Tetrahedron Letters,Vol.23,No.40,pp 4113-4114,1982 0040-4039/82/404113-02$03.00/0
Printed in Great Britain

A STEREOSPECIFIC SYNTHESIS OF 9,11-AZO-PGH_1 DERIVATIVES - POTENTIAL INHIBITORS OF BLOOD PLATELET AGGREGATION

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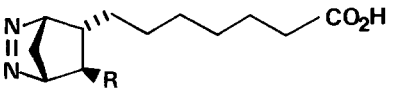
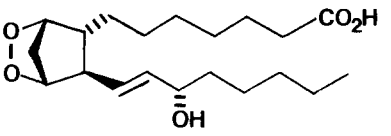
Abstract The stereospecific synthesis of the novel 9,11-azo-PGH_1 analogues 2 and 3 from the bicyclic intermediate 9 is reported

The 9,11-azo-PGH_1 analogue 1 is a potent inhibitor of human blood platelet aggregation which acts by blocking both thromboxane A_2 (TXA_2) synthetase and the PGH_2/TXA_2 receptors [1] Interestingly, the simple bicyclic compounds 4 and 5, which lack both side chains, also exhibit anti-aggregatory activity[2] whereas certain analogues lacking only the top side chain are inactive.[3] These findings prompted us to report our own work in this area and we describe herein a synthesis of the novel 9,11-azo-PGH_1 analogues 2 and 3 which lack the bottom side chain and the 15-hydroxy group of 1 respectively The synthesis proceeds via the key intermediate 9 which is easily prepared and purified on a large scale without recourse to tedious chromatography (cf. ref. 1) and can be used to prepare a variety of related analogues including the known[1] TXA_2 'synthetase inhibitor/receptor blocker'

Clearly analogues 2 and 3 will provide a deeper insight into the structure-activity relationship of this class of compound which in turn will define future objectives in the search for anti-thombotic drugs

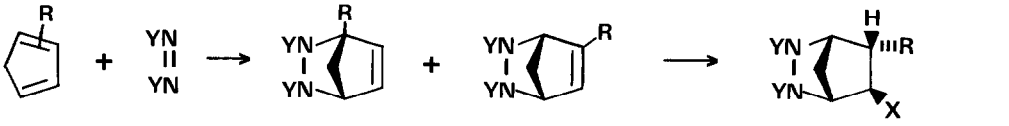


1 R = $OCH_2CH(OH)(CH_2)_4CH_3$
2 R = H
3 R = $O(CH_2)_6CH_3$



PGH_1

	X-X
4	O-O
5	N=N



6 7 8 9 10 X = H; 11 X = OH; 12 X = O(CH$_2$)$_6$CH$_3$

R = (CH$_2$)$_6$CO$_2$CH$_3$ Y = CO$_2$CH$_3$

Sequential treatment of cyclopentadiene with methyllithium (0.95 equiv., THF, 0°, 0.5 h) followed by methyl 7-bromoheptanoate (0.8 equiv., 23°, 4 5 h) afforded a mixture of the 2- and 3-alkylated cyclopentadienes 6 in 83% yield Treatment of crude 6 with dimethyl azodicarboxylate 7 (0 95 equiv., ether, 23°, 6 h) gave a 43 57 mixture of the two isomeric adducts 8 and 9 in quantitative yield. Separation of the required isomer 9 was achieved by simply cooling a solution of the isomeric mixture in ether (0 8 ml/g) at -4° for one to seven days which gave a crystalline precipitate of 9 Filtration followed by one recrystallisation from ether afforded 9 both isomerically and analytically pure[4] in 45% yield from 6 (78% recovery) [m p 70-71°, NMR/CDCl$_3$ δ6 03 (1H, bs, C=CH), δ5 04 (1H, bs, ⩾CH), δ4 98 (1H, bs, ⩾CH), δ3.77 (6H, s, CH$_3$O$_2$CN), δ3 65 (3H, s, CO$_2$CH$_3$), δ1 77 (2H, m, ⟨CH$_2$⟩), ν_{max}/cm^{-1} 1730, 1720, 1700, TLC (silica, ether) R_f 0 53 - red colour with phosphomolybdic acid (PMA), cf isomer 8 R_f 0 61 - blue colour with PMA]

Catalytic hydrogenation of 9 (Pd, THF) gave the reduced compound 10 (99%) derived from the *cis*-addition of hydrogen to the least hindered *exo*-face of 9[5] Hydrolysis of 10 (KOH, HO(CH$_2$)$_2$OH, 120°, 5 h) followed by the addition of excess aq. CuCl$_2$ at pH 7 afforded the copper complex of 2 as an insoluble red precipitate Treatment of this complex with aq NaOH liberated the required analogue 2 [m.p. 68-69°] in 76% yield from 9 Hydroboration - oxidation[6] of 9 afforded the *exo, trans*-alcohol 11 [85%, m p 67-68°] which was treated sequentially with NaH (2 equiv , DMSO, 30°, 0 5 h) followed by 1-iodoheptane (4 equiv , 23°, 7 h) to give 12 (55%) Hydrolysis of 12 followed by oxidation, as described above, gave the analogue 3 (51%) as a pale-yellow oil Biological evaluation of 2 and 3 will be reported at a later date [7]

REFERENCES AND NOTES

1 S T Kam, P S. Portoghese, J M Gerrard and E W. Dunham, *J. Med. Chem.*, *22*, 1402 (1979)

2 N A Porter, J H Roycroft, J Nixon, D. Gilmore and D B Mengel, *Fed. Proc Fed Am Soc Exp. Biol.*, *37*, 608 (1978)

3 S T Kam, R N Hanson and P S Portoghese, *J Pharm Sci , 69*, 1007 (1980).

4 All intermediates were characterised by 100 MHz PMR, IR, and high resolution mass spectra All stereochemical assignments were unambiguously confirmed by PMR spectroscopy.

5 M F Ansell, M P L Caton and P C North, *Tetrahedron Letters, 22*, 1723 (1981)

6 E L Allred, C L. Anderson and R.L Smith, *J Org Chem , 31*, 3493 (1966)

7. The financial support of a Science Research Council CASE award to P C North is gratefully acknowledged.

(Received in UK 16 July 1982)