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Synthesis of trihydroxylated pyrrolizidine and indolizidine alkaloids based on SmI_2-induced reductive coupling of chiral nitrones with methyl acrylate

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ABSTRACT

Synthesis of trihydroxylated pyrrolizidines, the enantiomer of 2-epihyacinthacine A_2 and indolizidine analogues of the natural alkaloids is reported. The key step of these syntheses is the stereoselective samarium diodide-induced coupling of the chiral nitrone prepared from D-ribose with methyl acrylate. The nitrone derived from D-ribose possessing C2/C3 *syn* configuration reacted with methyl acrylate in the presence of samarium diiodide in excellent yield and diastereoselectivity, with only the *anti*-diastereomer being detected.

1. Introduction

The polyhydroxylated alkaloids are a group of biologically active natural compounds that inhibit glycosidases and glycosyltransferases.[1] Selective inhibition of these enzymes is used in treating viral or microbial diseases and to treat cancer and metabolic disorders.[2] Asano et al. isolated a group of promising natural polyhydroxylated pyrrolizidines from plants of the genus *Hyacenthacea*.[3] These trihydroxylated alkaloids were found to inhibit a broad range of glycosidases and subsequently hyacinthacine A_1[4] and hyacinthacine A_2[5] were synthesized. In addition, to the natural products, attention has been paid to the preparation of stereoisomeric trihydroxylated pyrrolizidine analogues.[6]

Nitrones have become important building blocks in organic synthesis.[7] During recent years we have developed protocols for the preparation of optically active nitrone templates for the asymmetric 1,3-dipolar cycloadditions.[8] These nitrones have recently been used in a samarium diiodide-induced umpolung procedure, undergoing reductive coupling with α,β-unsaturated esters,[9a–d] ketones or aldehydes[9e–g] and alkylsulfinyl imines[9h] to afford intermediates suitable for the preparation of biologically active substances.[5d,10] Since this methodology represents a general route to γ-*N*-hydroxylamino esters, we turned our attention to the synthesis of chiral pyrrolidines from sugar-derived nitrones. Recently we have found that the reaction course of samarium diiodide-induced reductive coupling of chiral nitrones with methyl acrylate is dependent on the structure of the starting chiral nitrone.

Nitrones possessing a C2/C3 *syn* configuration reacted with methyl acrylate to give γ-*N*-hydroxylamino esters with high diastereocontrol.[11] On the other hand, the coupling of nitrones possessing C2/C3 *anti*-configuration with methyl acrylate proceeded more slowly and the γ-*N*-hydroxylamino esters were obtained as minor products along with products resulting from an unexpected reductive deoxygenation of the starting nitrone.

Herein we report the synthesis of trihydroxylated pyrrolizidine and indolizidine alkaloids, in particular the enantiomer of 2-epihyacinthacine **2** and indolizidine **20**,[11] structurally related to the hyacinthacine alkaloids.[3] Retrosynthetic analysis of target products **1** and **2** provided a suitably functionalized precursor pyrrolidine **3** (Scheme 1). The intermediate **3** possesses a primary hydroxyl group in position 1 protected as its *tert*-butyldimethylsilyl ether and a secondary hydroxyl group on carbon 2 activated for S_N2 substitution as a mesylate. For the preparation of 7a-*epi*-hyacinthacine A_1 **1**, a double inversion at the stereogenic center of the pyrrolidine **3** in position 2 is necessary. Alternatively, 3,7a-di-*epi*-hyacinthacine A_1 **2** could be available from the pyrrolidine **3** after a single inversion at the stereogenic center in position 2. Intermediate **3** can be prepared relatively straightforwardly from γ-*N*-hydroxyamino ester **4**, which can be obtained by SmI_2 induced reaction of nitrone **5** with methyl acrylate. On the basis of our

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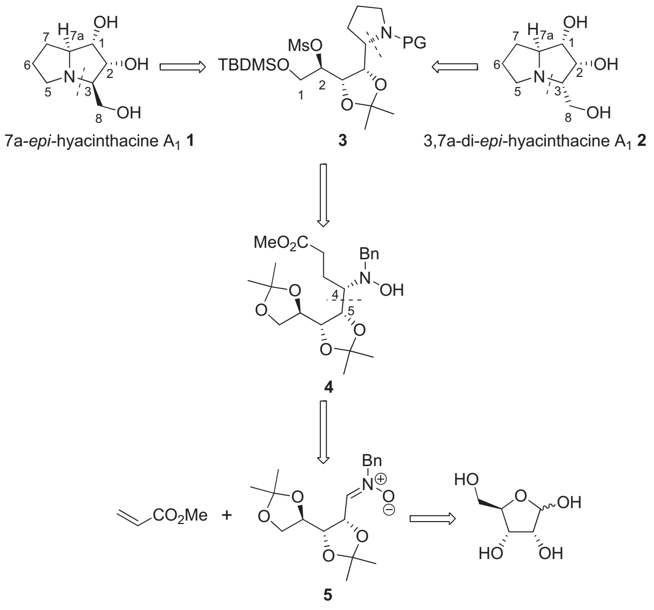
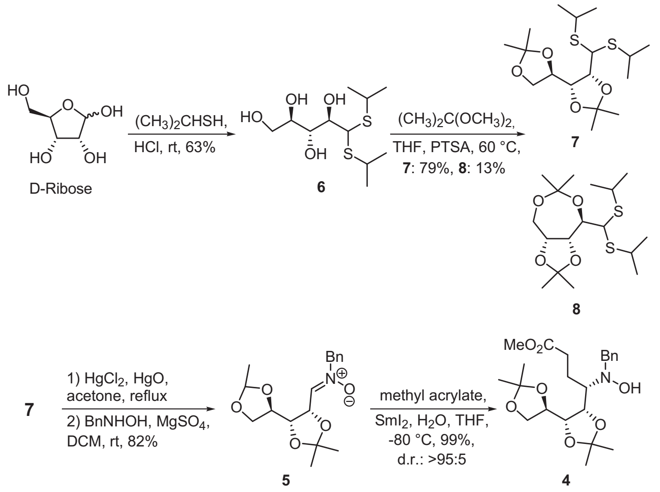


Scheme 1. Retrosynthetic pathway for 7a-*epi*-hyacinthacine A$_1$ **1** and 3,7a-di-*epi*-hyacinthacine A$_1$ **2**.

previous results we expected that γ-*N*-hydroxyamino ester **4** thus formed would have an *anti*-configuration for the new stereogenic centers.

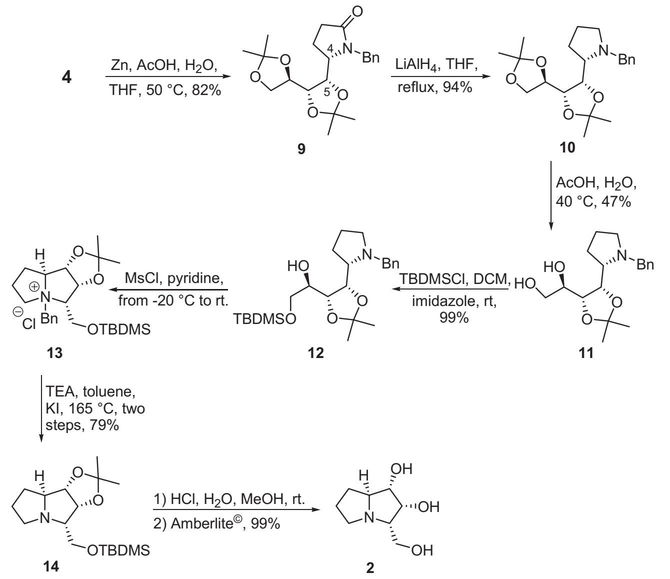
2. Results and discussion

The chiral D-*ribo* nitrone **5** was prepared starting from D-ribose that had been initially protected with propane-2-thiol in concentrated hydrochloric acid.[12] The D-*ribo* diisopropyl dithioacetal **6** obtained in 63% yield was next protected with 2,2-dimethoxypropane in THF in the presence of a catalytic amount of PTSA;[4a] the desired 2,3:4,5-di-*O*-isopropylidene-D-ribose diisopropyl-dithioacetal **7** being obtained in 79% yield. In addition to the expected product **7** 2,5:3,4-di-*O*-isopropylidene-D-ribose dithioacetal **8** was also isolated in a yield of 13% (Scheme 2).



Scheme 2. Preparation of nitrone **5**, followed by SmI$_2$ induced cross-coupling.

This finding is consistent with results of Edgar[13] and Kumar.[14] The structure of **7** and **8** was deduced by NMR spectroscopic analysis and definitively determined by X-ray structural analysis of the pyrrolidinones **9** and **23**. Next the dithioacetal protecting group was removed from di-*O*-isopropylidene-D-ribose dithioacetal **7** by the treatment with HgCl$_2$ and HgO in acetone.[15] The reaction afforded the chiral aldehyde that was directly used in condensation with *N*-benzylhydroxylamine to give **5** in 82% yield over two steps (Scheme 2).[16] The nitrone **5** was then used in the samarium diiodide-induced reductive coupling with methyl acrylate.[9–11] This reaction provided the expected adduct **4** in the excellent 95% yield and diastereoselectivity greater than 95:5, with only the *anti*-diastereomer being detected (Scheme 2). The chiral pure γ-*N*-hydroxylamino ester **4** was next transformed to the chiral pyrrolidinone **9** by reductive cleavage of the N–O bond of the *N*-hydroxylamino group with zinc in acetic acid in 82% yield (Scheme 3). Subsequent X-ray analysis of the pyrrolidinone **9** confirmed the *anti*-configuration of the new stereogenic centers at C3/C4, which is consistent with our previous observation,[9] as well as the results presented by Py and Vallee (Scheme 3, Fig. 1).[10,11]



Scheme 3. Preparation of pyrrolizidine **2**.

The pyrrolidinone **9** was finally reduced to pyrrolidine **10** using LiAlH$_4$ in an excellent yield of 94%. Next, we tried to remove the terminal isopropylidene group from the **10** using Zn(NO$_3$)$_2$·6H$_2$O[17] and InCl$_3$,[18] unsuccessfully with decomposition being observed. The required dihydroxypyrrolidine **11** could however be prepared

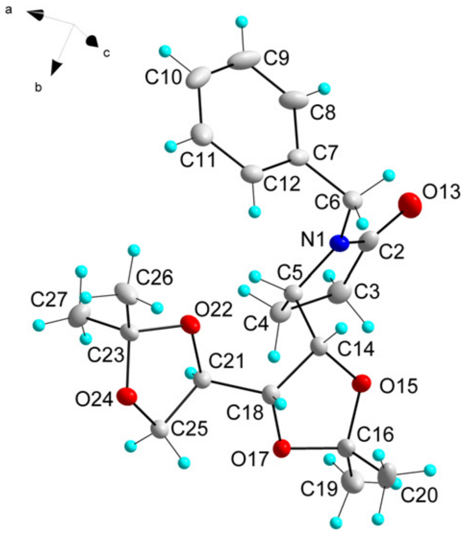


Fig. 1. X-ray structure of pyrrolidinone **9**.

only by slow hydrolysis of pyrrolidine **10** in 80% acetic acid at 40 °C in 47% yield and 85% conversion (Scheme 3). It should be mentioned that the temperature control is essential since the temperatures higher than 40 °C resulted in substantial decrease in yield. The primary hydroxyl group on dihydroxypyrrolidine **11** was subsequently selective protected with TBDMSCl in quantitative yield. For the final step, we had planned to activate the secondary hydroxyl group of TBDMS-pyrrolidine **12** as its mesylate and prepare the cyclization precursor by the reductive elimination of the benzyl group. Contrary to our expectations, in the reaction of **12** with MsCl in pyridine, instead of the mesyl activated intermediate we isolated directly the cyclized pyrrolizidine quaternary salt **13** (Scheme 3). This result shows that the benzyl protective group is not optimal for protecting the pyrrolidine in conditions where nucleophilic substitution is possible. Transformation of the pyrrolizidine quaternary salt **13** to pyrrolizidine **14** by Pd/C catalyzed reductive cleavage of benzyl group was not successful, but the required pyrrolizidine **14** was obtained by thermal decomposition of the quaternary pyrrolizidine salt **13** in the presence of triethylamine.[19] The yield of the **14** was 79% over two steps (Scheme 3). The final steps in the preparation of the trihydroxylated pyrrolizidine hyacinthacine analogue **2**, involved removing the isopropylidene and TBDMS protecting groups. The reaction was carried out in a methanolic solution of hydrochloric acid. This reaction provided the desired product **2** as its hydrochloride salt and the free pyrrolizidine was liberated by treatment with Amberlite® base in 99% yield (Scheme 3). The final product **2** was obtained in an overall yield of 13% from D-ribose.

The relative configuration at the stereogenic centers in pyrrolizidine **2** was determined by extensive NOE experiments (Fig. 2). Strong NOE effects between H-1 and H-2, between H-2 and H-3 and also between H-3 and H-1 indicate that H-1, H-2, and H-3 are on the same side of the ring. Irradiation of H-7a enhanced only the signal intensity of H-7. This indicates that H-7a and H-7 are on the same side of the ring. Thus, pyrrolizidine **2** was determined to be (1*S*,2*R*,3*S*,7a*S*)-1,2-dihydroxy-3-hydroxymethylpyrrolizidine. The opposite enantiomer of **2** was described by Clapés, $[\alpha]_D^{20}$ −34.0 (*c* 0.9, MeOH).[6d] The comparison of the optical rotation of our product **2** $[\alpha]_D^{20}$ +32.0 (*c* 0.2, MeOH) confirmed the preparation of the opposite enantiomer.

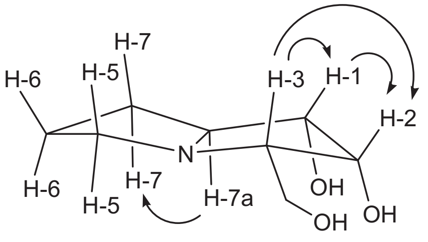
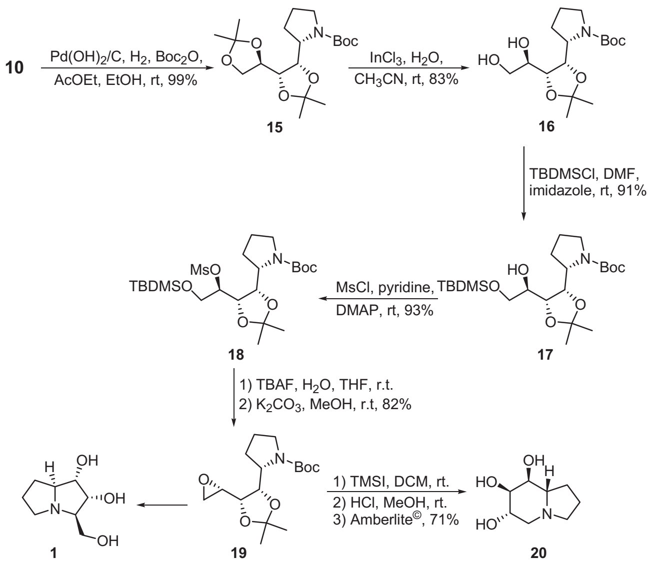


Fig. 2. NOE effects of pyrrolizidine **2**.

Next we have focused our attention on the synthesis of pyrrolizidine **1** (Scheme 4). We decided to change the benzyl protecting group of pyrrolidine **10** to a Boc group due to the observation of generation of the pyrrolizidine quaternary ammonium salt **13** on mesylation of **12**. Boc-protected pyrrolidine **15** was prepared in quantitative yield by (Pd/C–H_2) N-debenzylation of pyrrolidine **12** and in situ Boc-protection.[20] Next we used two Lewis acids for the selective deprotection of the terminal isopropylidene group of Boc-pyrrolidine **15**. $Zn(NO_3)_2 \cdot 6H_2O$ in acetonitrile provided selective, but deprotected pyrrolidine **16** only in 50% yield at 67% conversion.[17] Better results for selective deprotection of the pyrrolidine **15** were achieved with $InCl_3$ in acetonitrile. The dihydroxypyrrolidine **16**, obtained in 83% yield, was selectively protected with TBDMSCl in the presence of imidazole and DMF to provide the desired TBDMS protected pyrrolidine **17** in 95% yield. The free secondary hydroxyl group **17** was activated with mesyl chloride in pyridine giving **18** in 93% yield. Synthesis of pyrrolizidine **1** requires a double inversion of mesylate activated stereogenic center of the pyrrolidine **18**. An earlier procedure for the synthesis of similar compounds used a desilylation and subsequent cyclization of the free hydroxyl group to the corresponding oxirane with a double inversion. The intramolecular opening of the oxirane with subsequent cyclization gave the appropriate bicycle.[4a] In our case we were able to prepare the activated pyrrolidine **19** by desilylation of TBDMS-pyrrolidine **18** with TBAF in THF followed by alkaline activated cyclization. The yield of the oxirane **19** was 82% over two steps. The best method for preparation of the pyrrolizidine **1** appeared to be removal of the Boc group from **19** with TMSI in DCM followed by cyclization. Surprisingly, the reaction of the oxirane **19** with TMSI provided instead of the expected 7-*epi*-hyacinthacine A_1 **1**, a trihydroxyindolizidine **20** (Scheme 4). The syntheses of several stereoisomeric trihydroxyindolizidines have been published,[21] the product **20** has been described by Koskinen.[22]



Scheme 4. Preparation of indolizidine **20**.

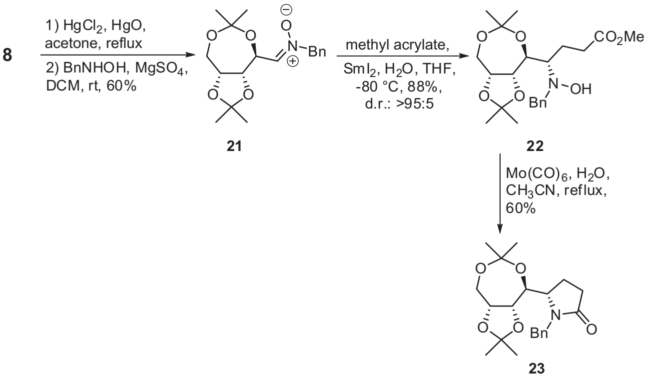
The formation of 6-*endo-tet* product **20** is not in accordance with Baldwin's rules and therefore we assume that the addition of iodine occurred to the less substituted and sterically hindered primary oxirane carbon,[23] followed by intramolecular nucleophilic substitution of iodine with the free-amine group.

Next we decided to convert the side product **8**, obtained in the protection of the free hydroxy groups of dithioacetal **6**, to the nitrone **21** and then examine the impact of its configuration on the SmI_2 induced cross-coupling with methyl acrylate. Removal of the dithioacetal from **8** by HgO/$HgCl_2$ in acetone[15] gave a chiral aldehyde that was directly used for the preparation of the desired nitrone **21** in 60% overall yield over two steps (Scheme 5). In the samarium diiodide-induced reaction with methyl acrylate chiral nitrone **21** afforded the expected adduct **22** in an excellent 88% yield and 95:5 diastereoselectivity. This enantiomerically pure adduct was then converted to the pyrrolidinone **23** by $Mo(CO)_6$ cleavage of N–O bond in 60% yield.

X-ray analysis of **23** confirmed the *anti*-configuration of the new formed stereogenic center (Fig. 3).[24]

3. Conclusions

The synthesis of trihydroxylated pyrrolizidine **2**, 3,7a-di-*epi*-hyacinthacine A_1 the enantiomer of 2-epihyacinthacine A_2 in overall yield 13% from commercial available D-ribose is reported.



Scheme 5. Preparation of pyrrolidinone **23**.

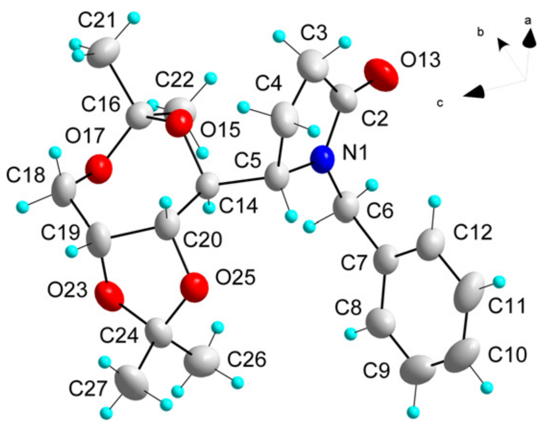


Fig. 3. X-ray structure of **23**.

The key step of this synthesis is the samarium diodide-induced coupling of the chiral nitrone prepared from D-ribose with methyl acrylate. The nitrone derived from D-ribose possessing C2/C3 *syn* configuration reacted with methyl acrylate in the presence of samarium diiodide in excellent yield and diastereoselectivity, with only the *anti*-diastereomeric adduct being detected. Furthermore, we have also prepared the (6*S*,7*R*,8*S*,8a*S*)-6,7,8-trihydroxyindolizidine **20** in 12% overall yield from D-ribose. The formation of the uncommon seven membered ring in product **8** was confirmed by X-ray analysis of the derived pyrrolidinone **23**.

4. Experimental section

4.1. General methods

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. TLC analysis was carried out using Merck TLC silica gel 60 F_{254} aluminum sheets and visualized by UV light or oxidized in $KMnO_4$ solution ($NaOH/KMnO_4/K_2CO_3/H_2O$ 1:8:80:1200). Specific rotations [α] were measured on an IBZ Messtechnik Polar-LμP polarimeter at the sodium D line (589 nm) using a 1 dm cell. ^1H NMR and ^{13}C NMR spectra were recorded on the Varian VRX-300 and Varian INOVA-600 in $CDCl_3$ or CD_3OD solution using TMS as internal standard. Chemical shifts are reported in ppm. IR spectra were recorded on an FTIR NICOLET MAGNA 750 instrument. HRMS analyses were determined on a Shimadzu, AXIMA TOF (MALDI-TOF/RTOF-MS). Elemental analyses were conducted using a Fisons EA 1108 Analysator.

*4.1.1. (2R,3R,4R)-5,5-bis(Isopropylthio)pentane-1,2,3,4-tetraol (**6**).* D-Ribose (10.0 g, 66.6 mmol) was dissolved in hydrochloric acid (10 mL) and this solution was cooled in an ice bath to 5 °C. Propane-2-thiol (10.1 g, 133.2 mmol, 12.3 mL) was then added dropwise. The temperature was kept at 5 °C for 40 min, and then the reaction mixture was stirred at room temperature for 1 h, progress of the reaction being monitored by TLC (EtOAc). After completion of the reaction, water (150 mL) was added, and solution was neutralized with $PbCO_3$ to pH 7. During addition of $PbCO_3$ CO_2 was evolved carrying with it excess propane-2-thiol. This gas was scrubbed by bubbling through an aqueous solution of $NaClO_4$. Inorganic solids were removed by filtration through a pad of Celite® and the solvent was removed under reduced pressure. The residue was separated by flash chromatography (silica gel, EtOAc) and **6** was obtained as colorless solid (12.0 g, 63%), mp 96–98 °C (lit.:[12] 97–97.5 °C); R_f (EtOAc) 0.26; $[\alpha]_D^{25}$ −63 (*c* 1, MeOH); ν_{max} (KBr): 3346, 3239, 2952, 2915, 2863, 1452, 1444 cm^{-1}; δ_H (300 MHz, CD_3OD) 1.24–1.31 (m, 12H), 3.02–3.22 (m, 2H), 3.66 (dd, *J*=6.0, 11.3 Hz, 1H), 3.75 (dd, *J*=3.3, 11.3 Hz, 1H), 3.79–3.84 (m, 1H), 3.88–3.91 (m, 2H), 3.33 (d, *J*=1.6 Hz, 1H); δ_C (75 MHz, CD_3OD) 23.7, 23.9, 24.1, 24.3, 35.9, 36.2, 54.1, 64.1, 73.1, 75.1, 77.1.

*4.1.2. (4R,4′R,5R)-5-(bis(Isopropylthio)methyl)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolane) (**7**) and (3aR,4R,8aR)-4-(bis(Isopropylthio)methyl)-2,2,6,6-tetramethyltetrahydro-[1,3]dioxolo[4,5-e][1,3]dioxepine (**8**).* Substrate **6** (5.0 g, 17.6 mmol) was dissolved in THF (100 mL) and 2,2-dimethoxypropane (20 mL) and PTSA (0.5 g) were added to the solution. The reaction mixture was stirred at 60 °C for 3 h. The reaction was confirmed to be complete by TLC analysis, whereupon a solution of Na_2CO_3 (100 mL, 1 M in water) was added. The mixture was extracted with EtOAc (4×100 mL) and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel: 100 g, 20% EtOAc/hexanes), 5.1 g (79%) of (4*R*,4′*R*,5*R*)-5-(*bis*(*Isopropylthio*)*methyl*)-2,2,2′,2′-*tetramethyl*-4,4′-*bi*(1,3-*dioxolane*) (7) was isolated as pale yellow crystals, mp 30–35 °C; R_f (20% EtOAc/hexanes, 1:4) 0.25; $[\alpha]_D^{25}$ −132.2 (*c* 0.202, $CHCl_3$); ν_{max} (KBr) 2985, 2958, 2929, 2867, 1455, 1381, 1371, 1255 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.27 (d, *J*=6.7 Hz, 3H), 1.29 (d, *J*=6.7 Hz, 3H), 1.31–1.35 (m, 12H), 1.41 (s, 3H), 1.51 (s, 3H), 3.16 (septet, *J*=6.7 Hz, 1H), 3.25 (septet, *J*=6.7 Hz, 1H), 3.91 (dd, *J*=5.3, 8.7 Hz, 1H), 4.09 (dd, *J*=6.9, 9.3 Hz, 1H), 4.16 (dd, *J*=6.2, 8.7 Hz, 1H), 4.38 (d, *J*=2.7 Hz, 1H), 4.60 (dd, *J*=2.7, 6.9 Hz, 1H), 4.72 (ddd, *J*=5.5, 6.0, 11.5 Hz, 1H); δ_C (150 MHz, $CDCl_3$) 22.8, 23.2, 23.3, 23.6, 24.4, 25.3, 26.1, 26.8, 34.7, 35.2, 48.7, 68.5, 73.1, 79.0, 81.3, 109.3, 109.6; HRMS calcd for: $C_{17}H_{32}O_4S_2Na$ $(MNa)^+$: 387.1640, found: 387.1642 and 0.8 g (13%) of (3a*R*,4*R*,8a*R*)-4-(*bis*(*Isopropylthio*)*methyl*)-2,2,6,6-*tetramethyltetrahydro*-[1,3]*dioxolo*[4,5-*e*][1,3]*dioxepine* (**8**) was isolated as pale yellow crystals, mp 58–60 °C; R_f (20% EtOAc/hexanes) 0.16; $[\alpha]_D^{25}$ −58.4 (*c* 0.209, $CHCl_3$); ν_{max} (KBr) 2989, 2962, 2948, 1456, 1441, 1369, 1336, 1296 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.25 (d, *J*=6.7 Hz, 3H), 1.29 (d, *J*=6.7 Hz, 3H), 1.32 (d, *J*=6.7 Hz, 3H), 1.33 (d, *J*=6.7 Hz, 3H), 1.34 (s, 3H), 1.37 (s, 3H), 1.45 (s, 3H), 1.48 (s, 3H), 3.02 (septet, *J*=6.7 Hz, 1H), 3.15 (septet, *J*=6.7 Hz, 1H), 3.95 (ddd, *J*=1.9, 14.2, 33.1 Hz, 2H), 4.00 (dd, *J*=1.2, 9.5 Hz, 1H), 4.10 (d, *J*=1.2 Hz, 1H), 4.14 (td, *J*=1.6, 5.7 Hz, 1H), 4.28 (dd, *J*=5.7, 9.5 Hz, 1H); δ_C (150 MHz, $CDCl_3$) 22.8, 23.1, 23.3, 24.1, 23.6, 25.3, 25.7, 28.3, 34.9, 35.1, 50.0, 58.2, 72.6, 76.2 (C-4), 101.8, 108.2; HRMS calcd for: $C_{17}H_{32}O_4S_2Na$ $(MNa)^+$: 387.1640, found: 387.1644.

*4.1.3. (Z)-1-Phenyl-N-(((4S,4′R,5S)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)methylene)methanamine oxide (**5**).* Compound **7** (3.64 g, 10 mmol) was dissolved in acetone (150 mL), water (4 mL), HgO (4.33 g, 20 mmol) and $HgCl_2$ (5.43 g, 20 mmol) were added and the resultant slurry was stirred at reflux for 2 h. Progress of the reaction was monitored by TLC (50% EtOAc/hexanes). On completion of reaction the mixture was cooled to room temperature, solids were removed by filtration through a pad of Celite® and the solvent was removed under reduced pressure. The residue was shaken with $CHCl_3$ (100 mL) resulting in a white precipitate. The mixture was filtered through a pad of Celite® and the filtrate was washed with aqueous KI (2×100 mL, 1 M) and brine (100 mL). The organic extracts were dried with Na_2SO_4, filtered and evaporated under reduced pressure. The residual yellow oil was dissolved in dichloromethane (100 mL) and anhydrous $MgSO_4$ (6 g, 50 mmol) and *N*-benzylhydroxylamine (1.35 g, 11 mmol) were added and the reaction mixture was stirred at room temperature for 15 h. After this period the $MgSO_4$ was filtered off and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel: 100 g, 75% EtOAc/hexanes then EtOAc) and nitrone **5** was obtained as colorless solid (2.75 g, 82%), mp 129–131 °C; R_f (50% EtOAc/hexanes) 0.2; $[\alpha]_D^{25}$ +108.4 (*c* 0.201, $CHCl_3$); ν_{max} (KBr) 3081, 3031, 2979, 2951, 2928, 2875, 1609, 1498, 1454, 1421 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.23 (s, 3H), 1.29 (s, 3H), 1.34 (s, 3H), 1.41 (s, 3H), 3.82–3.93 (m, 3H), 4.35 (t, *J*=7.1 Hz, 1H), 4.81–4.93 (2× d, *J*=13.9 Hz, 2H), 5.40 (t, *J*=6.2 Hz, 1H), 6.81 (d, *J*=6.1 Hz, 1H), 7.37–7.43 (m, 5H); δ_C (75 MHz, $CDCl_3$) 24.9, 25.3, 26.5, 27.4, 66.6, 69.4, 72.3, 74.0, 77.4, 109.3, 109.5, 128.9, 129.1, 129.7, 132.0, 134.6; Anal. Calcd for: $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18; Found: C, 64.73; H, 7.43; N, 3.96.

*4.1.4. Methyl 4-(benzyl(hydroxy)amino)-4-((4S,4′R,5S)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)butanoate (**4**).* A stirred and carefully deoxygenated solution of nitrone **5** (1.34 g, 4 mmol) in dry THF (40 mL) was cooled to −82 °C under a nitrogen atmosphere. Methyl acrylate and water were degassed by refluxing under a stream of nitrogen for 20 min, then methyl acrylate (0.504 mL, 5.6 mmol), water (0.574 mL, 32 mmol) and a solution of SmI_2 (120 mL, 0.1 M in THF) were added to the nitrone solution. The temperature was kept between −88 and −81 °C for 1 h, whereupon a solution of $Na_2S_2O_3$ (100 mL) was added. The mixture was extracted with EtOAc (4×100 mL) and the combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel: 50 g, 33% EtOAc/hexanes) and the adduct **4** was isolated as a colorless oil (1.68 g, 99%, dr: >95:5), R_f (20% EtOAc/hexanes) 0.66; $[\alpha]_D^{25}$ +23.3 (*c* 0.223, $CHCl_3$); ν_{max} (KBr) 3449, 3030, 2987, 2938, 2885, 1737, 1497, 1455 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.41 (s, 3H), 1.36 (s, 6H), 1.29 (s, 3H), 1.85–1.97 (m, 1H), 2.21–2.31 (m, 1H), 2.45–2.65 (m, 2H), 3.28–3.35 (m, 1H), 3.63 (s, 3H), 3.84–3.98 (m, 3H), 4.07–4.23 (m, 3H), 4.61 (t, 1H, *J*=6.2 Hz, 1H), 5.10–5.20 (br s, 1H), 7.22–7.37 (m, 5H); δ_C (75 MHz, $CDCl_3$) 23.2, 25.2, 25.5, 26.6, 27.6, 31.5, 51.6, 60.5, 62.9, 68.2, 73.7, 75.3, 79.3, 107.8, 109.8, 127.0, 128.1, 128.9, 138.3, 175.0; Anal. Calcd for: $C_{22}H_{33}NO_7$: C, 62.39; H, 7.85; N, 3.31; Found: C, 62.18; H, 7.92; N, 3.24.

*4.1.5. (S)-1-Benzyl-5-((4S,4′R,5S)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)pyrrolidin-2-one (**9**).* The γ-hydroxylamino ester **4** (1.66 g, 3.92 mmol) was dissolved in a mixture of AcOH/THF/H_2O (60/30/30 mL). Zinc dust (5.1 g, 78.4 mmol) was added and the reaction mixture was stirred at 50 °C for 1.5 h, monitoring by TLC. Water (200 mL) was added after reaction was complete and the mixture was treated with K_2CO_3 until basic (pH>10). The solution was extracted with EtOAc (4×100 mL), and the combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH (60 mL), K_2CO_3 was added and the mixture was stirred at room temperature for 10 h. At this point, water was added and solution was extracted with EtOAc (4×60 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel: 50 g, 80% EtOAc/hexanes, then EtOAc) and **9** was isolated as colorless crystals (1.18 g, 83%), mp 89–91 °C; R_f (80% EtOAc/hexanes) 0.36; $[\alpha]_D^{25}$ +4.8 (*c* 0.206, $CHCl_3$); ν_{max} (KBr) 2993, 2941, 2917, 2872, 1678, 1497, 1455, 1435, 1420 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.22 (s, 3H), 1.25 (s, 3H), 1.31 (s, 3H), 1.43 (s, 3H), 1.96–2.16 (m, 2H), 2.30–2.40 (m, 1H), 2.56–2.67 (m, 1H), 3.85 (dd, *J*=4.3, 8.4 Hz, 1H), 3.95–3.98 (m, 2H), 3.99–4.02 (m, 1H), 4.08 (dd, *J*=5.4, 8.4 Hz, 1H), 4.16 (d, *J*=15.1 Hz, 1H), 4.41 (d, *J*=5.7 Hz, 1H), 4.94 (d, *J*=15.1 Hz, 1H), 7.24–7.34 (m, 5H); δ_C (75 MHz, $CDCl_3$) 19.8, 24.3, 25.1, 26.3, 26.8, 30.8, 44.5, 56.7, 68.4, 73.3, 75.1, 77.3, 105.6, 108.9, 127.3, 128.1, 128.4, 136.6, 175.4; Anal. Calcd for: $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73; Found: C, 66.97; H, 7.81; N, 3.61.

*4.1.6. 1-Benzyl-2-((4S,4′R,5S)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)pyrrolidine (**10**).* Pyrrolidinone **9** (1.14 g, 3.03 mmol) was dissolved in dry THF (40 mL) and the mixture cooled in an ice bath to 0 °C under a nitrogen atmosphere. $LiAlH_4$ (0.576, 12.12 mmol) was added and the reaction mixture was heated to reflux for 2.5 h when reaction was confirmed to be complete by TLC analysis. The mixture was cooled to room temperature, MeOH (5 mL) and silica gel were added and the resultant slurry was dried under reduced pressure and the residue purified by column chromatography (silica gel: 50 g, 33% EtOAc/hexanes). Pyrrolidine **10** was isolated as yellow oil (1.09 g, 94%), R_f (50% EtOAc/hexanes) 0.43; $[\alpha]_D^{25}$ −34.2 (*c* 0.202, $CHCl_3$); ν_{max} (KBr) 3027, 2985, 2937, 2875, 2788, 1494, 1454, 1380, 1371 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.31 (s, 3H), 1.34 (s, 3H), 1.41 (s, 3H), 1.43 (s, 3H), 1.67–1.87 (m, 3H), 1.94–2.04 (m, 1H), 2.27 (dd, *J*=9.0, 16.0 Hz, 1H), 2.96–3.02 (m, 1H), 3.10–3.17 (m, 1H), 3.60 (d, *J*=13.0 Hz, 1H), 3.86 (dd, *J*=5.7, 8.3 Hz, 1H), 3.90–3.97 (m, 2H), 4.00–4.05 (m, 1H), 4.09 (dd, *J*=6.0, 8.7 Hz, 1H), 4.26 (dd, *J*=1.3, 6.4 Hz, 1H), 7.21–7.37 (m, 5H); δ_C (75 MHz, $CDCl_3$) 23.9, 24.6, 25.5, 26.8, 26.9, 25.8, 53.9, 59.1, 61.1, 68.5, 73.7, 77.7, 78.2, 108.1, 109.5, 126.8, 128.0, 129.5, 138.7; HRMS calcd for: $C_{21}H_{32}NO_4$ $(MH)^+$: 362.2331, found: 362.2336.

*4.1.7. (1R)-1-((4R,5S)-5-(1-Benzylpyrrolidin-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (**11**).* Pyrrolidine **10** (0.51 g, 1.41 mmol) was dissolved in a mixture of AcOH (20 mL) and water (5 mL) and the mixture was heated to 40 °C for 3 days monitoring by TLC. When a bis-deprotected product was detected, the reaction was quenched by adding water (100 mL) and treating with K_2CO_3 until basic (pH>10). The solution was extracted with EtOAc (5×60 mL), and the combined organic extracts were washed with brine (60 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: 50 g, 50% EtOAc/hexanes, then EtOAc) to furnish starting material **10** (0.08 g 15%) and desired pyrrolidine **11** (0.213 g, 47%) as colorless oils, R_f (80% EtOAc/hexanes) 0.25; $[\alpha]_D^{25}$ −13.0 (*c* 0.2, $CHCl_3$); ν_{max} (KBr) 3396, 2994, 2949, 2891, 1496, 1453, 1379, 1368 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.34 (s, 3H), 1.44 (s, 3H), 1.72–1.92 (m, 2H), 1.94–2.14 (m, 2H), 2.50 (td, *J*=7.3, 11.6 Hz, 1H), 2.79 (ddd, *J*=6.1, 8.0, 11.6 Hz, 1H), 3.25 (q, *J*=6.6 Hz, 1H), 3.41 (d, *J*=12.7 Hz, 1H), 3.69 (dd, *J*=5.8, 10.7 Hz, 1H), 3.78–3.84 (m, 1H), 3.89 (dd, *J*=3.42, 10.7 Hz, 1H), 4.08–4.16 (m, 2H), 4.22 (d, *J*=12.7 Hz, 1H), 7.25–7.40 (m, 5H); δ_C (75 MHz, $CDCl_3$) 21.1, 25.6, 28.3, 25.9, 51.5, 59.8, 63.9, 64.6, 68.4, 77.7, 78.2, 108.1, 127.5, 128.5, 129.3, 137.2; HRMS calcd for: $C_{18}H_{28}NO_4$ $(MH)^+$: 322.2013, found: 322.2019.

*4.1.8. (1R)-1-((4R,5S)-5-(1-Benzylpyrrolidin-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(tert-butyldimethylsilyloxy)ethanol (**12**).* Substrate **11** (0.21 g, 0.654 mmol) was dissolved in CH_2Cl_2 (15 mL) and imidazole (0.133 g, 1.635 mmol) was added, followed by TBDMSCl (0.117 g, 0.785 mmol) and the reaction mixture was stirred at room temperature for 19 h, monitoring by TLC. The solvent was removed and the crude mixture was purified by column chromatography (silica gel: 25 g, 20% EtOAc/hexanes) giving **12** as a colorless oil (0.28 g, 99%), R_f (50%, hexanes/EtOAc) 0.58; $[\alpha]_D^{25}$ −9.4 (*c* 0.32,

$CHCl_3$); ν_{max} (KBr) 3027, 2985, 2937, 2875, 2788, 1494, 1454, 1380, 1371 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.10 (s, 3H), 0.11 (s, 3H), 0.93 (s, 9H), 1.33 (s, 3H), 1.42 (s, 3H), 1.71–1.89 (m, 2H), 1.93–2.09 (m, 2H), 2.48 (td, J=6.9, 13.9 Hz, 1H), 2.76 (ddd, J=6.6, 7.7, 14.3 Hz, 1H), 3.23 (q, J=7.0 Hz, 1H), 3.42 (d, J=12.6 Hz, 1H), 3.71–3.78 (m, 2H, H-1), 3.92–3.97 (m, 1H), 4.05–4.11 (m, 2H), 4.15 (dd, J=5.4, 9.1 Hz, 1H), 7.23–7.38 (m, 5H); δ_C (75 MHz, $CDCl_3$) −5.3, −5.2, 18.5, 21.6, 25.5, 25.6, 28.2, 26.0, 51.1, 59.9, 63.9, 65.1, 69.5, 76.9, 77.9, 107.9, 127.3, 128.4, 129.5, 137.7; HRMS calcd for: $C_{24}H_{42}NO_4Si$ $(MH)^+$: 436.2883, found: 436.2887.

*4.1.9. (3aR,4S,8aS,8bS)-5-Benzyl-4-((tert-butyldimethylsilyloxy) methyl)-2,2-dimethyloctahydro-[1,3]dioxolo[4,5-a]pyrrolizin-5-ium chloride (**13**).* Pyrrolidine **12** (0.28 g, 0.64 mmol) was dissolved in pyridine (12 mL) and solution was cooled to −20 °C, whereupon MsCl (0.247 mL, 3.2 mmol) was added by microsyringe. The reaction was allowed to warm to room temperature, and was stirred for 15 h, when a solution of $CuSO_4$ (50 mL, 1 M in water) was added. The mixture was extracted with EtOAc (5×50 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The brown solid residue was used in the next step without further purification (0.31 g), mp 219–221 °C; $[\alpha]_D^{25}$ −65.4 (*c* 0.055, $CHCl_3$); ν_{max} (KBr) 3424, 2988, 2956, 2925, 2890, 2854, 1496, 1471 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.19 (s, 3H), 0.20 (s, 3H), 0.96 (s, 9H), 1.37 (s, 3H), 1.62 (s, 3H), 1.37–1.61 (m, 1H), 2.01–2.16 (m, 1H), 2.36–2.53 (m, 1H), 2.87–3.01 (m, 1H), 3.55 (td, J=8.4, 11.6 Hz, 1H), 4.15 (ddd, J=5.6, 7.7 12,6 Hz, 1H), 4.27–4.35 (m, 3H), 6.58 (d, J=12.6 Hz, 1H), 4.90 (d, J=12.6 Hz, 1H), 5.08 (q, J=6.5 Hz, 1H), 5.16 (d, J=6.5 Hz, 1H), 5.71 (t, J=5.2 Hz, 1H), 7.47–7.55 (m, 5H); δ_C (75 MHz, $CDCl_3$) −5.6, −5.1, 18.0, 22.2, 23.2, 25.3, 25.8, 26.4, 57.5, 58.7, 61.8, 74.2, 75.4, 80.1, 80.8, 112.1, 127.1, 129.6, 130.8, 133.4; HRMS calcd for: $C_{24}H_{40}NO_3Si$ $(M-Cl)^+$: 418.2777, found: 418.2781.

*4.1.10. (3aR,4S,8aS,8bS)-4-((tert-Butyldimethylsilyloxy)methyl)-2,2-dimethylhexahydro-3aH-[1,3]dioxolo[4,5-a]pyrrolizine (**14**).* Crude **13** (0.30 g) was transferred to a thick walled tube as a solution in CH_2Cl_2. the solvent was removed under reduced pressure. Toluene (30 mL) was used to dissolve solid residue, Et_3N (3 mL) and KI (0.104 g, 0.64 mmol) were added and tube was sealed and heated to 165 °C for 5 h. After this time, solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel: 25 g, EtOAc), giving the pyrrolizidine **14** as a yellow oil (0.166 g, 79% after two steps), R_f (80% EtOAc/hexanes) 0.19; $[\alpha]_D^{25}$ +29.7 (*c* 0.209, $CHCl_3$); ν_{max} (KBr) 2954, 2928, 2856, 1471, 1463, 1379, 1369 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.06 (s, 6H), 0.88 (s, 9H), 1.28 (s, 3H), 1.32–1.39 (m, 1H), 1.51 (s, 3H), 1.63–1.74 (m, 1H), 1.81–1.95 (m, 2H), 2.73 (dd, J=5.7, 11.9 Hz, 1H), 2.88–3.00 (m, 2H), 3.44 (t, J=8.5 Hz, 1H), 3.67 (dd, J=5.7, 9.9 Hz, 1H), 3.93 (dd, J=7.1, 9.9 Hz, 1H), 4.50 (d, J=5.9 Hz, 1H), 4.74 (dd, J=5.0, 5.7 Hz, 1H); δ_C (75 MHz, $CDCl_3$) −5.4, 5.3, 18.3, 24.2, 24.7, 26.5, 25.9, 28.2, 53.2, 62.9, 68.6, 72.2, 81.6, 83.1, 111.0; HRMS calcd for: $C_{17}H_{34}NO_3Si$ $(MH)^+$: 328.2308, found: 328.2302.

*4.1.11. (1S,2R,3S,7aS)-3-(Hydroxymethyl)hexahydro-1H-pyrrolizine-1,2-diol (**2**).* Pyrrolizidine **14** (0.166 g, 0.507 mmol) was dissolved in MeOH (10 mL), HCl (3 mL, 3.04 mmol, 3.6% in water) was added and the reaction mixture was stirred at room temperature for 2 days. The solvent was removed under reduced pressure and the crude residue was purified by column chromatography (Amberlite© (IRA-401 Serva): 25 g, MeOH). The target pyrrolizine **2** was isolated as a yellow solid (0.087 g, 99%), mp 169–171 °C; $[\alpha]_D^{25}$ +32.0 (*c* 0.2, MeOH); ν_{max} (KBr) 3354, 3041, 2914, 2871, 2544, 1456, 1360, 1321 cm^{-1}; δ_H (600 MHz, CD_3OD) 1.71–1.77 (m, 2H), 1.78–1.84 (m, 1H), 1.89–1.95 (m, 1H), 2.66–2.69 (m, 1H), 2.77 (ddd, J=3.3, 5.7, 7.3 Hz, 1H), 2.86 (ddd, J=5.6, 7.8, 10.9 Hz, 1H), 3.39 (dt, J=3.8, 7.9 Hz, 1H), 3.61 (dd, J=5.7, 10.7 Hz, 1H), 3.72 (dd, J=4.0, 8.1 Hz, 1H), 3.86 (dd, J=7.3, 10.7 Hz, 1H), 4.14 (t, J=3.6 Hz, 1H); δ_C (150 MHz, CD_3OD) 25.8, 31.1, 55.8, 62.2, 69.2, 71.3, 75.0, 79.2; HRMS calcd for: $C_8H_{16}NO_3$ $(MH)^+$: 174.1125, found: 174.1129.

*4.1.12. tert-Butyl 2-((4S,4′R,5S)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)pyrrolidine-1-carboxylate (**15**).* Substrate **10** (0.5 g, 1.38 mmol) was dissolved in a mixture of (EtOH/EtOAc, 10:10 mL), Boc_2O (0.321 g, 1.66 mmol) and 20% PdOH/C (0.05 g, 0.07 mmol) were added and the reaction mixture was stirred under a hydrogen atmosphere (balloon) at room temperature for 22 h. The PdOH/C was removed by filtration and the solution was concentrated under reduced pressure. The crude mixture was purified by column chromatography (silica gel: 50 g, 10% EtOAc/hexanes) to give **15** as a colorless oil (0.51 g, 99%), R_f (10% EtOAc/hexanes) 0.58; $[\alpha]_D^{25}$ −38.9 (*c* 0.213, $CHCl_3$); ν_{max} (KBr) 2983, 2935, 2879, 1697, 1479, 1456, 1393 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.30 (s, 3H), 1.34 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.45 (s, 9H), 1.71–1.82 (m, 1H), 1.87–2.04 (m, 3H), 3.30–3.40 (m, 2H), 3.81–3.92 (m, 1H), 4.01–4.14 (m, 3H), 4.25–4.35 (br s, 1H), 4.53–4.76 (m, 1H); δ_C (75 MHz, $CDCl_3$) 24.3, 24.6, 25.5, 26.2, 26.5, 26.8, 28.5, 46.1, 56.3, 68.5, 73.6, 78.1, 79.1, 79.3, 109.5, 109.7, 154.3; HRMS calcd for: $C_{19}H_{33}NO_6Na$ $(MNa)^+$: 394.2206, found: 394.2201.

*4.1.13. tert-Butyl 2-((4S,5R)-5-((R)-1,2-dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pyrrolidine-1-carboxylatea (**16**). Method A*: Substrate **15** (0.52 g, 1.37 mmol) was dissolved in acetonitrile (20 mL), $Zn(NO_3)_2 \cdot 6H_2O$ (4.05 g, 13.7 mmol) was added and the mixture was stirred at room temperature for 1 day, whereupon a solution of K_2CO_3 (100 mL, 1 M in water) was added. The mixture was extracted with EtOAc (3×100 mL) and the combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: 50 g, 33% EtOAc/hexanes) to provide starting material **15** (0.172 g 33%) and carboxylate **16** (0.227 g, 50%).

Method B: Water (0.017 mL, 1.05 mmol) and $InCl_3$ (0.134 g, 0.704 mmol) were added to a solution of substrate **15** (0.121 g, 0.352 mmol) in acetonitrile (10 mL) at room temperature and the reaction mixture was stirred for 1 day, monitoring by TLC. When the bis-deprotected product was detected, then the reaction was quenched with a solution of K_2CO_3 (50 mL, 1 M in water). The mixture was extracted with EtOAc (3×40 mL) and the combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: 25 g, 33% EtOAc/hexanes) to furnish **16** as a colorless oil (0.096 g, 83%), R_f (EtOAc) 0.36; $[\alpha]_D^{25}$ −41.2 (*c* 0.25, $CHCl_3$); ν_{max} (KBr) 3400, 2978, 2934, 2878, 1691, 1663, 1393, 1365 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.31 (s, 3H), 1.42 (s, 3H), 1.43 (s, 9H), 1.70–1.79 (m, 1H), 1.84–2.08 (m, 3H), 3.25–3.45 (m, 2H), 3.65 (dd, J=5.1, 10.5 Hz, 1H), 3.71 (ddd, J=5.1, 8.4, 8.8 Hz, 1H), 3.80 (dd, J=2.6, 10.4 Hz, 1H), 4.12–4.21 (m, 1H), 4.29–4.33 (m, 1H) 4.45–4.52 (br s, 1H); δ_C (75 MHz, $CDCl_3$) 24.5, 24.7, 26.6, 27.2, 28.5, 46.7, 56.1, 64.9, 69.6, 77.0, 78.8, 79.8, 107.9, 155.2; HRMS calcd for: $C_{16}H_{29}NO_6Na$ $(MNa)^+$: 354.1893, found: 354.1896.

*4.1.14. tert-Butyl 2-((4S,5R)-5-((R)-2-(tert-butyldimethylsilyloxy)-1-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pyrrolidine-1-carboxylate (**17**).* Diol **16** (0.168 g, 0.507 mmol) was dissolved in DMF (5 mL) and imidazole (0.09 g, 1.32 mmol) was added followed by TBDMSCl (0.091 g, 0.61 mmol) and the reaction mixture was stirred at room temperature for 5 h. Water (100 mL) was then added and the mixture was extracted with EtOAc (4×50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

The crude mixture was purified by column chromatography (silica gel: 25 g, 33% EtOAc/hexanes) giving **17** as a colorless oil (0.205 g, 91%), R_f (50% EtOAc/hexanes) 0.62; $[\alpha]_D^{25}$ −48.2 (*c* 0.19, $CHCl_3$); ν_{max} (KBr) 3411, 2928, 2856, 1694, 1671, 1471, 1456, 1391, 1365 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 0.07 (s, 6H), 0.89 (s, 9H), 1.30 (s, 3H), 1.43 (s, 3H), 1.44 (s, 9H), 1.72–1.77 (m, 1H), 1.85–1.92 (m, 1H), 1.95–2.04 (m, 2H), 2.40–2.70 (br s, 1H), 3.22–3.41 (m, 2H), 3.61–3.64 (m, 1H), 3.66–3.72 (m, 1H), 3.78 (dd, *J*=2.7, 9.7 Hz, 1H), 3.98–4.21 (m, 1H), 4.28–4.48 (m, 1H), 4.54–4.76 (m, 1H); δ_C (150 MHz, $CDCl_3$) −5.5, −5.4, 18.3, 24.5, 25.0, 25.6, 25.8, 26.2, 28.5, 46.6, 56.5, 64.3, 69.3, 75.4, 78.3, 79.1, 108.1, 154.9; HRMS calcd for: $C_{22}H_{43}NO_6SiNa$ $(MNa)^+$: 468.2752, found: 468.2752.

*4.1.15. tert-Butyl 2-((4S,5S)-5-((R)-2-(tert-butyldimethylsilyloxy)-1-(methylsulfonyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pyrrolidine-1-carboxylate (**18**).* MsCl (0.1 mL, 1.35 mmol) and DMAP (3.3 mg, 0.0269 mmol) were added to a solution of substrate **17** (0.12 g, 0.269 mmol) in pyridine (5 mL). The reaction mixture was stirred at room temperature for 15 h, whereupon a solution of $CuSO_4$ (50 mL, 1 M in water) was added. The mixture was extracted with EtOAc (5×50 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: 25 g, 33% EtOAc/hexanes) to provide **18** as a colorless oil (0.131 g, 93%), R_f (20% EtOAc/hexanes) 0.43; $[\alpha]_D^{25}$ −26.4 (*c* 0.265, $CHCl_3$); ν_{max} (KBr) 2954, 2932, 2884, 2858, 1684, 1390, 1361 cm^{-1}; δ_H (300 MHz, $CDCl_3$) −0.02 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.32 (s, 3H), 1.45 (s, 3H), 1.42 (s, 9H), 1.74–1.84 (m, 1H), 1.89–2.04 (m, 3H), 3.11–3.16 (m, 1H), 3.19 (s, 3H), 3.35–3.42 (m, 1H), 3.87 (dd, *J*=4.0, 12.0 Hz, 1H), 4.05–4.14 (m, 2H), 4.45–4.50 (m, 1H), 4.61–4.73 (m, 1H), 4.76–4.84 (m, 1H); δ_C (75 MHz, $CDCl_3$) −5.6, 5.5, 18.2, 24.4, 25.0, 25.7, 26.0, 26.3, 28.5, 39.3, 46.6, 56.6, 62.3, 72.9, 77.6, 79.2, 80.7, 108.2, 155.0; HRMS calcd for: $C_{23}H_{45}NO_8SSiNa$ $(MNa)^+$: 546.2527, found: 546.2529.

*4.1.16. (S)-tert-Butyl 2-((4S,5S)-2,2-dimethyl-5-((S)-oxiran-2-yl)-1,3-dioxolan-4-yl)pyrrolidine-1-carboxylate (**19**).* TBAF·$3H_2O$ was added to a solution of **18** (0.193 g, 0.368 mmol) in THF (15 mL) and the reaction mixture was stirred at room temperature for 2 h. A solution of K_2CO_3 (50 mL, 1 M in water) was added and the mixture was extracted with EtOAc (3×50 mL), the combined organic layers dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL), a solution of K_2CO_3 (5 mL, 1 M in water) was added and the reaction mixture was stirred at room temperature for 14 h monitoring by TLC (EtOAc). A solution of K_2CO_3 (50 mL, 1 M in water) was added on completion of reaction, the mixture was extracted with EtOAc (5×40 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: 25 g, 66% EtOAc/hexanes then EtOAc) and **19** was isolated as colorless crystals (0.095 g, 82%) mp 109–110 °C; R_f (EtOAc) 0.62; $[\alpha]_D^{25}$ −54.3 (*c* 0.21, $CHCl_3$); ν_{max} (KBr) 2987, 2942, 2869, 1683, 1475, 1458, 1393, 1379, 1370 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.33 (s, 3H), 1.46 (s, 9H), 1.52 (s, 3H), 1.73–1.94 (m, 2H), 2.02–2.15 (m, 2H), 2.68–2.76 (br s, 1H), 2.85 (t, *J*=4.2 Hz, 1H), 3.02–3.13 (m, 1H), 3.24–3.33 (m, 1H), 3.44 (ddd, *J*=3.2, 8.3, 11.1 Hz, 1H), 3.87 (t, *J*=7.0 Hz, 1H), 3.95–4.07 (m, 1H), 4.68 (d, *J*=7.6 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 24.4, 24.9, 26.0, 26.6, 28.5, 43.6, 46.7, 50.2, 57.5, 77.8, 78.7, 79.4, 108.9, 155.0; HRMS calcd for: $C_{16}H_{27}NO_5$ $(MNa)^+$: 336.1781, found: 336.1785.

*4.1.17. (6S,7R,8S,8aS)-Octahydroindolizine-6,7,8-triol (**20**).* Substrate **19** (0.17 g, 0.542 mmol) was dissolved in dichloromethane (10 mL), TMSI (0.37 mL, 2.71 mmol) was added and the mixture was stirred at room temperature for 4 h monitoring by TLC (EtOAc). On completion of reaction a solution of K_2CO_3 (50 mL, 1 M in water) was added and the mixture extracted with dichloromethane (3×50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude brown oil was dissolved in MeOH (15 mL), HCl (2 mL, 1 M) was added and the mixture was stirred at room temperature for 2 h. The solvent was removed by rotatory evaporator and the crude solid was purified by column chromatography (Amberlite© (IRA-401 Serva): 25 g, MeOH). The target indolizidine **20** was isolated as a pale brown solid (0.067 g, 71%), mp 155–157 °C; $[\alpha]_D^{25}$ +14.3 (*c* 0.51, MeOH); ν_{max} (KBr) 3372, 3038, 2916, 2871, 2544, 1456, 1361 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.46–1.54 (m, 1H), 1.64–1.71 (m, 1H), 1.71–1.81 (m, 1H), 1.95–2.01 (m, 1H), 2.16 (q, *J*=8.9 Hz, 1H), 2.23 (dt, *J*=6.3, 10.0 Hz, 1H), 2.46 (dd, *J*=1.4, 11.5 Hz, 1H), 2.83 (dd, *J*=1.7, 11.5 Hz, 1H), 2.97 (dt, *J*=2.5, 8.8 Hz, 1H), 3.59 (dd, *J*=2.5, 10.0 Hz, 1H), 3.77–3.81 (m, 2H); δ_C (150 MHz, $CDCl_3$) 21.7, 29.1, 54.0, 54.9, 63.7, 71.7, 72.8, 73.1; HRMS calcd for: $C_8H_{16}NO_3$ $(MH)^+$: 174.1125, found: 174.1124.

*4.1.18. (Z)-1-Phenyl-N-(((3aS,4S,8aR)-2,2,6,6-tetramethyltetrahydro-[1,3]dioxolo[4,5-e][1,3]dioxepin-4-yl)methylene)methanamine oxide (**21**).* Compound **8** (2.01 g, 5.5 mmol) was dissolved in acetone (100 mL), water (2 mL), HgO (2.38 g, 11 mmol) and $HgCl_2$ (2.99 g, 11 mmol) were added and the resultant slurry was stirred at reflux for 3 h. The mixture was then cooled to room temperature, solids were removed by filtration through pad of Celite® and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (50 mL) and the white precipitate formed was removed by filtration through a pad of Celite®. The filtrate was washed with aqueous KI (2×50 mL, 1 M) and brine (50 mL), the organic extracts were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The residual yellow oil was dissolved in dichloromethane (55 mL), anhydrous $MgSO_4$ (3.3 g, 27.5 mmol) and *N*-benzylhydroxylamine (0.68 g, 5.5 mmol) were added and the reaction mixture was stirred at room temperature for 14 h monitoring by TLC. On completion of the reaction, the $MgSO_4$ was removed by filtration and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel: 50 g, 75% EtOAc/hexanes) and nitrone **21** was obtained as a colorless solid (1.12 g, 60%), mp 150–152 °C; R_f (50% EtOAc/hexanes) 0.19; $[\alpha]_D^{25}$ −60.2 (*c* 0.201, $CHCl_3$); ν_{max} (KBr) 3030, 2993, 2932, 1576, 1498, 1462, 1445 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.34 (s, 3H), 1.49 (s, 3H), 1.51 (s, 6H), 3.93 (dd, *J*=5.2, 10.2 Hz, 1H), 3.98 (dd, *J*=1.5, 5.4 Hz, 2H), 4.09–4.11 (m, 1H), 4.91 (d, *J*=7.8 Hz, 1H), 4.96 (d, *J*=7.8 Hz, 1H), 5.20 (dd, *J*=7.8, 10.1 Hz, 1H), 6.74 (d, *J*=7.8 Hz, 1H), 7.35–7.41 (m, 5H); δ_C (150 MHz, $CDCl_3$) 23.3, 25.6, 25.8, 26.2, 58.3, 62.9, 70.2, 76.1, 77.5, 102.0, 109.0, 128.7, 128.8, 128.9, 132.7, 135.8; Anal. Calcd for: $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18; Found: C, 64.69; H, 7.84; N, 4.22.

*4.1.19. Methyl 4-(benzyl(hydroxy)amino)-4-((3aS,4S,8aR)-2,2,6,6-tetramethyltetrahydro-[1,3]dioxolo[4,5-e][1,3]dioxepin-4-yl)butanoate (**22**).* A stirred and carefully deoxygenated solution of the nitrone **21** (0.335 g, 1 mmol) in dry THF (10 mL) was cooled to −82 °C under a nitrogen atmosphere. Methyl acrylate and water were degassed by refluxing under a stream of nitrogen for 20 min, then methyl acrylate (0.126 mL, 1.4 mmol), water (0.144 mL, 8 mmol) and a solution of SmI_2 (30 mL, 0.1 M in THF) were then added. The temperature was kept at −82 °C until the reaction was judged to be complete by TLC analysis, whereupon a solution of $Na_2S_2O_3$ (50 mL) was added. The mixture was extracted with EtOAc (4×50 mL) and the combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (silica gel: 25 g, 33% EtOAc/hexanes) furnishing **22** as a colorless oil (0.376 g, 88%, dr: >95:5), mp 86–87 °C; R_f (50% hexanes/EtOAc) 0.6; $[\alpha]_D$ −38.5 (*c* 0.195, $CHCl_3$); ν_{max} (KBr) 3448, 2991, 2951, 2945, 2481, 1713, 1452, 1438 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.34 (s, 3H), 1.36 (s, 3H), 1.47 (s, 3H), 1.56 (s, 3H), 1.75–1.84 (br s, 1H), 2.27–2.35 (m, 1H), 2.47–2.51 (m, 2H), 2.86–2.92 (br s, 1H), 3.58 (s, 3H), 3.83 (d, J=13.2 Hz, 1H), 3.89–3.94 (m, 1H), 3.95–3.96 (m, 2H), 4.04 (d, J=13.2 Hz, 1H), 4.14–4.17 (m, 1H), 4.28 (d, J=9.4 Hz, 1H), 4.97–5.04 (br s, 1H), 7.24–7.42 (m, 5H); δ_C (150 MHz, $CDCl_3$) 20.9, 24.2, 25.4, 25.6, 28.2, 32.5, 51.6, 58.6, 60.9, 66.9, 68.2, 76.6, 77.3, 102.1, 108.2, 128.4, 128.5, 128.7, 134.4, 175.4; Anal. Calcd for: $C_{22}H_{33}NO_7$: C, 62.39; H, 7.85; N, 3.31; Found: C, 62.70; H, 7.91; N, 3.11.

4.1.20. 1-Benzyl-5-((3aS,4S,8aR)-2,2,6,6-tetramethyltetrahydro-[1,3]dioxolo[4,5-e][1,3]dioxepin-4-yl)pyrrolidin-2-one (***23***). $Mo(CO)_6$ (0.123 g, 0.462 mmol) and water (0.5 mL) were added to a solution of γ-hydroxylamino ester **22** (0.1 g, 0.231 mmol) in acetonitrile (5 mL) and the mixture was stirred at reflux for 3 h monitoring by TLC. Aqueous K_2CO_3 (40 mL, 1 M) was added, the mixture was extracted with EtOAc (4×40 mL) and the combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: 50 g, 20% EtOAc/hexanes then EtOAc) and **23** was isolated as colorless crystals (0.052 g, 60%), mp 141–144 °C; R_f (80% EtOAc/hexanes) 0.27; $[\alpha]_D^{25}$ +13.4 (c 0.209, $CHCl_3$); ν_{max} (KBr) 2987, 2891, 2862, 2821, 1681, 1676, 1496, 1462, 1445 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.29 (s, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 1.48 (s, 3H), 1.85–1.93 (m, 1H), 2.06–2.11 (m, 1H), 2.29 (ddd, J=1.5, 10.1, 16.6 Hz, 1H), 2.56 (td, J=9.8, 19.6 Hz, 1H), 3.73 (d, J=9.8 Hz, 1H), 3.76 (d, J=14.9 Hz, 1H), 3.84 (dd, J=5.6, 10.0 Hz, 1H), 3.96–3.99 (m, 3H), 4.15 (td, J=1.5, 5.6 Hz, 1H), 5.22 (d, J=14.9 Hz, 1H), 7.22–7.32 (m, 5H); δ_C (150 MHz, $CDCl_3$) 18.7, 23.8, 25.0, 25.5, 28.5, 30.8, 43.9, 56.5, 58.3, 68.3, 75.5, 76.6, 101.8, 108.5, 127.6, 128.0, 128.6, 136.4, 175.8; Anal. Calcd for: $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73; Found: C, 67.37; H, 8.12; N, 3.67.

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24. Crystallograhic Data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center and allocated the deposition numbers CCDC 800 702 and CCDC 800 703. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1E2, UK, (fax: +44 (0) 1223 336033 or email: deposit@ccdc.cam.ac.uk).