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An Efficient Enantioselective Synthesis of (*S*)-(−)-Acromelobic Acid

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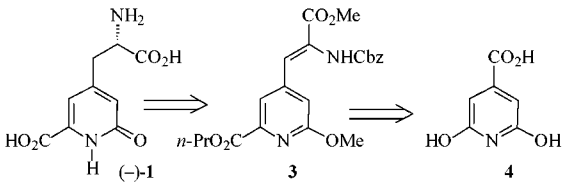
ABSTRACT



A highly efficient enantioselective synthesis of (*S*)-(−)-acromelobic acid (1) was achieved via asymmetric hydrogenation of dehydroamino acid derivative (3) using (*R*,*R*)-[Rh(DIPAMP)(COD)]BF_4 catalyst followed by removal of protective groups in >98% ee and good over all yield. The key intermediate (3) was prepared from the commercially available citrazinic acid (4) in six steps.

The poisonous mushroom *Clitocybe acromelalga*, found exclusively in Japan, has been the source of a variety of potent neuroexcitatory amino acids related to the kainoid family.[1] (*S*)-(−)-Acromelobic acid [3-(6-carboxy-2-oxo-4-pyridyl)-L-alanine, **1**] (Figure 1) was isolated by Shirahama et al.,[2a,b] from the fruit bodies of this mushroom by a combination of ion-exchange column chromatography and paper electrophoresis. Biosynthetically, this nonproteinogenic amino acid, (*S*)-(−)-**1**, was proposed to be derived from L-DOPA and exhibits depolarizing activity in the preparation of newborn rat spinal cord.[2b] The first synthesis of (*S*)-(−)-**1** was reported by chemical conversion of L-stizolobic acid (**2**), a related nonproteinogenic amino acid, which was isolated from *C. acromelalga*[2b] and *Stizolobium hassjoo*.[2c] Subsequently, Baldwin et al.[3] reported a racemic synthesis of (±)-**1** starting from catechol in 13 steps. We have been interested in the synthesis of nonproteinogenic amino acids,[4] particularly the kainoid family,[4a] for a variety of applications including in neuroscience research. In this context, we describe the first and highly efficient enantioselective synthesis of (*S*)-(−)-acromelobic acid (**1**) starting from a commercially available citrazinic acid (**4**).

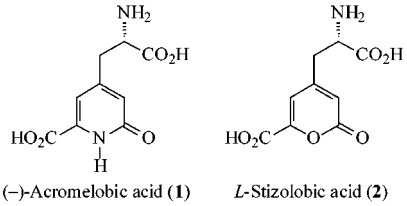


Figure 1. Structure of amino acids (**1** and **2**).

The foundation of our strategy for construction of (*S*)-(−)-**1** was based on the introduction of an α-amino acid chain

(1) (a) For a recent review on the kainoid amino acid chemistry, see: Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149−4174. (b) Also see: Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *J. Am. Chem. Soc.* **1988**, *110*, 4807−4815.

(2) (a) Yamano, K.; Hashimoto, K.; Shirahama, H. *Heterocycles* **1992**, *34*, 445−448. (b) Yamano, K.; Shirahama, H. *Tetrahedron* **1993**, *49*, 2427−2436. (c) Senoh, S.; Imamoto, S.; Maeno, Y.; Tokuyama, T.; Sakan, T.; Komamine, A.; Hattori, S. *Tetrahedron* **1964**, *46*, 3431−3436.

(3) Baldwin, J. E.; Spyvee, M. R.; Whitehead, R. C. *Tetrahedron Lett.* **1994**, *35*, 6575−6576.

(4) (a) Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *Tetrahedron: Asymmetry* **2000**, *11*, 3063−3068. (b) Adamczyk, M.; Akireddy, S. R.; Reddy, R. E. *Tetrahedron: Asymmetry* **1999**, *10*, 3107−3110. (c) Adamczyk, M.; Reddy, R. E. *Tetrahedron: Asymmetry* **2000**, *11*, 2289−2298. (d) Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *Angew. Chem., Int. Ed.* **1999**, *38*, 3537−3539.

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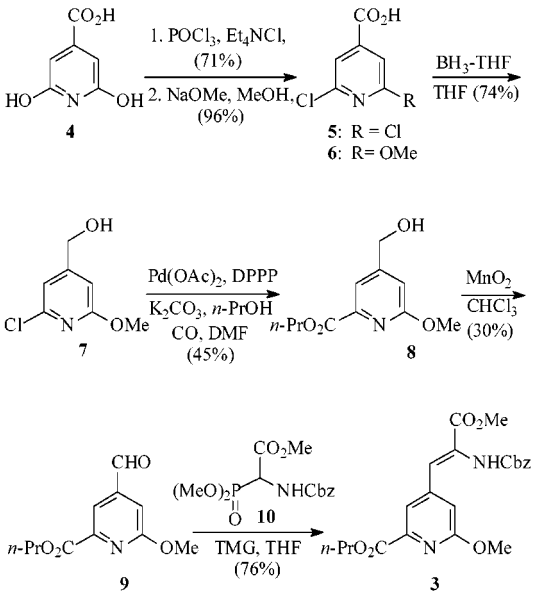
via asymmetric hydrogenation of the appropriately functionalized dehydroamino acid derivative **3** using a transition metal catalyst.[5] Although the application of hydrogenation protocol for the synthesis of (*S*)-(−)-**1** looked promising in light of recent success in the preparation of a variety of α-amino acids,[5] there were only a few reports in the literature related to the hydrogenation of pyridyl dehydroamino acid derivatives.[6] Catalytic asymmetric hydrogenation of heterocyclic systems appeared to be difficult due to the participation of a heteroatom (e.g., pyridine ring nitrogen) which blocked the formation of active metal−substrate complex.[6] The asymmetric hydrogenation reaction of 3,4-pyridyl dehydroamino acid derivatives, however, was facilitated either by higher temperature and pressure[6b] or by addition of HBF_4[6c] to provide the corresponding pyridylalanine derivatives in 70−99% ee.[6b,c] Our proposed asymmetric hydrogenation strategy for (*S*)-(−)-**1** was strengthened by the notion that a pyridine system such as **3**, which contains substituents at both the 2- and 6-positions, might reduce the participation of a ring nitrogen in the formation of an active metal−substrate complex due to steric hinderence. Nevertheless, our first goal in the commencement of asymmetric hydrogenation protocol for the synthesis of (*S*)-(−)-**1** was to prepare dehydroamino acid derivative **3**, which was envisioned from a commercially available inexpensive citrazinic acid (**4**).

Accordingly, citrazinic acid (**4**) (Scheme 1) was converted to the 2,6-dichloroisonicotinic acid (**5**) in 71% yield by

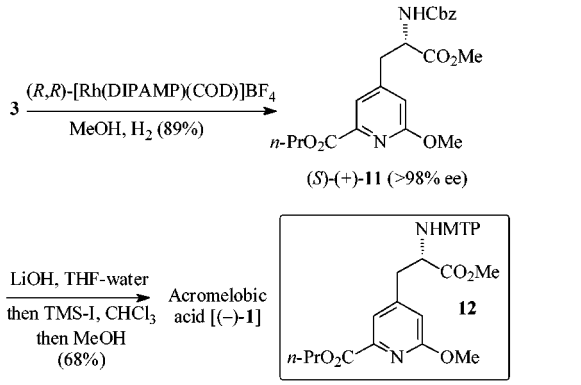
Scheme 1. Synthesis of Key Intermediate (**3**)



treatment with phosphorus oxychloride and tetramethylammonium chloride.[7] One of the chloro groups in **5** was then transformed to the corresponding methoxy derivative **6** in 96% yield[8] by treatment with sodium methoxide in refluxing MeOH for 48 h. The NaOMe was added in two portions in order to avoid the formation of the corresponding bismethoxy derivative. Reduction of the acid functionality in **6** by using a BH_3−THF complex in THF at room temperature for 5 h cleanly afforded the alcohol **7** in 74% yield after purification by silica gel column chromatography. The chloro functionality in alcohol **7** was then transformed into an ester by reaction with carbon monoxide (1 atm pressure) in the presence of palladium acetate, 1,3-bis(diphenylphosphino)-propane (DPPP), 1-propanol, and K_2CO_3 in DMF at 90 °C to obtain ester **8** in 45% yield. Compound **8** was oxidized to the corresponding aldehyde **9** in 30% yield using MnO_2 in chloroform at room temperature for 48 h. Finally, aldehyde **9** was reacted with *N*-(benzyloxycarbonyl) phosphonoglycine trimethyl ester (**10**) in the presence of *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) in THF at 0 °C to room temperature for 6 h to afford the dehydroamino acid derivative (**3**) as a mixture of *Z*/*E* isomers (ratio 93:7, determined by analysis of ^{1}H NMR of the crude compound). The *Z* and *E* geometrical isomers of **3** were separated by silica gel column chromatography (25% EtOAc in hexanes) to afford *Z*-isomer **3** in 76% yield.[9]

Next step in the synthesis of (*S*)-(−)-acromelobic acid (**1**) was the crucial asymmetric hydrogenation to introduce the α-amino acid chain. Thus, hydrogenation of dehydroamino acid derivative **3** was carried out (Scheme 2) using a catalytic

Scheme 2. Completion of the Synthesis of (*S*)-(−)-**1**



amount (0.05 equiv) of (*R*,*R*)-[Rh(DIPAMP)(COD)]BF_4 in anhydrous MeOH[10] at 48 °C and 65 psi of pressure. After

(5) (a) For recent studies on asymmetric hydrogenation, see: Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley and Sons: New York, 1994; Chapter 2, pp 16−94. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Hydrogenation*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 1, pp 1−110.

(6) (a) Cativiela, C.; Mayoral, J. A.; Melendez, E.; Oro, L. A.; Pinillos, M. T.; Uson, R. *J. Org. Chem.* **1984**, *49*, 2502−2504. (b) Bozell, J. J.; Vogt, C. E.; Gozum, J. *J. Org. Chem.* **1991**, *56*, 2584−2487. (c) Dobler, C.; Kreuzfeld, H.-J.; Machalik, M.; Krause, H. W. *Tetrahedron: Asymmetry* **1996**, *7*, 117−125.

(7) Henegar, K. E.; Ashford, S. W.; Baughman, T. A.; Sih, J. C.; Gu, Rui-Lin. *J. Org. Chem.* **1997**, *62*, 6588−6597.

(8) The spectroscopic and physical properties (e.g., ^{1}H NMR, ^{13}C NMR, HPLC, ESI-MS, HRMS) of all new compounds were fully consistent with those of the assigned structures.

(9) Dehydroamino acid derivative **3**: analytical RP HPLC, MeCN:0.05% aq acetic acid/60:40, 2.0 mL/min at 225 nm; t_R 5.95 min, 96%; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 1 H, J = 0.8 Hz), 7.36−7.25 (m, 5 H), 7.16 (s, 1 H), 6.91 (s, 1 H, J = 0.6 Hz). 6.74 (brs, 1 H), 5.07 (s, 2 H), 4.29 (t, 2 H, J =

the mixture was stirred for 16 h, the solvent was removed and the residue was purified by silica gel column chromatography to afford the amino acid derivative (*S*)-(+)-**11** in 89% yield[11] {$[\alpha]^{23}_D$ +50.5 (*c* 0.525, $CHCl_3$)}. The optical purity of compound (*S*)-(+)-**11** was determined by analysis of the corresponding Mosher amide **12** by ^{19}F NMR, which was found to be >98% ee. Mosher amide **12** was obtained in 81% yield in two steps from (*S*)-(+)-**11** by hydrogenation (10% Pd/C, MeOH, H_2, rt, 2 h) followed by treatment of the resulting amine with (*R*)-(−)-MTP-Cl (methylene chloride at room temperature, 3 h)[12] in 70% overall yield.

The final step in the synthesis of (*S*)-(−)-**1** was to remove all protective groups (i.e., methyl ether, Cbz group, *n*-propyl, and methyl esters) in (*S*)-(+)-**11** preferably in one-pot by using iodotrimethylsilane (TMS-I). However, reaction of (*S*)-(+)-**11** with excess TMS-I (10 equiv) in chloroform under reflux conditions cleaved only the Cbz and methyl ether groups. Alternately, (*S*)-(+)-**11** was first treated with LiOH in THF−water to hydrolyze the esters and the resulting diacid was then subjected to the reaction with TMSI in chloroform under reflux. After 7 h, MeOH was added to the reaction mixture and (*S*)-(−)-acromelobic acid (**1**) was isolated by Dowex CCR-3 ion exchange (eluent: water) followed by Biorad AG II A8 resin (eluent: water) chromatography in 68% yield. The synthetic (*S*)-(−)-**1** was consistent with the literature data including optical rotation,[2b] $[\alpha]^{23}_D$ −139.1 (*c* 0.0575, H_2O), lit.[2] $[\alpha]^{23}_D$ −131.0 (*c* 0.05, H_2O).

In summary, a highly efficient enantioselective synthesis of an important nonproteinigenic amino acid, (*S*)-(−)-acromelobic acid (**1**), was achieved starting from the commercially available citrazinic acid (**4**) by applying a catalytic asymmetric hydrogenation protocol.

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6.8 Hz), 4.01 (s, 3 H), 3.85 (s, 3 H), 1.84−1.72 (m, 2 H), 1.01 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 164.9, 164.8, 164.4, 152.7, 145.9, 145.0, 135.4, 128.5, 128.4, 128.2, 127.5, 125.4, 118.2, 114.2, 67.8, 67.1, 53.8, 53.1, 22.0, 10.4; ESI-MS (*m*/*z*) 429 $(M + H)^+$, 451 $(M + Na)^+$; HRMS (FAB, *m*/*z*) calcd for $C_{22}H_{25}N_2O_7$ $(M + H)^+$ 429.1662,obsd 429.1667.

(10) For a review on the asymmetric hydrogenation using chiral phosphine ligands, see: Knowles, W. S. *Acc. Chem. Res*. **1983**, *16*, 106−112.

(11) (*S*)-(+)-**11**: analytical RP HPLC, MeCN:0.05% aqueous acetic acid/60:40, 2.0 mL/min at 225 nm; t_R, 5.44 min, 99%; $[\alpha]^{23}_D$ +50.5 (*c* 0.525, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.47 (d, 1 H, *J* = 1.1 Hz), 7.38−7.30 (m, 5 H), 6.68 (d, 1 H, *J* = 0.8 Hz), 5.33 (d, 1 H, *J* = 7.9 Hz), 5.10 (s, 2 H), 4.69 (dd, 1 H, *J* = 13.4, 6.0 Hz), 4.30 (t, 2 H, *J* = 6.8 Hz), 3.99 (s, 3 H), 3.74 (s, 3 H), 3.17 (dd, 1 H, *J* = 13.7, 5.8 Hz), 3.07 (dd, 1 H, *J* = 13.7, 6.3 Hz), 1.86−1.74 (m, 2 H), 1.02 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 171.2, 165.0, 164.3, 155.5, 148.3, 145.9, 135.9, 128.5, 128.2, 128.0, 119.5, 115.3, 67.1, 53.9, 53.6, 52.6, 37.4, 22.0, 10.4; ESI-MS (*m*/*z*) 431 $(M + H)^+$, 453 $(M + Na)^+$; HRMS (FAB, *m*/*z*) calcd for $C_{22}H_{27}N_2O_7$ $(M + H)^+$ 431.1818, obsd 431.1824.

(12) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.