Pyrrolidine *N*-Oxides by Stereoselective Addition of Grignard and Lithium Compounds to 4,5-Dideoxy-2,3-*O*-isopropylidene-D-*erythro*-4-pentenose *N*-Benzyl Nitrone and Subsequent Cope−House Cyclization[‡]

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Dedicated to Professor Günter Helmchen on the occasion of his 60th birthday

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The addition of Grignard reagents to D-*erythro*-4-pentenose *N*-benzyl nitrone **5**, which is easily accessible from D-ribose, furnishes ω-unsaturated hydroxylamines that readily undergo Cope–House cyclization to afford pyrrolidine *N*-oxides. The stereoselectivity of the addition step is altered by either employing organolithium compounds or Lewis acids as complexing agents. The pyrrolidine *N*-oxides obtained by this sequence serve as key intermediates in the synthesis of 2,5-disubstituted pyrrolidine-3,4-diols (to be discussed in detail separately), both constituting new potential inhibitors of glycosidases.

Introduction

Glycosidase inhibitors hinder the enzymatic hydrolysis of oligo- and polysaccharides. Such inhibitors are therefore of considerable interest for the treatment of certain metabolic disorders, e.g. diabetes or inflammatory processes,[3−6] and many efforts have been undertaken to rationalize the characteristics that an effective inhibitor should possess. Two features seem to be of special relevance:[6−8] (i) The inhibitor should resemble the natural substrate (carbohydrate), i.e. it should possess several hydroxy groups in a distinct configuration; (ii) the inhibitor should mimic intermediate species such as the *exo*-protonated glycoside **A** (cf. the purported pyranosyl cation **B**),[4] or transition states like **C**, relevant in the course of the hydrolysis (Figure 1).[9] Thus, it should contain a basic function to accommodate the positive charge introduced by protonation.[5−7]

This concept is derived from many observations, notably that many potent inhibitors represent polyhydroxypiperidines (1,5-imino derivatives of the natural substrates) or polyhydroxypyrrolidines (1,4-iminoglycitols, ring-contracted analogues of the natural substrates).[10−14] Two examples are depicted in Figure 1: Nojirimycin (**D**), a potent inhibitor of several α-glucosidases,[15,16] and 1,4-dideoxy-1,4-imino-D-mannitol (**E**), which effectively inhibits some α-mannosidases.[17−21]

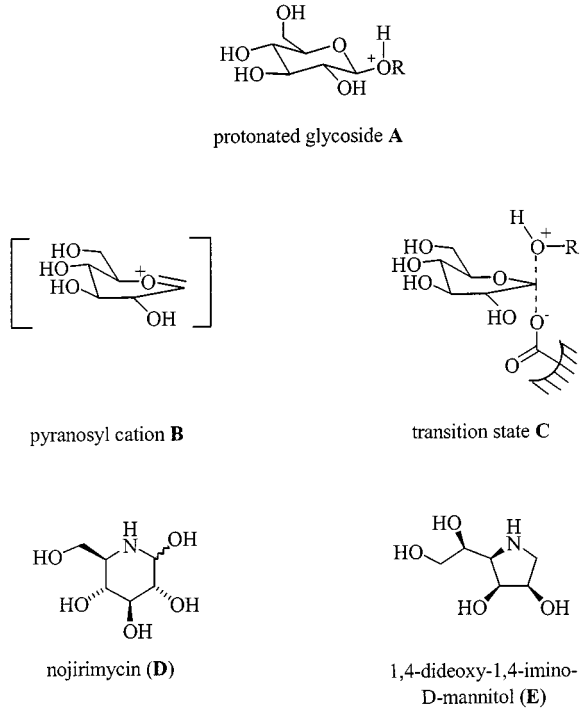

Figure 1. Intermediates and transition states proposed for enzymatic cleavage of glycosides. Iminoglycitols as examples of glycosidase inhibitors

The objective of the present work is the synthesis of 2,5-disubstituted pyrrolidinediols and pyrrolidinediol *N*-oxides, classes of compounds that meet the prerequisites outlined above and that, in our view, might give rise to new structures with high activities for inhibition, especially of α-L-fucosidases: The pyrrolidine *N*-oxides bring along a nega-

[‡] Synthesis of Glycosidase-Inhibiting Iminopolyols by Cope−House Cyclization of Unsaturated Hydroxylamines, III. − Part II: Ref.[1]
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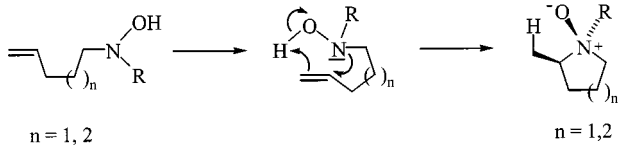
tively charged oxygen atom, presumably with the capability of forming additional hydrogen bonds within the active site while retaining the positively charged *N*-atom (or with *N*-hydroxypyrrolidines[22,23] allowing *N*-protonation to effect this).

The Cope−House cyclization of unsaturated hydroxylamines was expected to offer a convenient approach to these classes of heterocycles. This transformation was discovered in 1976 by House and co-workers and was originally thought to proceed by a radical pathway.[24,25] In the early nineties, Ciganek and Oppolzer proved this to be a concerted process (Scheme 1) with a planar five-membered transition state involving six electrons.[26−29] It is, of course, the reverse of the well-known thermal Cope elimination of tertiary amine *N*-oxides, mostly leading to separate ene and hydroxylamine products.[30,31] Thus, the mechanism of the Cope−House cyclization,[32,33] which has also been termed "Cope cyclization",[34] "retro- or reverse-Cope elimination",[27] "House reaction", or "1,3-azaprotio transfer",[32] resembles that of Alder's ene reaction.[35] As a consequence, the cyclization proceeds highly stereoselectively with respect to the mutual *cis*-orientation of the *N*-oxide function and the newly formed alkyl (methyl) group.



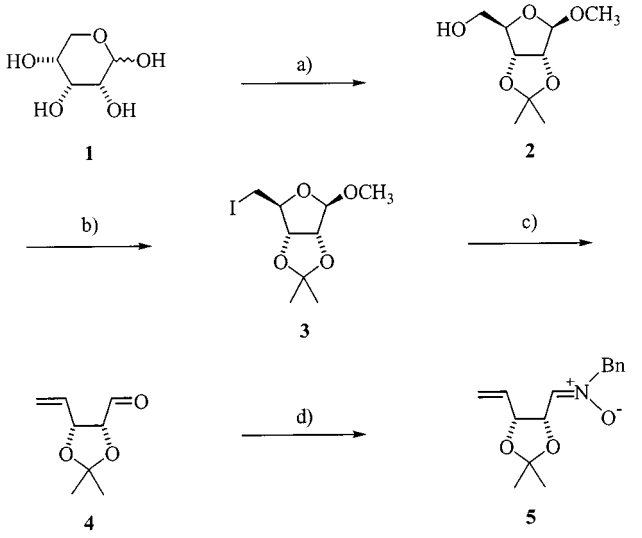
Scheme 1. Cope−House cyclization of unsaturated hydroxylamines

The use of unsaturated hydroxylamines derived from enantiomerically pure starting materials such as D-ribose or 1,2-epoxy-4-pentenols,[34,36,37] combined with the high diastereoselectivity of the Cope−House cyclization, therefore seemed a promising approach for the stereoselective synthesis of potential glycosidase inhibitors such as iminoglycitol *N*-oxides and, hence, of the parent polyhydroxypyrrolidines. We have developed four complementary approaches to obtain such *N*-oxy-pyrrolidines: (i) The "epoxypentenol route", involving the nucleophilic addition of hydroxylamines with subsequent Cope−House cyclization;[34,36,38,39] (ii) Bromocyclization of oximes followed by nucleophilic addition of *C*-nucleophiles to the intermediate cyclic nitrone (pyrroline *N*-oxide);[22,34] and (iii), (iv) Nucleophilic additions to unsaturated oximes and nitrones, respectively, generating alkenylhydroxylamines, which undergo cyclization.[34,38−40] In the following, details of our work concerning route (iv), the preparation of hydroxylamines from D-ribose (**1**) by the addition of a variety of Grignard or organolithium compounds to respective 4-pentenose nitrones, are described, along with the ensuing Cope−House cyclization. Transformation of selected products to the parent 2- or 2,5-(di)substituted dihydroxypyrrolidines along with results of the biological evaluation, mainly concerning fucosidase inhibition, are reported in the next paper of this series.[40]

Results and Discussion

Synthesis of D-*erythro*-4-Pentenose *N*-Benzyl Nitrone 5 − A Key Intermediate in the Synthesis of 2- and 2,5-Substituted Pyrrolidinediols

D-Ribose (**1**) was converted into 4,5-dideoxy-2,3-*O*-isopropylidene-D-*erythro*-4-pentenose (**4**) using a slight modification of a procedure that had been applied by the groups of Gallos[41,42] and Paquette[43] (Scheme 2). After protection of D-ribose (**1**) using 2,2-dimethoxypropane and methanolic hydrochloric acid,[44] the hydroxy group in **2** was transformed into the iodo compound **3** by means of triphenylphosphane/iodine.[45,46] Ring-opening of **3** to the unsaturated aldehyde **4** by reductive elimination (Boord elimination) was achieved with *n*-butyllithium.[22,34,47−49] The pentenose **4**, obtained in 58% overall yield from **1**, was dissolved in dichloromethane and condensed with one equivalent of *N*-benzylhydroxylamine, in the presence of magnesium sulfate as a dehydrating agent,[50] to afford the analytically pure *N*-benzyl nitrone **5** in 69% yield.[51] With this stoichiometric ratio of reactants, three minor by-products were formed and could be isolated by chromatography. Details of this unexpected formation of 5-azapyranoses are reported separately.[34,38,39]

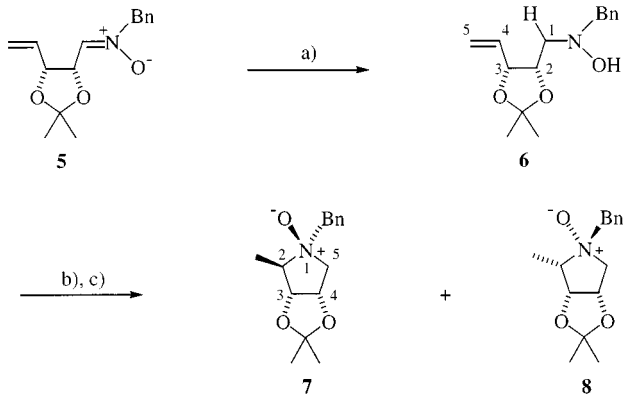


Scheme 2. Synthesis of the *N*-benzyl nitrone **5** from D-ribose (**1**): (a) 1. $Me_2C(OMe)_2$, MeOH, HCl, acetone, room temp., 21 h; 2. pyridine; 67%. − (b) PPh_3, imidazole, I_2, toluene, 70 °C, 2 h; 87%. − (c) *n*BuLi, THF, −80 °C, 2 h; quant. − (d) BnNHOH, $MgSO_4$, CH_2Cl_2, room temp., 19 h; 69%

Nucleophilic Addition of Hydride and Grignard Reagents to Nitrone 5; Cope−House Cyclization

Nitrones are rather sluggish electrophiles, but additions of hydride (from sodium borohydride and related agents) and particularly of Grignard reagents are well precedented.[52−55] Also, the reduction of oximes to provide *N*-alkenylhydroxylamines suitable for Cope−House cyclization is rather common.[25,28,56−58] However, only in few cases, nitrones were used as starting materials.[26,27,51,57] Here, in order to obtain the parent unsaturated hydroxylamine **6**, the *N*-benzyl nitrone **5** was reduced with

sodium borohydride in ethanol at 0 °C (Scheme 3). The ^{1}H NMR spectrum of the crude product, taken immediately after workup and extraction with chloroform, showed that the hydroxylamine **6** had been formed, as expected. However, some conversion of this into the cyclized *N*-oxides **7** and **8** was already evident, and this was brought to completion by allowing the solution to stand at room temperature for another 16 h. The pyrrolidine *N*-oxide products were obtained as a 92:8 mixture (93%), from which the major diastereomer **7** crystallized in 66% yield.



Scheme 3. Synthesis of the parent pyrrolidine *N*-oxides **7** and **8** by reduction of the nitrone **5**: (a) $NaBH_4$, EtOH, 0 °C, 4 h; (b) $CHCl_3$, room temp., 16 h, 93%, **7**/**8** = 92:8; (c) crystallization; **7**: 66%

The fact that only two isomers were formed is in agreement with the accepted concerted mechanism.[26−29] The configuration of these pyrrolidine *N*-oxides **7** and **8** was elucidated from NMR spectroscopic data (vide infra). The diastereomeric ratio of 92:8 observed clearly indicates that the acetonide function present at the α- and β-positions to the double bond causes effective asymmetric induction in the cyclization step.

For access to 2-substituted 5-methylpyrrolidine-3,4-diols, the addition of Grignard reagents proved feasible. A variety of reagents was used in order to explore structure−activity relationships with regard to the intended tests of fucosidase inhibition.[40] As indicated in Table 1, most additions occurred readily at low temperatures, typically requiring 2 to 8 h for completion. The cyclization of the intermediate hydroxylamines **9** and **10** was then carried out in chloroform as above; this had been described as the optimum solvent for the Cope−House cyclization.[26,27] In all cases, the conversion of the unsaturated, acyclic hydroxylamines **9a−h**,**k** and **10a−k** to the pyrrolidine *N*-oxides **11a−h**,**k**, **12a−k** and **13a**,**b**,**d**,**g** proceeded smoothly and completely within 16 h (Scheme 4).

The addition of *C*-nucleophiles to nitrone **5** and the subsequent Cope−House cyclization of the intermediate hydroxylamines **9a−h**,**k** and **10a−k** generate two stereocenters independently, so that product mixtures with up to four stereoisomers can be expected. In fact, upon reaction of the nitrone **5** with methylmagnesium bromide in diethyl ether three diastereomers, the 2,5-dimethylpyrrolidine *N*-oxides **11a**, **12a**, and **13a** were found (Table 1, entry 1; *dr* = 38:48:14), which could be separated by MPLC. The configurations of these heterocycles were derived from NMR spectroscopic data as depicted in Scheme 4 (vide infra).

As seen from Table 1 (entries 2−14), the addition of a representative set of other Grignard reagents to the nitrone **5** was studied likewise and in all cases, after Cope−House cyclization, led to the respective pyrrolidine *N*-oxides **11b−h**,**k** **12b−k**, and **13b**,**d**,**g**. With ethylmagnesium bromide and isopropylmagnesium chloride, the 2,3-*cis*-pyrrolidine *N*-oxides **12b** and **12c** were formed preferentially (Table 1, entries 2, 3). When using isobutylmagnesium bromide, the diastereomeric ratio of the products **11d−13d** depended more strongly on the reaction conditions (Table 1, entries 4 to 6). The question as to whether isomerization by Cope elimination/recyclization may occur was examined by stirring solutions of the pure isomers **11d** and **12d** in deuterated chloroform for 6 d at room temperature. The NMR spectra of **11d** and **12d** remained unchanged. Thus, it seems that the diastereoselectivity observed depends on the reaction conditions of the nucleophilic addition (temperature, time). Similarly, with the other alkyl cases, a general correlation between the steric demand of the nucleophile and the diastereoselectivity of the Grignard addition step does not seem to hold.

The reactions of **5** with *tert*-butyl- or neopentylmagnesium bromide furnished mixtures with two of the expected pyrrolidine *N*-oxides, **11e/12e** and **11f/12f**, respectively, in rather low yields (Table 1, entries 7 to 9). In the former case, the 2-unsubstituted pyrrolidine *N*-oxide **7**, resulting from Grignard reduction, was observed in an approximately equal amount; in the latter case the reaction did not go to completion. Again, the diastereomeric ratio observed strongly depended on the reaction conditions.

A tentative statement at this point may be that the addition of alkyl Grignard reagents to nitrone **5** proceeds with moderate diastereodifferentation, whereas the Cope−House cyclization proceeds highly stereoselectively. The Cope−House cyclization approach to pyrrolidine *N*-oxides using the "nitrone route" seems to be of preparative value mostly with primary and secondary alkyl nucleophiles for the preceding addition step.

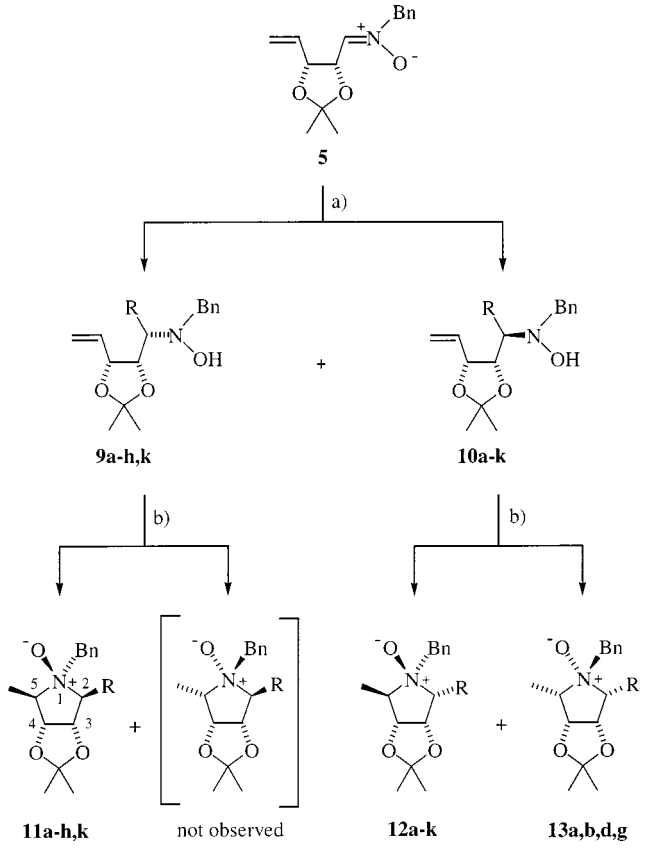
Good yields again were found for the phenyl and vinyl compounds, from which several of the individual stereoisomers were isolated. Upon addition of phenylmagnesium bromide to the nitrone **5**, the 2-epimers **11g/12g** were obtained in a diastereomeric ratio of 40:60 (Table 1, entry 10). With vinylmagnesium bromide, the similar pair of stereoisomers **11h/12h** was found, with a slight preference for the formation of **11h**, which has the 2-substituent oriented *trans* to the acetonide (Table 1, entry 11).

The delicate balance of the equilibrium between *N*-alkenylhydroxylamines and pyrrolidine *N*-oxides, comparable to ring-chain tautomerism, became evident in the case of the allyl and benzyl compounds: First, Grignard addition at low temperature and chloroform treatment at room temperature for 13 to 16 h led to single stereoisomers of the pyrrolidine *N*-oxides **12i** and **12j** in good yields (47 and 59%; entries 12, 13 in Table 1). These products, arising from the thermal Cope−House cyclization ("retro-Cope elimina-

Table 1. Addition of Grignard/organolithium reagents to *N*-benzyl nitrone **5** with ensuing Cope−House cyclization

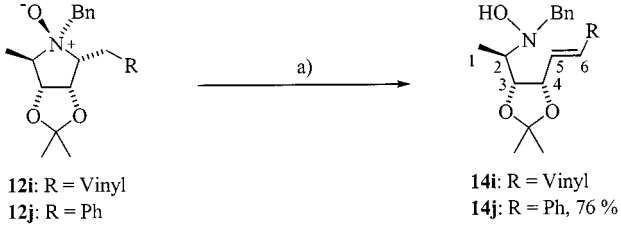
Entry	Reagent	Conditions [°C]	[h]	Products	*dr*[a] **11/12/13**	Yield [%][b]
1	MeMgBr	−40	2	**11a/12a/13a**	38:48:14	78 (**11a**: 27; **12a**: 37)
2	EtMgBr	−20 to −30	3.5	**11b/12b/13b**	22:67:11	74 (**11b**, **12b**: 64; **13b**: 8)
3	*i*PrMgCl	−30	4.75	**11c/12c**	15:85:<5	48
4	*i*BuMgBr	0 to room temp.	19	**11d/12d/13d**	27:65:8	74 (**11d**: 20; **12d**: 49)
5	*i*BuMgBr	−30 to room temp.	8.5	**11d/12d/13d**	46:48:6	87
6	*i*BuMgBr	−30 to −10	10	**11d/12d/13d**	26:67:7	not purified[c]
7	*tert*-BuMgBr	−30	7.5	**7/11e/12e**	24:76:<5	**7**: 24; **11e/12e**: 18
8	*neo*-PeMgBr	room temp.	48	**11f/12f**	50:50:<5	**12f**: 12
9	*neo*-PeMgBr	−10 to −30	11	**11f/12f**	20:80:<5	not purified[c]
10	PhMgBr	−20	1	**11g/12g/13g**	40:60:<5	70 (**11g**: 25; **12g**: 41; **13g**: 4)
11	VinylMgBr	−40	2	**11h/12h**	67:33:<5	91 (**11h**: 56; **12h**: [d]"35")
12	AllylMgBr	−40	0.75	**12i**	<5:>95:<5	47[e]
13	BnMgBr	−30	2	**12j**	<5:>95:<5	59[e]
14	ButenylMgBr	−20	3.5	**11k/12k/15**	22:37:41	59 (**11k**: 13; **12k**: 23; **15**: 23)
15	$MeMgBr/ZnCl_2{\cdot}Et_2O$	−30 to −10	6	**11a/12a/13a**	13:66:21	66 (**12a**: 49)[f]
16	$MeMgBr/Et_2AlCl$	−30	3.25	**11a/12a/13a**	18:64:18	59
17	$BnMgBr/Et_2AlCl$	−30 to −10	2.75	**12j**	<5:>95:<5	57[e]
18	$PhMgBr/Et_2AlCl$	−30	3.75	**11g/12g/13g**	58:42:<5	76 (**11g**: 46)
19	$VinylMgBr/ZnCl_2{\cdot}Et_2O$	−30 to −10	4.25	**11h/12h**	84:16:<5	75 (**11h**: 60)
20	$VinylMgBr/Et_2AlCl$	−30	3.5	**11h/12h**	84:16:<5	72
21	MeLi	−80	4.75	**11a/12a**	91:9:<5	58 (**11a**: 53)
22	PhLi	−80	3	**11g/12g/13g**	19:81:<5	51 (**12g**: 38)
23	VinylLi	−80	5.25	**11h/12h**	71:29:<5	62

[a] Diastereomeric ratios are calculated from the ^1H and ^{13}C NMR spectra of the crude product. Values <5 indicate that, although formation of these isomers is likely (cf. Experimental Section, case 10), characteristic signals of these minor products were not visible in the corresponding NMR spectra. − [b] Mixtures of diastereomers; yields given in brackets indicate the amount of pure stereoisomer isolated after MPLC separation. In entries 15 to 23 only the yield of the major isomer is given. − [c] Reaction did not go to completion. − [d] Viscous oil, still containing traces of solvent even after thorough drying. − [e] Only one pyrrolidine *N*-oxide was formed. − [f] Sample contained approximately 10% of the minor diastereomer **13a**.



Scheme 4. Cope−House cyclization of the unsaturated hydroxylamines **9a−h,k** and **10a−k** generated by Grignard addition to the nitrone **5**: (a) RMgBr or RLi; (b) $CHCl_3$; cf. Table 1

tion") as above, were not stable and, upon prolonged storage at −25 °C, slowly underwent ring-opening to form the acyclic isomeric hydroxylamines **14i** and **14j** (Scheme 5). This was demonstrated by ^1H NMR spectroscopy, when $[D_6]$DMSO solutions of the *N*-oxides **12i** or **12j** were heated to 80 °C for 15 to 30 min. The spectra showed that quantitative elimination had occurred, which was confirmed by a preparative run from which the phenyl compound **14j** was isolated in 76% yield. Since the *trans* orientation of the *N*-oxygen atom and the C-2 substituent present in these pyrrolidine *N*-oxides strongly disfavours formation of a planar transition state as required for the concerted Cope elimination,[59−61] this reaction might proceed in an *inter*molecular rather than in an *intra*molecular fashion, in a way related to the Hofmann degradation of quaternary ammonium salts.[31,62]

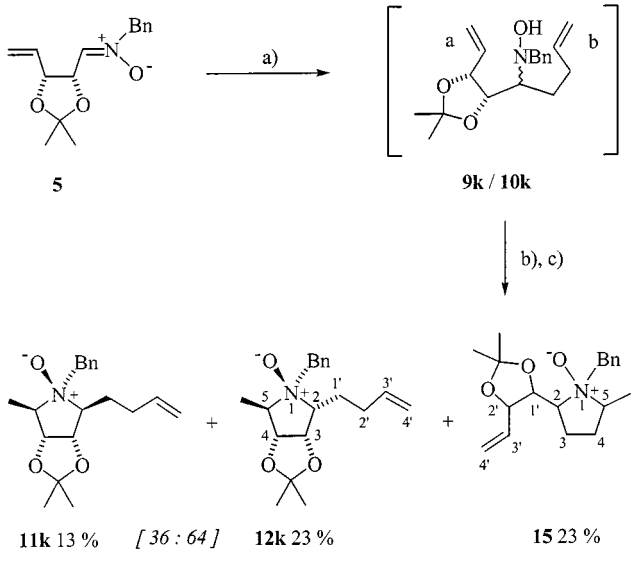


Scheme 5. Cope elimination of pyrrolidine *N*-oxides **12i** and **12j**: (a) Me_2SO, 80 °C, 15−30 min

Competition of Alkenyl Groups and the Influence of the Acetonide Group on the Rate of Cyclization

In the case of the vinyl compound, the progress of the Cope−House cyclization was monitored by ^1H NMR spec-

troscopy. It turned out that the reaction rates were different for the two diastereomeric hydroxylamines **9h** and **10h**, with **9h** reacting faster (15 min after workup: 56% cyclization, *dr* **11h/12h** = 82:18), and that the reaction was virtually complete within 90 min (>85% cyclization). According to literature reports, the cyclization of unsaturated hydroxylamines having alkenyl chains with no alkoxy functional group proceeds to 90% during work-up and goes to completion within 24 h.[27] Thus, it was of interest to evaluate the effect of the isopropylidenedioxy moiety on the cyclization, i.e. to study the internal competition of this functionalized chain with an unsubstituted 3-butenyl group. This was possible with the addition of 3-butenylmagnesium bromide: Two modes of Cope−House cyclization of the intermediate hydroxylamines **9k/10k** could occur, either involving the butenyl part or the dioxy-butenyl chain (Scheme 6). In fact, from the reaction with the 3-butenyl Grignard reagent carried out as above, three isomeric pyrrolidine *N*-oxides **11k**, **12k**, and **15** were obtained in a ratio of 22:37:41. The mixture was separated by MPLC, and the structures of the individual pyrrolidine *N*-oxides were established by NMR (H,H-COSY). Two of the isomers (**11k** and **12k**, 13% and 23% yield, respectively) resulted from cyclization to the dioxybutenyl part, the third isomer **15** (23% yield) constituted a 3,4-unsubstituted pyrrolidine *N*-oxide with an intact dioxybutenyl moiety. The configuration of the latter product **15**, a single stereoisomer, has thus far not been deduced.



Scheme 6. Cope−House cyclization of the unsaturated hydroxylamines **9k/10k** derived from nucleophilic addition of 3-butenylmagnesium bromide to the nitrone **5**: (a) 3-ButenylMgBr, Et_2O, −20 °C, 3.5 h; (b) $CHCl_3$, room temp., 5 d, isomer ratio **11k/12k/15** = 22:37:41; (c) MPLC; yields cf. above

Two opposing tendencies need to be considered: The CC double bond bearing an allylic alkoxy function is more electrophilic than that of the unsubstituted butenyl group,[63−66] and thus should react more readily with the nucleophilic hydroxylamine moiety. Also, the acetonide function serves as a clamp and might entropically facilitate the formation of the planar transition state required for the Cope−House cyclization. However, steric hindrance from the acetonide part and additional ring strain to form the fused bicycle might oppose this. Based on the experimental results, all these effects seem to balance, and the acetonide group is concluded to exhibit only a modest influence on the rate and regioselectivity of the Cope−House cyclization (Scheme 6).

Stereoselective Additions to the Nitrone 5 Using Organolithium and Grignard Reagents with Lewis Acids Added

Since the 2-methyl-, 2-phenyl-, and 2-vinylpyrrolidine *N*-oxides **11a/12a**, **11g**, and **11h** constitute key intermediates for access to iminopolyol inhibitors,[40,67−71] the stereoselectivity of the addition step was studied further by the use of additional Lewis acids in the Grignard reactions, and also by employing methyl-, phenyl-, and vinyllithium. For both variants, there is ample precedence in the literature concerning nitrone additions[55,72−76] and, for example, reactions with α-oxyimines.[77−79]

Complexation of the nitrone **5** with zinc chloride or diethylaluminium chloride prior to the addition of the methyl Grignard reagent led to somewhat enhanced diastereoselectivity, up to 13:66:21, and the 2,5-*trans* isomer **12a** was isolated in 49% yield (Table 1, entries 15 and 16). In the case of the benzyl compound, the addition of diethylaluminium chloride had no effect on the stereoselectivity of the reaction, and the 2,5-*trans*-isomer **12j** remained the sole product observed and isolated (57%; Table 1, entry 17).

Switching to methyllithium proved beneficial since this gave only two products with an increased ratio of 91:9, the *meso*-derivative **11a** (*cis*-2,5-dimethyl) being the major product (Table 1, entry 21). These observations suggest that organolithium compounds preferentially form the diastereomer **11** (2,5-*cis*) and, on the other hand, that an increase in the amount of the 2,5-*trans* isomer **12** formed would result from pre-complexation of the nitrone **5** with Lewis acids. Unfortunately, this simple guideline does not hold in the case of the vinyl and phenyl compounds: In the latter case, the use of the lithium derivative gave a better proportion (81:19) of the 2,5-*trans*-diastereomer **12g**, whereas the formation of 2,5-*cis*-pyrrolidine *N*-oxide **11g** was favoured in the presence of diethylaluminium chloride (Table 1, entries 18, 22). When adding vinylmagnesium bromide to the nitrone **5**, pre-complexed with diethylaluminium or zinc chloride, the major *N*-oxide product **11h** amounted to 84 parts of the two-isomer mixture, and was isolated in 60% yield (Table 1, entries 19 and 20). Switching from vinylmagnesium bromide to vinyllithium did not alter the diastereoselectivity of the addition (Table 1, entry 23).

Several models have been proposed by Dondoni, Merino, and co-workers in order to rationalize the stereochemical outcome of the addition of organometallic *C*-nucleophiles to α-alkoxy nitrones in the presence of Lewis acids.[55,72−76] However, the diastereoselectivities observed here are not satisfactorily explained by any of these and further detailed studies are necessary.

Determination of the Configuration and Conformation of the Pyrrolidine *N*-Oxides 7, 8 and 11a,b,d-h,k, 12a−k, 13a,b,g

Reduction of the nitrone **5** with sodium borohydride and ensuing Cope−House cyclization resulted in the formation of the 2-epimers **7** and **8** (vide supra). Here, the 2,3-*trans* configuration (methyl *trans* to the acetonide moiety) present in the major isomer **7** was readily assigned by comparison of the ^{13}C NMR chemical shifts of the 2-methyl groups, which for compound **7** appeared significantly downfield (δ = 11.5 in **7** vs. 8.2 in **8**).

The ^{1}H NMR spectroscopic data, chemical shifts, and coupling constants of the pyrrolidine *N*-oxides obtained in this work are collected in Table 2 and Table 3; ^{13}C NMR chemical shifts are given in Table 4. In each case, the configuration of the diastereomeric pyrrolidine *N*-oxides was established by comparison of the NMR spectroscopic data with those obtained for the 2,5-dimethylpyrrolidine *N*-oxides **11a**, **12a**, and **13a**, in which unambiguous assignment was based on the crystal structure obtained for the free *meso*-pyrrolidinediol *N*-oxide **16a**, as shown below.

Upon addition of methylmagnesium bromide to nitrone **5**, and cyclization, three pyrrolidine *N*-oxides **11a**, **12a**, and **13a** were formed. The NMR spectroscopic data obtained for these compounds clearly indicated that the two minor isomers **11a** and **13a** were *meso* derivatives (Figure 2).

Deprotection of one of these *meso* compounds (**11a**) was accomplished with hydrochloric acid in methanol/water (Scheme 7). Recrystallization of this deprotected pyrrolidine *N*-oxide **16a** from methanol/diethyl ether yielded crystals suitable for X-ray structure determination. The crystal structure of **16a**, shown in Figure 3, provided proof of the configuration of the *N*-oxide **11a** as determined above: The two methyl groups are oriented 2,5-*cis* and *trans* to the acetonide group. The other *meso* compound **13a** therefore constitutes the all-*cis* isomer which is also concluded from the distinct upfield signals for all the carbon atoms concerned.

Table 2. ^{1}H NMR chemical shifts δ of pyrrolidine *N*-oxides **11a**,**b**,**d**,**g**,**h**,**k**, **12a−k**, and **13a**,**b**,**g** (δ [ppm], 300.1 MHz or 500.1 MHz, $CDCl_3$)

	2-H	3-H	4-H	5-H	5-CH_3	$C(CH_3)_2$	CH_2Ph	Others (2-R)
11a	3.29	4.63	4.63	3.29	1.69	1.28 (6 H)	4.16 (CH_2), 7.32, 7.43 (Ph)	1.69 (CH_3)
11b	3.06	4.68	4.66	3.25	1.68	1.27, 1.28	4.12, 4.21 (CH_2), 7.31, 7.43 (Ph)	1.10 (CH_3) 1.99−2.16 (CH_aH_b), 2.24−2.34 (CH_aH_b)
11d	3.24	4.65	4.65	3.27	1.68	1.26, 1.27	4.14, 4.22 (CH_2), 7.34, 7.43 (Ph)	0.97 (CH_3), 1.10 (CH_3), 1.74 (CH_aH_b), 1.86 (CH), 2.38 (CH_aH_b)
11g	4.10	5.11	4.80	3.61	1.74	1.27, 1.38	3.99, 4.11 (CH_2), 7.30, 7.45, 7.99 (2 Ph)	[a]
11h	3.73	4.83	4.69	3.32	1.70	1.28, 1.32	4.13, 4.20 (CH_2), 7.34, 7.43 (Ph)	5.58 (CH_EH_Z), 5.68 (CH_EH_Z), 6.69 (CH)
11k	3.17	4.70	4.68	3.26	1.68	1.26, 1.28	4.14, 4.23 (CH_2), 7.31, 7.43 (Ph)	2.12, 2.36, 2.45 (CH_2CH_2), 5.07 (CH_EH_Z), 5.16 (CH_EH_Z), 5.92 (CH)
12a	3.81	4.91	4.63	3.83	1.35	1.37, 1.64	4.20, 4.48 (CH_2), 7.38, 7.73 (Ph)	1.52 (CH_3)
12b	3.52	4.89	4.60	3.86	1.27	1.39, 1.68	4.25, 4.55 (CH_2), 7.37, 7.70 (Ph)	1.12 (CH_3), 2.03 (CH_aH_b), 2.30 (CH_aH_b)
12c	3.36	4.84	4.50	3.87	1.22	1.36, 1.68	4.44, 4.65 (CH_2), 7.37, 7.70 (Ph)	1.17 (CH_3), 1.55 (CH_3), 2.56 (CH)
12d	3.65	4.88	4.61	3.84	1.29	1.37, 1.67	4.26, 4.53 (CH_2), 7.36, 7.71 (Ph)	0.96 (CH_3), 1.05 (CH_3), 1.79 (CH), 1.97 (CH_2)
12e	3.40	4.94	4.47	3.85	1.21	1.35, 1.70	4.75 (CH_2), 7.34, 7.74 (Ph)	1.48 [$C(CH_3)_3$]
12f	3.61	4.84	4.59	3.87	1.24	1.37, 1.68	4.27, 4.50 (CH_2), 7.35, 7.68 (Ph)	1.08[$(CH_3)_3$], 2.00 (CH_aH_b), 2.16 (CH_aH_b)
12g	4.81	5.24	4.80	4.04	1.47	1.40, 1.67	3.96, 4.52 (CH_2), 7.29, 7.41, 7.66, (2 Ph)	[a]
12h	4.26	5.09	4.71	3.80	1.43	1.37, 1.61	4.20, 4.43 (CH_2), 7.34, 7.69 (Ph)	5.46 (CH_EH_Z), 5.61 (CH_EH_Z), 5.99 (CH)
12i	3.61	4.81	4.58	3.87	1.26	1.37, 1.69	4.23, 4.60 (CH_2), 7.34, 7.70 (Ph)	2.74, 2.99 (CH_aH_b), 5.18 (CH_EH_Z), 5.31 (CH_EH_Z), 5.87 (CH)
12j	3.73	4.54	4.47	3.90	1.18	1.33, 1.74	4.35, 4.70 (N-CH_2), 7.26, 7.36, 7.47, 7.75 (2 Ph)	3.23, 3.55 (2-CH_2)[a]
12k	3.65	4.85	4.60	3.89	1.26	1.38, 1.67	4.28, 4.55 (CH_2), 7.36, 7.75 (Ph)	2.10, 2.19, 2.34 (CH_2CH_2), 5.04 (CH_EH_Z), 5.13 (CH_EH_Z), 5.89 (CH)
13a	3.18	4.51	4.51	3.18	1.63	1.28, 1.60	4.29 (CH_2), 7.34, 7.43 (Ph)	1.63 (CH_3)
13b	3.21	4.70	4.59	3.49	1.58	1.29, 1.52	4.52, 4.59 (CH_2), 7.43 (Ph)	1.10 (CH_3), 1.94 (CH_aH_b), 2.46 (CH_aH_b)
13g	4.22	4.75	4.72	3.58	1.73	1.27, 1.66	4.20, 4.76 (CH_2), 7.42, 7.95 (2 Ph)	[a]

[a] Signals of 2-Ph in column CH_2Ph.

Table 3. H,H-coupling constants of pyrrolidine *N*-oxides **11a**,**b**,**d**,**g**,**h**,**k**, **12a−k**, and **13a**,**b**,**g** (*J* [Hz], $CDCl_3$)

	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,5\text{-Me}}$	^2J (CH_2Ph)	Other
11a	–	–	–	6.4	–	J(2-*H*,C*H*$_3$) = 6.4
11b	5.5	7.3	6.3	6.3	14.0	J(2-*H*,C*H*$_a$H$_b$) = 11.3, J(2-*H*,CH$_a$*H*$_b$) = 3.3, J(C*H*$_2$CH$_3$) = 7.6
11d	5.5	n. d.	6.3	6.4	14.0	J(2-*H*,C*H*$_a$H$_b$) = 12.0, J(2-*H*,CH$_a$*H*$_b$) = 3.4, J(C*H*CH$_3$) = 6.5, J(CHCH$_3$) = 6.8
11g	7.1	7.2	6.1	6.3	13.8	
11h	6.6	7.1	6.3	6.3	13.8	J(2-*H*,C*H*) = 8.7, J(C*H*=CH$_E$*H*$_Z$) = 17.8, J(CH=C*H*$_E$H$_Z$) = 10.5
11k	5.9	7.4	6.5	6.4	14.0	J(2-*H*,C*H*$_a$H$_b$) = 11.4, J(2-*H*,CH$_a$*H*$_b$) = 3.0, J(C*H*=CH$_E$*H*$_Z$) = 10.2, J(C*H*=CH$_E$*H*$_Z$) = 17.2, ^2J(CH$_E$*H*$_Z$) = 1.7
12a	6.1	7.4	2.0	7.1	12.2	J(2-*H*,C*H*$_3$) = 7.2
12b	5.6	7.4	0.0	7.1	11.9	J(2-*H*,C*H*$_a$H$_b$) = 11.8, J(2-*H*,CH$_a$*H*$_b$) = 3.1, J(C*H*$_2$CH$_3$) = 7.6
12c	5.4	7.6	0.0	7.5	11.9	J(2-*H*,C*H*) = 10.3, J(C*H*CH$_3$) = 6.5, J(C*H*CH$_3$) = 6.6
12d	5.7	7.5	1.2	7.5	12.0	J(C*H*CH$_3$) = 6.6, J(C*H*CH$_3$) = 6.6
12e	5.5	7.6	0.0	7.5	–	
12f	5.7	7.4	0.0	7.4	12.1	J(2-*H*,C*H*$_a$H$_b$) = 11.0, J(2-*H*,CH$_a$*H*$_b$) = 1.5, ^2J(CH$_a$*H*$_b$) = 11.9
12g	5.9	7.4	3.0	7.0	12.3	
12h	6.3	7.3	3.3	6.9	12.3	J(2-*H*,C*H*) = 9.7, J(C*H*=CH$_E$*H*$_Z$) = 17.0, J(C*H*=CH$_E$*H*$_Z$) = 10.3, ^2J(CH$_E$*H*$_Z$) = 1.5
12i	5.4	7.5	0.8	7.4	11.9	J(2-*H*,C*H*$_a$H$_b$) = 12.2, J(2-*H*,CH$_a$*H*$_b$) = 3.4, ^2J(CH$_a$*H*$_b$) = 12.2, J(CH$_a$H$_b$C*H*) = 7.5, J(CH$_a$*H*$_b$C*H*) = 6.5, J(C*H*=CH$_E$H$_Z$) = 10.1, J(C*H*=CH$_E$*H*$_Z$) = 17.1, ^2J(CH$_E$*H*$_Z$) = 1.8
12j	5.4	7.4	0.0	7.5	11.9	J(2-*H*,C*H*$_a$H$_b$) = 12.1, J(2-*H*,CH$_a$*H*$_b$) = 2.6, ^2J(CH$_a$*H*$_b$) = 12.0
12k	5.7	7.4	0.0	7.4	12.0	J(2-*H*,C*H*$_a$H$_b$) = 11.7, J(2-*H*,CH$_a$*H*$_b$) = 2.5, J(C*H*=CH$_E$H$_Z$) = 10.2, J(C*H*=CH$_E$*H*$_Z$) = 17.1, ^2J(CH$_E$*H*$_Z$) = 1.8
13a	–	–	–	6.8	–	J(2-*H*,C*H*$_3$) = 6.8
13b	5.1	7.3	5.3	6.5	13.7	J(2-*H*,C*H*$_a$H$_b$) = 11.0, J(2-*H*,CH$_a$*H*$_b$) = 3.4, J(C*H*$_2$CH$_3$) = 7.5
13g	5.0	7.1	5.2	6.5	13.7	

Consequently, the isomer **12a** must have the 2,5-dimethyl groups in a *trans* orientation, as shown by the ^{13}C NMR signals at δ = 9.3 and 13.2; the individual assignment, however, is not possible from this. On the other hand, this can be done in a reliable way by comparison with the NMR spectroscopic data obtained for the 2-ethyl-5-methylpyrrolidine *N*-oxides **11b**, **12b**, and **13b** (cf. Figure 2), where characteristic shift changes of the 2- and 5-substituent are unequivocal: In **12a**, the 2-methyl group introduced by Grignard addition is oriented *cis* to the isopropylidenedioxy function and to the *N*-benzyl group, whereas the 5-methyl group formed by Cope−House cyclization is oriented *trans* to the acetonide moiety and *cis* to the *N*-oxido group. In all other cases, the configuration of the diastereomeric pyrrolidine *N*-oxides was established in a similar way by comparison of the NMR spectroscopic data obtained for the prevailing diastereomers with those obtained for the methyl compounds (cf. Table 2 to 4).

Several trends are obvious when comparing the ^{13}C NMR spectroscopic data of the diastereomeric pyrrolidine *N*-oxides (Table 4). When going from the pyrrolidine *N*-oxides **11** to their 2-epimers **12**, the relationship between 5-CH_3/NO (*cis*) and 5-CH_3/acetonide (*trans*) is retained, whereas the orientation between 2-R/NO (*cis*) and 2-R/acetonide (*trans*) is reversed. As a consequence, when comparing the NMR spectroscopic data of **11a**,**b**,**d−h**,**k** and **12a−k**, only a slight change in the chemical shifts of 5-CH_3, C-5, and C-4 (< 3 ppm) is observed, whereas significant changes in the chemical shifts of 2-R, C-2, and C-3 (3−5 ppm) are apparent. In order to pass from the pyrrolidine *N*-oxides **11** to their diastereomers **13**, the orientation of both 5-CH_3 and 2-R with respect to the acetonide and the NO-function has to be inverted. Consequently, all ring carbon atoms and the carbon atoms of the substituents adjacent to the ring in **13a**,**b**,**g** undergo an upfield shift in the range of 3 to 5 ppm. Interestingly, the chemical shift of the *N*-CH_2 part of the benzyl group of the pyrrolidine *N*-oxides **12a−k** is not affected by the proximity of 2-R, but the carbon atoms of the acetonide group give rise to signals distinctly upfield from those of **11a**,**b**,**d−h**,**k** (2 to 3 ppm).

In the ^1H NMR spectroscopic data of the pyrrolidine *N*-oxides **11a**,**b**,**d**,**g**,**h**,**k** and **12a−k** significant differences are also observed: (i) Two of the phenyl protons of **12a−k** are strongly deshielded (δ ca. 7.7). (ii) In the spectra of **12a−k**, the diastereotopic methylene protons of the benzyl group and the methyl groups of the acetonide are clearly differentiated (Δδ ca. 0.3 ppm). (iii) The signals for 2-H and 5-H of **12a−k** experience a net downfield shift relative to those for 2-H and 5-H of **11a**,**b**,**d**,**g**,**h**,**k**, whereas 5-CH_3 in **12a−k** is considerably more shielded than in **11a**,**b**,**d**,**g**,**h**,**k**. (iv) All coupling constants are of comparable magnitude with the exception of $J_{4,5}$ (**11b**,**d**,**g**,**h**,**k**: 6.1 to 6.5 Hz; **12a−k**: 0 to 3.3 Hz).

The information derived from these observations was used to establish suitable starting geometries for molecular models of the 2,5-dimethylpyrrolidine *N*-oxides **11a** and **12a** as representatives of the structural types **11** and **12**. The energies of these models were minimized by MM2/MOPAC calculations: Both pyrrolidine *N*-oxides **11a** and **12a** adopt *envelope* conformations (Figure 4). In the case of the 2,5-*cis*-isomer **11a**, the ring nitrogen atom is located out of the plane defined by the ring carbon atoms (1E).[80] This situation is also seen in the crystal structure of **16a**. The phenyl ring and the acetonide protecting group in **11a** are oriented symmetrically with respect to a plane (σ) perpendicular to the heterocycle and bisecting the nitrogen atom and the C-3/C-4 bond. This conformation relates to the fact that for all pyrrolidine *N*-oxides **11** similar chemical shifts were ob-

Table 4. ^{13}C NMR chemical shifts of pyrrolidine *N*-oxides **11a**,**b**,**d-h**,**k**, **12a−k**, and **13a**,**b**,**g** (δ [ppm], 125.8 MHz, $CDCl_3$)

	C-2	C-3	C-4	C-5	5-CH_3	$C(CH_3)_2$	CH_2Ph	Others (2-R)
11a	72.2	82.9	82.9	72.2	11.6	24.7, 26.7, 114.5	65.7 (CH_2), 129.4, 129.9, 130.0, 131.0 (Ph)	11.6 (CH_3)
11b	77.4	82.2	82.9	71.8	11.2	24.7, 26.8, 114.4	66.0 (CH_2), 129.3, 129.8, 130.2, 131.3 (Ph)	9.3 (CH_3), 19.8 (CH_2)
11d	74.9	82.3	83.0	72.0	11.4	24.9, 26.8, 114.3	65.8 (CH_2), 129.2, 129.9, 130.2, 131.5 (Ph)	21.9 (CH_3), 24.4 (CH_3), 24.7 (CH), 35.4 (CH_2)
11e	79.1	81.7	82.0	71.6	10.3	25.7, 27.5, 112.8	70.0 (CH_2), 128.2−132.0 (Ph)	29.2 [$(CH_3)_3$], 35.0 (C)
11f	75.1	82.0	83.1	71.3	11.3	24.8, 26.9, 113.9	65.8 (CH_2), 128.2, 129.1, 131.2, 133.3 (Ph)	30.4 [$(CH_3)_3$], 30.4, 39.8 (C, CH_2) [a]
11g	80.0	84.2	83.4	73.5	12.0	24.6, 26.8, 114.6	67.3 (CH_2), 128.5, 129.1, 129.6, 129.8, 130.2, 131.5, 131.6, 132.2 (2 Ph)	
11h	80.1	82.2	83.6	72.3	11.9	25.0, 27.1, 115.0	67.2 (CH_2), 129.6, 130.2, 130.4, 131.8 (Ph)	123.3 (CH_2), 131.8 (CH)
11k	75.6	82.4	83.0	72.1	11.4	24.8, 26.7, 114.5	66.0 (CH_2), 129.3, 129.9, 130.1, 131.1 (Ph)	26.2, 28.8 (2 CH_2), 115.9 (=CH_2), 137.2 (CH)
12a	74.8	77.6	82.4	70.5	13.2	23.5, 25.3, 112.2	65.3 (CH_2), 128.3, 128.8, 131.1, 132.9 (Ph)	9.3 (CH_3)
12b	80.5	75.7	81.3	70.0	13.7	23.1, 25.2, 111.3	66.2 (CH_2), 128.2, 128.7, 131.0, 133.3 (Ph)	11.0 (CH_3), 16.0 (CH_2)
12c	83.0	77.2	80.3	70.7	14.2	23.0, 25.3, 110.8	66.0 (CH_2), 128.1, 128.7, 131.6, 133.6 (Ph)	20.2 (CH_3), 21.7 (CH_3), 24.9 (CH)
12d	77.8	76.4	81.7	70.1	13.6	23.2, 25.3, 111.4	66.2 (CH_2), 128.2, 128.7, 131.4, 133.1 (Ph)	21.7 (CH_3), 24.0 (CH_3), 25.6 (CH), 31.2 (CH_2)
12e	80.3[b]	77.5	84.5[b]	70.8	14.6	22.9, 25.3, 110.8	69.1 (CH_2), 128.0, 128.7, 131.6, 133.3 (Ph)	30.8 [$(CH_3)_3$], 35.1 (C)
12f	76.7	76.9	81.5	69.0	14.0	23.0, 25.2, 111.0	66.0 (CH_2), 128.1, 128.8, 131.3, 133.4 (Ph)	30.1 [$(CH_3)_3$], 30.0, 35.2 (C, CH_2) [a]
12g	83.8	77.8	83.4	71.6	13.7	23.4, 25.4, 112.9	66.7 (CH_2), 127.8, 128.2, 128.6, 129.4, 130.2, 131.1, 132.6, 132.7 (2 Ph)	
12h	82.4	78.2	83.7	72.2	13.4	24.0, 25.9, 113.5	66.2 (CH_2), 128.4, 128.6, 129.3, 133.2 (Ph)	127.1 (CH), 127.3 (CH_2)
12i	77.4	75.9	81.4	70.1	13.6	23.1, 25.2, 111.4	66.4 (CH_2), 128.2, 128.7, 131.3, 133.3 (Ph)	27.2 (CH_2), 118.9 (=CH_2), 133.0 (CH)
12j	80.7	75.5	81.0	70.2	13.6	23.1, 25.2, 111.2	66.7 (*N*-CH_2), 126.8, 128.0, 128.2, 128.6, 128.8, 129.7, 131.2, 133.4, 137.1 (2 Ph)	28.8 (2-CH_2)[a]
12k	78.5	75.9	81.5	70.0	13.7	23.1, 25.2, 111.5	66.3 (CH_2), 128.2, 128.9, 131.1, 133.3 (Ph)	22.0 (CH_2), 30.6 (CH_2), 115.7 (=CH_2), 137.3 (CH)
13a	68.0	79.0	79.0	68.0	8.0	25.5, 25.9, 113.0	68.3 (CH_2), 129.3, 129.8, 131.5, 132.9 (Ph)	8.0 (CH_3)
13b	74.8	77.3	78.5	69.2	8.1	25.0, 25.9, 112.6	67.0 (CH_2), 129.4, 129.7, 130.2, 131.9 (Ph)	9.8 (CH_3), 16.5 (CH_2)
13g	75.6	78.7	79.2	69.0	8.5	25.0, 25.8, 113.1	67.3 (CH_2), 128.1, 128.4, 129.3, 129.5, 130.0, 130.3, 132.1, 133.5 (2 Ph)	[a]

[a] Signals of 2-Ph in column CH_2Ph. − [b] Signal assignment may be reversed.

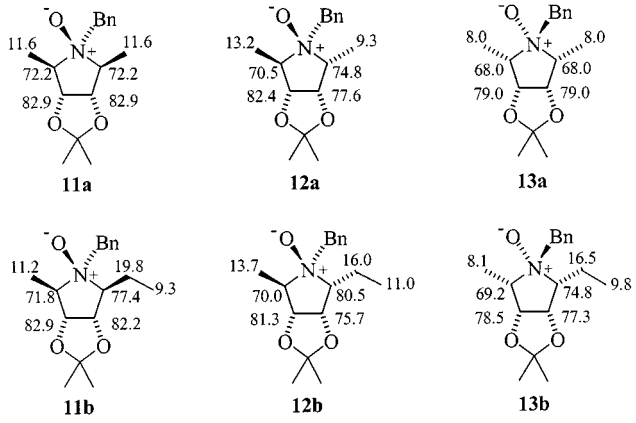
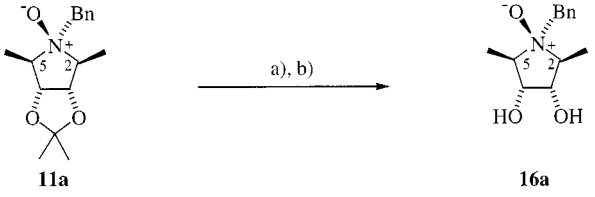


Figure 2. Comparison of ^{13}C NMR chemical shifts of 2-methyl- and 2-ethyl-substituted pyrrolidine *N*-oxides **11a−13a** and **11b−13b**



Scheme 7. *O*-deprotection of the pyrrolidine *N*-oxide **11a**: (a) conc. HCl, MeOH, H_2O (1:8:8), 1 d, room temp.; (b) Dowex 50WX8 (H^+ form); 84%

served for both diastereotopic methylene protons of the benzyl group, and for the carbon atoms C-3 and C-4 (vide supra). The dihedral angles estimated from this model are in perfect agreement with the coupling constants $J_{2,3}$, $J_{3,4}$, $J_{4,5}$ (Table 5).

Similarly, for the 2,5-*trans* isomers **12**, an envelope conformation 1E is suggested by the results of the calcula-

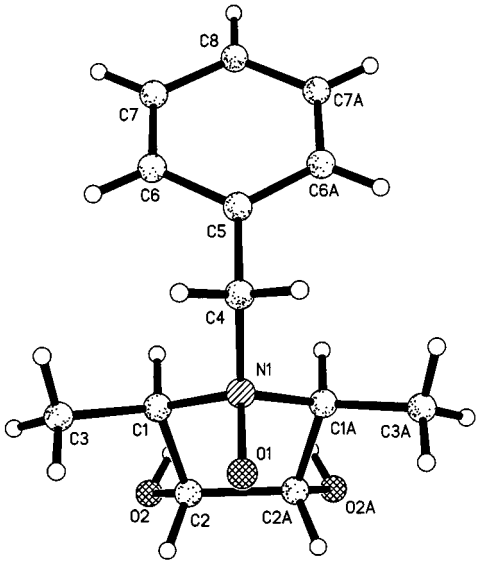


Figure 3. X-ray structure of the pyrrolidine *N*-oxide **16a**

Table 5. Comparison of the coupling values ^3J observed for pyrrolidine *N*-oxides **11a**,**b**,**d**,**g**,**h**,**k** and **12a−k** with the dihedral angles calculated for pyrrolidine *N*-oxides **11a** and **12a** (MOPAC)

Coupling Protons	Isomer **11**		Isomer **12**	
	^3J [Hz]	δ [°]	^3J [Hz]	δ [°]
2-H, 3-H	5.5 to 7.1	139	5.4 to 6.3	−33
3-H, 4-H	7.1 to 7.4	0	7.3 to 7.6	0
4-H, 5-H	6.1 to 6.5	−139	0 to 3.3	−104

tions.[80] This conformation would result in a perpendicular orientation (close to 90°) of 4-H and 5-H. Indeed, for all isomers **12a−k**, coupling values $J_{4,5}$ in the range of 0 to 3.3 Hz were observed (Table 5). The orientation of the 2-substituent with respect to the methylene protons of the benzyl group and to each of the methyl groups of the acetonide part differs considerably, hence the pronounced shift differences in the NMR signals of these groups. For the same reason, the C-3 and C-4 show different ^{13}C NMR chemical shifts.

Conclusion

The Cope−House cyclization of unsaturated hydroxylamines derived from D-ribose offers a quick, efficient, and stereoselective access to many (1*R*,2*S*,3*S*,4*R*,5*R*)- and (1*R*,2*R*,3*S*,4*R*,5*R*)-5-methyl-3,4-dihydroxypyrrolidine *N*-oxides (*allo* and L-*altro*/D-*talo* configurations with respect to 1,4-iminoglycitols). Since the side-chain at the 2-position of the pyrrolidine ring is introduced by nucleophilic addition of organometallic reagents to nitrone **5**, a large variety of substituents can be attached. Furthermore, by complexation of the nitrone **5** with Lewis acids or the use of organolithium compounds, in many cases both 2-epimers are accessible in good yields. The configuration and conformation of the parent pyrrolidine *N*-oxides **7**, **8**, **11**, **12**, and **13** was readily elucidated by analysis of the NMR spectroscopic data. Applying simple transformations to these pyrrolidine *N*-oxides, a variety of iminopolyols with glycosidase-inhibiting properties is available (to be described in detail in the following paper of this series).[40]

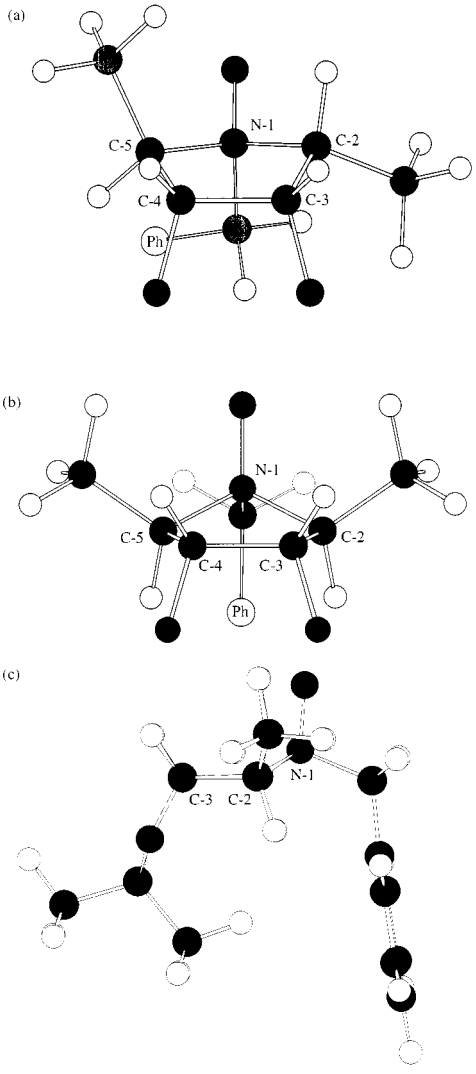


Figure 4. (a) and (b): Conformation of the pyrrolidine *N*-oxides **12a** and **11a**. The phenyl ring and the acetonide group are omitted for clarity. (c) The side view of the pyrrolidine *N*-oxide **11a** illustrates the symmetry of this conformer

Experimental Section

General Remarks: Melting points were determined on a Fisher−Johns 4017 heating block and are uncorrected. − ^{1}H and ^{13}C NMR spectra were recorded with Bruker AC 250, ARX 300, ARX 500 spectrometers using Me_4Si as internal standard. − IR spectra were recorded with a Perkin−Elmer 283 or a Bruker IFS 28 IR spectrometer. − Mass spectra and high-resolution mass spectra (HRMS) were obtained with Finnigan quadrupole-MS 4500 and Finnigan MAT 95 spectrometers, respectively. − Optical rotations were determined with a Perkin−Elmer polarimeter 241MC. − CHEM-3D 4.0 was used for molecular modelling (MM2, MOPAC).[81−83] − MPLC separations were carried out using a

Lewa FL 1 pump; the pyrrolidine *N*-oxides were monitored at 250 nm using a Knauer 97.00 diode array detector. The columns (26 cm × 3.2 cm, *N* = 5000 or 47 cm × 5 cm, *N* = 11700) were packed with LiChroprep Si 60 silica gel.[84]

Materials: Solvents were purified and dried by standard methods. For column chromatography, silica gel (40−63 μm, Merck) was used, and acidic resin Dowex 50WX8 (H^+ form) used for ion exchange purification was supplied from Fluka. Grignard reagents were freshly prepared from magnesium and the corresponding alkyl halide or purchased (Aldrich). MeLi and PhLi were purchased (Fluka, Acros); vinyllithium was prepared by transmetalation from tetravinyl tin (Aldrich) and PhLi.[85] The Lewis acids employed ($ZnCl_2{\cdot}Et_2O$, Et_2AlCl) are commercially available (Fluka, Aldrich). Chloroform (p.a.) used for Cope−House cyclizations was supplied by Merck.

Purity of the Pyrrolidine *N*-Oxides: Correct elemental analyses were only obtained for the pyrrolidine *N*-oxides **7**, **11a**, and **11g**. However, in all cases, spectroscopically pure compounds were obtained. The hygroscopic properties of amine *N*-oxides[86−88] and their capability to form hydrates[26,27,86−88] are well described in the literature, and deviations of the analyses can be explained by the presence of varying amounts of water. This assumption is confirmed by the following observations: (a) Several samples gained weight when exposed to air; (b) the presence of water was evident in the ^{1}H NMR spectra of several pyrrolidine *N*-oxides, e.g. in the spectrum of **11h** [$CDCl_3$; δ(OH_2) = 2.34 (bs, 2 H); compound analyzed for **11h**·1.0 H_2O]; (c) "correct" analyses are obtained when nonstoichiometric amounts of water are taken into account (cf. Experimental Section), which, however, is ambiguous. Deviations in the elemental analyses of **12h** (viscous oil) and **12i/12j** (thermally labile) are due to the fact that the chromatography solvent (CH_2Cl_2/MeOH) could not be completely removed. In all such cases, structures were confirmed by HRMS; in many cases, transformations of these hygroscopic pyrrolidine *N*-oxides were performed to yield products with correct analyses.[40]

Methyl 2,3-*O*-Isopropylidene-β-D-ribofuranoside (2): The furanoside **2** (45.5 g, 67%; ref.[44] 70% yield) was prepared from D-ribose (**1**, 50.0 g, 333 mmol) according to ref.[44] − $[\alpha]_D^{24}$ = −77 (*c* = 1.76, $CHCl_3$), {ref.:[44] $[\alpha]_D^{25}$ = −82 (*c* = 2, $CHCl_3$)}. − IR (film): $\tilde{\nu}$ = 3460, 2990, 2940, 1375, 1210, 1095, 1045 cm^{-1}. − ^{1}H NMR (250.1 MHz, $CDCl_3$): δ = 1.32, 1.49 [2 s, 6 H, $C(CH_3)_2$], 3.27 (dd, $J_{5a,OH}$ = 10.0, $J_{5b,OH}$ = 3.2 Hz, 1 H, OH), 3.44 (s, 3 H, OCH_3), 3.56−3.74 (m, 2 H, 5-H), 4.43 (m_c, 1 H, 4-H), 4.59 (d, $J_{2,3}$ = 5.9 Hz, 1 H, 3-H), 4.84 (d, $J_{2,3}$ = 5.9 Hz, 1 H, 2-H), 4.98 (s, 1 H, 1-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.7, 26.4 [$C(CH_3)_2$], 55.5 (OCH_3), 64.0 (C-5), 81.5, 85.8, 88.3 (C-2, C-3, C-4), 110.0 (C-1), 112.1 [$C(CH_3)_2$]. − $C_9H_{16}O_5$ (204.2): calcd. C 52.93, H 7.90; found C 52.93, H 7.88.

Methyl 5-Deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside (3): For the synthesis of **3**, a modification of the procedure given in ref.[46] was employed: The furanoside **2** (20.0 g, 98 mmol) was dissolved in toluene (650 mL). After the addition of imidazole (16.0 g, 235 mmol) and triphenylphosphane (30.9 g, 117 mmol), the solution was heated to 70 °C. At this temperature, iodine (29.8 g, 117 mmol) was added, and stirring continued for 2 h. The brown precipitate formed was decanted and the solution was evaporated to dryness. The remainders were extracted with diethyl ether (3 × 250 mL) and the solvent was evaporated in vacuo to afford a yellowish oil (44.8 g) which was purified by flash chromatography (SiO_2, CH_2Cl_2). The iodo sugar **3** was obtained as a colourless oil (26.8 g, 87% yield; ref.[46] 92%). − $[\alpha]_D^{20}$ = −72 (*c* = 1.95, CH_2Cl_2), {ref.:[22] $[\alpha]_D^{20}$ = −69 (*c* = 2.08, CH_2Cl_2)}. − IR (film): $\tilde{\nu}$ = 2988, 2936, 1373, 1210, 1194, 1104, 1066, 1018, 956 cm^{-1}. − ^{1}H NMR (250.1 MHz, $CDCl_3$): δ = 1.33, 1.49 [2 s, 6 H, $C(CH_3)_2$], 3.16 (t, $J_{4,5a}$ = $^2J_{5a,5b}$ = 10.0 Hz, 1 H, 5-H_a), 3.29 (dd, $J_{4,5b}$ = 6.3, $^2J_{5a,5b}$ = 10.0 Hz, 1 H, 5-H_b), 3.37 (s, 3 H, OCH_3), 4.45 (dd, $J_{4,5a}$ = 10.0, $J_{4,5b}$ = 6.3 Hz, 1 H, 4-H), 4.63 (d, $J_{2,3}$ = 5.9 Hz, 1 H, 2-H), 4.77 (d, $J_{2,3}$ = 5.9 Hz, 1 H, 3-H), 5.06 (s, 1 H, 1-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 6.7 (C-5), 25.0, 26.4 [$C(CH_3)_2$], 55.2 (OCH_3), 83.0, 85.3, 87.4 (C-2, C-3, C-4), 109.6 (C-1), 112.6 [$C(CH_3)_2$]. − $C_9H_{15}O_4I$ (314.1): calcd. C 34.41, H 4.81, I 40.40; found C 34.46, H 4.81, I 40.18.

4,5-Dideoxy-2,3-*O*-isopropylidene-D-*erythro*-4-pentenose (4): Following ref.,[22] compound **3** (6.3 g, 20 mmol) was dissolved in dry THF (90 mL) in a flame-dried flask under nitrogen. The solution was cooled to −80 °C and *n*-butyllithium (1.6 M in hexanes, 18.9 mL, 30 mmol) was added over a period of 15 min. The reaction mixture was stirred for 2 h at −80 °C and then quenched with NH_4Cl (2 g). The mixture was allowed to warm to −40 °C; water (50 mL) was added and the aqueous phase extracted with diethyl ether (3 × 50 mL). The combined organic solutions were dried with $MgSO_4$ and concentrated in vacuo (since the aldehyde **4** is somewhat volatile, the pressure should be kept above 20 mbar). The aldehyde **4** (3.8 g, "122%") was obtained as a colourless oil which was used without further purification. − ^{1}H NMR (250.1 MHz, $CDCl_3$): δ = 1.45, 1.62 [2 s, 6 H, $C(CH_3)_2$], 4.42 (dd, $J_{1,2}$ = 3.1, $J_{2,3}$ = 7.5 Hz, 1 H, 2-H), 4.86 (dd, $J_{2,3}$ = 7.5, $J_{3,4}$ = 6.8 Hz, 1 H, 3-H), 5.33 (dm, $J_{4,5E}$ = 10.3 Hz, 1 H, 5-H_E), 5.47 (dm, $J_{4,5Z}$ = 17.1 Hz, 1 H, 5-H_Z), 5.77 (ddd, $J_{3,4}$ = 6.8, $J_{4,5E}$ = 10.3, $J_{4,5Z}$ = 17.1 Hz, 1 H, 4-H), 9.56 (d, $J_{1,2}$ = 3.1 Hz, 1 H, 1-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 25.3, 27.4 [$C(CH_3)_2$], 79.1, 82.2 (C-2, C-3), 111.3 [$C(CH_3)_2$], 119.7 (C-5), 131.3 (C-4), 200.7 (C-1).

(*Z*)-4,5-Dideoxy-2,3-*O*-isopropylidene-D-*erythro*-4-pentenose *N*-Benzyl Nitrone (5): $MgSO_4$ (6.00 g, 50.0 mmol) was added to a solution of the crude aldehyde **4** [1.90 g, containing ca. 1.56 g (10.0 mmol) of **4**] and *N*-benzylhydroxylamine (1.23 g, 10.0 mmol) in CH_2Cl_2 (60 mL). The suspension was stirred at room temp. for 19 h, then $MgSO_4$ was removed by filtration and washed with CH_2Cl_2. The combined filtrates were evaporated to dryness. The remaining yellowish solid was purified by flash chromatography (SiO_2, ethyl acetate/petroleum ether = 7:3) affording analytically pure *N*-benzyl nitrone **5**, (1.80 g, 69% based on **3**), m.p. 96 °C. − Note: Three by-products (tetrahydro-1,2-oxazine derivatives) were isolated by further separation of the nonpolar fractions by column chromatography.[34,38,39] − $[\alpha]_D^{20}$ = +181 (*c* = 0.99, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3060, 1595, 1375, 1365, 1250, 1200, 1160, 1140, 1052, 1030 cm^{-1}. − ^{1}H NMR (250.1 MHz, $CDCl_3$,): δ = 1.37, 1.49 [2 s, 6 H, $C(CH_3)_2$], 4.80 and 4.88 (2 d, ^2J = 13.6 Hz, 2 H, CH_2Ph), 4.90 (ddt, $J_{2,3}$ = 6.9, $J_{3,4}$ = 6.3, $J_{3,5E}$ = $J_{3,5Z}$ = 1.1 Hz, 1 H, 3-H), 5.04 (ddd, $J_{3,5E}$ = 1.1, $J_{4,5E}$ = 10.4, $^2J_{5E,5Z}$ = 1.8 Hz, 1 H, 5-H_E), 5.32 (dd, $J_{1,2}$ = 5.5, $J_{2,3}$ = 6.9 Hz, 1 H, 2-H), 5.34 (ddd, $J_{3,5Z}$ = 1.1, $J_{4,5Z}$ = 17.1, $^2J_{5E,5Z}$ = 1.8 Hz, 1 H, 5-H_Z), 5.68 (ddd, $J_{3,4}$ = 6.3, $J_{4,5E}$ = 10.4, $J_{4,5Z}$ = 17.1 Hz, 1 H, 4-H), 6.74 (d, $J_{1,2}$ = 5.5 Hz, 1 H, 1-H), 7.39 (m_c, 5 H, C_6H_5). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.9, 27.4 [$C(CH_3)_2$], 69.2 (CH_2Ph), 74.4 (C-2), 78.6 (C-3), 109.5 [$C(CH_3)_2$], 117.5 (C-5), 128.9, 129.2, 129.5, 132.3 (C_6H_5), 132.7 (C-4), 136.5 (C-1). − $C_{15}H_{19}NO_3$ (261.3): calcd. C 68.94, H 7.32, N 5.36; found C 68.89, H 7.37, N 5.22.

(1*S*,2*R*,3*R*,4*S*)-*N*-Benzyl-3,4-*O*-isopropylidenedioxy-2-methylpyrrolidine *N*-Oxide 7: $NaBH_4$ (0.07 g, 1.9 mmol) was added to an ethanol solution (10 mL) of the *N*-benzyl nitrone **5** (1.00 g, 3.8 mmol) and the mixture was stirred for 4 h at 0 °C. A solution of citric acid (10 mL, 0.25 M) was added, then pH 8 was adjusted

by the addition of NaOH (6 N). The aqueous phase was saturated with NaCl and extracted with $CHCl_3$ (3 × 20 mL). The organic solutions were dried with $MgSO_4$, filtered, and then stirred for 16 h at room temp. to accomplish Cope−House cyclization of **6**. After evaporation of the solvent, a colourless solid remained, identified as **7** and **8** (*dr* = 92:8, 0.94 g, 93%). Colourless crystals (m.p. 120−122 °C) of the major isomer **7** (0.66 g, 66%) were isolated by crystallization of the crude product from ethyl acetate/heptane (2:1). − The intermediate unsaturated hydroxylamine **6** was observed when recording an NMR spectrum immediately after work-up: ^{1}H NMR ($CDCl_3$, 250.1 MHz): δ = 1.35, 1.45 [2 s, 6 H, $C(CH_3)_2$], 2.77 (dd, $^2J_{1a,1b}$ = 13.2, $J_{1a,2}$ = 4.3 Hz, 1 H, 1-H_a), 2.85 (dd, $^2J_{1a,1b}$ = 13.2, $J_{1b,2}$ = 7.2 Hz, 1-H_b), and 2.86 (bs, OH) [together 2 H], 3.81 and 3.89 (2 d, ^2J = 12.9 Hz, 2 H, CH_2Ph), 4.53−4.63 (m, 2 H, 2-H, 3-H), 5.20 (dd, $J_{4,5E}$ = 10.3, $^2J_{5E,5Z}$ = 1.8 Hz, 1 H, 5-H_E), 5.31 (dd, $J_{4,5Z}$ = 17.2, $^2J_{5E,5Z}$ = 1.8 Hz, 1 H, 5-H_Z), 5.80 (ddd, $J_{3,4}$ = 6.9, $J_{4,5E}$ = 10.3, $J_{4,5Z}$ = 17.2 Hz, 1 H, 4-H), 7.32 (m_c, 5 H, C_6H_5). − **7**: $[\alpha]_D^{20}$ = −5 (*c* = 0.56, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 2980, 1445, 1370, 1195, 1145, 1070 cm^{-1}. − ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.32, 1.40 [2 s, 6 H, $C(CH_3)_2$], 1.64 (d, $J_{2,2\text{-Me}}$ = 6.4 Hz, 3 H, 2-CH_3), 3.36 (quint, $J_{2,2\text{-Me}}$ = $J_{2,3}$ = 6.4 Hz, 1 H, 2-H), 3.40 (dd, $J_{4,5a}$ = 5.6, $^2J_{5a,5b}$ = 11.1 Hz, 1 H, 5-H_a), 3.65 (dd, $J_{4,5b}$ = 6.5, $^2J_{5a,5b}$ = 11.1 Hz, 1 H, 5-H_b), 4.26 and 4.31 (2 d, ^2J = 13.0 Hz, 2 H, CH_2Ph), 4.75 (dd, $J_{2,3}$ = 6.4, $J_{3,4}$ = 7.0 Hz, 1 H, 3-H), 5.09 (ddd, $J_{3,4}$ = 7.0, $J_{4,5a}$ = 5.6, $J_{4,5b}$ = 6.5 Hz, 1 H, 4-H), 7.44 (m_c, 5 H, C_6H_5). − ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 10.5 (2-CH_3), 23.6, 25.8 [$C(CH_3)_2$], 68.7 (CH_2Ph), 69.6 (C-5), 72.8 (C-2), 75.2 (C-4), 83.3 (C-3), 113.4 [$C(CH_3)_2$], 127.9, 128.7, 129.3, 130.8 (C_6H_5). − $C_{15}H_{21}NO_3$ (263.3): calcd. C 68.42, H 8.04, N 5.32; found C 68.16, H 8.04, N 5.27.

(3*S*,4*R*)-2-(*N*-Benzylhydroxylamino)-3,4-*O*-isopropylidenedioxy-5-hexene, (2*S*)-Isomer 9a or (2*R*)-Isomer 10a. − *N*-Benzyl-3,4-*O*-isopropylidenedioxy-2,5-dimethylpyrrolidine *N*-Oxides, (2*S*,3*S*,4*R*,5*R*)-Isomer 11a, (1*S*,2*R*,3*S*,4*R*,5*R*)-Isomer 12a, (2*R*,3*S*,4*R*,5*S*)-Isomer 13a

(a) By Addition of H_3CMgBr: A solution of *N*-benzyl nitrone **5** (290 mg, 1.11 mmol) in diethyl ether (10 mL) was placed in a flame-dried flask under nitrogen. At −40 °C, a solution of H_3CMgBr in diethyl ether (3.0 M, 0.57 mL, 1.7 mmol) was added. Within 5 min a colourless precipitate formed. The reaction mixture was kept at −40 °C for 2 h and then quenched by adding NH_4Cl (0.3 g) and ice water (20 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined extracts were dried with $MgSO_4$ and concentrated in vacuo. The residue (290 mg of a yellowish oil) was dissolved in $CHCl_3$ (10 mL) and the solution stirred for 14 h at room temp. After evaporation to dryness, the *dr* of the crude product was determined by ^{1}H and ^{13}C NMR spectroscopy (**11a/12a/13a** = 38:48:14) and the diastereomers were separated by MPLC (10 bar, SiO_2, CH_2Cl_2/MeOH = 9:1). Thus, spectroscopically pure samples of the pyrrolidine *N*-oxides **11a** (90 mg, 27%, m.p. 109−110 °C) and **12a** (120 mg, 37%, m.p. 97−100 °C) were obtained. The minor isomer **13a** (46 mg, 14%) was obtained in a mixture containing **11a**, **12a**, and **13a** in a ratio of 10:13:77. − One of the intermediate hydroxylamines **9a** or **10a** was observed in the NMR spectrum of the crude product recorded immediately after work-up: ^{1}H NMR ($CDCl_3$, 300.1 MHz): δ = 1.10 (d, $J_{1,2}$ = 7.2 Hz, 3 H, 1-H), 1.40, 1.52 [2 s, 6 H, $C(CH_3)_2$], 3.09 (m, 1 H, 2-H), 3.12 (bs, 1 H, OH), 3.87 and 3.99 (2 d, ^2J = 13.3 Hz, 2 H, CH_2Ph), 4.33 (dd, $J_{3,4}$ = 5.7, $J_{4,5}$ = 9.2 Hz, 1 H, 4-H), 5.22 (d, $J_{5,6E}$ = 10.2 Hz, 1 H, 6-H_E), 5.27 (d, $J_{5,6Z}$ = 17.9 Hz, 1 H, 6-H_Z), 5.89 (ddd, $J_{4,5}$ = 8.8, $J_{5,6E}$ = 10.0, $J_{5,6Z}$ = 17.1 Hz, 1 H, 5-H), 7.33 (m_c, 5 H, C_6H_5), signal of 3-H hidden by absorptions of the pyrrolidine *N*-oxides already present. − **11a** (monohydrate): $[\alpha]_D^{20}$ = 0 (*c* = 0.56, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3440 (H_2O), 3190 (H_2O), 2980, 1450, 1375, 1365, 1245, 1200, 1145, 1065, 1005 cm^{-1}. − **12a** (monohydrate): $[\alpha]_D^{20}$ = −13 (*c* = 1.03, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3400 (H_2O), 1375, 1195, 985 cm^{-1}. − ^{1}H and ^{13}C NMR spectroscopic data of **11a**, **12a**, and **13a**: see Table 2 to 4. − $C_{16}H_{23}NO_3$ (277.4): calcd. C 69.29, H 8.36, N 5.05; found for **11a** C 64.74, H 8.39, N 4.63 (correct for M + 1.0 H_2O); found for **12a** C 65.30, H 8.37, N 4.73 (correct for M + 1.0 H_2O).

(b) By Addition of H_3CLi: A solution of H_3CLi (1.6 M, 1.45 mL, 2.3 mmol) was added to a solution of the nitrone **5** (200 mg, 0.77 mmol) in diethyl ether (8 mL) under nitrogen at −80 °C and the mixture was kept at this temperature for 4.75 h. Work-up, Cope−House cyclization in $CHCl_3$ (18 h), and MPLC separation of the crude product (*dr* **11a/12a** = 91:9) were performed as described above, yielding analytically pure **11a** in the form of colourless crystals (112 mg, 53%, m.p. 121−123 °C). − **11a**: $C_{16}H_{23}NO_3$ (277.4): calcd. C 69.29, H 8.36, N 5.05; found C 68.98, H 8.44, N 4.97.

(c) By Complexation of the Nitrone 5 with Lewis Acids Prior to Grignard Addition: (*i*) A solution of $ZnCl_2{\cdot}Et_2O$ in CH_2Cl_2 (2.2 M, 0.42 mL, 0.9 mmol) was added to a suspension of the nitrone **5** (200 mg, 0.77 mmol) in diethyl ether (8 mL) under nitrogen. The resulting clear solution was stirred for 30 min at −10 °C, and then cooled to −30 °C. H_3CMgBr (3.0 M in diethyl ether, 1.54 mL, 4.6 mmol) was added. The reaction mixture was kept for 6 h between −30 °C and −10 °C. After work-up, Cope−House cyclization (16 h in $CHCl_3$ at room temp.), and MPLC separation of the crude product (*dr* **11a/12a/13a** = 13:66:21) as above, a wax consisting of **12a/13a** (109 mg, 49%, *dr* = 90:10) was isolated and analyzed as $C_{16}H_{23}NO_3{\cdot}(H_2O)_{0.75}$; (*ii*) complexation of the nitrone **5** (200 mg, 0.77 mmol) with Et_2AlCl (1.0 M in hexanes, 0.84 mL, 0.8 mmol) and addition of H_3CMgBr (3.0 M in diethyl ether, 0.77 mL, 2.3 mmol) was performed as described above. The mixture was stirred for 3.25 h at −30 °C. After work-up, Cope−House cyclization, and flash chromatography (SiO_2, CH_2Cl_2/MeOH = 9:1) of the crude product (**11a/12a/13a** = 18:64:18), an analytically pure mixture of **11a**, **12a**, and **13a** was isolated (130 mg, 59%, analyzing for $C_{16}H_{23}NO_3{\cdot}(H_2O)_{0.5}$, *dr* unchanged).

***N*-Benzyl-2-ethyl-3,4-*O*-isopropylidenedioxy-5-methylpyrrolidine *N*-Oxides, (1*R*,2*S*,3*S*,4*R*,5*R*)-Isomer 11b, (1*R*,2*R*,3*S*,4*R*,5*R*)-Isomer 12b, (1*S*,2*R*,3*S*,4*R*,5*S*)-Isomer 13b:** A suspension of the *N*-benzyl nitrone **5** (200 mg, 0.77 mmol) in diethyl ether (8 mL) was treated with H_5C_2MgBr (3.0 M in diethyl ether, 0.77 mL, 2.3 mmol) at −30 °C. The reaction mixture was stirred for 3.5 h between −20 °C and −30 °C. After work-up as above, Cope−House cyclization (15.5 h at room temp., *dr* of crude material **11b/12b/13b** = 22:67:11), and MPLC separation (10 bar, SiO_2, CH_2Cl_2/MeOH = 9:1), an analytically pure mixture of **11b** and **12b** (148 mg, 64%, *dr* = 24:76, m.p. 110−112 °C), and **13b** (18 mg, 8%, m.p. 56−58 °C) were obtained. − **11b** and **12b** (inseparable mixture, *dr* 24:76): $[\alpha]_D^{20}$ = −19 (*c* = 0.54, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3400 (b, H_2O), 2960, 1375, 1195, 1030, 1000 cm^{-1}. − $C_{17}H_{25}NO_3$ (291.4): calcd. C 70.07, H 8.65, N 4.81; found C 67.80, H 8.42, N 4.51 (correct for M + 0.5 H_2O). − MS (EI, 70 eV): *m*/*z* (%) = 291.2 (2.7) [M^+], 246.2 (25), 200.2 (16), 150.2 (19), 91.1 (100), 18.1 (13). − HRMS (EI, 70 eV): exact mass calcd. for $C_{17}H_{25}NO_3$: 291.1834; found 291.1834. − **13b**: $[\alpha]_D^{20}$ = −12 (*c* = 0.83, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3400 (b, H_2O), 1365, 1195, 1060, cm^{-1}. − MS (FAB, glycerol): *m*/*z* (%) = 292.2 (100) [MH^+], 91.0 (18). − HRMS (FAB, glycerol): exact mass calcd. for $C_{17}H_{25}NO_3$ + H: 292.1913; found 292.1906. − ^{1}H and ^{13}C NMR of **11b**, **12b**, and **13b**: see Table 2 to 4.

(1*R*,2*R*,3*S*,4*R*,5*R*)-*N*-Benzyl-2-isopropyl-3,4-*O*-isopropylidenedioxy-5-methylpyrrolidine *N*-Oxide (12c): A freshly prepared solution of *i*C_3H_7MgCl (2.3 mmol) in diethyl ether (5 mL) was added at −30 °C to a suspension of the *N*-benzyl nitrone **5** (200 mg, 0.77 mmol) in diethyl ether (5 mL). After stirring for 4.75 h, the usual work-up, Cope−House cyclization by standing at room temp. for 15 h, and flash chromatography (SiO_2, CH_2Cl_2/MeOH = 9:1) of the crude product (*dr* **11c/12c/13c** = 15:85:<5), a colourless solid was isolated (115 mg, 48%, m.p. 108 °C, mixture **11c/12c**, *dr* = 12:88). − $[\alpha]_D^{20}$ = −14 (*c* = 0.66, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 2950, 1378, 1370, 1195, 1030, 1000 cm^{-1}. − $C_{18}H_{27}NO_3$ (305.4): calcd. C 70.79, H 8.91, N 4.59; found C 69.70, H 8.78, N 4.43 (correct for M + 0.25 H_2O). − MS (EI, 70 eV): *m*/*z* (%) = 305.2 (<1) [M^+], 246.2 (92), 132.2 (18), 91.2 (100), 43.3 (11), 28.1 (18), 18.1 (55). − HRMS (EI, 70 eV): exact mass calcd. for $C_{18}H_{27}NO_3$: 305.1991; found 305.1989. − ^1H and ^{13}C NMR spectroscopic data of **12c**: see Table 2 to 4.

***N*-Benzyl-2-isobutyl-3,4-*O*-isopropylidenedioxy-5-methylpyrrolidine *N*-Oxides, (1*R*,2*S*,3*S*,4*R*,5*R*)-Isomer 11d, (1*R*,2*R*,3*S*,4*R*,5*R*)-Isomer 12d:** Three variations of the addition of freshly prepared *i*C_4H_9MgBr to *N*-benzyl nitrone **5** (200 mg, 0.77 mmol) were examined:

(a) Addition of the Grignard reagent in diethyl ether (2.3 mmol, 15 mL) at 0 °C, stirring over a period of 19 h at room temp., cyclization in $CHCl_3$. MPLC separation (SiO_2, CH_2Cl_2/MeOH = 9:1) of the crude product (*dr* **11d/12d/13d** = 27:65:8) afforded pure, colourless, crystalline samples of **11d** (50 mg, 20%, m.p. 97−99 °C) and **12d** (125 mg, 49%, m.p. 112−113 °C). − **11d**: $[\alpha]_D^{20}$ = +26 (*c* = 0.40, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3400 (b, H_2O), 3170 (b), 2940, 1460, 1370, 1360, 1245, 1200, 1140, 1060, 1010 cm^{-1}. − $C_{19}H_{29}NO_3$ (319.4): calcd. C 71.44, H 9.15, N 4.38; found C 69.29, H 9.04, N 4.24 (correct for M + 0.5 H_2O). − MS (EI, 70 eV): *m*/*z* (%) = 319.2 (3.4) [M^+], 261.2 (10), 246.2 (31), 228.2 (20), 150.1 (51), 91.1 (100). − HRMS (EI, 70 eV): exact mass calcd. for $C_{19}H_{29}NO_3$: 319.2147; found 319.2145. − **12d**: $[\alpha]_D^{20}$ = −43 (*c* = 0.46, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3400 (b, H_2O), 2940, 1370, 1195, 1025, 1000 cm^{-1}. − $C_{19}H_{29}NO_3$ (319.4): calcd. C 71.44, H 9.15, N 4.38; found C 68.69, H 9.04, N 4.18 (correct for M + 0.67 H_2O). − MS (EI, 70 eV): *m*/*z* (%) = 319.2 (2.4) [M^+], 286.2 (12), 246.1 (45), 228.2 (18), 91.1 (100), 41.3 (13), 18.1 (23). − HRMS (EI, 70 eV): exact mass calcd. for $C_{19}H_{29}NO_3$: 319.2147; found 319.2147. − ^1H and ^{13}C NMR spectroscopic data of **11d** and **12d**: see Table 2 to 4.

(b) *i*C_4H_9MgBr (3.1 mmol) was added at −30 °C to a solution of **5** in diethyl ether (8 mL). The solution was kept for 4.5 h between −30 °C and −10 °C, and was then allowed to warm to room temp. After a total reaction time of 8.5 h, work-up and Cope−House cyclization (10.5 h) were performed as above. The crude product (**11d/12d/13d** = 46:48:6) was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH = 9:1), yielding a colourless oil (214 mg, 87%, **11d/12d** = 50:50).

(c) After the addition of *i*C_4H_9MgBr (2.3 mmol) in ether (10 mL) at −25 °C, the reaction mixture was kept for 10 h between −30 °C and −10 °C. The crude product obtained after workup and Cope−House cyclization ($CHCl_3$, room temp., 10.5 h), was analyzed by ^1H and ^{13}C NMR spectroscopy: conversion 50%, products **11d/12d/13d** *dr* = 26:67:7.

***N*-Benzyl-2-*tert*-butyl-3,4-*O*-isopropylidenedioxy-5-methylpyrrolidine *N*-Oxides, (1*R*,2*S*,3*S*,4*R*,5*R*)-Isomer 11e, (1*R*,2*R*,3*S*,4*R*,5*R*)-Isomer 12e:** *tert*-C_4H_9MgBr (2.0 M in diethyl ether, 1.15 mL, 2.3 mmol) was added to a solution of the *N*-benzyl nitrone **5** (200 mg, 0.77 mmol) in diethyl ether (8 mL). The mixture was stirred for 7.5 h at −30 °C. Usual work-up, cyclization by stirring in $CHCl_3$ for 15 h, and flash chromatography (SiO_2, CH_2Cl_2/MeOH = 9:1) afforded a mixture of **11e** and **12e** (*dr* = 24:76, 43 mg, 18%) and colourless crystals of **7** (49 mg, 24%), resulting from Grignard reduction. Attempts to separate **11e** and **12e** by preparative HPLC resulted in the transformation into new products not yet fully characterized. − ^1H and ^{13}C NMR spectroscopic data of **11e** and **12e**: see Table 2 to 4.

***N*-Benzyl-3,4-*O*-isopropylidenedioxy-5-methyl-2-neopentylpyrrolidine *N*-Oxides, (1*R*,2*S*,3*S*,4*R*,5*R*)-Isomer 11f, (1*R*,2*R*,3*S*,4*R*,5*R*)-Isomer 12f: (a)** The Grignard addition of freshly prepared *neo*-$C_5H_{11}MgBr$ (2.3 mmol) in diethyl ether (15 mL) to the *N*-benzyl nitrone **5** (200 mg, 0.77 mmol) was performed at room temp. as described above. After a reaction time of 2 d, work-up, and Cope−House cyclization ($CHCl_3$, 3 d), conversion (66%) and *dr* (**11f/12f/13f** = 50:50:<5) were estimated from the NMR spectra. Flash chromatography (SiO_2, CH_2Cl_2/MeOH = 9:1) yielded pure **12f** (30 mg of a yellowish solid, 12%, m.p. 62 °C) and a mixture (31 mg) consisting of **11f**, **12f** (*dr* = 70:30), and another two unidentified products. − ^{13}C NMR spectroscopic data of **11f**: see Table 4. − **12f:** $[\alpha]_D^{20}$ = −22 (*c* = 0.33, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 2940, 1370, 1195, 1050, 1000 cm^{-1}. − ^1H and ^{13}C NMR spectroscopic data: see Table 2 to 4. − MS (EI, 70 eV): *m*/*z* (%) = 333.2 (4.1) [M^+], 246.1 (100), 160.1 (12), 132.0 (12), 91.0 (89), 70.0 (10), 57.0 (15), 28.0 (27), 18.0 (47). − HRMS (EI, 70 eV): exact mass calcd. for $C_{20}H_{31}NO_3$: 333.2304; found 333.2305.

(b) The reaction was run as described in (a), but with shorter reaction time (11 h) and at lower temperature (−30 °C and −10 °C). After Cope−House cyclization in $CHCl_3$ at room temp. (10.5 h), the *dr* of the crude product (**11f/12f/13f** = 20:80:<5) and conversion (ca. 32%) were determined from the NMR spectrum.

***N*-Benzyl-3,4-*O*-isopropylidenedioxy-5-methyl-2-phenylpyrrolidine *N*-Oxides, (1*R*,2*S*,3*S*,4*R*,5*R*)-Isomer 11g, (1*R*,2*R*,3*S*,4*R*,5*R*)-Isomer 12g, (1*S*,2*R*,3*S*,4*R*,5*S*)-Isomer 13g**

(a) By Addition of PhMgBr: PhMgBr (3.0 M in diethyl ether, 1.15 mL, 3.5 mmol) was added to a suspension of the *N*-benzyl nitrone **5** (300 mg, 1.15 mmol) in diethyl ether (15 mL) and the mixture kept at −20 °C for 1 h. The usual work-up, Cope−House cyclization in $CHCl_3$ at room temp. (16 h), and MPLC separation (SiO_2, 10 bar, CH_2Cl_2/MeOH = 93:7) of the crude product (*dr* **11g/12g/13g** = 40:60:<5) afforded colourless crystals of **11g** (96 mg, 25%, m.p. 135−137 °C), **12g** (160 mg, 41%, m.p. 45−47 °C), and **13g** (17 mg, 4%, m.p. 123 °C). − [Note: When kept neat, the pyrrolidine *N*-oxide **12g** underwent partial ring opening within several days to form the unsaturated hydroxylamine **10g** (ratio **10g/12g** = 33:67). Pure **12g** could be recovered by again stirring a $CHCl_3$ solution of this mixture for 4 d at room temp.] − Data of the unsaturated hydroxylamine **10g** from mixture of **10g/12g**: ^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.46, 1.58 [2 s, 6 H, $C(CH_3)_2$], 3.88 (d, $J_{1,2}$ = 9.7 Hz, 1 H, 1-H), 4.11 and 4.13 (2 d, ^2J = 14.3 Hz, 2 H, CH_2Ph), 4.21 (ddt, $J_{2,3}$ = 5.7, $J_{3,4}$ = 7.8, $^4J_{3,5}$ = 1.0 Hz, 1 H, 3-H), 4.86 (ddd, $^4J_{3,5Z}$ = 1.0, $J_{4,5Z}$ = 17.1, $^2J_{5E,5Z}$ = 1.7 Hz, 1 H, 5-H_Z), 4.95 (dd, $J_{1,2}$ = 9.7, $J_{2,3}$ = 5.7 Hz, 1 H, 2-H), 5.01 (ddd, $^4J_{3,5E}$ = 0.9, $J_{4,5E}$ = 10.3, $^2J_{5E,5Z}$ = 1.7 Hz, 1 H, 5-H_E), 5.69 (ddd, $J_{3,4}$ = 7.8, $J_{4,5E}$ = 10.3, $J_{4,5Z}$ = 17.1 Hz, 1 H, 4-H), 7.20−7.53 (m, 10 H, 2 C_6H_5). − **11g**: $[\alpha]_D^{20}$ = +12 (*c* = 0.56, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 2960, 2920, 1440, 1370, 1260, 1195, 1080, 1060 cm^{-1}. − $C_{21}H_{25}NO_3$ (339.4): calcd. C 74.31, H 7.42, N 4.13; found C 73.85, H 7.46, N 4.06. − **12g**: $[\alpha]_D^{20}$ = −53 (*c* = 0.52, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 2960, 2920, 1440, 1370, 1220, 1195, 1150, 1050

cm^{-1}. − MS (FAB, nitrobenzyl alcohol): *m/z* (%) = 340.2 (100) [MH$^+$], 212.1 (16), 91.0 (39). − HRMS (FAB, nitrobenzyl alcohol): exact mass calcd. for $C_{21}H_{25}NO_3$ + H: 340.1913; found 340.1912. − **13g**: $[\alpha]_D^{20}$ = −74 (*c* = 0.63, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3400, 2960, 2920, 1368, 1195, 1100 cm^{-1}. − MS (EI, 70 eV): *m/z* (%) = 339.2 (8.2) [M$^+$], 308.1 (15), 248.1 (22), 132.0 (75), 91.0 (100), 77.0 (22), 57.9 (14). − HRMS (EI, 70 eV): exact mass calcd. for $C_{21}H_{25}NO_3$: 339.1834; found 339.1835. − ^{1}H and ^{13}C NMR spectroscopic data of **11g**, **12g**, and **13g**: see Table 2 to 4.

(b) By Addition of PhLi: A solution of the nitrone **5** (200 mg, 0.77 mmol) in diethyl ether (10 mL) was treated with PhLi (2.0 M in cyclohexane/ether, 1.16 mL, 2.3 mmol) at a temp. of −80 °C. The reaction mixture was stirred for 3 h at −80 °C. The usual work-up including Cope−House cyclization (16.5 h in $CHCl_3$ at room temp.) afforded a mixture of **11g**, **12g**, and **13g** (19:81:<5) which was separated by MPLC (cf. above). Thus, spectroscopically pure samples of **11g** (25 mg, 9%, m.p. 134−136 °C), **12g** (100 mg, 38%, 50−53 °C), and **13g** (9 mg, 3%) were obtained.

(c) By Complexation of the Nitrone 5 with Et_2AlCl Followed by Grignard Addition: Et_2AlCl (1.0 M in hexanes, 0.91 mL, 0.9 mmol) was added to a solution of the nitrone **5** (200 mg, 0.77 mmol) in diethyl ether (10 mL). The mixture was stirred for 30 min at −30 °C, treated with PhMgBr (3.0 M in diethyl ether, 0.77 mL, 2.31 mmol), and stirred for another 3 h 45 min. From the usual work-up and Cope−House cyclization (16.5 h at room temp. in $CHCl_3$), a crude product consisting of **11g**, **12g**, and **13g** in a *dr* of 58:42:<5 was obtained. After MPLC separation (cf. above), analytically pure colourless crystals of **11g** (120 mg, 46%, m.p. 139−140 °C), spectroscopically pure crystals of **12g** (65 mg, 25%), and oily **13g** (12 mg, 5%) were isolated. − **11g**: $C_{21}H_{25}NO_3$ (339.4): calcd. C 74.31, H 7.42, N 4.13; found C 74.29, H 7.47, N 4.18.

N-Benzyl-3,4-*O*-isopropylidenedioxy-5-methyl-2-vinylpyrrolidine *N*-Oxides, (1*R*,2*S*,3*S*,4*R*,5*R*)-Isomer 11h, (1*R*,2*R*,3*S*,4*R*,5*R*)-Isomer 12h

(a) By Addition of Vinylmagnesium Bromide: Reaction of the *N*-benzyl nitrone **5** (200 mg, 0.77 mmol) with vinylmagnesium bromide (1.0 M in THF, 1.15 mL, 1.2 mmol) in diethyl ether (8 mL) [2 h, −40 °C], Cope−House cyclization in $CHCl_3$ at room temp. for 13 h (*dr* **11h/12h** = 67:33), and MPLC separation (SiO_2, 10 bar, CH_2Cl_2/MeOH = 92:8) afforded **11h** (131 mg of colourless crystals, 56%, m.p. 47 °C) and **12h** (82 mg of viscous oil, "35%", containing some solvent not removed by drying). [Note: The major isomer **11h** could be purified by Kugelrohr distillation (10^{-3} mbar, 60 °C) and distilled as the monohydrate. However, the minor diastereomer **12h** was not separated by this method.] − **11h**: $[\alpha]_D^{20}$ = −8 (*c* = 0.15, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3650−3000 (b, H_2O), 2970, 1375, 1200, 1150, 1065 cm^{-1}. − $C_{17}H_{23}NO_3$ (289.4): calcd. C 70.56, H 8.01, N 4.84; found C 66.14, H 8.14, N 4.46 (correct for M + 1.0 H_2O). − MS (EI, 70 eV): *m/z* (%) = 289.2 (1.4) [M$^+$], 170.2 (23), 91.2 (100), 43.3 (12), 18.1 (14). − HRMS (EI, 70 eV): exact mass calcd. for $C_{17}H_{23}NO_3$: 289.1678; found 289.1678. − **12h**: $[\alpha]_D^{20}$ = −51 (*c* = 0.52, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3365 (b, OH), 2988, 1381, 1209, 1099 cm^{-1}. − MS (EI, 70 eV): *m/z* (%) = 289.2 (3.6) [M$^+$], 273.2 (16), 170.2 (18), 134.2 (11), 91.2 (100), 43.0 (18), 28.1 (29), 18.1 (21). − HRMS (EI, 70 eV): exact mass calcd. for $C_{17}H_{23}NO_3$: 289.1678; found 289.1678. − ^{1}H and ^{13}C NMR spectroscopic data of **11h** and **12h**: see Table 2 to 4.

(b) By Addition of Vinyllithium: PhLi (2.0 M in cyclohexane/ether, 1.73 mL, 3.5 mmol) was added at room temp. to a solution of tetravinyltin (190 mg, 0.84 mmol) in diethyl ether (2.5 mL) which resulted in the immediate formation of a colourless precipitate.[85] The mixture was stirred for 45 min at room temp., diluted with diethyl ether (5 mL), cooled to −80 °C, treated with the *N*-benzyl nitrone **5** (300 mg, 1.15 mmol), and stirred for another 5.25 h at this temperature. The usual work-up, including Cope−House cyclization in $CHCl_3$ at room temp. (18.5 h, *dr* **11h/12h** = 71:29), and column chromatography (SiO_2, CH_2Cl_2/MeOH = 92:8) afforded a mixture of **11h/12h** (colourless oil, 205 mg, 62%, *dr* unchanged).

(c) By Complexation of the Nitrone 5 with Lewis Acids Followed by Grignard Addition: (*i*) Complexation of the *N*-benzyl nitrone **5** (200 mg, 0.77 mmol) with $ZnCl_2$·Et_2O (2.2 M in diethyl ether, 0.42 mL, 0.9 mmol) [30 min, −25 °C], subsequent addition of vinylmagnesium bromide (1.0 M in THF, 3.90 mL, 3.9 mmol) at −40 °C with stirring between −30 °C and −10 °C for 4.25 h, then cyclization in $CHCl_3$ at room temp. for 11.5 h (*dr* **11h/12h** = 84:16), and MPLC separation (SiO_2, 10 bar, CH_2Cl_2/MeOH = 92:8) afforded colourless crystals of **11h** [134 mg, 60%, m.p. 67−69 °C; analyzed as $C_{17}H_{23}NO_3$·$(H_2O)_{0.25}$]. − *(ii)* *N*-Benzyl nitrone **5** (200 mg, 0.77 mmol) was treated at −30 °C with Et_2AlCl (1.0 M in hexanes, 0.9 mmol) and, after 45 min vinylmagnesium bromide (1.0 M in THF, 2.31 mL, 2.3 mmol) was added at this temperature. After stirring for 3.5 h at −30 °C, work-up, and Cope−House cyclization (15 h at room temp. in $CHCl_3$) were performed as usual. The crude product (**11h/12h** = 84:16) was submitted to flash chromatography (SiO_2, CH_2Cl_2/MeOH = 92:8) to afford a mixture of **11h** and **12h** [163 mg, 72%, analyzes for $C_{17}H_{23}NO_3$·$(H_2O)_{0.25}$].

(1*R*,2*R*,3*S*,4*R*,5*R*)-2-Allyl-*N*-benzyl-3,4-*O*-isopropylidenedioxy-5-methylpyrrolidine *N*-Oxide (12i)

(1*R*,2*R*,3*S*,4*R*,5*R*)-2-Allyl-*N*-benzyl-3,4-*O*-isopropylidenedioxy-5-methylpyrrolidine *N*-Oxide (12i): A solution of the *N*-benzyl nitrone **5** (310 mg, 1.19 mmol) in diethyl ether (10 mL) was treated with allylmagnesium bromide (1.0 M in diethyl ether, 1.72 mL, 1.7 mmol). The mixture was stirred for 45 min at −40 °C. After work-up, Cope−House cyclization in $CHCl_3$ at room temp. (16 h), and MPLC separation (SiO_2, 10 bar, CH_2Cl_2/MeOH = 93:7), a colourless solid was isolated (**12i**, 181 mg, 47%) containing some solvent even after drying over P_4O_{10} at 10^{-3} mbar. Since **12i** was found to be thermally labile, no attempts were made to remove these traces by heating the sample. [Note: The NMR spectra of the nonpolar fractions obtained during MPLC showed the presence of the conjugated hydroxylamine **14i** (resulting from Cope elimination of **12i**). The hydroxylamine **14i** was also formed on prolonged storage of **12i**]. − ^{1}H and ^{13}C NMR spectroscopic data of **12i**: see Table 2 to 4.

(1*R*,2*R*,3*S*,4*R*,5*R*)-*N*,2-Dibenzyl-3,4-*O*-isopropylidenedioxy-5-methylpyrrolidine *N*-Oxide (12j)

(a) By Addition of BnMgBr: Freshly prepared BnMgBr (3.5 mmol) in diethyl ether (2.5 mL) was added at −30 °C to a solution of the *N*-benzyl nitrone **5** (200 mg, 0.77 mmol) in diethyl ether (8 mL); cf. methyl case, variant (a). After 2 h at −30 °C, work-up, and Cope−House cyclization in $CHCl_3$ at room temp. (11.5 h), the ^{1}H and ^{13}C NMR spectra of the crude product showed the presence of only one pyrrolidine *N*-oxide **12j** and of the unsaturated hydroxylamine **14j** (85:15). Flash chromatography (SiO_2, CH_2Cl_2/MeOH = 92:8) afforded **12j** (161 mg, 59%, m.p. 66−69 °C) as a colourless solid. − $[\alpha]_D^{20}$ = −25 (*c* = 0.51, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 2960, 2910, 1445, 1370, 1195, 1035, 1005 cm^{-1}. − ^{1}H and ^{13}C NMR spectroscopic data of **12j**: see Table 2 to 4. − MS (EI, 70 eV): *m/z* (%) = 353.2 (3.4) [M$^+$], 295.2 (10), 262.2 (36), 246.2 (62), 172.1 (19), 150.1 (39), 146.0 (11), 91.0 (100). − HRMS (EI, 70 eV): exact mass calcd. for $C_{22}H_{27}NO_3$: 353.1991; found 353.1995.

(b) By Complexation of the Nitrone 5 with Et_2AlCl Followed by Grignard Addition: A solution of *N*-benzyl nitrone **5** (200 mg, 0.77 mmol) in diethyl ether (8 mL) was treated with Et_2AlCl [1.0 M

in hexanes, 0.84 mL, 0.8 mmol; cf. methyl case, variant (c)] at −30 °C. The reaction was continued as described under (a) [reaction time: 2.75 h between −10 °C and −30 °C, crude product with ratio **12j/14j** = 83:17], yielding **12j** as a colourless solid (154 mg, 57%, m.p. 66−69 °C).

[Note: As described for the 2-allyl derivative **12i**, the solvent was not completely removed by drying **12j** over P_4O_{10} at 10^{-3} mbar. Due to the thermal lability of **12j**, no further attempts were made at this.]

***N*-Benzyl-2-(3-butene-1-yl)-3,4-*O*-isopropylidenedioxy-5-methylpyrrolidine *N*-Oxides, (1*R*,2*S*,3*S*,4*R*,5*R*)-Isomer 11k, (1*R*,2*R*,3*S*,4*R*,5*R*)-Isomer 12k, and *N*-Benzyl-2-(1,2-*O*-isopropylidenedioxy-3-butene-1-yl)-5-methylpyrrolidine *N*-Oxide (15):** According to the standard procedure, the *N*-benzyl nitrone **5** (200 mg, 0.77 mmol) was added at a temp. of −20 °C to a solution of freshly prepared butenylmagnesium bromide (2.3 mmol) in diethyl ether (10 mL). The mixture was kept for 3.5 h at −20 °C. The usual work-up, cyclization in $CHCl_3$ (5 d, *dr* **11k/12k/15** = 22:37:41), and MPLC separation (SiO_2, 10 bar, CH_2Cl_2/MeOH = 92:8) afforded spectroscopically pure samples of **11k** (colourless crystals, 33 mg, 13%, m.p. 92−94 °C), **12k** (colourless crystals, 58 mg, 23%, m.p. 108−110 °C), and **15** (viscous oil, 58 mg, 23%). − **11k**: $[\alpha]_D^{20}$ = +23 (*c* = 1.38, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3400 (b, H_2O), 2960, 2915, 1445, 1370, 1360, 1245, 1195, 1145, 1070 cm^{-1}. − MS (EI, 70 eV): *m*/*z* (%) = 317.2 (1) [M^+], 259.2 (12), 246.2 (18), 150.1 (55), 91.1 (100). − HRMS (EI, 70 eV): exact mass calcd. for $C_{19}H_{27}NO_3$: 317.1991; found 317.1988. − **12k**: $[\alpha]_D^{20}$ = −49 (*c* = 0.22, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3400 (b, H_2O), 2920, 1370, 1195, 1045, 1030, 1000 cm^{-1}. − MS (FAB positive ion, nitrobenzyl alcohol): *m*/*z* (%) = 318.2 (100) [MH^+], 91.0 (16). − HRMS (FAB positive ion, nitrobenzyl alcohol): exact mass calcd. for $C_{19}H_{27}NO_3$ + H: 318.2069; found 318.2065. − ^{1}H and ^{13}C NMR spectroscopic data of **11k** and **12k**: see Table 2 to 4. − $C_{19}H_{27}NO_3$ (317.4): calcd. C 71.89, H 8.57, N 4.42; found for **11k** C 69.78, H 8.54, N 4.31 (correct for M + 0.5 H_2O); found for **12k** C 70.06, H 8.48, N 4.23 (correct for M + 0.5 H_2O). − **15**: $[\alpha]_D^{20}$ = +45 (*c* = 1.46, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3386 (H_2O), 2985, 2935, 1380, 1217, 1044 cm^{-1}. − ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.51 (d, $J_{5,5\text{-Me}}$ = 7.1 Hz, 3 H, 5-CH_3), 1.52, 1.67 [2 s, 6 H, $C(CH_3)_2$], 1.71 (m_c, 3 H, 3-H, 4-H_a), 1.95 (m_c, 1 H, 4-H_b), 3.23 (m_c, 1 H, 5-H), 3.45 (m_c, 1 H, 2-H), 4.25 and 5.05 (2 d, ^2J = 13.4 Hz, 2 H, CH_2Ph), 4.44 (dd, $J_{1',2'}$ = 5.7, $J_{2',3'}$ = 9.0 Hz, 1 H, 2′-H), 5.19 (d, $J_{3',4'E}$ = 10.0 Hz, 1 H, 4′-H_E), 5.21 (dd, $J_{2,1'}$ = 9.1, $J_{1',2'}$ = 5.7 Hz, 1 H, 1′-H), 5.27 (d, $J_{3',4'Z}$ = 17.1 Hz, 1 H, 4′-H_Z), 5.81 (ddd, $J_{2',3'}$ = 9.0, $J_{3',4'E}$ = 10.0, $J_{3',4'Z}$ = 17.1 Hz, 1 H, 3′-H), 7.43 (m_c, 3 H, C_6H_5), 7.63 (m_c, 2 H, C_6H_5). − ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 12.3 (5-CH_3), 22.1 (C-3), 25.9, 28.4 [$C(CH_3)_2$], 27.7 (C-4), 66.9 (C-5), 67.0 (CH_2Ph), 68.6 (C-2), 76.4 (C-1′), 79.4 (C-2′), 110.1 [$C(CH_3)_2$], 119.5 (C-4′), 128.8, 129.3, 131.5, 132.5 (C_6H_5), 134.6 (C-3′). − $C_{19}H_{27}NO_3$ (317.4): calcd. C 71.89, H 8.57, N 4.42; found C 67.90, H 8.55, N 4.02 (correct for M + 1.0 H_2O). − MS (FAB positive ion, nitrobenzyl alcohol): *m*/*z* (%) = 318.2 (100) [MH^+], 91.0 (28). − HRMS (FAB positive ion, nitrobenzyl alcohol): exact mass calcd. for $C_{19}H_{27}NO_3$ + H: 318.2069; found 318.2060.

(5*E*)-(2*R*,3*R*,4*S*)-2-(*N*-Benzylhydroxylamino)-3,4-*O*-isopropylidenedioxy-5,7-octadiene (14i): An NMR tube containing **12i** (10 mg, 0.03 mmol) dissolved in [D_6]DMSO was placed into the spectrometer and heated to 80 °C. After 15 min, a ^{1}H NMR spectrum was recorded, showing quantitative transformation of **12i** into **14i**. − ^{1}H NMR (300.1 MHz, [D_6]DMSO, 80 °C): δ = 0.99 (d, $J_{1,2}$ = 6.5 Hz, 3 H, 1-H), 1.31, 1.42 [2 s, 6 H, $C(CH_3)_2$], 2.90 (m, 2-H), 3.82 and 3.90 (2 d, ^2J = 13.8 Hz, 2 H, CH_2Ph), 4.27 (dd, $J_{2,3}$ = 8.7, $J_{3,4}$ = 5.6 Hz, 1 H, 3-H), 4.49 (dd, $J_{3,4}$ = 5.6, $J_{4,5}$ = 8.1 Hz, 1 H, 4-H), 5.08 (d, $J_{7,8E}$ = 10.0 Hz, 1 H, 8-H_E), 5.21 (d, $J_{7,8Z}$ = 16.4 Hz, 1 H, 8-H_Z), 5.76 (dd, $J_{4,5}$ = 8.1, $J_{5,6}$ = 14.6 Hz, 1 H, 5-H), 6.22 (dd, $J_{5,6}$ = 14.6, $J_{6,7}$ = 10.3 Hz, 1 H, 6-H), 6.34 (dt, $J_{6,7}$ = $J_{7,8E}$ = 10.3, $J_{7,8Z}$ = 16.4 Hz, 1 H, 7-H), 7.25 (m_c, 5 H, C_6H_5). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.5 (C-1), 25.8, 28.4 [$C(CH_3)_2$], 59.5 (C-2), 59.9 (CH_2Ph), 79.1 (C-4), 79.8 (C-3), 108.9 [$C(CH_3)_2$], 118.5 (C-8), 127.1, 128.2, 129.5 (C_6H_5), 134.7 (C-6), 136.0 (C-7), 138.3 (C_6H_5).

(*E*)-(2*R*,3*R*,4*S*)-2-(*N*-Benzylhydroxylamino)-3,4-*O*-isopropylidenedioxy-6-phenyl-5-hexene (14j): A solution of **12j** (103 mg, 0.29 mmol) in DMSO was stirred for 30 min at 80 °C. After removal of the solvent under reduced pressure (50−60 °C, 0.25 mbar), the residue was purified by flash chromatography (SiO_2, ethyl acetate/petroleum ether = 1:1) yielding **14j** (82 mg, 76%) as a colourless oil. − $[\alpha]_D^{20}$ = +6 (*c* = 0.51, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3407 (b), 2986, 1453, 1371, 1245, 1216, 1064, 1040 cm^{-1}. − ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.09 (d, $J_{1,2}$ = 6.6 Hz, 3 H, 1-H), 1.43, 1.57 [2 s, 6 H, $C(CH_3)_2$], 3.08 (dq, $J_{1,2}$ = 6.6, $J_{2,3}$ = 9.3 Hz, 1 H, 2-H), 3.85 and 4.01 (2 d, ^2J = 13.1 Hz, 2 H, CH_2Ph), 4.35 (dd, $J_{2,3}$ = 9.3, $J_{3,4}$ = 5.7 Hz, 1 H, 3-H), 4.60 (dd, $J_{3,4}$ = 5.7, $J_{4,5}$ = 9.0 Hz, 1 H, 4-H), 6.09 (s, 1 H, OH), 6.17 (dd, $J_{4,5}$ = 9.0, $J_{5,6}$ = 15.8 Hz, 1 H, 5-H), 6.56 (d, $J_{5,6}$ = 15.8 Hz, 1 H, 6-H), 7.32 (m_c, 10 H, 2 C_6H_5). − ^{13}C NMR (125.8 MHz, [D_6]DMSO): δ = 10.0 (C-1), 25.8, 28.4 [$C(CH_3)_2$], 59.4 (C-2), 59.9 (CH_2Ph), 78.4 (C-4), 78.7 (C-3), 107.6 [$C(CH_3)_2$], 126.5 (C-5), 132.5 (C-6), 126.4, 127.7, 128.5, 129.0, 136.2, 139.5 (C_6H_5). − $C_{22}H_{27}NO_3$ (353.5): calcd. C 74.26, H 7.70, N 3.96; found C 71.31, H 7.74, N 3.71 (correct for M + 1.0 H_2O).

(2*S*,3*S*,4*R*,5*R*)-*N*-Benzyl-3,4-dihydroxy-2,5-dimethylpyrrolidine *N*-Oxide (16a): Under argon, **11a** (93 mg, 0.31 mmol) was dissolved in a mixture of water (2 mL), MeOH (2 mL), and conc. HCl (0.25 mL). The clear solution was stirred for 1 d at room temp. The crude product was purified using a column (5 cm × 1.2 cm) packed with Dowex 50WX8 (H^+ form). The resin was first washed with MeOH (50 mL) and water (50 mL), before **16a** was eluted using NH_3 (1 N, 50 mL). Concentration in vacuo afforded a colourless solid (75 mg), which was recrystallized from MeOH/diethyl ether. This yielded colourless needles of **16a** suitable for X-ray analysis (62 mg, 84%, m.p. 186 °C). − $[\alpha]_D^{20}$ = 0 (*c* = 0.10, MeOH). − IR (KBr): $\tilde{\nu}$ = 3190 (b, OH), 3050, 2980, 2940, 1495, 1455, 1445, 1430, 1365, 1165, 1135, 1090 cm^{-1}. − ^{1}H NMR (500.1 MHz, MeOD): δ = 1.57 (d, $J_{2,2\text{-Me}}$ = $J_{5,5\text{-Me}}$ = 6.4 Hz, 6 H, 2-CH_3, 5-CH_3), 3.18 (m_c, 2 H, 2-H, 5-H), 3.92 (m_c, 2 H, 3-H, 4-H), 4.23 (s, 2 H, CH_2Ph), 7.47 (m_c, 5 H, C_6H_5). − ^{13}C NMR (125.8 MHz, MeOD): δ = 11.5 (2-CH_3, 5-CH_3), 66.1 (CH_2Ph), 73.4 (C-2, C-5), 73.5 (C-3, C-4), 130.4, 131.2, 132.9 (C_6H_5). − $C_{13}H_{19}NO_3$ (237.3): calcd. C 65.80, H 8.07, N 5.90; found C 65.66, H 8.10, N 5.91.

X-ray Structural Analysis of 16a:[89] $C_{13}H_{19}NO_3$ (237.3), colourless needle (1.0 mm × 0.1 mm × 0.1 mm), *a* = 9.890(2) Å, *b* = 11.245(2) Å, *c* = 11.377(2) Å, *V* = 1265.3(4) Å^3, *T* = 293(2) K, orthorhombic, space group *P*nma, *Z* = 4, K: μ = 0.088 mm^{-1}. Intensity data were collected using a Nicolet P3 diffractometer with graphite-monochromated Mo-K_α radiation (0.71073 Å). The structure was solved with direct methods using SHELXS-86.[90] Refinement (full-matrix least-squares) was performed against F^2 using SHELXL-93.[91] 1173 measured reflections in the range of 2.55 to 24.99°, 1173 unique reflections and 932 with $F_O > 2\sigma(F_O)$. *R*1 [$F_O > 2\sigma(F_O)$] = 0.0645, *wR*2 for all data = 0.1315, GoF = 1.239, residual electron density: 0.19 e/Å^3.

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