A NEW ENTRY TO THE SYNTHETIC ROUTE FOR 6,7-SECOERGOLENE ALKALOIDS USING FRAGMENTATION REACTION OF γ-AMINOALCOHOLS

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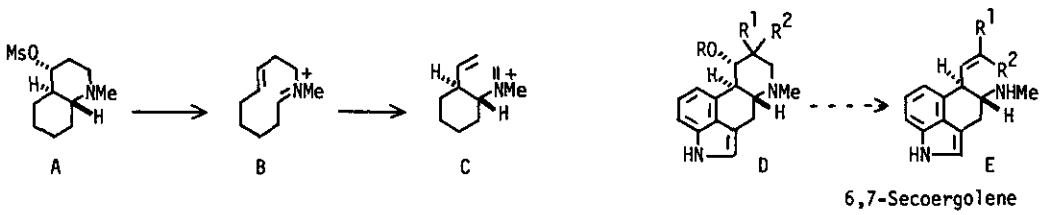
Abstract——A new synthetic route involving fragmentation reaction of γ-aminoalcohols for total synthesis of 6,7-secoergolene alkaloids was developed using the model compounds (1-5).

Heterolytic fragmentation reaction of the γ-aminoalcohol derivative (A) has been shown[1,2] to yield the cyclohexane (C) *via* the route involving the azecine (B). As an extension of our synthetic work on the ergot alkaloids,[3] we have investigated the fragmentation reaction of the γ-aminoalcohol derivatives (1-5) aiming at the application to the synthesis of 6,7-secoergolenes[4] (D → E).



The starting substrates (1-5) were prepared from the photocyclized lactams[5b] according to the reported procedure.[5] The mesylate (1) was first applied to the fragmentation reaction. Stirring an 80% ethanolic solution of the mesylate (1) at room temperature for 4 days followed by shaking the reaction solution with cold 10% aqueous ammonia and methylene dichloride furnished the E-*trans*- and E-*cis*-amines (6 and 8)[6] in 30% and 20% yields, respectively, together with a trace amount of the Z-*trans*-amine (7).[6] Heating of the mesylate (1) in either 80% ethanol or absolute ethanol at 50-70°C afforded three amines (6, 7, and 8) in combined 67-83% yields, while heating of the mesylate (1) without solvent at 110°C for 7 h gave the Z-amine (7) as a main product in 24% yield. The results obtained are summarized in Table 1.

In order to clarify the reaction course for the conversion of the mesylate (1) to the desired amines (6, 7, and 8), we treated the mesylate (1) with sodium borohydride in 80% ethanol at room temperature for 2 h and obtained the benzazecine (12)[6] in 79% yield. These findings indicated that 1 was subjected to facile fragmentation reaction to give an intermediate (13) which then underwent the aza-Cope rearrangement to give 14 when reducing agent was absent, as reported by Marshall.[2] Since the initially formed intermediate (13) would have a conformationally flexible ten-membered ring structure, the ratios of products (6, 7, and 8) were strongly influenced by the reaction conditions employed such as solvent and temperature (Table 1). Similarly, fragmentation of the 2-methyl-B/C-trans-mesylate (2) and 2-acetoxymethyl-B/C-cis-mesylate (3) proceeded smoothly to give the amines (9, 10, and 11)[6] and (6 and 8) in the yields and ratios as shown in Table 1, depending on the reaction conditions though 3 required a longer reaction time. Treatment of the mesylates (2 and 3) with sodium borohydride in 80% ethanol gave also the benzazecines (15 and 12) in 55-70% yields as a result of hydride reduction of the proposed intermediates (16 and 13). Interestingly, the 1,2-trans-2-acetoxymethyl- and 2-methyl-alcohols (4 and 5) underwent smooth fragmentation reaction under the mesylating condition shown in Table 1 and the E-amines (6 and 9) were obtained homogeneously in 34-54% yields respectively.
Structures of all products (6-11) obtained were established by the following chemical conversions. The acetates (6, 7, and 8) were converted into the known tricyclic benzo[f]quinolines (17 and 18)[7] via the route involving hydrolysis (c.HCl-MeOH) to the corresponding alcohols, followed by catalytic hydrogenation (PtO_2/H_2-dioxane) to the saturated alcohols (19a and 19b) and finally cyclization with thionyl chloride. The compounds (6, 7, 9, and 10) were further catalytically hydrogenated (PtO_2/H_2-dioxane) to give the identical amine (19c)[6] as a result of the allylic deoxygenation in 6 and 7. Similarly, the products (8 and 11) gave the identical amine (19d).[6]

Marked difference in the rates of fragmentation reaction between the stereoisomeric alcohols (4 and 5) and the mesylates (1, 2, and 3) can be explained as follows. Fragmentation of γ-aminoalcohol derivatives is known[1] to require an extended, anti-periplanar relationship between the leaving group (X), the C-C bond which is undergoing cleavage, and the nitrogen lone pair electrons as shown in the conformation (b). 1,2-trans-Alcohols (4 and 5) can exist preferentially in the

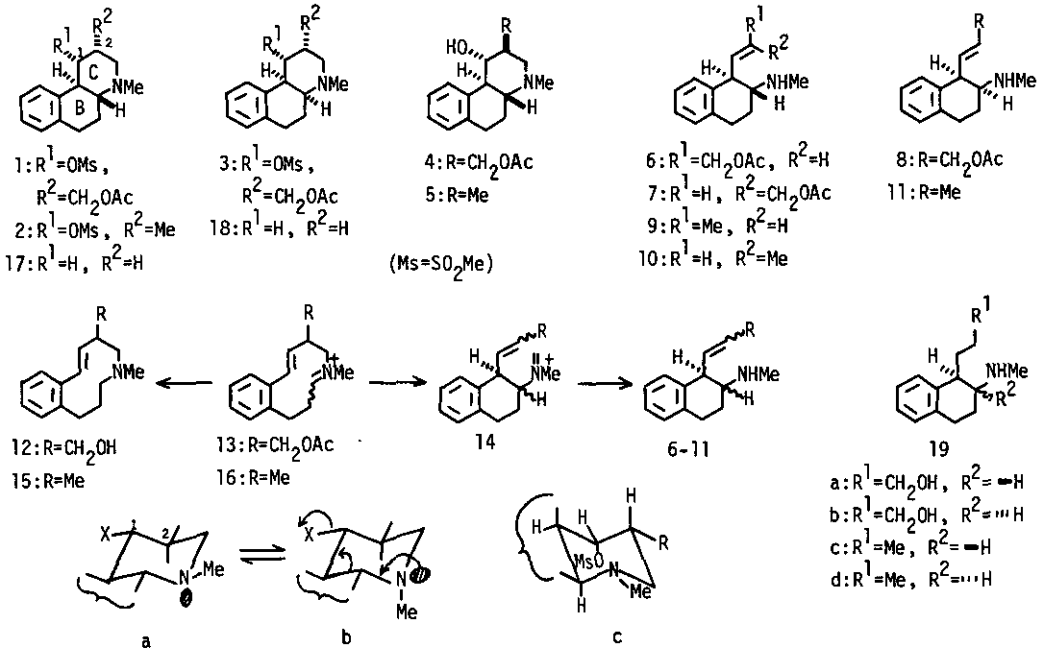


Table 1 Fragmentation Reaction of the γ-Aminoalcohol Derivatives (1-5)

Substrate	Reaction Condition			Yield (%) of Products 6 or 9	7 or 10	8 or 11	Recovered
1	80% EtOH	r.t.	4 days	30	trace	20	-
	80% EtOH	50°C	6 h	29	9	29	-
	80% EtOH	70°C	6 h	39	trace	44	-
	absolute EtOH	50°C	6 h	11	16	44	-
	neat	110°C	7 h	trace	24	trace	-
2	80% EtOH	70°C	4 h	27	20	31	-
	neat	110°C	5 h	trace	33	trace	-
3	80% EtOH	70°C	29 h	30	-	27	5
	neat	110°C	13 h	trace	-	11	20
4	MsCl in pyridine	0°C	3.5 h	34	-	-	-
	MsCl, Et_3N in CH_2Cl_2	0°C	5 h	39	-	-	-
	MsCl, Et_3N in toluene	0°C	2.5 h	54	-	-	-
5	MsCl, Et_3N in toluene	0°C	2 h	44	-	-	-

conformation (b) with α-axial N-methyl-β-equatorial lone pair electrons as compared with the mesylates (1 and 2), because there exists considerable steric repulsion between 2α-axial substituent and α-axial methyl group on nitrogen[8] in the conformation (b) of the mesylates (1 and 2). Therefore, fragmentation of the 1,2-trans-alcohols (4 and 5) would proceed readily even under the mesylating condition. The nmr spectrum of the B/C-cis-mesylate (3) suggests that the mesyloxy group at 1-position would be in an axial orientation (c) unfavorable to fragmentation, thus retarding the fragmentation of 3, compared with other mesylates (1 and 2).

Thus, we have developed a new and simple synthetic route for 6,7-secoergolenes using the fragmentation reaction of the γ-aminoalcohols (4 and 5) and γ-amino-mesylates (1, 2, and 3). E-trans-Amines (6 and 9) were effectively synthesized from the 1,2-trans-alcohols (4 and 5), the Z-trans-amines (7 and 10) from the 1,2-cis-B/C-trans-mesylates (1 and 2), and the E-cis-amines (8 and 11) from the 1,2-cis-mesylates (1, 2, and 3), respectively, though optimal reaction condition has not been established.

The application of the fragmentation reaction to the total synthesis of 6,7-secoergolenes is now in progress.

REFERENCES AND NOTES

1 C. A. Grob, Angew. Chem., Int. Ed. Engl., 1969, 8, 535.

2 J. A. Marshall and J. H. Babler, J. Org. Chem., 1969, 34, 4186.

3 I. Ninomiya, C. Hashimoto, T. Kiguchi, and T. Naito, J. Chem. Soc., Perkin Trans. 1, 1985, 941; T. Kiguchi, C. Hashimoto, and I. Ninomiya, Heterocycles, 1985, 23, 2891; references cited therein.

4 H. G. Floss, Tetrahedron, 1976, 32, 873.

5 (a) I. Ninomiya, C. Hashimoto, T. Kiguchi, and T. Naito, Chem. Pharm. Bull., 1986, 34, 2799. (b) I. Ninomiya, C. Hashimoto, T. Kiguchi, and T. Naito, J. Chem. Soc., Perkin Trans. 1, 1984, 2911.

6 All new compounds reported herein gave ir, nmr, and mass spectral data consistent with the assigned structures.

7 A. Kumar and J. M. Khanna, Indian J. Chem., 1976, 14B, 556; J. G. Cannon, G. J. Hatheway, J. P. Long, and F. M. Sharabi, J. Med. Chem., 1976, 19, 987.

8 C. A. Grob, W. Kunz, and P. R. Marbet, Tetrahedron Lett., 1975, 2613.

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