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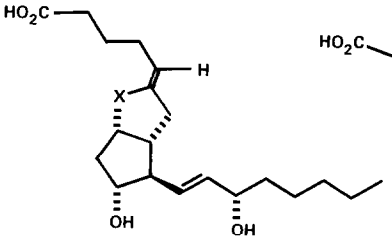
# SYNTHESIS OF BENZOPYRAN PROSTAGLANDINS, POTENT STABLE PROSTACYCLIN ANALOGS, VIA AN INTRAMOLECULAR MITSUNOBU REACTION

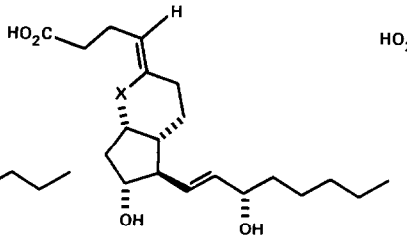
Paul A. Aristoff*, Allen W. Harrison and Anne M. Huber[1]
Lipids Research
The Upjohn Company
Kalamazoo, Michigan 49001

Summary. Short syntheses of the extremely potent benzopyran prostacyclin mimics 26 and 27 are described using a novel intramolecular Mitsunobu reaction (e.g. 20 → 22) in the key step. This mild cyclization method was also applied to the synthesis of some simple chromans and benzofurans (34 - 38).

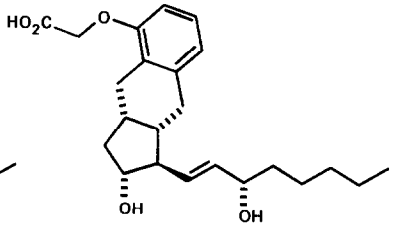
Prostacyclin ($PGI_2$, 1) is a powerful vasodilator and one of the most potent inhibitors of platelet aggregation known.[2] Replacement of the labile enol ether in 1 with a methylene group gives carbacyclin (2)[3], a chemically stable analog with one-tenth the biological activity of $PGI_2$ on platelets and blood pressure.[4] Interestingly, whereas the six-membered ring enol ether prostacyclin mimic 3 was nearly as effective as $PGI_2$ at inhibiting platelet aggregation,[5] the corresponding methylene analog 4 was a thousand times less active.[6] Several years ago we reported the synthesis and biological activity of the benzindene analog 5, a chemically stable compound which was twice as potent as carbacyclin on platelets.[7] We were therefore interested in replacing the methylene unit attached to C-9 in 5 with an oxygen so as to produce the corresponding benzopyran analog (i.e. 27). Herein is described the first reported synthesis of compounds 26 (an analog of 3 containing a fused benzene ring) and 27.




1 X = O
2 X = $CH_2$




3 X = O
4 X = $CH_2$

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The starting material for the preparation of the benzopyran analogs is the optically active enone 6,[8] an intermediate in the synthesis of interphenylene prostaglandins including benzindene 5.[7] Addition of the lithium diaryl cuprate derived from the treatment of aryl bromide 9 with t-butyllithium (2 equiv), copper iodide (0.5 equiv), and tri-n-butylphosphine (0.5 equiv) in ether at -78°C[8] to enone 6 afforded ketone 13[9] in 77% yield. Larger protecting

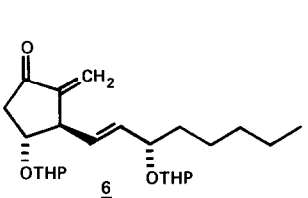
groups than methoxy on the aryl bromide 9 led to much lower yields in the cuprate addition, presumably due to steric hindrance. The aryl bromide 9[9] was readily prepared from the known bromo olefin 7[10] by alkylation of 7 to give 8 (KO*t*-Bu, *t*-BuOH, $CH_3I$, 88% yield) followed by hydroboration-oxidation and then protection of the resulting primary alcohol (9-BBN, THF; $H_2O_2$, KOH; dihydropyran, pyr•HCl, $CH_2Cl_2$, 72% overall yield).

Reduction of ketone 13 with sodium borohydride in methanol afforded approximately a 1:1 mixture of the desired alcohol 18[9] and its 9-epi isomer 15[9] in quantitative yield. Use of more hindered reducing agents gave mainly alcohol 15. Operationally this was not a problem since the alcohols were easily separated chromatographically, and 15 was converted to 18 in 77% yield using typical Mitsunobu conditions[11] ($Ph_3P$, $EtO_2CN{=}NCO_2Et$, $PhCO_2H$, THF, 0°C; NaOMe, MeOH).

Deprotection of the methyl ether in 18 was achieved in 83% yield using excess lithium n-butyl mercaptide in HMPA at 100°C.[12] Thus not only did the prostaglandin intermediate withstand the harsh conditions of the reaction, but also no protection of the alcohol at C-9 was necessary. The resulting diol 20[9] was directly cyclized to the benzopyran 22[9] in 94% yield by treatment with triphenylphosphine (3 equiv) and diethylazodicarboxylate (DEAD) (3 equiv) in dioxane at room temperature. There are several reports in the literature describing the intermolecular coupling of an alcohol and a phenol under Mitsunobu conditions[13]; however, this is the first example of the intramolecular variant of the process, and its success depends upon the phenol acting as an internal nucleophile. Interestingly, the phenol 17[9] (prepared by butyl mercaptide cleavage of ether 15) failed to cyclize even under forcing conditions, dehydration of the alcohol at C-9 taking place instead. Molecular models clearly indicate that backside displacement at C-9 with the phenol in an $S_N2$ sense is a much higher energy process in 17 than in 20.

To complete the synthesis, the THP protecting groups in 22 were removed under acidic conditions (THF, $H_2O$, HOAc, 45°C, 80% yield) and the primary alcohol in 23[9] selectively oxidized using platinum and oxygen in water and acetone[14] to give the benzopyran analog 26[9] (mp 135-137°C) in 82% yield (35% overall from ketone 6).

The 3-oxa benzopyran analog 27 was prepared using a very similar reaction sequence. The desired aryl bromide 12[9] for the cuprate reaction with enone 6 was prepared in overall 69% yield from *o*-vinyl ether 10 by ozonlysis, Baeyer-Villiger oxidation of 11[9] using *m*-chloroperbenzoic acid in methylene chloride,[15] and protection of the resulting phenol as a THP ether. We discovered that slowly eluting olefin 8[16] through a column of basic alumina (Woelm, akt I) produced 10[9] in nearly quantitative yield. This extremely simple method of bringing the olefin into conjugation with the aromatic ring is probably applicable to other systems. Using the diaryl cuprate derived from 12, enone 6 was converted to ketone 14 (69% yield) and then to phenol 21 (60% overall yield) as previously described. Cyclization of 21 under the modified Mitsunobu conditions afforded an 87% yield of 24[9] which was deprotected to 25[9], selectively alkylated (NaH, $BrCH_2CO_2CH_3$, DME) and the methyl ester hydrolyzed (KOH, $H_2O$, $CH_3OH$) to give the desired acid 27[9] (mp 132-134°C) in 72% yield.



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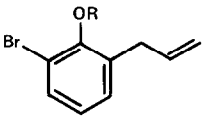
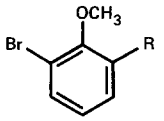
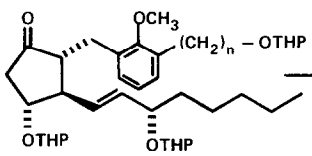


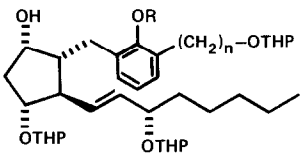
7 R = H
8 R = $CH_3$



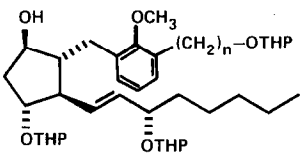
9 R = $(CH_2)_3OTHP$
10 R = $-CH \equiv CH-CH_3$
11 R = –CHO
12 R = –OTHP



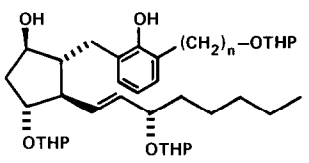
13 n = 3
14 n = 0



15 n = 3; R = $CH_3$
16 n = 0; R = $CH_3$
17 n = 3; R = H



18 n = 3
19 n = 0



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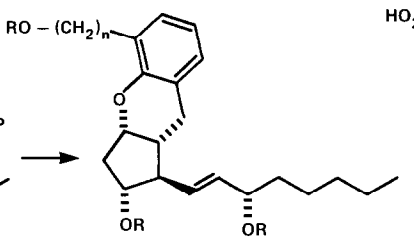
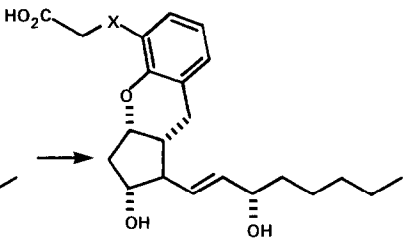
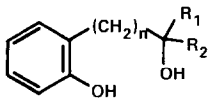
21 n = 0



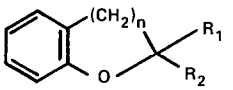
22 n = 3; R = THP
23 n = 3; R = H
24 n = 0; R = THP
25 n = 0; R = H



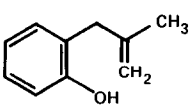
26 X = $CH_2$
27 X = O



28 n = 2; $R_1$ = $R_2$ = H
29 n = 1; $R_1$ = $R_2$ = H
30 n = 2; $R_1$ = $CH_3$; $R_2$ = H
31 n = 1; $R_1$ = $CH_3$; $R_2$ = H
32 n = 2; $R_1$ = $R_2$ = $CH_3$
33 n = 1; $R_1$ = $R_2$ = $CH_3$



34 n = 2; $R_1$ = $R_2$ = H
35 n = 1; $R_1$ = $R_2$ = H
36 n = 2; $R_1$ = $CH_3$; $R_2$ = H
37 n = 1; $R_1$ = $CH_3$; $R_2$ = H
38 n = 2; $R_1$ = $R_2$ = $CH_3$
39 n = 1; $R_1$ = $R_2$ = $CH_3$



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We also briefly investigated the intramolecular cyclization of phenols 28 - 33. As anticipated excellent yields (>90%) of chromans 34[9] and 36[9] as well as benzofurans 35[9] and 37[9] were obtained upon treatment of the corresponding primary or secondary alcohols with DEAD and triphenylphosphine in dioxane. Somewhat surprising was the discovery that even the tertiary alcohol 32 cyclized to chroman 38[9], albeit in low yield (30-40%). However, the major product upon Mitsunobu treatment of 33 was the dehydration product 40 (70% yield), less than 10% of 39 being formed.

In conclusion, application of a mild cyclization method has faciliatated a very brief synthesis of the benzopyran prostacyclin analogs 26 and 27 (6-7 steps from enone 6). As expected, these compounds turn out to be potent stable $PGI_2$ mimics. In particular, the 3-oxa analog 27 is essentially equiactive with prostacyclin at inhibiting platelet aggregation and lowering blood pressure.[17]

## REFERENCES AND NOTES


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9. This compound had satisfactory TLC behavior, NMR, IR, UV, combustion analysis and/or high resolution mass spectra. For 26: NMR ($CD_3COCD_3$, TMS) $\delta$ 0.90 (t, J=5 Hz, 3H), 1.10-3.30 (m, 18H), 3.82-4.23 (m, 2H), 4.30-4.53 (m, 1H), 4.97-5.80 (m, 5H), 6.70-7.13 (m, 3H); IR (mull) 3425, 3345, 3215, 1710, 1460, 1440, 1385, 1375, 1335, 1320, 1285, 1260, 1230, 1190, 1175, 1010, 975, 960, 745 $cm^{-1}$. For 27: NMR ($CDCl_3$, TMS) $\delta$ 0.90 (t, J=5, Hz, 3H), 1.03-2.96 (m, 17H), 3.77-4.23 (m, 2H), 4.35-4.52 (m, 1H), 4.62 (s, 2H), 5.40-5.62 (m, 2H), 6.63-6.91 (m, 3H), IR (mull) 3335, 1715, 1605, 1480, 1455, 1435, 1375, 1335, 1325, 1255, 1240, 1210, 970, 755, 725 $cm^{-1}$.
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15. I.M.Godfrey, M.W.Sargent, and J.A.Elix, J. Chem. Soc., Perkin Trans. 1, 1353 (1974).
16. A solution of 8 in 1% ethyl acetate in hexane was used.
17. Unpublished observations of R.R.Gorman, J.W.Aiken and co-workers, The Upjohn Company. We thank them for performing these experiments.


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