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Efficient and structurally controlled synthesis of novel polyhydroxylated indolizidine derivatives with an amino group

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ABSTRACT

Novel polyhydroxylated indolizidine derivatives containing an amino group have been efficiently and divergently synthesized from azasugar aldehyde. The key steps of the strategy involved an effectively microwave assisted 1,3-dipolar cycloaddition of azasugar nitrone and methacrylate for installing a potential amino group and an ester group with a extended chain, and a structurally controlled intramolecular cyclo-amidation for constructing the indolizidine ring system via a key tricyclic indolizinone-containing intermediate.

1. Introduction

Polyhydroxylated indolizidine alkaloids, such as the well known (−)-swainsonine (**A**) and (+)-castanospermine (**B**) (Fig. 1), are naturally occurring and typical bicyclic azasugar analoges,[1] and exhibited effective glycosidase inhibition and potential therapeutic applications as antidiabetic, antiviral, anticancer, and anti-metastatic immunoregulating agents.[2] Such promising applications and the interesting bicyclic structure of polyhydroxylated indolizidines have attracted great interests to approach the convenient and efficient synthetic methods and to build up the diversity of the compounds for studying the structure–activity relationship, improving their biological activity and selectivity, and diminishing toxicity.[3] In literature, considerable synthetic routes for synthesizing polyhydroxylated indolizidine derivatives have been well documented.[3–7] Of the most convenient methods are the intramolecular annulations of γ- or δ-amino acids,[4] or γ- or δ-amino alcohol derivatives.[5] However, to the best of our knowledge, most of the synthesized polyhydroxylated indolizidines were the alternative epimers and/or other structural analogues of the natural compounds, and those with the functional group other than hydroxyl, such as amino group, were scarce.[8] To meet the ever-growing requirements for diverse polyhydroxylated indolizidine derivatives in the structure–activity relationship study and the drug discovery, the design and stereoselective synthesis of novel structural variants of polyhydroxylated indolizidine with different functional groups and substituents are of high importance.

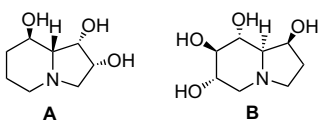

Figure 1. Swainsonine (**A**) and castanospermine (**B**).

Retrosynthetically, the target amino polyhydroxylated indolizidines (**T**) could be obtained from the reduction of the key intermediates (**C**) or (**G**), which would be generated from the 1,3-DC adducts (**D**)[9] via the process (*a*) or (*b*), respectively, as shown in Scheme 1. In the process (*a*), the reductive cleavage of N–O bond[10] would result in the γ- or δ-amino ester-like intermediate (**E**), which followed by competitively intermolecular cyclo-amidation in routes (*i*) or/and (*ii*), would produce the intermediates (**C**) or/and (**F**), respectively. However, the process (*b*) involving the tricyclic intermediate (**G**) produced by a trifluoroacetamide hydrolysis of (**D**) and then intermolecular cyclo-amidation would be in favor of exclusively resulting the indolizidine skeleton. The potential amino group in target molecule and the carboxyl group for constructing indolizidine ring could be simultaneously installed by the divergent and stereoselective 1,3-DC of an azasugar nitrone (**2**) and an acrylate.

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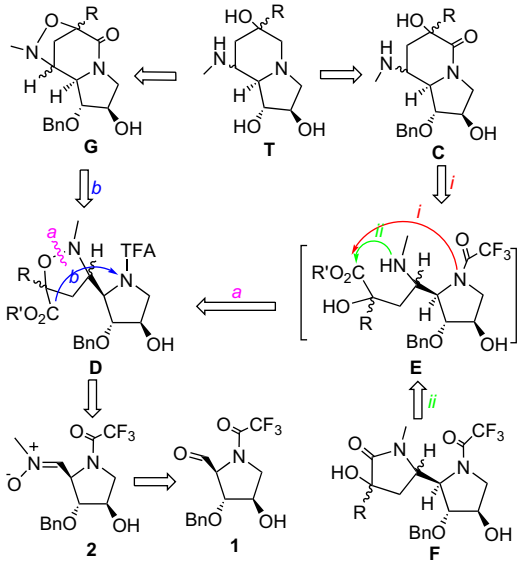


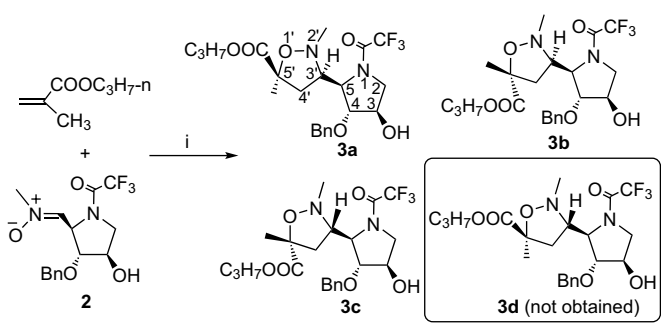
Scheme 1. Retrosynthetic analysis of amino polyhydroxylated indolizidines.

2. Results and discussion

The requisite azasugar nitrone (**2**) was prepared from the azasugar aldehyde (**1**)[11] following the Dondoni's procedure.[12] The 1,3-DC of nitrone (**2**) with propyl methacrylate was carried out at room temperature to afford the corresponding cycloadducts of the isoxazolidines **3a**, **3b**, and **3c** in total yield of 66.7% with the ratio of 1.47:0.81:1. Theoretically, the cycloaddition should produce four diastereomers of **3a**, **3b**, **3c**, and **3d**, but under both reaction conditions the reaction stereoselectively provided three isomers of **3a**, **3b**, and **3c** (Scheme 2).

The structure of **3a** was confirmed by its single-crystal X-ray analysis (Fig. 2), showing the newly generated chiral carbons of C-3′ and C-5′ to be in (*R*) and (*S*) configurations, respectively.[13] Similarly, the C-3′ and C-5′ in **3c** could be deduced to have (*S*) and (*R*) configurations, respectively, according to the single-crystal X-ray analysis of its derivative **5c** (Fig. 3)[13] generated from **3c** as shown in Scheme 3. The cycloadduct **3b** was determined to be of 3′-(*R*) and 5′-(*R*) based on the structures of **3a** and **3c** and by comparing the NOESY analyses of **3b** with those of **3a** and **3c** (Fig. 4).

As shown in Figure 4 of 2D-NOESY correlation analyses of **3a**, **3b**, and **3c**, the correlations between H-4/Ha-4′, H-5/H-3′, H-3′/Hb-4′, and Ha-4′/H-5′CH_3 in compound **3b** were observed, and no correlation between H-4/H-3′ and H-3′/Ha-4′ existed, indicating its structure to be identical to the proposed. Similarly, the correlations between H-4/Ha-4′, H-5/H-3′, H-3′/Hb-4′ and Hb-4′/H-5′CH_3 in compound **3a**, and H-4/H-3′, H-3′/Ha-4′, and Ha-4′/H-5′CH_3 in compound **3c** also matched to the structures of **3a** and **3c**, supporting the structural elucidation of compound **3b**.



Scheme 2. *Conditions and reagents*: (i) rt, 95 h, 66.7% (**3a**:**3b**:**3c**=1.47:0.81:1).

Firstly we explored the synthesis of the amino indolizinone derivative (**C**) via the intermediate (**E**) via the route of the reductive cleavage of the O–N bond (Scheme 1 step *a*) and cyclo-amidation (Scheme 1 step *i*) by treating **3** with Zn-AcOH-H_2O at room temperature following our previous report[10] as shown in Scheme 3. As expected in Scheme 1, the reaction should form a bipyrrolidinyl intermediate (**F**) (Scheme 1 step *ii*) or/and the amino indolizinone derivative (**C**) (Scheme 1 step *i*) via γ- or/and δ-cyclo-amidation of the intermediate (**E**), respectively. However, under the reductive treatment the cycloadduct **3b** gave the bipyrrolidinyl derivative **4b**, which might involve the generation of a γ,δ-diamino acid intermediate (**E**) (Scheme 1, step *a*) and then the favorite γ-cyclo-amidation (Scheme 1, attack *ii*) to form the product exclusively. In the cases of **3a** and **3c**, the tricyclic intermediates **5a** and **5c** were mainly obtained, respectively, via the acidic trifluoroacetamide hydrolysis and δ-cyclo-amidation by the step *b* as shown in Scheme 1, without the generation of O–N bond cleavage/cyclo-amidation products. These results implied that the reaction of **3** to form the tricyclic intermediates **5** may be depended upon the structure of **3**, namely being stereo-structurally controlled.

To explore the conversion of **3** to the tricyclic intermediates **5**, the cycloadduct **3c** was treated with NaOH/MeOH/H_2O solution (pH=12) to hydrolysize trifluoroacetamide and propyl ester, and then acidifying (pH=2) with hydrochloric acid to furnish the cyclo-amidation (Scheme 4, (i)). As a result, white solid of **5c** was afforded in 89.6% yield. With intermediate **5c**, the debenzylation and O–N bond cleavage were next investigated by catalytic hydrogenation with $Pd(OH)_2$/C in MeOH, which in the presence of an equivalent of hydrochloric acid afforded the amino polyhydroxylated indolizinone **6c** in 92.8% yield (Scheme 4, (ii)).

Following the same procedures, the tricyclic intermediate (**5a**) was obtained from **3a** in yields of 91.1%, which, followed by catalytic hydrogenation, gave the indolizinone derivative (**6a**) in 90.0% (Scheme 4). However, in the case of **3b**, following the same treatments the bipyrrolidinyl derivative (**6b**) was finally formed, and the corresponding intermediate (**5b**) was not generated in the first step (Scheme 4, (i)) according to the TLC monitoring. The results further indicated that the cyclo-amidation of **3** to form the intermediate **5** would be structurally controlled.

The structure of **5c** was confirmed by its single-crystal X-ray analysis (Fig. 3),[13] and the structure of **4b** was determined based on the structure of **3b** and the spectral analyses. The HMBC correlation between C(C=O) and H(CH_3–N) of **4b** indicated the existence of an amido *N*-methyl group, strongly supporting the pyrrolidinone structure of **4b**. Similar correlations were also observed in the HMBC spectra of **6b** (Scheme 4).

Moreover, in the supposed structure of **5b** (Fig. 5a) the N and O atoms in the isoxazolidine ring were antarafacial to the piperidone ring. According to its optimized conformation (Fig. 5b) by Chem3D Pro 10.0 (ChemOffice® 2006, CambridgeSoft® Corporation) calculation, the N-linked bridge sp^3carbon (inside the green circle) shared by the isoxazolindine ring and piperidinone ring could not build up a normal tetrahedron connection, that is, such structure was unfavorable and would be impossible, strongly indicating that the intramolecular cyclo-amidation was stereocontrolled by the structure of its product **5**.

It should be mentioned that in the absence of hydrochloric acid the hydrogenation of **5c** also generated the by-products of the debenzylated intermediate **7** and the methylated derivative **8**, besides the desired product **6c**, as shown in Scheme 5, probably because the new generated amine group in **6c** lowered the activity of the palladium catalyst by poisoning.

Toward the final amino polyhydroxylated indolizidine derivatives, the reduction of the carbonyl into methylene was

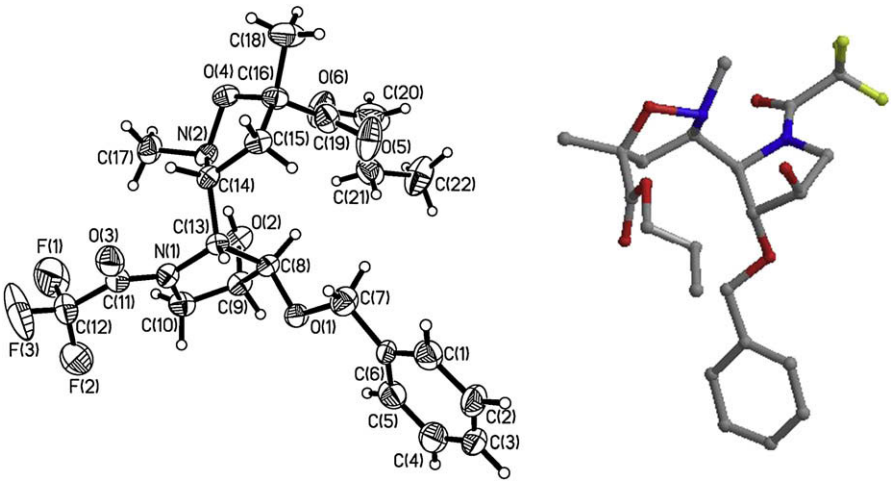


Figure 2. ORTEP drawings of compound **3a**.

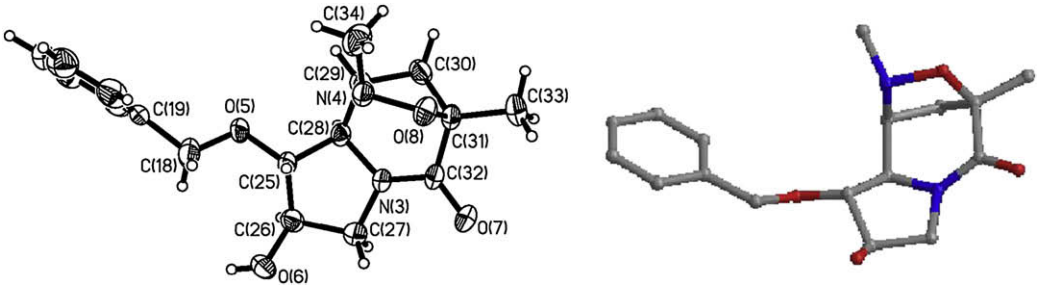
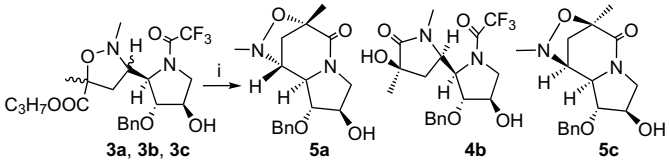


Figure 3. ORTEP drawings of compound **5c**.

approached with lithium aluminum hydride ($LiAlH_4$)[4h,6d,14] using the tricyclic indolizinone intermediates **5a**, instead of **6a** due to its poor solubility in THF. As shown in Scheme 6, under the condition **A** ($LiAlH_4$/THF, rt) the amido carbonyl of **5a** was reduced to afford the corresponding indolizidine derivative **9a** possessing a hemiacetal-like structure in 91.8% yield. Next, the exhaustively catalytic hydrogenation of **9a** involving the reductions of hemiacetal and O–N bond, and debenzylation provided the novel amino indolizidine derivatives **11a** in 90.2% yield (Scheme 6). Following the same procedure, **5c** was converted into the corresponding **11c** in 90% yield in two steps. However, in the presence of Lewis acid $AlCl_3$ (Scheme 6, condition **B**), the reduction of **5c** could proceed smoothly and directly gave the indolizidine derivative **10c** in 91.6% yield, but in the case of **5a**, the reaction produced the corresponding **10a** (41.0%), as well as the debenzylated derivative (**10a1**) (54.7%). Subsequently, the exhaustive hydrogenation of **10** provided the final product **11** in excellent yields (Scheme 6). The spectral data (^1H NMR, ^{13}C NMR, 2D NOESY, HRMS) of all the new compounds were matched to their proposed structures.



Scheme 3. *Conditions and reagents*: (i) AcOH/H_2O/Zn, 70 °C; **5a**: 66.2%, **5c**: 58.2%, **4b**: 27.8%.

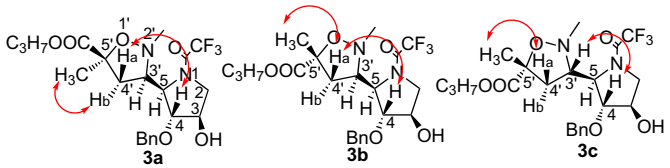
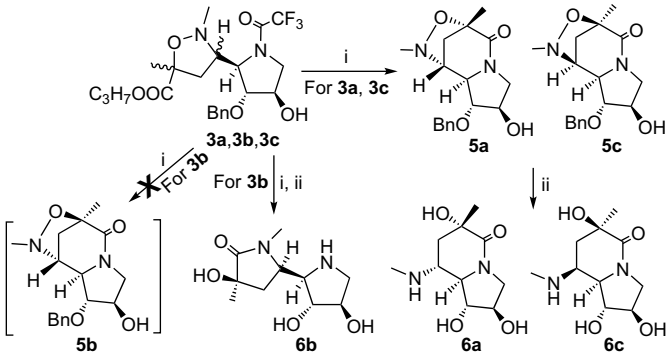


Figure 4. NOE correlations of compounds **3a**–**3c**.

Glycosidase inhibition and antitumor activities were preliminarily evaluated with compounds **6a**, **6c** and **11a**, **11c**. The cytotoxicity of the compounds against Hela cell lines (human cervical cancer cells) was examined by the modified Mosmann's protocol,[15] and the glycosidase inhibitory activities were measured on hydrolytic reactions of α-amylase, α-glucosidase, and β-glucosidase by colorimetric analysis and by comparison with acarbose, respectively. However, the compounds did not show obvious activities.

In conclusion, we have provided a new strategy of highly efficient synthesis of novel amino polyhydroxylated indolizidine and indolizinone derivatives from azasugar aldehyde by stereoselective 1,3-DC and structurally controlled cyclo-amidation. The divergent 1,3-DC of azasugar nitrone (**2**) and propyl methacrylate simultaneously introduced a carboxyl group for constructing the indolizidine ring and the potential amino group. The followed structurally dependent cyclo-amidation, which formed the key tricyclic indolizinone intermediates (**5**) determined the skeleton of polyhydroxylated indolizidine bearing an amino group. The preliminary biological evaluation of the synthesized compounds **6** and **11** showed weak glycosidase inhibitory activity, but no antitumor activities. The further application of the strategy to synthesize novel variants of such amino bicyclic azasugar and their biological testing are underway.



Scheme 4. *Conditions and reagents*: (i) NaOH/MeOH/H_2O, rt, then HCl (0.2 mol/L) (pH=2); **5a**: 91.1%, **5c**: 89.6%; (ii) $Pd(OH)_2$/C, H_2, MeOH/HCl; **6a**: 90.0%, **6c**: 92.8%, **6b**: 75.4% (two steps from **3b**).

3. Experimental

3.1. General methods

Melting points were measured on an SGW® X-4 micro melting point apparatus and were uncorrected. Optical rotations were determined on an SGW®-1 automatic polarimeter. NMR experiments were recorded on a FT-NMR Bruker AVANCE 400 (400 MHz) and Bruker AVANCE 600 (600 MHz) spectrometers, chemical shifts are given in parts per million using tetramethylsilane (Me_4Si) as an internal standard. X-ray crystallographic measurements were made on a Bruker SMART CCD diffractometer. Mass Spectra (MS) and High Resolution Mass Spectra (HRMS) were carried out on a FTICR-MS (Ionspec 7.0T) mass spectrometer with electrospray ionization (ESI). TLC was performed on silica gel plates (Qingdao GF_{254}) with detection by UV (254 nm) light or with phosphomolybdic reagent. Flash chromatography was performed using 200–300 mesh silica gel. Solvents were distilled and dried immediately prior to use.

3.2. Experimental procedures

*3.2.1. General procedure of 1,3-dipolar cycloaddition of nitrone (**2**) with propyl methacrylate (Scheme 2)*

A solution of nitrone **2** (1.34 g, 3.88 mmol) and methyl methacrylate (10 mL) was stirred under nitrogen atmosphere at room temperature for 95 h till the reaction completed. The reaction solution was concentrated in vacuo and the residue was subjected to silica gel column chromatography (petroleum ether/ethyl acetate v/v=8:1–6:1) to afford the adducts **3a** (white solid, 0.55 g, 29.9%), **3b** (colorless syrup, 0.30 g, 16.5%), **3c** (colorless syrup, 0.37 g 20.3%) (**a**:**b**:**c**=1.47:0.81:1) in total yield of 66.7%. A single crystal of **3a** for X-ray analysis was obtained from hexane solution.

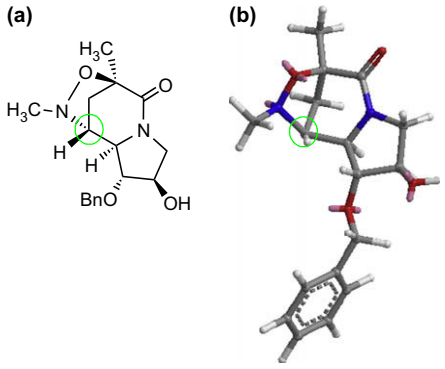
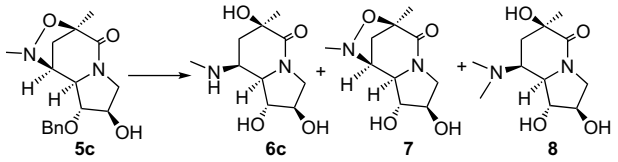


Figure 5. The supposed structure of **5b** (a) and its optimized conformation with minimum energy (b) by Chem3D Pro 10.0 calculation.



Scheme 5. *Conditions and reagents*: (i) $Pd(OH)_2$/C, H_2, MeOH, **6c**: 52.7%, **7**: 24.4%; **8**: 9.3%.

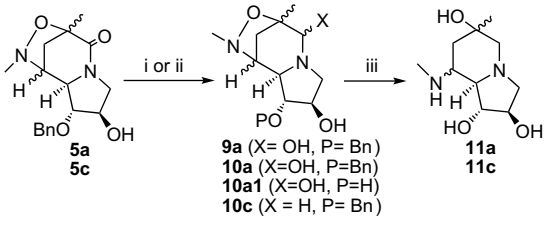
*3.2.1.1. Compound **3a**.* White solid, mp: 69–71 °C, $[\alpha]_D^{20}$ +3.91 (*c* 2.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.91 (t, *J*=7.4 Hz, 3H, CH_2CH_3), 1.49 (s, 3H, CH_3), 1.65 (m, 2H, CH_2CH_3), 2.42 (t, *J*=11.1 Hz, 1H, H-7a), 2.64 (s, 3H, N-CH_3), 2.71 (dd, *J*=13.2, 6.8 Hz, 1H, H-7b), 3.70–3.73 (m, 2H, H-2b, H-6), 3.94 (dd, *J*=12.4, 4.1 Hz, 1H, H-2a), 4.05 (m, 2H, CH_2O), 4.10 (s, 1H, H-4), 4.20 (m, 1H, H-3), 4.38 (d, *J*=2.3 Hz, 1H, H-5), 4.57 (s, 2H, $PhCH_2$), 6.32 (d, *J*=7.0 Hz, 1H, OH), 7.21–7.34 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 10.5, 22.1, 23.9, 42.9, 46.7, 56.5, 65.0, 67.8, 68.2, 72.1, 72.5, 82.4, 82.6, 116.4, 127.2–128.9, 137.6, 157.1, 174.3; HRMS (ESI): calcd for $C_{22}H_{29}F_3N_2O_6$ (M^+): 474.1978, found: 474.1983.

*3.2.1.2. Compound **3b**.* Colorless syrup, $[\alpha]_D^{20}$ −3.50 (*c* 3.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.87 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.15 (s, 3H, CH_3), 1.51–1.63 (m, 3H, H-7a, CH_2CH_3), 2.54 (s, 3H, N-CH_3), 3.19 (dd, *J*=11.1, 7.9 Hz, 1H, H-7b), 3.75 (d, *J*=11.1 Hz, 1H, H-2b), 3.86–3.90 (m, 2H, H-2a, H-6), 3.95 (s, 1H, H-4), 4.00 (m, 2H, OCH_2), 4.11 (s, 1H, H-3), 4.22 (d, 1H, *J*=3.8 Hz, H-5), 4.47 (d, *J*=11.8 Hz, 1H, $PhCH_2$), 4.61 (d, *J*=12.2 Hz, 1H, $PhCH_2$), 6.86 (s, 1H, OH), 7.22–7.28 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 10.6, 22.1, 23.4, 43.1, 48.2, 56.5, 65.6, 67.6, 69.4, 71.5, 72.3, 81.2, 84.2, 116.4, 128.4–129.0, 137.5, 157.2, 174.2; HRMS (ESI): calcd for $C_{22}H_{29}F_3N_2O_6$ (M^+): 474.1978, found: 474.1986.

*3.2.1.3. Compound **3c**.* Colorless syrup, $[\alpha]_D^{20}$ −8.53 (*c* 3.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.93 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.49 (s, 3H, CH_3), 1.69 (m, 2H, CH_2CH_3), 2.09 (dd, *J*=13.1, 8.7 Hz, 1H, H-7b), 2.75 (s, 3H, N-CH_3), 3.00 (dd, *J*=13.1, 7.2 Hz, 1H, H-7a), 3.49–3.56 (m, 2H, H-6, H-2a), 4.05–4.10 (m, 4H, H-2b, OCH_2, H-4), 4.26 (s, 1H, H-3), 4.37 (m, 1H, H-5), 4.58 (s, 2H, $PHCH_2$), 7.29–7.34 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 10.6, 22.3, 24.4, 40.8, 44.7, 53.7, 64.8, 67.1, 67.5, 72.1, 74.8, 82.2, 84.3, 116.5, 128.1–129.0, 138.1, 156.9, 175.2; HRMS (ESI): calcd for $C_{22}H_{30}F_3N_2O_6$ ($M+H^+$): 475.2050, found: 475.2056.

*3.2.2. Treatment of **3** with Zn/AcOH/H_2O (Scheme 3)*

A mixture of **3c** (538 mg, 1.14 mmol) and Zn (1.654 g, 25.3 mmol) in AcOH aqueous solution (30 mL, v_{AcOH}/v_{H_2O}=1:2) was stirred at 70 °C till the reactant disappeared on TLC. The



Scheme 6. *Conditions and reagents*: (i) $LiAlH_4$/THF, rt, **9a**: 91.8% (from **5a**); (ii) $LiAlH_4$/$AlCl_3$/THF, rt, **10a**: 41.5%, **10a1**: 54.7% (from **5a**), **10c**: 91.6% (from **5c**); (iii) $Pd(OH)_2$/C, H_2, MeOH/HCl, **11**: 90.2%–92.6% (from **9** or **10**).

solution was neutralized with $NaHCO_3$, filtered, and co-evaporated with toluene several times. The residue was extracted with CH_2Cl_2, concentrated, and then purified by chromatography (petroleum ether/ethyl acetate v/v=1:5) to afford **5c** (211 mg, 58.2%) as a white solid. The single crystal for X-ray analysis was obtained from ethyl acetate/hexane solution.

Following the same procedure, the cycloadduct **3a** (355 mg, 0.75 mmol) and **3b** (150 mg, 0.32 mmol) were treated, and **5a** (white solid, 158 mg, 66.2%) and **4b** (colorless syrup, 37 mg, 27.8%) were obtained, respectively.

*3.2.2.1. Compound **5a**.* White solid, mp: 142–144 °C, $[\alpha]_D^{25}$ +94.40 (*c* 2.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$), δ: 1.51 (s, 3H, CH_3), 2.12 (d, *J*=12.4 Hz, 1H, 7-Ha), 2.31 (dd, *J*=12.4, 4.3 Hz, 1H, 7-Hb), 2.73 (s, 3H, N-CH_3), 3.35 (dd, *J*=12.9, 6.1 Hz, 1H, 2-Hb), 3.42 (s, 1H, 6-H), 3.57 (d, *J*=6.6 Hz, 1H, 5-H), 3.75 (d, *J*=7.8 Hz, 1H, 4-H), 3.95 (d, *J*=12.7 Hz, 1H, 7-Ha), 4.33 (s, 1H, 3-H), 4.59 (d, *J*=11.8 Hz, 1H, $PhCH_2$), 4.81 (d, *J*=11.8 Hz, 1H, $PhCH_2$), 7.28–7.40(m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 19.0, 34.5, 47.3, 51.5, 63.4, 66.7, 69.1, 72.8, 75.0, 81.9, 85.5, 125.6–129.0, 138.1, 171.3; HRMS (ESI): calcd for $C_{17}H_{22}N_2O_4Na$ ($M+Na^+$): 341.1472, found: 341.1480.

*3.2.2.2. Compound **4b**.* Colorless syrup, $[\alpha]_D^{30}$ +13.61 (*c*, 2.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$), δ: 1.43 (s, 3H, CH_3), 2.03 (dd, *J*=14.7, 3.1 Hz, 1H, 7-H), 2.37 (dd, *J*=14.7, 9.5 Hz, 1H, 7-H), 2.88 (s, 3H, N-CH_3), 3.82 (d, *J*=11.9 Hz, 1H, 2-H), 4.03 (dd, *J*=12.0, 5.2 Hz, 1H, 2-H), 4.25 (s, 1H, 5-H), 4.42 (s, 1H, 3-H), 4.56 (m, 2H, 6-H, 4-H), 4.70 (s, 2H, $PhCH_2$), 7.25–7.39 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 23.4, 37.2, 31.3, 54.2, 57.7, 70.3, 71.6, 73.6, 73.8, 83.0, 116.4, 128.3–129.0, 137.9, 157.5, 177.5; HRMS (ESI): calcd for $C_{19}H_{23}F_3N_2O_5$ (M+): 416.1559, found: 416.1566.

*3.2.2.3. Compound **5c**.* White solid, mp: 155–156 °C, $[\alpha]_D^{26}$ −24.03 (*c* 2.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$), δ: 1.53 (s, 3H, CH_3), 2.33 (d, *J*=12.0 Hz, 1H, 7-Ha), 2.40 (dd, *J*=12.0, 6.0 Hz, 1H, 7-Hb), 2.68 (s, 3H, N-CH_3), 3.29 (dd, *J*=12.3, 3.5 Hz, 1H, 2-Ha), 3.39 (d, *J*=5.7 Hz, 1H, 6-H), 3.62 (s, 1H, 5-H), 3.83 (s, 1H, 4-H), 4.04 (d, *J*=12.3 Hz, 1H, 2-Hb), 4.15 (s, 1H, 5-H), 4.56 (d, *J*=11.8 Hz, 1H, $PhCH_2$), 4.71 (d, *J*=11.8 Hz, 1H, $PhCH_2$), 7.27–7.39 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 17.3, 38.6, 52.4, 63.7, 69.1, 72.6, 72.9, 81.0, 85.8, 128.2–129.0, 138.0, 169.7; HRMS (ESI): calcd for $C_{17}H_{23}N_2O_4$ ($M+H^+$): 319.1652, found: 319.1657.

*3.2.3. Treatment of **3** with NaOH/MeOH/H_2O (Scheme 4)*

The cycloadduct **3c** (317 mg, 0.67 mmol) was dissolved in MeOH (3.0 mL), to the solution was added NaOH aqueous solution (0.2 mol/L, 3 mL) with stirring. After the reaction completed within 1 h, the solution was acidified with diluted HCl solution (0.2 mol/L) to pH≈2, and then was stirred for 10 min at room temperature. The solution was neutralized with aqueous $NaHCO_3$ to pH≈7, concentrated in vacuo, and extracted with CH_2Cl_2. The organic solution was dried and concentrated. The residue was purified by column chromatography (petroleum ether/ethyl acetate v/v=1:5) to give **5c** (191 mg, 89.6%) as a white solid.

Similarly, 423 mg (91.1%) of **5a** was obtained as a white solid from 694 mg (1.46 mmol) of **3a**.

*3.2.4. Catalytic hydrogenation of **5** in the presence of hydrochloric acid (Scheme 4)*

A mixture of compound **5c** (213 mg, 0.67 mmol), $Pd(OH)_2/C$ (105 mg), and concentrated hydrochloric acid (60 μL, 0.7 mmol) in methanol (10 mL) was stirred under the atmospheric pressure of hydrogen for 2 h. After the reaction was complete, 0.5 g of solid $NaHCO_3$ was added to neutralize the acid, and the solid was removed by filtration through Celite. The filtrate was evaporated to give white solid, which was purified by silica gel column chromatography (ethyl acetate/methanol v/v=5:1 then 3:1) to give **6c** (143 mg, 92.8%) as a white solid.

Following the same procedure, the hydrogenation of **5a** (134 mg, 0.42 mmol) afforded **6a** (87 mg, 90.0%) as a white solid.

For cycloadduct **3b**, the above treatments were combined as follows: A solution of **3b** (392 mg, 0.83 mmol) in MeOH (4.0 ml) and 0.2 mol/L aqueous NaOH solution (4 ml) was stirred for 1 h and acidified with diluted HCl solution (0.2 mol/L) to pH≈2. The solution was again stirred for 10 min, neutralized with aqueous $NaHCO_3$ to pH≈7, concentrated in vacuo, and co-evaporated with toluene several times. The residue was extracted with MeOH (5 mL) two times. The resulting solution was hydrogenated in the presence of $Pd(OH)_2/C$ (92 mg) and concentrated hydrochloric acid (50 μL, 0.58 mmol). After usual work-up and chromatographic purification (ethyl acetate/methanol v/v=3:1), **6b** (144 mg, 75.4%) was obtained as a white solid.

*3.2.4.1. Compound **6a**.* White solid, mp: 75–77 °C, $[\alpha]_D^{25}$ −17.51 (*c* 2.0, MeOH); ^1H NMR (400 MHz, CD_3OD), δ: 1.43 (s, 3H, CH_3), 2.04 (dd, *J*=13.8, 8.1 Hz, 1H, 7-Ha), 2.23 (dd, *J*=13.8, 4.9 Hz, 1H, 7-Hb), 2.67 (s, 3H, N-CH_3), 3.36 (m, 1H, 2-Hb), 3.41 (dd, *J*=12.5, 5.5 Hz, 1H, 6-H), 3.58 (t, *J*=7.7 Hz, 1H, 5-H), 3.64 (dd, *J*=12.5, 2.2 Hz, 1H, 2-Ha), 3.97 (t, *J*=7.2 Hz, 1H, 4-H), 4.13 (dd, *J*=12.7, 5.7 Hz, 1H, 3-H); ^{13}C NMR (CD_3OD), δ: 25.5, 31.7, 39.1, 50.0, 56.5, 64.2, 70.5, 74.0, 80.6, 172.5; HRMS (ESI): calcd for $C_{10}H_{19}N_2O_4$ ($M+H^+$): 231.1339, found: 231.1347.

*3.2.4.2. Compound **6b**.* White solid, mp: 204–206 °C, $[\alpha]_D^{25}$ +16.10 (*c* 2.4, MeOH); ^1H NMR (400 MHz, D_2O), δ: 1.30 (s, 3H, CH_3), 2.18 (dd, *J*=14.7, 2.6 Hz, 1H, 7-Hb), 2.32 (dd, *J*=14.5, 8.7 Hz, 1H, 7-Ha), 2.82 (s, 3H, N-CH_3), 3.57 (d, *J*=12.9 Hz, 1H, 2-Ha), 3.42 (dd, *J*=12.4, 4.2 Hz, 1H, 2-Hb), 3.78 (t, *J*=3.8 Hz, 1H, 5-H), 4.06–4.08 (m, 2H, 6-H, 4-H), 4.23 (t, *J*=1.4 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, CD_3OD), δ: 21.8, 27.8, 35.2, 51.5, 57.3, 66.0, 72.8, 75.4, 77.3, 176.1; HRMS (ESI): calcd for $C_{10}H_{19}N_2O_4$ ($M+H^+$): 231.1339, found: 231.1342.

*3.2.4.3. Compound **6c**.* White solid, mp: 163–165 °C, $[\alpha]_D^{24}$ −18.11 (*c* 1.0, MeOH); ^1H NMR (400 MHz, CD_3OD), δ: 1.37 (s, 3H, CH_3), 1.96 (d, *J*=15.1 Hz, 1H, 7-Ha), 2.38 (dd, *J*=15.0, 3.6 Hz, 1H, 7-Hb), 2.53 (s, 3H, N-CH_3), 3.16 (d, *J*=3.03 Hz, 1H, 2-Ha), 3.48 (dd, *J*=11.6, 4.0 Hz, 1H, 6-H), 3.62 (m, 2H, 5-H, 2-H), 4.06 (m, 2H, 4-H, 3-H); ^{13}C NMR (100 MHz, CD_3OD), δ: 26.0, 33.9, 37.9, 50.3, 53.2, 67.4, 70.2, 73.7, 76.3, 172.5; HRMS (ESI): calcd for $C_{10}H_{19}N_2O_4$ ($M+H^+$): 231.1339, found: 231.1344.

*3.2.5. Catalytic hydrogenation of **5c** in the absence of hydrochloric acid (Scheme 5)*

A mixture of compound **5c** (151 mg, 0.47 mmol), $Pd(OH)_2/C$ (98 mg) in methanol (10 mL) was stirred under the atmospheric pressure of hydrogen for 8 h. The catalyst was removed by filtration through Celite and the filtrate was evaporated to give white solid, which was purified by silica gel column chromatography (ethyl acetate/methanol v/v=5:1 then 3:1) to provide **6c** (57 mg, 52.7%), the N–O bond remaining intermediate **7** (28 mg, 26.0%), and the methylated derivative **8** (10 mg, 8.7%) as white solids, probably because the newly generated amine group in **6c** lowered the activity of the palladium catalyst by poisoning.

*3.2.5.1. Compound **7**.* White solid, mp: 171–172 °C, $[\alpha]_D^{24}$ −41.71 (*c* 1.0, MeOH); ^1H NMR (400 MHz, CD_3OD), δ: 1.45 (s, 3H, CH_3), 2.36 (d, *J*=12.1 Hz, 1H, 7-Ha), 2.51 (dd, *J*=12.1, 6.0 Hz, 1H, 7-Hb), 2.74 (s, 3H, N-CH_3), 3.30 (m, 2H, 2-Ha, 6-H), 3.42 (dd, *J*=8.7, 2.1 Hz, 1H, 5-H), 3.57 (m, 1H, 2-H), 4.08 (m, 2H, 4-H, 3-H); ^{13}C NMR (100 MHz, CD_3OD), δ: 16.2, 29.7, 37.8, 46.6, 49.5, 61.8, 67.2, 74.6, 75.5, 80.4, 170.1; HRMS (ESI): calcd for $C_{10}H_{16}N_2O_4Na$ ($M+Na^+$): 251.1002, found: 251.1008.

*3.2.5.2. Compound **8**.* White solid, mp: 177–178 °C, $[\alpha]_D^{24}$ −13.97 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, D_2O), *δ*: 1.31 (s, 3H, CH_3), 2.20 (dd, *J*=15.9, 6.4 Hz, 1H, 7-Ha), 2.28 (dd, *J*=15.9, 4.2 Hz, 1H, 7-Hb), 2.5 (s, 6H, N-CH_3), 3.23 (dd, *J*=12.5, 6.7 Hz, 1H, 2-Ha), 3.65 (m, 2H, 5-H, 6-H), 3.81 (dd, *J*=8.1, 4.4 Hz, 1H, 2-H), 4.11 (m, 2H, 4-H, 3-H); ^{13}C NMR (100 MHz, CD_3OD), *δ*: 28.3, 34.5, 42.8, 49.9, 56.7, 65.2, 69.5, 73.9, 76.3, 174.5; HRMS (ESI): calcd for $C_{11}H_{21}N_2O_4$ ($M+H^+$): 245.1496, found: 245.1502.

*3.2.6. Reduction of **5** with $LiAlH_4$ in THF solution (Scheme 6, conditions A)*

To a solution of compound **5a** (150 mg, 0.47 mmol) in THF (2 mL) was added $LiAlH_4$ (30 mg, 0.79 mmol) with stirring under N_2 at room temperature. After 2 h ethyl acetate (0.5 mL) was added dropwise and the resulting mixture was evaporated in vacuo. The residue was applied to silica gel column chromatography (petroleum ether/ethyl acetate v/v=1:5) to give **9a** (138 mg, 91.8%) as a colorless syrup.

Similarly, the reduction of **5c** (172 mg, 0.54 mmol) with $LiAlH_4$ provided the corresponding **9c**, which, after work-up, was directly used in the next step of catalytic hydrogenation to afford the target compound **11c** (105 mg) in 90.0% yield (two steps) as a white solid.

*3.2.6.1. Compound **9a**.* White solid, mp: 115–116 °C, $[\alpha]_D^{29}$ +42.42 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), *δ*: 1.34 (s, 3H, CH_3), 1.68 (dd, *J*=11.8, 4.3 Hz, 1H, 7-Ha), 2.22 (dd, *J*=16.6, 4.3 Hz, 1H, 7-Hb), 2.73 (s, 3H, N-CH_3), 2.71–2.77 (br m, 1H, 2-Ha), 3.00 (d, *J*=10.4 Hz, 1H, 2-H), 3.18 (d, *J*=4.0 Hz, 1H, 6-H), 3.28 (d, *J*=4.3 Hz, 1H, 5-H), 3.46 (s, 1H, 4-H), 4.21 (s, 1H, 3-H), 4.38 (s, 1H, 9-H), 4.50 (dd, *J*=14.5, 11.9 Hz, 2H, $PhCH_2$), 7.29–7.38 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$), *δ*: 21.0, 30.3, 47.6, 58.4, 64.0, 68.8, 72.2, 76.1, 80.9, 81.3, 97.0, 128.1–129.0, 138.1; HRMS (ESI): calcd for $C_{17}H_{24}N_2O_4$ (M^+): 320.1736, found: 320.1741.

*3.2.7. Reduction of **5** with $LiAlH_4$ in THF solution in the presence of $AlCl_3$ (Scheme 6, conditions B)*

To a solution of compound **5c** (178 mg, 0.56 mmol) in THF (5 mL) were added $LiAlH_4$ (212 mg, 5.59 mmol) and anhydrate $AlCl_3$ (224 mg, 1.68 mmol) with stirring under N_2 at room temperature. After 2 h, ethyl acetate (2 mL) was added dropwise, the solution was neutralized to pH≈7 with 1 mol/L aqueous NaOH solution, and evaporated in vacuo. The residue was applied to silica gel column chromatography (petroleum ether/ethyl acetate v/v=1:5) to give **10c** (156 mg, 91.6%) as a colorless syrup.

Following the same procedure, the **5a** (170 mg, 0.53 mmol) was reduced with $LiAlH_4$ (84 mg, 2.2 mmol) in the presence of $AlCl_3$ (88 mg, 0.66 mmol) to afford a white solid of **10a** (66 mg, 41.0%) and the debenzylated **10a1** (62 mg, 54.7%) as a colorless syrup.

*3.2.7.1. Compound **10a**.* White solid, mp: 115–117 °C, $[\alpha]_D^{30}$ +59.27 (*c* 2.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD), *δ*: 1.32 (s, 3H, CH_3), 2.11 (s, 2H, 9-H), 2.63 (s, 3H, N-CH_3), 2.88 (d, *J*=11.4 Hz, 1H, 7-H), 2.94 (d, *J*=12.2 Hz, 1H, 2-H), 3.04 (d, *J*=11.4 Hz, 1H, 7-H), 3.25 (d, *J*=5.4 Hz, 1H, 2-H), 3.30 (m, 1H, 6-H), 3.43 (s, 1H, 5-H), 3.87 (d, *J*=7.0 Hz, 1H, 4-H), 4.35 (dd, *J*=3.4, 2.1 Hz, 1H, 3-H), 4.57 (d, *J*=11.7 Hz, 1H, $PhCH_2$), 4.75 (d, *J*=11.7 Hz, 1H, $PhCH_2$), 7.27–7.36 (m, 5H, ArH); ^{13}C NMR (100 MHz, CD_3OD), *δ*: 21.3, 33.6, 46.3, 60.1, 61.4, 64.7, 70.7, 72.3, 77.5, 80.7, 87.8, 127.9–128.5, 138.5; HRMS (ESI): calcd for $C_{17}H_{24}N_2O_3$ (M^+): 304.1787, found: 304.1790.

*3.2.7.2. Compound **10a1**.* Colorless syrup, $[\alpha]_D^{31}$ +5.74 (*c* 2.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD), *δ*: 1.40 (s, 3H, CH_3), 2.34 (s, 2H, 9-H), 2.73 (s, 3H, N-CH_3), 3.21 (d, *J*=6.5 Hz, 1H, 7-H), 3.25 (d, *J*=5.9 Hz, 1H, 7-H), 3.44 (d, *J*=12.2 Hz, 1H, 2-H), 3.57 (dd, *J*=7.6, 2.5 Hz, 1H, 6-H), 3.63 (dd, *J*=12.9, 5.8 Hz, 1H, 2-H), 3.79 (s, 1H, 5-H), 4.23 (d, *J*=7.6 Hz, 1H, 4-H), 4.28 (d, *J*=5.8 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, CD_3OD), *δ*: 20.6, 33.2, 46.2, 59.3, 61.1, 63.3, 72.8, 77.6, 78.5, 79.3; HRMS (ESI): calcd for $C_{10}H_{19}N_2O_3$ ($M+H^+$): 215.1390, found: 215.1396.

*3.2.7.3. Compound **10c**.* Colorless syrup, $[\alpha]_D^{27}$ +11.89 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$), *δ*: 1.33 (s, 3H, CH_3), 1.88 (d, *J*=11.6 Hz, 1H, 7-H), 2.25 (ddd, *J*=11.6, 5.6, 1.9 Hz, 1H, 7-H), 2.63 (s, 3H, N-CH_3), 2.68 (d, *J*=12.7 Hz, 1H, 2-H), 2.78 (d, *J*=12.8 Hz, 1H, 2-H), 2.92 (d, *J*=2.2 Hz, 1H, 6-H), 3.13 (d, *J*=10.4 Hz, 1H, 9-H), 3.18 (d, *J*=5.5 Hz, 1H, 5-H), 3.46 (dd, *J*=10.4, 6.0 Hz, 1H, 9-H), 3.81 (s, 1H, 4-H), 4.14 (d, *J*=5.8 Hz, 1H, 3-H), 4.56 (d, *J*=12.0 Hz, 1H, $PhCH_2$), 4.70 (d, *J*=12.0 Hz, 1H, $PhCH_2$), 7.27–7.34 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$), *δ*: 21.5, 40.3, 47.3, 60.0, 63.2, 65.0, 68.8, 72.0, 74.8, 81.4, 89.3, 128.1–128.8, 138.6; HRMS (ESI): calcd for $C_{17}H_{24}N_2O_3$ (M^+): 304.1787, found: 304.1795.

*3.2.8. Catalytic hydrogenation of **9** and **10** in the presence of hydrochloric acid (Scheme 6)*

A mixture of compound **9a** (125 mg, 0.39 mmol), $Pd(OH)_2/C$ (48 mg), and concentrated hydrochloric acid (20 μL, 0.23 mmol) in methanol (3 mL) was stirred under the atmospheric pressure of hydrogen for 2 h. After the reaction complete, 0.2 g of solid $NaHCO_3$ was added for neutralization, and the solid was removed by filtration through Celite. The filtrate was evaporated in vacuo and the residue was purified by silica gel column chromatography (ethyl acetate/methanol v/v=1:1) to afford the amino polyhydroxylated indolizidine **11c** (76 mg, 90.2%) as a white solid.

Following the same procedure, compounds **10a**, **10a1**, and **10c** were hydrogenated to afford the corresponding amino polyhydroxylated indolizidine **11a**, **11a**, and **11c** as white solids in yields of 91.2%, 92.3%, and 92.6%, respectively.

*3.2.8.1. Compound **11a**.* White solid, mp: 119–120 °C, $[\alpha]_D^{29}$ −8.71 (*c* 2.6, MeOH); ^{1}H NMR (400 MHz, D_2O), *δ*: 1.19 (s, 3H, CH_3), 1.38 (t, *J*=12.1 Hz, 1H, 9-H), 1.93 (d, *J*=14.7 Hz, 1H, 6-H), 1.98 (d, *J*=10.0 Hz, 1H, 9-H), 2.11 (dd, *J*=12.1, 3.8 Hz, 1H, 9-H), 2.60 (s, 3H, N-CH_3), 2.57–2.61 (m, 1H, 2-H), 2.70 (d, *J*=10.6 Hz, 1H, 7-H), 2.76 (dd, *J*=11.1, 4.2 Hz, 1H, 2-H), 3.17 (m, 1H, 5-H), 3.86 (dd, *J*=7.9, 2.7 Hz, 1H, 4-H), 3.96 (m, 1H, 3-H); ^{13}C NMR (100 MHz, D_2O), *δ*: 25.9, 30.6, 39.2, 57.4, 60.7, 62.6, 69.7, 69.8, 77.2, 81.9; HRMS (ESI): calcd for $C_{10}H_{21}N_2O_3$ ($M+H^+$): 217.1547, found: 217.1552.

*3.2.8.2. Compound **11c**.* White solid, mp: 63–65 °C, $[\alpha]_D^{28}$ +4.39 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, D_2O), *δ*: 1.18 (s, 3H, CH_3), 1.62 (d, *J*=15.5 Hz, 1H, 9-H), 2.17 (d, *J*=12.1 Hz, 1H, 7-H), 2.24 (d, *J*=16.2 Hz, 1H, 9-H), 2.31 (d, *J*=7.8 Hz, 1H, 2-H), 2.66 (t, *J*=10.3 Hz, 1H, 7-H), 2.74 (s, 3H, N-CH_3), 2.89 (s, 1H, 6-H), 2.92 (s, 1H, 2-H), 3.49 (s, 1H, 5-H), 4.02 (d, *J*=8.3 Hz, 1H, 4-H), 4.09 (d, *J*=6.3 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, D_2O) *δ*: 27.1, 32.4, 34.5, 54.6, 60.0, 63.3, 69.8, 70.1, 76.1, 77.7; HRMS (ESI): calcd for $C_{10}H_{21}N_2O_3$ ($M+H^+$): 217.1547, found: 217.1551.

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