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STEREOCHEMISTRY OF THE DITERPENOIDS—IV[1]

STRUCTURE AND STEREOCHEMISTRY OF SOME POLYCYCLIC DITERPENOIDS

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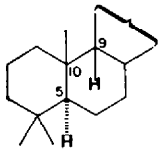
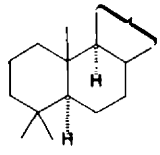
Abstract—Modification of the proposed stereochemistry of several diterpenoids is suggested using biogenetic analysis. Such conclusions are shown to be correct by derivation of the absolute stereochemistry of gibberellic acid, cafestol and kaurene using circular dichroism data and confirmed by X-ray crystallographic studies.

The analysis is extended to predict the stereochemistry of other terpenoids.

THE signal success attending codification of triterpenoid stereochemistry in terms of the Biogenetic Isoprene Rule[2,3] has not hitherto been attained in the diterpenoid family. In the past, reluctance to exercise rigorous application of the rule of anti-parallel cationic 1,2-addition, which has proved such a satisfying rationale for squalene cyclization, to the appropriate C_{20} precursors has been occasioned by the presence of a small but important group of diterpenoids with an apparently[4] exceptional common stereochemical feature. Thus, the proposed configuration at $C_{5,9}$ and C_{10} in each member of this irregular set results in the *trans-syn* (I) rather than the *trans-anti* (II) arrangement which would be expected by analogy with the mechanism proposed for other terpenoid cyclizations.[5,6]



I



II

At the outset of our work, the contradictions to the tenet of *trans-anti-trans* cyclization included members of the bicyclic, tricyclic and tetracyclic diterpenoids

[1] Part III—A. I. Scott, S. A. Sutherland, D. W. Young, G. A. Sim, L. Guglielmetti and D. Arigoni, *Proc. Chem. Soc.* 19 (1964).

[2] A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta* **38**, 1890 (1959).

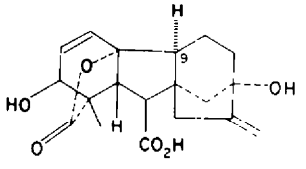
[3] L. Ruzicka, *Proc. Chem. Soc.* 341 (1959); *Idem, Perspektiven der Biogenese und der Chemie der Terpene* p. 493. International Symposium on the Chemistry of Natural Products, Prague (1962); Butterworths, London (1963).

[4] For a recent review see W. B. Whalley, *Tetrahedron* **18**, 43 (1962).

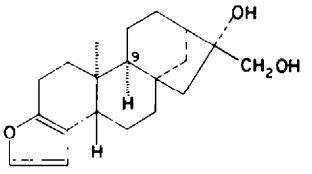
Refs. 5 and 6 at foot of p. 1340.

as portrayed in Chart I.* We proposed to seek extra support for the rigorous application of the all-*trans* cyclization rule rather than to plead a special case for each assignment of "unnatural" configuration.[6]

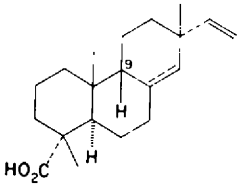
CHART I



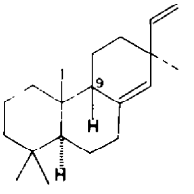
Gibberellic acid



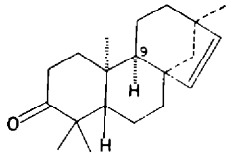
Cafestol
(Kahweol = 5,6-Dehydrocafestol)



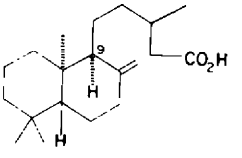
Isopimaric acid



Rimuene



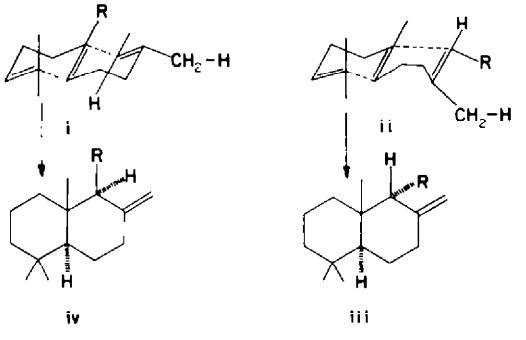
Stachenone



Eperuic acid

* In this context the rosenonolactone set (p. 1355) is not regarded as an exception.

[5] It should be noted that a *pseudo* two chair conformation (i) is required in the C_{20} precursor (e.g. geranylgeraniol) for development of this argument. Thus, cyclization of a potential ring B boat precursor (ii) would lead to configuration (iii) with the C_5 side chain (R) in the more encumbered *axial* conformation. Although apparent analogy for this event might be advocated with squalene



cyclization in mind, it must be pointed out that ring B in the triterpenoid-steroid series *eventually* realises a chair conformation by rearrangement and that so many examples of stereochemistry (iv)—a result of the cyclization of (i)—are on hand as to render the intervention of (iii) an unlikely event. As we shall show in the sequel, no authentic member of the latter type is now extant in the diterpenoid family.

[6] A possibility for the latter course is developed in footnote 5.

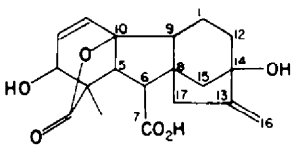
Since the only violation of the all-*trans* rule in each of the foregoing examples occurred in the allocation of C_9-stereochemistry we first examined the methods used in each case to assign configuration at this position.

Undoubtedly, the application of the tool of optical rotatory dispersion had been the only weapon which offered any real penetration to the least readily accessible centre of the cyclized diterpene array. Where comparison with valid model systems is possible such correlation is often quite straightforward. However, the method obviously suffers from the limitation that whereas the *sign* of an anomalous rotatory dispersion curve is seldom open to question, the *amplitude* and *shape* of the O.R.D. curve can be used for comparison only where contributions from asymmetric chromophores are well-resolved or where it is not required to assign subtle stereochemical features at a centre remote from the asymmetric chromophore. This inherent "impurity" of a rotatory dispersion curve, containing as it does unresolved contributions from both the background of $\sigma \rightarrow \sigma^*$ (—C—C—) transitions[7] and frequently rotatory donations from other centres, renders difficult extension of its interpretation beyond the valuable applications summarized in the Octant Rule[8] and in relatively uncomplicated comparison studies.[9]

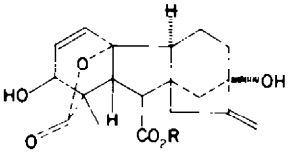
We therefore examined those cases where assignment of C_9-stereochemistry was first made by comparative O.R.D. studies and where a reasonable margin of error could be anticipated. As pointed out by the authors in some of these cases, the remoteness of the centre in question from the carbonyl chromophore left ambiguity in the assignment.[10] The resolution of this ambiguity will now be discussed for each case in turn under the headings *Stereochemical Analysis* and *Biogenetic Analysis*.

Gibberellic acid

Stereochemical analysis. The exhaustive studies of Grove *et al.*[11] defined the structure of gibberellic acid, the most important of the metabolites of *Gibberella fujikuroi* as III. Since the argument leading to stereochemistry IV for the acid will be required for our discussion, particularly with reference to the point at issue, the configuration of C_9, we summarize the evidence below.



III



IV

[7] For a summary of these effects, [a] S. F. Mason, *Quart. Rev.* **17**, 20 (1963); [b] C. Djerassi, *Optical Rotatory Dispersion; Applications to Organic Chemistry*. McGraw-Hill, New York (1960).

[8] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Amer. Chem. Soc.* **83**, 4013 (1961).

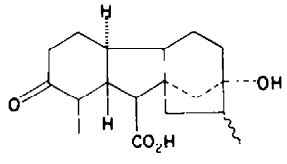
[9] For an excellent account of many correlative studies see Ref. 7*b*.

[10] Attempts have been made (Refs 15, 34) to remove background effects in such O.R.D. curves by subtraction methods. These gave unsatisfactory results.

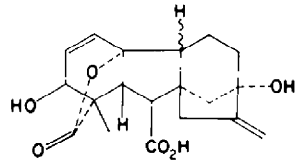
[11] Summarized by J. F. Grove in *Quart. Rev.* **15**, 56 (1961).

The conclusions reached by Stork and Newman, and the Imperial Chemical Industries group in 1959[12–15] are embodied in VI, and offer little by way of ambiguity, taken in conjunction with absolute configurational studies on V. We therefore now discuss the assignment of C_9 stereochemistry, which rested on less certain ground.

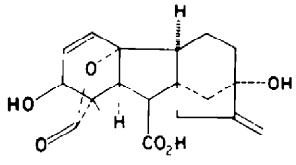
On the basis of rotatory dispersion data both groups[13,15] favoured the C_9-α-H orientation (VII). Thus Stork and Newman showed that there was a close correspondence in both shape and amplitudes of the R.D. curves of the *seco* esters (VIII and IX) derived from gibberellic and allogibberic acids respectively. Cross[15] *et al.* in addition to this observation commented on the *dissimilarity* of the R.D. curves of VIII and that of X, and thus deduced VII to be the relative and absolute stereochemistry of the acid. A separate study[16] using the atrolactic acid method defined the absolute stereochemistry at C_3 in harmony with expression VII.



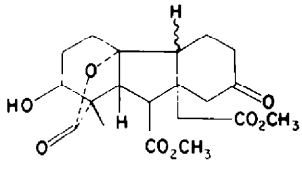
V



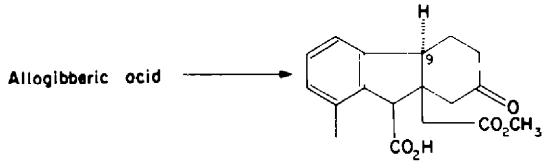
VI



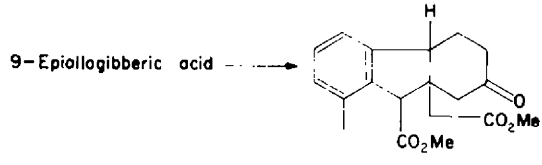
VII



VIII



IX

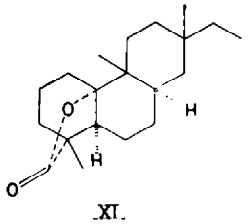


X

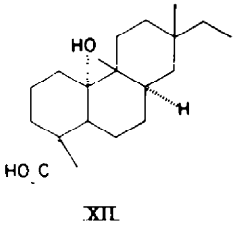
[12] G. Stork and H. Newman, *J. Amer. Chem. Soc.* **81**, 3168 (1959).
[13] G. Stork and H. Newman, *J. Amer. Chem. Soc.* **81**, 5518 (1959).
[14] P. W. Brian, J. F. Grove and J. Macmillan, *Progr. Chem. Org. Nat. Prod.* **18**, 350 (1960).
[15] B. E. Cross, J. F. Grove, P. McCloskey and T. P. C. Mulholland, *Chem. & Ind.* 1345 (1959).
[16] S. Masamune, *J. Amer. Chem. Soc.* **83**, 1515 (1961).

More recently the assignment of α-orientation to the lactone group has been questioned and on the basis of the rotation differences (large, negative) between certain diterpene lactones and their hydroxy acids, e.g. XI, XII and the corresponding difference (positive) in the case of 3-epitetrahydrogibberellic acid (XV) and its hydrolysis product, the stereochemistry XIII with the lactone ring β-oriented and hence the 3-hydroxyl in the α-configuration has been suggested.[17]

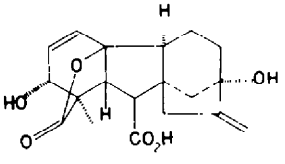
At the outset of our investigation the evidence for the stereochemistry of gibberellic acid (as outlined above) seemed to favour VII with XIII as a possible rival. The main point in favour of the latter appeared to be the ready explanation for the facile genesis of gibberellenic acid (XIV) in terms of the *trans* relationship of C_9—H and the lactone oxygen C_{10} bond. However, the expression XVI which explained the latter observation and all of the previous results (with the exception of the R.D. comparison data) seemed to us preferable to all other assignments in that it represented the result of rigorous application of the Biogenetic Isoprene Rule.[18]



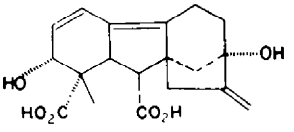
XI.



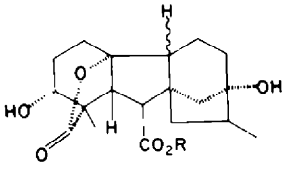
XII.



XIII.



XIV.



XV.

Biogenetic analysis. If we assume that the folding of the geranylgeraniol precursor (XVII) occurs in an all-*trans* fashion then XVIII[19] embodies the $C_{5,9,10}$ stereochemistry of *all bicyclic diterpenoids.* The derived carbonium ion (XIX)[20] now gives the tetracyclic parent (XX.) This represents an extension of the original scheme of Wenkert[25] in which

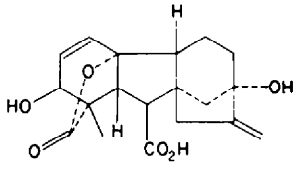
[17] O. E. Edwards *et al.*, *Chem. & Ind.* 624 (1960).

[18] Our views on this topic were first presented to the Organic Seminar, Glasgow University, November 1961, and subsequently at the I.U.P.A.C. Symposium on Natural Products, Brussels, June 1962.

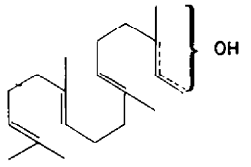
[19] Or its mirror image.

[20] A non-classical carbonium ion is not necessarily intended by this representation, but rather a working intermediate which leads mnemonically to all of the tri- and tetracyclic frameworks.

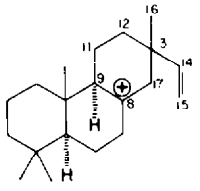
C_{12} and C_{14} are contiguous, the one carbon bridge is C_{15} and the two carbon bridge has C_{13} and C_{17} bearing the exocyclic methylene group (C_{16}). Since ring A is antipodal to the steroid ring A in absolute stereochemical terms we can write framework XXI for the skeleton on which the acid is based. This is now known to be the stereochemistry of (—)-kaurene.[21]



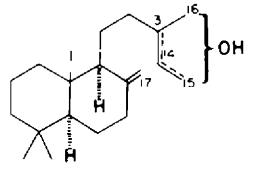
XVI



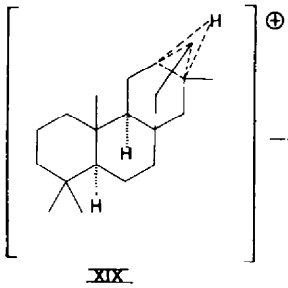
XVII



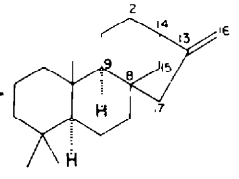
XVIII a



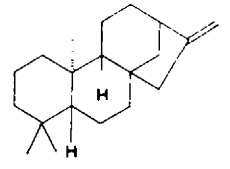
XVIII



XIX



XX

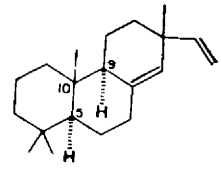


XXI

The removal of the C_{10}-methyl group in the biogenesis of gibberellic acid must now be considered. The situation in which this methyl group first migrates to C_9 seems most unlikely since this process generates the rosane skeleton (p. 1355) which would not be expected to afford an easy route to the tetracyclic diterpenoids. In other words we should not expect a *tetracyclic* member to subtend an angular methyl group at C_9 at *any* stage since the necessary carbonium ion (XIX) cannot be achieved in this way.[22] It therefore seemed to us that the assumption of kaurene stereochemistry

[21] B. E. Cross, R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.* 2944 (1963).

[22] A diametrically opposed argument has been advocated by Grove[15] in which the *normal* pimaradiene skeleton (i) serves as the precursor. Equilibration at C_8 (next to incipient carbonyl function at C_6) and loss of methyl at C_{10} leads to the $C_{5,9,10}$ *syn* backbone of XX. This also involves inversion at C_{10}.

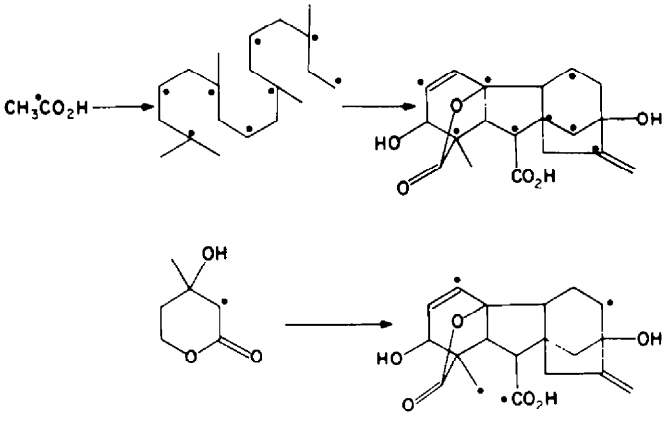


i

(XXI) in which all three centres are retained provided a sounder basis for consideration. By analogy with the lanosterol → cholesterol sequence[23] the loss of methyl from C_{10} should leave $C_{10}\alpha$-H and thence $C_{10}\alpha$-OH by the usual stereoselective bond insertion process of biological hydroxylation.[24]

The C/D ring formation takes place according to the Wenkert Scheme,[25] where stereochemical prediction cannot be made without prior knowledge of C_{13} stereochemistry. Partial stereochemistry (XXII) then follows from biogenetic analysis alone.[26] The results of feeding carboxy-^{14}C acetic acid and 2-^{14}C mevalonic acid to cultures of *G. fujikuori* indicate not only the diterpenoid nature of gibberellic acid, but also the changes depicted in XIX → XX. These are summarized in Chart II.

CHART II



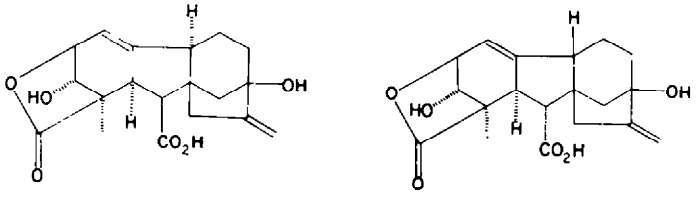
Subsequent to our preliminary communications on this subject[28,29] it was shown[21] that labelled (−)-kaurene (XXI) was incorporated into gibberellic acid in *G. fujikuroi*

[23] F. Guatschi and K. Bloch, *J. Amer. Chem. Soc.* **79**, 684 (1957); J. A. Olson, M. Lindberg and K. Bloch, *J. Biol. Chem.* **226**, 941 (1957).

[24] E. J. Corey, G. A. Gregoriou and D. H. Peterson, *J. Amer. Chem. Soc.* **80**, 2338 (1958).

[25] E. Wenkert, *Chem. & Ind.* **282**, (1955).

[26] Indeed an early expression (i) for gibberellic acid[27] embodied a *cis* relationship of C_5 and C_9. However, no distinction was made between the relative merits of (i) and (ii); in the latter the methyl group has migrated (cf. footnote 22).



[27] A. J. Birch, R. W. Rickards, H. Smith, A. Harris and W. B. Whalley, *Tetrahedron* **7**, 241 (1959).

[28] F. McCapra, A. I. Scott, G. A. Sim and D. W. Young, *Proc. Chem. Soc.* 185 (1962).

[29] A. I. Scott, G. A. Sim, G. Ferguson, D. W. Young and F. McCapra, *J. Amer. Chem. Soc.* **84**, 3197 (1962).

cultures, a result in full accord with the principles embodied in our present analysis.

With these concepts in mind we therefore began our re-examination of gibberellic acid stereochemistry with a study of the circular dichroism curves obtained from those carbonyl derivatives which had been used previously for O.R.D. studies. We expected that small differences (if any existed) between closely related ketones differing only in C_9 stereochemistry would be revealed in some way, however subtle, by the specific dichroism curve, which imparts rotatory information concerning only the *immediate environment* of the asymmetric carbonyl group.[30] The multi-banded nature of the dichroism curve for camphor[31] augured well for making such a distinction and we were able to show (Figs. 1–2) that suitable diterpenoid ketones showed considerable fine structure when measured in dioxan solution.[32]

When we compared the set of ketones (XXIII; XXIV) and (XXV; XXVI) (Figs 2, 3) it was at once apparent that although the intensities ($\epsilon_l - \epsilon_r$) of the various absorption bands could not be used in basing assignments, the position of maximal wavelength

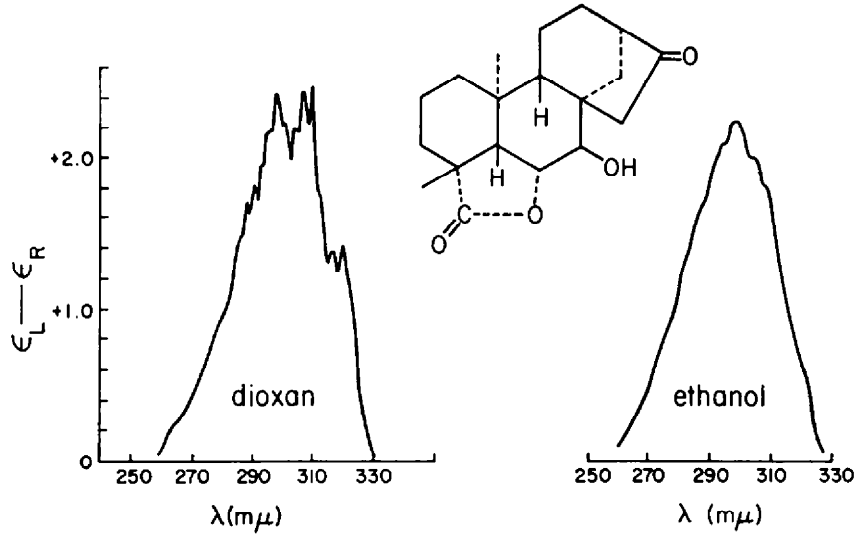
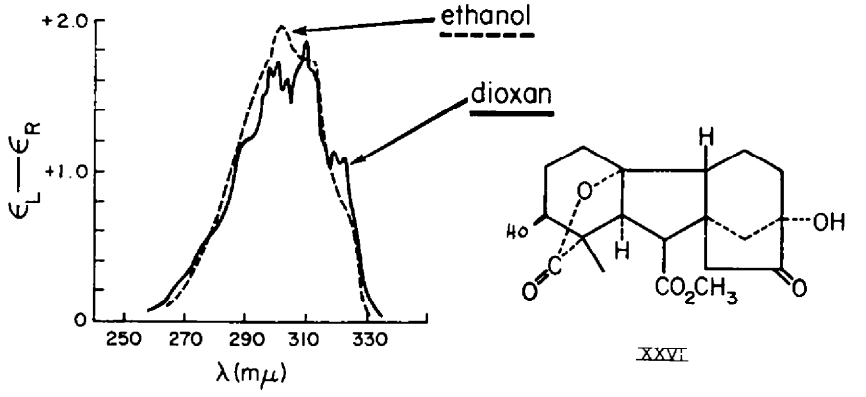


FIG. 1



XXVI

FIG. 2

[30] For reviews of this topic see Ref. 7*a* and also A. Moscowitz in Ref. 7*b*, Ch. 12.

[31] S. Mitchell, private communication.

[32] L. Velluz and M. Legrand, *Angew. Chem.* 73, 603 (1961).

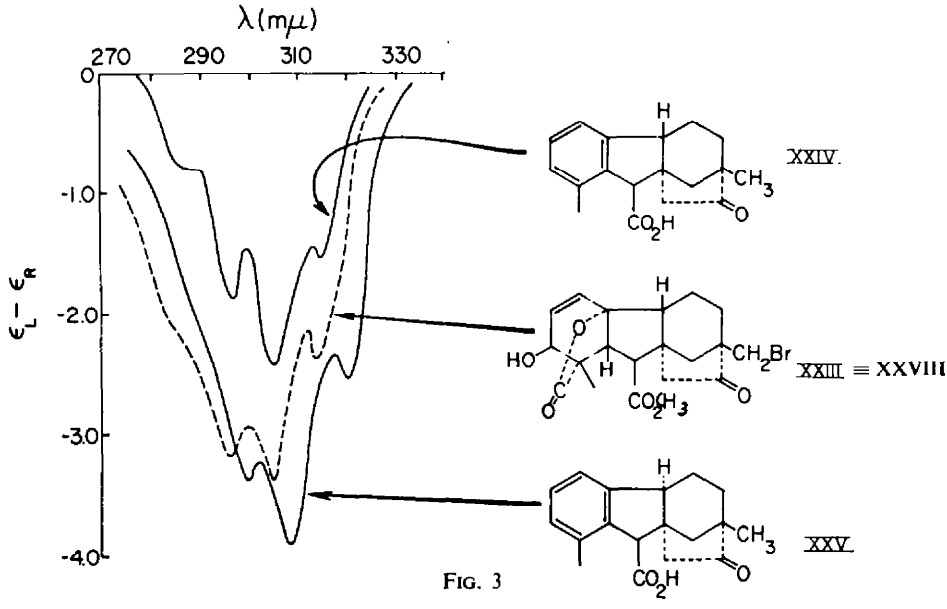
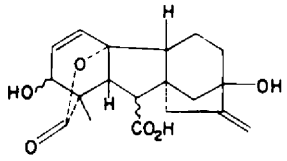


FIG. 3

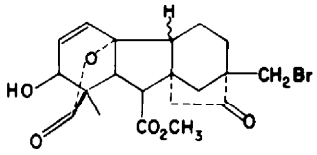
of each C.D. maximum showed that where the C-9 hydrogen and the two carbon bridge bearing the carbonyl group are in the *cis* relationship, the absorption is at longer wavelength than where the *trans* relationship exists. The difference is small but significant in that it represents the only method of differentiating such C_9 stereoisomerism. On this basis, the C_9-hydrogen in both XXIII and XXVI is β-oriented and these become XXVIII and XXVII respectively.

Thus, consideration of the dichroism data alone shows that the gibberellic acid series (XXIII, XXVI) is related to epigibberic acid (XXIV) with respect to C-9 stereochemistry whilst the enantiomeric relationship of XXV and XXVI reveals that the reflection of centres 8, 9 and 13 is also mirrored in the C.D. curves. So it becomes evident that the O.R.D. data is not only ambiguous but even leads to the incorrect choice of C-9 configuration (i.e. apparent identity with XXV) in this case. One possible explanation for the invalidity of O.R.D. comparisons in this instance is simply that the rotatory contributions from C_6 and C_9 in XXIV and XXV are twofold, there being an optically active transition (alkyl → ring; hyperconjugative) of the asymmetric benzilic carbon atoms at 265–270 mμ (ϵ 300) superimposed on the R.D. curve of XXIV and XXV but absent in XXIII and XXVI. Such effects are not observed in the corresponding C.D. curves of these ketones as the bands do not overlap and only the optically active $>C{=}O$ $n \rightarrow \pi^*$ transition was measured in our studies. It has been frequently observed that proper separation of different chromphoric contributions is often difficult in O.R.D. studies.[7b]

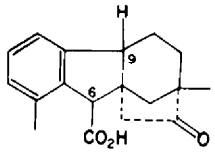
Since this finding represents the first allocation of stereochemistry by the C.D. method and also conflicts with previous assignments we sought independent proof of the validity of these conclusions. It was found that the crystalline bromide XXIII which could be formed by the reaction of pyridine perbromide on a solution of methyl gibberellate (a transformation unaffecting the C_9 stereochemistry) was eminently suitable for crystallographic studies. Full details of the crystallographic analysis will



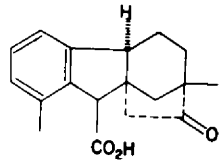
XXII



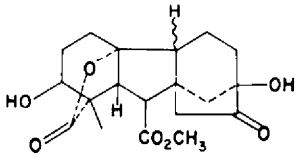
XXIII



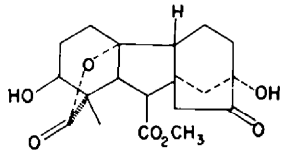
XXIV



XXV



XXVI



XXVII

be reported elsewhere,[33] the structure and stereochemistry XXVIII following at once for this bromide. The inversion of the C_2 bridge, an inevitable result of reaction of the ester of VI with bromonium ion was preferred to the preparation of other derivatives which bore the possibility of C_9 inversion. The formation of XXVIII is analogous to the acid catalysed allogibberic → gibberic acid change.[13] From this result, it is also apparent that the gibberellic → gibberellenic → allogibberic sequence involves not only *exchange* of C_9-H[13] but also *inversion* at this centre. The extreme facility of this rearrangement is now nicely rationalized for the first time in terms of a *trans*-stereochemistry of lactone opening coupled with α-configuration of the lactone group. The latter configuration was thus confirmed and the absolute configuration is also shown to be XVI since the O.R.D. data for ring A ketone (V) leaves no doubt of the antipodal relation of ring A to the steroid series.

Subsequent to the preliminary announcement[28] of the first correct allocation of stereochemistry to gibberellic acid, the Imperial Chemical Industries group published a paper on the stereochemistry of rings BCD of gibberellic acid[34] in which "evidence now presented and in part briefly reported before" shows that rings B/C/D of gibberellic acid have the same absolute configuration as they have in *epi*allogibberic acid. However, the previous brief report favoured the allogibberic stereochemistry as

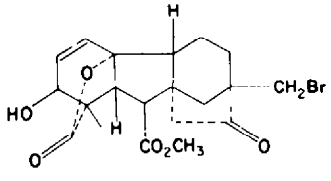
[33] G. A. Sim, F. McCapra, A. I. Scott and D. W. Young, *Acta Cryst.* in preparation.
[34] P. M. Bourn, J. F. Grove, T. P. C. Mulholland, B. K. Tidd and W. Klyne, *J. Chem. Soc.* 154 (1963).

in IV and included both O.R.D. and NMR arguments to this effect. In fact configuration XVI is not written as a possibility amongst those considered in this preliminary communication. The reasons for *now* preferring XVI to VII in fact seem to rest almost entirely on the same information as summarized in the earlier note.[35]

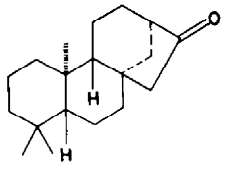
Kaurene

The biological conversion of (—)[17-^{14}C]kaurene into gibberellic acid[21] now places the inferred diterpenoid origin of the latter beyond doubt and confirms in a most satisfactory way the *trans-anti*-nature of the diterpenoid cyclization leading to the gibberellic series.

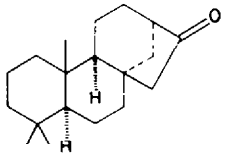
It was recently observed[21] that O.R.D. comparisons among ketones from gibberellic and allogibberic acids and those of the kaurene series did not provide consistently meaningful correlation. However, when we compare (Table 1) the C.D. curves of the norketones from kaurene and phyllocladene (XXIX and XXX) it is quite clear that with the full absolute stereochemistry of gibberellic acid in hand, we can confirm the $C_9\beta$-H configuration in both kaurene and phyllocladene. Thus norkaurene ketone (XXIX) exhibits the bathochromic shift in its C.D. curve compared with the *trans* compound (XXX) leading to allocation of *cis*-relationship of the C_2 bridge and the C_9-H. The total synthesis of DL-kaurene[36] confirms these conclusions fully. This "rule of shift" as summarized in Table 1 can now be extended to the solution of the stereochemistry of some of the remaining "C_9-exceptions".



XXVIII



XXIX



XXX

Cafestol

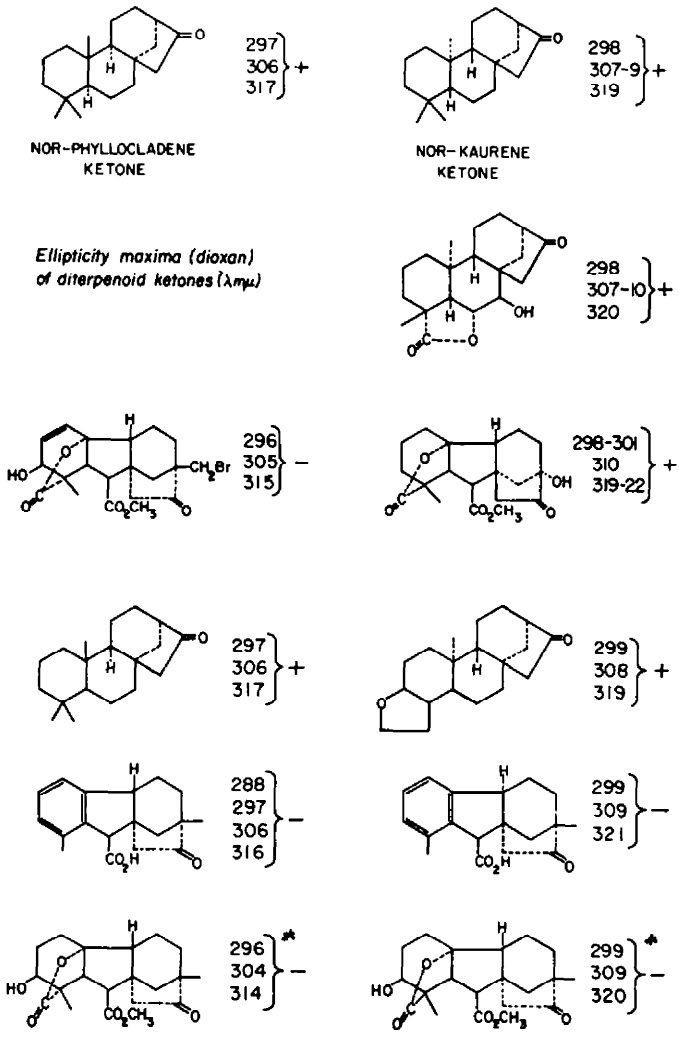
The earlier researches of Haworth[37] on cafestol, the diterpenoid constituent of coffee

[35] Careful examination of the argument embodied in Ref. 34 does not, in our view, allow unequivocal assignment of configuration XVI without taking into account the circular dichroism and X-ray data. This fact is scarcely acknowledged (footnote 16, Ref. 34) yet would appear to be the only criterion used by these authors for the reversal of the previously assigned stereochemistry.

[36] R. A. Bell, R. E. Ireland and R. A. Partyka, *J. Org. Chem.* **27**, 3741 (1962).

[37] R. D. Haworth and R. A. W. Johnstone, *J. Chem. Soc.* 1492 (1951), and earlier papers.

TABLE 1



were extended in a series of papers by Djerassi *et al.*[38,39] in which a clear definition of all the structural features of the compound was reached. In spite of carefully devised experiments it was not found possible to relate the cafestol skeleton to another diterpenoid of known stereochemistry although the following assignments could be made without ambiguity.

The demonstration of stereochemistry of ring A antipodal to that of the steroids allowed unequivocal assignment at C_5 and C_{10}. Furthermore a study of derived keto acids (as XXXI) narrowed the possibility of the ring B/C/D stereochemistry to XXXI, XXXII and XXXIII. However a final decision in favour of the C_9-α hydrogen (*syn* backbone) was made after comparison of the O.R.D. curves of epoxynorcafestanone (XXXIV) with that of phyllocladene norketone (XXXV). The coincidence of

[38] R. A. Finnegan and C. Djerassi, *J. Amer. Chem. Soc.* **82**, 4342 (1960).
[39] C. Djerassi, M. Cais and L. A. Mitscher, *J. Amer. Chem. Soc.* **81**, 2386 (1959).

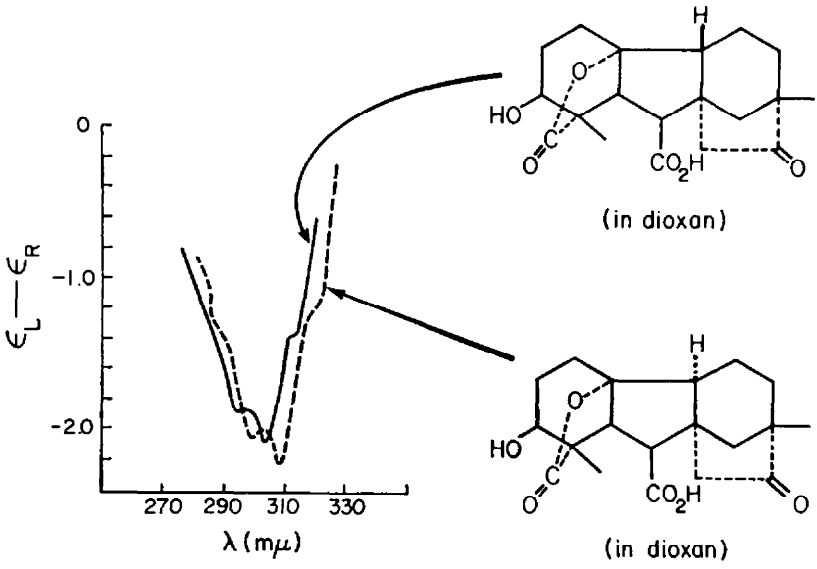
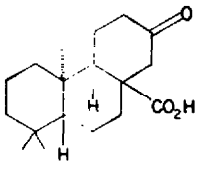
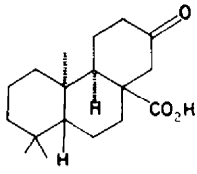


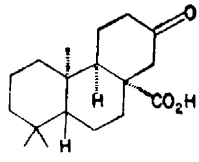
FIG. 4



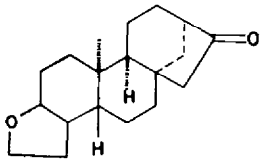
XXXI



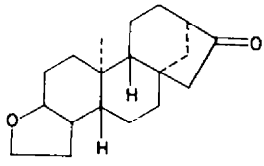
XXXII



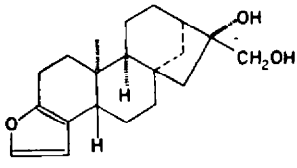
XXXIII



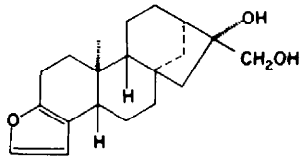
XXXIV



XXXV



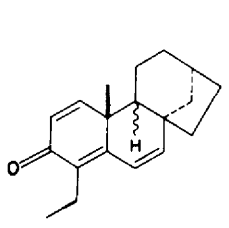
XXXVI



XXXVII

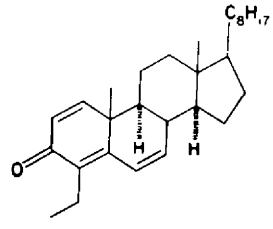
these curves was taken to provide evidence overwhelmingly in favour of stereochemistry XXXVI for cafestol.[40*] Certain features of cafestol chemistry seemed further to militate against the 'natural' *anti*-backbone formulation (XXXVII). In particular it was shown that the trienones (XXXVIII and XXXIX) displayed small but real differences in their UV maxima as shown. One possible explanation of this effect resided in a difference of C_9-stereochemistry, since a *syn*-backbone could conceivably move the principal electron transfer bands of the unsaturated ketone from their expected positions.

It was noted also that the C_4-carbomethoxy group in XL was relatively resistant to hydrolysis, a fact which could be explained on a boat B-ring conformation (XLI). On opening ring A this would lead to the favoured chair conformation with a resultant axial carboxyl group derived from C_4.



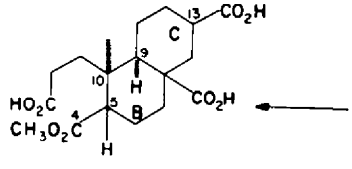
XXXVIII

λ 232, 256, 302·5 mμ

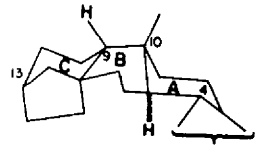


XXXIX

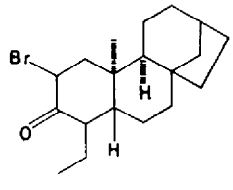
λ 227, 259 i, 305mμ



XL



XLI



XLII

Finally, the *relative* difficulty in removing the elements of hydrogen bromide from the 2β (equatorial) bromoketone (XLII) was reminiscent of friedelin chemistry[41]

* It should be noted that Djerassi *et al.*[39] had already drawn attention to this essential violation of the biogenetic isoprene rule, but as pointed out in Ref. 39 footnote 64, there were *apparent* exceptions to provide precedent at that time.

[40] R. A. Finnegan, *J. Org. Chem.* **26**, 3057 (1961) later defined the C_{16} stereochemistry as shown.

[41] E. J. Corey and J. J. Ursprung, *J. Amer. Chem. Soc.* **78**, 5041 (1950).

where the 9β-methyl group causes resistance to dehydrobromination. This again was considered supplementary evidence in favour of the ring B boat structure (XLI).

With the correlations available from the gibberellic acid and kaurene series, we felt that a crucial and immediate test of the "rule of shift" and also the ubiquitous presence of $C_{9,10}$ *anti* stereochemistry in the diterpenes lay in the direct comparison of the dichroism data for epoxynorcafestanone (XXXIV) and phyllocladene norketone (XXX) which were related in exactly the same way as XXIV and XXV.

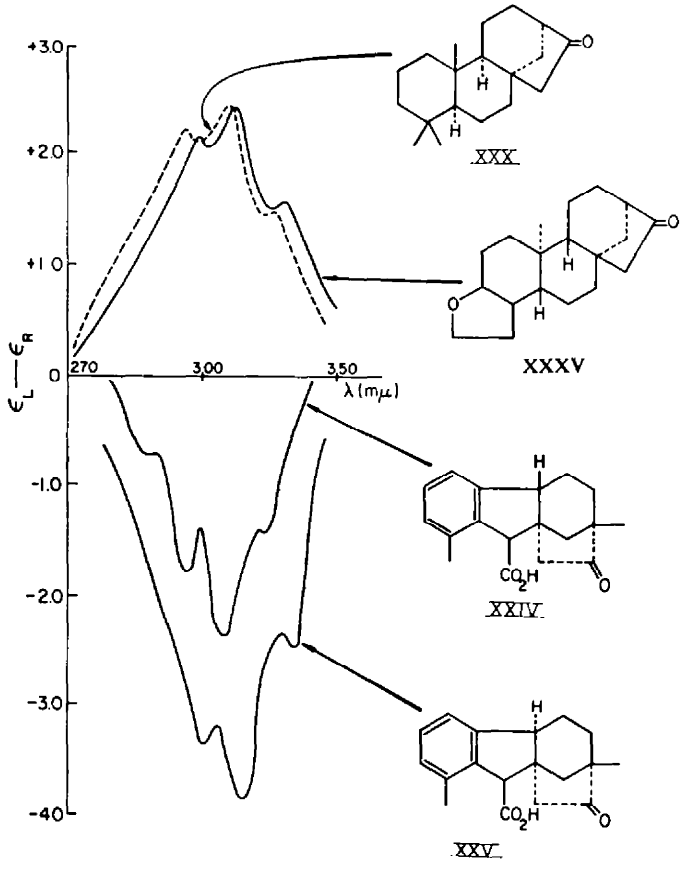


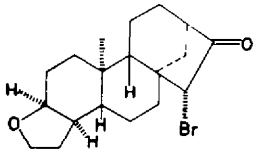
FIG. 5

When such a comparison was made (Fig. 5) it was at once evident that epoxynorcafestanone is XXXV and that cafestol must be represented as XXXVII i.e. with the same backbone as that of kaurene and gibberellic acid.*

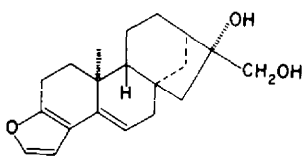
This result was again confirmed and the absolute configuration of cafestol established by X-ray crystallographic analysis of the bromoketone (XLIII). The details of the intensity measurements and calculations used in this study are being published

* For reasons of clarity we have not reproduced the appropriate UV spectrum for each of these cases. The UV curve often shows a *similar* band progression to the C.D. curve but is frequently shifted to the blue side of the latter. The rule of shift could not be applied in any systematic way to the corresponding UV data.

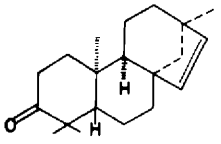
elsewhere[42] but lead unambiguously to stereochemistry XLIII for the bromoketone and XXXVII for cafestol. Hence kahweol may be written as XLIV.[39,43]



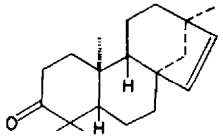
XLIII



XLIV



XLV



XLVI

Stachenone and several related compounds have been isolated from Tambooti wood. Structural studies have been followed by a proposal[44] XLV for the preferred stereochemistry. The *syn*-backbone (XLV) was favoured over the *trans* arrangement because of evidence for steric hindrance at C_1, a condition satisfied by the quasi-axial nature of the $C_{9,11}$-bond in XLV but not in XLVI.[44] However, the argument is not compelling and we predict that stachenone will have the *anti*-backbone as in XLVI.[45]

The tricyclic diterpenoids

Rosenonolactone and its derivatives. The absolute configuration (XLVII) for rosenonolactone, a metabolite of *Trichothecium roseum* link was proposed by Whalley *et al.*[46] Although XLVII embodies a *syn*-backbone (boat ring B) its existence, we feel, should not have been held in regard as exceptional.* As already pointed out[27] and emphasized in the above argument, the all-*trans* precursor (XLVIII) can suffer methyl migration and ring closure to give eventually a *syn*-backbone from the primary *anti*-cyclized precursor. These important implications for the eventual solution of diterpenoid biogenesis made it desirable to determine the complete absolute stereochemistry of the rosane series. Further, since no allocation of C_{13} stereochemistry had been made for rosenonolactone, and because the chemical proof for the location of the secondary hydroxyl group in rosololactone (XLIX) was somewhat lacking in rigour,[47,48] we studied the stereochemistry of the latter. First, the 6 position of the hydroxyl group was established by conversion of dihydrorosololactone to the same diosphenol (L) as that obtained from rosenonolactone *via* ozonization of the

* See for example, Refs. 4 and 39 for a discussion of this point.

[42] G. A. Sim, G. Ferguson, D. W. Young, A. I. Scott and F. McCapra, In preparation.

[43] For a recent discussion of kahweol chemistry see H. P. Kaufman and A. K. Sen Gupta, *Chem. Ber.* **96**, 2489 (1963).

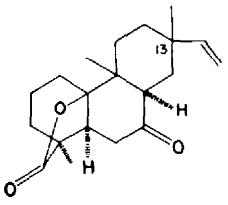
[44] W. H. Boarschers, D. H. Horn and LeRoy F. Johnson, *J. Chem. Soc.* 4046 (1962).

[45] Circular dichroism experiments bearing on this point are in hand in collaboration with Dr. D. H. Horn.

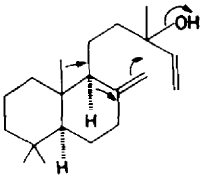
[46] W. B. Whalley, B. Green, D. Arigoni, J. Britt and C. Djerassi, *J. Amer. Chem. Soc.* **81**, 5520 (1959).

[47] A. Harris, A. Robertson and W. B. Whalley, *J. Chem. Soc.* 1799 (1958).

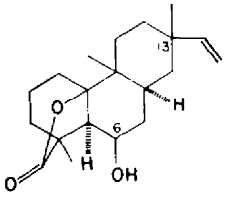
[48] A. Harris, A. Robertson and W. B. Whalley, *J. Chem. Soc.* 1807 (1958).



XLVII



XLVIII



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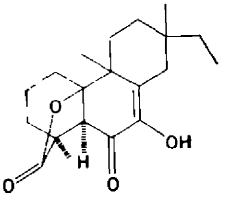
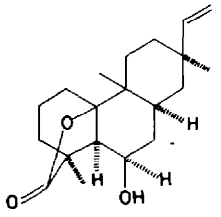
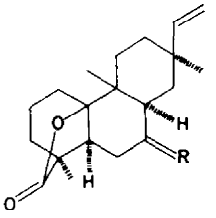


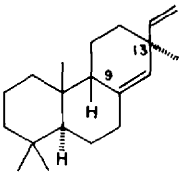
L



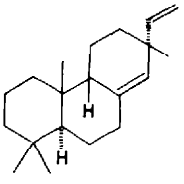
LI



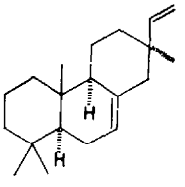
LII; R=O
LIII; R=H_2



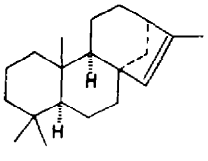
LIV



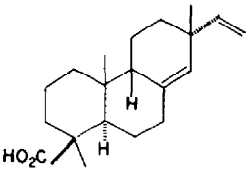
LV



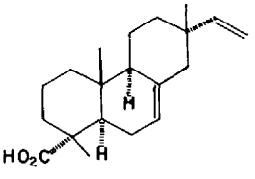
LVI



LVII



LVIII



LIX

appropriate furfurylidene derivative in each case. By both chemical and X-ray methods it was shown[1] that rosololactone had the absolute stereochemistry LI and hence rosenonolactone is LII and the 7-deoxy metabolite[46] LIII.

Rimuene and isopimaric acid. At the outset of our investigation (November, 1961) structure LIV had been proposed[49] for the diterpenoid hydrocarbon rimuene. However, towards the culmination of our investigations in the tetracyclic series, the total stereospecific synthesis[50] of *dl*-LIV and -LV corresponding to the proposals for rimuene, removed the latter exception by default when it was found that neither was identical with rimuene. Of the several remaining structural possibilities for this hydrocarbon we feel that LVI cannot be entirely neglected since at least one section of the published evidence for the structure will have to be called into question. For example it is difficult to envisage the genesis of isophyllocladene (LVII) from any but a close relative of LVI.

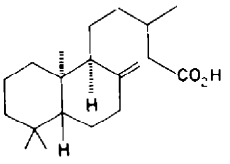
The removal of the principal enigma of diterpenoid stereochemistry was virtually completed by a recent announcement of the revision of isopimaric acid stereochemistry from LVIII to LIX in two independent studies.[51,52] There only remains for discussion a member of the bicyclic series.

Eperuic acid

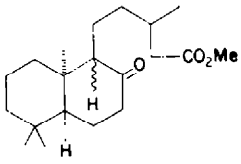
In a preliminary communication,[29] we proposed the constancy of $C_{9,10}$-*anti* stereochemistry throughout the diterpenoids and implied that eperuic acid would not long retain its exceptional stereochemistry[53] (LX). Indeed slight distortion from the complete mirror image relationship of the R.D. curves of methyl eperuate norketone (LXI) and that of the corresponding ketone (LXII) from labdanolic acid, which formed the basis for allocation of structure LX, does not appear in the corresponding dichroism curves.[54] Pending allocation of the C_{13} stereochemistry we can be confident that eperuic acid will have absolute stereochemistry LXIII.

Thus, with the present exceptions of rimuene and eperuic acid rigorous proof has been provided for the complete conformity of all diterpenoids to the Biogenetic Isoprene Rule. Indeed, by analogy with labdanolic acid and similar bicyclic diterpenoids we feel it appropriate to extend this analysis to a member of the sesquiterpenoid family. Thus farnesiferol A, has been allocated[55] probable stereochemistry LXIV, in which the side chain is in the axial configuration. We predict that the correct stereochemistry should in fact be LXV.[56] Experiments are in progress to verify this final application, although, as indicated earlier,[3] stereochemical analysis of the lower

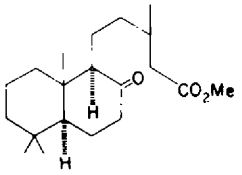
[49] E. Wenkert and P. Beak, *J. Amer. Chem. Soc.* **83**, 998 (1961).
[50] R. E. Ireland, *Tetrahedron Letters* No. 14, 493 (1961); *J. Org. Chem.* **28**, 17 (1963).
[51] W. Antkoviak, J. W. Apsimon and O. E. Edwards, *J. Org. Chem.* **27**, 1930 (1962).
[52] R. E. Ireland and R. Newbould, *J. Org. Chem.* **28**, 23 (1963).
[53] C. Djerassi and R. A. Marshall, *Tetrahedron* **1**, 238 (1957).
[54] Dr. K. H. Overton, private communication. We are indebted to Dr. Overton for discussion concerning the C_{13} stereochemistry of these compounds.
[55] L. Gaglioti, H. Naef, D. Arigoni and O. Jeger, *Helv. Chem. Acta* **41**, 2278 (1958).
[56] In footnote 4 we discussed the case of folding the precursor with a boat ring B, an event of almost certain *intermediacy* in the squalene → lanesterol cyclization. However in the latter case the initial intermediate rapidly undergoes methyl migration, 8:9 double bond formation and, in the case of cholesterol production, eventual establishment of the all chair conformation. We should expect *bicyclic* cases to reach this preferred state even more readily.



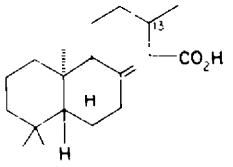
LX



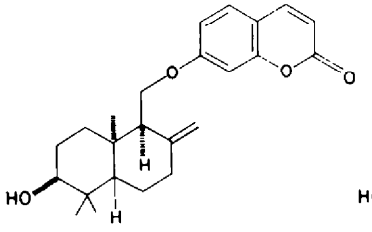
LXI



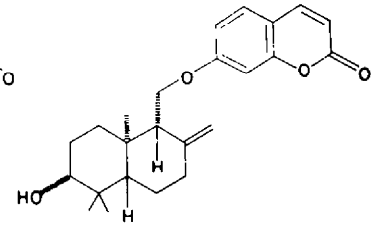
LXII



LXIII



LXIV



LXV

terpenes has been consistently more difficult than similar rationale of triterpene biosynthesis. We feel that the above evidence provides a satisfactory basis for regarding the diterpene family as an integrated unit, enjoying a constancy of stereochemical control in its origin.

EXPERIMENTAL

M.ps are uncorrected (Kofler). IR spectra were recorded on a Unicam S.P. 100 Spectrophotometer by Mrs. F. Lawrie. Circular dichroism measurements were made in dioxan solution (unless shown otherwise) with a Unicam S.P. 500 Spectrophotometer as described previously[57] only using specially constructed quartz $\lambda/4$ plates (Hilger and Watts) for the appropriate spectral region. Excellent results were also obtained at 280–320 mμ using Styrofoil (polystyrene) films in conjunction with a Glazebrook prism transparent to 250 mμ. A selected I.P. 28 photomultiplier (1050–1150 V) was used as a detector and the signal fed to a PYE Scalamp Galvanometer for successive readings of ϵ_l and ϵ_r. Dichroism was determined for 1% solutions in (a) conventional 1 cm quartz cuvettes, (b) in a specially constructed microcell (capacity 0·3 ml) of 1 cm path with quartz windows, or (c) in a Teflon insert (0·3 ml) used in the 1 cm cuvette. Intensity measurements on this instrument are accurate to within 10% of the data for suitable reference samples run on a similar instrument at Glasgow University, and with the Jouan-Russell Dichrograph. We thank Prof. G. Ourisson for his help in providing such reference spectra. The dichroism results in this paper are expressed directly as $\epsilon_l - \epsilon_r$. Subsequent circular dichroism data from this laboratory will be reported as both $\epsilon_l - \epsilon_r$ and $[\theta]$ in keeping with preferred current usage.*

* We thank Professor C. Djerassi for discussion on aspects of reporting C.D. and O.R.D. data. See *Proc. Chem. Soc.* 299 (1963).

[57] S. T. R. S. Mitchell, *J. Sci. Instr.* **34**, 89 (1957).

Methyl bromogibberellate (XXVIII). Methyl gibberellate (190 mg) and pyridine perbromide (135 mg) were dissolved in dioxan (3 cc) and after 30 min sufficient ether was added to precipitate the bromide (XLI) as white prisms m.p. 215–217° from ethanol. (Found: C, 54·7; H, 5·65. $C_{30}H_{23}O_6Br$ requires: C, 54·6; H, 5·25%). IR spectrum ($CHCl_3$) ν 3490 (OH), 1758 (γ-lactone) 1745 (5-ring ketone) and 1730 (ester) cm^{-1}.

Epigibberic acid (XXIV). The following modification of a previous method[58] was used. Gibberic acid (1 g) and palladized charcoal (10%; 1 g) were heated at 210° for 90 min in a stream of N_2. The product was cooled, extracted with ether and then extracted into $NaHCO_3$ aq. Recovery by acidification and ether extraction gave the epi-acid (XXXIX) as prisms m.p. 253–255°, $[\alpha]_D$ +131° (*c*, 1·0 in $CHCl_3$) [lit. m.p. 252–253°, $[\alpha]_D$ +131°].

Bromoepoxynorcafestanone (XLIII). Prepared by the method of Djerassi,[39] this had m.p. 197–198° (lit. m.p. 183–185°). $[\alpha]_D$ −33°. (*c*, 0·96 in $CHCl_3$).

Acknowledgements—This work was made possible by generous gifts of the following samples: epoxynorcafestanone and its bromo-derivative (Prof. C. Djerassi); gibberellic acid (Dr. B. A. Hems), phyllocladene norketone (Dr. R. Hodges), kaurene, kaurenolide and dihydrogibberellic acid derivatives (Dr. R. H. B. Galt). We thank the Carnegie Trust for the Universities of Scotland, D.S.I.R. and N.R.C. for studentships (to D. W. Y., G. F. and F. C. respectively). We also wish to acknowledge the help of Dr. S. Mitchell and Miss J. C. Moore in the design and operation of the dichroism apparatus and Dr. K. H. Overton for many helpful discussions.

[58] B. F. Cross, *J. Chem. Soc.* 4670 (1954).