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Synthesis of D-arabinose-derived polyhydroxylated pyrrolidine, indolizidine and pyrrolizidine alkaloids. Total synthesis of hyacinthacine A_2

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ABSTRACT

Several new polyhydroxylated alkaloids including pyrrolidines with a long side chain and 3-(hydroxymethyl) indolizidines were prepared from a common nitrone easily obtained from D-arabinose. In addition, a total synthesis of hyacinthacine A_2 has been achieved in five steps and 67.7% overall yield starting from the same D-*arabino*-derived nitrone. All synthesized compounds have a common structural feature consisting of a pyrrolidine ring with D-*arabino* configuration.

1. Introduction

Polyhydroxylated nitrogen saturated heterocycles, such as pyrrolidines, indolizidines, and pyrrolizidines constitute one of the most extensively examined family of compounds that have been shown to be potent inhibitors of a great variety of glycosidases.[1] This biological activity confers those compounds a well-recognized chemotherapeutic potential as antibacterial,[2] antidiabetic,[3] antitumoral,[4] and antiviral[5] agents and, as a consequence, they have been broadly studied subjects of synthetic chemistry for many years.[6] Among the pleyade of natural and unnatural polyhydroxylated alkaloids of biological interest, those found in *Hyacinthaceae* plants have received considerable attention from both biological[7] and synthetic[8] points of view. Most derivatives isolated from the leaves of bluebells (*Hyacinthoides non-scripta*) possess a common structural motif consisting of a pyrrolidine having D-*arabino* substitution pattern, that is, three contiguous centers bearing two hydroxyl groups and a hydroxymethyl group, all having R configuration. The simplest member of this family is DAB-1 **1**. Other structural variations reside in the side chain at C-1 of the pyrrolidine ring leading to DMDP **2** and homo-DMDP **3** among others like **4**–**6** (Fig. 1).[9] The same structural motif has also been found in radicamines A **7** and B **8**, both isolated from *Lobelia chinensis*.[10] The side chain at C-1 can also be linked to the nitrogen atom forming a bicyclic structure as in the

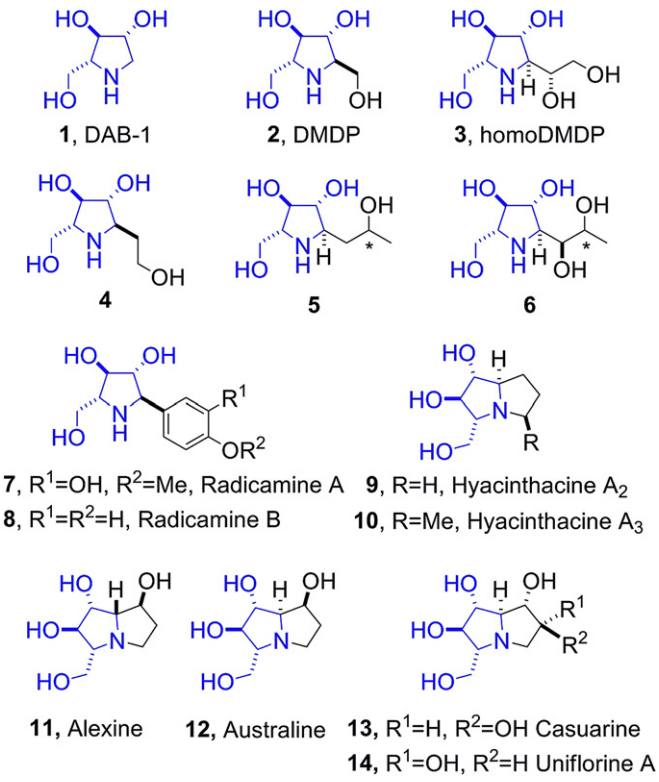

Figure 1. Alkaloids with D-*arabino* configuration.

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case of hyacinthacines A2 **9** and A3 **10**[11] as well as in the well-known pyrrolizidines alexine **11**,[12] australine **12**[13], casuarine **13**,[14] and uniflorine A **14**.[15]

Among the various approaches reported in the literature, nucleophilic additions to cyclic nitrones have demonstrated to be an expeditious and efficient method for preparing a variety of polyhydroxylated pyrrolidines and derivatives.[16] The main advantage of this approach resides in the fact that a variety of cyclic nitrones can be prepared from sugars having a different configuration in such a way that most of stereocenters are incorporated in the starting materials. Previous work in our laboratories[17] illustrated this concept and a variety of natural compounds including codonopsinine,[18] lentiginosine,[19] DAB-1,[20] DMDP,[21] and radicamine B[22] have been synthesized.

We describe herein the synthesis of the naturally occurring *hyacinthacine* A_2 **9** and the non-natural polyhydroxylated alkaloids **15**–**18**, compounds, which have the D-*arabino* configuration at the pyrrolidine ring (Fig. 2). We envisaged preparing compounds **15**–**18** using nitrone **19** as a suitable starting material. Nitrone **19** can be readily prepared from D-arabinose as described by one of us[22] in four steps and 21% overall yield,[23] and it has already been used in our laboratories for preparing DAB-1,[19] radicamine B,[20] and hyacinthacine A_2,[21] in the last case through a dipolar cycloaddition approach.

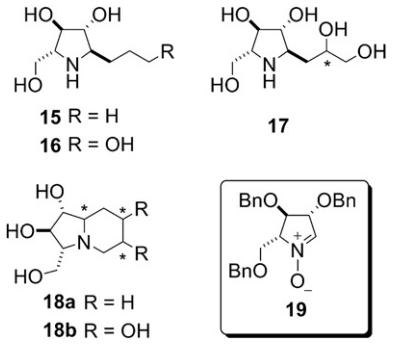


Figure 2. Target compounds from nitrone **19**.

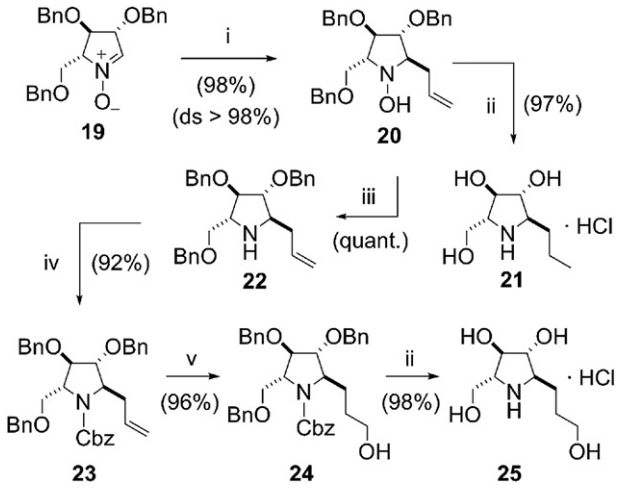
2. Results and discussion

2.1. Synthesis of pyrrolidines with a long side chain

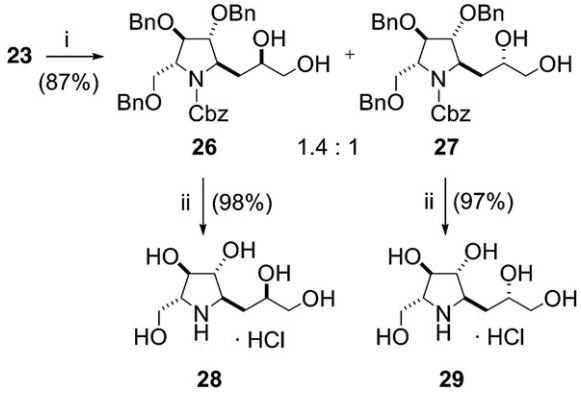
Allylation of nitrone **19** took place with complete selectivity and excellent chemical yield furnishing hydroxylamine **20** as the only product of the reaction (Scheme 1).[24] The configurational assignment of **20** was unambiguously determined by 2D NMR techniques (NOESY, COSY). Concomitant deoxygenation, reduction of the double bond, and removal of the benzyl groups were achieved by catalytic hydrogenation (Pearlman's catalyst, 3 bar) in acidic methanol. Purification of the resulting material afforded **21** (90% from **19**), which was characterized as the hydrochloride salt.

Selective deoxygenation of hydroxylamine **20** was achieved by using Zn in aqueous acetic acid as reducing system. The resulting pyrrolidine **22** was then protected at the nitrogen atom as the *N*-Cbz derivative **23**. The olefin **23** was then submitted to a typical hydroboration with 9-BBN[25] to afford primary alcohol **24** in 96% yield after purification (Scheme 1). Compound **24** was subjected to hydrogenolysis under 3 bar of hydrogen in acidic methanol to give **25** in 80.6% overall yield (six steps from **19**).

Compound **23** was treated with catalytic osmium tetroxide and *N*-methylmorpholine oxide (NMO) to give a 1.4:1 mixture of hydroxylated derivatives **26** and **27** in 87% combined yield. In seeking a higher selectivity for the hydroxylation reaction we checked different conditions including the use of AD-MIX α and β complexes.[26] In all cases the reaction proceeded with no selectivity, lower chemical yield and with the formation of a large number of by-products. The benzyl and benzyloxycarbonyl protecting groups in **26** and **27** could be removed in the same reaction vessel by treatment of those compounds with hydrogen at 3 bar under catalytic conditions (10% Pearlman's catalyst) in acidic methanol. Purification of **28** and **29** by C-18 reverse-phase chromatography and further liophylization afforded those target compounds in 98% and 97% yield, respectively (Scheme 2).

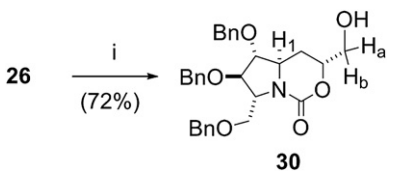


Scheme 1. Synthesis of pyrrolidines with a long side chain. (i) allylmagnesium bromide, THF, 0 °C. (ii) H_2, 3 bar, $Pd(OH)_2$–C, MeOH–HCl,. (iii) Zn, AcOH. (iv) Cbz_2O, dioxane. (v) 9-BBN, then H_2O_2.



Scheme 2. Synthesis of pyrrolidines with a long side chain. (i) OsO_4, NMO, acetone–H_2O. (ii) H_2, 3 bar, $Pd(OH)_2$–C, MeOH–HCl.

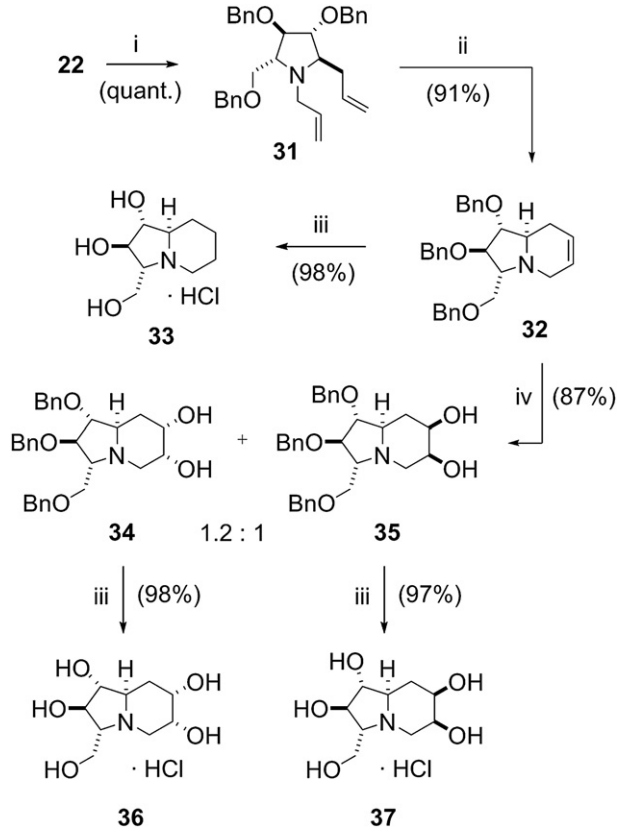
The relative stereochemistry of the newly created stereogenic center in **26** and **27** was determined by transforming the major isomer **26** into the bicyclic **30** through a NaH-mediated intramolecular cyclization (Scheme 3). 2D NMR NOESY experiments (C_6D_6, 500 MHz) indicated an NOE between H-1 and H-a and H-b of the hydroxymethyl group, thereby confirming that in **26** the hydroxyl group at the side chain possessed the indicated configuration.



Scheme 3. Determination of configuration for **26**. (i) NaH, THF, rt.

2.2. Synthesis of 3-(hydroxymethyl)indolizidines[27]

For the synthesis of the target analogs **18** we envisaged the formation of the six-membered ring from **22** via a Ring-Closing Metathesis (RCM), which had been successfully employed in the preparation of several bicyclic polyhydroxylated alkaloids.[28] The introduction of the second alkene residue in **22** was achieved through N-allylation under basic conditions (Scheme 4), which gave the RCM precursor **31** in quantitative yield. This precursor was then subjected to RCM using second generation Grubbs' catalyst[29] in toluene at 80 °C and bicycle **32** was obtained in 91% isolated yield.



Scheme 4. Synthesis of 3-(hydroxymethyl) indolizidines. (i) allyl bromide, DMF, K_2CO_3, Bu_4NI. (ii) Grubbs second generation catalyst, toluene, 80 °C. (iii) H_2, 3 bar, $Pd(OH)_2$–C, MeOH–HCl. (iv) OsO_4, NMO, acetone–H_2O.

Hydrogenolysis of **32** afforded 3-(hydroxymethyl) indolizidine **33** in an excellent yield after purification. Treatment of **32** with OsO_4/NMO in acetone–water gave *cis*-hydroxylated compounds **34** and **35** in 1.2:1 ratio and 79% combined yield. After chromatographic separation, 2D NMR NOESY on **34** and **35** confirmed both the α-*cis* configuration of the two newly introduced hydroxyl groups and the relative configuration of those groups with respect to the benzyloxy groups already present in the molecules (Fig. 3).

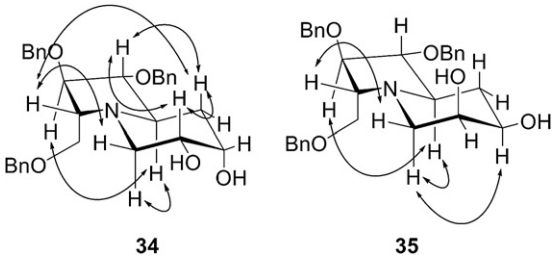
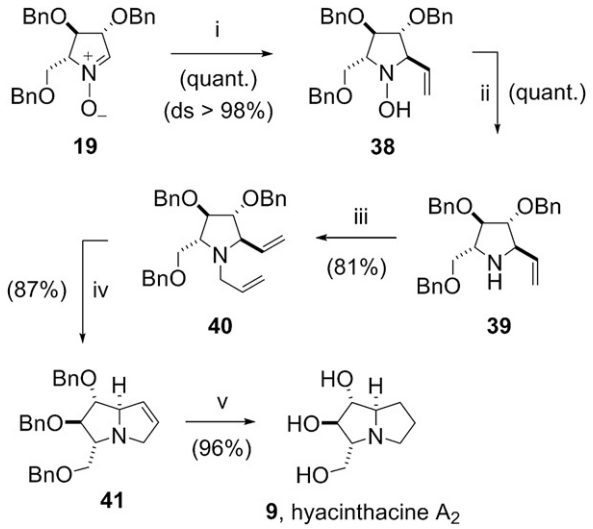


Figure 3. interactions found (2D NOESY) for **34** and **35**.

Again, any attempt of enhancing osmylation selectivity was unsuccessful; use of AD-MIX reagents led to the production of many polar products and lower yields without improving selectivity. Hydrogenolysis of compounds **34** and **35** produced the target 3-(hydroxymethyl) indolizidines **36** and **37**, respectively, as the hydrochloride salts in excellent yields.

2.3. Synthesis of hyacinthacine A_2[30]

Our approach to hyacinthacine A_2 **9** was based on the consecutive nucleophilic addition-RCM metathesis previously described for the preparation of 3-(hydroxymethyl) indolizidines **33**, **36**, and **37**. In the case of compound **9** the ring to be formed should have one less carbon atom that in the case of compounds **33**, **36**, and **37** in order to produce the pursued pyrrolizidine skeleton. Therefore, nucleophilic addition of vinylmangnesium bromide (VMB)[31] to **19** in diethyl ether at 0 °C was carried out to obtain hydroxylamine **38**. The reaction took place with quantitative yield and only one isomer could be detected by NMR (400 MHz). The relative stereochemistry between the vinyl group and the benzyloxy group at C-3 was determined to be *trans* by 2D NMR NOESY experiments. As expected, the nucleophile attacked by the less hindered *Re* face of the nitrone. Deoxygenation (Zn, aq acetic acid) of **38** to **39** followed by N-allylation as described for **22** furnished diallylamine **40** in 81% yield (overall two steps) (Scheme 5).



Scheme 5. Synthesis of Hyacinthacine A_2. (i), vinylmagnesium bromide, Et_2O, 0 °C. (ii) Zn, AcOH. (iii) allyl bromide, DMF, K_2CO_3, Bu_4NI. iv) Grubbs second generation catalyst, toluene, 80 °C. (v) H_2, 3 bar, $Pd(OH)_2$–C, MeOH–HCl, then Dowex 50WX8-200.

Compound **40** was subjected to RCM in toluene at 80 °C for 24 h and bicycle **41** was obtained in 87% isolated yield. In contrast to that reported for other chiral diallylamines[32] the RCM reaction of the basic nitrogen-containing substrate **40** took place smoothly without the assistance of any additive. Finally, catalytic hydrogenation of **41** under usual conditions gave hyacinthacine A_2, which was obtained as the free base after purification by ion-exchange chromatography. The overall yield for **9** was 67.7% (five steps from nitrone **19**).

3. Conclusions

Several polyhydroxylated saturated nitrogen heterocycles having a pyrrolidine ring with D-*arabino* configuration have been prepared. Incorporation of the side chain was achieved by completely stereoselective allylation of the starting nitrone. By introducing a second allylic chain it has been possible to prepare the scarcely

studied 3-(hydroxymethyl) indolizidines via RCM. Following a similar strategy a successful total synthesis of hyacinthacine A_2 has also been achieved in five steps and 67.7% overall yield.

4. Experimental section

4.1. General

The reaction flasks and other glass equipment were heated in an oven at 130 °C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F_{254}; the position of the spots was detected with 254 nm UV light or by spraying with 5% ethanolic phosphomolybdic acid. Preparative centrifugally accelerated radial thin-layer chromatography (radial chromatography) was performed with a Chromatotron® Model 7924 T (Harrison Research, Palo Alto, CA, USA) and with solvents that were distilled prior to use; the rotors (1 or 2 mm layer thickness) were coated with silica gel Merck grade type 7749, TLC grade, with binder and fluorescence indicator (Aldrich 34,644-6) and the eluting solvents were delivered by the pump at a flow-rate of 0.5–1.5 mL min^{-1}. Column chromatography was carried out in a Buchi 800 MPLC system using silica gel 60 μ. Melting points were uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 400 or 500 instruments in the stated solvent. Chemical shifts are reported in parts per million (δ) relative to $CHCl_3$ (δ=7.26) in $CDCl_3$. Optical rotations were taken on a Perkin–Elmer 241 polarimeter or on a JASCO DIP-370 polarimeter. Elemental analyses were performed on a Perkin–Elmer 240B microanalyzer or with a Perkin–Elmer 2400 instrument.

*4.1.1. (2R,3R,4R,5R)-2-Allyl-3,4-bis(benzyloxy)-5-(benzyloxy-methyl)pyrrolidin-1-ol (**20**).* To a cooled (0 °C) solution of nitrone **19** (1.0 g, 2.4 mmol) in anhydrous THF (30 mL), allylmagnesium bromide (7.2 mL of a 1 M solution in THF, 7.2 mmol) was added dropwise. After stirring for 13 h at 0 °C the reaction was quenched with satd aq NH_4Cl (20 mL). The reaction mixture was diluted with diethyl ether (20 mL), the organic layer was separated and the aqueous layer was extracted with diethyl ether (2×20 ml). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and the solvent was eliminated under reduced pressure to afford the crude product, which was purified by radial chromatography (Hexane–EtOAc, 7:3) to give pure **20** (1.15 g, 98%) as an oil. R_f (Hexane–EtOAc, 7:3)=0.55. $[\alpha]_D^{22}$ −3 (*c* 0.815, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.27–2.37 (m, 1H, CH_2CH=CH_2), 2.66–2.75 (m, 1H, CH_2CH=CH_2), 3.37 (dt, *J*=8.5, 5.1 Hz, 1H, H_2), 3.52–3.57 (m, 1H, H_5), 3.65 (dd, *J*=9.6, 6.5 Hz, 1H, CH_2OH), 3.80 (dd, *J*=9.6, 5.2 Hz, 1H, CH_2OH), 3.86 (dd, *J*=4.8, 2.5 Hz, 1H, H_3), 3.97 (dd, *J*=4.2, 2.5 Hz, 1H, H_4), 4.45 (d, *J*=11.8 Hz, 1H, CH_2Ph), 4.47 (d, *J*=11.9 Hz, 1H, CH_2Ph), 4.51 (d, *J*=11.8 Hz, 1H, CH_2Ph), 4.54 (d, *J*=12.0 Hz, 1H, CH_2Ph), 4.54 (d, 1H, *J*=12.0 Hz, 1H, CH_2Ph), 4.59 (d, *J*=12.0 Hz, 1H, CH_2Ph), 5.07–5.15 (m, 2H, CH_2CH=CH_2), 5.86 (dddd, *J*=16.9, 10.2, 7.5, 6.7 Hz, 1H, CH_2CH=CH_2), 7.27–7.38 (m, 15H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.6 (*C*H_2CH=CH_2), 68.4 (*C*H_2OBn), 69.5 (C_2), 69.9 (C_5), 71.7 (*C*H_2Ph), 71.7 (*C*H_2Ph), 73.4 (*C*H_2Ph), 84.2 (C_4), 85.3 (C_3), 117.1 (CH_2CH=*C*H_2), 127.6 (Ar), 127.7 (Ar), 127.7 (Ar), 127.9 (Ar), 127.9 (Ar), 128.3 (Ar), 128.3 (Ar), 128.4 (Ar), 135.5 (CH_2*C*H=CH_2), 138.1 (Ar), 138.2 (Ar), 138.5 (Ar). Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.73; H, 6.41; N, 3.24.

*4.1.2. (2R,3R,4R,5R)-2-(Hydroxymethyl)-5-propylpyrrolidine-3,4-diol hydrochloride (**21**).* A solution of hydroxylamine **20** (0.15 g, 0.32 mmol) in methanol (5 mL) was treated with HCl 1 M in methanol (0.5 mL) and $Pd(OH)_2$–C (50 mg). The resulting mixture was stirred under 3 bar of hydrogen for 6 h. The catalyst was eliminated by filtration through a pad of Celite, and the solvent was eliminated under reduced pressure to afford pure **21** (65 mg, 97%) as a white solid; mp84–86 °C. $[\alpha]_D^{21}$ +9 (*c* 0.28, H_2O). ^1H NMR (400 MHz, D_2O) δ 0.95 (t, *J*=7.3 Hz, 3H, $H_{3'}$), 1.38–1.53 (m, 2H, $H_{2'}$), 1.69–1.80 (m, 1H, $H_{1'a}$), 1.81–1.92 (m, 1H, $H_{1'b}$), 3.44 (td, *J*=8.4, 5.8 Hz, 1H, H_5), 3.56 (ddd, *J*=7.7, 6.1, 3.9 Hz, 1H, H_2), 3.86 (dd, *J*=12.6, 6.0 Hz, 1H, CH_2OH), 3.93 (dd, *J*=12.6, 3.8 Hz, 1H, CH_2OH), 3.96 (dd, *J*=7.9, 6.8 Hz, 1H, H_4), 4.05 (dd, *J*=7.7, 6.9 Hz, 1H, H_3). ^{13}C NMR (100 MHz, D_2O) δ 12.8 ($C_{3'}$), 18.6 ($C_{2'}$), 32.1 ($C_{1'}$), 57.9 (*C*H_2OH), 61.2 (C_5), 62.0 (C_2), 74.2 (C_3), 78.1 (C_4). Anal. Calcd for $C_8H_{18}ClNO_3$: C, 45.39; H, 8.57; N, 6.62. Found: C, 45.55; H, 8.70; N, 6.32.

*4.1.3. (2R,3R,4R,5R)-2-Allyl-3,4-bis(benzyloxy)-5-(benzyloxy-methyl)pyrrolidine (**22**).* A solution of hydroxylamine **20** (0.92 g, 2 mmol) in acetic acid (10 mL) was treated with water (10 mL) and Zn powder (2.6 g, 40 mmol). The resulting mixture was stirred at ambient temperature for 40 min, diluted with water (50 mL) and treated with Na_2CO_3 until bubbling of CO_2 stopped. The reaction mixture was extracted with dichloromethane (3×50 mL) and the combined organic extracts were washed with NaOH 3 M (50 mL) and brine, dried ($MgSO_4$) and evaporated under reduced pressure to give pure amine **22** (0.88 g, quant.), which did not need further purification. $[\alpha]_D^{27}$ −24 (*c* 1.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.20 (td, *J*=14.3, 7.3 Hz, 1H, CH_2CH=CH_2), 2.30 (td, *J*=13.1, 6.5 Hz, 1H, CH_2CH=CH_2), 3.11–3.17 (m, 1H, H_2), 3.35 (dt, *J*=6.0, 4.2 Hz, 1H, H_5), 3.42–3.48 (m, 2H, CH_2OBn), 3.68 (dd, *J*=3.1 Hz, *J*=4.8 Hz, 1H, H_3), 3.82 (dd, *J*=4.0, 3.2 Hz, 1H, H_4), 4.40–4.50 (m, 6H, CH_2Ph), 4.98–5.05 (m, 2H, CH_2CH=CH_2), 5.72 (ddt, *J*=17.2, 10.2, 7.1 Hz, 1H, CH_2CH=CH_2), 7.15–7.35 (m, 15H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.9 (*C*H_2CH=CH_2), 61.3 (C_2), 61.7 (C_5), 70.7 (*C*H_2OBn), 71.8 (*C*H_2Ph), 71.8 (*C*H_2Ph), 73.2 (*C*H_2Ph), 86.2 (C_4), 88.4 (C_3), 117.5 (CH_2CH=*C*H_2), 127.6 (Ar), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 127.9 (Ar), 128.4 (Ar), 128.4 (Ar), 135.1 (CH_2*C*H=CH_2), 138.1 (Ar), 138.1 (Ar), 138.2 (Ar). Anal. Calcd for $C_{29}H_{33}NO_3$: C, 78.52; H, 7.50; N, 3.16. Found: C, 78.42; H, 7.92; N, 3.35.

*4.1.4. (2R,3R,4R,5R)-Benzyl 2-allyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidine-1-carboxylate (**23**).* A solution of amine **22** (0.6 g, 1.35 mmol) in dioxane (15 mL) was treated with dibenzyl dicarbonate (0.57 g, 2 mmol) and sodium hydroxide (10 mg). After stirring for 2.5 h, the solvent was evaporated and the residue purified by radial chromatography (hexane–EtOAc, 7:3) to afford pure **23** (0.715 g, 92%) as an oil. $[\alpha]_D^{27}$ −27 (*c* 1.075, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, mixture of conformers) δ 2.38 (ddd, *J*=13.1, 11.6, 9.1 Hz, 0.5H, CH_2CH=CH_2^A), 2.47 (ddd, *J*=13.4, 11.3, 8.7 Hz, 0.5H, CH_2CH=CH_2^B), 2.67–2.74 (m, 0.5H, CH_2CH=CH_2^B), 2.99–3.07 (m, 0.5H, CH_2CH=CH_2^A), 3.55–3.65 (m, 1H, CH_2OBn^A, CH_2OBn^B), 3.83 (dd, *J*=8.9, 4.1 Hz, 0.5H, CH_2OBn^A), 3.94–4.02 (m, 1.5H, H_2^B, H_4^A, H_4^B), 4.05 (dd, *J*=11.3, 3.3 Hz, 0.5H, H_2^A), 4.15 (dd, *J*=4.2, 8.7 Hz, 0.5H, CH_2OBn^B), 4.23–4.28 (m, 1.5H, H_5^A, H_3^A, H_3^B), 4.37 (dd, *J*=10.5, 4.0 Hz, 0.5H, H_5^B), 4.41 (d, *J*=13.2 Hz, 0.5H, CH_2Ph), 4.43 (d, *J*=11.5 Hz, 0.5H, CH_2Ph), 4.49 (d, *J*=12.0 Hz, 0.5H, CH_2Ph), 4.52 (d, *J*=11.2 Hz, 0.5H, CH_2Ph), 4.53 (d, *J*=12.0 Hz, 0.5H, CH_2Ph), 4.54 (d, *J*=11.2 Hz, 0.5H, CH_2Ph), 4.57 (d, *J*=11.7 Hz, 0.5H, CH_2Ph), 4.65 (d, *J*=12.1 Hz, 0.5H, CH_2Ph), 4.69 (d, *J*=12.2 Hz, 0.5H, CH_2Ph), 4.72 (d, *J*=12.0 Hz, 0.5H, CH_2Ph), 5.04 (d, *J*=17.1 Hz, 0.5H, CH_2CH=CH_2^B), 5.09 (d, *J*=10.1 Hz, 0.5H, CH_2CH=CH_2^B), 5.11–5.18 (m, 2H, CH_2CH=CH_2^A, N(CO)OCH_2Ph), 5.25 (d, *J*=12.4 Hz, 0.5H, N(CO)OCH_2Ph), 5.28 (d, *J*=12.4 Hz, 0.5H, N(CO)OCH_2Ph), 5.74 (dddd, *J*=14.5, 10.1, 8.3, 6.0 Hz, 0.5H, CH_2CH=CH_2^B), 5.84 (dddd, *J*=14.6, 10.8, 8.8, 5.6 Hz, 0.5H, CH_2CH=CH_2^A), 7.24–7.41 (m, 20H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$, mixture of conformers) δ 34.8 (*C*H_2CH=CH_2^A), 36.1 (CH_2CH=CH_2^B), 63.0 (C_5^A), 63.3 (C_5^B), 64.0 (C_2^B), 64.1 (C_2^A), 67.0 (O(CO)OCH_2Ph), 67.0 (O(CO)OCH_2Ph), 67.8 (*C*H_2OH^B), 68.8 (*C*H_2OH^A), 71.0 (*C*H_2Ph), 71.0 (*C*H_2Ph), 71.1 (*C*H_2Ph), 71.2 (*C*H_2Ph), 73.1 (*C*H_2Ph), 73.1 (*C*H_2Ph), 82.0 (C_3^B), 82.7 (C_4^A), 83.1 (C_3^A), 83.8 (C_4^B), 117.9 (CH_2CH=*C*H_2^A), 117.9 (CH_2*C*H=CH_2^B), 127.6 (Ar), 127.6 (Ar), 127.7 (Ar), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 127.8 (Ar), 128.0 (Ar), 128.1 (Ar), 128.1 (Ar), 128.2

(Ar), 128.4 (Ar), 128.4 (Ar), 128.5 (Ar), 128.5 (Ar), 128.6 (Ar), 134.9 ($CH_2CH{=}CH_2^B$), 135.1 ($CH_2CH{=}CH_2^A$), 136.6 (Ar), 136.6 (Ar), 137.7 (Ar), 137.7 (Ar), 137.9 (Ar), 138.0 (Ar), 138.3 (Ar), 138.6 (Ar), 154.3 (*C*=O), 154.7 (*C*=O). Anal. Calcd for $C_{37}H_{39}NO_5$: C, 76.92; H, 6.80; N, 2.42. Found: C, 76.73; H, 6.99; N, 2.21.

*4.1.5. (2R,3R,4R,5R)-Benzyl 3,4-bis(benzyloxy)-2-(benzyloxy-methyl) -5-(3-hydroxypropyl)-pyrrolidine-1-carboxylate (**24**).* A solution of **23** (0.2 g, 0.346 mmol) in anhydrous THF (10 mL) was treated with 9-BBN (1.5 mL of a 0.5 M solution in THF, 0.75 mmol) under an argon atmosphere. The resulting mixture was stirred at ambient temperature until complete disappearance of the starting material (TLC), at which time 35% hydrogen peroxide (0.65 mL) and 3 M NaOH (0.5 mL) were added. Saturated aqueous ammonium chloride (10 mL) was added and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give a residue, which was purified by radial chromatography (hexane–EtOAc, 7:3) to afford alcohol **24** (0.195 g, 96%) as an oil. $[\alpha]_D^{20}$ −43 (*c* 0.363, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C) δ 1.46 (q, *J*=6.7 Hz, 2H, $H_{2'}$), 1.61–1.73 (m, 1H, $H_{1'a}$), 1.84–1.94 (m, 1H, $H_{1'b}$), 3.40 (t, *J*=6.4 Hz, 2H, $H_{3'}$), 3.51 (t, *J*=9.2 Hz, 1H, H_2), 3.78–3.86 (m, 2H, H_5, CH_2OBn), 3.96 (s, 1H, H_4), 4.05 (dd, *J*=9.7, 3.8 Hz, 1H, CH_2OH), 4.17 (s, 1H, H_3), 4.42 (d, *J*=12.2 Hz, 1H, CH_2Ph), 4.46–4.52 (m, 3H, CH_2Ph), 4.54 (d, *J*=12.1 Hz, 1H, CH_2Ph), 4.58 (d, *J*=2.1 Hz, 1H, CH_2Ph), 5.08 (d, *J*=12.5 Hz, 1H, CH_2Ph), 5.12 (d, *J*=12.5 Hz, 1H, CH_2Ph), 7.23–7.39 (m, 20H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6, 90 °C) δ 28.2 ($C_{1'}$), 29.9 ($C_{2'}$), 61.3 ($C_{3'}$), 63.7 (C_5), 65.1 (C_2), 66.6 (N(CO)OCH_2Ph), 68.9 (CH_2OBn), 69.0 (CH_2Ph), 71.1 (CH_2Ph), 71.2 (CH_2Ph), 83.3 (C_3), 84.5 (C_4), 127.7 (Ar), 127.8 (Ar), 127.8 (Ar), 127.9 (Ar), 127.9 (Ar), 127.9 (Ar), 128.1 (Ar), 128.2 (Ar), 128.5 (Ar), 128.6 (Ar), 128.7 (Ar), 136.4 (Ar), 137.6 (Ar), 137.8 (Ar), 138.2 (Ar), 154.6 (*C*=O). Anal. Calcd for $C_{37}H_{41}NO_6$: C, 74.60; H, 6.94; N, 2.35. Found: C, 74.86; H, 7.12; N, 2.63.

*4.1.6. (2R,3R,4R,5R)-2-(Hydroxymethyl)-5-(3-hydroxypropyl)-pyrrolidine-3,4-diol hydrochloride (**25**).* The hydrogenation of **24** (0.190 g, 0.32 mmol), as described above for **20** to give **21**, afforded pure **25** (71 mg, 98%) as a yellow oil. $[\alpha]_D^{22}$ +47 (*c* 0.27, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 1.55 (dc, *J*=8.7, 6.7 Hz, 2H, $H_{2'}$), 1.63–1.73 (m, 1H, $H_{1'a}$), 1.83 (dtd, *J*=9.1, 7.7, 6.1 Hz, 1H, $H_{1'b}$), 3.31 (dt, *J*=8.1, 6.3 Hz, 1H, H_5), 3.44 (ddd, *J*=7.5, 6.2, 3.8 Hz, 1H, H_2), 3.50 (t, *J*=6.3 Hz, 2H, $H_{3'}$), 3.71 (dd, *J*=12.6, 6.1 Hz, 1H, CH_2OH), 3.79 (dd, *J*=12.3, 3.8 Hz, 1H, CH_2OH), 3.84 (dd, *J*=7.8, 6.8 Hz, 1H, H_4), 3.91 (dd, *J*=7.6, 6.8 Hz, 1H, H_3). ^{13}C NMR (100 MHz, D_2O) δ 26.7 ($C_{1'}$), 27.7 ($C_{2'}$), 57.9 (CH_2OH), 60.8 ($C_{3'}$), 61.2 (C_5), 62.1 (C_2), 74.2 (C_3), 78.0 (C_4). Anal. Calcd for $C_8H_{18}ClNO_4$: C, 42.20; H, 7.97; N, 6.15. Found: C, 42.18; H, 8.14; N, 6.02.

*4.1.7. (2R,3R,4R,5R)-Benzyl 3,4-bis(benzyloxy)-2-(benzyloxy-methyl) -5-((R)-2,3-dihydroxypropyl)pyrrolidine-1-carboxylate (**26**) and (2R,3R,4R,5R)-benzyl 3,4-bis(benzyl-oxy)-2-(benzyloxymethyl)-5-((S)-2,3-dihydroxypropyl)-pyrrolidine-1-carboxylate (**27**).* A cooled (0 °C) solution of *N*-methylmorpholine oxide (0.106 g, 0.9 mmol) in 10:1 acetone–water (10 mL) was treated with osmium tetroxide (4.6 mg, 0.018 mmol) and a solution of **23** (0.35 g, 0.6 mmol) in acetone (5 mL). The resulting mixture was stirred at ambient temperature for 16 h at which time a 30% aqueous solution of $NaHSO_3$ (30 mL) was added. The solvent was partially evaporated and the residue was extracted with dichloromethane (3×30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude mixture of diols was purified by radial chromatography (hexane–EtOAc, 1:1).

Compound **26**: (0.186 g, 51%); Oil. $[\alpha]_D^{20}$ −31 (*c* 0.136, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (ddd, *J*=14.4, 10.0, 5.3 Hz, 1H, $H_{1'a}$), 2.04 (ddd, *J*=13.9, 8.8, 3.5 Hz, 1H, $H_{1'b}$), 3.48 (dd, *J*=10.2, 6.9 Hz, 1H, $H_{3'a}$), 3.51 (dd, *J*=10.5, 9.1 Hz, 1H, CH_2OBn), 3.59 (dd, *J*=11.2, 3.1 Hz, 1H, $H_{3'b}$), 3.72 (tdd, *J*=10.2, 6.8, 3.3 Hz, 1H, $H_{2'}$), 3.84 (dd, *J*=8.8, 4.1 Hz, 1H, CH_2OBn), 3.92 (s, 1H, H_4), 4.16 (dd, *J*=10.5, 3.6 Hz, 1H, H_2), 4.22 (s, 1H, H_3), 4.26 (dd, *J*=8.6, 5.2 Hz, 1H, H_5), 4.36 (d, *J*=12.1 Hz, 1H, CH_2Ph), 4.40 (d, *J*=12.0 Hz, 1H, CH_2Ph), 4.46 (d, *J*=12.0 Hz, 1H, CH_2Ph), 4.47 (d, *J*=12.1 Hz, 1H, CH_2Ph), 4.51 (d, *J*=12.2 Hz, 1H, CH_2Ph), 4.60 (d, *J*=12.2 Hz, 1H, CH_2Ph), 5.12 (d, *J*=12.2 Hz, 1H, CH_2Ph), 5.19 (d, *J*=12.2 Hz, 1H, CH_2Ph),7.19–7.42 (m, 20H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.7 ($C_{1'}$), 61.2 (C_5), 63.1 (C_2), 66.3 ($C_{3'}$), 67.5 (N(CO)OCH_2Ph), 68.4 (CH_2OBn), 68.9 ($C_{2'}$), 71.0 (CH_2Ph), 71.1 (CH_2Ph), 73.0 (CH_2Ph), 82.8 (C_3), 84.9 (C_4), 127.5 (Ar), 127.5 (Ar), 127.6 (Ar), 127.7 (Ar), 127.8 (Ar), 128.2 (Ar), 128.3 (Ar), 128.4 (Ar), 128.4 (Ar), 128.5 (Ar), 136.0 (Ar), 137.4 (Ar), 137.5 (Ar), 138.1 (Ar), 155.9 (*C*=O). Anal. Calcd for $C_{37}H_{41}NO_7$: C, 72.65; H, 6.76; N, 2.29. Found: C, 72.78; H, 6.46; N, 2.41.

Compound **27**: (0.133 g, 36 %); oil. $[\alpha]_D^{20}$ −52 (*c* 0.118, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.93–2.01 (m, 2H, $H_{1'}$), 3.44 (dd, *J*=11.2, 6.9 Hz, 1H, CH_2OBn), 3.52 (dd, *J*=10.6, 9.0 Hz, 1H, $H_{3'a}$), 3.58 (dd, *J*=11.2, 3.7 Hz, 1H, CH_2OBn), 3.70 (ddd, *J*=9.4, 6.8, 3.3 Hz, 1H, H_2), 3.75 (dd, *J*=8.9, 4.2 Hz, 1H, $H_{3'b}$), 3.96 (s, 1H, H_4), 4.15 (c, *J*=7.1 Hz, 1H, H_5), 4.19–4.22 (m, 2H, H_3, $H_{2'}$), 4.38 (d, *J*=12.1 Hz, 1H, CH_2Ph), 4.40–4.49 (m, 3H, CH_2Ph), 4.51 (d, *J*=12.8 Hz, 1H, CH_2Ph), 4.62 (d, *J*=12.2 Hz, 1H, CH_2Ph), 5.07 (d, *J*=12.3 Hz, 1H, CH_2Ph), 5.19 (d, *J*=12.3 Hz, 1H, CH_2Ph), 7.19–7.42 (m, 20H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.1 ($C_{1'}$), 61.5 ($C_{2'}$), 62.8 (C_5), 66.9 (CH_2OBn), 67.3 (N(CO)OCH_2Ph), 68.5 ($C_{3'}$), 69.8 (C_2), 71.1 (CH_2Ph), 71.3 (CH_2Ph), 73.1 (CH_2Ph), 83.1 (C_3), 85.1 (C_4), 127.5 (Ar), 127.6 (Ar), 127.7 (Ar), 127.8 (Ar), 127.8 (Ar), 127.9 (Ar), 128.2 (Ar), 128.2 (Ar), 128.4 (Ar), 128.5 (Ar), 128.5 (Ar), 128.6 (Ar), 136.2 (Ar), 137.5 (Ar), 137.5 (Ar), 137.5 (Ar), 138.2 (Ar), 154.7 (*C*=O). Anal. Calcd for $C_{37}H_{41}NO_7$: C, 72.65; H, 6.76; N, 2.29. Found: C, 72.51; H, 6.95; N, 2.34.

*4.1.8. (2R,3R,4R,5R)-2-((R)-2,3-Dihydroxypropyl)-5-(hydroxy-methyl)pyrrolidine-3,4-diol hydrochloride (**28**).* The hydrogenation of **26** (0.150 g, 0.25 mmol), as described above for **20** to give **21**, afforded pure **28** (60 mg, 98%) as an oil. $[\alpha]_D^{28}$ +5 (*c* 0.05, H_2O). ^{1}H NMR (500 MHz, D_2O) δ 1.70–1.74 (m, 2H, $H_{1'}$), 3.27 (dd, *J*=11.8, 6.3 Hz, 1H, $H_{3'a}$), 3.34–3.40 (m, 3H, H2, H5, $H_{3'b}$), 3.62 (dd, *J*=12.8, 5.8 Hz, 1H, CH_2OH), 3.63–3.66 (m, 1H, $H_{2'}$), 3.69 (dd, *J*=12.7, 3.6 Hz, 1H, CH_2OH), 3.78 (dd, *J*=8.5, 7.1 Hz, 1H, H_4), 3.83 (t, *J*=7.4 Hz, 1H, H_3). ^{13}C NMR (125 MHz, D_2O) δ 32.2 ($C_{1'}$), 57.9 (CH_2OH), 58.1 (C_2 or C_5), 61.8 (C_2 or C_5), 65.0 ($C_{3'}$), 67.8 ($C_{2'}$), 73.7 (C_3), 77.2 (C_4). Anal. Calcd for $C_8H_{18}ClNO_5$: C, 39.43; H, 7.45; N, 5.75. Found: C, 39.51; H, 7.68; N, 5.58.

*4.1.9. (2R,3R,4R,5R)-2-((S)-2,3-Dihydroxypropyl)-5-(hydroxy-methyl)pyrrolidine-3,4-diol hydrochloride (**29**).* The hydrogenation of **27** (0.120 g, 0.20 mmol), as described above for **20** to give **21**, afforded pure **29** (46 mg, 97%) as an oil. $[\alpha]_D^{21}$ +11 (*c* 0.285, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 1.70 (dt, *J*=14.7, 9.3 Hz, 1H, $H_{1'a}$), 1.92 (ddd, *J*=14.7, 5.1, 2.4 Hz, 1H, $H_{1'b}$), 3.35 (dd, *J*=11.5, 5.8 Hz, 1H, $H_{3'a}$), 3.39–3.49 (m, 3H, H_2, H_5, $H_{3'b}$), 3.69 (dd, *J*=12.6, 6.0 Hz, 1H, CH_2OH), 3.68–3.76 (m, 1H, $H_{2'}$), 3.77 (dd, *J*=12.6, 3.3 Hz, 1H, CH_2OH), 3.84 (t, *J*=7.0 Hz, 1H, H_4), 3.89 (t, *J*=6.9 Hz, 1H, H_3). ^{13}C NMR (100 MHz, D_2O) δ 32.8 ($C_{1'}$), 57.9 (CH_2OH), 60.0 (C_2 or C_5), 62.3 (C_2 or C_5), 65.2 ($C_{3'}$), 69.4 ($C_{2'}$), 74.0 (C_3), 78.1 (C_4). Anal. Calcd for $C_8H_{18}ClNO_5$: C, 39.43; H, 7.45; N, 5.75. Found: C, 39.19; H, 7.26; N, 5.90.

*4.1.10. (3R,4aR,5R,6R,7R)-5,6-Bis(benzyloxy)-7-(benzyloxy-methyl)-3-(hydroxymethyl)hexahydro-1H-pyrrolo[1,2-c][1,3]oxazin-1-one (**30**).* To a solution of **26** (20 mg, 0.033 mmol) in anhydrous THF (3 mL) under an argon atmosphere, sodium hydride (1.5 mg of a 60% dispersion in mineral oil, 0.04 mmol) was added at ambient temperature. The resulting mixture was stirred for 3 h at which time saturated aqueous ammonium chloride (3 mL) was carefully

added. The reaction mixture was extracted with diethyl ether (3×5 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by semipreparative HPLC (hexane–EtOAc, 1:1) to afford pure **30** (12 mg, 72%) as an oil. $[\alpha]_D^{22}$ +62 (*c* 0.11, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6) δ 1.28 (ddd, *J*=13.7, 10.4, 5.3 Hz, 1H, H_{4a}), 1.81 (ddd, *J*=13.7, 5.1, 2.8 Hz, 1H, H_{4b}), 3.41 (dd, *J*=11.5, 5.1 Hz, 1H, C*H*OH), 3.47 (dd, *J*=11.6, 5.9 Hz, 1H, C*H*OH), 3.66 (dd, *J*=8.3, 5.4 Hz, 1H, H_6), 3.73 (dd, *J*=9.5, 3.1 Hz, 1H, C*H*OBn), 3.82 (ddd, *J*=10.2, 8.4, 5.2 Hz, 1H, H_5), 3.94 (dd, *J*=9.5, 5.7 Hz, 1H, C*H*OBn), 4.01–4.06 (m, 1H, H_3), 4.39 (d, *J*=12.1 Hz, 1H, CH_2Ph), 4.40–4.43 (m, 1H, H_7), 4.46 (d, *J*=11.9 Hz, 1H, CH_2Ph), 4.48–4.55 (m, 3H, H_8, CH_2Ph), 4.60 (d, *J*=11.9 Hz, 1H, CH_2Ph), 4.62 (d, *J*=11.7 Hz, 1H, CH_2Ph), 7.18–7.39 (m, 15H, Ar). ^{13}C NMR (125 MHz, C_6D_6) δ 27.3 (C_5), 56.0 (C_4), 62.3 (C_8), 63.4 (*C*H_2OH), 69.3 (*C*H_2OBn), 72.1 (*C*H_2Ph), 72.2 (*C*H_2Ph), 73.3 (*C*H_2Ph), 76.3 (C_3), 83.7 (C_7), 88.6 (C_6), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 127.9 (Ar), 128.1 (Ar), 128.4 (Ar), 128.4 (Ar), 128.4 (Ar), 138.3 (Ar), 138.4 (Ar), 138.5 (Ar), 151.3 (*C*=O). Anal. Calcd for $C_{30}H_{31}NO_6$: C, 71.84; H, 6.23; N, 2.79. Found: C, 71.64; H, 6.38; N, 2.96.

*4.1.11. (2R,3R,4R,5R)-1,2-Diallyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidine (**31**).* A solution of amine **22** (555 mg, 1.25 mmol) in DMF (20 mL) was treated sequentially with potassium carbonate (275 mg, 2 mmol), allyl bromide (1.1 mL, 1.5 g, 12.5 mmol) and tetrabutylammonium iodide (10 mg) at ambient temperature under an argon atmosphere. The reaction mixture was stirred for additional 12 h, diluted with water (30 mL) and extracted with hexane (3×30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give pure **31** (0.595 mg, quant.) that did not need further purification. $[\alpha]_D^{25}$ −9 (*c* 0.59, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.07 (dt, *J*=13.9, 8.9 Hz, 1H, CH_2CH=CH_2), 2.30–2.39 (m, 1H, CH_2CH=CH_2), 3.03–3.17 (m, 3H, H_2, H_5, NCH_2CH=CH_2), 3.38–3.44 (m, 2H, CH_2OBn, CH_2CH=CH_2), 3.55 (dd, *J*=9.4, 4.7 Hz, 1H, CH_2OBn), 3.68 (s, 1H, H_3), 3.80 (s, 1H, H_4), 4.29 (d, *J*=12.0 Hz, CH_2Ph), 4.35 (d, *J*=12.1 Hz, CH_2Ph), 4.36 (d, *J*=12.1 Hz, CH_2Ph), 4.39 (d, *J*=12.2 Hz, CH_2Ph), 4.43 (sist. AB, CH_2Ph), 4.91 (dd, *J*=8.7, 1.6 Hz, 1H, CH$_2$CH=CH_2), 4.95 (s, 1H, CH$_2$CH=CH_2), 5.01 (d, *J*=10.2 Hz, 1H, NCH$_2$CH=CH_2), 5.12 (d, *J*=17.2 Hz, 1H, NCH$_2$CH=CH_2), 5.76–5.89 (m, 1H, CH$_2$*C*H=CH$_2$), 5.96–6.07 (m, 1H, NCH$_2$*C*H=CH$_2$), 7.31–7.44 (m, 15H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9 (*C*H$_2$CH=CH$_2$), 51.1 (NCH$_2$CH=CH$_2$), 65.0 (C_2), 65.6 (C_5), 69.3 (*C*H$_2$OBn), 71.3 (*C*H$_2$Ph), 71.4 (*C*H$_2$Ph), 73.3 (*C*H$_2$Ph), 85.7 (C_4), 85.7 (C_3), 116.6 (NCH$_2$*C*H=CH$_2$), 117.1 (CH$_2$*C*H=CH$_2$), 127.6 (Ar), 127.7 (Ar), 127.8 (Ar), 127.9 (Ar), 128.3 (Ar), 128.3 (Ar), 128.3 (Ar), 135.5 (CH$_2$*C*H=CH$_2$), 136.5 (NCH$_2$*C*H=CH$_2$), 138.4 (Ar), 138.4 (Ar), 138.4 (Ar). Anal. Calcd for $C_{32}H_{37}NO_3$: C, 79.47; H, 7.71; N, 2.90. Found: C, 79.61; H, 7.58; N, 3.04.

*4.1.12. (1R,2R,3R,8aR)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-1,2,3,5,8,8a-hexahydroindolizine (**32**).* To a solution of **31** (500 mg, 1.03 mmol) in anhydrous toluene (20 mL) the second generation Grubbs' catalyst (56 mg, 0.1 mmol) was added and the resulting mixture was stirred at 80 °C for 14 h. The solvent was evaporated under reduced pressure without exceeding 30 °C and the residue was purified by radial chromatography (hexane–EtOAc, 4:1) to give pure **32** (0.428 g, 91%) as an oil. $[\alpha]_D^{25}$ +32 (*c* 1.05, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.18–2.23 (m, 2H, H_8), 3.16 (td, *J*=7.3, 4.7 Hz, 1H, H_9), 3.38 (ddd, *J*=17.2, 3.9, 1.9 Hz, 1H, H_{5a}), 3.44 (td, *J*=5.3, 3.3 Hz, 1H, H_3), 3.48–3.54 (m, 1H, H_{5b}), 3.60 (dd, *J*=9.7, 5.6 Hz, 1H, CH_2OBn), 3.70 (dd, *J*=9.7, 5.0 Hz, 1H, CH_2OBn), 3.75 (dd, *J*=4.5, 2.5 Hz, 1H, H_1), 3.98 (t, *J*=2.8 Hz, 1H, H_2), 4.53 (d, *J*=12.1 Hz, 1H, CH_2Ph), 4.56 (s, 2H, CH_2Ph), 4.56 (d, *J*=12.1 Hz, 1H, CH_2Ph), 4.60 (d, *J*=12.0 Hz, 1H, CH_2Ph), 4.61 (d, *J*=12.1 Hz, 1H, CH_2Ph), 5.69–5.74 (m, 1H, H_6), 5.75–5.80 (m, 1H, H_7), 7.30–7.39 (m, 15H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5 (C_8), 45.8 (C_5), 59.8 (C_9), 65.0 (C_3), 69.4 (*C*H$_2$OBn), 71.6 (*C*H$_2$Ph), 71.7 (*C*H$_2$Ph), 73.4 (*C*H$_2$Ph), 86.2 (C_2), 88.9 (C_1), 124.0 (C_7), 125.2 (C_6), 127.6 (Ar), 127.6 (Ar), 127.6 (Ar), 127.7 (Ar), 127.8 (Ar), 127.9 (Ar), 128.3 (Ar), 128.4 (Ar), 128.4 (Ar), 138.3 (Ar), 138.4 (Ar), 138.4 (Ar). Anal. Calcd for $C_{30}H_{33}NO_3$: C, 79.09; H, 7.30; N, 3.07. Found: C, 79.18; H, 7.46; N, 3.21.

*4.1.13. (1R,2R,3R,8aR)-3-(Hydroxymethyl)octa-hydroindolizine-1,2-diol hydrochloride (**33**).* The hydrogenation of **32** (0.150 g, 0.25 mmol), as described above for **20** to give **21**, afforded pure **33** (63 mg, 98%) as a white solid; mp 111–113 °C. $[\alpha]_D^{28}$ +27 (*c* 0.05, H_2O). ^1H NMR (500 MHz, D_2O) δ 1.13–1.25 (m, 2H, H_{7a}, H_{8a}), 1.31–1.44 (m, 1H, H_{6a}), 1.47–1.55 (m, 1H, H_{6b}), 1.64–1.72 (m, 1H, H_{7b}), 1.72–1.80 (m, 1H, H_{8b}), 2.51 (td, *J*=11.5, 2.9 Hz, 1H, H_{5a}), 2.54–2.59 (m, 1H, H_9), 2.85 (dt, *J*=11.5, 3.3 Hz, 1H, H_{5b}), 2.90 (c, *J*=4.9 Hz, H_3), 3.61 (dd, *J*=7.8, 5.4 Hz, 1H, H_1), 3.67 (dd, *J*=11.9, 5.2 Hz, 1H, CH_2OH), 3.77 (dd, *J*=11.9, 5.2 Hz, 1H, CH_2OH), 3.83 (t, *J*=4.7 Hz, 1H, H_2). ^{13}C NMR (125 MHz, D_2O) δ 22.4 (C_7), 23.3 (C_6), 27.3 (C_8), 46.6 (C_5), 59.8 (*C*H$_2$OH), 64.0 (C_9), 67.4 (C_3), 78.0 (C_2), 81.1 (C_1). Anal. Calcd for $C_9H_{18}ClNO_3$: C, 48.32; H, 8.11; N, 6.26. Found: C, 48.27; H, 8.36; N, 6.13.

*4.1.14. (1R,2R,3R,6R,7S,8aR)-1,2-Bis(benzyloxy)-3-(benzyloxy-methyl)octa-hydroindolizine-6,7-diol (**34**) and (1R,2R,3R,6S, 7R,8aR)-1,2-bis(benzyloxy)-3-(benzyloxymethyl)octa-hydroindolizine-6,7-diol (**35**).* The osmylation of **32** (0.120 g, 0.20 mmol), as described above for **23** to give **26** and **27**, afforded pure **34** and **35** after purification by radial chromatography (hexane–EtOAc, 1:1).

Compound **34**: (151 mg, 43%). White solid; mp 108–110 °C. $[\alpha]_D^{26}$ −4 (*c* 1.06, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 1.63 (ddd, *J*=13.9, 11.5, 2.5 Hz, 1H, H_{8a}), 2.06 (dt, *J*=13.8, 3.5 Hz, 1H, H_{8b}), 2.83 (t, *J*=10.8 Hz, 1H, H_{5a}), 2.96 (dd, *J*=11.2, 5.1 Hz, 1H, H_{5b}), 3.22 (ddd, *J*=11.4, 5.8, 3.1 Hz, 1H, H_9), 3.36 (ddd, *J*=6.9, 5.3, 2.3 Hz, 1H, H_3), 3.53 (dd, *J*=9.4, 6.7 Hz, 1H, CH_2OBn), 3.65 (dd, *J*=5.9, 2.8 Hz, 1H, H_1), 3.68 (dd, *J*=9.4, 5.2 Hz, 1H, CH_2OBn), 3.81 (ddd, *J*=10.3, 5.1, 3.0 Hz, 1H, H_6), 3.90 (t, *J*=2.6 Hz, 1H, H_2), 4.01 (dd, *J*=6.0, 3.0 Hz, 1H, H_7), 4.47 (d, *J*=12.0 Hz, 1H, CH_2Ph), 4.49 (d, *J*=11.8 Hz, 1H, CH_2Ph), 4.53 (d, *J*=12.0 Hz, 1H, CH_2Ph), 4.54 (d, *J*=12.0 Hz, 1H, CH_2Ph), 4.57 (d, *J*=12.0 Hz, 1H, CH_2Ph), 4.60 (d, *J*=12.0 Hz, 1H, CH_2Ph), 7.29–7.39 (m, 15H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.1 (C_8), 47.7 (C_5), 57.5 (C_9), 65.1 (C_3), 67.6 (C_6), 68.0 (C_7), 68.7 (*C*H$_2$OBn), 71.6 (*C*H$_2$Ph), 71.7 (*C*H$_2$Ph), 73.4 (*C*H$_2$Ph), 86.6 (C_2), 88.3 (C_1), 127.6 (Ar), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 128.0 (Ar), 128.3 (Ar), 128.3 (Ar), 128.3 (Ar), 128.4 (Ar), 138.1 (Ar), 138.2 (Ar), 138.2 (Ar). Anal. Calcd for $C_{30}H_{35}NO_5$: C, 73.59; H, 7.21; N, 2.86. Found: C, 73.48; H, 7.01; N, 3.10.

Compound **35**: (126 mg, 36%); Oil. $[\alpha]_D^{25}$ +10 (*c* 0.10, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 1.47 (c, *J*=11.7 Hz, 1H), 2.14 (dddd, *J*=12.6, 5.2, 3.1, 0.6 Hz, 1H, H_{8a}), 2.70 (dd, *J*=12.1, 1.1 Hz, 1H, H_{8b}), 2.83 (ddd, *J*=10.3, 7.0, 2.8 Hz, 1H, H_{5a}), 3.16 (dd, *J*=12.1, 3.3 Hz, 1H, H_9), 3.40 (dt, *J*=5.4, 2.1 Hz, 1H, H_{5b}), 3.48–3.52 (m, 1H, H_7), 3.52 (dd, *J*=9.6, 5.7 Hz, 1H, CH_2OBn), 3.60 (dd, *J*=9.6, 5.3 Hz, 1H, CH_2OBn), 3.74 (dd, *J*=7.0, 3.4 Hz, 1H, H_1), 3.79 (s, 1H, H_6), 3.95 (dd, *J*=3.5, 2.3 Hz, 1H, H_2), 4.48 (d, *J*=11.8 Hz, 1H, CH_2Ph), 4.53 (s, 2H, CH_2Ph), 4.56 (s, 2H, CH_2Ph), 4.58 (d, *J*=11.8 Hz, 1H, CH_2Ph), 7.29–7.38 (m, 15H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.2 (C_8), 51.0 (C_5), 63.3 (C_9), 65.1 (C_3), 68.3 (C_6), 68.4 (*C*H$_2$OBn), 69.9 (C_7), 71.8 (*C*H$_2$Ph), 72.1 (*C*H$_2$Ph), 73.4 (*C*H$_2$Ph), 86.5 (C_2), 89.0 (C_1), 127.6 (Ar), 127.8 (Ar), 127.8 (Ar), 128.7 (Ar), 128.4 (Ar), 128.4 (Ar), 128.5 (Ar), 137.9 (Ar), 137.9 (Ar), 138.0 (Ar). Anal. Calcd for $C_{30}H_{35}NO_5$: C, 73.59; H, 7.21; N, 2.86. Found: C, 73.48; H, 7.40; N, 2.66.

*4.1.15. (1R,2R,3R,6S,7R,8aR)-3-(Hydroxymethyl)octahydro-indolizine-1,2,6,7-tetraol hydrochloride (**36**).* The hydrogenation of **34** (0.120 g, 0.251 mmol), as described above for **20** to give **21**,

afforded pure **36** (78 mg, 97%) as an oil. $[\alpha]_D^{28}$ +16 (*c* 0.12, H_2O). ^1H NMR (300 MHz, D_2O, 60 °C) δ 2.46 (ddd, *J*=13.5, 10.2, 2.5 Hz, 1H, H_{8a}), 2.60 (td, *J*=15.2, 5.3 Hz, 1H, H_{8b}), 3.83 (d, *J*=6.4 Hz, 2H, H_5), 4.01 (dd, *J*=9.0, 4.6 Hz, 1H, H_3), 4.18 (td, *J*=9.9, 4.8 Hz, 1H, H_9), 4.33 (dd, *J*=13.0, 5.4 Hz, 1H, CH_2OH), 4.42 (dd, *J*=13.0, 4.0 Hz, 1H, CH_2OH), 4.47–4.56 (m, 4H, H_1, H_2, H_6, H_7). ^{13}C NMR (75 MHz, D_2O, 60 °C) δ 27.8 (C_8), 48.2 (C_5), 58.3 (*C*H_2OH), 62.6 (C_9), 64.5 (C_6 or C_8), 64.6 (C_6 or C_8), 71.0 (C_3), 77.2 (C_1 or C_2), 77.4 (C_1 or C_2). Anal. Calcd for $C_9H_{18}ClNO_5$: C, 42.28; H, 7.10; N, 5.48. Found: C, 42.44; H, 7.03; N, 5.68.

*4.1.16. (1R,2R,3R,6R,7S,8aR)-3-(Hydroxymethyl)octahydro-indolizine-1,2,6,7-tetraol hydrochloride (**37**).* The hydrogenation of **35** (0.060 g, 0.12 mmol), as described above for **20** to give **21**, afforded pure **37** (31 mg, 98%) as an oil. $[\alpha]_D^{28}$ +7 (*c* 0.08, H_2O). ^1H NMR (300 MHz, D_2O, 45 °C) δ 2.22–2.51 (m, 2H, H_8), 3.61 (dd, *J*=13.7, 1.9 Hz, 1H, H_{5a}), 3.87 (dd, *J*=13.7, 4.4 Hz, 1H, H_{5b}), 3.91–3.96 (m, 1H, H_3), 4.10–4.41 (m, 6H, H_1, H_2, H_6, H_7, CH_2OH). ^{13}C NMR (75 MHz, D_2O, 45 °C) δ 34.8 (C_8), 39.9 (C_5), 59.2 (C_9), 59.23 (*C*H_2OH), 63.1 (C_6 or C_8), 64.1 (C_6 or C_8), 75.8 (C_3 or C_1 or C_2), 76.9 (C_3or C_1 or C_2), 79.7 (C_3 or C_1 or C_2). Anal. Calcd for $C_9H_{18}ClNO_5$: C, 42.28; H, 7.10; N, 5.48. Found: C, 42.50; H, 7.18; N, 5.38.

*4.1.17. (2R,3R,4R,5R)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-vinylpyrrolidin-1-ol (**38**).* To a cooled (0 °C) solution of nitrone **19** (1.0 g, 2.4 mmol) in anhydrous diethyl ether (30 mL), vinylmagnesium bromide (7.2 mL of a 1 M solution in THF, 7.2 mmol) was added dropwise. After stirring for 13 h at 0 °C the reaction was quenched with satd aq NH_4Cl (20 mL). The reaction mixture was diluted with diethyl ether (20 mL), the organic layer was separated and the aqueous layer was extracted with diethyl ether (2×20 ml). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent was eliminated under reduced pressure to afford the crude product, which was purified by radial chromatography (Hexane–EtOAc, 7:3) to give pure **20** (1.05 g, 98%) as an oil. $[\alpha]_D^{27}$ −198 (*c* 0.48, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 3.56 (dt, *J*=6.4, 4.7 Hz, 1H, H_2), 3.68 (dd, *J*=9.6, 6.4 Hz, 1H, CH_2OBn), 3.80 (dd, *J*=9.7, 4.9 Hz, 1H, CH_2OBn), 3.84 (dd, *J*=8.3, 5.4 Hz, 1H, H_5), 3.94 (dd *J*=5.3, 3.0 Hz, 1H, H_4), 4.01 (dd, *J*=4.1, 3.2 Hz, 1H, H_3), 4.50 (d, *J*=11.9 Hz, 2H, CH_2Ph), 4.55 (d, *J*=6.4 Hz, 1H, CH_2Ph), 4.57 (d, *J*=6.4 Hz, 1H, CH_2Ph), 4.59 (d, *J*=11.4 Hz, 2H, CH_2Ph), 5.31 (ddd, J*J*=10.2, 1.5, 0.6 Hz, 1H, CH=CHH_{trans}), 5.36 (ddd, *J*=17.2, 1.5, 1.0 Hz, 1H, CH=CHH_{cis}), 6.07 (ddd, *J*=17.2, 10.2, 8.3 Hz, 1H, C*H*=CH_2), 7.28–7.39 (m, 15H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 67.9 (*C*H_2OBn), 69.6 (C_2), 71.7 (*C*H_2Ph), 71.9 (*C*H_2Ph), 72.9 (C_5), 73.4 (*C*H_2Ph), 83.8 (C_3), 86.1 (C_4), 119.3 (CH=*C*H_2), 127.6 (Ar), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 127.9 (Ar), 128.0 (Ar), 128.4 (Ar), 128.4 (Ar), 128.4 (Ar), 135.5 (*C*H=CH_2), 137.9 (Ar), 138.0 (Ar), 138.2 (Ar). Anal. Calcd for $C_{28}H_{31}NO_4$: C, 75.48; H, 7.01; N, 3.14. Found: C, 74.29; H, 7.36; N, 3.29.

*4.1.18. (2R,3R,4R,5R)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-vinylpyrrolidine (**39**).* Deoxygenation of **38** (0.550 g, 1.2 mmol), as described above for **20** to give **22**, afforded pure **39** (0.52 g, quant.) as an oil. $[\alpha]_D^{26}$ −101 (*c* 1.11, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 3.46 (c, *J*=5.7 Hz, 1H, H_2), 3.53 (dd, *J*=9.3, 6.5 Hz, 1H, CH_2OBn), 3.57 (dd, *J*=9.3, 5.5 Hz, 1H, CH_2OBn), 3.71 (dd, *J*=6.9, 5.7 Hz, 1H, H_5), 3.89 (dd, *J*=5.4, 3.9 Hz, 1H, H_4), 3.92 (t, *J*=4.2 Hz, 1H, H_3), 4.54–4.58 (m, 5H, CH_2Ph), 4.63 (d, *J*=11.7 Hz, 1H, CH_2Ph), 5.16 (ddd, *J*=10.2, 1.2, 1.0 Hz, 1H, CH=CHH_{trans}), 5.29 (ddd, *J*=17.1, 1.3, 1.1 Hz, 1H, CH=CHH_{cis}), 5.96 (ddd, *J*=17.2, 10.2, 7.2 Hz, 1H, C*H*=CH_2), 7.29–7.41 (m, 15H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 61.4 (C_2), 64.5 (C_5), 70.9 (*C*H_2OBn), 71.9 (*C*H_2Ph), 72.1 (*C*H_2Ph), 73.3 (*C*H_2Ph), 85.9 (C_3), 89.3 (C_4), 116.1 (CH=*C*H_2), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 127.8 (Ar), 128.4 (Ar), 128.4 (Ar), 138.1 (Ar), 138.2 (Ar), 138.2 (Ar), 138.8 (*C*H=CH_2). Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26. Found: C, 78.45; H, 7.16; N, 3.12.

*4.1.19. (2R,3R,4R,5R)-1-Allyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-vinylpyrrolidine (**40**).* Allylation of **39** (0.520 g, 1.2 mmol), as described above for **22** to give **31**, afforded pure **40** (0.445 g, 81%) as an oil. $[\alpha]_D^{26}$ −14 (*c* 0.31, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 3.16 (dd, *J*=14.3, 7.8 Hz, 1H, NCH_2CH=CH_2), 3.31 (ddd, *J*=7.0, 4.1, 2.9 Hz, 1H, H_5), 3.39 (tdd, *J*=14.3, 4.5, 1.9 Hz, 1H, NCH_2CH=CH_2), 3.54 (dd, *J*=9.4, 6.9 Hz, 1H, CH_2OBn), 3.59 (dd, *J*=9.4, 4.2 Hz, 1H, H_2), 3.63 (dd, *J*=9.5, 4.3 Hz, 1H, CH_2OBn), 3.82 (dd, *J*=4.2, 2.4 Hz, 1H, H_3), 4.00 (t, *J*=2.7 Hz, 1H, H_4), 4.48 (m, 6H, CH_2Ph), 5.08 (dtd, *J*=10.2, 1.8, 0.9 Hz, 1H, NCH$_2$CH=CH_2), 5.15 (dtd, *J*=17.3, 1.8 ,1.0 Hz, 1H, NCH$_2$CH=CH_2), 5.20–5.29 (m, 2H, CH=CH_2), 5.81–5.93 (m, 2H, NCH$_2$C*H*=CH_2, C*H*=CH_2), 7.25–7.38 (m, 15H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.8 (NCH$_2$CH=CH_2), 64.8 (C_5), 68.8 (*C*H_2OBn), 70.4 (C_2), 71.4 (*C*H_2Ph), 71.6 (*C*H_2Ph), 73.3 (*C*H_2Ph), 85.7 (C_4), 88.1 (C_3), 116.4 (NCH$_2$CH=*C*H_2), 118.5 (CH=*C*H_2), 127.5 (Ar), 127.5 (Ar), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 127.8 (Ar), 128.3 (Ar), 128.3 (Ar), 136.4 (*C*H=CH_2), 137.9 (NCH$_2$*C*H=CH_2), 138.3 (Ar), 138.4 (Ar), 138.4 (Ar). Anal. Calcd for $C_{31}H_{35}NO_3$: C, 79.28; H, 7.51; N, 2.98. Found: C, 79.19; H, 7.42; N, 2.68.

*4.1.20. (1R,2R,3R,7aR)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-2,3,5,7a-tetrahydro-1H-pyrrolizine (**41**).* Ring-closing metathesis of **40** (0.50 g, 1.05 mmol), as described above for **31** to give **32**, afforded pure **41** (0.405 g, 87%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 2.87 (ddd, *J*=8.1, 5.9, 3.9 Hz, 1H, H_3), 3.43–3.52 (m, 2H, H_{5a}, CH_2OBn), 3.55 (dd, *J*=9.7, 3.9 Hz, 1H, CH_2OBn), 3.75–3.83 (m, 2H, H_1, H_{5b}), 3.96 (dd, *J*=6.5, 8.1 Hz, 1H, H_2), 4.05–4.10 (m, 1H, H_{7a}), 4.23–4.57 (m, 5H, CH_2Ph), 4.65 (d, *J*=11.6 Hz, 1H, CH_2Ph), 5.63–5.69 (m, 2H, H_6, H_7), 7.14–7.30 (m, 15H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.2 (C_5), 68.8 (C_3), 71.9 (*C*H_2OBn), 72.2 (*C*H_2Ph), 72.7 (*C*H_2Ph), 73.4 (*C*H_2Ph), 74.9 (C_{7a}), 83.7 (C_2), 87.6 (C_1), 127.4 (Ar), 127.6 (Ar), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 127.9 (C_6 or C_7), 128.3 (Ar), 128.3 (Ar), 128.5 (Ar), 129.2 (C_6 or C_7), 138.1 (Ar), 138.5 (Ar), 138.5 (Ar). Anal. Calcd for $C_{29}H_{31}NO_3$: C, 78.88; H, 7.08; N, 3.17. Found: C, 78.73; H, 7.35; N, 3.68.

*4.1.21. Hyacinthacine A_2 (**9**).* The hydrogenation of **41** (0.060 g, 0.12 mmol), as described above for **20** to give **21**, afforded pure **9** (40 mg, 96%) after purification by ion-exchange chromatography (Dowex 50WX8-200; eluent: 3 M methanolic ammonia) as an oil. $[\alpha]_D^{26}$ +12 (*c* 0.4, H_2O) [lit.[30c] $[\alpha]^{20}$ +11.2 (*c* 0.52, H_2O)]. ^1H NMR (400 MHz, $CDCl_3$) δ 1.65–1.94 (m, 4H, H_6, H_7), 2.61–2.72 (m, 2H, H_3, H_{5a}), 2.84 (ddd, *J*=11.0, 6.9, 5.9 Hz, 1H, H_{5b}), 3.08 (dt, *J*=7.5, 4.5 Hz, 1H, H_{7a}), 3.59 (dd, *J*=11.6, 6.6 Hz, 1H, CH_2OH), 3.67 (t, *J*=7.9 Hz, 1H, H_1), 3.70–3.76 (m, 2H, H_2, CH_2OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5 (C_6), 32.8 (C_7), 57.8 (C_5), 66.2 (*C*H_2OH), 68.9 (C_{7a}), 72.1 (C_3), 80.3 (C_2), 83.3 (C_1). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.60; H, 8.95; N, 7.75.

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