Pergamon

Tetrahedron Vol. 51, No. 19, pp. 5529-5542, 1995
Copyright © 1995 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4020/95 $9.50+0.00

0040-4020(95)00242-1

Synthesis of Novel Isocarbacyclins Containing a Phenylene Moiety in the α-Side Chain[1]

Masahiro Koga, Takao Fujii, and Toshio Tanaka*

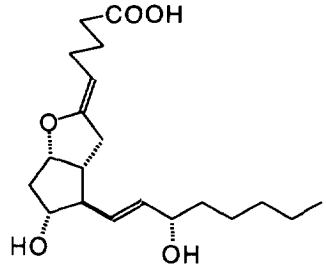
Iwakuni Pharmaceutical Factory, Chemicals Manufacturing Plant,
Teijin Ltd., 2-1, Hinode-cho, Iwakuni, Yamaguchi 740, Japan

Abstract: Synthesis of novel isocarbacyclin derivatives containing a phenylene moiety in the α-side chain has been achieved through the regioselective S_N2' substitution reaction of bicyclic allylic phosphates with ester-containing phenylic and benzylic zinc-copper reagents.

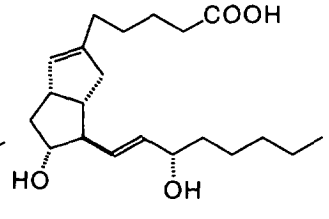
Introduction

Chemically stable analogs of prostacyclin[2] (prostaglandin I_2) (**1**) have been developed as effective therapeutic agents for treatment of various diseases.[3] Isocarbacyclin[4] [(+)-9(*0*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1] (**2**) is one of the most promising candidates for cardiovascular diseases because of both its potent prostaglandin-like activity and its chemical stability, and hence intensive efforts have been made focusing on the efficient synthesis of isocarbacyclin[4a,5] and its congeners.[6]

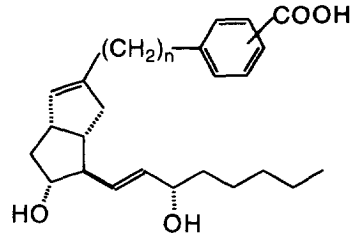
Prostaglandin derivatives are well known to be metabolized very quickly resulting in the loss of pharmacological activity. One of the main metabolic pathways is the β-oxidation reaction[7] of the α-carboxylic side chain. In order to block the metabolic β-oxidation reaction of prostaglandin derivatives, many studies have been reported on the introduction of such metabolically resistant functional groups as a hetero atom,[8] a double bond,[9] or a phenylene[10] moiety into the α-side chain. In this paper, we report the synthesis of both chemically and biologically stable novel isocarbacyclin derivatives (**3**, interphenylene



prostacyclin (prostaglandin I_2, **1**)

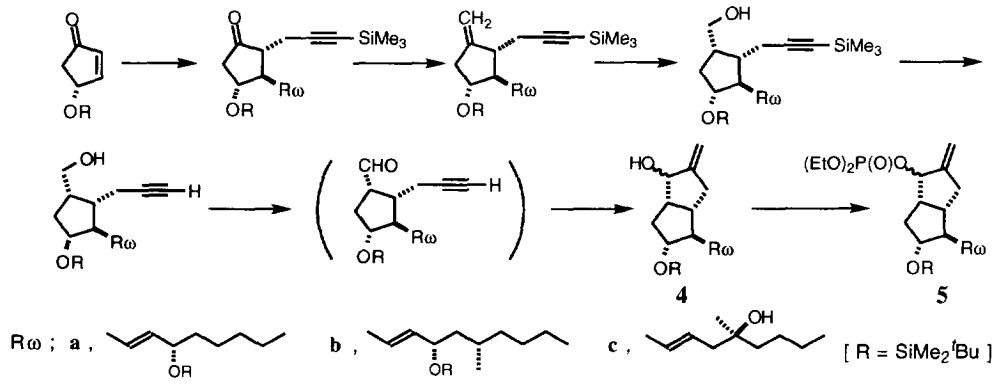


isocarbacyclin (**2**)



interphenylene isocarbacyclins (**3**)

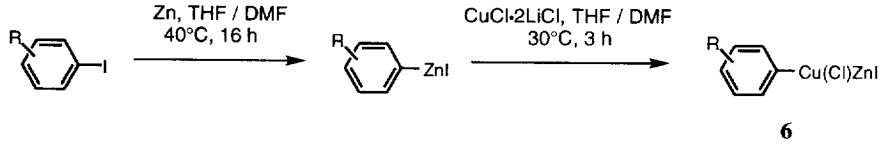
isocarbacyclins), which contain a phenylene moiety in the α-side chain. Previously, we reported the short synthesis of isocarbacyclin[5h,11,12] by regioselective S_N2' allylic alkylation reaction of bicyclic allylic phosphates (**5**) with an ester-containing zinc-copper reagent prepared from methyl 4-iodobutanoate. In the present studies, we prepared three types of bicyclic allylic phosphates **5a~5c** from the corresponding bicyclic allylic alcohols **4a~4c** according to the cited procedure[12a] (Scheme 1) and attempted their allylic substitution reactions with the following ester-containing phenylic and benzylic zinc-copper reagents to synthesize novel isocarbacyclins containing a phenylene moiety in the α-side chain.



Scheme 1. Synthetic route to bicyclic allylic phosphates **5**.

Results and Discussion

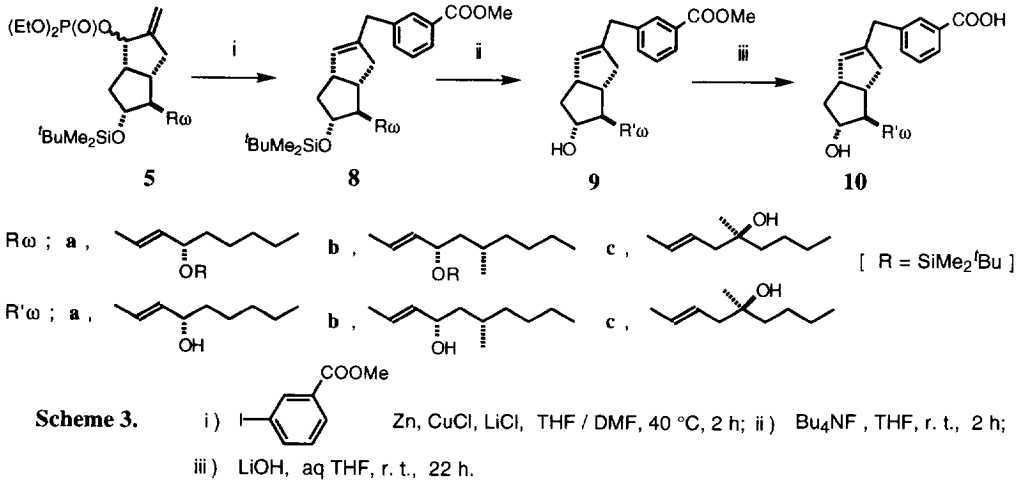
In the previous case for the preparation of alkylated zinc reagents starting with methyl 4-iodobutanoate, tetrahydrofuran (THF) was a suitable solvent. However, aromatic zinc derivatives could not be obtained from the corresponding aromatic halides in tetrahydrofuran. Recently, aromatic zinc compounds containing such functional groups as an ester group were reported to be obtained easily from the corresponding aromatic halides by reaction with activated zinc in *N,N*-dimethylformamide (DMF) or *N,N*-dimethylacetamide (DMAc).[13] Thus-obtained aromatic zinc compounds were converted into the corresponding aromatic zinc-copper reagents by treatment with cuprous cyanide (CuCN) in the presence of lithium chloride (LiCl) (Scheme 2).[13] This report prompted us to synthesize new phenylated isocarbacyclin skeletons by the reaction of the phosphates **5** with the phenylic zinc-copper reagents. Because cuprous chloride itself has already been found to be effective for the alkylation of the allylic phosphate **5a** with organozinc reagents,[11] we carried out the allylic phenylation by a modified procedure using harmless cuprous chloride instead of poisonous cuprous cyanide in this report. The modified phenylic zinc-copper reagents **6** were prepared under the reaction conditions shown in Scheme 2.



6

Scheme 2. Preparation of phenylic zinc-copper reagents **6**.

According to the highly regioselective procedure[11] using a phosphate group as a good leaving group, the phosphate **5a** was allowed to react with the phenylic zinc-copper reagent **6** (R = 3-COOMe) at 30°C for 16 h, affording the desired γ-adduct **8a** as an S_N2' substituted product in 96% yield (Scheme 3). Similarly, two other phosphates **5b** and **5c** were phenylated to provide the corresponding γ-adduct **8b** and **8c** in 98% and 92% yields, respectively (Table 1). These allylic substitution reactions resulted in the little formation of α-adducts (less than 0.5%) which could be detected by NMR and HPLC analyses.



Scheme 3. i) Zn, CuCl, LiCl, THF / DMF, 40 °C, 2 h; ii) Bu_4NF, THF, r. t., 2 h; iii) LiOH, aq THF, r. t., 22 h.

Deprotection of the isocarbacyclin silyl ethers **8a~8c** with tetrabutylammonium fluoride gave the corresponding desilyated products **9a~9c** in good yields (92~96%) (Table 1). Hydrolysis of the resulting methyl esters **9a** and **9b** with aqueous lithium hydroxide provided the corresponding isocarbacyclin derivatives **10a** and **10b** in good yields (95~98%) (Table 1), respectively, without isomerization of the *endo*-cyclic double bond into an *exo*-cyclic double bond of the carbacyclin type. The hydrolyzed product **10a**, as well as its precursor **9a**, showed an olefinic signal at δ 5.35 (or 5.30 in **9a**) which was assigned to an olefinic proton on the bicyclo[3.3.0]octene and a benzylic methylene signal at δ 3.35~3.40 in the ^1H NMR spectrum, whereas the carbacyclin derivatives **11** and **12** were reported by a Grünenthal researcher[14] to show the olefinic signals at δ 6.37 and 6.35 which were assigned to the conjugated olefinic protons (Figure 1). The other ^1H NMR and ^{13}C NMR signals of **10a** also supported the structure of the isocarbacyclin framework.

Table 1. Phenylation of Phosphates with Organozinc-Copper Reagents (**6**)

zinc-copper reagents	phosphates	phenylation products	phenylation yield (%)	desilylation products	desilylation yield (%)	hydrolysis products	hydrolysis yield (%)
	5a	**8a**	96	**9a**	96	**10a**	95
6	**5b**	**8b**	98	**9b**	95	**10b**	98
	5c	**8c**	92	**9c**	92		

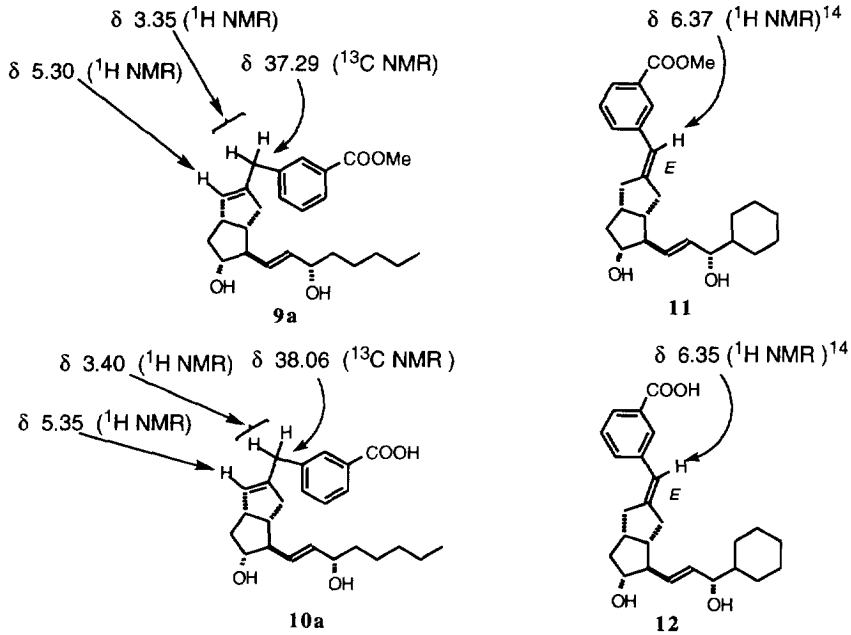
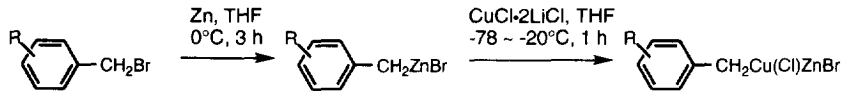


Figure 1. ^{1}H NMR and ^{13}C NMR signals of isocarbacyclin derivatives by comparison with those of a similar kind of carbacyclin derivatives.[14]

Benzylic zinc compounds were difficult to prepare under reaction conditions similar to those for phenylic derivatives, because the starting benzylic halides reacted with the resulting benzylic zinc compounds, resulting in the formation of coupling products even at low temperature.[15] This difficulty was found to be overcome by the choice of benzylic bromides as the starting halides according to P. Knochel *et al.*[15] Therefore, the preparation of benzylic zinc-copper reagents was performed starting with the corresponding benzylic bromide at lower temperature in the presence of cuprous chloride as shown in Scheme 4.



7

Scheme 4. Preparation of benzylic zinc-copper reagents **7**

The phosphate **5a** was allowed to react with the above benzylic zinc-copper reagent **7** (R = 4-COOMe) at -78°C for 2 h, furnishing the γ-adduct **13a** as an S_N2' substituted product in 92% yield (Scheme 5). The other allylic cross-coupling products **13b** and **13c** were also obtained from the corresponding phosphates **5b** and **5c** in 88% yield, respectively (Table 2). These benzylation reactions also resulted in the little formation of α-adducts as S_N2 products (less than 0.5%) by detection with NMR and HPLC analyses. A similar desilylation of the coupling products **13a~13c** gave the desilylated products **14a~14c** in high yields (94~95%), respectively, which were analogously hydrolyzed with aqueous lithium hydroxide, completing the synthesis of the corresponding isocarbacyclin derivatives **15a~15c** in high yields (89~96%) (Table 2).

Table 2. Benzylation of Phosphates with Organozinc-Copper Reagents (**7**)

zinc-copper		benzylation		desilylation		hydrolysis	
reagents	phosphates	products	yield (%)	products	yield (%)	products	yield (%)
	5a	**13a**	92	**14a**	94	**15a**	95
7	**5b**	**13b**	88	**14b**	95	**15b**	89
	5c	**13c**	88	**14c**	94	**15c**	96

Conclusion

Novel interphenylene isocarbacyclin derivatives, which are difficult to be obtained by the conventional methods, have been successfully synthesized with high S_N2' regioselectivity by the reaction of the bicyclic allylic phosphates **5** with ester-containing phenylic and benzylic zinc-copper reagents under modified reaction conditions. The choice of solvent (*N*,*N*-dimethylformamide) as a co-solvent was found to be crucial for the phenylic substitution reaction, and the selection of a bromide as the starting substrate was essential for the benzylic substitution reaction. Studies of the biological activities[16] of the present novel interphenylene isocarbacyclins are now in progress and will be published in due course.

*(1S,5S,6R,7R)-7-*tert*-Butyldimethylsilyloxy-6-[(*E,S*)-3-*tert*-butyldimethylsilyloxy-1-octenyl]-3-(3-methoxycarbonylbenzyl)bicyclo[3.3.0]-2-octene* (***8a***) was prepared from the phosphate **5a** in 96% yield (1.20 g, 1.92 mmol); IR (neat): 2956, 2932, 1715 (C=O), 1607 (C=C), 965, 735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.00~0.10 (12H, m), 0.85~0.95 (21H, m), 1.20~1.65 (9H, m), 1.80~1.95 (2H, m), 2.20~2.40 (3H, m), 2.95 (1H, m), 3.30 (2H, bs), 3.75 (1H, m), 3.85 (3H, s), 4.10 (1H, m), 5.30 (1H, d, J = 1.2 Hz), 5.40 (2H, m), 7.38 (2H, m), 7.85 (2H, m); High-resolution MS (*m/z*): Calcd for $C_{33}H_{53}O_4Si_2$ $(M-^tBu)^+$: 569.3484; Found: 569.3427.

*(1S,5S,6R,7R)-7-*tert*-Butyldimethylsilyloxy-6-[(*E,3S,5S*)-3-*tert*-butyldimethylsilyloxy-5-methyl-1-nonenyl]-3-(3-methoxycarbonylbenzyl)bicyclo[3.3.0]-2-octene* (***8b***) was also prepared from the phosphate **5b** in 98% yield (1.282 g, 1.96 mmol); IR (neat): 2955, 2920, 1725 (C=O), 1607 (C=C), 1590 (C=C), 965, 732 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.09 (18H, s), 0.80~0.90 (18H, m), 1.10~1.40 (10H, m), 1.80~1.95 (2H, m), 2.20~2.40 (3H, m), 3.00 (1H, m), 3.40 (2H, bs), 3.70 (1H, m), 3.90 (3H, s), 4.10 (1H, m), 5.30 (1H, d, J = 1.2 Hz), 5.45 (2H, m), 7.35 (2H, m), 7.85 (2H, m); EI-MS (*m/z*): 597 $(M-^tBu)^+$(100), 555 (9), 465 (9), 171 (3), 149 (9), 73 (19); High-resolution MS (*m/z*): Calcd for $C_{35}H_{57}O_4Si_2$ $(M-^tBu)^+$: 597.3797; Found: 597.3768.

*(1S,5S,6R,7R)-7-*tert*-Butyldimethylsilyloxy-6-[(*E,S*)-4-hydroxy-4-methyl-1-octenyl]-3-(3-methoxycarbonylbenzyl)bicyclo[3.3.0]-2-octene* (***8c***) was also prepared from the phosphate **5c** in 92% yield (968 mg, 1.84 mmol); IR (neat): 3340 (OH), 2956, 2930, 2915, 1682 (C=O), 1611 (C=C), 965, 735 cm^{-1}; ^1H NMR($CDCl_3$): δ 0.09 (9H, s), 0.80~1.95 (9H, m), 1.15 (3H, s), 1.11~1.60 (9H, m), 1.90~2.40 (8H, m), 2.80 (2H, t, J = 7.5 Hz), 3.70 (1H, m), 3.90 (3H, s), 5.25 (1H, d, J = 1.2 Hz), 5.45 (2H, m), 7.20 (2H, d, J = 7.5 Hz), 7.95 (2H, d, J = 7.5 Hz); EI-MS (*m/z*): 469 $(M-^tBu)^+$(88), 451 (44), 426 (6), 377 (75), 369 (41), 337 (16), 294 (100), 149 (63); High-resolution MS (*m/z*): Calcd for $C_{28}H_{41}O_4Si$ $(M-^tBu)^+$: 469.2775; Found: 469.2831.

General procedure for the S_N2' substitution reaction of allylic phosphates (5) with benzylic zinc-copper reagents

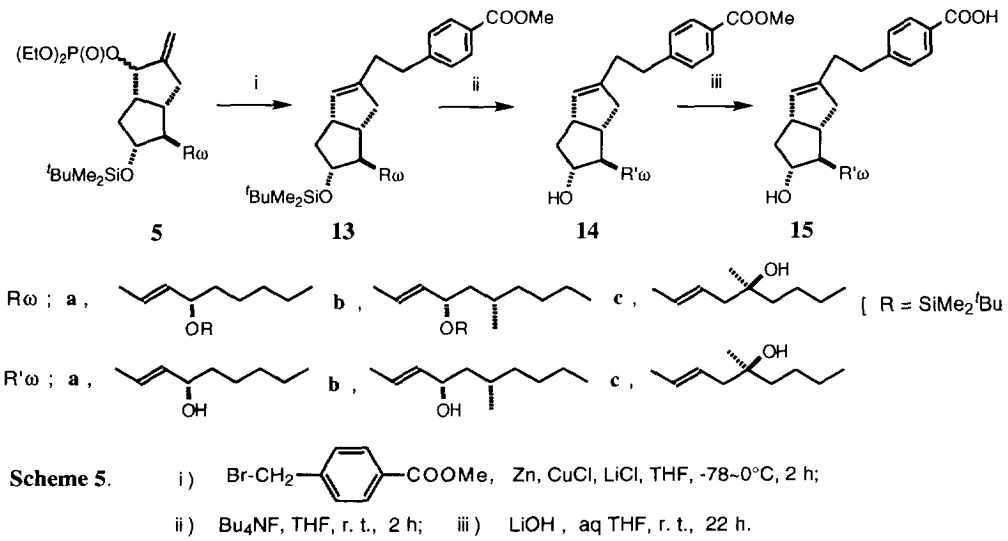
In a 50 ml flask were placed zinc powder (392 mg, 6.0 mmol) and THF (1 ml). 1,2-Dibromoethane (40 μl) was similarly added to the mixture and the resulting mixture was heated at 65°C for 1 min. The mixture was cooled to room temperature and stirred at the same temperature for 30 min. After chlorotrimethylsilane (80 μl) was added, the mixture was stirred at room temperature for 30 min. To the cooled reaction mixture was added methyl 4-(bromomethyl)benzoate (1.145 g, 5.0 mmol) in THF (10 ml) at 0°C. The resulting mixture was stirred at 0°C for 3 h, then cooled at -78°C. The supernatant of the thus-obtained organozinc bromide was added to a solution of copper (I) chloride (495 mg, 5.0 mmol) and dry LiCl (424 mg, 10.0 mmol) in THF (10 ml) at -78°C. The resulting mixture was warmed at -20°C, and then stirred at the same temperature for 30 min, and then cooled again to -78°C. To the resulting zinc-copper suspension was added a solution of **a phosphate** (**5**) (1.00 mmol) in THF (10 ml) at -78°C and the reaction mixture was stirred at -78°C for several hours, then at -20°C for additional several minutes. After

*(1S,5S,6R,7R)-7-*tert*-Butyldimethylsilyloxy-6-[(*E*,3S,5S)-3-*tert*-butyldimethylsilyloxy-5-methyl-1-nonenyl]-2-diethoxyphosphoryloxy-3-methylenebicyclo[3.3.0]octane (**5b**)* was similarly prepared in 78% yield using the (1*S*,5*S*,6*R*,7*R*)-7-*tert*-butyldimethylsilyloxy-6-[(*E*,3*S*,5*S*)-3-*tert*-butyldimethylsilyloxy-5-methyl-1-nonenyl]-2-hydroxy-3-methylenebicyclo[3.3.0]octane (**4b**) (5.36 g, 10.0 mmol), *n*-BuLi (1.55 M hexane solution, 7.7 ml, 11.9 mmol), and diethyl chlorophosphate (2.07 g, 12.0 mmol) in THF (100 ml); IR (neat): 2940, 2915, 2840, 1450, 1438, 1352, 1260, 1160, 1105, 1035, 1000, 975, 900, 855, 835 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.02 (12H, s), 0.75~0.90 (24H, m), 1.20~2.75 (22H, m), 3.75 (1H, m), 4.05~4.20 (5H, m), 4.67 (1H, d, *J* = 6 Hz), 5.18 (2H, d, *J* = 30 Hz), 5.45~5.50 (2H, m); High-resolution MS (*m/z*): Calcd for $C_{31}H_{60}O_6PSi_2$ $(M-^tBu)^+$: 615.3668; Found: 615.3696.

*(1S,5S,6R,7R)-7-*tert*-Butyldimethylsilyloxy-2-diethoxyphosphoryloxy-6-[(E,4S)-4-hydroxy-4-methyl-1-octenyl]-3-methylenebicyclo[3.3.0]octane (**5c**)* was also prepared in 67% yield using (1*S*,5*S*,6*R*,7*R*)-7-*tert*-butyldimethylsilyloxy-2-hydroxy-6-[(*E*,*S*)-4-hydroxyl-4-methyl-1-octenyl]-3-methylenebicyclo-[3.3.0]-octane (**4c**) (1.23 g, 3.00 mmol), *n*-BuLi (1.58 M hexane solution, 2.47 ml, 3.90 mmol), and diethyl chlorophosphate (0.78 g, 4.50 mmol) in THF (40 ml); IR (neat): 3425 (OH), 2940, 2915, 2880, 1450, 1438, 1384, 1352, 1250, 1160, 1105, 1050, 960, 900, 860, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.02 (6H, s), 0.85 (9H, s), 0.95 (3H, t, *J* = 4 Hz), 1.15 (3H, s), 1.20~1.55 (14H, m), 1.75~1.90 (2H, m), 2.15~2.35 (4H, m), 2.45~2.75 (2H, m), 3.60~3.80 (1H, m), 4.05~4.20 (4H, m), 4.65 (1H, d, *J* = 6 Hz), 5.15 (2H, d, *J* = 27 Hz), 5.35~5.58 (2H, m); High-resolution MS (*m/z*): Calcd for $C_{24}H_{44}O_6PSi$ $(M-^tBu)^+$: 487.2646; Found: 487.2615.

*General procedure for the S_N2' substitution reaction of allylic phosphates (**5**) with phenylic zinc-copper reagents*

In a 30 ml flask were placed zinc powder (850 mg, 13.0 mmol) and THF (2 ml). According to the cited procedure,[17] 1,2-dibromoethane (80 μl) was added to the mixture and the resulting mixture was heated at 65°C for 1 min. The mixture was cooled to room temperature and stirred at the same temperature for 30 min. After chlorotrimethylsilane (100 μl) was added, the mixture was stirred at room temperature for 30 min. To the activated zinc was added at room temperature methyl 3-iodobenzoate (2.62 g, 10.0 mmol) in DMF (10 ml) and the resulting mixture was stirred at 40°C for 16 h, and then cooled to 30°C. The supernatant of thus obtained organozinc iodide was added to a solution of copper (I) chloride (990 mg, 10.0 mmol), dry LiCl (848 mg, 20.0 mmol) in THF (10 ml) at 30°C, the resulting mixture was stirred at the same temperature for 3 h. To the resulting zinc-copper suspension was added a solution of **a phosphate** (**5**) (2.0 mmol) in THF (20 ml) at 30°C, and the reaction mixture was stirred at 30°C for 10~20 h. After the end point of this reaction was decided by tracing with TLC, the resulting reaction mixture was poured into a saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc (100 ml). The separated aqueous layer was extracted twice with EtOAc (2 x 50 ml). The combined organic extracts were washed with brine (100 ml). The separated organic layer was dried over $MgSO_4$, filtrated, and concentrated *in vacuo* to leave a residual oil, which was chromatographed on silica gel (60 g) with hexane and EtOAc (40 : 1) giving **the corresponding coupling product 8**.



Scheme 5. i) Br-CH_2-C$_6$H$_4$-COOMe, Zn, CuCl, LiCl, THF, -78~0°C, 2 h;
ii) Bu_4NF, THF, r. t., 2 h; iii) LiOH , aq THF, r. t., 22 h.

Experimental

^{1}H NMR and ^{13}C NMR spectra were obtained using a Varian Gemini 200 (200 MHz). Chemical shifts were reported as parts per million (ppm) relative to internal tetramethylsilane with $CDCl_3$ or CD_3OD. Mass spectra were taken at 70 eV using a HITACHI M-80B mass spectrometer. IR spectra were recorded on a Shimadzu FT-IR 8100 M Fourier transform infrared-spectrophotometer. UV spectra were recorded on a JASCO UV/VIS 660 spectrophotometer. The high-performance liquid chromatography (HPLC) was carried out on a Shimadzu Model LC-6A with a Shimadzu SPD-6A UV detector (210 nm or 240 nm) and a Shimadzu C-R6A Chromatopac. Column chromatography was performed using Daisogel IR-60 silica gel. Thin layer chromatography (TLC) was performed using Merck silica gel (Kieselgel 60 F_{254}). All reactions were carried out under an argon or a nitrogen atmosphere. Solvents for the reactions were purified, if necessary, before use by distillation from suitable drying agents. Solvents for extraction and chromatography were GR grades. Zinc powder was activated according to the P. Knochel's procedure.[17]

Preparation of allylic phosphates (5)

(*1S,5S,6R,7R*)-*7*-tert-*Butyldimethylsilyloxy-6*-[(E,S)-*3*-tert-*butyldimethylsilyloxy-1-octenyl]-2-diethoxy-phosphoryloxy-3-methylenebicyclo[3.3.0]octane* (***5a***) was prepared in 85% yield according to the cited procedure[11] using (*1S,5S,6R,7R*)-7-*tert*-butyldimethylsilyloxy-6-[(*E,S*)-3-*tert*-butyldimethyl-silyloxy-1-octenyl]-2-hydroxy-3-methylenebicyclo[3.3.0]octane (**4a**) (2.54 g, 5.00 mmol), *n*-BuLi (1.50 M hexane solution, 3.94 ml, 5.91 mmol), and diethyl chlorophosphate (1.30 g, 7.50 mmol) in THF (100 ml).

the end point of this reaction was decided by tracing with TLC, the resulting reaction mixture was poured into a saturated aqueous NH_4Cl solution. A similar extraction, washing, drying, evaporation, and separation by chromatography to the above phenylation reaction gave **the corresponding coupling product 13**.

*(1S,5S,6R,7R)-7-*tert*-Butyldimethylsilyloxy-6-[(E,S)-3-*tert*-butyldimethylsilyloxy-1-octenyl]-3-[2-(4-methoxycarbonylphenyl)ethyl]bicyclo[3.3.0]-2-octene* (***13a***) was prepared from the phosphate **5a** in 92% yield (559 mg, 0.92 mmol); IR (neat): 2955, 2920, 1724 (C=O), 1607 (C=C), 1590 (C=C), 965, 735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.00~0.10 (12H, m), 0.85~0.90 (21H, m), 1.20~1.40 (8H, m), 1.80~2.40 (7H, m), 2.80 (2H, t, J = 8 Hz), 3.00 (1H, m), 3.85 (1H, m), 3.85 (3H, s), 4.15 (1H, m), 5.25 (1H, d, J = 1.2 Hz), 5.50 (2H, m), 7.25 (2H, d, J = 7.5 Hz), 7.95 (2H, d, J = 7.5 Hz); High-resolution MS (*m/z*): Calcd for $C_{37}H_{61}O_4Si_2$ $(M\text{-}Me)^+$: 625.4110; Found: 625.4102.

*(1S,5S,6R,7R)-7-*tert*-Butyldimethylsilyloxy-6-[(E,3S,5S)-3-*tert*-butyldimethylsilyloxy-5-methyl-1-nonenyl]-3-[2-(4-methoxycarbonylphenyl)ethyl]bicyclo[3.3.0]-2-octene* (***13b***) was also prepared from the phosphate **5b** in 88% yield (578 mg, 0.88 mmol); IR (neat): 2955, 2920, 1724 (C=O), 1607 (C=C), 1590 (C=C), 965, 735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.00~0.10 (12H, m), 0.85~0.90 (24H, m), 1.20~1.40 (10H, m), 1.80~2.40 (7H, m), 2.80 (2H, t, J = 8 Hz), 3.00 (1H, m), 3.85 (1H, m), 3.85 (3H, s), 4.15 (1H, m), 5.25 (1H, d, J = 1.2 Hz), 5.50 (2H, m), 7.25 (2H, d, J = 7.5 Hz), 7.95 (2H, d, J = 7.5 Hz); EI-MS (*m/z*): 611 $(M\text{-}^tBu)^+$(100), 569 (6), 479 (6), 149 (10), 73 (20); High-resolution MS (*m/z*): Calcd for $C_{36}H_{59}O_4Si_2$ $(M\text{-}^tBu)^+$: 611.3954; Found: 611.3896.

*(1S,5S,6R,7R)-7-*tert*-Butyldimethylsilyloxy-6-[(E,S)-4-hydroxy-4-methyl-1-octenyl]-3-[2-(4-methoxycarbonylphenyl)ethyl]bicyclo[3.3.0]-2-octene* (***13c***) was prepared from the phosphate **5c** in 88% yield (496 mg, 0.88 mmol); IR (neat): 3340 (OH), 2956, 2930, 2915, 1682 (C=O), 1611 (C=C), 965, 735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.09 (9H, s), 1.80~1.95 (9H, m), 1.15 (3H, s), 1.10~1.60 (9H, m), 1.90~2.40 (8H, m), 2.80 (2H, t, J = 7.5 Hz), 3.00 (1H, m), 3.70 (1H, m), 3.90 (3H, s), 5.25 (1H, d, J = 1.2 Hz), 5.45 (2H, m), 7.20 (2H, d, J = 7.5 Hz), 7.95 (2H, d, J = 7.5 Hz); EI-MS (*m/z*): 483 $(M\text{-}^tBu)^+$(44), 465 (31), 391 (100), 383 (38), 351 (13), 308 (50), 159 (38); High-resolution MS (*m/z*): Calcd for $C_{29}H_{43}O_4Si$ $(M\text{-}^tBu)^+$: 483.2932; Found: 483.2948.

*General procedure for the desilylation of coupling products (**8** or **13**)*

Tetrabutylammonium fluoride (1.0 M solution of THF, 10 ml, 10.0 mmol) was added to a solution of **a silyl ether 8** or **13** (1.00 mmol) in THF (10 ml), and the mixture was stirred at room temperature for several hours. After deciding of the reaction end point by TLC, the resulting reaction mixture was poured into a saturated aqueous NH_4Cl solution (50 ml) and the organic layer was taken up in EtOAc (100 ml). The separated aqueous layer was extracted twice with EtOAc (2 x 50 ml). The combined organic extracts were washed with brine (50 ml). The separated organic layer was dried over $MgSO_4$, filtered, and

concentrated *in vacuo* to leave an oily residue, which was chromatographed on silica gel (60 g) with hexane and EtOAc (40 : 1) yielding **the corresponding desilylated product 9** or **14**.

(1S,5S,6R,7R)-7-Hydroxy-6-[(E,S)-3-hydroxy-1-octenyl]-3-(3-methoxycarbonylbenzyl)bicyclo[3.3.0]-2-octene (***9a***) was prepared from the disilyl ether **8a** in 96% yield (382 mg, 0.96 mmol); IR (neat): 3370 (OH), 2923, 1720 (C=O), 1601 (C=C), 1445, 1438, 1307, 1281, 1202, 1113, 1086, 972, 760 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (3H, t), 1.15~2.40 (16H, m), 3.00 (1H, m), 3.35 (2H, bs), 3.75 (1H, m), 3.90 (3H, s), 4.05 (1H, m), 5.30 (1H, d, *J* = 1.2 Hz), 5.50 (2H, m), 7.38 (2H, m), 7.85 (2H, m); ^{13}C NMR ($CDCl_3$); δ 14.58, 23.34, 29.51, 29.74, 37.29, 37.68, 39.42, 44.69, 44.80, 45.69, 52.52, 58.43, 72.01, 77.19, 127.76, 128.75, 130.29, 130.50, 131.20, 133.90, 134.10, 136.56, 140.47, 140.51, 167.70; EI-MS (*m/z*): 380 (M-H_2O)$^+$(18), 362 (M-2H_2O)$^+$(24), 281 (5), 149 (100), 117 (5), 91 (65), 79 (38); High-resolution MS (*m/z*): Calcd for $C_{25}H_{32}O_3$ (M-H_2O)$^+$: 380.2353; Found: 380.2330; UV (EtOH): λmax 231.6 (log ε 3.94), 211.2 (log ε 3.97) nm; HPLC analysis: *Rt* 14.94 min [column; Zorbax Sil (25 cm x 4.6 mm I.D.), detection; UV (210 nm), mobile phase; hexane / EtOH = 20 / 1, flow rate; 1.0 ml / min].

(1S,5S,6R,7R)-7-Hydroxy-6-[(E,3S,5S)-3-hydroxy-5-methyl-1-nonenyl]-3-(3-methoxycarbonylbenzyl)-bicyclo[3.3.0]-2-octene (***9b***) was also prepared from the disilyl ether **8b** in 95% yield (405 mg, 0.95 mmol); IR (neat): 3364 (OH), 2955, 2920, 2872, 1725 (C=O), 1607 (C=C), 1590 (C=C), 1446, 1435, 1281, 1200, 1105, 1088, 995, 970, 756, 704 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (6H, m), 1.10~1.40 (12H, m), 1.95~1.80 (2H, m), 2.20~2.40 (3H, m), 3.00 (1H, m), 3.38 (2H, bs), 3.70 (1H, m), 3.90 (3H, s), 4.10 (1H, m), 5.30 (1H, d, *J* = 1.2 Hz), 5.40 (2H, m), 7.35 (2H, m), 7.85 (2H, m); EI-MS (*m/z*): 408 (M-H_2O)$^+$ (33), 390 (22), 364 (44), 266 (33), 252 (27), 214 (47), 149 (100); High-resolution MS (*m/z*): Calcd for $C_{27}H_{36}O_3$ (M-H_2O)$^+$: 408.2666; Found: 408.2645; UV (EtOH): λmax 231.6 (log ε 3.94) nm; HPLC analysis: *Rt* 13.59 min (a similar HPLC condition to **9a**).

(1S,5S,6R,7R)-7-Hydroxy-6-[(E,S)-4-hydroxyl-4-methyl-1-octenyl]-3-(3-methoxycarbonylbenzyl)-bicyclo[3.3.0]-2-octene (***9c***) was prepared from the monosilyl ether **8c** in 92% yield (379 mg, 0.92 mmol); IR (neat): 3384 (OH), 2955, 2932, 2872, 1725 (C=O), 1607 (C=C), 1590 (C=C), 1447, 1439, 1397, 1283, 1200, 1107, 1090, 992, 974, 758 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (3H, t), 1.10 (3H, s), 1.15~2.40 (16H, m), 3.00 (1H, m), 3.40 (2H, bs), 3.75 (1H, m), 3.90 (3H, s), 5.30 (1H, d, *J* = 1.2 Hz), 5.45 (2H, m), 7.40 (2H, m), 7.85 (2H, m); EI-MS (*m/z*): 394 (M-H_2O)$^+$(9), 376 (10), 337 (12), 305 (12), 294 (100), 279 (18); High-resolution MS (*m/z*): Calcd for $C_{26}H_{34}O_3$ (M-H_2O)$^+$: 394.2509; Found: 394.2468; HPLC analysis: *Rt* 13.15 min (a similar HPLC condition to **9a**).

(1S,5S,6R,7R)-7-Hydroxy-6-[(E,S)-3-hydroxy-1-octenyl]-3-[2-(4-methoxycarbonylphenyl)-ethyl]-bicyclo[3.3.0]-2-octene (***14a***) was also prepared from the disilyl ether **13a** in 94% yield (387 mg, 0.94 mmol); IR (neat): 3425 (OH), 2953, 2928, 2863, 1720 (C=O), 1610 (C=C), 1437, 1416, 1285, 1194, 1179, 1113, 1086, 766 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (3H, t), 1.15~2.40 (18H, m), 2.80 (2H, t, *J* = 8 Hz), 3.00 (1H, m), 3.75 (1H, m), 3.90 (3H, s), 4.05 (1H, m), 5.30 (1H, d, *J* = 1.2 Hz), 5.55 (2H, m), 7.36 (2H, d, *J* = 7.5 Hz), 7.95 (2H, d, *J* = 10 Hz); EI-MS (*m/z*): 394 (M-H_2O)$^+$(27), 376 (46), 149 (100), 131 (58), 91 (70),

79 (80); High-resolution MS (*m/z*): Calcd for $C_{26}H_{34}O_3$ $(M-H_2O)^+$: 394.2509; Found: 394.2505; UV (EtOH): λ_{max} 239.2 (log ε 3.92), 210.2 (log ε 3.80) nm; HPLC analysis: *Rt* 17.28 min (a similar HPLC condition to **9a**).

(1S,5S,6R,7R)-7-Hydroxy-6-[(E,3S,5S)-3-hydroxy-5-methyl-1-nonenyl]-3-[2-(4-methoxycarbonyl-phenyl)ethyl]bicyclo[3.3.0]-2-octene ***(14b)*** was also prepared from the disilyl ether **13b** in 95% yield (418 mg, 0.95 mmol); IR (neat): 3400 (OH), 3435 (OH), 2955, 2928, 1723 (C=O), 1611 (C=C), 1457, 1485, 1416, 1377, 1310, 1192, 1179, 1111, 1021, 968, 991, 856, 768, 733 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (6H, m), 1.20~2.40 (19H, m), 2.80 (2H, t, *J* = 8 Hz), 3.00 (1H, m), 3.75 (1H, m), 3.90 (3H, s), 4.18 (1H, m), 5.32 (1H, d, *J* = 1.2 Hz), 5.55 (2H, m), 7.25 (2H, d, *J* = 7.5 Hz), 7.95 (2H, d, *J* = 7.5 Hz); EI-MS (*m/z*): 422 $(M-H_2O)^+$(26), 404 (62), 390 (14), 378 (24), 229 (50), 149 (100); High-resolution MS (*m/z*): Calcd for $C_{28}H_{38}O_3$ $(M-H_2O)^+$: 422.2822; Found: 422.2794; UV(EtOH): λ_{max} 238.8 (log ε 4.07), 209.0 (log ε 3.95) nm; HPLC analysis: *Rt* 12.56 min (a similar HPLC condition to **9a**).

(1S,5S,6R,7R)-7-Hydroxy-6-[(E,4S)-4-hydroxy-4-methyl-1-octenyl]-3-[2-(4-methoxycarbonylphenyl)-ethyl]bicyclo[3.3.0]-2-octene ***(14c)*** was also prepared from the monosilyl ether **13c** in 94% yield (400 mg, 0.94 mmol); IR (neat): 3380 (OH), 2953, 2932, 2872, 1723 (C=O), 1611 (C=C), 1455, 1435, 1310, 1281, 1192, 1179, 1113, 1021, 909, 768, 733, 708 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (3H, t), 1.15 (3H, m), 1.20~2.40 (18H, m), 2.80 (2H, t, *J* = 8 Hz), 3.00 (1H, m), 3.75 (1H, m), 3.90 (3H, s), 5.30 (1H, d, *J* = 1.2 Hz), 5.50 (2H, m), 7.25 (2H, d, *J* = 7.5 Hz), 7.95 (2H, d, *J* = 7.5 Hz); EI-MS (*m/z*): 408 $(M-H_2O)^+$(13), 390 (14), 326 (26), 308 (94), 293 (13), 159 (100); High-resolution MS (*m/z*): Calcd for $C_{27}H_{36}O_3$ $(M-H_2O)^+$: 408.2666; Found: 408.2715; UV (EtOH): λ_{max} 239.2 (log ε 4.16), 208.6 (log ε 4.04) nm; HPLC analysis: *Rt* 11.11 min (a similar HPLC condition to **9a**) .

*General procedure for the hydrolysis of esters (**9** or **14**)*

To a solution of **an ester 9** or **14** (0.20 mmol) in THF (10 ml) was added a 4 M aqueous solution of lithium hydroxide (0.5 ml, 2.0 mmol) and the reaction mixture was stirred at room temperature for 20~30 h. After diminishing the starting ester on TLC, the reaction mixture was neutralized by the addition of a 1 N HCl aqueous solution. The organic layer was taken up in EtOAc (100 ml). The organic layer was separated and the obtained aqueous layer was extracted twice with EtOAc (2 x 50 ml). The combined organic extracts were washed with brine (50 ml), dried over $MgSO_4$, filtered, and concentrated under vacuum. **The corresponding carboxylic acid 10** or **15** was obtained by chromatographic separation of the residual crude product on silica gel (30 g) with hexane and EtOAc (1 : 1 up to 1 : 9) containing 0.5 % of acetic acid.

(1S,5S,6R,7R)-3-(3-Carboxybenzyl)-7-hydroxy-6-[(E,S)-3-hydroxy-1-octenyl]bicyclo[3.3.0]-2-octene ***(10a)*** was prepared from the ester **9a** in 95% yield (74 mg, 0.19 mmol); IR (neat): 3300 (OH), 2957, 1717 (C=O), 1609 (C=C), 1590 (C=C), 1456, 1194, 968, 752 cm^{-1}; ^1H NMR (CD_3OD): δ 0.85 (3H, t), 1.15~2.40 (15H, m), 3.00 (1H, m), 3.40 (2H, bs), 3.65 (1H, m), 3.90 (1H, m), 4.20 (1H, m), 4.95 (2H, m),

5.25~5.55 (3H, m), 7.35 (2H, m), 7.85 (2H, m); ^{13}C NMR (CD_3OD): δ 14.52, 23.94, 30.29, 30.43, 38.06, 39.67, 40.69, 45.68, 45.78, 46.58, 58.47, 72.38, 77.96, 128.57, 129.43, 131.03, 131.83, 134.12, 134.45, 136.30, 141.64, 171.10; EI-MS (*m/z*): 366 $(M-H_2O)^+$(20), 348 (28), 267 (5), 135 (100), 117 (55), 91 (80), 79 (45); High-resolution MS (*m/z*): Calcd for $C_{24}H_{30}O_3$ $(M-H_2O)^+$: 366.2196; Found: 366.2174; UV (EtOH): λ_{max} 229.6 (log ε 3.97), 215.0 (log ε 3.95) nm; HPLC analysis: *Rt* 7.47 min [column; YMC A-303 (25 cm x 4.6 mm I.D.), detection; UV (240 nm), mobile phase; MeCN / H_2O / AcOH = 6 / 4 / 0.01, flow rate; 1.0 ml / min].

*(1S,5S,6R,7R)-3-(3-Carboxybenzyl)-7-hydroxy-6-[(E,3S,5S)-3-hydroxy-5-methyl-1-nonenyl]bicyclo-[3.3.0]-2-octene (**10b**)* was also prepared from the ester **9b** in 98% yield (83 mg, 0.195 mmol); IR (neat): 3360 (OH), 2957, 2928, 1696 (C=O), 1607 (C=C), 1559 (C=C), 1453, 1412, 1377, 1279, 1196, 1086, 997, 970, 839, 816 cm^{-1}; ^1H NMR (CD_3OD): δ 0.85 (6H, m), 2.1~2.40 (17H, m), 3.00 (1H, m), 3.30 (1H, m), 3.45 (2H, bs), 3.75 (1H, m), 4.05 (1H, m), 5.30~5.65 (3H, m), 7.40 (2H, m), 7.85 (2H, m); EI-MS (*m/z*): 394 $(M-H_2O)^+$(19), 376 (27), 350 (32), 291 (24), 265 (24), 252 (32), 200 (45), 135 (100); High-resolution MS (*m/z*): Calcd for $C_{26}H_{34}O_3$ $(M-H_2O)^+$: 394.2509; Found: 394.2498; UV (EtOH): λ_{max} 229.6 (log ε 3.94), 213.0 (log ε 3.95) nm; HPLC analysis: *Rt* 11.81 min (a similar HPLC condition to **10a**).

*(1S,5S,6R,7R)-3-[2-(4-Carboxyphenyl)ethyl]-7-hydroxy-6-[(E,S)-3-hydroxy-1-octenyl]bicyclo[3.3.0]-2-octene (**15a**)* was also prepared from the ester **14a** in 95% yield (76 mg, 0.19 mmol); IR (neat): 3325 (OH), 2928, 1717 (C=O), 1636 (C=C), 1589 (C=C), 1490, 1456, 1420, 1339, 1293, 1179, 1084, 972, 853 cm^{-1}; ^1H NMR (CD_3OD): δ 0.85 (3H, t), 1.15~2.45 (18H, m), 2.80 (2H, t, J = 8 Hz), 2.95 (1H, m), 3.70 (1H, m), 4.00 (1H, m), 5.30 (1H, d, J = 1.2 Hz), 5.55 (2H, m), 7.30 (2H, d, J = 7.5 Hz), 7.95 (2H, d, J = 7.5 Hz); EI-MS (*m/z*): 380 $(M-H_2O)^+$(10), 344 (12), 135 (100), 117 (40), 91 (72), 79 (63); High-resolution MS (*m/z*): Calcd for $C_{25}H_{32}O_3$ $(M-H_2O)^+$: 380.2353; Found: 380.2422; UV(EtOH): λ_{max} 238.0 (log ε 4.09), 208.6 (log ε 3.94) nm; HPLC analysis: *Rt* 9.05 min (a similar HPLC condition to **10a**).

*(1S,5S,6R,7R)-3-[2-(4-Carboxyphenyl)-ethyl]-7-hydroxy-6-[(E,3S,5S)-3-hydroxy-5-methyl-1-nonenyl]-bicyclo[3.3.0]-2-octene (**15b**)* was also prepared from the ester **14b** in 89% yield (76 mg, 0.178 mmol); IR (neat): 3325 (OH), 2955, 2924, 2872, 1692 (C=O), 1613 (C=C), 1424, 1318, 1289, 1179, 1090, 1015, 968, 839, 762, 708, 673 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (6H, m), 1.20~1.45 (10H, m), 1.80~2.45 (7H, m), 2.75 (2H, t, J = 7.5 Hz), 3.00 (1H, m), 3.75 (1H, m), 4.15 (1H, m), 5.25 (1H, d, J = 1.2 Hz), 5.45 (2H, m), 6.00 (2H, bs), 7.25 (2H, d, J = 7.5 Hz), 8.00 (2H, d, J = 7.5 Hz); EI-MS (*m/z*): 408 $(M-H_2O)^+$(2), 390 (12), 364 (10), 305 (6), 229 (19), 135 (100); UV (EtOH): λ_{max} 237.8 (log ε 4.38), 207.8 (log ε 4.29) nm; HPLC analysis: *Rt* 14.53 min (a similar HPLC condition to **10a**).

*(1S,5S,6R,7R)-3-[2-(4-Carboxyphenyl)-ethyl]-7-hydroxy-6-[(E,S)-4-hydroxy-4-methyl-1-octenyl]-bicyclo-[3.3.0]-2-octene (**15c**)* was also prepared from the ester **14c** in 96% yield (79 mg, 0.192 mmol); IR (neat): 3340 (OH), 2956, 2930, 2915, 2842, 2664, 1682 (C=O), 1611 (C=C), 1576, 1455, 1424, 1320, 1291, 1179, 1090, 972, 847, 762, 706, 677 cm^{-1}; ^1H NMR(CD_3OD): δ 0.90 (3H, t), 1.15 (3H, s), 1.20~1.50 (7H, m), 1.80~2.60 (9H, m), 2.80 (2H, t, J = 10 Hz), 3.00 (1H, m), 3.75 (1H, m), 5.25 (1H, d, J = 1.2 Hz), 5.42 (1H,

m), 5.55 (1H, m), 6.00 (2H, bs), 7.25 (2H, d, J = 7.5 Hz), 8.00 (2H, d, J = 7.5 Hz); EI-MS (*m/z*): 394 $(M-H_2O)^+$(2), 376 (15), 337 (11), 320 (12), 294 (100), 279 (12); High-resolution MS (*m/z*): Calcd for $C_{26}H_{34}O_3$ $(M-H_2O)^+$: 394.2509; Found: 394.2594; UV (EtOH): λ_{max} 237.8 (log ε 4.38), 207.8 (log ε 4.29) nm; HPLC analysis: *Rt* 12.14 min (a similar HPLC condition to **10a**).

ACKNOWLEDGEMENT

We would like to thank K. Kanemoto and M. Nakamura for their technical assistances.

References and Notes

1. Prostaglandin Chemistry Part XLIV. For Part XLIII; Koga, M.; Kageyama, H.; Tanaka, T.; Fujii, T. *Synth. Commun.* **1994**, *24*, 3321.
2. (a) Vane, J. R.; Bergström, S. *Prostacyclin* Raven Press, New York, **1979**; (b) Vane, J. R. *Angew.Chem. Int. Ed. Engl.* **1983**, *22*, 741.
3. (a) Lewis, P. L.; O'Grady, J. *Clinical Pharmacology of Prostaglandin* Raven Press, New York, **1981**; (b) Gryglewski, R. J.; Szczeklik, A.; McGiff, J. C. *Prostacyclin; Clinical Trials* Raven Press, New York, **1985**.
4. (a) Shibasaki, M.; Torisawa, Y.; Ikegami, S. *Tetrahedron Lett.* **1983**, *24*, 3493; (b) Noyori, R.; Suzuki, M. *Science* **1993**, *259*, 44.
5. (a) Shibasaki, M.; Fukasawa, H.; Ikegami, S. *Tetrahedron Lett.* **1983**, *24*, 3497; (b) Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1984**, 579; (c) Torisawa, Y.; Okabe, H.; Shibasaki, M.; Ikegami, S. *ibid.* **1984**, 1069; (d) Torisawa, Y.; Okabe, H.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1984**, 1602; (e) Ogawa, Y.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 1067; (f) Mase, T.; Sodeoka, M.; Shibasaki, M. *ibid.* **1984**, *25*, 5087; (g) Koyama, K.; Kojima, K. *Chem. Pharm. Bull.* **1984**, *32*, 2866; (h) Bannai, K.; Tanaka, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Tomimori, K.; Kurozumi, S. *Tetrahedron Lett.* **1986**, *27*, 6353; (i) Suzuki, S.; Koyano, H.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 5583; (j) Nagao, Y.; Nakamura, T.; Kume, M.; Ochiai, M.; Fuji, K.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1987**, 269; (k) Hashimoto, S.; Shinoda, T.; Shimada, Y.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1987**, *28*, 637; (l) Hashimoto, S.; Shinoda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1137; (m) Sodeoka, M.; Ogawa, Y.; Mase, T.; Shibasaki, M. *Chem. Pharm. Bull.* **1989**, *37*, 586; (n) Hemmerle, H.; Gais, H.-J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 349; (o) Hashimoto, S.; Kase, S.; Shinoda, T.; Ikegami, S. *Chem. Lett.* **1989**, 1063; (p) Hashimoto, S.; Miyazaki, Y.; Shinoda, T.; Ikegami, S. *Tetrahedron Lett.* **1989**, *30*, 7195; (q) Mandai, T.; Matsumoto, S.; Kohama, M.; Kawada, M.; Tsuji, J.; Saito, S.; Moriwake, T. *J. Org.Chem.* **1990**, *55*, 5671; (r) Tanaka, T.; Kurozumi, S. *J. Synth. Org. Chem. Jpn.* **1992**, *50*, 143.
6. (a) Amemiya, S.; Koyamo, K.; Saito, S.; Kojima, K. *Chem. Pharm. Bull.* **1986**, *34*, 4403; (b) Kojima, K.; Amemiya, S.; Koyama, K.; Saito, S.; Oshima, T.; Ito, T. *ibid.* **1987**, *35*, 4000; (c)

Shinoda, M.; Iseki, K.; Oguri, T.; Hayashi, Y.; Yamada, S.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 87; (d) Hashimoto, S.; Suzuki, A.; Shinoda, T.; Miyazaki, Y.; Ikegami, S. *Chem. Lett.* **1992**, 1835.

7. (a) Samuelsson, B.; Granstrom, E.; Green K.; Hamberg, M. *Ann. N. Y. Acad. Sct.* **1977**, *180*, 138; (b) Sum, F. F.; Taylor, B. M. *Prostaglandins* **1983**, *21*, 307.
8. (a) Kurozumi, S.; Toru, T. *J. Synth. Org. Chem. Jpn.* **1977**, *37*, 133; (b) Bundy, G.; Lincoln, F.; Nelson, N.; Pike, J.; Schneider, W. *Ann. N. Y. Acad. Sci.* **1977**, *180*, 76; (c) Skuballa, W.; Schillinger, E.; St. Sturzebecher, C.; Vorbrügen, H. *J. Med. Chem.* **1986**, *29*, 313; (d) Kojima, K.; Amemiya, S.; Koyama, K.; Saito, S.; Oshima, T.; Ito, T. *Chem. Pharm. Bull.* **1987**, *35*, 4000.
9. Shibasaki, M.; Iseki, K.; Shinoda, M.; Hayashi, Y. *Japan. Patent* **1992**, *04*, 19217.
10. (a) Ohno, K.; Ohtake, J.; Endo, T.; Ito, S.; Hoshi, K. *Japan. Patent* **1991**, *03*, 7275; (b) Larock, R. C.; Lee, N. H. *J. Org. Chem.* **1991**, *56*, 6253; (c) Ohno, K.; Nishiyama, H.; Nagase, H.; Matsumoto, K.; Ishikawa, M. *Tetrahedron Lett.* **1990**, *31*, 4489; (d) Nagase, H.; Mastumoto, K.; Yoshiwara, H.; Tajima, A.; Ohno, K. *Tetrahedron Lett.* **1990**, *31*, 4493.
11. Tanaka, T.; Bannai, K.; Hazato, A.; Koga, M.; Kurozumi, S.; Kato, Y. *Tetrahedron* **1991**, *47*, 1861.
12. (a) Bannai, K.; Tanaka, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Tomimori, K.; Kato, Y.; Kurozumi, S.; Noyori, R. *Tetrahedron* **1990**, *46*; 6689; (b) Koga, M.; Kageyama, H.; Tanaka, T.; Fujii, T. *Synth. Commun.* **1994**, *24*, 3321.
13. Majid, T. N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413.
14. Böhlke, H. *Japan. Patent* **1983**, *58*, 92637.
15. Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789.
16. Preliminary biological activities have been reported at the 9th International Conference on Prostaglandins and related compounds **1994**, 44, Florence (Italy) by M. Koga, T. Fujii, and T. Tanaka. Compounds of **9b**, **9c**, **14b** and **14c** were found to show inhibitory activities (92~78%) on cell proliferation by measurement of ^{3}H-thymidine incorporation into human aortic smooth muscle cells at 10^{-7}~10^{-5} M concentrations.
17. Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(*Received in Japan* 15 *February* 1995; *accepted* 20 *March* 1995)