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The combined use of stereoelectronic control and ring closing metathesis for the synthesis of (−)-8-*epi*-swainsonine

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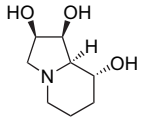
Abstract—A novel and efficient synthesis of (−)-8-*epi*-swainsonine **2** is reported. Stereocontrolled diol formation from the bicyclic alkene **3** followed by a stereoselective vinylation of the aldehyde and ring closing metathesis gave the indolizidine ring system, which was converted into (−)-8-*epi*-swainsonine **2**.

1. Introduction

The indolizidine alkaloids occur widely in nature and these together with many other structural analogues possess wide ranging and interesting biological activity.[1] Fleet et al. in a series of seminal papers have pointed the way to a therapy for tuberculosis based on the glycosidase inhibitor swainsonine and other indolizidine structures.[2] Other glycosidase inhibitors including castanospermine and deoxynojirimycin are useful agents in viral and cancer research.[3] Swainsonine **1**, which has been isolated from the fungus *Rhizoctonia leguminicola*,[4] and also isolated from other fungal[5] and plant sources,[6] has been found to possess properties, which include the inhibition of both lysosomal α-manosidase[7] and monosidase II.[8] Due to the fact that the glycosidases are involved in the degradation of carbohydrates associated with cell walls,[9] the synthesis of glycosidase inhibitors becomes important in the research areas and drug discovery. It is clear that the indolizidine alkaloids are an important class of compounds in the armoury of the drug discovery scientists, but they are often difficult to make on a scale, which would permit extensive biological evaluation.[10] Although over 30 syntheses of (−)-swainsonine **1** have been reported,[3,10,11] many of these utilise the asymmetry present in carbohydrate starting materials to engineer the synthesis of **1**. Non-carbohydrate based starting materials have also been used to construct (−)-swainsonine **1** and have often inspired useful solutions to tackle the problem of indolizidine ring formation. Fewer syntheses of (−)-8-*epi*-swainsonine **2** have been reported[12] hitherto and given the biological importance of the indolizidine family we developed a new route to (−)-8-*epi*-swainsonine **2**, which features a remarkable stereoselective hydroxylation reaction of the oxazolidinone **3**, followed later by a key ring closing metathesis reaction. There are many examples in the literature, which have shown the huge potential of the RCM reaction for the formation of heterocyclic rings,[13–15] and our approach to (−)-8-*epi*-swainsonine **2** further illustrates the power of this reaction.

We have now developed a procedure for the synthesis of (−)-8-*epi*-swainsonine **2** that is flexible and will allow the construction of a wide range of other members of the indolizidine alkaloid family.



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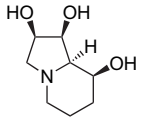

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2. Results and discussion

During our work on the synthesis of the excitatory amino acids including the kainates, we discovered that the light mediated addition of the oxazolidinone **3** to the acetal **4** resulted in the formation of the cyclobutane **5**.[16] The stereochemical outcome of the cycloaddition was a great surprise because the addition occurred on the most hindered face of the oxazolidinone **3** (Scheme 1).

Calculations from our laboratory have shown that the HOMO of alkene **3** reveals an unsymmetrical π-bond with a higher electronic density on its *endo* face (Fig. 1).[17] These data led us to devise new and effective routes to the indolizidine alkaloids including (−)-8-*epi*-swainsonine **2**.

Keywords: Stereoselective; Indolizidine synthesis; Stereoelectronic; Metathesis.
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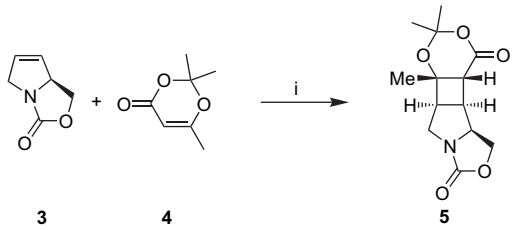


Scheme 1. Reagents: (i) *hν*, EtOAc (38%).

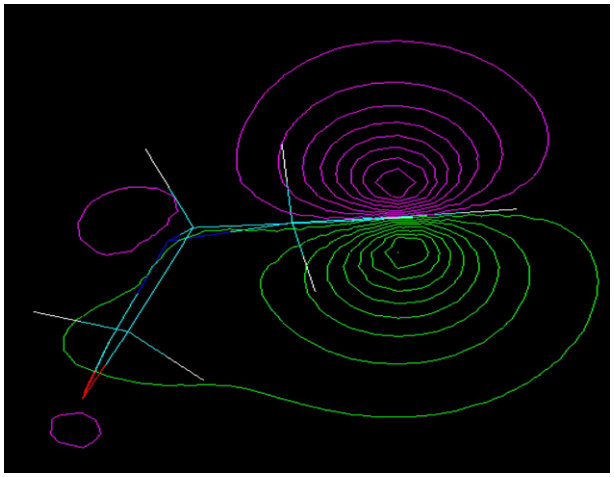
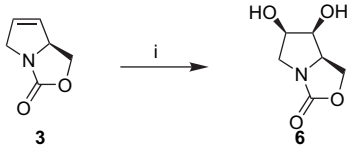


Figure 1. 6-31G representation of the HOMO of oxazolidinone **3**.[17]

Following our discovery that the photochemical additions to the oxazolidinone **3** occur from its most hindered face, we found that electrophilic reagents in general also add from the most hindered face of the alkene present in **3**. Pyne et al. have also reported similar results but overlooked our previous work in this area.[18] Treatment of the oxazolidinone **3** with osmium tetroxide[19] in tertiary butanol gave an excellent yield of the diol **6**,[17] which served as the starting point in our indolizidine alkaloid synthesis (Scheme 2).

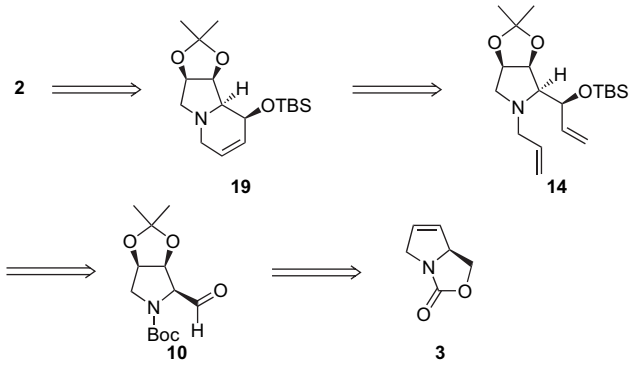


Scheme 2. Reagents: (i) OsO_4, ^tBuOH, H_2O, acetone, NMO (85%).

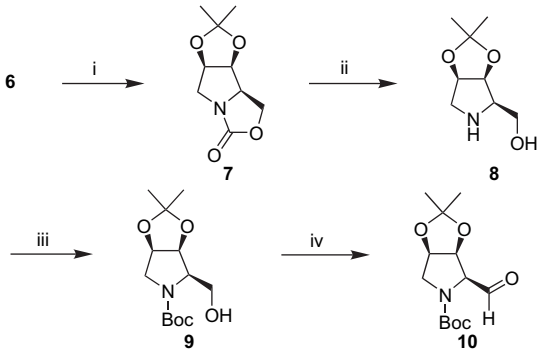
Retrosynthetic analysis of the indolizidine ring system revealed that alkene metathesis could be key to the construction of the six-membered ring present in the swainsonine **1** and *epi*-swainsonine **2** (Scheme 3).

After further functional group interconversions, stereoselective diol formation from **3** would provide the aldehyde **10**. It was envisaged that the aldehyde **10** could be converted into the allylamine **14** and that ring closing metathesis performed on **14** would furnish the *epi*-swainsonine precursor **19**.

In order to carry out the synthesis of *epi*-swainsonine **2** the diol **6** was converted into the acetonide **7**.[20] Smooth conversion of the diol **6** into the acetonide **7** was achieved using a refluxing mixture of acetone/2,2-dimethoxypropane (3:1) in the presence of pyridinium *p*-toluenesulfonate (Scheme 4).



Scheme 3.



Scheme 4. Reagents: (i) $(CH_3O)_2C(CH_3)_2$, PPTS, acetone, Δ (95%); (ii) LiOH, EtOH, Δ; (iii) $(Boc)_2O$, Et_3N, CH_3CN (85% over two steps); (iv) TPAP, 4 Å MS, NMO, CH_2Cl_2 (88%).

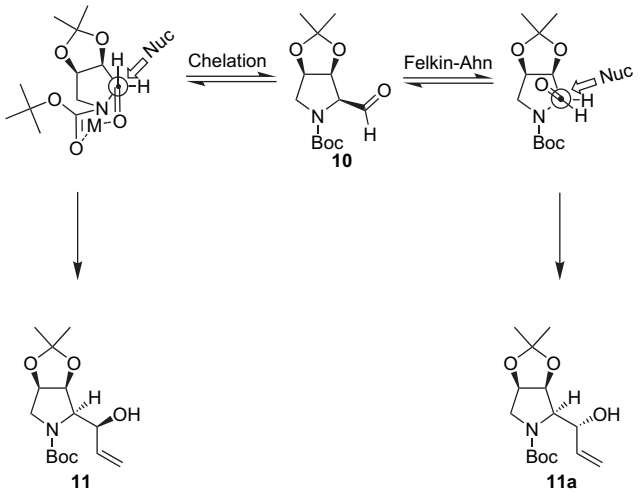
Conversion of the acetonide **7** into alcohol **8** was achieved using lithium hydroxide in hot ethanol. The resulting amino alcohol **8** was treated with di-*tert*-butyl dicarbonate to afford the *N*-Boc protected amine **9** in high yield. Under these reaction conditions only a small amount of carbonate formation was observed.[21] Treatment of the alcohol **9** with TPAP[22] in dry dichloromethane gave the aldehyde **10**, which proved to be configurationally stable. At this stage, we hoped to be able to control the stereochemistry of addition of a vinyl anion to the aldehyde **10**. Felkin–Ahn addition would lead to the stereochemistry required for the formation of swainsonine **1**, whereas chelation control would result in the stereochemistry required for the synthesis of *epi*-swainsonine **2** (Scheme 5).

Donohoe et al. studied the addition of a series of metalloalkenes to a related aldehyde and found that the stereochemistry of the resulting allylic alcohols depended on the metal counter ion selected.[23,24]

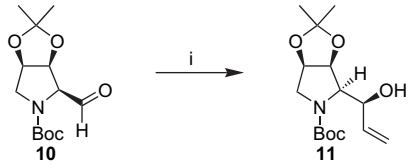
Encouraged by these results, we investigated the reaction of the aldehyde **10** with vinylmagnesium bromide, which under all conditions carried out, gave the allylic alcohol **11** as the exclusive product (Scheme 6; Table 1). The stereochemical outcome of alcohol **11** was later confirmed by X-ray analysis (Fig. 2).

The results were interesting but in contrast to Donohoe's observations on a related system.[23,24]

With the alcohol **11** in hand we were able to continue our synthesis of (−)-8-*epi*-swainsonine **2**.



Scheme 5.



Scheme 6. (i) See Table 1.

Table 1

Entry	Reaction conditions	Temp (°C)	Yield[a] (Conversion, %)	Product
1	CH_2=CHMgBr (1.5 equiv), THF	−78	69 (93)	**11**
2	CH_2=CHMgBr (2.5 equiv), THF	−78	87 (89)	**11**
3	CH_2=CHMgBr (1.5 equiv), THF	rt	85 (100)	**11**
4	CH_2=CHLi (2.0 equiv), Et_2O	−78	46 (77)	**11**
5	CH_2=CHLi (2.0 equiv), DMPU, Et_2O	−78	40 (65)	**11**
6	CH_2=CHLi (4.0 equiv), DMPU, Et_2O	−90	55 (40)	**11**

[a] Yield based on recovered starting material.

Boc deprotection of **11** was foreseen to be problematic, due to the presence of an acid labile acetonide moiety. As a result more contemporary approaches towards the deprotection of a Boc group were considered.[25]

Williams et al. successfully demonstrated the use of zinc bromide as a reagent to Boc deprotect a similarly acid sensitive system.[26] As alcohol functionality has been shown to reduce the reactivity of zinc bromide mediated reactions,[27] the alcohol **11** was protected as its TBS ether.

Treatment of the allylic alcohol **11** with *tert*-butyldimethylsilyl triflate gave the TBS protected acetonide **12** in high yield. The acetonide **12** was then treated with zinc dibromide in dichloromethane to afford the amine **13**.[28] Allylation of **13** was straightforward and the alkene metathesis precursor **14** was isolated in 91% yield (Scheme 7).

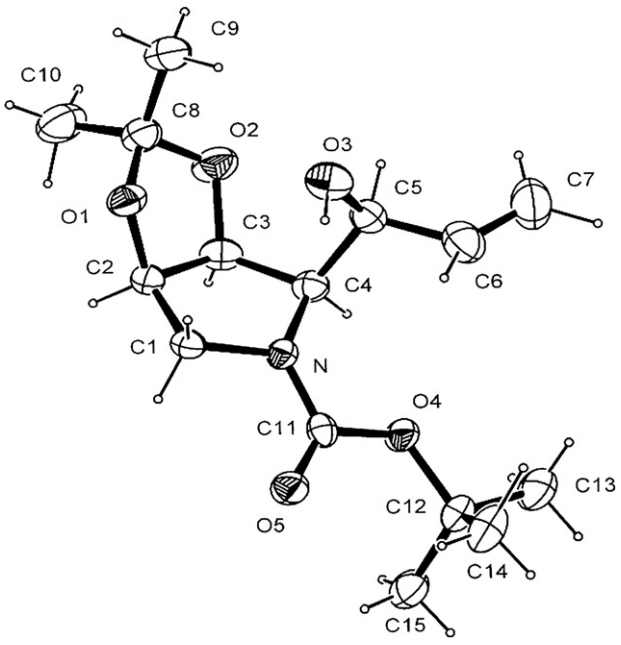
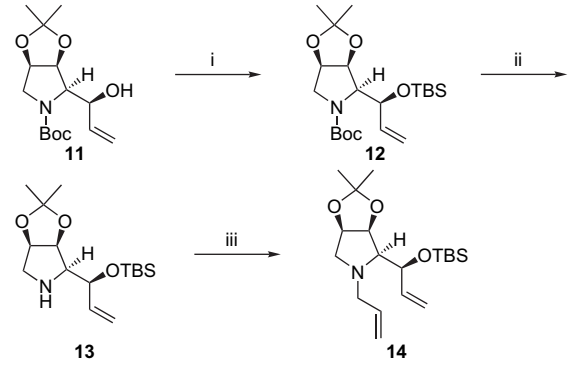


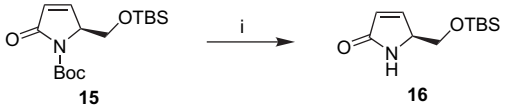
Figure 2. X-ray analysis of alcohol **11**.



Scheme 7. Reagents: (i) TBSOTf, Et_3N, CH_2Cl_2 (98%); (ii) $ZnBr_2$, CH_2Cl_2 (81%); (iii) CH_2CHCH_2Br, K_2CO_3, THF, Δ (91%).

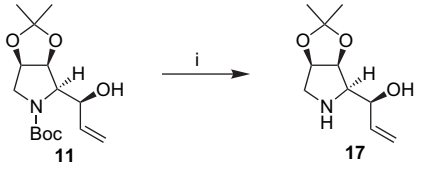
During this time period we were investigating the microwave assisted removal of Boc protecting group from amine systems. Previous work by Siro et al. showed that this could be accomplished when using a silica gel solution.[29] We intended to further expand this methodology by exploiting the benefits associated with a solvent free system. It was hoped that substrate adsorption onto silica, followed by microwave irradiation would furnish the desired free amine.

Studies in our laboratory showed that microwave irradiation of the readily available Boc protected lactam **15**[30] afforded the deprotected product **16** in good yield (Scheme 8). Hoping to demonstrate the synthetic usefulness of this methodology, microwave irradiation was used in the Boc deprotection of compound **11**.



Scheme 8. Reagents: (i) SiO_2, MW, 160 °C, 3 min (87%).

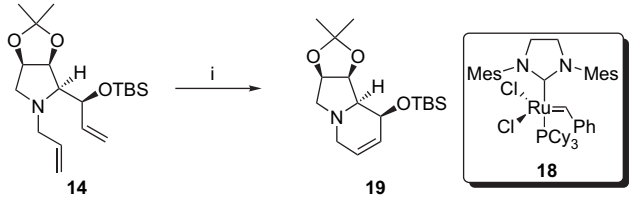
After using microwave heating to deprotect the *epi*-swainsonine intermediate **11**, the desired crude amine **17** was isolated in only 41% yield. It was found that extraction and purification of the desired product **17** from the dry loaded silica were both difficult and problematic. Although the presence of the crude amine **17** could be seen by ^{1}H NMR, ^{13}C NMR and mass spectroscopy, further evidence was provided by converting some of the alcohol **17** into the known TBS ether **13** (Scheme 9).



Scheme 9. Reagents: (i) SiO_2, MW, 200 °C, 4 min (41%).

Due to the problems associated with microwave irradiation, the zinc bromide mediated removal of the Boc protecting group remained the preferred method.

To continue the synthesis of *epi*-swainsonine **2**, diene **14** was treated with Grubbs' second generation catalyst **18** (Scheme 10).[31] As shown in Table 2, 20 mol % of catalyst **18**, added in two separate portions over 24 h, was needed to complete the ring closing metathesis of diene **14**.



Scheme 10. Reagents: (i) **18** (see Tables 2 and 3).

In order to increase the catalytic efficiency, efforts were made to first form the ammonium salt of **14**, before attempting the ring closing metathesis. Table 3 shows that although the camphorsulfonate salt did not undergo metathesis, the *para*-toluene sulfonate did yield indolizidine **19** under identical reaction conditions. Interestingly, complete conversion to **19** in 62% yield was only accomplished when benzene was used as the reaction medium, with only 5 mol % catalyst loading.

Table 2

Entry	**18**[a] (mol %)	Solvent	Temp	Yield[b] (Conversion, %)
1	5	C_6H_6	rt	29 (66)
2	2×5	CH_2Cl_2	rt	49 (72)
3	15	CH_2Cl_2	Δ	55 (91)
4	2×10	CH_2Cl_2	Δ	70 (100)

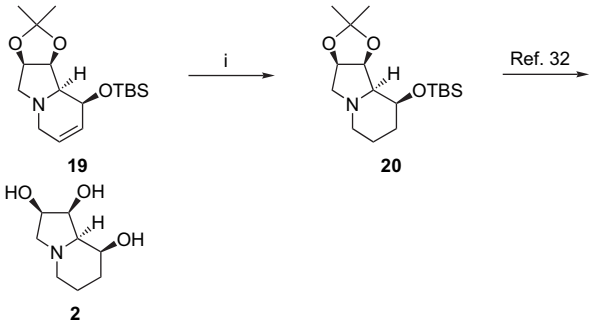
[a] With respect to the substrate.
[b] Yield based on recovered starting material.

Table 3

Entry	Acid	**18**[a] (mol %)	Solvent	Temp	Yield[b] (Conversion, %)
1	CSA	5	CH_2Cl_2	rt	SM
2	CSA	5	CH_2Cl_2	Δ	SM
3	*p*TsOH	5	CH_2Cl_2	rt	81 (40)
4	*p*TsOH	10	CH_2Cl_2	rt	53 (66)
5	*p*TsOH	5	C_6H_6	rt	62 (100)

[a] With respect to the substrate.
[b] Yield based on recovered starting material.

Hydrogenation of the acetonide **19** gave the (−)-8-*epi*-swainsonine precursor **20** (Scheme 11).



Scheme 11. Reagents: (i) 10% Pd/C, H_2, EtOAc, (54%).

The acetonide **20** has previously been converted into (−)-8-*epi*-swainsonine (**2**) using trifluoroacetic acid as the global deprotecting agent.[12a] This approach to (−)-*epi*-8-swainsonine **2** is efficient and can be tailored to the preparation of a range of indolizidine alkaloids.

3. Conclusions

We have developed an efficient route to (−)-8-*epi*-swainsonine **2**. The route is very flexible and allows the preparation of a wide range of indolizidines. Bhatacharjya et al. have now disclosed their synthesis of *epi*-swainsonine triacetate, which utilises ring closing metathesis but involves an entirely different route to the pyrrolidine core.[12a]

4. Experimental

4.1. General procedure

Unless otherwise stated, commercially available reagents were used without purification and solvents were dried according to standard procedures. Microwave reactions were carried out on a Biotage *Initiator 2.0*. Product purification was carried out using flash chromatography on silica gel (Merck silica gel 60 (230–400 mesh)). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) using $CDCl_3$ as the solvent and TMS as internal reference. Spectra were recorded in parts per million downfield from TMS (δ=0) for ^{1}H NMR and relative to the $CDCl_3$ resonance (δ=77.0) for ^{13}C spectra. Mass spectra were recorded on a Fisons VG Autospec Mass Spectrometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter.

4.1.1. (6*R*,7*S*,7a*R*)-6,7-Dihydroxy-tetrahydro-pyrrolo[1,2-*c*]oxazol-3-one (6). To a stirred solution of (*S*)-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*]oxazol-3-one **3** (6.60 g,

52.8 mmol) and 4-methylmorpholine *N*-oxide (6.80 g, 58.1 mmol) in acetone (60 mL) and water (60 mL) at 0 °C was added 0.1 M osmium tetroxide solution in *tert*-butanol (26.4 mL, 2.64 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 6 h, before concentrating under reduced pressure. The mixture was taken up in 10% methanol/dichloromethane (200 mL) and filtered through Celite. The Celite was further washed with 10% methanol/dichloromethane (3×100 mL) and the combined filtrates were concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography on silica, eluted with 5% methanol/dichloromethane to give **6** as a white solid (7.54 g, 90%). TLC (10% MeOH/$CHCl_2$) R_f=0.40. Mp 142–144 °C. $[\alpha]_D^{23}$ −8.6 (*c* 1.91, $CHCl_3$). *m/z* (EI): 159 (M^+, 6%), 142 ([M−OH]$^+$, 96%), 69 (88), 57 (100), 55 (85), 41 (87). HRMS (ESI): calcd for $C_9H_{13}NO_3Na$ [M+Na]$^+$ 206.0788, found 206.0785. ν_{max} (film/cm^{-1}): 3052, 3024, 2993, 2955 and 2885 (s, CH), 1744 (br, N–C=O), 1548, 1480, 1451, 1422, 1378, 1363, 1317, 1292, 1256, 1225, 1206, 1149, 1114, 1079, 1007, 981, 931, 892. δ_H (500 MHz, $CDCl_3$): 4.51 (1H, dd, *J* 8.8 and 4.2 Hz, 4-H^d), 4.36 (1H, dd, app. t, *J* 8.8 Hz, 4-H^u), 4.40 (1H, ddd, app. dt, *J* 7.7 and 3.3 Hz, 7-H), 4.02 (1H, ddd, *J* 9.3, 4.2 and 3.3 Hz, 5-H), 3.86 (1H, t, *J* 3.3 Hz, 6-H), 3.40 (1H, dd, *J* 10.7 and 7.8 Hz, 8-H^d), 3.20–3.24 (1H, m, 8-H^u). δ_C (75 MHz, $CDCl_3$): 165.4 (C-2), 75.6 (C-7), 72.5 (C-6), 65.2 (C-4), 63.3 (C-5), 51.3 (C-8).

4.1.2. (3a*S*,3b*R*,8a*R*)-2,2-Dimethyl-tetrahydro-1,3-dioxolo[3,4]pyrrolo[1,2-*c*]oxazol-6-one (7). To a stirred suspension of (6*R*,7*S*,7a*R*)-6,7-dihydroxy-tetrahydro-pyrrolo[1,2-*c*]oxazol-3-one **6** (5.30 g, 33.3 mmol) in dimethoxypropane (50 mL) and acetone (150 mL) at room temperature was added pyridinium *p*-toluenesulfonate (0.837 g, 3.33 mmol). The reaction mixture was heated to reflux and stirred for 20 h, before concentrating under reduced pressure. The resulting residue was subjected to flash column chromatography on silica, eluted with ethyl acetate to give **7** as a white solid (6.30 g, 95%). TLC (EtOAc) R_f=0.54. Mp 112–114 °C. $[\alpha]_D^{27}$ −4.92 (*c* 2.40, $CHCl_3$). *m/z* (EI): 199 (M^+, 9%), 184 (77), 140 (100), 86 (83), 69 (96), 41 (59). HRMS (ESI): calcd for $C_9H_{13}NO_4Na$ [M+Na]$^+$ 222.0737, found 222.0724. ν_{max} (film/cm^{-1}): 2973, 2991 and 2948 (s, CH), 1737 (s, N–C=O), 1699, 1552, 1480, 1438, 1396, 1377, 1366, 1339, 1321, 1277, 1257, 1208, 1167, 1147, 1101, 1073, 1045, 1024, 1011, 992, 925, 892, 878, 843, 810, 778, 770, 736, 667, 650, 634. δ_H (300 MHz, $CDCl_3$): 4.76 (1H, dd, app. t, *J* 4.5 Hz, 7-H), 4.57 (1H, dd, app. t, *J* 4.5 Hz, 6-H), 4.47–4.33 (2H, m 4-H), 3.92 (1H, ddd, *J* 7.5, 4.5 and 3.0 Hz, 5-H), 3.72 (1H, d, *J* 13.3 Hz, 8-H), 3.09 (1H, dd, *J* 13.3 and 4.5 Hz, 8-H), 1.24 and 1.31 (6H, 2×s, $C(CH_3)_2$). δ_C (75 MHz, CD_3OD): 164.2 (C-2), 113.3 ($C(CH_3)_2$), 83.1 (C-7), 81.1 (C-6), 64.2 (C-4), 63.6 (C-5), 52.5 (C-8), 24.1 and 26.5 ($C(CH_3)_2$).

4.1.3. ((3a*S*,4*R*,6a*R*)-2,2-Dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrol-4-yl)-methanol (8). To a stirred solution of (3a*S*,3b*R*,8a*R*)-2,2-dimethyl-tetrahydro-1,3-dioxolo[3,4]-pyrrolo[1,2-*c*]oxazol-6-one **7** (5.00 g, 25.1 mmol) in ethanol (100 mL) was added lithium hydroxide (3.01 g, 126 mmol) at room temperature. The reaction mixture was heated to reflux and stirred for 5 days, before concentrating under reduced pressure. The mixture was taken up in dichloromethane (100 mL) and filtered through Celite. The Celite was further washed with dichloromethane (3× 100 mL) and the combined filtrates were concentrated under reduced pressure to give **8** as a crude white solid (4.71 g). A small sample (0.500 g) was subjected to flash column chromatography on silica, eluted with 10% methanol/dichloromethane to give **8** as a white solid (0.438 g, 93%). TLC (10% MeOH/CH_2Cl_2) R_f=0.22. Mp 109–111 °C. $[\alpha]_D^{29}$ −54.0 (*c* 3.50, $CHCl_3$). *m/z* (EI): 158 (9%), 142 (100), 84 (42), 68 (37), 57 (34), 55 (35). HRMS (ESI): calcd for $C_8H_{15}NO_3Na$ [M+Na]$^+$ 196.0944, found 196.0942. ν_{max} (film/cm^{-1}): 3232 (s, OH), 2977, 2925 and 2874 (s, CH), 1605, 1474, 1440, 1385, 1367, 1307, 1272, 1251, 1242, 1207, 1193, 1166, 1126, 1112, 1098, 1062, 1043, 1032, 1015, 992, 956, 914, 883, 856, 826, 813, 766, 699. δ_H (300 MHz, $CDCl_3$): 4.60–4.53 (1H, m, 4-H), 4.53–4.42 (1H, m, 3-H), 3.70–3.51 (2H, m, CH_2OH), 2.87 (1H, dd, *J* 12.9 and 2.6 Hz, 5-H), 2.64 (1H, ddd, app. dt, *J* 6.4 and 3.9 Hz, 2-H), 2.53–2.42 (1H, m, 5-H), 3.13 and 2.83 (6H, 2×s, $C(CH_3)_2$). δ_C (75 MHz, $CDCl_3$): 111.9 ($C(CH_3)_2$), 82.7 (C-4), 82.0 (C-3), 65.8 (C-2), 60.9 (CH_2OH), 53.2 (C-5), 24.0 and 25.9 ($C(CH_3)_2$).

4.1.4. (3a*S*,4*R*,6a*R*)-4-Hydroxymethyl-2,2-dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrole-5-carboxylic acid *tert*-butyl ester (9). To a stirred solution of crude ((3a*S*,4*R*,6a*R*)-2,2-dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrol-4-yl)-methanol **8** (31.6 mmol) and triethylamine (8.82 mL, 63.3 mmol) in acetonitrile (200 mL) at 0 °C was added di-*tert*-butyl dicarbonate (6.84 g, 31.6 mmol) in acetonitrile (100 mL) dropwise over 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 15 h, before concentrating under reduced pressure. The resulting residue was subjected to flash column chromatography on silica, eluted with 50% diethyl ether/petrol 40:60 to give **9** as a colourless oil (7.40 g, 86%, over two steps). TLC (50% Et_2O/petrol) R_f=0.43. $[\alpha]_D^{25}$ −33.8 (*c* 2.10, $CHCl_3$). *m/z* (EI): 273 (M^+, 6%), 258 (13), 242 (11), 186 (28), 142 (61), 57 (100). HRMS (ESI): calcd for $C_{13}H_{23}NO_5Na$ [M+Na]$^+$ 296.1468, found 296.1449. ν_{max} (film/cm^{-1}): 3415 (br, OH), 2980 and 2936 (s, CH), 1743 (w, s), 1694 (br, N–C=O), 1478, 1456, 1404, 1369, 1279, 1249, 1212, 1165, 1135, 1086, 1048, 994, 925, 861, 821, 777, 749. δ_H (300 MHz, $CDCl_3$): 4.83–4.71 (1H, m, 3-H), 4.71–4.57 (1H, m, 4-H), 4.08–3.91 (1H, m, CH_2OH), 3.91–3.66 (3H, m, CH_2OH, 5-H and OH), 3.61–3.40 (2H, m, 2-H and 5-H), 1.45 (3H, s, $C(CH_3)_2$), 1.41 and 1.42 (9H, 2×s, $C(CH_3)_3$), 1.29 (3H, s, $C(CH_3)_2$). δ_C (75 MHz, $CDCl_3$): 112.6 ($C(CH_3)_2$), 81.1 ($C(CH_3)_3$), 80.8 (C-3), 77.9 (C-4), 62.8 (CH_2OH), 52.3 (C-5), 28.7 ($C(CH_3)_3$), 25.2 and 26.7 ($C(CH_3)_2$).

4.1.5. (3a*S*,4*S*,6a*R*)-4-Formyl-2,2-dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrole-5-carboxylic acid *tert*-butyl ester (10). To a stirred solution of (3a*S*,4*R*,6a*R*)-4-hydroxymethyl-2,2-dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrole-5-carboxylic acid *tert*-butyl ester **9** (2.12 g, 7.75 mmol) and 4-methylmorpholine *N*-oxide (1.32 g, 11.6 mmol) in dichloromethane (15 mL) over powdered molecular sieves 4 Å (4.00 g) at 0 °C was added tetrapropylammonium perruthenate (0.137 g, 0.387 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 3 h, before subjecting to flash column chromatography on silica, eluted with 30% diethyl ether/petrol 40:60 to give **10** as a

colourless oil, which formed a white solid when cooled below 0 °C (1.40 g, 88%). TLC (80% Et_2O/petrol) R_f= 0.63. Mp 64 °C. $[\alpha]_D^{27}$ −51.6 (*c* 3.06, $CHCl_3$). *m/z* (EI): 242 (6%), 186 (28), 142 (69), 57 (100), 41 (70), 28 (49). HRMS (ESI): calcd for $C_{13}H_{21}NO_5Na$ $[M+Na]^+$ 294.1312, found 294.1312. ν_{max} (film/cm^{-1}): 2981, 2938 (s, CH), 1740 (s, C═O), 1699 (br, N–C═O), 1478, 1458, 1395, 1292, 1259, 1212, 1163, 1131, 1088, 1053, 997, 969, 950, 924, 909, 856, 773, 750, 666. δ_H (300 MHz, $CDCl_3$): 9.51–9.40 (1H, m, CH═O), 5.15–4.92 (1H, m, 3-H), 4.86–4.76 (1H, m, 4-H), 4.17–3.94 (1H, m, 2-H), 3.87–3.43 (2H, m, 5-H), 1.47 (3H, s, $C(CH_3)_2$), 1.41 and 1.45 (9H, s, $C(CH_3)_3$), 1.30 (3H, s, $C(CH_3)_2$). δ_C (75 MHz, $CDCl_3$): 197.9 and 198.3 (C═O), 154.1 (N–C═O), 112.9 ($C(CH_3)_2$), 81.0 ($C(CH_3)_3$), 80.3 and 80.4 (C-3), 78.02 and 78.96 (C-4), 67.2 (C-2), 51.8 (C-5), 28.1 ($C(CH_3)_3$), 24.4 and 26.1 ($C(CH_3)_2$).

4.1.6. (3a*S*,4*R*,6a*R*)-4-((*S*)-1-Hydroxy-allyl)-2,2-dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrole-5-carboxylic acid *tert*-butyl ester (11). To a stirred solution of (3a*S*,4*S*,6a*R*)-4-formyl-2,2-dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrole-5-carboxylic acid *tert*-butyl ester **10** (5.85 g, 21.6 mmol) in tetrahydrofuran (100 mL) at 0 °C was added 1.6 M vinylmagnesium bromide solution in tetrahydrofuran (20.2 mL, 32.3 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 3 h, before adding saturated ammonium chloride solution (100 mL) and diethyl ether (100 mL). The phases were separated and the aqueous was further extracted with diethyl ether (3× 100 mL). The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography on silica, eluted with 30% diethyl ether/petrol 40:60 to give **11** as a colourless oil, which formed a white solid when cooled below 0 °C (5.47 g, 85%). TLC (80% Et_2O/petrol) R_f=0.67. Mp 56–58 C. $[\alpha]_D^{28}$ −52.1 (*c* 2.90, $CHCl_3$). *m/z* (EI): 288 (2%), 256 (10), 142 (100), 75 (17), 73 (15), 57 (10). HRMS (ESI): calcd for $C_{15}H_{25}NO_5Na$ $[M+Na]^+$ 322.1625, found 322.1614. δ_H (300 MHz, $CDCl_3$): 6.16–6.03 (1H, m, 7-H), 5.45 (1H, d, *J* 17.0 Hz, 8-H^{β}), 5.18 (1H, d, *J* 10.6 Hz, 8-H^{α}), 4.80–4.58 (2H, m, 3-H and 4-H), 4.54 (1H, dd app. t, *J* 6.2 Hz, 6-H), 3.96–3.60 (2H, m, 2-H and 5-H), 3.41 (1H, d, *J* 10.0, 5-H), 1.49 (3H, s, $C(CH_3)_2$), 1.43 (9H, s, $C(CH_3)_3$), 1.30 (3H, s, $C(CH_3)_2$). δ_C (75 MHz, $CDCl_3$): 156.0 (N–C═O), 137.9 (C-7), 115.9 (C-8), 112.6 ($C(CH_3)_2$), 80.9 ($C(CH_3)_3$), 80.2 (C-4), 77.1 (C-3), 71.5 (C-6), 65.5 (C-2), 52.1 (C-5), 28.3 ($C(CH_3)_3$), 25.0 and 26.8 ($C(CH_3)_2$).

4.1.7. (3a*S*,4*S*,6a*R*)-4-[(*S*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-allyl]-2,2-dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrole-5-carboxylic acid *tert*-butyl ester (12). To a stirred solution of (3a*S*,4*R*,6a*R*)-4-((*S*)-1-hydroxy-allyl)-2,2-dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrole-5-carboxylic acid *tert*-butyl ester **11** (4.64 g, 15.5 mmol) and triethylamine (2.16 mL, 15.5 mmol) in dichloromethane (100 mL) at 0 °C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.57 mL, 15.5 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h, before adding saturated ammonium chloride solution (100 mL). The phases were separated and the aqueous was further extracted with dichloromethane (3×50 mL). The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography on silica, eluted with 10% diethyl ether/petrol 40:60 to give **12** as a colourless oil (5.19 g, 81%). TLC (50% Et_2O/petrol) R_f=0.75. $[\alpha]_D^{26}$ −39.1 (*c* 3.80, $CHCl_3$). *m/z* (EI): 414 (M^+, 2%), 300 (23), 186 (49), 142 (92), 73 (39), 57 (100). HRMS (ESI): calcd for $C_{21}H_{39}NO_5SiNa$ $[M+Na]^+$ 436.2458, found 436.2440. ν_{max} (film/cm^{-1}): 2980, 2955, 2931, 2890 and 2858 (s, CH), 1701 (s, C═C), 1474, 1462, 1401, 1367, 1252, 1214, 1167, 1087, 1041, 996, 970, 923, 837, 813, 776, 673. δ_H (300 MHz, $CDCl_3$): 6.14 (1H, ddd, *J* 17.4, 10.4 and 7.0 Hz, 7-H), 5.16 (1H, d, *J* 17.4 Hz, 8-H^{β}), 5.06 (1H, d, *J* 10.4 Hz, 8-H^{α}), 4.75 (1H, dd, app. t, *J* 6.3 Hz, 3-H), 4.70–4.52 (2H, m, 4-H and 6-H), 4.01 (1H, dd, app. t, *J* 6.3 Hz, 2-H), 4.09–3.85 (1H, m, 5-H), 3.07 (1H, dd, *J* 11.7 and 6.6 Hz, 5-H), 1.51 (3H, s, $C(CH_3)_2$), 1.44 (9H, s, $C(CH_3)_3$), 1.30 (3H, s, $C(CH_3)_2$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.03 and 0.05 (6H, 2×s, $Si(CH_3)_2$). δ_C (75 MHz, $CDCl_3$): 154.1 (C═O), 139.9 (C-7), 115.6 (C-8), 113.0 ($C(CH_3)_2$), 80.3 (C-3), 79.7 ($C(CH_3)_3$), 77.4 (C-4), 72.4 (C-6), 62.7 (C-2), 51.1 (C-5), 28.4 ($C(CH_3)_3$), 27.2 ($C(CH_3)_2$), 25.8 ($SiC(CH_3)_3$), 25.2 ($C(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), −4.7 and −4.4 ($Si(CH_3)_2$).

4.1.8. (3a*S*,4*S*,6a*R*)-4-[(*S*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-allyl]-2,2-dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrole (13). To a stirred suspension of (3a*S*,4*S*,6a*R*)-4-[(*S*)-1-(*tert*-butyl-dimethyl-silanyloxy)-allyl]-2,2-dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrole-5-carboxylic acid *tert*-butyl ester **12** (0.839 g, 2.03 mmol) in dichloromethane (25 mL) at room temperature was added zinc(II) bromide (2.29 g, 10.2 mmol). The reaction mixture was stirred for 24 h, before adding diethyl ether (150 mL) and saturated sodium bicarbonate solution (150 mL). The phases were separated and the aqueous further extracted with diethyl ether (3×100 mL). The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography on silica, eluted with 30% diethyl ether/petrol 40:60 to give **13** as a colourless oil (5.13 g, 81%). TLC (50% Et_2O/petrol) R_f=0.75. $[\alpha]_D^{29}$ −40.0 (*c* 1.20, $CHCl_3$). *m/z* (EI): 242 (8%), 186 (45), 142 (64), 59 (29), 57 (100), 41 (27). HRMS (ESI): calcd for $C_{16}H_{32}NO_3Si$ $[M+H]^+$314.2146, found 314.2115. ν_{max} (film/cm^{-1}): 2955, 2930, 2857 and 2821 (CH, s), 1644 (s, C═C), 1473, 1463, 1422, 1403, 1380, 1371, 1254, 1208, 1165, 1125, 1089, 1015, 982, 926, 905, 838, 777, 671, 646. δ_H (300 MHz, $CDCl_3$): 6.04 (1H, ddd, *J* 17.0, 10.5 and 5.8 Hz, 7-H), 5.32 (1H, d, *J* 17.0 Hz, 8-H^{β}), 5.13 (1H, d, *J* 10.5 Hz, 8-H^{α}), 4.68–4.56 (1H, m, 4-H), 4.45 (1H, dd, *J* 5.4 and 4.2 Hz, 3-H), 4.41–4.31 (1H, m, 6-H), 3.12 (1H, d, *J* 12.2 Hz, 5-H), 2.66 (1H, dd, *J* 12.2 and 4.1 Hz, 5-H), 2.59 (1H, dd, *J* 8.1 and 4.2 Hz, 2-H), 2.13 (1H, br s, NH), 1.28 and 1.47 (6H, 2×s, $C(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.05 and 0.09 (6H, 2×s, $Si(CH_3)_2$). δ_C (75 MHz, $CDCl_3$): 139.0 (C-7), 115.3 (C-8), 110.7 ($C(CH_3)_2$), 81.0 (C-4), 80.2 (C-3), 73.5 (C-6), 69.0 (C-2), 52.4 (C-5), 26.0 ($SiC(CH_3)_3$), 24.4 and 25.9 ($C(CH_3)_2$), 18.3 ($SiC(CH_3)$, −4.7 and −4.3 ($Si(CH_3)_2$).

4.1.9. (3a*S*,4*S*,6a*R*)-5-Allyl-4-[(*S*)-1-(*tert*-butyl-dimethyl-silanyloxy)-allyl]-2,2-dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrole (14). To a stirred suspension of

(3a*S*,4*S*,6a*R*)-4-[(*S*)-1-(*tert*-butyl-dimethyl-silanyloxy)-allyl]-2,2-dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrole **13** (1.5 g, 4.79 mmol) and potassium carbonate (0.993 g, 7.19 mmol) in tetrahydrofuran (50 mL) at room temperature was added allyl bromide (0.456 mL, 5.27 mmol). The reaction mixture was refluxed for 24 h, before concentrating under reduced pressure. The residue was taken up in dichloromethane (150 mL) and filtered through Celite. The Celite was further washed with dichloromethane (3×50 mL) and the combined filtrates were concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography on silica, eluted with 10% diethyl ether/petrol 40:60 to give **14** as a colourless oil (1.63 g, 96%). TLC (30% Et_2O/petrol) R_f=0.66. $[\alpha]_D^{28}$ −50.5 (*c* 2.20, $CHCl_3$). *m*/*z* (EI): 338 (5%), 284 (12), 212 (12), 182 (100), 73 (42), 41 (35). HRMS (ESI): calcd for $C_{19}H_{36}NO_3Si$ $[M+H]^+$ 354.2459, found 354.2448. ν_{max} (film/cm^{-1}): 3080, 2956, 2931, 2858 and 2792 (s, CH), 1644 (ws, C=C), 1473, 1463, 1420, 1403, 1379, 1369, 1277, 1255, 1210, 1169, 1139, 1112, 1092, 1019, 1005, 926, 873, 838, 777, 676. δ_H (300 MHz, $CDCl_3$): 6.15 (1H, ddd, *J* 17.2, 10.8 and 5.9 Hz, 10-H), 5.96–5.72 (1H, m, 7-H), 5.30 (1H, d, *J* 17.2 Hz, 11-H), 5.22–4.91 (3H, m, 8-H and 11-H), 4.57–4.41 (3H, m, 3-H, 4-H, and 9-H), 4.09–3.98 (1H, m, 6-H), 3.22 (1H, d, *J* 11.5 Hz, 5-H), 2.63 (1H, dd, *J* 14.0 and 7.7 Hz, 6-H), 2.11 (1H, dd, *J* 7.8 and 3.4 Hz, 2-H), 2.02 (1H, dd, *J* 11.5 and 3.7 Hz, 5-H), 1.28 and 1.53 (6H, 2×s, $C(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.03 and 0.08 (6H, 2×s, $SiC(CH_3)_2$). δ_C (75 MHz, $CDCl_3$): −4.7 and −4.0 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 25.5 ($C(CH_3)_2$), 26.0 ($Si(C(CH_3)_3$), 26.3 ($C(CH_3)_2$), 58.1 (C-6), 60.5 (C-5), 71.6 (C-2), 81.5 (C-3, C-4 or C-9), 77.3 (C-3, C-4 or C-9), 74.4 (C-3, C-4 or C-9), 110.8 ($C(CH_3)_2$), 115.1 (C-11), 116.2 (C-8), 135.9 (C-7), 139.6 (C-10).

4.1.10. (*S*)-5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1,5-dihydro-pyrrol-2-one (16) and general procedure for microwave assisted removal of a Boc group. Silica (1.2 g) loaded with (*S*)-2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-oxo-2,5-dihydro-pyrrole-1-carboxylic acid *tert*-butyl ester **15** (0.500 g, 1.28 mmol) was heated using microwave irradiation to 160 °C for 5 min before adding dichloromethane (100 mL). The suspension was filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica, eluted with 90% ethyl acetate/petrol 40:60 to give **16** as a colourless oil (0.255 g, 87%).

Analysis in agreement with literature values.[26]

4.1.11. (3a*R*,9*S*,9a*S*,9b*S*)-9-(*tert*-Butyl-dimethyl-silanyloxy)-2,2-dimethyl-3a,4,6,9,9a,9b-hexahydro-1,3-dioxolo-[4,5-*a*]indolizidine (19). To a stirred solution of (3a*S*,4*S*,6a*R*)-5-allyl-4-[(*S*)-1-(*tert*-butyl-dimethyl-silanyloxy)-allyl]-2,2-dimethyl-tetrahydro-1,3-dioxolo[4,5-*c*]pyrrole **19** (0.193 g, 0.546 mmol) in dichloromethane (5 mL) at room temperature under an argon atmosphere was added Grubbs' second generation catalyst **18** (0.0464 g, 0.0546 mmol). The reaction mixture was heated to reflux and stirred for 24 h, before adding a further portion of Grubbs' second generation catalyst **18** (0.0464 g, 0.0546 mmol). The reaction mixture was heated to reflux for a further 24 h, before concentrating under reduced pressure. The resulting residue was purified by column chromatography on silica, eluted with 50% diethyl ether/petrol 40:60 to give **19** as a colourless oil (0.125 g, 70%). TLC (75% Et_2O/petrol) R_f=0.40. $[\alpha]_D^{38}$ 19.6 (*c* 1.50, $CHCl_3$). *m*/*z* (EI): 326 (M^+, 36%), 184 (87), 127 (100), 75 (61), 73 (65). HRMS (ESI): calcd for $C_{17}H_{32}NO_3Si$ $[M+H]^+$ 326.2146, found 326.2138. ν_{max} (film/cm^{-1}): 3037, 2952, 2928, 2856 and 2781 (s, CH), 1719 (br), 1660 (br), 1461, 1379, 1253, 1207, 1167, 1150, 1119, 1045, 1011, 961, 938, 901, 860, 836, 775, 653. δ_H (300 MHz, $CDCl_3$): 5.86–5.72 (2H, m, 3-H and 4-H), 4.69 (1H, dd, *J* 6.0 and 3.8 Hz, 8-H), 4.62 (1H, dd, app. t, *J* 6.0 Hz, 7-H), 4.53–4.47 (1H, m, 5-H), 3.68–3.58 (1H, m, 9-H), 3.33 (1H, d, *J* 11.4, 2-H), 2.59 (1H, d, *J* 17.1 Hz, 9-H), 2.14 (1H, dd, *J* 11.4 and 5.7 Hz, 2-H), 2.13–2.08 (1H, m, 6-H), 1.29 and 1.51 (6H, s, $C(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 0.11 and 0.13 (6H, s, $Si(CH_3)_2$). δ_C (75 MHz, $CDCl_3$): 127.5 (C-3 or C-4), 126.8 (C-3 or C-4), 111.2 ($C(CH_3)_2$), 80.8 (C-8), 77.8 (C-7), 67.2 (C-6), 65.3 (C-5), 61.9 (C-2), 53.3 (C-9), 26.5 ($C(CH_3)_2$), 26.1 ($SiC(CH_3)_3$), 24.2 ($C(CH_3)_2$), 18.8 ($SiC(CH_3)_3$), −5.3 and −4.4 ($Si(CH_3)_2$).

4.1.12. (3a*R*,9*S*,9a*S*,9b*S*)-9-(*tert*-Butyl-dimethyl-silanyloxy)-2,2-dimethyl-octahydro-1,3-dioxolo[4,5-*a*]indolizidine (20). To a stirred suspension of 10% palladium on carbon (0.025 g, 0.024 mmol) in ethyl acetate (1 mL) at room temperature was added (3a*R*,9*S*,9a*S*,9b*S*)-9-(*tert*-butyl-dimethyl-silanyloxy)-2,2-dimethyl-3a,4,6,9,9a,9b-hexahydro-1,3-dioxolo[4,5-*a*]indolizidine **19** (0.067 g, 0.26 mmol). A hydrogen atmosphere was introduced and the reaction mixture stirred for 16 h, before filtering through Celite. The Celite was further washed with dichloromethane (3×10 mL) and the combined filtrates were concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography on silica, eluted with ethyl acetate to give **20** as a colourless oil (0.036 g, 45%). TLC (EtOAc) R_f=0.40. $[\alpha]_D^{34}$ −44.1 (*c* 2.70, $CHCl_3$). *m*/*z* (EI): 327 (M^+, 6%), 270 (45), 212 (94), 156 (100), 120 (56), 75 (35). HRMS (ESI): calcd for $C_{17}H_{34}NO_3Si$ $[M+H]^+$ 328.2303, found 328.2304. ν_{max} (film/cm^{-1}): 2929, 2856 and 2785 (s, CH), 1472, 1463, 1379, 1370, 1329, 1321, 1255, 1206, 1168, 1156, 1141, 1125, 1115, 1077, 1036, 1006, 972, 956, 930, 907, 877, 853, 835, 813, 775, 735, 676. δ_H (300 MHz, $CDCl_3$): 4.66–4.51 (2H, m, 7-H and 8-H), 4.22 (1H, ddd, app. td, *J* 6.2 and 3.3 Hz, 5-H), 3.22 (1H, dd, *J* 6.4 and 3.4 Hz, 2-H), 3.16 (1H, d, *J* 11.8 Hz, 9-H), 2.22 (1H, dd, *J* 11.8 and 4.3 Hz, 9-H), 2.45–1.76 (4H, m, 2-H, 3-H, 4-H and 6-H), 1.50 (3H, s, $C(CH_3)_2$), 1.54–1.34 (2H, m, 3-H and 4-H), 1.26 (3H, s, $C(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.07 (6H, s, $Si(CH_3)_2$). δ_C (75 MHz, $CDCl_3$): 111.1 ($C(CH_3)_2$), 81.6 (C-7), 78.9 (C-8), 69.2 (C-6), 67.2 (C-5), 60.7 (C-9), 52.6 (C-2), 32.4 (C-4), 26.4 ($C(CH_3)_2$), 26.0 ($SiC(CH_3)_3$), 23.8 ($C(CH_3)_2$), 21.3 (C-3), 18.4 ($SiC(CH_3)_3$), −5.0 and −4.6 ($Si(CH_3)_2$).

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References and notes

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