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Enantiopure *N*-Boc piperidine-2-ethanol for the synthesis of (+)- and (−)-dumetorine, and (+)- and (−)-epidihydropinidine

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ABSTRACT

The convenient synthesis of both enantiomers of the piperidine alkaloids such as dumetorine and epidihydropinidine is described. Pure enantiomers of 2-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester are used as a common starting material. The syntheses are based on a RCM reaction and on methylation of the piperidine ring according to Beak–Lee methodology, respectively.

1. Introduction

We have previously reported the enzyme-catalyzed preparation of the enantiomers of 2-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl esters **1a** and **1b** starting from racemic piperidine-2-ethanol.[1]

These stereochemically stable compounds were used via the corresponding aldehydes **2a** and **2b** for the synthesis of diverse compounds inspired by naturally occurring and biologically active piperidine alkaloids (Scheme 1).

A simple diversity-generating strategy was applied,[2] based on the use of coupling reactions to attach various appendages to the aldehyde group.

Thus, the addition of MeMgBr and PhMgBr to both aldehydes gave rapid access to the pure (+)- and (−)-enantiomers of sedridine and allosedridine,[3] and of sedamine and allosedamine,[1] respectively.

Aldehyde **2b** was the starting material for obtaining (+)-ethyl-norlobenol and (−)-2′-*epi*-ethyl-norlobenol by reaction with EtMgBr,[3] as well as for (−)-coniine via a straightforward Wittig homologation and reduction.[3]

Finally, an ethylination reaction on aldehyde **2a** with a Grignard reagent prepared from trimethylsilylacetylene was crucial for the construction of the tetracyclic skeleton of the more complex aloperine.[4]

Herein, we further highlight the central role of the aldehydes **2a** and **2b** for the obtainment of piperidine alkaloids. In particular, we describe the synthesis of (+)-dumetorine **3** (Scheme 2) and of its non-natural enantiomer *ent*-**3** by the application of the ring-closing metathesis (RCM) reaction to form the 5,6-dihydro-4-methyl-pyran-2-one moiety, which is a typical feature of these compounds. In addition, the introduction of a methyl group at the 6-position of the piperidine alcohols by carbanion generation was used to form (−)- and (+)-epidihydropinidine (**4** and *ent*-**4**, Scheme 3), thus demonstrating the potential of this approach for the synthesis of natural compounds possessing a 2,6-disubstituted piperidine ring with defined stereochemistry.

2. Results and discussion

2.1. Synthesis of (+)- and (−)-dumetorine 3 and *ent*-3

(+)-Dumetorine **3** was isolated in 1985 from the tubers of *Dioscorea dumetorum* Pax, a West African yam whose extracts have found a notable use in folk medicine and arrow poisons.[5] The first synthesis of (±)-dumetorine used nitrone–olefin cycloaddition as the key step, and it confirmed this structure and relative configuration of the stereogenic carbons of this molecule.[6] Recently, an enantioselective synthesis of **3** by ring-rearrangement metathesis was reported by Bleckert.[7]

Our strategy is based on the constructive use of the aldehyde function to generate an acryloyl derivative of a homoallylic alcohol to be submitted to the RCM reaction.

We planned to harness the required homoallylic alcohol by the reaction of **2b** with methylallylmagnesium bromide. Two diastereoisomers **5b** and **6b** were obtained in a 3:2 ratio, and the configuration of the newly formed stereocenter was confirmed on the basis of the spectroscopic properties previously discussed in the case of the synthesis of sedridine.[3] The stereoselective formation of the newly formed stereocenter at the 2′-position to give almost exclusively the required compound **5b** (de >95%) was achieved by exploiting an asymmetric allylboration reaction with β-allyl-

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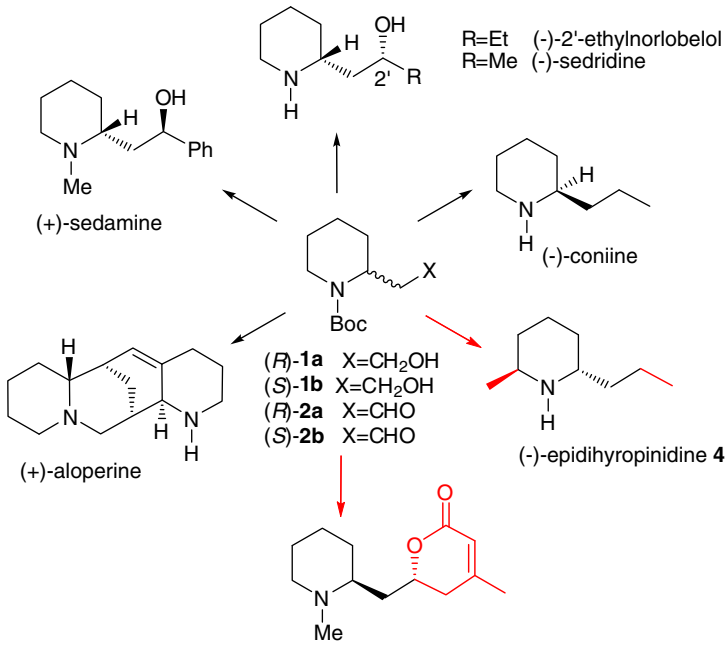
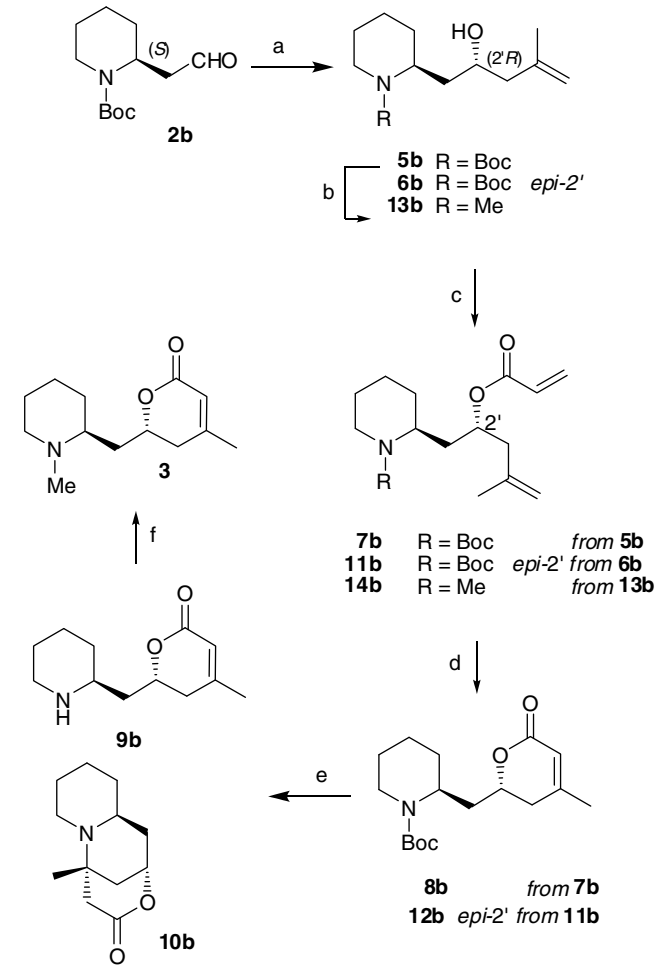
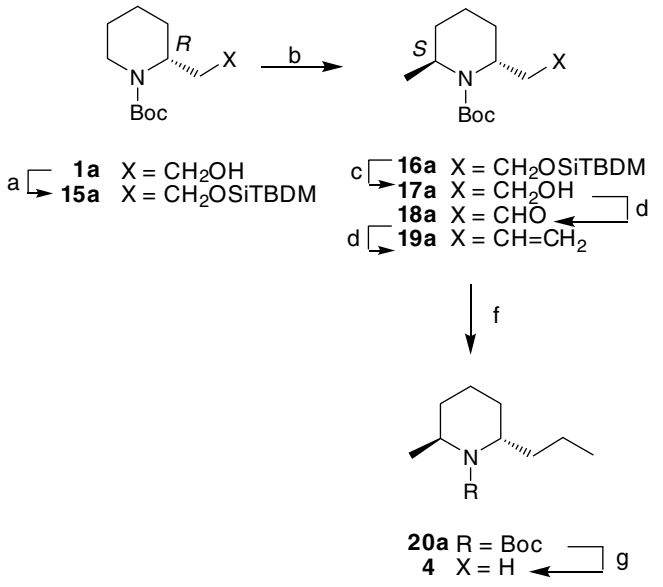


Scheme 1.



Scheme 2. Reagents and conditions: (a) THF, −78 °C, CH_2=$CHCH_3CH_2MgBr$; (b) $LiAlH_4$; (c) *i*-Pr_2Net, CH_2Cl_2, CH_2=CHCOCl; (d) 2nd Grubbs cat., CH_2Cl_2, 2 h, 40 °C; (e) TFA, CH_2Cl_2; (f) CH_2O, $NaBH_3CN$.



Scheme 3. Reagents and conditions: (a) imidazole, TBDMSCl, CH_2Cl_2; (b) TMEDA, *s*-BuLi, Et_2O, −78 °C, $MeSO_4$; (c) Na_2CO_3, MeOH; (d) Dess–Martin Reagent, CH_2Cl_2; (e) Ph_3P=CH_2, THF, 0 °C then rt; (f) MeOH, Pd/C, H_2, 24 h; (g) TFA, CH_2Cl_2, 3 h.

diisopinocamphenylborane[8] (obtained from (+)-β-methoxydiisopinocamphenylborane and methylallyl-magnesiumbromide). Reaction of **5b** with acryloyl chloride gave compound **7b** that presented the structural features for the ring-closing metathesis reaction.[9] The use of second generation Grubbs catalyst in CH_2Cl_2 at 40 °C allowed the formation of the dihydropyran ring in good yields (75%).[10] *N*-Boc deprotection was beset by dangers as reported on a similar structure.[7] The use of TFA resulted in the isolation of small amounts (10%) of desired product **9b** accompanied by tricyclic **10b** (60%) derived from an intramolecular Michael addition. The stereochemistry of the newly created stereocenter was deduced on the basis of manipulation of molecular models and on

NMR double resonance experiments. Compound **9b** was submitted to an N-methylation reaction by reductive amination with CH_2O in the presence of $NaBH_3CN$ to give the target natural (+)-dumetorine **3**, albeit in low yield. All spectroscopic data were consistent with those reported in literature $[\alpha]_D = +37$ (*c* 2.1, $CHCl_3$), {lit. $[\alpha]_D = +38$ (*c* 2.1, $CHCl_3$)}.

In order to avoid the formation of the undesired tricyclic compound **10b**, we planned to introduce the *N*-methyl group at the beginning of the reaction sequence. Thus, LAH reduction of **5b** gave **13b** which was then acryloylated to afford **14b**. Surprisingly, and in spite of many efforts, when we submitted compound **14b** to RCM reaction with different Grubbs catalysts, the substrate was not recovered and a complex reaction mixture of products was obtained, even in the presence of a stoichiometric amount of camphosulfonic acid to neutralize the basic character of the piperidine nitrogen.

The previously described sequence was repeated on aldehyde **2a** to afford the unnatural (−)-dumetorine *ent*-**3** {$[\alpha]_D = -35$ (*c* 2.1, $CHCl_3$)}. The use of compound **6b** as a substrate permitted the construction of the unsaturated lactone derivative **12b** on the way to preparation of 2′-epidumetorines and other analogues.

2.2. Synthesis of (−)- and (+)-epidihydropinidine 4 and *ent*-4

The presence in Nature of different compounds that present 2,6-*trans* disubstituted piperidine nucleus[11] drove us to consider the use of Beak's *N*-Boc-piperidine α-lithiation/alkylation methodology[12] to alkylate the enantiomers of compound **1**. We selected both enantiomers of epidihydropinidine as target compounds, as both of them are present in Nature.[13] Specifically, whereas the (−)-enantiomer **4** is less common, the (+)-enantiomer *ent*-**4** is the major volatile alkaloid of the Norwegian spruce *Picea abiens* (L) Karsten and a compenent of the Colorado blue spruce *Picea pungens* Englem and of many other *Picea* and *Pinus* species. Different accesses to (+)-epidihydropinidine[14] are reported in literature, whereas for (−)-epidihydropinidine[15] only one synthesis has been published. The TBDMS protected derivative **15a** from **1a** was treated with *s*-BuLi in ether at −78 °C, followed by reaction with dimethylsulfate at the same temperature to provide compound **16a** in ca. 39% yield.[16] The use of methyl iodide in the methylation reaction gave very poor yield. The ^{1}H NMR clearly indicated the relative *trans*-arrangement of substituents at C-2 and C-6 and proved the stereochemical course of the reaction that is based on the chelation of the lithium cation by the Boc protecting group. The use of the TBDMS hydroxyl protecting group was important in order to keep the C-2 chain at a distance from the reactive center. The use of other conventional protecting groups, such as a benzyl group, gave no acceptable results. After deprotection, a Dess–Martin oxidation provided the corresponding aldehyde **18a**, which we planned to use for the synthesis of (−)-epidihydropinidine. Reaction with a Wittig reagent $Ph_3P^+CH_3I^-$ in the presence of *t*BuOK afforded the 2-allyl-6-methyl-piperidine **19a,** which is the enantiomer of the compound described by Takahata and Momose.[15a] Catalytic hydrogenation led to *N*-Boc-epidihydropinidine **20a**, and the removal of the Boc group gave the desired product **4** {$[\alpha]_D = -2.7$ (*c* 0.2, $CHCl_3$)}[17] in good yield. The same sequence was applied to alcohol **1b** ending up with (+)-epidihydropinidine *ent*-**4** {$[\alpha]_D = +2.9$, (*c* 0.2, $CHCl_3$)}.

3. Conclusion

In conclusion, alcohols **1a** and **1b** have proven to be versatile chiral building blocks for the enantioselective synthesis of diversely 2-substituted piperidine derivatives via the corresponding aldehydes. Additionally, we have shown that the application of the stereocontrolled introduction of methyl group at the 6-position of the piperidine ring enables the preparation of new enantiopure aldehydic synthons (**18a** and its enantiomer), which are convenient starting points for the production of new collections of diverse compounds.

4. Experimental

4.1. Materials NMR spectra were recorded at 300/400 MHz (1H) and at 75/100 MHz (13C)

4.1.1. (*S*)-2-((*R*)-2-Hydroxy-4-methylpent-4-enyl)-piperidine-1-carboxylic acid *tert*-butyl ester 5b and (*S*)-2-((*S*)-2-Hydroxy-4-methylpent-4-enyl)piperidine-1-carboxylic acid *tert*-butyl ester 6b

A solution of 2-methylallylmagnesiumbromide (5.7 mL, 2.85 mmol) in THF was added dropwise to a solution of **2b** (538 mg, 2.4 mmol) in dry THF (20 mL) cooled at −78 °C. The solution was allowed to warm up to −78 °C and was left stirring for 4 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (15 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, 10:1) provided **5b** (230 mg, 34%) and **6b** (162 mg, 24%). Compound **5b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.50–1.70 (7H, m), 1.72 (3H, m), 1.80–1.95 (1H, m), 2.10 (1H, dd, *J* = 13.4, 5.1 Hz), 2.27 (1H, dd, *J* = 13.4, 7.4 Hz), 2.65 (1H, m), 3.75 (1H, m.), 3.92 (1H, m.), 4.43 (1H, br s), 4.76 (1H, 6s), 4.84 (1H, 6s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.6, 23.1, 25.5, 29.0 (3C), 29.9, 37.2, 40.0, 46.9, 47.8, 65.9, 80.8, 112.9, 143.9, 154.9; Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31; N, 4.94. Found: C, 67.88; H, 10.35; N, 4.90. $[\alpha]_D^{25} = -34$ (*c* 1, $CHCl_3$). Compound **6b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.50–1.65 (7H, m), 1.70 (3H, m), 1.80–2.00 (1H, m), 2.10 (1H, dd, *J* = 13.6, 5.2 Hz), 2.30 (1H, dd, *J* = 13.6, 7.6 Hz), 2.65 (1H, m), 3.50 (1H, br s), 3.95 (1H, m.), 4.45 (1H, br s), 4.80 (2H, d, *J* = 21.6 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.6, 23.1, 25.5, 29.0 (3C), 29.9, 37.2, 40.0, 46.9, 47.8, 65.9, 80.8, 112.9, 143.9, 154.9. Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31; N, 4.94. Found: C, 67.86; H, 10.37; N, 4.91. $[\alpha]_D^{25} = -47$ (*c* 1, $CHCl_3$).

4.1.2. (*R*)-2-((*S*)-2-Hydroxy-4-methylpent-4-enyl)-piperidine-1-carboxylic acid *tert*-butyl ester 5a and (*R*)-2-((*R*)-2-hydroxy-4-methylpent-4-enyl)piperidine-1-carboxylic acid *tert*-butyl ester 6a

See Section 4.1.1. Use of **2a** in the place of **2b**. Compound **5a**: $[\alpha]_D^{25} = +31$ (*c* 1, $CHCl_3$). **6a**: $[\alpha]_D^{25} = +44$ (*c* 1, $CHCl_3$).

4.1.3. (*S*)-2-((*R*)-2-Hydroxy-4-methylpent-4-enyl)-piperidine-1-carboxylic acid *tert*-butyl ester 5b

(+)-β-Methoxydiisopinocamphenylborane (95.6 mg, 0.3 mmol) was added to a solution of 2-methylallylmagnesium-bromide (0.58 mL, 0.29 mmol) in dry THF (3 ml) at 0 °C. The solution was allowed to warm up to 20 °C and left stirring for 1 h. The reaction mixture was concentrated. Then, the mixture was extracted with distilled pentane (2 × 3 mL). The solid was settled and the organic layer was transferred in a second vial and concentrated. The residue was dissolved in THF (2 ml) and a solution of **2b** (50 mg. 0.22 mmol) in dry THF (2 mL) was added at −78 °C. The mixture was stirred for 30 min at −78 °C. Then, MeOH (4.5 μL) was added and the solution was warmed to room temperature. After 30 min, NaOH 3 M (90 μL) and H_2O_2 35% (188 μL) were added. The mixture was heated at reflux for 2 h. The mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (hexane–AcOEt, 3:1) provided **5b** (87 mg, 77%).

4.1.4. (*S*)-2-((*R*)-2-Acryloyloxy-4-methylpent-4-enyl)-piperidine-1-carboxylic acid *tert*-butyl ester, 7b

i-Pr_2NEt (0.9 mL, 4.86 mmol) and acryloyl chloride (0.2 mL, 2.43 mmol) were added dropwise to a solution of **5b** (230 mg,

0.81 mmol) in dry CH_2Cl_2 (20 mL). After 4 h, the reaction mixture was quenched with a saturated solution of NH_4Cl (40 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, 9:1) provided **7b** (222 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (9H, s), 1.50–1.70 (7H, m), 1.70 (3H, s), 2.00–2.10 (1H, m), 2.27 (1H, dd, J = 13.7, 6.6 Hz), 2.43 (1H, dd, J = 13.7, 6.4 Hz), 2.70 (1H, br t, J = 12.9 Hz), 4.01 (1H, br s), 4.4 (1H, br s), 4.70 (1H, 6s), 4.78 (1H, 6s), 4.95–5.10 (1H, m), 5.8 (1H, d, J = 10.4 Hz), 6.10 (1H, dd, J = 17.3, 10.4 Hz), 6.38 (1H, d, J = 17.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.1, 22.5, 25.5, 28.3 (3C), 29.1, 33.4, 42.7, 47.8, 70.4, 79.2, 113.5, 128.9, 130.2, 141.6, 154.9, 165.5; Anal. Calcd for $C_{19}H_{31}NO_4$: C, 67.63; H, 9.26; N, 4.15. Found: C, 67.66; H, 9.28; N, 4.19. $[\alpha]_D^{25} = +44$ (c 1, $CHCl_3$).

4.1.5. (*R*)-2-((*S*)-2-Acryloyloxy-4-methylpent-4-enyl)-piperidine-1-carboxylic acid *tert*-butyl ester, 7a

See Section 4.1.4. The use of **5a** in the place of **5b** gave **7a**: $[\alpha]_D^{25} = -40$ (c 1, $CHCl_3$).

4.1.6. (*S*)-2-((*R*)-4-Methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-ylmethyl)piperidine-1-carboxylic acid *tert*-butyl ester, 8b

A solution of 2nd generation Grubbs catalyst (61 mg, 0.07 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a solution of **7b** (204 mg, 0.60 mmol) in dry CH_2Cl_2 (25 mL) at 40 °C. After 2 h, the solution was concentrated. Column chromatography (hexane–AcOEt, 3:1) gave **8b** (140 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37–1.42 (1H, m), 1.45 (9H, s), 1.50–1.70 (6H, m), 1.99 (3H, s), 2.23–2.60 (3H, m), 2.82 (1H, br t, J = 13.2 Hz), 3.99 (1H, br d, J = 12.0 Hz), 4.25–4.35 (1H, m), 4.40–4.50 (1H, m), 5.79 (1H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.0, 22.9, 25.5, 28.4 (3C), 29.1, 34.2, 34.9, 38.9, 46.4, 75.2, 79.6, 116.4, 136.4, 154.9, 165.2; Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.35. Found: C, 65.95; H, 8.83; N, 4.38; $[\alpha]_D^{25} = +64$ (c 1, $CHCl_3$).

4.1.7. (*S*)-2-((*R*)-4-Methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-ylmethyl)piperidine-1-carboxylic acid *tert*-butyl ester, 8a

See Section 4.1.6. The use of **7a** in the place of **7b** gave **8a**: $[\alpha]_D^{25} = -60$ (c 1, $CHCl_3$).

4.1.8. (*S*)-2-((*R*)-4-Methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-ylmethyl)piperidine, 9b

TFA (160 μl, 0.80 mmol) was added to a solution of **8b** (31.8 mg, 0.10 mmol) in dry CH_2Cl_2 (16 ml) at 0 °C. The solution was warmed to room temperature and stirred for 3 h. The organic layer was concentrated. Column chromatography (hexane–AcOEt 6:1) gave **10b** (12.6 mg, 60%) and **9b** (2 mg, 10%). Compound **10b** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, s), 1.27 (3H, s), 1.50–1.65 (3H, m), 1.72 (1H, br d, J = 11.2 Hz), 1.80–2.05 (3H, m), 2.13 (1H, d, J = 18.8 Hz), 2.20–2.30 (1H, m), 2.98 (1H, dd, J = 2.1, 18.9 Hz), 3.05 (1H, br d, J = 10.4 Hz), 4.75 (1H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.0, 26.8, 29.0, 30.3, 34.4 (2C), 39.8, 46.4, 52.9, 62.2, 74.8, 170.4. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69; O, 15.29. Found: C, 68.92; H, 9.10; N, 6.67; $[\alpha]_D^{25} = +3$ (c 0.26, $CHCl_3$). Compound **9b**: 1.20–1.70 (7H, m), 1.99 (3H, s), 2.29–2.56 (3H, m), 2.83 (1H, t, J = 13.2 Hz), 3.98 (1H, br d, J = 10.8 Hz), 4.28–4.33 (1H, m), 4.44–4.47 (1H, m), 5.81 (1H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.0, 22.9, 25.5, 29.1, 34.2, 34.9, 38.9, 46.4, 75.2, 116.4, 136.4, 165.2; Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.81; H, 9.19; N, 6.73; $[\alpha]_D^{25} = +54$ (c 1, $CHCl_3$).

4.1.9. (*R*)-2-((*S*)-4-Methyl-6-oxo-3,6-dihydro-2H-pyran-2-ylmethyl)piperidine, 9a

See Section 4.1.8. The use of **8a** in the place of **8b** gave **9a:** $[\alpha]_D^{25} = -51$ (c 1, $CHCl_3$). Compound **10a**: $[\alpha]_D^{25} = -2.5$ (c 0.24, $CHCl_3$).

4.1.10. (+)-Dumetorine, 3

$NaBH_3CN$ (18 mg) was added to a stirred solution of **9b** (30 mg, 0.143 mmol) and 0.5 ml of 37% aqueous formaldehyde in 4 ml of acetonitrile. The mixture was stirred for 25 min, and then acetic acid was added dropwise until the solution tested neutral. Stirring was continued for an additional 1 h, the solvent was evaporated in vacuo. Next, 10 ml of 0.2 M sodium hydroxide was added, and the mixture was extracted with CH_2Cl_2. Column chromatography (AcOEt–MeOH 10:1 + 0.5% Et_3N) gave **3** (12 mg, 39%). Compound **3** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (3H), 2.30–1.23 (12H, m), 2.25 (3H, s), 2.76 (1H, m), 4.20–4.35 (1H, m), 5.70 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.0, 23.2, 24.5, 28.9, 35.0, 42.1, 57.1, 60.1, 74.0, 157.1, 165.1; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.94; H, 9.45; N, 6.24; $[\alpha]_D^{25} = +37$ (c 1, $CHCl_3$).

4.1.11. (−)-Dumetorine, *ent*-3

See Section 4.1.9 using **9a** in the place of **9b**. ***ent*-3:** $[\alpha]_D^{25} = -35$ (c 1, $CHCl_3$).

4.1.12. (*S*)-2-((*S*)-2-Acryloyloxy-4-methylpent-4-enyl)-piperidine-1-carboxylic acid *tert*-butyl ester, 11b

See Section 4.1.4. Use of **6b** in the place of **5b**. Column chromatography (hexane–AcOEt, 3:1) provided **11b** (185 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.50–1.70 (7H, m), 1.78 (3H, s), 2.00–2.10 (1H, m), 2.27 (1H, dd, J = 13.7, 6.6 Hz), 2.43 (1H, dd, J = 13.7, 6.4 Hz), 2.71 (1H, br t, J = 12.9 Hz), 4.01 (1H, br s), 4.37 (1H, br s), 4.88 (1H, 6s), 4.74 (1H, 6s), 4.97–5.03 (1H, m), 5.81 (1H, d, J = 10.4 Hz), 6.12 (1H, dd, J = 17.3, 10.4 Hz), 6.39 (1H, d, J = 17.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.1, 22.5, 25.5, 28.3 (3C), 29.1, 33.4, 42.7 (2C), 47.8, 70.4, 79.3, 113.5, 129.0, 130.2, 141.6, 154.9, 165.5; Anal. Calcd for $C_{19}H_{31}NO_4$: C, 67.63; H, 9.26; N, 4.15. Found: C, 67.66; H, 9.28; N, 4.19; $[\alpha]_D^{25} = +51$ (c 0.9, $CHCl_3$).

4.1.13. (*S*)-2-((*S*)-4-Methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-ylmethyl)piperidine-1-carboxylic acid *tert*-butyl ester, 12b

See Section 4.1.6. Use of **11b** in the place of **7b**. Column chromatography (hexane–AcOEt, 3:1) gave **12b** (52 mg, 60%).^{1}H NMR (400 MHz, DMSO, 80 °C) δ 1.39 (9H, s), 1.56 (6H, br s), 1.72–1.80 (1H, m), 1.95 (3H, s), 2.03–2.12 (1H, m), 2.35 (2H, d, J = 7.3 Hz), 2.80 (1H, br t), 3.86 (1H, dd, J = 13.4, 3.5 Hz), 4.23–4.30 (1H, m), 4.35–4.45 (1H, m), 5.72 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 22.9, 25.5 (2C), 80.0, 28.4 (3C), 29.3, 34.9, 35.5, 47.2, 116.5, 136.4, 154.9, 157.1, 165.2; Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.35. Found: C, 65.95; H, 8.83; N, 4.38; $[\alpha]_D^{25} = +58$ (c 0.8, $CHCl_3$).

4.1.14. (*S*)-2-((*R*)-2-Hydroxy-4-methylpent-4-enyl)-piperidine-1-methyl, 13b

A solution of **5b** (285.7 mg, 1.01 mmol) in THF (10 mL) was added dropwise and under nitrogen atmosphere to a 1 mM solution of $LiAlH_4$ (5.1 mL, 5.1 mmol) in THF. After 4 h under reflux, the reaction mixture was quenched by addition of a 15% aqueous solution of NaOH (2 mL) and water (32 mL). The solution was then extracted several times with CH_2Cl_2, and the organic layers were dried over Na_2SO_4 and then concentrated in vacuo to afford **13b** (147.7 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.74 (9H, m), 1.76 (3H, s), 1.80–1.90 (1H, m), 2.13 (1H, dd, J = 13.6, 5.2 Hz), 2.22 (1H, dd, J = 13.6, 7.6 Hz), 2.42 (3H, s), 2.44–2.47 (1H, m), 2.62–2.65 (1H, m), 2.97–3.03 (1H, m), 4.77 (1H, d, J = 0.8 Hz), 4.83 (1H, d, J = 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 22.6, 22.8, 26.8, 37.4, 40.5, 46.9, 52.5, 60.8, 69.1, 112.8, 142.9. Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 65.91; H, 8.86; N, 4.34; $[\alpha]_D^{25} = -27$ (c 1, $CHCl_3$).

4.1.15. (*S*)-2-((*R*)-2-Acryloyloxy-4-methylpent-4-enyl)-piperidine-1-methyl, 14b

i-Pr_2NEt (0.7 mL, 4.15 mmol) and acryloyl chloride (160 μL, 2.08 mmol) were added dropwise to a solution of **13b** (136 mg, 0.69 mmol) in dry CH_2Cl_2 (15 mL). After 4 h, the reaction mixture was quenched with a saturated solution of NH_4Cl (40 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, 9:1) provided **14b** (120 mg, 66%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.25–1.74 (8H, m), 1.76 (3H, s), 1.83–2.15 (1H, m), 2.22 (1H, dd, J = 13.7, 6.0 Hz), 2.30 (3H, s), 2.38 (1H, dd, J = 13.7, 7.0 Hz), 2.40–2.55 (1H, br s), 2.82–2.90 (1H, m), 4.72 (1H, s), 4.78 (1H, s), 5.17–5.24 (1H, m), 5.83 (1H, dd, J = 10.4, 1.5 Hz), 6.10 (1H, dd, J = 17.3, 10.4 Hz), 6.39 (1H, dd, J = 17.3, 1.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.1, 24.4, 26.1, 31.4, 37.7, 43.5, 44.5, 57.3, 60.9, 70.6, 114.4, 129.5, 130.9, 141.9, 165.2. Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.64; H, 10.04; N, 5.53; $[\alpha]_D^{25} = -26$ (c 1, $CHCl_3$).

4.1.16. (*R*)-2-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-piperidine-1-carboxylic acid tert-butyl ester, 15a

TBDMSCl (440 mg. 2.9 mmol) and imidazole (329 mg, 4.8 mmol) were added to a solution of **1a** in dry CH_2Cl_2 (5 mL). The mixture was stirred for 1 h then washed with brine, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. Column chromatography (hexane–AcOEt, 4:1) provided **15a**. (652 mg, 90%). ^1H NMR (300 MHz, $CDCl_3$) δ 4.22–4.31 (1H, m), 3.95 (1H, br d), 3.51–3.86 (2H, m), 2.76 (1H, td, J = 13.5, 3 Hz), 1.84–2.02 (1H, m), 1.52–1.71 (7H, m), 1.42 (9H, s), 0.86 (9H, s), 0.05 (6H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.9, 79.0, 61.1, 48.0, 38.8, 33.2, 28.7, 28.4 (3C), 25.9 (3C), 25.6, 19.1, 18.3, −5.3 (2C); Anal. Calcd for $C_{18}H_{37}NO_3Si$: C, 62.92; H, 10.85; N, 4.08. Found: C, 62.97; H, 10.87; N, 4.11. $[\alpha]_D^{25} = +17.4$ (c 1, $CHCl_3$).

4.1.17. (*S*)-2-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester, 15b

See Section 4.1.16. Use of **1b** in the place of **1a**. $[\alpha]_D^{25} = -18.4$ (c 1, $CHCl_3$).

4.1.18. (2*R*,6*S*)-2-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester 16a

A solution of distillated TMEDA (354 μL, 2.3 mmol) and *s*-BuLi (2.2 mL, 2.9 mmol) was added at −78 °C to a solution of **15a** (652 mg, 2.9 mmol) in dry Et_2O (8 mL). The mixture was stirred for 3 h at −78 °C. Then $MeSO_4$ (331 μL, 3.5 mmol) in dry Et_2O (290 μL) was added. The mixture was warmed to room temperature, washed with brine, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. Column chromatography (hexane–AcOEt, 4:1) provided **16a** (261 mg, 39%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.9 (9H, s), 1.25 (3H, d, J = 6.7), 1.47 (9H, s), 1.59–1.5 (1H, m), 1.98–1.6 (7H, m), 3.67 (2H, t, J = 6.8 Hz), 3.92–3.85 (1H, m), 4.02–3.92 (1H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.3 (2C), 14.1, 18.3, 20.6, 24.6, 25.9 (3C), 26.9, 28.5 (3C), 37.7, 47.2, 49.3, 61.6, 78.8, 155.2; Anal. Calcd for $C_{19}H_{39}NO_3Si$: C, 63.82; H, 10.99; N, 3.92. Found: C, 63.87; H, 10.94; N, 3.91; $[\alpha]_D^{25} = +14.8$ (c 1, $CHCl_3$).

4.1.19. (2*S*,6*R*)-2-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester 16b

See Section 4.1.18. Use of **15b** in the place of **15a**. $[\alpha]_D^{25} = -15.6$ (c 1, $CHCl_3$).

4.1.20. (2*R*,6*S*)-2-(2-Hydroxyethyl)-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester, 17a

(A) Na_2CO_3 (92 mg, 0.87 mmol) was added to **16a** (63 mg, 0.17 mmol) in dry MeOH (3 mL). The mixture was stirred at room temperature for 16 h. Next, Na_2CO_3 was filtered and the solution concentrated. Brine (15 mL) was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. Column chromatography (hexane–AcOEt 4:1) provided **17a** (34 mg, 82.4%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.2–4.12 (1H, m), 3.95–3.87 (1H, m), 3.66–3.45 (2H, m), 3.33 (1H, br s), 2.123–1.95 (1H, m), 1.95–1.83 (1H, m), 1.79–1.62 (5H, m), 1.62–1.55 (1H, m), 1.48 (9H, s), 1.25 (3H, d, J = 6.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.2, 80.5, 59.8, 48.2, 48.1, 39.4, 29.1 (3C), 26.8, 25.8, 21.6, 13.6; Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 64.11; H, 10.31; N, 5.72; $[\alpha]_D^{25} = +32.7$ (c 1.15, $CHCl_3$).

4.1.21. (2*S*,6*R*)-2-(2-Hydroxyethyl)-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester, 17b

See Section 4.1.20. Use of **16b** in the place of **16a**. $[\alpha]_D^{25} = -34.5$ (c 1, $CHCl_3$).

4.1.22. (2*S*,6*R*)-2-(2-oxoethyl)-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester, 18a

A solution of **17a** (58 mg, 0.24 mmol) in dry CH_2Cl_2 (2 mL) was added to a solution of Dess–Martin reagent (263 mg, 0.62 mmol) in dry CH_2Cl_2 (1 mL). The mixture was stirred for 2.5 h at room temperature, then added to Et_2O (10 mL), and stirred for 5 min. In the end, a solution of the $NaHCO_3/Na_2S_2O_3$ 1:1 was added, and the solution was stirred for 30 min. The two phases were separated and the aqueous layer extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated to give **18a** (57.4 mg, 99%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, s), 4.45–4.23 (1H, m), 4.19–3.96 (1H, m), 2.92–2.73 (1H, m), 2.65–2.47 (1H, m), 2.05–1.55 (6H, m), 1.5 (9H, s), 1.21 (3H, d, J = 6.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.2, 155.2, 80.5, 45.7, 44.2, 44.1, 29.1(3C), 26.8, 25.8, 21.6, 13.6; Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.67; H, 9.58; N, 5.82; $[\alpha]_D^{25} = +17.5$ (c 1.15, $CHCl_3$).

4.1.23. (2*S*,6*R*)-2-(2-Oxoethyl)-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester, 18b

See Section 4.1.22. Use of **17b** in the place of **17a**. $[\alpha]_D^{25} = -18.5$ (c 1.10, $CHCl_3$).

4.1.24. (2*R*,6*S*)-2-Allyl-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester, 19a

A solution of *t*-BuOK (68.4 mg, 0.61 mmol) and **18a** (57.4 mg, 0.24 mmol) in dry THF (1 mL) was added to a solution of Ph_3PMeI (246.5 mg, 0.61 mmol) in dry THF (3 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 2 h, then water (1 mL) was added and the solution concentrated and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and concentrated. Column chromatography (hexane–AcOEt 3:1) provided **19a** (30 mg, 53%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.88–5.66 (1H, m), 5.13–5.04 (1H, dd, J = 17.1 Hz), 5.04–4.97 (1H, dd, J = 11.9 Hz), 4.10–3.90 (1H, m), 3.90–3.79 (1H, m), 2.5–2.38 (1H, m), 2.25–2.12 (1H, m), 2.00–1.86 (1H, m), 1.86–1.55 (5H, m), 1.48 (9H, s), 1.24 (3H, d, J = 6.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.8, 136.9, 117.0, 79.6, 51.8, 47.6, 39.8, 29.2 (3C), 27.5, 23.3, 21.5, 14.0; Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.29; H, 10.48; N, 5.81; $[\alpha]_D^{25} = +23.7$ (c 1.5, $CHCl_3$).

4.1.25. (2*S*,6R)-2-Allyl-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester, 19b

See Section 4.1.24. Use of **18b** in the place of **18a**. $[\alpha]_D^{25} = -25.0$ (c 1.4, $CHCl_3$).

4.1.26. (2*S*,6*S*)-2-Propyl-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester, 20a

Compound **19a** (30 mg, 0.13 mmol) in dry MeOH (4 mL) with Pd/C catalyst was reduced by H_2. After 1 day, the mixture was filtered on

Celite and washed with MeOH. The organic layer was concentrated. Column chromatography (hexane–AcOEt 19:1) provided **20a** (5 mg, 16%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.0–3.85 (1H, m), 3.85–3.7 (1H, m), 1.95–1.70 (4H, m), 1.70–1.49 (6H, m), 1.45 (9H, s), 1.23 (3H, d, J = 6.4 Hz), 0.9 (3H, t, J = 7.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.8, 14.2, 20.4, 20.9, 23.3, 27.0, 28.7 (3C), 36.6, 47.0, 51.5, 78.8, 155.4; Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.67; H, 11.27; N, 5.80. Found: C, 69.62; H, 11.31; N, 5.86.; $[\alpha]_D^{25} = +40.4$ (c 0.25, $CHCl_3$).

4.1.27. (2*R*,6*R*)-2-Propyl-6-methylpiperidine-1-carboxylic acid *tert*-butyl ester, 20b

See Section 4.1.26. Use of **19b** in the place of **19a**. $[\alpha]_D^{25} = -42.0$ (c 0.25, $CHCl_3$).

4.1.28. (−)-Epidihydropinidine 4

Trifluoric acetic acid (40 μL, 0.5 mmol) was added to a solution of **20a** (12 mg, 0.05 mmol) in dry CH_2Cl_2 (3 mL). The mixture was stirred for 3 h, then water and 5 M NH_4OH were added till basic pH. The solution was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated to give **4** (5 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15–3.00 (1H, m), 2.97–2.80 (1H, m), 1.90–1.15 (10H, m), 1.10–0.95 (3H, m), 0.93–0.80 (3H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.8, 14.2, 20.4, 20.9, 23.3, 27.0, 36.6, 47.0, 51.5; Anal. Calcd for $C_9H_{19}N$: C, 76.53; H, 13.56; N, 9.92. Found: 76.51; H, 13.50; N, 9.90; $[\alpha]_D^{25} = -2.7$ (c 0.2, $CHCl_3$).

4.1.29. (+)-Epidihydropinidine *ent*-4

See the sequence of reactions 4.1.16–4.1.22 using **1b** in the place of **1a**. $[\alpha]_D^{25} = +2.9$ (c 0.4, $CHCl_3$).

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