Preparation and 1,3-dipolar cycloadditions of chiral nitrones derived from D-xylose with vinyl acetate

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Dedicated to Professor Albert Padwa on his 65th birthday

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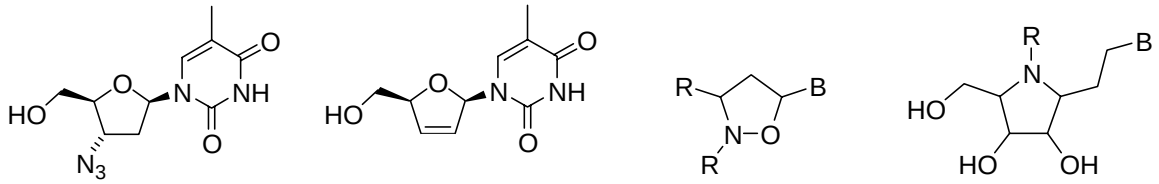
Abstract

New chiral nitrones **8** and **13**, easily prepared from D-xylose by multistep synthetic routes, undergo regioselective 1,3-dipolar cycloadditions with vinyl acetate giving 5-acetoxy isoxazolidines in good yields. Attack of the dipolarophile on the *Z*-configuration of the nitrone through an *endo* transition state from both prochiral faces of the nitrone affords C-3/C-5 *trans* isoxazolidines possessing C-1'/C-3 *erythro* (from *si*) and the C-1'/C-3 *threo* (from *re*) relative configuration as two major isomers.

Keywords: Chiral, dipolar cycloadditions, nitrones, isoxazolidines, saccharides

Introduction

Monosaccharides are powerful building blocks in the synthesis of polyhydroxylated compounds which are of interest in the search for various bioactive substances. Nucleoside analogues have received considerable attention over the last 10 years [1] due to the discovery of the antiviral effects of azidothymidine (AZT) **1** and dideoxynucleosides (ddN), for example d4T **2**, as inhibitors of *Reverse Transcriptase* and DNA *Polymerase* HIV viruses.[2] Insertion of the next heteroatom (O, S, N) to the furanosyl ring or its replacement for the another heterocycle gives the possibility of finding new structures (1,3-dioxolane,[3] 1,3-oxothiolane,[4] isoxazolines [5] and isoxazolidines,[6] thiazolidines,[7] pyrrolidines,[8] and nucleosides for example) with lower toxicity and higher biological effect.



1 **2** **3** **4**

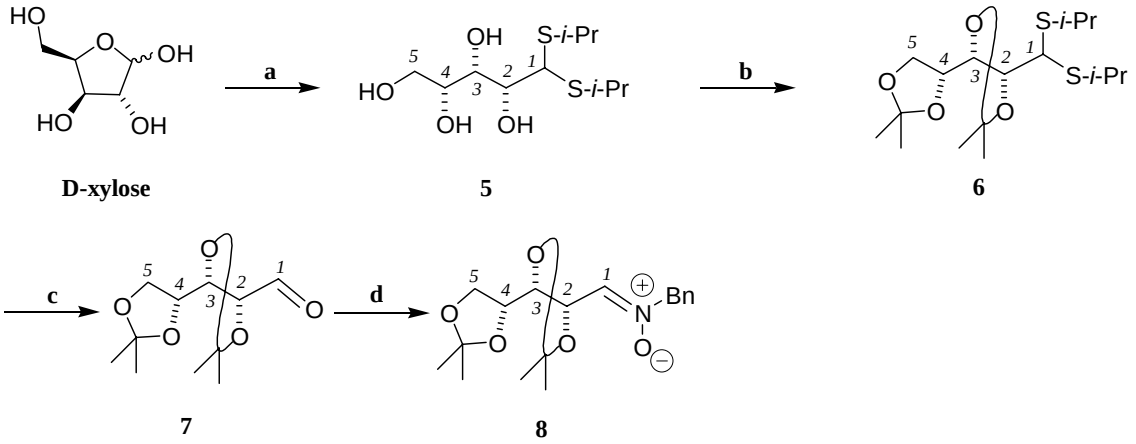
Figure 1

With our continuing efforts to utilize chiral 1,3-dipolar cycloadditions,[9] we focused our attention on developing simple routes to the synthesis of isoxazolidinyl nucleosides **3**.[10] The first example of an isoxazolidinyl nucleoside was synthesized in 1992 by Tronchet.[6a] Since this time many modified nucleosides possessing an isoxazolidinyl moiety have been created by a wide range of synthetic pathways, including Michael additions of hydroxylamines to α,β-unsaturated esters,[6b,11] additions of ketene acetals to nitrones,[6b,12] 1,3-dipolar cycloadditions of nitrones to vinyl acetate [6b,13] with the subsequent transformation of the formed isoxazolidines and direct 1,3-dipolar cycloaddition reactions of nitrones with *N*-vinylated bases.[5b,13b,14] In this paper we describe the detailed preparation of new chiral nitrones derived from D-xylose and their application in the 1,3-dipolar cycloaddition with vinyl acetate.

Results and Discussion

The 1,3-Dipolar cycloaddition of nitrones with vinyl acetate leads to the 5-acetoxy-isoxazolidines, which can by easily transformed to the isoxazolidinyl nucleosides by the Vorbrüggen method (silylated nucleosidic base, TMSOTf as Lewis acid).[15] In accordance with the our goal to prepare isoxazolidinyl nucleosides with the possibility of subsequent transformation toward novel aza-nucleosides **4** (Figure 1) possessing an ethylene bridge between the anomeric carbon and nitrogen, we have focused our attention on the preparation of new sugar-derived nitrones suitable for building pyrrolidine rings. Our preliminary results in this area have been the subject of a recent communication.[10]

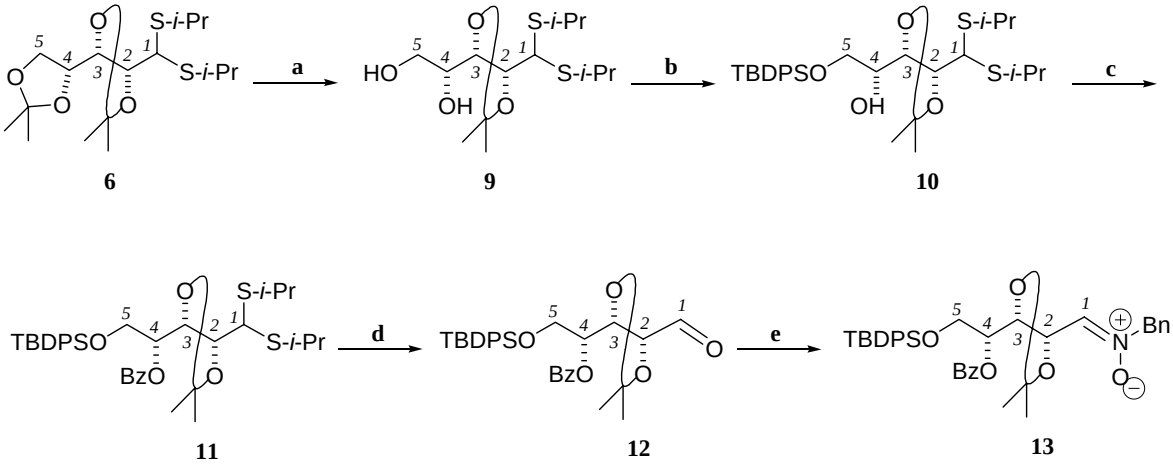
The chiral nitrone **8** was prepared from D-xylose in four steps (Scheme 1.). Thus, D-xylose was converted into D-xylose diisopropyldithioacetal **5** by treatment with 2-mercaptopropane. Reaction of the corresponding dithioacetal with acetone in the presence of a catalytic quantity of sulfuric acid gave the protected dithioacetal **6**. Deprotection of thiol group ($HgCl_2$/HgO) afforded aldehyde **7**,[16] which in turn reacted with *N*-benzylhydroxylamine according to the method of Dondoni and Merino *et al.*[17] to give nitrone **8**.



Reagents and reaction conditions: (a) *i*-PrSH, HCl, r.t, 2 h, 92%. (b) Acetone, H_2SO_4, r.t., 8 h, 52%. (c) Acetone, H_2SO_4, $HgCl_2$/HgO, 56 °C, 2 h. (d) BnNHOH, CH_2Cl_2, $MgSO_4$, r.t., 4 h, 42% in two steps.

Scheme 1

The chiral nitrone **13**, an alternative suitable for building the pyrrolidine moiety in the azanucleoside **4** (Figure 1) was prepared in five steps (Scheme 2). Selective removal of the primary acetonide of **6** (ethanol/water/HCl)[18] gave diol **9**. Silylation of the primary alcohol group with TBDPSCl/imidazole [19] in CH_2Cl_2 followed by benzoylation of the silylated dithioacetal **10** with benzoyl chloride [20] afforded the protected dithioacetal **11**. Deprotection of the thiol group ($HgCl_2$/HgO) and condensation of aldehyde **12** with *N*-benzylhydroxylamine gave nitrone **13.**



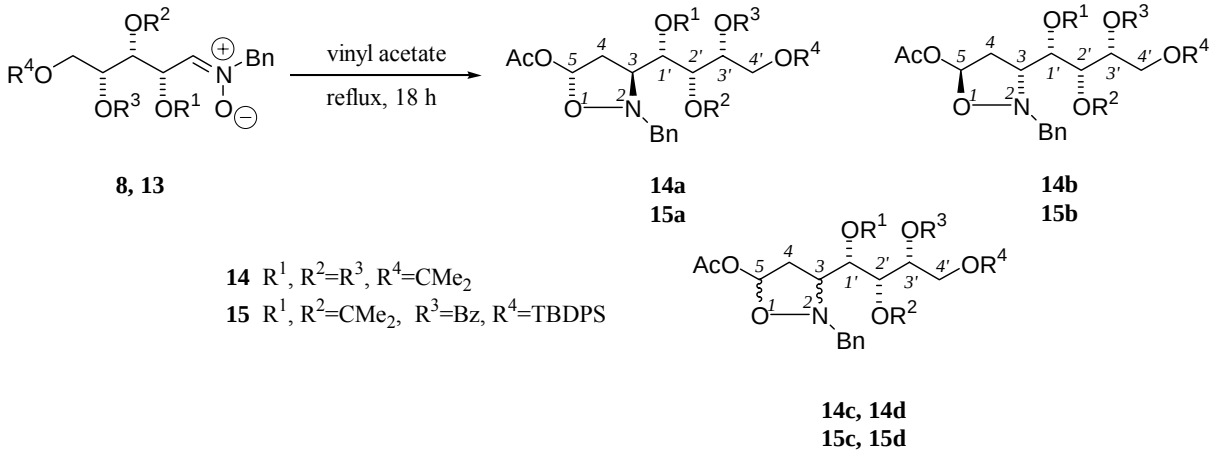
Reagents and reaction conditions: (a) EtOH/H_2O (80%), HCl, 40 °C, 4 h, 62%. (b) TBDPSCl, imidazole, CH_2Cl_2, °C to r.t., 30 min, 92%. (c) BzCl, pyridine, reflux, 24 h, 90%; (d)

$HgCl_2$/HgO, acetone, H_2O, 56 °C, 2 h; (e) BnNHOH, CH_2Cl_2, $MgSO_4$, r.t., 4 h, 63% in two steps.

Scheme 2

All structures described were determined by ^{1}H- and ^{13}C- NMR measurements. For the final nitrones, the H-1 proton is particularly diagnostic (d, 6.81 ppm, $J_{1,2}$ = 5.7 Hz) for nitrone **8** and (d, 6.74 ppm, $J_{1,2}$ = 5.4 Hz) in the case of nitrone **13**. In addition, a singlet for the benzyl methylene hydrogens is observed at 4.88 ppm in (**8**) and 4.83 ppm in (**13**). Only one *Z*-isomer of nitrone has been formed during the reaction (estimated from ^{1}H NMR spectra of crude reaction mixtures). The expected *Z*- configuration of the C=N double bond was confirmed by nuclear Overhauser effect (NOE) difference spectroscopy, this is in accord with the results previous described in the literature for the similar structures.[17]

Cycloadditions of nitrones **8** and **13** to vinyl acetate proceeded regioselectively and led to the isoxazolidines as a mixture of diastereoisomers (Table). Purification by flash chromatography allowed the isolation of pure *endo*-adducts **14a**, **14b** and **15a** with the C-3/C-5 *trans*- relative configuration identified by spectroscopic analysis, particularly NOE difference experiments.



Scheme 3

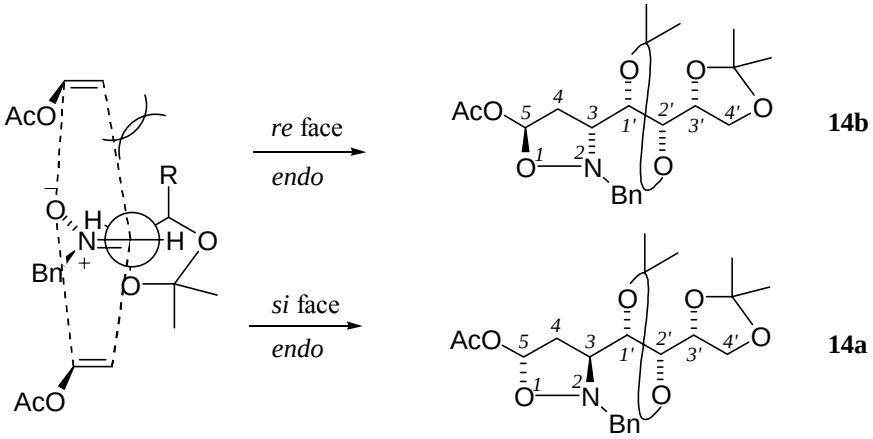
Table. 1,3-Dipolar cycloadditions of nitrones **8** and **13** to vinyl acetate

Entry	Nitrone	Total yield (%)	Adduct	**a** : **b** : **c** : **d** [a]
1	**8**	90	**15**	70 : 13 : 9 : 8
2	**13**	73	**16**	71 : 15 : 14 : -

[a] Ratios were determined by ^{1}H- NMR and ^{13}C- NMR (400 MHz) on the crude reaction mixture.

Based on our previous results from 1,3-dipolar cycloadditions of sugar nitrones bearing a protected hydroxy group in the α-position,[9] we assigned to isomer **14a** (and similarly **15a**) a C-

1′/C-3 *anti* relationship as a result of dipolarophile attack from the less sterically hindered *si* diastereotopic face of the nitrone and a C-1′/C-3 *syn*- relationship for isomer **14b**, resulting from attack of vinyl acetate from the *re*- face (Figure 2).



R: 2,2-dimethyl-1,3-dioxolane-4-yl

Figure 2

The determination of the configuration at the C-3 and C-5 positions of the isomers **14c**, **14d**, **15b** and **15c** was impossible, because we were not able to separate them in the pure form.
In conclusion, synthesis of the nitrones 8 and 13 starting from D-xylose, and their 1,3-dipolar cycloadditions with vinyl acetate have been investigated.

Experimental Section

General Procedures. All melting points were measured on a Kofler apparatus and are uncorrected. Specific rotations were measured at 25 °C with a Polar L-μP polarimeter (IBZ MESSTECHNIK). NMR spectra were recorded on a Varian VRX-300 (^{1}H, 300 MHz, and ^{13}C, 75 MHz) and a Bruker DRX-400 (^{1}H, 400 MHz, and ^{13}C, 125 MHz) spectrometers in $CDCl_3$ using TMS as the internal standard. All reactions were monitored by TLC Alugram SIL 50/UV_{254} (Macherey Nagel) with detection by UV or with an ethanolic solution of *p*-anisaldehyde (0.5 ml of *p*-anisaldehyde, 0.5 ml of concentrated sulfuric acid, 9 ml of ethanol and a few drops of acetic acid) followed by heating. Merck silica gel 60 (0.040–0.064 mm) was employed for column chromatography. All solvents were purified by standard methods. D-Xylose was purchased from Lachema, 2-mercaptopropane and imidazole from Aldrich, *tert*-butyldiphenylsilyl chloride from Fluka and were used without further purification. Vinyl acetate was freshly distilled before use.

D-Xylo-diisopropyldithioacetal (5). D-Xylose (4 g, 27.0 mmol) was dissolved in concentrated hydrochloric acid (4 ml) and the solution was cooled to 3 °C (ice-water bath). 2-

Mercaptopropane (4 g, 54.0 mmol) was added slowly. The mixture was stirred for 2 hours at 10–15 °C. Then 60 ml of water was added and the resulting solution was neutralized with solid $PbCO_3$. The mixture was filtered under suction and concentrated on a rotary evaporator. The product was separated by column chromatography (silica gel, ethyl acetate). The compound **5** was obtained as a pale-brown oil (6.9 g, 91%), $[\alpha]_D$ = +8.9 (CH_3OH; *c* 0.28). NMR data**:** δ_H (300 MHz, $CDCl_3$) 1.32 (d, 12 H, $SCH(CH_3)_2$), 3.22 (m, 2 H, $SCH(CH_3)_2$), 3.71 (dd, 1 H, H-3, $J_{2,3}$ = 7.8 Hz, $J_{3,4}$ = 2.4 Hz), 3.75 (d, 2 H, H-5, $J_{4,5}$ = 4.8 Hz), 3.85 (m, 5 H, H-1, 4 OH), 4.05 (dd, 1 H, H-4, $J_{3,4}$ = 2.4 Hz, $J_{4,5}$ = 4.8 Hz), 4.12 (d, 1 H, H-2, $J_{2,3}$ = 7.8 Hz). δ_C (75 MHz, $CDCl_3$) 23.5, 23.9, 24.0 ($SCH(CH_3)_2$), 35.0, 35.6 ($SCH(CH_3)_2$), 53.3 (C-1), 64.2 (C-5), 70.7 (C-2), 73.3 (C-4), 74.4 (C-3).

(2,3:4,5-Di-*O*-isopropylidene-D-xylo)-diisopropyldithioacetal (6). To a stirred solution of acetone (30 ml) and the concentrated sulfuric acid (0.8 ml) cooled to –5 °C, a solution of dithioacetal **5** (5 g, 18.0 mmol) in acetone (25 ml) was added. The mixture was stirred for 8 hours at the room temperature. Saturated ammonium hydroxide was added. The colorless precipitate was removed by filtration and the solvent was evaporated under reduced pressure using a rotary evaporator. The product was isolated by column chromatography (silica gel, hexanes:ethyl acetate=5:1). Compound **6** was obtained as a colorless solid (3.0 g, 52 %), mp 52–54 °C (crystallized from mixture MeOH/water), $[\alpha]_D$ = –39.2 ($CHCl_3$, *c* 0.17). (Anal. Calcd. for $C_{17}H_{32}O_4S_2$: C, 56.01; H, 8.85, S 17.59%. Found: C, 56.39; H, 8.77, S 17.79%): NMR data: δ_H (300 MHz, $CDCl_3$) 1.28–1.33 (m, 12 H, $SCH(CH_3)_2$), 1.38, 1.43, 1.44, 1.47 (4 × s, 4 × 3 H, $C(CH_3)_2$), 3.18–3.36 (m, 2 H, $SCH(CH_3)_2$), 3.94 (dd, 1 H, H-5a, $J_{4,5}$ = 7.9 Hz, $J_{5a,5b}$ = 7.9 Hz), 4.03 (d, 1 H, H-1, $J_{1,2}$ = 4.5 Hz), 4.05 (dd, 1 H, H-5b, $J_{4,5b}$ = 6.6 Hz, $J_{5a,5b}$ = 8.0 Hz), 4.15 (dd, 1 H, H-3, $J_{2,3}$ = 7.4 Hz, $J_{3,4}$ = 2.9 Hz), 4.35 (ddd, 1 H, H-4, $J_{3,4}$ = 2.9 Hz, $J_{4,5a}$ = $J_{4,5b}$ = 6.9 Hz), 4.41 (dd, 1 H, H-2, $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 7.5 Hz). δ_C (75 MHz, $CDCl_3$) 23.2, 23.4, 23.5, 23.6 ($SCH(CH_3)_2$), 25.7, 26.2, 27.2, 27.4 ($C(CH_3)_2$), 35.2, 35.5 ($SCH(CH_3)_2$), 50.7 (C-1), 66.0 (C-5), 75.4 (C-2), 78.1 (C-4), 80.0 (C-3), 109.4, 110.0 ($C(CH_3)_2$).

2,3:4,5-Di-*O*-isopropylidene-aldehydo-D-xylose (7). To a vigorously stirred solution of dithioacetal **6** (1.24 g, 3.4 mmol) in acetone/water (20 ml, 9:1 v/v) mercury(II) oxide (1.47 g, 6.8 mmol) and mercury(II) chloride (1.86 g, 6.8 mmol) were added. The contents of the flask were stirred for 2 hours under reflux. The resulting mixture was filtered through Celite®, washed with acetone and the solvent was removed on a rotary evaporator. Chloroform (10 ml) was added, the precipitate was collected by filtration and the filtrate was extracted with 1 *M* aqueous potassium iodide (2 x 10 ml) followed by water (10 ml). The organic layer was dried with sodium sulfate and solvent was evaporated under reduced pressure. The crude aldehyde obtained as a pale-yellow oil (0.37 g) was used in the next reaction without further purification.

(2,3-*O*-Isopropylidene-D-xylo)-diisopropyldithioacetal (9). Dithioacetal **6** (1 g, 2.74 mmol) was dissolved in ethanol (50 ml, 4:1 v/v with water) and concentrated hydrochloric acid (0.1 ml) was added dropwise. The temperature was raised to 50 °C and reaction mixture was stirred for 3 hours. The solution was neutralized with saturated Na_2CO_3 solution and the solvent was removed on a rotary evaporator. The product was isolated by column chromatography (silica gel,

hexanes:ethyl acetate=1:1). Compound **9** was obtained as a colorless solid (0,544 g, 62 %), mp 62–64 °C, $[\alpha]_D$ = –48.4 ($CHCl_3$, *c* 0.19). (Anal. Calcd. for $C_{14}H_{28}O_4S_2$: C, 51.82; H, 8.70, S 19.76%. Found: C, 52.14; H, 8.54, S 20.01%). NMR data: δ_H (300 MHz, $CDCl_3$) 1.29–1.34 (m, 12 H, $SCH(CH_3)_2$), 1.45, 1.48 (2 × s, 2 × 3 H, $C(CH_3)_2$), 2.40 (bs, 2 H, OH), 3.26 (m, 2 H, $SCH(CH_3)_2$), 3.72–3.83 (m, 2 H, H-5a, H-5b), 3.93 (ddd, 1 H, H-4, $J_{3,4}$ = 2.1 Hz, $J_{4,5a}$ = $J_{4,5b}$ = 4.5 Hz), 4.05 (d, 1 H, H-1, $J_{1,2}$ = 4.8 Hz), 4.17 (dd, 1 H, H-3, $J_{2,3}$ = 7.8 Hz, $J_{3,4}$ = 2.1 Hz), 4.46 (dd, 1 H, H-2, $J_{1,2}$ = 4.8 Hz, $J_{2,3}$ = 7.8 Hz). δ_C (75 MHz, $CDCl_3$) 23.2, 23.4, 23.4, 23.5 ($SCH(CH_3)_2$), 27.2 (2 × $C(CH_3)_2$), 35.2, 35.6 ($SCH(CH_3)_2$), 50.2 (C-1), 65.3 (C-5), 70.1 (C-2), 79.6 (C-4), 80.6 (C-3), 110.0 ($C(CH_3)_2$).

Isopropylidene-5-*O*-*tert*-butyldiphenylsilyl-D-xylo)-diisopropyldithioacetal (10). A solution of dithioacetal **9** (0.78 g, 2.46 mmol) and imidazole (0.37 g, 5.41 mmol) in dichloromethane (3 ml) was cooled to 0 °C (ice bath) and a solution of *tert*-butyldiphenylsilyl chloride (0.74 g, 2.71 mmol) in dichloromethane (2 ml) was added under argon. The reaction mixture was stirred for 30 minutes at the room temperature and colorless precipitate was removed by filtration and the filtrate was extracted with saturated ammonium chloride solution. The aqueous layer was subsequently extracted twice with dichloromethane. The combined organic layers were dried over sodium sulfate and solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes:ethyl acetate=1:1) giving **10** as a colorless oil (1.26 g, 92 %), $[\alpha]_D$ = –28.5 ($CHCl_3$, *c* 0.33). NMR data**:** δ_H (300 MHz, $CDCl_3$) 1.07 (s, 9 H, $OSiC(CH_3)_3$), 1.26–1.32 (m, 12 H, $SCH(CH_3)_2$), 1.42, 1.47 (2 × s, 2 × 3 H, $C(CH_3)_2$), 2.44 (bs, 1 H, OH), 3.18–3.32 (m, 2 H, $SCH(CH_3)_2$), 3.70 (dd, 1 H, H-5a, $J_{4,5a}$ = 6.6 Hz, $J_{5a,5b}$ = 9.9 Hz), 3.77 (dd, 1 H, H-5b, $J_{4,5b}$ = 6.2 Hz, $J_{5a,5b}$ = 9.9 Hz), 3.95 (ddd, 1 H, H-4, $J_{3,4}$ = 1.5 Hz, $J_{4,5a}$ = $J_{4,5b}$ = 6.6 Hz), 3.99 (d, 1 H, H-1, $J_{1,2}$ = 4.8 Hz), 4.32 (dd, 1 H, H-3, $J_{2,3}$ = 7.8 Hz, $J_{3,4}$ = 1.5 Hz), 4.42 (dd, 1 H, H-2, $J_{1,2}$ = 4.8 Hz, $J_{2,3}$ = 7.8 Hz), 7.41–7.68 (m, 10 H, Ph). δ_C (75 MHz, $CDCl_3$) 19.3 ($OSiC(CH_3)_3$), 23.3, 23.4, 23.5 ($SCH(CH_3)_2$), 26.6, 26.9, 27.2 ($OSiC(CH_3)_3$, $C(CH_3)_2$), 35.1; 35.4 ($SCH(CH_3)_2$), 50.5 (C-1), 65.5 (C-5), 70.3 (C-2), 78.4 (C-4), 79.6 (C-3), 109.6 ($C(CH_3)_2$), 127.7, 129.6, 129.8, 133.4, 134.8, 135.6 ($OSiPh_2$).

(2,3-*O*-Isopropylidene-4-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-D-xylo) diisopropyldithioacetal (11). A stirred solution of dithioacetal **10** (0.37 g, 0.66 mmol) and pyridine (0.08 ml, 0.98 mmol) in dichloromethane (4 ml) was cooled to 0 °C and benzoyl chloride (0.11 g, 0.13 ml, 0.79 mmol) was added dropwise. The mixture was heated for 24 hours under reflux. Then, the solution was diluted with saturated sodium bicarbonate solution, the organic layer was separated and extracted with brine followed by water and dried over sodium sulfate. The solvent was evaporated and the product was isolated by column chromatography (silica gel, hexanes:ethyl acetate=5:1). Compound **11** was obtained as a colorless oil (0.39 g, 90 %), $[\alpha]_D$ = –34.9 ($CHCl_3$, *c* 0.21). NMR data: δ_H (300 MHz, $CDCl_3$) 1.01 (s, 9 H, $OSiC(CH_3)_3$), 1.24–1.31 (m, 12 H, $SCH(CH_3)_2$), 1.44, 1.49 (2 × s, 2 × 3H, $C(CH_3)_2$), 3.10–3.26 (m, 2 H, $SCH(CH_3)_2$), 3.96–4.00 (m, 3 H, H-5a, H-5b, H-1), 4.22 (dd, 1 H, H-2, $J_{1,2}$ = 4.2 Hz, $J_{2,3}$ = 7.8 Hz), 4.59 (dd, 1 H, H-3, $J_{2,3}$ = 7.8 Hz, $J_{3,4}$ = 2.1 Hz), 5.58 (ddd, 1 H, H-4, $J_{3,4}$ = 1.9 Hz, $J_{4,5a}$ = $J_{4,5b}$ = 6.7 Hz), 7.30–8.10 (m, 15 H, $OSiPh_2$, COPh). δ_C (75 MHz, $CDCl_3$) 19.2 ($OSiC(CH_3)_3$), 23.3, 23.4, 23.5 ($SCH(CH_3)_2$), 26.6, 26.7, 27.2

($OSiC(CH_3)_3$, $C(CH_3)_2$), 35.2; 35.4 ($SCH(CH_3)_2$), 50.3 (C-1), 62.8 (C-5), 72.4 (C-2), 78.4 (C-4), 79.3 (C-3), 109.9 ($C(CH_3)_2$), 127.7–135.7 ($OSiPh_2$, COPh), 165.9 (COPh).

2,3-*O*-Isopropylidene-4-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-aldehydo-D-xylose (12). To a vigorously stirred solution of dithioacetal **11** (0.34 g, 0.52 mmol) in acetone/water (10 ml, 9:1 v/v) mercury(II) oxide (0.22 g, 1.03 mmol) and mercury(II)chloride (0.28 g, 1.03 mmol) were added. The contents of the flask were stirred for 2 hours under reflux. The resulting mixture was filtered through Celite®, washed with acetone and the solvent was removed on a rotary evaporator. Chloroform (10 ml) was added, the precipitate was collected by filtration and filtrate was extracted with 1 *M* aqueous potassium iodide (2 x 10 ml) followed by water (10 ml). The organic layer was dried with sodium sulfate and solvent was evaporated under reduced pressure to give the crude aldehyde as a pale-yellow oil (0.25 g) which was used in the next reaction without further purification.

(*Z*)-*N*-(1-Deoxy-2,3:4,5-di-*O*-isopropylidene-D-xylo-1-ylidene)-benzylamine-*N*-oxide (8). To a well-stirred solution of crude aldehyde **7** (0.3 g, 1.3 mmol) in dichloromethane (10 ml), anhydrous magnesium sulfate (0.24 g, 1.95 mmol) and *N*-benzylhydroxylamine (0.24 g, 1.95 mmol) were added. The reaction mixture was stirred for 4 hours at the room temperature. The progress of the reaction was monitored by TLC (hexanes:ethyl acetate=5:1). After the removal of magnesium sulfate by filtration, the solvent was evaporated under reduced pressure. The residue was treated with petroleum ether and the pale-yellow precipitate was crystallized from hexanes giving **8** as a colorless solid (0.31 g, 42 % over two steps). mp 95–97 °C, $[\alpha]_D$ = +41.3 ($CHCl_3$, *c* 0.22). (Anal. Calcd. for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51, N 4.18%. Found: C, 64.69; H, 7.37, N 4.45%). NMR data: δ_H (400 MHz, $CDCl_3$) 1.36, 1.38, 1.43, 1.48 (4 × s, 4 × 3 H, $C(CH_3)_2$), 3.73 (dd, 1 H, H-5a, $J_{4,5a}$ = 6.8 Hz, $J_{5a,5b}$ = 8.6 Hz), 3.95 (dd, 1 H, H-3, $J_{2,3}$ = 5.9 Hz, $J_{3,4}$ = 6.7 Hz), 4.09 (dd, 1 H, H-5b, $J_{4,5b}$ = 6.7 Hz, $J_{5a,5b}$ = 8.8 Hz), 4.40 (ddd, 1 H, H-4, $J_{3,4}$ = 6.7 Hz, $J_{4,5a}$ = $J_{4,5b}$ = 6.7 Hz), 4.89 (s, 2 H, NCH_2Ph), 5.07 (dd, 1 H, H-2, $J_{1,2}$ = $J_{2,3}$ = 6.2 Hz), 6.81 (d, 1 H, H-1, $J_{1,2}$ = 6.0 Hz), 7.41–4.42 (bs, 5 H, NCH_2Ph). δ_C (125 MHz; $CDCl_3$) 25.8, 26.8, 27.0, 27.4 ($C(CH_3)_2$), 66.1 (C-5), 70.1 (NCH_2Ph), 73.6 (C-2), 76.8 (C-4), 81.1 (C-3), 110.1; 111.3 ($C(CH_3)_2$), 129.4, 129.5, 129.7, 129.8, 130.0, 132.5 (NCH_2Ph), 137.4 (C-1).

(*Z*)-*N*-(1-Deoxy-2,3-*O*-isopropylidene-4-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-D-xylo-1-ylidene)-benzylamine-*N*-oxide (13). To a well-stirred solution of crude aldehyde **12** (0.25 g, 0.47 mmol) in dichloromethane (10 ml), anhydrous magnesium sulfate (0.28 g, 2.30 mmol) and *N*-benzylhydroxylamine (0.07 g, 0.52 mmol) were added. The reaction mixture was stirred for 4 hours at the room temperature. The progress of the reaction was monitored by TLC (hexanes:ethyl acetate=5:1). After the removal of magnesium sulfate by filtration, the solvent was evaporated on a rotary evaporator. The product was isolated by gradient elution column chromatography (initially hexanes:ethyl acetate=5:1, then hexanes:ethyl acetate=2:1). Compound **13** was obtained as a colorless oil (0.20 g, 63 % over two steps), $[\alpha]_D$ = +9.5 ($CHCl_3$, *c* 0.22). NMR data: δ_H (400 MHz, $CDCl_3$) 1.04 (s, 9 H, $OSiC(CH_3)_3$), 1.39, 1.50 (2 × s, 2 × 3 H, $C(CH_3)_2$), 3.99 (dd, 1 H, H-5a, $J_{4,5a}$ = 5.7 Hz, $J_{5a,5b}$ = 10.4 Hz), 4.10 (dd, 1 H, H-5b, $J_{4,5b}$ = 6.1

Hz, $J_{5a,5b}$ = 10.2 Hz), 4.50 (dd, 1 H, H-3, $J_{2,3}$ = 6.7 Hz, $J_{3,4}$ = 3.8 Hz), 4.86 (s, 2 H, NCH_2Ph), 5.23 (dd, 1 H, H-2, $J_{1,2}$ = $J_{2,3}$ = 6.3 Hz), 5.68 (ddd, 1 H, H-4, $J_{3,4}$ = 3.8 Hz, $J_{4,5a}$ = $J_{4,5b}$ = 5.8 Hz), 6.79 (d, 1 H, H-1, $J_{1,2}$ = 5.6 Hz), 7.28–8.11 (m, 20 H, NCH_2Ph, $OSiPh_2$). δ_C (125 MHz, $CDCl_3$) δ = 19.6 ($OSiC(CH_3)_3$), 27.0 ($C(CH_3)_2$), 27.2 ($OSiC(CH_3)_3$), 27.3 ($C(CH_3)_2$), 62.9 (C-5), 69.9 (NCH_2Ph), 72.9 (C-2), 74.0 (C-4), 78.6 (C-3), 111.0 ($C(CH_3)_2$), 128.0–136.1 (NCH_2Ph, $OSiPh_2$), 136.9 (C-1), 166.0 (COPh).

1, 3-Dipolar cycloaddition of nitrone 8 with vinyl acetate. A solution of nitrone **8** (1.3 g, 3.88 mmol) in vinyl acetate (5 ml) was stirred under reflux. The progress of reaction was monitored by TLC (hexanes:ethyl acetate=3:1). When no nitrone was observed (12 hours), the reaction mixture was concentrated under reduced pressure using a rotary evaporator and the products were separated by column chromatography (silica gel, hexanes:ethyl acetate=9:1).

(*3S,5S*)-5-Acetoxy-2-benzyl-3-[1,2:3,4-di-*O*-isopropylidene-D-xylo-1-yl]isoxazolidine (14a). Colorless oil (0.95 g, 58%), $[\alpha]_D$ = –88.9 (CH_3OH, *c* 0.54). NMR data: δ_H (400 MHz, $CDCl_3$) 1.32, 1.40, 1.41, 1.43 (4 × s, 4 × 3 H, $C(CH_3)_2$), 2.09 (s, 3H, $COCH_3$), 2.53–2.64 (m, 2H, H-4a, H-4b), 3.23 (ddd, 1H, H-3, $J_{3,4a}$ = 4.1 Hz, $J_{3,4b}$ = 7.5 Hz), 3.41 (dd, 1H, H-2', *J* = 4.6 Hz and 6.9 Hz), 3.91 (dd, 1H, H-4'a, $J_{3',4'a}$ = 7.6 Hz, $J_{4'a,4'b}$ = 8.5 Hz), 3.95 (d, 1H, NCH_2Ph, *J* = 12.8 Hz), 3.97 (dd, 1H, H-4'b, $J_{3',4'b}$ = 6.8 Hz, $J_{4'a,4'b}$ = 8.2 Hz), 4.11–4.17 (m, 2H, H-1', H-3'), 4.15 (d, 1H, NCH_2Ph, *J* = 12.8 Hz), 6.46 (dd, 1H, H-5, $J_{5,4a}$ = 5.5 Hz, $J_{5,4b}$ = 1.6 Hz), 7.34–7.35 (m, 5H, NCH_2Ph). δ_C (75 MHz, $CDCl_3$) 21.3 ($COCH_3$), 25.8, 26.3, 27.1, 27.4 ($C(CH_3)_2$), 36.4 (C-4), 62.7 (NCH_2Ph), 64.5 (C-3), 65.9 (C-4'), 76.0, 76.3 (C-1' and C-3'), 79.9 (C-2'), 96.5 (C-5), 109.6, 109.7 ($C(CH_3)_2$), 128.2, 128.5, 129.9 (CH-phenyl.), 135.5 (C-phenyl.), 170.3 (CO).

(*3R,5R*)-5-Acetoxy-2-benzyl-3-[1,2:3,4-di-*O*-isopropylidene-D xylo[l]isoxazolidine (14b). Colorless oil (0.13 g, 8%), $[\alpha]_D$ = +52.4 (CH_3OH, *c* 0.45). NMR data: δ_H (400 MHz, $CDCl_3$) 1.29, 1.37, 1.38, 1.40 (4 × s, 4 × 3 H, $C(CH_3)_2$), 2.11 (s, 3H, $COCH_3$), 2.68 (ddd, 1H, H-4b, $J_{3,4b}$ = 7.7 Hz, $J_{4a,4b}$ = 14.3 Hz, $J_{4b,5}$ = 2.6 Hz), 2.81 (ddd, 1H, H-4a, $J_{3,4a}$ = 3.4 Hz, $J_{4a,4b}$ = 14.2 Hz, $J_{4a,5}$ = 6.5 Hz), 3.37 (dd, 1H, H-2′, $J_{1',2'}$ = 6.6 Hz, $J_{2',3'}$ = 4.9 Hz), 3.41 (ddd, 1H, H-3, $J_{3,4a}$ = 3.2 Hz, $J_{3,4b}$ = $J_{1',3}$ = 7.9 Hz), 3.76 (dd, 1H, H-1′, $J_{1',2'}$ = 6.1 Hz, $J_{1',3}$ = 8.1 Hz), 3.85–3.93 (m, 2H, H-4'a, 4′b), 4.01 (d, 1H, NCH_2Ph, *J* = 12.4 Hz), 4.12 (ddd, 1H, H-3', $J_{2',3'}$ = 5.0 Hz, $J_{3',4'a}$ = $J_{3',4'b}$ = 6.9 Hz), 4.3 (d, 1H, NCH_2Ph, *J* = 12.3 Hz), 6.48 (dd, 1H, H-5, $J_{5,4a}$ = 6.5 Hz, $J_{5,4b}$ = 2.4 Hz), 7.34–7.35 (m, 5H, NCH_2Ph). δ_C (75 MHz, $CDCl_3$) 21.4 ($COCH_3$), 25.8, 26.5, 27.2, 27.6 ($C(CH_3)_2$), 37.8 (C-4), 63.9 (NCH_2Ph), 65.9 (C-3 and C-4'), 76.5 (C-3'), 77.8 (C-1'), 80.4 (C-2'), 99.1 (C-5), 109.6, 109.8 ($C(CH_3)_2$), 128.1, 128.7, 129.6 (CH-phenyl), 136.4 (C-phenyl), 170.1 (CO).

1, 3-Dipolar cycloaddition of nitrone 13 with vinyl acetate. A solution of nitrone **13** (0.21 g, 0.34 mmol) in vinyl acetate (5 ml) was stirred under reflux. The progress of reaction was monitored by TLC (hexanes:ethyl acetate=3:1). When no nitrone was observed (18 hours), the reaction mixture was concentrated under reduced pressure using a rotary evaporator and the products were separated by column chromatography (silica gel, hexanes:ethyl acetate=9:1).

(*3S,5S*)-5-Acetoxy-2-benzyl-3-[1,2-*O*-isopropylidene-3-*O*-benzoyl-4-*O*-*tert*butyldiphenylsilyl-D-xylo-1-yl]isoxazolidine (15a). Colorless oil (0.13 g, 54%), $[\alpha]_D$ = –62.9 (CH_3OH, *c* 0.32). NMR data: δ_H (400 MHz, $CDCl_3$) 1.02 (s, 9 H, $OSiC(CH_3)_3$), 1.37, 1.40

(2 × s, 2 × 3 H, $C(CH_3)_2$), 1.88 (s, 3H, $COCH_3$), 2.54–2.57 (m, 2H, H-4a and H-4b), 3.28 (ddd, 1H, H-3, $J_{3,4a} = J_{3,4b} = 6.7$ Hz, $J_{1',3} = 6.0$ Hz), 3.89 (dd, 1H, H-2', $J_{1',2'} = 10.5$ Hz, $J_{2',3'} = 5.3$ Hz), 3.95–3.98 (m, 2H, H-4'a and H-4'b), 4.02 (d, 1H, NCH_2Ph, $J = 13.5$ Hz), 4.08 (dd, 1H, H-1', $J_{1',3} = 5.9$ Hz, $J_{1',2'} = 8.0$ Hz), 4.11 (d, 1H, NCH_2Ph, $J = 13.5$ Hz), 5.60 (ddd, 1H, H-3', $J_{2',3'} = 5.2$ Hz, $J_{3',4'} = 2.2$ Hz and 7.5 Hz), 6.43 (dd, 1H, H-5, $J_{4,5} = 2.6$ Hz and 4.7 Hz), 7.20–7.72 and 8.10–8.13 (m, 20H, NCH_2Ph, $OSiPh_2$). δ_C (75 MHz, $CDCl_3$). 19.1 ($OSiC(CH_3)_3$), 21.0 ($COCH_3$), 26.7 ($OSiC(CH_3)_3$), 26.8, 27.3 ($C(CH_3)_2$), 36.8 (C-4), 62.6 (NCH_2Ph), 63.3 (C-4'), 64.4 (C-3), 72.8 (C-3'), 75.3 (C-1'), 77.7_(C-2'), 95.8 (C-5), 109.5 ($C(CH_3)_2$), 127.6 – 135.9 (NCH_2Ph, $OSiPh_2$), 165.7 (COPh), 170.3 ($COCH_3$).

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