.

Platelet aggregation in rabbits (ex vivo; *infusion*)

Male Japanese white rabbits (2.5–3.0 kg) were used. Under pentobarbital anesthesia (60 mg/kg i.m.), the carotid artery was cannulated. At the scheduled time after initiation of intravenous infusion, a blood sample was collected from the carotid artery in the syringe filled with one tenth volume of 3.18% sodium citrate solution and then 2-fold diluted with saline. Platelet aggregation was measured by whole blood aggregometer (Chrono-Log C540) and induced by addition of collagen (final concentration; 5 μg/ml). Test compounds were administered by intravenous infusion from the femoral vein for 20 min.

Table 11. Spectral data of 3-oxahomoisocarbacyclins (**43**)

compound	form (mp.)	yield (%)[a]	IR ν_{max} (cm^{-1})	^{1}H-NMR (δ)[b]	MS (*m/z*)	HR-MS (*m/z*)
43*b*	oil	26	neat: 3400, 2950, 1730, 1430, 1220, 1130, 1080, 1010.	0.80 ~ 1.40 (6H, m), 1.40 ~ 2.80 (18H, m), 3.35 ~ 4.30 (4H, m), 4.10 (2H, s), 5.40 ~ 5.70 (3H, m).	391 (M^+ + H), 373 (M^+ + H - H_2O), 355 (M^+ + H - $2H_2O$).[c]	found : 391.2463 calcd : 391.2484 for $C_{23}H_{35}O_5$, (M^+ + H).[c]
43*c*	oil	42	neat: 3400, 2970, 1740, 1430, 1370, 1240, 1135, 1040.	0.97 (6H, s), 3.66 (2H, t, J=6.0 Hz), 4.08 (2H, s), 5.38(1H, brs), 5.48 ~ 5.70 (2H, m).	404 (M^+), 386 (M^+ - H_2O).[d]	found : 404.2545 calcd : 404.2563 for $C_{24}H_{36}O_5$, (M^+).[d]
43*d*	oil	10	neat: 3400, 2970, 2930, 1740, 1430, 1380, 1240, 1140.	0.80 ~ 1.15 (3H, m), 1.63, 1.68 (each 3H, s), 3.30 ~ 4.35 (4H, m), 4.07 (2H, s), 5.10 (1H, t, J=6.0 Hz), 5.25 ~ 5.70 (3H, m).	402 (M^+ - H_2O), 384 (M^+ - $2H_2O$).[d]	found : 402.2778 calcd : 402.2770 for $C_{25}H_{38}O_4$, (M^+ - H_2O).[d]
43*e*	oil	36	neat: 3388, 2920, 1734, 1434, 1226, 1130, 970.	0.75 ~ 2.70 (24H, m), 3.50 ~ 4.25 (4H, m), 4.03 (2H, s), 5.20 ~ 5.58 (3H, m).	361 (M^+ + H - H_2O), 343 (M^+ + H - $2H_2O$).[c]	found : 361.2374 calcd : 361.2379 for $C_{22}H_{33}O_4$, (M^+ + H - H_2O).[c]
43*f*	122 ~ 126 °C	46	KBr: 3404, 2952, 2912, 1748, 1434, 1350, 1248, 1192, 1116, 1082, 970.	1.05 ~ 2.70 (22H, m), 3.43 ~ 4.20 (2H, m), 3.64 (2H, t, J=6.0Hz), 4.06 (2H, s), 5.30 ~ 5.75 (3H, m).	347 (M^+ + H - H_2O), 329 (M^+ + H - $2H_2O$).[c]	found : 347.2195 calcd : 347.2222 for $C_{21}H_{31}O_4$, (M^+ + H - H_2O).[c]
43*g*	112 ~ 116 °C	50	KBr: 3428, 2920, 2852, 1724, 1702, 1664, 1432, 1256, 1132, 1122, 972.	0.65 ~ 2.76 (24H, m), 3.43 ~ 4.30 (4H, m), 4.05 (2H, s), 5.20 ~ 5.75 (3H, m).	361 (M^+ + H - H_2O), 343 (M^+ + H - $2H_2O$).[c]	found : 361.2396 calcd : 361.2379 for $C_{22}H_{33}O_4$, (M^+ + H - H_2O).[c]

Table 11. *Continued*

compound	form (mp.)	yield (%)[a]	IR ν_{max} (cm^{-1})	^{1}H-NMR (δ)[b]	MS (*m/z*)	HR-MS (*m/z*)
43*h*	oil	43	neat: 3406, 2920, 1734, 1449, 1233, 1131, 975, 732.	0.90 (3H, t, J=6.0Hz), 3.40 ~ 3.93 (4H, m), 4.06 (2H, s), 5.20 ~ 5.58 (3H, m).	403 ($M^+ + H - H_2O$), 385 ($M^+ + H - 2H_2O$).[c]	found : 403.2858 calcd : 403.2849 for $C_{25}H_{39}O_4$, ($M^+ + H - H_2O$).[c]
43*i*	oil	48	neat: 3400, 2976, 2924, 2860, 1736, 1446, 1382, 1076.	1.56, 1.63 (each 3H, s), 3.40 ~ 3.90 (4H, m), 4.00 (2H, s), 4.86 (1H, d, J=9.0Hz), 5.20 ~ 5.53 (3H, m)	415 ($M^+ + H - H_2O$), 397 ($M^+ + H - 2H_2O$).[c]	found : 397.2747 calcd : 397.2743 for $C_{26}H_{37}O_3$, ($M^+ + H - 2H_2O$).[c]
43*j*	oil	43	neat: 3416, 2924, 1734, 1448, 1130, 1074, 910, 730.	3.64 (2H, t, J=6.0Hz), 4.06 (2H, s), 5.40 (1H, brs), 5.44 ~ 5.65 (2H, m), 7.07 ~ 7.43 (5H, m).	437 ($M^+ + H - H_2O$), 419 ($M^+ + H - 2H_2O$).[c]	found : 437.2705 calcd : 437.2691 for $C_{28}H_{37}O_4$, ($M^+ + H - H_2O$).[c]
43*k*	amorphous	55	KBr: 3416, 2924, 1732, 1244, 1128, 908, 764, 732.	3.55 (2H, t, J=6.0Hz), 3.70 ~ 4.20 (2H, m), 3.91 (2H, s), 5.33 (1H, brs), 5.55 ~ 5.80 (2H, m), 7.13 ~ 7.56 (9H, m).	431 ($M^+ + H - H_2O$).[c]	found : 431.2238 calcd : 431.2222 for $C_{28}H_{31}O_4$, ($M^+ + H - H_2O$).[c]
43*l*	oil	28	neat: 3400, 2920, 2850, 1730, 1450, 1120, 740, 690.	3.67 (2H, t, J=6.0Hz), 3.98 ~ 4.37 (2H, m), 4.09 (2H, s), 5.43 (1H, brs), 5.47 ~ 5.70 (2H, m), 7.12 ~ 7.30 (5H, m).	383 ($M^+ + H - H_2O$), 365 ($M^+ + H - 2H_2O$).[c]	found : 383.2228 calcd : 383.2222 for $C_{24}H_{31}O_4$, ($M^+ + H - H_2O$).[c]
43*m*	oil	35	neat: 3400, 2930, 1730, 1480, 1130, 1075, 1030, 970.	3.63 (2H, t, J=6.0Hz), 4.07 (2H, s), 5.35 (1H, brs), 5.45 ~ 5.80 (2H, m), 6.80 ~ 7.45 (4H, m).	394 ($M^+ - H_2O$).[d]	found : 394.2133 calcd : 394.2144 for $C_{25}H_{30}O_4$, ($M^+ - H_2O$).[d]

Table 11. *Continued*

compound	form (mp.)	yield (%)[a]	IR ν_{max} (cm^{-1})	^{1}H-NMR (δ)[b]	MS (*m/z*)	HR-MS (*m/z*)
43*n*	oil	41	neat: 3432, 2920, 1736, 1224, 1128, 1012, 972.	1.13 (3H, s), 3.60 (2H, t, J=6.0Hz), 4.13 (2H, s), 5.30 ~ 5.75 (3H, m), 7.00 ~ 7.30 (4H, m).	427 (M^+ + H), 409 (M^+ + H - H_2O), 391 (M^+ + H - $2H_2O$).[c]	found : 391.2280 calcd : 391.2276 for $C_{26}H_{31}O_3$, (M^+ + H - $2H_2O$).[c]
43*o*	oil	29	neat: 3400, 2940, 2860, 1735, 1450, 1130, 910, 730.	3.67 (2H, t, J=6.0Hz), 4.10 (2H, s), 5.40 (1H, brs), 5.50 ~ 5.85 (2H, m).	390 (M^+ - H_2O).[d]	found : 390.2408 calcd : 390.2406 for $C_{23}H_{34}O_5$, (M^+ - $2H_2O$).[d]
43*p*	oil	20	neat: 3400, 2940, 1730, 1600, 1500, 1140, 750, 690.	3.46 (2H, t, J=6.0Hz), 4.07 (2H, s), 5.43 (1H, brs), 5.55 ~ 5.80 (2H, m), 6.70 ~ 7.45 (5H, m).	403 (M^+ + H).[c]	found : 403.2079 calcd : 403.2120 for $C_{23}H_{31}O_6$, (M^+ + H).[c]
43*q*	oil	19	neat: 3400, 2920, 1730, 1500, 1250, 1210, 1120, 1030.	3.63 (2H, t, J=6.0Hz), 3.80 ~ 4.00 (3H, m), 4.08 (2H, s), 4.20 ~ 4.70 (1H, m), 5.42 (1H, brs), 5.58 ~ 5.80 (2H, m), 6.72 ~ 7.15 (4H, m).	421 (M^+ + H).[c]	found : 421.2008 calcd : 421.2027 for $C_{23}H_{30}O_6F$, (M^+ + H).[c]
43*r*	oil	17	neat: 3400, 2920, 1730, 1610, 1505, 1258, 1200, 1120.	3.63 (2H, t, J=6.0Hz), 3.78 ~ 4.20 (3H, m), 4.07 (2H, s), 4.40 ~ 4.80 (1H, m), 5.42 (1H, brs), 5.60 ~ 5.80 (2H, m), 6.75 ~7.17 (4H, m).	421 (M^+ + H), 403 (M^+ + H - H_2O), 385 (M^+ + H - $2H_2O$).[c]	found : 421.2012 calcd : 421.2027 for $C_{23}H_{30}O_6F$, (M^+ + H).[c]
43*s*	oil	21	neat: 3400, 2920, 1730, 1510, 1460, 1230, 1120, 1035.	3.61 (2H, t, J=6.0Hz), 3.78 (3H, s), 3.82 ~ 4.00 (3H, m), 4.09 (2H, s), 4.36 ~ 4.58 (1H, m), 5.41 (1H, brs), 5.60 ~ 5.77 (2H, m), 6.85 (4H, s).	433 (M^+ + H), 397 (M^+ + H - $2H_2O$).[c]	found : 433.2220 calcd : 433.2226 for $C_{24}H_{33}O_7$, (M^+ + H).[c]

Table 11. *Continued*

compound	form (mp.)	yield (%)[a]	IR ν_{max} (cm^{-1})	^{1}H-NMR (δ)[b]	MS (*m/z*)	HR-MS (*m/z*)
43*t*	oil	23	neat: 3400, 2920, 1730, 1590, 1500, 1250, 1120, 1020.	3.64 (2H, t, J=6.0Hz), 3.77 ~ 4.30 (3H, m), 3.88 (3H, s), 4.08 (2H,s), 4.40 ~ 4.65 (1H, m), 5.42 (1H, brs), 5.55 ~ 5.80 (2H, m), 6.75 ~ 7.10 (4H, m).	432 (M^+), 414 ($M^+ - H_2O$), 396 ($M^+ - 2H_2O$).[d]	found : 432.2158 calcd : 432.2148 for $C_{24}H_{32}O_7$, (M^+).[d]
43*u*	oil	29	neat: 3400, 2920, 2860, 1735, 1595, 1490, 1140, 750.	1.24 (3H, d, J=6.0Hz), 3.62 (2H, t, J=6.0Hz), 3.76 ~ 4.43 (3H, m), 4.05 (2H, s), 5.40 (1H, brs), 5.50 ~ 5.76 (2H, m), 6.80 ~ 7.07 (3H, m), 7.13 ~ 7.40 (2H, m).	417 ($M^+ + H$), 399 ($M^+ + H - H_2O$), 381 ($M^+ + H - 2H_2O$).[c]	found : 417.2275 calcd : 417.2277 for $C_{24}H_{33}O_6$, ($M^+ + H$).[c]
43*v*	oil	25	neat: 3400, 2970, 2930, 1740, 1600, 1585, 1495, 1240.	0.93 (3H, t, J=6.0Hz), 3.58 (2H, t, J=6.0Hz), 4.02 (2H, s), 5.32 (1H, brs), 5.45 ~ 5.80 (2H, m), 6.70 ~ 7.40 (5H, m).	412 ($M^+ - H_2O$).[d]	found : 412.2268 calcd : 412.2250 for $C_{25}H_{32}O_5$, ($M^+ - H_2O$).[d]
43*w* [e]	90 ~ 91 °C	64	KBr: 3400, 2920, 1730, 1590, 1490, 1370, 1130, 780.	1.23 (6H, s), 3.46 (2H, t, J=6.0Hz), 4.07 (2H, s), 5.43 (1H, brs), 5.50 ~ 5.76 (2H, m), 6.60 ~ 7.43 (5H, m).	431 ($M^+ + H$), 395 ($M^+ + H - 2H_2O$).[c]	found : 431.2437 calcd : 431.2440 for $C_{25}H_{35}O_6$, ($M^+ + H$).[c]
43*x*	oil	17	neat: 3400, 2920, 1730, 1625, 1595, 1255, 1210, 1120.	3.62 (2H, t, J=6.0Hz), 3.78 ~ 4.30 (4H, m), 4.06 (2H, s), 5.42 (1H, brs), 5.70 ~ 5.86 (2H, m), 7.05 ~ 7.60 (4H, m), 7.60 ~ 7.95 (3H, m).	453 ($M^+ + H$), 435 ($M^+ + H - H_2O$), 417 ($M^+ + H - 2H_2O$).[c]	found : 453.2304 calcd : 453.2277 for $C_{27}H_{33}O_6$, ($M^+ + H$).[c]
43*y*	oil	18	neat: 3400, 2920, 1730, 1595, 1495, 1270, 1125, 750.	3.32 ~ 3.80 (2H, m), 3.80 ~ 4.40 (5H, m), 4.08 (2H, s), 5.43 (1H, brs), 5.52 ~ 5.85 (2H, m), 6.68 ~ 7.10 (4H, m).	430 (M^+), 412 ($M^+ - H_2O$).[d]	found : 430.2003 calcd : 430.1992 for $C_{24}H_{30}O_7$, (M^+).[d]

[a]Overall yields from the alcohol (**37**) were shown.
[b]$CDCl_3$ was used as the solvent
[c]Mass spectrum was obtained using the fast atom bombardment (FAB) technique.
[d]Mass spectrum was obtained using the electron impact (EI) technique.
[e]^{13}C-NMR ($CDCl_3$) δ: 172.9, 154.2, 136.7, 132.8, 129.6, 128.9, 128.9, 127.5, 124.0, 124.0, 123.7, 82.6, 79.0, 77.5, 70.2, 67.8, 53.6, 40.2, 40.1, 37.9, 35.6, 24.5, 23.4, 23.3, 21.3.

Table 12. Spectral data of 4-(*Z*)-dehydrohomoisocarbacyclins (**51**)

compound	form (mp.)	yield (%)[a]	IR ν_{max} (cm^{-1})	^{1}H-NMR (δ)[b]	MS (*m/z*)	HR-MS (*m/z*)
51*a*	oil	29	neat: 3372, 2928, 2856, 1710, 1438, 1410, 1070, 968.	0.88 (3H, t, J=6.0Hz), 1.06 ~ 2.83 (23H, m), 3.60 ~ 4.25 (2H, m), 5.05 ~ 5.60 (4H, m), 5.80 (1H, d, J=12.0Hz).	345 ($M^+ + H - H_2O$), 327 ($M^+ + H - 2H_2O$).[c]	found : 345.2401 calcd : 345.2430 for $C_{22}H_{33}O_3$, ($M^+ + H - H_2O$).[c]
51*b*	oil	37	neat: 3376, 2968, 2920, 1710, 1435, 1070, 1014, 972.	0.80 ~ 1.40 (6H, m), 1.40 ~ 2.85 (20H, m), 3.60 ~ 4.16 (2H, m), 5.06 ~ 5.63 (4H, m), 5.80 (1H, d, J=12.0Hz).	369 ($M^+ + H - H_2O$), 351 ($M^+ + H - 2H_2O$).[c]	found : 369.2437 calcd : 369.2430 for $C_{24}H_{33}O_3$, ($M^+ + H - H_2O$).[c]
51*c*	oil	74	neat: 3400, 2970, 2930, 1705, 1270, 970, 910, 730.	0.98 (6H, s), 1.13 (3H, t, J=7.5Hz), 3.70 ~ 4.15 (2H, m), 5.10 ~ 5.75 (4H, m), 5.84 (1H, d, J=12.0Hz).	400 (M^+), 382 ($M^+ - H_2O$), 364 ($M^+ - 2H_2O$).[d]	found : 400.2607 calcd : 400.2614 for $C_{25}H_{36}O_4$, (M^+).[d]
51*d*	oil	14	neat: 3400, 2930, 1710, 1450, 1380, 1070, 970, 910.	0.92 (3H, d, J=6.0Hz), 1.62 (6H, d, J=.0Hz), 3.60 ~ 4.30 (2H, m), 4.90 ~ 5.63 (4H, m), 5.80 (1H, d, J=12.0 Hz).	416 (M^+), 398 ($M^+ - H_2O$), 380 ($M^+ - 2H_2O$).[d]	found : 416.2955 calcd : 416.2927 for $C_{26}H_{40}O_4$, (M^+).[d]
51*e*	oil	56	neat: 3380, 2948, 1712, 1412, 1342, 1264, 1076, 1040.	0.80 ~ 2.90 (26H, m), 3.70 ~ 4.40 (2H, m), 5.05 ~ 5.65 (4H, m), 5.78 (1H, d, J=12.0Hz).	357 ($M^+ + H - H_2O$), 339 ($M^+ + H - 2H_2O$).[c]	found : 357.2437 calcd : 357.2430 for $C_{23}H_{33}O_3$, ($M^+ + H - H_2O$).[c]
51*f*	106 ~ 112 °C	48	KBr: 3400, 2944, 2920, 2860, 1707, 1386, 1353, 1335, 1314, 1248, 1074.	1.00 ~ 2.80 (24H, m), 3.65 ~ 4.10 (2H, m), 5.10 ~ 5.65 (4H, m), 5.80 (1H, d, J=12.0Hz)).	343 ($M^+ + H - H_2O$), 325 ($M^+ + H - 2H_2O$).[c]	found : 343.2262 calcd : 343.2274 for $C_{22}H_{31}O_3$, ($M^+ + H - H_2O$).[c]

Table 12. *Continued*

compound	form (mp.)	yield (%)[a]	IR ν_{max} (cm^{-1})	^{1}H-NMR (δ)[b]	MS (*m/z*)	HR-MS (*m/z*)
51*g*	oil	54	neat: 3368, 2920, 2852, 1710, 1450, 1240, 1044, 970.	0.70 ~ 2.80 (26H, m), 3.60 ~ 4.00 (2H, m), 5.00 ~ 5.65 (4H, m), 5.80 (1H, d, J=12.0Hz).	357 ($M^+ + H - H_2O$), 339 ($M^+ + H - 2H_2O$).[c]	found : 357.2413 calcd : 357.2429 for $C_{23}H_{33}O_3$, ($M^+ + H - H_2O$).[c]
51*h*	oil	45	neat: 3400, 2924, 2856, 1714, 1448, 1152.	0.86 (1H, t, J=7.6Hz), 3.50 ~ 4.06 (2H, m), 5.10 ~ 5.56 (4H, m), 5.80 (1H, d, J=12.0Hz).	399 (M+ + H - H_2O), 381 ($M^+ + H - 2H_2O$).[c]	found : 399.2902 calcd : 399.2899 for $C_{26}H_{39}O_3$, ($M^+ + H - H_2O$).[c]
51*i*	amorphous	40	KBr: 3406, 2920, 2854, 1710, 1449, 1338.	3.83 (2H, t, J=7.0Hz), 5.10 ~ 5.38 (1H, m), 5.38 ~ 5.63 (3H, m), 5.80 (1H, d, J=12.0Hz), 7.00 ~ 7.32 (5H, m).	433 ($M^+ + H - H_2O$), 415 ($M^+ + H - 2H_2O$).[c]	found : 433.2782 calcd : 433.2743 for $C_{29}H_{37}O_3$, ($M^+ + H - H_2O$).[c]
51*j* [e]	91 ~ 92 °C	28	KBr: 3368, 2924, 1730, 1712, 1680, 1486, 1256, 1078, 968, 764.	3.73 ~ 3.95 (1H, m), 5.05 ~ 5.33 (2H, m), 5.50 (1H, brs), 5.70 ~ 5.95 (2H, m), 7.23 ~ 7.69 (9H, m).	427 ($M^+ + H - H_2O$), 409 ($M^+ + H - 2H_2O$).[c]	found : 427.2273 calcd : 427.2274 for $C_{29}H_{31}O_3$, ($M^+ + H - H_2O$).[c]
51*k*	134 ~ 139 °C	44	KBr : 3330, 2900, 2830, 1700, 1430, 1380, 1250, 970.	3.81 (1H, d, J=8.0Hz), 3.90 ~ 4.20 (2H, m), 5.00 ~ 5.63 (4H, m), 5.78 (1H, d, J=12.0Hz), 6.93 ~ 7.33 (5H, m).	391 ($M^+ + H - H_2O$), 373 ($M^+ + H - 2H_2O$).[c]	found : 373.2184 calcd : 373.2167 for $C_{26}H_{29}O_2$, ($M^+ + H - 2H_2O$).[c]
51*l*	oil	49	neat: 3400, 2930, 1710, 1430, 1270, 1160, 1060, 1010.	1.13 (3H, s), 3.82 (1H, d, J=8.0Hz), 3.90 ~ 4.18 (2H, m), 5.10 ~ 5.63 (4H, m), 5.78 (1H, d, J=12.0Hz), 7.00 ~ 7.16 (5H, m).	405 ($M^+ + H - H_2O$), 387 ($M^+ + H - 2H_2O$).[c]	found : 405.2456 calcd : 405.2430 for $C_{27}H_{33}O_3$, ($M^+ + H - H_2O$).[c]

[a]Overall yields from the alcohol (**45**) were shown.
[b]$CDCl_3$ was used as the solvent
[c]Mass spectrum was obtained using the fast atom bombardment (FAB) technique.
[d]Mass spectrum was obtained using the electron impact (EI) technique.
[e]^{13}C-NMR ($CDCl_3$) δ: 177.5, 142.1, 140.7, 140.2, 134.7, 134.2, 133.2, 132.8, 130.9, 128.7, 128.7, 127.3, 127.1, 127.1, 127.0, 127.0, 127.0, 126.5, 126.5, 77.3, 74.8, 53.5, 40.1, 39.6, 35.3, 34.6, 25.2, 24.2, 23.7.

Table 13. Spectral data of 5-methylene-3-oxahomoisocarbacyclins (**61**)

compound	form (mp.)	yield (%)[a]	IR ν_{max} (cm^{-1})	^{1}H-NMR (δ)[b]	MS (*m/z*)[c]	HR-MS (*m/z*)[c]
61*a*	oil	35	neat: 3364, 2924, 2856, 1734, 1436, 1226, 1120, 1074, 1034, 968, 900.	0.89 (3H, t, J=6.0Hz), 3.60 ~ 4.15 (2H, m), 4.04 (2H, s), 4.29 (2H, s), 5.10, 5.21 (each 1H, s), 5.32 ~ 5.65 (2H, m), 5.88 (1H, brs).	361 ($M^+ + H - H_2O$), 343 ($M^+ + H - 2H_2O$).	found : 343.2302 calcd : 343.2273 for $C_{22}H_{31}O_3$, ($M^+ + H - 2H_2O$).
61*b* [d]	oil	46	neat: 3400, 2940, 1730, 1630, 1605, 1460, 1360, 1230, 1120, 1030, 970.	0.97 (6H, s), 1.13 (3H, t, J=7.0Hz), 3.80 ~ 4.12 (2H, m), 4.04 (2H, s), 4.30 (2H, s), 5.10, 5.21 (each 1H, s), 5.50 ~ 5.68 (2H, m), 5.90 (1H, brs).	399 ($M^+ + H - H_2O$), 381 ($M^+ + H - 2H_2O$).	found : 399.2550 calcd : 399.2536 for $C_{25}H_{35}O_4$, ($M^+ + H - H_2O$).
61*c*	oil	44	neat: 3400, 2940, 1730, 1630, 1590, 1490, 1370, 1220, 1130, 1040, 970.	1.21 (3H, s), 1.24 (3H, s), 3.75 ~ 4.37 (2H, m), 4.03 (2H, s), 4.28 (2H, s), 5.08, 5.18 (each 1H, s), 5.50 ~ 5.70 (2H, m), 5.88 (1H, brs), 6.80 ~ 7.37 (5H, m).	443 ($M^+ + H$), 425 ($M^+ + H - H_2O$), 407 ($M^+ + H - 2H_2O$).	found : 407.2208 calcd : 407.2223 for $C_{26}H_{31}O_4$, ($M^+ + H - 2H_2O$).

[a]Overall yields from the alcohol (**60**) were shown.
[b]$CDCl_3$ was used as the solvent.
[c]Mass spectra were obtained using the fast atom bombardment (FAB) technique.
[d] ^{13}C-NMR ($CDCl_3$) δ: 172.8, 143.4, 135.2, 132.2, 131.7, 130.0, 113.6, 83.9, 79.4, 77.4, 77.1, 73.0, 66.4, 53.5, 39.8, 37.5, 35.8, 29.3, 23.5, 23.2, 22.5, 21.6, 14.5, 12.5.

Table 14. Spectral data of 13-dehydrohomoisocarbacyclins (**74, 75**)

compound	form (mp.)	yield (%)	IR ν_{max} (cm^{-1})	^{1}H-NMR (δ)[c]	MS (*m/z*)[d]	HR-MS (*m/z*)[d]
74a	oil	20[a]	neat: 3400, 2950, 2220,1740, 1450, 1215, 1140.	0.90 (3H, t, J=7.2Hz), 3.60 (2H, t, J=8.0Hz), 3.90 ~ 4.35 (2H, m) 4.04 (2H, s), 5.42 (1H, brs).	365 (M^+ + H), 347 (M^+ + H - H_2O), 329 (M^+ + H - $2H_2O$).	found : 329.2128 calcd : 329.2116 for $C_{21}H_{29}O_3$, (M^+ + H - $2H_2O$).
74c	oil	15[a]	neat: 3400, 2950, 2220, 1730, 1440, 1225, 1130, 1035.	0.96 (3H, d, J=7.2Hz), 1.60 (3H, s), 1.68 (3H, s), 3.65 (2H, t, J= 7.2Hz), 3.96 ~ 4.24 (2H, m), 4.06 (2H, s), 4.96 ~ 5.16 (1H, m), 5.40 (1H, brs).	419 (M^+ + H), 401 (M^+ + H - H_2O), 383 (M^+ + H - $2H_2O$).	found : 383.2590 calcd : 383.2586 for $C_{25}H_{35}O_3$, (M^+ + H - $2H_2O$).
74d	oil	32[a]	neat: 3400, 2924, 2856,1740, 1450, 1215, 1140.	3.60 (2H, t, J=6.0Hz), 3.90 ~ 4.35 (2H, m), 4.06 (2H, s), 5.40 (1H, brs).	377 (M^+ + H), 359 (M^+ + H - H_2O), 341 (M^+ + H - $2H_2O$).	found : 359.2220 calcd : 359.2223 for $C_{22}H_{31}O_4$, (M^+ + H - H_2O).
74e	oil	25[a]	neat: 3406, 2926, 2854, 1734, 1449, 1128, 988.	3.62 (2H, t, J=7.0Hz), 4.06 (2H, s), 4.13 ~ 4.32 (2H, m), 5.38 (1H, brs), 7.10 ~ 7.30 (5H, m).	435 (M^+ + H - H_2O), 417 (M^+ + H - $2H_2O$).	found : 417.2460 calcd : 417.2429 for $C_{28}H_{33}O_3$, (M^+ + H - H_2O).
74f	oil	25[a]	neat: 3400, 2925, 2850,2220, 1730, 1440, 1120, 1020.	0.82 (3H, t, J=7.6Hz), 3.65 (2H, t, J=8.1Hz), 4.10 (2H, s), 4.04 ~ 4.30 (2H, m), 5.44 (1H, brs).	419 (M^+ + H), 401 (M^+ + H - H_2O), 383 (M^+ + H - $2H_2O$).	found : 401.2680 calcd : 401.2692 for $C_{25}H_{37}O_4$, (M^+ + H - H_2O).
74g[e]	oil	25[a]	neat: 3400, 2920, 1734, 1449, 1128, 909, 732.	1.62 (3H, s), 1.67 (3H, s), 3.62 (2H, t, J=6.0Hz), 3.93 ~ 4.43 (2H, m), 4.05 (2H, s), 4.90 (1H, d, J=9.0Hz), 5.38 (1H, brs).	431 (M^+ + H), 413 (M^+ + H - H_2O), 395 (M^+ + H - $2H_2O$).	found : 395.2605 calcd : 395.2586 for $C_{26}H_{35}O_3$, (M^+ + H - $2H_2O$).

Table 14. *Continued*

compound	form (mp.)	yield (%)	IR ν_{max} (cm^{-1})	^{1}H-NMR (δ)[c]	MS (*m/z*)[d]	HR-MS (*m/z*)[d]
74*h*	oil	13[a]	neat: 3400, 2950, 2250, 1740, 1435, 1220, 1125, 1140.	3.60 (2H, t, J=7.2Hz), 4.00 (1H, q, J=6.0Hz), 4.04 (2H, s), 4.38 (dd, J=2.0, 6.0Hz), 5.35 (1H, brs), 7.00 ~ 7.20 (4H, m).	411 (M^+ + H), 375 (M^+ + H - $2H_2O$).	found : 375.1979 calcd : 375.1960 for $C_{25}H_{27}O_3$, (M^+ + H - $2H_2O$).
74*i*	oil	33[a]	neat: 3376, 2932, 1736, 1218, 1132, 1078, 1038.	0.70 ~ 2.70 (24H, m), 3.30 ~ 3.80 (3H, m), 3.80 ~ 4.30 (1H, m), 4.03 (2H, s), 5.36 (1H, brs).	377 (M^+ + H), 359 (M^+ + H - H_2O), 341 (M^+ + H - $2H_2O$).	found : 341.2106 calcd : 341.2116 for $C_{22}H_{29}O_3$, (M^+ + H - $2H_2O$).
74*j*	oil	17[a]	neat: 3400, 2900, 2220, 1730, 1590, 1490, 1220.	1.32 (3H, s), 1.38 (3H, s), 3.62 (2H, t, J=7.8Hz), 4.05 (2H, s), 4.16 (1H, q, J=6.4Hz), 4.44 (1H, d, J=2.0Hz), 5.40 (1H, brs), 6.90 ~ 7.34 (5H, m).	429 (M^+ + H), 411 (M^+ + H - H_2O).	found : 429.2271 calcd : 429.2278 for $C_{25}H_{33}O_6$, (M^+ + H).
75*a*	oil	24[b]	neat: 3450, 2940, 2220, 1710, 1440, 1260, 1120, 1030.	0.88 (3H, t, J=7.0Hz), 4.10 (1H, q, J=6.4Hz), 4.22 ~ 4.42 (1H, m), 5.14 ~ 5.40 (1H, m), 5.46 (1H, brs), 5.78 (1H, d, J=12.0Hz).	361 (M^+ + H), 343 (M^+ + H - H_2O), 325 (M^+ + H - $2H_2O$).	found : 343.2267 calcd : 343.2273 for $C_{22}H_{31}O_3$, (M^+ + H - H_2O).
75*b* [f]	oil	25[b]	neat: 3376, 2968, 2920, 1713, 1383, 1320, 1260, 1030.	1.00 (6H, s), 1.10 (3H, t, J=7.2Hz), 3.36 ~ 4.30 (2H, m), 5.10 ~ 5.38 (1H, m), 5.48 (1H, brs), 5.74 (1H, d J=12.0Hz).	399 (M^+ + H), 381 (M^+ + H - H_2O), 363 (M^+ + H - $2H_2O$).	found : 381.2408 calcd : 381.2430 for $C_{25}H_{33}O_3$, (M^+ + H - H_2O).
75*c*	oil	21[b]	neat: 3400, 2950, 2220, 1710, 1440, 1380, 1120.	0.94 (3H, d, J=7.2Hz), 1.60 (3H, s), 1.68 (3H,s), 4.10 (1H, q, J=6.0Hz), 4.22 ~ 4.50 (1H, m), 4.98 ~ 5.14 (1H, m), 5.14 ~ 5.38 (1H, m), 5.44 (1H, brs), 5.74 (1H, d, J=12.0Hz).	397 (M^+ + H - H_2O), 379 (M^+ + H - $2H_2O$).	found : 379.2648 calcd : 379.2637 for $C_{26}H_{35}O_2$, (M^+ + H - $2H_2O$).

Table 14. *Continued*

compound	form (mp.)	yield (%)	IR ν_{max} (cm^{-1})	^{1}H-NMR (δ)[c]	MS (*m/z*)[d]	HR-MS (*m/z*)[d]
75d	oil	9[b]	neat: 3450, 2950, 2870, 1710, 1450, 1260, 1120, 1010.	0.80 ~ 2.90 (24H, m), 4.00 ~ 4.20 (2H, m), 5.12 ~ 5.38 (1H, m), 5.46 (1H, brs), 5.78 (1H, d, J=12.0Hz).	373 (M^+ +H), 355 (M^+ + H - H_2O), 337 (M^+ + H - 2H_2O).	found : 337.2155 calcd : 337.2168 for $C_{23}H_{29}O_2$, (M^+ + H - 2H_2O).
75e	amorphous	24[b]	KBr: 3406, 2926, 2854, 1710, 1449, 1338, 1269, 1029.	3.96 ~ 4.70 (2H, m), 5.04 ~ 5.40 (1H, m), 5.50 (1H, brs), 5.80 (1H, d, J=12.0Hz), 7.00 ~ 7.40 (5H, m).	431 (M^+ + H - H_2O), 413 (M^+ + H - 2H_2O).	found : 431.2578 calcd : 431.2605, for $C_{29}H_{35}O_3$, (M^+ + H - H_2O).
75f	oil	14[b]	neat: 3392, 2920, 2230, 1718, 1448, 1382, 1118.	0.86 (3H, t, J=7.6Hz), 3.93 ~ 4.26 (2H, m), 5.10 ~ 5.46 (1H, m), 5.45 (1H, brs), 5.76 (1H, d, J=12.0Hz).	397 (M^+ + H - H_2O), 379 (M^+ + H - 2H_2O).	found : 397.2780 calcd : 397.2743 for $C_{26}H_{37}O_3$, (M^+ + H - H_2O).
75g	oil	16[b]	neat: 3400, 2900, 2220, 1700, 1420, 1380, 1110.	3.98 (1H, q, J=6.4Hz), 4.39 (1H, dd, J=2.0, 6.0Hz), 5.10 ~ 5.36 (1H, m), 5.44 (1H, brs), 5.76 (1H, d, J=12.0Hz), 7.00 ~ 7.20 (4H, m).	407 (M^+ + H), 389 (M^+ + H - H_2O), 371 (M^+ + H - 2H_2O).	found : 407.2227 calcd : 407.2223 for $C_{26}H_{31}O_4$, (M^+ + H).

[a]Overall yields from the alcohol (**37**) were shown.
[b]Overall yields from the alcohol (**45**) were shown.
[c]$CDCl_3$ was used as the solvent
[d]Mass spectrum was obtained using the fast atom bombardment (FAB) technique.
[e] ^{13}C-NMR ($CDCl_3$) δ: 173.0, 133.0, 130.6, 129.8, 127.0, 87.4, 81.6, 78.5, 70.0, 67.7, 67.2, 43.7, 41.9, 41.6, 39.8, 37.9, 37.1, 35.7, 32.7, 32.7, 28.4, 27.8, 25.7, 24.3, 23.5, 17.9.
[f] ^{13}C-NMR ($CDCl_3$) δ: 177.8, 133.4, 132.6, 130.4, 127.4, 87.6, 84.0, 81.0, 78.1, 76.7, 69.7, 42.0, 41.4, 39.7, 38.8, 35.4, 34.6, 28.5, 25.1, 24.2, 23.9, 23.1, 22.5, 14.4, 12.5.

Table 15. Spectral data of 13,14-dihydrohomoisocarbacyclins (**85**)

compound	form (mp.)	yield (%)	IR ν_{max} (cm^{-1})	^{1}H-NMR (δ)[c]	MS (*m/z*)[d]	HR-MS (*m/z*)[d]
85*b*	oil	12[a]	neat: 3406, 2926, 2854, 1713, 1449, 1269.	5.10 ~ 5.46 (1H, m), 5.53 (1H, brs), 5.82 (1H, d, J=12.5Hz), 7.07 ~ 7.30 (5H, m).	453 (M^+ + H), 417 (M^+ + H - $2H_2O$).	found : 453.2977 calcd : 453.3005 for $C_{29}H_{41}O_4$, (M^++ H).
85*c*	oil	31[a]	neat: 3350, 2970, 2940, 1705, 1450, 1320, 1260, 1065, 1040, 910.	0.80 ~ 2.90 (23H, m), 0.93 (6H, s), 1.13 (3H, t, J=7.5Hz), 3.25 ~ 3.60 (1H, m), 3.65 ~ 4.00 (1H, m), 5.10 ~ 5.43 (1H, m), 5.53 (1H, brs), 5.78 (1H, d, J=12.0Hz).	403 (M^+ + H), 385 (M^+ + H - H_2O), 367 (M^+ + H - $2H_2O$).	found : 367.2639 calcd : 367.2638 for $C_{25}H_{35}O_2$, (M^++ H - $2H_2O$).
85*d*	oil	22[b]	neat: 3432, 2924, 1732, 1246, 1130, 1044.	3.54 (2H, t, J=7.0Hz), 4.00 (2H, d, J=3.0Hz), 4.72 (1H, t, J=6.0Hz), 5.42 (1H, brs), 7.23 ~ 7.63 (9H, m).	433 (M^+ + H - H_2O), 415 (M^+ + H - $2H_2O$).	found : 433.2404 calcd : 433.2379 for $C_{28}H_{33}O_4$, (M^++ H - H_2O).
85*e*	amorphous	9[b]	KBr: 3406, 2920, 2854, 1734, 1449, 1233.	3.35 ~ 3.70 (3H, m), 4.05 (2H, s), 5.47 (1H, brs), 7.00 ~ 7.30 (5H, m).	457 (M^+ + H), 439 (M^+ + H - H_2O), 421 (M^+ + H - $2H_2O$).	found : 457.2962 calcd : 457.2954 for $C_{28}H_{41}O_5$, (M^++ H).

[a]Overall yields from the alcohol (**37**) were shown.
[b]Overall yields from the alcohol (**45**) were shown.
[c]$CDCl_3$ was used as the solvent.
[d]Mass spectra were obtained using the fast atom bombardment (FAB) technique.

Table 16. Spectral data of *cis*-bicylo[4.3.0]non-3-ene analogues of homoisocarbacyclin

compound	form (mp.)	yield (%)	IR vmax (cm^{-1})	^{1}H-NMR (δ)[d]	MS (*m/z*)[e]	HR-MS (*m/z*)[e]
104	oil	39[a]	neat: 3400, 2950, 1715, 1450, 1320, 1250, 970.	0.96 (6H, s), 1.20 (3H, t, J=7.3Hz), 3.70 ~ 4.15 (2H, m), 5.30 ~ 5.43 (1H, m), 5.43 ~ 5.70 (2H, m).	384 ($M^+ - H_2O$).	found : 384.2657 calcd : 384.2664 for $C_{25}H_{36}O_6$, ($M^+ - H_2O$).
111	oil	29[b]	neat: 3400, 2930, 1720, 1440, 1260, 1120, 970.	0.96 (6H, s), 1.13 (3H, t, J=7.1Hz), 3.68 ~ 4.04 (2H, m), 5.10 ~ 5.60 (4H, m), 5.80 (1H, d, J=12.0Hz).	400 (M^+), 382 ($M^+ - H_2O$).	found : 400.2628 calcd : 400.2613, for $C_{25}H_{36}O_4$, (M^+).
112	oil	48[c]	neat: 3400, 2950, 2860, 1740, 1430, 1320, 1130, 910.	0.95 (6H, s), 1.13 (3H, t, J=7.5Hz), 3.62 (2H, t, J=6.0Hz), 3.70 ~ 4.00 (2H, m), 4.06 (2H, s), 5.42 ~ 5.66 (3H, m).	404 (M^+), 386 ($M^+ - H_2O$), 368 ($M^+ - 2H_2O$).	found : 404.2563 calcd : 404.2562 for $C_{24}H_{36}O_5$, (M^+).

[a]Overall yield from the alcohol (**96**) was shown.
[b]Overall yield from the alcohol (**106**) was shown.
[c]Overall yield from the alcohol (**110**) was shown.
[d]$CDCl_3$ was used as the solvent.
[e]Mass spectra were obtained using the electron impact (EI) technique.

Platelet aggregation in rabbits (ex vivo; *oral administration*)

Male Japanese white rabbits (2.5–3.5 kg) were used. Under pentobarbital anesthesia (60 mg/kg i.m.), the carotid artery was cannulated by a polyethylene tube and deprived of food for 24 h up to the time of the subsequent experiments. A blood sample was collected from the cannula in the syringe filled with one tenth volume of 3.8% sodium citrate solution at the scheduled time before and after oral administration of the test compound. PRP was separated by centrifugation and the platelet count in the PRP was adjusted to 3.5 x 10^5/ml. Platelet aggregation was induced by addition of ADP (final concentration; 10 μM).

Hypotensive effect in rabbits

Male Japanese white rabbits (2.5–3.5 kg) were used, which were the same animals as in the ex *vivo* experiments on platelet aggregation. The left carotid artery was exposed under spontaneous respiration, and the blood pressure was measured using an electric pressure transducer (Nihon Kohden RP-5). Test compounds were administered by intravenous infusion from the left femoral vein.

Hypotensive effect in dogs

Male or female mongrel dogs (9–14kg) were anesthetized with sodium pentobarbital. Then, the left carotid artery was exposed under artificial respiration, and the blood pressure was measured using an electric pressure transducer (Nihon Kohden RP-5). Test compounds were administered from the left femoral vein.

Ethanol-induced gastric lesions

Male Wistar rats (170–270 g) were deprived of food except for drinking water freely for 24 h before the experiments. Gastric lesions were produced by giving orally 1ml of 99.5% ethanol to each rat. The rats were sacrificed by cervical vertebral luxation at 1 h after the ethanol administration, and the stomach was removed and fixed by 1% formalin solution for 30 min. The stomach was incised along the greater curvature, and the mucous membrane surface of the stomach was gently washed with flowing water. Then, the total length of damages appearing on the gastric glandular portion was obtained and used as the ulcer index. Test compounds or PGE_2 as a comparative compound were administered in an amount of three doses (1, 3, 10 or 30 mg/kg) orally at 0.5 or 3.5 h before ethanol administration. The inhibitory activities of a test compound were expressed by ED_{50} values at which the ulcer was inhibited by 50% relative to the ulcer index of the vehicle-treatment group. ED_{50} values were calculated by probit method from three dose groups of ten to fifteen animals.

HCl-induced gastric lesions

Male Wistar rats (210–270 g) were used, and the experimental procedures were performed in the same manner described in ethanol-induced gastric lesions, using a necrotizing agent of 0.6 N HCl solution instead of ethanol.

Indomethacin-induced gastric lesions

Male Wistar rats (210–270g) were deprived of food but allowed free access to water for 24 h before the experiments. Then, 30, 100 or 300 μg/kg of a test compound was orally administered to each rat, and 30 min later, 60 mg/kg of indomethacin suspended in 0.5% carboxymethyl cellulose sodium salt (CMC-Na) was orally administered. At six hours after the indomethacin administration, each rat was sacrificed by cervical vertebral luxation. The stomach was taken out and fixed, and the ulcer index was obtained in the same manner in the experiments of ethanol-induced gastric lesions.

Mepirizole-induced duodenal ulcers

Male Wistar rats (190–230g) were used. Meprizole suspended in 0.5% CMC-Na was administered orally at 200 mg/kg to non-fasted rats, which were then deprived of food and water. The rats were sacrificed 24 h later and examined for ulcers in the duodenum. Test compounds or the vehicle were adminisered orally twice at 30 min before and 9 h after the mepirizole treatment.

Water-immersion stress-induced gastric lesions

Male Wistar rats (190–230g) were deprived of food but allowed free access to water for 24 h before the experiments. The rats were placed in a restraint cage, and then immersed vertically to the level of the xiphoid process in a water bath (23 °C) for 6 h and sacrificed. The stomach of each rat was removed and inflated by injecting 8ml of 1% formalin to fix the inner and outer layers of the gastric wall. This formalin treatment was performed in all the following experiments. Subsequently, the stomach was incised along the greater curvature and examined for lesions in the glandular portion. Test compounds or the vehicle were administered orally at 30 min before the stress load.

Pentagastrin-stimulated secretion

Male Wistar rats (210–270g) were deprived of food but allowed free access to water for 24 h before the experiments. The rats were anesthetized with urethane (1.25 g/kg i.p.) and polyethylene tube was inserted into the trachea to facilitate spontaneous breathing. A midline laparotomy was then performed and the stomach was exteriolized. Through an incision in the forestomach the gastric contents were gently washed out with saline. A double-lumen cannula (outer: Tygon with a diameter of 7mm; inner: polyethylene with diameter of 2mm) was inserted into the forestomach and secured by a ligature. The pylorus was ligated and saline at room temperature was infused through the inner cannula at a rate of 1.0 ml/min and drained from the outer tube. The gastric secretion was stimulated by a constant infusion of pentagastrin (ICI, 10 μg/kg/h, intravenously). The gastric effluent was collected at 10 min intervals. The acid output (in microequivalents per minute) was determined by titration of the perfusate with 0.01N aqueous NaOH to pH 7.0 with an automatic titrator (AUT-201, TOA DENPA). Test compounds or the vehicle were administered from a femoral vein after the gastric acid secretion reached a plateau.

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C_1 carboxyl - C_{11} hydroxyl	**6**; 11.40 Å,	**10**; 11.41 Å
C_1 carboxyl - C_{15} hydroxyl	**6**; 13.54 Å,	**10**; 13.64 Å
C_{11} hydroxyl - C_{15} hydroxyl	**6**; 4.71 Å,	**10**; 5.03 Å.

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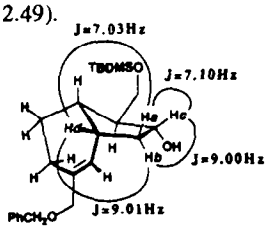

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19. The more polar fraction on TLC was assigned as the 15α-isomer (**32**) and the less polar one as the 15β-isomer (**33**), based on the known chromatographic behavior of synthetic PG intermediate.

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33. Reaction of **38** with dimethyl (1-chloro-2-oxo-heptyl)-phosphonate anion (**i**) according to the method reported by Iseki and co-workers gave the *Z*-chloroenone (**ii**) in 42% yield together with the *E*-chloroenone (**iii**) (45%) and only the *Z*-chloroenone (**ii**) was able to be converted into **74a**. See: Ref. 22.

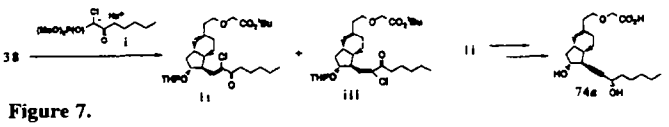

Figure 7.

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41. The enals (**21** and **93**) were independently converted to **vi** by the different routes shown in Fig. 8. Compound **vi** was obtained as an epimeric mixture at C_6, which could be separated by silica gel column chromatography (a ratio of epimers; less polar compound: more polar compound = 1:2.5 from **21**, 1:2.2 from **93**). The stereochemistry of the enal **93** was confirmed by comparing the spectral data of **vi** (more polar compound) prepared from **21** or **93**. Both products were identical to each other as shown below. A comparison of the less polar compounds also led to the same conclusion.

Spectral data of **vi** (more polar compound) synthesized from **21**:IR (neat):2928, 2856, 1742, 1462, 1438, 1114, 836cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.02 (12H, s), 0.88 (18H, s), 1.07–1.23 (5H, m), 1.24–1.36 (2H, m), 1.41–1.52 (3H, m), 1.54–1.63 (3H, m), 1.66–1.73 (1H, m), 1.76–1.87 (3H, m), 1.92–2.02 (1H, m), 2.30 (2H, t, J=7.46Hz), 3.59 (1H, dd, J=3.20, 10.20Hz), 3.64 (1H, dd, J=3.20, 10.30Hz), 3.66 (3H, s), 4.07 (1H, ddd, J=3.50, 5.80, 8.70Hz). MS (FAB) m/z: 513 (M^+ + H), 455 (M^+ + H - *tert*-Bu). HR-MS (FAB) m/z: 513.3778 (Calc'd for $C_{28}H_{57}O_4Si_2$, 513.3795, M^+ + H).

Spectral data of **vi** (more polar compound) synthesized from **93**:IR (neat):2928, 2856, 1744, 1462, 1438, 1112, 836cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.02 (12H, s), 0.86 (18H, s), 1.08–1.23 (5H, m), 1.27–1.36 (2H, m), 1.42–1.53 (3H, m), 1.56–1.65 (3H, m), 1.66–1.74 (1H, m), 1.76–1.87 (3H, m), 1.92–2.02 (1H, m), 2.30 (2H, t, J=7.45Hz), 3.59 (1H, dd, J=3.10, 10.10Hz), 3.64 (1H, dd, J=3.10, 10.40Hz), 3.66 (3H, s), 4.07 (1H, ddd, J=3.40, 5.80, 8.70Hz). MS (FAB) m/z: 513 (M^+ + H), 455 (M^+ + H - *tert*-Bu). HR-MS (FAB) m/z: 513.3785 (Calc'd for $C_{28}H_{57}O_4Si_2$, 513.3795, M^+ + H).

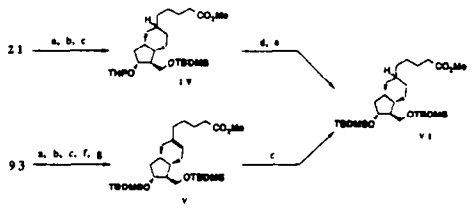

Figure 8. a) $Br^-Ph_3P^+CH_2(CH_2)_2CO_2H$, *tert*-BuOK, THF, r.t.; b) CH_2N_2 in Et_2O, 0 °C; c) H_2, 10%Pd-C, MeOH, r.t.; d) Et_2AlCl, CH_2Cl_2,-25°C; e) TBDMSCl, imidazole, DMF, r.t.; f) *p*-TsOH•H_2O, CH_3CN-H_2O(98:2), 50 °C; g) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C.

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50. Each analogue of **74b**, **75e** and **85a** was administered orally to some dose groups of five rats. **75e** induced loose bowels in four rats of 0.3 mg/kg dose group, and the same symptoms were observed in three rats of 3.0 mg/kg dose group of **85a**. Contrary to this, no gastrointestinal changes were observed in 10 mg/kg dose group of **74b**.