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Nucleophilic Additions to Cyclic Nitrones en Route to Iminocyclitols – Total Syntheses of DMDP, 6-deoxy-DMDP, DAB-1, CYB-3, Nectrisine, and Radicamine B

Pedro Merino,*[a] Ignacio Delso,[a,b] Tomás Tejero,[a] Francesca Cardona,[b] Marco Marradi,[a,b] Enrico Faggi,[a,b] Camilla Parmeggiani,[a,b] and Andrea Goti*[b]

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Highly diastereoselective nucleophilic additions to cyclic nitrones derived from L-malic acid and D-arabinose have been used for the construction of enantiomerically pure polyhydroxylated pyrrolidines. The synthetic strategy adopted was based on an oxidation/reduction protocol involving hydroxylamine/nitrone pairs and demonstrates the use of reagent- and substrate-derived stereocontrol. In most cases reactions took place with total diastereoselectivity and in quantitative yield, with no purification being necessary. By this strategy, 2-(hydroxymethyl)-, 2-(aminomethyl)-, and 2-aryl-substituted polyhydroxylated pyrrolidines have been prepared with abundant configurational diversity. The use of appropriate substrates and reagents allowed for approaches to DMDP, 6-deoxy-DMDP, DAB-1, CYB-3, nectrisine and radicamine B. Several analogues of these compounds with inverted configuration at one or more stereocenters were also prepared.

Introduction

A great variety of alkaloids possessing polyhydroxylated pyrrolidine structures, otherwise known as iminocyclitols, have been isolated from natural sources, including plants and microorganisms,[1] and many of them are powerful inhibitors of biologically important enzymes such as glycosidases and other enzymes closely associated with the metabolism of *N*-linked glycoproteins.[2] Because of that biological activity, iminocyclitols might constitute powerful tools against cancer,[3] viral infections,[4] or diabetes.[5] Naturally occurring DMDP (**1**), a fairly widespread secondary metabolite first isolated from *Derris elliptica* (Leguminosae)[6] and since then found in microorganisms and plant species of quite unrelated families,[7] together with its unnatural synthetic analogues, are known to be selective inhibitors of glycosidases and have proved to have potential for use as antiviral and anticancer therapeutic drugs, as well as immunomodulators.[8] Such a diverse array of potentially useful activities of DMDP and its analogues make them attractive targets for synthesis.[9] Of particular interest are several deoxy derivatives bearing lipophilic groups instead of the "usual" hydroxymethyl group at their 2-positions, several of which show potent α-L-fucosidase inhibitory activity.[10] Important members of this subclass of compounds are anisomycin, deoxyanisomycin, and analogues.[11]

The biological activities of iminocyclitols are due to the structural similarity of the corresponding protonated compounds under physiological conditions with the flattened half-chair conformation found for the transition structures involved in the mechanism of glycosidases (Figure 1).[12] In the particular case of the *N*-acetyl-β-hexosaminidases, important enzymes involved in osteoarthritis, the participation of the neighboring C-2 acetamido group of the substrate has been suggested.[13] Investigating this hypothesis, Wong and co-workers[14] found that *N*-acetyl-2-(aminomethyl)iminocyclitol **2** and its structural analogues are potent inhibitors of *N*-acetyl-β-hexosaminidases, and hence are expected to have potential as chondrotherapeutic agents.[15] Closely related derivatives of **2** bearing lipophilic aliphatic or aromatic amides attached to C1 have been found to inhibit β-glucosidase in the nanomolar range.[16] Simpler synthetic analogues of **2** are also inhibitors of several glycosidases, as reported by Vogel.[17] Other syntheses of polyhydroxylated 2-(aminomethyl)pyrrolidines have been reported by Jäger[18] and Correia.[19] Several of these compounds have also been used as ligands, forming chelates with a variety of metals including vanadium,[20] gold,[21] zinc,[22] palladium,[23]

[a] Laboratorio de Síntesis Asimétrica, Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Universidad de Zaragoza, CSIC,
50009 Zaragoza, Aragón, Spain
Fax: +34-976-762075
E-mail: pmerino@unizar.es
[b] Dipartimento di Chimica Organica Ugo Schiff and Hetero-BioLab, Università di Firenze, associated with ICCOM-CNR, via della Lastruccia 13, 50019 Sesto Fiorentino (FI), Italy
Fax: +39-055-4573531
E-mail: andrea.goti@unifi.it

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nickel,[24] ruthenium,[25] platinum,[26] rhodium,[27] titanium, and zirconium,[28] that served as catalysts in a variety of enantioselective reactions such as homocoupling of boronic acids[29] and hydrogenation.[30] Platinum complexes of 2-(aminomethyl)pyrrolidines have also been evaluated against several human cancer lines[26b] and their DNA-binding properties have been studied.[26c]

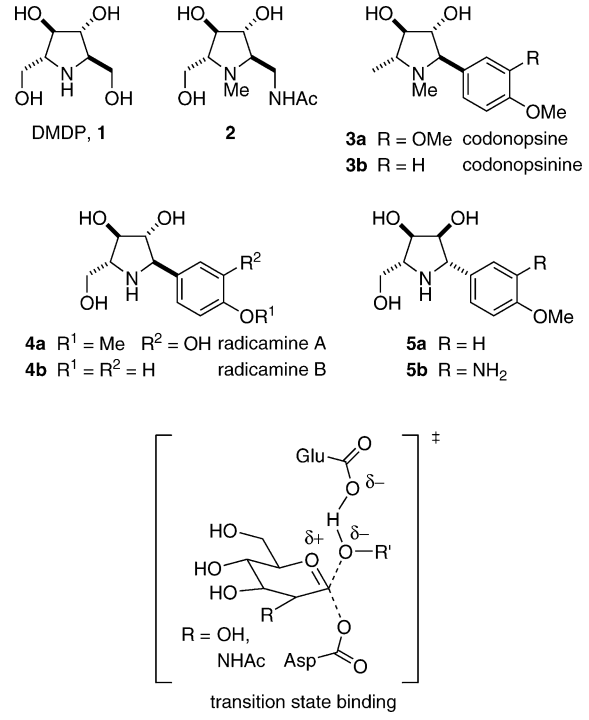


Figure 1. Polyhydroxylated pyrrolidines as inhibitors of glycosidases.

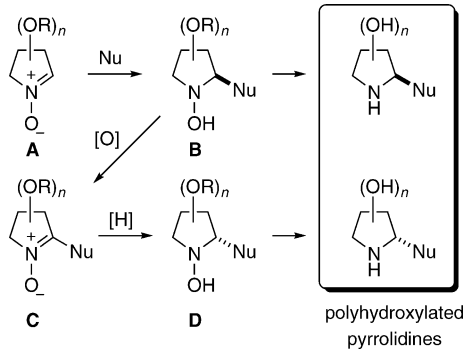
An unusual variety of natural polyhydroxylated pyrrolidines possessing an aromatic ring at C-2 of the pyrrolidine system have recently attracted great attention both from synthetic and from biological points of view. Among these compounds are codonopsine (**3a**) and codonopsinine (**3b**),[31] isolated from *Codonopsis clematidea* and displaying hypotensive activity,[32] the synthesis of the latter having been recently reported by us.[33] Radicamines A (**4a**) and B (**4b**) have been isolated[34] from *Lobelia chinensis*, a plant used in Chinese folk medicine, and syntheses of their enantiomers (as a result of a misassignment of the naturally occurring compounds) have recently been reported.[35] Other 2-aryliminocyclitols such as **5a** and **5b** have been shown to be inhibitors of nucleoside hydrolase and phosphorylase enzymes with inhibition constants in the picomolar range.[36] Several syntheses of these compounds have been reported.[37]

Among the structural variations of five-membered iminocyclitols reported in the literature,[1,2] relatively limited attention has been devoted to the obtainment of structural analogues with different configurations, particularly at C-2 and/or C-5, from common starting materials. Usually, a particular synthesis has been designed for each isomer to be prepared, without addressing possible stereochemical diversity.[38] As a continuation of our interest in the use of nitrones as versatile synthetic intermediates[39] here we describe in detail a concise, efficient, and stereochemically flexible approach to the preparation of a wide variety of polyhydroxylated pyrrolidines. The viability of this strategy was confirmed by the preparation of DMDP and analogues including 6-deoxy-DMDP, DAB-1, CYB-3, and nectrisine, of 2-(aminomethyl)pyrrolidines, and of 2-arylpyrrolidines, including radicamine B.[40]

Results and Discussion

Synthetic Plan

We opted to take advantage of the availability of a variable set of protected hydroxylated cyclic nitrones that can easily be prepared from carbohydrates and other natural sources,[41] thus providing the configuration(s) of one or more stereogenic centers of the pyrrolidine ring as derived from the chiral pool precursor. To obtain the target compounds we adopted the synthetic plan illustrated in Scheme 1, where nitrone **A** serves as electrophile in nucleophilic addition reactions. The additions would be expected to be highly stereoselective, according to our previous experience,[33a] by virtue of the presence of vicinal stereogenic centers that should discriminate between the two faces of the nitrone.



Scheme 1. Synthetic plan.

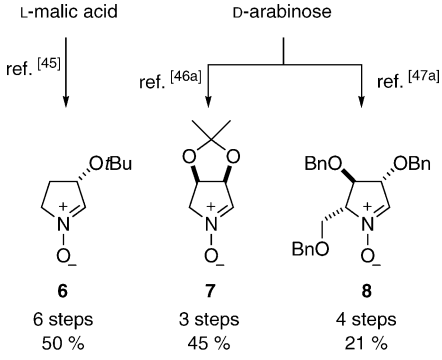
In order to introduce suitable groups we have chosen as nucleophiles hydroxymethyl anion synthetic equivalents,[42] cyanide (as an aminomethyl synthon equivalent),[43] and Grignard reagents.[44] To gain access to other isomers an oxidation/reduction protocol was implemented for the hydroxylamines **B** obtained immediately after the nucleophilic addition step. The route involved oxidation of compounds **B** to nitrones **C**, followed by stereoselective reduction to epimeric hydroxylamine **D**.

Finally, further elaboration of intermediates **B** and **D** would allow the obtention of the target polyhydroxylated pyrrolidines. It should be pointed out that the oxidation of **B** to furnish **C** may allow regioselectivity to be accounted for, since two possible isomers can be formed, it being possible to some extent to predict the major one. This feature, combined with a suitable study on the reduction scheme, gives our approach great flexibility, which should make it

possible to play around with a wide panel of substrates, leading to an abundant variety of configurational combinations.

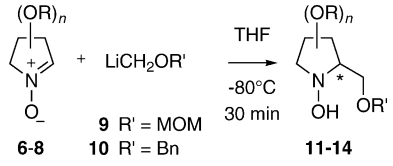
Synthesis of DMDP and Structural Analogues

The starting nitrones **6**–**8** used for this study were prepared from L-malic acid, for nitrone **6**,[45] and from D-arabinose for nitrones **7**[46] and **8**[47] (Scheme 2).



Scheme 2. Synthesis of cyclic nitrones.

Methoxymethyl- and benzyl-protected (hydroxymethyl)-lithium derivatives **9** and **10**, generated in situ from the corresponding tributyltin derivatives as described,[48] were chosen as the synthetic equivalents of the hydroxymethyl anion. The results of the nucleophilic additions of these reagents to nitrones **6**–**8**, illustrated in Scheme 3, are summarized in Table 1.



Scheme 3. Addition of protected hydroxymethyllithium derivatives.

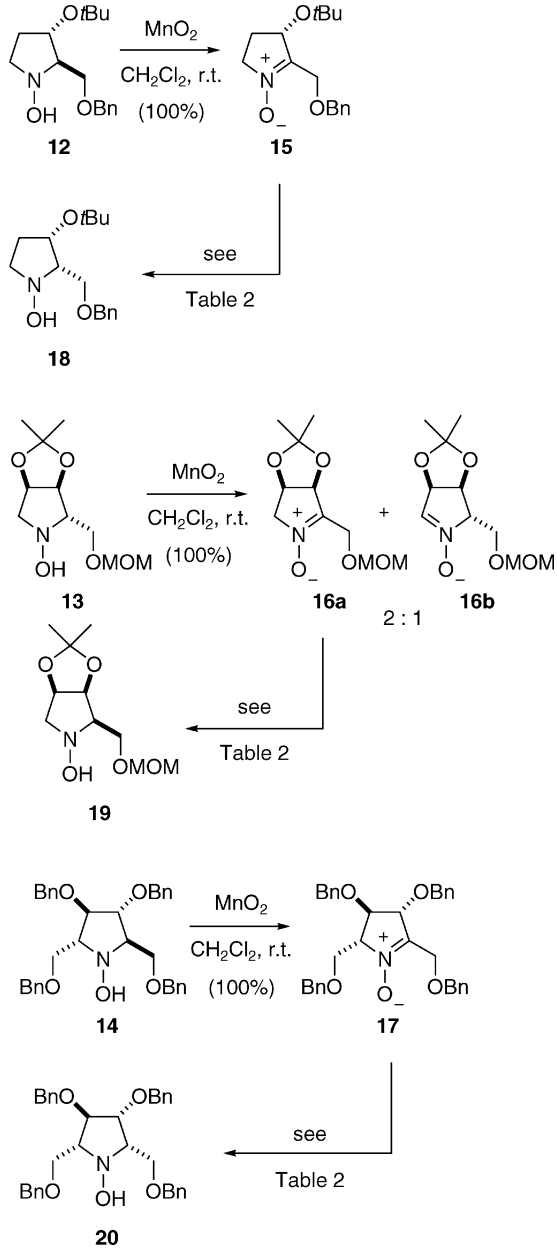
Table 1. Nucleophilic additions of $LiCH_2OR'$ to nitrones **6**–**8**.[a,b]

Entry	Nitrone	R′	Hydroxylamine	*cis*/*trans*[c,d]	% Yield[e]
1	**6**	MOM	**11**	≤5:95	35
2	**6**	Bn	**12**	≤5:95	80
3	**7**	MOM	**13**	≤5:95	70
4	**8**	Bn	**14**	5:95	71

[a] All reactions were carried out in THF at –80 °C. [b] 1.25 equiv. of $LiCH_2OR'$ were used. [c] Measured by ^1H NMR in the crude isolated mixture. [d] With reference to the relative configuration between substituents at C-2 and C-3 of the pyrrolidine ring. [e] Isolated yield after column chromatography.

For nitrones **6** and **7**, the OMOM derivative **9** was to be preferred (Table 1, Entries 1 and 3) in view of the potential for further deprotection in only one step under acidic conditions. For the same reason (simultaneous hydrogenolysis of all benzyl ethers), the OBn reagent **10** was used with nitrone **8**. The addition of **10** to **6** (Table 1, Entry 2) was carried out to provide the corresponding product in a higher yield (see below). In each case the reaction took place smoothly, the only exception being the addition of **9** to **6** (Table 1, Entry 1). Only one diastereoisomer, as detected by 400 MHz ^1H NMR, was obtained in the cases of additions to nitrones **6** and **7** (Table 1, Entries 1–3). Although excellent selectivity was also observed for nitrone **8**, it was possible in this case to identify the minor isomer, which was obtained in 5% yield.[49] This slight decrease in selectivity might arise from the fluxionality of the *O*-benzyl groups, which could, to some extent, interfere with the approach of the nucleophile to the less hindered face.[50]

Contrary to what has been found for acyclic α-alkoxy nitrones,[38c] stereocontrol of the nucleophilic additions to cyclic derivatives cannot be achieved by use of Lewis acids.[39,43a] In order to gain access to C-2 epimers of hydrox-



Scheme 4. Oxidation and reduction of cyclic hydroxylamines.

ylamines **12**–**14** it was then necessary to apply an oxidation (to nitrone) and reduction (to hydroxylamine) sequence, which had been successfully used in our laboratories for the synthesis of substituted prolines.[40,51] The oxidation of hydroxylamine **12** with manganese(IV) oxide[52] took place regioselectively, affording nitrone **15** (Scheme 4). On the other hand, the oxidation of hydroxylamine **13** showed lower regioselectivity, furnishing a 2:1 mixture of nitrones **16a** and **16b** (Scheme 4). Because of its C_2 symmetry, no regioselectivity issue applied for the oxidation of hydroxylamine **14**, which afforded nitrone **17** quantitatively. All oxidations were found to be clean and quantitative, no purification of the obtained nitrones being necessary after conventional workup.

The observed regioselectivity was in agreement with the model previously proposed by some of us.[45a,53] According to this model, the oxidation should occur preferentially at the side where a β-alkoxy group (to nitrogen) is present and if the α-hydrogen atom to be abstracted can be oriented in an antiperiplanar disposition with respect to the β-alkoxy group. This orientation allows an electron-donating hyperconjugative effect ($\sigma_{C-H} \rightarrow \sigma^*_{C-O}$) responsible for favoring the abstraction of the corresponding proton in the oxidation process. Thus, the oxidation of hydroxylamine **12** took place only on the side where two β-alkoxy groups are present.

For hydroxylamine **13**, a proton at both C-2 and C-5 can be accommodated antiperiplanar to a β-alkoxy substituent (Figure 2). The preferential formation of **16a** is due to the presence of an additional α-alkoxy group at the C-2 exocyclic chain, which can be more easily oriented into the appropriate conformation with 2-H than 5-$H_{antiperiplanar}$ with the α-alkoxy group at C-4.[54] The obtainment of **16a** as the major regioisomer may also result from the generally preferred formation of the more substituted ketonitrone with respect to its regioisomeric aldonitrone when hydroxylamines with different degrees of substitution at C-α and C-α′ are oxidized.[55]

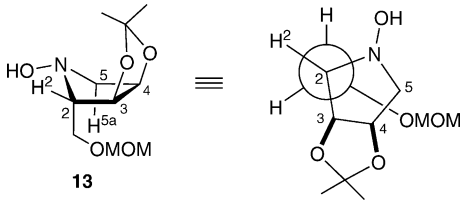


Figure 2. Antiperiplanar 2-H/OMOM conformation in **13**.

The reduction of nitrones **15**, **16a**, and **17** (Scheme 4) was carried out with sodium borohydride and L-selectride as listed in Table 2. In each case the reaction was quantitative, showing excellent diastereoselectivity.

Both sodium borohydride in methanol at 0 °C (Table 2, Entries 1 and 3) and L-selectride in THF at –80 °C (Table 2, Entries 2, 4, and 6) gave only one isomer, the only exception being the reduction of **17** with $NaBH_4$ (Table 2, Entry 5). In this case, attempts to increase the selectivity by lowering the temperature resulted in no reaction. Fortunately, the reduction with L-selectride was found to be completely selective towards the expected isomer. The absolute configurations of the newly created stereogenic centers in hydroxylamines **12**–**14** and **18**–**20** were unambiguously ascertained by 1D NOE and 2D NOESY and COSY NMR experiments, which unequivocally showed the expected interactions between the protons of the pyrrolidine ring. For compound **14** both the ^1H and ^{13}C spectra only showed signals consistent with the presence of a symmetry plane in the molecule.

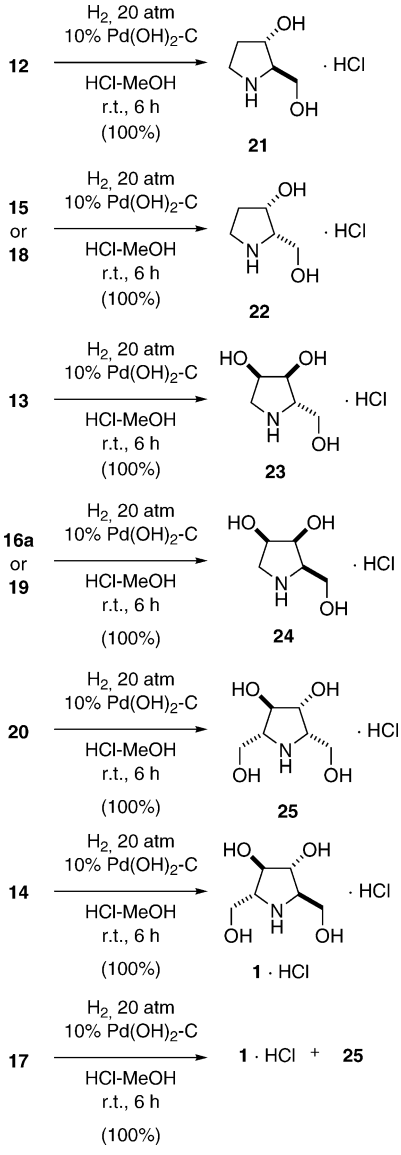
Table 2. Reduction of nitrones **15**, **16a**, and **17**.

Entry	Nitrone	Hydride[a]	*cis*/*trans*[b,c]	% Yield
1	**15**	$NaBH_4$	≥95:5[e]	100
2	**15**	L-selectride	≥95:5[e]	100
3	**16a**	$NaBH_4$	≥95:5[f]	66[d]
4	**16a**	L-selectride	≥95:5[f]	66[d]
5	**17**	$NaBH_4$	57:43[g]	100
6	**17**	L-selectride	≥95:5[g]	100

[a] $NaBH_4$/MeOH 2 h, 0 °C; L-selectride: THF, –80 °C, 14 h. [b] Measured by ^1H NMR in the crude isolated mixture. [c] With reference to the relative configuration between substituents at C-2 and C-3 in the pyrrolidine ring. [d] Isolated yield after column chromatography. [e] With reference to **18**:**12**. [f] With reference to **19**:**13**. [g] With reference to **20**:**14**.

The target polyhydroxylated pyrrolidines were finally obtained by concomitant reduction and deprotection of the precursor hydroxylamines. Compounds **12**–**14** and **18**–**20** were subjected to hydrogenolysis under hydrogen (20 atm) in concd. HCl/methanol and in the presence of Pearlman's catalyst (10%) to give the corresponding hydrochlorides in nearly quantitative yields. Thus, the hydrochloride of CYB-3 **21**[56] and its C-2 epimer **22**[56,57] were obtained in 80% overall yield from nitrone **6**. Hydrochlorides **23**[58] and **24**[58] were obtained in 70% overall yield from nitrone **7**, and the hydrochloride of DMDP **1**·HCl[9] and its C-2 epimer **25**[59] were obtained from nitrone **8** in 71% overall yield (Scheme 5).

The complete deprotection and reduction of **14** allowed, as in the other cases, an easy manipulation of the final compound as the corresponding hydrochloride **1**·HCl, which proved to be stable at 25 °C for months without appreciable decomposition. Nevertheless, in order to compare the spectroscopic and physical properties of DMDP with those reported in the literature, the obtained hydrochloride was also characterized as the free base after deposition onto a DOWEX 50W8–200 exchange resin and elution with NH_4OH in MeOH (3 N). Since there has been some controversy about the presence of hydrochloride salts and free bases with other isomers,[60] it is worth pointing out that a trivial analysis of the ^1H NMR showed more deshielded signals for the hydrochlorides than for the free bases. In addition, the typical signal corresponding to ammonium species is seen at 7–8 ppm in the spectrum of **1**·HCl (as a consequence of the high symmetry around the nitrogen atom), thus unequivocally confirming the presence of the hydrochloride salt. Also, the elemental analyses fully agree with both hydrochloride and free salt. The analytical and

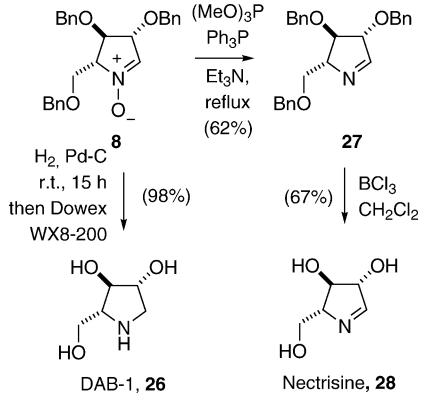


Scheme 5. Hydrogenation/deprotection of protected hydroxylamines.

spectroscopic data of **1** were in agreement, the NMR spectroscopic data being an exact match with those previously reported.[61]

It was also found that direct treatment of nitrones **15** and **16a** under the same hydrogenolytic conditions gave pyrrolidines **22** and **24**, respectively, also in quantitative yields (Scheme 5). Overall, it was found that the direct hydrogenation of ketonitrones was the more efficient route, providing **22** and **24** in overall yields of 80% and 70%, respectively, in three steps from the starting nitrones **6** and **7**. The hydrogenation of nitrone **17** was less selective, however, probably because of the presence of the benzyloxy group at C-4, affording a mixture of **1**·HCl and **25**, which were formed in 32% and 68% yields, respectively.

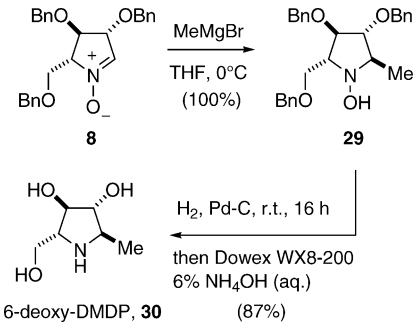
Nitrone **8** is also itself a direct precursor of polyhydroxylated pyrrolidines of interest. DAB-1 **26**, a potent inhibitor of α-glucosidases, α-D-arabinosidase, β-glucosidase, and α-mannosidase, isolated from *Angylocalyx* sp. (Leguminosae),[62,63] was obtained in high yield (86%) by direct hydrogenation of nitrone **8** with Pd/C in HCl/MeOH (Scheme 6).



Scheme 6. Syntheses of DAB-1 and nectrisine.

Nectrisine (**28**, also known as FR-900483), isolated from the fungus *Nectria lucida* F-4490 (Ascomycetes),[64] is an inhibitor of glucosidase and mannosidase, also possessing immunostimulating properties. Deoxygenation of nitrone **8** to provide imine **27** was achieved by a modification of a reported procedure.[65] Only the addition of triphenylphosphane (10 mol-%) to trimethylphosphite in triethylamine allowed **27**[66] to be afforded in good yield. Debenzylation of **27** with BCl_3,[66] in order to preserve the imine functionality, gave nectrisine **28**, which was found to be unstable in D_2O solution,[67] affording hydrated derivatives. On the other hand, ^{13}C NMR spectroscopic data of the crude compound were in agreement with those reported in the literature.[68]

The synthesis of 6-deoxy-DMDP (**30**), an inhibitor of β-mannosidase, β-galactosidase, and α-fucosidase isolated from *Angylocalyx* sp. (Leguminosae),[69] was achieved through quantitative and complete stereoselective addition of methylmagnesium bromide to nitrone **8** (Scheme 7). As expected, the Grignard reagent reacted with the cyclic nitrone at the less hindered face, opposite the C-3 OBn substituent, to afford hydroxylamine **29** quantitatively. Hydrogenation of **29** with Pd/C (10%) in HCl/MeOH, followed

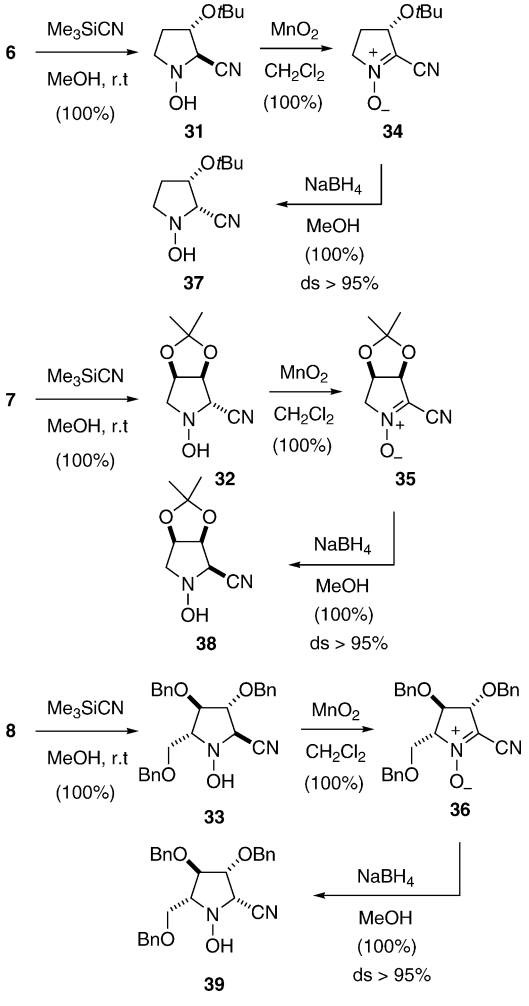


Scheme 7. Synthesis of 6-deoxy-DMDP.

by elution through DOWEX WX8–200 with ammonium hydroxide (6%), furnished the free amine **30** in 87% overall yield over two steps.

Synthesis of 2-(Aminomethyl)pyrrolidines

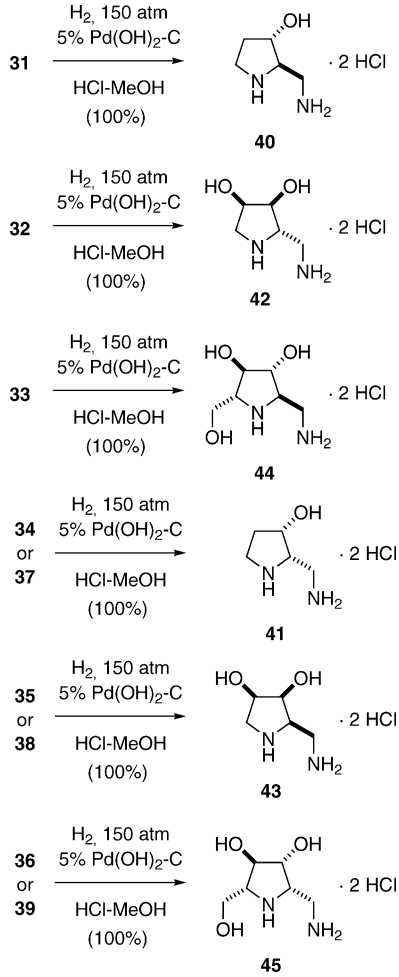
Nitrones **6**–**8** were converted into the corresponding α-cyano hydroxylamines **31**–**33** by treatment with trimethylsilyl cyanide in methanol (Scheme 8). In our previous study on hydrocyanation of cyclic nitrones,[43a] we described the reaction in dichloromethane as a solvent, providing the corresponding *O*-(trimethylsilyl) derivatives. Under these conditions an activating agent was needed,[43a,70] as well as an additional desilylation step also being necessary.[71] We have now improved the process: in methanol as solvent, trimethylsilyl cyanide was slowly converted in situ into HCN,[72] which reacted smoothly with nitrones, no additive being necessary,[73] to provide the free hydroxylamine in a single step.



Scheme 8. Synthesis of 2-cyano-*N*-hydroxypyrrolidines.

All the reactions took place with quantitative yields, and with no purification of the obtained free hydroxylamines being necessary. The selectivity of each reaction was complete, and only the isomer showing a *trans* disposition to the C-3 substituent could be detected by ^{1}H NMR (Scheme 8). Since attempts to invert the stereocontrol in the hydrocyanation of nitrones had been unsuccessful,[43a] we focused our attention on the oxidation/reduction protocol described above to obtain epimeric hydroxylamines at C-2. This was accomplished by oxidation of **31**–**33** to nitrones **34**–**36** with manganese(IV) oxide[52] as described above, followed by stereoselective reduction with sodium borohydride. The oxidation and reduction were found to be completely regio- and stereoselective, respectively. Presumably, the regioselectivity of the reaction was controlled by conjugation of the incipient nitrone functionality with the cyanide moiety, so that the oxidation was directed solely towards the cyanide side. The relative stereochemistry of all pyrrolidine substituents in **31**–**33**[43a] and **37**–**39**, and thus the absolute configurations of the new stereogenic centers, was confirmed by 2D NMR (NOESY and COSY) experiments and X-ray analysis in the case of **32**.[43a]

It was next attempted to apply the palladium-catalyzed hydrogenation/deprotection methodology used for the synthesis of **1** and **21**–**25** in Scheme 5 to the synthesis of 2-(aminomethyl)pyrrolidines. When compounds **31**–**33** and **37**–**39** were subjected to hydrogenolysis under hydrogen (150 bar) in HCl in MeOH (1 N), the corresponding dihy-



Scheme 9. Synthesis of 2-(aminomethyl)pyrrolidines.

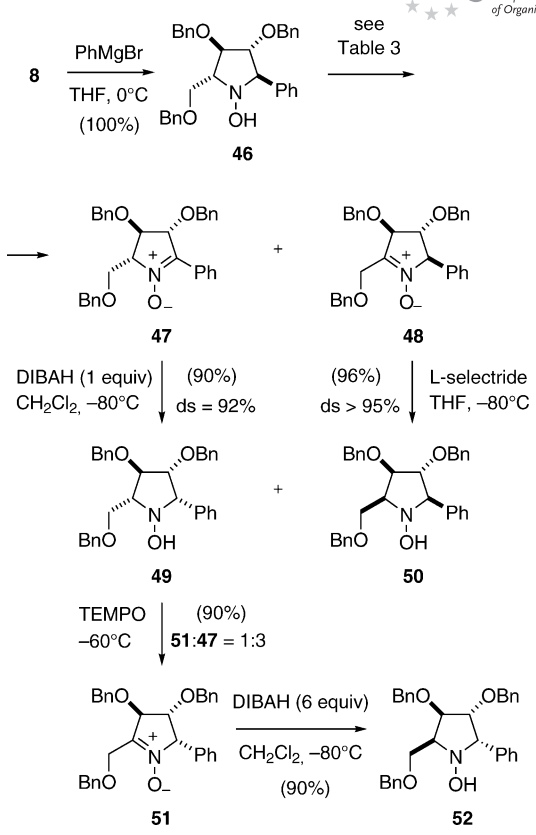
drochlorides **40**–**41**, **42**–**43**,[39a] **44**, and **45** were obtained in quantitative yield (Scheme 9). Similar results were obtained when a more direct approach to **41**, **43**, and **45** was attempted. Catalytic hydrogenation, under the above conditions, of nitrones **34**–**36** afforded the target compounds in quantitative yield and with complete stereoselectivity as determined by 400 MHz ^{1}H NMR spectroscopy. Overall, it is worth noting that all the processes described above and relating to the synthesis of 2-(aminomethyl)pyrrolidines **40**–**45** from nitrones **6**–**8** are clean and quantitative, both the intermediates and the final iminocyclitols being obtained analytically pure (as demonstrated by their spectra and elemental analyses) from crude reaction mixtures without any need for separation or purification.

Synthesis of 2-Aryl-substituted Polyhydroxylated Pyrrolidines

These compounds are a unique subset of iminocyclitols possessing four contiguous stereogenic centers, with the presence of an aryl group adjacent to the nitrogen atom (C-2) distinguishing this group from the larger class of polyhydroxylated pyrrolidines. In light of the above features, we turned our attention to the construction, in a stereoselective fashion starting from nitrone **8**, of all possible 2-phenyl-substituted polyhydroxylated pyrrolidines with different configurations at C-2 and C-5. According to the synthetic plan outlined in Scheme 1, the most evident approach was the addition of the corresponding aryl Grignard reagents.[74]

The nucleophilic addition of phenylmagnesium bromide to **8** gave the expected all-*trans* hydroxylamine **46** with complete selectivity and in quantitative yield (Scheme 10). We next tried oxidation of **46** to apply the protocol for inverting configuration at C-2. The oxidation of **46** with activated manganese(IV) oxide[52] as described above afforded regioisomeric nitrones **47** and **48** in a 1:1.4 ratio. Presumably, this lack of regioselectivity is due to the presence of the phenyl group, which favored, to an appreciable extent and through a conjugative effect, the formation of nitrone **47**, in spite of the absence of a proton at C-2 to be positioned antiperiplanar with respect to the C-3 benzyloxy substituent. Thus, the virtual lack of selectivity was the result of contrasting effects of the C-2 phenyl group (conjugation) and the C-5 benzyloxymethyl group (hyperconjugative effect to antiperiplanar 2-H), favoring the formation of **47** and **48**, respectively. An investigation of other oxidants was then undertaken in an effort to improve the regioselectivity of the oxidation. The results of this study are summarized in Table 3.

Evidence of thermodynamic control[75] of the oxidation reaction was provided when the process was performed at different temperatures. While at low temperature a more selective reaction was found (Table 3, Entries 1–4), on carrying out the oxidation at 80 °C a complete lack of selectivity was observed (Table 3, Entry 5). Similar results, although with slight differences, were obtained with mercury(II) oxide as the oxidant (Table 3, Entries 6 and 7). We therefore decided to check other typical oxidants employed in the synthesis of nitrones[40a] at 0 °C; lower temperatures usually led to poor conversions and low chemical yields. Oxidation with potassium permanganate[76] (Table 3, Entry 9) and *tert*-butyl hydroperoxide[77] (Table 3, Entry 10) afforded results similar to those obtained with MnO_2, showing a slight preference for regioisomer **48**. Increased regioselectivity ratios were found with urea/hydrogen peroxide complex[78] in the presence of a catalytic amount of sodium tungstate[79] (Table 3, Entry 11) and oxone (Table 3, Entry 12).



Scheme 10. Synthesis of protected 1-hydroxy-2-phenylpyrrolidines.

Table 3. Regioselective oxidation of hydroxylamine **46**.

Entry	Oxidant	*T* [°C]	*t* [h]	**48/47** ratio[a]	% Yield[b]
1	MnO_2	25	0.5	1.4	100
2	MnO_2	0	0.5	1.7	100
3	MnO_2	–20	24	2.6	100
4	MnO_2	–60	24	2.7	70
5	MnO_2	80	0.5	1.0	90
6	HgO	0	25	1.3	100
7	HgO	80	0.5	1.2	100
8	PDC	0	0.5	1.4	90
9	$KMnO_4$	0	0.5	1.8	100
10	TBHP	0	1	1.7	100
11	UHP[c]	0	24	2.6	40
12	Oxone	0	24	3.8	100
13	TEMPO	–60	3	6.7	100

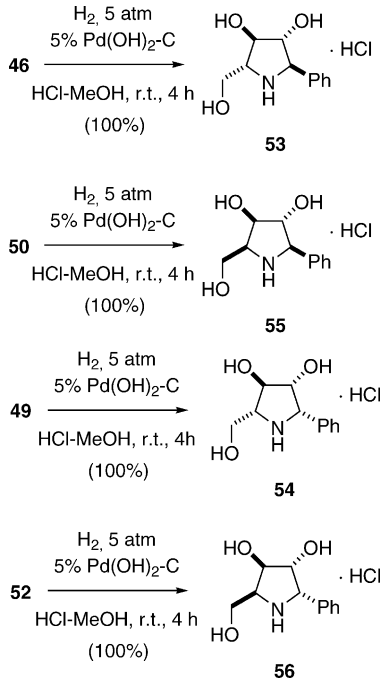
[a] Measured by ^{1}H NMR in the crude isolated mixture. [b] Isolated yield after column chromatography. [c] UHP: urea hydroperoxide complex used in the presence of a catalytic amount of $Na_2WO_4{\cdot}H_2O$.

The best result was obtained with TEMPO in dichloromethane as a solvent (Table 3, Entry 13), which gave rise to a 1:6.7 ratio of isomers **47** and **48**. After separation by MPLC, both nitrones **47** and **48** were subjected to reduction in order to obtain the corresponding hydroxylamines. The reduction of **47** was more difficult than expected, with the compound proving resistant to attack by both sodium borohydride and lithium aluminium hydride even at room temperature after 4 h, and only unchanged starting material was recovered from the reaction. It thus appeared that the C-2 phenyl group made the nitrone carbon of **47** simply too sterically hindered and/or weakly electrophilic to react with nucleophiles. However, upon treatment with a coordinating reducing agent such as DIBAH, nitrone **47** did react, providing a 92:8 mixture of hydroxylamines **49** and **46**. After chromatographic purification compound **49** was obtained in 81% isolated yield. On the other hand, the reduction of **48** with sodium borohydride afforded an almost equimolar mixture of hydroxylamines **50** and **46**. A rather more selective reduction was achieved with L-selectride at –80 °C, which furnished **50** in 96% yield and as a single diastereomer as observed by 400 MHz ^{1}H NMR spectroscopy.

In order to gain access to the last diastereomeric hydroxylamine (involving the configurations at C-2 and C-5), the regioselective oxidation at C-5 of **49** was now required. This was accomplished in 90% yield with TEMPO at –60 °C, which was selected as the oxidant of choice on the basis of the results reported in Table 3 for the oxidation of **46**. Under these conditions, nitrones **51** and **47** were obtained in 1:3 ratio. The lower regioselectivity ratio with respect to the oxidation of **46** was expected, in view of the fact that 2-H in **49** can be accommodated in an antiperiplanar fashion to the vicinal benzyloxy group. Surprisingly, reduction of **51** with L-selectride at –80 °C afforded hydroxylamine **49** as the only product of the reaction, thus providing evidence of an opposite steric preference with respect to nitrone **48**, the only structural difference being the configuration of the *N*-hydroxy pyrrolidine ring at C-2. After several attempts we found that the reduction of **51** with an excess of coordinating DIBAH (6 equiv.) provided **52** in 81% isolated yield and with complete diastereofacial selectivity (single diastereoisomer by 400 MHz ^{1}H NMR). The observed difference in selectivity between L-selectride and DIBAH can be interpreted in terms of the hydride delivery. Whereas reduction with L-selectride would be expected to proceed at the less hindered face through external delivery of the hydride, reduction with excess of a coordinating reagent such as DIBAH could invert the selectivity through coordination of the reagent by the less hindered face and a further external delivery of hydride from a second molecule of reagent by the opposite face.[80]

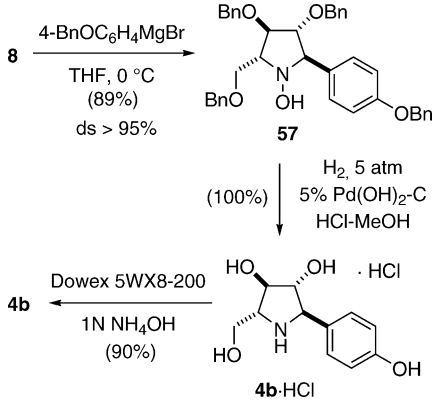
The absolute configurations of hydroxylamines **46**, **49**, **50**, and **52** were confirmed by 2D NOESY and COSY NMR experiments. All the observed signal enhancements (and their absence) were consistent with the configurations depicted in Scheme 10.

The diastereomeric hydroxylamines **46**, **49**, **50**, and **52** having been synthesized, the next transformations required were their reduction and complete deprotection. These were each accomplished in one step to afford 2-phenylpyrrolidine hydrochlorides **53**–**56** in quantitative yield, in all cases, by catalytic hydrogenation (Scheme 11).[81]



Scheme 11. Synthesis of 2-phenyl-substituted polyhydroxylated pyrrolidines.

With nitrone **8** to hand and the above strategy assessed, it was necessary to prepare the required Grignard reagent in order to synthesize radicamine B. A previous synthesis of the enantiomer of this compound by the same strategy has been reported very recently.[35] Nitrone **8** was thus transformed into hydroxylamine **57** by treatment with 4-benzyloxyphenylmagnesium bromide[82] (Scheme 12).



Scheme 12. Synthesis of radicamine B.

Consistently with the addition of phenylmagnesium bromide described above, the reaction showed complete diastereofacial selectivity, affording the all-*trans* compound **57**. This configuration was also established by 2D NMR experiments (NOESY and COSY). Finally, natural radicamine B was obtained by catalytic hydrogenolysis to provide its pure

hydrochloride **4b**·HCl, isolated in quantitative yield (Scheme 12). In order to allow comparisons with the literature data, this compound was deposited onto a DOWEX W8–200 exchange resin column and eluted with NH_4OH (1 N) to afford **4b** as the free base, which showed physical and spectroscopic data identical to those reported for the natural compound[34] and for the enantiomer,[35] in this case with the exception of the opposite sign of optical rotation.

Conclusions

The diastereoselective synthetic methodology reported above has allowed the preparation of several families of polyhydroxylated pyrrolidines and their variants with great versatility. The complete diastereoselectivity found in nucleophilic additions to cyclic nitrones and the possibility of configurational inversion at the newly created stereocenter, through an oxidation/reduction protocol, makes this methodology complementary to other Lewis-acid-tunable nucleophilic additions to acyclic nitrones. The approach was used to synthesize several 2-(hydroxymethyl)-, 2-(aminomethyl)-, and 2-aryl-substituted polyhydroxylated pyrrolidines enantiospecifically, offering a new route to such systems competing with previously reported strategies. Finally, the work provided access to the naturally occurring alkaloids DMDP, 6-deoxy-DMDP, DAB-1, CYB-3, nectrisine and radicamine B, as well as to several structural analogues. The total synthesis of other natural polyhydroxylated pyrrolidines and analogues by this methodology is under investigation in our laboratories.

Experimental Section

General Methods: The reaction flasks and other glass equipment were heated overnight in an oven at 130 °C and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the positions of the spots were detected with UV light (254 nm) or by spraying with one of the following staining systems: methanolic sulfuric acid (50%), ethanolic phosphomolybdic acid (5%), or iodine. Preparative centrifugally accelerated radial thin-layer chromatography (radial chromatography) was performed with a Chromatotron® Model 7924 T (Harrison Research, Palo Alto, CA, USA) and with solvents that were distilled prior to use; the rotors (1 or 2 mm layer thickness) were coated with silica gel Merck grade type 7749, TLC grade, with binder and fluorescence indicator (Aldrich 34,644–6) and the eluting solvents were delivered by the pump at a flow-rate of 0.5–1.5 mL min^{-1}. Column chromatography was carried out in a Büchi 800 MPLC system with silica gel SDS 60 microns. Melting points were uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 400 or 500 instruments or on a Varian Mercury 400 in the stated solvent. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ (δ = 7.26 ppm) in $CDCl_3$. Optical rotations were measured on a Perkin–Elmer 241 polarimeter or on a JASCO DIP-370 polarimeter. Elemental analysis were performed on a Perkin–Elmer 240B microanalyzer or with a Perkin–Elmer 2400 instrument.

(2*R*,3*S*)-3-(*tert*-Butoxy)-1-hydroxy-2-[(methoxymethoxy)methyl]pyrrolidine (11): Butyllithium (3.2 mL of a 1.6 M solution in hexanes, 2 mmol) was slowly added by syringe under argon to a cooled (–80 °C) solution of the stannane derivative of **9** (0.760 g, 2 mmol) in anhydrous THF (15 mL). The resulting solution was stirred for 6 min, at which point a cooled (–80 °C) solution of **6** (0.126 g, 0.8 mmol) in THF (5 mL) was added over a period of 5 min by cannula. After 15 min at –80 °C the reaction was quenched with satd. aq. NH_4Cl (1 mL) and the reaction mixture was allowed to warm to room temperature. The reaction mixture was treated with additional satd. aq. NH_4Cl (20 mL) and diethyl ether (30 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a crude product, which was purified by radial chromatography (hexane/EtOAc, 2:1). (65.4 mg, 35%); oil. $[a]_D^{25}$ = +53 (*c* = 0.23, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 [s, 9 H, C(CH_3)$_3$], 1.61–1.78 (m, 1 H, 4-H_a, 1.93–2.18 (m, 1 H, 4-H_b), 3.03 (q, *J* = 9.5 Hz, 1 H, 2-H), 3.23 (dt, *J* = 10.3, 2.2 Hz, 1 H, 5-H_a), 3.36 (s, 3 H, OCH$_2$OCH_3), 3.69 (dd, *J* = 10.3, 5.1 Hz, 1 H, CH_2OMOM), 3.79 (dd, *J* = 10.3, 2.9 Hz, 1 H, 5-H_b), 3.97 (dq, *J* = 8.1, 3.7 Hz, 1 H, 3-H), 4.65 (s, 2 H, OCH_2OCH$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 [*C*(CH$_3$)$_3$], 31.3 (C-4), 55.4 (OCH$_2$O*C*H$_3$), 56.5 (C-5), 65.2 (C-2), 69.6 (*C*H$_2$OMOM), 73.6 (C-3), 73.8 [C(*C*H$_3$)$_3$], 97.0 (O*C*H$_2$OCH$_3$) ppm. $C_{11}H_{23}NO_4$ (233.26): calcd. C 56.63, H 9.94, N 6.00; found C 56.49, H 10.05, N 5.89.

(2*R*,3*S*)-2-(Benzyloxymethyl)-3-(*tert*-butoxy)-1-hydroxypyrrolidine (12): Butyllithium (3.2 mL of a 1.6 M solution in hexanes, 2 mmol) was slowly added by syringe under argon to a cooled (–80 °C) solution of the stannane derivative of **10** (0.850 g, 2 mmol) in anhydrous THF (15 mL). The resulting solution was stirred for 6 min, at which point a cooled (–80 °C) solution of **6** (0.126 g, 0.8 mmol) in THF (5 mL) was added by cannula over a period of 5 min. After 15 min at –80 °C the reaction was quenched with satd. aq. NH_4Cl (1 mL) and the reaction mixture was allowed to warm to room temperature. The reaction mixture was treated with additional satd. aq. NH_4Cl (20 mL) and diethyl ether (30 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a crude product, which was purified by radial chromatography (hexane/EtOAc, 2:1). 0.178 g, 80%; oil. $[a]_D^{25}$ = +34 (*c* = 1.06, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 [s, 9 H, C(CH_3)$_3$], 1.61 (dddd, *J* = 12.9, 9.0, 3.2, 2.5 Hz, 1 H, 4-H_a), 1.89–2.03 (m, 1 H, 4-H_a), 2.72–2.79 (m, 1 H, 2-H), 2.93 (c, *J* = 9.6 Hz, 1 H, 5-H_a), 3.18 (ddd, *J* = 9.6, 8.0, 2.3 Hz, 1 H, 5-H_b), 3.51 (dd, *J* = 9.9, 4.3 Hz, 1 H, CH_2OBn), 3.63 (*J* = 10.0, 3.1 Hz, 1 H, CH_2OBn), 3.92 (ddd, *J* = 8.3, 7.3, 3.7 Hz, 1 H, 3-H), 4.41 (d, *J* = 11.9 Hz, 1 H, CH_2Ph), 4.52 (d, *J* = 11.9 Hz, 1 H, CH_2Ph), 7.17–7.32 (m, 15 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 [C(*C*H$_3$)$_3$], 31.3 (C-4), 56.6 (C-4), 67.3 (*C*H$_2$OBn), 69.6 (C-3), 73.4 (*C*H$_2$Ph), 73.5 (C-2), 73.8 [*C*(CH$_3$)$_3$], 127.7 (Ar), 128.1 (Ar), 128.3 (Ar), 138.1 (Ar) ppm. $C_{16}H_{25}NO_3$ (279.34): calcd. C 68.79, H 9.02, N 5.01; found C 68.84, H 9.27, N 4.86.

(2*S*,3*S*,4*R*)-1-Hydroxy-3,4-(isopropylidenedioxy)-2-[(methoxymethyloxy)methyl]pyrrolidine (13): Treatment of a solution of the stannane derivative of **9** (0.760 g, 2 mmol) with nitrone **7** (0.126 g, 0.8 mmol), as described above for nitrone **6** to give **11**, afforded pure **13** (0.131 g, 70%) as an oil. $[a]_D^{25}$ = –9 (*c* = 0.695, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 [s, 3 H, C(CH_3)$_2$], 1.54 [s, 3 H, C(CH_3)$_2$], 3.18 (dd, *J* = 11.0, 3.9 Hz, 1 H, 5-H_a), 3.32 (q, *J* = 4.5 Hz, 1 H, 2-H), 3.40 (s, 3 H, OCH$_2$OCH_3), 3.55 (dd, *J* = 11.0, 5.7 Hz, 1 H, 5-H_a), 3.76 (dd, *J* = 10.3, 4.5 Hz, 1 H, CH_2OMOM), 3.83 (dd, *J* = 10.3, 4.5 Hz, 1 H, CH_2OMOM), 4.58 (dd, *J* = 6.7, 4.5 Hz, 1 H, 3-H), 4.67 (s, 2 H, OCH_2OCH$_3$), 4.73–4.65 (m, 1 H, 4-H), 6.35 (br. s, 1 H, NO*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 4.6 [C(CH_3)$_2$], 26.9 [C(CH_3)$_2$], 55.4 (OCH$_2$OCH_3), 63.1 (C-5), 65.4 (CH_2OMOM), 71.7 (C-2), 77.3 (C-4), 80.2 (C-3), 96.8 (OCH_2OCH$_3$), 112.8 [C(CH$_3$)$_2$] ppm. $C_{10}H_{19}NO_5$ (233.21): calcd. C 51.49, H 7.21, N 6.00; found C 51.66, H 8.39, N 5.90.

(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-2,5-bis(benzyloxymethyl)-1-hydroxypyrrolidine (14): Treatment of a solution of the stannane derivative of **10** (0.850 g, 2 mmol) with nitrone **8** (0.334 g, 0.8 mmol), as described above for nitrone **6** to give **12**, afforded pure **14** (0.306 g, 71%); oil. $[\alpha]_D^{25}$ = +21 (c = 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (m, 2 H, 2-H), 3.63 (dd, J = 9.6, 6.2 Hz, 2 H, CH_2OBn), 3.78 (dd, J = 9.6, 4.8 Hz, 2 H, CH_2OBn), 4.00 (dd, J = 3.7, 1.5 Hz, 2 H, 3-H), 4.43 (d, J = 11.8 Hz, 2 H, CH_2Ph), 4.49 (d, J = 11.8 Hz, 2 H, CH_2Ph), 4.50 (d, J = 12.1 Hz, 2 H, CH_2Ph), 4.54 (d, J = 12.1 Hz, 2 H, CH_2Ph), 6.04 (s, 1 H, OH), 7.34–7.20 (m, 20 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.6 (CH_2OBn), 64.4 (C-2), 66.5 (CH_2Ph), 68.2 (CH_2Ph), 78.6 (C-3), 122.4 (Ar), 122.6 (Ar), 123.2 (Ar), 132.9 (Ar), 133.0 (Ar) ppm. $C_{34}H_{37}NO_5$ (539.59): calcd. C 75.67, H 6.91, N 2.60; found C 75.52, H 6.83, N 2.87.

(*S*)-5-(Benzyloxymethyl)-4-*tert*-butoxy-3,4-dihydro-2*H*-pyrrole 1-Oxide (15): Activated manganese(IV) oxide (2.09 g, 2.4 mmol) was added portionwise to a cooled (0 °C) solution of **12** (0.56 g, 2 mmol) in CH_2Cl_2 (30 mL). After 15 min of stirring at 0 °C the reaction mixture was allowed to warm to room temperature and stirring was continued until complete disappearance of the starting material (TLC, ca. 2 h). The reaction mixture was then filtered through a pad of Celite and anhydrous $MgSO_4$, and the resulting filtrate was evaporated under reduced pressure to give **15** (0.554 g, 100%), which did not need further purification; oil. $[\alpha]_D^{25}$ = –78, (c 1.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 [s, 9 H, C(CH_3)$_3$], 1.84 (dddd, J = 12.2, 8.7, 4.9, 3.0 Hz, 1 H, 3-H$_a$), 2.23 (dddd, J = 13.7, 9.2, 7.7, 6.2 Hz, 1 H, 3-H$_b$), 3.72 (ddd, J = 13.8, 9.3, 4.9 Hz, 1 H, 2-H$_a$), 3.96–4.05 (m, 1 H, 2-H$_b$), 4.07 (d, J = 12.7 Hz, 1 H, CH_2OBn), 4.45 (d, J = 11.7 Hz, 1 H, CH_2Ph), 4.52 (d, J = 11.7 Hz, 1 H, CH_2Ph), 4.60 (d, J = 12.7 Hz, 1 H, CH_2OBn), 4.76 (d, J = 7.4 Hz, 1 H, 4-H), 7.25 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2 [C(CH_3)$_3$], 28.5 (C-3), 61.0 (CH_2OBn), 61.7 (C-2), 71.8 (C-4), 73.7 (CH_2Ph), 74.9 [C(CH$_3$)$_3$], 127.9 (Ar), 128.0 (Ar), 128.4 (Ar), 137.7 (Ar), 144.0 (C-5) ppm. $C_{16}H_{23}NO_3$ (277.32): calcd. C 69.29, H 8.36, N 5.05; found C 69.40, H 8.48, N 4.93.

(3a*R*,6a*S*)-6-[(Methoxymethoxy)methyl]-2,2-dimethyl-4,6a-dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole 5-Oxide (16a) and (3a*S*,4*S*,6a*R*)-4-[(Methoxymethoxy)methyl]-2,2-dimethyl-4,6a-dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole 5-Oxide (16b): The oxidation of **13** (0.466 g, 2 mmol), as described above for hydroxylamine **12** to give **15**, afforded a 2:1 mixture of compounds **16a** and **16b**, which were separated by column chromatography (EtOAc/MeOH, 20:1).

Compound 16a: 0.305 g, 66%; oil. $[\alpha]_D^{25}$ = +1 (c = 0.91, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 [s, 3 H, C(CH_3)$_2$], 1.41 [s, 3 H, C(CH_3)$_2$], 3.38 (s, 3 H, OCH_3), 4.08 (dd, J = 14.9, 2.0 Hz, 1 H, 2-H$_a$), 4.19 (dd, J = 14.9, 6.2 Hz, 1 H, 2-H$_b$), 4.31 (d, J = 14.5 Hz, 1 H, CH_2OMOM), 4.69 (s, 2 H, OCH_2OCH$_3$), 4.71 (d, J = 14.5 Hz, 1 H, CH_2OMOM), 4.84 (td, J = 6.4, 2.0 Hz, 1 H, 4-H), 5.40 (d, J = 6.4 Hz, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6 [C(CH_3)$_2$], 27.1 [C(CH_3)$_2$], 55.5 (OCH_3), 59.6 (C-5), 68.1 (CH_2OMOM), 71.7 (C-4), 80.5 (C-3), 96.9 (OCH_2OCH$_3$), 112.1 [C(CH$_3$)$_2$], 142.6 (C-2) ppm. $C_{10}H_{17}NO_5$ (231.19): calcd. C 51.94, H 7.41, N 6.06; found C 51.84, H 7.62, N 6.13.

Compound 16b: 0.157 g, 34%; white solid; m.p. 50–52 °C. $[\alpha]_D^{25}$ = +6 (c = 0.29, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 [s, 3 H, C(CH_3)$_2$], 1.46 [s, 3 H, C(CH_3)$_2$], 3.33 (s, 3 H, OCH_3), 3.84 (d, J = 8.9 Hz, 1 H, 2-H), 4.19–4.08 (m, 2 H, CH_2OMOM), 4.59 (s, 2 H, OCH_2OCH$_3$), 4.85 (d, J = 6.1 Hz, 1 H, 3-H), 5.21 (d, J = 6.1 Hz, 1 H, 4-H), 6.92 (s, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8 [C(CH_3)$_2$], 27.3 [C(CH_3)$_2$], 55.5 (OCH_3), 63.7 (CH_2OMOM), 76.7 (C-2), 78.9 (C-3 or C-4), 79.0 (C-3 or C-4), 96.6 (OCH_2OCH$_3$), 111.8 [C(CH$_3$)$_2$], 133.3 (C-5) ppm. $C_{10}H_{17}NO_5$ (231.19): calcd. C 51.94, H 7.41, N 6.06; found C 51.90, H 7.53, N 6.11.

(2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2,5-bis(benzyloxymethyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (17): The oxidation of **14** (1.078 g, 2 mmol), as described above for hydroxylamine **12** to give **15**, afforded pure **17** (1.075 g, 100%) as an oil. $[\alpha]_D^{25}$ = –38 (c = 0.96, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.72 [dd, J = 3.3, 10.1 Hz, 1 H, (C(5)H)CH_2OBn], 3.87 [dd, J = 10.1, 5.8, Hz, 1 H, (C(5)H)CH_2OBn], 3.94–3.99 (m, 1 H, 5-H), 4.14 (dd, J = 2.9, 1.7, Hz, 1 H, 4-H), 4.25 [dt, J = 14.4, 1.3, Hz, 1 H, C(2)CH_2OBn], 4.35 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.39 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.41 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.47 (d, J = 11.7 Hz, 1 H, CH_2Ph), 4.47 (s, 2 H, CH_2Ph), 4.48 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.53 (d, J = 11.7 Hz, 1 H, CH_2Ph), 4.59 [d, J = 14.4 Hz, 1 H, C(2)CH_2OBn], 4.68 (s, 1 H, 3-H), 7.13–7.28 (m, 20 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.4 (CH_2Ph), 66.8 [C(2)HCH_2OBn], 71.6 [C(2)CH_2OBn], 72.1 (CH_2Ph), 73.5 (CH_2Ph), 73.6 (CH_2Ph), 78.2 (C-5), 78.9 (C-4), 83.4 (C-3), 127.0 (Ar), 127.6 (Ar), 127.7 (Ar), 127.9 (Ar), 128.0 (Ar), 128.0 (Ar), 128.1 (Ar), 128.4 (Ar), 128.5 (Ar), 128.5 (Ar), 137.2 (Ar), 137.2 (Ar), 137.5 (Ar), 137.7 (Ar), 143.9 (C-2) ppm. $C_{34}H_{35}NO_5$ (537.58): calcd. C 79.95, H 6.56, N 2.61; found C 79.88, H 6.73, N 2.90.

(2*S*,3*S*)-2-(Benzyloxymethyl)-3-(*tert*-butoxy)-1-hydroxypyrrolidine (18): Sodium borohydride (0.151 g, 4 mmol) was added to a cooled (0 °C) solution of nitrone **15** (0.277 g, 1 mmol) in MeOH (6 mL), and stirring was continued for an additional 2 h, at which point satd. aq. NH_4Cl (10 mL) was added. The resulting mixture was treated with diethyl ether (15 mL), the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give pure **18** (0.279 g, 100%) as an oil. $[\alpha]_D^{25}$ = +23 (c = 0.973, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 {s, 9 H, [C(CH_3)$_3$]}, 1.70 (dtd, J = 12.1, 8.8, 4.7 Hz, 1 H, 4-H$_a$), 2.18 (dddd, J = 13.4, 8.9, 7.6, 3.2 Hz, 4-H$_b$), 2.68 (c, J = 9.4 Hz, 1 H, 5-H$_a$), 2.95 (q, J = 6.4 Hz, 1 H, 2-H), 3.38 (ddd, J = 10.3, 8.4, 3.2 Hz, 1 H, 5-H$_b$), 3.70 (dd, J = 9.2, 6.3 Hz, 1 H, CH_2OBn), 3.76 (dd, J = 9.3, 6.5 Hz, 1 H, CH_2OBn), 4.17 (dt, J = 7.0, 3.4 Hz, 1 H, 3-H), 4.51 (s, 2 H, CH_2Ph), 7.27–7.39 (m, 5 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.2 [C(CH_3)$_3$], 31.9 (C-4), 54.4 (C-5), 66.8 (CH_2OBn), 66.9 [C(CH$_3$)$_3$], 68.2 (C-2), 70.3 (C-3), 72.4 (CH_2Ph), 126.5 (Ar), 126.7 (Ar), 127.3 (Ar), 137.1 (Ar) ppm. $C_{16}H_{25}NO_3$ (279.34): calcd. C 68.79, H 9.02, N 5.01; found C 68.88, H 9.15, N 5.27.

(2*R*,3*S*,4*R*)-1-Hydroxy-3,4-(isopropylidenedioxy)-2-[(methoxymethoxy)methyl]pyrrolidine (19): The reduction of nitrone **16a** (0.231 g, 1 mmol) as described above for nitrone **15** to give **18** afforded pure **19** (0.233 g, 100%) as an oil. $[\alpha]_D^{25}$ = –73 (c = 0.13, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 [s, 3 H, C(CH_3)$_2$], 1.45 [s, 3 H, C(CH_3)$_2$], 2.73 (dd, J = 11.0, 3.3 Hz, 1 H, 5-H$_a$), 2.83 (ddd, J = 8.1, 5.3, 4.5 Hz, 1 H, 2-H), 3.39 (s, 3 H), 3.52 (d, J = 11.1 Hz, 1 H, 5-H$_b$), 3.85 (dd, J = 9.6, 5.3 Hz, 1 H, CH_2OMOM), 3.93 (dd, J = 9.6, 8.1 Hz, 1 H, CH_2OMOM), 4.68 (s, 2 H, OCH_2-OCH$_3$), 4.69–4.66 (m, 2 H, 3-H and 4-H), 6.17 (s, NOH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3 [C(CH_3)$_2$], 25.8 [C(CH_3)$_2$], 55.3 (OCH_3), 62.5 (C-5), 65.1 (CH_2OMOM), 70.2 (C-2), 77.0 (C-3 and C-4), 96.8 (OCH_2OCH$_3$), 110.9 [C(CH$_3$)$_2$] ppm. $C_{10}H_{19}NO_5$

(233.21): calcd. C 51.49, H 8.21, N 6.00; found C 51.62, H 8.13, N 6.19.

(2*R*,3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-2,5-bis(benzyloxymethyl)-1-hydroxypyrrolidine (20): A cooled (–80 °C) solution of **17** (0.538 g, 1 mmol) in anhydrous THF (10 mL) was treated dropwise under argon with L-Selectride (2 mL of a 1 M solution in hexanes, 2 mmol). After stirring for 2 h at –80 °C the reaction mixture was warmed to 0 °C, at which point satd. aq. NH_4Cl (5 mL) was added. The resulting mixture was treated with diethyl ether (15 mL), the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure without exceeding 20 °C to give pure **20** (0.540 g, 100%) as an oil. This compound could not be characterized since it proved to be rather unstable, being oxidized immediately to the precursor nitrone **17**. Because of this it was used immediately in the next step without any purification.

(2*R*,3*S*)-2-(Hydroxymethyl)-3-hydroxypyrrolidine Hydrochloride (21, CYB-3): A solution of hydroxylamine **12** (0.277 g, 1 mmol) in methanol (10 mL) was treated with $Pd(OH)_2$-C (15 mg) and a solution of HCl in methanol (1 M). The resulting mixture was stirred under hydrogen (20 atm) for 6 h. The catalyst was eliminated by filtration through a pad of Celite, the filtrate was treated with HCl (3 M) in methanol, and the resulting solution was stirred at room temperature for an additional 10 min. The solvent was eliminated under reduced pressure to afford pure **21** (0.153 g, 100%) as a white solid; m.p. 110–112 °C (ref.[56c] m.p. 108–112 °C). $[\alpha]_D^{25}$ = +43 (*c* = 0.10, H_2O) [ref.[56c] $[\alpha]_D^{25}$ = +46.5 (*c* = 0.10, H_2O)]. ^1H NMR (500 MHz, D_2O): δ = 1.93–2.03 (m, 1 H, 4-H_a), 2.22 (dddd, *J* = 14.1, 8.3, 8.0, 6.0 Hz, 1 H, 4-H_b), 3.36–3.49 (m, 2 H, 5-H_a, 5-H_a), 3.57 (dt, *J* = 7.3, 4.0 Hz, 2-H), 3.67 (dd, *J* = 12.4, 7.3 Hz, CH_2OH), 3.84 (dd, *J* = 12.4, 4.3 Hz, 1 H, CH_2OH), 4.33 (dt, *J* = 6.0, 4.0 Hz, 3-H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 31.1 (C-4), 43.1 (C-5), 57.6 (*C*H_2OH), 66.3 (C-2), 70.0 (C-3) ppm. $C_5H_{12}ClNO_2$ (153.58): calcd. C 39.09, H 7.87, N 9.12; found C 38.86, H 7.95, N 8.90.

(2*R*,3*R*)-2-(Hydroxymethyl)-3-hydroxypyrrolidine Hydrochloride (22): The hydrogenation of **15** (0.277 g, 1 mmol) or **18** (0.279 g, 1 mmol), as described above for hydroxylamine **12** to give **21**, afforded pure **22** (0.153 g, 100%) as a white solid; m.p. >150 °C (dec.) (ref.[57b] m.p. 220 °C). $[\alpha]_D^{25}$ = +12 (*c* = 0.25, MeOH) [ref.[57b] $[\alpha]_D^{25}$ = –12.7 (*c* = 0.2, MeOH)]. ^1H NMR (400 MHz, D_2O): δ = 2.03 (dddd, *J* = 13.9, 7.5, 3.4, 1.5 Hz, 1 H, 4-H_a), 2.20 (dddd, *J* = 14.0, 9.4, 9.2, 4.6 Hz, 1 H, 4-H_b), 3.33–3.50 (m, 2 H, 5-H_a, 5-H_a), 3.57 (ddd, *J* = 8.8, 4.9, 3.7 Hz, 2-H), 3.81 (dd, *J* = 12.1, 8.5 Hz, CH_2OH), 3.94 (dd, *J* = 12.2, 4.9 Hz, 1 H, CH_2OH), 4.49–4.53 (m, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 32.6 (C-4), 43.2 (C-5), 57.6 (*C*H_2OH), 65.2 (C-2), 69.8 (C-3) ppm. $C_5H_{12}ClNO_2$ (153.58): calcd. C 39.09, H 7.87, N 9.12; found C 38.91, H 7.89, N 9.06.

(2*S*,3*S*,4*R*)-3,4-Dihydroxy-2-(hydroxymethyl)pyrrolidine Hydrochloride (23): The hydrogenation of **13** (0.233 g, 1 mmol), as described above for hydroxylamine **12** to give **21**, afforded pure **23** (0.169 g, 100%) as a white solid; m.p. 128–130 °C (ref.[58e] m.p. 124–126 °C). $[\alpha]_D^{25}$ = –52 (*c* = 0.41, H_2O) [ref.[58e] $[\alpha]_D^{25}$ = –52.0 (*c* = 0.6, H_2O)]. ^1H NMR (400 MHz, D_2O): δ = 3.36 (d, *J* = 12.8 Hz, 1 H, 5-H_a), 3.50 (dd, *J* = 12.8, 4.0 Hz, 1 H, 5-H_b), 3.63 (ddd, *J* = 8.3, 5.8, 3.5 Hz, 1 H, 2-H), 3.81 (dd, *J* = 12.6, 5.8 Hz, 1 H, CH_2OH), 3.97 (dd, *J* = 12.6, 3.5 Hz, 1 H, CH_2OH), 4.20 (dd, *J* = 8.3, 4.0 Hz, 1 H, 3-H), 4.38 (m, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 49.7 (C-5), 58.1 (CH_2OH), 61.9 (C-2), 69.5 (C-4), 71.2 (C-3) ppm. $C_5H_{12}ClNO_3$ (169.57): calcd. C 35.41, H 7.13, N 8.26; found C 35.18, H 7.16, N 8.20.

(2*R*,3*S*,4*R*)-3,4-Dihydroxy-2-(hydroxymethyl)pyrrolidine Hydrochloride (24): The hydrogenation of **16** (0.231 g, 1 mmol) or **19** (0.233 g, 1 mmol), as described above for nitrone **12** to give **21**, afforded pure **24** (0.170 g, 100%) as a white solid; m.p. 156–158 °C (ref.[58e] m.p. 157–159 °C). $[\alpha]_D^{25}$ = +20 (*c* = 0.32, H_2O) [ref.[58e] $[\alpha]_D^{25}$ = +21 (*c* = 0.70, H_2O)]. ^1H NMR (400 MHz, D_2O): δ = 3.11 (dd, *J* = 12.1, 7.3 Hz, 1 H, 5-H_a), 3.42 (dd, *J* = 12.1, 7.3 Hz, 1 H, 5-H_b), 3.63 (dt, *J* = 8.3, 4.0 Hz, 1 H, 2-H), 3.78 (dd, *J* = 12.1, 8.3 Hz, 1 H, CH_2OH), 3.88 (dd, *J* = 12.1, 4.0 Hz, 1 H, CH_2OH), 4.24 (t, *J* = 4.0 Hz, 1 H, 3-H), 4.38 (td, *J* = 7.3, 4.0 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 47.1 (C-5), 57.7 (*C*H_2OH), 62.5 (C-2), 69.8 (C-3 or C-4), 70.0 (C-3 or C-4) ppm. $C_5H_{12}ClNO_3$ (169.57): calcd. C 35.41, H 7.13, N 8.26; found C 35.26, H 7.14, N 8.22.

(2*R*,3*R*,4*R*,5*R*)-3,4-Dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine Hydrochloride (1, DMDP): The hydrogenation of **14** (0.540 g, 1 mmol), as described above for hydroxylamine **12** to give **21**, afforded pure **1** (0.2 g, 100%) as a white solid; m.p. >150 °C (dec.). $[\alpha]_D^{25}$ = +48 (*c* = 0.32, H_2O). ^1H NMR (400 MHz, D_2O): δ = 3.44–3.50 (m, 2 H, 2-H), 3.76 (dd, *J* = 12.7, 5.7 Hz, 2 H, CH_2OH), 3.84 (dd, *J* = 12.7, 3.7 Hz, 2 H, CH_2OH), 3.96–4.01 (m, 2 H, 3-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 57.8 (*C*H_2OH), 62.4 (C-2), 74.2 (C-3) ppm. $C_6H_{14}ClNO_4$ (199.63): calcd. C 36.10, H 7.07, N 7.02; found C 36.32, H 7.21, N 7.17.

In order to allow comparisons with the literature data an analytical sample of the free amine was obtained by passing the hydrochloride through a Dowex 50WX8 ion-exchange resin. Elution with ammonia in methanol (3 M) afforded, after evaporation, the free base of **1** as a white solid: m.p. 114–117 °C (ref.[9d] m.p. 115–117 °C). $[\alpha]_D^{25}$ = +53 (*c* = 0.95, H_2O) [ref.[9d] $[\alpha]_D$ = +55.4 (*c* = 1.3, H_2O)]. ^1H NMR (400 MHz, D_2O): δ = 2.92–2.99 (m, 2 H, 2-H), 3.53 (dd, *J* = 11.9, 4.3 Hz, 2 H, CH_2OH), 3.61 (dd, *J* = 11.9, 6.3 Hz, 2 H, CH_2OH), 3.72–3.77 (m, 2 H, 3-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 61.5 (C-2), 61.6 (*C*H_2OH), 77.5 (C-3) ppm. $C_6H_{14}ClNO_4$ (199.59): calcd. C 44.16, H 8.03, N 8.58; found C 43.87, H 8.05, N 8.53.

(2*S*,3*R*,4*R*,5*R*)-2,5-Bis(hydroxymethyl)-3,4-dihydroxypyrrolidine Hydrochloride (25): The hydrogenation of **20** (0.540 g, 1 mmol), as described above for hydroxylamine **12** to give **21**, afforded pure **25** (0.2 g, 100%) as a white solid; m.p. >150 °C (dec.). $[\alpha]_D^{25}$ = –5 (*c* = 0.75, MeOH) [ref.[59] $[\alpha]_D$ = –3.4 (*c* = 1.0, MeOH)]. ^1H NMR (400 MHz, D_2O): δ = 3.49 (ddd, *J* = 8.4, 4.6, 3.6 Hz, 1 H, 2-H), 3.70–3.92 (m, 5 H, 5-H, CH_2OH), 3.98 (dd, *J* = 3.6, 2.2 Hz, 1 H, 3-H), 4.16 (dd, *J* = 3.6, 2.2 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 56.7 (*C*H_2OH), 59.1 (*C*H_2OH), 62.9 (C-5), 66.6 (C-2), 74.3 (C-4), 75.8 (C-3) ppm. $C_6H_{14}ClNO_4$ (199.59): calcd. C 36.10, H 7.07, N 7.02; found C 35.83, H 7.15, N 6.86.

(2*R*,3*R*,4*R*)-3,4-Dihydroxy-2-(hydroxymethyl)pyrrolidine (26, DAB-1): A solution of nitrone **8** (0.430 g, 1.03 mmol) in methanol (8 mL) was treated with Pd/C (420 mg) and concentrated HCl (4 drops). The resulting mixture was stirred under hydrogen for 15 h. The catalyst was eliminated by filtration through a pad of Celite, and the filtrate was then concentrated under reduced pressure and passed through a short pad of Dowex WX8–200, with elution with water, MeOH, and finally with a NH_4OH solution (6%). Concentration of the fractions eluted with NH_4OH afforded a brown oil (135 mg, 98% yield). $[\alpha]_D^{23}$ = +5.6 (*c* = 0.285, H_2O) [ref.[63] $[\alpha]_D$ = +6.3 (*c* = 1, H_2O)]. ^1H NMR (400 MHz, D_2O): δ = 2.74 (dd, *J* = 12.3, 3.9 Hz, 1 H, 5-H_a), 2.90 (m, 1 H, 2-H), 3.02 (dd, *J* = 12.2, 5.7 Hz, 1 H, 5-H_b), 3.55 (dd, *J* = 11.5, 6.4 Hz, 1 H, CH_2OH), 3.63 (dd, *J* = 11.5, 4.9 Hz, 1 H, CH_2OH), 3.73 (dd, *J* = 5.7, 3.6 Hz, 1 H, 3-H), 4.03 (dt, *J* = 5.7, 3.9 Hz, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 49.6 (C-5), 61.0 (*C*H_2OH), 64.4 (C-2), 76.4

(C-4), 78.0 (C-3) ppm. $C_5H_{11}NO_3$ (133.12): calcd. C 45.10, H 8.33, N 10.52; found C 44.82, H 8.11, N 10.23.

(2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2*H*-pyrrole (27): Triphenylphosphane (75 mg, 0.30 mmol) was added to a solution of nitrone **8** (285 mg, 0.68 mmol) in a mixture of trimethyl phosphite and TEA (10:1, 20 mL), and the mixture was heated at reflux for 4 h. After evaporation under reduced pressure, purification by flash column chromatography (eluent petroleum ether/EtOAc, 1.5:1) afforded pure **27** (170 mg, 62%) as an oil. $[\alpha]_D^{22}$ = –10.4 (*c* = 0.76, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.58 (dd, *J* = 9.8, 6.3 Hz, 1 H, CH_2OH), 3.79 (dd, *J* = 9.8, 4.5 Hz, 1 H, CH_2OH), 4.14 (t, *J* = 3.8 Hz, 1 H, 3-H), 4.18–4.21 (m, 1 H, 2-H), 4.59–4.66 (m, 7 H, CH_2Ph, 4-H), 7.23–7.40 (m, 15 H, Ar), 7.64 (d, *J* = 2.34 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 71.1 (C-6), 72.1 (*C*H_2Ph), 72.4 (*C*H_2Ph), 73.4 (CH_2Ph), 76.9 (C-2), 84.5 (C-3), 90.7 (C-4), 127.6 (Ar), 127.7 (Ar), 127.8 (Ar), 127.9 (Ar), 128.0 (Ar), 128.2 (Ar), 128.3 (Ar), 128.4 (Ar), 128.5 (Ar), 137, 4 (Ar), 137.8 (Ar), 138.1 (Ar), 165.9 (C-5) ppm. $C_{26}H_{27}NO_3$ (401.45): calcd. C 77.78, H 6.78, N 3.49; found C 77.58, H 6.56, N 3.31.

(2*R*,3*R*,4*R*)-2-(Hydroxymethyl)-3,4-dihydro-2*H*-pyrrole-3,4-diol (28, Nectrisine): A solution of BCl_3 in CH_2Cl_2 (1 M, 1.75 mL) was added under nitrogen at –78 °C to a solution of **27** (0.1 g, 0.25 mmol) in dry CH_2Cl_2 (0.5 mL). The mixture was stirred for 3 h, while the temperature was raised to –40 °C. Then, a saturated aqueous solution of $NaHCO_3$ was added until neutral pH was reached. The solvent was evaporated under reduced pressure, and the residue was taken up with AcOEt (10 mL) and stirred for 10 min. After decantation, this procedure was repeated three times. The combined organic phases were concentrated, affording a white solid that was purified by flash column chromatography (eluent EtOAc/MeOH, 2:1) to afford pure **28** (22 mg, 67% yield) as an oil. ^{13}C NMR (50 MHz, D_2O): δ = 61.3 (t), 76.8 (d), 78.3 (d), 83.4 (d), 170.6 (d) ppm. Nectrisine (**28**) was found to be unstable in D_2O solution, due to formation of hydrated derivatives.[68]

(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-1-hydroxy-5-methylpyrrolidine (29): Methylmagnesium bromide (3 mL of a 3 M solution in THF, 3 mmol) was added dropwise under argon to a cooled (0 °C) solution of nitrone **8** (0.418 g, 1 mmol) in anhydrous THF (10 mL). The resulting solution was stirred at 0 °C for 3 h, at which point the reaction was quenched with satd. aq. NH_4Cl (10 mL). The reaction mixture was diluted with diethyl ether (10 mL), the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$, and filtered, and the solvent was eliminated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc, 4:1) to give pure **29** (0.434 g, 100%) as an oil. $[\alpha]_D^{24}$ = –12.5 (*c* = 0.135, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.4 Hz, 3 H, CH_3), 3.37–3.40 (m, 1 H, 5-H), 3.51–3.55 (m, 1 H, CH_2OBn), 3.62 (dd, *J* = 9.6, 6.5 Hz, 1 H, CH_2OBn), 3.72–3.76 (m, 2 H, 3-H, 4-H), 3.90 (dd, *J* = 4.1, 3.1 Hz, 1 H, 2-H), 4.45–4.56 (m, 6 H, CH_2Ph), 4.95 (br. s, 1 H, O*H*), 7.25–7.37 (m, 15 H, Ar) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.7 (*C*H_3), 62.3 (C-5), 67.2 (C-4), 69.4 (*C*H_2OBn), 69.7 (*C*H_2OPh), 71.1 (*C*H_2OPh), 71.4 (*C*H_2OPh), 81.8 (C-2), 85.0 (C-3), 125.4–126.8 (15 C, Ar), 135.3–135.6 (3 C, Ar) ppm. $C_{27}H_{31}NO_4$ (433.49): calcd. C 74.80, H 7.21, N 3.23; found C 74.78, H 6.91, N 3.44.

(2*R*,3*R*,4*R*,5*R*)-3,4-Dihydroxy-2-(hydroxymethyl)-5-methylpyrrolidine (6-Deoxy-DMDP, 30): A solution of hydroxylamine **29** (0.141 g, 0.32 mmol) in methanol (20 mL) was treated with Pd/C (10%, 170 mg), and concd. HCl (6 drops) was added. The resulting mixture was stirred under hydrogen at room temperature for 16 h. The catalyst was eliminated by filtration through a pad of Celite, and the filtrate was then passed through a Dowex 50WX8 ion-exchange resin. Elution with ammonia in methanol (3 M) afforded pure **30** (0.41 g, 87%) as a syrup after evaporation. $[\alpha]_D^{20}$ = +44.4 (*c* = 0.71, MeOH) [ref.[69a] $[\alpha]_D$ = +26.2 (*c* = 1.1, MeOH)] for the natural compound, $[\alpha]_D$ = +42.9 (*c* = 0.72, MeOH) for the synthetic compound. ^{1}H NMR (400 MHz, D_2O): δ = 1.06 (d, *J* = 6.4 Hz, 3 H, CH_3), 2.83 (dq, *J* = 8.2, 6.4 Hz, 1 H, 5-H), 2.92 (td, *J* = 6.6, 4.9 Hz, 1 H, 2-H), 3.51–3.45 (m, 2 H, CH_2, 4-H), 3.55 (dd, *J* = 11.4, 4.9 Hz, 1 H, CH_2), 3.69 (t, *J* = 7.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 17.4 (*C*H_3), 55.7 (C-5), 61.5 (C-2), 62.5 (*C*H_2), 78.2 (C-3), 82.7 (C-4) ppm. $C_6H_{13}NO_3$ (147.14): calcd. C 48.97, H 8.90, N 9.52; found C 48.59, H 9.02, N 9.78.

(2*R*,3*S*)-3-*tert*-Butoxy-1-hydroxypyrrolidine-2-carbonitrile (31): Trimethylsilyl cyanide (0.100 g, 1 mmol) was added under argon to a solution of nitrone **6** (0.157 g, 1 mmol) in MeOH (10 mL). The resulting solution was stirred at room temperature for 10 h, at which point the solvent was rotatory evaporated, without exceeding 35 °C, to give the pure hydroxylamine **31** (0.184 g, 100%), which did not need further purification. White solid; m.p. 127–129 °C. $[\alpha]_D^{25}$ = +20 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 [s, 9 H, C(CH_3)$_3$], 1.69 (ddt, *J* = 13.4, 3.7, 8.6 Hz, 1 H, 4-H_a), 2.22 (dq, *J* = 13.4, 8.6 Hz, 1 H, 4-H_b), 3.07 (dt, *J* = 11.7, 8.6 Hz, 1 H, 5-H_a), 3.18 (ddd, *J* = 11.7, 8.9, 3.7 Hz, 1 H, 5-H_b), 3.58 (d, *J* = 5.9 Hz, 1 H, 2-H), 4.33 (ddd, *J* = 8.9, 5.9, 3.7 Hz, 1 H, 3-H), 7.41 (s, 1 H, –NO*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 (*C*H_3), 31.6 (C-4), 56.2 (C-5), 67.7 (C-2), 73.3 (C-3), 74.9 [*C*-(CH_3)$_3$], 117.8 (*C*N) ppm. $C_9H_{16}N_2O_2$ (184.21): calcd. C 58.67, H 8.75, N 15.21; found C 58.73, H 8.90, N 15.14.

(2*S*,3*S*,4*R*)-1-Hydroxy-3,4-(isopropylidenedioxy)pyrrolidine-2-carbonitrile (32): The hydrocyanation of **7** (0.157 g, 1 mmol), as described above for nitrone **6** to give **31**, afforded pure **32** (0.184 g, 100%) as a white solid; m.p. 110–112 °C. $[\alpha]_D^{25}$ = +22 (*c* = 0.695, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 3.15 (dd, *J* = 11.4, 4.8 Hz, 1 H, 5-H_a), 3.42 (d, *J* = 11.4 Hz, 1 H, 5-H_b), 4.20 (s, 1 H, 2-H), 4.70–4.80 (m, 2 H, 3-H and 4-H), 6.18 (s, 1 H, NO*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3 (*C*H_3), 25.8 (*C*H_3), 60.5 (C-5), 62.9 (C-2), 76.1 (C-4), 80.1 (C-3), 112.6 [*C*(CH_3)$_2$], 114.8 (*C*N) ppm. $C_8H_{12}N_2O_3$ (184.16): calcd. C 52.17, H 6.57, N 15.21; found C 52.04, H 6.54, N 15.30.

(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-1-hydroxypyrrolidine-2-carbonitrile (33): The hydrocyanation of **8** (0.417 g, 1 mmol), as described above for nitrone **6** to give **31**, afforded a crude product that was purified by column chromatography (hexane/EtOAc, 4:1) to give pure **33** (0.444 g, 100%) as an oil. $[\alpha]_D^{25}$ = +9 (*c* = 1.08, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.32 (dt, *J* = 3.5, 7.0 Hz, 1 H, 5-H), 3.59 (dd, *J* = 10.6, 3.5 Hz, 1 H, CH_2OH), 3.76 (dd, *J* = 10.6, 3.5 Hz, 1 H, CH_2OH), 3.97 (dd, *J* = 6.7, 2.3 Hz, 1 H, 4-H), 4.19 (t, *J* = 2.4 Hz, 1 H, 3-H), 4.25 (d, *J* = 1.9 Hz, 1 H, 2-H), 6.51–6.42 (m, 4 H, CH_2Ph), 6.54 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 6.59 (d, *J* = 12.2 Hz, 1 H, CH_2Ph), 6.81 (s, 1 H, O*H*), 7.30 (m, 15 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.3 (C-2), 66.3 (*C*^{6}), 69.5 (C-5), 72.2 (*C*H_2Ph), 72.3 (*C*H_2Ph), 73.4 (*C*H_2Ph), 81.3 (C-4), 83.7 (C-3), 115.8 (*C*N), 127.9 (Ar), 128.0 (Ar), 128.0 (Ar), 128.1 (Ar), 128.1 (Ar), 128.4 (Ar), 128.5 (Ar), 128.5 (Ar), 128.8 (Ar), 136.6 (Ar), 137.4 (Ar), 137.5 (Ar) ppm. $C_{27}H_{28}N_2O_4$ (444.47): calcd. C 72.95, H 6.35, N 6.30; found C 73.05, H 6.28, N 6.48.

(*S*)-4-*tert*-Butoxy-5-cyano-3,4-dihydro-2*H*-pyrrole 1-Oxide (34): The oxidation of **31** (0.368 g, 2 mmol), as described above for hydroxylamine **12** to give **15**, afforded pure **34** (0.364 g, 100%) as a

white solid; m.p. 78–80 °C. $[\alpha]_D^{25}$ = +17 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 [s, 9 H, C(CH_3)$_3$], 2.19 (dddd, *J* = 13.6, 9.0, 5.3, 3.2 Hz, 1 H, 3-H_a), 2.65 (dddd, *J* = 14.0, 9.1, 7.6, 6.5 Hz, 1 H, 3-H_b), 3.95 (dddd, *J* = 15.0, 9.4, 5.5, 0.6 Hz, 1 H, 2-H_a), 4.26 (dddd, *J* = 14.9, 8.9, 6.5, 1.8 Hz, 1 H, 2-H_b), 4.99 (dddd, *J* = 5.0, 2.3, 1.1, 0.5 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7 (C-3), 30.0 (CH_3), 62.8 (C-2), 71.5 [C(CH$_3$)$_3$], 75.5 (C-4), 111.0 (C≡N), 120.2 (C-5) ppm. $C_9H_{14}N_2O_2$ (182.20): calcd. C 59.32, H 7.74, N 15.37; found C 59.48, H 7.90, N 15.21.

(3a*R*,6a*S*)-6-Cyano-2,2-dimethyl-4,6a-dihydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole 5-Oxide (35): The oxidation of **32** (0.368 g, 2 mmol), as described above for hydroxylamine **12** to give **15**, afforded pure **35** (0.364 g, 100%) as a white solid; m.p. 128–130 °C. $[\alpha]_D^{25}$ = –90 (*c* = 0.535, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 4.18 (dtd, *J* = 15.6, 1.2, 0.6 Hz, 1 H, 2-H_a), 4.29 (dd, *J* = 15.7, 6.4 Hz, 1 H, 2-H_b), 4.99 (dddd, *J* = 6.2, 4.9, 1.4, 0.6 Hz, 1 H, 3-H), 5.45 (d, *J* = 6.1 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7 (CH_3), 27.1 (CH_3), 69.1 (C-2), 73.0 (C-3), 79.3 (C-4), 110.4 (C≡N), 113.4 [C(CH$_3$)$_2$], 118.4 (C-5) ppm. $C_8H_{10}N_2O_3$ (182.14): calcd. C 52.74, H 5.53, N 15.38; found C 52.68, H 5.64, N 15.50.

(2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-cyano-3,4-dihydro-2*H*-pyrrole 1-Oxide (36): The oxidation of **33** (0.888 g, 2 mmol), as described above for hydroxylamine **12** to give **15**, afforded pure **36** (0.885 g, 100%) as an oil. $[\alpha]_D^{25}$ = –35 (*c* = 2.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.71 (dd, *J* = 3.2, 10.4 Hz, 1 H, CH_2OBn), 4.01 (dd, *J* = 10.4, 4.9 Hz, 1 H, CH_2OBn), 4.07–4.11 (m, 1 H, 2-H), 4.40 (dd, *J* = 3.6, 2.0 Hz, 1 H, 3-H), 4.50 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.51 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.55 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.59 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.65 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.76 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.84 (dd, *J* = 2.0, 0.6 Hz, 4-H), 7.10–7.35 (m, 15 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.7 (CH_2OBn), 72.1 (CH_2Ph), 72.2 (CH_2Ph), 73.6 (CH_2Ph), 79.3 (C-3), 79.5 (C-2), 82.0 (C-4), 111.1 (C≡N), 118.0 (C-5), 127.8 (Ar), 128.0 (Ar), 128.1 (Ar), 128.4 (Ar), 128.5 (Ar), 128.7 (Ar), 136.4 (Ar), 136.5 (Ar), 137.1 (Ar) ppm. $C_{27}H_{26}N_2O_4$ (442.45): calcd. C 73.28, H 5.92, N 6.33; found C 73.41, H 5.78, N 6.49.

(2*S*,3*S*)-3-*tert*-Butoxy-1-hydroxypyrrolidine-2-carbonitrile (37): Sodium borohydride (76 mg, 2 mmol) was added portionwise to a cooled (0 °C) solution of nitrone **34** (0.182 g, 1 mmol) in MeOH (6 mL). The reaction mixture was stirred for an additional hour and satd. aq. NH_4Cl (5 mL) was added. After stirring for 15 min the reaction mixture was diluted with diethyl ether (20 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, and filtered, and the solvent was eliminated under reduced pressure to give pure **37** (0.184 g, 100%), which did not need further purification; oil. $[\alpha]_D^{25}$ = +23 (*c* = 0.97, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.21 [s, 9 H, C(CH_3)$_3$], 1.86 (dddd, *J* = 12.1, 8.4, 8.3, 4.6 Hz, 1 H, 4-H_a), 2.25 (dtd, *J* = 12.8, 8.2, 4.5 Hz, 1 H, 4-H_b), 2.87 (dt, *J* = 10.1, 8.3 Hz, 1 H, 5-H_a), 3.37 (ddd, *J* = 9.9, 9.0, 4.6 Hz, 1 H, 5-H_b), 3.88 (d, *J* = 6.7 Hz, 1 H, 2-H), 4.30 (ddd, *J* = 7.9, 6.8, 4.7 Hz, 1 H, 3-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.4 [C(CH_3)$_3$], 31.3 (C-4), 54.7 (C-5), 64.4 (C-2), 68.3 (C-3), 74.5 [C(CH$_3$)$_3$], 115.6 (C≡N) ppm. $C_9H_{16}N_2O_2$ (184.21): calcd. C 58.67, H 8.75, N 15.21; found C 58.73, H 8.92, N 15.11.

(3aS,4*R*,6aR)-5-Hydroxy-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo-[4,5-*c*]pyrrole-4-carbonitrile (38): The reduction of **35** (0.182 g, 1 mmol), as described above for hydroxylamine **34** to give **37**, afforded pure **38** (0.184 g, 100%) as a white solid; m.p. 144–145 °C; $[\alpha]_D^{25}$ = –130 (*c* = 0.695, MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 2.77 (dd, *J* = 11.4, 4.4 Hz, 1 H, 5-H_a), 3.49 (s, 1 H, 2-H), 3.55 (d, *J* = 11.4 Hz, 1 H, 5-H_b), 4.72–4.79 (m, 2 H, 3-H and 4-H), 5.98 (br. s, 1 H, NO*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8 (CH_3), 25.9 (CH_3), 61.7 (C-5), 63.6 (C-2), 76.6 (C-4), 76.7 (C-3), 112.8 [C(CH$_3$)$_2$], 115.7 (C≡N) ppm. $C_8H_{12}N_2O_3$ (184.16): calcd. C 52.17, H 6.57, N 15.21; found C 52.31, H 6.43, N 15.30.

(2S,3*R*,4*R*,5R)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-1-hydroxypyrrolidine-2-carbonitrile (39): The reduction of **36** (0.442 g, 1 mmol), as described above for hydroxylamine **34** to give **37**, afforded pure **39** (0.444 g, 100%) as an oil. $[\alpha]_D^{25}$ = +11 (*c* = 0.27, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.03 (c, *J* = 5.4 Hz, 1 H, 5-H), 3.54 (dd, *J* = 10.0, 5.6 Hz, 1 H, CH_2OBn), 3.59 (dd, *J* = 10.0, 5.4 Hz, 1 H, CH_2OBn), 3.76 (d, *J* = 5.2 Hz, 1 H, 4-H), 3.95 (s, 2 H, 2-H and 3-H), 4.29 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.34 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.47 (s, 2 H, CH_2Ph), 4.48 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.60 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 7.08–7.33 (m, 15 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.1 (C-2), 68.7 (C-6), 71.8 (CH_2Ph), 71.9 (C-5), 72.6 (CH_2Ph), 73.4 (CH_2Ph), 79.7 (C-4), 81.7 (C-3), 116.3 (C≡N), 127.7 (Ar), 127.8 (Ar), 127.9 (Ar), 128.0 (Ar), 128.2 (Ar), 128.4 (Ar), 128.5 (Ar), 128.6 (Ar), 136.6 (Ar), 137.2 (Ar), 137.8 (Ar) ppm. $C_{27}H_{28}N_2O_4$ (444.47): calcd. C 72.95, H 6.35, N 6.30; found C 73.14, H 6.21, N 6.57.

(2*R*,3*S*)-2-(Aminomethyl)-3-hydroxypyrrolidine Dihydrochloride (40): The hydrogenation of **31** (0.184 g, 1 mmol), as described above for hydroxylamine **12** to give **21**, afforded pure **40** (0.189 g, 100%) as a white solid; m.p. >150 °C (dec.). $[\alpha]_D^{25}$ = +23 (*c* = 0.30, H_2O). ^1H NMR (500 MHz, D_2O): δ = 2.00 (ddddd, *J* = 14.3, 8.3, 5.9, 4.9, 0.6 Hz, 1 H, 4-H_a), 2.26 (dddd, *J* = 13.9, 8.4, 7.8, 6.0 Hz, 1 H, 4-H_b), 3.19 (dd, *J* = 13.9, 7.3 Hz, 2 H, CH_2NH$_2$), 3.40–3.44 (m, 2 H, 5-H_a, 5-H_b), 3.69 (dt, *J* = 7.0, 4.9 Hz, 1 H, 2-H), 4.37 (c, *J* = 5.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 30.8 (C-4), 38.4 (CH_2NH$_2$), 43.9 (C-5), 62.2 (C-2), 72.2 (C-3) ppm. $C_5H_{14}Cl_2N_2O$ (189.07): calcd. C 31.76, H 7.46, N 14.81; found C 31.60, H 7.60, N 14.78.

(2*S*,3*S*)-2-(Aminomethyl)-3-hydroxypyrrolidine Dihydrochloride (41): The hydrogenation of **34** (0.182 g, 1 mmol) or **37** (0.184 g, 1 mmol), as described above for hydroxylamine **12** to give **21**, afforded pure **41** (0.189 g, 100%) as a white solid; m.p. >150 °C (dec.). $[\alpha]_D^{25}$ = +66 (*c* = 1.0, H_2O). ^1H NMR (400 MHz, D_2O): δ = 2.03 (dddd, *J* = 14.3, 7.7, 3.5, 1.5 Hz, 1 H, 4-H_a), 2.16 (dtd, *J* = 14.0, 9.9, 4.2 Hz, 1 H, 4-H_b), 3.26–3.54 (m, 4 H, 5-H_a, 5-H_b and CH_2NH$_2$), 3.72 (dt, *J* = 6.6, 3.5 Hz, 1 H, 2-H), 4.53 (dd, *J* = 4.0, 1.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 31.7 (C-4), 35.4 (C-5 or CH_2NH$_2$), 43.5 (C-5 or CH_2NH$_2$), 59.9 (C-2), 69.0 (C-3) ppm. $C_5H_{14}Cl_2N_2O$ (189.07): calcd. C 31.76, H 7.46, N 14.81; found C 31.54, H 7.62, N 14.73.

(2*S*,3*S*,4*R*)-2-(Aminomethyl)-3,4-dihydroxypyrrolidine Dihydrochloride (42): The hydrogenation of **32** (0.184 g, 1 mmol), as described above for hydroxylamine **12** to give **21**, afforded pure **42** (0.204 g, 100%) as a white solid; m.p. >150 °C (dec.). $[\alpha]_D^{25}$ = –19 (*c* = 0.33, MeOH). ^1H NMR (400 MHz, D_2O): δ = 3.23 (dd, *J* = 13.2, 1.2 Hz, 1 H, 5-H_a), 3.31 (dd, *J* = 13.9, 5.7 Hz, 1 H, CH_2NH$_2$), 3.36 (dd, *J* = 14.0, 7.5 Hz, 1 H, CH_2NH$_2$), 3.43 (dd, *J* = 13.2, 4.1 Hz, 1 H, 5-H_b), 3.60 (dd, *J* = 9.4, 7.6, 6.1 Hz, 1 H, 2-H), 4.04 (dd, *J* = 9.5, 4.0 Hz, 1 H, 3-H), 4.18 (dt, *J* = 4.1, 1.0 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 40.3 (CH_2NH$_2$), 51.8 (C-5), 58.6 (C-2), 70.3 (C-4), 75.5 (C-3) ppm. $C_5H_{14}Cl_2N_2O_2$ (205.06): calcd. C 29.28, H 6.88, N 13.66; found C 28.48, H 6.95, N 13.42.

(2*R*,3*S*,4*R*)-2-(Aminomethyl)-3,4-dihydroxypyrrolidine Dihydrochloride (43): The hydrogenation of **35** (0.182 g, 1 mmol) or **38** (0.184 g,

1 mmol), as described above for hydroxylamine **12** to give **21**, afforded pure **43** (0.204 g, 100%) as a white solid; m.p. >150 °C (dec.). $[a]_D^{25}$ = –5 (*c* = 0.38, MeOH). ^{1}H NMR (400 MHz, D_2O): δ = 3.20 (dd, *J* = 13.2, 6.1 Hz, 1 H, 5-H_a), 3.38 (dd, *J* = 13.2, 5.6 Hz, 1 H, 5-H_b), 3.42 (dd, *J* = 12.6, 6.6 Hz, 1 H, CH_2NH$_2$), 3.53 (dd, *J* = 12.6, 7.1 Hz, 1 H, CH_2NH$_2$), 3.85 (q, *J* = 6.8 Hz, 1 H, 2-H), 4.35–4.45 (m, 2 H, 3-H and 4-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 36.6 (C-5), 48.2 (*C*H$_2$NH$_2$), 57.2 (C-2), 69.8 (C-3 or C-4), 70.0 (C-3 or C-4) ppm. $C_5H_{14}Cl_2N_2O_2$ (205.06): calcd. C 29.28, H 6.88, N 13.66; found C 28.97, H 6.95, N 13.42.

(2*R*,3*R*,4*R*,5*R*)-2-(Aminomethyl)-5-(hydroxymethyl)-3,4-dihydroxypyrrolidine Dihydrochloride (44): The hydrogenation of **33** (0.444 g, 1 mmol), as described above for hydroxylamine **12** to give **21**, afforded pure **44** (0.235 g, 100%) as a white solid; m.p. >150 °C (dec.). $[a]_D^{25}$ = +43 (*c* = 1.43, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 3.42 (dd, *J* = 13.9, 6.2 Hz, 1 H, CH_2NH$_2$), 3.54 (dd, *J* = 13.9, 6.8 Hz, 1 H, CH_2NH$_2$), 3.62 (ddd, *J* = 8.8, 4.9, 2.4 Hz, 1 H, 5-H), 3.76 (dd, *J* = 12.1, 8.8 Hz, 1 H, CH_2OH), 3.90 (dd, *J* = 12.1, 4.8 Hz, 1 H, CH_2OH), 4.02 (dt, *J* = 6.6, 3.6 Hz, 1 H, 2-H), 4.05 (dd, *J* = 2.7, 1.7 Hz, 1 H, 4-H), 4.27 (dd, *J* = 3.5, 1.4 Hz, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 35.4 (*C*H$_2$NH$_2$), 58.7 (C-2), 59.3 (*C*H$_2$OH), 68.3 (C-5), 74.5 (C-3), 75.6 (C-4) ppm. $C_6H_{16}Cl_2N_2O_3$ (235.07): calcd. C 30.65, H 6.86, N 11.92; found C 30.50, H 6.93, N 11.70.

(2*S*,3*R*,4*R*,5*R*)-2-(Aminomethyl)-5-(hydroxymethyl)-3,4-dihydroxypyrrolidine Dihydrochloride (45): The hydrogenation of **36** (0.442 g, 1 mmol) or **39** (0.444 g, 1 mmol), as described above for hydroxylamine **12** to give **21**, afforded pure **45** (0.235 g, 100%) as a white solid; m.p. >150 °C (dec.). $[a]_D^{25}$ = +43 (*c* = 1.43, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 3.54 (dd, *J* = 13.9, 6.2 Hz, 1 H, CH_2NH$_2$), 3.54 (dd, *J* = 13.9, 6.8 Hz, 1 H, CH_2NH$_2$), 3.62 (ddd, *J* = 8.8, 4.9, 2.4 Hz, 1 H, 5-H), 3.76 (dd, *J* = 12.1, 8.8 Hz, 1 H, CH_2OH), 3.90 (dd, *J* = 12.1, 4.8 Hz, 1 H, CH_2OH), 4.02 (dt, *J* = 6.6, 3.6 Hz, 1 H, 2-H), 4.05 (dd, *J* = 2.7, 1.7 Hz, 1 H, 4-H), 4.27 (dd, *J* = 3.5, 1.4 Hz, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 35.4 (CH_2NH$_2$), 58.7 (C-2), 59.3 (CH_2OH), 68.3 (C-5), 74.5 (C-3), 75.6 (C-4) ppm. $C_6H_{16}Cl_2N_2O_3$ (235.07): calcd. C 30.65, H 6.86, N 11.92; found C 30.89, H 7.01, N 11.83.

(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-1-hydroxy-5-phenylpyrrolidine (46): Phenylmagnesium bromide (6 mL of a 1 M solution in THF, 6 mmol) was added dropwise to a cooled (0 °C) solution of nitrone **8** (0.836 g, 2 mmol) in anhydrous THF. After stirring for 3 h at 0 °C the reaction was quenched with satd. aq. NH_4Cl (20 mL). The reaction mixture was diluted with diethyl ether (20 mL), the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$, and filtered, and the solvent was eliminated under reduced pressure to afford pure **46** (0.990 g, 100%), which did not need further purification. White solid; m.p. 80–82 °C (lit.[35b] value for the enantiomer m.p. 81–82 °C). $[a]_D^{24}$ = –15 (*c* = 0.15, $CHCl_3$) [lit.[35b] value for the enantiomer $[a]_D^{24}$ = +16.8 (*c* = 2.5, $CHCl_3$)]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.72–3.77 (m, 1 H, 5-H), 3.78 (dd, *J* = 9.0, 7.4 Hz, 1 H, CH_2OBn), 3.91 (dd, *J* = 9.1, 4.0 Hz, 1 H, CH_2OBn), 4.06 (dd, *J* = 7.3, 3.4 Hz, 1 H, 4-H), 4.12 (dd, *J* = 3.3, 2.8 Hz, 1 H, 3-H), 4.24 (d, *J* = 7.3 Hz, 1 H, 5-H), 4.32 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.36 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.51 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.56 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.59 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.61 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.85 (s, 1 H, NO*H*), 7.13 (dd, *J* = 6.5, 2. 5 Hz, 2 H, Ar), 7.23–7.42 (m, 16 H, Ar), 7.46 (dd, *J* = 7.4, 1.6 Hz, 2 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 66.8 (*C*H$_2$OBn), 68.8 (C-2), 71.7 (*C*H$_2$Ph), 72.0 (*C*H$_2$Ph), 73.5 (*C*H$_2$Ph), 74.1 (C-5), 83.6 (C-3), 87.6 (C-4), 127.6 (Ar), 127.6 (Ar), 127.7 (Ar), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 128.1 (Ar), 128.2 (Ar), 128.4 (Ar), 128.4 (Ar), 128.4 (Ar), 137.9 (Ar), 138.1 (Ar), 138.2 (Ar), 139.5 (Ar) ppm. $C_{32}H_{33}NO_4$ (495.55): calcd. C 77.55, H 6.71, N 2.83; found C 77.79, H 6.92, N 3.10.

(2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-phenyl-3,4-dihydro-2*H*-pyrrole 1-Oxide (47) and (2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-2-phenyl-3,4-dihydro-2*H*-pyrrole 1-Oxide (48): The oxidation of **46** (0.495 g, 1 mmol), as described above for hydroxylamine **34** to give **37**, afforded a 1 :1.4 mixture of nitrones **47** and **48**, which were separated by column chromatography (hexane/EtOAc, 3:2).

Compound 47: 0.207 g, 42%; oil. $[a]_D^{22}$ = –13 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.03 (dd, *J* = 9.9, 3.7 Hz, 1 H, CH_2OBn), 4.10 (dd, *J* = 9.9, 6.5 Hz, 1 H, CH_2OBn), 4.32 (ddd, *J* = 3.5, 2.3, 6.1 Hz, 1 H, 2-H), 4.36 (dd, *J* = 2.2, 1.1 Hz, 1 H, 3-H), 4.50 (d, *J* = 11.5 Hz, 1 H, CH_2Ph), 4.56 (d, *J* = 11.1 Hz, 1 H, CH_2Ph), 4.58 (d, *J* = 11.6 Hz, 1 H, CH_2Ph), 4.62 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.63 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.68 (d, *J* = 11.9 Hz, 1 H, CH_2Ph), 5.20 (s, 1 H, 4-H), 7.22 (dd, *J* = 3.0, 6.6 Hz, 2 H), 7.28–7.45 (m, 18 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 67.8 (*C*H$_2$OBn), 70.5 (*C*H$_2$Ph), 71.5 (*C*H$_2$Ph), 73.6 (*C*H$_2$Ph), 76.4 (C-3), 79.4 (C-2), 84.5 (C-4), 127.7 (Ar), 127.8 (Ar), 127.9 (Ar), 128.1 (Ar), 128.1 (Ar), 128.1 (Ar), 128.2 (C-5), 128.4 (Ar), 128.4 (Ar), 128.5 (Ar), 128.6 (Ar), 130.5 (Ar), 137.0 (Ar), 137.1 (Ar), 137.7 (Ar), 139.8 (Ar) ppm. $C_{32}H_{31}NO_4$ (493.54): calcd. C 77.87, H 6.33, N 2.84; found C 77.92, H 6.53, N 2.72.

Compound 48: 0.286 g, 58%; oil. $[a]_D^{21}$ = +12 (*c* = 3.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (dd, *J* = 2.3, 1.2 Hz, 1 H, 3-H), 4.42 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.48 (td, *J* = 14.1, 1.3 Hz, 1 H, CH_2OBn), 4.51 (d, *J* = 11.5 Hz, 1 H, CH_2Ph), 4.64 (s, 2 H, CH_2Ph), 4.67 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.72 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.76 (d, *J* = 14.6 Hz, 1 H, CH_2OBn), 4.86 (s, 1 H, 4-H), 4.99 (s, 1 H, 2-H), 7.21–7.25 (m, 2 H, Ar), 7.27–7.41 (m, 18 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.8 (*C*H$_2$OBn), 71.9 (*C*H$_2$Ph), 72.6 (*C*H$_2$Ph), 73.7 (*C*H$_2$Ph), 83.0 (C-4), 83.4 (C-2), 83.9 (C-3), 127.8 (Ar), 127.9 (Ar), 128.0 (Ar), 128.1 (Ar), 128.1 (Ar), 128.1 (Ar), 128.2 (Ar), 128.5 (Ar), 128.6 (Ar), 128.6 (Ar), 128.9 (Ar), 129.0 (Ar), 135.3 (Ar), 136.8 (Ar), 137.4 (Ar), 137.5 (Ar), 143.6 (C-5) ppm. $C_{32}H_{31}NO_4$ (493.54): calcd. C 77.87, H 6.33, N 2.84; found C 77.99, H 6.29, N 2.90.

(2*R*,3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-1-hydroxy-5-phenylpyrrolidine (49): DIBAH (1 mL of a 1 M solution in toluene, 1 mmol) was added dropwise under argon to a cooled (–80 °C) solution of nitrone **47** (0.493 g, 1 mmol) in anhydrous THF (20 mL). The resulting solution was stirred at –80 °C for 4 h, at which point the reaction mixture was quenched with water (1 mL) and allowed to warm to room temperature. The reaction mixture was partitioned between satd. aq. NH_4Cl (25 mL) and diethyl ether (30 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 250 mL). The combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$, and filtered, and the solvent was eliminated under reduced pressure to afford the crude product, which showed a 92:8 ratio of diastereomers by ^{1}H NMR. Purification of the crude product by radial chromatography (hexane/EtOAc, 4:1) gave pure **49** (0.401 g, 81%) as an oil. $[a]_D^{22}$ = –28 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.26 (q, *J* = 5.5 Hz, 1 H, 2-H), 3.79 (dd, *J* = 10.0, 5.4 Hz, 1 H, CH_2OBn), 3.84 (dd, *J* = 10.0, 5.5 Hz, 1 H, CH_2OBn), 3.95 (dd, *J* = 5.9, 1.5 Hz, 1 H, 3-H), 3.90 (dd, *J* = 5.7, 1.5 Hz, 1 H, 4-H), 3.96 (d, *J* = 11.9 Hz, 1 H, CH_2Ph),4.01 (d, *J* = 11.9 Hz,

1 H, CH_2Ph), 4.25 (d, J = 6.0 Hz, 1 H, 5-H), 4.48 (d, J = 11.8 Hz, 1 H, CH_2Ph), 4.52 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.62 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.66 (d, J = 12.0 Hz, 1 H, CH_2Ph), 5.01 (s, 1 H, NO*H*), 6.93 (dd, J = 6.4, 3.0 Hz, 2 H, Ar), 7.23 (dd, J = 4.9, 1.7 Hz, 1 H, Ar), 7.27–7.41 (m, 14 H, Ar),7.53 (d, J = 6.9 Hz, 1 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 70.2 (*C*H_2OBn), 71.6 (C-2), 71.7 (*C*H_2Ph), 72.1 (*C*H_2Ph), 73.4 (*C*H_2Ph), 74.8 (C-5), 82.5 (C-4), 83.2 (C-3), 127.6 (Ar), 127.6 (Ar), 127.6 (Ar), 127.7 (Ar), 127.8 (Ar), 127.8 (Ar), 127.9 (Ar), 128.1 (Ar), 128.2 (Ar), 128.4 (Ar), 128.4 (Ar), 129.2 (Ar), 136.9 (Ar), 137.7 (Ar), 138.0 (Ar), 138.3 (Ar) ppm. $C_{32}H_{33}NO_4$ (495.55): calcd. C 77.55, H 6.71, N 2.83; found C 77.48, H 6.80, N 2.68.

(2*S*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-1-hydroxy-5-phenylpyrrolidine (50): L-Selectride (1.5 mL of a 1 M solution in hexanes, 1.5 mmol) was added dropwise under argon to a cooled (–80 °C) solution of nitrone **48** (0.493 g, 1 mmol) in anhydrous THF (20 mL). The resulting solution was stirred at –80 °C for 16 h, at which point the reaction mixture was quenched with water (1 mL) and allowed to warm to room temperature. The reaction mixture was partitioned between satd. aq. NH_4Cl (25 mL) and diethyl ether (30 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 250 mL). The combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$, and filtered, and the solvent was eliminated under reduced pressure to afford the crude product, which was purified by radial chromatography (hexane/EtOAc, 4:1) to give pure **50** (0.476 g, 96%) as an oil. $[\alpha]_D^{22}$ = +14 (c = 0.835, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (dt, J = 7.3, 5.4 Hz, 1 H, 2-H), 3.86–3.93 (m, 3 H, CH_2OBn, 5-H, 4-H), 4.03 (dd, J = 9.1, 7.9 Hz, 1 H, CH_2OBn), 4.14 (dd, J = 6.7, 1.8 Hz, 1 H, 3-H), 4.31 (d, J = 11.7 Hz, 1 H, CH_2Ph), 4.37 (d, J = 11.7 Hz, 1 H, CH_2Ph), 4.60 (d, J = 11.8 Hz, 1 H, CH_2Ph), 4.61 (s, 2 H, CH_2Ph), 4.64 (d, J = 11.8 Hz, 1 H, CH_2Ph), 5.08 (s, 1 H, NO*H*), 7.12–7.15 (m, 2 H, Ar), 7.26–7.46 (m, 16 H, Ar), 7.47–7.52 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.1 (*C*H_2OBn), 69.4 (C-2), 71.9 (*C*H_2Ph), 72.2 (*C*H_2Ph), 73.5 (*C*H_2Ph), 77.4 (C-5), 80.3 (C-3), 88.0 (C-4), 127.6 (Ar), 127.7 (Ar), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 127.8 (Ar), 127.8 (Ar), 128.1 (Ar), 128.3 (Ar), 128.4 (Ar), 128.6 (Ar), 137.7 (Ar), 138.2 (Ar), 138.2 (Ar), 140.3 (Ar) ppm. $C_{32}H_{33}NO_4$ (495.55): calcd. C 77.55, H 6.71, N 2.83; found C 77.62, H 6.54, N 2.79.

(2*S*,3*R*,4*R*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-2-phenyl-3,4-dihydro-2*H*-pyrrole 1-Oxide (51): TEMPO (2 mmol) was added to a cooled (–60 °C) solution of hydroxylamine **49** (0.496 g, 1 mmol) in anhydrous CH_2Cl_2 (20 mL). The resulting solution was stirred for 48 h, at which point the solvent was evaporated under reduced pressure to give a 1:3 mixture of nitrones **51** and **47**. Purification of the mixture by radial chromatography (hexane/EtOAc, 3:2) afforded pure **51** (0.173 g, 23%) as an oil. $[\alpha]_D^{22}$ = –86 (c = 0.53, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.08 (s, 2 H, CH_2Ph), 4.31 (dd, J = 6.6, 2.4 Hz, 1 H, 3-H), 4.46 (ddd, J = 14.4, 2.3, 1.1 Hz, 1 H, CH_2OBn), 4.62 (d, J = 11.7 Hz, 1 H, CH_2Ph), 4.65 (d, J = 11.7 Hz, 1 H, CH_2Ph), 4.66 (d, J = 11.7 Hz, 1 H, CH_2Ph), 4.71 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.80 (dd, J = 14.4, 0.9 Hz, 1 H, CH_2OBn), 4.96 (dt, J = 2.1, 1.1 Hz, 1 H, 4-H), 5.42 (tdd, J = 6.4, 2.4, 1.3 Hz, 1 H, 2-H), 6.87–6.92 (m, 2 H, Ar), 7.22–7.45 (m, 18 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.5 (*C*H_2OBn), 72.4 (*C*H_2Ph), 72.9 (*C*H_2Ph), 73.7 (*C*H_2Ph), 79.4 (C-3), 79.8 (C-4), 83.3 (C-2), 127.9 (Ar), 128.0 (Ar), 128.0 (Ar), 128.0 (Ar), 128.0 (Ar), 128.1 (Ar), 128.4 (Ar), 128.4 (Ar), 128.5 (Ar), 128.6 (Ar), 128.9 (Ar), 129.7 (Ar), 131.4 (Ar), 136.7 (Ar), 137.4 (Ar), 137.5 (Ar), 143.4 (C-5) ppm. $C_{32}H_{31}NO_4$ (493.54): calcd. C 77.87, H 6.33, N 2.84; found C 77.79, H 6.234, N 2.89.

(2*S*,3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-1-hydroxy-5-phenylpyrrolidine (52): DIBAH (3 mL of a 1 M solution in toluene, 3 mmol) was added dropwise under argon to a cooled (–80 °C) solution of nitrone **51** (0.247 g, 0.5 mmol) in anhydrous THF (10 mL). The resulting solution was stirred at –80 °C for 16 h, at which point the reaction mixture was quenched with water (1 mL) and allowed to warm to room temperature. The reaction mixture was partitioned between satd. aq. NH_4Cl (25 mL) and diethyl ether (30 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$, and filtered, and the solvent was eliminated under reduced pressure to afford the crude product, which was purified by radial chromatography (hexane/EtOAc, 4:1) to give pure **52** (0.223 g, 90%) as an oil. $[\alpha]_D^{21}$ = +38 (c = 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88–3.95 (m, 2 H, 2-H, CH_2OBn), 2.98–4.03 (m, 1 H, CH_2OBn), 3.99 (d, J = 11.3 Hz, 1 H, CH_2Ph), 4.09 (d, J = 11.5 Hz, 1 H, CH_2Ph), 4.21–4.27 (m, 2 H, 5-H, 3-H), 4.57–4.67 (m, 4 H, CH_2Ph), 4.69 (d, J = 6.7 Hz, 1 H, 4-H), 6.88–6.93 (m, 2 H, Ar), 7.19–7.24 (m, 2 H, Ar), 7.29–7.39 (m, 14 H, Ar), 7.42–7.47 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.5 (*C*H_2OBn), 65.6 (C-2), 72.2 (*C*H_2Ph), 72.6 (*C*H_2Ph), 73.4 (C-5), 73.6 (*C*H_2Ph), 82.4 (C-4), 82.9 (C-3), 127.5 (Ar), 127.5 (Ar), 127.6 (Ar), 127.7 (Ar), 127.9 (Ar), 127.9 (Ar), 128.1 (Ar), 128.4 (Ar), 128.4 (Ar), 129.9 (Ar), 137.3 (Ar), 137.7 (Ar), 138.3 (Ar), 138.4 (Ar) ppm. $C_{32}H_{33}NO_4$ (495.55): calcd. C 77.55, H 6.71, N 2.83; found C 77.48, H 6.52, N 2.96.

(2*R*,3*R*,4*R*,5*R*)-3,4-Dihydroxy-2-(hydroxymethyl)-5-phenylpyrrolidine Hydrochloride (53): A solution of hydroxylamine **46** (0.248 g, 0.5 mmol) in methanol (6 mL) was treated with $Pd(OH)_2$-C (50 mg) and concentrated HCl (0.5 mL). The resulting mixture was stirred under hydrogen (5 atm) for 4 h. The catalyst was eliminated by filtration through a pad of Celite, and the filtrate was evaporated under reduced pressure to afford pure **53** (0.123 g, 100%) as a white solid; m.p. > 150 °C (dec.). $[\alpha]_D^{25}$ = +57 (c = 1.105, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 3.63 (ddd, J = 8.2, 5.5, 4.1 Hz, 1 H, 2-H), 3.83 (dd, J = 13.3, 6.3 Hz, 1 H, CH_2OH), 3.88 (dd, J = 13.3, 4.5 Hz, 1 H, CH_2OH), 4.11 (t, J = 7.5 Hz, 1 H, 3-H), 4.39 (d, J = 9.9 Hz, 1 H, 5-H), 4.43 (dd, J = 10.0, 6.9 Hz, 1 H, 4-H), 7.37–7.47 (m, 5 H, Ar) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 58.1 (*C*H_2OH), 61.9 (C-2), 63.2 (C-5), 73.7 (C-3), 77.5 (C-4), 128.3 (Ar), 128.5 (Ar), 130.3 (Ar), 131.3 (Ar) ppm. $C_{11}H_{16}ClNO_3$ (245.67): calcd. C 53.77, H 6.56, N 5.70; found C 53.82, H 6.49, N 5.83.

(2*R*,3*R*,4*R*,5*S*)-3,4-Dihydroxy-2-(hydroxymethyl)-5-phenylpyrrolidine Hydrochloride (54): The hydrogenation of **49** (0.248 g, 0.5 mmol), as described above for hydroxylamine **46** to give **53**, afforded pure **54** (0.123 g, 100%) as a white solid; m.p. >150 °C (dec.). $[\alpha]_D^{25}$ = +78 (c = 0.535, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 3.64 (ddd, J = 8.4, 4.8, 3.5 Hz, 1 H, 2-H), 3.85 (dd, J = 12.2, 8.6 Hz, 1 H, CH_2OH), 3.95 (dd, J = 12.2, 5.0 Hz, 1 H, CH_2OH), 4.11 (dd, J = 3.4, 1.3 Hz, 1 H, 3-H), 4.37 (dd, J = 3.3, 1.2 Hz, 1 H, 4-H), 4.85 (d, J = 3.3 Hz, 1 H, 5-H), 7.34–7.40 (m, 5 H, Ar) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 59.4 (*C*H_2OH), 64.8 (C-5), 67.5 (C-2), 75.9 (C-3), 76.6 (C-4), 127.5 (Ar), 128.9 (Ar), 129.1 (Ar), 130.3 (Ar) ppm. $C_{11}H_{16}ClNO_3$ (245.67): calcd. C 53.77, H 6.56, N 5.70; found C 53.86, H 6.52, N 5.59.

(2*S*,3*R*,4*R*,5*R*)-3,4-Dihydroxy-2-(hydroxymethyl)-5-phenylpyrrolidine Hydrochloride (55): The hydrogenation of **50** (0.248 g, 0.5 mmol), as described above for hydroxylamine **46** to give **53**, afforded pure **55** (0.122 g, 100%) as a white solid; m.p. >150 °C (dec.). $[\alpha]_D^{25}$ = +45 (c = 0.41, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 3.86–3.96 (m, 3 H, 2-H, CH_2OH), 4.35 (t, J = 3.3 Hz, 1 H, 3-

H), 4.41 (d, J = 5.9 Hz, 1 H, 5-H), 4.49 (dd, J = 5.9, 3.1 Hz, 1 H, 4-H), 7.40–7.50 (m, 5 H, Ar) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 56.9 (CH_2OH), 62.9 (C-2), 67.6 (C-5), 74.5 (C-3), 79.8 (C-4), 128.5 (Ar), 129.4 (Ar), 130.0 (Ar), 132.1 (Ar) ppm. $C_{11}H_{16}ClNO_3$ (245.67): calcd. C 53.77, H 6.56, N 5.70; found C 53.70, H 6.66, N 5.53.

(2*S*,3*R*,4*R*,5*S*)-3,4-Dihydroxy-2-(hydroxymethyl)-5-phenylpyrrolidine Hydrochloride (56): The hydrogenation of **52** (0.248 g, 0.5 mmol), as described above for hydroxylamine **46** to give **53**, afforded pure **56** (0.123 g, 100%) as a white solid; m.p. >150 °C (dec.). $[\alpha]_D^{25}$ = +27 (c = 0.08, H_2O). ^{1}H NMR (500 MHz, D_2O): δ = 3.90 (dd, J = 12.0, 8.2 Hz, 1 H, CH_2OH), 3.98 (dd, J = 12.1, 5.1 Hz, 1 H, CH_2OH), 3.98–4.06 (m, 1 H, 2-H), 4.30–4.34 (m, 1 H, 5-H), 4.46 (dd, J = 4.3, 1.3 Hz, 1 H, 3-H), 4.81–4.85 (s, 1 H, 4-H), 7.34–7.43 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 58.3 (CH_2OH), 62.5 (C-2), 64.0 (C-4), 75.0 (C-3), 77.4 (C-5), 127.8 (Ar), 128.8 (Ar), 131.3 (Ar) ppm. $C_{11}H_{16}ClNO_3$ (245.67): calcd. C 53.77, H 6.56, N 5.70; found C 53.88, H 6.38, N 5.90.

(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-[4-(benzyloxy)phenyl]pyrrolidine (57): A freshly prepared THF solution of 4-(benzyloxy)phenylmagnesium bromide[35b] (2 mmol) was added dropwise under argon to a cooled (0 °C) solution of nitrone **8** (0.209 g, 0.5 mmol) in anhydrous THF (10 mL). The resulting solution was stirred at 0 °C for 2 h, at which point the reaction was quenched with satd. aq. NH_4Cl (10 mL).The reaction mixture was diluted with diethyl ether (20 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$, and filtered and the solvent was eliminated under reduced pressure to afford the crude product, which was taken up in 1:1 hexane/diethyl ether. The resulting white solid was filtered off and dried to give pure **57** (0.268 g, 89%) as a white solid; m.p. 130–131 °C (lit.[35b] value for the enantiomer 131 °C). $[\alpha]_D^{25}$ = –19 (c = 1.0, $CHCl_3$) [lit.[35b] value for the enantiomer $[\alpha]_D^{25}$ = +18 (c = 0.55, $CHCl_3$)]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.71–3.75 (m, 1 H, 2-H), 3.79 (dd, J = 9.2, 7.3 Hz, 1 H, CH_2OBn), 3.91 (dd, J = 9.2, 4.2 Hz, 1 H, CH_2OBn), 4.08 (dd, J = 7.2, 3.4 Hz, 1 H, 4-H), 4.13 (t, J = 3.2 Hz, 1 H, 3-H), 4.22 (d, J = 7.2 Hz, 1 H, 5-H), 4.35 (d, J = 11.8 Hz, 1 H, CH_2Ph), 4.39 (d, J = 11.8 Hz, 1 H, CH_2Ph),4.53 (d, J = 12.0 Hz, 1 H, CH_2Ph),4.58 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.61 (d, J = 11.2 Hz, 1 H, CH_2Ph), 4.63 (d, J = 11.9 Hz, 1 H, CH_2Ph), 5.09 (s, 2 H, CH_2Ph), 6.98 (d, J = 8.7 Hz, 1 H, Ar), 7.11–7.14 (m, 2 H, Ar), 7.24–7.52 (m, 20 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 66.9 (CH_2OBn), 68.8 (C-2), 70.0 (CH_2Ph), 71.7 (CH_2Ph), 72.0 (CH_2Ph), 73.4 (CH_2Ph), 73.4 (C-5), 83.6 (C-3), 87.4 (C-4), 114.8 (Ar), 127.5 (Ar), 1267.6 (Ar), 127.6 (Ar), 127.7 (Ar), 127.7 (Ar), 128.0 (Ar), 128.1 (Ar), 128.2 (Ar), 128.4 (Ar), 128.4 (Ar), 128.6 (Ar), 129.6 (Ar), 131.6 (Ar), 137.1 (Ar), 137.9 (Ar), 138.1 (Ar), 138.2 (Ar), 158.5 (Ar) ppm. $C_{39}H_{39}NO_5$ (601.66): calcd. C 77.85, H 6.53, N 2.33; found C 77.54, H 6.47, N 2.44.

(2*R*,3*R*,4*R*,5*R*)-3,4-Dihydroxy-2-(hydroxymethyl)-5-(4-hydroxyphenyl)pyrrolidine (Radicamine B) Hydrochloride (4b): The hydrogenation of **57** (0.181 g, 0.3 mmol), as described above for hydroxylamine **12** to give **21**, afforded pure **4b** (79 mg, 100%) as a white solid; m.p. >150 °C (dec.). $[\alpha]_D^{25}$ = +81 (c = 0.25, H_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59 (ddd, J = 8.4, 5.5, 4.0 Hz, 1 H, 2-H), 3.82 (dd, J = 12.7, 5.7 Hz, 1 H, CH_2OH), 3.87 (dd, J = 12.8, 3.9 Hz, 1 H, CH_2OH), 4.09 (t, J = 7.7 Hz, 1 H, 3-H), 4.32 (d, J = 10.2 Hz, 1 H, 5-H), 4.39 (dd, J = 10.2, 7.4 Hz, 1 H, 4-H), 6.88 (d, J = 8.6 Hz, 2 H, Ar), 7.33 (d, J = 8.6 Hz, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 58.2 (CH_2OH), 61.5 (C-2), 62.8 (C-5), 73.6 (C-3), 77.1 (C-4), 116.1 (Ar), 122.8 (Ar), 130.2 (Ar), 157.0 (Ar) ppm. $C_{11}H_{16}ClNO_4$ (261.66): calcd. C 50.48, H 6.16, N 5.35; found C 50.39, H 6.38, N 5.24.

In order to allow comparisons with the literature data an analytical sample of the free amine was obtained by passing the hydrochloride through a Dowex 50WX8 ion-exchange resin. Elution with ammonia in methanol (3 M) afforded the free base of **4b** (61 mg, 90%) as a syrup after evaporation: $[\alpha]_D^{25}$ = +74 (c = 0.1, H_2O) [lit.[35b] value for the enantiomer $[\alpha]_D^{25}$ = –72.7 (c = 0.17, H_2O)]. ^{1}H NMR (400 MHz, D_2O): δ = 2.85–2.93 (m, 1 H, 2-H), 3.36 (dd, J = 11.1, 7.5 Hz, 1 H, CH_2OH), 3.42–3.57 (m, 3 H, 3-H, 5-H, CH_2OH), 3.75 (t, J = 8.3 Hz, 1 H, 4-H), 6.38 (d, J = 8.3 Hz, 2 H, Ar), 6.93 (d, J = 8.4 Hz, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 62.3 (C-2), 63.5 (CH_2OH), 63.8 (C-5), 78.4 (C-3), 82.9 (C-4), 118.7 (Ar), 126.1 (Ar), 128.8 (Ar), 165.6 (Ar) ppm. $C_{11}H_{15}NO_4$ (225.20): calcd. C 58.66, H 6.71, N 6.22; found C 58.71, H 6.59, N 6.14.

Supporting Information (see also the footnote on the first page of this article): ^{1}H, ^{13}C NMR and nOe spectra of new compounds.

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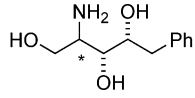
[81] Although the reaction took place quantitatively under the stated conditions, longer reaction times, especially under higher pressure, can lead to open-chain compounds because of the presence of a benzylic amine. By forcing the conditions with compounds **49** and **50** we have identified the following primary amine in a 25% yield.



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