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THE SYNTHESIS OF 15-DEOXY-9,11-(EPOXYIMINO)PROSTAGLANDINS- POTENT THROMBOXANE SYNTHETASE INHIBITORS

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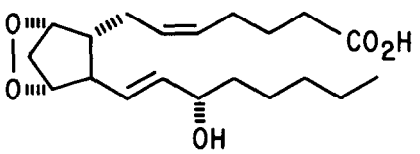
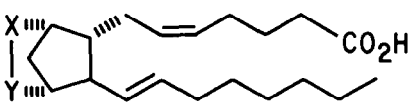
The central role of the prostaglandin endoperoxides PGG_2 and PGH_2[1] in arachidonic acid metabolism is becoming increasingly apparent. These unstable peroxides are the precursors not only for the classical prostaglandins[1] (PGE_2, $PGF_2\alpha$, PGD_2), but also for a hydroxylated C-17 fatty acid (HHT), the thromboxanes[2] (TXA_2 and TXB_2) and the recently discovered prostacyclin[3] (PGI_2). Current studies into the complex interactions between these various pathways in physiological systems have benefited from the availability of several chemically more stable endoperoxide analogs.[4] These analogs, similar in shape and polarity to the endoperoxides, exhibit a biological activity profile reminiscent of the less stable endoperoxides themselves.[5]

Recently, we have found that 9α,11α-azoprosta-5Z,13E-dienoic acid 3[6], which lacks the C-15 hydroxyl group of the natural prostaglandins and also most of the agonist activities typical of PGH_2[5] and its analogs, is a potent inhibitor of the enzyme which converts PGH_2 into thromboxane A_2 in human platelets.[6]

We report herein the synthesis of two 15-deoxy prostaglandin endoperoxide analogs 1 and 2, in which the chemically unstable peroxide linkage of PGH_2 has been replaced with the more stable epoxyimino (-NH-O-) group. Like 15-deoxy azo analog 3, these cyclic O,N-disubstituted hydroxylamine derivatives do not exhibit the biological activities typical of PGH_2, but rather are potent inhibitors of the thromboxane A_2 synthetase in human platelets.[7]



PGH_2



1, X = NH, Y = O
2, X = O, Y = NH
3, XY = -N=N-

The synthetic pathway to epoxyimino compounds 1 and 2, outlined in Figure I, begins in both cases with 15-deoxy-11β-$PGF_2\beta$, available in four steps and 53% overall yield from $PGF_2\alpha$ as described earlier.[6] Taking advantage of the different steric environments of the C-9 and C-11 hydroxyls in 15-deoxy-11β-$PGF_2\beta$ (4), conversion to the C-9 monotosylate 5 proceeded in 92% yield[8]

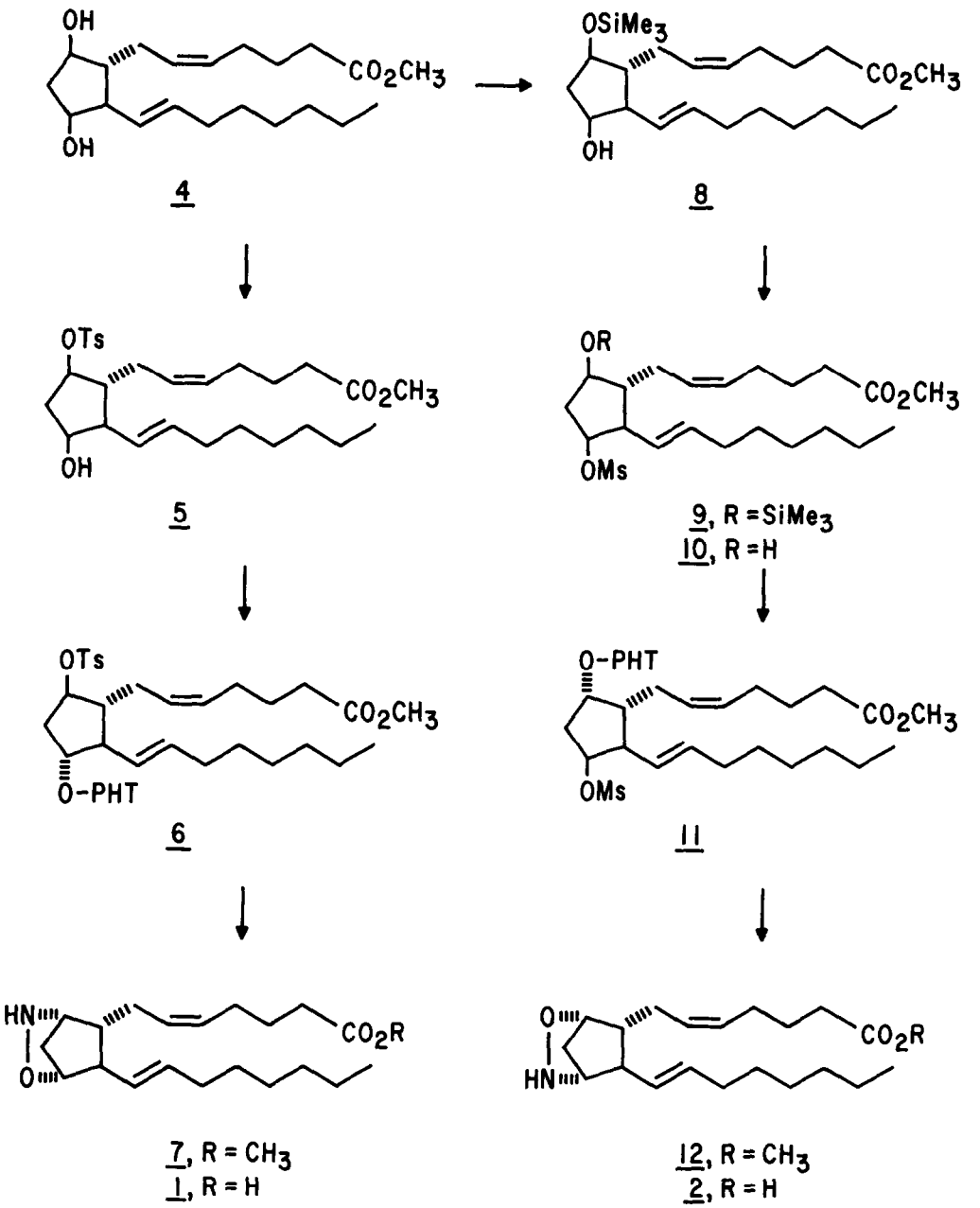

OH
CO2CH3
OH
4
OSiMe3
CO2CH3
OH
8
OTs
CO2CH3
OH
5
OR
CO2CH3
OMs
9, R = SiMe3
10, R = H
OTs
CO2CH3
O-PHT
6
O-PHT
CO2CH3
OMs
11
HN
O
CO2R
7, R = CH3
1, R = H
O
HN
CO2R
12, R = CH3
2, R = H

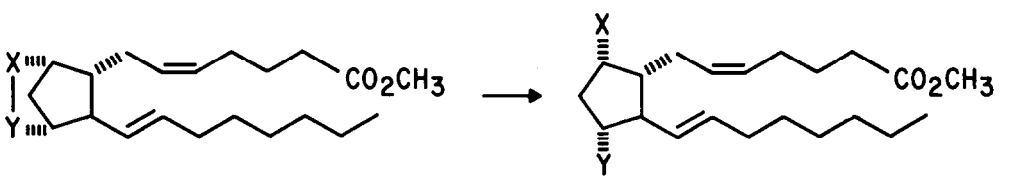
FIGURE I

(1.5 equiv of p-toluenesulfonyl chloride, pyridine, 0°, 4 days). That the regioselective tosylation had occurred at C-9 and not C-11 was inferred from several considerations. Inspection of molecular models indicates that the C-9 hydroxyl, trans to the adjacent side chain, is clearly the less hindered of the two. Analogous selectivity is observed in the silylation of 9α,11α-prostaglandin diols, where reaction occurs preferentially at the hydroxyl trans to the adjacent side chain [9] (in this case C-11). In addition, the minor product in the formation of 5, an isomeric hydroxytosylate isolated in 5% yield, was considerably more polar than 5 on thin layer chromatography. This increased polarity for the C-11 monotosylate by-product can be rationalized based on the greater accessibility of the C-9 hydroxyl for interaction with the silica.[15]

The monotosylate 5 was then treated with triphenylphosphine, N-hydroxyphthalimide and diethyl azodicarboxylate[10] in tetrahydrofuran (15 min, 0°), thereby affording N-alkoxyphthalimide 6 (45% yield after chromatography; PHT = phthalimido). Deprotection of the masked O-alkylhydroxylamine 6 with hydrazine (5 equiv, methanol, 25°, 1 hr) yielded epoxyimino ester 7 directly (77%), via the hydroxylamine tosylate, which could be seen by tlc early in the hydrazinolysis but which was never isolated. Standard ester hydrolysis with aqueous methanolic potassium hydroxide gave the 11α,9α-epoxyimino acid 1 in 90% yield: mp 53-54° (from 5% ether/hexane); r_f 0.39 (silica tlc plates, 50% ethyl acetate/hexane with 1% acetic acid); $\delta_{TMS}^{CDCl_3}$ 4.20 (C<u>H</u>O) and 3.65 ppm (C<u>H</u>N); mass spectrum of TMS derivative: M^+ 407.2832 (theoretical for $C_{23}H_{41}SiNO_5$: 407.2850).

The synthesis of 9α,11α-epoxyimino derivative 2 (O and NH interchanged from 1) required blocking the C-9 hydroxyl group temporarily and converting the more hindered C-11 hydroxyl to a sulfonate ester. Attempted selective silylation of C-9 using t-butyldimethylsilyl chloride under standard conditions[11] proved surprisingly unsuccessful. Even at -60° (7 days), a statistical array of products was obtained including starting material, both monosilyl derivatives and the disilyl derivative. Selective silylation of 15-deoxy-11β-$PGF_2\beta$ 4 could be achieved with trimethylsilyldiethyl amine[12], a sterically more discriminating silylating agent, yielding monosilyl derivative 8 (70% after rapid chromatographic purification).[15] Subsequent conversion to the C-11 mesylate (methanesulfonyl chloride, triethylamine, methylene chloride, 10 min, 0°) and removal of the silyl group (methanolic citric acid, 10 min, 20°) proceeded in essentially quantitative yield. Then, following the same sequence as before, monomesylate 10 was transformed into N-alkoxyphthalimide 11 (66%; mp 62-63°) and finally 9α,11α-epoxyimino derivative 12 and the corresponding acid 2: r_f 0.28 (silica plate, 50% ethyl acetate/hexane with 1% acetic acid) $\delta_{TMS}^{CDCl_3}$ 4.30 (C<u>H</u>O) and 3.55 ppm (C<u>H</u>N).

Epoxyimino derivatives 7 and 12 were further characterized by reduction of the N-O bond[13]



7, X = NH, Y = O
12, X = O, Y = NH

13, X = NHAc, Y = OAc
14, X = OAc, Y = NHAc

(zinc, acetic acid, 25°, 20 min) followed by acetylation (acetic anhydride, pyridine, 25°, 3 h), which afforded derivatives 13 (M^+ 435.2984) and 14 (M^+ 435.3003) respectively (theoretical for $C_{25}H_{41}NO_5$: 435.2984).

The epoxyimino derivatives 1 and 2 showed only very low levels of activity on rat blood pressure and gerbil colon. However, like 15-deoxy azo analog 3, the epoxyimino analogs 1 and 2 are both potent inhibitors of thromboxane synthetase from human platelets (active in the range of 10^{-5} to 10^{-6} M).[7]

In addition to providing biologically interesting analogs, the synthetic scheme in Figure I offers a generic solution to the problem of synthesizing cyclic O,N-disubstituted hydroxylamines, many of which are difficult to obtain by classical procedures.[14]

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15. Independent chemical confirmation of the regiochemical assignments for hydroxytosylate 5 and hydroxymesylate 10 was provided by the following observations. The carboxylic acid corresponding to mesylate ester 10, upon treatment with triphenylphosphine and 2,2'-dipyridyl disulfide and heating in dilute toluene solution at 100° for 6 hr, afforded the 1,9β-lactone in 50% yield.. [Method of E.J. Corey and K.C. Nicolaou, J. Am. Chem. Soc. 96, 5614 (1974)]. Under identical conditions, the carboxylic acid corresponding to tosylate ester 5 formed the activated pyridinethiol ester intermediate, but did not lactonize. Molecular models clearly show that lactonization with the 11β-hydroxyl should be much more difficult than with the 9β-hydroxyl, based on steric considerations.