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SYNTHESIS OF BENZINDENE PROSTAGLANDINS: A NOVEL POTENT CLASS OF STABLE PROSTACYCLIN ANALOGS

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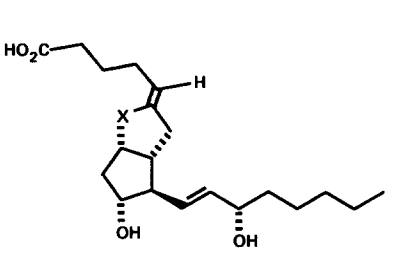
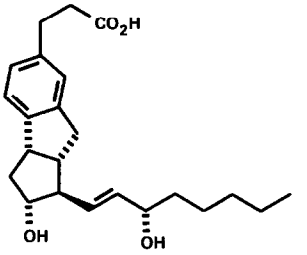
Summary. The phenols 13, 16, and 21, produced with remarkable regioselectivity by the cyclization of compounds 10 and 12, have been converted to the benzindene prostaglandin analogs 25, 20, and 24, respectively. Compounds 24 and 25 are potent prostacyclin mimics.

Prostacyclin (PGI_2, 1) is a powerful vasodilator and one of the most potent inhibitors of platelet aggregation known.[1] However, due to the labile enol ether portion, PGI_2 has a very short half-life, and a stable analog would be a much more useful drug in the treatment of cardiovascular disease. A number of chemically stable analogs have been prepared, with the carbon derivative 2, 6a-carbaprostaglandin I_2,[2] looking very promising.[3] A recent report[4] describing the preparation of the aromatic ring analog 3 of 6a-carba-PGI_2 prompts us to disclose the synthesis and biological activity of the benzindene prostaglandin analogs, a somewhat related class of stable, potent prostacyclin mimics.



1 X = O
2 X = CH_2



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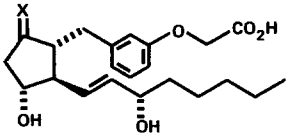


4 X = O
5 X = CH_2

Recently it was shown that the interphenylene prostaglandin 4[5] and the related 9-methylene compound 5,[6] though much less potent than PGI_2, had certain prostacyclin type activities. It was hypothesized that by making the interphenylene compounds more rigid by joining the aromatic ring to the cyclopentane ring (to give, for example, compounds 20, 24, or 25), the PGI_2-type activities of this series might be enhanced.

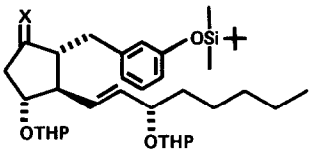
The starting material for the synthesis of these conformationally fixed interphenylene analogs is compound 6, an intermediate in the synthesis of 4.[5a] The methylene group was introduced using the two-step procedure of Johnson:[7] reaction of ketone 6 with the anion of methylphenyl-N-methyl-sulfoximine in THF followed by treatment of the resulting crude adduct with aluminum amalgam in 1:1:6 water-acetic acid-THF furnished compound 7[8] in 72% yield.

Hydroboration of 7 from the least hindered face with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by oxidation with basic hydrogen peroxide gave alcohol 8[8] in 92% yield.

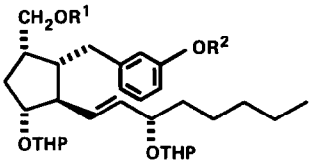
Treatment of alcohol 8 with methane sulfonyl chloride and triethylamine in methylene chloride afforded an 88% yield of mesylate 9 which was deprotected to 10[8] with tetra-n-butylammonium fluoride in THF. Intramolecular alkylation to give phenol 13[8] (mp 94-96°) was best accomplished (72% from 9) employing one equivalent of sodium hydride in glyme at reflux. None of the other possible isomer (i.e., the para-cyclized compound 26) could be detected. Similar results were obtained using n-butyllithium in refluxing THF or potassium hydride in refluxing glyme. These observations are in agreement with the work of Duggan and Murphy who showed that intramolecular alkylation of the anion of 4-m-hydroxyphenylbutyl toluene-p-sulfonate takes place predominantly at the ortho position.[9] Treatment of phenol 13 with sodium hydride and methyl bromoacetate in glyme gave ester 14 which was deprotected (1:2:4 THF-water-acetic acid at 45°) to give ester 15[8] (mp 82-84°) in 82% yield from 13. Finally, hydrolysis of the methyl ester with potassium hydroxide in methanol and water furnished (73% yield) the crystalline acid 25[8] (mp 131-133°).

The synthesis of acids 20 and 24 utilizes alcohol 8 as starting material. Collins exidation of 8 afforded a 79% yield of aldehyde 11.[8] In a one-pot procedure compound 11 was cyclized (73% yield) to phenol 16[8] by first fluoride cleavage of the silyl ether in THF at 0° followed by heating the resulting tetra-n-butylammonium phenoxide at reflux for several hours. In this novel intramolecular base-catalyzed aldol-type cyclization none of the corresponding ortho adduct 27 could be detected.[10] Treatment of phenol 16 with one equivalent of sodium hydride and methyl bromoacetate gave compound 17[8] in 84% yield. Dehydration of alcohol 17 to compound 18 presented some difficulty since most conventional methods met with failure. However, exposure of 17 to an excess of methane sulfonyl chloride in triethylamine (without a co-solvent) gave a 52% yield (85% based on recovered starting material) of compound 18. Hydrolysis of the THP protecting groups to 19[8] (mp 88-89°) followed by ester hydrolysis afforded (75% from 18) the desired crystalline acid 20[8] (mp 149-151°).

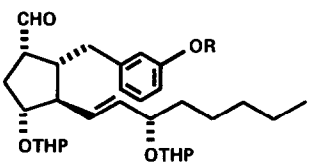
It was surmised that whereas the bulky tetra-n-butylammonium cation derived from 12 leads to only para attack because of steric hindrance, use of other counterions might lead to the ortho product 27. In particular, the magnesium cation could be particularly useful in directing the cyclization perhaps via an intermediate such as compound 28. In the event treatment of phenol 12[8] (produced in 90% yield from aldehyde 11 by fluoride-mediated silyl ether cleavage) with one equivalent of methyl magnesium chloride in glyme at -40° followed by several days at reflux furnished exclusively the ortho-vinylphenol 21[8] (60% yield). Thus the magnesium phenoxide not only cyclized in the desired manner, but the use of magnesium also promoted the dehydration of the resulting alcohol (which was actually the most difficult step in the synthesis of 20).[11] Introduction of the acetate side chain and hydrolysis of the THP and ester protecting groups as before via intermediates 22 and 23[8] (mp 96-98°) afforded the crystalline acid 24[8] (mp 146-148°) in overall about 50% yield.



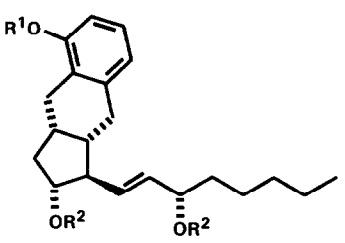
6 X = O
7 X = CH_2



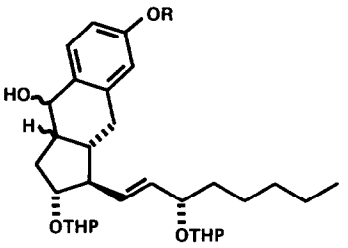
8 R^1 = H; R^2 = $SiMe_2$t–Bu
9 R^1 = SO_2CH_3; R^2 = $SiMe_2$t–Bu
10 R^1 = SO_2CH_3; R^2 = H



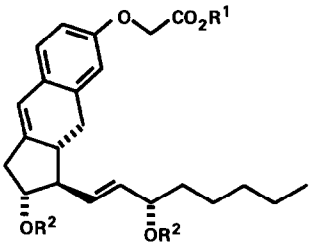
11 R = $SiMe_2$tBu
12 R = H



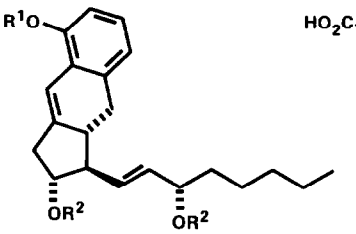
13 R^1 = H; R^2 = THP
14 R^1 = $CH_2CO_2CH_3$; R^2 = THP
15 R^1 = $CH_2CO_2CH_3$; R^2 = H



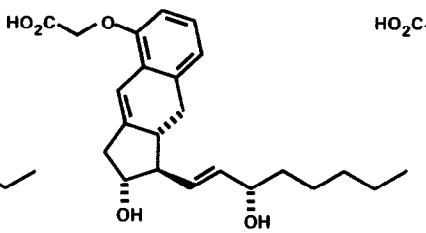
16 R = H
17 R = $CH_2CO_2CH_3$



18 R^1 = CH_3; R^2 = THP
19 R^1 = CH_3; R^2 = H
20 R^1 = R^2 = H



21 R^1 = H; R^2 = THP
22 R^1 = $CH_2CO_2CH_3$; R^2 = THP
23 R^1 = $CH_2CO_2CH_3$; R^2 = H



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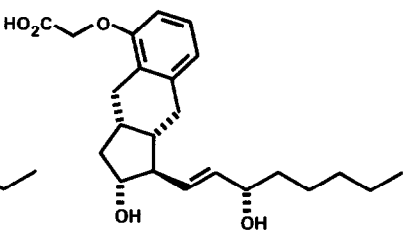

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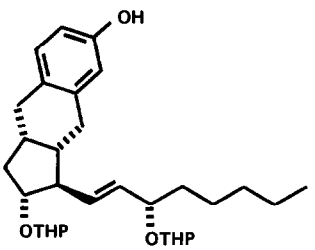

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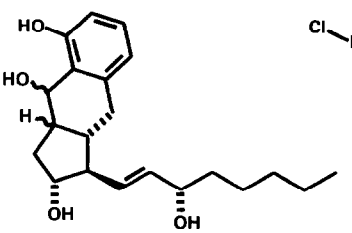

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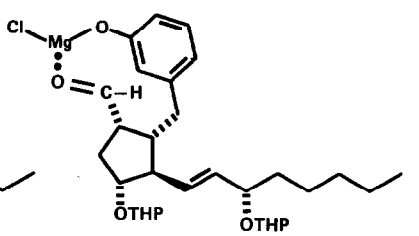

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While compound 20 did not appear to exhibit any prostacyclin-type activity, compounds 24 and 25 were potent inhibitors of platelet aggregation.[12] In particular, acid 25, which can be considered a carba-prostaglandin analog with a fused aromatic ring, is twice as active as 6a-carbaprostaglandin I_2.[12] These results along with those of Hayashi who reported that analog 3 was devoid of PGI_2-type properties,[4] serves to help pinpoint the position of the acid side chain in the prostacyclin receptor that is necessary for biological activity. In conclusion, conformationally rigid interphenylene (i.e., benzindene) prostaglandins of the type 24 and 25 represent a new class of potent, stable prostacyclin analogs.

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12. Unpublished observations of R.R.Gorman, J.W.Aiken, and co-workers, Experimental Biology Research, The Upjohn Co. We thank them for performing these experiments.

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