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Stereoselective total synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid

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Abstract—A concise, stereocontrolled synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid **1** is described. Key features involve diastereoselective oxazoline formation catalyzed by palladium(0) and intramolecular cyclization by catalytic hydrogenation of an oxazoline.

1. Introduction

3-Hydroxypipecolic acids, six-membered cyclic α-amino β-hydroxy acids, constitute the common structural sub-units of biologically important natural and non-natural compounds. Because of their biological importance, 3-hydroxypipecolic acids have been long standing synthetic targets and a number of synthetic approaches have recently reported.[1] (2*S*,3*R*)-3-Hydroxypipecolic acid **1** is the key component of tetrazomine **2**,[2a,b] the anti-tumor antibiotic (Fig. 1), which was isolated from *Saccharothrix mutabilis* by the Yamanouchi Pharmaceutical Co. in 1991.[2c] Despite recent improvements in the synthetic methodology for control of two stereocenters in the target molecule of 3-hydroxypipecolic acid,[3a] synthetic approaches for (2*S*,3*R*)-3-hydroxypipecolic acid could be found in only a few presentations.[2b,3b,d,e]

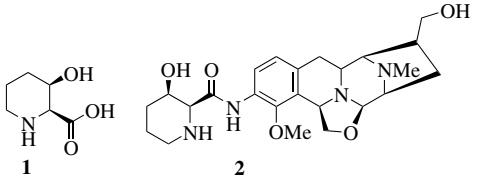
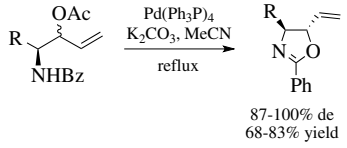


Figure 1. (2*S*,3*R*)-3-Hydroxypipecolic acid **1** and tetrazomine **2**.

In previous papers,[4] we described a new palladium(0)-catalyzed procedure for the stereoselective formation of an oxazoline ring from a homoallylic amide having a benzoyl substituent as an N-protecting group. The most significant point of this method is that it is based on the *trans*-oxazoline ring formation in palladium(0)-catalyzed conditions (Scheme 1). As part of a program directed at expanding the synthetic utility of oxazolines as chiral building blocks for the synthesis of natural products,[5] we herein report our synthetic efforts, which led to a concise and highly stereocontrolled total synthesis of **1**.



Scheme 1. Palladium(0)-catalyzed oxazoline formation.

The retro-synthesis proceeded as shown in Scheme 2. We envisioned that this method could be utilized to set the vicinal amino alcohol stereochemistry of **1** via the key intermediate **3**, which would be accessible via hydrogenolysis of oxazoline **4**. It was also anticipated that the pendant vinyl group of oxazoline **5** could be easily converted to ester **4** in three steps. The synthesis of *trans*-oxazoline **5** is made from D-serinol according to a known procedure.[5e]

2. Results and discussion

The synthesis of **1** commenced with ozonolysis of **5** to give the corresponding aldehyde, which was reacted with trimethylphosphonoacetate to yield the α,β-unsaturated methyl

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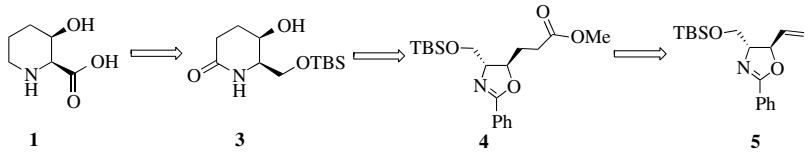
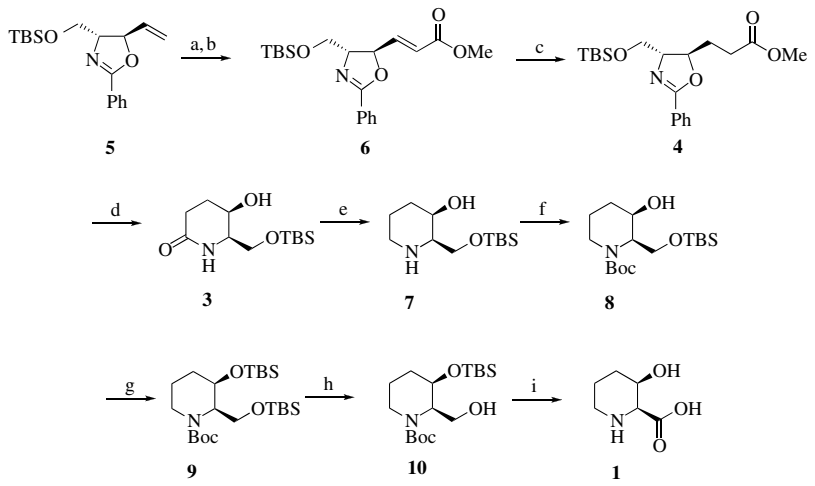


Scheme 2. Retrosynthetic analysis of (2*S*,3*R*)-3-hydroxypipecolic acid.



Scheme 3. Reagents and conditions: (a) O_3, MeOH, −78 °C then DMS; (b) $(MeO)_2POCH_2CO_2Me$, LiCl, DIPEA, CH_3CN, 95% for 2 steps; (c) L-Selectride, *t*-BuOH, THF, −78 °C, 86%; (d) $Pd(OH)_2/C$, H_2, MeOH + AcOH, 80%; (e) $BH_3{\cdot}SMe_2$, MeOH + THF, 83%; (f) $(Boc)_2O$, TEA, CH_2Cl_2, 91%; (g) TBSCl, Imid, DMF, 93%; (h) AcOH + H_2O + THF, 94%; (i) see Ref. 3b.

ester **6** in 95% yield (Scheme 3). 1,4-Reduction of **6** with L-Selectride gave the saturated methyl ester **4** in 86% yield. Hydrogenolysis of **4** with 20% $Pd(OH)_2/C$ in AcOH/MeOH (1/9, v/v) was performed under 70 psi of H_2 at ambient temperature to give the hydroxy piperidinone **3**, followed by reduction of **3** with borane–methyl sulfide complex to furnish **7** in good yield. The dihydroxyl piperidine monosilyl protected compound **7** was protected with Boc_2O to give compound **8**, and subsequent silyl protection led to disilyl *N*-Boc compound **9**, which was reacted with acetic acid to afford the selectively deprotected free primary alcohol **10** in good yield. Subsequent oxidation of the primary hydroxyl group including deprotection of the secondary silyl ether with $RuCl_3$ and $NaIO_4$ provided the corresponding carboxylic acid; acidic hydrolysis of the carbamate culminated in an efficient synthesis of the desired (2*S*,3*R*)-3-hydroxypipecolic acid **1**.[6] The spectroscopic (^1H and ^{13}C NMR) data for synthetic **1** were fully identical with those of synthetic one, and the properties of **1** showed good agreement with those reported.[3b]

3. Conclusion

In summary, we showed a concise and highly stereocontrolled total synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid that utilizes *trans*-oxazoline as a chiral building block. Moreover, starting from commercially available L-Serine and using the same strategy will permit the synthesis of (2*R*,3*S*)-3-hydroxypipecolic acid.

4. Experimental

4.1. General methods

Optical rotations were measured on a JASCO DIP 1020 digital polarimeter. ^1H NMR spectra were recorded on a Varian inova FT-NMR 500 MHz in $CDCl_3$. ^{13}C NMR spectra were recorded at 125 MHz in $CDCl_3$. Chemical shifts are reported as δ values in ppm relative to $CHCl_3$ (7.26) in $CDCl_3$. IR spectra were measured on a Bruker FT-IR spectrometer. Mass spectra were recorded on Mass spectrometer (Agilent MSD Trap SL). Flash chromatography was executed with Merck Kiesegel 60 (230–400 mesh) using mixtures of ethyl acetate and hexane as eluants. Ethyl acetate and hexane were dried and purified by distillation prior to use. Tetrahydrofuran (THF) was distilled over sodium and benzophenone (indicator). Methylene chloride (CH_2Cl_2) was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled. Commercially available compounds were used without further purification.

4.2. (*E*)-Methyl 3-((4*R*,5*R*)-4-((*tert*-butyldimethyl-silyloxy)methyl)-2-phenyl-4,5-dihydrooxazol-5-yl)acrylate 6

The *trans*-oxazoline **5** was synthesized according to Ref. 5e. A solution of **5** (1.0 g, 3.05 mmol) in dry methanol (50 mL) at − 78 °C was treated with ozone until the reaction was complete. The reaction mixture was quenched with $(CH_3)_2S$ (0.47 mL, 6.30 mmol) and allowed to warm to

room temperature. The solvents were evaporated under reduced pressure. The crude aldehyde was immediately employed in the next step without further purification. To a stirred solution of LiCl (164 mg, 3.78 mmol) in CH_3CN (20 mL) were added trimethyl-phosphonoacetate (0.54 mL, 3.78 mmol), diisopropyl-ethylamine (0.61 mL, 3.78 mmol) and stirring was allowed to continue for 1 h. The crude aldehyde in CH_3CN (10 mL) was added and the reaction mixture was stirred for 2 h. The reaction mixture was poured into H_2O (20 mL), extracted with EtOAc (50 mL). The organic extract was washed with brine, dried over $MgSO_4$ and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/6) gave **6** (1.13 g, 95% for 2 steps) as a colorless oil; $R_f = 0.3$ (ethyl acetate/hexane = 1/6); $[\alpha]_D^{25} = -75.2$ (*c* 1.0, $CHCl_3$); IR (neat) 839, 1174, 1264, 1653, 1727, 2859, 2943 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 3.69 (dd, $J = 3.5$, 10.5 Hz, 1H), 3.75 (s, 3H), 3.98 (dd, $J = 3.5$, 10.5 Hz, 1H) 4.14–4.16 (m, 1H), 5.18–5.19 (m, 1H), 6.11 (dd, $J = 1.5$, 15.5 Hz, 1H), 7.00 (dd, $J = 5.0$, 16.0 Hz, 1H) 7.40–7.43 (m, 2H), 7.48–7.49 (m, 1H), 7.95–7.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.12, 18.42, 26.01, 51.98, 64.87, 74.44, 80.90, 120.84, 127.53, 128.56, 131.84, 145.90, 163.97, 166.57; HRMS (M^++H) *m*/*z* calcd for $C_{20}H_{30}NO_4Si$: 376.1944; found, 376.1948.

4.3. Methyl 3-((4*R*,5*R*)-4-((*tert*-butyldimethylsilyloxy)-methyl)-2-phenyl-4,5-dihydrooxazol-5-yl)propanoate 4

A solution of **6** (1.0 g, 2.66 mmol) and *tert*-butyl alcohol (0.51 mL, 5.33 mmol) in dry THF (5 mL) was added over 5 min to L-Selectride (2.93 mL, 1 M solution in THF, 2.93 mmol) at −78 °C. After 20 min, the reaction was quenched with methanol (2 mL). The reaction mixture was then warmed to room temperature and solvent was removed under reduced pressure. Then the reaction mixture was diluted with hexanes (30 mL), cooled to 0 °C, followed by addition of 10% NaOH (3.5 mL) and 30% H_2O_2 (2.5 mL) and the reaction mixture was stirred for 4 h at room temperature. The aqueous layer was then separated and extracted with hexanes (30 mL × 3). The combined organic layer was washed twice with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (ethyl acetate/hexane = 1/4) gave **4** (865 mg, 86%) as a colorless oil; $R_f = 0.3$ (ethyl acetate/hexane = 1/4); $[\alpha]_D^{25} = +47.6$ (*c* 1.0, $CHCl_3$); IR (neat) 841, 1173, 1252, 1649, 1740, 2860, 2943 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 2.01–2.05 (m, 2H), 2.52–2.56 (m, 2H), 3.59 (dd, $J = 7.0$, 10.0 Hz, 1H), 3.67 (s, 3H), 3.92–3.98 (m, 2H), 3.98–4.64 (m, 1H), 7.38–7.42 (m, 2H), 7.46–7.49 (m, 1H), 7.19–7.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.15, −5.13, 18.45, 26.05, 30.06, 30.85, 51.87, 65.28, 73.54, 82.23, 128.08, 128.47, 128.49, 131.56, 164.07, 173.54. HRMS (M^++H) *m*/*z* calcd for $C_{20}H_{32}NO_4Si$: 378.2101; found, 378.2102.

4.4. (5*R*,6*R*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-5-hydroxypiperidin-2-one 3

A solution of **4** (600 mg, 1.59 mmol) in AcOH/MeOH (1:9, 10 mL), to which was added 300 mg of 20% $Pd(OH)_2/C$, was vigorously shaken under 70 psi H_2 for 3 days at ambient temperature. The mixture was then filtered through a pad of silica and concentrated in vacuo. Then the reduced mixture was diluted with ethyl acetate (30 mL). A saturated solution of $NaHCO_3$ was added slowly, stirred for 30 min. The aqueous layer was then separated and extracted with ethyl acetate (30 mL × 3).The combined organic layer was washed twice with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography over silica gel ($CHCl_3$/MeOH = 9/1) gave **3** (330 mg, 80%) as a white solid; $R_f = 0.5$ ($CHCl_3$/MeOH = 9/1); $[\alpha]_D^{25} = +10.0$ (*c* 1.0, $CHCl_3$); mp 85 °C; IR (neat) 838, 1095, 1648, 2941, 3394 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06–0.07 (m, 6H), 0.88–0.92 (m, 9H), 1.80–1.86 (m, 1H), 2.00–2.06 (m, 1H), 2.26–2.33 (m, 1H), 2.57–2.64 (m, 1H), 3.44–3.46 (m, 1H), 3.79–3.81 (m, 2H), 4.13–4.14 (m, 1H), 6.32 (s, 1H); ^{13}C NMR (125MHz, $CDCl_3$) δ −5.30, −5.29, 18.35, 26.01, 26.52, 27.77, 57.78, 64.20, 64.37, 172.66; HRMS (M^++H) *m*/*z* calcd for $C_{12}H_{26}NO_3Si$: 260.1682; found, 260.1678.

4.5. (2*R*,3*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-piperidin-3-ol 7

To a 0 °C solution of **3** (200 mg, 0.77 mmol) in dry THF (8 mL) was added $BH_3{\cdot}SMe_2$ (1.93 mL, 2 M solution in THF, 3.86 mmol) dropwise under argon, and the reaction mixture was kept at room temperature for 4 h. The excess of reducing agent was quenched by slow addition of EtOH (8 mL). After evaporation of the solvent, the residue was dissolved in EtOH (20 mL) and heated at reflux for 2 h. The cooled mixture was then evaporated and purified by column chromatography ($CHCl_3$/MeOH = 4/1) to afford **7** (157 mg, 83%) as a white solid; mp 265 °C; $R_f = 0.3$ ($CHCl_3$/MeOH = 4/1); $[\alpha]_D^{25} = +3.0$ (*c* 1.0, $CHCl_3$); IR (neat) 838, 1093, 1620, 2352, 2937 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.011–0.014 (m, 6H), 0.92–0.96 (m, 9H), 1.48–1.52 (m, 1H), 1.60–1.66 (m, 1H), 1.86–1.93 (m, 2H), 2.72 (td, $J = 3.15$, 12.35 Hz, 1H), 2.81 (td, $J = 1.8$, 8.1 Hz, 1H), 3.10 (dt, $J = 1.88$, 10.48 Hz, 1H), 3.17–3.33 (m, 1H), 3.73–3.75 (m, 2H), 3.91–3.93 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ −6.57, −6.50, 18.00, 19.55, 25.21, 30.78, 45.33, 60.90, 63.40, 64.07; HRMS (M^++H) *m*/*z* calcd for $C_{12}H_{28}NO_2Si$: 246.1889; found, 246.1891.

4.6. (2*R*,3*R*)-*tert*-Butyl 2-((tert-butyldimethylsilyloxy)-methyl)-3-hydroxypiperidine-1-carboxylate 8

To a solution of **7** (100 mg, 0.41 mmol) in CH_2Cl_2 (4.0 mL) was added triethylamine (0.23 mL, 1.63 mmol) via syringe followed by di(*tert*-butyl)dicarbonate (107 mg, 0.49 mmol) in one portion. The reaction mixture was stirred for 4 h after which the resulting yellow solution was poured into 5 mL of water. The layer was separated, and the organic layer was washed with 5 mL of water. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude compound was purified by flash column chromatography to afford **8** (128 mg, 91 %) as a colorless oil; $R_f = 0.3$ (ethyl acetate/hexane = 1/2); $[\alpha]_D^{25} = +29.25$ (*c* 0.5, $CHCl_3$); IR (neat) 842, 1152, 1423, 1670, 2938, 3436 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ

0.12 (d, $J = 5.6$ Hz, 6H), 0.92 (s, 9H), 1.48 (s, 9H), 1.63–1.73 (m, 3H), 1.93–1.96 (m, 1H), 2.68 (t, $J = 12.5$ Hz, 1H), 3.63 (s, 1H), 3.78 (dd, $J = 5.2$, 11.2 Hz, 1H), 3.84 (dd, $J = 5.2$, 11.7 Hz, 1H), 3.93 (d, $J = 11.5$ Hz, 1H), 4.13 (t, $J = 9.5$ Hz, 1H), 4.46–4.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.39, −5.32, 18.35, 24.14, 26.04, 28.66, 29.16, 60.87, 70.58, 80.08, 155.05; HRMS (M^++H) m/z calcd for $C_{17}H_{36}NO_4Si$: 346.2414; found, 346.2417.

4.7. (2*R*,3*R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-((*tert*-butyldimethylsilyloxy)methyl)piperidine-1-carboxylate 9

t-BuMe_2SiCl (26 mg, 0.17 mmol) and imidazole (12 mg, 0.17 mmol) was added to solution of **8** (50 mg, 0.14 mmol) in DMF (1.5 mL) under argon. The mixture was stirred at 40 °C for 12 h and diluted with Et_2O (3.0 mL) after cooling. An aqueous solution of $NaHCO_3$ (3.0 mL) was added and the product was extracted four times with Et_2O. After washing of the organic layers with H_2O, usual workup and purification by preparative TLC (ethyl acetate/hexane = 1/15), the disilyloxy derivative **9** was obtained (63 mg, 95%) as a colorless oil; $R_f = 0.3$ (ethyl acetate/hexane = 1/8); $[\alpha]_D^{25} = -13.6$ (c 0.5, $CHCl_3$); IR (neat) 774, 1102, 1256, 1695, 2862, 2939 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05–0.01 (m, 12H), 0.90–0.92 (m, 18H), 1.47 (s, 9H), 1.62–1.67 (m, 4H), 2.80–3.05 (br, 1H), 0.374 (br, 1H), 3.80–3.86 (m, 1H), 3.95 (br, 2H), 4.28 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.20, −5.12, −4.71, −4.60, 18.29, 18.49, 24.48, 25.87, 26.01, 26.19, 28.70, 29.93, 37.66, 39.58, 56.14, 58.14, 58.36, 69.83, 79.32, 155.50; HRMS (M^++H) m/z calcd for $C_{23}H_{50}NO_4Si_2$: 460.3278; found, 460.3275.

4.8. (2*R*,3*R*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(hydroxymethyl)piperidine-1-carboxylate 10

Disilyl derivative **9** (100 mg, 0.22 mmol) in a mixture AcOH + THF + H_2O 13:3:7 (2.0 mL) was stirred at 30 °C for 12 h. After dilution with CH_2Cl_2 (3.0 mL) and the addition of Na_2CO_3, the organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. After the usual workup, the product was purified by flash column chromatography (ethyl acetate/hexane = 1/2) to afford the primary alcohol **10** (71 mg, 94%) as a colorless oil; $R_f = 0.3$ (ethyl acetate/hexane = 1/2); $[\alpha]_D^{25} = -17.1$ (c 1.0, $CHCl_3$); IR (neat) 774, 1100, 1418, 1687, 2863, 2941, 3452 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (d, $J = 12.0$ Hz, 6H), 0.91 (s, 9H), 1.48 (s, 9H), 1.67–1.76 (m, 4H), 2.39 (dd, $J = 4.0$, 8.0 Hz, 1H), 2.65–2.79 (br, 1H), 3.72 (br, 1H), 3.85–4.15 (m, 3H), 4.38–4.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.80, −4.55, 18.25, 24.17, 25.99, 28.63, 29.18, 31.13, 38.34, 39.73, 56.07, 56.83, 59.59, 70.28, 71.07, 80.29, 155.41; HRMS (M^++H) m/z calcd for $C_{17}H_{36}NO_4Si$: 346.2414; found, 346.2418.

4.9. (2*S*,3*R*)-3-Hydroxypiperidine-2-carboxylic acid 1

Spectral data of compound **1**:[6] mp 233–238 °C (decomp); $R_f = 0.30$ (EtOAc/MeOH/30%NH_4OH = 5/5/1); $[\alpha]_D^{25} = -53.8$ (c 0.6, H_2O) {lit. see Ref. 3e: $[\alpha]_D^{25} = -52.8$ (c 0.6, H_2O)}; IR (neat) 993, 1401, 1621, 3375 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 1.63–1.73 (m, 2H), 1.86–1.94 (m, 2H), 2.89–2.95 (m, 1H), 3.31–3.35 (m, 1H), 3.58 (d, $J = 2.0$ Hz, 1H), 4.42–4.43 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 17.30, 30.12, 45.02, 63.67, 65.53, 173.66; HRMS (M^++H) m/z calcd for $C_6H_{12}NO_3$: 146.0817; found, 146.0819.

Acknowledgments

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6. The conversion of **10** to **1** has been reported earlier by Liang and Datta, see Ref. 3b.