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Synthesis of casuarine-related derivatives via 1,3-dipolar cycloaddition between a cyclic nitrone and an unsaturated γ-lactone

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ABSTRACT

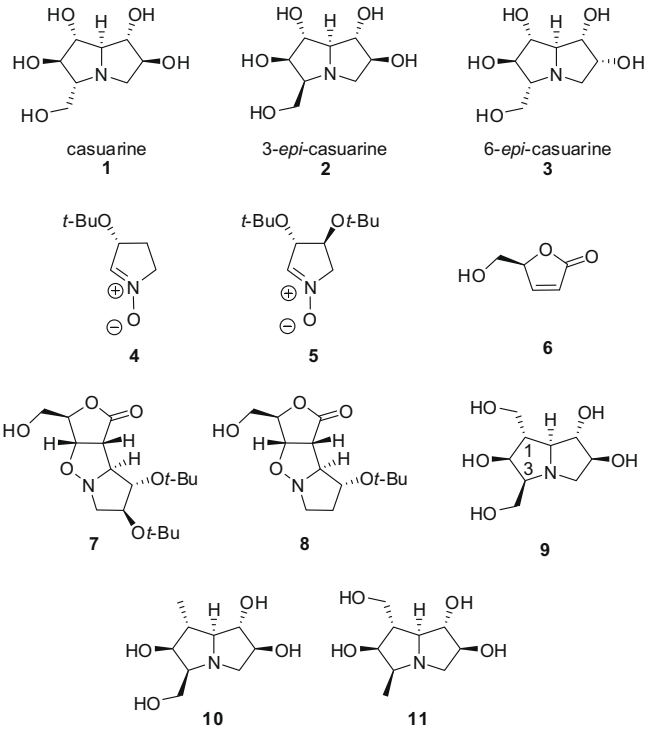
The 1,3-dipolar cycloaddition of the cyclic nitrone derived from tartaric acid and (*S*)-5-hydroxymethyl-2(5*H*)-furanone leads to the single adduct **7** which can be transformed into the 3-*epi*-1-homo-casuarine via a reaction sequence involving reduction of the lactone moiety and *N*–*O* bond hydrogenolysis, followed by intramolecular alkylation of the nitrogen atom. The adduct **7** can also be used in the synthesis of 1-methyl- or 3-methyl analogues of 3-*epi*-casuarine.

1. Introduction

Casuarine **1** is a polyhydroxylated pyrrolizidine alkaloid isolated from *Casuarina equisetifolia*, which exhibits some activity against α-glucosidase and trehalase.[1,2] Two other isomeric compounds, 3-*epi*-casuarine **2** and 6-*epi*-casuarine **3**, have also been found in plant materials. The former one was isolated from *Myrtus communis* in 2006[3] and the latter one from *Eugenia unifloria* in 2000.[4,5] Both compounds show an inhibition of β-D-glucosidase.[3–5]

In our previous studies, we have shown that the 1,3-dipolar cycloadditions of five-membered cyclic nitrones (i.e., **4** and **5**[6]) to α,β-unsaturated δ-lactones are an attractive route to pyrrolizidine, indolizidine and quinolizidine iminosugars.[7,8]

Very recently, we have demonstrated that γ-lactones (e.g., **6**) may also be used for this purpose.[9,10] Generally, the cycloadditions involving five-membered lactones show less diastereoselectivity in comparison to their six-membered analogues, due to the possible formation of endo adducts and the reversibility of reaction.[11] However, a proper choice of both the reaction's components may afford the formation of a single product in the case when the endo approach of reactants is hindered.[11] For example, the cycloadducts **7** and **8**, available from the reaction of D-*glycero* lactone **6** and the nitrones **4** and **5**, respectively (both matching pairs), are formed as sole products. Particularly attractive is the adduct **7** since it is



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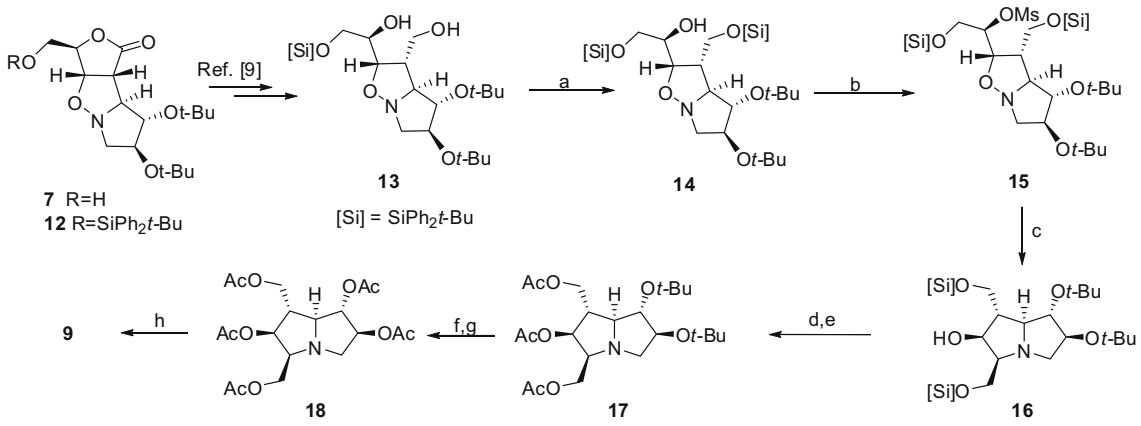
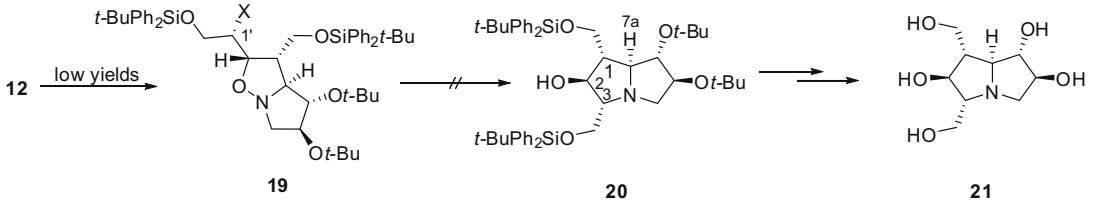


Scheme 1. Reagents and conditions: (a) *t*-BuPh$_2$SiCl, imidazole, CH_2Cl_2, −15 °C up to rt, 92%; (b) MsCl, Et_3N, CH_2Cl_2, −15 °C to rt, 84%; (c) H_2, Pd/C, 4:1 EtOAc–MeOH, rt, 80%; (d) TBAF, THF, rt; (e) Ac_2O, Et_3N, rt, 72% (2 steps); (f) CF_3COOH, rt; (g) Ac_2O, Et_3N, rt, 78% (2 steps); (h) 1%NH_3 in MeOH, rt, 89%.



Scheme 2.

easily accessible starting from relatively inexpensive substrates,[11a] and provides entry to the casuarines' 1-homo derivative **9**.

The two hydroxymethyl groups present in pyrrolizidine **9**, obtained via transformation of the adduct **7**, also offer an easy access to the corresponding methyl analogues, that is, compounds **10** and **11**.

A methyl group occurs in many polyhydroxylated alkaloids, that is, iminoalditols,[12a] iminosugars from hyacinthacine group[12b] and others.[13,14] Interesting biological properties of methyliminosugars[12,14] encourage us to propose a synthetic route to the mentioned methyl derivatives of **9** from the adduct **7**.

2. Results and discussion

2.1. Synthesis of 3-*epi*-1-homocasuarine (9)

The synthesis of **9** is depicted in Scheme 1. The free hydroxy group in **7** was protected with a *t*-BuPh$_2$Si residue to yield the known lactone **12**.[9] Subsequently, lactone **12** was transformed into **14** via a two-step procedure described previously, which involves reduction with the BH_3–Me_2S complex to afford **13**,[9] followed by silylation of the hydroxymethyl group. Subsequently, the remaining free hydroxy group was mesylated to afford compound **15**, which after hydrogenolysis of the *N–O* bond promptly formed the pyrrolizidine **16** via intramolecular alkylation of the nitrogen atom. The latter step proceeds with an inversion of the configuration at the C-3 carbon atom of the pyrrolizidine skeleton.

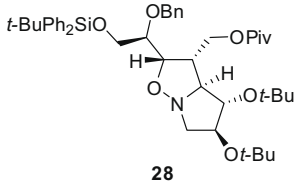
Compound **16** was subjected to a deprotection–acetylation sequence to provide the peracetylated derivative **18** of the target compound. The structure and configuration of **18** were confirmed by ^{1}H NMR and NOE experiments. The final deprotection was performed by treatment of **18** with a 1% solution of ammonia in methanol to afford the pyrrolizidine **9**.

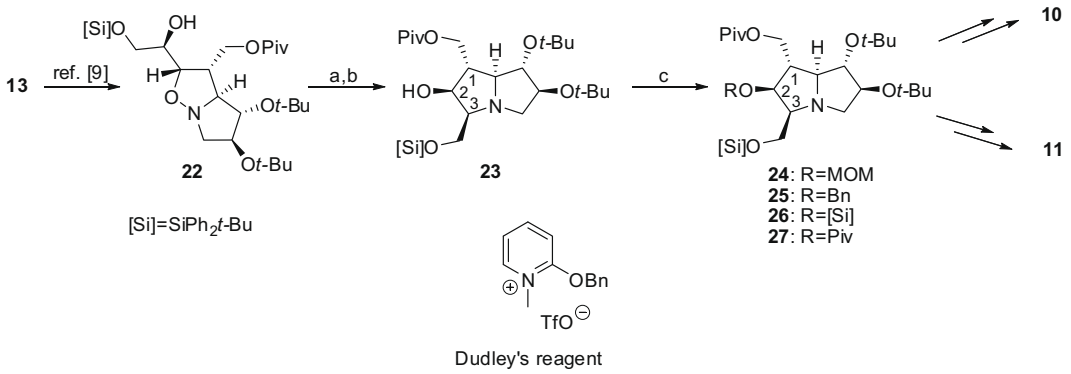
Deeper analysis of the synthetic route led us to conclude that inversion of configuration at C-1′ in **14**, prior to the N–O bond cleavage and N-alkylation, may afford **20**, the precursor of 1-homo-casuarine **21** (Scheme 2). However, the planned synthesis failed due to problems arising during the inversion step. Numerous experiments, using a variety of procedures to introduce a halogen atom with inversion of configuration at C-1′ in **12**, provided the product **19** in only a very low yield.

2.2. Synthesis of the methyl analogues 10 and 11

The first task in the synthesis of the methyl pyrrolizidines **10** and **11** was the discrimination of both hydroxymethyl groups obtained via reduction of the lactone moiety in **7**. A detailed approach is shown in Scheme 3. As we reported recently,[9] the primary hydroxy group in the diol **13** can be easily protected with a pivaloyl residue to give **22**. This pivalate can be transformed into the pyrrolizidine **23** using a standard reaction sequence. Protection of the hydroxy group in **23**, followed by the selective deprotection of one hydroxymethyl group, should allow to obtain either **10** or **11**. The hydroxy group in **23** is, however, not accessible for benzylation (**25**) or MOM protection (**24**) under standard conditions.[15†]

† Benzylation of **23** under standard Williamson's conditions affords quarternary ammonium salt, which proceeds rapidly to Hoffman degradation under basic condition. On the other hand, reaction under neutral condition, BnX in presence of Ag_2O, stops at the salt step and does not proceed further. An alternative way of protection by treatment with benzyl 2,2,2-trichloroacetimidate cannot be done due to presence of acid labile groups. Similar problems were observed in case of MOM protection. It must be underlined that the discussed problem has a general character and the same difficulties with benzylation, as well as MOM protection, were observed also for isoxazolidine **22**. Only treatment of **22** with Dudley's reagent afforded the desired benzylated derivative **28** with 95% yield.



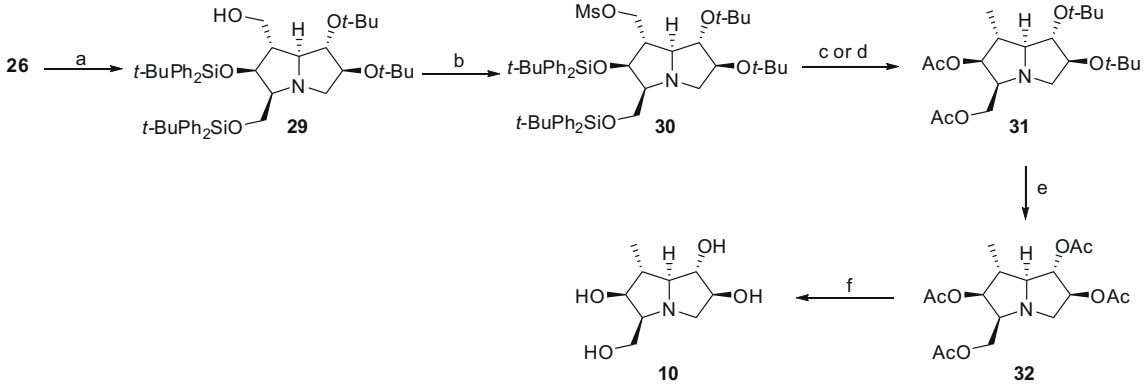


Scheme 3. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, rt, 89%; (b) H_2, Pd/C, 4:1 EtOAc–MeOH, rt, 75%; (c) for **24**: MOMCl, *i*-Pr_2NEt, CH_2Cl_2, decomposition of the starting material; for **25**: Dudley's reagent, MgO, benzene, reflux, 95%; for **26**: *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, −15 °C then rt, 60%; for **27**: PivCl, DMAP, CH_2Cl_2, rt, 60%.

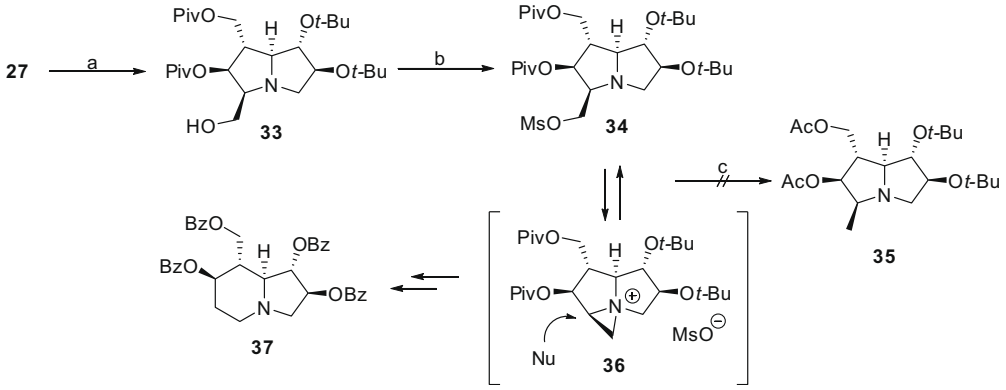
However, this group can be easily protected either by *t*-$BuPh_2SiCl$ to give **26** or by PivCl to give **27**. When both syntheses leading to **10** and **11** were completed, we were able to find a successful way to benzylate the hydroxy group in **23** by using Dudley's reagent, *N*-methyl-2-benzyloxypyridinium triflate.[16] The reaction proceeds in boiling benzene in the presence of 1.2–1.3 equiv of reagent to give the corresponding benzylated product **25** in about 95% yield.

The pivaloyl protection in **26** was removed with *i*-Bu_2AlH in toluene, and the free hydroxy group in **29** was mesylated to afford **30** (Scheme 4). Reduction of the mesylate function in **30** with $LiAlH_4$ also removed both silyl groups and provided the respective diol in only 54% yield, which was characterized as the diacetate **31**. Replacement of $LiAlH_4$ by $LiEt_3BH$ followed by desilylation and acetylation gave **31** in 68% yield. A subsequent desilylation–acetylation sequence led to the tetraacetate **32** and then to the free 1-methyl-pyrrolizidine **10**.

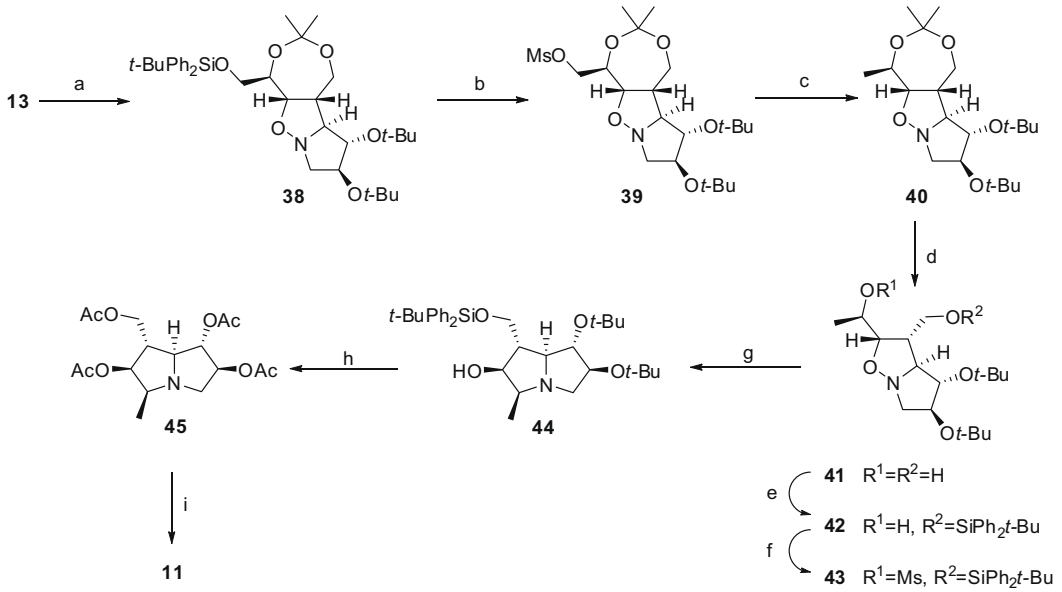
A parallel strategy was attempted for introduction of a methyl group at the C-3 carbon atom of the pyrrolizidine skeleton (Scheme 5). Desilylation of **27** with TBAF followed by mesylation and reduction of the mesylate **34** gave a mixture of products. The crude post-



Scheme 4. Reagents and conditions: (a) DIBAL-H, toluene, −78 °C, 90%; (b) MsCl, Et_3N, CH_2Cl_2, −15 °C then rt, 93%; (c) (i) $LiAlH_4$, Et_2O, rt; (ii) Ac_2O, Et_3N, 0 °C then rt, 54% (2 steps); (d) (i) $LiEt_3BH$, THF, rt; (ii) TBAF, THF, rt; (iii) Ac_2O, Et_3N, 0 °C then rt, 68% (3 steps); (e) (i) CF_3COOH; (ii) Ac_2O, Et_3N, 0 °C then rt, 86% (2 steps); (f) 1%NH_3 in MeOH, rt, 91%.



Scheme 5. Reagents and conditions: (a) TBAF, THF, rt, 93%; (b) MsCl, Et_3N, CH_2Cl_2, −15 °C then rt, 92%; (c) (i) $LiAlH_4$, Et_2O, rt; (ii) Ac_2O, Et_3N, 0 °C then rt.



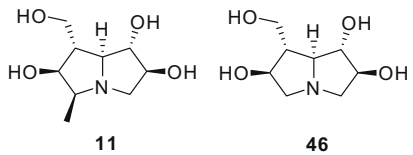
Scheme 6. Reagents and conditions: (a) 2,2-dimethoxypropane, *p*-TsOH, reflux, 70%; (b) (i) TBAF, THF, rt; (ii) MsCl, Et_3N, CH_2Cl_2, −15 °C then rt, 85% (2 steps); (c) $LiEt_3BH$, THF, rt, 87%; (d) *p*-TsOH (10 mol %), 9:1 MeOH–water, reflux, 80%; (e) *t*-BuSiPh$_2$Cl, imidazole, CH_2Cl_2, −15 °C then rt, 90%; (f) MsCl, Et_3N, CH_2Cl_2, −15 °C then rt, 90%; (g) H_2, 10% Pd/C, 4:1 EtOAc–MeOH; (h) (i) TBAF, THF, rt; (ii) CF_3COOH, rt; (iii) Ac_2O, Et_3N, −15 °C then rt, 75% (3 steps); (i) 1%NH_3 in MeOH, rt, 97%.

reaction mixture was subjected to the two-step deprotection, which was followed by benzoylation and chromatographic purification providing only one product **37** in 20% yield with low purity. An analogous result was observed when $LiEt_3BH$ was used to reduce **34**.

The observed rearrangement is a known reaction. Compound **37** is formed from the mesylate **34** via the intermediate aziridine **46**, which is subsequently opened by the hydride ion (Scheme 5). The transformation of activated hydroxymethyl pyrrolidines into the corresponding piperidines has been investigated by Cossy et al.[17] and used in a variety of syntheses of natural products.[18]

Since a simple deoxygenation at the pyrrolizidine stage failed, we attempted to carry it out earlier, before the opening of the isoxazolidine ring (Scheme 6). Both hydroxy groups in **13** were protected via an isopropylidene group affording compound **38**.[10] Desilylation of **38** followed by mesylation and reduction with $LiEt_3BH$ gave the methyl derivative **40**. After releasing the diol, the primary hydroxy group in **41** was silylated, whereas the secondary one was mesylated. Subsequent standard transformations led to the pyrrolizidine **11** (Scheme 6).

All of the obtained pyrrolizidines (i.e., **9**, **10** and **11**) were tested against bovine kidney α-L-fucosidase, bovine liver β-D-galactosidase, bovine liver β-D-glucuronidase, rice α-D-glucosidase, almond β-D-glucosidase and jack bean α-D-mannosidase inhibition. Under the procedures described previously,[19] compounds **9** and **10** displayed no activity against the tested enzymes. On the other hand, the pyrrolizidine **11** revealed a weak inhibition of almond β-D-glucosidase (IC_{50} 13 mM). It is worth to note that the recently reported[9] 2,6-dihydroxyhastanecine **46**, which is structurally related to the pyrrolizidine **11**, showed an inhibition of rice α-D-glucosidase (IC_{50} 9.9 mM).[9]



3. Conclusion

In this work, we have presented a strategy for the synthesis of polyhydroxylated pyrrolizidines starting from the cycloadduct of (5*S*)-5-hydroxymethyl-2(5*H*)-furanone and five-membered nitrone derived from L-tartaric acid. The synthesis extends our approach to iminosugars based on the 1,3-dipolar cycloaddition of nitrones to the unsaturated γ- and δ-lactones.[7,9,10] We demonstrated that a sequence of reactions, leading to the final products, has to be carefully planned since the multifunctional character of the intermediary compounds may preclude the use of standard transformations in certain cases.

4. Experimental

4.1. General methods

Melting points were determined using a Köfler hot-stage apparatus with a microscope and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker 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. Infrared spectra were obtained on an FT-IR-1600 Perkin–Elmer spectrophotometer. The optical rotations were measured with a JASCO J-1020 digital polarimeter. High-resolution mass spectra were recorded on an ESI-TOF Mariner spectrometer (Perspective Biosystem). Thin layer chromatography (TLC) 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). TLC spots were visualized in UV (254 nm) and by treatment with an alcoholic solution of ninhydrine.

All solvents were dried and purified applying standard techniques.[20] Compounds **7**,[11a] **12**,[9] **13**[9] and **22**[9] were prepared following our previously published procedures.

Tests of the inhibitory activity of pyrrolizidines **9**, **10** and **11** against bovine kidney α-L-fucosidase, bovine liver β-D-galactosidase, bovine liver β-D-glucuronidase, rice α-D-glucosidase, almond β-D-glucosidase and jack bean α-D-mannosidase were performed according to the procedures described previously.[19]

4.2. (*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-((2*S*,3*S*,3a*S*,4*S*,5*S*)-4,5-di-*tert*-butoxy-3-(*tert*-butyldiphenylsilyloxymethyl)-hexahydropyrrolo[1,2-*b*]-isoxazol-2-yl)ethanol (14)

The soln of diol **13** (1.79 g, 2.97 mmol) and imidazole (0.40 g, 5.95 mmol) in 50 mL of CH_2Cl_2 was cooled to −15 °C, and *t*-$BuPh_2SiCl$ was added (0.57 g, 3.23 mmol). The progress of the reaction was monitored by TLC (4:1 hexane–EtOAc). Subsequently, the reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water (50 mL), brine (30 mL) and dried over anhyd Na_2SO_4. After solvent removal, the residue was purified by column chromatography on a silica gel column (4:1 hexane–EtOAc) affording 2.25 g (92%) of compound **14** as a colourless oil; $[\alpha]_D$ +17.5 (*c* 0.34, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 8.00–7.00 (20H, 4 × Ph), 4.52 (1H, dd, *J* 9.1, 5.2 Hz, H_2), 4.30–4.20 (3H, $H_{1'}$,H_5, C*H*HOSi), 4.07 (1H, dd, *J* 10.3, 6.0 Hz, $H_{2'a}$), 3.89–3.73 (3H, H4, CH*H*OSi, $H_{2'b}$), 3.57–3.50 (2H, H_6,$H_{6'}$), 3.46 (1H, dd, *J* 4.8, 2.1 Hz, H_{3a}), 3.04 (1H, m, H_3), 1.22 (9H, s, *t*-Bu), 1.20 (9H, s, *t*-Bu), 1.09 (9H, s, *t*-Bu), 1.00 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6, without Ph groups): δ 81.5, 76.3, 75.4, 73.9, 73.7, 72.6, 69.6, 66.3, 63.3, 60.2, 51.8, 29.0, 28.5, 26.9, 26.8, 19.4, 19.1; IR (film) *v:* 3480, 1112 cm^{-1}; HRESI-TOFMS: calcd for [M+H$^+$] $C_{49}H_{70}NO_6Si_2$: 824.4736. Found: *m/z* 824.4771. Anal. Calcd for $C_{49}H_{69}O_6Si_2$: C, 71.40; H, 8.44; N, 1.70. Found: C, 71.51; H, 8.44; N, 1.71.

4.3. (*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-((2*S*,3*S*,3a*S*,4*S*,5*S*)-4,5-di-*tert*-butoxy-3-(*tert*-butyldiphenylsilyloxymethyl)-hexahydropyrrolo[1,2-*b*]-isoxazol-2-yl)ethyl mesylate (15)

A soln of alcohol **14** (1.40 g, 1.70 mmol) and Et_3N (0.34 g, 3.40 mmol) in 50 mL of CH_2Cl_2 was cooled to −15 °C, and MsCl was added (0.29 g, 2.55 mmol). After disappearance of the starting material, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with water and brine and dried over anhyd Na_2SO_4. After removal of the solvent, the residue was chromatographed on a silica gel column (4:1 hexane–EtOAc) to afford 1.22 g (84%) of mesylate **15** as colourless crystals; mp 53–55 °C (1:1 benzene–hexane); $[\alpha]_D$ +36.6 (*c* 0.21, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 8.00–7.20 (20H, 4 × Ph), 5.28 (1H, ddd, *J* 5.8, 5.6, 3.1 Hz, $H_{1'}$), 4.72 (1H, dd, *J* 6.0, 5.8 Hz, H_2), 4.27 (1H, dd, *J* 10.5, 5.7 Hz, C*H*HOSi), 4.20–4.00 (3H, dd, *J* 11.9, 3.1 Hz, for $H_{2'a}$, dd, *J* 11.9, 5.6 Hz, for $H_{2'b}$, dd, *J* 10.5, 8.2 Hz, for CH*H*OSi), 3.89 (1H, m, H_{3a}), 3.85–3.75 (2H, H_4,H_5), 3.57 (1H, dd, *J* 12.2, 5.0 Hz, H_6), 3.13–3.03 (2H, H_3,$H_{6'}$), 2.48 (3H, s, Ms), 1.26 (9H, s, *t*-Bu), 1.18 (9H, s, *t*-Bu), 1.11 (9H, s, *t*-Bu), 1.01 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6, without Ph groups): δ 82.5, 80.4, 77.1, 75.8, 73.9, 73.8, 73.5, 64.4, 62.1, 51.8, 38.5, 29.0, 28.4, 27.3, 27.1, 19.6, 19.5; HRESI-TOFMS: calcd for [M+H$^+$] $C_{50}H_{72}NO_8Si_2S$: 902.4511. Found: *m/z* 902.4555; Anal. Calcd for $C_{50}H_{71}O_8SSi_2$: C, 66.55; H, 7.93; N, 1.55; S, 3.55. Found: C, 66.67; H, 7.96; N, 1.56; S, 3.56.

4.4. (1*S*,2*S*,3*S*,6*S*,7*S*,7a*S*)-6,7-Di-*tert*-butoxy-1,3-bis(*tert*-butyldiphenylsilyloxymethyl)-2-hydroxypyrrolizidine (16)

Mesylate **15** (0.15 g, 0.17 mmol) was dissolved in 10 mL of 4:1 EtOAc–MeOH, 10% Pd/C was added (20 mg) and the reaction mixture was saturated with hydrogen at atmospheric pressure. The disappearance of substrate was monitored by TLC (4:1 hexane–EtOAc). Subsequently, the reaction mixture was filtered through Celite and concentrated. The crude residue was chromatographed on a short silica gel pad (2:1 hexane–EtOAc) to afford 0.11 g (80%) of pyrrolizidine **16** as a colourless oil; $[\alpha]_D$ +13.1 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82–7.30 (20H, 4 × Ph), 4.29 (1H, dd, *J* 8.8, 3.8 Hz, H_2), 4.10 (1H, dd, *J* 9.8, 7.9 Hz, C_3C*H*HOSi), 4.00 (1H, dd, *J* 9.8, 5.7 Hz, C_3CH*H*OSi), 3.84 (1H, ddd, *J* 4.9, 2.9, 1.7 Hz, H_6), 3.81–3.72 (2H, m, for H_7; dd, *J* 10.3, 5.0 Hz, for C_1C*H*HOSi), 3.59 (1H, dd, *J* 10.3, 6.4 Hz, C_1CH*H*OSi), 3.38 (1H, ddd, *J* 8.8, 7.9, 5.7 Hz, H_3), 3.14–3.06 (2H, dd, *J* 5.3, 1.7 Hz, for H_{7a}; dd, *J* 11.8, 4.9 Hz, for H_5), 2.98 (1H, dd, *J* 11.8, 2.9 Hz, $H_{5'}$), 2.36 (1H, dddd, *J* 6.4, 5.3, 5.0, 3.8 Hz, H_1), 1.13 (9H, s, *t*-Bu), 1.11 (9H, s, *t*-Bu), 1.07 (9H, s, *t*-Bu), 1.05 (9H, s, *t*-Bu); IR (film) *v:* 3401, 1111 cm^{-1}; HRESI-TOFMS: calcd for [M+H$^+$] $C_{49}H_{70}NO_5Si_2$: 808.4787. Found: *m/z* 808.4856; Anal. Calcd for $C_{49}H_{69}NO_5Si_2$: C, 72.81; H, 6.80; N, 1.73. Found: C, 72.83; H, 6.81; N, 1.74.

4.5. (1*S*,2*S*,3*S*,6*S*,7*S*,7a*S*)-2-Acetoxy-1,3-bis(acetoxymethyl)-6,7-di-*tert*-butoxy-pyrrolizidine (17)

A soln of TBAF (0.10 g, 0.31 mmol) in 5 mL of THF was added to a soln of compound **16** (0.30 g, 0.37 mmol) in 20 mL of THF. After 1 h, the solvent was removed and the residue was dissolved in Et_3N (10 mL). After cooling to −5 °C, Ac_2O was added (2 mL) and the reaction mixture was stirred for 2 h. After removal of solvents, the residue was purified chromatographically (4:1, then 1:1 hexane–EtOAc) affording 122 mg (72%) of triacetate **17** as a colourless oil; $[\alpha]_D$ +2.6 (*c* 0.79, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 5.39 (1H, dd, *J* 4.8, 2.4 Hz, H_2), 4.50 (1H, dd, *J* 11.3, 6.8 Hz, C_3C*H*HOSi), 4.42 (1H, dd, *J* 11.3, 7.0 Hz, C_3CH*H*OSi), 4.30 (1H, dd, *J* 11.4, 4.8 Hz, C_1C*H*HOSi), 4.15 (1H, ddd, *J* 8.3, 6.6, 5.3 Hz, H_6), 4.02 (1H, dd, *J* 11.4, 7.5 Hz, C_1CH*H*OSi), 3.94 (1H, dd, *J* 5.3, 3.9 Hz, H_7), 3.42 (1H, ddd, *J* 7.0, 6.2, 4.8 Hz, H_3), 3.20 (1H, dd, *J* 8.3, 6.6 Hz, H_5), 3.10 (1H, dd, *J* 6.9, 3.9 Hz, H_{7a}), 3.01 (1H, t, *J* 8.3 Hz, $H_{5'}$), 2.58 (1H, dddd, *J* 7.5, 6.9, 4.8, 2.4 Hz, H_1), 1.74 (3H, s, Ac), 1.72 (3H, s, Ac), 1.58 (3H, s, Ac), 1.20 (9H, s, *t*-Bu), 1.09 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.08, 170.00, 169.5, 82.4, 79.8, 79.6, 73.7, 73.4, 71.5, 64.1, 62.8, 60.4, 53.6, 51.1, 29.2, 28.6, 20.4, 20.3; IR (film) *v:* 1745, 1231 cm^{-1}; HRESI-TOFMS: calcd for [M+H$^+$] $C_{23}H_{40}NO_8$: 458.2748. Found: *m/z* 458.2736.

4.6. (1*S*,2*S*,3*S*,6*S*,7*S*,7a*S*)-2,6,7-Triacetoxy-1,3-bis(acetoxymethyl)-pyrrolizidine (18)

The triacetate **17** (65 mg, 0.14 mmol) dissolved in trifluoroacetic acid (5 mL) was stirred overnight. After solvent removal, the residue was acetylated following standard conditions. Chromatographic purification on silica gel (1:4 hexane–EtOAc) afforded 47 mg (78%) of peracetylated pyrrolizidine **18** as a colourless oil; $[\alpha]_D$ −1.5 (*c* 3.05, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 5.54 (1H, m, H_6), 5.30–5.22 (2H, H_7, H_2), 4.36–4.24 (2H, C_3C*H*HOSi, C_1C*H*HOSi), 4.19–4.11 (2H, C_3CH*H*OSi, C_1CH*H*OSi), 3.27 (1H, dd, *J* 9.3, 7.0 Hz, H_5), 3.1 (1H, m, H_3), 2.99–2.91 (2H, $H_{5'}$, H_{7a}), 2.54 (1H, m, H_1), 1.68 (3H, s, Ac), 1.66 (3H, s, Ac), 1.62 (3H, s, Ac), 1.61 (3H, s, Ac), 1.54 (3H, s, Ac); ^{13}C NMR (125 MHz, C_6D_6): δ 170.2, 170.0, 169.9, 169.6, 169.2, 81.0, 78.8, 78.7, 71.4, 63.5, 62.5, 60.3, 51.2, 50.6, 30.1, 20.30, 20.27, 20.23, 20.22; IR (film) *v:* 1740, 1234 cm^{-1}; HRESI-TOFMS: calcd for [M+H$^+$] $C_{19}H_{28}NO_{10}$: 430.1707. Found: *m/z* 430.1724.

4.7. (1*S*,2*S*,3*S*,6*S*,7*S*,7a*S*)-2,6,7-Hydroxy-1,3-bis(hydroxymethyl)-pyrrolizidine (9)

Compound **18** (40 mg, 0.09 mmol) was dissolved in 5 mL of a 1% soln of ammonia in MeOH. After disappearance of the substrate, the reaction mixture was filtered through a Florisil pad and concentrated to afford 18 mg (89%) of the pyrrolizidine **9** as a colourless oil; $[\alpha]_D$ −5.2 (*c* 2.8, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3OD): δ 3.94 (1H, dd, *J* 11.5, 6.0 Hz, C_3C*H*HOH), 3.88 (1H, dd, *J* 11.5, 6.9 Hz, C_3CH*H*OH), 3.57–3.50 (2H, C_1CH_2OH); 3.22 (1H, dd, *J* 9.7, 7.8 Hz, H_5), 3.14–3.08 (2H, $H_{5'}$,H_3), 4.17 (1H, dd, *J* 4.2, 2.2 Hz, H_2), 4.06 (1H, ddd, *J* 7.6, 6.2, 5.9 Hz, H_6), 4.00 (1H, dd, *J* 5.9, 5.1 Hz, H_7), 3.00 (1H, t, *J* 5.1 Hz, H_{7a}), 2.34 (1H, dddd, *J* 7.1,

6.6, 5.1, 2.2 Hz, H_1); ^{13}C NMR (125 MHz, CD_3OD): δ 83.3, 78.8, 77.4, 73.4, 67.9, 63.9, 59.1, 56.3, 53.7; IR (film) *v:* 3342 cm^{-1}; HRESI-TOFMS: calcd for $[M+H^+]$ $C_9H_{18}NO_5$: 220.1179. Found: *m/z* 220.1170.

4.8. (1*S*,2*S*,3*S*,6*S*,7*S*,7*aS*)-6,7-Di-*tert*-butoxy-3-(*tert*-butyldiphenylsilyloxymethyl)-2-hydroxy-1-(pivaloyloxymethyl)-pyrrolizidine (23)

A soln of alcohol **22** (0.5 g, 0.75 mmol) and Et_3N (0.15 g, 1.50 mmol) in 25 mL of CH_2Cl_2 was cooled to −15 °C, and MsCl was added (0.13 g, 1.13 mmol). The progress of the reaction was controlled by TLC (1:1 hexane–EtOAc). Subsequently, the reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with water, brine and dried over anhyd Na_2SO_4. After solvent removal, the residue was purified on silica gel (1:1 hexane–EtOAc) affording 0.50 g (89%) of mesylate which was directly used for the next step. A soln of the mesylate in 20 mL of 4:1 EtOAc–MeOH was treated with 10% Pd/C (40 mg) and saturated with hydrogen under atmospheric pressure. After disappearance of the starting material the post-reaction mixture was filtered through Celite pad and concentrated. Chromatographic purification of the residue on silica gel (1:1 hexane–EtOAc) gave 0.32 g (75%) of pyrrolizidine **23** as a colourless oil. $[\alpha]_D$ +14.2 (*c* 0.39, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 7.92–7.20 (10H, 2 × Ph), 4.34–4.20 (3H, H_2, C*H*HOPiv, C*H*HOSi), 4.00 (1H, dd, *J* 11.2, 7.9 Hz, CH*H*OPiv), 3.91 (1H, m, H_7), 3.86 (1H, m, H_6), 3.51 (1H, m, H_3), 3.46 (1H, d, *J* 8.0 Hz, CH*H*OSi), 3.20 (1H, dd, *J* 11.0, 5.0 Hz, H_5), 3.16–3.08 (2H, $H_{5'}$, H_{7a}), 2.56 (1H, m, H_1), 1.20 (9H, s, *t*-Bu), 1.19 (9H, s, *t*-Bu), 1.30 (9H, s, *t*-Bu), 0.97 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.6, 135.6, 133.4, 129.6, 127.7, 81.9, 79.9, 77.6, 75.0, 74.1, 73.9, 67.5, 65.2, 61.0, 54.5, 51.2, 38.9, 28.6, 28.2, 27.2, 26.8, 19.2; IR (film) *v:* 3396, 1731, 1112 cm^{-1}; HRESI-TOFMS: calcd for $[M+H^+]$ $C_{38}H_{60}NO_6Si$: 654.4184. Found: *m/z* 654.4187. Anal. Calcd for $C_{38}H_{59}O_6Si$: C, 69.79; H, 9.09; N, 2.14. Found: C, 69.72; H, 9.12; N, 2.15.

4.9. (1*S*,2*S*,3*S*,6*S*,7*S*,7*aS*)-2-Benzyloxy-6,7-di-*tert*-butoxy-3-(*tert*-butyldiphenylsilyloxymethyl)-1-(pivaloyloxymethyl)-pyrrolizidine (25)

A suspension of alcohol **23** (0.50 g, 0.77 mmol), MgO (0.06 g, 1.55 mmol) and Dudley's reagent (0.35 g, 1.00 mmol) in 20 mL of benzene was refluxed under argon atmosphere. After disappearance of the substrate the post-reaction mixture was filtered through Celite and concentrated. The residue was chromatographed on silica gel (1:1 hexane–EtOAc with addition of 1% of Et_3N) to afford 0.56 g (97%) of product **25** as a low-melting solid. $[\alpha]_D$ +5.4 (*c* 0.37, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.70–7.30 (15H, 3 × Ph), 4.96 (1H, d, *J* 5.1 Hz, H_2), 4.79 (1H, d, *J* 12.6 Hz, OC*H*HPh), 4.56 (1H, d, *J* 12.6 Hz, OCH*H*Ph), 4.46 (1H, dd, *J* 13.5, 3.8 Hz, C*H*HOSi), 4.38 (1H, m, H_3), 4.25 (1H, dd, *J* 13.5, 9.0 Hz, CH*H*OSi), 4.10–3.90 (4H, H_6, H_7, CH_2OPiv), 3.79 (1H, dd, *J* 12.6, 7.4 Hz, H_5), 3.69 (1H, dd, *J* 8.0, 1.8 Hz, H_{7a}), 3.51 (1H, dd, *J* 12.6, 6.7 Hz, $H_{5'}$), 2.62 (1H, m, H_1), 1.18 (9H, s, *t*-Bu), 1.05 (9H, s, *t*-Bu), 0.99 (9H, s, *t*-Bu), 0.90 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6, without Ph groups): δ 177.8, 80.5, 77.7, 77.1, 76.7, 75.4, 72.8, 71.3, 67.2, 63.2, 61.0, 60.0, 48.6, 38.7, 28.4, 28.3, 27.1, 26.9, 19.2; IR (film) *v:* 1731, 1111 cm^{-1}; HRESI-TOFMS: calcd for $[M+H^+]$ $C_{45}H_{66}NO_6Si$: 744.4654. Found: *m/z* 744.4628.

4.10. (1*S*,2*S*,3*S*,6*S*,7*S*,7*aS*)-6,7-Di-*tert*-butoxy-2-(*tert*-butyldiphenylsilyloxy)-3-(*tert*-butyldiphenylsilyloxymethyl)-1-(pivaloyloxmethyl)-pyrrolizidine (26)

The alcohol **23** (0.30 g, 0.46 mmol) and imidazole (0.09 g, 1.38 mmol) were dissolved in 1 mL of CH_2Cl_2 and cooled to −15 °C. Subsequently, *tert*-butyldiphenylsilyl chloride was added (0.63 g, 2.30 mmol). After disappearance of the substrate, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with water, brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified on silica gel (9:1 hexane–EtOAc) to afford 0.25 g (60%) of disilylated pyrrolizidine **26** as a colourless oil, $[\alpha]_D$ +24.1 (*c* 0.55, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 8.00–7.10 (20H, 4 × Ph), 4.49 (1H, d, *J* 3.2 Hz, H_2), 4.44 (1H, dd, *J* 10.6, 7.3 Hz, C*H*HOSi), 4.36 (1H, dd, *J* 10.6, 5.9 Hz, CH*H*OSi), 4.16 (1H, m, H_6), 4.02 (1H, m, H_7), 3.83 (1H, dd, *J* 11.5, 5.9 Hz, C*H*HOPiv), 3.63 (1H, dd, *J* 11.5, 5.3 Hz, CH*H*OPiv), 3.52 (1H, m, H_5), 3.42 (1H, m, H_3), 3.34 (1H, m, $H_{5'}$), 3.24 (1H, m, H_{7a}), 2.48 (1H, m, H_1), 1.24 (9H, s, *t*-Bu), 1.13 (9H, s, *t*-Bu), 1.11 (9H, s, *t*-Bu), 1.09 (9H, s, *t*-Bu), 1.04 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6, without Ph groups): δ 177.6, 82.6, 80.7, 78.5, 73.3, 72.9, 70.4, 68.2, 64.9, 61.9, 54.0, 52.7, 38.7, 29.4, 28.7, 27.30, 27.26, 27.25, 27.19, 26.8, 19.6, 19.5; IR (film) *v:* 1731, 1111 cm^{-1}; HRESI-TOFMS: calcd for $[M+H^+]$ $C_{54}H_{78}NO_6Si_2$: 892.5262. Found: *m/z* 892.5371. Anal. Calcd for $C_{54}H_{77}O_6Si_2$: C, 72.68; H, 8.70; N, 1.57. Found: C, 72.81; H, 8.74; N, 1.59.

4.11. (1*S*,2*S*,3*S*,6*S*,7*S*,7*aS*)-6,7-Di-*tert*-butoxy-2-(*tert*-butyldiphenylsilyloxy)-3-(*tert*-butyldiphenylsilyloxymethyl)-1-hydroxymethyl-pyrrolizidine (29)

A soln of compound **26** (0.24 g, 0.27 mmol) in toluene (10 mL) was cooled to −78 °C and treated with 1 M solution of DIBAL-H in hexane (1.1 mL). After disappearance of the substrate, water was added (60 μL) and the suspension was stirred for 30 min. After filtration though a Celite pad and solvent evaporation, the residue was chromatographed on silica gel (1:1 hexane–EtOAc) affording 0.20 g (90%) of liquid alcohol **29**. $[\alpha]_D$ +25.2 (*c* 0.67, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 8.00–7.20 (20H, 4 × Ph), 4.42 (1 H, dd, *J* 10.7, 8.0 Hz, C*H*HOSi), 4.35 (1H, dd, *J* 3.9, 1.6 Hz, H_2), 4.29 (1H, dd, *J* 10.7, 4.8 Hz, CH*H*OSi), 4.18 (1H, m, H_6), 4.11 (1H, m, H_7), 3.56 (1H, m, H_5), 3.28 (1H, m, $H_{5'}$), 3.20 (1H, ddd, *J* 8.0, 4.8, 3.9 Hz, H_3), 3.09–3.01 (2H, H_{7a}, C*H*HOH), 2.95 (1H, m, CH*H*OH), 2.33 (1H, m, H_1), 1.24 (9H, s, *t*-Bu), 1.18 (9H, s, *t*-Bu), 1.13 (9H, s, *t*-Bu), 1.09 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6, without Ph groups): δ 82.5, 80.6, 79.1, 73.6, 73.0, 71.5, 67.8, 63.9, 63.0, 55.7, 54.8, 29.5, 28.9, 27.3, 27.2, 19.6, 19.5; IR (film) *v:* 3245, 1111 cm^{-1}; HRESI-TOFMS: calcd for $[M+H^+]$ $C_{49}H_{70}NO_5Si_2$: 808.4787. Found: *m/z* 808.4826.

4.12. (1*S*,2*S*,3*S*,6*S*,7*S*,7*aS*)-6,7-Di-*tert*-butoxy-2-(*tert*-butyldiphenylsilyloxy)-3-(*tert*-butyldiphenylsilyloxymethyl)-1-mesyloxymethyl-pyrrolizidine (30)

Alcohol **29** (0.19 g, 0.24 mmol) was dissolved in CH_2Cl_2 (20 mL), treated with Et_3N (0.05 g, 0.48 mmol) and cooled to −15 °C. Subsequently, mesyl chloride (0.06 g, 0.48 mmol) was added. After disappearance of the substrate, the reaction mixture was diluted with CH_2Cl_2, washed with water, brine and dried over anhyd Na_2SO_4. Purification on silica gel (2:1 hexane–EtOAc) afforded 0.19 g (93%) of mesylate **30** as a yellowish oil. $[\alpha]_D$ +31.1 (*c* 0.51, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 8.00–7.19 (20H, 4 × Ph), 4.41 (1H, dd, *J* 10.8, 8.4 Hz, C*H*HOSi), 4.33 (1H, d, *J* 3.2 Hz, H_2), 4.29–4.16 (2H, CH*H*OSi, H_6), 4.09 (1H, m, H_7), 3.63–3.50 (3H, H_5, CH_2OH), 3.42 (1H, m, $H_{5'}$), 3.24 (1H, m, H_3), 3.14 (1H, m, H_{7a}), 2.50 (1H, m, H_1), 1.26 (9H, s, *t*-Bu), 1.16 (9H, s, *t*-Bu), 1.13 (9H, s, *t*-Bu), 1.11 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6, without Ph groups): δ 82.2, 79.9, 73.6, 73.2, 69.1, 67.6, 61.9, 53.9, 52.6, 36.4, 29.5, 28.7, 27.23, 27.20, 19.6, 19.5; HRESI-TOFMS: calcd for $[M+H^+]$ $C_{50}H_{72}NO_7Si_2S$: 886.4563. Found: *m/z* 886.4593.

4.13. (1*R*,2*S*,3*S*,6*S*,7*S*,7*aS*)-2-Acetoxy-6,7-di-*tert*-butoxy-3-(acetoxymethyl)-1-methyl-pyrrolizidine (31)

4.13.1. Method A

To a soln of mesylate **30** (0.10 g, 0.11 mmol) in Et_2O (5 mL) cooled to 0 °C, 1 M solution of $LiAlH_4$ in diethyl ether (0.40 mL) was added. After disappearance of the substrate, an excess of hydride was decomposed by addition of water (50 μL). After filtration through Celite and solvent evaporation, the residue was acetylated under standard conditions. Chromatographic purification on silica gel (1:3 hexane–EtOAc) gave 24 mg (54%) of diacetate **31**.

4.13.2. Method B

To a soln of mesylate **30** (0.10 g, 0.11 mmol) in THF (5 mL) cooled to 0 °C, 1 M soln of $LiEt_3BH$ in THF (0.88 mL) was added. After disappearance of the substrate, an excess of hydride was decomposed by addition of MeOH. After solvent removal, the residue was evaporated with toluene. Subsequently, the residue was dissolved in THF (10 mL) and a soln of TBAF (0.08 g, 0.25 mmol) in 5 mL of THF was added. After 1 h, the solvent was removed and the residue was acetylated under standard conditions. Purification on silica gel column (4:1, then 1:4 hexane–EtOAc) afforded 30 mg (68%) of compound **31**. Colourless oil, $[\alpha]_D$ +23.3 (*c* 0.29, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 4.96 (1H, dd, *J* 4.8, 2.9 Hz, H_2), 4.47 (1H, dd, *J* 11.4, 6.5 Hz, C*H*HOAc), 4.40 (1H, dd, *J* 11.4, 6.9 Hz, CH*H*OAc), 4.13 (1H, ddd, *J* 8.4, 6.7, 5.5 Hz, H_6), 3.85 (1H, dd, *J* 5.5, 4.3 Hz, H_7), 3.36 (1H, ddd, *J* 6.5, 6.1, 4.8 Hz, H_3), 3.14 (1H, dd, *J* 8.2, 6.7 Hz, H_5), 3.00 (1H, dd, *J* 8.4, 8.2 Hz, $H_{5'}$), 2.88 (1H, dd, *J* 6.6, 4.3 Hz, H_{7a}), 2.21 (1H, m, *J* 7.2, 6.6, 2.9 Hz, H_1), 1.74 (3H, s, Ac), 1.60 (3H, s, Ac), 1.16 (9H, s, *t*-Bu), 1.09 (9H, s, *t*-Bu), 1.3 (3H, d, *J* 7.2 Hz, Me); ^{13}C NMR (125 MHz, C_6D_6): δ 169.9, 169.7, 83.8, 82.4, 79.6, 76.4, 73.4, 73.3, 62.0, 60.7, 53.5, 45.7, 29.2, 28.7, 20.4, 18.1; IR (film) *v:* 1743, 1232 cm^{-1}; HRESI-TOFMS: calcd for $[M+H^+]$ $C_{21}H_{38}NO_6$: 400.2699. Found: *m/z* 400.2704.

4.14. (1*R*,2*S*,3*S*,6*S*,7*S*,7*aS*)-2,6,7-Triacetoxy-3-(acetoxymethyl)-1-methyl-pyrrolizidine (32)

Diacetate **31** (26 mg, 60 μmol) was dissolved in trifluoroacetic acid (10 mL) and the resulting soln was stirred overnight. After solvent removal, the residue was acetylated in standard condition. Purification on silica gel (1:4 hexane–EtOAc) afforded 21 mg (86%) of the peracetylated pyrrolizidine **32** as a low-melting solid; $[\alpha]_D$ +24.1 (*c* 0.45, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 5.54 (1H, ddd, *J* 7.0, 7.0, 4.9 Hz, H_6), 5.24 (1H, dd, *J* 4.9, 4.6 Hz, H_7), 4.93 (1H, dd, *J* 5.4, 3.8 Hz, H_2), 4.30 (1H, dd, *J* 11.5, 6.1 Hz, C*H*HOAc), 4.18 (1H, dd, *J* 11.5, 7.1 Hz, CH*H*OAc), 3.27 (1H, dd, *J* 9.4, 7.0 Hz, H_5), 3.19 (1H, ddd, *J* 7.1, 6.1, 5.4 Hz, H_3), 3.00 (1H, dd, *J* 9.4, 7.0 Hz, $H_{5'}$), 2.67(1H, dd, *J* 7.6, 4.6 Hz, H_{7a}), 2.28 (1H, m, *J* 7.6, 7.0, 3.8 Hz, H_1), 1.70 (3H, s, Ac), 1.64 (3H, s, Ac), 1.63 (3H, s, Ac), 1.59 (3H, s, Ac), 1.06 (3H, d, *J* 7.1 Hz, Me); ^{13}C NMR (125 MHz, C_6D_6): δ 170.1, 169.9, 169.6, 169.4, 82.9, 81.0, 78.9, 75.8, 61.7, 60.7, 51.4, 45.1, 20.3, 16.8; IR (film) *v:* 1731, 1111 cm^{-1}; HRESI-TOFMS: calcd for $[M+Na^+]$ $C_{17}H_{25}NO_8Na$: 394.1472. Found: *m/z* 394.1492.

4.15. (1*R*,2*S*,3*S*,6*S*,7*S*,7*aS*)-2,6,7-Trihydroxy-3-(hydroxymethyl)-1-methyl-pyrrolizidine (10)

Pyrrolizidine **32** (21 mg, 56 μmol) was dissolved in a 1% soln of NH_3 in MeOH (5 mL) and stirred under argon. The progress of the reaction was monitored by mass spectrometry. Filtration through a small Florisil pad and evaporation of the solvent afforded 10.5 mg (91%) of pyrrolizidine **10** as a colourless oil; $[\alpha]_D$ +16.5 (*c* 0.33, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_3OD): δ 4.02 (1H, m, H_6), 3.96–3.83 (3H, H_7, CH_2OH), 3.18 (1H, m, H_5), 3.13–3.02 (2H, H_3, $H_{5'}$), 2.80 (1H, m, H_{7a}), 2.17 (1H, m, H_1), 1.05 (1H, d, *J* 7.2 Hz, Me); ^{13}C NMR (125 MHz, CD_3OD): δ 83.1, 81.7, 78.7, 77.4, 66.7, 59.2, 53.6, 47.2, 18.4; IR (film) *v:* 3324 cm^{-1}; HRESI-TOFMS: calcd for $[M+H^+]$ $C_9H_{18}NO_4$: 204.1230. Found: *m/z* 204.1232.

4.16. (1*S*,2*S*,3*S*,6*S*,7*S*,7*aS*)-6,7-Di-*tert*-butoxy-3-(*tert*-butyldiphenylsilyloxymethyl)-2-(pivaloyloxy)-1-(pivaloyloxymethyl)-pyrrolizidine (27)

To a soln of alcohol **23** (0.50 g, 0.77 mmol) and DMAP (0.19 g, 1.55 mmol) in CH_2Cl_2 (2 mL) PivCl was added (0.15 g, 1.20 mmol). After disappearance of the substrate, the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with saturated Na_2CO_3, water, brine and dried over anhyd Na_2SO_4. After solvent evaporation, the residue was purified on silica gel (2:1 hexane–EtOAc) to give 0.57 g (60%) of dipivalate **27** as a colourless oil. $[\alpha]_D$ +28.0 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 7.90–7.20 (10H, 2 × Ph), 5.50 (1H, d, *J* 2.6 Hz, H_2), 4.44 (1H, dd, *J* 11.5, 5.1 Hz, C*H*HO-Piv), 4.24 (1H, ddd, *J* 8.7, 7.4, 6.7 Hz, H_6), 4.16–4.10 (2H, CH_2OSi), 4.06–3.96 (2H, H_3, CH*H*OPiv), 3.93 (1H, m, H_7), 3.47 (1H, m, H_{7a}), 3.41 (1H, dd, *J* 8.7, 6.7 Hz, H_5), 3.06 (1H, dd, *J* 9.3, 8.7 Hz, $H_{5'}$), 2.72 (1H, m, H_1), 1.27 (9H, s, *t*-Bu), 1.20 (9H, s, *t*-Bu), 1.17 (9H, s, *t*-Bu), 1.07 (9H, s, *t*-Bu), 1.06 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6, without Ph groups): δ 177.7, 176.5, 81.8, 79.1, 77.6, 73.8, 73.6, 68.7, 65.0, 63.9, 59.9, 52.3, 50.7, 38.9, 38.8, 293, 29.6, 27.4, 27.1, 27.0, 19.5; IR (film) *v:* 1734, 1147, 1112 cm^{-1}; HRESI-TOFMS: calcd for $[M+H^+]$ $C_{43}H_{68}NO_7Si$: 738.4759. Found: *m/z* 738.4726. Anal. Calcd for $C_{43}H_{67}O_7Si$: C, 69.97; H, 9.15; N, 1.90. Found: C, 69.99; H, 9.17; N, 1.89.

4.17. (1*S*,2*S*,3*S*,6*S*,7*S*,7*aS*)-6,7-Di-*tert*-butoxy-3-(mesyloxymethyl)-2-(pivaloyloxy)-1-(pivaloyloxymethyl)-pyrrolizidine (34)

To a soln of dipivalate **27** (0.20 g, 0.27 mmol) in THF (25 mL), TBAF (0.07 g, 0.29 mmol) in THF (5 mL) was added and the mixture was stirred for 2 h. Subsequently, the solvent was evaporated and the residue was chromatographed on silica gel (1:4 hexane–EtOAc) affording 0.13 g (93%) of alcohol **33**, which was directly used for the next step. Alcohol **33** was dissolved in CH_2Cl_2 (15 mL), and Et_3N (0.05 g, 0.50 mmol) was added. After cooling to −15 °C MsCl was added (0.06 g, 0.50 mmol). Standard work-up and purification on silica gel column (4:1 EtOAc–hexane) afforded 0.13 g (92%) of mesylate **34** as a yellowish oil. $[\alpha]_D$ +3.6 (*c* 1.78, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 5.32 (1H, dd, *J* 4.5, 2.2 Hz, H_2), 4.49 (1H, dd, *J* 10.4, 7.4 Hz, C*H*HOMs), 4.39 (1H, dd, *J* 11.5, 4.3 Hz, C*H*HOPiv), 4.34 (1H, dd, *J* 10.4, 6.2 Hz, CH*H*OMs), 4.13 (1H, ddd, *J* 8.2, 6.8, 5.1 Hz, H_6), 3.95 (1H, dd, *J* 11.5, 7.2 Hz, CH*H*OPiv), 3.89 (1H, dd, *J* 5.1, 4.0 Hz, H_7), 3.44 (1H, ddd, *J* 7.4, 6.2, 4.5 Hz, H_3), 3.23 (1H, dd, *J* 8.3, 6.8 Hz, H_5), 3.13 (1H, dd, *J* 6.7, 4.0 Hz, H_{7a}), 2.96 (1H, dd, *J* 8.3, 8.2 Hz, $H_{5'}$), 2.54 (1H, dddd, *J* 7.2, 6.7, 4.3, 2.2 Hz, H_1), 2.30 (3H, s, Ms), 1.18 (9H, s, *t*-Bu), 1.17 (9H, s, *t*-Bu), 1.13 (9H, s, *t*-Bu), 1.06 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 177.6, 176.9, 82.2, 79.5, 79.4, 73.8, 73.4, 71.3, 64.5, 63.8, 63.3, 53.7, 51.1, 38.9, 38.8, 37.2, 29.2, 28.6, 27.3, 27.1; IR (film) *v:* 1732, 1177, 1151 cm^{-1}; HRESI-TOFMS: calcd for $[M+Na^+]$ $C_{28}H_{51}NO_9SNa$: 600.3177. Found: m/*z* 600.3170.

4.18. (1*S*,2*S*,7*R*,8*S*,8*aS*)-1,2,7-Tribenzoyloxy-8-(benzoyloxymethyl)-indolizidine (37)

To a cooled soln of mesylate **34** (0.10 g, 0.17 mmol) in 10 mL of Et_2O, a 1 M soln of $LiAlH_4$ in Et_2O (2.7 mL) was added. After disappearance of the substrate, an excess of hydride was decomposed by addition of water. The organic layer was filtered through Celite and evaporated. The residue was treated with trifluoroacetic acid and stirred overnight. Subsequently, the solvent was removed, and

the residue dissolved in dry pyridine (15 mL), cooled and treated with BzCl (2 mL). After 12 h, the reaction mixture was diluted with CH_2Cl_2, washed with water, brine and dried over anhyd Na_2SO_4. After solvent removal, the residue was chromatographed on silica gel column (2:1 hexane–EtOAc) affording 17 mg of tetrabenzoate **37** containing ca. 10% inseparable impurities (according to NMR spectra) as a colourless oil; ^{1}H NMR (500 MHz, C_6D_6, without Ph groups): δ 5.93 (1H, ddd, *J* 6.9, 6.6, 3.5 Hz, H_2), 5.71 (1H, dd, *J* 3.5, 2.5 Hz, H_1), 4.32 (1H, d, *J* 6.6 Hz, H_7), 4.25 (1H, dd, *J* 12.1, 4.3 Hz, C*H*HOSi), 4.07 (1H, dd, *J* 12.1, 9.2 Hz, CH*H*OSi), 3.95–3.85 (2H, H_5, H_{8a}), 3.80–3.71 (2H, H_3, $H_{5'}$), 2.75 (1H, dd, *J* 11.0, 6.6 Hz, $H_{3'}$), 2.65 (1H, m, *J* 14.0, 9.2, 6.6, 4.3 Hz, H_8), 1.47–1.38 (1H, m, H_6), 1.30 (1H, ddd, *J* 13.5, 7.0, 4.1 Hz, $H_{6'}$) H; ^{13}C NMR (125 MHz, C_6D_6, without Ph groups): δ 166.2, 166.1, 165.9, 165.4, 81.2, 78.9, 72.7, 66.3, 63.7, 60.1, 49.9, 40.9, 29.1, IR (film) *v:* 1736 cm^{-1}; HRESI-TOFMS: calcd for [M+H$^+$] $C_{37}H_{34}NO_8$: 620.2284. Found: *m/z* 620.2279.

4.19. (1*aS*,2*R*,6*aS*,6*bS*,7*S*,8*S*)-7,8-di-*tert*-butoxy-2-(*tert*-butyldiphenylsilyloxymethyl)-3,3-dimethyloctahydro-[1,3]dioxepino[5,6-*d*]pyrrolo[1,2-*b*]isoxazole (38)

A soln of diol **13** (1.1 g, 1.88 mmol) and *p*-TsOH (35 mg, 0.18 mmol) in 30 mL of 2,2-dimethoxypropane was refluxed for 1.5 h. After cooling and neutralizing of the acid by Et_3N (1 mL), the solvent was removed under diminished pressure. The obtained residue was purified by column chromatography (silica gel, 4:1 hexane–EtOAc) affording 0.82 g (70%) of **38** as a colourless oil; $[\alpha]_D$ +22.4 (*c* 0.65, CH_2Cl_2); ^{1}H NMR (500 MHz, toluen-d_8): δ 7.70–7.20 (10H, 2 × Ph), 4.11 (1H, ddd, *J* 9.9, 6.8, 2.0 Hz, H_2), 4.01 (1H, dd, *J* 10.7, 2.0 Hz, C*H*HOSi), 3.97–3.81 (4H, H_{1a},H_6,H_{6b},H_8), 3.78 (1H, m, H_7), 3.72 (1H, dd, *J* 10.7, 6.8 Hz, CH*H*OSi), 3.54–3.46 (2H, $H_{6'}$,H_9), 3.12 (1H, dd, *J* 12.5, 4.5 Hz, $H_{9'}$), 2.65 (1H, m, H_{6a}), 1.33 (3H, s, Me), 1.28 (3H, s, Me), 1.12 (9H, s, *t*-Bu), 1.03 (9H, s, *t*-Bu), 0.97 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, toluene-d_8): δ 136.2, 132.9, 129.5, 127.3, 101.7, 80.2, 79.0, 74.4, 73.9, 71.9, 69.7, 63.8, 63.1, 56.9, 49.6, 28.5, 28.4, 25.6, 24.8, 24.5; HRESI-TOFMS: calcd for [M+Na$^+$] $C_{36}H_{55}NO_6SiNa$: 648.3696. Found: *m/z* 648.3690. Anal. Calcd for $C_{36}H_{55}NO_6Si$: C, 69.08; H, 8.86; N, 2.24. Found: C, 69.10; H, 8.87; N, 2.23.

4.20. (1*aS*,2*R*,6*aS*,6*bS*,7*S*,8*S*)-7,8-Di-*tert*-butoxy-2-(mesyloxymethyl)-3,3-dimethyloctahydro-[1,3]dioxepino-[5,6-*d*]pyrrolo[1,2-*b*]isoxazole (39)

A soln of compound **38** (0.50 g, 0.8 mmol) in 25 mL of THF was treated with TBAF (0.31 g, 0.96 mmol) in 10 mL of THF. The mixture was stirred at room temperature for 3 h. After that time, the solvent was removed under diminished pressure and the residue was chromatographed on a silica gel column (2:1 hexane–EtOAc with 1% of Et_3N then EtOAc 100%) to afford 0.34 g (90%) of the alcohol, which was directly used in the next step. It was dissolved in CH_2Cl_2 (15 mL) and treated with Et_3N (0.18 g, 1.74 mmol, 242 μL). After cooling to −15 °C, MsCl (0.15 g, 100 μL, 1.30 mmol) was added dropwise. Then, while stirring for 15 min, the temperature was allowed to rise to room temperature. After disappearance of the substrate, the post-reaction mixture was washed with water (2 × 5 mL), brine (5 mL) and the organic phase was dried over anhyd Na_2SO_4. After filtration and removal of the solvent, the residue was purified on a silica gel column (1:1 hexane–EtOAc) to afford 0.32 g (94%) of mesylate **39** as a yellowish oil; $[\alpha]_D$ +119.8 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 4.43 (1H, ddd, *J* 8.5, 1.9, 1.8 Hz, H_2), 4.27–4.22 (2H, H_{1a}, H_7), 4.01 (1H, br d, *J* 9.5 Hz, H_6), 3.40–3.82 (3H, $H_{6'}$,H_{6b},H_8), 3.72 (1H, dd, *J* 13.4, 1.8 Hz, CH*H*OMs), 3.56 (1H, dd, *J* 13.1, 4.9 Hz, H_9), 3.45 (1H, dd, *J* 13.4, 1.9 Hz, C*H*HOMs), 3.23 (1H, dd, *J* 13.1, 3.3 Hz, $H_{9'}$), 2.64 (1H, m, H_{6a}), 2.22 (3H, s, $MeSO_2$), 1.21 (3H, s, Me), 1.17 (3H, s, Me), 1.10 (9H, s, *t*-Bu), 1.02 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 101.8, 81.3, 79.9, 77.7, 74.1, 73.5, 72.0, 70.7, 68.5, 63.4, 57.1, 50.3, 36.6, 28.5, 28.4, 24.6, 24.3; HRESI-TOFMS: calcd for [M+H$^+$] $C_{21}H_{40}NO_8S$: 466.2469. Found: *m/z* 466.2459.

4.21. (1*aS*,2*R*,6*aS*,6*bS*,7*S*,8*S*)-7,8-Di-*tert*-butoxy-2,3,3-trimethylooctahydro[1,3]dioxepino[5,6-*d*]pyrrolo[1,2-*b*]isoxazole (40)

A soln of mesylate **39** (0.20 g, 0.32 mmol) in THF (10 mL) was treated with 1 M $LiEt_3BH$ in THF (2.5 mL). After disappearance of the substrate, an excess of the hydride was decomposed by addition of MeOH. After solvent removal, the residue was chromatographed on silica gel (1:1 hexane–EtOAc with addition of 1% of Et_3N) to afford 0.10 g (87%) of **40** as a colourless oil; $[\alpha]_D$ +104.2 (*c* 0.37, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 4.18 (1H, m, H_2), 4.06 (1H, br d, *J* 9.8 Hz, H_{1a}), 3.96 (1H, ddd, *J* 5.2, 4.3, 2.4 Hz, H_7), 3.92–3.84 (2H, H_5, H_6), 3.82 (1H, dd, *J* 9.6, 7.1 Hz, $H_{5'}$), 3.65 (1H, dd, *J* 12.5, 5.2 Hz, H_8), 3.54 (1H, br s, H_{5b}), 3.25 (1H, dd, *J* 12.5, 4.3 Hz, $H_{8'}$), 2.66 (1H, m, H_{5a}), 1.40 (3H, d, *J* 6.3 Hz, C^{2}Me), 1.26 (3H, s, Me), 1.21 (3H, s, Me), 1.53 (9H, s, *t*-Bu), 1.04 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6): δ 101.1, 83.6, 81.3, 80.0, 73.9, 73.4, 71.9, 66.6, 63.5, 57.1, 50.3, 28.7, 28.5, 24.8, 24.4, 19.5; HRESI-TOFMS: calcd [M+H$^+$] $C_{20}H_{38}NO_5$: 372.2745. Found: *m/z* 372.2727.

4.22. (*R*)-1-((2*S*,3*S*,3*aS*,4*S*,5*S*)-4,5-Di-*tert*-butoxy-3-(hydroxymethyl)-hexahydropyrrolo[1,2-*b*]isoxazol-2-yl)ethanol (41)

To a soln of **40** (0.15 g, 0.40 mmol) in 5 mL of MeOH–water (9:1), *p*-TsOH (7 mg, 0.04 mmol) was added and the mixture was maintained under a gentle reflux. After disappearance of the substrate, the solvents were removed and the residue was chromatographed on a short silica gel pad (4:1 EtOAc–hexane), affording 0.11 g (80%) of diol **41** as a colourless oil; $[\alpha]_D$ +60.0 (*c* 0.55, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.10–3.97 (2H, $H_{1'}$, H_2), 3.88 (1H, dd, *J* 10.9, 10.5 Hz, C*H*HOH), 3.84–3.78 (2H, H_4, H_5), 3.61 (1H, dd, *J* 10.9, 3.6 Hz, CH*H*OH), 3.46 (1H, dd, *J* 11.5, 4.9 Hz, H_6), 3.06 (1H, m, H_{3a}), 2.92 (1H, dd, *J* 11.5, 6.6 Hz, $H_{6'}$), 2.84 (1H, m, H_3), 1.30 (3H, d, *J* 6.1 Hz, Me), 1.21 (9H, s, *t*-Bu), 1.18 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ 81.7, 75.9, 74.2, 74.0, 73.7, 65.2, 61.8, 60.6, 51.2, 29.7, 28.9, 28.4, 20.6; IR (film) *v:* 3351, 1192, 1105, 1060 cm^{-1}; HRESI-TOFMS: calcd for [M+H$^+$] $C_{17}H_{34}NO_5$: 332.2432. Found: *m/z* 332.2422.

4.23. (*R*)-1-((2*S*,3*S*,3*aS*,4*S*,5*S*)-4,5-Di-*tert*-butoxy-3-(*tert*-butyldiphenylsilyloxymethyl)-hexahydropyrrolo[1,2-*b*]isoxazol-2-yl)ethanol (42)

To a cooled soln of diol **41** (80 mg, 0.24 mmol) and imidazole (20 mg, 0.30 mmol) in CH_2Cl_2 (5 mL), *t*-$BuPh_2SiCl$ (70 mg, 0.26 mmol) was added. After disappearance of the starting diol, the reaction mixture was diluted with CH_2Cl_2, washed with water, brine and dried over anhyd Na_2SO_4. After solvent removal, the residue was chromatographed on a silica gel column (4:1, then 1:1 hexane–EtOAc) affording 0.11 g (90%) of alcohol **42** as a colourless oil; $[\alpha]_D$ +60.7 (*c* 1.45, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6): δ 7.80–7.17 (10H, 2 × Ph), 4.29–4.23 (2H, $H_{1'}$, H_2), 4.18 (1H, dd, *J* 10.6, 10.0 Hz, C*H*HOSi), 3.80–3.70 (2H, H_5, H_4), 3.64 (1H, dd, *J* 10.6, 4.61H, M, H_{3a}Hz, CH*H*OSi), 3.50 (1H, dd, *J* 11.1, 5.6 Hz, H_6), 3.16 (1H, dd, *J* 4.8, 2.2 Hz, H_{3a}), 3.04 (1H, dd, *J* 11.1, 7.3 Hz, $H_{6'}$), 2.96 (1H, m, *J* 10.0, 4.6, 4.6, 2.2 Hz, H_3), 1.53 (3H, d, *J* 5.5 Hz, Me), 1.12 (9H, s, *t*-Bu), 1.03 (9H, s, *t*-Bu), 1.00 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6, without Ph groups): δ 82.5, 82.2, 76.3, 73.9, 73.6, 73.4, 65.7, 64.3, 60.7, 52.7, 29.1, 28.5, 26.9, 21.5, 19.2; IR

(film) *v:* 3480, 1112, 1068 cm^{-1}; HRESI-TOFMS: calcd for $[M+Na^+]$ $C_{33}H_{51}NO_5SiNa$: 592.3429. Found: *m/z* 592.3425.

4.24. (*R*)-1-((2*S*,3*S*,3a*S*,4*S*,5*S*)-4,5-Di-*tert*-butoxy-3-(*tert*-butyldiphenylsilyloxymethyl)-hexahydropyrrolo[1,2-*b*]isoxazol-2-yl)ethyl mesylate (43)

To a cooled soln of alcohol **42** (90 mg, 0.16 mmol) and Et_3N (30 mg, 0.32 mmol) in CH_2Cl_2 (5 mL), MsCl was added (30 mg, 0.24 mmol). After disappearance of the substrate, the reaction mixture was diluted with CH_2Cl_2, washed with water, brine and dried over anhyd Na_2SO_4. After solvent removal, the residue was chromatographed on silica gel (2:1 hexane–EtOAc) affording 90 mg (90%) of mesylate **43** as a yellowish oil; $[\alpha]_D$ +45.0 (*c* 0.50, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 7.80–7.17 (10H, 2 × Ph), 5.08 (1H, m, *J* 6.4, 5.8 Hz, $H_{1'}$), 4.33 (1H, t, *J* 5.8 Hz, H_2), 4.17 (1H, dd, *J* 10.4, 6.1 Hz, C*H*HOSi), 3.98 (1H, dd, *J* 10.4, 8.2 Hz, CH*H*OSi), 3.87 (1H, dd, *J* 3.7, 3.3 Hz, H_{3a}), 3.82–3.76 (2H, H_4, H_5), 3.56 (1H, dd, *J* 12.5, 5.1 Hz, H_6), 3.11 (1H, dd, *J* 12.5, 4.7 Hz, $H_{6'}$), 2.96 (1H, dddd, *J* 8.2, 6.1, 5.8, 3.3 Hz, H_3), 2.24 (3H, s, Ms), 1.40 (3H, d, *J* 6.4 Hz, Me), 1.22 (9H, s, *t*-Bu), 1.10 (9H, s, *t*-Bu), 1.01 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6, without Ph groups): δ 82.8, 79.1, 77.6, 76.6, 74.5, 73.8, 73.6, 62.6, 62.5, 51.9, 28.9, 28.4, 27.2, 19.5, 18.8; HRESI-TOFMS: calcd for $[M+Na^+]$ $C_{34}H_{53}NO_7SiSNa$: 670.3204. Found: *m/z* 670.3211.

4.25. (1*S*,2*S*,3*S*,6*S*,7*S*,7a*S*)-6,7-Di-*tert*-butoxy-1-(*tert*-butyldiphenylsilyloxymethyl)-2-hydroxy-3-methyl-pyrrolizidine (44)

To a soln of mesylate **43** (90 mg, 0.14 mmol) in 5 mL 4:1 EtOAc–MeOH, 10% Pd/C (5 mg) was added and the suspension was saturated with hydrogen under atmospheric pressure. After disappearance of the substrate, the reaction mixture was filtered through Celite and concentrated. The residue was chromatographed on silica gel (20:1 CH_2Cl_2–MeOH) affording 70 mg (93%) of pyrrolizidine **44** as a colourless oil; $[\alpha]_D$ +7.1 (*c* 0.49, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6, without Ph groups): δ 4.27–4.20 (2H, H_2, H_6), 4.11 (1H, t, *J* 5.3 Hz, H_7), 3.91 (1H, m, H_{7a}), 3.81 (1H, m, H_3), 3.76–3.66 (3H, H_5, CH_2OSi), 3.44 (1H, dd, *J* 10.3, 8.4 Hz, $H_{5'}$), 2.83 (1H, m, H_1), 1.46 (3H, d, *J* 6.6 Hz, Me), 1.21 (9H, s, *t*-Bu), 1.10 (9H, s, *t*-Bu), 1.09 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6, without Ph groups): δ 79.6, 75.2, 74.0, 73.6, 69.5, 63.4, 61.4, 52.6, 50.3, 38.6, 27.9, 27.3, 26.2, 18.5, 9.2; IR (film) *v:* 3303, 1192, 1112 cm^{-1}; HRESI-TOFMS: calcd for $[M+H^+]$ $C_{33}H_{52}NO_4Si$: 554.360. Found: *m/z* 554.3683.

4.26. (1*S*,2*S*,3*S*,6*S*,7*S*,7a*S*)-2,6,7-Triacetoxy-1-(acetoxymethyl)-3-methyl-pyrrolizidine (45)

To a soln of pyrrolizidine **44** (60 mg, 0.11 mmol) in 1 mL of THF, a soln of TBAF (40 mg, 0.13 mmol) was added and the mixture was stirred for 1 h. After evaporation of the solvent, the residue was treated with trifluoroacetic acid and stirred overnight. Subsequently, the solvent was removed and the residue was acetylated under standard conditions. Evaporation of the solvent provided a residue, which was chromatographed on silica gel (1:1 then 1:5 hexane–EtOAc) to give 30 mg (75%) of pyrrolizidine **45** as a low-melting solid; $[\alpha]_D$ +19.2 (*c* 0.49, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6): δ 5.58 (1H, ddd, *J* 8.0, 7.0, 5.2 Hz, H_6), 5.29 (1H, dd, *J* 5.2, 3.6 Hz, H_7), 5.10 (1H, dd, *J* 5.1, 2.7 Hz, H_2), 4.32 (1H, dd, *J* 11.2, 6.4 Hz, C*H*HOAc), 4.19 (1H, dd, *J* 11.2, 6.1 Hz, CH*H*OAc), 3.29 1H, dd, *J* 9.1, 7.0 Hz, H_5), 3.00–2.92 (2H, dd, *J* 7.6, 3.6 Hz, for H_{7a}; dd, *J* 6.8, 5.1 Hz, for H_3), 2.89 (1H, dd, *J* 9.1, 8.0 Hz, $H_{5'}$), 2.59 (1H, dddd, *J* 7.6, 6.4, 6.1, 2.7 Hz, H_1), 1.69 (3H, s, Ac), 1.62 (3H, s, Ac), 1.61 (3H, s, Ac), 1.56 (3H, s, Ac), 0.95 (3H, d, *J* 6.9 Hz, Me); ^{13}C NMR (125 MHz, C_6D_6): δ 170.2, 170.0, 169.6, 169.3, 81.8, 80.7, 78.4, 71.4, 65.0, 59.9, 51.3, 50.8, 20.3, 11.3; IR (film) *v:* 1735, 1111 cm^{-1}; HRESI-TOFMS: calcd for $[M+H^+]$ $C_{17}H_{26}NO_8$: 372.1653. Found: *m/z* 372.1668.

4.27. (1*S*,2*S*,3*S*,6*S*,7*S*,7a*S*)-2,6,7-Trihydroxy-1-(hydroxymethyl)-3-methyl-pyrrolizidine (11)

Pyrrolizidine **45** (30 mg, 81 μmol) was dissolved in 10 mL of 1% NH_3 in MeOH and stirred under an argon atmosphere. The progress of deprotection was monitored by mass spectrometry. Filtration through a short Florisil pad and evaporation of the solvent afforded 16 mg (97%) of the pyrrolizidine **11** as a colourless oil; $[\alpha]_D$ −9.1 (*c* 0.84, MeOH); ^1H NMR (500 MHz, CD_3OD): δ 4.04 (1H, ddd, *J* 7.8, 6.1, 5.8 Hz, H_6), 3.99–3.95 (2H, H_2, H_7), 3.57–3.49 (2H, CH_2OH), 3.17 (1H, dd, *J* 9.9, 7.8 Hz, H_5), 3.11 (1H, m, *J* 7.0, 4.0 Hz, H_3), 3.01 (1H, dd, *J* 9.9, 6.1 Hz, $H_{5'}$), 2.97 (1H, t, *J* 4.9 Hz, H_{7a}), 2.32 (1H, dddd, *J* 7.2, 6.7, 4.9, 2.1 Hz, H_1), 1.24 (3H, d, *J* 7.0 Hz, Me); ^{13}C NMR (125 MHz, CD_3OD): δ 83.7, 78.9, 78.7, 73.2, 64.0, 61.6, 56.4, 53.2, 11.2; IR (film) *v:* 3342 cm^{-1}; HRESI-TOFMS: calcd for $[M+H^+]$ $C_9H_{18}NO_4$: 204.1236. Found: *m/z* 204.1234.

4.28. (2*S*,3*S*,3a*S*,4*S*,5*S*)-4,5-Di-*tert*-butoxy-2-((*R*)-1′-benzyloxy-2′-*tert*-butyldiphenylsilyloxyethyl)-3-(pivaloyloxymethyl)-hexahydropyrrolo[1,2-*b*]isoxazole (28)

The reaction was performed according to the procedure described for **25**. Starting from the alcohol **22** (0.10 g, 0.15 mmol), after chromatography on silica gel (1:2 hexane–EtOAc), 0.11 g of compound **28** (95%) was obtained as a low-melting solid; $[\alpha]_D$ +36.2 (*c* 0.45, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6, without Ph groups): δ 5.18–5.08 (3H, H_2, OCH_2Ph), 4.85 (1H, dd, *J* 14.5, 5.1 Hz, H_6), 4.71 (1H, dd, *J* 11.6, 4.8 Hz, C*H*HOPiv), 4.63 (1H, d, *J* 5.7 Hz, H_5), 4.47 (1H, d, *J* 4.8 Hz, H_{3a}), 4.31–4.23 (2H, $H_{1'}$, H_4), 3.95 (1H, dd, *J* 11.1, 4.5 Hz, C*H*HOSi), 3.89 (1H, dd, *J* 11.1, 4.6 Hz, CH*H*OSi), 3.72–3.61 (2H, $H_{6'}$, CH*H*OPiv), 3.45 (1H, m, H_3), 1.32 (9H, s, *t*-Bu), 1.19 (9H, s, *t*-Bu), 1.15 (9H, s, *t*-Bu); 1.10 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6, without Ph groups): δ 177.2, 85.7, 84.5, 79.4, 76.5, 76.2, 75.7, 74.6, 73.0, 69.5, 66.1, 62.5, 46.5, 38.6, 28.2, 27.8, 27.3, 27.1, 19.4; IR (film) *v:* 1734, 1279, 1260, 1152, 1113 cm^{-1}; HR ESI-TOFMS: calcd for $[M+H^+]$ $C_{45}H_{66}NO_7Si$: 760.4603. Found: *m/z* 760.4619. Anal. Calcd for $C_{45}H_{65}NO_7Si$: C, 71.11; H, 8.62; N, 1.84. Found: C, 71.10; H, 8.63; N, 1.83.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.10.016.

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