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THE SYNTHESIS OF FURAN-BASED SECOPROSTACYCLINS

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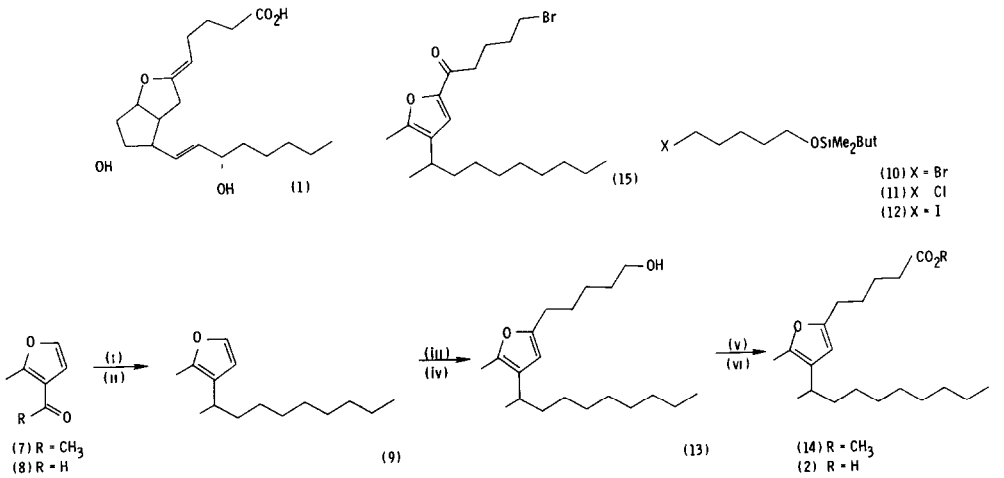
Summary Furan-based secoprostacyclins (2-6) have been synthesised by two routes differing in the stage at which the furan ring is generated.

In contrast to the classical prostaglandins (PG), prostacyclin (PGI_2, 1) has a direct effect on the tuberular reabsorption of sodium in the kidney.[1] Since the Merck group had shown[2] useful, PG-like activity may still be retained in very simple prostanoid derivatives (termed secoprostaglandins), we decided to make simpler, stable analogues of PGI_2 to test as novel diuretic agents. Furan-based secoprostacyclins (2-6) combined these features, the furan ring provides the critical[3] sp^2-character at C-6 (PG-numbering) and also incorporates the enol-ether functionality into a more stable environment

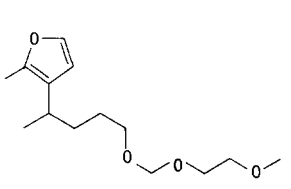
In principle, compound 2 could be synthesised from the parent furan 7 by introduction of the bottom side-chain by Wittig olefination of the carbonyl group followed by alkylation of the resulting furan at the 5-position to give the C_{20} skeleton. However, reaction of the anion of 9 with ethyl bromovalerate gave 15[4] rather than 14. The problem was solved by introduction of the c-5 chain in reduced form as follows. 5-Bromo-1-pentanol was reacted immediately with an excess of dimethyl t-butylsilyl chloride to give (by GC/MS) a 4 1 mixture of the bromide 10 and the chloride 11. Since only the bromide reacted with



Reagents· i. $Ph_3P^+(CH_2)_7CH_3Br^-$,$KOBu^t$, PhMe, 90°, furan added at 25°, ii. H_2, 10% Pd-C, abs. EtOH, iii. n-BuLi, THF, -5°, 2.5h; 12 added at -60°, iv. $n\text{-}Bu_4N^+F^-$, 0°, THF, 0.5h, v. $C_5H_5NH^+ClCrO_3^-$, CH_3CO_2Na, CH_2Cl_2, 20°, 3h, vi. 2N-NaOH, $AgNO_3$, H_2O, 20°, 2h.

the metalated derivative of 9, the mixture was converted to the iodide 12 prior to use, desilylation of the resulting furan gave the alcohol 13 ready for oxidation to the acid. This was most conveniently accomplished in two steps with pyridinium chlorochromate in methylene dichloride followed by silver oxide oxidation of the intermediate aldehyde. For purification the crude acid was immediately esterified with diazomethane, following chromatography and saponification of the ester the pure acid 2 was isolated as its sodium salt.

Application of this sequence to a furan with a functionalised lower side-chain (eg 16, prepared in two steps from 7 and the phosphonium salt 17) failed at the metalation stage regardless of the protecting group[5] and the ratio of base to furan that was used. Addition of the top side-chain in two stages enabled the synthesis to be completed. The furan 22 was prepared via the usual Wittig reaction between 7 and 18 (to give 20) followed by hydrogenation and acetylation. Formylation gave 23 and this reacted selectively at the aldehyde function with the ylid from 24. Hydrogenation of the Wittig product generated the alcohol 25 which was oxidised to give 3. Olefination of 7 with the phosphorane from 19[6] gave 21 and repetition of the steps described above afforded 4.



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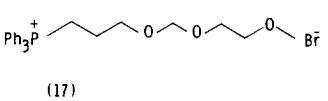

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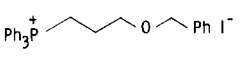

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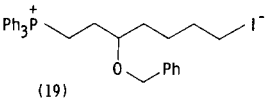

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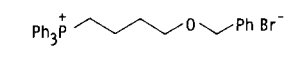

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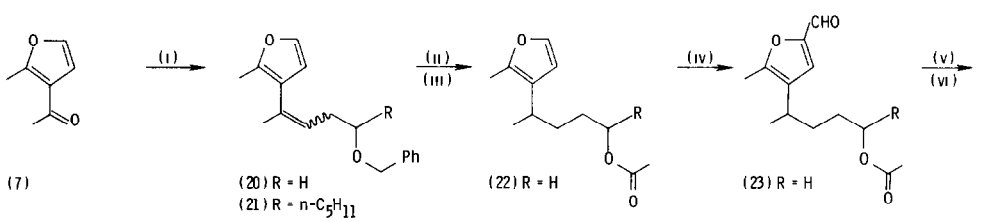
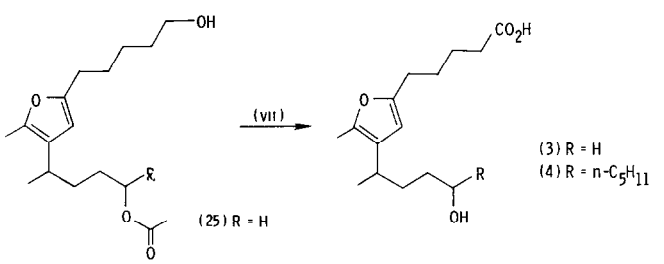


(7) → (i) → (20) R = H; (21) R = n-C_5H_{11} → (ii), (iii) → (22) R = H → (iv) → (23) R = H → (v), (vi)

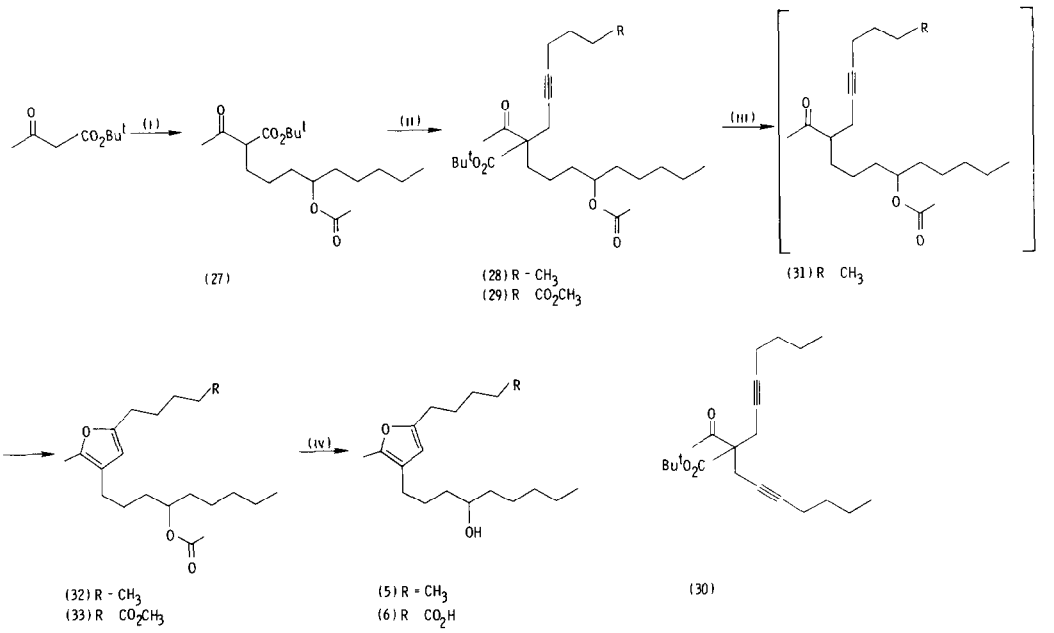


(25) R = H → (vii) → (3) R = H; (4) R = n-C_5H_{11}

Reagents. i 18 or 19, n-BuLi, THF, -10° to 25°, 0.5h, furan added at -10°, ii. H_2, 10% Pd-C, iii. Ac_2O, Et_3N, 4-$(CH_3)_2NC_5H_4N$, 25°, 3h, iv. $POCl_3$, DMF, 5°, 1h, then Na_2CO_3, v. 24, n-BuLi, THF, -10°, furan added at -55°, vi. H_2, 10% Pd-C, vii. oxidation as above.

Clearly this route could also be applied to the preparation of 5 and 6 from the aldehyde 8. However, we also wished to exploit the well-documented[7] furan synthesis based on the acid- or base-catalysed ring closure of α,γ-ketoalkynes. The intermediate 31

required for the crucial cyclisation reaction was obtained by sequential alkylation of t-butyl acetoacetate first with 1-bromo-2-heptyne and then with the iodoacetate 26[2], the dialkylated material 30 was the major product. Reverse addition of the side-chains using the more reactive propargylic bromide in the second step avoided this problem Exposure of 28 to a trace of acid gave the furan 32 in 65% yield and this was hydrolysed to 5. If the reaction was interrupted after only two hours, the intermediate 31 could be isolated. Substitution of 1-bromo-2-heptyne by methyl 7-bromoheptynoate[8]. in the alkylation of 27 followed by acid treatment of the product 29 afforded the ester 33, saponification completed the synthesis of 6[9].



Reagents: i. NaH, THF, 0°, 1-iodo-4-acetoxynonane (26), then reflux, 16h, ii NaH, THF, 5°, propargylic bromide added at 5° then reflux, 3h, iii. PhMe, Ac_2O, p-TsOH, reflux, 16h, iv. 2N-NaOH, MeOH, 25°, 48h.

References and Notes.

1. P.M. Bolger, G.M. Eisner, P.W. Ramwell, L.M. Slotkoff and E.J. Corey, Nature, 1978, 271, 467.

2 J.B. Bicking, C.M. Robb, R.L. Smith, E.J. Cragoe, F.A. Kuehl and L.R. Mandel, J.Medicin. Chem., 1977, 20, 35.

3 K.C. Nicolaou, W.E. Barnette and R.L. Magolda, J.Amer.Chem.Soc , 1979, 101, 766.

4. All new compounds gave spectra (IR, NMR, MS) consistent with the assigned structure and satisfactory accurate mass measurement or combustion analysis

5 Similar results were obtained when either benzyl or tetrahydropyranyl was used as protecting group.

6. 1-chloro-3-octanol, required in the synthesis of 19, was prepared by two alternative routes The first involved sequential alkylation of 1,3-dithiane with 1-bromopentane and the tetrahydropyranyl ether of 2-bromoethanol followed by desulphurisation, chlorination and borohydride reduction of the ketone. This same intermediate was also available from acrolein by addition of hydrogen chloride followed by pentylation of

the aldehyde with pentyl magnesium bromide.

7. e.g. K.E. Schulte, J. Reisch and A. Mock, Arch.Pharm., 1962, 295, 627. During the course of this part of our programme we became aware of the accidental synthesis of a close analogue of 6 by the Merck group - J.Medicin.Chem., 1978, 21, 1011.

8 E.J. Corey and H.S. Sachdev, J.Amer.Chem.Soc., 1973, 95, 8483.

9 All compounds were tested for their ability to inhibit the aggregation of human platelets induced by ADP in platelet-rich plasma (Dr. M. Johnson) and as diuretic agents (Dr S.T. Kau) which involved oral dosing to salt-loaded male Wistar rats. No compound was sufficiently active to merit further study.

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