Asymmetric Synthesis of (*S*)-(−)-Acromelobic Acid

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(*S*)-(–)-Acromelobic acid (**1**) was synthesized in nine steps in enantiomerically pure form from citrazinic acid (**4**) in an overall yield of 21%. The key steps of this synthesis are the introduction of the amino function by the bis(lactim) ether method and the introduction of the acid function by Stille coupling.

Introduction

The mushroom *Clitocybe acromelalga* has been a source of a variety of potent neuroexcitatory amino acids related to the kainoids[1] such as (*S*)-(−)-acromelobic acid (**1**). Therefore, an efficient synthesis of this amino acid and its derivatives is of high pharmacological interest, for example in neuroscience research.

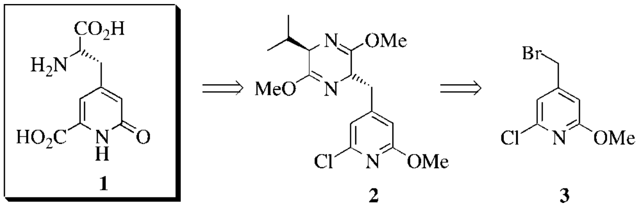
(*S*)-(−)-Acromelobic acid (**1**), isolated in 1992 by Shirama et al.[2,3] from the fruiting bodies of this mushroom, was prepared for the first time from (*S*)-stizolobic acid (a related naturally occurring nonproteinogenic amino acid), again by Shirama et al.[2] Baldwin et al. reported the first total synthesis of racemic (±)-**1** in 13 steps and an overall yield of 9% starting from catechol.[4] So far, there has been only one enantioselective synthesis of (*S*)-(−)-acromelobic acid (**1**) reported. In 2001 Adamczyk et al. reported an asymmetric synthesis of (−)-**1** in eight steps with an enantiomeric excess of greater than 98% and an overall yield of 3% by asymmetric hydrogenation.[5a−5c]

The bis(lactim) ether method is well established in amino acid synthesis as an alternative to asymmetric hydrogenation, and generally proceeds with excellent yields and high enantioselectivities.[6] This method has been successfully employed for the synthesis of many nonproteinogenic amino acids, such as tryptophan analogues,[7] 2-amino-3-methyl-4-phosphobutanoic acids,[8] 3-hetarylalanines,[9] 5-hydroxylysine,[10] homocysteine and homocystine,[11] clavipitic acid,[12] and 2,6-diamino-3-fluoropimelic acid[13] among many others. In 2002 Adamczyk et al. reported a synthesis of acromelobic acid by employing the bis(lactim) ether method. Unfortunately, after hydrolytic cleavage of the bis(lactim) ether ring, complete racemization of a precursor to acromelobic acid took place during the introduction of an ester group at C-2 of the pyridine ring.[5c]

Consequently, in our approach towards acromelobic acid, we decided to use the bis(lactim) ether heterocycle both as a protecting group for the amine and the carboxylic acid functions, in order to avoid racemization and decomposition after the alkylation step.[14,15] According to our experience, the lactim ether bonds should survive the reaction conditions for both Stille coupling and ozonolysis, among many other transformations. Furthermore, no epimerization can occur. Our strategy was therefore to carry out these operations prior to hydrolysis. In the final reaction, it should be possible to liberate acromelobic acid **1** under mildly acidic reaction conditions without any racemization.[16]

Results and Discussion

Our synthetic approach to the synthesis of (*S*)-(−)-**1** was envisioned through the retrosynthetic route shown in Scheme 1. The ester function was thought to be a good precursor for the target molecule, which in turn could be obtained from the Stille coupling of the corresponding chloride **2** with (α-ethoxyvinyl)tributyltin and subsequent ozonolysis. The chloride **2** itself could be derived from the bromide **3** through alkylation with the bis(lactim) ether **8**. The bromide **3** finally should easily be available from citrazinic acid (**4**).



Scheme 1. Retrosynthetic route towards (*S*)-(−)-acromelobic acid (**1**)

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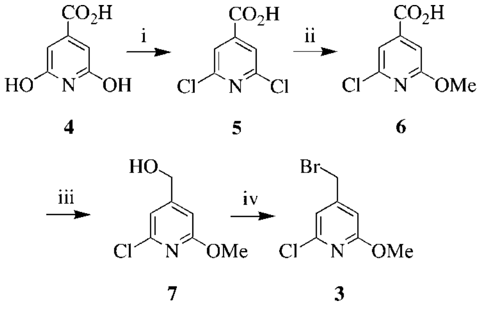
The successful synthesis of (*S*)-(−)-acromelobic acid (**1**) described herein is based on the bis(lactim) ether method[6,17] and the introduction of an enol ether by the Stille coupling[18] of **2** and subsequent ozonolysis to the corresponding ester.

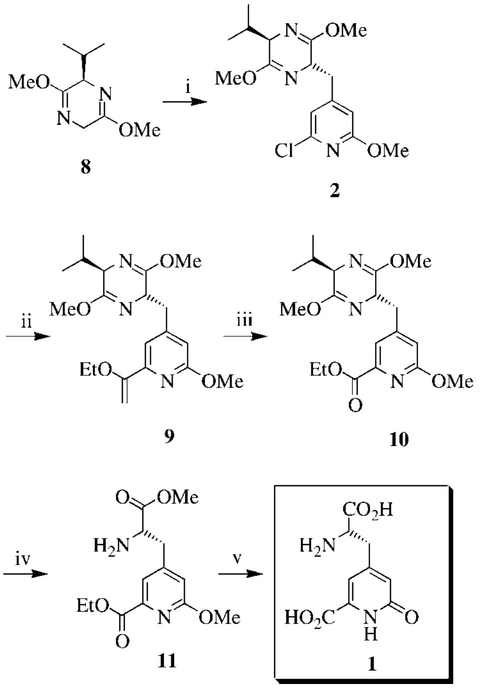
The detailed synthetic route with reagents and reaction conditions is provided in Schemes 2 and 3. Our synthesis of target molecule **1** started from citrazinic acid (**4**), which was converted into the known compound **5** in 85% yield and compound **6** in 95% yield according to known protocols.[19,20] Reduction of the acid group in compound **6** with a mixture of BH_3·SMe_2 complex and $B(OMe)_3$ in THF at room temperature afforded the alcohol **7** in 86% yield after purification by chromatography. Alcohol **7** was then transformed into a bromide by reaction with PPh_3 and CBr_4 in benzene at room temperature, to give benzyl bromide **3** in 98% yield.



Scheme 2. Reagents and conditions: (i) ref.[19] 85%; (ii) ref.[20] 95%; (iii) BH_3·SMe_2, $B(OMe)_3$, THF, 16 h, room temp., 86%; (iv) CBr_4, PPh_3, benzene, 16 h, room temp., 98%

The bis(lactim) ether of *cyclo*(-L-Val-Gly-) (**8**),[17] was lithiated at −78 °C with *n*-butyllithium and alkylated with the bromide **3**, to provide the chloride **2**. This material was obtained with a diastereomeric ratio of 91:9, as determined by ^1H NMR spectroscopy. After chromatography, (2*R*,5*S*)-(+)-**2** was isolated in 84% yield in an enantiomerically and diastereomerically pure form. The mechanism of related alkylations as well as their stereochemical outcomes has been discussed in detail by Schöllkopf.[21,22]

Our next concern was the introduction of the ester functionality.[5] Adamczyk et al. were able to obtain a similar ester by reaction with carbon monoxide (at 1 atm) in the presence of palladium acetate, 1,3-bis(diphenylphosphanyl)propane (DPPP), 1-propanol and K_2CO_3 in DMF at 90 °C, but in only 45% yield. We therefore tried an indirect route to the ester (2*R*,5*S*)-(+)-**10**, employing a Stille cross-coupling. A mixture of the chloride (2*R*,5*S*)-(+)-**2**, tributyl(α-ethoxyvinyl)tin and $[Pd(Ph_3)_4]$ in deoxygenated toluene was refluxed for 72 h to give the enol ether (2*R*,5*S*)-(+)-**9** in 87% yield. Treatment of a solution of (2*R*,5*S*)-(+)-**9** in CH_2Cl_2 with ozone at −78 °C, with Sudan III as an indicator afforded the desired ester (2*R*,5*S*)-(+)-**10** in 69% yield. Acid hydrolysis of (2*R*,5*S*)-(+)-**10** with HCl in MeCN at room temperature for 45 min, yielded methyl L-valinate and the amino acid methyl ester (*S*)-(+)-**11** (86%), which were separated by flash chromatography.



Scheme 3. Reagents and conditions: (i) (a) **8**, *n*BuLi, toluene, −78 °C, 15 min, (b) **3**, toluene, −78 °C, 16 h, 84%, 91:9 de; (ii) **2**, tributyl(α-ethoxyvinyl)tin, $Pd(PPh_3)_4$, toluene, reflux, 3 d, 87%; (iii) (a) O_3, Sudan III, CH_2Cl_2, −78 °C, 5 min, (b) Me_2S, room temp., 30 min, 69%; (iv) 0.5 N HCl, MeCN, room temp., 45 min, 86%; (v) (a) LiOH, $MeOH/H_2O$ (3:1), 16 h, room temp., (b) TMSI, $CHCl_3$, 16 h, reflux, (c) MeOH, 16 h, reflux, 71%

The final step in the synthesis of (*S*)-(−)-**1** was the removal of the protecting groups in (*S*)-(+)-**11**. Thus, alkaline hydrolysis of both the methyl and ethyl esters in (*S*)-(+)-**11** was carried out with LiOH in MeOH/water. The resulting crude diacid was dried and subsequently treated with TMSI in $CHCl_3$ under reflux to cleave the methyl ether group. After 16 h, MeOH was added to the reaction mixture. Purification of the crude compound by Dowex® MAC-3 ion exchange resin was followed by Dowex® Retardion® resin chromatography. Lyophilization afforded (*S*)-(−)-acromelobic acid **1** in 71% yield as a pale yellow powder with an optical rotation of $[\alpha]_D^{23} = -133.1$ ($c = 0.051$, H_2O), consistent with the literature data.[2,3]

Conclusion

In conclusion, a short, high-yielding and efficient asymmetric synthesis of the nonproteinogenic amino acid (*S*)-(−)-acromelobic acid (**1**) has been achieved starting from the commercially available citrazinic acid (**4**) by applying the bis(lactim) ether protocol for the introduction of the amino acid functionality. The introduction of the acid functionality was achieved by a Stille coupling and subsequent ozonolysis, a reaction which so far has only been shown for aliphatic systems[23,24] A short reaction sequence and high overall yield (21%) of (*S*)-(−)-acromelobic acid (**1**) renders our strategy a good alternative to the method described by Adamzcyk. By employing the bis(lactim) ether method, the synthesis of derivatives of **1** with even better pharmacological profiles (such as its α-methyl derivative) could be achieved very easily from the bis(lactim) ether of *cyclo*(-L-Val-DL-Ala-).[25] Of course the above-mentioned α-methyl derivative cannot be prepared by asymmetric hydrogenation due to its tetrasubstituted central carbon atom.

Experimental Section

General Remarks: The bis(lactim) ether of *cyclo*(-L-Val-Gly-) (**8**) was prepared according to a literature method.[17] Infrared (IR) spectra were obtained using a Perkin−Elmer 1600 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained using a JEOL 400 GX JNM or a Bruker Advance DRX 600 spectrometer. Chemical shifts are given in ppm (δ) using tetramethylsilane as internal standard. Mass spectra were recorded with a Varian MAT 312 spectrometer. Optical rotations were measured with a Perkin−Elmer model 241 MC polarimeter. The melting points were measured in open capillary tubes with a Gallenkamp Melting Point Apparatus and are not corrected. TLC analyses were performed with Polygram Sil G/UV$_{254}$ silica gel plates (Macherey−Nagel & Co.). Merck silica gel 60 (0.040−0.063 mm, 230−400 mesh) was used for flash chromatography. Combustion analyses were carried out by the microanalytical laboratory of the University of Konstanz. All reactions were carried out under argon except those involving hydrolysis. All reagents were, if necessary, purified and dried before use.

2,6-Dichloroisonicotinic Acid (5):[19] A mixture of citrazinic acid (**4**) (10.0 g, 64.5 mmol) and tetramethylammonium chloride (7.35 g, 67.1 mmol) in phosphorous oxychloride (29.7 g, 139.5 mmol) was refluxed at 130 °C for 18 h. After cooling, the mixture was poured onto ice (150 g) and stirred for 2 h. The precipitate was filtered off and dried in vacuo to afford **5** (10.54 g, 85%) as a pale brown solid. The spectroscopic and physical properties (^{1}H NMR, ^{13}C NMR, m.p., IR, MS) are consistent with those reported in the literature.[19]

2-Chloro-6-methoxyisonicotinic Acid (6):[20] A mixture of NaOMe (52.2 mmol) and 2,6-dichloroisonicotinic acid (**5**) (5.0 g, 26.1 mmol) in dry MeOH (20 mL) was refluxed for 6 h. The solution was hydrolyzed with water (5 mL). The solvent was removed under reduced pressure and H_2O (50 mL) was added to the residue. The solution was acidified with 2 N HCl (200 mL) and the resulting solid was filtered. This was dried in vacuo to give **6** (4.65 g, 95%) as a pale brown solid. The spectroscopic and physical properties (^{1}H NMR, ^{13}C NMR, m.p., IR, MS) are consistent with those reported in the literature.[20]

2-Chloro-4-hydroxymethyl-6-methoxypyridine (7): Borane−methyl sulfide (1.11 mL, 11.7 mmol) was added to a solution of **6** (2.0 g, 10.7 mmol) trimethyl borate (3 mL) in dry THF (6 mL) under argon over a period of 30 min. The reaction mixture was stirred at room temperature for 16 h. MeOH (10 mL) was then added over a period of 10 min. After stirring for 30 min, the solution was concentrated to dryness in vacuo. The residue was purified by silica gel column chromatography using EtOAc as eluent to give **7** (1.60 g, 86%) as a pale brown solid. M.p. 92−93 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.80 (s, 3 H, OCH_3), 4.46 (d, $^{3}J_{\mathrm{H,H}}$ = 5.1 Hz, 2 H, CH_2), 5.59 (t, $^{3}J_{\mathrm{H,H}}$ = 5.4 Hz, 1 H, OH), 6.71 (s, 1 H, 3-H), 6.97 (s, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 54.1 (OCH_3), 61.2 (CH_2), 106.0 (C-3), 114.2 (C-5), 147.3 (C-2), 158.8 (C-4), 163.8 (C-6) ppm. IR (KBr): $\tilde{\nu}$ = 3244 (O−H), 2953, 1611, 1561, 1460, 1392, 1174, 1045 (CH_2−O), 866, 840, 668 cm^{-1}. MS (70 eV): *m*/*z* (%) = 173 (77) [M$^+$], 172 (100) [M$^+$] , 143 (55) [M$^+$ − HCO], 80 (46), 39 (48). $C_7H_8ClNO_2$ (173.60): calcd. C 48.43, H 4.64, N 8.07; found C 48.27, H 4.74, N 8.32.

4-Bromomethyl-2-chloro-6-methoxypyridine (3): A mixture of CBr_4 (1.34 g, 4.00 mmol) and PPh_3 (1.06 g, 4.00 mmol) in dry benzene (5 mL) was stirred under argon for 10 min. **7** (0.5 g, 2.90 mmol) was added in small portions over a period of 15 min, and the solution stirred at room temperature for 16 h. The precipitate was filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography using EtOAc as eluent to give **3** (0.68 g, 98%) as a pale brown solid. M.p. 51−51.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 4.21 (s, 2 H, CH_2), 6.57 (s, 1 H, 3-H), 6.85 (s, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4 (CH_2), 54.2 (OCH_3), 109.0 (C-3), 116.4 (C-5), 148.8 (C-2), 151.0 (C-4), 164.1 (C-6) ppm. IR (KBr): $\tilde{\nu}$ = 2955, 2359, 1602, 1557, 1468, 1389, 1328, 1181, 1131, 1043, 848 (C−Cl) cm^{-1}. MS (70 eV): *m*/*z* (%) = 237 (82) [M$^+$], 236 (100) [M$^+$], 235 (69) [M$^+$], 234 (74) [M$^+$], 156 (84) [M$^+$ − Br], 126 (58) [M$^+$ − Br − OCH_3], 51 (89). $C_7H_7BrClNO$ (236.49): calcd. C 35.55, H 2.98, N 5.92; found C 35.93, H 3.24, N 5.48.

(2*R*,5*S*)-5-[(2-Chloro-6-methoxy-4-pyridyl)methyl]-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (2): A solution of *n*-butyllithium in hexane (1.6 M, 1.45 mL, 2.32 mmol) was added at −78 °C to a stirred solution of the bis(lactim) ether (*R*)-(−)-**8** (0.39 g, 2.11 mmol) in dry toluene (10 mL). After 15 min, a solution of **3** (0.5 g, 2.11 mmol) in dry toluene (5 mL) was added over a period of 3 h. After stirring at −78 °C for 16 h, saturated NH_4Cl solution (30 mL) was added and the solution was warmed up to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (100:1) as eluent to give **2** (0.60 g, 84%) as a pale yellow oil in diastereomerically pure form. $[\alpha]_{\mathrm{D}}^{23}$ = +41.6 (*c* = 1.2, EtOH). Ratio of diastereomers before purification: 91:9, as determined by ^{1}H NMR spectroscopy. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.58 (d, $^{3}J_{\mathrm{H,H}}$ = 6.6 Hz, 3 H, $CHCH_3$), 0.92 (d, $^{3}J_{\mathrm{H,H}}$ = 6.6 Hz, 3 H, $CHCH_3$), 2.13 (dsept, $^{3}J_{\mathrm{H,H}}$ = 3.1 Hz, 1 H, $CHCH_3$), 2.94 (dd, $^{3}J_{\mathrm{H,H}}$ = 5.9, $^{2}J_{\mathrm{H,H}}$ = 12.9 Hz, 2 H, CH_2), 3.60 (s, 3 H, OCH_3), 3.61−3.64 (m, 1 H, 2-H), 3.65 (s, 3 H, OCH_3), 3.82 (s, 3 H, py-OCH_3), 4.19 (m, 1 H, 5-H), 6.37 (s, 1 H, py-3-H), 6.66 (s, 1 H, py-5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5 (CH_3), 18.9 (CH_3), 31.7 [$CH(CH_3)_2$], 39.0 (CH_2), 52.4 (OCH_3), 52.5 (OCH_3), 53.9 (py-OCH_3), 55.5 (C-2), 60.7 (C-5), 110.0 (py-C-3), 118.1 (py-C-5), 147.6 (py-C-2), 152.3 (py-C-4), 161.8 and 163.6 (C=N), 164.2 (py-C-6) ppm. IR (film): $\tilde{\nu}$ = 2945, 1695 (C=N), 1605, 1551, 1461, 1391, 1312, 1240, 1171, 1050, 1015 cm^{-1}. MS (70 eV): *m*/*z* (%) = 339 (23) [M$^+$], 296 (48) [M$^+$ − $CH(CH_3)_2$], 183 (100) [$C_9H_{15}N_2O_2^+$], 157 (43) [$C_7H_7ClNO^+$], 141 (71) [$C_6H_8N_2O_2^+$]. $C_{16}H_{22}ClN_3O_3$ (339.82): calcd. C 56.55, H 6.53, N 12.37; found C 56.99, H 6.36, N 12.28.

(2*R*,5*S*)-5-[(1-Ethoxyvinyl-6-methoxy-4-pyridyl)methyl]-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (9): A solution of **2** (1.34 g, 3.95 mmol), tributyl(α-ethoxyvinyl)tin (1.57 g, 4.34 mmol) and tetrakis(triphenylphosphane)palladium(0) (0.15 g, 0.01 mmol) in deoxygenated toluene (25 mL) was refluxed for 72 h. The solvent was removed, and the crude product was treated with H_2O (5 mL) and then extracted with diethyl ether (3 × 20 mL). Removal of the solvent under reduced pressure afforded a crude product which was purified by silica gel column chromatography using petroleum ether/EtOAc (10:1) as eluent to give **9** (1.29 g, 87%) as a colorless oil. $[\alpha]_{\mathrm{D}}^{23}$ = +43.1 (*c* = 1.02, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61 (d, $^{3}J_{\mathrm{H,H}}$ = 6.6 Hz, 3 H, $CHCH_3$), 0.94 (d, $^{3}J_{\mathrm{H,H}}$ = 6.6 Hz, 3 H, $CHCH_3$), 1.38 (t, $^{3}J_{H,H}$ = 7.0 Hz, 3 H, CH_3CH_2O), 2.13 (dsept, $^{3}J_{H,H}$ = 3.5 Hz, 1 H, $CHCH_3$), 3.01 (d, $^{3}J_{H,H}$ = 4.7 Hz, 2 H, CH_2), 3.56 (t, $^{3}J_{H,H}$ = 3.5 Hz, 1 H, 2-H), 3.66 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.88 (s, 3 H, py-OCH_3), 3.90 (q, $^{3}J_{H,H}$ = 7.0 Hz, 2 H, CH_3CH_2O), 4.26 (s, 1 H, $C{=}CH_{(Z)}H$), 4.29 (q, $^{3}J_{H,H}$ = 4.7 Hz, 1 H, 5-H), 5.40 (s, 1 H, $C{=}CH_{(E)}H$), 6.43 (s, 1 H, py-3-H), 7.10 (s, 1 H, py-5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_3CH_2O), 16.5 (CH_3), 18.9 (CH_3), 31.5 [$CH(CH_3)_2$], 39.3 (CH_2), 52.2 and 52.4 (OCH_3), 53.0 (py-OCH_3), 55.7 (C-2), 60.5 (C-5), 63.2 (CH_3CH_2O), 83.9 ($C{=}CH_2$), 111.5 (py-C-3), 114.0 (py-C-5), 149.7 (py-C-2), 149.8 (py-C-4), 158.7 (C=N), 161.9 (C=N), 162.9 (py-C-6), 163.9 ($C{=}CH_2$) ppm. IR (CCl_4): $\tilde{\nu}$ = 2944, 1696 (C=COR), 1604, 1462, 1438, 1393, 1371, 1313, 1286, 1240, 1198, 1174, 1054 cm^{-1}. MS (70 eV): *m*/*z* (%) = 375 (61) [M^+], 360 (50) [$M^+ - CH_3$], 332 (36) [$M^+ - CH(CH_3)_2$], 193 (100) [$C_{11}H_{14}NO_2^+$], 141 (99) [$C_6H_8N_2O_2^+$]. $C_{20}H_{29}N_3O_4$ (375.46): calcd. C 63.98, H 7.79, N 11.19; found C 64.05, H 7.27, N 11.35.

(2*R*,5*S*)-5-[(2-Ethoxycarbonyl-6-methoxy-4-pyridyl)methyl]-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (10): Ozonized oxygen was bubbled through a cooled solution (−78 °C) of (1-ethoxyvinyl)pyridine **9** (0.26 g, 0.70 mmol) and a few milligrams of Sudan III in CH_2Cl_2 (25 mL) until the red colour disappeared. Dimethyl sulfide (0.09 g, 1.40 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. Solvent removal in vacuo gave a crude product which was purified by chromatography using petroleum ether/EtOAc (10:1) as eluent to give **10** (0.18 g, 69%) as a colorless oil. $[\alpha]_D^{23}$ = +30.7 (*c* = 0.99, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61 (d, $^{3}J_{H,H}$ = 6.8 Hz, 3 H, $CHCH_3$), 0.93 (d, $^{3}J_{H,H}$ = 7.0 Hz, 3 H, $CHCH_3$), 1.37 (t, $^{3}J_{H,H}$ = 7.0 Hz, 3 H, CH_3CH_2O), 2.13 (dsept, $^{3}J_{H,H}$ = 3.5 Hz, 1 H, $CHCH_3$), 3.06 (dd, $^{3}J_{H,H}$ = 5.8, $^{2}J_{H,H}$ = 12.9 Hz, 2 H, CH_2), 3.57 (t, $^{3}J_{H,H}$ = 3.4 Hz, 1 H, 2-H), 3.64 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.95 (s, 3 H, py-OCH_3), 4.27 (q, $^{3}J_{H,H}$ = 4.4 Hz, 1 H, 5-H), 4.31 (q, $^{3}J_{H,H}$ = 7.0 Hz, 2 H, CH_3CH_2O), 6.66 (d, $^{4}J_{H,H}$ = 1.2 Hz, 1 H, py-3-H), 7.53 (d, $^{4}J_{H,H}$ = 0.8 Hz, 1 H, py-5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (CH_3CH_2O), 16.5 (CH_3), 18.9 (CH_3), 31.6 [$CH(CH_3)_2$], 39.1 (CH_2), 52.3 (OCH_3), 52.4 (OCH_3), 53.5 (OCH_3), 55.5 (C-5), 60.6 (C-2), 61.4 (CH_3CH_2O), 115.7 (py-C-3), 121.0 (py-C-5), 144.7, 150.3, 161.7, 163.9, 164.2, 165.3 ppm. IR (CCl_4): $\tilde{\nu}$ = 2961, 1744, 1719, 1701, 1616, 1564, 1440, 1373, 1244 (C-OR), 1057 cm^{-1}. MS (70 eV): *m*/*z* (%) = 377 (40) [M^+], 334 (54) [$M^+ - CH(CH_3)_2$], 195 (99) [$C_{10}H_{12}NO_3^+$], 183 (97) [$C_9H_{15}N_2O_2^+$], 141 (100) [$C_6H_8N_2O_2^+$], 122 (59) [$C_7H_7NO^+$]. $C_{19}H_{27}N_3O_5$ (377.43): calcd. C 60.46, H 7.21, N 11.13; found C 60.15, H 7.03, N 11.00.

4-[(2-Ethoxycarbonyl-6-methoxy-4-pyridyl)methyl]-L-alanine Methyl Ester (11): 0.5 N HCl (1 mL) was added to a stirred solution of **10** (80.4 mg, 0.21 mmol) in MeCN (5 mL). The reaction mixture was stirred at room temperature for 45 min. The solvent was removed under reduced pressure, CH_2Cl_2 (5 mL) was added to the residue, and the solution was adjusted to pH = 9 by the addition of concd. ammonia. Solvent removal in vacuo gave a crude yellow oil which was purified by chromatography using petroleum ether/EtOAc (1:500) as eluent to give **11** (51.7 mg, 86%) as a pale yellow solid. $[\alpha]_D^{23}$ = −2.9 (*c* = 0.72, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, $^{3}J_{H,H}$ = 7.4 Hz, 3 H, CH_3CH_2O), 1.71 (br. s, 2 H, NH_2), 2.83 (dd, $^{3}J_{H,H}$ = 5.5, $^{2}J_{H,H}$ = 13.3 Hz, 1 H, CH_2), 3.06 (dd, $^{3}J_{H,H}$ = 5.1, $^{2}J_{H,H}$ = 13.7 Hz, 1 H, CH_2), 3.72 (s, 3 H, CO_2CH_3), 3.69−3.76 (m, 1 H, $CHNH_2$), 3.98 (s, 3 H, py-OCH_3), 4.38 (q, $^{3}J_{H,H}$ = 7.4 Hz, 2 H, CH_3CH_2O), 6.75 (s, 1 H, py-3-H), 7.54 (s, 1 H, py-5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (CH_3CH_2O), 40.1 (CH_2), 52.3 (CO_2CH_3), 53.7 (py-OCH_3), 54.9 (NH_2CH), 61.3 (CH_3CH_2O), 115.3 (py-C-3), 119.7 (py-C-5), 145.8 (py-C-2), 149.9 (py-C-4), 164.3 (py-C-6), 165.1 (py-CO_2), 174.8 (NH_2CHCO_2) ppm. IR (CCl_4): $\tilde{\nu}$ = 2963, 1745 (CO_2R), 1717 (CO_2R), 1613, 1461, 1371, 1355, 1253, 1178, 1057, 1029 cm^{-1}. MS (70 eV): *m*/*z* (%) = 282 (5) [M^+], 223 (66) [$M^+ - CO_2CH_3$], 195 (94) [$M^+ - C_3H_6NO_2$], 177 (23) [$M^+ - CO_2CH_2CH_3 - OCH_3$], 149 (100) [$M^+ - CO_2CH_2CH_3 - CO_2CH_3$], 121 (49) [$M^+ - CO_2CH_2CH_3 - C_3H_6NO_2$], 88 (38) [$C_3H_6NO_2^+$]. $C_{13}H_{18}N_2O_5$ (282.29): calcd. C 55.31, H 6.43, N 9.92; found C 55.15, H 6.78, N 9.55.

3-(6-Carboxy-2-oxo-4-pyridyl)-L-alanine [(*S*)-(−)-Acromelobic Acid] (1): A solution of **11** (0.03 g, 0.11 mmol) and LiOH (0.06 g, 1.59 mmol) in MeOH/H_2O (3:1, 5 mL) was stirred at room temperature for 16 h. The reaction mixture was neutralized with 2 N HCl and the solvent was removed in vacuo. The residue was dissolved in $CHCl_3$ (5 mL), treated with TMSI (0.11 g, 0.53 mmol) and refluxed for 16 h. After addition of MeOH (20 mL), the solution was refluxed for a further 16 h. Solvent removal in vacuo and purification of the crude compound by DOWEX® MAC-3 ion exchange resin using water as eluent followed by DOWEX® Retardion® 11A8 resin chromatography and lyophilization afforded (*S*)-(−)-acromelobic acid (**1**, 0.02 g, 71%) as a pale yellow solid. $[\alpha]_D^{23}$ = −133.1 (*c* = 0.051, H_2O). ^{1}H NMR (600 MHz, D_2O): δ = 3.09 (dd, $^{3}J_{H,H}$ = 7.7, $^{2}J_{H,H}$ = 14.5 Hz, 1 H, CH_2), 3.22 (dd, $^{3}J_{H,H}$ = 5.9, $^{2}J_{H,H}$ = 14.5 Hz, 1 H, CH_2), 4.18 (dd, $^{3}J_{H,H}$ = 5.9, $^{3}J_{H,H}$ = 7.8 Hz, 1 H, $CHNH_2$), 6.75 (s, 1 H, py-3-H), 7.05 (s, 1 H, py-5-H) ppm. ^{13}C NMR (150 MHz, D_2O): δ = 35.1 (CH_2), 52.8 (NH_2CH), 111.4 (py-C-3), 122.7 (py-C-5), 137.2 (py-C-2), 150.9 (py-C-4), 163.6 (py-C-6), 164.0 (CO_2H), 171.2 (CO_2H) ppm. IR (KBr): $\tilde{\nu}$ = 3181, 3174, 3169, 3167, 3163, 1620 cm^{-1}. UV: λ_{max} (H_2O) = 225 and 310 nm. $C_9H_{10}N_2O_5$ (226.19): calcd. C 47.79, H 4.46, N 12.39; found C 47.92, H 4.23, N 12.08.

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[1] A. F. Parsons, *Tetrahedron* **1996**, *52*, 4149−4174.
[2] K. Yamano, K. Hashimoto, H. Shirahama, *Heterocycles* **1992**, *34*, 445−448.
[3] K. Yamano, H. Shirahama, *Tetrahedron* **1993**, *49*, 2427−2436.
[4] J. E. Baldwin, M. R. Spyvee, R. C. Whitehead, *Tetrahedron Lett.* **1994**, *35*, 6575−6576.
[5] [5a] M. Adamczyk, S. R. Akireddy, R. E. Reddy, *Org. Lett.* **2000**, *2*, 3421−3423. [5b] M. Adamczyk, S. R. Akireddy, R. E. Reddy, *Tetrahedron: Asymmetry* **2001**, *12*, 2385−2387. [5c] M. Adamczyk, S. R. Akireddy, R. E. Reddy, *Tetrahedron* **2002**, *58*, 6951−6963.
[6] For a review, see: R. M. Williams, *Synthesis of optically active α-amino acids*, Pergamon Press, New York, **1989**, p. 1 ff.
[7] C. Ma, X. Liu, X. Li, J. Flippen-Anderson, S. Yu, J. M. Cook, *J. Org. Chem.* **2001**, *66*, 4525−4542.
[8] V. Ojea, M. Ruiz, G. Shapiro, E. Pombo-Villar, *J. Org. Chem.* **2000**, *65*, 1984−1995.
[9] P. Dalla Croce, C. La Rosa, E. Pizzatti, *Tetrahedron: Asymmetry* **2000**, *11*, 2635−2642.

[10] B. Löhr, S. Orlich, H. Kunz, *Synlett* **1999**, 1139−1141.

[11] M. Adamczyk, J. R. Fishpaugh, M. Thiruvazhi, *Tetrahedron: Asymmetry* **1999**, *10*, 4151−4156.

[12] H. Shinohara, T. Fukuda, M. Iwao, *Tetrahedron* **1999**, *55*, 10989−11000.

[13] A. Sutherland, J. C. Vederas, *Chem. Commun.* **1999**, 1739−1740.

[14] U. Groth, U. Schöllkopf, T. Tiller, *Liebigs Ann. Chem.* **1991**, 857−860.

[15] U. Groth, W. Halfbrodt, U. Schöllkopf, *Liebigs Ann. Chem.* **1992**, 351−355.

[16] T. Beulshausen, U. Groth, U. Schöllkopf, *Liebigs Ann. Chem.* **1992**, 523−526.

[17] U. Schöllkopf, U. Groth, C. Deng, *Angew. Chem.* **1981**, *93*, 793−795; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 798−799.

[18] J. K. Stille, *Angew. Chem.* **1986**, *98*, 504−519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508−523.

[19] K. E. Henegar, S. W. Ashford, T. A. Baughman, J. C. Sih, R.-L. Gu, *J. Org. Chem.* **1997**, *62*, 6588−6597.

[20] Y. Okajima, I. Seki, *Yakugaku Zasshi* **1953**, *73*, 845−847.

[21] U. Schöllkopf, *Pure Appl. Chem.* **1983**, *55*, 1799−1806.

[22] U. Schöllkopf, *Top. Curr. Chem.* **1983**, *109*, 65−84.

[23] E. M. Carreira, J. Du Bois, *J. Am. Chem. Soc.* **1994**, *116*, 10825−10826.

[24] E. M. Carreira, J. Du Bois, *J. Am. Chem. Soc.* **1995**, *117*, 8106−8125.

[25] U. Schöllkopf, U. Groth, K. O. Westphalen, C. Deng, *Synthesis* **1981**, 969−971.

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