TILDEN LECTURE*

The Initiation of Cyclization Using 3-Methylcyclohex-2-enone Derivatives

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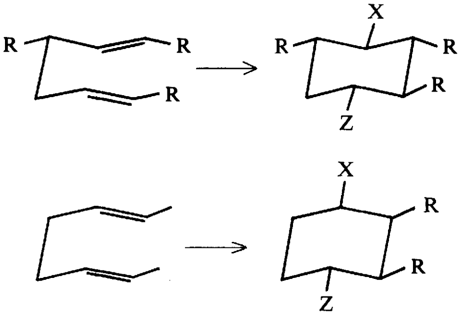
1 Introduction

Since the publication[1] of the Stork–Eschenmoser hypothesis in 1955 there have been many attempts to translate these ideas into viable synthetic routes to alicyclic compounds. The attractiveness of the method of polyene cyclization lies in the potential control of stereochemistry and the readiness with which highly substituted carbon–carbon bonds may be formed; it is these bonds, linking tertiary–tertiary, tertiary–secondary, and secondary–secondary centres, which, due to steric hindrance, are difficult to form using organometallic methods. Some of the basic tenets of the Stork–Eschenmoser hypothesis are illustrated (Scheme 1), *viz* cyclization of a 1,5-diene in a defined conformation (chair or boat) by anti-periplanar addition to the double bonds. It is now clear that these postulates are upheld in many cases and are the foundations for viable synthetic methods. However, the transformation of ideas into practice was not without difficulty, not the least being the discovery of satisfactory methods for the initiation of



Scheme 1

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*First presented at the Scientific Societies' Lecture Theatre, London, on 18th January 1979.

[1] A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, 1955, **38**, 1890; G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, 1955, **77**, 5068.

cyclization. It is not possible in the confines of this lecture to give a comprehensive review of this large area, especially the early work in the field, and apologies are necessary to those whose work is not mentioned. In addition, heterocyclizations are excluded and emphasis is placed on cyclizations where more than one ring is formed.

2 Initiation of Cyclization

In much of the early pioneering work cyclizations were initiated by protonation of double bonds or interaction with Lewis acids[2] and excellent results were obtained in certain cases, particularly for monocyclizations. Addition of other electrophiles, such as HOBr,[3] $PhSBF_4$,[4] $Tl(ClO_4)_3$,[5] $Hg(OAc)_2$,[6] CH_3COCl,[7] and $CH_3CO.BF_4$,[4] to double bonds has led to cyclization in varying yields, but in cases where these reagents have been tested for polycyclizations they do not appear to afford any significant advantages other than introduction of an additional functional group. The ionization of alcohols and their derivatives has been used to initiate cyclization and has been most successful with tertiary derivatives. In particular, Landsbury has used this method in his work on chloro-olefin annulation.[8] Cyclization induced by the cleavage of epoxides has been extensively studied by van Tamelen[9] and by Goldsmith[10] with results which give valuable insights into biosynthesis of terpenes.

These, and many other reactions not mentioned, gave chemically interesting and, in some cases, preparatively useful results but it was only with the introduction by Johnson[11] of stabilized carbonium ion initiators that a general synthetic methodology was developed. Oxonium ions (from acetals or aldehydes) were developed by Johnson[12] and his collaborators, and later by Ireland[13] and Marshall.[14] However, the most flexible initiators appear to be the allylic carbonium ions (derived from the alcohols in Scheme 2) also introduced by Johnson.[15] These have led to elegant steroid syntheses.[16] Other promising initiating ions (Scheme 3) would appear to be the acyliminium ion (1) used by

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[2] P. A. Stachler, A. Eschenmoser, H. Schinz, and G. Stork, *Helv. Chim. Acta*, 1957, **40**, 2191.

[3] E. E. van Tamelen and E. J. Hessler, *J.C.S. Chem. Comm.*, 1966, 411.

[4] W. A. Smit, A. V. Semenovsky, V. F. Kuchrov, T. N. Chemova, M. Z. Krimer, and O. V. Lubinskaya, *Tetrahedron Letters*, 1971, 3101.

[5] Y. Yamada, H. Sanjoh, and K. Iguchi, *J.C.S. Chem. Comm.*, 1976, 997.

[6] M. Julia and J. D. Fourneron, *Tetrahedron*, 1976, **32**, 1113.

[7] S. Kumazawa, Y. Nakano, T. Kato, and Y. Kitahara, *Tetrahedron Letters*, 1974, 1757.

[8] P. T. Landsbury, *Accounts Chem. Res.*, 1972, **5**, 311.

[9] E. E. van Tamelen, *Accounts Chem. Res.*, 1975, **8**, 152.

[10] D. J. Goldsmith and C. F. Phillips, *J. Amer. Chem. Soc.*, 1969, **91**, 5862.

[11] W. S. Johnson, *Bio-org. Chem.*, 1976, **5**, 51.

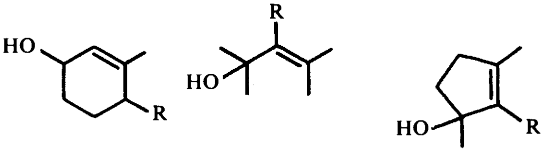
[12] A. van der Gen, K. Weidhaup, J. J. Swoboda, H. Dunathan, and W. S. Johnson, *J. Amer. Chem. Soc.*, 1973, **95**, 2656.

[13] R. E. Ireland, C. A. Libinski, C. J. Kowalski, J. W. Tilley, and D. M. Walba, *J. Amer. Chem. Soc.*, 1974, **96**, 3333.

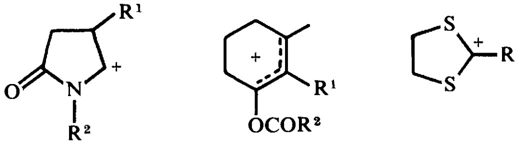
[14] J. A. Marshall and P. G. M. Wuts, *J. Org. Chem.*, 1977, **42**, 1794.

[15] W. S. Johnson, W. H. Lunn, and K. Fitzi, *J. Amer. Chem. Soc.*, 1964, **86**, 1972.

[16] W. S. Johnson, M. F. Semmelhack, M. U. S. Sultanbawa, and L. A. Dolak, *J. Amer. Chem. Soc.*, 1968, **90**, 2944; W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *J. Amer. Chem. Soc.*, 1971, **93**, 4332.



Scheme 2



(1) (2) (3)

Scheme 3

Speckamp,[17] the allylic ion (2) of Harding,[18] and the sulphur-stabilized species (3) introduced by Corey and used by Andersen and Brinkmeyer.[19] Other allyl, homoallyl,[20] and iminium[21] ions have been used successfully. The greater success of stabilized carbonium ions perhaps results from the alternative reaction pathways to cyclization (elimination or intermolecular nucleophilic attack) being reversible under the reaction conditions. With less stable ions, especially those produced under solvolytic conditions, this would not be the case. Once the initial cyclization has occurred then further cyclization could be concerted or involve intermediate carbonium ions which, though not stabilized, are formed in the absence of a counterion, thus prolonging their lifetimes.

3 Regio- and Stereo-chemistry of Cyclizations

It is implicit in Scheme 1 that an electronically unbiased 1,5-diene will cyclize to a six-membered ring and that stereochemistry at all positions in the ring can be controlled if three postulates are upheld; these are antiperiplanar addition to the double bonds, cyclization in a single defined conformation (chair or boat), and the adoption by sp^3-borne substituents of a single orientation (pseudo-axial or -equatorial). There is evidence that all of these postulates are valid to a greater or lesser extent. There is overwhelming evidence that cyclization of a 1,5-diene to a six-membered ring (6-*endo*-trig) is favoured over five-ring formation (5-*exo*-trig) except when the diene is electronically biased towards the latter. One of the few exceptions is a recent report[22] summarized in Scheme 4. Cyclization *via* a chair-like transition state is consistent with most of the results reported where this is

[17] J. Dijkink and W. N. Speckamp, *Tetrahedron Letters*, 1977, 935.

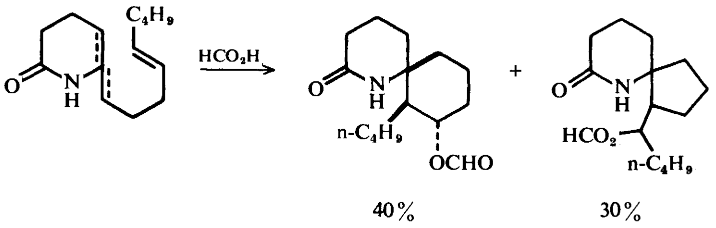
[18] J. L. Cooper and K. E. Harding, *Tetrahedron Letters*, 1977, 3321.

[19] E. J. Corey and S. W. Walinsky, *J. Amer. Chem. Soc.*, 1972, **94**, 8932; N. H. Anderson, Y. Yamamoto, and A. D. Denniston, *Tetrahedron Letters*, 1975, 4547; R. S. Brinkmeyer, *ibid.*, 1979, 207.

[20] G. Stork and M. Gregson, *J. Amer. Chem. Soc.*, 1969, **91**, 2373.

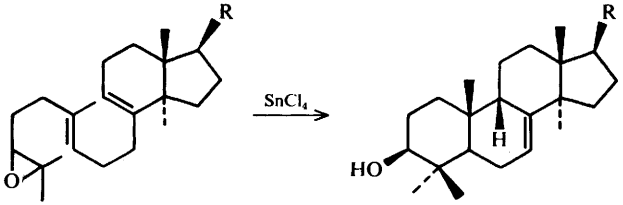
[21] G. Demailly and G. Solladié, *Tetrahedron Letters*, 1977, 1885.

[22] D. A. Evans and E. W. Thomas, *Tetrahedron Letters*, 1979, 411.



Scheme 4

discernible; a likely exception has been reported in a sterically congested cyclization[23] (Scheme 5). Again the majority of examples of carbon–carbon bond formation involve antiperiplanar addition to a double bond. In order to establish whether this arises from the stereoselective reaction of an intermediate or is demanded by the mechanism of the reaction it is necessary to examine the reaction of pairs of *Z*- and *E*-isomers. This has been done in a number of cases using the polyenes in Scheme 6, which all cyclized to a greater or lesser extent to bicyclo[3.3.0]decane derivatives. Cyclization of *Z*- and *E*-(4) gave the same *trans* fused products,[24] but the *Z*- and *E*-pairs of (5),[25] (6),[12] (7),[26] (8),[17] and (9)[10] showed no crossover between the two series, the *Z*-isomer giving *cis* fusion and the *E*-isomer the *trans* ring junction. *Z*-(10) gave a *cis–trans* ratio of 80:20 and *E*-(10) a ratio of 7:93.[27a] Elegant experiments on the cyclization of (*E*,*E*)- and (*Z*,*Z*)-octa-2,5-diene demonstrated that while proton attack and carbon–carbon bond formation were stereospecific the attack of nucleophile terminating cyclization was stereoselective.[27b] These results indicate that, while the principle of antiperiplanar addition is a powerful one, it cannot always be assumed. The formation of the 'wrong' isomers can arise in a number of different ways which will be discussed later.



Scheme 5

When a 1,5-diene is electronically biased towards five-membered ring formation

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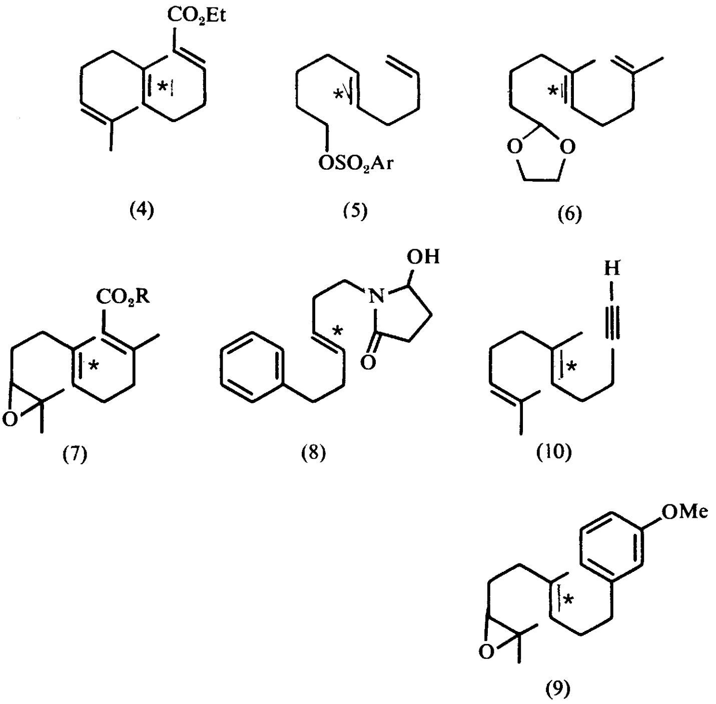
[23] E. E. van Tamelen and J. H. Freed, *J. Amer. Chem. Soc.*, 1970, **92**, 7206.

[24] P. A. Stadler, A. Nechvatel, A. J. Frey, and A. Eschenmoser, *Helv. Chim. Acta*, 1957, **40**, 1373.

[25] W. S. Johnson and J. K. Crandall, *J. Org. Chem.*, 1965, **30**, 1785.

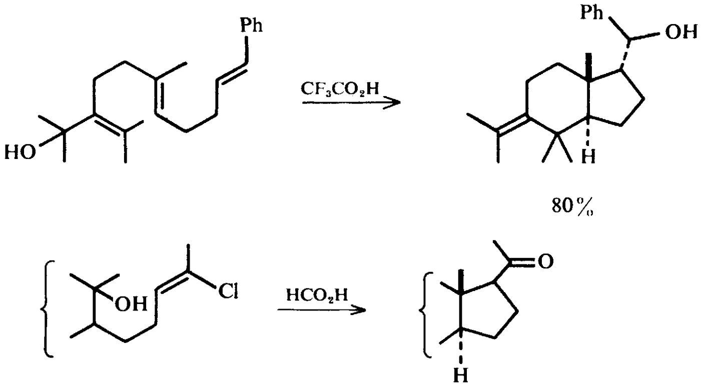
[26] E. E. van Tamelen and J. P. McCormick, *J. Amer. Chem. Soc.*, 1969, **91**, 1847.

[27] (*a*) G. Ohloff, F. Näf, E. Decorzant, W. Thommen, and E. Sundt, *Helv. Chim. Acta*, 1973, **56**, 1414; (*b*) H. E. Vlery and J. H. Richards, *J. Amer. Chem. Soc.*, 1964, **86**, 3113.



Scheme 6

then such cyclizations can occur but are frequently followed by other processes such as hydride or alkyl migrations. These can, in some cases, be prevented by stabilizing the cyclized carbonium ion (Scheme 7).[8,28] Recently, Johnson has



Scheme 7

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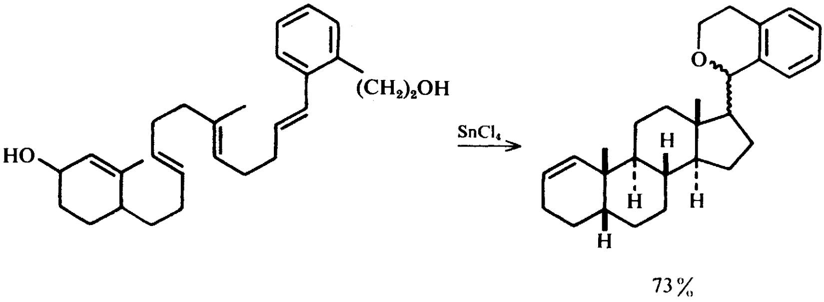
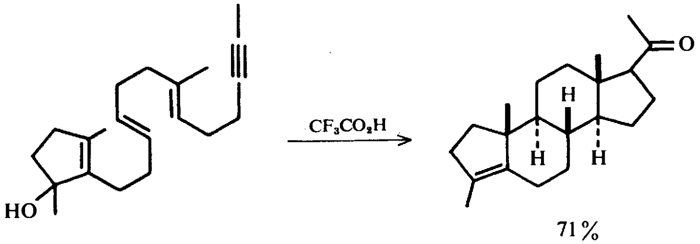
[28] W. S. Johnson, M. B. Gravestock, R. J. Parry, R. F. Meyers, T. A. Bryson, and D. H. Miles, *J. Amer. Chem. Soc.*, 1971, 93, 4330.

combined the carbonium ion stabilization device with internal nucleophilic capture (Scheme 8).[29] The cyclopentane ring can also be formed by cyclization of



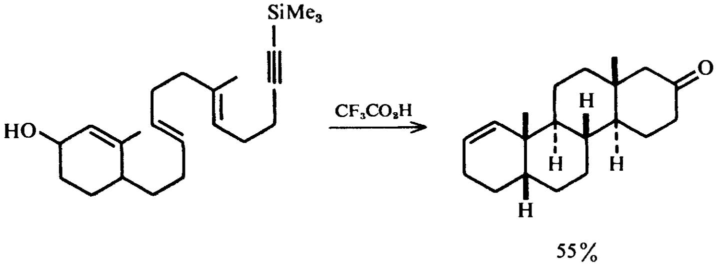
Scheme 8

1,5-enynes where the acetylene is dialkylated (Scheme 9);[16] terminal acetylenes



Scheme 9

(and their trimethyl silyl derivatives) cyclize to cyclohexane derivatives (Scheme 10).[30] This cyclization also illustrates the general phenomenon of axial attack on the cyclohexenyl cation leading to a *cis*-bicyclo[3.3.0]decane ring system. Allenes



Scheme 10

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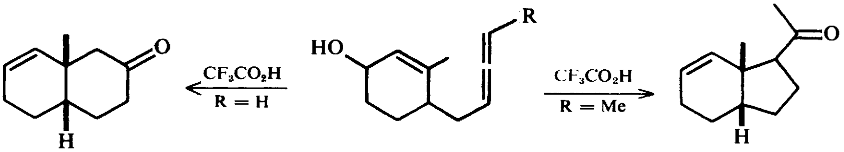
[29] M. E. Garst, Y.-F. Cheung, and W. S. Johnson, *J. Amer. Chem. Soc.*, 1979, **101**, 4404.
[30] W. S. Johnson, T. M. Yarnell, R. F. Myers, and D. R. Morton, *Tetrahedron Letters*, 1978, 2549.

appear to show similar behaviour, the monoalkyl compounds forming six-membered rings, the 1,3-dialkylated allenes giving five-membered rings (Scheme 11).[31] Examples of the formation of rings larger than six-membered are relatively rare, but a few cases of cyclization to cycloheptane derivatives have been reported.[32,33]



Scheme 11

Substituents at C-3 or -4 of a 1,5-diene system show, to a greater or lesser extent, a preference for equatorial orientation in the cyclization transition state (Scheme 12).[14,34,35]

4 Termination of Cyclization

If polyene cyclization is to be preparatively useful then cyclization should be terminated by a single process, and not routes which give rise to multiple products. Elimination or inter- or intra-molecular nucleophilic attack are the two reactions which terminate cyclization. Frequently the two occur together. It is not easy to predict whether proton elimination from cyclohexyl cations will occur regiospecifically or give rise to a mixture of isomers; apparently closely related intermediates behave differently. However, the predominant product is usually that formed by elimination of a proton originally allylic to the double bond. In many cases this is probably the thermodynamically more stable product but it may also indicate a kinetic preference for allyl proton elimination.[36] The control of the direction of elimination by use of trimethylsilyl substituents is a most promising device (Scheme 13)[37] and may only be limited by the availability of synthetic routes to the precursors. There are a number of cases where elimination to form partially cyclized olefins followed by further proton-initiated cyclization accounts for the formation of 'wrong' isomers, *i.e.* apparent *cis* addition (Scheme 14).[1,2] This can frequently be tested by use of a medium containing $^2H^+$. When an aromatic (or heterocyclic) ring participates in cyclization there is no problem with the direction of elimination, but often *o*- and *p*-attack compete.

Termination by intermolecular nucleophilic attack is common and is usually stereoselective when a secondary centre is being attacked, but often gives

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[31] K. E. Harding, P. M. Puckett, and J. L. Cooper, *Bio-org. Chem.*, 1978, 7, 221.

[32] K. E. Harding, J. L. Cooper, P. M. Puckett, and J. D. Ryan, *J. Org. Chem.*, 1978, **43**, 4363.

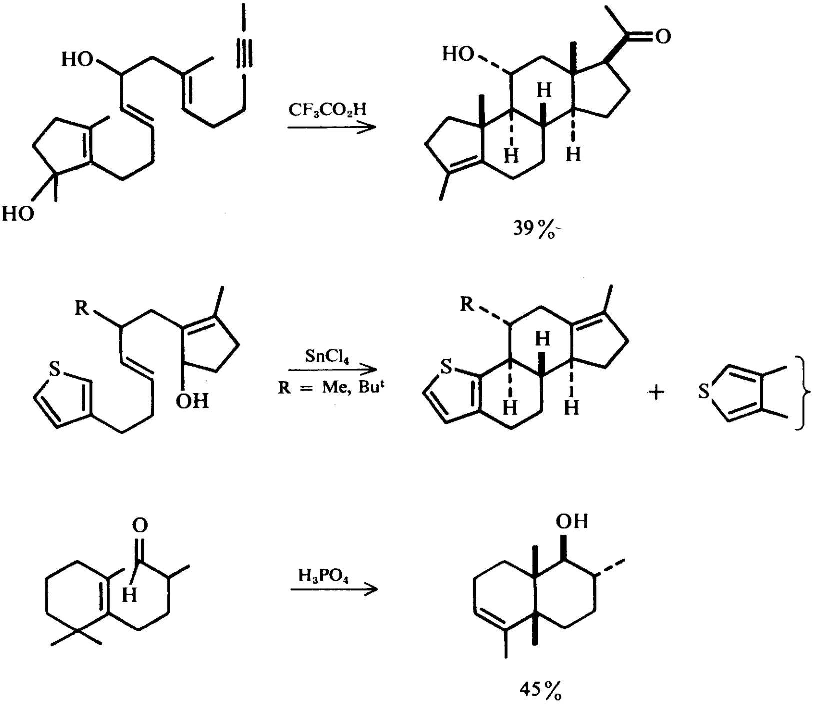
[33] S. Hashimoto, A. Itoh, Y. Kitagawa, H. Yamamoto, and H. Nozaki, *J. Amer. Chem. Soc.*, 1977, 99, 4192.

[34] W. S. Johnson, S. Escher, and B. W. Metcalf, *J. Amer. Chem. Soc.*, 1976, **98**, 1039.

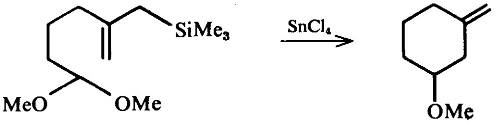
[35] A. A. Marco, R. J. de Brouwer, P. M. N. Nossin, E. F. Godefroi, and H. M. Buck, *J. Org. Chem.*, 1978, **43**, 1591.

[36] I. M. Cunningham and K. H. Overton, *J.C.S. Perkin I*, 1975, 2140.

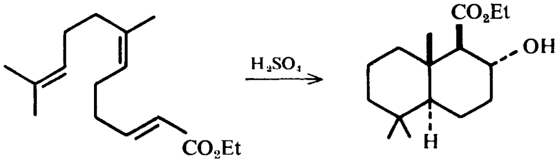
[37] I. Fleming, A. Pearce, and R. L. Snowden, *J.C.S. Chem. Comm.*, 1976, 182.



Scheme 12

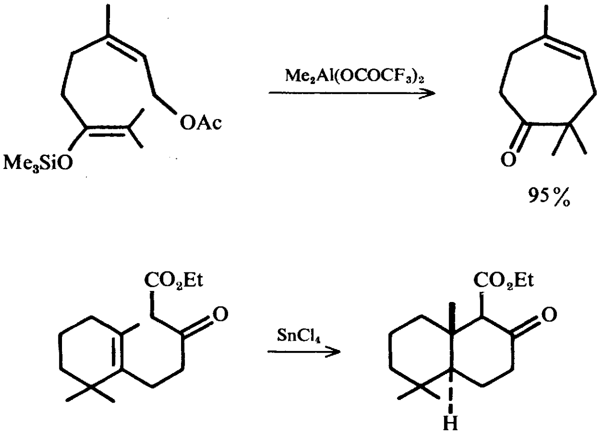


Scheme 13



Scheme 14

mixtures when a tertiary ion is neutralized. A major problem in polyene cyclizations is the interception of partially cyclized intermediates with nucleophiles before cyclization is complete. There can thus be a delicate balance between having a nucleophile efficient enough to terminate cyclization without on the one hand elimination becoming dominant or, on the other, cyclization being interrupted. If the final cation formed is vinylic then nucleophilic attack is the only termination mechanism. The most successful protocol for polyene cyclization at present appears to be a stable initiating ion, conditions of low nucleophilicity, double bonds of adequate nucleophilicity (not deactivated by electron-withdrawing groups), and termination by nucleophilic addition to either a vinyl cation or a resonance-stabilized cation. Use of the latter requires a delicate balance such that the electrophile inducing formation of the initiating ion does not irreversibly transform the double bond which is the precursor of the final stabilized cation. From the viewpoint of stabilization the enol–ether function has desirable properties as the final double bond in a cyclization, but it is clear that it can be transformed independently of the cyclizations under many conditions However, two interesting cyclizations are illustrated (Scheme 15).[33,38]

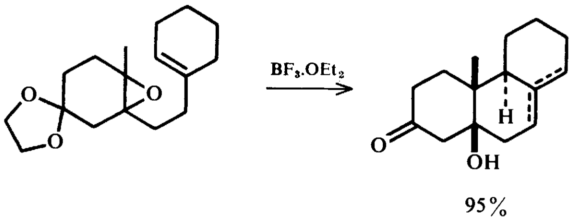


Scheme 15

5 3-Methylcyclohex-2-enone Derivatives as Initiators of Cyclization

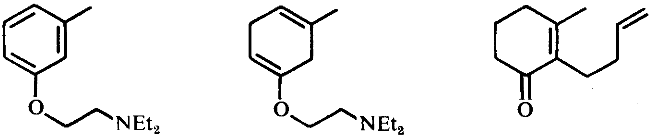
Our own interest in this area followed the demonstration (Scheme 16)[39] that the epoxide was efficiently cyclized to the mixture shown. We decided to investigate whether such cyclohexene epoxides were generally useful initiators of cyclization and concurrently examine the synthetically more accessible epoxides (11). Initially we prepared the enone precursors (12) by the Hagemann's ester route, but when this route failed or gave poor results in a number of cases we developed the method shown (Scheme 17),[40] which has proved satisfactory in all the cases we have examined so far. The demonstration by Harding[18] that enolacetates of the enones (12) were suitable substrates for the initiation of cyclization caused us to

[38] R. W. Skeen, G. L. Trammell, and J. D. White, *Tetrahedron Letters*, 1976, 525.
[39] P. Marsham, D. A. Widdowson, and J. K. Sutherland, *J.C.S. Perkin I*, 1974, 238.
[40] J. Amupitan and J. K. Sutherland, *J.C.S. Chem. Comm.*, 1978, 852.



(11) (12)

Scheme 16



Scheme 17

study cyclization of the related enoltrifluoroacetates in parallel with the epoxide cyclizations.[41] These will be contrasted and compared. Epoxide cyclizations were usually carried out at −78 °C in CH_2Cl_2 using the Lewis acids indicated, while the enones were cyclized using $(CF_3CO)_2O$–CF_3CO_2H at 0 °C.

The least substituted of the epoxides (13) was studied in some detail and the results are summarized in Table 1. Two processes were observed (Scheme 18), the

Table 1

Lewis acid	*Solvent*	*Ratio* dione*:(15)
$TiCl_4$	CH_2Cl_2	∞
$AlCl_3$	CH_2Cl_2	3.0
$FeCl_3$	CH_2Cl_2	1.1
$SnCl_4$	CH_2Cl_2	0.6
$ZnCl_2$	CH_2Cl_2	0.3
$BF_3.OEt_2$	CH_2Cl_2	0.8
$BF_3.OEt_2$	C_6H_6	0.6
$BF_3.OEt_2$	Et_2O	0.1
$ZnCl_2$	Et_2O	0.1

*Ratios determined by g.l.c.

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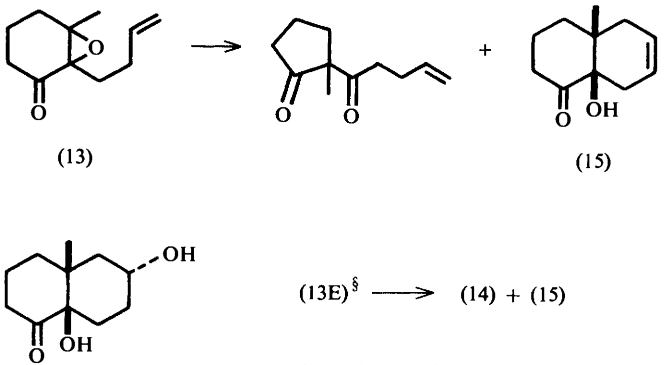
[41] E. Huq, M. Mellor, E. G. Scovell, and J. K. Sutherland, *J.C.S. Chem. Comm.*, 1978, 526; E. G. Scovell and J. K. Sutherland, *ibid*, 1978, 529; M. Mellor, A. Santos, E. G. Scovell, and J. K. Sutherland, *ibid*, 1978, 528.



(13)

(15)

(14)

$(13E)^{\S} \longrightarrow (14) + (15)$

§The suffix E indicates the enone corresponding to that numbered epoxide.

Scheme 18

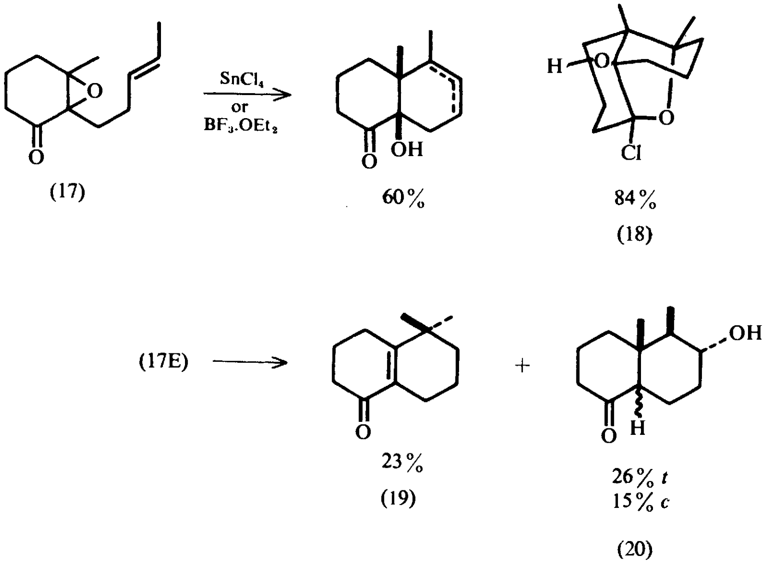
desired cyclization and ring contraction to the dione. If it is accepted that metal–oxygen bond strengths in the gas-phase[42] are a reasonable measure of Lewis acidity of related halides for oxygen, then it is clear that the stronger the Lewis acid, the higher is the yield of cyclization product. With $TiCl_4$ no ring-contraction product was formed, but there was an appreciable amount of the hydrate (14) formed (25%) in addition to the cycloalkene (15). Surprisingly, cyclization of the enone with $(CF_3CO)_2O$–CF_3CO_2H also gave (14) and (15). We have been unable to ascertain exactly at what stage the oxidation occurs.

Cyclization of the epoxide (17) with an unpolarized double bond gave only the mixture of isomeric cycloalkenes derived by six-membered ring formation (Scheme 19). Use of BCl_3 gave some of the alkenes but the major product was assigned the structure (18). The related enone on reaction with $(CF_3CO)_2O$–CF_3CO_2H also gave a mixture of products, unrearranged (19), and rearranged (20); that hydride and methyl migrations produced (20) followed from cyclization using $CF_3CO_2{}^2H$ when only one ^2H was incorporated into the product. The deuteron was exchangeable with NaOH–H_2O. When the participating double bond was polarized in order to produce a five-membered ring (Scheme 20) then cyclization of the enone gave only rearranged product (21) while the epoxide gave the unexpected (22). Some clue as to its mode of formation came from the demonstration that (23) was the kinetic product of reaction. This, in turn, might be formed from (24) which is the product of an 'ene' reaction between the carbonyl and isopropylidene groups of the epoxide.

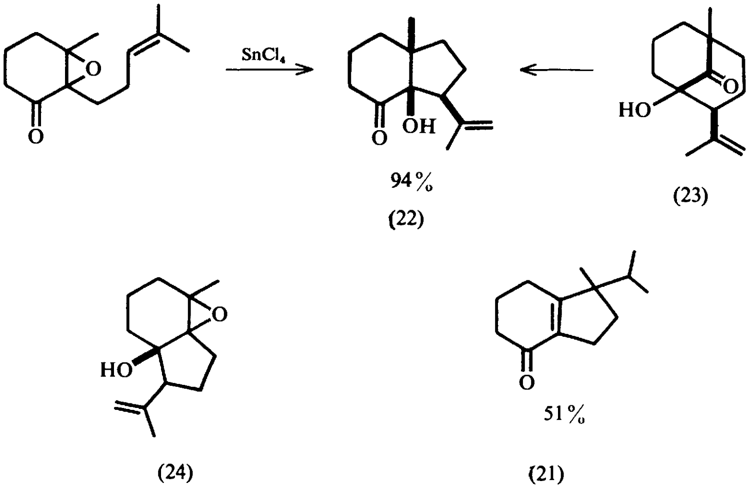
Anisyl groups can participate efficiently in the cyclizations (Scheme 21) but there is little discrimination between reaction at the *o*- and *p*-positions. With $TiCl_4$ the epoxide gave the two ketols as minor products, the major one being the dihydrophenanthrene (25).

Participation of acetylenic groups in cyclizations followed the expected paths

[42] L. H. Brewer and G. M. Rosenblatt, 'Advances in High Temperature Chemistry', Vol. II, Academic Press, New York, 1969.



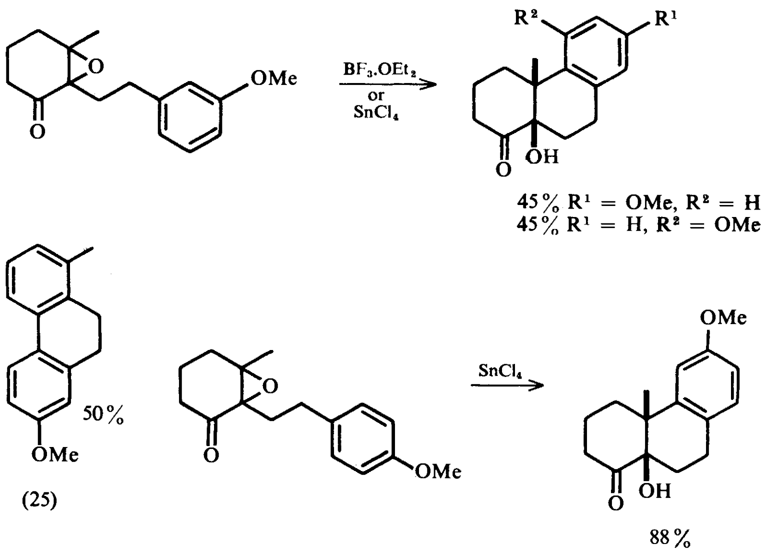
Scheme 19



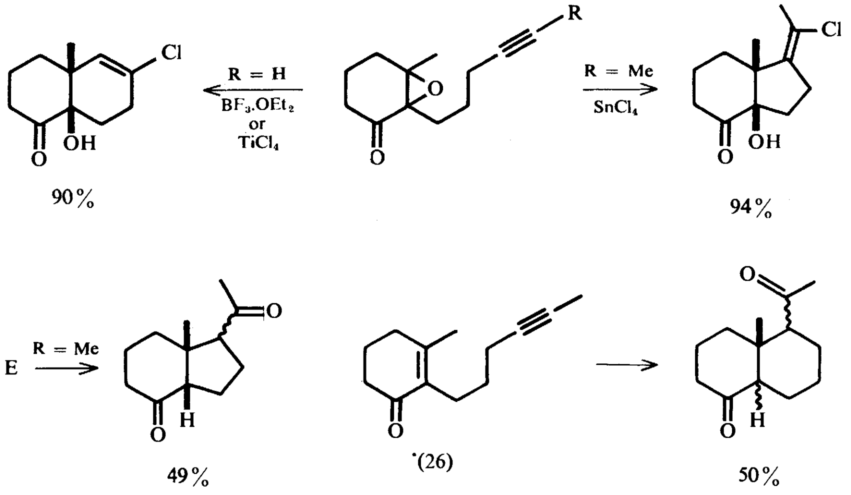
Scheme 20

(Scheme 22). It is notable that the enone (26) cyclized readily but the related epoxide only underwent ring contraction.

These and other monocyclisations demonstrate that both the epoxide and the dienoltrifluoroacetate could function as efficient initiators in forming single rings. Cyclization of the epoxide (27) to the tricycle (28) (Scheme 23) showed that

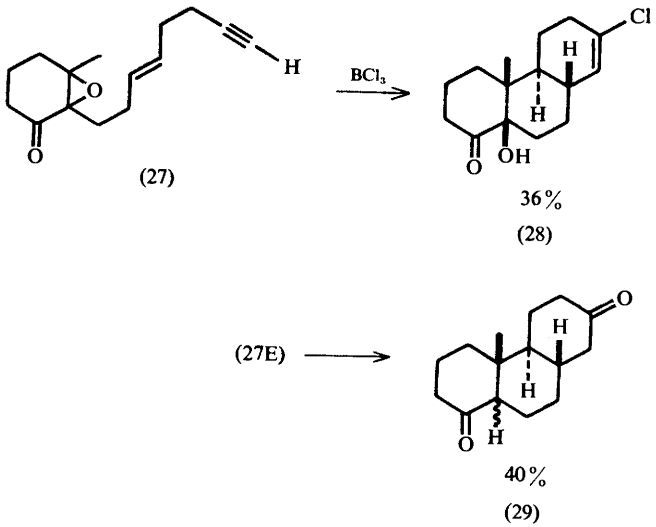


Scheme 21



Scheme 22

consecutive ring formation could take place. The corresponding enone was also cyclized in comparable yield to the *cis*- and *trans*-diones (29). However, the anisyl derivatives (30) and (31) (Scheme 24) gave disappointing results; tetracyclic products were obtained but in very low yield. The major products were (33) and (34),



Scheme 23

arising from single cyclizations. The corresponding enones cyclized much more efficiently to tetracyclic products. A comparison was also made with Johnson's method by cyclizing the alcohol (38) to the tetracycle (39) (Scheme 25).

From these results it is apparent that the 3-methylcyclohex-2-enone group is versatile in that it can be transformed into at least three functionalities capable of initiating cyclization. There are other possibilities as yet unexplored.

6 Mechanism

It is unlikely that any single mechanism operates over the diversity of polyene cyclizations. The range of possible mechanisms are (*a*) completely concerted cyclizations, (*b*) stepwise cyclization with equatorial attack on the carbonium ion intermediates being favoured, and (*c*) stepwise cyclization with products being formed under thermodynamic control. The latter can be rejected conclusively only in the few cases where pairs of *Z*- and *E*-isomers have been cyclized and shown to lead to different stereochemical series and where the manifestly thermodynamically less stable product is formed. With stepwise mechanism (*b*) it is necessary to account for the stereochemical integrity of the intermediate and for the preference for equatorial attack. With intermediates where ring flipping is possible it is necessary to make the not unreasonable assumption that this process is slower than the rate of nucleophilic attack. The intermediacy of bridged ions[43] and purely steric effects[44] have been advanced to account for the preference for equatorial attack. The most convincing evidence for a concerted cyclization has

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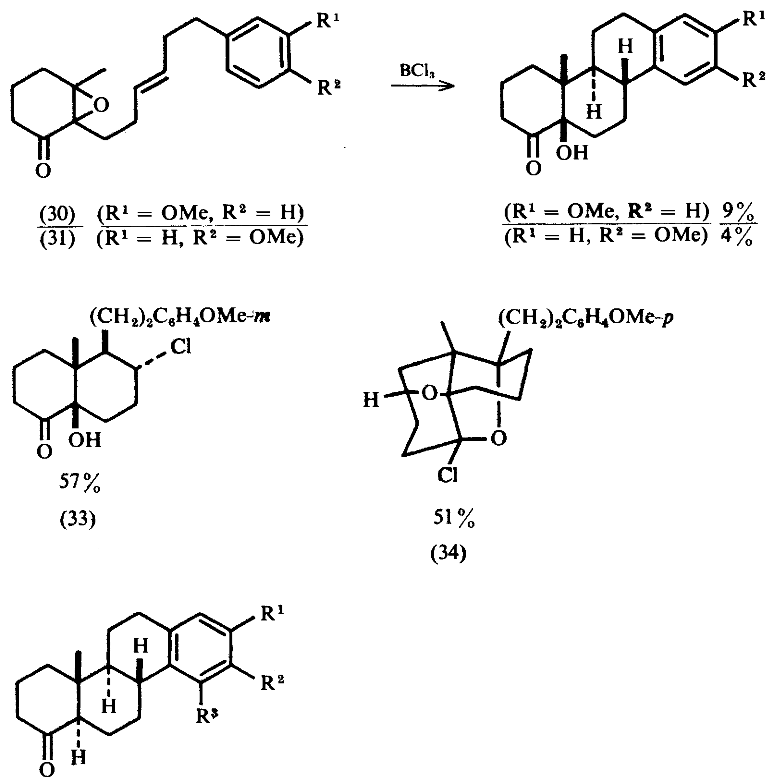
[43] W. S. Johnson, *Trans. New York Acad. Sci.*, 1967, **29**, 1001.

[44] K. E. Harding, *Bio-org. Chem.*, 1973, **2**, 248.



(30) (R^1 = OMe, R^2 = H)
(31) (R^1 = H, R^2 = OMe)

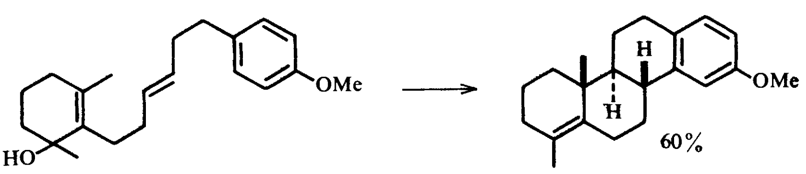
(R^1 = OMe, R^2 = H) 9%
(R^1 = H, R^2 = OMe) 4%

57%
(33)

51%
(34)

(30E) $\longrightarrow$ 56% (35) (R^1 = OMe, R^2 = R^3 = H)
(30E) $\longrightarrow$ 14% (36) (R^1 = R^2 = H, R^3 = OMe)
(31E) $\longrightarrow$ 81% (37) (R^1 = R^3 = H, R^2 = OMe)

Scheme 24



60%

(38) (39)

Scheme 25

been supplied by Johnson[45] who showed that the rates of cyclization of the aryl compounds (Scheme 26) varied with the nature of the substituents (X). The only

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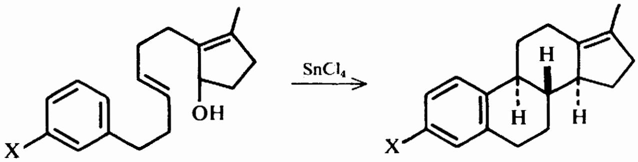
[45] P. A. Bartlett, J. I. Brauman, W. S. Johnson, and R. A. Volkman, *J. Amer. Chem. Soc.*, 1973, 95, 7502.



Scheme 26

feasible explanation, other than concerted cyclization, of these results is the *reversible* formation of a monocyclized carbonium ion; there appears to be little precedent for such reversibility. Our results do not yet allow any differentiation between these mechanisms. In the epoxide cyclizations diaxial ring opening is, as expected, preferred† leading to a steroid decalone conformation. However, the stable conformation, when it can be adopted, is the 'non-steroid' where hydrogen bonding of the hydroxyl to the carbonyl group is observed.

Finally, I would like to thank my collaborators who contributed much to the work: they are Drs. J. Amupitan, E. Huq, M. Mellor, A. Santos, E. G. Scovell, and Mr. P. M. Bishop.

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†This is established by the *X*-ray structure determination of (28) carried out by Mr. O. S. Mills