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SYNTHESES OF ISOCARBACYCLIN BY HIGHLY REGIOSELECTIVE ALKYLATION OF ALLYLIC ALCOHOLS[†]

Kiyoshi Bannai, Toshio Tanaka, Noriaki Okamura, Atsuo Hazato,
Satoshi Sugiura, Kenji Manabe, Koji Tomimori, Yoshinori Kato,
Seizi Kurozumi*, and Ryoji Noyori[§]

1st Bio-Medical Research Laboratories, Teijin Ltd.,
Asahigaoka, Hino, Tokyo 191, Japan

[§]Department of Chemistry, Nagoya University,
Chikusa, Nagoya 464, Japan

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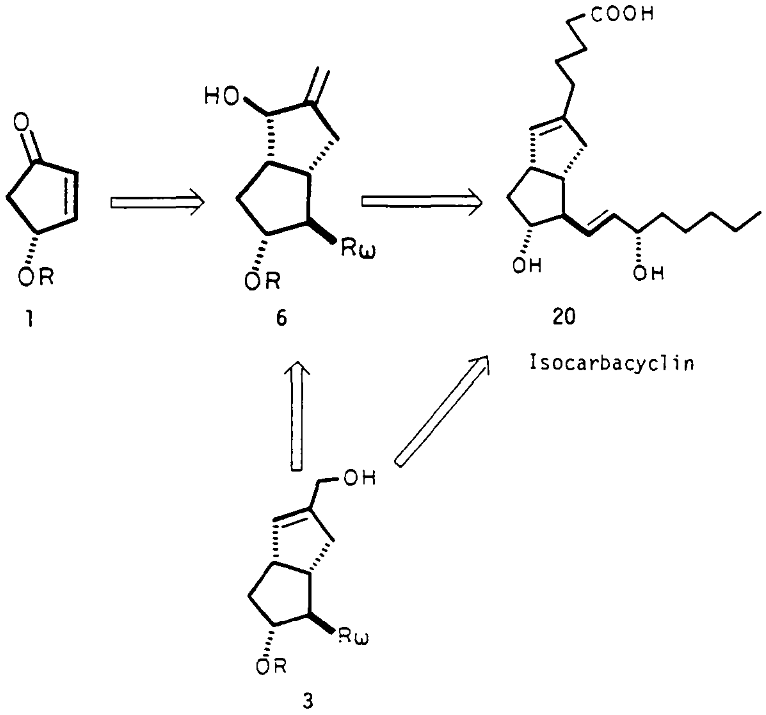
Abstract: Syntheses of isocarbacyclin (**20**) using highly regioselective alkylation of the new allylic alcohol intermediate **6** having an exocyclic double bond are described. The allylic alcohol **6** was prepared by (i) allylic rearrangement of the allylic alcohol **3** having an endocyclic double bond and (ii) reductive cyclization of γ-ethynyl aldehyde **11a** which was synthesized from (*R*)-4-hydroxy-2-cyclopentenone derivative **1** in 5 steps. γ-Alkylation of the allylic alcohol **6** was achieved by the use of Murahashi's method to result in the highly regioselective formation of isocarbacyclin (regioselectivity > 99%). α-Alkylation of the allylic alcohol **3** was also achieved to construct isocarbacyclin.

Stable analogs of prostacyclin (PGI_2) have been believed to be effective therapeutic agents for cardiovascular diseases.[1] Isocarbacyclin [9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1] (**20**)[2] is one of the most promising candidates because of its high chemical stability and the prostacyclin-like activity, hence several syntheses of this important analog have been reported to date.[3] In the course of our synthetic studies of isocarbacyclin,[3,4] we paid our attention to the method of Shibasaki *et al.*,[5] which involves regioselective S_N2 type alkylation (α-alkylation) toward an allylic alcohol intermediate of bicyclo[3.3.0]octene **3**. It was anticipated that other new and efficient syntheses of isocarbacyclin would be achieved by the use of the S_N2' type alkylation (γ-alkylation) reactions toward an allylic alcohol intermediate of a newly designed 3-methylenebicyclo[3.3.0]octane **6**.

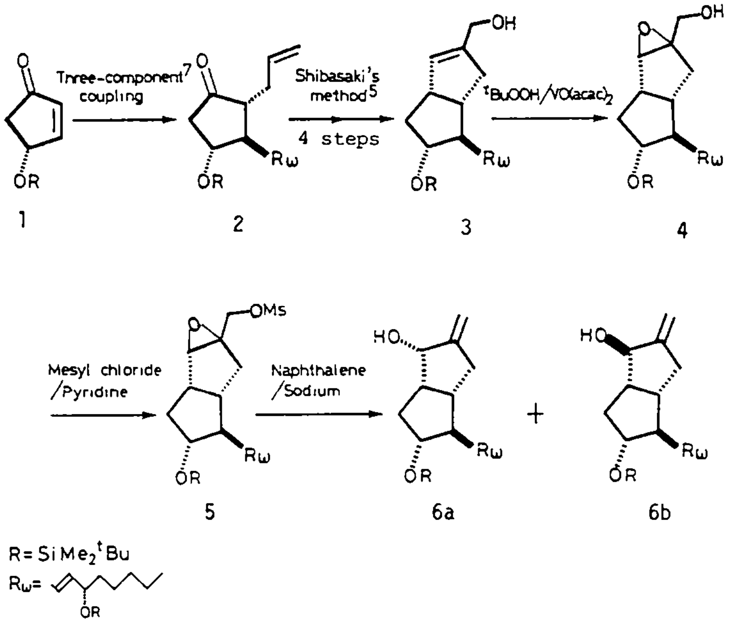
In this report, the improved syntheses of isocarbacyclin are described involving (i) syntheses of the new allylic alcohol intermediate **6** having an exocyclic double bond from (*R*)-4-*t*-butyldimethylsilyloxy-2-cyclopentenone (**1**), and (ii) highly regioselective alkylation toward **6** to construct the isocarbacyclin skeleton.



I. Syntheses of the allylic alcohol intermediate 6

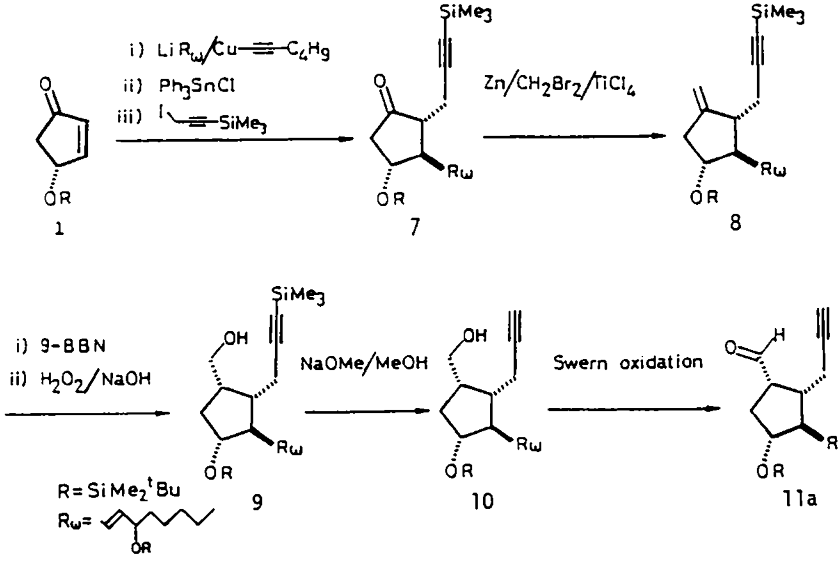
Firstly, we directed our efforts to the synthesis of the new allylic alcohol derivative of bicyclo[3.3.0]-octane **6** as a key intermediate. Construction of the 2-hydroxy-3-methylenebicyclo[3.3.0]octane skeleton was achieved by two routes; (A) allylic rearrangement of the allylic alcohol **3** by the use of the Nozaki's method[6] (Scheme I), (B) reductive cyclization of γ-ethynyl aldehyde **11a** (Scheme III).

The starting material of the first route (Scheme I), the allylic alcohol **3**, was easily obtained according to the method of Shibasaki *et al.*[5] *via* the three-component coupling[7] product **2** from the chiral 4-hydroxy-cyclopentenone derivative **1**. Epoxidation of **3** with *t*-butyl hydroperoxide/vanadyl acetylacetonate [$VO(acac)_2$] followed by mesylation gave epoxy mesylate **5** in 78% yield. The resultant mesylate **5** was then reduced with sodium naphthalene to afford the desired allylic alcohol derivatives of less polar (*S*)-isomer **6a** and more polar (*R*)-isomer **6b** in 26% and 34% yields, respectively, after chromatographic separation. The stereochemistry at $C_{6(9\alpha)}$ (PG numbering) in **6a** and **6b** was determined by measurement of the CD spectra of their corresponding benzoates **6c** and **6d**.[8] The positive Cotton effect of the benzoate **6c** [$\Delta\epsilon_{225} = +3.7$ (cyclohexane)] indicated *S*-configuration of the less polar alcohol **6a** and the negative Cotton effect of the benzoate **6d** [$\Delta\epsilon_{224} = -6.7$ (cyclohexane)] indicated *R*-configuration of the more polar alcohol **6b**.



(Scheme I)

The second efficient method to obtain the allylic alcohol **6** involved a reductive cyclization[9] of γ-ethynyl aldehyde **11a** derived from (*R*) 4-*t*-butyldimethylsilyloxy-2-cyclopentenone (**1**) in 55% yield (Scheme II).



(Scheme II)

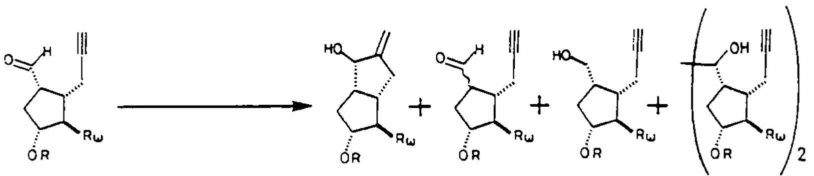
Firstly the three-component coupling reaction[7] was effected using the organo-copper reagent prepared from (*E,S*)-3-*t*-butyldimethylsilyloxy-1-lithiooctene, the optically active cyclopentenone **1**, and 3-iodo-1-trimethylsilylpropyne to afford the disubstituted cyclopentanone **7** in 86% yield. Methylenation of **7** with the Nozaki-Lombardo reagent[10] gave methylene cyclopentane **8** in 93% yield. Hydroboration of **8** with 9-borabicyclo[3.3.1]nonane (9-BBN) and subsequent oxidation with alkaline hydrogen peroxide was effected in a stereo- and regioselective manner to afford the cyclopentane carbinol **9** in 80% yield. The trimethylsilyl group of **9** was effectively removed by the use of sodium methoxide in 92% yield without affecting the silyl protecting groups of C-11 and C-15 (PG numbering) alcohols. The resulting cyclopentane carbinol **10** was then subjected to the Swern oxidation reaction to result in the formation of the γ-ethynyl aldehyde **11a** in 94% yield.

The reductive cyclization of **11a** was studied under several conditions (Scheme III). Firstly, we examined zinc metal as the reducing agent, which had been reported to be a good reagent for the reductive cyclization of γ-ethynyl ketones.[9b] When a tetrahydrofuran solution of the γ-ethynyl aldehyde **11a** was treated with zinc dust in the presence of chlorotrimethylsilane and 2,6-lutidine, desired allylic alcohol trimethylsilyl ether **13** was obtained accompanied with enol silyl ether **14** as an oily mixture. Acid hydrolysis of the reaction mixture afforded the epimeric mixture of the allylic alcohol **6** and γ-ethynyl aldehyde **11** (**11a**/**11b** = 1/1) in 28% and 51% yields, respectively. The formation of the enol silyl ether by-product **14** could be attributed to the relatively low electron-donating activity of zinc metal under the heterogeneous reaction conditions.

In order to avoid the enolization of the formyl compound **11a**, alkali metal naphthalene of a strong homogeneous reducing agent[9c] was then used for this cyclization reaction. Treatment of **11a** with lithium naphthalene in the presence of *t*-butyl alcohol as a proton donor gave the desired allylic alcohol **6** in 65% yield as a epimeric mixture at $C_{6(9\alpha)}$ (PG numbering; α/β = 13/52). In this reaction, the competitive enolization reaction was suppressed to 15% and was obtained the epimeric mixture of γ-ethynyl aldehyde **11** (**11a**/**11b** = 1/2).

Since the enolization reaction could be ascribed to the strong basicity of the reaction system, samarium (II) iodide was chosen as an appropriate reducing agent because it is described as a neutral homogeneous reducing agent with moderate reducing ability.[11] When the γ-ethynyl aldehyde **11a** was treated with samarium iodide in the presence of *t*-butyl alcohol, the desired cyclized product **6** was obtained in 71% yield as a epimeic mixture of **6a** and **6b** (**6a**/**6b** = 1/9). In this cyclization reaction the side product **11** which could be formed *via* enolization was not detectable, but the alcohol **10** and dimerized product **12** were obtained as by-products in both 8% yields.

The reductive cyclization of **11a** was also achieved by photochemical method.[9d] UV (254 nm) irradiation of **11a** in acetonitrile in the presence of 5 equiv. of triethylamine as an electron donor afforded desired allylic alcohol **6** in 60% yield as a mixture of the stereoisomers (**6a**/**6b** = 1/2). In this reaction, the β-aldehyde **11b** was obtained in 20% yield as a by-product.



11a 6 11 10 12

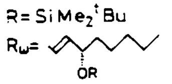
(Scheme III)

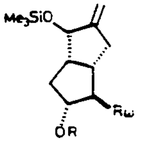
Reductive cyclization of γ-ethynyl aldehyde **11a**

Reagent	Conditions	Yields			
		6	**11**	**10**	**12**
Zn-TMSCl-2,6-Lutidine	THF, reflux, 5 h	28%*	51%*	-	-
Li-Naphthalene-^{t}BuOH	THF, -70°, 0.5 h	65%	15%	3%	-
SmI_2-^{t}BuOH	THF, -70°, 0.5 h	71%	-	8%	8%
hν-Et_3N	CH_3CN, r.t., 2 h	60%	20%**	-	-

*Analyzed after hydrolysis of silyl ethers (**13** and **14**)

Only β-aldehyde **11b was obtained.





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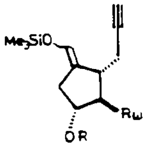

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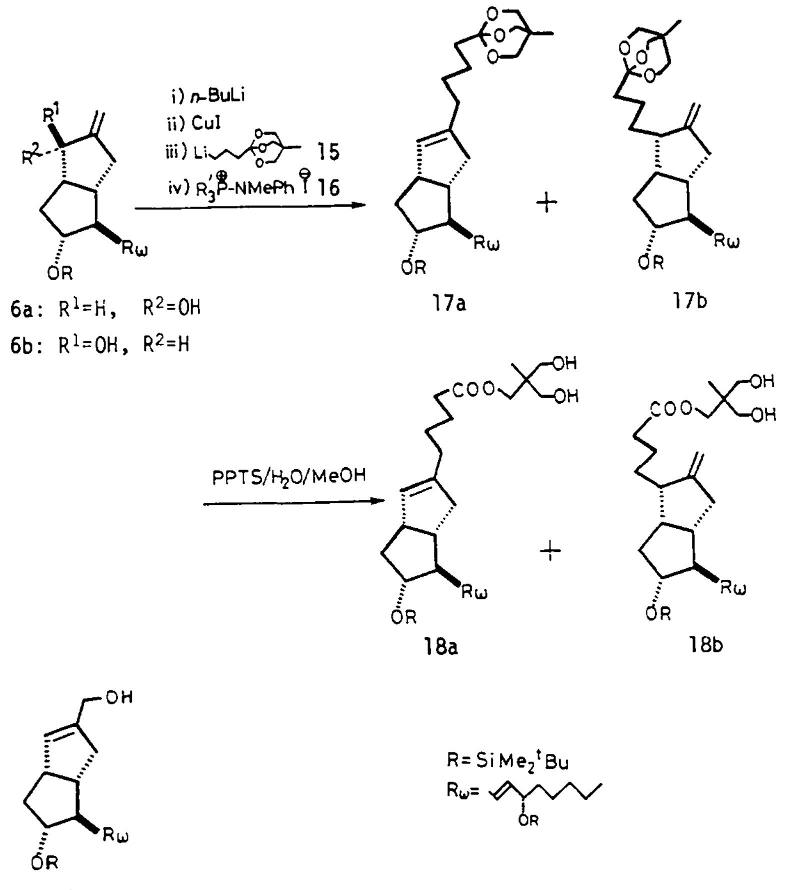
The resulting cyclized product of allylic alcohol **6** is a new synthon for the isocarbacyclin synthesis (*vide infra*).

II. Regioselective alkylation of the allylic alcohols 6 and 3 --- Regioselective syntheses of isocarbacyclin.

Now with the allylic alcohol **6** in our hand, our attention is turned to the regioselective introduction of the butanoic acid moiety of α-side chain to complete the isocarbacyclin synthesis. The regioselective γ-alkylation of the allylic alcohol **6** was studied using the procedure of Murahashi *et al.*[12] (Scheme IV). According to their procedure of regioselective γ-alkylation,[12b] both isomers of allylic alcohol **6a** and **6b** were treated successively with (i) *n*-butyllithium (ii) cuprous iodide (iii) lithiated orthoester **15**[13] (1.2 equiv.) and (iv) (methylphenylamino)tributylphosphonium iodide (**16a**) to result in the preferential formation of the orthoester form of isocarbacyclin **17a**. Without purification the resulting orthoester **17** was hydrolyzed with a catalytic amount of pyridinium *p*-toluenesulfonate to afford trimethylol ester **18a** in 82% and 76% yield from **6a** and **6b**, respectively, with a trace amount formation of by-product **18b** *via* α-alkylation, which was detected by HPLC analysis (**18a**/**18b** ≥ 99/1). When the excess equivalency of the lithiated orthoester **15** was used in this reaction, the regioselectivity of the alkylation was decreased[14].



(Scheme IV)

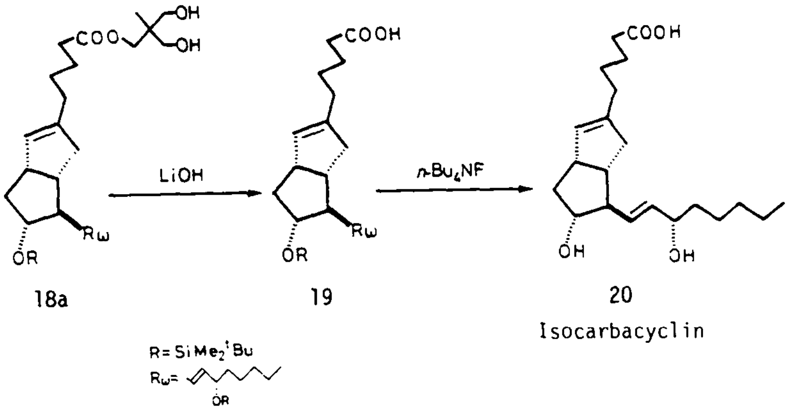
Regioselective alkylation of the allylic alcohols **6** and **3**

Run	Starting material	Equivalency of 15^{13}	R'(Phosphonium salt)	Yield (%)	**18a/18b**
1	**6a**	1.2	^{n}Bu(**16a**)	82	>99/1
2	**6b**	1.2	^{n}Bu(**16a**)	76	99/1
3	**6b**	6	^{n}Bu(**16a**)	70	99/5
4	**3**	4	Ph(**16b**)	62	99/1
5	**3**	1.8	Ph(**16b**)	61	48/52
6	**3**	<5*	^{n}Bu(**16a**)	66	13/87

*Lithium naphthalene was used instead of ^{t}BuLi to form **15**.

The regioselective α-alkylation of the allylic alcohol **3** was also accomplished according to the α-alkylation procedure of Murahashi *et al.*[12a] (Scheme IV). Similar treatment of allylic alcohol **3** with lithiated orthoester **15** (4 equiv.) in the presence of (methylphenylamino)triphenylphosphonium iodide (**16b**), gave the trimethylol ester of isocarbacyclin **18a** in 62% overall yield with excellent regioselectivity (**18a/18b** = 99/1). In this reaction the use of 1.8 equiv. of lithiated orthoester **15** resulted in the diminished regioselectivity of the alkylation (**18a/18b** = 48/52). When tributylphosphonium salt **16a** was used instead of triphenylphosphonium salt **16b**, the regioselectivity of the reaction reversed to result in the preferential formation of **18b** (**18a/18b** = 13/87). These results indicated that the combination of the equivalency of lithiated orthoester **15** and the sort of phosphonium salt played an important role on the regioselectivity of the alkylation reaction.[12,14]

The resultant trimethylol ester **18a** was finally converted into isocarbacyclin (**20**) in 90% yield after ester hydrolysis (95%) and desilylation (95%). Thus the highly regioselective synthesis of isocarbacyclin from the new allylic alcohol intermediate **6** as well as the known allylic alcohol **3** has become feasible.



(Scheme V)

Experimental

Melting point (uncorrected) was observed with a Yanaco micro melting point apparatus. IR spectra were recorded on a JASCO A102 spectrometer ^{1}H- and ^{13}C-NMR spectra were obtained on a JEOL JNM-GX400 (400 MHz), HITACHI R-90H (90 MHz) or a Varian EM360A (60 MHz) spectrometer. Chemical shifts are reported as parts per million (ppm) relative to internal tetramethylsilane. Mass spectra were taken at 70 or 20 eV on a HITACHI M-80B mass spectrometer. Optical rotations were measured on a Union Giken PM-101 automatic polarimeter. For high pressure liquid chromatography (HPLC) analysis, a Shimadzu Model LC-6A liquid chromatography equipped with a Shimadzu SPD-6A UV detector (210 nm), and a Zorbax Sil (5 μm) column (25 cm x 4.6 mm I.D.) were employed. Silica gel column chromatography was performed using Daisogel IR-60 silica gel. Thin layer chromatography (TLC) was performed using Merck silica gel (Kieselgel 60 F_{254}) analytical or preparative plates. All reactions were carried out under argon or nitrogen. Solvents for reactions were purified if necessary before use by distillation from suitable drying agents. Solvents for extraction and chromatography were GR grades.

Conversion of (1*S*,5*S*,6*R*,7*R*)-7-*t*-butyldimethylsilyloxy-6-{(*E*,*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl}-3-hydroxymethylbicyclo[3.3.0]-2-octene (3) into (1*S*,5*S*,6*R*,7*R*)-7-*t*-butyldimethylsilyloxy-6-{(*E*,*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl}-2-hydroxy-3-methylenebicyclo[3,3,0]octane (6)

Epoxidation of 3 — (1*S*,5*S*,6*R*,7*R*)-7-*t*-butyldimethylsilyloxy-6-{(*E*,*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl}-2,3-epoxy-3-hydroxymethylbicyclo[3,3,0]octane (4)

To a stirred solution of **3** (1.0 g, 1.97 mmol) in benzene (8 ml) was added vanadyl acetylacetonate [VO(acac)$_2$] (10 mg, 0.038 mmol) and 3.0 M solution of *t*-butyl hydroperoxide in dichloromethane (1.2 ml, 3.6 mmol) successively. The reaction mixture was stirred and heated at refluxing temperature for 20 min. After evaporation of the solvent *in vacuo*, the residual oil was chromatographed on silica gel eluting with hexane-ethyl acetate (6 : 1) to give epoxy alcohol **4** (801 mg, 78%) as an oil; IR (film) 3440, 3000, 1255, 1115, 1060, 1000, 965, 860, 830, 770 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 0.04 (12H, s), 0.8-1.0 (21H), 1.0-1.6 (8H, m), 1.6-2.7 (8H, m), 3.31 (1H, m), 3.4-4.1 (2H, m), 3.67 (2H, m), 5.15-5.35 (2H, m); MS m/e 467 (M-^{t}Bu), 393, 375, 261, 243, 215.

Mesylation of 4 — (1*S*,5*S*,6*R*,7*R*)-7-*t*-butyldimethylsilyloxy-6-{(*E*,*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl}-2,3-epoxy-3-methanesulfonyloxymethylbicyclo[3.3.0]octane (5)

To a cooled solution of epoxy alcohol **4** (801 mg, 1.53 mmol) and triethylamine (230 μl, 1.68 mmol) in dichloromethane (3 ml) at -26°C was added a dichloromethane (3 ml) solution of methanesulfonyl chloride (130 μl, 1.68 mmol), and the reaction mixture was stirred at the same temperature for 1 h. Ice-water was added and then extracted with ethyl acetate twice. The combined extracts were washed with brine and dried over MgSO$_4$. After evaporation of the solvent *in vacuo*, 917 mg of epoxy mesylate **5** was obtained as an oil (99%); IR (film) 3000, 1735, 1355, 1250, 1175, 1115, 1060, 1000, 960, 830, 770 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 0.04 (12H), 0.84 (21H), 1.0-1.7 (8H, m), 1.7-2.7 (7H, m), 2.94 (3H, s), 3.30 (1H, m), 3.6-4.1 (2H, m), 4.0-4.6 (2H, m), 5.15-5.35 (2H, m); MS m/e 545 (M-^{t}Bu), 507, 449.

Reductive cleavage of 5 — (2*S*)-allylic alcohol 6a and (2*R*)-allylic alcohol 6b

Sodium metal (1.45 mg, 63 mmol) cut in small pieces was added to a solution of naphthalene (9.01 g, 70 mmol) in tetrahydrofuran (210 ml) and this was stirred at room temperature for 1 h. The color of the solution has changed to dark green in a few minutes which indicates the formation of sodium naphthalene anion radicals. To this solution was added a solution of epoxy sulfonate **5** (7.71 g, 12.8 mmol) in tetrahydrofuran (40 ml), and the reaction mixture was stirred at room temperature for 15 min. Saturated NH$_4$Cl solution was added and then extracted with ethyl acetate twice (300 ml, 200 ml). The combined extracts were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The residual oil was chromatographed on silica gel eluting with hexane-ethyl acetate (92:8) to give less polar allylic alcohol **6a** (1,705 g, 26%) as an oil; $[\alpha]_D^{23}$+32.1°(c, 0.74, MeOH); IR (film) 3420, 3080, 1665, 1255, 1110, 1000, 965, 935, 835, 770 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 0-0.1 (12H), 0.8-1.0 (21H), 1.2-1.35 (6H, m), 1.35-1.55 (2H, m), 1.61-1.70 (1H, m), 1.82-1.91 (1H, m), 1.98-2.05 (1H, m), 2.10-2.24 (2H, m), 2.35-2.45 (1H, m), 2.63-2.73 (1H, m), 3.86 (1H, q; J=6 Hz), 4.03 (1H, m), 4.36 (1H, d; J=8.7 Hz), 4.95 (1H, bs), 5.06 (1H, bs), 5.43 (2H, m); ^{13}C-NMR (CDCl$_3$) δ -4.7 and -4.6 and -4.6 and -4.5 (Si-(CH$_3$)$_2$ x 2), 14.1 (C$_{20}$), 18.1 and 18.3 (Si-C≑ x 2), 22.7 (C$_{19}$), 25.1 (C$_{17}$), 25.9 and 26.0 (Si-c-(CH$_3$)$_3$ x 2), 31.9 (C$_{18}$), 34.3 and 35.4 (C$_7$, C$_{10}$), 38.6 (C$_{16}$), 43.6 and 44.3 (C$_8$, C$_9$), 57.9 (C$_{12}$), 73.3 (C$_{15}$), 74.6 (C$_{6(9\alpha)}$), 79.2 (C$_{11}$), 106.6 (C$_5$), 130.8 (C$_{13}$), 134.1 (C$_{14}$), 153.7 (C$_6$): (PG Numbering); MS (EI, m/e) 451 (M-^{t}Bu), 433, 359. Calc. for C$_{25}$H$_{47}$O$_3$Si$_2$ 451.3063, Found 451.3058.

Further elution with hexane-ethyl acetate (85:15) gave more polar allylic alcohol **6b** (2.216 g, 34%) as an oil; $[\alpha]_D^{23}$ −15.5° (c, 0.84, MeOH); IR (film) 3350, 3080, 1660, 1460, 1258, 1115, 1000, 968, 935, 835, 775 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 0-0.1 (12H), 0.8-1.0 (21H), 1.20-1.36 (7H, m), 1.36-1.54 (2H, m), 1.88-1.97 (1H, m), 2.08 (1H, d, J=15 Hz), 2.12-2.30 (3H, m), 2.61-2.70 (1H, m), 3.76 (1H, m), 4.04 (1H, m), 4.16 (1H, bs), 4.96 (1H, bs), 5.08 (1H, bs), 5.46 (2H, m); ^{13}C-NMR (CDCl$_3$) δ -4.6 and -4.5 and -4.5 and -4.4 (Si-(CH$_3$)$_2$ x 2), 14.1 (C$_{20}$), 18.2 and 18.3 (Si-C≑ x 2), 22.7 (C$_{19}$), 25.2 (C$_{17}$), 25.9 and 26.0 (Si-c-(CH$_3$)$_3$ x 2), 31.9 (C_{18}), 35.2 and 39.2 (C_7, C_{10}), 38.7 (C_{16}), 43.0 and 47.2 (C_8, C_9), 56.9 (C_{12}), 73.2 (C_{15}), 78.4 (C_{11}), 82.0 ($C_{6(9\alpha)}$), 108.5 (C_5), 130.5 (C_{13}), 134.6 (C_{14}), 153.9 (C_6): (PG Numbering); Mass (EI, m/e) 451 (M-^{t}Bu), 319, 305. Calc. for $C_{25}H_{47}O_3Si_2$ 451.3063, Found 451.3115.

Benzoylation of **6a** — (1*S*,2*S*,5*S*,6*R*,7*R*)-2-benzoyloxy-7-*t*-butyldimethylsilyloxy-6-{(*E*,*S*)-3-t-butyldimethylsilyloxy-1-octenyl}-3-methylenebicyclo[3.3.0]octane (**6c**)

Benzoyl chloride (68 µl, 0.59 mmol) was added to a stirred solution of **6a** (23 mg, 0.045 mmol) in pyridine (0.2 ml) at room temperature. The reaction mixture was stirred at the same temperature for 7 h. At the end of this period, the reaction was quenched by the addition of water and extracted with ether twice. The combined extracts were washed with saturated $KHSO_4$ solution, saturated $NaHCO_3$ solution and brine successively. After dryness over $MgSO_4$ and evaporation of the solvent *in vacuo*, the residual oil was purified by preparative TLC (benzene) to give **6c** (16 mg, 58%) as an oil; CD $\Delta\epsilon_{225}$ = +3.7 (cyclohexane); IR (film) 1722, 1272, 1253, 1118, 836, 772, 708 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 0.8-1.0 (21H), 3.74 (1H, m), 4.05 (1H, m), 5.07 (1H, bs), 5.16 (1H, bs), 5.52 (2H, m), 5.70 (1H, m), 7.57 (3H, m), 8.16 (2H, m).

Benzoylation of **6b** — (1*S*,2*R*,5*S*,6*R*,7*R*)-2-benzoyloxy-7-*t*-butyldimethylsilyloxy-6-{(*E*,*S*)-3-t-butyldimethylsilyloxy-1-octenyl}-3-methylenebicyclo[3.3.0]octane (**6d**)

The benzoylation of **6b** (24 mg, 0.047 mmol) was carried out by the same method described above (as in the case of the benzoylation of **6a**) to give 14 mg (51%) of **6d** as an oil; CD $\Delta\epsilon_{224}$ = −6.7 (cyclohexane); IR (film) 1720, 1268, 1255, 1108, 838, 775, 710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.8-1.0 (21H), 3.76 (1H, m), 4.06 (1H, m), 5.15 (1H, bs), 5.27 (1H, bs), 5.37 (1H, bs), 5.49 (2H, m), 7.52 (3H, m), 8.08 (2H, m).

Preparation of the γ-ethynyl aldehyde 11a from (*R*)-4-*t*-butyldimethylsilyloxy-2-cyclopentenone (1)

Three-component coupling reaction — (2*R*,3*R*,4*R*)-4-*t*-butyldimethylsilyloxy-3-{(*E*,*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl}-2-(3-trimethylsilyl-2-propynyl)cyclopentanone (7)

To a 1.51 M pentane solution of *t*-butyllithium (210 ml, 315 mmol) was added at -78°C a solution of (*E*,*S*)-3-*t*-butyldimethylsilyloxy-1-iodo-1-octene (60.4 g, 164 mmol) in anhydrous ether (100 ml), which had been cooled at -78°C previously. The resulting mixture was stirred at -78°C for 2 h. A solution of 1-hexynylcopper (23.8 g, 165 mmol) and hexamethylphosphorous triamide (60.0 ml, 330 mmol) in anhydrous ether (150 ml) was then added at -78°C. The whole was stirred at -78°C for 1 hr, then a solution of (*R*)-4-*t*-butyldimethylsilyloxy-2-cyclopentenone (**1**) (31.9 g, 150 mmol) in anhydrous tetrahydrofuran (200 ml) was added slowly at -78°C for 1.5 h by the use of a microfeeder. After the mixture was stirred at -40°C for 20 min, then at -78°C for 10 min, *N*-methyl-2-pyrrolidone (144 ml, 1.50 mol) was added and stirred at -78°C for 30 min. A solution of triphenyltin chloride (72.3 g, 188 mmol) in anhydrous tetrahydrofuran (100 ml) was added at -78°C, and then stirred at -30°C for 5 min. To the resulting mixture was added at -30°C a solution of 3-iodo-1-trimethylsilylpropyne (53.6 g, 225 mmol), and then stirred at -30°C for 30 min. After acetic acid (45.0 g, 750 mmol) was added, the reaction mixture was poured into a stirred solution (400 ml) of acetate buffer. [The buffer solution (400 ml) was prepared by dissolving sodium acetate (23.6 g) and acetic acid (78.7 g) in water]. This was extracted with hexane twice (1 l, 0.5 l). The combined extracts were washed successively with saturated NH_4Cl solution twice and brine twice, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel with hexane-dichloromethane (3 : 1) to give **7** (73.1 g, 86%) as an oil; $[\alpha]_D^{26}$−5.7° (c, 0.98, MeOH); IR (film) 2190, 1752, 1462, 1250, 967, 838, 778 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0-0.1 (12H), 0.13 (9H, s), 0.8-1.0 (21H), 3.95-4.2 (2H, m), 5.57 (2H, m); MS (EI, m/e) 564 (M^+), 550, 507 (M-^{t}Bu), 493. Calc. for $C_{27}H_{51}O_3Si_3$ 507.3146, Found 507.3091.

Methylenation of 7 — (1*R*,2*R*,3*R*)-2-{(E,S)-3-*t*-butyldimethylsilyloxy-1-octenyl}-4-methylene-3-(3-trimethylsilyl-2-propynyl)cyclopentanol *t*-butyldimethylsilyl ether (8)

Preparation of the methylenating agent[10]

To a stirred suspension of zinc dust (182.8 g, 2.80 mmol) in dry dibromomethane (159.3 g, 916 mmol) and anhydrous tetrahydrofuran (1.2 l) at -40°C was added dropwise titanium tetrachloride (74 g, 664 mmol) over 1 h. The mixture was stirred at -40°C for 2.5 h then allowed to stand at -20°C for 16 h to give a thick grey slurry of an active species, which was stored in a freezer (-20°C) until required.

Methylenation of 7

Some part of the slurry of the methylenating agent thus prepared was added to an ice cold stirred solution of the ketone **7** (37.4 g, 66.3 mmol) in dichloromethane (150 ml) and stirred at room temperature about half an hour. If it was found by a TLC monitor that the starting ketone **7** still remained at this point, the mixture was ice cooled again and the slurry agent was added, then stirred at room temperature again. These procedures were repeated until the TLC monitor indicates complete reaction. The reaction mixture and 2 M hydrochloric acid (300 ml) was successively poured into a stirred mixture of ice and hexane (400 ml). The resulting water layer was extracted with hexane again. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was purified by silica gel column chromatography eluting with hexane-ethyl acetate (99 : 1) to give **8** (34.7 g, 93%) as an oil; IR (film) 2190, 1658, 1460, 1250, 1002, 968, 838, 773 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 0-0.1 (12H), 0.14 (9H, s), 0.8-1.0 (21H), 3.7-4.2 (2H, m), 4.98 (1H, bs), 5.10 (1H, bs), 5.51 (2H, m); MS (EI, m/e) 562 (M^+), 547, 505.

Hydroboration of **8** — (1*R*,2*R*,3*S*,4*S*)-2-{(*E*,*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl}-4-hydroxymethyl-3-(3-trimethylsilyl-2-propynyl)cyclopentanol 1-*t*-butyldimethylsilyl ether (**9**)

To a stirred solution of **8** (106.0 g, 0.189 mole) in anhydrous tetrahydrofuran (400 ml) cooled on ice-water bath was added 0.5 M solution of 9-borabicyclo[3.3.1]nonane (9-BBN) in tetrahydron (547 ml, 0.274 mole), and the reaction mixture was stirred at room temperature for 1 h. After the mixture was cooled on ice-water bath, aqueous sodium hydroxide solution (9.4 M, 100 ml) was added, and then aqueous hydrogen peroxide solution (35%, 60 ml) was added at a rate that the reaction might not proceed so vigorously. After stirring at 60°C for 30 min the reaction mixture was poured on ice-water (500 ml) and extracted with ethyl acetate (2 x 400 ml). The combined extracts were washed successively with saturated $KHSO_4$ solution (300 ml), saturated $NaHCO_3$ solution (300 ml) and brine (2 x 300 ml), and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was chromatographed on silica gel eluting with hexane-ethyl acetate (19 : 1) to give 87.7 g of **9** (80%) as an oil; IR (film) 3450, 2190, 1460, 1252, 967, 835, 772 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 0-0.1 (12H), 0.13 (9H, s), 0.8-1.0 (21H), 2.8-3.0 (1H, br), 3.7-4.2 (4H, br), 5.44 (2H, m); MS (EI, m/e) 523 (M^+-^{t}Bu), 391, 317.

Removal of the trimethylsilyl group of **9** — (1*R*,2*R*,3*S*,4*S*)-2-{(*E*,*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl}-4-hydroxymethyl-3-(2-propynyl)cyclopentanol 1-*t*-butyldimethylsilyl ether (**10**)

To an ice cooled solution of **9** (109.3 g, 0.189 mol) in methanol (450 ml) was added a 28% solution of sodium methoxide in methanol (164 g, 0.850 mol). The reaction mixture was stirred at room temperature for 2 h. At the end of this period, saturated NH_4Cl solution (400 ml) was added and the mixture was extracted with dichloromethane (2 x 400 ml). The combined extracts were washed successively with saturated $KHSO_4$ solution (400 ml), saturated $NaHCO_3$ solution (400 ml) and brine (2 x 300 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product with silica gel eluted with hexane-ethyl acetate (25 : 1) afforded **10** as an oil (88.3 g, 92%): $[\alpha]_D^{26}$ −0.28° (c, 0.73, MeOH); IR (film) 3450, 3320, 2120, 1460, 1252, 965, 835, 775 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 0-0.1 (12H), 0.8-1.0 (21H), 1.94 (1H, t; J=3 Hz), 2.85-3.1 (1H, br), 3.7-4.2 (4H, br), 5.44 (2H, m); MS (EI, m/e) 508 (M^+), 451 (M-^{t}Bu), 319. Calc. for $C_{25}C_{47}O_3Si_2$ 451.3063, Found 451.3074.

Swern oxydation of **10** — (1*R*,2*R*,3*R*,4*S*)-2-{(*E*,*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl}-4-formyl-3-(2-propynyl)cyclopentanol *t*-butyldimethylsilyl ether (**11a**)

Dimethylsulfoxide (6.46 ml, 94 mmol) was added dropwise to a stirred solution of oxalyl chloride (3.89 ml, 44 mmol) in dry dichloromethane (140 ml) at -55°C, and the mixture was stirred for 20 min at the same temperature. A solution of **10** (11.68 g, 23 mmol) in dry dichloromethane (50 ml) was added and the mixture was stirred at -55°C for 30 min, then triethylamine (15.8 ml, 114 mmol) was added at -55°C. After the reaction mixture was stirred at -55°C for 30 min, the reaction was quenched by the addition of acetic acid (7.7 ml, 135 mmol). After stirring at -55°C for 30 min, saturated NH_4Cl solution (150 ml) was added and extracted with dichloromethane twice (100 ml, 200 ml). The combined extracts were washed successively with saturated $KHSO_4$ solution (150 ml), saturated $NaHCO_3$ solution (150 ml) and brine (2 x 150 ml), dried over $MgSO_4$ and then concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography eluting with hexane-ethyl acetate (4 : 1) to afford 11.03 g (94%) of aldehyde **11a** as an oil; $[\alpha]_D^{24}$ +2.3° (c, 0.60, $CHCl_3$); IR (film) 3320, 2970, 2950, 2860, 2120, 1722, 1252, 1120, 965, 835, 775 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0-0.1 (12H), 0.8-1.0 (21H), 2.8-3.1 (1H, m), 3.85-4.2 (2H, m), 5.50 (2H, m), 10.00 (1H, d; J=3 Hz); MS (EI, m/e) 465, 449 (M-^{t}Bu), 317, 303. Calc. for $C_{25}H_{45}O_3Si_2$ 449.2907, Found 449.2876.

Preparation of the allylic alcohol 6 from 11a by reductive cyclization

Reductive cyclization of 11a using zinc metal as a reducing agent

Zinc dust was activated before use by rinsing with 1.2 M hydrochloric acid for 4 min. After decantation, the zinc dust was washed successively with water, acetone (twice) and ether, and then dried at reduced pressure for 2 h. The activated zinc dust (262 mg, 4 gram atom) was added to a solution of the ethynyl aldehyde **11a** (100 mg, 0.20 mmol) in absolute tetrahydrofuran (2 ml). 2,6-Lutidine (70 µl, 0.60 mmol) and trimethylchlorosilane (152 µl, 0.12 mmol) was added and the mixture was stirred at reflux for 4 h. During this period irradiation of ultrasound was effected intermittently in order to crush a solid mass formed during the reaction. At the end of this period, ether and water was added and the mixture was filtered through Celite. After washing the Celite with ether, combined filtrate was transferred into a separatory funel. The water layer was extracted with ether again and the combined organic solution was washed successively with saturated $KHSO_4$ solution, saturated $NaHCO_3$ solution and brine. After dryness with $MgSO_4$ and concentration *in vacuo*, the resulting oily residue which contained enol trimethylsilylether of **11** and trimethylsilylether of **6** was dissolved in methanol (3 ml). To this solution was added a catalytic amount of pyridinium *p*-toluenesulfonate and the mixture was stirred at room temperature for 10 min to hydrolyzed the trimethylsilylethers. Saturated $NaHCO_3$ solution was poured and this was extracted with ether twice. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product with silica gel eluted with hexane-ethyl acetate (40:1) furnished 51 mg (51%) of a epimeric mixture of aldehyde **11** as an oil. The ratio of α-isomer **11a** and β-isomer **11b** was about 1:1 according to the ^{1}H-NMR study; ^{1}H-NMR ($CDCl_3$) δ 0-0.1 (12H), 0.8-1.0 (21H), 2.8-3.1 (1H, m), 3.85-4.2 (2H, m), 5.55 (2H, m), 9.71 (0.5 H, d, J=2 Hz; -CHO of β-aldehyde **11b**), 10.00 (0.5 H, d, J=3 Hz; -CHO of α-aldehyde **11a**).

Further elution with hexane-ethyl acetate (19 : 1) afforded a epimeric mixture of the cyclized alcohol **6** (23.5 mg, 23%) as an oil.

Reductive cyclization of 11a using lithium naphthalene as a reducing agent

Naphthalene (70.3 g, 550 mmol) was added to an ice cold stirred suspension of lithium (15.3 g of 25% dispersion in mineral oil containing about 0.5% of sodium, 552 gram atom) in absolute tetrahydrofuran (550 ml). Several minutes later the color of the solution became dark green, which indicates the presence of anion radical. After stirring on ice bath for 3 hr, the mixture was cooled to -70°C. To this cooled solution was added the mixture of the aldehyde **11a** (25.1 g, 49.7 mmol) and *t*-butyl alcohol (18.7 ml, 198 mmol) in absolute tetrahydrofuran (120 ml) cooled to -70°C in advance. The mixture was stirred at -70°C for 10 min, and then ethanol was added until the dark green color has disappeared. After addition of saturated NH_4Cl solution (600 ml), the mixture was extracted with ethylacetate (2 x 500 ml). The combined extracts were washed with brine (2 x 400 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was separated by silica gel column chromatography eluting with hexane-ethyl acetate (19 : 1) to give 3.77 g (15%) of the epimeric mixture of aldehyde **11**. The ratio of α-isomer **11a** and β-isomer **11b** was about 1 : 2 according to the ^{1}H-NMR study; ^{1}H-NMR ($CDCl_3$) δ 0-0.1 (12H), 0.8-1.0 (21H), 2.8-3.1 (1H, m), 3.85-4.2

(2H, m), 5.55 (2H, m), 9.71 (0.65 H, d, J=2 Hz; -CHO of β-aldehyde **11a**), 10.00 (0.35 H, d, J=3 Hz; -CHO of α-aldehyde **11a**).

Further elution with hexane-ethyl acetate (9:1 - 4:1) gave 17.34 g of oil containing the cyclized alcohols, **6a** and **6b**, and the alcohol **10**. According to the HPLC analysis [column; Zorbax Sil (25 cm x 4.6 mm I.D.), Mobil phase; 0.2% EtOH-Hexane, Flow rate; 1.0 ml/min: the retention times of **6a**, **6b** and **10** were 19.6 min, 33.4 min and 24.8 min, respectively]. The ratio of **6a**, **6b** and **10** were 19:77:4 (which means the yields of the three products were 13%, 52% and 3%, respectively).

Reductive cyclization of 11a using samarium (II) iodide as a reducing agent

Preparation of tetrahydrofuran solution of samarium iodide[11b]

A solution of 1,2-diiodoethane (5.64 g, 20 mmol) in absolute tetrahydrofuran (200 ml) was added at 0°C to samarium powder (6.0 g, 39.9 gram atom). After the mixture was stirred at room temperature for 5 h, the resulting blue-green supernatant was used as a 0.1 M solution of samarium iodide.

Reductive cyclization

The solution of samarium iodide thus prepared (60 ml, 6 mmol) was transferred into another flask and then cooled to -70°C. To this solution was added a solution of the aldehyde **11a** (508 mg, 1 mmol) and *t*-butyl alcohol (283 μl, 3 mmol) in absolute tetrahydrofuran (12 ml), which had been cooled to -70°C in advance. After stirring at the same temperature for 45 min, the reaction mixture was quenched by the addition of saturated NH_4Cl solution. This was then extracted with ethyl acetate twice, and the combined extracts were washed successively with saturated $KHSO_4$ solution, saturated $NaHCO_3$ solution and brine. After dryness with $MgSO_4$ and concentration *in vacuo*, the resulting oil was chromatographed on silica gel eluting with hexane-ethyl acetate (97 : 3) to give 41 mg (8%) of **12** as an oil (the dimer of **11a**); IR (film) 3350, 3320, 2950, 2120, 1258, 837, 775 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 0-0.1 (24H), 0.8-1.0 (42H), 3.65 (2H, br; OH), 3.7-4.2 (6H, m), 5.40 (4H, m); MS (EI, m/e) 1014 (M^+), 957, 827, 507, 375. Further elution with hexane-ethyl acetate (19:1 - 10:1) gave 372 mg of oil containing the allylic alcohols **6a** and **6b**, and the alcohol **10**. According to the HPLC analysis, the ratio of **6a**, **6b** and **10** were 9 : 81 : 10 (which means the yields of the three products were 7%, 64% and 8%, respectively).

Photo-reductive cyclization of 11a

The reaction was carried out in a cold room (4°C). A solution of aldehyde **11a** (106 mg, 0.21 mmol) in acetonitrile (5.8 ml) in 10 mm o.d. quartz tube was degased by 1 h nitrogen bubbling. After the addition of triethylamine (143 μl, 1.03 mmol), irradiation was conducted in a merry-go-round type system (Rayonet Photochemical Reactor) equipped with 14 low-pressure mercury lamps (Rayonet Photochemical Reaction Lamp; RPR 2537A) for 3.5 h. The solvent was distilled off, and the crude product was separated by silica gel column chromatography. Elution with hexane-ethyl acetate (19:1) gave 22 mg (20%) of aldehyde **11b**, which was a epimer of starting aldehyde **11a**; ^{1}H-NMR ($CDCl_3$) δ 0-0.1 (12H), 0.8-1.0 (21H), 2.8-3.1 (1H, m), 3.88 (1H, q, J=7 Hz), 4.06 (1H, m), 5.57 (2H, m), 9.71 (1H, d, J=2 Hz); MS (EI, m/e) 449 (M-^{t}Bu), 317, 303. Further elution with the same solvent gave the cyclized product **6** (64 mg, 60%) as a epimeric mixture at $C_{6(9\alpha)}$ carbon (PG numbering; α : β ratio is about 1:2 according to the HPLC study).

Regioselective alkylation of the allylic alcohol 6

Preparation of 9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 11,15-bis-*t*-butyldimethylsilyl ether 3-hydroxy-2-hydroxymethyl-2-methylpropyl ester (18a) *via* 1-nor-2-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octyl)-9(*O*)-metano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 11,15-bis-*t*-butyldimethylsilyl ether (17a)

Preparation and quantitative analysis of 1-(3-lithiopropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane (15)

Preparation

2.0 M solution of *t*-butyllithium in pentane (1.5 ml, 3.0 mmol) was added to a flask containing 7 ml of ether at -78°C. To this solution was added an ethereal solution (4 ml) of 1-(3-bromopropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**21**) (502 mg, 2.0 mmol) at -78°C for 3 min. The mixture was stirred at the same temperature for 1.5 h to afford the ethereal solution of lithiated orthoester **15**.

Quantitative analysis

Benzaldehyde was added to the above prepared solution of lithiated orthoester **15** at -78°C and the mixture was stirred at the same temperature for 1 h. Saturated NH_4Cl solution (20 ml) was added and then extracted with ether (2 x 20 ml). The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residual oil was chromatographed on silica gel eluting with hexane-ethyl acetate (1 : 1) containing 0.05% of triethylamine to give 332 mg of 1-(4-hydroxy-4-phenylbutyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**22**) (60%) as an oil; ^{1}H-NMR ($CDCl_3$) δ 0.7 (3H, s), 3.80 (6H, s), 4.60 (1H, br), 7.30 (5H, m). Since the yield of the coupling product **22** was roughly considered as the yield of lithiated orthoester **15** from bromoorthoester **21** in the lithiation the yield of **15** was estimated about 60%.

Alkylation of the (*S*)-allylic alcohol **6a**

Preparation of lithiated orthoester solution

To a stirred solution of bromoorthoester **21** (1.12 g, 4.46 mmol) in anhydrous ether (23 ml) was added 2.0 M pentane solution of *t*-butyllithium (3.35 ml, 6.7 mmol) at -78°C. This was then stirred at the same temperature for 1.5 h and was used as the ethereal solution of lithiated orthoester **15**.

Alkylation of **6a** using 1.2 equiv. of **15**

n-Butyllithium (1.56 M in hexane; 1.72 ml, 1.68 mmol) was added to a stirred solution of **6a** (1.134 g, 2.23 mmol) in anhydrous tetrahydrofuran (36 ml) at 0°C. After stirring at room temperature for 30 min, the reaction mixture was poured into a suspension of cuprous iodide (638 mg, 3.34 mmol) in anhydrous tetrahydrofuran (13 ml) and then stirred at room temperature for 30 min. At the end of this period this was cooled at -78°C, to which was added all of the cold ethereal solution of lithiated orthoester **15** prepared above (2.67 mmol). After stirring at the same temperature for 25 min, (methylphenylamino)tributylphosphonium iodide (**16a**) (1.46 g, 3.35 mmol) in anhydrous dimethylformamide (7 ml) was added and the mixture was stirred at room temperature for 2 h. At the end of this period, saturated NH_4Cl solution (100 ml) was added and the mixture was extracted with ether (2 x 150 ml). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was chromatographed on silica gel eluting with hexane-ethyl acetate (20 : 1) containing 0.05% of triethylamine to afford **17a** (1.50 g) as a crude oil; ^{1}H-NMR ($CDCl_3$) δ 0-0.1 (12H), 0.76 (3H, s), 0.8-1.0 (21H), 3.5-4.2 (2H, m), 3.80 (6H, s), 5.28 (1H, bs), 5.50 (2H, m).

Hydrolysis of **17a**

All the crude oil **17a** obtained was dissolved in methanol (60 ml) containing 0.6 ml of water. To this solution was added pyridinium *p*-toluenesulfonate (38 mg), and the reaction mixture was stirred at room temperature for 15 h. After addition of $NaHCO_3$ solution, the solvent was concentrated *in vacuo*. The oily residue was partitioned between ethyl acetate-water, and the water layer was extracted with ethyl acetate again. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel eluting with hexane-ethyl acetate (7:3 - 1:1) furnished 1.32 g (82% from **6a**) of ester **18a** as an oil. No α-alkylated by-product **18b** was detected by HPLC analysis [column; Zorbax Sil (25 cm x 4.6 mm I.D.); Mobil phase: 2.5% EtOH-Hexane, Flow rate; 1.2 ml/min: the peak of **18a** appeared at 17.3 min, but that of **18b** (which must have appeared at 18.6 min) did not appear on the flow chart.], which indicates the content of **18b** was less than 1%; **18a** IR (film) 3420, 2970, 2950, 2880, 1735, 1255, 1110, 1050, 970, 850, 835, 770 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0-0.1 (12H), 0.8-1.0 (21H), 2.7-3.1 (1H, m), 3.53 (4H, s), 3.5-3.9 (1H, m), 3.9-4.1 (1H, m), 4.18 (2H, s), 5.25 (1H, bs), 5.47 (2H, m); MS (EI, m/e) 623 (M-^{t}Bu), 605, 492. Calc. for $C_{34}H_{63}O_6Si_2$ 623.4163, Found 623.4194.

Alkylation of the (*R*)-allylic alcohol **6b**

Alkylation of **6b** using 1.2 equiv. of **15**

Alkylation of **6b** and hydrolysis of the resulting orthoester **17** was carried out as the same method described in the case of the less polar allylic alcohol **6a** (*vide supra*). The yield of **18** from the allylic alcohol **6b** was 76%, and the ratio of **18a** and **18b** was determined as 99/1 by the HPLC analysis.

Alkylation of **6b** using 6 equiv. of **15**

Alkylation of **6b** and hydrolysis **17** was carried out as the same method described above without using 6 equiv. of **15** instead of 1.2 equiv. The yield of **18** from **6b** was 70%, and the ratio of **18a** and **18b** was determined as 99/5 by the HPLC analysis.

Regioselective alkylation of the allylic alcohol 3

Alkylation of 3 using **16b** and 4 equiv. of **15**

Preparation of lithiated orthoester solution

t-Butyllithium (2.0 M solution in pentane; 5.17 ml, 10.4 mmol) was added to a flask containing 5 ml of anhydrous ether at -78°C. To this solution, bromoorthoester **21** (1.73 g, 6.9 mmol) in anhydrous ether (32 ml) was added at -78°C in the period of 2 min. The mixture was then stirred at the same temperature for 1.5 h to afford the ethereal solution of orthoester lithium **15**.

Alkylation of 3

To an ice cold solution of allylic alcohol **3** (508 mg, 1 mmol) in anhydrous tetrahydrofuran (20 ml) was added 0.75 ml (1.2 mmol) of *n*-butyllithium in hexane (1.6 M). After stirring at room temperature for 15 min, the mixture was transferred into another flask containing a suspension of cuprous iodide (228 mg, 1.2 mmol) in anhydrous tetrahydrofuran (17 ml) and then stirred at room temperature for 30 min. At the end of this period, when the cuprous iodide was dissolved, the solution was cooled at -78°C. To this cold solution was added at -78°C for 4 min all of the cold solution of lithiated orthoester **15** (4.1 mmol) prepared above. After stirring at -78°C for 15 min, (methylphenylamino)triphenylphosphonium iodide (**16b**) (594 mg, 1.2 mmol) in anhydrous dimethylformamide (14 ml) was added to the solution. The reaction mixture was stirred at -78°C for 5 min, at -30°C for 1 h, then at room temperature for 2 h. Saturated NH_4Cl solution (80 ml) was added and the mixture was extracted with hexane (2 x 100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was chromatographed on silica gel eluting with hexane-ethyl acetate (20:1 - 10:1) containing 0.05% of triethylamine to afford **17a** (662 mg) as a crude oil.

Hydrolysis of 17a

Pyridinium *p*-toluenesulfonate (54 mg, 0.12 mmol) was added to a solution of all the crude oil **17a** in methanol (40 ml) containing 0.4 ml of water. This was stirred at room temperature for 1 h and was concentrated *in vacuo*. The oily residue was partitioned between ethyl acetate (50 ml) and water (30 ml), and the water layer was extracted with ethyl acetate (30 ml) again. The combined extracts were washed with brine (2 x 30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography of the crude product on silica gel eluting with hexane-ethyl acetate (3 : 2) furnished 421 mg (62% from **3**) of ester **18a** as an oil. The content of the γ-alkylated by-product **18b** was determined as 1% by the HPLC analysis.

Alkylation of 3 using **16b** and 1.8 equiv. of **15**

Alkylation of **3** was carried out as the same method described above using *t*-butyllithium (2.0 M in pentane; 1.13 ml, 2.25 mmol), bromoorthoester **21** (337 mg, 1.5 mmol), **3** (254 mg, 0.5 mmol), *n*-butyllithium (1.56 M in hexane; 385 µl, 0.6 mmol), cuprous iodide (143 mg, 0.75 mmol) and (methylphenylamino)triphenylphosphonium iodide (**16b**) (458 mg, 0.93 mmol). Hydrolysis of the crude orthoester **17** with pyridinium *p*-toluenesulfonate as described above afforded the mixture of esters **18a** and **18b** (207 mg, 61% from **3**) as an oil. The ratio of the esters **18a** and **18b** was determined as 48 to 52 by HPLC analysis of the product mixture.

Alkylation of 3 using **16a**

Preparation of lithiated orthoester solution

A solution of naphthalene (1.01 g, 7.91 mmol) in anhydrous tetrahydrofuran (10 ml) was added to lithium metal (55 mg, 7.91 mmol) cut in small pieces. This was stirred on ice bath for 4 h and then cooled at -78°C. To this stirred solution was added bromoorthoester **21** (992 mg, 3.96 mmol) in anhydrous tetrahydrofuran (10 ml). The mixture was stirred at -78°C for 20 min to afford the tetrahydrofuran solution of lithiated orthoester **15**.

Alkylation of 3

To an ice cold solultion of **3** (798 mg, 1.57 mmol) in anhydrous tetrahydrofuran (10 ml) was added 1.21 ml (1.88 mmol) of *n*-butyllithium in hexane (1.56 M). After stirring at room temperature for 10 min, the mixture was transferred to another flask containing cuprous iodide (449 mg, 2.36 mmol). This was stirred at room temperature for 30 min and then cooled to -78°C. To this cold solution was added all of the solultion of lithiated orthoester **15** (<7.91 mmol) prepared above. After stirring at -78°C for 15 min, (methylphenylamino)tributylphosphonium iodide (**16a**) (2.05 g, 4.71 mmol) in anhydrous dimethylformamide (10 ml) was added to the solution. The reaciton mixture was stirred at -30°C for 1.5 h. Saturated NH_4Cl solution was added and the mixture was extracted with hexane. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was chromatographed on silica gel eluting with hexane-ethyl acetate (20:1 - 7:1) containilng 0.05% of triethylamine to afford **17** as a crude oil.

Hydrolysis of 17

Hydrolysis of the crude orthoester **17** with pyridinium *p*-toluenesulfonate as described above afforded the mixture of esters **18a** and **18b** (708 mg, 66% from **3**) as an oil. The ratio of the esters **18a** and **18b** was determined as 13 to 87 by HPLC analysis of the product mixtue. A part of the product mixture was separated by HPLC (YMC-PACK SH-043 S-15 SIL column; 25 cm x 20 mm I.D.) using 3% ethanol-hexane as a mobil phase to obtain pure **18b**; IR (film) 3420, 2970, 2950, 2870, 1735, 1255, 1112, 1055, 970, 835, 775 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0-0.1 (12H), 0.8-1.0 (21H), 3.53 (4H, s), 3.5-3.9 (1H, m), 3.9-4.1 (1H, m), 4.18 (2H, s), 4.74 (1H, bs), 4.82 (1H, bs), 5.45 (2H, m); MS (EI, m/e) 623 (M-^{t}Bu), 605, 491. Calc. for $C_{34}H_{63}O_6Si_2$ 623.4163, Found 623.4180.

Hydrolysis of the ester 18a

To a solution of ester **18a** (1.32 g, 1.94 mmol) in tetrahydrofuran (15 ml) was added an 4 M aqueous solution of lithium hydroxide (10 ml, 40 mmol), and the mixture was stirred at 30 40°C for 3 h. After concentration *in vacuo*, the residual oil was dissolved in water (20 ml)-ether (20 ml) which was neutralized by the addition of saturated $KHSO_4$ solution. After extraction with ethyl acetate (2 x 40 ml), the combined extracts were washed with brine (2 x 30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was chromatographed on silica gel with hexane-ethyl acetate (95 : 5) containing 0.5% of acetic acid gave 1.07 g of **19** (95%) as an oil; IR (film) 2860, 2830, 3000-2400, 1710, 1250, 1110, 830, 765 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0-0.2 (12H), 0.8-1.0 (21H), 2.8-3.1 (1H, br), 3.5-4.2 (2H, br), 5.27 (1H, bs), 5.4-5.6 (2H, m); MS m/e 578 (M^+), 521, 389.

Desilylation of 19 — Isocarbacyclin (20)

Tetrabutylammonium fluoride trihydrate (3.16 g, 10 mmol) was added to a solution of **19** (1.12 g, 1.94 mmol) in tetrahydrofuran (16 ml), and the mixture was stirred at room temperature for 14 h. After the addition of saturated NH_4Cl solution (50 ml), the mixture was extracted wih ethyl acetate (2 x 50 ml). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was chromatographed on silica gel with ethyl acetate containing 0.04% of acetic acid gave 645 mg of isocarbacyclin (**20**) (95%) as an oil, which could be crystalized from acetonitril; m.p. 78-81°C (CH_3CN); $[\alpha]_D^{25}$ + 8.6° (c, 0.24, MeOH); IR (KBr) 3400, 3000, 2880, 3000-2400, 1702, 1662, 1345, 1255, 962 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.89 (3H, t, J=7 Hz; C_{20}-H_3), 1.2-1.38 (7H, m; C_{10}-H, C_{17}-H_2, C_{18}-H_2, C_{19}-H_2), 1.38-1.53 (3H, m; C_4-H_2, C_{16}-H), 1.53-1.70 (3H, m; C_3-H_2, C_{16}-H), 1.89 (1H, q, J=9 Hz; C_{12}-H), 1.96 (1H, d, J=16 Hz; $C_{7\alpha}$-H), 2.05 (2H, t, J=7 Hz; C_5-H_2), 2.18-2.45 (5H, m; C_2-H_2, $C_{7\beta}$-H, C_8-H, C_{10}-H), 2.98 (1H, m; C_9-H), 3.72 (1H, m; C_{11}-H), 4.02 (1H, q, J=7 Hz; C_{15}-H), 5.28 (1H, s; $C_{6(9\alpha)}$-H), 5.45 (1H, dd, J=15 Hz, 8 Hz,; C_{13}-H), 5.51 (1H, dd, J=15 Hz, 7 Hz; C_{14}-H), 5.3-6.0 (3H, br; disappeared by the addition of D_2O); ^{13}C-NMR ($CDCl_3$) δ 14.01 (C_{20}), 22.62 (C_{19}), 24.73 (C_3), 25.21 (C_{17}), 27.23 (C_4), 29.98 (C_5), 31.69 (C_{18}), 33.97 (C_2), 36.90 (C_{16}), 39.07 (C_7 or C_{10}), 39.42 (C_7 or C_{10}), 44.32 (C_8), 45.31 (C_9), 57.91 (C_{12}), 73.36 (C_{15}), 77.15 (C_{11}), 128.96 ($C_{6(9\alpha)}$), 133.30 (C_{13}), 135.58 (C_{14}), 141.10 (C_6) 178.33 (C_1); MS (EI, m/e), 332 (M-H_2O), 314, 288. Calc. for $C_{21}H_{32}O_3$ (M-H_2O) 332.2351, Found 332.2365.

References and Notes

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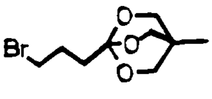

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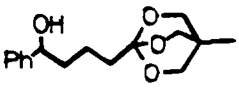

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