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Enantioselective synthesis of (+)-(2*S*,4*S*,6*S*)-1-ethoxycarbonyl-6-hydroxymethyl-4-methylpipecolate

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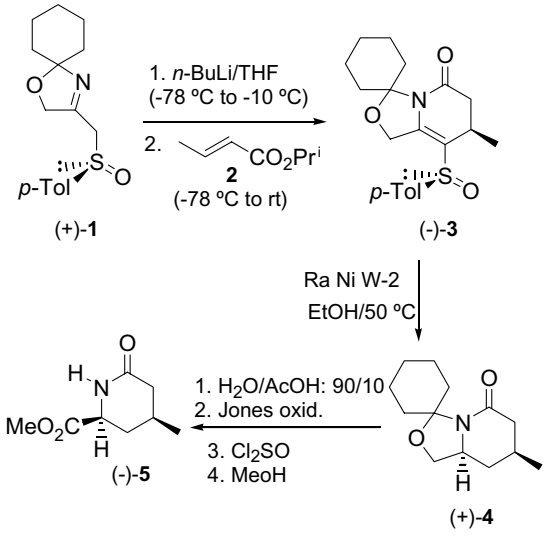
Abstract—The enantioselective synthesis of (+)-(2*S*,4*S*,6*S*)-1-ethoxycarbonyl-6-hydroxymethyl-4-methylpipecolamide **16** is described. The absolute configuration of stereocenters introduced in (+)-**16** was assigned on the basis of ^{1}H NMR data. The results extend the chirality transfer with complete control of stereoselectivity from the sulfinyl group to the 4-position and, hence, to the 6- and 2-positions of the piperidine ring via asymmetric induction.

1. Introduction

Substituted pipecolic acids are the subject of many current investigations and have found uses as building blocks in the synthesis of peptidomimetics,[1] immunosuppresor agents,[2] enzyme inhibitors,[3] and NMDA antagonists.[4] On the other hand, procedures for easy transformations of 6-oxopipecolic acids through the lactam enolate and further ring functionalization have been described[5,6] and several methods for the preparation of 6-oxopipecolic acid derivatives have previously been reported.[7–16]

We have recently reported an efficient synthesis of 6-oxopipecolate (−)-**5** by the reaction of α-sulfinylketimine (+)-**1** and isopropyl (*E*)-crotonate **2**, which in turn gives the intermediate lactam (−)-**3** in 70% yield with total stereoselectivity. The Ra–Ni reduction led to piperidin-2-one (+)-**4** (de = 100%), which yielded (−)-**5** (de >97%) by hydrolysis (aq AcOH 10% v/v), oxidation of the resultant amino alcohol derivative and further esterification of the resultant carboxylic acid (Scheme 1).[17] Since the *p*-tolylsulfinyl group has been shown to be a very efficient chiral auxiliary by transferring its chirality to the 4-position of piperidine ring and, hence, to the 6-position, we have now developed the α-amidocarboxylation of (+)-(4*S*,6*S*)-piperidin-2-one derivative (+)-**4** as an alternative method for the synthesis of 4.6-disubstituted L-pipecolamides. The synthesis of *trans*-configured 6-alkyl substituted pipecolic acid derivatives is of current interest[18] as they represent key precursors for antibiotics such as *solenopsin* A.[19]



Scheme 1.

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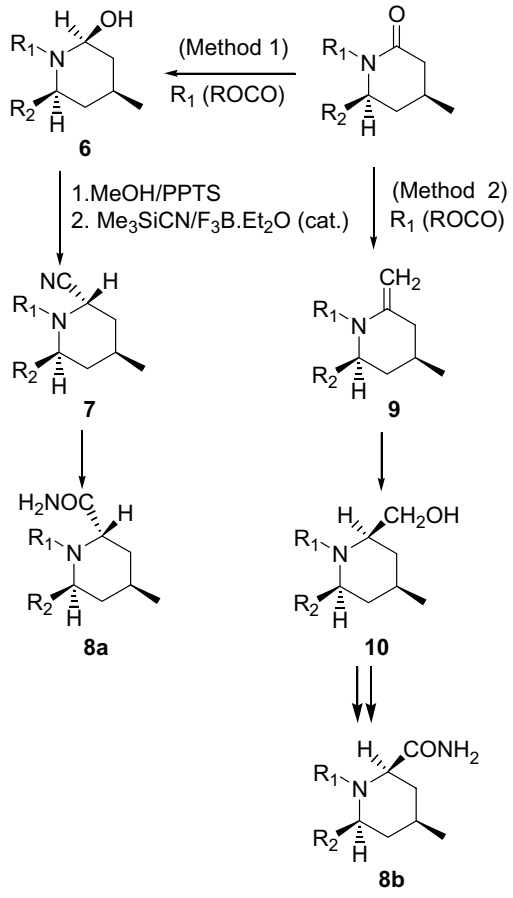
2. Results and discussion

2.1. Synthesis of pipecolamide (+)-16

The transformation of amide carbonyl groups in six-membered lactams into the carboxylic function can be achieved in two ways. First, by reduction of carbonyl group to an α-hydroxycarbamate such as **6** ($R^1 = ROCO$), trapping of the acyl iminium derivative,[20] generated by the BF_3 catalyzed OMe-elimination from **6**, with trimethylsilyl cyanide and hydrolysis of the resulting nitrile to the carboxamide **8a** (Scheme 2; Method 1). The formation of α-cyanocarbamate **7** occurs with high *trans*-diastereoselectivity.[21] The second method involves the methylenation of the carbonyl group and hydroboration/oxidation of the ene carbamate **9**, which furnishes a *cis*-configured hydroxymethyl piperidine **10**, which can be transformed into the epimeric carboxamide **8b** (Scheme 2; Method 2).[22]

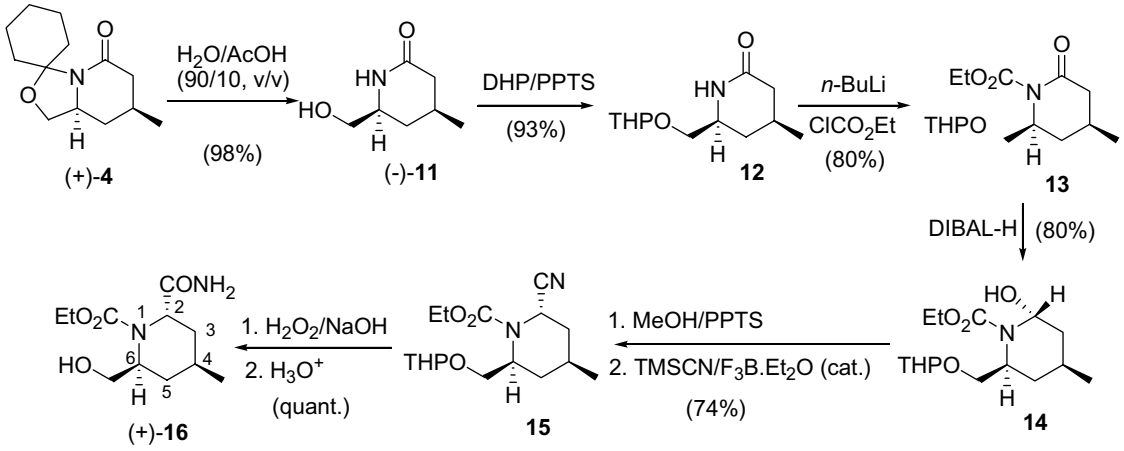


Scheme 2.

Since our goal is to synthesize L-pipecolates, analogous to the natural occurring ones,[23] we selected the first strategy (Scheme 3). Thus, compound (+)-**4** was hydrolyzed to the amino alcohol (−)-**11** (aqueous AcOH 10%).[17] Next, the orthogonal protection of derivative (−)-**11** was achieved by conventional methods to give **13** in 74% overall yield. Reduction of **13** with DIBAL-H led to the hemiaminal **14** (80% yield), which was purified by flash chromatography on deactivated silica gel (EtOAc/hexane: 2/1). Next, the introduction of the required nitrile group with retention of configuration was accomplished by in situ transformation of **14** in its acyl iminium derivative[24] and subsequent cyanosilylation ($TMSCN/F_3B{\cdot}Et_2O$) to afford **15** (74% yield). This α-amino nitrile was transformed without previous purification to pipecolamide (+)-**16** by one-pot hydrolysis of nitrile (H_2O_2/NaOH 1 M)[25] and a THP protecting group (74% overall yield from **14**).

2.2. Structural analysis and configurational assignment

The stereochemistry of compounds **14** and **15** could not be easily established on the basis of their ^1H NMR spectra owing to extensive signal overlapping of the stereoisomers (rotamers and diastereomers). However, the proton spectrum (500 MHz) of pipecolamide **16** allowed the precise assignment of the relative (and, hence, absolute) stereodisposition of the molecule. In particular, the vicinal coupling constants between H-6 and H-5/H-5′ ($^3J = 3.1$, 11.4 Hz) and H-2 and H-3/H-3′ hydrogens ($^3J = 1.3$, 6.2 Hz) confirmed a pseudo-axial conformation for H-6 and a pseudo-equatorial one for



Scheme 3.

H-2 and hence, the *trans*-relative configuration for these hydrogens.

Coming back to the analysis of the ^{1}H NMR spectra of **14** and **15**, similar values for vicinal coupling constants for H-2 were observed. Thus, compound **15** appeared as a mixture of three isomers **A**:**B**:**C** = 60:20:20 (two epimers on acetalic carbon of THP group; one of them could be constituted by two rotamers) with signals at δ 5.327, 5.513, and 5.129 ppm, respectively (dd, $^3J = 2.3$, 5.0 Hz), which could be assigned to H-2$_{eq}$. Similarly, compound **14** (two epimers, four rotamers) showed analogous values for the vicinal coupling constants of H-2 (5.65–6.67 ppm; dd, $^3J = 2.7$, 5.5 Hz). Probably, the equatorial attack of DIBAL-H on the compound **13** would be induced on the basis of the most stable conformation **A** for **13** (Fig. 1).

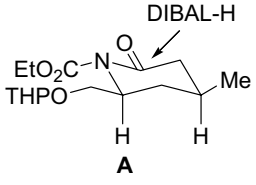


Figure 1. Equatorial attack of DIBAL-H on the most stable conformation **A** of compound **13**.

The observed diastereoselectivity in the cyanation reaction can be rationalized by assuming that the cyanide addition proceeds preferentially via axial attack on the intermediate iminium ion in a half-chair conformation **B** as outlined in Figure 2.

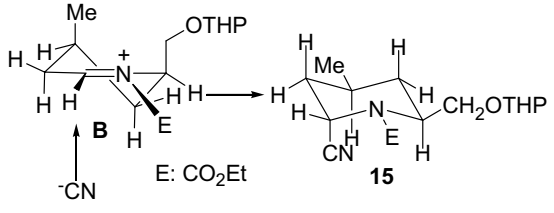


Figure 2. Stereochemical pathway for cyanation reaction of acyl iminium derivative from **14**.

3. Conclusions

The enantioselective synthesis of (+)-(2*S*,4*S*,6*S*)-1-ethoxycarbonyl-6-hydroxymethyl-4-methylpipecolamide (+)-**16** was accomplished from (+)-**4** in six steps (41% overall yield) with total stereoselectivity. Functionalized piperidines such as 2-hydroxy- and 2-aminomethylpiperidines are valuable building blocks in the preparation of several pharmaceuticals.[26]

4. Experimental

4.1. General

Melting points were determined in a Gallenkamp apparatus in open capillary tubes and are uncorrected. Optical rotations were measured at room temperature (20–23 °C) using a Perkin Elmer 241 MC polarimeter (concentration in g/100 mL). Infrared spectra were recorded on a Perkin Elmer 781 IR Spectrophotometer. The ^{1}H and ^{13}C NMR were recorded at 200 or 500 MHz and 50 or 125 MHz, in a Bruker AC-200 or Bruker AM-500 spectrometer, respectively, using $CDCl_3$, and the chemical shifts (δ) refer to TMS (^{1}H) or deuterated chloroform (^{13}C) signals. Coupling constants (J) are reported in hertz. Multiplicities in proton spectra are indicated as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Elemental analyses were performed with a Perkin Elmer 2400 C, H, N, analyzer.

All reactions in nonaqueous media were carried out in flame-dried glassware under an argon atmosphere. Reagents and solvents were handled by using standard syringe techniques. Tetrahydrofuran (THF) was distilled from sodium and benzophenone, and dichloromethane from P_2O_5. In all other cases commercially available reagent-grade solvents were employed without purification. Analytical TLC was routinely used to monitor reactions. Plates precoated with Merck silica gel 60 F_{254} of 0.25 mm thickness were used, and visualized with UV light or vanillin (acid solution in ethanol) or phosphomolibdic acid solution (PMA, 10% in ethanol). Flash column chromatography was carried out using Merck silica gel (grade 60, 230–400 mesh). Deactivated silica gel was performed by eluting with 2% aqueous solution of $NaHCO_3$/MeOH (5/95, v/v) until the pH of the eluent was basic, and then passing through it dry acetone. Chemicals for reactions were used as purchased from the Aldrich Chemical Co. Starting compounds (−)-**3** and its derivatives (+)-**4** and (−)-**11** have previously been described.[17]

4.2. Orthogonal protection of (−)-(4*S*,6*S*)-6-hydroxymethyl-4-methylpiperidin-2-one, (−)-11

To a stirred solution of (−)-**11** (0.433 g, 3.02 mmol) in anhydrous methylene chloride (15 mL) at room temperature under argon, 3,4-dihydro-2*H*-pyran (0.76 g, 91.0 mmol) was added, followed by the addition of pyridinium *p*-toluene sulfonate (0.076 g, 0.302 mmol). The reaction mixture was stirred overnight at room temperature, after which EtOAc (10 mL) and NaCl (saturated aqueous solution, 5 mL) were added. The organic layer was separated and the aqueous one extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with water and dried on anhydrous $MgSO_4$. After filtration and elimination of the solvent at reduced pressure, the crude product was purified by flash chromatography (EtAcO/EtOH = 13/1 as eluent) to give the piperidin-2-one derivative **12** (93% yield) as a mixture of diastereomers **A**/**B** = 44/56: white solid, mp 75–78 °C. IR ($CHCl_3$) 3209, 2928, 2895, 1661, 1032 cm^{-1}. ^{1}H NMR

(200 MHz) Isomer **A**: δ 1.052 (d, 3H, $^3J = 6.6$, Me), 1.895 (t, 1H, $^2J = {}^3J = 12.0$, H-3$_{ax}$), 2.11–2.52 (m, 9H, H-4, H-5, H-5′, 6H-THP), 2.463 (dd, 1H, $^2J = 12.5$, $^3J = 2.4$, H-3′$_{eq}$), 3.56–3.72 (m, 2H, H-6, 1H-THP), 3.493 (dd, 1H, $^2J = 9.3$, $^3J = 8.3$, CH_2O), 3.816 (dd, 1H, $^2J = 9.3$, $^3J = 3.2$, CH_2O), 3.866 (dt, 1H, $^2J = {}^3J = 6.9$, $^3J = 3.4$, CH_2O-THP), 4.586 (dd, 1H, $^3J = 7.7$, 3.3, 1H-THP), 6.381 (br s, 1H, NH). Isomer **B** (distinguishable signals): δ 1.033 (d, 3H, $^3J = 6.6$, Me), 3.147 (t, 1H, $^2J = {}^3J = 9.5$, CH_2O), 3.511 (dd, 1H, $^2J = 9.5$, $^3J = 8.5$, CH_2O), 3.817 (dt, 1H, $^2J = {}^3J = 12.4$, $^3J = 3.1$, 1H-THP), 4.594 (dd, 1H, $^3J = 9.6$, 4.3, 1H-THP), 6.292 (br s, 1H, NH). ^{13}C NMR (50 MHz) δ 19.28, 21.44, 25.22, 27.34, 30.39, 33.31, 39.75, 52.50, 62.40, 71.59, 99.49, 171.83. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.9; H, 9.80; N, 6.70.

To a stirred solution of compound **12** (0.721 g, 3.18 mmol) in anhydrous THF (17 mL) at −60 °C under argon, 2.08 mL (3.33 mmol) of 1.6 M solution of BuLi in hexane was added dropwise. The mixture was stirred for 20 min at −60 °C after which ethyl chloroformiate (0.85 mL, 8.89 mmol) in dry THF (0.1 mL) was slowly added. The mixture was allowed to warm up to 0 °C (ice bath) and then hydrolyzed with a saturated aqueous solution of ammonium chloride. The aqueous layer was extracted with EtAcO (4×20 mL) and the combined organic extracts washed with brine, dried on anhydrous $MgSO_4$, filtered, and the solvent evaporated at reduced pressure. The crude product was chromatographied on silica gel (EtOAc/EtOH = 13/1 as eluent) to give **13** (80% yield) as an oil (mixture of diastereomers **A**/**B** = 48/52). IR ($CHCl_3$) 1773, 1719 cm^{-1}. ^{1}H NMR (200 MHz) δ Isomer **A**: 1.027 (d, 3H, $^3J = 6.4$, Me), 1.338 (t, 3H, $^3J = 7.1$, Me ester), 1.4–1.7 (m, 7H, H-5, 6H-THP), 1.8–2.0 (m, 1H, H-4), 2.05–2.25 (m, 1H, H-5′), 2.191 (dd, 1H, $^2J = 12.8$, $^3J = 5.7$, H-3$_{ax}$), 2.537 (dd, 1H, $^2J = 12.8$, $^3J = 2.7$, H-3′$_{eq}$), 3.331 (dd, 1H, $^2J = 9.8$, $^3J = 3.7$, CH_2O), 3.41–3.53 (m, 1H, H-6), 3.65–3.75 (m, 1H, THP), 3.890 (dd, 1H, $^2J = 9.8$, $^3J = 4.4$, CH_2O), 4.295 (q, 2H, $^3J = 7.1$, CH_2 ester), 4.36–4.51 (m, 1H, THP), 4.630 (t, 1H, $^3J = 2.9$, THP). Isomer **B**: 1.027 (d, 3H, $^3J = 6.4$, Me), 1.338 (t, 3H, $^3J = 7.1$, Me ester), 1.4–1.7 (m, 7H, H-5, 6H-THP), 1.8–2.0 (m, 1H, H-4), 2.05–2.25 (m, 1H, H-5), 2.118 (dd, 1H, $^2J = 16.6$, $^3J = 5.6$, H-3$_{ax}$), 2.515 (dd, 1H, $^2J = 16.6$, $^3J = 3.2$, H-3′$_{eq}$), 3.41–3.53 (m, 1H, H-6), 3.65–3.75 (m, 1H, THP), 3.567 (dd, 1H, $^2J = 10.3$, $^3J = 3.9$, CH_2O), 3.730 (dd, 1H, $^2J = 10.3$, $^3J = 2.9$, CH_2O), 4.301 (q, 2H, $^3J = 7.1$, CH_2 ester), 4.36–4.51 (m, 1H, THP), 4.529 (t, 1H, $^3J = 3.5$, THP). ^{13}C NMR (50 MHz) (mixture of diastereomers) δ 14.15, 20.64, 20.73, 25.29, 25.32, 25.98, 26.03, 30.26, 33.08, 33.27, 42.11, 54.17, 61.4, 62.29, 63.00, 69.67, 70.14, 98.22, 99.25, 154.54, 154.60, 172.62, 173.14. Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.70; H, 8.91; N, 5.20.

4.3. DIBAL-H reduction of lactam 13

To a solution of lactam **13** (0.114 g, 3.18 mmol) in anhydrous THF (2.4 mL) at −78 °C under argon, 1.33 mL (1.33 mmol) of 1 M solution of DIBAL-H in hexane was added and the mixture stirred for 1 h at −78 °C. The mixture was allowed to warm up to 0 °C (ice bath) and then 0.06 mL of a solution of NaOH (aqueous solution, 25%) added. The salts were filtered through a short pad of Celite and the filtrate washed with brine and dried on anhydrous Na_2SO_4. After filtration and elimination of the solvent at reduced pressure, the crude product was purified by flash chromatography on deactivated silica gel (hexane/EtOAc = 2/1 as eluent) to give the expected hemiaminal **14** (80% yield) as an oil that was identified as a mixture of four isomers (diastereomers and rotamers): **A** (11%), **B** (23%), **C** (41%), **D** (25%). ^{1}H NMR (200 MHz) δ 1.098 (**A**), 1.049 (**B**), 0.993 (**C**), 0.979 (**D**) (d, 3H, $^3J = 7.4$, Me), 1.208 (**A**), 1.204 (**B**), 1.218 (**C**), 1.239 (**D**) (t, 3H, $^3J = 7.2$, Me ester), 1.4–2.3 (m, 12H, OH, H-3, H-3′, H-4, H-5, H-5′, 6H-THP), 3.25–3.85 (m, 4H, H-6, CH_2O, 1H-THP), 4.098 (**A**), 4.102 (**B**), 4.124 (**C**), 4.152 (**D**), (q, 2H, $^3J = 7.2$, CH_2 ester), 4.35–4.60 (m, 1H, THP), 4.79–4.90 (m, 1H, THP), 5.65 (**B***), 6.67 (**A**, **C**, **D***) (dd, 1H, $^3J = 2.7$, 5.5, H-2) (* interchangeable assignments).

4.4. Ethyl (2*S*,4*R*,6*S*)-2-cyano-4-methyl-6-[(tetrahydro-2*H*-piran-2-yloxy)methyl]piperidin-1-carboxylate, 15

To a solution of compound **14** (0.090 g, 0.298 mmol) in distilled MeOH (4 mL) at room temperature under argon, pyridinium *p*-toluenesulfonate (0.011 mg, 0.042 mmol) was added and the reaction mixture stirred for 48 h. EtAcO (5 mL) and HCl (3% aqueous solution, 15 mL) were then added and the aqueous layer extracted with EtAcO (4×20 mL). The organic extracts were washed with $NaHCO_3$ (saturated aqueous solution, 3×10 mL) and then with brine (3×10 mL), dried on anhydrous Na_2SO_4, filtered, and the solvent removed at reduced pressure to give a crude product (oil), which was used in the next step without further purification.

To a stirred solution of the crude product previously obtained (90 mg, 0.286 mmol) in anhydrous methylene chloride at −40 °C under argon, $F_3B{\cdot}Et_2O$ (0.011 mL, 0.085 mmol) and TMSCN (0.08 mL, 0.600 mmol) were added. The reaction mixture was stirred at −40 °C for 1 h and then allowed to warm up to room temperature. Two milliliters of an aqueous solution (10%, w/v) of Na_2CO_3 were then added and the aqueous layer separated and extracted with methylene chloride (2×5 mL). The combined organic extracts were washed with brine (3×10 mL), dried on anhydrous $MgSO_4$ and the solvent removed at reduced pressure to give 90 mg of a crude product of the expected nitrile **15**, which was used in the next step without further purification (74% yield from **14**). The crude compound was characterized as a mixture of two diastereomers in the acetalic stereocenter (one of them as two rotamers): **A**:**B**:**C** = 60:20:20. ^{1}H NMR (200 MHz) δ 0.942 (**A**), 0.867 (**B**), 0.859 (**C**) (d, 3H, $^3J = 6.3$–6.6, Me), 1.224 (**A**), 1.230 (**B**), 1.217 (**C**) (t, 3H, $^3J = 7.1$, Me ester), 1.4–2.0 (m, 11H, H-3, H-3′, H-4, H-5, H-5′, 6H-THP), 3.4–3.9 (m, 4H, CH_2O, 2H-THP), 4.138 (**A**), 4.113 (**B**), 4.097 (**C**) (q, 2H, $^3J = 7.1$, CH_2 ester), 4.30–4.60 (m, 2H, H-6, 1H-THP), 5.327 (**A**), 5.513 (**B**), 5.129 (**C**) (dd, 1H, $^3J = 2.3$, 4.8–5.0, H-2).

4.5. (2*S*,4*S*,6*S*)-1-Ethoxycarbonyl-6-hydroxymethyl-4-methylpipecolamide, (+)-16

To a solution of the crude nitrile **15** (90 mg) in absolute ethanol (4 mL) at room temperature were added H_2O_2 (0.24 mL, 30%) and NaOH (1 M solution, 0.28 mL). The reaction mixture was stirred for 1 h at room temperature and then hydrolyzed with water (1 mL). EtOAc (5 mL) was added and the aqueous layer extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine, dried on anhydrous Na_2SO_4, filtered, and the solvent removed at reduced pressure to give a solid residue.

To a stirred cooled solution of this crude product in methylene chloride (10 mL), a solution of HCl (3% v/v, 1 mL) was added then left to stir at 0 °C for 12 h. Finally, water (5 mL) was added and the organic layer washed with brine (3×5 mL), dried on anhydrous Na_2SO_4, filtered, and the solvent removed at reduced pressure to give a solid residue. The crude product was purified by flash chromatography to give 52 mg of **16** (74% yield from **14**) as a colorless oil. $[\alpha]_D = +14.3$ (*c* 1.4, $CHCl_3$). IR (film): 3450–3220, 1730, 1640 cm^{-1}. ^1H NMR (500 MHz) δ 0.985 (d, 3H, $^3J = 6.4$, Me), 1.259 (t, 3H, $^3J = 7.2$, Me ester), 1.79–1.83 (m, 4H, H-3, H-4, H-5, H-5′), 2.268 (tdd, 1H, $^2J = 13.5$, $^4J = {}^3J = 1.3$, $^3J = 3.1$, H-3′), 3.946 (dd, 1H, $^2J = 7.6$, $^3J = 6.3$, CH_2OH), 3.973 (dddd, 1H, $^3J = 11.4$, 7.6, 6.3, 3.1, H-6), 4.121 (q, 2H, $^3J = 7.2$, CH_2 ester), 4.487 (t, 1H, $^2J = {}^3J = 7.6$, CH_2OH), 4.526 (dd, 1H, $^3J = 6.2$, 1.3, H-2), 5.741 (br s, 1H, $CONH_2$), 6.409 (br s, 1H, $CONH_2$). ^{13}C NMR (125 MHz) δ 14.21, 21.87, 25.93, 32.97, 38.21, 52.46, 52.83, 60.41, 68.72, 157.81, 172.21. Anal. Calcd for $C_{11}H_{20}N_2O_4$: C, 54.80; H, 8.25; N, 11.47. Found: C, 54.71; H, 7.98; N, 11.58.

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