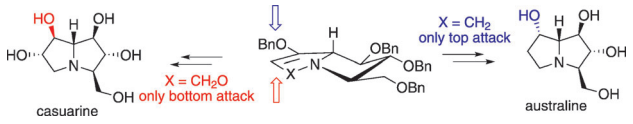

Ring size matters! Complete control of the configuration at C-7 of polyhydroxy pyrrolizidine alkaloids has been achieved by carrying out addition reactions to an endocyclic double bond in a six-membered 1,2-oxazine adduct, or after ring contraction to a five-membered pyrrolidine (see scheme). Versatility and reliability of the strategy allowed high yield syntheses of both casuarine and australine.

Alkaloids

C. Parmeggiani, F. Cardona, L. Giusti, H.-U. Reissig, A. Goti** .... ▮▮▮▮–▮▮▮▮

Stereocomplementary Routes to Hydroxylated Nitrogen Heterocycles: Total Syntheses of Casuarine, Australine, and 7-*epi*-Australine

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Stereocomplementary Routes to Hydroxylated Nitrogen Heterocycles: Total Syntheses of Casuarine, Australine, and 7-*epi*-Australine

Camilla Parmeggiani,[a, b, c] Francesca Cardona,[a] Leonardo Giusti,[a, b] Hans-Ulrich Reissig,*[b] and Andrea Goti*[a]

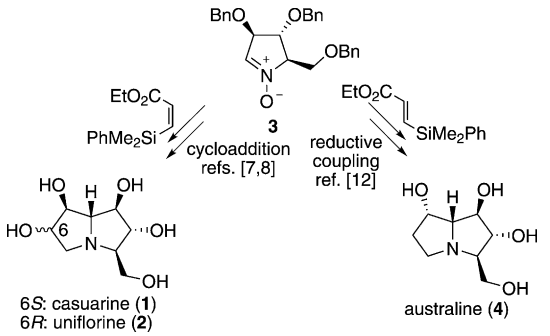
Abstract: Addition of lithiated 1-benzyloxyallene to a D-arabinose-derived cyclic nitrone occurred with perfect diastereoselectivity furnishing a bicyclic 1,2-oxazine derivative, which is an excellent precursor for pyrrolizidine alkaloids hydroxylated at C-7 with optional configuration at this stereogenic center. Depending on the stage of the N–O bond cleavage and ring re-closure, 7-hydroxypyrrolizidines with 7*R* or 7*S* configuration were obtained, as a result of completely selective addition reactions occurring complementarily at the bottom or top face of the endocyclic C–C double bond in six- and five-membered B rings, respectively. Applicability of these stereodivergent routes to obtain polyhydroxy pyrrolizidine alkaloids is demonstrated by the efficient syntheses of casuarine and australine as examples of the two classes of diversely configured 7-hydroxypyrrolizidine alkaloids. An alternative synthesis of australine and two strategies for the preparation of 7-*epi*-australine are also reported, which demonstrate that the stereoselectivity of hydride reduction of an exocyclic C–O double bond is independent of the ring size, occurring preferentially from the top face either in a six- or five-membered ring.

Keywords: alkaloids · allenes · nitrones · nucleophilic attack · stereoselectivity

Introduction

Iminosugars (polyhydroxypiperidines and pyrrolidines) and related bicyclic compounds belonging to the privileged classes of indolizidines, pyrrolizidines, and nortropanes have recently emerged as potential therapeutic agents towards a large variety of diseases (diabetes, cancer, viral and bacterial infections, lysosomal storage diseases) in view of their well-established bioactivity as inhibitors of glycosyl hydrolases.[1]

This interesting behavior has stimulated intense synthetic activity in the last decades to access natural products belonging to these classes and their unnatural congeners for structure/activity relationship studies.[2] In this context, we have addressed the synthesis of natural products and analogues, mainly by the use of chiral cyclic nitrones as intermediates for 1,3-dipolar cycloadditions[2d] and nucleophilic additions of organometallic reagents.[3,4,5,6] In the field of pyrrolizidine alkaloids, we have recently succeeded in synthesizing casuarine (**1**) and its 6-*O*-glucosyl conjugate,[7] and uniflorine (**2**),[8] as well as a number of unnatural relatives,[9] by cycloaddition of a suitably designed dipolarophile to D-arabinose-derived nitrone **3** (Scheme 1) and related carbohydrate-derived nitrones.[7,10,11] While this manuscript was in preparation, Py and co-workers reported a synthesis of australine (7a-*epi*-alexine) (**4**)[12] based on their SmI_2-mediated reductive coupling of nitrones with acrylates[13] by starting with the same precursor **3** (Scheme 1). One of the most challenging points of both of these synthetic strategies rested in placing the hydroxyl substituent at C-7 of the pyr-



Scheme 1. Synthetic strategies to polyhydroxylated pyrrolizidine alkaloids from carbohydrate-derived cyclic nitrone **3**.

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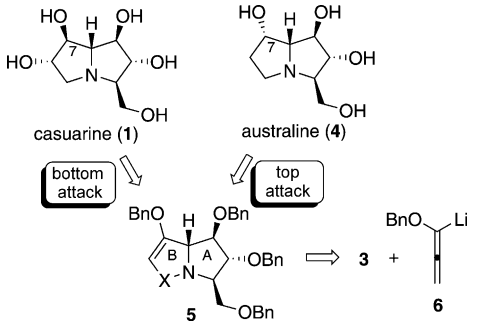
rolizidine ring, which was achieved by silicon to oxygen replacement with a Tamao–Fleming reaction.[7,12] Interestingly, diastereomeric β-*C*-silyl acrylates, *Z* and *E*, respectively, were necessary to achieve the opposite configuration required at C-7 of the target alkaloids **1** and **4** (Scheme 1).

Results and Discussion

Placing a hydroxyl group at C-7 of a pyrrolizidine is not a trivial task unless it is already part of a starting material from the chiral pool as a carbohydrate. As mentioned before, ours and Py's group have both managed to accomplish this aim by a Tamao–Fleming reaction.[7,12] Other researchers have devised different routes; for example, Fleet, Yu and co-workers achieved this purpose by introducing a dithiane heterocycle that was then deprotected to a carbonyl and reduced;[4g] Pyne and co-workers introduced the oxygen atom at C-7 by oxidation of an endocyclic double bond through dihydroxylation or epoxidation followed by hydrolysis or reduction;[14] Huang and co-workers also employed a dihydroxylation of a double bond installed in turn by a selenylation/elimination procedure.[15] However, all these procedures suffer from some drawbacks, requiring several distinct synthetic steps and/or the use of expensive or unpleasant stoichiometric reagents. In addition to the length of these approaches, the key transformations do not always give good yields of products or display complete regio- and/or stereoselectivity. Moreover, they did not allow for control of the stereoselectivity for installing each one of the two possible configurations at the newly created C-7 stereocenter, a highly desirable target. We envisaged that nucleophilic addition of an appropriate lithiated 1-alkoxyallene derivative **6** to the same nitrone **3**, according to a well-established methodology developed by one of the groups,[16] would allow a more direct access to 7-hydroxypyrrolizidines (Scheme 2). Even more importantly, the intermediate adduct **5** might

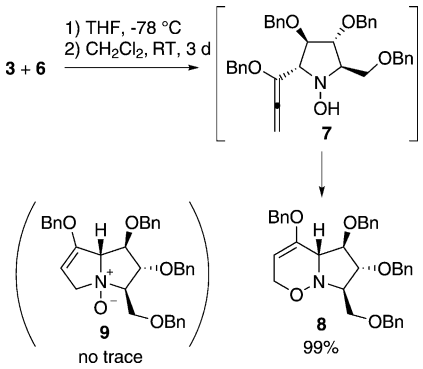


Scheme 2. Retrosynthetic analysis for casuarine (**1**) and australine (**4**).

give the opportunity to access both classes of pyrrolizidine derivatives belonging to the casuarine (**1**)[17] or the australine (**4**)[18] classes, with opposite configuration at C-7, depending on the diastereofacial preference of addition to the double bond (Scheme 2).

We show herein that addition of the organolithium derivative **6** to nitrone **3** is a very straightforward key reaction to directly install the hydroxy group at C-7 of the polyhydroxypyrrolizidine skeleton and that the diastereofacial preference for addition to the endocyclic double bond can be completely controlled by the size of ring B of the bicyclic intermediate. The power of this strategy is exemplified by the short and efficient syntheses of australine[19,20] and casuarine.[21]

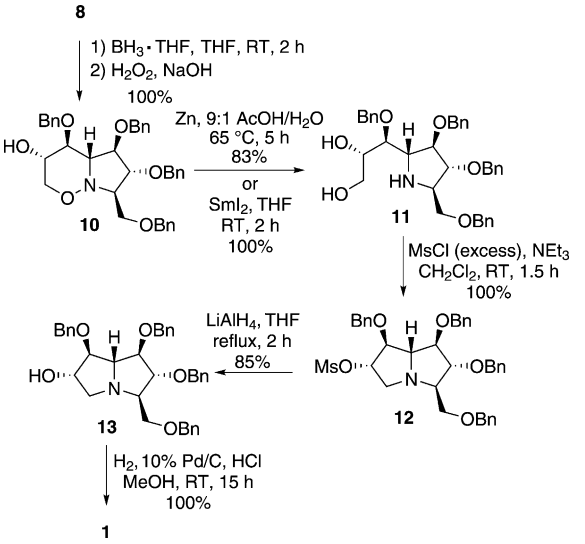
The addition of lithiated 1-benzyloxyallene (**6**) to nitrone **3** occurred successfully with exclusive *trans* stereoselectivity (with respect to the vicinal benzyloxy group at C-3 of the nitrone), as expected on the basis of previous findings collected by us and other groups on related nucleophilic additions,[3,4,22] which were established to be efficiently controlled by steric and stereoelectronic effects.[23] Contrary to the only precedent additions of a lithiated alkoxyallene to related tartaric or malic acid derived nitrones,[3a] the primary adduct **7** was barely detectable and chromatography aimed to its isolation led to extensive decomposition. Extraction of the reaction mixture with dichloromethane immediately after quenching proved to be advantageous. After drying with Na_2SO_4 and storage in CH_2Cl_2 solution for three days a complete cyclization to **8** was observed. Albeit it was reported earlier that related hydroxylamines may cyclize to two isomeric bicyclic adducts, that is, either a pyrrolo-1,2-oxazine or a pyrrolizidine *N*-oxide, in a concentration dependent manner,[3a] only adduct **8** was obtained in our case, with no trace of the pyrrolizidine *N*-oxide **9** being detected (Scheme 3), even when increasing the concentration of the solution. However, the 1,2-oxazine ring of **8** could be converted into a pyrrolidine ring as well (see below).



Scheme 3. Stereoselective addition of lithiated 1-benzyloxyallene (**6**) to nitrone **3**.

Firstly, an addition to the C–C double bond of 1,2-oxazine **8** was studied. On the basis of the previous study[3a] it was anticipated that additions would occur with efficient regio- and stereocontrol. Indeed, hydroboration/oxidation of **8** following the established protocol[24] occurred with complete regio- and stereoselectivity in quantitative yield (Scheme 4).

Careful analysis of the NMR spectroscopic data showed that the diastereoisomer **10** was formed exclusively, which



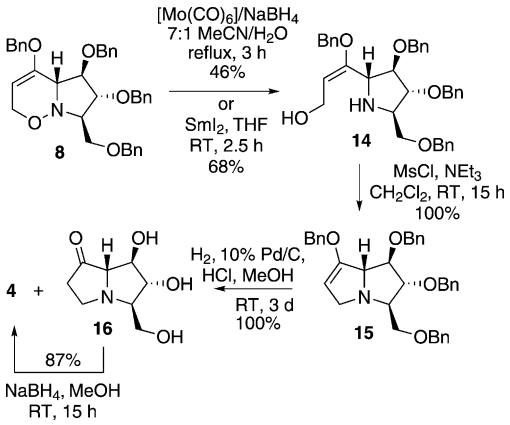
Scheme 4. Hydroboration of bicyclic 1,2-oxazine derivative **8** and synthesis of casuarine (**1**).

indicated a preferential addition to the *Si* face, anti to the bridgehead hydrogen atom. This approach installed, therefore, the correct configuration required for casuarine (**1**) at the two newly created stereogenic centers. Indeed, casuarine was easily obtained by reductive ring opening of **10** with Zn/H^+ or SmI_2,[24,25] followed by cyclization of **11** with an excess of MsCl to pyrrolizidine **12** and final reductive steps for demesylation to **13** with $LiAlH_4$ and deprotection by Pd/C-catalyzed hydrogenation. The resulting product displayed physical and spectroscopic data in good agreement with those reported in the literature.[21] This accomplished the most straightforward and high yielding total synthesis of casuarine reported to date, with an 84% overall yield of the alkaloid and six steps from nitrone **3** (ten steps, 47% from commercially available tribenzyl-protected D-arabinose).

The same synthetic sequence had been preliminarly carried out by starting with the parent 1-methoxyallene as a model substrate. Essentially analogous results have been obtained (see Supporting Information) for the preparation of the corresponding products **8**–**13** with a methoxy instead of a benzyloxy group at C-4 (dihydro-1,2-oxazines) or C-7 (pyrrolizidines). Of course, final hydrogenation of the pyrrolizidine corresponding to **13** furnished the methylated analogue 7-*O*-methylcasuarine (**1b**, see the Supporting Information). Interestingly, bioassays of this compound towards a set of 12 commercial glycosidases showed that it behaved similarly to casuarine itself, displaying good and selective inhibition of amyloglucosidase from *Aspergillus niger* (97% inhibition at 1 mM, $IC_{50}=9.7$ μM).[26]

The stereoselectivity of the key addition to **8**, occurring from the bottom face, may be attributed to a preferential conformation of the six-membered ring, in which the top face is more encumbered. In other words, a pyrrolo-1,2-oxazine bicyclic system does not present a pronounced convex face, contrary to a ring-contracted pyrrolizidine heterocycle. We reasoned therefore that, inverting the order of the events, that is, operating the ring-opening/cyclization steps before the addition reaction, would switch the diastereofacial preference for the addition, thus providing access to the australine class of alkaloids possessing the opposite configuration at C-7.

The pyrrolo-1,2-oxazine **8** was first subjected to a chemoselective reduction of the N–O bond to pyrrolidine **14**, which was successful with both $[Mo(CO)_6]/NaBH_4$[27] and SmI_2,[24,25,28] with the latter reagent being more satisfactory (Scheme 5).



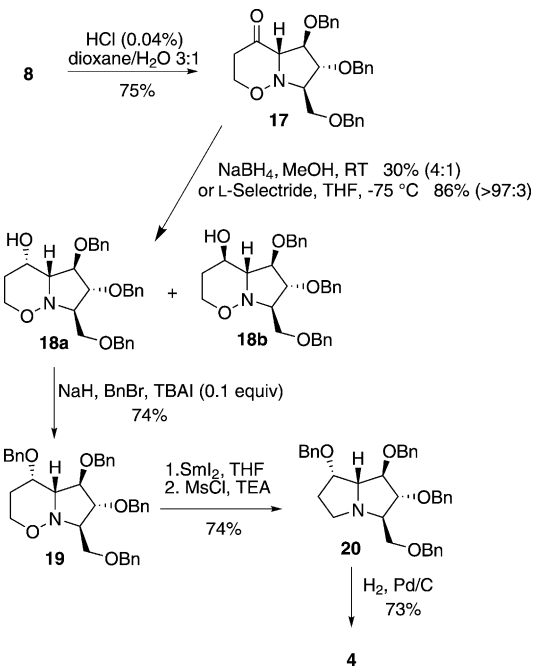
Scheme 5. Ring contraction of bicyclic 1,2-oxazine **8** to pyrrolizidine **15** and synthesis of australine (**4**).

Pyrrolidine **14** smoothly cyclized after mesylation to quantitatively afford pyrrolizidine **15**. Hydrogenation of **15** over Pd/C occurred quantitatively, but furnished a mixture of the desired australine (**4**) and its 7-oxo relative **16** in an approximately 3:1 ratio. Formation of this mixture indicates that debenzylation of the hydroxy group at C-7 competes with hydrogenation of the double bond in **15**: when debenzylation occurs first, the resulting enol readily isomerizes to its keto tautomer, which is inert to hydrogenation under these conditions.[29] Attempted selective debenzylation to **16** with BCl_3 led to a complex mixture of products. However, only australine (**4**) was isolated in good yield (87%) when the reaction mixture resulting from work up of the hydrogenation step was treated directly with $NaBH_4$ in methanol. This result derives from complete stereoselectivity in the hydrogenation of the double bond of **15** and in the hydride reduction of the carbonyl group of **16**, with reagents always approaching from the upper convex face of the pyrrolizidine ring as anticipated. NMR spectroscopic data and optical rotation of the synthesized alkaloid were in good agreement with those previously reported for australine.[18] Thus, we completed this novel total synthesis of australine in four steps from nitrone **3** with 59% overall yield (eight steps, 33% from commercial tribenzyl protected D-arabinose), which compares very well with the previously reported syntheses.[19]

Prompted by the observed complete stereoselectivity in the hydride reduction of ketone **16**, yet another approach

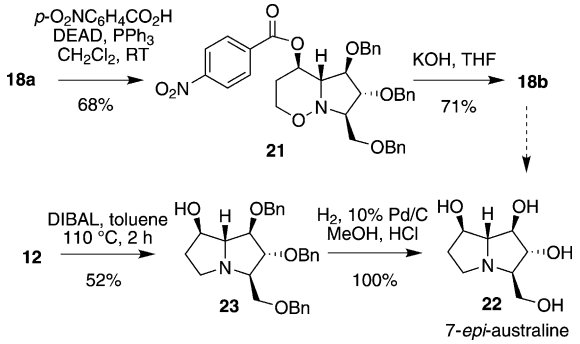
has been envisaged aiming at an alternative synthesis of australine. We expected that the benzyl enol ether in **8** might undergo acid-catalyzed hydrolysis to the ketone **17**, which would be reduced to the corresponding secondary alcohol. We speculated that hydride reagents would attack from the same face as for ketone **16**, as a consequence of the shift of the double bond from the *endo* (in **8**) to the *exo* position which should give a chair conformation in which equatorial attack to C-4 would be favored.

Hydrolysis of **8** to the ketone **17** was challenging.[30] A set of different solvents (methanol, acetonitrile, dioxane) in a mixture with H_2O were tested, as well as different strong protic acids (HCl, $HClO_4$) at different concentrations. None of the conditions employed allowed clean and complete conversion to the ketone. Concentration of the acid had to be kept low to avoid decomposition; consequently, long reaction times were required and it was found convenient to stop the reaction before complete consumption of the starting material. Moreover, the dimethyl ketal of **17** (in CH_3OH) and a mixed benzyl methyl ketal were detected besides the desired product and unreacted starting material. After extensive experimentation, dioxane/water and HCl were selected as the most satisfactory reaction mixture, which at least did not form ketal byproducts. Also in this case, however, complete conversion of the enol ether **8** was not achieved. The advancement of the reaction had to be monitored by ^{1}H NMR spectroscopy and the reaction was stopped at about 80% conversion; moreover, in our hands the reaction suffered from scarce reproducibility. Under the optimized conditions, a 75% yield of the desired ketone **17** was isolated from the reaction mixture by flash column chromatography (Scheme 6). Reduction of **17** with sodium borohydride gave a low yield of a 4:1 diastereomeric mixture of alcohols **18**, with the major alcohol **18a** deriving from hydride attack *syn* to the bridgehead hydrogen atom as anticipated. Structural assignment of **18a**,**b** was based on analysis of the coupling constants, as well as on subsequent synthetic elaboration (see below). Increase of the reagent bulkiness by use of L-selectride in THF at −75 °C allowed complete control of diastereoselectivity, affording alcohol **18a** exclusively in a satisfactory 86% yield. Benzylation of the free hydroxyl group of **18a** followed by cleavage of the N−O bond with SmI_2 and re-closure to a pyrrolizidine upon mesylation furnished the tetra-*O*-benzylated australine precursor **20** in 55% overall yield. The final deprotection by hydrogenation with Pd/C furnished the natural alkaloid **4** in 73% yield in high purity.



Scheme 6. Acid-catalyzed hydrolysis of benzyl enol ether **8** and synthesis of australine (**4**).

The second strategy also gave access to intermediates which may be useful for achieving complementary targets. As an example, we envisaged that the alcohol **18b** would serve as a suitable precursor of 7-*epi*-australine (7,7a-di-*epi*-alexine), a tetrahydroxylated pyrrolizidine yet unidentified from natural samples.[31] This compound has been previously synthesized[34] for structural correlation to isolated natural products[31] and was found to be a weak inhibitor of several glycosidases.[33b] The result described above for the reduction of ketone **17** with $NaBH_4$ discouraged us to test other reducing agents for the selective synthesis of **18b**. Alternatively, inversion of configuration at C-4 from alcohol **18a** through a Mitsunobu reaction was deemed a better solution. Indeed, treatment of **18a** under Mitsunobu conditions with *p*-nitrobenzoic acid afforded ester **21**, which was hydrolyzed to alcohol **18b** under basic conditions (Scheme 7). This alcohol, through the same transformations reported above for its diastereoisomer **18a** (Scheme 6), should afford 7-*epi*-australine. However, it was simultaneously evaluated to access 7-*epi*-australine via intermediates obtained in the strategy illustrated in Scheme 4, which is fairly more efficient and reliable. Unfortunately, attempted protodeboration of the borane obtained by hydroboration of adduct **8** was unsuccessful. Then, we turned our attention to the mesylate **12**, which should undergo a reductive deoxygenation as previously observed for a related compound in our synthesis of



Scheme 7. Synthesis of 7-*epi*-australine (**22**) by starting from precursors **18a** or **12**.

hyacinthacine A_2.[9a] Indeed, treatment of **12** with diisobutylaluminium hydride (DIBAL) in refluxing toluene for 2 h led to the desired deoxygenation at C-6. As previously observed on related benzyl-protected carbohydrate derivatives,[35] DIBAL promoted the concomitant selective debenzylation of the hydroxy group at C-7, affording the tri-*O*-benzylated 7-*epi*-australine **23** in reasonable yield (Scheme 7). Final debenzylation with hydrogen over Pd/C quantitatively provided the desired 7-*epi*-australine **22**, which displayed spectroscopic and physical data in good agreement with the literature.[34] Subjected to inhibition assays towards the same set of glycosidic enzymes, 7-*epi*-australine **22** showed a good inhibition of amyloglucosidase from *Aspergillus niger* (95% inhibition at 1 mM, IC_{50} = 3.5 μM)[26] with a potency lower than that of casuarine, but much higher (>1 order of magnitude) than that reported earlier.[33b] It also showed significant inhibition (80% inhibition at 1 mM) of α-glucosidase from yeast, in good agreement with the literature.[33b]

Conclusion

We have developed an efficient and straightforward strategy for accessing the 7-hydroxy pyrrolizidine skeleton and have proved that control of the configuration at C-7 can be achieved by carrying out additions to the endocyclic C–C double bond either to the initial 6-membered 1,2-oxazine adduct, or after ring contraction to a five-membered dihydropyrrole. In contrast, the stereoselectivity of the hydride reduction of an exocyclic C–O double bond preferentially occurred from the top face in six- and five-membered heterocycles. These results represent a considerable improvement and extension of the methodology based on addition of organometallic reagents to chiral cyclic nitrones for accessing alkaloid-like pyrrolizidine heterocycles by: 1) allowing direct placement of a protected hydroxyl substituent at C-7 without the need of additional synthetic elaborations, 2) providing efficient access to both 7*R* and 7*S*-configured compounds (with the additional option of stereocontrol at C-6) as a result of completely stereocontrolled addition reactions that occur with opposite preference depending on the size of ring B. Versatility and reliability of the strategy were demonstrated by high-yield syntheses of both casuarine and australine as examples of the two classes of 7-hydroxypyrrolizidine alkaloids. In particular, the high efficacy of our casuarine synthesis, with an overall yield doubled compared to the best previously published total syntheses,[21] should facilitate further biological investigations and lead to possible applications in view of its excellent inhibition of human digestive glycosidase enzymes.[7]

Experimental Section

General methods: Commercial reagents were used as received. All reactions were carried out under magnetic stirring and monitored by TLC analysis on 0.25 mm silica gel plates (Merck F_{254}). Column chromatographies were carried out on silica gel 60 (32–63 μm) or on silica gel (230–400 mesh, Merck). Yields refer to spectroscopically and analytically pure compounds unless otherwise stated. ^{1}H NMR spectra were recorded on a Varian Mercury-400, on a Varian INOVA 400, on Bruker (AC 250, WH 270, AC 500, AVIII), or JEOL (ECX 400, Eclipse 500) instruments at 25 °C. ^{13}C NMR spectra were recorded on a Varian Gemini-200 or on a Varian Gemini-300. Chemical shifts are reported relative to TMS (^{1}H: δ = 0.00 ppm) and $CDCl_3$ (^{13}C: δ = 77.0 ppm). Integrals are in accordance with assignments, coupling constants are given in Hz. For detailed peak assignments 2D spectra were measured (COSY, HMQC, HMBC, NOESY, and NOE as necessary). IR spectra were recorded with a Perkin–Elmer Spectrum BX FT-IR System spectrophotometer, with a Nicolet 5 SXC FTIR spectrometer, or with a Nexus FTIR spectrometer equipped with a Nicolet Smart DuraSample IR ATR. Mass spectra were recorded on a QMD 1000 Carlo Erba instrument by direct inlet. HRMS analyses were performed with a Varian Ionspec QFT-7 (ESI-FT ICRMS) instrument. Elemental analyses were performed with a Perkin–Elmer 2400 analyzer or with CHN-Analyzer 2400 (Perkin–Elmer), Vario EL, or Vario EL III. Optical rotation measurements were performed on a JASCO DIP-370 polarimeter.

(4a*S*,5*R*,6*R*,7*R*)-4,5,6-Tris(benzyloxy)-7-[(benzyloxy)methyl]-4a,5,6,7-tetrahydro-2*H*-pyrrolo[1,2-b]-1,2-oxazine (8): A solution of *n*BuLi in hexane (1.6 M, 3.30 mL, 5.28 mmol) was added at −40 °C to a stirred solution of 1-benzyloxyallene[5d] (815 mg, 5.58 mmol) in dry THF (20 mL) under an argon atmosphere. The mixture was stirred at −40 °C for 10 min, and then a solution of nitrone **3**[10] (1.27 g, 3.00 mmol) in dry THF (15 mL) was added at −78 °C. The mixture was stirred at −78 °C for 2 h. TLC control (CH_2Cl_2/AcOEt 8:1) showed the disappearance of the starting material (R_f = 0.11) and the appearance of a new product (R_f = 0.82), and then H_2O (30 mL) was added dropwise and the mixture was warmed up to RT. The mixture was extracted with dichloromethane (3× 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and stirred at RT for 3 d. Evaporation under reduced pressure and purification of the residue by flash column chromatography on silica gel (hexane/AcOEt 4:1) afforded pure **8** (1.67 g, 2.97 mmol, 99%) as a yellow oil. R_f = 0.26 (hexane/AcOEt 4:1); $[\alpha]_D^{20}$ = −21 (c = 1.4 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.25 (m, 20H; Ar-H), 4.93–4.87 (m, 3H, H-3; Bn-H), 4.74–4.53 (m, 6H; Bn-H), 4.51–4.49 (m, 2H, H-5; Ha-2), 4.42 (dd, ^2J(H,H) = 14.7, ^3J(H,H) = 3.3 Hz, 1H; Hb-2), 4.23 (t, ^3J(H,H) = 4.2 Hz, 1H; H-6), 3.97 (d, ^3J(H,H) = 6.3 Hz, 1H; H-4a), 3.78–3.74 (m, 2H; H-7, Ha-8), 3.66 ppm (dd, ^2J(H,H) = 11.3, ^2J(H,H) = 7.7 Hz, 1H; Hb-8); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.2 (s, C-4), 138.4–136.9 (s, 4C; Ar-C), 128.7–127.7 (d, 16C; Ar−C), 93.0 (d, C-3), 87.9 (d, C-5), 86.3 (d, C-6), 73.6, 72.4, 72.1 (t, Bn-C), 69.6 (t, C-8), 69.4 (t, Bn-C), 68.3 (d, C-7), 66.3 (d, C-4a), 63.6 ppm (t, C-2); IR (KBr): $\tilde{\nu}$ = 3029, 2897, 1673, 1496, 1453, 1361, 1349, 1216, 1199, 1074, 732, 694 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{36}H_{37}NO_5+H^+$: 564.2705 [M+H$^+$]; found: 564.2742; elemental analysis calcd (%) for $C_{36}H_{37}NO_5$: C 76.71, H 6.62, N 2.48; found: C 76.76, H 6.58, N 2.50.

(3*S*,4*S*,4a*S*,5*R*,6*R*,7*R*)-4,5,6-Tris(benzyloxy)-7-[(benzyloxy)methyl]hexahydro-2*H*-pyrrolo[1,2-b]-1,2-oxazin-3-ol (10): A solution of BH_3·THF in THF (1 M, 2.92 mL, 2.92 mmol) was added at −30 °C to a stirred solution of **8** (410 mg, 0.73 mmol) in dry THF (15 mL) under an argon atmosphere. The solution was stirred at −30 °C for 5 min and then at RT for 2 h. TLC control (hexane/AcOEt 2:1) showed the disappearance of the starting material (R_f = 0.35) and the appearance of a new product (R_f = 0.63), then a 2 N solution of NaOH (4.38 mL) and 35% H_2O_2 (1.46 mL) were added dropwise at −10 °C and the mixture was stirred for 15 h at RT. After this time, a saturated aqueous solution of $Na_2S_2O_3$ (5 mL) was added dropwise and the mixture was stirred for 10 min and then extracted with Et_2O (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/AcOEt 2:1) afforded pure **10** (425 mg, 0.73 mmol, 100%) as a colorless oil. R_f = 0.16 (hexane/AcOEt 2:1); $[\alpha]_D^{20}$ = −26 (c = 0.41 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.21 (m, 20H; Ar-H), 4.70–4.44 (m, 8H; Bn-H), 4.31–4.25 (m, 1H; H-5), 4.06 (t, ^3J(H,H) = 2.8 Hz, 1H; H-6), 4.03 (d, ^3J(H,H) = 3.3 Hz, 1H; Ha-2), 3.77–3.69 (m,

4H; Hb-2, H-3, H-7, Ha-8), 3.59 (t, ^3J(H,H) = 6.1 Hz, 1H; H-4), 3.54 (dd, ^2J(H,H) = 8.9, ^3J(H,H) = 7.4 Hz, 1H; Hb-8), 3.35 (t, ^3J(H,H) = 6.5 Hz, 1H; H-4a), 2.39 ppm (br s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.3, 138.2, 138.0, 137.9 (s; Ar-C), 128.6–127.8 (d, 16C; Ar-C), 85.4 (d; C-6), 84.7 (d; C-5), 76.9 (d; C-4), 73.6, 73.1, 71.9, 71.7 (t; Bn-C), 69.0 (d; C-3), 68.9, 68.8 (t; C-2, C-8), 67.9 ppm (d, 2C; C-7, C-4a); IR (KBr): $\tilde{\nu}$ = 3432, 3029, 2910, 2864, 1495, 1453, 1362, 1206, 1093, 750, 734 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{36}H_{39}NO_6+H^+$: 582.2811 [M+H$^+$]; found: 582.2861; elemental analysis calcd (%) for $C_{36}H_{39}NO_6$: C 74.33, H 6.76, N 2.41; found: C 74.17, H 6.98, N 2.42.

(2′*S*,3′*S*)-3′-(Benzyloxy)-3′-{(2*R*,3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-[(benzyloxy)- methyl]pyrrolidin-2-yl}-propan-1′,2′-diol (11):

Procedure A: Zn dust (100 mg, 1.53 mmol) was added to a stirred solution of **10** (166 mg, 0.30 mmol) in 9:1 acetic acid/H_2O (3 mL) at RT. The mixture was heated at 65 °C for 5 h. TLC control (petroleum ether/AcOEt 1:1) showed the disappearance of the starting material (R_f = 0.41) and the appearance of a new product (R_f = 0.00). The mixture was cooled to RT and a saturated aqueous solution of $NaHCO_3$ was added until a basic pH was reached. The mixture was extracted with AcOEt (3× 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (AcOEt/CH_3OH 40:1) afforded pure **11** (146 mg, 0.25 mmol, 83 %) as an orange oil.

Procedure B:[24a] Sm powder (232 mg, 1.54 mmol) was added to a stirred solution of 1,2-diiodoethane (376 mg, 1.33 mmol) in dry THF (9 mL) at RT under an argon atmosphere. The solution was stirred at RT for 2 h, and then a solution of **10** (216 mg, 0.37 mmol) in dry THF (9 mL) was added and the mixture was stirred at RT for a further 2 h. TLC control (hexane/AcOEt 1:1) showed the disappearance of the starting material (R_f = 0.55) and the appearance of a new product (R_f = 0.02). At this point, a saturated aqueous solution of $NaHCO_3$ (6.5 mL) was added and the mixture was extracted with Et_2O (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2/CH_3OH 20:1) afforded pure **11** (216 mg, 0.37 mmol, 100 %) as an orange oil. R_f = 0.69 (AcOEt/CH_3OH 40:1); R_f = 0.38 (CH_2Cl_2/CH_3OH 20:1); $[\alpha]_D^{20}$ = −7 (*c* = 0.49 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.22 (m, 20H; Ar-H), 4.66 (d, *J* = 11.4 Hz, 1H; Bn-H), 4.54–4.42 (m, 7H; Bn-H), 4.05–4.01 (m, 2H; H-3, H-2′), 3.98 (dd, ^3J(H,H) = 5.7, ^3J(H,H) = 2.7 Hz, 1H; H-4), 3.78 (d, ^3J(H,H) = 5.4 Hz, 2H; Ha,b-1′), 3.68 (dd, ^3J(H,H) = 9.5, ^3J(H,H) = 3.8 Hz, 1H; H-3′), 3.57–3.56 (m, 1H; H-2), 3.56 (d, ^3J(H,H) = 4.5 Hz, 2H; Ha,b-6), 3.36 ppm (dd, ^3J(H,H) = 10.0, ^3J(H,H) = 4.6 Hz, 1H; H-5); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.2, 138.1, 137.9, 137.8 (s; Ar-C), 128.6–127.8 (d, 16C; Ar-C), 86.9 (d; C-3), 88.8 (d; C-4), 76.4 (d; C-3′), 73.3, 72.9 (t; Bn-C), 72.2 (d; C-2′), 72.1, 71.5 (t; Bn-C), 68.7 (t; C-6), 64.4 (d; C-2), 63.4 (t; C-1′), 62.4 ppm (d; C-5); IR (KBr): $\tilde{\nu}$ = 3312, 3029, 2862, 1495, 1452, 1070, 695 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{36}H_{41}NO_6+H^+$: 584.2967 [M+H$^+$]; found: 584.3011; elemental analysis calcd (%) for $C_{36}H_{41}NO_6$: C 74.04, H 7.08, N 2.40; found: C 73.61, H 7.01, N 2.33.

(1*R*,2*R*,3*R*,6*S*,7*S*,7a*S*)-1,2,7-Tris(benzyloxy)-3-[(benzyloxy)methyl]hexahydro-1*H*-pyrrolizin-6-yl methanesulfonate (12): Triethylamine (108 μL, 0.78 mmol) and MsCl (44 μL, 0.57 mmol) were added to a stirred solution of **11** (151 mg, 0.26 mmol) in dry CH_2Cl_2 (20 mL) at RT under an argon atmosphere. The solution was stirred at RT for 1.5 h. TLC control (CH_2Cl_2/CH_3OH 9:1) showed the disappearance of the starting material (R_f = 0.54) and the appearance of a new product (R_f = 0.88). Water (5.0 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/AcOEt 1:1) afforded pure **12** (167 mg, 0.26 mmol, 100 %) as a colorless oil. R_f = 0.54 (hexane/AcOEt 1:1); $[\alpha]_D^{20}$ = −7 (*c* = 1.3 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 20H; Ar-H), 5.17 (dt, ^3J(H,H) = 5.3, ^3J(H,H) = 3.1 Hz, 1H; H-6), 4.69–4.46 (m, 8H; Bn-H), 4.22 (dd, ^3J(H,H) = 3.8, ^3J(H,H) = 3.5 Hz, 1H; H-7), 4.04 (t, ^3J(H,H) = 5.2 Hz, 1H; H-1), 4.01 (dd, ^3J(H,H) = 12.2, ^3J(H,H) = 5.8 Hz, 1H; H-2), 3.59 (dd, ^2J(H,H) = 9.5, ^3J(H,H) = 4.6 Hz, 1H; Ha-8), 3.54–3.49 (m, 3H; Hb-8, H-7a, Ha-5), 3.37 (dd, ^2J(H,H) = 13.2, ^3J(H,H) = 3.1 Hz, 1H; Hb-5), 3.28 (td, ^3J(H,H) = 6.4, ^3J(H,H) = 4.8 Hz, 1H; H-3), 2.89 ppm (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.4, 138.2, 138.0, 137.5 (s, Ar-C), 128.6–127.7 (d, 16C; Ar-C), 85.9 (d; C-7), 85.8 (d; C-1), 85.3 (d; C-2), 85.3 (d; C-6), 73.5, 72.8 (t; Bn-C), 72.5 (t; C-8), 72.4, 72.1 (t; Bn-C), 68.2 (d; C-3), 57.2 (t; C-5), 38.6 ppm (q, CH_3); IR ($CDCl_3$): $\tilde{\nu}$ = 3029, 2893, 2863, 1342, 1175, 1090, 1071, 750, 696 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{37}H_{41}NO_7S+H^+$: 644.2637 [M+H$^+$]; found: 644.2678; elemental analysis calcd (%) for $C_{37}H_{41}NO_7S$: C 69.03, H 6.42, N 2.18; found: C 69.50, H 6.03, N 2.60.

(1*R*,2*R*,3*R*,6*S*,7*S*,7a*R*)-1,2,7-Tris(benzyloxy)-3-[(benzyloxy)methyl]hexahydro-1*H*-pyrrolizin-6-ol (13): A solution of $LiAlH_4$ in THF (1 M, 0.88 mL, 0.88 mmol) was added to a stirred solution of **12** (140 mg, 0.22 mmol) in dry THF (4 mL) at 0 °C under an argon atmosphere. The solution was stirred at reflux for 2 h. TLC control (hexane/AcOEt 1:1) showed the disappearance of the starting material (R_f = 0.44) and the appearance of a new product (R_f = 0.16). Then, a saturated aqueous solution of Na_2SO_4 (0.7 mL) was added and the mixture was filtered over Celite and evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/AcOEt 1:3) afforded pure **13** (106 mg, 0.19 mmol, 85 %) as a colorless oil. R_f = 0.43 (hexane/AcOEt 1:3); $[\alpha]_D^{20}$ = −7 (*c* = 0.14 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 20H; Ar-H), 4.60–4.48 (m, 8H; Bn-H), 4.26 (q, ^3J(H,H) = 4.0 Hz, 1H; H-6), 4.12 (t, ^3J(H,H) = 4.4 Hz, 1H; H-1), 4.08 (t, ^3J(H,H) = 4.6 Hz, 1H; H-2), 3.87 (t, ^3J(H,H) = 3.7 Hz, 1H; H-7), 3.56–3.50 (m, 3H; H-7a Ha,b-8), 3.43–3.38 (m, 2H; H-3, Ha-5), 2.98 ppm (dd, ^2J(H,H) = 12.0, ^3J(H,H) = 3.9 Hz, 1H; Hb-5); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.5, 138.3, 138.2, 137.8 (s; Ar-C), 128.6–127.6 (d, 16C; Ar-C), 88.6 (d; C-7), 86.5 (d; C-1), 85.7 (d; C-2), 77.6 (d; C-6), 73.6 (d; C-7a), 73.4, 72.4 (t; Bn-C), 72.2 (t; C-8), 71.8, 71.1 (t; Bn-C), 70.3 (d; C-3), 61.1 ppm (t; C-5); HRMS (ESI): *m*/*z*: calcd for $C_{36}H_{39}NO_5+H^+$: 566.2901 [M+H$^+$]; found: 566.2904; elemental analysis calcd (%) for $C_{36}H_{39}NO_5$: C 76.43, H 6.95, N 2.48; found: C 75.79, H 7.00, N 2.43.

(1*R*,2*R*,3*R*,6*S*,7*S*,7a*R*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,6,7-tetrol (Casuarine) (1): Conc. HCl (4 drops) and 10 % Pd/C (34 mg) were added to a stirred solution of **13** (57 mg, 0.10 mmol) in CH_3OH (10 mL). The suspension was stirred under a H_2 atmosphere for 15 h, and then filtered through Celite and washed with CH_3OH. Evaporation under reduced pressure afforded a viscous oil that was transferred to a column of DOWEX 50WX8 and washed with CH_3OH (20 mL) and H_2O (20 mL) to remove nonamine-containing products and then with 7 % NH_4OH (30 mL) to elute casuarine (**1**). Evaporation of the solvent afforded casuarine (**1**) as a white solid (21 mg, 0.10 mmol, 100 %) with physical and spectroscopic data in good agreement with those reported in the literature.[21] $[\alpha]_D^{20}$ = +13.6 (*c* = 0.66 in CH_3OH) (lit. $[\alpha]_D^{20}$ = +14 (*c* = 0.52 in H_2O));[7] ^{1}H NMR (500 MHz, D_2O): δ = 4.20–4.17 (m, 2H; H-6, H-7), 4.14 (t, ^3J(H,H) = 8.2 Hz, 1H; H-1), 3.79–3–74 (m, 2H; H-2, Ha-8), 3.60 (dd, ^2J(H,H) = 11.8, ^3J(H,H) = 6.6 Hz, 1H; Hb-8), 3.25 (dd, ^2J(H,H) = 12.3, ^3J(H,H) = 4.4 Hz, 1H; Ha-5), 3.06 (dd, ^3J(H,H) = 8.2, ^3J(H,H) = 3.3 Hz, 1H; H-7a), 3.04–3.01 (m, 1H; H-3), 2.91 ppm (dd, ^2J(H,H) = 12.3, ^3J(H,H) = 3.8 Hz, 1H; Hb-5); ^{13}C NMR (50 MHz, D_2O): δ = 79.3 (d; C-7), 78.2 (d; C-1), 77.9 (d; C-6), 77.1 (d; C-2), 72.7 (d; C-7a), 70.5 (d; C-3), 62.7 (t; C-8), 58.6 ppm (t; C-5).

(2′*E*)-3′-(Benzyloxy)-3′-{(3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-[(benzyloxy)-methyl]-pyrrolidin-2-yl}prop-2′-en-1′-ol (14):

Procedure A:[27] $[Mo(CO)_6]$ (111 mg, 0.42 mmol) was added at RT to a stirred solution of **8** (153 mg, 0.27 mmol) in 7:1 CH_3CN/H_2O (4 mL); then, after 5 min, $NaBH_4$ (5.2 mg, 0.14 mmol) was added at RT and the mixture was heated at reflux for 3 h. TLC control (petroleum ether/AcOEt 1:1) showed the disappearance of the starting material (R_f = 0.60) and the appearance of a new product (R_f = 0.07). The mixture was cooled to RT and filtered over Celite and then evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (petroleum ether/AcOEt 2:3) afforded pure **14** (70 mg, 0.12 mmol, 46 %) as a colorless oil.

Procedure B:[28] SmI_2 in THF (0.1 M, 9.9 mL, 0.99 mmol) was added to **8** (155 mg, 0.27 mmol) under a nitrogen atmosphere at RT and the mixture was stirred for 2.5 h until disappearance of the starting material was ob-

served as above. Then a saturated aqueous solution of $NaHCO_3$ (4.5 mL) was added and the mixture was extracted with Et_2O (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (petroleum ether/AcOEt 1:4) afforded pure **14** (104 mg, 0.18 mmol, 68%) as a colorless oil. R_f=0.07 (petroleum ether/AcOEt 1:1); $[\alpha]_D^{20}$=+15 (c=1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34–7.22 (m, 20H; Ar-H), 5.13 (t, ^3J(H,H)=8.0 Hz, 1H; H-2′), 4.75, 4.72 (AB system, J(H,H)=11.5 Hz, 2H; Bn-H), 4.59–4.48 (m, 6H; Bn-H), 4.18–3.39 (m, 5H; Ha-1′, Hb-1′, H-2, H-3, H-4), 3.56–3.49 (m, 2H; Ha-6, H-b-6), 3.49–3.42 ppm (m, 1H; H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ=156.7 (s, C-3′), 138.0, 137.4, 136.4 (s, 4C; Ar-C), 128.4–127.5 (d, 20C; Ar-C), 101.4 (d; C-2′), 87.1 (d; C-3), 86.6 (d; C-4), 73.4, 72.6, 72.1 (t; Bn-C), 71.4 (t; C-6), 69.4 (t; Bn-C), 61.7 (d; C-5), 60.2 (d; C-2), 57.2 ppm (t; C-1′); IR ($CDCl_3$): $\tilde{\nu}$=3450, 3350, 3066, 3031, 2932, 2867, 2243, 1654, 1495, 1454, 1362, 1220, 1094, 1076 cm^{-1}; MS (ESI): m/z: 588.43 (100) [M+Na$^+$], 566.45 (88) [M+H$^+$]; elemental analysis calcd (%) for $C_{36}H_{39}NO_5$: C 76.43, H 6.95, N 2.48; found: C 76.00, H 7.47, N 2.94.

(1*R*,2*R*,3*R*,7a*S*)-1,2,7-Tris(benzyloxy)-3-[(benzyloxy)methyl]-2,3,5,7a-tetrahydro-1*H*-pyrrolizine (15): Triethylamine (0.3 mL, 2.01 mmol) and MsCl (0.08 mL, 1.00 mmol) were added to a stirred solution of **14** (380 mg, 0.67 mmol) in dry CH_2Cl_2 (25 mL) under a nitrogen atmosphere at RT and the mixture was stirred at RT for 15 h. Then, H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3×20 mL). The collected organic layers were dried over Na_2SO_4, filtered, and then evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (petroleum ether/AcOEt 3:1) afforded pure **15** (367 mg, 0.67 mmol, 100%) as a pale-yellow oil. R_f=0.57 (petroleum ether/AcOEt 1:1); $[\alpha]_D^{20}$=−18 (c=0.63 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30–7.12 (m, 20H; Ar-H), 4.81 (AB system, ^2J(H,H)=11.6 Hz, 2H; Bn-H), 4.66–4.57 (m, 2H; Bn-H), 4.51–4.39 (m, 5H, H-6; Bn-H), 4.08 (m, 1H; H-7a), 4.02–3.96 (m, 2H; H-1, H-2), 3.87–3.84 (m, 1H; Ha-5), 3.56 (dd, ^2J(H,H)=9.7, ^3J(H,H)=3.9 Hz, 1H; Ha-8), 3.51–3.45 (m, 2H; Hb-8, Hb-5), 2.97–2.93 ppm (m, 1H, H-3); ^{13}C NMR (50 MHz, $CDCl_3$): δ=138.2–136.2 (s, 4C; Ar-C), 128.4–127.3 (d, 20C; Ar-C), 100.9 (s; C-7), 91.7 (d; C-6), 85.2 (d; C-1), 84.3 (d; C-2), 73.4 (t; Bn-C), 72.9 (d; C-7a), 72.6, 72.5, 71.9 (t; Bn-C), 71.1 (t; C-8), 68.9 (d; C-3), 58.6 ppm (t; C-5); MS (ESI): m/z: 570.35 (95) [M+Na$^+$], 548.40 (100) [M+H$^+$]; elemental analysis calcd (%) for $C_{36}H_{37}NO_4$: C 78.95, H 6.81, N 2.56; found: C 78.92, H 6.54, N 2.36.

(1*R*,2*R*,3*R*,7*S*,7a*R*)-3-(Hydroxymethylhexahydro-1*H*-pyrrolizine-1,2,7-triol (Australine) (4): Conc. HCl (3 drops) and 10% Pd/C (50 mg) were added to a stirred solution of **15** (111 mg, 0.20 mmol) in CH_3OH (10 mL) at RT under a nitrogen atmosphere. The mixture was stirred at RT under H_2 for 3 d. NMR spectroscopic control showed the disappearance of the signals of the benzyl groups and the formation of two products identified as **4** and **16** in an approximately 3:1 ratio. The mixture was filtered over Celite and evaporated under reduced pressure, and then fresh CH_3OH (10 mL) and $NaBH_4$ (30 mg) were added and the suspension was stirred for 15 h. After addition of conc. HCl (4 drops), the mixture was filtered over Celite and evaporated under reduced pressure. Then the crude product was transferred to a column of DOWEX 50WX8 and washed with CH_3OH (20 mL) and H_2O (20 mL) to remove nonamine-containing products and then with 7% NH_4OH (30 mL) to elute australine (**4**). After evaporation, **4** was obtained (33 mg, 0.17 mmol, 87%) as a colorless vitreous solid, with physical and spectroscopic data in good agreement with those reported in the literature.[19] $[\alpha]_D^{20}$=+15 (c=0.62 in CH_3OH) (lit. $[\alpha]_D^{20}$=+17.1 (c=2.9 in CH_3OH)];[12] ^{1}H NMR (400 MHz, D_2O): δ=4.25 (dt, ^3J(H,H)=4.4, ^3J(H,H)=2.4 Hz, 1H; H-7), 4.11 (t, ^3J(H,H)=7.8 Hz, 1H; H-1), 3.78 (dd, ^3J(H,H)=9.5, ^3J(H,H)=7.8 Hz, 1H; H-2), 3.67 (dd, ^2J(H,H)=11.7, ^3J(H,H)=3.4 Hz, 1H; Ha-8), 3.50 (dd, ^2J(H,H)=11.7, ^3J(H,H)=6.5 Hz, 1H; Hb-8), 3.11–3.03 (m, 2H; H-7a, Ha-5), 2.66–2.59 (m, 2H; H-3, Hb-5), 1.95–1.89 (m, 1H; Ha-6), 1.87–1.77 ppm (m, 1H; Hb-6); ^{13}C NMR (50 MHz, D_2O): δ=78.4 (d, C-2), 72.8 (d, C-1), 70.9 (d, C-7a), 70.5 (d, C-3), 69.3 (d, C-7), 61.7 (t, C-8), 51.8 (t, C-5), 35.0 ppm (t, C-6); MS (ESI): m/z: 212.17 (100) [M+Na$^+$], 190.15 (36) [M+H$^+$]; elemental analysis calcd (%) for $C_8H_{15}NO_4$: C 50.78, H 7.99, N 7.40; found: C 50.87, H 7.82, N 7.20.

(4a*S*,5*R*,6*R*,7*R*)-5,6-Bis(benzyloxy)-7-(benzyloxymethyl)hexahydro-4*H*-pyrrolo[1,2-b][1,2]oxazin-4-one (17): Concentrated HCl (0.2 mL) was added to a stirred solution of **8** (1.12 g, 1.98 mmol) in water/dioxane (1:3, 200 mL). The solution was stirred for 78 h at RT. TLC control (hexane/AcOEt 2:1) showed the disappearance of the starting material (R_f=0.64) and the appearance of a new compound (R_f=0.55). A saturated aqueous solution of $NaHCO_3$ (20 mL) was added and the mixture was evaporated under reduced pressure and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/AcOEt 1:4) afforded starting material **8** (232 mg, 0.411 mmol, 21% yield) and pure **17** (705 mg, 1.49 mmol, 75% yield) as an orange oil. R_f=0.21 (hexane/AcOEt 1:4); $[\alpha]_D^{20}$=−41 (c=1.0 in $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): δ=7.38–7.26 (m, 15H; Ar-H), 4.63–4.49 (m, 7H; Bn-H, H-5), 4.25 (m, 2H; Ha,b-2), 4.12 (dd, ^3J(H,H)=3.8, ^3J(H,H)=3.1 Hz, 1H; H-6), 3.83 (d, ^3J(H,H)=8.4 Hz, 1H; H-4a), 3.72 (td, ^3J(H,H)=6.1, ^3J(H,H)=3.0 Hz, 1H; H-7), 3.58 (dd, ^2J(H,H)=9.8, ^3J(H,H)=5.5 Hz, 1H; Ha-8), 3.50 (dd, ^2J(H,H)=9.8, ^3J(H,H)=6.6 Hz, 1H; Hb-8), 2.63 (dt, ^2J(H,H)=16.3, ^3J(H,H)=8.0 Hz, 1H; Ha-3), 2.53 ppm (dt, ^2J(H,H)=16.6, ^3J(H,H)=4.5 Hz, 1H; Ha-3); ^{13}C NMR (175 MHz, $CDCl_3$): δ=204.1 (s; C-4), 137.8, 137.7, 137.0 (s; Ar-C), 128.4–127.7 (d, 15C; Ar-C), 86.2 (d; C-6), 85.6 (d; C-5), 76.9 (d; C-4a), 73.4, 72.2, 71.9 (t; Bn-C), 71.2 (d; C-7), 68.9 (t; C-8), 66.2 (t; C-2), 37.8 ppm (t, C-3); IR ($CHCl_3$): $\tilde{\nu}$=2957 (str. C−H), 1699 cm^{-1} (str. C=O); HRMS (ESI): m/z: calcd for $C_{29}H_{31}NO_5$+H$^+$ 474.2280 [M+H$^+$]; found 474.2288; elemental analysis calcd (%) for $C_{29}H_{31}NO_5$: C 73.55, H 6.60, N 2.96; found: C 73.58, H 6.64, N 2.96.

(4a*S*,4a*R*,5*R*,6*R*,7*R*)-5,6-bis(Benzyloxy)-7-[(benzyloxy)methyl]hexahydro-2*H*-pyrrolo[1,2-b][1,2]oxazin-4-ol (18a): L-Selectride 1M solution in THF (2.7 mL, 2.7 mmol) was added to a stirred solution of **17** (705 mg, 1.49 mmol) in dry THF (15 mL) at −75°C under an argon atmosphere. After 3 h, a TLC control (hexane/AcOEt 2:1) showed the disappearance of the starting material (R_f=0.55) and the appearance of a new compound (R_f=0.19); then water (3 mL) was added and the temperature was allowed to rise to RT. The mixture was extracted with Et_2O (3×20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/AcOEt 1:2) afforded the pure reduction product (616 mg, 1.29 mmol, 86% yield, diastereomeric ratio (d.r.) >97:3) as a pale-yellow oil. R_f=0.19 (hexane/AcOEt 2:1); $[\alpha]_D^{20}$=−16 (c=0.9 in $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): δ=7.37–7.24 (m, 15H; Ar-H), 4.65–4.43 (m, 6H; Bn-H), 4.39 (s, 1H; H-5), 4.18 (s, 1H; H-4), 4.12–4.06 (m, 2H; Ha-2, H-6), 3.85–3.80 (m, 1H; Hb-2), 3.73–3.66 (m, 2H; Ha-8, H-7), 3.56 (t, ^2J(H,H)=^3J(H,H)=7.9 Hz, 1H; Hb-8), 3.38 (dd, ^3J(H,H)=8.6, ^3J(H,H)=2.8 Hz, 1H; H-4a), 2.76 (br s, 1H; OH), 1.85–1.74 ppm (m, 2H; Ha-3, Hb-3); ^{13}C NMR (175 MHz, $CDCl_3$): δ=138.0, 137.8, 137.7 (s; Ar-C), 128.5–127.7 (d, 15C; Ar-C), 85.1 (d; C-6), 82.4 (d; C-5), 73.4, 72.3, 71.6 (t; Bn-C), 69.4 (d; C-7), 68.1 (d; C-4a), 65.9 (t; C-2), 64.8 (d; C-4), 31.3 ppm (t; C-3); IR ($CHCl_3$): $\tilde{\nu}$=3521, 3064, 3032, 3011, 2981, 2952, 2918, 2866, 1494, 1451, 1361, 1258, 1094 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{29}H_{33}NO_5$+H$^+$: 476.2436 [M+H$^+$]; found: 476.2435; elemental analysis calcd (%) for $C_{29}H_{33}NO_5$: C 73.24, H 6.99, N 2.95; found: C 73.24, H 6.99, N 3.03.

(4a*S*,4a*R*,5*R*,6*R*,7*R*)-4,5,6-Tris(benzyloxy)-7-[(benzyloxy)methyl]hexahydro-2*H*-pyrrolo[1,2-b][1,2]oxazine (19): NaH (60% in mineral oil, 86 mg, 2.14 mmol), tetrabutylammonium iodide (TBAI) (44 mg, 0.119 mmol), and benzyl bromide (305 mg, 1.78 mmol) were added to a stirred solution of **18a** (565 mg, 1.19 mmol) in dry THF (50 mL). The suspension was stirred at RT overnight under an argon atmosphere. TLC control (hexane/AcOEt 2:1) showed the disappearance of the starting material (R_f=0.19) and the appearance of a new compound (R_f=0.45). Then, a saturated aqueous solution of NH_4Cl (15 mL) was added. The mixture was extracted with Et_2O (3×20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/AcOEt 1:3) afforded pure **19** (502 mg, 0.887 mmol, 74% yield) as a pale-yellow oil. R_f=0.33 (hexane/AcOEt 1:3); $[\alpha]_D^{20}$=−56 (c=1.1 in $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): δ=7.43–7.21 (m, 20H; Ar-H), 4.73–4.50 (m, 9H; Bn-H, H-5), 4.21–4.15 (m, 2H; Ha-2, H-6), 4.06 (dt, ^3J-

(H,H) = 8.6, ^3J(H,H) = 4.3 Hz, 1H; H-4), 3.87 (ddd, ^2J(H,H) = 12.0, ^3J-(H,H) = 9.0, ^3J(H,H) = 3.1 Hz, 1H; Hb-2), 3.78–3.75 (m, 1H; H-7), 3.72 (dd, ^2J(H,H) = 9.6, ^3J(H,H) = 5.4 Hz, 1H; Ha-8), 3.65–3.61 (m, 1H; H-4a), 3.56 (dd, ^2J(H,H) = 9.5, ^3J(H,H) = 7.6 Hz, 1H; Hb-8), 2.02 (dtd, ^2J-(H,H) = 13.0, ^3J(H,H) = 8.8, ^3J(H,H) = 4.0 Hz, 1H; Ha-3), 1.88–1.83 ppm (m, 1H; Hb-3); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 138.5, 138.4, 138.2, 138.1 (s; Ar-C), 128.5–127.4 (d, 20C; Ar-C), 87.1 (d; C-6), 83.9 (d; C-5), 73.4, 72.6 (t; Bn-C), 71.6 (d, 1C; C-4, t, 1C; Bn-C), 70.6 (t; Bn-C), 70.0 (d; C-7), 68.5 (t; C-8), 67.3 (d; C-4a), 66.3 (t; C-2), 28.0 ppm (t; C-3) ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3066, 3034, 3007, 2928, 2863, 2252, 1496, 1453, 1356, 1101, 1028 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{36}H_{39}NO_5+H^+$: 566.2906 [*M*+H$^+$]; found: 566.2889; elemental analysis calcd (%) for $C_{36}H_{39}NO_5$: C 76.43, H 6.95, N 2.48; found: C 76.18, H 6.64, N 2.65.

(1*R*,2*R*,3*R*,7*S*,7a*R*)-1,2,7-Tris(benzyloxy)-3-[(benzyloxy)methyl]hexahydro-1*H*-pyrrolizine (20): A solution of SmI_2 in THF 0.13 M (23.8 mL, 3.19 mmol) was added to a stirred solution of **19** (502 mg, 0.887 mmol) in dry and degassed THF (15 mL) under an argon atmosphere. The solution was stirred at RT overnight. TLC control (hexane/AcOEt 1:1) showed the disappearance of the starting material (R_f = 0.76) and the appearance of a new compound (R_f = 0.03). Then, a saturated aqueous solution of $NaHCO_3$ (4 mL) was added and the mixture was extracted with Et_2O (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product obtained (489 mg) was dissolved in dry CH_2Cl_2 (25 mL) and methanesulfonyl chloride (0.2 mL, 2.58 mmol) and triethylamine (0.45 mL, 3.44 mmol) were added. The solution was stirred under an argon atmosphere for 14 h. When TLC control (hexane/AcOEt 1:1) showed the disappearance of the starting material (R_f = 0.03) and the appearance of a new compound (R_f = 0.35), water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/AcOEt 1:1, 1:3 then AcOEt) afforded pure **20** (360 mg, 0.655 mmol, 74% yield) as a pale-yellow oil. R_f = 0.35 (hexane/AcOEt 1:1); $[\alpha]_D^{20}$ = +22 (*c* = 0.92 in $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 20H; Ar-H), 4.79–4.39 (m, 9H; Bn-H, H-1), 4.21 (dd, ^3J(H,H) = 9.0, ^3J(H,H) = 7.2 Hz, 1H; H-2), 3.93–3.90 (m, 1H; H-7), 3.67 (dd, ^2J(H,H) = 9.8, ^3J(H,H) = 3.1 Hz, 1H; Ha-8), 3.61–3.56 (m, 2H; Hb-8, H-7a), 3.30 (m, 1H; Ha-5), 3.03 (m, 1H; H-3), 2.77 (ddd, ^2J(H,H) = 13.6, ^3J(H,H) = 10.5, ^3J(H,H) = 6.0 Hz, 1H; Hb-5), 2.24–2.20 (m, 1H; Ha-6), 1.90–1.84 ppm (m, 1H; Hb-6); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 138.6, 138.5, 138.4, 138, 3 (s; Ar-C), 128.4–127.4 (d, 20C; Ar-C), 85.9 (d; C-2), 80.9 (d; C-1), 78.1 (d; C-7), 73.4, 72.8, 72.2 (t; Bn-C), 71.3 (t, 1C; C-8, d, 1C; C-7), 70.7 (t; Bn-C), 68.9 (d; C-3), 52.3 (t; C-5), 32.1 ppm (t; C-6); HRMS (ESI): *m*/*z*: calcd for $C_{36}H_{39}NO_4+H^+$: 550.2957 [*M*+H$^+$]; found: 550.2950; elemental analysis calcd (%) for $C_{36}H_{39}NO_4$: C 78.66, H 7.15, N 2.55; found: C 78.65, H 7.18, N 2.58.

(1*R*,2*R*,3*R*,7*S*,7a*R*)-3-(Hydroxymethylhexahydro-1*H*-pyrrolizine-1,2,7-triol (australine) (4): Conc. HCl (4 drops) and 10% Pd/C (185 mg) were added to a stirred solution of **20** (175 mg, 0.318 mmol) in CH_3OH (15 mL). The suspension was stirred under H_2 for 67 h and then filtered through a pad of Celite and washed with CH_3OH. Evaporation under reduced pressure afforded a viscous oil that was transferred to a column of DOWEX 50WX200. The column was washed with CH_3OH (20 mL) and H_2O (20 mL) to remove nonamine-containing products and then with 5% NH_4OH (40 mL) to elute australine (**4**). Evaporation of the solvent afforded australine **4** (44 mg, 0.232 mmol, 73%) as a yellowish solid, with spectroscopic data identical to those given above. $[\alpha]_D^{21}$ = = +21 (*c* = 2.2 in CH_3OH).

(4*R*,4a*R*,5*R*,6*R*,7*R*)-5,6-Bis(benzyloxy)-7-[(benzyloxy)methyl]hexahydro-2*H*-pyrrolo[1,2-b][1,2]oxazin-4-yl-4-nitrobenzoate (21): A stirred solution of **18a** (31 mg, 0.07 mmol), *p*-nitrobenzoic acid (27 mg, 0.16 mmol), and PPh_3 (80 mg, 0.31 mmol) in dry THF (10 mL) was cooled to 0°C and stirred for 5 min under an argon atmosphere. Then diethyl azodicarboxylate (DEAD) (48 μL, 0.31 mmol) was added dropwise and the temperature brought to RT. The solution was stirred at RT for 1 day. TLC control (hexane/AcOEt 1:2) showed the disappearance of the starting material (R_f = 0.19) and the appearance of a new compound (R_f = 0.54). Then, water (6 mL) was added and the mixture was extracted with Et_2O (3× 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/AcOEt 1:3) afforded pure **21** (28 mg, 0.05 mmol, 68% yield) as a pale yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 8.24–8.15 (m, 4H; Ar-H), 7.38–7.08 (m, 15H; Ar-H), 5.38–5.35 (m, 1H; H-4), 4.67 (d, ^2J(H,H) = 12.0 Hz, 1H; Bn-H), 4.60 (m, 2H; Bn-H), 4.50 (d, ^2J(H,H) = 11.1 Hz, 1H; Bn-H), 4.48 (d, ^2J(H,H) = 12.0 Hz, 1H; Bn-H), 4.41 (d, ^2J(H,H) = 11.1 Hz, 1H; Bn-H), 4.26 (t, ^3J(H,H) = 7.4 Hz, 1H; H-5), 4.16–4.09 (m, 2H; Ha-2, H-6), 3.99 (ddd, ^2J(H,H) = 11.3, ^3J(H,H) = 7.2, ^3J(H,H) = 3.7 Hz, 1H; Hb-2), 3.77–3.73 (m, 2H; H-7, Ha-8,), 3.58 (t, ^2J(H,H) = ^3J(H,H) = 10.2 Hz, 1H; Hb-8), 3.36 (dd, ^3J(H,H) = 8.8, ^3J(H,H) = 6.0 Hz, 1H; H-4a), 2.14–2.09 (m, 1H; Ha-3), 1.82–1.75 ppm (m, 1H, Hb-3); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 164.0 (s; C=O), 150.4 (s; Ar-NO_2), 138.0, 137.8, 137.7 (s; Ar-C), 135.6 (s; Ar-C), 131.0–123.4 (d, 19C; Ar-C), 85.1 (d, 2C; C-6, C-5), 73.5, 72.1, 71.8 (t; Bn-C), 70.3 (d; C-4), 69.2 (d; C-7), 68.0 (d; C-4a), 67.9 (t; C-8), 65.1 (t; C-2), 30.9 ppm (t, C-3); HRMS (ESI): *m*/*z*: calcd for $C_{36}H_{36}N_2O_8+H^+$: 625.2544 [*M*+H$^+$]; found: 625.2519.

(4*R*,4a*R*,5*R*,6*R*,7*R*)-5,6-Bis(benzyloxy)-7-[(benzyloxy)methyl]hexahydro-2*H*-pyrrolo[1,2-b][1,2]oxazin-4-ol (18b): KOH (100 mg, 1.8 mmol) was added to a stirred solution of **21** (28 mg, 0.05 mmol) in THF (5 mL). After 3 h, a TLC control (hexane/AcOEt 2:1) showed the disappearance of the starting material (R_f = 0.54) and the appearance of a new compound (R_f = 0.19). Then, water (5 mL) was added. The mixture was extracted with Et_2O (3×5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/AcOEt 1:2) afforded pure **18b** (15 mg, 0.03 mmol, 71% yield) as a pale-yellow oil. R_f = 0.19 (hexane/AcOEt 2:1); ^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 15H; Ar-H), 4.65 (d, ^2J(H,H) = 11.9 Hz, 1H; Bn-H), 4.59 (m, 2H; Bn-H), 4.54 (m, 2H; Bn-H), 4.46 (d, ^2J(H,H) = 12.2 Hz, 1H; Bn-H), 4.18 (dd, ^3J(H,H) = 8.2, ^3J(H,H) = 3.2 Hz, 1H; H-5), 4.06 (dd, ^3J(H,H) = 3.2, ^3J(H,H) = 2.5 Hz, 1H; H-6), 4.05–4.02 (m, 1H; Ha-2), 3.95–3.91 (m, 1H; H-4), 3.88 (ddd, ^2J(H,H) = 11.5, ^3J(H,H) = 7.2, ^3J(H,H) = 3.8 Hz, 1H; Hb-2), 3.72 (dd, ^2J(H,H) = 11.5, ^3J(H,H) = 4.8 Hz, 1H; Ha-8), 3.68–3.65 (m, 1H; H-7), 3.52 (dd, ^2J(H,H) = 9.3, ^3J(H,H) = 7.7 Hz, 1H; Hb-8), 3.10 (dd, ^3J(H,H) = 8.2, ^3J(H,H) = 6.1 Hz, 1H; H-4a) 1.97–1.92 (m, 1H, Ha-3), 1.59–1.54 ppm (m, 1H, Hb-3); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 138.2, 138.1, 137.9 (s; Ar-C), 128.5–127.6 (d, 15C; Ar-C), 85.5 (d; C-6), 85.0 (d; C-5), 73.5, 72.0, 71.7 (t; Bn-C), 70.3 (d; C-7), 70.1 (d; C-4a), 68.1 (t; C-8), 67.0 (d; C-5), 66.3 (d, C-4), 65.4 (t; C-2), 31.2 ppm (t, C-3); HRMS (ESI): *m*/*z*: calcd for $C_{29}H_{33}NO_5+H^+$: 476.2436 [*M*+H$^+$]; found: 476.2434.

(1*R*,2*R*,3*R*,7*R*,7a*R*)-1,2-Bis(benzyloxy)-3-[(benzyloxy)methyl]hexahydro-1*H*-pyrrolizin-7-ol (23): DIBAL (2 M sol. in toluene, 0.8 mL, 1.6 mmol) was added dropwise at 0°C to a stirred solution of **12** (67 mg, 0.10 mmol) in dry toluene (4 mL) under an argon atmosphere and then the resulting mixture was heated to reflux temperature. The mixture was stirred at reflux temperature for 2 h. TLC analysis (hexane/AcOEt 1:1) showed the disappearance of the starting material (R_f = 0.64) and the appearance of a new product (R_f = 0.00). The mixture was cooled to RT and a saturated aqueous solution of Na_2SO_4 was added (0.42 mL) at 0°C. The mixture was filtered on Celite and evaporated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (AcOEt) afforded pure **23** (24 mg, 0.05 mmol, 52%) as a colorless oil. R_f = 0.50 (AcOEt/MeOH 30:1); $[\alpha]_D^{20}$ = −27 (*c* = 0.33 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 15H; Ar-H), 4.70–4.48 (m, 6H; Bn-H), 4.07 (dd, ^3J(H,H) = 6.9, ^3J(H,H) = 6.2 Hz, 1H; H-2), 3.94 (dt, ^3J-(H,H) = 5.2, ^3J(H,H) = 4.0 Hz, 1H; H-7), 3.78 (t, ^3J(H,H) = 5.9 Hz, 1H; H-1), 3.60–3.56 (m, 2H; Ha,b-8), 3.46 (dd, ^3J(H,H) = 5.9, ^3J(H,H) = 3.5 Hz, 1H; H-7a), 3.15–3.10 (m, 1H; Ha-5), 2.79 (dt, ^3J(H,H) = 7.1, ^3J-(H,H) = 3.6 Hz, 1H; H-3), 2.77–2.72 (m, 1H; Hb-5), 2.00–1.93 (m, 1H; Ha-6), 1.91–1.86 ppm (m, 1H; Hb-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.3, 138.2, 138.1 (s; Ar-C), 128.5–127.8 (d, 12C; Ar-C), 86.4 (d; C-1), 84.1 (d; C-2), 83.4 (d; C-7), 73.3 (d; C-7a), 73.0, 71.9, 71.3 (t; Bn-C), 69.3 (d; C-3), 60.6 (t; C-8), 51.7 (t; C-5), 30.5 (t; C-6), 58.6 ppm (t; C-5); IR (KBr): $\tilde{\nu}$ = 3029, 2922, 2867, 1453, 1361, 1108, 734, 696 cm^{-1}; HRMS

(ESI): *m/z*: calcd for $C_{29}H_{33}NO_4+H^+$: 460.2443 [$M+H^+$]; found: 460.2495.

(1*R*,2*R*,3*R*,7*R*,7a*R*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,7-triol (7-*epi*-australine, 22): Conc. HCl (4–5 drops) and 10% Pd/C (104 mg) were added to a stirred solution of **23** (58 mg, 0.13 mmol) in MeOH (6 mL),. The suspension was stirred under a hydrogen atmosphere overnight, and then filtered through Celite and washed several times with MeOH. Evaporation under reduced pressure afforded a viscous oil that was transferred to a column of DOWEX 50WX8 and then washed with MeOH (20 mL) and H_2O (20 mL) to remove nonamine-containing products and then with 7% NH_4OH (30 mL) to elute 7-*epi*-australine **22**. Evaporation of the solvent under reduced pressure afforded pure **22** (24 mg, 0.13 mmol, quantitative yield) as a yellow solid. M.p. 176–177 °C (dec.); $[\alpha]_D^{20}=-6$ ($c=0.49$ in MeOH), lit. $[\alpha]_D^{23}=-13.0$ ($c=0.55$ in H_2O);[34a] ^{1}H NMR (400 MHz, D_2O): $\delta=4.25$ (dt, $^3J(H,H)=4.6$, $^3J(H,H)=2.6$ Hz, 1H; H-7), 3.69–3.59 (m, 3H; H-1, H-2, Ha-8), 3.53 (dd, $^2J(H,H)=11.7$, $^3J(H,H)=6.3$ Hz, 1H; Hb-8), 3.00 (td, $^2J(H,H)=^3J(H,H)=11.4$, $^3J(H,H)=7.7$ Hz 1H; Ha-5), 2.95 (dd, $^3J(H,H)=7.7$, $^3J(H,H)=1.7$ Hz, 1H; H-7a), 2.80 (ddd, $^2J(H,H)=11.1$, $^3J(H,H)=7.1$, $^3J(H,H)=3.4$ Hz 1H; Hb-5), 2.60 (ddd, $^3J(H,H)=9.2$, $^3J(H,H)=6.2$, $^3J(H,H)=3.7$ Hz,1H; H-3), 2.02–1.93 (m, 1H; Ha-6), 1.71–1.65 ppm (m, 1H; Hb-6); ^{13}C NMR (50 MHz, D_2O): $\delta=77.1$ (d; C-1), 75.5 (d; C-2), 74.4 (d; C-7), 73.9 (d; C-7a), 68.2 (d; C-3), 61.5 (t; C-8), 51.8 (t; C-5), 31.3 ppm (t; C-6); IR (KBr): $\tilde{\nu}=3357$, 3307, 3243, 2912, 1443, 1340, 1316, 1261, 1035, 978, 530 cm^{-1}; HRMS (TOF): *m/z*: calcd for $C_8H_{15}NO_4+H^+$: 190.1074 [$M+H^+$]; found: 190.1087.

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