

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 B¹ (**1**), isolated by Konno, Shirahama, and Matsumoto² along with acromelic acid¹ 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 acid⁵ and acromelic acid A⁶ (**2**), we now describe a more direct route to acromelic acid B (**1**) employing the same methodology.

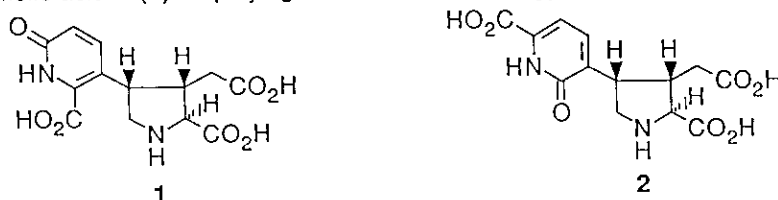
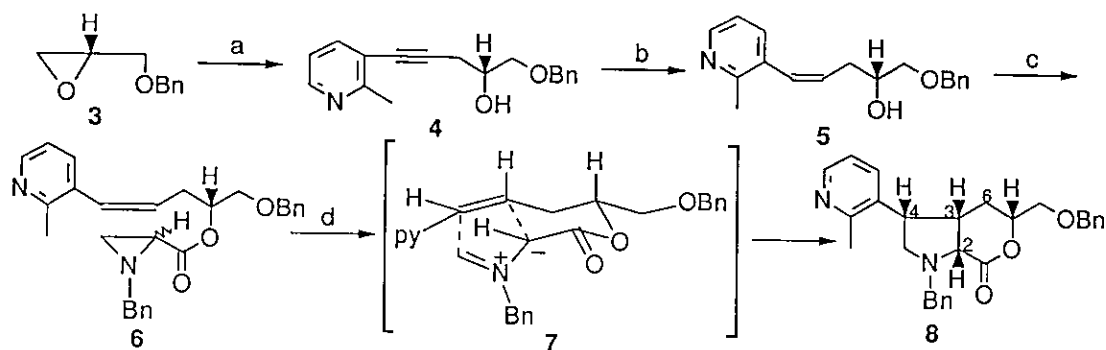


Fig. 1

Treatment of (*S*)-*O*-benzylglycidol⁷ (**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**, $[\alpha]_D^{23} -18.2^\circ$ (*c* 1.25, CHCl₃), in 84% yield. Catalytic hydrogenation using Lindlar catalyst gave the *Z*-olefin **5** (97%), $[\alpha]_D^{24} -14.8^\circ$ (*c* 1.11, CHCl₃), which was treated with 2,3-dibromopropionyl chloride and triethylamine followed by benzylamine in dichloromethane at room temperature⁸ 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**, $[\alpha]_D^{23} -102.6^\circ$ (*c* 1.95, CHCl₃), in 66% yield as a single

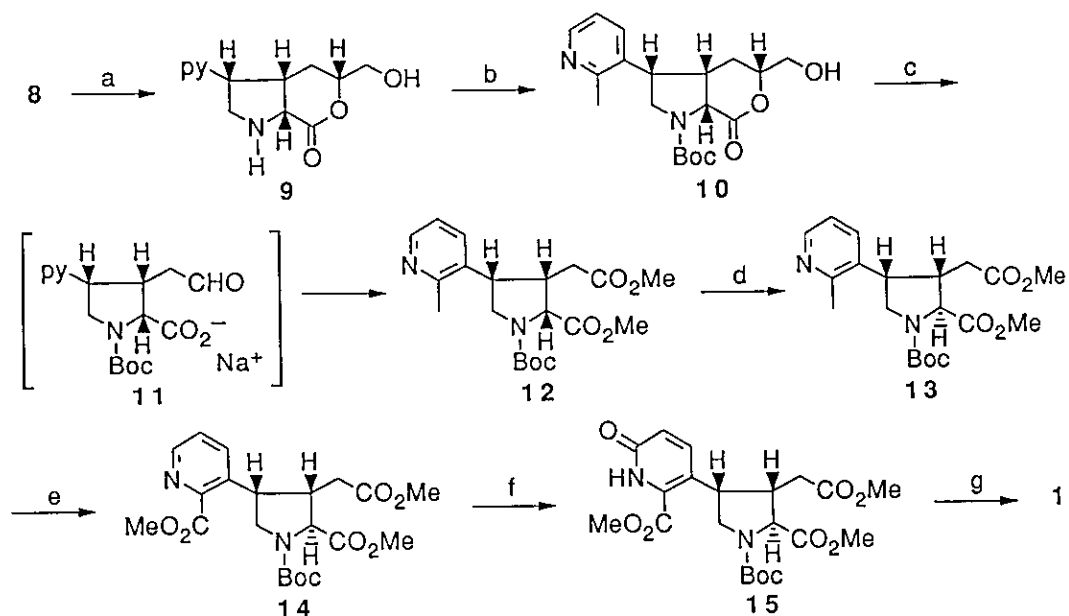


Scheme 1

a, 3-ethynyl-2-methylpyridine, $n\text{BuLi}$, HMPA, THF, $-25\text{ }^\circ\text{C}$ \rightarrow r. t.; b, H_2 , Pd/BaSO₄, MeOH; c, 2,3-dibromopropionyl chloride, Et₃N then BnNH₂; d, xylene, sealed tube, 200 $^\circ\text{C}$, 1.5 h.

stereoisomer. Stereochemistry of the product was deduced to be all *cis*-configuration by comparison of its ¹H-nmr spectrum (500 MHz) with that of the isomeric compound⁶ [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 6 α -proton (δ 0.90), indicated the stereochemistry of the product as shown. The product 8 may be formed *via* transient formation of the azomethine ylide⁸ 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), [α]_D²³ -128.7° (*c* 1.10, CHCl₃). 10 was sequentially saponified, cleaved, oxidized, and methylated in the same flask to afford the dimethyl ester 12, [α]_D²⁴ -34.1° (*c* 2.80, CHCl₃), 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 C₂ center to give the 2(*S*)-ester 14, [α]_D²⁴ -27.6° (*c* 1.00, CHCl₃), 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 C₂-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 seleno 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), [α]_D²⁴ -32.1° (*c* 0.455, CHCl₃) [lit.^{2b} [α]_D²⁴ -35.5° (*c* 0.85, CHCl₃)], of which spectral data (ir, ¹H-nmr, and mass) were identical with the reported values. Employing the established method,^{2,4} 14 was converted into the pyridone 15 (54% overall), [α]_D²⁷ -30.6° (*c* 0.17, CHCl₃) [lit.^{2b} [α]_D²⁷ -28.0° (*c* 0.15, CHCl₃)] by sequential *N*-oxidation and rearrangement. Finally, 15 was sequentially saponified and de-*N*-protected to afford acromelic acid B (1), [α]_D²⁷ -74.0° (*c* 0.1, H₂O) [natural⁹: [α]_D²⁸ -79.6° (*c* 0.29, H₂O); lit.^{2b,4}: [α]_D²⁸ -50.1° (*c* 0.45, H₂O)]¹⁰ in 67.5% yield.



Scheme 2

a, H₂, Pd/C, MeOH, HCl; b, Boc₂O, Et₃N, CH₂Cl₂; c, NaOH, THF, H₂O then NaIO₄, KMnO₄ then CH₂N₂; d, NaH, DBU, benzene, r. t.; e, (i) SeO₂, pyridine, (ii) CH₂N₂; f, (i) MCPBA, (ii) TFAA, DMF; g, KOH then TFA.

The synthetic material was identical with natural acromelic acid B⁹ (1) isolated from *Clitocybe acromelalga*.

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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 v (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 v (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 v (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 v (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 v (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 v (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 v (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 v (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 v (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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