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PRENYL SUBSTITUTED CYCLOBUTANONES AS SQUALENE SYNTHETASE INHIBITORS[1]

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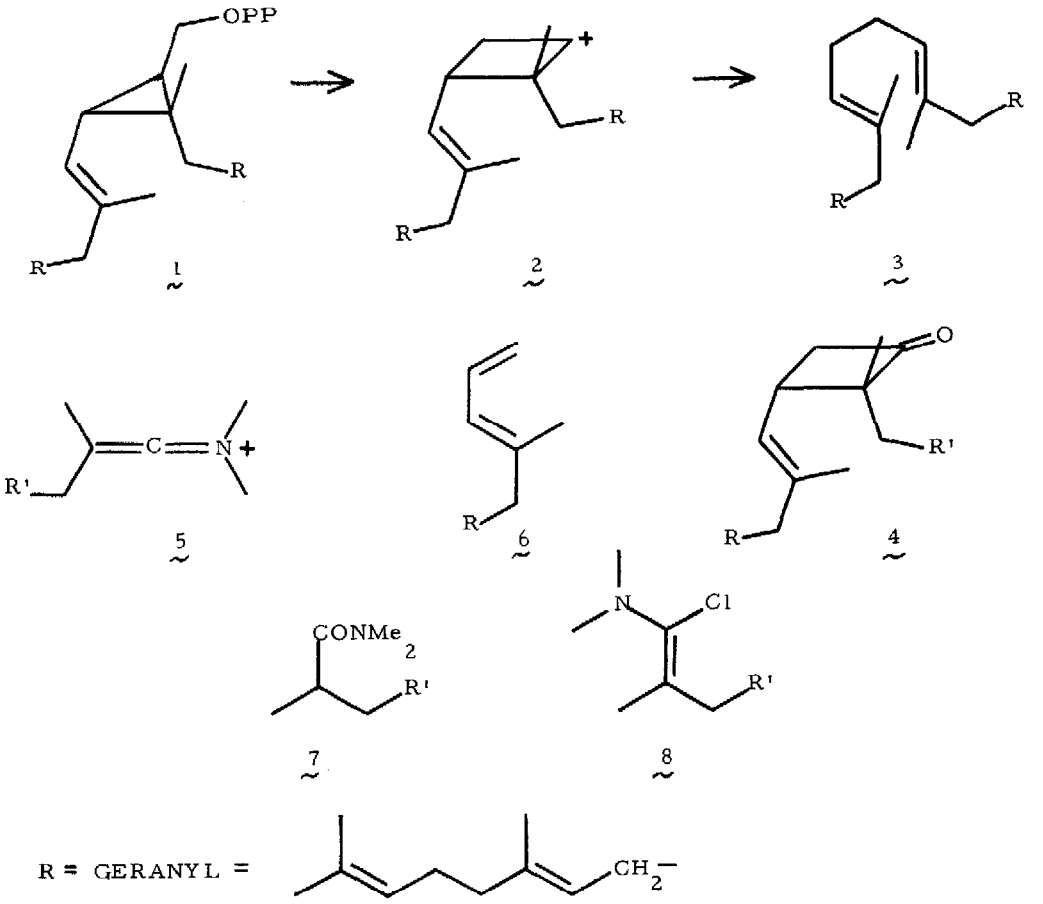
Although virtually no direct information is available on the enzymatic mechanism by which presqualene pyrophosphate (1) is transformed into squalene (3),[2] solvolysis studies with small (ten carbon) model compounds have been used to define thermodynamically favored pathways.[3] These formally entail pyrophosphate loss to a cyclopropylmethylene carbonium ion, multiple rearrangement to the squalene skeleton, and quenching of the cation by hydride transfer. The model studies suggest that the highest energy barrier in the rearrangement sequence lies near cyclobutyl cation 2,[3a] the pyrophosphate of which has been mentioned as a possible discrete intermediate.[4] If model studies do, in fact, reflect the enzymatic mechanism, the transition state for the enzymatic rearrangement sequence should also approximate 2.[5] Cyclobutanone analogs of cation 2, in which the charged atom is replaced by a similarly hybridized and polarized carbonyl carbon, might therefore function as "transition state" inhibitors of the enzyme squalene synthetase.[6] The cyclobutanones would also be useful as precursors to cyclobutanol derivatives for mechanistic and model studies. We report here the synthesis and preliminary bioassay of 3-(2,6,10-trimethylundeca-1,5,9-trienyl)-2,2-dimethylcyclobutanone (4a) and 3-(2,6,10-trimethylundeca-1,5,9-trienyl)-2-methyl-2-(4,8-dimethyl-1-nonyl)cyclobutanone (4b), as well as a functional group incompatibility in 5c which has prevented synthesis of 4c.

The cyclobutanones were assembled by polar cycloaddition of keteneimmonium cations[7] 5a and 5b to 4,8,12-trimethyl-1,3,7,11-tridecatetraene (6). Diene 6 was prepared in 94% yield by Wittig condensation of methylenetriphenylphosphorane and E,E-farnesal.[8] N,N-Dimethyl-1-chloro-2-methylpropenylamine (8a), the precursor of 5a, was prepared from N,N-dimethylisobutyramide (7a)[9] by sequential treatment with gaseous phosgene[10] and triethylamine.[7] Addition of 8a

(3 mmol) to a CH_2Cl_2 solution of 6 (2.99 mmol) and $AgBF_4$ (3.23 mmol) at -78°C, warming the mixture slowly to room temperature, filtration, aqueous base workup, silica gel chromatography, and bulb-to-bulb distillation gave cyclobutanone 4a (59%), a single peak on glc (13.99 min, 175°C);[11] ir (film) 1790 cm^{-1}; nmr ($CDCl_3$) 1.03 and 1.22 (s, 6H, cyclobutyl methyls), 1.63 and 1.68 (s, 12H, allyl methyls), 1.88-2.23 (m, 8H, allyl methylenes), 2.68-3.35 (m, 3H, cyclobutyl H), and 4.87-5.33 ppm (m, 3H, vinyl H); CIMS m/e 289 (molec. ion + 1). Anal. ($C_{20}H_{32}O$): calcd., C, 83.27; H, 11.18; found C, 82.98, H, 11.05. The nmr signal at 1.03 ppm is attributed to the cyclobutyl methyl cis to the farnesyl group, and that at 1.21 ppm to the trans methyl, by correlation with pertinent literature examples.[12]

The α-chloroenamine 8b was prepared from dimethylamide 7b in 99% yield (allowing for recovered starting material) as described for 8a.[8] Amide 7b was obtained by catalytic hydrogenation of 7c (10% Pd/C, ethanol, 97.5% yield), which in turn was made in 92% yield by stepwise reaction of the known free acid[13] with 1,1-carbonyldiimidazole and dimethylamine.[8,14] Treatment of 8b and 6 with $AgBF_4$ in CH_2Cl_2, as described above, gave a mixture of products from which 4b (cyclobutyl Z:E ratio 6:4 by glc) was isolated in 35% yield by high vacuum removal of volatile components and silica gel chromatography: ir (film) 1785 cm^{-1}; CIMS m/e 429 (molec. ion + 1); calc. exact mass for $C_{30}H_{52}O$, 428.4018; observed 428.4016.[15] The isomer mixture, although difficult to separate, gave each isomer with 30% contamination of the other on careful column chromatography through silica gel. These enriched mixtures showed that the two isomers had similar nmr spectra except for the position of the cyclobutyl methyl signals. The common portion of the spectrum is as follows: 0.87 (d, J=5.8 Hz, 9H, aliphatic methyls), 0.96-1.54 (m, 14H, aliphatic CH_2 and CH), 1.62 and 1.68 (s, 12H, allylic methyls), 1.70-2.40 (m, 8H, allylic CH_2), 2.60-3.34 (m, 3H, cyclobutyl H), and 5.17 ppm (m, 3H, vinyl H). The cyclobutyl methyl group appeared at 1.21 ppm in the major isomer of the product mixture (glc 8.70 min, 240°C),[11] and at 1.03 ppm in the minor isomer (glc 10.01 min, 240°C).[11] Correlation of these signals with those of the methyl groups in 4a allows assignment of the cyclobutyl-Z configuration to the major isomer.

Synthesis of 4c by analogous condensation of 8c with 6 gave a complex mixture, in which products with infrared absorption appropriate to cyclobutanones did not have thirty-carbon skeletons. Analysis of the product mixture by nmr indicated substantial loss of vinyl protons, suggesting that intramolecular cyclizations of 5c may have occurred. The use of keteneimmonium cations for cyclobutanone synthesis thus appears limited to compounds without vicinal unsaturation.



R' = a) H b) TETRAHYDROGERANYL c) GERANYL

Cyclobutanones 4a and 4b are weak inhibitors of yeast squalene synthetase compared with farnesyl pyrophosphate analogs.[16] A 10-15% inhibition was observed in our bioassay[16] with the cyclobutanones at about 5 mM concentration, although the quantitative accuracy of the data is clouded by the water insolubility of the compounds.

REFERENCES AND NOTES

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