SESQUITERPENES - BIOSYNTHETIC STUDIES WITH ^{13}C AND ^{2}H MAGNETIC RESONANCE - A SYNTHETIC APPROACH VIA HOMOENOLIZATION

J. B. Stothers

Department of Chemistry, University of Western Ontario, London, Ontario, N6A 5B7, Canada

Abstract - Studies of the sesquiterpenes isolated from species of the Solanaceae under the stress of fungal infection are reviewed with emphasis on the biosynthetic pathways leading to their formation. These pathways have been examined primarily through incorporation experiments using doubly-labelled sodium acetate-^{13}C$_2$ with ^{13}Cmr characterization of the stress metabolites. Complementary evidence obtained from mevalonolactone-4,4-d_2 incorporation and ^{2}Hmr is also described. The use of ^{2}Hmr to monitor deuterium exchange in a variety of bicyclic ketones under homoenolization conditions is discussed. Certain of these homoenolization experiments lead to the development of a new synthesis for hirsutene and congeners which is outlined.

STRESS METABOLITES FROM THE SOLANACEAE (with A. Stoessl, Research Institute, Agriculture Canada, London, Canada)

The metabolism of plant cells can be profoundly altered by stress such that the generation of substances not normally found in substantial concentrations, if at all, is induced in the affected tissue. Stresses include injury and infection by bacteria, viruses or fungi and the stress compounds produced may be primary or secondary metabolites (1). Many stress metabolites of the latter type, often with no known immediate precursors in the plant, appear to arise by *de novo* synthesis from the usual elementary building blocks, acetate and/or mevalonate. These materials have been attracting increasing attention recently because (a) several have been implicated in the toxicity of diseased food plants, (b) their potential relevance to mechanisms of plant disease and (c) their possible function, in some cases, as natural defensive agents. Fungal infection in a number of species of the Solanaceae has been found to lead to the production of a family of sesquiterpenes, now known to include some thirty examples. The isolation, characterization and structural determination of many of these stress metabolites, together with studies directed toward elucidation of the biosynthetic pathways leading to these substances have been actively pursued in these laboratories for several years (2) and some results of this work will be surveyed.

Stress metabolites induced by fungal interactions with potatoes, sweet peppers, eggplant and jimson weed have been examined; other groups have investigated interactions with potatoes, tomatoes and tobacco. The most extensive studies, however, have been performed with potatoes from which twenty members of the family have been identified; these include six different skeletal types while one acyclic, one monocyclic and ten polycyclic skeletons occur within the family. The single known monocyclic compound and some examples having the principal bicyclic skeletons are shown in Fig. 1. In general, these compounds are not induced singly nor are all those known for a given species produced in detectable amounts in a given situation. The relative proportions in which these are induced appears to be a function of incubation time, the fungal species used as inducer and other, mostly undetermined, factors.

The close structural relationships between members of this series must reflect closely related biosynthetic pathways for their genesis and all can be, at least formally, derived from eudesmane precursors, as outlined for a few examples in Fig. 2. Sesquiterpenes arise from farnesylpyrophosphate which itself is generated from three isopentenylpyrophosphate units (see Fig. 3) each of which is produced by decarboxylation of mevalonate; thus, of the three acetate moieties utilized for mevalonate, one suffers cleavage. If acetate, doubly-labelled with ^{13}C, is used as a tracer the labelling patterns in Figs. 2 and 3 result. Pairs of carbons arising from intact acetate units are indicated by heavy bonds while heavy circles denote carbons which have lost their original labelled neighbor. The presence of more than three of the latter signifies cleavage and/or rearrangement at a later stage in the sequence,
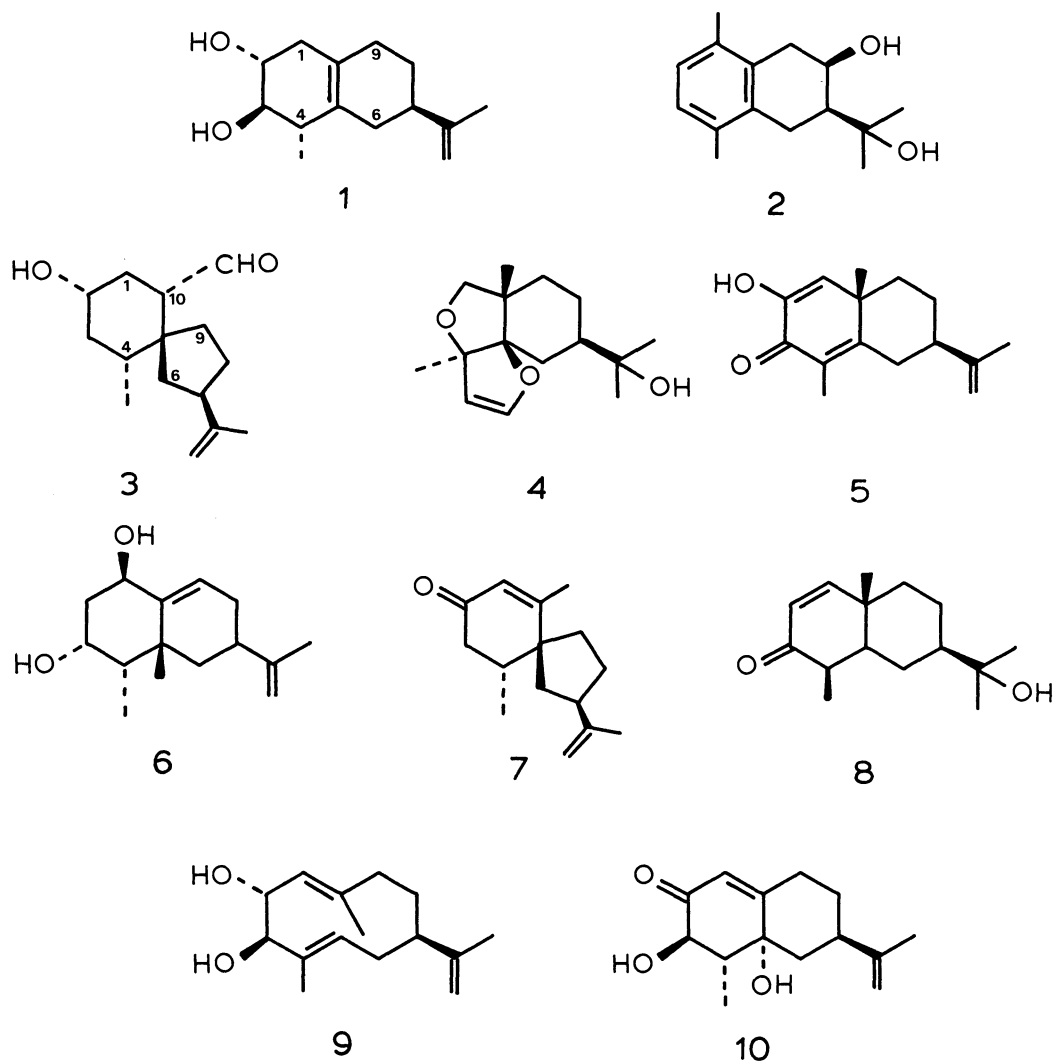
Fig. 1. Specific stress metabolites from the Solanaceae illustrating the major carbon skeletons encountered.
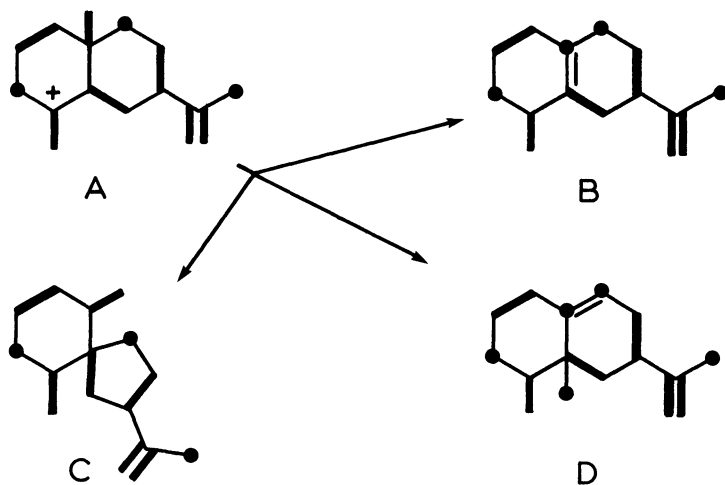

Fig. 2. Biosynthetic relationships of sesquiterpenes from the Solanaceae.

e.g., B and D in Fig. 2, although subsequent skeletal rearrangement may not involve cleavage of an acetate unit, e.g. C (Fig. 2). In any event these labelling patterns are readily identified by examination of the stress metabolites produced by incorporation experiments
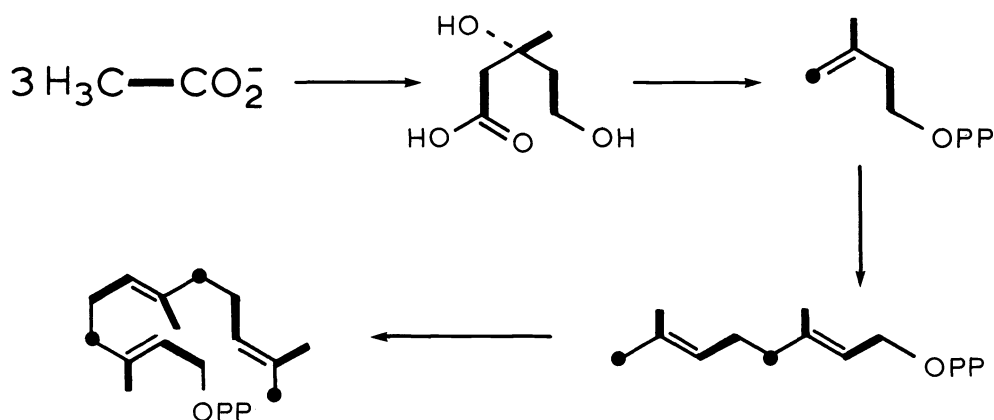

Fig. 3. Biosynthesis of farnesylpyrophosphate.

utilizing acetate-$^{13}C_2$. The ^{13}C magnetic resonance spectra of the labelled products contain distinctive patterns for the two types of carbon. The pairs of carbon atoms from intact acetate units give rise to doublets for each centre, which flank the natural abundance signal for each, while the signal for a carbon lacking its original neighbor coincides with, and therefore enhances, the natural abundance signal. The spectrum of rishitin-$^{13}C_x$ (1), isolated from such an incorporation experiment (3), is illustrative (Fig. 4). Four signals clearly
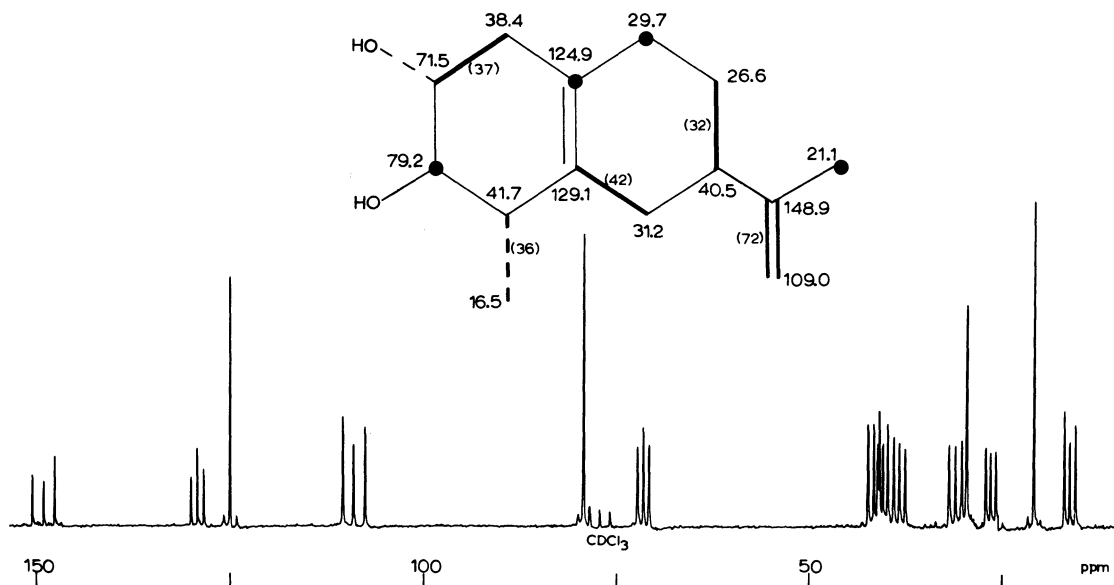

Fig. 4. ^{13}Cmr spectrum of 1 biosynthesized from 1,2-^{13}C-acetate.

lack the prominent flanking doublets exhibited by each of the other ten patterns. It may be noted that the separation of the components of each doublet represents the ^{13}C-^{13}C spin coupling constant between the coupled carbons, thus these separations can be matched to identify the individual pairs of carbons for unequivocal assignments. The individual shieldings and one bond coupling constants (in parentheses) are noted in Fig. 4. The intensity of the doublet relative to that of the central signal provides a reliable quantitative measure of the level of enrichment (4) which for 1 (Fig. 4) was found to be 4%.

Before details of the biosynthetic routes to these bicyclic stress compounds were
investigated through incorporation experiments with labelled precursors, a number of
different, although essentially equivalent, speculative schemes were considered; the first of
which proposed links between five of the compounds (5). The isolation of germacrenediol 9
from *Datura stramonium* (6) suggested that a germacrene derivative may function as a direct
precursor for the majority of the members of the series. The flexible cyclodecadiene
skeleton can adopt different conformations, consideration of which led to the proposal of
Scheme 1 accounting for the formation 1, 3 (R = H or OH), 7 and 8.

Aubergenone (8), a stress metabolite isolated from eggplant together with lubimin (3) and
three acyclic sesquiterpenes (7), was originally viewed as the 4α-epimer, contrary to
Scheme 1, since it was assumed that the more stable epimer was the more probable product.
Our scheme indicated that the less stable 4β-methyl epimer would result from the 3 → 4
hydride shift and this was subsequently established by synthesis. Two groups (8) have
described syntheses of 4-*epi*-aubergenone which was found to differ from natural 8. It was
found that treatment of 8 with base gave quantitative conversion to the synthetic material
whose structure was unequivocally established by its synthesis from carrisone (8a) (Fig. 5).
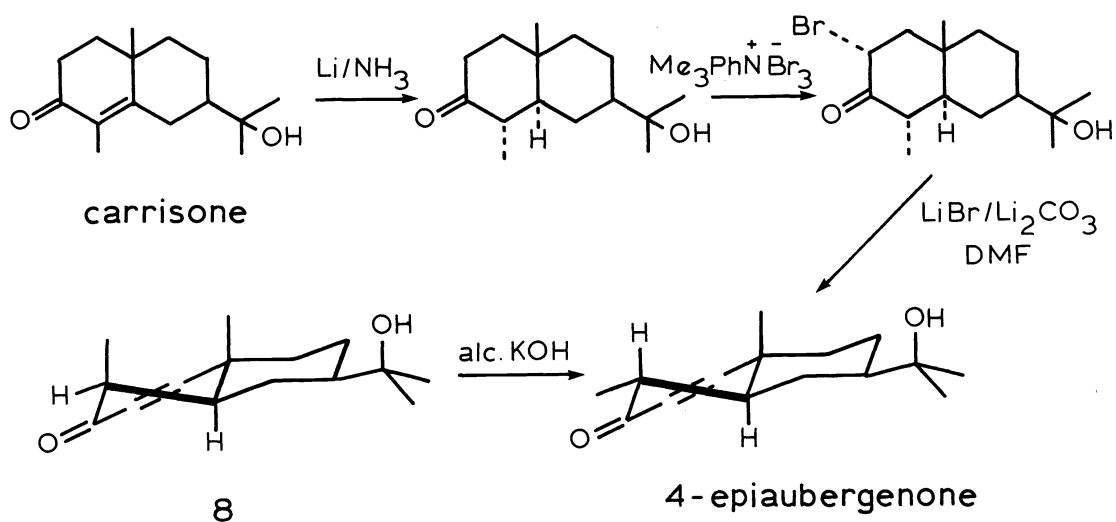

Fig. 5. Structure proof of 8 by conversion to 4-*epi*-8 synthesized from
carrisone (8a).

Rishitin (1), lubimin (3) and solavetivone (7) are stress metabolites from potato and
straightforward transformations of 3 and 7 account readily for nine additional members of the
series (see below). Feeding experiments, with doubly-labelled acetate-$^{13}C_2$, gave 3 and 7
containing six intact acetate units since prominent doublets for 12 of the 15 ^{13}Cmr signals
were apparent in the ^{13}C spectra. This finding limits the possible modes of formation of the
spirovetivane skeleton from a farnesyl chain which is almost assuredly the prime C_{15}
precursor.

Rishitin (1) and rishitinol (2) were the first members of the series (9), isolated in 1968,
and subsequently the formation of 1 has been found to be a general response to inoculation
with a variety of fungi in the several potato cultivars tested. Lubimin (3) was
characterized as the third example (10) in 1971, but its structure was not established until
1974 (5,11). This later work also revealed the formation of 3 in eggplant and jimson weed
upon fungal invasion (5). In addition, its 3-hydroxy derivative 11, was isolated in the
latter experiments as well as from potatoes (11). About the same time another group (12)
reported the isolation and identification of solavetivone (7) and the closely-related anhydro-
β-rotunol (12). With increasing activity in this area, several more spirovetivane derivatives
were found from potato-fungi interactions and plausible relationships of 3 and 7 with the

SCHEME 1
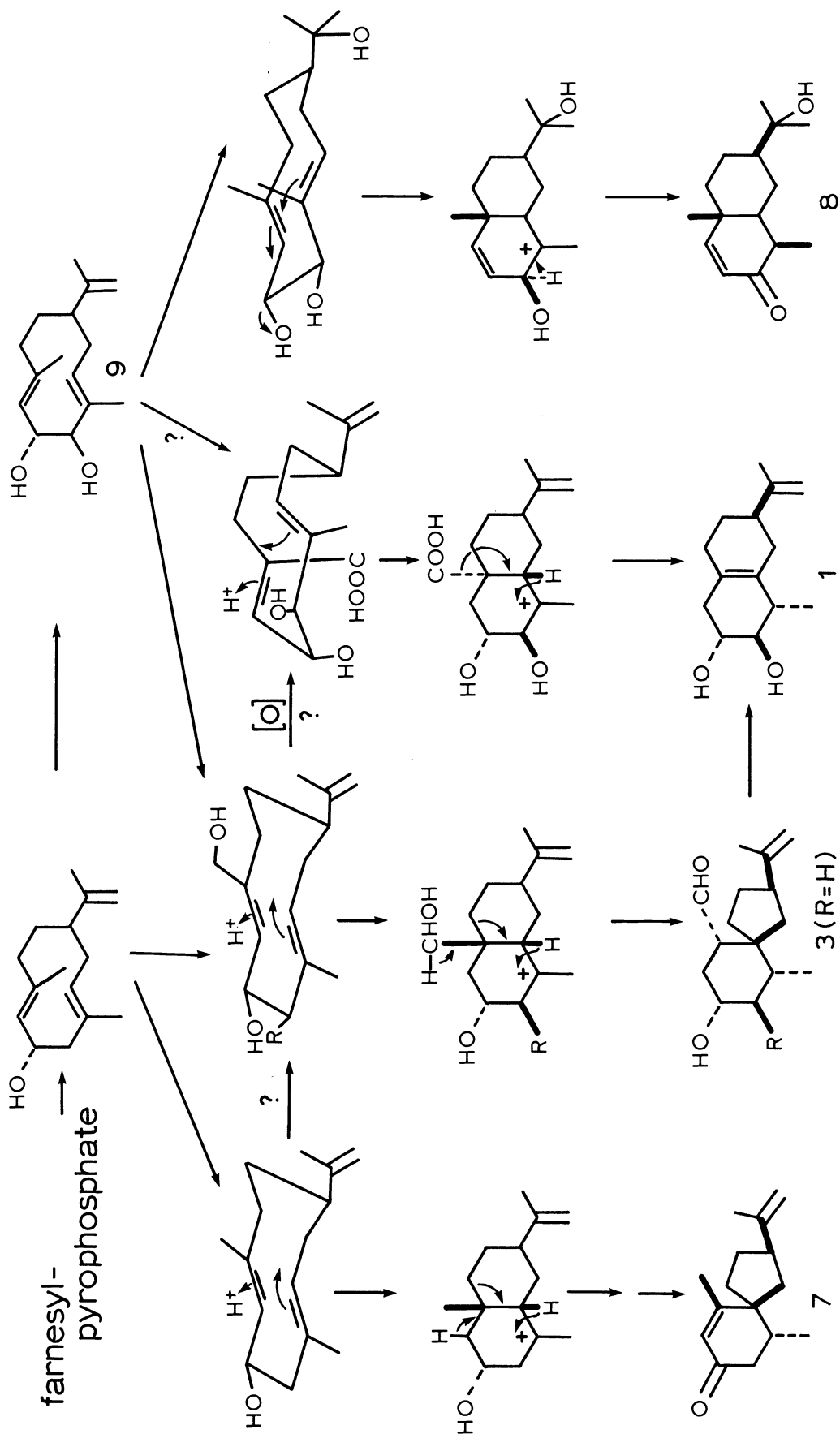
other known congeners in the series are outlined in Fig. 6. Reduction of 3 to 15-dihydro-
lubimin (13), initially isolated from potatoes by Masamune's group (13), has been shown to
occur in pure cultures of fungi supplemented with 3 (14); thus, 13 is mainly a product of
fungal reduction. The 10-epimer of 3, 10-epilubimin (14), was first described by Masamune's
group as well (15), and subsequent isolation of its reduction product 15 was not surprising.
While 3 and 14 could be in equilibrium in diseased plants, conclusive evidence has not been
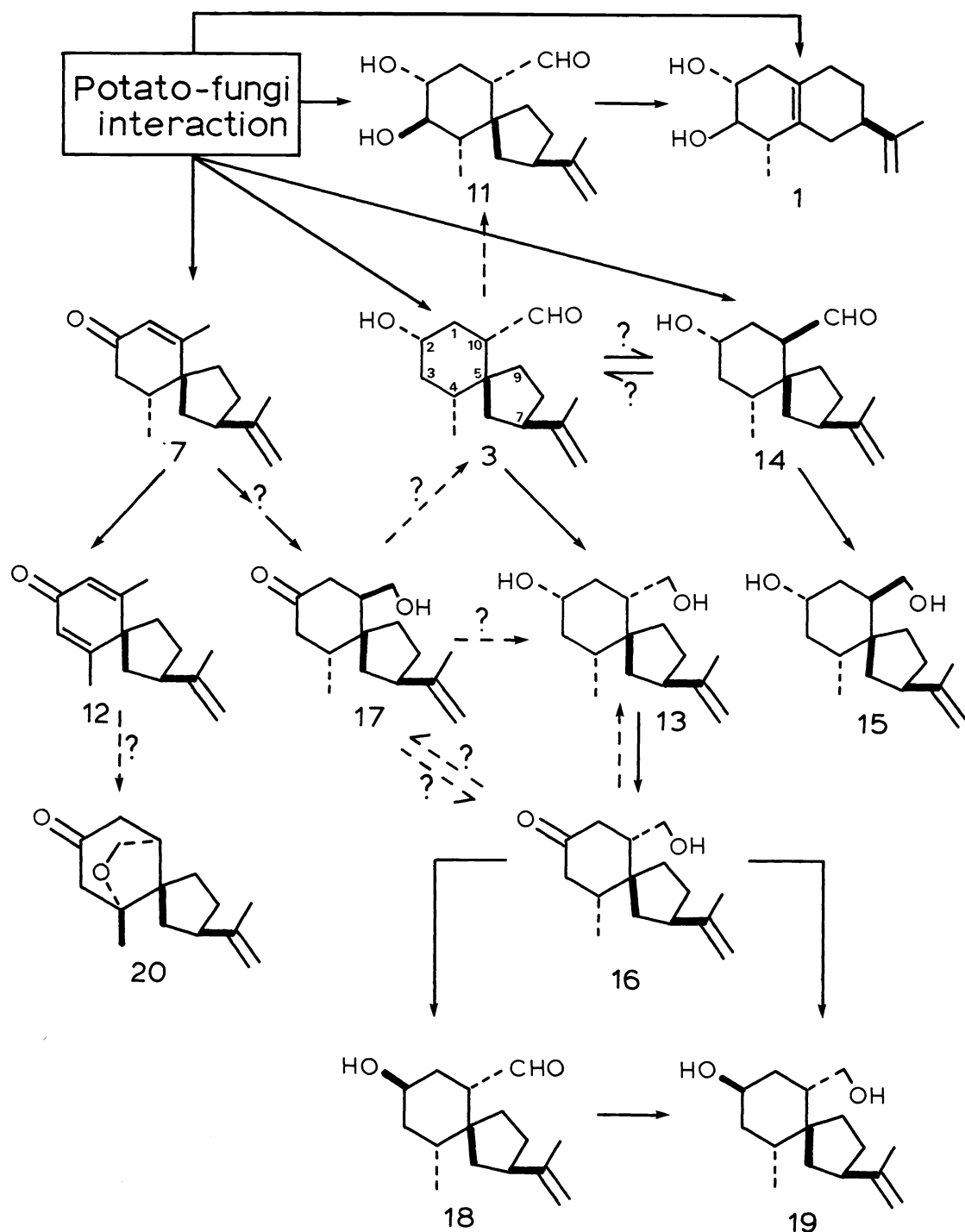provided.

Fig. 6. Known and postulated interrelations of several sesquiterpenes from
potato-fungi interactions.

Another member of the series, isolubimin (16), was initially reported to arise from metabolism of 7 on potato slices (16a) in the absence of fungi. In these experiments, lubimin and rishitin were also isolated and these authors suggested that the sequence 7 → 16 (17) → 13 → 3 → 11 → 1 was followed (16); however, the requisite studies with labelled 7 were not carried out and the sequence remains questionable. It may be noted, however, that, as postulated for this sequence, radioactive 11 indeed affords radioactive 1 on potato slices infected with fungi (17). On the other hand we have very recently (18) shown that ^{13}C-enriched dihydrolubimin (13) is transformed into labelled isolubimin (16) but not into lubimin (3). A further complication is that, after isolation of authentic 16 (3), Masamune and coworkers (19) showed that the material originally described as 16 (16a) is in fact 17. A third epimer of 3, 2-epilubimin (18), has recently been characterized together with the corresponding 2-epi-15-dihydrolubimin (19) (20). Another member of this series from the potato experiments has the tricyclic structure 20 (21) and conceivably arises from 12 but no supportive evidence is available.

In the earlier work on potato-fungi interactions, an example having another skeleton was isolated (22) although structure 4 was not established for a few years (23). This interesting tricyclic system of phytuberin can be envisaged to arise via the sequence shown in Fig. 7. After publication of this proposal (3), a synthesis of 4 was described (24) which in its critical stages mimics the proposed biosynthetic route (see Fig. 8) offering support for the suggested scheme in Fig. 7.
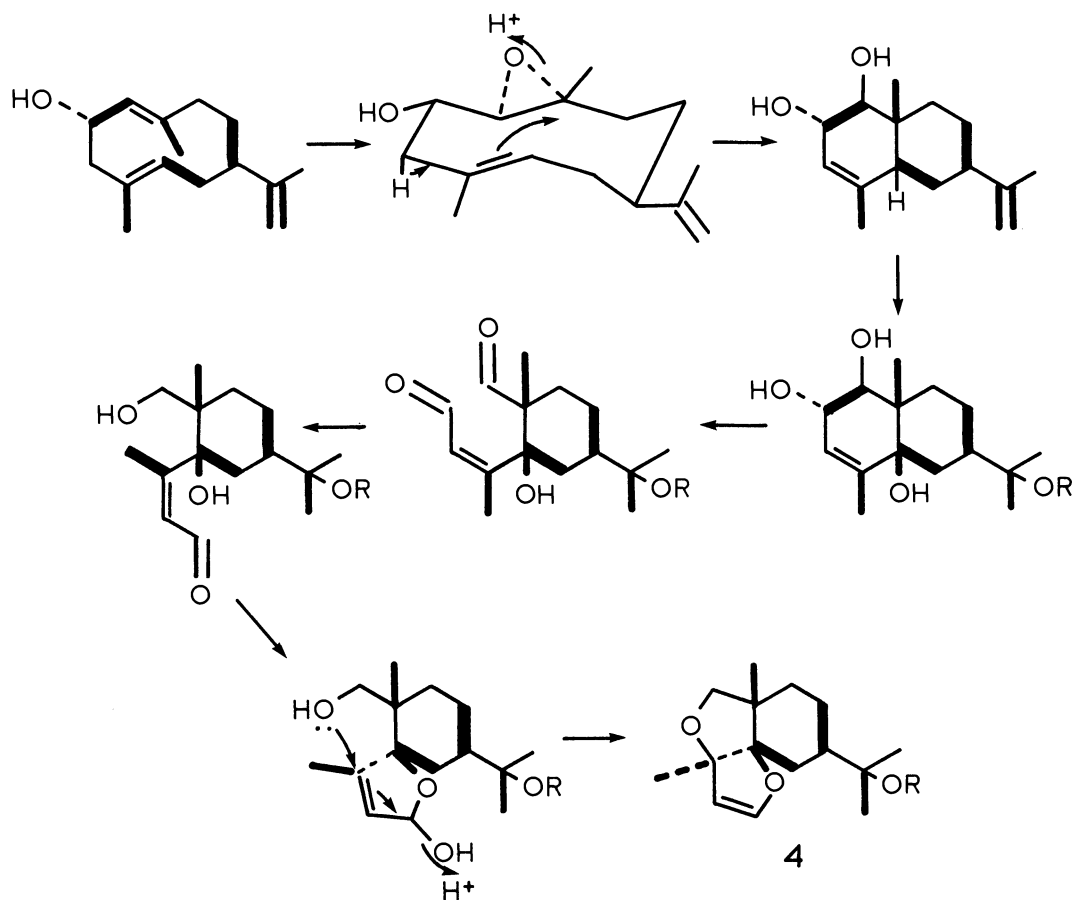

Fig. 7. A proposed biosynthesis of 4 (3).

Since the publication of our proposed biosynthetic sequences for various members of this family of sesquiterpenes, alternative suggestions for a number of these compounds have been put forward (8b, 25). The alternative scheme invokes a germacrene oxide (the first oxide in Fig. 7, lacking the hydroxyl group) as the primary precursor for compounds 1, 2, 4, 6, 8, 10 and 11.
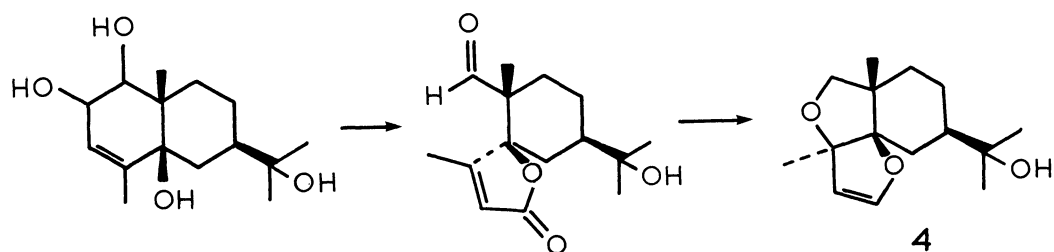
Fig. 8. Final steps in the synthesis of 4 (24).

The occurrence of another skeletal modification within the series was established with the isolation and characterization of capsidiol (6) from sweet pepper-fungi interactions. The structure and stereochemistry of 6 was deduced from ^{1}H and ^{13}Cmr data and confirmed by x-ray analysis (26). Its skeleton is interesting because the vicinal methyl groups are *trans*, in contrast to all other previously described eremophilanes. Its biosynthesis from acetate was investigated through feeding experiments using doubly-labelled acetate-^{13}C$_2$ which confirmed that the pathway involves migration of the angular methyl group of an eudesmane-type intermediate to C-5 in the capsidiol skeleton (27). The ^{13}Cmr spectrum of the enriched material from the incorporation experiments established the presence of five intact acetate units with five carbons which had lost their enriched neighbor. A spectrum obtained from material induced in similar experiments in these laboratories is shown in Fig. 9, the inset
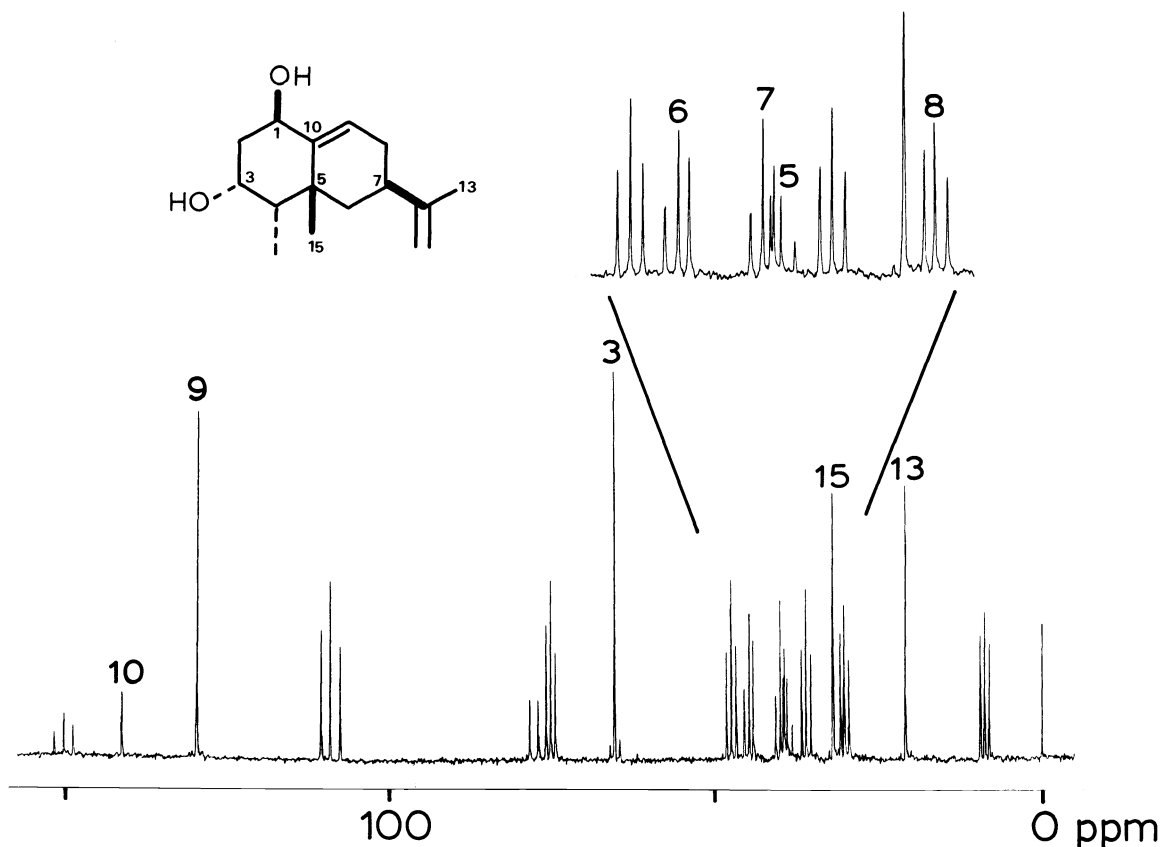

Fig. 9. ^{13}Cmr spectrum of 6 biosynthesized from 1,2-^{13}C-acetate.

of which displays an expanded view of the 30-50 ppm region. The latter is interesting since the signals for C-5,-6,-7 and -8 exhibiting similar J_{CC} values can be readily and unequivocally matched from the relative intensities of the doublets for each. In effect these are simple AB patterns and there is no difficulty in matching the appropriate pairs.

Fruits of sweet pepper were found to metabolize exogenously supplied capsidiol (6). This led to the isolation of the major metabolite and its identification as the 13-hydroxy derivative 21 (28). Similarly, healthy potato tissue has been found to convert rishitin (1) to its 13-hydroxy derivative 22 as well as the dihydro analog 23 (28,29). Experiments with radioactive 1 and 6 confirmed the origins of the hydroxylated metabolites. To gain additional

OH

21   22   23
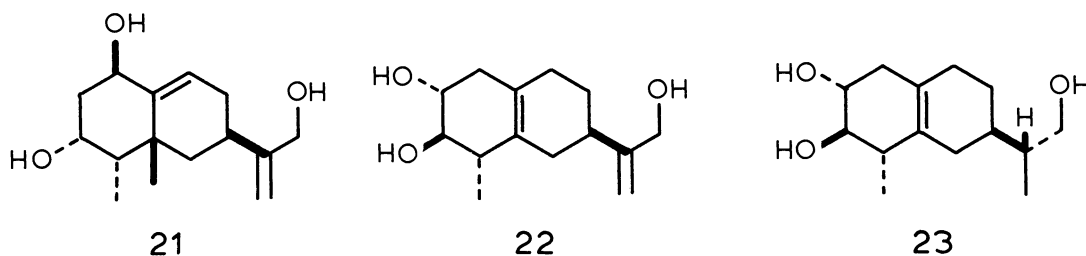
information on the mechanism of biological hydroxylation of 6, the metabolism of samples of ^{13}C-enriched 6 from the acetate-^{13}C$_2$ incorporations was studied. The ^{13}C spectrum of 21-^{13}C$_x$ obtained from these experiments clearly revealed that hydroxylation occurs only at C-13 of 6; the highest field singlet in Fig. 9 at 21 ppm is shifted to 65.4 ppm in the spectrum of 21 while the remaining absorptions are little affected apart from the position of the patterns for C-7 and -11, as expected upon introduction of a hydroxyl group. These results indicate that neither an allylic rearrangement nor the formation of an epoxide intervene in the process.

By analogy with the foregoing examples, a biosynthetic sequence leading to 6 from a germacrene derivative was readily envisaged (2) as set out in Fig. 10 which includes sequential *syn*
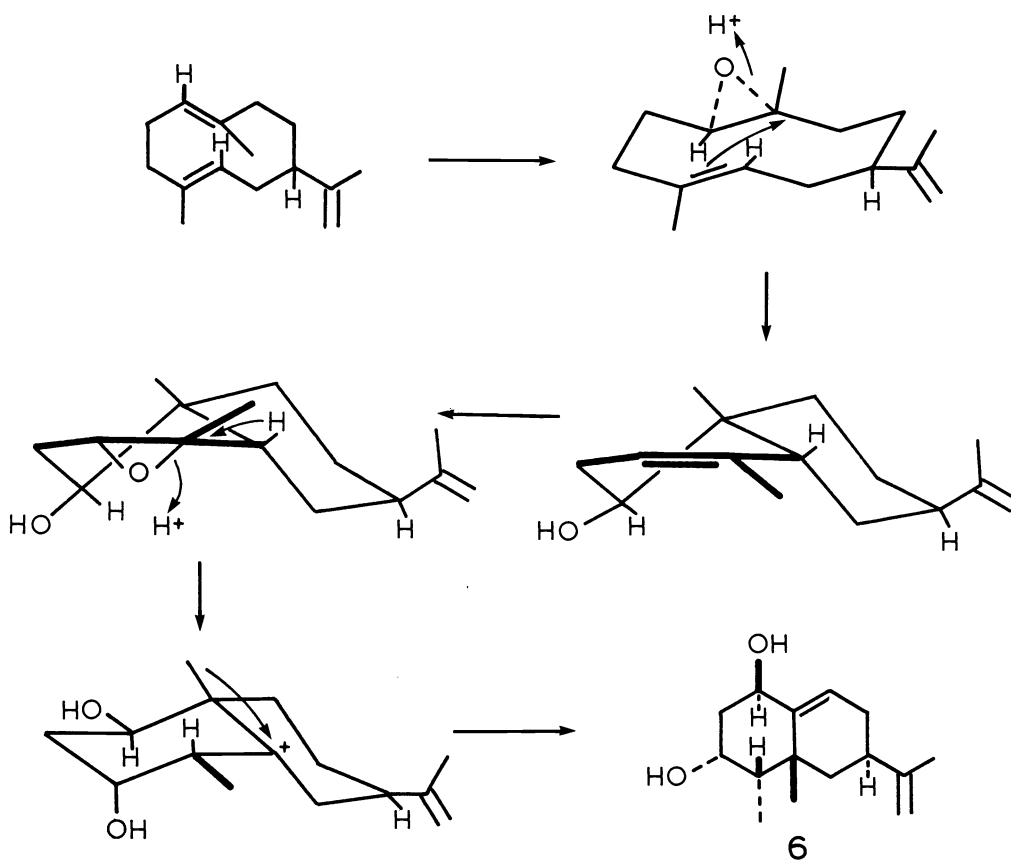
OH

6

Fig. 10. Postulated biosynthetic scheme for 6 (2).

migration of hydrogen (C-5 → C-4) and methyl (C-10 → C-5), similar to the postulated biosynthesis of occidentalol (30). To obtain supportive evidence for this proposal, incorporation experiments utilizing mevalonolactone-4,4-d_2 were carried out (31). After isolation of $\underline{6}$-d_x and conversion to the diacetate, the ^{2}Hmr spectrum of the product was found to contain three deuterium signals (Fig. 11), one of which is significantly deshielded relative to the others. Clearly the deuterium atom from each of the three mevalonate units involved in the genesis of $\underline{6}$ is retained. Since the angular methyl group is bonded to a carbon originating from C-4 in mevalonate, a hydride (deuteride) shift has occurred. The low specific incorporation (0.3%) of mevalonate clearly precludes other possible interpretations. The lowest field signal in the ^{2}H spectrum arises from deuterium on C-1 and highest from that on C-4. The remaining signal is the allylic deuterium at C-7 and its lower relative intensity may be attributed to allylic exchange. These results offer strong support for sequential *syn* migration of hydride and methyl. The data rule out an earlier suggestion that $\underline{6}$, an *epi*eremophilane, arises by a trivial epimerization of an eremophilane (30).
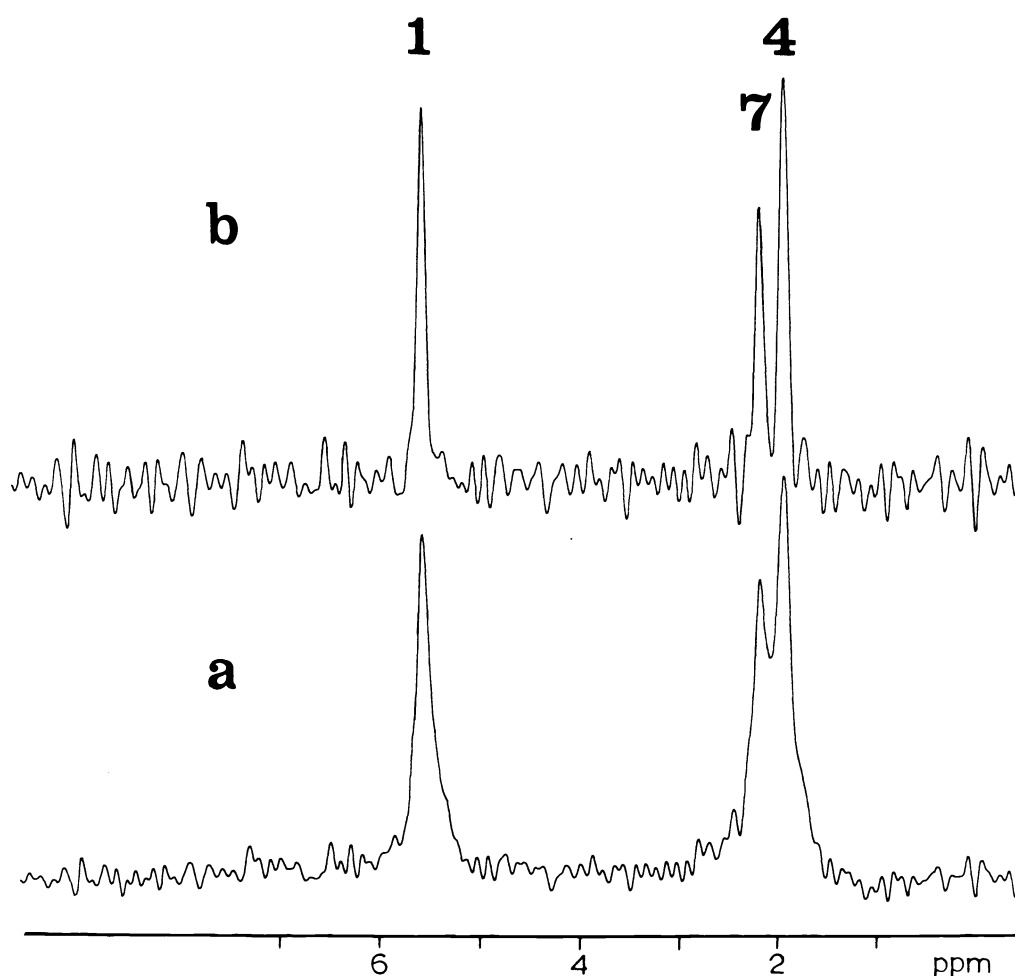

Fig. 11. ^{2}Hmr spectra of the diacetate of $\underline{6}$-d_x at 30.7 MHz in CFCl$_3$: (a) normal data processing, (b) resolution enhanced spectrum. (Courtesy of W.C. Jankowski, Varian Associates.)

REARRANGEMENT AND DEUTERIUM EXCHANGE IN KETONES VIA HOMOENOLIZATION

Finding that base-catalyzed racemization and deuterium exchange occurred at the same rates when camphenilone (24) was treated with potassium t-butoxide and t-butyl alcohol-O-d at 185° Nickon and Lambert (32) proposed that a symmetric homoenolate anion 25 was involved and
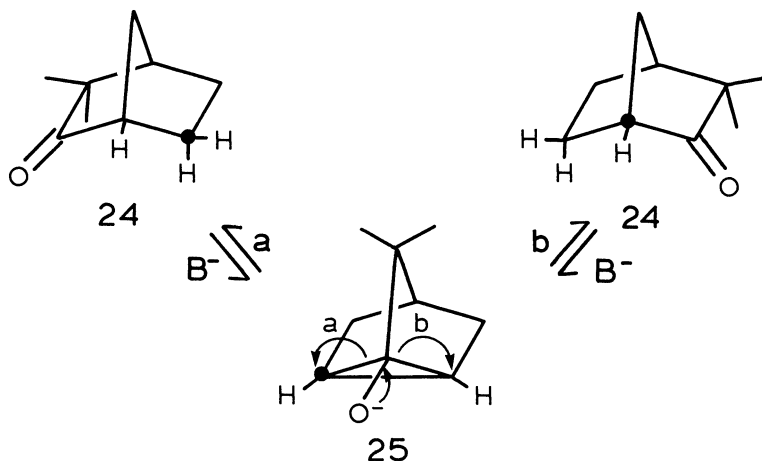
introduced the term homoenolization for this process. Homoketonization was suggested for the reverse reaction, cleavage of the cyclopropoxide ion. These processes have received some attention over the past twenty years and this work has been reviewed recently (33); thus, only certain aspects will be considered here. In 25, C-1 and -6 become equivalent, and hence scrambled, leading to the incorporation of up to three deuterium atoms. In the early work, homoketonization of 26, readily generated from 1-acetoxynortricyclene under mild conditions, was found (34) to yield norcamphor-6-exo-d with high stereoselectivity (> 95%). Some other
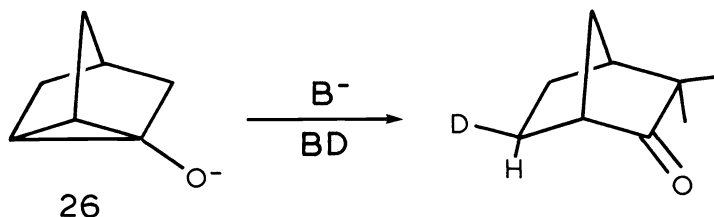
examples of bicyclic systems subsequently examined are collected in Fig. 12. In contrast to 24 the additional methyl group in fenchone (27) renders the intermediate homoenolate anion unsymmetric such that rearrangement to the 3,3,6-trimethylated analog 28 is possible. Although the equilibrium mixture of ketones favors 27 it is significant that 6-$endo$-methyl-28 predominates over its 6-exo-methyl counterpart by a factor of 3 (35). This is consistent with preferred inversion of configuration at C-6 in the cleavage of the homoenolate, in agreement with the ring opening of 26 noted above. The lower stereoselectivity in the fenchone system probably results from different temperature dependencies for the two modes of ring opening, i.e., inversion and retention. Deuterium incorporation at C-6 in 27 was readily monitored by ^{2}Hmr spectra and found, as expected, to favor exo over $endo$ incorporation in a 3:1 ratio (35). Equilibration of the two α,α-dimethylbicyclooctanones 29 and 30 was found to favor the latter by $ca.$ 4:1 (36). Furthermore, the ratio of $exo/endo$ ^{2}H incorporation at C-6(-7) in 29 is 10:1, while in 30 only exo-deuterium was detected at C-4 at an incorporation rate similar to that found for $endo$-^{2}H uptake in 29. Introduction of the double bond into the bicyclooctanone skeleton has a profound effect on the rate of rearrangement. Whereas the half-life for equilibration of 29 ⇌ 30 is some hundreds of hours at 185° (36), for the system 31 ⇌ 32 + 33, the half-life is 7 h at the same temperature (37). It may be noted that in addition to exchange via homoenolate anions, vinylic and bridgehead exchange also occur in 31-33. Hence ^{2}Hmr spectroscopy is particularly useful since incorporation of deuterium at the several sites is readily monitored. All of these systems 24, 27-33 exhibit exchange at the methyl groups as well, albeit at distinctly different rates spanning two orders of magnitude. Exchange at the exo-methyl sites in 30, 32 and 33 is at least 100 times faster than at the $endo$-methyl carbons; the rates for the latter are similar to those for the methyl carbons in 29 and for the bridgehead and $endo$-methyl in 27. The mechanism of methyl exchange in these cases, is considered in more detail later.
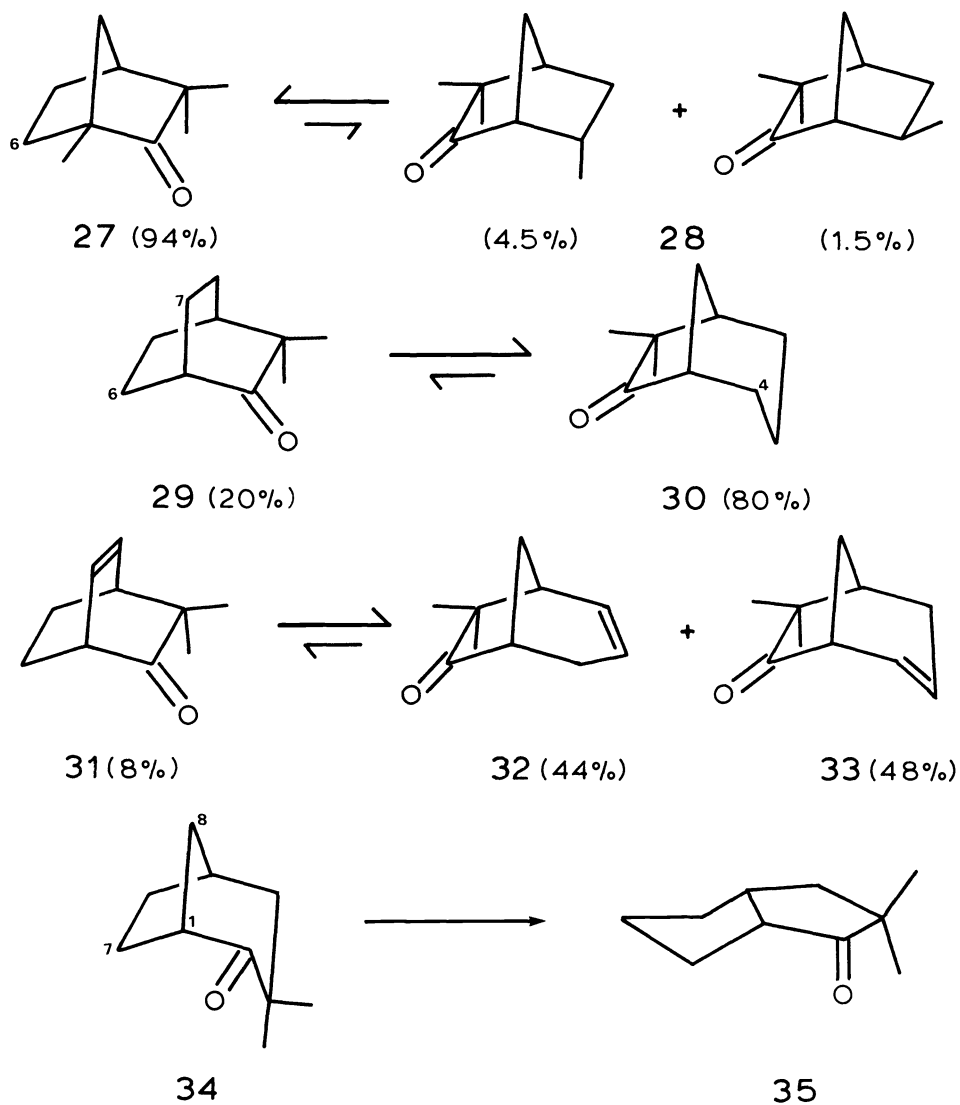
Fig. 12. Homoenolization results for some bicyclic ketones.

The remaining example in Fig. 12 is an irreversible rearrangement whereby the [3.2.1] skeleton is converted smoothly, but slowly, to the [3.3.0] system (38). In deuterated media, 34 takes up deuterium at C-1,-7 and the methyl carbons; none was detected at C-8, at which proton abstraction must occur to produce the rearranged ketone 35. Under homoenolization conditions 35 yields no detectable 34, which is consistent with the lack of ^{2}H at C-8 in 34, but exhibits exchange at C-1,-6,-7,-8 and both methyl carbons. A ^{2}Hmr spectrum of this material is reproduced in Fig. 13 which includes a spectrum of 35-d_x generated from 34. The former spectrum clearly shows that quantitative assays of ^{2}H incorporation at eight sites in the same molecule are essentially straightforward. The most significant feature of this system is the fact that proton abstraction (and ^{2}H uptake) occurs at γ-positions with respect to the carbonyl group, clearly indicating that the molecule can adopt conformations in which the γ-carbons (C-6 and -7) can be relatively close to the carbonyl group. Hence, 35 was the first example of γ-exchange in ketones involving a flexible system. Although earlier illustrations of γ-exchange had been described, these occur in systems in which the γ-carbon is constrained by molecular geometry to a position close to the carbonyl function (39).

As noted above, the α-methyl groups in a variety of mono- and bicyclic ketones exhibit deuterium exchange under homoenolization conditions (33-37a). The process can be envisaged to involve a cyclopropoxide intermediate such as 36 (Fig. 14). Although 36 can undergo
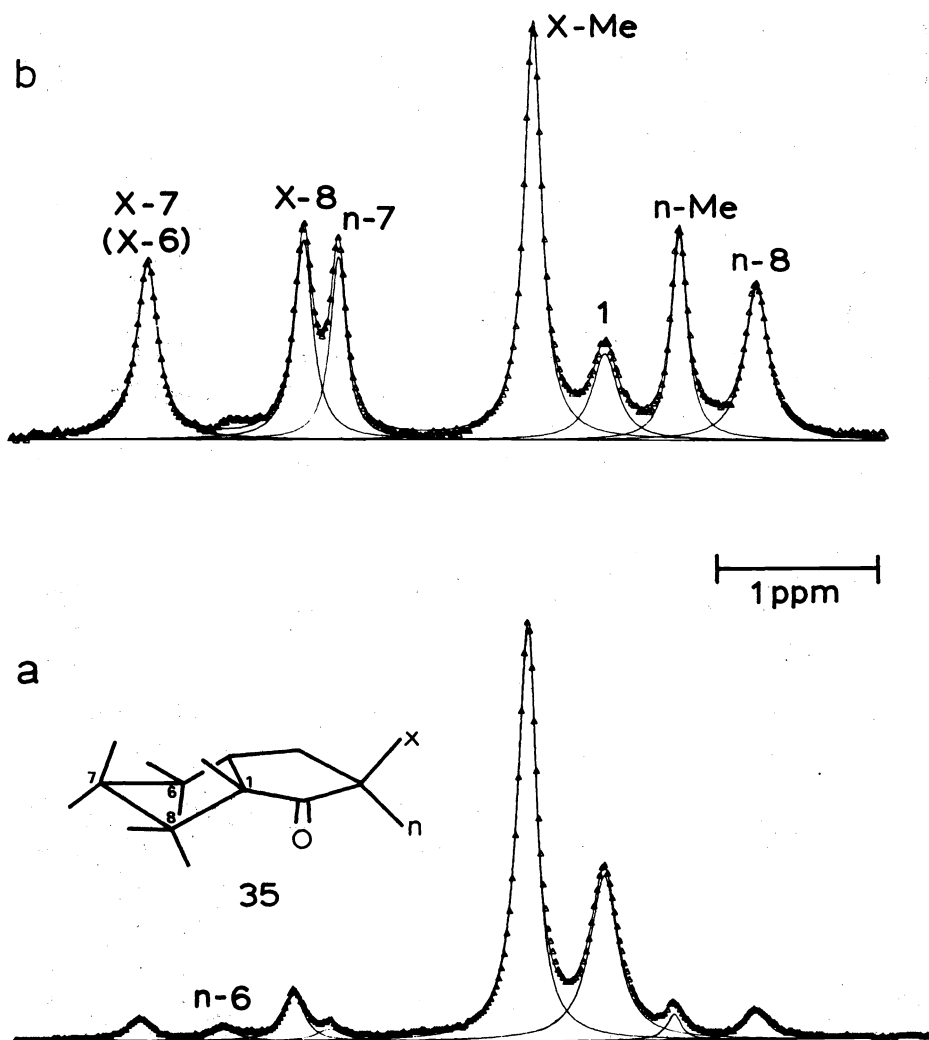
b

1 ppm

a

35

Fig. 13. 15.4 MHz ^{2}Hmr spectra of 35-d_x in CHCl$_3$-C$_6$F$_6$ containing Pr(fod)$_3$, observed (Δ) and computer-fitted (full line) spectra. (a) 35 treated with t-BuO$^-$/t-BuOD at 185°, (b) 35 generated from 34 under the same conditions.
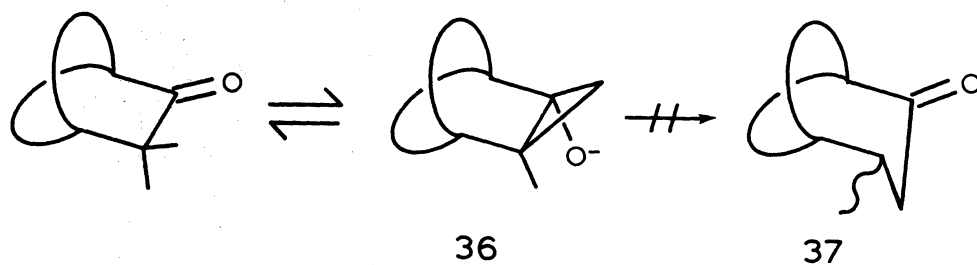

36   37

Fig. 14. Generalized scheme for H/D exchange at α-methyl sites in bicyclic ketones.

cleavage in two ways, to regenerate the initial ketone or to furnish a ring-expanded product 37, there was no evidence for the formation of such products in any of the reported studies, indicating that 36 → 37 is a minor process under the reaction conditions. The first direct evidence that species akin to 36 may be involved in α-methyl exchange was the finding that acyclic ketones such as 38 (R = Me, n-Bu or Ph) slowly rearrange to 39 (40,41). With R = Me, 38 and 39 afforded trace amounts of 40 (40) demonstrating that a second rearrangement via a
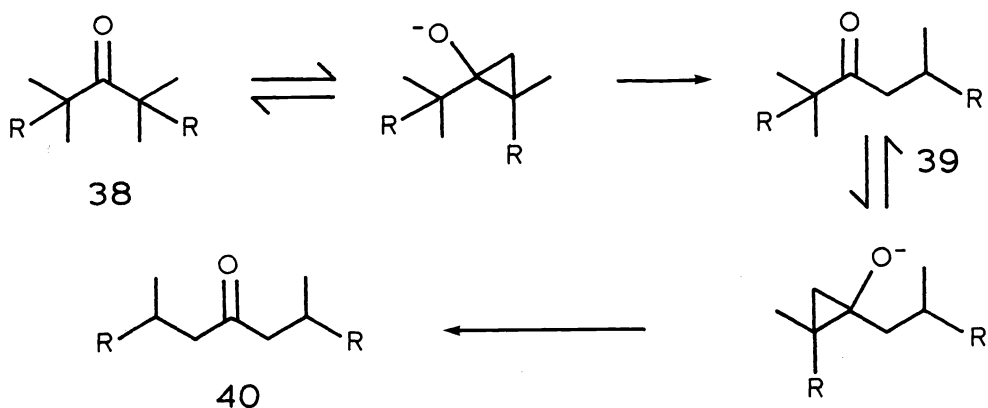
homoenolizable methyl can occur; with R = Ph, 38 and 39 furnished 40 in substantial amounts
(41). However, the balance between factors governing the regioselectivity of cleavage of the
cyclopropoxide intermediates in the acyclic systems may differ from those controlling ring
opening in their cyclic counterparts such as 36. To test for the existence of species 36, a
series of the corresponding substituted cyclopropanols was prepared and their base-catalyzed
homoketonizations examined (42). The appropriate α-methyl ketone 41 (R = Me) was converted
to the corresponding cyclopropanol 42 (R = Me) using the sequence in Fig. 15 modeled after
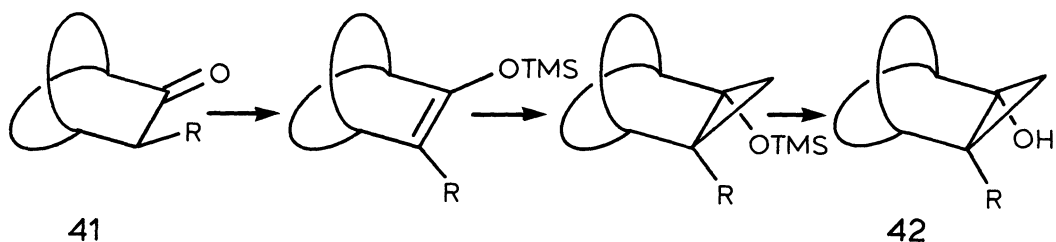the literature method for simpler systems (43). In the development of our synthetic

Fig. 15. Preparative scheme employed for substituted cyclopropanols.

procedures, the series for the parent ketones 41 (R = H) was also prepared. Some of the
results of the ring opening experiments are collected in Figs. 16 and 17; these homoketon-
izations utilized potassium t-butoxide/t-butyl alcohol at 25° and, in some instances, 82°,
the reflux temperature. For the methylated series of general formula 42 (R = Me) the major

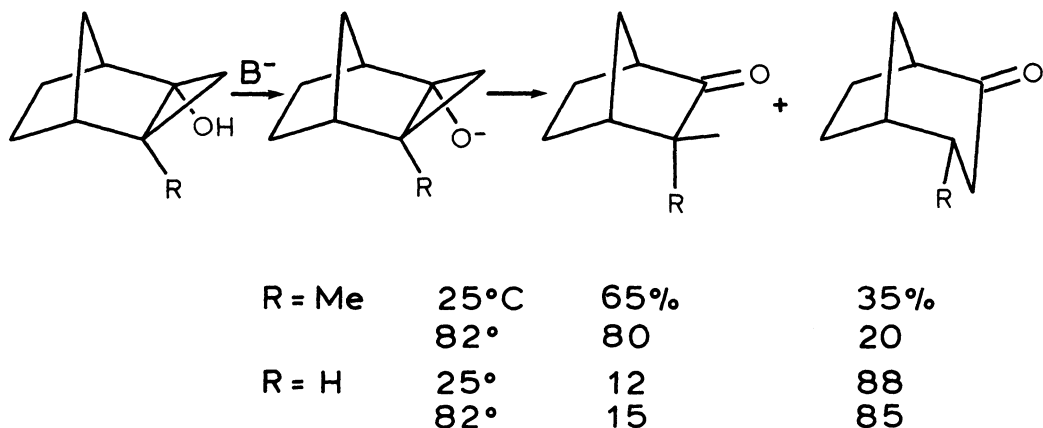| R = Me	25°C	65%	35%
	82°	80	20
R = H	25°	12	88
	82°	15	85

Fig. 16. Homoketonization results for two tricyclo[3.2.1.0^{2,4}]octane systems.

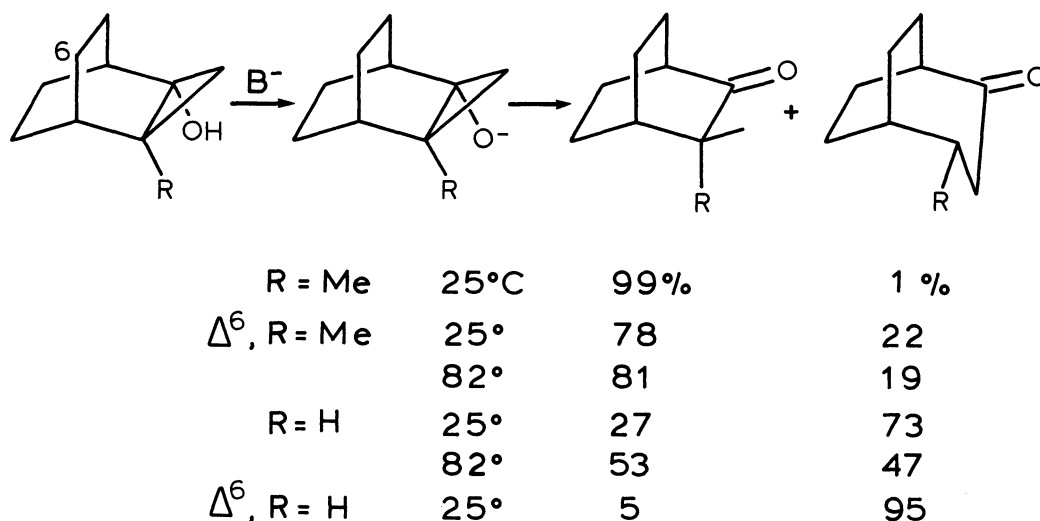|			
R = Me	25°C	99%	1 %
Δ^6, R = Me	25°	78	22
	82°	81	19
R = H	25°	27	73
	82°	53	47
Δ^6, R = H	25°	5	95

Fig. 17. Homoketonization results for some tricyclo[3.2.2.0^{2,4}]nonane systems.

product was found to be the corresponding dimethyl ketone, i.e., preferential opening to the incipient primary carbanion, with increasing regioselectivity with increasing temperature. From these results it is apparent that 36 is a reasonable intermediate for α-methyl exchange under homoenolization conditions. The minor product in each case was found to be a single ring-expanded β-methyl analog arising by ring opening with inversion of configuration, the anticipated mode of cleavage. While ring expansion is the minor process in the methylated series, the less highly substituted cyclopropanols corresponding to 42 (R = H) exhibited the opposite regioselectivity in homoketonization (42), as the data in Figs. 16 and 17 show, although a similar temperature dependence appears to hold. Thus, at the lower temperatures, ring-expansion is highly favored but it must be noted that ring expansion is decreasingly favored in the saturated bicyclic systems in the order [2.2.1], [2.2.2], [3.2.1], [3.2.2] (44). These results indicate that two opposing major factors may govern the regioselectivity for a given system. Opening to the α-methyl ketone may be inherently favored because the primary carbanion generated is more stable and less hindered for protonation than the alternative secondary carbanion but relief of ring strain resulting from the latter mode of cleavage may, in certain cases, render it the preferred mode. In any event, the preponderance of ring expansion for the three systems having R = H in Figs. 16 and 17 provides a new synthetic method for these and closely related cases. As an example of the synthetic utility of homoketonization for ring expansion it has been found that homologation of tricyclo[5.2.1.0^{2,6}]decan-8-one is straightforward as shown in Fig. 18 (45).
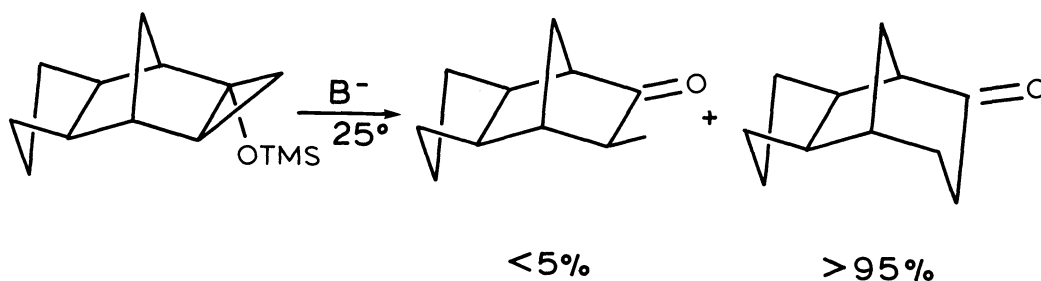

<5%   >95%

Fig. 18. Homoketonization of 8-trimethylsilyloxytetracyclo[5.3.1.0^{2,6}.0^{8,10}]-undecane.

A NEW SYNTHETIC APPROACH TO THE HIRSUTANES VIA HOMOENOLIZATION

Two of the major findings in our studies of the homoenolization reaction have led to the design and development of a new stereocontrolled synthetic route to naturally occurring tricyclopentanoids of the *cis*, *anti*, *cis*-tricyclo[6.3.0.0^{2,6}]undecane system. This is the carbon skeleton of a group of sesquiterpenes known as the hirsutanes, some of which have been shown to possess antibiotic and antitumor properties. As the initial objective, hirsutene (43) was chosen and the proposed route is set out in Scheme 2.

Scheme 2
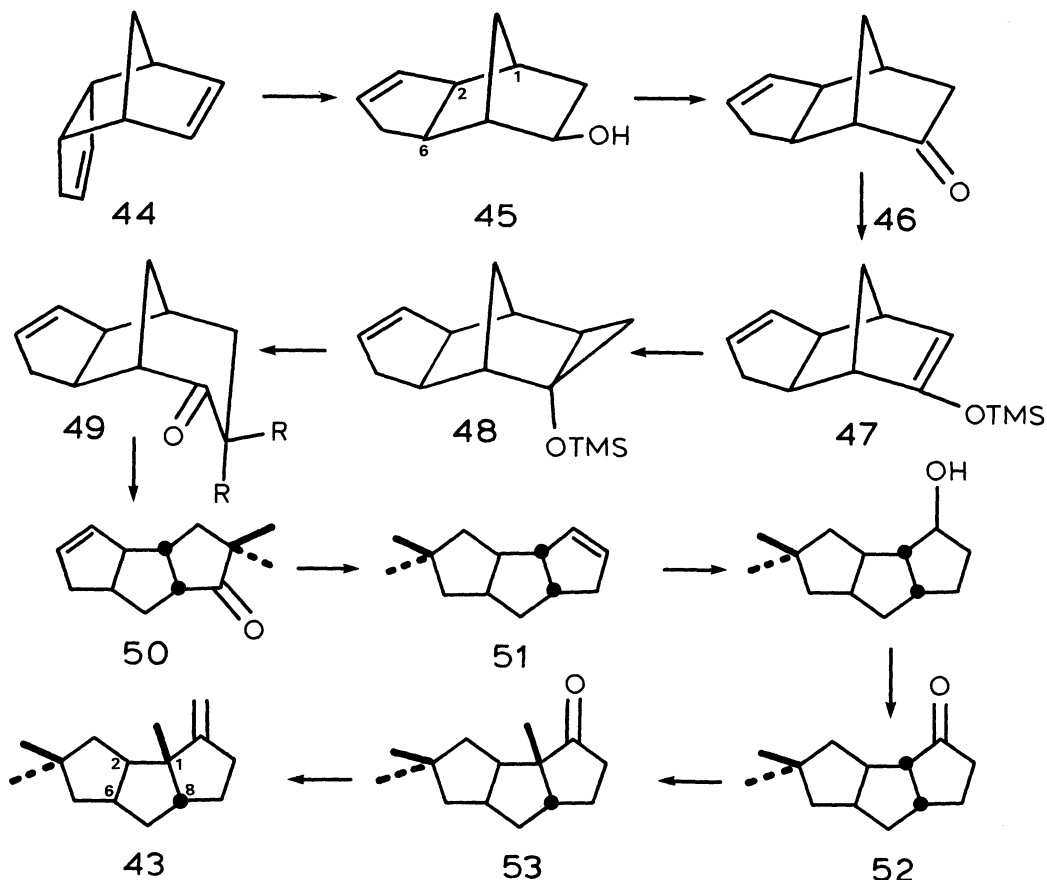
From dicyclopentadiene (44), alcohol 45 was readily generated (46) as a mixture of double bond isomers having the required *exo*-orientation of the unsaturated ring. [In Scheme 2, the Δ^3 isomer is illustrated while the Δ^4 analog is omitted for simplicity.] In 45 the three centres (C-1,-2 and -6) which become C-2,-1 and -8, respectively, in hirsutene (43) have the required stereochemistry. Oxidation of 45 gave 46 in high yield (47). Conversion to the enol ether 47, followed by cyclopropanation, afforded the tetracycloether 48. Homoketon- ization of 48 at room temperature furnished 49 (R = H) as the sole product with no evidence of the presence of the α-methyl derivative of 46 (48). Dimethylation with lithium diisopropylamide and methyl iodide gave 49 (R = Me) in good yield, completing the first subgoal of the proposed synthesis.

Rearrangement of 49 (R = Me) under homoenolization conditions (potassium *t*-butoxide/*t*-butyl alcohol, 185°) led smoothly to 50 (48), as anticipated from our earlier work (38) with the bicyclic analog 34 (see Fig. 12). The generation of 50 is the key step in the sequence furnishing the required ring system of the hirsutane family. The stereochemistry of the rearrangement is predestined to give the correct configuration at the fourth bridgehead because of the constraints of the ring system. The desired *cis* ring fusion results (C-2,-6 in 43) because the alternative *trans* arrangement is too strained and is energetically precluded. As an additional benefit, the gem-dimethyl substitution, necessary as a blocking group for the rearrangement, leads directly to the correct positioning of these groups in the target skeleton. It should be noted that, under the strongly basic conditions of the rearrangement, the allylic methylene carbon will undergo exchange, thus equilibrating the two double bond isomers. Separation of the isomeric mixtures 45-49 is, therefore, unnecessary.

To complete the synthesis of 43 from 50, the following steps are envisaged. Reduction of the carbonyl group through, for example, a Wolff-Kishner reaction will afford olefin 51. [In Fig. 19, a 180° rotation of the skeleton has been done to simplify comparison with the conventional display of the hirsutene skeleton.] Hydration of the double bond followed by oxidation should lead to ketone 52, angular methylation of which will afford 53. This would complete the first objective of this study since 53 has been converted to 43 by other workers (49).

REFERENCES

1. J. Kuć in *Microbial Toxins*, S. Kadis, A. Ciegler and S.J. Ajl, eds. Vol. 8, Academic Press, New York, 1972, pp. 211; J.D. Bu'Lock, *The Biosynthesis of Natural Products*, McGraw-Hill, 1965, New York, p. 1.

2. A. Stoessl, J.B. Stothers and E.W.B. Ward, *Phytochem.* 15, 855 (1976); A. Stoessl, E.W.B. Ward and J.B. Stothers in *Host plant resistance to pests*, P.A. Hedin, ed. American Chem. Soc., Washington, 1977, Chap. 5, p. 61-77.

3. A. Stoessl, J.B. Stothers and E.W.B. Ward, *Can. J. Chem.* 56, 645 (1978).

4. R.E. London, V.H. Kollman and N.A. Matwiyoff, *J. Am. Chem. Soc.* 97, 3565 (1975).

5. A. Stoessl, J.B. Stothers and E.W.B. Ward, *J. Chem. Soc. Chem. Comm.* 709 (1974).

6. A. Stoessl, J.B. Stothers and E.W.B. Ward, *J. Chem. Soc. Chem. Comm.* 431 (1975).

7. A. Stoessl, J.B. Stothers and E.W.B. Ward, *Can. J. Chem.* 53, 3351 (1975).

8. (a) R.B. Kelly, S.J. Alward, K.S. Murty and J.B. Stothers, *Can. J. Chem.* 56, 2508 (1978); (b) A. Murai, A. Abiko, M. Ono and T. Masamune, *Chem. Lett.* 1209 (1978).

9. N. Katsui, A. Murai, M. Takasugi, K. Imaizumi and T. Masamune, *J. Chem. Soc. Chem. Comm.* 43 (1968); T. Masamune, A. Murai, M. Takasugi, A. Matsunaga, N. Katsui, N. Sato and K. Tomiyama, *Bull. Chem. Soc. Jap.* 50, 1201 (1977).

10. L.V. Metlitskii, O.L. Ozeretskovskaya, N.S. Vul'fson and L.I. Chalova, *Doklady Akad Nauk SSSR* 200, 1970 (1971).

11. N. Katsui, A. Matsunaga, H. Kitahara, T. Masamune, F. Yagihashi, A. Murai and N. Sato, *Bull. Chem. Soc. Jap.* 50, 1217 (1977).

12. D.T. Coxon, K.R. Price, B. Howard, S.F. Osman, E.B. Kalan and R.M. Zacharius, *Tetrahedron Lett.* 2921 (1974).

13. N. Katsui, A. Matsunaga and T. Masamune, *Tetrahedron Lett.* 4483 (1974).

14. E.W.B. Ward and A. Stoessl, *Phytopathology* 67, 468 (1977).

15. N. Katsui, F. Yagihashi, A. Matsunaga, K. Orito, A. Murai and T. Masamune, *Chem. Lett.* 723 (1977).

16. (a) E.B. Kalan and S.F. Osman, *Phytochem.* 15, 775 (1976); (b) E.B. Kalan, J.M. Patterson and D.P. Schwartz, *Plant Physiology* 57 (Supplement) Abst. 473 (1976).

17. A. Murai, N. Katsui and T. Masamune, *Phytochem.* 17, 1901 (1978).

18. A. Stoessl and J.B. Stothers, unpublished results.

19. N. Katsui, F. Yagihashi, A. Murai and T. Masamune, *Chem. Lett.* 1205 (1978).

20. A. Stoessl and J.B. Stothers, *Can. J. Chem.*, in press (1980).

21. D.T. Coxon, K.R. Price, J.B. Stothers and A. Stoessl, *J. Chem. Soc. Chem. Comm.* 348 (1979).

22. J.L. Varns, J. Kuć and E.B. Williams, Phytopathology 61, 174 (1971).

23. D.L. Hughes and D.T. Coxon, J. Chem. Soc. Chem. Comm. 822 (1974).

24. A. Murai, M. Ono, A. Abiko and T. Masamune, J. Am. Chem. Soc. 100, 7751 (1978).

25. T. Masamune, A. Murai and N. Katsui, Kagaku to Seibutsu 16, 648 (1978).

26. G.I. Birnbaum, A. Stoessl, S.H. Grover and J.B. Stothers, Can. J. Chem. 52, 993 (1974).

27. F.C. Baker, C.J.W. Brooks and S.A. Hutchinson, J. Chem. Soc. Chem. Comm. 293 (1975);
     F.C. Baker and C.J. Brooks, Phytochem. 15, 689 (1976).

28. E.W.B. Ward, A. Stoessl and J.B. Stothers, Phytochem. 16, 2024 (1977).

29. Y. Ishiguri, K. Tomiyama, N. Koke, A. Murai, N. Katsui, F. Yagihashi and T. Masamune,
     Phytopathology 68, 720 (1978); A. Murai, N. Katsui, F. Yagihashi, T. Masamune,
     Y. Ishiguri and K. Tomiyama, J. Chem. Soc. Chem. Comm. 670 (1977).

30. R.M. Coates, Fortsch. Chem. Org. Naturst. 33, 73 (1976).

31. Y. Hoyano, A. Stoessl and J.B. Stothers, Can. J. Chem., in press (1980).

32. A. Nickon and J.L. Lambert, J. Am. Chem. Soc. 84, 4604 (1962); 88, 1905 (1966).

33. D.H. Hunter, J.B. Stothers and E.W. Warnhoff in Rearrangements in Ground and Excited
     States, Vol. 1, Academic Press, New York, Chap. 6, p. 410-437.

34. A. Nickon, J.H. Hammons, J.L. Lambert and R.O. Williams, J. Am. Chem. Soc. 85, 3713
     (1963); A. Nickon, J.L. Lambert, R.O. Williams and N.H. Werstiuk, ibid. 88, 3354 (1966).

35. A.L. Johnson, J.B. Stothers and C.T. Tan, Can. J. Chem. 53, 212 (1975).

36. A.K. Cheng, J.B. Stothers and C.T. Tan, Can. J. Chem. 55, 447 (1977).

37. A.K. Cheng and J.B. Stothers, Can. J. Chem. 56, 1342 (1978).

38. A.L. Johnson, N.O. Petersen, M.B. Rampersad and J.B. Stothers, Can. J. Chem. 52, 4143
     (1974).

39. R. Howe and S. Winstein, J. Am. Chem. Soc. 87, 915 (1965); T. Fukunaga, ibid. 87, 916
     (1965); A. Nickon, J.L. Lambert, J.E. Oliver, D.F. Covey and J. Morgan, J. Am. Chem.
     Soc. 98, 2593 (1976); T. Fukunaga and R.A. Clement, J. Org. Chem. 42, 270 (1977).

40. M.B. Rampersad and J.B. Stothers, J. Chem. Soc. Chem. Comm. 709 (1976).

41. R.A. Dyllick-Brenzinger and J.B. Stothers, ibid. 108 (1979).

42. V. Patel and J.B. Stothers, Can. J. Chem., in press (1980).

43. C. Girard and J. Conia, J. Chem. Res. (M) 2346 (1978).

44. Y. Hoyano, V. Patel and J.B. Stothers, Can. J. Chem., in press (1980).

45. B.A. Dawson, A.J. Ragauskas and J.B. Stothers, unpublished results.

46. F. Bergman and H. Japhe, J. Am. Chem. Soc. 69, 1826 (1947); S.J. Cristol, W.K. Seifert
     and S.B. Solway, ibid. 82, 2351 (1960).

47. H.C. Brown, C.P. Garg and K-T. Liu, J. Org. Chem. 36, 387 (1971).

48. B.A. Dawson and J.B. Stothers, unpublished results.

49. S. Nozoe, J. Furukawa, V. Sankawa and S. Shibata, Tetrahedron Lett. 195 (1976).