tion about the $C_1$–$C_2$ bond in **14** will retain the specific orientation of $H_a$ and $H_b$.[12,16,19] The cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement should then occur with expected inversion of configuration at $C_1$ and $C_4$.[20,21] Model studies indicate that cation **15** rearranges to allylic ion **16**[22] followed by stereospecific hydride transfer to $C_4$ from NADPH*[2b] to give squalene.

Most of the stereospecific steps shown in Scheme II do not require special orientation by an enzyme, although the efficiency of the overall transformation obviously depends on enzyme catalysis at several points. It is also interesting to note that models indicate the entire sequence of molecular rearrangements shown in Scheme II can take place with little movement of the long isoprenoid side chains.

**Acknowledgments.** The technical assistance of Mrs. E. K. Davis is gratefully acknowledged. We also wish to thank the Research Corporation, the Petroleum Research Fund (1694-G1), administered by the American Chemical Society, the National Science Foundation, and the National Institutes of Health (GM 08 321 and Research Career Development Award 2-K3-GM-6354).

(19) D. S. Kabakoff and E. Namanworth, *J. Amer. Chem. Soc.*, **92**, 3234 (1970).

(20) (a) K. B. Wiberg and G. Szeimies, *ibid.*, **91**, 571 (1970); (b) J. E. Baldwin and W. D. Foglesong, *ibid.*, **90**, 4303 (1968).

(21) The possibility of a puckered cyclobutyl cation intervening between **14** and **15** cannot be ruled out:[16a] C. D. Poulter and S. Winstein, *ibid.*, **91**, 3650 (1969).

(22) Hydride attack of **16** at $C_4$ should proceed with inversion,[12,16a] giving the wrong absolute configuration. We have preliminary evidence that a delicate balance exists between vinyl-substituted cyclopropylcarbinyl cations similar to **14** and **15** and their allylic isomers. Thus, the rearrangement **14** → **15** → **16** is quite plausible: C. D. Poulter and S. Moesinger, unpublished results.

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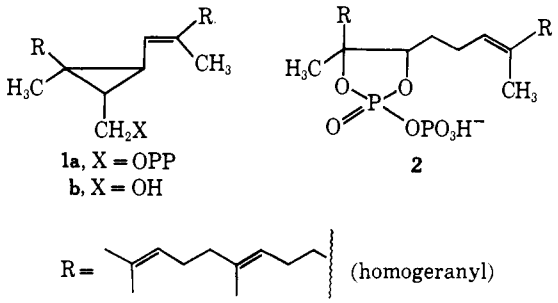
## Stereoselective Total Synthesis of (±)-Presqualene Alcohol

*Sir:*

The mechanism of the enzymatic coupling of two molecules of farnesyl pyrophosphate to squalene has been a subject of considerable interest and conjecture.[1–5] The recent discovery[2a] of a C-30 intermediate (presqualene) in the biosynthetic process has, owing to the possible mechanistic implications, focused attention upon the structure of this new triterpene. Structural investigations with enzymatically produced material have led to two independent proposals, **1a**[2b,c] and **2**,[3b] for the constitution of presqualene. We wish to report a stereoselective total synthesis of racemic presqualene alcohol[2] which confirms structure **1b** for this dephosphorylated derivative of presqualene, and in particular defines the relative stereochemistry about the cyclopropane ring.[6,7]




Copper-catalyzed decomposition (cupric acetylacetonate or copper powder in refluxing toluene) of *trans,trans*-farnesyl diazoacetate (**4**, $\nu_{max}$ 2100 $cm^{-1}$),[8a,b] prepared in 76% yield from *trans,trans*-farnesol (**3**)[9] by reaction with glyoxalyl chloride tosylhydrazone and triethylamine in methylene chloride,[10] affords the cyclopropyl lactone **5** ($\nu_{max}$ 1775 $cm^{-1}$, $M^+$ 262)[8a,b] in about 20% yield after purification by column chromatography and hydrolysis–relactonization (dicyclohexylcarbodiimide in methylene chloride). The γ-lactone ring must be cis fused to the three-membered ring and, in view of the stereospecificity of intermolecular copper-catalyzed diazo ester cycloadditions,[11] the trans relationship between the side chain and the oxymethylene group should be retained; hence the stereochemistry of **5** is assigned. The corresponding hydroxy acid **6a** (mp 58.5–60.5°)[8b] was esterified with diazomethane and then oxidized to the *cis*-aldehyde ester **7** [69%; $\nu_{max}$ 1730, 1700 $cm^{-1}$; δ 9.58 (1 H, d, $J$ = 6 Hz); 1.52 (3 H, s)],[8a,b] with the chromium trioxide–dipyridine complex in methylene chloride.[12] Exposure of **7** to 5% sodium hydroxide in aqueous methanol (1:1) at room temperature effects first rapid ester hydrolysis followed by a slower ($t_{1/2}$ ~ 2 hr) epimerization of the aldehyde group; reesterification with diazomethane gives the more stable *trans*-aldehyde ester **8** [92%; $\nu_{max}$ 1730, 1700; δ 9.56 (1 H, apparent t, $J$ ~ 1 Hz), 1.32 (3 H, s)].[8a–c,13,13a]

(1) Reviews: R. B. Clayton, *Quart. Rev., Chem. Soc.*, **19**, 168 (1965); I. D. Franz and G. J. Schroepfer, *Annu. Rev. Biochem.*, **36**, 691 (1967).

(2) (a) H. C. Rilling, *J. Biol. Chem.*, **241**, 3233 (1966); (b) H. C. Rilling and W. W. Epstein, *J. Amer. Chem. Soc.*, **91**, 1041 (1969); (c) W. W. Epstein and H. C. Rilling, *J. Biol. Chem.*, **245**, 4597 (1970).

(3) (a) J. W. Cornforth, R. H. Cornforth, C. Donninger, and G. Popjak, *Proc. Roy. Soc., Ser. B*, **163**, 492 (1966); (b) G. Popjak, J. Edmond, K. Clifford, and V. Williams, *J. Biol. Chem.*, **244**, 1897 (1969).

(4) (a) G. Krishna, H. W. Whitlock, Jr., D. H. Feldgruegge, and J. W. Porter, *Arch. Biochem. Biophys.*, **114**, 200 (1966); (b) G. E. Risinger and H. D. Durst, *Tetrahedron Lett.*, 3133 (1968).

(5) (a) B. M. Trost and R. LaRochelle, *ibid.*, 3327 (1968); (b) J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *J. Amer. Chem. Soc.*, **90**, 4758 (1968); (c) G. M. Blackburn, W. D. Ollis, C. Smith, and I. O. Sutherland, *Chem. Commun.*, 99 (1969).

(6) The relative and absolute stereochemistry of (−)-**1b** has recently been established by degradative studies: H. C. Rilling, W. W. Epstein, and B. Larsen, *J. Amer. Chem. Soc.*, submitted for publication. We are grateful to Professor Epstein for advance disclosure of these results and a preprint of the manuscript.

(7) Two concurrent and independent syntheses of presqualene alcohol have been completed: L. J. Altman, R. C. Kowerski, and H. C. Rilling, *J. Amer. Chem. Soc.*, **93**, 1782 (1971); L. Crombie and coworkers, private communication from Professor Rilling.

(8) (a) This compound gave infrared and nmr spectra compatible with the structure shown. Only the key data are cited. (b) A satisfactory combustion analysis was obtained. (c) Elemental composition was verified by exact mass determination (with ±0.0003) either on the molecular ion, or indirectly by the metastable defocusing technique.

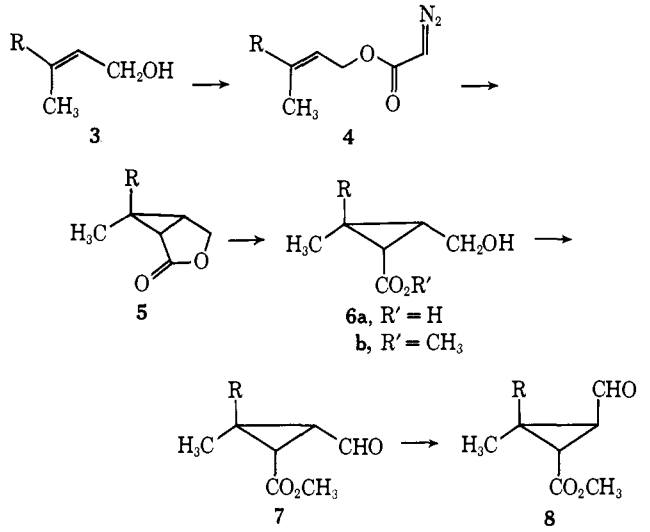
(9) R. B. Bates, D. M. Gale, and B. J. Gruner, *J. Org. Chem.*, 28, 1086 (1963).

(10) H. O. House and C. J. Blankley, *ibid.*, **33**, 53 (1968).

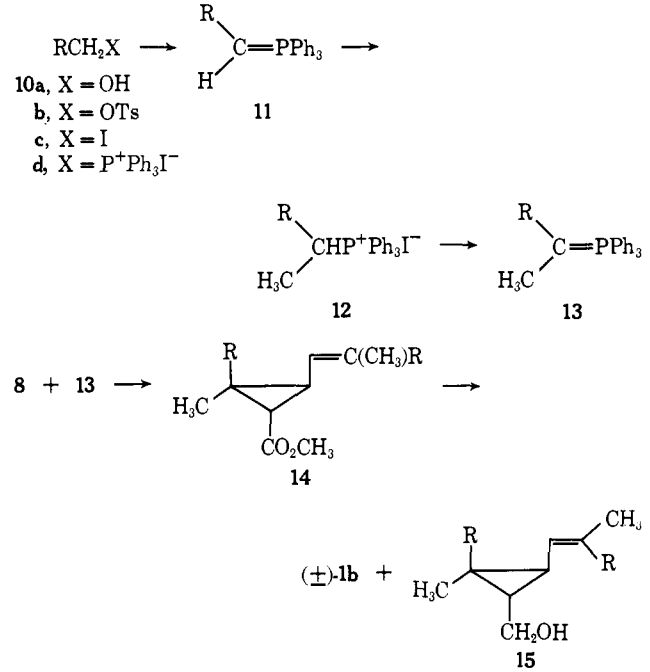
(11) W. von E. Doering and T. Mole, *Tetrahedron*, **10**, 65 (1960).

(12) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968); R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

(13) At equilibrium <5% of original cis isomer **7** remains. There seems little doubt that epimerization has occurred only at the aldehyde position, since cyclopropane carboxylate undergoes <10% exchange in 0.25 *M* sodium deuteroxide–deuterium oxide at 150° for 5 days: J. G. Atkinson, J. J. Csakvary, G. T. Herbert, and R. S. Stuart, *J. Amer. Chem. Soc.*, **90**, 498 (1968).



Phosphorane **13**, required for attachment of the second side chain, was prepared from geranylacetic acid (**9**)[14] as follows. Successive reactions with lithium aluminum hydride,[14a] tosyl chloride, sodium iodide–acetone, and triphenylphosphine in benzene gave the primary phosphonium iodide **10d** (mp 92–93°, 34% overall).[8a,b] Deprotonation with *n*-butyllithium in ether and subsequent methylation of the monosubstituted ylide **11** with a large excess of methyl iodide produced the secondary phosphonium iodide **12**;[15] addition of a second equivalent of *n*-butyllithium to **12** (after removal of the excess methyl iodide) in tetrahydrofuran furnished the disubstituted ylide **13**.



The Wittig reaction between the transaldehyde ester **8** and phosphorane **13** in tetrahydrofuran provided a mixture of esters **14** (57%)[8a,c] isomeric about the newly formed double bond. Reduction with lithium aluminum hydride yielded the corresponding alcohols (67%)[8c] which were separated by preparative tlc on silica gel impregnated with 7% silver nitrate.[16] The more polar and major (~2/3) isomer gave the following spectral data:[16] $\delta_{220}^{CDCl_3}$ 5.12 (4 H, m), 4.94 (1 H, d, $J \sim 8$ Hz), 3.82 (1 H, 2 d, $J \sim 6$, 10 Hz), 3.56 (1 H, 2 d, $J \sim 9$, 10 Hz), 1.9–2.2 (14 H, m), 1.70 (3 × 3 H, s), 1.62 (4 × 3 H, s), 1.3–1.5 (m), 1.16 (3 H, s), 0.8–1.0 (m); *m/e* 426 ($m^+$), 408, 395, 357, 339, 289, 273, 271. The less polar isomer had very similar properties. The data are in good accord with those reported for presqualene alcohol.[3]

Radioactive samples of the two C-30 alcohol isomers, prepared by reduction of **14** with lithium aluminum tritide, were compared directly with presqualene alcohol by Professor Rilling at the University of Utah. The tlc and glc mobilities of the synthetic and natural materials were found to be essentially identical. While the pyrophosphate of the minor isomer **15** was essentially devoid of enzymatic activity, the derivative of the major isomer (±)-**1b** was converted into squalene in 33% yield (66% if only one enantiomer is active). This synthesis, therefore, confirms the structure of presqualene alcohol proposed by Rilling and Epstein[3] and establishes the relative cyclopropane stereochemistry depicted in **1b**.[17]

**Acknowledgments.** We are very grateful to Professor Rilling for performing the comparisons, phosphorylations, and enzymatic assays and to H. D. Pigott for the purification of **3**. Financial support from the National Institutes of Health, Eli Lilly and Company, and E. I. du Pont and Company is appreciated. Funds contributing to the purchase of the HA 220 nmr spectrometer were provided by the National Science Foundation.

(16) Although ostensibly homogeneous on tlc and glc (as TMS derivative, 3% SE-30, 240°), small extraneous absorptions can be discerned in the nmr spectra [$\delta$ 4.33 (t, $J$ = 7 Hz), and excessive integration in the regions $\delta$ 1.3–1.5 and 0.8–1.0] and ir spectra ($\nu_{max}$ 1730 $cm^{-1}$).

(17) Since the reaction between **8** and **14** is evidently the first synthesis of a trisubstituted olefin with an unsymmetrical dialkylphosphorane, the geometry about the double bond cannot be assigned with certainty at this time.

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(13a) NOTE ADDED IN PROOF. Equilibration in methanol-*O*-*d* has been found to occur with incorporation of one deuterium atom (90%) adjacent to the formyl group (nmr,-CHO, s).

(14) (a) I. N. Nazarov, S. M. Makin, O. A. Shavrgin, and V. A. Smirnyagin, *Zh. Obshch. Khim.*, **30**, 443 (1960); *J. Gen. Chem. USSR*, **30**, 467 (1960). (b) The acid was purified *via* the *S*-benzylisothiouronium salt: D. W. Dicker and M. C. Whiting, *J. Chem. Soc.*, 1994 (1958).

(15) *Cf.* C. T. Eyles and S. Trippett, *ibid.*, *C*, 67 (1966).

## Chemistry of the Copper–Dithiooxalate Complexes. The Synthesis of a New Carbonyl Sulfide Complex

*Sir:*

Dithiooxalato complexes in which the dithiooxalate ligands are sulfur bonded to the central metal ions interact with coordinatively unsaturated metal complexes, giving rise to polynuclear coordination compounds. These interactions, which stem from the ability of the carbonyl groups to function as donors for Lewis acids, are manifested in the electronic and structural characteristics of the ternary complexes.[1,2] A study of the chemistry of the bis(dithiooxalato)copper-

(1) D. Coucouvanis, *J. Amer. Chem. Soc.*, **92**, 707 (1970).

(2) D. Coucouvanis, R. E. Coffman, and D. Piltingsrud, *ibid.*, **92**, 5004 (1970).