

A concise and fully selective synthesis of the ant venom alkaloid (3*S*,5*R*,8*S*,9*S*)-3-butyl-5-propyl-8-hydroxyindolizidine†

Geng-Jie Lin^a and Pei-Qiang Huang^{*a,b}

Received 22nd June 2009, Accepted 23rd July 2009

First published as an Advance Article on the web 24th August 2009

DOI: 10.1039/b912190k

A seven-step synthesis of (3*S*,5*R*,8*S*,9*S*)-3-butyl-5-propyl-8-hydroxyindolizidine (**2**), an ant venom alkaloid isolated from *Myrmecaria melanogaster*, is disclosed with an overall yield of 28.9%. The key feature of the synthesis is the use of the iodocyclization for the introduction of the hydroxyl group of the 3-piperidinol. Remarkably, all the reaction steps proceeded with excellent chemo-, regio- and/or diastereoselectivities.

Introduction

Nitrogen-containing heterocycles are typical components found in the venoms of ants of the subfamily Myrmicinae, genera *Megalomyrme*, *Monomorium* and *Solenopsis*.¹ 3,5-Dialkylindolizidines (e.g. **1**, monomorphine I)² are one of the earliest reported structural classes of these compounds (Fig. 1). 3,5-Dialkylindolizidines, in addition to 2,5-disubstituted pyrrolidines, 3,5-disubstituted pyrrolizidines and 2,6-disubstituted piperidines, are also often found among the skin alkaloids of dendrobatid frogs, and occasionally occur in other amphibians.³ Recently, (3*S*,5*R*,8*S*,9*S*)-3-butyl-5-propyl-8-hydroxyindolizidine (**2**) was isolated from *Myrmecaria melanogaster* (Emery), a species reported only in Borneo and collected in the sultanate of Brunei Darussalam.⁴ The structure was established by comparison with authentic samples obtained by a non-stereoselective synthesis. Vapour phase infrared analysis revealed the Bohlmann bands and an intramolecular hydrogen bond that allowed the assignment of the relative stereochemistry. Soon after its isolation, the first enantioselective synthesis of **2** was reported, which allowed the determination of its absolute configuration.⁵ This is the first reported ring-hydroxylated acetate-derived ant venom alkaloid. Although the bioactivity of this indolizidine alkaloid has not yet been studied, it has been reported to be involved in ant warfare. In addition, since the stereochemistry of **2** is the same as that of the major alkaloid

5*Z*,9*Z*-223AB isomer (**3**) present in *Myrmecaria melanogaster*,⁶ its isolation has allowed the advance of a biogenetic relationship between the mono- and bicyclic ring systems. In continuation of our general interest in the asymmetric synthesis of bioactive alkaloids,⁷ we now report a concise enantioselective synthesis of **2**.

In our retrosynthetic analysis, the piperidine ring was projected to be built by the intramolecular reductive alkylation⁸ of **11**. The hydroxyl group was envisioned to be introduced by halonium-initiated cyclization⁹ of allylic urethane **8**. The latter can be prepared, in turn, from known *N*-Boc-(*S*)-pyroglutamate **4** via Martin's *cis*-diastereoselective reductive alkylation method.¹⁰

The synthesis started from known *N*-Boc-(*S*)-pyroglutamate **4**, which is both commercially available and easily synthesized from (*S*)-pyroglutamic acid.¹¹ Treatment of imide **4** with *n*-butyl magnesium bromide at $-78\text{ }^{\circ}\text{C}$ gave the desired keto urethane ester **5** chemoselectively,¹² which was then subjected to an intramolecular reductive carbamoylation under Martin's conditions¹⁰ to give 2,5-disubstituted pyrrolidine derivative **6** as the only observable isomer in 82% yield from **4** (Scheme 1). It is worthy of mention that $\text{B}(\text{C}_6\text{F}_5)_3$ is a milder Lewis acid than $\text{BF}_3\cdot\text{OEt}_2$, which can promote the reductive alkylation without concomitant cleavage of the *tert*-butyl urethane moiety. Regarding the stereochemistry of the product, the rotamerism of the product prevented determination of the stereochemistry by NOE experiments. It was assumed to

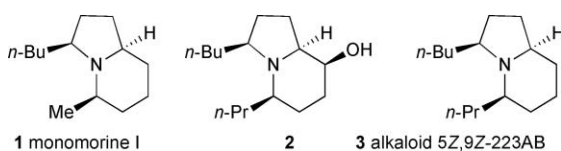
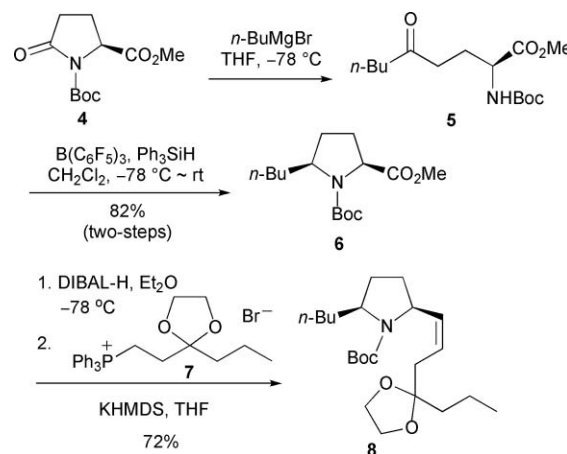


Fig. 1 The structure of 3,5-dialkylindolizidine alkaloids.



Scheme 1 The synthesis of allylic urethane **8**.

^aDepartment of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, P. R. China

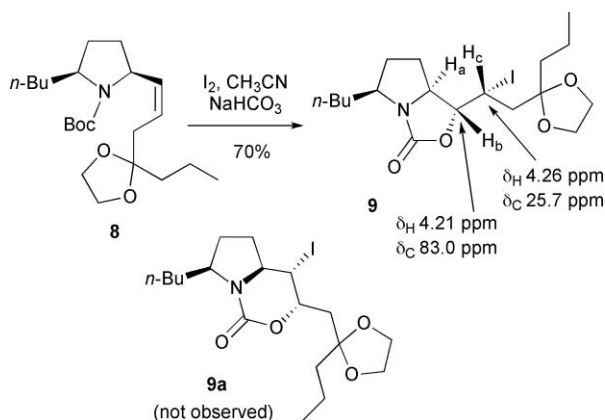
^bState Key Laboratory of Bioorganic and Natural Products Chemistry, 354 Fenglin Lu, Shanghai 200032, P. R. China. E-mail: pqhuang@xmu.edu.cn; Fax: +86 592-2186400; Tel: +86 592-2180992

† Electronic supplementary information (ESI) available: NMR spectra and data. CCDC reference number 734883. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b912190k

be *cis* by analogy with literature precedents,^{5,8d,10} and confirmed by a X-ray diffraction analysis of an advanced intermediate (compound **10**).

The treatment of **6** with diisobutyl aluminum hydride (DIBAL-H) in Et₂O at -78 °C allowed chemoselective reduction of the ester group to provide the corresponding aldehyde, which was subjected to a Wittig reaction with an ylide, *in situ*-generated from phosphonium **7** and KHMDS. This one-pot transformation afforded (*Z*)-olefin **8** as the sole stereoisomer in 72% overall yield. Due to rotamerism, measuring the coupling constant accurately was not possible. However, the coupling constant range of <14 Hz is an indication of a *Z*-geometry, which could also be deduced by analogy with literature precedents.^{8c,13}

Now, the stage was set for the key electrophile-mediated heterocyclization.^{9,14} Iodocyclization of allylic urethane **8** with I₂ proceeded smoothly in acetonitrile at 0 °C to produce iodooxazolidone **9** as the sole regio- and diastereomer in 70% yield (Scheme 2).



Scheme 2 The I₂-mediated iodocyclization of allylic urethane **8**.

The structure of compound **9** was assigned on the basis of NMR experiments. Firstly, the characteristic resonance of the carbon bound to iodine at high field ($\delta_C = 25.7$) allowed an unambiguous localization of the carbon (C–I). Secondly, the HSQC correlation clearly distinguished the protons H_b ($\delta_H = 4.21$) with H_c ($\delta_H = 4.26$). Further inspection of the ¹H NMR spectrum of **9** showed a splitting of a doublet of doublets for H_b and a doublet of doublets for H_c. Thus, five membered oxazolidone **9** was formed instead of its regioisomer **9a**. Thus the oxygen–carbon bond was formed from **8** in a highly regio- and diastereoselective manner.

The observed diastereospecificity in the formation of compound **9** is in agreement with literature precedents,^{9,14} and may result from an A^(1,3) strain-controlled¹⁵ facial differentiation of the alkene. As shown in Fig. 2, the stereoselectivity of the reaction can be rationalized on the basis of favored conformer **A**, which avoids the

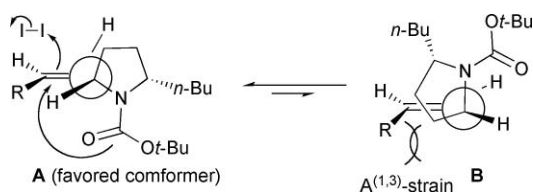
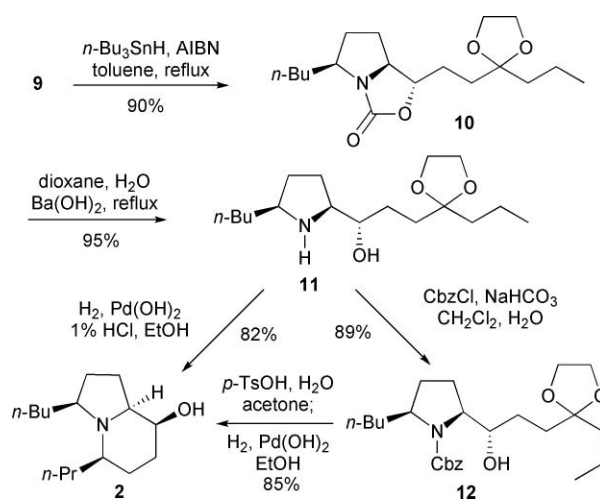


Fig. 2 The stereochemical course of I₂-mediated iodocyclization.

A^(1,3) strain between the pyrrolidine moiety and the bulky carbon side chain R, as shown in conformer **B**. The iodine then approaches the less hindered β -face of the C=C double bond in **A** to form an iodonium ion intermediate. Subsequent attack by the carbonyl oxygen in a 5-*exo-trig*¹⁶ fashion then gives oxazolidone **9**.

The radical-initiated reduction (*n*-Bu₃SnH, AIBN, toluene, reflux) of **9** then afforded oxazolidone **10** in 90% yield (Scheme 3). The stereochemistry of **10** was confirmed by single-crystal X-ray diffraction analysis (Fig. 3). By refluxing **10** with Ba(OH)₂ in dioxane and water, the oxazolidone ring was smoothly hydrolyzed to give amino alcohol **11** in 95% yield. Re-protection of the amine group (CbzCl, NaHCO₃, CH₂Cl₂, H₂O), followed by hydrolysis of the ketal (*p*-TsOH, H₂O, acetone) and a subsequent Pd(OH)₂-catalyzed reductive amination (H₂, 1 atm), produced desired indolizidine **2**. Alternatively a one-pot reaction was achieved by the subjection of pyrrolidine derivative **11** to hydrogenolysis conditions in the presence of 1% HCl (10% Pd/C, 1% HCl, H₂, 1 atm, rt, 3 d), which provided **2** in 82% yield as the sole diastereomer. The physical and spectral data of our synthetic product are in agreement with that reported for the natural product^{4,5} { $[\alpha]_D^{24} -47.8$ (*c* 0.84 in CHCl₃); lit.⁵ $[\alpha]_D^{24} -48.92$ (*c* 0.62 in CHCl₃)}



Scheme 3 The synthesis of indolizidine alkaloid (3*S*,5*R*,8*S*,9*S*)-**2**.

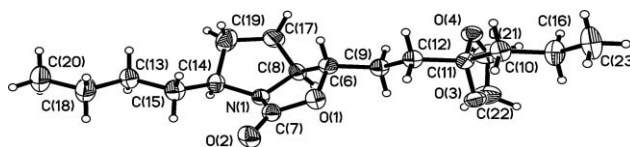


Fig. 3 The X-ray crystal structure of compound **10**.

Conclusions

In summary, starting from known (*S*)-pyroglutamate derivative **4**, a concise seven-step synthesis of hydroxylated indolizidine alkaloid **2** was achieved with an overall yield of 28.9%. It is noteworthy that all the reactions progressed with excellent chemo-, regio- and/or diastereoselectivities. To the best of our knowledge, while electrophile-mediated heterocyclization is a popular methodology for the synthesis of heterocycles, its use in

the stereoselective installation of a 3-piperidinol hydroxyl group is rare.¹⁷ We believe that this powerful and highly regio- and diastereoselective reaction will find applications in the synthesis of other 3-piperidinol-containing alkaloids.¹⁸

Experimental

General

Melting points were determined on a Yanaco MP-500 micro melting point apparatus and were uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ¹H NMR spectra were recorded in CDCl₃ on a Bruker 400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. ¹³C NMR spectra were determined at 100 MHz. Mass spectra were recorded on a Bruker Dalton ESquire 3000 Plus liquid chromatography–mass spectrum (direct injection) instrument. HRMS spectra were recorded on a Shimadzu LCMS-IT-TOF apparatus. Optical rotations were measured with a Perkin-Elmer 341 automatic polarimeter. Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with an ethyl acetate/petroleum ether (PE) (60–90 °C) mixture. Diethyl ether and THF were distilled over sodium benzophenone ketyl under N₂. Dichloromethane was distilled over calcium hydride under N₂.

(2S)-1-tert-Butoxycarbonylamino-5-oxononanoic acid methyl ester (5)

To a cooled solution (–78 °C) of compound **4** (2.00 g, 8.23 mmol) in anhydrous THF (65 mL) was added a solution of *n*-BuMgBr (16.5 mmol, 33 mL, 0.5 M) in THF. The mixture was stirred for 3.5 h at –78 °C and then quenched with a saturated NH₄Cl solution (20 mL). The reaction mixture was poured into a mixture of H₂O (150 mL) and Et₂O (50 mL). The aqueous layer was extracted with Et₂O (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under a reduced pressure. Flash column chromatography of the residue (EtOAc : PE = 1 : 7) afforded product **5** (2.20 g, 90%) as a colorless oil. $[\alpha]_D^{24} +8.5$ (*c* 1.93 of CHCl₃). $[\alpha]_D^{24} +4.7$ (*c* 1.39 of CH₂Cl₂). $[\alpha]_D^{25} -16.9$ (*c* 2.32 of CH₃CN). $\nu_{\max}/\text{cm}^{-1}$: 3369, 2959, 2934, 2873, 1745, 1715, 1513, 1438, 1367, 1250, 1213, 1167, 1050 and 1026. δ_{H} (CD₃CN): 0.85 (3H, s), 1.20–1.30 (2H, m), 1.37 (9H, s), 1.40–1.51 (2H, m), 1.68–1.80 (1H, m), 1.90–2.02 (1H, m), 2.36 (2H, t, *J* = 7.4 Hz), 2.40–2.57 (2H, m), 3.63 (3H, s), 4.00–4.10 (1H, m) and 5.55–5.65 (1H, m). δ_{C} (CD₃CN): 14.7, 23.5, 26.9, 27.1, 29.1, 39.4, 43.5, 53.2, 54.4, 80.4, 157.0, 174.4 and 211.3. MS (ESI): *m/z* 324 [M + Na⁺, 100%]. Found: C, 59.56; H, 9.02; N, 4.64. Calc. for C₁₅H₂₇NO₅: C, 59.78; H, 9.03; N, 4.65%.

tert-Butyl-(2S,5S)-2-methoxycarbonyl-5-butylpyrrolidine-1-carboxylate (6)

A CH₂Cl₂ (15 mL) solution of B(C₆F₅)₃ (645 mg, 1.26 mmol) was added to a CH₂Cl₂ (20 mL) solution of Ph₃SiH (5.22 g, 20.1 mmol) at room temperature. The solution was stirred for 10 min and then transferred to a stirred solution of compound **5** (2.00 g, 6.64 mmol) at –78 °C. The mixture was allowed to slowly warm

to room temperature and stirred for a further 2 d. A saturated aqueous solution of NaHCO₃ (15 mL) was added, the organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 × 40 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under a reduced pressure. Flash column chromatography of the residue (EtOAc : PE = 1 : 10) gave compound **6** (1.630 g, 86%) as a colorless oil. $[\alpha]_D^{24} -22.5$ (*c* 0.97 of CHCl₃). $\nu_{\max}/\text{cm}^{-1}$: 2956, 2922, 2873, 1755, 1702, 1455, 1431, 1392, 1366, 1282, 1257, 1202, 1169, 1127, 1105 and 1033. δ_{H} (DMSO-*d*₆ at 343 K): 0.88 (3H, t, *J* = 7.1 Hz), 1.22–1.35 (5H, m), 1.36 (9H, s), 1.60–1.70 (1H, m), 1.72–1.81 (1H, m), 1.81–1.86 (1H, m), 1.86–1.96 (1H, m), 2.11–2.19 (1H, m), 3.63 (3H, s), 3.70–3.78 (1H, m) and 4.17 (1H, t, *J* = 7.8 Hz). δ_{C} (DMSO-*d*₆ at 343 K): 13.5, 21.7, 27.7, 27.8, 27.9, 33.2, 51.2, 57.8, 59.2, 78.4, 152.9 and 172.8. MS (ESI): *m/z* 308 [M + Na⁺, 100%]. Found: C, 63.23; H, 9.51; N, 4.91. Calc. for C₁₅H₂₇NO₄: C, 63.13; H, 9.54; N, 4.91%.

tert-Butyl-(2S,5S)-2-butyl-5-[(Z)-3-(2-propyl-1,3-dioxolan-2-yl)prop-1-enyl]pyrrolidine-1-carboxylate (8)

A solution of DIBAL-H (1.0 M in toluene, 6.2 mL, 6.2 mmol) was added dropwise over 30 min to a solution of compound **6** (960 mg, 3.37 mmol) in toluene (20 mL) at –78 °C. After stirring for 10 min, Et₂O (30 mL), H₂O (12 mL) and 15% NaOH (18 mL) were added successively, and the resultant mixture was stirred at room temperature for 30 min. The reaction mixture was extracted with Et₂O (3 × 40 mL). The organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and evaporated to dryness under a reduced pressure. The residue was dissolved in THF (5 mL) and added at 0 °C to a pre-prepared solution of phosphonium **7** (4.616 g, 9.53 mmol) and KHMDS (0.5 M in toluene, 9.50 mmol, 19 mL) in THF (20 mL) that had been stirred at 0 °C for 1 h. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with a saturated NH₄Cl solution (20 mL) and the mixture extracted with EtOAc (3 × 30 mL). The filtrate was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under a reduced pressure. Flash column chromatography of the residue (EtOAc : PE = 1 : 10) gave compound **8** (911 mg, 71%) as a colorless oil. $[\alpha]_D^{24} +107.4$ (*c* 1.26 of CHCl₃). $\nu_{\max}/\text{cm}^{-1}$: 2959, 2926, 2874, 1753, 1694, 1454, 1387, 1365, 1255, 1170 and 1103. δ_{H} : 0.90 (3H, t, *J* = 6.5 Hz), 0.91 (3H, t, *J* = 7.4 Hz), 1.20–1.50 (7H, m), 1.42 (9H, s), 1.55–1.70 (4H, m), 1.70–1.95 (2H, m), 2.00–2.10 (1H, m), 2.28–2.45 (1H, m), 2.50–2.62 (1H, m), 3.75–3.85 (1H, m), 3.88–3.99 (4H, m), 4.43–4.46 (1H, m) and 5.03–5.05 (2H, m). δ_{C} : 14.3, 14.5, 17.0, 22.9, 28.8, 29.0, 29.5, 31.6, 35.5, 35.9, 40.1, 55.6, 58.9, 65.2, 65.3, 79.1, 111.6, 123.0–124.0 (br s), 136.0–136.4 (br s) and 155.0. MS (ESI): *m/z* 404 [M + Na⁺, 100%]. Found: C, 69.44; H, 10.32; N, 3.63. Calc. for C₂₂H₃₉NO₄: C, 69.25; H, 10.30; N, 3.67%.

(1R,5S,7aS)-5-Butyl-tetrahydro-1-[(R)-1-iodo-2-(2-propyl-1,3-dioxolan-2-yl)ethyl]pyrrolo[1,2-*c*]oxazol-3(1H)-one (9)

To a vigorously stirred solution of compound **8** (850 mg, 2.23 mmol) in CH₃CN at 0 °C (5.5 mL) was added fine powdered NaHCO₃ (756 mg, 9.00 mmol) together with I₂ (1.143 g, 4.50 mmol). The resulting mixture was stirred at 0 °C for 1 h. A

saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) was added and the mixture stirred for 10 min. The aqueous layer was separated and extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under a reduced pressure. Flash column chromatography of the residue (EtOAc : PE = 1 : 2) gave compound **9** (704 mg, 70%) as a colorless oil. $[\alpha]_{\text{D}}^{24} +8.6$ (*c* 1.11 of CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$: 2958, 2929, 2873, 1756, 1465, 1406, 1378, 1259, 1167 and 1055. δ_{H} : 0.91 (3H, t, *J* = 7.1 Hz), 0.92 (3H, t, *J* = 7.3 Hz), 1.22–1.50 (7H, m), 1.58–1.72 (3H, m), 1.87–1.95 (1H, m), 2.02–2.12 (1H, m), 2.12–2.21 (1H, m), 2.29–2.39 (1H, m), 2.36 (1H, dd, *J* = 7.0 and 15.5 Hz), 2.45 (1H, dd, *J* = 5.3 and 15.5 Hz), 3.50–3.58 (1H, m), 3.86 (1H, ddd, *J* = 6.0, 7.1 and 9.2 Hz), 3.91–4.02 (4H, m), 4.21 (1H, dd, *J* = 3.4 and 7.1 Hz) and 4.26 (1H, ddd, *J* = 3.4, 5.3 and 7.0 Hz). δ_{C} : 14.2, 14.4, 17.1, 22.8, 25.9, 29.0, 29.9, 30.0, 33.1, 39.9, 41.3, 57.0, 64.9, 65.0, 65.8, 83.1, 110.9 and 155.4. MS (ESI): *m/z* 474 [$\text{M} + \text{Na}^+$, 100%]. HRMS (ESI): calc. for $\text{C}_{18}\text{H}_{31}\text{INO}_4$ [$\text{M} + \text{H}^+$]: 452.1292; found: 452.1290.

(1S,5S,7aS)-5-Butyl-tetrahydro-1-[2-(2-propyl-1,3-dioxolan-2-yl)ethyl]pyrrolo[1,2-c]oxazol-3(1H)-one (10)

To a solution of compound **9** (660 mg, 1.46 mmol) and AIBN (35 mg, 0.22 mmol) in toluene (20 mL) was added tributyltin hydride (2.130 g, 7.3 mmol). The resulting mixture was refluxed under an atmosphere of nitrogen overnight. After cooling to room temperature, the solvent was evaporated under a reduced pressure. Flash column chromatography of the residue (EtOAc : PE = 1 : 3) gave compound **10** (465 mg, 98%) as white crystals. mp 86–87 °C (EtOAc/PE). $[\alpha]_{\text{D}}^{24} -3.1$ (*c* 0.93 of CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$: 2958, 2929, 2874, 1753, 1465, 1404, 1367, 1263 and 1071. δ_{H} : 0.91 (3H, t, *J* = 7.1 Hz), 0.92 (3H, t, *J* = 7.3 Hz), 1.20–1.47 (7H, m), 1.53–1.68 (4H, m), 1.70–1.96 (5H, m), 2.09–2.22 (1H, m), 2.23–2.34 (1H, m), 3.47–3.55 (1H, m), 3.74 (1H, ddd, *J* = 5.6, 8.2 and 9.1 Hz), 3.90–3.97 (4H, m) and 4.18 (1H, dt, *J* = 5.6 and 7.7 Hz). δ_{C} : 14.2, 14.5, 17.3, 22.8, 28.6, 28.7, 29.0, 30.4, 32.4, 33.6, 39.7, 56.5, 65.2 (2C), 66.6, 82.3, 111.2 and 156.1. MS (ESI): *m/z* 348 [$\text{M} + \text{Na}^+$, 100%]. Found: C, 66.37; H, 9.58; N, 4.31. Calc. for $\text{C}_{18}\text{H}_{31}\text{NO}_4$: C, 66.43; H, 9.60; N, 4.30%.

(2S,5S)-2-Butyl-5-[(S)-1-hydroxy-3-(2-propyl-1,3-dioxolan-2-yl)propyl]pyrrolidine (11)

A suspension of $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ (2.465 g, 7.80 mmol) in H_2O (40 mL) was added in one portion to a solution of **10** (420 mg, 1.30 mmol) in 1,4-dioxane (60 mL). The resulting mixture was refluxed for 48 h at 120 °C. After cooling to room temperature, the precipitated inorganic salts were filtered off through a glass frit and washed with MeOH (3×10 mL). The solution was concentrated under a reduced pressure. Flash column chromatography of the residue ($\text{CH}_3\text{OH} : \text{CH}_2\text{Cl}_2 : \text{NH}_3 \cdot \text{H}_2\text{O} = 10 : 100 : 1$) gave compound **11** (361 mg, 93%) as a pale yellow oil. $[\alpha]_{\text{D}}^{24} -14.0$ (*c* 0.77 of CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$: 3354, 2957, 2931, 2873, 1530, 1466, 1407, 1195 and 1075. δ_{H} : 0.89 (3H, t, *J* = 7.1 Hz), 0.91 (3H, t, *J* = 7.3 Hz), 1.20–1.54 (11H, m), 1.54–1.70 (4H, m), 1.75–1.95 (3H, m), 2.90–3.14 (4H, m), 3.21 (1H, ddd, *J* = 3.5, 5.8 and 9.0 Hz) and 3.92–3.96 (4H, m). δ_{C} : 14.3, 14.6, 17.3, 23.0, 28.6, 29.7, 30.0, 31.5, 33.6, 36.9, 39.6, 59.2, 62.6, 65.0, 65.1, 73.9 and 111.9. MS (ESI):

m/z 300 [$\text{M} + \text{H}^+$, 100%]. HRMS (ESI) calc. for $\text{C}_{17}\text{H}_{34}\text{NO}_3$ [$\text{M} + \text{H}^+$]: 300.2533; found: 300.2549.

(2S,5S)-Benzyl-2-butyl-5-[(S)-1-hydroxy-3-(2-propyl-1,3-dioxolan-2-yl)propyl]pyrrolidine-1-carboxylate (12)

A mixture of compound **11** (200 mg, 0.67 mmol) and CbzCl (0.70 mmol) in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (10/10 mL) was stirred in the presence of NaHCO_3 (2.0 mmol, 170 mg) for 2 h. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under a reduced pressure. Flash column chromatography of the residue (EtOAc : PE = 1 : 1) gave compound **12** (258 mg, 89%) as a colorless oil. $[\alpha]_{\text{D}}^{24} -31.9$ (*c* 1.27 of CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$: 3441, 2958, 2930, 2873, 1697, 1669, 1498, 1453, 1412, 1352, 1306, 1190 and 1099. δ_{H} : 0.84 (3H, t, *J* = 6.8 Hz), 0.91 (3H, t, *J* = 7.3 Hz), 1.18–1.45 (8H, m), 1.53–1.75 (7H, m), 1.80–2.03 (3H, m), 3.46 (1H, dt, *J* = 2.4 and 8.7 Hz), 3.80–3.90 (1H, m), 3.92 (4H, s, overlapped), 3.90–4.01 (1H, m, overlapped), 5.10 (1H, d, *J* = 12.4 Hz), 5.19 (1H, d, *J* = 12.4 Hz) and 7.28–7.38 (5H, m). δ_{C} : 14.1, 14.6, 17.3, 22.7, 27.4, 28.7, 29.0, 29.7, 32.6, 35.3, 39.6, 59.4, 64.4, 65.0 (2C), 67.6, 111.9, 128.1, 128.2, 128.6 and 136.6. MS (ESI): *m/z* 456 [$\text{M} + \text{Na}^+$, 100%]. Anal. calc. for $\text{C}_{25}\text{H}_{39}\text{NO}_5$: C, 69.25; H, 9.07; N, 3.23. Found: C, 69.14; H, 9.05; N, 3.23%.

(3S,5R,8S,9S)-3-Butyl-5-propyl-8-hydroxyindolizidine (2)

Preparation via compound 12. A solution of compound **12** (96 mg, 0.22 mmol) in acetone/ H_2O (15 : 1, 5 mL) containing TsOH· H_2O (30 mg) was stirred at room temperature for 1 d. The mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under a reduced pressure. To the residue were added EtOH (10 mL) and 20% Pd(OH)₂ (20 mg). The resulting suspension was hydrogenated at 1 atm for 24 h. The catalyst was filtered off, washed with MeOH (3×10 mL) and the filtrate evaporated. Flash column chromatography of the residue ($\text{CH}_3\text{OH} : \text{CH}_2\text{Cl}_2 : \text{NH}_3 \cdot \text{H}_2\text{O} = 20 : 100 : 1$) gave compound **2** (45 mg, 86%) as a pale yellow oil.

Direct preparation from compound 11. In the presence of HCl (1M in H_2O , 0.05 mL) and a catalytic amount of Pearlman's catalyst (20% Pd(OH)₂/C, 10 mg), compound **11** (30 mg, 0.1 mmol) in ethanol (5 mL) was hydrogenated under an atmosphere of hydrogen for 3 d. The catalyst was filtered off, washed with MeOH (3×10 mL) and the filtrate evaporated. Flash column chromatography of the residue ($\text{CH}_3\text{OH} : \text{CH}_2\text{Cl}_2 : \text{NH}_3 \cdot \text{H}_2\text{O} = 20 : 100 : 1$) gave compound **2** (19 mg, 82%) as a pale yellow oil. $[\alpha]_{\text{D}}^{24} -47.8$ (*c* 0.84 of CHCl_3) {lit.⁵ $[\alpha]_{\text{D}}^{24} -48.92$ (*c* 0.62 of CHCl_3)}. $\nu_{\text{max}}/\text{cm}^{-1}$: 3483, 2957, 2933, 2872, 2855, 1465, 1446, 1403, 1378, 1313, 1199, 1130, 1107, 1088 and 1054. δ_{H} : 0.90 (3H, t, *J* = 7.2 Hz), 0.92 (3H, t, *J* = 7.3 Hz), 1.14–1.53 (12H, m), 1.54–1.66 (3H, m), 1.68–1.88 (3H, m), 2.27 (1H, apparent t, *J* = 9.7 Hz, NCH), 2.42 (1H, dd, *J* = 4.5 and 10.7 Hz, NCH), 2.76 (1H, apparent t, *J* = 8.1 Hz, NCH), 3.05 (1H, br, D₂O exchangeable, OH) and 3.75 (1H, br, CHOH). δ_{C} : 14.3, 14.6, 19.3, 23.1, 26.0, 26.7, 28.9, 29.1, 32.3, 37.9, 39.5, 60.7, 64.4, 65.6 and 70.4. MS (ESI): *m/z* 240 [$\text{M} + \text{H}^+$, 100%]. HRMS (ESI) calc. for $\text{C}_{15}\text{H}_{30}\text{NO}$ [$\text{M} + \text{H}^+$]: 240.2322; found: 240.2330.

Acknowledgements

The authors are grateful to the NSF of China (20832005) and the National Basic Research Program (973 Program) of China (Grant no. 2010CB833206) for financial support.

Notes and references

- 1 A. Numata, and T. Ibuka, Alkaloids from Ants and Other Insects, in *The Alkaloids: Chemistry and Pharmacology*, ed. A. Brossi, Elsevier Science, Oxford, 1987, vol. 31, pp. 193–315.
- 2 F. J. Ritter, I. E. M. Rotgans, E. Talman, P. E. Verwiel and F. Stein, *Cell. Mol. Life Sci.*, 1973, **29**, 530–531.
- 3 For two comprehensive reviews, see: (a) J. W. Daly, T. F. Spande and H. M. Garraffo, *J. Nat. Prod.*, 2005, **68**, 1556–1575; (b) J. W. Daly, *J. Med. Chem.*, 2003, **46**, 445–452.
- 4 T. H. Jones, H. L. Voegtle, H. M. Miras, R. G. Weatherford, T. F. Spande, H. M. Garraffo, J. W. Daly, D. W. Davidson and R. R. Snelling, *J. Nat. Prod.*, 2007, **70**, 160–168.
- 5 N. Toyooka, D. J. Zhou, H. Nemoto, Y. Tezuka, S. Kadota, T. H. Jones, H. M. Garraffo, T. F. Spande and J. W. Daly, *Synlett*, 2008, 1894–1896.
- 6 (a) M. W. Edwards, J. W. Daly and C. W. Myers, *J. Nat. Prod.*, 1988, **51**, 1188–1197; (b) H. M. Garraffo, T. F. Spande, J. W. Daly, A. Baldessari and E. G. Gros, *J. Nat. Prod.*, 1993, **56**, 357–373.
- 7 For an account, see: (a) P.-Q. Huang, *Synlett*, 2006, 1133–1149; For a recent example, see: (b) P.-Q. Huang, Z.-Q. Guo and Y.-P. Ruan, *Org. Lett.*, 2006, **8**, 1435–1438.
- 8 For representative examples on the use of reductive amination in the synthesis of 3,5-dialkylindolizidine alkaloids, see: (a) R. V. Stevens and A. W. M. Lee, *J. Chem. Soc., Chem. Commun.*, 1982, 102–103; (b) J. Royer and H.-P. Husson, *J. Org. Chem.*, 1985, **50**, 670–673; (c) S. H. Zhang, L. Xu, L. Miao, H. Shu and M. L. Trudell, *J. Org. Chem.*, 2007, **72**, 3133–3136; (d) Z. Sun, S. Yu, Z. Ding and D. Ma, *J. Am. Chem. Soc.*, 2007, **129**, 9300–9301; (e) N. Toyooka, D. J. Zhou and H. Nemoto, *J. Org. Chem.*, 2008, **73**, 4575–4577.
- 9 For excellent reviews on halocyclocarbamation and related cyclizations, see: (a) G. Cardillo and M. Orena, *Tetrahedron*, 1990, **46**, 3321–3408; (b) S. Robin and G. Rousseau, *Tetrahedron*, 1998, **54**, 13681–13736.
- 10 J. B. Brenneman, R. Machauer and S. F. Martin, *Tetrahedron*, 2004, **60**, 7301–7314.
- 11 E. Coudert, F. Acher and R. Azerad, *Synthesis*, 1997, 863–865.
- 12 A. Giovannini, D. Savoia and A. Umami-Ronchi, *J. Org. Chem.*, 1989, **54**, 228–234.
- 13 (a) P. L. Beaulieu, J.-S. Duceppe and C. Johnson, *J. Org. Chem.*, 1991, **56**, 4196–4204; (b) W. S. Saari and T. E. Fisher, *Synthesis*, 1990, 453–454.
- 14 For selected examples, see: (a) H. W. Pauls and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1980, **102**, 3956–3957; (b) Y. F. Wang, T. Izawa, S. Kobayashi and M. Ohno, *J. Am. Chem. Soc.*, 1982, **104**, 6465–6466; (c) K. A. Parker and R. O'Fee, *J. Am. Chem. Soc.*, 1983, **105**, 654–655; (d) M. Georges, D. MacKay and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1982, **104**, 1101–1103; (e) A. Agami, F. Couty and O. Venier, *Synlett*, 1995, 1027–1028; (f) C. Agami, F. Couty, L. Hamon and O. Venier, *J. Org. Chem.*, 1997, **62**, 2106–2112; (g) J. M. Jordá-Gregori, M. E. Gonzalez-Rosende, J. Sepulveda-Arques, R. Galeazzi and M. Orena, *Tetrahedron: Asymmetry*, 1999, **10**, 1135–1143; (h) J. M. Jordá-Gregori, M. E. Gonzalez-Rosende, P. Cava-Montesinos, J. Sepulveda-Arques, R. Galeazzi and M. Orena, *Tetrahedron: Asymmetry*, 2000, **11**, 3769–3777; (i) D. L. Comins and A. L. Williams, *Tetrahedron Lett.*, 2000, **41**, 2839–2842; (j) A. L. Williams, T. A. Grillo and D. L. Comins, *J. Org. Chem.*, 2002, **67**, 1972–1973.
- 15 R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841–1860.
- 16 (a) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734–736; (b) C. D. Johnson, *Acc. Chem. Res.*, 1993, **26**, 476–482.
- 17 C. Caderas, R. Lett, L. E. Overman, M. H. Rabinowitz, L. A. Robinson, M. J. Sharp and J. Zablocki, *J. Am. Chem. Soc.*, 1996, **118**, 9073–9082.
- 18 For selected reviews on the synthesis of piperidine alkaloids, see: (a) N. Toyooka, in *Asymmetric Synthesis of Nitrogen Heterocycles*, ed. J. Royer, Wiley-VCH, Weinheim, 2009, pp. 95–138; (b) D. L. Comins and S. P. Joseph, in *Advances in Nitrogen Heterocycles*, ed. C. J. Moody, JAI Press Inc., Greenwich, CT, 1996, vol. 2, pp. 251–294; (c) J. P. Michael, *Nat. Prod. Rep.*, 1999, **16**, 675–696; (d) S. Laschat and T. Dickner, *Synthesis*, 2000, 1781–1813; (e) N. Toyooka and H. Nemoto, *Drugs of the Future*, 2002, **27**, 143–158; (f) P. M. Weintraub, J. S. Sabol, J. M. Kane and D. R. Borcharding, *Tetrahedron*, 2003, **59**, 2953–2989; (g) F.-X. Felpin and J. Lebreton, *Eur. J. Org. Chem.*, 2003, 3693–3712; (h) M. G. P. Buffat, *Tetrahedron*, 2004, **60**, 1701–1729; (i) R. P. Hsung, A. V. Kurdyumov and N. Sydorenko, *Eur. J. Org. Chem.*, 2005, 23–44.