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# A NEW BIOGENETIC-TYPE CYCLIZATION OF CITRAL TO α-CYCLOCITRAL VIA AN ENAMINE

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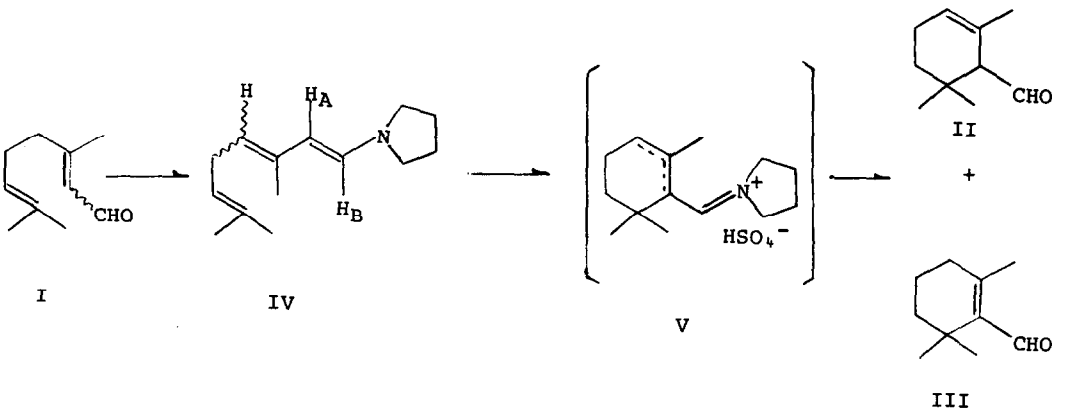
Several representatives of terpene structural types have been synthesized by the non-enzymic cationic cyclization reactions which are recognized as a model reaction for biosynthesis of cyclic terpenes from acyclic ones and are called biogenetic-type cyclization reaction.[1,2]

We report here a versatile biogenetic-type cyclization reaction which has been found to convert citral (a mixture of cis- and trans-isomers)(I),[3] an acyclic monoterpene carrying no asymmetric carbon, to α-cyclocitral(II) having an asymmetric center. Being different from the reported procedure[4] featuring the acid-catalyzed cyclization of the citral-aniline Schiff base, which usually




I IV V II III

gives a mixture of II and β-cyclocitral(III) in a ratio of 2:1, our new method developed here, exclusively afforded II with concomitant formation of the trace amount of III.

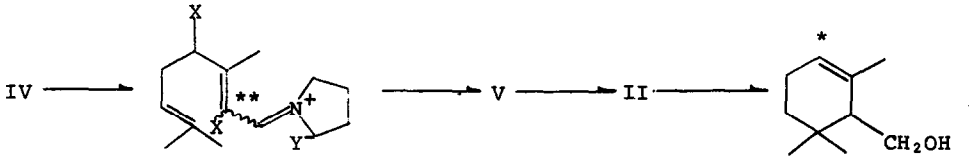
Reflux of a benzene solution of I(1.0 eq.) and pyrrolidine(2.0 eq.) in the presence of Molecular Sieves 4A[5] for 1 hr, followed by the filtration and evaporation in vacuo, gave the crude pyrrolidine enamine(IV) as a pale brown oil in a quantitative yield. The structure of IV was tentatively assigned as shown in the Chart due to its spectral data.[6] IR$\nu_{max}^{cap}$ $cm^{-1}$: 1639, 1631, 1618, 1613(olefinic double bonds), 930(trans disubstituted olefin). NMR(in $CDCl_3$): δ6.33, 6.41(two sets of doublet, $J_{AB}$=14 cps, 1H, $H_A$), δ4.48-5.28(multiplets, 3H, other olefinic protons). Cyclization of the crude IV was accomplished by treating with a mixture of conc. sulfuric acid and water(ratio by vol. 10:1) at 0° for 3 hr, and the formed imminium salt(V) was directly hydrolyzed without isolation by refluxing the whole reaction mixture after the pH of the aqueous solution was adjusted to be 3-4 with 10% sodium hydroxide solution. Usual extractive isolation, followed by the purification with silica gel column chromatography(solvent benzene-n-hexane 4:1), afforded pure II as a colorless oil in 41% yield. The isolated II was identified with the authentic sample[4] by comparing their spectral data(IR) and their behaviors on tlc and glc analyses. The glc analysis(15% SE-30 on Diasolid L, 1.0 m, 110°) of the crude reaction product obtained after the extractive isolation, clearly disclosed that III[4] (retention time 5.2 min) was also produced in 0.8% yield in addition to II (retention time 3.0 min).[7]

The use of a variety of secondary amines in place of pyrrolidine, gave results as follows(yields of II(isolated) and III(determined by glc)): piperidine, 33 and 1.4%; morphorine, 12 and 0.5%; dibenzylamine, 8.0 and 1.0%.

Although the cyclization reaction of IV was further carried out under several different reaction conditions in order to improve the yield of II, these examinations simply afforded II, accompanied with the trace amount of III(detected by glc), in lower yields than that observed before(reaction conditions, yield of II): 99% formic acid-conc. sulfuric acid(ratio by vol. 8:5), 30°, 0.75 hr, 26%; 85% phosphoric acid-conc. sulfuric acid(ratio by vol. 1.1:1), 30°,0.75

hr, 14%; boron trifluoride etherate-benzene(ratio by vol. 1:3.3), 80°, 24 hr, 6%.

It is generally accepted that the dienamine such as IV easily affords the conjugated imminium salt($VI_a$) in conc. sulfuric acid.[8] Aiming to elucidate whether this novel cyclization proceeds through $VI_a$, the same reaction as that cited above, was carried out using conc. deuteriosulfuric acid($D_2SO_4$). NMR spectrum of the reaction product isolated as α-cyclogeraniol(VII)[9] by the usual work-up, followed by the reduction with sodium borohydride, cleanly showed that the olefinic proton(* position) was replaced by deuterium in 78% conversion. This result discloses that the cyclization reaction has undoubtedly taken place from the salt($VI_a$), since the treatment of IV with conc. deuteriosulfuric acid should afford the deuterated imminium salt($IV_b$).[10]




VI a: X=H, Y=$HSO_4$
b: X=D, Y=$DSO_4$

A successful application of this novel reaction to the asymmetric synthesis of cyclic terpenes is reported in the accompanying paper.[11]

## REFERENCES

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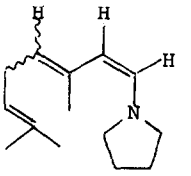
2) M.A. Schwartz, J.D. Crowell, and J.H. Musser, J. Am. Chem. Soc., 94, 4361 (1972) and references therein.

3) The ratio of cis- and trans-I was determined to be 5:6 by the glc analysis.

4) L. Colombi, A. Bosshard, H. Schniz, and C.F. Seidel, Helv. Chim. Acta, 34, 265(1951).

5) K. Taguchi, and F.H. Westheimer, J. Org. Chem., 36, 1570(1971).

6) The other possible structure of the enamine such as i might be excluded from the steric reason and the spectral data.



i

7) Other reaction product was a dark-colored tar which remained at the origin on tlc analysis(silica gel, benzene-n-hexane 4:1).

8) R.A. Raphael, E.C. Taylor, and H. Wynberg, Advances in Org. Chem. Methods and Results, 4, 84(1963).

9) Identified with the authentic sample prepared by the reduction of α-cyclogeranic acid(I) with lithium aluminium hydride in ether.

10) Substitution of the olefinic hydrogen of $VI_b$(** position) by deuterium can be deduced from the mechanistic point of view. However the precise determination of the degree of the substitution could not be attained in the isolated VII.

11) S. Yamada, M. Shibasaki, and S. Terashima, Tetrahedron Letters, accompanying paper.