strong, albeit destabilizing, orbital mixing involving the isotopic bond and the π cloud may be important.

Acknowledgment. We wish to thank Professors F. W. Dahlquist, C. E. Klopfenstein, T. Koenig, and J. E. Baldwin for valuable suggestions and stimulating discussion.

(16) National Institutes of Health Postdoctoral Fellow, 1971–1972.

(17) We thank the National Science Foundation for partial support of this investigation.

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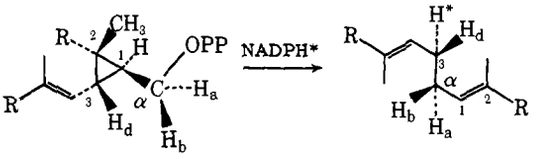
Received March 27, 1972

Model Studies of Terpene Biosynthesis. Stereoselective Ionization of *N*-Methyl-4-[(αS,1*R*,3*R*)-chrysanthemyloxy]pyridinium-d_1 Iodide[1]

Sir:

The stereospecific head-to-head condensation of two molecules of farnesyl pyrophosphate during the biosynthesis of squalene (**2**) is known to proceed through a

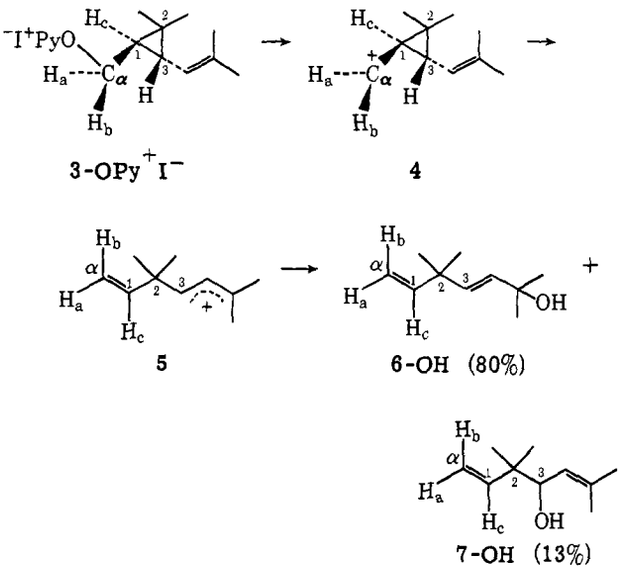


1-OPP **2**

C_{30} cyclopropylcarbinyl intermediate, presqualene pyrophosphate (**1**-OPP, R = homogeranyl).[2,3] We have proposed a mechanism in which the stereochemistry of all but the last step leading from **1**-OPP to **2** can be attributed to the solvolytic properties of cyclopropylcarbinyl cations with minimal special orientation by an enzyme.[2a] Recently, Trost and coworkers demonstrated that the skeletal rearrangements required for biosynthesis of squalene from presqualene pyrophosphate were possible under normal solvolysis conditions in a C_{10} model system.[4] If the configuration of C_α is to be inverted during a solvolytic rearrangement in a manner analogous to that found for squalene, C_α must assume a specific orientation with respect to the cyclopropane ring during heterolysis of the C_α–O bond. Based on work with alkyl-substituted cyclopropylcarbinyl derivatives,[5] we suggested that a conformation in which the leaving group was trans to the C_1–C_3 cyclopropane bond would facilitate ionization by utilizing the vinyl substituent at C_3 for delocalization of charge. Subsequent inversion of C_α is consistent with stereochemical studies of cyclopropylcarbinyl rearrangements.[6] However, in a recent paper Kispert and coworkers[7] reported, on the basis of semiempirical calculations (INDO approximation), that interaction between positively charged C_α and the vinyl substituent at C_3 through the cyclopropane ring is expected to be very small or nonexistent.

N-Methyl-4-[chrysanthemyloxy]pyridinium iodide (**3**-OPy$^+$I$^-$) should provide a suitable C_{10} model system with which to determine the preferred stereochemistry at C_α during ionization of presqualene pyrophosphate.[8] Hydrolysis of **3**-OPy$^+$I$^-$ is known to give a mixture of alcohols with two major components, yomogi alcohol (**6**-OH), 80%, and artemisia alcohol (**7**-OH), 13%, in which only the C_1–C_3 cyclopropane bond has been ruptured (Scheme I).[9] Although two cationic intermediates are thought to precede formation of alcohols **6**-OH and **7**-OH,[10] the stereochemistry of C_α during ionization of **3**-OPy$^+$I$^-$ should determine the relative positions of H_a, H_b, and H_c in the allylic alcohols. Rotation about the C_α–C_1 bond cannot occur during the solvolytic lifetime of **4**,[5,11] and the rearrangement **4** → **5** does not alter the relative positions of protons at C_α and C_1. Therefore, the preferred orientation for C–O bond heterolysis can be deduced by replacing H_a with deuterium and examining the proton distribution at C_α in hydrolysis products **6**-OH and **7**-OH.

Scheme I. Hydrolysis of *N*-Methyl-4-[chrysanthemyloxy]pyridinium Iodide



(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.

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(8) Replacing the homogeranyl substituents by methyl groups should not alter the reactivity of the cyclopropylcarbinyl core of **1**-OPP.

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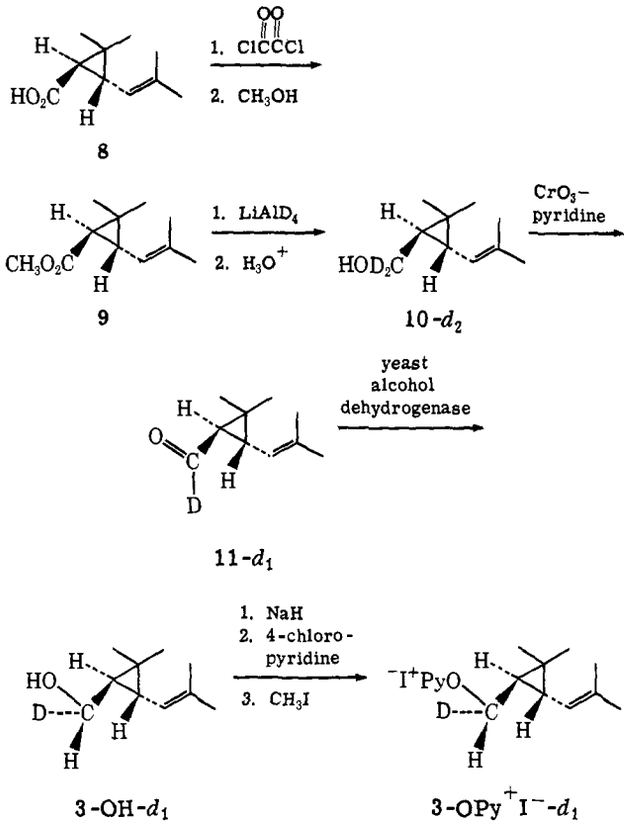
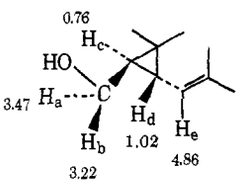
(1*R*,3*R*)-Chrysanthemic acid (97% optically pure)[12] was converted to (1*R*,3*R*)-chrysanthemol-d_2 (**10**) by the sequence of reactions outlined in Scheme II. Chro-

Scheme II. Synthesis of *N*-Methyl-4-[(α*S*,1*R*,3*R*)-chrysanthemyloxy]pyridinium-d_1 Iodide



mium trioxide–pyridine oxidation[14] gave a 95:5 mixture of aldehyde **11** and unoxidized alcohol **10** which was introduced without additional purification[15] into an aqueous suspension of actively fermenting yeast.[16] Glpc analysis of **3**-OH-d_1 using conditions (500-ft Carbowax 20M) which cleanly separated *cis*- and *trans*-chrysanthemol gave no evidence (<0.5%) of the undesired cis isomer. From nmr spectra[17] of **3**-OH-d_1 it is obvious that the yeast alcohol dehydrogenase reduction



$|J_{a,b}| = 11.4$ Hz $\quad |J_{c,d}| = 5.5$ Hz
$|J_{a,c}| = 6.2$ Hz $\quad |J_{d,e}| = 7.5$ Hz
$|J_{b,c}| = 8.3$ Hz

was stereospecific. Protons H_a and H_b of chrysanthemol are intrinsically nonequivalent[2e,18] with a chemical-shift separation of 0.25 ppm in carbon tetrachloride. By replacing H_a with deuterium the eight-line pattern for H_a and H_b is reduced to a doublet of triplets at 3.22 ppm ($J_{b,c} = 8.3$ Hz, $J_{a,b} = 1.6$ Hz[19]) which is further simplified to a doublet by irradiation at the deuterium resonance position. At high spectrum amplitudes with deuterium decoupling, a weak doublet at 3.47 ppm ($J_{a,c} = 6.2$ Hz) was also observed. Yeast alcohol dehydrogenase is known to stereospecifically reduce deuterioaldehydes to the corresponding *S* primary alcohols.[16] Since chrysanthemic acid (**8**) used to prepare **3**-OH-d_1 was a 97:3 mixture of 1*R*,3*R* and 1*S*,3*S* enantiomers, the weak doublet at the H_a resonance position was expected. A comparison of intensities for H_a and H_b indicated 4.8% of the α*S*,1*S*,3*S* diastereomer, in good agreement with the optical purity of **8**. Preparation of **3**-OPy$^+$I$^-$-d_1 from **3**-OH-d_1 does not alter the configuration of C_α.[20]

Hydrolysis of *N*-methyl-4-[(α*S*,1*R*,3*R*)-chrysanthemyloxy]pyridinium iodide and isolation of **6**-OH and **7**-OH were carried out as previously described[9] using conditions where the initially formed allylic alcohols are stable. A deuterium-decoupled ^{1}H spectrum of yomogi alcohol gave two AB quartets of unequal intensity (85 and 15%) for protons at positions H_a, H_b, and H_c (Scheme I). The larger AB quartet results from protons at 4.89 and 5.74 ppm coupled by 17.4 Hz, and the smaller quartet results from protons at 4.84 and 5.74 ppm coupled by 10.6 Hz. From the relative magnitudes of J_{AB}[21] we conclude that the major quartet corresponds to a structure with protons at positions H_b and H_c and deuterium at H_a, while the minor quartet represents a structure with protons at H_a and H_c and deuterium at H_b. The ^{1}H nmr spectrum of artemisia alcohol also gave two unequal AB quartets (87 and 13%). The larger quartet (δ 4.97 and 5.87 ppm) had $J_{AB} = 17.6$ Hz and the smaller (δ 4.96 and 5.87 ppm) had $J_{AB} = 10.6$ Hz. Again the proton attached to C_α was found predominantly in the H_b position.

It is clear from the nmr spectra of **6**-OH-d_1 and **7**-OH-d_1 that 3-OPy$^+$I$^-$-d_1 ionizes stereoselectively from the conformation shown in Scheme I. After correction for 5% of the α*S*,1*S*,3*S* diastereomer, the stereoselectivity of **3**-OPy$^+$I$^-$-d_1 during hydrolysis is 91 ± 2%, congruent with a rate factor of 9 in favor of the predicted stereochemistry of ionization. I prefer to ascribe the stereoselectivity to electronic control by the vinyl substituent at C_3 since steric interactions between the leaving group and the endo methyl group at C_2 would be expected to give the opposite result. By analogy one should expect parallel behavior of presqualene pyrophosphate.

(12) Measured $[\alpha]^{25}$D +13.4 (*c* 5.4, C_2H_5OH) and +24.3° (*c* 5.0. $CHCl_3$) as compared with reported values of $[\alpha]^{23}$D +14.4 (*c* 3, C_2H_5OH) and +25.9° (*c* 3, $CHCl_3$) for optically pure acid.[13]

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(17) Nmr spectra were taken in carbon tetrachloride on a Varian A-60 spectrometer or a Varian XL-100-12 spectrometer. Chemical shifts are reported in δ, parts per million, relative to internal tetramethylsilane.

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Received April 10, 1972