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Synthesis of D-Erythrose and D-Threose Derived Nitrones and Cycloadditions to Styrene

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Abstract: The new nitrones derived from cyclic acetals of D-erythrose (**2a-c**) and D-threose (**8**) react with styrene to afford the corresponding 3,5-disubstituted diastereomeric isoxazolidines **3-6** and **9-12**. The stereoselectivity was dependent on the steric hindrance of the nitrone. The major products **3a-c** (55-58 %) and **9** (73 %) were found to have the C-3/C-4′ *erythro* and C-3/C-5 *cis* relative configuration by X-ray analysis. Its formation can be rationalized by less hindered *endo* attack of the *Z*-nitrone in an antiperiplanar manner with respect to the largest group of the cyclic acetal.

INTRODUCTION

The nitrone-olefin 1,3-dipolar cycloaddition is a powerful reaction in that it can create as many as three new contiguous stereogenic centers in a single step.[1] Based on an evaluation of the nitrone cycloaddition, it was felt that the configuration of these new centers could be influenced if the reaction system was properly designed.[2] Regio- and stereoselective nitrone cycloaddition, followed by reduction of the N–O bond, to produce both an amino and a hydroxy function, allows the synthesis of many products of potential interest.[3]

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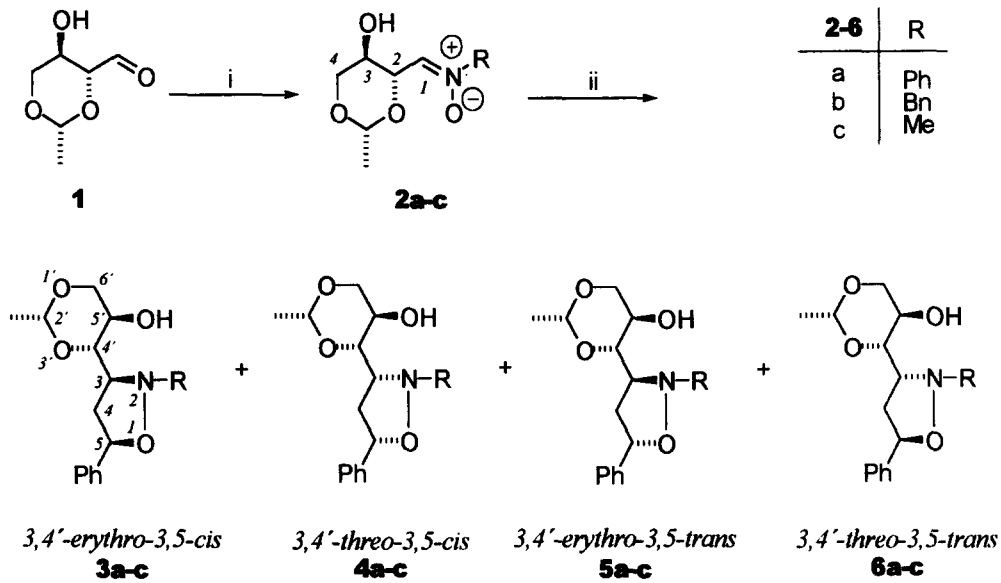
Over the years, nitrones have become important building blocks in organic synthesis.[1,4] However, in spite of that well-documented utility there are only scattered reports dealing with the preparation of nitrones with a chiral *C*-substituent.[5,6] With the goal of developing a simple route to polyhydroxylated derivatives of pyrrolizidines,[7] which have been shown to display antiviral activity,[8] *via* an asymmetric 1,3-dipolar cycloaddition we have prepared chiral sugar-derived nitrones as template for cycloaddition.

In this paper we report in detail the preparation of new D-erythrose- and D-threose- derived nitrones and the stereoselectivity of their cycloadditions to styrene as a model dipolarophile; our preliminary results in this area have been the subject of a recent communication.[9]

Our first step of this approach is indicated in **Scheme 1**. 2,4-*O*-Ethylidene-D-erythrose (**1**) was prepared from 4,6-*O*-ethylidene-D-glucose (readily available from D-glucose in 70 % yield) by oxidation with periodate in almost quantitative yield.[10] However, no aldehydic resonance appeared in ^{1}H and ^{13}C NMR spectra of **1**, since the protected β-hydroxy-aldehyde exists and was isolated as a crystalline dimer, in accordance with previous papers.[10-12] Reformation of the monomer **1** was facilitated in our case by adding a catalytic amount of 2-pyridone,[12b] and from this more rapidly equilibrating mixture the aldehyde **1** underwent smooth condensation with the respective hydroxylamine in increased yield (50% *versus* 73% for nitrone **2b**). Likewise, treatment of the dimer with ethyl acetate containing a catalytic amount of glacial acetic acid or 100 % phosphoric acid is reported to afford the monomer **1**.[11] The nitrones **2a-c**, with a "chiral" *C*-substituent, were prepared from the aldehyde **1** by the reaction with the appropriate *N*-substituted hydroxylamine in dichloromethane in the presence of anhydrous magnesium sulfate, according to the procedure of Dondoni *et al.* used for the preparation of chiral *N*-benzyl nitrones.[13] A catalytic amount of 2-pyridone for the formation of aldehyde monomer **1** proved beneficial to improve the yield of nitrone **2**. In the case of the *N*-methyl nitrone **2c** this procedure was modified by adding DABCO to the reaction mixture. Single, diastereomerically pure nitrones **2a-c** were isolated in pure state as crystalline solids in all cases, and the expected *Z* configuration[2] was confirmed by nuclear Overhauser enhancement difference spectroscopy (NOEDS).

The nitrones **2a-c** were subjected to 1,3-dipolar cycloaddition with styrene. Our concern was to study the asymmetric induction from the nitrone part. There are eight possible products, *cis*- and *trans*-isomers for each pair of regioisomers from *anti* and *syn* attack (**Scheme 1**, only 5-substituted regioisomers are depicted). With each of the nitrones the reaction proceeded smoothly in a highly regioselective manner; 3,4-disubstituted adducts were not detected in crude reaction mixture by NMR spectra. The cycloadditions of the nitrones **2a-c** to styrene carried out in boiling toluene for 10

h gave a mixture of four diastereomeric isoxazolidines **3-6** in excellent yield (82-94%). The major adducts **3a-c** could be separated and isolated by flash chromatography. The regiochemical assignments came straightforwardly from the analysis of diagnostic signals in the NMR spectra. The resonance positions of the isoxazolidine ring protons serve as sensitive probes for regiochemical assignment.[1] The proton 5-H in **3-6** resonates at lower field as compared to the proton 3-H; *e.g.* 5.19 *vs.* 4.17 ppm for **3a**.



i, RNHOH, CH_2Cl_2, 2-pyridone (cat.), rt
ii, styrene, toluene, 110°C

Scheme 1

The ratio of diastereoisomers was determined from quantitative ^{13}C NMR spectra, by integration of the peaks from C-4 of the isoxazolidines. The 500 MHz NMR spectrum of the crude product mixture from the nitrone **2a** and styrene was well resolved and showed four peaks for C-4 at δ 39.05, 37.88, 37.16 and 36.09 in the ratio of 82 : 9 : 5 : 4 (**Table 1**). The structure of the separated major isomer **3a** was unambiguously assigned the *cis*-3,5-configuration by means of a detailed NMR analysis including 2D experiments. The *cis* relationship of substituents at C-3 and C-5 in **3a** is assigned on the basis of NOEDS. A 2.5 % enhancement on signal 3-H following saturation of signal 5-H shows a *cis* relationship between these protons; irradiation of 3-H causes a similar enhancement

(1.8 %) confirming this *cis* relationship. Finally, the *erythro* C-3/C-4′ relative configuration in **3a** was elucidated by X-ray analysis (Figure 1).[21] This also clearly proved the suggested *cis* relationship between3-H and 5-H. That **3b** and **3c** have the same configuration as **3a** is inferred from the diagnostic signals and NOEDS results.

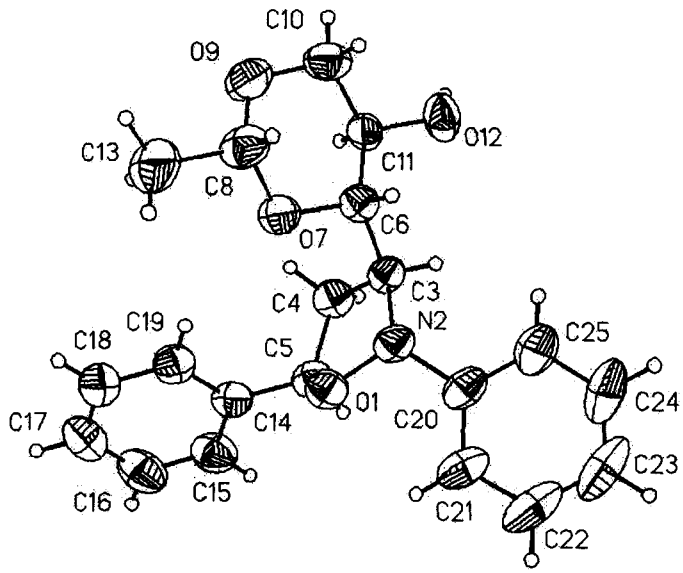


Fig. 1. X-ray analysis of **3a**

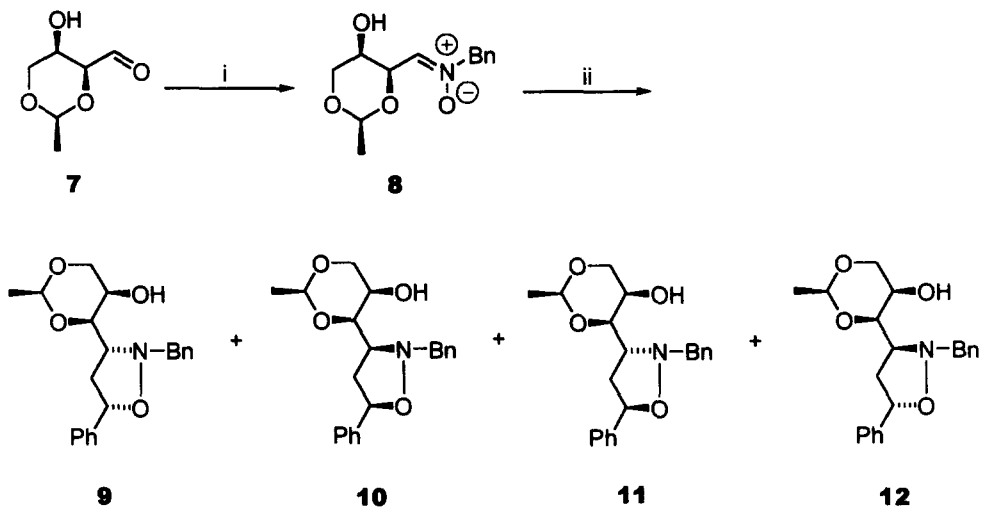
Table 1. 1,3-Dipolar Cycloaddition of *C*-α-Alkoxyalkyl-substituted Nitrones to Styrene

Entry	Nitrone	Yield (%)	*erythro-cis*	*threo-cis*	*erythro-trans*	*threo-trans*	*erythro:threo*	*cis:trans*
1	**2a**	94	82	9	5	4	87 : 13	91 : 9
2	**2b**	82	81	12	7	-	88 : 12	93 : 7
3	**2c**	85	69	17	10	4	79 : 21	86 : 14
4	**8**	84	90	5	3	2	93 : 7	95 : 5
5	**14**[a]	78	73	11	9	7	82 : 18	84 : 16
6	**15**[a]	89	39	30	20	11	59 : 41	69 : 31

[a]Ref.[8b]

The use of D-galactose as starting material gave access to the D-*threo* nitrone **8**, as indicated in Scheme 2. D-galactose was converted to the 4,6-*O*-ethylideneacetal which was treated with

periodate to give 2,4-*O*-ethylidene-D-threose (**7**) in almost quantitative yield.[14] The D-threose nitrone **8** was prepared from the aldehyde **7** on treatment with *N*-benzylhydroxylamine in 73% yield after crystallization, as a stable crystalline material, by the route indicated above for the preparation of the erythrose nitrones **2a-c**.



i, BnNHOH, CH_2Cl_2, 2-pyridone, rt
ii, styrene, toluene, 110°C

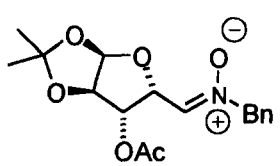
Scheme 2

The nitrones **2a-c** and **8** could be stored in a refrigerator at 4 °C for several months without notable decomposition. The *Z*-configuration of the nitrone **8** was assigned on the basis of NOEDS. The nitrone **8** reacted with styrene in boiling toluene within 10 h in a highly regioselective fashion to furnish the diastereomeric cycloadducts **9-12** in 84% combined yield. The highest diastereoselectivities in this series were observed here with the D-*threo* nitrone **8** and stereoisomeric products were found in a ratio of 90 : 5 : 3 : 2 (**Table 1**). The ratio of stereoisomers **9-12** was determined from quantitative carbon NMR spectra (500 MHz) by integration of peaks at δ 40.29 (2%), 39.59 (90%), 39.29 (3%) and 38.05 (5%), arising from the absorptions of C-4 atom of the isoxazolidines. The major adduct **9** could be separated by flash column chromatography and was isolated in 73% yield. The ^{1}H NMR spectrum of this material was well resolved, and its analysis confirmed the indicated regioselectivity. The stereostructure of isoxazolidine **9** was assigned based on NOE experiments and the comparison of **9** with isoxazolidine **3a**, whose structure had been determined by X-ray analysis. In particular, the interactions were observed between 3-H and both 5-

H and 4-H_a, and between 5-H and each of 3-H, 4-H_a and 4-H_b. That the isoxazolidine **9** has the same relative configuration as **3a** is inferred from the close agreement of resonance positions and coupling constants for the key signals.

The analysis of product configuration indicates that **3a-c** and **9** arise from a cycloaddition which has occurred on the more sterically-accessible face of the nitrone, *via* an *endo*-transition state with antiperiplanar relationship of the phenyl and *N*-alkyl(aryl) group. The stereoselectivity of the nitrone/alkene cycloaddition is difficult to predict, and would appear to depend on minor structural changes in either component.[1,2] Dipolar cycloaddition of *C*-α-alkoxy-substituted nitrones had been shown to occur preferentially *via* transition states in which the developing carbon-carbon bond avoids steric interaction with the more bulky group.[2,15] In the cases studied here, three structural features may influence the stereochemical outcome of such cycloadditions: *E/Z*-isomerization around the C=N bond, nitrone facial selectivity, and *endo/exo* preference.[1] We have therefore focused our attention on the potential interconversion of the *Z*- and *E*-isomers of the starting nitrones. Heating a toluene solution of nitrones **2b** and **8** for 10h, respectively, proceeded without any isomerization, the corresponding *E*-nitrones were not detected by ^{1}H NMR spectra. There was no thermal interconversion between the prepared adducts in refluxing toluene, thus indicating that the cycloaddition proceeded irreversibly under the reaction conditions to give the kinetically controlled products **3-6** and **9-12**, respectively.

As previously observed in 1,3-dipolar cycloadditions with *C*-α-alkoxy substituted nitrones **13**,[2,6a] **14**[6b] and **15**[6b], the *anti*-facial preference accounts for formation of the isoxazolidines **3**, **5**, **9** and **11**, and that an *endo* approach of the dipole occurs to provide the isoxazolidines **3**, **4**, **9** and **10**. On the other hand, an *exo* approach of the dipole is involved in the generation of the isoxazolidines **5**, **6**, **11** and **12**.



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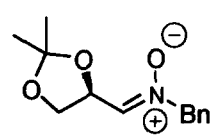

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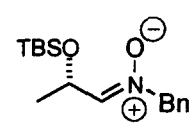

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The high diastereoselectivity found with **2b** and styrene can be ascribed to the more favoured approach of the dipole **2b** to styrene, to give *erythro-cis* **3b** and *threo-cis* **4b** as depicted in Figure

2. It is reasonable that attack of *Z*-**2b** proceeds *via* the less hindered *endo* transition state and in an antiperiplanar manner with respect to the largest group of the heterocyclic acetal to give the major product isoxazolidine **3b** possessing C-3/C-4′ *erythro* and C-3/C-5 *cis*-configuration. The more pronounced steric hindrance present in the approach leading to the *threo-cis* diastereomer **4b** might explain the observed ratio *erythro/threo* 88 : 12 (Table 1). It is noteworthy that the transition states shown have the α-oxygen of the nitrone in "outside" and "inside" orientation, thus avoiding the unfavourable interaction of σ*(C-O) with the HOMO - π-system (if C-O were *anti*-periplanar).[16]

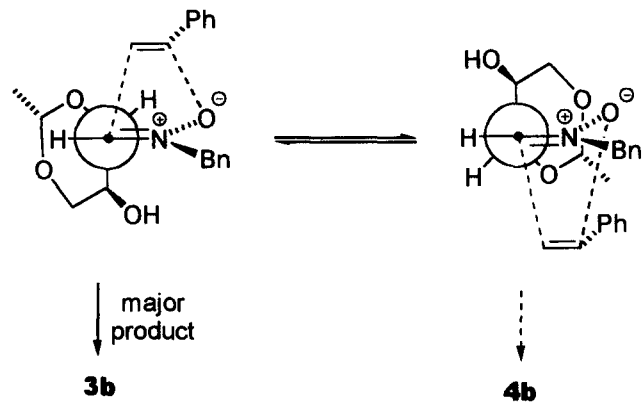

Fig. 2

These suggested transition states can also explain the observed preponderance of the adducts *cis* C-3/C-5 *vs.* the products *trans* C-3/C-5. The ratios found 93 : 7 (*N*-Bn), 91 : 9 (*N*-Ph), and 86 : 14 (*N*-Me), point out that the steric hindrance between the phenyl group in the dipolarophile and the *N*-substituent in the dipole in the *exo* approach, leading to the 3,5-*trans*-isoxazolidine adducts **5** and **6** is responsible for the high diastereoselectivity of the nitrones **2a-c** in the order **2b**(*N*-Bn) > **2a**(*N*-Ph) > **2c**(*N*-Me) (Table 1). A similar explanation was first used by Brandi *et al.* for the cycloaddition of the nitrone **14** to 2,3-dihydro-1-phenyl-1*H*-phosphole-1-oxide.[17] This explanation, that steric factors are clearly important for the orientation of the dipoles **2** in the cycloaddition to styrene, is also supported by the fact, that the cycloaddition of the D-*threo* nitrone **8** proceeds with the best *anti*-facial (93 : 7) and *endo*-facial (95 : 5) preference in this series (entry 4, Table 1). The results on the stereoselectivity of the chiral nitrones **14** and **15** to styrene, published previously by us, are in accord with the aforementioned importance of steric factors (entries 5 and 6, Table 1).[6b]

In conclusion, 1,3-dipolar cycloadditions of *C*-α-alkoxy-substituted chiral nitrones would appear to proceed with useful diastereoselectivity, but the degree of stereodifferentiation also depends upon the respective *N*-substituent present in the nitrone. The stereoselectivity of the cycloaddition is influenced by the steric hindrance of both the *N*- and *C*-substituent of the nitrone, *i.e.* the selectivity increases as the nitrogen substituent of the nitrone becomes bulkier. The best diastereoselectivity was achieved with the *N*-benzyl nitrones **2b** and **8** derived from D-erythrose and D-threose. The major products **3** and **9** were found to have the *erythro* - configuration at C-3/C-4′ and *cis* - substitution at C-3/C-5. Its favoured formation can be rationalized *via* the less hindered *endo* approach of the *Z*-nitrone antiperiplanar to the largest substituent of the heterocyclic acetal moiety.

EXPERIMENTAL

All starting materials and reagents are commercially available (Fluka, Merck or Avocado) and were used without further purification. Solvents were dried using standard procedures. Thin-layer chromatography (TLC) was used for monitoring of reaction courses and was carried out on aluminium plates coated with silica $60F_{254}$ (0.25 mm thickness, Merck). Eluents are indicated in the text. All column chromatography was done by using the flash chromatography technique, and was carried out on silica 60 (0.040—0.063 mm, Merck). Melting points were determined on a Kofler hot plate apparatus and are uncorrected. Elemental analyses were performed by the microanalysis service of the Department of Analytical Chemistry, Slovak University of Technology, Bratislava.

The ^{1}H and ^{13}C NMR spectra of deuterochloroform solutions were measured with Varian VXR 300 (300 MHz) and VXR-500 (500 MHz) instruments, tetramethylsilane being the internal reference. Optical rotations [α] were measured on an IBZ Messtechnik Polar-LμP polarimeter at the sodium D line (589 nm) using a 1 dm cell with dichloromethane as solvent. Previously described methods were used to prepare *N*-benzylhydroxylamine,[18] **1**,[10-12] and **7**.[14]

(*Z*)-*N*-(1-Deoxy-2,4-*O*-ethylidene-D-*erythro*-1-ylidene)methylamine *N*-oxide (2c). **{(*2R,4S,5R*)-(*Z*)-*N*-[(2-methyl-1,3-dioxan-4-yl)methylene]methylamine *N*-oxide}.** To a well–stirred solution of the D-erythrose acetal **1** (3.03 g, 20.5 mmol) with a catalytic amount of 2-pyridone (100 mg) in CH_2Cl_2 (25 mL), *N*-methylhydroxylamine hydrochloride (2.21 g, 2.3 mmol), 1,4-diazabicyclo[2.2.2]octane (DABCO, 4.55 g, 31.0 mmol), and anhydrous $MgSO_4$ (2.91 g, 24.1 mmol) were added and stirring was maintained at room temperature overnight (16 h). The precipitate was then filtered off and the filtrate poured into water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 25 mL), dried (over $MgSO_4$), and evaporated. The crude product (2.89 g, 79%) was purified by recrystallization from MeOH/EtOAc (20 : 80) to give the nitrone **2c** (2.60 g, 71% yield after crystallization) as a colourless crystalline material., m.p. = 171–172 °C, $[\alpha]_D^{25}$ =

+138.2 (*c* 0.22, CH_2Cl_2), R_f = 0.55 in MeOH/EtOAc (30 : 70) or 0.40 in MeOH/EtOAc (20 : 80). For $C_7H_{13}NO_4$, MW 175.18: calc. C 47.99 %, H 7.48 %, N 8.00 %; found C 47.64 %, H 7.25 %, N 8.01 %. IR: ν / cm^{-1}: 3415 br w ν(OH), 3059 s, 3034 m, 2990 m, 2930 s, 2876 s, 2806 m, 1630 s ν(C=N), 1508 m, 1464 m, 1453 m, 1429 s, 1412 s, 1393 m, 1379 m, 1360 m, 1340 w, 1289 m, 1234 m, 1186 vs, 1136 vs ν(N-O), 1123 vs, 1115 s, 1092 vs, 1065 m, 1049 s, 1036 vs, 955 s, 901 m, 885 vs, 851 m, 826 m, 718 m, 696 m. ^{1}H NMR (300 MHz), δ: 6.92 (d, 1 H, $J_{1,2}$ = 4.3 Hz, 1-H), 5.97 (br s, 1 H, OH), 4.75-4.71 (m, 1 H, 2-H), 4.71 (q, 1 H, J = 5.1 Hz, C<u>H</u>CH_3), 4.18 (dd, 1 H, $J_{3,4e}$ = 5.2 Hz, $J_{4a,4e}$ = 11.1 Hz, 4-H_e), 3.82 (ddd, 1 H, $J_{2,3}$ = 9.2 Hz, $J_{3,4a}$ = 10.1 Hz, 3-H), 3.75 (s, 3 H, NCH_3), 3.47 (dd, 1 H, 4-H_a), 1.33 (d, 3 H, CH<u>CH_3</u>). ^{13}C NMR (75 MHz), δ: 141.56 (C-1), 98.78 (<u>C</u>HCH_3), 76.77 (C-2), 70.82 (C-4), 65.75 (C-3), 52.13 (NCH_3), 20.12 (CH<u>CH_3</u>).

(*Z*)-*N*-(1-Deoxy-2,4-*O*-ethylidene-D-*erythro*-1-ylidene)phenylamine *N*-oxide (2a). **{(*2R,4S,5R*)-(*Z*)-*N*-[(2-methyl-1,3-dioxan-4-yl)methylene]phenylamine *N*-oxide}.** According to the procedure described for 2c; with the exception that DABCO was omitted. The crude product was purified by recrystallization from EtOAc/*i*-hexane (66 : 34) and gave the nitrone 2a (66 %) as a colourless crystalline material with m.p. = 156–157 °C., $[\alpha]_D^{25}$ = +33.6 (*c* 0.25, CH_2Cl_2), and R_f = 0.60 in MeOH/EtOAc (10 : 90) or 0.34 in EtOAc/*i*-hexane (80 : 20). For $C_{12}H_{15}NO_4$, MW: 237.24 calc. C 60.75 %, H 6.37 %, N 5.90 %; found C 60.56 %, H 6.34 %, N 5.95 %. IR: ν / cm^{-1}: 3421 br w ν(OH), 3214 m, 3092 m, 3069 m, 2996 m, 2928 m, 2872 m, 1618 w, 1607 w ν(C=N), 1578 m, 1489 m, 1460 s, 1418 s, 1381 m, 1356 w, 1289 m, 1269 w, 1229 w, 1202 s, 1184 n, 1169 m, 1144 vs, 1130 s, 1111 s, 1092 vs, 1071 vs, 1042 m, 1022 vs, 918 s, 895 m, 858 m, 833 m, 760 vs, 689 m, 681 m. ^{1}H NMR (300 MHz), δ: 7.74–7.70 (m, 2 H, NC_6H_5), 7.51–7.47 (m, 3 H, NC_6H_5), 7.44 (d, 1 H, $J_{1,2}$ = 4.4 Hz, 1-H) 5.95 (br s, 1 H, OH), 4.98 (dd, 1 H, $J_{2,3}$ = 9.3 Hz, 2-H), 4.77 (q, 1 H, J = 5.1 Hz, C<u>H</u>CH_3), 4.23 (dd, 1 H, $J_{3,4e}$ = 5.2 Hz, $J_{4a,4e}$ = 11.1 Hz, 4-H_e), 3.95 (ddd, 1 H, $J_{3,4a}$ = 10.0 Hz, 3-H), 3.55 (dd, 1 H, 4-H_a), 1.37 (d, 3 H, CH<u>CH_3</u>). ^{13}C NMR (75 MHz), δ: 140.32 (C-1), 145.56, 130.98, 129.52 and 121.42 (NC_6H_5), 98.75 (<u>C</u>HCH_3), 77.40 (C-2), 71.03 (C-4), 66.26 (C-3), 20.22 (CH<u>CH_3</u>).

(*Z*)-*N*-(1-Deoxy-2,4-*O*-ethylidene-D-*erythro*-1-ylidene)benzylamine *N*-oxide (2b). **{(*2R,4S,5R*)-(*Z*)-*N*-[(2-methyl-1,3-dioxan-4-yl)methylene]benzylamine *N*-oxide}.** According to the procedure described for 2a. The crude product was purified by recrystallization from mixture of MeOH/*i*-hexane (50 : 50) and gave the nitrone 2b (73 %) as a colourless crystalline material with m.p. = 145–146 °C. $[\alpha]_D^{25}$ = +87.1 (*c* 0.20, CH_2Cl_2), and R_f = 0.57 in MeOH/EtOAc (10 : 90) or 0.34 in EtOAc. For $C_{13}H_{17}NO_4$, MW: 251.16 calc. C 62.14 %, H 6.82 %, N 5.57 %; found C 62.15 %, H 6.86 %, N 5.57 %. IR: ν / cm^{-1}: 3252 br s ν(OH), 3079 s, 3034 m, 2990 s, 2938 m, 2921 m, 2884 s, 1605 s ν(C=N), 1583 w, 1499 m, 1474 w, 1455 s, 1408 s, 1379 m, 1294 m, 1264 m, 1236 s, 1202 s, 1194 s, 1154 s, 1132 vs, 1113 vs, 1084 vs, 1038 s, 1022 vs, 974 w, 945 s, 903 m, 891 m, 847 w, 812 w, 748 m, 733 s, 706 s. ^{1}H NMR (300 MHz), δ: 7.48-7.38 (m, 5 H, $NCH_2C_6H_5$), 6.83 (d, 1 H, $J_{1,2}$ = 4.1 Hz, 1-H), 5.90 (br s, 1 H, OH), 4.93 (s, 2 H, N<u>CH_2</u>C_6H_5), 4.75 (dd, 1 H, $J_{2,3}$ = 9.2 Hz, 2-H), 4.67 (q, 1 H, J = 5.1, C<u>H</u>CH_3), 4.17 (dd, 1 H, $J_{3,4e}$ = 5.2 Hz, $J_{4a,4e}$ = 11.1 Hz, 4-H_e), 3.82 (ddd, 1 H, $J_{3,4a}$ =

10.1 Hz, 3-H), 3.46 (dd, 1 H, 4-H_a), 1.30 (d, 3 H, CHC$\underline{H}_3$). ^{13}C NMR (75 MHz), δ: 141.00 (C-1), 131.47, 129.60, 129.53 and 129.27 ($NCH_2C_6H_5$), 98.78 (C$\underline{H}$$CH_3$), 77.27 (C-2), 71.09 (C-4), 69.11 (N$\underline{C}H_2C_6H_5$), 66.15 (C-3), 20.28 (CH$\underline{C}H_3$).

(*Z*)-*N*-(1-Deoxy-2,4-*O*-ethylidene-D-*threo*-1-yliden)benzylamine *N*-oxide (8). {(*2S,4R,5R*)-(*Z*)-*N*-[(2-methyl-1,3-dioxan-4-yl)methylene]benzylamine *N*-oxide}. According to the procedure described for 2a from D-threose. The crude product was purified by recrystallization from mixture of EtOAc/*i*-hexane (60 : 40) and gave the nitrone 8 (73 % after crystallization) as a colourless crystalline material, m. p. = 181–182 °C, $[\alpha]_D^{25}$ = -116.1 (*c* 0.19, CH_2Cl_2), and R_f = 0.51 in MeOH/EtOAc (20 : 80) or 0.26 in MeOH/EtOAc (10 : 90). For $C_{13}H_{17}NO_4$, MW: 251.16 calc. C 62.14 %, H 6.82 %, N 5.57 %; found C 62.27 %, H 6.93 %, N 5.51 %. IR: ν / cm^{-1}: 3445 br s ν(OH), 3081 m, 3032 w, 2994 m, 2965 w, 2940 w, 2909 w, 2874 w, 1609 m, 1603 m ν(C=N), 1497 w, 1458 m, 1426 m, 1408 m, 1256 w, 1206 s, 1142 vs, 1128 vs, 1107 m, 1086 vs, 1067 s, 1051 m, 1030 w, 983 m, 941 m, 914 m, 862 m, 833 s, 764 m, 708 vs. ^{1}H NMR (300 MHz), δ: 7.44–7.35 (m, 5 H, $NCH_2C_6H_5$), 6.79 (d, 1 H, $J_{1,2}$ = 4.9 Hz, 1-H), 4.97 (d, 1 H, 2-H), 4.89 (s, 2 H, N$\underline{C}H_2C_6H_5$), 4.82 (q, 1 H, J = 5.1 Hz, C$\underline{H}$$CH_3$), 4.02 (s, 1 H, 3-H), 4.00 (d, 1 H, $J_{4a,4e}$ = 11.1 Hz, 4-H_e), 3.91 (d, 1 H, 4-H_a), 3.15 (br s, 1 H, OH), 1.34 (d, 3 H, CHC$\underline{H}_3$). ^{13}C NMR (75 MHz), δ: 136.83 (C-1), 132.22, 129.43, 129.14 and 129.02 ($NCH_2C_6H_5$), 99.68 (C$\underline{H}$$CH_3$), 75.97 (C-2), 71.61 (C-4), 69.46 (N$\underline{C}H_2C_6H_5$), 62.67 (C-3), 20.85 (CH$\underline{C}H_3$).

Cycloaddition of nitrones 2a-c, 8 to styrene. General procedure.

To a stirred solution of the nitrone (4.0 mmol) in toluene (12 mL) was added styrene (1.15 eq.) and the reaction mixture was heated at reflux (110 °C) for 10 h. The resulting brown mixture was evaporated under reduced pressure.

Cycloaddition of nitrone 2a to styrene. (*3S,5R,2'R,4'S,5'R*)-3-(5'-hydroxy-2'-methyl-1',3'-dioxanyl)-2,5-diphenylisoxazolidine (3a) The crude mixture (1.40 g, ~100 %) of four diastereomers in the ratio 82 : 9 : 5 : 4 (by ^{13}C NMR) was purified and separated by column chromatography on silica (40 g, 2.0 cm × 21 cm) eluting with EtOAc/*i*-hexane (5 : 95) to give the major product 3a as a first fraction (812 mg, 58 %), and the mixture of the major and three minor diastereoisomers 4a-6a (507 mg, 36%) as the second fraction. Combined yield 1.32 g (94 %). Data for 3a, colourless crystals, m.p. = 141–142 °C, $[\alpha]_D^{25}$ = -68.5 (c 0.29, CH_2Cl_2), R_f = 0.59 in EtOAc/*i*-hexane (70 : 30) or 0.38 in EtOAc/*i*-hexane (40 : 60). For $C_{20}H_{23}NO_4$, MW: 341.40 calc. C 70.36 %, H 6.79 %, N 4.10 %; found C 70.42 %, H 6.80 %, N 3.99 %. ^{1}H NMR (500 MHz), δ: 7.46-7.33 (m, 7 H, C_6H_5); 7.23-7.21 (m, 2 H, C_6H_5); 7.09-7.05 (m, 1 H, C_6H_5); 5.19 (dd, 1 H, $J_{4a,5}$ = 8.5 Hz, $J_{4b,5}$ = 8.3 Hz, 5-H); 4.71 (q, 1 H, J = 5.1 Hz, C$\underline{H}$$CH_3$); 4.37 (br s, 1 H, OH); 4.21 (dd, 1 H, $J_{5',6e'}$ = 5.4 Hz, $J_{6a',6e'}$ = 11.1 Hz, 6'-H_e); 4.17 (ddd, 1 H, $J_{3,4a}$ = 3.3 Hz, $J_{3,4b}$ = 8.4 Hz, $J_{3,4'}$ = 9.0 Hz; 3-H); 3.95 (ddd, 1 H, $J_{4',5}$ = 9.0 Hz, $J_{5',6a'}$ = 10.0 Hz; 5'-H); 3.56 (dd, 1 H, 4'-H); 3.47 (dd, 1 H, 6'-H_a); 2.78 (ddd, 1 H, $J_{4a,4b}$ = 13.0 Hz, 4-H_b); 2.30

(ddd, 1 H, 4-H_a); 1.23 (d, 3 H, (CHC$\underline{H}_3$). ^{13}C NMR (125 MHz), δ: 149.70, 138.36, 129.41, 128.74, 128.37, 126.65, 123.24 and 115.05 (C_6H_5); 99.34 (C$\underline{H}$CH$_3$); 81.00 (C-4'); 79.72 (C-5); 70.70 (C-3); 70.10 (C-6'); 66.69 (C-5'); 40.20 (C-4); 20.56(CH$\underline{C}$H$_3$).

Cycloaddition of nitrone 2b to styrene. (*3S,5R,2'R,4'S,5'R*)-3-(5'-hydroxy-2'-methyl-1',3'-dioxanyl) -2-benzyl-5-phenylisoxazolidine (3b). The crude mixture (1.42 g, ~100 %) of three diastereomers in the ratio 81 : 12 : 7 (by ^{13}C NMR) was purified and separated by column chromatography on silica (40 g, 2.2 cm × 19 cm) eluting with EtOAc/*i*-hexane (5 : 95) to give as first major product 3b (782 mg, 55 %), diastereomer 5b (85 mg, 6%) and the mixture of the major and two minor diastereoisomers **4b**, **5b** (298 mg, 21 %) as second fraction. Combined yield 1.16 g (82 %). Data for 3b, colourless crystals, m.p. = 162–163 °C, $[\alpha]_D^{25}$ = -30.9 (c 0.18, CH_2Cl_2), R_f = 0.54 in EtOAc/i-hexane (60 : 40) or 0.38 in EtOAc/i-hexane (40 : 60). For $C_{21}H_{25}NO_4$, MW: 355.43 calc. C 70.96 %, H 7.09 %, N 3.94 %; found C 70.68 %, H 7.22 %, N 4.01 %. ^{1}H NMR (500 MHz), δ: 7.40-7.32 (m, 10 H, C_6H_5); 5.49 (br s, 1 H, OH); 5.45 (dd, 1 H, $J_{4a,5}$ = 7.5 Hz, $J_{4b,5}$ = 8.8 Hz, 5-H); 4.57 (q, 1 H, J = 5.1 Hz, C$\underline{H}$CH$_3$); 4.28 (d, 1 H, J = 12.2 Hz, NC$\underline{H}_2$C$_6$H$_5$); 4.06 (dd, 1 H, $J_{5',6e'}$ = 4.1 Hz, $J_{6a',6e'}$ = 10.7 Hz, 6'-H_e); 3.94 (d, 1 H, NC$\underline{H}_2$C$_6$H$_5$); 3.49-3.46 (m, 1 H, 3-H); 3.36 (dd, 1 H, $J_{6a',5'}$ = 9.7 Hz, 6-H_a), 3.32-3.26 (m, 2 H, 4'-H, 5'-H); 3.00 (ddd, 1 H, $J_{3,4b}$ = 8.4 Hz, $J_{4a,4b}$ = 13.4 Hz, 4-H_b); 2.35 (ddd, 1 H, $J_{3,4a}$ = 2.6 Hz, 4-H_a); 1.23 (d, 3 H, CHC$\underline{H}_3$). ^{13}C NMR (125 MHz), δ: 139.41, 135.09, 129.58, 128.88, 128.66, 128.28, 128.05, and 126.42 (C_6H_5); 99.14 (C$\underline{H}$CH$_3$); 80.38 (C-4'); 78.99 (C-5); 69.92 (C-6'); 68.70 (C-3); 66.25 (C-5'); 60.92 (NC$\underline{H}_2$C$_6$H$_5$); 38.98 (C-4); 20.47 CH$\underline{C}$H$_3$). Data for minor isoxazolidine 5b. Yield 6 %, m.p. = 128–130 °C, $[\alpha]_D^{25}$ = +14.0 (c 0.17, CH_2Cl_2), R_f = 0.47 in EtOAc/i-hexane (60 : 40) or 0.33 in EtOAc/i-hexane (40 : 60). ^{1}H NMR (300 MHz), δ: 7.41-7.33 (m, 10 H, C_6H_5); 5.47 (br s, 1 H, OH); 5.29 (dd, 1 H, $J_{4a,5}$ = 10.1 Hz, $J_{4b,5}$ = 7.0 Hz, 5-H); 4.69 (q, 1 H, J = 5.1 Hz, C$\underline{H}$CH$_3$); 4.31 (d, 1 H, J = 12.2 Hz, N-C$\underline{H}_2$C$_6$H$_5$); 4.01 (dd, 1 H, $J_{6'a,6'e}$ = 10.5 Hz, $J_{5',6'e}$ = 4.7 Hz, 6'-H_e); 3.81 (d, 1 H, N-C$\underline{H}_2$C$_6$H$_5$); 3.55 (dd, 1 H, $J_{3,4'}$ = 9.3 Hz, $J_{3,4a}$ = 6.8 Hz, 3-H); 3.47-3.21 (m, 3 H, 4'-H, 5'-H, 6'-H_a); 2.88 (dd, 1 H, $J_{4a,4b}$ = 13.1 Hz, 4-H_b); 2.48 (ddd, 1 H, 4-H_a); 1.30 (d, 3 H, J = 5.1 Hz, CHC$\underline{H}_3$). ^{13}C NMR (62 MHz), δ: 141.15, 135.63, 129.52, 128.93, 128.66, 128.25, 127.83 and 125.96 (C_6H_5); 99.21 (C$\underline{H}$CH$_3$); 81.38 (C-4'); 78.18 (C-5); 70.03 (C-6'); 68.80 (C-3); 65.96 (C-5'); 63.88 (NC$\underline{H}_2$C$_6$H$_5$); 37.02 (C-4); 20.61 (CH$\underline{C}$H$_3$).

Cycloaddition of nitrone 2c with styrene. (*3S,5R,2'R,4'S,5'R*)-3-(5'-hydroxy-2'-methyl-1',3'-dioxanyl)-2-methyl-5-phenyl isoxazolidine (3c). The crude mixture (1.16 g, ~100 %) of four diastereomers in the ratio 69 : 17 : 10 : 4 (by ^{13}C NMR) was purified and separated by column chromatography on silica (35 g, 2.0 cm × 21 cm) eluting with EtOAc/*i*-hexane (5 : 95) to give major product 3c as a first fraction (638 mg, 55%) and the mixture of the major and three minor diastereoisomers **4c-6c** (348 mg, 30%) as the second fraction. Combined yield 986 mg (85%). Data for 3c, colourless crystals, m.p. = 65–67 °C, $[\alpha]_D^{25}$ = -16.3 (c 0.19, CH_2Cl_2), R_f = 0.38 in EtOAc/*i*-hexane (80 : 20) or 0.25 in EtOAc/*i*-hexane (60 : 40). For $C_{15}H_{21}NO_4$, MW: 279.33 calc. C 64.50 %, H 7.58 %, N 5.01 %; found C 64.63 %, H 7.33 %, N 5.27 %. ^{1}H NMR (500 MHz), δ:

7.37-7.29 (m, 5 H, C_6H_5); 5.49 (br s, 1 H, OH); 5.34 (dd, 1 H, $J_{4a,5}$ = 7.8 Hz, $J_{4b,5}$ = 8.6 Hz, 5-H); 4.61 (q, 1 H, J = 5.1 Hz, $\underline{CH}CH_3$); 4.15 (dd, 1 H, $J_{5',6e'}$ = 5.4 Hz, $J_{6a',6e'}$ = 11.0 Hz, 6'-H_e); 3.67 (ddd, 1 H, $J_{4',5'}$ = 8.5 Hz, $J_{5',6a'}$ = 10.0 Hz, 5'-H); 3.40 (dd, 1 H, 6'-H_a); 3.30-3.28 (m, 2 H, 3-H, 4'-H); 2.94 (ddd, 1 H, $J_{3,4b}$ = 8.0 Hz, $J_{4a,4b}$ = 13.2 Hz, $J_{4b,5}$ = 8.6 Hz,, 4-H_b); 2.82 (s, 3 H, $N\underline{CH_3}$); 2.30 (ddd, 1 H, $J_{3,4a}$ = 2.4 Hz, $J_{4a,5}$ = 7.8 Hz, 4-H_a); 1.27 (d, 3 H, $CH\underline{CH_3}$). ^{13}C NMR (125 MHz), δ: 139.27, 128.54, 128.04, and 126.49 (C_6H_5); 99.21 ($\underline{CH}CH_3$); 80.51 (C-4'); 77.90 (C-5); 72.08 (C-3); 70.17 (C-6'); 66.97 (C-5'); 44.84 ($N\underline{CH_3}$); 39.17 (C-4); 20.52 ($CH\underline{CH_3}$).

Cycloaddition of nitrone 8 to styrene. ***(3R,5R,2'S,4'R,5'R)*****-3-(5'-hydroxy-2'-methyl-1',3'-dioxanyl) -2-benzyl-5-phenylisoxazolidine (9).** The crude mixture (1.45 g, ~100 %) of four diastereomers in the ratio 90 : 5 : 3 : 2 (by ^{13}C NMR) was purified and separated by column chromatography on silica gel (40 g, 1.5 cm × 36 cm) eluting with EtOAc/*i*-hexanes (15 : 85) to give as first major product 9 (1.06 g, 73 %) and the mixture of major and three minor diastereoisomers 10-12 (160 mg, 11 %) as the second fraction. Combined yield 1.22 g (84 %). Data for 9, colourless crystals, m.p. = 110–112 °C, $[\alpha]_D^{25}$ = +51.0 (c 0.19, CH_2Cl_2), R_f = 0.40 in EtOAc/*i*-hexane (50 : 50) or 0.21 in EtOAc/*i*-hexane (30 : 70). For $C_{21}H_{25}NO_4$, MW: 355.43 calc. C 70.96 %, H 7.09 %, N 3.94 %; found C 70.75 %, H 7.00 %, N 4.07 %. ^{1}H NMR (500 MHz), δ: 7.42-7.29 (m, 10 H, C_6H_5); 5.28 (dd, 1 H, $J_{4a,5}$ = 8.8 Hz, $J_{4b,5}$ = 7.2 Hz, 5-H); 4.67 (q, 1 H, J = 5.1 Hz, $\underline{CH}CH_3$); 4.21 (d, 1 H, J = 13.2 Hz, $N\underline{CH_2}C_6H_5$); 4.05 (d, 1 H, $N\underline{CH_2}C_6H_5$); 4.04 (dd, 1 H, $J_{5',6e'}$ = 2.1 Hz, $J_{6a',6e'}$ = 12.1 Hz, 6'-H_e or 6'-H_a); 3.79-3.77 (m, 1 H, 5'-H); 3.78 (dd, 1 H, $J_{5',6a'}$ = 1.4 Hz, 6'-H_a or 6'-H_e); 3.67 (ddd, 1 H, $J_{3,4a}$ = 5.6 Hz, $J_{3,4b}$ = 7.9 Hz, $J_{3,4'}$ = 8.8 Hz, 3-H); 3.58 (dd, 1 H, $J_{4',5'}$ = 1.1 Hz, 4'-H); 2.83 (ddd, 1 H, $J_{4a,4b}$ = 12.9 Hz, 4-H_b); 2.73 (br s, 1 H, OH); 2.28 (ddd, 1 H, 4-H_a); 1.31 (d, 3H, $CH\underline{CH_3}$). ^{13}C NMR (125 MHz), δ: 139.38, 137.20, 129.46, 129.45, 128.42, 127.90, 127.52, and 126.53 (C_6H_5); 99.70 ($\underline{CH}CH_3$); 80.63 (C-4'); 78.46 (C-5); 71.92 (C-6'); 64.96 (C-3); 63.60 (C-5'); 61.65 ($N\underline{CH_2}C_6H_5$); 39.59 (C-4); 20.89 $CH\underline{CH_3}$).

X-ray diffraction study: X-ray structure determination of 3a $C_{20}H_{23}O_4N$: colourless crystal (0.40 x 0.45 x 0.80 mm^3, grown from diethyl ether), $C_{20}H_{23}O_4N$, M_r = 341.39, hexagonal, space group P 6_1, a = 10.03376(1) Å, c = 32.3577(4) Å, γ = 120 °, V = 2823.37(5) $Å^3$, Z = 6, D_x = 1.205 g cm^{-3}, T = 297K. A Siemens SMART diffractometer (CCD area detector) and graphite monochromated Mo Kα radiation, λ = 0.71069 Å, was used for all measurements. The cell dimensions were refined using 8192 strong reflections. A whole sphere of reciprocal space was collected by ω-scans (0.3° wide frames, 30 sec. exposure each) by combination of 8 sets with 4 different settings of φ angle (0°, 90°, 180°, 270°) and two settings of detector angle (-25° and -55°). The collected data range is $3.8° \le 2\Theta \le 67.64°$ ($-15 \le h \le 15$, $-15 \le k \le 15$, $-50 \le l \le 50$). The crystal-to-detector distance was 6.21 cm. 46 603 reflections were collected and 7543 unique reflections [R_{int} = 0.0195, R (σ) = 0.0145] were obtained after correction for polarization and Lorents effects. Empirical psi-scan absorption (SADABS, μ = 0.84 cm^{-1}) was done. The structure was solved by directs methods (SHELXS86)[19] and refined by full-matrix least-squares SHELXL93 software[20] using anisotropic temperature factors for non-hydrogen atoms, hydrogen atoms with isotropic temperature factors in idealized positions riding on the atom

to which they are attached (C-H = 0.96 Å for CH_3, C-H = 0.97 Å for CH_2, C-H = 0.98 Å for CH sp^3 hybridization, C-H = 0.93 Å for CH sp^2 hybridization and O-H = 0.82 Å for OH), 5914 reflections with $F_o > 4\sigma(F_o)$, weights $w = 1/[\sigma^2(F_o^2) + (0.0762P)^2 + 0.0814P]$ where $P = (F_o^2 + 2F_c^2)/3$. Final R = 0.0473 and wR = 0.1213. Maximum shift/σ in final least-square cycle < 0.02. Minimum and maximum difference electron densities were -0.17 and 0.24 e $Å^{-3}$. As Flack parameter x = 0.50(65), absolute structure cannot be determined reliably, but is taken from the known absolute configuration of D-erythrose (and its precursor D-glucose). The ORTEP drawing of **3a** is shown in Figure 1. [21]

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