

**Factors governing the Ratio of Isomeric Oxabicyclo[3.2.1]octanones formed on Baeyer–Villiger Oxidation of Some 5-*endo*,7-*anti*-Disubstituted Bicyclo[2.2.1]heptan-2-ones**

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It was found that the outcome of Baeyer–Villiger oxidation of 5-*endo*,7-*anti*-disubstituted bicyclo[2.2.1]heptan-2-ones was influenced by at least three factors: (i) the electronegativity of the substituent at C-7; (ii) the hydrogen-bonding capability of the substituent at C-5; and (iii) the peracid employed. The optimum substituents and reaction conditions for oxidation of a bicycloheptanone to the corresponding 2-oxabicyclo[3.2.1]octan-3-one were delineated and used in the synthesis of a prostaglandin intermediate.

THE peracid oxidation of a ketone to an ester was first reported by Baeyer and Villiger<sup>1</sup> and the generally accepted two-step mechanism for the reaction (Scheme 1) was proposed by Criegee.<sup>2</sup> For unsymmetrical acyclic ketones, that group which is better able to support positive charge migrates preferentially.<sup>3</sup>

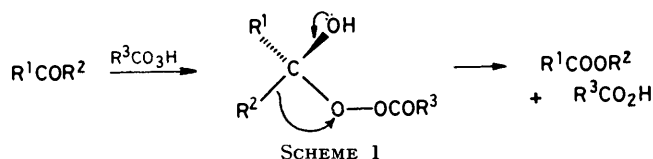
It is for the purpose of oxidation of cyclic ketones to lactones that the Baeyer–Villiger oxidation has been used most frequently in recent years, particularly in

<sup>1</sup> A. von Bayer and V. Villiger, *Ber.*, 1899, **32**, 3625.

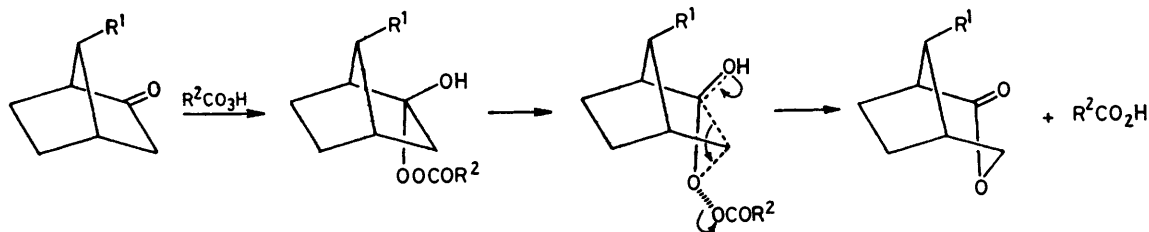
<sup>2</sup> R. Criegee, *Annalen*, 1948, **560**, 127.

<sup>3</sup> J. B. Lee and B. C. Uff, *Quart. Rev.*, 1967, **21**, 429.

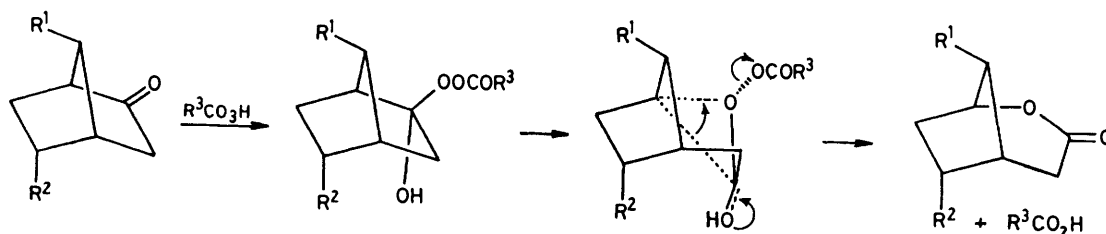
synthetic routes to prostaglandins,<sup>4</sup>  $\alpha$ -methylene- $\gamma$ -lactones,<sup>5</sup> and macrocyclic lactones.<sup>6</sup> For relatively inflexible cyclic ketones, steric factors can profoundly



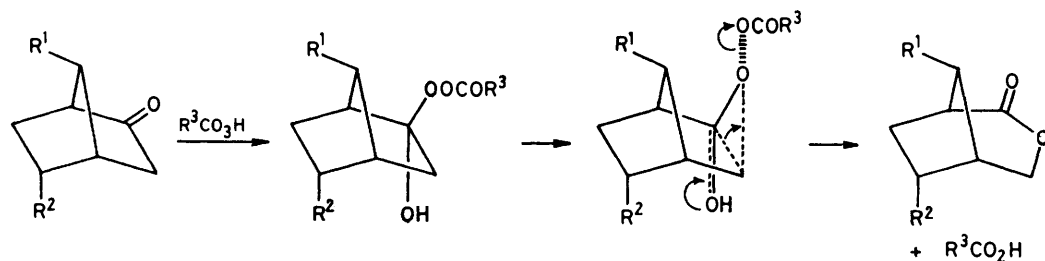
influence the mode of ring expansion to the extent that electronic preferences can be over-ridden. For instance,



7-*syn*-substituted bicyclo[2.2.1]heptan-2-ones are oxidised to the lactones derived from methylene group migration rather than to those expected to be formed on



electronic grounds through methine group (bridgehead) migration.<sup>7</sup> This has been rationalised<sup>8</sup> by assuming that the 7-substituent prohibits the approach of the



oxidant to the carbonyl carbon atom from the *exo*-face. Attack by the peracid thus takes place from the *endo*-face and rearrangement through a 'chair-like' transition state leads to the 3-oxabicyclo[3.2.1]octanone (Scheme 2).

<sup>4</sup> P. H. Bentley, *Chem. Soc. Rev.*, 1973, 2, 29; 'Chem. Soc. Specialist Periodical Reports,' K. B. Mallion, 'Aliphatic Chemistry,' 1976, vol. 4, p. 243.

<sup>5</sup> S. M. Ali and S. M. Roberts, *J.C.S. Perkin I*, 1976, 1934, and references therein.

<sup>6</sup> B. D. Mookherjee, R. W. Trenkle, and R. R. Patel, *J. Org. Chem.*, 1972, 37, 3846.

In the absence of a bulky 7-*syn*-substituent (e.g. for 5-*endo*,7-*anti*-disubstituted bicycloheptanones) peracid attack from the *exo*-face and rearrangement through a 'chair-like' transition state leading to the 2-oxabicyclo[3.2.1]octanone (Scheme 3) would be expected to be preferred to the formation of the 3-oxabicyclo[3.2.1]octanone through a 'boat-like' transition state (Scheme 4).

We had occasion to study the Baeyer-Villiger oxidation of various 5-*endo*,7-*anti*-disubstituted bicyclo[2.2.1]heptan-2-ones and we now report the influence of

substituents at these sites on the mode of ring expansion.

7-*anti*-Cyano-5-*endo*-methoxybicyclo[2.2.1]heptan-2-one (1)<sup>9</sup> gave only the 3-oxabicyclo-octanone (2) on

treatment with *m*-chloroperbenzoic acid. The product was identified by <sup>1</sup>H n.m.r. spectroscopy and particularly by the presence of the low field, geminally coupled

signals from the protons attached to C-4. 5-*endo*-Bromo-7-*anti*-cyanobicyclo[2.2.1]heptan-2-one (3) under the same oxidation conditions gave a mixture of isomeric lactones in the ratio 1 : 4. The isomers were separated

<sup>7</sup> R. R. Sauers and G. P. Ahearn, *J. Amer. Chem. Soc.*, 1961, 83, 2759; P. A. Grieco, C. S. Pogonowski, M. Nishizawa, and C.-L. J. Wang, *Tetrahedron Letters*, 1975, 254.

<sup>8</sup> H. O. House, 'Modern Synthetic Reactions,' Benjamin, New York, 1972, 2nd edn., p. 323.

<sup>9</sup> T. V. Lee, S. M. Roberts, and R. F. Newton, preceding paper.

by chromatography and the major product was identified as the lactone (4), while the minor component showed a low field signal due to H-1 in the n.m.r. spectrum consistent with this compound being the lactone (5).

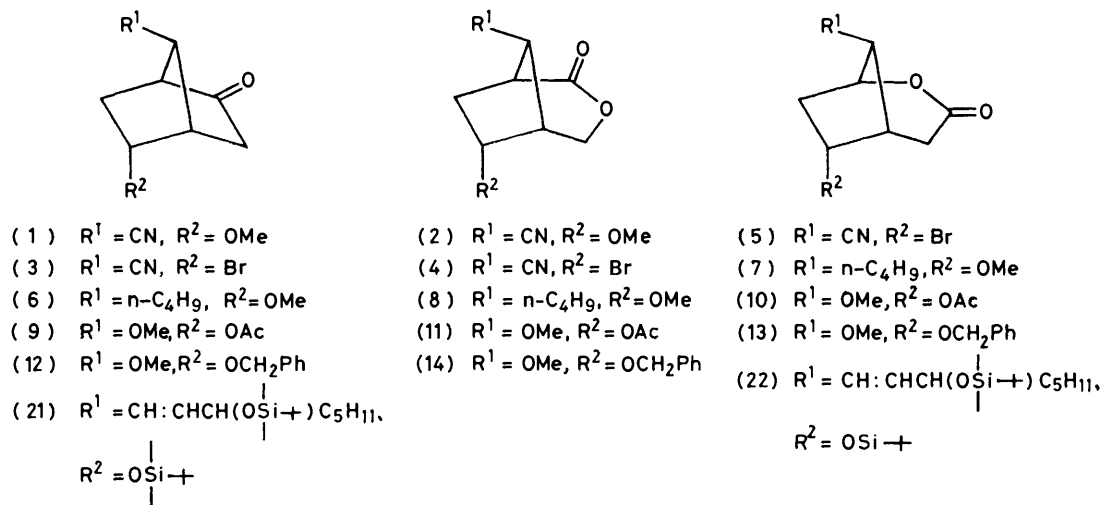
In contrast *m*-chloroperbenzoic acid oxidation of the 7-*anti*-butyl-5-*endo*-methoxybicycloheptanone (6)<sup>9</sup> gave mainly the lactone (7) resulting from bridgehead migration but n.m.r. spectroscopy and g.l.c. analysis indicated the presence of *ca.* 20% of an isomer, presumably the lactone (8).

Treatment of 5-*endo*-acetoxy-7-*anti*-methoxybicyclo-[2.2.1]heptan-2-one (9) with the same peracid gave a

and, secondly, integration of the <sup>1</sup>H n.m.r. spectra and determination of the ratio of protons resonating at high field ( $\delta < 3.5$ ) to those resonating at low field ( $5.5 > \delta > 3.5$ ). The estimations of the ratios of isomeric lactones by these two methods agreed to within  $\pm 3\%$ .

The reasons for the observed changes in the ratios of the lactones can be accommodated within the framework of the generally accepted mechanism of the Baeyer-Villiger reaction and may be summarised as follows.

Nucleophilic peracid attack at the carbonyl carbon atom is assumed to occur from the less hindered *exo*-face



mixture containing the lactones (10) and (11) in the ratio 7 : 3. This mixture was analysed most decisively by <sup>13</sup>C n.m.r. spectroscopy, with offset decoupling. The signal due to C-1 (doublet) in the lactone (10) appears at low field ( $\delta$  78.08) while that due to C-4 (triplet) is observed at high field ( $\delta$  36.98). For the lactone (11) the signals are interchanged; that due to C-1 appears at high field ( $\delta$  45.05) and the signal due to C-4 is found at low field ( $\delta$  66.03); the lower field signal indicates bonding of that carbon atom to the ring oxygen atom. Performic acid oxidation of the ketone (9) gave the lactone (10) only.

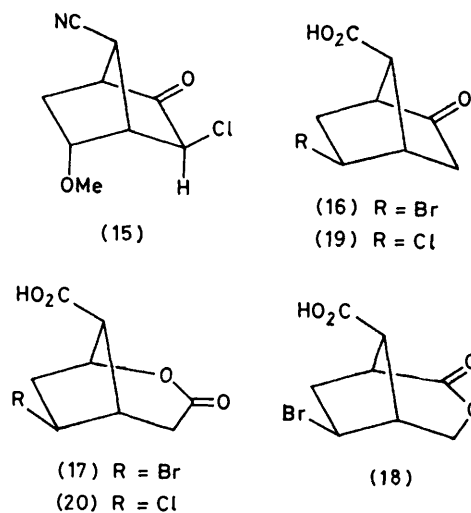
5-*endo*-Benzyloxy-7-*anti*-methoxybicycloheptanone (12) with *m*-chloroperbenzoic acid gave a mixture containing roughly equal amounts of the lactones (13) and (14). Other peracids gave mixtures rich in the 2-oxabicyclo-octanone (13) (Table). The ratios of the

Ratios of isomeric lactones (13) and (14) formed on oxidation of ketone (12) with peracid

Peracid	Solvent	Ratio (13) : (14)
<i>m</i> -Chlorobenzoic	CH <sub>2</sub> Cl <sub>2</sub>	55 : 45
Maleic <sup>10</sup>	CH <sub>2</sub> Cl <sub>2</sub>	67 : 33
Phthalic <sup>11</sup>	CHCl <sub>3</sub>	73 : 27
Formic	HCO <sub>2</sub> H	85 : 15
Acetic	CH <sub>3</sub> CO <sub>2</sub> H	92 : 8

isomeric lactones were assessed in two ways, first, integration of the signals in the <sup>13</sup>C n.m.r. spectra of the mixtures, after addition of chromium acetylacetonate

of the molecule: bridgehead migration and formation of a 2-oxabicyclo-octanone takes place through a 'chair-like' transition state (Scheme 3), methylene group migration, and 3-oxabicyclo-octanone formation *via* a 'boat-like' transition state (Scheme 4). Specific attack



from the *exo*-face in the oxidation of the ketones (1), (3), (6), (9), and (12) is substantiated by the unreactivity of

<sup>10</sup> R. W. White and W. D. Emmons, *Tetrahedron*, 1962, **17**, 31.

<sup>11</sup> E. E. Royals and L. L. Harrell, jun., *J. Amer. Chem. Soc.*, 1955, **77**, 3405.

the 3-*exo*-chloro-ketone (15) even under forcing oxidation conditions.

(a) The propensity for methylene group migration is increased on introducing an electron-withdrawing group at C-7 [cf. the oxidation of ketones (1), (6), and (12)]. The electron demand of the group at C-7 is obviously transmitted to C-1 which is then less able to support a build-up of positive charge as required for the migrating group in the rearrangement step. This effect has been observed previously; oxidation of the ketone (16) with peracetic acid gave the 2-oxa- (17) and the 3-oxa-bicyclo-octanones (18) in the ratio 7:2.<sup>12</sup> The later report of the 'clean' oxidation of the chloro-analogue (19) to the lactone (20) only is anomalous.<sup>13</sup>

(b) A pendant group at C-5 that is capable of hydrogen bonding to the transannular pseudoaxial hydroxy group at C-2 in the chair-like transition state (Scheme 3) encourages bridgehead (C-1) migration [cf. the oxidation of ketones (1), (3), and (9), (12)].

(c) The ease of loss of carboxylate anion from the Criegee intermediate and/or the ease of protonation of the acylperoxy unit in this intermediate will profoundly influence the rate of the second, rearrangement step of the oxidation. It has been argued that this rate should be slower and hence the rearrangement more selective on decreasing the acidity of the parent carboxylic acid.<sup>3</sup> In those cases in which a relatively safe comparison may be made, our findings are consistent with this postulate [cf. the oxidation of the ketone (12) (a) with permaleic acid or perphthalic acid in CHCl<sub>3</sub> or CH<sub>2</sub>Cl<sub>2</sub> and (b) with performic acid or peracetic acid in the corresponding alkanolic acid]. While other work has demonstrated that the bulk of the peracid oxidant can influence the outcome of a Baeyer-Villiger reaction,<sup>14</sup> it is difficult to assess the importance of this factor in the present study.

The above studies were undertaken to determine the optimum conditions for oxidation of the bicycloheptanone (21) to the lactone (22), a prostaglandin precursor. Hence, the most favourable oxidising medium for selective bridgehead migration, namely hydrogen peroxide in acetic acid buffered with sodium acetate, was applied to ketone (21). After chromatography, the lactone (22) was isolated in an acceptable yield (65%); also obtained was a trace amount of isomeric lactone and small amounts of more polar materials probably resulting from the loss of the acid-sensitive silyl protecting group(s) under the reaction conditions.

#### EXPERIMENTAL

<sup>13</sup>C N.m.r. spectra were recorded on a Varian CFT-20 spectrometer and are reported as chemical shifts downfield from tetramethylsilane. <sup>1</sup>H N.m.r. spectra were recorded on Varian A 60, Varian EM 360, or Perkin-Elmer R32 spectrometers in carbon tetrachloride unless otherwise stated. I.r. spectra were obtained on a Perkin-Elmer 257 spectrophotometer. Silica gel MFC was used for column

chromatography and silica gel G for t.l.c. Anhydrous magnesium sulphate was used as a drying agent for solutions in organic solvents. *m*-Chloroperbenzoic acid (Koch-Light) was used without further purification and ketones (1), (3), (6), (9), (12), and (21) were prepared by methods described elsewhere.<sup>9,15</sup>

*Oxidation of the Bicyclic Ketones (1), (3), (6), (9), and (12) using Peracid.—Method A.* To the appropriate bicyclic ketone (0.015 mol) in methylene chloride (15 ml) was added sodium hydrogencarbonate (0.1 mol) and *m*-chloroperbenzoic acid (0.025 mol). The mixture was stirred at room temperature. The excess peracid was decomposed by washing with aqueous 10% sodium sulphite. Finally the organic phase was washed with saturated sodium hydrogencarbonate solution, dried, and evaporated.

*Method B.* The bicyclic ketone (0.015 mol) in glacial acetic acid (10 ml) containing sodium acetate (0.1 mol) was treated with hydrogen peroxide (30% in water; 0.1 mol). After 36 h at room temperature sodium sulphite (0.2 mol) was added followed by water (20 ml). The aqueous solution was extracted with chloroform (4 × 10 ml) and the chloroform extracts were washed with water (3 × 10 ml) and saturated sodium hydrogencarbonate solution (15 ml). The aqueous extracts were back-extracted with chloroform (2 × 10 ml) and the combined organic fractions were dried and evaporated.

*Method C.* Hydrogen peroxide (30% in water; 1 mol) was added to a solution of ketone (0.1 mol) in 90% aqueous acetic acid (100 ml) containing anhydrous sodium acetate (0.1 mol). After stirring for 30 h at 50° the mixture was treated as described in method B.

*Method D.* To the ketone (0.02 mol) in formic acid (10 ml) was added hydrogen peroxide (30% in water; 0.1 mol). After 12 h the solution was treated as described in method B.

*Method E.* Maleic acid (0.6 g) was dissolved in dimethylformamide (1 ml) and hydrogen peroxide (30% in water; 0.2 g) was added. After 4 h at room temperature the ketone (0.5 g) in methylene chloride (10 ml) was added. After 9 h the solution was filtered and the filtrate was washed with saturated sodium sulphite solution (10 ml), saturated sodium hydrogencarbonate solution (10 ml), and water (4 × 5 ml). The aqueous washings were back-extracted with methylene chloride (2 × 10 ml) and the combined organic extracts were dried and evaporated.

*Method F.* Phthalic anhydride (0.96 g) was dissolved in dimethylformamide (1 ml) and methylene chloride (1 ml). Hydrogen peroxide (90% in water; 0.17 g) was added to the stirred solution at 40°. After 1 h, the ketone (0.5 g) in chloroform (10 ml) was added. Stirring was continued for 9 h at 40° whereupon the solution was treated as described in method E.

8-anti-Cyano-6-endo-methoxy-3-oxabicyclo[3.2.1]octan-2-one (2), from the bicyclic ketone (1) (method A; 3 h), was a solid (65%), m.p. 93–97° (from carbon tetrachloride);  $\nu_{\max}$  2 260 and 1 750 cm<sup>-1</sup>;  $\delta$ (CDCl<sub>3</sub>) 4.55 (1 H, d, *J* 11.5 Hz, H-4-endo), 4.23 (1 H, m, H-6), 3.84 (1 H, dd, *J* 11.5, 4 Hz, H-4-exo), 3.32 (3 H, s, OMe), 3.30 (1 H, m, H-8), 3.05 (1 H, d, *J* 7 Hz, H-1), 2.88 (1 H, m, H-5), 2.60 (1 H, m, H-7-exo), and 1.83br (1 H, d, *J* 15.0 Hz, H-7-endo) (Found: C, 59.2; H, 6.1; N, 7.4. C<sub>9</sub>H<sub>11</sub>NO<sub>2</sub> requires C, 59.7; H, 6.1; N, 7.7%).

<sup>12</sup> R. Peel and J. K. Sutherland, *J.C.S. Chem. Comm.*, 1974, 151.

<sup>13</sup> J. S. Bindra, A. Grodski, T. K. Schaaf, and E. J. Corey, *J. Amer. Chem. Soc.*, 1973, **95**, 7522.

<sup>14</sup> M. A. Winnik and V. Stoute, *Canad. J. Chem.*, 1973, **51**, 2788.

<sup>15</sup> T. V. Lee, S. M. Roberts, M. J. Dimsdale, R. F. Newton, D. K. Rainey, and C. F. Webb, *J.C.S. Perkin I*, 1978, 1176.

6-endo-Bromo-8-anti-cyano-2-oxabicyclo[3.2.1]octan-3-one (5) and -3-oxabicyclo[3.2.1]octan-2-one (4).—Oxidation of the ketone (3) (method A; 9 h) gave two products separated by fractional crystallization and chromatography over silica, using chloroform–light petroleum (b.p. 60–80°) (1 : 4) as eluant, into the lactone (5) (10%) m.p. 147–148°;  $\nu_{\max}$  2 255 and 1 745  $\text{cm}^{-1}$ ;  $\delta$  4.79br (1 H, d,  $J$  5 Hz, H-1), 4.61 (1 H, m, H-6), 3.30 (1 H, d,  $J$  18 Hz, H-4-endo), 3.28 (1 H, m, H-8), 2.92 (1 H, dd,  $J$  18, 5.5 Hz, H-4-exo), 3.0–2.8 (2 H, m, H-5 and -7-exo), and 2.40 (1 H, ddd,  $J$  16, 6, 2 Hz, H-7-endo) (Found: C, 42.1; H, 3.6.  $\text{C}_8\text{H}_8\text{BrNO}_2$  requires C, 41.7; H, 3.6%), and the lactone (4) (50%), m.p. 158–159°;  $\nu_{\max}$  2 250 and 1 750  $\text{cm}^{-1}$ ;  $\delta$  4.96 (1 H, d,  $J$  12 Hz, H-4-endo), 4.82 (1 H, m, H-6), 4.51 (1 H, dd,  $J$  12, 3 Hz, H-4-exo), 3.69br (1 H, s, H-8), 3.40–3.00 (3 H, m, H-1, -5, and -7-exo), and 2.33 (1 H, m, H-7-endo) (Found: C, 41.7; H, 3.6%).

8-anti-Butyl-6-endo-methoxy-2-oxabicyclo[3.2.1]octan-3-one (7) from ketone (6) [method B and chromatography of the residue over silica with ethyl acetate–light petroleum (2 : 3) as eluant] was an oil (73%);  $\nu_{\max}$  1 735  $\text{cm}^{-1}$  (Found: C, 67.7; H, 9.4.  $\text{C}_{12}\text{H}_{20}\text{O}_3$  requires C, 67.9; H, 9.5%).

Oxidation of ketone (6) using method A gave two products; the major component (80% by g.l.c. analysis) was the lactone (7). Spectroscopic data were consistent for the minor component being the isomeric lactone (8).

6-endo-Acetoxy-8-anti-methoxy-2-oxabicyclo[3.2.1]octan-3-one (10) was obtained from the ketone (9) (method D) as an oil (80.5%), b.p. 114° at 0.003 mmHg;  $\nu_{\max}$  1 740  $\text{cm}^{-1}$ ;  $\delta$  5.2 (1 H, m, H-6), 4.54 (1 H, d, H-1), 3.98 (1 H, s, H-8), 3.37 (3 H, s, OMe), and 2.95–2.35 (4 H, m, H-4-exo, -4-endo, -5, and -7-endo);  $\delta_{\text{C}}(\text{CCl}_4)$  166.97 (s, C-3), 83.24 (d, C-8),

78.08 (d, C-1), 73.86 (d, C-6), 38.43 (d, C-5), 36.98 (t, C-4), and 31.58 (t, C-7) (Found:  $M^+$ , 214.0851.  $\text{C}_{10}\text{H}_{14}\text{O}_5$  requires  $M$ , 214.0841).

Oxidation of the ketone (9) using method A gave two products. The major component (70%) was the lactone (10), and the  $^{13}\text{C}$  n.m.r. data for the minor component was consistent with that expected for the lactone (11),  $\delta_{\text{C}}(\text{CCl}_4)$  171.61 (s, C-2), 81.17 (d, C-8), 72.49 (d, C-6), 66.03 (t, C-4), 45.05 (d, C-1), 41.25 (d, C-5), and 33.32 (t, C-7).

6-endo-Benzoyloxy-8-anti-methoxy-2-oxabicyclo[3.2.1]octan-3-one (13) was obtained (method C) from the bicyclic ketone (12) as an oil (70%), b.p. 155° at 0.001 mmHg;  $\nu_{\max}$  1 740 952, and 930  $\text{cm}^{-1}$ ;  $\delta(\text{CDCl}_3)$  7.29 (5 H, s,  $\text{C}_6\text{H}_5$ ), 4.50 (1 H, m, H-1), 4.44 (2 H, s,  $\text{OCH}_2\text{Ph}$ ), 4.28 (1 H, m, H-6), 3.87br (1 H, s, H-8), 3.28 (3 H, s, OMe), 3.50–2.25 (3 H, m, H-4-exo, -4-endo, and -7-exo), and 1.92 (1 H, dm,  $J$  15 Hz, H-7-endo);  $\delta_{\text{C}}(\text{CHCl}_3)$  169.44 (s, C-3), 83.40 (d, C-8), 78.59 (d, C-1), 78.43 (d, C-6), 38.48 (d, C-5), 37.00 (t, C-4), and 31.23 (t, C-7) (Found: C, 68.7; H, 7.1.  $\text{C}_{15}\text{H}_{18}\text{O}_4$  requires C, 68.7; H, 6.9%).

Oxidation of the ketone (12) using method A gave two products (81%). The major component (55%) was the lactone (13); the minor component was identified as the isomeric lactone (14) by spectral data,  $\delta_{\text{C}}(\text{CHCl}_3)$  173.33 (s, C-2), 81.19 (d, C-8), 76.90 (d, C-6), 66.40 (t, C-4), 45.14 (d, C-1), 41.59 (d, C-5), and 33.33 (t, C-7).

The ratios of 2- (13) to 3-oxabicyclo-octanone (14) obtained from other methods of oxidation were as follows: method B (72%) (92 : 8), method D (78%) (85 : 15), method E (85%) (67 : 33), method F (83%) (73 : 27).

We thank Mrs. L. Phillips for  $^{13}\text{C}$  n.m.r. measurements.

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