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Total Synthesis of Uniflorine A, Casuarine, Australine, 3-*epi*-Australine, and 3,7-Di-*epi*-australine from a Common Precursor

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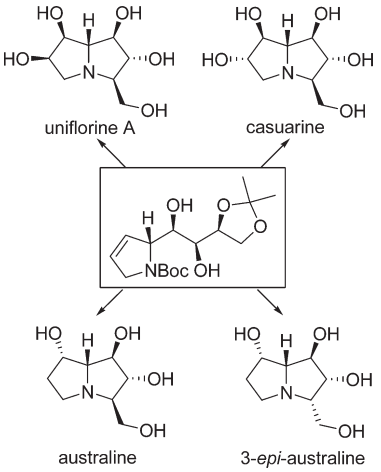

A flexible method for the diastereoselective total synthesis of the pyrrolizidine alkaloids uniflorine A, casuarine, australine, and 3-*epi*-australine and the unnatural epimer 3,7-di-*epi*-australine from a common chiral 2,5-dihydropyrrole precursor is described.

Introduction

Uniflorine A (**1**, 6-*epi*-casuarine),[1−3] casuarine (**2**),[4] australine (**3**),[5] and 3-*epi*-australine (**4**)[6] are members of the expanding group of polyhydroxylated 3-hydroxymethylpyrrolizidine natural products (Figure 1).[7] This group also includes alexine[8] (7a-*epi*-australine), several other *epi*-australines (1-*epi*-australine, 3-*epi*-australine, 2,3-di-*epi*-australine and 2,3,7-tri-*epi*-australine),[9] 1-*epi*-australine-2-*O*-β-glucoside, 3-*epi*-casuarine,[10] casuarine-6-*O*-α-glucoside,[11] and the more recently isolated hyacinthacine alkaloids of which 19 novel compounds have been identified.[12] This group, along with the polyhydroxylated pyrrolidine, piperidine, indolizidine, and

(1) Matsumura, T.; Kasai, M.; Hayashi, T.; Arisawa, M.; Momose, Y.; Arai, I.; Amagaya, S.; Komatsu, Y. *Pharm. Biol.* **2000**, *38*, 302–307.
(2) Davis, A. D.; Ritthiwigrom, T.; Pyne, S. G. *Tetrahedron* **2008**, *64*, 4868–4879.
(3) For a preliminary communication on the synthesis of (+)-uniflorine A, see: Ritthiwigrom, T.; Pyne, S. G. *Org. Lett.* **2008**, *10*, 2769–2771.
(4) Nash, R. J.; Thomas, P. I.; Waigh, R. D.; Fleet, G. W. J.; Wormald, M. R.; de Q. Lilley, P. M.; Watkin, D. J. *Tetrahedron Lett.* **1994**, *35*, 7849–7852.
(5) Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198–1206.
(6) Nash, R. J.; Fellows, L. E.; Plant, A. C.; Fleet, G. W. J.; Derome, A. E.; Baird, P. D.; Hegarty, M. P.; Scofield, A. M. *Tetrahedron* **1988**, *44*, 5959–5964.
(7) Asano, N. In *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*; Fattorusso, E., Taglialatela-Scafati, O., Eds.; Wiley-VCH Verlag: Weinheim, Germany, 2008; pp 111−138.
(8) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. *Tetrahedron Lett.* **1988**, *29*, 2487–2490.
(9) Kato, A.; Kano, E.; Adachi, I.; Molyneux, R. J.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Wormald, M. R.; Kizu, H.; Ikeda, K.; Asano, N. *Tetrahedron: Asymmetry* **2003**, *14*, 325–331.
(10) Van Ameijde, J.; Horne, G.; Wormald, M. R.; Dwek, R. A.; Nash, R. J.; Jones, P. W.; Evinson, E. L.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2006**, *17*, 2702–2712.
(11) Wormald, M. R.; Nash, R. J.; Watson, A. A.; Bhadoria, B. K.; Langford, R.; Sims, M.; Fleet, G. W. J. *Carbohydr. Lett.* **1996**, *2*, 169–174.
(12) Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res.* **1999**, *316*, 95–103. Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1–8. Yamashita, T.; Yasuda, K.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Asano, N. *J. Nat. Prod.* **2002**, *65*, 1875–1881. Kato, A.; Kato, N.; Adachi, I.; Hollinshead, J.; Fleet, G. W. J.; Kuriyama, C.; Ikeda, K.; Asano, N.; Nash, R. J. *J. Nat. Prod.* **2007**, *70*, 993–997. Asano, N.; Ikeda, K.; Kasahara, M.; Arai, Y.; Kizu, H. *J. Nat. Prod.* **2004**, *67*, 846–850.

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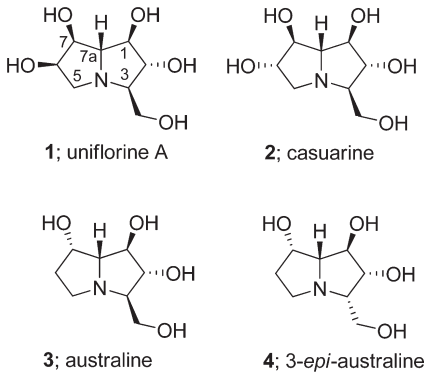
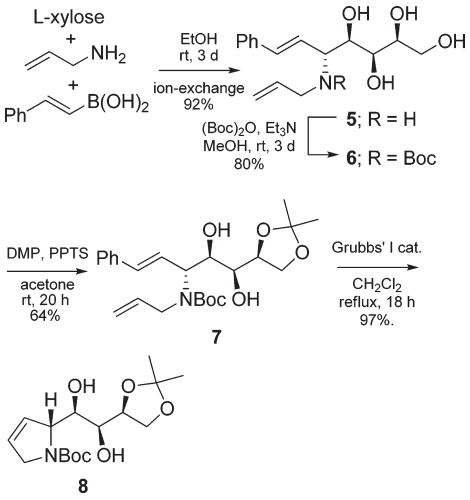


FIGURE 1. Structures of uniflorine A (**1**), casuarine (**2**), australine (**3**), and 3-*epi*-australine (**4**).

nortropane alkaloids, have glycosidase inhibitory activities and thus have potential utility as antiviral, anticancer, antidiabetic, and antiobesity drugs.[7] Three structurally related synthetic compounds have been marketed as antidiabetic drugs to treat type-2 diabetes based on their potent α-glucosidase inhibitory activities while others have been identified as candidates for therapeutics to treat type-1 Gaucher disease.[7] A comparative study of the inhibitory activities of alexine, australine, casuarine, and their aforementioned epimers and *O*-α- and *O*-*β*-glucoside derivatives against a panel of glycosidase enzymes revealed that casuarine and 1-*epi*-australine-2-*O*-*β*-glucoside were the most potent compounds.[9] These alkaloids showed low micromolar activities against several α-glucosidases while casuarine had an IC_{50} value of 0.7 μM against amylglucosidase from *Aspergillus niger*. In a separate study, uniflorine A (**1**) was shown to have moderate inhibitory activity against the α-glucosidases, rat intestinal maltase and sucrase, with IC_{50} values of 12 and 3.1 μM, respectively.[1] These potentially useful biological activities along with the stereochemical richness of these alkaloids (uniflorine A and casuarine have six contiguous stereogenic carbons) have made these compounds attractive and important synthetic targets.[13−15]

We recently reported the revised structures of uniflorines A and B from initially proposed pentahydroxyindolizidines[1] to 1,2,6,7-tetrahydroxy-3-hydroxymethylpyrrolizidines from a reinvestigation of their originally published NMR spectroscopic data.[2] Uniflorine B was the known alkaloid casuarine (**2**), while uniflorine A was tentatively assigned as 6-*epi*-casuarine (**1**); this was confirmed in a preliminary communication by the total synthesis of its enantiomer, (+)-uniflorine A (*ent*-**1**), from D-xylose.[3] In this paper, we report the full details of the synthesis of natural (−)-uniflorine A (**1**) from the chiral 2-substituted-2,5-dihydropyrrole **8** (Scheme 1), which is readily prepared in four synthetic steps from L-xylose. We also demonstrate here that compound **8** is a versatile precursor for the diastereoselective synthesis of the alkaloids casuarine (**2**), australine (**3**), and 3-*epi*-australine (**4**) and the unnatural epimer, 3,7-*epi*-australine **36**.

SCHEME 1



Results and Discussion

Total Synthesis of (−)-Uniflorine A (1). The synthesis of (−)-uniflorine A (**1**) is shown in Schemes 1 and 2. The known tetrol **5**[16] was prepared in one step from the boronic acid-Mannich reaction (Petasis reaction)[16,17] of L-xylose, allylamine, and (*E*)-styrene boronic acid and then converted to its *N*-Boc derivative **6**[16] (Scheme 1). The terminal diol functionality of **6** was selectively protected as the acetonide derivative **7** under standard conditions. The modest yield (64%) for this step was a result of the poor regioselectivity of this reaction. The other regioisomer was recycled back to **6** by hydrolysis with TFA (0.5 equiv) in MeOH/water (3:1, 10 mL/mmol) at rt for 36 h and the crude product was reprotected to give **7** in 49% overall yield. A ring-closing metathesis reaction of the diene **7** with use of Grubbs' first generation ruthenium catalyst provided the 2,5-dihydropyrrole **8** in 97% yield (Scheme 1). This intermediate can be readily prepared on a 4 g scale from L-xylose in 4 steps and in 46% overall yield.

The 2,5-dihydropyrrole **8** underwent an osmium(VIII)-catalyzed *syn*-dihydroxylation (DH) reaction to furnish the tetrol **9** as a single diastereomer in 72% yield (Scheme 2). The stereochemical outcome of this DH reaction was expected due to the stereodirecting effect of the C-2 pyrrolidine substituent in **8**.[2,16,18,19] The configuration of this diol was established from ROESY NMR studies on the final product **1**. The tetrol **9** was readily converted to its per-*O*-benzyl-protected derivative **10** in 96% yield, using standard reaction conditions.[16] Treatment of **10** under acidic conditions (HCl/MeOH)

(13) For previous syntheses of casuarine see: Denmark, S. E.; Hurd, A. R. *Org. Lett.* **1999**, *1*, 1311–1314. Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875–2886. Izquierdo, I.; Plaza, M. T.; Tamayo, J. A. *Tetrahedron* **2005**, *61*, 6527–6533. Cardona, F.; Parmeggiani1, C.; Faggi, E.; Bonaccini, C.; Gratteri, P.; Sim, L.; Gloster, T. M.; Roberts, S.; Davies, G. J.; Rose, D. R.; Goti, A. *Chem.—Eur. J.* **2009**, *15*, 1627–1636.

(14) For previous syntheses of australine see: (a) Pearson, W. H.; Hines, J. V. *Tetrahedron Lett.* **1991**, *32*, 5513–5516. (b) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359–7360. (c) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046–3056. (d) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785–5793. (e) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129–9142. (f) Romero, A.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 8264–8268. (g) Ribes, C.; Falomir, E.; Carda, M.; Marco, J. A. *Org. Lett.* **2007**, *9*, 77–80. (h) Trost, B. M.; Aponick, A.; Stanzl, B. N. *Chem.—Eur. J.* **2007**, *13*, 9547–9560. (i) For a synthesis of australine from castanospermine see: Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C. *Tetrahedron* **1994**, *50*, 2131–2160.

(15) For previous syntheses of 3-*epi*-australine see: refs 14c and 14f.

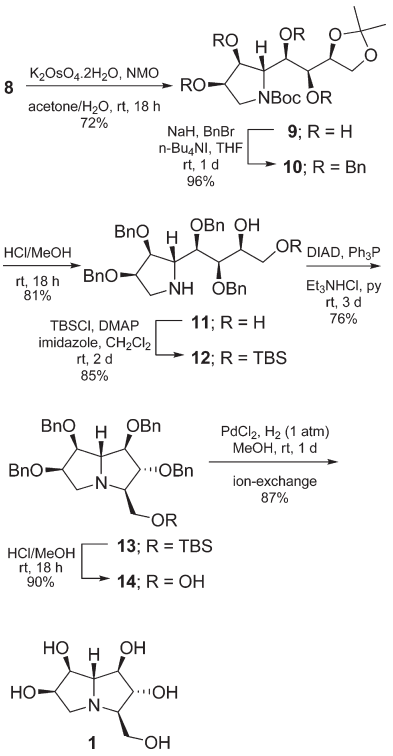
(16) Davis, A. S.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2004**, *69*, 3139–3143.

(17) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798–11799.

(18) Lindsay, K. B.; Tang, M.; Pyne, S. G. *Synlett* **2002**, 731–734.

(19) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774–7780.

SCHEME 2



resulted in *N*-Boc and acetonide hydrolysis and gave the amino diol **11** in 81% yield. Regioselective *O*-silylation of **11** with TBSCl/imidazole/DMAP gave the primary silyl ether **12** in 85% yield. In our earlier synthesis of (+)-uniflorine A, the compound *ent*-**12** underwent cyclization under Mitsunobu reaction conditions with pyridine[2,20,21] as the solvent to give a mixture (ca. 4:1) of the desired pyrrolizidine *ent*-**13** and an indolizidine product (structure not shown) in a combined yield of about 30% after purification of the crude reaction mixture by column chromatography. The undesired indolizidine product arose from first base catalyzed *O*-TBS migration to the secondary hydroxyl group in *ent*-**12** followed by Mitsunobu cyclization onto the primary carbon of the butyl side chain. We have now found, using **12**, that the yield of **13** could be dramatically improved to 76% with little or no formation of the undesired product by buffering the reaction mixture with $Et_3N \cdot HCl$.[22] Acid hydrolysis of **13** gave the primary alcohol **14** in 90% yield, which upon hydrogenolysis with $PdCl_2/H_2$[2,20,23] gave uniflorine A (**1**) ($[\alpha]_D^{22}$ −3.7 (*c* 1.2, H_2O) {lit.[1] $[\alpha]_D$ −4.4 (*c* 1.2, H_2O)}), in 87% yield after ion-exchange chromatography in a total of 11 synthetic steps and 13% overall yield from L-xylose.

The ^1H NMR spectral data (D_2O) of **1** and those of the natural product were essentially identical ($\Delta\delta_H$ = 0.00−0.02 ppm, see Table 1 of the Supporting Information).

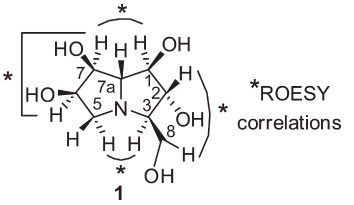


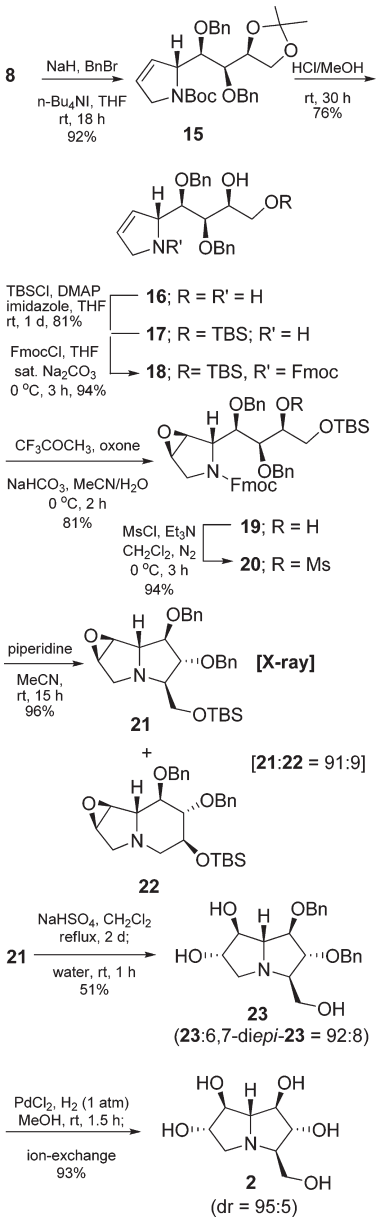
FIGURE 2. ROESY NMR correlations for uniflorine A (**1**).

The ^{13}C NMR signals of **1** (in D_2O with MeCN as an internal reference at δ 1.47), however, were all consistently 2.1−2.2 ppm upfield of those reported for the natural product (Supporting Information). We[2] noted earlier that while the ^1H NMR spectroscopic data reported for uniflorine B and casuarine were also essentially identical, the ^{13}C NMR shifts reported for casuarine were all consistently 3.0−3.2 ppm upfield of the corresponding ^{13}C NMR resonances reported for uniflorine B.[1] We suggested that alternative referencing between the two samples accounts for this consistent discrepancy.[2] The ^{13}C NMR spectrum of casuarine was referenced to acetone at δ 29.80 while that of uniflorines A and B was apparently referenced to TMS as an internal standard (a standard not known for its water (D_2O) solubility).[1] Thus the consistent differences in the ^{13}C NMR chemical shifts between synthetic **1** and those of uniflorine A can also be ascribed to the differences in referencing between the different samples.[24] The observed cross-peaks in the ROESY spectrum of **1** were fully consistent with the configurational assignment of **1** as shown in Figure 2. Thus our synthesis of **1** provides unequivocal proof that uniflorine A is 6-*epi*-casuarine. Uniflorine A and 3-*epi*-casuarine therefore represent the two known natural product epimers of casuarine.[4,10]

Total Synthesis of Casuarine (2). The synthesis of casuarine (**2**) from the chiral 2,5-dihydropyrrole **8** is shown in Scheme 3. This synthesis required a modified strategy to that for uniflorine A to secure the 6α,7β-configuration of the target molecule. To achieve this goal the synthetic plan involved a regioselective ring-opening reaction of the epoxide **21** with an oxygen nucleophile (Scheme 3). To obtain the key epoxide **21**, the two unprotected secondary hydroxyl groups in **8** were first protected as their *O*-benzyl ethers and the resulting dibenzyl ether **15** (92% yield) was treated under acidic conditions to effect hydrolysis of both the acetonide and *N*-Boc protecting groups and to provide amino diol **16** in 76% yield. Regioselective *O*-silylation of **16** at the primary hydroxyl group gave the TBS ether **17** (81% yield), which was efficiently *N*-protected as its Fmoc derivative **18** in 94% yield. Epoxidation of the alkene moiety of **18** with 1,1,1-trifluoroacetone and oxone[25] provided the epoxide **19** in 81% yield as a single diastereomer. Mesylation of the free secondary hydroxyl of **19** followed by treatment of the mesylate **20** (94% yield) with piperidine resulted in smooth *N*-Fmoc deprotection and then cyclization of the free cyclic secondary amine to give in 96% yield a 91:9 mixture of the desired pyrrolizidine **21** and the undesired indolizidine **22**, respectively. We assume that **22** arose from *O*-TBS migration under the basic conditions of the *O*-mesylation reaction; however, this was difficult to ascertain

(20) Tang, M.; Pyne, S. G. *J. Org. Chem.* **2003**, *68*, 7818–7824.
(21) Mulzer, J.; Dehmlow, H. *J. Org. Chem.* **1992**, *57*, 3194–3202. Casiraghi, G.; Ulgheri, F.; Spanu, P.; Rassu, G.; Pinna, L.; Gasparri, F. G.; Pelosi, F. M. G. *J. Chem. Soc., Perkin Trans. I* **1993**, 2991–2997. Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358–1364.
(22) Anderson, J. C.; Chapman, H. A. *Org. Biomol. Chem.* **2007**, *5*, 2413–2422.
(23) Zhao, H.; Hans, S.; Chemg, X.; Mootoo, D. R. *J. Org. Chem.* **2001**, *66*, 1761–1767. Zhou, W.-S.; Xie, W.-G.; Lu, Z.-H.; Pan, X.-F. *Tetrahedron Lett.* **1995**, *36*, 1291–1294.
(24) Unfortunately we have not been able to obtain a copy of the NMR spectra of uniflorine A for comparison purposes from the original authors.[1]
(25) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887–3889.

SCHEME 3



since NMR analysis of the mesylate intermediate **20** was made difficult because of *N*-Fmoc rotamers. A small amount of pure **21** could be obtained by further separation of the mixture by column chromatography. Compound **22** could not be obtained pure but was fully characterized as its derivative **26a** (Supporting Information). The structure of the epoxide **21** was confirmed by a single-crystal X-ray analysis (Supporting Information).[26]

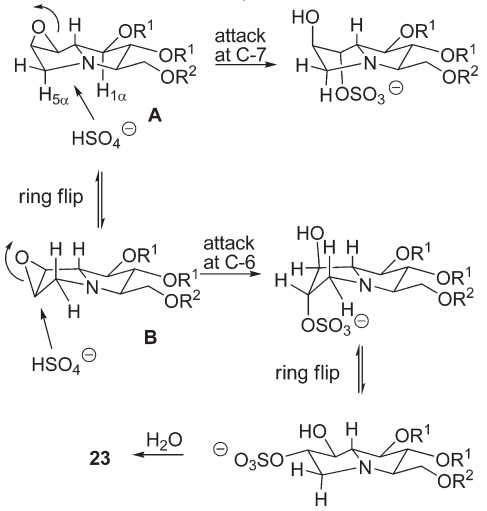
Several attempts in our laboratory to ring-open the epoxide group of compounds related to **21** using aqueous acid conditions (for example, H_2SO_4, water) led to complex mixtures and low yields of diol products. However, when **21** was treated under the conditions reported by Saracoglu,[27] using $NaHSO_4$ as both the acid catalyst and the nucleophilic species in dichloromethane at reflux, followed by the addition of water to hydrolyze the intermediate sulfate, then the desired diol **23** was obtained as an 86:14 crude mixture of regioisomers. Purification of this mixture by column chromatography gave a 92:8 mixture of the diastereomeric diols **23** and 6,7-di-*epi*-**23**, respectively, in 51% yield. The regiochemistry of this ring-opening reaction was consistent with that reported on related epoxy-pyrrolizidines[28] and was expected from stereoelectronic considerations as shown in Scheme 4. For *trans*-1,2-diaxial ring-opening of epoxide **21** by HSO_4^-, the two reactive conformations **A** and **B** are possible. Attack on conformation **A** at C-7 is inhibited by 1,3-diaxial interactions between the nucleophile (HSO_4^-) and the pseudoaxial protons H-1α and H-5α and thus addition to conformation **B** at C-6 predominates resulting in **23** as the major regioisomeric product. Hydrogenolysis of **23** over $PdCl_2/H_2$ gave casuarine (**2**) ($[\alpha]_D^{23}$ +18.1 (*c* 1.0, H_2O) {lit.[4] $[\alpha]_D^{24}$ +16.9 (*c* 0.8, H_2O)}) in 93% yield after purification by ion-exchange chromatography in a total of 13 synthetic steps and 8% overall yield from L-xylose. The diastereomeric purity of **2** was 95:5 from ^{1}H NMR spectroscopic analysis. The ^{1}H NMR spectroscopic data (D_2O) of **2** and that of the natural product[4] were essentially identical ($\Delta\delta_H$ = 0.00−0.01 ppm, see Table 2 of the Supporting Information). The ^{13}C NMR signals of **2** in D_2O, however, were all consistently 1.0−1.3 ppm downfield of those reported for the natural product (see Table 2 of the Supporting Information). Consistent differences in the ^{13}C NMR chemical shifts of the related alkaloid australine **3** have also been reported (see Table 3 of the Supporting Information and the Supporting Information in ref 14g).

Total Synthesis of Australine (3). The epoxide **21** also provided ready access to australine (**3**) as shown in Scheme 5. Reductive ring-opening of a 91:9 mixture of the epoxides **21** and **22** respectively with lithium aluminum hydride at 0 °C gave a mixture of the pyrrolizidines **24** and **25** (27% yield, **24**:**25** = 88:12), a mixture of the pyrrolizidines **26** and **27** (64% yield, **26**:**27** = 92:8), and the indolizidine corresponding to the ring-opening of **22** (2% yield, structure **26a** in the Supporting Information).

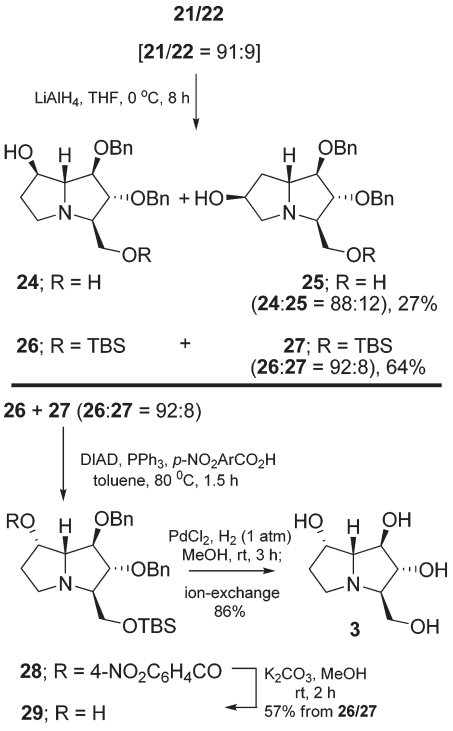
The regioisomeric mixture of **24** and **25** could be converted to a mixture of **26** and **27** by treatment with TBSCl in 61% yield. Fortunately, the regioisomers **26** and **27** could be readily separated as their C-7α and C-6α 4-nitrobenzoate esters, respectively, which were obtained from their Mitsunobu reactions with 4-nitrobenzoic acid.[29] In this way the 92:8 regioisomeric mixture of **26** and **27** was converted to a mixture of the C-7 and C-6 inverted 4-nitrobenzoate esters, respectively, from which the major regioisomer **28** was isolated pure after separation by column chromatography. Base hydrolysis of **28** gave the diastereomerically pure alcohol **29** in 57% overall yield for the two synthetic steps. Hydrogenolysis of **29** over $PdCl_2/H_2$, which also resulted in hydrolysis of the TBS ether due to in situ formation of HCl, gave diastereomerically pure australine **3** ($[\alpha]_D^{22}$ +9.4 (*c* 2.4, H_2O) {lit.[14d] $[\alpha]_D^{25}$ +8 (*c* 0.35, H_2O)}) in 86% yield after ion-exchange chromatography in a total of 16 synthetic steps and 5% overall yield from L-xylose. The ^{1}H NMR

(26) Crystal/refinement data have been deposited with the Cambridge Crystallographic Data Centre as CCDC 752850.
(27) Cavdar, H.; Saracoglu, N. *Tetrahedron* **2009**, *65*, 985–989.
(28) Ahn, J.-B.; Yun, C.-S.; Kim, H.; Ha, D.-C. *J. Org. Chem.* **2000**, *65*, 9249–9251. Papaioannou, N.; Blank, J. T.; Miller, S. J. *J. Org. Chem.* **2003**, *68*, 2728–2734.
(29) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017–3020.

SCHEME 4. Formation of 23 (R^1 = Bn, R^2 = TBS or OH)



SCHEME 5

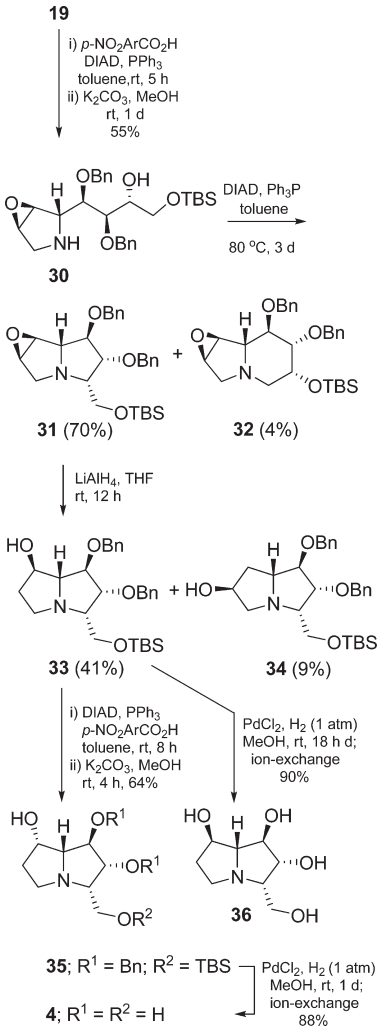


spectroscopic data (D_2O) of **3** and that of the natural product[30,31] were essentially identical ($\Delta\delta_H$ = 0.06−0.10 ppm, see Table 3 of the Supporting Information). The ^{13}C NMR signals of **3** in D_2O, however, were all consistently 2.0−2.3 ppm upfield of those reported for the natural product[9,30] (see Table 3 of the Supporting Information). Our ^{13}C NMR signals, however, matched more closely with those reported for synthetic australine by Pearson ($\Delta\delta_C$ = 0.1−0.4 ppm)[14d] and Denmark ($\Delta\delta_C$ = 0.8−1.3 ppm).[14c] Our ^{13}C NMR assignments, based on 2D NMR experiments (COSY, HSQC, and HMBC), also agreed

(30) Wormald, M. R.; Nash, R. J.; Hrnciar, P.; White, J. D.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2549–2558.

(31) For a comparison of the differences in the ^1H and ^{13}C NMR chemical shifts for natural and synthetic australine see the Supporting Information in ref 14g.

SCHEME 6



with those made by Denmark and differ from those reported on the natural product (see Table 3 of the Supporting Information).

Total Synthesis of 3-*epi*-Australine (4) and 3,7-Di-*epi*-australine (36). The syntheses of naturally occurring 3-*epi*-australine (**4**) and the unnatural analogue 3,7-d-i*epi*-australine (**36**) from the epoxide **19** are shown in Scheme 6. These syntheses required an inversion of configuration of the butyl side-chain secondary hydroxyl group in **19**. This was achieved by the Mitsunobu reaction of **19** with 4-nitrobenzoic acid.[29] Base treatment (K_2CO_3/MeOH, rt, 1 d) of the resulting secondary 4-nitrobenzoate ester resulted in benzoate hydrolysis and *N*-Fmoc cleavage giving the amino alcohol **30** in 55% overall yield for the two synthetic steps. This compound underwent cyclization under Mitsunobu reaction conditions with toluene as the solvent to give a separable mixture of the desired pyrrolizidine **31** in 70% yield and the indolizidine product **32** in 4% yield. Reductive ring-opening of the epoxide **31** with lithium aluminum hydride at rt gave a separable mixture of the regioisomeric pyrrolizidines **33** and **34**, in yields of 41% and 9%, respectively. In contrast to the reductive ring-opening reaction of **21**, the more hindered TBS group in these products remained intact. In the final steps of the synthesis, the configuration at C-7 in **33** was

inverted by the two-step sequence described above for the synthesis of australine. Thus treatment of **33** under the Mitsunobu reaction conditions with 4-nitrobenzoic acid followed by base treatment of the resulting 4-nitrobenzoate gave the C-7 inverted alcohol **35** in 64% overall yield. This compound underwent hydrogenolysis under acidic conditions with $PdCl_2/H_2$ to deliver diastereomerically pure 3-*epi*-australine (**4**) ($[\alpha]_D^{23}$ −10.5 (*c* 0.7, H_2O)) in 88% yield after ion-exchange chromatography in a total of 16 synthetic steps and 1.7% overall yield from L-xylose. Its hydrochloride salt, **4**·HCl, had $[\alpha]_D^{23}$ −37 (*c* 0.7, H_2O), which was of the same sign as the natural product but significantly larger in magnitude {lit.[6] for 3-*epi*-australine·HCl, $[\alpha]_D^{20}$ −3.5 (*c* 1.35, H_2O)}. The ^1H NMR spectroscopic data (D_2O) of **4** and those of the natural product[6] matched closely ($\Delta\delta_H$ = 0.13−0.19 ppm, see Table 4 of the Supporting Information). The ^{13}C NMR signals of **4** in D_2O, however, were all consistently 0.4−0.9 ppm downfield of those reported for the natural product (see Table 4 of the Supporting Information).

For the synthesis of 3,7-di-*epi*-australine (**36**), the direct hydrogenolysis of **33** under acidic conditions gave diastereomerically pure 3,7-di-*epi*-australine (**36**) ($[\alpha]_D^{24}$ −9.3 (*c* 1.1, H_2O)) in 90% yield after ion-exchange chromatography in a total of 14 synthetic steps and 2.6% overall yield from L-xylose. Its hydrochloride salt, **36**·HCl, had $[\alpha]_D^{21}$ −21 (*c* 0.63, H_2O), which was of opposite sign to that of its synthetic enantiomer, 1,2-di-*epi*-alexine·HCl {lit.[32] $[\alpha]_D^{20}$ +33 (*c* 0.1, H_2O)}. The ^1H NMR spectroscopic data (D_2O) of **36**·HCl and those reported in the literature for 1,2-di-*epi*-alexine·HCl were essentially identical ($\Delta\delta_H$ = 0.03−0.04 ppm, see Table 5 of the Supporting Information). The ^{13}C NMR signals of **36**·HCl in D_2O, however, were all consistently 1.7−2.1 ppm upfield of those reported for its enantiomer (see Table 5 of the Supporting Information).

Conclusions

In conclusion, we have developed a flexible method to prepare the pyrrolizidine alkaloids uniflorine A, casuarine, australine, and 3-*epi*-australine and the unnatural epimer 3,7-di-*epi*-australine from the common chiral 2,5-dihydropyrrole precursor **8**, which is available in gram quantities in four synthetic steps from L-xylose.[33] The synthesis of **1** confirmed our earlier configurational assignment to this natural product.[3] The synthesis of the latter four target compounds involved regioselective epoxide ring-opening reactions which proceeded with diastereoselectivities ranging from 91:9 (Scheme 5) to 82:18 (Scheme 6) in favor of the desired regioisomeric products. In contrast to our earlier work[3,20] efficient methods for the cyclization of 2-substituted pyrrolidines to pyrrolizidines have been developed by using the Mitsunobu reaction with either Et_3N·HCl as an additive (Scheme 2) or by using toluene as the solvent (Scheme 6). Alternatively, the cyclization of an Fmoc-protected pyrrolidine having a tethered *O*-mesylate to the corresponding pyrrolizidine worked efficiently upon exposure to base (Scheme 3). This methodology should prove versatile for the synthesis of other, more complex pyrrolizidine alkaloids and stereodefined epimeric derivatives for future structure−activity relationship studies.[34]

Experimental Section[35]

(1*R*,2*R*,3*R*,6*R*,7*S*,7a*R*)-1,2,6,7-Tetrabenzyloxy-3-((*tert*-butyldimethylsilyloxy)methyl)hexahydro-1*H*-pyrrolizine, 13. To a solution of **12** (0.792 g, 1.136 mmol) in pyridine (11 mL) was added triphenylphosphine (0.301 g, 1.148 mmol), triethylamine·hydrochloride (0.156 g, 1.136 mmol), and diisopropyl azodicarboxylate (0.56 mL, 2.841 mmol). The mixture was stirred at rt for 3 days. The volatiles were removed in vacuo then satd $CuSO_4$ solution (20 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined CH_2Cl_2 extracts were washed with satd $CuSO_4$ solution (20 mL) and water (20 mL), dried (Na_2CO_3), filtered, and then evaporated. Flash column chromatography (FCC) (100% petrol to 20:80 EtOAc/petrol) gave **13** as a yellow viscous oil (0.587 g, 76%). $[\alpha]_D^{20}$ −34 (*c* 0.4, $CHCl_3$). ν_{max}/cm^{-1} 3070, 3040, 2924, 2852, 1454, 1120, 1097. This compound had the same R_f, MS, and NMR spectroscopic data as reported for (+)-**13**.[3]

((1*R*,2*R*,3*R*,6*R*,7*S*,7a*R*)-1,2,6,7-Tetrabenzyloxyhexahydro-1*H*-pyrrolizin-3-yl)methanol, 14. To a solution of **13** (1.417 g, 2.087 mmol) in MeOH (50 mL) was added dropwise concd HCl solution (12.5 mL) and the mixture was stirred at rt for 18 h. The mixture was basified at 0 °C with aqueous NH_3 solution (28%). The mixture was extracted with EtOAc, dried (Na_2CO_3), evaporated, and purified by FCC (50:50 EtOAc/petrol) to give **14** (1.058 g, 90%) as a pale yellow viscous oil. R_f 0.11 (50:50 EtOAc/petrol). $[\alpha]_D^{20}$ −35 (*c* 1.3, $CHCl_3$) [lit.[3] for (+)-**14**; $[\alpha]_D^{23}$ +34 (*c* 1.3, $CHCl_3$)]. ν_{max}/cm^{-1} 3446, 3050, 2893, 2858, 1449, 1107, 1097. This compound had the same R_f, MS, and NMR spectroscopic data as reported for (+)-**14**.

(1*R*,2*R*,3*R*,6*R*,7*S*,7a*R*)-Hexahydro-3-(hydroxymethyl)-1*H*-pyrrolizine-1,2,6,7-tetraol (Uniflorine A, 1). To a solution of **14** (0.636 g, 1.126 mmol) in MeOH (12 mL) was added $PdCl_2$ (0.300 g, 1.690 mmol). The mixture was stirred at rt under an atmosphere of H_2 (balloon) for 1 day. The mixture was filtered through a Celite pad and the solids were washed with MeOH. The combined filtrates were evaporated in vacuo and the residue was dissolved in water (3 mL) and applied to a column of Amberlyst (OH^-) A-26 resin (7 cm). Elution with water followed by evaporation in vacuo gave uniflorine A (**1**) (0.201 g, 87%) as a white solid, mp 163.2−164.8 °C (lit.[1] mp 174−178 °C). $[\alpha]_D^{23}$ −3.7 (*c* 1.2, H_2O) [lit.[1] for (−)-uniflorine A: $[\alpha]_D$ −4.4 (*c* 1.2, H_2O)]. This compound had the same R_f, MS, IR, and NMR spectroscopic data as reported for (+)-**1**.[1]

(*R*)-(9*H*-Fluoren-9-yl)methyl 2-((1*R*,2*R*,3*S*)-1,2-Bis(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxybutyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate, 18. To a solution of **17** (6.05 g, 0.013 mol) in THF (125 mL) and satd Na_2CO_3 solution (60 mL) was added 9-fluorenylmethyl chloroformate (3.89 g, 15.03 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. Water (20 mL) was added and the solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 × 70 mL). The combined extracts were washed with brine, dried (Na_2CO_3), and then evaporated to leave a residue that was chromatographed on silica gel by FCC (10:90 to 30:70 EtOAc/petrol) to

(32) Chikkanna, D.; Singh, O. V.; Kong, S. B.; Han, H. *Tetrahedron Lett.* **2005**, *46*, 8865–8868.

(33) For a flexible synthetic strategy for preparing several hyacinthacine alkaloids and epimers and 2,3,7-tri-*epi*-australine see: Donohoe, T. J.; Thomas, R. E.; Cheeseman, M. D.; Rigby, C. L.; Bhalay, G.; Linney, I. D. *Org. Lett.* **2008**, *10*, 3615–3618.

(34) After submission of this manuscript an alternative synthesis of uniflorine A was published, see: Parmeggiani, C.; Martella, D.; Cardona, F.; Goti, A. *J. Nat. Prod.* **2009**, *72*, 2058–2060.

(35) For general experimental details see the Supporting Information. All ^1H (500 MHz) and ^{13}C NMR (125 MHz) spectra were run in $CDCl_3$ solution unless otherwise indicated. NMR assignments are based upon COSY and HSQC, and sometimes HMBC and NOESY, NMR experiments. All IR spectra were run on neat samples.

give **18** (8.31 g, 94%) as a colorless viscous oil. R_f 0.47 (20:80 EtOAc/petrol). $[\alpha]_D^{24}$ +125 (*c* 2.0, $CHCl_3$). ν_{max}/cm^{-1} 3061, 3028, 2945, 2924, 1700, 1413, 1107. δ_H (major rotamer) 7.78−7.59 (m, 4H, Ar), 7.42−7.16 (m, 14H, Ar), 5.97−5.95 (m, 1H, H-3), 5.92−5.89 (m, 1H, H-4), 4.90 (d, 2H, *J* = 11.0 Hz, 2 × C*H*HPh), 4.91−4.89 (m, 1H, H-2), 4.67−4.63 (m, 1H, C*H*HPh), 4.47 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.45 (d, 1H, *J* = 8.0 Hz, H-1′ or H-2′), 4.39 (dd, 2H, *J* = 7.0, 2.3 Hz, CH_2 (Fmoc)), 4.26−4.20 (m, 1H, C*H* (Fmoc)), 4.26−4.07 (m, 2H, 2 × H-5), 3.88 (dd, 1H, *J* = 13.5, 7.5 Hz, H-3′), 3.77 (d, 1H, *J* = 7.5 Hz, H-1′ or H-2′), 0.90 (s, 9H, *t*-Bu), 0.07 (s, 3H, CH_3), 0.06 (s, 3H, CH_3). δ_C (major rotamer) 154.3 (CO), 144.0 (C), 143.9 (C), 141.3 (C), 141.2 (C), 138.4 (C), 138.2 (C), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 126.9 (CH), 125.0 (CH), 119.9 (CH), 78.3 (C-1′), 77.8 (C-2′), 74.7 (CH_2), 74.3 (CH_2), 70.8 (C-3′), 66.9 (CH_2 (Fmoc)), 66.2 (C-2), 63.6 (C-4′), 53.4 (C-5), 47.2 (*C*H (Fmoc)), 25.8 (C(CH_3)$_3$), 18.1 (C), −5.4 (CH_3), −5.5 (CH_3). δ_C (minor rotamer) 154.3, 144.0, 143.8, 141.3, 141.2, 138.3, 138.2, 128.2, 127.8, 127.7, 127.6, 126.7, 126.5, 125.5, 124.7, 119.9, 80.2, 78.6, 74.9, 74.8, 71.0, 65.9, 65.5, 63.5, 54.2, 47.7, 25.7, 18.0, −5.4. HRMS (ESI+ve) calcd for $C_{43}H_{52}NO_6Si$ $(M + H)^+$ 706.3564, found 706.3537.

(1*S*,2*S*,5*R*)-(9*H*-Fluoren-9-yl)methyl 2-((1*R*,2*R*,3*S*)-1,2-Bis-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxybutyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate, 19. To a solution of the olefin **18** (2.37 g, 3.37 mmol) in MeCN (35 mL) was added Na_2EDTA (13.5 mL, 4×10^{-4} M) and $CF_3C(O)CH_3$ (6.8 mL, 7.60 mmol). The reaction was chilled to 0 °C before the portionwise addition of a mixture of $NaHCO_3$ (4.24 g, 50.47 mmol) and oxone (4.14 g, 6.73 mmol) over 15 min. After stirring for 2 h at 0 °C, the mixture was poured into water followed by removed of the volatiles under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 40 mL) and the combined extracts were washed with brine, dried (Na_2CO_3), and then evaporated to leave a residue that was chromatographed on silica gel by FCC (10:90 to 20:80 EtOAc/petrol) to give **19** (1.95 g, 81%) as a pale yellow oil. R_f 0.42 (20:80 EtOAc/petrol). $[\alpha]_D^{25}$ +99 (*c* 1.1, $CHCl_3$). ν_{max}/cm^{-1} 3062, 2945, 2924, 2858, 1700, 1454, 1110. δ_H (major rotamer) 7.76−7.54 (m, 4H, Ar), 7.41−7.16 (m, 14H, Ar), 4.86 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.67 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.64 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.36 (d, 1H, *J* = 11.0 Hz, C*H*HPh), 4.36−4.30 (m, 3H, CH_2 (Fmoc) and H-2), 4.26 (br s, 1H, H-1′), 4.19−4.15 (m, 1H, C*H* (Fmoc)), 3.91−3.86 (m, 1H, H-3′), 3.86−3.80 (m, 2H, H-2′ and H-3), 3.74−3.67 (m, 2H, H-4′ and H-5), 3.63 (d, 1H, *J* = 2.0 Hz, H-4), 3.59−3.53 (m, 1H, H-4′), 3.24−3.20 (m, 1H, H-5), 0.88 (s, 9H, *t*-Bu), 0.04 (s, 3H, CH_3), 0.03 (s, 3H, CH_3). δ_C (major rotamer) 154.9 (CO), 143.7 (C), 141.3 (C), 138.0 (C), 137.8 (C), 128.7 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.1 (CH), 127.0 (CH), 125.0 (CH), 124.9 (CH), 119.9 (CH), 79.1 (C-1′), 77.2 (C-2′), 74.9 (CH_2), 74.4 (CH_2), 70.6 (C-3′), 67.1 (CH_2 (Fmoc)), 63.5 (C-4′′), 60.1 (C-2), 56.3 (C-3), 55.6 (C-4), 47.8 (C-5), 47.1 (*C*H (Fmoc)), 25.8 (C(CH_3)$_3$), 18.1 (C), −5.4 (CH_3), −5.5 (CH_3). δ_C (minor rotamer) 155.0, 144.0, 141.2, 137.9, 137.7, 127.8, 127.7, 127.69, 127.64, 127.63, 127.5, 127.4, 125.0, 124.7, 120.0, 80.6, 78.0, 75.0, 74.8, 70.8, 66.2, 63.4, 59.8, 56.4, 54.9, 48.2, 47.6, 25.7, 18.07, −5.45, −5.48. HRMS (ESI+) calcd for $C_{43}H_{51}NO_7SiNa$ $(M + Na)^+$ 744.3333, found 744.3360.

(1*S*,2*S*,5*R*)-(9*H*-Fluoren-9-yl)methyl 2-((1*R*,2*S*,3*S*)-1,2-Bis-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3-(methylsulfonyloxy)-butyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate, 20. To a solution of **19** (0.414 g, 0.574 mmol) in anhydrous CH_2Cl_2 (6 mL) was added anhydrous Et_3N (0.24 mL, 1.723 mmol) and methanesulfonyl chloride (0.089 mL, 1.148 mmol). The reaction mixture was stirred at 0 °C under an atmosphere of N_2 for 3 h, followed by the evaporation of all volatiles in vacuo. Water (20 mL) was added and the residue was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with brine, dried (Na_2CO_3), and then evaporated to leave a residue that was chromatographed on silica gel by FCC (10:90 to 30:70 EtOAc/petrol) to give **20** (0.433 g, 94%) as a pale yellow oil. R_f 0.5 (30:70 EtOAc/petrol). $[\alpha]_D^{25}$ +64 (*c* 1.1, $CHCl_3$). ν_{max}/cm^{-1} 2950, 2924, 2888, 2852, 1695, 1360, 1328, 1175, 1110. δ_H (major rotamer) 7.70−7.66 (m, 2H, Ar), 7.45 (app t, 2H, *J* =6.8 Hz, Ar), 7.35−7.11 (m, 14H, Ar), 4.76−4.73 (m, 1H, H-3′), 4.64 (d, 1H, *J* = 10.5 Hz, C*H*HPh), 4.64−4.61 (m, 2H, 2 × C*H*HPh), 4.34 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.31−4.29 (m, 2H, CH_2 (Fmoc)), 4.16 (br s, 1H, H-2), 4.13 (app t, 1H, *J* = 7.0 Hz, C*H* (Fmoc)), 4.02−4.00 (m, 2H, H-1′ and H-2′), 3.97−3.94 (m, 2H, 2 × H-4′), 3.74−3.72 (m, 1H, H-3), 3.68 (d, 1H, *J* = 12.0 Hz, H-5), 3.58−3.56 (m, 1H, H-4), 3.20 (d, 1H, *J* = 13.0 Hz, H-5), 3.04 (s, 3H, CH_3 (Ms)), 0.82 (s, 9H, *t*-Bu), 0.04 (s, 6H, CH_3). δ_C (major rotamer) 154.9 (CO), 144.0 (C), 143.7 (C), 141.3 (C), 141.2 (C), 137.9 (C), 137.5 (C), 128.5 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.0 (CH), 125.0 (CH), 124.9 (CH), 120.0 (CH), 81.5 (C-3′), 79.1 (C-1′), 78.6 (C-2′), 75.7 (CH_2), 75.0 (CH_2), 67.1 (CH_2 (Fmoc)), 61.1 (C-4′), 60.6 (C-2), 56.0 (C-3), 55.6 (C-4), 47.8 (C-5), 47.2 (*C*H (Fmoc)), 38.4 (CH_3 (Ms)), 25.8 (C(CH_3)$_3$), 18.1 (C), −5.4 (CH_3), −5.5 (CH_3). HRMS (ESI+) calcd for $C_{44}H_{54}NO_9SSi$ $(M + H)^+$ 800.3289, found 800.3273.

(1a*R*,4*R*,5*R*,6*R*,6a*S*,6b*S*)-5,6-Bis(benzyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)hexahydro-1a*H*-oxireno[2,3-*a*]pyrrolizine, 21. To a solution of **20** (470.3 mg, 0.589 mmol) in MeCN (6 mL) was added piperidine (0.12 mL, 1.12 mmol). The reaction was stirred for 15 h at rt, the volatiles were removed under reduced pressure, and the residue was purified by FCC (10:90 to 30:70 EtOAc/petrol) to give a mixture of **21** and **22** (91:9) as a pale yellow oil (271.0 mg, 96%). A pure sample of **21** was obtained by further purification of this mixture by FCC to give **21** as yellow needles. R_f 0.27 (30:70 EtOAc/petrol). Mp 40.9−43.1 °C (yellow needles). $[\alpha]_D^{24}$ +12 (*c* 1.0, $CHCl_3$). ν_{max}/cm^{-1} 3032, 2945, 2924, 2858, 1255, 1109. δ_H 7.36−7.24 (m, 10H, Ar), 4.61 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.60 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.54 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.51 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.15 (app t, 1H, *J* = 3.8 Hz, H-2), 3.91 (dd, 1H, *J* = 7.3, 3.8 Hz, H-1), 3.69−3.68 (m, 1H, H-6), 3.66 (dd, 1H, *J* = 10.0, 6.0 Hz, H-8), 3.64−3.62 (m, 2H, H-7 and H-7a), 3.50 (app t, 1H, *J* = 10.0 Hz, H-8), 3.45 (d, 1H, *J* = 11.5 Hz, H-5), 3.08−3.04 (m, 1H, H-3), 2.98 (d, 1H, *J* = 12.0 Hz, H-5), 0.88 (s, 9H, *t*-Bu), 0.04 (s, 3H, CH_3), 0.03 (s, 3H, CH_3). δ_C 138.1 (C), 137.7 (C), 128.4 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.64 (CH), 127.6 (CH), 88.7 (C-2), 85.9 (C-1), 72.1 (CH_2), 71.8 (CH_2), 70.8 (C-3), 69.0 (C-7a), 64.4 (C-8), 58.5 (C-7), 57.0 (C-6), 55.6 (C-5), 25.9 (C(CH_3)$_3$), 18.2 (C), −5.4 (CH_3), −5.43 (CH_3). HRMS (CI+) calculated for $C_{28}H_{40}NO_4Si$ $(M + H)^+$ 482.2727, found 482.2729.

(1*S*,2*S*,5*R*,6*R*,7*R*,7a*R*)-6,7-Bis(benzyloxy)-5-(hydroxymethyl)-hexahydro-1*H*-pyrrolizine-1,2-diol, 23. To a solution of the epoxide **21** (37.4 mg, 0.078 mmol) in anhydrous CH_2Cl_2 (4 mL) was added $NaHSO_4$ (46.7 mg, 0.389 mmol). The reaction mixture was stirred and heated at reflux for 2 days under an atmosphere of N_2. The reaction was quenched by the addition of water (5 mL) and stirred for 1 h. The solvent was removed under reduced pressure and the residue was extracted with EtOAc (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and evaporated. NMR analysis of this crude reaction mixture showed an 86:14 mixture of regioisomers. The crude mixture was purified by FCC (100% EtOAc to 8.5:1:0.5 EtOAc/MeOH/NH_3) to give **23** (as a 92:8 mixture of diastereomers) as a pale yellow oil (15.3 mg, 51%). **23** (as a 92:8 mixture of diastereomers): R_f 0.34 (8.6:1.0:0.4 EtOAc/MeOH/NH_3). $[\alpha]_D^{23}$ +19 (*c* 1.1, $CHCl_3$). ν_{max}/cm^{-1} 3390, 3027, 2929, 2873, 1449, 1103, 1063. δ_H (CD_3OD) δ 7.36−7.24 (m, 10H, Ar), 4.68 (d, 2H, *J* = 12.0 Hz, 2 × C*H*HPh), 4.60 (d, 1H, *J* = 11.5 Hz, C*H*HPh), 4.54 (d, 1H, *J* = 12.0 Hz, C*H*HPh), 4.19 (app t, 1H, *J* = 5.3 Hz, H-1), 4.08 (dd, 1H, *J* = 10.5, 5.5 Hz, H-2), 4.04 (app t, 1H, *J* = 5.3 Hz, H-7), 3.98 (dd, 1H, *J* = 6.5, 5.5 Hz, H-6), 3.62 (dd, 1H, *J* = 11.0, 4.8 Hz, H-8), 3.51 (dd, 1H, *J* = 11.3, 5.8 Hz, H-8), 3.30 (m, 1H, H-5), 3.27 (app t, 1H, *J* = 5.0 Hz, H-7a), 3.18 (app dt, 1H,

J = 5.8, 5.0 Hz, H-3), 2.87 (dd, 1H, J = 11.3, 5.8 Hz, H-5). δ_C (CD_3OD) 139.6 (C), 139.5 (C), 129.4 (CH), 129.3 (CH), 128.95 (CH), 129.5 (CH), 128.7 (CH), 128.5 (CH), 87.2 (C-1), 85.6 (C-6), 81.4 (C-7), 79.2 (C-2), 75.2 (C-7a), 73.3 (CH_2), 72.9 (CH_2), 72.6 (C-3), 63.5 (C-8), 60.1 (C-5). HRMS (ESI+) calcd for $C_{22}H_{28}NO_5$ $(M + H)^+$ 386.1967, found 386.1967.

(1*R*,2*R*,3*R*,6*S*,7*S*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,6,7-tetraol (Casuarine, 2). To a solution of 92% diastereomerically pure **23** (21.0 mg, 0.055 mmol) in MeOH (2 mL) was added $PdCl_2$ (10.0 mg, 0.055 mmol). The mixture was stirred at rt under an atmosphere of H_2 (balloon) for 1.5 h. The mixture was filtered through a Celite pad and the solids were washed with MeOH. The combined filtrates were evaporated in vacuo and the residue was dissolved in water (1 mL) and applied to a column of Amberlyst (OH^-) A-26 resin (3 cm). Elution with water followed by evaporation in vacuo gave casuarine (**2**) (dr = 95:5) as a brown foamy solid (10.4 mg, 93%). $[\alpha]_D^{23}$ +18.1 (c 1.0, H_2O) [lit.[4] $[\alpha]_D^{24}$ +16.9 (c 0.8, H_2O)]. ν_{max}/cm^{-1} 3284, 2919, 1378, 1128, 1102, 1029. δ_H (D_2O) 4.22−4.18 (m, 2H, H-6 and H-7), 4.16 (t, 1H, $J_{1,2}$ = $J_{1,7a}$ = 8.7 Hz, H-1), 3.79 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 8.0 Hz, H-2), 3.77 (dd, 1H, $J_{8,8'}$ = 10.0, $J_{3,8}$ = 3.5 Hz, H-8), 3.61 (dd, 1H, $J_{8,8'}$ = 11.3, $J_{3,8'}$ = 6.8 Hz, H-8′), 3.27 (dd, 1H, $J_{5\alpha,5\beta}$ = 12.3 Hz, $J_{5\beta,6}$ = 4.3 Hz, H-5β), 3.06 (dd, 1H, $J_{1,7a}$ = 8.0 Hz, $J_{7,7a}$ = 3.0 Hz, H-7a), 3.04−3.00 (m, 1H, H-3), 2.90 (dd, 1H, $J_{5\alpha,5\beta}$ = 11.8 Hz, $J_{5\alpha,6}$ = 4.3 Hz, H-5α). δ_C (D_2O) 79.9 (C-7), 78.9 (C-1), 78.5 (C-6), 77.8 (C-2), 73.1 (C-7a), 71.0 (C-3), 63.5 (C-8), 59.0 (C-5). HRMS (ESI+) calcd for $C_8H_{16}NO_5$ $(M + H)^+$ 206.1028, found 206.0953.

(1*R*,2*R*,3*R*,7*S*,7a*R*)-3-Hydroxymethylhexahydro-*1H*-pyrrolizine-1,2,7-triol (Australine, 3). To a solution of **29** (74.6 mg, 0.155 mmol) in MeOH (3 mL) was added $PdCl_2$ (41.1 mg, 0.232 mmol). The mixture was stirred at rt under an atmosphere of H_2 (balloon) for 3 h, follow by the dropwise addition of concd HCl (10 drops) and stirring was continued at rt for 21 h. The mixture was filtered through a Celite pad and the solids were washed with MeOH. The combined filtrates were evaporated in vacuo and the residue was dissolved in water (2 mL) and applied to a column of Amberlyst (OH^-) A-26 resin (4 cm). Elution with water followed by evaporation in vacuo gave australine **3** as a yellow oil (25.1 mg, 86%). $[\alpha]_D^{22}$ +9.4 (c 2.4, H_2O) [lit.[14d] $[\alpha]_D^{25}$ +8 (c 0.35, H_2O)]. ν_{max}/cm^{-1} 3318, 2944, 2873, 2484, 1388, 1332, 1123, 1041. δ_H (D_2O) 4.37−4.35 (m, 1H, H-7), 4.22 (t, 1H, $J_{1,2}$ = $J_{1,7a}$ = 7.8 Hz, H-1), 3.89 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 3.79 (dd, 1H, $J_{8,8'}$ = 12.0 Hz, $J_{3,8}$ = 3.5 Hz, H-8), 3.61 (dd, 1H, $J_{8,8'}$ = 11.5 Hz, $J_{3,8'}$ = 7.0 Hz, H-8′), 3.17 (dd, 1H, $J_{1,7a}$ = 7.8 Hz, $J_{7,7a}$ = 4.8 Hz, H-7a), 3.15−3.12 (m, 1H, H-5), 2.74−2.69 (m, 2H, H-3 and H-5), 2.05−2.00 (m, 1H, H-6), 1.97−1.89 (m, 1H, H-6). δ_C NMR (D_2O) 79.5 (C-2), 73.7 (C-1), 71.3 (C-7a), 71.1 (C-3), 70.1 (C-7), 63.5 (C-8), 52.4 (C-5), 35.8 (C-6). **3**·HCl salt: δ_H (D_2O) 4.72−4.69 (m, 1H, H-7), 4.51 (app t, 1H, J = 7.5 Hz, H-1), 4.18 (dd, 1H, J = 10.0, 8.0 Hz, H-2), 4.02 (dd, 1H, J = 13.0, 2.5 Hz, H-8), 3.95−3.92 (m, 1H, H-7a), 3.92 (dd, 1H, J = 13.8, 4.3 Hz, H-8), 3.84 (app br t, 1H, J = 9.8 Hz, H-5), 3.45−3.38 (m, 2H, H-5 and H-3), 2.36−2.31 (m, 1H, H-6), 2.05−2.00 (m, 1H, H-6), 2.29−2.27 (m, 1H, H-6). δ_C (D_2O) 76.2 (C-2), 73.3 (C-7a), 72.1 (C-1), 71.4 (C-3), 68.7 (C-7), 56.5 (C-8), 52.9 (C-5), 35.0 (C-6). HRMS (EI) calcd for $C_8H_{15}NO_4$ (M^+) 189.1001, found 189.0994.

((2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-4-((1*S*,2*S*,5*R*)-6-oxa-3-azabicyclo[3.1.0]hexan-2-yl)-1-(*tert*-butyldimethylsilyloxy)butan-2-ol, 30. To a solution of **19** (0.095 g, 0.131 mmol) in toluene (2 mL) was added triphenylphosphine (0.086 g, 0.328 mmol) and *p*-nitrobenzoic acid (0.055 g, 0.328 mmol). The mixture was cooled to 0 °C and diisopropyl azodicarboxylate (64.5 μL, 0.28 mmol) was added. The mixture was stirred at rt for 5 h. The volatiles were removed in vacuo then satd $CuSO_4$ solution (20 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with water (5 mL), dried (Na_2CO_3), filtered and then evaporated to give **30a** as a pale yellow oil that was used in the next step without further purification. (1*S*,2*S*,5*R*)-(9*H*-Fluoren-9-yl)methyl 2-((1*R*,2*S*,3*R*)-1,2-bis(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3-(4-nitrobenzoyloxy)butyl)-6-oxa-3-azabicyclo-[3.1.0]hexane-3-carboxylate (**30a**): R_f 0.41 (30:70 EtOAc/petrol). $[\alpha]_D^{22}$ +35 (c 2.6, $CHCl_3$). ν_{max}/cm^{-1} 2950, 2940, 2857, 1720, 1701, 1529, 1271, 1101. δ_H 8.29−8.23 (m, 2H, Ar), 7.79−7.57 (m, 2H, Ar), 7.42−7.20 (m, 18H, Ar), 5.45 (dd, 1H, J = 9.0, 5.5 Hz, H-3′), 4.91 (d, 1H, J = 11.0 Hz, C*H*HPh), 4.84 (d, 1H, J = 11.5 Hz, C*H*HPh), 4.60 (d, 1H, J = 11.0 Hz, C*H*HPh), 4.45 (d, 2H, J = 6.5 Hz, CH_2 (Fmoc)), 4.37 (d, 1H, J = 11.5 Hz, C*H*HPh), 4.28−4.14 (m, 5H, H-1′ or H-2′, H-3 or H-4, 2 × H-4′ and C*H* (Fmoc)), 4.07 (d, 1H, J = 3.0 Hz, H-3 or H-4), 3.78 (br s, 1H, H-1′ or H-2′), 3.76 (d, 1H, J = 12.0, Hz, H-5), 3.68 (br d, 1H, J = 2.0 Hz, H-2), 3.25 (d, 1H, J = 11.5 Hz, H-5), 0.91 (s, 9H, *t*-Bu), 0.08 (s, 3H, CH_3), 0.07 (s, 3H, CH_3). δ_C 163.9 (CO), 154.8 (CO), 150.5 (C), 143.8 (C), 143.5 (C), 141.2 (C), 141.1 (C), 137.6 (C), 137.4 (C), 135.2 (C), 130.7 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.0 (CH), 126.9 (CH), 124.7 (CH), 123.4 (CH), 119.9 (CH), 80.7 (C-1′), 79.0 (C-2′), 75.8 (C-3′), 74.5 (CH_2), 74.8 (CH_2), 67.0 (CH_2 (Fmoc)), 61.8 (C-2), 60.5 (C-4′), 56.4 (C-3 or C-4), 55.7 (C-3 or C-4), 47.6 (C-5), 47.1 (*C*H (Fmoc)), 25.7 ($C(CH_3)_3$), 18.0 (C), −5.4 (CH_3), −5.5 (CH_3). HRMS (ESI+) calcd for $C_{50}H_{55}N_2O_{10}Si$ $(M + H)^+$ 871.3626, found 871.3611. To a solution of crude **30a** (0.131 mmol) in MeOH (2 mL) was added K_2CO_3 (0.015 g, 0.109 mmol). After stirring at rt for 1 day, the mixture was evaporated and dissolved in CH_2Cl_2. The solution was washed with water (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine, dried (Na_2CO_3), and evaporated. The residue was purified by FCC (50:50 EtOAc/petrol to 100% EtOAc) to give **30** as a yellow oil (36 mg, 55%). R_f 0.08 (30:70 EtOAc/petrol). $[\alpha]_D^{23}$ +53 (c 2.8, $CHCl_3$). ν_{max}/cm^{-1} 3362, 2930, 1449, 1250, 1100. δ_H (major rotamer) 7.33−7.25 (m, 10H, Ar), 4.86 (d, 1H, J = 11.0 Hz, C*H*HPh), 4.71 (d, 1H, J = 11.5 Hz, C*H*HPh), 4.62 (d, 1H, J = 11.0 Hz, C*H*HPh), 4.57 (d, 1H, J = 11.0 Hz, C*H*HPh), 3.81 (br s, 3H, H-2′, H-3′, and H-4′), 3.73 (dd, J = 9.5, 3.5 Hz, 1H, H-4′), 3.67 (d, 1H, J = 2.5 Hz, H-3 or H-4), 3.55 (dd, 1H, J = 9.5, 2.0 Hz, H-1′), 3.42 (d, 1H, J = 9.5 Hz, H-2), 3.39 (d, 1H, J = 2.5 Hz, H-3 or H-4), 3.02 (d, 1H, J = 13.5 Hz, H-5), 2.70 (d, 1H, J = 13.0 Hz, H-5), 0.91 (s, 9H, *t*-Bu), 0.08 (s, 6H, 2 × CH_3). δ_C (major rotamer) 138.3 (C), 138.2 (C), 128.4 (CH), 128.3 (CH), 128.22 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 79.4 (C-2′), 78.5 (C-1′), 74.52 (CH_2), 74.5 (CH_2), 71.7 (C-3′), 64.4 (C-4′), 59.9 (C-2), 58.0 (C-3 or C-4), 55.8 (C-3 or C-4), 46.9 (C-5), 25.9 ($C(CH_3)_3$), 18.3 (C), −5.28 (CH_3), −5.3 (CH_3). HRMS (ESI+) calcd for $C_{28}H_{42}NO_5Si$ $(M + H)^+$ 500.2832, found 500.2836.

(1a*R*,4*S*,5*R*,6*R*,6b*S*)-5,6-Bis(benzyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)hexahydro-1a*H*-oxireno[2,3-*a*]pyrrolizine, 31, and (1a*R*,5*R*,6*S*,7*R*,7a*S*,7b*S*)-6,7-Bis(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)octahydrooxireno[2,3-*a*]indolizine, 32. To a solution of **30** (0.500 g, 1.002 mmol) in toluene (10 mL) was added triphenylphosphine (0.657 g, 2.505 mmol). The mixture was cooled to 0 °C and diisopropyl azodicarboxylate (0.49 mL, 2.505 mmol) was added. The mixture was heated and stirred at 80 °C for 12 h. The volatiles were removed in vacuo then satd $CuSO_4$ solution (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were washed with water (20 mL), dried (Na_2CO_3), filtered, and then evaporated. The residue was purified by FCC (50:50 EtOAc/petrol to 100% EtOAc) to give **31** as a yellow oil (0.337 g, 70%) and **32** as a yellow oil (0.02 g, 4%). **31**: R_f 0.26 (70:30 EtOAc/petrol). $[\alpha]_D^{25}$ +43 (c 1.6, $CHCl_3$). ν_{max}/cm^{-1} 2952, 2930, 2850, 1447, 1250, 1095. δ_H 7.38−7.25 (m, 10H, Ar), 4.55 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.53 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.51 (d, 1H, J = 11.5 Hz, C*H*HPh), 4.48 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.09 (d, 1H, J = 4.0 Hz, H-2), 3.99 (app t, 1H, J = 9.3 Hz, H-8), 3.91 (dd, 1H, J = 10.0, 5.0 Hz, H-8), 3.80 (d, 1H, J = 4.5 Hz, H-1), 3.68−3.66 (m, 2H, H-6 or H-7 and H-7a), 3.60

(d, 1H, J = 2.0 Hz, H-6 or H-7), 3.39 (app dt, 1H, J = 8.5, 4.3 Hz, H-3), 3.19 (d, 1H, J = 10.5 Hz, H-5), 3.03 (d, 1H, J = 11.5 Hz, H-5), 0.09 (s, 9H, *t*-Bu), 0.06 (s, 6H, 2 × CH_3). δ_C 138.3 (C), 137.6 (C), 128.5 (CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 86.9 (C-2), 85.3 (C-1), 72.2 (CH_2), 71.9 (C-7a), 71.7 (CH_2), 65.7 (C-3), 58.5 (C-8), 57.6 (C-6 or C-7), 57.3 (C-6 or C-7), 48.1 (C-5), 25.9 (C(CH_3)$_3$), 18.2 (C), −5.4 (CH_3), −5.5 (CH_3). **32**: R_f 0.25 (70:30 EtOAc/petrol). δ_H 7.78−7.26 (m, 10H, Ar), 4.97 (d, 1H, J = 11.5 Hz, C*H*HPh), 4.73 (d, 1H, J = 11.5 Hz, C*H*HPh), 4.65 (d, 2H, J = 11.5 Hz, 2 × C*H*HPh), 4.15 (m, 1H, H-6), 3.63 (app t, 1H, J = 7.8 Hz, H-8), 3.55 (d, 1H, J = 3.0 Hz, H-1 or H-2), 3.52 (d, 1H, J = 10.5 Hz, H-3), 3.45 (d, 1H, J = 3.0 Hz, H-1 or H-2), 3.38 (dd, 1H, J = 10.0, 3.0 Hz, H-7), 3.20 (d, 1H, J = 10.5 Hz, H-3), 3.15 (d, 1H, J = 9.5 Hz, H-8a), 2.96 (dd, 1H, J = 15.0, 1.5 Hz, H-5), 2.86 (br d, 1H, J = 15.0 Hz, H-5), 0.91 (s, 9H, *t*-Bu), 0.10 (s, 3H, CH_3), 0.07 (s, 3H, CH_3). δ_C 138.5 (C), 138.3 (C), 133.2 (CH), 133.0 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 84.1 (C-7), 75.0 (CH_2), 72.7 (C-8), 72.2 (CH_2), 71.3 (C-6), 61.8 (C-8a), 57.8 (C-1 or C-2), 54.7 (C-1 or C-2), 52.0 (C-3), 50.3 (C-5), 28.6 (C(CH_3)$_3$), 18.2 (C), −4.6 (CH_3), −4.7 (CH_3). HRMS (ESI+) calcd for $C_{28}H_{40}NO_4Si$ $(M + H)^+$ 482.2727, found 482.2717.

(1*R*,5*S*,6*R*,7*R*,7a*R*)-6,7-Bis(benzyloxy)-5-((*tert*-butyldimethylsilyloxy)methyl)hexahydro-1*H*-pyrrolizin-1-ol, 33, and (2*S*,5*S*,6*R*,7*R*,7a*R*)-6,7-Bis(benzyloxy)-5-((*tert*-butyldimethylsilyloxy)methyl)-hexahydro-1*H*-pyrrolizin-2-ol, 34. To a solution of crude **31** (0.037 g, 0.098 mmol) in anhydrous THF (2 mL) was added dropwise a solution of lithium aluminum hydride (1 M in THF, 0.1 mL, 0. 1 mmol). The mixture was stirred at rt for 12 h. The solvent was evaporated and the mixture was chromatographed on silica gel by FCC (80:20 EtOAc/petrol to 10:90 MeOH/EtOAc) to give **33** as a pale yellow oil (15.3 mg, 41%) and **34** (3.3 mg, 9%) as a pale yellow oil. **33**: R_f 0.31 (5:95 MeOH/EtOAc). $[\alpha]_D^{22}$ −4 (*c* 1.4, $CHCl_3$). ν_{max}/cm^{-1} 3390, 2923, 2858, 1260, 1095. δ_H 7.34−7.25 (m, 10H, Ar), 4.59 (d, 1H, J = 11.5 Hz, C*H*HPh), 4.57 (d, 1H, J = 10.5 Hz, C*H*HPh), 4.52 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.48 (d, 1H, J = 11.5 Hz, C*H*HPh), 4.16 (app dt, 1H, J = 6.5, 5.5 Hz, H-7), 4.04 (dd, 1H, J = 4.5, 2.0 Hz, H-2), 3.95 (dd, 1H, J = 10.0, 7.3 Hz, H-8), 3.89−3.86 (m, 2H, H-1 and H-8), 3.35 (app dt, 1H, J = 6.5, 4.8 Hz, H-3), 3.30 (app t, 1H, J = 4.5 Hz, H-7a), 3.09 (ddd, 1H, J = 9.3, 7.0, 6.5 Hz, H-5), 2.91−2.87 (m, 1H, H-5), 2.19−2.13 (m, 1H, H-6), 1.84−1.78 (m, 1H, H-6), 0.88 (s, 9H, *t*-Bu), 0.40 (s, 6H, 2 × CH_3). δ_C 138.4 (C), 138.1 (C), 128.4 (CH), 128.3 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 85.9 (C-1), 85.6 (C-2), 77.7 (C-7a), 75.6 (C-7), 72.1 (CH_2), 71.4 (CH_2), 65.3 (C-3), 58.8 (C-8), 46.1 (C-5), 35.6 (C-6), 25.9 (C(CH_3)$_3$), 18.3 (C), −5.4 (CH_3), −5.5 (CH_3). HRMS (ESI+) calcd for $C_{28}H_{42}NO_4Si$ $(M + H)^+$ 484.2883, found 484.2868. **34**: R_f 0.1 (5:95 MeOH/EtOAc). $[\alpha]_D^{25}$ +10.3 (*c* 1.1, $CHCl_3$). ν_{max}/cm^{-1} 3236, 2952, 2923, 1250, 1096. δ_H 7.36−7.24 (m, 10H, Ar), 4.56 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.53 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.48 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.45 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.43 (br t, 1H, J = 4.0 Hz, H-6), 4.10 (dd, 1H, J = 4.5, 2.0 Hz, H-2), 3.91 (d, 2H, J = 6.0 Hz, 2 × H-8), 3.88−3.83 (m, 2H, H-1 and H-7a), 3.54 (app dt, 1H, J = 6.0, 5.0 Hz, H-3), 3.23 (dd, 1H, J = 10.0, 3.5 Hz, H-5), 2.96 (d, 1H, J = 10.0 Hz, H-5), 2.18 (dd, 1H, J = 13.0, 7.3 Hz, H-7), 1.86−1.81 (m, 1H, H-7), 0.89 (s, 9H, *t*-Bu), 0.05 (s, 6H, 2 × CH_3). δ_C 138.0 (C), 137.9 (C), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 86.8 (C-1), 85.7 (C-2), 73.7 (C-6), 72.4 (CH_2), 71.5 (CH_2), 68.7 (C-7a), 64.5 (C-3), 58.5 (C-8), 56.2 (C-5), 39.5 (C-7), 25.9 (C(CH_3)$_3$), 18.3 (C), −5.4 (CH_3), −5.5 (CH_3). HRMS (ESI+) calcd for $C_{28}H_{42}NO_4Si$ $(M + H)^+$ 484.2883, found 484.2863.

(1*S*,5*S*,6*R*,7*R*,7a*R*)-6,7-Bis(benzyloxy)-5-((*tert*-butyldimethylsilyloxy)methyl)hexahydro-1*H*-pyrrolizin-1-ol, 35. To a solution of **33** (0.040 g, 0.083 mmol) in toluene (2 mL) was added triphenylphosphine (0.055 g, 0.021 mmol) and *p*-nitrobenzoic acid (0.035 g, 0.021 mmol). The mixture was stirred at 0 °C and diisopropyl azodicarboxylate (41.1 μL, 0.021 mmol) was added. The mixture was stirred at rt for 8 h. The volatiles were removed in vacuo then satd $CuSO_4$ solution (20 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with water (5 mL), dried (Na_2CO_3), filtered, and then evaporated to give **35a** as a brown oil that was used in the next step without further purification. (1*S*,5*S*,6*R*,7*R*,7a*R*)-6,7-Bis(benzyloxy)-5-((*tert*-butyldimethylsilyloxy)methyl)hexahydro-1*H*-pyrrolizin-1-yl-4-nitrobenzoate (**35a**): R_f 0.39 (50:50 EtOAc/petrol). $[\alpha]_D^{26}$ +31 (*c* 3.0, $CHCl_3$). ν_{max}/cm^{-1} 2926, 2853, 1726, 1528, 1272, 1096. δ_H 7.95 (s, 4H, Ar), 7.37−7.12 (m, 10H, Ar), 5.63 (app t, 1H, J = 5.8 Hz, H-7), 4.56 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.51 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.49 (d, 1H, J = 13.0 Hz, C*H*HPh), 4.47 (d, 1H, J = 13.5 Hz, C*H*HPh), 4.13 (dd, 1H, J = 4.5, 1.5 Hz, H-2), 4.07 (dd, 1H, J = 10.3, 7.3 Hz, H-8), 4.05 (dd, 1H, J = 4.3, 2.3 Hz, H-1), 4.00 (dd, 1H, J = 10.3, 6.8 Hz, H-8), 3.68 (app t, 1H, J = 4.8 Hz, H-7a), 3.40 (app dt, 1H, J = 6.0, 5.0 Hz, H-3), 3.30−3.25 (m, 1H, H-5), 2.81 (app br t, 1H, J = 6.5 Hz, H-5), 2.30−2.23 (m, 1H, H-6), 2.05 (br d, 1H, J = 12.0 Hz, H-6), 0.90 (s, 9H, *t*-Bu), 0.08 (s, 3H, CH_3), 0.07 (s, 3H, CH_3). δ_C 163.8 (CO), 150.4 (C), 138.3 (C), 137.7 (C), 135.2 (C),130.6 (CH), 128.4 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 126.9 (CH), 123.3 (CH), 86.9 (C-2), 81.7 (C-1), 74.3 (C-7), 73.7 (C-7a), 72.3 (CH_2), 71.7 (CH_2), 65.4 (C-3), 59.9 (C-8), 46.2 (C-5), 34.7 (C-6), 25.9 (C(CH_3)$_3$), 18.3 (C), −5.3 (CH_3), −5.4 (CH_3). HRMS (ESI+) calcd for $C_{35}H_{45}N_2O_7Si$ $(M + H)^+$ 633.2996, found 633.2986. To a solution of crude **35a** (0.083 mmol) in MeOH (2 mL) was added K_2CO_3 (0.023 g, 0.1669 mmol). After stirring at rt for 4 h, the mixture was evaporated and dissolved in CH_2Cl_2 then washed with water. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with brine, dried (Na_2CO_3), and evaporated. The residue was purified by FCC (80:20 EtOAc/petrol to 10:90 MeOH/EtOAc) to give **35** as a pale yellow oil (26 mg, 64%). R_f 0.19 (10:90 MeOH/EtOAc). $[\alpha]_D^{24}$ −5.3 (*c* 1.2, $CHCl_3$). ν_{max}/cm^{-1} 3418, 2930, 2850, 1673, 1250, 1089. δ_H 7.36−7.26 (m, 10H, Ar), 4.68 (d, 1H, J = 11.5 Hz, C*H*HPh), 4.62 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.57 (d, 1H, J = 11.5 Hz, C*H*HPh), 4.56 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.25 (app t, 1H, J = 5.0 Hz, H-1), 4.23 (app t, 1H, J = 5.0 Hz, H-2), 4.12 (app br t, 1H, J = 2.5 Hz, H-7), 3.97 (dd, 1H, J = 10.8, 5.3 Hz, H-8), 3.82 (dd, 1H, J = 10.8, 5.3 Hz, H-8), 3.49 (app t, 1H, J = 4.3 Hz, H-7a), 3.31 (app dt, 1H, J = 4.8, 4.0 Hz, H-3), 3.04−2.99 (m, 1H, H-5), 2.81 (br t, 1H, J = 7.8 Hz, H-5), 1.96−1.94 (m, 2H, 2 × H-6), 0.88 (s, 9H, *t*-Bu), 0.05 (s, 3H, CH_3), 0.04 (s, 3H, CH_3). δ_C 138.4 (C), 137.9 (C), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 85.5 (C-2), 79.5 (C-1), 73.2 (C-7a), 73.0 (CH_2), 71.9 (CH_2), 71.2 (C-7), 62.5 (C-3), 59.3 (C-8), 43.9 (C-5), 36.9 (C-6), 26.0 (C(CH_3)$_3$), 18.6 (C), −5.3 (CH_3), −5.8 (CH_3). HRMS (ESI+) calcd for $C_{28}H_{42}NO_4Si$ $(M + H)^+$ 484.2883, found 484.2882.

(1*R*,2*R*,3*S*,7*S*,7a*R*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,7-triol (3-*epi*-Australine, 4). To a solution of **35** (21 mg, 0.045 mmol) in MeOH (1 mL) was added $PdCl_2$ (12 mg, 0.065 mmol). The mixture was stirred at rt under an atmosphere of H_2 (balloon) for 3 h, follow by the dropwise addition of concd HCl (5 drops). Stirring at rt was continued for 21 h. The mixture was filtered through a Celite pad and the solids were washed with MeOH. The combined filtrates were evaporated in vacuo and the residue was dissolved in water (1 mL) and applied to a column of Amberlyst (OH^-) A-26 resin (3 cm). Elution with water followed by evaporation in vacuo gave 3-*epi*-australine (**4**) as a brown viscous oil (7.2 mg, 88%). $[\alpha]_D^{23}$ −10.5 (*c* 0.7, H_2O). ν_{max}/cm^{-1} 3279, 2924, 2888, 1429, 1357, 1058. δ_H (D_2O) 4.41 (br t, 1H, $J_{6,7}$ = $J_{7,7a}$ = 4.0 Hz, H-7), 4.30 (t, 1H, $J_{1,2}$ = $J_{1,7a}$ = 3.3 Hz, H-1), 4.15 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 4.0 Hz, H-2), 4.01 (dd, 1H, $J_{8,8'}$ = 11.8 Hz, $J_{3,8}$ = 5.8 Hz, H-8), 3.92 (dd, 1H, $J_{8,8'}$ = 11.8 Hz, $J_{3,8'}$ = 6.3 Hz, H-8′), 3.38 (t, 1H, $J_{1,7a}$ = $J_{7,7a}$ = 4.3 Hz, H-7a), 3.30 (dt, 1H, $J_{3,8'}$ = 5.3 Hz, $J_{2,3}$ = $J_{3,8}$ = 4.5 Hz, H-3), 3.15−3.10 (m, 1H, H-5α), 2.88 (t, 1H, $J_{5,5}$ = $J_{5,6}$ = 8.0 Hz, H-5*β*), 2.00−1.87 (m, 2H, 2 × H-6). ^{13}C NMR (D_2O) δ 79.3 (C-2),

75.2 (C-7a), 74.7 (C-1), 70.4 (C-7), 63.9 (C-3), 57.8 (C-8), 45.3 (C-5), 35.6 (C-6). HRMS (ESI+) calcd for $C_8H_{16}NO_4$ $(M + H)^+$ 190.1079, found 190.1086. **4**·HCl salt: $[\alpha]_D^{23}$ −37 (*c* 0.7, H_2O). [lit.[6] $[\alpha]_D^{20}$ −3.5 (*c* 1.35, H_2O)]. δ_H (D_2O) 4.77−4.73 (m, 1H, H-7), 4.65 (s, 1H, H-1), 4.34 (d, 1H, J = 3.5 Hz, H-2), 4.29 (d, 1H, J = 5.5 Hz, H-7a), 4.16 (dd, 1H, J = 12.0, 4.5 Hz, H-8), 4.13−4.04 (m, 2H, H-8 and H-3), 3.74 (dd, 1H, J = 11.3, 5.3 Hz, H-5), 3.71−3.65 (m, 1H, H-5), 2.28 (dd, 1H, J = 14.0, 5.0 Hz, H-6), 2.21−2.13 (m, 1H, H-6). δ_C (D_2O) 79.3 (C-7a), 77.4 (C-2), 74.2 (C-1), 69.3 (C-7), 67.1 (C-3), 56.1 (C-8), 48.4 (C-5), 35.0 (C-6).

(1*R*,2*R*,3*S*,7*R*,7a*R*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,7-triol (3,7-Di-*epi*-australine, 36). To a solution of **33** (20 mg, 0.041 mmol) in MeOH (1 mL) was added $PdCl_2$ (11 mg, 0.062 mmol). The mixture was stirred at rt under an atmosphere of H_2 (balloon) for 3 h, followed by the dropwise addition of concd HCl (5 drops) at rt for 15 h. The mixture was filtered through a Celite pad and the solids were washed with MeOH. The combined filtrates were evaporated in vacuo and the residue was dissolved in water (1 mL) and applied to a column of Amberlyst (OH^-) A-26 resin (3 cm). Elution with water followed by evaporation in vacuo gave 3,7-di-*epi*-australine (**36**) as a white solid (7.0 mg, 90%). $[\alpha]_D^{24}$ −9.3 (*c* 1.1, H_2O). ν_{max}/cm^{-1} 3370, 3309, 2509, 1454, 1202, 1060. δ_H (D_2O) 4.30 (dt, 1H, $J_{6,7}$ = $J_{7,7a}$ = 6.5 Hz, $J_{6,7}$ = 6.0 Hz, H-7), 4.16 (br d, 1H, $J_{2,3}$ = 3.5 Hz, H-2), 4.13 (s, 1H, H-1), 3.97 (dd, 1H, $J_{8,8'}$ = 11.8 Hz, $J_{3,8}$ = 7.0 Hz, H-8), 3.92 (dd, 1H, $J_{8,8'}$ = 12.0 Hz, $J_{3,8'}$ = 7.0 Hz, H-8′), 3.28 (ddd, 1H, $J_{2,3}$ = 9.0 Hz, $J_{3,8}$ = 7.0 Hz, $J_{2,3}$ = 4.0 Hz, H-3), 3.11 (ddd, 1H, $J_{5,5}$ = 10.0 Hz, $J_{5,6}$ = 10.0 Hz, $J_{5,6}$ = 6.0 Hz, H-5α), 3.06 (dd, 1H, $J_{7,7a}$ = 2.0 Hz, $J_{1,7a}$ = 5.5 Hz, H-7a), 2.98 (t, 1H, $J_{5,5}$ = $J_{5,6}$ = 8.5 Hz, H-5*β*), 2.23−2.18 (m, 1H, H-6α), 1.80−1.72 (m, 1H, H-6*β*). δ_H (D_2O) 80.5 (C-1), 79.8 (C-2), 78.2 (C-7a), 75.1 (C-7), 64.9 (C-3), 57.6 (C-8), 46.4 (C-5), 34.5 (C-6). **36**·HCl salt: $[\alpha]_D^{21}$ −21 (*c* 0.63, H_2O), HCl salt [lit.[31] for *ent*-**36**·HCl; $[\alpha]_D^{20}$ +33 (*c* 0.1, H_2O)]. δ_H (D_2O) 4.63 (dt, 1H, $J_{6,7}$ = 8.0 Hz, $J_{6,7}$ = $J_{7,7a}$ = 6.0 Hz, H-7), 4.41 (br s, 1H, H-1), 4.35 (d, 1H, $J_{1,2}$ = 2.5 Hz H-2), 4.13 (dd, 1H, $J_{8,8'}$ = 12.5 Hz, $J_{3,8}$ = 5.0 Hz, H-8), 4.10 (d, 1H, $J_{8,8'}$ = 9.0 Hz, H-8), 4.06−4.02 (m, 1H, H-3), 3.84 (d, 1H, $J_{7,7a}$ = 6.5 Hz, H-7a), 3.75 (dd, 1H, $J_{5,5}$ = 11.3 Hz, $J_{5,6}$ = 6.3 Hz, H-5), 3.73 (dd, 1H, $J_{5,5}$ = 10.8 Hz, $J_{5,6}$ = 6.3 Hz, H-5), 2.54−2.48 (m, 1H, H-6), 2.07−1.99 (m, 1H, H-6). δ_C (D_2O) 80.1 (C-7a), 77.6 (C-1), 77.1 (C-2), 73.1 (C-7), 67.7 (C-3), 55.8 (C-8), 48.6 (C-5), 33.1 (C-6). HRMS (ESI+) calcd for $C_8H_{16}NO_4$ $(M + H)^+$ 190.1079, found 190.1074.

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Supporting Information Available: General experimental procedures and full experimental procedures and characterization data as well as copies of the ^1H NMR and ^{13}C NMR spectra of all new compounds and crystal/refinement data and an ORTEP plot of compound **21** (CCDC 752850). This material is available free of charge via the Internet at http://pubs.acs.org.