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OXYALLYLS IN SYNTHESIS: PREPARATION OF TRICYCLIC THROMBOXANE A_2 ANALOGUES

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ABSTRACT: We describe the formation of 1-(dimethoxymethyl)-2-(2-phenylethenyl)-8-oxabicyclo[3.2.1]oct-6-en-3-ol (4) using oxyallyl methodology, and conversion of this into two 2,6-dioxatricyclo[3.3.1.$0^{3,7}$] nonanes (9) and (10) via iodoetherification and reduction. These compounds were then elaborated into the novel thromboxane analogues (11) and (12).

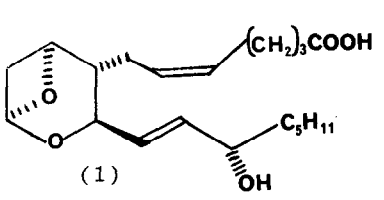
The thromboxanes are probably the least studied of the arachidonate metabolites, not least because the first formed species, thromboxane A_2(TXA_2,1) has a biological half-life of only 30 seconds.[1] A number of analogues have been prepared,[2] and a few of these either inhibit the formation of TXA_2, or antagonise its vasoconstrictive and platelet aggregating activities. Most of these compounds overcome the inherent instability of the dioxabicyclo system through replacement of one or both of the oxygen atoms with carbon, nitrogen or sulphur atoms. Our strategy was to produce structural analogues which possessed a different combination of ring-sizes.

The basic oxabicyclo[3.2.1] ring system was established by means of a cycloaddition between the oxyallyl (2)[3] [from 3-bromo-5-phenylpent-4(E)-ene-2-one in CF_3CH_2OH containing one equiv. of Et_3N] and furfural dimethyl acetal (15-fold excess). The major product (3) (overall yield of 26% for the bromination and cycloaddition steps) was the one anticipated on the basis of our own[4] and Hoffmann's[3] previous work (first bond forms between the least substituted carbon centres in non-synchronous cycloadditions). Reduction with $K^+(sec\text{-}Bu)_3\overset{\ominus}{B}H$ in THF at -78°C produced axial alcohol (4) almost exclusively (olefinic H at 6.40 p.p.m.) with only traces of the corresponding equatorial alcohol (olefinic H at 6.10 p.p.m.). Formation of the axial alcohol (5) is always favoured when cycloadducts of general structure (6) are reduced (even with $NaBH_4$ in alcohol solvents ratios of axial:equatorial of 6:1 or better are produced), and the relative positions of the olefinic ^1H-signals is also of general utility for structure assignment.

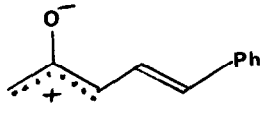
Iodoetherification of (4) (I_2/CH_2Cl_2/aq. $NaHCO_3$) provided the two

iodoethers (7) and (8) in the ratio of 3:2 (combined yield 72%). Structure assignment was achieved through n.m.r. analysis: methoxyl signals for (7) at 3.44 and 3.58 p.p.m. ($\Delta\delta$ 0.14 p.p.m.), and for (8) at 3.50 and 3.54 p.p.m. ($\Delta\delta$ 0.04 p.p.m.); and 7-H signal for (7) at 4.97 p.p.m. (d, $J_{3,7}$, 3.5Hz), and for (8) at 4.52 p.p.m. (singlet). Each isomer was reduced to yield the desired dioxatricyclic systems (9) and (10) in near quantitative yield (Bu_3SnH/toluene/AIBN). These were then converted into the TXA_2 analogues (11) and (12) using standard prostanoid methodology[5].

Both analogues (as mixtures of C-15 epimers) had potent TXA_2-like activity, and these biological results will be described elsewhere.



(1)



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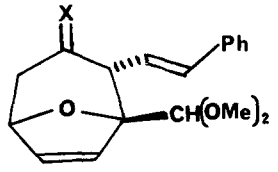
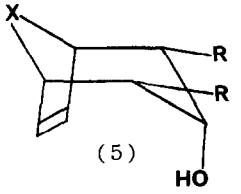


(3) X=O

(4) X=αOH, βH



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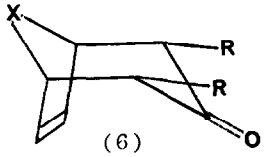
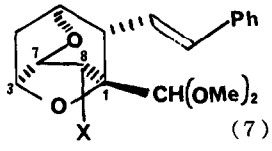


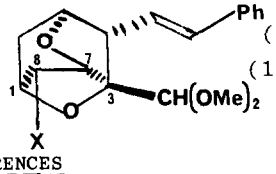
(6)



(7) X=I

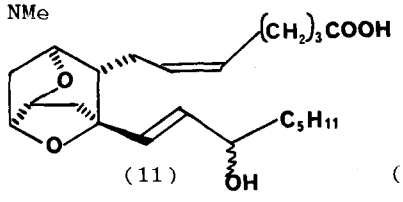
(9) X=H

R = alkyl or aryl, X = O, NMe

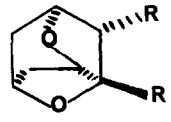


(8) X=I

(10) X=H



(11)



(12) side-chains as in (11)

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1. M.Hamberg, J.Svensson, and B.Samuelsson, Proc.Nat.Acad.Sci.USA, 1975, 72, 2994.
2. R.J.K.Taylor in 'New Synthetic Routes to Prostaglandins and Thromboxanes', (S.M.Roberts and F.Scheinmann, eds.), Chapter 7, Wiley, 1982.
3. H.M.R.Hoffmann, Angewandte Chemie, 1984, 1.
4. 1-Bromo-1-phenylpropanone and furfural dimethylacetal give exclusively 1-(dimethoxymethyl)-2-phenyl-8-oxabicyclo[3.2.1]oct-6-en-3-one.
5. The sequence was:
   (i) O_3 then Me_2S (74%);
   (ii) Ph_3P = CHOMe (74%);
   (iii) $Hg(OAc)_2$ (86%);
   (iv) Ph_3P = $CH(CH_2)_3CO_2^{\ominus}K^{\oplus}$ then CH_2N_2 (70%);
   (v) H^+ then $(MeO)_2PO.\overset{\ominus}{C}HCO.C_5H_{11}$ (21%);
   (vi) $NaBH_4$ (97%)

[The yields given are for the conversion of (9) into (11). Yields for the sequence (10) to (12) were identical within a few percent]

All new compounds were fully characterised by IR, NMR (400 MHz), and high resolution *mass spectrometry or microanalytical methods.*

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