A CONCISE ENANTIOSELECTIVE SYNTHESIS OF ACROMELIC ACID B FROM (*S*)-*O*-BENZYLGLYCIDOL

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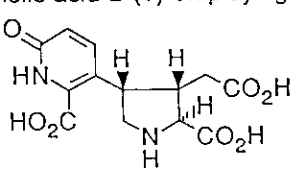
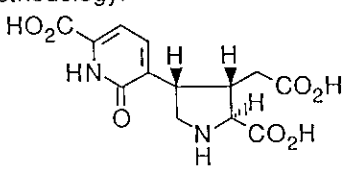
Abstract——— The potent neurotoxin, acromelic acid B, has been synthesized by an enantioselective route employing an intramolecular 1,3-dipolar cyclization as the key step.

Acromelic acid B[1] (**1**), isolated by Konno, Shirahama, and Matsumoto[2] along with acromelic acid[1] A (**2**) from the Japanese poisonous mushroom *Clitocybe acromelalga*, possesses extremely potent depolarizing activity on glutamate-mediated neurotransmission.[3] Hashimoto, Konno, Ohfune, Shirahama, and Matsumoto[2b,4] have converted kainic acid into **1** and **2** to clarify their structures by employing an interesting method. Although this conversion implies the formal total synthesis of these amino acids since kainic acid has been synthesized enantioselectively by a variety of methods,[1] more straightforward route to the former alkaloid has not been reported to date. Following the development of an enantio- and stereo-selective intramolecular 1,3-dipolar cycloaddition route to kainic acid[5] and acromelic acid A[6] (**2**), we now describe a more direct route to acromelic acid B (**1**) employing the same methodology.



1

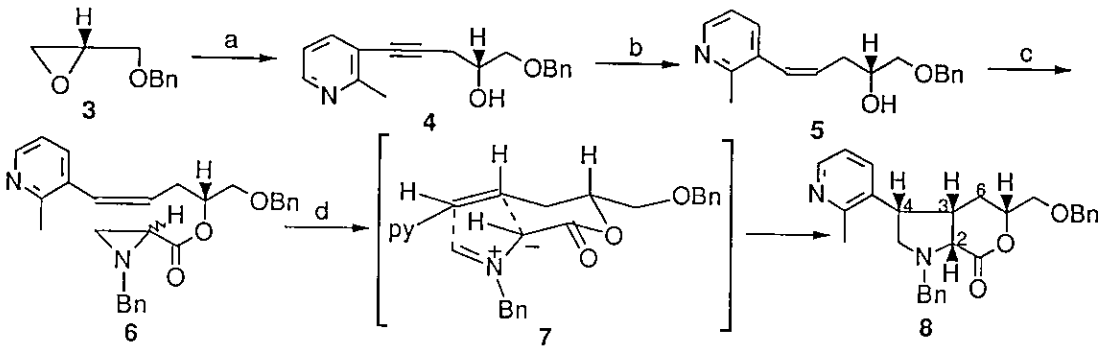


2

Fig. 1

Treatment of (*S*)-*O*-benzylglycidol[7] (**3**) with the lithium acetylide, generated by exposure of 3-ethynyl-2-methylpyridine to *n*-butyllithium in tetrahydrofuran (THF) containing hexamethylphosphoric triamide (HMPA), afforded the acetylene-alcohol **4**, $[\alpha]_D^{23}$ –18.2° (*c* 1.25, $CHCl_3$), in 84% yield. Catalytic hydrogenation using Lindlar catalyst gave the *Z*-olefin **5** (97%), $[\alpha]_D^{24}$ –14.8° (*c* 1.11, $CHCl_3$), which was treated with 2,3-dibromopropionyl chloride and triethylamine followed by benzylamine in dichloromethane at room temperature[8] to furnish the aziridine ester **6** in 62% yield as a 1:1 mixture of epimers.

Upon thermolysis in degassed xylene (15% w/v) at 200 °C for 1.5 h using a glass sealed-tube **6** afforded the trisubstituted pyrrolidine **8**, $[\alpha]_D^{23}$ –102.6° (*c* 1.95, $CHCl_3$), in 66% yield as a single

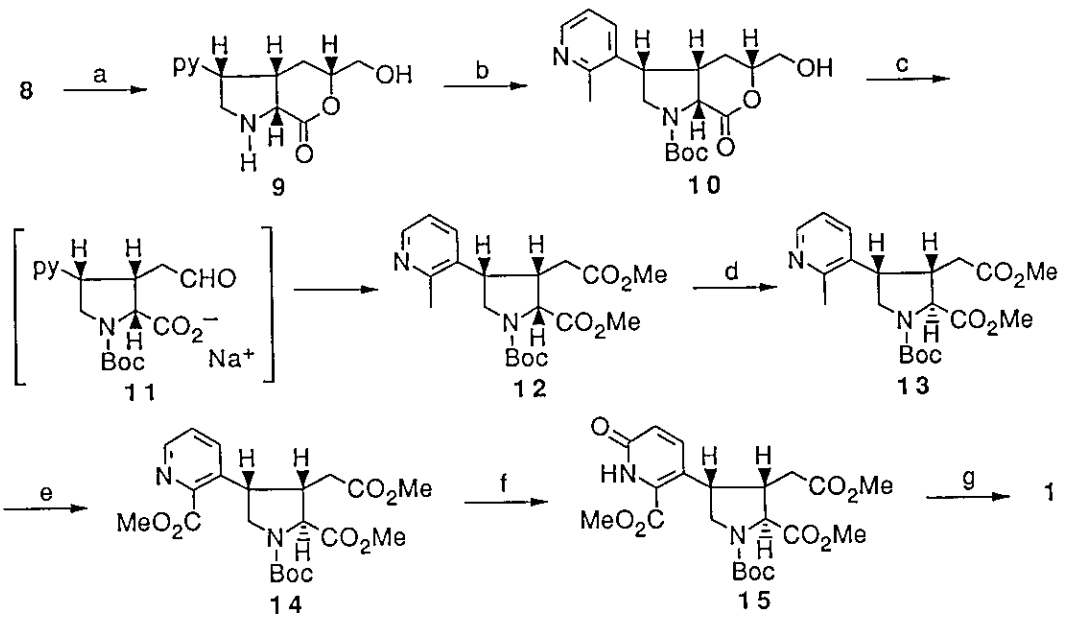


Scheme 1

a, 3-ethynyl-2-methylpyridine, ^{n}BuLi, HMPA, THF, –25 °C → r. t.; b, H_2, Pd/$BaSO_4$, MeOH; c, 2,3-dibromopropionyl chloride, Et_3N then $BnNH_2$; d, xylene, sealed tube, 200 °C, 1.5 h.

stereoisomer. Stereochemistry of the product was deduced to be all *cis*-configuration by comparison of its ^{1}H-nmr spectrum (500 MHz) with that of the isomeric compound[6] [**8**: 3-(6-pyridylmethyl)- in place of 3-(2-pyridylmethyl)-] which was served as the key intermediate of acromelic acid A (**2**). Close resemblance between two spectra, especially anomalous high field shift of 6α-proton (δ 0.90), indicated the stereochemistry of the product as shown. The product **8** may be formed *via* transient formation of the azomethine ylide[8] **7** taking single reactive conformation owing to the presence of bulky benzyloxymethyl group on the chiral center. At any rate, it was noteworthy that three new chiral centers could be generated stereoselectively in a single step by the directive group on a single chiral center.

Having succeeded in the intramolecular 1,3-dipolar cyclization, the product **8** was double debenzylated using palladized carbon (10%) and the amino-alcohol **9** obtained was immediately acylated to give the lactone-carbamate **10** (73% overall), $[\alpha]_D^{23}$ –128.7° (*c* 1.10, $CHCl_3$). **10** was sequentially saponified, cleaved, oxidized, and methylated in the same flask to afford the dimethyl ester **12**, $[\alpha]_D^{24}$ –34.1° (*c* 2.80, $CHCl_3$), in 77% overall yield. On exposure to a mixture of sodium hydride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene[5,6] at room temperature, **13** epimerized cleanly at C_2 center to give the 2(*S*)-ester **14**, $[\alpha]_D^{24}$ –27.6° (*c* 1.00, $CHCl_3$), possessed the requisite stereochemistry for acromelic acid B (**1**), in 84% yield. The 2,3-*trans* configuration was supported by comparison[2,4,5] of chemical shift of C_2-proton between **12** and **13** the former of which appeared at δ 4.08, while the latter of which appeared at δ 4.60, respectively. Treatment of **13** with selene dioxide[2,4,5] in refluxing pyridine, followed by methylation of the resulting carboxylic acid in the same flask furnished the known triester **14** (52% overall), $[\alpha]_D^{24}$ –32.1° (*c* 0.455, $CHCl_3$) [lit.[2b] $[\alpha]_D^{24}$ –35.5° (*c* 0.85, $CHCl_3$)], of which spectral data (ir, ^{1}H-nmr, and mass) were identical with the reported values. Employing the established method,[2,4] **14** was converted into the pyridone **15** (54% overall), $[\alpha]_D^{27}$ –30.6° (*c* 0.17, $CHCl_3$) [lit.[2b] $[\alpha]_D$ –28.0° (*c* 0.15, $CHCl_3$)] by sequential *N*-oxidation and rearrangement. Finally, **15** was sequentially saponified and de-*N*-protected to afford acromelic acid B (**1**), $[\alpha]_D^{27}$ –74.0° (*c* 0.1, H_2O) [natural[9]: $[\alpha]_D^{28}$ –79.6° (*c* 0.29, H_2O); lit.[2b,4]: $[\alpha]_D$ –50.1° (*c* 0.45, H_2O)[10]] in 67.5% yield.



Scheme 2

a, H_2, Pd/C, MeOH, HCl; b, Boc_2O, Et_3N, CH_2Cl_2; c, NaOH, THF, H_2O then $NaIO_4$, $KMnO_4$ then CH_2N_2; d, NaH, DBU, benzene, r. t.; e, (i) SeO_2, pyridine, (ii) CH_2N_2; f, (i) MCPBA, (ii) TFAA, DMF; g, KOH then TFA.

The synthetic material was identical with natural acromelic acid B[9] (**1**) isolated from *Clitocybe acromelalga*.

ACKNOWLEDGMENT

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8. P. A. DeShong, D. A. Kell, and D. R. Sidler, *J. Org. Chem.*, 1985, **50**, 2309.
9. Kindly donated by Professors S. Nozoe and G. Kusano, and Dr. S. Fushiya, Pharmaceutical Institute, Tohoku University.
10. The sign of specific rotations was missing in the references 2b and 4: Private letter from Professor H. Shirahama, Faculty of Science, Hokkaido University.
11. All the products isolated gave satisfactory spectral data as follows:

4: ir ν (neat) cm^{-1}: 2200, 3250; nmr ($CDCl_3$) δ 2.55 (1H, br s, exchangeable with D_2O), 2.60 (3H, s), 2.83 (2H, d, *J*=6.4 Hz), 3.62 (2H, m), 4.08 (1H, m), 4.60 (2H, s), 7.35 (5H, s), 7.05 (1H, dd, *J*=4.9, 7.5 Hz), 7.60 (1H, dd, *J*=7.5, 1.7 Hz), 8.37 (1H, dd, *J*=4.9, 1.7 Hz).

5: ir ν (neat) cm^{-1}: 3300; nmr ($CDCl_3$) δ 2.31 (2H, td, *J*=6.8, 1.5 Hz), 2.47 (3H, s), 2.70 – 3.10 (1H, m, exchangeable with D_2O), 3.30 (1H, dd, *J*=9.3, 7.3 Hz), 3.48 (1H, dd, *J*=9.3, 3.4 Hz), 3.90 (1H, m), 4.52 (2H, s), 5.91 (1H, dt, *J*=11.5, 7.3 Hz), 6.52 (1H, d, *J*=11.5 Hz), 7.06 (1H, dd, *J*=7.6, 4.9 Hz), 7.31 (5H, s), 7.50 (1H, dd, *J*=7.6, 1.7 Hz), 8.36 (1H, dd, *J*=4.9, 1.7 Hz).

6: ir ν (neat) cm^{-1}: 1730; nmr ($CDCl_3$) δ 2.45 (3H, s), 1.62 – 2.62 (5H, m), 3.40 – 3.66 (4H, m), 4.50 (2H, s), 5.18 (1H, m), 5.54 – 5.94 (2H, m), 6.51 (2H, br d, *J*=11.3 Hz), 6.91 – 7.57 (12H, m), 8.48 (1H, br d, *J*=4.2 Hz).

8: ir ν (neat) cm^{-1}: 1745; nmr ($CDCl_3$) δ 0.90 (1H, m), 1.76 (1H, m), 2.47 (3H, s), 2.89 (1H, m), 3.06 (1H, m), 3.16 (1H, m), 3.37 (1H, m), 3.50 – 3.59 (2H, m), 3.65 (1H, d, *J*=12.8 Hz), 4.36 (1H, m), 4.49 (2H, m), 4.54 (1H, d, *J*=12.8 Hz), 4.55, 4.60 (1H, m), 7.13 (1H, dd, *J*=7.6, 4.9 Hz), 7.30 (10H, m), 7.53 (1H, dd, *J*=7.6, 1.5 Hz), 8.41 (1H, dd, *J*=4.9, 1.5 Hz).

10: ir ν (neat) cm^{-1}: 3400, 1760, 1705; nmr ($CDCl_3$) δ 1.00 (1H, m), 1.52 (9H, br s), 1.83 (1H, m), 2.48 (3H, s), 3.40 – 3.55 (4H, m), 3.62 (1H, m), 3.70 – 3.82 (2H, m), 3.93 (1H, m), 4.20 – 4.50 (1H, m), 4.50 – 4.80 (1H, m), 7.13 (1H, dd, *J*=7.8, 4.9 Hz), 7.57 (1H, dd, *J*=7.8, 1.7 Hz), 8.32 (1H, dd, *J*=4.9, 1.7 Hz).

12: ir ν (neat) cm^{-1}: 1750, 1705; nmr ($CDCl_3$) δ 1.43 (9H, br s), 1.80 – 2.44 (2H, m), 2.59 (3H, s), 3.39 (3H, s), 3.69 (3H, s), 3.26 – 4.00 (4H, m), 4.51 – 4.72 (1H, m), 7.15 (1H, dd, *J*=7.6, 4.9 Hz), 7.53 (1H, dd, *J*=7.6, 1.5 Hz), 8.41 (1H, dd, *J*=4.9, 1.5 Hz).

13: ir ν (neat) cm^{-1}: 1695, 1738; nmr ($CDCl_3$) δ 1.48, 1.45 (9H, s), 1.90 – 2.35 (2H, m), 2.54 (3H, s), 3.00 – 3.30 (1H, m), 3.81 (3H, s), 3.54 (3H, s), 3.60 – 4.00 (2H, m), 7.15 (1H, dd, *J*=7.6, 4.9 Hz), 7.53 (1H, dd, *J*=7.6, 1.5 Hz), 8.41 (1H, dd, *J*=4.9, 1.5 Hz).

14: ir ν (neat) cm^{-1}: 1700, 1738; nmr ($CDCl_3$) δ 1.46 (6H, s), 1.52 (3H, s), 2.10 – 2.30 (2H, m), 3.10 – 3.40 (1H, m), 3.45 – 4.22 (3H, m), 3.58 (3H, s), 3.80 (3H, s), 3.97 (3H, s), 4.25 – 4.60 (1H, m), 7.40 (1H, dd, *J*=5.0, 8.0 Hz), 7.61 (1H, dd, *J*=1.5, 8.0 Hz), 8.61 (1H, dd, *J*=1.5, 5.0 Hz).

15: ir ν (neat) cm^{-1}: 1695, 1735; nmr ($CDCl_3$) δ 1.45 (9H, s), 2.10 – 2.40 (2H, br m), 3.00 – 3.10 (1H, m), 3.61 (3H, br s), 3.80 (3H, br s), 3.99 (3H, br s), 3.40 – 4.20 (4H, m), 4.40 – 4.80 (1H, m), 6.80 (1H, br d), 8.00 (1H, br d).

1: nmr (D_2O) δ 2.42 (1H, dd, *J*=9.14, 17.1 Hz), 2.62 (1H, dd, *J*=17.1, 6.10 Hz), 3.36 (1H, m), 3.72 (1H, t, *J*=11.60 Hz), 3.84 (1H, dd, *J*=11.9, 7.93 Hz), 4.22 (1H, d, *J*=5.4 Hz), 4.65 (1H, m), 6.78 (1H, d, *J*=9.16 Hz), 7.73 (1H, d, *J*=9.16 Hz).

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