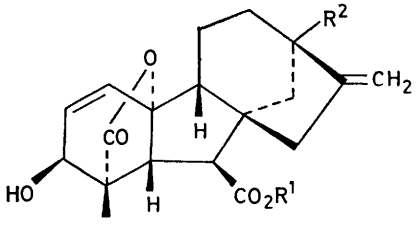
Rearrangement of the Lactone Ring of Gibberellin A_3 in Aqueous Alkali; Participation of the Ionised 3-Hydroxy-group in an *anti* S_N2' Reaction

By **Paul S. Kirkwood**, **Jake MacMillan**,* and **Michael L. Sinnott**, School of Chemistry, University of Bristol, Bristol BS8 1TS

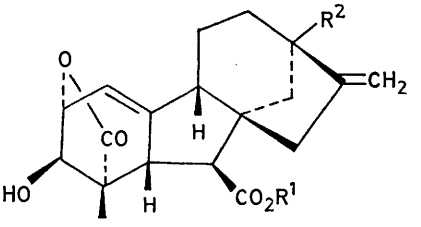
Whereas gibberellin A_3 is completely rearranged by 0.01 M-aqueous sodium hydroxide at 22 °C to the 19,2-lactone, the methyl ethers of both reactant and product, the 3-epimer (as its 13-acetate), and 3-deoxygibberellin A_3 methyl ester are all inert to aqueous base. A 2β,3β-epoxy-19-carboxylate intermediate in the rearrangement is proposed.

THE isomerisation of gibberellin A_3 (1) in weak alkali to give the 19,2-lactone (4) has been known for many years.[1] Using 0.01M-alkali, only (4) was detected;[1] with stronger alkaline conditions (>0.1M), opening of the lactone occurred to give the diacid (7).[2] That the product of isomerisation contained an intact lactone ring, even in the alkaline reaction medium, was established[1] by direct solvent extraction of the ester (5) from such a reaction medium. The 19,2-lactone methyl ester (5) was also obtained[2] by relactonisation of the diacid (7) followed by methylation, using diazomethane. The same rearrangement has been observed[3] with gibberellin A_7 (3) and its methyl ester in alkaline conditions.

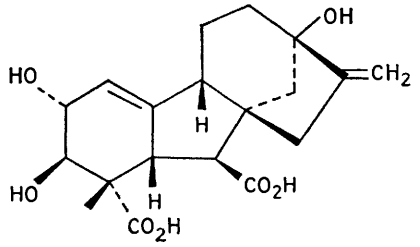
The 1,2-double bond seems to be essential for the lactone rearrangement; the methyl esters of C_{19}-gibberellins which possess a 3β-hydroxy-group in a saturated A-ring, such as gibberellins A_1 and A_4 *methyl* esters (8) and (9), are converted in *ca.* 70% yield to the 3α(*eq*)-alcohol (10) by treatment with aqueous, dilute alkali.[1,4,5] A retro-aldol mechanism (Scheme 1) has been proposed for this rearrangement.[6,7] However, 3-epimerisation has not been reported for gibberel-



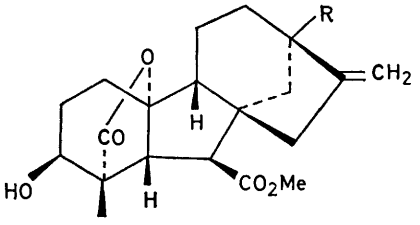
(1) R^1 = H, R^2 = OH
(2) R^1 = Me, R^2 = OH
(3) R^1 = R^2 = H



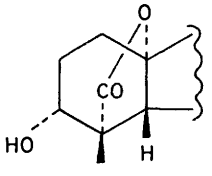
(4) R^1 = H, R^2 = OH
(5) R^1 = Me, R^2 = OH
(6) R^1 = R^2 = H



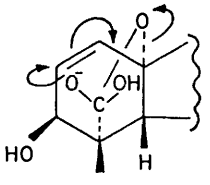
(7)



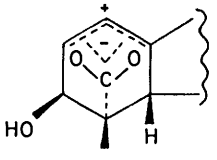
(8) R = OH
(9) R = H



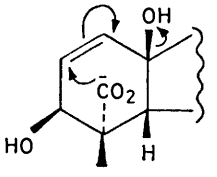
(10)



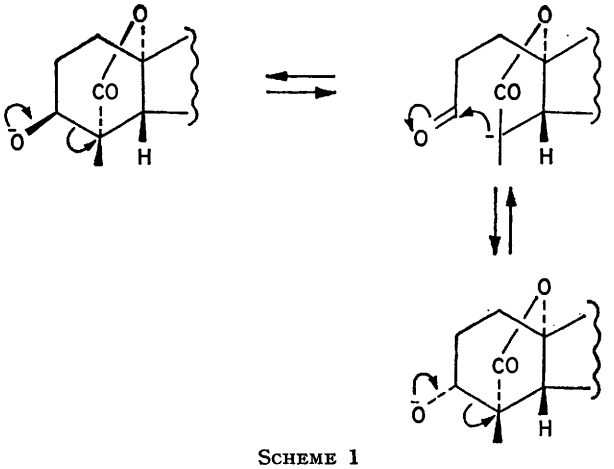
(11)



(12)



(13)

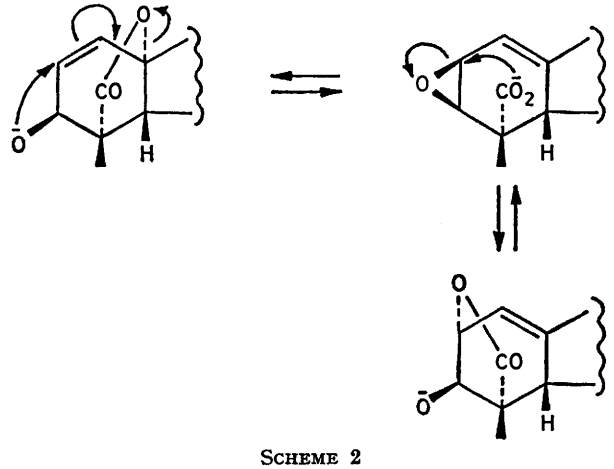


SCHEME 1

lins A_3 (1) and A_7 (3), which possess a 1,2-double-bond; only rearrangement of the lactone with retention of the 3β-configuration to form (4) and (6) has been observed.[1,3,4,8]

Two mechanisms have been proposed in the literature [9] for the formation of the 19,2-lactone (4) from gibberellin A_3 (1) in aqueous alkali: an electrocyclic reaction of the tetrahedral intermediate (11) formed by addition of hydroxide ion to the lactone carbonyl group, or a non-concerted, allylic shift involving an ion-pair intermediate (12). The latter mechanism is untenable since it cannot explain the necessity of base for rearrangement to occur. The rate of such an S_N1 ionisation process to give (12) would be independent of any nucleophile or its concentration. Also the S_N2 attack of a hydroxide ion at the tertiary 10-position *via* (13), followed by attack of the carboxylate anion at the 2α-position is highly unlikely. The rearrangement does not occur at room temperature in aqueous solution, buffered at pH 5.2, 7.0, and 8.0 (see Experimental section). A Cope rearrangement (14) is therefore improbable. Furthermore, since the 7-oic acid is fully ionised at pH 7, and since the rearrangement occurs with the methyl ester (2), a remote carboxylate anion is unimportant.

Apart from the proposed intermediate (11), there is another plausible mechanism: an *anti* S_N2' process *via* a 2β,3β-epoxy-intermediate (Scheme 2). Since this latter mechanism requires that a free 3-hydroxy-group be present, protection of this group should prevent any rearrangement by way of an *anti*-S_N2' mechanism. We now report data compatible with this mechamism and incompatible with previously suggested ones.



SCHEME 2

RESULTS AND DISCUSSION

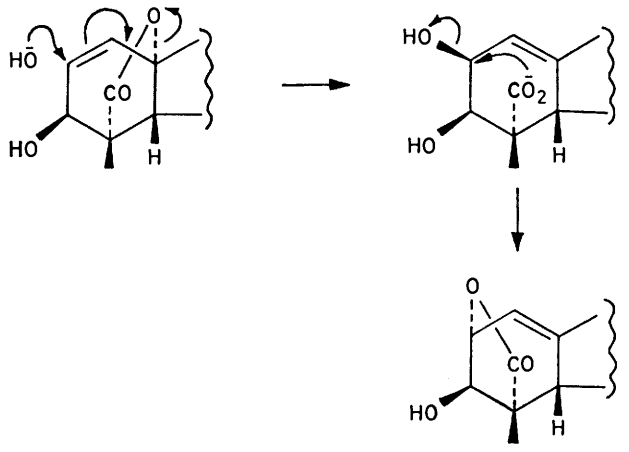
The permethylation of gibberellins using sodium hydride and methyl iodide in dimethylformamide has been shown, by work in this laboratory,[10] to give clean reaction products. The 3,13-dimethyl ether of gibberellin A_3 methyl ester (15) was prepared, in 58% yield, from gibberellin A_3 methyl ester (2) using this method. Treatment of the dimethyl ether (15) with aqueous potassium hydroxide (0.8M), remethylation of the 7-oic acid using diazomethane, and analysis by n.m.r. and g.l.c.–mass spectrometry revealed that only starting material had been isolated. The n.m.r. spectrum showed two one-proton signals at δ 6.34 and 6.04 with the characteristic splitting associated with a 1,2-double bond and a 3β-substituent.

The base-catalysed isomerisation of (1) to (4), or (2) to (5), proceeds to completion ($K > 10^2$). However, conceivably, permethylation could alter the position of equilibrium such that the dimethyl ether (15) was thermodynamically more stable than the rearranged ether (20); that this was not the case was shown by demonstrating that the 19,2-lactone (20) was also inert to base.

These observations show that failure to observe the rearrangement of (15) to (20) is a kinetic, not a thermodynamic phenomenon, and establish the necessity for a 3-hydroxy-group if this isomerisation to the 19,2-lactone, (4) or (5), is to occur. They also eliminate the possibility of (11) as an intermediate and support a mechanism involving deprotonation of the allylic alcohol.

Further support for such a mechanism comes from the inert nature of 3-deoxygibberellin A_3 methyl ester (16) to aqueous base. Although the ester (16) was only available as a mixture with its 2,3-double-bond isomer (23) in the ratio of 3 : 7, the presence of (16) could be readily established and quantified by n.m.r. spectroscopy. The stability of the ester (16) would not be expected if isomerisation occurred by way of hydroxide attack at the carbonyl group of the lactone. It also renders unlikely an intermolecular *anti* S_N2' mechanism involving hydroxide attack at the 2β-position (Scheme 3). . Such a process could possibly have allowed for the inert nature of the dimethyl ether (15) to alkali by the additional steric hindrance of the 3β-methoxy-group.

The 3α-alcohol (17), upon treatment with aqueous alkali, was hydrolysed to the diol (18). That isomerisation had not occurred was shown by the unaltered pattern of signals at δ 4.2—6.2, characteristic of a 1,2-double bond with a 3α-substituent. This shows that not only must a free 3-hydroxy-group be present for the

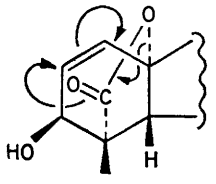


SCHEME 3

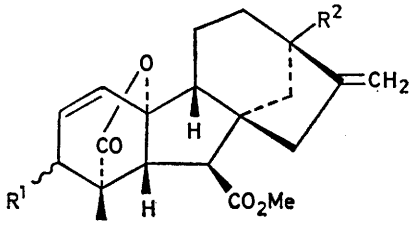
lactone rearrangement to occur, but that it must have the β-configuration. Therefore, any mechanism for this rearrangement which involves cleavage of the C(3)–C(4) bond in a retro-aldol condensation of the type shown in Scheme 1 can be discounted. However, on the basis of the mechanism shown in Scheme 2, any 2α,3α-epoxide (21) formed from (18) would not be susceptible to intramolecular nucleophilic attack by carboxylate, since this would require a *syn* S_N2 reaction.

Work in connection with the total synthesis of gibberellin A_3 [11,12] has shown that the 2β,3β-epoxide, proposed here as an intermediate in the lactone rearrangement, when generated by a completely different route, does indeed lead to a product with the 19,2-lactone ring. Epoxidation of diene (22) with *m*-chloroperbenzoic acid [11] in methylene chloride or peracetic acid at pH 9 [12] yields the lactone (5) as an isolated product.

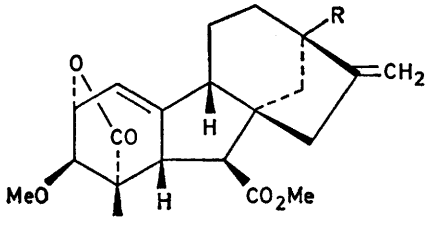
It may therefore be concluded that the isomerisation of gibberellin A_3 (1), gibberellin A_7 (3), and their methyl esters in aqueous alkali proceeds (Scheme 2) by an intramolecular *anti* S_N2' reaction to give a 2β,3β-epoxide intermediate which is then opened by the newly liberated C(19)-carboxylate group in a conventional S_N2 reaction. The driving force is presumably



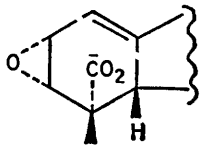
(14)



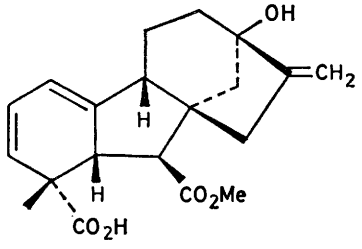
(15) R^1 = β-OMe, R^2 = OMe
(16) R^1 = H, R^2 = OH
(17) R^1 = α-OH, R^2 = OAc
(18) R^1 = α-OH, R^2 = OH



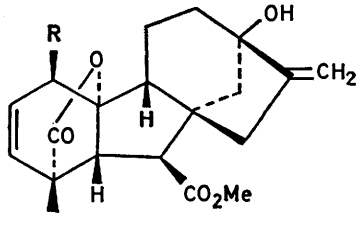
(19) R = OH
(20) R = OMe



(21)



(22)



(23) R = H
(24) R = Cl

the relief of strain in going from the *trans* A/B ring fusion to an exocyclic double bond.

Both steps have chemical precedent. The literature on the stereochemistry of the S_N2' reaction is contradictory. Although early work [13] indicated a *syn*-stereochemistry for the S_N2' reaction of a cyclohexenyl ester with amines, *anti*-stereochemistry [14] was observed with thiolate nucleophiles in the same system. The reaction of a cyclobutenyl chloride with methoxide gave products of *syn*-attack,[15] and both *syn*- [16] and *anti*- [17] stereochemistries have been observed in acyclic systems. Pathways for *syn* and *anti* S_N2' attack clearly have similar free-energy maxima, and in accord with this idea participation by the PhS group in an intramolecular S_N2' reaction in both a *syn*- and *anti*-sense has been considered to be comparably effective.[18] In the light of these findings, the second step in Scheme 2 is orthodox.

Neighbouring-group participation in the ring-opening of epoxides is well recognised,[19] although examples of the participation of ionised carboxylate are scarce. The best precedent for such a reaction is perhaps the alkylation of active-site aspartate residues of glycosidases in their non-covalent complexes with suitably substituted cyclohexene oxides.[20]

A corollary to the mechanism in Scheme 2 is that protection of the 3-hydroxy-group as a base-stable derivative renders ring A of gibberellin A_3 stable to alkali. Thus future syntheses of gibberellin A_3 need not be based on strategies in which ring A is the last to be assembled.[12]

EXPERIMENTAL

For general experimental details, see ref. 21.

ent-10-*Hydroxy*-3α,13-*dimethoxy*-7-*methoxycarbonyl*-20-*norgibberella*-1,16-*dien*-19-*oic Acid* 19,10-*Carbolactone* (15).—Gibberellin A_3 (1) (500 mg) was dissolved in methanol and ethereal diazomethane was added until the yellow colouration persisted. After removal of the solvent, the methyl ester (2) was dissolved in dimethylformamide (20 ml) and methyl iodide (120 ml), both freshly redistilled and dried, to which sodium hydride (500 mg; 60% in oil, washed several times with light petroleum) was added, with stirring. After 28 h, excess of methanol was added and the solvents were removed *in vacuo*. Addition of water and extraction into ethyl acetate at pH 3 gave the crude product which, after evaporation of the solvent, was fractionated by p.l.c. using ethyl acetate–light petroleum (3 : 2). Elution of the band at R_F 0.5—0.6 yielded the dimethyl ether (15) (312 mg), recrystallised from ethyl acetate–light petroleum, m.p. 152—153 °C (lit.,[22] 151—152 °C) (Found: C, 68.1; H, 7.7. $C_{22}H_{28}O_6$ requires C, 68.0; H, 7.2%); [22] $\nu_{max.}$ 1 771, 1 730, 1 660w, and 1 077; δ 6.34 (d, *J* 10 Hz, 1-H), 6.04 (dd, *J* 3 and 10 Hz, 2-H), 5.14 (m, 17-H), 5.06 br (s, 17-H), 3.77 (s, CO_2Me), 3.67 (d, *J* 3 Hz, 3-H), 3.49 (s, 3-OMe), 3.30 (d, *J* 10 Hz, 5-H), 3.20 (s, 13-OMe), 2.78 (d, *J* 10 Hz, 6-H), and 1.25 (s, 18-Me); *m/e* 388 (M^+, 100%), 359 (12), 357 (13), 329 (11), 312 (16), 180 (26), 150 (23), 149 (13), and 135 (20).

ent-2β-*Hydroxy*-3α,13-*dimethoxy*-7-*methoxycarbonyl*-20-*norgibberella*-1(10),16-*dien*-19-*oic Acid* 19,2-*Carbolactone* (20).—Gibberellin A_3 (1) (700 mg) was dissolved in potassium hydroxide solution (5 ml; 0.05M) and, after 20 h, extracted into ethyl acetate at pH 3. The solvent was removed *in vacuo* and treated with ethereal diazomethane to give the 19,2-lactone methyl ester (5).

The ester (5) (550 mg) was permethylated according to the procedure described in the previous experiment. P.l.c. of the reaction product, using ethyl acetate–light petroleum (7 : 3) gave, at R_F 0.65—0.75, the dimethyl ether (20) (272 mg) (Found: M^+ 388.188; $C_{22}H_{28}O_6$ requires M^+ 388.188); $\nu_{max.}$ ($CHCl_3$) 1 773, 1 728, 1 681w and 956; δ 5.72 (quin, *J* 2.5 Hz, 1-H), 5.00br and 4.94br (each s, 17-H_2), 4.78 (t, *J* 5 Hz, 2-H), 3.84 (d, *J* 5 Hz, 3-H), 3.71 (s, CO_2Me), 3.42 (s, 3-OMe), 3.11 (s, 13-OMe), 3.29 (dd, *J* 2.5 and 6 Hz, 5-H), 2.55 (d, *J* 6 Hz, 6-H), and 1.21 (s, 18-Me); *m/e* 388 (M^+, 100%), 359 (15), 357 (13), 312 (28), 180 (37), 150 (9), and 149 (14).

Elution of the band at R_F 0.5—0.6 gave the 3-methyl ether (19) (180 mg) (Found: M^+ 374.171; $C_{21}H_{26}O_6$ requires M^+ 374.171); $\nu_{max.}$ ($CHCl_3$) 3 590, 1 778, 1 730, 1 680w, and 948 cm^{-1}; δ 5.78 (quin, *J* 2.5 Hz, 1-H), 5.11br and 4.96br (each s, 17-H_2), 4.82 (t, *J* 5 Hz, 2-H), 3.87 (d, *J* 5 Hz, 3-H), 3.75 (s, CO_2Me), 3.46 (s, 3-OMe), 3.32 (dd, *J* 2.5 and 6 Hz, 5-H), 2.66 (m, 9-H), 2.52 (d, *J* 6 Hz, 6-H), and 1.24 (s, 18-Me); *m/e* 446 (M^+, 100%), 431 (8), 417 (15), 415 (15), 387 (8), 371 (13), 370 (14), 311 (7), 239 (12), 238 (24), and 73 (71).

Base Treatment Experiments

(a) ent-10-*Hydroxy*-3α,13-*dimethoxy*-7-*methoxycarbonyl*-20-*norgibberella*-1,16-*dien*-19-*oic Acid* 19,10-*Carbolactone* (15).—The compound (20 mg) was dissolved in dioxan (1 ml) and 0.8M-potassium hydroxide (5 ml). After 40 h, concentrated hydrochloric acid was added (pH 3). The product was extracted into ethyl acetate and the solvent was removed under vacuum to give a gum (18 mg). This gum was re-methylated using diazomethane and analysed by g.l.c.–mass spectrometry and n.m.r. spectrometry from which it was identified as starting material (15).

(b) ent-2β-*Hydroxy*-3α,13-*dimethoxy*-7-*methoxycarbonyl*-20-*norgibberella*-1(10),16-*dien*-19-*oic Acid* 19,2-*Carbolactone* (20).—The compound (20 mg) was treated as in (a). N.m.r. and g.l.c.-mass spectrometry of the product showed it to be starting material (20).

(c) ent-10,13-*Dihydroxy*-7-*methoxycarbonyl*-20-*norgibberella*-1,16-*dien*-19-*oic Acid* 19,10-*Carbolactone* (16).—A mixture of gibberellin A_5 methyl ester (23) (70%) and its 1,2-double-bond isomer (16) (30%), obtained [23] by tri-n-butylstannane reduction of 1β-chlorogibberellin A_5 methyl ester (24), was dissolved in dioxan (1 ml) and 2M-potassium hydroxide (1 ml). After 2 h, water was added. The solution was then adjusted to pH 3 with concentrated hydrochloric acid and extracted with ethyl acetate. Evaporation of the ethyl acetate and re-methylation with diazomethane gave the starting mixture (7 : 3) (by n.m.r.).

(d) ent-13-*Acetoxy*-3β,10-*dihydroxy*-7-*methoxycarbonyl*-20-*norgibberella*-1,16-*dien*-19-*oic Acid* 19,10-*Carbolactone* (17).—The acetate [21] (20 mg) was treated as in (a) to give *ent*-3β,10,13-trihydroxy-7-methoxycarbonyl-20-norgibberella-1,16-dien-19-oic acid 19,10-carbolactone (18) as the sole product (15 mg); δ 6.18br (d, *J* 10 Hz, 1-H), 5.82br (d, *J* 10 Hz, 2-H), 5.24br and 4.93br (each s, $W_{\frac{1}{2}}$ 8 Hz, 17-H_2), 4.26br (s, $W_{\frac{1}{2}}$ 8 Hz, 3-H), 3.73 (s, CO_2Me), 2.96 (d, *J* 10 Hz, 5-H), 2.76 (d, *J* 10 Hz, 6-H), and 1.29 (s, 18-Me); *m/e* [MeTMSi]: 504 (M^+, 68), 489 (3), 475 (5), 445 (5), 347 (12), 238 (18), 208 (38), 193 (13), 167 (7), 157 (14), and 73 (100).

Treatment of ent-3α,10,13-*Trihydroxy*-20-*norgibberella*-

1,16-diene-7,19-dioic Acid 19,10-*Carbolactone* (1) *with Aqueous Buffer*.—In separate experiments the acid (1) (20 mg) was dissolved in (i) 1% aqueous disodium hydrogen phosphate (5 ml), buffered at pH 8.0; (ii) dioxan (0.5 ml) and 1% aqueous disodium hydrogen phosphate solution (4.5 ml), buffered at pH 7.0; and (iii) as in (ii) but buffered at pH 5.2. In each case, after 12 h, the pH was reduced to 3.0 using 2M-hydrochloric acid and the mixture extracted with ethyl acetate. Evaporation of the ethyl acetate gave pure starting material as indicated by the ^{1}H n.m.r. spectra of it and its methyl ester (diazomethane).

We thank Dr. L. Rivier and Mrs. K. S. Albone for providing details of the permethylation procedure prior to publication. We also thank Mrs. K. S. Albone for the preparation of the permethylated compounds, used in this work, and Dr. J. R. Bearder for helpful advice. One of us (P. S. K.) thanks the S.R.C. for a Research Studentship.

[9/1649 *Received*, 17*th October*, 1979]

REFERENCES

[1] B. E. Cross, J. F. Grove, and A. Morrison, *J. Chem. Soc.*, 1961, 2498.
[2] B. E. Cross, *J. Chem. Soc.*, 1960, 3022.
[3] D. C. Aldridge, J. R. Hanson, and T. P. C. Mulholland, *J. Chem. Soc.*, 1965, 3539.
[4] B. E. Cross, J. F. Grove, J. MacMillan, T. P. C. Mulholland, and N. Sheppard, *Proc. Chem. Soc.*, 1958, 221.
[5] B. E. Cross, J. F. Grove, J. MacMillan, J. S. Moffatt, T. P. C. Mulholland, J. C. Seaton, and N. Sheppard, *Proc. Chem. Soc.*, 1959, 302.
[6] R. H. Cornforth, *Chem. and Ind.*, 1959, **78**, 184.
[7] J. MacMillan and R. J. Pryce, *J. Chem. Soc.* (*C*), 1967, 740.
[8] B. E. Cross, J. F. Grove, P. McCloskey, and T. P. C. Mulholland, *Chem. and Ind.*, 1959, **78**, 1345.
[9] D. C. Aldridge, J. F. Grove, R. N. Speake, B. K. Tidd, and W. Klyne, *J. Chem. Soc.*, 1963, 143.
[10] K. S. Albone, P. Gaskin, L. Rivier, and J. MacMillan, *Phytochemistry*, submitted for publication.
[11] E. J. Corey, T. M. Brennan, and R. L. Carney, *J. Amer. Chem. Soc.*, 1971, **93**, 7316.
[12] E. J. Corey, R. L. Danheiser, S. Chandrasekaran, G. E. Keck, B. Gopalan, S. D. Larsen, P. Siret, and J.-L. Gras, *J. Amer. Chem. Soc.*, 1978, **100**, 8034.
[13] G. Stork and W. N. White, *J. Amer. Chem. Soc.*, 1956, **78**, 4609.
[14] G. Stork and A. Kreft, *J. Amer. Chem. Soc.*, 1977, **99**, 3850.
[15] W. Kirmse, F. Scheidt, and H.-J. Vater, *J. Amer. Chem. Soc.*, 1978, **100**, 3945.
[16] R. M. Magid and O. S. Fruchey, *J. Amer. Chem. Soc.*, 1977, **99**, 8368.
[17] S. Godtfredsen, J. P. Obrecht, and D. Arigoni, *Chimia*, 1977, **31**, 62.
[18] J. J. Hebel, R. F. Milaszewski, and R. E. Arlt, *J. Org. Chem.*, 1977, **42**, 585.
[19] J. G. Buchanan and H. Z. Sable in 'Selective Organic Transformations,' B. S. Thyagarajan (ed.), John Wiley, New York and London, 1972, vol. 2, pp. 1—95.
[20] G. Legler, *Mol. Cell Biochem.*, 1973, **2**, 31.
[21] M. H. Beale and J. MacMillan, *J.C.S. Perkin I*, 1980, 877.
[22] D. C. Wheatley, B.Sc. Thesis, University of Bristol, 1964.
[23] J. R. Bearder, P. S. Kirkwood, and J. MacMillan, *J.C.S. Perkin I*, in the press.