ment of authentic dihydro-$\Delta^{13(17)}$-protolanosterol (**4**) (or its acetate)[24] resulted in formation (70–80%) of dihydroparkeol (**5**)[25] (or acetate), the realization of the same transformation (vpc and gas chromatographic–mass spectral comparisons) when synthetic tetracycle **4** was subjected to such conditions confirms its identification as **4**. In that terpenoid **5** has been previously converted[26] to 24,25-dihydrolanosterol (**17**), the present work also constitutes a direct total synthesis of the latter natural product.[27]

Although generation of either the 9,10 trans or cis rearrangement in the hydronaphthalene framework arising from polycyclization of terpenoid terminal epoxides has been previously observed,[28] the formation of tetracycles **4**, **5**, and **8** from epoxides **2a** and **7a** represents the first *tric*yclization 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 **3**, **4**, **5**, **6**, **8**, and **17**, 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.

Acknowledgment. Thanks are due to the National Science Foundation (GP23019) and the National Institutes of Health (GM10421) for financial assistance, Dr. J. Trudell for gas chromatographic–mass spectral data, Dr. L. Durham for nmr consultation, Professors D. Arigoni, ETH, and J. Kutney, University of British Columbia, for samples of natural products, and Dr. M. Suffness for cooperation in the synthesis of intermediate **10d**.

(24) The observation that $SnCl_4$–CH_3NO_2 also effects, albeit in lower yield, conversion of **4** to **5** permits that **5** may be generated from **4** under the conditions when **4** is formed from 2.

(25) S. Uyeo, J. Okada, S. Matsunaga, and J. W. Rowe, *Tetrahedron*, 24, 2859 (1968).

(26) Despite the considerable difference in melting point from literature values and the unmistakable mass spectral retro Diels–Alder cleavage exhibited by the derived Δ^1-3-ketone indicative of a Δ^7 double bond, the epoxide cyclization product reported by E. E. van Tamelen and J. W. Murphy, *J. Amer. Chem. Soc.*, **92**, 7204 (1970), is indistinguishable from dihydroparkeol (**5**).

(27) The synthesis of lanosterol from cholesterol was achieved by R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *ibid.*, **79**, 1131 (1957).

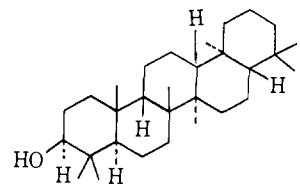
(28) Cis and/or trans: E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *ibid.*, **85**, 3295 (1963); E. E. van Tamelen and R. M. Coates, *Chem. Commun.*, 13, 413 (1966); E. E. van Tamelen and J. P. McCormick, *J. Amer. Chem. Soc.*, **91**, 1847 (1969). Trans: E. E. van Tamelen and R. G. Nadeau, *ibid.*, **89**, 176 (1967); E. E. van Tamelen, G. M. Milne, M. I. Suffness, M. C. Rudler-Chauvin, R. J. Anderson, and R. S. Achini, *ibid.*, **92**, 7202 (1970). Cis: ref 17.

E. E. van Tamelen,* R. J. Anderson
Department of Chemistry, Stanford University
Stanford, California 94305
Received June 12, 1972

Biogenetic-Type Total Synthesis. *dl*-Tetrahymanol

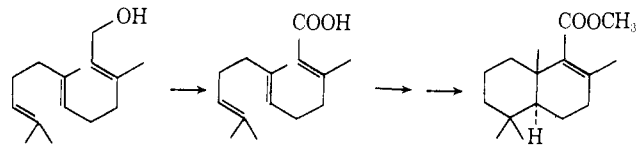
Sir:

Incorporating five carbocyclic rings and nine asymmetric centers, the protozoan metabolite tetrahymanol (**1**)[1,2] presents a considerable challenge for



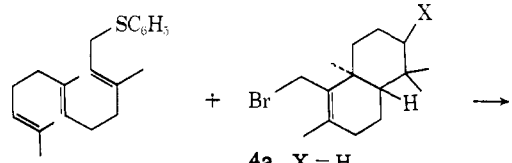
1

laboratory construction by efficient means. We have now completed a *dl*-tetrahymanol total synthesis—the first of a pentacarbocycle featuring ring formation solely by polyolefin cyclization methods—which comprises ten steps starting from farnesol (**2**), or seven steps from previously described, available starting material **3**.[3a]

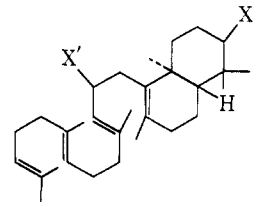


2 **3**

Bicyclic bromide **4a**, prepared by $LiAlH_4$ reduction of **3** to allyl alcohol followed by treatment with hydrobromic acid,[3b] was used without purification to alkylate (THF for several hours in the range −35 to 20°) the anion of phenyl thioether **5**,[4] prepared by sequential



5 **4a**, X = H
b, X = $OCH_2C_6H_5$



6a, X′ = SC_6H_5; X = H
b, X′ = H; X = H
c, X′ = SC_6H_5; X = $OCH_2C_6H_5$
d, X′ = H; X = OAc

in situ treatment of *trans,trans*-farnesol with methyllithium, *p*-toluenesulfonyl chloride, and lithium thiophenoxide. The trans,trans alkylation product **6a** [nmr (CCl_4) δ 7.07 (5, s), 4.97 (3, m), 3.90 (1, m), 0.87 (12, m)] (65%) was reductively desulfurized (100%)[4] with Li–$C_2H_5NH_2$ at −78° to a *ca.* 50:50 mixture of the desired 2,6,10,14-tetraene **6b** [nmr (CCl_4) δ 5.02 (3, m), 0.92 (3, s), 0.87 (3, s), 0.82 (3, s)] and the 2,6,11,14 isomer [nmr (CCl_4) δ 2.65 (2, d, J = 2 Hz)], separated by gc or preparative tlc ($AgNO_3$–SiO_2). Presumably because of adverse steric influences in the environment of the Δ^{14} tetrasubstituted bond, selective oxidative attack[5] on the terminal Δ^2 trisubstituted site

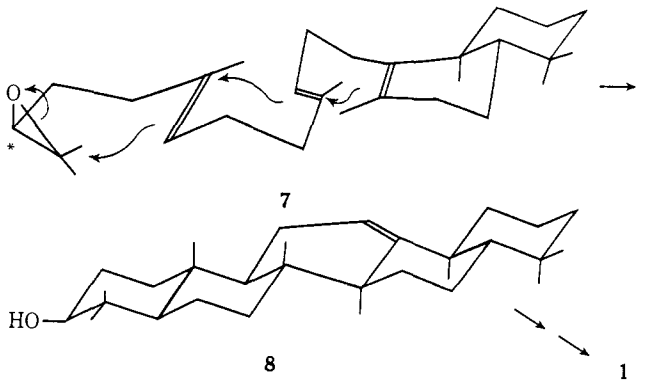
(1) F. B. Mallory, J. T. Gordon, and R. L. Conner, *J. Amer. Chem. Soc.*, **85**, 1362 (1963).

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

(3) (a) G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **77**, 5068 (1955); (b) M. A. Schwartz, Ph.D. Dissertation, Stanford University, 1965.

(4) J. F. Bielmann and J. B. Ducep, *Tetrahedron Lett.*, 3707 (1969).

(5) E. E. van Tamelen and T. J. Curphey, *ibid.*, 121 (1962).

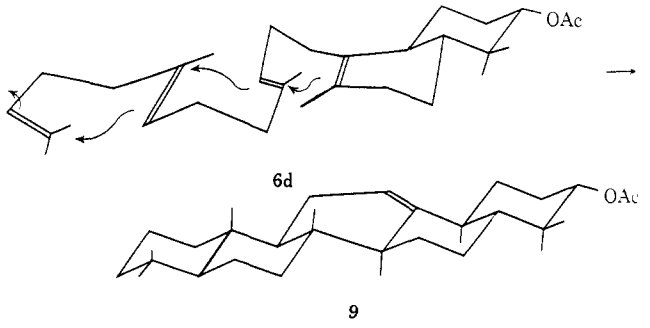


7

8 1

could be achieved, providing epoxide **7**, believed to be a 50:50 mixture of C-3(*) epimers [nmr (CCl_4) δ 5.15 (2, m), 2.53 (1, t, J = 6 Hz), 1.23 (3 s), 1.20 (3, s)]. Cyclization of **7**, carried out by means of $SnCl_4$ in CH_3NO_2 for 0.5 hr at 0°, yielded, after thin layer chromatographic separation, *dl*-Δ^{12}-dehydrotetrahymanol (**8**), mp 252–254°, [M^+ *m/e* 426.3896 (calcd, 426.3861); ir 3330 (br), 2920, 1701, 1254, 1084 cm^{-1}; nmr ($CDCl_3$) δ 5.25 (1, m), 3.25 (1, m), 1.13, 1.10, 0.97, 0.90, 0.87, 0.82, 0.78 (aliphatic methyl)] (yield 20%, based on the utilizability of one C-3 epimer).

In an alternative approach which more nearly approximates the established biological pathway,[6] the bicyclic polyene acetate **6d** was synthesized and cyclized. Under conditions similar to those described above, the known[7] bicyclic bromo ether **4b** was coupled with thioether **5**, providing thioether **6c** [nmr (CCl_4) δ 7.17 (10, s), 4.98 (3, m), 4.45 (2, q, J = 11 Hz), 3.95 (1, m), 2.82 (1, m), 0.97 (6, s), 0.83 (3, s)], which on reduction (Li–$C_2H_5NH_2$) and acetylation afforded tetraene **6d** [nmr (CCl_4) δ 5.05 (3, m), 3.11 (1, m), 0.98 (3, s), 0.93 (3, s), 0.77 (3, s)]. Although H_3PO_4 or $SnCl_4$ was ineffectual, CH_3CO_2H–H_2SO_4 or $BF_3 \cdot (C_2H_5)_2O$ served to convert (2%) **6d** to *dl*-$\Delta^{9(11)}$-dehydrotetrahymanyl acetate (**9**), identified at the microgram level by its nmr, ir, gc, and tlc properties, which were essentially identical with those of *dl*-Δ^{12}-dehydrotetrahymanyl acetate, and by its characteristic mass spectrum [*m/e* 468 (2%), 276 (33%), 216 (55%), 201 (67%), 191 (100%)].



6d

9

Conversion of synthetic *dl*-Δ^{12}-dehydrotetrahymanyl acetate, mp 249–251°, [M^+ *m/e* 468.3994 (calcd 468.3969 (7%), 249 (5%), 218 (100%), 203 (67%), 189 (55%)] to *dl*-tetrahymanol, patterned after a published relay,[8] involved initial CF_3CO_3H oxidation (80%), carried out in CH_2Cl_2 in the presence of Na_2CO_3,[9] to the acetate of *dl*-tetrahymanol-12-one, mp 290–292° [ir 1723, 1694 cm^{-1}; nmr (CCl_4) δ 2.05 (3, m), 1.95 (3, s); M^+ *m/e* 484.4010 (calcd 484.3916)]. On Wolff–Kishner reduction,[10] the ketone afforded (85%) *dl*-tetrahymanol, mp 271–274° [M^+ *m/e* 428.4048 (calcd 428.4018)] identical, except for melting point and optical properties, with naturally occurring tetrahymanol (mass spectral, nmr, ir, gc, and tlc comparison).[11]

Acknowledgment. The authors are grateful to Dr. J. R. Trudell, Stanford Medical Center, for gas chromatographic–mass spectral data, Dr. Alan Duffield for high-resolution mass spectral data, and Dr. F. B. Mallory, Bryn Mawr College, and Dr. E. Caspi, Worcester Foundation for Experimental Biology, for kindly supplying generous samples of natural tetrahymanol. Financial support was provided by the National Science Foundation (GP 23019).

(6) J. M. Zander, J. B. Greig, and E. Caspi, *J. Biol. Chem.*, **245**, 1247 (1970).

(7) E. E. van Tamelen, M. A. Schwartz, E. J. Hessler, and A. Storni, *Chem. Commun.*, 409 (1966).

(8) Y. Tsuda and coworkers (ref 2) have reported the conversion of α-onocerin diacetate to tetrahymanol.

(9) R. A. Micheli, *J. Org. Chem.*, 27, 666 (1962).

(10) Satisfactory results were achieved only by carrying out the reaction at 130° for 48 hr in the presence of anhydrous diethylene glycol, anhydrous hydrazine, and hydrazine hydrochloride, then adding sodium diethylene glycolate–diethylene glycol and warming to 210° for 24 hr; see W. Nagata and H. Itazaki, *Chem. Ind. (London)*, 1194 (1964); K. Schaffner, L. Cagliotti, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, 41, 152 (1958).

(11) All new compounds gave satisfactory elemental analyses.

(12) National Science Foundation fellow.

E. E. van Tamelen,* R. A. Holton, R. E. Hopla,[12] W. E. Konz
Department of Chemistry, Stanford University
Stanford, California 94305
Received June 12, 1972

Biogenetic-Type Total Synthesis. δ-Amyrin, β-Amyrin, and Germanicol

Sir:

We wish to announce the total biogenetic-type synthesis[1] of the pentacyclic triterpenoids δ-amyrin (**2**),[2] β-amyrin (**3**),[3] and germanicol (**4**),[4] all produced in nature presumably from squalene 2,3-oxide (**1**).[5] The laboratory reaction sequence features two separate polyolefin cyclization operations: in one, five asymmetric centers are generated during intramolecular annulation of the tetraene epoxide **5**, and in the second, a key intermediate **8a** is built up by means of a Linstead-type reaction carried out on triene **7**.

To initiate the synthesis of the D–E component, the Michael addition of ethyl 1-methallylmalonate to 3-chloro-2,5,5-trimethylcyclohex-2-one[6] was carried out

(1) Treatise on biogenetic-type synthesis: E. E. van Tamelen, *Fortschr. Chem. Org. Naturst.*, **19**, 242 (1961).

(2) Natural occurrence: O. C. Musgrave, J. Stark, and F. S. Spring, *J. Chem. Soc.*, 4393 (1952).

(3) Previous synthetic accomplishments in the β-amyrin area: (a) production of δ-amyrene-iso-β-amyrin from (+)-ambreinolide, J. A. Barltrop, J. D. Littlehailes, J. D. Rushton, and N. A. J. Rogers, *Tetrahedron Lett.*, 429 (1962); E. J. Corey, H. J. Hess, and S. Proskow, *J. Amer. Chem Soc.*, **81**, 5258 (1959); **85**, 3979 (1963); E. Ghera and F. Sondheimer, *Tetrahedron Lett.*, 3887 (1964); (b) conversion of δ-amyrene to β-amyrin, D. H. R. Barton, E. F. Lier, and J. F. McGhie, *J. Chem. Soc. C*, 1031 (1968).

(4) Synthesis of *dl*-germanicol: R. E. Ireland, S. W. Baldwin, D. J. Dawson, M. I. Dawson, J. E. Dolfini, J. Newbould, W. S. Johnson, M. Brown, R. J. Crawford, P. F. Hudrlik, G. H. Rasmussen, and K. K. Schmiegel, *J. Amer. Chem. Soc.*, **92**, 5743 (1970).

(5) The oxide has been established as a progenitor of β-amyrin in pea seedlings: E. J. Corey and P. R. Ortiz de Montellano, *ibid.*, **89**, 3362 (1967)

(6) T. G. Halsall and D. B. Thomas, *J. Chem. Soc.*, 2431 (1956).