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BIOGENETIC-LIKE CYCLIZATION OF FARNESOL AND NEROLIDOL TO BISABOLENE BY THE USE OF 2-FLUOROBENZOTHIAZOLIUM SALT

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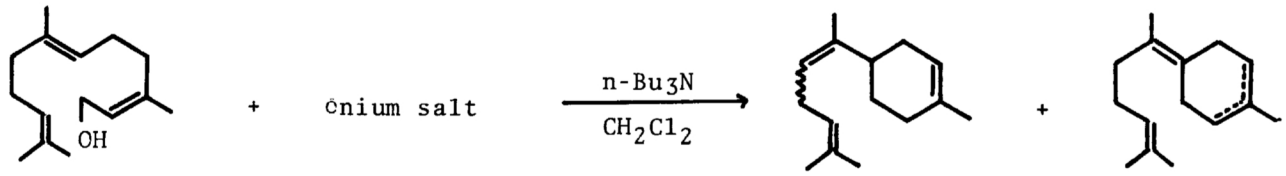
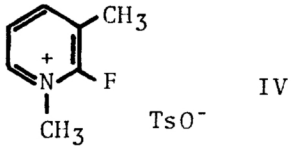
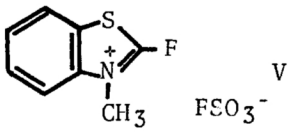
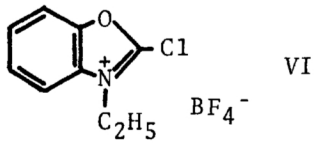
Treatment of trans, cis-farnesol or nerolidol with 2-fluorobenzothiazolium salt in the presence of tri-n-butylamine afforded monocyclic sesquiterpenes, mainly α-bisabolene, in good yields.

In the previous communication, non-enzymic biogenetic-like cyclization of nerol and geraniol to limonene using 2-fluoropyridinium salt was reported.[1] There have been known several examples for the cyclization of sesquiterpene alcohols by the promotion of protonic acids[2] or Lewis acids[3]. However, the cyclization under rather basic media has not been reported. We now wish to report here the cyclization of farnesol and nerolidol to bisabolene, monocyclic sesquiterpene hydrocarbon, with 2-fluorobenzothiazolium salt in the presence of a slight excess amount of tertiary amine.

In the first place, we examined the reaction of trans, cis-farnesol[4] with 1,3-dimethyl-2-fluoropyridinium salt (IV), but the yield of cyclized product, bisabolene, was low and many undetermined by-products were formed. Since several more active onium salts of 2-haloazaaromatics have been developed in our laboratory, we tried the cyclization of trans, cis-farnesol using active onium salts such as 2-fluorobenzothiazolium salt,[5] 2-chlorobenzoxazolium salt.[6] The results are summarized in the following Table.

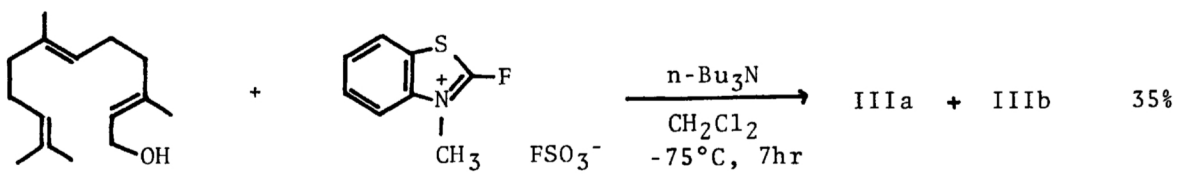


Ia IIIa IIIb

Onium Salt	Temp. (°C)	Time (hr)	Yield (%) IIIa + IIIb
 IV	-40	4	58
 V	-78	6	54
	-40	2	75
	-15	1.5	71
	0	1.5	74
	15	1.5	74
 VI	-78	3	56
	-40	2	46

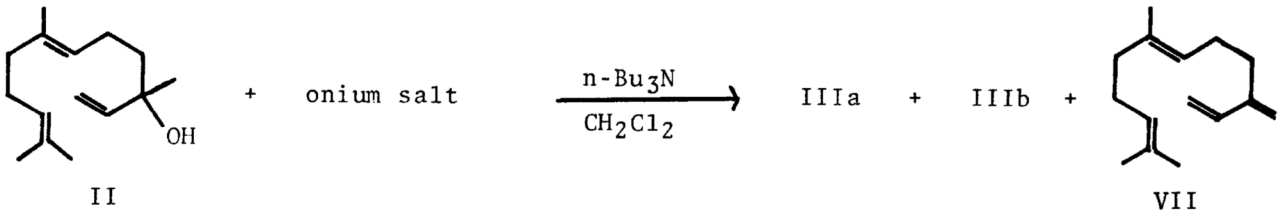
As shown in the Table, the optimum yield was obtained when trans, cis-farnesol was treated with 2-fluorobenzothiazolium salt (V) in CH_2Cl_2 at -40°C for 2 hr. In the case of the cyclization with 2-chlorobenzoxazolium salt (VI), the reaction mixture was rather complex even at -78°C and many by-products were formed. In these cyclization reactions, trans, cis-farnesol afforded mainly α-bisabolene (IIIa) (about 1:1 E,Z mixture) and small amount (less than 5% yield) of γ-bisabolene (IIIb), and none of β-bisabolene or polycyclic sesquiterpene was detected. The structures of α- and γ-bisabolene were confirmed by n.m.r. and mass spectra[7] after separation of the products by $AgNO_3$-impregnated silica gel column chromatography.

On the other hand, when trans, trans-farnesol[4] (Ib) was treated with 2-fluorobenzothiazolium salt, bisabolene was obtained in only 35% yield similar to the result obtained in the case of geraniol.[1]



It was found that the formation of 2-alkoxybenzothiazolium salt was very slow in the case of the cyclization of nerolidol (II). Therefore, the use of excess

amount of 2-fluorobenzothiazolium salt was necessary to obtain bisabolene in good yield. When nerolidol was treated with 5 molar amounts of 2-fluorobenzothiazolium salt in CH_2Cl_2 at -20°C for 7 hr, sesquiterpene hydrocarbons, α- and γ-bisabolene and farnesene (VII) (less than 10% yield), were obtained in 79% yield. In the case of nerolidol, the allylic cation is more easily generated compared to the case of farnesol, so the competitive deprotonation would lead to the formation of farnesene.



II VII

Onium Salt	Temp. (°C)	Time (hr)	Yield (%)
IV	r.t.	overnight	37
V	-40	8	70
	-20	7	79

A typical procedure is described for the cyclization of trans, cis-farnesol (Ia) using 2-fluorobenzothiazolium salt (V). To a suspension of V (320 mg, 1.2 mmol) in CH_2Cl_2 (1 ml) was added a CH_2Cl_2 solution (1 ml) of Ia (222 mg, 1.0 mmol) and tri-n-butylamine (444 mg, 2.4 mmol) under an argon atmosphere, and the mixture was stirred at -40°C for 2 hr. After addition of water, an organic layer was extracted with hexane (20 ml). The organic layer was washed successively with water and saturated sodium chloride solution, and condensed under reduced pressure. Then the product was separated by silica gel column chromatography.

Among various onium salts of 2-haloazaaromatics developed in our laboratory, 2-fluorobenzothiazolium salt was found to be the most effective reagent for the dehydrative cyclization of sesquiterpene alcohols under weakly basic conditions, and farnesol and nerolidol are converted to bisabolene in good yield. Application to the synthesis of bicyclic sesquiterpene is now in progress.

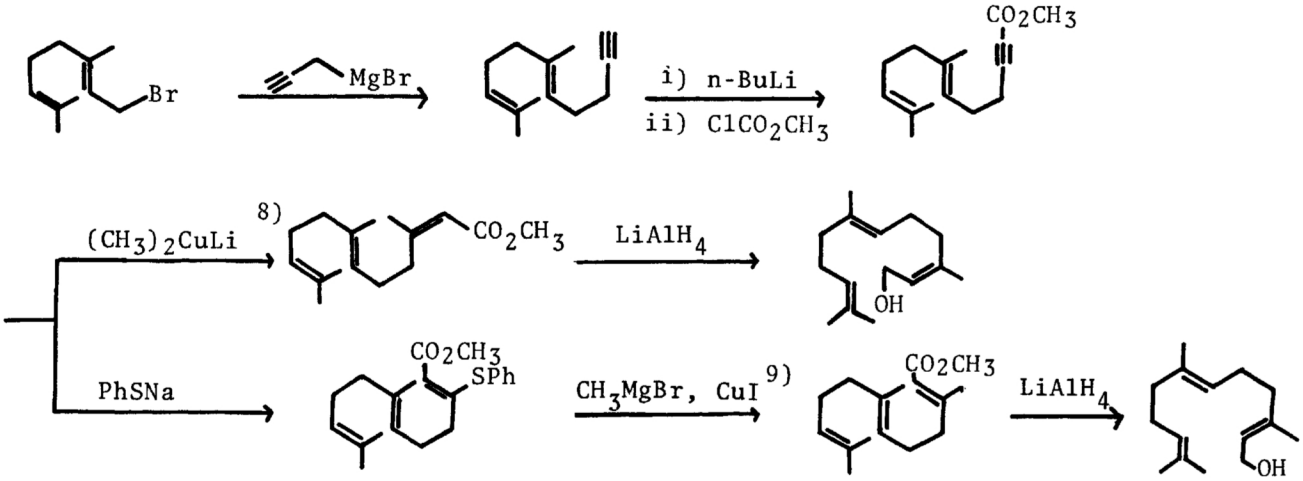
REFERENCES AND NOTES

1) S. Kobayashi, M. Tsutsui, and T. Mukaiyama, Chem. Lett., 1976, 1137.

2) L. Ruzicka and E. Capato, Helv. Chim. Acta, 8, 259 (1925).
Y-R. Naves, ibid., 49, 1029 (1966).
C. D. Gutshe, J. R. Maycock, and C. T. Chang, Tetrahedron, 24, 859 (1968).
G. Brieger, T. J. Nestrick, and C. Mckenna, J. Org. Chem., 34, 3789 (1969).
N. H. Andersen and D. D. Syrdal, Tetrahedron Lett., 1972, 2455.

3) Y. Ohta and Y. Hirose, Chem. Lett., 1972, 263.

4) trans, cis-Farnesol and trans, trans-farnesol were prepared from geraniol stereoselectively as depicted in the following scheme.



5) T. Mukaiyama and K. Hojo, Chem. Lett., 1976, 267, 893.
K. Hojo and T. Mukaiyama, ibid., 1976, 619.

6) T. Mukaiyama, S. Shoda, and Y. Watanabe, Chem. Lett., 1977, 383.
Y. Echigo, Y. Watanabe, and T. Mukaiyama, ibid., 1977, 697.
Y. Echigo, Y. Watanabe, and T. Mukaiyama, ibid., in press.

7) α-bisabolene (IIIa, E,Z mixture): m/e 204 (M^+), 93 (100%), 41; ppm (CCl_4) 5.30 (1H), 5.05 (2H), 2.60 (2H), 1.90 (6H), 1.60 (13H).
γ-bisabolene (IIIb, E,Z mixture): m/e 204 (M^+), 93 (100%), 41, 107; ppm (CCl_4) 5.30 (1H), 5.05 (1H), 2.65 (2H), 2.20 (2H), 1.95 (6H), 1.65, 1.55 (12H).

8) E. J. Corey and J. A. Katzenellenbogen, J. Am. Chem. Soc., 91, 1851 (1969).
J. B. Siddal, M. Biskup, and J. H. Fried, ibid., 91, 1853 (1969).

9) S. Kobayashi and T. Mukaiyama, Chem. Lett., 1974, 1425.

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