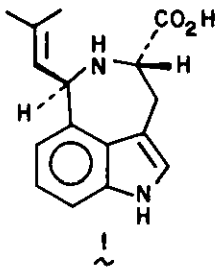
IAC REACTIONS IN THE INDOLE SERIES: TOTAL SYNTHESIS OF CLAVICIPITIC ACID

Alan P. Kozikowski*† and Michael N. Greco
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

Abstract - The first total synthesis of clavicipitic acid (1), a derailment product of ergoline biosynthesis, has been accomplished through an intramolecular azide cycloaddition reaction. The 3,4-disubstituted indole required for this work was assembled from indole-4-carboxaldehyde. The single imine generated from the [3+2] cycloaddition reaction was subjected to bromination, dehydrobromination, reduction and hydrolysis to afford clavicipitic acid (~1:1 mixture of the cis and trans-isomers).

We have reported recently an intramolecular azide [3+2] cycloaddition approach to the skeleton of clavicipitic acid, a metabolite of Claviceps strain SD58.[1] This compound, which is isolated as a mixture of isomers (1, the major constituent in Floss' samples), appears to represent a derailment product of ergoline biosynthesis after the first pathway-specific step, the isoprenylation of tryptophan.[2] Since fermentation processes produce this compound in relatively low yield an efficient high-yielding synthesis might be of some health-related value.



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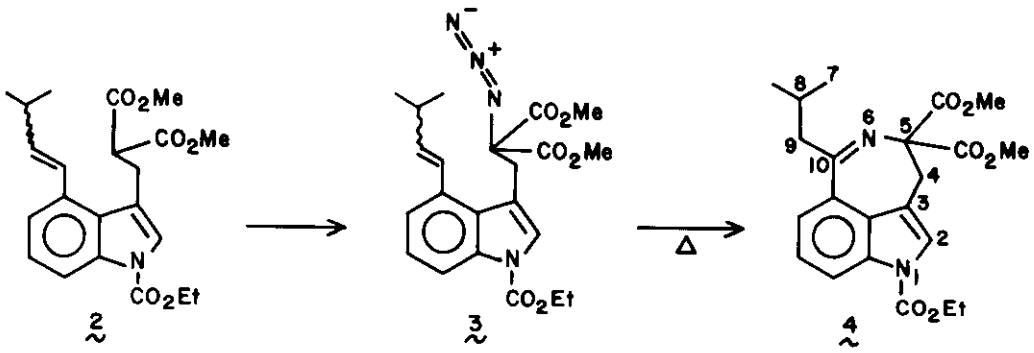
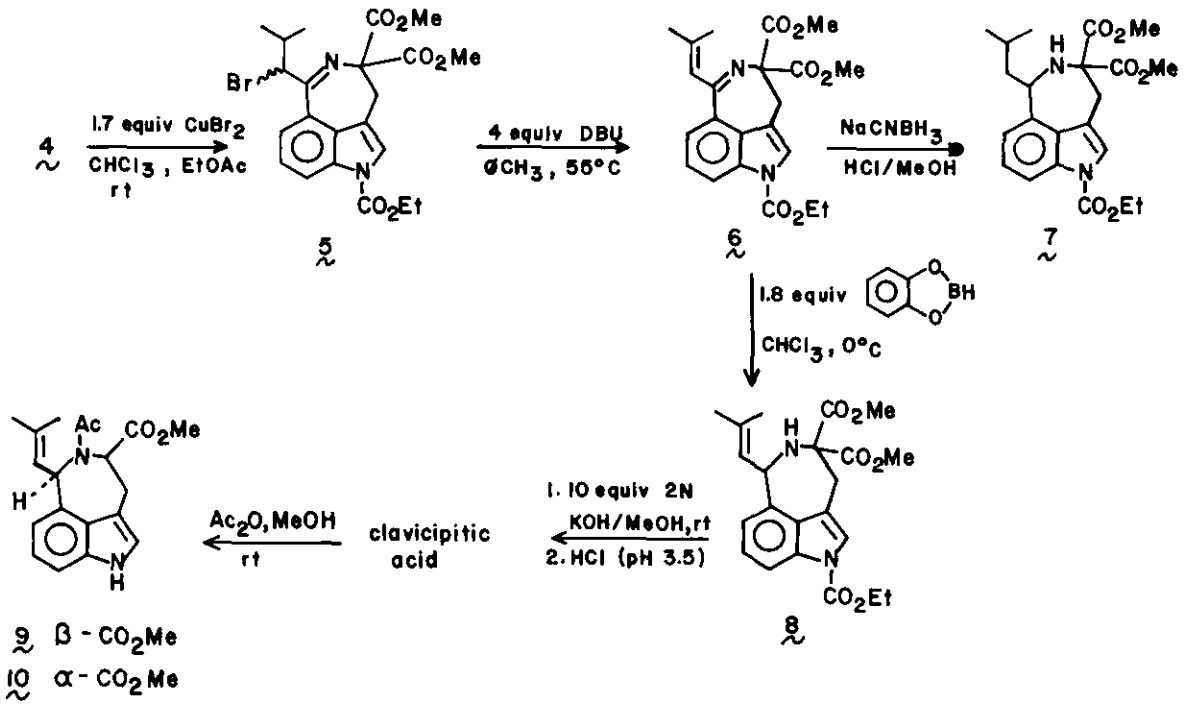
The 3,4-disbustituted indole 2 was thus prepared and converted by conventional chemistry to the azidomalonate 3. On heating 3 in o-dichlorobenzene at 190-195°C for 8 h, a good yield of the single imine 4 was obtained as reported.[1] To complete the synthesis, it was now necessary to relocate the unsaturation from the N_6 - C_{10} position to the C_8 - C_9 position.



While construed as a reaction of relatively low probability, the imine was exposed to $RhCl_3 \cdot 3H_2O$ with the hope of effecting a direct isomerization.[3] Since this reaction led only to decomposition of the imine, we opted instead to investigate the functionalization of C-9 with the idea of producing through a subsequent elimination reaction an ene-imine. Selective reduction of the imine double bond might then yield the targeted intermediate. Although 4 could be selenylated at C-9 in high yield (NaH, then ϕSeCl), the oxidation of selenide to selenoxide using several different reagents proved to be a very poor reaction. Enough of the selenoxide was generated, however, to be able to carry out the elimination reaction and to discover that the desired ene-imine 6 could be formed.

A bromination/dehydrobromination sequence has, on the other hand, been found to give workable yields of 6. On exposing 4 to cupric bromide[4] in $CHCl_3$/EtOAc at room temperature, bromide 5 was obtained in 77% isolated yield. Dehydrobromination with DBU (4 equiv) in toluene at 55°C for 72 h yielded 6 (32% unoptimized yield after chromatography).[5] While subsequent treatment of this ene-imine with acidic cyanoborohydride[6] resulted in formation of the over-reduced product 7, use of



catecholborane gave the desired product 8 cleanly (89%).[7] Hydrolysis and decarboxylation of 8 with 2 N KOH/MeOH for 5 h at rt followed by acidification to *pH 3.5 (HCl) yielded clavicipitic acid* [both isomers, ratio ~1:1; mp 239-244°C (d)]. The R_f values of these isomeric acids were identical to those of the natural product generously provided by Dr. Heinz Floss and Dr. Jon Clardy. The mass spectrum [(15 eV) m/e 270, 269, 255, 225, 215, 196, 183, 182, 169, 167, 154] and UV [(EtOH) λ_{max} = 221, 288 nm] of the mixture were *also* identical to those obtained for the natural product. Since it is difficult to obtain an NMR of these acids for reasons of insolubility,[2] both the synthetic and natural acids were derivatized by treatment with acetic anhydride/methanol following the procedure of Morris, Williams and Ambler[8] as described by Mantle[2] to yield a chromatographically homogeneous product (9 or 10, stereochemistry not assigned) possessing *identical* R_f, *IR and 300 MHz* ^1H NMR characteristics.[9] The physical properties of the N-acetyl methyl ester prepared from synthetic clavicipitic acid are as follows:

mp (CCl_4/hexanes) 117-119°C; UV ($CHCl_3$) λ_{max} = 285 nm; IR ($CHCl_3$) 3485, 1736, 1636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31 (br s, 1 H); 6.85-7.29 (m, 4 H), 5.86 (d, 1 H, J = 7 Hz), 5.23, (d, 1 H, J = 7 Hz), 4.44 (dd, 1 H, J = 6.05, 4.03 Hz), 3.72 (s, 3 H), 3.37, 3.93 (AB portion of ABX, 2 H, J_{AB} = 16.0 Hz, J_{AX} = 6.05 Hz, J_{BX} = 4.03 Hz), 2.17 (s, 3 H), 1.91 (s, 3 H), 1.75 (s, 3 H); mass spectrum (15 eV) m/e 326, 311, 283.

The work reported herein defines a very direct approach to clavicipitic acid. This route, which should be quite amenable to analogue production, further demonstrates the power and versatility of dipolar cycloaddition strategies for natural product total synthesis.[10]

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REFERENCES AND NOTES

†Camille and Henry Dreyfus Teacher Scholar, 1982-1987; Fellow of the Alfred P. Sloan Foundation, 1978-1982.

1. A. P. Kozikowski and M. N. Greco, Tetrahedron Lett., 1982, 23, 2005.
2. J. E. Robbers, H. Otsuka, H. G. Floss, E. V. Arnold, and J. Clardy, J. Org. Chem., 1980, 45, 1117; G. S. King, P. G. Mantle, C. A. Szczyrbak, and E. S. Waight, Tetrahedron Lett., 1973, 215; G. S. King, E. S. Waight, P. G. Mantle, and C. A. Szczyrbak, J. Chem. Soc., Perkin Trans. 1, 1977, 209. The latter authors indicate that clavicipitic acid is comprised of two approximately equal fractions.
3. P. A. Grieco, M. Nishizawa, and N. Marinovic, J. Am. Chem. Soc., 1976, 98, 7102.
4. L. C. King and G. K. Ostrum, J. Org. Chem., 1964, 29, 3459.
5. H. Oediger, F. Moller, and K. Eiter, Synthesis, 1972, 591.
6. R. F. Borch, M. D. Bernstein, and H. D. Durst, J. Am. Chem. Soc., 1971, 93, 2897.

7. G. W. Kabalka, J. D. Baker, and G. W. Neal, J. Org. Chem., 1977, 42, 512.

8. H. R. Morris, D. H. Williams, and R. P. Ambler, Biochem. J., 1971, 125, 189.

9. Since the N-acetyl methyl ester derivative appears to be a single isomer by HPLC and 300 MHz ^{1}H NMR, epimerization may occur under the reaction conditions. Additional studies are being carried out in order to further probe this possibility.

10. For other recent examples of the use of dipoles in synthesis, see: A. P. Kozikowski and Y. Y. Chen, J. Org. Chem., 1981, 46, 5248; A. P. Kozikowski and H. Ishida, J. Am. Chem. Soc., 1980, 102, 4265; S. H. Andersen, N. B. Das, R. D. Jorgensen, G. Kjeldsen, J. S. Knudsen, S. C. Sharma, and K. B. G. Torssel, Acta Chem. Scand. B., 1982, 36, 1; P. M. Wovkulich and W. R. Uskokovic, J. Am. Chem. Soc., 1981, 103, 3956; A. Padwa, K. F. Koehler, and A. Rodriguez, ibid., 1981, 103, 4974; J. J. Tufariello and G. E. Lee, ibid., 1980, 102, 373; I. Nagakura, Heterocycles, 1981, 16, 1495.

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