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A new approach for the asymmetric synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid

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ABSTRACT

An efficient stereoselective synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid was achieved from (*S*)-glutamic acid via the furylation of an N-protected 6-hydroxy-2-piperidinone using furan as a nucleophile and the oxidation of the furyl group to a carboxylic group as the key steps.

1. Introduction

Chiral hydroxylated piperidines are important core structures that can be found in many bioactive natural and non-natural compounds. These compounds have received considerable attention on account of their many pharmacological properties.[1] 3-Hydroxypipecolic acid is an interesting natural compound since it may be seen as a conformationally constrained serine derivative, or a hydroxylated homoproline,[2] and has shown inhibitory activity against β-*N*-acetylglucosaminidase as well as *Escherichia coli* β-glucuronidase.[3] Moreover, this 3-hydroxypiperidine unit is found in a number of biologically important products. For example, the *cis*-isomer **1** forms a part of the structure of tetrazomine **3**,[4] an antitumor antibiotic, while the *trans*-isomer **2** is a precursor of (−)-swainsonine **4**, which has shown potent and specific α-D-mannosidase inhibitory activity,[5] and can be found in the structure of febrifugine **5**, a potent antimalarial agent. In addition, 3-hydroxypiperidine unit also is found in polyhydroxylated nitrogen heterocycles (azasugars) representing sugar analogues. Many of these azasugars, which are frequently inhibitors of carbohydrate-processing enzymes, have the potential for use in a wide range of potential therapeutic strategies including the treatment of viral infections, cancer, diabetes, tuberculosis, and lysosomal storage diseases, as well as being inhibitors of the growth of parasitic protozoa (Fig. 1).[6]

Recently, we have shown that protected (*S*)-3-hydroxyglutarimides **7** and **8** (P = PMB, Bn) were versatile building blocks for the asymmetric synthesis of 3-hydroxy and 3-amino-piperidines.[7] Starting from **7** and **8**, different methods have been developed for establishing (2*S*,3*S*)-, (2*R*,3*R*)- or (2*R*,3*S*)-stereochemistry of 2-substituted 3-hydroxypiperidines.[8]

In continuation of our interest in the amino acid chiral template-assisted synthesis of natural and non-natural bioactive compounds, as a part of our research program aimed at developing enantioselective syntheses of naturally occurring bioactive compounds, we decided to explore the introduction of the carboxyl group at the C-2 of **8** and we became interested in developing a simple and feasible route to 3-hydroxypipecolic acid.[9] Herein, we report an enantioselective synthesis of **2** employing the furylation and oxidation of a furyl group to a carboxylic group as the key steps.

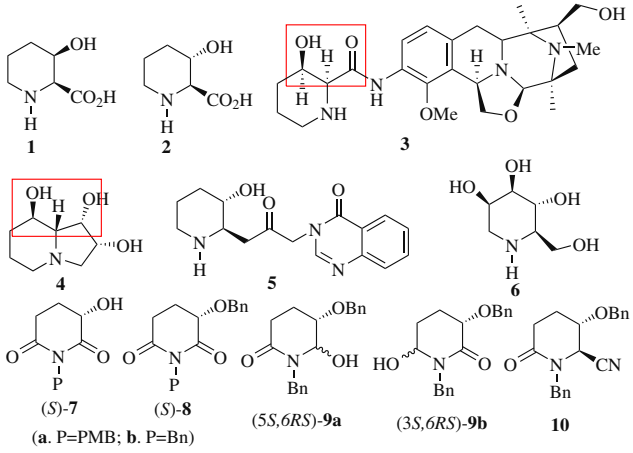

Figure 1.

2. Results and discussion

The requisite (*S*)-3-benzyloxyglutarimide **8** (P = Bn) was prepared essentially by the known procedure from inexpensive commercially available (*S*)-glutamic acid in 57% yield (three steps).[8a] Controlled reduction of (*S*)-**8** with sodium borohydride (MeOH, CH_2Cl_2, 0.5 h, −15 °C) led to the formation of both C-2 and C-6

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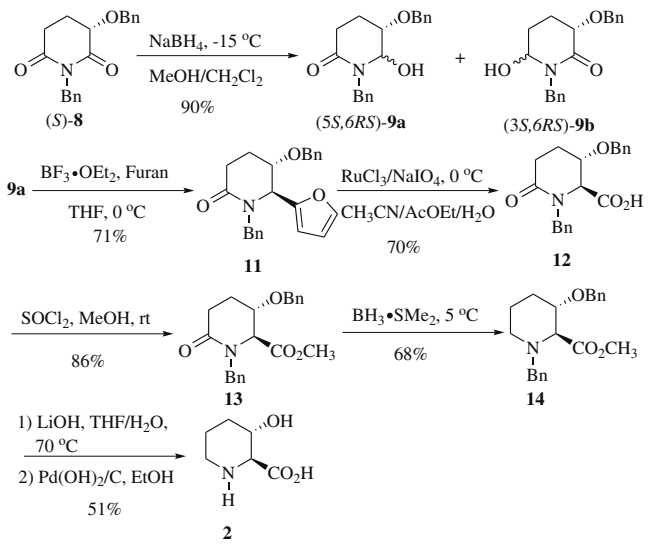
partially reduced products **9a** and **9b** in a 95:5 ratio with a combined yield of 90% (Scheme 1).



Scheme 1.

With **9a** in hand, two routes to the 6-carboxyl-2-piperidinone were possible. Considering the corresponding amide could be obtained when **10** being hydrolyzed,[10] the oxidation of the furyl group to a carboxyl group with $RuCl_3/NaIO_4$ was initially tried. Initially, we introduced the furyl group in **11**. Treatment of **9a** with furan and borontrifluoride etherate in THF at rt for 12 h led to the **11** in 65% yield, but the diastereoselectivity was low [(5*S*,6*S*)-**11**/(5*S*,6*R*)-**11** diastereoselective ratio: ~1:1]. After several unsuccessful attempts, including using Me_3SiCl as a Lewis acid, we were delighted to find that the reaction at lower temperature provided a better result. Compound **9a** was treated with furan and borontrifluoride etherate in THF at 0 °C for 24 h, the desired product **11** was obtained in 71% yield as a 80:20 mixture of diastereomers (determined by ^1H NMR analysis). The stereochemistry of the major diastereomer **11** was assigned as *trans*-**11**, according to the observed small vicinal coupling constants ($J_{5,6}$ = 1.0 Hz),[8] which was further confirmed by converting **11** to the known compound **2**. Since the major stereomer (5*S*,6*S*)- and minor (5*S*,6*R*)-piperidinone **11** which could only be separated partly by column chromatography while the *cis*-ester **14** could only be inverted partly to the corresponding diastereomer *trans*-ester **14** under basic conditions, the diastereomeric mixture was used directly without further separation in the next step. Oxidation of **11** with $RuCl_3/NaIO_4$ in a mixture of $CH_3CN/EtOAc/H_2O$ in a ratio of 4.5/4.5/2 at 0 °C for 5 min afforded **12** in 70% yield. Its vicinal coupling constants ($J_{5,6}$ = 1.2 Hz) is consistent with (5*S*,6*S*)-**11** ($J_{5,6}$ = 1.0 Hz).

With the 2-piperidinone-6-carboxylic acid **12** in hand, the esteration of **12** with $SOCl_2$/MeOH proceeded easily to afford ester **13** in 86% yield. Use of the borane dimethyl sulfide complex as reductant led to piperidine-2-carboxylic acid methyl ester **14** in 68% yield.

Methyl ester **14** was hydrolyzed under basic conditions (LiOH, THF, H_2O, 70 °C, 3 h) to afford the corresponding acid. It is fortunate that the minor protected (5*S*,6*R*)-piperidine-2-carboxylic acid or its ester could be inverted partly to corresponding diastereomer (5*S*,6*S*)-piperidine-2-carboxylic acid or its ester under basic conditions. Finally, deprotection afforded the desired (2*S*,3*S*)-3-hydroxypipecolic acid **2** {mp 228–235 °C; lit.[11] mp 230–238 °C. $[\alpha]_D^{25} = +13.3$ (*c* 0.7, 10% aq HCl); lit.[11] $[\alpha]_D^{20} = +12.9$ (*c* 0.23, 10% aq HCl)} in 51% yield (two steps).

3. Conclusion

In conclusion, we have described a concise and straightforward asymmetric synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid **2** using a versatile chiral building block (*S*)-3-hydroxyglutarimide **8**. The overall yield of **2** from (*S*)-glutamic acid was 13.3%. Piperidinone **11** should be useful as a chiral building block for the synthesis of piperidine-related alkaloids, especially polyhydroxylated nitrogen heterocycles (azasugars) representing sugar analogues.

4. Experimental

4.1. General

Melting points were determined on a Yanaco MP-500 micro melting point apparatus and are uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker 400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by a Bruker Dalton ESquire 3000 plus liquid chromatography–mass spectrum (direct injection). Optical rotations were measured with Perkin–Elmer 341 automatic polarimeter. Flash column chromatography was carried out with silica gel (300–400 mesh). THF was distilled over sodium benzophenone ketyl under N_2.

4.2. (5*S*,6*RS*)-1-Benzyl-5-benzyloxy-6-hydroxy-2-piperidinone 9a

To a cooled solution of **8** (1.28 g, 4.14 mmol) in $MeOH/CH_2Cl_2$ (3:1, 40 mL) was added $NaBH_4$ (0.47 g, 12.37 mmol). After being stirred for 30 min, the reaction mixture was quenched by the successive addition of saturated aqueous $NaHCO_3$ (15 mL) and brine (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (eluent: EtOAc/PE = 1:2) to give 1.11 g of *cis*-**9a** and *trans*-**9a** (combined yield 86%). Major diastereoisomer: White solid. Mp 135–137 °C (EtOAc/PE = 1:1). $[\alpha]_D^{20} = -29.8$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3183, 2864, 1604, 1478, 1454 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.78 (dddd, *J* = 15.6, 6.6, 5.8, 3.3 Hz, 1H, H-4), 2.16 (dddd, *J* = 15.6, 9.7, 9.0, 5.8 Hz, 1H, H-4), 2.36 (ddd, *J* = 17.8, 9.0, 6.6 Hz, 1H, H-3), 2.60 (ddd, *J* = 17.8, 5.8, 5.8 Hz, 1H, H-3), 3.61 (ddd, *J* = 9.4, 3.4, 3.3 Hz, 1H, H-5), 3.96 (d, *J* = 6.0 Hz, 1H, OH), 4.18 (d, *J* = 14.8 Hz, 1H, NCH_2), 4.46 (d, *J* = 11.7 Hz, 1H, OCH_2), 4.55 (d, *J* = 11.7 Hz, 1H, OCH_2), 4.81 (dd, *J* = 6.0, 3.4 Hz, 1H, H-6), 5.20 (d, *J* = 14.8 Hz, 1H, NCH_2), 7.13–7.35 (m, 10H, Ph–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.59 (C-4), 28.65 (C-3), 46.42 (NCH_2), 70.76, 73.53, 78.07 (C-6), 127.08, 127.57 (2C), 127.86, 127.95 (2C), 128.34 (2C), 128.35 (2C), 137.10, 137.25, 169.68 (C=O). MS (ESI): 312 (M^++1, 10), 334 (M^++23, 100). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.16; H, 6.52; N, 4.09. Regioisomer **9b** (57 mg, 4%): White crystal. Mp 67–70 °C (EtOAc/PE = 1:1). $[\alpha]_D^{20} = -83.5$ (*c* 1.1, $CHCl_3$). IR (film) ν_{max}: 3316, 2930, 1620, 1496, 1454 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.85–1.95 (m, 1H, H-5), 2.15–2.36 (m, 1H, H-5), 2.33 (ddd, *J* = 17.9, 4.5, 1.7 Hz, 1H, H-4), 2.62 (ddd, *J* = 17.9, 6.8, 5.1 Hz, 1H, H-4), 3.65 (dd, *J* = 4.3, 2.2 Hz, 1H, H-3), 4.13 (d, *J* = 15.4 Hz, 1H, NCH_2), 4.31 (d, *J* = 11.7 Hz, 1H, OCH_2), 4.41 (d, *J* = 11.7 Hz, 1H, OCH_2), 4.80–4.88 (m, 1H, H-6), 5.18 (d, *J* = 15.4 Hz, 1H, NCH_2), 5.26 (s, 1H, OH), 7.13–7.35 (m, 10H, Ph–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.21, 27.27, 46.78 (NCH_2), 70.52, 74.22, 79.72 (C-6), 127.08, 127.52 (2C), 127.97 (2C), 128.23 (2C), 128.38 (2C), 128.56 (2C), 128.69, 137.03,

137.82, 170.80 (C=O). MS (ESI): 312 (M^++1, 5), 334 (M^++23, 100). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 72.96; H, 6.84; N, 4.43.

4.3. (5*S*,6*S*)-1-Benzyl-5-benzyloxy-6-(2-furyl)-2-piperidinone 11

To a stirred solution of **9a** (190 mg, 0.61 mmol) and furan (0.22 mL, 3.05 mmol) in anhydrous THF (5 mL) at 0 °C under a nitrogen atmosphere was added borontrifluoride etherate (0.23 mL, 1.85 mmol) dropwise. After being stirred for 24 h at that temperature, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution (5 mL) and H_2O (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine and dried over Na_2SO_4. Solvent was removed under vacuum, and the residue was purified by flash column chromatography (EtOAc/hexane = 1:6) to yield **11** (156 mg, 71%) as a colorless oil. $[\alpha]_D^{25} = -54.9$ (c 0.8, $CHCl_3$). IR (neat) ν_{max}: 3030, 2929, 1656, 1453, 1070 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.96 (dddd, J = 18.3, 7.2, 4.5, 2.5 Hz, 1H, H-4), 2.05 (dddd, J = 18.3, 8.9, 6.8, 2.1 Hz, 1H, H-4), 2.53 (ddd, J = 17.9, 8.9, 2.5 Hz, 1H, H-3), 2.79 (ddd, J = 17.9, 7.2, 6.8 Hz, 1H, H-3), 3.58 (d, J = 15.3 Hz, 1H, NCH_2), 3.86 (ddd, J = 4.5, 2.1, 1.0 Hz, 1H, H-5), 4.36 (d, J = 11.7 Hz, 1H, OCH_2), 4.42 (d, J = 11.7 Hz, 1H, OCH_2), 4.64 (d, J = 1.0 Hz, 1H, H-6), 5.62 (d, J = 15.3 Hz, 1H, NCH_2), 6.21 (d, J = 3.2Hz, 1H), 6.36 (dd, J = 3.2, 1.9 Hz, 1H), 7.16–7.34 (m, 10H, Ph–H), 7.36 (d, J = 1.9Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.26, 27.32, 47.59 (NCH_2), 57.59 (OCH_2), 70.42, 73.81, 108.18, 110.51, 127.26 (2C), 127.32, 127.67, 127.87 (2C), 128.37 (2C), 128.54 (2C), 136.83, 137.77, 142.66, 151.88, 169.96 (C=O). MS (ESI): 362 (M^++1, 100). Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.86; H, 6.71; N, 4.01.

4.4. (5*S*,6*S*)-1-Benzyl-5-benzyloxy-2-piperidinone-6-carboxylic acid 12

To an ice-cold solution of $NaIO_4$ (711 mg, 3.32 mmol) in EtOAc (2.5 mL), CH_3CN (4.5 mL) and H_2O (2 mL) was added $RuCl_3$ (0.05 M solution in H_2O, 0.33 mL, 0.017 mmol). After 10 min, piperidinone **11** (120 mg, 0.33 mmol) in EtOAc (2 mL) was added. The resultant mixture was stirred at 0 °C for 5 min and then poured into H_2O, and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. Silica gel column chromatography using EtOAc/MeOH (9:1) as eluent gave **12** (79 mg, 70%) as a waxy solid. $[\alpha]_D^{25} = -109.9$ (c 1.0, $CHCl_3$); IR (film) ν_{max}: 3450, 1693, 1650, 1495, 1450 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ1.85–1.98 (m, 1H, H-4), 1.98–2.07 (m, 1H, H-4), 2.57 (ddd, J = 18.0, 6.4, 1.0 Hz, 1H, H-3), 2.75 (ddd, J = 18.0, 6.8, 4.5 Hz, 1H, H-3), 3.68 (d, J = 15.3 Hz, 1H, NCH_2), 4.07–4.12 (m, 1H, H-5), 4.22 (d, J = 1.2 Hz, 1H, H-6), 4.26 (d, J = 11.6 Hz, 1H, OCH_2), 4.31 (d, J = 11.6 Hz, 1H, OCH_2), 5.68 (d, J = 15.3 Hz, 1H, NCH_2), 7.15–7.35 (m, 10H, Ph–H), 9.30 (br s, 1H, CO_2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.24, 26.70, 49.15 (NCH_2), 61.43 (OCH_2), 70.37, 71.87, 127.37 (2C), 127.58, 127.75, 128.09 (2C), 128.38 (2C), 128.66 (2C), 135.85, 137.38, 171.38 (C=O), 171.73 (C=O). MS (ESI): 340 (M^++1, 100). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.66; H, 6.51; N, 4.15.

4.5. (5*S*,6*S*)-1-Benzyl-5-benzyloxy-2-piperidinone-6-carboxylic acid methyl ester 13

To an ice-cold solution of **12** (300 mg, 0.88 mmol) in dry MeOH (8 mL) was added $SOCl_2$ (0.14 mL, 1.92 mmol). After being stirred for 24 h at room temperature, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL) and H_2O (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine and dried over Na_2SO_4. Solvent was removed under vacuum, and the residue was purified by flash column chromatography (EtOAc/hexane = 1:1) to yield **13** (269 mg, 86%) as a colorless oil. $[\alpha]_D^{20} = -52.9$ (c 2.1, $CHCl_3$). IR (neat) ν_{max}: 2982, 1732, 1641, 1496, 1064 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.88 (ddd, J = 16.4, 4.9, 2.0 Hz, H-4), 2.04 (ddd, J = 16.4, 7.0, 2.0 Hz, H-4), 2.50 (ddd, J = 18.0, 6.9, 2.0 Hz, H-3), 2.75 (ddd, J = 18.0, 7.0, 4.9 Hz, H-3), 3.72 (s, 3H, OCH_3), 3.74 (d, J = 15.2 Hz, 1H, NCH_2), 4.01 (dt, J = 4.4, 2.1 Hz, 1H, H-5), 4.24 (t, J = 2.1 Hz, 1H, H-6), 4.32 (d, J = 11.7 Hz, 1H, OCH_2), 4.37 (d, J = 11.7 Hz, 1H, OCH_2), 5.55 (d, J = 15.2 Hz, 1H, NCH_2), 7.18–7.40 (m, 10H, Ph–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.61, 27.06, 48.84 (NCH_2), 52.71 (OCH_3), 61.72 (OCH_2), 70.35, 72.10, 127.30 (2C), 127.45, 127.75, 128.15 (2C), 128.36 (2C), 128.54 (2C), 136.26, 137.34, 169.72 (C=O), 170.56 (C=O). MS (ESI): 354 (M^++1, 100). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 70.89; H, 6.57; N, 3.78.

4.6. (2*S*,3*S*)-1-Benzyl-3-benzyloxypiperidine-2-carboxylic acid methyl ester 14

To an ice-cold solution of **13** (125 mg, 0.35 mmol) in dry THF (4 mL) was added borane dimethyl sulfide complex (0.10 mL, 1.05 mmol). After being stirred for 24 h at 5 °C, the reaction mixture was quenched by the addition of MeOH (1 mL) and the mixture was stirred for another 4 h at room temperature. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine and dried over Na_2SO_4. Solvent was removed under vacuum, and the residue was purified by flash column chromatography (EtOAc/hexane = 1:8) to yield **14** (81 mg, 68%) as a colorless oil. $[\alpha]_D^{25} = -19.0$ (c 1.5, $CHCl_3$). IR (neat) ν_{max}: 2930, 1745, 1453, 1256, 1152 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25–1.37 (m, 1H), 1.44–1.56 (m, 1H), 1.69 (ddd, J = 17.3, 7.7, 3.9 Hz, 1H), 1.97 (ddd, J = 11.3, 3.0, 3.0 Hz, 1H, H-6), 2.10 (ddd, J = 17.3, 8.1, 4.0 Hz, 1H), 2.84 (ddd, J = 11.3, 3.9, 3.8 Hz, 1H, H-6), 3.05 (d, J = 8.3 Hz, 1H, H-2), 3.33 (d, J = 13.4 Hz, 1H, NCH_2), 3.72 (s, 3H, OCH_3), 3.74 (d, J = 13.4 Hz, 1H, NCH_2), 3.77 (ddd, J = 8.3, 4.2, 4.2 Hz, 1H, H-3), 4.46 (d, J = 11.7 Hz, 1H, OCH_2), 4.59 (d, J = 11.7 Hz, 1H, OCH_2), 7.20–7.40 (m, 10H, Ph–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.28, 28.70, 50.64, 51.77, 60.23, 70.90, 70.94, 76.65, 127.12, 127.53 (2C), 127.63, 128.10 (2C), 128.25 (2C), 129.23 (2C), 137.40, 138.25, 173.05 (C=O). MS (ESI): 340 (M^++1, 100). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.51; H, 7.36; N, 4.52.

4.7. (2*S*,3*S*)-3-Hydroxypipecolic acid 2

To a solution of **14** (200 mg, 0.59 mmol) in THF (9 mL) and H_2O (3 mL) was added $LiOH{\cdot}H_2O$ (125 mg, 2.98 mmol). The reaction mixture was stirred at 70 °C for 3 h. The reaction mixture was neutralized by addition of 10% solution of $KHSO_4$ and diluted with CH_2Cl_2. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to a crude product.

To a mixture of $Pd(OH)_2$/C (110 mg, 20% Pd) in ethanol (5 mL) was added this crude product in EtOH (3 mL). After being stirred at room temperature under an atmosphere of H_2 for 72 h, the mixture was filtered over Celite and concentrated to provide **2** (51 mg, 51%) as a white solid. $[\alpha]_D^{25} = +13.3$ (c 0.7, 10% aq HCl) [lit.[11] $[\alpha]_D^{20} = +12.9$ (c 0.23, 10% aq HCl)]. Mp: 228–235 °C (lit.[11] mp 230–238 °C). IR (film) ν_{max}: 3410, 1685, 1450, 1137 cm^{-1}. ^1H NMR (400 MHz, D_2O): δ 1.60–1.66 (m, 2H), 1.92–1.95 (m. 2H), 2.80–2.95 (m, 1H), 3.80–3.83 (m, 1H), 4.10–4.15 (m, 1H), 4.33 (br s, 1H). ^{13}C NMR (100 MHz, D_2O): δ 20.12, 30.05, 46.46, 62.10,

66.38, 176.46. MS (ESI): 146 (M^++1, 100). HRESIMS calcd for $[C_6H_{11}NO_3+H]^+$: 146.0817; Found: 146.0818.

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