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Asymmetric aza-Michael addition: synthesis of (−)-allosedridine and (−)-2-*epi*-ethylnorlobelol

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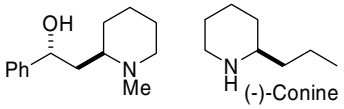
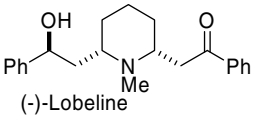
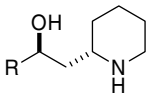
Abstract—The combination of cross-metathesis and aza-Michael addition is an efficient method for generating piperidine alkaloids. Allosedridine and 2-*epi*-ethylnorlobelol were synthesized in six steps with ca. 25% overall yield. The aza-Michael addition is reversible for phenyl and alkyl ketones; however, the epimerization is not observed for the corresponding ester and amide.

1. Introduction

Piperidine alkaloids,[1] such as lobeline,[2] coniine,[3] and sedamine,[4] represent a large, important family of natural products. Many of these compounds are biologically active, and the piperidine moiety is frequently found in the structure of drug candidates.[5] Therefore, the development of an efficient, stereoselective access to the piperidine alkaloids continues to attract the attention of organic chemists.[6] Recently, several research groups have shown that asymmetric aza-Michael addition to generate β-aminoketones or esters is a good entry to alkaloids.[7] For example, O'Brien et al. have applied the tandem S_N2 substitution and intramolecular aza-Michael addition to prepare ethyl 2-piperidineacetate as a key intermediate in their synthesis of (−)-sparteine.[7d,8] We felt that this approach would be applicable to our current studies in synthesizing piperidine alkaloids. Thus, we applied the intramolecular aza-Michael addition to the synthesis of (−)-allosedridine **1** and (−)-2-*epi*-ethylnorlobelol **2**, and report our results herein.







R = Me, (-)-allosedridine, **1**
R = Et, (-)-2'-*epi*-ethylnorlobelol, **2**

2. Results and discussion

Cross-metathesis (CM) of commercially available 6-chloro-1-hexene and methyl acrylate quickly generates the 7-chloro-hept-2-enoate **3** in good yield; the yield is lower (47%) without *p*-cresol as the beneficial additive.[9] Compared to the reported method for preparing 7-chloro- and 7-iodo-hept-2-enoate,[7f,10] our preparation utilizing CM methodology decreases the number of synthetic steps. By using phase transfer catalysis, substitution, and intramolecular Michael addition of **3** and (*R*)-α-methylbenzylamine, methyl 2-(piperidin-2-yl)acetates **4** and **5** were obtained in a diastereomeric ratio of 2:1 (Scheme 1). This ratio is consistent with O'Brien's observation using 7-iodo-hept-2-enoate.[7d] The diastereomers were separable by flash column chromatography. Other chiral auxiliaries, (*R*)-1-(1-naphthyl)ethylamine and (*R*)-α-ethylbenzylamine, gave **4**:**5** in the ratios of 3:1 and 1.5:1, respectively. However, the reactions with these chiral amines were sluggish and the diastereomers produced were more difficult to separate. The reversibility of this intramolecular aza-Michael addition was examined by re-subjecting **4** to the reaction conditions. Under these conditions, we found that **4** does not epimerize to **5**, as shown by ^{1}H NMR spectroscopy. This result supports the conclusion that the diastereomeric ratio of **4**:**5** is determined at the cyclization step, which is in contrast to

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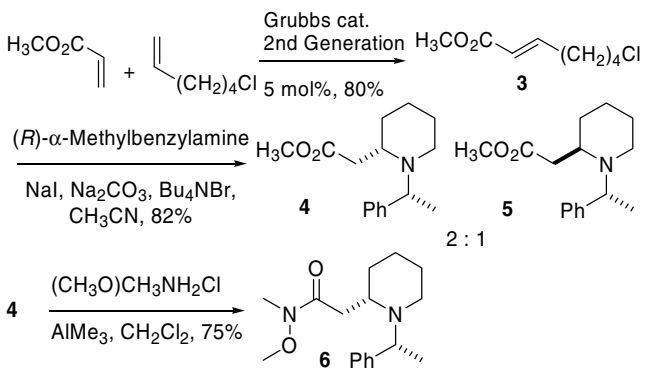
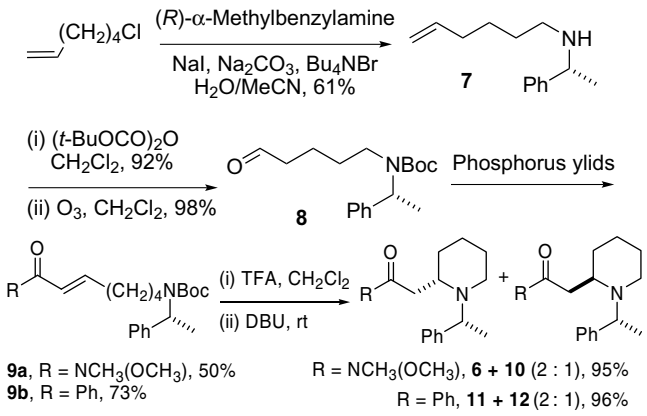


Scheme 1.

the finding that the aza-Michael addition is reversible when an α,β-unsaturated phenyl ketone is the acceptor (vide infra). Compound **4** was further converted to the Weinreb amide **6** at −10 °C.[11]

Alternatively, compound **6** was prepared from 6-chloro-1-hexene by a sequence involving amination, ozonolysis, Horner–Emmons olefination, and aza-Michael addition (Scheme 2). This method was also applied to the preparation of phenyl ketone **9b** and the corresponding β-ketopiperidines **11** and **12**. Unfortunately, neither **9a** nor **9b** provided an improved diastereomeric ratio for the intramolecular aza-Michael addition compared to that obtained with **3**. Nonetheless, the mixture of **6** and **10** was separable by column chromatography. Pure **6** does not undergo epimerization to form **10** under the reaction conditions. Thus, the formation of both compounds **4** and **6** is irreversible. On the other hand, efforts to isolate pure **11** or **12** always gave a 2:1 mixture even though these diastereomers have distinct R_f values on TLC. This phenomenon suggests a facile epimerization process for interconverting the two phenyl ketones. This was confirmed when it was found that the acyl substitution of pure **6** with phenyllithium at −40 °C (Eq. 1 and entries 1 and 2, Table 1) generated both **11** and **12** in a ratio that approached 2:1 as the reaction time increased. Thus, the behavior of **11** is analogous to that of lobeline[12] in that the epimerization occurs via a retro-Michael addition. Phenyl Grignard and Gilman



Scheme 2.

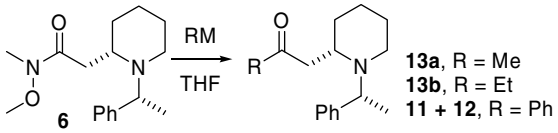
Table 1. Reaction of **6** and organometallic reagents

Entry	Reagent	Temp. (°C)	Time (min)	Yield (%)
1	PhLi	−40	30	71[a]
2	PhLi	−40	60	65[b]
3	PhMgBr	−40	60	18
4	Ph_2CuLi	−40	60	0
5	CH_3MgCl	25	90	91
6	C_2H_5MgCl	25	90	94

[a] **11**:**12** = 4: 1.
[b] **11**:**12** = 2: 1.

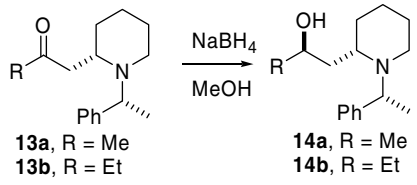
reagents only gave poor yields or decomposed product when used in place of phenyllithium (Table 1, entries 3 and 4).

Although the stereolability of **11** limits its suitability for our purposes, methyl and ethyl ketones **13ab** can be prepared from **6** with retained stereochemistry and in good yields (Table 1, entries 5 and 6). Epimerization of these ketones **13ab** is much slower. Thus, at room temperature, four days was required for diastereomerically pure **13a** and **13b** in $CDCl_3$ to reach an equilibrium ratio of 2:1. Therefore, isolation, purification, and further chemical modification of ketones **13** are practical. The differences in the rates of epimerization of **4**, **6**, **11**, and **13** correlate qualitatively with their relative acidities.[13]



(1)

Ketones **13** were reduced to the corresponding alcohols with sodium borohydride (Eq. 2 and Table 2). We found that the addition of Lewis acids such as zinc chloride and manganese(II) chloride improves the diastereoselectivity up to 17:1 via chelation control.[14] As seen in Eq. 3, hydrogenolysis to remove the chiral auxiliary generated (−)-allosedridine **1** and (−)-2′-*epi*-ethylnorlobelol **2**.

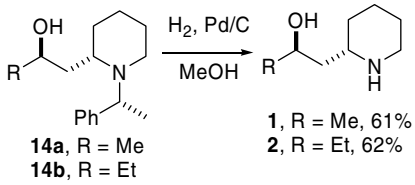


(2)

Table 2. Reduction of ketones **13**

Entry	Compound	Additive	Temp. (°C)	Time (h)	dr[a]	Yield (%)
1	**13a**	—	25	2	3:1	62
2	**13a**	—	0	3	4:1	71
3	**13a**	$MnCl_2$	0	3	7:1	66
4	**13a**	$ZnCl_2$	0	16	17:1	95
5	**13b**	$MnCl_2$	0	3	5:1	46
6	**13b**	$ZnCl_2$	0	16	14:1	99

[a] Diastereomeric ratio, determined by ^1H NMR spectroscopy.



14a, R = Me
14b, R = Et

1, R = Me, 61%
2, R = Et, 62%

(3)

3. Conclusion

In conclusion, the asymmetric synthesis of **1** and **2** was achieved in six steps and 25–27% overall yield. The efficacy of this sequence shows that the combination of cross-metathesis and aza-Michael addition is a useful way to prepare the piperidine alkaloids. We also demonstrated that the reversibility of the intramolecular aza-Michael addition is influenced by the carbonyl group, that is, the epimerization rate of phenyl ketone **11** is faster than that of alkyl ketones **13ab**, while ester **4** and Weinreb amide **6** do not epimerize under the reaction conditions. Consequently, the diastereomeric ratios obtained from the intramolecular aza-Michael additions of **3** and **9a** were determined at the stage of the initial cyclization.

4. Experimental

4.1. (*E*)-Methyl 7-chloro-2-heptenoate 3[7f]

To a solution of 6-chloro-1-hexene (100 mg, 0.84 mmol), methyl acrylate (726 mg, 8.4 mmol), and *p*-cresol (46 mg, 0.42 mmol) was added the second generation Grubbs catalyst[15] (18 mg, 0.02 mmol) in toluene (0.5 mL). The reaction mixture was heated in an oil bath (120 °C) for 3 h, and then excess solvent was removed under vacuum. Purification by column chromatography (SiO_2: EtOAc/hexane 1:4; R_f 0.67) provided **3** (119 mg, 0.67 mmol, 80%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45–1.90 (m, 4H), 2.12–2.31 (m, 2H), 3.51 (t, $J = 6.4$ Hz, 2H), 3.70 (s, 3H), 5.81 (dt, $J = 15.6$ Hz and 1.4 Hz, 1H) 6.92 (dt, $J = 15.6$ Hz and 7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.21, 31.30, 31.83, 44.54, 51.41, 121.44, 148.50, 166.94.

4.2. Methyl (2*S*)-1-[(1*R*)-1-phenylethyl]piperidineacetate 4 and (*R*,*R*)-diastereomer 5

A solution of **3** (100 mg, 0.57 mmol), tetrabutylammonium bromide (50% in water, 255 mg), sodium iodide (255 mg, 1.7 mmol), sodium carbonate (300 mg, 2.9 mmol), and (*R*)-α-methylbenzylamine (68.6 mg, 0.57 mmol) in acetonitrile (10 mL) was heated at reflux for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with ether (15 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2: EtOAc/hexane/Et_3N, 1:4:0.05; R_f 0.67) to give **4** (81 mg, 0.31 mmol, 55%) as a colorless oil; $[\alpha]_D^{20} = +39.2$ (*c* 1, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25–1.32 (d, $J = 6.7$ Hz, 3H), 1.35–1.85 (m, 6H), 2.1–2.4 (m, 2H), 2.5–2.63 (m, 2H), 3.38–3.55 (m, 1H), 3.6–3.75 (m, 4H), 7.15–7.4 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.87, 20.80, 25.59, 29.99, 31.98, 44.59, 51.55, 52.37, 59.29, 126.51, 127.28, 128.13, 146.13, 173.64; HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for ($C_{16}H_{24}NO_2$) 262.1807; found 262.1802. Diastereomer **5** (39 mg, 0.15 mmol, 26%) was eluted later (R_f 0.45). $[\alpha]_D^{20} = +9.7$ (*c* 1.5, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.25–2.35 (d, $J = 6.7$ Hz, 3H), 2.35–2.75 (m, 6H), 2.4–2.75 (m, 4H), 3.1–3.23 (m, 1H), 3.58 (s, 3H), 3.75–3.9 (q, $J = 6.7$ Hz, 1H), 7.15–7.4 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.2, 21.3, 24.9, 29.0, 32.7, 43.4, 51.4, 52.7, 59.1, 126.7, 127.3, 128.1, 144.7, 173.4.

4.3. *N*-Methoxy-*N*-methyl (2*S*)-1-[(1*R*)-1-phenylethyl]-piperidineacetamide 6

Trimethylaluminum (2.0 M in toluene, 1.67 mL, 3.3 mmol) was added dropwise to a solution of *N*,*O*-dimethyl-hydroxylamine hydrochloride (325 mg, 3.3 mmol) and CH_2Cl_2 (4 mL) under nitrogen at −10 °C. The reaction mixture was stirred at room temperature for another 30 min and re-cooled to −10 °C. A solution of **4** (290 mg, 1.1 mmol) in CH_2Cl_2 (2.0 mL) was added, and the mixture was stirred for 2 h at −10 °C. It was then quenched with water (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic solution was dried over Na_2SO_4, filtered, and concentrated to give crude **6** (241.7 mg, 75%).

Alternatively, to the solution of **9a** (77 mg, 0.2 mmol) and CH_2Cl_2 (0.7 mL) was added trifluoroacetic acid (114 mg, 1.0 mmol) at 0 °C, and the mixture was stirred for 1 h. It was then concentrated under vacuum, redissolved in CH_2Cl_2 (0.7 mL), after which DBU (500 μL, 0.33 mmol) was added, and the solution was stirred at rt for 16 h. After being concentrated, purification by column chromatography (SiO_2, $CH_3OH/CHCl_3/Et_3N$, 1:1:0.02; R_f 0.50) afforded **6** (36 mg, 0.12 mmol, 64%) as a colorless oil; $[\alpha]_D^{20} = +20.4$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28–1.32 (d, $J = 6.6$ Hz, 3H), 1.32–1.50 (m, 3H), 1.51–1.6 (m, 2H), 1.70–1.80 (m, 1H), 2.15–2.35 (m, 2H), 2.55–2.8 (m, 2H), 3.54–3.60 (m, 1H), 3.65–3.75 (m, 4H), 7.15–7.4 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 20.8, 25.5, 29.3, 32.1, 45.2, 52.2, 59.5, 61.3, 126.8, 127.5, 128.3, 146.5, 173.5; HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for ($C_{17}H_{27}N_2O_2$), 291.2073; found, 291.2071.

4.4. (*R*)-*N*-(1-Phenylethyl)-5-hexenyl amine 7[16]

(*R*)-α-Methylbenzylamine (2.04 g, 16.9 mmol) was added to a solution of 6-chloro-1-hexene (1.0 g, 8.4 mmol), tetrabutylammonium bromide, 50% in water, 544 mg, 0.84 mmol, sodium iodide (2.53 g, 16.9 mmol), sodium carbonate (2.68 g, 25.3 mmol), and acetonitrile (15 mL). After being heated at reflux for 16 h, the reaction mixture was diluted with water (20 mL), extracted with ether (15 mL × 3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (SiO_2, EtOAc/hexanes/Et_3N, 2:3:0.05; R_f 0.45) gave **7** (1.04 g, 5.1 mmol, 61%) as a light yellow oil; $[\alpha]_D^{20} = +46.8$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30–1.32 (d, $J = 6.6$ Hz, 3H), 1.32–1.55 (m, 5H), 1.95–2.05 (q, $J = 7.05$ Hz, 2H), 2.35–2.55 (m, 2H), 3.70–3.80 (q, $J = 6.6$ Hz, 1H), 4.98–5.02 (m, 2H), 5.70–5.85 (m,

1H), 7.20–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.3, 26.6, 29.8, 33.6, 47.7, 58.4, 114.4, 126.5, 126.8, 128.4, 138.8, 145.9; HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for ($C_{14}H_{22}N$), 204.1752; found, 204.1747.

4.5. *tert*-Butyl 5-oxopentyl (*R*)-(1-phenylethyl)carbamate 8

Di-*tert*-butyl dicarbonate (1.23 g, 5.6 mmol) was added to a solution of **7** (1.04 g, 5.1 mmol) and CH_2Cl_2 (20 mL). The solution was stirred at rt for 16 h, and excess reagent and by-product were removed by washing with water (10 mL × 3). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give the Boc-protected **7** as a light-yellow oil (1.43 g, 4.7 mmol). $[\alpha]_D^{20} = +71.1$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18–1.25 (m, 2H), 1.41 (s, br, 9H), 1.49–1.52 (m, 5H), 1.90–2.00 (m, 2H), 2.70–3.40 (m, br, 2H), 4.85–5.00 (m, 2H), 5.60–5.80 (m, 1H), 7.15–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.43, 27.39, 28.48, 33.30, 79.37, 85.15, 114.37, 126.95, 128.21, 138.66, 146.73; HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for ($C_{19}H_{30}NO_2$), 304.2277; found, 304.2274.

Ozone was bubbled into a solution of **7** the Boc-protected (500 mg, 1.65 mmol) and methanol (50 mL) at −78 °C until a light-blue color was observed. Dimethyl sulfide (0.61 mL, 8.24 mmol) was added at −78 °C. The solution was stirred overnight and warmed to rt during this period. After the removal of methanol under vacuum, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (10 mL × 3). The organic solution was dried over Na_2SO_4, filtered, and concentrated to give **8** (493 mg, 98%) as a light yellow oil. $[\alpha]_D^{20} = +71.7$ (*c* 1, $CHCl_3$); ^{1}H NMR(500 MHz, $CDCl_3$) δ 1.35–1.55 (m, 16H), 2.27–3.05 (m, 2H), 2.75–3.1 (m, br, 2H), 5.2–5.7 (m, br, 1H), 7.20–7.40 (m, 5H), 9.65 (t, $J = 1.63$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.4, 19.5, 27.4, 28.5, 29.3, 43.4, 79.6, 85.2, 127.0, 128.3, 141.9, 155.7, 202.2; HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for ($C_{18}H_{28}NO_3$), 306.2069; found, 306.2067; IR(cm^{-1}): 3063, 3030, 2975, 2938, 2805, 2719, 1725, 1686, 1603, 1454, 1159, 1131.

4.6. *tert*-Butyl 7-[methoxy(methyl)amino]-7-oxo-(5,*E*)-hepten-yl-(*R*)-(1-phenylethyl) carbamate 9a

To a solution of dimethyl [2-(methoxymethylamino)-2-oxoethyl]phosphonate[17] (510 mg, 2.1 mmol) and THF (3 mL) was added *n*-butyllithium (1.6 M in hexanes, 1.4 mL, 2.1 mmol) at 0 °C. The ylid solution was stirred for 15 min, and **8** (650 mg, 2.1 mmol) dissolved in THF (1.6 mL) was added at 0 °C. The reaction mixture was stirred at rt for 16 h, quenched with water (5 mL), and extracted with diethyl ether (5 mL × 3). The combined organic layers were washed with satd $NaCl_{(aq)}$ (10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (SiO_2, EtOAc/hexanes/Et_3N, 1:1:0.02; R_f 0.50) yielded **9a** (416 mg, 1.1 mmol, 50%) as a light-yellow oil. $[\alpha]_D^{20} = +54.0$ (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20–1.60 (m, 16H), 2.10–2.20 (m, 2H), 2.70–3.10 (m, br, 2H), 3.19 (s, 3H), 3.64 (s, 3H), 5.00–5.50 (m, br, 1H), 6.25–6.35 (d, $J = 15.4$ Hz, 1H), 6.80–6.95 (dt, $J = 6.95$ Hz, 15.4 Hz, 1H), 7.2–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.5, 25.8, 28.4, 29.5, 32.0, 32.3, 43.3, 52.8, 61.5, 79.4, 118.7, 126.9, 127.9, 128.2, 141.9, 147.2, 155.7, 166.9; HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for ($C_{22}H_{35}N_2O_4$), 391.2597; found, 391.2599; IR(cm^{-1}): 3063, 3028, 2973, 2936, 1686, 1666, 1635, 1157, 1024.

4.7. *tert*-Butyl (7-oxo-7-phenyl-(5,*E*)-heptenyl)-(*R*)-(1-phenylethyl)carbamate 9b

To a solution of **8** (388 mg, 1.27 mmol) and benzene (5 mL) was added 1-phenyl-2-(triphenylphosphoranylidene)ethanone[18] (483 mg, 1.27 mmol). The solution was heated at reflux for 16 h. The solvent was removed under vacuum, and purification by column chromatography (SiO_2, EtOAc/hexanes, 1:4; R_f 0.40) gave **9b** (378 mg, 0.93 mmol, 73%) as a light-yellow oil. $[\alpha]_D^{20} = +49.0$ (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30–1.60 (m, 16H), 2.10–2.30 (q, $J = 6.8$ Hz, 2H), 2.70–3.20 (m, br, 2H), 5.10–5.65 (m, br, 1H), 6.70–7.10 (m, 2H), 7.15–7.30 (m, 5H), 7.35–7.6 (m, 3H), 7.85–7.95 (dd, $J = 1.36$ Hz, 7.96 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.5, 25.7, 28.5, 29.4, 32.3, 43.5, 79.5, 126.0, 127.0, 128.2, 128.5, 132.5, 137.9, 141.9, 149.3, 155.7, 190.8; HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for ($C_{26}H_{34}NO_3$), 408.2539; found, 408.2534; IR(cm^{-1}): 3063, 3030, 2973, 2933, 1683, 1671, 1636, 1156, 1024.

4.8. (2*S*)-(1-(*R*)-Phenylethyl-2-piperidyl)acetophenone 11 and the (*R*,*R*)-diastereomer 12

Trifluoroacetic acid (1.4 mL, 1.85 mmol) was added to a solution of **9b** (150 mg, 0.37 mmol) and CH_2Cl_2 (1.2 mL) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was concentrated and combined with a solution of DBU (0.9 mL, 0.62 mmol) in CH_2Cl_2 (1.2 mL). The reaction was stirred at rt for another 16 h, concentrated, and DBU was removed by flash column chromatography (SiO_2, EtOAc/hexanes, 3:7) to give the two inseparable diastereomers **11** and **12** (2:1, 109 mg, 0.35 mmol, 96%) as a yellow oil (R_f 0.6 and 0.5, respectively, on SiO_2-TLC plate eluted by EtOAc/hexanes/Et_3N, 1:4:0.05). Diastereomer **11**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15–1.85 (m, 9H), 2.30–2.45 (m, 2H), 3.10–3.30 (m, 2H), 3.65–3.77 (m, 2H), 7.15–8.15 (m, 5H); diastereomer **12**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15–1.85 (m, 4.5H), 2.5–2.65 (m, 0.5H), 2.75–2.85 (m, 0.5H), 2.95–3.3 (m, 1H), 3.77–3.85 (m, 0.5H), 7.15–8.15 (m, 2.5H); HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for ($C_{21}H_{26}NO$), 308.2014; found, 308.2011. ^{13}C NMR (mixture of **11** and **12**, 75 MHz, $CDCl_3$) δ 18.2, 19.7, 21.1, 22.2, 25.4, 25.6, 29.0, 30.2, 35.7, 35.9, 43.7, 45.2, 52.1, 52.7, 59.5, 60.2, 126.6, 126.9, 127.3, 127.5, 128.1, 128.2, 128.5, 128.7, 132.8, 133.0, 137.0, 137.7, 145.0, 146.2, 200.3, 200.7.

4.9. *N*-Methoxy-*N*-methyl (2*R*)-1-[(1*R*)-1-phenylethyl]-piperidineacetamide 10

Trifluoroacetic acid (750 μL, 1 mmol) was added to a solution of **9a** (77 mg, 0.20 mmol) and CH_2Cl_2 (0.7 mL) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was concentrated and combined with a solution of DBU (500 μL, 0.3 mmol) in CH_2Cl_2 (0.7 mL). The mixture was stirred at rt for 16 h and concentrated. Purification by column chromatography (SiO_2, $CH_3OH/CHCl_3/Et_3N$,

1:4:0.05) provided diastereomers **6** (R_f 0.5, 36 mg, 0.1 mmol, 64%) and **10** (R_f 0.3, 18 mg, 0.06 mmol, 32%) as colorless oils. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30–1.35 (d, $J = 6.5$ Hz, 3H), 1.35–1.45 (m, 2H), 1.50–1.70 (m, 4H), 2.50–2.65 (m, 3H), 2.70–2.80 (m, 1H), 3.08 (s, 3H), 3.18–3.25 (q, $J = 4.6$ Hz, 1H), 3.50 (s, 3H), 3.80–3.91 (q, $J = 6.5$ Hz, 1H), 7.15–7.4 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 21.3, 25.4, 29.5, 30.4, 32.0, 43.8, 52.4, 59.2, 61.1, 126.6, 127.4, 128.1, 144.7, 173.9.

4.10. 1-[(2*S*)-1-[(1*R*)-1-Phenylethyl]-2-piperidinyl]-2-propanone 13a

Methylmagnesium chloride (3 M in THF, 175 μL, 0.52 mmol) was added to a solution of **6** (50 mg, 0.17 mmol) and THF (0.5 mL) at 25 °C. After being stirred for 1.5 h at 25 °C, the reaction mixture was cooled in an ice-water bath, satd $NH_4Cl_{(aq)}$ and 1 M $HCl_{(aq)}$ (1:1, 0.6 mL) were added, and the mixture was diluted with water (5 mL) Following extraction with CH_2Cl_2 (5 mL × 3), the combined organic solution was dried over Na_2SO_4, filtered, and concentrated to give **13a** (38.4 mg, 0.15 mmol, 91%) as a light-yellow oil. $[\alpha]_D^{20} = +41.4$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.30 (d, $J = 6.6$ Hz, 3H), 1.30–1.60 (m, 5H), 1.68–1.72 (m, 1H), 2.15 (s, 3H), 2.18–2.40 (m, 2H), 2.60–2.70 (m, 2H), 3.45–3.55 (m, 1H), 3.55–3.68 (q, $J = 6.6$ Hz, 1H), 7.15–7.4 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 20.9, 25.5, 30.0, 30.9, 41.3, 44.9, 51.4, 59.3, 126.5, 127.3, 128.2, 146.1, 208.7; HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for ($C_{16}H_{24}NO$), 246.1858; found, 246.1863; IR(cm^{-1}): 3060, 3024, 2970, 2932, 1710, 1601,1453.

4.11. 1-[(2*S*)-1-[(1*R*)-1-Phenylethyl]-2-piperidinyl]-2-butanone 13b

Ethylmagnesium chloride (1 M in THF, 525 μL, 0.52 mmol) was added to a solution of **6** (50 mg, 0.17 mmol) and THF (0.5 mL) at 25 °C. Following the same procedure as with **13a**, compound **13b** (38.4 mg, 0.16 mmol, 94%) was obtained as a light-yellow oil. $[\alpha]_D^{20} = +32.6$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00–1.10 (t, $J = 7.3$ Hz, 3H), 1.22–1.28 (d, $J = 6.7$ Hz, 3H), 1.3–1.55 (m, 5H), 1.68–1.78 (m, 1H), 2.18–2.37 (m, 2H), 2.37–2.50 (m, 2H), 2.6–2.65 (d, $J = 6.5$ Hz, 2H), 3.46–3.55 (m, 1H), 3.58–3.65 (q, $J = 6.7$ Hz, 1H), 7.15–7.20 (m, 1H), 7.22–7.29 (m, 2H), 7.31–7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.8, 17.9, 20.9, 25.6, 30.2, 37.0, 39.9, 45.0, 51.5, 59.3, 126.5, 127.3, 128.1, 146.2, 211.2; HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for ($C_{17}H_{26}NO$), 260.2014; found, 260.2011; IR(cm^{-1}): 3060, 3024, 2970, 2932, 1709, 1601, 1453.

4.12. (*R*)-1-((*S*)-1-((*R*)-1-Phenylethyl)-2-piperidinyl)propan-2-ol 14a

Sodium borohydride (31 mg, 0.8 mmol) was added to a solution of **13a** (50 mg, 0.2 mmol), zinc chloride (14 mg, 0.1 mmol), and methanol (0.5 mL) at 0 °C. The reaction mixture was stirred at rt for 16 h, quenched with water (5 mL), and extracted with CH_2Cl_2 (5 mL × 3). The combined organic solution was dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (SiO_2, $CH_3OH/CHCl_3/Et_3N$, 1:9:0.01; R_f 0.50) gave impure alcohol (47.5 mg, 0.19 mmol, 95%). Repeating the column chromatography provided diastereomerically pure **14a** (25 mg, 0.1 mmol, 50%) as a light-yellow oil. $[\alpha]_D^{20} = +13.5$ (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90–1.00 (m, 2H), 1.04–1.08 (d, $J = 6.1$ Hz, 3H), 1.22–1.28 (m, 1H), 1.30–1.35 (d, $J = 6.5$ Hz, 3H), 1.55–1.70 (m, 3H), 1.82–1.92 (m, 1H), 2.01–2.11 (m, 1H), 2.75–2.85 (m, br, 2H), 3.02–3.20 (m, 2H), 3.52–3.6 (m, 1H), 4.06–4.14 (q, $J = 6.5$ Hz, 1H), 6.55–7.05 (s, br, 1H), 7.16–7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.13, 20.04, 22.05, 23.48, 23.65, 37.44, 41.07, 54.64, 57.94, 68.72, 127.13, 127.29, 128.69, 145.29; HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for ($C_{16}H_{26}NO$), 248.2014; found, 248.2009.

4.13. (*R*)-1-((*S*)-1-((*R*)-1-Phenylethyl)-2-piperidinyl)butan-2-ol 14b

Sodium borohydride (29 mg, 0.77 mmol) was added to a solution of **13b** (50 mg, 0.19 mmol), zinc chloride (13 mg, 0.1 mmol), and methanol (0.5 mL) at 0 °C. The reaction mixture was stirred at rt for 16 h, quenched with water (5 mL), and extracted with CH_2Cl_2 (5 mL × 3). The combined organic solution was dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (SiO_2, $CH_3OH/CHCl_3/Et_3N$, 1:9:0.01; R_f 0.45) gave impure alcohol (49.4 mg, 0.2 mmol, 99%). Repeating the column chromatography provided diastereomerically pure **14b** (30 mg, 0.11 mmol, 60%) as a light-yellow oil. $[\alpha]_D^{20} = +5.8$ (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80–0.87 (t, $J = 7.5$ Hz, 3H), 0.92–1.03 (m, 1H), 1.20–1.30 (m, 2H), 1.30–1.35 (d, $J = 6.3$ Hz, 3H), 1.40–1.50 (m, 1H), 1.60–1.75 (m, 2H), 1.82–1.93 (m, 1H), 1.96–2.1 (m, 1H), 2.75–2.9 (m, br, 1H), 3.02–3.21 (m, 2H), 3.27–3.4 (m, 1H), 4.05–4.20 (q, $J = 6.3$ Hz, 1H), 6.70–7.05 (s, br, 1H), 7.2–7.45 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.8, 19.1, 20.0, 22.1, 23.8, 30.6, 35.1, 41.1, 54.6, 57.9, 73.9, 127.1, 127.4, 128.7, 145.2; HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for ($C_{17}H_{28}NO$), 262.2171; found, 262.2172.

4.14. (−)-Allosedridine 1

A suspension of **14a** (25 mg, 0.1 mmol), palladium (5% on activated carbon, 5 mg) in methanol (2 mL) was stirred at 25 °C for 3 h under a hydrogen atmosphere (1 atm). The suspension was filtered and concentrated to give **1** (8.8 mg, 0.06 mmol, 61%). Mp 61.5–63.0 °C (crystallized from diethyl ether); $[\alpha]_D^{20} = +20.7$ (*c* 0.22, MeOH);[6c] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11–1.15 (d, $J = 6.16$ Hz, 3H), 1.30–1.70 (m, 7H), 1.75–1.85 (m, 1H), 2.65–2.75 (m, 1H), 2.85–2.96 (m, 1H), 3.15–3.21 (m, br, 1H), 3.95–4.06 (m, 1H), 4.58 (s, br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.45, 24.03, 24.86, 32.06, 43.08, 45.39, 57.87, 68.11; HRMS-FAB (*m*/*z*): $[M+H]^+$ calcd for ($C_8H_{18}NO$), 144.1388; found, 144.1389.

4.15. (−)-2′-*epi*-Ethylnorlobelol 2

A suspension of **14b** (30 mg, 0.1 mmol), palladium (5% on activated carbon, 5 mg) in methanol (2 mL) was stirred at 25 °C for 3 h under a hydrogen atmosphere (1 atm). The

suspension was filtered and concentrated to give **2** (11.0 mg, 0.07 mmol, 62%). $[\alpha]_D^{20} = -6.8$ (*c* 0.24, EtOH);[6c] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84–0.90 (t, $J = 7.47$ Hz, 3H), 1.12–1.25 (m, 1H), 1.30–1.52 (m, 6H), 1.55–1.70 (m, 2H), 1.75–1.85 (m, 1H), 2.56–2.65 (m, 1H), 2.72–2.80 (m, 1H), 3.05–3.13 (m, 1H), 3.65–3.75 (m, 1H), 4.04 (s, br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.8, 24.1, 26.3, 30.9, 33.4, 41.5, 45.7, 58.1, 74.0; HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for ($C_9H_{20}NO$), 158.1545; found, 158.1547.

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