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INFLUENCE OF THE POSITION OF THE SIDE CHAIN HYDROXY GROUP ON THE BIOLOGICAL PROPERTIES OF PROSTAGLANDINS[1]

P W Collins, E Z Dajani, M S Bruhn, C H Brown, J R Palmer and R Pappo*

Departments of Chemical and Biological Research,
Searle Laboratories, P O Box 5110, Chicago, Illinois 60680

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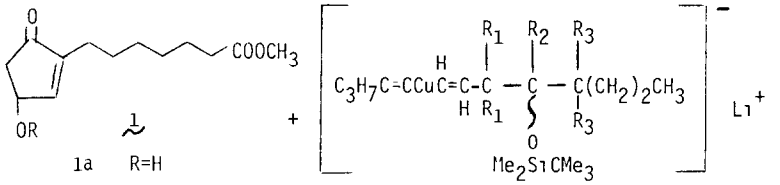
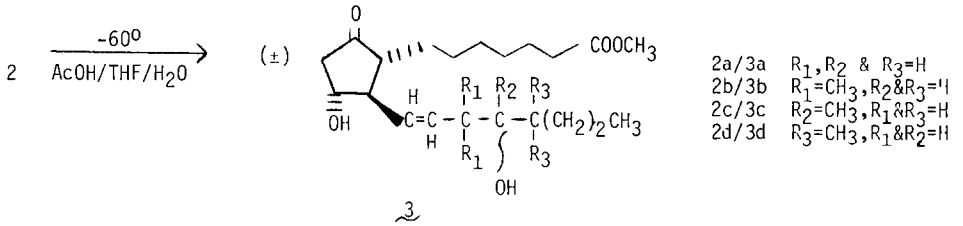
In our efforts to eliminate the unwanted side effects and to enhance the oral activity of prostaglandins we studied the influence of the position of the side chain hydroxy group on the biological properties of prostaglandin E_1

The preparation of (±)-15-deoxy-16-hydroxy PGE_1 methyl ester (3a), PMR δ=5 74, C_{14} [d(15 5 t(7 0)], δ=5 4, C_{13}[d(15 5) d(7 3)], δ=4 06, C_{11}[t(9 2) d(7 5)] was accomplished utilizing the stereospecific 1,4 addition reaction of the cuprate reagent 2a with 1b[2] followed by mild acidic hydrolysis and purification by chromatography Yield of 3a from 1b was 55%



1a R=H
1b R=THP

2



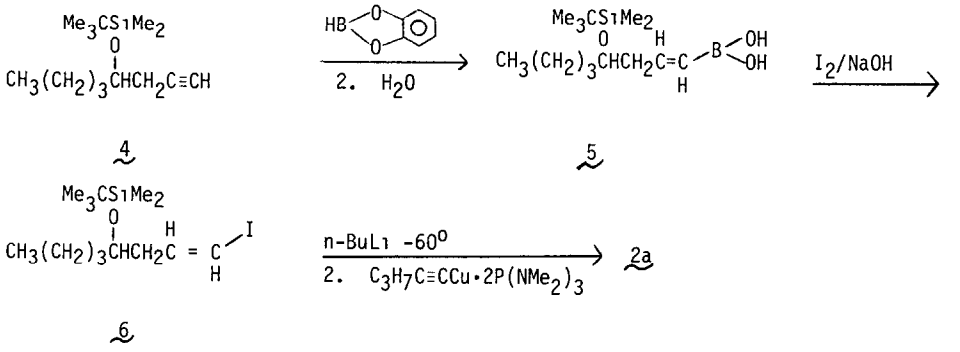
2a/3a R_1,R_2 & R_3=H
2b/3b R_1=CH_3,R_2&R_3=H
2c/3c R_2=CH_3,R_1&R_3=H
2d/3d R_3=CH_3,R_1&R_2=H

3

To prepare the cuprate reagent 2a, the t-butyldimethylsilyl ether of 1-octyn-4-ol 4 was allowed to react neat at room temperature with catechol borane[3] followed by hydrolysis to obtain the trans-boronic acid[4] 5. Iodine and sodium hydroxide treatment of 5 yielded the trans vinyl iodide 6, PMR δ6 58 C_2 m, δ6 01 C_1[d(15)] Treatment of 6 with one equivalent of n-butyl lithium at -60°, followed by addition of an ethereal solution of pentynyl copper solubilized with hexamethyl phosphorus triamide[5], gave 2a Yield of 6 from 4 was 45%

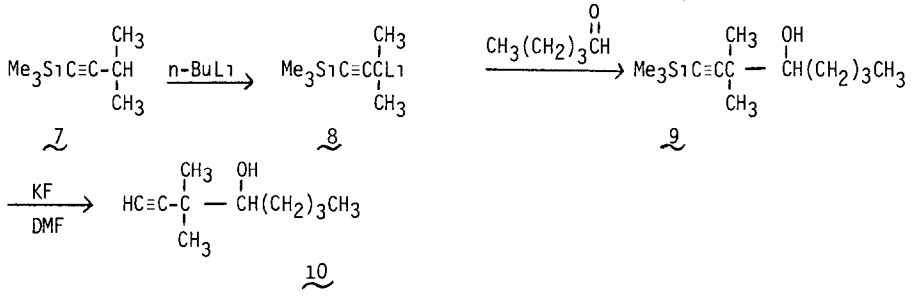
Although 3a was only weakly active in typical prostaglandin screening tests such as the gerbil colon stimulation and platelet aggregation inhibition assays, it was as active as PGE_1 methyl ester in inhibiting stimulated gastric acid secretion in the Heidenhain pouch dog assay[6] Additionally it had a lower degree of side effects than PGE_1 methyl ester These findings encouraged us to prepare some alkylated derivatives of 3a

Three alkylated derivatives, 3b, PMR (CD_3OD) δ5 69, C_{14}[d(16 0)], δ5 46, C_{13}[d(16 0)



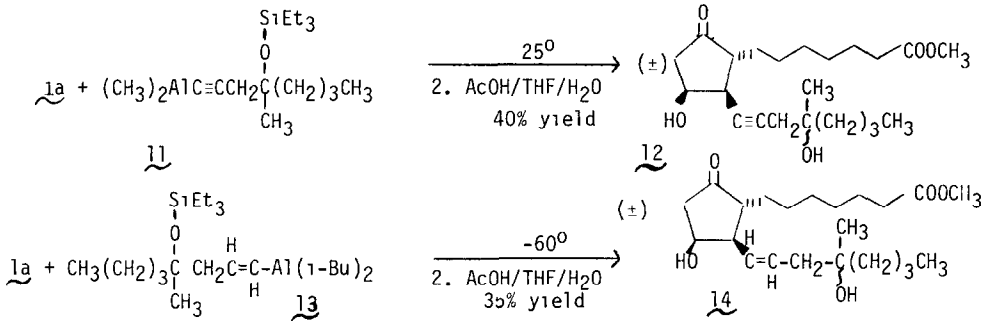
d(7 5)]; δ1 01, 1 03, 1 05, 1 05(S) CH_3 groups at C_{15}, 3c, PMR δ4 07, C_{11}[d(8 ?)t(7 5)], δ2 73 C_{10} [d(18 0) d(7 5)], δ1 19, CH_3 at C_{16}(s), 3d, PMR δ3 44, C_{16}[d(6 5)d(1 0)], δ 87, δ 89 CH_3's at 17] were synthesized via the mixed cuprate reaction just described The appropriate trans-vinyl iodides were prepared from the corresponding acetylenes by use of either catechol borane/iodide-sodium hydroxide or diisobutylaluminum hydride-iodine [7]

The 1-alkyn-4-ols employed in this work were prepared by addition of the grignard reagent derived from propargyl bromide to the appropriate carbonyl compound Synthesis of 3,3-dimethyl-1-octyn-4-ol 10, however, required a different approach The trimethylsilyl derivative of 3-methyl-1-butyne[8] was treated with one equivalent of n-butyl lithium, and the solution refluxed 24 hours to generate the lithio derivative 8. Addition of valeraldehyde followed by overnight stirring, acid work up and fractional distillation yielded 9 It is noteworthy that the silicon-carbon bond survived the 24 hour butyl lithium treatment [9] The trimethylsilyl group was removed by treatment with potassium fluoride in dimethylformamide[10] to give 10, PMR δ2 16, C_1, δ1 22, δ1 18, CH_3 groups at C_3 Yield of 10 from 7 was 15%



Taking advantage of our discovery that organoaluminum acetylenic reagents add 1,4 to 1d with participation of the hydroxy function to yield 11-epi prostaglandin derivatives[2], we used dimethyl 4-methyl-4-triethylsilyloxy-1-octynylalane[11] 11 to obtain 12, PMR δ4 45, C_{11}[d(1 0) t(4 0)], δ2 27, C_{12} [d(11 6)d(3 8) t(1 8)], δ1 18, C_{16} methyl group,(s) Similarly, we have recently found that the diisobutylaluminum hydride adduct of 4-methyl-4-triethylsilyloxy-1-octyne (13) upon reaction at -60° with 1a gives the 11-epi compound 14, PMR δ4 37, C11[m, w½~8], δ6 68, C_{13} and C_{14}(m) This very facile reaction was totally unexpected, especially when we

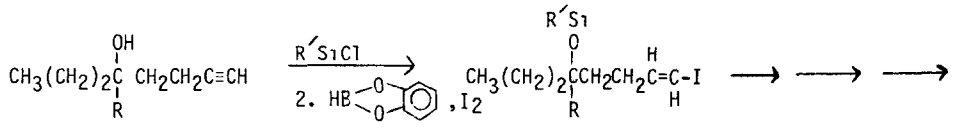
discovered that at room temperature 1,2 addition occurs exclusively [12] The implication is that at low temperature a free radical mechanism operates[13], whereas an ionic mechanism prevails at higher temperature



Of these alkylated derivatives, the 16-methyl compound 3c was found to be an extremely potent antisecretory agent when administered either intravenously or intragastrically [14] Surprisingly, it was devoid of antifertility properties at doses which inhibited gastric secretion Smooth muscle stimulant activity (gerbil colon) was minimal Interestingly, 3d was inactive as an antisecretory agent

Because of this important discovery, we decided to prepare the pure stereoisomer responsible for the activity of 3c Racemic 2c was added to (3R)-1b[15] to give a mixture of (11R, 16R)-3c ($[\alpha]_D^{25°}$(MeOH)= -55 5°) and (11R, 16S) -3c ($[\alpha_D^{25°}$(MeOH) = -54°) which were separated by chromatography In the same manner (11S, 16 S)-3c ($[\alpha]_D^{25°}$(MeOH)=+56 5°) and (11S, 16R)- 3c ($[\alpha]_D^{25°}$(MeOH) =+47.5°) were prepared from (3S)-1b and 2c. Only one of these isomers, (11R, 16S) -3c was active in the Heidenhain pouch dog assay [16]

The discovery of the unexpectedly potent and selective antisecretory activity in the 16-hydroxy series prompted us to investigate the effect of moving the hydroxy group further along the chain. Starting from 1-octyn-5-ol (15a) and 5-methyl-1-octyn-5-ol (15b) respectively, the conversion to the corresponding trans-vinyl iodides (16a & 16b) proceeded smoothly utilizing the catechol borane-iodine sequence. The respective lithium cuprate reagents were prepared from 16a and 16b and added to 1b to form 17a (PMR δ4.04,C11



15

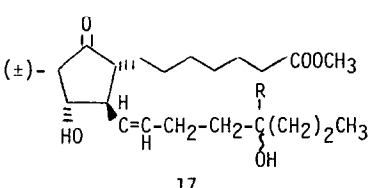
16

15,16,17a R=H

15,16,17b R=CH_3

R′= Me_3CMe_2 when R=H

R′= Et_3 when R=CH_3



17

Yield from 1b was 40%

[t(9.2) d(7.5)], and 17b (PMR δ5.72, C_{14}[d(15.5) t (6.3)], δ5.36, C_{13}[d(15.5) d(8)], δ1.19 (s), CH_3 group at C_{17}. Both 17a and 17b were essentially inactive in the gastric antisecretory and smooth muscle stimulation assays.

In conclusion, we found that shifting the 15-hydroxy group to carbon 16 of prostaglandins results not only in improving the antisecretory properties of the compounds but also in practically eliminating their unwanted smooth muscle stimulating action. Further displacement to the 17 position caused almost complete loss of activity in both areas

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4. The success of this reaction was highly dependent on the particular protecting group employed. Use of the relatively small trimethylsilyl group or groups containing oxygen such as tetrahydropyranyl resulted in either slight reaction or cleavage of the protecting group. An alternative method of producing trans- vinyl iodides (diisobutylaluminum hydride followed by iodine (G. Zweifel, J. Am. Chem. Soc., 89, 2754 (1967) was generally unsuccessful with this particular acetylenic alcohol With the exception of the bulky triphenylmethyl derivative which reacted quite smoothly, all protecting groups tried gave either a mixture of products or cleavage of the protecting group.
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7. Again the nature of the protecting group played an important role. With both reagents poor results were realized when either the trimethylsilyl group or oxygenated protecting groups were employed, whereas more bulky trialkysilyl groups provided the products in good yield. The triethylsilyl protecting group was preferred for these hindered alcohols because the reaction conditions required to remove the t-butyldimethylsilyl group following the cuprate reaction were too stringent to permit survival of the prostaglandin structure. The triethylsilyl group was readily cleaved under mild hydrolytic conditions.
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10. E.J. Corey, G.W.J. Fleet and M. Kato, Tetrahedron Letters, 3963 (1973).
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15. R. Pappo, P. Collins and C. Jung, Tetrahedron Letters, 943 (1973).
16. The 16S configuration was assigned solely on the basis of biological activity.