

Bioorganic Chemistry: Total Synthesis of Tetra- and Pentacyclic Triterpenoids

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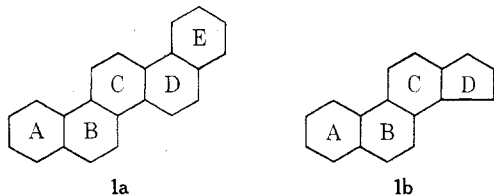
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Biogenetic-type synthesis,¹ which may be defined as the design and execution of laboratory reactions based upon established or presumed biochemical transformations, implies advances of three types: the discovery of chemical changes new to the abiological area; the development of elegant total syntheses of various natural products; and the uncovering of biochemical findings, experiments leading to which having been suggested in the first place by successful biogenetic-type synthesis attempts.

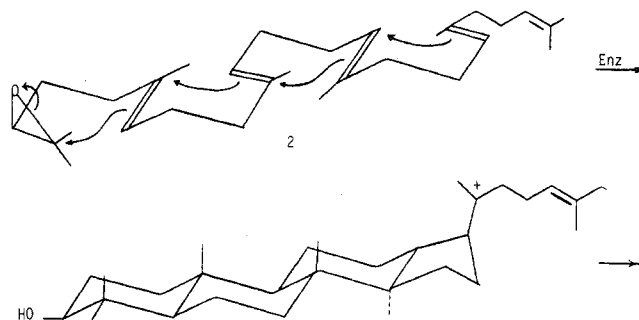
The principle is not confined to organic chemistry. In our own laboratory we have utilized this approach not only in alkaloid and terpenoid synthesis, but also in the pursuit of transition metal promoted nitrogen fixation under mild conditions,² a program based generally on the presumed workings of the enzymic process.

In both organic and inorganic areas, the old "hammer-and-tong" approach, depending on high temperatures, powerful reagents, and/or other drastic means for the unwieldy, multistage fashioning of desired structures, is abandoned in the quest of short, efficient, low-energy pathways to the desired end, quite often a structure of considerable complexity. In short, an aim of biogenetic-type synthesis is making difficult work easy, and not vice versa; and the means involve taking cues from Nature.

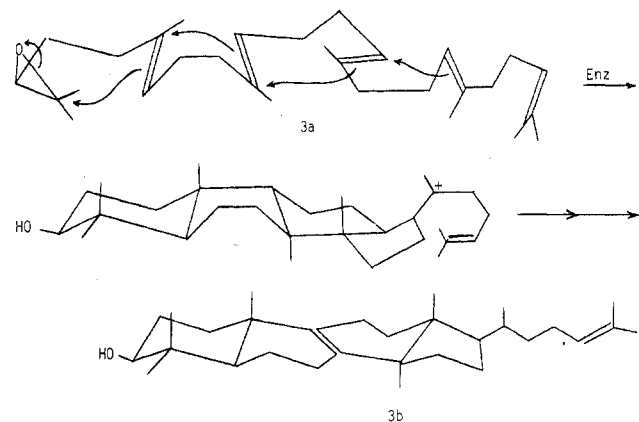
Polycyclic triterpenoids found in plant sources possess various carbon skeletons, for example **1a** or **1b**, whereas animal-derived members, such as the



steroids, are characterized almost exclusively by the tetracyclic framework **1b**. It is generally accepted that the typical plant triterpenoid is built up in Nature through all-chair folding (**2**)^{3a,b} and subsequent



cyclization of squalene 1,2-oxide, whereas the sterol precursor, lanosterol (**3b**), represents a type which emerges by chair-boat-chair folding (**3a**),³ followed by generation of a chair-boat-chair proto structure, which then undergoes methyl-hydrogen migration and final proton loss.



As the culmination of a project started more than 10 years ago,⁴ we summarize in this Account⁵ total biogenetic-type syntheses of various complex polycyclic triterpenoids by means which not only parallel most closely the biosynthetic pathways but also provide important clues to the intimate character of the reference enzymic changes.

In much earlier related work both Stork^{3b} and Eschenmoser^{3a} achieved stereoselective elaboration of

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(1) E. E. van Tamelen, *Fortschr. Chem. Org. Naturst.*, **19**, 245 (1961).

(2) E. E. van Tamelen, *Acc. Chem. Res.*, **3**, 361 (1970).

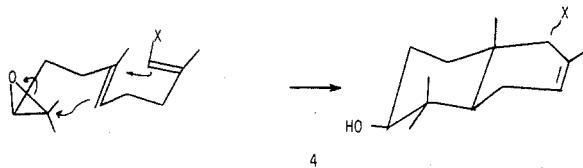
(3) (a) P. A. Stadler, A. Nechvatal, A. J. Frey, and A. Eschenmoser, *Helv. Chim. Acta*, **40**, 1373 (1957); (b) G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, **77**, 5068 (1955); (c) W. S. Johnson, *Acc. Chem. Res.*, **1**, 1 (1968); R. L. Markezich, W. E. Willy, B. E. McCarry, and W. S. Johnson, *J. Am. Chem. Soc.*, **95**, 4414 (1973); B. E. McCarry, R. L. Markezich, and W. S. Johnson, *ibid.*, **95**, 4416 (1973); D. R. Morton, M. B. Gravestock, R. J. Parry, and W. S. Johnson, *ibid.*, **95**, 4417 (1973); D. R. Morton and W. S. Johnson, *ibid.*, **95**, 4419 (1973); W. S. Johnson, K. Weidhaup, S. F. Brady, and G. L. Olson, *ibid.*, **96**, 3979 (1974).

(4) For the first publication in this series, see E. E. van Tamelen and T. J. Curphey, *Tetrahedron Lett.*, 121 (1962).

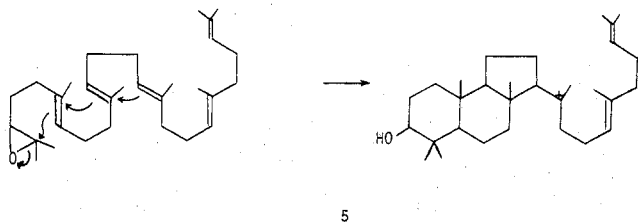
(5) For an earlier summary of related investigations, see E. E. van Tamelen, *Acc. Chem. Res.*, **1**, 111 (1968).

3-deoxy model bicyclic (A-B) systems by purely chemical cyclization of farnesic ester type precursors. More recently, Johnson and coworkers,^{3c} by departing markedly from the biosynthetic pathway (3a → 3b), were able to utilize nonenzymic cyclization methods for the production of hormonal steroids, metabolic products of the central precursor lanosterol. In many cases excellent yields of polycyclic material could be obtained by employing various novel devices in the cyclization process. For example, instead of initiating reaction by the means used in Nature, i.e., ring opening of a terminal epoxide unit, such carbonium ion sources as acetals or allylic alcohols were brought into play. Also, by omitting from starting polyene or -enyne those methyls which are excised from lanosterol during the biosynthetic production of hormonal nonaromatic steroids, the Johnson group gained ready control over the site of developing carbonium ions and therefore ring size. Sterol-like structures with the desired all-trans tetracyclic framework thus can emerge during the nonenzymic, stereoselective annelation process, in effect resulting from all-chair folding of starting material. The total synthesis is completed by appropriate changes in ring size, if necessary, and in the oxidation level at certain positions (e.g., C-3).

In the design stage of a total biogenetic-type synthesis in this area, we first raised the question: how much of the biosynthetic operation can one expect to simulate in the organic laboratory? To begin with, generation of the entire, functionalized A-B ring portion, including the correct stereochemistry of the hydroxyl and the ring juncture, follows reliable organic chemical principles and in fact had been realized in our laboratory with sesquiterpenoid models, e.g., 4.⁶



On the other hand, size of the C ring poses a problem in that the methyl substitution pattern in squalene, under nonenzymic chemical conditions, dictates carbonium ion center development during cyclization, and thereby is responsible for generation of a five-membered C ring (5), and not the six-membered



type an enzyme system forces in almost every cyclization case.⁷

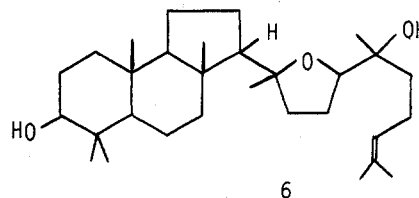
To underscore the abiological result, we recently carried out a series of laboratory cyclizations with radiolabeled 22,23-dihydrosqualene 2,3-oxide, the product being cocrystallized with an authentic sam-

(6) E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *J. Am. Chem. Soc.*, **85**, 3295 (1963).

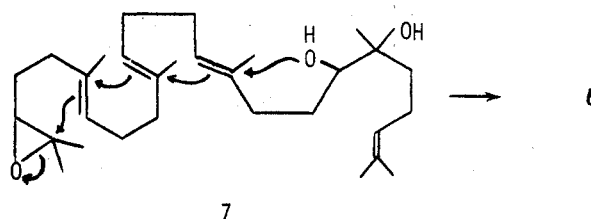
(7) E. E. van Tamelen, J. Willett, M. Schwartz, and R. Nadeau, *J. Am. Chem. Soc.*, **88**, 5937 (1966).

ple of isotirucallenol, isoeuphenol, dihydro- Δ^7 -lanosterol, dihydro- Δ^8 -lanosterol, tirucallenol, euphenol, dihydro- $\Delta^{13(17)}$ -protosterol, or dihydroparkeol.⁸ Even with this sensitive method, no trace of authentic natural product, and therefore no indication of six-membered C-ring formation, could be detected.

Advantage has been taken of this purely chemical cyclization tendency in the synthesis of malabaricol (6),⁹ a natural product which in fact possesses a

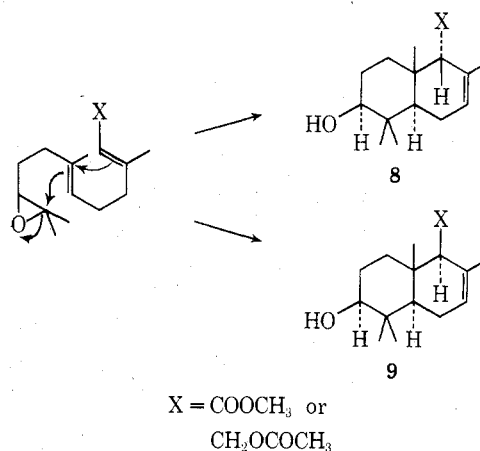


five-membered C ring. As one issue of the terpenoid terminal epoxide cyclization program, 18,19-dihydroxysqualene 2,3-oxide (7) prepared from squalene,



was converted under laboratory conditions to, inter alia, *dl*-malabaricol.¹⁰

Less clear-cut are predictions of the emerging C-9/C-10 stereochemistry, a crucial matter in that, under biological conditions, the *trans* arrangement leads to the typical all-*trans*-fused tetra- or pentacycle of the plant triterpenoid class, whereas the 9,10 *cis* relationship in the B-boat intermediate is needed for generation of lanosterol³ and thence other sterols. Under normal circumstances, a process leading to the 9,10-*trans* type would be considered the lower energy pathway. However, we observed some years ago that, depending on conditions, either the *cis* (8) or the *trans* (9) arrangement results from cyclization of the methyl *trans,trans*-10,11-oxidofarnesate or *trans,trans*-10,11-oxidofarnesyl acetate.⁶



In more recent studies,¹¹ we accumulated support for the view that the stereochemical outcome in such

(8) Unpublished results, B. Boire, Stanford University.

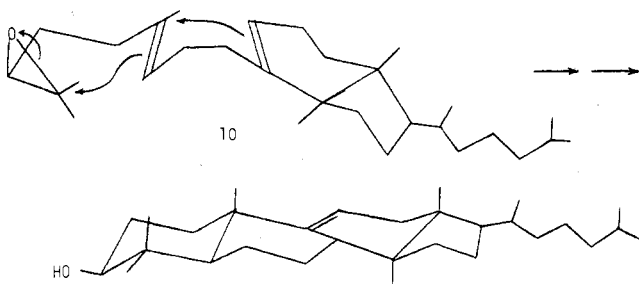
(9) A. Chawla and S. Dev, *Tetrahedron Lett.*, 4837 (1967).

(10) K. B. Sharpless, *J. Am. Chem. Soc.*, **92**, 6999 (1970).

(11) E. E. van Tamelen and J. P. McCormick, *J. Am. Chem. Soc.*, **91**, 1847 (1969).

cases is determined by the solvent-dependent conformation of the reacting epoxide—more specifically the conformation of the transition state leading to formation of the B ring. Thus one can justifiably imagine nonenzymic circumstances under which an appropriate tetracyclic precursor might generate the 9,10-cis stereochemistry in the B ring and then be converted to sterol product.

In a special case, just this result was observed.¹² Cyclization with SnCl_4 of polyene terminal epoxide **10** apparently proceeded mainly through a chair-



boat intermediate (**10**), since dehydroparkeol was the only detectable tetracyclic product—neither of the all-trans cases, euphenol or isoeuphenol, was in evidence. Presumably cyclization through chair-chair conformations is prevented by the severe steric interaction existing between the C-6, olefinic methyl group, and either angular methyl in the bicyclic moiety. Chair-boat conformation avoids these restraints and permits formation of the 9,10-cis isomer. Thus, in the above cases, generation of this biologically crucial 9,10-cis stereochemical arrangement is achieved nonenzymatically by means of either conformational constraints or solvent effects, factors which might play a role in still other epoxide cyclizations, including the biological ones.

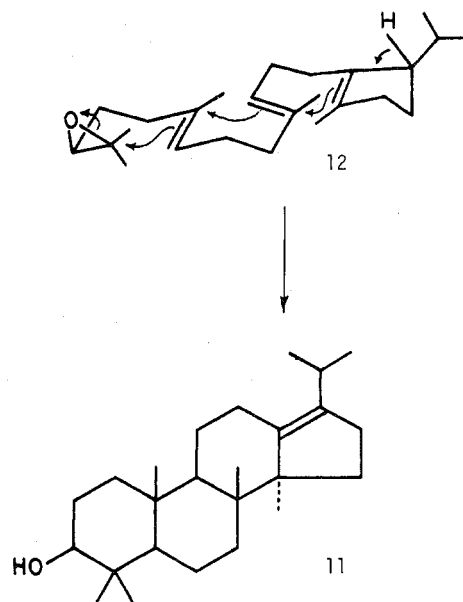
The Isoeuphenol System

Bearing the above considerations in mind, we first sought to project a model synthesis route which would lead to a naturally occurring system and in addition serve as a prototype for biogenetically patterned total syntheses of diverse tetra- and pentacyclic triterpenoids. The result was successful construction of the pentanor (C_{25}) isoeuphenol system (**11**),¹³ featuring the stereoselective generation of no fewer than five asymmetric centers during cyclization of epoxide **12**. This step represents the closest nonenzymic approach thus far to the basic biosynthetic (all-chair) cyclization scheme.

In order simultaneously to elaborate the desired tetracyclic framework (**11**) and achieve C-3 functionalization, a polyene terminal epoxide having a *preformed* D ring (**12**) was selected as the key intermediate. Because it is tetrasubstituted, the π bond in the D ring would permit control of carbonium ion behavior and consequent generation of a six-, rather than a five-membered C ring. Also, the construction of a tetracycle would be simplified, since only three new rings need then be formed in the cyclization process. Finally, in the C_{30} series, the established D ring should act as an "insulator" and deter involve-

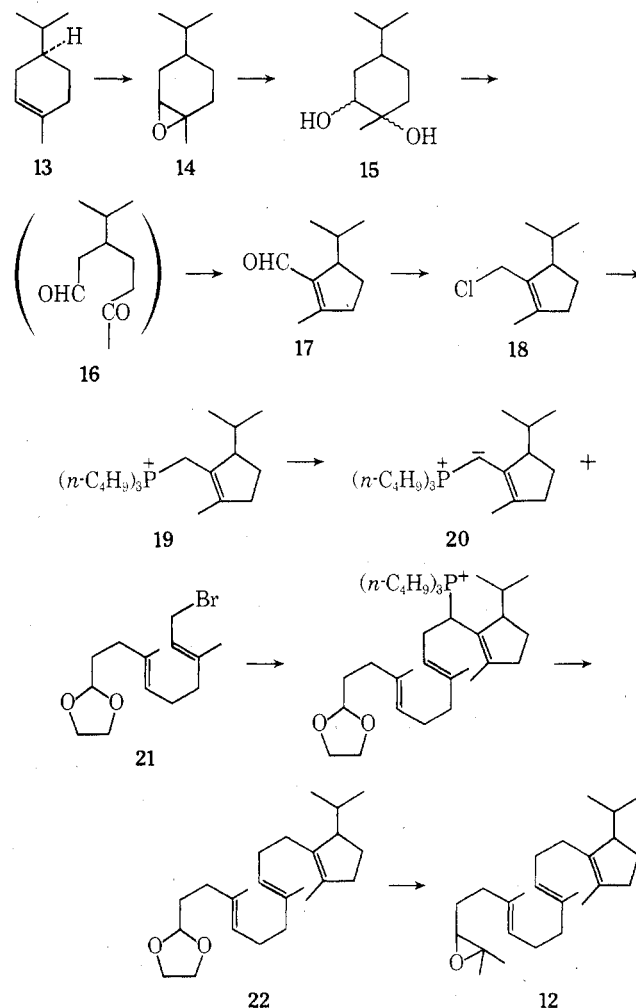
(12) E. E. van Tamelen and J. W. Murphy, *J. Am. Chem. Soc.*, **92**, 7204 (1970).

(13) E. E. van Tamelen, G. M. Milne, M. I. Suffness, M. C. Rudler-Chauvin, R. J. Anderson, and R. S. Achini, *J. Am. Chem. Soc.*, **92**, 7202 (1970).



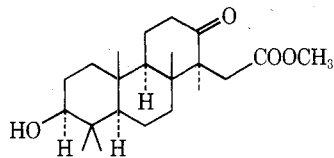
ment of the side-chain π bond with any carbonium ion developing during cyclization.

The synthesis of the monocyclic epoxide **22** was carried out by the coupling of a C_{10} unit derived from (*S*)-(-)-limonene with farnesyl bromide trisnoracetal (**21**). Oxidation of 8,9-dihydro-(*S*)-(-)-limonene (**13**) with peracetic acid gave the expected epoxide (**14**), which on hydrolysis with 3% perchloric acid was converted to crystalline diastereomeric diol **15**. The keto aldehyde (**16**) prepared by the NaIO_4



cleavage of diol 15 was cyclized to give α,β -unsaturated aldehyde 17, which was reduced to the corresponding allylic alcohol. The allylic chloride 18 was converted to the phosphonium chloride 19, the ylide (20) from which was coupled¹⁴ with trisnoracetol 21 to give, on reduction with lithium-ethylamine, monocyclic acetal 22 (55%). The aldehyde obtained by perchloric acid hydrolysis of 22 was converted to desired epoxide 12 by treatment with diphenylsulfonium isopropylide.

Treatment of epoxide 12 with $\text{BF}_3\text{-Et}_2\text{O}$ or SnCl_4 in different solvents was found to give varying amounts of tetracycle 11. In the best run, 5 equiv of SnCl_4 in CH_3NO_2 provided a 70% yield of alcoholic material comprising at least seven products. The major, optically inactive product, 11 (35% yield), was identified as tetracycle 11 by various means, including stepwise degradation to keto ester 23, identi-



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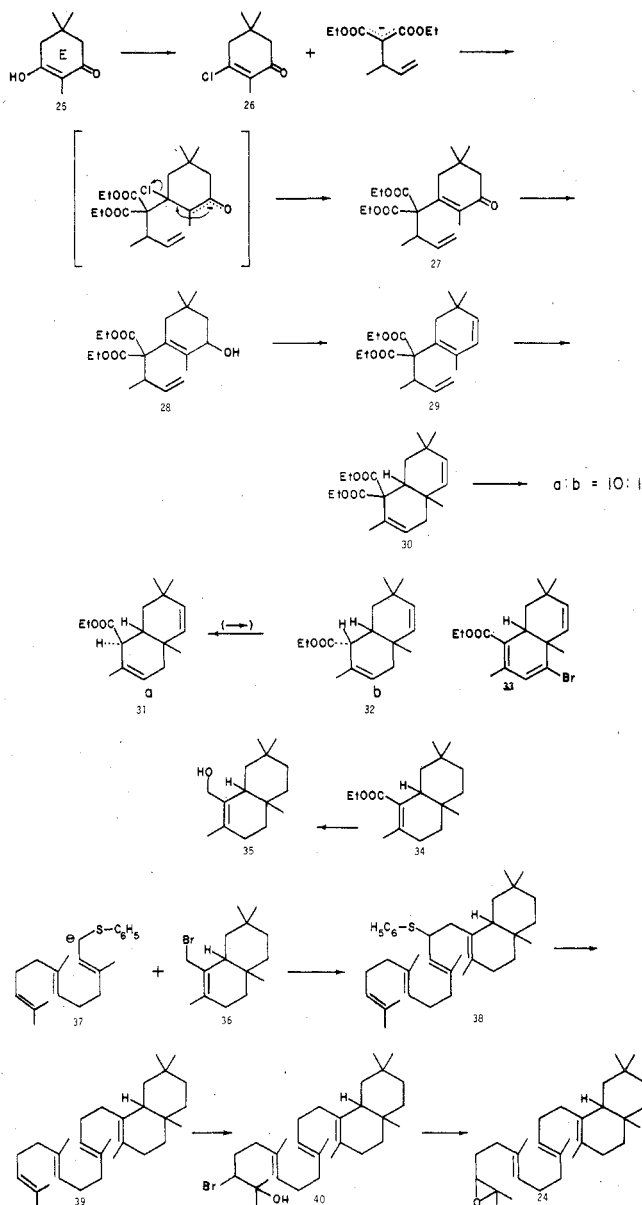
cal, except for optical activity, with the product obtained from isoeuphol itself. This synthetic work, along with the earlier nonenzymic, selective terminal oxidation of squalene, represents an overall, close simulation of the squalene \rightarrow tetracyclic triterpene bioconversion and defines the purely organic chemical basis for operation of enzymes therein.

β -Amyrin, δ -Amyrin, and Germanicol

With the above results in hand, application of the synthesis approach to more complicated, naturally occurring polycyclic triterpenes became realistic. One of the targets selected was the amyirin system, which would result, it was hoped, from laboratory cyclization of tetraene epoxide 24.¹⁵

To initiate the synthesis of the preformed D-E component (Scheme I), the Michael addition of diethyl 1-methylmalonate to 2,5,5-trimethyl-3-chlorocyclohex-2-en-1-one (26; prepared from methylidmedone 25), was carried out, resulting in the formation, after in situ β elimination of chloride ion, of the diene keto diester 27. After NaBH_4 reduction of 27, acidification, and work-up, distillation of crude intermediate alcohol 28 afforded directly the triene diester 29. On exposure to a large excess of $\text{BF}_3 \cdot (\text{C}_2\text{H}_5)_2\text{O}$, 29 was transformed to the cis-bicyclic diene diester 30, which after decarboethoxylation provided a 10:1 mixture of diene esters a and b (31 and 32, respectively). Since the β,γ -unsaturated ester could not be converted by base or acid to the α,β isomer, the latter, required system had to be secured by indirect means. The crude bromination production which resulted from heating of 31-32 with 2.5 equiv of *N*-bromosuccinimide (NBS) in refluxing CCl_4 (benzoyl peroxide initiator) was subjected to DBN elimination, yielding the bromo triene ester 33. Catalytic hydrogenation provided the

Scheme I



monounsaturated ester 34. Further reduction with AlH_3 , followed by treatment of the resulting allyl alcohol with 48% hydrobromic acid-petroleum ether, gave rise to the bicyclic allyl bromide 36.

In order to complete the synthesis of epoxide 24, the carboacyclic moiety was introduced through alkylation¹⁶ of bromide 36 with the phenyl thioether anion 37. The resulting product 38, on treatment with $\text{Li-C}_2\text{H}_5\text{NH}_2$ at -78° , was converted to tetraene 39. The latter, upon selective oxidation with *N*-bromosuccinimide-water, was transformed to terminal bromohydrin 40 and thence to terminal epoxide 24, unquestionably an ca. 50:50 mixture of racemates differing stereochemically at C-3.

$\text{SnCl}_4\text{-CH}_3\text{NO}_2$ at 0° for 2 hr effected transformation of epoxide 24 to *dl*- δ -amyrin (41; 8%, based on the consumption of one of the two epoxide racemates). Resolution was accomplished through the (*S*)-methoxytrifluoromethylphenylacetate¹⁷ (MTPA), identical with the MTPA of authentic

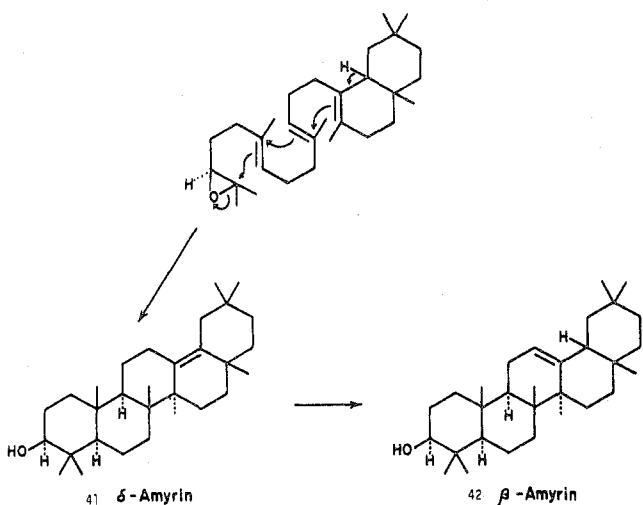
(14) E. H. Axelrod, G. M. Milne, and E. E. van Tamelen, *J. Am. Chem. Soc.*, **92**, 2139 (1970).

(15) E. E. van Tamelen, M. Seiler, and W. Wierenga, *J. Am. Chem. Soc.*, **94**, 8229 (1972).

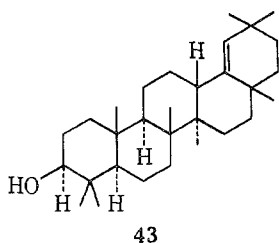
(16) J. F. Biemann and J. B. Ducep, *Tetrahedron Lett.*, 3707 (1969).

(17) J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).

δ -amyrin. (-)- δ -amyrin was regenerated from the ester by LiAlH_4 reduction. In view of the prior conversion of δ -amyrin from natural sources to δ -amyrene,¹⁸ and the transformation of the latter to β -amyrin,¹⁹ the δ -amyrin synthesis described herein also constitutes a formal synthesis of β -amyrin (42). Fi-



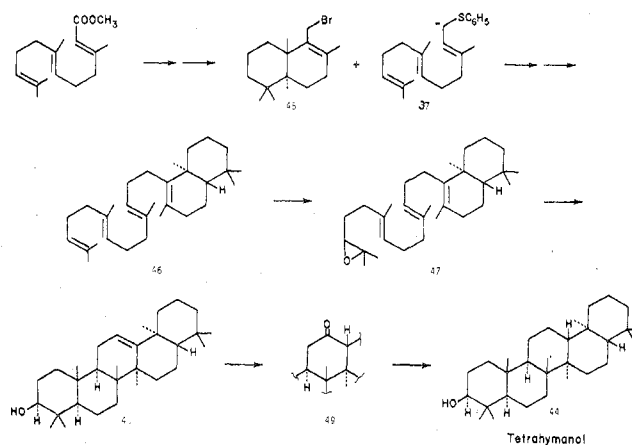
nally, the laboratory production of 41 also embraces germanicol (43), since the latter is isolated as the predominant product when δ -amyrin is photolyzed in the presence of *p*-xylene.



Tetrahymanol

Incorporating five carbocyclic rings and nine asymmetric centers, the protozoan metabolite tetrahymanol (44) presents a considerable challenge for laboratory construction by efficient means. As part of the terpenoid terminal epoxide program, we developed an economical nine-step stereoselective total synthesis of this natural product (in the racemic form), the first of a pentacarbocycle to be achieved solely by polyolefin cyclization methods.²⁰

Trans,trans bicyclic bromide 45, obtained as previously described²¹ by initial cyclization of methyl *trans,trans*-farnesate^{3b} followed by conversion of conjugated ester to allyl bromide, was allowed to react with the anion of phenyl thioether 37. The *trans,trans* alkylation product was reductively desulfurized with $\text{Li-C}_2\text{H}_5\text{NH}_2$ to an ca. 50:50 mixture of the desired 2,6,10,14-tetraene 46 and the 2,6,11,14 isomer, separated by GC or preparative TLC. Selective oxidation with NBS-water to terminal bromohydrin again was applied here, making available epoxide 47, believed to be an ca. 50:50 mixture of C-3 epimers. Cyclization of the epoxide carried out



by means of SnCl_4 in CH_3NO_2 for 0.5 hr at 0° , yielded 20% *dl*- Δ^{12} -dehydrotetrahymanol (48).

Conversion of the synthetic dehydrotetrahymanol acetate to *dl*-tetrahymanol, patterned after a published relay,²² involved initial $\text{CF}_3\text{CO}_3\text{H}$ oxidation to the acetate of tetrahymanol-12-one (49). On Wolff-Kishner reduction, the ketone afforded *dl*-tetrahymanol, identical, except for melting point and optical properties, with naturally occurring tetrahymanol.

24,25-Dihydrolanosterol, 24,25-Dihydro- $\Delta^{13(17)}$ -protosterol, Isoeuphenol, (-)-Isotirucallol, and Parkeol

Returning to the tetracyclic category, we describe next our experiences in extending the isoeuphol model work to cases featuring the full side chain, characteristic of the natural products. Apparently because of the availability of naturally occurring substances (or products derived from these) which, as comparison compounds, facilitated the search for cyclization products formed in minor amounts, we encountered results which provided new information about mechanistic and conformational behavior during polyolefin epoxide cyclizations, nonenzymic and, by implication, enzymic.²³ To summarize, the totally synthetic epoxide epimer 50a is transformed by Lewis acid to not only isoeuphenol (51), presumably reflecting the polychair conformation (50a α) of reacting epoxide, but also 24,25-dihydro- $\Delta^{13(17)}$ -protosterol (52) and 24,25-dihydroparkeol (53), apparently arising as a consequence of chair-boat-chair folding (50a β), cyclization, and (in the case of 53) termination by a CH_3/H migration sequence akin to that occurring in the biological process. Abiological tricyclization of 50b, the C-3 epimer of 50a, yields only (-)-isotirucallenol (54) (the enantiomer of naturally derived material), again a consequence of the all-chair arrangement (50b α). Similarly, synthetic epoxide 55a affords the natural product parkeol (56), while 55b, the C-3 epimer of 55a, gives rise to (-)-isotirucallol (57).

Construction of the required tetraene epoxides followed the lines laid down in the model series. The cyclohexenyl alcohol 58 was converted by the Lee method²⁴ to the corresponding bromide 59, which, on treatment with malonic ester anion, gave rise to

(18) G. Brownlie, M. B. E. Favez, F. S. Spring, R. Stevenson, and W. S. Strachen, *J. Chem. Soc.*, 1377 (1956).

(19) D. H. R. Barton, E. F. Lier and J. F. McGhie, *J. Chem. Soc.*, 1031 (1968).

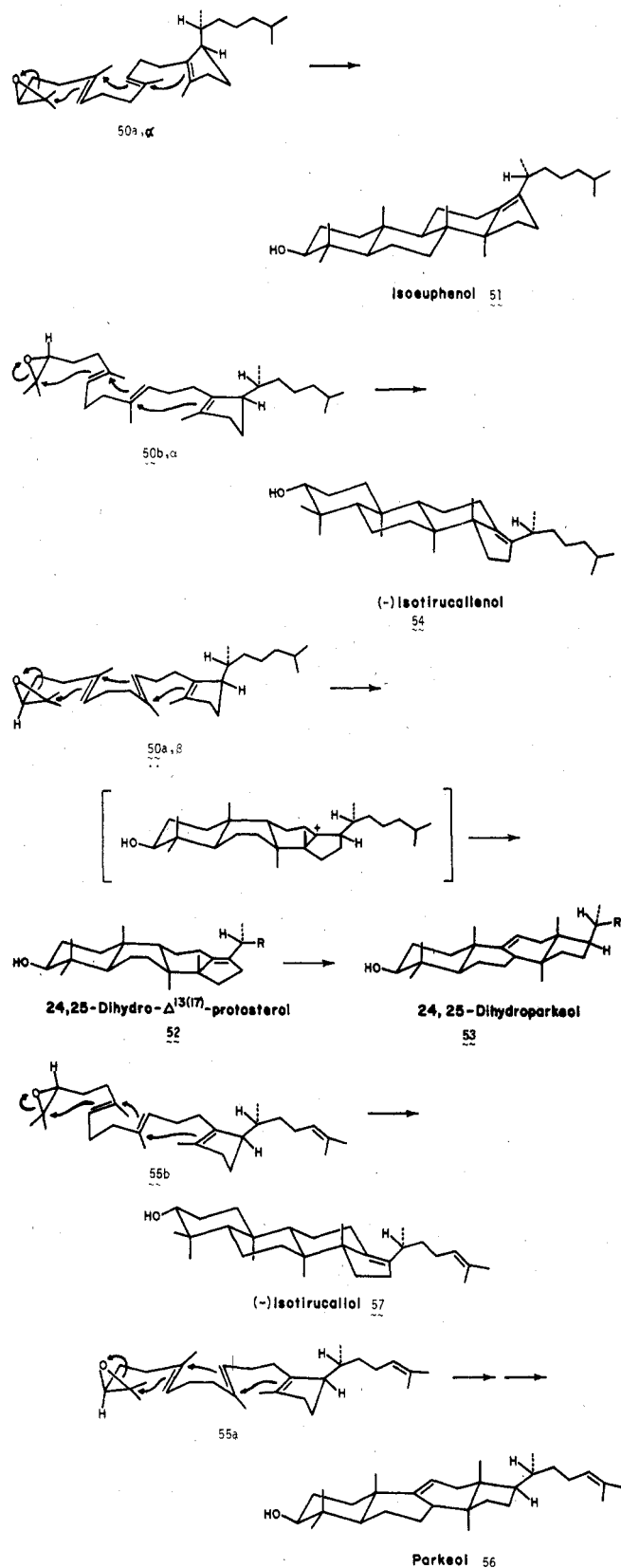
(20) E. E. van Tamelen, R. A. Holton, R. E. Hapla, and W.-E. Konz, *J. Am. Chem. Soc.*, 94, 8228 (1972).

(21) M. A. Schwartz, Ph.D. Dissertation, Stanford University, 1965.

(22) Y. Tsuda, A. Morimoto, T. Sano, and Y. Inubushi, *Tetrahedron Lett.*, 1427 (1965).

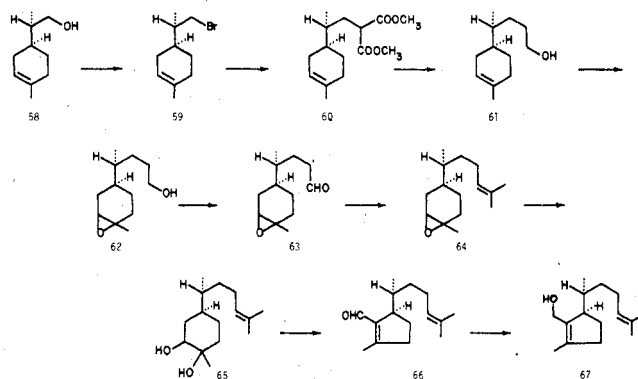
(23) E. E. van Tamelen and R. J. Anderson, *J. Am. Chem. Soc.*, 94, 8225 (1972).

(24) J. B. Lee and T. J. Nolan, *Can. J. Chem.*, 44, 1331 (1966).

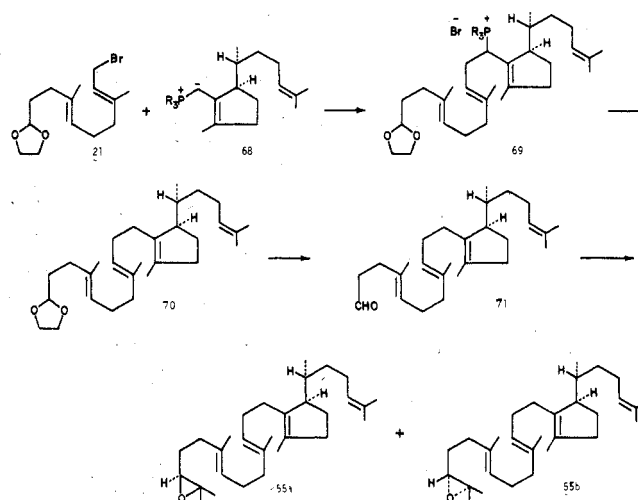


the diester 60. Decarbomethoxylation of 60 was carried out by heating with NaCN in Me_2SO solution, and the resulting monoester was quantitatively reduced by LiAlH_4 to the corresponding alcohol 61. On oxidation with *m*-chloroperbenzoic acid 61 was transformed to a 1:2.2 mixture of α, β -epoxides 62 (separable by GLC), which mixture was further oxidized by Collins reagent to the aldehyde level (63). By means of a Wittig reaction, aldehyde 63 was con-

verted to diene monoxide mixture 64. Treatment of the epoxide mixture 64 with dilute HClO_4 effected conversion to a 8.4:1 (diaxial:diequatorial hydroxyls) mixture of diastereoisomeric trans glycols (65), which was subjected to the action of sodium meta-periodate. The resulting unisolated keto aldehyde was transformed by piperidine-acetic acid to the cyclopentenecarboxaldehyde 66, which was reduced directly by means of NaBH_4 to the alcohol 67.

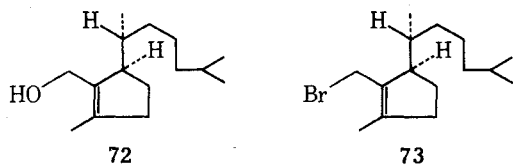


After formation of allyl bromide and then phosphonium salt from this alcohol, coupling was carried out between trisnor acetal 21 and the ylide 68 derived by treatment with phenyllithium of the phosphonium salt. The coupling product 69 was reduced with lithium-ethylamine to tetraene acetal 70, convertible to aldehyde 71 and thence to epoxide 55 by means similar to those employed in the isoeuphenol model work. Epoxide 55 is, again, presumably an *ca.* 50:50 mixture of C-3 epimers (55a,b), inseparable by chromatographic means.



Exposure of epoxide 55a,b to 2.5 equiv of SnCl_4 in CH_3NO_2 at 0° for 1.5 hr resulted in formation of product complex from which there was isolated by means of a combination of TLC and preparative VPC methods, (-)-isotirucallol (57; 18%). A second product was identified as the natural product parkeol (56; 2%) by comparison of its acetate with authentic parkeyl acetate.

Results secured in the saturated side chain series were even more revealing. In order to obtain dihydro epoxide 50, the cyclopentenyl alcohol 67 was selectively hydrogenated to allylic alcohol 72, and the corresponding bromide 73 was subjected to a reduc-



tive coupling sequence similar to ones already described.^{15,20} Attachment of the terminal epoxide unit, as above with **55a,b**, completed the synthesis of the **50a,b** mixture.

As with **55a,b**, cyclization of epoxide **50a,b**, followed by TLC separation of products, yielded a tetracycle fraction comprising isoeuphenol (**51**; 3.5%), 24,25-dihydro- $\Delta^{13(17)}$ -protolanosterol (**52**; 2%), and 24,25-dihydroparkeol (**53**; 3.5%), all from epoxide **50a**, and (-)-isotirucallenol (**54**; 43%) from epimer **50b**. Since $\text{SnCl}_4\text{-CH}_3\text{NO}_2$ or $\text{BF}_3\cdot\text{Et}_2\text{O-CH}_3\text{NO}_2$ treatment of authentic dihydro- $\Delta^{13(17)}$ -protolanosterol (**52**) (or its acetate) resulted in formation of dihydroparkeol (**53**) (or acetate), the latter may well be generated from the former during the original cyclization conditions. In that dihydroparkeol (**53**) has been previously converted¹² to 24,25-dihydrolanosterol, the present work also constitutes a direct total synthesis of the latter natural product.

Although generation of either the 9,10-trans or -cis arrangement in the hydronaphthalene framework arising from polycyclization of terpenoid terminal epoxides has been previously observed (vide supra), the formation of tetracycles **52**, **53**, and **56** from epoxides **50a** and **55a** represents the first tricyclization featuring the 9,10-cis outcome and thus emerges as a

close simulation of the biosynthetic conversion of squalene oxide to the presterol, and thence to the lanosterol level. The results described herein thus not only constitute total syntheses of tetracycles **51**, **52**, **53**, **54**, **56**, and **57**, but also suggest that biological chair-boat-chair construction rests on a palpable, purely chemical foundation, the function of the lanosterol cyclase enzyme being in part to optimize this particular folding-cyclization process. As revealed by examination of Dreiding models, a distinct steric interaction between the C-10 (vinyl) methyl and the side chain exists in epoxides **50a** and **55a**, but not in epoxides **50b** and **55b**. As a consequence, formation of the isotirucallol system from **50b** or **55b** proceeds in much higher yield than does that of the isoeuphol type from **50a** or **55a**, where the aforementioned steric interference inhibits the all-trans folding which must precede cyclization to the all-trans tetracycle. This C-10 methyl-side chain interaction in compounds **50a** and **55a** can be alleviated by chair-boat-chair folding, which permits then competitive cyclization to A-B-C chair-boat-chair tetracyclic carbonium ion, the requisite precursor of protosterol (**52**), dihydroparkeol (**53**), and parkeol (**56**), all observed products from the epimer-b series of epoxides. These results and considerations suggest that, during enzymic formation of lanosterol from squalene oxide, steric crowding between the C-10 methyl and some portion of the enzyme on the β -side of the substrate could inhibit all-chair folding and force the epoxide to assume the chair-boat conformation required for lanosterol production.

Synthesis of the *Cephalotaxus* Alkaloids

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Cephalotaxus is a plant genus in the family *Taxaceae*,¹ which includes several species and varieties such as *Cephalotaxus harringtonia* var. *drupacae* (Japanese plumyew), native to Japan and China.

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This genus is the sole known source of the cephalotaxine family of alkaloids, some members of which are promising for leukemia chemotherapy.

Clinical testing will require larger quantities of the interesting constituents than are now available from natural sources because the biologically active alkaloids such as harringtonine and isoharringtonine are only minor constituents and the trees appear only in small numbers for ornamental purposes in the United States. The problem of supplying the active compounds in sufficient quantities for clinical testing therefore falls to organic chemists to solve via chemi-

(1) Some workers have placed *Cephalotaxus* in a separate family, the *Cephalotaxaceae*: W. Dallimore and A. B. Jackson, revised by S. G. Harrison, "A Handbook of Coniferales and Ginkgoaceae", St. Martin's Press, New York, N.Y., 1967, pp 146-152.