A stereoselective total synthesis of *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid

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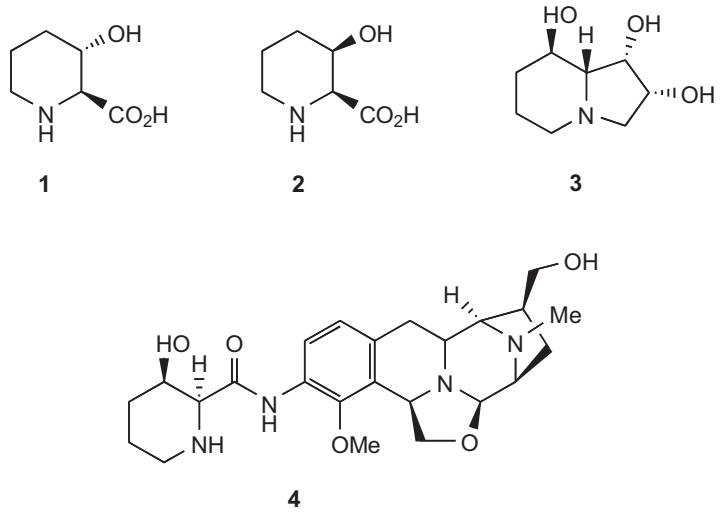
A stereoselective total synthesis of (2*R*,3*S*)-3-hydroxypipecolic acid starting from an enantiomerically pure α-amino alcohol is reported. The synthesis involved a regioselective mesylation and subsequent cyclisation as key steps.

Keywords: L-serine, amino alcohol, hydroxypipecolic acid, piperidine

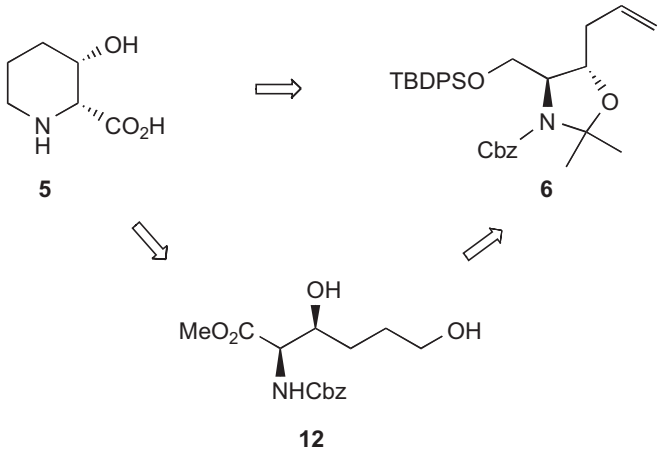
3-Hydroxypipecolic acid is a nonproteinogenic cyclic α-amino acid whose structure is found in a variety of biologically-active natural and non-natural compounds. For instance, the *trans*-3-hydroxypipecolic acid **1** is an advanced intermediate in the synthesis of (–)-swainsonine **3**,[1] a potent α-D-mannosidase inhibitor,[2] while the related *cis*-isomer **2** structure is contained in tetrazomine **4**,[3] an antitumor antibiotic (Scheme 1).

The 3-hydroxypipecolic acid framework has been used as a conformationally constrained α-amino β-hydroxy acid in the synthesis of peptidomimetics,[4] and has been incorporated in the preparation of biologically active compounds such as immunosupressants,[5] enzyme inhibitors,[6] and anticancer[7] or anti-HIV[8] agents. Consequently, a number of synthetic studies have been directed towards the synthesis of *cis*- or *trans*-3-hydroxypipecolic acid.[9] Among the four possible isomers of 3-hydroxypipecolic acid, only few syntheses of the (2*R*,3*S*)-enantiomer **5** have been reported.[9f] As part of a program directed towards the synthesis of biologically-active products using the enantiomerically pure α-amino alcohol **6** (derived from L-serine) as a chiral building block,[10] we report an efficient synthesis of *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid **5** (Scheme 2).

Thus, the target compound would be obtained from **6** *via* alcohol **12** through a cyclisation reaction.



Scheme 1 Structures of *trans*- and *cis*-3-hydroxypipecolic acid **1** and **2**, swainsonine **3** and tetrazomine **4**.



Scheme 2 Retrosynthetic analysis for *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid **5**.

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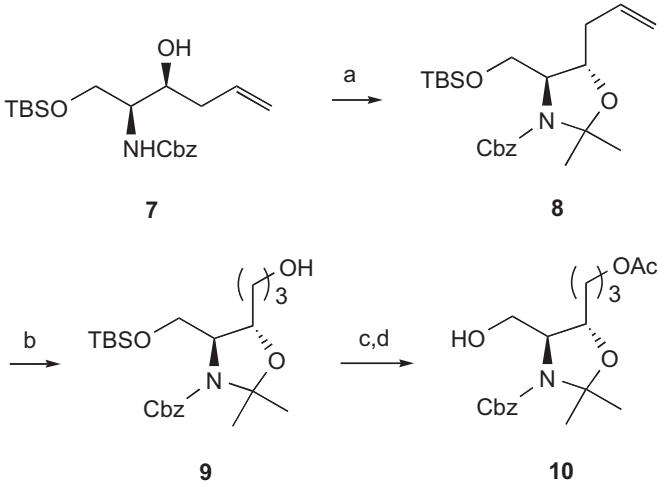
Results and discussion

The synthesis of compound **12** required hydroboration of **6** in order to introduce the primary alcohol function. However, first attempts of hydroboration of the alkene **6** using either 9-BBN or BH_3:Me_2S resulted in cleavage of the *tert*-butyldiphenylsilyl (TBDPS) protecting group, affording the corresponding diol, thus impeding the remainder of the synthesis. We decided to replace the TBDPS group by a *tert*-butyldimethylsilyl (TBS) group. Thus, the parent compound **8** was prepared from the known amino alcohol **7**[11] by treatment with 2,2-dimethoxypropane in the presence of catalytic *p*-toluenesulfonic acid (Scheme 3).

Hydroboration of compound **8** was initially carried out with 9-BBN which afforded non-reproducible results. However, the use of BH_3:Me_2S gave the expected alcohol **9** in 76% yield. After protection of **9** as an acetate, removal of the TBS group by treatment with tetrabutylammonium fluoride afforded the corresponding alcohol **10** in 78% yield.

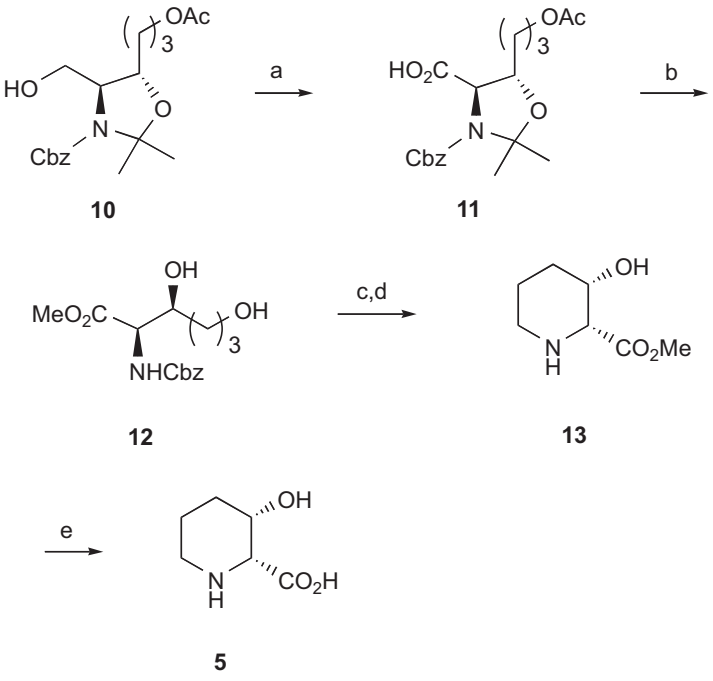
With the selectively protected alcohol **10** in hand, the synthesis of *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid **5** was continued as depicted in Scheme 4. Conversion of **10** into the corresponding carboxylic acid **11** was performed using sodium periodate and catalytic ruthenium chloride in carbon tetrachloride/acetonitrile/water (1/1/1.5) at room temperature.[12] Subsequent concomitant esterification of the carboxylic acid, deprotection of the amino alcohol moiety and hydrolysis of the acetate function were then obtained by simply heating compound **11** in methanol in the presence of a catalytic amount of hydrochloric acid. Under these conditions, the corresponding diol **12** was obtained with a satisfactory 90% yield.

Initial attempts to achieve a one-pot selective mesylation of the primary alcohol and cyclisation were unsuccessful. Indeed, treatment of **12** with methanesulfonyl chloride and triethylamine at –78°C afforded the corresponding mesylate but no cyclisation was observed. Increasing the reaction temperature to 0°C gave the expected piperidine in only



7 **8** **9** **10**

Scheme 3 *Reagents and conditions*: (a) Dimethoxypropane, cat. PTSA, benzene, Δ, 3 h, 95%; (b) BH_3:Me_2S, THF, 0°C, 3 h then EtOH, 3M NaOH, 30% aq. H_2O_2, rt, 3 h, 76%; (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0°C to rt, 14 h; (d) $n$$Bu_4NF$, THF, rt, 3 h, 78% (2 steps).



10 **11** **12** **13** **5**

Scheme 4 *Reagents and conditions*: (a) $RuCl_3.H_2O$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$, r.t., 8 h, 82%; (b) MeOH, cat. HCl, Δ, 8 h, 90%; (c) MsCl, Et_3N, CH_2Cl_2, –78°C, 3 h; (d) H_2, Pd/C, MeOH, rt, 12 h, 60% (2 steps); (e) NaOH, EtOH, H_2O, rt, 12 h then Dowex 50W-X8, 80%.

30% yield, with a lot of side-products being formed. Finally, the hydroxypipecolic acid core was prepared in stages. Thus, the mesylation reaction was quenched at –78°C and the crude product was subjected to hydrogenolysis in the presence of Pd/C to afford the corresponding primary amine, which in turn led to the expected cyclisation product **13** in 60% overall yield. After saponification and purification on Dowex 50W-X8, *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid **5** was finally obtained in 80% yield. The spectroscopic data of **5** were found to be in agreement with those reported previously.[3]

Conclusion

In conclusion, a short and efficient synthesis of *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid **5** has been achieved using the enantiomerically pure α-amino alcohol **7** as a chiral building block. In terms of efficiency (9 steps from **7**, 20% overall yield), our synthetic route to **5** compares favourably with the other reported syntheses. Moreover, since the antipode of **7** is easily available (from D-serine), the synthesis developed here can be applied to the preparation of *ent*-**5**.

Experimental

All solvents were reagent grade and distilled under argon prior to use. Amines were distilled from potassium hydroxide and CH_2Cl_2 from calcium hydride. THF was distilled from sodium benzophenone. All commercially available reagents were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded either at 400 and 100 MHz, respectively, on an Avance 400 Bruker spectrometer, or at 300 and 75 MHz, respectively, on an Avance 300 Bruker spectrometer. IR spectra were recorded on an IRFT Nicolet 210 spectrometer. Mass spectra (MS) were measured on a Nermag R10-10C mass spectrometer (DCI/NH_3). Flash column chromatography was performed on Merck silica gel (0.040–0.063 mesh). TLC analysis was performed on Merck silica gel 60 PF 254 and sprayed with either phosphomolybdic acid or ninhydrin. Specific rotations were recorded on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Service Régional de Microanalyse de l'Université Pierre et Marie Curie.

(*4S,5S)-5-Allyl-4-(tert-butyldimethylsilanyloxymethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid benzyl ester* (**8**): A mixture of amino alcohol **7** (5.7 g, 15 mmol), 2,2-dimethoxypropane (5.5 ml, 45 mmol) and *p*-toluenesulfonic acid (28.5 mg, 15 mmol) in dry benzene (100 ml) was heated for 3 h under azeotropic conditions. Ether (80 ml) was added to the cooled reaction mixture and the solution was washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification of the residue by flash chromatography (cyclohexane/ethyl acetate: 9/1) afforded **8** (5.0 g, 80%) as an oil. $[\alpha]_D^{25}$ = + 10.3 (*c* 2.7, CH_2Cl_2). IR (neat): 3069, 2933, 2889, 2854, 1708, 1642, 1466, 1405, 1352, 1256, 850 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6, 50°C) δ 0.90 (s, 9H), 1.59 (s, 3H), 1.71 (s, 3H), 2.35 (t, 2H, J = 6.4 Hz), 3.70–4.05 (m, 3H), 4.30 (q, 1H, J = 6.4 Hz), 5.00 (dd, 1H, $^3J_{cis}$ = 10.2 and ^2J = 1.7 Hz), 5.03 (d, 1H, ^2J = 12.4 Hz), 5.06 (dd, 1H, $^3J_{trans}$ = 17.1 and ^2J = 1.7 Hz), 5.14 (d, 1H, ^2J = 12.4 Hz), 5.84 (ddt, 1H, $^3J_{trans}$ = 17.1, $^3J_{cis}$ = 10.2 and ^3J = 6.4 Hz), 7.06–7.25 (m, 5H). ^{13}C NMR (100 MHz, C_6D_6, 50°C) δ –5.3, 18.4, 26.0, 26.8, 27.8, 39.4, 53.2, 63.2, 66.9, 77.7, 94.9, 117.3, 128.5, 128.7, 134.6, 137.3, 152.6. MS (DCI/NH_3) *m/z* 420 [M + H]$^+$.

(*4S,5S)-4-(tert-Butyldimethylsilyloxymethyl)-5-(3-hydroxy-propyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid benzyl ester* (**9**): To a solution of **8** (4.7 g, 11.2 mmol) in THF (50 ml) was added at 0°C borane-methyl sulfide complex (10M, 2.8 ml, 28 mmol). The reaction mixture was stirred at this temperature for 24 h, then 30% aqueous H_2O_2 (3.6 ml), 3M NaOH (4 ml) and EtOH (4 ml) were added. After stirring at room temperature for 3 h, water (100 ml) was added and the solution was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (cyclohexane/ethyl acetate: 7/3) afforded **9** (3.72 g, 76%) as a colourless oil. $[\alpha]_D^{25}$ = + 4.9 (*c* 1.2, CH_2Cl_2). IR (neat): 3445, 2955, 2927, 2879, 2855, 1703, 1472, 1408, 1257, 838 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6, 70°C) δ 0.02 (s, 6H), 0.90 (s, 9H), 1.00–1.15 (m, 1H), 1.50–1.90 (m, 10H), 3.34–3.50 (m, 2H), 3.62–3.72 (m, 1H), 3.76–3.98 (m, 2H), 4.15–4.28 (m, 1H), 5.10 (AB system, 2H, J = 12.2 Hz), 7.00–7.30 (m, 5H). ^{13}C NMR (100 MHz, C_6D_6, 60°C) δ –5.3, 18.4, 26.1, 26.9, 28.0, 29.6, 31.8, 62.4, 62.6, 64.0, 67.0, 78.3, 94.8, 128.5, 128.6. MS (DCI/NH_3) *m/z* 438 [M + H]$^+$. Anal. Calcd. for $C_{23}H_{39}NSiO_5$: C, 63.1; H, 9.0; N, 3.2. Found: C, 63.1; H, 9.2; N, 3.3%.

(4S,5S)-5-(3-Acetoxypropyl)-4-hydroxymethyl-2,2-dimethyl-oxazolidine-3-carboxylic acid benzyl ester (**10**): To a solution of alcohol **9** (2.0 g, 4.57 mmol) in CH_2Cl_2 (50 ml) were added Et_3N (1.28 ml, 9.14 mmol), acetic anhydride (648 µl, 6.85 µmol) and a catalytic amount of 4-DMAP (40 mg). The reaction mixture was stirred at room temperature for 4 h, quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$and concentred to afford the expected acetate as a yellow oil which was used in the next reaction without further purification. To a solution of the acetate in THF (30 ml) was added dropwise nBu$_4$NF (1M solution in THF, 6.85 ml). After stirring at room temperature for 8 h, water (50 ml) was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (cyclohexane/ethyl acetate: 6/4) afforded **10** (1.30 g, 78%) as a viscous oil. $[\alpha]_D^{25}$ = –1.8 (*c* 2.5, MeOH). IR (neat): 3460, 2934, 1736, 1700, 1408 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6, 60°C) δ 1.34–1.74 (m, 4H), 1.45 (s, 3H), 1.57 (s, 3H), 1.70 (s, 3H), 3.50–3.72 (m, 3H), 3.73–3.89 (m, 1H), 3.90–4.05 (m, 2H), 5.05 (AB system, 2H, J = 12.2 Hz), 7.00–7.30 (m, 5H). ^{13}C NMR (100 MHz, C_6D_6, 70°C) two conformers δ 25.4, 25.8, 26.3, 26.6, 27.5, 28.0, 30.9, 61.5, 63.5, 64.0, 65.4, 67.2, 67.4, 76.5, 77.3, 94.9, 128.5, 128.7, 137.1, 153.7, 169.9. MS (CI, NH_3) *m/z* 383 [M + NH_4]$^+$, 366 [M + H]$^+$. Anal. Calcd. for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.4; N, 3.8. Found: C, 62.9; H, 7.6; N, 3.9%.

(2R,3S)-2-Benzyloxycarbonylamino-3,6-dihydroxy-hexanoic acid methyl ester (**12**): To a suspension of **10** (1.25 g, 3.42 mmol) and sodium periodate (2.2 g, 10.26 mmol) in a 1/1/1.5 mixture of CCl_4/MeCN/H_2O (28 ml) was added ruthenium trichloride hydrate (35 mg, 0.16 mmol) and the mixture was stirred vigorously for 4 h at room temperature. The dark solution was filtered through a Celite pad and rinsed with CH_2Cl_2. The organic phase was separated, dried over $MgSO_4$ and concentrated. The crude acid was dissolved in MeOH (40 ml), conc. HCl (1 drop) was added, and the mixture was refluxed overnight. After evaporation of the solvent, water (60 ml) was added and the mixture was extracted with AcOEt. Purification of the residue by flash chromatography (cyclohexane/ethyl acetate: 2/8) afforded **12** (0.8 g, 75%) as an oil. $[\alpha]_D^{25}$ = –2.4 (*c* 1.5, CH_2Cl_2). IR (neat): 3380, 2955, 2919, 2847, 1716, 1531 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–1.70 (m, 4H), 3.42–3.76 (m, 2H), 3.67 (s, 3H), 4.05 (d, 1H, J = 7.8 Hz), 4.29 (d, 1H, J = 9.3 Hz), 5.04 (s, 2H), 5.70 (d, 1H, J = 9.3 Hz), 7.10–7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 31.3, 52.5, 58.4, 62.5, 67.1, 71.8, 128.0, 128.1, 128.5, 136.2, 156.8, 171.7. MS (CI, NH_3) *m/z* 329 [M + NH_4]$^+$, 312 [M + H]$^+$. Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.9; H, 6.8; N, 4.5. Found: C, 58.1; H, 7.0; N, 4.5%.

(2R,3S)-3-Hydroxypiperidine-2-carboxylic acid methyl ester (**13**): To a solution of **12** (1.09, 3.5 mmol) in CH_2Cl_2, were added triethyl-amine (1.0 ml, 7.0 mmol) and mesyl chloride (285 µL, 3.67 mmol) at –78°C. The mixture was stirred at –78°C for 3 h, then water (40 ml) was added. The organic phase was separated and washed with brine, dried over $MgSO_4$ and concentrated to afford the crude mesylate. To a degassed solution of the crude mesylate in MeOH (30 ml) was added 10% Pd/C (30 mg). The resulting mixture was purged three times with hydrogen and stirred at room temperature for 12 h under hydrogen at atmospheric pressure. The reaction mixture was then filtered on Celite, rinsed with MeOH, and concentrated. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH: 9/1) afforded pure **13** (557 mg, 60%) as an oil. $[\alpha]_D^{25}$ + 12.7 (*c* 1.6, MeOH). IR (neat) 3359, 3025, 2965, 2923, 1750 cm^{-1}. ^{1}H NMR (400 MHz, MeOD) δ 1.69 (br d, 1H, J = 14.2 Hz), 1.83 (tdd, 1H, J = 13.7, 4.2 and 2.3 Hz), 1.98 (br d, 1H, J = 14.2 Hz), 2.12 (qt, 1H, J = 13.7 and 4.2 Hz), 3.05 (td, 1H, J = 12.9 and 3.1 Hz), 3.30–3.43 (m, 1H), 3.88 (s, 3H), 4.15 (d, 1H, J = 1.8 Hz), 4.48 (br s, 1H). ^{13}C NMR (75 MHz, MeOD) δ 31.3, 49.0, 54.2, 63.0, 65.8, 170.7. MS (CI, NH_3) *m/z* 160 [M$^+$ + 1].

(2R, 3S)-3-Hydroxypipecolic acid (**5**): To a solution of **13** (240 mg, 1.5 mmol) in EtOH (10 ml), was added 3M NaOH (2 ml) and the mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated and acidified with 3M HCl. The remaining aqueous solution was eluted with 5% NH_4OH through a column packed with Dowex 50W-X8 resin (100–200 mesh, 20 g). The ninhydrin positive fractions were collected and lyophilised to furnish the low-melting solid **5** (175 mg, 80%). $[\alpha]_D^{25}$ + 17.5 (*c* 0.6, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 1.70–1.85 (m, 2H), 1.91-2.01 (m, 2H), 2.99 (dt, 1H, J = 12.9 and 3.1 Hz), 3.38 (m, 1H), 3.65 (d, 1H, J = 2.0 Hz), 4.49 (br s, 1H). ^{13}C NMR (75 MHz, D_2O) δ 16.5, 29.4, 44.1, 62.8, 64.6, 173.0. MS (CI, NH_3) *m/z* 146 [M$^+$ + 1].

Received 2 May 2007; accepted 4 June 2007
Paper 07/4629 doi: 10.3184/030823407X218020

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