Bioorganic Chemistry: Total Synthesis of Tetra- and Pentacyclic Triterpenoids

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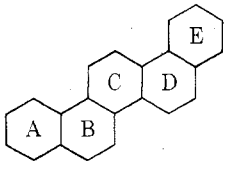
Biogenetic-type synthesis,[1] which may be defined as the design and execution of laboratory reactions based upon established or presumed biochemical transformations, implies advances of three types: the discovery of chemical changes new to the abiological area; the development of elegant total syntheses 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.

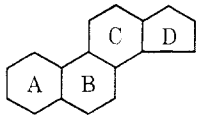
The principle is not confined to organic chemistry. In our own laboratory we have utilized this approach not only in alkaloid and terpenoid synthesis, but also in the pursuit of transition metal promoted nitrogen fixation under mild conditions,[2] a program based generally on the presumed workings of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

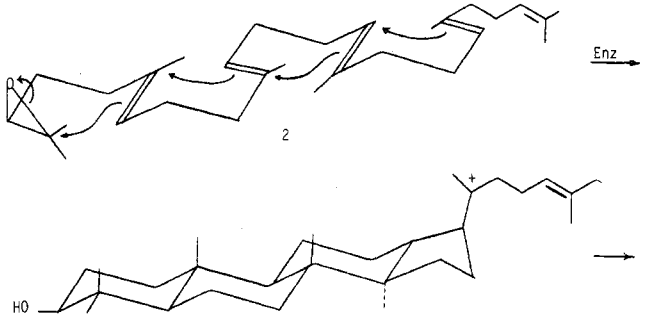


1a

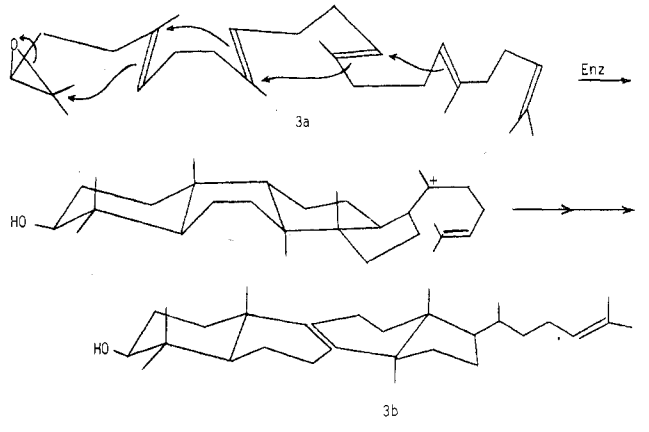


1b

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 Account[5] 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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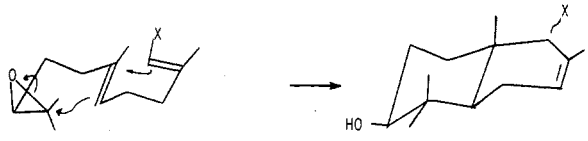
(1) E. E. van Tamelen, *Fortschr. Chem. Org. Naturst.*, 19, 245 (1961).
(2) E. E. van Tamelen, *Acc. Chem. Res.*, 3, 361 (1970).
(3) (a) P. A. Stadler, A. Nechvatal, A. J. Frey, and A. Eschenmoser, *Helv. Chim. Acta*, 40, 1373 (1957); (b) G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, 77, 5068 (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]



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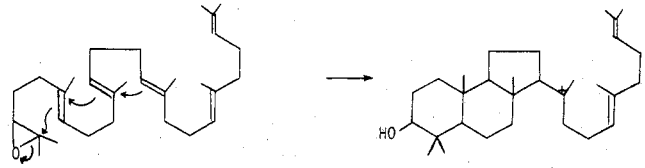
On the other hand, size of the C ring poses a problem in that the methyl substitution pattern in squalene, under nonenzymic chemical conditions, dictates carbonium ion center development during cyclization, and thereby is responsible for generation of a five-membered C ring (**5**), and not the six-membered



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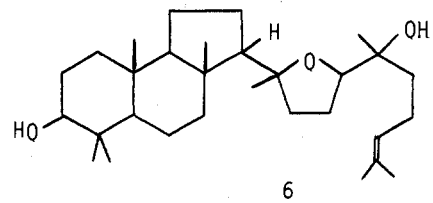
type an enzyme system forces in almost every cyclization case.[7]

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 sample 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



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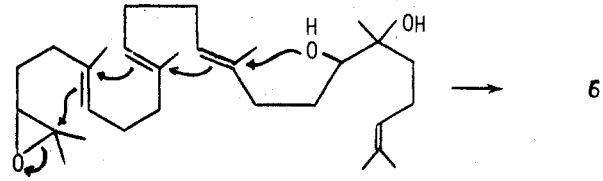
five-membered C ring. As one issue of the terpenoid terminal epoxide cyclization program, 18,19-dihydroxysqualene 2,3-oxide (**7**) prepared from squalene,



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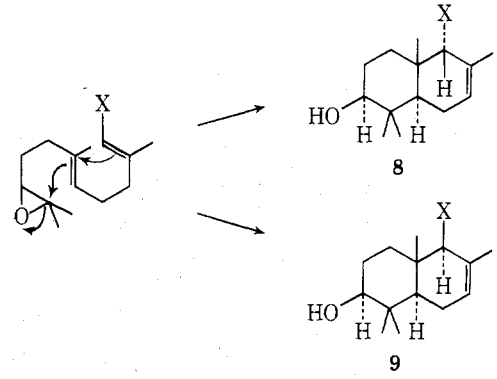
was converted under laboratory conditions to, inter alia, *dl*-malabaricol.[10]

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 lanosterol[3] 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]



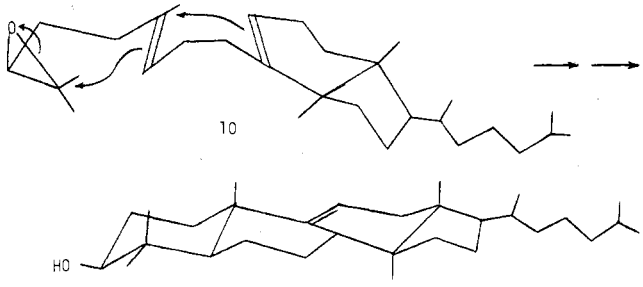
X = $COOCH_3$ or CH_2OCOCH_3

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

(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).
(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–

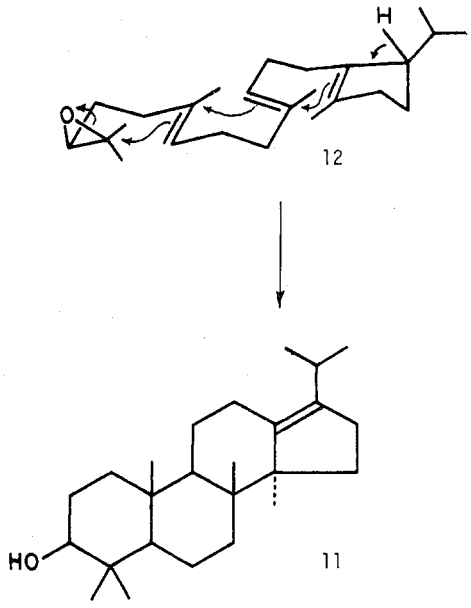


boat intermediate (**10**), since dehydroparkeol was the only detectable tetracyclic product—neither of the all-trans cases, euphenol or isoeuphenol, was in evidence. Presumably cyclization through chair–chair conformations is prevented by the severe steric interaction existing between the C-6, olefinic 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.

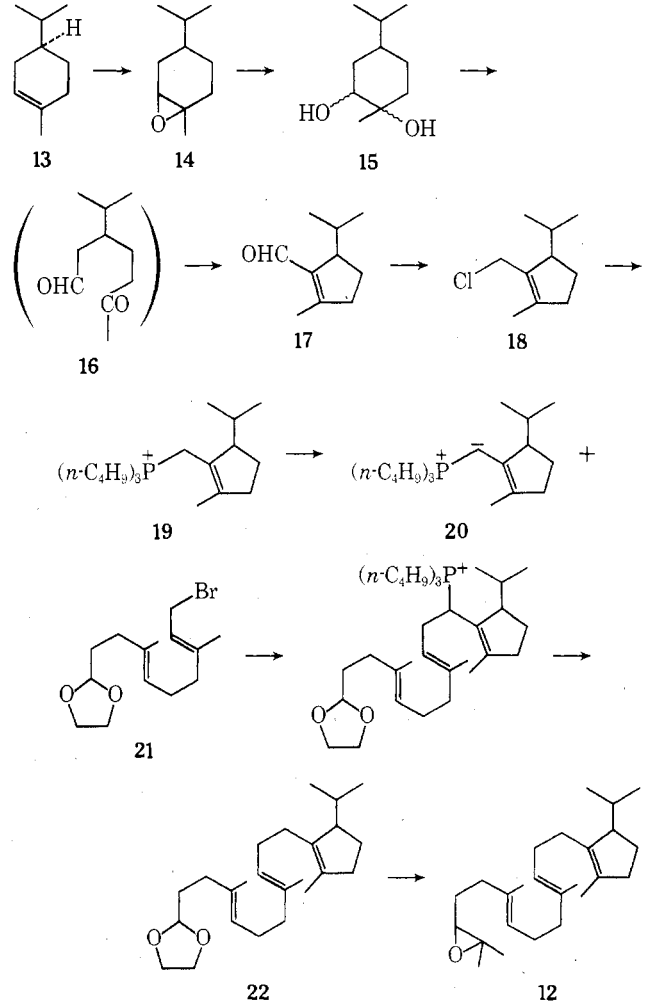
The Isoeuphenol System

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 involvement 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 $NaIO_4$

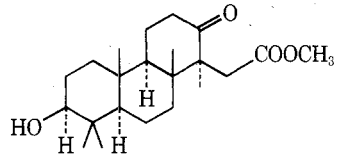


(12) E. E. van Tamelen and J. W. Murphy, *J. Am. Chem. Soc.*, 92, 7204 (1970).

(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).

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 coupled[14] with trisnoracetal **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 BF_3–Et_2O 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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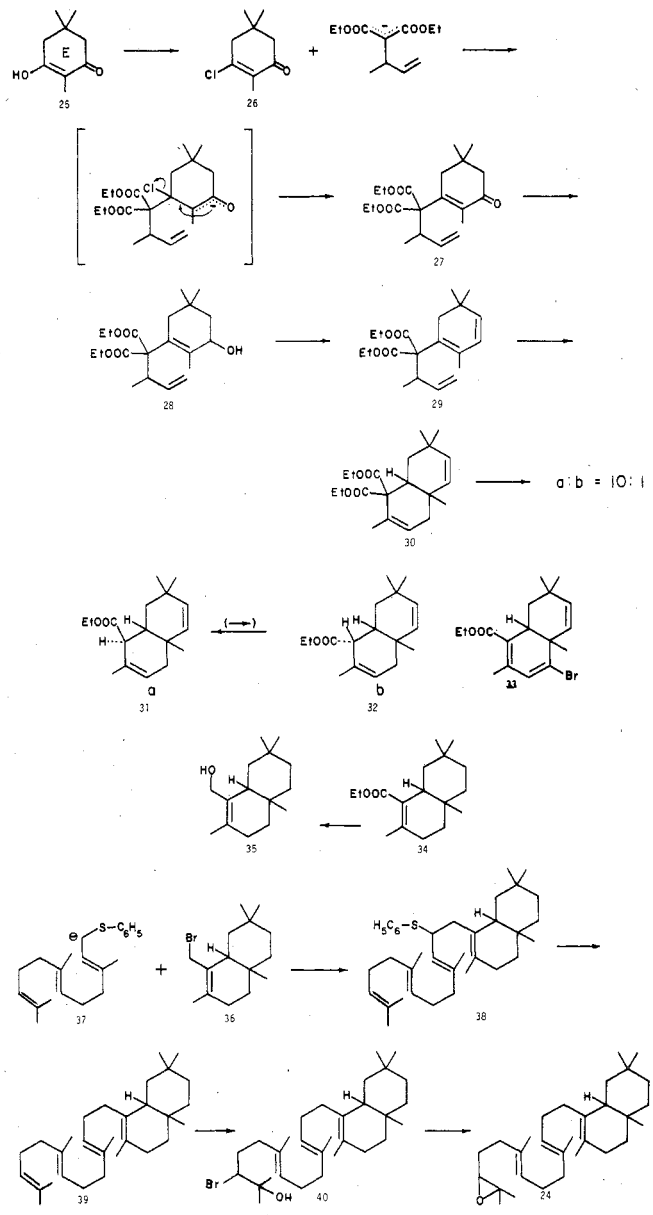
cal, except for optical activity, with the product obtained from isoeuphol itself. This synthetic work, along with the earlier nonenzymic, selective terminal oxidation of squalene, represents an overall, close simulation of the squalene → tetracyclic triterpene bioconversion and defines the purely organic 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 amyrin 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-methallylmalonate to 2,5,5-trimethyl-3-chlorocyclohex-2-en-1-one (**26**; prepared from methyldimedone **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 $BF_3 \cdot (C_2H_5)_2O$, **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



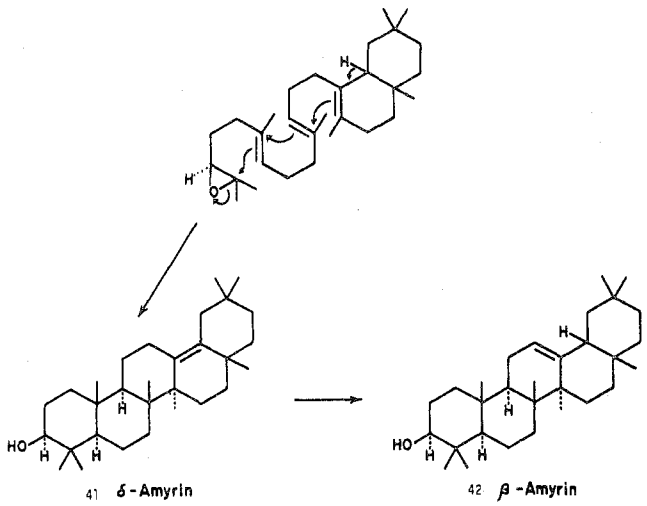
monounsaturated ester **34**. Further reduction with AlH_3, followed by treatment of the resulting allyl alcohol with 48% hydrobromic acid–petroleum ether, gave rise to the bicyclic allyl bromide **36**.

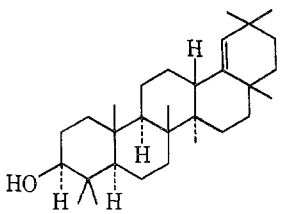
In order to complete the synthesis of epoxide **24**, the carboacyclic moiety was introduced through alkylation[16] of bromide **36** with the phenyl thioether anion **37**. The resulting product **38**, on treatment with Li–$C_2H_5NH_2$ at −78°, was converted to tetraene **39**. The latter, upon selective 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.

$SnCl_4$–CH_3NO_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*)-methoxytrifluoromethylphenylacetate[17] (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. Bielmann 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). Finally, 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.





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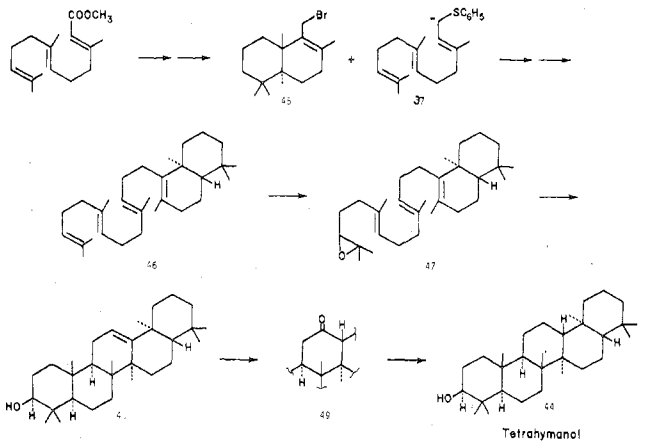
Tetrahymanol

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 syntesis 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 described[21] 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 $Li-C_2H_5NH_2$ 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 avaliable 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).

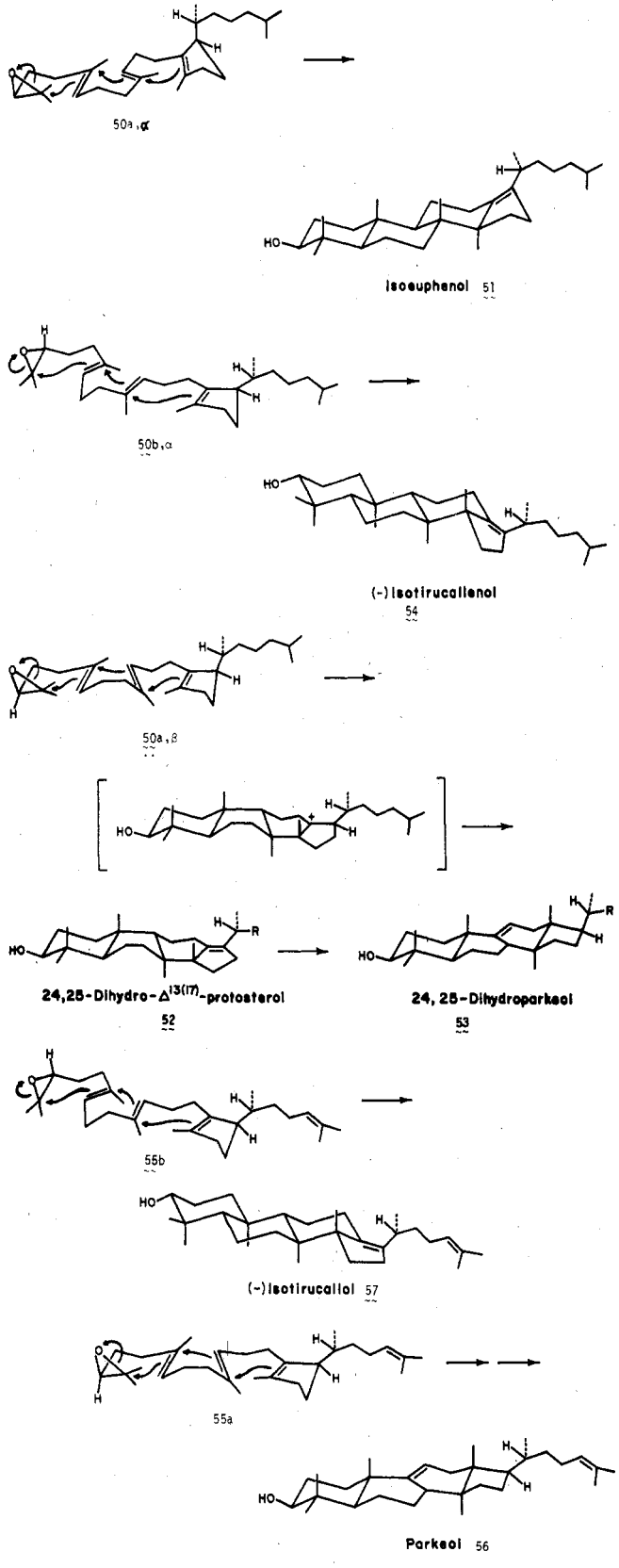
Conversion of the synthetic dehydrotetrahymanyl acetate to *dl*-tetrahymanol, patterned after a published relay,[22] involved initial CF_3CO_3H oxidation to the acetate of tetrahymanol-12-one (49). On Wolff–Kishner reduction, the ketone afforded *dl*-tetrahymanol, identical, except for melting point and optical properties, with naturally occurring tetrahymanol.

24,25-Dihydrolanosterol, 24,25-Dihydro-$\Delta^{12(17)}$-protosterol, Isoeuphenol, (−)-Isotirucallol, and Parkeol

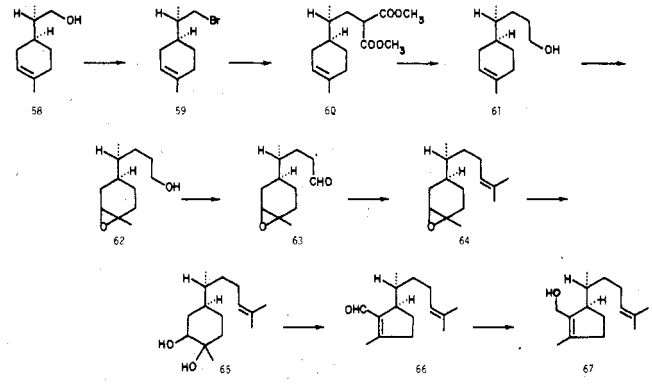
Returning to the tetracyclic category, we describe next our experiences in extending the isoeuphol model work to cases featuring the full side chain, characteristic of the natural products. Apparently because of the availability of naturally occurring substances (or products derived from these) which, 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 method[24] to the corresponding bromide **59**, which, on treatment with malonic ester anion, gave rise to

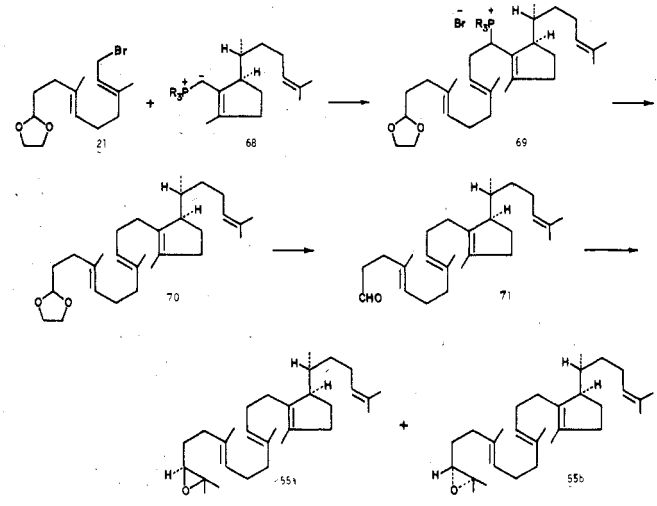
(18) G. Brownlie, M. B. E. Fayez, F. S. Spring, R. Stevenson, and W. S. Strachen, *J. Chem. Soc.*, 1377 (1956).
(19) D. H. R. Barton, E. F. Lier and J. F. McGhie, *J. Chem. Soc.*, 1031 (1968).
(20) E. E. van Tamelen, R. A. Holton, R. E. Hapla, and W.-E. Konz, *J. Am. Chem. Soc.*, 94, 8228 (1972).
(21) 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 converted 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 metaperiodate. 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**.

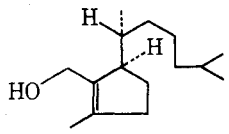


After formation of allyl bromide and then phosphonium salt from this alcohol, coupling was carried out between trisnor acetal **21** and the ylide **68** derived by treatment with phenyllithium of the phosphonium salt. The coupling product **69** was reduced with lithium–ethylamine to tetraene acetal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

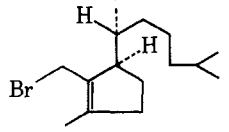


Exposure of epoxide **55a,b** to 2.5 equiv of $SnCl_4$ in CH_3NO_2 at 0° for 1.5 hr resulted in formation of product complex from which there was isolated by means of a combination of TLC and preparative VPC methods, (−)-isotirucallol (**57**; 18%). A second product was identified as the natural product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



72



73

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 $SnCl_4$–CH_3NO_2 or $BF_3 \cdot Et_2O$–CH_3NO_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 converted[12] 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 *tri*cyclization 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 preceed 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 *Taxacae,*[1] which includes several species and varieties such as *Cephalotaxus harringtonia* var. *drupacae* (Japanese plumyew), native to Japan and China. 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-

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