Pure & Appl. Chem., Vol.53, pp.1259-1270.
Printed in Great Britain.

0033-4545/81/061259-12$02/00/0
Pergamon Press Ltd.

THE ROLE OF ORGANIC SYNTHESIS IN BIOORGANIC CHEMISTRY

Eugene E. van Tamelen

Department of Chemistry, Stanford University, Stanford, California 94305, USA

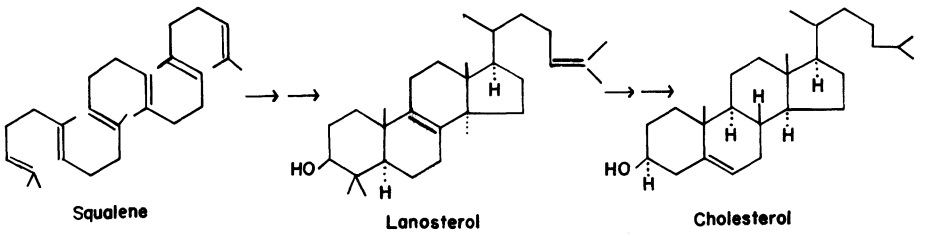
Abstract - Among the various applications of non-enzymic synthesis in the bioorganic area, biogenetic-type synthesis has proved to be a far-reaching, fruitful endeavor. In this exposition emphasis is placed on the terpene family, including total syntheses of naturally occurring diterpenoids, triterpenoids and steroids, especially approaches involving polyene epoxide polycyclizations, reactions closely akin to the biochemical processes by which such natural products are built up.

INTRODUCTION

Within the bioorganic chemical area, non-enzymic organic synthesis serves various useful purposes, including I) the preparation of radiolabelled potential substrates for enzymic reactions, II) the provision of comparison materials needed for biosynthetic studies, III) elaboration of modified, unnatural substrates for biosynthesis studies, IV) design and execution of new reactions as models for biosynthetic steps, and subsequent enzymic testing thereof, and V) biogenetic-type, or biomimetic, synthesis, including (a) non-enzymic simulation of enzyme structures and behavior with normal substrates and (b) abiological mimesis of established or presumed substrate behavior, with either genuine substrate or modifications thereof. It is the last area (Vb) with which this exposition will be principally concerned, although allusion and reference will be made to the other activities listed. In order to set the stage for presentation of our latest results, it is instructive to review past activities having to do with the bioorganic chemistry of terpenoids and steroids which were initiated in our laboratory during the early 1960's.

BIOSYNTHESIS OF 3-OXYGENATED TRITERPENOIDS AND STEROIDS

Although the biological conversion of squalene (1) to lanosterol (2) and thence to cholesterol (3) and other sterols was securely established (1) at the time our interest was aroused, the exact chemical means by which the overall oxidation/cyclization conversion proceeded remained unknown. Following the discovery in our laboratory of the highly selective,



Squalene — Lanosterol — Cholesterol

1 — 2 — 3

general terminal oxidation of acyclic polyunsaturated terpenes (2) and the demonstration (3) that non-enzymic cyclization of epoxides resulting from such oxidations generated polycyclic systems bearing considerable structural and stereochemical resemblance to naturally occurring 3-oxygenated terpenoids, it became reasonable and readily possible to test the conjecture that squalene-2,3-oxide (4b) is a genuine intermediate in sterol biosynthesis. Thus, as illustrated in Fig. 1, N-bromosuccinimide oxidation of radiolabelled squalene followed by treatment with base provided radiolabelled squalene-2,3-oxide, which was converted in high yield by rat or pig liver enzyme to lanosterol (4,5). Further, extensive biochemical studies

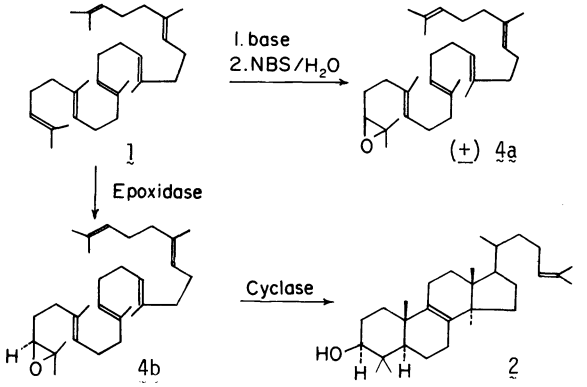


Fig. 1

of radiolabelled modified substrates revealed (6) that deletions and insertion of various groups, as illustrated in Fig. 2, do not preclude enzymic cyclizations to sterol-like structures, results which define the minimum structural requirements for cyclase action, i.e., the 2-alkylundeca-2,6,10-triene-2,-3-oxide moiety.

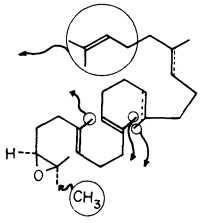


Fig. 2

Physical organic mechanism of lanosterol biosynthesis

Superimposition of the intermediacy of oxide 4b on the theoretical treatment put forth earlier (7,8) leads to the stereochemical interpretation shown in Fig. 3 for the biosynthesis of lanosterol, via 5. A parallel "all-chair" folding of 4b leads to the all-chair 3-oxygenated triterpene class. More recently, various chemical and biochemical studies as well as newer theoretical considerations have led to the view (9) that the overall annulation process is not completely concerted, but involves a series of conformationally rigid carbocyclic intermediates (Fig. 4).

BIOGENETIC-TYPE TOTAL SYNTHESIS OF POLYCYCLIC TERPENES VIA POLYENE EPOXIDE POLYCYCLIZATIONS AND RELATED PROCESSES

3-Oxygenated tetra- and pentacyclic triterpenes

What about the non-enzymic cyclization of squalene oxide? Extensive tests with radiolabelled starting material have revealed that not even traces of any one of a variety of tetracyclic terpene types is generated (Fig. 5) when the oxide is subjected to acid conditions normally employed for di- and tricyclization of many other terpene oxides. Moreover, the tricyclic products isolated were found to be derived from carbocation 6, bearing a five-membered C-ring, formed by reason of the greater tertiary carbonium ion stability in the product resulting from the third cyclization step. The problem of controlling C-ring size in non-enzymic cyclizations was solved by employing a simple device (Fig. 6), namely the incorporation of a preformed D-ring in the starting oxide (7), thereby virtually eliminating preferential carbonium stability in product resulting from tricyclization and thus permitting formation of the normally more stable six-membered third ring (8). By such means, total

biogenetic-type synthesis of β-amyrin (9), tetrahymanol (10), isoeuphenol (11), isotirucallol (12), parkeol (13) and dihydrolanosterol (14) were completed in our laboratories during the 1970's (10).

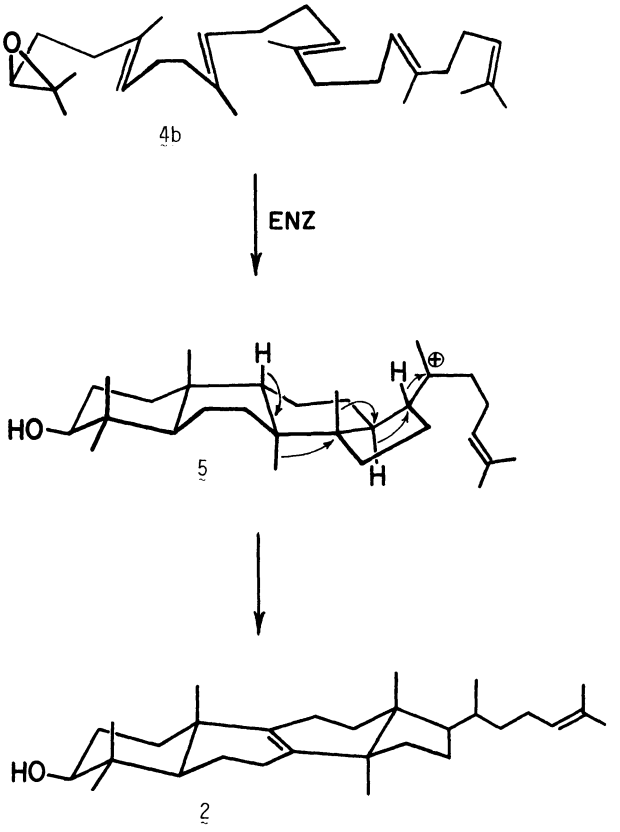


Fig. 3

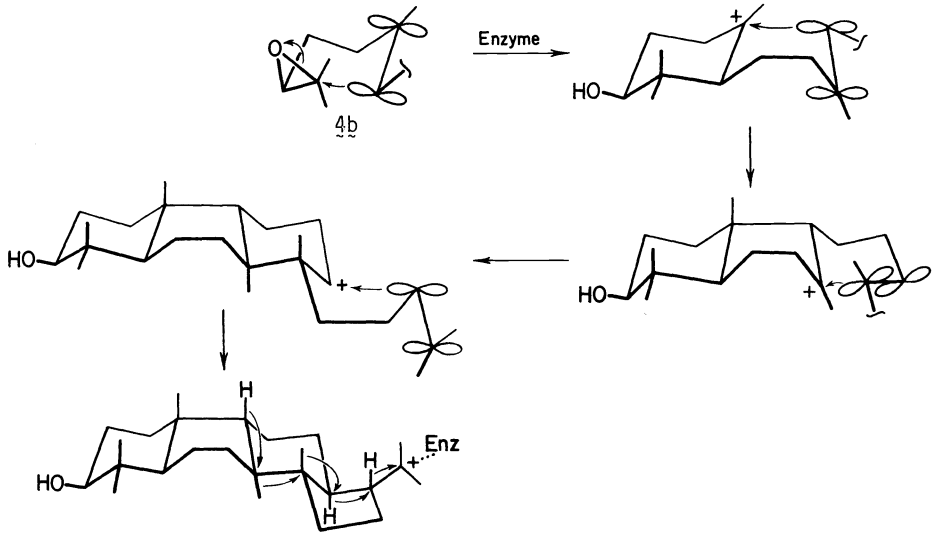
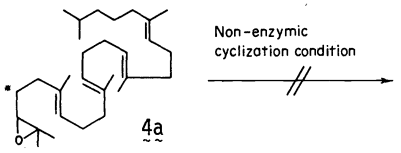


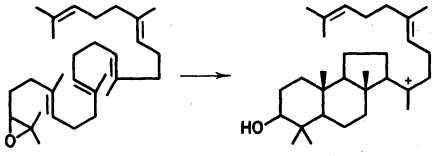
Fig. 4



4a

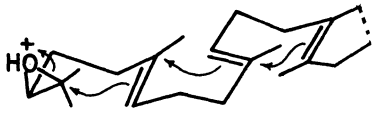
Isotirucallenol
Isoeuphenol
Dihydro-Δ^{8}-lanosterol
Dihydro-Δ^{7}-lanosterol
Tirucallenol
Euphenol
Dihydro-$\Delta^{13(17)}$-protosterol
Dihydroparkeol

Fig. 5



4a 6

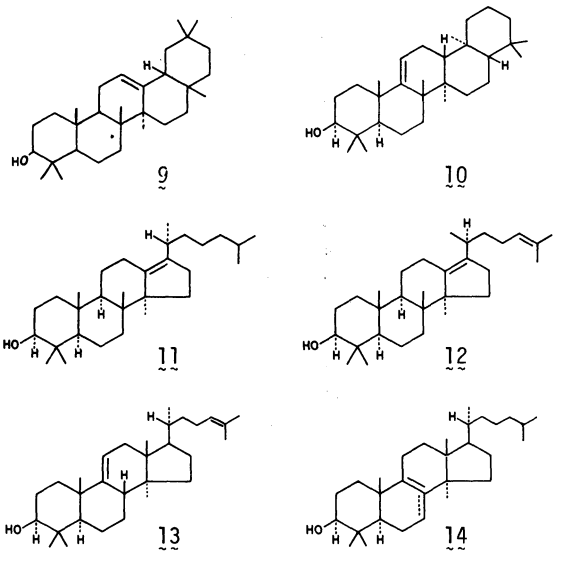
4a



7

8

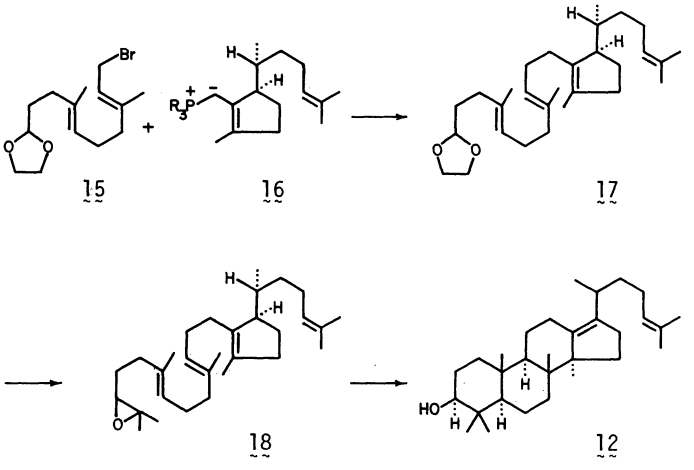
Fig. 6



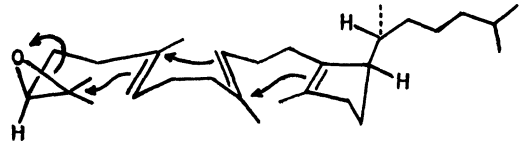
9 10 11 12 13 14

In order to illustrate the approach, we now describe the preparation and cyclization of 1,2-oxides 18 and 18a. By straight-forward means, detailed elsewhere, (11), allylic bromide 15 was prepared by selective degradation and transformation of trans,trans-farnesol; while ylide 16 was elaborated by a process featuring the oxidation cleavage and recyclization of limonene. Alkylation of 16 by 15 yielded, after reductive removal of the phosphorus entity, polyene acetal 17, which was transformed to 18. Cyclization of the epoxide yielded in part isoeuphenol (12) presumably resulting from overall reaction in the expected all-chair mode. Interestingly, reaction of oxide 18a led to protosterol 20 and dihydroparkeol (21), the structure and stereochemistry of which suggest cyclization in the chair-boat-chair fashion, giving 19, which spontaneously undergoes either simple proton loss to 20 or two-fold methyl migration, with final formation of 21.

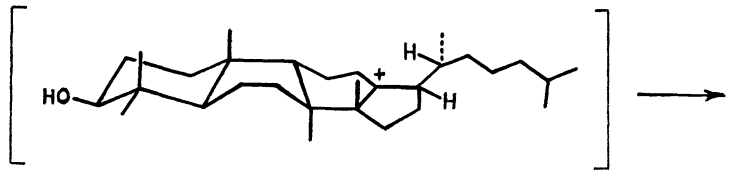
In all of the above pursuits, cyclizations involved starting materials bearing the terminal trisubstituted epoxide unit corresponding to that in squalene oxide itself. In the sections below, which summarize results completed and/or published during the calendar year 1980, variants of this natural unit are employed in order to achieve expeditious construction of other desired natural products.



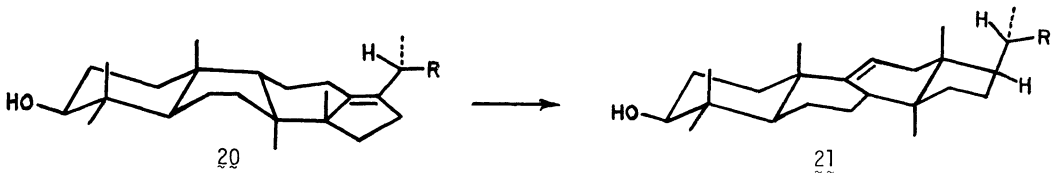
15 16 17 18 12



18a



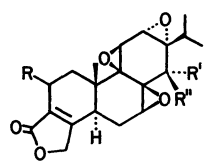
19

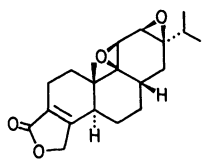


20 21

Diterpenes triptolide, triptonide and stemolide

Triptolide (22) and tripdiolide (23), accompanied in nature by triptonide (24), were reported in 1972 to possess promising potent cytotoxic properties (12), and because of their scarcity and unusual structures emerged as worthwhile targets for organic synthesis. In 1976, the structurally related stemolide (25) was reported as a constituent of a different plant source (13). Herein we describe total syntheses of 22, 24 and 25, achieved by various means which embody striking contrasts between biogenetic-type and traditional synthesis (14, 15, 16).

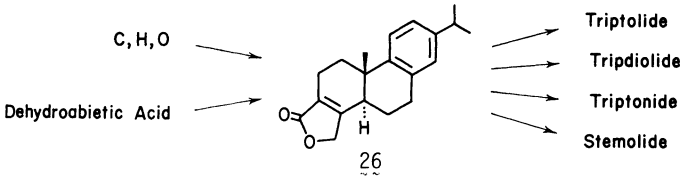




Triptolide (R, R' = H; R'' = OH) 22
Tripdiolide (R, R'' = OH; R' = H) 23
Triptonide (R = H; R', R'' = O) 24

Stemolide 25

In our laboratory, two total synthesis lines were followed, one involving construction from the elements and the other depending upon partial synthesis from the available, optically active dehydroabietic acid (Fig. 7). As plans, both approaches featured generation of a key intermediary tetracyclic lactone (26) or modification thereof, which would be convertible to the desired natural product. Obviously, in the route starting from the resin acid, considerable modification in the A-ring is required, as depicted in Fig. 8. In reduction to practice, dehydroabietic acid (26) was first converted by known procedures (17) to exocyclic olefin 27, which was carried through intermediates 28 and 29 to sulfide 30. The ylide derived from the corresponding sulfonium salt 31 readily underwent electrocyclic conversion to the isomeric thioether 32, which possesses the carbon skeleton needed for the final target molecule.



26

Fig. 7

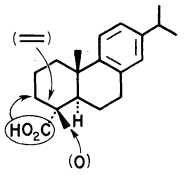
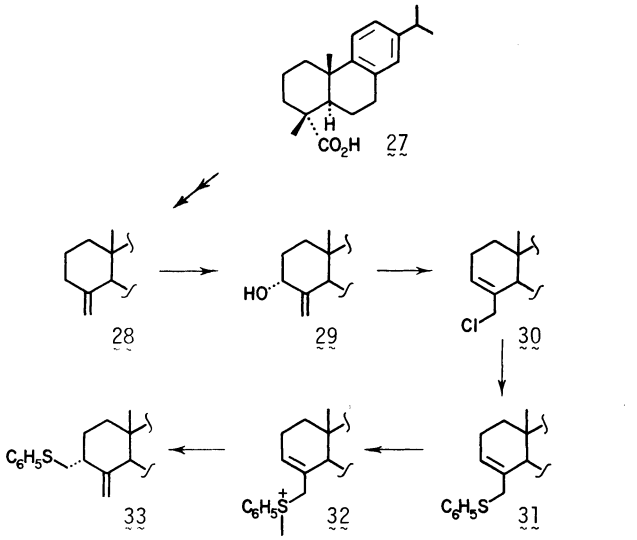
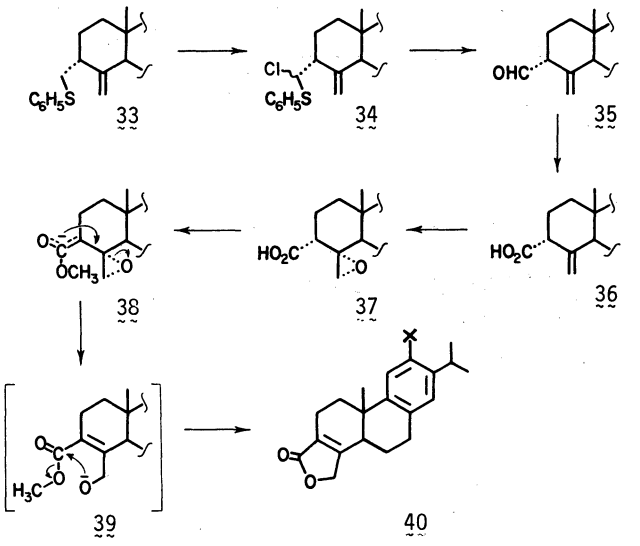


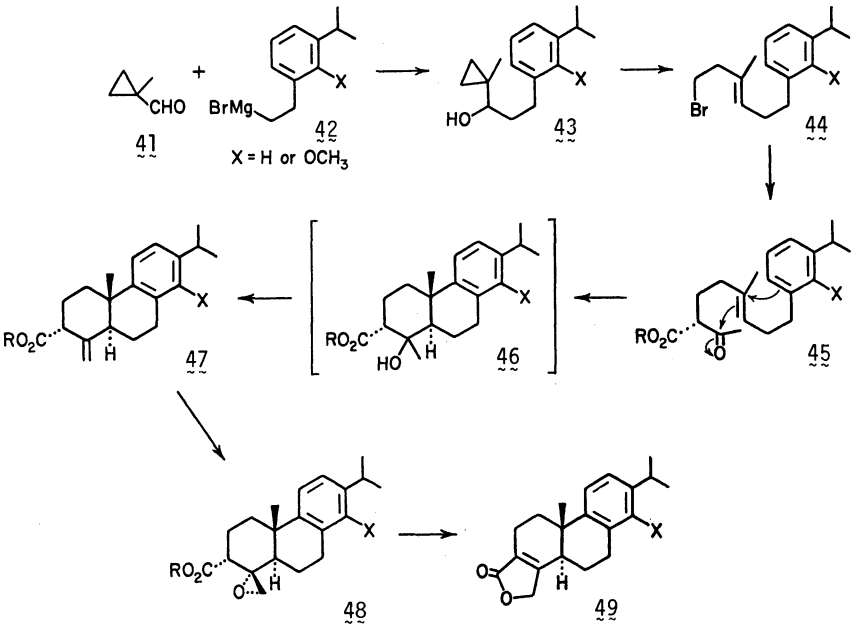
Fig. 8



In order to complete construction of the lactone moiety, thioether 33 was successively oxidized by way of intermediates 34 and 35 to β,γ-unsaturated carboxylic acid 36. Epoxidation of the latter provided 37, which after conversion to the methyl ester 38, easily suffered elimination by base to 39, the immediate precursor of lactone 40 (X = H or OCH_3).

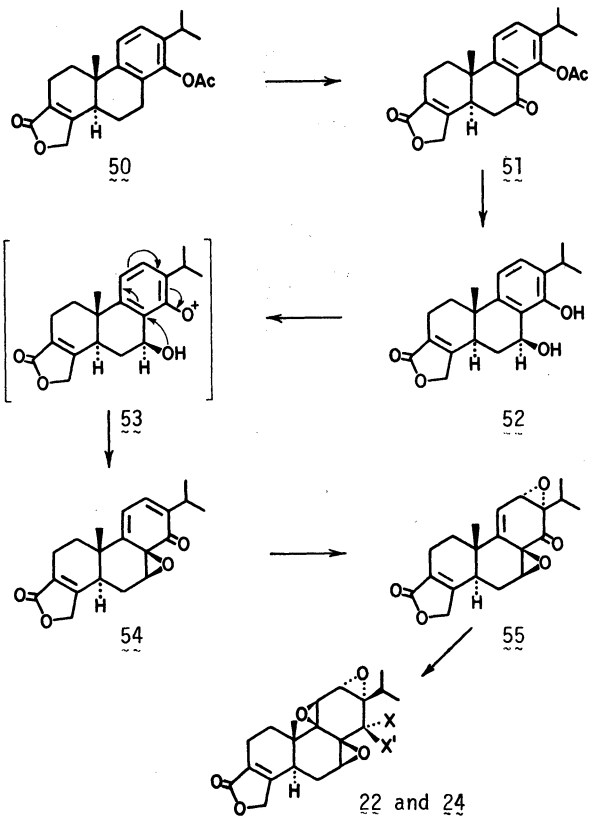
While the above series of steps bears no relation to biological pathways, a second approach to tetracyclic lactones of the type 26 depends upon a biomimetic carbocyclization triggered by a β-keto ester unit, never before employed as an initiator. The desired key intermediate for cyclization was readily assembled starting from two available building blocks, α-methylcyclopropylaldehyde (41) and the Grignard reagent (42) derived from a substituted β-phenethyl bromide. Skeletal rearrangement of the intermediate cyclopropylcarbinol 43 led to the butenyl bromide 44, which was used to alkylate acetoacetic ester, thereby giving 45. Stannic chloride-induced cyclization led to the isolable β-hydroxester 46, readily dehydrated to the β,γ-unsaturated ester 47. As in the earlier synthesis, epoxidation afforded 48, which was convertible by base to lactone 49.

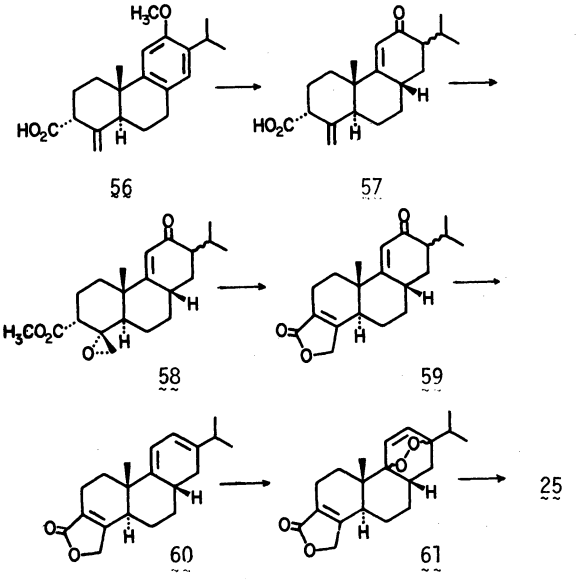




Completion of this triptolide synthesis depends, as does that of Berchtold and collaborators (18), upon earlier studies (19) of phenol oxidation which may well parallel the terminal steps in the biogenesis of triptolide and congeners. In order to prepare for execution of the appropriate biogenetic-type sequence, lactone 50 was oxidized at the benzylic methylene site, giving ketone 51, which was reduced and hydrolyzed to 52. Periodate oxidation presumably generates the equivalent of species 53, well set-up for participation of the benzylic hydroxyl, leading as shown to epoxycyclohexadienone 54. Additional separate oxidations afford, successively, diepoxide 55 and triepoxide 24 (triptonide), reducible to triptolide (22).

As far as stemolide is concerned, again we note that completion of the total synthesis depends upon oxidation chemistry which, as pointed out already (13), may correspond to final stages in the biosynthesis of the natural product. Since the required modification of the aromatic C-ring could not be made with the unsaturated lactone ring intact, initial reduction of an anisole unit was carried out on the unsaturated acid 56, giving cyclohexenone 57.





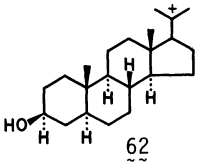
The isolated double bond in the latter could be safely oxidized to the oxirane 58, which as before was transformed by base directly to lactonic ketone 59. The tosylhydrazone of the latter was converted by base to diene 60, which underwent reaction with singlet oxygen to peroxide 61 (α- and β-). On being heated, the β-peroxide smoothly gave rise to stemolide (25). Both formation of the peroxide and its rearrangement to diepoxide have transition-metal promoted analogies and thus might be readily accomplished under biological conditions.

Traditional steroids

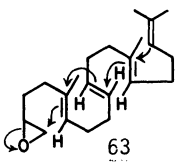
In light of the demethylations and other changes involved in the biochemical conversion of lanosterol (2) to cholesterol (3) and other traditional C_{30} sterols, close duplication of this overall transformation under non-enzymic conditions appears, by any sane view, impractical. Thus acceptable production of classical steroids through biogenetic-type synthesis calls for distinct departure from the biological pathway. Thus, by employing initiators other than the natural, epoxide type, W. S. Johnson and coworkers have been able to develop efficient polycyclization routes to various aromatic and non-aromatic sterols (20). However, heretofore no synthesis of a common sterol involving polycyclization of a polyene oxide has been reported. Merely conceptually, the simplest possible cyclization route to a traditional sterol system (62) would start from a mono-substituted epoxide such as 63; however, acid-promoted ring opening of the oxide would not, in the normal course of events, be expected to lead to formation of a six-membered A-ring.

In order to create a surrogate for a carboacyclic epoxide, we sought to employ in this connection the same device resorted to earlier (vide supra), viz., a preformed carbocyclic ring—in this case, ring A—on which is fused the epoxide initiator, as in 64. Insofar as carbonium stability is concerned, direction of the acid-catalyzed oxide ring-opening is largely immaterial; but both stereoelectronic and overall thermodynamic factors favor formation of the desired six-membered B-ring, after which, one hopes, additional cyclizations would occur, finally affording tetracyclic product of type 65. Optimism along these lines was fortified by the prior observation that at least monocyclizations of cyclohexene oxides closely similar to the butenylcyclohexene oxide portion of structure 64 were successful (21), proceeding in around 90% yield.

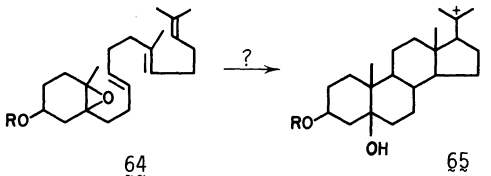
Toward this end, the sulfur ylide 66 was alkylated with trans-1,4-dichloro-2-butene, giving



62



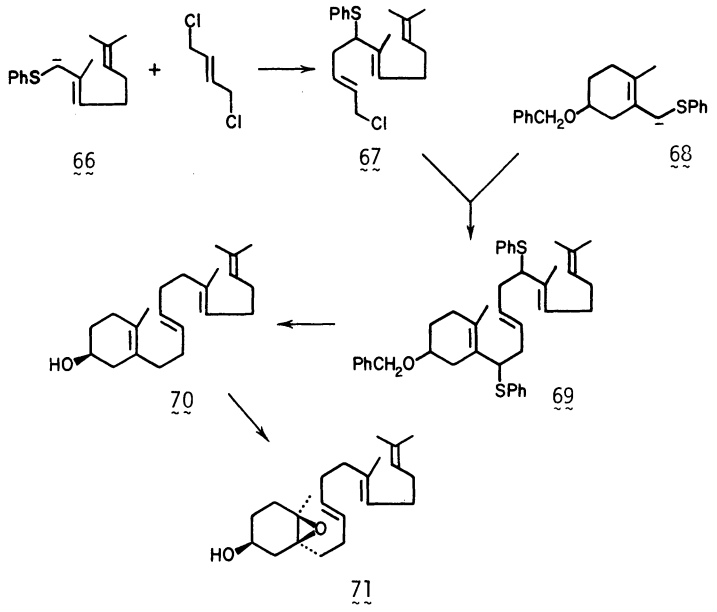
63

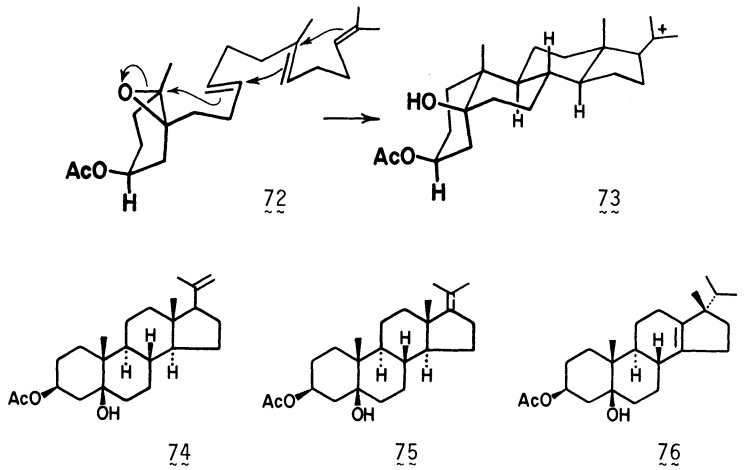


64 65

67, which was in turn used to alkylate a second thioether anion, 68, thereby producing the substituted polyene bisthioether 69. Reductive removal of sulfur resulted in formation of the simpler polyene alcohol 70, which, through transition-metal catalyzed regio- and stereoselective epoxidation (22), gave rise to the cyclohexenol oxide 71.

Behaving entirely in accordance with stereoelectronic theories of epoxide ring opening and polyene cyclization, the acetate (72) of 71 undergoes an uncommon tricyclization to the A/B cis 3,5-dioxygenated steroidal cation 73. Although there was some reason to expect that olefin 74 or 75 would be produced by simple proton loss from the cation 73, such was not the

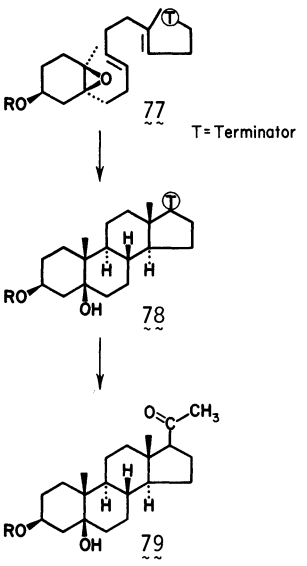




case; and, by comparison with authentic material it was demonstrated that the final product of the cyclization was the abnormal steroid 76, resulting from sequential hydrogen and methyl migration (23).

In order to realize a genuine sterol synthesis by the above cyclization means, a terminator other than isopropylidene was needed; and we therefore set about to investigate oxides of type 77, where T = e.g. $CH_3C{\equiv}C$- or $CH_3CO(COOR)CH$-. We can now report that such efforts have been successful, with intermediate cyclization product 78 being convertible to (±) pregnan-3β,5β-diol-20-one (79), indistinguishable by the usual spectral means from authentic, naturally derived material. Oxidation of 79 to the C-3 ketone followed by dehydration led to formation of (±) progesterone. Thus by means of a two-step oxidation-cyclization sequence, as in the biosynthetic process, typical sterols containing up to eight asymmetric centers can be assembled from a relatively simple polyene alcohol bearing but one chiral center.

In view of the intrinsic stereoselectivity and functionalization capabilities which characterize the synthesis approach outlined above, adaptation to various other sterol systems seems practicable and worthwhile. Such targets include the C-11 functionalized, adrenal cortical hormones as well as members of the cardenolide class which are oxygenated at C-3, C-5 and possibly C-19. Pursuit of such projects in this laboratory is planned.



Acknowledgment - Various portions of this work were supported separately through grants from the National Institutes of Health, the National Science Foundation and the American Cancer Society.

REFERENCES

1. (a) T. T. Tchen and K. Bloch, J. Am. Chem. Soc. 77, 6085 (1955); (b) R. B. Clayton and K. Bloch, J. Biol. Chem. 218, 305, 319 (1956).
2. E. E. van Tamelen and T. J. Curphey, Tetrahedron Lett. 121 (1962).
3. E. E. van Tamelen, A. Storni, E. J. Hessler and M. Schwartz, J. Am. Chem. Soc. 85, 3295 (1963).
4. E. J. Corey and W. E. Russey, J. Am. Chem. Soc. 88, 4750, 4751 (1966).
5. E. E. van Tamelen, J. D. Willett, R. B. Clayton and K. E. Lord, J. Am. Chem. Soc. 88, 4752 (1966).
6. E. E. van Tamelen and R. E. Hopla, J. Am. Chem. Soc. 101, 6112 (1979) and earlier references.
7. A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, Helv. Chim. Acta 38, 1890 (1955).
8. G. Stork and A. W. Burgstahler, J. Am. Chem. Soc. 77, 5068 (1955).
9. E. E. van Tamelen and D. R. James, J. Am. Chem. Soc. 99, 950 (1977).
10. E. E. van Tamelen, Acc. Chem. Res. 8, 152 (1975).
11. E. E. van Tamelen and R. J. Anderson, J. Am. Chem. Soc. 94, 8225 (1972).
12. S. M. Kupchan, W. A. Court, R. G. Dailey, Jr., C. J. Gilmore and R. F. Bryan, J. Am. Chem. Soc. 94, 7194 (1972).
13. P. S. Manchand and J. F. Blout, Tetrahedron Lett. 2489 (1976).
14. E. E. van Tamelen, E. G. Taylor, T. M. Leiden and A. F. Kreft III, J. Am. Chem. Soc. 101, 7423 (1979).
15. E. E. van Tamelen and E. G. Taylor, J. Am. Chem. Soc. 102, 1202 (1980).
16. E. E. van Tamelen, J. Demers, E. G. Taylor and K. Koller, J. Am. Chem. Soc. 102, 5424 (1980).
17. J. W. Huffman and R. F. Stockel, J. Org. Chem. 28, 506 (1963).
18. R. S. Buckanin, S. J. Chen, D. M. Frieze, F. T. Sher and G. A. Berchtold, J. Am. Chem. Soc. 102, 1200 (1980).
19. H. D. Becker, T. Bremholt and E. Adler, Tetrahedron Lett. 4205 (1972).
20. W. S. Johnson, Bioorg. Chem. 5, 51 (1976).
21. P. Marsham, D. A. Widdowson and J. K. Sutherland, J. Chem. Soc. Perkin 1, 238 (1974).
22. K. B. Sharpless and R. C. Michaelson, J. Am. Chem. Soc. 95, 6136 (1973).
23. E. E. van Tamelen and D. G. Loughhead, J. Am. Chem. Soc. 102, 869 (1980.