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Synthesis of Acromelic Acid B, a Toxic Principle of Clitocybe acromelalga

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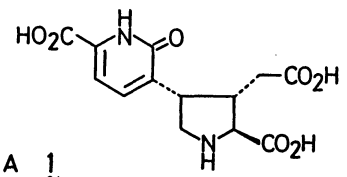
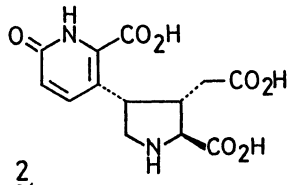
Acromelic acid B was synthesized from kainic acid through our newly developed method of pryidine synthesis.

Acromelic acid A (1) and B (2) are the toxic principles of Clitocybe acromelalga Ichimura.[1] The synthesis of these compounds have been attempted in our laboratory in order to provide not only proof for the proposed structures but also samples available for biological assays. Thus, the synthesis of 1 was accomplished recently, which demonstrated the correctness of the assigned formula and the potent neuroexcitatory activity of 1.[2] In this communication, we report the synthesis of acromelic acid B (2).



acromelic acid A 1



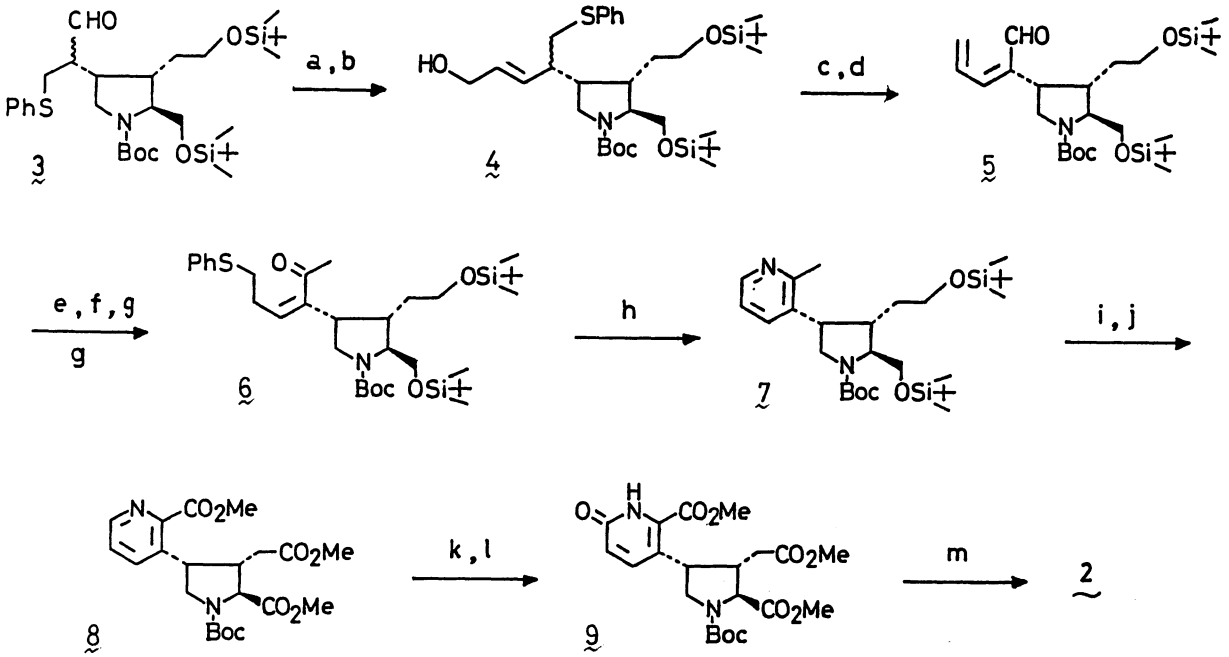
acromelic acid B 2

The strategy is basically the same as that for the synthesis of 1. The aldehyde 3[2] was subjected successively to the Horner-Emmons reaction and DIBAH reduction to afford allylic alcohol 4 as a mixture of diastereoisomers. The alcohol 4 was then led to α, β, γ, δ -unsaturated aldehyde 5[3] in good yield by the Pummerer reaction and subsequent dehydration. 1, 6-Conjugate addition of thiophenol to aldehyde 5 proceeded smoothly[4] and the adduct was successively reacted with MeLi and PDC to yield ketosulfide 6.[3] Conversion of the ketosulfide 6 to methylpyridine 7[5] was carried out along the way of our newly developed pyridine synthesis.[6] Transformation of the methylpyridine 7 to acromelic acid B (2) was performed in a similar procedure as in the case of 1. Selenium dioxide oxidation of 7 gave the corresponding carboxylic acid, which was then esterified and desilylated. Treatment of the resulting diol-ester successively with PDC and diazomethane afforded triester 8.[5] Conversion of 8 to pyridone 9[5] was achieved by our improved method for pyridone synthesis via N-oxide.[7] Finally, removal of the protective groups of 9 gave acromelic acid B(2). The synthetic compound was identical with natural product in all respects (^{1}H NMR, UV, CD and chromatographic mobilities).

Thus, the structure of acromelic acid B was established, including absolute configuration, as shown by 2.[8]

In the neurobiological test using crayfish neuromuscular preparation,

acromelic acid B (2) showd the potent depolarizing action comparable to that of acromelic acid A (1).[9]



(a) $EtO_2CCH_2PO(OEt)_2$/NaH/THF, 0 °C, 20 min (98%). (b) DIBAH, 0 °C, 20 min (99%). (c) i $NaIO_4$-Na_2HPO_4, 40 °C, 1 h; ii TFAA/Py, 0 °C, 10 min→rt, 30 min; iii Na_2CO_3aq., 0 °C, 10 min→rt, 1 h. (d) MsCl/Et_3N/CH_3CN, 0 °C, 20 min. (e) PhSH/Et_3N/DMF, 0 °C, 15 min (48%, 4 steps). (f) MeLi/THF, -15 °C, 20 min (87%). (g) PDC/DMF, rt, 16 h (83%). (h) i $NaIO_4$-Na_2HPO_4, 40 °C, 1 h ii TFAA/Py, 0 °C, 20 min iii NH_3aq, 0 °C→rt, 16 h (62%). (i) i SeO_2/Py, 100 °C, 16 h; ii CH_2N_2; iii pTsOH/MeOH, rt, 30 min (52%). (j) i PDC/DMF, 40 °C, 16 h; ii CH_2N_2 (48%). (k) mCPBA, rt, 16 h (75%). (l) TFAA/DMF, rt, 16 h (62%). (m) i KOH/MeOH, rt, 16 h; ii TFA, rt, 30 min (73%).

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References

1) K. Konno, H. Shirahama and T. Matsumoto, Tetrahedron Lett., 24, 939 (1983).
2) K. Konno, K. Hashimoto, Y. Ohfune, H. Shirahama, and T. Matsumoto, Tetrahedron Lett., 27, 607 (1986).
3) These compounds were obtained as a mixture of geometrical isomers about the double bond.
4) In this step, the 1, 6-adduct was yielded exclusively, no 1, 4-adduct being obtained.
5) 7: $[\alpha]_D$ -53.5° (c 0.65, $CHCl_3$); UV(EtOH), 264(3,910) nm. 8: $[\alpha]_D$ -35.5°(c 0.85, $CHCl_3$); UV(EtOH), 268(2,400) nm. 9: $[\alpha]_D$ -28.0°(c 0.15, $CHCl_3$); UV(EtOH) 317(2,600) nm.
6) K. Konno, K. Hashimoto, H. Shirahama, and T. Matsumoto, Tetrahedron Lett., in press.
7) K. Konno, K. Hashimoto, H. Shirahama and T. Matsumoto, Heterocycles, 20, No.8 (1986)
8) 2: $[\alpha]_D$ 50.1 (c 0.45, H_2O); SIMS: m/z 311 $(M+H)^+$; UV: (pH 7) 239(5,150) and 311(3,250), (pH 2) 241(4,650) and 312(2,960), (pH 12) 236(6,320) and 302(2,920) nm; FT-IR: 3165-3045, 1715, 1695, 1620 cm^{-1}; CD (H_2O): 225 (3,500) nm
9) Thanks are due to Dr. H. Shinozaki (the Tokyo Metropolitan Institute of Medical Science) for informing us the unpublished results.

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