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SYNTHESIS OF STABLE FURAN PROSTACYCLIN ANALOGS[1]

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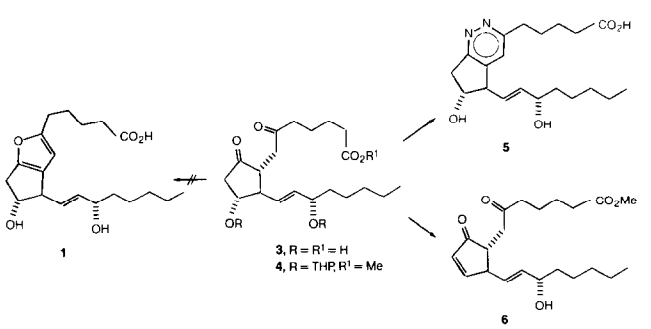
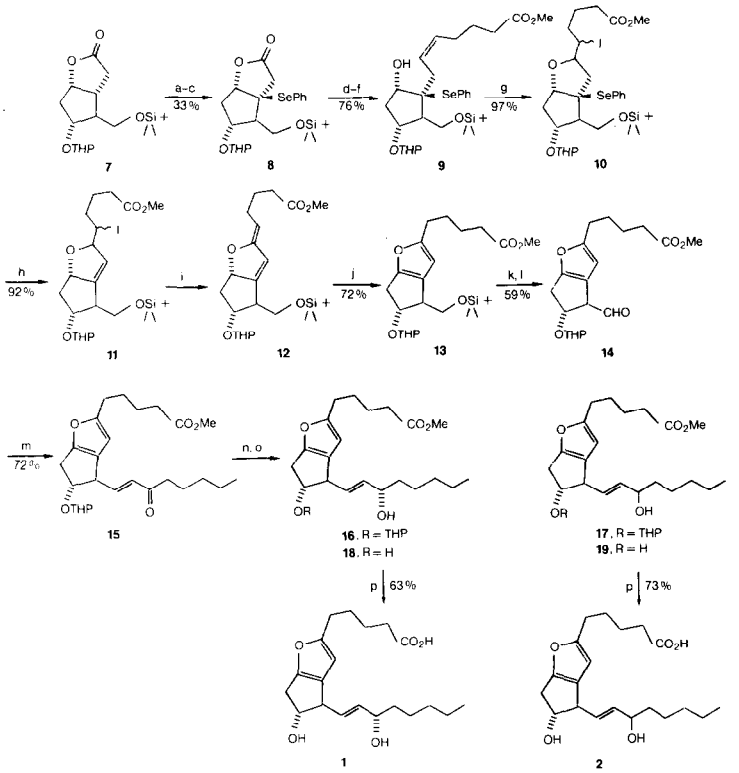
Summary: Starting from γ-lactone intermediates, a novel method for the synthesis of the 5,6-dihydro-4H-cyclopenta[b]furan system has been developed which was utilized to prepare furanoprostacyclin derivatives.

Because of the inherent instability of prostacyclin towards hydrolytic conditions [2] and its rapid decomposition into 6-ketoprostaglandin $F_{1\alpha}$[3], we have been engaged in a program to develop syntheses of stable prostacyclin analogs which would be suitable for treating hypertension and/or occlusive circulatory disorders[4]. An obvious structural modification which would confer stability to the prostacyclin structure would be the modification of the enol ether moiety into a fully-aromatic furan derivative 1.

Nicolaou[5] has described the synthesis of the "first" aromatic prostacyclin analog, 6,9-pyridazaprostacyclin 5, by treatment of the 6,9-diketone 3 with hydrazine and subsequent dehydrogenation with platinum dioxide. Our attempts to cyclize the diketones 3 or 4 under acidic conditions[6] furnished, however, only the PGA_1 derivative 6 and no trace of the desired furan. It therefore became necessary to develop a new approach for the preparation of strained, polyfunctionalized cyclopenta[b]furan derivatives[7] starting from γ-lactone intermediates.



Scheme I Synthesis of Furan Prostacyclins [a]



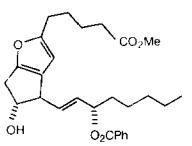
[a] (a) HMDS, n-C_4H_9Li, THF, PhSeCl, -70 °C. (b) H_2O_2, CH_2Cl_2, room temperature. (c) $NaBH_4$, PhSeSePh, EtOH, room temperature. (d) DIBAL, $PhCH_3$, -70 °C. (e) HMDS. n-C_4H_9Li, 4-carboxybutyltriphenylphosphonium bromide, THF, 45 °C. (f) CH_2N_2, ether, 20 °C. (g) I_2, $NaHCO_3$, ether, H_2O, 0 °C. (h) H_2O_2, THF, room temperature. (i) DBU, $PhCH_3$, 40 °C. (j) $MgSO_4$, PhH, reflux. (k) n-Bu_4NF, THF, room temperature. (l) DCC, DMSO, pyridinium trifluoroacetate, room temperature. (m) Dimethyl 2-oxoheptylphosphonate, NaH, DME, -25 °C. (n) $NaBH_4$, MeOH, -30 °C. (o) AcOH, THF, H_2O 35:10:65, 20 °C. (p) NaOH, MeOH, H_2O, room temperature.

Phenylselenylation[8] of 7[9] at the α position of the lactone followed by elimination of the phenylseleno moiety under oxidative conditions and subsequent reintroduction of phenylselenate yielded the ß-phenylseleno lactone 8[8] in 33 % overall yield. Reduction with DIBAL followed by Wittig reaction[10] and treatment of the resulting carboxylic acid with diazomethane resulted in the formation of the ester 9 in 76 % yield.

The bicyclic iodo ether 10 was prepared in nearly quantitative yield[3] and subsequently subjected to oxidative conditions to furnish the dihydrofuran 11. Dehydroiodination of 11 yielded the extremely labile dienol ether 12 which was immediately isomerized to the furan

derivative 13 by treatment with magnesium sulfate in refluxing benzene[11]. The tert-butyldimethylsilyl ether was removed to give the free alcohol in quantitative yield which was oxidized according to the Pfitzner-Moffat method[12] to give the relatively labile aldehyde 14. Further reaction with dimethyl 2-oxoheptylphosphonate[12] resulted in formation of the enone 15 which was reduced to give the 15α- and 15ß-alcohols 16 and 17 in 53 % and 39 % yield, resp., after separation. The tetrahydropyranyl protective groups were removed to afford the diols 18 and 19[13] in 93 % and 98 % yield, resp. which were hydrolyzed to afford the free acids 1 and 2.

The configurations of the alcohols at C-15 were determined by analysis of the CD spectra of the 15-monobenzoates 20 and 21[14] according to the method of Johnson[15]. The 15α-configuration was assigned to the benzoate 20 exhibiting the less negative Cotton effect[16] between 226 - 229 nm.



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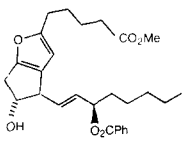

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The biological properties of these furan prostacyclin analogs are being presently investigated.

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(1) Prostaglandin Analogs, Part 5. Part 4: Skuballa, W.; Vorbrüggen, H. Angew. Chem. Int. Ed. Engl. 1981, 20, 1046.

(2) Moncada, S.; Vane, J.R. In "Biochemical Aspects of Prostaglandins and Thromboxanes"; Kharash, N.; Fried, J., Eds.; Academic Press: New York, 1977; p 155.

(3) Johnson, R.A.; Lincoln, F.H.; Nidy, E.G.; Schneider, W.P.; Thompson, J.L.; Axen, U. J. Am. Chem. Soc. 1978, 100, 7690.

(4) For a review of the current clinical uses of prostacyclin, see: Moncada, S.; Vane, J.R. Phil. Trans. R. Soc. London 1981, 294, 305.

(5) Nicolaou, K.C.; Barnette, W.; Magolda, R.L. J. Am. Chem. Soc. 1979, 101, 766.

(6) A number of novel furan syntheses have appeared in the recent literature. See, for example: Galesloot, W.G.; Schreurs, P.H.M.; Brandsma, L. Rec. Trav. Chim. 1975, 94, 70 and references cited therein. Grieco, P.; Pagnowski, C.S.; Burke, S. J. Org. Chem. 1975, 40, 542. Wender, P.; Letendre, L.J. J. Org. Chem. 1980, 45, 367. Lie Ken Jie, M.S.; Ahmad, F. J. Chem. Soc., Chem. Commun. 1981, 1110. Ley, S.V.; Mahon, M. Tetrahedron Lett. 1981, 4747. Cormier, R.A.; Francis, M.D. Synth. Commun. 1981, 11, 365. Jommi, G.; Bernasconi,S.;

Gariboldi, P.; Sisti, M.; Montanari, S. J. Chem. Soc., Perkin Trans. 1 1981, 2394. Nakano, T.; Maillo, M.A. Synth. Commun. 1981, 11, 463.

(7) Syntheses of relatively simple 5,6-dihydro-4H-cyclopenta[b]furans are known. See, for example: Wolters, E.; Schaaf, H.-D. Angew. Chem. 1976, 88, 718. Machinskaya, I.V.; Smirnova, G.P.; Barkhash, V.A. Zh. Obshch. Khim. 1962, 32, 1248 as cited in Chem. Abstr. 1963, 58, 3377. Synthetic entries into the 5,6-dihydro-4H-cyclopenta[c]furan system have also been reported. See: Baldwin, J.W. J. Am. Chem. Soc. 1980, 102, 1198. Münzenmaier,W.; Straub, H. Liebigs Ann. Chem. 1977, 313.

(8) Performed in analogy to a similar reaction sequence previously reported by Sih, J.C.; Graber, D.R. J. Org. Chem. 1978, 43, 3798.

(9) Anderson, N.H.; Imamoto, S.; Picker, D.H. Prostaglandins 1977, 14, 61.

(10) The ylid of 4-carboxybutyltriphenylphosphonium bromide was generated in tetrahydrofuran using hexamethyldisilazane-lithium as base. A similar procedure has been described to attach the upper side chain of thromboxane B_2. See: Hanessian, S.; Lavallee, P. Can. J. Chem. 1981, 59, 870. Attempts to carry out the Wittig condensation with the ß-phenylseleno lactol in DMSO as solvent were not successful.

(11) In analogy to the previously described isomerization of PGI_2 into Δ^6-PGI_1, see: DOS 28 50 304(1979) and Jap. Patent 5 31 44-565(1977).

(12) Bindra, J.S.; Bindra, R. "Prostaglandin Synthesis"; Academic Press, Inc.: New York, 1977; p 200.

(13) The furan chromophore of methyl 5-{(4R,5R)-4-[(3S)-(E)-3-hydroxyoct-1-enyl]-5-hydroxy-5,6-dihydro-4H-cyclopenta[b]furan-2-yl}-pentanoate (18) and related derivatives exhibits a UV absorption at λ_{max} 223 nm (ε = 9000). All derivatives were characterized by IR, 400 MHz ^{1}H NMR and, where appropriate, UV and MS spectroscopy. The ^{1}H NMR data (benzene) for the furan diol 18 are as follows: δ5,93 (s,1H,7-H), 5,72 (m,2H,13,14-H,$J_{13,14}$=15 Hz), 4,38 (q,1H,11ß-H,J=5,5 Hz), 4,03 (q,1H,15ß-H,J=6 Hz), 3,45 (t,1H,12α-H,J=5 Hz), 3,36 (s,3H, methyl ester), 2,98 (dd,1H,10α-H,$J_{10\alpha,10\beta}$=15 Hz,$J_{10\alpha,11\beta}$=7 Hz), 2,57 (dd,1H,10ß-H, $J_{10\beta,11\beta}$=5 Hz), 2,48 (t,2H,5-H,J=6,5 Hz), 2,07 (t,2H,2-H,J=6 Hz), 0,92 (t,3H,20-H,J=6 Hz). The NMR data for the furan diol 19 with the 15ß configurated alcohol are quite similar to those obtained for the 15α isomer with the following exceptions: δ5,94 (s,1H,7-H), 5,78 (dd,1H,13-H,$J_{13,14}$=15 Hz, $J_{13,12\alpha}$=6,5 Hz), 5,71 (dd,1H,14-H,$J_{14,15}$=5,5 Hz), 2,50 (dd,1H, 10ß-H,$J_{10\beta,10\alpha}$=15 Hz, $J_{10\beta,11\beta}$=5 Hz).

(14) These derivatives were prepared by benzoylation of the alcohols 16 and 17 (PhCOCl, pyridine) followed by removal of the tetrahydropyranyl ethers.

(15) Johnson, R.A.; Krueger, W.C.; Nidy, E.G.; Pschigoda, L.M.; Garry, M.J. J. Org. Chem. 1980, 45, 1528.

(16) The 15α-benzoate 20 exhibits a slightly negative cotton effect at 229 nm (θ=-1300) whereas the epimeric benzoate 21 exhibits a more pronounced negative adsorption at 226 nm (θ = -21000). The CD spectra of these two derivatives are not mirror images of one another due to the moderately negative Cotton adsorption shown by the furan chromophore. For example, the furan diol 19 (Scheme I) exhibits a negative adsorption at 224 nm (θ =-7300).

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