

## An Unequivocal Synthesis of an *exo*-2-Methylbicyclo[3.3.1]nonan-9-one

Archibald J. Baker\* and Donald V. Frazer

Department of Chemistry, The University, Glasgow G12 8QQ, Scotland, U.K.

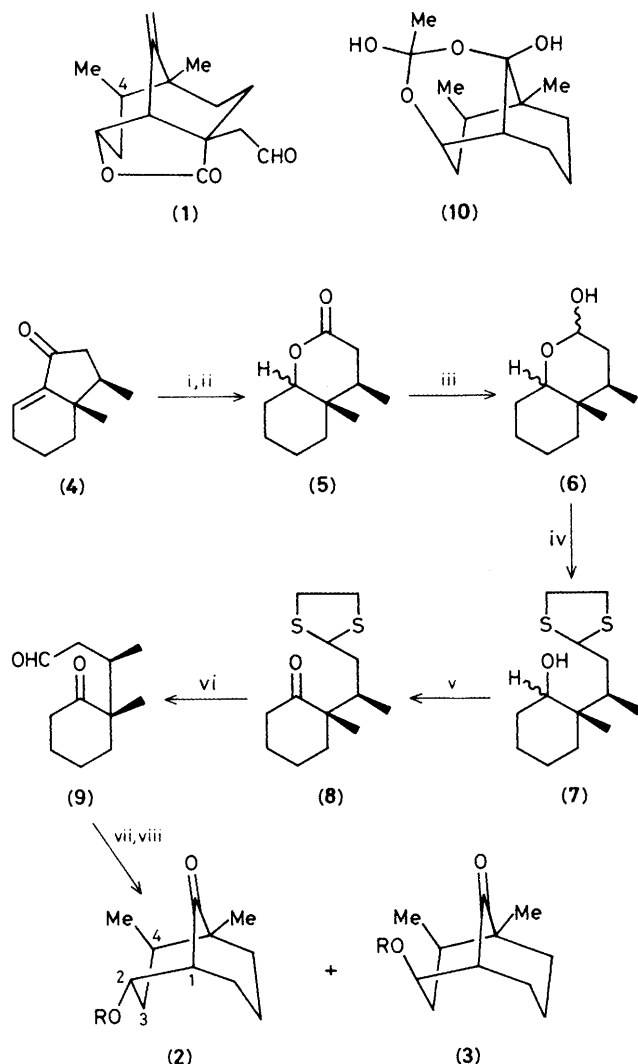
*endo*- and *exo*-2-Acetoxy-4(*exo*),5-dimethylbicyclo[3.3.1]nonan-9-ones have been prepared by a novel route and shown to adopt twin chair conformations.

---

Among the metabolites isolated from the marine sponge genus *Dysidea* are some interesting sesquiterpenoids based on the rare (in nature) bicyclo[3.3.1]nonane skeleton, one of which, upial, (**1**), has been assigned the structure shown.<sup>1</sup>

It was apparent from knowledge of this bicyclic system that the crucial stereospecific attainment of an *exo* configuration

for the C-4 methyl group was unlikely to be achieved by currently available methods of synthesis.<sup>2</sup> We therefore sought an alternative synthesis of the bicyclo[3.3.1]nonane framework which would offer a solution to this problem and yet afford the flexibility of extension to a synthesis of upial itself.



**Scheme 1.** Reagents and conditions (yields not optimised): i, Li, NH<sub>3</sub>, Bu<sup>t</sup>OH, -78 °C (55%); ii, *m*-chloroperbenzoic acid, CH<sub>2</sub>Cl<sub>2</sub> (70%); iii, Dibal, CH<sub>2</sub>Cl<sub>2</sub>, -25 °C (75%); iv, TiCl<sub>4</sub>, (CH<sub>2</sub>SH)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 62 h (42%); v, PDC, *N,N*-dimethylformamide, 0 °C, 6 h (60%); vi, BF<sub>3</sub>·OEt<sub>2</sub>, HgO(red), tetrahydrofuran, 4 h (75%); vii, HCl, AcOH, H<sub>2</sub>O; viii, Ac<sub>2</sub>O, pyridine [30% from (9)].

We report an unambiguous synthesis of *endo*-2-acetoxy-4(*exo*),5-dimethylbicyclo[3.3.1]nonan-9-one (**2**; R = Ac) and its 2(*exo*) epimer (**3**; R = Ac) and show that both compounds adopt the twin chair conformation (Scheme 1).

4,5-*cis*-Dimethylbicyclo[4.3.0]non-9-en-2-one (**4**),<sup>3</sup> readily obtainable from 2-methylcyclohexanone and butyn-3-ol, was converted by reduction and peracid oxidation into a mixture of  $\delta$ -lactones (**5**),<sup>†</sup> di-isobutylaluminium hydride (Dibal) reduction of which afforded the lactols (**6**) in good overall yield. The lactols (**6**), which were resistant to ring opening acetalisation with ethylene glycol, reacted smoothly but slowly (62 h) with ethanedithiol and titanium(IV) chloride<sup>4</sup> to give the 1,3-

dithiolanes (**7**). Oxidation of (**7**) to a single ketone (**8**) could only be effected using pyridinium dichromate (PDC)<sup>5</sup> as oxidant, other methods giving complex mixtures of products. Removal of the dithiolane group with red mercury(II) oxide<sup>6</sup> in the presence of BF<sub>3</sub>·Et<sub>2</sub>O provided the key keto aldehyde (**9**), ( $\nu_{\max}$  1730 and 1708 cm<sup>-1</sup>) from which the bicyclo[3.3.1]nonane system could be obtained by conventional acid catalysed cyclisation.<sup>7</sup> After complete acetylation of the resulting mixture of *endo*- and *exo*-2-ols (**2**; R = H) and (**3**; R = H), and their corresponding acetates, chromatographic separation afforded the individual epimeric acetates (**2**; R = Ac) and (**3**; R = Ac) in a ca. 1:1 ratio.

That both the *endo*-acetate (**2**; R = Ac) ( $\nu_{\max}$  CCl<sub>4</sub> 1742 and 1720 cm<sup>-1</sup>) and the *exo*-acetate (**3**; R = Ac) ( $\nu_{\max}$  CCl<sub>4</sub> 1739 and 1720 cm<sup>-1</sup>) adopt a twin chair conformation was evidenced by the abnormal C-H vibrational modes at 2997 and 1490 cm<sup>-1</sup>, characteristic of this conformation, in their i.r. spectra.<sup>8,9</sup> The chair conformation of the acetoxy substituted ring in both epimers was also evident from their 200 MHz <sup>1</sup>H n.m.r. spectra. Thus the equatorial orientation of the acetoxy group in (**2**; R = Ac) was indicated by the coupling of the axial C-2 proton at  $\delta$  5.30 to the three vicinal protons with *J* values of 12, 6, and 6 Hz; the corresponding *J* values for the equatorial C-2 proton ( $\delta$  5.26) in (**3**; R = Ac) were 5, 3, and 3 Hz.<sup>9</sup> In (**2**; R = Ac) the acetoxy methyl group resonated at  $\delta$  2.06 and the axial C-4 methyl group at  $\delta$  0.96 (d, *J* 9 Hz); in (**3**; R = Ac) the corresponding signals were at  $\delta$  1.97 and at  $\delta$  0.97 (d, *J* 9 Hz). Further evidence for the diaxial relationship at C-2 and C-4 in the *exo*-acetate (**3**; R = Ac) came from the observation that (**3**; R = Ac) readily underwent hydrolysis to (**3**; R = H) in unpurified CDCl<sub>3</sub> (H<sub>2</sub>O and HCl present), possibly *via* the intermediate (**10**), whereas the *endo* acetate was stable to these conditions. Our findings are in agreement with the observed diaxial twin chair conformation for *exo-exo*-2,4-dimethoxybicyclo[3.3.1]nonan-9-one and with force field calculations on this compound and the (unknown) dimethyl analogue.<sup>10</sup>

We acknowledge financial support from the S.E.R.C. (to D. V. F.).

Received, 12th November 1984; Com. 1601

## References

- G. Schulte, P. J. Scheuer, and O. J. McConnell, *J. Org. Chem.*, 1980, **45**, 552.
- G. L. Buchanan in 'Topics in Carbocyclic Chemistry,' ed. D. Lloyd, Logos Press, 1969, vol. 1, p. 199; J. A. Peters, *Synthesis*, 1979, 321.
- T. Hiyama, M. Shinoda, and H. Nozaki, *J. Am. Chem. Soc.*, 1979, **101**, 1599.
- P. C. Bulman-Page, R. A. Roberts, and L. A. Paquette, *Tetrahedron Lett.*, 1983, **24**, 3555.
- E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, **20**, 399.
- E. J. Corey and H. L. Pearce, *J. Am. Chem. Soc.*, 1979, **101**, 5841; E. Vedejs and P. L. Fuchs, *J. Org. Chem.*, 1971, **36**, 366.
- A. C. Cope and M. E. Synerholm, *J. Am. Chem. Soc.*, 1950, **72**, 5228; A. C. Cope, F. S. Fawcett, and G. Munn, *J. Am. Chem. Soc.*, 1950, **72**, 3399.
- G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc.*, 1965, 1243.
- J. Martin, W. Parker, B. Shroote, and T. Stewart, *J. Chem. Soc. C*, 1967, 101.
- C. Jaime, Y. Takeuchi, P. Camps, and E. Osawa, *J. Org. Chem.*, 1983, **48**, 4514.

<sup>†</sup> All new compounds gave satisfactory spectral, microanalytical, and/or accurate mass data.