

## A Photochemical Route to a Thromboxane A<sub>2</sub> Ring Analogue

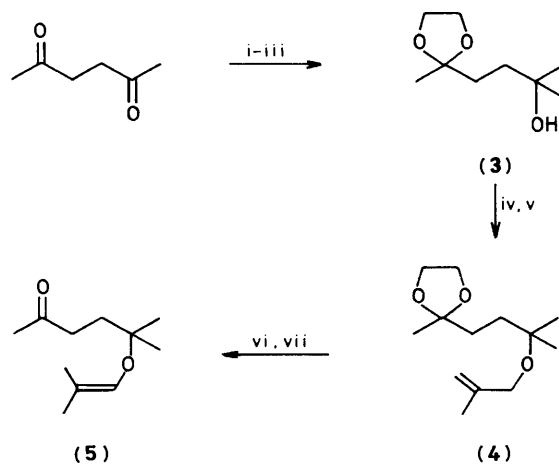
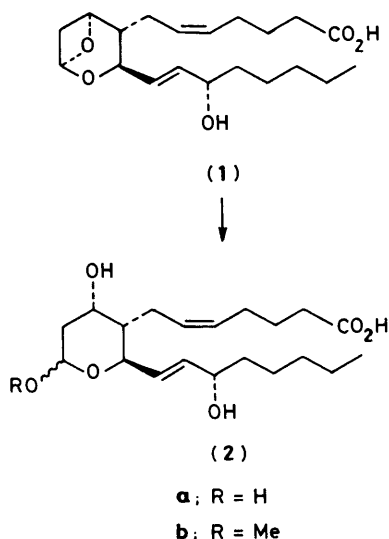
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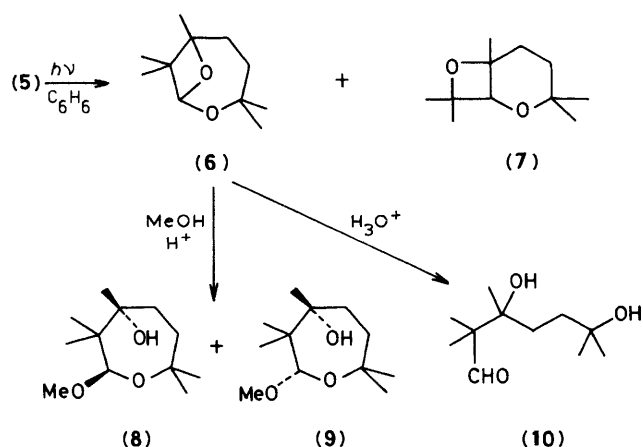
Two examples of methyl-substituted 2,7-dioxabicyclo[4.1.1]octanes (**6**) and (**12**) have been prepared by intramolecular photocycloaddition of the vinyloxycarbonyl compounds (**5**) and (**11**), respectively.

There is much interest in the role of prostaglandins and thromboxanes in important physiological processes.<sup>1,2</sup> In contrast with the well-characterized prostaglandins and prostacyclin, thromboxane A<sub>2</sub> is an unstable substance (half-life *ca.* 32 s at 37 °C and pH 7.4). Its structure was proposed as (**1**), a derivative of the 2,6-dioxabicyclo[3.1.1]heptane ring, by Samuelsson and co-workers,<sup>3</sup> on the basis of its ready reaction

with nucleophiles such as water or methanol to give thromboxane B<sub>2</sub> (**2a**) or the methyl derivative (**2b**), respectively. The combination of a highly strained oxetane ring and the acetal function has so far defeated synthetic efforts, and analogues produced have replaced one<sup>4</sup> or both<sup>5</sup> ring oxygen atoms by carbon, or by sulphur,<sup>6</sup> or have replaced the oxetane ring by tetrahydrofuran.<sup>7</sup> In fact, the only syntheses of 2,6-



**Scheme 1.** Reagents: i, HOCH<sub>2</sub>CH<sub>2</sub>OH, H<sup>+</sup>, C<sub>6</sub>H<sub>6</sub>; ii, MeMgI, Et<sub>2</sub>O; iii, H<sub>2</sub>O; iv, NaH, tetrahydrofuran; v, CH<sub>2</sub>=C(Me)CH<sub>2</sub>Br; vi, CF<sub>3</sub>CO<sub>2</sub>H, H<sub>2</sub>O, dioxane; vii, Pd-C, toluene, reflux.



dioxabicyclo[3.1.1]heptanes are those reported by Schuerch for some protected 1,3-anhydro-glucopyranose and -mannopyranose derivatives.<sup>8</sup> Our interest in photochemical [2 + 2] cycloadditions<sup>9</sup> suggested to us that the 2-alkoxyoxetane core of a thromboxane might be constructed by intramolecular reaction of a carbonyl group to a vinyl ether. We now describe a synthesis of the previously unknown 2,7-dioxabicyclo[4.1.1]octane ring system which relies on this reaction.

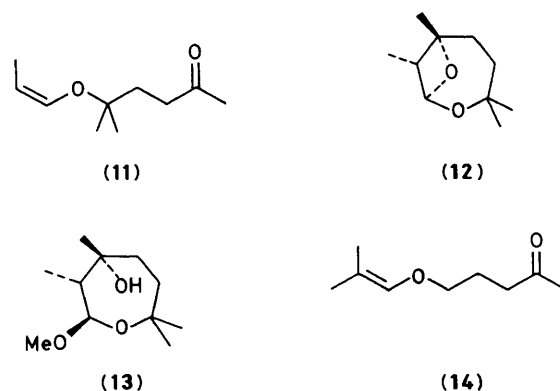
The synthesis of the vinyloxyketone (5)<sup>†</sup> is shown in Scheme 1. Hexane-2,5-dione was first converted to the hydroxyacetal (3). After alkylation of the hydroxy group to give (4), the carbonyl group was deprotected. Finally, isomerisation of the allyl ether to the vinyl ether (5) was effected by palladium on carbon.<sup>10</sup> Irradiation of (5) in benzene solution<sup>‡</sup> gave two intramolecular adducts, (6) and (7) (11% and 54%, respectively), which were isolated by flash column chromatography.<sup>11</sup> The orientation of addition in (6) was easily shown from its <sup>1</sup>H n.m.r. spectrum, which showed a low-field 1-H singlet at  $\delta$  5.02.<sup>12</sup>

In contrast with thromboxane A<sub>2</sub>, the bicyclic dioxaoctane (6) proved to be relatively stable towards pure methanol. However, it reacted extremely readily with nucleophiles in the presence of traces of acid: reaction with acidic (0.002 M trifluoroacetic acid) methanol occurred within 5 minutes at room temperature to give two hydroxyacetals (8) and (9),<sup>§</sup> isolated in 22% and 45% yields, respectively. There is a close analogy here to the proposed reaction of thromboxane A<sub>2</sub> with methanol, which also gave two epimeric acetals (2b).<sup>3</sup> The reaction of (6) with aqueous trifluoroacetic acid gave the dihydroxyaldehyde (10) in quantitative yield.

<sup>†</sup> The structure of new compounds was supported by <sup>1</sup>H and <sup>13</sup>C n.m.r. spectroscopic methods, and by elemental analysis or mass spectrometry.

<sup>‡</sup> A solution of (5) (1.5 g) in benzene (600 ml) in the presence of sodium carbonate (20 mg) was irradiated using quartz apparatus and a centrally-positioned 450 W medium-pressure mercury arc lamp.

<sup>§</sup> N.m.r. data: (8) <sup>1</sup>H (200 MHz, CDCl<sub>3</sub>)  $\delta$  0.92, 0.96, 1.19, 1.24 and 1.32 (each 3 H, s, Me), 1.27–1.49 (2 H, m, CH<sub>2</sub>), 1.62 (1 H, br. s, OH), 1.91–2.16 (2 H, m, CH<sub>2</sub>), 3.35 (3 H, s, OMe), and 4.44 (1 H, s, CH-OMe);  $\delta_c$  (C<sub>6</sub>D<sub>6</sub>) 17.8, 19.4, 27.0, 27.5 and 28.8 (5  $\times$  Me), 34.0 and 34.1 (C-4 and C-5), 47.2 (C-2), 54.9 (OMe), 73.0 and 73.7 (C-3 and C-6), and 99.6 (C-1) p.p.m.; (9) <sup>1</sup>H (200 MHz, CDCl<sub>3</sub>)  $\delta$  0.90, 1.04, 1.17, 1.28 and 1.30 (each 3 H, s, Me), 1.44–2.08 (5 H, m, 2  $\times$  CH<sub>2</sub> and OH), 3.43 (3 H, s, OMe), and 4.20 (1 H, s, CH-OMe);  $\delta_c$  (C<sub>6</sub>D<sub>6</sub>) 18.1, 21.5, 25.2, 27.9, and 30.4 (5  $\times$  Me), 35.5 (C-4 and C-5), 47.0 (C-2), 56.2 (OMe), 74.7 and 75.0 (C-3 and C-6), and 105.3 (C-1) p.p.m.



Similar behaviour was observed on irradiation of the *cis*-unsaturated ketone (11), which yielded the *trans*-isomer of (11) (11%), two bicyclic isomers analogous to (7) (31%), and a single stereoisomer assigned the structure (12) (9%). The latter appeared to react with methanol even in the absence of added acid to give the hydroxyacetal (13) as a major adduct.

One limitation on the photocycloaddition at present is the need to retain substituents at the carbon  $\gamma$  to the carbonyl group, in order to prevent the Norrish type II photoreaction. Thus, irradiation of the vinyloxyketone (14) led efficiently to the production of 2-methylprop-1-enyl vinyl ether and acetone, detected by n.m.r. spectroscopy. It is possible that the irradiation of suitable cyclic vinyloxy carbonyl compounds may overcome this difficulty.

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