which in large measure are dictated by the size and shape of the sieves and their supporting network, i.e., HZSM5.[38]

## Summary

Several tools have been developed which are useful in diagnosing the relative utility of very strong acids (often called superacids) as catalysts, as well as the relative ability of solid acids to support carbonium ion processes.

The ability of strong acids to stabilize carbonium ions which isomerize rather than deprotonate is one measure of their usefulness. Another lies in their capacity to stabilize relatively unsolvated carbonium ions. The latter can be assessed when hydride-transfer equilibria can be measured or estimated. This has been done for equilibria involving adamantyl and *tert*-butyl ions.

The freedom of intermediates participating in acid catalyzed reactions on solids can also be probed by determining the way by which they partition themselves into different reaction channels. Paths requiring the development of an increasing amount of carbonium-ion-like character appear to be preferentially aided as catalyst activity and probably acidity increase. These considerations have been used to establish the relative rates of converting an olefin into a methyl shifted and a double bond shifted product as an important characterizing selectivity parameter for solid acids.

(38) Argauer, R. J.; Landolt, R. G. U.S. Patent 3 702 886. Chang, C. D.; Lang, W. H.; Silvestri, A. J. U.S. Patent 3 894 106. Butter, S. A., Kaeding, W. W.; Jurewicz, A. T. U.S. Patent 3 894 107. Chang, C. D., Silvestri, A. J.; Smith R. U.S. Patent 3 928 483.

# Naturally Occurring Cyclohexene Oxides

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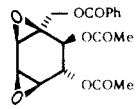
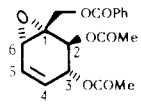
Cyclohexene oxides are a small group of natural products which have aroused widespread interest amongst natural product and synthetic chemists in the last 10 years owing to their unusual structures, biogenesis, and biological activity.




1

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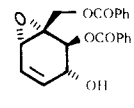
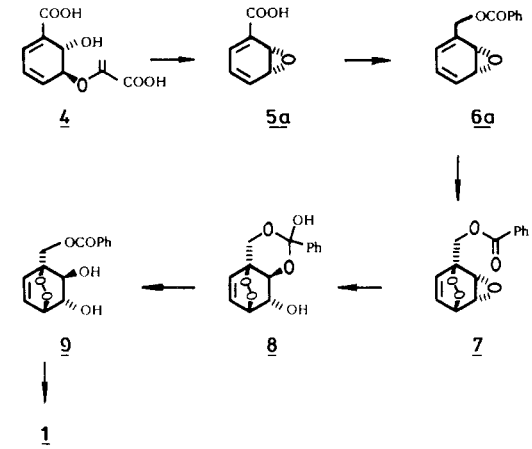


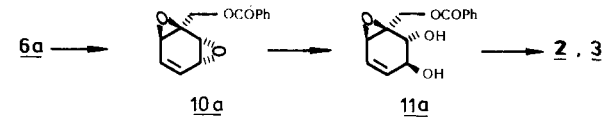

3

Crotepoxide 1, senepoxide 2, and pipoxide 3 were discovered during the period between 1968–1970 from *Croton macrostachys*,[1,2] *Uvaria catocarpa*,[3] and *Piper hookeri*,[4] respectively. Due to the report by the late Professor Kupchan that crotepoxide (1) has a significant inhibitory activity against Lewis lung carcinoma in mice, the compound has become very well-known and is thus responsible for generating interest in this field. Consequently, in the following years the chemical community saw several syntheses of crotepoxide[5–7] and senepoxide,[8–11] including, also, the proposal of a biogenetic pathway to this family of compounds.[12] However, it was to be another decade before new members of the family were discovered which clarified their biogenesis.

**Scheme I**




**Scheme II**




In the meantime the absolute stereostructures of crotepoxide (1), and subsequently of senepoxide (2), were conclusively established by X-ray crystallography.[13,14] The stereostructure of pipoxide (3) was also proposed,[4] albeit based on that of senepoxide (2), which was later proved to be incorrect.

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Yodhathai Thebtaranonth was born in 1943 in Bangkok, Thailand. He received his B.Sc. and M.Sc. degrees from the University of Medical Sciences, Bangkok, and his Ph.D. degree from Sheffield University, where he worked under Professor W. D. Ollis, F.R.S. In 1975 he spent a year at Cornell University doing postdoctoral work with Professor M. F. Semmelhack. He is now Associate Professor at Mahidol University. His research interests lie mainly in natural products and synthetic chemistry.

(1) S. M. Kupchan, R. J. Hemingway, P. Coggon, A. T. McPhail, G. A. Sim, *J. Am. Chem. Soc.* **1968**, *90*, 2982.
(2) S. M. Kupchan, R. J. Hemingway, R. M. Smith, *J. Org. Chem.* **1969**, *34*, 3898.
(3) R. Hollands, D. Becher, A. Gaudemer, J. Polonsky, *Tetrahedron* **1968**, *24*, 1633.

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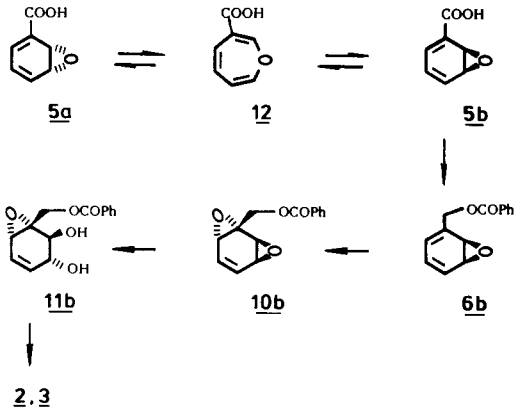
**Scheme III**




At about this time Professor Ganem put forward an ingenious scheme to rationalize the biogenetic pathway to these cyclohexene oxides (Scheme I).[12] Starting from (−)-(2*S*,3*S*)-isochorismic acid (**4**)[15] Ganem suggested that the arene oxide **5a** is formed by an intramolecular $S_N2$ displacement of the enol pyruvate by the adjacent hydroxy group and then undergoes enzymatic reduction to an alcohol followed by acylation to give **6a**. Subsequent photooxygenation of the diene **6a** to the endoperoxide **7** was envisaged, followed by epoxide ring opening with anchimeric assistance from the neighboring benzoate carbonyl to yield **9** via the hemiorthoester **8**. Acetylation and rearrangement of the endoperoxide function in **9** finally completed the biogenetic scheme to give rise to crotepoxide (**1**). The biogeneses of senepoxide (**2**) and pipoxide (**3**) were also conveniently explained via intermediate **6a** (Scheme II). Thus, proposed epoxidation at the reactive 1,6-double bond of the arene oxide **6a** to afford **10a**, followed by selective epoxide ring opening and acylation of the resulting alcohol finally led to **2** and **3**.

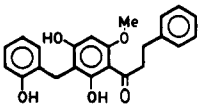
One drawback of this proposal, as pointed out by Ganem himself, was that the scheme resulted in **2** and **3** having the opposite configuration to that found in nature, unless, of course, the plant produced the antipodal (2*R*,3*R*)-isochorismate.

This led Ganem[16] to consider the possibility of arene oxide isomerization (**5a** ⇄ **5b**), a conversion that can be easily envisaged via the oxepin intermediate **12** (Scheme III). According to the scheme, senepoxide (**2**) and pipoxide (**3**) with the "correct" absolute configuration would result from the enantiomeric arene oxide **5b**. Despite this problem the idea of the arene oxide **6** as the common precursor in the biogenesis of these natural products remained very attractive and viable.

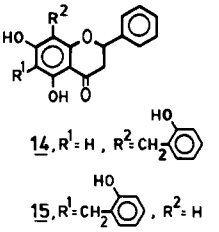
To support his proposal Ganem also performed various biomimetic transformations in his laboratory, including the total synthesis of (±)-senepoxide (**2**) from **6**.[9,10,17]

## Recent Developments

After a lapse of almost 10 years during which no new addition was made to the known family of three cyclohexene oxides, research in this area suddenly took a new leap not long after the discovery of the biologically active (*o*-hydroxybenzyl)dihydrochalcone (uvaretin) (**13**) in *Uvaria acuminata*[18] and flavanones (chamanetin and isochamanetin) (**14** and **15**) in *U. chamae*[19] by two independent groups in 1976, which triggered

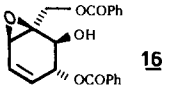



**13**




intensive chemical investigation of plants in the *Uvaria* genus and led to the isolation of a large number of cyclohexene oxides and related metabolites, besides several other types of compounds (i.e., alkaloids,[20,21] aromatic compounds,[22] and oxygen heterocycles[23] including those derived from syncarpic acid[24]). In retrospect it was no mere coincidence, therefore, that senepoxide (**2**) was isolated from *U. catocarpa* in the first systematic investigation of the *Uvaria* plant made in 1968.

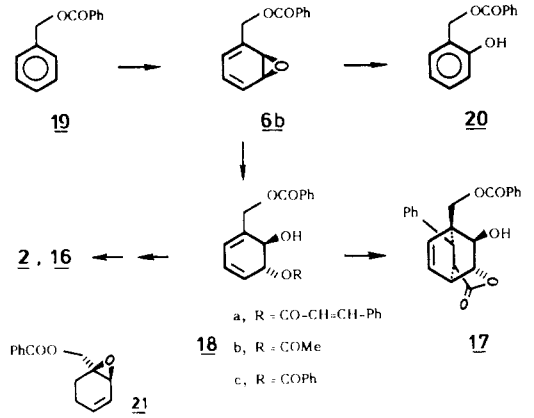
A significant observation was made in 1979 when a collaborative program between American and Thai chemists resulted in the isolation of a large amount of a compound from *U. purpurea*, which was found to be identical with the known pipoxide (**3**) but with an NMR spectrum that was inconsistent with the relative stereochemistry and position of the secondary benzoate group as depicted in pipoxide (**3**). A comparison of the $H_2$–$H_3$ coupling constant in the NMR spectrum of pipoxide (8 Hz, diaxial hydrogens) with that of senepoxide (**2**) (2.5 Hz) suggested that the orientations of the $C_2$, $C_3$ substituents were different in these two compounds, which would be the case if the stereochemistry of the epoxide rings were different in these two molecules (crotepoxide's $H_2$–$H_3$ coupling constant is 9 Hz). Total synthesis and X-ray crystallography were finally employed to resolve the structure of pipoxide,[25] and the revised or correct structure of pipoxide is now established as **16**.




**16**

(4) J. Singh, K. L. Dhar, C. K. Atal, *Tetrahedron*, **1970**, *26*, 4403.
(5) K. Oda, A. Ichihara, S. Sakamura, *Tetrahedron Lett.* **1975**, 3187.
(6) M. R. Demuth, P. E. Garrett, J. D. White, *J. Am. Chem. Soc.* **1976**, *98*, 634.
(7) M. Matsumoto, S. Dobashi, K. Kuroda, *Tetrahedron Lett.* **1977**, 3361.
(8) A. Ichihara, K. Oda, M. Kobayashi, S. Sakamura, *Tetrahedron Lett.* **1974**, *4235*.
(9) G. W. Holbert, B. Ganem, *J. Am. Chem. Soc.* **1978**, *100*, 352.
(10) B. Ganem, G. W. Holbert, L. B. Weiss, K. Ishizumi, *J. Am. Chem. Soc.* **1978**, *100*, 6483.
(11) A. Ishihara, K. Oda, M. Kobayashi, S. Sakamura, *Tetrahedron* **1980**, *36*, 183.
(12) B. Ganem, G. W. Holbert, *Bioorg. Chem.* **1977**, *6*, 393.
(13) P. Coggon, A. T. McPhail, G. A. Sim, *J. Chem. Soc. B* **1969**, 534.
(14) A. Ducruix, C. Pascard, J. Polonsky, *Acta Crystallogr., Sect. B* **1976**, *32*, 1589.
(15) I. G. Young, T. J. Batterham, F. Gibson, *Biochim. Biophys. Acta* **1969**, 177, 389.
(16) B. Ganem, *Tetrahedron* **1978**, *34*, 3353.
(17) G. W. Holbert, L. B. Weiss, B. Ganem, *Tetrahedron Lett.* **1976**, 4435.
(18) J. R. Cole, S. J. Torrance, R. M. Wiedhopf, S. K. Arora, R. B. Bates, *J. Org. Chem.* **1976**, *41*, 1852.
(19) C. D. Hufford, W. L. Lasswell, Jr., *J. Org. Chem.* **1976**, *41*, 1297.
(20) K. Panichpol, R. D. Waigh, P. G. Waterman, *Phytochemistry* **1977**, *16*, 621.
(21) H. Achenbach, B. Raffelsberger, *Tetrahedron Lett.* **1979**, 2571.
(22) W. L. Lasswell, Jr., C. D. Hufford, *Phytochemistry* **1977**, *16*, 1439.
(23) C. D. Hufford, B. O. Oguntimein, D. V. Engen, D. Muthard, J. Clardy, *J. Am. Chem. Soc.* **1980**, *102*, 7365.
(24) C. D. Hufford, B. O. Oguntimein, J. K. Baker, *J. Org. Chem.* **1981**, *46*, 3073.
(25) G. W. Holbert, B. Ganem, D. V. Engen, L. Borsub, K. Chantrapromma, C. Sadavongvivad, Y. Thebtaranonth, *Tetrahedron Lett.* **1979**, 715.

**Scheme IV**



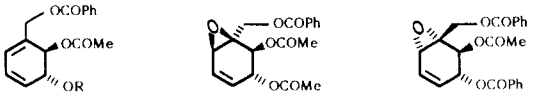

Shortly afterwards pipoxide was also studied by an Indian–Swiss group[26] who employed high-resolution NMR techniques and eventually confirmed the revised structure **16**.

In 1981 investigation of *U. zeylanica* by the Cole and Bates group resulted in the discovery of a new and very interesting compound, zeylena (**17**).[27] A close examination of **17** pointed to its formation by an intramolecular Diels–Alder reaction from the diene precursor **18a**, which, in turn, could have resulted from epoxide ring opening of the arene oxide **6b** by cinnamic acid. The isolation of **17** stimulated Cole and Bates to map out a simple yet very attractive biogenetic pathway to the cyclohexene oxides (Scheme IV), via the same arene oxide precursor proposed by Ganem.[12] According to this scheme benzyl benzoate **19** is epoxidized to the arene oxide intermediate **6b** which can then add cinnamic acid, acetic acid, or benzoic acid, to give, respectively, the dienes **18a**, **18b**, or **18c**. Subsequent acetylation and further epoxidation of **18b** would yield senepoxide (**2**). In the same way the formation of pipoxide **16** can be similarly explained. On the other hand, **18a** can undergo an intramolecular cycloaddition reaction to give rise to **17**. Cole and Bates not only used their biogenetic scheme to explain the biogenesis of cyclohexene oxides but also to explain the origin of the *o*-hydroxybenzyl group in uvaretin (**13**), chamanetin (**14**), and isochamanetin (**15**), all of which have been found in plants of the *Uvaria* genus. Here the arene oxide **6b** is perceived to easily rearrange to *o*-hydroxybenzyl benzoate **20**, thus providing the plants with a pool of *o*-hydroxybenzyl groups.

Although the arene oxide **6** was postulated as the key metabolic intermediate in both the biogenetic routes that were proposed by Ganem[12] (Scheme I) and by Cole and Bates[27] (Scheme IV), the two schemes differed considerably in their concepts of formation and subsequent transformations of this key intermediate. Ganem speculated that the arene oxide **6** resulted from isochorismic acid (**4**) while Cole and Bates postulated direct epoxidation of benzyl benzoate **19** to give **6b**. The latter then proposed direct epoxide ring opening to give the diene intermediate **18**. In fact an alternative route to the diene involving conjugate addition to the arene oxide **21** was also considered but thought to be less likely.[28] The isolation of zeylena (**17**) clearly indicated derivation from the diene **18a**, hence it was only logical to propose that senepoxide (**2**) and pipoxide **16** should also arise from this same type of intermediate, the dienes **18b** and **18c**, respectively, and not from the diepoxide **10** as formerly proposed by Ganem (Schemes II and III).

Cole and Bates' biogenetic route appeared attractive, simple, and highly feasible. However, up until that time there had been no report on the isolation of the key intermediate (the "missing link") diene **18** from nature, even though its stability was expected to be far greater than that of the arene oxide **6**.

It was not until 1982 that further investigation of plants in the *Uvaria* genus finally provided convincing evidence for the Cole and Bates biogenetic pathway. The first missing link diene **18c** [mp 90–91 °C; $[\alpha^{25}_D$ −276° (*c* 0.145, $CHCl_3$)] was discovered in the roots of *U. purpurea*,[29] whereas the dienes **22** and **23** together with their oxidized products senepoxide **2**,[30] β-senepoxide (**24**), and tingtanoxide (**25**) were isolated from the roots of *U. ferruginea* in the following year.[31] It should be noted that **24** is, in fact, the epoxide stereoisomer of the well-known senepoxide **2**, here arbitrarily assigned as α-senepoxide; hence **24** becomes β-senepoxide.




The absolute stereochemistry of these compounds was determined by chemical correlations with natural products of known absolute configurations as briefly outlined below.

The diene **18c** was converted to pipoxide **16** by direct epoxidation (synthetic **16**, $[\alpha^{20}_D$ +36.3°; natural, $[\alpha^{20}_D$ +37.9°).[29] Acetylation of **18c** afforded the diene **23** (synthetic **23**, $[\alpha^{28}_D$ −285°; natural, $[\alpha]^{28}_D$ −298°).[31] Epoxidation of the diene **22** isolated from *U. ferruginea* yielded α-senepoxide (**2**) (synthetic **2**, $[\alpha]^{28}_D$ −185°; natural, $[\alpha]^{?}_D$ −197°)[3,30] and β-senepoxide (**24**) (synthetic **24**, $[\alpha]^{28}_D$ +60°; natural, $[\alpha]^{25}_D$ +62°).[31,32] A similar reaction of the natural diene **23** gave tingtanoxide (**25**) (synthetic **25**, $[\alpha]^{27}_D$ −221°; natural, $[\alpha]^{28}_D$ −306°) and pipoxide acetate **26** ($[\alpha]^{28}_D$ + 9°).[31,32]

A close examination of the natural products from *U. purpurea* (**16** and **18c**) and from *U. ferruginea* (**2** and **22–25**) revealed that they all possessed the same absolute configuration at $C_2$ and $C_3$, which is strongly indicative of a common origin, possibly the arene oxide **6b**. However, the varying stereochemistry of the epoxide ring at $C_1$–$C_6$, and especially the cooccurrence of α- and β-senepoxide (**2**) and **24**, indicates that at least the last epoxidation step (of the diene **18**) in the biosynthesis of these compounds must be nonstereospe-

(26) B. S. Joshi, D. H. Gawad, H. Fuhrer, *Tetrahedron Lett.* **1979**, 2427.

(27) S. D. Jolad, J. J. Hoffmann, K. H. Schram, J. R. Cole, M. S. Tempesta, R. B. Bates, *J. Org. Chem.* **1981**, *46*, 4267. Zeylena **17** has also been isolated from *U. purpurea*: M. Kodpinid, C. Thebtaranonth, Y. Thebtaranonth, unpublished results. We are grateful to Professor R. B. Bates for the comparison of zeylena samples.

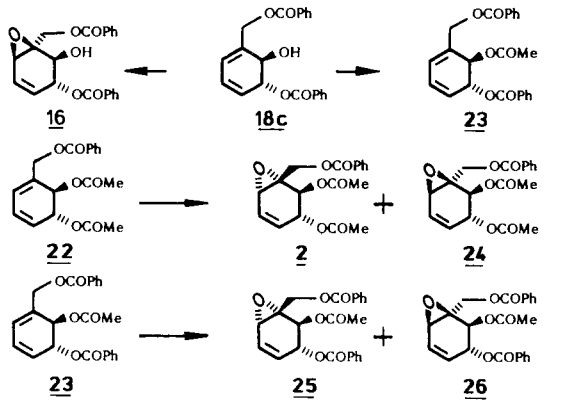
(28) See ref 3 in 27.

(29) G. R. Schulte, M. Kodpinid, C. Thebtaranonth, Y. Thebtaranonth, *Tetrahedron Lett.* **1982**, *23*, 4303.

(30) α-Senepoxide from *U. ferruginea* ($[\alpha^{28}_D$ −192.5°) is identical in all respects with that reported.[3]

(31) M. Kodpinid, C. Sadawongvivad, C. Thebtaranonth, Y. Thebtaranonth, *Tetrahedron Lett.* **1983**, *24*, 2019.

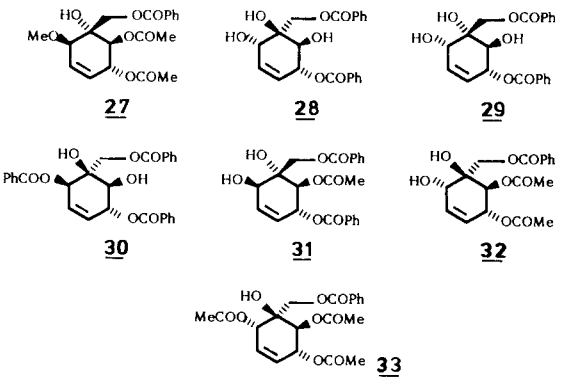
(32) The 4,5-epoxide has also been isolated.



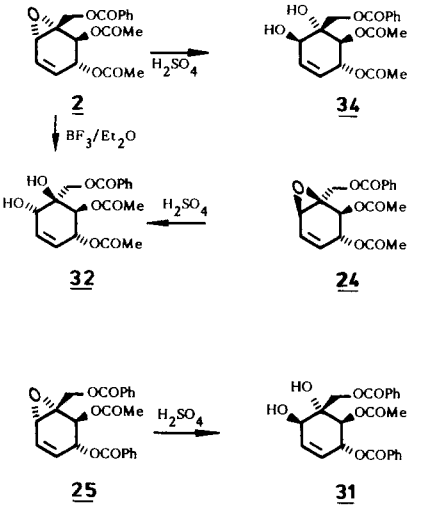
cific, making possible at once the formation of both α- and β-epoxides. The coisolation of these dienes and their oxidized products from the same plant is thus highly significant in providing the missing evidence for the proposed biogenetic pathway shown in Scheme IV.

## Metabolites of Cyclohexene Oxides

In the initial investigation of the *Uvaria* genus, the French group[3] not only isolated α-senepoxide (**2**) from *U. catocarpa* but also reported the identification of its metabolite, seneol (**27**). The structure of **27** infers methanolysis of the epoxide ring in α-senepoxide (**2**). Later work on other *Uvaria* plants has yielded several more such metabolites, viz: zeylenol (**28**) and epizeylenol (**29**) from the roots of *U. zeylanica*,[27,33,34] ferrudiol (**30**) from the leaves of *U. ferruginea*,[35] and metabolites of tingtanoxide and β-senepoxide and the alcohols **31–33**, from the roots of *U. ferruginea*.[36]

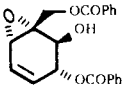


Although the identification of **28–30** rested mostly on NMR techniques, chemical correlations, on the other hand, played a major role in the determination of the stereochemical structures of **31–33**. Thus it was shown that the diol **31** can be formed from acid hydrolysis of natural tingtanoxide (**25**), while the diol **32** can be obtained from the reaction of β-senepoxide (**24**) with sulfuric acid. Despite the fact that the diol **32** was not a known natural product prior to its isolation from *U. ferruginea*, it had been synthesized by Holland's group[3] by a simple chemical transformation of its precursor. In their study it was shown that hydrolysis of α-senepoxide (**2**) with 4 N sulfuric acid yielded **34**, but treatment of **2** with $BF_3/Et_2O$ gave rise to the diol **32** as a result of a different mode of epoxide ring opening.[3] Acetylation ($MeCOCl/NEt_3$) of **32** simply gave the triacetate **33**.[36]



The results of these chemical transformations firmly established the structures and stereochemistry of the metabolites **31–33**.

Certain conclusions that can be drawn from the work on the *Uvaria* metabolites deserve special mention. First of all, from specially controlled isolation procedures it can be concluded that diols **31–33** are not artifacts,[36] which is to say that opening of the epoxide rings to yield **27–33** occurred within the plants and not during the extraction and purification procedures. Second, as mentioned above, it can be concluded from the varying stereochemistry of the epoxide rings and from the cooccurrence of the α- and β-cyclohexene oxide isomers, that the biosynthetic oxidation of diene **18** to cyclohexene oxide is not stereospecific. Third, studies on in vitro cyclohexene oxide ring openings have shown that at this stage it is not yet possible to discern whether or not the related cyclohexene oxides (e.g., **16** and **35**) are biogenetic precursors of the cis diols (epizeylenol (**29**) and ferrudiol (**30**)). More information will be required before the biogenetic process to give the 1,6-cis disubstitution pattern on the cyclohexene nucleus can be clearly understood.



## Benzyl Benzoates and *o*-Hydroxybenzyl-Containing Compounds

The proposed biogenetic pathway to cyclohexene oxides as shown in Scheme IV postulates an enzymatic epoxidation of benzyl benzoate to the arene oxide **6b**, which can then either undergo a nucleophilic epoxide ring opening to the diene **18** or rearrange to *o*-hydroxybenzyl benzoate **20**.[27] The scheme further extends to evoke **20** as the common source of the *o*-hydroxybenzyl grouping(s) present in the various compounds found in plants of the *Uvaria* genus. Indeed, investigations of several such plants have provided valuable data in support of this biogenetic scheme. Altogether, nine benzyl benzoates, **19** and **36–43**, have been isolated from *U. purpurea* and *U. ferruginea*,[37,38]

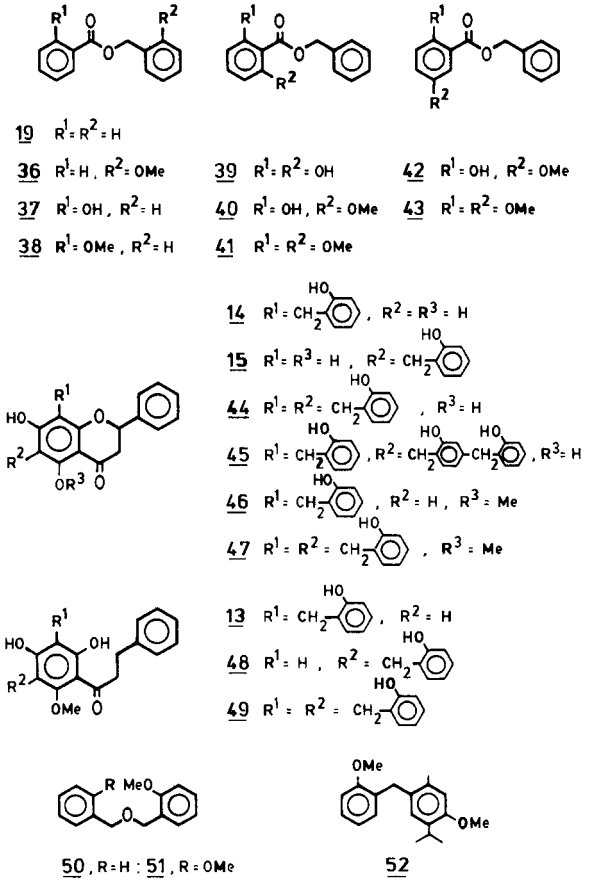
(33) S. D. Jolad, J. J. Hoffmann, J. R. Cole, M. S. Tempesta, R. B. Bates, *Phytochemistry* **1984**, *23*, 935.

(34) 1-Epizeylenol is also found in the roots of *U. purpurea*: M. Kodpinid, C. Thebtaranonth, Y. Thebtaranonth, unpublished work. See ref 33.

(35) G. R. Schulte, B. Ganem, K. Chantrapromma, M. Kodpinid, K. Sudsuansri, *Tetrahedron Lett.* **1982**, *23*, 289.

(36) M. Kodpinid, Ph.D. Thesis, Mahidol University, Bangkok, Thailand, 1984.

while C-benzylated flavanones **14**, **15**, and **44–47** and dihydrochalcones **13**, **48**, and **49** have been found as constituents of *U. chamae*,[19,39–42] *U. acuminata*,[18] *U. ferruginea*,[38] and *U.* Angolensis.[43] Interestingly, some

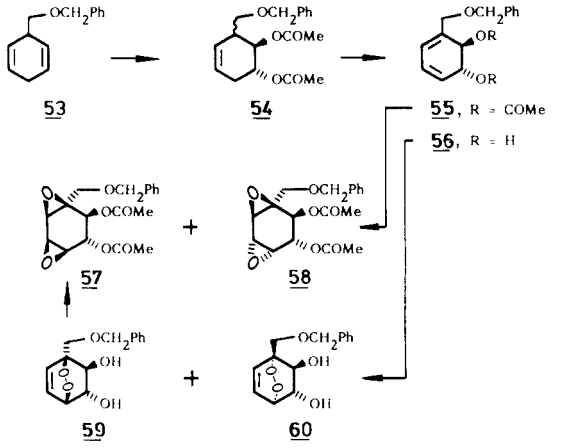



of these *o*-hydroxybenzyl flavanones and dihydrochalcones are not only active in vivo against P-388 lymphocytic leukemia but also display strong antimicrobial activity.[44] Other compounds bearing the *o*-hydroxybenzyl group which have also been isolated include the benzyl ethers **50** and **51** and the monoterpene, chamanen (**52**).[22] The coisolation of several different types of *o*-hydroxybenzyl compounds from *U. ferruginea* certainly makes it seem highly probable that the *o*-hydroxybenzyl moiety in all the compounds mentioned here have their origin in the same precursor.

## Synthesis of Cyclohexene Oxides

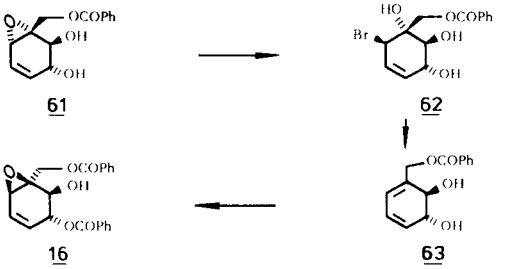
A brief review of earlier work on the synthesis of cyclohexene oxides has already appeared as part of a report on the development of natural products from the shikimate pathway.[16] This includes total syntheses of crotepoxide (**1**) by Ichihara,[5] White,[6] and Matsumoto,[7] those of $\alpha$-senepoxide (**2**) by Ichihara[8,11] and Ganem,[9,10] and, perhaps most adventurous of all, the preparation of the surprisingly stable arene oxide **6** by Ganem, who also successfully converted **6** to $\alpha$-senepoxide (**2**) and seneol (**27**).[9,10]

Later work has shown that the most convenient entry to cyclohexene oxides is by a biomimetic synthesis via the dienes, e.g., **18**, **22**, or **23**. This approach was originally explored by White,[6] whose synthesis of crotepoxide (**1**) involved the preparation of dienes **55** and **56** as follows: monoepoxidation of the dihydrobenzene **53** followed by treatment of the resulting epoxide with acetic anhydride produced the trans diacetate **54** as a mixture of two diastereomers; bromination and subsequent dehydrohalogenation of **54** gave a single diene **55**, which, upon epoxidation under forcing conditions yielded the cis and trans dioxides **57** and **58** in a ratio of 1:8; finally, hydrogenolysis and subsequent benzoylation of the cis dioxide **57** gave the required crotepoxide (**1**).




An alternative route to **57** involved singlet oxygen photooxygenation of the diol **56** (obtained from LAH reduction of **55**), which yielded the endoperoxides **59** and **60** in a ratio of 1:1, the diacetate **55** being surprisingly unreactive under these conditions. Acetylation of **59** followed by thermal rearrangement of the resulting endoperoxide diacetate eventually furnished the crotepoxide precursor **57**.

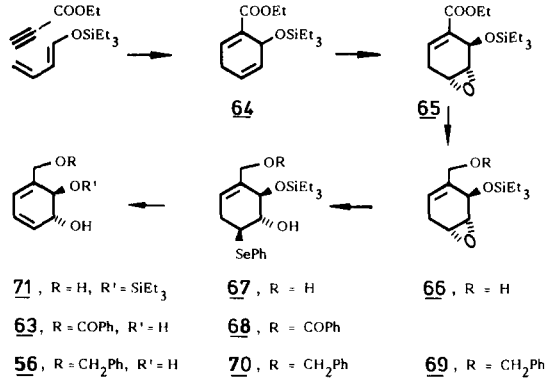
The timely synthesis of pipoxide **16** by Ganem in 1979 served to unambiguously confirm its newly revised structure.[25] Employing the epoxy diol **61**[9] as the starting material, it was first converted to the bromohydrin **62** and then treated with zinc in acetic acid to yield the diene **63**. Regiospecific and stereospecific monoepoxidation of **63** at the trisubstituted double bond followed by monobenzoylation subsequently afforded pipoxide **16**.




Diene diols **56** and **63** have recently been prepared by Schlessinger[45] who used the regiospecific Diels–Alder addition approach. The reaction of 1-(triethylsiloxy)-buta-1,3-diene with ethyl propiolate gave a good yield

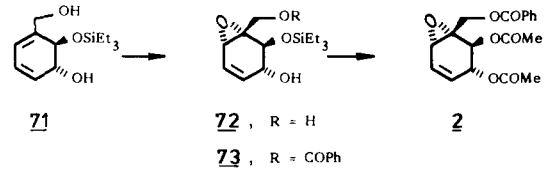
(37) M. Kodpinid, C. Sadavongvivad, C. Thebtaranonth, Y. Thebtaranonth, *Phytochemistry* **1984**, *23*, 199.
(38) M. Kodpinid, C. Thebtaranonth, Y. Thebtaranonth, *Phytochemistry* **1985**, *24*, 3071.
(39) W. L. Lasswell, Jr., C. D. Hufford, *J. Org. Chem.* **1977**, *42*, 1295.
(40) C. D. Hufford, W. L. Lasswell, Jr., *Lloydia* **1978**, *41*, 151.
(41) C. D. Hufford, W. L. Lasswell, Jr., K. Hirotsu, J. Clardy, *J. Org. Chem.* **1979**, *44*, 4709.
(42) H. N. El-Sohly, W. L. Lasswell, Jr., C. D. Hufford, *J. Nat. Prod.* **1979**, *42*, 264.
(43) C. D. Hufford, B. O. Oguntimein, *Phytochemistry* **1980**, *19*, 2036.
(44) C. D. Hufford, W. L. Lasswell, Jr., Lloydia **1978**, *41*, 156.
(45) R. H. Schlessinger, A. Lopes, *J. Org. Chem.* **1981**, *46*, 5252.

of the hexa-1,4-diene **64**, which upon monoepoxidation gave **65** together with a small amount of the corresponding β-isomer. Reduction of the ester side chain



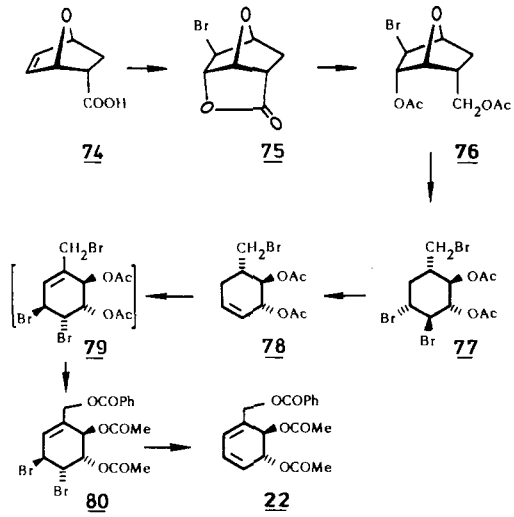
and removal of the contaminating β-isomer led to pure **66**, from which regiospecific ring opening of the epoxide residue by sodium phenyl selenide afforded **67**. Subsequent benzoylation of **67** at the primary alcohol site followed by oxidative elimination of the phenyl selenide group and finally disilylation eventually furnished the diene diol **63**. In an analogous manner diene **56** was prepared by first converting **66** into its benzyl ether **69** and then subjecting the ether to consecutive ring opening, elimination, and desilylation reactions.

Having accomplished the formal synthesis of crotepoxide (**1**) and pipoxide **16** via the dienes **56** and **63**, Schlessinger then proceeded to the total synthesis of racemic α-senepoxide (**2**). Here he took advantage of the bulky triethylsiloxy group to control the stereochemistry of the epoxidation reaction. Thus oxidation of the triethylsiloxy diene diol **71** with 95% *m*-CPBA in methylene chloride at −40 °C gave the α-epoxide **72** in 77% yield. Subsequent esterification of the primary alcohol function in **72** with benzoyl chloride yielded **73**, which, after desilylation followed by exhaustive acetylation finally gave α-senepoxide **2**.



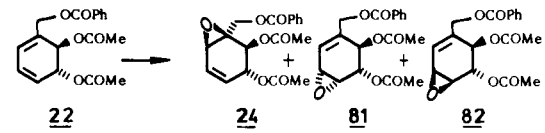
The most recent cyclohexene oxide synthesis is the report by Ogawa who prepared optically active pipoxide **16**, β-senepoxide **24**, and dienes **18c**, **22**, and **23**.[46] As a result of extensive synthetic work on multisubstituted cyclohexane derivatives[47-50] the Japanese group has developed an attractive method for the preparation of optically active diene **22** from optically active furan–acrylic acid cycloadduct **74**, as outlined below.

Bromolactonization of **74** gave the bromo lactone **75**, which after reduction with LAH followed by acetylation afforded the bromo diacetate **76**.[47] Cleavage of the oxygen bridge in **76** with HBr in acetic acid gave the tribromide **77** which could be debrominated to **78** with zinc dust. Interestingly, treatment of this bromo

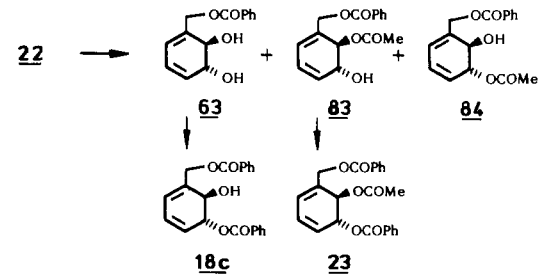


acetate **78** with *N*-bromosuccinimide in carbon tetrachloride in the presence of α,α-azobisisobutyronitrile yielded the tribromide **79**, which the authors then converted to the benzoate **80** without further purification. The conversion of **78** to **79** is believed to proceed via initial allylic bromination to an intermediate diene, which subsequently reacted with the bromine generated in situ.[46] The required diene **22** was finally obtained by treatment of **80** with zinc dust.

Having prepared the optically active diene **22**, Ogawa then subjected it to epoxidation with *m*-CPBA and obtained β-senepoxide (**24**) together with its isomers **81** and **82** in 19%, 24%, and 14% yields, respectively.



On the other hand, treatment of **22** with *p*-toluenesulfonic acid in methanol at room temperature effected deacetylation and gave the diol **63** together with the monoacetate **83**, with only a trace amount of **84**. Monobenzoylation of **63** yielded the optically active diene **18c**, which could be converted to pipoxide **16**.[29] Moreover, benzoylation of **83** yielded the diene **23** which is the precursor of tingtanoxide (**25**).[31]



## Conclusion

Although the first three cyclohexene oxides **1**, **2**, and **16** were found scattered in plants of different families, later work has discovered that a rich source of this class of compounds can be found in the *Uvaria* genus. Interestingly, although crotepoxide (**1**) is distributed in many plants, namely, *Croton macrostachys*,[12] *Piper attenuatum*,[26] *Piper galeatum*,[26] *Piper hookeri*,[26] and *Piper futokadzura*,[51] and *Boesenbergia sp.* (Zingibera-

(46) S. Ogawa, T. Takagaki, *J. Org. Chem.* **1985**, *50*, 2356.
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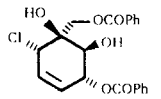
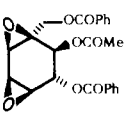
ceae),[52] neither this compound nor any of its relatives (bearing the cis diepoxide structure) has been found in the *Uvaria* plant. This has raised the suspicion that despite their rich pool of benzyl benzoates (e.g., **36–43**) and dienes (e.g. **18**), the *Uvaria* plants probably lack the biological means to synthesize the cis diepoxides. The possibility that these mono- and diepoxides should arise from different biogenetic pathways is considered unlikely since it has been established that crotepoxide (**1**), α-senepoxide (**2**), pipoxide **16**, zeylenol (**28**), and ferrudiol (**30**) all have identical 2*S*,3*R* absolute configurations, a fact highly suggestive of a unified biosynthesis via a common key intermediate, the diene **18**.[53] Results from the study of *Piper hookeri*, from which crotepoxide (**1**), pipoxide **16**, and pipoxide chlorohydrin **85** have been isolated,[26] lend further support to these deductions.

Deserving special mention among the *Uvaria* species is *Uvaria ferruginea* which was collected from northeastern Thailand. With the exception of the arene oxide **6b**, all of the compounds postulated in Scheme IV[27] have been isolated from this plant. These are the benzyl benzoates (**19** and **37**),[38] the *o*-(hydroxybenzyl)flavanones (**14** and **46**),[38] the missing link dienes (**22** and **23**),[31] and the cyclohexene oxides (**2**, **24**, and **25**)[31] as well as their various metabolites (**30–33**).[35,36] These findings have put the Cole and Bates biogenetic pathway (Scheme IV) on firm ground.

Last of all it might be mentioned that the latest addition (unpublished) to the family of naturally occurring cyclohexene oxides is a new cyclohexene diepoxide, boesenoxide **86**, from *Boesenbergia sp.* (Zingibereceae) from Thailand.[54]




**85**




**86**

(52) O. Pancharoen, V. A. Patrik, V. Reutrakul, P. Tuntiwachwuttikul, A. H. White, *Aust. J. Chem.* **1984**, *37*, 221.
(53) G. R. Shulte, B. Ganem, *Tetrahedron Lett.* **1982**, *23*, 4299.
(54) Personal communication with Dr. P. Tuntiwachwuttikul of the Department of Medical Science, Ministry of Public Health, Bangkok, Thailand.

# Cooperative Binding to Macromolecules. A Formal Approach

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Many macromolecules are able to bind a variety of ligand molecules to one or more specific sites. The importance of this phenomenon lies in the fact that the binding of one ligand often influences the binding strength of the macromolecule toward a subsequent ligand (or ligands). When this happens, one speaks of *cooperative binding*. This effect is the basis of enzyme control and many other vital biological processes. If we were to elaborate on this theme, we could only repeat what has been ably presented elsewhere.[1-5]

In view of the importance of cooperative binding, it is not surprising that much effort should have been devoted not only to the elucidation of the mechanism by which the phenomenon might arise in a specific case[1] but also to the development of general methods by which cooperative binding can be recognized and subjected to mathematical or graphical representation. What *is* surprising is the seeming lack of coordination between papers dealing with different aspects of the topic, so that there is even some confusion about the very definition of the term "cooperativity". Wrong, or, at least, misleading statements seem never to have been challenged, and the interesting results of some theoretical treatments[6-8] have not yet found their way into the literature which deals with more practical aspects.

In this Account, we present a short review of the *formal* aspects of cooperative binding as we see them, confining ourselves to homotropic binding, i.e., the multiple binding of like molecules. We shall employ a consistent nomenclature and point out some of the various pitfalls presented by this subject. We also believe to have some original contributions to make to various aspects of the topic.

## Stoichiometric Binding Constants and Binding Equations

We shall use the following definitions for the stoichiometric binding constants[3,5,9]

$$K_1 = \frac{[PX]}{[P][X]}, K_2 = \frac{[PX_2]}{[PX][X]}, \ldots, K_n = \frac{[PX_n]}{[PX_{n-1}][X]}, \ldots, K_t = \frac{[PX_t]}{[PX_{t-1}][X]} \quad (1)$$

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