A Concise and Diastereoselective Synthesis of Piperidine and Indolizidine Alkaloids via Aza-Prins Cyclization

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Abstract: The synthesis of 2-substituted and 2,4-disubstituted piperidine alkaloids such as (±)-coniine, (±)-hydroxypipecolic acid, (±)-pipecolic acid, (±)-coniceine, and (±)-4-hydroxy-2-hydroxymethyl piperidine have been accomplished in a highly diastereoselective manner by employing aza-Prins cyclization as a key step to construct the piperidine core of these alkaloids.

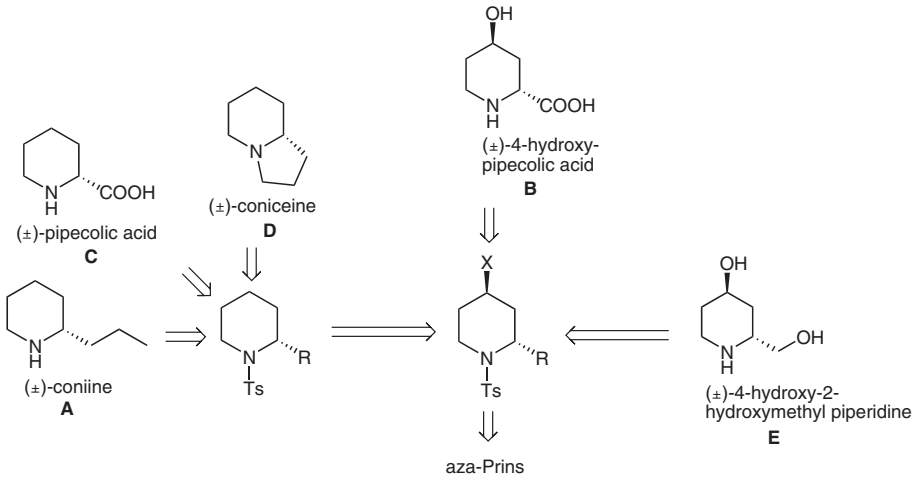
Key words: aza-Prins cyclization, diastereoselective, piperidine, alkaloids, natural products

Piperidine and indolizidine subunits are common structural motifs in naturally occurring alkaloids and constitute the basic skeleton of several drug candidates for the treatment of a wide range of diseases.[1,2] As a result, various methods have been developed for the stereo- and enantioselective synthesis of piperidine derivatives.[3] Of these, the coupling of homoallylic amines with aldehydes – the so-called aza-Prins cyclization – is a versatile and direct method for the synthesis of *trans*-2,4-disubstituted piperidines.[4] As part of our ongoing research project on the development of new chemical entities, recently, we have reported the synthesis of 4-iodo- and 4-hydroxypiperidines by means of aza-Prins cyclization.[5] Herein, we report an extension of this work to the total synthesis of several piperidine and indolizidine alkaloids. The 4-iodo- and 4-hydroxypiperidines could be used as key intermediates in the synthesis of five representative alkaloids. To the best of our knowledge, this is the first report on the synthesis of (±)-coniine (**A**),[6] (±)-4-hydroxypipecolic acid (**B**),[7] (±)-pipecolic acid (**C**),[8] (±)-coniceine (**D**),[9] and (±)-4-hydroxy-2-hydroxymethylpiperidine (**E**)[10] using aza-Prins cyclization (Scheme 1).

Coniine (**A**)[11] is a hemlock alkaloid that was used in ancient Greece to execute criminals. Initially, we prepared the piperidine key intermediate 4-iodopiperidine **1** in 92% yield using aza-Prins cyclization between *N*-tosylhomoallylic amine and *n*-butyraldehyde,[5a] which was transformed into coniine by a known reaction sequence.

Piperidine intermediate **2** was achieved by radical reduction of **1** in 95% yield by refluxing with *n*-tributyltinhydride in toluene.[12] The exposure of **2** to a dark-green sodium naphthalenide solution at –78 °C in anhydrous tetrahydrofuran resulted in deprotection of the *N*-tosyl group to give coniine (**A**) in 90% yield (Scheme 2).[13] The data of product **A** was identical to that reported in the literature.[6d]

The 4-hydroxypipecolic acid (**B**)[14] motif is the most prevalent subunit of this type in bioactive molecules such as SS20846A[15] and palinavir,[16] which is a highly potent HIV protease inhibitor. Both pipecolic acid and 4-hydroxypipecolic acid, being unnatural amino acids, are useful in peptide synthesis.



Scheme 1 Retrosynthetic analysis for the synthesis of piperidine and indolizidine alkaloids

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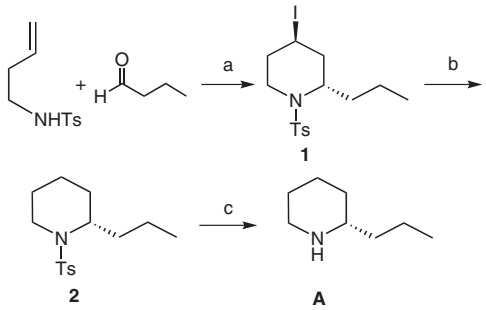
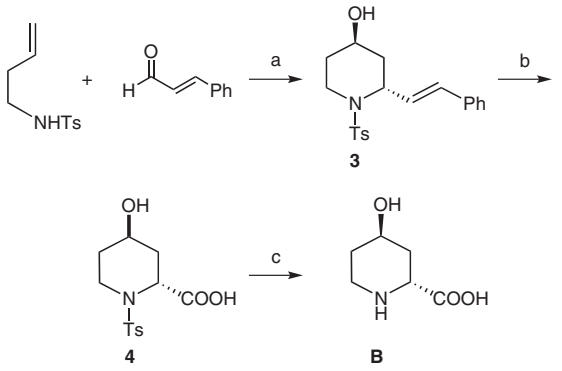


Scheme 2 Synthesis of (±)-coniine (**A**). *Reagents and conditions*: (a) GaI_3, I_2, anhydrous CH_2Cl_2, 0 °C to r.t., 7 h, 92%; (b) Bu_3SnH, AIBN, toluene, 4 h, reflux, 95%; (c) Na/naphthalene, anhydrous THF, –78 °C, 6 h, 90%.

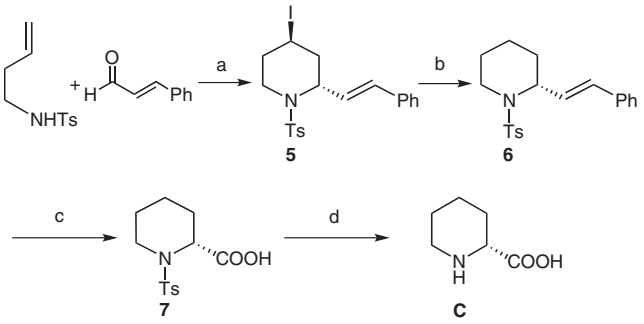
The key intermediate, 4-hydroxypiperidine **3**, was synthesized in 85% yield by means of an aza-Prins cyclization between *N*-tosyl homoallylic amine and cinnamaldehyde.[5b] Oxidative cleavage of olefin **3** with $RuCl_3{\cdot}2H_2O$ gave the corresponding carboxylic acid **4** in 68% yield without affecting the hydroxy group.[8a,17] Treatment with sodium/naphthalene at –78 °C in anhydrous tetrahydrofuran deprotected the tosyl group to give the target product **B** in 80% yield (Scheme 3).[13] The data of product **B** was identical with respect to its ^{1}H NMR spectrum to that reported in the literature.[7a]



Scheme 3 Synthesis of (±)-4-hydroxypipecolic acid (**B**). *Reagents and conditions*: (a) PMA (10 mol%), anhydrous CH_2Cl_2, reflux, 10 h, 85%; (b) $RuCl_3{\cdot}2H_2O$, $NaIO_4$, MeCN–CCl_4–H_2O (1:1:10), r.t., 8 h, 68%; (c) Na/naphthalene, anhydrous THF, –78 °C, 6 h, 80%.

Pipecolic acid (**C**)[18] is a naturally occurring non-proteinogenic α-amino acid that is frequently found in plants, fungi, and human physiological fluids. It is a key structural unit in many biologically active natural and synthetic molecules, for instance anticonvulsant pipradol,[19] immunosuppressants FK 506[20] and rapamycin,[21] amyloglucosidase inhibitor lentiginosine,[22] enzyme inhibitors, and *N*-methyl-D-aspartic acid (NMDA)[23] antagonists.

The key precursor, 4-iodopiperidine **5** was also prepared by means of an aza-Prins cyclization.[5a] Removal of iodide with *n*-tributyltinhydride in the presence of AIBN gave the (*E*)-2-styryl-*N*-tosylpiperidine **6** in 93% yield.[12] Oxidative cleavage of the olefin was achieved using $RuCl_3{\cdot}2H_2O$ and $NaIO_4$ to afford the corresponding carboxylic acid **7** in 70% yield.[8a,17] Deprotection of the *N*-tosyl group was carried out using sodium/naphthalene at –78 °C in anhydrous tetrahydrofuran to afford (±)-pipecolic acid (**C**) in 89% yield (Scheme 4).[13] The data for product **C** was in agreement with the those reported in the literature.[8a]

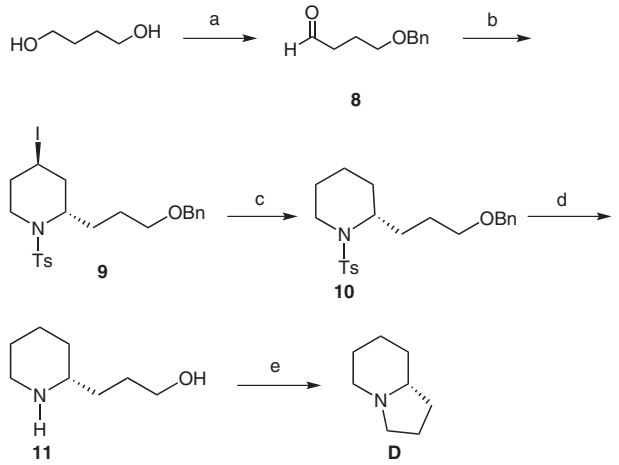


Scheme 4 Synthesis of (±)-pipecolic acid (**C**). *Reagents and conditions*: (a) GaI_3, I_2, anhydrous CH_2Cl_2, 0 °C to r.t., 7 h, 90%; (b) Bu_3SnH, AIBN, toluene, 3 h, reflux, 93%; (c) $RuCl_3{\cdot}2H_2O$, $NaIO_4$, MeCN–CCl_4–H_2O (1:1:10), r.t., 8 h, 70%; (d) Na/naphthalene, anhydrous THF, –78 °C, 6 h, 89%.

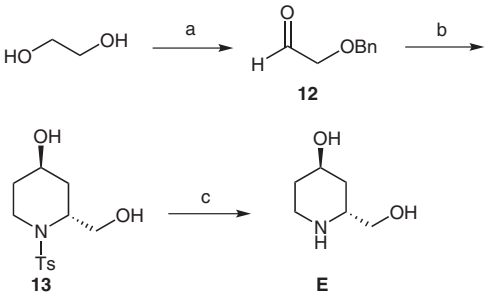
Bicyclic alkaloid coniceine (**D**)[24] is a representative member of the biologically active indolizidine alkaloids. It acts as a non-competitive blocker for muscle and ganglionic nicotinic receptor channels that have been isolated from the skin secretions of neotropical amphibians.

The synthesis of coniceine (**D**) began from aldehyde **8**, which was prepared from 1,4-butanediol by mono-benzylation, followed by oxidation of the free hydroxy group with pyridinium chlorochromate. The resulting aldehyde was subjected to aza-Prins cyclization with homoallylic amine using gallium iodide and iodine to give 4-iodopiperidine **9** in 85% yield. Radical reduction of **9** was achieved by treatment of tributyltin hydride in the presence of AIBN at reflux in toluene to give piperidine **10** in 80% yield.[12] Both *N*-tosyl and *O*-benzyl groups underwent smooth cleavage upon treatment with sodium/naphthalene at –78 °C in anhydrous tetrahydrofuran to afford compound **11** in 85% yield.[13] Cyclization of **11** was achieved by treatment with iodine, triphenylphosphine and imidazole followed by aqueous sodium bicarbonate to give coniceine (**D**) in 60% yield (Scheme 5).[25] The data of product **D** was in agreement with those reported in the literature.[9a]

4-Hydroxy-2-hydroxymethylpiperidine (**E**) was prepared from piperidine **13** by tosyl deprotection upon treatment with sodium/naphthalene at –78 °C. Piperidine **13** was synthesized in 65% yield by aza-Prins cyclization between aldehyde **12** and homoallylic amine with PMA at reflux temperature for 18 hours,[5b] with concomitant debenzylation. It should be noted that the *N*-tosyl group was stable under these conditions.[26] Aldehyde **12** was prepared in good yield from ethylene glycol through monobenzylation followed by oxidation of the free alcohol with pyridinium chlorochromate (Scheme 6). The



Scheme 5 Synthesis of (±)-coniceine (D). *Reagents and conditions*: (a) (i) NaH, BnBr, DMF, cat. TBAI, 0 °C to r.t., 12 h, 90%; (ii) PCC–Celite (1:1), anhydrous CH_2Cl_2, r.t., 12 h, 80%; (b) *N*-tosyl homoallylic amine, GaI_3, I_2, anhydrous CH_2Cl_2, 0 °C to r.t., 11 h, 85%; (c) Bu_3SnH, AIBN, toluene, 10 h, reflux, 80%; (d) Na/naphthalene, anhydrous THF, –78 °C, 6 h, 85%; (e) I_2, TPP, imidazole, r.t., 4 h, then sat. $NaHCO_3$, 3 h, 60%.



Scheme 6 Synthesis of (±)-4-hydroxy-2-hydroxymethylpiperidine (**E**). *Reagents and conditions*: (a) (i) NaH, BnBr, DMF, cat. TBAI, 0 °C to r.t., 14 h, 85%; (ii) PCC–Celite (1:1), anhydrous CH_2Cl_2, r.t., 10 h, 70%; (b) *N*-tosylhomoallylic amine, PMA (10 mol%), anhydrous CH_2Cl_2, reflux, 20 h, 65%; (c) Na/naphthalene, anhydrous THF, –78 °C, 70%.

data of product **E** was in agreement with those reported in the literature.[10]

In summary, we have demonstrated a modular and concise route to the total synthesis of (±)-coniine, (±)-4-hydroxypipecolic acid, (±)-pipecolic acid, (±)-coniceine, and (±)-4-hydroxy2-hydroxymethylpiperidine via aza-Prins cyclization.

Commercial reagents were used without further purification and all solvents were purified by standard techniques. IR spectra were recorded with a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. NMR spectra were recorded in $CDCl_3$ with Varian Gemini 200, Bruker 300, or Varian Unity 400 NMR spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to tetramethylsilane (TMS) as internal standard; coupling constants (*J*) are quoted in hertz. Column chromatographic separations were carried out on silica gel (60–120 mesh) and flash chromatographic separations were carried out using 230–400 mesh silica gel. MS were recorded with a Micromass VG-7070H for EI and a VG Autospec M for FAB-MS.

***trans*-4-Iodo-2-propyl-*N*-tosylpiperidine (1)**

A mixture of *N*-tosylhomoallylic amine (0.430 g, 1.91 mmol), *n*-butyraldehyde (0.178 g, 2.48 mmol), iodine (0.485 g, 1.90 mmol) and gallium iodide (0.008 g, 0.019 mmol) in CH_2Cl_2 (25 mL) was stirred at 0 °C for 10 min and then at r.t. for 7 h. After completion of the reaction (indicated by TLC), the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent, followed by purification on silica gel (EtOAc–hexane, 5:95) gave the product.

Yield: 0.715 g (92%); colorless oil.

IR (neat): 2923, 2853, 1739, 1461, 1374, 1216, 1170, 1119, 759, 668 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 7.9 Hz, 2 H), 4.24 (tt, *J* = 12.4, 3.8 Hz, 1 H), 3.89 (br q, 1 H), 3.63 (ddt, *J* = 14.6, 4.4, 2.3 Hz, 1 H), 3.02 (ddd, *J* = 15.2, 12.4, 2.9 Hz, 1 H), 2.40 (s, 3 H), 2.12–2.20 (m, 2 H), 2.02 (ddt, *J* = 13.4, 4.2, 2.1 Hz, 1 H), 1.87 (dq, *J* = 4.6, 12.3 Hz, 1 H), 1.25–1.60 (m, 4 H), 0.90 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 19.6, 21.4, 31.6, 37.9, 41.3, 42.2, 55.1, 126.8, 129.6, 138.1, 143.2.

LC-MS: *m*/*z* = 408 [M + H], 430 [M + Na].

(±)-2-Propyl-*N*-tosylpiperidine (2)

In an oven-dried, single-neck 25 mL round-bottom flask equipped with reflux condenser, magnetic stirring bar, rubber septum and nitrogen inlet, was placed **1** (0.575 g, 1.41 mmol) and anhydrous toluene (20 mL). Bu_3SnH (0.570 mL, 2.12 mmol) was added and the mixture was heated at reflux for 4 h (130 °C), then AIBN (10 mg) was added to the reaction mixture at 80 °C. After completion of the reaction, as indicated by TLC, the mixture was cooled to r.t. and then concentrated to give a syrup. The resulting crude product was purified by column chromatography (EtOAc–petroleum ether, 15:85) to give **2**.

Yield: 0.378 g (95%); colorless oil.

IR (neat): 2930, 2862, 1734, 1456, 1334, 1156, 1093, 931, 815, 654 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.3 Hz, 2 H), 7.25 (d, *J* = 7.5 Hz, 2 H), 3.97–4.05 (m, 1 H), 3.73 (dd, *J* = 3.0, 13.6 Hz, 1 H), 2.95 (ddd, *J* = 15.6, 13.5, 2.2 Hz, 1 H), 2.43 (s, 3 H), 1.20–1.61 (m, 10 H), 0.90 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 18.2, 19.5, 21.3, 24.2, 27.2, 31.4, 40.4, 52.5, 126.7, 129.4, 138.8, 142.5.

LC-MS: *m*/*z* = 282 [M + H], 299 [M + NH_4].

(±)-Coniine (A)

To a stirred solution of naphthalene (0.732 g, 5.72 mmol) in anhydrous THF (20 mL) in a two-neck 50 mL, round-bottom flask equipped with magnetic stirring bar, a rubber septum and a nitrogen inlet, was added sodium (0.132 g, 5.73 mmol) at r.t. and the mixture was stirred until the formation of sodium naphthalide was complete (indicated by the formation of a persistent navy-blue color; sodium naphthalide was formed within 40 min), and then cooled to –78 °C. A solution of **2** (0.268 g, 0.953 mmol) in anhydrous THF (15 mL) was added to the above solution at –78 °C and the resulting mixture was stirred at the same temperature for 45 min. The reaction was quenched by the addition of sat. aq NH_4Cl (15 mL) and the organic layer was washed with H_2O (2 × 10 mL), brine (3 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the crude product by column chromatography (EtOAc–petroleum ether, 35:65) gave the target molecule **A**.

Yield: 0.109 g (90%); syrup.

IR (neat): 3447, 2925, 2855, 1735, 1458, 1335, 1155, 1093, 927, 687 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.74–3.79 (m, 1 H), 3.65 (dddd, *J* = 11.5, 4.0, 2.1, 1.7 Hz, 1 H), 3.50 (ddd, *J* = 11.5, 11.3, 2.4 Hz, 1 H), 2.30–2.36 (m, 1 H), 2.12–2.17 (m, 1 H), 1.77–1.81 (m, 2 H), 1.57–1.70 (m, 3 H), 1.25–1.36 (m, 4 H), 0.93 (dd, *J* = 7.0, 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 19.6, 26.1, 32.3, 33.8, 40.6, 46.1, 50.7.

LC-MS: *m*/*z* = 150 [M + Na].

***trans*-2-Styryl-*N*-tosylpiperidin-4-ol (3)**

A mixture of *N*-tosylhomoallylic amine (0.338 g, 1.50 mmol), *trans*-cinnamaldehyde (0.257 g, 1.95 mmol) and phosphomolybdic acid (0.027 g, 0.015 mmol) in CH_2Cl_2 (25 mL) was stirred at reflux temperature for 10 h. After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (EtOAc–hexane, 18:82) gave the product.

Yield: 0.456 g (85%); white solid; mp 170–173 °C.

IR (neat): 3452, 2929, 2854, 1598, 1448, 1334, 1156, 1081, 1022, 929, 755, 669 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.2 Hz, 2 H), 7.00–7.20 (m, 7 H), 6.34 (d, *J* = 16.6 Hz, 1 H), 5.85 (dd, *J* = 5.8, 15.6 Hz, 1 H), 4.78–4.84 (m, 1 H), 3.75–3.83 (m, 2 H), 3.02 (ddd, *J* = 15.1, 13.2, 2.7 Hz, 1 H), 2.35 (s, 3 H), 2.01 (ddd, *J* = 13.0, 3.8, 1.8 Hz, 1 H), 1.80 (dddd, *J* = 11.9, 2.5, 3.7, 3.9 Hz, 1 H), 1.61 (ddd, *J* = 12.8, 11.3, 5.5 Hz, 1 H), 1.35 (dddd, *J* = 12.0, 11.9, 4.5, 3.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 34.0, 38.9, 40.3, 55.0, 64.3, 125.9, 127.1, 127.6, 128.3, 129.4, 130.5, 132.0, 136.5, 137.1, 143.1.

LC-MS: *m*/*z* = 358 [M + H].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{20}H_{24}NO_3S$: 358.1478; found: 358.1476.

***trans*-4-Hydroxy-*N*-tosylpiperidine-2-carboxylic Acid (4)**

To a stirred solution of $NaIO_4$ (0.209 g, 0.976 mmol) in MeCN–CCl_4–H_2O (1:1:10, 12 mL) was added $RuCl_3·2H_2O$ (0.011 g, 0.048 mmol) and the resulting mixture was stirred at r.t. for 1 h. Compound **3** (0.174 g, 0.488 mmol) was dissolved in MeCN (10 mL) and this solution was added to the above reaction mixture, followed by the addition of a second portion of $NaIO_4$ (0.105 g, 0.490 mmol). The resulting mixture was stirred at r.t. for 30 min and then filtered through Celite. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (MeOH–$CHCl_3$, 1:9 to 2:8) to yield acid **4**.

Yield: 0.099 g (68%); colorless oil.

IR (neat): 3460, 2924, 2855, 1726, 1454, 1273, 1161, 1097, 708 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.3 Hz, 2 H), 7.28 (d, *J* = 8.2 Hz, 2 H), 5.05 (d, *J* = 5.4 Hz, 1 H), 4.90–4.99 (br s, 1 H), 3.96–4.00 (m, 1 H), 3.52 (ddd, *J* = 4.5, 10.9, 13.7 Hz, 1 H), 2.71–2.75 (m, 2 H), 2.49–2.56 (m, 1 H), 2.40–2.49 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 39.6, 41.5, 41.9, 55.4, 60.3, 127.1, 129.6, 135.8, 143.9, 171.3.

LC-MS: *m*/*z* = 300 [M + H], 322 [M + Na].

(±)-4-Hydroxypipecolic Acid (B)

Compound **4** (0.049 g, 0.163 mmol) was subjected to tosyl deprotection using the procedure described above (synthesis of **A** from **2**) with naphthalene (0.126 g, 0.984 mmol) and sodium metal (0.023 g, 1 mmol) to give the target molecule **B**.

Yield: 0.019 g (80%); viscous oil.

IR (neat): 3430, 2927, 1630, 1028, 764 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 10.4 (s, 1 H), 5.04–5.07 (m, 2 H), 3.74–3.85 (m, 7 H).

LC-MS: *m*/*z* = 168 [M + Na].

***trans*-4-Iodo-2-styryl-*N*-tosylpiperidine (5)**

A mixture of *N*-tosylhomoallylic amine (0.193 g, 0.857 mmol), *trans*-cinnamaldehyde (0.147 g, 1.11 mmol), iodine (0.218 g 0.858 mmol) and gallium iodide (0.0038 g, 0.008 mmol) in CH_2Cl_2 (15 mL) was stirred at 0 °C for 10 min and then at r.t. for 7 h. After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent and purification on silica gel (EtOAc–hexane, 5:95) gave the product.

Yield: 0.360 g (90%); yellow syrup.

IR (KBr): 2918, 2858, 1646, 1492, 1383, 1334, 1189, 1155, 1087, 931, 700, 651 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.7 Hz, 2 H), 7.13–7.25 (m, 7 H), 6.43 (d, *J* = 16.2 Hz, 1 H), 5.92 (dd, *J* = 5.6, 16.1 Hz, 1 H), 4.63–4.73 (m, 1 H), 4.27 (tt, *J* = 12.3, 3.9 Hz, 1 H), 3.67 (ddt, *J* = 14.5, 4.3, 2.3 Hz, 1 H), 3.10 (ddd, *J* = 15.1, 12.2, 2.8 Hz, 1 H), 2.10–2.55 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 32.1, 33.7, 38.9, 44.3, 55.5, 125.9, 127.2, 128.3, 129.2, 130.5, 133.1, 134.5, 136.2, 137.1, 143.2.

LC-MS: *m*/*z* = 490 [M + Na].

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{20}H_{22}NO_2SNa$: 490.0287; found: 490.0308.

(±)-2-Styryl-*N*-tosylpiperidine (6)

Compound **5** (0.259 g, 0.555 mmol) was subjected to the same reaction conditions (synthesis of **2** from **1**) with Bu_3SnH (0.24 mL, 0.831 mmol) and AIBN (10 mg) to give compound **6**.

Yield: 0.176 g (93%); syrup.

IR (neat): 2927, 2864, 1709, 1450, 1340, 1213, 1158, 1054, 964, 815, 696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 7.5 Hz, 2 H), 7.10–7.25 (m, 7 H), 6.38 (d, *J* = 15.8 Hz, 1 H), 5.93 (dd, *J* = 6.7, 16.6 Hz, 1 H), 4.69 (dd, *J* = 11.5, 4.5 Hz, 1 H), 3.72 (dd, *J* = 12.8, 2.3 Hz, 1 H), 2.98 (ddd, *J* = 15.8, 12.4, 3.7 Hz, 1 H), 2.34 (s, 3 H), 1.79 (ddd, *J* = 3.7, 7.5, 18.1 Hz, 2 H), 1.49–1.66 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 21.3, 30.1, 34.0, 40.1, 54.9, 125.3, 126.3, 127.1, 128.3, 129.6, 132.7, 143.3.

LC-MS: *m*/*z* = 340 [M – H].

(±)-*N*-Tosylpiperidine-2-carboxylic Acid (7)

Compound **6** (0.131 g, 0.384 mmol) was subjected to the same reaction conditions (synthesis of **4** from **3**) with $RuCl_3·2H_2O$ (0.009 g, 0.040 mmol), $NaIO_4$ (0.171 g, 0.799 mmol), and a second portion of $NaIO_4$ (0.086 g, 0.401 mmol) to give **7**.

Yield: 0.092 g (70%); viscous oil.

IR (neat): 3430, 2926, 2856, 1724, 1666, 1595, 1411, 1356, 1282, 168, 1092, 1064, 1039, 939, 812, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.52 (br s, 1 H), 7.62 (d, *J* = 8.7 Hz, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 5.19–5.21 (dd, *J* = 2.9, 5.8 Hz, 1 H), 3.68 (ddt, *J* = 3.6, 13.1, 17.5 Hz, 1 H), 3.31–3.38 (ddd,

J = 2.9, 11.7, 16.1 Hz, 1 H), 2.41 (s, 3 H), 2.15 (dddd, J = 2.9, 13.1, 15.3, 18.3 Hz, 1 H), 1.24–1.67 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 21.2, 38.8, 40.1, 42.4, 56.3, 127.1, 129.6, 135.2, 143.8, 171.2.

LC-MS: m/z = 282 [M – 1].

(±)-Pipecolic Acid (C)

Compound **7** (0.042 g, 0.148 mmol) was subjected to tosyl deprotection using the same reaction conditions (synthesis of **A** from **2**) with naphthalene (0.114 g, 0.890 mmol) and sodium metal (0.020 g, 0.869 mmol) to give the target molecule **C**.

Yield: 0.017 g (89%); syrup.

IR (neat): 3452, 2926, 1723, 1655, 1158, 1036, 822 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.05 (br s, 1 H), 3.82–3.89 (m, 1 H), 3.71–3.74 (m, 1 H), 3.51–3.54 (m, 1 H), 3.29–3.31 (m, 1 H), 2.78–2.83 (m, 2 H), 2.51–2.63 (m, 3 H).

LC-MS: m/z = 130 [M + H].

4-(Benzyloxy)butanal (8)

To a stirred solution of 1,4-butanediol (0.283 g, 3.14 mmol) in anhydrous DMF (35 mL) in a single-necked, round-bottom 100 mL flask equipped with nitrogen inlet, was added NaH (0.090 g, 3.77 mmol) at 0 °C and stirring was continued for 30 min. To the above mixture, benzyl bromide (0.27 mL, 3.11 mmol) was added dropwise at 0 °C, then TBAI (0.0011 g, 0.0031 mmol) was added and the reaction was stirred at r.t. for 12 h. After completion of the reaction, as indicated by TLC, the mixture was quenched with H_2O (5 mL) and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were concentrated in vacuo and the resulting syrup was purified by column chromatography (EtOAc–petroleum ether, 15:85) to give the mono-protected alcohol.

Yield: 0.509 g (90%); syrup.

IR (neat): 3383, 2940, 2865, 1714, 1451, 1364, 1275, 1102, 1064, 742, 706, 611 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.34 (m, 5 H), 4.49 (s, 2 H), 3.61 (t, J = 6.1 Hz, 2 H), 3.49 (t, J = 6.1 Hz, 2 H), 1.61–1.75 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1, 29.4, 61.9, 70.1, 72.6, 127.7, 128.2, 128.1, 137.8.

LCMS: m/z = 181 [M + H].

HRMS (ESI): m/z [M + Na] calcd for $C_{11}H_{16}O_2Na$: 203.1042; found: 203.1042.

This product (0.410 g, 2.27 mmol) was directly oxidized over PCC (0.979 g, 4.55 mmol) and Celite (0.979 g) in CH_2Cl_2 (40 mL) at r.t. for about 12 h. After completion of the reaction, as indicated by TLC, the reaction mixture poured on silica gel and purified by column chromatography (EtOAc–hexane, 7:93) to give aldehyde **8**.

Yield: 0.324 g (80%); oil.

IR (neat): 2949, 2858, 1720, 1600, 1452, 1274, 1106, 1027, 711, 609 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.04 (s, 1 H), 7.29–7.35 (m, 5 H), 4.50 (s, 2 H), 4.35 (t, J = 6.8 Hz, 2 H), 3.50–3.56 (m, 2 H), 1.79–1.98 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2, 64.6, 69.6, 72.7, 127.4, 128.8, 129.3, 129.5, 134.2, 138.3, 192.1.

***trans*-2-[3-(Benzyloxy)propyl]-*N*-tosyl-piperidine-4-ol (9)**

A mixture of *N*-tosylhomoallylic amine (0.219 g, 0.973 mmol), 4-(benzoloxy)butanal (**8**; 0.225 g, 1.26 mmol), iodine (0.247 g, 0.973 mmol) and gallium iodide (0.004 g, 0.009 mmol) in CH_2Cl_2 (25 mL) was stirred at 0 °C to r.t. for 11 h. After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent, followed by purification on silica gel (EtOAc–hexane, 10:90) gave the product.

Yield: 0.424 g (85%); yellow syrup.

IR (neat): 2936, 1722, 1598, 1451, 1334, 1157, 1075, 1031, 931, 814, 722, 676 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, J = 7.9 Hz, 2 H), 7.21–7.30 (m, 7 H), 4.44 (s, 2 H), 4.34 (tt, J = 12.2, 3.7 Hz, 1 H), 4.10–4.25 (m, 1 H), 3.79 (ddt, J = 14.7, 4.6, 2.3 Hz, 1 H), 3.44–3.50 (dd, J = 4.8, 10.5 Hz, 2 H), 2.96 (ddd, J = 2.5, 9.6, 13.5 Hz, 1 H), 2.40 (s, 3 H), 1.49–1.70 (m, 4 H), 0.82–1.25 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 26.6, 27.6, 32.4, 36.8, 39.3, 42.1, 56.5, 63.1, 72.7, 126.8, 127.5, 128.3, 129.7, 133.1, 135.2, 138.8, 143.2.

LCMS: m/z = 514 [M + H].

(±)-2-[3-(Benzyloxy)propyl]-*N*-tosylpiperidine (10)

Compound **9** (0.302 g, 0.588 mmol) was subjected to the procedure described (synthesis of **2** from **1**) with Bu_3SnH (0.257 mL, 0.883 mmol) and AIBN (10 mg) to give compound **10**.

Yield: 0.183 g (80%); syrup.

IR (neat): 2926, 2855, 1595, 1453, 1336, 1215, 1161, 1058, 934, 735, 660 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.3 Hz, 2 H), 7.28–7.33 (m, 7 H), 4.46 (s, 2 H), 4.20 (dd, J = 11.0, 5.5 Hz, 1 H), 3.90 (ddt, J = 3.7, 14.3, 18.1 Hz, 1 H), 3.44–3.50 (m, 2 H), 3.10 (ddd, J = 2.2, 15.1, 12.8 Hz, 1 H), 2.42 (s, 3 H), 1.99 (dddd, J = 2.2, 4.5, 14.3, 16.6 Hz, 2 H), 1.25–1.65 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 21.5, 26.6, 27.5, 29.8, 32.8, 39.1, 53.5, 69.4, 72.8, 126.9, 127.6, 128.4, 129.8, 138.2, 138.5, 143.3.

LCMS: m/z = 386 [M – H].

Amino Alcohol (11)

Compound **10** (0.133 g, 0.344 mmol) was subjected to tosyl deprotection (synthesis of **A** from **2**) using naphthalene (0.264 g, 2.062 mmol) and sodium metal (0.047 g, 2.043 mmol) to give piperidine **11**.

Yield: 0.042 g (86%); syrup.

IR (neat): 3448, 2923, 2853, 1637, 1460, 1375, 770 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.23–6.91 (br s 1 H), 4.46–4.44 (m, 2 H), 4.09–4.18 (m, 1 H), 3.54–3.60 (m, 1 H), 3.29–3.41 (m, 1 H), 3.11–3.25 (m, 1 H), 3.00–3.12 (m, 1 H), 1.53–2.03 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 26.2, 29.8, 32.2, 32.8, 42.8, 51.9, 63.2.

LCMS: m/z = 166 [M + Na].

(±)-Coniceine (D)

To a stirred solution of **11** (0.021 g, 0.147 mmol) in anhydrous CH_2Cl_2 (15 mL) in a 100 mL single-neck round-bottom flask were added Ph_3P (0.115 g, 0.440 mmol), iodine (0.112 g, 0.440 mmol) and imidazole (0.029 g, 0.440 mmol) at 0 °C. The resulting mixture was stirred at r.t. for 4 h and then quenched with sat. aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), the combined organic layers were concentrated in vacuo, and the resulting syrup was purified by column chromatography (EtOAc–petroleum ether, 10:90) to give the target molecule **D**.

Yield: 0.011 g (60%); syrup.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.06–4.13 (m, 1 H), 3.57–3.63 (m, 1 H), 2.26–2.33 (m, 1 H), 2.13–2.17 (m, 1 H), 2.02–2.06 (m, 2 H),

1.83–1.92 (m, 1 H), 1.61–1.72 (m, 1 H), 1.47–1.55 (m, 1 H), 1.31–1.41 (m, 1 H), 1.17–1.29 (m, 5 H).

LCMS: *m*/*z* = 124 [M – H].

2-(Benzyloxy)acetaldehyde (12)

To a stirred solution of ethylene glycol (0.150 g, 2.41 mmol) in anhydrous DMF (25 mL) in a single-neck, round-bottom 100 mL flask equipped with a nitrogen inlet, was added NaH (0.071 g, 2.95 mmol) at 0 °C and stirring was continued for 30 min. To the above mixture, benzyl bromide (0.21 mL, 2.388 mmol) was added dropwise at 0 °C, then TBAI (0.0017 g, 0.0048 mmol) was added and the mixture was stirred at r.t. for 14 h. After completion of the reaction, as indicated by TLC, the mixture was quenched with H_2O (5 mL) and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were concentrated in vacuo and the resulting syrup was purified by column chromatography (EtOAc–petroleum ether, 15:85) to give the mono-protected alcohol.

Yield: 0.311 g (85%); syrup.

IR (neat): 3413, 2926, 2863, 1496, 1453, 1358, 1209, 1112, 1067, 891, 741, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.27 (m, 5 H), 4.47 (s, 2 H), 3.63 (t, *J* = 4.7 Hz, 2 H), 3.48 (t, *J* = 4.9 Hz, 2 H), 3.04 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 61.4, 71.2, 73.2, 127.6, 128.2, 137.7.

LCMS: *m*/*z* = 170 [M + NH_4], 175 [M + Na].

This product (0.216 g, 1.42 mmol) was directly oxidized over PCC (0.611 g, 2.84 mmol) and Celite (0.611 g) in CH_2Cl_2 (30 mL) at r.t. for about 10 h. After completion of the reaction, as indicated by TLC, the reaction mixture was passed through a silica gel column (EtOAc–hexane, 5:95) to give the pure aldehyde **12**.

Yield: 0.149 g (70%); oil.

IR (neat): 2867, 1704, 1613, 1498, 1455, 1351, 1310, 1260, 1047, 967, 869, 744, cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.28 (s, 1 H), 7.28–7.34 (m, 5 H), 5.14 (d, *J* = 2.9 Hz, 1 H), 5.09 (d, *J* = 2.9 Hz, 1 H), 4.90 (s, 2 H).

LCMS: *m*/*z* = 149 [M – H].

***trans*-2-Hydroxymethyl-*N*-tosylpiperidin-4-ol (13)**

A mixture of *N*-tosylhomoallylic amine (0.2 g, 0.888 mmol), 2-(benzyloxy)acetaldehyde (**12**; 0.086 g, 0.575 mmol) and phosphomolybdic acid (0.008 g, 0.004 mmol) in CH_2Cl_2 (30 mL) was stirred at reflux temperature for 20 h. After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (EtOAc–hexane, 25:75) gave piperidine **13**.

Yield: 0.082 g (65%); colorless oil.

IR (neat): 3448, 2988, 2886, 1595, 1342, 1256, 1161, 1098, 1008, 968, 868, 818, 688 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.1 Hz, 2 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 4.51–4.53 (m, 1 H), 4.36–4.41 (m, 1 H), 3.64–3.70 (m, 1 H), 3.52 (dd, *J* = 3.5, 9.4 Hz, 1 H), 3.25 (d, *J* = 9.4 Hz, 1 H), 2.82–2.92 (m, 1 H), 2.45 (s, 3 H), 1.80–1.89 (m, 2 H), 1.63–1.69 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 30.6, 37.2, 39.8, 55.8, 69.1, 73.6, 126.9, 129.5, 134.8, 143.3.

LCMS: *m*/*z* = 285 [M^+], 268 [M – OH].

(±)-4-Hydroxy-2-hydroxymethylpiperidine (E)

Compound **13** (0.040 g, 0.140 mmol) was subjected to tosyl deprotection using the same reaction conditions (synthesis of **A**) with naphthalene (0.107 g, 0.842 mmol) and sodium metal (0.019 g, 0.842 mmol) to give the target molecule **E**.

Yield: 0.009 g (50%); syrup.

IR (neat): 3471, 2923, 1622, 1615, 1051, 1010, 722 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 4.27 (br s, 1 H), 4.19 (dd, *J* = 9.06, 11.2 Hz, 1 H), 3.86–3.88 (m, 1 H), 3.62–3.72 (ddd, *J* = 13.1, 3.5, 2.3 Hz, 1 H), 2.56–2.69 (m, 2 H), 2.37–2.40 (m, 1 H), 1.74–1.76 (m, 1 H), 1.57–1.59 (m, 1 H), 1.23–1.25 (m, 1 H), 0.86–0.89 (m, 1 H).

LCMS: *m*/*z* = 149 [M + Na].

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