Total Synthesis of Carboprostacyclin, a Stable and Biologically Active Analogue of Prostacyclin (PGI_2)

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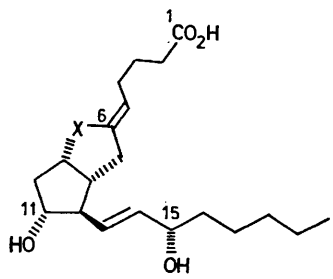
Summary The total synthesis of the carbocyclic analogue (**2**) of prostacyclin (**1**) from *cis*-bicyclo[3.3.0]octane-3,7-dione (**3**) is described.

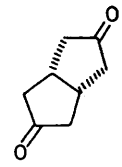
IN 1976 Vane and his associates announced the discovery of prostacyclin (**1**),[1,2] a rather unstable but exciting substance owing to its potent antithrombotic and vasodilatory properties. Since then an increasing number of analogues have been reported in search of potentially therapeutic agents.[3] We now report the total synthesis of the carbocyclic analogue (**2**) of this important biomolecule.

cis-Bicyclo[3.3.0]octane-3,7-dione (**3**) was converted into the mono-acetal (**4**)† (95% yield based on 70% conversion)

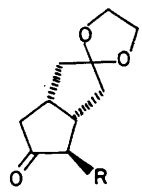
by careful deacetalization of its diacetal (AcOH–tetrahydrofuran–H_2O; 3:1:1, 45 °C, 1 h). Treatment of (**4**) with an excess of sodium hydride in dimethyl carbonate in the presence of traces of ethanol at 25 °C resulted in the formation of the keto-ester (**5**) in 81% yield. Reduction of (**5**) with sodium borohydride in ethanol at −45 °C gave the alcohol (**6**) (91%) which was protected as the t-butyldimethylsilyl ether (**7**) in 95% yield under standard conditions. Exposure of the ester (**7**) to Bu_2AlH in methylene chloride at −78 °C furnished the alcohol (**8**) (90%) which was oxidized to the aldehyde (**9**) with pyridinium chlorochromate (88%). Condensation of this aldehyde with the sodium salt of dimethyl 2-oxoheptylphosphonate led to the enone (**10**) in 81% yield, which after reduction with zinc borohydride furnished a 1:1 mixture of epimeric alcohols from which the (15*S*)-isomer (fast moving) (**11**) was separated chromatographically. Deprotection of (**11**) (AcOH–tetrahydrofuran–H_2O, 3:1:1, 45 °C) led to the dihydroxyketone (**12**) which underwent Wittig reaction with the sodium salt of 4-carboxybutyl(triphenyl)phosphorane (6 equiv.) in Me_2SO leading to carboprostacyclin (**2**) in 45% yield together with its 5(*E*)-isomer (less polar) from which it was separated chromatographically. The corresponding 15-*epi*-carboprostacyclin analogues were similarily obtained from the 15-epimer of (**11**).



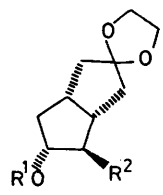
(1), X = O
(2), X = CH_2



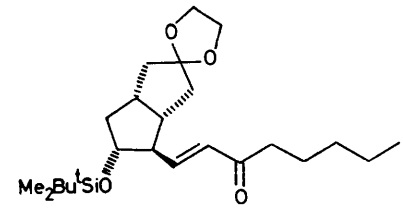
(3)



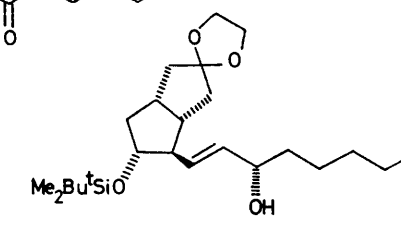
(4), R = H
(5), R = CO_2Me



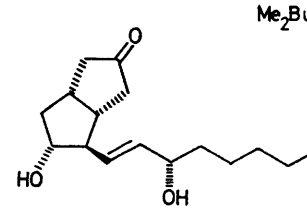
(6), R^1 = H, R^2 = CO_2Me
(7), R^1 = Si^tBuMe_2, R^2 = CO_2Me
(8), R^1 = Si^tBuMe_2, R^2 = CH_2OH
(9), R^1 = Si^tBuMe_2, R^2 = CHO



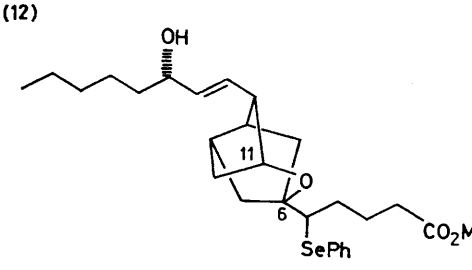
(10)



(11)



(12)



(13)

The α stereochemistry of the 11-hydroxy group in (**2**) was confirmed by phenyl selenide formation[4] (PhSeCl, −78 °C; CH_2Cl_2) of its methyl ester to afford the cage-type compound (**13**), the structure of which was based on spectroscopic data and conversion into the corresponding enone on treatment with MnO_2.

The stable carbocyclic analogue (**2**) of prostacyclin is a potent inhibitor of platelet aggregation‡ and its 5(*Z*) geometry is tentatively based on this property, since its geometrical isomer is relatively inactive.

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† All new compounds exhibited satisfactory spectral and analytical data.

‡ Tests on platelet aggregation were carried out in Professor J. B. Smith's laboratories, Thomas Jefferson University, Philadelphia, PA 19107.

[1] S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature*, 1976, **263**, 663.
[2] R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Sun, N. Wittaker, S. Bunting, J. Salmon, S. Moncada, and J. R. Vane, *Prostaglandins*, 1976, **12**, 915.
[3] For a review see: K. C. Nicolaou, G. P. Gasic, and W. E. Barnette, *Angew. Chem. Internat. Edn.* 1978, **17**, 293.
[4] K. C. Nicolaou and Z. Lysenko, *Tetrahedron Letters*, 1977, 1257.