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SYNTHESIS OF 14-PHENYLPROSTAGLANDINS E_1, A_1 AND $F_{2\alpha}$

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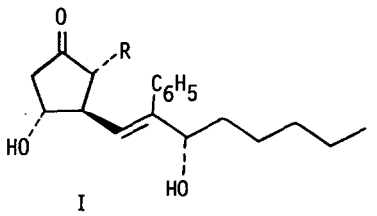
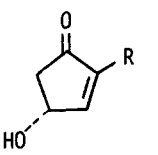
In searching for prostaglandins of more specific biological activities, we chose to make analogs having a 14-phenyl substitutent. An examination of space-filling molecular models suggested that such a structural transformation might constrain the lower arm of the PG skeleton in a conformation favoring increased interaction between the two arms. Such interaction would reduce the number of possible conformations and perhaps lead to a sharper profile of pharmacological activities.

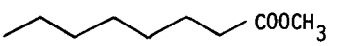
The synthetic route chosen for the E-type prostaglandins I was based on the conjugate addition of the organo cuprate III to the known cyclopentenones II. This reaction is known to produce E-type prostaglandins possessing the all-*trans* stereochemistry at the ring atoms.[1]

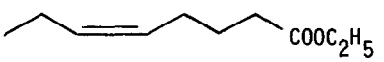


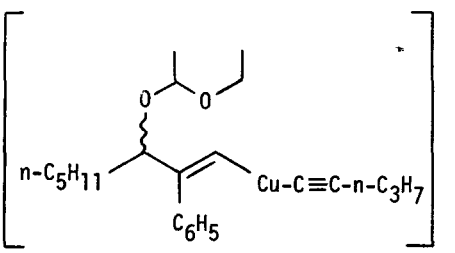
I



II

a; R = 

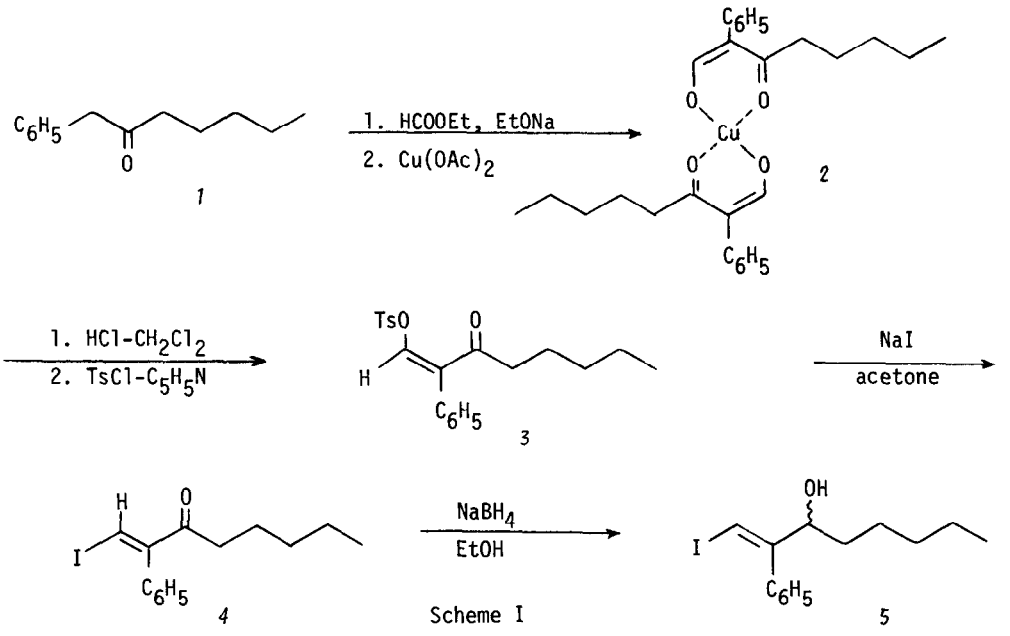
b; R = 

Li 

III

The precursor of cuprate III, the *E*-iodovinyl alcohol 5, was prepared from 1-phenyl-2-heptanone *1*[2] as shown in Scheme I. Condensation of *1* with ethyl formate produced 1-formyl-1-phenyl-2-heptanone, isolated and characterized as the copper-chelated *Z*-isomer *2* (recry from hexane, mp 85-88°C, 50%).[3] The free enol of *2* was liberated with HCl-CH_2Cl_2 and treated with *p*-toluene-sul-

fonyl chloride-pyridine. This produced the enol tosylate 3 (mp 90-92°C, recry from hexane), assigned the Z configuration on the basis of the shift of the vinyl proton in its ^{1}H NMR spectrum



Scheme I

(7.4 δ, $CDCl_3$). Vinyl protons β-*trans* to carbonyl functions exhibit chemical shifts in the range 7.2 δ to 7.4 δ. Protons β-*cis* to carbonyl groups are deshielded and shifted downfield to about 8.1 δ[4].

The acid-catalyzed reaction of 3 with 2 equivalents of NaI in acetone gave the *E*-iodovinyl ketone 4 (vinyl H at 8.0 δ, $CDCl_3$), which was not characterized but reduced directly ($NaBH_4$-ethanol) to give *dl*-E-3-hydroxy-1-iodo-1-octene 5, isolated as a pale golden oil (vinyl H at 7.2 δ, $CDCl_3$, 22% yield overall). Alcohol 5 was protected as the ethyl vinyl ether adduct, lithiated (*t*-BuLi, -70°C, ether), and combined with the hexamethyl phosphorous triamide complex of copper *n*-propyl acetylide to generate the cuprate cluster III[1]. This reactant transfered the vinyl species (-40°C, 2 hrs, ether) to the protected 4-hydroxycyclopentenones II to produce, after deblocking, the PGE esters Ia and Ib.

It was not possible to resolve alcohol 5. However, we were able to obtain the 4-hydroxycyclopentenones as the optically active *R*-enantiomers IIa and IIb by the published procedures[5]. Thus the 14-phenyl PGEs Ia and Ib were obtained as a mixture of two isomers, epimeric at C-15. These were separated by column chromatography on silica gel, eluting with benzene-ethyl acetate. The first-eluted isomer in each case was assigned the structure of the 15-*epi* isomer (15 *R*) and the second-eluted one as the *natural* (15 *S*) isomer on the basis of the known chro-

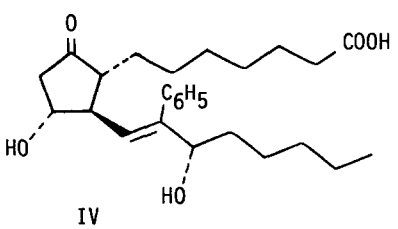
matographic behavior of the natural PGs.[6] In this way we made 180 mg (12% yield) of 14-phenyl PGE_1 methyl ester Ia (oil $\alpha_D = -34.9^o$, rf = 0.60, m/e 444 [M+], 426 [M+ $-H_2O$]) and 115 mg (10% yield) of the ethyl ester of 14-phenyl PGE_2Ib (oil, $\alpha_D = -17.5^o$, rf = 0.62, m/e 465 [M+], 438 [M+ $-H_2O$]).

The ester Ia, 200 mg was hydrolyzed to its corresponding free acid using the enzyme *hog liver carboxylic ester hydrolase* (EC 3.1.1.1) in 0.1 M phosphate buffer (pH 7.4, 37°C). By this we obtained 75 mg of 14-phenyl PGE_1 IV [oil, $\alpha_D = -29.0^o$, rf = 0.51, m/e 412 (M+ $-H_2O$)].

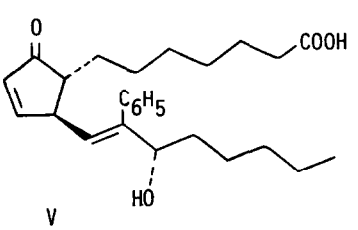
50 Mg of the acid IV was dehydrated in aqueous acetic acid (50°C, 2 hrs) to give 10 mg of 14-phenyl PGA_1 V [oil, $\alpha_D = 85.4^o$, rf = 0.65, m/e 412 (M+)].

900 Mg of ester Ib was stereoselectively reduced using lithium perhydro-9b-borophenalyl-hydride (PBPH)[7] to give 278 mg of the ethyl ester of 14-phenyl $PGF_{2\alpha}$ VIa [oil, $\alpha_D = -19.2^o$, rf = 0.57, m/e 458 [M+], 440 (M+ $-H_2O$)]. A 200 mg portion of this was saponified (KOH-MeOH) to give 131 mg of the free acid, 14-phenyl $PGF_{2\alpha}$ VIb [oil, $\alpha_D = -23.1^o$, rf = 0.48, m/e 430 (M+), 412 (M+ $-H_2O$)].

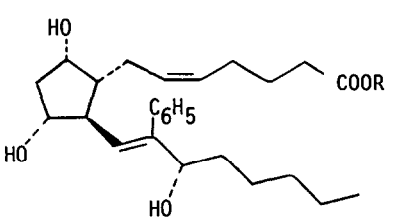
These PG analogs were examined in a number of pharmacological screens. Although they display some antagonism to natural PGs, their own prostaglandin-like activities are some thousand-fold less than the natural substances.



IV



V



VI

a, R = C_2H_5

b, R = H

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