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1,3-Dipolar Cycloaddition Reactions of Homochiral Cyclic Nitrones Derived from 1-Deoxynojirimycin

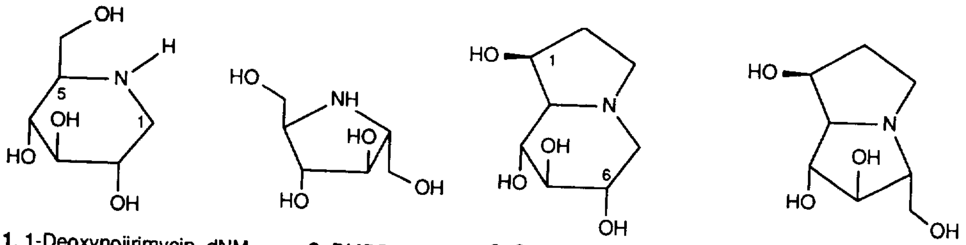
Leon A.G.M. van den Broek

Scientific Development Group, Department of Medicinal Chemistry III,
N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands.

Abstract: The synthesis of nitrones **12**, **19** and **20**, derived from 1-deoxynojirimycin (**1**, dNM), using 2,2-dimethyldioxirane, is reported. In subsequent 1,3-dipolar cycloaddition reactions of nitrones **12** and **19** with phenyl isocyanate and trichloro acetonitrile the cycloadducts **13** and **15**, ring-closed to C-1, and **14**, **16**, **21** and **22**, which are ring-closed to C-5 of the dNM ring, were obtained. Cycloaddition reaction of **19** and **20** with methyl vinylacetate at 15 kbar pressure, provided the cycloadducts **23**, **24** and **25**, which are highly functionalized dNM derivatives with various possibilities for further synthesis.

INTRODUCTION

There has been much interest in recent years in the chemistry and biological properties of polyhydroxylated piperidines (e.g. 1-deoxynojirimycin, dNM, **1**), pyrrolidines (e.g. DMDP, **2**), indolizidines (e.g. castanospermine, CAS, **3**) and pyrrolizidines (e.g. australine, **4**) (Figure 1) isolated from natural sources[1].

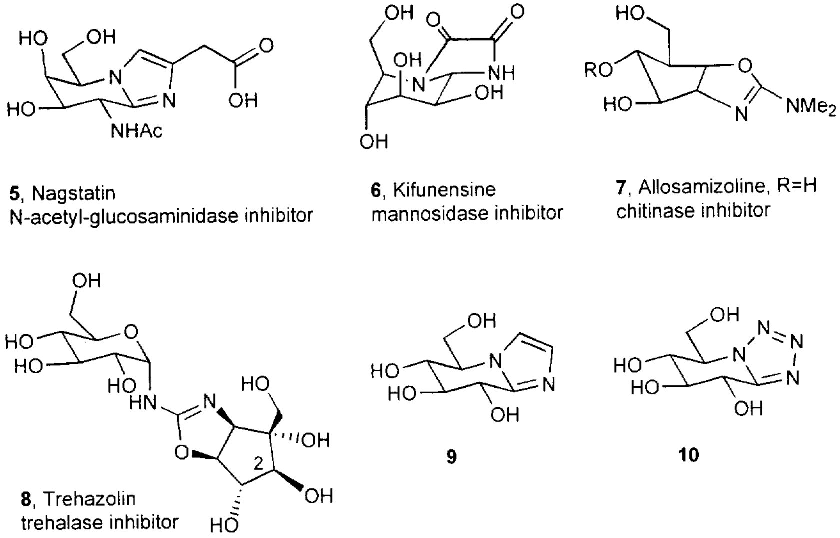


1, 1-Deoxynojirimycin, dNM **2**, DMDP **3**, Castanospermine, CAS **4**, Australine

Figure 1

This is in large part due to the recognition that compounds of this type can act as potent and specific inhibitors of glycosidases, e.g. α-glucosidase I, and that this inhibition has potential application in a number of areas of medicinal importance. This is perhaps most notably illustrated by the anti-HIV activity shown by some compounds of these classes, e.g. N-butyl-dNM and 6-O-butyryl-CAS[1].

Furthermore, several other potent and highly functionalized glycosidase inhibitors, such as nagstatin (**5**)[2], kifunensine (**6**)[3], allosamizoline (**7**)[4] and trehazolin (**8**)[5] (Figure 2) have been isolated recently from nature, that possess interesting heterobicyclic structures much different from those of CAS and australine. The heterobicyclic compounds **9**[6] and **10**[7] (Figure 2) were synthesized recently.



5, Nagstatin
N-acetyl-glucosaminidase inhibitor

6, Kifunensine
mannosidase inhibitor

7, Allosamizoline, R=H
chitinase inhibitor

8, Trehazolin
trehalase inhibitor

9

10

Figure 2

There has been much synthetic activity directed towards the classes of highly functionalized mono- and bicyclic azasugars depicted in Figure 1. The published syntheses of dNM have been reviewed recently[8]. However, a need for structural analogues of glycosidase inhibitors, with high enzyme activity and selectivity, still remains.

We reasoned that a dNM-derived nitrone, where the double bond could be directed either towards C-1 or C-5 (seeScheme1), could be a valuable synthon for a series of ring-annulated heterobicyclic dNM derivatives to be obtained via a 1,3-dipolar cycloaddition reaction[9-11]. In addition, several nucleophilic addition reactions have been reported on the nitrone functionality, such as Grignard[12,13], 2-lithiothiazole[14] and lithiated methyl phenyl sulfoxide[15] reactions, and these could yield either C-1 or C-5 derivatized dNM analogues. We intended to prepare the nitrone functionality starting from a secondary amine, a properly protected dNM derivative, using the novel, versatile and easy to use oxidizing agent 2,2-dimethyldioxirane.

The synthesis of C-arylnitrones using 2,2-dimethyldioxirane, starting from a linear (substituted) benzyl secondary amine, was reported recently.[16] 2,2-Dimethyldioxirane has been used earlier to oxidize amines, but never for the synthesis of cyclic nitrones. Furthermore, 2,2-dimethyldioxirane was reported to convert amino sugars, possessing a primary amine, into the corresponding hydroxylamines (R-NH-OH) using one equivalent of oxidizing agent[17,18]. Using an excess of 2,2-dimethyldioxirane cyclic secundary amines were converted into the corresponding hydroxamic acids (-N(OH)-C(O)-)[19]. This oxidation proceeds via the cyclic nitrone derivatives, but these were not isolated and characterized.

Recently, the synthesis of indolizidine and pyrrolizidine derivatives related to swainsonine and CAS were reported, that used cyclic pyrrolidine- and piperidine-based nitrones. These cyclic nitrones were derived from either D- or L-arabinopyranose[20] or D-xylose[21] and were isolated as a mixture of enantiomers or diastereomers, respectively. The nitrone functionality was either obtained by oxidation of a pyrrolidine analogue with 2-(phenylsulfonyl)-3-phenyloxaziridine[20] or by intramolecular conjugate addition of an oxime[21], respectively. Less functionalized cyclic nitrones were prepared using H_2O_2/SeO_2[12], NMO/cat TPAP[22] or HgO[23] starting from a secundary amine or hydroxylamine.

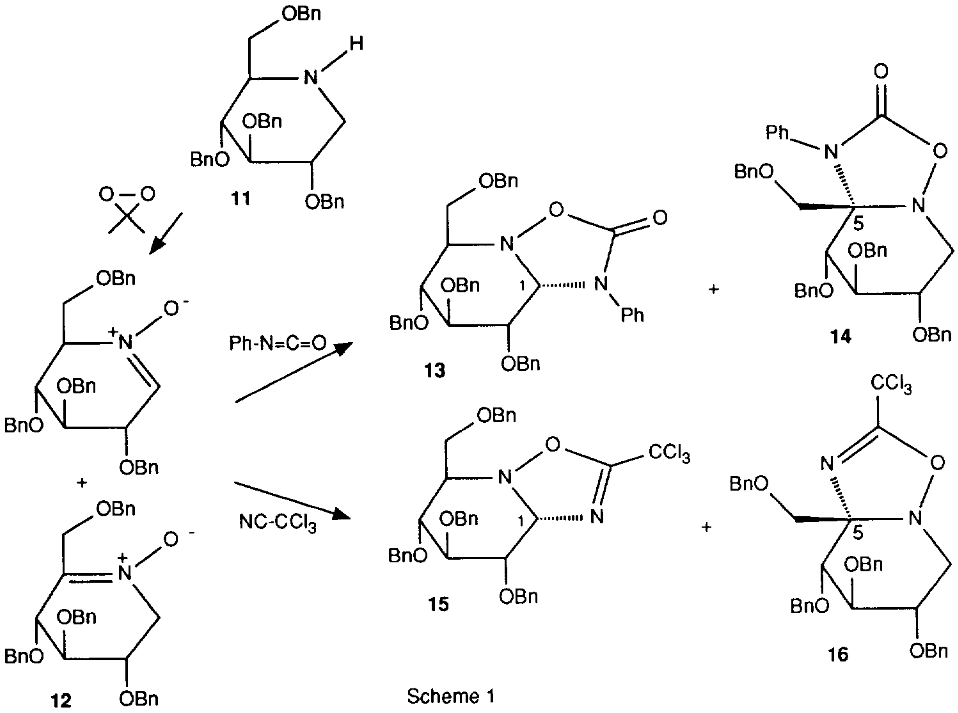
In this report, we describe the synthesis and use of homochiral cyclic nitrones derived from the α-glucosidase inhibitor 1-deoxynojirimycin (**1**, dNM) in 1,3-dipolar cycloaddition reactions with phenyl isocyanate and trichloroacetonitrile as dipolarophiles. Further, we show that cycloaddition reaction with methyl vinylacetate yields various cycloadducts, which are useful intermediates to various C-1 or C-5 substituted or ring-annulated dNM analogues.

RESULTS AND DISCUSSION

The first objective was the synthesis of two nitrones derived from 1-deoxynojirimycin (**1**, dNM), in which the hydroxyl groups were either protected with benzyl (Bn) or tert-butyldimethylsilyl (TBDMS) groups.

The nitrone precursor **11** was synthesised in two steps from dNM (**1**) in 90% overall yield (Scheme 1)[24]. Oxidation of the secondary amine **11** to nitrone **12** proceeded smoothly in 79% isolated yield using 2,2-dimethyldioxirane which was generated in situ from potassium monoperoxysulfate (i.e. Oxone)[25]. Nitrone **12** is a mixture of the C-1 and C-5 nitrone, which could not be separated or purified to homogeneity. That nitrones **12** indeed were formed was concluded from subsequent 1,3-dipolar cycloaddition reactions with very reactive dipolarophiles, such as phenyl isocyanate and trichloro acetonitrile.

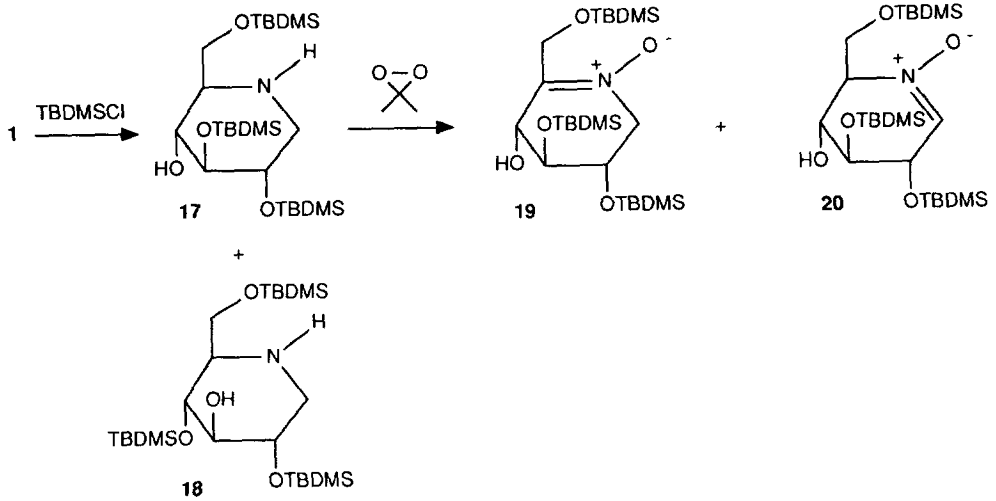
Reaction of nitrone **12** with these reactive dipolarophiles proceeded smoothly in toluene at room temperature in ca. 3 hours (Scheme 1). From the reaction of **12** with phenyl isocyanate the C-1 and C-5 cycloadducts **13** and **14** were isolated in 30% and 10% yield, respectively; with trichloro acetonitrile the corresponding C-1 and C-5 cycloadducts **15** and **16** were isolated in 48% and 16% yield, respectively. The C-1 nitrone **12** and compound **16** were not stable at room temperature and decomposed upon standing[12]. The formation of the C-5 cycloadducts **14** and **16** was confirmed by ^{1}H-NMR showing an AB quartet for H-6/H-6a at 3.78 and 3.91 ppm and with a coupling constant of J_{AB}=11 and 10 Hz for compounds **14** and **16**, respectively. For **14**, the ABX system H-1/H-1a/H-2 shows two double doublets for H-1/H1a at 3.29 and 3.59 ppm. In the cycloadducts **13** and **15**, a doublet at 5.33 and 5.39 ppm with a coupling constant of $J_{1\text{-}2}$=2.5 and 3.5 Hz for H-1 were found, respectively. For **13**, an NOE between H-1 and H-2, together with the small coupling constant of 2.5 Hz, confirms the α-configuration at C-1.



Scheme 1

Next, the synthesis of TBDMS protected dNM nitrones was undertaken. Reaction of **1** with TBDMSCl in dry pyridine did not lead to the fully silyl ether protected derivative, but led to the formation of the tri-substituted silyl ethers **17** and **18** in 46% and 20% yield, respectively (Scheme 2). It was anticipated that the remaining free hydroxyl group in **17** and **18** would not interfere with nitrone formation. Oxidation of **17** with 2,2-dimethyldioxirane generated in situ[25] now gave a mixture of the two regioisomeric nitrones[26-29] **19** and **20** in 64% and 32% yield, respectively. Now, contrary to the formation of the C-1 nitrone **12**, the more highly substituted C-5 nitrone **19** was formed in excess. The silyl ether protected nitrones **19** and **20** could be separated easily[26] on silica gel by column chromatography and were each fully characterized. For **19**, H-6 and H-6a each showed up as a doublet at 4.64 and 4.90 ppm with a coupling constant of $^2J=16$ Hz in the ^{1}H- and C-5 at 147.4 ppm in the ^{13}C-NMR spectrum. For **20**, H-1 appeared as a doublet at 7.00 ppm with a coupling constant of $^3J_{1\text{-}2}=3$ Hz in the ^{1}H- and C-1 at 135.7 ppm in the ^{13}C-NMR spectrum.

At first, nitrone **19** was allowed to react with phenyl isocyanate in toluene at room temperature (Scheme 3). The reaction of **19** with phenyl isocyanate was slower (overnight at room temperature) than the reaction of nitrone **12** with phenyl isocyanate (3 h at room temperature) and gave the endo cycloadduct **21** and the exo cycloadduct **22** in 10% and 30% yield, respectively. The exo cycloadduct **22** thus was formed in excess of the expected endo cycloadduct **21**. The stereochemistry at C-5 was confirmed by NOE experiments. For **21**, NOE's between H-6 and H-1β, H-6 and H-2 or H-4 and for **22** an NOE between H-6 and OH were observed. In addition, in the ^{1}H-NMR spectrum of **22** the OH group is found at higher field, i.e. a doublet at 3.11 ppm with J=8.5 Hz, than for **21** (doublet at 4.01 ppm with J=9.5 Hz), due to the presence of the proximal C-6 tert-butyldimethylsilyl group.

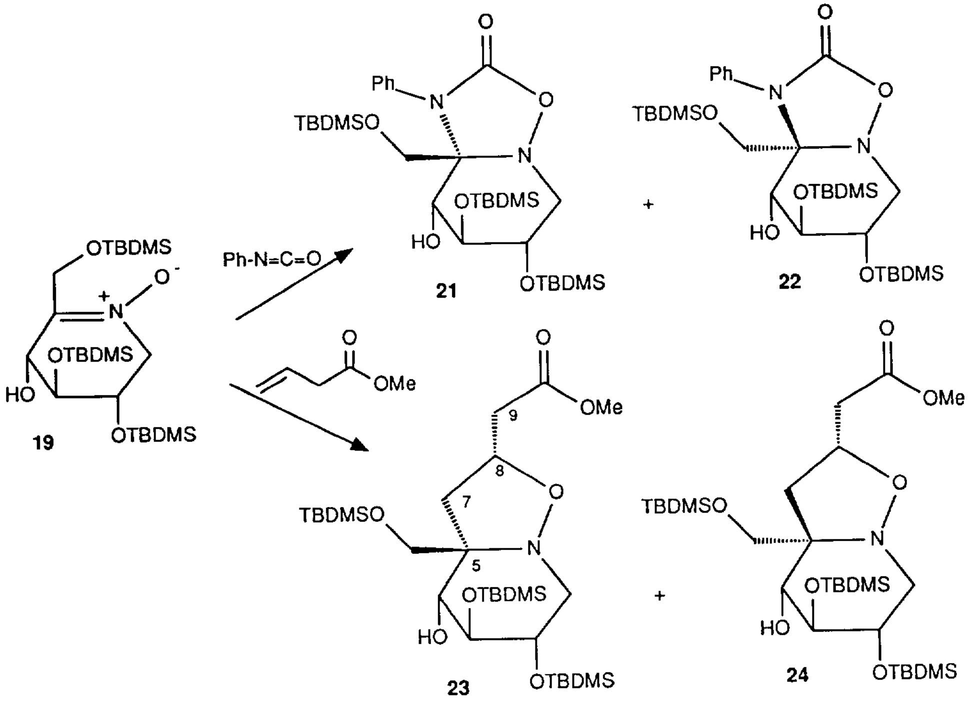


Scheme 2

Next, 1,3-dipolar cycloaddition reactions of benzyl ether protected C-1 nitrone **12** with nonactivated alkenes like vinylacetic acid and allyl trimethylsilyl ether were attempted, but even at 80 °C in toluene no cycloaddition reaction occurred, instead, decomposition of the nitrone took place. Nitrone **12** even did not react smoothly with the relatively reactive dipolarophile maleic anhydride at room temperature and gave decomposition of the starting material. Also, C-5 nitrone **19** did not react with methyl vinylacetate at 80 °C in toluene, but gave decomposition of the starting material.

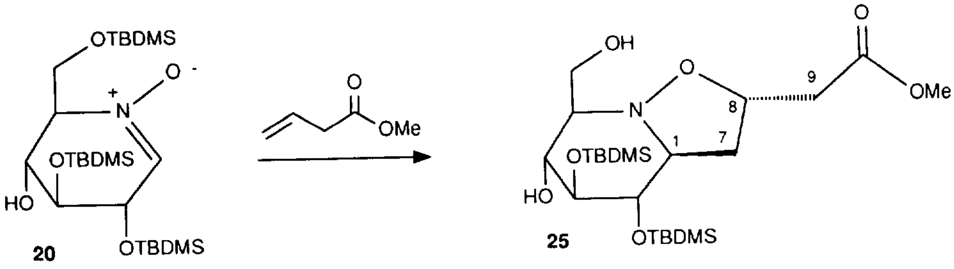
Therefore, nitrone **19** was allowed to react with the nonactivated dipolarophile methyl vinylacetate in chloroform at high pressure (i.e. 15 kbar)[30] at room temperature (Scheme 3). The reaction was allowed to proceed for 16 hours and after work-up, two isomeric cycloadducts **23** and **24** were isolated in 39% and 11% yield, respectively.

As expected, the endo cycloadduct **23** was formed in excess. The stereochemistry at C-5 was established by NOE's between H-6 and H-4, H-7α and OH, H-7β and H-6 and at C-8 by an NOE between H-7β and H-8. In compound **23**, probably the 6-membered ring is in the boat conformation following the coupling constants observed for the sugar ring protons. For compound **24**, NOE's between H-4 and H-7β, H-4 and H-8, H-7α and H-6, H-7α and H-9 and H-7β and H-8 confirm the stereochemistry as indicated at C-5 and C-8. In addition, like observed for **22**, in compound **24** the signal for the OH group is found at higher field, i.e. a doublet at 2.33 ppm with J=6 Hz, than in **23** (doublet at 3.39 ppm with J=2.5 Hz), due to the presence of the proximal C-6 tert-butyldimethylsilyl group. Reaction of nitrone **19** with methyl acrylate at 15 kbar in chloroform for 16 hours at room temperature gave an inseparable mixture of isomers.



Scheme 3

Finally, 1,3-dipolar cycloaddition reaction of the C-1 nitrone **20** with methyl vinylacetate at 15 kbar for 16 hours in chloroform at room temperature gave a single exo cycloadduct, i.e. **25**, in 29% yield (Scheme 4). According to mass spectroscopy, the C-6 tert-butyldimethylsilyl group was lost during this reaction. The configuration at C-1 is β, according to NOE's between H-1α and H-5 and H-1α and H-9; for C-8 an NOE between H-8 and 6-OH is observed.



Scheme 4

In conclusion, we have shown that mixtures of homochiral cyclic C-1 and C-5 nitrones derived from dNM, i.e. **12**, **19** and **20**, can be synthesized easily, in one step and in good to excellent yield, using 2,2-dimethyldioxirane as the oxidizing agent. Our first attempts at 1,3-dipolar cycloaddition reactions of these nitrones with reactive dipolarophiles gave the desired cycloadducts, i.e. **13-16**, **21** and **22**, in reasonable yield. Furthermore, cycloaddition reactions of **19** and **20** with methyl vinylacetate, which did not react at high temperature, provided the desired cycloadducts, i.e. **23**, **24** and **25**, by carrying out the reaction under high-pressure (i.e. 15 kbar). Cycloadduct **25** is structurally similar to the glycosidase inhibitor nagstatin (**5**, Figure 2) isolated from nature. These novel cycloadducts are highly functionalized dNM derivatives and one can see various possibilities in going further to synthesize interesting dNM or CAS analogues[21,26-29].

EXPERIMENTAL

The Chemical Abstracts nomenclature was used for the scientific names. dNM (**1**) is: 1,5-dideoxy-1,5-imino-D-glucitol. In the text, Figures, Schemes and NMR spectral data, the sugar numbering is employed as indicated in structure **1** (Figure 1). ^{1}H NMR (360, 400 or 600 MHz) and ^{13}C NMR (50 or 100 MHz) spectra were measured in $CDCl_3$ unless stated otherwise using a Bruker AM-360, DRX-400 or DRX 600 Avance spectrometer; chemical shifts are given in ppm (δ) relative to TMS for spectra run in $CDCl_3$ or relative to C_6D_6. Fast atom bombardment (FAB), using glycerol or 3-nitrobenzyl alcohol (NBA) as the matrix and electron impact (EI) mass spectra were recorded on a Finnigan MAT 90 mass spectrometer. FAB exact mass determinations were recorded in NBA using PEG. Field desorption (FD) mass spectra. Electrospray ionization (ESI) spectra were recorded on a VGBio-Q spectrometer (RU Gent). Optical rotations were recorded at ambient temperature on a Perkin-Elmer 241 polarimeter. The IR spectrum was recorded on a Biorad FTS 60 apparatus using diffuse reflection infrared fourier transform (DRIFT) spectroscopy. The melting point (mp) was determined on a Reichert hot stage and is uncorrected. TLC analysis was performed on Merck DC-Fertigplatten (Kieselgel 60 F_{254}). Compounds were visualized by spraying with H_2SO_4-EtOH, 1:9 or Cl_2-TMB. For column chromatography Merck Kieselgel 60 (230-400 mesh) was used.

(2β,3α,4β,5α)-2,3,4,5-Tetrahydro-3,4,5-tri(phenylmethoxy)-2-[(phenylmethoxy)methyl]pyridine 1-oxide (12)

The amine **11**[24] (2.45 g, 4 mmol) was dissolved in 20 ml of CH_2Cl_2 and 20 ml of acetone. To this solution $NaHCO_3$ (1.51 g, 18 mmol) in 20 ml of water was added and the mixture was cooled to 0 ^{0}C. A catalytic amount of cis-dicyclohexano-18-crown-6 was added and the mixture was stirred vigorously. A solution of Oxone (potassium peroxymonosulfate) (6.12 g, 10 mmol) in 20 ml of water was added dropwise.[25] According to TLC, the reaction was complete after 2 h. A saturated $NaHSO_4$ solution was added and the product was extracted with CH_2Cl_2. The organic layer was separated and washed with a saturated $NaHCO_3$ solution, separated, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent CH_2Cl_2, 0.1 to 3% MeOH-CH_2Cl_2) to give the desired product **12** as a colorless oil in 79% yield. The C-1 nitrone was not stable and decomposed on standing or was transformed into the C-5 nitrone. TLC Rf 0.47 (eluent MeOH-CH_2Cl_2, 5:95). The product could not be purified to homogeneity according to its ^{1}H and ^{13}C NMR spectra. FAB$^+$ MS (glycerol) 538 [M+H], 522 [538-O], 1075 [2M+H]; (NBA) 538 [M+H]. FAB$^-$ MS (glycerol) 554 [M+H_2O-H], 628 [M+glycerol-H], 1109 [2x555-H]. Exact mass: measured 538.2568 for [M+H], calculated 538.2593. IR DRIFT 2860, 1100-900 cm^{-1}. ^{13}C NMR for C-5 nitrone (DEPT, 100 MHz) 60.0 (C-6), 65.0, 65.8, 71.7 and 72.7 (4x CH_2Ph), 73.2, 73.4, 73.6 and 75.4 (C-1, C-2, C-3, C-4), 126.9-128.4 (Ph), 137.2, 137.3, 137.5 and 137.6 (4x Ph), 144.3 (C-5); the signals for the C-1 nitrone could not be interpreted.

(5β,6α,7β,8α,8aβ)-Hexahydro-1-phenyl-6,7,8-tri(phenylmethoxy)-5-[(phenylmethoxy)methyl]-2H-[1,2,4]oxadiazolo[2,3-a]pyridine-2-one (13) and (5α,6β,7α,8β)-4-Phenyl-5,6,7-tri(phenylmethoxy)-8-[(phenylmethoxy)methyl]-2-oxa-1,4-diazabicyclo-[3.3.1]nonan-3-one (14)

A solution of nitrones 12 (350 mg, 0.65 mmol) and phenyl isocyanate (353 µl, 3.25 mmol) in 10 ml of dry toluene was stirred at room temperature for 2.5 h until completion of the reaction. The reaction product was concentrated in vacuo and purified over silica gel (eluent EtOAc-heptane, 15:85) to give the cycloaddition products **13** (colorless oil) and **14** (white semi-solid on long standing) in 30% and 10% yield, respectively. TLC Rf 0.22 and 0.19, respectively (eluent EtOAc-heptane, 2:8).

Compound **13**: ^{1}H NMR (COSY) 3.70-3.75 (m, H-5), 3.77 (dd, H-2, $J_{2\text{-}1}$=2.5 Hz, $J_{2\text{-}3}$=3 Hz), 3.84-3.91 (m, H-3, H-4, H-6, H-6a), 4.24-4.74 (4x ABq, CH$_2$Ph), 5.57 (d, H-1, $J_{1\text{-}2}$=2.5 Hz), 7.00-7.40 (m, Ph). Characteristic signals in ^{1}H NMR spectrum taken in C$_6$D$_6$ (200 MHz): 3.12 (t, H-3, J=4.5 Hz), 3.40 (t, H-4, J=4.5 Hz), 3.65 (t, H-2, J=2.5 Hz), 5.33 (d, H-1, J=2.5 Hz). NOESY: an NOE between H-1 and H-2 together with the small coupling of $J_{1\text{-}2}$=2.5 Hz confirms the α-configuration at C-1 with a β-positioned proton. ^{1}H-^{13}C correlation and ^{13}C DEPT: ^{13}C NMR (100 MHz) 63.7 (C-5), 66.0 (C-6), 72.6, 72.8, 73.8, 74.3 (4x CH$_2$Ph), 74.3 (C-2), 76.0 (C-1, C-4), 80.7 (C-3), 122.1-129.4 (Ph, NPh), 127.8 (s, NPh), 136.0, 136.6, 137.5 and 138.0 (4x s,Ph), 155.0 (C(O)). $[\alpha]_D^{20}$ -56.0° (c 1.0, CH$_2$Cl$_2$) and -59.4° (c 1.0, CHCl$_3$). FAB$^+$ MS (NBA) 657 [M+H], 1313 [2M+H]. FAB$^-$ MS 809 [M+NBA].

Compound **14**: ^{1}H NMR (COSY, C$_6$D$_6$) 3.29 (dd, H-1, ^{3}J=9 Hz, ^{2}J=11 Hz), 3.46-3.52 (ddd, H-5), 3.59 (dd, H-1a, ^{3}J=4 Hz, ^{2}J=11 Hz), 3.78 (ABq, H-6, H-6a, J_{AB}=11 Hz), 3.98-4.06 (m, H-3, H-4), 4.23-4.72 (4x ABq, CH$_2$Ph), 6.48 (dd, N-Ph, ^{3}J=8 Hz, ^{4}J=2 Hz), 6.95-7.30 (m, Ph).^{1}H-^{13}C correlation: ^{13}C NMR (100 MHz) 54.3 (C-6), 68.7 (C-1), 72.6, 73.8, 74.1 and 75.38 (4x CH$_2$Ph), 75.44 (C-5), 76.3 (C-4), 80.9 (C-3), 86.4 (C-2), 126.1-129.4 (Ph, NPh), 127.0 (s, NPh), 136.0, 137.3, 137.61 and 137.63 (4x s, Ph), 157.6 (C(O)). An NOE (NOESY, 600 MHz) between H-6/6a and H-4 and 3-OCH$_2$ confirms the product most probably as the endo-cycloadduct. $[\alpha]_D^{20}$ +23.9° (c 1.0, CH$_2$Cl$_2$) and +17.2° (c 1.0, CHCl$_3$). FAB$^+$ MS 657 [M+H], 565 [M-C$_7$H$_7$], 535 [M-CH$_2$OC$_7$H$_7$]. FAB$^-$ MS 809 [M+NBA].

(5β,6α,7β,8α,8aβ)-2-(Trichloromethyl)-6,7,8,8a-tetrahydro-6,7,8-tri(phenylmethoxy)-5-[(phenylmethoxy)methyl]-5H-[1,2,4]oxadiazolo[2,3-a]pyridine (15) and (5α,6β,7α,8β)-5,6,7-tri(Phenylmethoxy)-8-[(phenylmethoxy)methyl]-3-(trichloromethyl)-2-oxa-1,4-diazabicyclo[3.3.1]non-3-ene (16)

A solution of nitrones 12 (25 mg, 0.04 mmol) and trichloro acetonitrile (47 µl, 0.46 mmol) in 2.5 ml of dry toluene was stirred at room temperature overnight; the reaction was nearly complete after 2-3 h. The reaction mixture was concentrated and the residue purified over silica gel to give the cycloadducts **15** and **16**, both as colorless oils, in 48% and 16% yield, respectively. Compound **16** was not stable and decomposes upon standing. TLC Rf 0.07 and 0.15, respectively (eluent CH$_2$Cl$_2$-heptane, 1:1).

Compound **15**: ^{1}H NMR (C$_6$D$_6$) 3.61-3.66 (m, H-5), 3.72 (dd, H-2, $J_{2\text{-}1}$=3.5 Hz, $J_{2\text{-}3}$=6 Hz plus coupling of ca. 1 Hz), 3.82-3.86 (m, H-6, H-3, H-4), 3.93 (dd, H-6a), ^{3}J=2.5 Hz, ^{2}J=11 Hz), 4.31-4.80 (4x ABq, CH$_2$Ph), 5.39 (d, H-1, $J_{1\text{-}2}$=3.5 Hz plus small coupling of ca. 1 Hz), 7.05-7.35 (m, Ph). FAB$^+$ MS 681 [M+H] (CCl$_3$ isotopic pattern). FAB$^-$ MS 679 [M-H]. EI MS 589 [M-C$_7$H$_7$] (CCl$_3$ isotopic pattern). $[\alpha]_D^{20}$ -18.4° (c 1.0, CHCl$_3$).

Compound **16**: In the ^{1}H NMR spectrum (C$_6$D$_6$) the absence of a signal at 5.39 ppm and the ABq, J_{AB}=10 Hz at 3.91 ppm are indicative of its formation. FAB$^+$ MS 681 [M+H] (CCl$_3$ isotopic pattern), 575 [M-OC$_7$H$_7$+2H], 559 [M-CH$_2$OC$_7$H$_7$]. FAB$^-$ MS 679 [M-H] (CCl$_3$ isotopic pattern). EI MS 559 [M-CH$_2$OC$_7$H$_7$] (CCl$_3$ isotopic pattern). $[\alpha]_D^{20}$ +42.1° (c 1.0, CHCl$_3$).

2,3,6-tri-O-[(1,1-Dimethylethyl)dimethylsilyl]-1,5-dideoxy-1,5-imino-D-glucitol (17) and 2,4,6-tri-O-[(1,1-Dimethylethyl)dimethylsilyl]-1,5-dideoxy-1,5-imino-D-glucitol (18)

To a solution of dNM (**1**) (2 g, 12.2 mmol) in 20 ml of dry DMF was added imidazole (5 g, 73.8 mmol) and TBDMSCl (11 g, 73.2 mmol) and the reaction mixture was stirred at room temperature overnight. The mixture was concentrated in vacuo, dissolved in CH$_2$Cl$_2$ and extracted with a saturated NaHCO$_3$ solution and a saturated NaCl solution. The organic layer was separated, dried and concentrated in vacuo to give a yellow oil. The products were separated by column chromatography over silica gel to give **17** and **18**, both as colorless oils, in 46% and 20% yield, respectively. TLC Rf 0.39 and 0.56, respectively (eluent CH$_2$Cl$_2$-acetone, 97:3).

Compound **17**: ^{1}H NMR 0.00, 0.06, 0.10, 0.11, 0.12 and 0.13 (6x s, SiCH$_3$), 0.90, 0.91 and 0.92 (3x s, CCH$_3$), 1.70 (br s, NH), 2.45 (br d, OH, J=3.5 Hz), 2.50 (dd, H-1ax, $J_{1\text{-}2}$=8.5 Hz, ^{2}J=12 Hz), 2.63 (ddd, H-5, 19 Hz), 3.13 (dd, H-1eq, $J_{1\text{-}2}$=4 Hz, ^{2}J=12 Hz), 3.25 (br dt, H-4, $J_{4\text{-}3}$=7.5 Hz, $J_{H\text{-}4,OH}$=3.5 Hz), 3.41 (t, H-3, $J_{3\text{-}4}$=7.5 Hz), 3.49 (ddd, H-2, 21 Hz), 3.72 (dd, H-6, ^{3}J=7 Hz, ^{2}J=10 Hz), 3.83 (dd, H-6a, ^{3}J=4 Hz, ^{2}J=10 Hz). ^{13}C NMR 18.3 and 18.4 (3x SiC), 26.0, 26.1 and 26.2 (SiCH$_3$, CCH$_3$), 50.0 (C-5), 60.8 and 63.7 (C-1, C-6), 73.1, 73.2 and 79.5 (C-2, C-3, C-4).

Compound **18**: ^{1}H NMR 0.05, 0.06, 0.08, 0.09, 0.11 and 0.13 (6x s, SiCH$_3$), 0.87, 0.89 and 0.90 (3x s, CCH$_3$), 1.70 (br s, NH), 2.23 (d, OH, J=2 Hz), 2.49 (dd, H-1ax, J_{1-2}=10 Hz, ^{2}J=11.5 Hz), 2.49-2.54 (ddd, H-5), 3.05 (dd, H-1eq, J_{1-2}=5 Hz, ^{2}J=11.5 Hz), 3.26-3.29 (m, H-3, H-4), 3.44 (ddd, H-2, 24 Hz), 3.54 (dd, H-6, ^{3}J=7 Hz, ^{2}J=9.5 Hz), 3.89 (dd, H-6a, ^{3}J=3 Hz, ^{2}J=9.5 Hz). Characteristic signals in ^{1}H NMR spectrum taken in C_6D_6 2.30 (d, OH, J=2 Hz), 2.41 (dd, H-1ax, J_{1-2}=10 Hz, ^{2}J=11.5 Hz), 2.65 (ddd, H-5, 19 Hz), 2.94 (dd, H-1eq, J_{1-2}=5 Hz, ^{2}J=11.5 Hz), 3.40 (dt, H-3, ^{3}J=9 Hz, $J_{H-3,OH}$=2 Hz), 3.53 (t, H-4, J=8.5 Hz), 3.52-3.59 (ddd, H-2, 23 Hz), 3.75 (dd, H-6, ^{3}J=7 Hz, ^{2}J=9.5 Hz), 4.07 (dd, H-6a, ^{3}J=3 Hz, ^{2}J=9.5 Hz). ^{13}C NMR 17.8 and 18.1 (3x SiC), 25.4, 25.6, 25.7 and 25.8 (SiCH$_3$, CCH$_3$), 50.4 (C-5), 62.0 and 63.8 (C-1, C-6), 72.9, 73.6 and 80.0 (C-2, C-3, C-4). FAB$^+$ MS 506 [M+H], 448 [M-C$_4$H$_9$], 374 [M+H-tBuMe$_2$SiOH]. FAB$^-$ MS 504 [M-H], 390 [M-H-tBuMe$_2$SiOH]. FD$^+$ MS 505 [M, 100%], 448 [M-C$_4$H$_9$].

(3α,4β,5α)-2,3,4,5-Tetrahydro-5-hydroxy-3,4-bis[(1,1-dimethylethyl)dimethylsilyloxy]-6-[[(1,1-dimethylethyl)dimethyl]methyl]pyridine 1-oxide (19) and (3α,4β,5α,6β)-3,4,5,6-Tetrahydro-5-hydroxy-3,4-bis[(1,1-dimethylethyl)dimethylsilyloxy]-6-[[(1,1-dimethylethyl)dimethyl]methyl]pyridine 1-oxide (20)

The nitrones **19** and **20** were prepared from the amine **17** (505 mg, 1 mmol) according to the procedure described for compound **12**. After separation over silica gel the nitrones **19** and **20** were obtained both as colorless oils in 64% and 32% yield, respectively. Both compounds became white semi-solids on long standing. TLC Rf 0.55 and 0.47, respectively (eluent MeOH-CH$_2$Cl$_2$, 5:95).

Compound **19**: ^{1}H NMR 0.05-0.15 (6x s, SiCH$_3$), 0.85-0.90 (3x s, CCH$_3$), 3.42 (d, OH, J=9.5 Hz), 3.71 (br dd, H-1, ^{3}J=1.5 Hz, ^{2}J=14 Hz), 4.00 (dd, H-3, J_{3-2}=2 Hz, J_{3-4}=4 Hz), 4.06-4.09 (ddd, H-2), 4.13 (br dq, H-1a), 4.44 (br d, H-4, J=9.5 Hz), 4.64 (br d, H-6, J=16 Hz), 4.90 (br d, H-6a, J=16 Hz). NOE's: between H-1, H-1a and H-6, H-6a; H-4 and 4-OH, H-3 and H-2. ^{13}C NMR (APT) 17.9, 18.0 and 18.2 (3x SiC), 25.6, 25.7 and 25.8 (SiCH$_3$, CCH$_3$), 60.2 and 61.3 (C-1, C-6), 67.2, 68.1 and 70.0 (C-2, C-3, C-4), 147.4 (C-5). FAB$^+$ MS 520 [M+H], 634 [2M+H], 504 [M+H-O], 462 [M-C$_4$H$_9$]. FAB$^-$ MS 518 [M-H], 672 [M+NBA]. Exact mass: measured 520.3265 for [M+H], calculated 520.3310.

Compound **20**: ^{1}H NMR 0.05-0.15 (6x s, SiCH$_3$), 0.85-0.90 (3x s, CCH$_3$), 3.12 (d, OH, J=7 Hz), 3.80-3.87 (m, H-5), 3.86 (dd, H-3, J_{3-2}=5.5 Hz, J_{3-4}=7 Hz), 4.13 (dd, H-6, ^{3}J=4 Hz, ^{2}J=10 Hz), 4.16-4.23 (m, H-4, H-2, H-6a), 7.00 (d, H-1, ^{3}J=3 Hz plus additional coupling of ca. 1 Hz). ^{13}C NMR (APT) 18.0 (SiC), 25.6 (SiCH$_3$, CCH$_3$), 60.7 (C-6), 67.7, 69.7, 71.7 and 74.8 (C-2, C-3, C-4, C-5), 135.7 (C-1). FAB$^+$ MS 520 [M+H], 504 [M+H-O], 462 [M-C$_4$H$_9$]. FAB$^-$ MS 518 [M-H], 672 [M+NBA]. Exact mass: measured 520.3272 for [M+H], calculated 520.3310.

(6α,7β,8α,8aβ)-6,7-bis[(1,1-dimethylethyl)dimethylsilyloxy]-8a-[[(1,1-dimethylethyl)dimethylsilyloxy]-methyl]-1-phenyl-hexahydro-8-hydroxy-2H-[1,2,4]oxadiazolo[2,3-a]pyridine-2-one (21) and (6α,7β,8α,8aα)-6,7-bis[(1,1-dimethylethyl)dimethylsilyloxy]-8a-[[(1,1-dimethylethyl)dimethylsilyloxy]-methyl]-1-phenyl-hexahydro-8-hydroxy-2H-[1,2,4]oxadiazolo[2,3-a]pyridine-2-one (22)

A solution of nitrone **19** (100 mg, 0.19 mmol) and phenyl isocyanate (209 μl, 1.9 mmol) in 4 ml of dry toluene was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and the residue purified by column chromatography over silica gel (eluent EtOAc-heptane, 1:1) to give the cycloadducts **21** (colorless oil) and **22** (white crystalline) in 10% and 30% yield, respectively. TLC Rf 0.30 and 0.65, respectively (eluent CH$_2$Cl$_2$).

Compound **21**: ^{1}H NMR 0.07, 0.09 (double intensity), 0.10, 0.18 and 0.20 (6x s, SiCH$_3$), 0.89, 0.90 and 0.95 (3x s, CCH$_3$), 3.44 (dd, H-4, J_{4-3}=4.5 Hz, $J_{H-4,OH}$=9.5 Hz), 3.53 (d, H-6, J=12 Hz), 3.57 (dd, H-1, ^{3}J=3 Hz, ^{2}J=15.5 Hz), 3.63 (dd, H-1a, ^{3}J=3.5 Hz, ^{2}J=15.5 Hz), 3.71 (q, H-2, J=4 Hz), 4.01 (d, OH, J=9.5 Hz), 4.05 (d, H-6a, J=12 Hz), 4.09 (t, H-3, J=4.5 Hz), 7.30-7.65 (m, Ph). Characteristic signals in ^{1}H NMR spectrum (C_6D_6): 3.19 (d, OH, J=8 Hz), 3.49 (dd, H-1α, ^{3}J=6.5 Hz, ^{2}J=13 Hz), 3.61 (dd, H-1β, ^{3}J=3.5 Hz, ^{2}J=13 Hz), 3.63-3.68 (ddd, H-2), 3.65 (dd, H-4, J_{4-3}=6 Hz, $J_{H-4,OH}$=8 Hz), 3.82 (d, H-6, J=11.5 Hz), 4.04 (t, H-3, J=6 Hz), 4.10 (d, H-6a, J=11.5 Hz). NOE's: between H-6a and H-1β and H-2 or H-4; H6a and H-2 or H-4; H-1β and only H-6a; H-1α and H-3, H-1β and H-2 or H-4; OH and H-3 and H-4. ^{13}C NMR (APT) 17.9 and 18.3 (SiC), 25.7 (SiCH$_3$, CCH$_3$), 51.0 and 61.7 (C-1, C-6), 69.2 and 70.8 (C-2, C-3, C-4), 85.7 (C-5), 127.8 and 128.9 (Ph), 135.2 (Ph), 156.2 (C(O)). EI MS 638 (weak) [M], 594 [M-CO$_2$], 581 [M-C$_4$H$_9$], 537 [581-CO$_2$], 493 [M-tBuMe$_2$SiOCH$_2$], 462 [594-tBuMe$_2$SiOH], 330 [462-tBuMe$_2$SiOH]. $[\alpha]_D^{20}$ +57.5° (c 1.0, CH$_2$Cl$_2$). Exact mass: measured 639.3642 for [M+H], calculated 639.3681.

Compound **22**: ^{1}H NMR 0.05, 0.09, 0.12, 0.13, 0.15 and 0.20 (6x s, SiCH$_3$), 0.88, 0.90 and 0.93 (3x s, CCH$_3$), 3.11 (d, OH, J=8.5 Hz), 3.45 (dd, H-1, ^{3}J=4.5 Hz, ^{2}J=12 Hz), 3.53 (dd, H-1a, ^{3}J=3 Hz, ^{2}J=12 Hz), 3.92 (t, H-3, J=4.5 Hz), 3.95 (d, H-6, J=11 Hz), 3.96-4.00 (m, H-2, w-coupling 1 Hz), 4.04 (dd, H-4, J_{4-3}=4.5 Hz, $J_{H-4,OH}$=8.5 Hz, w-coupling 1 Hz), 4.17 (d, H-6a, J=11 Hz), 7.25-7.50 (m, Ph). Characteristic signals in ^{1}H NMR spectrum (C_6D_6) 3.04 (d, OH, J=7.5 Hz), 3.38 (dd, H-1α, ^{3}J=4.5 Hz, ^{2}J=13 Hz), 3.48 (dd, H-1β, ^{3}J=3

Hz, ^{2}J=13 Hz), 3.85-3.89 (m, H-2, w-coupling 1 Hz), 4.05 (t, H-3, J=5.5 Hz), 4.12 (d, H-6, J=11 Hz), 4.13-4.17 (m, H-4, w-coupling 1 Hz), 4.37 (d, H-6a, J=11 Hz); OH signal is at higher field than in compound **21** due to proximal additional C-6 silyl group. NOE's: between H-6a and OH; H-1β and H-2 and H-4; H-1α and H-2 and H-3; OH and H-3, H-4 and H-6. ^{13}C NMR (APT) 18.1 and 18.4 (SiC), 25.9 and 26.2 ($SiCH_3$, CCH_3), 54.2 and 66.5 (C-1, C-6), 71.7, 72.6 and 72.9 (C-2, C-3, C-4), 84.7 (C-5), 127.8, 128.2 and 129.1 (Ph), 135.4 (Ph), 157.0 (C(O)). EI MS 638 (weak) [M], 594 [M-CO_2], 581 [M-C_4H_9], 537 [581-CO_2], 493 [M-$tBuMe_2SiOCH_2$], 462 [594-$tBuMe_2SiOH$], 330 [462-$tBuMe_2SiOH$]. $[\alpha]_D^{20}$ -8.0° (c 1.0, CH_2Cl_2); mp 189-190 °C. Exact mass: measured 639.3682 for [M+H], calculated 639.3681.

Methyl (2α,3aβ,4α,5β,6α)-Hexahydro-4-hydroxy-5,6-bis[(1,1-dimethylethyl)dimethylsilyloxy]-3a-[[(1,1-dimethylethyl)dimethylsilyloxy]methyl]-2H-isoxazolo[2,3-a]pyridine-2-acetate (23) and
Methyl (2α,3aα,4α,5β,6α)-Hexahydro-4-hydroxy-5,6-bis[(1,1-dimethylethyl)dimethylsilyloxy]-3a-[[(1,1-dimethylethyl)dimethylsilyloxy]methyl]-2H-isoxazolo[2,3-a]pyridine-2-acetate (24)

A solution of the nitrone **19** (519 mg, 1 mmol) and methyl vinylacetate (300 mg, 3 mmol) in 7.5 ml of $CHCl_3$ and a catalytic amount of a radical scavenger was kept under 15 kbar pressure overnight. The reaction mixture was concentrated in vacuo and the residue chromatographed over silica gel to afford the cycloadducts **23** (white semi-solid) and **24** (colorless oil) in 39% and 11% yield, respectively. TLC Rf 0.82 and 0.65, respectively (eluent MeOH-CH_2Cl_2, 4:96).

Compound **23**: ^{1}H NMR (C_6D_6) 0.00, 0.05, 0.15, 0.28 and 0.32 ($SiCH_3$), 0.85, 0.95 and 1.10 (CCH_3), 2.06 (dd, H-7α, ^{3}J=5.5 Hz, ^{2}J=13 Hz), 2.44 (dd, H-9, ^{3}J=7 Hz, ^{2}J=15 Hz), 2.59 (dd, H-7β, ^{3}J=9 Hz, ^{2}J=13 Hz), 2.70 (dd, H-9a, ^{3}J=6.5 Hz, ^{2}J=15 Hz), 2.92 (t, H-1β, J=10 Hz), 3.39 (d, OH, J=2.5 Hz), 3.40 (s, OCH_3), 3.46 (dd, H-1α, ^{3}J=3.5 Hz, ^{2}J=10 Hz), 3.73 (t, H-3, J=7.5 Hz), 3.76-3.81 (m, H-2), 3.81 (d, H-6, J=10 Hz), 3.86 (d, H-6a, J=10 Hz), 4.05 (dd, H-4, ^{3}J=2.5 Hz, ^{2}J=8 Hz), 4.79-4.88 (m, H-8). NOE's: between H-8 and H-7β and H-1β; H-4 and H-6, H-2, H-3 and OH; H-6 and H-4, H-2, H-7, H-9 and H-9a; H-7α and OH, H-6 and H-7β. 6-Membered ring probably in boat conformation. ^{13}C NMR (APT, C_6D_6) 18.2 and 19.0 (SiC), 25.9, 26.2 and 26.5 ($SiCH_3$, CCH_3), 36.2 and 40.4 (C-7, C-9), 51.2 (OCH_3), 55.7 (C-1), 69.7, 72.5, 76.1 and 76.9 (C-2, C-3, C-4, C-8), 70.8 (C-6), 72.8 (C-5), 170.4 (C(O)). EI MS 619 [M], 562 [M-C_4H_9], 474 [M-$tBuMe_2SiOCH_2$] (Si M+2 isotopic pattern). $[\alpha]_D^{20}$ +20.2° (c 1.0, $CHCl_3$). Exact mass: measured 620.3776 for [M+H], calculated 620.3834.

Compound **24**: ^{1}H NMR (C_6D_6) 0.05, 0.07, 0.14 and 0.30 ($SiCH_3$), 0.95, 0.98 and 1.05 (CCH_3), 1.55 (dd, H-7β, ^{3}J=5 Hz, ^{2}J=13 Hz), 2.33 (d, OH, J=6 Hz), 2.35 (dd, H-9, ^{3}J=5.5 Hz, ^{2}J=15.5 Hz), 2.54 (dd, H-7α, ^{3}J=8.5 Hz, ^{2}J=13 Hz), 2.79 (dd, H-9a, ^{3}J=7 Hz, ^{2}J=15.5 Hz), 3.29 (s, OCH_3), 3.35 (dd, H-1, ^{3}J=9 Hz, ^{2}J=14.5 Hz), 3.61 (dd, H-1a, ^{3}J=4 Hz, ^{2}J=14.5 Hz), 3.65 (d, H-6, J=10 Hz), 3.79 (dd, H-4, ^{3}J=5 Hz, ^{2}J=9 Hz), 4.07 (d, H-6a, J=10 Hz), 4.18-4.24 (m, H-2), 4.25 (t, H-3, J=9 Hz), 4.47-4.55 (m, H-8); OH signal is at higher field than in compound **23** due to proximal additional C-6 silyl group. NOE's: between H-4 and H-7β and H-8; H-7α and H-6, H-6a, H-9 and H-9a; H-6 and H-7α; H-7β and H-8. 6-Membered ring probably in chair conformation. EI MS 619 [M], 562 [M-C_4H_9], 474 [M-$tBuMe_2SiOCH_2$] (Si M+2 isotopic pattern). $[\alpha]_D^{20}$ -13.6° (c 0.25, $CHCl_3$). Exact mass: measured 620.3776 for [M+H], calculated 620.3834.

Methyl (2α,3α,4α,5β,6α,7β)-hexahydro-4,5-bis[(1,1-dimethylethyl)dimethylsilyloxy]-7-[[(1,1-dimethylethyl)dimethylsilyloxy]methyl]-6-hydroxy-2H-isoxazolo[2,3-a]pyridine-2-acetate (25)

A solution of the nitrone **20** (467 mg, 0.9 mmol) and methyl vinylacetate (300 mg, 3.0 mmol) in 7.5 ml of $CHCl_3$ and a catalytic amount of a radical scavenger was kept under 15 kbar pressure overnight. The reaction mixture was concentrated in vacuo and the residue chromatographed over silica gel to afford compound **25** as a colorless oil in 23% yield. TLC Rf 0.32 (eluent EtOAc-heptane, 4:6). ^{1}H NMR 0.11, 0.12 and 0.13 ($SiCH_3$), 0.90 and 0.92 (CCH_3), 1.66 (br s, OH), 1.99-2.06 (m, H-7), 2.43-2.53 (m, H-7a), 2.55 (dd, H-9, ^{3}J=7 Hz, ^{2}J=15.5 Hz), 2.60-2.68 (m, H-5), 2.66 (dd, H-9a, ^{3}J=6 Hz, ^{2}J=15.5 Hz), 2.98-3.12 (br s, OH), 3.42-3.49 (m, H-4), 3.66-3.70 (m, H-1, H-3), 3.70 (s, OCH_3), 3.77-3.84 (m, H-6), 3.86 (dd, H-2, ^{3}J=4.5 Hz, ^{2}J=7 Hz), 4.58-4.66 (m, H-8). Configuration at C-1 is β according to NOE's between H-1 and H-5 and H-1 and H-9; an NOE between H-8 and 6-OH is observed. ^{13}C NMR (APT) 18.0 (SiC), 25.9 and 26.0 ($SiCH_3$, CCH_3), 34.2 and 39.3 (C-7, C-9), 51.7 (OCH_3, C-1), 60.8 (C-6), 63.6 (C-8), 70.7, 71.0, 72.3 and 74.3 (C-2, C-3, C-4, C-5), 170.7 (C(O)). EI MS 505 [M], 490 [M-CH_3], 474 [M-OCH_3, 100%], 448 [M-tBu]. FAB^+ MS 506 [M+H], 528 [M+Na], 474 [M-OCH_3]. FAB^- MS 504 [M-H], 658 [M+NBA]. FD^+ MS 505 [M, 100%]. ESI^+ MS 506 $[M+H]^+$, 571 $[M+2H]^{++}$ (Gramicidin as internal standard). Exact mass: measured 506.2929 for [M+H], calculated 506.2969.

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30. These reactions were carried out at the Department of Organic Chemistry of the University of Nijmegen. A test reaction was carried out in deuterated chloroform in order to be able to follow the reaction by ^{1}H-NMR.

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