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Synthesis of polyhydroxylated 7-aminopyrrolizidines and 8-aminoindolizidines

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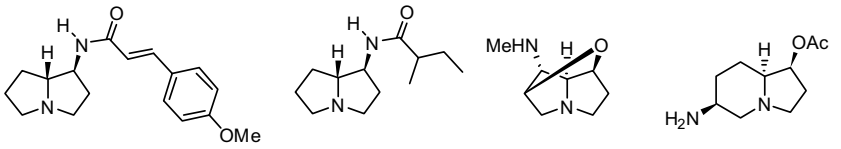
ABSTRACT

The ammonolysis of a lactone moiety in tricyclic cycloadducts derived from non-racemic five-membered cyclic nitrone and 2(5*H*)-furanones furnishes an amido function, which after subsequent Hofmann rearrangement, leads to a protected amino group attached to the bicyclic isoxazolidine skeleton. A successive simple transformation, involving cleavage of N–O bond followed by intramolecular N-alkylation, provides an access to the polyhydroxylated 7-aminopyrrolizidines and 8-aminoindolizidines, potential glycosidases inhibitors.

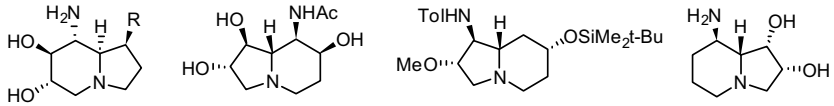
1. Introduction

Compounds containing the amino-pyrrolizidine and amino-indolizidine motifs are widespread in nature.[1,2] Their potential bioactivity as antidepressant, analgesic, antiviral, antibacterial, or antitumor agents makes them a particularly attractive synthetic target for academic and industrial research laboratories. This trend can be exemplified by the recent reports of syntheses of absouline **1** and its geometric isomer **2**,[3] laburnamine **3**,[4] loline **4**,[5] and slafr-amine **5**.[2h,m]

Although, there are numerous strategies applicable to the synthesis of simple amino-pyrrolizidine and amino-indolizidine alkaloids,[2g,h,m,6] examples reporting preparation of their polyhydroxylated analogues, such as amino-iminosugars, are limited.[7–12] The indolizidines **6** and **7** were synthesized by Tyler and co-workers through modification of the castanospermine structure.[7]



1 *E*-isomer, absouline
2 *Z*-isomer, isoabsouline
3 laburnamine
4 loline
5 slaframine



6 R: OH
8 R: H
7
9
10

On the other hand, Pandey and co-workers[8] synthesized the 1-deoxy derivative of **6** (**8**) via a photoinduced electron transfer radical cyclization of pyrrolidine with a chiral acetylene derived from tartaric acid. It is noteworthy, that compound **8** is a weak inhibitor of almonds' β-glucosidase, whereas alkaloid **6** displays no activity. Recently, Alcaide and Almendros[9] presented the asymmetric synthesis of highly functionalized indolizidine systems based on the combination of the aza-Diels–Alder reaction of

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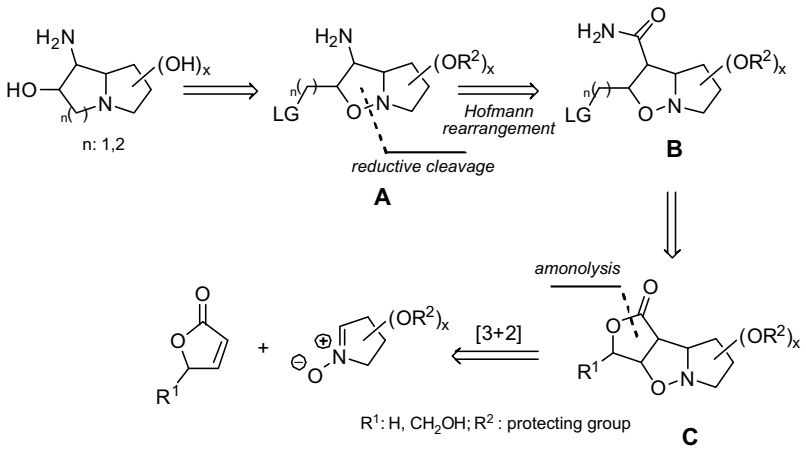


Scheme 1.

2-azetidinone-tethered imines and subsequent rearrangement of the 2-azetidinone ring. Following this strategy, compound **9** and its 8a-epimer were obtained.[9] A similar synthetic approach has also been applied for the synthesis of 7-amino-indolizidine derivatives.[10] Another example of amino-iminosugar is the amino analogue of swansonine (**10**) synthesized by Hashimoto and coworkers.[11]

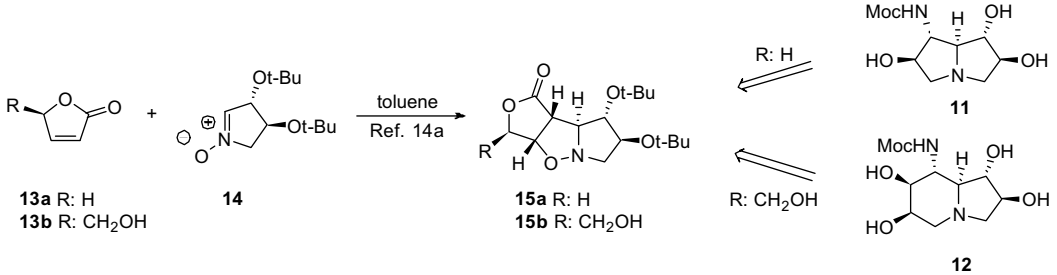
Recognizing the potential of unexplored biological activity of amino-iminosugars[7] and our ongoing research program directed at the search for novel glycomimetics,[8] we have developed an attractive strategy of the synthesis for 7-amino-pyrrolizidines and 8-amino-indolizidines. In contrast to the known literature protocols[7,8] of amino-iminosugars synthesis, the amino function is introduced at the early stage of the synthesis, prior to the formation of the pyrrolizidine or indolizidine skeleton. The general approach is depicted in Scheme 1. Both types of amino alkaloids can be obtained from the amino-isoxazolidine **A** by N–O bond cleavage, followed by intramolecular N-alkylation. The aminoisoxazolidine **A** can be derived from the amide **B**. The attractive precursor of **B** is the cycloadduct **C** easily accessible by the 1,3-dipolar cycloaddition reaction between a five-membered cyclic nitrone and 2(5*H*)-furanone. The cycloaddition step is the most important for the entire synthesis because of the formation of three new stereogenic centers. The proper selection of cycloaddition components enables the formation of the initial cycloadduct with a high diastereoselectivity[14] and provides an entry to the stereocontrolled synthesis of a highly functionalized amino-azabicycloalkanes.

2. Results and discussion

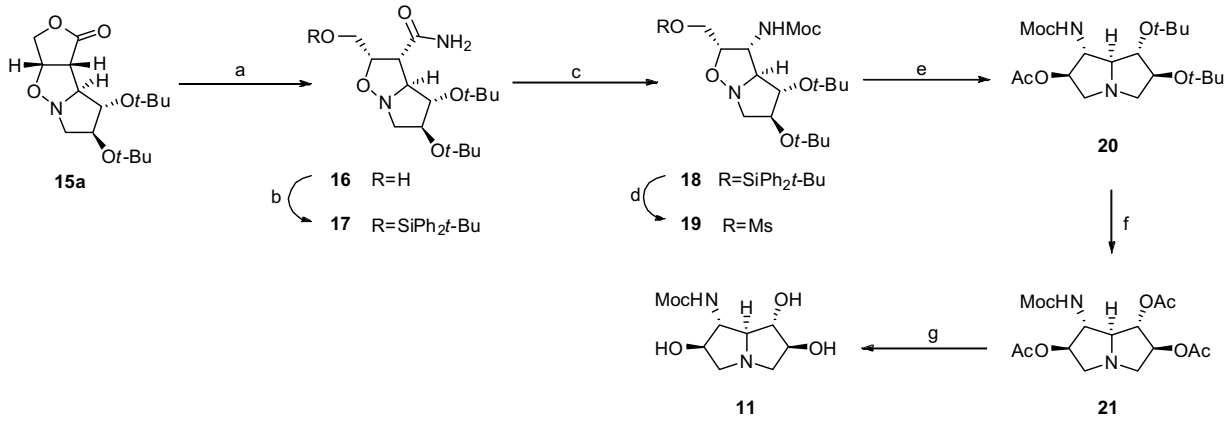
To demonstrate the applicability of our methodology, we synthesized the amino-iminosugars **11** and **12** that belong to the pyrrolizidine and indolizidine groups, respectively (Scheme 2). These compounds may also be regarded as potential glycosidase inhibitors.

The synthesis of **11** was carried out following the steps shown in Scheme 3. The cycloadduct **15a** was obtained as a single product by the 1,3-dipolar cycloaddition between nitrone **14** and lactone **13a**, following the protocol developed in our group.[14a] Treatment of lactone **15a** with ammonia gave amide **16** in 75% yield. Initially, the 7 N solution of ammonia in methanol was used. However, during the scale-up optimization steps, it was found that a better result could be obtained when the lactone, dissolved in small amount of MeOH, is treated with liquid ammonia. After opening of the lactone moiety, the free hydroxy group in **16** was silylated immediately to avoid a re-cyclization process leading back to the starting lactone. The protection of the hydroxyl group also prevents the intramolecular cyclization, which may occur during the next step (Hofmann rearrangement). The treatment of the amide **17** with $PhI(OAc)_2$ in MeOH,[15] led to the Hofmann rearrangement with the retention of configuration at C-3 and the methoxycarbonyl protected amine **18** was obtained in 80% yield. The configuration at C-3 in **18** was proved by $J_{2,3}$=6.3 Hz and spin–spin interaction between H-2 and H-3 protons (NOE). Unfortunately, this protocol worked only when the reaction was carried out in MeOH leading to the *N*-Moc derivative. Replacement of MeOH by *t*-BuOH or BnOH failed, and the starting material was recovered. The analogous procedure involving $PhI(CF_3COO)_2$ in acetonitrile/water mixture did not succeed either.[16] On the other hand, the standard Hofmann rearrangement conditions (RONa or NaOH, Br_2 in ROH) caused the decomposition of the substrate. Similarly, the other protocol, involving treatment of **17** with $Pb(OAc)_4$ in DMF in presence of *t*-BuOH[17] was not successful.

The desilylation of **18** with tetrabutylammonium fluoride in THF followed by mesylation led to the mesylate **19**, which was hydrogenated under atmospheric pressure in the presence of palladium on charcoal. The resulted pyrrolizidine was isolated as the acetate **20**. Subsequently, the *tert*-butyl protection in **20** was removed by treatment with trifluoroacetic acid and both hydroxy groups were acetylated to give **21**, which was easily purified by chromatography.



Scheme 2.



Scheme 3. Reactants and conditions: (a) NH_3 (liquid), MeOH, rt, 75%; (b) *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, −15 °C then rt, 91%; (c) $PhI(OAc)_2$, MeOH, rt, 80%; (d) i. TBAF, THF, rt, ii. MsCl, Et_3N, CH_2Cl_2, −15 °C then rt; (e) i. H_2, Pd/C, AcOEt/MeOH (4:1), rt; ii. Ac_2O, Et_3N, 0 °C then rt, 65% (4 steps); (f) i. CF_3COOH, rt; ii. Ac_2O, Et_3N, 0 °C then rt, 79% (2 steps); (g) 1% NH_3 in MeOH, rt, 85%.

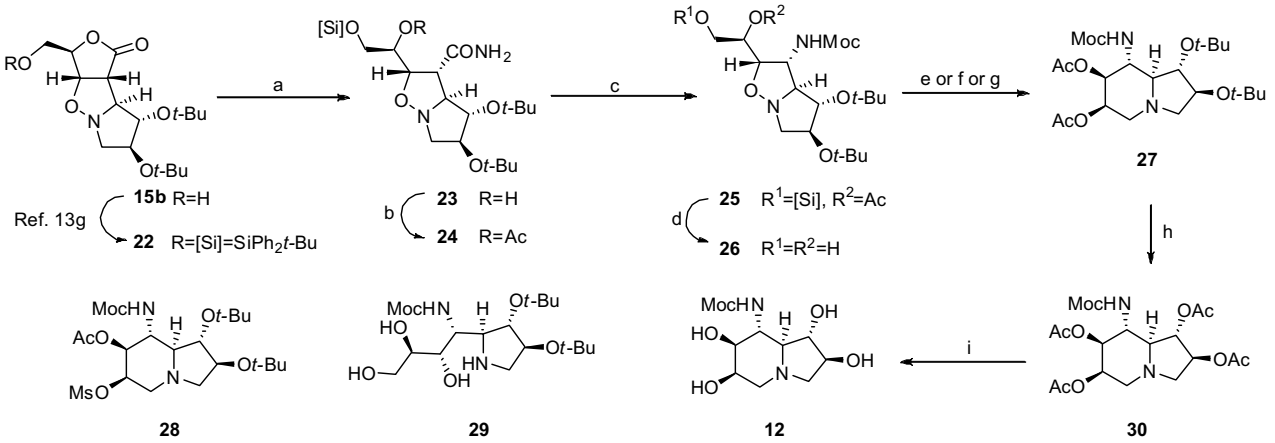
The final deacetylation using a protocol well established by our group[13] (1% NH_3 in MeOH) gave the desired amino-pyrrolizidine **11** in 24% overall yield.

The synthesis of indolizidine **12** is shown in Scheme 4. The starting **15b** was obtained by the cycloaddition of nitrone **14** and lactone **13b** according to the reported procedure.[14a] After protection of the free hydroxy group in **15b** with a *tert*-butyldiphenylsilyl group,[13g] the lactone **22** was treated with liquid ammonia. Next, the free hydroxyl group in **23** was immediately protected to avoid the re-cyclization process. According to the planned synthetic sequence, the benzyl group was chosen as the most attractive protection, which could be easily removed during hydrogenolysis of the N–O bond step. The standard benzylation of **23**, however, did not succeed and only the re-cyclization product **15b** was formed with further N-benzylation and decomposition.[13h] On the other hand, the benzylation carried out under neutral conditions by treatment with Dudley's reagent[13h,18] did not proceed as expected and the starting material was recovered. Finally, this problem was resolved by acetylation of hydroxyl group in **23**, which led to the amide **24** in 91% yield.

The Hofmann rearrangement carried out with **24** and $PhI(OAc)_2$ in MeOH led to the *N*-Moc protected amine **25** in 83% yield. As for **18**, the configuration at C-3 in **25** was proved by $J_{2,3}$=4.4 Hz and spin–spin interaction between H-2 and H-3 protons (NOE). The presence of acetyl protection at the C-1′ hydroxyl group forced a revision of the original cyclization strategy leading to the indolizidine skeleton. Initially, desilylation of the primary hydroxyl group followed by its mesylation was planned. In the case of **25**, however, to avoid the unwanted migration of the acetyl group from the secondary hydroxyl to the primary one, the desilylation, and deacetylation sequence were performed to provide diol **26** in 80% yield.

Subsequently, diol **26** was submitted to the reaction sequence leading to formation of the indolizidine skeleton. The mesylation using 1 equiv of MsCl, followed by hydrogenolysis and acetylation gave the desired indolizidine **27** in 62% yield but with a low purity. Additionally, a small quantity of compound **28** was isolated as a by-product. This compound, derived from the dimesylate of diol **26**, was not stable, and underwent decomposition within a few days. Because of the unsatisfactory result of the presented transformations, several alternate strategies of cyclization were considered.

An alternative approach assumed a reductive cleavage of the N–O bond in **26** followed by the intramolecular cyclization under Mitsunobu conditions. Unexpectedly, this bond turned out to be relatively strong and hydrogenolysis under standard conditions did not proceed at all (Pd/C, H_2, 1.5 bar). Another reduction method, involving the treatment with zinc in acetic acid[19] also failed. Finally, when hydrogenolysis was carried out under elevated pressure (Pd/C in EtOH, 60 bar) the desired aminoalcohol **29** was obtained, albeit only in a 50% yield after 7 days. The subsequent Mitsunobu reaction



Scheme 4. Reagents and conditons: (a) NH_3 (liquid), MeOH, rt, 70%; (b) Ac_2O, Et_3N, 0 °C then rt, 91%; (c) $PhI(OAc)_2$, MeOH, rt, 83%; (d) i. TBAF, THF, rt, ii. 1% NH_3 in MeOH, rt, 80%; (e) i. CBr_4, PPh_3, CH_2Cl_2, 0 °C then rt, ii. H_2, Pd/C, EtOH, iii. Ac_2O, Et_3N, 0 °C then rt, 70% (3 steps); (f) MsCl, Et_3N, CH_2Cl_2, ii. H_2, Pd/C, EtOH, iii. Ac_2O, Et_3N, 0 °C then rt, 62% (3 steps); (g) H_2, Pd/C, 60 bar, EtOH, ii. DEAD, PPh_3, THF, iii. Ac_2O, Et_3N, 0 °C then rt, 10% (3 steps); (h) i. CF_3COOH, rt, ii. Ac_2O, Et_3N, 0 °C rt, 86% (2 steps); (i) 1% NH_3 in MeOH, rt, 75%.

with **29** followed by the acetylation gave a poor yield of **27** (less then 20%, overall after 3 steps 10%).

The best yield of **27** was achieved applying the third alternate cyclization strategy involving the Appel reaction followed by hydrogenolysis and acetylation. Here, the desired indolizidine **27** was obtained in a 70% yield (3 steps) and with a high purity.

Subsequently, the *tert*-butyl groups were removed by treatment with CF_3COOH and the product was isolated after acetylation as compound **30**. The final deacetylation was carried out as previously described (1% NH_3 in MeOH) affording the target indolizidine **12** in a 19% overall yield starting from **15b**.

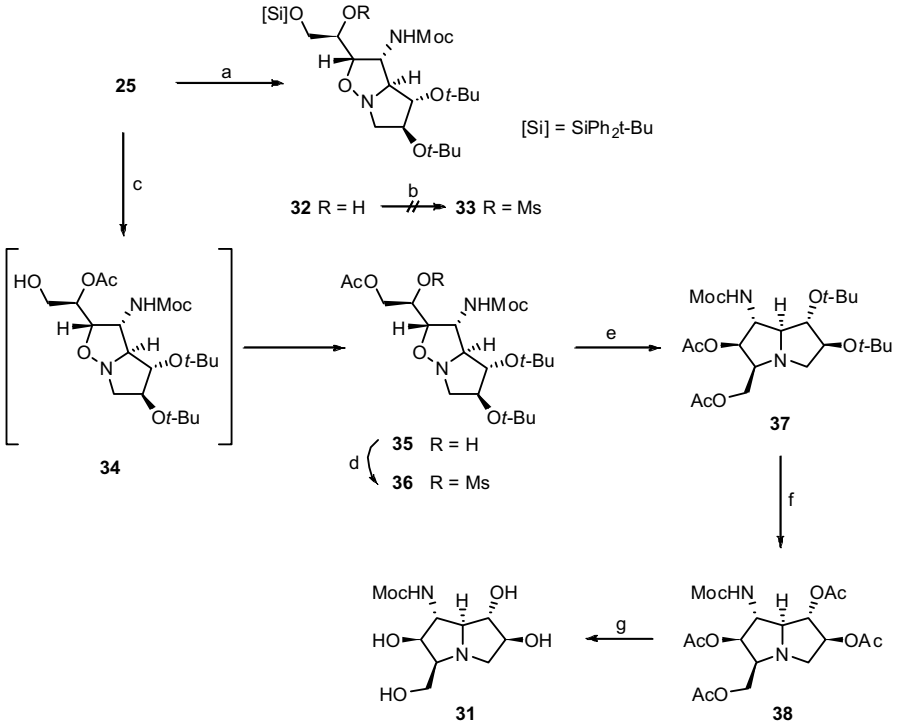
Recently, we have demonstrated that compound **22** is not only an attractive substrate for the synthesis of polyhydroxylated indolizidines but also provides an entry to the pyrrolizidine class of iminosugars.[13g–i] This can be achieved by changing the cyclization step strategy.[13g–i] We decided to apply the new strategy to prepare the 7-aminopyrrolizidine **31** from **25**. For this purpose, the acetate **25** was submitted to selective deprotection of the secondary hydroxyl group by treatment with 10% ammonia solution in methanol (Scheme 5). Subsequently, the alcohol **32** was treated with mesyl chloride. Unexpectedly, this reaction did not proceed as expected under standard condition and starting material was recovered. The same result was also observed when the reaction was performed in neat MsCl as a solvent and DMAP as a base. The elevation of reaction temperature from ambient to 40 °C caused consumption of the starting material, but only a trace of the desired product **33** was noticed. As a result, a complex mixture of unidentified products was obtained. The failure of mesylation at low temperature can be explained due to the steric hindrance, which restricts an access to the hydroxy group. The elevated reaction temperature may initially lead to the formation of expected mesyl product, but simultaneously it also promotes the participation of neighboring substituents, which likely cause further reactions, involving nucleophilic substitution or elimination, leading finally to decomposition.

To overcome these difficulties we decided to modify the reaction sequence and start with the removal of the silyl protection. The altered route leading to **31** is outlined in Scheme 5. The treatment of **25** with TBAF in THF gave the primary alcohol **34** which immediately underwent intramolecular acetyl migration leading to the secondary alcohol **35**. The crude alcohol **35** was treated with mesyl chloride to afford mesylate **36**, which was hydrogenated in the presence of Pd/C causing cleavage of the N–O bond followed by the intramolecular alkylation of nitrogen atom. The crude 7-aminopyrrolizidine was acetylated and purified as acetate **37**. The comparison of its ^1H NMR spectra with that of **27** confirmed the presence of the pyrrolizidine skeleton in acetate **37**. Finally, the pyrrolizidine **37** was transformed into target molecule **31** applying the standard deprotection sequence described before. The overall yield of the process from **15b**, was ca. 16% (11 steps).

The resulting amino-iminosugars (**11**, **12** and **31**) were tested as potential inhibitors of several standard glycosidase enzymes: α-L-fucosidase (bovine kidney), β-D-galactosidase (bovine liver), β-D-glucuronidase (bovine liver), α-D-glucosidase (rice), β-D-glucosidase (almond), and α-D-mannosidase (jack bean). Unfortunately, only compound **31** displayed weak activity toward one of tested enzymes (inhibition of β-D-galactosidase IC_{50} 0.9 mM). It must be stressed, however, that the bicyclic amino-iminosugars are still a relatively unexplored class of glycomimetics and the relation between their substitution patterns, their absolute configuration and their biological activity is hard to predict. The preliminary unsatisfactory results do not exclude the possibility of finding bioactivity in this class of compounds.

3. Conclusions

To conclude, we have established an attractive synthetic strategy leading to the formation of amino-iminosugars. The strategy involves the 1,3-dipolar cycloaddition between the five-membered cyclic nitrone and 2(5*H*)-furanones, ammonolysis of the lactone moiety and Hofmann rearrangement as the key steps. The general value of this method was demonstrated by the synthesis of polyhydroxy-alkaloids with both indolizidine and pyrrolizidine skeleton.



Scheme 5. Reagents and conditons: (a) 10% NH_3 in MeOH, rt, 98%; (b) MsCl, Et_3N, CH_2Cl_2 or MsCl, DMAP; (c) TBAF, THF, rt; 75%; (d) MsCl, Et_3N, CH_2Cl_2, rt, 80%, 0 °C then rt; (e) i. H_2, Pd/C, EtOH, rt, ii. Ac_2O, Et_3N, 0 °C then rt, 70% (2 steps); (f) i. CF_3COOH, rt, ii. Ac_2O, Et_3N, 0 °C then rt, 85% (2 steps),(g) 1%NH_3 in MeOH, 90%.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Brucker DRX 500 Avance Spectrometer at 500 MHz and 125 MHz, respectively, using deuterated solvents and TMS as an internal standard. Chemical shifts are reported as δ values in ppm and coupling constants are in hertz. Proton assignment was done based on COSY experiments. Infrared spectra were recorded on a FT-IR-1600 Perkin–Elmer spectrophotometer. The optical rotations were measured with JASCO J-2000 digital polarimeter. High-resolution mass spectra were recorded on ESI-TOF Mariner Spectrometer (Perspective Biosystem). Thin layer chromatography was performed on aluminium sheet Silica Gel 60 F_{254} (20×20×0.2) from Merck. Column chromatography was carried out using Merck silica gel (230–400 mesh) and Florisil (100–200 mesh). All solvents were purified by standard techniques.[20]

4.2. (2*S*,3*R*,3a*S*,4*S*,5*S*)-4,5-Di-*tert*-butoxy-2-(*tert*-butyldiphenylsilyloxymethyl)hexahydropyrrolo[1,2-*b*]isoxazolo-3-carboxyamide (17)

A solution of compound **15a** (0.31 g, 1.0 mmol) in MeOH (10 mL) was put into ampoule (cooled to −20 °C) equipped with dry-ice condenser connected with ammonia bottle. After condensing of ca. 30 mL of liquid ammonia, the ampoule was closed and warmed up to room temperature. After 48 h ammonia and MeOH were carefully removed and a residue was chromatographed on a silica gel (CH_2Cl_2/MeOH, 30:1). Afforded amide **16** (0.25 g, 75%) was dissolved in CH_2Cl_2 (10 mL) and transferred to a solution of imidazole (0.14 g, 2.0 mmol) in CH_2Cl_2 (10 mL). After cooling to −15 °C, *t*-$BuPh_2SiCl$ (0.25 g, 0.9 mmol) was added and obtained mixture was stirred at room temperature till disappearance of starting alcohol (TLC, CH_2Cl_2/MeOH, 1:1). Then solvent was removed and obtained residue was purified on silica gel (CH_2Cl_2/MeOH, 30:1) affording amide **17** (0.39 g, 91%) as a colourless oil. $[\alpha]_D$ +42.1 (*c* 0.15, CH_2Cl_2); IR (film) ν: 3330, 3190, 1670, 1112 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70–7.25 (10H, Ar), 6.21 (1H, br s, CON*H*H), 5.19 (1H, br s, CONH*H*), 4.58 (1H, ddd, *J* 6.6, 5.8, 4.8 Hz, H-2), 3.95 (1H, dd, *J* 11.2, 4.8 Hz, C*H*HOSi), 3.90 (1H, ddd, *J* 6.0, 5.6, 2.3 Hz, H-5), 3.84 (1H, dd, *J* 11.2, 6.6 Hz, CH*H*OSi), 3.76–3.72 (2H, H-3a, H-4), 3.56 (1H, dd, *J* 12.4, 5.6 Hz, H-6a), 3.20 (1H, br d, *J* 5.8 Hz, H-3), 3.04 (1H, dd, *J* 12.4, 6.0 Hz, H-6b), 1.20 (9H, s, *t*-Bu), 1.18 (9H, s, *t*-Bu), 1.05 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz,C_6D_6) δ: 172.5, 135.6, 135.5, 133.2, 133.1, 129.8, 129.7, 127.7, 127.6, 81.8, 78.4, 76.5, 74.8, 74.4, 74.3, 62.3, 61.5, 56.5, 28.8, 28.5, 26.8, 19.2; HRMS (ESI): *m*/*z* calcd for $C_{32}H_{48}N_2O_5NaSi$ [M+Na$^+$]: 591.3225; found: 591.3206. Anal. Calcd for $C_{32}H_{48}N_2O_5Si$: C, 67.57; H, 8.51; N, 4.92. Found: C, 67.54; H, 8.48; N, 4.90.

4.3. Methyl (2*S*,3*R*,3a*S*,4*S*,5*S*)-4,5-di-*tert*-butoxy-2-(*tert*-butyldiphenylsilyloxymethyl)hexahydropyrrolo[1,2-*b*]isoxazol-3-ylcarbamate (18)

Diacetoxyiodobenzene (0.34 g, 1.06 mmol) was added to solution of amide **17** (0.3 g, 0.53 mmol) in MeOH (20 mL) and obtained mixture was stirred at room temperature. The progress of reaction was controlled by TLC. Then a solvent was removed and residue was purified on a silica gel (hexane/AcOEt, 1:1) affording *N*-protected amine **18** (0.25 g, 80%) as a colourless oil. $[\alpha]_D$ +43.5 (*c* 0.55, CH_2Cl_2); IR (film) ν: 3325, 1725, 1113 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ: 8.00–7.20 (10H, Ar), 6.14 (1H, d, *J* 9.6 Hz, NH), 5.05 (1H, ddd, *J* 9.6, 6.3, 4.3 Hz, H-3), 4.26 (1H, ddd, *J* 6.3, 3.9, 3.6 Hz, H-2), 4.18 (1H, m, H-4), 3.98 (1H, dd, *J* 11.5, 3.9 Hz, C*H*HOSi), 3.89 (1H, ddd, *J* 6.1, 5.8, 3.7 Hz, H-5), 3.80 (1H, dd, *J* 11.5, 3.6 Hz, CH*H*OSi), 3.66 (1H, m, H-3a), 3.62 (1H, dd, *J* 11.5, 5.8 Hz, H-6a), 2.95 (1H, dd, *J* 11.5, 6.1 Hz, H-6b), 1.22 (9H, s, *t*-Bu), 1.19 (9H, s, *t*-Bu), 1.02 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, benzen-d_6) δ: 156.8, 136.2, 135.9, 133.7, 133.1, 130.1, 130.0, 127.9, 127.8, 80.9, 79.4, 77.4, 77.3, 74.2, 73.6, 62.6, 61.6, 60.9, 51.8, 28.8, 28.4, 26.9, 19.4; HRMS (ESI): *m*/*z* calcd for $C_{33}H_{50}N_2O_6NaSi$ [M+Na$^+$]: 621.3330; found: 621.3309. Anal. Calcd for $C_{33}H_{50}N_2O_6Si$: C, 66.19; H, 8.42; N, 4.68. Found: C, 66.14; H, 8.40; N, 4.65.

4.4. (1*S*,2*S*,6*R*,7*R*,7a*S*)-6-Acetoxy-1,2-di-*tert*-butoxy-7-(methoxycarbonylamino)-pyrrolizidine (20)

A solution of TBAF (0.11 g, 0.36 mmol) in THF (5 mL) was added to a solution of **18** (0.2 g, 0.33 mmol) in THF (5 mL). The progress of reaction was monitored by TLC. Subsequently, solvent was removed and residue was chromatographed on a silica gel (CH_2Cl_2/MeOH, 25:1 with 1% Et_3N). Afforded alcohol was dissolved in CH_2Cl_2 (5 mL), Et_3N was added (67 mg, 0.66 mmol) and after cooling to −15 °C, MsCl was added slowly (49 mg, 0.43 mmol). When substrate was consumed, solvent was removed and residue was purified on a silica gel (CH_2Cl_2/MeOH, 25:1 with 1% Et_3N). Obtained mesylate **19**, was immediately dissolved in mixture AcOEt/MeOH (1:1, 10 mL), Pd/C was added (100 mg) and vigorously stirred solution was saturated with hydrogen at atmospheric pressure. After disappearance of mesylate, post-reaction mixture was filtrated through Celite, and solvents were removed under diminished pressure. Residue was dissolved in Et_3N (5 mL), cooled and Ac_2O (2 mL) was added. After 1 h solvents were removed and residue purified on a silica gel (CH_2Cl_2/MeOH, 25:1 with 1% Et_3N) affording pyrrolizidine **20** (83 mg, 65%) as a yellowish oil. $[\alpha]_D$ +4.1 (*c* 0.35, CH_2Cl_2); IR (film) ν: 3325, 1730, 1723, 1239 cm^{-1}; ^{1}H NMR (500 MHz, toluene-d_8) δ: 5.30 (1H, br m, H-7), 5.19 (1H, m, H-6), 4.66 (1H, m, H-2), 4.32 (1H, br s, NH), 3.84 (1H, m, H-1), 3.51 (1H, dd, *J* 8.5, 7.1 Hz, H-5a), 3.43 (3H, s, Me), 3.22 (1H, dd, *J* 11.4, 4.0 Hz, H-3a), 3.15 (1H, br d, *J* 8.5 Hz, H-5b), 3.07 (1H, m, H-7a), 2.61 (1H, dd, *J* 11.2, 2.4 Hz, H-3b), 1.61 (3H, s, Ac), 1.19 (9H, s, *t*-Bu), 1.11 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, toluene-d_8) δ: 170.2, 157.0, 80.2, 79.7, 76.9, 75.4, 74.0, 73.6, 60.3, 58.7, 57.3, 51.6, 28.7, 28.4, 19.9; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{35}N_2O_6$ [M+H$^+$]: 387.2489; found: 387.2473.

4.5. (1*S*,2*S*,6*S*,7*R*,7a*S*)-1,2,6-Triacetoxy-7-(methoxycarbonylamino)-pyrrolizidine (21)

Pyrrolizidine **20** (55 mg, 0.14 mmol) was dissolved in CF_3COOH (5 mL) and stirred overnight. After removal of solvent under diminished pressure, residue was dissolved in Et_3N (3 mL), cooled and Ac_2O (1 mL) was added slowly. After 1 h solvent was removed and residue was chromatographed on a silica gel (hexane/AcOEt, 1:4) affording pyrrolizidine **21** (40 mg, 79%) as a yellowish oil. $[\alpha]_D$ +9.1 (*c* 1.09, CH_2Cl_2); IR (film) ν: 1731, 1723 cm^{-1}; ^{1}H NMR (500 MHz, toluene-d_8) δ: 5.48 (1H, m, H-7), 5.27 (1H, m, H-6), 5.20 (1H, br s, NH), 5.12 (1H, q, H-2), 4.40 (1H, m, H-1), 3.44 (3H, s, Me), 3.39 (1H, dd, *J* 9.6, 6.7 Hz, H-5a), 3.28 (1H, dd, *J* 12.2, 5.0 Hz, H-3a), 3.13 (1H, dd, *J* 7.5, 2.0 Hz, H-7a), 2.76–2.65 (2H, H-3b, H-5b), 1.68 (3H, s, Ac), 1.65 (3H, s, Ac), 1.63 (3H, s, Ac); ^{13}C NMR (125 MHz, toluene-d_8) δ: 170.1, 169.5, 169.2, 157.0, 80.2, 78.9, 77.3, 73.6, 59.2, 57.9, 57.5, 51.9, 30.3; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{22}N_2O_8Na$ [M+Na$^+$]: 381.1274; found: 381.1269.

4.6. (1*S*,2*S*,6*S*,7*R*,7a*S*)-1,2,6-Trihydroxy-7-(methoxycarbonylamino)-pyrrolizidine (11)

Pyrrolizidine **21** (30 mg, 84 μmol) was dissolved in 5 mL of 1% soln NH_3 in MeOH and stirred overnight under argon atmosphere. The progress of reaction was monitored by mass spectrometry. After filtration through Florisil, solvent was removed affording target pyrrolizidine **11** (16 mg, 85%) as yellowish oil. $[\alpha]_D$ −9.0 (*c* 0.49, MeOH); IR (film) ν: 3330, 1720 cm^{-1}; ^{1}H NMR (500 MHz,

metanol-d_4) δ: 4.19 (1H, m, H-1), 4.11–4.06 (2H, H-2, H-6), 4.03 (1H, t, *J* 7.7 Hz, H-7), 3.65 (3H, s, Me), 3.24 (1H, dd, *J* 9.5, 5.8 Hz, H-5a), 3.18 (1H, dd, *J* 11.5, 4.6 Hz, H-3a), 3.03 (1H, dd, *J* 7.7, 3.2 Hz, H-7a), 2.90 (1H, dd, *J* 9.5, 8.3 Hz, H-5b), 2.85 (1H, dd, *J* 11.5, 4.0 Hz, H-3b); ^{13}C NMR (125 MHz, metanol-d_4) δ: 159.6, 81.3, 79.6, 76.3, 75.9, 62.2, 61.0, 60.4, 52.5; IR (film) ν: 3330, 1720 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_9H_{17}N_2O_5$ [M+H$^+$]: 233.1132; found: 233.1143.

4.7. (2*S*,3*R*,3a*S*,4*S*,5*S*,1′*R*)-2′-(*tert*-Butyldiphenylsilyloxy)-1′-(4,5-di-*tert*-butoxy-3-carbamoylhexahydro-pyrrolo[1,2-*b*]isoxazol-2-yl)ethyl acetate (24)

Ammonolysis of **22** (1.0 g, 1.72 mmol) was carried out in the same way like for **17**. After chromatographically purification on a silica gel (CH_2Cl_2/MeOH, 25:1 with 1% Et_3N) 0.72 g (70%) of amide **23** was obtained. This compound was immediately dissolved in Et_3N (25 mL), cooled and Ac_2O (10 mL) was added slowly. After 3 h solvents were removed and residue was chromatographed on a silica gel (AcOEt 100%) affording amide **24** (0.7 g, 91%) as a colourless oil. $[\alpha]_D$ +38.5 (*c* 0.65, CH_2Cl_2); IR (film) ν: 3416, 1747, 1639 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ: 8.00–7.20 (10H, Ar), 5.66 (1H, s, NH), 5.50 (1H, ddd, *J* 8.9, 4.8, 2.6 Hz, H-1′), 5.37 (1H, s, NH), 4.90 (1H, dd, *J* 8.9, 6.2 Hz, H-2), 4.24 (1H, dd, *J* 11.4, 2.6 Hz, H-2′a), 4.09 (1H, dd, *J* 11.4, 4.8 Hz, H-2′b), 3.87 (1H, dd, *J* 4.5, 2.6 Hz, H-3a), 3.77 (1H, ddd, *J* 6.0, 5.1, 4.1 Hz, H-5), 3.72 (1H, dd, *J* 4.5, 4.1 Hz, H-4), 3.42 (1H, dd, *J* 12.1, 5.1 Hz, H-6a), 3.37 (1H, dd, *J* 6.2, 2.6 Hz, H-3), 3.07 (1H, dd, *J* 12.1, 6.0 Hz, H-6b), 1.96 (3H, s, Ac), 1.19 (9H, s, *t*-Bu), 1.05 (9H, s, *t*-Bu), 0.95 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6, carbon atoms of Ph groups omitted) δ: 172.5, 169.2, 82.6, 77.6, 75.6, 75.5, 74.1, 73.7, 72.3, 64.4, 61.6, 57.6, 28.8, 28.4, 27.1, 20.7, 19.6; HRMS (ESI): *m*/*z* calcd for $C_{35}H_{52}N_2O_7SiNa$ [M+Na$^+$]: 663.3436; found: 663.3453. Anal. Calcd for $C_{35}H_{52}N_2O_7Si$: C, 65.59; H, 8.18; N, 4.37. Found: C, 65.54; H, 8.13; N, 4.36.

4.8. (2*S*,3*R*,3a*S*,4*S*,5*S*,1′*R*)-2′-(*tert*-Butyldiphenylsilyloxy)-1′-(4,5-di-*tert*-butoxy-3-(methoxycarbonyl-amino)hexahydropyrrolo[1,2-*b*]isoxazol-2-yl)ethyl acetate (25)

Diacetoxyiodobenzene (0.3 g, 0.94 mmol) was added to a solution of amide **24** (0.3 g, 0.47 mmol) in MeOH (20 mL) and stirred at room temperature. The progress of reaction was monitored by TLC. After disappearance of substrate MeOH was removed and residue was chromatographed on a silica gel (hexane/AcOEt, 4:1 then 1:1) affording amide **25** (0.26 g, 83%) as colourless oil. $[\alpha]_D$ +4.4 (*c* 5.3, CH_2Cl_2); IR (film) ν: 3333, 1747, 1724, 1255 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ: 7.9–7.20 (10H, Ar), 5.95 (1H, d, *J* 10.3 Hz, NH), 5.47 (1H, dd, *J* 10.3, 4.4 Hz, H-3), 5.02 (1H, ddd, *J* 9.1, 4.9, 2.5 Hz, H-1′), 4.68 (1H, dd, *J* 9.1, 4.4 Hz, H-2), 4.16 (1H, dd, *J* 11.4, 2.5 Hz, H-2′a), 4.01 (1H, dd, *J* 11.4, 4.9 Hz, H-2′b), 3.87–3.77 (2H, H-4, H-5), 3.57 (1H, dd, *J* 11.4, 5.7 Hz, H-6a), 3.49 (4H, H-3a, MeO), 3.03 (1H, dd, *J* 11.4, 7.2 Hz, H-6b), 2.03 (3H, s, Ac), 1.19 (9H, s, *t*-Bu), 1.11 (9H, s, *t*-Bu), 0.98 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6, carbon atoms of Ph groups omitted) δ: 169.3, 156.5, 81.1, 78.6, 76.1, 75.1, 74.1, 73.6, 70.4, 64.6, 61.1, 60.3, 28.9, 28.4, 27.0, 21.1, 19.6; HRMS (ESI): *m*/*z* calcd for $C_{36}H_{54}N_2O_8SiNa$ [M+Na$^+$]: 693.3542; found: 693.3562. Anal. Calcd for $C_{36}H_{54}N_2O_8Si$: C, 64.45; H, 8.11; N, 4.18. Found: C, 64.40; H, 8.08; N, 4.17.

4.9. Methyl (2*S*,3*R*,3a*S*,4*S*,5*S*,1′*R*)-4,5-Di-*tert*-butoxy-2-(-1′,2′-dihydroxyethyl)hexahydro-pyrrolo[1,2-*b*]isoxazol-3-ylcarbamate (26)

A solution of tetrabutylammonium fluoride (0.14 g, 0.43 mmol) in THF (5 mL) was added to a solution of amide **25** (0.25 g, 0.36 mmol) in THF (15 mL). After consumption of substrate, solvent was removed under diminished pressure and residue was dissolved in 1% soln of NH_3 in MeOH (10 mL) and stirred 24 h. After removal of solvent residue was chromatographed on a silica gel (hexane/AcOEt, 1:1 then AcOEt 100%) affording diol **26** (91 mg, 80%) as a colourless oil. $[\alpha]_D$ +94.3 (*c* 1.60, CH_2Cl_2); IR (film) ν: 3363, 1708 cm^{-1}; ^{1}H NMR (500 MHz, metanol-d_4) δ: 4.67 (1H, dd, *J* 5.1, 2.5 Hz, H-3), 4.23 (1H, dd, *J* 7.6, 5.1 Hz, H-2), 4.02 (1H, dd, *J* 4.1, 3.9 Hz, H-4), 3.84 (1H, ddd, *J* 5.5, 5.3, 3.9 Hz, H-5), 3.74 (1H, ddd, *J* 7.6, 6.1, 3.5 Hz, H-1′), 3.67–3.60 (4H, singlet for Me, and dd, *J* 11.5, 3.5 Hz, for H-2′a), 3.52 (1H, dd, *J* 11.5, 6.1 Hz, H-2′b), 3.45 (1H, dd, *J* 12.5, 5.5 Hz, H-6a), 3.29 (1H, dd, *J* 4.1, 2.5 Hz, H-3a), 2.95 (1H, dd, *J* 12.5, 5.3 Hz, H-6b), 1.22 (9H, s, *t*-Bu), 1.20 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, metanol-d_4) δ: 159.2, 81.8, 80.4, 78.4, 77.5, 75.7, 70.5, 65.0, 62.5, 61.6, 52.7, 29.1, 28.8; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{35}N_2O_7$ [M+H$^+$]: 391.2444; found: 391.2440. Anal. Calcd for $C_{18}H_{35}N_2O_7\cdot H_2O$: C, 52.93; H, 8.88; N, 6.82. Found: C, 52.90; H, 8.86; N, 6.81.

4.10. (1*S*,2*S*,6*R*,7*S*,8*R*,8a*S*)-6,7-Diacetoxy-1,2-di-*tert*-butoxy-8-(methoxycarbonylamino)-indolizidine (27)

A solution of CBr_4 (0.12 g, 0.36 mmol) in CH_2Cl_2 (2 mL) was added to cooled solution of diol **26** (90 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) containing Ph_3P (95 mg, 0.36 mmol). After consumption the substrate solvent was removed and residue was dissolved in EtOH and 10% Pd/C (100 mg) was added. Obtained solution was saturated with hydrogen under atmospheric pressure. Subsequently, post-reaction mixture was filtered through Celite and solvent was removed. Residue was dissolved in Et_3N (2 mL), cooled and Ac_2O was added (1 mL). After 1 h solvents were removed and residue purified on a silica gel (hexane/AcOEt, 1:1) affording diacetate **27** (75 mg, 70%) as a colourless oil. $[\alpha]_D$ −20.1 (*c* 0.94, CH_2Cl_2); IR (film) ν: 3363, 1746, 1708 cm^{-1}; ^{1}H NMR (500 MHz, toluene-d_8) δ: 5.29 (1H, ddd, *J* 3.1, 2.7, 1.7 Hz, H-6), 4.65 (1H, dd, *J* 10.4, 3.1 Hz, H-7), 4.44 (1H, m, H-8), 4.33 (1H, br s, NH), 4.07 (1H, dd, *J* 6.3, 2.6 Hz, H-1), 3.72 (1H, ddd, *J* 6.3, 2.6, 2.0 Hz, H-2), 3.45 (3H, s, MeO), 2.87 (1H, dd, *J* 9.7, 2.0 Hz, H-3b), 2.83 (1H, dd, *J* 13.1, 2.7 Hz, H-5a), 2.27 (1H, dd, *J* 9.7, 6.3 Hz, H-3b), 2.00 (1H, dd, *J* 13.1, 1.7 Hz, H-5b), 1.82 (4H, H-8a, Ac), 1.71 (3H, s, Ac), 1.19 (9H, s, *t*-Bu), 1.03 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, toluene-d_8) δ: 170.0, 156.4, 83.5, 79.2, 74.6, 74.1, 73.5, 68.9, 60.3, 52.9, 51.6, 29.1, 29.0, 20.5, 20.4; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{38}N_2O_8Na$ [M+Na$^+$]: 481.2526; found: 481.2521.

4.11. (1*S*,2*S*,6*R*,7*S*,8*R*,8a*S*)-1,2,6,7-Tetraacetoxy-8-(methoxycarbonylamino)-indolizidine (30)

Indolizidine **27** (50 mg, 0.11 mmol) was dissolved in CF_3COOH (2 mL) and stirred overnight. Subsequently, solvent was removed under diminished pressure and residue was acetylated affording, after chromatography on a silica gel (AcOEt/hexane, 5:1), indolizidine **30** (40 mg, 86%) as a colourless oil. $[\alpha]_D$ −25.8 (*c* 0.73, CH_2Cl_2); IR (film) ν: 3363, 1739, 1713, 1232 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ: 5.58 (1H, dd, *J* 7.6, 2.5 Hz, H-6), 5.31 (1H, m, H-2), 5.13 (1H, dd, *J* 5.5, 2.5 Hz, H-7), 4.79 (1H, m, H-1), 4.32 (1H, m, H-8), 3.35 (3H, s, MeO), 2.76–2.63 (2H, H-3a, H-5a), 2.26 (1H, m, H-3b), 1.95–1.80 (2H, H-5b, H-8a), 1.82 (3H, s, Ac), 1.77 (3H, s, Ac), 1.76 (3H, s, Ac), 1.67 (3H, s, Ac); ^{13}C NMR (125 MHz, C_6D_6) δ: 170.5, 170.0, 169.8, 169.7, 156.3, 80.4, 77.5, 72.4, 68.5, 67.8, 57.7, 52.3, 51.5, 51.4, 20.0, 19.9, 19.8, 19.7; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{26}N_2O_{10}Na$ [M+Na$^+$]: 453.1480; found: 453.1486.

4.12. (1*S*,2*S*,6*R*,7*S*,8*R*,8a*S*)-1,2,6,7-Tetrahydroxy-8-(methoxycarbonylamino)-indolizidine (12)

Indolizidine **30** (40 mg, 93 μmol) was dissolved in 1% soln of NH_3 in MeOH (5 mL) and stirred at room temperature under argon atmosphere. The progress of reaction was controlled by mass

spectrometry. After filtration through Florisil, solvent was removed affording indolizidine **12** (18 mg, 75%) as a colourless oil. $[\alpha]_D$ −33.0 (*c* 0.64, MeOH); IR (film) *ν*: 3363, 1713 cm^{-1}; ^1H NMR (500 MHz, metanol-d_4) *δ*: 3.98 (1H, br d, *J* 6.7 Hz, H-1), 3.90–3.84 (2H, H-2, H-6), 3.77 (1H, m, H-7), 3.37 (1H, dd, *J* 10.5, 2.7 Hz, H-8), 3.34 (3H, s, MeO), 3.01 (1H, dd, *J* 12.1, 2.5 Hz, H-5a), 2.80 (1H, br d, *J* 10.1 Hz, H-3a), 2.56 (1H, dd, *J* 10.1, 5.3 Hz, H-3b), 2.31 (1H, br d, *J* 12.1 Hz, H-5b), 1.84 (1H, dd, *J* 10.4, 6.7 Hz, H-8a); ^{13}C NMR (125 MHz, metanol-d_4) *δ*: 160.1, 83.9, 79.7, 75.0, 73.7, 70.2, 60.6, 56.1, 55.3; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{19}N_2O_6$ [M+H^+]: 263.1238; found: 263.1231.

4.13. (1*S*,2*S*,5*S*,6*S*,7*R*,7a*S*)-6-Acetoxy-5-acetoxymethyl-1,2-di-*tert*-butoxy-7-(methoxycarbonylamino)-pyrrolizidine (37)

A solution of tetrabutylammonium fluoride (0.14 g, 0.43 mmol) in THF (5 mL) was added to a solution of amide **25** (0.25 g, 0.36 mmol) in THF (15 mL). After consumption of substrate, solvent was removed under diminished pressure and residue was chromatographed on a silica gel (EtOAc/hexane 4:1). Resulting alcohol **35** (0.27 mmol, 75% yield) was dissolved in CH_2Cl_2 (5 mL) and Et_3N (60 mg, 0.60 mmol) was added. After cooling to −15 °C MsCl (34 mg, 0.30 mmol) was added dropwise. After 3 h solvent was removed and residue was chromatographed through short silica gel pad (AcOEt/hexane 1:1) to afford mesylate **36** (110 mg, 80%) which was immediately used in next step. Its solution in AcOEt (5 mL) containing 10 mg of 10% Pd/C was saturated with hydrogen under atmospheric pressure. After 24 h reaction mixture was filtered and solvent was removed. Residue was dissolved in Et_3N (1 mL), cooled and Ac_2O (0.5 mL) was added. After 1 h solvent was removed and residue was chromatographed on a silica gel (EtOAc/hexane 9:1) to afford pyrrolizidine **37** as a yellowish oil. $[\alpha]_D$ +34.4 (*c* 0.45, CH_2Cl_2); IR (film) *ν*: 3360, 1740, 1235 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) *δ*: 5.46–5.34 (3H, H-1, H-2, H-6), 4.67 (1H, s, NH), 4.42 (1H, dd, *J* 11.5, 6.5 Hz, C*H*HOAc), 4.34 (1H, dd, *J* 11.5, 6.7 Hz, CH*H*OAc), 4.15 (1H, m, H-7), 3.60 (1H, m, H-5), 3.39 (3H, s, MeO), 3.12 (1H, m, H-3a), 3.04 (1H, m, H-7a), 2.92 (1H, m, H-3b), 1.75 (3H, s, Ac), 1.58 (3H, s, Ac), 1.19 (9H, s, *t*-Bu), 1.08 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) *δ*: 170.4, 170.0, 168.4, 81.1, 79.6, 73.9, 73.5, 66.1, 61.5, 61.0, 53.4, 52.6, 51.9, 28.9, 28.6, 22.8, 20.5, 20.3; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{38}N_2O_8Na$ [M+Na^+]: 481.2520; found: 481.2534.

4.14. (1*S*,2*S*,5*S*,6*S*,7*R*,7a*S*)-1,2,6-Triacetoxy-5-(acetoxymethyl)-7-(methoxycarbonylamino)-pyrrolizidine (38)

Pyrrolizidine **37** (50 mg, 0.11 mmol) was dissolved in CF_3COOH (2 mL) and stirred overnight. Subsequently, solvent was removed under diminished pressure and residue was acetylated affording, after chromatography on a silica gel (AcOEt/hexane, 6:1), pyrrolizidine **38** (40 mg, 85%) as a colourless oil. $[\alpha]_D$ +11.1 (*c* 1.45, CH_2Cl_2); IR (film) *ν*: 3354, 1742, 1234 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) *δ*: 5.53 (1H, ddd, *J* 7.0, 5.7, 5.0 Hz, H-2), 5.48–5.40 (2H, H-1, H-6), 5.28 (1H, br s, NH), 4.29 (1H, dd, *J* 11.7, 5.9 Hz, C*H*HOAc), 4.24 (1H, m, H-7), 4.13 (1H, dd, *J* 11.7, 6.9 Hz, CH*H*OAc), 3.40 (3H, s, MeO), 3.28 (1H, dd, *J* 9.6, 5.7 Hz, H-3a), 3.20 (1H, m, H-7a), 2.97 (1H, dd, *J* 9.6, 7.0 Hz, H-3b), 1.74 (3H, s, Ac), 1.66 (3H, s, Ac), 1.65 (3H, s, Ac), 1.61 (3H, s, Ac); ^{13}C NMR (125 MHz, C_6D_6) *δ*: 170.2, 169.9, 169.7, 169.5, 156.7, 80.2, 79.8, 78.4, 72.9, 61.7, 61.2, 60.2, 51.9, 51.2, 20.34, 20.32, 20.28, 20.17; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{26}N_2O_{10}Na$ [M+Na^+]: 453.1480; found: 453.1483.

4.15. (1*S*,2*S*,5*S*,6*S*,7*R*,7a*S*)-1,2,6-Trihydroxy-5-(hydroxymethyl)-7-(methoxycarbonylamino)-pyrrolizidine (31)

Pyrrolizidine **38** (40 mg, 93 μmol) was dissolved in 1% soln of NH_3 in MeOH (5 mL) and stirred at room temperature under argon atmosphere. The progress of reaction was controlled by mass spectrometry. After filtration through Florisil, solvent was removed affording pyrrolizidine **31** (21 mg, 90%) as a colourless oil. $[\alpha]_D$ +0.7 (*c* 1.0, CH_2Cl_2); IR (film) *ν*: 3334, 1748 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) *δ*: 4.10–3.98 (3H, H-1, H-2, H-6), 3.93 (1H, dd, *J* 11.5, 5.9 Hz, C*H*HOH), 3.88 (1H, dd, *J* 11.5, 6.6 Hz, CH*H*OH), 3.35 (3H, s, MeO), 3.21 (1H, dd, *J* 9.3, 8.0 Hz, H-3a), 3.14 (1H, ddd, *J* 6.6, 5.9, 4.0 Hz, H-5), 3.08 (1H, dd, *J* 9.3, 5.8 Hz, H-3b), 3.03 (1H, dd, *J* 5.8, 4.0 Hz, H-7a); ^{13}C NMR (125 MHz, CD_3OD) *δ*: 159.2, 81.9, 79.9, 77.9, 76.0, 66.5, 64.0, 58.6, 53.5, 52.6; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{18}N_2O_6Na$ [M+Na^+]: 285.1057; found: 285.1045.

References and notes

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