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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME PGE_1 CARBINOLS

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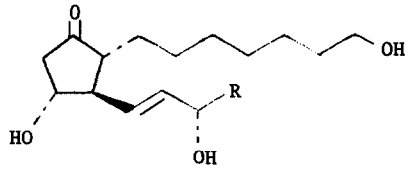
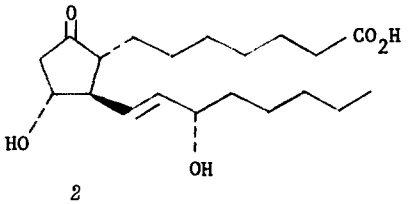
Broad prostaglandin-like activity has been reported for 1-prostanols such as the PGE_1-carbinol, *1a*.[1] However, when *1a* was prepared in our laboratories it was found to show marked selectivity in its biological activity as compared to PGE_1, *2*.[2] The carbinol was found to be a relaxant of guinea pig tracheal tissue at levels similar to those observed for PGE_1. On the other hand, the activity in the rat uterine strip *in vitro* and the cat and dog cardiovascular systems *in vivo* for *1a* was significantly less than that observed for *2*.



1a, R=n-C_5H_{11}



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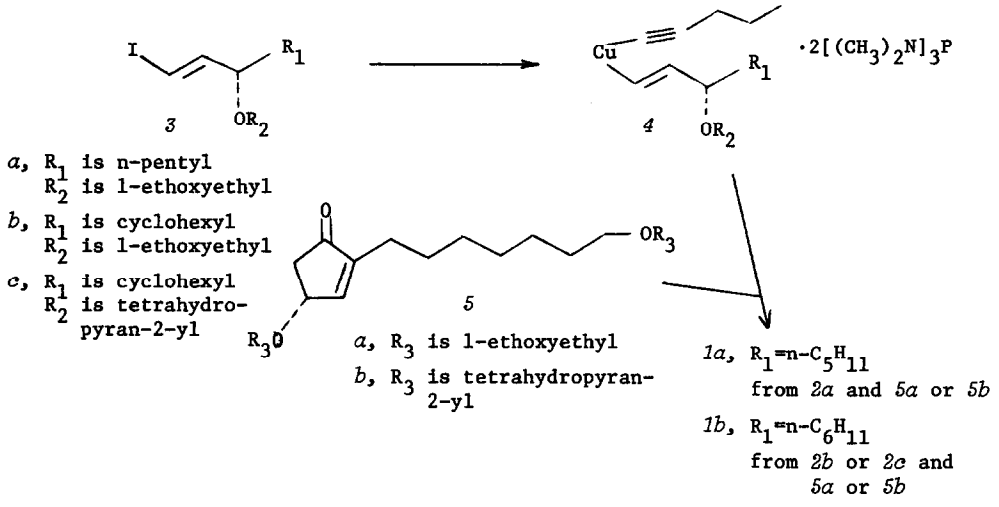
With these encouraging results in hand we set out to synthesize even more specifically-active analogs of *1a*. PGE_1, *2*, is used as a starting material in the original Pike process[1] for the preparation of *1a*. PGE_1 is an expensive material. A separate total synthesis would have to be conducted of each analog acid (or ester) if the Pike process were used for carbinol analog preparation. An efficient convergent synthesis of carbinol analogs is described in this communication.

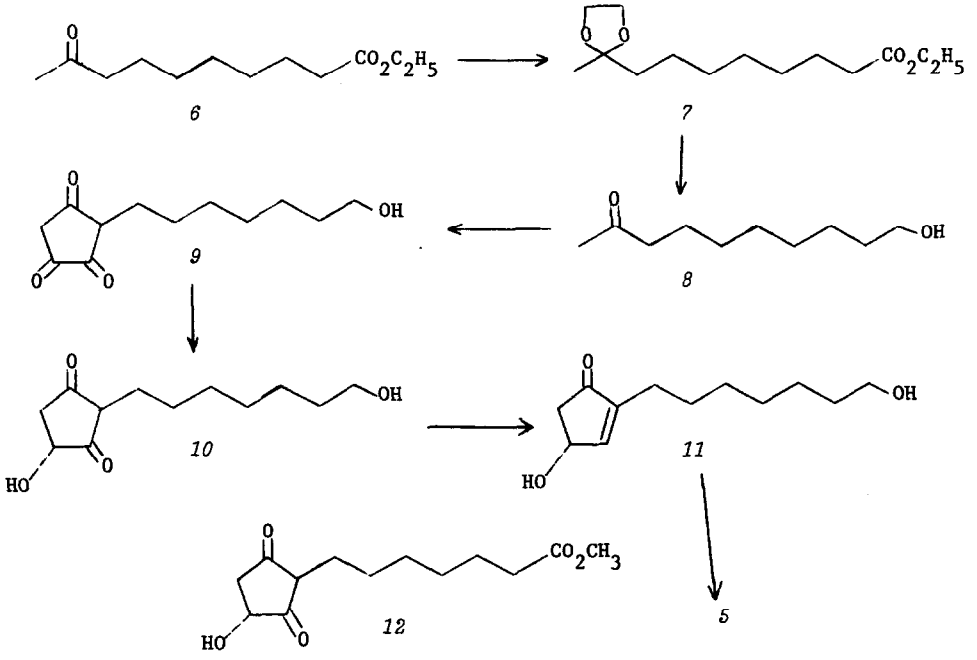
The key reaction in the synthetic sequence is the 1,4-conjugate addition of a Corey type alkenyl copper (I) reagent[3] of structure *4* to a cyclopentenone *5* followed by acid hydrolysis of the protecting groups to yield analogs of type *1*. Such reactions leading to ester analogs are well documented in the prostaglandin literature.[4] The syntheses of compounds having structure *3* are also well documented.[5] We herein report the preparation of key intermediate *5* an its use in the preparation of pharmacologically-interesting 1-prostanols.



Reaction of ethyl 9-oxodecanoate *6*[6] with ethylene glycol in benzene containing a trace of p-toluenesulfonic acid (reflux,Dean Stark trap) yielded *7* (84%, bp 101-110°/0.2 mm).[7] Reduction of *7* with Red-al[8] in ether followed by hydrolysis in 10% hydrochloric acid-methanol (2:1) afforded 9-oxodecan-1-ol, *8* (100%, bp 14-150°/0.2 mm). Basic condensation (ethanol, sodium ethoxide, 0° to reflux) of *8* with diethyl oxylate followed by reflux with 10% HCl yielded intermediate *9* (31%, mp 121-4°) which crystallized as the crude reaction mixture was cooled. Intermediate *9* was exposed to a culture of *Dipodascus uninucleatus* essentially as described by Sih[4] for the corresponding C-1 ester intermediate. The product *10* (70%, mp 101-4°) had the natural 11*R* configuration as evidenced by its CD spectrum $[\theta]_{281}$ -95,400° (*c*0.85, $CHCl_3$) which was identical to that observed for the corresponding C-1 ester intermediate, *12*, prepared by the Sih route. Compound *10* was treated sequentially with one equivalent of 2-mesitylenesulfonyl chloride and triethylamine (THF, 0°), Red-al[8] (THF, -78°) and chloroform/oxalic acid/sodium oxalate to yield *11* (38-50%, mp 62-4°). Finally *11* was converted to *5* by treatment with a trace of p-toluenesulfonic acid and ethyl vinyl ether (yielding *5A*) or dihydropyran (yielding *5B*) in ether. Prostaglandins with R_1=n-pentyl (*1a*) and R_1=cyclohexyl (*1b*) were prepared by treating *3a*, *3b*, or *3c* sequentially with two equivalents of t-butyllithium (ether-pentane, -78°, 2hr, argon), one equivalent of hexamethylphosphoroustriamide-solublized copper (I) pentyne[3] (ether, -78°, 15 min), 0.6-0.9 equivalent of either *5a* or *5b* (-78° to 0°, 2 to 4 hr) and then acetic acid-water-tetrahydrofuran (65:35:10, 30 min to 24 hr, room temperature).

The use of 1-ethoxyethyl rather than tetrahydropyran-2-yl protecting groups on *3* and/or *5* usually afforded higher yields of *1* (typical yields 20-50% based on *5*).

Analog *1b* (R_1=cyclohexyl) is a specific gastric antisecretory agent comparable to PGE_1 in this activity with only low or undetectable side-activities. Significant tracheal relaxant activity as observed with *1a* is not observed with *1b*. Analog *1b* does not cause diarrhea in the rat at 2 mg/kg and does not effect smooth muscle at doses at least 200 times those at which PGE_1 causes significant effects.[9,10]



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1. J. E. Pike; U. S. Patents 3,636,120 - Jan. 18, 1972; 3,723,528 - March 27, 1973; For a summary of these patents see J. C. Colbert, "Prostaglandins - Isolation and Synthesis" Noyes Data Corporation, Park Ridge, N.J., 1973, p 64-67.
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3. E. J. Corey and D. J. Beames, *J. Amer. Chem. Soc.*, 94, 7210 (1972).

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7. All compounds described herein were obtained as chromatographically homogeneous samples and had infrared, pmr and standard mass spectral data consistent with their assigned structures. Exact mass of parent or parent minus water signals and/or elemental analyses were also found to be within specifications on all compounds. R_f data was obtained on silica gel 60 F-254 plates and non-distillable intermediates were chromatographed on either silica gel 60 or silicic acid-Celite (8:2). In most cases no attempts were made to maximize yields.
8. Trademark of Aldrich Chemical Company, Inc., Milwaukee, Wisconsin 53233.
9. a) Gastric antisecretory test: H. J. Lipmann, *J. Pharm. Pharmacol.*, 21, 335 (1968).
   b) Smooth muscle tests: E. Hong, *Prostaglandins*, 8, 213 (1974).
10. We wish to thank the leaders of the prostaglandin pharmacology screening effort of Miles Laboratories for their contributions. They are:
    E. Hong - Instituto Miles De Terapeutica Experimental - Mexico City
    C. E. Myers - Miles Laboratories, Inc. - Elkhart, Indiana
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