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TETRAHEDRON: *ASYMMETRY*

# Asymmetric synthesis of (*S*)-(−)-acromelobinic acid

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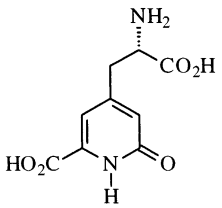
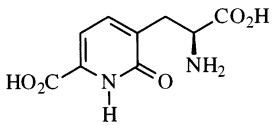
**Abstract**—A total synthesis of (*S*)-(−)-acromelobinic acid **2**, which was isolated from *clitocybe acromelalga*, was achieved via an asymmetric hydrogenation protocol. Dehydroamino acid derivative **12** was prepared from 2,5-lutidine **5** and subjected to asymmetric hydrogenation using (*S*,*S*)-[Rh(Et-DuPHOS)(COD)]$BF_4$ to give the (*S*)-(+)-pyridylalanine derivative **13** in 93% yield and >96% e.e. Removal of the protecting groups in (*S*)-(+)-**13** afforded (*S*)-(−)-acromelobinic acid **2**. 

## 1. Introduction

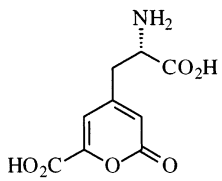
The poisonous mushroom *clitocybe acromelalga* found exclusively in Japan has been the source for a variety of potent neuroexcitatory non-proteinogenic amino acids related to the kainoid family.[1] Shirahama et al.[2] isolated (*S*)-(−)-acromelobic acid [3-(6-carboxy-2-oxo-4-pyridyl)-L-alanine, **1**] and (*S*)-(−)-acromelobinic acid [3-(6-carboxy-2-oxo-3-pyridyl)-L-alanine, **2**][3] (Fig. 1)



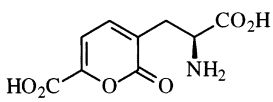
(*S*)-(−)-Acromelobic acid **1**



(*S*)-(−)-Acromelobinic acid **2**



Stizolobic acid **3**



Stizolobinic acid **4**

**Figure 1.** Structure of non-proteinogenic amino acids (*S*)-(−)-**1** and (*S*)-(−)-**2**.

from the fruit bodies of this mushroom by a combination of ion-exchange column chromatography and paper electrophoresis. It was proposed that these non-proteinogenic amino acids (*S*)-(−)-**1** and (*S*)-(−)-**2** are biosynthetically derived from L-DOPA and are the precursors for various acromelic acids.[2] The amino acids (*S*)-(−)-**1** and (*S*)-(−)-**2** exhibit weak depolarizing activity in the preparation of newborn rat spinal cord.[2] Shirahama et al.[2b] also prepared (*S*)-(−)-**1** and (*S*)-(−)-**2** from L-stizolobic acid **3** and L-stizolobinic acid **4** (Fig. 1), respectively, by chemical conversion. L-Stizolobic acid **3** and L-stizolobinic acid **4** were also isolated from *Clitocybe acromelalga*,[2b] and other sources, *Stizolobium hassjoo*[4a,b] and *Amanita pantherina*.[4c] Our interest in non-proteinogenic heterocyclic α-amino acids for applications in the areas of osteoporosis[5] and neuroscience research[6] led to an enantioselective synthesis of (*S*)-(−)-acromelobic acid **1**.[6b] In this context, we herein describe the first total synthesis of (*S*)-(−)-acromelobinic acid **2** starting from 2,5-lutidine **5** via an asymmetric hydrogenation protocol.

## 2. Results and discussion

The strategy for synthesis of (*S*)-(−)-**2** was based on asymmetric hydrogenation[7] of a dehydroamino acid derivative **12**, formation of which was envisaged from commercially available 2,5-lutidine **5**. Accordingly, **5** was first reacted (Scheme 1) with selenium dioxide followed by treatment with sulfuric acid in methanol to afford 5-methylpicolic acid methyl ester,[8] which was subsequently converted to the corresponding *N*-oxide **6**

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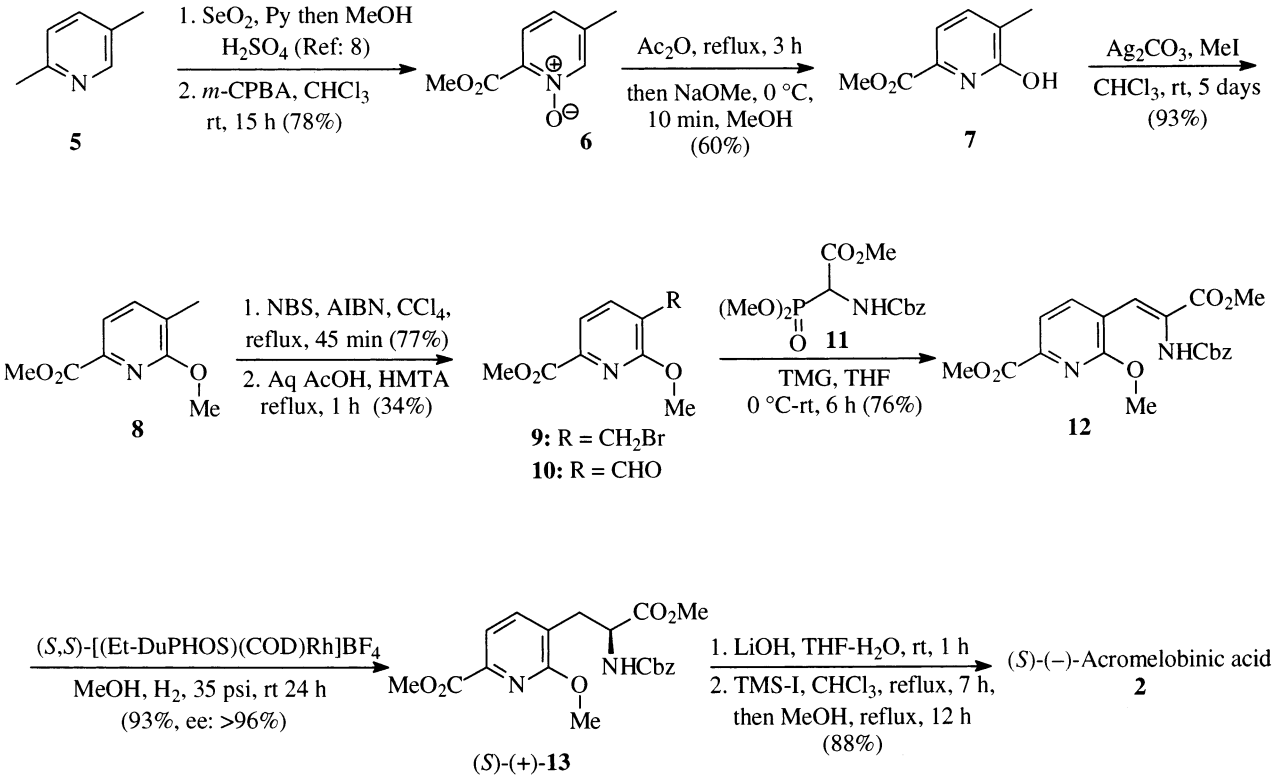


**Scheme 1.** Synthesis of (*S*)-(−)-acromelobinic acid **2**.

in 79% yield by treatment with *m*-CPBA.[9] The *N*-oxide **6** was then treated with acetic anhydride under reflux conditions followed by treatment with NaOMe in methanol to afford compound **7** in 60% yield. We decided to protect the newly generated 2-hydroxyl group in **7** as the methyl ether in order to avoid its interference in the synthesis of (*S*)-(−)-**2**. Thus, **7** was treated with silver carbonate and iodomethane in chloroform, and the crude compound was purified by silica gel column chromatography to afford **8** in 93% yield. The next step in the synthesis of (*S*)-(−)-**2** was the transformation of the C(3)-methyl group in **8** into an aldehyde functionality. Direct oxidation of the methyl group in **8** using selenium dioxide to form the corresponding aldehyde **10** gave a complex mixture, and therefore, a two-step protocol was devised. Thus, bromination of the 3-methyl group in **8** using NBS and AIBN[10] in carbon tetrachloride afforded the bromomethyl compound **9** in 77% yield. Bromide **9** was then treated with hexamethylenetetramine (HMTA) in aqueous acetic acid (Sommelet reaction)[11] to afford the desired aldehyde **10** in 34% yield and >99% purity. Treatment of aldehyde **10** with *N*-(benzyloxycarbonyl)phosphonoglycine trimethyl ester **11** in the presence of *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) afforded the dehydroamino acid derivative **12** in 76% yield as a mixture of (*Z*)/(*E*) isomers (ratio 9:1) in 66% yield.

The crucial asymmetric hydrogenation[7] of dehydroamino acid derivative **12** was initially carried out by using catalytic (*R*,*R*)-[Rh(DIPAMP)(COD)]$BF_4$ in MeOH at 48°C and a hydrogen pressure of 65 psi to afford the amino acid derivative (*S*)-(+)-**13** in 97% yield and 92% e.e. The enantiomeric purity of (*S*)-(+)-**13** was determined by the analysis of $^{19}F$ NMR and HPLC of the Mosher's amide, which was prepared from (*S*)-(+)-**13** by hydrogenation (10% Pd/C, HCl, MeOH) followed by reaction of the corresponding amine with (*R*)-MTPCl. Alternatively, we decided to carry out the hydrogenation of **12** using (*S*,*S*)-[Rh(Et-DUPHOS)(COD)]$BF_4$ catalyst, which was reported to reduce both (*Z*)/(*E*) isomers with generally high degrees of selectivity.[12] Accordingly, hydrogenation of **12** using (*S*,*S*)-[Rh(Et-DUPHOS)(COD)]$BF_4$ catalyst (0.011 equiv.) in a mixture of MeOH–EtOAc at a hydrogen pressure of 35 psi at room temperature afforded (*S*)-(+)-**13** in 93% yield,[13] and with improved enantiomeric purity (>96% e.e.). Compound (*S*)-(+)-**13** has the required amino acid side chain and functionalized pyridine ring, and unmasking the protective groups would complete the synthesis of (*S*)-(−)-**2**. Thus, alkaline hydrolysis of methyl esters in (*S*)-(+)-**13** (e.e. >96%) was carried out using LiOH and the resulting crude acid was subsequently treated with TMS-I to cleave the methyl ether and Cbz protective groups. The mixture was concentrated and the resulting residue was suspended in water, and basified (pH 10) using 1.0N aqueous NaOH. Purification of the crude compound by Dowex CCR-3 ion exchange resin (eluent: water) followed by Biorad AG 11 A8 resin chromatography (eluent: water) and lyophilization afforded (*S*)-(−)-acromelobinic acid **2** in 88% yield as a pale yellow powder.[14]

In summary, a total synthesis of (*S*)-(−)-acromelobinic acid **2** was developed starting from commercially available 2,5-lutidine **5** and using a catalytic asymmetric hydrogenation protocol as the key step.

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13. **(+)-Methyl *N*-(benzyloxycarbonyl)-3-(methoxycarbonyl-6-methoxy-5-pyridinyl)-L-alaninate (*S*)-13**: Viscous oil; $R_f$: 0.29 (30% EtOAc in hexanes). Analytical RP HPLC (Waters, Symmetry, RCM, C18, 7.0 μ, 8×100 mm column): MeCN:0.05% aqueous acetic acid/45:55, 2.0 mL/min at 225 nm, $t_R$: 8.81 min, 99%; $[\alpha]_D^{23}$ +25.1 (*c* 0.74, $CHCl_3$); $^1$H NMR ($CDCl_3$): $\delta$ 7.61 (d, 1H, $J$=7.1 Hz), 7.43 (d, 1H, $J$=7.4 Hz), 7.36–7.26 (m, 5H), 5.51 (d, 1H, $J$=7.9 Hz), 5.08–5.00 (m, 2H), 4.71–4.63 (m, 1H), 4.01 (s, 3H), 3.94 (s, 3H), 3.70 (s, 3H), 3.18 (dd, 1H, $J$=13.7, 6.0 Hz), 3.04 (dd, 1H, $J$=13.7, 7.7 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ 171.8, 165.4, 161.8, 155.5, 144.0, 139.6, 136.0, 128.4, 128.0, 127.9, 123.8, 118.7, 66.8, 53.7, 53.2, 52.4, 52.3, 32.7; ESI–MS ($m/z$): 403 $(M+H)^+$, 805 $(2\times M+H)^+$, 822 $(2\times M+NH_4)^+$; HRMS (FAB, $m/z$): calcd for $C_{20}H_{23}N_2O_7$, 403.1505 $(M+H)^+$; observed, 403.1514.
14. **(*S*)-(−)-Acromelobinic acid 2**: Pale yellow powder, $[\alpha]_D^{23}$ −56 (*c* 0.15, $H_2O$), lit.[2b] $[\alpha]_D^{23}$ −5.8 (*c* 0.13, $H_2O$). Analytical RP HPLC (Waters, Symmetry, RCM, C18, 7.0 μ, 8×100 mm column): MeCN:0.05% aqueous trifluoroacetic acid/2:98, 1.0 mL/min at 225 nm, $t_R$: 6.13 min, 98%; $^1$H NMR ($D_2O$): $\delta$ 7.50 (d, 1H, $J$=7.1 Hz), 6.86 (d, 1H, $J$=7.1 Hz), 3.76 (dd, 1H, $J$=7.9, 4.6 Hz), 3.01 (dd, 1H, $J$=14.5, 4.6 Hz), 2.77 (dd, 1H, $J$=14.5, 8.2 Hz); $^{13}$C NMR ($D_2O$+0.05 mL of $CD_3OD$): $\delta$ 176.7, 167.4, 164.8, 143.6, 140.0, 131.1, 110.5, 55.6, 34.1; ESI–MS ($m/z$): 225 $(M-H)^-$, 451 $(2\times M-H)^-$.