Tetrahedron: *Asymmetry* 22 (2011) 1000–1005

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Stereoselective total synthesis of the piperidine alkaloids, (+)-coniine, (+)-pseudoconhydrine, and (+)-sedamine through a common intermediate ☆

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ARTICLE INFO

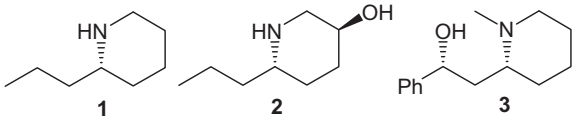
Article history:
Received 19 April 2011
Accepted 9 June 2011

ABSTRACT

The stereoselective total synthesis of the piperidine alkaloids, (+)-coniine, (+)-pseudoconhydrine and (+)-sedamine has been achieved through a common intermediate generated from butane-1,4-diol. The synthetic sequence involves a Maruoka asymmetric allylation and ring-closing metathesis as the key steps.

1. Introduction

Piperidine alkaloids are widespread in Nature and many of these compounds are known to possess interesting biological properties.[1] Much effort has been devoted to the isolation and characterization of these bases. However, these compounds are generally obtained in small quantities from natural sources. As a result, several synthetic methods have been discovered for the preparation of these alkaloids.[2] In a continuation of our work[3] on asymmetric routes to the natural bioactive compounds, we herein report the total synthesis of three piperidine alkaloids, (+)-coniine **1**, (+)-pseudoconhydrine **2** and (+)-sedamine **3**. The first two compounds **1** and **2** were isolated from *Conium maculatum*[4a] while the other three from *Sedum acre*.[4b,4c] All of these three alkaloids, **1**,[5] **2**[6] and **3**[7] have attracted the attention of organic chemists.



1 **2** **3**

2. Results and discussion

The retrosynthetic analysis of compounds **1**–**3** (Scheme 1) revealed that these compounds can be prepared from a common intermediate **4** which, in turn, can be obtained from the homoallylic alcohol **5** generated from readily available butane-1,4-diol **6**.

The synthesis of (+)-coniine was initiated by converting butane-1,4-diol **6** into *mono*-silylated ether **7** by treatment with TBSCl and imidazole (Scheme 2). The silylated ether **7** underwent oxidation with PCC followed by Maruoka allylation[8] with allyltributylstannane in the presence of the (*S*)-Binol complex (*S*,*S*)-I to produce the chiral homoallylic alcohol **5** (96% ee). The latter was treated with MsCl and this mesylate underwent nucleophilic displacement by a S_N2 process with allylamine in DMF at 50 °C to afford the amine derivative **8** (92% ee) with an inverse configuration of the required stereocenter of the target molecule **1**. This was supported by its opposite specific rotation value, $[\alpha]_D^{25} = +11.6$ (*c* 0.5, $CHCl_3$), compared to that of homoallylic alcohol **5**, $[\alpha]_D^{25} = -5.4$ (*c* 0.5, $CHCl_3$). Amine **8** was treated with $(Boc)_2O$ to form **9** and the TBS ether group of the latter was deprotected. The resulting compound **10** was subjected to a ring-closing metathesis (RCM) reaction[9] using a Grubbs' second generation catalyst to give the cyclic tetrahydropyridine derivative **4**, a common intermediate useful for the synthesis of **1**–**3**. Compound **4** was treated with I_2 and imidazole to form the corresponding iodide derivative, which was reduced with Zn/AcOH[10] to produce (+)-coniine derivative **11**. The reduction of the olefinic double bond of **11** with H_2/Pd–C followed by treatment with aqueous HCl and washing with NaOH solution afforded (+)-coniine **1**.[4a] This compound was treated with a 2 M solution of dry HCl in EtOH and the resulting residue was recrystallized from ether. The melting point of this hydrochloride salt of **1** was 195–197 °C (lit. mp 195 °C) and $[\alpha]_D^{25} = +8.6$ (*c* 0.8, EtOH) {lit. $[\alpha]_D^{22} = +8.3$ (*c* 0.7, EtOH)}. Its spectroscopic data also matched well with those of the reported compound.[5c]

Compound **11** derived from the common intermediate **4** was used for the synthesis of (+)-pseudoconhydrine **2** (Scheme 3). The double bond of **11** was selectively hydrated[11] using BH_3·DMS and H_2O_2 to produce the Boc-protected (+)-pseudoconhydrine **13** and its diastereoisomer in a 9:1 ratio. Both diastereoisomers were separated. Compound **13** upon treatment with aqueous HCl, followed by washing with a NaOH solution yielded (+)-pseudoconhydrine **2**. By following the above procedure, the hydrochloride salt of **2** was prepared. The melting point of this compound was 204–206 °C (lit. mp 208 °C) and $[\alpha]_D^{25} = +3.0$ (*c* 0.4, MeOH) {lit.

☆ Part 46 in the series 'Synthetic studies on natural products'.

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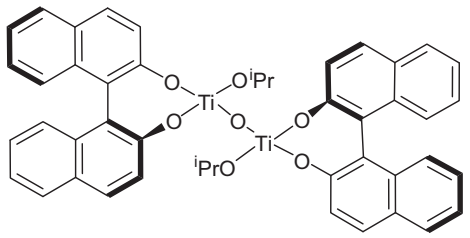
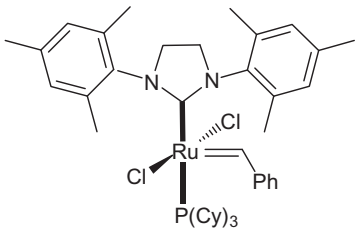
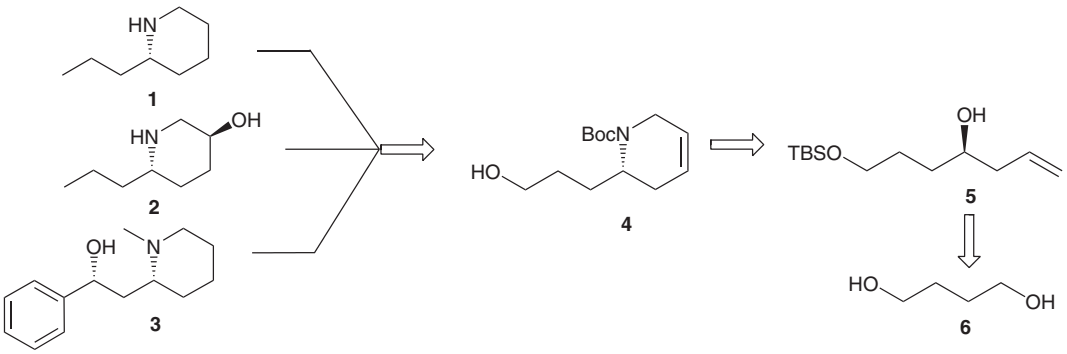
doi:10.1016/j.tetasy.2011.06.011



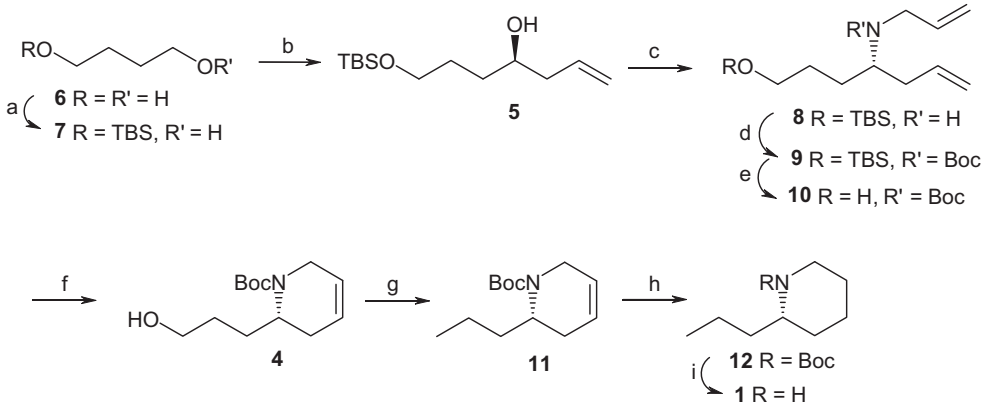
(*S*,*S*)-**I**



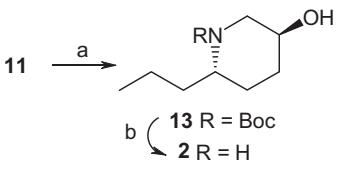
Grubbs' II generation catalyst



Scheme 1. Retrosynthetic analysis of **1–3**.



Scheme 2. Synthesis of (+)-coniine **1**. Reagents and conditions: (a) TBSCl, imidazole, DCM, 0 °C to rt, 0.5 h, 90%; (b) (i) PCC, DCM, 0 °C to rt, 0.5 h, 90%, (ii) (*S*,*S*)-**I**, $CH_2{=}CHCH_2SnBu_3$, DCM, −15 to 0 °C, 72 h, 85%; (c) (i) MsCl, Et_3N, DMAP, DCM, 0 °C to rt, 1 h, (ii) allylamine, DMF, H_2O, 50 °C, 30 h, 78% (over two steps); (d) $(Boc)_2O$, Et_3N, DCM, rt, 3 h, 92%; (e) *p*TSA, THF/H_2O (3:1), rt, 0.5 h; 89%; (f) Grubbs' II catalyst (10 mol %), DCM, reflux at 50 °C, 4 h, 90%; (g) (i) I_2, TPP, imidazole, CH_3CN/ether (1:3), 0 °C to rt 15 min; (ii) Zn, DCM, rt, 30 min, then AcOH, 0 °C to rt, 0.5 h, 80% (over two steps); (h) H_2/Pd–C, EtOAc, rt, 2 h, 91%; (i) 5 M HCl, THF, rt, 89%.



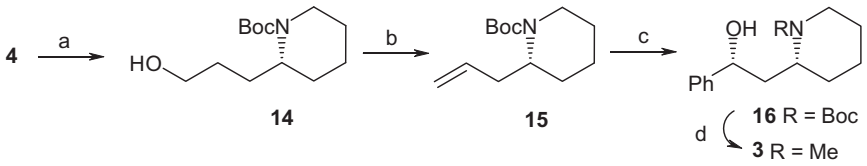
Scheme 3. Synthesis of (+)-pseudoconhydrine **2**. Reagents and conditions: (a) $BH_3.SMe_2$, THF, −78 °C to rt, 20 h, then H_2O, 20% NaOH, 30% H_2O_2, rt, 2 h, 90%; (b) 5 N HCl, THF, rt, 0.5 h, 87%.

$[\alpha]_D^{20} = +2.6$ (*c* 0.47, MeOH)}. The spectroscopic data of this compound matched well with the previous report.[6c]

Finally, the synthesis of (+)-sedamine **3** was achieved from the common intermediate **4** by saturating its olefinic double bond with H_2/Pd–C to afford product **14** (Scheme 4). Treatment of **14** with I_2 and imidazole and subsequently with ^{t}BuOK generated the olefinic compound **15**.[12] The latter was treated with $RuCl_3$ and $NaIO_4$ and the resulting aldehyde with PhMgBr to produce alcohol **16** and its diastereoisomer in a 95:5 ratio.[13] The major product **16** was separated and then treated with $LiAlH_4$ to afford (+)-sedamine **3** with a melting point of 56–58 °C (lit. mp 54–56 °C), $[\alpha]_D^{25} = +86.3$ (*c* 1.0, EtOH) {lit. $[\alpha]_D^{20} = +86.8$ (*c* 1.0, EtOH)}. The spectroscopic properties of **3** were identical to those reported in the literature.[7e]

3. Conclusion

In conclusion, we have synthesized the piperidine alkaloids, (+)-coniine, (+)-pseudoconhydrine and (+)-sedamine starting from a



Scheme 4. Synthesis of (+)-sedamine **3**. Reagents and conditions: (a) H_2/ Pd–C, EtOAc, rt, 2 h, 91%; (b) (i) I_2, TPP, imidazole, CH_3CN/ether (1:3), 15 min, (ii) ^{t}BuOK, THF, 0 °C to rt, 15 min, 85% (over two steps); (c) (i) $RuCl_3$, $NaIO_4$, CH_3CN/H_2O (6:1), 1 h; (ii) PhMgBr, THF, −78 °C, 56% (over two steps); (d) $LiAlH_4$, THF, rt, 8 h, 78%.

common intermediate generated from butane-1,4-diol, involving Maruoka allylation and RCM as the key steps. This method can be utilized for the synthesis of several other related piperidine alkaloids.

4. Experimental

4.1. General

Silica gel F_{254} plates were used for thin layer chromatography (TLC) in which the spots were examined under UV light and then developed by an iodine vapor. Column chromatography was performed with silica gel (BDH 100–200 mesh). Solvents were purified according to standard procedures. The spectra were recorded with the following instruments; IR: Perkin-Elmer RX FT-IR spectrophotometer; NMR: Varian Gemini 200 MHz (^{1}H) and 50 MHz (^{13}C) spectrometer; ESIMS: VG-Autospec micromass. Organic extracts were dried over anhydrous Na_2SO_4. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C.

4.1.1. 4-(*tert*-Butyldimethylsilyloxy)butan-1-ol 7

To a stirred solution of butanediol **6** (2.25 g, 25 mmol) in CH_2Cl_2 (50 mL) was added imidazole (2.04 g, 30 mmol) at room temperature. After 15 min, to this stirred solution, TBDMS–Cl (3.75 g, 25 mmol) was added. The reaction mixture was stirred for 30 min. It was then concentrated in vacuo and the reaction mixture purified by column chromatography (ethyl acetate/hexane, 2:8) to afford pure 4-(*tert*-butyldimethylsilyloxy)butan-1-ol **7** (4.59 g, 90%) as a colorless liquid. IR: ν 3387,1467, 1255, 1117 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.61 (2H, t, J = 7.0 Hz), 3.54 (2H, t, J = 7.0 Hz), 2.75 (1H, br s), 1.62–1.51 (4H, m), 0.83 (9H, s), 0.01 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 63.5, 62.6, 30.0, 29.7, 25.8, 18.2, −3.8; ESIMS: m/z 205 $[M+H]^+$ Anal. Calcd for $C_{10}H_{24}O_2Si$: C, 58.77; H, 11.84. Found: C, 58.67; H, 11.89.

4.1.2. (*R*)-7-(*tert*-Butyldimethylsilyloxy)hept-1-en-4-ol 5

To a stirred suspension of Celite in CH_2Cl_2 (20 mL) was added a solution of compound **7** (4.56 g, 22.3 mmol) in CH_2Cl_2 (30 mL) at room temperature. To this suspension pyridinium chlorochromate (8.63 g, 40.14 mmol) was added at 0 °C and the mixture was warmed to room temperature. After 1 h, the reaction mixture was filtered off through a Celite pad. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (1:9). The purified aldehyde (4.059 g, 90%) was directly subjected to allylation.

To a stirred solution of $TiCl_4$ (0.189 g, 1 mmol) in CH_2Cl_2 (15 mL) was added dried $Ti(O^iPr)_4$ (0.852 g, 3 mmol) at 0 °C under a nitrogen atmosphere and the mixture was allowed to warm to room temperature. After 1 h, silver(I) oxide (0.462 g, 2 mmol) was added and the reaction was continued for 5 h under the exclusion of direct light. The mixture was diluted with CH_2Cl_2 (30 mL) and treated with (*S*)-BINOL (1.144 g, 4 mmol) at room temperature for 2 h to furnish the chiral bis-Ti(IV)oxide (*S*,*S*)-**I**. This complex was cooled to −15 °C and treated sequentially with a solution of aldehyde (4.04 g, 20 mmol) in dry CH_2Cl_2 (20 mL) and allyltributyltin (8.606 g, 26 mmol) at the same temperature. The mixture was allowed to warm to 0 °C and stirred for 20 h. The mixture was quenched with aqueous saturated $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvents and purification of the residue by column chromatography (ethyl acetate/hexane, 2:8) gave pure (*R*)-7-(*tert*-butyldimethylsilyloxy)hept-1-en-4-ol **5** (4.148 g, 85%) as a colorless liquid. $[\alpha]_D^{25} = -5.4$ (*c* 0.5, $CHCl_3$); IR: ν 3449, 1619, 1457, 1401, 1250 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.79 (1H, m), 5.12–5.03 (2H, m), 3.67–3.56 (3H, m), 2.51 (1H, br s), 2.25–2.10 (2H, m), 1.68–1.52 (3H, m), 1.41 (1H, m), 0.89 (9H, s), 0.02 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.2, 117.5, 70.7, 63.5, 42.2, 34.0, 29.2, 26.1, 18.5, −5.2; ESIMS: m/z 245 $[M+H]^+$ Anal. Calcd for $C_{13}H_{28}NOSi$: C, 63.87; H, 11.55%. Found: C, 63.94; H, 11.49%.

4.1.3. (*S*)-*N*-allyl-7-(*tert*-Butyldimethylsilyloxy)hept-1-en-4-amine 8

To a stirred solution of alcohol **5** (4.1 g, 16.8 mmol) in CH_2Cl_2 (30 mL) was added dried Et_3N (2.206 g, 21.84 mmol) at room temperature under a nitrogen atmosphere. To this solution, a catalytic amount of DMAP was added and the mixture was stirred for 15 min. The reaction mixture was cooled to 0 °C, after which mesyl chloride (2.298 g, 20.16 mmol) was added and stirred for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude mesylate (4.97 g, 92%) thus obtained was used without further purification. The crude mesylate (4.97 g, 15.2 mmol) was dissolved in dry DMF (60 mL) and to this was added allylamine (17.33 g, 304 mmol) at room temperature. This reaction mixture was warmed to 50 °C and refluxed for 36 h. The reaction mixture was allowed to cool to room temperature and extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 4:6) afforded pure (*S*)-*N*-allyl-7-(*tert*-butyldimethylsilyloxy)hept-1-en-4-amine **8** (3.66 g, 85%) as a yellow liquid. $[\alpha]_D^{25} = +11.6$ (*c* 0.5, $CHCl_3$); IR: ν 3425, 1639, 1560, 1459, 1220 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.89 (1H, m), 5.72 (1H, m), 5.28–5.07 (2H, m), 3.68-3.55 (3H, m), 3.39–3.32 (2H, m), 2.72 (1H, m), 2.30–2.22 (2H, m), 1.62–1.51 (3H, m), 1.38 (1H, m), 0.83 (9H, s), 0.02 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.0, 136.2, 117.4, 115.9, 63.0, 55.1, 46.0, 38.9, 29.8, 27.7, 26.2, 18.8, −5.1; ESIMS: m/z 284 $[M+H]^+$ Anal. Calcd for $C_{16}H_{33}NOSi$: C, 67.78; H, 11.73; N, 4.94. Found: C, 67.84; H, 11.67; N, 4.86%.

4.1.4. (*S*)-*tert*-Butyl allyl(7-(*tert*-butyldimethylsilyloxy)hept-1-en-4-yl)carbamate 9

To a stirred solution of amine **8** (3.6 g, 12.7 mmol) in dry CH_2Cl_2 (25 mL) under a nitrogen atmosphere at room temperature was added Et_3N (1.67 g, 16.5 mmol). The reaction mixture was stirred for 15 min, after which was added $(Boc)_2O$ (3.045 g, 13.97 mmol) and further stirred for 3 h. The reaction mixture was quenched with aqueous saturated NH_4Cl (15 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue on

purification by column chromatography (ethyl acetate/hexane, 0.5:9:5) afforded pure (*S*)-*tert*-butyl allyl(7-(*tert*-butyldimethylsilyloxy)hept-1-en-4-yl)carbamate **9** (4.48 g, 92%) as a colorless liquid. $[\alpha]_D^{25} = +45.4$ (*c* 0.6, $CHCl_3$); IR: *ν* 1693, 1457, 1365, 1250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 5.91–5.62 (2H, m), 5.16–4.94 (4H, m), 3.70 (1H, m), 3.62–3.51 (4H, m), 2.32–2.11 (2H, m), 1.54–1.50 (2H, m), 1.46 (9H, s), 1.38–1.24 (2H, m), 0.89 (9H, s), 0.02 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 156.4, 137.4, 136.5, 117.1, 115.5, 79.2, 62.6, 55.1, 45.7, 38.3, 29.6, 28.4, 27.8, 26.0, 18.5, −0.51; ESIMS: *m*/*z* 384 $[M+H]^+$ Anal. Calcd for $C_{21}H_{41}NO_3Si$: C, 65.75; H, 10.77; N, 3.65. Found: C, 65.81; H, 10.82; N, 3.58%.

4.1.5. (*S*)-*tert*-Butyl allyl(7-hydroxyhept-1-en-4-yl)carbamate 10

To a stirred solution of compound **9** (4.44 g, 11.6 mmol) in THF/H_2O (20 mL, 3:1) was added *p*-TSA (0.199 g, 1.16 mmol) at room temperature. The reaction mixture was stirred for 15 min and quenched with aqueous saturated solution of $NaHCO_3$ (15 mL). The reaction mixture was extracted with EtOAc (2 × 40 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 2:8) afforded pure (*S*)-*tert*-butyl allyl(7-hydroxyhept-1-en-4-yl)carbamate **10** (2.775 g, 89%) as colorless liquid. $[\alpha]_D^{25} = +39.6$ (*c* 0.4, $CHCl_3$); IR: *ν* 3442, 1681, 1451, 1366, 1247, 1169 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 5.90–5.61 (2H, m), 5.18–4.96 (4H, m), 3.71 (1H, m), 3.64–3.52 (4H, m), 2.38–2.10 (2H, m), 1.64–1.52 (4H, m), 1.46 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 156.2, 136.4, 135.8, 117.0, 116.1, 79.4, 62.8, 54.9, 45.2, 38.1, 29.1, 28.5, 25.8; ESIMS: *m*/*z* 270 $[M+H]^+$ Anal. Calcd for $C_{15}H_{27}NO_3$: C, 66.88; H, 10.10; N, 5.20%. Found: C, 66.81; H, 10.15; N, 5.28%.

4.1.6. (*S*)-*tert*-Butyl 6-(3-hydroxypropyl)-5,6-dihydropyridine-1(2*H*)-carboxylate 4

A solution of compound **10** (0.7 g, 2.6 mmol) in dry CH_2Cl_2 (150 mL) was first bubbled with a nitrogen flow, after which Grubb's second generation catalyst (10 mol %) was added and the resulting mixture was heated under nitrogen at 50 °C for 6 h. After cooling, the solvent was evaporated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 0.5:9.5) afforded pure (*S*)-*tert*-butyl 6-(3-hydroxypropyl)-5,6-dihydropyridine-1(2*H*)-carboxylate **4** (0.564 g, 90%) as a colorless liquid. $[\alpha]_D^{25} = +32.5$ (*c* 0.6, $CHCl_3$); IR: *ν* 3380, 1697, 1634, 1457, 1364 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 5.76–5.53 (2H, m), 4.47–4.08 (3H, m), 3.69–3.55 (2H, m), 3.46 (1H, m), 2.50–2.33 (2H, m), 1.91 (1H, m), 1.66 (1H, m), 1.59–1.43 (2H, m), 1.41 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 156.2, 123.5, 122.9, 80.0, 62.3, 60.1, 48.1, 29.7, 29.0, 28.3, 27.7; ESIMS: *m*/*z* 242 $[M+H]^+$ Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.78; H, 9.55; N, 5.88.

4.1.7. (*S*)-*tert*-Butyl 6-propyl-5,6-dihydropyridine-1(2*H*)-carboxylate 11

To a stirred solution of alcohol **4** (0.25 g, 1.04 mmol) in acetonitrile/ether (8 mL, 3:1) were added imidazole (0.163 g, 2.39 mmol), TPP (0.545 g, 2.08 mmol) and iodine (0.526 g, 2.08 mmol) separately at 0 °C under nitrogen. After 15 min the reaction was quenched by an aqueous saturated sodium thiosulfate ($Na_2S_2O_3$) solution (4 mL). The organic portions were extracted with CH_2Cl_2 (3 × 20 mL) and the extract was washed with brine solution (20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (ethyl acetate/hexane, 0.2:9.8) to afford iodide (0.349 g, 96%) as a yellow viscous liquid. This iodide was used for the next step without characterization.

4.1.7.1. Activation of zinc.

Zinc dust was treated with 10% HCl for 10 min, then the dark solution was filtered, washed with water and acetone. The solid collected was dried at 50–60 °C for 30 min and stored in desiccators.

To a stirred solution of iodide (0.34 g, 0.97 mmol) in dry CH_2Cl_2 (2 mL) at room temperature was added zinc dust (0.252 g, 3.88 mmol) under nitrogen. The suspension was stirred for 30 min and at 0 °C, after which 0.4 mL of glacial acetic acid was added slowly. The reaction mixture was warmed to room temperature and stirred for another 30 min. After completion of the reaction (monitored with TLC), the reaction mixture was filtered through a Celite pad with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2 (3 × 15 mL) and washed with an aqueous saturated $NaHCO_3$ (10 mL) solution and brine solution (8 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography (ethyl acetate/hexane, 0.1:9.9) to afford (*S*)-*tert*-butyl 6-propyl-5,6-dihydropyridine-1(2*H*)-carboxylate **11** (0.183 g, 84%) as a colorless liquid. $[\alpha]_D^{25} = +15.7$ (*c* 0.6, $CHCl_3$); IR: *ν* 1693, 1460, 1370, 1256, 1119 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 5.70–5.49 (2H, m), 4.42–4.01(2H, m), 3.40 (1H, m), 2.38 (1H, m), 1.82 (1H, m), 1.46 (9H, s), 1.33–1.12 (4H, m), 0.85 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 153.4, 123.8, 122.9, 79.3, 64.2, 48.4, 39.3, 33.9, 28.4, 19.5, 14.0; ESIMS: *m*/*z* 226 $[M+H]^+$ Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22%. Found: C, 69.19; H, 10.33; N, 6.29%.

4.1.8. (*S*)-*tert*-Butyl 2-propylpiperidine-1-carboxylate 12

To a solution of compound **11** (0.08 g, 0.36 mmol) in EtOAc (3 mL) was added 10% Pd/C under hydrogen. After 2 h the reaction mixture was filtered through Celite and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 0.1:9.9) afforded (*S*)-*tert*-butyl 2-propylpiperidine-1-carboxylate **12** (0.074 g, 91%) as colorless liquid. $[\alpha]_D^{25} = +16.1$ (*c* 0.4, $CHCl_3$); IR: *ν* 1683, 1356, 1252, 1112, 952 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 3.50 (1H, m), 3.12–2.89 (2H, m), 2.01–1.70 (5H, m), 1.69–1.52 (2H, m), 1.51–1.33 (12H, m), 0.91 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 152.3, 79.2, 57.2, 44.1, 34.8, 28.3, 22.6, 22.3, 19.4, 13.7; ESIMS: *m*/*z* 128 $[M+H]^+$ Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16%. Found: C,68.55; H, 11.15; N, 6.21.

4.1.9. (*S*)-2-Propylpiperidine 1

To a stirred solution of compound **12** (0.05 g, 0.22 mmol) in THF (1 mL) was added 0.5 mL of 5 M HCl at room temperature. After completion of the reaction, the reaction mixture was basified with 5% NaOH solution. The reaction mixture was extracted with EtOAc (3 × 10 mL) and washed with brine solution. The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was free amine **1** (0.026 g, 89%). This free amine was used to prepare a HCl salt by adding dry ethanolic HCl. After 10 min., the reaction was completed and the reaction mixture was filtered through Wattman filter paper. The white solid obtained (0.033 g) was the HCl salt of coniine **1**. The spectroscopic data of the compound were found to be identical to those reported earlier.[5c]

4.1.10. (2*S*,5*S*)-*tert*-Butyl 5-hydroxy-2-propylpiperidine-1-carboxylate 13

To a stirred solution of compound **11** (0.08 g, 0.36 mmol) in dry THF (33 mL) was added BH_3.DMS (2.7 g, 36 mmol) under nitrogen at −78 °C. The reaction mixture was warmed to room temperature and stirred for 36 h. Next, were added H_2O (0.55 mL), 20% aq NaOH (0.8 mL) and 30% aq H_2O_2 (0.8 mL) and stirred for 2 h, after which H_2O (4 mL) was added. The organic layer was extracted with EtOAc (3 × 10 mL) and dried over anhydrous Na_2SO_4. The organic layer

was concentrated in vacuo and the residue on purification by column chromatography (ethyl acetate/hexane, 4:6) afforded (2*S*,5*S*)-*tert*-butyl 5-hydroxy-2-propylpiperidine-1-carboxylate **13** (0.077 g, 90%) as a colorless liquid. $[\alpha]_D^{25} = +9.3$ (*c* 0.4, $CHCl_3$); IR: *ν* 3446, 1689, 1459, 1369, 1247 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 5.12 (1H, br s), 4.28 (1H, m), 4.08 (1H, m), 3.92–3.48 (2H, m), 1.94 (1H, m), 1.72–1.52 (4H, m), 1.48 (9H, s), 1.39–1.25 (3H, m), 0.91 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 155.5, 79.8, 68.9, 62.0, 49,1, 37.0, 31.8, 28.4, 25.5, 19.2, 13.9; ESIMS: *m*/*z* 266 $[M+Na]^+$ Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76%. Found: C, 64.21; H, 10.25; N, 5.69%.

4.1.11. (3*S*,6*S*)-6-Propylpiperidin-3-ol 2

The HCl salt of pseudoconhydrine **2** (0.031 g, 87%, white precipitate) was prepared from **13** following the same procedure as that described for the synthesis of the HCl salt of coniine **1**. The spectroscopic data of the compound were found to be identical to those reported earlier.[6c]

4.1.12. (*R*)-*tert*-Butyl 2-(3-hydroxypropyl)piperidine-1-carboxylate 14

To a solution of compound **4** (0.280 g, 1.16 mmol) in EtOAc (5 mL) was added 10% Pd/C under hydrogen. After 2 h the reaction mixture was filtered through Celite and concentrated in vacuo. The residue on purification by column chromatography (ethyl acetate/hexane, 2:8) afforded (*R*)-*tert*-butyl 2-(3-hydroxypropyl)piperidine-1-carboxylate **14** (0.57 g, 91%) as a colorless liquid. $[\alpha]_D^{25} = +33.8$ (*c* 0.5, $CHCl_3$); IR: *ν* 3422, 1676, 1420, 1368, 1266 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 4.52–4.25 (2H, m), 3.95 (1H, m), 3.80–3.62 (2H, m), 1.86–1.52 (10H, m), 1.48 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 153.5, 79.8, 62.2, 56.3, 40.8, 29.6, 29.4, 28.5, 26.4, 25.7, 19.1; ESIMS: *m*/*z* 244 $[M+H]^+$ Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76%. Found: C, 64.22; H, 10.33; N, 5.68%.

4.1.13. (*R*)-*tert*-Butyl 2-allylpiperidine-1-carboxylate 15

To a stirred solution of alcohol **14** (0.230 g, 0.95 mmol) in acetonitrile/ether (5 mL, 3:1) were added imidazole (0.148 g, 2.18 mmol), TPP (0.498 g, 1.9 mmol) and iodine (0.481 g, 1.9 mmol) separately at 0 °C under nitrogen. After 15 min. the reaction was quenched by an aq saturated hypo solution (6 mL). The organic portions were extracted with CH_2Cl_2 (3 × 20 mL) and washed with brine solution (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane, 0.2:9.8) to afford the iodide (0.32 g, 96%) as a yellow viscous liquid. This iodide was used for the next step without characterization.

To a stirred solution of the iodide (0.32 g, 0.91 mmol) in dry THF was added ^{t}BuOK (0.254 g, 2.27 mmol) at 0 °C under nitrogen. The reaction was warmed to room temperature and stirred for 20 min. After completion of reaction, it was quenched with aqueous saturated NH_4Cl (6 mL). The reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The organic portion was concentrated under reduced pressure and the residue was purified by column chromatography (ethyl acetate/hexane, 0.2:9.8) to afford (*R*)-*tert*-butyl 2-allylpiperidine-1-carboxylate **15** (0.179 g, 88%) as a light yellow viscous liquid. IR: *ν* 1684, 1444, 1249 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 5.73 (1H, m), 5.12–4.96 (2H, m), 4.28 (1H, m), 4.16–3.91 (2H, m), 2.48–2.17 (2H, m), 1.78–1.50 (6H, m), 1.47 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 153.4, 135.4, 116.3, 79.6, 53.4, 45.1, 34.2, 32.0, 28.6, 25.6, 19.2; ESIMS: *m*/*z* 226 $[M+H]^+$ Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22%. Found: C, 69.38; H, 10.23; N, 6.29%.

4.1.14. (*R*)-*tert*-Butyl 2-((*R*)-2-hydroxy-2-phenylethyl)piperidine-1-carboxylate 16

To a stirred solution of compound **15** (0.150 g, 0.67 mmol) and $RuCl_3$ (1 mL, 0.0235 mmol, 3.5 mol %) in CH_3CN (4 mL) and distilled water (0.67 mL) was added $NaIO_4$ (0.286 g, 1.34 mmol) at room temperature. After 1 h, the reaction was quenched with an aq saturated solution of hypo (5 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL) and washed with brine solution (6 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 0.2:9.8) to afford (0.106 g, 70%) as a colorless liquid. Without characterization this aldehyde was used for the next step.

Magnesium metal turnings (0.027 g, 1.125 mmol) were placed into a two necked round bottom flask after which were added dry THF (2 mL) and then bromobenzene (0.118 g, 0.75 mmol) slowly under nitrogen at room temperature. The reaction mixture was stirred until the solution became an ash color. The solution of the aldehyde (0.106 g, 0.47 mmol) in dry THF (2 mL) was added dropwise to the above freshly prepared Grignard reagent at −78 °C. The reaction mixture was stirred for 4 h at −78 °C. The reaction was quenched with aqueous saturated NH_4Cl solution (3 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL) and washed with a brine solution (8 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 2:8) to afford (*R*)-*tert*-butyl 2-((*R*)-2-hydroxy-2-phenylethyl)piperidine-1-carboxylate **16** (0.114 g, 80%) as a colorless liquid. $[\alpha]_D^{25} = +63.6$ (*c* 0.5, $CHCl_3$); IR: *ν* 3408, 1673, 1606, 1504, 1205 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 7.41–7.20 (5H, m), 4.86 (1H, dd, *J* = 7.0, 2.0 Hz), 4.71 (1H, br s), 3.19–2.96 (2H, m), 2.68 (1H, m), 2.12 (1H, m), 1.81 (1H, m), 1.73–1.38 (15H, m); ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 156.2, 145.1, 128.9, 127.8, 126.3, 78.4, 73.0, 61.9, 53.0, 29.9, 29.1, 26.5, 22.3, 21.2; ESIMS: *m*/*z* 306 $[M+H]^+$ Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59%. Found: C, 70.85; H, 8.88; N, 4.66%.

4.1.15. (*R*)-2-((*R*)-1-Methylpiperidin-2-yl)-1-phenylethanol 3

To a suspension of $LiAlH_4$ (0.053 g, 1.4 mmol) in dry THF (4 mL) was added a solution of **16** (0.086 g, 0.28 mmol) in dry THF at room temperature under nitrogen. The reaction mixture was stirred for 6 h at reflux. After completion, the reaction was quenched with an aqueous saturated solution of Na_2SO_4 (6 mL) followed by the addition of 15% aqueous NaOH solution (1 mL). The reaction mixture was filtered through Celite and the filtrate was extracted into EtOAc (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane, 3:7) to afford sedamine **3** (0.048 g, 78%) as white solid. The spectroscopic data of the compound were found to be identical to those reported earlier.[7e]

Acknowledgments

The authors thank CSIR and UGC, New Delhi for their financial assistance.

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