Grignard Addition to Aldonitrones. Stereochemical Aspects and Application to the Synthesis of C_2-Symmetric Diamino Alcohols and Diamino Diols

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A new example of the stereoselective installation of the amino group at a saturated carbon center via organometallic addition of chiral aldehydes to nitrones is illustrated by the synthesis of 1,3-diamino propanol **1** and 1,4-diamino butandiol **2** units. Three diamino alcohol **1** stereotriads were obtained by stereoselective addition of alkylmagnesium halides (benzyl, cyclohexylmethyl, and metallyl) to the *N*-benzyl nitrones derived from *β*-amino-α-hydroxy aldehydes followed by reduction of the resulting *N*-benzylhydroxylamines. Three 1,4-dibenzyl substituted stereoisomers of type **2** with fixed *S* configuration at C2 and C3 were prepared by sequential and simultaneous amination in two directions starting from L-threose nitrone and L-tartraldehyde bis-nitrone, respectively. The *R*,*S*,*S*,*R* isomer obtained by the former route was converted into a seven-membered ring cyclic urea (1,3-diazapin-2-one), i.e., a compound that belongs to a class of nonpeptide HIV-1 protease inhibitors.

Introduction

Our group has been investigating in recent years an approach in which aldonitrones are used as convenient iminium derivatives of aldehydes for the synthesis of amino compounds.[1] The method consists of the substrate-stereocontrolled addition of a carbon nucleophile to the nitrone functionality and reduction of the resulting hydroxylamine (Scheme 1). Tunable syn/anti stereoselectivity of the addition reaction was achieved by precomplexation of the nitrone with various metal halides, such as magnesium, zinc, or aluminum chloride or bromide.

Initially, this synthetic pathway was directed to the simultaneous introduction of the amino group and another functionality by the use of organometallic reagents as carbon nucleophiles whose organic moiety was transformable into a functional group. Remarkable examples of this procedure are provided by the synthesis of α-amino aldehydes[2] and α-amino acids[3] by the use of 2-lithiothiazole and 2-lithiofuran as masked equivalents of the formyl and carboxylate carbanions, respectively. Our total synthesis of the peptidyl nucleoside antibiotic Polyoxin J stemmed from the application of this methodology.[4] More recently, we have considered this amination method for the synthesis of 1,3-diamino alcohols **1** and 1,4-diamino 2,3-diols **2** (Figure 1) by the use of alkyl Grignard reagents as carbon nucleophiles.[5] Compounds **1** and **2** can exist as different stereoisomers and therefore are interesting synthetic targets for testing the scope of the nitrone-based stereocontrolled amination of suitable substrates. Numerous compounds with C_2-symmetry have been reported in recent years mainly for their potential utility in the area of asymmetric catalysis.[6] By contrast, diamino alcohols **1** and diols **2** are receiving special attention in medicinal chemistry because they are the key core units of C_2-symmetric peptidic and nonpeptidic HIV-1 protease inhibitors.[7,8] Examples of these types of inhibitors are shown by the modified peptide[7a,b] A-74704 incorporating the structural motif of

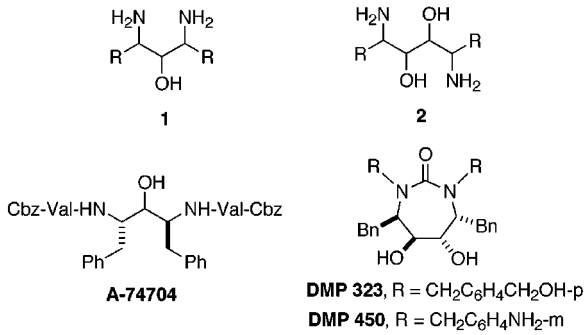
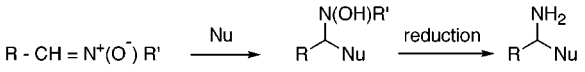


Figure 1. Structures of the HIV-1 protease inhibitors A-74704, DMP 323, and DMP 450 and their core units **1** and **2**.

Scheme 1



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(1) (a) Dondoni, A.; Perrone, D. *Aldrichimica Acta* **1997**, *30*, 35−46. (b) Dondoni, A.; Marra, A. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp 173−205. (c) Dondoni, A. *Synthesis* **1998**, 1681−1706.

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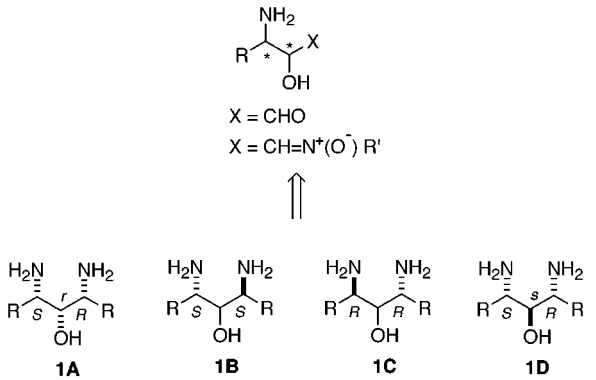
Scheme 2



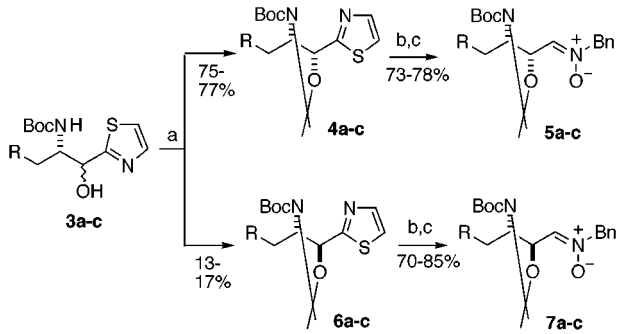
1 and the cyclic ureas[8c,e] DMP 323 and DMP 450 incorporating the motif of **2**. It is worth recalling that the rational design and synthesis of these new potent protease inhibitors have been stimulated by the recognition that the aspartic protease encoded by the HIV-1 exists in its active form as a 2-fold symmetric homodimer.[9] Consequently, compounds with C_2-symmetry matching the characteristics of the enzyme structure may act as potent and selective inhibitors of that enzyme which is essential for the maturation of fully infectious virion particles.

After the recent reports[5] on the synthesis of some stereoisomers of type **1** and **2** (R = Bn), we have since expanded the scope of our investigation and report here *in extenso* the results of the earlier and recent work.

Results and Discussion

Synthesis of 1,3-Diamino Alcohols 1. A symmetrically substituted diamino alcohol **1** exists as four stereoisomers **1A**−**D** (stereotriads),[10] i.e., two meso and two pseudo-C_2-symmetric compounds (Scheme 2). Therefore, the challenge lay in demonstrating the potential of the nitrone-based amination methodology for the synthesis of various stereotriads carrying different groups

Scheme 3[a,b]



[a] Key: **3a**−**7a**, R = Ph; **3b**−**7b**, R = *c*-C_6H_{11}; **3c**−**7c**, R = *i*-C_3H_7. [b] Reagents and conditions: (a) 2-methoxypropene, PPTS, toluene, 100 °C; (b) 1. MeOTf, MeCN; 2. $NaBH_4$, MeOH; 3. CuO, $CuCl_2$, H_2O, MeCN; (c) BnNHOH, $MgSO_4$, CH_2Cl_2.

R. According to the reaction sequence outlined in Scheme 1, a straightforward entry to these compounds would require the tunable stereoselective addition of organometallic reagents RM to nitrones of *β*-amino-α-hydroxy aldehydes. The easy access to this type of chiral aldehydes from α-amino acids by the thiazole-based aldehyde synthesis has been amply documented.[1]

Thus, the amino alcohols **3a**−**c** (Scheme 3) were prepared in good yield (ca. 80%) by addition of 2-(trimethylsilyl)thiazole (2-TST) to the *N*-Boc-α-amino aldehydes derived from L-phenylalanine,[11] L-cyclohexylalanine,[12] and L-leucine,[11] as described.[13] Acetonation of these amino alcohols and column chromatography of the mixtures of 2-thiazolyl oxazolidine epimers gave pure products **4a**−**c** and **6a**−**c**. Each individual compound was then subjected to the standard thiazole-to-formyl deblocking protocol,[14] and the resulting crude aldehyde was condensed with *N*-benzylhydroxylamine in the presence of magnesium sulfate as dehydrating agent. The *N*-benzyl nitrones **5a**−**c** and **7a**−**c** were characterized as being *Z* isomers by NOE (8−10% enhancement) between the C*H*=N and C*H*$_2$Ph signals.[2] These compounds were white solids which were storable for months without appreciable decomposition.

Each nitrone of type **5** was reacted with the suitable Grignard reagent under the same conditions (Et_2O/THF, −78 °C, 3 h), i.e., **5a** with benzylmagnesium chloride, **5b** with cyclohexylmethylmagnesium bromide, and **5c** with metallylmagnesium chloride (Scheme 4). Each reaction produced a mixture of syn and anti hydroxylamines **8** and **9** in good overall yield (Table 1). The reactions of **5a** and **5b** showed good levels of syn selectivity to give the corresponding hydroxylamines **8a** and **8b** as major products.[15] A reversal of the diastereoselectivity to give the anti adducts **9a** and **9b** as main products was achieved by complexation of the nitrones **5a** and **5b** with

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(10) The central carbon of **1B** and its enantiomer **1C**, by virtue of its symmetrical characteristics, is nonstereogenic.

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(13) Given the syn stereoselective addition of 2-TST to α-amino aldehydes whose nitrogen is singly protected (see refs 1 and 11), the amino alcohols **3a**−**c** were obtained as mixtures of syn/anti isomers in ca. 80:20 ratio. The stereochemical assignment followed the conversion of each pair of these amino alcohols into the corresponding oxazolidinones and NMR analysis as described (ref 11).

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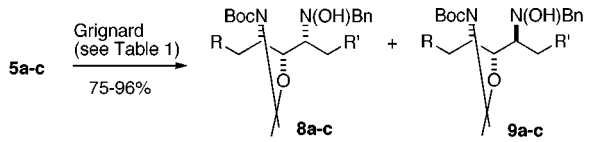
(15) The stereochemistry of the hyroxylamines obtained in this section was assigned following their conversion into the final products **1**.

Scheme 4[a]



[a] Key: **8a** and **9a**, R = R′ = Ph; **8b** and **9b**, R = R′ = *c*-C_6H_{11}; **8c** and **9c**, R = *i*-C_3H_7, R′ = $C(CH_3)$=CH_2.

diethylaluminum chloride (Et_2AlCl) prior to the Grignard addition. These stereochemical outcomes match those of other organometal additions to nitrones[2,3] and therefore are consistent with the same nonchelate Houk-type and metal chelate transition-state models **A** and **B**, respectively (Figure 2). Tunable selectivity as above could not be achieved in the addition of metallylmagnesium chloride to the nitrone **5c** because this reaction afforded the anti hydroxylamine **9c** as the major diastereomer even in the absence of Et_2AlCl.[16] The activating agent trimethylsilyl chloride (Me_3SiCl)[2,17] or the complex-destroying agent dimethylpropylene urea (DMPU)[18] had no substantial effect on the stereochemical outcome of this reaction. The same exceptional behavior had been registered[2] in the addition of 2-lithiothiazole to the nitrone derived from D-arabinose. Hence, a similar transition-state model **C** may be adopted in the metallylmagnesium chloride addition to **5c**. This type of model was earlier proposed by Kita and co-workers for the addition of O-silylated ketene acetals to nitrones.[19] Its recourse is justified when the increased size of R makes model **A** improbable because of the severe steric interaction of R with the incoming nucleophile.

Having isolated the individual *N*-benzylhydroxylamines **8a**−**c** (syn adducts) and **9a**−**c** (anti adducts), each compound was converted into the corresponding unprotected 2,3-diamino alcohol **1** (Scheme 5). The general procedure that was adopted involved the reduction of the *N*-benzylhydroxylamino group to the amino group by hydrogenolysis over $Pd(OH)_2$ and the removal of the isopropylidene and *tert*-butoxycarbonyl (Boc) protective groups by acid treatment. Thus, compounds **8a**−**c** gave the meso isomers **1Aa**−**c** and compounds **9a**−**c** gave the *S*,*S* isomers **1Ba**−**c** in satisfactory yields up to 84%. These stereoisomers were easily characterized through their NMR spectra.

Although the *R*,*R* stereoisomers **1Ca**−**c** (not shown) can be prepared using the enantiomers of nitrones **5a**−**c**, the synthesis of the meso compounds **1Da**−**c** had to be demonstrated. The anti addition of the Grignard reagents to nitrones **7a**−**c** was considered as a possible approach for the synthesis of the latter class of stereoisomers. Guided by the above results, benzylmagnesium chloride and cyclohexylmethylmagnesium bromide were added to the Et_2AlCl-precomplexed nitrones **7a** and **7b**, respectively (Scheme 6). On the other hand, the addition of metallylmagnesium chloride to **7c** was carried out in the absence of any complexing agent. These reactions afforded the expected anti adducts **10a**−**c** with high levels of selectivity, and the yields ranged from modest to good values (Table 1). The reduction of these compounds and removal of the protective groups as described above gave the meso 2,3-diamino alcohols **1Da**−**c** in comparable overall yields. These products showed NMR spectra consistent with their configuration.

In conclusion, the 1,3-diamino propanol stereotriads **1A**, **1B**, and **1D** with R = benzyl, methylcyclohexyl, and isobutyl have been prepared, and a route to **1C** has been delineated. Some of these compounds have been previously prepared by different methods employing either α-amino acid derivatives[20] or suitable chiral precursors as starting materials.[21] Instead, we have carried out the synthesis of various compounds of type **1** by a single synthetic scheme.

Synthesis of 1,4-Diamino 2,3-Diols 2 (R = Bn). Because compounds **2** can exist as a large number of stereoisomers, we decided to focus only on the synthesis of stereotetrads **2a**−**c** with the fixed *S*,*S* configuration of the diol moiety and a benzyl group at both sides of the chain (Scheme 7). These structural features are those embodied in the above-mentioned HIV-1 protease inhibitors.[7,8]

A simultaneous double amination via Grignard addition to a bis-nitrone **11** incorporating the diol moiety was envisaged as a first approach to compounds **2a**−**c.** This appealing route would allow the symmetrical extension of the diol chain in two directions by a single operation.[22] The double elaboration of symmetrically substituted diols, such as bis-epoxides,[23] bis-hydrazones,[8b,24] bis-aziridines,[25] and bis-enones[26] has been employed to introduce either the amino or the alkyl groups by suitable reactions. The *O*-isopropylidene (*S*,*S*)-tartraldehyde dinitrone **11a** (Scheme 8) was designed to allow the planned two-dimensional synthetic approach. This compound was prepared in a multigram scale starting from dimethyl L-tartrate, by protection of the hydroxy groups by acetonation and reduction of the ester to formyl groups with DIBAL as described.[27] The dialdehyde was not isolated. Instead, the resulting bis-aluminum acetal intermediate was treated with excess *N*-benzylhydroxylamine to give the pure bis-nitrone **11a** as a white solid in 51% isolated yield by chromatography. This compound was characterized as a *Z*,*Z* isomer by NOE (8% enhancement) between the C*H*=N and CH_2Ph signals.[2]

The addition of excess benzylmagnesium chloride (4 equiv) to **11a** under the above standard conditions (Et_2O/

(16) The same diastereoselectivity was obtained by addition of 2-methylvinylmagnesium chloride to **5c**, whereas *i*-butylmagnesium bromide proved to be unreactive.

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Table 1. Addition of Grignard Reagents to Nitrones 5 and 7[a]

nitrone	Grignard R′CH_2MgX	additive	product	yield[b]	ratio or dr%[c]
5a, R = Ph	R′ = Ph		**8a** + **9a**	90%	95:5
5a, R = Ph	R′ = Ph	Et_2AlCl	**8a** + **9a**	89%	6:94
5b, R = *c*-C_6H_{11}	R′ = *c*-C_6H_{11}		**8b** + **9b**	75%	80:20
5b, R = *c*-C_6H_{11}	R′ = *c*-C_6H_{11}	Et_2AlCl	**8b** + **9b**	75%	15:85
5c, R = *i*-C_3H_7	R′ = C(Me)=CH_2		**8c** + **9c**	86%	20:80
5c, R = *i*-C_3H_7	R′ = C(Me)=CH_2	Me_3SiCl	**8c** + **9c**	85%	15:85
5c, R = *i*-C_3H_7	R′ = C(Me)=CH_2	DMPU[d]	**9c**	96%	≥95
7a, R = Ph	R′ = Ph	Et_2AlCl	**10a**	96%	≥95
7b, R = *c*-C_6H_{11}	R′ = *c*-C_6H_{11}	Et_2AlCl	**10b**	65%	≥95
7c, R = *i*-C_3H_7	R′ = C(Me)=CH_2		**10c**	62%	≥95

[a] All reactions were carried out in Et_2O/THF or Et_2O at −78 °C; additivies were added to the nitrone at room temperature. [b] Isolated chemical yields of mixtures of **8** and **9** or **10** only. [c] Diastereomeric ratios (dr) were determined by ^{1}H NMR analysis of the crude mixture. [d] DMPU = dimethylpropylene urea.

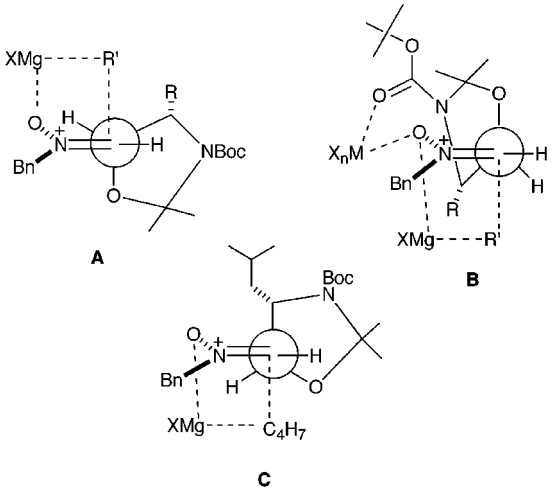
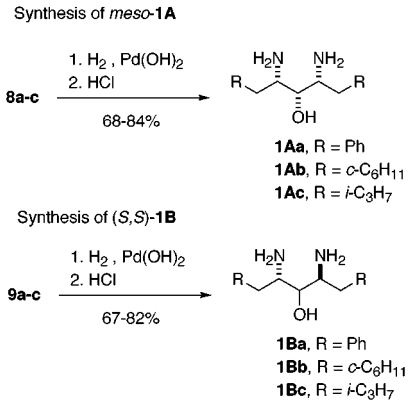


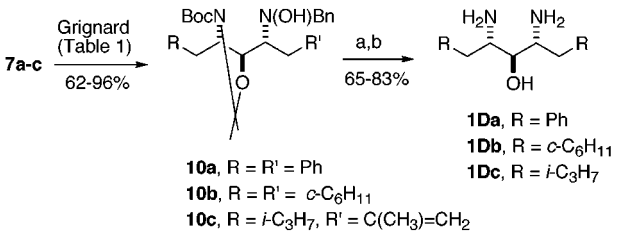
Figure 2. Proposed transition-state models for the Grignard addition to nitrones **5a**−**c**.

Scheme 5



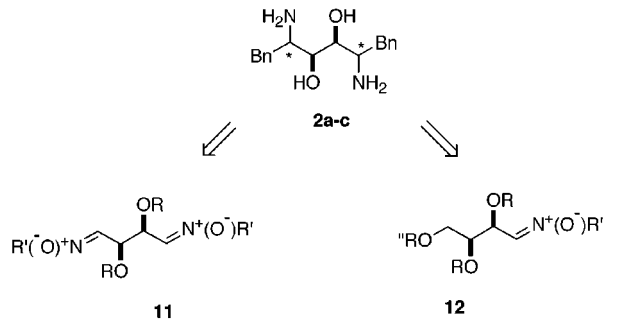
THF, −78 °C, 3 h) afforded a complex mixture of products from which the bis-hydroxylamines **13** and **14** were isolated in 60:40 ratio and 40% overall yield (Scheme 9). Similar ratios and yields were obtained in reactions performed in the presence of dimethylpropylene urea (DMPU) or by precomplexation of **11a** with $MgBr_2$ and $ZnBr_2$. The use of Et_2AlCl and $CeCl_3$ increased substantially the diastereomeric ratio of **13** to **14** (80:20 and 86:14) and to some extent the overall yield (43% and 68%). Overall, these results show that the BnMgCl addition to the bis-nitrone **11a** occurs with a double facial anti selectivity either in the absence of any additive or in the presence of chelate complex-destroying (DMPU) or complex-inducing ($MgBr_2$ and $ZnBr_2$) agents. This preferential stereochemical outcome contrasts with the syn addition of the same Grignard reagent to the nitrone **5a** in the absence of complexing agents (see Scheme 4 and Table 1). By analogy with the models that have been employed to rationalize the stereochemical outcomes in double Michael addition reactions to bis-enones[26] and bis-enoates,[28] the four ground-state conformations **D**−**G** of the nitrone **11a** can be considered (Figure 3). The double

Scheme 6[a]

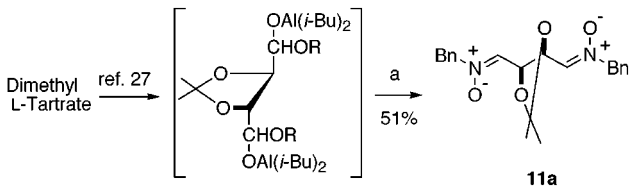


[a] Reagents and conditions: (a) H_2, $Pd(OH)_2$; (b) HCl.

Scheme 7

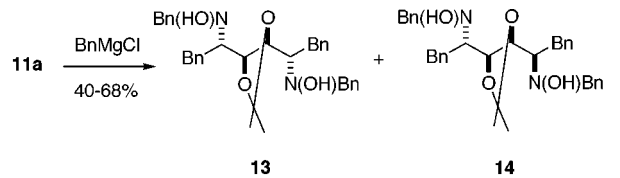


Scheme 8[a]



[a] Reagents and conditions: (a) BnNHOH, CH_2Cl_2.

Scheme 9



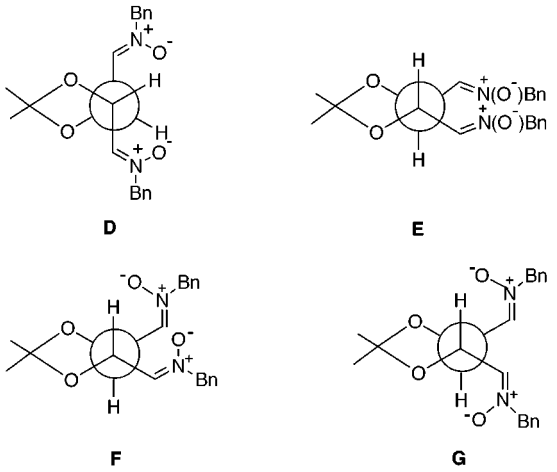


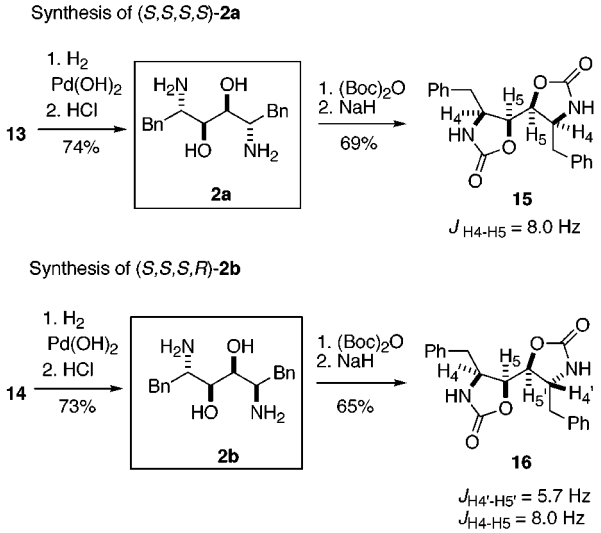
Figure 3. Newman projections of some ground-state conformations of **11a**.

anti selectivity is consistent with either **D** and **E** and Grignard double attack from the outside faces of the nitrone groups. Semiempirical calculations[29] indicate that **D** is a lower energy conformation than **E**. However, the equilibrium between these forms can easily occur by inversion of the twist conformation of the 1,3-dioxolane ring. The double interaction of Lewis acids with both nitrone groups might concur to further stabilize these forms, thus explaining the anti selectivity under these conditions as well. The formation of the minor syn,anti adduct **14** may be due to the attack from outside to the nitrone diastereofaces of conformation **F**. On the other hand, since the bis-hydroxylamine arising from a double syn addition was not observed, the conformation **G** can be reasonably ruled out in this context. The above explanations are merely tentative.[30] Other approaches based on accurate calculations of transition-state models should be considered in future studies.

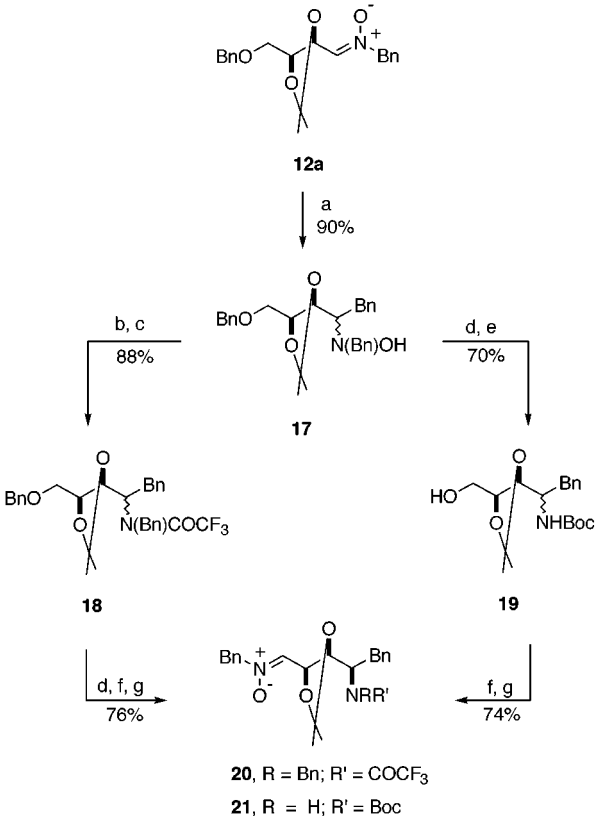
The elaboration of bis-hydroxylamines **13** and **14** to diamino diol (*S*,*S*,*S*,*S*)-**2a** (74%) and (*R*,*S*,*S*,*S*)-**2b** (73%) was carried out by the standard two-step protocol, i.e., reduction of the *N*-benzylhydroxylamino to amino groups by low-pressure hydrogenolysis over $Pd(OH)_2$ and deacetonation by aqueous hydrochloric acid (Scheme 10). In addition to consistent NMR spectra, the structures of these compounds were demonstrated from selected coupling constants in the NMR spectra of the corresponding bis-oxazolidinones **15** and **16**. Consistent with its symmetrical structure, compound **15** showed a single coupling constant value ($J = 8.0$ Hz) for the two pairs of H_4 and H_5 protons, whereas **16** showed different values for each pair ($J = 8.0$ and 5.7 Hz).

The inherent anti selectivity of the double Grignard addition to the bis-nitrone **11a** restricted the use of this reagent to the convenient synthesis of the diamino diol **2a**. Therefore, we envisaged a different approach to stereoisomers **2b** and **2c** featuring syn/syn/anti and syn/syn/syn motifs, via sequential double amination starting from a mono-nitrone of type **12** (Scheme 7). The known[2] L-threose nitrone **12a**, readily available in enantiomerically pure form from dimethyl L-tartrate, appeared to be

Scheme 10



Scheme 11[a]



[a] Reagents and conditions: (a) BnMgCl, −78 °C, Et_2O, THF; (b) $(AcO)_2Cu$, Zn, AcOH, H_2O; (c) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2; (d) $Pd(OH)_2$, H_2; (e) $(Boc)_2O$, dioxane; (f) $(COCl)_2$, DMSO, *i*-Pr_2NEt, −78 °C, CH_2Cl_2; (g) BnNHOH, $MgSO_4$, CH_2Cl_2.

a suitable starting material in this approach. The Grignard addition to this nitrone proceeded smoothly in THF at −78 °C to give the hydroxylamine **17** as a mixture of diastereoisomers in 87:13 ratio and 90% overall yield (Scheme 11). Because the separation of these isomers turned out to be quite difficult by normal column chromatography, the mixture was first converted into the N,N-diprotected amine **18**. This transformation of the nitrogen functionality involved the removal of the hydroxy group by reduction with $Zn/Cu(OAc)_2$ and then

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(29) We thank Dr. H. Banks (U.S. Army ERDEC) for the AM1 results obtained using Spartan 5.0.

(30) The ground-state conformation control on a Grignard addition reaction has been recently discussed (see ref 18).

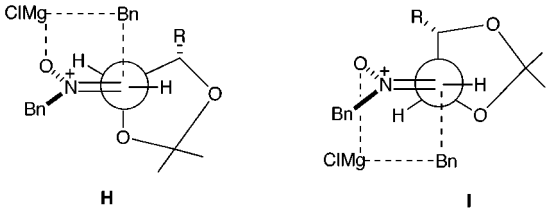
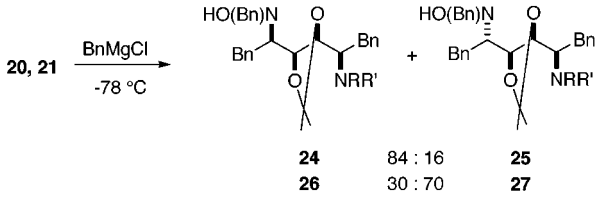


Figure 4. Proposed transition-state models for the addition of BnMgCl to nitrones **20** and **21**.

Scheme 12[a]

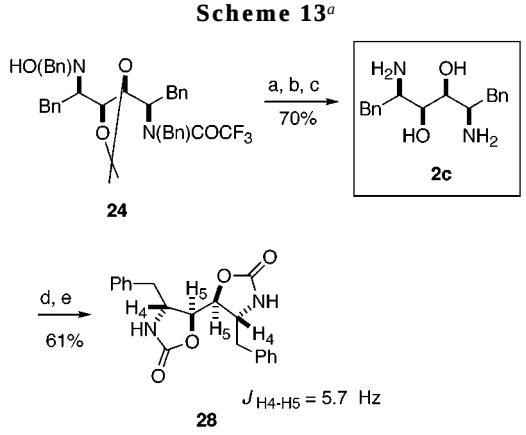


[a] Key: **24** and **25**, R = Bn, R′ = $COCF_3$ (overall yield 89%). **26** and **27**, R = H, R′ = Boc (overall yield 78%).

reaction with trifluoroacetic anhydride to introduce the $COCF_3$ protective group.[4] On the other hand, attempted double protection with the bulkier Boc was very difficult and therefore was abandoned. Alternatively, the mixture of hydroxylamines **17** was converted into a mixture of N-monoprotected (*N*-Boc) amines **19**. This transformation was carried out in the usual way, i.e., hydrogenolysis over $Pd(OH)_2$ followed by reaction with the pyrocarbonate $(Boc)_2O$. Obviously, the reductive step induced also the removal of the *O*-benzyl group. Both compounds **18** and **19** were proven by ^1H NMR analysis as being mixtures of diastereoisomers in the same 87:13 ratio as **17**. Thus, the first amino group appeared to have been inserted in the carbon chain with a satisfactory stereoselectivity. It will become evident soon that the major stereoisomer of each pair of epimers **18** and **19** possessed the anticipated[31] syn relationship between the amino and the adjacent alkoxy group. Compounds **18** and **19** were ready to face the conversion to nitrones that served for the installation of the second amino group. Accordingly, the removal of the *O*-benzyl group from **18** by hydrogenolysis over $Pd(OH)_2$, followed by the Swern oxidation and condensation of the resulting aldehyde with *N*-benzylhydroxylamine, afforded the pure *N*-benzyl nitrone **20** as the main product in 76% isolated yield by column chromatography. The same oxidation−condensation sequence was applied to the alcohol **19** to give the pure nitrone **21** in 74% yield. The all-syn relationship at the three contiguous stereocenters of nitrones **20** and **21** was demonstrated at a later point. Also isolated were the minor products **22** (not shown), epimer of **20**, and **23**, epimer of **21**. All these compounds were proved to be *Z* isomers by NOE (8−10% enhancement) between the C*H*=N and CH_2Ph signals.[2]

The Grignard addition to nitrones **20** and **21** was the second crucial step. In the event, the N,N-diprotected nitrone **20** was treated with excess benzylmagnesium chloride in THF at −78 °C (Scheme 12) as described for **12a**. The resulting mixture of products consisted of syn and anti *N*-benzylhydroxylamines **24** and **25** in 84:16 ratio and 89% overall yield. The syn selectivity parallels that observed in the same Grignard addition to the nitrone **12a**. Rather surprisingly, the benzylmagnesium chloride addition to the N-monoprotected nitrone **21** afforded a mixture of *N*-benzylhydroxylamines **26** and **27** in 78% overall yield with the anti adduct **27** as major diastereomer (dr 70%). Nevertheless, these opposite stereochemical outcomes paved the way to a more efficient synthesis of **2b** and, even more important, to the so far elusive stereotetrad **2c**. The isolated hydroxylamine **24** was converted into the diamino diol **2c** by sequential $NaBH_4$ reduction, hydrogenolysis, and acid hydrolysis (Scheme 13). A conclusive proof of the structure of **2c** came from the NMR spectra of the corresponding bis-oxazolidinone **28**. The *N*-benzylhydroxylamine **27** was elaborated in a similar way to give the diamino diol **2b** that was identical in all respects to the product obtained as described in Scheme 10. Also the minor isomers **25** and **26** were adequately characterized by conversion into the corresponding free diamino diols **2b** and **2c**, respectively. From these results, we can safely conclude that the main stereochemical outcome of the Grignard addition to the nitrone **12a** corresponds to a syn addition, and therefore compounds **17**, **18**, and **19** are mixtures of syn and anti diastereisomers in the observed 87:13 ratio. For the same reasons, the structure of nitrones **20** and **21** is as depicted.

Scheme 13[a]



[a] Reagents and conditions: (a) $NaBH_4$, EtOH, 60 °C; (b) H_2, $Pd(OH)_2$; (c) HCl; (d) $(Boc)_2O$, dioxane; (e) NaH, THF, 50 °C.

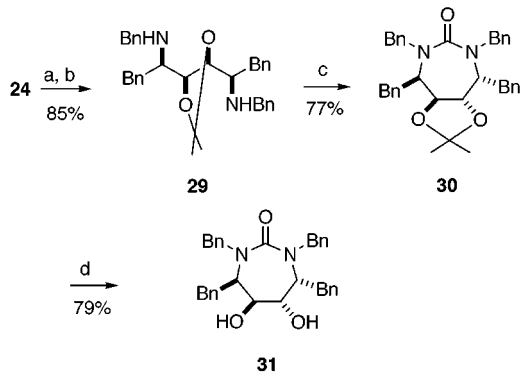
The reversal of diastereoselectivity of the Grignard addition to nitrones **20** and **21** was intriguing since the only difference between these compounds was represented by the differentially protected amino group, which however was three carbon atoms remote from the reaction site. Nevertheless, the syn addition to **20** can be explained by the Houk-type transition-state[32] model **H** previously applied to other reactions of α-alkoxy nitrones,[2] whereas the anti addition to **21** is consistent with model **I** where the antiperiplanar position is occupied by the alkyl chain and the attack of the organometal occurs from the opposite site (Figure 4). The increased congestion around the nitrone group in **H** by the bulky *N*-Boc that is present in **21** justifies switching to **I**. Evidently, models **H** and **I** are essentially identical to models **A** and **C**, respectively, depicted in Figure 2.

Collectively, these examples show that it is possible to construct the 1,4-diamino 2,3-butandiol stereotetrads **2a**−**c** by double and sequential addition of BnMgCl to a

(31) The syn addition of BnMgCl to **12a** was expected to be the main stereochemical outcome on the basis of earlier organometallic additions to the same nitrone (see ref 2).

(32) Houk, K. N.; Paddon-Row, N. M.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108−1117.

Scheme 14[a]



[a] Reagents and conditions: (a) $(AcO)_2Cu$, Zn, AcOH, H_2O; (b) $NaBH_4$, 60 °C, EtOH; (c) $COCl_2$, *N*-methylmorpoline, toluene, 100 °C; (d) HCl, dioxane.

bis- and mono-nitrone, respectively. The sequential method appears to be wider in scope because it allows the differentiation of the stereochemical outcome of the first and second addition reaction. It is worth noting that compound **2a** has been previously reported[7d,20a] and considered to be the nonscissile core unit of a peptide HIVp inhibitor.[33] The isomer **2c** featuring the syn/syn/syn motif is also a very interesting product because it represents the scaffold for the construction of cyclic ureas endowed with similar HIVp inhibitory activity.

Synthesis of a Cyclic Urea. Seven-membered ring cyclic urea derivatives (1,3-diazapin-2-ones) incorporating a chiral *S*,*S*-butandiol moiety have been designed as small, rigid, C_2-symmetrical HIVp inhibitors by a DuPont Merck group.[8a,b] Compound DMP 323 (Figure 1) was chosen as a clinical candidate, but unfortunately that clinical trial was terminated due to highly variable human oral bioavailability. Compound DMP 450 is presently in human clinical trials.[34] The efficient synthesis of these cyclic ureas is far from being a trivial problem because it involves the cyclization of suitably protected diamino diols with carbonyldiimidazole or similar reagents.[8c] The protection of the diol functionality is required in order to avoid the formation of bis-oxazolidinones of type **28**. Among the numerous protective groups that were screened for this purpose, the acetonide proved to be of little utility because the five-membered dioxolane ring imposes such a strain on the intermediate that cyclization to 1,3-diazapin-2-one becomes very difficult.[8b,c] Nevertheless, cyclic ureas with the acetonide-protected diol were convenient intermediates, for example, for the synthesis of DMP 323. Therefore, we investigated the conversion of **24** into a cyclic urea. The best route involved the dibenzylamine **29** as an intermediate (Scheme 14). This compound was obtained from **24** by methods that were applied above, i.e., reduction with $Zn/Cu(OAc)_2$ and then with $NaBH_4$ for the sequential removal of the hydroxy group and for deacetylation. The cyclic urea **30** (77%) was obtained by adding via syringe pumping toluene solutions of **29** and phosgene to *N*-methylmorpholine at 100 °C. Deacetonation of **30** to **31** was carried out by treatment with hydrochloric acid in dioxane without any apparent cleavage of the seven-membered ring cyclic urea. The overall yield of **31** from **24** was 52%.

Conclusions

The above results demonstrate that the nitrone-based amination method can be effectively employed for the synthesis of diamino alcohols and diols in different configurational arrays. The flexibility of the method relies on the Lewis acid mediated tunable stereoselectivity of the Grignard addition to the nitrone. However, in some cases, the stereochemical outcome of this key reaction could not be controlled. Current research is devoted to examining the possibilities of better stereochemical control on the 2-fold amination with bis-nitrones.

Experimental Section

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Solvents were dried over standard drying agents[35] and freshly distilled prior to use. Flash column chromatography[36] was performed on silica gel 60 (230−400 mesh), under positive pressure from a compressed air line. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with alcoholic solutions of ninhydrin or sulfuric acid. After extractive workup, organic solutions were dried over Na_2SO_4, filtered through a cotton plug, and evaporated under reduced pressure. Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded at room temperature for $CDCl_3$ solutions, unless otherwise specified. Benzylmagnesium chloride and cyclohexylmethylmagnesium bromide were prepared according to the typical literature procedure. Metallylmagnesium chloride was prepared as reported.[37]

2-[(4*S*,5*R*)- and (4*S*,5*S*)-4-Benzyl-3-*tert*-butoxycarbonyl-2,2-dimethyl-1,3-oxazolidin-5-yl]-1,3-thiazole (4a and 6a). To a solution of **3a**[11] (1.0 g, 3.0 mmol) in toluene (15.0 mL) were added 2-methoxypropene (3.0 mL, 30.0 mmol) and PPTS (catalytic). The solution was refluxed for 18 h and then concentrated to dryness. The crude residue was chromatographed on silica gel with cyclohexane/EtOAc (10:1) to give as first eluted the (4*S*,5*R*)-1,3-oxazolidine derivative **4a** (0.75 g, 67%) and then the *S*,*S* epimer **6a** (0.22 g, 20%). **4a**: mp 84−85 °C; $[\alpha]_D$ −53.3 (*c* 1.4, $CHCl_3$); ^1H NMR (DMSO-d_6, 120 °C) δ 1.37 (s, 3 H), 1.45 (s, 3 H), 1.56 (s, 9 H), 3.13 (dd, 1 H, J = 7.5, 13.5 Hz), 3.18 (dd, 1 H, J = 4.5, 13.5 Hz), 4.62 (ddd, 1 H, J = 4.0, 4.5, 7.5 Hz), 5.21 (d, 1 H, J = 4.0 Hz), 7.17−7.34 (m, 5 H), 7.63 (d, 1 H, J = 3.2 Hz), 7.72 (d, 1 H, J = 3.2 Hz). Anal. Calcd for $C_{20}H_{26}N_2O_3S$: C, 64.14; H, 7.00; N, 7.48; S, 8.56. Found: C, 64.36; H, 6.89; N, 7.54; S, 8.63. **6a**: mp 103−106 °C; $[\alpha]_D$ +34.1 (*c* 0.7, $CHCl_3$); ^1H NMR (DMSO-d_6, 120 °C) δ 1.35 (s, 9 H), 1.64 (s, 3 H), 1.70 (s, 3 H), 2.65 (dd, 1 H, J = 7.0, 14.0 Hz), 2.72 (dd, 1 H, J = 6.0, 14.0 Hz), 4.59 (ddd, 1 H, J = 5.5, 6.0, 7.0 Hz), 5.57 (d, 1 H, J = 5.5 Hz), 6.80−6.86 (m, 2 H), 7.02−7.15 (m, 3 H), 7.61 (d, 1 H, J = 3.2 Hz), 7.67 (d, 1 H, J = 3.2 Hz). Anal. Calcd for $C_{20}H_{26}N_2O_3S$: C, 64.14; H, 7.00; N, 7.48; S, 8.56. Found: C, 64.42; H, 7.25; N, 7.38; S, 8.58.

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(37) Tius, M. A.; Kannangara, G. S. K. *Org. Synth.* **1992**, *71*, 158−166.

2-[(4*S*,5*R*)- and (4*S*,5*S*)-3-*tert*-Butoxycarbonyl-4-cyclohexylmethyl-2,2-dimethyl-1,3-oxazolidin-5-yl]-1,3-thiazole (4b and 6b). The reaction was carried out as described above for **4a**, starting from the mixture of the thiazole derivative **3b**[12] (1.90 g, 5.61 mmol). Chromatography on silica gel of the crude residue with cyclohexane/EtOAc (10:1) gave as first eluted the (4*S*,5*R*)-1,3-oxazolidine derivative **4b** (1.53 g, 72%) and then the *S*,*S* epimer **6b** (0.38 g, 18%). **4b**: mp 80−83 °C; $[\alpha]_D$ −65.3 (*c* 0.4, $CHCl_3$); ^{1}H NMR δ 0.90−1.46 (m, 7 H), 1.48 (s, 9 H), 1.55 (s, 3 H), 1.61 (s, 3 H), 1.62−1.90 (m, 6 H), 4.54 (dt, 1 H, *J* = 2.8, 10.5 Hz), 5.14 (d, 1 H, *J* = 2.8 Hz), 7.36 (d, 1 H, *J* = 3.2 Hz), 7.76 (d, 1 H, *J* = 3.2 Hz); ^{13}C NMR δ 26.0, 26.2, 26.4, 27.8, 28.5, 32.3, 34.4, 34.9, 41.8, 60.7, 80.0, 95.7, 119.8, 142.6, 151.5, 172.0. Anal. Calcd for $C_{20}H_{32}N_2O_3S$: C, 63.13; H, 8.48 N, 7.36; S, 8.43. Found: C, 63.34; H, 8.69; N, 7.57; S, 8.25. **6b**: mp 55−65 °C; $[\alpha]_D$ −5.1 (*c* 0.7, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.55−1.40 (m, 11 H), 1.48 (s, 9 H), 1.46−1.60 (m, 2 H), 1.61 (s, 3 H), 1.64 (s, 3 H), 4.29 (ddd, 1 H, *J* = 4.5, 5.5, 8.0 Hz), 5.52 (d, 1 H, *J* = 5.5 Hz), 7.67 (d, 1 H, *J* = 3.2 Hz), 7.83 (d, 1 H, *J* = 3.2 Hz); ^{13}C NMR δ 24.2, 26.1, 26.3, 26.4, 27.3, 28.5, 32.8, 33.9, 34.0, 38.7, 57.8, 77.1, 93.7, 119.1, 142.6, 151.6, 167.0. Anal. Calcd for $C_{20}H_{32}N_2O_3S$: C, 63.13; H, 8.48; N, 7.36; S, 8.43. Found: C, 63.21; H, 8.45; N, 7.43; S, 8.37.

2-[(4*S*,5*R*)- and (4*S*,5*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-4-isobutyl-1,3-oxazolidin-5-yl]-1,3-thiazole (4c and 6c). The reaction was carried out as described above for **4a**, starting from the mixture of the thiazole derivative **3c**[11] (1.50 g, 5.0 mmol). Chromatography on silica gel of the crude residue with cyclohexane/Et_2O (6:1) gave as first eluted the (4*S*,5*R*)-1,3-oxazolidine derivative **4c** (1.28 g, 72%) and then the *S*,*S* epimer **6c** (0.22 g, 13%). **4c**: mp 44.5−46.0 °C; $[\alpha]_D$ −66.1 (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 0.95 (d, 6 H, *J* = 6.5 Hz), 1.47 (s, 9 H), 1.56 (s, 3 H), 1.60 (s, 3 H), 1.60−1.84 (m, 3 H), 4.45−4.53 (m, 1 H), 5.14 (d, 1 H, *J* = 2.8 Hz), 7.33 (d, 1 H, *J* = 3.2 Hz), 7.75 (d, 1 H, *J* = 3.2 Hz); ^{13}C NMR δ 21.4, 23.9, 25.6, 27.7, 28.1, 28.5, 43.5, 61.2, 79.7, 80.0, 95.7, 119.7, 142.7, 151.4, 166.5. Anal. Calcd for $C_{17}H_{28}N_2O_3S$: C, 59.97; H, 8.29; N, 8.22; S, 9.40. Found: C, 60.17; H, 8.56; N, 8.28; S, 9.08. **6c**: mp 101−103 °C; $[\alpha]_D$ +17.9 (*c* 0.6, CH_3OH); ^{1}H NMR δ 0.60 (s, 3 H), 0.80 (s, 3 H), 1.05−1.60 (m, 3 H), 1.50 (s, 9 H), 1.65 (s, 3 H), 1.70 (s, 3 H), 4.20−4.45 (m, 1 H), 5.50 (d, 1 H, *J* = 5.2 Hz), 7.35 (d, 1 H, *J* = 3.2 Hz), 7.80 (d, 1 H, *J* = 3.2 Hz); ^{13}C NMR δ 21.9, 23.5, 24.3, 25.4, 27.3, 28.5, 40.3, 58.3, 76.8, 80.1, 93.7, 119.2, 142.6, 151.6, 166.9. Anal. Calcd for $C_{17}H_{28}N_2O_3S$: C, 59.97; H, 8.29; N, 8.22; S, 9.40. Found: C, 59.84; H, 8.40; N, 8.01; S, 9.62.

(*Z*)-*N*-[(4*S*,5*R*)-4-Benzyl-3-*tert*-butoxycarbonyl-2,2-dimethyl-5-methylenyl-1,3-oxazolidine]benzylamine *N*-oxide (5a). A mixture of **4a** (1.0 g, 2.67 mmol), activated 4 Å powdered molecular sieves (5.30 g), and anhydrous MeCN (26.0 mL) was stirred at room temperature for 10 min, and then methyl triflate (0.39 mL, 3.47 mmol) was added. The suspension was stirred for 15 min and then concentrated to dryness. The residue was suspended in MeOH (26.0 mL), cooled to 0 °C, and then treated with $NaBH_4$ (0.22 g, 5.90 mmol). The mixture was stirred at room temperature for 10 min, diluted with acetone (0.50 mL), filtered through Celite, and concentrated. To a solution of the residue in MeCN/H_2O (10:1, 26.0 mL) were added CuO (1.70 g, 21.40 mmol) and then $CuCl_2 \cdot H_2O$ (0.45 g, 2.67 mmol) portionwise and under vigorous stirring. The mixture was stirred for 15 min and then filtered through Celite. After the removal of the solvent (bath temperature not exceeding 40 °C), the crude brown residue was taken up in Et_2O (5 × 26.0 mL) and sonicated by an ultrasonic cleaning bath. The liquid layer was pipetted and filtered through a pad of Florisil (100−200 mesh). The almost colorless filtrate was concentrated to give the crude aldehyde, which was dissolved in CH_2Cl_2 (15.0 mL) and treated with anhydrous $MgSO_4$ (0.50 g) and *N*-benzylhydroxylamine (0.27 g, 2.17 mmol). The resulting mixture was stirred at room temperature for 30 min, filtered through Celite, and concentrated. Chromatography on silica gel of the residue with cyclohexane/EtOAc (7:3) gave the nitrone **5a** as a white solid (0.61 g, 78%): mp 125−126 °C; $[\alpha]_D$ +17.7 (*c* 0.6, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.25 (s, 3 H), 1.47 (s, 9 H), 1.50 (s, 3 H), 2.97−3.08 (m, 2 H), 4.11 (ddd, 1 H, *J* = 4.0, 5.0, 6.5 Hz), 4.87 (d, 1 H, *J* = 13.0 Hz), 4.92 (d, 1 H, *J* = 13.0 Hz), 4.99 (dd, 1 H, *J* = 4.0, 6.5 Hz), 7.14−7.31 (m, 6 H), 7.32−7.40 (m, 5 H). Anal. Calcd for $C_{25}H_{32}N_2O_4$: C, 70.74; H, 7.60; N, 6.59. Found: C, 70.58; H, 7.71; N, 6.73.

(*Z*)-*N*-[(4*S*,5*R*)-3-*tert*-Butoxycarbonyl-4-cyclohexylmethyl-2,2-dimethyl-5-methylenyl-1,3-oxazolidine]benzylamine *N*-oxide (5b). The same procedure as described for the synthesis of **5a** was applied to **4b** (1.0 g, 2.63 mmol). Chromatography on silica gel of the crude product with cyclohexane/EtOAc (2:1) gave the nitrone **5b** as a white solid (0.85 g, 75%): mp 109−111 °C; $[\alpha]_D$ +26.7 (*c* 1.1, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.84−1.42 (m, 8 H), 1.44 (s, 9 H), 1.49 (s, 3 H), 1.53 (s, 3 H), 1.55−1.82 (m, 5 H), 3.96 (ddd, 1 H, *J* = 2.5, 4.0, 9.0 Hz), 4.84 (dd, 1 H, *J* = 2.5, 6.0 Hz), 4.96 (s, 2 H), 7.30 (d, 1 H, *J* = 6.0 Hz), 7.35−7.45 (m, 5 H). Anal. Calcd for $C_{25}H_{38}N_2O_4$: C, 69.74; H, 8.90; N, 6.50. Found: C, 69.98; H, 9.17; N, 6.51.

(*Z*)-*N*-[(4*S*,5*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-4-isobutyl-5-methylenyl-1,3-oxazolidine]benzylamine *N*-oxide (5c). The same procedure as described for the synthesis of **5a** was applied to **4c** (1.70 g, 5.0 mmol). Chromatography on silica gel of the crude product with cyclohexane/CH_2Cl_2/EtOAc (6.5:1:2.5) gave the nitrone **5c** as a white solid (1.43 g, 73%): mp 91−92 °C; $[\alpha]_D$ +45.2 (*c* 0.7, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.89 (d, 3 H, *J* = 6.5 Hz), 0.91 (d, 3 H, *J* = 6.5 Hz), 1.45 (s, 9 H), 1.49 (s, 3 H), 1.54 (s, 3 H), 1.51−1.59 (m, 2 H), 1.65−1.80 (m, 1 H), 3.93 (ddd, 1 H, *J* = 2.5, 4.5, 8.5 Hz), 4.86 (dd, 1 H, *J* = 2.5, 6.5 Hz), 4.96 (s, 2 H), 7.30−7.45 (m, 6 H). Anal. Calcd for $C_{22}H_{34}N_2O_4$: C, 67.67; H, 8.77; N, 7.17. Found: C, 67.99; H, 8.64; N, 7.28.

(*Z*)-*N*-[(4*S*,5*S*)-4-Benzyl-3-*tert*-butoxycarbonyl-2,2-dimethyl-5-methylenyl-1,3-oxazolidine]benzylamine *N*-oxide (7a). The same procedure as described for the synthesis of **5a** was applied to **6a** (0.56 g, 1.50 mmol). Chromatography on silica gel of the crude product with cyclohexane/Et_2O (4:1.5) gave the nitrone **7a** as a white solid (0.44 g, 70%): mp 153−154 °C; $[\alpha]_D$ −108.9 (*c* 0.3, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.35 (s, 9 H), 1.50 (s, 6 H), 2.66 (dd, 1 H, *J* = 5.5, 14.0 Hz), 2.74 (dd, 1 H, *J* = 7.0, 14.0 Hz), 4.51 (dt, 1 H, *J* = 5.5, 7.0 Hz), 4.68 (d, 1 H, *J* = 13.5 Hz), 4.84 (d, 1 H, *J* = 13.5 Hz), 5.02 (t, 1 H, *J* = 5.5 Hz), 7.10−7.45 (m, 11 H). Anal. Calcd for $C_{25}H_{32}N_2O_4$: C, 70.74; H, 7.60; N, 6.59. Found: C, 70.87; H, 7.52; N, 6.68.

(*Z*)-*N*-[(4*S*,5*S*)-3-*tert*-Butoxycarbonyl-4-cyclohexylmethyl-2,2-dimethyl-5-methylenyl-1,3-oxazolidine]benzylamine *N*-oxide (7b). The same procedure as described for the synthesis of **5a** was applied to **6b** (0.50 g, 1.31 mmol). Chromatography on silica gel of the crude product with cyclohexane/EtOAc (2:1) gave the nitrone **7b** (0.43 g, 76%) as a white solid: mp 98−101 °C; $[\alpha]_D$ −62.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.65−1.20 (m, 9 H), 1.45 (s, 9 H), 1.50 (s, 3 H), 1.52 (s, 3 H), 1.52−1.70 (m, 4 H), 4.21 (ddd, 1 H, *J* = 5.0, 6.5, 10.5 Hz), 4.92 (d, 1 H, *J* = 14.0 Hz), 4.93−4.98 (m, 1 H), 4.99 (d, 1 H, *J* = 14.0 Hz), 7.25 (d, 1 H, *J* = 5.0 Hz), 7.32−7.42 (m, 3 H), 7.43−7.52 (m, 2 H). Anal. Calcd for $C_{25}H_{38}N_2O_4$: C, 69.74; H, 8.90; N, 6.50. Found: C, 69.83; H, 8.89; N, 6.34.

(*Z*)-*N*-[(4*S*,5*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-4-isobutyl-5-methylenyl-1,3-oxazolidine]benzylamine *N*-oxide (7c). The same procedure as described for the synthesis of **5a** was applied to **6c** (0.50 g, 1.48 mmol). Chromatography on silica gel of the crude product with cyclohexane/CH_2Cl_2/EtOAc (6.5:1:2.5) gave the nitrone **7c** (0.49 g, 85%) as a white solid: mp 78−81 °C; $[\alpha]_D$ −52.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.74 (d, 3 H, *J* = 6.5 Hz), 0.79 (d, 3 H, *J* = 6.5 Hz), 1.10−1.40 (m, 3 H), 1.44 (s, 9 H), 1.49 (s, 3 H), 1.53 (s, 3 H), 4.13−4.20 (m, 1 H), 4.91 (d, 1 H, *J* = 13.0 Hz), 4.94−4.97 (m, 1 H), 5.00 (d, 1 H, *J* = 13.0 Hz), 7.23−7.30 (m, 1 H), 7.34−7.50 (m, 5 H). Anal. Calcd for $C_{22}H_{34}N_2O_4$: C, 67.67; H, 8.77; N, 7.17. Found: C, 67.41; H, 8.90; N, 6.93.

(2*R*,3*R*,4*S*)-2-*N*-Benzylhydroxylamine-4-*tert*-butoxycarbonylamino-1,5-diphenyl-4*N*,3*O*-isopropylidene-3-pentanol (8a). To a cold (−78 °C) solution of nitrone **5a** (0.50 g,

1.18 mmol) in Et_2O/THF (3:1, 6.0 mL) was added dropwise a freshly prepared solution of BnMgCl (0.5 M in Et_2O, 12.0 mL). The reaction solution was stirred for 3 h at −78 °C, treated with aqueous phosphate buffer (pH 7, 6.0 mL), and allowed to warm to room temperature. The white suspension was filtered through Celite, and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 5.0 mL), and the combined organic phases were dried and concentrated. Chromatography on silica gel of the residue with cyclohexane/EtOAc (9:1) afforded **8a** (0.55 g, 90%) as a syrup: $[\alpha]_D$ +15.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($C_2D_2Cl_4$, 120 °C) δ 1.28 (s, 3 H), 1.63 (s, 9 H), 1.72 (s, 3 H), 2.72 (ddd, 1 H, *J* = 5.0, 7.0, 9.0 Hz), 2.83 (dd, 1 H, *J* = 8.0, 13.0 Hz), 2.93 (dd, 1 H, *J* = 9.0, 14.0 Hz), 3.07 (dd, 1 H, *J* = 3.0, 13.0 Hz), 3.20 (dd, 1 H, *J* = 5.0, 14.0 Hz), 3.76 (d, 1 H, *J* = 14.0 Hz), 4.02 (dd, 1 H, *J* = 3.0, 7.0 Hz), 4.16 (d, 1 H, *J* = 14.0 Hz), 4.36 (dt, 1 H, *J* = 3.0, 8.0 Hz), 4.90 (s, 1 H), 6.83 (d, 2 H, *J* = 6.1 Hz), 7.10−7.20 (m, 5 H), 7.25−7.48 (m, 8 H). Anal. Calcd for $C_{32}H_{40}N_2O_4$: C, 74.39; H, 7.80; N, 5.42. Found: C, 74.11; H, 7.65; N, 5.48.

(2*S*,3*R*,4*S*)-2-*N*-Benzylhydroxylamine-4-*tert*-butoxycarbonylamino-1,5-diphenyl-4*N*,3*O*-isopropylidene-3-pentanol (9a). To a solution of nitrone **5a** (0.50 g, 1.18 mmol) in Et_2O/THF (3:1, 6.0 mL) was added a solution of Et_2AlCl (1 M in hexane, 1.18 mL). The resulting mixture was stirred at room temperature for 15 min, cooled (−78 °C), and treated as described above for **8a**. Chromatography on silica gel of the crude residue with cyclohexane/Et_2O (9:1) gave as first eluted **8a** (30.5 mg, 5%) and then **9a** (0.51 g, 84%) as a white solid: mp 114−116 °C; $[\alpha]_D$ −107.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($C_2D_2Cl_4$, 120 °C) δ 1.55 (s, 6 H), 1.60 (s, 9 H), 2.78 (dd, 1 H, *J* = 10.1, 12.8 Hz), 2.94−3.06 (m, 2 H), 3.18 (dd, 1 H, *J* = 8.3, 15.6 Hz), 3.39 (dd, 1 H, *J* = 3.2, 12.8 Hz), 3.59 (d, 1 H, *J* = 13.8 Hz), 3.71 (d, 1 H, *J* = 13.8 Hz), 4.17 (dd, 1 H, *J* = 3.2, 7.3 Hz), 4.39 (dt, 1 H, *J* = 3.2, 10.1 Hz), 7.05−7.45 (m, 15 H). Anal. Calcd for $C_{32}H_{40}N_2O_4$: C, 74.39; H, 7.80; N, 5.42. Found: C, 74.40; H, 7.76; N, 5.35.

(2*R*,3*R*,4*S*)-2-*N*-Benzylhydroxylamine-4-*tert*-butoxycarbonylamino-1,5-dicyclohexyl-4*N*,3*O*-isopropylidene-3-pentanol (8b). To a cold (−78 °C) solution of nitrone **5b** (0.40 g, 0.93 mmol) in Et_2O/THF (10:1, 5.0 mL) was added dropwise a freshly prepared solution of cyclohexylmethylmagnesium bromide (1 M in Et_2O, 4.65 mL). The reaction solution was stirred for 3 h at −78 °C, quenched, and processed as described above for **8a**. Chromatography on silica gel of the residue with cyclohexane/Et_2O (9:1) gave as first eluted **9b** (0.07 g, 14%; see below) and then **8b** (0.30 g, 61%) as a white solid: mp 54−56 °C; $[\alpha]_D$ −9.7 (*c* 0.5, CH_3OH); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.90−1.40 (m, 14 H), 1.45 (s, 12 H), 1.53 (s, 3 H), 1.54−1.84 (m, 12 H), 2.87−2.94 (m, 1 H), 3.91 (d, 1 H, *J* = 14.0 Hz), 3.98 (d, 1 H, *J* = 14.0 Hz), 4.04−4.11 (m, 2 H), 6.95 (s, 1 H), 7.20−7.40 (m, 5 H). Anal. Calcd for $C_{32}H_{52}N_2O_4$: C, 72.68; H, 9.91; N, 5.29. Found: C, 72.45; H, 9.63; N, 5.32.

(2*S*,3*R*,4*S*)-2-*N*-Benzylhydroxylamine-4-*tert*-butoxycarbonylamino-1,5-dicyclohexyl-4*N*,3*O*-isopropylidene-3-pentanol (9b). To a solution of nitrone **5b** (0.10 g, 0.23 mmol) in Et_2O/THF (10:1, 2.0 mL) was added a solution of Et_2AlCl (1 M in hexane, 0.23 mL). The resulting mixture was stirred at room temperature for 15 min, cooled (−78 °C), and treated as described above for **8b**. Chromatography on silica gel of the crude residue with cyclohexane/Et_2O (9:1) gave as first eluted **9b** (0.08 g, 64%) as a white solid and then **8b** (0.01 g, 11%). **9b**: mp 136−138 °C; $[\alpha]_D$ −7.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.90−1.30 (m, 11 H), 1.46 (s, 12 H), 1.51 (s, 3 H), 1.58−1.90 (m, 15 H), 2.90−2.97 (m, 1 H), 3.85 (d, 1 H, *J* = 14.0 Hz), 3.92 (d, 1 H, *J* = 14.0 Hz), 4.03−4.12 (m, 2 H), 7.12 (s, 1 H), 7.18−7.37 (m, 5 H). Anal. Calcd for $C_{32}H_{52}N_2O_4$: C, 72.68; H, 9.91; N, 5.29. Found: C, 72.89; H, 9.74; N, 5.50.

(4*R*,5*R*,6*S*)- and (4*S*,5*R*,6*S*)-4-*N*-Benzylhydroxylamine-6-*tert*-butoxycarbonylamino-6*N*,5*O*-isopropylidene-8-methyl-2-vinyl-5-nonanol (8c and 9c). To a cold (−78 °C) slurry of freshly prepared metallylmagnesium chloride (1 M in Et_2O, 25.6 mmol) was added dropwise a solution of the nitrone **5c** (1.0 g, 2.56 mmol) in Et_2O/THF (3:1, 13.0 mL). The reaction mixture was stirred for 3 h at −78 °C, quenched, and processed as described above for **8a**. Chromatography on silica gel of the crude residue with cyclohexane/Et_2O (9:1) gave as first eluted **9c** (0.79 g, 69%) as a white solid and then **8c** (0.21 g, 17%) as a syrup. **8c**: $[\alpha]_D$ +9.2 (*c* 0.4, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.92 (d, 3 H, *J* = 6.0 Hz), 1.43 (s, 3 H), 1.45 (s, 3 H), 1.40−1.65 (m, 3 H), 1.78 (s, 3 H), 2.13 (dd, 1 H, *J* = 7.5, 15.0 Hz), 3.08 (ddd, 1 H, *J* = 4.5, 5.7, 7.5 Hz), 3.83 (d, 1 H, *J* = 14.0 Hz), 4.04 (dd, 1 H, *J* = 4.0, 5.7 Hz), 4.05 (d, 1 H, *J* = 14.0 Hz), 4.13 (ddd, 1 H, *J* = 3.5, 4.0, 8.5 Hz), 4.81 (s, 1 H), 4.84 (s, 1 H), 7.10 (s, 1 H), 7.15−7.45 (m, 5 H). Anal. Calcd for $C_{26}H_{42}N_2O_4$: C, 69.93; H, 9.48; N, 6.27. Found: C, 70.14; H, 9.61; N, 6.05. **9c**: mp 75−77 °C; $[\alpha]_D$ +13.9 (*c* 0.6, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.93 (d, 3 H, *J* = 6.5 Hz), 0.95 (d, 3 H, *J* = 6.5 Hz), 1.45 (s, 12 H), 1.51 (s, 3 H), 1.53−1.60 (m, 2 H), 1.67−1.79 (m, 1 H), 1.80 (s, 3 H), 2.29 (dd, 1 H, *J* = 4.0, 15.0 Hz), 2.60 (dd, 1 H, *J* = 7.5, 15.0 Hz), 3.05 (ddd, 1 H, *J* = 4.0, 6.5, 7.5 Hz), 3.95 (s, 2 H), 4.04 (dd, 1 H, *J* = 3.5, 6.5 Hz), 4.06−4.12 (m, 1 H), 4.80 (s, 1 H), 4.85 (s, 1 H), 7.03 (s, 1 H), 7.15−7.35 (m, 5 H). Anal. Calcd for $C_{26}H_{42}N_2O_4$: C, 69.93; H, 9.48; N, 6.27. Found: C, 70.06; H, 9.77; N, 5.93.

(2*R*,3*S*,4*S*)-2-*N*-Benzylhydroxylamine-4-*tert*-butoxycarbonylamino-1,5-diphenyl-4*N*,3*O*-isopropylidene-3-pentanol (10a). The reaction was carried out as described above for the synthesis of the compound **9a**, starting from the nitrone **7a** (0.10 g, 0.24 mmol). Chromatography on silica gel of the crude residue with cyclohexane/Et_2O (5:1) gave **10a** (0.12 g, 96%) as a white solid: mp 88−90 °C; $[\alpha]_D$ +10.1 (*c* 0.3, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.20 (s, 9 H), 1.51 (s, 6 H), 2.58 (dd, 1 H, *J* = 8.4, 13.5 Hz), 2.96 (dd, 1 H, *J* = 4.1, 14.5 Hz), 3.01 (dd, 1 H, *J* = 4.9, 13.5 Hz), 3.31 (dd, 1 H, *J* = 6.0, 14.5 Hz), 3.39 (ddd, 1 H, *J* = 4.1, 6.0, 9.3 Hz), 3.63 (d, 1 H, *J* = 14.0 Hz), 3.83 (d, 1 H, *J* = 14.0 Hz), 4.25 (dd, 1 H, *J* = 4.5, 9.3 Hz), 4.41 (ddd, 1 H, *J* = 4.5, 4.9, 8.4 Hz), 7.05−7.49 (m, 16 H). Anal. Calcd for $C_{32}H_{40}N_2O_4$: C, 74.39; H, 7.80; N, 5.42. Found: C, 74.56; H, 7.63; N, 5.55.

(2*R*,3*S*,4*S*)-2-*N*-Benzylhydroxylamine-4-*tert*-butoxycarbonylamino-1,5-dicyclohexyl-4*N*,3*O*-isopropylidene-3-pentanol (10b). The reaction was carried out as described above for the synthesis of the compound **9b**, starting from the nitrone **7b** (0.32 g, 0.74 mmol). Chromatography on silica gel of the crude residue with cyclohexane/Et_2O (9:1) gave **10b** (0.25 g, 65%) as a syrup: $[\alpha]_D$ −4.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.80−1.45 (m, 12 H), 1.46 (s, 9 H), 1.48 (s, 3 H), 1.50 (s, 3 H), 1.51−1.98 (m, 14 H), 2.93 (ddd, 1 H, *J* = 5.0, 5.0, 9.0 Hz), 3.74 (d, 1 H, *J* = 14.0 Hz), 3.89 (d, 1 H, *J* = 14.0 Hz), 4.07 (dd, 1 H, *J* = 4.5, 9.0 Hz), 4.17 (ddd, 1 H, *J* = 4.5, 5.5, 8.0 Hz), 7.18−7.38 (m, 5 H). Anal. Calcd for $C_{32}H_{52}N_2O_4$: C, 72.68; H, 9.91; N, 5.29. Found: C, 72.44; H, 9.71; N, 4.94.

(4*R*,5*S*,6*S*)-4-*N*-Benzylhydroxylamine-6-*tert*-butoxycarbonylamino-6*N*,5*O*-isopropylidene-8-methyl-2-vinyl-5-nonanol (10c). The reaction was carried out as described above for the synthesis of the compounds **8c** and **9c**, starting from the nitrone **7c** (0.20 g, 0.51 mmol). Chromatography on silica gel of the crude residue with cyclohexane/Et_2O (9:1) gave **10c** (0.14 g, 62%) as syrup: $[\alpha]_D$ +10.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 0.87 (d, 3 H, *J* = 6.5 Hz), 0.92 (d, 3 H, *J* = 6.5 Hz), 1.20−1.32 (m, 1 H), 1.45 (s, 9 H), 1.48 (s, 3 H), 1.50 (s, 3 H), 1.50−1.58 (m, 1 H), 1.64−1.82 (m, 1 H), 1.82 (s, 3 H), 2.25 (dd, 1 H, *J* = 4.5, 15.0 Hz), 2.76 (dd, 1 H, *J* = 5.5, 15.0 Hz), 3.09 (ddd, 1 H, *J* = 4.5, 5.5, 9.5 Hz), 3.79 (d, 1 H, *J* = 13.5 Hz), 3.97 (d, 1 H, *J* = 13.5 Hz), 4.07 (dd, 1 H, *J* = 4.5, 9.5 Hz), 4.13−4.21 (m, 1 H), 4.79 (s, 1 H), 4.86 (s, 1 H), 7.20−7.35 (m, 5 H), 8.19 (s, 1 H). Anal. Calcd for $C_{26}H_{42}N_2O_4$: C, 69.93; H, 9.48; N, 6.27. Found: C, 70.15; H, 9.39; N, 6.54.

(2*R*,3*r*,4*S*)-2,4-Diamino-1,5-diphenyl-3-pentanol (1Aa). To a solution of **8a** (0.20 g, 0.39 mmol) in AcOH/EtOH (9:1, 4.0 mL) was added $Pd(OH)_2$ (20% on C, 0.10 g). The resulting mixture was stirred at room temperature under 3 atm of H_2 for 18 h, filtered through Celite, and concentrated. To the residue was added an aqueous solution of HCl (6.0 M, 3.0 mL), and the resulting suspension was heated to 90 °C for 3 h and then concentrated. The crude residue was neutralized with an aqueous solution of NaOH (3.0 M) and extracted with $CHCl_3$ (3 × 5.0 mL). The combined organic layers were dried

and concentrated. Chromatography on silica gel with CH_2Cl_2/MeOH/NH_4OH (89:10:1) gave pure **1Aa** (90.0 mg, 84%) as a white solid: mp 105−107 °C; ^{1}H NMR δ 2.59 (dd, 2 H, J = 9.0, 13.5 Hz), 2.92 (dd, 2 H, J = 5.0, 13.5 Hz), 3.09 (ddd, 2 H, J = 3.5, 5.0, 9.0 Hz), 3.31 (t, 1 H, J = 3.5 Hz), 7.15−7.40 (m, 10 H); ^{13}C NMR δ 42.1, 55.3, 74.0, 126.3, 128.5, 129.3, 138.9. Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.34; H, 8.32; N, 10.28.

(2*R*,3*r*,4*S*)-2,4-Diamino-1,5-dicyclohexyl-3-pentanol (1Ab). The same procedure as described above for **1Aa** was applied to **8b** (0.15 g, 0.29 mmol). Chromatography on silica gel of the crude product with CH_2Cl_2/MeOH/NH_4OH (86:13:1) gave pure **1Ab** (56.0 mg, 69%) as a syrup: ^{1}H NMR δ 0.80−1.95 (m, 26 H), 2.84 (ddd, 2 H, J = 4.0, 4.3, 8.3 Hz), 2.99 (t, 1 H, J = 4.0 Hz); ^{13}C NMR δ 26.1, 26.3, 26.5, 32.7, 34.2, 34.3, 43.3, 50.0, 76.2. Anal. Calcd for $C_{17}H_{34}N_2O$: C, 72.29; H, 12.13; N, 9.91. Found: C, 72.34; H, 11.95; N, 9.65.

(4*R*,5*r*,6*S*)-4,6-Diamino-2,8-dimethyl-5-nonanol (1Ac). The same procedure as described above for **1Aa** was applied to **8c** (0.21 g, 0.47 mmol). Chromatography on silica gel of the crude product with CH_2Cl_2/MeOH/NH_4OH (89:10:1) gave pure **1Ac** (65.0 mg, 68%) as a syrup: ^{1}H NMR δ 0.90 (d, 6 H, J = 6.5 Hz), 0.94 (d, 6 H, J = 6.5 Hz), 1.20−1.38 (m, 4 H), 1.68−1.82 (m, 2 H), 2.76−2.86 (m, 2 H), 3.03 (t, 1 H, J = 4.0 Hz); ^{13}C NMR δ 21.85, 23.5, 24.6, 44.7, 51.0, 75.9. Anal. Calcd for $C_{11}H_{26}N_2O$: C, 65.30; H, 12.95; N, 13.84. Found: C, 65.35; H, 13.16; N, 14.07.

(2*S*,4*S*)-2,4-Diamino-1,5-diphenyl-3-pentanol (1Ba). The same procedure as described above for **1Aa** was applied to **9a** (0.18 g, 0.35 mmol). Chromatography on silica gel of the crude compound with CH_2Cl_2/MeOH/NH_4OH (89:10:1) gave pure **1Ba** (78.0 mg, 82%) as a white solid: mp 138−139 °C from cyclohexane/EtOAc (lit.[20a] 135−137 °C); $[\alpha]_D$ −11.1 (*c* 0.4, $CHCl_3$); ^{1}H NMR δ 2.50 (dd, 1 H, J = 9.7, 13.4 Hz), 2.65 (dd, 1 H, J = 9.4, 13.4 Hz), 2.91 (dd, 1 H, J = 4.6, 13.4 Hz), 3.01 (dd, 1 H, J = 3.2, 13.4 Hz), 3.14 (ddd, 1 H, J = 3.2, 4.8, 9.7 Hz), 3.31−3.43 (m, 2 H), 7.15−7.45 (m, 10 H); ^{13}C NMR δ 40.0, 41.5, 52.5, 55.8, 75.2, 126.3, 126.4, 128.5, 128.6, 129.2, 138.9, 139.2. Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.47; H, 8.29; N, 10.43.

(2*S*,4*S*)-2,4-Diamino-1,5-dicyclohexyl-3-pentanol (1Bb). The same procedure as described above for **1Aa** was applied to **9b** (0.07 g, 0.14 mmol). Chromatography on silica gel of the crude compound with CH_2Cl_2/MeOH/NH_4OH (86:13:1) gave pure **1Bb** (26.0 mg, 67%) as a white solid: mp 63−65 °C; $[\alpha]_D$ −25.5 (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 0.75−1.90 (m, 26 H), 2.99 (ddd, 2 H, J = 4.1, 4.5, 8.8 Hz), 3.14 (t, 1 H, J = 4.1 Hz); ^{13}C NMR δ 26.1, 26.3, 26.4, 26.5, 32.4, 32.7, 34.1, 34.2, 34.6, 40.2, 42.8, 48.1, 50.8, 76.7. Anal. Calcd for $C_{17}H_{34}N_2O$: C, 72.29; H, 12.13; N, 9.91. Found: C, 72.47; H, 12.38; N, 9.69.

(4*S*,6*S*)-4,6-Diamino-2,8-dimethyl-5-nonanol (1Bc). The same procedure as described above for **1Aa** was applied to **9c** (0.50 g, 1.12 mmol). Chromatography on silica gel of the crude compound with CH_2Cl_2/MeOH/NH_4OH (89:10:1) gave pure **1Bc** (0.18 g, 79%) as a white solid: mp 60−61 °C; $[\alpha]_D$ −27.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 0.88 (d, 3 H, J = 6.5 Hz), 0.94 (d, 3 H, J = 6.5 Hz), 0.96 (d, 3 H, J = 6.5 Hz), 1.16−1.40 (m, 4 H), 1.62−1.78 (m, 2 H), 2.94−3.60 (m, 2 H), 3.18 (t, 1 H, J = 4 Hz); ^{13}C NMR δ 21.5, 21.8, 23.4, 23.9, 24.5, 24.6, 41.4, 43.9, 49.1, 51.7, 76.0. Anal. Calcd for $C_{11}H_{26}N_2O$: C, 65.30; H, 12.95; N, 13.84. Found: C, 65.20; H, 12.84; N, 13.95.

(2*R*,3*s*,4*S*)-2,4-Diamino-1,5-diphenyl-3-pentanol (1Da). The same procedure as described above for **1Aa** was applied to **10a** (0.11 g, 0.21 mmol). Chromatography on silica gel of the crude compound with CH_2Cl_2/MeOH/NH_4OH (89:10:1) gave pure **1Da** (47.0 mg, 83%) as a white solid: mp 131−133 °C; ^{1}H NMR δ 2.52 (dd, 2 H, J = 10.1, 13.5 Hz), 3.17 (dd, 2 H, J = 3.0, 13.5 Hz), 3.29 (ddd, 2 H, J = 3.0, 5.7, 10.1 Hz), 3.39 (t, 1 H, J = 5.7 Hz), 7.17−7.40 (m, 10 H); ^{13}C NMR δ 38.5, 53.5, 76.0, 126.3, 128.5, 129.4, 139.1. Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.69; H, 8.11; N, 10.22.

(2*R*,3*s*,4*S*)-2,4-Diamino-1,5-dicyclohexyl-3-pentanol (1Db). The same procedure as described above for **1Aa** was applied to **10b** (0.20 g, 0.38 mmol). Chromatography on silica gel of the crude compound with CH_2Cl_2/MeOH/NH_4OH (86:13:1) gave pure **1Db** (73.0 mg, 68%) as a white solid: mp 136−140 °C from $CHCl_3$/AcOEt; ^{1}H NMR δ 0.75−2.00 (m, 26 H), 3.02 (ddd, 2 H, J = 2.5, 5.5, 10.0 Hz), 3.19 (t, 1 H, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 26.1, 26.4, 26.5, 32.2, 34.1, 34.9, 39.8, 49.2, 78.8. Anal. Calcd for $C_{17}H_{34}N_2O$: C, 72.29; H, 12.13; N, 9.91. Found: C, 72.54; H, 12.55; N, 9.95.

(4*R*,5*s*,6*S*)-4,6-Diamino-2,8-dimethyl-5-nonanol (1Dc). The same procedure as described above for **1Aa** was applied to **10c** (0.10 g, 0.22 mmol). Chromatography on silica gel of the crude compound with CH_2Cl_2/MeOH/NH_4OH (89:10:1) gave pure **1Dc** (29.0 mg, 65%) as a white solid: mp 121−124 °C from EtOAc; ^{1}H NMR δ 0.92 (d, 6 H, J = 6.5 Hz), 0.97 (d, 6 H, J = 6.5 Hz), 1.27 (ddd, 2 H, J = 4.0, 10.0, 14.0 Hz), 1.40 (ddd, 2 H, J = 3.0, 10.0, 14.0 Hz), 1.66−1.82 (m, 2 H), 2.99 (ddd, 2 H, J = 3.0, 5.5, 10.0 Hz), 3.17 (t, 1 H, J = 5.5 Hz); ^{13}C NMR δ 21.3, 24.2, 24.6, 41.3, 50.0, 78.9. Anal. Calcd for $C_{11}H_{26}N_2O$: C, 65.30; H, 12.95; N, 13.84. Found: C, 65.23; H, 12.71; N, 13.79.

(*Z*,*Z*)-*N*,*N*-[(4*S*,5*S*)-2,2-dimethyl-4,5-dimethylenyl-1,3-dioxolane]-bis(benzylamine *N*-oxide) (11a). To a cold (−40 °C) solution of dimethyl isopropylidene L-tartrate[27] (3.50 g, 16.0 mmol) in CH_2Cl_2 (50.0 mL) was added dropwise a solution of DIBAL (1.5 M, 21.30 mL). The solution was stirred at this temperature for 2 h and then treated with MeOH (1.25 mL). When the H_2 evolution was completed, the reaction mixture was allowed to warm to −5 °C and then a solution of *N*-benzylhydroxylamine (4.13 g, 33.60 mmol) in CH_2Cl_2 (5.0 mL) was added. The resulting mixture was stirred at this temperature for 30 min and at room temperature for 2 h and then treated with an aqueous solution of NaOH (1 M, 50.0 mL). The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15.0 mL). The combined organic layers were washed with a solution of aqueous phosphate buffer (pH 7, 50.0 mL), dried, and concentrated. Chromatography of the residue on silica gel with EtOAc/MeOH (9:1) gave the bis-nitrone **11a** (3.0 g, 51%) as a white solid: mp 105−106 °C from Et_2O; $[\alpha]_D$ +78.9 (*c* 0.4, $CHCl_3$); ^{1}H NMR δ 1.40 (s, 6 H), 4.90 (s, 4 H), 5.02−5.10 (m, 2 H), 6.86−6.94 (m, 2 H), 7.36−7.46 (m, 10 H); ^{13}C NMR δ 26.3, 69.3, 73.4, 110.6, 128.9, 129.0, 129.4, 132.0, 135.4. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.20; H, 6.26; N, 7.67.

(2*S*,3*S*,4*S*,5*S*)- and (2*R*,3*S*,4*S*,5*S*)-2,5-Bis(*N*-benzylhydroxylamine)-3,4-*O*-isopropylidene-1,6-diphenyl-3,4-hexandiol (13 and 14). To a cold (−78 °C) solution of nitrone **11a** (0.50 g, 1.36 mmol) in THF/Et_2O (1:1, 7.0 mL) was added dropwise a freshly prepared solution of BnMgCl (0.5 M in Et_2O, 10.9 mL). The reaction was stirred for 3 h at −78 °C, treated with a solution of aqueous phosphate buffer (pH 7, 15.0 mL), and allowed to warm to room temperature. The white suspension was filtered through Celite, and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 5.0 mL), and the combined organic phases were dried and concentrated. Chromatography on silica gel of the residue with cyclohexane/Et_2O (9:1) gave as first eluted the compound **13** (0.18 g, 24%) as a white solid and then **14** (0.12 g, 16%) as a white solid. **13**: mp 91−92 °C; $[\alpha]_D$ −80.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 1.35 (s, 6 H), 3.09 (dd, 2 H, J = 2.6, 15.0 Hz), 3.14 (ddd, 2 H, J = 2.6, 6.1, 9.3 Hz), 3.46 (dd, 2 H, J = 6.1, 15.0 Hz), 3.46 (d, 2 H, J = 12.8 Hz), 3.85 (d, 2 H, J = 12.8 Hz), 4.10 (d, 2 H, J = 9.3 Hz), 6.83−6.89 (m, 4 H), 7.09 (s, 2 H), 7.15−7.35 (m, 16 H); ^{13}C NMR δ 26.9, 31.5, 61.3, 72.5, 81.7, 108.6, 125.7, 127.5, 128.4, 129.3, 129.4, 136.4, 142.3. Anal. Calcd for $C_{35}H_{40}N_2O_4$: C, 76.06; H, 7.29; N, 5.07. Found: C, 75.96; H, 7.27; N, 5.46. **14**: mp 136−138 °C from cyclohexane/EtOAc; $[\alpha]_D$ −62.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 1.35 (s, 3 H), 1.50 (s, 3 H), 2.63 (dd, 1 H, J = 6.0, 15.0 Hz), 3.08−3.23 (m, 3 H), 3.33−3.54 (m, 3 H), 3.40 (d, 1 H, J = 13.0 Hz), 3.80 (d, 1 H, J = 13.0 Hz), 4.01 (d, 1 H, J = 13.5 Hz), 4.25 (dd, 1 H, J = 7.0, 10.0 Hz), 4.62−4.70 (m, 1 H), 6.78−6.90 (m, 2 H), 7.00−7.50 (m, 20 H); ^{13}C NMR δ 26.6, 27.3, 31.9, 33.0 61.0, 61.6, 70.5, 72.0, 78.7, 79.1, 108.6, 125.8, 126.2, 127.2, 127.3, 128.2, 128.4, 128.6, 128.8, 128.9, 129.1, 129.2, 136.4, 137.3, 140.8, 142.0. Anal. Calcd for $C_{35}H_{40}N_2O_4$: C, 76.06; H, 7.29; N, 5.07. Found: C, 75.99; H, 7.36; N, 5.19

Addition of BnMgCl to the Bis-nitrone 11a with DMPU. A cold (−78 °C) solution of nitrone **11a** (0.10 g, 0.27 mmol) in THF/DMPU (1:1, 2.0 mL) was treated as described above for the synthesis of **13** and **14**. Chromatography on silica gel of the crude residue afforded **13** (54.0 mg, 36%) and **14** (36.0 mg, 24%).

Addition of $CeCl_3$/BnMgCl to the Bis-nitrone 11a. To a cold (−78 °C) suspension of anhydrous $CeCl_3$ (0.67 g, 2.71 mmol) in THF (6.0 mL) was added a solution of freshly prepared BnMgCl in Et_2O (0.5 M, 10.8 mL). The resulting yellow slurry was stirred at this temperature for 1 h, and then a solution of the bis-nitrone **11a** (0.10 g, 0.27 mmol) in THF (1.35 mL) was added. The reaction was stirred at −78 °C for 1 h and then slowly allowed to warm to 0 °C. A solution of aqueous phosphate buffer (pH 7, 17.0 mL) was added, and the mixture was processed as described above for **13** and **14**. Chromatography on silica gel of the crude residue afforded **13** (88.0 mg, 59%) and **14** (13.0 mg, 9%).

Addition of BnMgCl to the Bis-nitrone 11a Precomplexed with Et_2AlCl. To a solution of nitrone **11a** (0.10 g, 0.27 mmol) in THF (1.50 mL) was added a solution of Et_2AlCl (1 M in hexane, 0.27 mL). The resulting mixture was stirred at room temperature for 15 min, cooled (−78 °C), and treated as described above for **13** and **14**. Chromatography on silica gel of the crude residue afforded **13** (54.0 mg, 36%) and **14** (13.0 mg, 9%).

Addition of BnMgCl to the Bis-nitrone 11a Precomplexed with $MgBr_2$. To a solution of nitrone **11a** (0.10 g, 0.27 mmol) in THF (1.50 mL) was added anhydrous $MgBr_2$ (0.05 g, 0.27 mmol). The resulting mixture was stirred at room temperature for 15 min, cooled (−78 °C), and treated as described above for **13** and **14**. Chromatography on silica gel of the crude residue afforded **13** (40.0 mg, 27%) and **14** (27.0 mg, 18%).

Addition of BnMgCl to the Bis-nitrone 11a Precomplexed with $ZnBr_2$. To a solution of nitrone **11a** (0.10 g, 0.27 mmol) in THF (1.50 mL) was added anhydrous $ZnBr_2$ (60.8 mg, 0.27 mmol). The resulting mixture was stirred at room temperature for 15 min, cooled (−78 °C), and treated as described above for **13** and **14**. Chromatography on silica gel of the crude residue afforded **13** (49.0 mg, 33%) and **14** (25.0 mg, 17%).

(2*S*,3*S*,4*S*,5*S*)-2,5-Diamino-1,6-diphenyl-3,4-hexandiol (2a). The same procedure as described above for the synthesis of **1Aa** was applied to **13** (0.15 g, 0.27 mmol). Chromatography on silica gel of the crude compound with $CHCl_3$/MeOH/NH_4OH (89:10:1) afforded **2a** (60.0 mg 74%) as a white solid: mp 183−185 °C (dec) [lit.[7d] 150 °C (dec)]; $[\alpha]_D$ −31.7 (c 0.3, $CHCl_3$) [lit.[7d] −33.0 (*c* 0.18, $CHCl_3$)]; ^{1}H NMR δ 2.64 (dd, 2 H, J = 10.6, 13.4 Hz), 2.85 (dd, 2 H, J = 3.5, 13.4 Hz), 3.60 (ddd, 2 H, J = 2.8, 3.5, 10.6 Hz), 3.92 (d, 2 H, J = 2.8 Hz), 7.15−7.42 (m, 10 H); ^{13}C NMR δ 38.5, 56.8, 72.8, 126.7, 128.8, 129.0, 138.5. Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.32. Found: C, 71.69; H, 8.18; N, 9.52.

(2*R*,3*S*,4*S*,5*S*)-2,5-Diamino-1,6-diphenyl-3,4-hexandiol (2b). The same procedure as described above for the synthesis of **1Aa** was applied to **14** (0.15 g, 0.27 mmol). Chromatography on silica gel of the crude compound with $CHCl_3$/MeOH/NH_4OH (89:10:1) afforded **2b** (59.0 mg 73%) as a white solid: mp 114−115 °C; $[\alpha]_D$ −45.6 (*c* 0.75, $CHCl_3$); ^{1}H NMR δ 2.60 (dd, 1 H, J = 10.3, 13.3 Hz), 2.72 (dd, 1 H, J = 3.3, 11.5 Hz), 2.80 (dd, 1 H, J = 4.2, 13.3 Hz), 2.94 (dd, 1 H, J = 5.4, 11.5 Hz), 2.95−3.01 (m, 1 H), 3.52 (ddd, 1 H, J = 3.6, 4.2, 10.3 Hz), 3.60 (dd, 1 H, J = 1.2, 3.6 Hz), 3.96 (bs, 1 H), 7.10−7.36 (m, 10 H); ^{13}C NMR δ 38.6, 43.3, 56.7, 57.5, 71.0, 76.2, 126.4, 126.6, 128.6, 128.7, 129.0, 129.3, 138.6, 138.8. Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.32. Found: C, 72.04; H, 7.85; N, 9.32.

(4*S*,5*S*,4′*S*,5′*S*)-5,5′-Bis(4-benzyloxazolidin-2-one) (15). To a solution of **2a** (20.0 mg, 0.07 mmol) in dioxane (2.0 mL) was added $(Boc)_2O$ (34.0 mg, 0.15 mmol). The solution was stirred at room temperature for 18 h and then concentrated. The residue was dissolved in THF (2.0 mL) and treated with NaH (60% oil dispersion, 6.0 mg, 0.15 mmol). The resulting suspension was refluxed for 3 h, treated with MeOH (2 drops), and concentrated. Chromatography on silica gel of the residue with $CHCl_3$/EtOAc (3:2) afforded **15** (17.0 mg 69%) as a white solid: mp 270 °C (dec) from $CHCl_3$; $[\alpha]_D$ +168.0 (*c* 0.5, DMSO); ^{1}H NMR δ 3.03 (dd, 2 H, J = 4.4, 14.0 Hz), 3.11 (dd, 2 H, J = 10.5, 14.0 Hz), 4.29 (ddd, 2 H, J = 4.4, 8.0, 10.5 Hz), 4.94 (d, 2 H, J = 8.0 Hz), 5.00 (s, 2 H), 7.00−7.50 (m, 10 H); ^{13}C NMR δ 36.9, 56.3, 75.2, 127.5, 128.8, 129.3, 136.4, 156.9. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.45; H, 5.57; N, 7.94.

(4*R*,5*S*,4′*S*,5′*S*)-5,5′-Bis(4-benzyloxazolidin-2-one) (16). The reaction was carried out as described above for the synthesis of the bis-oxazolidinone **15**, starting from **2b** (20.0 mg, 0.07 mmol). Chromatography on silica gel of the residue with $CHCl_3$/EtOAc (3:2) afforded **16** (16.0 mg, 65%) as a white solid: mp 167−170 °C from $CHCl_3$; $[\alpha]_D$ +66.0 (*c* 0.5, DMSO); ^{1}H NMR δ 2.73 (dd, 1 H, J = 7.5, 13.5 Hz), 2.95 (dd, 1 H, J = 6.0, 14.0 Hz), 2.97 (dd, 1 H, J = 6.5, 13.5 Hz), 3.08 (dd, 1 H, J = 9.0, 14.0 Hz), 4.05 (d, 1 H, J = 8.0 Hz), 4.10 (ddd, 1 H, J = 5.7, 6.5, 7.5 Hz), 4.20 (ddd, 1 H, J = 6.0, 8.0, 9.0 Hz), 4.41 (d, 1 H, J = 5.7 Hz), 5.40 (s, 1 H), 6.00 (s, 1 H), 6.95−7.10 (m, 2 H), 7.12−7.20 (m, 2 H), 7.20−7.40 (m, 6 H); ^{13}C NMR δ 36.4, 41.5, 55.7, 77.2, 78.5, 127.4, 127.6, 128.7, 128.9, 129.2, 134.9, 136.5, 156.8, 157.1. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.83; H, 5.84; N, 8.18.

(2*S*,3*S*,4*R*)- and (2*S*,3*S*,4*S*)-4-*N*-Benzylhydroxylamine-1-*O*-benzyl-2,3-*O*-isopropylidene-5-phenyl-1,2,3-pentantriol (17). To a cold (−78 °C) solution of the nitrone **12a**[2] (3.0 g, 8.50 mmol) in Et_2O/THF (1:2, 35.0 mL) was added a solution of freshly prepared BnMgCl in Et_2O (0.5 M, 34.0 mL). The resulting mixture was stirred at this temperature for 2 h, quenched with a solution of aqueous phosphate buffer (pH 7, 30.0 mL), and allowed to warm to room temperature. The white suspension was filtered through Celite, and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10.0 mL), and the combined organic phases were dried and concentrated. Chromatography on silica gel of the residue with cyclohexane/EtOAc (9:1) gave **17** (3.41 g, 90%) as a mixture of (2*S*,3*S*,4*R*)- and (2*S*,3*S*,4*S*)-*N*-benzylhydroxylamines in a 87:13 ratio (by ^{1}H NMR analysis). Attempts to separate these compounds by flash chromatography failed. NMR for the major 2*S*,3*S*,4*R* isomer: ^{1}H NMR δ 1.38 (s, 3 H), 1.50 (s, 3 H), 2.95−3.14 (m, 2 H), 3.24−3.31 (m, 1 H), 3.32 (dd, 1 H, J = 4.7, 10.3 Hz), 3.41 (dd, 1 H, J = 4.7, 10.3 Hz), 3.84 (d, 1 H, J = 13.2 Hz), 3.98 (dd, 1 H, J = 1.5, 8.5 Hz), 4.17 (d, 1 H, J = 13.2 Hz), 4.38 (s, 2 H), 4.38−4.45 (m, 1 H), 5.35 (s, 1 H), 7.05−7.15 (m, 2 H), 7.15−7.35 (m, 13 H); ^{13}C NMR δ 26.7, 27.2, 30.6, 61.0, 65.0, 70.5, 73.4, 76.0, 79.2, 108.8, 137.8, 138.1, 140.1. Anal. Calcd for $C_{28}H_{33}NO_4$: C, 75.14; H, 7.43; N, 3.13. Found: C, 74.84; H, 7.07; N, 3.08.

(2*S*,3*S*,4*R*)- and (2*S*,3*S*,4*S*)-1-*O*-Benzyl-2,3-*O*-isopropylidene-5-phenyl-4-(*N*-trifluoroacetyl)benzylamine-1,2,3-pentantriol (18). To a solution of $(AcO)_2Cu\cdot H_2O$ (0.18 g, 0.90 mmol) in AcOH (20.0 mL) was added Zn dust (3.0 g, 45.9 mmol). The resulting suspension was vigorously stirred at room temperature for 15 min, and then a solution of benzylhydroxylamines **17** (4.0 g, 9.0 mmol) in AcOH/H_2O (3:1, 32.0 mL) was added. The stirring was continued for 1 h; the suspension was filtered through Celite; and the collected solution was neutralized with an aqueous solution of NaOH (3 M), extracted with EtOAc (3 × 20.0 mL), and washed with a saturated aqueous solution of EDTA. The organic phase was dried and concentrated to give 3.90 g of the corresponding crude benzylamines. To a suspension of these and activated 4 Å powdered molecular sieves (3.0 g) in CH_2Cl_2 (35.0 mL) were added Et_3N (7.50 mL, 54.0 mmol) and $(CF_3CO)_2O$ (3.80 mL, 27.0 mmol). The resulting mixture was stirred at room temperature for 1.5 h, treated with MeOH (3.0 mL), filtered through Celite, and concentrated. The crude residue was chromatographed with cyclohexane/EtOAc (4:1) to give a mixture of the expected trifluoroacetylbenzylamines **18** (4.15 g, 88%) as a syrup. Attempts to separate these compounds by flash chromatography failed. ^{1}H NMR for the major 2*S*,3*S*,4*R* isomer: (DMSO-d_6, 160 °C) δ 1.25 (s, 3 H), 1.32 (s, 3 H), 2.95 (dd, 1 H, J = 5.5, 14.0 Hz), 3.06 (dd, 1H, J = 8.5, 14.0 Hz), 3.60 (dd, 1 H, J = 5.0, 11.5 Hz), 3.66 (dd, 1 H, J =

4.0, 11.5 Hz), 4.04−4.12 (m, 1 H), 4.21−4.36 (m, 2 H), 4.53 (s, 2 H), 4.50−4.60 (m, 1 H), 4.68 (d, 1 H, J = 16.0 Hz), 7.02−7.10 (m, 2 H), 7.12−7.35 (m, 13 H). Anal. Calcd for $C_{30}H_{32}F_3NO_4$: C, 68.30; H, 6.11; N, 2.65. Found: C, 67.98; H, 6.48; N, 2.89.

(2*S*,3*S*,4*R*)- and (2*S*,3*S*,4*S*)-4-*tert*-Butoxycarbonylamino-2,3-*O*-isopropylidene-5-phenyl-1,2,3-pentantriol (19). To a solution of the benzylhydroxylamines **17** (2.0 g, 4.47 mmol) in MeOH (15.0 mL) was added $Pd(OH)_2$ (20% on C, 0.60 g). The resulting mixture was stirred at room temperature under 1 atm of H_2 for 8 h, filtered through Celite, and concentrated. To the residue dissolved in dioxane (15.0 mL) was added $(Boc)_2O$ (1.17 g, 5.36 mmol), and the resulting solution was stirred at room temperature for 18 h and then concentrated. Chromatography on silica gel of the crude residue with cyclohexane/EtOAc (3:2) gave a mixture of the expected *tert*-butoxycarbonylamines **19** (1.11 g, 70%). Careful chromatography of a portion of the mixture **19** with cyclohexane/Et_2O (3:2) provided a pure sample of the major 2*S*,3*S*,4*R* isomer as a colorless syrup: $[\alpha]_D$ +19.1 (*c* 1.1, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 160 °C) δ 1.34 (s, 9 H), 1.36 (s, 3 H), 1.40 (s, 3 H), 2.79 (dd, 1 H, J = 8.5, 13.8 Hz), 2.89 (dd, 1 H, J = 5.5, 13.8 Hz), 3.56 (d, 2 H, J = 4.0 Hz), 3.80−3.97 (m, 3 H), 3.98−4.12 (m, 1 H), 5.58 (d, 1 H, J = 8.0 Hz), 7.12−7.30 (m, 5 H). Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.94; H, 8.32; N, 3.99. Found: C, 64.74; H, 7.96; N, 3.72.

(*Z*)-*N*-[(2*S*,3*S*,4*R*)- and (2*S*,3*S*,4*S*)-2,3-Isopropylidenedioxy-5-phenyl-4-(*N*-trifluoroacetylbenzylamine)pentylidene]benzylamine *N*-oxide (20 and 22). To a solution of **18** (4.0 g, 7.58 mmol) in EtOAc (25.0 mL) was added $Pd(OH)_2$ (20% on C, 0.80 g). The resulting mixture was stirred at room temperature under 1 atm of H_2 for 24 h, filtered through Celite, and concentrated to give 3.25 g of crude alcohols which were employed for the Swern oxidation without purification. To a cold (−78 °C) solution of $(COCl)_2$ (0.70 mL, 8.10 mmol) in CH_2Cl_2 (35.0 mL) was added DMSO (1.10 mL, 15.30 mmol) in CH_2Cl_2 (1.50 mL). The solution was stirred at −78 °C for 20 min, and then the above crude alcohols (3.25 g) in CH_2Cl_2 (8.0 mL) were added. After the reaction solution had been stirred at this temperature for 1 h, *i*-Pr_2NEt (6.30 mL, 37.0 mmol) was added. The cooling bath was removed, and the reaction flask was allowed to warm to 0 °C over 10 min. The reaction solution was neutralized with ice-cold 1 M HCl solution. The two phases were separated; the aqueous phase was extracted with CH_2Cl_2 (3 × 20.0 mL); and the combined organic phases were washed with aqueous phosphate buffer (pH 7, 4 × 20.0 mL), dried, and concentrated. The crude aldehydes were dissolved in CH_2Cl_2 (35.0 mL) and treated with anhydrous $MgSO_4$ (1.0 g) and *N*-benzylhydroxylamine (1.02 g, 8.30 mmol). The resulting mixture was stirred at room temperature for 4 h, filtered through Celite, and concentrated. Chromatography on silica gel of the residue with cyclohexane/EtOAc (3:1) gave as first eluted the nitrone **22** (0.60 g 16%) as a white solid and then the nitrone **20** (3.14 g, 76%) as a syrup which solidified on standing. **20**: mp 59−62 °C; $[\alpha]_D$ −19.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 180 °C) δ 1.29 (s, 3 H), 1.33 (s, 3 H), 2.86 (dd, 1 H, J = 4.5, 14.0 Hz), 2.97 (dd, 1 H, J = 9.5, 14.0 Hz), 4.18−4.29 (m, 1 H), 4.34 (t, 1 H, J = 7.5 Hz), 4.42 (d, 1 H, J = 15.0 Hz), 4.62 (d, 1 H, J = 15.0 Hz), 4.93 (d, 1 H, J = 13.0 Hz), 4.98 (d, 1 H, J = 13.0 Hz), 4.94−5.02 (m, 1 H), 7.00−7.10 (m, 2 H), 7.15−7.45 (m, 14 H); ^{13}C NMR δ 26.4 (CH_3), 26.5 (CH_3), 32.0 (CH_2Ph), 53.6 (PhCH_2N), 64.5 (*C*HNCOCF_3), 70.3 (N^+CH_2Ph), 73.8 (O*C*H), 78.1 (O*C*H), 109.9 (*C*(CH_3)$_2$), 116.2 (q, J = 288.0 Hz), 126.6, 127.8, 128.3, 128.5, 128.9, 129.2, 131.9, 133.8, 134.7 (*C*H=N^+), 137.1, 157.2 (q, J = 36.0 Hz); ^{19}F NMR (DMSO-d_6, 180 °C) δ −66.1. Anal. Calcd for $C_{30}H_{31}F_3N_2O_4$: C, 66.66; H, 5.78; N, 5.18. Found: C, 66.82; H, 5.90; N, 5.04. **22**: mp 113−115 °C; $[\alpha]_D$ −46.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 180 °C) δ 1.20 (s, 3 H), 1.35 (s, 3 H), 3.12 (dd, 1 H, J = 8.5, 15.0 Hz), 3.18 (dd, 1 H, J = 5.0, 15.0 Hz), 4.28 (dd, 1 H, J = 3.5, 7.5 Hz), 4.54 (d, 1 H, J = 16.0 Hz), 4.63 (ddd, 1 H, J = 3.5, 5.0, 8.5 Hz), 4.71 (d, 1 H, J = 16.0 Hz), 4.94 (d, 1 H, J = 14.0 Hz), 4.99 (d, 1 H, J = 14.0 Hz), 5.01 (t, 1 H, J = 7.0 Hz), 7.08−7.50 (m, 16 H); ^{19}F NMR (DMSO-d_6, 180 °C) δ −66.1. Anal. Calcd for $C_{30}H_{31}F_3N_2O_4$: C, 66.66; H, 5.78; N, 5.18. Found: C, 66.32; H, 5.46; N, 5.13.

(*Z*)-*N*-[(2*S*,3*S*,4*R*)- and (2*S*,3*S*,4*S*)-4-*N*-*tert*-Butoxycarbonylamine-2,3-isopropylidenedioxy-5-phenylpentylidene]benzylamine *N*-oxide (21 and 23). A mixture of the alcohols **19** (1.0 g, 2.84 mmol) was oxidized as described above for **20** and **22**. The crude aldehydes were dissolved in CH_2Cl_2 (15.0 mL) and treated with $MgSO_4$ (0.50 g) and *N*-benzylhydroxylamine (0.39 g, 3.17 mmol). The resulting mixture was stirred at room temperature for 4 h, filtered through Celite, and concentrated. Chromatography on silica gel of the residue with cyclohexane/EtOAc (3.5:2) gave as first eluted the nitrone **21** (0.95 g, 74%) as a colorless syrup and then the nitrone **23** (0.19 g, 15%) as a colorless syrup. **21**: $[\alpha]_D$ +23.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.28 (s, 9 H), 1.37 (s, 3 H), 1.42 (s, 3 H), 2.69 (dd, 1 H, J = 9.5, 14.0 Hz), 2.88 (dd, 1 H, J = 4.5, 14.0 Hz), 3.99 (dd, 1 H, J = 4.5, 7.0 Hz), 4.07 (ddd, 1 H, J = 4.5, 9.0, 9.5 Hz), 4.90−5.00 (m, 1 H), 4.94 (d, 1 H, J = 13.0 Hz), 5.00 (d, 1 H, J = 13.0 Hz), 6.07 (d, 1 H, J = 9.0 Hz), 7.12−7.28 (m, 6 H), 7.30−7.48 (m, 5 H). Anal. Calcd for $C_{26}H_{34}N_2O_5$: C, 68.70; H, 7.54; N, 6.16. Found: C, 68.91; H, 7.29; N, 6.41. **23**: $[\alpha]_D$ +12.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 1.35 (s, 3 H), 1.37 (s, 9 H), 1.43 (s, 3 H), 2.78 (dd, 1 H, J = 7.0, 13.5 Hz), 2.98 (dd, 1 H, J = 5.4, 13.5 Hz), 3.94 (t, 1 H, J = 6.0 Hz), 4.06−4.20 (m, 1 H), 4.90 (s, 2 H), 5.08 (t, 1 H, J = 6.0 Hz), 5.40 (d, 1 H, J = 7.5 Hz), 6.81 (d, 1 H, J = 5.5 Hz), 7.10−7.35 (m, 5 H), 7.42 (s, 5 H); ^{13}C NMR δ 27.0, 27.2, 28.3, 36.2, 52.7, 69.6, 73.4, 79.0, 80.7, 110.4, 126.2, 128.2, 129.1, 129.3, 129.5, 129.6, 131.9, 137.4, 137.7, 155.6. Anal. Calcd for $C_{26}H_{34}N_2O_5$: C, 68.70; H, 7.54; N, 6.16. Found: C, 68.99; H, 7.48; N, 6.21.

(2*R*,3*S*,4*S*,5*R*)- and (2*S*,3*S*,4*S*,5*R*)-2-*N*-Benzylhydroxylamine-1,6-diphenyl-3,4-*O*-isopropylidene-5-(*N*-trifluoroacetyl)benzylamine-3,4-hexandiol (24 and 25). To a cold (−78 °C) solution of nitrone **20** (0.80 g, 1.48 mmol) in THF (15.0 mL) was added a solution of freshly prepared BnMgCl in Et_2O (0.5 M, 7.40 mL). The resulting solution was stirred at this temperature for 3 h, treated with a solution of aqueous phosphate buffer (pH 7, 15.0 mL), and allowed to warm to room temperature. The white suspension was filtered through Celite, and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10.0 mL), and the combined organic phases were dried and concentrated. Chromatography on silica gel of the residue with cyclohexane/Et_2O (9:1) gave as first eluted the hexandiol **25** (0.14 g, 15%) as a white solid and then the epimer **24** (0.69 g, 74%) as a white solid. **24**: mp 65−68 °C; $[\alpha]_D$ +10.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 180 °C) δ 1.28 (s, 3 H), 1.34 (s, 3 H), 2.68 (dd, 1 H, J = 5.5, 9.5 Hz), 2.90 (dd, 1 H, J = 9.0, 14.5 Hz), 2.95 (dd, 1 H, J = 10.0, 14.5 Hz), 3.25−3.34 (m, 2 H), 3.91 (d, 1 H, J = 13.5 Hz), 3.93 (dd, 1 H, J = 2.5, 8.0 Hz), 4.12 (d, 1 H, J = 13.5 Hz), 4.23−4.33 (m, 1 H), 4.57−4.64 (m, 1 H), 4.61 (s, 2 H), 6.85−6.98 (m, 2 H), 7.10−7.34 (m, 19 H); ^{19}F NMR (DMSO-d_6, 180 °C) δ −65.9. Anal. Calcd for $C_{37}H_{39}F_3N_2O_4$: C, 70.24; H, 6.21; N, 4.43. Found: C, 70.11; H, 6.27; N, 4.44. **25**: mp 94−97 °C; $[\alpha]_D$ +4.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 180 °C) δ 1.25 (s, 3 H), 1.34 (s, 3 H), 2.91 (dd, 1 H, J = 5.0, 15.0 Hz), 2.97 (dd, 1 H, J = 9.5, 15.0 Hz), 3.09 (dd, 1 H, J = 5.0, 14.5 Hz), 3.17 (dd, 1 H, J = 7.0, 14.5 Hz), 3.34−3.41 (m, 1 H), 4.17 (t, 1 H, J = 7.0 Hz), 4.43 (dd, 1 H, J = 4.5, 7.5 Hz), 4.46−4.54 (m, 1 H), 4.58 (d, 1 H, J = 15.0 Hz), 4.67 (d, 1 H, J = 15.0 Hz), 7.04−7.10 (m, 2 H), 7.11−7.30 (m, 19 H); ^{19}F NMR (DMSO-d_6, 180 °C) δ −65.9. Anal. Calcd for $C_{37}H_{39}F_3N_2O_4$: C, 70.24; H, 6.21; N, 4.43. Found: C, 70.62; H, 6.52; N, 4.80.

(2*R*,3*S*,4*S*,5*R*)- and (2*S*,3*S*,4*S*,5*R*)-2-*N*-Benzylhydroxylamine-5-*tert*-butoxycarbonylamine-1,6-diphenyl-3,4-*O*-isopropylidene-3,4-hexandiol (26 and 27). To a cold (−78 °C) solution of nitrone **21** (0.50 g, 1.10 mmol) in THF (11.0 mL) was added a solution of freshly prepared BnMgCl in Et_2O (0.5 M, 17.7 mL). The resulting solution was stirred at this temperature for 5 h, treated with a solution of aqueous phosphate buffer (pH 7, 15.0 mL), and allowed to warm to room temperature. The white suspension was filtered through Celite, and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10.0 mL), and the combined

organic phases were dried and concentrated. Chromatography on silica gel of the residue with cyclohexane/Et_2O (3:2) gave as first eluted the hexandiol **26** (0.33 g, 55%) as a white solid and then the epimer **27** (0.14 g, 23%) as a colorless syrup. **26**: mp 53−55 °C; $[\alpha]_D$ +10.8 (*c* 0.7, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.24 (s, 9 H), 1.55 (s, 3 H), 1.57 (s, 3 H), 2.76 (d, 2 H, J = 7.8 Hz), 2.84 (dd, 1 H, J = 7.0, 13.5 Hz), 3.14 (dd, 1 H, J = 6.5, 13.5 Hz), 3.26 (ddd, 1 H, J = 4.5, 6.5, 7.0 Hz), 3.88 (d, 1 H, J = 14.0 Hz), 3.91−3.98 (m, 1 H), 4.01 (dd, 1 H, J = 4.5, 8.5 Hz), 4.05 (d, 1 H, J = 14.0 Hz), 4.21 (dd, 1 H, J = 2.1, 8.5 Hz), 5.64 (d, 1 H, J = 7.5 Hz), 7.10−7.30 (m, 21 H). Anal. Calcd for $C_{33}H_{42}N_2O_5$: C, 72.50; H, 7.74; N, 5.12. Found: C, 72.27; H, 7.78; N, 5.12. **27**: $[\alpha]_D$ −7.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 120 °C) δ 1.26 (s, 3 H), 1.31 (s, 9 H), 1.39 (s, 3 H), 2.81−2.93 (m, 3 H), 3.08 (ddd, 1 H, J = 4.0, 6.5, 7.5 Hz), 3.24 (dd, 1 H, J = 6.5, 14.5 Hz), 3.70 (d, 1 H, J = 14.0 Hz), 3.82 (d, 1 H, J = 14.0 Hz), 3.86 (dd, 1 H, J = 2.0, 7.5 Hz), 3.98 (t, 1 H, J = 7.5 Hz), 4.18−4.28 (m, 1 H), 6.11 (d, 1 H, J = 8.0 Hz), 7.02 (s, 1 H), 7.05−7.30 (m, 15 H); ^{13}C NMR δ 26.9, 28.3, 31.7, 40.1, 52.1, 62.0, 70.1, 77.4, 80.4, 82.3, 107.8, 125.5, 126.5, 126.8, 128.0, 128.2, 128.4, 128.8, 129.3, 129.6, 138.0, 142.4, 157.2. Anal. Calcd for $C_{33}H_{42}N_2O_5$: C, 72.50; H, 7.74; N, 5.12. Found: C, 72.63; H, 7.58; N, 5.52.

(2*R*,3*S*,4*S*,5*R*)-2,5-Diamino-1,6-diphenyl-3,4-hexandiol (2c). To a solution of **24** (0.90 g, 1.42 mmol) in EtOH (9.0 mL) was added $NaBH_4$ (0.22 g, 5.70 mmol). The resulting mixture was stirred at 60 °C for 1 h, treated with acetone (3−4 drops), and concentrated. To the residue dissolved in AcOH/EtOH (9:1, 5.0 mL) was added $Pd(OH)_2$ (20% on C, 0.30 g). The mixture was stirred at room temperature under 3 atm of H_2 for 18 h, filtered through Celite, and concentrated. To the crude residue was added an aqueous solution of HCl (6 M, 5.0 mL), and the resulting suspension was heated to 90 °C for 1 h and then concentrated. The crude salts were neutralized with an aqueous solution of NaOH (3.0 M) and extracted with $CHCl_3$ (3 × 5.0 mL). The combined organic layers were dried and concentrated. Chromatography on silica gel with $CHCl_3$/MeOH/NH_4OH (89:10:1) afforded **2c** (0.30 g, 70%) as a white solid: mp 96−100 °C; $[\alpha]_D$ −48.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 2.73 (dd, 2 H, J = 9.0, 13.2 Hz), 2.93 (dd, 2 H, J = 5.7, 13.2 Hz), 3.04 (dd, 2 H, J = 5.7, 9.0 Hz), 3.10−3.65 (m, 6 H), 3.70 (s, 2 H), 7.15−7.37 (m, 10 H); ^{13}C NMR δ 43.0, 57.5, 74.3, 126.3, 128.6, 129.3, 138.7. Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.32. Found: C, 71.86; H, 7.84; N, 8.98.

Synthesis of 2b from 25. The same procedure as described above for the synthesis of **2c** was applied to **25** (0.3 g, 0.47 mmol). Chromatography on silica gel of the crude compound with $CHCl_3$/MeOH/NH_4OH (89:10:1) afforded **2b** (92.0 mg, 65%).

Synthesis of 2c from 26. The same procedure as described above for the synthesis of **1Aa** was applied to **26** (0.25 g, 0.46 mmol). Chromatography on silica gel of the crude compound with $CHCl_3$/MeOH/NH_4OH (89:10:1) gave pure **2c** (0.11 g, 79%).

Synthesis of 2b from 27. The same procedure as described above for the synthesis of **1Aa** was applied to **27** (0.25 g, 0.46 mmol). Chromatography on silica gel of the crude compound with $CHCl_3$/MeOH/NH_4OH (89:10:1) gave pure **2b** (0.10 g, 75%).

(4*R*,5*S*,4′*R*,5′*S*)-5,5′-Bis(4-benzyloxazolidin-2-one) (28). The reaction was carried out as described above for the synthesis of the bis-oxazolidinone **15** starting from **2c** (20.0 mg, 0.07 mmol). Chromatography on silica gel of the crude compound with $CHCl_3$/EtOAc (3:2) afforded **28** (15.0 mg, 61%) as a white solid: mp 171−172 °C from EtOAc; $[\alpha]_D$ +106.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 2.76 (dd, 2 H, J = 6.3, 14.0 Hz), 2.86 (dd, 2 H, J = 7.6, 14.0 Hz), 3.99 (d, 2 H, J = 5.8 Hz), 4.04−4.15 (m, 2 H), 4.98 (s, 2 H), 7.05−7.15 (m, 4 H), 7.30−7.40 (m, 6 H); ^{13}C NMR δ 41.3, 54.5, 79.6, 127.5, 129.1, 134.9, 157.4. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.85; H, 5.40; N, 7.81.

(2*R*,3*S*,4*S*,5*R*)-2,5-Bis(phenylmethylamino)-3,4-*O*-isopropylidene-1,6-diphenyl-3,4-hexandiol (29). To a solution of $(AcO)_2Cu\cdot H_2O$ (0.03 g, 0.13 mmol) in AcOH (5.0 mL) was added Zn dust (0.45 g, 6.85 mmol). The resulting suspension was vigorously stirred at room temperature for 15 min, and then a solution of benzylhydroxylamine **24** (0.85 g, 1.34 mmol) in AcOH/H_2O (3:1, 8.0 mL) was added. The stirring was continued for 4 h, the suspension was filtered through Celite, and the collected solution was neutralized with an aqueous solution of NaOH (3 M) and extracted with EtOAc (3 × 10.0 mL). The combined organic phases were washed with a saturated aqueous solution of EDTA, dried, and concentrated to give 0.83 g of the corresponding crude benzylamine which was suspended in EtOH (15.0 mL) and treated with $NaBH_4$ (0.20 g, 5.36 mmol). The resulting mixture was stirred at 60 °C for 18 h, quenched with acetone (3−4 drops), and concentrated. The crude residue was partitioned with CH_2Cl_2 (3 × 5.0 mL) and saturated aqueous $NaHCO_3$ (15.0 mL). The combined organic layers were dried and concentrated. Chromatography on silica gel of the residue with cyclohexane/EtOAc (4:1) afforded the bisbenzylamine **29** (0.59 g, 85%) as a white solid: mp 106−108 °C; $[\alpha]_D$ −9.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 1.43 (s, 6 H), 2.58−2.72 (m, 4 H), 2.86 (dd, 2 H, J = 9.5, 16.0 Hz), 3.52 (d, 2 H, J = 13.0 Hz), 3.68 (d, 2 H, J = 13.0 Hz), 4.15 (s, 2 H), 7.00−7.30 (m, 20 H); ^{13}C NMR δ 27.3, 38.3, 51.6, 57.9, 77.6, 107.9, 126.0, 126.7, 128.1, 128.3, 129.3, 139.5, 140.6. Anal. Calcd for $C_{35}H_{40}N_2O_2$: C, 80.73; H, 7.74; N, 5.38. Found: C, 80.85; H, 7.47; N, 5.05.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-isopropylidenedioxy-4,7-bis(phenylmethyl)-1,3-bis(phenylmethyl)-2*H*-1,3-diazapin-2-one (30). To a solution of *N*-methylmorpholine (0.09 mL, 0.81 mmol) in toluene (10.0 mL) were added under vigorous stirring the amine **29** (0.10 g, 0.19 mmol) in toluene (0.83 mL) and phosgene (1.28 M in toluene, 0.30 mL) simultaneously by two syringe pumps within 4 h at 100 °C. After an additional 1 h at 100 °C, *N*-methylmorpholine (0.09 mL, 0.81 mmol) and H_2O (0.30 mL) were added. The resulting mixture was filtered through Celite and then concentrated. Chromatography on silica gel of the residue with cyclohexane/EtOAc (8:1) gave the pure cyclic urea **30** (0.08 g, 77%) as a white solid: mp 126−129 °C; $[\alpha]_D$ +77.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR δ 1.34 (s, 6 H), 2.86−3.00 (m, 4 H), 3.08 (d, 2 H, J = 14.6 Hz), 3.74−3.83 (m, 2 H), 3.84 (s, 2 H), 5.00 (d, 2 H, J = 14.6 Hz), 7.10−7.20 (m, 8 H), 7.20−7.40 (m, 12 H); ^{13}C NMR δ 26.7, 33.5, 56.3, 60.8, 75.5, 110.1, 126.6, 127.5, 128.5, 128.6, 129.1, 129.4, 138.3, 138.9, 161.6. Anal. Calcd for $C_{36}H_{38}N_2O_3$: C, 79.09; H, 7.01; N, 5.12. Found: C, 78.99; H, 6.95; N, 4.80.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-1,3-bis(phenylmethyl)-2*H*-1,3-diazapin-2-one (31). To a solution of cyclic urea **30** (0.08 g, 0.15 mmol) in MeOH (1.0 mL) was added a solution of HCl in dioxane (4.8 M, 0.50 mL). The solution was stirred at room temperature for 3 h, neutralized with an aqueous solution of NaOH (1 M), and extracted with CH_2Cl_2 (3 × 5.0 mL). The combined organic phases were dried and concentrated. Chromatography on silica gel with $CHCl_3$/MeOH (94:6) afforded pure urea **31** (0.06 g, 79%) as a white crystal: mp 164−165 °C from cyclohexane/EtOAc; $[\alpha]_D$ +134.1 (*c* 0.6, MeOH);^{1}H NMR (CD_3OD) δ 2.92 (dd, 2 H, J = 10.0, 13.5 Hz), 2.94 (d, 2 H, J = 14.2 Hz), 3.04 (dd, 2 H, J = 2.2, 13.5 Hz), 3.53−3.65 (m, 4 H), 4.74 (d, 2 H, J = 14.2 Hz), 7.03−7.40 (m, 20 H); ^{13}C NMR (CD_3OD) δ 33.5, 57.1, 67.2, 72.0, 127.5, 128.8, 129.6, 129.7, 130.5, 130.6, 139.3, 141.1, 163.9. Anal. Calcd for $C_{33}H_{34}N_2O_3$: C, 78.23; H, 6.76; N, 5.53. Found: C, 78.32; H, 6.42; N, 5.64.

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