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Stereocontrolled syntheses of *trans*-3-hydroxypipecolic acids and application to (−)-swainsonine

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Summary — The enantioselective syntheses of both enantiomers of *trans*-3-hydroxypipecolic acid are described from a prochiral starting material: the methyl 3-oxo-7-methyloct-6-enoate. The stereocenters of the piperidine ring are created by enantioselective hydrogenation of the β-ketoester and by diastereoselective electrophilic amination of the β-hydroxyester enolate. (2*R*,3*R*)-3-Hydroxypipecolic acid methyl ester is the precursor for the synthesis of (−)-swainsonine.

piperidine / indolizidine / chiral ruthenium complex / electrophilic amination

Résumé — Synthèses stéréocontrôlées des acides *trans*-3-hydroxypipécoliques, et application à la (−)-swainsonine. Les synthèses énantiosélectives des deux énantiomères de l'acide *trans*-3-hydroxypipécolique ont été réalisées à partir du 3-oxo-7-méthyloct-6-énoate de méthyle. La chiralité est introduite par hydrogénation énantiosélective du β-cétoester en présence de catalyseurs chiraux du ruthénium et par amination électrophile de l'énolate du β-hydroxyester obtenu. L'ester méthylique de l'acide (2*R*,3*R*)-3-hydroxypipécolique est le précurseur pour la synthèse de la (−)-swainsonine.

pipéridine / indolizidine / complexe chiral du ruthénium / amination électrophile

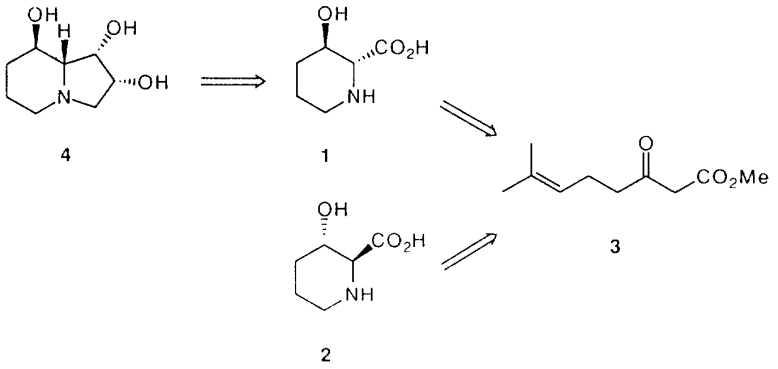
The piperidine ring is present in many natural products such as simple piperidine alkaloids displaying significant activities [1]. 3,4-Dihydroxy and 3,4,5-trihydroxypipecolic acids have been screened as potential inhibitors of HIV replication [2]. The synthesis and the activity of monohydroxylated piperidine as 3-hydroxypipecolic acid is less well documented. We proposed recently diastereoselective routes to both enantiomers **1** and **2** of the *trans*-3-hydroxypipecolic acid starting from the prochiral β-ketoester **3** [3]. We describe here these syntheses and the application to the synthesis of (−)-swainsonine **4**.

Since its initial isolation from the fungus *Rhizoctonia leguminicola* [4], **4** has aroused considerable interest, primarily due to its potent and highly specific α-D-mannosidase inhibitory activity [5]. More recently, **4** has been shown to exhibit immunoregulative properties [6,7] and antimetastatic activity [7,8]. Its chemical preparation as a practical alternative to natural sources is highly desirable. Most of the previously reported methodologies utilized the chiral pool as starting material: carbohydrates, [4a–b, 9], α-amino [10] and α-hydroxyacids [11]. Only two approaches to (−)-swainsonine have been reported using respectively an achiral and a racemic compound as starting material. The first employed Sharpless asymmetric epoxidation of an allylic alcohol and the Masamune/Sharpless iterative methodology [12]. The second utilized as key steps the kinetic resolution of an α-furfurylamide and the Sharpless asymmetric dihydroxylation reaction [13]. The development of flexible technologies for the synthesis of (−)-swainsonine and its analogs remains of great interest.

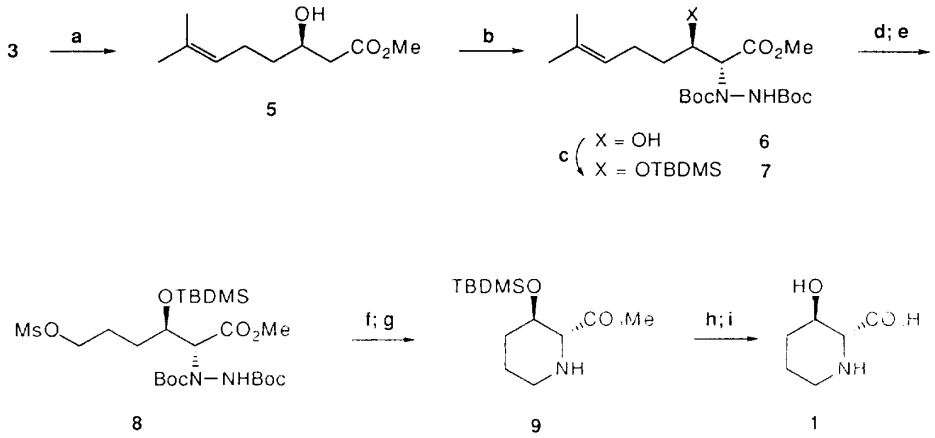
Our strategy is illustrated in scheme 1: the key intermediate is the optically pure (2*R*,3*R*)-3-hydroxypipecolic acid **1**, whereas (2*S*,3*S*)-3-hydroxypipecolic acid **2** could be a precursor of 8,8a-diepiswainsonine and other diastereoisomers.

Compound **1** has the same configuration as the piperidine ring of (−)-swainsonine **4** and can be used at its precursor. The carbons of the pyrrolidine ring can be introduced by homologation of the carboxylic function of **1**. The acid **1** was obtained from the β-ketoester **3** using as key steps the enantioselective hydrogenation in the presence of a chiral ruthenium catalyst followed by the diastereoselective electrophilic amination to create the hydroxyl and amino functions in *anti* relationship.

The β-ketoester **3** was hydrogenated under mild conditions at atmospheric pressure in the presence of $RuBr_2$[(*R*)-Binap] catalyst prepared in situ from commercially available Ru(Cod)(2-methylallyl)$_2$ [14]. This reaction was quantitative and proceeded with high



Scheme 1

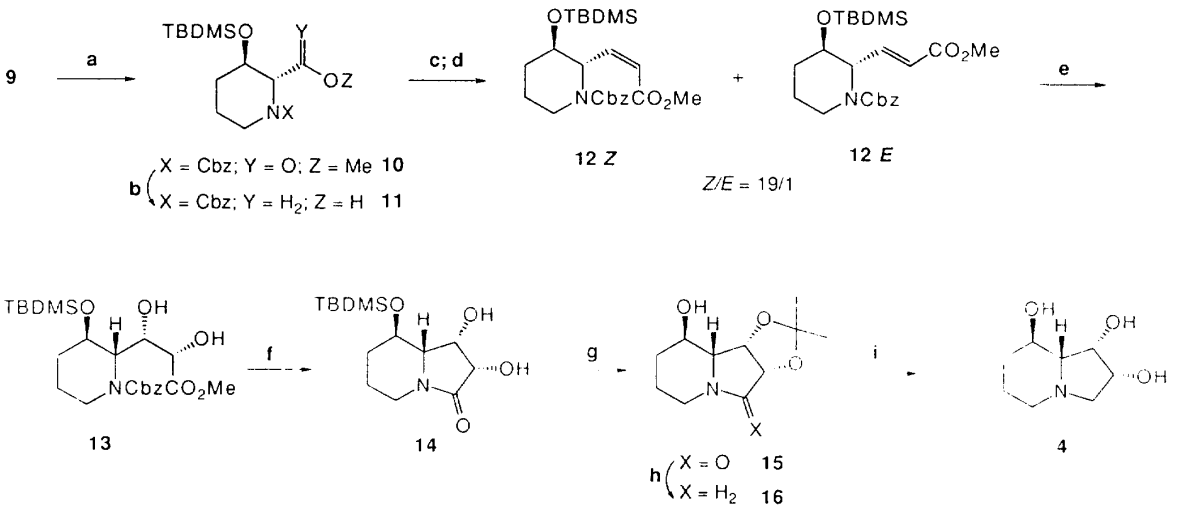


Scheme 2. (a) $RuBr_2[(R)$-Binap] in situ (2%), H_2 (1 atm), MeOH, 2 h, 50 °C (98%, ee = 97%). (b) 1. MeZnBr (1.1 equiv), THF, 30 min, 0 °C; 2. LDA (2.2 equiv), THF, 1 h, −78 °C; 3. DBAD (2 equiv), THF, 30 min, −78 °C (66%, de > 95%). (c) 2,6-lutidine (2 equiv), TBDMSOTf (1.5 equiv), CH_2Cl_2, 2 h, −78 °C (77%). (d) 1. O_3, CH_2Cl_2, 1 h, −78 °C; 2. BH_3–Me_2S (4 equiv), CH_2Cl_2, −78 °C → room temperature, then 16 h (96%). (e) MsCl (1.5 equiv), pyridine, 1 h, 0 °C (86%). (f) TFA, CH_2Cl_2, 0 °C → room temperature, then 2 h. (g) 1. Raney Ni, H_2 (1 atm), ultrasound, MeOH, room temperature, 2 h; 2. Et_3N, CH_2Cl_2, 30 min, room temperature (75% from **8**). (h) HF, CH_3CN, 50 °C. (i) K_2CO_3, MeOH, H_2O then Amberlite CG 50 (80% from **9**).

enantio- and chemoselectivity. The electrophilic amination of the ester enolate was carried out with di-*tert*-butyl azodicarboxylate (DBAD) in the presence of MeZnBr to produce exclusively the *anti* diastereoisomer **6** [15]. The resulting α-hydrazino β-hydroxyester was then protected as a silyl ether. Reductive ozonolysis of the double bond and subsequent mesylation of the primary alcohol provided **8** in 64% yield from **6**. Deprotection and cleavage of the hydrazine bond followed by a basic treatment gave the cyclic product **9** which constituted the piperidine ring of (−)-swainsonine **4**.

(2*S*,3*S*)-3-Hydroxypipecolic acid **2** has been obtained using the same reaction sequence. $RuBr_2[(S)$-Binap] was used as chiral catalyst for the hydrogenation of **3** to afford the corresponding (*S*)-methyl 3-hydroxy-7-methyloct-6-enoate in 98% yield and 97% ee. Recently another synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid has been described starting from (*R*)-phenylglycinol [16].

The synthetic goals were then achieved through the homologation of the ester function and dihydroxylation of the resulting double bond. The piperidine **9** was first protected as a benzyl carbamate. The ester function of compound **10** was then reduced with $Ca(BH_4)_2$ and the corresponding alcohol was oxidized to the aldehyde under classical Swern conditions. The formation of the double bond was run under kinetic control using Clark–Still's reagent: potassium salt of methyl bis(trifluoroethyl)phosphonoacetate [17] to afford the *Z*-alkene **12** as the major stereoisomer (*Z*/*E* = 19:1). The *Z*–*E* mixture was not separable by flash or medium-pressure chromatography. The use of stabilized ylide : ethyl (triphenylphosphoranylidene) acetate inverted the *Z*/*E* ratio to 1:15.



Scheme 3. (a) CbzCl (1.1 equiv), DMAP (1.1 equiv), CH_3CN, 0 °C → room temperature, then 2.5 h (74%). (b) $Ca(BH_4)_2$ (6 equiv), THF/EtOH (2:3), −20 °C → room temperature, then 45 min (91%). (c) 1. $(COCl)_2$ (3 equiv), DMSO (4 equiv), CH_2Cl_2, 10 min, −60 °C; 2. Et_3N (8 equiv), 30 min, −60 °C, then H_2O (100%). (d) $(CF_3CH_2O)_2P(O)CH^-COOMe$, K^+ (1 equiv), 18-crown-6 (5 equiv), THF, 2 h, −78 °C (83%, Z/E = 19:1). (e) OsO_4 (0.2 equiv), Me_3NO (2.2 equiv), acetone–H_2O (19:1), ultrasound, 2 h, room temperature, then chromatography (71%). (f) Pd/C, H_2 (1 atm), AcONa (2.2 equiv), MeOH, 1 h, room temperature, then 2 h, 35 °C (90%). (g) 2,2-dimethoxypropane, Dowex H^+, 4 h, room temperature (97%). (h) 1. BH_3–Me_2S (5 equiv), THF, 14 h, room temperature, then EtOH and vacuum; 2. EtOH, 2 h, reflux (81%). (i) HCl, 1 M, 30 min, reflux, then Dowex OH^- (96%).

The dihydroxylation of the double bond of **12** with OsO_4 in the presence of trimethylamine *N*-oxide was unsuccessful. However, under ultrasound the reaction proceeded smoothly. The desired optically pure diastereoisomer **13** was separated from the mixture of stereoisomers by flash chromatography and isolated in 71% yield. The use of Sharpless asymmetric dihydroxylation reagent did not increase the diastereoselectivity. The stereochemical assignments for this product were based on allylic 1,3-strain [18]. Similar results were observed by Kibayashi et al for lactams α-substituted with a *Z*-olefinic system [11b].

The stereochemistry of **13** was correlated by transformation to the known compound **16** and to (−)-swainsonine **4**. Cleavage of the benzyl carbamate under classical hydrogenolysis conditions provided the bicyclic product **14** with 90% yield. In a first attempt, the lactam **14** has been directly reduced by $LiAlH_4$ at 0 °C and the silyl ether cleaved using acidic ion exchange resin (Dowex H^+) in methanol at room temperature. (−)-Swainsonine **4** was obtained in 47% yield from **14**. This moderate yield resulted from the reduction step.

To improve the chemical yield, the 1,2-diol of the lactam **14** was converted into acetonide by treatment with 2,2-dimethoxypropane in the presence of an acidic ion exchange resin. The silyl ether was simultaneously cleaved by the acidic conditions of the reaction mixture. The lactam **15** was then reduced with BH_3–Me_2S to give the known product **16**. The (1*S*,2*R*) configuration was confirmed at this stage by comparison with the spectrometric data of the literature [11b]. Finally, deprotection of the acetonide produced (−)-swainsonine **4** in 75% yield from **14**. The ^1H and ^{13}C NMR spectra of synthetic **4** were identical with those described in the literature. The observed optical rotation and melting point were found to be in accordance with the reported values [4b,c].

In conclusion, the first stereoselective synthesis of *trans*-3-hydroxypipecolic acid and a new chiral route to (−)-swainsonine have been developed starting from the prochiral β-ketoester **3**. The asymmetry was introduced by enantioselective hydrogenation in the presence of $RuBr_2$[(*R*)-Binap] as catalyst, followed by a diastereoselective electrophilic amination. The use of the (*S*)-Binap in the hydrogenation step and the formation of the *E* double bond instead of the *Z* one for compound **12** would extend our strategy to the other diastereoisomers of (−)-swainsonine. Further studies using this methodology, aiming at the synthesis of polyhydroxylated indolizidine or pyrrolizidine compounds, are now in progress in our group.

Experimental section

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 589 nm. Infrared spectra (IR) were taken using a Bruker 45 FTIR instrument. NMR spectra were recorded on a Bruker AC200 spectrometer. ^1H spectra were run at 200 MHz and ^{13}C spectra at 50.3 MHz. Elemental analyses were performed by the Service Régional de Microanalyses de l'Université Pierre et Marie Curie. MS data were recorded on a ZAB-HSQ instrument by the Service de Spectrométrie de l'Université Pierre et Marie Curie. Column chromatographic separations were carried out over Merck

silica gel 60 (0.040–0.063 mm); analytical thin layer chromatography (TLC) experiments were performed on Merck silica gel TLC plates F254.

(R) Methyl 3-hydroxy-7-methyloct-6-enoate **5**

Methyl 3-oxo-7-methyloct-6-enoate 3 (0.92 g, 4.95 mmol) was diluted under argon in degassed methanol (4 mL). This solution was canulated into a Schlenk tube containing the [(*R*)-BinapRu]Br_2 complex (2 mol%). The system was purged 3 times with hydrogen and the reaction mixture was stirred under hydrogen (1 atm) at 50 °C for 2 h. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved with hexane and filtrated on celite pad. The filtrate was concentrated under reduced pressure. The brownish oil was distilled (95 °C, 0.5 mm Hg) to give **5** as a colourless oil (0.9 g, 98%).

$[\alpha]_D^{20} = +15$ ($c = 1.2$, $CHCl_3$).

IR ν_{max}: 3 430, 2 953, 2 917, 1 736, 1 623 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 5.1 (ddt, $J = 7.1, 1.4, 1.4$ Hz, 1H), 4 (m, 1H), 3.7 (s, 3H), 2.92 (broad d, $J = 3.1$ Hz, 1H), 2.52 (dd, $J = 16.5$, 4 Hz, 1H), 2.4 (dd, $J = 16.5$, 8.4 Hz, 1H), 2.10 (dt, $J = 7.1$, 7.1 Hz, 2H), 1.61 (s, 3H), 1.55 (dt, $J = 8$, 7.1 Hz, 2H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.3, 132.2, 123.5, 67.5, 51.6, 41.1, 36.4, 25.6, 23.9, 17.5.

Anal Calc for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.42; H, 9.76.

(2R,3R) Methyl 2-[1,2-bis(tert-butoxycarbonyl)hydrazino]-3-hydroxy-7-methyloct-6-enoate **6**

To **5** (5.48 g, 29 mmol) in dry THF (29 mL) at 0 °C, was added dropwise a solution of MeZnBr (30 mmol) prepared from $ZnBr_2$ (6.75 g, 30 mmol) in dry THF (30 mL) and MeLi (24.3 mL, 30 mmol, 1.2 M sol in Et_2O). After stirring for 1 h, the mixture was cooled at −78 °C and a solution of lithium diisopropylamide (60 mmol) in THF was added dropwise. After further stirring for 1 h at −78 °C, a solution of DBAD (13.8 g, 60 mmol) in THF (15 mL) was added dropwise. The reaction mixture was stirred until no more starting material was detectable by TLC, hydrolysed at −78 °C with a saturated aqueous solution of NH4Cl (30 mL), warmed at room temperature, extracted into Et_2O, dried and evaporated. The crude product was purified by flash chromatography eluting with cyclohexane/AcOEt (4:1) to give **6** (8 g, 66%).

$[\alpha]_D^{20} = -22$ ($c = 1$, EtOH).

IR ν_{max}: 3 401, 3 053, 2 981, 1 743 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 6.6 (m, 1H), 5.1 (t, $J = 6.5$ Hz, 1H), 4.75 (m, 1H), 4.1 (m, 1H), 3.76 (s, 3H), 3.66 (broad s, 1H), 2.15 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.55 (m, 2H), 1.47 (s, 18H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.5, 155.6, 154.9, 132, 123.6, 82.3, 81.9, 70.1, 63.4, 52.1, 33.6, 28, 27.9, 25.6, 24.8, 17.5.

Anal Calc for $C_{20}H_{36}N_2O_7$: C, 57.67; H, 8.71; N, 6.72. Found: C, 57.59; H, 8.71; N, 6.84.

(2R,3R) Methyl 2-[1,2-bis(tert-butoxycarbonyl) hydrazino]-3-[(tert-butyldimethylsilyl)oxy]-7-methyloct-6-enoate **7**

tert-Butyldimethylsilyl triflate (0.25 mL, 1.08 mmol) was added dropwise in 15 min at −78 °C to a solution of **6** (0.3 g, 0.72 mmol) in CH_2Cl_2 (3 mL) containing 2,6-lutidine (0.17 mL, 1.44 mmol). The solution was stirred for 2 h at −78 °C, MeOH (1 mL) was added and the mixture was warmed to room temperature. The solvents were removed under reduced pressure and the residue was purified by chromatography eluting with cyclohexane/AcOEt (9:1) in presence of 2% of Et_3N, to give **7** as a colorless oil (0.294 g, 77%).

$[\alpha]_D^{20} = -15$ ($c = 0.95$, $CHCl_3$).

IR ν_{max}: 3 331, 2 927, 2 856, 1 745, 1 709 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 6.51 (broad s, 1H), 5.1 (t, $J = 7.4$ Hz, 1H), 4.75 (m, 1H), 4.13 (m, 1H), 3.7 (s, 3H), 2.06 (td, $J = 7.4$, 7.4, 2H), 1.75 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.47 (s, 9H), 1.45 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.9, 154.8, 131.8, 123.7, 82, 80.8, 70.8, 63, 51.7, 35.1, 28.1, 28, 25.6, 22.8, 17.8, 17.6, −4.3, −5.2.

Anal Calc for $C_{26}H_{50}N_2O_7Si$: C, 58.83; H, 9.49; N, 5.28. Found: C, 58.96; H, 9.49; N, 5.22.

(2R,3R) Methyl 2-[1,2-bis(tert-butoxycarbonyl) hydrazino]-3-[(tert-butyldimethylsilyl)oxy]-6-(mesyloxy)hexanoate **8**

7 (5.45 g, 10.3 mmol) was dissolved under argon in anhydrous CH_2Cl_2 (100 mL) and the solution was cooled at −78 °C. Ozone was bubbled through the solution until the blue colour persisted. The solution was stirred 1 h and purged with argon until the blue colour disappeared. BH_3–Me_2S (2 M in THF, 20.3 mL, 40.6 mL) was added dropwise. The solution was warmed to room temperature and stirred for 16 h. The reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl (5 mL). After 30 min, solid $NaHCO_3$ was added to obtain pH = 8–9 for the aqueous layer. The organic layer was separated, dried over $MgSO_4$, filtrated and concentrated under reduced pressure to give the crude (2*R*,3*R*) methyl 2-[*N*,*N*′-(di-*tert*-butoxycarbonyl) hydrazino]-3-[*tert*-butyldimethylsilyl)oxy]-6-hydroxyhexanoate as a yellow oil. The crude product was dissolved in anhydrous pyridine (30 mL) and cooled at 0 °C. Mesyl chloride (1.2 mL, 15.4 mmol) was added dropwise and the reaction mixture was stirred for 1 h. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography eluting with cyclohexane/AcOEt (3:1) in the presence of 1% of Et_3N to give **8** (4.93 g, 86%) as a colourless solid.

$[\alpha]_D^{20} = -13$ ($c = 0.97$, $CHCl_3$).

IR ν_{max}: 3 333, 2 951, 2 930, 1 744, 1 708 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 6.55 (broad s, 1H), 4.76 (m, 1H), 4.23 (t, $J = 5.5$ Hz, 2H), 4.2 (m, 1H), 3.69 (s, 3H), 2.99 (s, 3H), 1.82 (m, 4H), 1.68 (s, 3H), 1.61 (s, 3H), 1.45 (s, 9H), 1.43 (s, 9H), 0.83 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.6, 155, 154.7, 82.3, 81.1, 69.8, 62.4, 51.8, 37.2, 30.7, 28.1, 28, 25.5, 23.4, 17.8, −4.4, −5.2.

Anal Calc for $C_{24}H_{48}N_2O_{10}SSi$: C, 49.29; H, 8.26; N, 4.79. Found: C, 49.11; H, 8.14; N, 4.60.

(2R,3R)-3-[(tert-Butyldimethylsilyl)oxy]-2-(methoxycarbonyl)piperidine **9**

Trifluoroacetic acid (3 mL) was added at 0 °C to a solution of **8** (0.184 g, 0.31 mmol) in anhydrous CH_2Cl_2 (3 mL). The solution was stirred 15 min at 0 °C and 2 h at room temperature. The solvents were evaporated under reduced pressure. The residue was dissolved in absolute methanol (3 mL), a small amount of Raney-Ni was added and the reaction mixture was placed under hydrogen (1 atm). The reaction was

performed in an ultrasonic cleaner for 2 h. After filtration over Celite, the solvent was evaporated, the residue was dissolved in CH_2Cl_2 (10 mL) and Et_3N (0.52 mL, 3.8 mmol) was added. The solution was stirred 30 min and a 10% aqueous solution of Na_2CO_3 (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL), the organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with CH_2Cl_2/Et_3N (49:1) to give **9** (64 mg, 75%) as a yellow oil.

$[\alpha]_D^{20} = -41$ ($c = 1.16$, $CHCl_3$).

IR ν_{max}: 3 313, 2 928, 2 855, 1 737 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.69 (m, 1H), 3.21 (d, $J = 8.7$ Hz, 1H), 2.99 (d, $J = 11.6$ Hz, 1H), 2.54 (ddd, $J = 11.6, 11.6, 3.2$ Hz, 1H), 1.97 (m, 1H), 1.84 (broad s, 1H), 1.72 (m, 1H), 1.45 (m, 2H), 0.85 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.1, 70.6, 65.1, 51.7, 44.8, 33.7, 25.5, 17.7, −4.4, −5.2.

Anal Calc for $C_{13}H_{27}NO_3Si$: C, 57.10; H, 9.95; N, 5.12. Found: C, 57.61; H, 9.91; N, 5.01.

(2R,3R)-3-Hydroxypipecolic acid ***1***

A solution of **9** (29 mg, 0.11 mmol) in CH_3CN/48% aqueous HF (3:2) was stirred for 3 h at 50 °C. The solution was cooled at 0 °C, CH_2Cl_2 (50 mL) was added and the pH adjusted to 8–9 with solid $NaHCO_3$. The solution was dried over $MgSO_4$, filtrated and the solvents evaporated under reduced pressure. The crude product was purified by flash chromatography eluting with Et_2O/MeOH (12:1) in the presence of 2% of Et_3N to give the (2*R*,3*R*)-3-hydroxypipecolic acid methyl ester (15 mg, 89%) as a yellow solid. K_2CO_3 (14 mg, 0.1 mmol) was added to a solution of the ester (15 mg, 0.094 mmol) in H_2O/MeOH (4:1) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 5 h. The solution was lyophilized and the residue was eluted with water from an acidic ion exchange resin (Amberlite CG50) to give **1** (11.7 mg, 86%) as a white solid.

$[\alpha]_D^{20} = -14$ ($c = 0.54$, 10% aqueous HCl).

IR ν_{max}: 3 441, 2 985, 2 959, 2 874, 1 627 cm^{-1}.

^1H NMR (200 MHz, D_2O) δ 3.97 (ddd, $J = 7.1, 7.1, 3.1$ Hz, 1H), 3.47 (d, $J = 7.1$ Hz, 1H), 3.16 (m, 1H), 2.92 (m, 1H), 1.8 (m, 2H), 1.53 (m, 1H).

^{13}C NMR (50.3 MHz, D_2O) δ 172.9, 66.8, 62.9, 43.4, 29.1, 19.3.

MS (EI) exact mass calc for ($C_6H_{11}NO_3$–CO_2) 101.0841, found 101.0840; calc for ($C_6H_{11}NO_3$–CO_2H) 100.0762, found 100.0762.

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

$[\alpha]_D^{20} = +13$ ($c = 0.43$, 10% aqueous HCl).

(2R,3R)-1-(Benzyloxycarbonyl)-3-[(tert-butyldimethylsilyl)oxy]-2-(methoxycarbonyl)piperidine ***10***

To a solution of **9** (27 mg, 0.1 mmol) and 4-(1-dimethylamino)pyridine (13 mg, 0.11 mmol) in anhydrous acetonitrile (0.5 mL) at 0 °C, was added dropwise benzyl chloroformate (0.016 mL, 0.11 mmol). The reaction mixture was warmed to room temperature, stirred for 2.5 h and quenched with absolute methanol (0.5 mL). The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography eluting with cyclohexane/AcOEt (9:1) in the presence of 2% of Et_3N to give **10** (30 mg, 74%) as a yellow oil.

$[\alpha]_D^{20} = +8$ ($c = 1$, $CHCl_3$).

IR ν_{max}: 3 353, 3 032, 2 950, 2 855, 1 746, 1 702 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 7.34 (s, 5H), 5.15 (s, 2H), 4.84 (m, 1H), 4.4 (m, 1H), 3.73 (s, 3H), 3.02 (m, 1H), 1.97 (m, 1H), 1.7 (m, 1H), 1.43 (m, 2H), 0.87 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.2, 156.5, 136.7, 128.3, 127.7, 127.6, 67.1, 65.8, 61.1, 52.1, 42.1, 28.5, 25.5, 18.1, 17.9, −5.1, −5.2.

Anal Calc for $C_{21}H_{33}NO_5Si$: C, 61.88; H, 8.16; N, 3.44. Found: C, 61.86; H, 8.17; N, 3.41.

(2R,3R)-1-(Benzyloxycarbonyl)-3-[(tert-butyldimethylsilyl)oxy]-2-(hydroxymethyl)piperidine ***11***

A solution of **10** (407 mg, 1 mmol) in absolute EtOH (6 mL) is added to a suspension of dry $CaCl_2$ (777 mg, 7 mmol) in anhydrous THF (4 mL). The mixture was cooled at −20 °C, $NaBH_4$ (462 mg, 12 mmol) was added in one portion and stirring was performed at −20 °C for 15 min, at room temperature for 45 min, cooled to 0 °C and hydrolysed with an aqueous solution of citric acid (1 M, 10 mL). Et_2O (40 mL) was added and the aqueous layer was extracted with Et_2O (3 × 40 mL). The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$ (80 mL) and brine (2 × 80 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product purified by flash chromatography eluting with cyclohexane/AcOEt (4:1) in the presence of 1% of Et_3N to give **11** (344 mg, 91%) as a yellow solid.

$[\alpha]_D^{20} = +13$ ($c = 1$, $CHCl_3$).

IR ν_{max}: 3 424, 3 062, 3 009, 2 950, 2 883, 1 676 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 7.36 (s, 5H), 5.21 (d, $J = 12.5$ Hz, 1H), 5.11 (d, $J = 12.5$ Hz, 1H), 4.26 (ddd, $J = 8.2, 6.5, 3$ Hz, 1H), 4.06 (d, $J = 11.5$ Hz, 1H), 3.92 (ddd, $J = 3, 3, 3$ Hz, 1), 3.78 (dd, $J = 11.2, 8.2$ Hz, 1H), 3.68 (dd, $J = 11.2, 6.5$ Hz, 1H), 2.96 (dd $J = 11.5, 11.5$ Hz, 1H), 1.93 (m, 1H), 1.65 (m, 2H), 1.37 (m, 1H), 0.86 (s, 9H), 0.47 (s, 6H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ 156.9, 136.9, 128.5, 127.9, 127.8, 67.2, 65.2, 60.6, 40.2, 28.3, 25.7, 19.3, 18, −4.8, −5.

Anal Calc for $C_{20}H_{33}NO_4Si$: C, 63.29; H, 8.76; N, 3.69. Found: C, 63.35; H, 8.82; N, 3.60.

(2R,3R)-1-(Benzyloxycarbonyl)-3-[(tert-butyldimethylsilyl)oxy]-2-[(Z)-2-(methoxycarbonyl)ethenyl]-piperidine ***12***

A solution of DMSO (0.15 mL, 2.04 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was cooled at −60 °C and canulated on a solution of oxalyl chloride (0.135 mL, 1.53 mmol) in anhydrous CH_2Cl_2. The mixture was stirred for 15 min at −60 °C and a solution of **11** (194 mg, 0.51 mmol) in CH_2Cl_2 (2.5 mL) was added. After another 10 min, Et_3N (0.58 mL, 4.08 mmol) was added dropwise. The mixture was stirred for 30 min at −60 °C, hydrolysed with 0.75 mL of water and diluted with hexane (25 mL). The aqueous layer was extracted with AcOEt (3 × 25 mL). The organic layers were combined, acidified with an aqueous 20% solution of $KHSO_4$ (10 mL) and washed with an aqueous saturated solution of $NaHCO_3$ (2 × 10 mL), water (3 × 10 mL) and brine (2 × 10 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude aldehyde was obtained as a yellow oil (193 mg).

At −78 °C, potassium hexamethyldisilazide (1.17 mL, 0.59 mmol, 0.5 M solution in toluene) was added to a solution of methyl bis(trifluoroethyl)phophonoacetate (178 mg, 0.56 mmol) and 18-crown-6 (712 mg, 2.8 mmol) in THF

(10 mL). The mixture was stirred for 1 h at −78 °C and a solution of the crude aldehyde in THF (2.5 mL) was added. After another 2 h at −78 °C, the mixture was hydrolysed with an aqueous saturated solution of NH_4Cl (2.5 mL). The aqueous layer was extracted with AcOEt (3 × 15 mL), the organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with cyclohexane/AcOEt (9:1) in the presence of 2% of Et_3N to give the olefine **12** (Z/E = 19:1) as a yellow oil (184 mg, 83%).

IR ν_{max}: 2 948, 2 926, 2 853, 1 720, 1 697 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 7.32 (s, 5H), 6.29 (dd, J = 11.6, 8.4 Hz, 1H), 5.87 (dd, J = 11.6, 1.5 Hz, 1H), 5.77 (m, 1H), 5.16 (d, J = 12.6 Hz, 1H), 5.08 (d, J = 12.6 Hz, 1H), 4.16 (dd, J = 13.5, 4.1 Hz, 1H), 3.95 (m, 1H), 3.67 (s, 3H), 3.03 (ddd, J = 13.5, 13.5, 3.0 Hz, 1H), 2.04 (m, 1H), 1.5 (m, 3H), 0.87 (s, 9H), 0.14 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ 165.3, 156, 142.9, 136.9, 128.2, 127.5, 127.4, 120.7, 67.8, 66.8, 56.7, 51.3, 39.1, 28.3, 25.6, 18.5, 17.8, −4.9, −5.2.

Anal Calc for $C_{23}H_{35}NO_5Si$: C, 63.71; H, 8.13; N, 3.23. Found: C, 63.83; H, 8.14; N, 3.18.

(2R,3R)-1-(Benzyloxycarbonyl)-3-[(tert-butyldimethylsilyl)oxy]-2-[(1S,2S)-1,2-dihydroxy-2-(methoxycarbonyl)ethyl]piperidine **13**

A solution of OsO_4 (216 mg, 0.085 mmol, 2.5% in t-butanol), trimethylamine N-oxide dihydrate (104 mg, 0.94 mmol) and **12** (180 mg, 0.42 mmol) in acetone/water (19:1), was treated under ultrasound for 2 h. An aqueous saturated solution of $Na_2S_2O_5$ (10 mL) was added at room temperature and the mixture was stirred for 1 h. The aqueous layer was extracted with CH_2Cl_2 (5 × 30 mL). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with cyclohexane/AcOEt (11:9) in the presence of 4% of Et_3N to give **13** (136 mg, 71%).

$[\alpha]_D^{20}$ = +30 (c = 1, $CHCl_3$).

IR ν_{max}: 3 412, 2 949, 2 926, 2 854, 1 740, 1 669 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.16 (d, J = 12.6 Hz, 1H), 5.08 (d, J = 12.6 Hz, 1H), 5.1 (m, 1H), 4.24 (m, 1H), 4 (m, 4H), 3.84 (s, 3H), 3.5 (m, 1H), 3.29 (ddd, J = 13.4, 13.4, 4.0 Hz, 1H), 1.97 (m, 2H), 1.66 (m, 1H), 1.39 (m, 1H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.9, 158.4, 136.4, 128.4, 127.9, 127.5, 74.2, 71.4, 67.8, 67.5, 58.4, 52.6, 41.8, 28.5, 25.6, 18.8, 17.8, −5, −5.1.

Anal Calc for $C_{23}H_{37}NO_7Si$: C, 59.09; H, 7.97; N, 2.99. Found: C, 59.16; H, 7.98; N, 2.89.

(1S,2S,8R,8aR)-8-[(tert-Butyldimethylsilyl)oxy]-1,2-dihydroxy-3-oxoindolizidine **14**

A suspension of **13** (163 mg, 0.35 mmol), sodium acetate (63 mg, 0.77 mmol) and Pd/C (0.34 mg) in absolute methanol (1.5 mL) was stirred under hydrogen (1 atm) for 1 h at room temperature and for 2 h at 35 °C. The mixture was filtrated over Celite and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (19:1) in the presence of 4% of Et_3N to give **14** as a colorless solid (94 mg, 90%).

Mp = 204 °C.

$[\alpha]_D^{20}$ = −129 (c = 0.15, $CHCl_3$).

IR ν_{max}: 3 532, 2 949, 2 926, 2 855, 1 709 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 4.4 (m, 4H), 3.95 (m, 2H), 3.12 (dd, J = 8.9, 3.3 Hz, 1H), 2.55 (dd, J = 10.4, 10.4 Hz, 1H), 2.02 (m, 1H), 1.72 (m, 1H), 1.43 (m, 1H), 0.89 (s, 9H), 0.13 (s, 3H), 0.1 (s, 3H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.1, 71.6, 65.5, 64.9, 63.4, 39, 33, 25.6, 21.9, 17.8, −4.5, −5.

Anal Calc for $C_{14}H_{27}NO_4Si$: C, 55.78; H, 9.03; N, 4.65. Found: C, 55.88; H, 9.10; N, 4.69.

(1S,2S,8R,8aR)-8-Hydroxy-1,2-(isopropylidenedioxy)-3-oxoindolizidine **15**

A small amount of acidic ion exchange resin (Dowex 50W400) was added to a solution of **14** (90 mg, 0.3 mmol) in 2,2-dimethoxypropane (15 mL) and the mixture was stirred for 4 h at room temperature. After filtration over Celite, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (9:1) to give **15** as a white solid (66 mg, 97%).

Mp = 195 °C.

$[\alpha]_D^{20}$ = −44 (c = 0.39, MeOH).

IR ν_{max}: 3 412, 2 991, 2 934, 2 853, 1 681 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 4.87 (dd, J = 6.5, 5.5 Hz, 1H), 4.68 (dd, J = 6.5, 1.2 Hz, 1H), 4.08 (ddd, J = 12.9, 4.3, 2 Hz, 1H), 3.78 (ddd, J = 9.3, 9.3, 4.3, 1H), 3.29 (dd, J = 9.3, 5.5 Hz, 1H), 2.57 (ddd, J = 12.9, 12.9, 3.5 Hz, 1H), 2.5 (broad s, 1H), 2.14 (m, 1H), 1.8 (m, 1H), 1.5 (m, 2H), 1.46 (s, 3H), 1.4 (s, 3H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ 169, 113.2, 72.6, 66.8, 63.3, 39, 32, 26.5, 25.4, 22.6.

Anal Calc for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.99; H, 7.56; N, 6.18.

(1S,1R,8R,8aR)-8-Hydroxy-1,2-(isopropylidenedioxy)-indolizidine **16**

BH_3–Me_2S (0.63 mL, 1.25 mmol, 2 M solution in THF) was added to a solution of **15** (57 mg, 0.25 mmol) in anhydrous THF (8 mL). The mixture was stirred for 14 h at room temperature, hydrolysed with EtOH (5 mL) and the solvents were evaporated under reduced pressure. The residue was dissolved in EtOH (8 mL) and refluxed for 2 h. The solvents were evaporated under reduced pressure and the crude product was purified by flash chromatography eluting with CH_2Cl_2/MeOH (9:1) to give **16** as a white solid (43 mg, 81%).

Mp = 103 °C (lit [4b] Mp = 105–107 °C; lit [9e] Mp = 100–103 °C; lit [11a] Mp = 106–108 °C; lit [11b] Mp = 101–104 °C).

$[\alpha]_D^{20}$ = −75 (c = 0.48, MeOH) (lit [4b] $[\alpha]_D^{24}$ = −75.1; lit [9e] $[\alpha]_D^{25}$ = −72.76; lit [11a] $[\alpha]_D^{20}$ = −65.8; lit [11b] $[\alpha]_D^{26}$ = −67.3).

IR ν_{max}: 3 197, 2 938 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) δ 4.7 (dd, J = 6.3, 4.4 Hz, 1H), 4.6 (dd, J = 6.3, 4.1 Hz, 1H), 3.82 (ddd, J = 10.2, 4, 4 Hz, 1H), 3.15 (d, J = 10.7 Hz, 1H), 2.98 (ddd, J = 10.2, 4.4, 4.4 Hz, 1H), 2.25 (br. s, 1H), 2.25 (m, 1H), 2.13 (dd, J = 10.7, 4.1 Hz, 1H), 2.04 (m, 1H), 1.84 (m, 1H), 1.65 (m, 3H), 1.5 (s, 3H), 1.33 (s, 3H).

^{13}C NMR (50.3 MHz, $CDCl_3$) δ 111.2, 79, 78.1, 73.6, 67.3, 59.7, 51.5, 32.9, 25.8, 24.7, 24.

(1S,2R,8R,8aR)-1,2,8-Trihydroxyindolizidine-[(-)-swainsonine] **4**

A solution of **16** in aqueous HCl (2 mL, 1 M solution) was refluxed for 30 min. The mixture was concentrated under reduced pressure and the residue was eluted with water over a basic ion exchange resin (Dowex 1X8-200). Water was evaporated under reduced pressure to give **4** as a colorless solid (19.5 mg, 96%). After sublimation, **4** was obtained as a white solid.

Mp = 144 °C (lit [4b] Mp = 144–145 °C; lit [11b] Mp = 141–143 °C).

$[\alpha]_D^{20} = -79$ (0.62, MeOH) (lit [4b] $[\alpha]_D^{25} = -87.2$; lit [11b] $[\alpha]_D^{26} = -82.6$).

IR ν_{max}: 3 197, 2 938 cm^{-1}.

^1H NMR (200 MHz, D_2O) δ 4.18 (app td, 1H), 4.09 (m, 1H), 3.64 (ddd, J = 10.8, 10.8, 3.6 Hz, 1H), 2.72 (m, 2H), 2.39 (dd, J = 11, 7.7 Hz, 1H), 1.85 (m, 3H), 1.4 (m, 2H), 1.1 (m, 1H).

^{13}C NMR (50.3 MHz, D_2O) δ 73.4, 70.2, 69.6, 66.8, 61.1, 52.3, 39, 23.7.

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