# Preparation of *N*-Glycosylhydroxylamines and Their Oxidation to Nitrones for the Enantioselective Synthesis of Isoxazolidines[‡]

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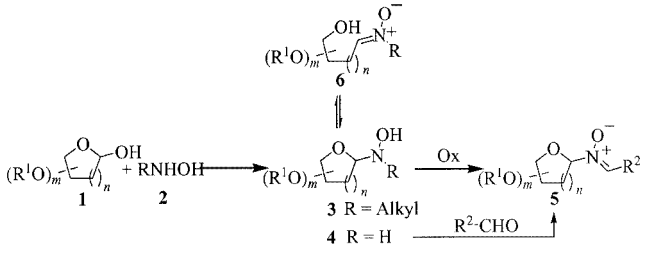
**Keywords:** Hydroxylamines / Sugars / Nitrones / Chiral auxiliaries / Enantioselectivity

*N*-benzyl- and *N*-methyl-*N*-glycosylhydroxylamines **3a–i** were conveniently obtained by reaction of sugars with *N*-substituted hydroxylamines according to a novel procedure. Subsequent oxidation occurred at the alkyl group, selectively affording the corresponding *C*-phenyl- and *C*-unsubstituted *N*-glycosylnitrones. *C*-phenyl-*N*-glycosylnitrones **10** and **13** underwent highly stereoselective 1,3-dipolar cycloaddition with dimethyl maleate, with the sugar moiety acting as a chiral auxiliary. Final removal of the glycosyl moiety afforded enantiopure enantiomeric isoxazolidines **17** and ***ent*-17** which are oxa-analogues of proline diester derivatives.



## Introduction

Suitably protected carbohydrate derivatives, and lactols in general, are valuable tools for the synthesis of chiral nitrogen heterocycles. In particular, they can be readily converted into chiral cyclic nitrones,[1] or into *N*-glycosylhydroxylamines, which, in turn, are precursors of chiral acyclic nitrones.[2] With this in mind, *N*-glycosylhydroxylamines **4** (R = H) (Scheme 1) have received considerable attention as chiral equivalents of simple hydroxylamine. The glycosyl moiety acts as an auxiliary which can be easily removed by acid treatment at an advanced stage of a synthetic sequence, i.e. after the hydroxylamine moiety has reacted. This concept was introduced by Vasella,[3] and then extensively applied by the same group[4] and others,[5] thus demonstrating the synthetic utility of intermediates **4**. The reaction between a suitably protected sugar **1** with a free OH at the anomeric carbon atom (more generally a lactol) and hydroxylamine hydrochloride (**2**, R = H) affords *N*-glycosylhydroxylamines **4** (Scheme 1). Ribosyl and mannofuranosyl derivatives were isolated as *E*/*Z*-oxime mixtures;[3][4a] however, they can be more conveniently employed directly in the synthesis of *C*-unsubstituted-, *C*-alkoxycarbonyl-, *C*-alkyl-, *C*-phosphonoyl- and *C*-aryl-*N*-glycosylnitrones **5** by condensation with a carbonyl compound.[3–5] These nitrones have usually been prepared in situ, and reacted with olefins in 1,3-dipolar cycloadditions, to afford, ultimately, enantioenriched isoxazolidines.[3,4a–4e,5a–5f] Alternatively, they have undergone nucleophilic addition reactions with dialkyl phosphites, affording *N*-hydroxy-*N*-glycosylaminophosphonates.[4f–4i]




Scheme 1

Conversely, to the best of our knowledge, *N*-substituted *N*-glycosylhydroxylamines **3** (R = Alkyl) have been the subject of only a few reports, and these deal specifically with *N*-benzyl derivatives. Merino and co-workers have performed the synthesis of several compounds of structure **3** (R = $CH_2Ph$) by reaction of the corresponding monosaccharides **1** with 1.5 equiv. of *N*-benzylhydroxylamine in the presence of $MgSO_4$ (3 equiv.) and $ZnCl_2$ (1.5 equiv.) (Scheme 1).[6] Dondoni and co-workers have synthesized *N*-arabinosyl-*N*-benzylhydroxylamine by a modification of the above procedure,[7] and have also, while this work was in progress, reported a convenient solventless transformation of four pentofuranosyl derivatives into the corresponding hydroxylamines in short times by heating the reagents at high temperature.[8]

In this paper, we report full details of our own results on the synthesis of several *N*-benzyl-*N*-glycosylhydroxylamines **3** (R = $CH_2Ph$), using a methodology which can be extended to other *N*-alkyl congeners (Scheme 1 and Table 1).[9] These compounds are versatile intermediates in

[‡] Chiral Nitrones from Lactols, 1.

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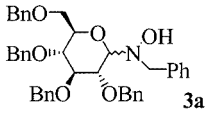
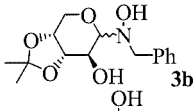
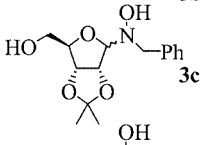
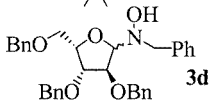
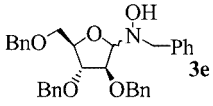
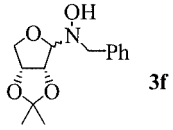
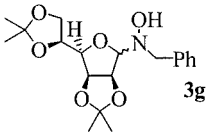
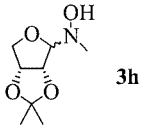
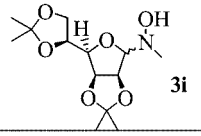
organic synthesis: they can be oxidized to *N*-glycosylnitrones **5** where the glycosyl moiety behaves as a chiral auxiliary, or they themselves can act as masked acyclic chiral nitrones.[8,9] Exemplification of the former behaviour is also reported in this article.

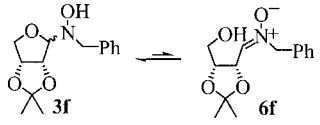
Table 1. Synthesis of *N*-alkyl-*N*-glycosylhydroxylamines from the corresponding lactols

| Entry | Lactol | RNHOH | Product | Yield | α/β |
|---|---|---|---|---|---|
| 1 | **1a** | **2a** R = Bn |  **3a** | 79% | 0/100 |
| 2 | **1b** | **2a** |  **3b** | 61% | 75/25 |
| 3 | **1c** | **2a** |  **3c** | 66% | 0/100 |
| 4 | **1d** | **2a** |  **3d** | 60% | 80/20 |
| 5 | **1e** | **2a** |  **3e** | 66% | 85/15 |
| 6 | **1f** | **2a** |  **3f** | 88% | 0/100 |
| 7 | **1g** | **2a** |  **3g** | 73% | 100/0 |
| 8 | **1f** | **2b** R = Me |  **3h** | 71% | 0/100 |
| 9 | **1g** | **2b** |  **3i** | 70% | 100/0 |

## Results and Discussion

The *N*-benzyl-*N*-glycosylhydroxylamines **3a**−**g** (Table 1, Entries 1−7) were generally obtained by reacting the corresponding sugar derivative **1a**−**g** with 1.2 equiv. of *N*-benzylhydroxylamine hydrochloride (**2a**) in dry pyridine at room temperature for 12−15 h. The same method can be extended to the synthesis of other *N*-alkyl-*N*-glycosylhydroxylamines, as demonstrated by the synthesis of *N*-methyl-*N*-glycosylhydroxylamines **3h**−**i** (Table 1, Entries 8−9) when *N*-methylhydroxylamine hydrochloride (**2b**) was used. The products were isolated simply by filtration and removal of the solvent, and were found to be spectroscopically pure, except for some residual pyridinium salts, which were readily eliminated by elution through a short pad of silica gel. The *N*-glycosylhydroxylamines were obtained as mixtures of the two equilibrating anomers. In several cases, the equilibrium lies far over to one side, with the thermodynamically most stable anomer being the one only detectable by $^1$H NMR spectroscopy (Table 1, Entries 1, 3 and 6−9). The differences in experimental conditions with respect to the above reported alternative procedures may account for the observed discrepancies between our results and the previously reported anomeric composition of compounds **3a**, **3d** and **3e**.[10]

The anomeric equilibration must occur through an open-chain nitrone, according to previous hypotheses[6] and findings,[7] in analogy to the well-known behaviour of *N*-(2-hydroxyalkyl)nitrones, which undergo a ring-chain tautomerism to the corresponding *N*-hydroxyoxazolidines via a formal intramolecular 1,3-OH addition to the nitrone group.[11] The open-chain tautomer (i.e. the nitrone form) of *N*-glycosylhydroxylamines is usually hardly detectable in the equilibrium mixture by NMR spectroscopy, meaning that the ring-chain equilibrium is heavily shifted towards the cyclic forms (Scheme 2). However, in a few cases, a signal (doublet) of low intensity in the range δ = 7.0−6.5 ppm, which may be assigned to the $Csp^2$-H resonance, demonstrates the presence of the open-chain nitrone. Among compounds **3** in Table 1, these signals are most evident for compounds **3d**, **3f** and **3h**. For example, the $^1$H NMR spectrum of compound **3f** in $CDCl_3$ solution at equilibrium showed 6% of the open-chain nitrone **6f** (Scheme 2, see Exp. Sect.).[9] An analogous observation has recently been reported for tribenzyl xylosyl-, ribosyl- and lyxosylhydroxylamine derivatives, which showed doublets resonating at δ = 6.75, 6.93, and 6.81 ppm, respectively.[8]



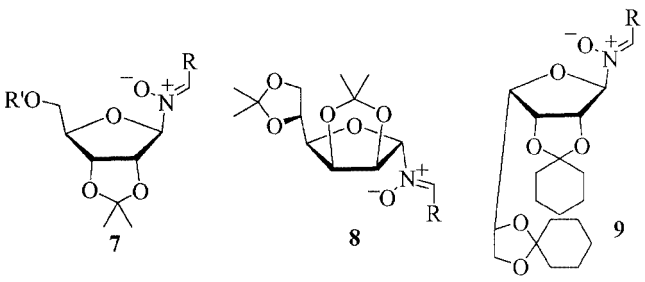

Scheme 2

Oxidation of *N*-glycosylhydroxylamines **3** gives an alternative access to *N*-glycosylnitrones,[3−5] particularly to *C*-phenyl and *C*-unsubstituted ones. Indeed, it has been observed that oxidation of **3g** occurs with complete regioselectivity affording the corresponding *C*-phenyl-*N*-mannofuranosylnitrone.[6] The utility of *N*-glycosylnitrones in enantioselective synthesis has been investigated in reactions with dipolarophiles[3,4a] and nucleophiles,[4f−4i] and both cycloaddition reactions[4c,4e,5a−5f] and nucleophilic additions[4h,5g−5i] have found applications to the synthesis of relevant chiral compounds. Concerning cycloaddition reactions, it has mainly been *N*-glycosylnitrones derived from

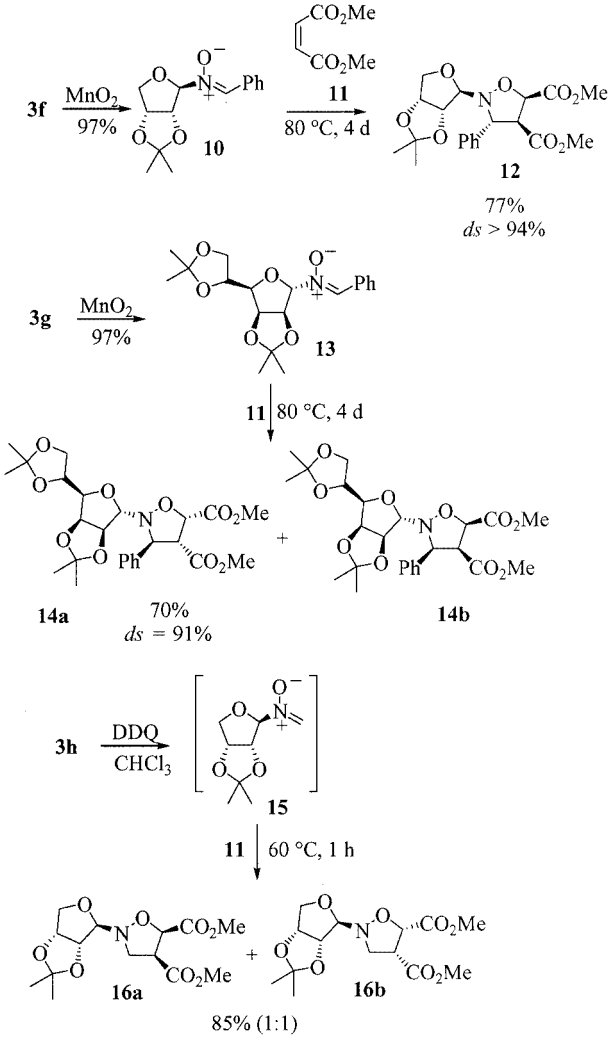
formaldehyde (*C*-unsubstituted)[3,5a,5f] or from glyoxylates (*C*-alkoxycarbonyl)[4c,4e,5b−5e] which have been used, and these compounds usually showed very interesting stereoselectivities. Conversely, *C*-aryl-*N*-glycosylnitrones have been synthesized,[4h,4i,6] but their behaviour in cycloaddition reactions has not been studied, the only exception being the cycloadditions of unprotected *C*-phenyl-*N*-glucosylnitrone to monosubstituted alkenes and maleimides, which generally afforded low yields of adducts.[12] Moreover, among aldonitrones with simple *C*-substituents, only *C*-methyl-*N*-ribosyl- and *N*-mannosyl- nitrones, derived from acetaldehyde, have been used in cycloaddition to methyl methacrylate, and these reactions gave a complex mixture of all four possible adducts.[3,4a] The cycloadditions showed good diastereocontrol over the formation of the isoxazolidine C5 stereogenic center, since the two main components derived from attack at the same diastereoface of methacrylate, but very poor, if any, control of chirality at the C3 carbon. *E*/*Z* Configurational isomerization of nitrones under the reaction conditions was invoked in order to account for this lack of selectivity.[3,4a] Thus, we decided to study the degree of asymmetric induction that could be achieved in the cycloaddition of *C*-phenyl-*N*-glycosylnitrones to dimethyl maleate, leading to simple trisubstituted isoxazolidines with simultaneous formation of three new stereogenic centers.

In addition, we wanted to clarify the structural features of the glycosyl moiety required for optimal stereoselectivity. From the literature data, it is apparent that 2,3-*cis*-dioxyfuranosides protected as ketals all perform well in terms of diastereocontrol (Scheme 3).[3−5] The opposite diastereofacial preference, with similar selectivities, shown by *N*-D-ribosyl- **7** and *N*-D-mannosyl- **8** nitrones,[4a] suggests that the configuration at C2 and C3 of the sugar moiety is crucial in determining the face of attack of the dipolarophile, while the branch and stereochemistry at C4 play a negligible role. Confirmation of this assumption rests in the finding that *N*-D-gulosylnitrone **9** showed analogous stereofacial preference as *N*-D-ribosylnitrone **7** (and *N*-L-gulosylnitrone, which can be synthesized from D-glucurono-6,3-lactone, the same preference as the D-mannose derivative **8**).[5b] The simplest way to prove this assumption was to test the behaviour of the nitrone obtained by oxidation of *N*-D-erythrosylhydroxylamine **3f**, and to prove its complementarity, in terms of diastereoselectivity, to that derived from *N*-D-mannosylhydroxylamine **3g** (i.e. **8**, R = Ph).




Scheme 3

As anticipated, oxidation of *N*-benzyl-*N*-glycosylhydroxylamines **3f** and **3g** with $MnO_2$ [13] occurred with complete regioselectivity, affording the corresponding nitrones **10** and **13** in nearly quantitative yields as stable, crystalline compounds (Scheme 4). These *N*-glycosylnitrones reacted smoothly with dimethyl maleate (**11**) by heating at 80 °C in toluene (Scheme 4).




Scheme 4

The reaction of nitrone **10** with **11** afforded, in high yield and selectivity, the isoxazolidine **12**, which was by far the major isomer (> 94% diastereoselectivity). Traces of two minor isomers were identified in the reaction mixture, and they were collected as an inseparable mixture. The structure of compound **12** was unambiguously assigned on the basis of X-ray analysis (Figure 1). The $^1$H NMR spectrum of **12** shows that the proton at C4 of the isoxazolidine ring resonates at δ 3.83 ppm as a triplet with the same coupling constant $J$ = 9.0 Hz as the vicinal protons at C5 and C3, even though it has opposite relative relationships with them (*cis* and *trans*, respectively). This finding is in agreement with the large dihedral angle H−C3−C4−H measured in the crystal structure (164.4°), suggesting that the H,H-anti-

periplanar conformation around the C3−C4 bond should also be the most stable in solution.

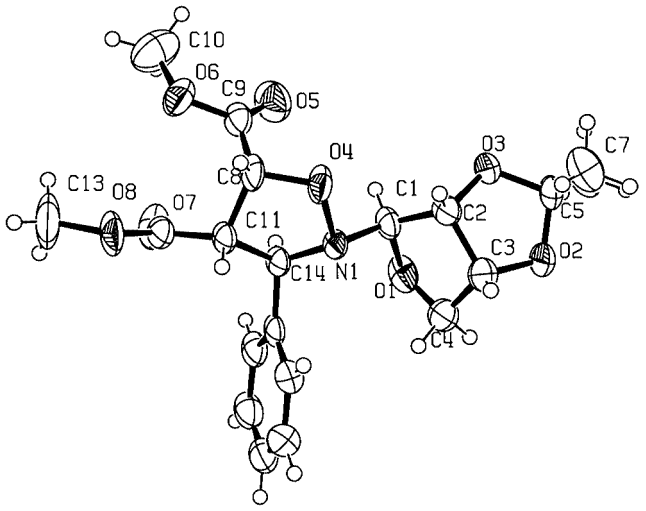



Figure 1. Crystal structure of cycloadduct **12**

The cycloaddition of nitrone **13** afforded, in good yield, a mixture of the two diastereoisomeric isoxazolidines **14a**−**b** in a 11.6:1 ratio. A third isomer, present in traces in the reaction mixture, was recovered in 0.5% yield after separation by flash column chromatography.[14] The major isomer **14a** was assigned the structure depicted in Scheme 4, after comparison of its $^1$H NMR spectrum with that of **12**. The two spectra show striking similarities: H3, H4 and H5 protons of the isoxazolidine ring resonate at almost the same frequencies (δ = 4.62 vs. 4.50 ppm, 3.83 vs. 3.76 ppm and 4.93 vs. 4.91 ppm in **12** and **14a**, respectively) and with almost identical coupling constants ($J_{3-4} = J_{4-5} = 9.0$ Hz vs. 8.9 Hz in **12** and **14a**, respectively). This suggests that both adducts possess the same relative stereochemistry at the isoxazolidine ring, which was ultimately proved by detachment of the *N*-glycosyl chiral auxiliary (see below). The minor isomer **14b** was assigned the all-*cis* relative configuration at the isoxazolidine stereocenters on the basis of the high difference in the chemical shifts of the two methyl signals of the methoxycarbonyl groups (δ = 3.78 ppm and 3.21 ppm for **14b** vs. δ = 3.78 ppm and 3.65 ppm for **12** and 3.76 ppm and 3.62 ppm for **14a**). The strong upfield shift of one methyl signal suggests that it falls in the shielding cone of the phenyl group, thus disclosing the *cis* phenylmethoxycarbonyl relationship. The absolute stereochemistry at the isoxazolidine stereocenters of **14b** as reported in Scheme 4 has been tentatively assigned on the basis of considerations on the preferred approach of reagents (see below).

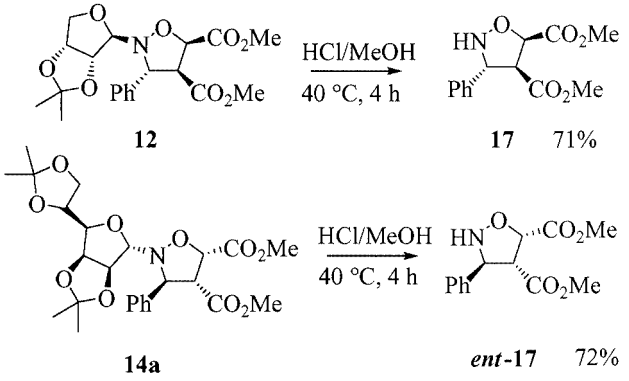
These results clearly show that both cycloadditions of nitrones **10** and **13** with dimethyl maleate occur with exceptionally high diastereoselectivity, unprecedented for cycloadditions of related *N*-glycosyl aldonitrones.

We also wanted to test the possibility of accessing *C*-unsubstituted *N*-glycosylnitrones from *N*-methyl-*N*-glycosylhydroxylamines. The regioselectivity of such an oxidation was by no means certain, having never been carried out before. Oxidation of hydroxylamine **3h** with $MnO_2$ in $CH_2Cl_2$ led to a complex mixture of products. However, when treated with DDQ in $CHCl_3$, **3h** rapidly gave the corresponding aldonitrone **15** with complete regioselectivity. Nitrone **15** was identified by the signal at δ = 6.60 ppm in the $^1$H NMR spectrum of the reaction mixture, but its complete characterization was prevented by its instability. Indeed, it decomposed on attempted purification on silica or alumina, and it was unstable even on standing in solution or on concentration of the product mixture. However, when dimethyl maleate (**11**) was added to the reaction mixture, nitrone **15** reacted directly, and very quickly, to afford the adducts **16** in excellent yield (Scheme 4). In contrast with the above results, the reaction of nitrone **15** with **11** is characterized by a virtually complete absence of diastereoselectivity, adducts **16a** and **16b** being formed in ca. 1:1 ratio. The two diastereomeric adducts were not separable by column chromatography, and were characterized by their spectroscopic data in the mixture, which were very similar. Their diastereomeric nature was ascertained by recording $^1$H and $^{13}$C NMR spectra at high temperatures, thus excluding the possibility of their being rotamers or invertomers.

A few, but nevertheless striking, differences, which deserve to be noted here, arise from a comparison of the above findings with the results of cycloadditions of related *N*-glycosylnitrones to methyl methacrylate reported by Vasella:[3,4a,4i] (*i*) the high diastereoselectivity of additions of nitrones **10** and **13** to **11** vs. the poor selectivity reported for a *C*-methyl-substituted nitrone;[4a] (*ii*) the lack of stereoselectivity in the reaction of nitrone **15** with **11** vs. the good selectivity reported for a related *C*-unsubstituted nitrone.[3,4a] Thus, the outcome of the cycloadditions to *N*-glycosylnitrones appears to be dramatically influenced either by the nature of the dipolarophile or the substituents at the nitrone carbon atom. However, the sense of chiral induction at C5 of the isoxazolidine ring is the same when selective additions occur, i.e. both compound **14a** and the major adduct obtained from the *C*-unsubstituted nitrone with the same *N*-mannosyl chiral auxiliary residue with methyl methacrylate[4a] possess the (5*S*) absolute configuration. This feature makes *N*-glycosylnitrones useful tools for enantioselective synthesis of isoxazolidines with predictable selectivity.

In order to get a decisive proof of the opposite chiral induction achieved by use of *N*-D-erythrosyl and *N*-D-mannosyl auxiliaries, and, at the same time, to demonstrate their utility in enantioselective synthesis, the adducts **12** and **14a** were separately subjected to acidic treatment according to Vasella's method (Scheme 5).[3,4] Removal of the glycosyl residue with HCl afforded, respectively, 2-unsubstituted isoxazolidines **17** and ***ent*-17** which, as anticipated, were enantiomers. Compounds **17**, which possess three stereogenic centers, newly-created with high stereocontrol, can be considered as oxa-analogues of proline diesters, besides being valuable chiral intermediates suitable for further synthetic transformations. This result, besides confirming the structure of compound **14a**, demonstrates that maleate **11** ap-




Scheme 5

proaches the opposite diastereofaces of the two nitrones **10** and **13**, due to the complementary behaviour of the two glycosidic fragments.

The stereoselectivity of the cycloadditions to *N*-glycosylnitrones has been rationalized by Vasella in terms of a preferred attack of the dipolarophile to the less sterically-hindered face of the nitrone, in a conformation which puts the ring oxygen *anti* and the nitrone oxygen atom in the "endo" position. This conformation of the nitrone allows a coplanar arrangement of the C1−O bond σ*-orbital with the doubly-occupied nonbonding orbital developing at the nitrogen atom during the reaction, and should be the more reactive based on a stabilizing "kinetic anomeric effect".[4a,4i] Semi-empirical AM1 calculations on a model nitrone suggested that the proposed reacting conformation is also very close to the most stable conformer in terms of both geometry and energy.[4i] However, rationalization of selectivities based on different models has also been proposed.[5b]

In order to get an insight into the mechanism of the reactions performed in the present study, an ab initio computational study was performed on the nitrones **10** and **13** (Figure 2) and on the transition-state of the cycloaddition of **10** to dimethyl maleate (**11**) (Figure 3).[15]

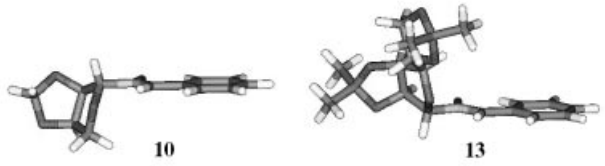



Figure 2. Minimum energy conformers of nitrones **10** and **13**

The two structures depicted in Figure 2, the lowest energy conformers of **10** and **13** respectively (dihedral drive along the N−C1 bond, HF STO-3G), show that the less hindered face of the nitrone double bond is the *Re* face for **10** and the *Si* face for **13**, according to the experimental results. The obtained lowest energy conformers are in perfect agreement with that reported by Vasella for a similar model nitrone[4i] [dihedral angle φ(O-*N*−C−O) = 219° for nitrone **10** vs. 221°].

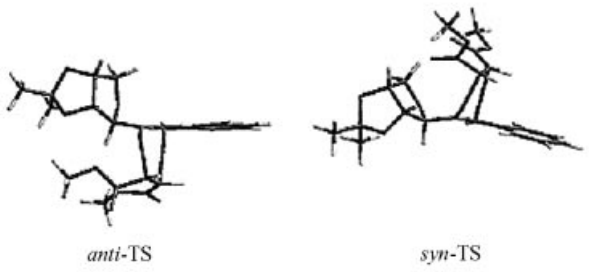



Figure 3. Minimum energy transition-states for the cycloaddition of **10** with **11** (*endo* approaches)

Transition-state modeling (HF STO-3G level)[15] for the two possible *endo* approaches of maleate to nitrone **10** gave the minimized structures depicted in Figure 3 for the approaches to the *Re* face (*anti*-TS) and to the *Si* face (*syn*-TS) of nitrone, respectively. Calculations resulted in a lower activation energy ($\Delta\Delta E^{\neq}$ = 0.8 kcal·mol$^{-1}$) for the former TS, in qualitatively good agreement with the observed selectivity. The two transition-structures were found to have only one negative eigenvalue, with the corresponding eigenvector involving the formation of the newly created C−C and C−O bonds (imaginary frequencies ν = −339 for both *anti*-TS and *syn*-TS). The structures of the two transition-states are consistent with a rather asynchronous process: in both cases the C−O bond length (*anti*-TS: 2.044 Å; *syn*-TS: 1.962 Å) is much shorter than that of the forming C−C bond (*anti*-TS: 2.766 Å; *syn*-TS: 2.782 Å), in agreement with the results of a previous study on 1,3 dipolar cycloaddition reaction of nitrones with electron poor olefins.[16] That we found the *anti*-TS structure to be preferred, substantiates the TS model proposed by Vasella.[4i] However, these results suggest that the diastereofacial selectivity is determined mainly by steric factors, since the early nature of the TS, with negligible nitrogen pyramidalization, appears to make stereoelectronic factors less important.

## Conclusion

A highly diastereo- and enantioselective synthesis of 3,4,5-trisubstituted isoxazolidines has been accomplished by means of a carbohydrate-derived chiral auxiliary approach, which demonstrates the great potential of cycloaddition reactions applied to *C*-phenyl-*N*-glycosylnitrones. The high degree of diastereoselectivity induced by the sugar moiety allows the synthesis of adducts which are readily converted into the enantiopure targets by removal of the chiral auxiliary. The sense of chiral induction in the final isoxazolidine is easily predictable on the basis of the configuration at C2 and C3 of the sugar, locked in its furanosidic form, as proved by the complementary behaviour of *N*-erythrosyl and *N*-mannosyl nitrones.

This study demonstrates that isopropylidene erythrose is a convenient, versatile and low molecular-weight chiral auxiliary for nitrone reactions. The *N*-erythrosyl nitrone has the obvious advantage of being easily accessible in both en-

antiomeric forms, which therefore must lead exactly to the same results and opposite configuration in reactions with achiral substrates, starting from D-arabinose and L-arabinose, both equally inexpensive, using the same synthetic procedure.

## Experimental Section

**General Remarks:** All reactions requiring anhydrous conditions were carried out under nitrogen, and solvents were appropriately dried before use. $R_f$ values refer to TLC on 0.25-mm silica gel plates (Merck $F_{254}$) obtained using the same eluent as in the separation of the compound by flash column chromatography (FCC), except where indicated. Melting points (m.p.) were determined with an RCH Kofler apparatus. Optical rotation measurements were performed (at the equilibrium for tautomeric compounds) with a Jasco DIP-370 polarimeter. $^1$H and $^{13}$C NMR spectra (in $CDCl_3$ solution, unless otherwise stated) were recorded at 200 MHz and 50.3 MHz, respectively, with a Varian Gemini spectrometer; the chemical shifts for $^1$H and $^{13}$C NMR spectra are given in ppm from TMS. IR spectra were recorded with a Perkin−Elmer 881 spectrophotometer. Mass spectra (EI, 70 eV) were recorded with a QMD 1000 Carlo Erba instrument by direct inlet. Elemental analyses were performed with a Perkin−Elmer 240 C instrument.

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (**1a**) was purchased from Aldrich, 3,4-*O*-isopropylidene-D-arabinopyranose (**1b**),[17] 2,3-*O*-isopropylidene-D-ribofuranose (**1c**),[18] 2,3,5-tri-*O*-benzyl-L-xylofuranose (**1d**),[19] 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**1e**),[20] 2,3-*O*-isopropylidene-D-erythrose (**1f**)[21]and (2,3:5,6)-di-*O*-isopropylidene-D-mannofuranose (**1g**)[22] were prepared according to published procedures.

**General Procedure for the Synthesis of *N*-Alkyl-*N*-glycosylhydroxylamines:** *N*-Benzylhydroxylamine hydrochloride (1.2 equiv.) and 3 Å molecular sieves (800 mg) were added to a 0.3 M solution of lactol **1** (1 mmol) in dry pyridine. The mixture was stirred at room temperature overnight , then diluted with $CH_2Cl_2$ (3 mL), filtered through Celite, and concentrated. The resulting product was purified by chromatography over a short pad of silica using the eluent reported for $R_f$ values. Variations from the general procedure, which were applied in the syntheses of **3a**, **3c** and **3d**, are given in the relevant Exp. Sect.

***N*-Benzyl-2,3,4,6-tetra-*O*-benzyl-*N*-hydroxy-β-D-glucopyranosylamine (3a):** From *N*-benzylhydroxylamine hydrochloride (2.2 equiv.), 48 h. White solid, 510 mg, 79% yield. $R_f$ (ethyl acetate/petroleum ether, 1:3) = 0.49. M.p. 113−114 °C. $[\alpha]_D^{26}$ = +20.5 (*c* = 1.10, $CH_2Cl_2$). IR ($CHCl_3$): $\tilde{\nu}$ = 3545, 3511, 3034, 2911, 1450, 1362, 1054, 1028 cm$^{-1}$. $^1$H NMR: δ = 7.48−7.17 (m, 25 H), 5.11−4.74 (m, 5 H), 4.67−4.53 (m, 3 H), 4.33−4.04 (m, 3 H), 3.90−3.84 (m, 1 H), 3.82−3.42 (m, 5 H) ppm. $^{13}$C NMR: δ = 139.0 (s), 138.4 (s), 138.3 (s), 137.5 (s, 2 C), 129.4−127.6 (d, 25 C), 93.0 (d), 86.1 (d), 78.5 (d), 78.0 (d), 76.6 (d), 75.9 (t), 75.2 (t), 74.7 (t), 73.7 (t), 69.3 (t), 60.4 (t) ppm. MS: *m*/*z* (%) = 645 (0.6) [M$^+$], 181 (29), 91 (100). $C_{41}H_{43}NO_6$ (645.82): calcd. C 76.25, H 6.71, N 2.17; found C 75.86, H 6.90, N 2.11.

***N*-Benzyl-*N*-hydroxy-3,4-*O*-(1-methylethylidene)-D-arabinopyranosylamine (3b):** White solid, 180 mg, 61% yield (as a 3:1 α/β anomeric mixture in $CDCl_3$ solution). $R_f$ (ethyl acetate) = 0.26. M.p. 144−157 °C. $[\alpha]_D^{27}$ = −68.0 (*c* = 1.00, $CH_2Cl_2$). IR ($CDCl_3$): $\tilde{\nu}$ = 3550, 3400, 3040, 2990, 2910, 1455, 1380, 1218, 1125, 1080 cm$^{-1}$. $^1$H NMR: δ = 7.38−7.29 (m, 5 H), 4.49−3.69 (m, 8 H), 1.38 (s, 3 H), 1.35 (s, 3 H) ppm. $^{13}$C NMR: δ = (*major anomer*) 136.7 (s), 129.8 (d, 2 C), 128.4 (d, 2 C), 127.6 (d), 109.9 (s), 91.9 (d), 78.9 (t), 73.4 (d), 69.7 (d), 65.3 (d), 59.7 (t), 28.0 (q), 26.0 (q); (*minor anomer*) 136.3 (s), 129.6 (d, 2 C), 129.1 (d, 2 C), 128.6 (d), 111.9 (s), 85.1 (d), 80.4 (t), 71.4 (d), 69.0 (d), 64.8 (d), 60.5 (t), 27.0 (q), 24.6 (q) ppm. MS: *m*/*z* (%) = 295 (1) [M$^+$], 280 (4), 115 (20), 91 (100), 59 (55). $C_{15}H_{21}NO_5$ (295.38): calcd. C 61.00, H 7.17, N 4.74; found C 60.51, H 7.34, N 4.57.

***N*-Benzyl-*N*-hydroxy-2,3-*O*-(1-methylethylidene)-β-D-ribofuranosylamine (3c):** From *N*-benzylhydroxylamine (2.2 equiv.). White solid, 195 mg, 66% yield. $R_f$ (ethyl acetate) = 0.45. M.p. 102−103 °C. $[\alpha]_D^{24}$ = −43.2 (*c* = 1.00, $CH_2Cl_2$). IR ($CDCl_3$): $\tilde{\nu}$ = 3244, 3050, 2991, 2905, 1455, 1371, 1100, 1076 cm$^{-1}$. $^1$H NMR: δ = 7.46−7.28 (m, 5 H), 4.84 (m, 2 H), 4.61 (s, 1 H), 4.39−4.34 (m, 1 H), 3.97 (m, 2 H), 3.69 (m, 2 H), 1.51 (s, 3 H), 1.32 (s, 3 H) ppm. $^{13}$C NMR: δ = 136.1 (s), 129.7 (d, 2 C), 128.3 (d, 2 C), 127.5 (d), 112.4 (s), 101.0 (d), 87.2 (d), 83.5 (d), 81.7 (d), 63.8 (t), 59.9 (t), 26.8 (q), 25.1 (q) ppm. MS: *m*/*z* (%) = 295 (0.6) [M$^+$], 280 (0.7), 265 (2), 173 (38), 91 (100), 59 (40). $C_{15}H_{21}NO_5$ (295.38): calcd. C 61.00, H 7.17, N, 4.74; found C 61.32, H 7.32, N 4.58.

***N*-Benzyl-2,3,5-tri-*O*-benzyl-*N*-hydroxy-L-xylofuranosylamine (3d):**[8] From *N*-benzylhydroxylamine hydrochloride (1.8 equiv.). Dark green oil, 315 mg, 60% yield (as a 4:1 α/β anomeric mixture in $CDCl_3$ solution containing ca. 10% of the open-chain nitrone tautomer). $R_f$ (ethyl acetate/petroleum ether, 1:2) = 0.65. $[\alpha]_D^{26}$ = +24.8 (*c* = 0.11, $CH_2Cl_2$). IR ($CDCl_3$): $\tilde{\nu}$ = 3574, 3432, 3034, 2925, 2865, 1448, 1353, 1100 cm$^{-1}$. $^1$H NMR: δ = (selected signals of the open-chain nitrone isomer) 6.78 (d, *J* = 6.7 Hz, 1 H), 5.16 (t, *J* = 6.8 Hz, 1 H) ppm. $^{13}$C NMR: δ = (*major anomer*) 137.9 (s), 137.6 (s), 137.5 (s), 137.1 (s), 129.2−126.8 (d, 20 C), 98.7 (d), 82.5 (d), 81.5 (d), 78.6 (d), 73.3 (t), 71.9 (t), 71.5 (t), 68.4 (t), 60.3 (t); (*minor anomer, selected signals*) 91.4 (d) ppm. MS: *m*/*z* (%) = 525 (4) [M$^+$], 510 (2), 181 (17), 91 (100). $C_{33}H_{35}NO_5$ (525.71): calcd. C 75.41, H 6.71, N 2.66; found C 75.10, H 6.39, N 2.43.

***N*-Benzyl-2,3,5-tri-*O*-benzyl-*N*-hydroxy-D-arabinofuranosylamine (3e):**[8] Colourless oil, 347 mg, 66% yield (as a 6:1 α/β anomeric mixture in $CDCl_3$ solution). $R_f$ (ethyl acetate/petroleum ether, 1:3) = 0.60. $[\alpha]_D^{26}$ = +23.7 (*c* = 2.15, $CH_2Cl_2$). IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3566, 3032, 2914, 2870, 1452, 1362, 1078 cm$^{-1}$. $^1$H NMR: δ = 7.42−7.20 (m, 20 $H_\alpha$+20 $H_\beta$), 4.76−4.51 (m, 4 $H_\alpha$+4 $H_\beta$), 4.50−4.40 (m, 2 $H_\beta$), 4.34−4.23 (m, 4 $H_\alpha$), 4.22−4.39 (m, 2 $H_\alpha$ + 4 $H_\beta$), 3.96−3.85 (m, 2 $H_\beta$), 3.75−3.66 (m, 2 $H_\alpha$), 3.64−3.55 (m, 2 $H_\beta$), 3.54−3.49 (m, 2 $H_\alpha$) ppm. $^{13}$C NMR: δ = (*major anomer*) 138.3 (s), 138.2 (s), 138.1 (s), 137.5 (s), 129.5−127.4 (d, 20 C), 98.0 (d), 85.2 (d), 83.5 (d), 81.9 (d), 73.5 (t), 72.3 (t), 72.1 (t), 70.1 (t), 60.1 (t); (*minor anomer*) 138.4 (s), 138.1 (s), 138.0 (s), 137.8 (s), 129.3−127.3 (d, 20 C), 91.1 (d), 83.7 (d), 82.7 (d), 79.2 (d), 73.5 (t), 72.7 (t), 72.5 (t), 71.0 (t), 58.9 (t) ppm. MS: *m*/*z* (%) = 418 (3), 388 (2), 310 (7), 280 (8), 253 (21), 181 (61), 107 (31), 105 (30), 91 (100), 77 (67), 65 (99). $C_{33}H_{35}NO_5$ (525.71): calcd. C 75.41, H 6.71, N 2.66; found C 75.04, H 6.58, N 2.63.

**(3a*R*,4*R*,6a*R*)-*N*-Benzyl-tetrahydro-*N*-hydroxy-2,2-dimethylfuro-[3,4-*d*]-1,3-dioxol-4-amine (3f):** White solid, 233 mg, 88% yield (as a 16:1 mixture with the open-chain nitrone tautomer in $CDCl_3$ solution). $R_f$ (ethyl acetate/petroleum ether, 1:3) = 0.35. M.p. 86−87 °C. $[\alpha]_D^{20}$ = −70.0 (*c* = 1.00, $CHCl_3$). IR (CHCl3): $\tilde{\nu}$ = 3580, 3040, 2981, 2943, 1380, 1371, 1098, 1057 cm$^{-1}$. $^1$H NMR (500 MHz): δ = (*N-glycosylhydroxylamine*) 7.43−7.27 (m, 5 H), 4.92 (d, *J* = 6.0 Hz, 1 H), 4.88 (dd, *J* = 6.0, 4.2 Hz, 1 H), 4. 73 (s, 1 H), 4.68 (br. s, 1 H), 4.27 (dd, *J* = 9.5, 4.2 Hz, 1 H), 4.09 (d, *J* =

13.5 Hz, 1 H), 4.07 (d, $J$ = 9.5 Hz, 1 H), 3.88 (d, $J$ = 13.5 Hz, 1 H), 1.51 (s, 3 H), 1.35 (s, 3 H); *(open-chain nitrone)* 6.89 (d, $J$ = 6.0 Hz, 1 H), 5.32 (t, $J$ = 5.5 Hz, 1 H), 5.06 (s, 1 H), 1.43 (s, 3 H), 1.39 (s, 3 H) ppm. $^{13}$C NMR: δ = 137.0 (s), 129.5 (d, 2 C), 128.5 (d, 2 C), 127.5 (d), 112.1 (s), 99.7 (d), 83.9 (d), 81.1 (d), 76.4 (t), 59.4 (t), 26.5 (q), 24.8 (q) ppm. MS: *m*/*z* (%) = 265 (4) [M$^+$], 159 (4), 143 (22), 91 (100), 57 (52) ppm. $C_{14}H_{19}NO_4$ (265.37): calcd. C 63.38, H 7.22, N 5.28; found C 63.33, H 7.24, N 5.20.

***N*-Benzyl-*N*-hydroxy-2,3:5,6-di[*O*-(1-methylethylidene)]-α-D-mannofuranosylamine (3g):**[6] White solid, 266 mg, 73% yield. $R_f$ ($CH_2Cl_2$/$CH_3OH$, 30:1) = 0.68. $^1$H NMR: δ = 7.36−7.28 (m, 5 H), 5.52 (br. s, 1 H), 4.96 (d, $J$ = 6.1 Hz, 1 H), 4.84 (dd, $J$ = 6.1, 3.2 Hz, 1 H), 4.66 (s, 1 H), 4.42−4.28 (m, 2 H), 4.20−4.08 (m, 2 H), 4.00 (d, $J$ = 13.2 Hz, 1 H), 3.86 (d, $J$ = 13.2 Hz, 1 H), 1.48 (s, 6 H), 1.40 (s, 3 H), 1.37 (s, 3 H) ppm.

**(3a*R*,4*R*,6a*R*)-Tetrahydro-*N*-hydroxy-*N*,2,2-trimethylfuro[3,4-*d*]-1,3-dioxol-4-amine (3h):** White solid, 134 mg, 71% yield (as a 6:1 mixture with the open-chain nitrone tautomer in $CDCl_3$ solution). $R_f$ (ethyl acetate/petroleum ether, 1:2) = 0.23. M.p. 101−102 °C. $[\alpha]_D^{20}$ = −65.1 ($c$ = 1.04, $CH_2Cl_2$). IR ($CHCl_3$): ν̃ = 3166, 2999, 2974, 2946, 1456, 1383, 1203, 1108, 1057 cm$^{-1}$. $^1$H NMR: δ = *(N-glycosylhydroxylamine)* 4.88 (m, 2 H), 4. 52 (s, 1 H), 4.16 (dd, $J$ = 9.8, 3.4 Hz, 1 H), 4.02 (d, $J$ = 9.8 Hz, 1 H), 2.68 (s, 3 H), 1.51 (s, 3 H), 1.35 (s, 3 H); *(open-chain nitrone)* 6.94 (d, $J$ = 5.1 Hz, 1 H), 5.33 (dd, $J$ = 7.3, 5.1 Hz, 1 H), 4.60 (td, $J$ = 7.3, 3.7 Hz, 1 H), 3.74 (s, 3 H), 3.72 (dd, $J$ = 11.7, 3.7 Hz, 1 H), 3.55 (dd, $J$ = 11.7, 7.3 Hz, 1 H), 1.51 (s, 3 H), 1.41 (s, 3 H) ppm. $^{13}$C NMR: δ = *(N-glycosylhydroxylamine)* 112.0 (s), 101.0 (d), 82.8 (d), 80.9 (d), 75.7 (t), 42.9 (q) 26.4 (q), 24.7 (q); *(open-chain nitrone)* detected signals 79.5 (d), 73.8 (d), 61.5 (t), 52.0 (q), 27.0 (q), 24.3 (q) ppm. MS: *m*/*z* (%) = 189 (1) [M$^+$], 171 (2), 143 (30), 114 (19), 84 (75), 56 (100). $C_8H_{15}NO_4$ (189.21): calcd. C 50.78, H 7.99, N 7.40; found C 51.13, H 7.96, N 7.54.

***N*-Hydroxy-*N*-methyl-2,3:5,6-di[*O*-(1-methylethylidene)]-α-D-mannofuranosylamine (3i):** White solid, 202 mg, 70% yield. $R_f$ (eluent ethyl acetate/petroleum ether, 1:2) = 0.26. M.p. 61−62 °C. $[\alpha]_D^{22}$ = +20.3 ($c$ = 1.00, $CH_2Cl_2$). IR ($CHCl_3$): ν̃ = 3582, 2992, 2937, 1454, 1372, 1205, 1060 cm$^{-1}$. $^1$H NMR: δ = 5.70 (br. s, 1 H), 4.92 (d, $J$ = 6.1 Hz, 1 H), 4.82 (dd, $J$ = 6.1, 3.2 Hz, 1 H), 4.48 (s, 1 H), 4.40−4.20 (m, 2 H), 4.12−4.05 (m, 2 H), 2.68 (s, 3 H), 1.44 (s, 3 H), 1.42 (s, 3 H), 1.38 (s, 3 H), 1.37 (s, 3 H) ppm. $^{13}$C NMR: δ = 112.6 (s), 109.2 (s), 100.8 (d), 83.9 (d), 83.7 (d), 80.8 (d), 73.8 (d), 66.9 (t), 43.1 (q), 27.0 (q), 26.2 (q), 25.3 (q), 24.6 (q) ppm. MS: *m*/*z* (%) = 274 (15) [M − $CH_3^+$], 258 (5), 231 (6), 101 (44), 99 (36), 84 (100). $C_{13}H_{23}NO_6$ (289.34): calcd. C 53.97, H 8.01, N 4.84; found C 53.99, H 8.28, N 4.83.

**General Procedure for the Synthesis of *C*-Phenyl-*N*-glycosylnitrones:** Commercially available "activated' $MnO_2$ (90% purity, 1.5 equiv.) was added to a stirred 0.5 M solution of *N*-benzyl-*N*-glycosylhydroxylamine **3f**−**g** (1 mmol) in $CH_2Cl_2$ which was cooled to 0 °C.[13] The mixture was stirred at room temperature for 12 h, then filtered through a short pad of Celite and $Na_2SO_4$. The resulting solution was concentrated to afford the corresponding pure *C*-phenylnitrone.

**(3a*R*,4*R*,6a*R*)-Tetrahydro-2,2-dimethyl-*N*-(phenylmethylene)furo-[3,4-*d*][1,3]dioxol-4-amine *N*-Oxide (10):** White solid, 255 mg, 97% yield. M.p. 110−112 °C. $[\alpha]_D^{20}$ = −148.2 ($c$ = 1.09, $CHCl_3$). IR ($CHCl_3$): ν̃ = 2991, 1582, 1448, 1375, 1100 cm$^{-1}$. $^1$H NMR: δ = 8.26−8.23 (m, 2 H), 7.59 (s, 1 H), 7.46−7.42 (m, 3 H), 5.49 (s, 1 H), 5.32 (d, $J$ = 6.2 Hz, 1 H), 5.01 (dd, $J$ = 6.2, 4.1 Hz, 1 H), 4.52 (dd, $J$ = 9.8, 4.1 Hz, 1 H), 4.31 (d, $J$ = 9.8 Hz, 1 H), 4.10 (m, 2 H), 1.51 (s, 3 H), 1.43 (s, 3 H), 1.38 (s, 3 H), 1.36 (s, 3 H) ppm. $^{13}$C NMR: δ = 132.8 (d), 131.0 (d, 2 C), 129.6 (s), 128.9 (d, 2 C), 128.5 (d), 112.9 (s), 104.0 (d), 84.4 (d), 80.5 (d), 77.2 (t), 26.3 (q), 24.7 (q) ppm. MS: *m*/*z* (%) = 263 (4) [M$^+$], 248 (2), 143 (67), 85 (39), 59 (41), 57 (100). $C_{14}H_{17}NO_4$ (263.35): calcd. C 63.87, H 6.51, N 5.32; found C 63.64, H 6.49, N 5.21.

**2,3:5,6-Di[*O*-(1-methylethylidene)]-*N*-(phenylmethylene)-α-D-mannofuranosylamine *N*-Oxide (13):**[6] White solid, 350 mg, 97% yield. M.p. 179−181 °C. $[\alpha]_D^{25}$ = +62.7 ($c$ = 1.00, $CHCl_3$). [ref. m.p. 182−183 °C, $[\alpha]_D$ = +66.4 ($c$ = 1.50, $CHCl_3$);[4h] m.p. 184 °C, $[\alpha]_D$ = +62.1 ($c$ = 1.50, $CHCl_3$).[6] $^1$H NMR: δ = 8.26−8.23 (m, 2 H), 7.59 (s, 1 H), 7.46−7.42 (m, 3 H), 5.49 (s, 1 H), 5.32 (d, $J$ = 6.2 Hz, 1 H), 5.01 (dd, $J$ = 6.2, 4.1 Hz, 1 H), 4.52 (dd, $J$ = 9.8, 4.1 Hz, 1 H), 4.31 (d, $J$ = 9.8 Hz, 1 H), 4.10 (m, 2 H), 1.51 (s, 3 H), 1.43 (s, 3 H), 1.38 (s, 3 H), 1.36 (s, 3 H) ppm.

**General Procedure for the Cycloadditions of *C*-Phenyl-*N*-glycosylnitrones with Dimethyl Maleate (11):** Dimethyl maleate (**11**) (2 equiv.) was added to a 0.5 M suspension of *C*-phenyl-*N*-glycosylnitrone **10** or **13** (0.5 mmol) in toluene in a Sovirel vial. The mixture was heated at 80 °C in the sealed vial in an oven for 4 days, then concentrated and purified by FCC.

**Dimethyl (3*R*,4*S*,5*R*)-2-[(3a*R*,4*R*,6a*R*)-Tetrahydro-2,2-dimethyl-3-phenylfuro[3,4-*d*][1,3]dioxol-4-yl]isoxazolidine-4,5-dicarboxylate (12):**[23] White solid, 157 mg, 77% yield. $R_f$ (ethyl acetate/petroleum ether, 1:2) = 0.35. M.p. 70−71 °C. $[\alpha]_D^{20}$ = −62.1 ($c$ = 0.59, $CHCl_3$). $^1$H NMR: δ = 7.43−7.29 (m, 5 H), 5.13 (d, $J$ = 6.2 Hz, 1 H), 4.93 (d, $J$ = 9.0 Hz, 1 H), 4.86 (s, 1 H), 4.81 (dd, $J$ = 6.2, 4.5 Hz, 1 H), 4.62 (d, $J$ = 9.0 Hz, 1 H), 3.83 (t, $J$ = 9.0 Hz, 1 H), 3.80 (d, $J$ = 10.0 Hz, 1 H), 3.78 (s, 3 H), 3.73 (dd, $J$ = 10.0, 4.5 Hz, 1 H), 3.65 (s, 3 H), 1.43 (s, 3 H), 1.34 (s, 3 H) ppm. $^{13}$C NMR: δ = 169.5 (s), 169.2 (s), 136.7 (s), 128.8 (d, 2 C), 128.3 (d), 127.7 (d, 2 C), 112.1 (s), 98.8 (d), 82.4 (d), 80.7 (d), 77.7 (d), 74.3 (d), 68.7 (t), 58.9 (d), 52.6 (q), 52.5 (q), 26.3 (q), 24.8 (q) ppm. IR (KBr): ν̃ = 3003, 2957, 2895, 1740, 1436, 1373, 1265, 1157, 1092 cm$^{-1}$. MS: *m*/*z* (%) = 407 (9) [M$^+$], 146 (60), 143 (47), 91 (100), 85 (43), 59 (54), 57 (72). $C_{20}H_{25}NO_8$ (407.48): calcd. C 58.96, H 6.18, N 3.44; found C 59.03, H 6.22, N 3.33.

**Dimethyl (3*S*,4*R*,5*S*)-2-[2,3:5,6-Di-*O*-(1-methylethylidene)-α-D-mannofuranosyl]-3-phenylisoxazolidine-4,5-dicarboxylate (14a):** White solid, 178 mg, 70% yield. $R_f$ (ethyl acetate/petroleum ether, 1:3) = 0.35. M.p. 115−116 °C. $[\alpha]_D^{25}$ = +46.1 ($c$ = 1.00, $CH_2Cl_2$). $^1$H NMR: δ = 7.48−7.28 (m, 5 H), 5.08 (d, $J$ = 6.0 Hz, 1 H), 4.92 (s, 1 H), 4.91 (d, $J$ = 8.9 Hz, 1 H), 4.77 (dd, $J$ = 6.0, 3.7 Hz, 1 H), 4.50 (d, $J$ = 8.9 Hz, 1 H), 4.11 (ddd, $J$ = 8.4, 4.8, 2.6 Hz, 1 H), 3.76 (t, $J$ = 8.9 Hz, 1 H), 3.76 (s, 3 H), 3.66 (dd, $J$ = 8.8, 2.6 Hz, 1 H), 3.62 (s, 3 H), 3.56 (dd, $J$ = 8.4, 3.7 Hz, 1 H), 2.78 (dd, $J$ = 8.8, 4.8 Hz, 1 H), 1.43 (s, 3 H), 1.33 (s, 3 H), 1.26 (s, 3 H), 1.25 (s, 3 H) ppm. $^{13}$C NMR: δ = 169.4 (s), 168.5 (s), 137.2 (s), 128.7 (d, 2 C), 128.1 (d), 127.3 (d, 2 C), 112.4 (s), 108.9 (s), 100.0 (d), 83.5 (d), 82.5 (d), 80.2 (d), 77.6 (d), 72.5 (d), 69.6 (d), 66.4 (t), 59.7 (d), 52.5 (q), 52.4 (q), 26.7 (q), 26.0 (q), 25.3 (q), 24.6 (q) ppm. IR (KBr): ν̃ = 3050, 2989, 2957, 1740, 1465, 1380, 1202, 1062 cm$^{-1}$. MS: *m*/*z* (%) = 507 (0.5) [M$^+$], 294 (22), 185 (29), 115 (29), 101 (100), 85 (53), 69 (42), 59 (68). $C_{25}H_{33}NO_{10}$ (507.60): calcd. C 59.16, H 6.55, N 2.76; found C 59.27, H 6.99, N 2.83.

**Dimethyl (3*S*,4*S*,5*R*)-2-[2,3:5,6-Di-*O*-(1-methylethylidene)-α-D-mannofuranosyl]-3-phenyl-4,5-isoxazolidinedicarboxylate (14b):** White solid, 15 mg, 6% yield. $R_f$ (ethyl acetate/petroleum ether, 1:3) = 0.20. M.p. 94−97 °C. $[\alpha]_D^{21}$ = +7.6 ($c$ = 0.50, $CH_2Cl_2$). $^1$H NMR: δ = 7.40−7.28 (m, 5 H), 5.13 (d, $J$ = 6.2 Hz, 1 H), 4.96 (d, $J$ = 6.6 Hz, 1 H), 4.77 (dd, $J$ = 6.2, 3.7 Hz, 1 H), 4.63 (d, $J$ = 8.4 Hz,

1 H), 4.60 (s, 1 H), 4.12 (ddd, $J$ = 8.4, 6.6, 4.8 Hz, 1 H), 4.03 (dd, $J$ = 8.4, 6.6 Hz, 1 H), 3.78 (s, 3 H), 3.67 (dd, $J$ = 8.4, 6.6 Hz, 1 H), 3.59 (dd, $J$ = 8.4, 3.7 Hz, 1 H), 3.21 (s, 3 H), 2.78 (dd, $J$ = 8.4, 4.8 Hz, 1 H), 1.43 (s, 3 H), 1.33 (s, 3 H), 1.26 (s, 3 H), 1.21 (s, 3 H) ppm. $^{13}$C NMR: δ = 168.5 (s), 168.4 (s), 136.2 (s), 128.2 (d, 2 C), 128.0 (d), 127.2 (d, 2 C), 112.4 (s), 109.0 (s), 100.0 (d), 84.2 (d), 82.4 (d), 80.1 (d), 77.6 (d), 72.4 (d), 70.8 (d), 66.4 (t), 57.8 (d), 52.4 (q), 51.7 (q), 26.6 (q), 26.0 (q), 25.3 (q), 24.5 (q) ppm. IR (KBr): ṽ = 3055, 2988, 2956, 1737, 1453, 1381, 1199, 1065 cm$^{-1}$. MS: *m*/*z* (%) = 507 (4) [M$^+$], 294 (49), 185 (50), 115 (70), 101 (97), 85 (100). $C_{25}H_{33}NO_{10}$ (507.60): calcd. C 59.16, H 6.55, N 2.76; found C 58.91, H 6.55, N 2.78.

**One-Pot Oxidation of Hydroxylamine 3h. − Cycloaddition with Dimethyl Maleate (11):** A solution of hydroxylamine **3h** (55 mg, 0.29 mmol) in $CHCl_3$ (5 mL) was cooled to 0 °C in an ice-bath and DDQ (73 mg, 0.32 mmol) was added. The cold-bath was removed and then, after 5 min, dimethyl maleate (**11**, 75 μL, 0.50 mmol) was added. The mixture was then refluxed for 1 h. The solution was concentrated and purified by flash column chromatography, to afford a 1:1 mixture of diastereoisomers **16a**−**b** as a colourless oil (82 mg, 85% yield, $R_f$ (ethyl acetate/pentane, 1:3) = 0.17).

**Dimethyl (4*S*,5*R*)-2-{(3a*R*,4*R*,6a*R*)-Tetrahydro-2,2-dimethylfuro-[3,4-*d*][1,3]dioxol-4-yl}isoxazolidine-4,5-dicarboxylate (16a) and Dimethyl (4*R*,5*S*)-2-{(3a*R*,4*R*,6a*R*)-Tetrahydro-2,2-dimethylfuro[3,4-*d*][1,3]dioxol-4-yl}isoxazolidine-4,5-dicarboxylate (16b):** IR ($CH_2Cl_2$): ṽ = 2987, 2954, 1744, 1437, 1374, 1210, 1096 cm$^{-1}$. $^1$H NMR ([D$_6$]DMSO, 70 °C, 400 MHz): δ = (the signals of the two diastereoisomers are not discernible and are reported together) 4.85−4.75 (m, 3 H), 4.67 (s, 1 H), 4.58 (s, 1 H), 4.02 (dd, $J$ = 6.1, 3.9 Hz, 1 H), 3.99 (dd, $J$ = 6.1, 3.9 Hz, 1 H), 3.94−3.86 (m, 4 H), 3.65 (s, 3 H), 3.64 (s, 3 H), 3.63 (s, 3 H), 3.62 (s, 3 H), 3.49 (dd, $J$ = 13.4, 8.1 Hz, 1 H), 3.47 (dd, $J$ = 13.4, 7.8 Hz, 1 H), 3.31 (dd, $J$ = 11.5, 8.1 Hz, 1 H), 3.27 (dd, $J$ = 11.5, 8.1 Hz, 1 H), 1.41 (s, 3 H), 1.40 (s, 3 H), 1.29 (s, 3 H), 1.28 (s, 3 H) ppm. $^{13}$C NMR: δ = (the signals of the two diastereoisomers are not discernible and are reported together) 112.3 (s), 112.2 (s), 100.5 (d), 97.3 (d), 83.9 (d), 83.8 (d), 80.6 (d), 80.4 (d), 77.9 (d), 77.1 (d), 75.8 (t), 75.0 (t), 52.4 (q, 2 C), 52.4 (q, 2 C), 52.4 (t), 51.3 (t), 50.6 (d), 49.3 (d), 26.5 (q), 26.3 (q), 24.8 (q), 24.7 (q) ppm. MS: *m*/*z* (%) = 331 (1) [M$^+$], 256 (5), 218 (17), 143 (36), 85 (80), 57 (100).$C_{14}H_{21}NO_8$ (331.32): calcd. C 50.75, H 6.39, N 4.23; found C 51.13, H 6.46, N 4.26.

**General Procedure for Cleavage of the *N*-Glycosyl Bond:** A 0.1 M solution of isoxazolidine **12** or **14a** in HCl (1 M in MeOH) was stirred at 40 °C for 4 h. After cooling and neutralization with cold 1 M $Na_2CO_3$, the mixture was extracted with $Et_2O$. The collected organic phases were washed with 0.5 M $Na_2CO_3$, dried with $Na_2SO_4$, concentrated and purified by FCC.

**Dimethyl (3*R*,4*S*,5*R*)-3-Phenylisoxazolidine-4,5-dicarboxylate (17):**[24] Colourless oil, 38 mg, 71% yield. $R_f$ (ethyl acetate/diethyl ether/petroleum ether, 1:2:3) = 0.31. $[\alpha]_D^{22}$ = −169.4 ($c$ = 0.28, $CH_2Cl_2$). IR ($CH_2Cl_2$): ṽ = 3688, 3052, 2971, 1741, 1446, 1365, 1198, 1080 cm$^{-1}$. $^1$H NMR: δ = 7.46−7.25 (m, 5 H), 4.92 (d, $J$ = 4.0 Hz, 1 H), 4.90 (d, $J$ = 8.4 Hz, 1 H), 3.82 (dd, $J$ = 8.4, 4.0 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H) ppm. $^{13}$C NMR: δ = 171.0 (s), 170.3 (s), 140.0 (s), 128.9 (d, 2 C), 127.8 (d), 126.3 (d, 2 C), 80.6 (d), 66.2 (d), 60.8 (d), 52.8 (t), 52.5 (t) ppm. MS: *m*/*z* (%) = 265 (1) [M$^+$], 146 (100), 120 (31), 104 (51), 84 (62), 77 (43), 51 (61). $C_{13}H_{15}NO_5$ (265.27): calcd. C 58.86, H 5.70, N 5.28; found C 58.81, H 5.82, N 5.37.

**Dimethyl (3*S*,4*R*,5*S*)-3-Phenylisoxazolidine-4,5-dicarboxylate (*ent*-17):** Colourless oil, 38 mg, 72% yield. $[\alpha]_D^{22}$ = +166.2 ($c$ = 0.28, $CH_2Cl_2$). $C_{13}H_{15}NO_5$(265.27): calcd. C 58.86, H 5.70, N 5.28; found C 58.71, H 5.81, N 4.95.

**X-ray Crystallographic Study of Compound 12:** $C_{20}H_{25}NO_8$, M = 407.41, Triclinic, space group $P1$, $a$ = 6.247(1), $b$ = 9.807(1), $c$ = 9.346(1) Å, α = 106.48(1)°, β = 105.14(2)°, γ = 95.08(1)°, $V$ = 521.75(11) Å$^3$, $Z$ = 1 $D_{calcd.}$ = 1.297, μ = 0.847 mm$^{-1}$, $F$(000) = 216.

Analysis of a single crystal was carried out with a Siemens P4 X-ray diffractometer at room temperature. Graphite-monochromated Cu-$K_\alpha$ radiation was used for cell parameter determination and data collection. The intensities of three standard reflections were monitored during data collection to check the stability of the crystal: no loss of intensity was recognized. The integrated intensities, measured using the θ/2θ scan mode, were corrected for Lorentz and polarization effects.[25] The reflection collected were 1421 with a $4.78 < \theta < 49.92$ range; 1421 were indipendent and the parameters were 288. The final $R$ index was 0.0350 for reflections having $I > 2\sigma I$, and 0.0355 for all data. The non-hydrogen atoms were refined anisotropically; aromatic, methylene and methyl hydrogen atoms were assigned in calculated positions while the others (H$^1$, H$^2$, H$^3$, H$^8$, H$^{11}$ and H$^{14}$) were found in the Fourier difference synthesis; all of them were refined as isotropic. This structure was solved by direct methods of SIR97[26] and refined using the full-matrix least-squares on $F^2$ provided by SHELXL-97.[27]

CCDC-209316 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk].

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