Communications to the Editor

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Studies on Prostaglandins. III.[1] Synthesis of Bicyclo[4.3.0]nonane Derivatives

3-(4-Carboxybutylidene)-7α,9α-dihydroxy-4-hexyl-1βH,6αH-bicyclo[4.3.0]nonane (III) and 3-(4-carboxybutylidene)-7α,9α-dihydroxy-4-(1-hydroxyhexyl)-1βH,6αH-bicyclo[4.3.0]-nonane (IV) were synthesized as prostaglandin-derivatives which were related to steroids. Preliminary *in vitro* studies on isolated guinea pig ileum have shown that IV possessed weakly PG-like contraction activity (1/300 of $PGF_{2\alpha}$) and III did not possess the PG-like activity.

The structural and biological relationships between prostaglandins (PGs) and steroids have been discussed by many investigators.[2-4] Recently, D.L. Venton, *et al.*[4] synthesized 17β-hydroxy-5α-androstane-2α-carboxylic acid (IIa) and 6β,17β-dihydroxy-5α-androstane-2α-carboxylic acid (IIb) as steroid-like PG-derivatives, and they reported that IIa showed weakly specific PG-antagonistic activity. However, the natural steroids possess the opposite absolute configuration to natural PGs as written in Chart 1. Therefore, we have planned to synthesize the derivatives which possess the opposite absolute configuration to natural steroids. This report describes on the synthesis of PG-derivatives (III and IV) possessed a bicyclo[4.3.0]-nonane skeleton as the first attempt of our project and the biological activity of them.

The synthetic scheme was shown in Chart 2. The synthesis was started from the Corey's intermediate V[5] (mp 97—98 ° $[\alpha]_D^{25}$ −85.6°)[6a] for the synthesis of PGs. Deacylation of V with an equimolar amount of potassium carbonate in methanol at 30° for 3 hr gave VI with a

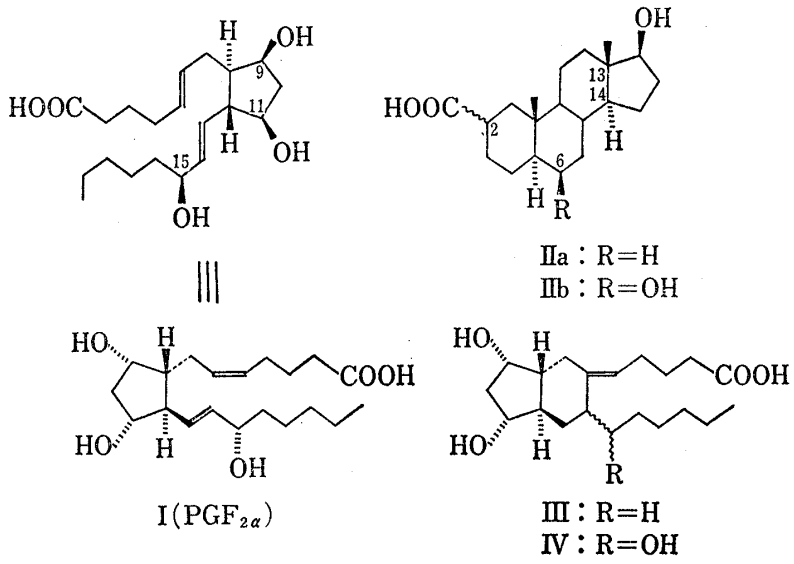

Chart 1

1) Part II: N. Inukai, H. Iwamoto, N. Nagano, I. Yanagisawa, T. Tamura, Y. Ishii, and M. Murakami, *Chem. Pharm. Bull.* (Tokyo), "in press."
2) S.V. Sunthankar and S.D. Meheudale, *Tetrahedron Letters*, **1972**, 2481.
3) D. Brewster, M. Myers, J. Ormerod, P. Otter, A.C.B. Smith, M.S. Spinner, and S. Turner, *J. Chem. Soc. Perkin Trans.* I, **1973**, 2796.
4) D.L. Venton, R.E. Counsell, T.H. Sanner, and K. Sierra, *J. Med. Chem.*, **18**, 9 (1975).
5) E.J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T.K. Schaaf, *J. Am. Chem. Soc.*, **93**, 1490 (1971); E.J. Corey, S.M. Albonico, U. Koelliker, T.K. Schaaf, and R.K. Varma, *ibid.*, **93**, 1491 (1971).
6) $[\alpha]_D$ was measured in chloroform with following concentration: *a*) $c=1.0$; *b*) $c=0.5$; *c*) $c=0.05$.

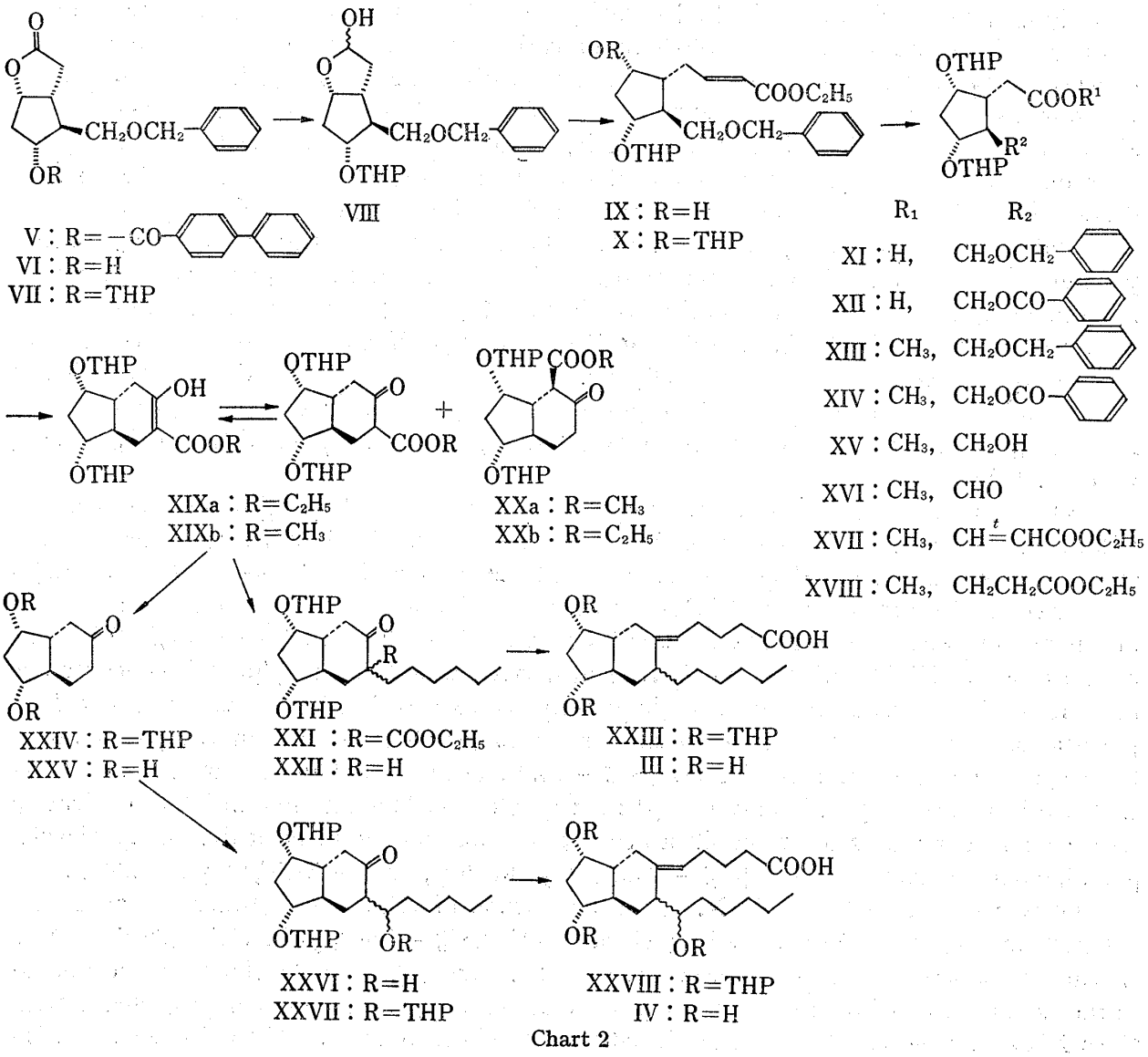

Chart 2

quantitative yield $[\alpha]_D^{20}$ −7.2°),[6a,7] which was converted with a 98% yield into the tetrahydropyranyl derivative VII ($[\alpha]_D^{20}$ −28.2°)[6a,7] using 2,3-dihydropyran (1.5 eq)[8] in methylene chloride containing *p*-toluenesulfonic acid (0.007 eq) at room temperature for 30 min. Reduction of VII by means of 1.4 eq of diisobutylaluminum hydride[9] in toluene at −70° for 30 min gave the lactol VIII ($[\alpha]_D^{22}$ −27.6°, yield 97%)[6a,7] which was condensed with ethoxycarbonylmethylene-triphenylphosphorane[10] in benzene at 80° for 4.5 hr to form IX ($[\alpha]_D^{23}$ +12.6°, yield 89.5%).[6a,7] IX was treated with 2,3-dihydropyran (1.5 eq) in methylene chloride containing *p*-toluenesulfonic acid (0.007 eq) to obtain ditetrahydropyranyl derivative X ($[\alpha]_D^{22}$ +15.1°, yield 77%).[6a,7] The oxidation of X with sodium metaperiodate and potassium permanganate[11] in a mixture of acetone and water at pH 4.6—4.7 overnight followed by column chromatography on silica gel[12a] yielded the acid XI ($[\alpha]_D^{22}$ +6.3°, yield 46%)[6a,7] and XII ($[\alpha]_D^{22}$ +8.07, yield 13%).[6a,7] XI and XII were converted respectively to the methyl ester

7) Infrared, nuclear magnetic resonance and mass spectra were in agreement with the assigned structure.
8) The abbreviation of "eq" means "equivalent".
9) J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **46**, 2799 (1963).
10) D.B. Denney and S.T. Ross, *J. Org. Chem.*, **27**, 998 (1962).
11) R.U. Lemieux and E. Von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).
12) An eluting solvent: *a*) ether–*n*-hexane (1:1); *b*) ethylacetate–*n*-hexane (1:2); *c*) ethylacetate–methanol–acetic acid (100:2:1).

XIII ($[\alpha]_D^{22}$ +33.7°)[6a,7] and XIV ($[\alpha]_D^{22}$ +2.96°)[6a,7] with a quantitative yield. The catalytic hydrogenation of XIII with 10% palladium on carbon in methanol containing small amounts of acetic acid at 1 atm gave the primary alcohol XV with a quantitative yield ($[\alpha]_D^{22}$ +13.2°).[6a,7] XV was also obtained from XIV by treating with 1 eq potassium carbonate in methanol at 25° overnight. Oxidation of alcohol XV using 12 eq of the Collins reagent[13] in methylene chloride at 0° for 6 min produced the unstable aldehyde XVI, which without purification was condensed with 1.5 eq the sodio derivative of diethylcarbethoxymethyl-phosphonate[14] in tetrahydrofuran at room temperature for 1 hr to form the *trans*-vinyl ester XVII ($[\alpha]_D^{22}$ +27.9°, yield 40% from XIV).[6a,7] Catalytic hydrogenation of XVII with 10% palladium on carbon in methanol gave XVIII with a quantitative yield ($[\alpha]_D^{26}$ +28.6°).[6a,7] The treatment of XVIII with sodio methylsulfinylcarbanide (1.2 eq)[15] in dimethylsulfoxide at room temperature for 1.5 hr gave the two kinds of bicyclo[4.3.0]nonane derivatives (XIXa, b and XXa, b).[7] These were separated by column chromatography on silica gel[12a]: XIXa containing about 30% XIXb ($[\alpha]_D^{26}$ −45.5°, yield 37.5%),[6a] XXa [($[\alpha]_D^{26}$ +12.4°, yield 34.2%)[6a] and XXb ($[\alpha]_D^{26}$ −7.85°, yield 13.8%).[6a]

XIX was converted to XXI by treating it with sodium hydride (1 eq) in dimethoxyethane followed by reacting with *n*-hexyliodide at 85° for 19 hr. XXI was the mixture of two stereoisomers which showed $[\alpha]_D^{19}$ −47.7°[6a] (yield 26.3%) and $[\alpha]_D^{19}$ −54.0°[6a] (yield 18%) respectively. Decarboxylation of XXI with large excess of barium hydroxide in a mixture of ethanol and water under reflux for 2 hr yielded XXII ($[\alpha]_D^{17}$ −12.2°, yield 15%).[6b,7] The condensation of XXII with the Wittig reagent derived from 5-triphenylphosphoniopentanoic acid and sodio methylsulfinylcarbanide in dimethylsulfoxide[5,15] at 55° for 2.5 hr followed by purification with column chromatography on silica gel[12a] gave the ditetrahydropyranyl-bicyclo[4.3.0]nonane derivative XXIII ($[\alpha]_D^{20}$ −15.0°, yield 7.6%).[6b,7] Hydrolysis of XXIII with acetic acid-tetrahydrofuran-water (19: 11: 3) at 40—45° for 2 hr followed by purification with column chromatography on silica gel[12c] gave two stereoisomers of dihydroxy-bicyclo-[4.3.0]nonane derivative III[7] ($[\alpha]_D^{20}$ −33.2°,[6c] yield 30% and −37.5°,[6c] yield 20%).

IV was synthesized from XIX. Decarboxylation of XIX with 1,4-diazabicyclo[2.2.2]-octane[16] in *o*-xylene at 140° for 2 hr yielded XXIV ($[\alpha]_D^{25}$ −1.94°, yield 71.5%).[6a,7] XXIV was able to be separated two stereoisomer ($[\alpha]_D^{25}$ +26.0° and $[\alpha]_D^{25}$ −23.5°) which were originated in the asymmetric carbon atom of tetrahydropyranyl group, and the same deprotected derivatives XXV ($[\alpha]_D^{25}$ −63.7°)[6b,7] was produced from the both isomers. The aldol condensation of XXIV with *n*-hexylaldehyde by House's method[17] gave the XXVI ($[\alpha]_D^{25}$ −1.5°)[6c,7] with 8.5% yields which was converted to the tetrahydropyranyl-derivative XXVII ($[\alpha]_D^{25}$ −12.0°)[6c,7] using 2,3-dihydropyran (1.5 eq) in methylene chloride containing *p*-toluenesulfonic acid (0.007 eq). The condensation of XXVII with the Wittig reagent derived from 5-triphenylphosphonio-pentanoic acid and sodio methylsulfinylcarbanide in dimethylsulfoxide[5,15] at 50—60° for 4 hr followed by column chromatography on silica gel[12] gave XXVIII ($[\alpha]_D^{25}$ −4.6°, yield 17.2%).[6c,7] Hydrolysis of XXVIII with acetic acid-tetrahydrofuran-water (19: 11: 3) at 45° for 1 hr followed by purification with column chromatography on silica gel[12c] gave the trihydroxy-bicyclo[4.3.0]nonane derivative IV ($[\alpha]_D^{28}$ −11.2°, *Rf*=0.21, yield 53%)[6c,7,18] in accompany with the minor product XXIX ($[\alpha]_D^{28}$ −9.0°, *Rf*=0.16).[6c,18,19]

The biological activities of III, and IV were investigated. Preliminary *in vitro* studies on isolated guinea pig ileum have shown that IV possessed weakly PG-like contraction activity

13) J.C. Collins, W.W. Hess, and F.J. Frank, *Tetrahedron Letters*, **1968**, 3363.
14) *a*) P. Nylén, *Chem. Ber.*, **57**, 1023 (1924); *b*) A.E. Arbusow and A.A. Dunin, *ibid.*, **60**, 291 (1927).
15) R. Greenwald, M. Chaykovsky, and E.J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).
16) B-S. Huang, E.J. Parish, and D. Howard, *J. Org. Chem.*, **39**, 2647 (1974).
17) H.O. House, D.S. Crumrine, A.Y. Teranishi, and H.D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973.)
18) Developing solvent: chloroform–methanol–acetic acid–water (95: 5: 0.65: 1). (*Rf* of $PGF_{2\alpha}$=0.16).
19) The structure of XXIX is investigating.

(1/300 of $PGF_{2\alpha}$) and III did not possess the PG-like activity. This fact was shown that the hydroxy group of 15-position of PGs was also very important for such bicyclo[4.3.0]nonane derivatives.

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N-(3-Fluoranthyl)maleimide (FAM): A Medium Lifetime Fluorescent Thiol Reagent[1)]

N-(3-Fluoranthyl)maleimide (FAM) is a fluorescent probe for thiols with a medium lifetime (~20 nsec), which can be used for studies of time-dependent processes of biopolymers.

Fluorescent probes have been effectively employed to map the microenvironments of biological macromolecules such as proteins and polynucleotides and to clock the dynamics of intramolecular interactions.[2)] The general idea behind a fluorescent probe is that fluorescence emission, sensitive to changes in microenvironments, will display distinct fluorescent properties which will characterize uniquely each environment. A number of different aspects of the fluorescence emission include spectral distribution of emission, the degree of polarization, and the time dependence of emission or polarized components of emission. In a series of systematic study we have developed several fluorescent thiol reagents of maleimide-type which satisfy the above requirements to varying degrees: *e.g.*, N-(*p*-(2-benzimidazolyl)phenyl)-maleimide (BIPM)[1,3)] is a reagent for microdetermination; N-(1-anilinonaphthyl-4)maleimide (ANM)[4)] is a hydrophobic probe; N-(7-dimethylamino-4-methylcoumarinyl)maleimide (DACM)[5)] has emission maximum at a longer wave region. Those reagents have proved useful

1) Fluorescent Thiol Reagents. XI. For Part X, see: T. Sekine, K.A. Kato, K. Takamori, M. Machida, and Y. Kanaoka, *Biochim. Biophys. Acta*, **354**, 139 (1974).
2) For example, see: *a*) G. Weber and F.W.J. Teale, "The Proteins," ed. by H. Neurath, Academic Press, New York, Vol. 3, 1965, p. 445; *b*) L. Brand and B. Witholt, "Methods in Enzymology," Academic Press, New York, Vol. 11, 1967, p. 776; *c*) C.R. Cantor and T. Tao, "Procedures in Nucleic Acid Research," Vol. 2, ed. by G.L. Cantoni and D.R. Davis, Harper & Row, Publishers, New York, 1971, p. 31; *d*) L. Brand and J.R. Gohlke, *Ann. Rev. Biochem.*, **41**, 843 (1972).
3) *a*) Y. Kanaoka, M. Machida, K. Ando, and T. Sekine, *Biochem. Biophys. Acta*, **207**, 269 (1970), and papers cited therein; *b*) T. Sekine, T. Ohyashiki, M. Machida, and Y. Kanaoka, *ibid.*, **351**, 205 (1974); *c*) K. Kimura, A. Watanabe, M. Machida, and Y. Kanaoka, *Biochem. Biophys. Res. Comm.*, **43**, 882 (1971); *d*) T. Sekine, K. Ando, M. Machida, and Y. Kanaoka, *Anal. Biochem.*, **48**, 557 (1972); *e*) M. Machida, T. Sekine, and Y. Kanaoka, *Chem. Pharm. Bull.* (Tokyo), **22**, 2642 (1974).
4) *a*) Y. Kanaoka, M. Machida, M.I. Machida, and T. Sekine, *Biochim. Biophys. Acta.*, **317**, 563 (1973); *b*) T. Ohyashiki, T. Sekine, and Y. Kanaoka, *ibid.*, **420**, 27 (1976).
5) *a*) M. Machida, N. Ushijima, M.I. Machida, and Y. Kanaoka, *Chem. Pharm. Bull.* (Tokyo), **23**, 1385 (1975); *b*) T. Sekine, *Seikagaku*, **47**, 441 (1975).