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REVIEW ARTICLE

A SURVEY OF SOME IRREGULAR MONOTERPENES AND THEIR BIOGENETIC ANALOGIES TO PRESQUALENE ALCOHOL

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Key Word Index—Irregular monoterpenes; occurrence; biosynthesis; review.

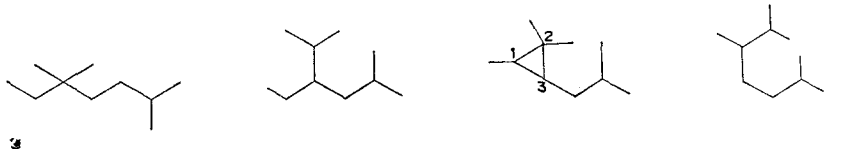
Abstract—A survey of all naturally occurring irregular monoterpenes which may bear structural analogies to presqualene alcohol is presented. Attention is focused on structural and stereochemical relationships among these compounds. A critical analysis of biogenetic proposals is made.

INTRODUCTION

A GENERAL pathway for the biosynthesis of regular monoterpenes that proceeds through geranyl or neryl pyrophosphate has received considerable support.[1] The vast majority of monoterpenes can be explained in this fashion; however, a group of irregular 10-carbon isoprenoids appears to be biogenetic anomalies in that they are not really derived from head-to-tail precursors. Although individual members of this class of compounds have been discussed[1] in conjunction with regular monoterpenes, they have not been treated in depth as a separate biogenetic family as recent work with presqualene and prephytoene alcohols suggests.[2] This review is divided into two sections. The first section deals with the carbon skeletal variations and their plant sources. The second considers the various alternative biogenetic pathways.

STRUCTURES AND OCCURRENCE

All of the compounds considered in this review are listed in Table 1. Since four basic carbon skeletons are involved—artemisyl (I), santolinyl (II), chrysanthemyl (III) and lavandulyl (IV)—the individual monoterpenes are grouped in this manner.



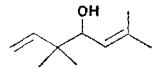
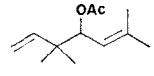
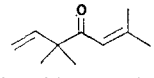
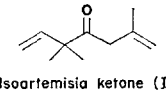
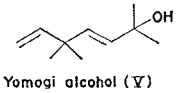
(I) Artemisyl (II) Santolinyl (III) Chrysanthemyl (IV) Lavandulyl

[1] BANTHORPE, D. V., CHARLWOOD, B. V. and FRANCIS, M. J. O. (1972) *Chem. Rev.* **72**, 115.

[2] (a) RILLING, H. C. and EPSTEIN, W. W. (1969) *J. Am. Chem. Soc.* **91**, 1041; (b) EPSTEIN, W. W. and RILLING, H. C. (1970) *J. Biol. Chem.* **18**, 4597; (c) VAN TAMELEN, E. E. and SCHWARTZ, M. A. (1971) *J. Am. Chem. Soc.* **93**, 1780; (d) RILLING, H. C., POULTER, C. D., EPSTEIN, W. W. and LARSEN, B. (1971) *J. Am. Chem. Soc.* **93**, 1783; (e) ALTMAN, L., ASH, L., KOWERSKI, R. C., EPSTEIN, W. W., LARSEN, B., RILLING, H. C., MUSCIO, F. and GREGONIS, D. (1972) *J. Am. Chem. Soc.* **94**, 3257.

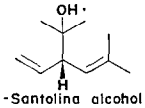
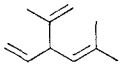
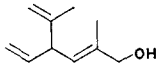
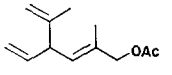
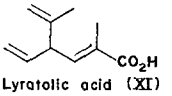
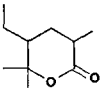
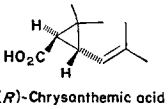
There are six reported compounds in the artemisyl group which range in oxidation states from a hydrocarbon to ketones and esters. All are acyclic and have three functional groups, two of which are double bonds. Members of the santolinyl series occur in both acyclic and cyclic modifications with either three or four functional groups in various stages of oxidation. Chrysanthemic acid and chrysanthemic dicarboxylic acid (chrysanthemyl) are found as the acid portion of pyrethin ester insecticides. All of the above irregular monoterpenes are genetically related in that they are only reported to occur in the *Anthemideae*

TABLE 1. IRREGULAR MONOTERPENES AND THEIR NATURAL SOURCES

	Compound	Source	Ref.
Artemisyl	 Artemisia alcohol (I)	*Artemisia japonica*	31
		Artemisia ludiviciana	32
	 Artemisia acetate (II)	*Artemisia annua*	30
	 Artemisia ketone (III)	*Artemisia annua*	22,30,33
		Artemisia apiacae	31
		Artemisia arbuscula	32
		Artemisia frigida	32
		Artemisia japonica	31
		Artemisia ludiviciana	32
		Artemisia princepts	34
		Chrysanthemum tanacetum	35
		Chrysanthemum vulgare	35
		Santolina chamaecyparissus	22,36
	 Isoartemisia ketone (IV)	*Artemisia annua*	30
	 Yomogi alcohol (V)	*Artemisia feddi*	37
	 Artemisia triene (VI)	*Artemisia arbuscula*	32
		Artemisia tridentata	32
		Santolina chamaecyparisuss	38

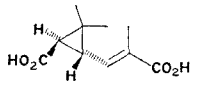
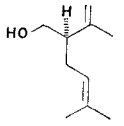
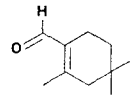
[31] YANO, K. (1970) *Flavour Ind.* **1**, 328.
[32] Unpublished observations from this laboratory.
[33] RUZICKA, L., REICHSTEIN, T. and PULVER, R. (1936) *Helv. Chim. Acta* **19**, 646.
[34] TSUBAKI, N., NISHMURA, K. and HIROSE, Y. (1966) *Bull. Chem. Soc. Japan* **39**, 312.
[35] STAHL, E. and SCHEN, D. (1965) *Naturwissenschaften* **52**, 394.
[36] ZALKOW, L. H., BRANNON, D. and VECKE, J. W. (1964) *J. Org. Chem.* **29**, 2786.
[37] HAYASHI, S., YANO, K. and MATSURA, T. (1968) *Tetrahedron Letters* 6241.
[38] THOMAS, A. F. and WILLHALM, B. (1964) *Tetrahedron Letters* 3775.

TABLE 1—*continued*

Compound	Source	Ref.
Santolinyl		
 (*S*)-Santolina alcohol (VII)	*Ormenis multicaulis*	39
 Santolina triene (VIII)	*Artemisia arbuscula* *Artemisia nova* *Artemisia tridentata* *Santolina chamaecyparissus*	32 32 32 37
 Lyratol (IX)	*Cyathocline lyrata*	40
 Lyratol acetate (X)	*Cyathocline lyrata*	40
 Lyratolic acid (XI)	*Cyathocline lyrata*	41
 (XII)	*Chrysanthemum flosculosum*	42
Chrysanthemyl		
 1(*R*),3(*R*)-Chrysanthemic acid (XIII) (as an ester)	*Chrysanthemum balsamita* *Chrysanthemum canescens* *Chrysanthemum carneum* *Chrysanthemum chyliophyllum* *Chrysanthemum cinerariaefolium* *Chrysanthemum macrophyllum* *Cgrysanthemum myriophyllum* *Chrysanthemum parthenifolium* *Chrysanthemum pulverilentum* *Chrysanthemum punctatum* *Chrysanthemum roseum* *Chrysanthemum szowitssi* *Chrysanthemum tamrutense*	43 43 43 43 24 43 43 43 43 43 43 43 43

[39] BESSIERE-CHRETIEN, Y., PEYRON, L., BEMEZET, L. and GARNERO, J. (1968) *Bull. Soc. Chim. Fr.* 2018.
[40] DEVGAN, O. N., BOKADIA, M. M., BOSE, A. K., TRIVEDI, G. K. and CHAKRAVATI, K. K. (1969) *Tetrahedron* **25**, 3217.
[41] DEVGAN, O. N. and BOKADIA, M. M. (1967) *Curr. Sci.* **36**, 205.
[42] BOHLMANN, F. and GRENZ, M. (1969) *Tetrahedron Letters* 2413.
[43] GNADINGER, C. B. (1936) *Pyrethrum Flowers*, 2nd Edn, p. 419, McLaughlin-Gormley-King, Minneapolis, Minnesota.

TABLE 1—*continued*

Compound	Source	Ref.
Chrysanthemyl		
 1(*R*), 3(*R*)-Chrysanthemic dicarboxylic acid (XIV) (as an ester)	*Chrysanthemum cinerariaefolium*	24
Lavandulyl		
 (*R*)-Lavandulol (XV)	*Lavandula officinalis* *Lavandula vera*	6,44 45
 *β*-Cyclolavandulal (XVI)	*Seseli indicum*	46

[44] SCHINZ, H. and SEIDEL, C. F. (1942) *Helv. Chim. Acta* **25**, 1572.
[45] SEIDEL, C. F., SCHINZ, H. and MULLER, P. H. (1944) *Helv. Chim. Acta* **27**, 663.
[46] LOGANI, M. K., VARSHNEY, I. P., PANDEY, R. C. and DEV, S. (1967) *Tetrahedron Letters* 2645.

tribe of the Compositae. Lavandulyl, the fourth class, is represented by one acyclic and one cyclic member. Both of these natural products are found in plants which are outside of the Compositae.

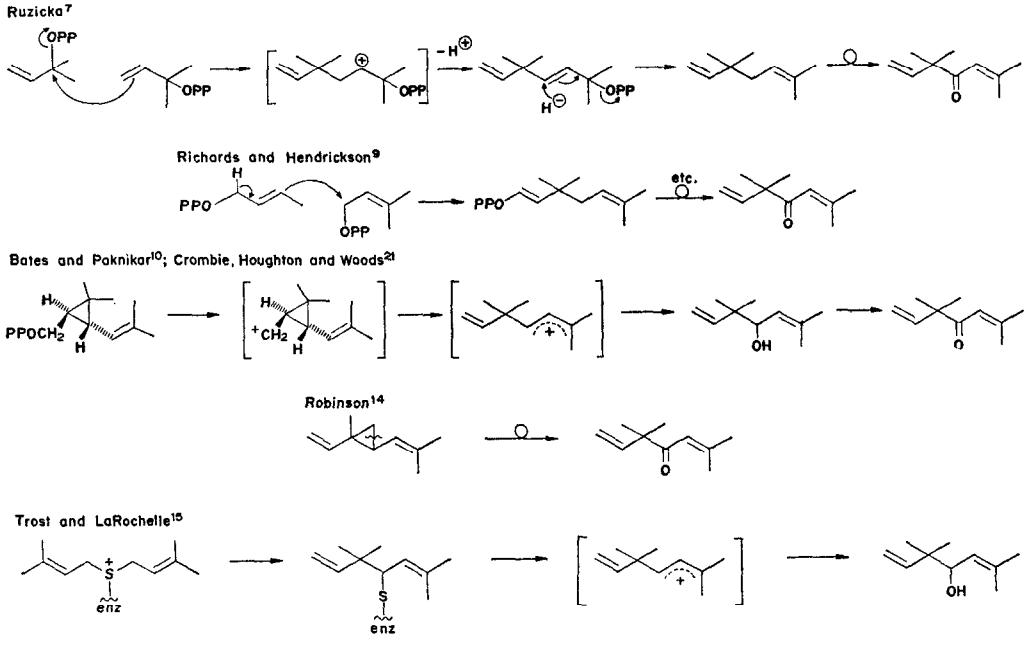
All of the compounds in Table 1 with asymmetric centers are optically active. In contrast to the regular monoterpenes where either antipode frequently is found in varying degrees of optical purity, only one enantiomer has thus far been reported for each of the irregular compounds. The optical purity and absolute configurations of santolina alcohol (VII),[3] chrysanthemic acid (XIII),[4] chrysanthemic dicarboxylic acid (XVI),[5] and lavandulol (XV)[6] have been determined. In each case the natural product was optically pure.

BIOSYNTHESIS

Several different routes for the biosynthesis of the compounds listed in Table 1 have been suggested. Most of the proposals are specific for a particular carbon skeleton. However, recent modifications have evolved into schemes which attempt to interrelate the biogenetic origin of most of the irregular monoterpenes. It should be emphasized that there is very little direct experimental verification of any pathway. All of the labeling studies have used intact plants with resulting experimental difficulties[1] such as lack or low incorpora-

[3] POULTER, C. D., GOODFELLOW, R. J. and EPSTEIN, W. W. (1972) *Tetrahedron Letters* 71.
[4] CROMBIE, L. and HARPER, S. H. (1954) *J. Chem. Soc.* 470.
[5] CROMBIE, L., HARPER, S. H. and SLEEP, K. C. (1957) *J. Chem. Soc.* 2743.
[6] SOUCEK, M. and DOLYS, C. (1959) *Coll. Czech. Chem. Commun.* **24**, 2802.

tion of labeled substrate or problems involved with transportation of substrates to the site of synthesis. Further complications may involve cleavage of phosphate precursors by plant phosphatases, and the resulting alcohols oxidized or otherwise modified.



SCHEME 1. PROPOSED ROUTES TO ARTEMISYL MONOTERPENES.

Proposed Routes to Artemisyl Monoterpenes

Five methods for generating the artemisyl skeleton have appeared and are outlined in Scheme 1. Ruzicka[7] envisions dimerization of two 5-carbon equivalents of linalool where the double bond of one functions as a nucleophile in displacing the pyrophosphate of the other. The cationic intermediate suffers loss of a proton to give the pyrophosphate ester of yomogi alcohol. Artemisia ketone is produced by an S_N2' displacement of pyrophosphate by hydride and subsequent oxidation of the resulting diene. The original dimerization, while chemically feasible, has no biological analogy in other irregular terpenoid systems.[8] The latter steps appear to be an added complication in view of the ease of allylic ester and alcohol interconversions.

Richards and Hendrickson[9] outlined a dimerization scheme which rationalizes the formation of the artemisyl skeleton. However, in view of the lack of detail and analogy, it does not warrant further consideration.

Chrysanthemyl pyrophosphate was proposed as a biogenetic precursor for artemisia alcohol and artemisia ketone by Bates and Paknikar.[10] They postulated heterolysis of the carbon–oxygen bond, giving a cyclopropylcarbinyl cation, followed by cleavage of the appropriate cyclopropane bond, and hydroxylation of the allylic intermediate to produce

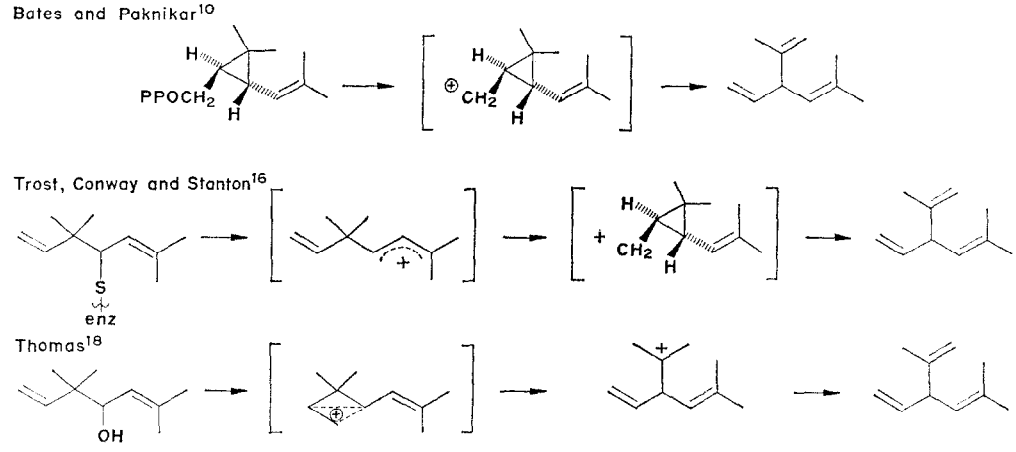
[7] RUZICKA, L. (1963) *Pure Appl. Chem.* **6**, 493.
[8] SOFER, S. S. and RILLING, H. C. (1969) *J. Lip. Res.* **10**, 183.
[9] RICHARDS, J. H. and HENDRICKSON, J. B. (1964) *The Biosynthesis of Steroids, Terpenes and Acetogens* p. 211, Benjamin, New York.
[10] BATES, R. B. and PAKNIKAR, S. K. (1965) *Tetrahedron Letters* 1453.

artemisia alcohol. This suggestion has found subsequent chemical analogy.[11–13] The cyclopropylcarbinyl cation has now been shown to give products with artemisyl carbon skeletons under a wide variety of conditions. Recently, C_{30} and C_{40} cyclopropylcarbinyl pyrophosphates with analogous structures have been established as intermediates in irregular terpene biosynthesis.[2] Of historical interest is a route to the artemisyl system proposed by Sir Robert Robinson[14] which involves cleavage of a cyclopropane bond.

A Steven's rearrangement of a sulfonium salt followed by solvolysis has been suggested by Trost and LaRochelle[15] as a logical route to artemisia alcohol. Although this pathway is attractive from a chemical viewpoint and the individual steps have been carried out in the laboratory,[16,17] the acceptance of pyrophosphate intermediates in terpene biosynthesis generally, and the occurrence of presqualene and prephytoene pyrophosphates in particular, argue against this hypothesis.

Routes to Santolinyl Monoterpenes

The three proposed routes to santolinyl monoterpenes proceed through the cyclopropylcarbinyl cation obtained by ionization of chrysanthemyl pyophosphate (Scheme 2). The routes are elaborations of the proposals for biosynthesis of artemisyl monoterpenes. Chemical simulation leading to santolinyl derivatives has been observed for both cyclopropylcarbinyl[13] and artemisyl precursors.[16,18]



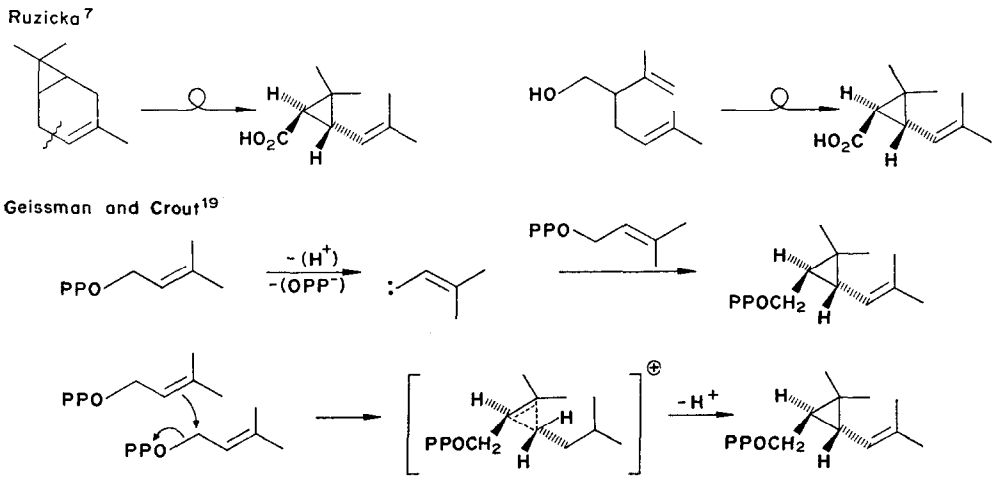
SCHEME 2. PROPOSED ROUTES TO SANTOLINYL MONOTERPENES.

Routes to Chrysanthemyl Monoterpenes

Four approaches to the biosynthesis of chrysanthemic acid have appeared in the literature (Scheme 3). Two very early precursors were offered by Ruzicka[7] to rationalize the

[11] CROMBIE, L., FIRTH, P. A., NOUGHTON, R. P., WHITING, D. A. and WOODS, D. K. (1972) *J. Chem. Soc. Perkin Trans, I*, 642.
[12] BATES, R. B. and FELD, D. (1967) *Tetrahedron Letters* 1453.
[13] POULTER, C. D., MOESINGER, S. G. and EPSTEIN, W. W. (1972) *Tetrahedron Letters* 67.
[14] ROBINSON, R. (1955) *Structural Relations of Natural Products*, p. 14, Clarendon Press, Oxford.
[15] TROST, M. B. and LAROCHELLE, R. (1968) *Tetrahedron Letters* 3327.
[16] TROST, M. B., CONWAY, P. and STANTON, J. (1971) *Chem. Commun.* 1639.
[17] BALDWIN, J. E., HACKLER, R. E. and KELLEY, D. P. (1968) *J. Am. Chem. Soc.* **90**, 4758.
[18] THOMAS, A. F. (1970) *Chem. Commun.* 1054; *ibid.* (1971) *Helv. Chim. Acta* **54**, 1822.

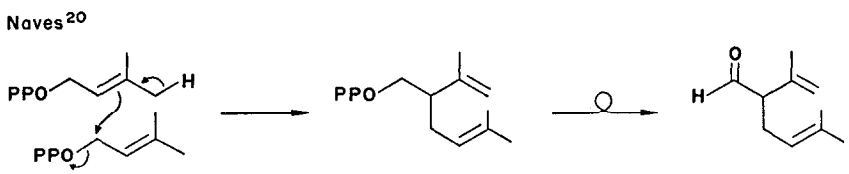
then unusual vinyl cyclopropyl carbon skeleton. Using chemical analogies for the synthesis of cyclopropane systems, Geissman and Crout[19] presented a carbene and a carbonium ion mechanism. The authors pointed out, ". . . the addition of carbenes to olefinic double bonds are well known reactions. Whether they in fact occur in nature is still open to conjecture."



SCHEME 3. PROPOSED ROUTES TO CHRYSANTHEMYL MONOTERPENES.

Routes to Lavandulyl Monoterpenes

Naves[20] has outlined an approach to the lavandulyl monoterpenes which involves the head-to-middle dimerization of two molecules of dimethylallyl pyrophosphate (Scheme 4). As depicted the coupling involves simultaneous loss of pyrophosphate and proton. Crombie *et al.*[11,21] pointed out that rupture of the C_2–C_3 bond of the chrysanthemyl cyclopropane ring (III) will give monoterpenes of the lavandulyl type (IV), although they did not specifically suggest this route as a biosynthetic possibility. For a C_2–C_3 cleavage to occur during a carbonium ion reaction, the 2-methylpropenyl side chain must be functionalized in a manner which permits generation of positive charge at the carbon atom adjacent to C_3.



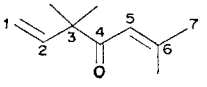
SCHEME 4. POSSIBLE ROUTES TO LAVANDULYL MONOTERPENES.

Labeling Studies

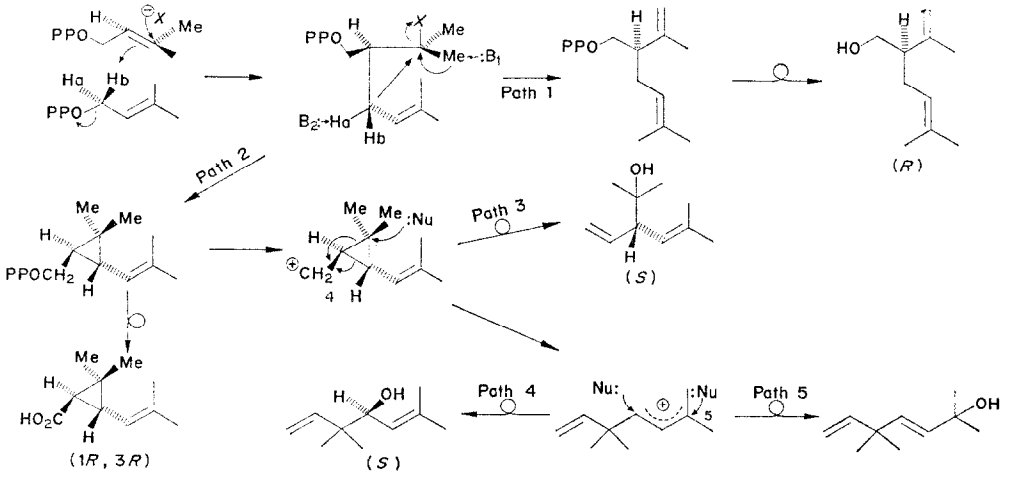
Labeling experiments have been carried out with only three of the compounds listed in Table 1. Biosynthesis of artemisia ketone in *Santolina chamaecyparissus* has been studied

[19] GEISSMAN, T. A. and CROUT, D. H. G. (1969) *Organic Chemistry of Secondary Plant Metabolism*, p. 254, Freeman, Cooper, San Francisco.
[20] NAVES, Y. R. (1960) *Bull. Soc. Chim. Fr.* 1741.
[21] CROMBIE, L., HOUGHTON, R. P. and WOODS, D. K. (1967) *Tetrahedron Letters* 4553.

by two groups. The initial investigation in this area[22] revealed no significant incorporation of [1-^{14}C]acetate or [2-^{14}C]mevalonate in artemisia ketone. It was pointed out by the authors that all of the label could have resided in the less than 1% impurity which accompanied artemisia ketone. Crombie *et al.*[11] also reported no significant incorporations with [1-^{14}C]acetate, [2-^{14}C]mevalonate, [carboxy-^{14}C]chrysanthemate, or [CH_2-^{14}C]chrysanthemyl phosphates. Low incorporations of [2-^{14}C]mevalonate (0·001–0·01%) in artemisia ketone from *Artemisia annua* were found by Banthorpe and Charlwood.[23] In this instance degradation of the ketone suggested an asymmetric incorporation of label in the individual isoprene units with 90% of the activity at C_2 and the geminal dimethyl substituents, and 10% of the activity at C_7 and the methyl group at C_6.



Higher incorporations of [2-^{14}C]mevalonate and [1-^{14}C]acetate (up to 1·4%) were found in chrysanthemic acid and chrysanthemic dicarboxylic acid isolated from *Chrysanthemum cinerariaefolium*.[24] The label was found to be equally distributed between the isobutenyl and the cyclopropyl methyl groups in chrysanthemic acid. In this instance labeled precursors were administered by soaking isolated ovules in a nutrient solution.



SCHEME 5. A UNIFIED APPROACH TO IRREGULAR MONOTERPENE BIOSYNTHESIS.

A Unified Approach to Irregular Monoterpene Biogenesis

An analysis of available data leads to an amalgamation of many of the previously suggested pathways into a unified hypothesis, as depicted in Scheme 5. The initial step requires the dimerization of two molecules of dimethylallyl pyrophosphate as suggested by Naves[20] to give an activated intermediate. This process can be interpreted as similar to

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the well-understood prenyl transfer reactions for aliphatic head-to-tail terpene biosynthesis.[25] Rather than activation of an isopentenyl pyrophosphate by an electron donating X[26] group, we suggest activation of C_2 of dimethylallyl pyrophosphate, and nucleophilic attack at C_1 of a second dimethylallyl pyrophosphate, displacing a pyrophosphate ion, presumably with inversion. The overall reaction would then involve a *trans* addition of one dimethylallyl group and of X to the double bond of a second dimethylallyl moiety.

The second step in prenyl transfer is a *trans* 1,2-elimination of X and an H. By analogy two modes of elimination can be envisioned for the intermediate. Path 1 would require a 1,2-elimination of H and X presumably assisted by a base ($:B_1$) to give lavandulyl pyrophosphate. Attack by $:B_1$ could occur at either methyl group, but labeling studies which would permit this distinction have not been reported. An alternative *trans* 1,3(W)-elimination[27] of H and X would generate chrysanthemyl pyrophosphate which has been suggested to be the precursor of chrysanthemyl, artemisia and santolina carbon skeletons. Although there are two modes of *trans* addition of one DMAPP to another and therefore two of 1,3-elimination, the known absolute configuration of lavandulol and chrysanthemic acid allows only the path shown.

The route to chrysanthemic acid is similar to those outlined for presqualene and prephytoene terpenoids.[2a,b,e] It has been established that presqualene pyrophosphate results from the coupling of two molecules of farnesyl pyrophosphate, the 15-carbon analog of DMAPP.[2b,8]

The proposed route to artemisia and santolina derivatives is thought to proceed by ionization of highly reactive chrysanthemyl pyrophosphate. The (*S*)-santolina system would result from cleavage of the C_1–C_2 cyclopropane bond (Scheme 5). At this juncture several mechanistic routes to oxygenated and olefinic systems are possible. For example hydroxylation of the cyclopropylcarbinyl cation could give (*S*)-santolina alcohol directly as shown in path 3 of Scheme 5. One could argue that artemisia and yomogi alcohols are also derived directly from the cation by appropriate hydroxylations. However, stereochemical considerations argue against this possibility. Nucleophilic attack of the cyclopropylcarbinyl cation to give artemisia alcohol would be predicted to proceed with inversion of configuration*,[28] giving the R absolute configuration at C_3. The rotations of (*S*)-2,2,5-trimethylhexan-3-ol[29] and tetrahydroartemisia alcohol[30] obtained by hydrogenation of artemisia alcohol from natural sources are both negative, suggesting the S absolute configuration for the artemisia system.† To accommodate the presumed absolute configuration of artemisia alcohol and artemisia acetate, we propose that the cyclopropylcarbinyl cation rearranges to an allylic cation which is then stereospecifically attacked (path 4) to give (*S*)-artemisia alcohol. It has been shown that a delicate balance exists between the two cations and therefore, the rearrangement of a vinyl-substituted cyclopropylcarbinyl cation to its allylic isomer is

* For simplicity the cation is represented by a classical, charge-localized structure; however, one should remember that the real structure involves considerable delocalization of positive charge.

† The absolute configurations of naturally occurring artemisia derivatives remain to be conclusively established.

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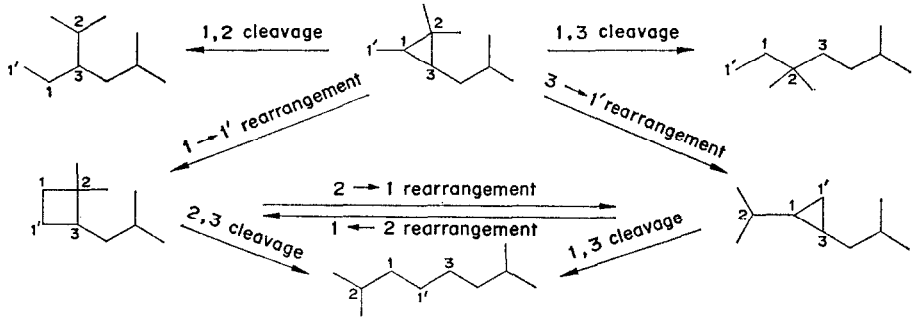
[28] POULTER, C. D., FRIEDRICH, E. C. and WINSTEIN, S. (1970) *J. Am. Chem. Soc.* **92,** 4274; POULTER, C. D. and WINSTEIN, S. (1970) *J. Am. Chem. Soc.* **92,** 4282.
[29] FOLEG, W. M., WELSH, F. J., LACOMBE, E. M. and MOSHER, H. S. (1961) *J. Am. Chem. Soc.* **81,** 2779.
[30] TAKEMOTO, T. and NAKAJIMA, T. (1957) *Yakugaku Zasshi* **77,** 1307, 1310.

quite plausible.[13] Yomogi alcohol could result from hydroxylation of the allylic cation as outlined by path 5. The *trans* double bond geometry in naturally occurring yomogi alcohol was also obtained exclusively during *in vitro* studies by normal solvolysis techniques.[13]

Of the four irregular carbon systems, the chrysanthemyl, artemisyl, and santolinyl types are found exclusively in closely related members of the Compositae family. The notable exception is the lavandulyl system, found in the Labiatae and Umbelliferae families. The above observations as well as mechanistic considerations suggest that the lavandulyl skeleton is derived directly by coupling of two molecules of DMAPP and prior to 1,3-elimination, in contrast to the suggestion that lavandulyl derivatives could be produced by an abnormal cleavage of the chrysanthemyl cyclopropane ring.[11,21]

From the preceding discussion it can be seen that the overall stereochemistry for the biosynthesis of irregular monoterpenes should be an important part of any proposed biogenetic sequence. The stereochemistry shown in Scheme 5 is developed on the basis of the known absolute configurations of chrysanthemic acid, chrysanthemic dicarboxylic acid, santolinyl alcohol and lavandulol, whose asymmetry can be related to C_1 and C_3 of chrysanthemic acid. If the hypothesis is correct, there are two major stereochemical consequences. Only one of two possible enantiomers would be expected for most of the optically active non-head-to-tail monoterpenes. The available evidence shows this to be true.* All of the irregular monoterpenes in Table 1 of known absolute configuration belong to the same enantiomeric series and are optically pure.



SCHEME 6. ROUTES TO NON-HEAD-TO-TAIL CARBON SKELETONS BY RING CLEAVAGE AND REARRANGEMENT.

If indeed the biosynthesis of some irregular monoterpenes proceeds as outlined in Scheme 5, then one could anticipate that carbon skeletons other than those already reported might occur naturally, as depicted in Scheme 6. Of the seven possible primary carbon skeletons, four already have been found in various states of oxidation. One test of the ideas presented would be to search for examples of the three remaining systems in various plant sources known to have non-head-to-tail terpenes, particularly Compositae. It is surprising that 10-carbon analogs of the important triterpene squalene have not been observed. Since chrysanthemyl pyrophosphate is postulated as a key intermediate, it is likely that the corresponding alcohol might also occur naturally.

If a unified biosynthetic pathway exists for irregular monoterpenes analogous to higher irregular terpenoids, a dichotomy is apparent in the labeling results involving artemisia

* Both enantiometers of many head-to-tail monoterpenes are known to occur naturally, and it is possible that dual enantiomeric pathways may also exist for non-head-to-tail monoterpenes.

ketone and chrysanthemic acid. If two molecules of dimethylallyl pyrophosphate are involved, label should be evenly distributed between the two 5-carbon isoprene units. This is in agreement with the work with chrysanthemic acid but is inconsistent with the labeling pattern in artemisia ketone. The development of experimental techniques which give better incorporations of labeled precursors must be developed before these inconsistencies can be resolved. Work with plant tissue cultures or cell-free enzyme systems offers potential long-range solutions.

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