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An enantioselective synthesis of (+)-azimic acid

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ABSTRACT

Herein we report a concise enantioselective synthesis of (+)-azimic acid starting from (5*S*,6*S*)-6-methyl-5-benzyloxy-2-piperidinone **8a**, which was prepared from protected (*S*)-3-hydroxyglutarimide **6** according to a method recently disclosed in our laboratory. The key step is a stepwise regioselective reductive alkylation of the imide **10**, which established the 2,6-*cis*-stereochemistry in excellent diastereoselectivity.

1. Introduction

2,6-Disubstituted piperidin-3-ol **1** represents a characteristic structural feature of many alkaloids,[1] which exhibit a wide range of bioactivities.[1,2] While these alkaloids generally exist as monomers, azimine[3] **2** and carpaine[4] **3** are macrocyclic dilactones, which were isolated, respectively, from *Azima tetracantha* L. and *Carica papaya* L. (Fig. 1). Carpaine **3** was shown to possess interesting antitumor activity.[5] Structurally, azimine **2** and carpaine **3** consist of two 2-methyl-3-piperidinol skeletons with a carboxyl group as a terminal substituent at the C-6 side chain, namely, azimic acid **4** and carpamic acid **5**, respectively. The latter are both ready synthetic precursors[6,7] and presumed biosynthetic precursors of the former. Several methods have been developed for the synthesis of enantio-enriched azimic acid[6,8] **4**, carpamic acid[7,9] **5**, and other 2,6-disubstituted piperidin-3-ol alkaloids, which share the same 'all *cis*' stereochemistry **1**.[10] The synthesis of azimine **2** and carpaine **3** via azimic acid[6] **4** and carpamic acid[6,7] (**5**) in both racemic and enantio-enriched forms has also been reported.

Previously, we have developed the protected (*S*)-3-hydroxyglutarimides **6** as versatile building blocks for the asymmetric synthesis of a variety of 2,6-disubstituted 2,3-*trans*-piperidin-3-ols via *trans*-6-alkyl-5-benzyloxy-2-piperidinone derivatives **7**.[11,12] Recently, this methodology was extended to the synthesis of *cis*-6-alkyl-5-benzyloxy-2-piperidinone derivatives **8** (Scheme 1).[13] Herein we report an application of this new variation to the asymmetric synthesis of (+)-azimic acid **4**.

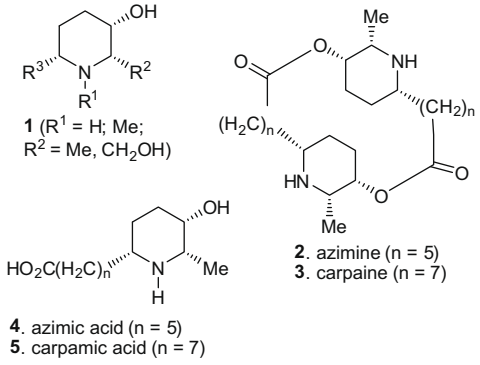
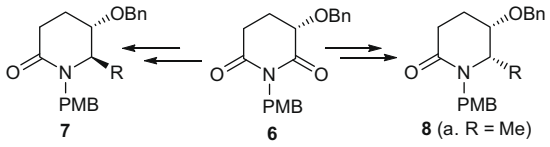


Figure 1. Structures of some 2,6-disubstituted piperidin-3-ol containing alkaloids.



Scheme 1.

2. Results and discussion

Our synthetic route to (+)-azimic acid **4** is outlined in Scheme 2. The synthesis started from the *cis*-6-methyl-5-benzyloxy-2-piperidinone derivative **8a**, which was synthesized from the protected (*S*)-3-hydroxyglutarimide **6** (overall yield: 74%; ds = 80:20) as described in a previous report.[13] Cleavage of the protecting group (PMB) by treatment of **8a** with ceric ammonium nitrate (CAN)

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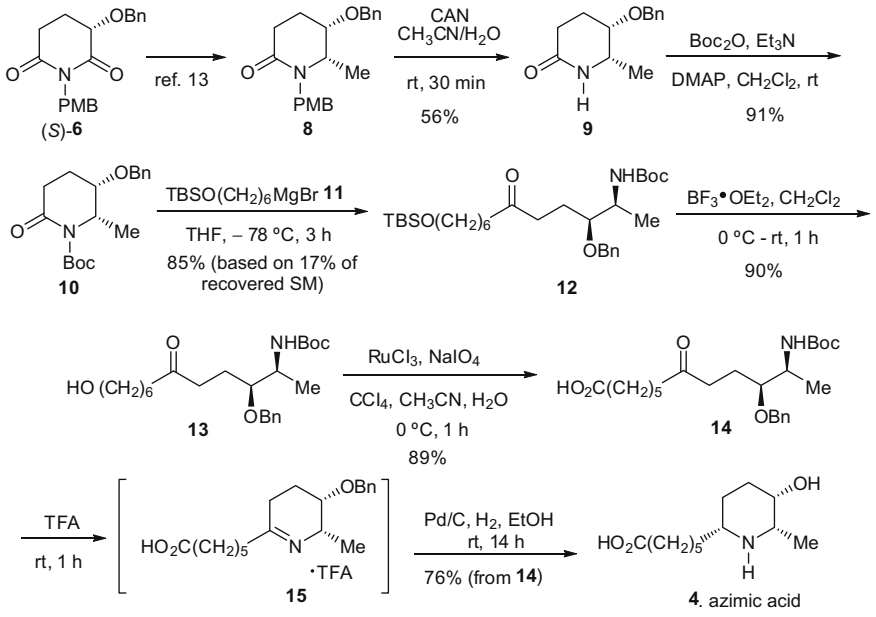

Scheme 2.

(CH_3CN/H_2O = 3:1, rt, 30 min) gave lactam **9** {$[\alpha]_D^{20} = +9.4$ (*c* 0.5, $CHCl_3$)} in 56% yield. Carbamation [$(Boc)_2O$, TEA, DMAP (cat.), rt, overnight] of lactam **9** led to imide **10** {$[\alpha]_D^{20} = +8.9$ (*c* 1.1, $CHCl_3$)} in 91% yield. To introduce the C-6 substituent (numbered based on **4**), the method of Savoia[14a] was employed. Thus treatment of **10** with Grignard reagent **11** (0.5 M in THF) (−78 °C for 2 h, then −50 °C for 40 min) produced the ring-opening product **12** {$[\alpha]_D^{20} = -13.5$ (*c* 0.9, $CHCl_3$)} in 85% yield (based on 17% of the recovered starting material **10**). Desilylation of **12** with $BF_3{\cdot}OEt_2$[11e,15] (CH_2Cl_2, 0 °C–rt, 1 h) produced the desired product **13** {$[\alpha]_D^{20} = -24.6$ (*c* 0.8, $CHCl_3$)} in 90% yield. Selective oxidation of the hydroxyl group in ketol **13** to a carboxylic acid group was achieved with $RuCl_3/NaIO_4$ in CH_3CN–EtOAc–H_2O[16] (2:2:3) at 0 °C for 1 h, which gave the carboxylic acid **14** {$[\alpha]_D^{20} = -15.9$ (*c* 1.0, $CHCl_3$)} in 89% yield.

Finally, treatment of **14** with trifluoroacetic acid (TFA) (rt, 1 h) generated imine **15**, which, was subjected to catalytic hydrogenation (10% Pd/C, H_2, EtOH, rt, 14 h) to give the desired azimic acid **4** as a single isomer in 76% yield over two steps. Both the physical and spectroscopic data of the synthetic product are in accordance with those reported {mp 212–214 °C; lit. mp 214–215 °C;[8f] mp 212–215 °C;[6] $[\alpha]_D^{20} = +7.7$ (*c* 0.5, MeOH); lit. $[\alpha]_D^{20} = +8.0$ (*c* 1.0, MeOH);[8f] $[\alpha]_D^{23} = +7.45$ (*c* 0.49, MeOH)[6]}. The enantiospecificity of the hydrogenation of iminium salt **15** is in agreement with literature precedents.[9e,10b,e,i,k–m]

3. Conclusion

In conclusion, the enantioselective synthesis of (+)-azimic acid **4** was achieved in six steps with 26% overall yield starting from (5*S*,6*S*)-6-methyl-5-benzyloxy-2-piperidinone **8a**, which was easily available from the known protected (*S*)-3-hydroxyglutarimide **6**. By using other Grignard reagents, this method may be extended for the asymmetric synthesis of other piperidine alkaloids such as carpamic acid **5**.

4. Experimental

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 on a Bruker Dalton ESquire 3000 plus liquid chromatography–mass spectrum (direct injection). HRMS spectra were recorded on a Shimadzu LCMS-IT-TOF apparatus. Optical rotations were measured with a Perkin–Elmer 341 automatic polarimeter. Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with an ethyl acetate/petroleum ether (PE) (60–90 °C) mixture. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

4.1. (5*S*,6*S*)-5-Benzyloxy-6-methyl-2-piperidinone 9

To a solution of **8a** (220 mg, 0.65 mmol) in CH_3CN (18 mL) and H_2O (6 mL), prepared as described in a previous paper,[12] was added ceric ammonium nitrate (1.78 g, 3.24 mmol), and the mixture was stirred at room temperature for 30 min. The resulting reaction mixture was diluted with water (30 mL) and extracted with AcOEt (5 × 10 mL). The combined organic layers were washed successively with saturated aqueous sodium bicarbonate (5 × 3 mL), brine (5 mL), then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue and *p*-TsOH (cat.) were resolved in CH_2Cl_2 (15 mL) and the mixture was stirred at room temperature overnight. The resultant mixture was basified with a saturated sodium bicarbonate solution to reach pH 7 and was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/$NH_3{\cdot}H_2O$/MeOH = 100:1:5) to yield the 2-piperidinone **9** (80 mg, yield: 56%) as a colorless oil. $[\alpha]_D^{20} = +9.4$ (*c* 0.5, $CHCl_3$). IR (film) ν_{max}: 3211, 3065, 2927, 1661, 1453, 1405, 1091 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.5 Hz, 3H, CH_3), 1.78 (dddd, *J* = 13.9, 10.7, 6.5, 2.1 Hz, 1H, H-4), 2.16 (dddd, *J* = 13.9, 6.5, 5.7, 3.9 Hz, 1H, H-4), 2.31 (ddd, *J* = 17.6, 6.5, 3.9 Hz, 1H, H-3), 2.50 (ddd, *J* = 17.6, 10.7, 6.5 Hz, 1H, H-3), 3.58–3.66 (m, 2H, H-5 and H-6), 4.48 (d, *J* = 11.9 Hz, 1H, OCH_2), 4.65 (d, *J* = 11.9 Hz, 1H, OCH_2), 5.78 (br s, 1H, NH), 7.20–7.36 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.7, 23.3, 26.6, 51.8 (C-6), 70.6 (OCH_2), 76.7

(C-5), 127.5 (2C), 127.7, 128.4 (2C), 138.0, 171.7 (C=O). MS (ESI): 220 (MH^+, 100). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.01; H, 7.44; N, 6.26.

4.2. (5*S*,6*S*)-5-Benzyloxy-1-(*tert*-butyloxycarbonyl)-6-methyl-2-piperidinone 10

To a cooled (0 °C) solution of **9** (145 mg, 0.66 mmol) and DMAP (cat.) in CH_2Cl_2 (5 mL) was added Et_3N (0.20 mL, 1.45 mmol) under a nitrogen atmosphere. After stirring for 10 min at that temperature, $(Boc)_2O$ (0.30 mL, 1.32 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The resultant mixture was quenched with saturated aqueous NH_4Cl (0.5 mL), diluted with CH_2Cl_2 (2 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: EtOAc/PE = 1:6) to give **10** (192 mg, yield: 91%) as a white solid. Mp 39–41 °C (PE/CH_2Cl_2) (PE/CH_2Cl_2); $[\alpha]_D^{20} = +8.9$ (*c* 1.1, $CHCl_3$). IR (film) ν_{max}: 2979, 2929, 1768, 1716, 1368, 1289, 1250, 1152 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (d, *J* = 6.5 Hz, 3H, CH_3), 1.51 (s, 9H, *t*-Bu-H), 2.02–1.96 (m, 2H, H-4), 2.49 (ddd, *J* = 17.8, 9.6, 8.2 Hz, 1H, H-3), 2.62 (ddd, *J* = 17.8, 7.1, 4.1 Hz, 1H, H-3), 3.78 (ddd, *J* = 10.1, 5.8, 4.8 Hz, 1H, H-5), 4.39 (dq, *J* = 4.8, 6.5 Hz, 1H, H-6), 4.58 (s, 2H, OCH_2), 7.28–7.38 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.1, 27.9, 31.6, 52.6 (C-6), 70.8 (OCH_2), 73.5 (C-5), 82.9 (O–C), 127.4 (2C), 127.8, 128.4 (2C), 137.7, 152.3 (C=O), 170.2 (C=O). MS (ESI): 320 (MH^+, 100). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.61; H, 8.24; N, 4.41.

4.3. *tert*-Butyl [(2*S*,3*S*)-3-Benzyloxy-12-(*tert*-butyldimethylsilyloxy)-6-oxododecan-2-yl]carbamate 12

To a cooled (−78 °C) solution of **10** (280 mg, 0.88 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise a solution of $TBSO(CH_2)_6MgBr$ (**11**) in THF (0.5 M, 5.3 mL, 2.63 mmol). After being stirred for 2 h at that temperature, the mixture was allowed to warm to −50 °C over 40 min. The mixture was quenched with saturated aqueous NH_4Cl (5 mL), and the aqueous phase was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: EtOAc/PE = 1:10) to give **12** (321 mg, yield: 68%) as a pale yellow oil, and recovered **10** (47 mg, 17%). $[\alpha]_D^{20} = -13.5$ (*c* 0.9, $CHCl_3$). IR (film) ν_{max}: 3447, 2930, 2857, 1713, 1493, 1450, 1365, 1252, 1170, 1097 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.40 (s, 6H, $SiCH_3$), 0.88 (s, 9 H, *t*-Bu), 1.16 (d, *J* = 6.8 Hz, 3H, CH_3), 1.24–1.36 (m, 4H), 1.42 (s, 9H, *t*-BuO), 1.44–1.56 (m, 4H), 1.70 (dddd, 1H, *J* = 14.1, 6.6, 6.6, 6.5 Hz, H-4), 1.86 (dddd, 1H, *J* = 14.1, 7.0, 7.0, 6.8 Hz, H-4), 2.32 (t, *J* = 7.5 Hz, 2H, H-7), 2.38–2.52 (m, 2H, H-5), 3.33 (ddd, 1H, *J* = 6.8, 6.5, 2.6 Hz, 1H, H-3), 3.59 (t, *J* = 6.5 Hz, 2H, CH_2OTBS), 3.79–3.86 (m, 1H, H-2), 4.53 (d, *J* = 11.4 Hz, 1H, OCH_2), 4.58 (d, *J* = 11.4 Hz, 1H, OCH_2), 4.70 (d, *J* = 8.0 Hz, 1H, NH), 7.28–7.38 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.3, 14.0, 17.8, 18.3, 23.8, 25.6, 25.9, 28.4, 29.0, 32.6, 38.4, 42.8, 47.5 (C-2), 63.1 (OCH_2), 72.2 (OCH_2), 79.1 (C-3), 80.5 (O–C), 127.7 (2C), 127.9, 128.3 (2C), 138.3, 155.6 (C=O), 210.8 (C=O). MS (ESI): 558 (MNa^+, 100). HRESIMS calcd for $[C_{30}H_{53}NO_5Si + Na]^+$: 558.3592; found: 558.3604.

4.4. *tert*-Butyl [(2*S*,3*S*)-3-Benzyloxy-12-hydroxy-6-oxododecan-2-yl]carbamate 13

To a cooled (0 °C) solution of **12** (260 mg, 0.48 mmol) in anhydrous CH_2Cl_2 (5 mL) was added $BF_3{\cdot}OEt_2$ (0.1 mL, 0.72 mmol). The mixture was stirred at 0 °C for 3 h and quenched with a saturated aqueous $NaHCO_3$ (4 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1:2) to yield **13** (182 mg, yield: 90%) as a colorless oil. $[\alpha]_D^{20} = -24.6$ (*c* 0.8, $CHCl_3$). IR (film) ν_{max}: 3446, 3361, 2931, 2859, 1710, 1497, 1450, 1365, 1252, 1170, 1097, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (d, *J* = 6.8 Hz, 3H, CH_3), 1.24–1.36 (m, 4H), 1.43 (s, 9H, *t*-Bu), 1.52–1.59 (m, 4H), 1.70 (dddd, *J* = 13.6, 6.2, 6.0, 6.0 Hz, 1H, H-4), 1.86 (dddd, *J* = 13.6, 7.1, 7.1, 6.8 Hz, 1H, H-4), 2.36 (t, *J* = 7.4 Hz, 2H, H-7), 2.40–2.54 (m, 2H, H-5), 3.34 (ddd, 1H, *J* = 6.8, 6.2, 2.4 Hz, 1H, H-3), 3.62 (t, *J* = 6.5 Hz, 2H, CH_2OH), 3.79–3.86 (m, 1H, H-2), 4.53 (d, *J* = 11.5 Hz, 1H, OCH_2), 4.59 (d, *J* = 11.5 Hz, 1H, OCH_2), 4.71 (d, *J* = 7.6 Hz, 1H, NH), 7.28–7.38 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 23.7, 24.2, 25.5, 28.4, 28.9, 32.5, 38.5, 42.7, 47.5 (C-2), 62.8 (OCH_2), 72.3 (OCH_2), 79.2 (C-3), 80.5 (O–C), 127.7 (2C), 127.9, 128.4 (2C), 138.3, 155.6 (C=O), 210.8 (C=O). MS (ESI): 422 (MH^+, 5), 444 (MNa^+, 100). Anal. Calcd for $C_{24}H_{39}NO_5$: C, 68.38; H, 9.32; N, 3.32. Found: C, 68.36; H, 9.03; N, 3.31.

4.5. (10*S*,11*S*)-10-Benzyloxy-11-(*tert*-butoxycarbonylamino)-7-oxo-dodecanoic acid 14

Compound **13** (253 mg, 0.60 mmol) was dissolved in a mixed solvent system: CCl_4 (0.7 mL), CH_3CN (0.7 mL), distilled H_2O (1.1 mL), and the mixture was cooled to 0 °C. To the mixture was added $NaIO_4$ (385 mg, 1.80 mmol) in one portion. The resulting mixture was vigorously stirred, and an aqueous solution of $RuCl_3$ (0.05 M, 0.58 mL, 0.024 mmol) was added into the reaction mixture. The mixture was stirred at room temperature for 2 h. The reaction was quenched with brine (4 mL), and then filtered. The aqueous solution was extracted with ethyl acetate (4×3 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent EtOAc/PE = 1:2) to afford acid **14** (232 mg, yield: 89%) as a colorless oil. $[\alpha]_D^{20} = -15.9$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3449, 2931, 1710, 1504, 1455, 1366, 1246, 1167, 1056 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (d, *J* = 6.8 Hz, 3H, CH_3), 1.24–1.36 (m, 3H), 1.43 (s, 9H, *t*-Bu), 1.52–1.64 (m, 3H), 1.70 (dddd, *J* = 13.2, 6.2, 5.9, 5.9 Hz, 1H, H-4), 1.87 (dddd, *J* = 13.2, 7.4, 7.0, 6.8 Hz, 1H, H-4), 2.34 (t, *J* = 7.3 Hz, 2H, H-7), 2.36 (t, *J* = 7.4 Hz, 2H, H-5), 2.40–2.54 (m, 2H), 3.34 (ddd, *J* = 6.8, 6.2, 2.5 Hz, 1H, H-3), 3.79–3.86 (m, 1H, H-2), 4.53 (d, *J* = 11.3 Hz, 1H, OCH_2), 4.59 (d, *J* = 11.3 Hz, 1H, OCH_2), 4.74 (d, *J* = 8.1 Hz, 1H, NH), 7.28–7.38 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 23.3, 24.1, 24.4, 28.4, 28.5, 33.7, 38.5, 42.4, 47.5 (C-2), 72.3 (OCH_2), 79.3 (C-3), 80.5 (O–C), 127.7 (2C), 127.9, 128.4 (2C), 138.3, 155.8 (C=O), 178.5 (C=O), 210.7 (C=O). MS (ESI): 458 (MNa^+, 100). HRESIMS calcd for $[C_{24}H_{37}NO_6 + Na]^+$: 458.2519; found: 458.2524.

4.6. 6-[(2*S*,3*S*,6*R*)-5-Hydroxy-6-methylpiperidin-2-yl]hexanoic acid (azimic acid) 4

Trifluoroacetic acid (1.0 mL) was added dropwise to compound **14** (85 mg, 0.20 mmol) at 0 °C. After stirring at room temperature for 1 h, the resulting mixture was concentrated under reduced pressure to give a residue, which without further purification, was dissolved in methanol (2 mL) and hydrogenolyzed in the presence of Pd/C (10% Pd, 80 mg) under an atmosphere of H_2 for 14 h. The resulting mixture was filtered and washed with methanol. The filtrate was basified with a 1 M sodium hydroxide solution to reach pH 11. The resulting mixture was concentrated under reduced

pressure, and extracted with methanol several times. The combined organic layers were concentrated to afford azimic acid **4** (34 mg, yield: 76%) as a pale yellow solid {mp 212–214 °C (MeOH); lit. mp 214–215 °C;[8f] mp 212–215 °C;[6] $[\alpha]_D^{20} = +7.7$ (*c* 0.5, MeOH); lit. $[\alpha]_D^{20} = +8.0$ (*c* 1.0, MeOH);[8f] $[\alpha]_D^{23} = +7.45$ (*c* 0.49, MeOH)[6]}. IR (film) ν_{max}: 3339, 1709, 2853, 1409, 1260, 1200, 1090, 1020 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 1.36 (d, J = 6.5 Hz, 3H, CH_3), 1.42–1.89 (m, 11H), 1.95–2.05 (m, 1H), 2.35 (t, J = 7.3 Hz, 2H, $COCH_2$), 3.08–3.16 (m, 1H, H-6), 3.26 (dq, J = 6.5, 1.4 Hz, 1H, H-2), 3.88 (t, J = 1.4 Hz, 1H, H-3). ^{13}C NMR (100 MHz, CD_3OD): δ 15.9, 23.5, 25.7, 25.9, 29.8, 31.0, 34.5, 34.8, 57.5 (NCH), 58.5 (NCH), 65.8 (C-3), 177.6 (C=O). MS (ESI): 230 (MH^+, 100). HRESIMS calcd for $[C_{12}H_{23}NO_3 + H]^+$: 230.1751; found: 230.1750.

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