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†

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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 *Myrmicaria 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 *Megalomyrmex*, *Monomorium* and *Solenopsis*.[1] 3,5-Dialkylindolizidines (*e.g.* **1**, monomorine 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 *Myrmicaria 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 *Myrmicaria 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 alkylation[8] of **11**. The hydroxyl group was envisioned to be introduced by halonium-initiated cyclization[9] 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 °C gave the desired keto urethane ester **5** chemoselectively,[12] which was then subjected to an intramolecular reductive carbamoylation under Martin's conditions[10] 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 $B(C_6F_5)_3$ is a milder Lewis acid than $BF_3{\cdot}OEt_2$, 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

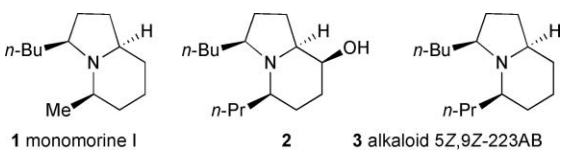
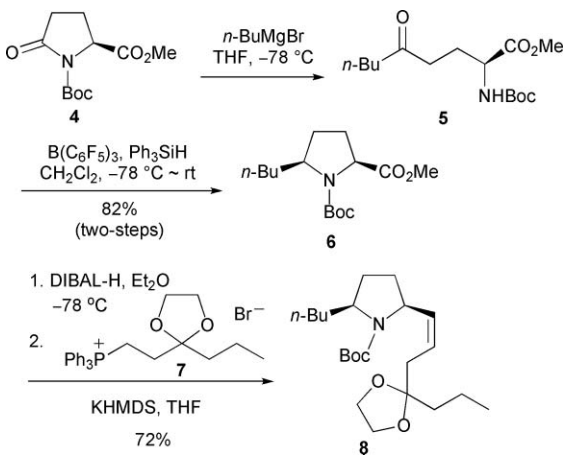


Fig. 1 The structure of 3,5-dialkylindolizidine alkaloids.



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

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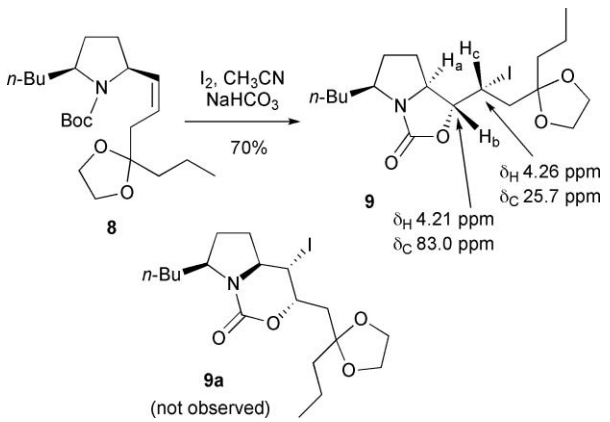
† Electronic supplementary information (ESI) available: NMR spectra and data. CCDC reference number 734883. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b912190k

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 Et_2O 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 I_2 proceeded smoothly in acetonitrile at 0 °C to produce iodo-oxazolidone **9** as the sole regio- and diastereomer in 70% yield (Scheme 2).



Scheme 2 The I_2-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 ^{1}H NMR spectrum of **9** showed a splitting of a doublet of doublets for H_b and a doublet of 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-controlled[15] 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

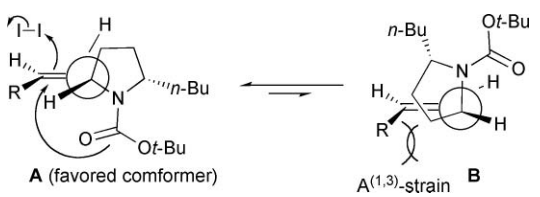
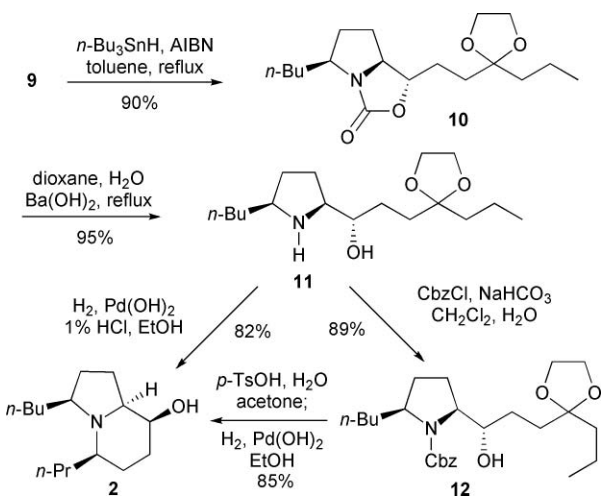


Fig. 2 The stereochemical course of I_2-mediated iodocyclization.

$A^{(1,3)}$ 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*-Bu_3SnH, 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, $NaHCO_3$, CH_2Cl_2, H_2O), followed by hydrolysis of the ketal (*p*-TsOH, H_2O, acetone) and a subsequent $Pd(OH)_2$-catalyzed reductive amination (H_2, 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, H_2, 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 $CHCl_3$); lit.[5] $[\alpha]_D^{24}$ −48.92 (*c* 0.62 in $CHCl_3$)}.



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

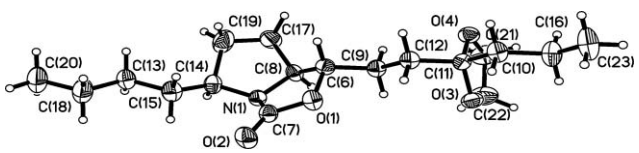


Fig. 3 The X-ray crystal structure of compound **10**.

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. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker 400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. ^{13}C 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 N_2. Dichloromethane was distilled over calcium hydride under N_2.

(2*S*)-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 NH_4Cl solution (20 mL). The reaction mixture was poured into a mixture of H_2O (150 mL) and Et_2O (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 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 : 7) afforded product **5** (2.20 g, 90%) as a colorless oil. $[\alpha]_D^{24}$ +8.5 (*c* 1.93 of $CHCl_3$). $[\alpha]_D^{24}$ +4.7 (*c* 1.39 of CH_2Cl_2). $[\alpha]_D^{24}$ −16.9 (*c* 2.32 of CH_3CN). ν_{max}/cm^{-1}: 3369, 2959, 2934, 2873, 1745, 1715, 1513, 1438, 1367, 1250, 1213, 1167, 1050 and 1026. δ_H (CD_3CN): 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 (CD_3CN): 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 $C_{15}H_{27}NO_5$: C, 59.78; H, 9.03; N, 4.65%.

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

A CH_2Cl_2 (15 mL) solution of $B(C_6F_5)_3$ (645 mg, 1.26 mmol) was added to a CH_2Cl_2 (20 mL) solution of Ph_3SiH (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 $NaHCO_3$ (15 mL) was added, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 40 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 : 10) gave compound **6** (1.630 g, 86%) as a colorless oil. $[\alpha]_D^{24}$ −22.5 (*c* 0.97 of $CHCl_3$). ν_{max}/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 $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91%.

tert-Butyl-(2*S*,5*S*)-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, Et_2O (30 mL), H_2O (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 Et_2O (3 × 40 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, 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 NH_4Cl solution (20 mL) and the mixture extracted with EtOAc (3 × 30 mL). The filtrate was 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 : 10) gave compound **8** (911 mg, 71%) as a colorless oil. $[\alpha]_D^{24}$ +107.4 (*c* 1.26 of $CHCl_3$). ν_{max}/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 $C_{22}H_{39}NO_4$: C, 69.25; H, 10.30; N, 3.67%.

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

To a vigorously stirred solution of compound **8** (850 mg, 2.23 mmol) in CH_3CN at 0 °C (5.5 mL) was added fine powdered $NaHCO_3$ (756 mg, 9.00 mmol) together with I_2 (1.143 g, 4.50 mmol). The resulting mixture was stirred at 0 °C for 1 h. A

saturated aqueous solution of $Na_2S_2O_3$ (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. $[\alpha]_D^{24}$ +8.6 (*c* 1.11 of $CHCl_3$). ν_{max}/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 [M + Na^+, 100%]. HRMS (ESI): calc. for $C_{18}H_{31}INO_4$ [M + H^+]: 452.1292; found: 452.1290.

(1*S*,5*S*,7*aS*)-5-Butyl-tetrahydro-1-[2-(2-propyl-1,3-dioxolan-2-yl)ethyl]pyrrolo[1,2-*c*]oxazol-3(1*H*)-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). $[\alpha]_D^{24}$ −3.1 (*c* 0.93 of $CHCl_3$). ν_{max}/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 [M + Na^+, 100%]. Found: C, 66.37; H, 9.58; N, 4.31. Calc. for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30%.

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

A suspension of $Ba(OH)_2{\cdot}8H_2O$ (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 (CH_3OH : CH_2Cl_2 : $NH_3{\cdot}H_2O$ = 10 : 100 : 1) gave compound **11** (361 mg, 93%) as a pale yellow oil. $[\alpha]_D^{24}$ −14.0 (*c* 0.77 of $CHCl_3$). ν_{max}/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 [M + H^+, 100%]. HRMS (ESI) calc. for $C_{17}H_{34}NO_3$ [M + H^+]: 300.2533; found: 300.2549.

(2*S*,5*S*)-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 CH_2Cl_2/H_2O (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. $[\alpha]_D^{24}$ −31.9 (*c* 1.27 of $CHCl_3$). ν_{max}/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 [M + Na^+, 100%]. Anal. calc. for $C_{25}H_{39}NO_5$: C, 69.25; H, 9.07; N, 3.23. Found: C, 69.14; H, 9.05; N, 3.23%.

(3*S*,5*R*,8*S*,9*S*)-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 $TsOH{\cdot}H_2O$ (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 (CH_3OH : CH_2Cl_2 : $NH_3{\cdot}H_2O$ = 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 (CH_3OH : CH_2Cl_2 : $NH_3{\cdot}H_2O$ = 20 : 100 : 1) gave compound **2** (19 mg, 82%) as a pale yellow oil. $[\alpha]_D^{24}$ −47.8 (*c* 0.84 of $CHCl_3$) {lit.[5] $[\alpha]_D^{24}$ −48.92 (*c* 0.62 of $CHCl_3$)}. ν_{max}/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, NC*H*), 2.42 (1H, dd, *J* = 4.5 and 10.7 Hz, NC*H*), 2.76 (1H, apparent t, *J* = 8.1 Hz, NC*H*), 3.05 (1H, br, D_2O exchangeable, O*H*) and 3.75 (1H, br, C*H*OH). 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 [M + H^+, 100%]. HRMS (ESI) calc. for $C_{15}H_{30}NO$ [M + 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.

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