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Exploring Nitrone Chemistry: Towards the Enantiodivergent Synthesis of 6-Substituted 4-Hydroxypipecolic Acid Derivatives

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A methodology for the stereoselective preparation of all-*cis* 6-substituted 4-hydroxypipecolic acid derivatives using nitrone chemistry, involving both nucleophilic additions and cycloadditions, is presented. The *N*-benzyl nitrone derived from 1,2-di-*O*-isopropylidene-D-glyceraldehyde was shown to undergo stereocontrolled allylation reactions to provide enantiomerically pure homoallyl hydroxylamines. Further transformation of these substrates into *N*-alkenyl nitrones was achieved in high yields and regioselectivities by oxidation with manganese(IV) oxide. The oxidation reaction is thermodynamically controlled and directed by a phenyl group which became the 6-substituent. A transoximation reaction of the intermediate *N*-alkenyl-*C*-phenyl nitrone was needed to add versatility to the methodology by varying the substituent at the 6-position. The resulting *N*-alkenyl nitrones underwent stereoselective intramolecular 1,3-dipolar cycloaddition reactions to provide the immediate precursors of the target compounds. The selectivity observed in the intramolecular cycloaddition was dictated by both the steric preference and the electronic nature of the substrate, which promoted a hitherto unknown aza-Cope rearrangement of the *N*-alkenyl nitrone. The chiral induction exerted by the dioxolane moiety as well as its synthetic equivalence with the carboxy group provided the basis for the enantiodivergency achieved in the synthesis of 6-substituted (2*R*,4*S*,6*R*)-4-hydroxypipecolic acids and their enantiomers.

Introduction

The synthesis of polysubstituted piperidine derivatives is still a challenging field of ongoing interest as demonstrated by very recent publications.[1] Several synthetic methodologies have been applied so far and the subject of the synthesis of piperidines has been covered in several dedicated reviews.[2] In the domain of piperidines, pipecolic acid derivatives have been widely used as chiral intermediates for the synthesis of drugs,[3] unnatural amino acids and peptides[4] and several pipecolic acid containing natural products.[5] For this reason, the study of synthetic methods directed towards the preparation of enantiomerically pure pipecolic acid derivatives has attracted much attention in recent years.[6] Of particular interest are pipecolic acid derivatives bearing hydroxy or amino groups. Because of their structural diversity and interesting functionalities, some interest has been directed towards devising strategies for the synthesis of such compounds. Several 4- and 5-hydroxypipecolic acids have been isolated from the leaves of species of *Bikinia* and *Tetraberlinia* (Leguminosae: Caesalpiniodeae).[7] In particular, (2*S*,4*S*)-hydroxypipecolic acid (**1**) was isolated from *Acacia* species and the (2*S*,4*R*) isomer **2** was obtained from the leaves of *Calliandra pittieri* and *Strophantus scandeu*.[8] Compound **2** is also a constituent of antibiotics such as virginiamicin S[9] as well as a key intermediate in the synthesis of NMDA receptor antagonists[10] and the HIV protease inhibitor palinavir.[11] 4-Oxygenated pipecolic acids have also been used as key intermediates in the synthesis of several constrained amino acids and peptidomimetics.[12] Pipecolic acids **1** and **2** have been synthesized from dihydropyridones,[13] amino acid derived *N*-acyliminium ions,[14] imines,[15] vinylglycinols,[16] and nitrones.[17] Davies et al. reported the stereoselective synthesis of all four stereoisomers of 4-hydroxypipecolic acids.[18] A protected derivative of **2** served to prepare (2*S*,4*R*)-4-aminopipecolic acid (**3**).[19] Compounds **3** and **4**, isolated from *Strophantus scandeus* (Apocinacea)[20] and *Calliandra haematocephala* (Leguminosae),[21] are representative of endocyclic-N$^{\alpha}$/exocyclic-N$^{\gamma}$ basic constrained amino acids. Other 4-aminopipecolic acids have been prepared through catalytic imino-Diels–Alder reactions of 2-aminodienes.[22] (2*S*,3*S*)-3-Hydroxypipecolic acid and its enantiomer have been prepared starting from D- and L-glyceraldehyde imines, respectively.[23] The (2*R*,3*R*) isomer has also been synthesized from methyl mandelate as the chiral source.[24] The *cis*-(2*S*,3*R*) and (2*S*,3*R*) derivatives have been obtained by enzymatic resolution.[25]

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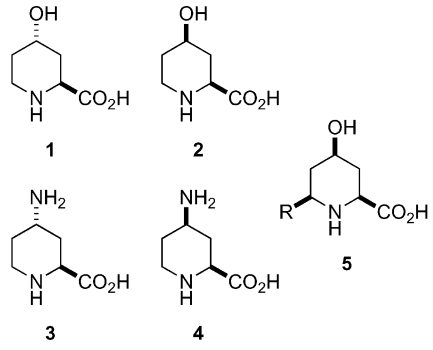
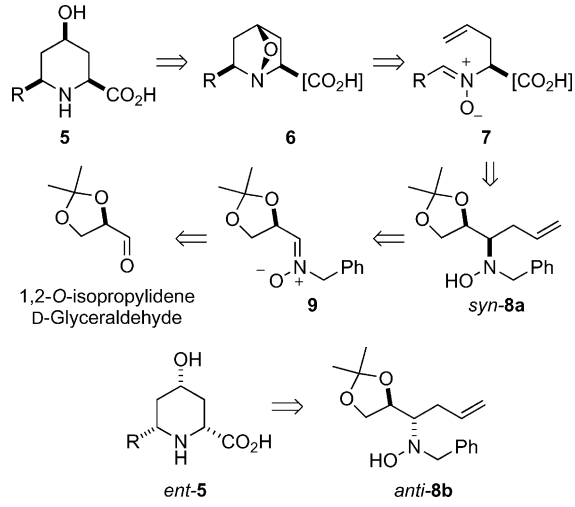
Several syntheses of 3-hydroxypipecolic acids have been reported because of their importance in biologically active molecules.[26] 5-Hydroxypipecolic acids, available from *trans*-4-hydroxyproline,[27] have recently been used as intermediates in the preparation of chimeric peptide nucleic acids[28] and (+)-epiquinamide.[29]



The introduction of additional substituents at the 6-position in 4-hydroxypipecolic acids and their derivatives gives an entry to a variety of natural alkaloids of biological importance.[30] The synthesis of several isomers of 6-substituted 4-hydroxypipecolic acids **5** have been reported starting from suitable precursors depending on the desired isomer.[31] Only in one case has a diastereodivergent reduction of 4-oxo derivatives allowed the preparation of C-4 epimeric 6-substituted (2*R*,6*S*)-4-hydroxypipecolic acids.[32] In this paper we describe in detail the enantiodivergent synthesis of 6-substituted (2*S*,4*R*,6*R*)-4-hydroxypipecolic acids and their enantiomers by using a strategy based on nitrone chemistry that involves both nucleophilic additions and 1,3-dipolar cycloaddition reactions.



Scheme 1. Retrosynthetic analysis for 6-substituted 4-hydroxypipecolic acid derivatives.

Results and Discussion

Synthetic Plan

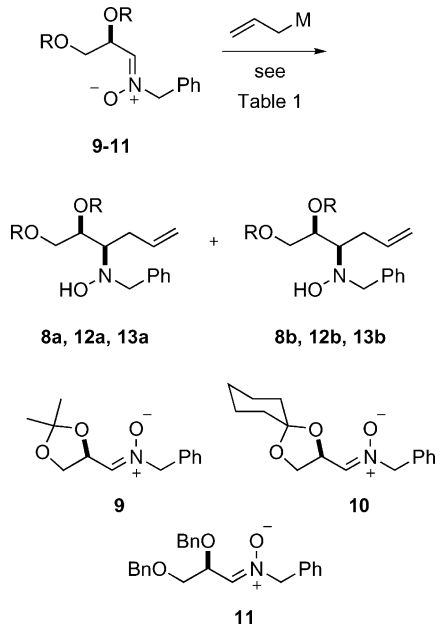
Our approach to the synthesis of 6-substituted derivatives (2*S*,4*R*,6*R*)-**5** is illustrated by the retrosynthetic analysis depicted in Scheme 1 and envisaged the use of *N*-benzyl-1,2-di-*O*-isopropylidene-D-glyceraldehyde nitrone **9**, which can be easily obtained in a multigram scale from protected D-glyceraldehyde[33] as the starting material.

As shown in Scheme 1 the stereoselective allylation of nitrone **9** could allow the preparation of hydroxylamine *syn*-**8a**. Work from this laboratory has previously shown that nucleophilic addition to **9** could be stereocontrolled by the appropriate use of Lewis acids.[34] Based on these previous observations it can be assumed that the corresponding *anti* isomer **8b** will also be available.[35] Elaboration of the homoallyl hydroxylamines would then involve oxidation of the hydroxyamino moiety and intramolecular cycloaddition of the resulting alkenyl nitrone **7**. The phenyl substituent at the site of oxidation is of particular interest as this is required for directing the oxidation to the aldo nitrone **7**. To give versatility to the methodology it will also be necessary to develop a suitable procedure for exchanging the phenyl group with other radicals. As discussed in this work (see below), this is possible through a transoximation reaction. The last steps towards the targeted pipecolic acid derivatives **5** involves the reduction of the N–O bond by standard procedures and transformation of the dioxolane ring into the carboxy group, as we[36] and others[37] have previously described. In this way, one could take advantage of the loss of the chiral dioxolane unit because, by preparing the *anti* isomer **8b**, the enantiomer of **5** would be expected, thus achieving an enantiodivergent approach from nitrone **9**.[38]

Synthesis of Homoallyl Hydroxylamines

We decided first to study the allylation reaction of nitrone **9** with a series of allyl metals and Lewis acids, with the expectation that the reaction could be stereocontrolled.[35a] In spite of the numerous studies on the allylation of imines, the allylation of nitrones has scarcely been investigated.[39] In order to evaluate the influence of the protecting groups on stereofacial discrimination, nitrones **10** and **11**, in addition to **9**, were also considered (Scheme 2, Table 1).

The reaction protocol involved of the slow addition of a solution of nitrone to a solution of the corresponding allyl metal derivative. In the case of reactions carried out in the presence of Lewis acids, the nitrone complex was preformed by admixing the Lewis acid and nitrone in the stated solvent for 5 min at room temperature, later subjecting it to a specified temperature for sequential addition to the allyl metal solution. The reaction progress was easily monitored by TLC analysis, and purification of the crude product by flash chromatography and determination of the diastereomeric ratio by NMR spectroscopy provided assessment of the efficiency of the reaction.



Scheme 2. Allylation of D-glyceraldehyde nitrones.

First, the addition of allyllithium, prepared in situ from allyltriphenyltin and phenyllithium,[40] to nitrone **9** was tested.

Whereas the reaction in the absence of any additive (Table 1, entry 1) led to an almost equimolar mixture of isomers, the addition of 1 equiv. of TMEDA (Table 1 entry 2) or TMSOTf (Table 1, entry 3) proved to be more efficient. However, the best *syn* selectivity was obtained in the presence of Zn_2Br (Table 1, entry 4). In accord with our previous studies on nucleophilic addition to nitrones,[34] the reaction was also carried out in the presence of $TiCl_4$ (Table 1, entry 5), Et_2AlCl (Table 1, entry 6) and $BF_3{\cdot}Et_2O$ (Table 1, entry 7), typical Lewis acids that promote *anti* addition. However, only a very slight inversion of the selectivity was observed. In addition, lower chemical yields were obtained. This behaviour was not observed with nitrone **10** (Table 1, entries 18–20), which also afforded *syn*-**12a** even in the presence of diethylaluminium chloride. Nitrone **11** (Table 1, entries 24–26) exhibited stereocontrol of the reaction, but with lower diastereoselectivities, and therefore is not synthetically useful. On the other hand, an acceptable 50% chemical yield was obtained with allyltributyltin in the presence of 1.0 equiv. of trimethylsilyl triflate (Table 1, entry 8), a modest *anti* selectivity also being achieved. Gratifyingly, when the reaction was carried out in the presence of boron trifluoride etherate (Table 1, entry 9), excellent *anti* selectivity and chemical yield were obtained. Although in this case stereocontrol of the reaction was achieved (Table 1, entries 4 and 9), we tested the commercially avail-

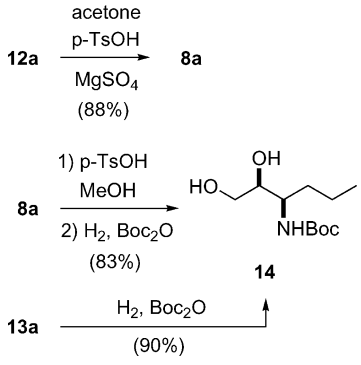
Table 1. Stereocontrolled allylation of D-glyceraldehyde nitrones **9**–**11**.

Entry	Nitrone	M[a]	Lewis acid[b]	Solvent	*T* [°C]	*t* [h]	Hydroxylamine[c]	*syn*/*anti*[d]	Yield [%][e]
1	**9**	Li	none	THF	–80	1	**8**	55:45	86
2	**9**	Li[f]	none	Et_2O	–80	1	**8**	71:29	90
3	**9**	Li	TMSOTf	Et_2O	–80	1	**8**	81:19	50
4	**9**	Li	$ZnBr_2$	Et_2O	–80	1	**8**	90:10	75
5	**9**	Li	$TiCl_4$	Et_2O	–80	1	**8**	37:63	43
6	**9**	Li	Et_2AlCl	Et_2O	–80	1	**8**	52:48	64
7	**9**	Li	$BF_3{\cdot}Et_2O$	Et_2O	–80	1	**8**	44:56	69
8	**9**	S-*n*Bu_3	TMSOTf	CH_2Cl_2	25	72	**8**	31:69	50
9	**9**	S-*n*Bu_3	$BF_3{\cdot}Et_2O$	CH_2Cl_2	25	72	**8**	≤ 5:95	90
10	**9**	MgBr	none	Et_2O	–50	8	**8**	76:24	100
11	**9**	MgBr	TMSOTf	Et_2O	0	2	**8**	45:55	70
12	**9**	MgBr	$ZnBr_2$	Et_2O	–50	8	**8**	>95:5	100
13	**9**	MgBr	$TiCl_4$	Et_2O	0	3	**8**	17:83	43
14	**9**	MgBr	Ti(*i*PrO)$_2Cl_2$	Et_2O	–50	8	**8**	45:55	78
15	**9**	MgBr	Ti(*i*PrO)$_4$	Et_2O	–50	8	**8**	55:45	80
16	**9**	MgBr	Et_2AlCl	Et_2O	–50	8	**8**	35:65	90
17	**9**	MgBr	$BF_3{\cdot}Et_2O$	THF	–50	10	**8**	5:95	90
18	**10**	Li	none	Et_2O	–80	1	**12**	72:28	86
19	**10**	Li	$ZnBr_2$	Et_2O	–80	1	**12**	76:24	87
20	**10**	Li	Et_2AlCl	Et_2O	–80	1	**12**	64:36	80
21	**10**	MgBr	none	Et_2O	0	2	**12**	74:26	78
22	**10**	MgBr	$ZnBr_2$	Et_2O	–50	8	**12**	91:9	93
23	**10**	MgBr	$BF_3{\cdot}Et_2O$	THF	–50	8	**12**	8:92	85
24	**11**	Li	none	THF	–80	1	**13**	60:40	90
25	**11**	Li	$ZnBr_2$	Et_2O	–80	1	**13**	61:39	80
26	**11**	Li	Et_2AlCl	Et_2O	–80	1	**13**	37:63	86
27	**11**	MgBr	none	Et_2O	0	2	**13**	62:38	100
28	**11**	MgBr	$ZnBr_2$	Et_2O	–50	8	**13**	69:31	90
29	**11**	MgBr	Et_2AlCl	Et_2O	0	2	**13**	48:52	90
30	**11**	MgBr	$BF_3{\cdot}Et_2O$	THF	–50	8	**13**	29:71	90

[a] 2.0 equiv. of organometallic reagent were used. [b] 1.0 Equiv. of Lewis acid was used. [c] In the text, **a** series refers to *syn* compounds and **b** series refers to *anti* compounds. [d] Measured by ^1H NMR of isolated crude mixtures. [e] Isolated yield after column chromatography. [f] 1.0 equiv. of TMEDA was added.

able allylmagnesium bromide as a more advisable and easy-to-handle reagent.[41] The addition of such a reagent to **9** at –50 °C in the absence of any additive (Table 1, entry 10) or in the presence of TMSOTf (Table 1, entry 11) provided *syn*-**8a** in good yield but only modest diastereoselectivity. A change of solvent or reduction of the reaction temperature did not lead to better results. On the other hand, the reaction in the presence of Zn_2Br (Table 1, entry 12) proved to be quantitative and only the *syn* isomer **8a** could be detected in the crude product by 400 MHz NMR spectroscopy. In an effort to invert the stereochemical course of the reaction with the same reagent, several Lewis acids, including $TiCl_4$ (Table 1, entry 13), $Ti(iPrO)_2Cl_2$ (Table 1, entry 14), $Ti(iPrO)_4$ (Table 1, entry 15), Et_2AlCl (Table 1, entry 16) and $BF_3{\cdot}Et_2O$ (Table 1, entry 17) were tested. In most cases only modest selectivities were obtained. However, by using 1.0 equiv. of $BF_3{\cdot}Et_2O$, essentially complete *anti* selectivity (ds > 95%) with 90% yield was obtained. Similar results were observed with nitrones **10** (Table 1, entries 21–23) and **11** (Table 1, entries 27–30). Even though lower selectivities were obtained, some stereocontrol was still present. Hence, complete stereocontrol of the allylation reaction was achieved with nitrone **9** by using allylmagnesium bromide and by changing the Lewis acid from Zn_2Br to $BF_3{\cdot}Et_2O$. Under these conditions multigram quantities (1–5 g) of enantiomerically pure *syn*-**8a** and *anti*-**8b** could be obtained without loss of selectivity.[42]

The structures of **8a** and **8b** were assigned by comparison of their physical and spectroscopic properties, including optical rotations, with previously prepared compounds.[41] The configurations of hydroxylamines **12** and **13** were determined by using the chemical correlation method. The adduct **12a** was transformed through a transacetalization reaction into **8a** (Scheme 3). Compounds **8a** and **13a** were converted into the known[43] compound **14** by catalytic hydrogenation. In this way, the hydroxyamino and α-alkoxy groups of adducts **12a** and **13a** were unequivocally found to exist in a *syn* orientation. In the diastereomers **12b** and **13b**, these groups adopt an *anti* orientation. The stereodivergent allylation of nitrone **9** was also ascertained and its utility demonstrated[44] by synthesizing both enantiomers of allylglycine, as described in a preliminary communication.[35a]



Scheme 3. Structural assignment of homoallyl hydroxylamines.

The stereochemical course of the allylation reaction was attributed to different conformations depending on the Lewis acid employed. No proof was found for the existence of α- or β-chelation between the nitrone and the Lewis acids. Although chelated models can be invoked to explain the Lewis acid dependent stereocontrol,[45] further NMR studies confirmed that nitrone **9** coordinated to the Lewis acids as a monodentate ligand.[46] From these experiments we believe that the nature of the Lewis acid plays a crucial role in stabilizing different conformations, leading to opposite diastereomers through classical Houk[47] models **A** and **B** in which either the oxygen atom or the methylene group can act as the large group, respectively (Figure 1).

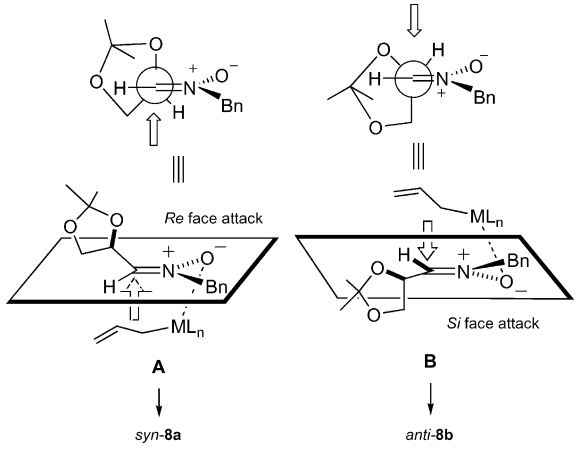
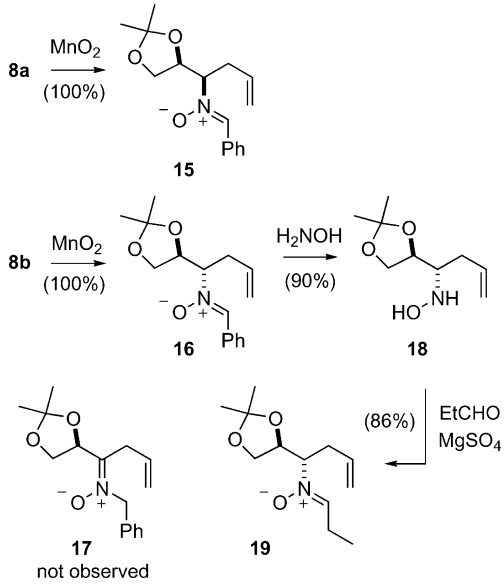


Figure 1. Models for the allylation of D-glyceraldehyde nitrones.

Synthesis of *N*-Alkenyl Nitrones and Intramolecular 1,3-Dipolar Cycloaddition Reactions

Hydroxylamines **8a** and **8b** were subjected to MnO_2 oxidation,[48] which provided nitrones **15** and **16**, respectively, in quantitative yield (Scheme 4). The *Z* configuration of the



Scheme 4. Synthesis of *N*-alkenyl nitrones.

nitrone was confirmed by NOESY experiments, which showed for both **15** and **16** an interaction between the azomethine proton of the nitrone functionality and the proton attached to the C_α atom of the nitrogen atom. This assignment was confirmed for **15** by a single-crystal X-ray analysis (Figure 2).[49] Our method provided ready access to *N*-alkenyl-*C*-phenyl nitrones, which are precursors of the corresponding 4-hydroxy-6-phenylpipecolic acids (see below). The fact that only the *C*-phenyl nitrones were formed in the oxidation reactions is a consequence of the driving force exerted by the phenyl group, which favours the formation of the more stable aldo nitrone instead of the keto nitrone **17** (not observed in any case).

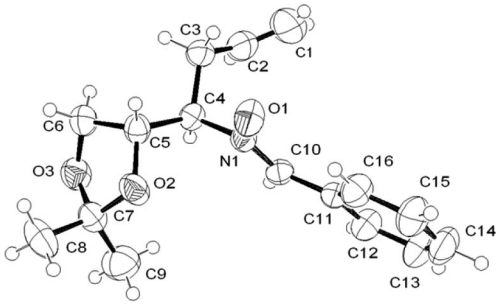
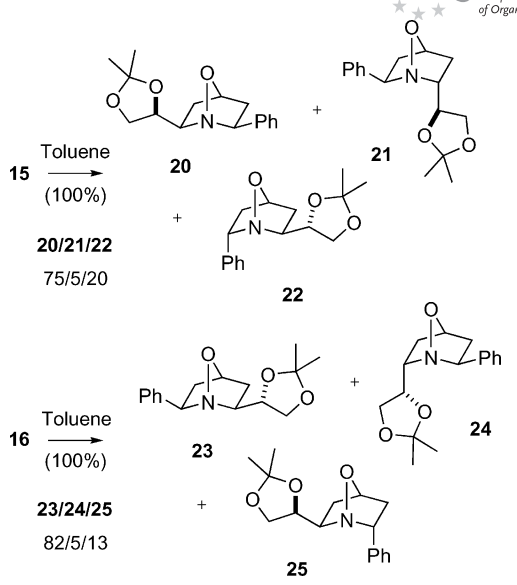


Figure 2. ORTEP drawing of the X-ray structure corresponding to **15** (ellipsoids drawn at the 50% probability level).

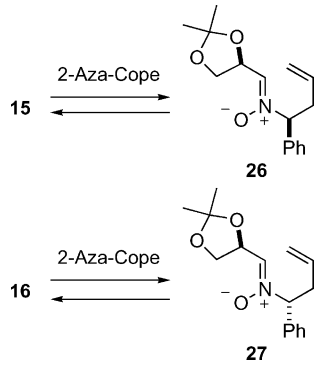
As explained in the synthetic plan (see above) we needed to be able to prepare different *C*-alkyl- and *C*-aryl-*N*-alkenyl nitrones in order to gain access to different 6-substituted 4-hydroxypipecolic acids. Starting with other *N*-substituted nitrones instead of **9** would have two significant drawbacks: i) complete stereocontrol of the allylation reaction could not be guaranteed as different substrates would be used and ii) the oxidation reaction in the case of *N*-alkyl-substituted hydroxylamines could afford mixtures of regioisomeric *N*-alkenyl nitrones. For these reasons we decided to carry out a transhydroximation[50] of nitrone **16**, which led to the formation of the free hydroxylamine **18**. This compound can be condensed with an aldehyde to give *C*-(substituted)-*N*-alkenyl nitrones, which can be converted, as discussed below, into the corresponding 6-substituted 4-hydroxypipecolic acids. As an example, compound **18** was condensed with *n*-propanal under typical conditions to yield nitrone **19** in 86% isolated yield (Scheme 4).

The intramolecular 1,3-dipolar cycloaddition of *N*-alkenyl nitrones has been employed before to obtain cyclic nitrogen derivatives,[51] many of which form a part of natural product structures such as alkaloids.[52] The intramolecular cycloaddition of nitrone **15** proceeded quantitatively in toluene at 100 °C to give, unexpectedly, the three adducts **20**, **21** and **22** in a 75:5:20 ratio, respectively. Similarly, heating nitrone **16** afforded, also quantitatively, the adducts **23**, **24** and **25** in an 82:5:13 ratio, respectively (Scheme 5). All of these cycloadducts were separated by radial chromatography and fully characterized.



Scheme 5. Intramolecular cycloaddition reactions of nitrones **15** and **16**.

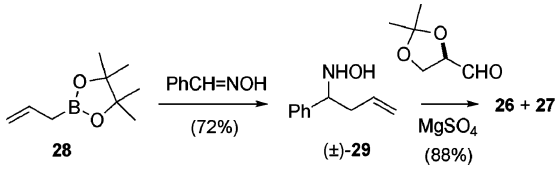
This cycloaddition reaction revealed an intriguing aspect. From the intramolecular cycloaddition reactions of nitrones **15** and **16**, and according to their configuration, only cycloadducts **20** and **21** (from **15**) and **23** and **24** (from **16**) were expected. The major compounds **20** and **23** arose from intramolecular attack at the *Re* face of the *syn* nitrones **15** and **16**, respectively. The minor compounds **21** and **24** were formed by attack at the *Si* face of the same nitrones. Only these products were expected, in principle, because in all cases, for steric reasons, only the *endo* approach of the double bond to the two diastereotopic faces of the nitrone is allowed. In principle there are two possible explanations for the formation of cycloadducts **22** and **25**: i) the nitrone **15** epimerizes to **16** and then this compound isomerizes[53] to the corresponding (*E*)-nitrone,[54] which could lead to adduct **22** (the same applies to **16**: epimerization to **15** and isomerization to the (*E*)-nitrone could explain the formation of **25**) or ii) a 2-aza-Cope rearrangement takes place to form nitrone **26** from **15** and **27** from **16** (Scheme 6). Intramolecular cycloaddition of these rearranged nitrones should afford cycloadducts **20** and **22** (from **26**) and **23** and **25** (from **27**).



Scheme 6. Intramolecular cycloaddition reactions of nitrones **15** and **16**.

Compounds **20** and **23** should be formed by *endo* attack on the *Si* faces of nitrones **26** and **27**, respectively. The unexpected adducts **22** and **25** should be formed by *endo* attack on the *Re* faces of nitrones **26** and **27**, respectively.[55] These assumptions were discerned by analyzing the stereochemical course of the reaction. Thus, the epimerization/isomerization route is negligible as the first process should occur in opposite senses, that is, from **15** and **16**, which contradicts the basic rules of thermodynamics. In addition, if partial epimerization (or even isomerization) took place a cross-mixture of products from the *syn* and *anti* series should be obtained. Moreover, other diastereomers should also have been observed. Such a contamination of diastereomers was not detected at all in either case.[55]

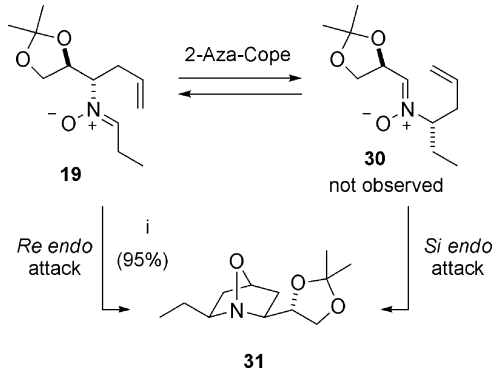
The 2-aza-Cope rearrangement[56] has previously been reported for iminium salts[57] and for nitrones protonated or coordinated to Lewis acids,[58] which actually were oxyiminium salts. The thermal rearrangement of nitrones has also been suggested[59] but never demonstrated because of the use of racemic products that prevent discrimination between the rearrangement and *E*/*Z* isomerization processes (see below). We have reported the preliminary results of the 2-aza-Cope rearrangement of nitrones **15** and **16**, including a theoretical study.[60] It was observed that the activation energies for the aza-Cope rearrangement are very similar to those of the cycloaddition processes, which explains why nitrones **26** and **27** were not detected in the course of the reactions. In order to confirm the above hypothesis we synthesized nitrones **26** and **27** in an alternative way. As their preparation by a homochiral route would not be easy we decided to prepare them as a diastereomeric mixture by condensation of racemic hydroxylamine **29** (obtained from the addition of allylboronate **28** to benzaldoxime)[59a] with 1,2-di-*O*-isopropylidene-D-glyceraldehyde (Scheme 7).



Scheme 7. Synthesis of nitrones **26** and **27**.

Unfortunately, nitrones **26** and **27** could not be separated and careful column chromatography under a variety of conditions was in vain; only enriched mixtures were obtained. Nevertheless, when these mixtures were subjected to cycloaddition conditions (toluene, 110 °C, sealed tube) identical results were observed[61] to those obtained separately from nitrones **15** and **16**, which confirms the connection between the nitrone pairs **15**/**26** and **16**/**27** through a reversible 2-aza-Cope thermal rearrangement. As expected, nitrones **15** and **16** could not be detected during the course of these experiments and only the final adducts **20** and **23** were obtained preferentially in diastereomeric ratios of 75 and 82%, respectively.

The intramolecular cycloaddition of **19** afforded the cycloadduct **31** (Scheme 8) as the only isomer, as detected by 400-MHz NMR spectroscopy. The compound obtained should be formed by *endo* attack of the double bond on the *Re* face of the nitrone **19**. Of course compound **31** could also be formed by *endo* attack on the *Si* face of the rearranged nitrone **30**. In this case we think that there is no reason for ruling out the 2-aza-Cope rearrangement. However, it cannot strictly be demonstrated for **19** as no other cycloadducts were detected in the reaction mixture.



Scheme 8. Intramolecular cycloaddition reaction of nitrone **19**.

The structures of cycloadducts **20**–**25** and **31** were determined by a combination of X-ray crystallography and NMR techniques. The stereochemistries of compounds **20** and **25** was proven by single-crystal X-ray analysis (see Figures 3 and 4).[49]

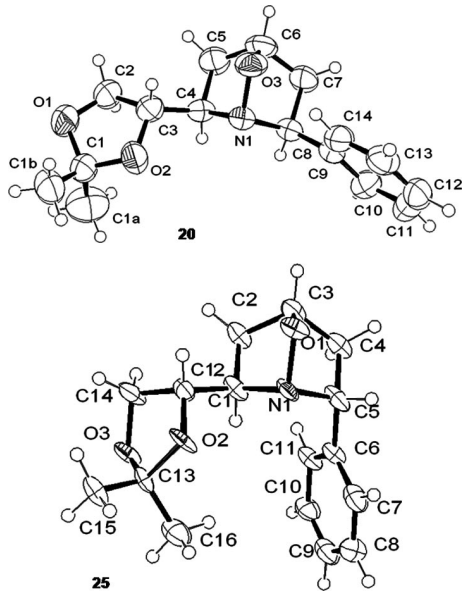


Figure 3. ORTEP drawings of the X-ray structures of **20** and **25** showing ellipsoids at the 50% probability level.

The NMR signals of all the adducts were assigned by COSY and HSQC (or HMQC) 2D-NMR experiments. The NOE difference spectra of the adducts were compared for complete structural assignment (Figure 4). For compounds **20**, **23** and **31**, correlations of 2-H with both 3en-H and 6-H as well as those found between 6-H and 5en-H, and 5en-

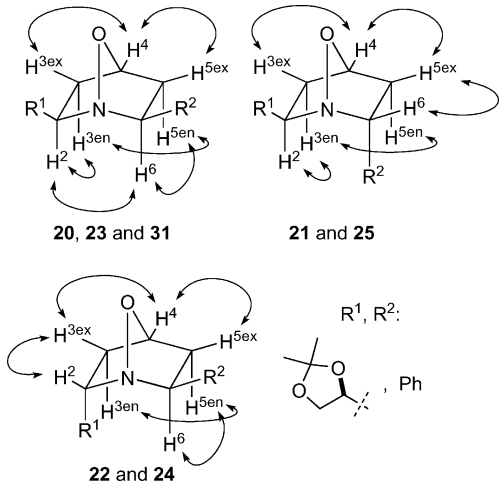
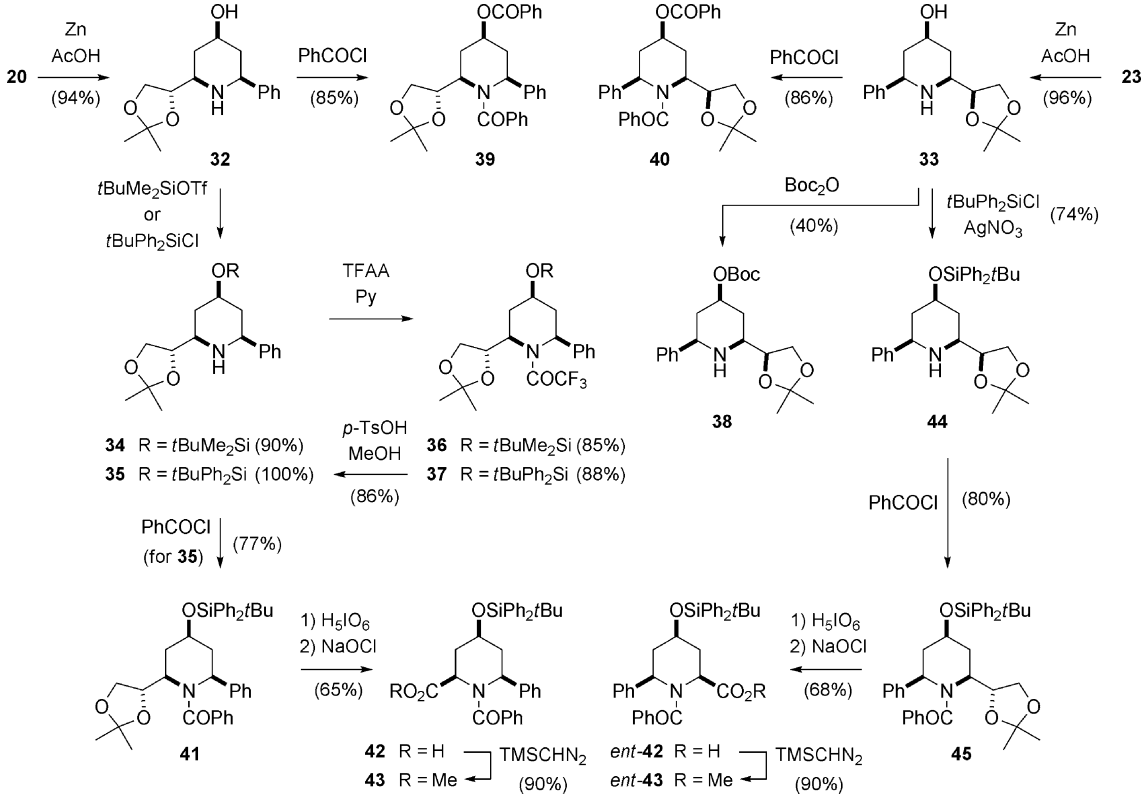


Figure 4. NOE relationships of cycloadducts **20**–**25** and **31**.

H and 3en-H allowed us to assign the *exo*,*exo* configuration (further confirmed by X-ray analysis of **20**). For compounds **21** and **25**, no correlation was observed between 6-H and 5en-H. These data, together with the interactions shown in Figure 1, suggest that the C-6 substituent is in an *endo* disposition. As discussed above, the configuration of **25** was confirmed by X-ray analysis. Similarly, the observed correlations for **22** and **24** as well as the lack of correlation between 2-H and 3en-H indicate an *endo* orientation of the substituent at C-2.

Synthesis of Pipecolic Acid Derivatives

Having in hand enantiomerically pure cycloadducts **20** and **23** we pursued the synthesis of 4-hydroxy-6-phenylpipecolic acids. From compounds **20** and **23**, two key operations should be performed: i) reduction of the N–O bond to form the 4-hydroxypiperidine skeleton and ii) unmasking of the carboxylic group by oxidation of the dioxolane moiety. Bicyclics **20** and **23** were first reduced with Zn in acetic acid to furnish piperidines **32** and **33** in 94 and 96% yields, respectively (Scheme 9). By carrying out the reaction at ambient temperature over 4 h the integrity of the dioxolane moiety was completely maintained. With the aim of establishing an orthogonal protection protocol, compound **32** was converted into *O*-silyl derivatives **34** and **35**. Although the formation of the *O*-(*tert*-butyldimethylsilyl) derivative took place in 85% yield under conventional conditions (TBSCl; 2,6-lutidine), protection as the *O*-(*tert*-butyldiphenylsilyl) derivative proved to be more difficult. Indeed, by using TBDPSCl in the presence of imidazole, triethylamine or DMAP,[62] compound **35** was isolated in a low yield (at best 25%). In contrast, by carrying out the reaction in the presence of silver nitrate,[63] the same compound was obtained in quantitative yield. Nitrogen protection in **34** and **35** allowed us to isolate the trifluoroacetamido derivatives **36** and **37** in good yields. At ambient temperature the ^{1}H and ^{13}C NMR spectra of these compounds showed an equilibrium between amide rotamers, but on heating to 55 °C coalescence was observed although in the case of **36** broad signals were still present.



Scheme 9. Synthesis of pipecolic acid derivatives (route 1).

To transform the dioxolane ring into a carboxylic acid, we needed to subject compounds **36** and **37** to acidic conditions. Unfortunately, treatment of **36** with *p*-toluenesulfonic acid in methanol resulted in a very sluggish reaction and only complex mixtures were obtained. Subjecting **37** to the same reaction conditions resulted in the recovery of **35** in 86% isolated yield. From these experiments we concluded that the *O*-(*tert*-butyldimethylsilyl) and, more disappointingly, *N*-trifluoroacetyl protecting groups were not compatible with the required conditions for unmasking the carboxy group. We also attempted an initial *N*-(*tert*-butoxycarbonyl) protection of compound **33**. However, after several attempts, only the *O*-Boc derivative **38** was isolated in 40% yield.[64] We then turned our attention to the amide group to protect the nitrogen atom. Attempts at chemoselective *N*-benzoylation of **32** and **33** only led to dibenzoylated adducts **39** and **40**, which were obtained in good yields when an excess of benzoyl chloride was employed. As before for compounds **36** and **37**, the ^{1}H and ^{13}C NMR spectra of **39** and **40** showed a complexity characteristic of compounds presenting slow conformational equilibria.

Indeed, previous studies with *N*-acyl-4-acetyl-2,6-diphenylpiperidines showed two preferential conformations[65] due to a pseudo-allylic A(1,3) strain. Allylic A(1,3) strain[66] can feature in *N*-acylpiperidines due to the partial double bond character of the amide N–CO bond. It has been known for some time that a ring substituent at the 2-position of *N*-acylpiperidines preferentially adopts a pseudoaxial arrangement.[67] Such a conformational preference has been found in nature to be related to biological activity[68] and it has also been used to predict a high level of asymmetric induction in several chemical reactions.[69] Following from these considerations, conformation **A** for 2,6-disubstituted *N*-acyl-4-hydroxypiperidines, like those considered in this work, should present unfavourable steric interactions between the amide moiety and the adjacent substituents (Figure 5). The two conformations **B** and **C** should be preferred. These conformational preferences serve to explain both the difficulty in protecting the nitrogen atom as a Boc derivative and the observed lability of the trifluoroacetamido group.

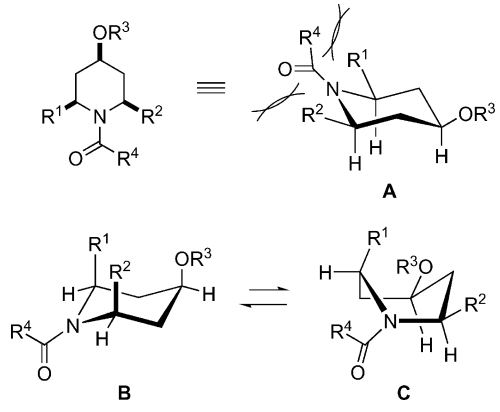
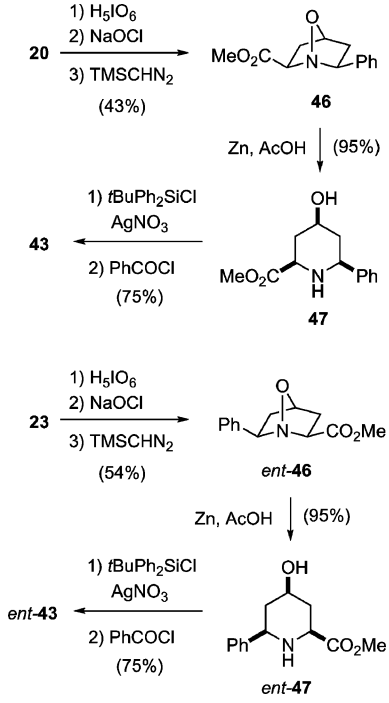


Figure 5. Preferred conformations for 2,5-disubstituted *N*-acyl-4-hydroxypiperidine.

In order to differentiate oxygen and nitrogen protecting groups, compound **35** was benzoylated. An excess of benzoyl chloride (2.5 equiv.) was needed, which also indicates steric hindrance at the nitrogen atom. Under these conditions the fully protected derivative **41** was obtained in 77% yield. The same protocol was applied to **33**; after silylation and benzoylation, compound **45** was isolated in 73% overall yield (two steps). Finally, unmasking of the carboxy group was carried out by one-pot oxidation of the dioxolane ring by using periodic acid in diethyl ether.[70] The resulting intermediate amino aldehyde was oxidized in situ with sodium chlorite under neutral conditions.[71] Esterification of the carboxylic acid **42** with trimethylsilyldiazomethane furnished the targeted, fully protected (2*R*,4*S*,6*S*)-4-silyloxy-6-phenylpipecolic acid **43**. Similarly, transformation of **45** into *ent*-**43** was carried out in 61% overall yield. As expected, physical and spectroscopic properties of this compound were identical to those of its enantiomer with the only exception the sign of the optical rotation. Thus, the enantiodivergent synthesis of **43** and *ent*-**43** has been achieved in 32 and 30% overall yields (nine steps) from the starting nitrone **9**.

With the aim of simplifying the synthetic process we also considered the possibility of unmasking the carboxy group before reducing the N–O bond in cycloadducts **20** and **23**. Bicyclic amino ester **46** was synthesized from **20** by the above-mentioned sequence featuring oxidative cleavage of the dioxolane ring and oxidation of the emerging aldehyde (Scheme 10). The complete protocol took place with a relatively low yield of 43%, presumably due to the presence of a nucleophilic nitrogen atom, which might lead to undesired oxidation byproducts. Zinc-mediated cleavage of the N–O bond afforded methyl ester **47**, which was differentially pro-



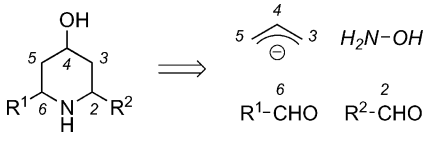
Scheme 10. Synthesis of pipecolic acid derivatives (route 2).

tected to furnish **43**. Application of the same reaction sequence to **23** provided *ent*-**43** via bicyclic *ent*-**46** and pipecolic acid *ent*-**47**. By this route compounds **43** and *ent*-**43** were obtained in 23 and 27% overall yields from nitrone **9** in nine steps. The approach depicted in Scheme 10 provided the target compounds in lower overall yields than that illustrated in Scheme 9. Nevertheless, the initial unmasking of the carboxy group in **46** and its enantiomer offers the possibility of introducing acid-sensitive protecting groups in **47** and *ent*-**47** that could not be used for protecting **32** and **33**. The two routes can be defined as being complementary as the first provides access not only to pipecolic acid derivatives but also to substituted piperidines because of the different synthetic elaborations that can be achieved with the dioxolane ring.

Conclusions

The combination of two typical reactions of nitrones, that is, nucleophilic addition and cycloaddition chemistry, has allowed the development of an enantiodivergent strategy directed towards the synthesis of all-*cis* orthogonally protected 6-substituted 4-hydroxypipecolic acids. The methodology involves the stereocontrolled allylation of *N*-benzyl-1,2-di-*O*-isopropylidene-D-glyceraldehyde nitrone **9**, oxidation of the resulting hydroxylamines and stereoselective intramolecular cycloaddition of the thus formed *N*-alkenyl nitrones. During the course of the research, experimental evidence for a thermal 2-aza-Cope rearrangement of nitrones was found. The final steps of the synthetic methodology required the use of suitable protecting groups due to the particular structural features of the 2,4,6-trisubstituted piperidine precursor of the target compounds.

Taking into account the fact that the starting nitrone is easily prepared by condensation of an aldehyde and an *N*-substituted hydroxylamine, which, in turn, is obtained by reduction of the corresponding oxime formed by condensation of an aldehyde and hydroxylamine hydrochloride, it can be concluded that the primary raw materials of 6-substituted 4-hydroxypipecolic acids are two aldehydes, an allyl reagent and hydroxylamine, the latter being the source of the nitrogen atom and the hydroxy group (Scheme 11).



Scheme 11. General approach to 6-substituted 4-hydroxypipecolic acid derivatives.

The major benefits of this synthetic approach include large amounts of the intermediate *N*-alkenyl nitrones, less than three days work, a very stereoselective two-step sequence from D-glyceraldehyde nitrone, efficient isolation of the product in an enantiomerically pure form and the ease of their conversion into different *C*-substituted nitrones through a typical transoximation protocol. This methodology should thus be of general utility for the preparation of a large number of polysubstituted 4-hydroxypiperidines (including 2,3,5,6-tetrasubstituted 4-hydroxypiperidines if substituted allylic compounds are considered) and provides a highly stereoselective route to the preparation of highly substituted 4-hydroxypipecolic acids.

Experimental Section

General Methods: The reaction flasks and other glass equipment were heated in an oven at 130 °C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the positions of the spots were detected with 254 nm UV light or by spraying with one of the following staining systems: 50% methanolic sulfuric acid, 5% ethanolic phosphomolybdic acid and iodine. Preparative centrifugally accelerated radial thin-layer chromatography (radial chromatography) was performed with a Chromatotron® Model 7924 T instrument (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 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 with a MPLC system (max. pressure: 40 bar) using 5–60 micron silica gel. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with Bruker 300, 400 and 500 instruments in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ (δ = 7.26 ppm) in $CDCl_3$ and coupling constants are given in Hz. Optical rotations were measured at 25 °C on a Perkin-Elmer 241 or Jasco polarimeter. Elemental analyses were performed with a Perkin-Elmer 240B microanalyzer. D-Glyceraldehyde nitrone **9** was prepared as described previously.[33] Nitrones **10** and **11** were prepared by condensation of the corresponding protected D-glyceraldehyde with *N*-benzylhydroxylamine following the same procedure reported for **9**.

Allylation of Nitrones. General Procedure: A Lewis acid (1.0 equiv.), where appropriate, was added to a solution of the nitrone (1.0 equiv.) in the stated solvent (Table 1), and the mixture stirred for 5 min at ambient temperature and then cooled to the stated temperature (Table 1). The corresponding allylic metal (2.0 equiv.) was added and the reaction mixture was stirred at the corresponding temperature until no more nitrone (TLC) was observed (see Table 1). Saturated aq. NH_4Cl was added and the resulting mixture was diluted with diethyl ether. The organic layer was separated and the aqueous layer extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to furnish the crude product, which was purified by radial chromatography.

(2*S*,3*R*)-3-(Benzylhydroxyamino)-1,2-di-*O*-isopropylidenehex-5-ene-1,2-diol (8a): R_f (hexane/ethyl acetate, 4:1) = 0.48; white solid, m.p. 79–80 °C. $[\alpha]_D^{20}$ = +13 (*c* = 1.70, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.20 (m, 5 H), 5.98–5.81 (m, 1 H), 5.25–5.00 (m, 3 H), 4.50–4.38 (m, 1 H), 4.15–3.95 (m, 3 H), 3.82 (t, ^3J = 8.1 Hz, 1 H), 3.05–2.95 (m, 1 H), 2.62–2.40 (m, 1 H), 2.38–2.25 (m, 1 H), 1.46 (s, 3 H), 1.41 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 136.3, 129.1, 128.4, 127.2, 116.5, 108.6, 75.6, 66.8, 65.6, 61.1, 30.8, 26.6, 25.5 ppm. $C_{16}H_{23}NO_3$ (277.36): calcd. C 69.29, H 8.36, N 5.05; found C 69.57, H 8.34, N 5.07.

(2*S*,3*S*)-3-(Benzylhydroxyamino)-1,2-di-*O*-isopropylidenehex-5-ene-1,2-diol (8b): R_f (hexane/ethyl acetate, 4:1) = 0.47; white solid, m.p. 74–75 °C. $[\alpha]_D^{20}$ = –8 (*c* = 0.84, $CHCl_3$). ^{1}H NMR (300 MHz,

$CDCl_3$): δ = 7.34–7.22 (m, 5 H), 6.11–5.95 (m, 1 H), 5.25–5.05 (m, 2 H), 5.00 (br., 1 H), 4.35 (q, ^3J = 6.5 Hz, 1 H), 4.11 (dd, ^3J = 8.5, 6.5 Hz, 1 H), 3.98 (d, ^2J = 13.4 Hz, 1 H), 3.85 (d, ^2J = 13.4 Hz, 1 H), 3.79 (dd, ^3J = 8.5, 6.5 Hz, 1 H), 2.93–2.77 (m, 1 H), 2.72–2.55 (m, 1 H), 2.55–2.40 (m, 1 H), 1.43 (s, 3 H), 1.37 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.1, 137.0, 129.5, 128.2, 127.2, 116.0, 108.9, 75.8, 68.3, 67.9, 60.3, 30.8, 26.6, 25.4 ppm. $C_{16}H_{23}NO_3$ (277.36): calcd. C 69.29, H 8.36, N 5.05; found C 69.52, H 8.22, N 4.88.

(2*S*,3*R*)-3-(Benzylhydroxyamino)-1,2-di-*O*-cyclohexylidenehex-5-ene-1,2-diol (12a): R_f (hexane/ethyl acetate, 4:1) = 0.55; oil. $[\alpha]_D^{20}$ = –10 (c = 3.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.16 (m, 5 H), 5.96 (ddt, ^2J = 17.2, ^3J = 10.1, 7.1 Hz, 1 H), 5.08 (ddt, ^2J = 17.2, ^3J = 1.8, 1.2 Hz, 1 H), 5.00 (d, ^3J = 10.1 Hz, 1 H), 4.71 (br., 1 H), 4.26 (q, ^3J = 6.6 Hz, 1 H), 4.03 (dd, ^3J = 8.3, 6.4 Hz, 1 H), 3.92 (d, ^2J = 13.4 Hz, 1 H), 3.81–3.74 (m, 2 H), 2.81 (q, ^3J = 6.5 Hz, 1 H), 2.59 (dt, ^2J = 14.4, ^3J = 6.8 Hz, 1 H), 2.42 (dt, ^2J = 14.4, ^3J = 6.2 Hz, 1 H), 1.61–1.45 (m, 8 H), 1.39–1.27 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 137.2, 129.3, 128.4, 127.3, 116.1, 109.5, 75.8, 88.3, 68.1, 60.1, 36.4, 35.0, 31.1, 25.3, 24.1, 23.9 ppm. $C_{19}H_{27}NO_3$ (317.42): calcd. C 71.89, H 8.57, N 4.41; found C 72.01, H 8.39, N 4.47.

(2*S*,3*S*)-3-(Benzylhydroxyamino)-1,2-di-*O*-cyclohexylidenehex-5-ene-1,2-diol (12b): R_f (hexane/ethyl acetate, 4:1) = 0.54; oil. $[\alpha]_D^{20}$ = +8 (c = 1.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = (400 MHz, $CDCl_3$): 7.42–7.37 (m, 2 H), 7.37–7.31 (m, 2 H), 7.31–7.25 (m, 1 H), 5.93 (ddt, ^2J = 17.1, ^3J = 10.1, 7.0 Hz, 1 H), 5.13 (dt, ^2J = 17.1, ^3J = 1.5 Hz, 1 H), 5.08 (d, ^3J = 10.1 Hz, 1 H), 4.44 (q, ^3J = 6.2 Hz, 1 H), 4.07 (s, 2 H), 4.02 (t, ^3J = 6.2 Hz, 1 H), 3.81 (t, ^3J = 6.1 Hz, 1 H), 3.00 (q, ^3J = 6.4 Hz, 1 H), 2.51 (dt, ^2J = 14.7, ^3J = 6.8 Hz, 1 H), 2.32 (dt, ^2J = 14.7, ^3J = 6.7 Hz, 1 H), 1.70–1.56 (m, 8 H), 1.46–1.38 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 136.3, 129.0, 128.3, 127.2, 116.5, 109.4, 75.4, 66.6, 65.9, 61.1, 36.2, 35.0, 31.2, 25.2, 24.1, 24.0 ppm. $C_{19}H_{27}NO_3$ (317.42): calcd. C 71.89, H 8.57, N 4.41; found C 71.77, H 8.49, N 4.37.

(2*S*,3*R*)-3-(Benzylhydroxyamino)-1,2-di-*O*-benzylhex-5-ene-1,2-diol (13a): R_f (hexane/ethyl acetate, 4:1) = 0.63; oil. $[\alpha]_D^{20}$ = –5 (c = 1.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = (400 MHz, $CDCl_3$): δ = 7.28–7.14 (m, 15 H), 5.91 (ddt, ^2J = 17.2, ^3J = 10.1, 7.1 Hz, 1 H), 5.07–4.92 (m, 2 H), 4.64 (d, ^3J = 11.4 Hz, 1 H), 4.51 (d, ^3J = 11.4 Hz, 1 H), 4.48 (s, 2 H), 3.92 (d, ^2J = 13.5 Hz, 1 H), 3.84 (d, ^2J = 13.5 Hz, 1 H), 3.81 (q, ^3J = 5.2 Hz, 1 H), 3.71 (dd, ^3J = 9.9, 5.1 Hz, 1 H), 3.64 (dd, ^3J = 9.9, 4.7 Hz, 1 H), 2.94 (q, ^3J = 6.1 Hz, 1 H), 2.62 (dt, ^2J = 13.8, ^3J = 6.8 Hz, 1 H), 2.38 (dt, ^2J = 13.8, ^3J = 6.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 138.5, 138.0, 137.8, 129.0, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 127.1, 115.7, 79.3, 73.5, 72.4, 71.3, 67.0, 60.9, 30.8 ppm. $C_{27}H_{31}NO_3$ (417.54): calcd. C 77.67, H 7.48, N 3.35; found C 77.52, H 7.37, N 3.43.

(2*S*,3*S*)-3-(Benzylhydroxyamino)-1,2-di-*O*-benzylhex-5-ene-1,2-diol (13b): R_f (hexane/ethyl acetate, 4:1) = 0.62; oil. $[\alpha]_D^{20}$ = –20 (c = 0.37, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = (400 MHz, $CDCl_3$): δ = 7.28–7.12 (m, 15 H), 5.76–5.62 (m, 1 H), 4.97–4.89 (m, 2 H), 4.69 (dd, ^3J = 11.5 Hz, 1 H), 4.59 (br., 1 H), 4.47 (d, ^3J = 11.5 Hz, 1 H), 4.42 (d, ^3J = 11.9 Hz, 1 H), 4.37 (d, ^3J = 11.9 Hz, 1 H), 4.01 (d, ^2J = 13.2 Hz, 1 H), 3.80–3.74 (m, 1 H), 3.72–3.65 (m, 3 H), 2.94–2.87 (m, 1 H), 2.57–2.39 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 138.3, 138.1, 136.5, 129.6, 129.0, 128.3, 128.1, 127.7, 127.6, 127.5, 127.0, 121.3, 116.8, 78.9, 73.3, 73.2, 71.2, 64.8, 60.6, 28.4 ppm. $C_{27}H_{31}NO_3$ (417.54): calcd. C 77.67, H 7.48, N 3.35; found C 77.62, H 7.43, N 3.39.

Transacetalization of 12a: A solution of **12a** (0.095 g, 0.3 mmol) in acetone (15 mL) was treated with *p*-TsOH (2 mg) and $MgSO_4$ (1 g) and the resulting mixture was stirred at ambient temperature for 16 h. The reaction mixture was then filtered and the solvents evaporated to dryness. The residue was purified by radial chromatography (hexane/ethyl acetate, 4:1) to furnish pure **8a**. The physical and spectroscopic properties of this compound were identical to those observed for the same product prepared by allylation of nitrone **9** as described above.

(2*S*,3*R*)-3-(*tert*-Butoxycarbonylamino)hexane-1,2-diol 14 from 8a: A solution of **8a** (0.069 g, 0.25 mmol) in methanol (10 mL) was treated with *p*-TsOH (5 mg) and stirred at ambient temperature for 6 h. The reaction mixture was then neutralized with Amberlyst basic ion-exchange resin and filtered. The filtrate was then treated with $Pd(OH)_2$/C (24 mg) and di-*tert*-butyl dicarbonate (0.109 g, 0.5 mmol) and the mixture stirred under hydrogen at ambient temperature and 2000 psi. After 24 h the reaction mixture was filtered through a pad of Celite, which was washed with methanol. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 2:1) to afford pure **14** (48 mg, 83%) as a white solid; m.p. 63–65 °C. $[\alpha]_D^{20}$ = –14 (c = 0.21, $CHCl_3$) {lit.:[43] $[\alpha]_D^{20}$ = –12 (c = 1, $CHCl_3$)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = (400 MHz, $CDCl_3$): δ = 4.65 (br. d, ^3J = 5.3 Hz, 1 H); 3.64–3.70 (m, 2 H), 3.44–3.52 (m, 2 H), 2.48 (br. s, 2 H), 1.43–1.55 (m, 4 H), 1.48 (s, 9 H), 0.98 (t, ^3J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 80.0, 72.5, 64.3, 51.7, 34.8, 28.7, 19.2, 13.4 ppm. $C_{11}H_{23}NO_4$ (233.31): calcd. C 56.63, H 9.94, N 6.00; found C 56.59, H 10.04, N 5.89.

(2*S*,3*R*)-3-(*tert*-Butoxycarbonylamino)hexane-1,2-diol 14 from 13a: A solution of **13a** (0.104 g, 0.25 mmol) in methanol (10 mL) was treated with $Pd(OH)_2$/C (24 mg) and di-*tert*-butyl dicarbonate (0.109 g, 0.5 mmol), and the mixture was stirred under hydrogen at ambient temperature and 2000 psi. After 24 h the reaction mixture was filtered through a pad of Celite, which was washed with methanol. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 2:1) to afford pure **14** (52 mg, 90%). The physical and spectroscopic properties of this compound were identical to those observed for the same product prepared from **8a** as described above.

(*R*,*Z*)-*N*-Benzylidene-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]but-3-en-1-amine Oxide (15): Activated manganese(IV) oxide (0.65 g, 7.6 mmol) was added in portions to an ice-cooled solution of hydroxylamine **8a** (1.75 g, 6.3 mmol) in dichloromethane (100 mL). The reaction was stirred for 8 h at 0 °C. The solution was then filtered through anhydrous sodium sulfate and concentrated under reduced pressure. The NMR analysis of the crude product revealed the presence of only one regioisomer. The crude product was purified by flash chromatography (hexane/ethyl acetate, 4:1; R_f = 0.13) to give pure **15** (1.73 g, 100%); white solid, m.p. 104–105 °C. $[\alpha]_D^{20}$ = –30 (c = 0.72, methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32–8.24 (m, 2 H), 7.48–7.38 (m, 3 H), 7.36 (s, 1 H), 5.85–5.68 (m, 1 H), 5.20 (ddt, ^2J = 16.9, ^3J = 2.6, 1.3 Hz, 1 H), 5.10 (d, ^3J = 10.1 Hz, 1 H), 4.61 (q, ^3J = 6.6 Hz, 1 H), 4.18 (ddd, ^3J = 8.5, 6.4, 0.9 Hz, 1 H), 3.95–3.81 (m, 2 H), 2.96–2.82 (m, 1 H), 2.28–2.16 (m, 1 H), 1.44 (s, 3 H), 1.36 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.8, 132.2, 130.0, 129.9, 128.5, 128.0, 118.5, 109.1, 78.3, 74.9, 65.8, 32.1, 26.4, 24.8 ppm. $C_{16}H_{21}NO_3$ (275.34): calcd. C 69.79, H 7.69, N 5.09; found C 70.02, H 7.76, N 4.98.

(*S*,*Z*)-*N*-Benzylidene-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]but-3-en-1-amine Oxide (16): Oxidation of hydroxylamine **8b** (1.75 g, 6.3 mmol) as described above for **8a** afforded nitrone **16** (1.73 g, 100%) after purification by flash chromatography (hexane/ethyl

acetate, 4:1; R_f = 0.24); white solid, m.p. 38–39 °C. $[\alpha]_D^{20}$ = +18 (*c* = 1.71, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20–8.12 (m, 2 H), 7.38–7.26 (m, 4 H), 5.71 (ddt, ^2J = 17.1, ^3J = 10.1, 7.2 Hz, 1 H), 5.11 (d, ^2J = 17.1 Hz, 1 H), 4.99 (d, ^3J = 10.1 Hz, 1 H), 4.46 (dt, ^3J = 7.4, 5.6 Hz, 1 H), 4.00 (dd, ^3J = 8.9, 6.1 Hz, 1 H), 3.90 (dd, ^3J = 8.9, 4.9 Hz, 1 H), 3.81–3.72 (m, 1 H), 2.90–2.74 (m, 1 H), 2.61–2.49 (m, 1 H), 1.34 (s, 3 H), 1.28 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.1, 132.9, 130.3, 129.8, 128.5, 128.3, 118.5, 109.6, 77.7, 75.8, 66.3, 33.4, 26.7, 25.0 ppm. $C_{16}H_{21}NO_3$ (275.34): calcd. C 69.79, H 7.69, N 5.09; found C 69.68, H 7.65, N 5.13.

***N*-{(*S*)-1-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]but-3-enyl}hydroxylamine (18):** A well-stirred and cooled (0 °C) solution of hydroxylamine hydrochloride (0.051 g, 0.73 mmol) in methanol (5 mL) was sequentially treated with NaOH (0.029 g, 0.73 mmol) and AcOH (0.044 g, 0.734 mmol). The resulting solution was stirred for 15 min after which time the nitrone **16** (0.185 g, 0.67 mmol) was added. The resulting mixture was stirred at room temperature for 24 h and then concentrated under reduced pressure. The crude product was purified by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.19) to give pure **18** (0.112 g, 90%); oil. $[\alpha]_D^{20}$ = +4 (*c* = 2.49, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.27 (br., 1 H), 5.82 (ddt, ^2J = 17.1, ^3J = 10.2, 7.2 Hz, 1 H), 5.15 (d, ^2J = 17.1 Hz, 1 H), 5.13 (d, ^3J = 10.2 Hz, 1 H), 4.21 (q, ^3J = 6.4 Hz, 1 H), 4.08 (t, ^3J = 7.6 Hz, 1 H), 3.86 (t, ^3J = 7.6 Hz, 1 H), 3.01 (dt, ^3J = 8.8, 4.8 Hz, 1 H), 2.37 (dt, ^2J = 14.2, ^3J = 5.2 Hz, 1 H), 2.26 (dt, ^2J = 14.2, ^3J = 8.4 Hz, 1 H), 1.42 (s, 3 H), 1.36 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 134.6, 118.2, 108.7, 76.0, 66.9, 62.4, 32.3, 26.4, 25.2 ppm. $C_9H_{17}NO_3$ (187.24): calcd. C 57.73, H 9.15, N 7.48; found C 57.84, H 9.03, N 7.36.

(*S*,*Z*)-1-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-*N*-propylidenebut-3-en-1-amine Oxide (19): Hydroxylamine **18** (0.050 g, 0.27 mmol) and anhydrous magnesium sulfate (0.033 g, 0.27 mmol) were added to a well-stirred solution of propionaldehyde (0.021 mL, 0.29 mmol) in dichloromethane (4 mL) and the resulting mixture was stirred at room temperature for 4 h. The mixture was filtered and the filtrate evaporated under reduced pressure to yield the crude product which was purified by chromatography on silica gel (hexane/ethyl acetate, 4:1; R_f = 0.17) to afford the corresponding pure nitrone **19** (0.053 g, 86%); oil. $[\alpha]_D^{20}$ = –5 (*c* = 1.59, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.63 (t, ^3J = 5.8 Hz, 1 H), 5.70 (ddt, ^2J = 17.2, ^3J = 10.1, 7.3 Hz, 1 H), 5.16 (dd, ^2J = 17.2, ^3J = 1.2 Hz, 1 H), 5.09 (d, ^3J = 10.1 Hz, 1 H), 4.47 (ddd, ^3J = 7.9, 5.9, 5.3 Hz, 1 H), 4.06 (dd, ^3J = 9.0, 6.2 Hz, 1 H), 3.86 (dd, ^3J = 9.0, 4.8 Hz, 1 H), 3.57 (ddd, ^3J = 10.7, 8.1, 3.3 Hz, 1 H), 2.77 (ddd, ^2J = 14.4, ^3J = 10.7, 7.3 Hz, 1 H), 2.58–2.52 (m, 1 H), 2.51–2.42 (m, 2 H), 1.41 (s, 3 H), 1.34 (s, 3 H), 1.09 (t, ^3J = 7.6, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.5, 133.1, 118.5, 109.7, 76.3, 75.6, 66.4, 33.3, 26.9, 25.1, 19.6, 10.0 ppm. $C_{12}H_{21}NO_3$ (227.30): calcd. C 63.41, H 9.31, N 6.16; found C 63.20, H 9.25, N 6.26.

Intramolecular 1,3-Dipolar Cycloaddition of Nitrone 15: Nitrone **15** (0.63 g, 2.3 mmol) was dissolved in toluene (20 mL) and the corresponding solution was heated with stirring at 110 °C for 72 h in a sealed tube. After this time the solution was concentrated under reduced pressure. The NMR analysis of the crude product revealed the presence of the three regioisomeric cycloadducts **20**, **21** and **22** in a 75:5:20 ratio, respectively. The crude mixture was purified by radial chromatography to give the corresponding pure cycloadducts.

20: Yield: 0.472 g (75%). R_f (hexane/ethyl acetate, 4:1) = 0.38; white solid, m.p. 98–99 °C. $[\alpha]_D^{20}$ = –34 (*c* = 0.41, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 2 H), 7.32–7.27 (m, 2 H), 7.22–7.14 (m, 1 H), 4.95 (t, ^3J = 4.8 Hz, 1 H), 4.26 (q, ^3J = 6.9 Hz, 1 H), 3.99 (dd, ^3J = 8.1, 6.9 Hz, 1 H), 3.93 (dd, ^3J = 8.3, 4.8 Hz, 1 H), 3.72 (dd, ^3J = 8.1, 6.9 Hz, 1 H), 3.18 (td, ^3J = 7.6, 4.8 Hz, 1 H), 2.15 (dd, ^2J = 11.8, ^3J = 8.3 Hz, 1 H), 2.05–1.94 (m, 1 H), 1.75 (dd, ^2J = 11.8, ^3J = 8.0 Hz, 1 H), 1.68–1.57 (m, 1 H), 1.41 (s, 3 H), 1.33 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.7, 128.4, 126.9, 126.8, 109.3, 78.7, 77.2, 70.5, 69.9, 65.7, 42.7, 34.8, 26.7, 25.1 ppm. $C_{16}H_{21}NO_3$ (275.34): calcd. C 69.79, H 7.69, N 5.09; found C 69.88, H 7.76, N 5.03.

21: Yield: 0.031 g (5%). R_f (hexane/ethyl acetate, 4:1) = 0.30; white solid, m.p. 148–149 °C. $[\alpha]_D^{20}$ = +31 (*c* = 0.07, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.42 (m, 2 H), 7.37–7.33 (m, 2 H), 7.27–7.21 (m, 1 H), 5.05–5.00 (m, 1 H), 4.61 (t, ^3J = 6.5 Hz, 1 H), 4.28 (dt, ^3J = 8.5, 6.9 Hz, 1 H), 4.14 (dd, ^3J = 8.0, 6.3 Hz, 1 H), 3.77 (t, ^3J = 7.6 Hz, 1 H), 3.58 (ddd, ^3J = 10.0, 8.5, 6.3 Hz, 1 H), 2.19–2.08 (m, 3 H), 1.50 (s, 3 H), 1.40 (s, 3 H), 1.26 (dd, ^2J = 11.2, ^3J = 6.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.9, 128.4, 126.9, 126.7, 110.0, 80.4, 75.4, 67.9, 67.7, 62.9, 43.3, 35.3, 26.7, 25.4 ppm. $C_{16}H_{21}NO_3$ (275.34): calcd. C 69.79, H 7.69, N 5.09; found C 69.74, H 7.65, N 5.03.

22: Yield: 0.126 g (20%). R_f (hexane/ethyl acetate, 4:1) = 0.33; white solid, m.p. 94–96 °C. $[\alpha]_D^{20}$ = –34 (*c* = 0.23, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.29 (m, 5 H), 5.03 (t, ^3J = 5.0 Hz, 1 H), 4.75 (dd, ^3J = 10.2, 6.4 Hz, 1 H), 4.13 (dd, ^3J = 8.0, 6.5, 5.7 Hz, 1 H), 3.97 (dd, ^3J = 8.5, 6.5 Hz, 1 H), 3.64 (dd, ^3J = 8.5, 5.7 Hz, 1 H), 3.17 (td, ^3J = 8.0, 5.5 Hz, 1 H), 2.47–2.34 (m, 1 H), 1.75 (dd, ^2J = 11.6, ^3J = 6.4 Hz, 1 H), 1.62 (dd, ^2J = 11.6, ^3J = 8.0 Hz, 1 H), 1.58–1.49 (m, 1 H), 1.33 (s, 3 H), 1.26 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.5, 128.6, 128.5, 127.6, 109.3, 81.3, 77.4, 70.2, 65.7, 62.3, 36.5, 35.7, 26.5, 25.1 ppm. $C_{16}H_{21}NO_3$ (275.34): calcd. C 69.79, H 7.69, N 5.09; found C 69.93, H 7.80, N 5.11.

Intramolecular 1,3-Dipolar Cycloaddition of Nitrone 16: The intramolecular cycloaddition of nitrone **16** (0.63 g, 2.3 mmol) was carried out as described above for **15**. The NMR analysis of the crude product revealed the presence of the three regioisomeric cycloadducts **23**, **24** and **25** in an 82:5:13 ratio, respectively. Purification by radial chromatography of the crude product afforded the pure cycloadducts.

23: Yield: 0.516 g (82%). R_f (hexane/ethyl acetate, 4:1) = 0.54; white solid, m.p. 76–77 °C. $[\alpha]_D^{20}$ = +54 (*c* = 1.28, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 2 H), 7.24–7.21 (m, 2 H), 7.17–7.10 (m, 1 H), 4.91 (t, ^3J = 4.9 Hz, 1 H), 4.09 (dd, ^3J = 8.6, 5.9 Hz, 1 H), 3.92 (dd, ^3J = 8.6, 4.7 Hz, 1 H), 3.90–3.80 (m, 2 H), 2.89 (td, ^3J = 8.5, 4.0 Hz, 1 H), 2.07 (dd, ^2J = 11.8, ^3J = 8.4 Hz, 1 H), 1.96–1.86 (m, 2 H), 1.76 (dd, ^2J = 11.8, ^3J = 7.8 Hz, 1 H), 1.35 (s, 3 H), 1.25 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.7, 128.4, 126.8, 126.5, 109.0, 79.4, 78.6, 70.1, 70.0, 68.8, 42.4, 36.8, 27.1, 25.2 ppm. $C_{16}H_{21}NO_3$ (275.34): calcd. C 69.79, H 7.69, N 5.09; found C 69.81, H 7.75, N 5.22.

24: Yield: 0.031 g (5%). R_f (hexane/ethyl acetate, 4:1) = 0.45; white solid, m.p. 140–141 °C. $[\alpha]_D^{20}$ = –51 (*c* = 0.09, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.38 (m, 2 H), 7.37–7.29 (m, 2 H), 7.28–7.19 (m, 1 H), 5.04 (t, ^3J = 5.2 Hz, 1 H), 4.57 (dd, ^3J = 8.3, 4.6 Hz, 1 H), 4.43 (ddd, ^3J = 8.2, 6.5, 3.6 Hz, 1 H), 4.16 (dd, ^3J = 8.2, 6.5 Hz, 1 H), 3.66 (t, ^3J = 8.2 Hz, 1 H), 3.55 (ddd, ^3J = 9.7, 5.9, 3.6 Hz, 1 H), 2.20 (dd, ^2J = 11.2, ^3J = 8.3 Hz, 1 H), 2.16–2.00 (m, 2 H), 1.69 (dd, ^2J = 11.2, ^3J = 5.9 Hz, 1 H), 1.47 (s, 3 H), 1.42 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.3, 128.4, 126.7, 126.6, 110.0, 81.2, 73.4, 68.4, 68.1, 64.3, 43.5, 33.0, 26.4, 25.9 ppm. $C_{16}H_{21}NO_3$ (275.34): calcd. C 69.79, H 7.69, N 5.09; found C 69.65, H 7.58, N 5.13.

25: Yield: 0.081 g, 13%). R_f (hexane/ethyl acetate, 4:1) = 0.50; white solid, m.p. 80–81 °C. $[a]_D^{20}$ = +83 (*c* = 0.11, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.30 (m, 5 H), 5.08 (t, ^3J = 5.1 Hz, 1 H), 4.68 (dd, ^3J = 10.1, 6.5 Hz, 1 H), 4.14 (dd, ^3J = 8.3, 6.1 Hz, 1 H), 3.95 (dt, ^3J = 9.0, 6.1 Hz, 1 H), 3.56 (dd, ^3J = 8.3, 6.1 Hz, 1 H), 2.91 (ddd, ^3J = 8.6, 8.2, 4.7 Hz, 1 H), 2.40–2.26 (m, 1 H), 2.01–1.90 (m, 1 H), 1.82 (dd, ^2J = 11.9, ^3J = 6.5 Hz, 1 H), 1.76 (dd, ^2J = 11.9, ^3J = 8.0 Hz, 1 H), 1.29 (s, 3 H), 1.25 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.9, 128.7, 128.5, 128.0, 108.9, 82.0, 78.6, 70.4, 68.6, 62.4, 38.6, 35.0, 26.7, 25.3 ppm. $C_{16}H_{21}NO_3$ (275.34): calcd. C 69.79, H 7.69, N 5.09; found C 70.00, H 7.96, N 5.07.

(±)-*N*-Hydroxy-1-phenylbut-3-en-1-amine (29): A solution of benzaldoxime (3.634 g, 30 mmol) and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**28**) (3.70 g, 33 mmol), synthesized as described by Hoffmann and Endesfelder,[59a] in carbon tetrachloride (50 mL) was heated at reflux for 7 h. The reaction mixture was diluted with diethyl ether (100 mL) and 1 M HCl (100 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The aqueous layer was cooled in an ice bath and adjusted to pH 10 by addition of 6 M aqueous KOH, and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with brine, dried with magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate, 4:1; R_f = 0.48) to afford pure **29** (3.525 g, 72%); oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.28 (m, 5 H), 5.74 (dddd, ^2J = 16.7, ^3J = 10.1, 7.9, 6.3 Hz, 1 H), 5.15–5.05 (m, 2 H), 4.05 (t, ^3J = 7.1 Hz, 1 H), 2.57 (dt, ^2J = 14.8, ^3J = 7.7 Hz, 1 H), 2.46 (dt, ^2J = 14.8, ^3J = 6.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8, 134.5, 128.5, 127.7, 127.6, 117.9, 66.1, 38.1 ppm. $C_{10}H_{13}NO$ (163.22): calcd. C 73.59, H 8.03, N 8.58; found C 73.69, H 8.07, N 8.77.

(*S*,*Z*)-*N*-{[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methylene}-1-phenylbut-3-en-1-amine Oxide (26) and (*R*,*Z*)-*N*-{[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methylene}-1-phenylbut-3-en-1-amine Oxide (27): Amine **29** (0.326 g, 2 mmol) and anhydrous magnesium sulfate (0.241 g, 2 mmol) were added to a well-stirred solution of 1,2-di-*O*-isopropylidene-D-glyceraldehyde[72] (0.260 g, 2 mmol) in dichloromethane (15 mL) and the stirring was maintained at room temperature for 4 h. The mixture was filtered and the filtrate evaporated under reduced pressure to yield the crude product, which was purified by flash chromatography (hexane/ethyl acetate, 4:1; R_f = 0.08) to afford a 1:1 mixture of nitrones **26** and **27** (0.485 g, 88%) that could not be separated by chromatographic methods; oil. ^1H NMR (400 MHz, $CDCl_3$; mixture of diastereoisomers): δ = 7.52–7.34 (m, 10 H), 7.03 (d, ^3J = 4.5 Hz, 1 H), 7.00 (d, ^3J = 4.7 Hz, 1 H), 5.83–5.67 (m, 2 H), 5.27–5.06 (m, 6 H), 4.81 (dd, ^3J = 9.0, 5.8 Hz, 1 H), 4.77 (dd, ^3J = 9.4, 5.4 Hz, 1 H), 4.43 (dd, ^3J = 8.6, 7.2 Hz, 1 H), 4.37 (dd, ^3J = 8.7, 7.1 Hz, 1 H), 3.88 (dd, ^3J = 8.6, 5.9 Hz, 1 H), 3.77 (dd, ^3J = 8.7, 5.8 Hz, 1 H), 3.28–3.16 (m, 2 H), 2.74–2.62 (m, 2 H), 1.44 (s, 3 H), 1.43 (s, 3 H), 1.39 (s, 3 H), 1.38 (s, 3 H) ppm.

Intramolecular 1,3-Dipolar Cycloaddition of Nitrone 19: The intramolecular cycloaddition of nitrone **19** (0.053 g, 0.23 mmol) was carried out as described above for **15**. The NMR analysis of the crude product revealed the presence of cycloadduct **31** as the only product of the reaction. Purification by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.73) of the crude product afforded pure **31** (0.050 g, 95%) as an oil. $[a]_D^{20}$ = +5 (*c* = 0.47, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.85 (t, ^3J = 4.9 Hz, 1 H), 4.18 (dd, ^3J = 8.6, 6.0 Hz, 1 H), 4.00 (dd, ^3J = 8.6, 4.7 Hz, 1 H), 3.90 (ddd, ^3J = 9.3, 6.0, 4.7 Hz, 1 H), 2.78 (ddd, ^3J = 9.3, 7.9, 4.2 Hz, 1 H), 2.65 (tdd, ^3J = 7.9, 6.4, 4.5 Hz, 1 H), 1.92–1.84 (m, 1 H), 1.74 (dd, ^2J = 11.4, ^3J = 7.7 Hz, 1 H), 1.71 (dd, ^2J = 11.4, ^3J = 7.8 Hz, 1 H), 1.58 (dq, ^2J = 13.8, ^3J = 7.5 Hz, 1 H), 1.52–1.44 (m, 1 H), 1.42 (s, 3 H), 1.34 (s, 3 H), 1.25 (dq, ^2J = 13.8, ^3J = 7.1 Hz, 1 H), 0.95 (t, ^3J = 7.4, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.9, 79.3, 78.7, 69.9, 69.5, 68.7, 39.4, 36.8, 29.5, 27.2, 25.2, 11.2 ppm. $C_{12}H_{21}NO_3$ (227.30): calcd. C 63.41, H 9.31, N 6.16; found C 63.37, H 9.45, N 6.08.

(2*R*,4*S*,6*S*)-2-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-phenylpiperidin-4-ol (32): Compound **20** (0.450 g, 1.63 mmol) was taken up in 70% aq. acetic acid (10 mL) and Zn powder (2.120 g, 32.6 mmol) was added portionwise to the resulting suspension. The resulting mixture was stirred at room temperature for 4 h, filtered and the solid washed with water. The filtrate was neutralized by the addition of 5 M NaOH and then extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed sequentially with a saturated aq. solution of EDTA and brine. The organic layer was separated, dried with magnesium sulfate, filtered and evaporated under reduced pressure. The resulting crude product was purified by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.1) to give pure **32** (0.424 g, 94%); white solid, m.p. 124–125 °C. $[a]_D^{20}$ = –45 (*c* = 0.62, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.40 (m, 2 H), 7.38–7.32 (m, 2 H), 7.31–7.25 (m, 1 H), 4.11–4.00 (m, 2 H), 3.85 (tt, ^3J = 10.8, 4.5 Hz, 1 H), 3.77–3.69 (m, 2 H), 2.79 (ddd, ^3J = 10.9, 8.2, 2.3 Hz, 1 H), 2.29 (br., 1 H), 2.13 (ddt, ^2J = 11.9, ^3J = 4.5, 2.2 Hz, 1 H), 1.82 (ddt, ^2J = 11.9, ^3J = 4.5, 2.2 Hz, 1 H), 1.65–1.45 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.23 (q, ^3J = 11.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.5, 128.3, 127.3, 126.7, 109.2, 79.0, 68.8, 66.5, 59.0, 58.5, 43.3, 36.7, 26.7, 25.3 ppm. $C_{16}H_{23}NO_3$ (277.36): calcd. C 69.29, H 8.36, N 5.05; found C 69.16, H 8.59, N 5.23.

(2*S*,4*R*,6*R*)-2-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-phenylpiperidin-4-ol (33): The reduction of **23** (0.500 g, 1.82 mmol), as described for **20** in the synthesis of **32**, gave after purification by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.10) pure **33** (0.485 g, 96%); white solid, m.p. 98–99 °C. $[a]_D^{20}$ = +33 (*c* = 0.84, $CHCl_3$). ^1H NMR (400 MHz, [D$_6$]acetone): δ = 7.34–7.16 (m, 5 H), 4.10–3.99 (m, 2 H), 3.92 (t, ^3J = 6.1 Hz, 1 H), 3.72 (tt, ^2J = 11.4, ^3J = 4.3 Hz, 1 H), 3.61 (dd, ^2J = 11.4, ^3J = 2.2 Hz, 1 H), 2.96 (dt, ^2J = 11.4, ^3J = 2.9 Hz, 1 H), 2.19 (br., 1 H), 2.02 (ddt, ^2J = 11.7, ^3J = 4.3, 2.1 Hz, 1 H), 1.94 (ddt, ^2J = 11.7, ^3J = 4.3, 2.0 Hz, 1 H), 1.36–1.28 (m, 1 H), 1.32 (s, 3 H), 1.30 (s, 3 H), 1.01 (q, ^3J = 11.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 146.7, 129.6, 129.3, 128.0, 110.7, 80.2, 70.0, 66.7, 60.4, 57.5, 46.3, 39.1, 27.4, 26.1 ppm. $C_{16}H_{23}NO_3$ (277.36): calcd. C 69.29, H 8.36, N 5.05; found C 69.19, H 8.43, N 4.92.

(2*R*,4*S*,6*S*)-4-*tert*-Butyldimethylsiloxy-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-6-phenylpiperidine (34): 2,6-Lutidine (0.535 g, 5 mmol) was added to a cooled (0 °C) solution of **32** (0.277 g, 1 mmol) in anhydrous dichloromethane (10 mL) under argon. The resulting mixture was cooled to –40 °C and *tert*-butyldimethylsilyl triflate (0.793 g, 3 mmol) was added through a syringe. After 5 min of stirring at –40 °C, the reaction mixture was warmed slowly to room temperature. Then the reaction was quenched with saturated aq. ammonium chloride (10 mL). The organic layer was separated, washed with brine, dried with magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was filtered through a short pad of silica gel (hexane/ethyl acetate, 4:1; R_f = 0.17) to give pure **34** (0.333 g, 85%); oil. $[a]_D^{20}$ = +10 (*c* = 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 55 °C): δ = 7.49–7.17 (m, 5 H), 4.10–3.94 (m, 2 H), 3.82–3.55 (m, 4 H), 2.18 (br., 1 H), 2.2–1.86 (m, 2 H), 1.66–1.44 (m, 2 H), 1.37 (s, 1.5 H), 1.36 (s, 1.5 H),

1.32 (s, 1.5 H), 1.31 (s, 1.5 H), 1.30–1.18 (m, 1 H), 0.88–0.84 (m, 9 H), 0.06–0.03 (m, 3 H), 0.02–0.01 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 55 °C): δ = 143.4, 128.3, 127.6, 126.3, 109.3, 79.9, 70.6, 67.1, 59.6, 58.1, 44.2, 37.5, 26.7, 26.6, 25.1, 19.4, –4.7, –4.9 ppm. $C_{22}H_{37}NO_3Si$ (391.62): calcd. C 67.47, H 9.52, N 3.58; found C 67.32, H 9.33, N 3.70.

(2*R*,4*S*,6*S*)-4-*tert*-Butyldiphenylsiloxy-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-6-phenylpiperidine (35): Pyridine (0.171 g, 2.16 mmol) and silver nitrate (0.08 g, 0.473 mmol) were added sequentially to a well-stirred solution of **32** (0.120 g, 0.43 mmol) in anhydrous dichloromethane (5 mL). After 10 min of stirring, *tert*-butyldiphenylsilyl chloride (0.155 g, 0.56 mmol) was added and stirring was maintained for 18 h. After this time the solution was filtered trough a short pad of Celite®, diluted with dichloromethane (10 mL), washed with saturated aq. $CuSO_4$ (15 mL) and water (15 mL), dried with anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.59) to afford pure **35** (0.222 g, 100%); oil. $[\alpha]_D^{20}$ = +8 (c = 1.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 55 °C): δ = 7.79–7.68 (m, 4 H), 7.52–7.24 (m, 11 H), 4.02–3.91 (m, 2 H), 3.84 (tt, ^3J = 10.7, 4.5 Hz, 1 H), 3.54 (dd, ^2J = 11.5, ^3J = 2.1 Hz, 1 H), 3.47 (dd, ^3J = 7.4, 6.4 Hz, 1 H), 2.54 (ddd, ^3J = 10.4, 8.0, 1.8 Hz, 1 H), 2.51 (br., 1 H), 2.07–2.00 (m, 1 H), 1.69 (q, ^3J = 11.4 Hz, 1 H), 1.53–1.45 (m, 1 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 1.36–1.24 (m, 1 H), 1.10 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 135.7, 135.6, 134.4, 134.1, 129.7, 129.6, 128.3, 127.6, 127.5, 127.2, 126.8, 109.1, 79.1, 70.7, 65.5, 59.1, 58.5, 43.8, 37.0, 26.9, 26.8, 25.3, 19.0 ppm. $C_{32}H_{41}NO_3$ (487.67): calcd. C 74.52, H 8.01, N 2.72; found C 74.49, H 7.94, N 2.62.

(2*R*,4*S*,6*S*)-4-*tert*-Butyldimethylsiloxy-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-6-phenyl-*N*-(trifluoroacetyl)piperidine (36): pyridine (0.073 g, 0.93 mmol) and TFAA (0.097 mL, 0.62 mmol) were added sequentially to a stirred solution of **34** (0.120 g, 0.31 mmol) in anhydrous dichloromethane (2 mL) and the resulting solution was stirred for 3 h. After this time saturated aq. sodium hydrogen carbonate (5 mL) was added and the resulting mixture was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with saturated aq. $CuSO_4$ (45 mL) and brine (45 mL). The organic layer was separated, dried with magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.88) to give pure **36** (0.136 g, 90%). The NMR analysis revealed the presence of several conformers; only signals corresponding to the major one are given; oil. $[\alpha]_D^{20}$ = –61 (c = 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 55 °C): δ = 5.72–5.52 (br. s, 1 H), 4.34–4.19 (m, 1 H), 4.15–4.05 (m, 2 H), 3.94–3.85 (m, 1 H), 3.42–3.33 (m, 1 H), 2.53–2.41 (m, 1 H), 2.29–2.20 (m, 1 H), 2.16–2.05 (m, 1 H), 1.45–1.36 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 143.6, 128.2, 127.5, 126.4, 114.1, 109.6, 76.1, 67.8, 65.5, 57.9, 54.1, 46.5 34.9, 27.2, 26.4, 25.0, 19.0, –4.9, –5.1 ppm. $C_{24}H_{36}F_3NO_4Si$ (487.63): calcd. C 59.11, H 7.44, N 2.87; found C 59.36, H 7.40, N 2.91.

(2*R*,4*S*,6*S*)-4-*tert*-Butyldiphenylsiloxy-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-6-phenyl-*N*-(trifluoroacetyl)piperidine (37): The protection of **35** (0.160 g, 0.31 mmol), as described above for **34** in the synthesis of **36**, using pyridine (0.073 g, 0.93 mmol) and TFAA (0.097 mL, 0.62 mmol) afforded pure **37** (0.167 g, 88%) after purification by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.75); oil. $[\alpha]_D^{20}$ = –56 (c = 1.33, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 2 H), 7.62–7.55 (m, 2 H), 7.53–7.35 (m, 8 H), 7.33–7.22 (m, 3 H), 5.52 (br., 1 H), 4.45–3.95 (m, 3 H), 3.86 (t, ^3J = 6.5 Hz, 1 H), 3.29 (t, ^3J = 7.5 Hz, 1 H), 2.49 (dt, ^2J = 12.8, ^3J = 6.6 Hz, 1 H), 2.20 (ddd, ^2J = 12.8, ^3J = 7.6, 4.2 Hz, 1 H), 2.05–1.92 (m, 1 H), 1.37 (s, 3 H), 1.37–1.27 (m, 1 H), 1.11 (s, 3 H), 1.08 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 140.2, 135.8, 135.6, 133.5, 133.4, 130.1, 130.0, 128.0, 127.9, 127.8, 126.9, 126.7, 116.8, 109.8, 75.7, 67.5, 65.1, 57.5, 53.8, 49.6 35.2, 27.1, 26.3, 25.2, 19.1 ppm. $C_{34}H_{40}F_3NO_4Si$ (611.77): calcd. C 66.75, H 6.59, N 2.29; found C 66.69, H 6.45, N 2.33.

***tert*-Butyl (2*S*,4*R*,6*R*)-2-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-phenylpiperidin-4-yl Carbonate (38):** Boc_2O (0.746 g, 3.42 mmol) was added to a well-stirred solution of **33** (0.315 g, 1.14 mmol) in dioxane (30 mL) and the resulting solution was stirred for 48 h, after which time the solvent was removed under reduced pressure. The NMR analysis of the crude revealed the presence of the starting material and the product. After purification by radial chromatography (hexane/ethyl acetate, 4:1), compounds **33** (0.189 g, 60%) and **38** (0.172 g, 40%) were obtained.

38: R_f (hexane/ethyl acetate, 4:1) = 0.13; oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.37 (m, 2 H), 7.37–7.31 (m, 2 H), 7.30–7.24 (m, 1 H), 4.74 (tt, ^2J = 11.2, ^3J = 4.2 Hz, 1 H), 4.17–4.07 (m, 2 H), 3.99 (dd, ^3J = 6.8, 6.0 Hz, 1 H), 3.76 (dd, ^2J = 11.5, ^3J = 2.2 Hz, 1 H), 3.10 (ddd, ^2J = 11.8, ^3J = 5.2, 2.2 Hz, 1 H), 2.23 (ddt, ^2J = 11.8, ^3J = 4.2, 2.2 Hz, 1 H), 2.14 (ddt, ^2J = 11.5, ^3J = 4.2, 2.2 Hz, 1 H), 1.75 (br., 1 H), 1.54 (q, ^2J = 11.6 Hz, 1 H), 1.49 (s, 9 H), 1.39 (s, 3 H), 1.37 (s, 3 H), 1.25 (q, ^2J = 11.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 143.7, 128.5, 127.4, 126.6, 109.0, 82.1, 78.4, 74.4, 65.1, 58.8, 55.2, 40.4, 33.4, 27.8, 26.4, 25.2 ppm. $C_{21}H_{31}NO_5$ (377.48): calcd. C 66.82, H 8.28, N 3.71; found C 66.99, H 8.17, N 3.59.

(2*R*,4*S*,6*S*)-2-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-phenyl-*N*-benzoylpiperidin-4-yl Benzoate (39): Benzoyl chloride (0.133 g, 0.95 mmol) was added to a cooled (0 °C) solution of **32** (0.120 g, 0.43 mmol) in pyridine (2 mL). The resulting solution was stirred at room temperature for 4 h after which time the reaction was quenched with saturated aq. $CuSO_4$ (2 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed sequentially with water (30 mL), 5% HCl (30 mL), 5% NaOH (30 mL) and brine (30 mL). The organic layer was separated, dried with magnesium sulfate and evaporated under reduced pressure. The crude product was purified by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.10) to give pure **39** (0.177 g, 85%); oil. $[\alpha]_D^{20}$ = –65 (c = 1.87, methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.45 (m, 4 H), 7.44–7.27 (m, 6 H), 7.22–7.10 (m, 5 H), 6.10 (br., 1 H), 5.46–5.41 (m, 1 H), 4.31–4.22 (m, 1 H), 4.22 (br., 1 H), 3.40 (t, ^3J = 6.0 Hz, 1 H), 3.06–2.94 (m, 2 H), 2.32–2.21 (m, 1 H), 2.09–1.99 (m, 1 H), 1.57 (d, ^2J = 14.9 Hz, 1 H), 1.19 (s, 3 H), 0.97 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 165.7, 140.5, 136.7, 133.1, 129.4, 129.3, 129.2, 128.2, 128.1, 127.9, 126.9, 126.6, 126.3, 109.4, 75.6, 67.4, 66.7, 30.8, 30.1, 26.4, 25.1 ppm (C-2 and C-6 of the piperidine cycle could not be detected probably due to the formation of a conformational equilibrium). $C_{30}H_{31}NO_5$ (485.57): calcd. C 74.21, H 6.43, N 2.88; found C 74.50, H 6.57, N 2.89.

(2*S*,4*R*,6*R*)-2-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-phenyl-*N*-benzoylpiperidin-4-yl Benzoate (40): The reaction of **33** (0.120 g, 0.43 mmol), as described for **32** in the synthesis of **39**, gave, after purification by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.13), pure **40** (0.180 g, 86%); oil. $[\alpha]_D^{20}$ = +60 (c = 1.20, methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.65 (m, 2 H), 7.44–7.10 (m, 13 H), 5.66 (br., 1 H), 5.48–5.41 (m, 1 H), 4.42 (br., 1 H), 4.14–4.00 (m, 1 H), 3.69 (br., 2 H), 2.90 (d, ^2J = 14.7 Hz, 1 H), 2.41 (d, ^2J = 14.1 Hz, 1 H), 2.34–2.23 (m, 1 H), 2.03 (dt, ^2J = 14.7,

^3J = 5.6 Hz, 1 H), 1.10 (br., 3 H), 0.82 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 166.0, 141.2, 136.3, 132.9, 130.1, 129.6, 129.5, 128.7, 128.2, 128.1, 127.0, 126.5, 126.0, 109.2, 75.6, 67.7, 67.4, 29.6, 29.1, 26.5, 24.5 ppm (C-2 and C-6 of the piperidine cycle could not be detected, probably due to the formation of a conformational equilibrium). $C_{30}H_{31}NO_5$ (485.57): calcd. C 74.21, H 6.43, N 2.88; found C 74.38, H 6.60, N 2.72.

(2*R*,4*S*,6*S*)-*N*-Benzoyl-4-*tert*-butyldiphenylsiloxy-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-6-phenylpiperidine (41): The reaction of **35** (0.516 g, 1 mmol), as described for **32** in the synthesis of **39**, gave, after purification by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.26), pure **41** (0.477 g, 77%); oil. $[\alpha]_D^{20}$ = –82 (c = 1.81, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70–7.66 (m, 2 H), 7.64–7.60 (m, 2 H), 7.55–7.48 (m, 3 H), 7.47–7.40 (m, 5 H), 7.38–7.30 (m, 7 H), 7.27–7.21 (m, 1 H), 5.90 (br., 1 H), 4.41–4.31 (m, 2 H), 4.06 (br., 1 H), 3.70 (dd, ^3J = 7.6, 6.2 Hz, 1 H), 2.98 (t, ^3J = 7.9 Hz, 1 H), 2.58 (dt, ^2J = 14.1, ^3J = 5.2 Hz, 1 H), 2.22 (ddd, ^2J = 14.1, ^3J = 7.7, 3.8 Hz, 1 H), 1.80 (ddd, ^2J = 13.8, ^3J = 7.7, 4.4 Hz, 1 H), 1.32–1.25 (m, 1 H), 1.28 (s, 3 H), 1.09 (s, 3 H), 1.04 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 141.5, 137.0, 135.8, 135.5, 133.5, 133.3, 130.0, 129.9, 128.9, 128.0, 127.8, 127.7, 127.6, 126.8, 126.8, 126.3, 109.2, 76.0, 67.4, 65.5, 55.7, 50.9, 34.4, 34.0, 27.0, 26.4, 25.2, 19.0 ppm. $C_{39}H_{45}NO_4Si$ (619.87): calcd. C 75.57, H 7.32, N 2.26; found C 75.51, H 7.39, N 2.22.

(2*R*,4*S*,6*S*)-*N*-Benzoyl-4-*tert*-butyldiphenylsiloxy-6-phenylpiperidine-2-carboxylic Acid (42): H_5IO_6 (0.180 g, 0.79 mmol) was added to a well-stirred solution of **41** (0.477 g, 0.77 mmol) in diethyl ether (10 mL) and the resulting suspension was stirred at room temperature for 4 h. After this time the mixture was filtered through a short pad of silica gel and the filtrate was evaporated under reduced pressure. The crude product was taken up in acetonitrile (3 mL) and then added to a cooled (0 °C) and freshly prepared solution of NaH_2PO_4 (0.022 g, 0.183 mmol) and sodium chlorite (0.099 g, 1.10 mmol) in water (2 mL). The resulting mixture was stirred for 5 min after which time H_2O_2 30% (0.077 mL, 0.82 mmol) was added. The stirring was maintained for an additional hour at 0 °C after which time Na_2SO_3 (0.007 g, 0.05 mmol) was added. After 5 min of stirring the solution was acidified to pH 2–3 with 10% HCl. The resulting solution was diluted with dichloromethane (30 mL) and saturated aq. ammonium chloride. The organic layer was separated, washed with brine (3 × 50 mL), dried with magnesium sulfate, filtered and evaporated at reduced pressure. The crude product was purified by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.07) to give pure **42** (0.282 g, 65%); oil. $[\alpha]_D^{20}$ = –6 (c = 0.42, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.80 (br., 1 H), 7.78–7.52 (m, 5 H), 7.50–7.30 (m, 12 H), 7.29–7.19 (m, 3 H), 4.97 (t, ^3J = 5.9 Hz, 1 H), 4.43 (dd, ^3J = 9.6, 5.4 Hz, 1 H), 4.22–4.14 (m, 1 H), 2.41 (ddd, ^2J = 14.6, ^3J = 6.8, 5.6 Hz, 1 H), 2.33 (dt, ^2J = 14.6, ^3J = 7.9 Hz, 1 H), 2.19–2.08 (m, 2 H), 0.99 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.5, 173.7, 142.7, 135.8, 135.7, 135.6, 135.4, 133.8, 133.7, 130.4, 129.9, 129.8, 128.4, 127.8, 127.7, 127.0, 126.9, 126.7, 65.4, 57.3, 55.4, 38.7, 33.8, 26.8, 19.0 ppm. $C_{35}H_{37}NO_4Si$ (563.76): calcd. C 74.57, H 6.62, N 2.48; found C 74.44, H 6.78, N 2.42.

Methyl (2*R*,4*S*,6*S*)-*N*-Benzoyl-4-*tert*-butyldiphenylsiloxy-6-phenylpiperidine-2-carboxylate (43): Compound **42** (0.282 g, 0.50 mmol) was dissolved in methanol (5 mL) and treated with $TMSCHN_2$ (0.75 mmol) under vigorous stirring. After 3 h the solvent was eliminated under reduced pressure and the resulting crude product was purified by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.33) to give pure **43** (0.260 g, 90%); oil. $[\alpha]_D^{20}$ = –14 (c = 1.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.66 (m, 2 H), 7.62–7.57 (m, 2 H), 7.56–7.51 (m, 2 H), 7.48–7.22 (m, 14 H), 4.91 (dd, ^3J = 8.2, 4.7 Hz, 1 H), 4.46 (dd, ^3J = 8.6, 5.2 Hz, 1 H), 4.21–4.13 (m, 1 H), 3.80 (s, 3 H), 2.38 (ddd, ^2J = 14.4, ^3J = 8.2, 5.6 Hz, 1 H), 2.29 (ddd, ^2J = 14.4, ^3J = 8.6, 6.0 Hz, 1 H), 2.12 (ddd, ^2J = 14.4, ^3J = 7.5, 4.8 Hz, 1 H), 2.04 (ddd, ^2J = 14.4, ^3J = 7.4, 5.2 Hz, 1 H), 0.92 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 172.9, 143.0, 135.7, 135.6, 135.5, 133.6, 133.5, 130.2, 129.8, 129.7, 128.3, 128.2, 127.7, 127.6, 126.9, 126.8, 126.6, 65.2, 56.5, 55.1, 52.4, 38.8, 34.3, 26.7, 19.0 ppm. $C_{36}H_{39}NO_4Si$ (577.79): calcd. C 74.84, H 6.80, N 2.42; found C 74.64, H 6.66, N 2.35.

(2*S*,4*R*,6*R*)-4-*tert*-Butyldiphenylsiloxy-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-6-phenylpiperidine (44): The reaction of **33** (0.277 g, 1 mmol), as described for **32** in the synthesis of **35**, afforded after purification by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.62) pure **44** (0.490 g, 74%); oil. $[\alpha]_D^{20}$ = +45 (c = 0.84, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.55 (m, 4 H), 7.39–7.25 (m, 6 H), 7.24–7.19 (m, 4 H), 7.18–7.12 (m, 1 H), 3.99 (t, ^3J = 7.0 Hz, 1 H), 3.91 (td, ^3J = 6.6, 3.8 Hz, 1 H), 3.85 (dd, ^3J = 7.0, 6.2 Hz, 1 H), 3.69 (tt, ^3J = 10.6, 4.4 Hz, 1 H), 3.39 (dd, ^2J = 11.5, ^3J = 2.4 Hz, 1 H), 2.73 (ddd, ^2J = 11.9, ^3J = 3.7, 2.4 Hz, 1 H), 1.86 (ddt, ^2J = 12.2, ^3J = 4.4, 2.2 Hz, 1 H), 1.70 (ddt, ^2J = 11.9, ^3J = 4.4, 2.2 Hz, 1 H), 1.63 (br., 1 H), 1.44 (q, ^2J = 11.5 Hz, 1 H), 1.24 (s, 6 H), 1.08 (q, ^2J = 11.5 Hz, 1 H), 0.96 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 135.8, 134.4, 134.3, 129.7, 129.6, 128.4, 127.6, 127.2, 126.7, 108.7, 78.7, 71.1, 65.0, 59.0, 55.1, 44.6, 37.3, 27.0, 26.5, 25.3, 19.1 ppm. $C_{32}H_{41}NO_3Si$ (515.76): calcd. C 74.52, H 8.01, N 2.72; found C 74.77, H 8.14, N 2.90.

(2*S*,4*R*,6*R*)-*N*-Benzoyl-4-*tert*-butyldiphenylsiloxy-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-6-phenylpiperidine (45): The reaction of **44** (0.382 g, 0.74 mmol), as described for **35** in the synthesis of **41**, afforded after purification by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.37) pure **45** (0.367 g, 80%); oil. $[\alpha]_D^{20}$ = +39 (c = 0.79, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 55 °C): δ = 7.78–7.66 (m, 4 H), 7.52–7.20 (m, 14 H), 7.18–7.13 (m, 2 H), 5.44 (t, ^3J = 7.0 Hz, 1 H), 4.30–4.13 (m, 3 H), 3.68–3.54 (m, 2 H), 2.49 (dt, ^2J = 14.4, ^3J = 7.3 Hz, 1 H), 2.25–2.15 (m, 1 H), 2.08–1.99 (m, 1 H), 1.94 (dt, ^2J = 13.5, ^3J = 6.6 Hz, 1 H), 1.21 (s, 3 H), 1.19 (s, 3 H), 1.11 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 55 °C; mixture of conformers): δ = 173.1, 142.3, 137.1, 136.0, 135.9, 134.2, 134.1, 133.5, 130.2, 129.9, 129.8, 129.1, 128.5, 128.2, 127.7, 127.6, 127.1, 126.9, 126.0, 109.4, 77.5, 67.4, 66.7, 54.4, 35.4, 32.7, 29.7, 27.1, 26.7, 25.3, 19.2 ppm. $C_{39}H_{45}NO_4Si$ (619.87): calcd. C 75.57, H 7.32, N 2.26; found C 75.46, H 7.28, N 2.41.

Methyl (2*S*,4*R*,6*R*)-*N*-Benzoyl-4-*tert*-butyldiphenylsiloxy-6-phenylpiperidine-2-carboxylate (*ent*-43): Starting from **45** (0.367 g, 0.59 mmol) and applying, sequentially, the methodologies used to synthesize **42** and **43**, pure *ent*-**43** (0.198 g, 58%) was obtained; oil. $[\alpha]_D^{20}$ = –39 (c = 0.83, $CHCl_3$). The R_f, m.p. and NMR data were identical to those found for its enantiomer **43**.

Methyl (2*R*,4*S*,6*S*)-6-Phenyl-7-oxa-1-azabicyclo[2.2.1]heptane-2-carboxylate (46): Starting from **20** (0.6 g, 2.18 mmol) and applying the methodology used to synthesize **43**, pure **46** was obtained after radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.38); white solid, m.p. 88–89 °C. $[\alpha]_D^{20}$ = –6 (c = 1.49, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.30 (m, 2 H), 7.26–7.20 (m, 2 H), 7.17–7.12 (m, 1 H), 5.00 (t, ^3J = 4.9 Hz, 1 H), 3.89 (dd, ^3J = 8.3, 5.0 Hz, 1 H), 3.69 (s, 3 H), 3.64 (dd, ^3J = 8.6, 4.7 Hz, 1 H), 2.32 (dtd, ^2J = 11.9, ^3J = 4.8, 2.7 Hz, 1 H), 2.13 (dd, ^2J = 11.9, ^3J = 8.3 Hz, 1 H), 2.00–1.93 (m, 1 H), 1.90 (dd, ^2J = 11.9, ^3J = 8.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 143.2, 128.4, 127.0, 126.7, 78.7, 70.1, 68.3, 52.6, 42.4, 36.5 ppm. $C_{13}H_{15}NO_3$

(233.26): calcd. C 66.94, H 6.48, N 6.00; found C 66.75, H 6.44, N 5.99.

Methyl (2*R*,4*S*,6*S*)-4-Hydroxy-6-phenylpiperidine-2-carboxylate (47): The reduction of **46** (0.030 g, 0.13 mmol), as described for **20** in the synthesis of **32**, gave, after purification by radial chromatography (hexane/ethyl acetate, 4:1; R_f = 0.25), pure **47** (0.029 g, 95%); white solid, m.p. 128–129 °C. $[\alpha]_D^{20}$ = –24 (*c* = 0.11, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 2 H), 7.30–7.24 (m, 2 H), 7.24–7.18 (m, 1 H), 3.80 (tt, ^2J = 11.0, ^3J = 4.5 Hz, 1 H), 3.67 (s, 3 H), 3.63 (dd, ^2J = 11.4, ^3J = 2.3 Hz, 1 H), 3.47 (dd, ^2J = 11.8, ^3J = 2.6 Hz, 1 H), 2.35 (ddt, ^2J = 12.1, ^3J = 4.5, 2.4 Hz, 1 H), 2.07 (ddt, ^2J = 12.1, ^3J = 4.5, 2.3 Hz, 1 H), 1.96 (br., 2 H), 1.45 (td, ^2J = 11.5, ^3J = 3.3 Hz, 1 H), 1.40 (td, ^2J = 11.5, ^3J = 3.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 142.9, 128.6, 127.6, 126.8, 69.3, 59.1, 57.4, 52.2, 43.1, 37.6 ppm. $C_{13}H_{17}NO_3$ (235.28): calcd. C 66.36, H 7.28, N 5.95; found C 66.48, H 7.13, N 5.78.

Methyl (2*S*,4*R*,6*R*)-6-Phenyl-7-oxa-1-azabicyclo[2.2.1]heptane-2-carboxylate (*ent*-46): Starting from **23** (0.6 g, 2.18 mmol) and applying the methodology used to synthesize **43**, pure *ent*-**46** (0.276 g, 54%) was obtained. $[\alpha]_D^{20}$ = +6 (*c* = 1.42, $CHCl_3$). The R_f, m.p. and NMR data were identical to those found for its enantiomer **46**. $C_{13}H_{15}NO_3$ (233.26): calcd. C 66.94, H 6.48, N 6.00; found C 66.82, H 6.49, N 6.05.

Methyl (2*S*,4*R*,6*R*)-4-Hydroxy-6-phenylpiperidine-2-carboxylate (*ent*-47): Starting from *ent*-**46** (0.030 g, 0.13 mmol) and applying the methodology used to synthesize **32**, pure *ent*-**47** (0.029 g, 95%) was obtained. $[\alpha]_D^{20}$ = +24 (*c* = 1.05, $CHCl_3$). The R_f, m.p. and NMR data were identical to those found for its enantiomer **47**. $C_{13}H_{17}NO_3$ (235.28): calcd. C 66.36, H 7.28, N 5.95; found C 66.45, H 7.49, N 5.86.

Supporting Information (see also the footnote on the first page of this article): Full analysis of the stereochemical course of the intramolecular cycloadditions and ^1H and ^{13}C NMR spectra of the new compounds.

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