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Note

Synthesis of protected 2-amino-2-deoxy-D-xylothionolactam derivatives and some aspects of their reactivity

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Abstract

The synthesis of polyfunctionalized δ-lactams as key intermediates of glycomimetics in the 2-acetamido-2-deoxy sugar series is presented. Starting from a chiral γ-amino vinylic ester synthesized from Garner's aldehyde and after regioselective reduction, 1-azido-3-(*N*-*tert*-butyloxycarbonyl-2,2-dimethyloxazolidin-4-yl)-2-propene was obtained. Next, a cis-dihydroxylation reaction provided the protected D-xylitol and L-arabinitol azides. A simple protection-deprotection sequence, followed by an oxidation and a reductive cyclization, led to protected 2-amino-δ-lactams bearing a *tert*-butyloxycarbonyl group on the amine functionality. To explore the reactivity of such compounds, activation of the lactam into the corresponding thionolactam was performed. The resulting 2-amino-D-xylothionolactam derivative, a versatile intermediate, allowed access to a first generation of protected 2-amino-D-xylosamidoxime derivatives which are of interest as precursors of *N*-acetylhexosaminidase and *N*-acetylglucosaminyltransferase inhibitors. In this series of compounds, epimerization at C-2 was observed. AM_1 calculations performed on these analogs showed that they adopted a $B_{2,5}$ conformation and that the axial epimer was favored in the protected series whereas the equatorial epimer was preferred in the unprotected series.

Keywords: Glycomimetics; *N*-Acetamido-sugar amidoxime; Xylose and arabinose analogs

1. Introduction

Due to their implication in a number of biological and pathological processes,[1] glycosidases and glycosyltransferases have raised increasing interest.[2,3] Recent emergence of glycosyltransferase three dimensional structures[4] stressed mechanistic similarities between both types of enzymes and strengthened the hypothesis that they shared a common oxocarbenium ion-like transition state.[3a,4a,4c,5,6]

The quest for glycosidase inhibitors has provided a wide variety of structures[7] such as piperidinols like 1-deoxynojirimycin **1**[8]and isofagomine **2**,[9] or pyrrolidinol derivatives such as **3**,[10] and neutral[8b,11] **4** or positively charged[12] **5** transition state analogues (Scheme 1).

More recently, imidazole derivatives[13] like **6** have proved to be good mechanistic probes by bringing out information concerning the direction of protonation in the active site.[7a,14]

Concerning glycosyltransferases inhibitors, various structures have recently emerged[15] and compounds such as **2** and **3** have been used as basic scaffolds to generate selective and efficient inhibitors.

Compared to the wide variety of structures in the glucose, mannose, galactose and even fucose series, fewer examples of glycomimetics bearing an acetamido function at C-2 position have been described.[16] Yet, such derivatives could be of interest considering the key role of enzymes such as *N*-acetylhexosaminidases[17a] or *N*-acetylglucosaminyltransferases.[17b] δ-Lactams have already proved their potentiality in the glucose, galactose and mannose series, giving access to piperidinol,[8,11b] imidazole[14] or glycoamidoxime[12] derivatives.

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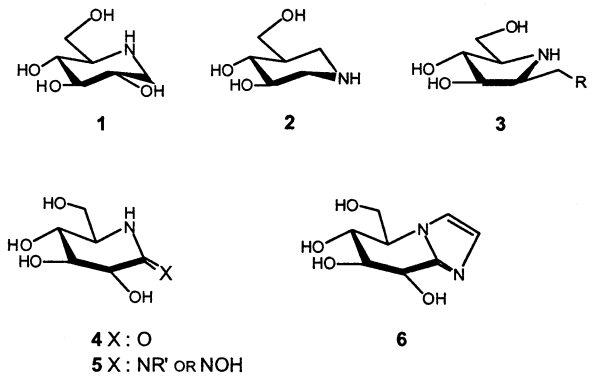


Scheme 1.

The use of this functionality remains little explored in the case of 2-acetamido analogs as evidenced by a paucity of reports in the literature.[18] In the present work, we report the synthesis of polyfunctionalized 2-acetamido-2-deoxy-δ-lactams in their protected form as precursors of glycomimetics in the *N*-acetyl series. From Garner's synthon,[19,20] the synthesis of D-xylonolactams is described as well as the stability of such derivatives toward epimerization.

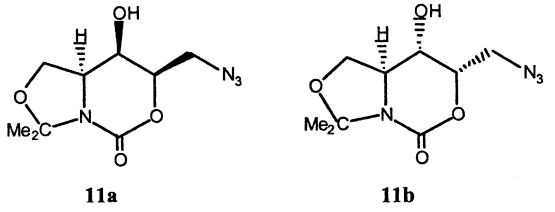
2. Results and discussion

The unsaturated ester **7**, obtained by homologation of Garner's aldehyde, was reduced to the allylic alcohol **8** (Scheme 2).

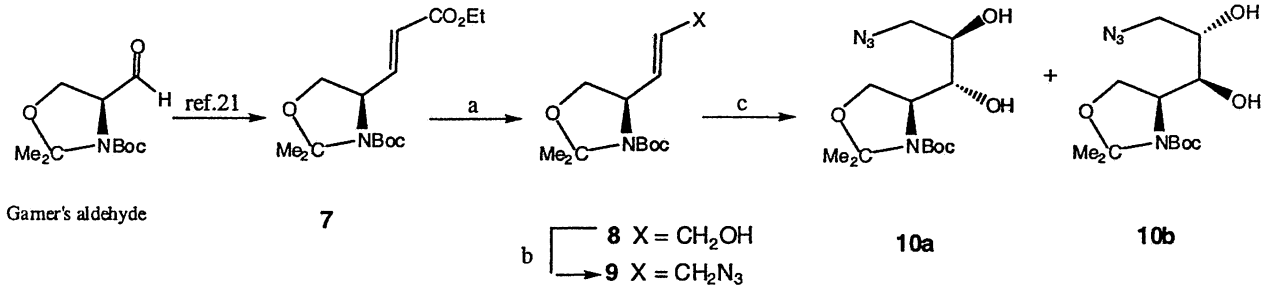
The reduction of a γ-aminovinylic ester such as **7** has been previously described in the literature[22] by using diisobutylaluminum hydride (DIBAL-H) in dichloromethane at −70 °C. When these conditions were applied, a mixture of starting material, saturated aldehyde and allylic alcohol was obtained in a 55% yield. Nevertheless, the allylic alcohol **8** was obtained with an excellent yield (93%) by performing the reaction at 0 °C in tetrahydrofuran[23] avoiding the conjugated reduction. One-step methods[24] to introduce the azido function proved to be unfruitful. Therefore, the alcohol function was activated as the corresponding mesylate which was then reacted with sodium azide to give the allylic azide **9** in 76% yield. A subsequent cis-dihydroxylation reaction was carried out using osmium tetroxide in catalytic amount.[25] Diastereoisomers **10a** (major) and **10b** were obtained in a low diastereoisomeric excess (de 10%). The reaction was then conducted in presence of chiral ligands using mixtures such as Admix-α and Admix-β.[26] In the presence of hydroquinidine 1,4-phtalazinediyl diether $(DHQD)_2PHAL$, the diol diastereoisomer **10b** was isolated with a 80% diastereoisomeric excess. In return, with hydroquinine 1,4-phtalazinediyl diether $(DHQ)_2PHAL$, no enhancement in favor of **10a** was observed as the diastereoisomeric excess of 10% remained unchanged. To explain this result, a match–mismatch effect[27] in favor of **10b** may be considered. Thus the dihydroxylation was conducted without a chiral ligand.

The relative configuration of the newly formed stereogenic centers in **10a** and **10b** was attributed after their cyclization into the bicyclic compounds **11a** and **11b** upon addition of sodium hydride (Scheme 3). In this rigidified system, the relative configurations of the three contiguous asymmetric centers could be established by measuring the H-2–H-3 and H-3–H-4 coupling constants ($J_{2,3}$ and $J_{3,4}$ 1.5 Hz for **11a** and $J_{2,3}$ 6 Hz and $J_{3,4}$ 9 Hz, for **11b**).

The xylitol derivative **10a**, which has the correct configuration for the construction of the D-xylonolactam skeleton, was further transformed into the corresponding di-O-benzyl derivative **12a** (Scheme 4). In order to prevent the aforementioned cyclization reaction, benzyl bromide was added prior to the addition of

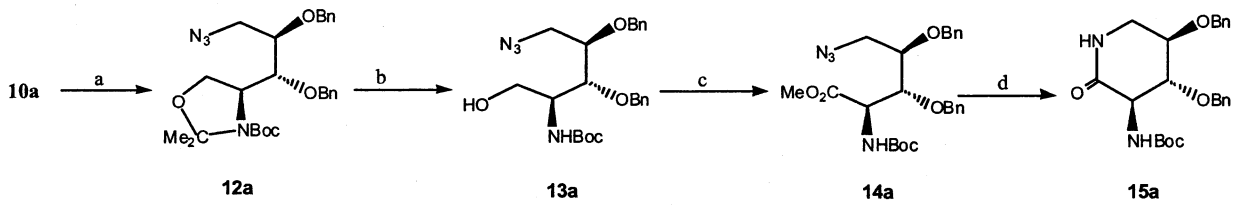


Scheme 3.



a) DIBAL-H, THF, 0 °C, 1.5 h b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 15 min then NaN_3, DMF, rt, 1.5 h
c) OsO_4, NMO, tBuOH, water, THF, rt, 24 h.

Scheme 2.



a) BnBr, DMF, 0 °C, then NaH,rt, 3h b) Dowex H^+, MeOH, rt, 48 h c) TEMPO, NaOCl, KBr, $NaHCO_3$ 5% aq acetone, 0 °C, 40 min then CH_2N_2, MeOH d) $Pd/CaCO_3$, H_2, MeOH, 12 h.

Scheme 4.

sodium hydride. Next, the oxazolidine ring was subjected to acid-catalysed opening,[28] thus unmasking the primary hydroxyl function.

Several reaction conditions were tested for the oxidation of **13a**, including treatment with pyridinium dichromate (PDC)[29] or ruthenium tetraoxide.[30] The highest yield was obtained by using the 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO reagent)[31] in catalytic amount. The resulting carboxylic acid was directly esterified with freshly prepared diazomethane to give the azido ester **14a** in a good yield (75%). Regioselective reduction of the azide function was achieved by hydrogenation in the presence of Lindlar's catalyst,[32] leading to **15a** in 85% yield.

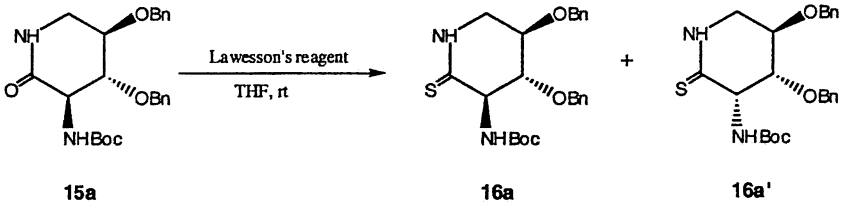
Activation of δ-lactam carbonyl functions into their corresponding thionocarbonyl derivatives has been previously achieved for glycomimetics by transforming the amido functionality into thioamide. This method has notably been employed to synthesize various glycoamidines and glycoamidoximes.[12,33] To have access to the protected 2-acetamido-xylothionolactam **17a** (see Scheme 7), we chose to maintain the carbamate and introduce the acetamido group at a later stage of the synthesis. Lactam **15a** was first treated with the Lawesson's reagent[34] in the presence of pyridine at reflux in toluene. Under these conditions, transformation of the lactam into the thionolactam did not give the expected product **16a**[35] but was accompanied by epimerization at C-2, leading to the thionolactam derivative **16a′** as the only product. The epimerization reaction was partially avoided by carrying out the reaction at room temperature and in the absence of base. The expected thionolactam **16a** was thus obtained as the major product (81% yield) with a small proportion of the C-2 epimer **16a′** (Scheme 5).

The two diastereoisomers **16a** and **16a′** were nicely separated by crystallization. As they did not diffract properly, the structure of **16a′** was further confirmed by the preparation of its enantiomer **16b** from the L-*arabino* diol **10b** following a parallel reaction sequence (Scheme 6). When the thionylation reaction was applied to the L-*arabino* derivative **15b**, the epimerization reaction was not observed, and the corresponding thionolactam **16b** was isolated in 56% yield.

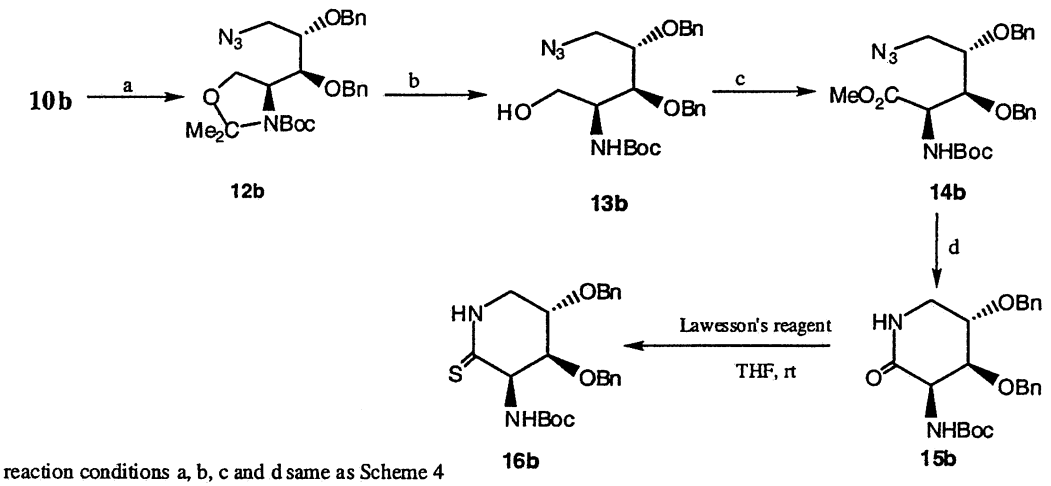
Thionolactam **16b** was crystallized, and its structure was resolved by single-crystal X-ray diffraction analysis. The relative configuration of the three contiguous centers was confirmed from this structure (Fig. 1).

Attempts to cleave the carbamate group in **16a** using TFA followed by acetylation of the resulting amine led to a complex mixture, from which the expected *N*-acetylxylothionolactam derivative **17a** could not be isolated. Considering furthermore the observed epimeric instability of **16a**, it appeared necessary to find milder conditions to convert the carbamate group into the acetamido group. Compound **17a** could be obtained after treatment of **16a** with TBDMSOTf in the presence of 2,6-lutidine following the method reported by Ohfune and coworkers[36] and further reaction with a fluoride-ion donor in presence of methanol and acetic anhydride (Scheme 7).

The moderate yield (43%) of this reaction was balanced by the ease to isolate the product directly by precipitation and recrystallization. However the *N*-acetylxylothionolactam (**17a**) turned out to be unstable and partial epimerization took place. Thus, pure **17a** was engaged rapidly in the next step and was converted into amidoxime **18a** in basic medium upon reaction with hydroxylamine. To limit the epimerization at the C-2 leading to **18a′**, the best conditions were the use of



Scheme 5.



Scheme 6.

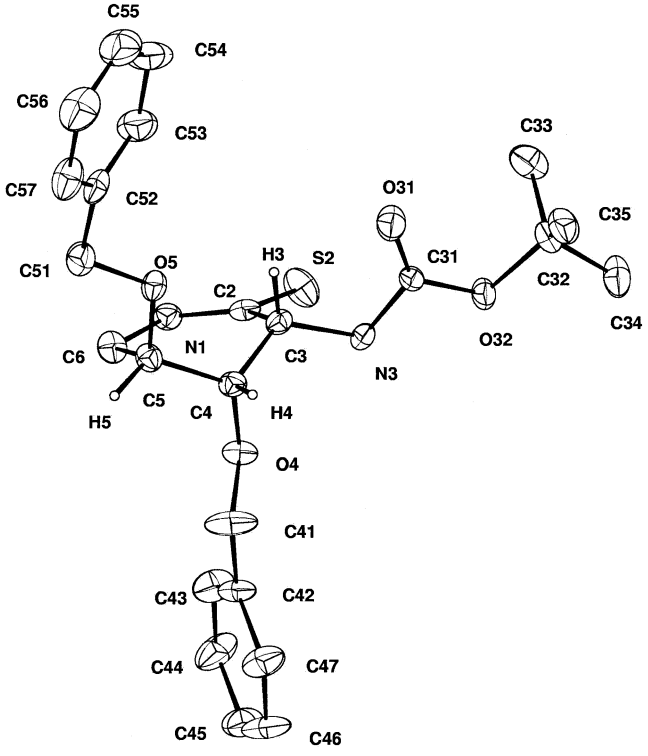
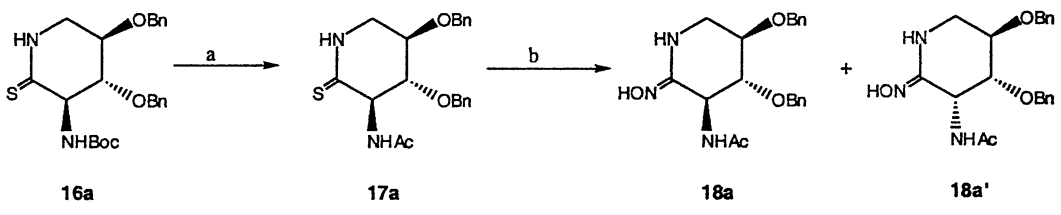


Fig. 1. ORTEP view of **16b**.

cesium carbonate as a base in dimethylformamide. In that case, a 4:1 ratio in favor of the expected *N*-acetylxylosamidoxime derivative **18a** was obtained.

As partial epimerization at C-2 limits the access to the desired D-*xylo* series, calculations using AM_1 method were achieved on the lactam and thionolactam derivatives. From the results obtained (data not shown), the epimerization can be rationalized by two main factors. First, steric hindrance due to bulky protecting groups and second, an increase of the α-proton acidity for the thionolactam derivatives. Indeed, the concurrent presence of bulky protecting groups on the amine and the hydroxyl functions shifts the equilibrium toward the axial epimer. By contrast, when the hydroxyl groups are unprotected, the equatorial epimer always displayed a higher stability whatever the C-2 nitrogen substituent may be. The greater stability (6.2 kcal/mol) for the equatorial epimer was also attributed to a favorable hydrogen bonding between the C-3 hydroxyl group and the carbonyl of the carbamate or the acetamido group. A conformational effect was ruled out as the preferred conformation was found to be a boat conformation ($B_{2,5}$) for both the protected and unprotected compounds. As expected, the thionolactam derivatives were



Scheme 7.

more susceptible to epimerization and the presence of the 2-acetamido group had an additional effect on the enhancement of the α-proton acidity. This result was in agreement with our experimental observations, as **17a** was rather unstable and proned to epimerization.

3. Conclusion

A synthetic route allowing access to polyfunctionalized lactam glycomimetics was developed. An example of activation of the pseudo-anomeric position in 2-amino series was also described allowing access to O-protected *N*-acetylxylosamidoximes.

The main problem we had to face was the epimeric instability at the C-2 position. It clearly appears that the nature of protecting groups on the amino group and on the two hydroxyl functions drastically influence this side reaction. Tuning the nature of these protecting groups might therefore limit this epimerization reaction. Work is in progress to explore such a difference in reactivity.

4. Experimental

4.1. General methods

Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone and kept over 4 Å molecular sieves. Dimethyl sulfoxide, triethylamine, dichloromethane and toluene were distilled from CaH_2. Dry *N*,*N*-dimethylformamide and other reagents were commercially available from Fluka, Aldrich or Acros. Anhydrous reactions were performed under argon atmosphere, and all glassware was flame-dried under a stream of nitrogen prior to use. The course of the reactions was monitored by thin-layer chromatography with E. Merck 60F-250 precoated silica gel (0.2 mm) on glass. Chromatography was performed with E. Merck Kieselgel-60, 0.040–0.063 mm (flash). ^1H and ^{13}C NMR spectra were recorded on Brucker DMX-500, ARX-400, AC-250, AC-200. Chemical shifts are reported in ppm with residual chloroform, methanol or water as internal reference. Optical rotations were measured at 21 °C on a Perkin–Elmer 241C polarimeter with sodium (589 nm) lamp. Melting points were determined on a Reichert Heizbank (Kofler) apparatus, and are uncorrected. Mass spectra were recorded on a NERMAG R30-10 in the CI ionization mode, and ammonia was used as ionizing gas. Microanalysis was obtained from the University Pierre et Marie Curie and from CNRS (Vernaison) laboratories.

4.2. 3-(*N*-*tert*-Butyloxycarbonyl-2,2-dimethyloxazolidin-4-yl)-prop-2-en-1-ol (8)

In a three-necked flask, the unsaturated ester **7** (11.3 g, 37.7 mmol) was dissolved in dry THF (100 mL). The reaction mixture was cooled to 0 °C and DIBAL-H (89 mL, 89 mmol, 1 M soln in THF) was added dropwise. After 1.5 h at 0 °C, the mixture was poured in cold MeOH (100 mL). After a few min, a saturated soln of sodium potassium tartrate (100 mL), water (150 mL) and EtOAc (150 mL) were successively added and stirred overnight. The aq layer was then extracted with EtOAc (3 × 100 mL), and the organic phase washed with brine (250 mL), dried ($MgSO_4$) and concentrated. The pale-yellow oil was purified by chromatography (3:7 EtOAc–cyclohexane) to give **8** as colorless oil (9 g, 93%). R_f 0.30 (3:7 EtOAc–cyclohexane); $[\alpha]_D^{25}$ −13.5° (*c* 0.35, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ major rotamer 5.75 (m, 1 H, H-2), 5.66 (dd, 1 H, $J_{3,4}$ 6.6 Hz, $J_{2,3}$ 15.2 Hz, H-3), 4.28 (m, 1 H, H-4), 4.13 (m, 2 H, H-1), 4.02 (dd, 1 H, $J_{4,5}$ 6.5 Hz, $J_{5,5'}$ 8.8 Hz, H-5), 3.72 (dd, 1 H, $J_{4,5'}$ 1.5 Hz, $J_{5,5'}$ 8.8 Hz, H-5′), 2.10 (br s, 1 H, OH), 1.56, 1.49 (2 × s, 6 H, C(CH_3)$_2$), 1.46 (s, 9 H, C(CH_3)$_3$); minor rotamer 5.75 (m, 1 H, H-2). 5.66 (dd, 1 H, $J_{3,4}$ 6.6 Hz, $J_{2,3}$ 15.2 Hz, H-3), 4.40 (m, 1 H, H-4), 4.13 (m, 2 H, H-1), 4.02 (dd, 1 H, $J_{4,5}$ 6.5 Hz, $J_{5,5'}$ 8.8 Hz, H-5), 3.72 (dd, 1 H, $J_{4,5}$ 1.5 Hz, $J_{5,5'}$ 8.8 Hz, H-5′), 2.44 (br s, 1 H, OH), 1.59, 1.49 (2 × s, 6 H, C(CH_3)$_2$), 1.41 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ major rotamer 150.68 (*CO*), 129.74 (C-2), 128.32 (C-3), 92.14 (*C*(CH_3)$_2$), 78.88 (*C*(CH_3)$_3$), 66.63 (C-5), 61.17 (C-1), 57.22 (C-4), 26.93 (C(CH_3)$_3$), 25.07, 22.11 (C(CH_3)$_2$); minor rotamer 150.40 (*CO*Boc), 129.74 (C-2), 128.68 (C-3), 92.43 (*C*(CH_3)$_2$), 78.13 (*C*(CH_3)$_3$), 66.63 (C-5), 61.17 (C-1), 57.22 (C-4), 26.93 (C(CH_3)$_3$), 27.67, 23.29 (C(CH_3)$_2$); Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.53; H, 9.17; N, 5.47.

4.3. 1-Azido-3-(*N*-*tert*-butyloxycarbonyl-2,2-dimethyloxazolidin-4-yl)-2-propen (9)

To a soln of alcohol **8** (5 g, 11.46 mmol) in CH_2Cl_2 (40 mL) was added triethylamine (3.3 mL, 23.9 mmol). The mixture was cooled to 0 °C and methanesulfonyl chloride (1.9 mL, 23.9 mmol) was added dropwise. After 15 min, water (15 mL) was added. The aq phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The yellow oil was taken up in DMF (40 mL) and sodium azide (1.9 g, 30 mmol) was added rapidly. After stirring 1.5 h at rt, water (40 mL) and EtOAc (40 mL) were added. After extracting the aq phase with EtOAc (3 × 30 mL), washing the organic layer with brine (100 mL), and drying ($MgSO_4$), the solvent was evaporated. The yellow oil was purified by

chromatography (95:5 EtOAc–cyclohexane) to lead to pure azide **9** (2.45 g, 76%). R_f 0.30 (95:5 EtOAc–cyclohexane); $[\alpha]_D^{25}$ −26.7° (*c* 0.88, $CHCl_3$); IR (thin film): *v* 2103 (N_3), 1690 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ major rotamer 5.68 (m, 2 H, H-2, H-3), 4.33 (m, 1 H, H-4), 4.02 (dd, 1 H, $J_{4,5}$ 6 Hz, $J_{5,5'}$ 9 Hz, H-5), 3.74 (m, 2 H, H-1, H-5′), 1.53, 1.41 (2 × s, 6 H, $C(CH_3)_2$), 1.37 (s, 9 H, $C(CH_3)_3$); minor rotamer 5.77 (m, 2 H, H-2, H-3), 4.46 (m, 1 H, H-4), 4.02 (dd, 1 H, $J_{4,5}$ 6 Hz, $J_{5,5'}$ 9 Hz, H-5), 3.74 (m, 2 H, H-1, H-5′), 1.55, 1.44 (2 × s, 6 H, $C(CH_3)_2$), 1.38 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ major rotamer 152.11 (*CO*), 134.38, 125.21 (C-2, C-3), 93.99 ($C(CH_3)_2$), 80.69 ($C(CH_3)_3$), 68.51 (C-5), 58.83 (C-4), 52.40 (C-1), 29.00 ($C(CH_3)_3$), 26.98, 23.89 ($C(CH_3)_2$); minor rotamer 152.11 (*CO*Boc), 134.98, 125.21 (C-2, C-3), 94.44 ($C(CH_3)_2$), 80.14 ($C(CH_3)_3$), 68.51 (C-5), 58.83 (C-4), 52.40 (C-1), 29.00 ($C(CH_3)_3$), 27.77, 25.06 ($C(CH_3)_2$); CIMS: *m/z* 300 $[MNH_4]^+$, 283 $[MH]^+$; Anal. Calcd for $C_{13}H_{22}N_4O_3$: C, 55.30; H, 7.85; N, 19.84. Found: C, 55.55; H, 7.92; N, 19.68.

4.4. 2-Amino-5-azido-2-(*N*-*tert*-butyloxycarbonyl)-2,5-dideoxy-1,2-*N*,*O*-isopropylidene-D-xylitol (10a) and 4-amino-1-azido-4-(*N*-*tert*-butyloxycarbonyl)-1,4-dideoxy-4,5-*N*,*O*-isopropylidene-L-arabinitol (10b)

To a soln of *tert*-butanol (21 mL), water (2 mL), morpholine N-oxide (2.8 g, 23.8 mmol) and OsO_4 (0.21 mmol, 2.5% in *tert*-butanol) in THF, a soln of azide **9** (6.1 g, 21.6 mmol) in THF (50 mL) was added and stirred for 24 h at rt. A soln of NaSH (50 mL) and fluorisil (15 g) were added and the mixture was stirred for 2 h. After filtration over celite and several washings with EtOAc, the aq phase was extracted with EtOAc (3 × 30 mL). The organic layer was washed with brine (100 mL) and dried ($MgSO_4$). After concentration, the yellow oil was purified by chromatography (3:7 EtOAc–cyclohexane) yielding a white solid (5.14 g, 75%) as a mixture of **10a** and **10b** (55:45). The two diastereoisomers could be separated by adding warm pentane, **10b** was filtered off and **10a** cristallized out at room temperature.

Compound **10a** (2.33 g, 39%); R_f 0.35 (3:7 EtOAc–cyclohexane); mp 116 °C; $[\alpha]_D^{25}$ −63.3° (*c* 1, $CHCl_3$); IR (thin film): *v* 3303 (OH), 2106 (N_3), 1653 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.88 (br s, 1 H, OH), 4.14 (m, 1 H, H-2), 3.93 (m, 1 H, H-1), 3.80 (m, 1 H, H-1′), 3.61 (m, 2 H, H-3, H-4), 3.44 (dd, 1 H, $J_{4,5}$ 8 Hz, $J_{5,5'}$ 12 Hz, H-5), 3.25 (dd, 1 H, $J_{4,5'}$ 5 Hz, $J_{5,5'}$12 Hz, H-5′), 2.75 (br s, 1 H, OH), 1.53, 1.48, 1.45, 1.43 (4 × s, 15 H, ($C(CH_3)_3$), ($C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.17 (*CO*), 94.84 ($C(CH_3)_2$), 82.55 ($C(CH_3)_3$), 74.60 (C-3), 71.24 (C-2), 65.18 (C-5), 60.10 (C-4), 54.52 (C-1), 28.72, 24.61 ($C(CH_3)_3$), 27.49, 27.28 ($C(CH_3)_2$); CIMS: *m/z* 317 $[MH]^+$, 278 $[MNH_4-56]^+$, 261 $[MH-56]^+$; Anal. Calcd for $C_{13}H_{24}N_4O_5$: C, 49.36; H, 7.65; N, 17.71. Found: C, 49.49; H, 7.77; N, 17.57.

Compound **10b** (1.79 g, 31%); R_f 0.35 (3:7 EtOAc–cyclohexane); Mp 92 °C; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 4.58 (br s, 1 H, OH), 4.06 (dd, 1 H, $J_{4,5}$ 9 Hz , $J_{5,5'}$ 9 Hz, H-5), 3.91 (dd, 1 H, $J_{4,5'}$ 5 Hz, $J_{5,5'}$ 9 Hz, H-5′), 3.75 (dd, 1 H, $J_{4,5'}$ 5 Hz, $J_{4,5}$ 9 Hz, H-4), 3.61 (m, 1 H, H-2), 3.48 (dd, 1 H, $J_{1,2}$ 8 Hz, $J_{1,1'}$ 12 Hz, H-1), 3.28 (dd, 1 H, $J_{2,3}$ 9 Hz, $J_{3,4}$ 9 Hz, H-3), 3.21 (dd, 1 H, $J_{1',2}$ 5 Hz, $J_{1,1'}$ 12 Hz, H-1′), 2.29 (br s, 1 H, OH), 1.49–1.44, (2 × s, 15 H, ($C(CH_3)_3$), ($C(CH_3)_2$)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.06 (*CO*Boc), 94.52 ($C(CH_3)_2$), 82.43 ($C(CH_3)_3$), 72.60 (C-3), 69.12 (C-2), 66.15 (C-5), 59.41 (C-4), 53.02 (C-1), 28.70 ($C(CH_3)_3$), 28.03, 24.37 ($C(CH_3)_2$); Anal. Calcd for $C_{13}H_{24}N_4O_5$: C, 49.36; H, 7.65; N, 17.71. Found: C, 49.38; H, 7.82; N, 17.70.

4.5. 2-Amino-5-azido-2,4-*N*,*O*-carbonyl-2,5-dideoxy-1,2-isopropylidene-D-xylitol (11a) and 4-amino-1-azido-2,4-*N*,*O*-carbonyl-1,4-dideoxy-4,5-isopropylidene-L-arabinitol (11b)

To a soln of diastereoisomers **10a** and **10b** (1:9, 0.074 g, 0.23 mmol) in DMF (1 mL) was added NaH (60% dispersion in oil, 0.025 g, 0.62 mmol) by small portions. The mixture was stirred at rt for 2 h and a soln of 0.1 M HCl (1 mL) was added. The reaction mixture was extracted with EtOAc (3 × 2 mL) and the organic layer was washed with brine (2 mL), dried ($MgSO_4$) and concentrated. The orange oil was purified by chromatography (2:3 EtOAc–cyclohexane) and **11a** and **11b** was isolated as a 2:3 mixture (0.021 g, 38%).

Compound **11a** R_f 0.30 (2:3 EtOAc–cyclohexane); ^1H NMR (400 MHz, $CDCl_3$, D_2O exchange): δ 4.35 (ddd, 1 H, $J_{3,4}$ 1.5 Hz, $J_{4,5}$ 6 Hz, $J_{4,5'}$ 6 Hz, H-4), 4.14 (dd, 1 H, $J_{2,3}$ 1.5 Hz, $J_{3,4}$ 1.5 Hz, H-3), 4.11 (dd, 1 H, $J_{1,2}$ 6 Hz, $J_{1,1'}$ 9 Hz, H-1), 4.04 (d, 1 H, $J_{1,1'}$ 9 Hz, H-1′), 3.85 (dd, 1 H, $J_{2,3}$ 1.5 Hz, $J_{1,2}$ 6 Hz, H-2), 3.68 (m, 2 H, H-5, H-5′), 1.61, 1.57 (2 × s, 6 H, ($C(CH_3)_2$)).

Compound **11b** R_f 0.30 (2:3 EtOAc–cyclohexane); ^1H NMR (400 MHz, $CDCl_3$, D_2O exchange): δ 4.49 (ddd, 1 H, $J_{1,2}$ 4 Hz, $J_{1',2}$ 6 Hz, $J_{2,3}$ 6 Hz, H-2), 4.35 (dd, 1 H, $J_{4,5}$ 6 Hz, $J_{5,5'}$ 8.5 Hz, H-5), 4.03 (dd, 1 H, $J_{2,3}$ 6 Hz, $J_{3,4}$ 9 Hz, H-3), 3.84 (ddd, 1 H, $J_{3,4}$ 9 Hz, $J_{4,5}$ 6 Hz, $J_{4,5'}$ 9 Hz, H-4), 3.77 (dd, 1 H, $J_{1,2}$ 4 Hz, $J_{1,1'}$ 13 Hz, H-1), 3.68–3.63 (m, 2 H, H-5, H-1′), 1.63, 1.57 (2 × s, 6 H, ($C(CH_3)_2$)); CIMS: *m/z* 260 $[MNH_4]^+$, 243 $[MH]^+$.

4.6. 2-Amino-5-azido-3,4-di-*O*-benzyl-2-(*N*-*tert*-butyloxycarbonyl)-2,5-dideoxy-1,2-*N*,*O*-isopropylidene-D-xylitol (12a) and 4-amino-1-azido-2,3-di-*O*-benzyl-4-(*N*-*tert*-butyloxycarbonyl)-1,4-dideoxy-4,5-*N*,*O*-isopropylidene-L-arabinitol (12b)

Benzylbromide (2.6 mL, 22.12 mmol) was added to a soln of **10a** or **10b** (1.4 g, 4.42 mmol) in DMF (9

mL).The reaction mixture was cooled to 0 °C and NaH (0.44 g, 11 mmol, 60% dispersion in oil) was added by small portions. After 3 h, water (10 mL) and EtOAc (20 mL) were added. The aq phase was extracted with EtOAc (3 × 20 mL) and the organic phase was washed with brine (20 mL) and dried ($MgSO_4$). After evaporation of solvent, the crude product was purified by chromatography (5:95 EtOAc–cyclohexane) to yield a pale yellow oil (2.06 g, 94%).

Compound **12a** R_f 0.50 (5:95 EtOAc–cyclohexane); $[\alpha]_D^{25}$ −25.4° (*c* 1, $CHCl_3$); IR (thin film): *v* 2103 (N_3), 1691 (CO), 715 (Ph) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ major rotamer 7.40–7.31 (m, 10 H, 2 × *Ph*), 4.69 (m, 4 H, 2 × CH_2Ph), 4.34 (m, 2 H, H-1, H-2), 3.95 (m, 1 H, H-1′), 3.81 (m, 2 H, H-3, H-4), 3.40 (m, 2 H, H-5, H-5′), 1.72, 1.62 (2 × s, 6 H, C(CH_3)$_2$), 1.53 (s, 9 H, C(CH_3)$_3$)); minor rotamer 7.40–7.31 (m, 10 H, 2 × *Ph*), 4.69 (m, 4 H, 2 × CH_2Ph), 4.34 (m, 1 H, H-1), 4.14 (m, 1 H, H-2), 3.95 (m, 1 H, H-1′), 3.40 (m, 2 H, H-5, H-5′), 1.53 (s, 6 H, C(CH_3)$_2$), 1.45 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ major rotamer 153.52 (*CO*), 138.56, 138.26, 128.81, 128.65, 128.25 (2 × *Ph*) , 94.38 (*C*(CH_3)$_2$), 80.85 (*C*(CH_3)$_3$), 77.84 , 77.63 (C-3, C-4), 74.26, 73.77 (2 × CH_2Ph), 64.99 (C-1), 57.73 (C-2), 52.22 (C-5), 28.78 (C(CH_3)$_3$), 27.69, 24.51 (C(CH_3)$_2$) minor rotamer 152.84 (*CO*), 138.56, 138.26, 128.81, 128.65, 128.25 (2 × *Ph*), 94.84 (*C*(CH_3)$_2$), 80.63 (*C*(CH_3)$_3$), 78.08, 77.41 (C-3, C-4), 74.26, 73.77 (2 × CH_2Ph), 64.99 (C-1), 59.79 (C-2), 52.22 (C-5), 28.78 (C(CH_3)$_3$), 27.10, 22.89 (C(CH_3)$_2$); CIMS: *m*/*z* 514 $[MNH_4]^+$, 497 $[MH]^+$, 469 $[MH-28]^+$, 458 $[MNH_4-56]^+$, 441 $[MH-56]^+$; Anal. Calcd for $C_{27}H_{36}N_4O_5$: C, 65.30; H, 7.31; N, 11.28. Found: C, 65.46; H, 7.48; N, 11.08.

Compound **12b** R_f 0.50 (5:95 EtOAc–cyclohexane); ^1H NMR (400 MHz, $CDCl_3$): δ major rotamer 7.36–7.28 (m, 10 H, 2 × *Ph*), 4.72–4.46 (m, 4 H, 2 × CH_2Ph), 4.21 (m, 1 H, H-5′), 4.17 (m, 1 H, H-3), 3.95 (m, 1 H, H-4), 3.84 (dd, 1 H, $J_{4,5}$ 7 Hz, $J_{5,5'}$ 8.5 Hz, H-5), 3.52 (m, 1 H, H-4), 3.29 (m, 2 H, H-1, H-1′), 1.64, 1.57 (2 × s, 6 H, (C(CH_3)$_2$), 1.49 (s, 9 H, (C(CH_3)$_3$); minor rotamer 7.36–7.28 (m, 10 H, 2 × *Ph*), 4.72–4.46 (m, 4 H, 2 × CH_2Ph), 4.21 (m, 1 H, H-5′), 3.99 (m, 1 H, H-4), 3.84 (dd, 1 H, $J_{4,5}$ 7 Hz, $J_{5,5'}$ 8.5 Hz, H-5), 3.64 (m, 1 H, H-4), 3.38 (m, 1 H, H-2), 3.20 (m, 2 H, H-1, H-1′), 1.61, 1.53 (2 × s, 6 H, (C(CH_3)$_2$), 1.53 (s, 9 H, (C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ major rotamer 153.36 (*CO*), 138.44, 138.09, 128.75, 128.61, 128.57, 128.21 (2 × *Ph*), 93.97 (*C*(CH_3)$_2$), 80.79 (*C*(CH_3)$_3$), 79.82 (C-2), 78.75 (C-3), 75.43, 73.81 (2 × CH_2Ph), 63.88 (C-5), 59.50 (C-4), 52.18 (C-1), 28.86 (C(CH_3)$_3$), 26.92, 25.28 (C(CH_3)$_2$); minor rotamer 153.36 (*CO*), 138.44, 138.09, 128.75, 128.61, 128.57, 128.21 (2 × *Ph*), 93.97 (*C*(CH_3)$_2$), 80.79 (*C*(CH_3)$_3$), 79.82 (C-2), 77.00 (C-3), 75.43 , 73.81 (2 × CH_2Ph), 63.88 (C-5), 59.50 (C-4), 51.30 (C-1), 28.86 (C(CH_3)$_3$), 26.35, 23.26 (C(CH_3)$_2$).

4.7. 2-Amino-5-azido-3,4-di-*O*-benzyl-2-(*N*-*tert*-butyloxycarbonyl)-2,5-dideoxy-D-xylitol (13a) and 4-amino-1-azido-2,3-di-*O*-benzyl-4-(*N*-*tert*-butyloxycarbonyl)-1,4-dideoxy-4-L-arabinitol (13b)

To a soln of **12a** or **12b** (2.9 g, 5.84 mmol) in MeOH (20 mL) was added DOWEX resin 50W (H^+) (5 g). The mixture was stirred at rt for 48 h and filtered. The resin was abundantly washed with MeOH and CH_2Cl_2. After solvent evaporation, the oil was purified by chromatography (3:7 EtOAc–cyclohexane) and the primary alcohol was isolated as a colorless oil (2.0 g, 75%).

Compound **13a** (75%) R_f 0.35 (3:7 EtOAc–cyclohexane); $[\alpha]_D^{25}$ −21.3° (*c* 1, $CHCl_3$); IR (thin film): *v* 2103 (N_3), 1702 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.18 (m, 10 H, 2 × *Ph*), 4.91 (d, 1 H, $J_{2,NH}$ 10 Hz, NH), 4.68, 4.61, 4.56, 4.49 (4 × d, 4 H, J_{gem} 11 Hz, 2 × CH_2Ph), 3.80 (d, 1 H, $J_{3,4}$ 7 Hz, H-3), 3.73 (m, 1 H, H-2), 3.63 (ddd, 1 H, $J_{4,5}$ 3 Hz, $J_{4,5'}$ 5.5 Hz, $J_{3,4}$ 7 Hz, H-4), 3.52 (dd, 1 H, $J_{1,2}$ 7.5 Hz, $J_{1,1'}$ 11 Hz, H-1), 3.42 (dd, 1 H, $J_{4,5}$ 3 Hz, $J_{5,5'}$ 13 Hz, H-5), 3.39 (m, 1 H, H-1′), 3.27 (dd, 1 H, $J_{5,5'}$ 13 Hz, $J_{4,5'}$ 5.5 Hz, H-5′), 2.62 (br s, 1 H, OH), 1.34 (s, 9 H, (C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.46 (*CO*), 138.20, 128.96, 128.91, 128.75, 128.55, 128.41, 128.33 (2 × *Ph*), 80.38 (*C*(CH_3)$_3$,), 80.00 (C-4), 77.45 (C-3), 75.45, 73.70 (2 × CH_2Ph), 63.52 (C-1), 52.34 (C-2), 51.53 (C-5), 28.76 (C(CH_3)$_3$); CIMS: *m*/*z* 474 $[MNH_4]^+$, 457 $[MH]^+$, 429 $[MH-28]^+$, 418 $[MNH_4-56]^+$, 401 $[MH-56]^+$; Anal. Calcd for $C_{24}H_{32}N_4O_5$: C, 63.14; H, 7.06; N, 12.27. Found: C, 63.16; H, 7.26; N, 12.00.

Compound **13b** R_f 0.30 (3:7 EtOAc–cyclohexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.44–7.32 (m, 10 H, 2 × *Ph*) 5.43 (d, 1 H, $J_{2,NH}$ 7 Hz, NH), 4.76–4.68 (m, 4 H, 2 × CH_2Ph), 3.91 (m, 1 H, H-3), 3.78 (m, 3 H, H-2, H-4, H-5), 3.66 (m, 1 H, H-5′), 3.50 (m, 2 H, H-1, H-1′), 3.04 (br s, 1 H, OH), 1.49 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.69 (*CO*), 137.95, 137.80, 128.99, 128.77, 128.70, 128.55 (2 × CH_2Ph), 80.06 (*C*(CH_3)$_3$), 78.96 (C-2), 77.89 (C-3), 73.95, 73.84 (2 × CH_2Ph), 63.06 (C-5), 52.63 (C-4), 51.72 (C-1), 28.77 (C(CH_3)$_3$).

4.8. 2-Amino-5-azido-3,4-di-*O*-benzyl-2-(*N*-*tert*-butyloxycarbonyl)-2,5-dideoxy-D-methylxylonate (14a) and 4-amino-1-azido-4-(*N*-*tert*-butyloxycarbonyl)-2,3-di-*O*-benzyl-1,4-dideoxy-L-methylarabinonate (14b)

To a soln of alcohol **13a** or **13b** (1.8 g, 3.94 mmol) in acetone (20 mL), were added successively TEMPO (60 mg, 0.4 mmol), potassium bromide (50 mg, 0.4 mmol) and a 5% soln of $NaHCO_3$ (10 mL). The reaction mixture was cooled to 0 °C and sodium hypochlorite (9.7 mL, 157.6 mmol) was added dropwise. After 40

min, the temperature was raised to rt and EtOAc (20 mL) was added. The aq phase was acidified to pH 2 by using a 6 M HCl soln and extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine (40 mL), dried ($MgSO_4$) and concentrated. The orange oil was taken up with MeOH (20 mL) and an excess of CH_2N_2 in Et_2O was added. After stirring overnight, the reaction mixture was concentrated and the crude product was purified by chromatography (1:9 EtOAc–cyclohexane) to yield a colorless oil (1.42 g, 75%).

Compound **14a** R_f 0.7 (3:7 EtOAc–cyclohexane); $[\alpha]_D^{25}$ −19.7° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.11 (m, 10 H, 2 × *Ph*), 5.20 (d, 1 H, $J_{2,\ NH}$ 10 Hz, NH), 4.56 (m, 3 H, CH_2Ph), 4.40 (d, 1 H, J_{gem} 11.5 Hz, CH_2Ph), 4.37 (dd, 1 H, $J_{2,\ 3}$ 7.5 Hz, $J_{2,\ NH}$ 10 Hz, H-2), 4.08 (dd, 1 H, $J_{3,\ 4}$ 2 Hz, $J_{2,\ 3}$ 7.5 Hz, H-3), 3.64 (ddd, 1 H, $J_{3,\ 4}$ 2 Hz, $J_{4,\ 5}$ 3 Hz, $J_{4,\ 5'}$ 6 Hz, H-4), 3.56 (s, 3 H, OCH_3), 3.47 (dd, 1 H, $J_{5,\ 5'}$ 14 Hz, $J_{4,\ 5}$ 3 Hz, H-5), 3.30 (dd, 1 H, $J_{5,\ 5'}$ 14 Hz, $J_{4,\ 5'}$ 6 Hz, H-5′), 1.37 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.80 (C-1), 156.21 (*CO*), 138.03, 137.87, 128.85, 128.59, 128.41, 128.33 (2 × *Ph*), 80.77 (*C*(CH_3)$_3$), 79.88 (C-4), 79.05 (C-3), 75.09, 73.87 (2 × CH_2Ph), 54.34 (C-2), 52.88 (OCH_3), 51.43 (C-5), 28.66 (C(CH_3)$_3$); CIMS: *m*/*z* 502 $[MNH_4]^+$, 485 $[MH]^+$; 457 $[MH-28]^+$, 446 $[MNH_4-56]^+$, 429 $[MH-56]^+$.

Compound **14b** R_f 0.6 (3:7 EtOAc–cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.28 (m, 10 H, 2 × *Ph*), 5.77 (d, 1 H, $J_{4,\ NH}$ 8.5 Hz, NH), 4.76 (dd, 1 H, $J_{3,\ 4}$ 4.5 Hz, $J_{4,\ NH}$ 8.5 Hz, H-4), 4.71, 4.69, 4.59, 4.56 (4 × d, 4 H, J_{gem} 11.7 Hz, CH_2Ph), 3.92 (dd, 1 H, $J_{2,\ 3}$ 4.5 Hz, $J_{3,\ 4}$ 4.5 Hz, H-3), 3.75 (s, 3 H, OCH_3), 3.70 (m, 1 H, H-2), 3.52 (m, 2 H, H-1, H-1′), 1.44 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.80 (C-5), 156.69 (*CO*), 137.95, 137.80, 128.99, 128.77, 128.70, 128.55 (2 × *Ph*), 80.06 (*C*(CH_3)$_3$), 78.96 (C-2), 77.89 (C-3), 73.95, 73.84 (2 × CH_2Ph), 63.06 (C-4), 52.63 (OCH_3), 51.72 (C-1), 28.77 (C(CH_3)$_3$).

4.9. 2,5-Diamino-3,4-di-*O*-benzyl-2*N*-*tert*-butyloxycarbonyl-2,5-dideoxy-D-xylono-1,5-lactam (15a) or 2,5-diamino-3,4-di-*O*-benzyl-2*N*-*tert*-butyloxycarbonyl-2,5-dideoxy-L-arabinol-1,5-lactam (15b)

To a soln of ester **14a** (0.83 g, 1.71 mmol) in MeOH (20 mL) was added Pd/Ca(CO_3)$_2$ (0.25 g, 25% weight). After degassing, the mixture was stirred under a hydrogen atmosphere during 12 h. The reaction mixture was filtered and washed thoroughly with MeOH. The solvent was evaporated and **15a** was isolated as a white solid (0.619 g, 85%). The solid was recristallized from Et_2O and pure **15a** isolated quantitatively. For **15b**, the procedure as described above was applied except that **15b** was recristallized from 1:1 ether–pentane giving a white solid (0.575 g, 79%).

Compound **15a** R_f 0.3 (EtOAc); Mp 148 °C; $[\alpha]_{Hg}^{25}$ −15° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.31 (m, 10 H, 2 × *Ph*), 6.45 (br s, 1 H, NH), 5.29 (d, 1 H, $J_{2,\ NH}$ 7 Hz, NH), 4.78, 4.74 (2 × d, 2 H, J_{gem} 11.7 Hz, CH_2Ph), 4.60 (s, 2 H, CH_2Ph), 4.21 (dd, 1 H, $J_{2,\ NH}$ 7 Hz, $J_{2,\ 3}$ 7 Hz, H-2), 3.82 (m, 2 H, H-3, H-4), 3.55 (d, 1 H, $J_{5,\ 5'}$ 13 Hz, H-5), 3.36 (dd, 1 H, $J_{5,\ 5'}$ 13 Hz, $J_{4,\ 5'}$ 5 Hz, H-5′), 1.47 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.38 (C-1), 156.01 (*CO*), 138.22, 137.81, 128.98, 128.79, 128.45, 128.33, 128.21, 128.09 (2 × Ph), 80.17 (*C*(CH_3)$_3$), 79.57 (C-3), 75.28 (C-4), 73.16, 71.96 (2 × CH_2Ph), 54.61 (C-2), 42.25 (C-5), 28.62 (C(CH_3)$_3$); CIMS: *m*/*z* 427 $[MH]^+$, 371 $[MH-56]^+$; Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.54; H, 7.06; N, 6.61.

Compound **15b** R_f 0.5 (4:1 EtOAc–cyclohexane); Mp 89 °C; $[\alpha]_D^{25}$ −6° (*c* 1, $CHCl_3$) and $[\alpha]_{Hg}^{25}$ −22° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.17 (m, 10 H, 2 × *Ph*) 6.15 (br s, 1 H, NH), 5.34 (d, 1 H, $J_{2,\ NH}$ 7 Hz, NH), 4.57–4.40 (m, 5 H, 2 × CH_2Ph, H-2), 4.24 (dd, 1 H, $J_{2,\ 3}$ 3 Hz, $J_{3,\ 4}$ 3 Hz, H-3), 3.66 (m, 1 H, H-4), 3.49 (ddd, 1 H, $J_{5,\ 5'}$ 13 Hz, $J_{4,\ 5}$ 2 Hz, $J_{5,\ NH}$ 2.5 Hz, H-5), 3.22 (ddd, 1 H, $J_{5,\ 5'}$ 13 Hz, $J_{4,\ 5'}$ 5 Hz, $J_{5',\ NH}$ 2.5 Hz, H-5′), 1.39 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.38 (C-1), 155.89 (*CO*), 137.84, 137.46, 128.66, 128.16, 128.08, 127.99, 127.91 (2 × *Ph*), 79.76 (*C*(CH_3)$_3$), 75.56 (C-2), 73.48 (CH_2Ph), 71.86 (C-4), 71.19 (CH_2Ph), 51.97 (C-3) , 43.11 (C-5), 28.54 (C(CH_3)$_3$); Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.07; H, 7.18; N, 6.56.

4.10. 2,5-Diamino-3,4-di-*O*-benzyl-2-*N*-*tert*-butyloxycarbonyl-2,5-dideoxy-D-xylothiono-1,5-lactam (16a) and 2,5-diamino-3,4-di-*O*-benzyl-2-*N*-*tert*-butyloxycarbonyl-2,5-dideoxy-D-arabinothiono-1,5-lactam (16a′)

To a soln of lactam **15a** (1.23 g, 2.88 mmol) in dry THF (30 mL) was added the Lawesson's reagent (0.7 g, 1.73 mmol). After stirring at rt for 1 h, the mixture was concentrated, dissolved in CH_2Cl_2 (3 mL) and purified by chromatography (0.1:0.9:9 Et_3N–EtOAc–cyclohexane). After recrystallization from Et_2O, **16a** and **16a′** were isolated as a white solid (1.03 g, 81%) in a ratio 9:1. The two epimers were separated by a second recristallization from hot Et_2O.

Compound **16a** R_f 0.25 (0.1:2.9:7 Et_3N–EtOAc–cyclohexane); Mp 127 °C; $[\alpha]_D^{25}$ −34° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (br s, 1 H, NH), 7.31–7.21 (m, 10 H, 2 × *Ph*), 5.38 (d, 1 H, $J_{2,\ NH}$ 8 Hz, NH), 4.61, 4.55, 4.48, 4.45 (4 × d, 4 H, J_{gem} 11.7 Hz, 2 × CH_2Ph), 4.40 (dd, 1 H, $J_{2,\ NH}$ 8 Hz, $J_{2,\ 3}$ 8 Hz, H-2), 3.84 (m, 1 H, H-3), 3.55 (m, 1 H, H-4), 3.50 (m, 1 H, H-5), 3.38 (ddd, 1 H, $J_{5,\ 5'}$ 14 Hz, $J_{4,\ 5'}$ 4 Hz, $J_{5',\ NH}$ 4 Hz, H-5′), 1.39 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.89 (C-1), 156.43 (*CO*), 138.62, 138.23,

129.29, 129.11, 128.69, 128.65, 128.59 (2 × *Ph*), 80.70 (*C*(CH_3)$_3$) 80.56 (C-3), 75.80 (C-4), 73.39, 72.17 (2 × CH_2Ph), 59.65 (C-2), 45.90 (C-5), 28.92 (*C*(CH_3)$_3$); CIMS: *m/z* 460 $[MNH_4]^+$, 443 $[MH]^+$, 387 $[MH-56]^+$; Anal. Calcd for $C_{24}H_{30}N_2O_4S$: C, 65.13; H, 6.83; N, 6.33. Found: C, 65.04; H, 6.86; N, 6.43.

Compound **16a′** R_f 0.35 (0.1:2.9:7 Et_3N–EtOAc–cyclohexane); Mp 143 °C; $[\alpha]_D^{25}$ +5° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (br s, 1 H, NH) , 7.28–7.19 (m, 10 H, 2 × *Ph*), 5.61 (d, 1 H, $J_{2,\ NH}$ 6 Hz, NH), 4.59–4.44 (m, 5 H, 2 × CH_2Ph, H-2), 4.16 (dd, 1 H, $J_{2,\ 3}$ 3 Hz, $J_{3,\ 4}$ 3 Hz, H-3), 3.79 (m, 1 H, H-4), 3.56 (ddd, 1 H, $J_{5,\ 5'}$ 14 Hz, $J_{5,\ NH}$ 3 Hz, $J_{4,\ 5}$ 4.5 Hz, H-5), 3.28 (ddd, 1 H, $J_{5,\ 5'}$ 14 Hz, $J_{5',\ NH}$ 3 Hz, $J_{4,\ 5'}$ 3 Hz, H-5′) 1.39 (s, 9 H, (C(*CH*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.61(C-1), 156.07(*CO*), 138.45, 138.17, 129.25, 128.71, 128.58 (2 × *Ph*), 80.30 (*C*(CH_3)$_3$), 76.29(C-3), 74.13(*CH*$_2$Ph), 72.98 (C-4), 72.03 (*CH*$_2$Ph), 56.62 (C-2), 45.75(C-5), 28.89 (C(*CH*$_3$)$_3$); Anal. Calcd for $C_{24}H_{30}N_2O_4S$: C, 65.13; H, 6.83; N, 6.33. Found: C, 64.98; H, 7.02; N, 6.19.

4.11. 2,5-Diamino-3,4-di-*O*-benzyl-2-*N*-*tert*-butyloxycarbonyl-2,5-dideoxy-L-arabinothiono-1,5-lactam (16b)

Same physical characteristics as (**16a′**) (0.79 g, 56%). $[\alpha]_D^{25}$ −7° (*c* 1, $CHCl_3$). Resolution of the RX structure was performed at the Centre de Resolution de Structures, UPMC, Paris.

4.12. 2,5-Diamino-3,4-di-*O*-benzyl-2-*N*-acetamido-2,5-dideoxy-D-xylo-1,5-thionolactam (17a) and 2,5-diamino-3,4-di-*O*-benzyl-2-*N*-acetamido-2,5-dideoxy-D-arabinothiono-1,5-lactam (17a′)

To a soln of **16a** (0.77 g, 1.74 mmol) in anhyd CH_2Cl_2 (5 mL) were successively added 2,6-lutidine (0.5 mL, 4.35 mmol) and TBDMSOTf (0.88 mL, 3.83 mmol). After stirring for 2 h at rt, MeOH (3 mL) was added, followed by acetic anhydride (1.6 mL, 17.4 mmol) and tetrabutylammonium fluoride (1.9 mL, 1.9 mmol). The soln was stirred for 1 h and a white precipitate appeared. The mixture was filtered and the solid recristallized from EtOAc leading to **17a** as a white solid (0.290 g, 43%).

Compound **17a** R_f 0.6 (9:1 CH_2Cl_2–MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (br s, 1 H, NH) 7.39–7.34 (m, 10 H, 2 × *Ph*), 6.28 (d, 1 H, $J_{2,\ NH}$ 8 Hz, *NH*Ac), 4.88 (dd, 1 H, $J_{2,\ 3}$ 5.5 Hz, $J_{2,\ NH}$ 8 Hz, H-2), 4.65, 4.57, 4.48, 4.42 (4 × d, 4 H, J_{gem} 11.7 Hz, CH_2Ph), 3.84 (m, 1 H, H-4), 3.64 (m, 1 H, H-3), 3.57 (d, 1 H, $J_{5,\ 5'}$ 13.2 Hz, H-5), 3.40 (dd, 1 H, $J_{5,\ 5'}$ 13.2 Hz, $J_{5',\ NH}$ 3.5 Hz, H-5′), 1.92 (s, 3 H, CO*CH*$_3$); ^{13}C NMR (100 MHz, Me_2SO d_6): δ 200.02 (C-1), 169.34 (*CO*CH_3), 138.56, 138.34, 128.59, 128.51, 128.07, 127.87 (2 × *Ph*), 80.71 (C-4), 76.08 (C-3), 71.99 , 70.34 (2 × *CH*$_2$Ph), 58.85 (C-2), 44.52 (C-5), 23.06 (CO*CH*$_3$); CIMS: *m/z* 402 $[MNH_4]^+$, 385 $[MH]^+$, 294 $[MNH_4-108]^+$, 277 $[MH-108]^+$.

4.13. 2,5-Diamino-3,4-di-*O*-benzyl-2-*N*-acetamido-2,5-dideoxy-D-xylosamidoxime (18a) and 2,5-diamino-3,4-di-*O*-benzyl-2*N*-acetamido-2,5-dideoxy-D-arabinosamidoxime (18a′)

A soln of **17a** (0.231 g, 0.6 mmol), hydroxylamine hydrochloride (0.083 g, 1.2 mmol) and cesium carbonate (0.391 g, 1.2 mmol) in DMF was stirred at rt for 48 h. The mixture was then concentrated under diminished pressure and filtered. The solid was thoroughly washed with MeOH and the filtrate was concentrated. The crude product was purified by chromatography (9:1 CH_2Cl_2–EtOH) and a mixture of **18a** and **18a′** was isolated (0.078 g, 34%) in a 4:1 ratio.

Compound **18a** R_f 0.38 (9:1 CH_2Cl_2–MeOH); ^{1}H NMR (200 MHz, CD_2Cl_2): δ 7.25–7.18 (m, 10 H, 2 × *Ph*), 6.72 (d, 1 H, $J_{2,\ NH}$ 9 Hz, NH), 4.92 (dd, 1 H, $J_{2,\ NH}$ 9 Hz, $J_{2,\ 3}$ 4.5 Hz, H-2), 4.64–4.47 (m, 4 H, 2 × CH_2Ph), 3.82 (m, 1 H, H-4), 3.76 (m, 1 H, H-3), 3.49 (dd, 1 H, $J_{5,\ 5'}$ 13 Hz, $J_{4,\ 5}$ 7 Hz, H-5), 3.36 (dd, 1 H, $J_{5,\ 5'}$ 13 Hz, $J_{4,\ 5'}$ 3 Hz, H-5′), 1.84 (s, 3 H, CO*CH*$_3$); ^{13}C NMR (50 MHz, CD_2Cl_2): δ 170.40 (*CO*CH_3), 152.08 (C-1), 138.67, 138.47, 129.31, 129.15, 128.99, 128.77, 128.65, 128.56 (2 × *Ph*), 77.53 (C-3), 75.79 (C-4), 73.00, 72.33 (2 × *CH*$_2$Ph), 47.90 (C-2), 42.22 (C-5), 23.78 (CO*CH*$_3$).

Compound **18a′** R_f 0.35 (9:1 CH_2Cl_2–MeOH); ^{1}H NMR (200 MHz, CD_2Cl_2): δ 7.25–7.18 (m, 10 H, 2 × *Ph*), 6.42 (d, 1 H, $J_{2,\ NH}$ 8 Hz, NH), 5.15 (dd, 1 H, $J_{2,\ NH}$ 8 Hz, $J_{2,\ 3}$ 3.5 Hz, H-2), 4.64–4.47 (m, 4 H, 2 × CH_2Ph), 4.11 (m, 1 H, H-3), 3.76 (m, 1 H, H-4), 3.46 (dd, 1 H, $J_{5,\ 5'}$ 13 Hz, $J_{4,\ 5}$ 2.5 Hz, H-5), 3.29 (d, 1 H, $J_{5,\ 5'}$ 13 Hz, H-5′), 1.93 (s, 3 H, CO*CH*$_3$); ^{13}C NMR (50 MHz, CD_2Cl_2): δ 170.87 (*CO*CH_3), 151.84 (C-1), 138.67, 138.47, 129.31, 129.15, 128.99, 128.77, 128.65, 128.56 (2 × *Ph*), 76.33 (C-3), 73.71 (C-4), 72.73, 71.92 (2 × *CH*$_2$Ph), 46.75 (C-2), 42.22 (C-5), 23.56 (CO*CH*$_3$); CIMS: *m/z* (mixture of the two epimers): 384 $[MH]^+$, 368 $[MH-16]^+$, 276 $[MH-108]^+$.

4.14. Energy minimization calculations

The structure of lactams and thionolactams was optimized using AM_1 parametrization AMPAL version 2.14. This program runs on RISK 6000 computers at the CCR Jussieu. All optimizations were carried out using the BFGS procedure. As all species have an even number of electrons, the default RHF calculations were performed. Since the 2.14 version is limited to 59 atoms, the isopropyl group was used instead of the *tert*-butyl group on the 2-amino functionality, in such a way that

the steric interactions of the methyl groups could mimic those of a *tert*-butyl group.

5. Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 207472. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk.

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