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REGIOSPECIFIC CYCLIZATION OF N-BENZOYL-N-METHOXYMETHYL-1-METHYL-α,β-DEHYDRO-TRYPTOPHAN METHYL ESTER TO A 5,6-DIHYDROAZEPINO[5,4,3-cd]INDOLE DERIVATIVE. A NEW METHOD FOR INTRODUCING SUBSTITUENTS ONTO THE 4-POSITION OF INDOLE NUCLEUS

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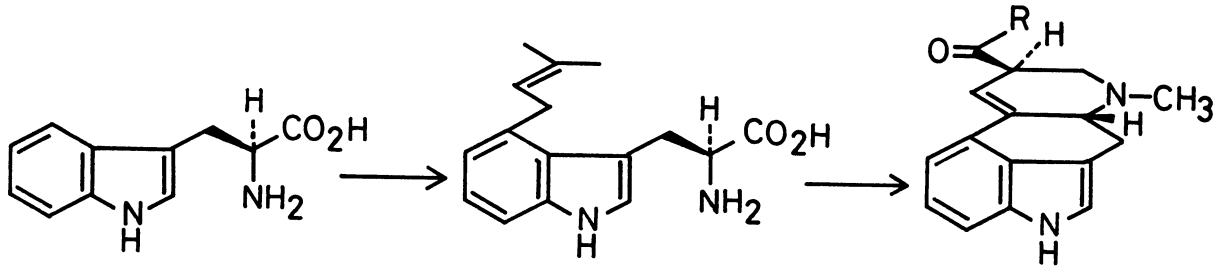
A novel cyclization of the N-protected dehydrotryptophan 7 at the 4-position was achieved in excellent yield. Selective hydrogenation of the cyclized compound 10 gave the 3,4,5,6-tetrahydroazepinoindole derivative 11, which contains the same ring system as clavicipitic acid (12).

All attempts introducing an alkyl group onto the 4-position of tryptophan nucleus similar to the biogenetic process of the ergot alkaloids (Scheme I) have been completely unsuccessful[1] except photochemical pathway.[2] In our recent paper[3] we reported a novel cyclization of a protected neoechinulin A to a 5,6-dihydroazepino[5,4,3-cd]indole derivative. In this case, however, the starting material has a bulky group which may inhibit the usual cyclization at the 2-position. Here we report a novel cyclization of the N-protected α,β-dehydrotryptophan 7 to 5,6-dihydroazepinoindole 10, instead of to usual dihydropyridoindole. This regiospecific cyclization is generally applicable to α,β-dehydrotryptophan derivatives.[3,4]

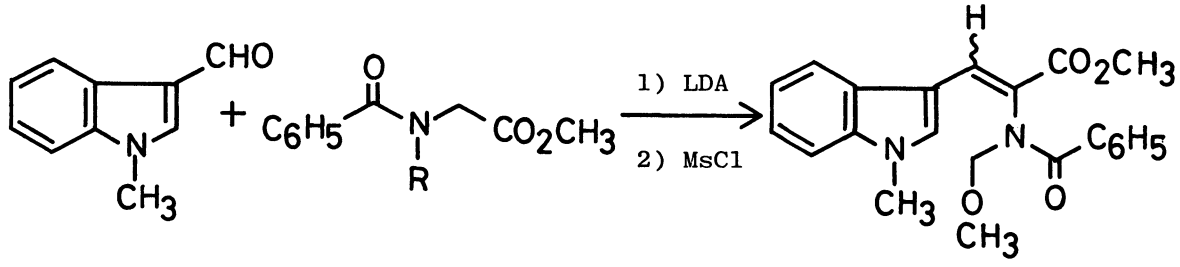
Scheme I



Tryptophan (1) 2 Ergot alkaloids (3)

N-Benzoylglycine methyl ester (4) was treated with sodium hydride in dimethyl formamide at room temp. The reaction mixture was cooled to -78°C and chloromethyl methyl ether was added. The solution was warmed up to room temp. to afford the methoxymethyl derivative 5 (75%), oil [m/e 237 (M^+); nmr (DMSO-d_6, 150°C) δ 3.26 (3H, s), 3.76 (3H, s), 4.29 (2H, s), 4.80 (2H, s), 7.61 (5H, s)]. Knoevenagel condensation between 5 and N-methylindole-3-aldehyde (6)[5] was achieved as reported previously[3] [(1) 1.2 eq lithium diisopropylamide, (2) 1.2 eq methanesulfonyl-chloride]. Chromatography of the product on a silica gel column gave Z-dehydro-tryptophan derivative 7Z[6,7] (77%), mp 142-143°C [m/e 378 (M^+); λ_{max} (MEOH) nm (ε) 224 (30,300), 270 (11,200), 357 (21,700); nmr ($CDCl_3$) δ 3.54 (3H, s), 3.66 (3H, s) 3.90 (3H, s), 5.00 (1H, d, J=9 Hz), 5.33 (1H, d, J=9 Hz), 7.0-7.5 (8H, m), 7.75 (1H, br. d, J=7 Hz), 7.84 (1H, s), 7.89 (1H, s)], and the E-isomer 7E (8%), oil [m/e 378 (M^+)].

Scheme II

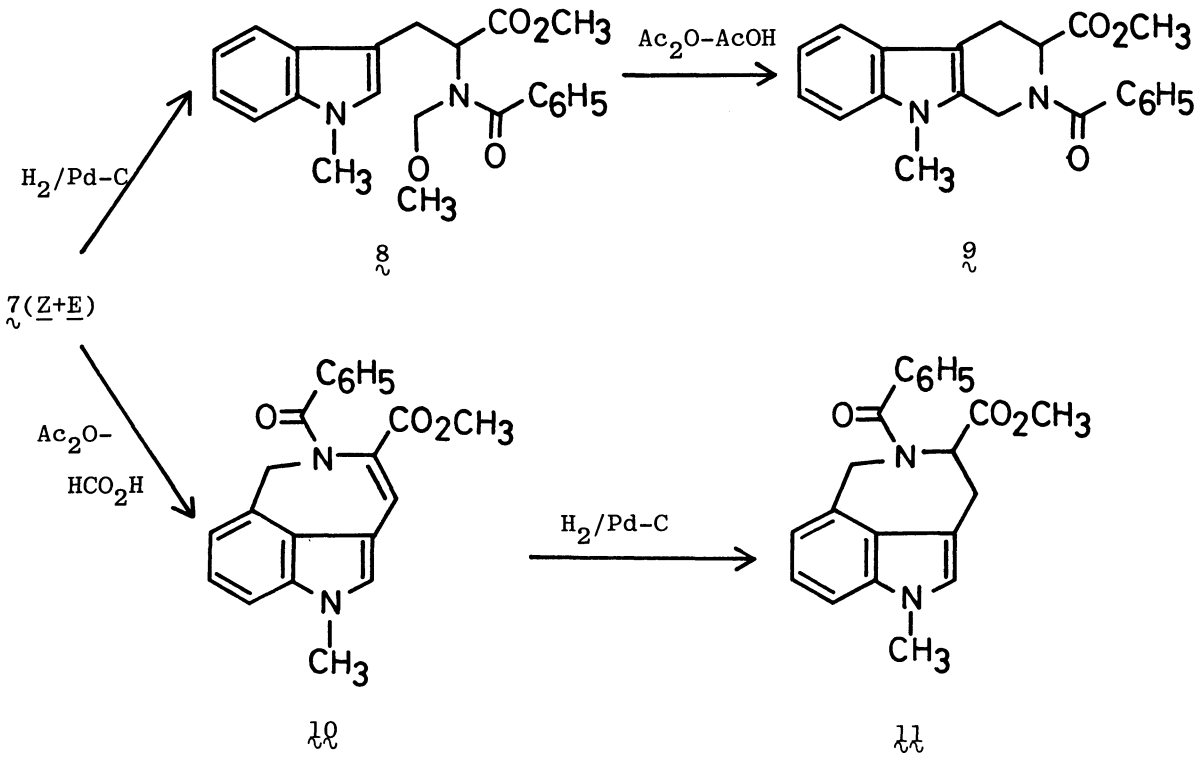


6 4 R=H
5 R=CH_2OCH_3 7(Z+E)

Catalytic hydrogenation of 7Z over 10% Pd-C in MeOH at 60°C gave N-methoxy-methyltryptophan derivative 8 (95%), oil [m/e 380 (M^+); nmr (DMSO-d_6, 130°C) δ 3.15 (3H, s), 3.52 (2H, m), 3.78 (3H, s), 3.81 (3H, s), 4.62 (1H, d, J=11Hz), 4.70 (1H, d, J=11 Hz), 4.98 (1H, m), 7.1-7.8 (10H, m)]. Treatment of 8 in Ac_2O-AcOH at 120 °C or in DMSO at 150°C resulted the Pictet Spengler type cyclization at the 2-position to afford the tetrahydropyrido[3,4-b]indole 9[7] (92% or 90%) mp 175-176°C m/e 348 (M^+); nmr (DMSO-d_6, 150°C) δ 3.0-3.6 (2H, m), 3.61 (3H, s), 3.66 (3H, s), 4.68 (1H, d, J=17 Hz), 5.15 (1H, d, J=17 Hz), 5.37 (1H, m), 7.0-7.8 (9H, m)].

On the other hand, heating the solution of 7Z in o-dichlorobenzene at 180°C recovered the starting material unchanged. But, treatment of 7Z and 7E with a mixture of formic acid and acetic anhydride (1:1) at 80°C gave almost a single product, which was obtained as crystals[7] (89% from 7Z and 87% from 7E), mp 211-213

Scheme III

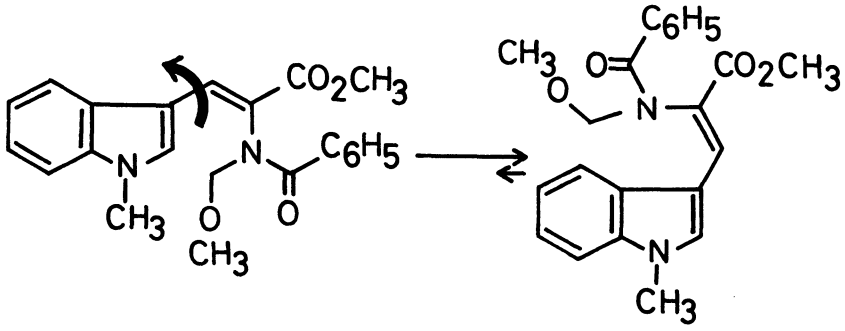


°C [m/e 346 (M^+); λ_{max}(MeOH) nm (ε) 225 (28,300), 272 (9,800), 353 (22,400); nmr ($CDCl_3$) δ 3.48 (3H, s), 3.81 (3H, s), 3.97 (1H, d, J=15 Hz), 6.01 (1H, d, J=15 Hz) 7.1-7.3 (8H, m), 7.29 (1H, s), 7.52 (1H, s)]. The spectral data indicate the structure shown in 10, which was formed by cyclization at the 4-position of the indole nucleus. We assume that the E-isomer (7E) was cyclized after isomerization to the Z-isomer in the acidic conditions. The structure of 10 was further confirmed by hydrogenation of 10 with H_2/10% Pd-C in MeOH at 60°C to 3,4,5,6-tetrahydroazepinoindole derivative 11[7] (95%), mp 160-161°C [m/e 348 (M^+); λ_{max}(MeOH) nm (ε) 225 (35,300), 293 (6,900); nmr ($CDCl_3$) δ 3.52 (2H, m), 3.74 (3H, s), 3.82 (3H, s), 4.62 (1H, d, J=18 Hz), 5.00 (1H, m), 5.10 (1H, d, J=18 Hz), 6.47 (1H, br. d, J =7 Hz), 6.89 (1H, s), 6.9-7.5 (7H, m)], which contains the same ring system as clavicipitic acid 12.[8]

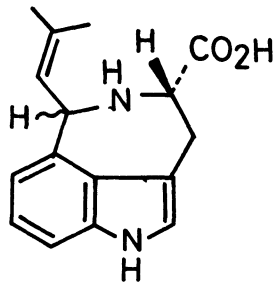
Regiospecificity of the cyclization of dehydrotryptophan derivatives[9] seems to be controlled by the stereochemical factor [the transoid form (B) may be more stable than the cisoid form (A) and in the former the methoxymethyl group is closer to the 4-position than to the 2-position of the indole] and/or electronic factor[10] (conjugation between the ester carbonyl and the indole moiety

diminishes the reactivity of the 2-position of the indole nucleus). Application of this cyclization to the synthesis of some alkaloids such as 3 and 12 is now in progress.

Scheme IV



A (cisoid) B (transoid)



Clavicipitic acid (12)

7Z

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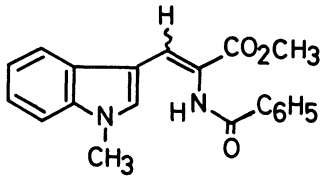
4. S. Nakatsuka, K. Yamada, H. Miyazaki and T. Goto, in preparation.
5. H. Wieland, W. Konz and H. Mittasch, Ann., 513, 1 (1934).
6. Stereochemistry of 7Z and 7E was determined by the methoxymethylation of 13 (Z and E) and the comparison of those nmr spectra.[11]
7. Satisfactory elemental analysis was obtained.
8. (a) J. E. Robbers and H. G. Floss, Tetrahedron Lett., 1857 (1969); J. E. Robbers, H. Otsuka and H. G. Floss, J. Org. Chem., 45, 1117 (1980).
   (b) G. S. King, P. G. Mantle, C. A. Szczyrbak and E. S. Waight, Tetrahedron Lett., 215 (1973); G. S. King, E. S. Waight, P. G. Mantle and C. A. Szczyrbak, J. Chem. Soc. Perkin I, 2099 (1977).
9. We assume that the reactivity of α,β-dehydrotryptophan derivatives has some connection with the isoprenylation at the 6-position of dehydrotryptophan containing diketopiperazine in biosynthesis of neoechinulin in comparison with that at the 5- and 7-position in the case of echinulin.
10. We thank Prof. S. Sakai for pointing out this factor.
11. U. Hengartner, D. Valentine, K. K. Johnson, M. E. Larscheid, F. Pigott, F. Scheidl, J. W. Scott, R. C. Sun, J. M. Townsent and T. H. Williams, J. Org. Chem., 44, 3741 (1979).



13 (Z and E)

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