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Short enantioselective synthesis of sedridines, ethylnorlobelols and coniine via reagent-based differentiation

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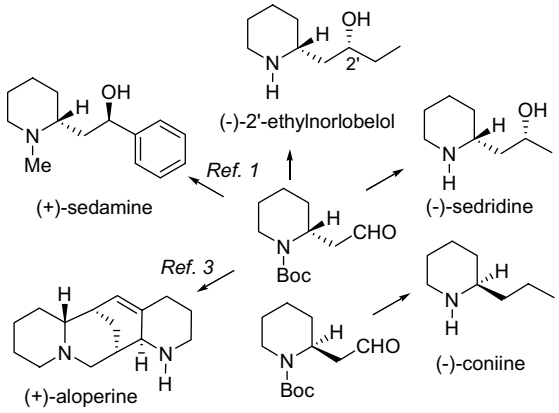
Abstract—The preparation of collections of structurally diverse small molecules is a useful tool for studying biology and medicine with chemistry. Herein, we demonstrate the versatility of the pure enantiomers of 2-(2-oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester to prepare the biological active alkaloids sedridine, allosedridine, methylsedridine, methylallosedridine, ethylnorlobelol, and coniine in two steps and in a stereoselective way via a reagent-based differentiation. The described syntheses are a demonstration of the versatility of 2-(2-oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl esters as chiral building blocks.

1. Introduction

Recently, we reported the easy preparation of the enantiomers of 2-(2-oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester **1** starting from racemic piperidine-2-ethanol.[1] In order to achieve the synthesis of diverse compounds[2] inspired by naturally occurring and biologically active piperidine alkaloids (Scheme 1), we decided to apply the simplest diversity-generating process, which is the use of coupling reactions to attach different groups to a common molecular skeleton that presents a configurationally defined stereogenic center.[2a] We used this strategy for the preparation of the pure enantiomers of sedamine and allosedamine[1] and more recently for the enantioselective synthesis of (+)-aloperine.[3] In the case of sedamine and allosedamine, the aldehyde group was submitted to an addition reaction with phenylmagnesium bromide, while for aloperine an ethylation reaction with a Grignard reagent prepared from trimethylsilylacetylene was crucial for the construction of the tetracyclic skeleton.

Herein, we report the elongation of the chain at the 2-position of the piperidine ring by reactions of the aldehyde group with alkylmagnesium bromides, dialkylzinc in the presence of 1,2-amino alcohols, and phosphonium ylides.



Scheme 1.

2. Results and discussion

The configurational stability of **1a** and **1b** was demonstrated by the high enantiomeric excess obtained in the preparation of sedamine, allosedamine, and aloperine; this feature together with the wide spectrum of reactivity of the aldehyde group prompted us to employ compounds **1** as starting materials for a number of natural products.

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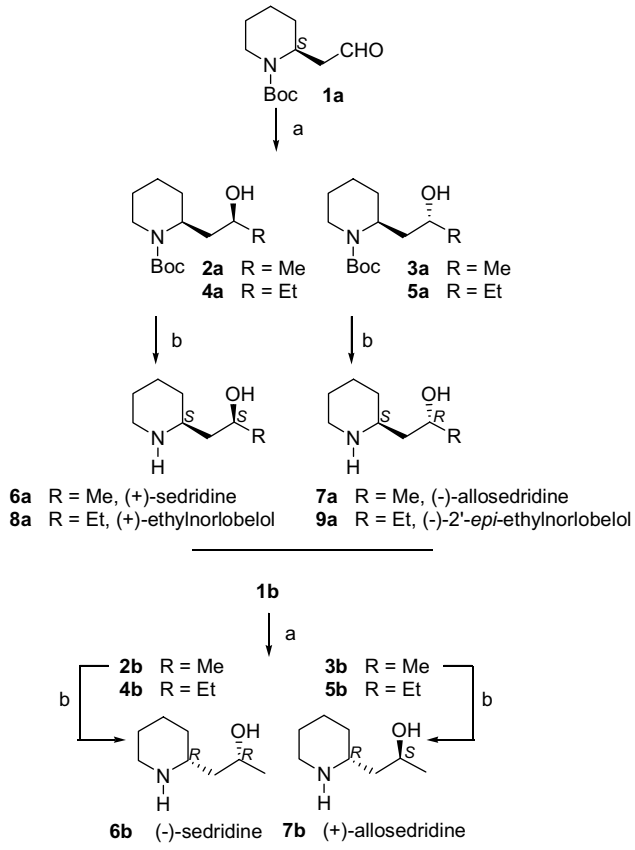
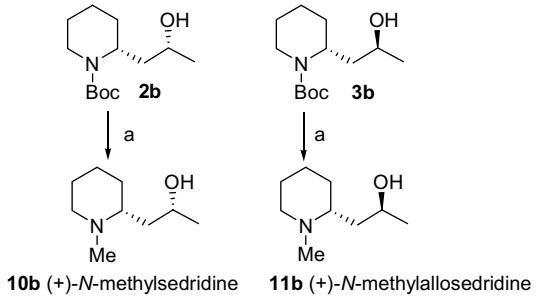
It is worthy of note that the availability of the enantiopure aldehydes **1** allowed us to achieve the synthesis of structurally related compounds simply by changing the nature of the nucleophilic reagent without changing the synthon (Scheme 2). For example, the reaction of aldehyde (*S*)-**1a** with methylmagnesium bromide at −78 °C gave two diastereoisomeric alcohols **2a** and **3a** with a global yield of 61% in a 1:1 ratio.



Scheme 2. Reagents and conditions: (a) RMgBr, THF, −78 °C; (b) TFA, CH_2Cl_2.

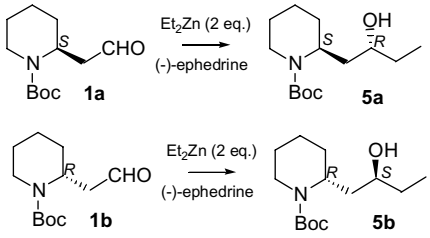
The structural assignments of the relative configuration of the obtained alcohols were possible only after the conversion to the corresponding natural products. HPLC analysis of compounds **2a** and **3a** showed that the enantiomeric excesses (**2a** 94% and **3a** 93%) were the same as that of the starting piperidine-2-ethanol. After separation of **2a** and **3a**, the simple cleavage of the Boc group (TFA in CH_2Cl_2 at room temperature for 2 h) gave (+)-sedridine **6a** in 75% yield {$[\alpha]_D$ = +26.2 (*c* 0.85, EtOH)}[4] and (−)-allosedridine **7a** (59% yield, $[\alpha]_D$ = −16.4, (*c* 0.80, MeOH)}.[5,6] Moreover, the reaction of EtMgBr with aldehyde **1a** gave compounds **4a** and **5a** which were separately submitted to reaction with TFA to give (+)-ethylnorlobelol **8a** {$[\alpha]_D$ = +17.5 (*c* 0.8, EtOH)}[7] and (−)-2′-*epi*-ethylnorlobelol **9a** {$[\alpha]_D$ = −6.6 (*c* 0.8, EtOH)}. Analogously, aldehyde (*R*)-**1b** treated with MeMgBr gave the conversion to a 1:1 mixture of compounds **2b** and **3b** that allowed access to (−)-sedridine **6b** {$[\alpha]_D$ = −25.6 (*c* 0.95, EtOH)}[8] and (+)-allosedridine **7b** {$[\alpha]_D$ = +15.5 (*c* 0.95, EtOH)}.[9]

Additionally, the reduction of **2b** and **3b** with $LiAlH_4$ in refluxing THF for 4 h gave the corresponding *N*-methyl derivatives: (+)-*N*-methylsedridine **10b** {77% yield, $[\alpha]_D$ = +34.5 (*c* 0.85, EtOH)}, (+)-*N*-methylallosedridine **11b** {69% yield, $[\alpha]_D$ = +67.5 (*c* 0.65, EtOH)} (Scheme 3).[10]



Scheme 3. Reagent: (a) $LiAlH_4$.

We then studied the possibility of inducing a diastereoselective addition of an organometallic reagent to the enantiomerically enriched aldehydes **1a** and **1b**. Using **1a** as a substrate with dimethylzinc in the presence of $TiCl_4$,[11] we obtained a 1:1 mixture of **2a** and **3a**, a result which suggested that the presence of the C2-piperidine stereogenic center was located too far away from the reactive group to influence the new stereogenic carbon even in the presence of a coordinating reagent. We then decided to use diethyl zinc in the presence of a 1,3-amino alcohol as a ligand.[12] Unsuccessful results were obtained with phenylglycinol or quinine, but the use of (−)-ephedrine showed a high degree of stereoselectivity to give just compound **5a** (65%) with no traces of **4a**. We performed the same reaction using **1b** as substrate and (−)-ephedrine as ligand to ascertain the influence of the configuration of the ligand on the formation of the second stereogenic center (Scheme 4). The formation of compound **5b** confirmed the exclusive influence of the configuration of the stereogenic carbon at the 2-position in the approach of the nucleophile. We reasoned that the diastereoselection is the consequence of the coordination of Boc and aldehyde groups by diethylzinc. The second equivalent of diethylzinc, coordinated by the ligand, attacks the less hindered *pro-R* face of the aldehyde (Fig. 1).[13]



Scheme 4.

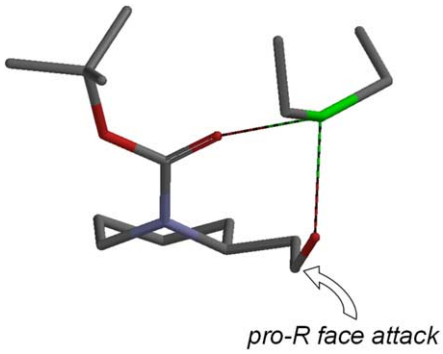
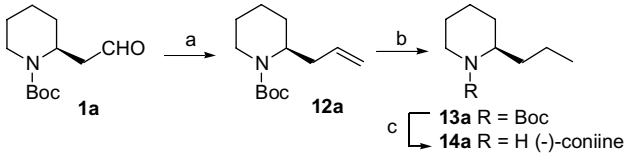


Figure 1.

Finally, our desire to increase the diversity of the compounds deriving from synthons **1a** and **1b** led us to consider the possibility of employing a Wittig reaction to lengthen the alkyl chain on the 2-position.

A Wittig reaction could allow the introduction of differently functionalized appendages, which could lead to the enantioselective synthesis of many piperidine derivatives. To demonstrate the potential of this methodology, we pursued the synthesis of (*R*-(−)-coniine **14a** (Scheme 5),[14] the enantiomer of the major alkaloid extracted from *Poison hemlock* and responsible for its toxicity.



Scheme 5. Reagents and conditions: (a) $Ph_3P^+CH_3I^-$, BuLi; (b) H_2, $Pd(OH)_2$; (c) TFA.

Aldehyde **1a** was treated with the Wittig reagent $Ph_3P^+CH_3I^-$ in the presence of BuLi to afford the 2-allyl-piperidine **12a**. Catalytic hydrogenation of **12a** led to *N*-Boc-coniine, while the removal of the Boc group gave the desired product **14a** {$[\alpha]_D = -9.7$ (*c* 0.93, $CHCl_3$)}.[15] It is noteworthy that racemic **12a** is a crucial intermediate in different racemic synthesis of compounds with interesting biological activities reported in the literature.[16]

3. Conclusion

In conclusion, aldehydes **1a** and **1b** have proven to be versatile chiral building blocks for the enantioselective synthesis of diversely 2-substituted piperidine derivatives. They also allow the stereocontrolled formation of C–C bonds while elongating the chain at the 2-position of the piperidine ring. We are of the opinion that this approach represents the easiest entry to this type of piperidine alkaloids. This strategy appears as a folding pathway for the synthesis of piperidine alkaloid-like skeletons, which continues to be a demanding challenge for synthetic chemists and an interesting target for the pharmaceutical industry.

4. Experimental

4.1. Materials

Enantiomeric excesses were determined by chiral HPLC.

4.1.1. 2-(2-Hydroxy-alkyl)-piperidine-1-carboxylic acid *tert*-butyl ester, 2a or 2b and 3a or 3b. A solution of MeMgBr (3 M, 2.85 mL, 8.36 mmol) in Et_2O was added dropwise to a solution of **1a** or **1b** (960 mg, 4.2 mmol) in THF (16 mL) and cooled at −78 °C. The solution was allowed to warm up to −20 °C and then left stirring for 4 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (hexane–AcOEt, 4:1) provided **2a** (or **2b**) (321 mg, 31%) and **3a** (or **3b**) (315 mg, 30%). Compounds **2a** and **2b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, d, $J = 6.7$ Hz), 1.42 (9H, s), 1.48–1.68 (7H, m), 1.69–1.80 (1H, m), 2.00 (1H, td, $J = 12.3$, 2 Hz), 2.70 (1H, td, $J = 12.3$, 2 Hz), 3.55 (1H, br s), 3.90–4.05 (1H, m), 4.42–4.54 (1H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.2, 22.5, 25.5, 28.4, 29.3, 39.4, 46.5, 63.3, 80.1, 110.6. Compound **2a**: mp 52 °C; ee 94%; $[\alpha]_D = -38.9$ (*c* 1, $CHCl_3$). Compound **2b**: mp 48 °C; ee 89%; $[\alpha]_D = +34.7$ (*c* 1, $CHCl_3$). Chiral HPLC Analysis (Analytical). Column: Chiralcel OJ chiral column; UV detector: λ 210 nm; solvent: petroleum ether–*i*-PrOH, 99.9:0.1; flow rate: 0.5 mL/min; retention time: **2b**, 11.58 min; **2a**, 12.48 min. Compounds **3a** or **3b:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, d, $J = 7.4$ Hz), 1.42 (9H, s), 1.51 (dt, $J = 14.7$, 7.4 Hz), 1.52–1.64 (5H, m), 1.78–1.86 (1H, m), 2.65 (1H, br s), 2.82 (1H, t, $J = 14.7$), 3.82 (1H, m), 3.95 (1H, br d), 4.30–4.38 (1H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.1, 23.5, 25.5, 28.4, 29.7, 40.0, 48.6, 66.4, 79.7; **3a** ee 95%, $[\alpha]_D = -60.2$ (*c* 1.025, $CHCl_3$); **3b** ee 85%, $[\alpha]_D = +56$ (*c* 1.15, $CHCl_3$). Chiral HPLC Analysis (Analytical). Column: Chiralcel OD chiral column; UV detector: λ 210 nm; solvent: petroleum ether–*i*-PrOH, 99:1; flow rate: 0.7 mL/min; retention time: **3b**, 16.76 min; **3a**, 19.78 min.

4.1.2. (+)-1-(1-Methyl-piperidin-2-yl)-propan-2-ol (*N*-methylsedridine), 10b. A solution of $LiAlH_4$ (1 M, 2.05 mL, 2.05 mmol) in THF was added dropwise to solution of **2b** (100 mg, 0.41 mmol) in dry THF (7 mL). After being heated for 4 h at reflux, the reaction mixture was quenched by addition of a 15% aqueous solution of NaOH (2 mL) and water (10 mL). The solution was then extracted with CH_2Cl_2. The organic layers gave, after concentration, **10b** (50 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (3H, d, $J = 5.4$ Hz), 1.20–1.34 (2H, m), 1.50–1.58 (3H, m), 1.62–1.78 (2H, m), 1.86–2.00 (2H, m), 2.12–2.22 (1H, m), 2.32 (3H, s), 2.88 (1H, br d, $J = 12.5$ Hz), 4.12–4.24 (1H, m); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.1, 23.6, 24.4, 25.7, 29.7, 38.9, 43.8, 57.4, 62.8, 65.1, 111.2; $[\alpha]_D = +34.5$

(c 0.85, EtOH). Anal. Calcd for $C_{13}H_{25}NO_3$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.79; H, 12.24; N, 8.88.

4.1.3. (+)-1-(1-Methyl-piperidin-2-yl)-propan-2-ol (*N*-methylallosedridine), 11b. The treatment of **3b** (115 mg, 0.47 mmol) with the same procedure described for the preparation of **10b** gave **11b** (50 mg, 0.32 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (3H, d, J = 7.4 Hz), 1.22 (1H, ddd, J = 15.7, 4 Hz), 1.25–1.34 (1H, m), 1.42–1.58 (3H, m), 1.62–1.76 (2H, m), 1.84 (1H, ddd, J = 15.7, 9.8, 9.5 Hz), 2.42 (3H, s), 2.44–2.50 (1H, m), 2.60–2.66 (1H, m), 2.98 (1H, ddd, J = 11.7, 7.5, 4 Hz), 3.92–3.99 (1H, m), 4.72 (1H, br s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.0, 23.0, 24.1, 25.6, 29.7, 39.2, 40.0, 53.0, 60.9, 68.1; $[\alpha]_D$ = +67.5 (c 0.65, EtOH). Anal. Calcd for $C_{13}H_{25}NO_3$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.79; H, 12.24; N, 8.88.

4.1.4. 1-Piperidin-2-yl-propan-2-ol (sedridine), 6a or 6b. TFA (1.04 mL, 13.6 mmol), was added to a solution of **2a** or **2b** (220 mg, 0.9 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The solution was warmed to room temperature and left stirring for 3 h. The reaction was then quenched with H_2O (2,5 mL) and 5 M NH_4OH to reach pH 9. The concentration of the organic layer gave **6a** or **6b** as a white crystalline solid (97 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (3H, d, J = 5.6 Hz), 1.38–1.56 (4H, m), 1.58–1.68 (3H, m), 1.76–1.86 (1H, m), 2.62 (1H, dt, J = 11.2, 3.7 Hz), 2.90–3.00 (1H, m), 3.12 (1H, br d, J = 11.2 Hz), 3.74 (2H, br s), 4.05–4.16 (1H, m); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 23.4, 24.1, 25.0, 30.8, 43.2, 46.3, 54.5, 64.4; **6a** $[\alpha]_D$ = +26.2 (c 0.85, EtOH). Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.15; H, 11.89; N, 9.80; **6b** $[\alpha]_D$ = −25.6 (c 0.95, EtOH). Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.16; H, 11.90; N, 9.72.

4.1.5. 1-Piperidin-2-yl-propan-2-ol (allosedridine), 7a and 7b. The treatment of **3a** or **3b** (200 mg, 0.82 mmol) with the same procedure described for the preparation of **6a** or **6b** gave **7a** or **7b** (69 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06–1.12 (1H, m), 1.13 (3H, s), 1.22–1.33 (2H, m), 1.45–1.52 (2H, m), 1.53–1.65 (2H, m), 1.77–1.84 (1H, m), 2.54–2.62 (1H, m), 2.71 (1H, tt, J = 10.7, 2.6 Hz), 3.03 (1H, dq, J = 13.5, 2 Hz), 3.95–4.03 (1H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.8, 24.5, 27.4, 34.4, 44.6, 46.0, 58.1, 68.9. Compound **7a** $[\alpha]_D$ = −16.4 (c 0.80, MeOH). Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.14; H, 11.92; N, 9.80. Compound **7b** $[\alpha]_D$ = +15.5 (c 0.95, EtOH). Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.21; H, 11.99; N, 9.76.

4.1.6. 2-(2-Hydroxy-butyl)-piperidine-1-carboxylic acid *tert*-butyl ester, 4a and 5a. A solution of EtMgBr (1 M, 3.7 mL, 3.7 mmol) in Et_2O was added dropwise to a solution of **1a** (420 mg 1.85 mmol) in THF (15 mL) at −78 °C. The solution was allowed to warm up to −20 °C and left stirring for 5 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give by flash column chromatography (hexane–AcOEt, 4:1) **4a** (206 mg, 43%) and **5a** (131 mg, 28%). Compound **4a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (3H, d, J = 6.8 Hz), 1.14–1.22 (1H, m), 1.39–1.64 (7H, m), 1.46 (9H, s), 1.67–1.78 (1H, m), 2.01 (dt, J = 12.3, 2 Hz), 2.69 (1H, td, J = 13, 2.5 Hz), 3.15–3.28 (1H, m), 3.82 (1H, br s), 3.91–4.01 (1H, m), 4.42–4.54 (1H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.0, 19.9, 26.2, 29.1, 30.2, 30.3, 37.9, 40.0, 47.3, 69.5, 80.7; $[\alpha]_D$ = +37.7 (c 1, $CHCl_3$). Compound **5a**: mp 75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (3H, d, J = 7.6 Hz), 1.46 (9H, s), 1.38–1.66 (8H, m), 1.69–1.82 (2H, m), 2.85 (1H, t, J = 13 Hz), 3.53–3.62 (1H, m), 3.96 (1H, br d, J = 11.5 Hz), 4.34–4.40 (1H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.1, 19.0, 25.5, 28.4, 29.5, 30.1, 37.7, 48.4, 71.6, 79.6; $[\alpha]_D$ = +53.3 (c 1, $CHCl_3$).

4.1.7. Stereoselective synthesis of 5a or 5b. A solution of Et_2Zn (1 M, 440 μL, 0.44 mmol) in toluene was added at 0 °C to a solution of (−)-ephedrine (0.22 mmol) in toluene (3 mL). The solution was stirred for 15 min at 0 °C, then a solution of **1a** or **1b** (50 mg, 0.22 mmol) in toluene (1 mL) was added. The resulting solution was stirred for 24 h at room temperature. The mixture was washed with 1 M HCl, and extracted with AcOEt. The concentration of the organic layer gave **5a** {$[\alpha]_D$ = +51.4 (c 1, $CHCl_3$)} or **5b** {$[\alpha]_D$ = −48.7 (c 1, $CHCl_3$)} (65%).

4.1.8. (+)-1-Piperidin-2-yl-butyl-2-ol (ethylnorlobelol), 8a. The treatment of **4a** (200 mg, 0.78 mmol) with the same procedure described for the preparation of **6a** or **6b** gave **8a** (75 mg, 67%) as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, t, J = 7.2 Hz), 1.35–1.52 (6H, m), 1.53–1.62 (3H, m), 1.77–1.82 (1H, m), 2.57 (1H, dt, J = 11.8, 3 Hz), 2.85–2.92 (1H, m), 3.02–3.08 (1H, m), 3.70 (2H, br s), 3.72–3.82 (1H, br s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 9.9, 24.6, 25.9, 30.5, 31.5, 41.6, 46.7, 54.7, 70.2; mp 63 °C; $[\alpha]_D$ = +17.5 (c 0.80, EtOH). Anal. Calcd for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.78; H, 12.16; N, 8.95.

4.1.9. (−)-1-Piperidin-2-yl-butyl-2-ol (2′-*epi*-ethylnor lobelol), 9a. The treatment of **5a** (130 mg, 0.51 mmol) with the same procedure described for the preparation of **6a** or **6b** gave **9a** (35 mg, 48%) as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, t, J = 7.5 Hz), 1.11–1.22 (1H, m), 1.23–1.55 (7H, m), 1.57–1.70 (1H, m), 1.76–1.84 (1H, m), 2.62 (1H, dt, J = 12.2, 3 Hz), 2.76 (1H, tt, J = 10.7, 2.5 Hz), 3.04–3.10 (1H, m), 3.67–3.75 (1H, m), 4.10 (2H, br s); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.3, 24.9, 27.3, 31.6, 34.4, 42.5, 46.5, 58.7, 74.7; $[\alpha]_D$ = −6.6 (c 0.80, EtOH).

4.1.10. 2-Allyl-piperidine-1-carboxylic acid *tert*-butyl ester, 12a. BuLi (1.9 mL, 3.04 mmol) was added to a suspension of $Ph_3P^+CH_3I^-$ (1.23 g, 3.04 mmol) in THF (15 mL) cooled at 0 °C. The mixture was allowed to stir for 15 min at 0 °C after which a solution of **1a** (300 mg, 1.32 mmol) in THF (5 mL) was added. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched with a saturated

solution of NH_4Cl and then extracted with EtOAc. The organic layers were washed with brine, dried over $NaSO_4$, and concentrated to give after flash column chromatography (hexane–EtOAc, 24:1) **12a** (145 mg, 48.7%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.32–1.44 (1H, m), 1.45 (9H, s), 1.52–1.65 (5H, m), 2.19–2.27 (1H, m), 2.36–2.45 (1H, m), 2.77 (1H, dt, $J = 14.3$, 2.5 Hz), 3.98 (1H, br d, $J = 13.5$ Hz), 4.24–4.31 (1H, m), 5.00 (1H, dd, $J_1 = 10$, 1.5 Hz), 5.05 (1H, dq, $J = 15$, 1.5 Hz), 5.75 (1H, qt, $J = 7$, 10 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 18.8, 25.5, 27.6, 28.4, 34.4, 38.9, 50.1, 79.1, 116.5, 135.6, 155.1; $[\alpha]_D = -49.2$ (*c* 0.9, $CHCl_3$).

4.1.11. 2-Propyl-piperidine-1-carboxylic acid *tert*-butyl ester, 13a. $Pd(OH)_2$ (15 mg) was added to a solution of **12a** (130 mg, 0.58 mmol) in MeOH (10 mL). The suspension was allowed to react under H_2 atmosphere at room temperature for 1 h. The suspension was filtered on Celite and the solvent removed to afford **13a** (122 mg, 94%). ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, t, $J = 6.5$ Hz), 1.18–1.72 (10H, m), 1.44 (9H, s), 2.72 (1H, dt, $J = 4$, 12.9 Hz), 3.95 (1H, br d, $J = 12.9$ Hz), 4.12–4.25 (1H, m); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.0, 19.0, 19.5, 25.7, 28.5, 31.9, 38.6, 50.1, 77.4, 155.1; $[\alpha]_D = -39.8$ (*c* 0.6, $CHCl_3$).

4.1.12. (−)-2-Propyl-piperidine (coniine), 14a. Compound **13a** (25 mg, 0.11 mmol) was treated with the same procedure described for the preparation of **4a** or **4b** to give (−)-coniine (**14a**) (12 mg, 95%). ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, t, $J = 7$ Hz), 1.05–1.54 (6H, m), 1.56–1.72 (4H, m), 2.44–2.58 (1H, m), 2.64 (1H, t, $J = 13.5$ Hz), 2.68 (1H, s all), 3.10 (1H, br d, $J = 13$ Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.1, 18.9, 24.4, 25.7, 31.9, 38.8, 46.7, 56.7; $[\alpha]_D = -9.7$ (*c* 0.93, $CHCl_3$).

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