Tetrahedron Letters No. 26, pp 2627 - 2630, 1972. Pergamon Press. Printed in Great Britain.

# SYNTHESIS OF PROSTAGLANDIN ANALOGS BY NOVEL 1,4 ADDITION REACTIONS

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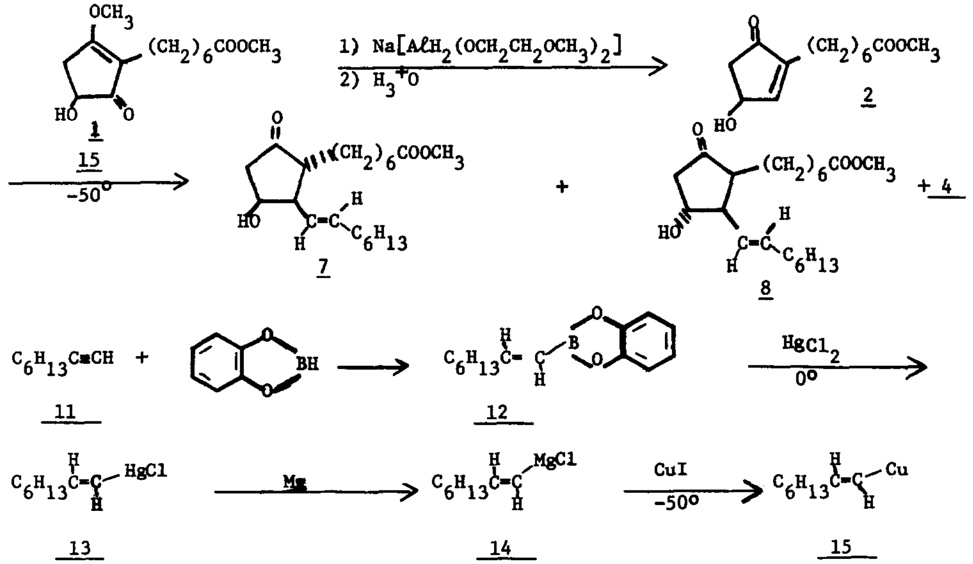
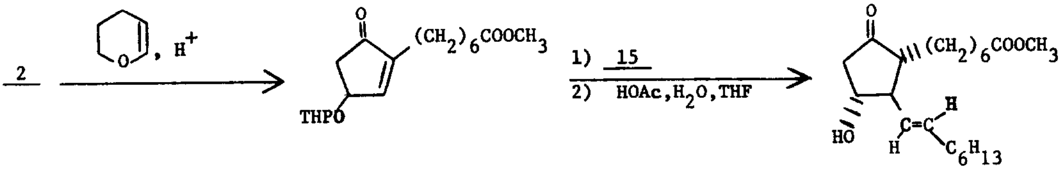
(Received in USA 1 May 1972; received in UK for publication 22 May 1972)

In 1969 we initiated a program to study the application of 1,4 addition reactions to the synthesis of prostaglandins. Recent publications [1,2] corroborating some of our work have prompted us to report the preliminary results of our efforts.

The key intermediate 2 mp 49-51° [1,3] was prepared by reduction of 1[4] with sodium dihydro-bis(2-methoxyethoxy)aluminate in toluene at -60° followed by acidification. Treatment of 2 directly with trans 1-octenylcopper (15) in tetrahydrofuran at -50° gave a mixture of three isomers which were separated by column chromatography and identified by PMR analysis [5] as (±)-11-epi-15-deoxy $PGE_1$ methyl ester (7), PMR: δ=5.59, $C_{13}$ and $C_{14}$ [m]; δ=4.30, $C_{11}$ [d (1.9) t (3.5)], (±)-15-deoxy $PGE_1$ methyl ester (4), PMR: δ=5.67, $C_{14}$ [d (15.2) t (6.3)]; δ=5.30, $C_{13}$ [d (15.2) d (8.0)]; δ=4.03, $C_{11}$ [d (9.3) t (7.5)]; δ=2.72, $C_{10}$ [d (18.1) d (7.5)], and (±)-8-iso-15-deoxy $PGE_1$ methyl ester (8) which isomerized to 4 on standing.



However conversion of 2 to its tetrahydropyranyl ether 3 prior to treatment with 15 resulted in a stereospecific synthesis of (±)-15-deoxy $PGE_1$ methyl ester 4 which was obtained after removal of the tetrahydropyranyl group [6] (yield of 4 was 50% after chromatography).



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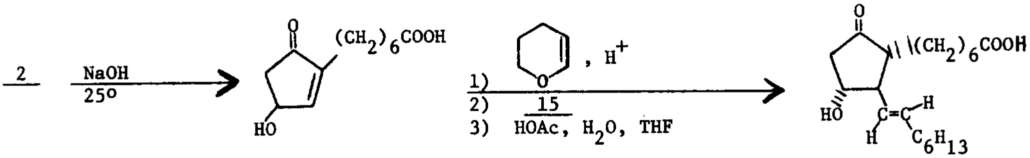
Treatment of 2 with one equivalent of sodium hydroxide at 25° gave the free acid 5 [3]. The bis-tetrahydropyranyl derivative of 5 yielded (±)-15-deoxy $PGE_1$ (6) mp 34-35° upon reaction with 15 and subsequent hydrolysis. In an analogous manner (±)-11,15-bisdeoxy $PGE_1$ (10), PMR[5]: $\delta$=5.41, $C_{13}$, $C_{14}$ [m], was prepared by treatment of 2-(6'-carboxyhexyl)-2-cyclopenten-1-one (9)[7] with 15.



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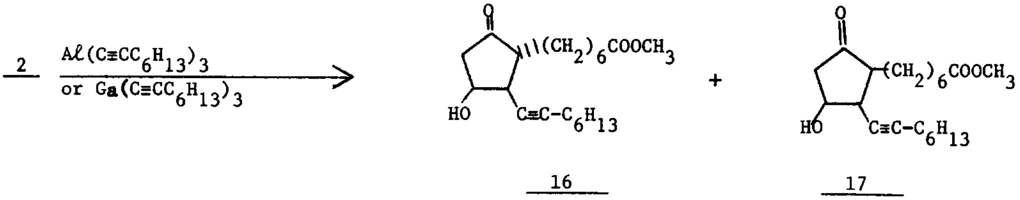
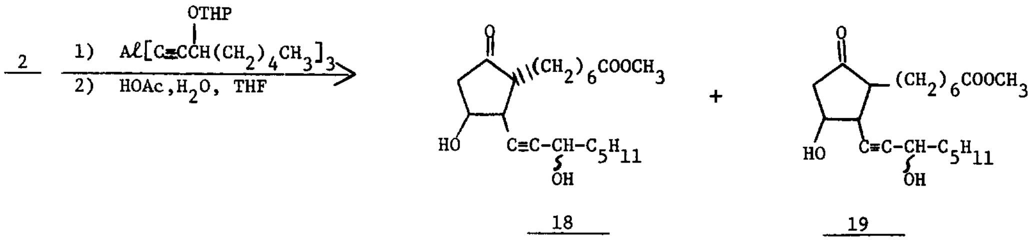
The synthesis of 15 was begun by treatment of 1-octyne 11 with catechol borane [8] in refluxing tetrahydrofuran to produce stereospecifically the trans 1-octenylborane derivative 12. Without isolation, 12 was treated with mercuric chloride at 0° to give trans 1-octenylmercuric chloride (13) mp 104-105°. Reaction of 13 with powdered magnesium in tetrahydrofuran at toom temperature gave the Grignard reagent 14. When contacted with cuprous iodide at -50°, 14 was converted to the required 15 which was used *in situ* at -50°.

Our attention was also turned to the study of the addition of metal acetylides, to $\alpha,\beta$ unsaturated ketones in general and to 2 and 9 in particular. We found that, although copper acetylides were too unreactive, trioctynylboron [9] and trioctynylaluminum [9] would add readily 1,4 to pregnenolone acetate yielding the 16-octynyl derivative. However 17-acetoxy-1-androstene-3-one and 9 did not give the expected 1,4 addition products with trioctynylaluminum.

Interestingly when 2 was treated with trioctynylaluminum in ether at room temperature 1,4 addition did occur to yield a mixture of two isomers. These were separated by chromatography and identified by PMR [5] as methyl (±)-11$\beta$-hydroxy-9-oxoprost-13-ynoate (16) mp 32°, PMR: δ=4.40, $C_{11}$ [d (1.0) t (4.0)]; δ=2.78, $C_{12}$ [d (11.2) d (3.7) t (2.0)]; δ=2.56, $C_{10}$ [d (18.2) d (1.0)]; δ=2.27, $C_{10}$ [d (18.2) d (4.5)] and methyl (±)-11β-hydroxy-9-oxo-8-isoprost-13-ynoate (17) mp 41-42°, PMR: δ=4.32, $C_{11}$ [d (8.0) d (6.5) d (5.5)]; δ=3.41, $C_{12}$ [d (7.5) d (5.5) t (1.5)]; δ=2.61, $C_{10}$ [d (18.5) d (7.0)]; δ=2.27, $C_{10}$ [d (18.5) d (8.5)] which could be isomerized to 16 on treatment with potassium acetate in ethanol. 16 and 17 were obtained in approximately a 1:2 ratio. Interestingly, use of the corresponding trioctynylgallium reagent reversed this ratio. The fact that the entering octynyl radical added cis to the hydroxy group of 2 indicated participation of that neighboring group in the 1,4 addition process probably by way of a cyclic intermediate. Moreover, blockage of the hydroxy group of 2 by a tetrahydropyranyl group prevented reaction with the aluminum reagent.

In an analogous fashion 2 was allowed to react with tri(3-tetrahydropyranyloxy-1-octynylaluminum)[9] to give, after hydrolysis and chromatography, methyl (±)-11β,(15RS)-dihydroxy-9-oxoprost-13-ynoate (18), PMR: δ=4.39, $C_{11}$, $C_{15}$ [m]: δ=2.74, $C_{12}$ [d (11.2) t (1.8)] and methyl (±)-11β,(15RS)-dihydroxy-9-oxo-8-iso-prost-13-ynoate (19) mp 84-85°, PMR: δ=4.39, $C_{11}$ [m]; δ=3.45, $C_{12}$ [t (6.5)]; δ=2.64, $C_{10}$ [d (18.6) d (7.0)][5]. The corresponding gallium reagent did not react with 2. The reaction of 2 with trioctynylboron is currently under study: preliminary results indicate the presence in the reaction mixture of 16, 17 and methyl (±)-11α-hydroxy-9-oxo-8-isoprost-13-ynoate, PMR: δ=4.56, $C_{11}$ [d (5.1)]; δ=3.16, $C_{12}$ [broadened d (ca. 8)]; δ=2.66, $C_{10}$ [d (18.5) d (5.0)][5].





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5. Centers of bands are given in PPM with reference to internal tetramethylsilane. Splittings are given in Hertz and are not necessarily coupling constants.

   The PMR analyses were done in collaboration with R. H. Bible and L. Swenton and will be reported in detail at a later date: the arrangement of the 2 side-chains at $C_8$ and $C_{12}$ was deduced from the magnitude of $J_{C\text{-}12H,C\text{-}8H}$ (about 7Hz for the cis and 11Hz for the trans). The relationship of the $C_{11}$ hydroxyl group to the $C_{12}$ proton was determined primarily by the coupling of the $C_{11}$ proton to neighboring protons and by the position of the $C_{12}$ proton signal.
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9. Conveniently prepared by reaction of the appropriate metal trichloride with the appropriate 1-octynyllithium.