

REGIOSELECTIVE CYCLIZATION OF 1-TRIMETHYLACETYLINDOLE DERIVATIVES
AT THE 4-POSITION OF INDOLE NUCLEUS

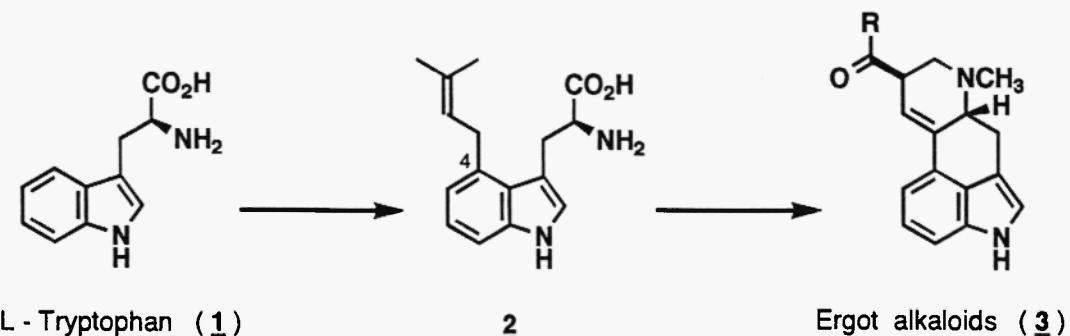
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Abstract: 1-Trimethylacetyl derivatives 9 and 10 of 3-(2-butenyl)indole 7 and 3-(3-methyl-2-butenyl)indole 8 were regioselectively cyclized at the 4-position of indole nucleus.

In the biosynthesis of ergot alkaloids 3, a prenyl group is first introduced at 4-position of tryptophan as shown in the scheme(1). Although many attempts to introduce a such substituent at the position of indole nucleus have been studied for a long time, no successful method has been reported except a few cases(2,3).

Biosynthesis of ergot alkaloids.



In our studies on synthesis of indole alkaloids, we developed novel intra- and intermolecular cyclizations of dehydrotryptophan derivatives at the 4-position(3a~c). Furthermore, we succeeded in the facile synthesis of Uhle's ketone by regioselective Friedel-Crafts cyclization of 3-(1-trimethylacetyl-indo-3-yl)propionic acid(3d). In this paper, we describe another type of AlCl_3 -catalyzed regioselective cyclization of 5, 9 and 10.

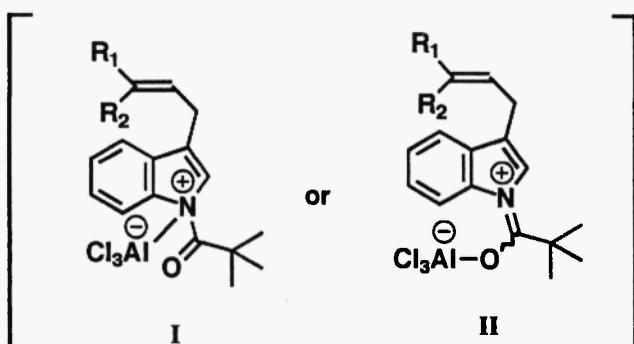
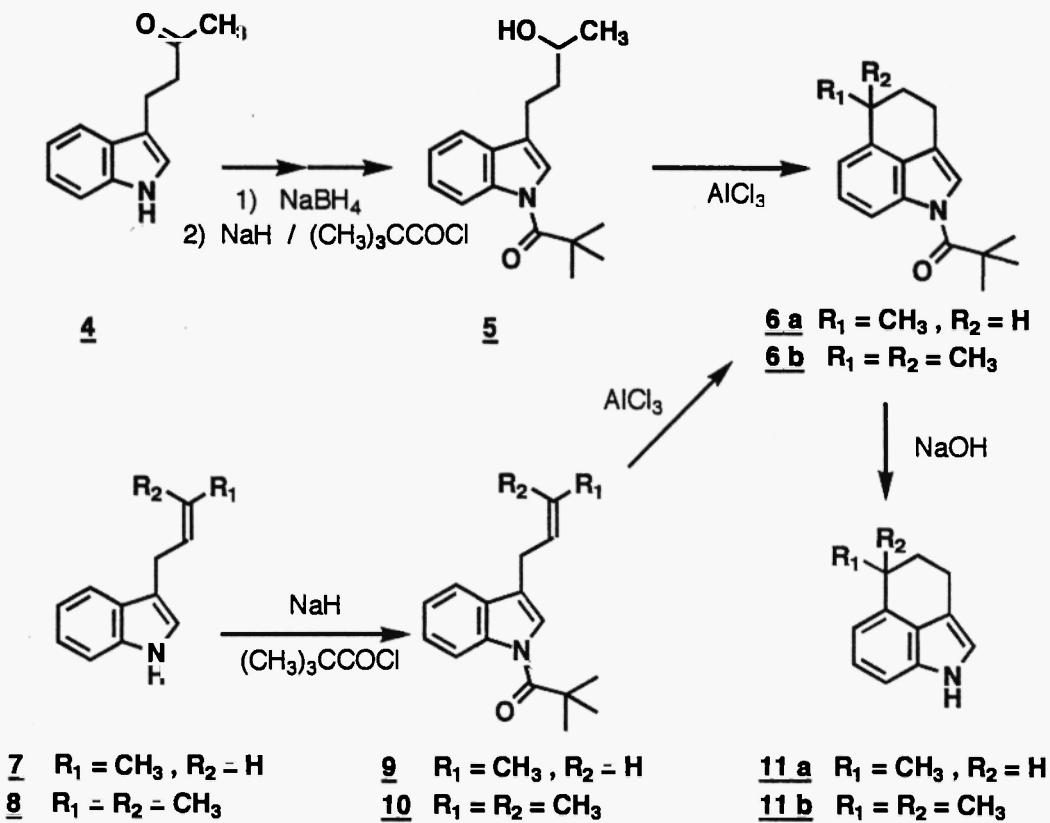
As the starting materials, we chose an alcohol 5 and 3-allylindole derivatives 9 and 10. An alcohol 5 was synthesized by reduction of ketone 4 (4) and subsequent trimethylacetylation of 1-position with 1 eq. NaH /trimethylacetylchloride in DMF in 70% overall yield(5). 1-Trimethylacetyl derivatives 9 and 10 were also prepared from 3-allylindole derivatives 7 and 8 (6) with NaH /trimethylacetylchloride in DMF in 76% and 82% yields, respectively(9,10).

AlCl_3 -catalyzed cyclization of alcohol 5 in dichloroethane in the presence of 5 eq. AlCl_3 at 60°C for 1 h gave our desired cyclization product 6a at 4-position of indole nucleus in 17% yield(7). No cyclization product at 2-position was obtained. Similarly, monomethyl- and dimethylallyl derivatives 9 and 10 were treated with AlCl_3 in dichloromethane at 25°C to afford the corresponding monomethyl- and dimethyl- cyclization products 6a and 6b. Cyclization of 9 and 10 proceeded faster than that of alcohol 5.

Tricycles 6a and 6b were obtained in 15% and 70% yields, respectively, after purification by silica gel column chromatography(7, 8). The structures of 6a and 6b were determined by their $^1\text{H-NMR}$ spectra. Hydrolysis of 6a and 6b with 1N- NaOH in MeOH afforded 5-methyl- and 5,5-dimethyl-3,4-dihydro($1H$)benz[*c, d*]-indole 11a and 11b in quant. yields, respectively(11,12).

When we used less than 2 eq. of AlCl_3 as catalyst, such cyclization products were not produced and 3~5 eq. of AlCl_3 were suitable for the selective cyclization at the 4-position. We assumed that nucleophilic pyrrole part (1, 2 and 3-position) of 5, 9 and 10 was deactivated by formation of AlCl_3 -complex such as I or II, and relatively reactive 4-position attacked a cationic site on the side chain at its 3'-position to afford those products.

Further application of our novel cyclization at the 4-position of indole nucleus to the biomimetic total synthesis of ergot alkaloids(3) and study of reaction mechanism are now in progress.

AlCl₃ complex of **9** and **10**

REFERENCES AND FOOTNOTES

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- (2) J. Szmuszkovicz, *J. Org. Chem.*, **29**, 843(1964) and references cited in (3cd).

- (3) a) S. Nakatsuka, H. Miyazaki and T. Goto, *Tetrahedron Lett.*, **21**, 2817(1980); b) S. Nakatsuka, H. Miyazaki and T. Goto, *Chem. Lett.*, 407(1981); c) S. Nakatsuka, K. Yamada and T. Goto, *Tetrahedron Lett.*, **27**, 4757(1986); d) K. Teranishi, S. Hayashi, S. Nakatsuka and T. Goto, *ibid.*, **35**, 8173(1994) and *Synthesis*, 506(1995).
- (4) J. B. Brown, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 3172(1952).
- (5) 5; MS m/z 273(M^+), 201. 1H -NMR($CDCl_3$) δ 1.27(3H, d, $J=7Hz$), 1.51(9H, s), 1.87(2H, q, $J=8Hz$), 2.81(2H, m), 3.92(1H, m), 7.24~7.37(3H, m), 7.52(1H, d, $J=8Hz$), 8.51(1H, d, $J=8Hz$).
- (6) J. Szmuszkovicz, *J. Am. Chem. Soc.*, **79**, 2819(1957).
- (7) 6a; mp 144~145°C(sealed tube); MS m/z 255(M^+), 156. 1H -NMR($CDCl_3$) δ 1.38(3H, d, $J=7Hz$), 1.51(9H, s), 1.76(1H, m), 2.08(1H, m), 2.82(2H, m), 3.07(1H, m), 7.10(1H, br. d, $J=8Hz$), 7.29(1H, t, $J=8Hz$), 7.36(1H, br. s), 8.18(1H, br. d, $J=8Hz$).
- (8) 6b; mp 121~122°C; MS m/z 269(M^+), 170. 1H -NMR($CDCl_3$) δ 1.34(6H, s), 1.51(9H, s), 1.84(2H, t, $J=6Hz$), 2.84(2H, t, $J=6Hz$), 7.17(1H, br. d, $J=8Hz$), 7.30(1H, t, $J=8Hz$), 7.38(1H, br. s), 8.18(1H, br. d, $J=8Hz$).
- (9) 9; oil; MS m/z 255(M^+). 1H -NMR($CDCl_3$) δ 1.51(9H, s), 1.71(3H, m), 3.39(2H, m), 5.66(2H, m), 7.21~7.39(2H, m), 7.47(1H, br. s), 7.52(1H, br. d, $J=8Hz$), 8.51(1H, br. d, $J=8Hz$).
- (10) 10; oil; MS m/z 269(M^+). 1H -NMR($CDCl_3$) δ 1.45(9H, s), 1.78(6H, m), 3.39(2H, d, $J=7Hz$), 5.40(1H, m), 7.22~7.38(2H, m), 7.43(1H, br. s), 7.50(1H, br. d, $J=8Hz$), 8.50(1H, br. d, $J=8Hz$).
- (11) 11a; mp 63~64°C; MS m/z 171(M^+), 156. 1H -NMR($CDCl_3$) δ 1.40(3H, d, $J=7Hz$), 1.78(1H, m), 2.10(1H, m), 2.88(2H, m), 3.10(1H, m), 6.85(1H, m), 6.92(1H, m), 7.14~7.17(2H, m), 7.83(1H, br. s).
- (12) 11b; mp 130~131°C(sealed tube); MS m/z 185(M^+), 170. 1H -NMR($CDCl_3$) δ 1.35(6H, s), 1.86(2H, t, $J=7Hz$), 2.89(2H, t, $J=7Hz$), 6.86(1H, m), 6.99(1H, br. t, $J=8Hz$), 7.16(2H, m), 7.84(1H, br. s).

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