

A VERSATILE SYNTHESIS OF ANGULARLY SUBSTITUTED CIS-2-METHOXY- $\Delta^{1,6}$ -HEXALINS

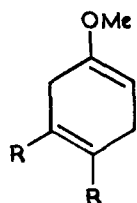
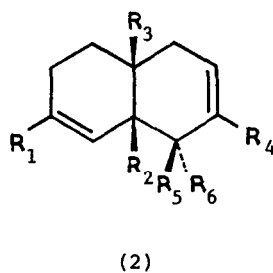
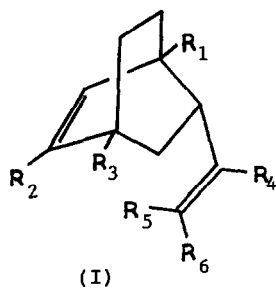
By A. Peter Johnson* and Motiur Rahman

(Department of Chemistry, The Polytechnic of North London, London N7 8DB)

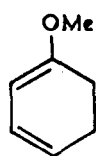
(Received in UK 16 November 1973; accepted for publication 18 December 1973)

Hitherto, the methods which have been used for the synthesis of terpenoids with skeletons based on cis-decalin have been fairly diverse. One approach which might be more generally applicable involves a Cope rearrangement of 2-endo-vinylbicyclo [2.2.2] oct-5-enes such as (1) to the corresponding unsaturated cis-decalins (2). The overall stereochemistry of this process is likely to be as indicated because the rigid bicyclic skeleton of (1) forces the transition state of the Cope rearrangement to be boat-like. A few simple examples of this process have already been reported¹ but its synthetic utility has been restricted because of the lack of a good preparative route to suitably substituted derivatives of (1).² We have found that such compounds can be readily synthesised from aromatic precursors and in most cases do smoothly undergo the desired Cope rearrangement.

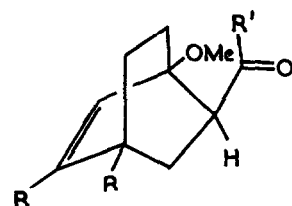
Birch reduction of anisole and 3,4-dimethylanisole yielded the corresponding dihydro derivatives (3a) and (3b) respectively. Heating (3a) with methyl vinyl ketone in a sealed tube at 110^o led to the formation of an epimeric mixture (83%) of the Diels-Alder adducts (5a) and (6a) (28 : 72) which have previously been prepared by a similar route.³ Presumably the Diels-Alder reaction is preceded by equilibration of (3a) with (4) and it has been suggested that this process is catalysed by glass and/or dienophiles.^{4,5} As previously observed,³ the exo adduct (5a) and endo adduct (6a) are readily distinguished by their p.m.r. spectra since only in the endo case are the olefinic double bond and the carbonyl group suitably disposed to cause the upfield shifts in the positions of signals due to the acetyl methyl group and the vinyl hydrogens which are observed for one of the isomers.



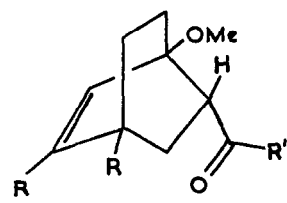
R=H (3a)
R=Me (3b)



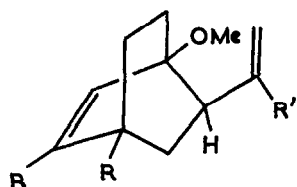
(4)



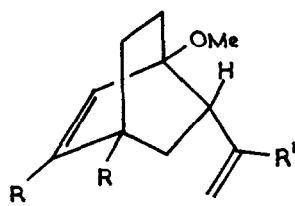
R=H, R'=Me (5a)
R=R'=Me (5b)
R=Me, R'=CHMe₂ (5c)



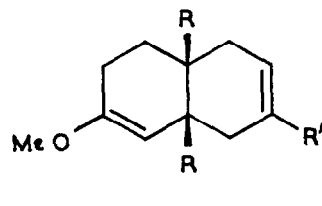
(6a)
(6b)
(6c)



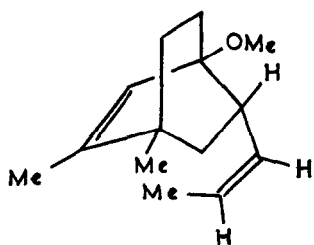
R=H, R'=Me (7a)
R=R'=Me (7b)
R=Me, R'=CHMe₂ (7c)



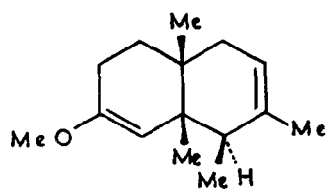
(8a)
(8b)
(8c)



(9a)
(9b)
(9c)



(10)



(II)

In similar fashion, the reaction between (3b) and methyl vinyl ketone yielded a mixture (96%) of (5b) and (6b), (31 : 69). Isopropyl vinyl ketone reacted similarly with (3b) to yield (5c) and (6c), (65%; 35 : 65).

All these bicyclic ketones were converted in high yields (72 - 83%) to the corresponding dienes by treatment in dimethyl sulphoxide with the ylid derived from methyltriphenylphosphonium bromide. The more hindered ketones (5c and 6c) reacted rather sluggishly and required higher temperatures (70 - 80°) and longer reaction times (3 - 4 days). In all cases there was some increase in the *exo* : *endo* ratio in going from ketone to diene, presumably as a result of base-catalysed epimerisation at the ketone stage. The structural assignments again follow from the p.m.r. data, the same shielding effects being observed as was the case with the corresponding ketones.

When the *endo*-dienes (8a), (8b) and (8c) were heated in an alkali-washed sealed tube at 250° they were smoothly rearranged to the enol ethers (9a), (9b) and (9c) respectively whereas the *exo* isomers (7a), (7b) and (7c) remained unchanged when subjected to these conditions. In contrast to the situation found in some oxy-Cope rearrangements,^{1,2} under the conditions employed for their formation the products of our Cope reactions do not undergo migration of the enol ether double bond. Thus the method results in the regiospecific formation of an enol ether and an additional double bond both of which are valuable sites for further synthetic transformations. The enol ethers (9a), (b) and (9c) were rather labile compounds being readily hydrolysed to the corresponding ketones by treatment with aqueous acid or more slowly by exposure to the laboratory atmosphere.

The examples quoted so far have not utilised the full potential of the Cope rearrangement for stereospecifically generating chiral centres as implied in the formal conversion of (1) to (2). In this connection we have synthesised (10) by minor variations in the standard route and attempted to convert it to (11). However (10) does not undergo rearrangement at 250° and at higher temperatures decomposes by fragmentation. Examination of models suggests that this failure

may be due to destabilisation of the transition state by severe steric compression between the methyl group at C-4 and the allylic methyl group in the side chain.

References

1. J.A.Berson and M.Jones, J. Amer. Chem. Soc., 1964, **86**, 5017 and 5019;
J.A.Berson and E.J.Walsh, ibid., 1968, **90**, 4729 and 4730.
2. The synthetic utility of the oxy-Cope rearrangement has recently been extended by the development of new methods for the synthesis of substituted 2-hydroxy-2-vinylbicyclo[2.2.2]oct-5-enes. D.A.Evans, W.L.Scott and L.K.Truesdale, Tetrahedron Letters, 1972, 137.
3. A.J.Birch and J.S.Hill, J. Chem. Soc. C, 1966, 419.
4. I. Alfaro, W.Ashton, L.D.McManus, R.C.Newstead, K.L.Rabone, N.A.J.Rogers and W.Kernick, Tetrahedron, 1970, **26**, 201.
5. A.J.Birch and K.P.Dastur, Tetrahedron Letters, 1972, 4195.