Tetrahedron Letters,Vol.24,No.44,pp 4871-4874,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF A NEW SULPHUR-CONTAINING CARBAPROSTACYCLIN ANALOGUE

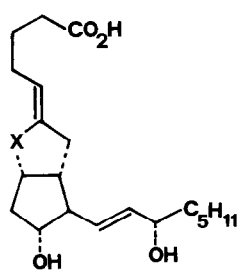
P.G. Baraldi[a], A. Barco[b], S. Benetti[b], C.A. Gandolfi[c], G.P. Pollini[a] and D. Simoni[a]

a) Istituto di Chimica Farmaceutica, Ferrara b) Istituto Chimico, Ferrara
c) C. Erba - Farmitalia S.p.A., Milano

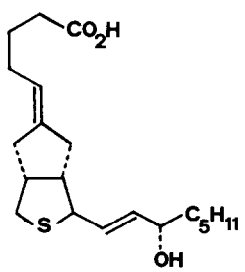
ABSTRACT: The synthesis of tetrahydro-cis-cyclopenta[c]thiophen-5-one ethylene ketal 5 and its transformation into 11-thia-carbacyclin analogues are described.

Most of the biological and pharmacological activities of prostacyclin (PGI_2) 1 are still retained when its characteristic bicyclo[3.3.0] octane framework was replaced by a perhydropentalene nucleus[1]. Other changes made in the same skeleton (for instance 4-oxabicyclo-[2] and 2-thiabicyclo[3.3.0]-octane[3] analogues) did not appear fortunate enough to yield close mimics of the natural substance. The presence of a C-11 hydroxy group seems to be an essential requisite for a biological response[4]. A recent report[5] showed that in one case the lack of the C-11 hydroxy group in carbaanalogs seems to induce *in vivo* a selective antagonism against blood pressure lowering activity of the PGI_2 putting out in evidence the dramatic role of this C-11 appendix in recognizing the receptor site.

To furtherly probe this matter, we planned the synthesis of the novel stable analogue 3, carrying a sulphur atom in place of the hydroxymethine group in C-11 position.



1 X = O
2 X = CH_2



3

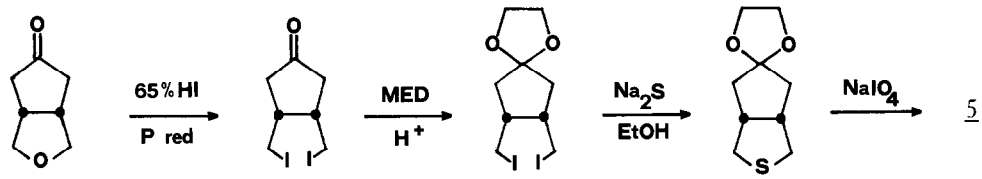
4

5

We chose the sulphur analogue 5 of the monoketal of cis-bicyclo [3.3.0] octane-3,7-dione 4, a classical intermediate in carbacyclin synthesis[1], as a bifunctional starting material.

This synthon offers the opportunity to introduce the required side-chains taking advantage of the protected carbonyl group and of the acidity of the hydrogen atoms adjacent to the sulphoxide moiety.

The preparation of 5 was achieved as outlined in the scheme starting from the known tetrahydro-cis-cyclopenta[c]furan-5-one, 6[6], which was transformed by standard steps into the bicyclic sulphide 9.*

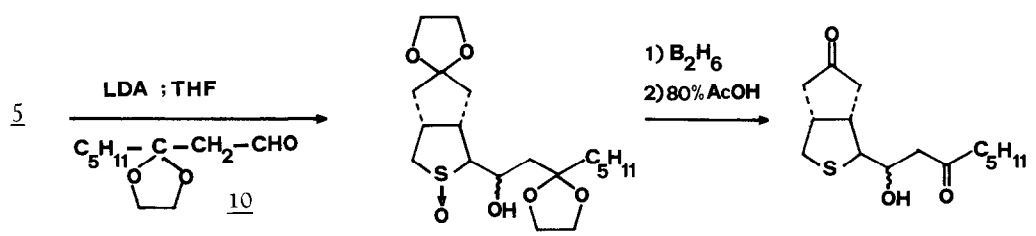


6 7 8 9 5

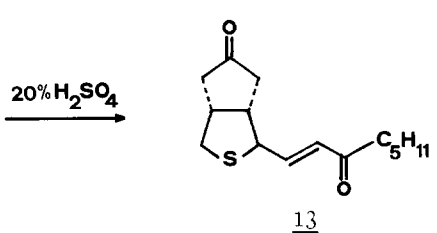
Oxidation of 9 with sodium metaperiodate proceeded cleanly to give almost exclusively 5, where the S-O bond is cis to the junction hydrogens as can be deduced from the NMR studies on related compounds[7].

The introduction of the ω-chain was performed by reaction of the carbanion generated from 5 with LDA in THF with the protected aldehyde (10)[8] producing an 80% yield of an unseparable mixture of aldols 11.

Diborane promoted deoxygenation followed by deketalization (80% aqueous acetic acid) led to the β-hydroxyketone 12, which was dehydrated with 20% sulfuric acid to afford the αβ-trans-enone 13 (75% overall yield from 5).**

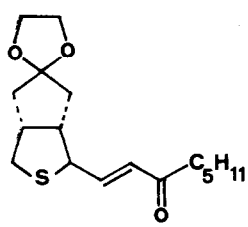


11 12

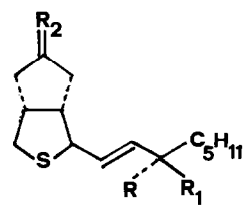


13

The two carbonyl functions of 13 were chemoselectively differentiated by ketal exchange with 2-methyl-2-ethyl-1,3-dioxolane (MED) at room temperature to produce quantitatively 14, which was reduced with $NaBH_4$ at 0°C to give an unseparable mixture of the epimeric alcohols 15a,b. Removal of the ketal protective group by action of dilute sulfuric acid allowed the separation of the epimers 16a and 16b by column chromatography on silica gel, as oils with almost identical spectroscopic properties. Condensation of the single C-15 epimers with (4-carboxybutylene)triphenylphosphorane in DMSO in the presence of K tert-butoxide for 3h at 30°C gave rise to 3 and its 15(R)-epimer, which were obtained as homogeneous oils after chromatography on silica gel (eluent Et_2O-Petroleum ether 3:1), in 30% and 16% yield respectively, as unseparable E/Z mixture.



14



15a R=OH;R_1=H;R_2=O$(CH_2)_2$O
15b R=H;R_1=OH;R_2=O$(CH_2)_2$O
16a R=OH;R_1=H;R_2=O
16b R=H;R_1=OH;R_2=O

The two new 11-deoxy-11-thia carbaprostacyclin analogues are characterized by a very weak antiaggregatory activity and are not able to antagonize prostacyclin in vivo.***

References and Notes

1. W. Bartmann and G. Beck, Angew.Chem.Int.Ed., 1982, 21, 751 and references reported therein.
2. S. Ohuchida, S. Hashimoto, H. Wakatsuda, Y. Arai and M. Hayashi, IV Int. Prostagl. Conference Washington D.C., May 27-31, 1979, Abstracts pag. 88.
3. K.C. Nicolaou, G.P. Gasic and W.E. Barnette, Angew.Chem.Int.Ed., 1978, 17, 293.

4. K. Shimoji, Y. Arai, H. Wakatsuka and M. Hayashi, IV Int.Prostagl. Conference Washington D.C., May 27-31, 1979, Abstracts pag. 106.

5. N. Mongelli, O. Magni, C.A. Gandolfi, M. Grossoni and R. Ceserani, Adv.Prostagl.Thromb.Leukot.Res., Raven Press, N.Y., 1983, 11, 281.

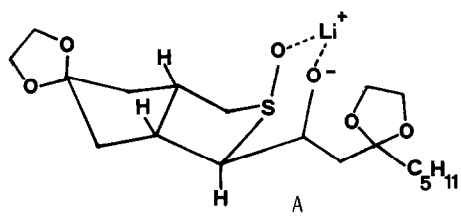
6. P.G. Baraldi, A. Barco, S. Benetti, G.P. Pollini and D. Simoni, Tetrahedron, in press.

* All new compounds gave satisfatory elemental analysis and spectra consistent with the assigned structures.

7. S. Lavielle, S. Bory, B. Moreau, M.J. Luche and A. Marquet, J.Am.Chem. Soc., 1978, 100, 1558.

8. K. Sakai, T. Kabori and T. Fujisawa, Tetrahedron Lett., 1981, 22, 115.

** The preferential formation of 13 may be accounted for by the chair-like six center transition state A in the aldolization process which favours the delivering of the chain cis to the S — O bond and trans to the cyclopentane ring.



A

NMR ($CDCl_3$) and IR data are given for:

5: δ=1.5-2.3 (m, 4H); 2.5-2.8 (m, 2H); 2.9-3.5 (m, 4H); 3.9 (s, 4H). m.p. 70-71°C.

13: δ=0.9 (t, 3H, J=4Hz); 1.1-1.9 (m, 8H); 2.1-3.5 (m, 8H); 3.7 (dd, 1H, J=8Hz), 6.1 (d, 1H, J=15Hz); 6.6 (dd, 1H, J=15, J=8Hz).
IR (film): 1740, 1720, 1620, 990 cm^{-1}.

3: δ=0.9 (t, 3H, J=4Hz); 1-3.3 (m, 23H); 3.4-3.7 (m, 1H); 3.9-4.2 (m, 1H); 4.5-5.3 (m, 3H); 5.4-5.6 (m, 2H).
I.R. (film): 3300, 1710 cm^{-1}.

*** We thank Dr. R. Ceserani and M. Bergamaschi for these preliminary biological results.

(Received in UK 30 June 1983)