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Short synthesis, X-ray and conformational analysis of a cyclic peracetylated L-sorbose-derived nitrone, a useful intermediate towards N–O-containing D-gluco-iminosugars†

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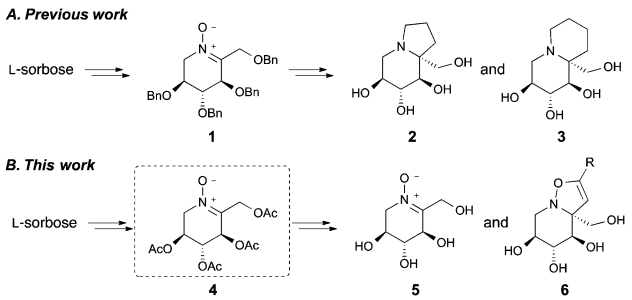
The synthesis of the peracetylated ketonitrone **4** is described in four steps from L-sorbose. This cyclic nitrone is crystalline and proved to preferentially adopt a $^4H_3$ conformation with all acetate groups in pseudo-axial orientation. Nitrone **4** undergoes regioselective cycloadditions with alkynes, affording tetra-*O*-acetyl-isoxazolines with good yields and stereoselectivities (4 : 1 to 9 : 1 diastereomeric ratio). Nitrone **4** and the obtained isoxazolines were smoothly deacetylated to produce the polyhydroxylated nitrone **5** and novel iminosugars containing an isoxazoline motif. Evaluation of their glycosidase inhibitory activity demonstrated their rather weak, but selective affinity for a variety of enzymes.

Introduction

Carbohydrate-derived nitrones[1] are key intermediates for the synthesis of polyhydroxylated alkaloids and iminosugars, which are sugar analogues with a nitrogen atom in place of the endocyclic oxygen atom. Iminosugars are a major class of synthetic targets due to their therapeutic potential, generally associated with their ability to inhibit glyco-processing enzymes.[2]

Among the cyclic nitrones described to date, the vast majority is *O*-benzyl-protected due to the compatibility of benzyl ethers with the steps involved in their preparation from carbohydrates. Moreover, easy conversion of benzyl ethers into hydroxyls by hydrogenolysis is usually performed in the last stages of iminosugar syntheses. A few years ago, we applied tetra-*O*-benzyl-protected ketonitrones (prepared from inexpensive D-fructose[3] or L-sorbose[4]) to the synthesis of original iminosugars bearing a quaternary center α to their nitrogen atom. In particular, the L-sorbose benzylated ketonitrone **1** was successfully used in the synthesis of the polyhydroxylated indolizidine **2**[4] and quinolizidine **3**,[5] which were revealed to be potent and selective α-glucosidase inhibitors with nanomolar K_i values (Scheme 1). Such carbohydrate derived-nitrones could also give access to iminosugars containing a N–O bond, for which little is known concerning glycosidase inhibition potency.[6] Although such compounds could in principle be obtained through cleavage of benzyl ethers using BCl_3 to avoid N–O bond destructive hydrogenolysis,[3,7] we thought that the use of *O*-acyl-protected nitrones could be advantageous to allow a hydroxyl-deprotection step under mild conditions. We thus intended to prepare nitrone **4**, the *O*-acetylated analogue of nitrone **1**, and to study its reactivity in cycloaddition reactions with alkynes to form 4-isoxazolines, a class of compounds for which glycosidase inhibition has yet not been reported. Noteworthily, examples of *O*-acylated nitrones are very scarce in the literature.[8]



Scheme 1 Ketonitrones as intermediates for new iminosugar synthesis.

Results and discussion

While three steps are necessary for the synthesis of tetra-*O*-benzyl-L-sorbose from L-sorbose,[4] only one step is required to prepare tetra-*O*-acetyl-L-sorbose (**7**). This protected ketose has been previously obtained in 65% yield by treating L-sorbose

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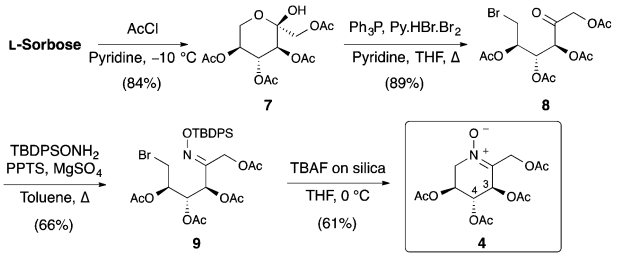


Scheme 2 Synthesis of nitrone **4** from L-sorbose.

with acetic anhydride in pyridine.[9] We found that acylation of L-sorbose in the presence of acetyl chloride yielded the protected derivative **7** (84%) with better efficiency (Scheme 2).[10] In the next step, the *in situ* generation of the $PPh_3{\cdot}Br_2$ brominating reagent was preferred to the commercially available complex as the latter exhibited variable efficiency depending on the batches. Thus, triphenylphosphine and pyridinium tribromide in the presence of pyridine were used to perform concomitant hemiketal ring opening and C-6 bromination of **7**,[11] allowing the isolation of bromoketone **8** in excellent yield (89%). The direct transformation of **8** into nitrone **4** by using the same protocol used for the synthesis of **1** was not possible in this case. Treating bromoketone **8** with hydroxylamine only led to complex mixtures, in which the presence of **4** could not be detected by NMR analysis. A significant loss of material after extraction suggested deacetylation in the presence of hydroxylamine.[12] Bromoketone **8** was thus treated with *tert*-butyldimethylsilyloxyamine[13] in the presence of $MgSO_4$ in refluxing toluene to yield the bromo-oxime **9** in 66% yield. Remarkably, only the *E* stereoisomer was formed in this case. Finally, the target nitrone **4** was obtained in 61% yield by a desilylation/cyclisation sequence induced by treatment with TBAF on silica at 0 °C.[14] The crystalline and stable nitrone **4** was thus synthetized in 4 steps from L-sorbose in 30% overall yield. Its preparation can be applied to the multigram scale.

The analysis by X-ray diffraction of a monocrystal of nitrone **4** unambiguously confirmed its structure and depicted a half-chair conformation in which the acetate substituents are in pseudo-axial orientations (Fig. 1).[15] NMR data also support the preference for pseudo-axial positioning of the acetate groups in solution (broad singlet for ^3H, meaning that $J^3H,^4H < 2$ Hz in $CDCl_3$). This conformation could be favored over the half-chair exhibiting pseudo-equatorial acetate groups due to through-space electrostatic stabilization of the $(C{=}N)^+$ function by axial acyloxy groups, as previously demonstrated for 6-membered cyclic oxocarbeniums.[16] DFT calculations confirmed that the half-chair conformation with all acetate substituents in pseudo-axial orientation is more stable than that bearing all-equatorial acetates, although the free energy difference is small (ΔG_{298} = 1 kcal mol^{-1}, see ESI†).[17]

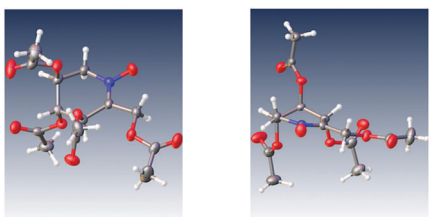
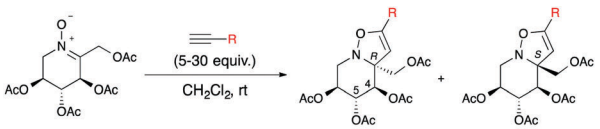


Fig. 1 Views of the X-ray structure of nitrone **4**.

Nitrone **4** was engaged in cycloaddition reactions with various alkynes to prepare isoxazolines (Table 1). The cycloadditions with phenylacetylene, cyclohexylacetylene, trimethylsilylacetylene, propargyl acetate, 1-pentyne and 1-hexyne were slow, but occurred smoothly at room temperature, and led to isoxazolines **10a–f** and **10′a–f** in good yields (78–97%). These reactions proved to be completely regioselective, yielding only the C-5 substituted isoxazolines **10a–f**. However, cycloadditions with nitrone **4** were not as diastereoselective as with nitrone **1**,[18] and minor diastereoisomers **10′a–f** could not be separated by chromatography from **10a–f** (**10** : **10′** = 4 : 1 to 9 : 1).

Table 1 Cycloaddition of nitrone **4** with alkynes at room temperature



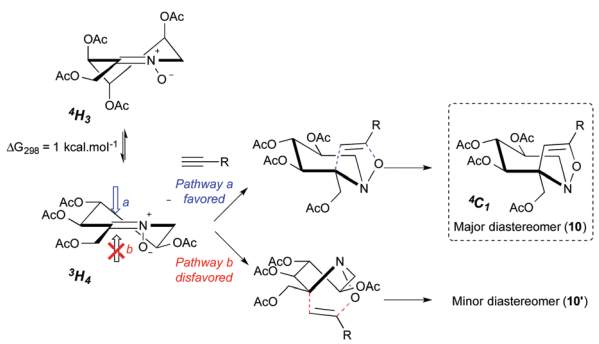
Entry	Alkyne	Cycloadduct	Reaction time (days)	Global yield (%)	dr **10** : **10′**
1	—Ph	**10a**	3	90	4 : 1
2[a]	—Cy	**10b**	4	78	9 : 1
3	—TMS	**10c**	2	97	9 : 1
4	—OAc	**10d**	2	92	4 : 1
5[a]		**10e**	17	Not purified	9 : 1
6[a]		**10f**	12	Not purified	9 : 1

[a] A small volume of dichloromethane was added to solubilize the reactants, nitrone **4** being poorly soluble in the alkyne.

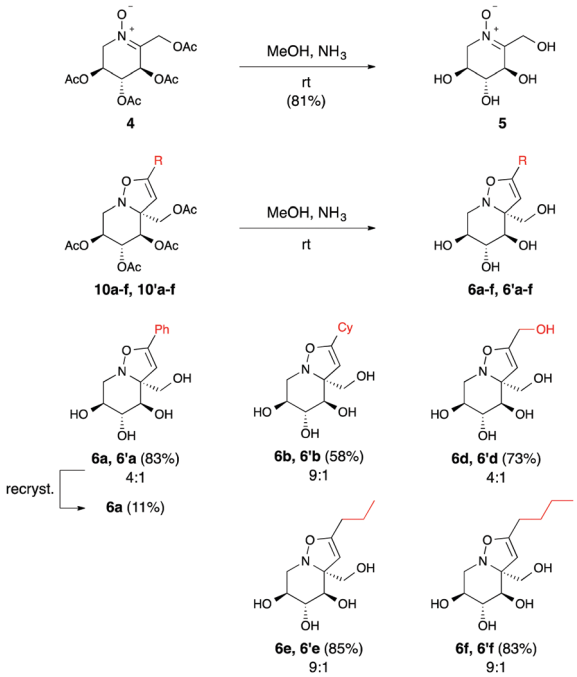
Interestingly, the major isoxazolines **10a–f** (of *R* configuration at the quaternary center as deduced from nOe analyses, see ESI†) exhibit the D-gluco configuration that proved essential for the biological activities of **2** and **3**.[4,5] The dominant reaction pathway thus results from the preferential approach of the alkyne from the *Si* face of the nitrone. This is consistent with an axial approach of the alkyne on the minor $^3H_4$ conformer of nitrone **4**, forming a favored chair-like transition (pathway a) state rather than the higher-energy twist boat that would result from addition of the alkyne through the other axial trajectory (pathway b), *i.e. anti* to the C-3 acetoxy substituent (Scheme 3). The axial approach favoring chair-like transition states is known to be favored in nucleophilic additions to both 6-membered oxonium[19] and iminium[20] ions.

The stereochemical outcome of the cycloaddition of alkynes to nitrone **4** thus suggests a fast equilibrium between its $^4H_3$ and $^3H_4$ conformers, and a faster cycloaddition of the latter, exhibiting pseudo-equatorial acetate groups, over the slightly more stable $^4H_3$ conformer. The formation of the minor diastereoisomers **10′** could arise either from an axial approach of the alkyne to develop a chair-like transition state on the $^4H_3$ conformer of the nitrone (not shown), or from the disfavored twist-boat transition state occurring in pathway b from the $^3H_4$ conformer (Scheme 3). In contrast to the numerous studies on cycloadditions involving 5-membered ring nitrones and alkenes,[21] cycloadditions to cyclic 6-membered ring nitrones are less common and their stereoselectivity has rarely been discussed.[22] The model proposed here, involving addition of the dipolarophile to the nitrone *via* a favored axial trajectory, can also explain previous results reported by van den Broek[23] and by Peer and Vasella (with dipolarophiles different from alkynes).[24] In light of these results, DFT energy minimization calculations were also performed on the two half-chair conformations of nitrone **1** (see ESI†).[17,18] The most stable conformer is also the $^3H_4$ conformer exhibiting pseudo axial benzyloxy groups, and in this case, the free energy difference (ΔG_{298} = 0.5 kcal mol^{-1}) between conformers is smaller.

According to NMR data, the major isoxazolines **10** formed from the cycloaddition of nitrone **4** with alkynes all adopt a chair $^4C_1$ conformation in the piperidine ring. Indeed, the ^{4}H–^{5}H coupling constants in these compounds exhibit typical values for diaxial proton coupling (10.1 Hz < J^4H–^{5}H < 10.6 Hz).



Scheme 3 Stereochemical model for alkyne cycloadditions to nitrone **4**.



Scheme 4 Deacetylation of nitrone **4** and isoxazolines **10**.

Nitrone **4** and isoxazolines **10**,**10′** were next easily deprotected under mild conditions by treatment with a saturated solution of ammonia in methanol, affording the polyhydroxylated nitrone **5** in good yield (81%, Scheme 4).[25] The polyhydroxylated isoxazolines **6a–f** and **6′a–f** could also be obtained in good yields under the same conditions. Gratifyingly, after deacetylation, the major diastereomer **6a** could be isolated pure by recrystallization in methanol. Here again, the measured coupling constant J^4H–^{5}H of 8.8 Hz (δ 3.92 ppm) for **6a** suggests that this compound adopts mostly a $^4C_1$ conformation in d4-methanol.

Biological activities

The polyhydroxylated nitrone **5** and isoxazolines **6** synthesized from nitrone **4** were next evaluated as glycosidase inhibitors using a panel of commercial enzymes.[26] Nitrone **5** and isoxazoline **6a** were tested as pure compounds (single stereoisomer), whereas isoxazolines **6b** and **6d–f** were tested as mixtures of diastereomers. Inhibition of rice α-glucosidase, yeast α-glucosidase, almond β-glucosidase, β-glucosidase from *Aspergillus niger*, β-galactosidase from *Aspergillus oryzae*, Jack bean α-mannosidase, bovine liver α-fucosidase and α-rhamnosidase from *Aspergillus niger* was first evaluated at 1 mM concentration of inhibitor (Table 2). When almost complete inhibition (>95%) occurred at this concentration, IC_{50} (the concentration of inhibitor affording half the initial rate of the considered glycosidase) was further determined. In the case of an inhibition rate between 90% and 95%, an additional assay was performed at a concentration of 100 μM (see footnotes of Table 2).

Nitrone **5** and isoxazolines **6a**,**b**,**e**,**f** are all inhibitors of α-glucosidase from rice at 1 mM concentration. Nitrone **5** and isoxazoline **6a** are the most active, with IC_{50} values of 16 and 50 μM, respectively. However, these values are three orders

Table 2 Glycosidase inhibition[a,b]

Enzyme	5	6a	6b/6′b	6d/6′d	6e/6′e	6f/6′f
α-glucosidase (rice)	95%[c]	96%[d]	92%[e]	43%	92%[f]	91%[g]
α-glucosidase (*Sac. cerevisiae*)	5%	49%	74%	−26%[j]	11%	30%
β-glucosidase (almond)	16%	94%[h]	−7%[j]	−7%[j]	−24%[j]	−8%[j]
β-glucosidase (*Asp. niger*)	11%	93%[i]	NI	NI	NI	NI
β-galactosidase (*Asp. orizae*)	15%	37%	15%	NI	NI	NI
α-mannosidase (Jack bean)	8%	NI	−13%[j]	−8%[j]	−6%[j]	−12%[j]
α-rhamnosidase (*Asp. niger*)	33%	46%	8%	NI	10%	7%

[a] % inhibition at 1 mM concentration of inhibitor (less than 5% inhibition/activation was regarded as no impact of the inhibitor on enzyme activity). [b] NI means no impact on enzyme activity. [c] IC_{50} = 16 μM. [d] IC_{50} = 50 μM. [e] 39% inhibition at 100 μM. [f] 33% inhibition at 100 μM. [g] 41% inhibition at 100 μM. [h] 20% inhibition at 100 μM. [i] 18% inhibition at 100 μM. [j] Negative values mean increase of enzyme activity.

of magnitude higher than other D-gluco-configured bicyclic iminosugars bearing a hydroxymethyl substituent at the ring junction (IC_{50} in the nanomolar range).[4,5] Isoxazolines **6b,e,f** are less efficient inhibitors, with IC_{50} values above 100 μM, as reflected by the remaining α-glucosidase activity measured at this concentration. Compound **6d**, which features an extra hydroxymethyl group, is only a moderate inhibitor of α-glucosidase from rice (43% at 1 mM) and it has no inhibition capacity towards all other tested enzymes. Such a detrimental impact of additional hydroxyl groups onto the fused cycle has already been observed previously with hydroxylated analogues of indolizidine **2**[4] and quinolizidine **3**.[5] Compounds **5** and **6b,d,e,f** only marginally interfere with the other glycosidases. Only **6a**, which features an aromatic moiety on the isoxazoline ring, proved active against β-glucosidases from almond and from *Aspergillus niger* (94% and 93% inhibition, respectively). However, a sharp decrease of inhibition potency occurred in a dose-dependent manner affording only 20% remaining inhibition at 100 μM for both enzymes. The weak basicity of the nitrogen atom in isoxazolines **6** (in comparison to that of iminosugars such as **2** and **3**) probably disfavours protonation under the assay conditions, and could account for their limited performance as transition state mimics.

Unexpectedly, a significant increase in the activity of α-glucosidase (yeast) was observed in the presence of **6d** at 1 mM concentration (26% activation). Similarly, isoxazolines **6b,d,e,f** behave as activators of β-glucosidase and of α-mannosidase. This phenomenon is quite commonly encountered while performing glycosidase assays in the presence of carbohydrate analogues,[27] but it is not systematically included in the tables reporting inhibition values (for the sake of simplicity, it is sometimes referred to as NI, no inhibition). The mechanism of activation of glycosidases by saccharides or analogues is currently unknown but allosteric regulation or modification of the assay-solution properties by the activator has been suggested as a possible explanation.[28]

Conclusions

In conclusion, a short synthetic route to the peracetylated ketonitrone **4** was developed from L-sorbose. The latter was used in cycloaddition reactions with alkynes, which afforded the corresponding bicyclic isoxazolines in high yields, with excellent regioselectivity and significant stereoselectivity in favour of the D-gluco-configured compounds. An easy deprotection through methanolic aminolysis of acetates gave access to the polyhydroxylated nitrone **5** and to unprecedented iminosugars **6a–f** containing an isoxazoline motif. These compounds were evaluated as glycosidase inhibitors and most of them were found to be weak but selective inhibitors of rice α-glycosidase.

Experimental

General remarks

Reactions were performed under a positive pressure of dry argon in oven-dried glassware equipped with a magnetic stir bar. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. THF and toluene were freshly distilled from sodium; CH_2Cl_2 and pyridine were distilled from CaH_2. Purchased reagents were used without purification. Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel plates. TLC spots were viewed under ultraviolet light and by heating the plate after treatment with a 3% solution of potassium permanganate in 10% aqueous potassium hydroxide (w/v). Product purification by gravity column chromatography was performed using Silica Gel 60 (70–230 mesh). Optical rotations were measured on a Perkin Elmer 341 polarimeter. Infrared spectra were obtained from neat compounds on a Nicolet "Magna 550" spectrometer using an ATR (attenuated total reflexion) module. The data are reported in reciprocal centimeters (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 (^1H: 500 MHz, ^{13}C: 125 MHz) spectrometer. Chemical shifts for ^1H spectra are values from residual chloroform in $CDCl_3$ (δ 7.26 ppm), residual acetone in $(CD_3)_2CO$ (δ 2.05 ppm) or residual methanol in CD_3OD (δ 3.31 ppm). Chemical shifts for ^{13}C spectra are values from $CDCl_3$ (δ 77.16 ppm), $(CD_3)_2CO$ (δ 29.84 ppm) or CD_3OD (δ 49.00 ppm). ^1H NMR spectra are reported as following: chemical shift (ppm), multiplicity (br: broad; s: singlet; d: doublet; dd: doublet of doublets; ddd: dedoubled doublet of doublets; t: triplet; ps t: pseudo triplet; td: triplet of doublets; m: multiplet), coupling constants (Hz) and integration. Proton and carbon signal assignments were established using COSY, HSQC, and HMBC experiments. High-resolution mass spectra (HRMS) were recorded on a Waters G2-S Q-TOF mass spectrometer.

Experimental protocols

(2*R*,3*S*,4*R*,5*S*)-2-(Acetoxymethyl)-2-hydroxytetrahydro-2*H*-pyran-3,4,5-triyl triacetate (7). L-Sorbose (10.0 g, 55.5 mmol) was

dissolved in dry pyridine (150 mL) at room temperature. The solution was cooled to −10 °C and kept for 1 h at this temperature. Acetyl chloride (16.2 mL, 228 mmol) was then added dropwise (in around 45 min), the temperature of the mixture being kept at −5 °C. The final solution was stirred at −10 °C for 3 h and at room temperature for 40 min. After dilution in dichloromethane, the mixture was poured into a 2 M HCl aqueous solution. The organic phase was then separated and washed twice with HCl solution followed by washing with a saturated aqueous $NaHCO_3$ solution. After drying over anhydrous $MgSO_4$, the organic phase was filtered and concentrated under vacuum to give a residue, which was purified by chromatography (pentane/ether 9 : 1) affording tetra-*O*-acetylated-L-sorbose **7** (16.16 g, 84%) as a white solid. M.p. 91–93 °C. $[\alpha]_D^{20} = -21.6$ (c = 1.02, $CHCl_3$). IR ν = 3551, 2977, 1750, 1736, 1700, 1369, 1218, 1168, 1036 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 5.52 (ps t, J = 9.8 Hz, 1H, ^4CH), 5.07 (d, J = 9.9 Hz, 1H, ^3CH), 5.02 (ddd, J = 6.2, 9.8, 10.6 Hz, 1H, ^5CH), 4.18 (d of AB system, J = 11.8 Hz, 1H, $^1CH_2$), 3.97 (d of AB system, J = 11.8 Hz, 1H, $^1CH_2$), 3.90–3.80 (m, 2H, $^6CH_2$), 3.41 (s, 1H, OH), 2.12 (s, 3H, $^{Ac}CH_3$), 2.09 (s, 3H, $^{Ac}CH_3$), 2.03 (s, 3H, $^{Ac}CH_3$), 2.02 (s, 3H, $^{Ac}CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.1 (^{Ac}CO), 170.3 (^{Ac}CO), 170.1 (^{Ac}CO), 169.8 (^{Ac}CO), 95.8 (^2Cq), 70.7 (^4CH), 70.4 (^3CH), 69.2 (^5CH), 65.9 ($^1CH_2$), 59.5 ($^6CH_2$), 20.8 ($^{Ac}CH_3$), 20.8 ($^{Ac}CH_3$), 20.7 ($^{Ac}CH_3$), 20.7 ($^{Ac}CH_3$). HRMS (ESI^+): calcd for $C_{14}H_{20}NaO_{10}$ $[M + Na]^+$ 371.0954; found 371.0957.

(3*S*,4*S*,5*R*)-6-Bromo-2-oxohexane-1,3,4,5-tetrayl tetraacetate (8). To a solution of triphenylphosphine (9.09 g, 34.6 mmol) in THF (90 mL) was added pyridinium tribromide (11.04 g, 34.5 mmol) and the mixture was stirred for 20 minutes at room temperature. Compound **7** (6 g, 17.2 mmol) in THF (45 mL) and pyridine (5.5 mL, 69.0 mmol) were then added and the resultant mixture was heated at reflux for 1 h. After dilution in ethyl acetate, the organic phase was washed successively with a saturated $Na_2S_2O_3$ aqueous solution, aqueous 2 M HCl solution and with brine. After drying over $MgSO_4$, the organic phase was filtered and concentrated under vacuum. The crude solid was washed with ether and discarded. The ethereal solution was evaporated to give an oily residue that was purified by chromatography (pentane/ether 3 : 7) to afford bromoketone **8** (6.26 g, 89%) as a yellow oil. $[\alpha]_D^{20}$ = +21.1 (c = 0.99, $CHCl_3$). IR ν = 2941, 1750, 1431, 1371, 1200, 1042 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 5.71 (dd, J = 3.7 Hz, J = 5.6 Hz, 1H, ^4CH), 5.43 (d, J = 3.7 Hz, 1H, ^3CH), 5.27 (ddd, J = 5.3, 5.3, 11.0 Hz, 1H, ^5CH), 4.83 (d of AB system, J = 17.1 Hz, 1H, $^1CH_2$), 4.77 (d of AB system, J = 17.1 Hz, 1H, $^1CH_2$), 3.52 (dd of ABX system, J = 5.3, 11.0 Hz, 1H, $^6CH_2$), 3.41 (dd of ABX system, J = 5.3, 11.0 Hz, 1H, $^6CH_2$), 2.20 (s, 3H, $^{Ac}CH_3$), 2.16 (s, 3H, $^{Ac}CH_3$), 2.12 (s, 3H, $^{Ac}CH_3$), 2.09 (s, 3H, $^{Ac}CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 197.1 (^{Ac}CO), 169.9 (^{Ac}CO), 169.8 (^{Ac}CO), 169.72 (^{Ac}CO), 169.66 (^{Ac}CO), 73.8 (^3CH), 70.3 (^5CH), 70.0 (^4CH), 66.7 ($^1CH_2$), 29.3 ($^6CH_2$), 20.7 ($^{Ac}CH_3$), 20.6 ($^{Ac}CH_3$), 20.56 ($^{Ac}CH_3$), 20.54 ($^{Ac}CH_3$) ppm. HRMS (ESI^+): calcd for $C_{14}H_{19}BrNaO_9$ $[M + Na]^+$ 433.0110; found 433.0113.

(3*R*,4*S*,5*R*,*E*)-6-Bromo-2-(*tert*-butyldiphenylsilyloxyimino)-hexane-1,3,4,5-tetrayl tetraacetate (9). To a solution of bromoketone **8** (3.06 g, 7.44 mmol) in toluene (150 mL), $MgSO_4$ (25.5 g), *O-tert*-butyldiphenylsilyl hydroxylamine (2.42 g, 8.93 mmol) and pyridinium *p*-toluenesulfonate (374 mg, 1.49 mmol) were added successively. The mixture was heated at reflux for 1 h whereupon solid $NaHCO_3$ was added to neutralise PPTS. After filtration over Celite, the solids were rinsed with dichloromethane and the filtrate was concentrated under vaccum to give a residue, which, upon chromatography (pentane/ether 9 : 1 to 7 : 3), yielded oxime **9** (3.24 g, 66%) as a brown oil. $[\alpha]_D^{20} = -9.2$ (c = 1.08, $CHCl_3$). IR ν = 3072, 2958, 2935, 2859, 1746, 1428, 1371, 1207, 1115, 1044, 966, 948 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.68–7.58 (m, 4H, ^{Ar}CH), 7.47–7.32 (m, 6H, ^{Ar}CH), 5.74–5.63 (m, 2H, ^3CH and ^4CH), 5.22 (d of AB system, J = 15.9 Hz, 1H, $^1CH_2$), 5.16 (td, J = 5.5, 6.7 Hz, 1H, ^5CH), 5.11 (d of AB system, J = 15.9 Hz, 1H, $^1CH_2$), 3.28 (d, J = 5.6 Hz, 2H, $^6CH_2$), 2.16 (s, 3H, $^{Ac}CH_3$), 2.04 (s, 3H, $^{Ac}CH_3$), 1.92 (s, 3H, $^{Ac}CH_3$), 1.89 (s, 3H, $^{Ac}CH_3$), 1.10 (s, 9H, $^{t\text{-}Bu}CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.9 (^{Ac}CO), 169.9 (^{Ac}CO), 169.8 (^{Ac}CO), 169.8 (^{Ac}CO), 156.2 (^2Cq), 135.6 (^{Ar}CH), 135.6 (^{Ar}CH), 132.8 (^{Ar}Cq), 132.8 (^{Ar}Cq), 130.1 (^{Ar}CH), 130.0 (^{Ar}CH), 127.9 (^{Ar}CH), 127.8 (^{Ar}CH), 70.7 (^5CH), 70.5 (^4CH), 69.1 (^3CH), 58.5 ($^1CH_2$), 27.1 ($^6CH_2$), 20.9 ($^{Ac}CH_3$), 20.7 ($^{Ac}CH_3$), 20.6 ($^{Ac}CH_3$), 20.5 ($^{Ac}CH_3$) ppm. HRMS (ESI^+): calcd for $C_{30}H_{38}BrNaNO_9Si$ $[M + Na]^+$ 686.1397; found 686.1385.

(3*S*,4*R*,5*R*)-3,4,5-Triacetoxy-6-(acetoxymethyl)-2,3,4,5-tetrahydropyridine 1-oxide (4). To a solution of bromide **9** (4.02 g, 6.05 mmol) in THF (135 mL), TBAF supported on silica gel (6.7 g, 8.28 mmol) was added at 0 °C, and the mixture was stirred for 1 h. After filtration, the solid was rinsed with THF. The filtrate was concentrated under vacuum and the residue was purified by chromatography (AcOEt/MeOH 95 : 5) to afford nitrone **4** (1.27 g, 61%) as a white solid. M.p. 106–107 °C. $[\alpha]_D^{20} = -63.5$ (c = 1.07, $CHCl_3$). IR ν = 2981, 2950, 1737, 1434, 1370, 1208, 1047, 1022 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 5.72 (br s, 1H, ^3CH), 5.23 (d, J = 16.6 Hz, 1H, $^1CH_2$), 5.22–5.16 (m, 2H, ^4CH and ^5CH), 4.95 (d, J = 16.6 Hz, 1H, $^1CH_2$), 4.23 (dd, J = 1.6, 16.1 Hz, 1H, $^6CH_2$), 4.01 (br d, J = 16.1 Hz, 1H, $^6CH_2$), 2.11 (s, 3H, $^{Ac}CH_3$), 2.08 (s, 3H, $^{Ac}CH_3$), 2.06 (s, 3H, $^{Ac}CH_3$), 2.04 (s, 3H, $^{Ac}CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.2 (^{Ac}CO), 169.4 (^{Ac}CO), 169.0 (^{Ac}CO), 168.7 (^{Ac}CO), 138.5 (^2Cq), 65.8 (^4CH), 65.4 (^5CH), 65.3 (^3CH), 60.0 ($^1CH_2$), 59.4 ($^6CH_2$), 20.7 ($^{Ac}CH_3$), 20.7 ($^{Ac}CH_3$), 20.6 ($^{Ac}CH_3$), 20.6 ($^{Ac}CH_3$) ppm. HRMS (ESI^+): calcd for $C_{14}H_{20}NO_9$ $[M + H]^+$ 346.1138; found 346.1133.

(3*aR*,4*R*,5*R*,6*S*)-3*a*-(Acetoxymethyl)-2-phenyl-3*a*,4,6,7-tetrahydro-5*H*-isoxazolo[2,3-*a*]pyridine-4,5,6-triyl triacetate (10a). A mixture of nitrone **4** (264 mg, 0.76 mmol) and phenylacetylene (1.3 mL, 11.5 mmol) was stirred at room temperature for 3 days. After concentration under reduced pressure, the residue was purified by chromatography over silica gel (pentane/EtOAc 7 : 3) to give cycloadducts **10a** and **10′a** (310 mg, 90%) as a white foam (mixture of two unseparated diastereoisomers, dr = 4 : 1). M.p. 43–45 °C. IR ν = 2969, 1750, 1649, 1494, 1448, 1367, 1212, 1031 cm^{-1}. Major diastereoisomer: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.55–7.47 (m, 2H, ^{Ar}CH), 7.37–7.31 (m, 3H, ^{Ar}CH), 5.48 (d, J = 10.1 Hz, 1H, ^4CH), 5.31–5.24 (m, 2H, ^3CH, ^5CH), 5.05 (td, J = 4.6, 6.5 Hz, 1H, ^6CH), 4.08 (d of AB system, J = 11.6 Hz, 1H, $^8CH_2$), 3.95 (d of AB system, J = 11.6 Hz, 1H, $^8CH_2$), 3.60 (dd o f ABX system, J = 4.5, 13.4 Hz, 1H, $^7CH_2$), 3.39 (dd of ABX system, J = 6.5, 13.4 Hz, 1H, $^7CH_2$), 2.08 (s, 3H, $^{Ac}CH_3$), 2.06 (s, 3H, $^{Ac}CH_3$),

1.99 (s, 3H, $^{Ac}CH_3$), 1.86 (s, 3H, $^{Ac}CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.8 (^{Ac}CO), 170.1 (^{Ac}CO), 170.0 (^{Ac}CO), 169.6 (^{Ac}CO), 157.0 ($^{2}C_q$), 130.1 (^{Ar}CH), 128.6 (^{Ar}CH), 127.8 ($^{Ar}C_q$), 126.0 (^{Ar}CH), 91.7 (^{3}CH), 74.7 ($^{3a}C_q$), 73.0 (^{5}CH), 69.9 (^{6}CH), 67.9 (^{4}CH), 64.4 ($^{8}CH_2$), 53.1 ($^{7}CH_2$), 20.9 ($^{Ac}CH_3$), 20.8 ($^{Ac}CH_3$), 20.8 ($^{Ac}CH_3$), 20.7 ($^{Ac}CH_3$) ppm. NOESY correlation between $^{8}CH_2$ and ^{4}CH. Minor diastereoisomer significative signals: ^1H NMR (400 MHz, $CDCl_3$) δ = 5.41–5.36 (m, 1H, $^{5'}CH$), 5.22–5.16 (m, 2H, $^{3'}CH$, $^{6'}CH$), 4.23 (d of AB system, J = 11.4, 1H, $^{8'}CH_2$), 4.19 (d of AB system, J = 11.2, 1H, $^{8'}CH_2$), 3.69 (dd, of ABX system, J = 4.8, 14.3 Hz, 1H, $^{7'}CH_2$), 3.33 (dd of ABX system, J = 7.7, 14.3 Hz, 1H, $^{7'}CH_2$), 2.09 (s, 3H, $^{Ac}CH_3$), 2.05 (s, 3H, $^{Ac}CH_3$), 2.00 (s, 3H, $^{Ac}CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6 (^{Ac}CO), 170.2 (^{Ac}CO), 169.7 (^{Ac}CO), 169.6 (^{Ac}CO), 156.0 ($^{2'}C_q$), 130.0 (^{Ar}CH), 127.5 ($^{Ar}C_q$), 126.1 (^{Ar}CH), 94.7 ($^{3'}CH$), 73.4 ($^{3a'}C_q$), 72.3 ($^{4'}CH$), 71.8 ($^{5'}CH$), 68.5 ($^{6'}CH$), 65.6 ($^{8'}CH_2$), 52.4 ($^{7'}CH_2$), 21.1 ($^{Ac}CH_3$), 21.1 ($^{Ac}CH_3$), 21.0 ($^{Ac}CH_3$), 20.9 ($^{Ac}CH_3$) ppm. NOESY correlation between $^{8'}CH_2$ and $^{5'}CH$. HRMS (ESI^+): calcd for $C_{22}H_{26}NO_9$ $[M + H]^+$ 448.1608; found 448.1608.

(3*aR*,4*R*,5*R*,6*S*)-3*a*-(Acetoxymethyl)-2-cyclohexyl-3*a*,4,6,7-tetrahydro-5*H*-isoxazolo[2,3-*a*]pyridine-4,5,6-triyl triacetate (10b). A mixture of nitrone **4** (44 mg, 0.13 mmol) and cyclohexylacetylene (0.5 mL, 3.7 mmol) was stirred at room temperature for 4 days. After concentration under reduced pressure, the residue was purified by column chromatography over silica gel (pentane/EtOAc 9 : 1) to give cycloadducts **10b** and **10′b** (45 mg, 78%) as a colourless oil (mixture of diasteroisomers, dr = 9 : 1). IR ν = 2933, 2855, 1742, 1668, 1450, 1368, 1215, 1033 cm^{-1}. Major diastereoisomer: ^1H NMR (400 MHz, $CDCl_3$) δ = 5.32 (d, J = 10.5 Hz, 1H, ^{4}CH), 5.29–5.21 (m, 1H, ^{5}CH), 5.02 (dd, J = 5.8, 12.0, 1H, ^{6}CH), 4.46 (s, 1H, ^{3}CH), 3.90 (d of AB system, J = 11.6 Hz, 1H, $^{8}CH_2$), 3.76 (d of AB system, J = 11.6 Hz, 1H, $^{8}CH_2$), 3.45 (dd of ABX system, J = 4.9, 13.4 Hz, 1H, $^{7}CH_2$), 3.21 (dd of ABX system, J = 6.0, 13.4 Hz, 1H, $^{7}CH_2$), 2.15–2.05 (m, 1 H, ^{Cy}CH), 2.03 (s, 3H, $^{Ac}CH_3$), 1.98 (s, 3H, $^{Ac}CH_3$), 1.98 (s, 3H, $^{Ac}CH_3$), 1.95 (s, 3H, $^{Ac}CH_3$), 1.91–1.57 (m, 6H, $^{Cy}CH_2$), 1.31–1.15 (m, 4H, $^{Cy}CH_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6 (^{Ac}CO), 170.0 (^{Ac}CO), 169.9 (^{Ac}CO), 169.4($n^{Ac}CO$), 164.1 ($^{2}C_q$), 89.6 (^{3}CH), 73.6 ($^{3a}C_q$), 72.3 (^{5}CH), 70.1 (^{4}CH), 67.7 (^{6}CH), 64.9 ($^{8}CH_2$), 53.1 ($^{7}CH_2$), 35.6 (^{Cy}CH), 30.6 ($^{Cy}CH_2$), 30.3 ($^{Cy}CH_2$), 25.9 ($^{Cy}CH_2$), 25.7 ($^{Cy}CH_2$), 25.6 ($^{Cy}CH_2$), 20.8 ($^{Ac}CH_3$), 20.8 ($^{Ac}CH_3$), 20.7 ($^{Ac}CH_3$), 20.5 ($^{Ac}CH_3$) ppm. NOESY correlation between $^{8}CH_2$ and ^{4}CH. Minor diastereoisomer significative signals: ^1H NMR (400 MHz, $CDCl_3$) δ = 5.15–5.09 (m, 1H, $^{6'}CH$), 4.38 (s, 1H, $^{3'}CH$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.4 (^{Ac}CO), 170.1 (^{Ac}CO), 169.5 (^{Ac}CO), 169.3 (^{Ac}CO), 163.3 ($^{2'}C_q$), 92.3 ($^{3'}CH$), 72.7 ($^{5'}CH$), 71.7 ($^{4'}CH$), 68.1 ($^{6'}CH$), 66.0 ($^{8'}CH_2$), 52.2 ($^{7'}CH_2$), 35.3 (^{Cy}CH), 30.4 ($^{Cy}CH_2$), 30.4 ($^{Cy}CH_2$) ppm. HRMS (ESI^+): calcd for $C_{22}H_{32}NO_9$ $[M + H]^+$ 454.2077; found 454.2072.

(3*aR*,4*R*,5*R*,6*S*)-3*a*-(Acetoxymethyl)-2-(trimethylsilyl)-3*a*,4,6,7-tetrahydro-5*H*-isoxazolo[2,3-*a*]pyridine-4,5,6-triyl triacetate (10c). Nitrone **4** (204 mg, 0.59 mmol) and trimethylsilylacetylene (1.6 mL, 11.2 mmol) were dissolved in CH_2Cl_2 (1.5 mL) and stirred at room temperature for 2 days. After concentration under reduced pressure, the crude product was purified on silica gel (CH_2Cl_2) to afford cycloadducts **10c** and **10′c** (253 mg, 97%) as a yellow oil (mixture of diastereoisomers, dr = 9 : 1). IR ν = 2962, 1741, 1367, 1230, 1031 cm^{-1}. Major diastereoisomer: ^1H NMR (400 MHz, $CDCl_3$) δ = 5.44 (d, J = 10.4 Hz, 1H, ^{4}CH), 5.30–5.21 (m, 1H, ^{5}CH), 5.13–5.05 (m, 1H, ^{6}CH), 4.97 (s, 1H, ^{3}CH), 3.96 (d of AB system, J = 11.6 Hz, 1H, $^{8}CH_2$), 3.75 (d of AB system, J = 11.6 Hz, 1H, $^{8}CH_2$), 3.52 (dd of ABX system, J = 5.0, 13.2 Hz, 1H, $^{7}CH_2$), 3.20 (dd of ABX system, J = 6.4, 13.2 Hz, 1H, $^{7}CH_2$), 2.09 (s, 3H, $^{Ac}CH_3$), 2.06 (s, 3H, $^{Ac}CH_3$), 2.03 (s, 3H, $^{Ac}CH_3$), 2.01 (s, 3H, $^{Ac}CH_3$), 0.22 (s, 9H, $^{TMS}CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.8 (^{Ac}CO), 170.2 (^{Ac}CO), 170.0 (^{Ac}CO), 169.6 (^{Ac}CO), 162.6 ($^{2}C_q$), 106.1 (^{3}CH), 73.4 ($^{3a}C_q$), 72.4 (^{5}CH), 69.9 (^{6}CH), 67.7 (^{4}CH), 64.8 ($^{8}CH_2$), 53.2 ($^{7}CH_2$), 21.0 ($^{Ac}CH_3$), 20.9 ($^{Ac}CH_3$), 20.8 ($^{Ac}CH_3$), 20.7 ($^{Ac}CH_3$), −2.3 ($^{TMS}CH_3$) ppm. NOESY correlation between $^{8}CH_2$ and ^{4}CH. Minor diastereoisomer significative signals: ^1H NMR (400 MHz, $CDCl_3$) δ = 4.88 (s, 1H, $^{3'}CH$), 4.12 (d of AB system, J = 11.1 Hz, 1H, $^{8'}CH_2$), 4.00 (d of AB system, J = 11.1 Hz, 1H, $^{8'}CH_2$), 3.46 (dd, J = 4.6, 14.3 Hz, 1H, $^{7'}CH_2$), 3.26 (dd, J = 8.2, 14.3 Hz, 1H, $^{7'}CH_2$), 0.21 (s, 9H, $^{TMS}CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6 (^{Ac}CO), 170.2 (^{Ac}CO), 169.4 (^{Ac}CO), 161.9 ($^{2'}C_q$), 108.4 ($^{3'}CH$), 73.0 ($^{5'}CH$), 71.8 ($^{3a'}Cq$), 71.3 ($^{6'}CH$), 68.2 ($^{4'}CH$), 66.2 ($^{8'}CH_2$), 52.3 ($^{7'}CH_2$), 21.0 ($^{Ac}CH_3$), 21.0 ($^{Ac}CH_3$), −0.18 ($^{TMS}CH_3$) ppm. HRMS (ESI^+): calcd for $C_{19}H_{30}NO_9Si$ $[M + H]^+$ 444.1690; found 444.1699.

(3*aR*,4*R*,5*R*,6*S*)-3*a*-Bis(acetoxymethyl)-3*a*,4,6,7-tetrahydro-5*H*-isoxazolo[2,3-*a*]pyridine-4,5,6-triyl triacetate (10d). A mixture of nitrone **4** (98 mg, 0.28 mmol) and prop-2-yn-1-yl acetate (0.15 mL, 1.5 mmol) was stirred at room temperature for 2 days. After concentration under reduced pressure, the crude product was purified by column chromatography over silica gel (pentane/EtOAc 7 : 3) to give cycloadducts **10d** and **10′d** (115 mg, 92%) as a colourless oil (mixture of diastereoisomers, dr = 4 : 1). IR ν =3054, 2957′, 1740, 1431, 1372, 1213, 1033 cm^{-1}. Major diastereoisomer: ^1H NMR (500 MHz, $CDCl_3$) δ = 5.40 (d, J = 10.3 Hz, 1H, ^{4}CH), 5.27 (dd, J = 6.8, 10.2 Hz, 1H, ^{5}CH), 5.11–5.06 (m, 1H, ^{6}CH), 4.94 (s, 1H, ^{3}CH), 4.66 (br s, 2H, $^{9}CH_2$), 4.01 (d of AB system, J = 11.6 Hz, 1H, $^{8}CH_2$), 3.91 (d of AB system, J = 11.6 Hz, 1H, $^{8}CH_2$), 3.54 (dd of ABX system, J = 4.9, 13.8 Hz, 1H, $^{7}CH_2$), 3.35 (dd of ABX system, J = 5.7, 13.8 Hz, 1H, $^{7}CH_2$), 2.13 (s, 3H, $^{Ac}CH_3$), 2.10 (s, 3H, $^{Ac}CH_3$), 2.06 (s, 3H, $^{Ac}CH_3$), 2.06 (s, 3H, $^{Ac}CH_3$), 2.02 (s, 3H, $^{Ac}CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.8 (^{Ac}CO), 170.3 (^{Ac}CO), 170.2 (^{Ac}CO), 169.7 (^{Ac}CO), 169.6 (^{Ac}CO), 154.1 ($^{2}C_q$), 96.4 (^{3}CH), 74.1 ($^{3a}C_q$), 72.5 (^{5}CH), 70.5 (^{6}CH), 67.7 (^{4}CH), 64.8 ($^{8}CH_2$), 56.9 ($^{9}CH_2$), 53.3 ($^{7}CH_2$), 21.1 ($^{Ac}CH_3$), 21.0 ($^{Ac}CH_3$), 20.9 ($^{Ac}CH_3$), 20.9 ($^{Ac}CH_3$), 20.8 ($^{Ac}CH_3$) ppm. NOESY correlation between $^{8}CH_2$ and ^{4}CH. Minor diastereoisomer significative signals: ^1H NMR (500 MHz, $CDCl_3$) δ = 5.21 (d, J = 5.9 Hz, 1H, $^{4'}CH$), 5.19–5.16 (m, 1H, $^{6'}CH$), 4.91 (s, 1H, $^{3'}CH$), 4.71 (d of AB system, J = 13.5, 1H, $^{9'}CH_2$), 4.58 (d of AB system, J = 13.5, 1H, $^{9'}CH_2$), 4.17 (d of AB system, J = 11.2 Hz, 1H, $^{8'}CH_2$), 4.12 (d of AB system, J = 11.2 Hz, 1H, $^{8'}CH_2$), 3.57 (dd of ABX system, J = 4.6, 14.5 Hz, 1H, $^{7'}CH_2$), 3.28 (dd of ABX system, J = 8.7, 14.5 Hz, 1H, $^{7'}CH_2$), 2.11 (s, 3H, $^{Ac}CH_3$), 2.11 (s, 3H, $^{Ac}CH_3$), 2.08 (s, 3H, $^{Ac}CH_3$), 2.07 (s, 3H, $^{Ac}CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.6 (^{Ac}CO), 170.5 (^{Ac}CO), 170.2 (^{Ac}CO), 169.8 (^{Ac}CO), 169.4 (^{Ac}CO), 153.3 ($^{2'}C_q$), 99.6 ($^{3'}CH$), 72.7 ($^{5'}CH$), 71.5 ($^{4'}CH$), 67.9 ($^{6'}CH$), 65.8 ($^{8'}CH_2$), 56.5 ($^{9'}CH_2$), 52.4 ($^{7'}CH_2$), 21.2 ($^{Ac}CH_3$), 21.1 ($^{Ac}CH_3$), 21.1 ($^{Ac}CH_3$), 20.9 ($^{Ac}CH_3$)

ppm. HRMS calcd for $C_{19}H_{25}NO_{11}$ $[M + H]^+$ 444.1500; found 444.1495.

(3*aR*,4*R*,5*R*,6*S*)-3*a*-(Acetoxymethyl)-2-propyl-3*a*,4,6,7-tetrahydro-5*H*-isoxazolo[2,3-*a*]pyridine-4,5,6-triyl triacetate (10e). Nitrone **4** (38 mg, 0.11 mmol) and 1-pentyne (165 μL, 1.67 mmol) were disolved in CH_2Cl_2 (60 μL) and stirred at room temperature for 17 days. The reaction was monitored by TLC. When the conversion of nitrone was completed, the mixture was concentrated under reduced pressure. The diastereomeric cycloadducts **10e** and **10′e** (dr = 9 : 1) were obtained as a colourless oil. Note that these compounds are not stable and should be used immediately in the next step. IR ν = 2977, 2876, 1754, 1672, 1432, 1362, 1225, 1056 cm^{-1}. Major diastereoisomer: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ = 5.38 (d, J = 10.5 Hz, 1H, ^{4}CH), 5.37–5.32 (m, 1H, ^{5}CH), 5.10–5.05 (m, 1H, ^{6}CH), 4.67 (s, 1H, ^{3}CH), 3.98 (d of AB system, J = 11.4 Hz, 1H, ^{8}CH_2), 3.84 (d of AB system, J = 11.3 Hz, 1H, ^{8}CH_2), 3.63 (dd of ABX system, J = 5.1, 14.3 Hz, 1H, ^{7}CH_2), 3.31 (dd of ABX system, J = 4.8, 14.3 Hz, 1H, ^{7}CH_2), 2.21–2.16 (m, 2H, ^{9}CH_2), 2.03 (br s, 6H, ^{Ac}CH_3), 1.99 (s, 3H, ^{Ac}CH_3), 1.96 (s, 3H, ^{Ac}CH_3), 1.64–1.53 (m, 2H, ^{10}CH_2), 1.00 (t, J = 7.4 Hz, ^{11}CH_3) ppm. ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ = 170.6 (^{Ac}CO), 170.4 (^{Ac}CO), 170.1 (^{Ac}CO), 170.1 (^{Ac}CO), 159.7 (^{2}C_q), 92.8 (^{3}CH), 74.6 (^{3a}C_q), 72.9 (^{5}CH), 71.9 (^{6}CH), 68.7 (^{4}CH), 66.2 (^{8}CH_2), 53.8 (^{7}CH_2), 28.7 (^{9}CH_2), 20.8 (^{Ac}CH_3), 20.7 (^{10}CH_2), 20.7 (^{Ac}CH_3), 20.6 (^{Ac}CH_3), 20.6 (^{Ac}CH_3), 14.0 (^{11}CH_3) ppm. NOESY correlation between ^{8}CH_2 and ^{4}CH. Minor diastereoisomer significative signals: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ = 5.30–5.27 (m, 1H, $^{5'}$CH), 5.22–5.17 (m, 2H, $^{4'}$CH, $^{6'}$CH), 4.69 (s, 1H, $^{3'}$CH), 4.08 (d of AB system, J = 11.1 Hz, 1H, $^{8'}$$CH_2$), 4.06 (d of AB system, J = 11.1 Hz, 1H, $^{8'}$$CH_2$), 3.53 (dd of ABX system, J = 4.6, 14.3 Hz, 1H, $^{7'}$$CH_2$), 3.22 (dd of ABX system, J = 8.6, 14.4 Hz, 1H, $^{7'}$$CH_2$), 2.00 (s, 3H, ^{Ac}$CH_3$), 2.00 (s, 3H, ^{Ac}$CH_3$), 0.97 (t, J = 7.4 Hz, $^{11'}$$CH_3$) ppm. ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ = 96.1 ($^{3'}$CH), 73.3 ($^{5'}$CH), 72.6 ($^{4'}$CH), 68.8 ($^{6'}$CH), 66.6 ($^{8'}$$CH_2$), 52.8 ($^{7'}$$CH_2$), 28.3 ($^{9'}$$CH_2$), 13.9 ($^{11'}$$CH_3$) ppm. HRMS ($ESI^+$): calcd for $C_{19}H_{28}NO_9$ $[M + H]^+$ 414.1764; found 414.1760.

(3*aR*,4*R*,5*R*,6*S*)-3*a*-(Acetoxymethyl)-2-butyl-3*a*,4,6,7-tetrahydro-5*H*-isoxazolo[2,3-*a*]pyridine-4,5,6-triyl triacetate (10f). Nitrone **4** (40 mg, 0.115 mmol) and 1-hexyne (0.2 mL, 1.73 mmol) were dissolved in CH_2Cl_2 (60 μL) and stirred at room temperature for 12 days. The reaction was monitored by TLC. When the conversion of nitrone was completed, the mixture was concentrated under reduced pressure. The diastereomeric cycloadducts **10f** and **10′f** (dr = 9 : 1) were obtained as a colourless oil. Note that these compounds are not stable and should be used immediately in the next step. IR ν = 2955, 2927, 2866, 1758, 1679, 1435, 1369, 1230, 1024 cm^{-1}. Major diastereoisomer: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ = 5.38 (d, J = 10.6 Hz, 1H, ^{4}CH), 5.36–5.32 (m, 1H, ^{5}CH), 5.07 (td, J = 5.0, 6.4 Hz, 1H, ^{6}CH), 4.66 (s, 1H, ^{3}CH), 3.98 (d of AB system, J = 11.4 Hz, 1H, ^{8}CH_2), 3.84 (d of AB system, J = 11.4 Hz, 1H, ^{8}CH_2), 3.63 (dd of ABX system, J = 5.1, 14.3 Hz, 1H, ^{7}CH_2), 3.31 (dd of ABX system, J = 4.7, 14.3 Hz, 1H, ^{7}CH_2), 2.27–2.15 (m, 2H, ^{9}CH_2), 2.03 (br s, 6H, ^{Ac}CH_3), 1.99 (s, 3H, ^{Ac}CH_3), 1.96 (s, 3H, ^{Ac}CH_3), 1.60–1.38 (m, 2H, ^{10}CH_2), 1.47–1.38 (m, 2H, ^{11}CH_2), 0.93 (t, J = 7.3 Hz, ^{12}CH_3) ppm. ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ = 170.7 (^{Ac}CO), 170.5 (^{Ac}CO), 170.2 (^{Ac}CO), 170.2 (^{Ac}CO), 160.0 (^{2}C_q), 92.7 (^{3}CH), 74.7 (^{3a}C_q), 73.0 (^{5}CH), 72.0 (^{6}CH), 68.8 (^{4}CH), 66.3 (^{8}CH_2), 53.9 (^{7}CH_2), 29.7 (^{10}CH_2), 26.5 (^{9}CH_2), 23.0 (^{11}CH_2), 20.9 (^{Ac}CH_3), 20.8 (^{Ac}CH_3), 20.7 (^{Ac}CH_3), 20.7 (^{Ac}CH_3), 14.2 (^{12}CH_3) ppm. Minor diastereoisomer significative signals: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ = 5.30–5.25 (m, 1H, $^{5'}$CH), 5.22–5.17 (m, 2H, $^{4'}$CH, $^{6'}$CH), 4.68 (s, 1H, $^{3'}$CH), 3.53 (dd of ABX system, J = 4.6, 14.3 Hz, 1H, $^{7'}$$CH_2$), 3.22 (dd of ABX system, J = 8.6, 14.4 Hz, 1H, $^{7'}$$CH_2$), 2.00 (s, 3H, ^{Ac}$CH_3$), 2.00 (s, 3H, ^{Ac}$CH_3$), 1.98 (s, 3H, ^{Ac}$CH_3$), 1.97 (s, 3H, ^{Ac}$CH_3$) ppm. ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ = 170.6 (^{Ac}CO), 170.4 (^{Ac}CO), 170.0 (^{Ac}CO), 169.9 (^{Ac}CO), 159.3 ($^{2'}$$C_q$), 96.0 ($^{3'}$CH), 73.4 ($^{5'}$CH), 72.6 ($^{6'}$CH), 68.6 ($^{4'}$CH), 65.5 ($^{8'}$$CH_2$), 52.9 ($^{7'}$$CH_2$), 26.1 ($^{9'}$$CH_2$), 22.9 ($^{11'}$$CH_2$), 20.9 (^{Ac}$CH_3$), 20.8 (^{Ac}$CH_3$), 14.1 ($^{12'}$$CH_3$) ppm. HRMS ($ESI^+$): calcd for $C_{20}H_{30}NO_9$ $[M + H]^+$ 428.1915; found 428.1917.

(3*S*,4*R*,5*R*)-3,4,5-Trihydroxy-6-(hydroxymethyl)-2,3,4,5-tetrahydropyridine 1-oxide (5). Nitrone **4** (82 mg, 0.24 mmol) was dissolved in 3.0 mL of methanol saturated with ammonia. The reaction mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure and the residue was purified by chromatography (silica gel, CH_2Cl_2/MeOH 4 : 1) to afford **5** (35 mg, 81%) as a colourless oil. $[\alpha]_D^{20}$ = −49.2 (*c*, 0.16, MeOH). IR ν = 3253, 2904, 1616, 1426, 1160, 1065, 1005 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD) δ = 4.66 (d of AB system, J = 16.6 Hz, 1H, ^{1}CH_2), 4.46 (d of AB system, J = 16.9 Hz, 1H, ^{1}CH_2), 4.43–4.38 (m, 1H, ^{3}CH), 4.08–3.98 (m, 2H, ^{5}CH, ^{6}CH_2), 3.89–3.82 (m, 1H, ^{4}CH), 3.72 (br d of AB system, J = 13.1 Hz, 1H, ^{6}CH_2) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ = 153.3 (^{2}Cq), 70.7 (^{4}CH), 69.8 (^{3}CH), 68.0 (^{5}CH), 62.6 (^{6}CH_2), 59.6 (^{7}CH_2). HRMS (ESI^+): calcd for $C_6H_{12}NO_5$ $[M + H]^+$ 178.0715; found 178.0716.

(3*aR*,4*R*,5*R*,6*S*)-3*a*-(Hydroxymethyl)-2-phenyl-3*a*,4,6,7-tetrahydro-5*H*-isoxazolo[2,3-*a*]pyridine-4,5,6-triol (6a). Cycloadducts **10a** and **10′a** (120 mg, 0.268 mmol) were dissolved in methanol saturated with ammonia (4 mL) and the solution was stirred at room temperature. After 2 hours, the solvent was evaporated under reduced pressure and the residue was purified by chromatography (silica gel, CH_2Cl_2/MeOH 4 : 1) to afford compounds **6a** and **6a′** (62 mg, 83%) as a white solid (dr = 4 : 1). By recrystalisation in methanol, iminosugar **6a** (8 mg, 11%) was obtained as a single diastereoisomer. M.p. 123–125 °C. $[\alpha]_D^{20}$ = +42.0 (*c* 0.52, MeOH). IR ν = 3373, 2929, 2887, 1447, 1390, 1123, 1016 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD) δ = 7.57–7.50 (m, 2H, ^{Ar}CH), 7.40–7.31 (m, 3H, ^{Ar}CH), 5.53 (s, 1H, ^{3}CH), 3.92 (d, J = 8.8 Hz, 1H, ^{4}CH), 3.56 (d of AB system, J = 11.2 Hz, 1H, ^{8}CH_2), 3.47 (dd, J = 2.7, 10.0 Hz, 1H, ^{7}CH_2), 3.42–3.38 (m, 2H, ^{5}CH, ^{6}CH), 3.36 (d of AB system, J = 11.3 Hz, 1H, ^{8}CH_2), 2.91–2.83 (m, 1H, ^{7}CH_2) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ = 156.3 (^{2}Cq), 130.4 (^{Ar}Cq), 130.4 (^{Ar}CH), 129.5 (^{Ar}CH), 126.6 (^{Ar}CH), 96.4 (^{3}CH), 79.6 (^{3a}Cq), 77.4 (^{5}CH), 70.5 (^{4}CH), 67.7 (^{6}CH), 63.8 (^{8}CH_2), 57.6 (^{7}CH_2) ppm. NOESY correlation between ^{8}CH_2 and ^{4}CH. HRMS (ESI^+): calcd for $C_{14}H_{18}NO_5$ $[M + H]^+$ 280.1185; found 280.1185.

(3*aR*,4*R*,5*R*,6*S*)-2-Cyclohexyl-3*a*-(hydroxymethyl)-3*a*,4,6,7-tetrahydro-5*H*-isoxazolo[2,3-*a*]pyridine-4,5,6-triol (6b). Cycloadducts **10b** and **10′b** (60 mg, 0.132 mmol) were dissolved in methanol saturated with ammonia (3 mL) and the solution was stirred at

room temperature. After 6 hours, the solvent was evaporated under reduced pressure and the residue was purified by chromatography (silica gel, CH_2Cl_2/MeOH 4 : 1) to afford **6b** and **6′b** (22 mg, 58%) as a colourless oil (dr = 9 : 1). IR ν = 3313, 2927, 2857, 1663, 1448, 1093, 1040, 1027 cm^{-1}. Major diastereoisomer: ^{1}H NMR (500 MHz, CD_3OD) δ = 4.72 (s, 1H, ^{3}CH), 3.83 (d, J = 9.0 Hz, 1H, ^{4}CH), 3.43 (d of AB system, J = 11.2 Hz, 1H, $^8CH_2$), 3.36–3.28 (m, 3H, ^{5}CH, ^{6}CH, $^7CH_2$), 3.19 (d of AB system, J = 11.2 Hz, 1H, $^8CH_2$), 2.82–2.74 (m, 1H, $^7CH_2$), 2.16–2.06 (m, 1H, ^{Cy}CH), 1.92–1.15 (m, 10H, $^{Cy}CH_2$) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ = 163.5 (^{2}Cq), 93.7 (^{3}CH), 78.5 (^{3a}Cq), 77.3 (^{5}CH), 70.3 (^{4}CH), 67.7 (^{6}CH), 64.2 ($^8CH_2$), 57.4 ($^7CH_2$), 36.9 (^{Cy}CH), 31.8 ($^{Cy}CH_2$), 31.8 ($^{Cy}CH_2$), 27.1 ($^{Cy}CH_2$), 26.8 ($^{Cy}CH_2$) ppm. NOESY correlation between $^8CH_2$ and ^{4}CH. Minor diastereoisomer significative signals: ^{1}H NMR (500 MHz, CD_3OD) δ = 3.80–3.63 (m, 5H, $^{4'}$CH, $^{5'}$CH, $^{6'}$CH, $^{8'}CH_2$), 3.15–3.09 (m, 1H, $^{7'}CH_2$) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ = 77.9 ($^{5'}$CH), 76.7 ($^{4'}$CH), 70.1 ($^{6'}$CH), 65.0 ($^{8'}CH_2$), 56.0 ($^{7'}CH_2$) ppm. HRMS (ESI$^+$): calcd for $C_{14}H_{24}NO_5$ $[M + H]^+$ 286.1649; found 286.1653.

(3*aR*,4*R*,5*R*,6*S*)-2,3*a*-bis(Hydroxymethyl)-3*a*,4,6,7-tetrahydro-5*H*-isoxazolo[2,3-*a*]pyridine-4,5,6-triol (6d). Cycloadducts **10d** and **10′d** (70 mg, 0.158 mmol) were dissolved in methanol saturated with ammonia (2.5 mL) and the solution was stirred at room temperature. After 2.5 hours, the solvent was evaporated under reduced pressure and the residue was purified by chromatography (silica gel, CH_2Cl_2/MeOH 4 : 1) to afford **6d** and **6′d** (27 mg, 73%) as a yellow oil (dr = 4 : 1). IR ν = 3304, 2923, 2868, 1671, 1421, 1102, 1015 cm^{-1}. Major diastereoisomer: ^{1}H NMR (500 MHz, CD_3OD) δ = 5.01 (s, 1H, ^{3}CH), 4.12 (d of AB system, J = 14.3 Hz, 1H, $^9CH_2$), 4.08 (d of AB system, J = 14.3 Hz, 1H, $^9CH_2$), 3.84 (d, J = 8.9 Hz, 1H, ^{4}CH), 3.47 (d of AB system, J = 11.2 Hz, 1H, $^8CH_2$), 3.39–3.33 (m, 3H, ^{5}CH, ^{6}CH, $^7CH_2$), 3.27 (d of AB system, J = 11.2 Hz, 1H, $^8CH_2$), 2.90–2.83 (m, 1H, $^7CH_2$) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ = 158.2 (^{2}Cq), 97.7 (^{3}CH), 78.6 (^{3a}Cq), 77.2 (^{5}CH), 70.3 (^{4}CH), 67.9 (^{6}CH), 64.0 ($^8CH_2$), 57.5 ($^7CH_2$), 56.8 ($^9CH_2$) ppm. Minor diastereoisomer significative signals: ^{1}H NMR (500 MHz, CD_3OD) δ = 5.00 (s, 1H, $^{3'}$CH), 4.08 (d of AB system, J = 14.5 Hz, 1H, $^9CH_2$), 4.05 (d of AB system, J = 14.5 Hz, 1H, $^9CH_2$), 3.82–3.66 (m, 5H, $^{4'}$CH, $^{5'}$CH, $^{6'}$CH, $^{8'}CH_2$), 3.16 (dd, J = 8.6, 14.1 Hz, 1H, $^{7'}CH_2$) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ = 101.8 ($^{3'}$CH), 77.5 ($^{5'}$CH), 76.7 ($^{4'}$CH), 75.6 ($^{3a'}$Cq), 70.0 ($^{6'}$CH), 64.7 ($^{8'}CH_2$), 56.6 ($^{9'}CH_2$), 56.0 ($^{7'}CH_2$) ppm. HRMS (ESI$^+$): calcd for $C_9H_{16}NO_6$ $[M + H]^+$ 234.0972; found 234.0973.

(3*aR*,4*R*,5*R*,6*S*)-3*a*-(Hydroxymethyl)-2-propyl-3*a*,4,6,7-tetrahydro-5*H*-isoxazolo[2,3-*a*]pyridine-4,5,6-triol (6e). Cycloadducts **10e** and **10′e** (44 mg, 0.106 mmol) were disolved in methanol saturated with ammonia (2 mL) and the solution was stirred at room temperature. After 5 hours, the solvent was evaporated under reduced pressure and the residue was purified by chromatography (silica gel, CH_2Cl_2/MeOH 4 : 1) to afford **6e** and **6′e** (23 mg, 85%) as a colourless oil (dr = 9 : 1). IR ν = 3341, 1651, 1466, 1433, 1102, 1017 cm^{-1}. Major diastereoisomer: ^{1}H NMR (500 MHz, CD_3OD) δ = 4.76 (s, 1H, ^{3}CH), 3.83 (d, J = 9.0 Hz, 1H, ^{4}CH), 3.44 (d of AB system, J = 11.2 Hz, 1H, $^8CH_2$), 3.37–3.33 (m, 3H, ^{5}CH, ^{6}CH, $^7CH_2$), 3.22 (d of AB system, J = 11.2 Hz, 1H, $^8CH_2$), 2.84–2.77 (m, 1H, $^7CH_2$), 2.14 (t, J = 7.3 Hz, 2H, $^9CH_2$), 1.59–1.47 (m, 2H, $^{10}CH_2$), 0.96 (t, J = 7.3 Hz, 3H, $^{11}CH_3$) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ = 158.9 (^{2}Cq), 95.8 (^{3}CH), 78.7 (^{3a}Cq), 77.2 (^{5}CH), 70.4 (^{4}CH), 67.7 (^{6}CH), 64.1 ($^8CH_2$), 57.6 ($^7CH_2$), 29.3 ($^9CH_2$), 21.1 ($^{10}CH_2$), 14.0 ($^{11}CH_3$) ppm. NOESY correlation between $^8CH_2$ and ^{4}CH. Minor diastereoisomer significative signals: ^{1}H NMR (500 MHz, CD_3OD) δ = 3.80–3.64 (m, 5H, $^{4'}$CH, $^{5'}$CH, $^{6'}$CH, $^{8'}CH_2$), 3.13 (dd, J = 8.5, 14.1 Hz, 1H, $^{7'}CH_2$) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ = 157.5 ($^{2'}$Cq), 100.2 ($^{3'}$CH), 78.0 ($^{5'}$CH), 76.6 ($^{4'}$CH), 76.6 ($^{3a'}$Cq), 70.1 ($^{6'}$CH), 64.9 ($^{8'}CH_2$), 56.0 ($^{7'}CH_2$), 29.0 ($^{9'}CH_2$), 21.0 ($^{10'}CH_2$) ppm. HRMS (ESI$^+$): calcd for $C_{11}H_{20}NO_5$ $[M + H]^+$ 246.1336; found 246.1337.

(3*aR*,4*R*,5*R*,6*S*)-2-Butyl-3*a*-(hydroxymethyl)-3*a*,4,6,7-tetrahydro-5*H*-isoxazolo[2,3-*a*]pyridine-4,5,6-triol (6f). Cycloadducts **10f** and **10′f** (43 mg, 0.1 mmol) were dissolved in methanol saturated with ammonia (2.5 mL) and the solution was stirred at room temperature. After 5 hours, the solvent was evaporated under reduced pressure and the residue was purified by chromatography (silica gel, CH_2Cl_2/MeOH 4 : 1) to afford **6f** and **6′f** (25 mg, 83%) as a colourless oil (dr = 9 : 1). IR ν = 3320, 2968, 2932, 2862, 1667, 1152, 1039, 1002 cm^{-1}. Major diastereoisomer: ^{1}H NMR (500 MHz, CD_3OD) δ = 4.75 (s, 1H, ^{3}CH), 3.83 (d, J = 8.6 Hz, 1H, ^{4}CH), 3.44 (d of AB system, J = 11.3 Hz, 1H, $^8CH_2$), 3.37–3.32 (m, 3H, ^{5}CH, ^{6}CH, $^7CH_2$), 3.22 (d of AB system, J = 11.2 Hz, 1H, $^8CH_2$), 2.85–2.75 (m, 1H, $^7CH_2$), 2.22–2.10 (m, 2H, $^9CH_2$), 1.54–1.44 (m, 2H, $^{10}CH_2$), 1.43–1.33 (m, 2H, $^{11}CH_2$), 0.92 (t, J = 7.3 Hz, 3H, $^{12}CH_3$) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ = 159.1 (^{2}Cq), 95.6 (^{3}CH), 78.7 (^{3a}Cq), 77.2 (^{5}CH), 70.4 (^{4}CH), 67.7 (^{6}CH), 64.1 ($^8CH_2$), 57.6 ($^7CH_2$), 30.0 ($^9CH_2$), 27.0 ($^{10}CH_2$), 23.3 ($^{11}CH_2$), 14.1 ($^{12}CH_3$) ppm. NOESY correlation between $^8CH_2$ and ^{4}CH. Minor diastereoisomer significative signals: ^{1}H NMR (500 MHz, CD_3OD) δ = 3.80–3.64 (m, 5H, $^{4'}$CH, $^{5'}$CH, $^{6'}$CH, $^{8'}CH_2$), 3.13 (dd, J = 8.4, 14.1 Hz, 1H, $^{7'}CH_2$) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ = 157.7 ($^{2'}$Cq), 100.0 ($^{3'}$CH), 77.5 ($^{5'}$CH), 75.6 ($^{4'}$CH), 70.1 ($^{6'}$CH), 64.9 ($^{8'}CH_2$), 56.0 ($^{7'}CH_2$), 29.9 ($^{9'}CH_2$), 26.6 ($^{10'}CH_2$) ppm. HRMS (ESI$^+$): calcd for $C_{12}H_{21}NO_5Na$ $[M + H]^+$ 282.1312; found 282.1310.

Conflicts of interest

There are no conflicts to declare.

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