CHEMISTRY LETTERS, pp. 175-176, 1980. © The Chemical Society of Japan 1980

SYNTHESIS OF NOVEL PROSTANOIDS HAVING A CYCLOPENTA[*c*]FURAN STRUCTURE WITH A HEMITHIOACETAL SIDE CHAIN FROM AUCUBIN[1)]

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The titled prostanoids, methyl (*Z*)-7-[(3aR,5S,6R,6aR)-1-(2-substituted-2-hydroxyethylthio)-5-hydroxy-hexahydro-1*H*-cyclopenta-[*c*]furan-6-yl]-5-heptenoates, were prepared from aucubin *via* hemithioacetalization in construction of the alkyl-end(C_{13}-C_{20}) side chain.

In previous papers[1a-d)] we have reported the synthesis of chiral prostanoids from aucubin 1[2)] through two different routes concerning the introduction of alkyl-end(C_{13}-C_{20}) side chain to the intramolecular bicyclic acetal moiety of the tetrahydroanhydroaucubigenin derivatives. One includes the titanium tetrachloride promoted aldol condensation of the acetal with an enol acetate.[1a,c,d)] In the other one stepwise cleavage of the acetal was accomplished by utilizing thioacetal-acetal exchange *via* the cyclic hemithioacetal intermediate.[1b)] In connection with our interest in the structure-activity relationship of prostaglandin congeners, we attempted the synthesis of the titled compounds having a thioacetal-type alkyl-end (C_{13}-C_{20}) side chain from the hemithioacetal intermediate 3, easily prepared from aucubin 1 by the reported method.[1b)]

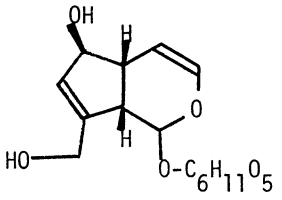
The benzoate of tetrahydroanhydroaucubigenin-epimer, 2[1a)] (1 mmol), derived from aucubin 1, was treated with an excess of ethanethiol(0.5 ml) in the presence of boron trifluoride etherate(2.4 mmol) in 1,2-dimethoxyethane(10 ml) at 20 °C for 20 h to give the hemithioacetal 3[3,4)] [colorless oil, NMR(δ ppm);1.30(3H, t, 7.5Hz), 1.7-3.0(10H), 3.8-3.9(3H), 4.20(1H, dd, 9Hz, 6Hz), 5.5(1H), 5.57(1H, d, 4Hz), 7.3-7.7(3H), 7.9-8.2(2H)] in quantitative yield. The Collins oxidation(CrO_3·2Py 57 mmol in dichloromethane 150 ml) of 3(9.42 mmol) at 0 °C for 30 min and subsequent alkaline hydrolysis(0.33 M KOH in MeOH-H_2O 2:1 30 ml) at 20 °C for 17 h produced the hemiacetal 4[3)] in 70% yield.

The Wittig condensation of crude 4(6.52 mmol) with the ylide from (4-carboxybutyl)-triphenylphosphonium bromide(19.5 mmol) and sodium methylsulfinylmethide(37 mmol) in dimethyl sulfoxide[8)] (40 ml) at 20 °C for 5 h followed by esterification with diazomethane and deprotection of hemithioacetal using $CuCl_2$(1 eq)-CuO(2 eq) in aqueous acetone(1% H_2O) at 20 °C for 2 h[5)] afforded the hemiacetal 5[3,4)] [colorless oil, NMR(δ ppm); 1.4-2.6(15H), 3.67(3H, s), 3.7-4.1(3H), 5.4(2H), 5.53(1H, d, 3Hz)] in 45% yield from 4.

The common intermediate 5, obtained above, could be readily converted into the prostanoid 6 or 7 by hemithioacetalization using 2-substituted-2-hydroxyethane-1-thiols[6)] in a good yield. Thus, treatment of 5(0.53 mmol) with 2 eq of 3-(3-chlorophenoxy)-2-hydroxypropane-1-thiol and excess boron trifluoride etherate(3.2 mmol)

in 1,2-dimethoxyethane(10 ml) in the presence of molecular sieves 4A for 17 h at 20 °C followed by purification by silica gel chromatography(cyclohexane-ethyl acetate) afforded a 1:1 C-15 epimeric mixture of the prostanoid 7[3,4] in 85% yield [polar C-15 epimer 7a: colorless oil, NMR(δ ppm); 1.5-3.1(15H), 3.67(3H, s), 3.7-4.4(7H), 5.44(2H), 5.52(1H, d, 3Hz), 6.7-7.3(4H), IR(ν cm^{-1}); 3450, 2935, 2860, 1740, 1595, 1480, 1435, 1280, 1240, 1070, 1030, 970, 905, 860, 775, less polar C-15 epimer 7b: colorless oil, NMR(δ ppm); 1.5-3.1(15H), 3.67(3H, s), 3.7-4.4(7H), 5.4(2H), 5.55(1H, d, 3Hz), 6.7-7.3(4H)]. Further, the reaction of 5 with 2-hydroxyheptane-1-thiol produced the prostanoid 6[3,4] in 86% yield. The acetal carbons of 6 and 7 have tentatively be assigned the (R) configuration in consideration of the preferential nucleophilic attack of the thiol from less hindered β-side of the molecule.

Bioassay of the polar isomer 7a on the termination of pregnancy(hamster) exhibited about 1/10 activity of prostaglandin $F_{2\alpha}$, while exhibiting only 1/500 activity on the contraction of smooth muscle(hamster stomach fundus).[7] Details of biological activity for these prostanoids will be reported elsewhere.



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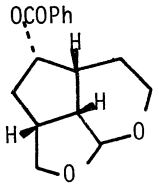

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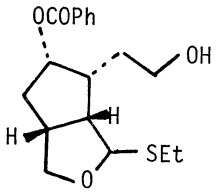

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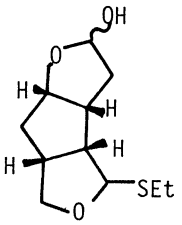

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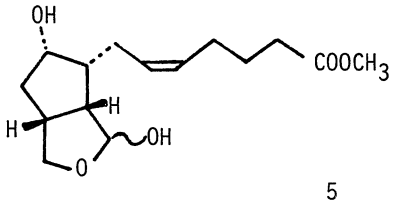

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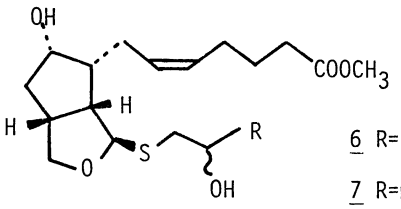

6 R=n-C_5H_{11}-

7 R=m-$ClC_6H_4OCH_2$-

References and Notes

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(Received November 28, 1979)