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NEW PROSTAGLANDIN SYNTHON FROM AN 4-OXA-TRICYCLO[4.3.0.0^{3,7}]-NON-8-ENE SYSTEM. A TOTAL SYNTHESIS OF (±)-PROSTAGLANDIN F$_{2\alpha}$*

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The C-9 tricyclic heterocycle(1) is shown to be a new starting material for a synthesis of (±)-prostaglandin F$_{2\alpha}$ through the C-9 acetylenic intermediate(10).

The synthesis of the C-9 prostaglandin intermediate(11), which may serve as a versatile synthon comparable to the Corey prostaglandin aldehyde(12)[1], from 5-trichloromethyl-4-oxa-tricyclo[4.3.0.0.^{3,7}]non-8-ene(1)[2] has recently been reported by this group.[3] This communication deals with a further utility of the C-9 tricyclic heterocycle(1) to allow the alternative approach to prostaglandins *via* the C-9 acetylenic intermediate(10)[4].

The tricyclic heterocycle(1), prepared by following Fritz et al.,[2] was treated with 3.3 molar equiv of n-butyllithium in a 1:1 mixture of ether and tetrahydrofuran[5] at -78° for 2h to give the bicyclic acetylene(2)[6] as a colorless oil, bp 29-30°(0.09 torr), ν_{max}^{neat} 3540, 3400, 3275, 3050, 2110, 1570, 1055, δ^{CDCl_3} 1.90 (2H, m), 2.30(1H, d, J=2.5 Hz), 2.69(1H, br.s), 2.80(1H, br.s,

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*Dedicated to Emeritus Professor Dr. Shigehiko Sugasawa, University of Tokyo, on his 80th birthday.

disappeared with D_2O), 2.94(2H, br.s), 3.83(1H, br.s), 6.59(2H, m), m/e 134(M^+), 90(base peak), in 82 % yield. This compound, upon treatment with *p*-toluenesulfonyl chloride in pyridine at room temperature, yielded the practically pure tosylate(3) almost quantitatively, as a pale yellow oil, ν_{max}^{neat} 3265, 3050, 1595, 1570, 1350, 1170, δ^{CDCl_3} 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, dd, J=6.5 and 3.5 Hz), 6.14(1H, dd, J=6.5 and 3.0 Hz), 7.72(2H, d, J=8.5 Hz), 7.80(2H, d, J=8.5 Hz), which without purification was warmed at 55 to 57° for 63 h in acetic acid in the presence of potassium acetate to give the oily tricyclic acetate(4) exclusively in 92 % yield as a 1:1 inseparable mixture, bp 53-55°(0.55 torr), ν_{max}^{neat} 3265, 3050, 2115, 1725, 1235, δ^{CDCl_3} 1.19-1.67(3H, m), 1.83(1H, br.s), 1.95-2.26(2H, m), 2.01 (3H, s), 2.07(1H, d, J=2.5 Hz), 2.49(0.5H, br.s), 2.91(0.5 H, br.s), 4.57(0.5H, br.s), 4.73(0.5H, br.s), m/e 176(M^+), 43(base peak). Since the epimeric center was lost in the later synthetic stage, an exclusive formation of the tricyclic acetate(4) which could be resulted from a steric effect of the acetylenic group in the solvolysis[3] was very advantageous for the present research. Cleavage of the acetoxyl group in <u>4</u> with potassium carbonate in ethanol at room temperature for 3.5 h afforded an epimeric mixture of alcohols(5) in 98 % yield as a colorless oil, bp 53.5-54.0°(0.16 torr), ν_{max}^{neat} 3300, 3275, 3050, 2110, 1070, δ^{CCl_4} 1.00-1.53(3H, m), 1.63-2.00(3H, m), 1.90(1H, d, J=2.5 Hz), 2.29(0.5 H, br.s), 2.89(0.5H, br.s), 3.36(1H, br.s, disappeared with D_2O), 3.68(0.5H, br.s), 3.83(0.5 H, br.s), m/e 134(M^+), 116(base peak), which on oxidation with Jones reagent at room temperature gave a 61 % yield of the ketone(6) as a colorless oil, bp 38-40° 0.18 torr), ν_{max}^{neat} 3270, 1755, δ^{CCl_4} 1.29(1H, t), 1.73-2.40(5H, m), 2.07(1H, d, J=2.5 Hz), 2.90(1H, br.s), m/e 132(M^+), 103(100 %). Exposure of the tricyclic ketone(6) to 1.1 molar equiv of 48 % hydrobromic acid in boiling acetic acid[7] for 3 h brought about a highly regio- and stereospecific cleavage of the cyclopropane ring to give an 87 % yield of the bicyclic bromo ketone(7) as colorless needles, mp 68-69°, ν_{max}^{Nujol} 3270, 1740, δ^{CDCl_3} 2.05(2H, m), 2.40(1H, d, J=2.5 Hz), 2.42(1H, m), 2.80(2H, m), 3.06(2H, m), 4.03(1H, m), m/e 214, 212(M^+), 40(base peak).

Baeyer-Villiger oxidation of the bromo ketone(7) using 1.2 molar equiv of *m*-chloroperbenzoic acid in methylene chloride at room temperature for 72 h produced the bromo lactone(8) in 79 % yield as colorless needles, mp 127-129°, ν_{max}^{Nujol} 3245, 1735, 1155, δ^{CDCl_3} 2.40(1H, d, J=2.5 Hz), 2.66-3.25(6H, m), 4.27(1H, m), 4.88 (1H, br.s), m/e 230, 228(M^+), 39(base peak), which on heating in boiling ethanol in the presence of a catalytic amount of *p*-toluenesulfonic acid for 4h afforded the oily monocyclic bromo ester(9), ν_{max}^{neat} 3480, 3280, 2110, 1720, 1180, δ^{CDCl_3} 1.32(3H, t, J=7.2 Hz), 2.21-3.28(8H, m, disappeared 1H with D_2O), 4.25(4H, m), m/e 276, 274(M^+), 91(base peak), in a 96 % yield. Baeyer-Villiger oxidation of the bromo ketone(7) with 1.2 molar equiv of *m*-chloroperbenzoic acid in chloroform at room temperature for 72 h, followed by refluxing the reaction mixture with ethanol for 4 h led directly to the bromo ester(9) in a 98 % over-all yield.

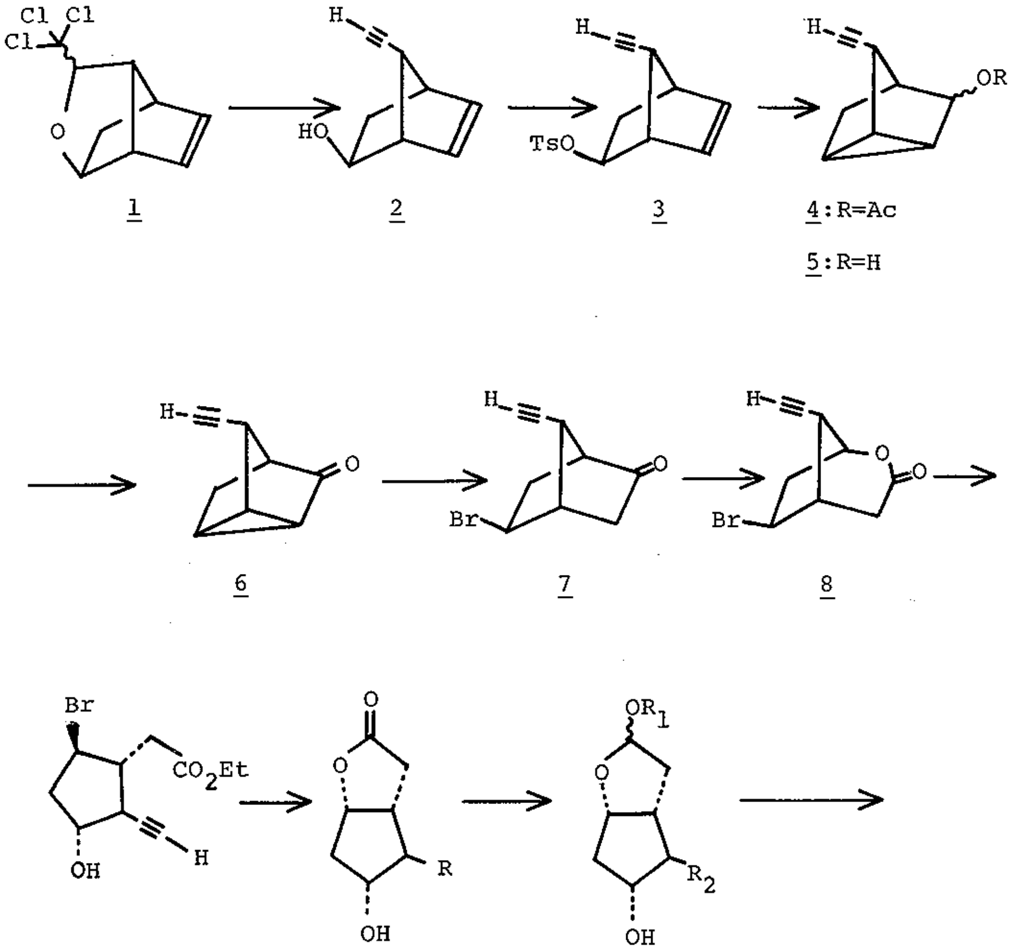
Conversion of the bromo ester(9) into the bicyclic γ-lactone (10) was accomplished by two methods, though both in dissatisfactory yield. In the first method, the lactone(10), colorless needles, mp 79-80°, ν_{max}^{Nujol} 3400, 3260, 3240, 1755, 1215, 1085, δ^{CDCl_3} 2.20(1H, d, J=2.5 Hz), 2.36(2H, m), 2.57(1H, br.s, disappeared with D_2O), 2.63-2.90(3H, m), 3.08(1H, m), 4.41(1H, m), 5.14(1H, m), m/e 166(M^+), 77(base peak), was obtained in a 10 % yield by treating 9 with 1.2 molar equiv of silver perchlorate in aqueous dimethoxyethane at room temperature[3] for 4 h, while in the second method, 10 was obtained in an 18 % yield by refluxing 9 with sodium hydroxide in aqueous ethanol for 2.5 h.

Transformation of the bicyclic lactone(10) into the known prostaglandin intermediate[1](16) was carried out in a 20 % over-all yield by the following sequence. Reduction of the lactone(10) with diisobutylaluminum hydride in a 1:1 mixture of benzene and toluene at -15 to -20° for 1 h gave an epimeric mixture of lactols(13), ν_{max}^{neat} 3375, 3270, 2100, 1080, 1030, which, without purification, was converted into an epimeric mixture of acetals(14), an oil, ν_{max}^{neat} 3380, 3270, 2100, 1090, 1040, δ^{CDCl_3} 2.07(1H, d, J=2.5 Hz), 1.93-3.13(6H, m), 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), in a 47 % over-all yield, by treating with methyl orthoformate in boiling methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid. Metalation of 14 with 2.2 molar equiv of n-butyllithium in a 1:1 mixture of ether and tetrahydrofuran[4] at -78° for 1.5 h, followed by treating with 2.2 molar equiv of n-hexanal at the same temperature and stirring at room temperature for 2 h produced an epimeric mixture of acetylene diols(17) as a colorless oil in a 52 % yield, ν_{max}^{neat} 3300, 2220, 1090, 1050, δ^{CDCl_3} 0.93(3H, t, J=5 Hz), 1.13-1.93(8H, m), 1.97-3.06(6H, m), 3.35(1.8H, s), 3.40(1.2H, s), 3.97(3H, m), 5.12(1H, m), m/e 251(M^+-31), 41(base peak).

The epimeric mixture of acetylene diols(17) was also obtained by a similar conversion from the ketene dichloride intermediate (11) which has been synthesized from the C-9 tricyclic·heterocycle (1)[3]. Thus the ketene dichloride(11) was reduced with diisobutylaluminum hydride in a mixture of toluene and benzene(1:1) at -20° for 30 min to form an epimeric mixture of the lactols(15), colorless oil, ν_{max}^{neat} 3350, 3020, 1615 cm^{-1}, which was treated with methyl orthoformate as above to give an epimeric mixture of the cyclic acetals(16) in 78 % overall yield, colorless oil, ν_{max}^{neat} 3380, 1615, 1090, 1040 cm^{-1}, δ^{CDCl_3} 1.88-2.87(7H, m), 3.28(1.8H, s), 3.36(1.2H, s), 3.91, 4.53, 5.10(each 1H, each m), 5.70(1H, d, J=9 Hz),m/e 221, 223, 225(M^+-OMe), 58(100 %). Upon treating with 3.3 molar equiv of n-butyllithium at -78° in a mixture of ethyl ether and tetrahydrofuran[4](1:1), followed by with 3.3 molar equiv of n-hexanal as above, the cyclic acetals(16) afforded an epimeric mixture of acetylene diols(17) in 58 % yield. Stereoselective reduction of the acetylene group in the compounds(17) was carried out by treating with lithium aluminum hydride in boiling tetrahydrofuran to afford the known trans allyl alcohol(18)[8] in an 84 % yield, ν_{max}^{neat} 3350, 1090, 1050, 970, δ^{CDCl_3} 0.94(3H, t, J=5.0 Hz), 1.12-1.75(8H, br.s), 1.91-2.63(6H, m), 2.92(2H, s, disappeared with D_2O), 3,35(1.8H, s), 3.39(1.2H, s), 3.95(2H, m), 4.56(1H, m), 5.13(1H, m), 5.57(2H, m), m/e 253(M^+-31), 99(base peak), accompanied with a 10 % yield of the allenic by-product (20), a colorless oil, ν_{max}^{neat} 3350, 1950, 1090, 1050, δ^{CDCl_3} 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), m/e 235(M^+-31), 80(base peak).

By following Corey's procedure[9], the acetal(18) was hydrolyzed with diluted hydrochloric acid to give an epimeric mixture of lactols(19) which upon treatment with the Wittig reagent prepared from 5-triphenylphosphoniopentanoic acid and sodio methylsulfinylcarbanide in dimethylsulfoxide gave a 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), mp 15-20°[10], and (±)-15epi-prostaglandin $F_{2\alpha}$(21, C-15epi), an oil, which were identical spectroscopically and chromatographically with the authentic materials[11].

Since the ketal(18) has been successfully transformed into prostaglandin E_2[11], the C-9 acetylenic compound(10) obtained as described may also be used as a synthon for the E, A and B series of prostaglandins.



1 2 3

4: R=Ac

5: R=H

6 7 8

9

10: R=C≡CH

11: R=CH=CCl$_2$

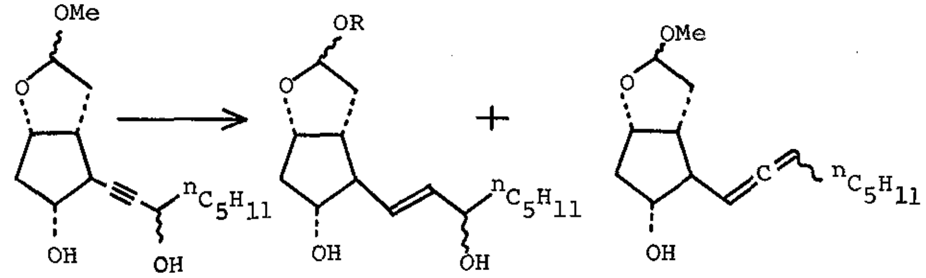
12: R=CHO

13: R$_1$=H, R$_2$=C≡CH

14: R$_1$=Me, R$_2$=C≡CH

15: R$_1$=H, R$_2$=CH=CCl$_2$

16: R$_1$=Me, R$_2$=CH=CCl$_2$

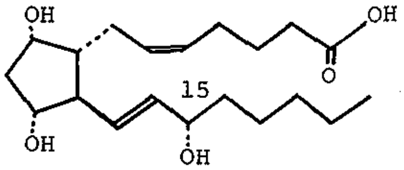


17

18: R=Me

19: R=H

20



21

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4 Synthesis of the C-9 acetylenic compound(10) from the Corey aldehyde(12) *via* the ketene dichloride(11) and its conversion into the prostaglandin derivatives have been claimed by the Ciba-Geigy group in a patent(Japan Kokai 49-82650).

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