[Chem. Pharm. Bull. 27(11)2582—2588(1979)]

UDC 547.896.04 : 547.473.04

# A New Prostaglandin Synthon from the 4-Oxatricyclo[4.3.0.0$^{3,7}$]non-8-ene System. A Total Synthesis of (±)-Prostaglandin $F_{2\alpha}$[1]

Seiichi Takano, Noboru Kubodera, Hiromitsu Iwata, and Kunio Ogasawara

*Pharmaceutical Institute, Tohoku University*[2]

(Received February 3, 1979)

The synthesis of a new prostaglandin synthon(**14**) from 5-trichloromethyl-4-oxatricyclo[4.3.0.0$^{3,7}$]non-8-ene(**2**) and its conversion to prostaglandin $F_{2\alpha}$(**21**) are described. Compound(**2**) was transformed into the acetylene derivative(**5**) which was then led to the C-9 acetylene lactone(**14**) *via* a 6-step, 8-stage reaction.

A new synthesis of (±)-prostaglandin $F_{2\alpha}$(**21**) was completed through a 5-step reaction starting from the C-9 lactone(**14**).

**Keywords**——prostaglandin; prostaglandin synthon; β,β,β-trichloroethyl ether; solvolysis; Baeyer-Villiger oxidation; lactonization; dichloroketene; silver perchlorate

Recently, a new synthesis of the Corey prostaglandin intermediate (**4**) from 5-trichloromethyl-4-oxatricyclo[4.3.0.0$^{3,7}$]non-8-ene (**2**) *via* the C-9 ketene dichloride intermediate (**3**) was reported by our group.[3] In the present report, the application of the compound (**2**) for synthesis of prostaglandin $F_{2\alpha}$(**21**) *via* the C-9 acetylene intermediate (**14**) is described.

The tricyclic compound (**2**), prepared from norbornadiene (**1**) and chloral in the presence of aluminum chloride,[4] was treated with 3.3 molar equivalents of *n*-butyllithium in a 1:1 mixture of ether and tetrahydrofuran[5] at −78° to give the bicyclic acetylene (**5**) in 82% yield. This compound, upon treatment with *p*-toluenesulfonyl chloride in pyridine gave the practically pure tosylate (**6**) in excellent yield. Solvolysis of the tosylate (**6**) in acetic acid in the presence of potassium acetate at 55—57° for 63 hr resulted in regiospecific substitution to give a 1:1 epimeric mixture of the tricyclic acetates (**8**) in 92% yield, presumably through a non-classical carbonium ion (**7**). Production of epimeric acetates was not a serious problem from the synthetic point of view, since the epimeric center could be lost in a later stage of the synthesis. Thus, the epimeric mixture of the acetates (**8**) was hydrolyzed with ethanolic potassium carbonate to give an epimeric mixture of the tricyclic alcohols (**9**) quantitatively, and on treatment with Jones reagent, this gave a 61% yield of the tricyclic ketone (**10**) in crystalline form.

Cleavage of the cyclopropane ring system of (**10**) was carried out in a highly regio- and stereospecific manner to give the bicyclic bromoketone (**11**) in 87% yield, employing Sutherland's conditions,[6] which have been successfully applied for cleavage of a related ring system. Baeyer-Villiger oxidation of the bromoketone (**11**) using 1.2 molar equivalents of *m*-chloroperbenzoic acid in methylene chloride gave the bicyclic lactone (**12**) exclusively, in 79% yield. As the lactone (**12**) was very sensitive to alcoholic solvents, the oxidation product was isolated as the monocyclic ethyl ester (**13**) by brief heating of the reaction mixture with a small amount of ethanol.

1) A preliminary communication of this work appeared in: S. Takano, N. Kubodera, H. Iwata, and K. Ogasawara, *Heterocycles*, **8**, 325 (1977).
2) Location: *Aobayama, Sendai 980, Japan.*
3) S. Takano, N. Kubodera, and K. Ogasawara, *J. Org. Chem.*, **42**, 786 (1977).
4) H. Fritz, C.D. Weis, and T. Winkler, *Helv. Chim. Acta*, **58**, 1345 (1975).
5) J. Villieras, P. Perriot, and J.F. Normant, *Synthesis*, **1975**, 458.
6) R. Peel and J.K. Sutherland, *Chem. Commun.*, **1974**, 151.

Lactonization of the ester (**13**) by intramolecular nucleophilic reaction was very difficult under various conditions, including the use of the metal salt catalysis[7] which had been very effective in the formation of the dichloroketene analog (**3**)[3] of the acetylene lactone (**14**). Under these conditions the desired lactone (**14**) was obtained at best in yields of 10 and 18% using silver perchlorate and sodium hydroxide, respectively. The best yield (73%) was obtained by simply refluxing the ester (**13**) with a catalytic amount of *p*-toluenesulfonic acid in ethanol containing a small amount of water. This simple and efficient lactonization is noteworthy.[8]

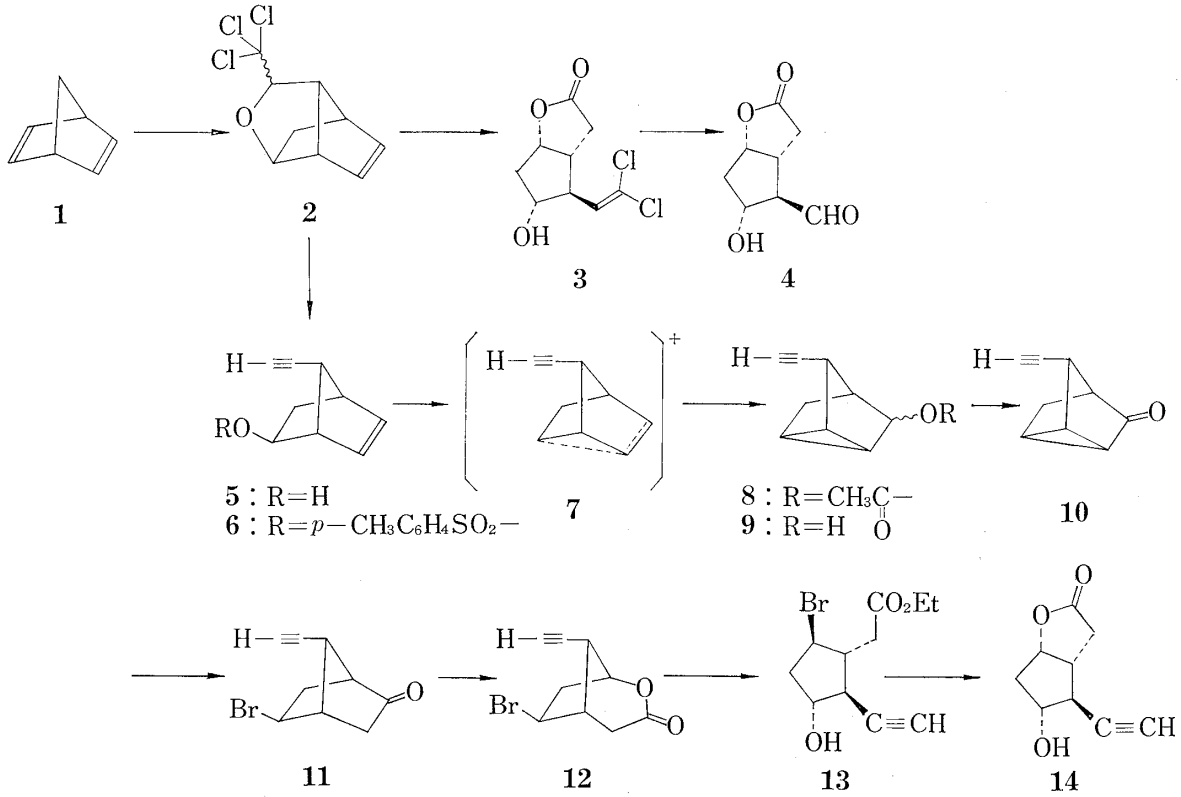
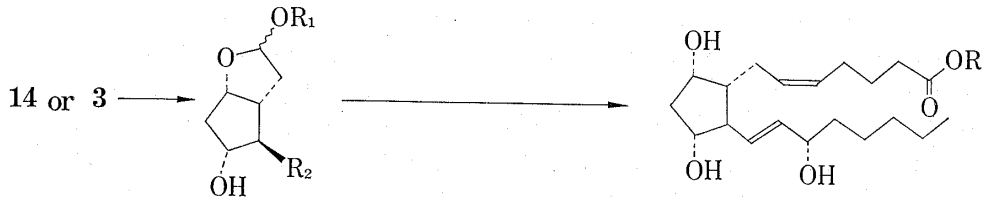



Chart 1

The structure of the C-9 acetylene lactone (**14**) was determined by correlation with its dichloroketene analog (**3**). Thus, the acetylene lactone (**14**) was reduced with diisobutylaluminum hydride to give an epimeric mixture of lactols (**15a**), which was converted without separation into an epimeric mixture of the cyclic acetals (**16a**) in 47% overall yield from (**14**) by treatment with trimethyl orthoformate in the presence of *p*-toluenesulfonic acid. Similar treatment of the corresponding ketene dichloride[9] (**3**) afforded an epimeric mixture of the cyclic acetals (**16b**) in 78% overall yield *via* the lactol (**15b**). Both compounds, (**16a**) and (**16b**), were treated with *n*-butyllithium in a 1:1 mixture of ether and tetrahydrofuran[5] at −78°, followed by treatment with *n*-hexanal to yield the same acetylene diol (**17**) as an epimeric mixture in yields of 52 and 58%, respectively.

The acetylene diol (**17**) thus obtained was then treated with lithium aluminum hydride in boiling tetrahydrofuran to give the known *trans* allyl alcohol (**18**)[10] as a mixture of epimers

7) A. McKillop and M.E. Ford, *Tetrahedron*, **30**, 2467 (1974).
8) *Cf.* S. Takano, H. Iwata, and K. Ogasawara, *Heterocycles*, **12**, 699 (1979).
9) An alternative synthesis of the dichloroketene(3) from the Corey aldehyde(4) and its conversion into prostaglandin derivatives have been claimed by the Ciba-Geigy group in a patent (Japan Kokai 49-82650).
10) J. Fried, C.H. Lin, J.C. Sih, P. Dalven, and G.F. Cooper, *J. Am. Chem. Soc.*, **94**, 4342 (1972).




**15a** : $R_1=H$, $R_2=C\equiv CH$
**15b** : $R_1=H$, $R_2=CH=CCl_2$
**16a** : $R_1=CH_3$, $R_2=C\equiv CH$
**16b** : $R_1=CH_3$, $R_2=CH=CCl_2$
**17** : $R_1=CH_3$, $R_2=C\equiv CCHC_5H_{11}^{n}$ (OH)
**18** : $R_1=CH_3$, $R_2=CH=^{t}CHCHC_5H_{11}^{n}$ (OH)
**19** : $R_1=CH_3$, $R_2=CH=C=CHC_5H_{11}^{n}$
**20** : $R_1=H$, $R_2=CH=^{t}CHCHC_5H_{11}^{n}$ (OH)

**21** : R=H
**22** : $R=CH_3$

Chart 2

in 84% yield, accompanied by the allenic by-product (**19**) in 10% yield as a mixture of geometric isomers.

Following Corey's procedure,[11,12] the acetal (**18**) was hydrolyzed with diluted hydrochloric acid to give an epimeric mixture of lactols, (**20**) which, upon treatment with the Wittig reagent prepared from 5-triphenylphosphoniopentanoic acid[13] and sodio methylsulfinylcarbanide in dimethylsulfoxide, gave a roughly 1:1 mixture of (±)-prostaglandin $F_{2\alpha}$(**21**) and its C-15 epimer.

Chromatographic separation of this mixture gave (±)-prostaglandin $F_{2\alpha}$(**21**) and (±)-15-epi-prostaglandin $F_{2\alpha}$(**21**; C-15 *epi*); these, as well as their corresponding methyl esters, (**22**) and (**22**; C-15 epi), were spectroscopically and chromatographically identical with the authentic materials.[14]

The present route to the C-9 synthon for the synthesis of prostaglandin $F_{2\alpha}$(**21**) from (**2**) is practically attractive because of its simplicity and stereoselectivity.

## Experimental

Melting points are not corrected. Infrared (IR) spectra were recorded with a Shimadzu IR 400 grating spectrometer or a Hitachi EPI-3 grating spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained with JEOL PMX-60 or JEOL PS-100 instruments in deuteriochloroform with $Me_4Si$ as an internal standard, unless otherwise indicated. Mass spectra (MS) were recorded on a Hitachi RMU-7 spectrometer.

**7-Ethynyl-5-hydroxy-2-norbornene** (**5**)——Compound **2** (11.98 g, 50 mmol) was added rapidly to a stirred solution of *n*-butyllithium (10 w/v% in hexane, 154 ml, 165 mmol) in ether (150 ml) and THF (150 ml) at −78° under nitrogen. After 2 hr the reaction was quenched by addition of $NH_4Cl$ (10 g), and the temperature was then allowed to rise slowly to room temperature. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was extracted with methylene chloride and the extract was washed with saturated NaCl and dried over $Na_2SO_4$. Removal of the solvent *in vacuo* left a yellow oil, which was

11) E.J. Corey and R. Noyori, *Tetrahedron Lett.*, **1970**, 311.
12) E.J. Corey, N.M. Weinshenker, T.K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).
13) We thank Dr. Masayasu Kurono, Ono Pharmaceutical Co. Ltd., for providing a substantial amount of this compound.
14) We thank Dr. Hiromasa Nakamoto, Fuji Yakuhin Co. Ltd., and Professor Susumu Tsurufuji, Pharmaceutical Institute, Tohoku University, for providing samples of optically active prostaglandin $F_{2\alpha}$ and its 15 epimer.

distilled to give 7-ethynyl-5-hydroxy-2-norbornene(**5**) (5.50 g, 82.1%) as a colorless oil: bp 29—30° (0.09 Torr); IR $\nu_{max}^{neat}$ $cm^{-1}$: 3540, 3400, 3275, 3050, 2110, 1570, 1055. NMR $\delta$: 1.90(2H, m), 2.30(1H, d, $J$=2.5 Hz), 2.69(1H, br.s), 2.80(1H, br.s, disappeared with $D_2O$), 2.94(2H, br.s), 3.83(1H, br.s), 6.05(2H, m); MS *m/e*: 134, 90(100%); *Anal.* Calcd. for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.31; H, 7.57.

**3-Acetoxy-7-ethynyltricyclo[2.2.1.0]heptane** (**8**)——A solution of (**5**) (4.67 g, 34.85 mmol) in dry pyridine (93 ml) was cooled to 0° and treated with *p*-toluenesulfonyl chloride (19.94 g, 104.55 mmol) with stirring under nitrogen for 2 hr. After 12 hr at room temperature, the reaction mixture was diluted with water and the mixture was extracted with benzene. The extract was washed with 10% HCl and saturated NaCl and dried over $Na_2SO_4$. Removal of the solvent *in vacuo* left the oily tosylate (**6**) (10.02 g, 99.8%) in a practically pure state: IR $\nu_{max}^{neat}$ $cm^{-1}$: 3265, 3050, 1595, 1570, 1350, 1170; NMR $\delta$: 1.70 (2H, m), 2.04(1H, d, $J$=2.5 Hz), 2.43(3H, s), 2.63(1H, m), 2.87(1H, m). 3.05(1H, m), 4.48(1H, m), 5.86(1H, d, d, $J$=6.5, 3.5 Hz), 6.14(1H, d, d, $J$=6.5, 3. 0Hz), 7.27(2H, d, $J$=8.5 Hz), 7.80(2H, d, $J$=8.5 Hz).

The crude (**6**) (10.02 g, 34.79 mmol) thus obtained and fused potassium acetate (6.82 g, 69.58 mmol) were dissolved in acetic acid (282 ml), and the mixture was heated at 55—57° for 63 hr with stirring under nitrogen. After cooling, the reaction mixture was diluted with ice-water and extracted with ether. The extract was washed with saturated $NaHCO_3$ and saturated NaCl, then dried over $Na_2SO_4$. Removal of the solvent *in vacuo* left the oily tricyclic acetate (**8**) (5.61 g, 91.6%) as a 1:1 epimeric mixture, which was used without further purification. Purification by thin layer chromatography (TLC) (silica gel) afforded an analytically pure mixture of the epimers (**8**): IR $\nu_{max}^{neat}$ $cm^{-1}$: 3265, 3050, 2115, 1725, 1235; NMR $\delta$: 1.19—1.67 (3H, m), 1.83 (1H, br.s), 1.95—2.26(2H, m), 2.10(3H, s), 2.07(1H, d, $J$=2.5 Hz), 2.49(0.5H, br.s, *endo* isomer), 2.91 (0.5H, br.s, *endo* isomer), 2.91(0.5H, br.s, *exo* isomer), 4.57(0.5H, br.s, *endo* isomer), 4.73(0.5H, br.s, *exo* isomer); MS *m/e*: 176, 43(100%); *Anal.* Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.65; H, 6.61.

**7-Ethynyl-3-hydroxytricyclo[2.2.1.0]heptane** (**9**)——A solution of an epimeric mixture of (**8**) (5.59 g, 31.76 mmol) in ethanol (500 ml) was stirred with anhydrous potassium carbonate (10.96 g, 63.25 mmol) under nitrogen at room temperature for 3.5 hr. The reaction mixture was concentrated *in vacuo* and the residue was extracted with methylene chloride. The extract was washed with 10% HCl and saturated NaCl, then dried over $Na_2SO_4$. Removal of the solvent *in vacuo* left a practically pure oily compound (**9**) (4.18 g, 98.2%) as a 1:1 epimeric mixture, which was used without further purification. Purification by TLC (silica gel) afforded an analytically pure oil; IR $\nu_{max}^{neat}$ $cm^{-1}$: 3300, 3275, 3050, 2110, 1070; NMR ($CCl_4$) $\delta$: 1.00—1.53 (3H, m), 1.63—2.00 (3H, m), 1.90 (1H, d, $J$=2.5 Hz), 2.29 (0.5H, br.s, *endo* isomer), 2.89 (0.5H, br.s, *exo* isomer), 3.36 (1H, br.s, disappeared with $D_2O$), 3.68 (0.5H, br.s, *endo* isomer), 3.83 (0.5H, br.s, *exo* isomer); MS *m/e*: 134, 116 (100%); *Anal.* Calcd. for $C_9H_{10}O$; C, 80.56; H, 7.51. Found: C, 80.69; H, 7.64.

**7-Ethynyltricyclo[2.2.1.0]hept-3-one** (**10**)——A solution of an epimeric mixture of (**9**) (2.86 g, 95.97 mmol) in acetone (140 ml) was treated with Jones reagent (prepared by mixing $CrO_3$ (14.90 g, 143.95 mmol) on $H_2O$ (140 ml) with 98% $H_2SO_4$ (17.28 ml) at 0°) with stirring at 0° and the mixture was stirred for 12 hr at room temperature. The reaction was quenched by addition of isopropyl alcohol (*ca.* 7 ml) and the reaction mixture was extracted with methylene chloride, The extract was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $Na_2SO_4$, and concentrated *in vacuo* to leave a yellow oil. The crude product was distilled to give (**10**) (7.75 g, 61.2%) as a colorless oil: bp 38—40° (0.18 Torr); IR $\nu_{max}^{neat}$ $cm^{-1}$: 3270, 1755; NMR ($CCl_4$) $\delta$: 1.29(1H, m), 1.73—2.40(5H, m), 2.01(1H, d, $J$=2.5 Hz), 2.90(1H, br.s); MS *m/e*: 132, 103(100%). *Anal.* Calcd. for $C_9H_8O$: C, 81.79; H, 6.10. Found: C, 81.44; H, 6.19.

**5-Bromo-7-ethynylnorbornan-2-one** (**11**)——A solution of (**10**) (7.75 g, 58.7 mmol) in a mixture of 47% HBr (11.13 g, 64.6 mmol) and acetic acid (300 ml) was refluxed for 3 hr. The reaction mixture was poured into ice-water (*ca.* 300 ml) and extracted with methylene chloride. The extract was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $Na_2SO_4$, and concentrated *in vacuo* to leave a crystalline residue which was recrystallized from *n*-hexane to give (**11**) (10.82 g, 86.54%) as colorless needles: mp 68—69°; IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3270, 1740; NMR $\delta$: 2.05 (2H, m), 2.40 (1H, d, $J$=2.5 Hz), 2.42 (1H, m), 2.80(2H, m)m 3.06 (2H, m), 4.03(1H, m); MS *m/e*: 214, 212, 40(100%); *Anal.* Calcd. for $C_9H_9BrO$: C, 50.73; H, 4.26. Found: C, 50.99; H, 4.28.

**6-Bromo-8-ethynyl-2-oxabicyclo[3.2.1]oct-3-one** (**12**)——A solution of (**11**) (2.13 g. 1 mmol) in methylene chloride (100 ml) was stirred with 70% *m*-chloroperbenzoic acid (3.71 g, 15 mmol) at room temperature for 72 hr. The reaction mixture was washed with 2% $Na_2S_2O_4$, saturated $NaHCO_3$, and saturated NaCl, dried over $Na_2SO_4$, and concentrated *in vacuo* to give a crystalline residue, which on recrystallization from a mixture of *n*-hexane and benzene gave (**12**) (1.80 g, 78.6%) as colorless needles: mp 127—129°; IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3245, 1735, 1155; NMR $\delta$: 2.40 (1H, d, $J$=2.5 Hz), 2.66—3.25 (6H, m), 4.27(1H, m), 4.88(1H, br.s); MS *m/e*: 230, 228, 39(100%); *Anal.* Calcd. for $C_9H_9BrO_2$: C, 47.19; H, 3.96. Found: C, 47.18; H, 3.92.

**Ethyl 5β-Bromo-2β-ethynyl-3α-hydroxycyclopentane-1-acetate** (**13**)——A solution of (**11**) (0.180 g, 0.85 mmol) in chloroform (4 ml) was stirred with 70% *m*-chloroperbenzoic acid (0.206 g, 1.01 mmol) at room temperature for 72 hr. Ethanol (1 ml) was added, the mixture was refluxed for 4 hr, and the solvent was removed *in vacuo*. The residue was extracted with methylene chloride and the extract was washed with 2% $Na_2S_2O_4$, saturated $NaHCO_3$, and saturated NaCl, then dried over $Na_2SO_4$. Removal of the solvent *in vacuo* left practically pure (**13**) (0.228 g, 98.1%) as a pale yellow oil, which was used without further puri-

fication. Preparative TLC (silica gel) afforded analytically pure **13** as a pale yellow oil: IR $\nu_{max}^{neat}$ cm$^{-1}$: 3400, 3280, 2110, 1720, 1180; NMR $\delta$: 1.32 (3H, t, $J$=7.2 Hz), 2.21—3.28 (8H, m, disappeared 1H with $D_2O$), 4.25(4H, m); MS *m/e*: 276, 274, 91(100%); *Anal.* Calcd. for $C_{11}H_{15}BrO_3$: C, 48.02; H, 5.50; Found: C, 48.44; H, 5.50.

**2β-Ethynyl-3α,5α-dihydroxycyclopentane-1α-acetic Acid γ-Lactone (14)**——A. $AgClO_4$-Catalyzed Reaction: A solution of (**13**) (0.515 g, 1.87 mmol) in 1,2-dimethoxyethane (10 ml) was added to a mixture of $AgClO_4$ (0.409 g, 1.87 mmol), water (0.43 ml) and 1,2-dimethoxyethane (10 ml) with stirring at room temperature under nitrogen. After stirring for 4 hr, the insoluble precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was extracted with methylene chloride and the extract was washed with saturated NaCl, then dried over $Na_2SO_4$. Removal of the solvent *in vacuo* left a brown oil, which was purified by preparative TLC (silica gel) to give a crystalline residue. Recrystallization from a mixture of *n*-hexane and benzene gave (**14**) (0.031 g, 10.0%) as colorless needles: mp 78—80°; IR $\nu_{max}^{neat}$ cm$^{-1}$: 3400, 3260, 3240, 1755, 1215, 1085; NMR $\delta$: 2.20(1H, d, $J$=2.5 Hz), 2.36(2H, m), 2.57(1H, br.s, disappeared with $D_2O$), 2.63—2.90(3H, m), 3.08(1H, m), 4.41(1H, m); MS *m/e*: 166, 77(100%). *Anal.* Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.97; H, 5.95.

B. NaOH-Catalyzed Reaction: A solution of (**13**) (0.952 g, 3.36 mmol) in a mixture of 30% NaOH (5.8 ml) and ethanol (70 ml) was refluxed for 25 hr. The reaction mixture was made acidic (pH 3—4) by addition of 10% HCl at 0° and the mixture was stirred at room temperature for 30 min, then the solvent was removed *in vacuo*. The residue was extracted with methylene chloride and the extract was washed with saturated NaCl, dried over $Na_2SO_4$, and concentrated *in vacuo* to leave a brown oil, which on crystallization from a mixture of *n*-hexane and benzene gave (**14**) (0.102 g, 18.3%) as colorless needles.

C. *p*-TsOH-Catalyzed Reaction: A mixture of bromolactone (**13**) (229 mg, 1 mmol) and a catalytic amount of *p*-toluenesulfonic acid in 95% EtOH (20 ml) was refluxed for 30 hr. Removal of the slovent left a crystalline mass, which on recrystallization from a mixture of *n*-hexane and benzene gave (**14**) (68 mg, 41.0 %). The mother liquor was evaporated down and the residue was dissolved in methylene chloride, washed with saturated $NaHCO_3$ and dried over $Na_2SO_4$. Concentration followed by crystallization afforded additional (**14**) (53 mg, 31.9%) (total 121 mg, 72.9%).

**2β-Ethynyl-3α,5α-dihydroxycyclopentane-1α-acetaldehyde γ-Lactol-methylether (16a)**——A stirred solution of the lactone (**14**) (0.102 g, 0.61 mmol) in a mixture of benzene (10 ml) and toluene (10 ml) was treated with diisobutylaluminum hydride (1.15 ml of 25 w/v% toluene solution, 2.30 mmol) at −20° to −15° under nitrogen. After 1 hr 10% HCl (5 ml) was added at −20° to −15° and the mixture was stirred for 30 min at room temperature. The organic layer was separated and the aqueous layer was extracted with benzene. The combined organic layer was washed with saturated NaCl and dried over $Na_2SO_4$. Removal of the solvent left (**15a**) (0.069 g) as a pale yellow oil, which was used without further purification: IR $\nu_{max}^{neat}$ cm$^{-1}$: 3375, 3270, 2100, 1080, 1030.

The crude (**15a**) (0.078 g, 0.74 mmol), methyl orthoformate (0.078 g, 0.74 mmol) and a catalytic amount of *p*-toluenesulfonic acid were dissolved in methanol (12 ml) and the mixture was refluxed for 2 hr with stirring under nitrogen. The reaction mixture was concentrated *in vacuo* and the residue was extracted with methylene chloride. The extract was washed with saturated $NaHCO_3$ and saturated NaCl, then dried over $Na_2SO_4$. Removal of the solvent *in vacuo* left (**16a**) (0.025 g, 46.5% from (**14**)) as a yellow oil, which was used without further purification: IR $\nu_{max}^{neat}$ cm$^{-1}$: 3380, 3270, 2100, 1090, 1040; NMR $\delta$: 1.93—3.13 (6H, m), 2.07(1H, d, $J$=2.5 Hz), 3.24(1.8H, s), 3.29(1.2H, s), 3.57(1H, br.s, disappeared with $D_2O$), 4.20(1H, m), 4.57(1H, m), 5.06(1H, m); MS *m/e*: 151($M^+$−OMe), 58(100%). *Anal.* Calcd. for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 66.24; H, 7.79.

**2β-(2,2-Dichlorovinyl)-3α,5α-dihydroxycyclopentane-1α-acetaldehyde γ-Lactol-methylether (16b)**——A stirred solution of the lactone (**3**) (3.555 g, 15 mmol) in a mixture of benzene (100 ml) and toluene (30 ml) was treated with diisobutylaluminum hydride (18.75 ml of 25 w/v% toluene solution, 33 mmol) at −20° to −15° under nitrogen. After 30 min 10% HCl(20 ml) was added at −20° to −15° and the mixture was stirred for 30 min at room temperature. The organic layer was separated and the aqueous layer was extracted with benzene. The combined organic layer was washed with saturated NaCl and dried over $Na_2SO_4$. Removal of the solvent left (**15b**) (3.455 g) as a pale yellow oil, which was used without further purification: IR $\nu_{max}^{neat}$ cm$^{-1}$: 3350, 3020, 1615.

The crude (**15b**) (3.455 g), methyl orthoformate (1.908 g, 18 mmol) and a catalytic amount of *p*-toluenesulfonic acid were dissolved in methanol (170 ml) and the mixture was refluxed for 4 hr with stirring under nitrogen. The reaction mixture was concentrated *in vacuo* and the residue was extracted with methylene chloride. The extract was washed with saturated $NaHCO_3$ and saturated NaCl, and dried over $Na_2SO_4$. Removal of the solvent *in vacuo* left (**16b**) (3.05 g, 80.4% from (**3**)) as a pale yellow oil, which was used without further purification. Preparative TLC (silica gel) of the crude (**16b**) afforded an analytically pure oil: IR $\nu_{max}^{neat}$ cm$^{-1}$: 3390, 1615, 1019, 1040: NMR $\delta$: 1.88—2.87(7H, m), 3.28(1.8H, s, $-OCH_3$), 3.36(1.2H, s, $-OCH_3$), 3.91(1H, m), 4.53(1H, m), 5.10(1H, m), 5.70(1H, d, $J$=9.0 Hz); MS *m/e*: 225, 223, 221($M^+$−OMe), 58(100%). *Anal.* Calcd. for $C_{10}H_{14}Cl_2O_3$: C, 47.45; H, 5.58. Found: C, 47.51; H, 5.41.

**3α,5α-Dihydroxy-2β(3-hydroxy-1-octynyl)cyclopentane-1α-acetaldehyde γ-Lactol-methylether (17)**——A. Compound **16a** (0.025 g, 0.29 mmol) in a mixture of ether (5 ml) and THF (5 ml) was added dropwise

to a stirred solution of *n*-butyllithium (10 w/v% in hexane, 0.58 ml, 0.63 mmol) in ether (5 ml) and tetrahydrofuran (THF) (5 ml) at −78° under nitrogen. After 1.5 hr *n*-hexanal (0.064 g, 0.63 mmol) in a mixture of ether (4 ml) and THF (4 ml) was added dropwise and the temperature was then allowed to rise slowly to room temperature. After 1.5 hr the reaction was quenched by addition of saturated $NH_4Cl$, and the organic layer was separated. The organic layer was washed with saturated NaCl, dried over $Na_2SO_4$ and concentrated *in vacuo* to leave a yellow oil which was purified by preparative TLC (silica gel) to give (**17**) (0.025 g, 52.1%) as a pale yellow oil: IR $\nu_{max}^{neat}$ $cm^{-1}$: 3300, 2200, 1090, 1050; NMR $\delta$: 0.93 (3H, t, $J$=5.0 Hz), 1.13—1.93 (8H, m), 1.97—2.06(6H, m), 3.00(2H, s, disappeared with $D_2O$), 3.35(1.8H, s), 3.40(1.2H, s), 3.97—4.80(3H, m), 5.12(1H, m),; MS *m/e*: 251($M^+$—OMe), 41(100%). *Anal.* Calcd. for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 67.29; H, 9.07.

B. Compound **16b** (0.320 g, 1.26 mmol) in a mixture of ether(7 ml) and THF(7 ml) was added dropwise to a stirred solution of *n*-butyllithium (3.87 ml of 10 w/v% hexane solution 4.17 mmol) in ether (7 ml) and THF(7 ml) at −78° under nitrogen. After 1.5 hr *n*-haxanal (0.417 g, 4.17 mmol) in a mixture of ether (7 ml) and THF(7 ml) was added dropwise and the temperature was then allowed to rise slowly to room temperature. After 1.5 hr the reaction was quenched by addition of saturated $NH_4Cl$ and the organic layer was separated. The organic layer was washed with saturated NaCl, dried over $Na_2SO_4$ and concentrated *in vacuo* to leave a yellow oil, which was purified by preparative TLC (silica gel) to give a yellow oil (0.207 g, 51.15%). The spectral data and *Rf* value of this material were compatible with those of the product obtained from (**16a**).

**3α,5α-Dihydroxy-2β(3-hydroxy-*trans*-1-octenyl)cyclopentane-1α-acetaldehyde γ-Lactol-methylether (18)**——A stirred suspension of lithium aluminum hydride (0.1 g) in THF(10 ml) was treated with (**17**) (0.106 g, 0.38 mmol) in THF(5 ml) at 0° under nitrogen, and the reaction mixture was refluxed for 4 hr. After cooling, the reaction was quenched by addition of wet ether at 0° with stirring and the mixture was concentrated *in vacuo*. The residue was extracted with methylene chloride and the extract was washed with saturated NaCl, dried over $Na_2SO_4$ and concentrated *in vacuo* to leave a colorless oil. The crude product was purified by preparative TLC(silica gel) to give an epimeric mixture of the allylic alcohols (**18**) (0.090 g, 84.33%), as a colorless oil: IR $\nu_{max}^{neat}$ $cm^{-1}$: 3300, 1090, 1050, 970; NMR $\delta$: 0.94 (3H, t, $J$=5.0 Hz), 1.12—1.75(8H, m), 1.91—2.63(6H, m), 2.29(2H, s, disappeared with $D_2O$), 3.35(1.8H, s,) 3.40(1.2H, s), 3.95(2H, m), 4.56(1H, m), 5.13(1H, m), 5.57(2H, m); MS *m/e*: 253($M^+$—OMe), 66(100%), and a mixture of the isomeric allenes (**19**) (0.010 g, 10.0%) as a colorless oil: IR $\nu_{max}^{neat}$ $cm^{-1}$: 3350, 1950; NMR $\delta$: 0.89 (3H, t, $J$=5.0 Hz), 1.11—1.60(8H, m), 1.71—2.79(7H, m, disappeared 1H with $D_2O$), 3.30(1.8H, s), 3.36(1.2H, s), 3.89(1H, m), 4.54(1H, m), 5.10(3H, m); MS *m/e*: 235($M^+$−OMe), 80(100%).

**Prostaglandin $F_{2\alpha}$ (21) and Its C-15 Epimer**——The acetal (**18**) (0.115 g, 0.405 mmol) was dissolved in aqueous acetonitrile containing hydrochloric acid (preparared from conc. HCl (0.12 ml), $H_2O$(12.5 ml) and acetonitrile(25 ml)) and the mixture was stirred at room temperature for 2.5 hr. The reaction mixture was concentrated and the residue was extracted with methylene chloride. The extract was washed with saturated $NaHCO_3$, followed by saturated NaCl, and dried over $Na_2SO_4$. Removal of the solvent *in vacuo* left the crude hemiacetal (**20**) (0.095 g, 86.9%) as a colorless oil: IR $\nu_{max}^{neat}$ $cm^{-1}$: 3350, 3040, 970.

5-Triphenylphosphoniopentanoic acid (0.832 g, 2.02 mmol) in dimethyl sulfoxide (8 ml) was added dropwise at 0° to a stirred solution containing sodio methylsulfinylcarbanide prepared from NaH(0.177 g, 7.37 mmol) and dimethyl sulfoxide (5 ml), and stirring was continued for 10 min at room temperature. The crude hemiacetal (**20**) (0.095 g, 0.35 mmol) in dimethyl sulfoxide (6 ml) was then added dropwise and the mixture was stirred for 2 hr at room temperature. The reaction mixture was treated with saturated $NaHCO_3$ and washed thoroughly with methylene chloride. The aqueous layer was made acidic (pH 2—3) by addition of 10% HCl and was then extracted with methylene chloride. The extract was washed with water, dried over $Na_2SO_4$, and concentrated *in vacuo* to leave a pale yellow oil (0.707 g), which was purified on a silica gel preparative plate, developing with a mixture of chloroform, methanol, and acetic acide (700 ml: 100 ml: 100 drops) to give a mixture of (±)-prostaglandin $F_{2\alpha}$–(**21**) and its C-15 epimer (110 mg, 76.9% from the acetal (**18**)): IR $\nu_{max}^{neat}$ $cm^{-1}$: 3600—2300, 2900, 1700, 1432, 1145.

This mixture was separated on a silica gel preparative plate, developing 6 times with a mixture of chloroform and methanol(7: 3), to give pure (±)-prostaglandin $F_{2\alpha}$ (**21**) (12 mg) as a colorless semisolid, mp 30—31°, and its C-15 isomer (2 mg) as a colorless oil accompanied by unseparated material (*ca.* 50 mg) (the fact that these compounds cannot be detected by ultraviolet made their separation extremely difficult). The IR spectra in chloroform and the TLC behavior of the purified compounds identical with those of authentic materials. Although TLC indicated roughly 1: 1 formation of (±)-prostaglandin $F_{2\alpha}$ (**21**) and its C-15 epimer, the actual ratio was determined as the corresponding methyl esters. Thus, a mixture of (**21**) and its C-15 epimer (270 mg, 0.76 mmol), prepared as above, in ether (30 ml) was treated with excess diazomethane in ether, and after 24 hr the mixture was filtered and concentrated to leave a pale yellow oil (225 mg) which was separated by silica gel centrifugal chromatography (Servo PX-2) using a mixtute of benzene and methanol (20: 1) as an eluent to give (±)-prostaglandin $F_{2\alpha}$ methyl ester (**22**) (62 mg, 22.2%) as a colorless oil: IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3510, 2950, 2865, 1735, 1165, 1100, 972. NMR $\delta$: 0.9(3H, br.t), 1.07—2.77 (28H, m; 3H, disapp. with $D_2O$), 3.67(3H, s), 3.60—4.47(3H, m), 5.27—6.20(4H, m), and its C-15 epimer (75 mg, 26.8%) as a colorless oil: IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3500, 2950, 2865, 1730, 1100. NMR $\delta$: 0.88(3H, br.t), 1.05—3.10

(23H; 3H, disapp. with $D_2O$), 3.67(3H, s), 3.30—4.47(3H, m), 5.20—6.35(4H, m). The products thus obtained were identical spectroscopically and chromatographically with authentic samples obtained from (**21**) and its C-15 epimer.

**Acknowledgements** The author is grateful to Mr. Kazuyoshi Kawamura and Misses Chieko Koyanagi, Harumi Koizumi, and Aiko Sato of this institute for physical data.