Tetrahedron Letters, Vol.27, No.5, pp 607-610, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

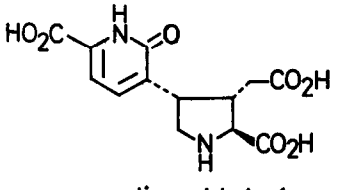
SYNTHESIS OF ACROMELIC ACID A, A TOXIC PRINCIPLE OF CLITOCYBE ACROMELALGA.

Katsuhiro Konno, Kimiko Hashimoto, +Yasufumi Ohfune,
Haruhisa Shirahama and Takeshi Matsumoto

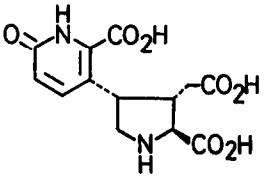
Department of Chemistry, Faculty of Science, Hokkaido University,
Sapporo 060, Japan
+Suntory Institute for Bioorganic Research, Shimamoto-cho,
Mishima-gun, Osaka 618, Japan

Abstract; Acromelic acid A, a toxic principle of Clitocybe acromelalga, was synthesized from L-α-kainic acid. The synthesis established the previously inferred structure, and determined the absolute configuration as shown by 1.

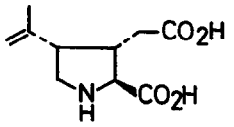
The poisonous mushroom Clitocybe acromelalga Ichimura, distributed in Japan only, exhibits unique symptoms similar to erythromelalgia and acromelalgia. Its remarkable physiological properties prompted us to study chemical constituents of this fungus[1]. As a result, we isolated new amino acids acromelic acid A and B as the toxic principles, and inferred their structures to be 1 and 2 respectively by spectral analyses[2]. Due to the limited sample quantity, however, the spectral data available were those of ^{1}H NMR and UV spectra only. Therefore, the inferred structures had to be supported further by other experimental findings. Moreover, because of its structural relationship to kainic acid 3 and domoic acid 4, it was expected (for 1 and 2) to show some neurobiological activities[3]. We report here the synthesis of acromelic acid A from L-α-kainic acid, which unambiguously established the structure, including absolute configuration, as shown by 1.



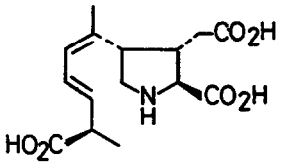
acromelic acid A 1



acromelic acid B 2



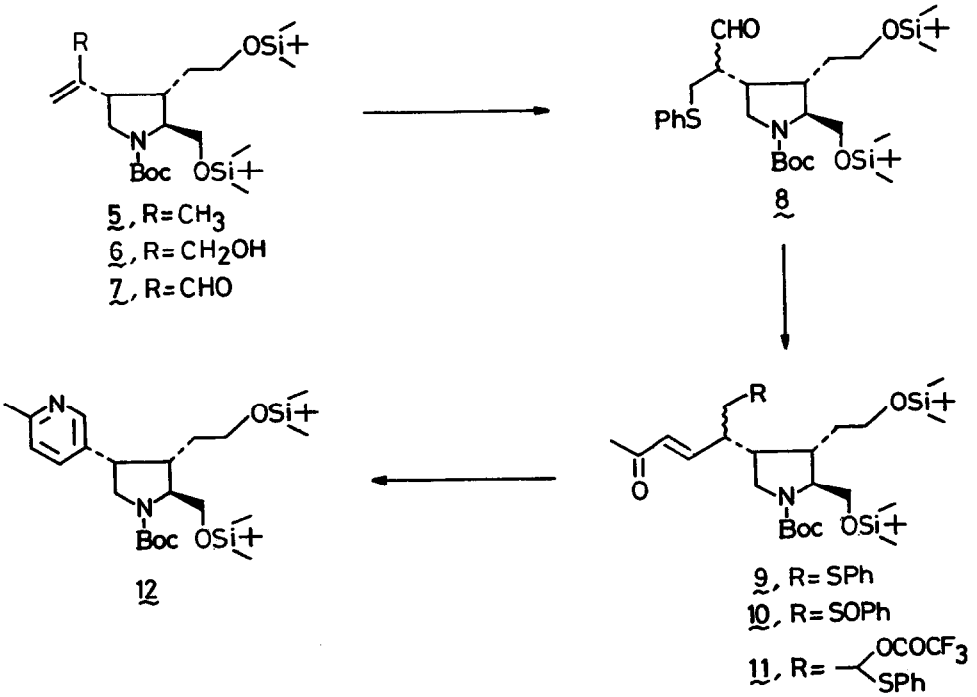
kainic acid 3



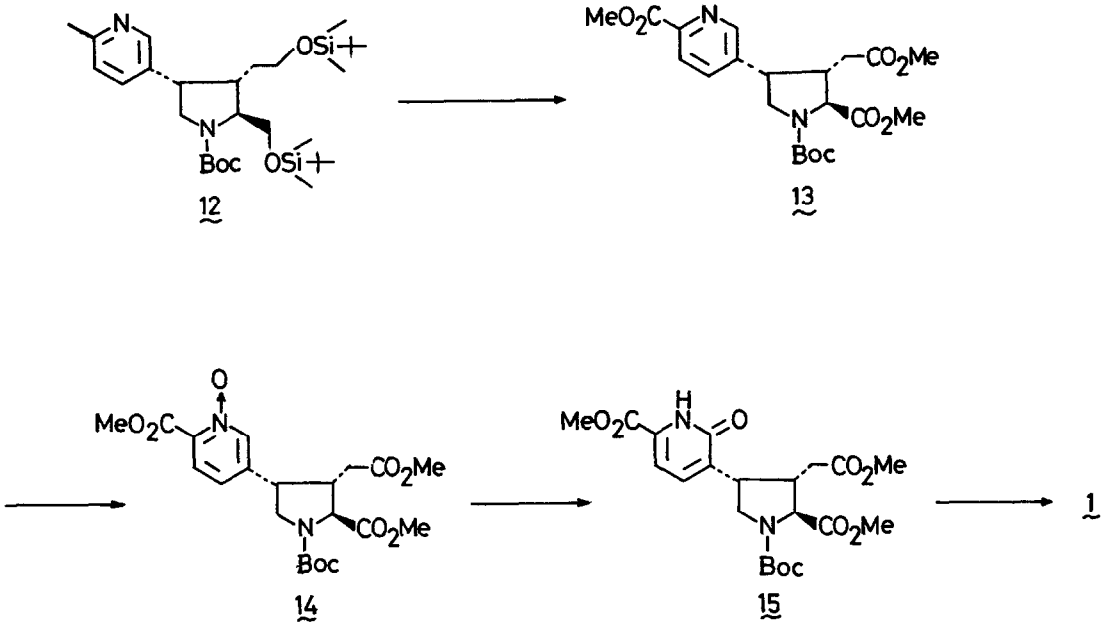
domoic acid 4

Successive protection[4] of imino (Boc-ON) and carboxyl (CH_2N_2) groups of L-α-kainic acid 3, followed by reduction ($LiAlH_4$) and silylation (ClSi≡, imidazole) afforded 5, $[\alpha]_D$ -27.8° (C 1.0, $CHCl_3$) in 70% overall yield. Since allylic oxidation of 5 using SeO_2 gave undesired results, oxidation of methyl group in 5 was carried out through sequential epoxidation of 5 (mCPBA, 97%), isomerization of the resulting epoxide to allylic alcohol 6 (lithium 2,2,6,6-tetramethylpiperidide/ether, 60%), and oxidation of 6 by MnO_2 to aldehyde 7, $[\alpha]_D$ -27.0° (C 1.15, $CHCl_3$), in 86% yield.

To construct pyridine nucleus from α,β-unsaturated carbonyl compounds, we found a mild and efficient method that involved (1) 1,4-addition by thiophenol (2) connection of C_3-unit by a Hornér-Emmons reaction (3) preparation of 1,5-dicarbonyl compound by a Pummerer reaction (4) cyclization to pyridine by ammonia[5]. The α,β-unsaturated aldehyde 7 was subjected to this method. The adduct 8 was obtained as a diastereomixture ($PhSH/Et_3N$, 0°, 1h, 93%), which was converted to ketone 9



[$CH_3COCH_2PO(OEt)_2$/NaH/THF, 0°, 16h, 79%]. Pummerer reaction of 10, obtained by oxidation of 9 with $NaIO_4$-Na_2HPO_4, was smoothly proceeded under neutral condition (TFAA/py[6] in CH_2Cl_2, 0°, 1h) to furnish rearranged product 11 in excellent yield. 11 was rather unstable, so that it was immediately cyclized by NH_3/MeOH (rt, 16 h), in one-pot operation, to methylpyridine 12, $[\alpha]_D$ -31.5° (C 0.80, $CHCl_3$), λ_{max}^{EtOH} 268 nm (log ε 3.66), in 64% overall yield from 9.



In order to transform 12 to pyridonecarboxylic acid derivative, 12 was treated sequentially with (1) SeO_2/Py (2) CH_2N_2 (3) nBu_4NF (4) PDC/DMF (5) CH_2N_2 to afford pyridinecaboxylic acid dervative 13, $[\alpha]_D$ +6.5° (C 0.73, $CHCl_3$) λ_{max}^{EtOH} 269 nm (log ε 3.71), in 20% overall yield, which in turn was led to N-oxide 14 by mCPBA in 77% yield. Formation of 2-pyridone from 14 was realized by our modified method using TFAA/DMF instead of hot Ac_2O[7], that is, treatment of 14 with excess TFAA in DMF at room temp gave pyridone 15, $[\alpha]_D$ -114.3 (C 0.74, $CHCl_3$) λ_{max}^{EtOH} 241 (log ε 3.90), 231 (4.22) nm, in 68% yield. Deprotection of 15 in usual manner [(1) KOH (2) TFA, in 71% yield] afforded 1[8], all of the data of which were completely identical with those of natural 1 (NMR, UV. SIMS[9], CD, chromatographic mobilities). Thus, the structure of acromelic acid A was establised to be 1.

In the neurobiological tests employing crayfish neuromuscular preparation, 1 showed the most potent depolarizing effect among the compounds related to L-glutamic acid known so far[10].

Acknowledgement

We are indebted to Dr. Y. Naya and H. Naoki (Suntory Institute for Bioorganic Research) for the measurement of SIMS, and to Dr. A. Ichihara (Faculty of Agriculture, Hokkaido University) for the measurement of optical rotations.

References and Notes

1) a. K. Konno, K. Hayano, H. Saito, H. Shirahama and T. Matsumoto, Tetrahedron, 38, 3281 (1982).
b. K. Konno, H. Shirahama and T. Matsumoto, Phytochemistry, 23, 1003 (1984).
2) K. Konno, H. Shirahama and T. Matsumoto, Tetrahedron Letters, 24, 939 (1983).
3) H. Shinozaki, "Kainic Acid as a Tool in Neurobiology", Ed. by E. G. McGeer, J. W. Olney and P. L. McGeer, Raven Press, New York (1978).
4) Y. Ohfune and M. Tomita, J. Am. Chem. Soc., 104, 3511 (1982).
5) K. Konno, K. Hashimoto, Y. Ohfune, H. Shirahama and T. Matsumoto, 17th Congress of Heterocyclic Chemistry, Sapporo Japan (1985), Abstr., p. 133.
6) a. T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, S. Matsumoto and S. Nishida, J. Am. Chem. Soc., 90, 3280 (1968).
b. T. Matsumoto, H. Shirahama, F. Sakan and K. Takigawa, Bull, Chem. Soc. Jpn., 50, 325 (1977).
7) E. Ochiai, "Aromatic Amine Oxides", Elsevier, Amsterdom, (1967).
8) White crystals, mp.>310°C, $[\alpha]_D$ +27.8° (C 0.35, H_2O), SIMS: m/z 311 $[(M+H)^+]$. IR(nujol): 3600-2400, 1705, 1650, 1620 cm^{-1}.UV:$\lambda_{max}^{pH\ 7}$ 240(log ε 3.71), 313 (3.98); $\lambda_{max}^{pH\ 2}$ 242 (3.64), 317 (3.95); $\lambda_{max}^{pH\ 12}$ 242 (3.71), 313 (3.96) nm, CD(H_2O): $[\theta]_{205}$ -14600, $[\theta]_{245}$ +4600, $[\theta]_{313}$ +5800.
9) The sample of natural 1 was extracted from fruiting bodies of C. acromelalga collected in 1983.
10) Thanks are due to Dr. H. Shinozaki (the Tokyo Metropolitan Institute of Medical Science) for informing us the unpublished results.

(Received in Japan 26 November 1985)