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Efficient Syntheses of Acromelic Acids B and E, Which Are Potent Neuroexcitatory Amino Acids

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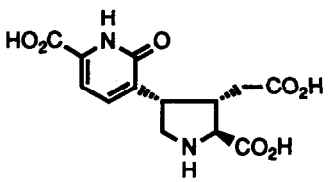
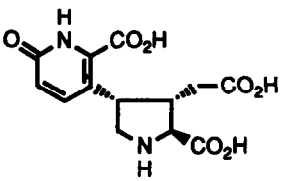
Summary: (–)-Acromelic acid B(2) was synthesized from 2-cyano-3-(2-hydroxyethyl)pyridine(4) in 21% overall yield. Acromelic acid E(3) was also prepared on the way of above synthesis.

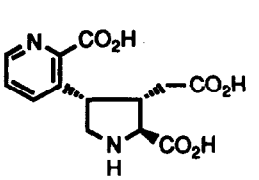
Acromelic acids A~E are very potent neuroexcitatory amino acids which are isolated from a poisonous mushroom *Clitocybe acromelalga*(Japanese name: Dokusasako).[1] Because of their strong biological activity, pharmacologists and physiologists are very much interested in their neurophysiological functions and expect them to be good tools in their studies.[2]



acromelic acid A(1)



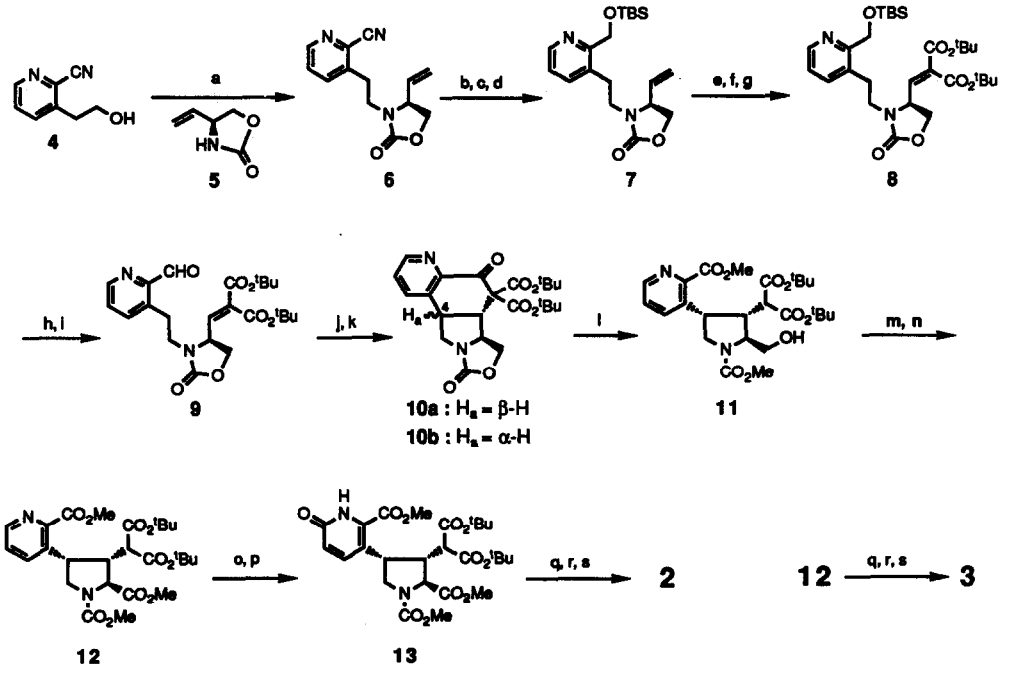
acromelic acid B(2)



acromelic acid E(3)

In 1987, a serious outbreak of food poisoning occurred in Canada. Symptoms of the poisoning included confusion, memory loss, disorientation and coma. It was attributed to shellfishes, blue mussels, from which domoic acid was isolated as the cause of poisoning.[3] The domoic acid has been known as a neuroexcitatory amino acid which interacts with a kainate type glutamate receptor.[2] The unfortunate accident endorses that the glutamate receptor takes part deeply in memory and learning. Acromelic acids A(1) and B(2) interact with the kainate type glutamate receptor[2] which is eagerly studied in these days. Since the acids are anxiously asked in the field of physiology, the development of the method for their effective synthesis has been requested. Acromelic acids A(1) and B(2) were already synthesized by us[1a] and others,[4] but they were still short to supply them as the reagents for pharmacology. In this report we wish to describe an efficient synthetic procedure of acromelic acids B(2) and E(3).

Scheme [a]



[a] reagents and conditions

a) Tf_2O, CH_2Cl_2; then **5**, KH, rt, b) 50% BF_3•MeOH, 120°C, c) $NaBH_4$, d) TBSCl, imidazole, e) O_3, MeOH, -78°C, f) $CH_2(CO_2{}^tBu)_2$, NaH, CH_2Cl_2, -78°C, g) MsCl, Et_3N, h) CSA, EtOH, i) Dess-Martin periodinane(DMP), j) hν, toluene, -78°C, k) DMP, l) MeONa, MeOH, m) DMP, n) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, then CH_2N_2, o) mCPBA, p) TFAA, DMF, q) HCO_2H, r) H_2O, 140°C, s) 3N KOHaq, 120°C

Alkylation of the optically active vinyl glycinol derivative **5**[5] with the triflate of **4**[6] was carried out using KH in CH_2Cl_2 to give rise to adequately protected secondary amine **6** in 70% yield. Treatment of **6** with 50% BF_3•MeOH, followed by reduction and silylation afforded the silyloxymethylpyridine **7** in 88% yield. A hydroperoxyhemiacetal provided by ozonization of **7** was combined with sodium di-*tert*-butyl malonate to give β-hydroxydiester, which was converted to α,β-unsaturated diester **8** by treatment with MsCl and Et_3N in 92% yield from **7**. The diester **8** was then desilylated and oxidized with Dess-Martin periodinane(DMP)[7] to afford aldehyde **9** in 90% yield. Intramolecular Diels-Alder reaction of **9**, which contains photoinduced enolization of pyridinecarbaldehyde, was carried out under irradiation of light using a medium pressure mercury lamp in toluene at -78°C.[8] The reaction occurred smoothly and stereoselectively. The resulting secondary alcohol was oxidized with DMP to furnish the desired ketone **10a**[9](mp 182~185°C, $[\alpha]^{24}_D$+57°(c 0.80, $CHCl_3$)) and its C-4 epimer **10b**[9](mp 85~87°C, $[\alpha]^{25}_D$–83°(c 0.75, $CHCl_3$))(**10a** : **10b** = 6 : 1) in 73% yield from **9**. Cleavage of β-ketodiester and cyclic carbamate groups of **10a** took place at once by treatment with NaOMe in MeOH to give **11** in 98% yield. The primary alcohol **11** was oxidized stepwise, with DMP to an aldehyde first and then with $NaClO_2$[10] to an acid which was converted to ester **12** in 81% yield through three steps. Treatment of **12** with mCPBA in

CH_2Cl_2, followed by TFAA in DMF, afforded pyridone **13** in 88% yield.[1a, 11] The pyridone **13** was converted to acromelic acid B(**2**) in 81% yield through the following sequential treatment: (1) hydrolysis of *tert*-butyl ester with HCO_2H; (2) decarboxylation with reflux in water; (3) removal of methyl carbamate group with 3N KOHaq. Synthetic acid **2** was completely identical to the natural product spectroscopically(IR, NMR, $[\alpha]_D$) and chromatographically. This synthetic process is very effective and overall yield of the acromelic acid B(**2**)[12](mp>300°C, $[\alpha]^{21}_D$–57°(c 0.35, H_2O)) from **4** amounts to 21%. Acromelic acid E(**3**)[13](mp>300°C, $[\alpha]^{25}_D$–107°(c 0.25, H_2O)) was also synthesized from **12** through the similar process.

References and Notes

1) (a) **Acromelic acids A and B**: Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *J. Amer. Chem. Soc.* **1988**, *110*, 4807. (b) **C**: Fushiya, S.; Sato, S.; Kanazawa, T.; Kusano, G.; Nozoe, S. *Tetrohedron Lett.* **1990**, *31*, 3901. (c) **D and E**: Fushiya, S.; Sato, S.; Kera, Y.; Nozoe, S. *Heterocycles* **1992**, *34*, 1277.

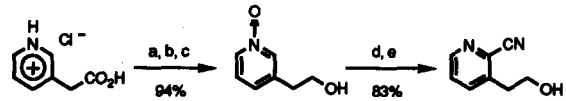
2) Ishida, M.; Shinozaki, H. *Br. J. Pharmacol.* **1991**, *104*, 873; Shinozaki, H.; Ishida, M. *Asia Pacific J. Pharmacol.* **1991**, 293 and literatures cited therein.

3) Quilliam, M. A.; Wright, J. L. C. *Anal. Chem.* **1989**, *61*, 1053A and literatures cited therein.

4) (a) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Amer. Chem. Soc.* **1987**, *109*, 5523. (b) Baldwin, J. E.; Li, C. S. *J. Chem. Soc., Chem. Commun.* **1988**, 261. (c) Takano, S.; Tomita, S.; Iwabuchi, Y.; Ogasawara, K. *Heterocycles* **1989**, *29*, 1473.

5) The optically active **5** was synthesized by treatment of (2S)-N-Boc-amino-3-butenol with $SOCl_2$ in benzene at 100°C in 80% yield. The synthesis of (2S)-N-Boc-amino-3-butenol has been reported by: Ohfune, Y; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1071.

6) The cyanate **4** was prepared from 3-pyridylacetic acid hydrochloride through five steps: (a) esterification with $SOCl_2$ in MeOH; (b) reduction with $LiAlH_4$; (c) oxidation with mCPBA; (d) cyanation with TMSCN and Me_2NCOCl in CH_2Cl_2; (e) desilylation with MeOH. For references of cyanation: Fife, W. K. *J. Org. Chem.* **1983**, *48*, 1375. Fife, W. K.; Boyer, B. D. *Heterocycles* **1984**, *22*, 1121.



7) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

8) This key step reaction is essentially the same as one employed in our previous synthesis of hydroxy and methoxyphenyl kainoids: Hashimoto, K.; Horikawa, M.; Shirahama, H. *Tetrahedron Lett.* **1990**, *31*, 7047. However, the Diels-Alder reaction based on photoinduced enolization of pyridinecarbaldehyde, which is less reactive than previous case, has not been recorded so far.

9) ^{1}H NMR for **10a**: (500MHz, $CDCl_3$)δ 3.26(1H, dd, J=7.8,9.8Hz), 3.27((1H, dd, J=2.5, 11.3Hz), 4.03(1H, ddd, J=2.5, 7.8, 8.8Hz), 4.19(1H, ddd, J=5.4, 8.3, 9.8Hz), 4.28(1H, dd, J=8.8, 11.7Hz), 4.45(1H, dd, J=5.4, 10.3Hz), 4.74(1H, dd, J=8.3, 10.3Hz), 7.54(1H, dd, J=4.4, 7.8Hz), 7.64(1H, dd, J=~1, 7.8Hz), 8.78(1H, dd, J=~1, 4.4Hz).; ^{1}H NMR for **10b**: (500MHz, $CDCl_3$)δ 2.70(1H, dd, J=9.3, 12.2Hz), 3.59(1H, dd, J=7.8, 10.3Hz), 3.63(1H, dd, J=5.4, 10.3Hz), 4.05(1H, ddd, J=5.4, 7.8, 12.2Hz), 4.52(1H, dd, J=7.8, 8.3Hz), 4.69(1H, dd, J=4.9, 8.3Hz), 4.72(1H, ddd, J=4.9, 7.8, 9.3Hz), 7.50(1H, dd, J=4.4, 7.8Hz), 7.57(1H, dd, J=1.5, 7.8Hz), 8.81(1H, dd, J=1.5, 4.4Hz).

10) Lindgren, B. O.; Hilsson, T. *Acta Chem. Scand.* **1973**, *27*, 880.

11) Konno, K.; Hashimoto, K. ; Shirahama, H.; Matsumoto, T. *Heterocycles* **1986**, *24*, 2169.

12) ^{1}H NMR for **2**:(500MHz, D_2O)δ 2.33(1H, dd, J=8.8, 16.9Hz), 2.53(1H, dd, J=5.9, 16.9Hz), 3.23(1H, ddt, J=5.9, 8.1, 8.8Hz), 3.60(1H, t, J=11.7Hz), 3.75(1H, dd, J=8.1, 11.7Hz), 4.07(1H, d, J=5.9Hz), 4.63(1H, dt, J=11.7, 8.1Hz), 6.67(1H, d, J=9.5Hz), 7.63(1H, d, J=9.5Hz). In our previous report,[1a] the datum $[\alpha]_D$ of **2** was misprinted. $[\alpha]_D$ 50.1° should read $[\alpha]_D$–50.1°.

13) ^{1}H NMR for **3**:(500MHz, D_2O)δ 2.42(1H, dd, J=8.8, 16.6Hz), 2.62(1H, dd, J=6.3, 16.6Hz), 3.56(1H, dddd, J=4.9, 6.3, 7.8, 8.8Hz), 3.95(1H, t, J=11.7Hz), 4.01(1H, dd, J=7.8, 11.7Hz), 4.26(1H, d, J=4.9Hz), 5.04(1H, dt, J=11.7, 7.8Hz), 8.10(1H, dd, J=5.9, 8.3Hz), 8.58(1H, d, J=8.3Hz), 8.74(1H, d, J=5.9Hz). These data are not completely coincident with those of natural **3** reported in the reference 1c. The chemical shifts of the ^{1}H NMR signal of **3** depend on pH of the sample solution which is not found in the literature 1c.

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