A Photochemical Synthesis of a Thromboxane A_2 Analogue *via* Intramolecular Trapping of an Oxacarbene by an Hydroxy Group

Stephen W. Jones,[a] Feodor Scheinmann,[a] Basil J. Wakefield,[a] David Middlemiss,[b] and Roger F. Newton*[b]

[a] *The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT, U.K.*

[b] *Chemistry Division, Glaxo Group Research Ltd., Ware, Herts SG12 0DJ, U.K.*

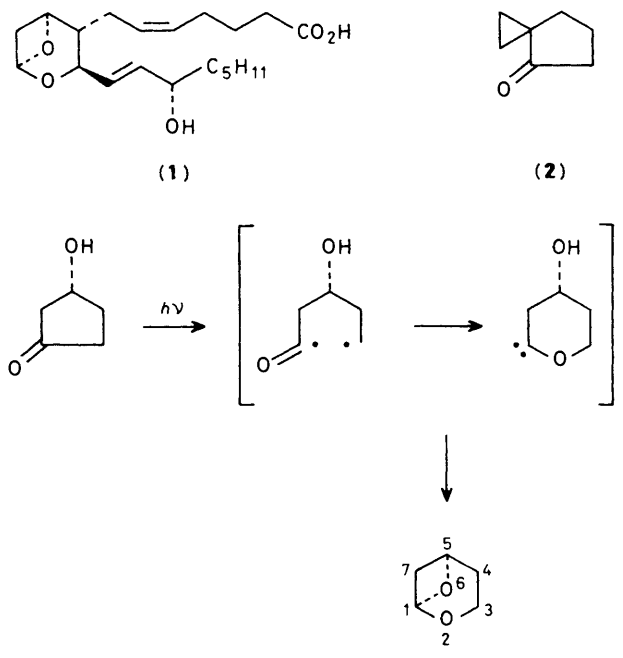
A spiro substituted 2,6-dioxabicyclo[3.1.1]heptane (the thromboxane A_2 ring system) has been prepared by intramolecular trapping of a photochemically generated oxacarbene.

The 2,6-dioxabicyclo[3.1.1]heptane ring system of thromboxane A_2 (**1**) is very labile under acidic and mildly basic conditions.[1] The recent syntheses of this ring system[2] and of thromboxane A_2 itself[3] have overcome this problem by using the more stable 7-heterosubstituted dioxabicycloheptanes and removing the heteroatoms at a late stage. An alternative and novel strategy would be to trap a photochemically generated oxacarbene intramolecularly by an hydroxy group (Scheme 1).

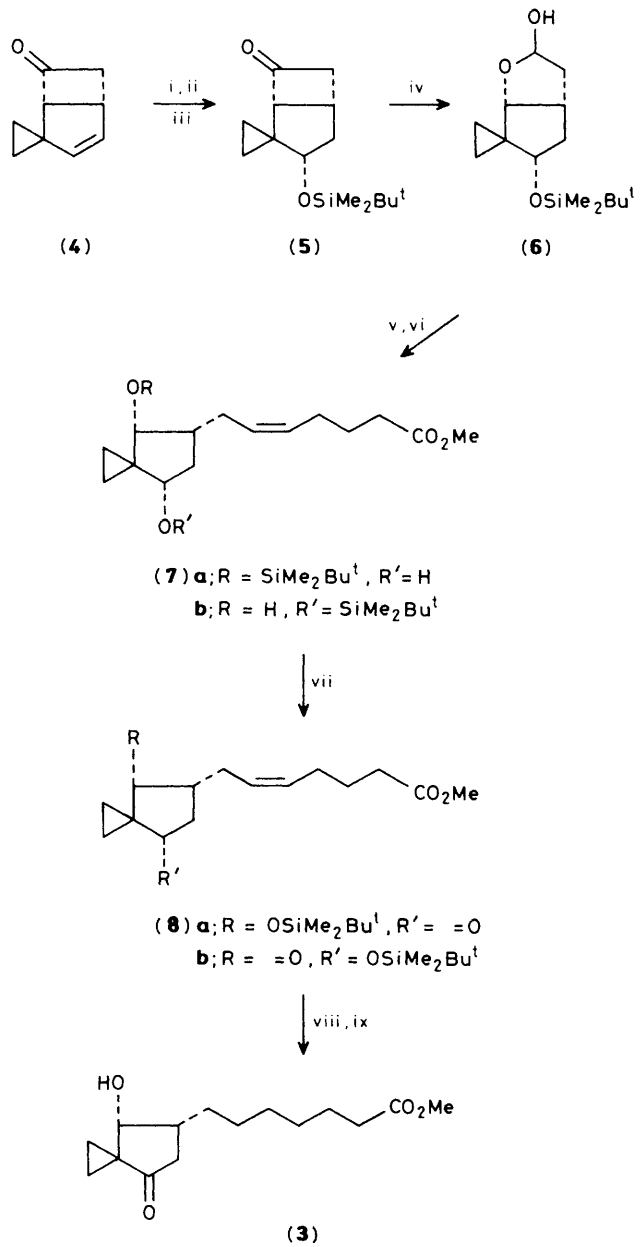
Since, unlike cyclobutanones, unsubstituted cyclopentanones do not undergo photochemically induced ring expansion[4] the unusual photochemical behaviour of the spiro cyclopentanone system (**2**) was utilised.[5] The required model compound (**3**) was synthesised from the corresponding bicyclo[3.2.0]heptanone (**4**)[6] as shown in Scheme 2.

Photolysis of the derived ketone (**5**) in aqueous acetonitrile[7] afforded the lactol (**6**) which was subjected to a Wittig reaction and esterification. Under the conditions of the Wittig reaction silyl migration occurred[8] to give a mixture of alcohols (**7a**) and (**7b**). Oxidation produced the ketones (**8a**) and (**8b**) which were separated by chromatography. Deprotection and reduction of (**8a**) then afforded the required model compound (**3**).

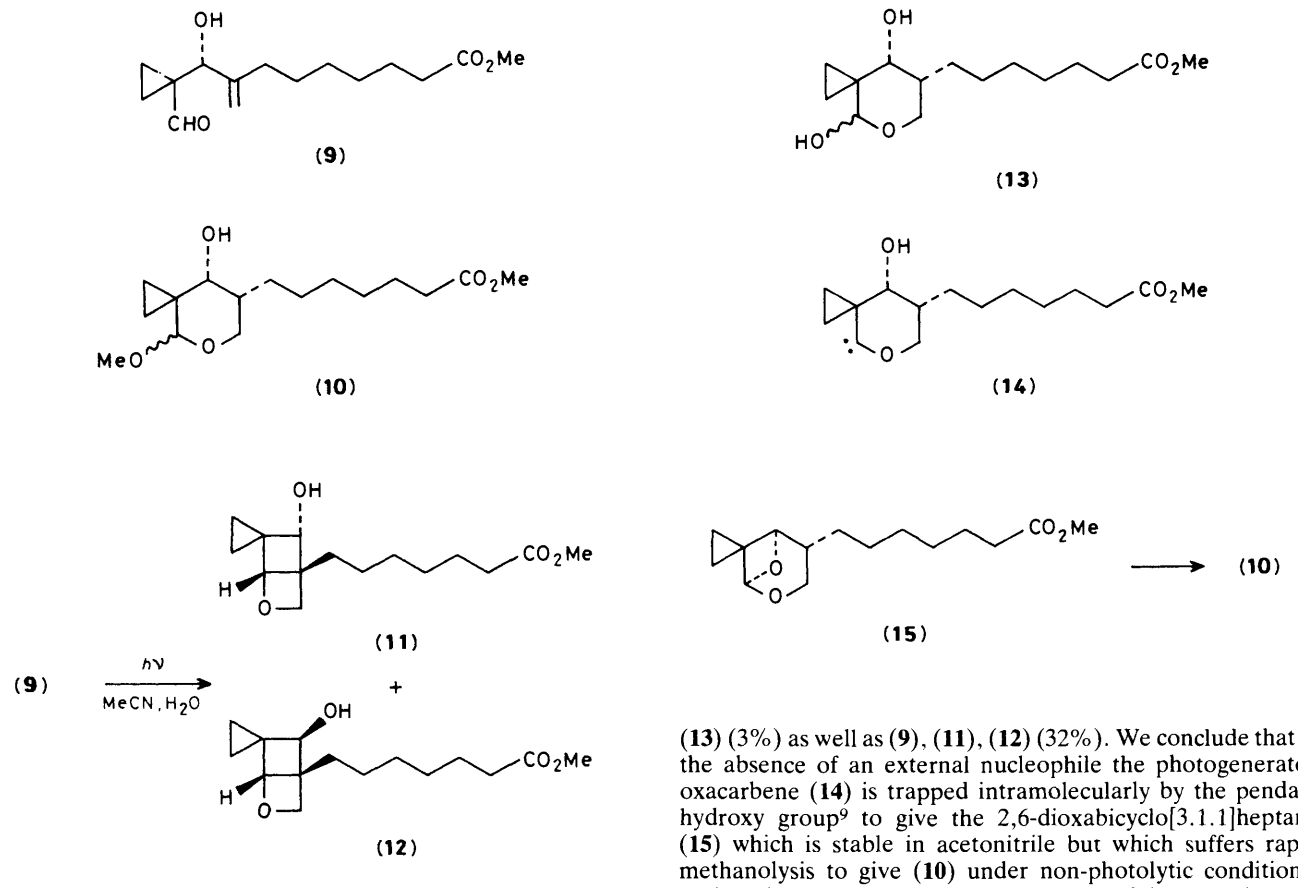
Photolysis of (**3**) in dry methanol using a 125 W medium pressure mercury arc and quartz apparatus gave as the major products the unsaturated aldehyde (**9**) and the hydroxy acetal



Scheme 1



Scheme 2. *Reagents:* i, *N*-bromo-acetamide (NBA), H_2O, Me_2CO; ii, Bu_3SnH, azoisobutyronitrile (AIBN); iii, Bu^tMe_2SiCl, imidazole, dimethylformamide (DMF); iv, *hν*, MeCN, H_2O; v, $BrPh_3P(CH_2)_4CO_2H$, $KOBu^t$, tetrahydrofuran (THF); vi, CH_2N_2; vii, pyridinium chlorochromate (PCC), NaOAc, CH_2Cl_2 then chromatography; viii, HF, H_2O, MeCN; ix, Pt, H_2.



Scheme 3

(**10**) which were isolated chromatographically in yields of 27% and 17% and fully characterised.†

The oxetanes (**11**) and (**12**) were identified as minor products and in a separate experiment (Scheme 3) shown to arise by an intramolecular cycloaddition reaction of the initially formed aldehyde (**9**), which itself is presumably formed by rearrangement of a diradical intermediate (*cf.* Scheme 1). Photolysis of (**3**) in aqueous acetonitrile solvent gave the unsaturated aldehyde (**9**) and the lactol (**13**). The formation of (**10**) and (**13**) clearly indicated that the required oxacarbene intermediate (**14**) was being generated and trapped by the methanol and water respectively.

Photolysis of the ketone (**3**) in dry acetonitrile and quenching the reaction with methanol up to four hours after the photolysis period gave the acetal (**10**) (25%) and the lactol (**13**) (3%) as well as (**9**), (**11**), (**12**) (32%). We conclude that in the absence of an external nucleophile the photogenerated oxacarbene (**14**) is trapped intramolecularly by the pendant hydroxy group[9] to give the 2,6-dioxabicyclo[3.1.1]heptane (**15**) which is stable in acetonitrile but which suffers rapid methanolysis to give (**10**) under non-photolytic conditions. Although our evidence for the formation of the thromboxane A_2 analogue (**15**) is strong, we have not succeeded in isolating it; presumably the additional ring strain arising from the spirocyclopropyl group makes it even less stable than thromboxane A_2 itself.

We thank S.E.R.C. for a CASE award to S. W. J., and S. M. Roberts for valuable discussions.

Received, 21st April 1986; Com. 521

† Compound (**10**). Isomer *cis* 9-OH, 11-OMe: δ_H (250.13 MHz, $CDCl_3$) 1.90 (1H, m, H-8), 2.29 (2H, t, H-2), 2.89 (1H, br.d, H-9), 3.23 (1H, d, OH), 3.36 (3H, s, C-11-O*Me*), 3.52 (1H, dd, H-13), 3.67 (s, COO*Me*), 3.72 (t, H-13), 3.84 (1H, s, H-11); δ_C (62.9 MHz, $CDCl_3$) 8.4 and 10.1 (C-14 and C-15), 25.4 (C-10), 39.9 (C-8), 51.3 (COO*Me*), 55.1 (C-11-O*Me*), 59.3 (C-13), 74.2 (C-9), 105.5 (C-11), 174.1 (C-1).

Isomer *trans* 9-OH, 11-OMe: δ_H 3.41 (s, C-11-O*Me*), 4.65 (s, H-11); δ_C 5.5 and 7.0 (C-14 and C-15), 26.7 (C-10), 40.8 (C-8), 56.4 (C-11-O*Me*), 64.9 (C-13), 74.5 (C-9), 101.0 (C-11).

References

1 M. Hamserg, J. Svensson, and B. Samuelsson, *Proc. Natl. Acad. Sci. USA*, 1975, **72**, 2994.
2 S. S. Bhagwat, P. R. Hamann, and W. C. Still, *Tetrahedron Lett.*, 1985, 1955; J. Fried, E. A. Hallinan, and M. J. Szwedo, *J. Am. Chem. Soc.*, 1984, **106**, 3872.
3 S. S. Bhagwat, P. R. Hamann, and W. C. Still, *J. Am. Chem. Soc.*, 1985, **107**, 6372.
4 P. Yates and R. O. Loutfy, *Acc. Chem. Res.*, 1975, **8**, 209.
5 D. R. Morton, E. Lee-Ruff, R. M. Southam, and N. J. Turro, *J. Am. Chem. Soc.*, 1970, **92**, 4349.
6 K. Jarowicki and T. Jaworski, *Monatsh. Chem.*, 1984, **115**, 605.
7 N. M. Crossland, D. R. Kelly, S. M. Roberts, D. P. Reynolds, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 682.
8 C. Howard, R. F. Newton, D. P. Reynolds, and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2049.
9 M. Pirrung, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1043; H. G. Davies, S. M. Roberts, B. J. Wakefield, and J. A. Winders, *J. Chem. Soc., Chem. Commun.*, 1985, 1166, and references therein.