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Enantiodivergent synthesis of the quinolizidine poison frog alkaloid **195C**

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ABSTRACT

Herein, we describe the enantiodivergent synthesis of the 1,4-*cis*-disubstituted quinolizidine alkaloid **195C**. Although the stereoselectivity of the final hydrogenation reaction was low, we have proposed the first chiral total synthesis of both (−)- and (+)-**195C** as an enantiodivergent process.

1. Introduction

The poison frog alkaloid quinolizidine **195C** has been detected in numerous skin extracts from certain dendrobatid, bufonid, mantellid, and myobatrachid anurans,[1] and an extract of a Brazilian myrmicine ant.[2] The presence of alkaloids in poison frogs is a direct result of dietary uptake from certain alkaloid-containing arthropods, including ants, mites, millipedes, and beetles.[3] The quinolizidine alkaloids are relatively rare in nature, but have a 4,6-*cis*-disubstitution and exhibit intriguing biological activities. There have been some synthetic studies of **195C**,[2,4] however the enantioselective synthesis of this alkaloid has not been reported to date. As part of our program directed at studying the synthesis of poison frog alkaloids,[5] we report here the enantiodivergent synthesis of **195C** (Fig. 1).

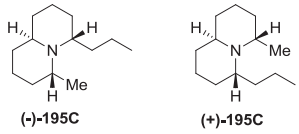
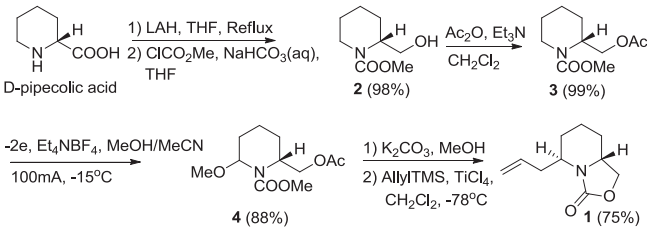


Fig. 1. Structure of **195C**.

2. Results and discussion

From the pseudo symmetric property of **195C**, we planned the enantiodivergent synthesis of **195C**. The synthesis began with known allyl derivative **1**,[6] which was prepared from D-pipecolic acid as shown in Scheme 1. Reduction of D-pipecolic acid with $LiAlH_4$ followed by protection of the resulting aminoalcohol with $ClCO_2Me$ afforded alcohol **2** in good overall yield. After conversion of **2** to the acetate **3**,[7] the anodic oxidation of **3** provided the methoxy derivative **4**. Treatment of **4** with base yielded the corresponding oxazolizinone, which was transformed into the allyl derivative **1** via the acyliminium ion[8] as the single isomer in 75% yield.



Scheme 1. Synthesis of key intermediate **1**.

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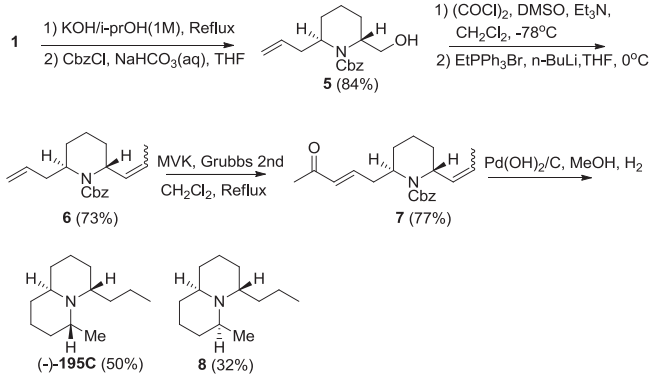
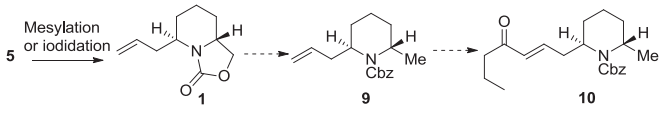
Next we examined the synthesis of (−)-**195C** starting from the common precursor **1**. Hydrolysis of **1** followed by protection of the resulting amine with CbzCl gave rise to the alcohol **5**.[9] Swern oxidation of **5**, and then the Wittig reaction of the resulting aldehyde afforded the olefin **6** as the *E*, *Z* mixture. The cross-metathesis reaction of the olefin **6** with methyl vinyl ketone proceeded smoothly to yield the desired unsaturated ketone **7**. Finally, the hydrogenation reaction of **7** furnished the (−)-**195C** ($[\alpha]_D^{26}$ −14.1) along with the epimer **8** on the 4-position as a 1.4:1 mixture. The structure of (−)-**195C** was determined by the ^{1}H, ^{13}C NMR, MS, and HRMS spectra. The spectral data of the epimer **8** were completely identical with those of the reported values[4b] (Scheme 2).



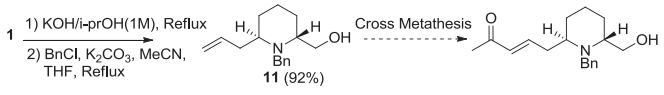
Scheme 2. Synthesis of (−)-**195C**.

For the synthesis of (+)-**195C**, we first tried to synthesize the unsaturated ketone **10** from **5**. However, all attempts to convert **5** to the corresponding mesylate or iodide, which could have then been converted to the corresponding methyl derivative **9**, resulted in the formation of **1** (Scheme 3).



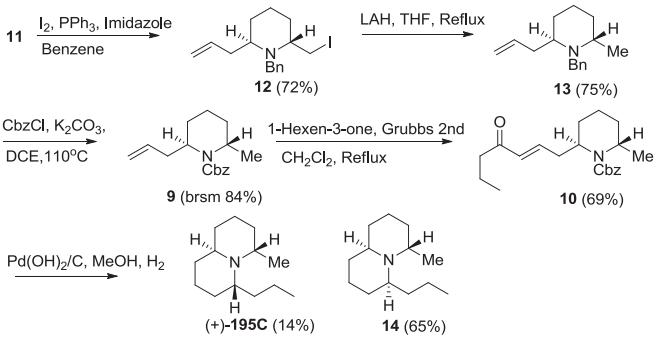
Scheme 3. Attempt to synthesize of **10** via mesylation of iodination of **5**.

To avoid the formation of **1** as shown in Scheme 3, we next investigated the use of benzyl derivative **11**, which was synthesized from **1** in two steps as shown in Scheme 3. Treatment of **11** with methyl vinyl ketone in the presence of Grubbs' second-generation catalyst or Grubbs–Hoveyda catalyst did not proceed, and the results were recovery of only **11**[10] (Scheme 4).



Scheme 4. Attempt to synthesize of homologated ketone via cross metathesis.

In an alternative attempt to synthesize (+)-**195C**, we tried to convert **11** to the methyl derivative **13** via iodide **12**. Treatment of **11** with iodine and Ph_3P afforded the iodide **12**, which was reduced with $LiAlH_4$ to give rise to the desired reduction product **13**.[11] The benzyl group in **13** was then transformed into the Cbz group by thermal conditions to provide **9**. The olefin cross-metathesis reaction of **9** with 1-hexen-3-one in the presence of Grubbs' second-generation catalyst yielded the unsaturated ketone **10**. Finally, hydrogenation reaction of **10** provided the two quinolizidines as a 1:4.6 mixture. The structure of the minor product was determined to be (+)-**195C** ($[\alpha]_D^{26}$ +14.6) by comparing it to the ^{1}H and ^{13}C NMR spectra of (−)-**195C** (Scheme 5).



Scheme 5. Synthesis of (+)-**195C**.

In the favorable conformation on A and B, the *n*-propyl or methyl substituent on the 4-position would occupy in the pseudo-axial orientation due to the A[1,3] strain between the substituent on the iminium moiety. In the conformer A, hydrogenation would occur from the less hindered β-face to give rise to (−)-**195C** as a major product. On the other hand, in the confomer B, the propenyl or *n*-propyl substituent on the iminium moiety would occupy the upper face due to the steric repulsion with methyl group at the 4-position, and hydrogenation would occur from the α-face to afford **14** as the major product (Fig. 2).[12]

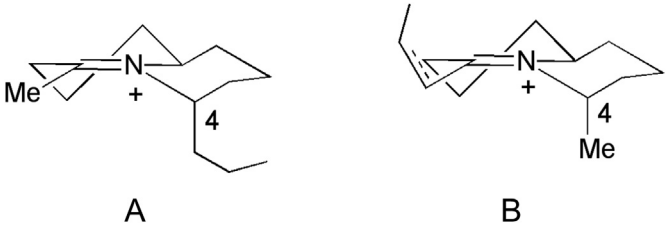


Fig. 2. Stereoselectivity of the final hydrogenation step for **7** and **10**.

3. Conclusions

This study represents the first chiral synthesis of the quinolizidine alkaloid **195C**. We have achieved the enantiodivergent synthesis of both (−)- and (+)-**195C** starting from the common precursor of oxazolizinone **1**. The antagonist activities of both enantiomers of this alkaloid against nicotinic acetylcholine receptors are now in progress.

4. Experimental section

4.1. General

Flash chromatography was performed with Kanto Kagaku silica gel 60N (63–210 mm). NMR spectra were recorded on a JEOL JNM-A400 or JEOL JNM-ECX500 spectrometer in the solvent indicated. Chemical shifts (δ) are given in parts per million downfield from TMS and referenced with $CHCl_3$ (7.26 ppm) as an internal standard. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. Coupling constants are given in (J) Hertz. High resolution mass spectral data was obtained on a JEOL JMS-GC MATE II or JEOL JMS-AX505HAD. All commercial reagents were used as received unless otherwise noted.

4.2. (*R*)-Methyl 2-(hydroxymethyl)piperidine-1-carboxylate (2)

$LiAlH_4$ (3.42 g, 30.00 mmol) was added to a stirred solution of D-pipecolic acid (3.87 g, 30.00 mmol) in THF (40 mL) at 0 °C, and the

resulting suspension was refluxed for 2 h. After cooling, the reaction was quenched with 10% NaOH (aq), and the aqueous mixture was extracted with hot ethyl acetate (10 mL×5). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give a colorless oil, which was used directly in the next step. Saturated $NaHCO_3$ (aq) (40 mL) and $ClCO_2Me$ (2.5 mL, 33.00 mmol) were added to a stirred solution of the above alcohol in THF (40 mL) at room temperature, and the resulting mixture was stirred overnight. The reaction mixture was diluted with CH_2Cl_2, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL×3). The organic layer and extracts were combined, dried over Na_2SO_4, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (30 g, hexane/acetone=8:1) to afford 2 (5.1 g, 98%) as a colorless oil.

IR (neat) 3414, 2939, 1695, 1450, 1271, 770 cm^{-1}; ^1H NMR (400 MHz) δ 1.25–1.53 (2H, m), 1.56–1.71 (4H, m), 2.92 (1H, t-like, J=10.9 Hz), 3.61–3.67 (1H, m), 3.70 (3H, s), 3.83 (1H, td-like, J=10.9, 4.0 Hz), 3.96 (1H, br), 4.30–4.33 (1H, m); ^{13}C NMR (125 MHz) δ 19.40, 25.07, 25.26, 40.00, 52.65 (two carbons), 60.81, 157.14; MS (EI): m/z 173 $[M]^+$; HRMS: Calcd for $C_8H_{15}NO_3$ $[M]^+$ 173.1052; found 173.1051; $[\alpha]_D^{26}$ +40.2 (c 2.90, $CHCl_3$).

4.3. (*R*)-Methyl 2-(acetoxymethyl)piperidine-1-carboxylate (3)[7]

Et_3N (1.8 mL, 12.60 mmol) and Ac_2O (0.95 mL, 10.10 mmol) were added to a stirred solution of alcohol **2** (1.46 g, 8.40 mmol) in CH_2Cl_2 at 0 °C, and the resulting mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was chromatographed on silica gel (30 g, hexane/acetone=30:1) to afford **3** (1.8 g, 99%) as a pale yellow oil.

^1H NMR (400 MHz) δ 1.39–1.54 (2H, m), 1.56–1.68 (4H, m), 2.04 (3H, s), 2.87 (1H, t-like, J=13.2 Hz), 3.69 (3H, s), 4.04 (1H, br), 4.14 (1H, dd, J=11.0, 6.6 Hz), 4.24 (1H, dd, J=11.0, 8.4 Hz), 4.51 (1H, br s); $[\alpha]_D^{26}$ +41.0 (c 1.00, $CHCl_3$), Ref. 7: $[\alpha]_D^{28}$ −45.6 (c 1.10, $CHCl_3$).

4.4. (*R*)-Methyl 2-(acetoxymethyl)-6-methoxypiperidine-1-carboxylate (4)

Et_4NBF_4 (540 mg, 1.82 mmol) was added to a solution of **3** (800 mg, 3.70 mmol) in MeOH (9 mL) and MeCN (36 mL) at room temperature. The resulting mixture was stirred at −15 °C for 2 h, with 100 mA of electricity passing through it. The solvent was evaporated and the residue was chromatographed on silica gel (30 g, hexane/acetone=40:1) to afford **4** (802 mg, 88%) as a pale yellow oil.

^1H NMR (400 MHz) δ 1.40–1.66 (3H, m), 1.74–1.91 (3H, m), 2.05 (3H, s), 3.27 & 3.32 (3H, br s), 3.73 (3H, s), 4.02–4.18 (1H, m), 4.37 & 4.51 (2H, br s), 5.30 & 5.48 (1H, br s).

4.5. (5*R*, 8*aR*)-5-Allyltetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (1)[6]

K_2CO_3 (360 mg, 2.60 mmol) was added to a stirred solution of **4** (640 mg, 2.60 mmol) in MeOH (12 mL) at room temperature, and the resulting mixture was stirred for 1 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, filtered by Celite, and evaporated to give a pale yellow oil.

Allyltrimethylsilane (1.85 mL, 11.70 mmol) and $TiCl_4$ (0.28 mL, 2.60 mmol) was added to a stirred solution of the above oil in CH_2Cl_2 (15 mL) at −78 °C, and the resulting mixture was stirred and allowed to warm to room temperature over 1 h. The reaction was quenched with saturated $NaHCO_3$, and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were combined, dried over $NaSO_4$, and evaporated to give a residue, which was chromatographed on silica gel (25 g, hexane/acetone=10:1) to give **1** (356 mg, 75%) as a colorless oil.

^1H NMR (500 MHz) δ 1.24–1.36 (1H, m), 1.58–1.86 (5H, m), 2.24–2.30 (1H, m), 2.39–2.45 (1H, m), 3.73–3.79 (1H, m), 3.85–3.88 (1H, m), 4.01–4.05 (1H, m), 4.38 (1H, t, J=8.1 Hz), 5.06–5.14 (2H, m), 5.73–5.80 (1H, m); ^{13}C NMR (125 MHz) δ 17.37, 26.11, 30.10, 34.08, 48.42, 50.05, 67.91, 116.85, 134.14, 156.50; $[\alpha]_D^{26}$ +27.0 (c 1.00, MeOH), Ref. 6: $[\alpha]_D^{25}$ −28.8 (c 1.02, MeOH).

4.6. (2*R*, 6*R*)-Benzyl 2-allyl-6-(hydroxymethyl)piperidine-1-carboxylate (5)[8]

Oxazolidinone **1** (195 mg, 1.10 mmol) was added to a solution of KOH (1M in ^{i}PrOH) (10.8 mL, 10.80 mmol) at room temperature, and the resulting solution was refluxed for 24 h. After cooling, the solvent was evaporated, and then H_2O (2 mL) was added to the residue. After saturation with NaCl, the aqueous layer was extracted with CH_2Cl_2 (10 mL×5). The organic extracts were combined, dried over $NaSO_4$, and evaporated to give a pale yellow oil, which was used directly in next step.

Saturated $NaHCO_3$ (aq) (3 mL) and $ClCO_2Bn$ (0.15 mL, 1.10 mmol) were added to a stirred solution of the above oil in THF (3 mL) at room temperature, and the resulting mixture was stirred overnight. The reaction mixture was diluted with CH_2Cl_2, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL×3). The organic layer and extracts were combined, dried over Na_2SO_4, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (15 g, hexane/ethyl acetate=10:1) to afford **5** (260 mg, 84%) as a colorless oil.

^1H NMR (400 MHz) δ 2.20–2.27 (1H, m), 2.24–2.50 (1H, m), 3.54 (1H, br), 3.77–3.84 (2H, m), 4.30 (1H, br), 5.00–5.17 (4H, m), 5.63–5.72 (1H, m), 7.30–7.39 (5H, m); $[\alpha]_D^{26}$ +30.7 (c 1.00, MeOH), Ref. 3: $[\alpha]_D^{23}$ −32.0 (c 0.99, MeOH).

4.7. (2*R*, 6*R*)-Benzyl 2-allyl-6-(prop-1-en-1-yl)piperidine-1-carboxylate (6)

DMSO (0.18 mL, 2.60 mmol) was added to a stirred solution of $(COCl)_2$ (0.11 mL, 1.30 mmol) in CH_2Cl_2 (5 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 5 min. To the resulting mixture, a solution of the alcohol **5** (250 mg, 0.86 mmol) in CH_2Cl_2 (5 mL) was added dropwise via a double-tripped stainless steel needle at −78 °C, and the reaction mixture was stirred at the same temperature for 30 min. Triethylamine (0.54 mL, 3.89 mmol) was added to the reaction mixture, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with water, and the organic layer was separated. The aqueous mixture was extracted with CH_2Cl_2 (10 mL×2), and the organic layer and extracts were combined, dried over Na_2SO_4, and evaporated to give a pale yellow oil, which was used directly in the next step.

n-BuLi (1.58 M in THF, 1.59 mL, 2.51 mmol) was added to a stirred suspension of ethyltriphenylphosphonium bromide (962 mg, 2.59 mmol) in THF (5 mL) and to the resulting orange solution was added the above aldehyde in THF (5 mL) via a double-tripped stainless steel needle at 0 °C. After stirring the reaction mixture for 1 h, the reaction was quenched with water. The aqueous mixture was extracted with Ethyl acetate (10 mL×3), and the organic extracts were combined, dried over Na_2SO_4, and evaporated to give a colorless oil, which was chromatographed on silica gel (15 g, hexane/ethyl acetate=50:1–30:1) to afford **6** (190 mg, 73%) as a colorless oil.

IR (neat) 2941, 1693, 1404, 1267, 1065 cm^{-1}; ^1H NMR (500 MHz) δ 1.14–1.77 (7H, m), 1.81–1.94 (1H, m), 2.19–2.31 (1H, m), 2.33–2.43 (1H, m), 2.50–2.54 (1H, m), 3.95–4.02 (1H, m), 4.69–4.71 (1H, m), 5.00–5.09 (2H, m), 5.13–5.18 (2H, m), 5.44–5.57 (2H, m), 5.66–5.79 (1H, m), 7.22–7.50 (5H, m); ^{13}C NMR (125 MHz) δ 12.66 & 12.74, 14.19 & 14.32, 22.41 & 26.47, 27.23 & 30.21, 38.67 & 39.07, 47.30 & 48.91, 50.39 & 51.69, 66.51 & 66.82,

116.67 & 116.77, 124.24 & 125.46, 127.69, 128.20, 131.01, 132.22, 135.61 & 135.97, 136.80 & 136.83, 155.63 & 155.70; MS (EI): *m*/*z* 299 $[M]^+$; HRMS: Calcd for $C_{19}H_{25}NO_2$ $[M]^+$ 299.1885; found 299.1883; $[\alpha]_D^{26}$ −45.4 (*c* 1.00, $CHCl_3$).

4.8. (2*R*, 6*R*)-Benzyl 2-((*E*)-4-oxopent-2-en-1-yl)-6-(prop-1-en-1-yl)piperidine-1-carboxylate (7)

Methyl vinyl ketone (0.22 mL, 2.67 mmol) and Grubbs' second catalyst (45 mg, 0.05 mmol) were added to a stirred solution of **6** (160 mg, 0.53 mmol) in CH_2Cl_2 (15 mL), and the resulting mixture was refluxed for 12 h. After cooling, the solvent was evaporated, and the residue was chromatographed on silica gel (10 g, hexane/ethyl acetate=10:1) to give **7** (140 mg, 77%) as a pale yellow oil.

IR (neat) 2947, 1682, 1404, 1254, 1099 cm^{-1}; ^1H NMR (500 MHz) δ 1.61 (3H, d, *J*=8.6 Hz), 1.63–1.73 (4H, m), 1.80–1.92 (2H, m), 2.18 (3H, s), 2.42–2.48 (1H, m), 2.69–2.74 (1H, m), 4.06–4.10 (1H, m), 4.73–4.76 (1H, m), 5.10 & 5.13 (2H, ABq, *J*=11.8 Hz), 5.46–5.54 (2H, m), 6.04–6.07 (1H, d, *J*=15.9 Hz), 6.74 (1H, td, *J*=7.7, 15.9 Hz), 7.28–7.47 (5H, m); ^{13}C NMR (125 MHz) δ 12.82, 14.47, 24.72, 26.73, 27.22, 37.77, 49.24, 51.39, 66.90, 125.17, 127.84, 128.41, 131.65, 132.90, 136.73, 137.84, 145.08, 155.80, 198.56; MS (EI): *m*/*z* 341$[M]^+$; HRMS: Calcd for $C_{21}H_{27}NO_3$ $[M]^+$ 341.1991; found 341.1994; $[\alpha]_D^{26}$ −31.8 (*c* 0.75, $CHCl_3$).

4.9. (4*R*, 6*S*, 9a*S*)-4-Methyl-6-propyloctahydro-1*H*-quinolizine ((−)-195C)

20% $Pd(OH)_2/C$ (5 mg) was added to a stirred solution of **7** (60 mg, 0.15 mmol) in MeOH (5 mL), and the resulting suspension was stirred for 12 h under H_2 atmosphere. The catalyst was filtered off by Celite and the filtrate was evaporated to afford a 1.6:1 mixture of the crude product, which was chromatographed on silica gel (5 g, CH_2Cl_2/MeOH=6:1 (in the presence of Et_3N)) to give (−)-**195C** (17 mg, 50%) and **8** (11 mg, 32%), whose spectral data were identical with those reported for the racemic compound.[4b]

IR (neat) 2932, 2864, 2793, 1450, 1366, 1030 cm^{-1}; ^1H NMR (500 MHz) δ 0.90 (3H, t, *J*=7.5 Hz), 1.06 (3H, d, *J*=6.3 Hz), 1.08–1.14 (2H, m), 1.23–1.40 (2H, m), 1.43–1.72 (11H, m), 1.75–1.86 (1H, m), 2.94–3.09 (1H, m), 3.10–3.15 (1H, m), 3.16–3.25 (1H, m); ^{13}C NMR (125 MHz) δ 14.32, 19.79, 20.04, 20.24, 20.61, 22.27, 24.45, 29.88, 33.39, 34.03, 47.14, 49.40, 52.50; MS (EI): *m*/*z* 195 $[M]^+$; HRMS: Calcd for $C_{13}H_{25}N$ $[M]^+$ 195.1987; found 195.1989; $[\alpha]_D^{26}$ −14.1 (*c* 1.00, $CHCl_3$).

4.10. (4*S*, 6*S*, 9*aS*)-4-Methyl-6-propyloctahydro-1*H*-quinolizine (8)[4b]

IR (neat) 2930, 2862, 2792, 1457, 1374, 1104 cm^{-1}; ^1H NMR (500 MHz) δ 0.94 (3H, t, *J*=7.3 Hz), 1.06 (3H, d, *J*=6.3 Hz), 1.09–1.38 (5H, m), 1.44–1.63 (9H, m), 1.65–1.82 (2H, m), 2.31 (1H, t-like, *J*=10.8 Hz), 2.46–2.52 (1H, m), 3.12–3.19 (1H, m); ^{13}C NMR (125 MHz) δ 14.50, 18.56, 20.04, 20.40, 22.42, 24.51, 27.92, 34.59, 35.29, 35.61, 52.94, 53.04, 54.03; MS (EI): *m*/*z* 195 $[M]^+$; HRMS: Calcd for $C_{13}H_{25}N$ $[M]^+$ 195.1987; found 195.1989; $[\alpha]_D^{26}$ +13.8 (*c* 0.25, $CHCl_3$).

4.11. (2*R*, 6*R*)-6-Allyl-1-(benzylpiperidin-2-yl)methanol (11)

Oxazolidinone **1** (237 mg, 1.31 mmol) was added to a solution of KOH (1 M in ^{i}PrOH) (13.1 mL, 13.10 mmol) at room temperature, and the resulting solution was refluxed for 24 h. After cooling, the alcohol was evaporated, and the residue was added to H_2O (4 mL) saturated with NaCl, and extracted with CH_2Cl_2 (10 mL×5). The organic layer and extracts were combined, dried and evaporated to give a pale yellow oil, which was used directly in next step.

K_2CO_3 (250 mg, 1.81 mmol) was added to a stirred solution of the above oil in MeCN (10 mL) and stirred for 15 min at room temperature. BnCl (0.15 mL, 1.33 mmol) was then added to the resulting mixture and refluxed overnight. The reaction solution was diluted with CH_2Cl_2, and the insoluble materials were filtered off by Celite and the filtrate was evaporated to give a pale yellow oil, which was chromatographed on silica gel (15 g, hexane/ethyl acetate=10:1) to afford **11** (280 mg, 92%) as a colorless oil.

IR (neat) 2931, 2854, 1444, 1450, 1179, 910, 732 cm^{-1}; ^1H NMR (500 MHz) δ 1.14–1.22 (1H, m), 1.45–1.50 (2H, m), 1.57–1.80 (3H, m), 2.19–2.25 (1H, m), 2.34–2.42 (1H, m), 2.87–2.94 (1H, m), 2.95–3.00 (1H, m), 3.25–3.28 (1H, m), 3.65 & 3.90 (2H, ABq, *J*=13.5 Hz), 3.71 (1H, t, *J*=10.3 Hz), 5.05–5.09 (2H, m), 5.76–5.85 (1H, m), 7.16–7.47 (5H, m); ^{13}C NMR (125 MHz) δ 20.43, 20.55, 24.35, 36.81, 48.88, 53.48, 54.52, 59.66, 116.27, 126.89, 128.29, 128.55, 136.11, 139.75; MS (EI): *m*/*z* 246 $[M+H]^+$; HRMS: Calcd for $C_{16}H_{24}NO$ $[M+H]^+$ 246.1858; found 246.1857; $[\alpha]_D^{26}$ −22.6 (*c* 1.70, $CHCl_3$).

4.12. (2*R*, 6*R*)-2-Allyl-1-benzyl-6-(iodomethyl)piperidine (12)

Imidazole (34 mg, 0.50 mmol), PPh_3 (132 mg, 0.51 mmol), and I_2 (103 mg, 0.40 mmol) were added to a stirred solution of **11** (50 mg, 0.20 mmol) in benzene (3 mL), and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with 10% $Na_2S_2O_3$ in satd $NaHCO_3$ (aq), and the aqueous layer was extracted with CH_2Cl_2 (5 mL×3). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (10 g, hexane/ethyl acetate=100:1) to give **12** (52 mg, 72%) as a colorless oil.

IR (neat) 2931, 2854, 1444, 1450, 1179, 910, 732 cm^{-1}; ^1H NMR (500 MHz) δ 1.33–1.35 (1H, m), 1.58–1.70 (3H, m), 2.12–2.18 (1H, m), 2.33–2.38 (1H, m), 2.75–2.82 (2H, m), 3.31–3.38 (2H, m), 3.61 & 3.81(2H, ABq, *J*=12.5 Hz), 4.96–5.00 (2H, m), 5.70–5.77 (1H, m), 7.23 (1H, t, *J*=6.9 Hz), 7.30 (2H, t, *J*=7.5 Hz), 7.41 (2H, d, *J*=7.5 Hz); ^{13}C NMR (125 MHz) δ 10.76, 19.19, 26.16, 26.96, 34.54, 51.21, 53.90, 55.41, 115.99, 126.75, 128.13, 128.55, 136.40, 139.92; MS (EI): *m*/*z* 314 $[M-C_3H_5]^+$; HRMS: Calcd for $C_{13}H_{17}IN$ $[M-C_3H_5]^+$ 314.0406; found 314.0407; $[\alpha]_D^{26}$ −12.0 (*c* 2.50, $CHCl_3$).

4.13. (2*R*, 6*S*)-2-Allyl-1-benzyl-6-methylpiperidine (13)[10]

$LiAlH_4$ (27 mg, 0.72 mmol) was added to a stirred solution of **12** (85 mg, 0.24 mmol) in THF (8 mL) at 0 °C, and the resulting suspension was refluxed for 13 h. After cooling, the reaction was quenched with 10% NaOH (aq), and the aqueous mixture was extracted with hot ethyl acetate (3 mL×6). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a colorless oil, which was chromatographed on silica gel (10 g, hexane/ethyl acetate=30:1) to give **13** (41 mg, 75%) as a colorless oil.

^1H NMR (500 MHz) δ 1.03 (3H, t, *J*=6.6 Hz), 1.25–1.31 (2H, m), 1.40–1.50 (1H, m), 1.54–1.59 (3H, m), 2.21–2.27 (1H, m), 2.32–2.37 (1H, m), 2.76–2.84 (1H, m), 2.85–2.90 (1H, m), 3.55 & 3.90 (2H, ABq, *J*=14.2 Hz), 4.95–5.00 (2H, m), 5.67–5.76 (1H, m), 7.21 (1H, t, *J*=7.5 Hz), 7.29 (2H, t, *J*=7.5 Hz), 7.37 (2H, d, *J*=7.5 Hz); $[\alpha]_D^{26}$ +33.0 (*c* 1.30, $CHCl_3$), Ref. 10: $[\alpha]_D^{26}$ −35.8 (*c* 1.30, $CHCl_3$).

4.14. (2*R*, 6*S*)-Benzyl 2-allyl-6-methylpiperidine-1-carboxylate (9)

K_2CO_3 (72 mg, 0.52 mmol) and CbzCl (0.15 mL, 1.05 mmol) was added to a stirred solution of **13** (24 mg, 0.11 mmol) in 1,2-dichloroethane (10 mL) at room temperature, and the resulting suspension was refluxed for 24 h. Additional K_2CO_3 (72 mg,

0.52 mmol) and CbzCl (0.15 mL, 1.05 mmol) were added to the reaction mixture, and the resulting mixture was refluxed an additional 48 h. After cooling, the insoluble materials were filtered off by Celite and the filtrate was evaporated to give a colorless oil, which was chromatographed on silica gel (10 g, hexane/ethyl acetate=40:1) to give **9** (11 mg, 38%) as a colorless oil, and the starting material **13** (13 mg, 54%) was recovered.

IR (neat) 2945, 2360, 1695, 1405 cm^{-1}; ^1H NMR (500 MHz) δ 1.26 (3H, d, J=6.9 Hz), 1.55–1.75 (4H, m), 1.78–1.85 (1H, m), 2.17–2.23 (1H, m), 2.47–2.53 (1H, m), 3.93–3.96 (1H, m), 4.04–4.08 (1H, m), 4.99–5.05 (2H, m), 5.11 & 5.16 (2H, ABq, J=11.9 Hz), 5.71–5.79 (1H, m), 7.21–7.47 (5H, m); ^{13}C NMR (125 MHz) δ 13.08, 20.85, 22.36, 26.58, 38.92, 47.27, 51.36, 66.56, 116.67, 127.73, 128.26, 128.37, 135.78, 137.07, 155.59; MS (EI): m/z 232 $[M-C_3H_5]^+$; HRMS: Calcd for $C_{14}H_{18}NO$ $[M-C_3H_5]^+$ 232.1338; found 232.1339; $[\alpha]_D^{26}$ +24.7 (c 1.60, $CHCl_3$).

4.15. (2*S*, 6*R*)-Benzyl 2-methyl-6-((*E*)-4-oxohept-2-en-1-yl)piperidine-1-carboxylate (10)

1-Hexen-3-one (0.13 mL, 1.12 mmol) and Grubbs' second catalyst (19 mg, 0.02 mmol) was added to a stirred solution of **9** (61 mg, 0.22 mmol) in CH_2Cl_2 (7 mL), and the resulting mixture was refluxed for 12 h. After cooling, the solvent was evaporated and the residue was chromatographed on silica gel (10 g, hexane/ethyl acetate=10:1) to give **10** (53 mg, 69%) as a pale yellow oil.

R (neat) 2936, 1694, 1404, 1088 cm^{-1}; ^1H NMR (500 MHz) δ 0.92 (3H, t, J=7.5 Hz), 1.26 (3H, d, J=6.6 Hz), 1.55–1.76 (7H, m), 1.85–1.93 (1H, m), 2.35–2.42 (1H, m), 2.47 (2H, t, J=7.3 Hz), 2.61–2.67 (1H, m), 4.02–4.09 (2H, m), 5.11 & 5.15 (2H, ABq, J=12.5 Hz), 6.08 (1H, d, J=15.7 Hz), 6.72–6.80 (1H, m), 7.29–7.47 (5H, m); ^{13}C NMR (125 MHz) δ 13.10, 13.77, 17.63, 20.74, 23.26, 26.49, 37.75, 41.80, 47.38, 50.91, 66.78, 127.80, 127.90, 128.46, 132.08, 136.84, 143.67, 155.58, 200.65; MS (EI): m/z 343 $[M]^+$; HRMS: Calcd for $C_{13}H_{25}NO$ $[M]^+$ 343.2147; found 343.2148; $[\alpha]_D^{26}$ +21.5 (c 1.00, $CHCl_3$).

4.16. (4*S*, 6*R*, 9a*R*)-4-Methyl-6-propyloctahydro-1*H*-quinolizine ((+)-195C)

20% $Pd(OH)_2/C$ (5 mg) was added to a stirred solution of **10** (49 mg, 0.14 mmol) in MeOH (5 mL), and the resulting suspension was stirred for 12 h under H_2 atmosphere. The catalyst was filtered off by Celite and the filtrate was evaporated to afford a 1:4.6 mixture of crude product, which was chromatographed on silica gel (5 g, CH_2Cl_2/MeOH=6:1 (Et_3N drops)) to give (+)-**195C** (4 mg, 14%) and **14** (18 mg, 65%).

(+)-**195C**: ^1H NMR (500 MHz) δ 0.90 (3H, t, J=7.4 Hz), 1.04 (3H, d, J=6.3 Hz), 1.04–1.32 (4H, m), 1.48–1.72 (11H, m), 1.76–1.86 (1H, m), 2.95–3.05 (1H, m), 3.06–3.12 (1H, m), 3.16–3.23 (1H, m); ^{13}C NMR (125 MHz) δ 14.33, 19.87, 20.15, 20.24, 20.68, 22.30, 24.52, 29.96, 33.46, 34.10, 47.15, 49.38, 52.49; MS (EI): m/z 195 $[M]^+$; HRMS: Calcd for $C_{13}H_{25}N$ $[M]^+$ 195.1987; found 195.1985; $[\alpha]_D^{26}$ +14.6 (c 0.10, $CHCl_3$).

4.17. (4*S*, 6*S*, 9a*R*)-4-Methyl-6-propyloctahydro-1*H*-quinolizine (14)

IR (neat) 2930, 2868, 2793, 1456, 1383, 1096 cm^{-1}; ^1H NMR (500 MHz) δ 0.90 (3H, t, J=7.3 Hz), 0.95 (3H, d, J=5.9 Hz), 1.09–1.72 (15H, m), 1.72–1.85 (1H, m), 2.21–2.26 (1H, m), 2.36–2.39 (1H, m), 3.41–3.47 (1H, m); ^{13}C NMR (125 MHz) δ 8.47, 14.59, 18.55, 18.75, 24.40, 31.29, 32.48, 34.29, 34.57, 47.49, 53.73, 58.10; MS (EI): m/z 195 $[M]^+$; HRMS: Calcd for $C_{13}H_{25}N$ $[M]^+$ 195.1987; found 195.1989; $[\alpha]_D^{26}$ +13.8 (c 0.25, $CHCl_3$).

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.10.009.

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