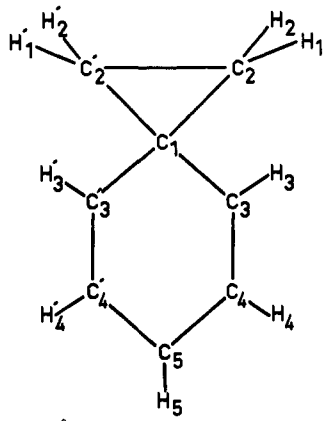

$r(C_1C_2) = 1.598$ Å
$r(C_2C_2') = 1.460$ Å
$r(C_3C_4) = (1.400$ Å)
$r(C_2H_1) = (1.080$ Å)
$r(C_4H_4) = (1.080$ A)
$\angle C_2C_1C_2' = 54.4°$
$\angle C_1C_3C_4 = 122.1°$
$\angle C_4C_5C_4' = (120.0°)$
$\angle H_{12}C_2C_2'$[12] $= 158.2°$
$\angle H_3C_3C_1 = 118.3°$
$\angle H_5C_5C_4 = (120.0°)$

$r(C_1C_3) = 1.431$ Å
$r(C_4C_5) = (1.400$ Å)
$r(C_3H_3) = (1.080$ Å)
$r(C_5H_5) = (1.080$ A)
$\angle C_3C_1C_3' = 115.8°$
$\angle C_3C_4C_5 = (120.0°)$
$\angle H_1C_2H_2 = 115.7°$
$\angle H_4C_4C_3 = (120.0°)$

Table I. Energy Data (kcal/mol)

Molecule	STO-3G
Bridged ethylenebenzenium (V)	0
Orthogonal perpendicular ethylenebenzenium (II)	35.4
Orthogonal staggered ethylenebenzenium (I)	42.3
Planar perpendicular ethylenebenzenium (IV)	46.5
Planar staggered ethylenebenzenium (III)	48.8

the relative energies of the open ions will be lowered some 10–15 kcal/mol by further geometric optimization and by extension of the basis function beyond minimal.[13] It is not anticipated, however, that such an effect will alter the stated conclusions.

In this and in the preceding communication[7] we have provided two examples of the interaction of an electron-deficient center with an area rich in density. The similarity is striking and we believe extends well beyond our present applications.

Acknowledgments. The author gratefully acknowledges Professor Lionel Salem (Orsay) for his comments and criticisms on the manuscript.

(12) $H_{12}C_2$ refers to the line bisecting the plane formed by carbon 2 and hydrogens 1 and 2.

(13) This latter behavior is to be expected in light of our experience with the homoallyl–cyclopropylcarbinyl system; see ref 7.

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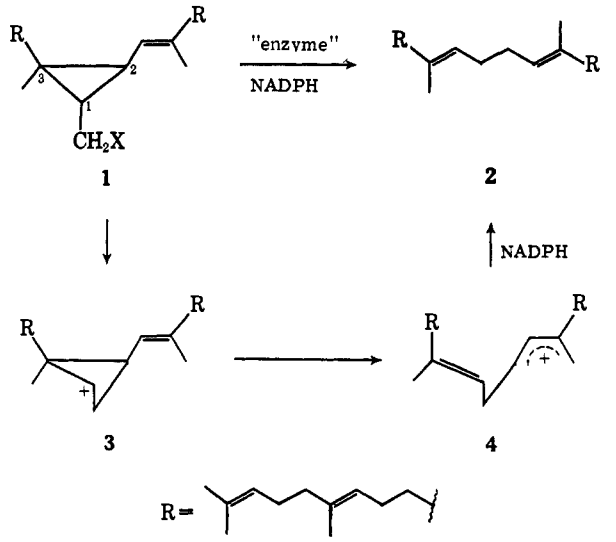
Solvolysis of *trans*-2,2-Dimethyl-3-(2′-methylpropenyl)cyclobutyl Tosylate. Model Reactions Relevant to Squalene Biosynthesis

Sir:

The reductive coupling of farnesyl pyrophosphate to squalene (**2**) proceeds through the C-30 intermediate, presqualene pyrophosphate,[1] the structure of which (**1**, X = OPP) now seems firmly established.[2,3] The rearrangement pathway **1** → **3** (or equivalent delocalized species) → **4**, terminated by a stereospecific hydride transfer from NADPH (Scheme I), has been suggested[1b,2,3b,4] as a mechanism for the **1** → **2** transformation.[5]

Scheme I



While this mechanism finds precedent in the rearrangements of cyclopropylcarbinyl compounds,[6] the heterolytic reactions of *trans*-chrysanthemol derivatives (**1**, R = CH_3) in solution lead principally to ring cleavage products.[7,8] In order to determine whether the subsequent steps in Scheme I would occur in the absence of enzymatic control, we have investigated the reactions of the C-10 cyclobutyl tosylate, **6**-OTs, a potential precursor to cation **3** (R = CH_3).[9] The corresponding C_{30} pyrophosphate has in fact been proposed as an additional enzymic intermediate between presqualene pyrophosphate and squalene.[2b] The trans isomer was selected in view of the stereochemistry

(1) (a) H. C. Rilling, *J. Biol. Chem.*, **241**, 3233 (1966); (b) W. W. Epstein and H. C. Rilling, *ibid.*, **245**, 4597 (1970).

(2) (a) H. C. Rilling, C. D. Poulter, W. W. Epstein, and B. Larsen, *J. Amer. Chem. Soc.*, **93**, 1783 (1971); (b) J. Edmond, G. Popjàk, S-M. Wong, and V. P. Williams, *J. Biol. Chem.*, **246**, 6254 (1971).

(3) (a) R. V. M. Campbell, L. Crombie, and G. Pattenden, *Chem. Commun.*, 218 (1971); (b) L. Altman, R. C. Kowerski, and H. C. Rilling, *J. Amer. Chem. Soc.*, **93**, 1782 (1971); (c) R. M. Coates and W. H. Robinson, *ibid.*, **93**, 1785 (1971).

(4) E. E. van Tamelen and M. A. Schwartz, *ibid.*, **93**, 1780 (1971).

(5) A similar scheme, but with ultimate deprotonation, may be involved in the biosynthetic coupling of geranyl–geranyl pyrophosphate to phytoene (dehydro **2**, R = *trans,trans*-homofarnesyl): W. W. Epstein, private communication; R. J. H. Williams, G. Britton, J. M. Charlton, and T. W. Goodwin, *Biochem. J.*, **104**, 767 (1967). The synthesis of prephytoene and its role in carotene biosynthesis have recently been reported: L. J. Altman, L. Ash, R. C. Kowerski, W. W. Epstein, B. R. Larsen, H. C. Rilling, F. Muscio, and D. E. Gregonis, *J. Amer. Chem. Soc.*, **94**, 3257 (1972).

(6) For leading references, see G. A. Olah, C. L. Jeuell, D. P. Kelly, and R. D. Porter, *J. Amer. Chem. Soc.*, **94**, 146 (1972).

(7) (a) L. Crombie, R. P. Houghton, and D. K. Woods, *Tetrahedron Lett.*, 4553 (1967); (b) R. B. Bates and D. Feld, *ibid.*, 4875 (1967); (c) C. D. Poulter, S. G. Moesinger, and W. W. Epstein, *ibid.*, 67 (1972).

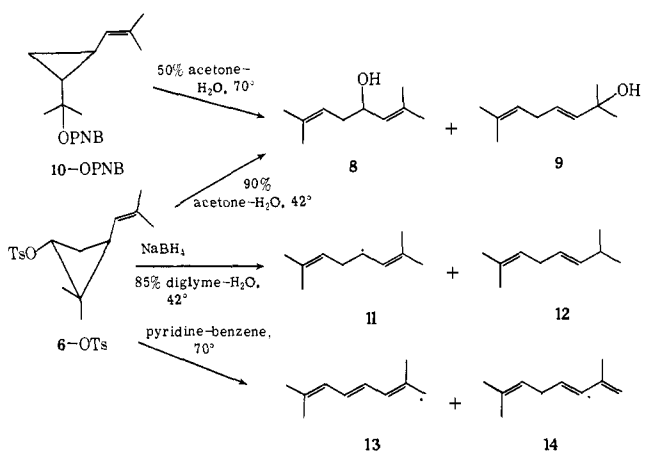
(8) A small amount of 2,7-dimethyl-2,6-octadien-4-yl methyl ether (methyl ether of 8) has recently been obtained from methanolysis of 2,5,5-trimethyl-2,6-heptadien-4-yl dimethylsulfonium fluoroborate, presumably by way of **1** (R = CH_3, X = +) and **4** (R = CH_3): B. M. Trost, P. Conway, and J. Stanton, *Chem. Commun.*, 1639 (1971).

(9) A similar investigation has been independently carried out by C. D. Poulter, *et al.*, *J. Amer. Chem. Soc.*, **94**, 5921 (1972).

of **1**-OPP[1b,2,3] and the known stereospecificity of cyclopropylcarbinyl rearrangements.[10]

Cycloaddition of dimethylketene (generated *in situ* from dimethylmalonic anhydride)[11] to 4-methyl-1,3-pentadiene at 125° afforded 2,2-dimethyl-3-(2′-methylpropenyl)cyclobutanone (**5**; 60%; ν_{max} 1780 cm^{-1}; δ 5.12 (d, sept, 1 H, J = 1.5, 7 Hz), 1.75, 1.64 (d, 3 H, J = 1.5 Hz), 1.15, 0.99 (s, 3 H)).[12,13] Reduction of **5** with aluminum isopropoxide in isopropyl alcohol gave a 40:60 mixture of **6**-OH (δ 5.13 (d, sept, 1 H, J = 1.5, 7 Hz), ~3.9 (m, 1 H), 1.07, 0.89 (s, 3 H)) and its cis isomer **7**-OH (δ 5.00 (d, sept, 1 H, J = 1.5, 7 Hz), ~3.7 (m, 1 H), 1.04, 0.89 (s, 3 H))[14] which was converted to a mixture of the tosylates since the epimeric alcohols could not be separated.

Hydrolysis of **6**-OTs in 90% acetone–water (sodium acetate buffer) afforded a mixture of the acyclic dienols **8** (27%; δ 5.00 (br t, 2 H, J = 7 Hz), 4.15 (m, 1 H), 2.08 (br t, 2 H, J = 7 Hz), 1.8–1.5 (12 H)) and **9** (55%; δ 5.62 (m, 2 H), 5.03 (br t, 1 H, J = 7 Hz), 2.62 (m, 2 H), 1.71, 1.60 (br s, 3 H), 1.21 (s, 6 H)). The cis tosylate (mp 48–49°) proved to be much less reactive than the trans ($k_{6\text{-OTs}}^{42°}$ = 4.5 × 10^{-4} sec^{-1}, $k_{6\text{-OTs}}^{42°}/k_{7\text{-OTs}}^{42°}$ = 250) as expected[15a] and was efficiently recovered (95%) after complete hydrolysis of **6**-OTs. The same dienol mixture was formed from hydrolysis of the *trans*-cyclopropylcarbinyl ester, **10**-OPNB (mp 64–65°).[16]



(10) (a) K. B. Wiberg and G. Szeimies, *J. Amer. Chem. Soc.*, **92**, 571 (1970); (b) Z. Majerski and P. von R. Schleyer, *ibid.*, **93**, 665 (1971).

(11) (a) W. E. Hanford and J. C. Sauer, *Org. React.*, 135 (1946); (b) H. Staudinger, *Helv. Chim. Acta*, 8, 306 (1925); (c) H. M. Frey and N. S. Issacs, *J. Chem. Soc. B*, 830 (1970).

(12) H. Bestian and D. Günther, *Angew. Chem., Int. Ed. Engl.*, **2**, 608 (1963).

(13) All compounds gave nmr, ir, and mass spectra in accord with the indicated structures; only key data are cited. All new compounds except the unstable tosylates, 6-OTs and 7-OTs, gave satisfactory combustion analyses.

(14) The stereochemical assignments are based upon the stereoselectivity of lithium aluminum hydride reduction of **5** (**6**-OH/**7**-OH ~ 1/4),[15a-e] the nmr chemical shifts for C*H*OH in **6**-OH and **7**-OH,[15f] and the greater solvolytic reactivity of **6**-OTs.[15a,c,e]

(15) (a) K. B. Wiberg and G. L. Nelson, *Tetrahedron Lett.*, 4385 (1969); (b) G. M. Lampman, G. D. Hager, and G. L. Couchman, *J. Org. Chem.*, **35**, 2398 (1970); (c) C. F. Wilcox, Jr., and R. J. Engen, *Tetrahedron Lett.*, 2759 (1966); (d) R. Huisgen and L. A. Feiler, *Chem. Ber.*, **102**, 3391 (1969); (e) I. Lllien and L. Handlosser, *J. Amer. Chem. Soc.*, **93**, 1682 (1971); (f) I. Lllien and R. A. Doughty, *ibid.*, **89**, 155 (1967).

(16) Alcohol **9**-OH was prepared from ethyl diazoacetate and 4-methyl-1,3-pentadiene ($CuSO_4$, 50°, 2:1 trans:cis esters, 40%) followed by reaction with methylmagnesium iodide and column chromatographic separation of the isomers. The stereochemical assignments are based upon the chemical shift of the vinyl protons as compared to *cis*- and *trans*-chrysanthemol and chrysanthemates (A. F. Bramwell, L. Crombie, P. Hemesley, G. Pattenden, M. Elliott, and N. F. Janes, *Tetrahedron*, **25**, 1727 (1969)).

Reductive solvolysis of **6**-OTs in the presence of sodium borohydride (1.6 M)[17] gave, in addition to the dienols **8** and **9** (39%), the two known[18] dienes **11** (34%) and **12** (12%), **7**-OTs again being recovered unchanged. The identity of **11** was established by direct comparison with an independently prepared specimen,[18b] while that of **12** relies upon the correspondence of its nmr spectral data with the literature values.[18a] The acyclic trienes **13** (56%; λ_{max} 281 (57,200); δ 6.3–5.5 (m, 4 H), 1.80, 1.73 (s, 6 H)) and **14** (28%; λ_{max} 233 (21,800); δ 6.2–4.8 (m, 3 H), 4.75 (br s, 2 H), 2.73 (br t, 2 H, J = 7 Hz), 1.77 (t, 3 H, J = 1 Hz), 1.70, 1.60 (br s, 3 H)) were obtained when **6**-OTs was heated in pyridine–benzene,[19] a transformation analogous to phytoene biosynthesis.[5]

The facile ring opening reactions of **6**-OTs and **10**-OPNB indicate that the steps subsequent to formation of cyclobutyl intermediate **3** are inherently favorable. Thus, the overt functions of the enzyme(s) in Scheme I would appear to be chiefly avoidance of the thermodynamically favored ring opening of **1**[7] and maintenance of specificity in the final hydride transfer. We suggest that the former function may be accomplished if the plane of the adjacent double bond of **1**-OPP is fixed within the active site so that the π orbitals are aligned perpendicular to the 1,2-cyclopropane bent bond. Since allylic resonance stabilization of the incipient positive charge would not be possible in this conformation, premature ring opening would be avoided. In this same orientation, the π bonds are aligned parallel to the 2,3-cyclopropane bond and may thus assist the ring scission of **3** to **4**.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for financial assistance.

(17) H. M. Bell and H. C. Brown, *J. Amer. Chem. Soc.*, 88, 1473 (1966); Z. Majerski, S. Borčič, and D. E. Sunko, *Tetrahedron*, **25**, 301 (1969).

(18) (a) J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *J. Amer. Chem. Soc.*, **90**, 4758 (1968); (b) U. T. Bhalerao and H. Rapoport, *ibid.*, **93**, 5311 (1971). We are grateful to Professor Rapoport for a copy of the nmr spectrum of **11**.

(19) M. Sakai, H. H. Westberg, H. Yamaguchi, and S. Masamune, *ibid.*, **93**, 4611 (1971).

(20) A. P. Sloan Foundation Fellow, 1971–1973.

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Model Studies of Terpene Biosynthesis. Cationic Rearrangements Leading to Head-to-Head Terpenes[1]

Sir:

It is now evident that cyclopropylcarbinyl pyrophosphates are key intermediates in the biosyntheses of the symmetric head-to-head terpenes, squalene (C_{30})[2] and

(1) We wish to acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Research Corporation, and the University of Utah Research Fund for support of this work.

(2) (a) H. C. Rilling, C. D. Poulter, W. W. Epstein, and B. Larsen, *J. Amer. Chem. Soc.*, **93**, 1783 (1971); (b) L. J. Altman, R. C. Kowerski, and H. C. Rilling, *ibid.*, **93**, 1782 (1971); (c) R. M. Coates and W. H. Robinson, *ibid.*, **93**, 1785 (1971); (d) J. Edmond, G. Popják, S. M. Wong, and V. P. Williams, *J. Biol. Chem.*, **246**, 6254 (1971); (e) R. V. M. Campbell, L. Crombie, and G. Pattenden, *Chem. Commun.*, 218 (1971).