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Nonproteinogenic amino acids: an efficient asymmetric synthesis of (*S*)-(−)-acromelobic acid and (*S*)-(−)-acromelobinic acid

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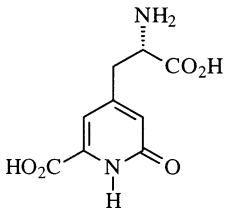
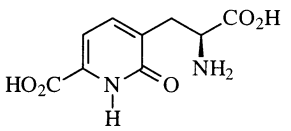
Abstract—An efficient synthesis of (*S*)-(−)-acromelobic acid (**1**) and (*S*)-(−)-acromelobinic acid (**2**) is described via asymmetric hydrogenation protocol. Asymmetric hydrogenation of dehydroamino acid derivative **23** using (*R*,*R*)-[Rh(DIPAMP)(COD)]BF_4 catalyst followed by removal of the protective groups afforded (*S*)-(−)-acromelobic acid (**1**) in >98% ee. The key intermediate **23** was prepared from citrazinic acid (**8**). The dehydroamino acid derivative **33** required for the synthesis of (*S*)-(−)-**2** was prepared from 2,5-lutidine (**27**), which upon hydrogenation using (*S*,*S*)-[Rh(Et-DuPHOS)(COD)]BF_4 catalyst afforded (*S*)-(+)-**34** in 93% yield and >96% ee. Removal of protective groups in (*S*)-(+)-**34** afforded (*S*)-(−)-acromelobinic acid (**2**) in good overall yield.

1. Introduction

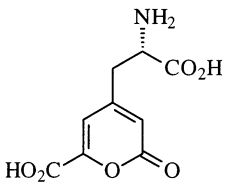
Interest in nonproteinogenic α-amino acids[1] continues to arise due to their importance in medicinal and biotechnological fields.[2] The nonproteinogenic α-amino acids, which are also the constituents of a number of peptides and proteins, are shown to have exceptional utility as chiral building blocks.[3] Synthesis of nonproteinogenic amino acids is critically important not only for their production but also for the preparation structural analogs, since in many cases, only small quantities of were isolated from natural sources. Since the chirality of α-amino acids is critically important for molecular recognition and biological activity, the synthesis must be designed to produce them in high enantiomeric purity.[4] The poisonous mushroom *Clitocybe acromelalga* found exclusively in Japan has been the source for a variety of potent neuroexcitatory nonproteinogenic amino acids related to the kainoid family.[5] Shirahama et al.[6] 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**],[7] (Fig. 1) from the fruit bodies of this mushroom (*C. acromelalga*) by a combination of ion-exchange column chromatography, and paper electrophoresis. The amino acids (*S*)-(−)-**1** and (*S*)-(−)-**2** are isomers and differ in the attachment of α-amino acid side chain on the pyridone ring. It was proposed that these two nonproteinogenic amino acids (*S*)-(−)-**1** and (*S*)-(−)-**2** are biosynthetically derived from L-DOPA and are the precursors for various acromelic acids.[6] These amino acids exhibit weak depolarizing activity in the preparation of newborn rat spinal cord.[6] The first synthesis of (*S*)-(−)-**1** and (*S*)-(−)-**2** was achieved by chemical conversion[6b] of L-stizolobic acid (**3**) and L-stizolobinic acid (**4**) (Fig. 1), respectively, a related nonproteinogenic amino acids. The amino acids **3** and **4** were also isolated from *C. acromelalga*,[6b] and from other sources such as, *Stizolobium hassjoo*[8a,b] and *Amanita pantherina*.[8c] Subsequently, Baldwin et al.[9] reported the first chemical synthesis of **1** in a racemic form starting from catechol in thirteen steps. Our interest in nonproteinogenic amino acids led to the synthesis of a number of heterocyclic



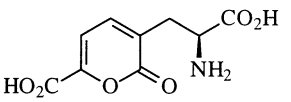
(*S*)-(−)-Acromelobic acid (**1**)



(*S*)-(−)-Acromelobinic acid (**2**)



Stizolobic acid (**3**)



Stizolobinic acid (**4**)

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

Keywords: nonproteinogenic amino acids; total synthesis; acromelobic acid; acromelobinic acid.

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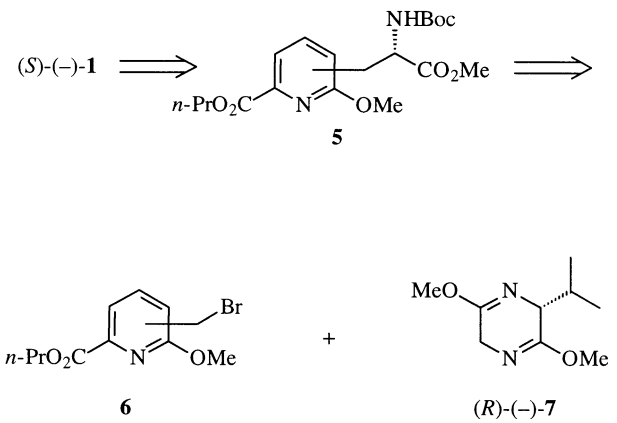


Figure 2. Retrosynthetic analysis of (*S*)-(−)-**1** and (*S*)-(−)-**2** via asymmetric alkylation approach.

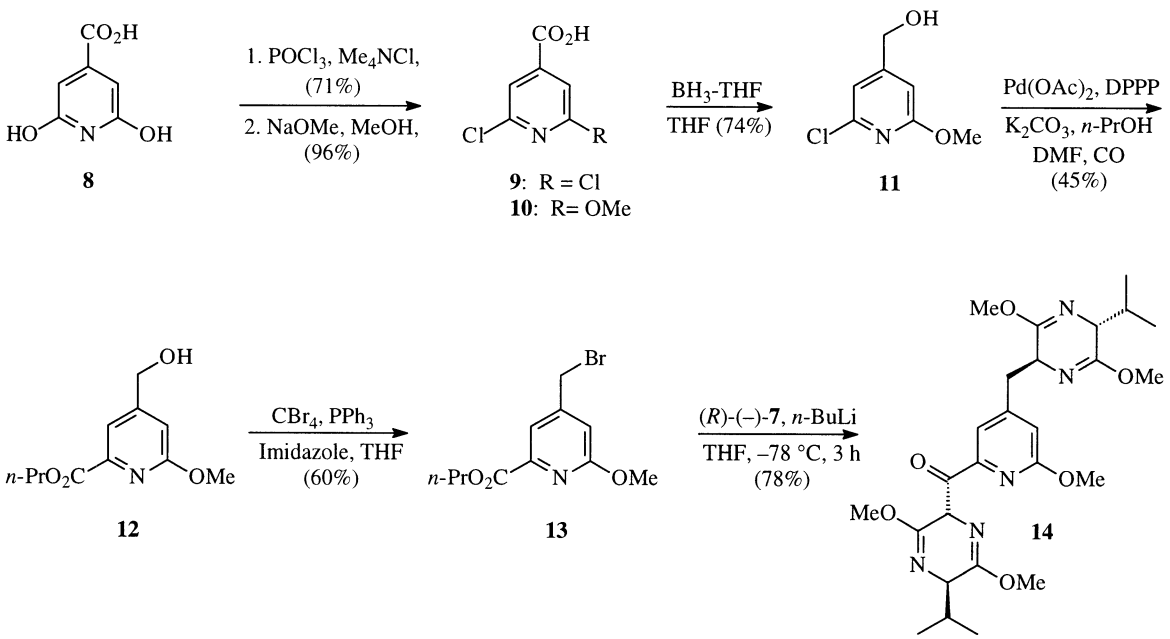
α-amino acids[10,11] for applications in the area of osteoporosis and neuroscience research. In this context, we describe an efficient enantioselective synthesis of (*S*)-(−)-**1** and (*S*)-(−)-**2** starting from commercially available citrazinic acid (**8**) and 2,5-lutidine (**27**), respectively.[12]

2. Results and discussion

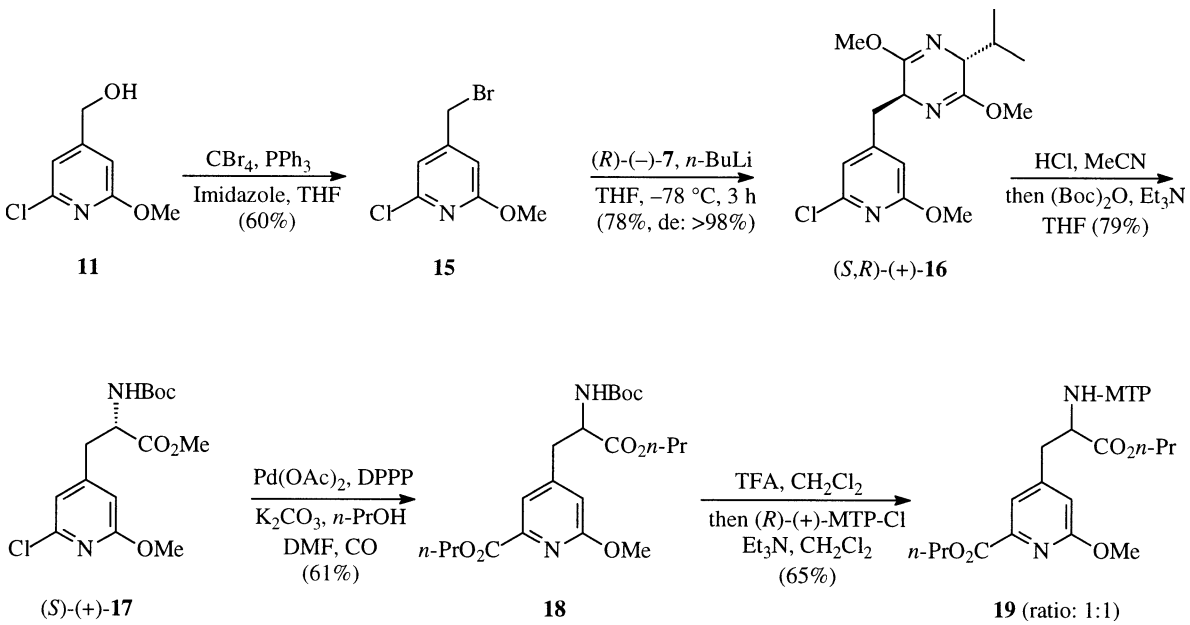
The two nonproteinogenic amino acids (*S*)-(−)-**1** and (*S*)-(−)-**2** have common structural feature, e.g. 2-pyridone-6-carboxylic acid, and therefore, we envisioned a general strategy (Fig. 2) for their synthesis. The exceptional utility of (2*R*)-(−)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (Schollkopf's reagent, **7**)[13] in asymmetric synthesis of α-amino acids, coupled with our recent success in utilization this remarkable reagent for synthesis of a bone collagen cross-link,[14] prompted us to make use (*R*)-(−)-**7** for the synthesis of (*S*)-(−)-**1** and (*S*)-(−)-**2**. Accordingly, the strategy (Fig. 2) for the synthesis of (*S*)-(−)-**1** and (*S*)-(−)-**2** first involves the preparation of an appropriately functionalized bromo compound **6**, which is suitable for alkylation with the lithiated (*R*)-(−)-**7**. The bromo compound **6** contains a methoxy group at the 2-position of pyridine ring, which can be cleaved at the final stages of the synthesis to form the pyridone ring, and a carboxylic acid group in the form of an ester at the 6-position. Thus, the stereoselective alkylation of Schollkopf's reagent (*R*)-(−)-**7** with bromo compound **6** followed by hydrolysis of the resulting dihydropyrazine ring and cleavage of protective groups should yield (*S*)-(−)-**1** and (*S*)-(−)-**2**. Initially, we directed our efforts to implement this strategy for the synthesis of (*S*)-(−)-acromelobic acid (**1**).

3. Studies on the synthesis of (*S*)-(−)-1 via asymmetric alkylation approach

The bromo compound **13** required for the synthesis of (*S*)-(−)-**1** was envisioned from a commercially available citrazinic acid (**8**). Thus, **8** was treated (Scheme 1) with phosphorous oxychloride and tetramethylammonium chloride to obtain 2,6-dichloroisonicotinic acid (**9**) in 71% yield.[15] Treatment of **9** with 4.0 equiv. of NaOMe, which was added in two portions, in refluxing MeOH afforded 2-chloro-6-methoxyisonicotinic acid (**10**) in excellent yield (96%). Interestingly, addition of NaOMe 2,6-dichloroisonicotinic acid (**9**) in one portion resulted in the formation of the corresponding bis-methoxy compound (2,6-dimethoxyisonicotinic acid). The carboxylic acid group in **10** was reduced using BH_3–THF to afford the alcohol **11** in 74% yield after purification by silica gel column chromatography. The hydroxy compound **11** was then subjected to the carbonylation reaction using palladium acetate, 1,3-bis(diphenylphosphino)propane (DPPP), anhydrous potassium carbonate and 1-propanol in DMF and carbon monoxide at 90°C to afford the ester **12** in 45% yield. The



Scheme 1. Studies on the synthesis of (*S*)-(−)-**1** via asymmetric alkylation approach.



Scheme 2. Studies on the synthesis of (*S*)-(−)-**1** via asymmetric alkylation approach.

ester **12** was then converted to the bromide **13** by treatment with carbon tetrabromide, triphenylphosphine and imidazole in THF in 60% yield. The crucial step in the synthesis of (*S*)-(−)-**1**, alkylation of (*R*)-(−)-Schollkopf's reagent (**7**, 2.0 equiv.) with bromo compound **13**, was carried out by using *n*-BuLi in THF at −78°C. After 2.5 h, the reaction was quenched at −78°C and the crude product was purified by silica gel column chromatography to afford a compound, which did not correspond to the desired product. In the ^{1}H NMR spectrum, the resonance corresponding to the *n*-propyl ester was missing and four doublets at 1.07, 0.96, 0.79 and 0.64 with integration of three protons each, were present. The ESI-MS of this undesired compound showed $(M+H)^+$ at 516 corresponding to the compound **14**, which was apparently formed by nucleophilic substitution at both bromo and ester groups. When the alkylation reaction using bromo compound **13** was carried out with one equivalent of (*R*)-(−)-**7**, a mixture of **14** and unreacted starting material **13** were isolated and thus indicating that there was no selectivity in the reactivity between the bromide and *n*-propyl ester groups with lithiated (*R*)-(−)-**7** reagent.

Alternately, we thought that the ester functionality at 2-position of pyridine ring could be installed after the introduction of amino acid side chain at 4-position in order to avoid the reaction of (*R*)-(−)-**7** with ester group. Thus, alcohol **11** was first converted (Scheme 2) to the bromo compound **15** in 60% yield. Alkylation of bromo compound **15** with the lithium anion of (*R*)-(−)-**7** in THF at −78°C afforded (*S*,*R*)-(−)-**16** in 78% yield as a single isomer (de: > 98%). The next step in the synthesis of (*S*)-(−)-**1** was to transform the dihydropyrazine ring in (*S*,*R*)-(+)-**16** into the amino acid moiety. Thus, (*S*,*R*)-(+)-**16** was first hydrolyzed with HCl in acetonitrile and the resulting crude amine hydrochloride was treated with $(Boc)_2O$ and triethylamine in THF to afford the amino acid derivative (*S*)-(+)-**17** in 79% yield. The palladium catalyzed carbonylation of (*S*)-(+)-**17** in *n*-propanol and DMF, under the conditions optimized for preparation of **12**, gave **18** in 61% yield. In this transformation, the methyl ester of α-amino acid was *trans*-esterified into *n*-propyl ester. The compound **18** has all functional groups that are present in (*S*)-(−)-**1** and thus the cleavage of the protective groups should complete its synthesis. In order to determine if any racemization has occurred during the carbonylation and to ensure the integrity of the stereocenter in **18**, we determined the optical purity of **18** by converting it to the Mosher's amide. Thus, Boc group in **18** was first hydrolyzed with trifluoroacetic acid and the resulting amine was treated with (*R*)-MTP-Cl to afford the Mosher's amide **19**. Analysis of ^{1}H and ^{19}F NMR of Mosher's amide **19** showed a diastereomeric mixture in a 1:1 ratio, indicating that complete racemization has occurred presumably during the transformation of (*S*)-(+)-**17** to **18**. From these results, it became clear that having an ester group at the 2-position of pyridine ring during the alkylation of **13** with (*R*)-(−)-Schollkopf's reagent (**7**) or introduction of ester group via carbonylation in (*S*)-**17** after the installation of α-amino acid chain, is problematic. Therefore, we devised a different strategy for the synthesis of (*S*)-(−)-**1**.

4. Synthesis of (*S*)-(−)-1 via asymmetric hydrogenation protocol

Synthesis of α-amino acids via catalytic asymmetric hydrogenation protocol[16] has become increasingly valuable in recent years mainly due to this protocol's ability to produce them in excellent enantiomeric purities in good yields and also its compatibility with various functional groups to the reaction conditions. Although, application of hydrogenation protocol for the synthesis of (*S*)-(−)-**1** (Fig. 3) looked promising in light of the recent success in the preparation of a variety of α-amino acids by various research groups,[16] a careful literature survey revealed that there were only few reports[17] related to the catalytic asymmetric hydrogenation of pyridyldehydroamino acid derivatives. The catalytic asymmetric hydrogenation of

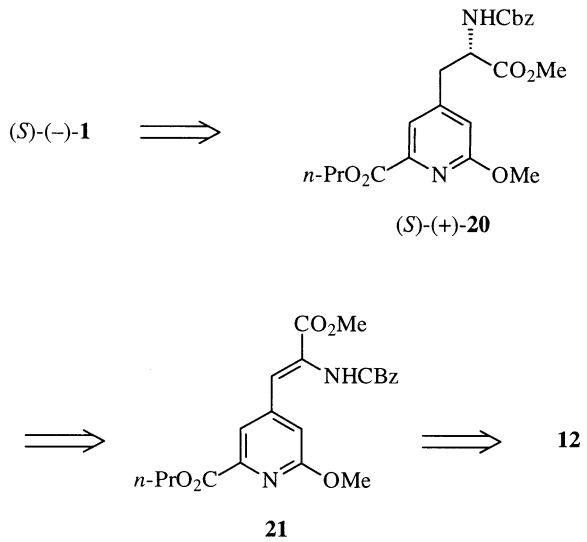
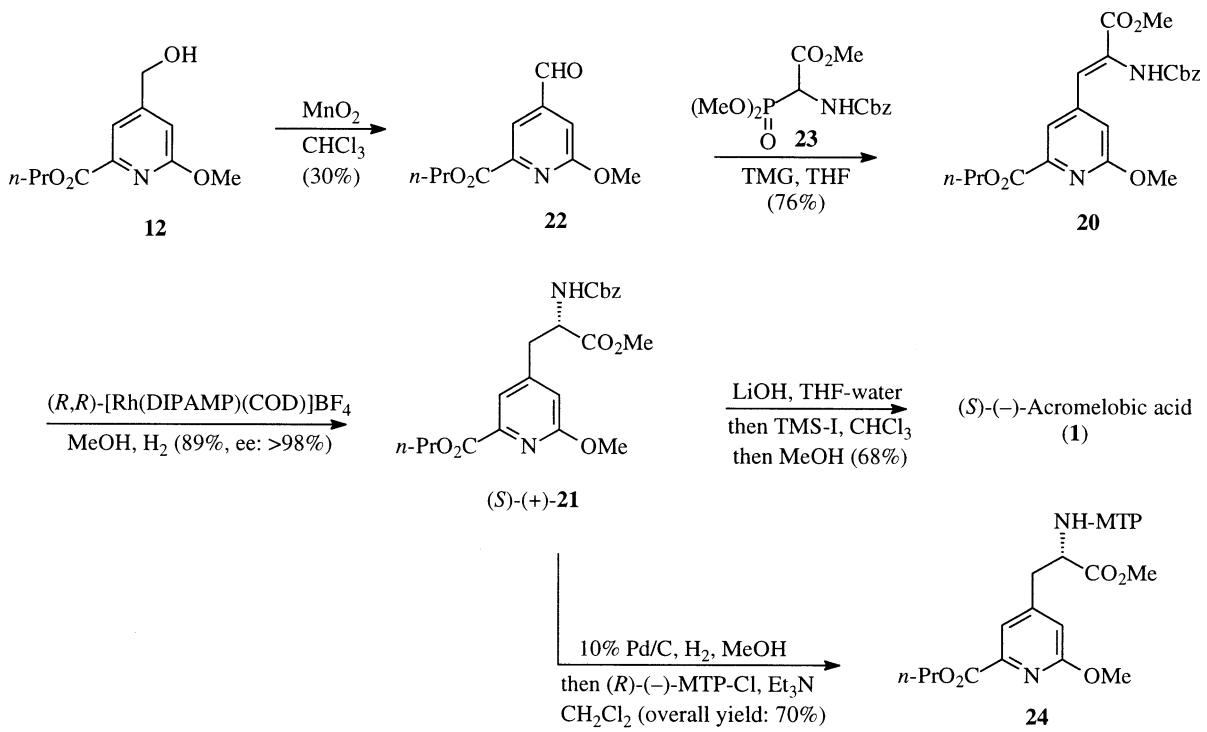


Figure 3. Asymmetric hydrogenation approach to the synthesis of (*S*)-(−)-**1**: retrosynthetic analysis.

heteroaromatic dehydroamino acid was reported[17] to be difficult due to the participation of hetero-atom, e.g. pyridine ring nitrogen, in blocking the formation of an active metal–substrate complex. Asymmetric hydrogenation of 3- and 4-pyridyldehydroamino acid derivatives was carried out at high temperature/pressure[17a,b] or in the presence of noncomplexing acids such as HBF_4.[17c,d] The required pyridyldehydroamino acid derivative **23** for implementation of the asymmetric hydrogenation protocol to synthesize (*S*)-(−)-**1** was envisioned from *n*-propyl 4-(hydroxymethyl)-6-methoxy-2-pyridinecarboxylate (**12**), which was prepared in four steps from commercially available citrazinic acid (**8**) as described in Scheme 1.

Accordingly, the hydroxy compound **12** was first oxidized with MnO_2 to the corresponding aldehyde **22**, and then reacted with *N*-(benzyloxycarbonyl)phosphonoglycine trimethyl ester (**23**) in the presence of *N*,*N*,*N*,*N*-tetramethylguanidine (TMG) to afford dehydroamino acid derivative **20** as a mixture of *Z*/*E* isomers (ratio 93:7) (Scheme 3). The minor *E*-isomer was separated during silica gel column chromatography (25% EtOAc in hexanes) to afford *Z*-isomer **20** in 76% yield. Asymmetric hydrogenation of dehydroamino acid derivative **23** was carried out by using a catalytic amount of (*R*,*R*)-[Rh(DIPAMP)(COD)]BF_4 in MeOH[18] and hydrogen (65 psi) at 48°C for 16 h to afford the amino acid derivative (*S*)-(+)-**21** in 89% yield. The enantiomeric purity of (*S*)-(+)-**21** was found to be >98% by the analysis of its Mosher's amide **24**, which was obtained in 81% yield by hydrogenation of (*S*)-(+)-**21** followed by reaction of the resulting amine with (*R*)-(−)-MTP-Cl. We were gratified with the successful outcome of the hydrogenation approach to install the α-amino acid chain in an excellent optical purity (>98%) and proceeded to complete the synthesis of (*S*)-(−)-**1**. Accordingly, the next step in the synthesis of (*S*)-(−)-**1** was to remove all the protecting groups in (*S*)-(+)-**21**, which we thought of achieving in one-pot by using iodotrimethylsilane (TMS-I). However, treatment of (*S*)-(+)-**21** with 10 equiv. of TMS-I in chloroform under reflux conditions cleaved only the urethane and methyl ether groups leaving the *n*-propyl and methyl esters intact. Alternately, (*S*)-(+)-**21** was first treated with lithium hydroxide in a mixture of THF–water to give the corresponding di-acid, which without purification was subjected to a reaction with TMS-I in $CHCl_3$. Purification of the crude product by Dowex CCR-3 ion exchange resin followed by Biorad AG 11 A8 resin chromatography and lyophilization afforded (*S*)-(−)-acromelobic acid (**1**) in 68% yield as a white fluffy solid.

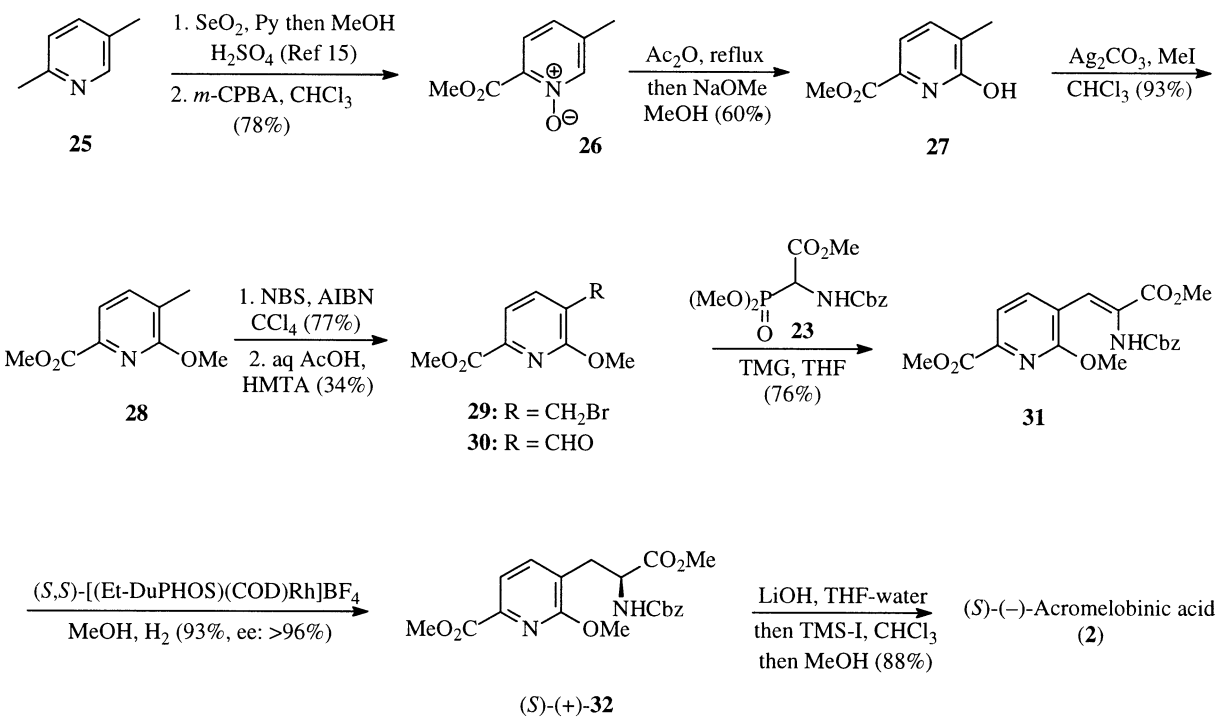


Scheme 3. Synthesis of (*S*)-(−)-**1** via asymmetric hydrogenation protocol.

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

Having successfully achieved the enantioselective synthesis of (*S*)-(−)-acromelobic acid (**1**) via asymmetric hydrogenation protocol, we proceeded to the synthesis of second nonproteinogenic amino acid, (−)-acromelobinic acid (**2**). A similar asymmetric hydrogenation strategy was envisioned for the synthesis of (*S*)-(−)-**2**, which required 3-pyridyldehydroamino acid derivative **31** for implementation of this protocol (Scheme 4). The key dehydroamino acid derivative **31** was envisioned from a commercially available and inexpensive 2,5-lutidine (**25**). Thus, **25** was first reacted with selenium dioxide followed by treatment with sulfuric acid in methanol to afford 5-methylpicolic acid methyl ester,[19] which was subsequently converted to the corresponding *N*-oxide **26** in 79% yield. The *N*-oxide **26** was then treated with acetic anhydride under reflux conditions followed by treatment with NaOMe to afford compound **27** in 60% yield. We decided to protect the newly generated 2-phenolic group as a methyl ether in order to avoid its interference in the synthesis of (*S*)-(−)-**2**. Thus, **27** was treated with silver carbonate and methyl iodide and the crude compound was purified by silica gel column chromatography to afford **28** in 93% yield. The next step in the synthesis was the oxidation of 3-methyl group into aldehyde functionality. Direct oxidation of methyl group in **28** using selenium dioxide to form the aldehyde **30** was unsuccessful. Therefore, a two-step protocol was devised for the conversion of **28** to the aldehyde **30**. Thus, bromination[20] of the 5-methyl group in **28** using NBS and AIBN in CCl_4 afforded the bromomethyl compound **29**, which was then treated with hexamethylenetetramine in aqueous acetic acid (Sommelet reaction)[21] to afford the aldehyde **30**. Treatment of **30** with *N*-(benzyloxycarbonyl) phosphonoglycine trimethyl ester (**23**) in the presence of TMG under the conditions developed for **20**, afforded the dehydroamino acid derivative **31** in 76% yield as a mixture of *Z*/*E* isomers in 9:1 ratio. Our attempts to separate the *Z*/*E* mixture of **31** by silica gel column chromatography were not successful. The asymmetric hydrogenation of dehydroamino acid **31** was initially carried out with (*R*,*R*)-[Rh(DIPAMP)(COD)]BF_4 catalyst in MeOH and hydrogen gas (65 psi) at 48°C to afford the amino acid derivative (*S*)-(+)-**32** in 97% yield. Disappointingly, the enantiomeric purity of (*S*)-(+)-**32** was found to be 92% as determined by the analysis of ^{19}F NMR and HPLC of the Mosher's amide, which was prepared from (*S*)-(+)-**32** by hydrogenation followed by reaction of the corresponding amine with (*R*)-MTP-Cl. Alternatively, the hydrogenation of dehydroamino acid derivative **31** was carried out using (*S*,*S*)-[Rh(Et-DUPHOS)(COD)]BF_4 catalyst[22] in a mixture of MeOH–EtOAc and hydrogen at 35 psi afforded (*S*)-(+)-**32** in 93% yield. To our delight, the enantiomeric purity of (*S*)-(+)-**32** was found to be >96% as determined by the analysis of ^{19}F NMR and HPLC of its Mosher's amide. Finally, alkaline hydrolysis of methyl esters in (*S*)-(+)-**32** was carried out using lithium hydroxide and the resulting crude acid was treated with TMS-I to cleave the methyl ether and Cbz protecting groups. Purification of the crude product by Dowex CCR-3 ion exchange resin followed by Biorad AG 11 A8 resin chromatography and lyophilization afforded (*S*)-(−)-acromelobinic acid (**2**) in 88% yield as pale yellow powder.

In summary, an efficient asymmetric synthesis of two nonproteinogenic amino acids, (*S*)-(−)-acromelobic acid (**1**) and (*S*)-(−)-acromelobinic acid (**2**) was developed via catalytic asymmetric hydrogenation protocol starting from commercially available and inexpensive materials.



Scheme 4. Synthesis of (*S*)-(−)-acromelobinic acid (**2**).

6. Experimental

6.1. General methods and materials

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz) and the chemical shifts (δ) were reported in ppm relative to TMS and coupling constants (J) were reported in Hz. Electrospray ionization mass spectrometry (ESI-MS) were carried out on a Perkin–Elmer (Norwalk, CT) Sciex API 100 Benchtop system employing Turbo Ionspray ion source and HRMS were obtained on a Nermang 3010 MS-50, JEOL SX102-A mass spectrometer. Thin layer chromatography was performed on a pre-coated Whatman MK6F silica gel 60 Å plates (layer thickness: 250 μm) and visualized with UV light and/or using $KMnO_4$ solution (prepared from $KMnO_4$ (2.0 g) and $NaHCO_3$ (8.0 g) in water (200 mL)) or phosphomolybdic acid reagent (20 wt% solution in ethanol). Column chromatography was performed on silica gel, Merck grade 60 (230–400 mesh). THF was freshly distilled from a purple solution of sodium and benzophenone under nitrogen. CH_2Cl_2 was freshly distilled from CaH_2 under nitrogen. Analytical reversed phase (RP) HPLC was performed using a Waters Symmetry, RCM C18, particle size: 7.0 μm, pore size: 100 Å, 8×100 mm column. Optical rotations were measured on Autopol III polarimeter from Rudolph Research, Flanders, NJ. Melting points were recorded in open capillary tubes on an Electrothermal Melting Point Apparatus and were uncorrected. IUPAC names of all new compounds were obtained using the ACD/Ilab Web service version 3.5 at http://www.acdlabs.com/ilab.

6.1.1. 2,6-Dichloroisonicotinic acid (9). Citrazinic acid (**8**, 51.0 g, 0.329 mol) and tetramethylammonium chloride (37.7 g, 0.342 mol, 1.04 equiv.) were suspended in $POCl_3$ (92 mL, 0.987 mol, 3.0 equiv.) and the mixture was heated to 140°C (bath temperature). The reaction mixture became homogenous in 30 min, which was stirred 28 h and then heated at 150°C for an additional 1 h. The mixture was cooled to room temperature, poured over ice (700 g) and the contents were stirred for 2 h. The resulting solid was filtered, washed with water (50 mL) and dried under vacuum. The solid was suspended in EtOAc (500 mL), stirred for 15 min, and the insoluble material was filtered. The solid was collected and dried under vacuum (0.1 mm Hg) to afford 45.0 g of **9** in 71% yield as a pale brown solid.[15] Analytical RP HPLC: MeCN–0.05% aq acetic acid/30:70, 2.0 mL/min at 225 nm, t_R: 10.55 min, 98%; ^{1}H NMR (DMSO-d_6): δ 7.80 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 163.7, 150.2, 144.7, 122.9; ESI-MS (m/z): 190 $(M-H)^-$.

6.1.2. 2-Chloro-6-methoxyisonicotinic acid (10). NaOMe (25 wt% solution in MeOH, 47.0 mL, 219.89 mmol, 3.5 equiv.) was added to a solution of 2,6-dichloroisonicotinic acid (**9**, 12.0 g, 62.8 mmol) in MeOH (200 mL) and the mixture was heated to reflux for 24 h. An additional amount of NaOMe solution (7.0 mL, 32.0 mmol, 0.5 equiv.) was added to the reaction mixture and was refluxed for an additional 24 h. The mixture was cooled to room temperature, acidified to pH 6.5 using 6.0N aqueous HCl (45 mL, 270.0 mmol, 4.2 equiv.) and the mixture was concentrated on a rotary evaporator. The residue was partitioned between water (100 mL) and EtOAc (600 mL). Organic layer was separated and the aqueous layer was extracted with EtOAc (200 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford 11.3 g of **10** in 96% yield as a pale brown solid. Mp: 213–215°C; Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/30:70, 2.0 mL/min at 225 nm, t_R: 11.91 min, 96%; ^{1}H NMR ($CDCl_3$): δ 7.36 (d, J=1.0 Hz, 1H,), 7.14 (d, J=1.0 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 164.6, 164.0, 148.1, 144.2, 115.5, 109.3, 54.5; ESI-MS (m/z): 186 $(M-H)^-$, 373 $(2\times M-H)^-$.

6.1.3. (2-Chloro-6-methoxy-4-pyridinyl)methanol (11). A solution of BH_3–THF (1.0 M solution in THF, 120 mL, 120.0 mmol, 3.0 equiv.) was added to compound **10** (7.5 g, 40.1 mmol) in THF (150 mL) at 0°C under nitrogen over a period of 15 min. After the addition was complete, cooling bath was removed, the mixture was allowed to warm to room temperature and stirred for 5 h. The mixture was cooled to 0°C and quenched with 1.0N aqueous NaOH (65 mL). The mixture was then diluted with saturated aqueous NH_4Cl (150 mL) solution and ether (200 mL). Organic layer was separated and the aqueous layer was extracted with ether (200 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator. Purification of the crude compound by silica gel column chromatography (30–35% EtOAc in hexanes) afforded 5.1 g of **11** as a colorless solid. R_f: 0.53 (40% EtOAc in hexanes); Mp: 100–101°C; Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/30:70, 2.0 mL/min at 225 nm, t_R: 5.22 min, 99%; ^{1}H NMR ($CDCl_3$): δ 6.90 (s, 1H), 6.65 (d, J=0.8 Hz, 1H), 4.67 (d, J=5.8 Hz, 2H), 3.94 (s, 3H), 1.86 (t, J=6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 164.2, 155.4, 148.6, 113.9, 105.9, 63.0, 54.1; ESI-MS (m/z): 174 $(M+H)^+$, 191 $(M+NH_4)^+$; HRMS (FAB, m/z): Calcd for $C_7H_9ClNO_2$, 174.0322 $(M+H)^+$, observed, 174.0328.

6.1.4. *n*-Propyl 4-(hydroxymethyl)-6-methoxy-2-pyridinecarboxylate (12). A mixture of chloro compound **11** (100 mg, 0.578 mmol), $Pd(OAc)_2$ (6.5 mg, 0.029 mmol, 0.05 equiv.), 1,3-bis(diphenylphosphino)propane (DPPP, 13.0 mg, 0.032 mmol, 0.055 equiv.), anhydrous K_2CO_3 (120 mg, 0.867 mmol, 1.5 equiv.) in a mixture of *n*-propanol (2.2 mL) and DMF (1.1 mL) was purged with nitrogen and then with carbon monoxide. The mixture was then stirred at 90°C (bath temperature) under carbonmonoxide atmosphere (15 psi). The reaction mixture was cooled to room temperature, filtered through celite powder and washed with THF (30 mL). The combined filtrates were concentrated on a rotary evaporator and the residue was partitioned between methyl-*tert*-butylether (MTBE, 50 mL) and water (50 mL). Organic layer was separated and the aqueous layer was extracted with MTBE (20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated on a rotary evaporator and the crude product was purified by silica gel column chromatography (40–50% EtOAc in hexanes) to afford 0.059 g of **12** in 45% yield as viscous oil. R_f: 0.29 (30% EtOAc in hexanes); Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/30:70, 2.0 mL/min at 225 nm, t_R: 7.71 min, 99%; ^{1}H NMR ($CDCl_3$): δ 7.55 (s, 1H), 6.85 (d, J=1.1 Hz, 1H), 4.66 (s, 2H), 4.24 (t, J=6.8 Hz, 2H), 3.95 (s, 3H), 3.08 (br s, 1H, OH), 1.81–1.69 (m, 2H), 0.98 (t, J=7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 165.4, 164.3, 153.9, 145.4, 116.4, 111.8, 67.1,

63.0, 53.7, 21.9, 10.3; ESI-MS (*m/z*): 226 $(M+H)^+$, 243 $(M+NH_4)^+$, 451 $(2\times M+H)^+$; HRMS (FAB, *m/z*): Calcd for $C_{11}H_{16}NO_4$, 226.1079 $(M+H)^+$, observed, 226.1071.

6.1.5. *n*-Propyl 4-(bromomethyl)-6-methoxy-2-pyridinecarboxylate (13). Triphenylphosphine (0.463 g, 1.766 mmol, 1.5 equiv.), imidazole (0.12 g, 1.766 mmol, 1.5 equiv.) and carbon tetrabromide (0.586 g, 1.766 mmol, 1.5 equiv.) were added sequentially to a solution of hydroxy compound **12** (0.265 g, 1.177 mmol) in THF (15 mL) at room temperature under nitrogen. After stirring the mixture for 3.5 h, the solvent was removed on a rotary evaporator and the crude product was purified by silica gel column chromatography (20% EtOAc in hexanes) to afford 0.25 g of **13** in 74% as viscous oil. R_f: 0.52 (15% EtOAc in hexanes); Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/60:40, 2.0 mL/min at 225 nm, t_R: 6.34 min, 99%; ^{1}H NMR ($CDCl_3$): δ 7.70 (d, J=1.3 Hz, 1H), 6.92 (d, J=1.3 Hz, 1H), 4.38 (s, 2H), 4.33 (t, J=6.8 Hz, 2H), 4.02 (s, 3H), 1.88–1.76 (m, 2H), 1.04 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 164.8, 164.4, 149.4, 146.4, 118.7, 114.5, 67.2, 53.9, 29.8, 22.0, 10.4; ESI-MS (*m/z*): 288 $(M+H)^+$, 310 $(M+Na)^+$; HRMS (FAB, *m/z*): Calcd for $C_{11}H_{15}^{79}BrNO_3$, 288.0235 $(M+H)^+$, observed, 288.0235; HRMS (FAB, *m/z*): Calcd for $C_{11}H_{15}^{81}BrNO_3$, 290.0215 $(M+H)^+$, observed, 290.0227.

6.1.6. [(2*S*,5*R*)-5-Isopropyl-3,6-dimethoxy-2,5-dihydro-2-pyrazinyl](4-{[(2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydro-2-pyrazinyl]methyl}-6-methoxy-2-pyridinyl) methanone (14). *n*-BuLi (2.5 M solution in hexanes, 0.654 mL, 1.637 mmol, 2.0 equiv.) was added dropwise to a solution of (*R*)-(−)-Schollkopf's reagent (**7**, 0.293 g, 1.637 mmol, 2.0 equiv.) in THF (15 mL) at −78°C under nitrogen. The resulting pale yellow solution was stirred for 20 min. A solution of bromo compound **13** (0.235 g, 0.82 mmol) in THF (15 mL) was added dropwise at −78°C via double ended needle over a 5 min period. The reaction mixture was then stirred for 4 h and quenched with saturated aqueous NH_4Cl solution (1 mL) at −78°C. The mixture was allowed to warm to room temperature and diluted with EtOAc (30 mL) and H_2O (20 mL). Organic layer was separated and the aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated on a rotary evaporator. The crude compound was purified by silica gel column chromatography (15% EtOAc in hexanes) to afford 0.265 g of bis-dihydropyrazine compound **14** in 64% yield as colorless viscous oil. R_f: 0.21 (15% EtOAc in hexanes); Analytical RP HPLC: MeCN–0.05% aqueous trifluoroacetic acid/80:20, 2.0 mL/min at 225 nm, t_R: 9.57 min, 96%; ^{1}H NMR ($CDCl_3$): δ 7.54 (d, J=1.1 Hz, 1H), 6.73 (d, J=1.1 Hz, 1H), 5.94 (d, J=3.54 Hz, 1H), 4.32–4.27 (m, 1H), 4.13–4.09 (m, 1H), 3.88 (s, 3H), 3.71 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 3.63–3.60 (m, 4H), 3.16 (dd, J=13.2, 4.4 Hz, 1H), 3.04 (dd, J=13.2, 6.3 Hz, 1H), 2.36–2.25 (m, 1H), 2.23–2.12 (m, 1H), 1.07 (d, J=6.9 Hz, 3H), 0.96 (d, J=6.9 Hz, 3H), 0.79 (d, J=6.9 Hz, 3H), 0.64 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 195.0, 165.3, 164.2, 163.2, 161.9, 160.1, 150.5, 148.8, 119.0, 116.2, 61.3, 60.7, 60.5, 55.6, 53.6, 52.9, 52.7, 52.5, 52.4, 39.3, 32.2, 31.7, 19.1, 18.9, 16.9, 16.5; ESI-MS (*m/z*): 516 $(M+H)^+$, 1031 $(2\times M+H)^+$.

6.1.7. 4-(Bromomethyl)-2-chloro-6-methoxypyridine (15). Triphenylphosphine (2.72 g, 10.40 mmol, 1.5 equiv.), imidazole (0.71 g, 10.40 mmol, 1.5 equiv.) and carbon tetrabromide (3.45 g, 10.40 mmol, 1.5 equiv.) were added sequentially to a solution of hydroxy compound **11** (1.2 g, 6.94 mmol) in THF (60 mL) at room temperature under nitrogen. After stirring the mixture for 4 h, the solvent was removed on a rotary evaporator and the crude product was purified by silica gel column chromatography (10% EtOAc in hexanes) to afford 0.25 g of **15** in 60% as a pale yellow solid. R_f: 0.88 (25% EtOAc in hexanes); Mp: 55–56°C; Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/60:40, 2.0 mL/min at 225 nm, t_R: 6.60 min, 99%; ^{1}H NMR ($CDCl_3$): δ 6.93 (d, J=1.1 Hz, 1H), 6.65 (d, J=1.1 Hz, 1H), 4.29 (s, 2H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 164.1, 151.0, 148.8, 116.4, 109.0, 54.2, 29.4; ESI-MS (*m/z*): 236 $(M+H)^+$.

6.1.8. (+)-(2*S*,5*R*)-2-[(2-Chloro-6-methoxy-4-pyridinyl)-methyl]-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (16). *n*-BuLi (2.5 M solution in hexanes, 1.46 mL, 3.66 mmol, 2.0 equiv.) was added dropwise to a solution of (*R*)-(−)-Schollkopf's reagent (**7**, 0.674 g, 3.66 mmol, 2.0 equiv.) dissolved in THF (25 mL) at −78°C under nitrogen. The resulting pale yellow solution was stirred for 20 min. A solution of bromo compound **15** (0.43 g, 1.83 mmol) in THF (25 mL) was added dropwise via double ended needle over a 5 min period. The reaction mixture was then stirred for 2.5 h and quenched with saturated aqueous NH_4Cl solution (10 mL) at −78°C. The mixture was allowed to warm to room temperature and diluted with EtOAc (50 mL) and H_2O (20 mL). The aqueous layer was separated and extracted with EtOAc (25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated on a rotary evaporator. The crude compound was purified by silica gel column chromatography (10% EtOAc in hexanes) to afford 0.485 g of (*S*,*R*)-(+)-**16** in 78% yield (>98% de) as colorless viscous oil. R_f: 0.37 (15% EtOAc in hexanes); Analytical RP HPLC: MeCN–0.05% aqueous trifluoroacetic acid/60:40, 2.0 mL/min at 225 nm, t_R: 17.51 min, 99%; $[\alpha]_D^{23}$=+28.8 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 6.73 (d, J=0.8 Hz, 1H), 6.44 (d, J=0.8 Hz, 1H), 4.29–4.24 (m, 1H), 3.89 (s, 3H), 3.72 (s, 3H), 3.70–3.67 (m, 4H), 3.05 (dd, J=12.9, 4.39 Hz, 1H), 2.95 (dd, J=13.2, 6.0 Hz, 1H), 2.24–2.14 (m, 1H), 0.99 (d, J=6.8 Hz, 3H), 0.65 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 164.2, 163.6, 161.7, 152.3, 147.6, 118.1, 110.1, 60.7, 55.5, 53.9, 52.4, 52.3, 39.0, 31.7, 18.9, 16.5; ESI-MS (*m/z*): 340 $(M+H)^+$; HRMS (FAB, *m/z*): Calcd for $C_{16}H_{23}N_3O_3Cl$, 340.1428 $(M+H)^+$, observed, 340.1433.

6.1.9. (+)-Methyl *N*-(*tert*-butoxycarbonyl)-3-(2-chloro-6-methoxy-4-pyridinyl)-L-alaninate (17). 1.0N aqueous HCl (6.0 mL) was added to a solution of (*S*,*R*)-(+)-**16** (0.45 g, 1.22 mmol) in acetonitrile (20 mL) at room temperature. After stirring the mixture for 1 h 10 min, it was concentrated on a rotary evaporator. The resulting crude amine–TFA salt was dissolved in acetonitrile (20 mL) and Et_3N (0.85 mL, 6.10 mmol, 5.0 equiv.) followed by $(Boc)_2O$ (0.80 g, 3.66 mmol, 3.0 equiv.) were added to the reaction mixture. After stirring the mixture for 16 h at room temperature, it was concentrated on a rotary evaporator and purified by silica gel column chromatography (15% EtOAc in hexanes)

to give 0.36 g of (*S*)-(+)-**17** in 79% yield as a colorless solid. R_f: 0.28 (15% EtOAc in hexanes); Mp: 90–91°C; Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/60:40, 2.0 mL/min at 225 nm, t_R: 5.67 min, 99%; $[\alpha]_D^{23}$=+47.0 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.71 (s, 1H), 6.44 (s, 1H), 5.07 (d, *J*=7.4 Hz, 1H), 4.63–4.55 (m, 1H), 3.91 (s, 3H), 3.75 (s, 3H), 3.09 (dd, *J*=13.7, 5.5 Hz, 1H), 3.94 (dd, *J*=13.7, 6.6 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 171.5, 163.9, 154.9, 150.5, 148.5, 117.2, 109.6, 80.3, 54.0, 53.5, 52.5, 37.3, 28.2; ESI-MS (*m*/*z*): 345 $(M+H)^+$, 689 $(2\times M+H)^+$; HRMS (FAB, *m*/*z*): Calcd for $C_{15}H_{22}N_2O_5$, $(M+H)^+$ 345.1217, observed, 345.1214.

6.1.10. *n*-Propyl *N*-(*tert*-butoxycarbonyl)-3-(2-*n*-propyloxycarbonyl-6-methoxy-4-pyridinyl) alaninate (18). A mixture of chloro compound (*S*)-(+)-**17** (300 mg, 0.87 mmol), $Pd(OAc)_2$ (9.8 mg, 0.0436 mmol, 0.05 equiv.), 1,3-bis(diphenylphosphino)propane (DPPP, 20.0 mg, 0.048 mmol, 0.055 equiv.), anhydrous K_2CO_3 (180 mg, 1.31 mmol, 1.5 equiv.) in a mixture of *n*-propanol (6.6 mL) and DMF (3.3 mL) was purged with nitrogen and then with carbon monoxide. The mixture was then stirred at 90°C under carbon monoxide atmosphere (15 psi). The reaction mixture was cooled to room temperature, filtered through celite powder and washed with THF (50 mL). The combined filtrates were concentrated on a rotary evaporator and the residue was partitioned between methyl-*tert*-butylether (MTBE, 100 mL) and water (75 mL). Organic layer was separated and the aqueous layer was extracted with MTBE (50 mL). The combined organic extracts were dried (Na_2SO_4), concentrated on a rotary evaporator and the crude product was purified by silica gel column chromatography (20% EtOAc in hexanes) to afford 0.225 g of **18** in 61% yield as viscous oil. R_f: 0.57 (20% EtOAc in hexanes); Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/60:40, 2.0 mL/min at 225 nm, t_R: 9.71 min, 99%; ^1H NMR ($CDCl_3$): δ 7.49 (d, *J*=1.1 Hz, 1H), 6.71 (d, *J*=0.8 Hz, 1H), 5.07 (d, *J*=7.7 Hz, 1H), 4.64–4.56 (m, 1H), 4.31 (d, *J*=6.8 Hz, 2H,), 4.12–4.07 (m, 2H), 4.00 (s, 3H), 3.17 (dd, *J*=13.73, 6.0 Hz, 1H), 3.05 (dd, *J*=13.73, 6.2 Hz, 1H), 1.87–1.75 (m, 1H), 1.71–1.59 (m, 1H), 1.42 (s, 9H), 1.03 (t, *J*=7.4 Hz, 3H), 0.92 (t, *J*=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.1, 165.1, 164.2, 154.9, 148.7, 145.7, 119.7, 115.7, 80.2, 67.3, 67.1, 53.6, 37.5, 28.2, 22.0, 21.8, 10.4, 10.3; ESI-MS (*m*/*z*): 425 $(M+H)^+$, 447 $(M+Na)^+$; HRMS (FAB, *m*/*z*): Calcd for $C_{21}H_{33}N_2O_7$, 425.2288 $(M+H)^+$, observed, 425.2293.

6.1.11. Mosher's amide 19. Trifluoroacetic acid (1.2 mL) was added to a solution of **18** (0.026 g, 0.061 mmol) in methylenechloride (1.0 mL) at room temperature. After stirring the mixture for 1 h, it was concentrated on a rotary evaporator and dried under vacuum (0.1 mm/Hg) to afford the corresponding amine as its TFA salt of (0.022 g, 82%). Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/30:70, 2.0 mL/min at 225 nm, t_R: 3.69 min, 99%; ^1H NMR (CD_3OD): δ 7.55 (br s, 1H), 6.90 (br s, 1H), 4.42–4.33 (m, 1H), 4.26 (t, *J*=6.6 Hz, 2H), 4.12 (t, *J*=6.6 Hz, 2H), 3.92 (s, 3H), 3.31 (br d, *J*=5.2 Hz, 2H), 1.84–1.72 (m, 2H), 1.66–1.54 (m, 2H), 1.01 (t, *J*=7.4 Hz, 3H), 0.85 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (CD_3OD): δ 168.5, 165.2, 164.5, 147.1, 146.0, 119.3, 115.2, 68.6, 67.5, 54.0, 53.3, 35.3, 21.9, 21.5, 10.3, 10.0; ESI-MS (*m*/*z*): 325 $(M+H)^+$, 649 $(2\times M+H)^+$.

The above prepared crude amine–TFA salt (0.021 g, 0.049 mmol) was dissolved in CH_2Cl_2 (5.0 mL) and cooled to 0°C. Et_3N (0.034 mL, 0.245 mmol, 5.0 equiv.) followed by (*R*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid chloride (MTP-Cl, 0.014 mL, 0.0735 mmol, 1.5 equiv.) were added and the mixture was stirred for 45 min. The reaction was quenched with water (10 mL), mixture was stirred for an additional 10 min and extracted with CH_2Cl_2 (2×25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator to afford 0.024 g of Mosher amide **19** in 92% yield as a 1:1 diastereomeric mixture. Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/62:38, 2.0 mL/min at 225 nm, t_R: 12.37 min, 96%; ^1H NMR ($CDCl_3$): δ 7.52 (m, 5H), 7.19 (d, *J*=8.24 Hz, 1H), 6.72 (d, *J*=1.1 Hz, 1H), 6.52 (d, *J*=1.1 Hz, 1H), 5.02–4.89 (m, 1H), 4.34–4.27 (m, 2H), 4.15–4.09 (m, 2H), 4.01 and 3.98 (two s, 3H), 3.44–3.42 and 3.30–3.27 (two m, 3H), 3.24–3.01 (m, 2H), 1.88–1.74 (m, 2H), 1.73–1.59 (m, 2H), 1.06–1.00 (m, 3H), 0.96–0.90 (m, 3H); ^{19}F NMR ($CDCl_3$+2.0 μL of α,α,α-trifluorotoluene): δ −6.04 and −6.00; ESI-MS (*m*/*z*): 541 $(M+H)^+$, 1081 $(2\times M+H)^+$.

6.1.12. *n*-Propyl 4-formyl-6-methoxy-2-pyridinecarboxylate (22). MnO_2 (6.5 g, 63.55 mmol, 13.0 equiv.) was added to a solution of **12** (1.1 g, 4.88 mmol) in $CHCl_3$ (45 mL) at room temperature and the mixture was stirred for 24 h. An additional amount of MnO_2 (2.0 g, 2.0 equiv.) was added to the reaction mixture and the stirring was continued for an additional 24 h at room temperature. The mixture was filtered through celite powder and washed with $CHCl_3$ (50 mL). The combined filtrates were concentrated on a rotary evaporator and the residue was purified by silica gel column chromatography (10–20% EtOAc in hexanes) to afford 0.32 g of aldehyde **22** in 30% yield as pale yellow solid. R_f: 0.37 (15% EtOAc in hexanes); Mp: 86–87°C; Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/60:40, 2.0 mL/min at 225 nm, t_R: 3.76 min, 99%; ^1H NMR ($CDCl_3$): δ 10.07 (s, 1H), 8.08 (d, *J*=1.1 Hz, 1H), 7.32 (d, *J*=1.1 Hz, 1H), 4.36 (t, *J*=6.8 Hz, 2H), 4.09 (s, 3H), 1.89–1.78 (m, 2H), 1.05 (t, *J*=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 190.3, 165.0, 164.3, 147.4, 145.3, 116.0, 115.4, 67.5, 54.4, 22.0, 10.4; ESI-MS (*m*/*z*): 224 $(M+H)^+$, 241 $(M+NH_4)^+$; HRMS (FAB, *m*/*z*): Calcd for $C_{11}H_{14}NO_4$, 224.0923 $(M+H)^+$, observed, 224.0920.

6.1.13. *n*-Propyl 4-((1*Z*)-2-{[(benzyloxy)carbonyl]-amino}-3-methoxy-3-oxo-1-propenyl)-6-methoxy-2-pyridinecarboxylate (20). *N*,*N*,*N*′,*N*′-Tetramethylguanidine (TMG, 0.127 mL, 1.01 mmol, 1.1 equiv.) followed by a solution of aldehyde **22** (0.205 g, 0.92 mmol) in THF (4.0 mL) were added to a solution of and *N*-(benzyloxycarbonyl)phosphonoglycine trimethyl ester (**23**, 0.335 g, 1.01 mmol, 1.1 equiv.) in THF (6.0 mL) at 0°C under nitrogen. The cooling bath was removed, the mixture was allowed to warm to room temperature and stirred for 6 h. The mixture was then quenched with water (50 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were dried (Na_2SO_4), concentrated on a rotary

evaporator and the residue was purified by silica gel column chromatography (25% EtOAc in hexanes) to afford 0.301 g of dehydro amino acid derivative **20** in 76% yield (*Z*-isomer, >98%). R_f: 0.15 (25% EtOAc in hexanes); Analytical RP HPLC: MeCN–0.05% aqueous 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, J=0.8 Hz, 1H), 7.36–7.25 (m, 5H), 7.16 (s, 1H), 6.91 (s, J=0.6 Hz, 1H). 6.74 (br s, 1H), 5.07 (s, 2H), 4.29 (t, J=6.8 Hz, 2H), 4.01 (s, 3H), 3.85 (s, 3H), 1.84–1.72 (m, 2H), 1.01 (t, J=7.4 Hz, 3H); ^{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 $C_{22}H_{25}N_2O_7$, 429.1662 $(M+H)^+$; observed 429.1667.

Also, 0.025 g of the *E*-isomer of **20** in 6% yield was isolated. R_f: 0.21 (25% EtOAc in hexanes); Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/60:40, 2.0 mL/min at 225 nm, t_R: 6.79 min, 91%; ^{1}H NMR ($CDCl_3$): δ 7.59 (br s, 1H), 7.44 (m, 1H), 7.33–7.27 (m, 5H), 7.17 (s, 1H), 7.12 (br s, 1H), 6.65 (m, 1H), 5.09 (s, 2H), 4.22 (t, J=6.8 Hz, 2H), 3.93 (s, 3H), 3.54 (s, 3H), 1.78–1.66 (m, 2H), 0.94 (t, J=7.4 Hz, 3H); ESI-MS (*m/z*): 429 $(M+H)^+$.

6.1.14. (+)-Methyl *N*-(benzyloxycarbonyl)-3-(*n*-propyloxycarbonyl-6-methoxy-4-pyridinyl)-L-alaninate (21). Dehydroamino acid derivative **20** (0.117 g, 0.27 mmol) was dissolved in MeOH (10 mL) and nitrogen was bubbled. (*R*,*R*)-[Rh(DIPAMP)(COD)]BF_4 (13.0 mg, 0.018 mmol, 0.065 equiv.) was added under nitrogen atmosphere and the mixture was degassed using vacuum. The mixture was then hydrogenated (65 psi) at 48°C for 16 h. The reaction mixture was cooled to room temperature, concentrated on a rotary evaporator and the residue was purified by silica gel column chromatography (25% EtOAc in hexanes) to afford 0.105 g of (*S*)-(+)-**21** in 89% yield as viscous oil. R_f: 0.15 (25% EtOAc in hexanes); Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/60:40, 2.0 mL/min at 225 nm, t_R: 5.44 min, 99%; $[\alpha]_D^{23}$=+50.5 (*c* 0.525, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.47 (d, J=1.1 Hz, 1H), 7.38–7.30 (m, 5H), 6.68 (d, J=0.8 Hz, 1H), 5.33 (d, J=7.9 Hz, 1H), 5.10 (s, 2H), 4.69 (dd, J=13.4, 6.0 Hz, 1H), 4.30 (t, J=6.8 Hz, 2H), 3.99 (s, 3H), 3.74 (s, 3H), 3.17 (dd, J=13.7, 5.8 Hz, 1H), 3.07 (dd, J=13.7, 6.3 Hz, 1H), 1.86–1.74 (m, 2H), 1.02 (t, J=7.4 Hz, 3H); ^{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 $C_{22}H_{27}N_2O_7$, 431.1818 $(M+H)^+$, observed, 431.1824.

6.1.15. Preparation of Mosher's amide (24). 1.0N aqueous HCl solution (0.046 mL, 0.046 mmol, 1.1 equiv.) was added dropwise to a stirred solution of (*S*)-(+)-**21** (0.018 g, 0.0418 mmol) in MeOH (5 mL). After the addition was complete, the mixture was concentrated on a rotary evaporator to dryness. The residue was dissolved in MeOH (5 mL) and hydrogenated in presence of 10% Pd/C (50% wet with water, 4.0 mg, 10% wt/wt) at 30 psi for 2 h. The reaction mixture was filtered through celite powder and the filtrate was concentrated to afford 0.011 g of the corresponding amine as its hydrochloride salt in 88% yield. Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/20:80, 2.0 mL/min at 225 nm, t_R: 6.49 min, 99%; ^{1}H NMR (CD_3OD): δ 7.52 (d, J=0.8 Hz, 1H), 6.85 (s, 1H), 4.21 (t, J=6.6 Hz, 2H), 3.87 (s, 3H), 3.72 (s, 3H), 3.23–3.33 (m, 2H), 1.77–1.65 (m, 2H), 0.94 (t, J=7.1 Hz, 3H); ^{13}C NMR (CD_3OD): δ 170.1, 166.5, 166.1, 148.8, 147.4, 120.4, 116.7, 68.4, 54.4, 54.2, 53.8, 36.4, 23.1, 10.7; ESI-MS (*m/z*): 297 $(M+H)^+$, 593 $(2\times M+H)^+$.

The above prepared crude amine hydrochloride salt (0.011 g, 0.033 mmol) was dissolved in CH_2Cl_2 (5.0 mL) and cooled to 0°C. Et_3N (0.019 mL, 0.132 mmol, 4.0 equiv.) followed by (*R*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid chloride (MTP-Cl, 0.0093 mL, 0.0497 mmol, 1.5 equiv.) were added to the above solution and the mixture was stirred for 2.5 h. The reaction was quenched with water (10 mL), stirred for an additional 10 min and extracted with CH_2Cl_2 (10 mL). Organic layer was separated, washed with saturated $NaHCO_3$ (10 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator. The residue was purified by silica gel column chromatography (30% EtOAc in hexanes) to afford 0.013 g of Mosher amide **24** in 78% yield. R_f: 0.46 (30% EtOAc in hexanes); Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/55:45, 2.0 mL/min at 225 nm, t_R: 11.92 min, 99%; ^{1}H NMR ($CDCl_3$): δ 7.41 (d, J=1.3 Hz, 1H), 7.39–7.33 (m, 5H), 7.18 (d, J=8.5 Hz, 1H), 6.50 (d, J=1.0 Hz, 1H), 5.02–4.95 (m, 1H), 4.32–4.27 (m, 2H), 3.98 (s, 3H), 3.79 (s, 3H), 3.45–3.22 (m, 3H), 3.20 (dd, J=14.0, 5.2 Hz, 1H), 3.03 (dd, J=14.0, 7.4 Hz, 1H), 1.86–1.74 (m, 2H), 1.03 (t, J=7.4 Hz, 3H); ^{19}F NMR ($CDCl_3$+2.0 μL of α,α,α-trifluorotoluene): δ −6.03; ESI-MS (*m/z*): 513 $(M+H)^+$, 1025 $(2\times M+H)^+$.

6.1.16. (*S*)-(−)-Acromelobic acid (1). A solution of LiOH (monohydrate, 0.024 g, 0.558 mmol, 4.0 equiv. in 2.0 mL of water) was added to a solution of (*S*)-(+)-**21** (0.06 g, 0.139 mmol) in THF (5.0 mL) at room temperature. After stirring the mixture for 2 h, it was concentrated on a rotary evaporator to about 2.0 mL volume and diluted with water (2.0 mL) and EtOAc (15 mL). 2.0N aqueous HCl (0.28 mL, 0.558 mmol, 4.0 equiv.) was added to the above mixture with stirring. Organic layer was separated and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic extracts were washed with water (5.0 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to afford the corresponding di-acid (0.05 g) in 96% yield.

The above isolated crude di-acid (0.05 g, 0.133 mmol) was suspended in $CHCl_3$ (24 mL), iodotrimethylsilane (0.19 mL, 1.336 mmol, 10.0 equiv.) was added and the mixture was refluxed under nitrogen for 7 h. The reaction mixture became homogeneous in 10 min of heating. MeOH (16 mL) was added and the reflux was continued for an additional 12 h. The mixture was concentrated to dryness on a rotary evaporator and the residue was triturated with CH_3CN (2×10 mL) and the CH_3CN layer was separated using a pipette. The resulting solid was suspended in water (5.0 mL) and basified to pH 11 using 1.0N aqueous NaOH. The resulting clear solution was then passed through Dowex, CCR-3 ion exchange (Aldrich Chemical Co.) resin column (eluent: water). The fractions containing the product were combined and lyophilized. Analysis of the

product by RP HPLC (MeCN–0.05% aqueous acetic acid/2:98, 1.0 mL, 225 nm, t_R: 2.69 min (NaI) and t_R: 4.18 min, 80%;), indicated that approximately 20% NaI was present. The lyophilized product was further purified with AG11A8 (Biorad Laboratories) resin (eluent: water) to afford 0.019 g of (*S*)-(−)-acromelobic acid (**1**) in 63% yield. $[\alpha]_D^{23}=-139.1$ (*c* 0.0575, H_2O), Lit.[6b] $[\alpha]_D^{23}=-131.0$ (*c* 0.05, H_2O); Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/2:98, 1.0 mL/min at 225 nm, t_R: 4.57 min, 98%; ^{1}H NMR (D_2O): δ 6.86 (s, 1H), 6.48 (s, 1H), 3.54 (dd, *J*=7.9, 5.5 Hz, 1H,), 2.91 (dd, *J*=13.7, 5.5 Hz, 1H,), 2.71 (dd, *J*=13.7, 8.2 Hz, 1H); ^{13}C NMR (D_2O+0.05 mL of CD_3OD): δ 180.3, 167.2, 165.1, 155.9, 140.7, 122.0, 112.3; ESI-MS (*m*/*z*): 225 $(M-H)^-$, 451 $(2\times M-H)^-$.

6.1.17. Methyl 5-methyl-2-pyridinecarboxylate *N*-oxide (26). A mixture of 2,5-lutidine (**25**, 20.0 g, 0.187 mol) and SeO_2 (31.1 g, 0.28 mol, 1.5 equiv.) in pyridine (100 mL) was heated to reflux for 26 h. The mixture was then cooled to room temperature, filtered and the solid was washed with pyridine (20 mL) and water (2×20 mL). The combined filtrate was concentrated on a rotary evaporator and the resulting residue was suspended in water (200 mL). Activated carbon (5 g) was added to the suspension and the mixture was heated to reflux for 15 h. The warm mixture was then filtered and filtrate was concentrated to dryness on a rotary evaporator to afford 5-methylpicolic acid, which was used in the next step without purification.

The above prepared crude 5-methylpicolic acid was dissolved in methanol (130 mL) and conc H_2SO_4 (15 mL) was added. After refluxing the mixture for 8 h, it was cooled to room temperature and basified carefully with $NaHCO_3$ (20 g). The mixture was concentrated on a rotary evaporator and the residue was partitioned between water (200 mL) and ether (200 mL). The organic layer was separated and aqueous layer was extracted with ether (2×200 mL). The combined organic extracts were dried (Na_2SO_4), concentrated on a rotary evaporator and the residue was purified by silica gel column chromatography to afford 8.2 g of the 5-methylpicolic acid methyl ester in 34% yield. Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/25:75, 2.0 mL/min at 225 nm, t_R: 3.14 min, 95%; ^{1}H NMR ($CDCl_3$): δ 8.57 (m, 1H), 8.04 (d, *J*=7.9 Hz, 1H,), 7.66–7.62 (m, 1H), 4.00 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.7, 150.2, 145.3, 137.4, 137.2, 124.7, 52.6, 18.5; ESI-MS (*m*/*z*): 152 $(M+H)^+$.

m-CPBA (70%, 16.6 g, 67.54 mmol, 1.5 equiv.) was added to a solution of above prepared 5-methylpicolic acid methyl ester (6.8 g, 45.0 mmol) in $CHCl_3$ (200 mL) and the mixture was stirred at room temperature for 15 h. The reaction was quenched with saturated aqueous Na_2SO_3 (75 mL) and the mixture was stirred for 10 min. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (100 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to afford 5.84 g of 5-methylpicolic acid-*N*-oxide methyl ester (**26**) in 78% yield. Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/20:80, 1.0 mL/min at 225 nm, t_R: 4.08 min, 98%; ^{1}H NMR ($CDCl_3$): δ 8.12 (d, *J*=0.8 Hz, 1H,), 7.55 (d, *J*=8.2 Hz, 1H)), 7.12–7.08 (m, 1H), 3.99 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 162.0, 140.7, 138.8, 138.7, 126.7, 126.0, 53.1, 18.3; ESI-MS (*m*/*z*): 168 $(M+H)^+$, 190 $(M+Na)^+$.

6.1.18. Methyl 6-hydroxy-5-methyl-2-pyridinecarboxylate (27). 5-Methylpicolic acid-*N*-oxide methyl ester (**26**, 0.225 g, 1.347 mmol) was dissolved in acetic anhydride (5.0 mL) and the mixture was heated to reflux for 3 h. The reaction was cooled to room temperature and acetic anhydride was removed on a rotary evaporator. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL). Organic layer was dried (Na_2SO_4) and concentrated on a rotary evaporator. The residue was dissolved in methanol (10 mL) and cooled to 0°C. NaOMe (25 wt% solution in methanol, 0.288 mL, 1.347 mmol) was added to the above solution and the mixture was stirred 10 min. The reaction was quenched with solid NH_4Cl (1.0 g) and the mixture was concentrated on a rotary evaporator. The residue was partitioned between CH_2Cl_2 (50 mL) and water (30 mL). Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated on a rotary evaporator and purified by silica gel column chromatography (70–80% EtOAc in hexanes) to obtain 0.115 g of **27** in 51% yield as a pale yellow solid. R_f: 0.71 (80% EtOAc in hexanes); Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/10:90, 2.0 mL/min at 225 nm, t_R: 11.12 min, 99%; ^{1}H NMR ($CDCl_3$): δ 9.86 (brs, 1H), 7.33–7.30 (m, 1H), 6.92 (d, *J*=6.9 Hz, 1H), 3.95 (s, 3H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 162.4, 161.5, 137.3, 136.6, 131.0, 109.7, 53.1, 17.1; ESI-MS (*m*/*z*): 168 $(M+H)^+$, 190 $(M+Na)^+$.

6.1.19. Methyl 6-methoxy-5-methyl-2-pyridinecarboxylate (28). Ag_2CO_3 (11.52 g, 41.91 mmol, 2.0 equiv.) followed by MeI (1.3 mL, 20.95 mmol, 1.0 equiv.) were added to a solution of **27** in $CHCl_3$ (140 mL) at room temperature under nitrogen. After stirring the mixture for 3 days an additional amount of MeI (2.6 mL, 41.9 mmol, 2.0 equiv.) was added in portions over two days period. After stirring the reaction mixture for a total of five days, it was filtered and the filtrate was concentrated concentrated on a rotary evaporator. Purification of the crude product by silica gel column chromatography (20% EtOAc in hexanes) afforded 3.5 g of methyl ether **28** in 93% yield as a pale yellow solid. R_f: 0.80 (40% EtOAc in hexanes); Mp: 124–125°C; Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/45:55, 2.0 mL/min at 225 nm, t_R: 5.82 min, 98%; ^{1}H NMR ($CDCl_3$): δ 7.63 (d, *J*=7.4 Hz, 1H,), 7.49–7.46 (m, 1H), 4.04 (s, 3H), 3.95 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.9, 162.1, 142.7, 138.5, 126.1, 118.8, 53.6, 52.5, 16.2; ESI-MS (*m*/*z*): 182 $(M+H)^+$.

6.1.20. Methyl 5-(bromomethyl)-6-methoxy-2-pyridinecarboxylate (29). AIBN (0.041 g, 0.248 mmol, 0.045 equiv.) was added to a refluxing mixture of compound **28** (1.0 g, 5.53 mmol) and NBS (1.08 g, 6.077 mmol, 1.1 equiv.) in CCl_4 (30 mL) at room temperature. After stirring the mixture for 15 min, an additional amount of AIBN (0.123 g in three portions over a period of 1.5 h and the stirring was continued for 0.5 h. The reaction mixture was cooled to room temperature, filtered and the solid was washed with CCl_4 (50 mL). The combined filtrates were washed with water (100 mL), dried (Na_2SO_4) and

concentrated on a rotary evaporator. The crude compound was purified by silica gel column chromatography (15% EtOAc in hexanes) to afford 1.1 g of **29** in 77% yield as a pale yellow solid. R_f: 0.36 (10% EtOAc in hexanes); Mp: 94–95°C; Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/45:55, 2.0 mL/min at 225 nm, t_R: 7.48 min, 98%; ^{1}H NMR ($CDCl_3$): δ 7.73 (d, J=7.4 Hz, 1H,), 7.69 (d, J=7.4 Hz, 1H,),4.49 (s, 2H), 4.11 (s, 3H), 3.96 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.3, 161.1, 145.3, 139.4, 124.9, 118.8, 54.1, 52.7, 26.8; ESI-MS (m/z): 260 $(M+H)^+$.

6.1.21. Methyl 5-formyl-6-methoxy-2-pyridinecarboxylate (30). A mixture of bromo compound **29** (1.1 g, 4.23 mmol) and hexamethylenetetramine (1.3 g, 9.3 mmol, 2.2 equiv.) in 50% aqueous acetic acid (25 mL) was heated to reflux. After 1 h, the mixture was cooled to room temperature, neutralized carefully with solid $NaHCO_3$ (~35 g) diluted with water (200 mL) and extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were dried (Na_2SO_4), concentrated on a rotary evaporator and purified by silica gel column chromatography (15% EtOAc in hexanes) to afford 0.285 g of **30** in 34% yield as a pale yellow solid. R_f: 0.50 (20% EtOAc in hexanes); Mp: 82–83°C; Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/45:55, 2.0 mL/min at 225 nm, t_R: 3.42 min, 99%; ^{1}H NMR ($CDCl_3$): δ 10.41 (d, J=0.8 Hz, 1H), 8.22 (d, J=7.4 Hz, 1H), 7.79 (d, J=7.7, 0.8 Hz, 1H), 4.17 (s, 3H), 4.00 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 188.5, 164.6, 163.9, 149.7, 138.5, 121.1, 118.4, 54.2, 52.9; ESI-MS (m/z): 196 $(M+H)^+$, 391 $(2\times M+H)^+$, 408 $(2\times M+NH_4)^+$; HRMS (FAB, m/z): Calcd for $C_9H_{10}NO_4$, 196.0610 $(M+H)^+$, observed, 196.0615.

6.1.22. Methyl 5-((1*Z*)-2-{[(benzyloxy)carbonyl]amino}-3-methoxy-3-oxo-1-propenyl)-6-methoxy-2-pyridinecarboxylate (31). *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG, 0.194 mL, 1.55 mmol, 1.1 equiv.) followed by a solution of aldehyde **20** (0.275 g, 1.41 mmol) in THF (6.0 mL) were added to a solution of and *N*-(benzyloxycarbonyl)phosphonoglycine trimethyl ester (**23**, 0.514 g, 1.55 mmol, 1.1 equiv.) in THF (9.0 mL) at 0°C under nitrogen. The cooling bath was removed and the mixture was allowed warm to room temperature and stirred for 6 h. The mixture was then quenched with water (50 mL) and extracted with EtOAc (2×40 mL). The combined organic extracts were dried (Na_2SO_4), concentrated on a rotary evaporator and the residue was purified by silica gel column chromatography (40% EtOAc in hexanes) to afford 0.375 g of dehydroamino acid derivative **31** in 66% yield as a mixture of *Z*/*E* isomers (ratio 9:1). R_f: 0.27 (30% EtOAc in hexanes); Analytical RP HPLC: MeCN–0.05% aq acetic acid/45:55, 2.0 mL/min at 225 nm, t_R: 9.93 min (90%) and 11.47 min (10%); ^{1}H NMR ($CDCl_3$) of *Z*-isomer (major): δ 7.77 (d, J=7.7 Hz, 1H,), 7.62 (d, J=7.7 Hz, 1H), 7.41–7.26 (m, 6H), 6.79 (br s, 1H), 5.06 (s, 2H), 4.06 (s, 3H), 3.97 (s, 3H), 3.85 (s, 3H); ESI-MS (m/z): 401 $(M+H)^+$, 801 $(2\times M+H)^+$; HRMS (FAB, m/z): Calcd for $C_{20}H_{21}N_2O_7$, 401.1349 $(M+H)^+$, observed, 401.1337.

6.1.23. (+)-Methyl *N*-(benzyloxycarbonyl)-3-(methoxycarbonyl-6-methoxy-5-pyridinyl)-L-alaninate (32) using DIPAMP catalyst. Dehydroamino acid derivative **31** (0.184 g, 0.46 mmol) was dissolved in MeOH (15 mL) and bubbled with nitrogen. (*R*,*R*)-[Rh(DIPAMP)-(COD)]BF_4 (17.4 mg, 0.023 mmol, 0.05 equiv.) was added under nitrogen atmosphere and the mixture was degassed using vacuum. The mixture was then hydrogenated (65 psi) at 45°C for 17 h. The reaction mixture was cooled to room temperature, concentrated on a rotary evaporator and residue was purified by silica gel column chromatography (40% EtOAc in hexanes) to afford 0.18 g of (*S*)-(+)-**32** in 97% yield as viscous oil. R_f: 0.29 (30% EtOAc in hexanes); Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/45:55, 2.0 mL/min at 225 nm, t_R: 8.84 min, 99%; $[\alpha]_D^{23}$=+24.2 (*c* 0.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.61 (d, J=7.1 Hz, 1H), 7.43 (d, J=7.4 Hz, 1H), 7.36–7.26 (m, 5H), 5.51 (d, J=7.9 Hz, 1H), 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, J=13.7, 6.0 Hz, 1H), 3.04 (dd, J=13.7, 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 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 $(2\times M+NH_4)^+$.

6.1.24. (+)-Methyl *N*-(benzyloxycarbonyl)-3-(methoxycarbonyl-6-methoxy-5-pyridinyl)-L-alaninate (32) using DuPHOS catalyst. Dehydroamino acid derivative **31** (0.16 g, 0.40 mmol) was dissolved in MeOH–EtOAc (10 mL, 7:3) and bubbled with nitrogen. (*S*,*S*)-[Rh(Et-DuPHOS)(COD)]BF_4 (3.0 mg, 0.0045 mmol, 0.011 equiv.) was added under nitrogen atmosphere and the mixture was degassed using vacuum. The mixture was then hydrogenated (35 psi) at room temperature for 24 h. The reaction mixture was concentrated on a rotary evaporator and residue was purified by silica gel column chromatography (40% EtOAc in hexanes) to obtain 0.15 g of (*S*)-(+)-**32** in 93% yield as a viscous oil. R_f: 0.29 (30% EtOAc in hexanes); Analytical RP HPLC: 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 ($CDCl_3$): δ 7.61 (d, J=7.1 Hz, 1H), 7.43 (d, J=7.4 Hz, 1H), 7.36–7.26 (m, 5H), 5.51 (d, J=7.9 Hz, 1H), 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, J=13.7, 6.0 Hz, 1H), 3.04 (dd, J=13.7, 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 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.

6.1.25. Preparation of the Mosher amide of (*S*)-(+)-32. 1.0N aqueous HCl solution (0.14 mL, 0.14 mmol, 2.1 equiv.) followed by 10% Pd/C (50% wet with water, 11.0 mg, 20% wt/wt) were added to a solution of (*S*)-(+)-**32** (0.027 g, 0.0671 mmol) in MeOH (5 mL). The mixture was hydrogenated at 30 psi for 1 h. The reaction mixture was filtered through celite powder and the filtrate was concentrated to afford the corresponding amine hydrochloride (19.0 mg, 84%). Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/15:85, 2.0 mL/min at 225 nm, t_R: 4.69 min, 95%; ESI-MS (m/z): $(M+H)^+$, $(2\times M+H)^+$.

The above prepared crude amine hydrochloride (15.0 mg, 0.044 mmol) was suspended in CH_2Cl_2 (7.0 mL) and cooled to 0°C. Et_3N (0.025 mL, 0.176 mmol, 4.0 equiv.) followed

by (*R*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid chloride (MTP-Cl, 0.0123 mL, 0.066 mmol, 1.5 equiv.) were added to the above solution and the mixture was stirred for 1 h. The reaction was quenched with water (10 mL). After stirring reaction for an additional 10 min, the mixture was extracted with CH_2Cl_2 (20 mL). The aqueous layer was separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator. The residue was purified by silica gel column chromatography (40% EtOAc in hexanes) to afford 0.021 g of Mosher amide of **32** in 98% yield. R_f: 0.24 (30% EtOAc in hexanes); Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/50:50, 2.0 mL/min at 225 nm, t_R: 10.30 min, 98%; ^{1}H NMR ($CDCl_3$): δ 7.53 (d, J=7.4 Hz, 1H), 7.36–7.27 (m, 7H), 4.98–4.90 (m, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.75 (s, 3H), 3.50–3.47 (m, 3H), 3.16 (dd, J=14.01, 5.5 Hz, 1H), 3.07 (dd, J=14.01, 8.5 Hz, 1H); ^{19}F NMR ($CDCl_3$+2.0 μL of α,α,α-trifluorotoluene): δ −6.04; ESI-MS (*m*/*z*): 485 $(M+H)^+$, 502 $(M+NH_4)^+$, 986 $(2\times M+NH_4)^+$.

6.1.26. (*S*)-(−)-Acromelobinic acid (2). LiOH (monohydrate, 0.046 g, 0.1.09 mmol, 4.0 equiv. in 3.0 mL of water) was added to a solution of (*S*)-(+)-**32** (0.11 g, 0.27 mmol) in THF (7.0 mL) at room temperature. After stirring the mixture for 1 h, it was concentrated on a rotary evaporator to 3.0 mL volume and diluted with water (5.0 mL) and EtOAc (30 mL). 1.0N aqueous HCl (1.1 mL, 1.1 mmol, 4.0 equiv.) was added to the above mixture with vigorous stirring. Organic layer was separated and the aqueous layer was extracted with EtOAc (15 mL). The combined organic extracts were washed with water (10 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to obtain the corresponding di-acid (0.10 g) in 98% yield.

The above prepared crude di-acid (0.10 g, 0.267 mmol) was suspended in $CHCl_3$ (40 mL), iodotrimethylsilane (0.38 mL, 2.67 mmol, 10.0 equiv.) was added and the mixture was heated to reflux under nitrogen for 7 h. The reaction mixture became homogeneous in 10 min of heating. MeOH (26 mL) was added and the reflux was continued for an additional 12 h. The mixture was concentrated to dryness on a rotary evaporator and the residue was triturated with CH_3CN (10 mL). CH_3CN layer was separated using a pipette. The resulting solid was suspended in water (5.0 mL) and basified to pH 10 with 1.0N aqueous NaOH. The resulting clear solution was then passed through Dowex, CCR-3 ion exchange (Aldrich Chemical Co.) resin column (eluent: water). The fractions containing the product were combined and lyophilized. The lyophilized product was further purified with AG11A8 (Biorad Laboratories) resin (eluent: water) to afford 0.053 g of (*S*)-(−)-acromelobinic acid (**2**) in 88% yield. $[\alpha]_D^{23}$=−56 (*c* 0.15, H_2O), Lit.[6b] $[\alpha]_D^{23}$=−5.8 (*c* 0.13, H_2O); Analytical RP HPLC: MeCN–0.05% aqueous acetic acid/2:98, 1.0 mL/min at 225 nm, t_R: 6.13 min, 98%; ^{1}H NMR (D_2O): δ 7.50 (d, J=7.1 Hz, 1H), 6.86 (d, J=7.1 Hz, 1H), 3.76 (dd, J=7.9, 4.6 Hz, 1H), 3.01 (dd, J=14.5, 4.6 Hz, 1H), 2.77 (dd, J=14.5, 8.2 Hz, 1H); ^{13}C NMR (D_2O+0.05 mL of CD_3OD): δ 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 $(2\times M-H)^-$.

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