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Internally Protected Amino Sugar Equivalents from Enantiopure 1,2-Oxazines: Synthesis of Variably Configured Carbohydrates with C-Branched Amino Sugar Units

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Dedicated to Professor Richard R. Schmidt on the occasion of his 75th birthday

Abstract: A stereodivergent synthesis of differently configured C2-branched 4-amino sugar derivatives was accomplished. The Lewis acid mediated rearrangement of phenylthio-substituted 1,2-oxazines delivered glycosyl donor equivalents that can directly be employed in glycosidation reactions. Treatment with methanol provided internally protected amino sugar equivalents that have been transformed into the stereoisomeric methyl glycosides **28**, *ent*-**28**, **29**, *ent*-**29** and **34** in two simple reductive steps. Reaction with natural carbohydrates or bicyclic amino sugar precursors allowed the synthesis of homo-oligomeric di- and trisaccharides **44**, **46** and **47** or a hybrid trisaccharide **51** with natural carbohydrates. Access to a bivalent amino sugar derivative **54** was accomplished by reaction of rearrangement product **10** with 1,5-pentanediol. Alternatively, when a protected L-serine derivative was employed as glycosyl acceptor, the glycosylated amino acid **60** was efficiently prepared in few steps. In this report we describe the synthesis of unusual amino sugar building blocks from enantiopure 1,2-oxazines that can be attached to natural carbohydrates or natural product aglycons to produce new natural product analogues with potential applications in medicinal chemistry.

Keywords: allenes · amino sugars · carbohydrates · glycosidation · rearrangement

Introduction

The occurrence of amino sugar moieties in the glycome of animals and humans is mainly restricted to glucosamine, galactosamine, and sialic acids.[1] However, an enormous diversity of amino sugars, including several C-branched derivatives, can be found in many natural products and in a variety of antibiotics.[2] By replacing these carbohydrates by synthetic analogues a large number of antibacterial compounds such as aminoglycoside and glycopeptide mimetics with a decreased resistance and toxicity profile has been discovered.[3] This has led to remarkable success in the therapy of bacterial infections and genetic disorders.[4]

There are two major possibilities to synthesize new amino sugar derivatives: one is the chemical or enzymatic modification of existing carbohydrates, the second involves the de novo strategy.[5] The construction of sugars from smaller fragments by C–C-bond forming reactions allows to employ cheap starting materials and to synthesize structurally related carbohydrates from common precursors. Particularly advantageous is the preparation of carbohydrate building blocks that can directly be used in the synthesis of oligosaccharides or other glycoconjugates without further protecting group transformations.[6]

In this context, we recently described de novo approaches towards different classes of amino sugars and their mimetics starting from enantiopure 1,2-oxazines,[7] which are surprisingly versatile intermediates for the stereoselective synthesis of a variety of carbohydrate related compounds such as polyhydroxylated pyrrolidines, azetidines or polyols.[8] Among these differently configured C2-branched 4-amino sugars **A** have been generated from bicyclic compounds **B** by a sequence of glycosidation reaction, stereoselective carbonyl reduction and reductive cleavage of the N–O bond (Scheme 1).[9] A novel Lewis acid mediated rearrangement

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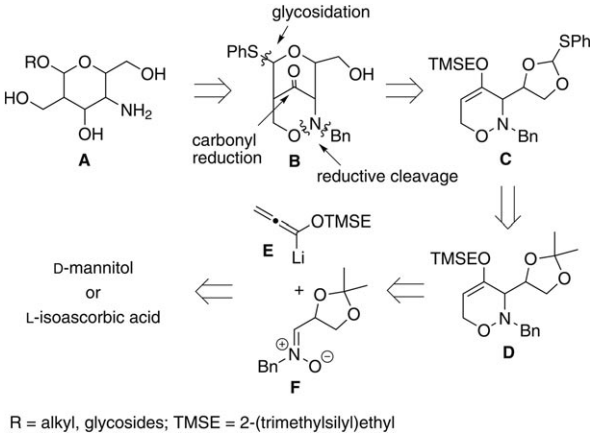
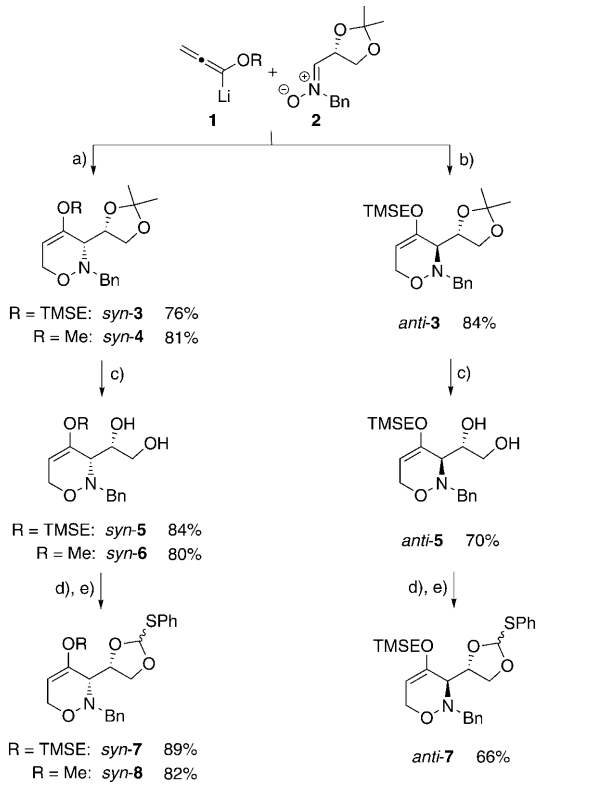
of 1,2-oxazines **C** delivered these key intermediates by an aldol-type C–C-bond forming reaction. As crucial precursors for the transformation into phenylthio-substituted compounds **C**, the required enantiomerically pure 1,2-oxazines **D** can be obtained by a [3+3]-cyclization of lithiated alkoxyallenes **E** and glyceraldehyde-derived nitrones **F**.[10] Since protected glyceraldehyde is easily available in both enantiomeric forms our concept allows the preparation of all compounds and hence the desired final product **A** as D- or as L-configured compound.



Scheme 1. Retrosynthetic analysis of C2-branched D- or L-amino sugars **A**.



Scheme 2. Synthesis of phenylthio-substituted 1,2-oxazines *syn*-**7**, *anti*-**7** and *syn*-**8**. a) THF, −78 °C, 2 h; b) **2** + Et_2AlCl, Et_2O, then to **1**, −78 °C, 2 h; c) $InCl_3$, H_2O, MeCN, 2 h; d) $HC(OMe)_3$, CAN, CH_2Cl_2, 1 h; e) $PhSSiMe_3$, TMSOTf, CH_2Cl_2, 3 h. CAN = cerium ammonium nitrate; TMSOTf = trimethylsilyl trifluoromethanesulfonate.

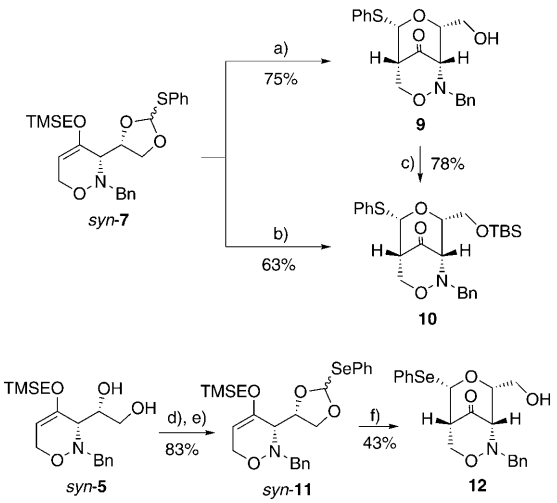
Herein, we disclose our detailed results on the Lewis acid mediated rearrangement of phenylthio-substituted 1,2-oxazines **C**, and on the application of the resulting glycosyl donor equivalents **B** towards the stereocontrolled synthesis of diversely configured amino sugars as components of oligosaccharides and glycosylated amino acids.

Results and Discussion

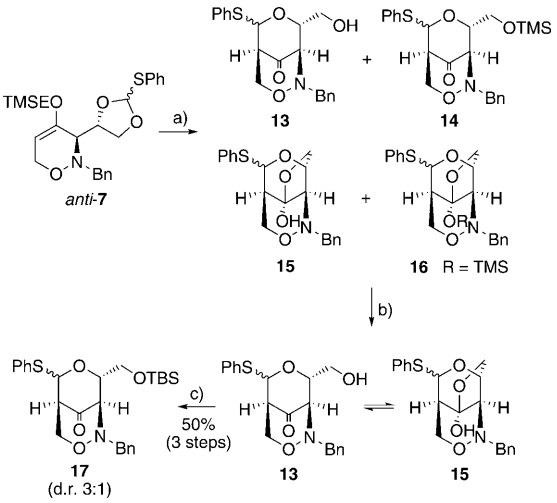
Starting points for our synthetic route were 1,2-oxazines *syn*-**3**, *anti*-**3** and *syn*-**4**, which are smoothly accessible in a stereodivergent manner from lithiated alkoxyallenes **1** and D-glyceraldehyde-derived nitrone **2** (Scheme 2).[7] In order to exchange the dimethyl substituents in the dioxolane ring by a phenylthio group a new method for the mild cleavage of acetonides was developed providing diols *syn*-**5**, *anti*-**5** and *syn*-**6** in good yields.[11] Formation of the corresponding orthoesters with trimethyl orthoformate[12] followed by Lewis-acid-catalyzed substitution of the methoxy by a phenylthio group[13] delivered the desired rearrangement precursors *syn*-**7**, *syn*-**8** and *anti*-**7**.

To achieve the desired rearrangement to the bicyclic compound **9** 1,2-oxazine derivative *syn*-**7** was exposed to different Lewis acids. Treatment with $SnCl_4$, which was the reagent of choice in similar reactions,[9b] was not successful in this case, but the use of two equivalents of trimethylsilyl trifluoromethanesulfonate (TMSOTf) smoothly afforded bicyclic 1,2-oxazinone **9** in good yield (Scheme 3). The TBS-protected derivative **10** could be obtained by either protection of **9** with *tert*-butyldimethylsilyl chloride or directly from 1,2-oxazine *syn*-**7**, when this compound was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf). The closely related 1,2-oxazine *syn*-**11** bearing a phenylseleno substituent at the C2 atom of the dioxolane moiety was also exposed to TMSOTf as Lewis acid thus furnishing the desired product **12** in moderate yield (not yet optimized). This result reveals that the phenylseleno substituent also provides suitable electronic properties for a successful rearrangement. Although we did not investigate the reactivity of compounds such as **12** it is evident that the phenylseleno group offers new synthetic options. It may be used for radical reactions or—after oxidation and elimination—may allow the preparation of novel C2-branched glycals.

When 1,2-oxazine *anti*-**7** was treated with TMSOTf quite a number of different compounds has been detected in the NMR spectra of the crude product mixture (Scheme 4). These could be assigned to compounds **13**–**16**. The products are formed as unprotected and TMS-protected hydroxyketones or as internal hemiketals (each as a mixture of two diastereomers). For simplification of the mixture it was first treated with tetra-*n*-butylammonium fluoride (TBAF) to



Scheme 3. Rearrangement of 1,2-oxazine *syn*-**7** into bicyclic ketones **9** and **10**. Rearrangement of phenylseleno-substituted 1,2-oxazine *syn*-**11** into **12**. a) TMSOTf (2 equiv), CH_2Cl_2, −30 °C to RT, 16 h; b) TBSOTf, −30 °C to RT, CH_2Cl_2, 16 h; c) TBSCl, imidazole, THF, 4 h; d) $HC(OMe)_3$, CAN, CH_2Cl_2, 1 h; e) $PhSeSiMe_3$, TMSOTf, CH_2Cl_2, 3 h; f) TMSOTf (2 equiv), CH_2Cl_2, −30 °C to RT, 16 h.

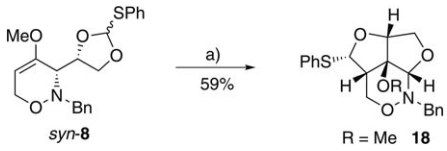


Scheme 4. Conversion of 1,2-oxazine *anti*-**7** into bicyclic ketone **17**. a) TMSOTf (2.5 equiv), CH_2Cl_2, −30 °C to RT, 21 h; b) TBAF, THF, 7 h; c) TBSOTf, NEt_3, CH_2Cl_2, 3 h. TBAF = tetra-*n*-butylammonium fluoride; TBSOTf = *tert*-butyldimethylsilyl triflate.

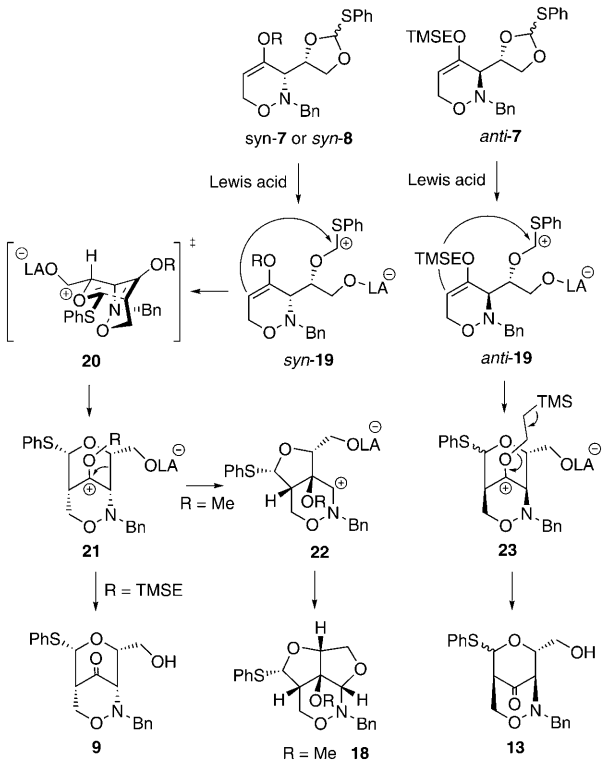
give compound **13** being in equilibrium with its hemiketal **15**. Subsequent protection with TBSOTf provided the final rearrangement product **17** as a 3:1 mixture of diastereomers.

The 1,2-oxazine *syn*-**8**, which bears the 4-methoxy instead of the (2-trimethylsilyl)ethoxy (TMSEO) substituent, rearranged under Lewis acidic conditions into tricyclic compound **18**, which is in analogy to previously observed transformations (Scheme 5).[14,15]

Plausible reaction pathways leading to rearrangement products **9**, **13** and **18** are depicted in Scheme 6. Coordination of the Lewis acid to the distal oxygen of the dioxolane ring of the precursor 1,2-oxazines leads to a ring opening followed by an aldol-type cyclization of the resulting carbenium ions *syn*-**19** or *anti*-**19** to give key intermediates **21** or **23**. The excellent diastereoselectivity in the formation of **21** can be explained by a chair-like transition state **20** where the phenylthio substituent adopts an equatorial position. Depending on the nature of the group R two different succeeding sequences are possible. In the case of R = TMSE, this group undergoes a very fast fragmentation into ethene and a TMSX species leading to bicyclic ketone **9**. On the other hand, simple alkoxy groups such as methoxy in **21** do not undergo a similarly fast fragmentation and therefore a 1,2-alkyl shift under retention of configuration generates the more stable carbenium ion **22**. This rearranged intermediate finally produced tricyclic compound **18** by *N*,*O*-acetal formation of the remaining oxygen with the cationic centre. In contrast to compounds **9** and **18**, which were isolated as single diastereomers, rearrangement product **13** derived in the *anti*-series was obtained as a mixture of diastereomers.



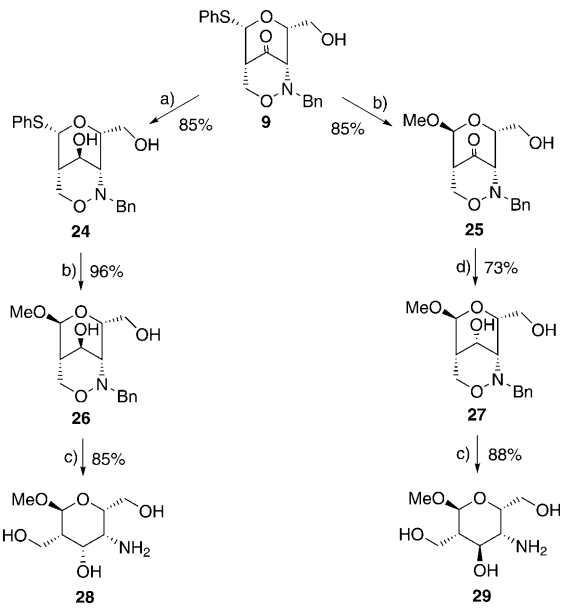
Scheme 5. Rearrangement of methoxy-substituted 1,2-oxazine *syn*-**8** into tricyclic compound **18**. a) TMSOTf (2 equiv), CH_2Cl_2, −30 °C to RT, 16 h.



Scheme 6. Proposed reaction pathways leading to compounds **9**, **13** and **18**.

The cyclization of carbenium ion *anti*-**19** leading to intermediate **23** can not proceed via a chair-like transition state (similar to **20**), since the bulky hydroxymethyl group would have to occupy an axial position. Therefore a twisted boat-like transition state of this subunit probably leads to the poor selectivity for the position of the phenylthio group as observed for product **13**.

Rearrangement products **9** and **17** can be regarded as internally protected amino sugar equivalents which can directly be used for the formation of glycosides. This feature was first demonstrated by the stereodivergent synthesis of simple C-branched amino sugars **28** and **29**. Starting with bicyclic 1,2-oxazine **9** as common precursor these two diastereomeric methyl glycosides were efficiently prepared in three steps (Scheme 7). Stereoselective reduction of the carbonyl group of **9** with sodium borohydride followed by NBS-activated substitution of the phenylthio moiety using methanol and subsequent hydrogenolytic cleavage of the N–O bond with concurrent debenzylation furnished C2-branched amino sugar derivative **28** featuring D-talose configuration.



Scheme 7. Stereodivergent synthesis of C2-branched amino sugar derivatives **28** and **29**. a) $NaBH_4$, EtOH, −40 °C, 3 h; b) NBS, MeOH, 30 min; c) H_2, Pd/C, MeOH, 18 h; d) Li(*s*Bu)$_3$BH, THF, −30 °C, 3 h. NBS = *N*-bromosuccinimide.

Most remarkably, change of the order of the first two steps afforded the epimeric amino sugar derivative **29** with inverted configuration at C3. Now the reaction of **9** with NBS in methanol followed by the stereoselective reduction of the carbonyl group of **25** with L-selectride gave compound **27**, an epimer of **26**. The final hydrogenolysis step afforded C2-branched methyl glycoside **29** with D-idose configuration.

Plausible explanations for the observed stereoselectivities of the reductions of **9** and **25** with the employed hydride reagents as well as for the stereoselective generation of **25** and **26** are presented in Figure 1. Apparently, the hydride reagent has to attack compound **9** from the side of the pyran moiety, since the *N*-benzyl group of the 1,2-oxazine unit efficiently shields this direction. On the other hand, when the axially positioned methoxy group has been introduced first to give **25**, this substituent sufficiently blocks the pyran side, hence leading to an attack of the hydride reagent from the opposite direction. It should be mentioned here that the use of sodium borohydride gave an 8:1 mixture of epimers, only the very bulky L-selectride allowed stereoselective reduction at low temperature.

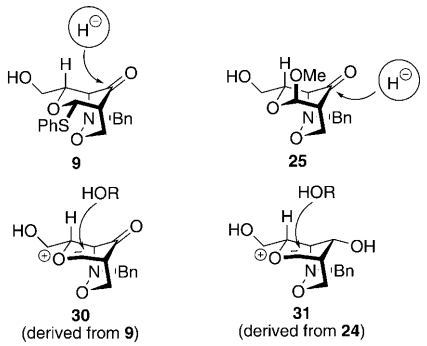
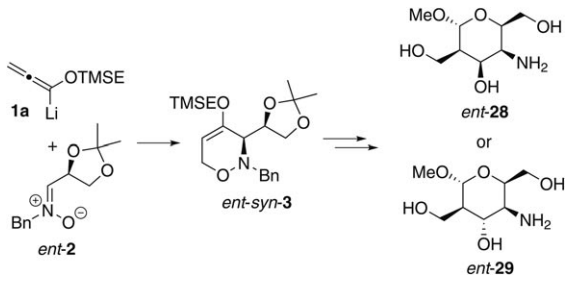


Figure 1. Crucial intermediates in the stereodivergent syntheses of amino sugar derivatives **28** and **29**.

The activation of **9** and **24** by *N*-bromosuccinimide very likely generates oxocarbenium ions **30** and **31**, respectively, which should have a halfchair-like conformation of the pyran moiety. The stereoelectronically favored axial attack of the alcohol directly generates the pyran chairs of **25** and **26** which directly benefit by the anomeric effect.

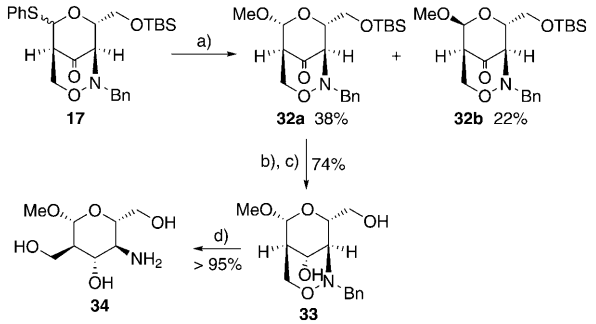
Starting from L-glyceraldehyde-derived nitrone *ent*-**2**,[16] the two enantiomeric amino sugars *ent*-**28** (L-talose configuration) and *ent*-**29** (L-idose configuration) have analogously been prepared, demonstrating that all described compounds are easily accessible in either of the two enantiomeric series via *ent-syn*-**3** (Scheme 8).



Scheme 8. Syntheses of enantiomeric amino carbohydrate derivatives *ent*-**28** and *ent*-**29**.

Aminopyrans **28** and *ent*-**28** have already been evaluated towards their potential as components of new multivalent anti-inflammatory agents[17] and compared with the corresponding dimethyl-substituted analogues which exhibited most remarkable properties as ligands of gold nanoparticles in their binding abilities to selectins.[18]

When rearrangement product **17** was treated with NBS in methanol, the expected products **32a/b** were formed only in low yield (Scheme 9). However, when a standard glycosylation protocol[19] for thio donors was employed, the diastereomers **32a/b** were obtained which could be easily separated by column chromatography.



Scheme 9. Synthesis of amino sugar derivative **34**. a) NIS, cat. TfOH, MeOH, MeCN, 4 Å molecular sieves, 2.5 h; b) TBAF, THF, 18 h; c) $NaBH_4$, EtOH, 2 h; d) H_2, Pd/C, MeOH, 18 h. NIS = *N*-iodosuccinimide; TfOH = trifluoromethanesulfonic acid.

We propose that after NIS/TfOH activation of the phenylthio group the pyran ring in cationic intermediate **35** is generated in a halfchair-like conformation, with the siloxymethyl substituent in a pseudoaxial position (Figure 2) which allows the attack of the alcohol from both sides. Depending on the solvent used diastereomeric ratios of 1.2:1 (CH_2Cl_2) to 1.7:1 (MeCN) were obtained. After separation of the diastereomers the major isomer **32a** was treated with TBAF giving the corresponding desilylated product that was subsequently reduced with sodium borohydride to furnish bicyclic alcohol **33** as a single diastereomer in good yield. The hydride reagent attacks intermediate **36** exclusively from the side of the 1,2-oxazine moiety, since the opposite side apparently is strongly shielded by the hydroxymethyl and the methoxy group (Figure 2). A final hydrogenolysis provided the desired C2-branched amino sugar derivative **34** having a D-glucose configuration.[20] As in glucose itself all substituents adopt equatorial positions in a chair-like conformation,

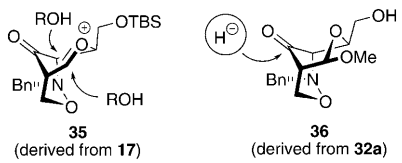
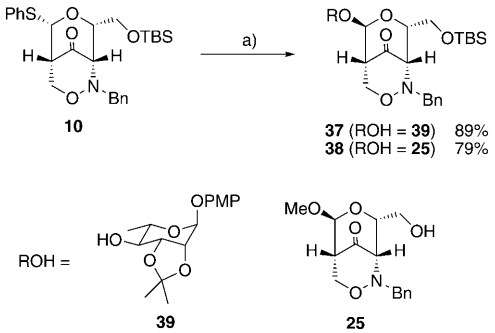


Figure 2. Crucial intermediates in the stereoselective synthesis of amino sugar derivative **34**.

which is in contrast to amino sugars **28** and **29** (Scheme 8) where the two *cis*-hydroxymethyl groups force the ring into a slightly twisted boat-like conformation. This was proven by X-ray crystallographic analysis of compound **29**.[9a]

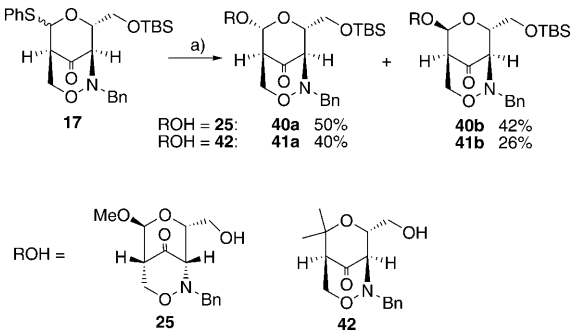
Protected rearrangement products **10** and **17** can directly be employed as glycosyl donor equivalents. This was demonstrated by reacting them not just with methanol or other simple alcohols but with suitably protected rhamnose derivative **39**[21] or with amino sugar precursor **25** using the NIS/TfOH activation protocol (Scheme 10). The resulting disaccharide precursors **37** and **38** were obtained as single diastereomers in very good yields; they were further elaborated to disaccharides as described below.



Scheme 10. Reactions of glycosyl donor equivalent **10**. a) **25** or **39**, NIS, TfOH, CH_2Cl_2, 4 Å molecular sieves, 2-4 h. PMP = 4-methoxyphenyl.

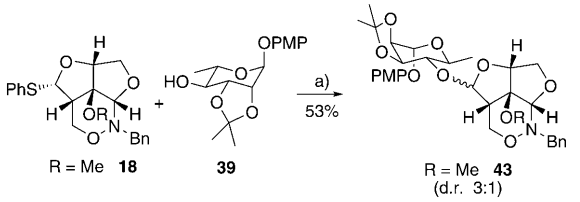
Likewise, the reaction of the diastereomeric product **17** with glycosyl acceptors **25** or **42**[9b] provided the coupled disaccharide precursors **40** and **41** in good yield but as mixtures of the two possible anomers (Scheme 11). In the reaction of **17** with methanol (Scheme 9) the alcohol was used in large excess and there the diastereomeric ratio could be improved by switching from CH_2Cl_2 to MeCN as solvent. This was not possible for the examples depicted in Scheme 11. No conversion to the expected products was observed in MeCN which probably traps the intermediate oxocarbenium ion.

Tricyclic rearrangement product **18** also reacted smoothly with alcohols. For example, NIS-promoted reaction with



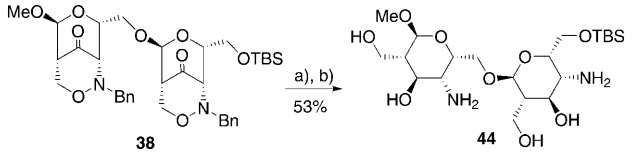
Scheme 11. Reactions of glycosyl donor equivalent **17**. a) alcohol **25** or **42**, NIS, TfOH, CH_2Cl_2, 4 Å molecular sieves, 4 h.

rhamnose derivative **39** furnished **43** as a 3:1 mixture of diastereomers in moderate yield (Scheme 12). Compound **18** was considerably more reactive than glycosyl donor equivalents **10** and **17** making further activation of NIS by TfOH unnecessary. Since the two resulting isomers could not be separated by column chromatography, further transformations of **43**, which may lead to new unusual carbohydrate mimetics, have not yet been examined. We assume that the major isomer is formed by the attack of the rhamnose derivative **39** to the sterically more open *exo*-face of **18** (*cis* to the three bridge-head hydrogens).



Scheme 12. Reaction of glycosyl donor equivalent **18** with L-rhamnose derivative **39**. a) NIS, CH_2Cl_2, 4 Å molecular sieves, 1 h.

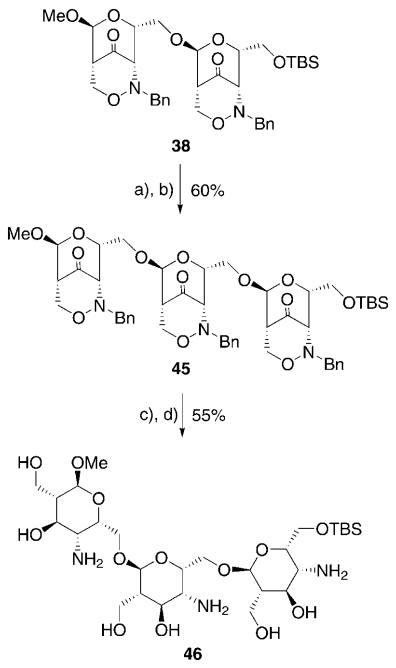
After glycosylation reactions of the rearrangement products the resulting dimeric compounds **38** and **41a** have been used for the synthesis of di- and trisaccharides containing C2-branched 4-amino sugar units. First, disaccharide equivalent **38** was stereoselectively transformed into **44** by reduction of the carbonyl groups with L-selectride and subsequent hydrogenolysis which induces debenzylation and cleavage of the N–O bonds (Scheme 13). The overall yield for the three steps leading to the novel disaccharide **44** is good.



Scheme 13. Synthesis of disaccharide **44**. a) Li(*s*Bu)$_3$BH, THF, 0 °C, 2 h; b) 1 bar H_2, Pd/C, MeOH, 19 h.

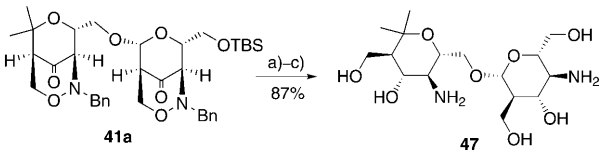
When compound **38** was desilylated with TBAF it can serve as a glycosyl acceptor. Glycosidation with glycosyl donor equivalent **10** delivered the trimeric compound **45** which was stereoselectively converted into trisaccharide **46** by the reductive steps as already described for the preparation of dimer **44** (Scheme 14).[22] Considering the complexity of trisaccharide **46** the overall yield of 55% for the three steps is again remarkable. The reactions described in Schemes 13 and 14 underscore the potential of our protocol to generate oligosaccharides of type **44** and **46** in a repetitive manner.

A disaccharide mimetic containing a D-glucose configured C2-branched amino sugar unit is also accessible. Dimeric



Scheme 14. Synthesis of trisaccharide **46**. a) TBAF, THF, 18 h; b) **10**, NIS, TfOH, 4 Å molecular sieves, CH_2Cl_2, 4 h; c) Li(*s*Bu)$_3$BH, THF, 0 °C to RT, 3 h; d) 1 bar H_2, Pd/C, MeOH, 42 h.

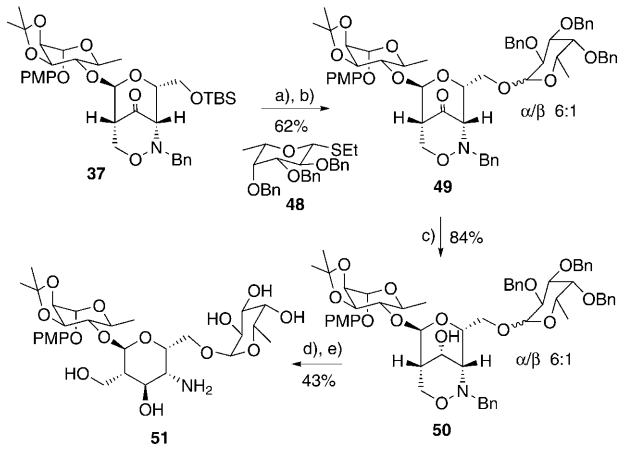
compound **41a** was smoothly transformed by three simple steps into fully deprotected disaccharide mimetic **47** in very good overall yield (Scheme 15). As in all previous cases the two carbonyl groups of **41a** were reduced to give the corresponding secondary alcohols with perfect levels of stereocontrol. All described oligosaccharides bearing amino sugar units of different configurations may have potential as aminoglycoside mimetics.[23]



Scheme 15. Synthesis of disaccharide mimetic **47**. a) $NaBH_4$, EtOH, 0 °C, 1 h; b) TBAF, THF, 18 h; c) 1 bar H_2, Pd/C, MeOH, 18 h.

Syntheses of hybrid systems of the presented amino sugar derivatives with natural carbohydrates are also easily possible. This was exemplarily demonstrated by using the desilylated intermediate derived from **37** as glycosyl acceptor in the reaction with commercially available L-fucosyl donor **48** (Scheme 16). The resulting trisaccharide equivalent **49** was stereoselectively reduced to furnish **50** and a final hydrogenolysis with palladium on charcoal provided partially protected trisaccharide **51**.

The option to employ rearrangement products such as **10** as protected amino sugar equivalents has been followed to prepare bivalent amino sugar derivatives such as **54**

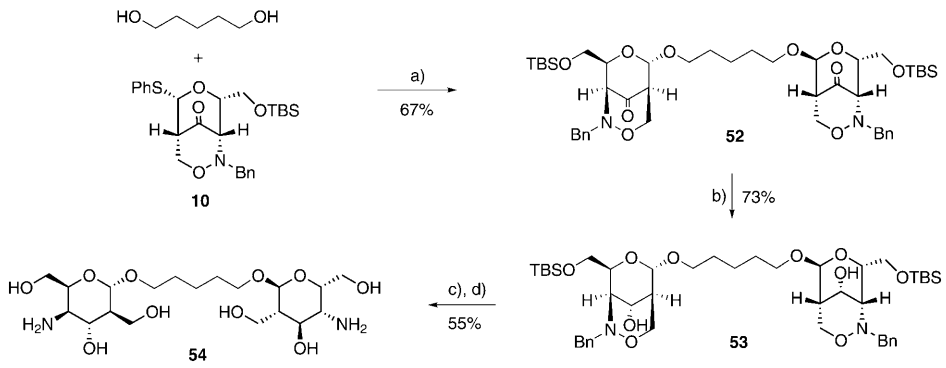


Scheme 16. Synthesis of hybrid trisaccharide **51**. a) TBAF, THF, RT, 18 h; b) NIS, 4 Å molecular sieves, CH_2Cl_2, RT, 1 h; c) Li(*s*Bu)$_3$BH, THF, −30 °C, 3 h; d) Crystallization of α-Fuc anomer from Et_2O (64 %); e) 1 bar H_2, Pd/C, MeOH/EtOAc, RT, 16 h (67 %).

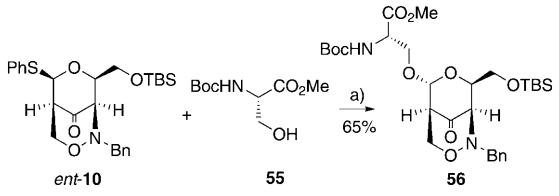
(Scheme 17). Compound **10** was combined with 1,5-pentanediol generating product **52** in good yield, which connects the two internally protected amino sugar units by a polymethylene linker. Stereoselective reduction of the carbonyl groups, deprotection by removal of the TBS groups, and subsequent hydrogenolysis furnished the desired bivalent carbohydrate derivative **54** in reasonable overall yield.[24]

Finally, we examined the possibility to use the available glycosyl donor for the synthesis of carbohydrate–peptide conjugates. For this purpose N-Boc-protected L-serine derivative **55** was employed as glycosyl acceptor. Glycosidation with rearrangement product *ent*-**10** furnished the expected coupling product **56** in good yield (Scheme 18).

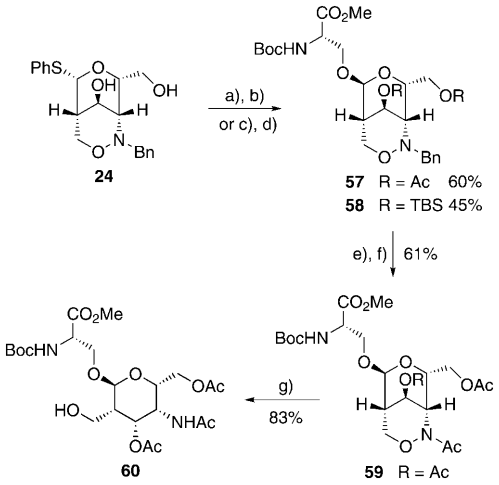
Further transformations of **56** should allow the preparation of various glycosylated L-serine derivatives. This has already been demonstrated by the synthesis of glycosylated L-serine derivative **60** bearing an amino sugar unit with D-talose configuration (Scheme 19). Protection of **24** with acetic acid anhydride or with TBSOTf provided excellent precursors for the NIS/TfOH-promoted coupling with L-serine derivative **55** to give the desired products **57** and **58**



Scheme 17. Synthesis of bivalent amino sugar derivative **54**. a) NIS, TfOH, CH_2Cl_2, 4 Å molecular sieves, 5 h; b) Li(*s*Bu)$_3$BH, THF, 0 °C, 2 h; c) TBAF, THF, 12 h; d) 1 bar H_2, Pd/C, MeOH, 24 h.



Scheme 18. Reaction of glycosyl donor equivalent *ent*-**10** with L-serine derivative **52**. a) NIS, TfOH, CH_2Cl_2, 4 Å molecular sieves, 4 h.



Scheme 19. Synthesis of glycosylated L-serine derivative **60**. a) Ac_2O, DMAP, pyridine, 4 h; b) **55**, NIS, TfOH, CH_2Cl_2, 4 Å molecular sieves, 2 h; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 5 h; d) **55**, NIS, TfOH, CH_2Cl_2, 4 Å molecular sieves, 1 h; e) 1 bar H_2, Pd/C, EtOAc, 12 h; f) Ac_2O, DMAP, pyridine, 2 h; g) SmI_2, THF, 1 h. DMAP = *N*,*N*-dimethylaminopyridine.

as single diastereomers in moderate to good yields. Since a smooth removal of the TBS-protection group in **58** was not possible, further studies were performed with acetylated intermediate **57**. Hydrogenolysis of **57** by Pd/C catalysis did not lead to cleavage of the N–O bond, but only to debenzylation of the starting material. Gratifyingly, the N–O bond of the resulting 1,2-oxazine **59** could smoothly be cleaved by samarium diiodide in tetrahydrofuran after N-acetylation of the obtained intermediate.[8a,25] The resulting glycosylated L-serine derivative **60** should be a good building block for the incorporation into peptides providing novel compounds being of interest for chemical biology.[26]

Conclusion

A fairly efficient approach to variably configured C2-branched 4-amino sugars is presented. The Lewis acid mediated rearrangement of enantiopure 1,2-oxazines directly deliv-

ers internally protected amino sugar building blocks as common intermediates, which are suitable for the smooth incorporation into oligosaccharides or glycosylated amino acids. Rearrangement products such as **10** and **17** can directly be used as glycosyl donor equivalents in glycosidations with simple alcohols, natural carbohydrate derivatives, carbohydrate mimetics, or with amino acid derivatives. Simple subsequent reductive transformations deliver the free amino sugar units under mild conditions. By this strategy methyl glycosides with various configurations (**28**, **29**, *ent*-**28**, *ent*-**29** and **34**), di- and trisaccharides (**44**, **46**, **47** and **51**), a bivalent amino sugar derivative (**54**), and a glycosylated L-serine derivative (**60**) have been synthesized with a minimum of protective group transformations. Of particular importance is the fact that the amino sugar equivalents are easily available in both enantiomeric series. In addition, due to the easy availability of the starting 1,2-oxazines such as *syn*-**3** many compounds are smoothly accessible in fair scale (up to gram quantities).

The presented results complement our previous reports about the synthesis of enantiopure aminopyrans and aminooxepanes such as **61**–**64** which are available via Lewis acid mediated cyclizations of 1,2-oxazines[9b,c] or related 1,3-dioxolanyl-substituted enol ethers[27] (Figure 3).

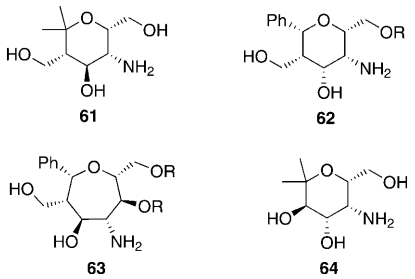
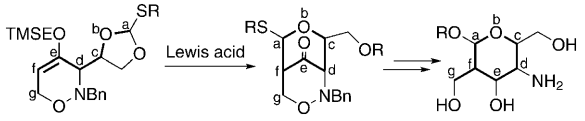


Figure 3. Enantiopure aminopyrans **61**, **62** and **64**, and aminooxepane **63**.

These compounds have been termed as carbohydrate mimetics since they represent C-glycosides of the C2-branched amino sugars described here. The use of thiophenyl-substituted 1,2-oxazine derivatives now allows not only the synthesis of mimetics but of "real" carbohydrates bearing an anomeric center (Scheme 20). The pyranose skeleton of the branched amino sugars, comprising atoms a–g, is derived from their linear arrangement in the precursor 1,2-oxazines which rearrange in an aldol-type reaction.

Our methods should be very useful for chemical glycodiversifications where the original carbohydrates in natural products are modified or replaced by synthetic analogues. Unusual amino sugar building blocks such as presented in this work can, for example, be incorporated into new aminoglycoside mimetics in order to improve the understanding of the molecular mechanism of aminoglycoside–RNA interactions.[28]



Scheme 20. Synthesis of amino sugar derivatives by Lewis acid promoted rearrangement of 1,2-oxazines.

Experimental Section

General Methods: See Supporting Information.

(3*S*,4′*S*)-(2-Benzyl-3-(2-phenylthio-[1,3]dioxolan-4-yl)-4-(2-trimethylsilylethoxy)-3,6-dihydro-2*H*-[1,2]oxazine (*syn*-7): Diol *syn*-**5** (4.50 g, 12.8 mmol), cerium ammonium nitrate (577 mg, 1.05 mmol) and trimethyl orthoformate (4.21 mL, 4.08 g, 38.4 mmol) were dissolved in CH_2Cl_2 (170 mL) and the mixture was stirred for 1 h. After addition of a saturated solution of Na_2CO_3, the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and concentrated to dryness. The resulting colorless oil was dissolved in CH_2Cl_2 (90 mL). Freshly distilled (phenylthio)trimethylsilane (6.05 mL, 5.84 g, 32.0 mmol) and trimethylsilyl triflate (139 μL, 171 mg, 0.768 mmol) were added and the mixture was stirred for 3 h. The reaction mixture was quenched by addition of 10% aqueous NaOH solution and after separation of the layers the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Fast flash column chromatography (silica gel, EtOAc/hexane 1:20) afforded *syn*-**7** (d.r. 1:1) as colorless oil (5.40 g, 89%), which should be stored in the freezer due to its low stability. $[\alpha]_D^{22} = -55.8$ ($c = 1.35$, $CHCl_3$); diastereomer **a**: ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 0.06$ (s, 9H, $SiMe_3$), 0.96–1.15 (m, 2H, CH_2Si), 3.33 (dd, $J = 6.8$, 1.0 Hz, 1H, 3-H), 3.71–3.89 (m, 2H, OCH_2), 4.09–4.19 (m, 5H, NCH_2, 5′-H, 6-H), 4.39–4.45 (m, 1H, 6-H), 4.74 (dd, $J = 3.4$, 1.8 Hz, 1H, 5-H), 4.94 (dd, $J = 13.6$, 6.8 Hz, 1H, 4′-H), 6.63 (s, 1H, 2′-H), 7.21–7.37 (m, 6H, Ph), 7.38–7.42 (m, 1H, Ph), 7.43–7.46 (m, 1H, Ph), 7.50–7.55 (m, 1H, Ph), 7.56–7.61 ppm (m, 1H, Ph); ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta = -1.3$ (q, $SiMe_3$), 17.6 (t, CH_2Si), 58.4 (t, NCH_2), 60.5 (t, C-6), 62.8 (d, C-3), 64.7 (t, OCH_2), 66.7 (t, C-5′), 74.6 (d, C-4′), 93.5 (d, C-5), 112.2 (d, C-2′), 127.2–133.7 (several d, s, Ph), 150.0 ppm (s, C-4); diastereomer **b**: ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 0.08$ (s, 9H, $SiMe_3$), 0.96–1.15 (m, 2H, CH_2Si), 3.43 (dd, $J = 7.7$, 1.1 Hz, 1H, 3-H), 3.71–3.89 (m, 2H, OCH_2), 4.06 (dd, $J = 9.3$, 6.0 Hz, 1H, 5′-H), 4.09–4.19 (m, 1H, 6-H), 4.23 (t, $J = 9.3$ Hz, 1H, 5′-H), 4.39–4.45 (m, 3H, NCH_2, 6-H), 4.59 (ddd, $J = 9.3$, 7.7, 6.0 Hz, 1H, 4′-H), 4.76 (dd, $J = 3.4$, 1.8 Hz, 1H, 5-H), 6.65 (s, 1H, 2′-H), 7.21–7.37 (m, 6H, Ph), 7.38–7.42 (m, 1H, Ph), 7.43–7.46 (m, 1H, Ph), 7.50–7.55 (m, 1H, Ph), 7.56–7.61 ppm (m, 1H, Ph); ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta = -1.3$ (q, $SiMe_3$), 17.6 (t, CH_2Si), 58.4 (t, NCH_2), 60.5 (t, C-6), 63.7 (d, C-3), 66.1 (t, C-5′), 64.7 (t, OCH_2), 76.4 (d, C-4′), 93.5 (d, C-5), 112.4 (d, C-2′), 127.2–133.7 (several d, s, Ph), 150.0 ppm (s, C-4); IR (film): $\tilde{\nu} = 3090$–2840 (=C–H, C–H), 1670 cm^{-1} (C=C); ESI-TOF: m/z: calcd for $[C_{25}H_{33}NO_4SSi+H]^+$: 472.1972; found: 472.1945.

(1*S*,5*S*,6*S*,8*S*)-2-Benzyl-8-hydroxymethyl-6-phenylthio-3,7-dioxa-2-aza-bicyclo[3.3.1]nonan-9-one (9): 1,2-Oxazine *syn*-**7** (4.50 g, 9.54 mmol) was dissolved in CH_2Cl_2 (100 mL), cooled to −30 °C and treated with trimethylsilyl triflate (3.47 mL, 4.25 g, 19.1 mmol). The mixture was allowed to reach RT over 16 h without removing the cooling bath. After quenching the reaction mixture with H_2O, the layers were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Column chromatography (silica gel, EtOAc/hexane 1:3) provided **9** as colorless oil (2.67 g, 75%). $[\alpha]_D^{22} = +57.5$ ($c = 0.44$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta =$ 2.29 (br s, 1H, OH), 2.98 (ddt, $J = 6.4$, 3.2, 1.5 Hz, 1H, 5-H), 3.34 (t, $J =$ 1.5 Hz, 1H, 1-H), 3.69 (dd, $J = 10.9$, 5.5 Hz, 1H, 8-CH_2), 3.73 (td, $J = 5.5$, 1.5 Hz, 1H, 8-H), 3.94 (d, $J = 13.3$ Hz, 1H, NCH_2), 3.98 (dd, $J = 10.9$, 5.5 Hz, 1H, 8-CH_2), 4.19 (d, $J = 13.3$ Hz, 1H, NCH_2), 4.52 (ddd, $J = 12.0$, 6.4, 0.9 Hz, 1H, 4-H), 4.76 (dd, $J = 12.0$, 3.2 Hz, 1H, 4-H), 5.07 (s, 1H, 6-

H), 7.24–7.37 (m, 8H, Ph), 7.45–7.51 ppm (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 54.4 (d, C-5), 61.2 (t, NCH_2), 62.6 (t, 8-CH_2), 68.5 (t, C-4), 71.5 (d, C-1), 81.1 (d, C-8), 88.4 (d, C-6), 128.0, 128.3, 128.7, 129.1, 129.4, 132.1, 132.9, 135.5 (6 d, 2 s, Ph), 204.1 ppm (s, C-9); IR (film): $\tilde{\nu}$ = 3450 (OH), 3090–2860 (=C–H, C–H), 1730 cm^{-1} (C=O); ESI-TOF: *m*/*z*: calcd for $[M+H]^+$: 372.1264; found: 372.1264; elemental analysis calcd (%) for $C_{20}H_{21}NO_4S$ (371.5): C 64.67, H 5.70, N 3.77, S 8.63, found: C 64.85, H 5.42, N 3.79, S 8.41.

(1*S*,5*S*,6*S*,8*S*)-2-Benzyl-8-(*tert*-butyldimethylsiloxymethyl)-6-phenylthio-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-one (10):

Method A: 1,2-Oxazine *syn*-**7** (105 mg, 0.222 mmol) was dissolved in CH_2Cl_2 (2 mL), cooled to −30 °C and treated with *tert*-butyldimethylsilyl triflate (155 μL, 178 mg, 0.666 mmol). The mixture was allowed to reach RT over 16 h without removing the cooling bath. After cooling to 0 °C, NEt_3 (47 μL, 34 mg, 0.333 mmol) was added followed by addition of a saturated solution of NH_4Cl. The layers were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, EtOAc/hexane 1:10) provided **10** as colorless crystals (68 mg, 63 %).

Method B: Compound **9** (570 mg, 1.53 mmol) was dissolved in THF (6 mL). Imidazole (209 mg, 3.07 mmol) and TBSCl (345 mg, 2.30 mmol) were added and the resulting reaction mixture was stirred for 4 h at RT. The mixture was filtered and after addition of water the mixture was extracted three times with Et_2O. The combined organic layers were dried with Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, EtOAc/hexane 1:10) provided **10** as colorless crystals (580 mg, 78 %). M.p. 81 °C; $[\alpha]_D^{22}$ = +22.9 (*c* = 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.00, 0.03 (2 s, 6H, $SiMe_2$), 0.84 (s, 9H, *t*Bu), 3.02 (m, 1H, 5-H), 3.57 (t, *J* = 1.6 Hz, 1H, 1-H), 3.71 (ddd, *J* = 8.0, 5.5, 1.6 Hz, 1H, 8-H), 3.86 (dd, *J* = 9.8, 5.5 Hz, 1H, 8-CH_2), 3.94 (dd, *J* = 9.8, 8.0 Hz, 1H, 8-CH_2), 3.98 (d, *J* = 14.2 Hz, 1H, NCH_2), 4.15 (d, *J* = 14.2 Hz, 1H, NCH_2), 4.43 (ddd, *J* = 11.9, 7.2, 0.4 Hz, 1H, 4-H), 4.71 (dd, *J* = 11.9, 3.3 Hz, 1H, 4-H), 5.04 (m, 1H, 6-H), 7.26–7.39 (m, 8H, Ph), 7.47–7.50 ppm (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = −5.5 (q, $SiMe_2$), 18.1, 25.8 (s, q, *t*Bu), 54.7 (d, C-5), 61.2 (t, 8-CH_2), 61.7 (t, NCH_2), 68.1 (t, C-4), 71.8 (d, C-1), 81.6 (d, C-8), 88.5 (d, C-6), 127.5, 128.0, 128.4, 128.7, 129.2, 131.9, 133.2, 136.3 (6 d, 2 s, Ph), 204.5 ppm (s, C-9); IR (KBr): $\tilde{\nu}$ = 3070–2840 (=C–H, C–H), 1720 cm^{-1} (C=O); ESI-TOF: *m*/*z*: calcd for $[M+H]^+$: 486.2129; found: 486.2130; elemental analysis calcd (%) for $C_{26}H_{35}NO_4SSi$ (485.7): C 64.29, H 7.26, N 2.88, S 6.60, found: C 64.28, H 7.36, N 2.85, S 6.74.

(1*R*,5*S*,6*S*,8*S*,9*R*)-2-Benzyl-8-hydroxymethyl-6-phenylthio-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (24): Ketone **9** (1.10 g, 2.96 mmol) was dissolved in EtOH (22 mL) and the solution was cooled to −40 °C. Sodium borohydride (198 mg, 5.21 mmol) was added and the mixture was stirred at this temperature for 3 h. Then the solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 and H_2O. The layers were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Recrystallisation from EtOAc/hexane provided **24** as colorless crystals (1.00 g, 90 %). M.p. 167 °C; $[\alpha]_D^{22}$ = −48.7 (*c* = 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.23 (dd, *J* = 7.6, 3.4 Hz, 1H, OH), 2.27 (s, 1H, 5-H), 3.06 (s, 1H, 1-H), 3.67 (d, *J* = 10.7 Hz, 1H, OH), 3.69–3.75 (m, 2H, 8-H, 8-CH_2), 3.84 (dt, *J* = 10.7, 2.9 Hz, 1H, 9-H), 4.03 (d, *J* = 14.0 Hz, 1H, NCH_2), 4.06 (m, 1H, 8-CH_2), 4.23 (d, *J* = 14.0 Hz, 1H, NCH_2), 4.26–4.33 (m, 2H, 4-H), 5.03 (s, 1H, 6-H), 7.24–7.36 (m, 8H, Ph), 7.45–7.49 ppm (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 40.4 (d, C-5), 61.2 (d, C-1), 62.1 (t, NCH_2), 63.4 (t, 8-CH_2), 66.0 (t, C-4), 70.3 (d, C-9), 80.5 (d, C-8), 86.9 (d, C-6), 127.6, 127.7, 128.6, 128.7, 129.2, 131.2, 134.2, 137.1 ppm (6 d, 2 s, Ph); IR (KBr): $\tilde{\nu}$ = 3305 (OH), 2960–2855 cm^{-1} (C–H); ESI-TOF: *m*/*z*: calcd for $[M+H]^+$: 374.1421; found: 374.1433; elemental analysis calcd (%) for $C_{20}H_{23}NO_4S$ (373.5): C 64.32, H 6.21, N 3.75, S 8.59; found: C 64.31, H 6.02, N 3.76, S 8.99.

(1*S*,5*R*,6*S*,8*S*)-2-Benzyl-8-hydroxymethyl-6-methoxy-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-one (25): Ketone **9** (1.50 g, 4.03 mmol) was dissolved in MeOH (50 mL). *N*-Bromosuccinimide (899 mg, 5.26 mmol) was added and the mixture was stirred for 30 min at RT. The reaction mixture was quenched by the addition of a saturated solution of $NaHCO_3$. After addition of CH_2Cl_2 the layers were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Column chromatography (silica gel, EtOAc/hexane 1:2) provided **25** as colorless crystals (1.01 g, 85 %). M.p. 96 °C; $[\alpha]_D^{22}$ = +172.2 (*c* = 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.69 (m, 1H, 5-H), 3.19 (t, *J* = 2.0 Hz, 1H, 1-H), 3.37 (s, 3H, OMe), 3.88 (dd, *J* = 11.8, 5.0 Hz, 1H, 8-CH_2), 3.96 (d, *J* = 12.9 Hz, 1H, NCH_2), 4.01 (dd, *J* = 11.8, 5.0 Hz, 1H, 8-CH_2), 4.11 (td, *J* = 5.0, 2.0 Hz, 1H, 8-H), 4.19 (d, *J* = 12.9 Hz, 1H, NCH_2), 4.42 (ddd, *J* = 12.0, 2.5, 2.0 Hz, 1H, 4-H), 4.68 (ddd, *J* = 12.0, 4.1, 1.4 Hz, 1H, 4-H), 5.25 (s, 1H, 6-H), 7.26–7.35 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 53.6 (d, C-5), 55.1 (q, OMe), 58.6 (t, NCH_2), 63.4 (t, 8-CH_2), 70.2 (d, C-1), 70.4 (t, C-4), 74.2 (d, C-8), 104.3 (d, C-6), 128.1, 128.8, 129.1, 135.1 (3 d, s, Ph), 204.0 ppm (s, C-9); IR (KBr): $\tilde{\nu}$ = 3490 (OH), 2990–2820 (C–H), 1725 cm^{-1} (C=O); ESI-TOF: *m*/*z*: calcd for $[M+H]^+$: 294.1336; found: 294.1344; elemental analysis calcd (%) for $C_{15}H_{19}NO_5$ (293.3): C 61.42, H 6.53, N 4.78, found: C 61.09, H 6.41, N 4.97.

(1*R*,5*S*,6*S*,8*S*,9*R*)-2-Benzyl-8-hydroxymethyl-6-methoxy-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (26): Compound **24** (250 mg, 0.670 mmol) was dissolved in MeOH (10 mL). *N*-Bromosuccinimide (171 mg, 1.01 mmol) was added and the mixture was stirred for 30 min at RT. The reaction mixture was quenched by the addition of a saturated solution of $NaHCO_3$. After addition of CH_2Cl_2 the layers were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, EtOAc/hexane 1:1) and recrystallisation from EtOAc/hexane provided **26** as colorless crystals (190 mg, 96 %). M.p. 137 °C; $[\alpha]_D^{22}$ = +126.8 (*c* = 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.03 (m, 1H, 5-H), 2.79 (s, 1H, OH), 3.02 (m, 1H, 1-H), 3.37 (s, 3H, OMe), 3.39 (s, 1H, OH), 3.80 (dt, *J* = 12.1, 0.8 Hz, 1H, 4-H), 3.81–3.84 (m, 1H, 8-CH_2), 3.97 (ddd, *J* = 6.1, 4.4, 1.4 Hz, 1H, 8-H), 4.03 (dd, *J* = 11.0, 6.1 Hz, 1H, 8-CH_2), 4.08 (d, *J* = 13.9 Hz, 1H, NCH_2), 4.27 (dt, *J* = 9.6, 3.3 Hz, 1H, 9-H), 4.31 (d, *J* = 13.9 Hz, 1H, NCH_2), 4.38 (dd, *J* = 12.1, 4.5 Hz, 1H, 4-H), 5.05 (d, *J* = 1.2 Hz, 1H, 6-H), 7.26–7.30, 7.31–7.36 ppm (2 m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 39.1 (d, C-5), 55.0 (q, OMe), 61.1 (t, NCH_2), 61.9 (d, C-1), 64.0 (t, 8-CH_2), 64.3 (d, C-9), 66.1 (t, C-4), 73.9 (d, C-8), 102.6 (d, C-6), 127.6, 128.6, 128.7, 137.4 ppm (3 d, s, Ph); IR (KBr): $\tilde{\nu}$ = 3330 (OH), 3000–2830 cm^{-1} (C–H); ESI-TOF: *m*/*z*: calcd for $[M+H]^+$: 296.1492; found: 296.1506; elemental analysis calcd (%) for $C_{15}H_{21}NO_5$ (295.3): C 61.00, H 7.17, N 4.74; found: C 61.16, H 7.09, N 4.77.

(1*R*,5*S*,6*S*,8*S*,9*S*)-2-Benzyl-8-hydroxymethyl-6-methoxy-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (27): Compound **25** (130 mg, 0.440 mmol) was dissolved in THF (3 mL) and the solution was cooled to −30 °C. A solution of L-selectride (1.0 M in THF, 1.45 mL, 1.45 mmol) was added carefully and the mixture was stirred at this temperature for 3 h. After quenching the reaction mixture with a saturated solution of NH_4Cl, EtOAc and H_2O were added. The layers were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, EtOAc/hexane 2:1) and recrystallisation from EtOAc/hexane provided **27** as colorless crystals (95 mg, 73 %). M.p. 112 °C; $[\alpha]_D^{22}$ = +147.1 (*c* = 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.17 (m, 1H, 5-H), 2.88 (m, 1H, 1-H), 3.43 (s, 3H, OMe), 3.68 (dd, *J* = 9.3, 2.0 Hz, 1H, OH), 3.87 (ddd, *J* = 11.9, 9.3, 3.9 Hz, 1H, 8-CH_2), 3.92 (dd, *J* = 12.2, 1.5 Hz, 1H, 4-H), 3.97 (ddd, *J* = 11.9, 3.9, 2.0 Hz, 1H, 8-CH_2), 4.16 (d, *J* = 13.1 Hz, 1H, NCH_2), 4.20 (dt, *J* = 5.9, 3.9 Hz, 1H, 8-H), 4.29 (d, *J* = 13.1 Hz, 1H, NCH_2), 4.34 (dd, *J* = 12.2, 2.6 Hz, 1H, 4-H), 4.39 (dd, *J* = 8.6, 3.7 Hz, 1H, 9-H), 4.46 (d, *J* = 8.6 Hz, 1H, OH), 5.05 (s, 1H, 6-H), 7.24–7.34 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 37.8 (d, C-5), 55.1 (q, OMe), 56.8 (t, NCH_2), 59.5 (d, C-1), 61.8 (d, C-9), 64.8 (t, 8-CH_2), 66.1 (t, C-4), 66.5 (d, C-8), 102.3 (d, C-6), 127.7, 128.5, 128.6, 136.3 ppm (3 d, s, Ph); IR (KBr): $\tilde{\nu}$ = 3400, 3350 (OH), 3010–2830 cm^{-1} (C–H); ESI-TOF: *m*/*z*: calcd for $[M+H]^+$: 296.1492; found: 296.1496; elemental analysis calcd (%) for $C_{15}H_{21}NO_5$ (293.5): C 61.00, H 7.17, N 4.74; found: C 60.98, H 7.21, N 4.71.

Methyl 4-amino-2,4-dideoxy-2-hydroxymethyl-α-D-talopyranoside (28): A suspension of palladium on charcoal (10 % Pd, 100 mg) in MeOH (3 mL)

was saturated with hydrogen for 1 h. After addition of bicyclic alcohol **26** (62 mg, 0.210 mmol) in MeOH (2 mL), hydrogen was bubbled through the mixture for another 30 min and the reaction mixture was stirred under an atmosphere of hydrogen for 18 h. Filtration through a short pad of celite and concentration of the solution to dryness afforded methyl glycoside **28** as pale yellowish oil (37 mg, 85%). Purity according to NMR: >95%. $[\alpha]_D^{22}=+92.8$ ($c=1.06$, H_2O); ^{1}H NMR (D_2O, 500 MHz): $\delta=2.07$ (td, $J=5.9$, 3.8 Hz, 1H, 2-H), 3.14 (dd, $J=4.1$, 2.3 Hz, 1H, 4-H), 3.37 (s, 3H, OMe), 3.70 (dd, $J=11.8$, 3.6 Hz, 1H, 6-H), 3.71 (dd, $J=11.4$, 5.9 Hz, 1H, 2-CH_2), 3.75 (dd, $J=11.4$, 3.8 Hz, 1H, 2-CH_2), 3.77 (dd, $J=11.8$, 7.8 Hz, 1H, 6-H), 3.91 (ddd, $J=7.8$, 3.6, 2.3 Hz, 1H, 5-H), 4.22 (dd, $J=5.9$, 4.1 Hz, 1H, 3-H), 4.88 ppm (s, 1H, 1-H); ^{13}C NMR (D_2O, 126 MHz): $\delta=44.7$ (d, C-2), 49.5 (d, C-4), 54.5 (q, OMe), 57.3 (t, 2-CH_2), 61.5 (t, C-6), 66.0 (d, C-3), 70.1 (d, C-5), 100.4 ppm (d, C-1); IR (film): $\tilde{\nu}$ = 3600–3000 (OH, NH), 2990–2730 cm^{-1} (C–H); ESI-TOF: m/z: calcd for $[C_8H_{17}NO_5+H]^+$: 208.1179; found: 208.1180.

Methyl 4-amino-2,4-dideoxy-2-hydroxymethyl-α-D-idopyranoside (29): A suspension of palladium on charcoal (10% Pd, 80 mg) in MeOH (3 mL) was saturated with hydrogen for 1 h. After addition of bicyclic alcohol **27** (60 mg, 0.203 mmol) in MeOH (2 mL) hydrogen was bubbled through the mixture for another 30 min and the reaction mixture was stirred under an atmosphere of hydrogen for 18 h. Filtration through a short pad of celite and concentration of the solution to dryness afforded methyl glycoside **29** as colorless crystals (37 mg, 88%). Purity according to NMR: >95%. M.p. 142°C; $[\alpha]_D^{22}=+74.7$ ($c=0.18$, H_2O); ^{1}H NMR (D_2O, 500 MHz): $\delta=1.77$ (m, 1H, 2-H), 2.96 (dd, $J=6.5$, 4.3 Hz, 1H, 4-H), 3.46 (s, 3H, OMe), 3.67 (t, $J=6.5$ Hz, 1H, 3-H), 3.74 (dd, $J=7.9$, 3.6 Hz, 1H, 2-CH_2), 3.75–3.80 (m, 2H, 6-H), 3.81 (dd, $J=8.7$, 3.6 Hz, 1H, 2-CH_2), 4.18 (ddd, $J=8.1$, 4.3, 4.2 Hz, 1H, 5-H), 5.77–5.85 ppm (m, 1H, 1-H, hidden by the solvent residue peak); ^{13}C NMR (D_2O, 126 MHz): $\delta=45.0$ (d, C-2), 50.9 (d, C-4), 53.5 (q, OMe), 57.1, 58.0 (2 t, C-6, 2-CH_2), 67.9 (d, C-3), 68.5 (d, C-5), 97.4 ppm (d, C-1); IR (KBr): $\tilde{\nu}$ = 3360–3175 (OH, NH), 2980–2820 cm^{-1} (C–H); ESI-TOF: m/z: calcd for $[C_8H_{17}NO_5+H]^+$: 208.1179; found: 208.1185.

Disaccharide precursor 38: To a solution of ketone **10** (500 mg, 1.03 mmol) and alcohol **25** (400 mg, 1.34 mmol) in CH_2Cl_2 (20 mL) were added 4 Å molecular sieves (700 mg) and *N*-iodosuccinimide (463 mg, 2.06 mmol). After stirring the mixture for 30 min at RT it was cooled to 0°C and trifluoromethanesulfonic acid (17 μL, 0.206 mmol) was added. The mixture was stirred at RT for 4 h, then diluted with CH_2Cl_2 and filtered through a short pad of celite. The solution was subsequently washed with a saturated solution of $NaHCO_3$ and a 1M solution of $Na_2S_2O_3$, dried with $MgSO_4$, filtered and concentrated. Column chromatography (silica gel, EtOAc/hexane 1:3) provided **38** as colorless crystals (543 mg, 79%). M.p. 58°C; $[\alpha]_D^{22}=+117.2$ ($c=0.15$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=0.02$, 0.04 (2 s, 6H, $SiMe_2$), 0.83 (s, 9H, *t*Bu), 2.03 (m_c, 1H, 5′-H), 2.65 (m_c, 1H, 5-H), 3.14 (m, 1H, 1-H), 3.29 (m_c, 1H, 1′-H), 3.34 (s, 3H, OMe), 3.84 (dd, $J=8.9$, 4.9 Hz, 1H, 8′-CH_2), 3.89–3.93 (m, 3H, 8-CH_2, NCH_2), 3.98 (d, $J=12.4$ Hz, 1H, NCH_2), 4.04 (t, $J=8.9$ Hz, 1H, 8′-CH_2), 4.07–4.20 (m, 4H, 4′-H, 8′-H, NCH_2), 4.20 (dd, $J=6.5$, 2.2 Hz, 1H, 8-H), 4.38 (dd, $J=10.4$, 1.6 Hz, 1H, 4′-H), 4.40 (dd, $J=11.8$, 5.4 Hz, 1H, 4-H), 4.71 (dd, $J=11.8$, 3.8 Hz, 1H, 4-H), 4.97 (d, $J=1.5$ Hz, 1H, 6′-H), 5.04 (d, $J=1.4$ Hz, 1H, 6-H), 7.21–7.36 ppm (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta=-5.5$ (q, $SiMe_2$), 18.1, 25.8 (s, q, *t*Bu), 53.2 (d, C-5′), 53.8 (d, C-5), 54.9 (q, OMe), 58.5, 59.4 (2 t, NCH_2), 61.2 (t, 8′-CH_2), 65.6 (t, 8-CH_2), 67.6 (d, C-1), 69.9 (t, C-4′), 70.1 (d, C-1′), 70.9 (t, C-4), 72.8 (d, C-8), 75.3 (d, C-8′), 103.5 (d, C-6′), 104.2 (d, C-6), 127.5, 127.8, 128.4, 128.5, 128.8, 129.6, 135.4, 136.0 (6 d, 2 s, Ph), 204.1, 204.9 ppm (2 s, C-9, C-9′); IR (KBr): $\tilde{\nu}$ = 3090–2830 (=C-H, C–H), 1760, 1730 cm^{-1} (C=O); ESI-TOF: m/z: calcd for $[M+H]^+$: 669.3202; found: 669.3195; elemental analysis calcd (%) for $C_{35}H_{48}N_2O_9Si$ (668.8): C 62.85, H 7.23, N 4.19; found: C 62.82, H 7.34, N 4.07.

Reduction of disaccharide precursor 38: Compound **38** (75 mg, 0.112 mmol) was dissolved in THF (2.5 mL) and the solution was cooled to 0°C. A solution of L-selectride (1.0M in THF, 336 μL, 0.336 mmol) was added and the mixture was stirred at this temperature for 2 h. After quenching the mixture with a saturated solution of NH_4Cl, EtOAc and H_2O were added. The layers were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered and concentrated. Column chromatography (silica gel, EtOAc/hexane 2:1) provided the product as a colorless oil (55 mg, 73%). $[\alpha]_D^{22}=+119.6$ ($c=0.43$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=0.06$, 0.07 (2 s, 6H, $SiMe_2$), 0.86 (s, 9H, *t*Bu), 1.92 (m_c, 1H, 5′-H), 2.17 (m_c, 1H, 5-H), 2.79 (m_c, 1H, 1-H), 3.00 (m_c, 1H, 1′-H), 3.34 (s, 3H, OMe), 3.56 (dd, $J=9.8$, 4.8 Hz, 1H, 8-H), 3.78, 3.85 (dd, $J=11.8$, 1.5 Hz, 1H, dd, $J=12.2$, 1.6 Hz, 1H, 4-H, 4′-H), 3.90 (dd, $J=9.7$, 6.0 Hz, 1H, 8′-CH_2), 4.02 (dd, $J=9.7$, 8.0 Hz, 1H, 8′-CH_2), 4.10–4.20 (m, 1H, 4′-H), 4.12 (d, $J=13.2$ Hz, 1H, NCH_2), 4.17 (d, $J=13.2$ Hz, 1H, NCH_2), 4.24–4.31 (m, 3H, 4-H, NCH_2, OH), 4.34 (dd, $J=9.1$, 4.7 Hz, 1H, 9′-H), 4.37 (dd, $J=8.0$, 6.0 Hz, 1H, 8′-H), 4.39–4.45 (m, 2H, 8-CH_2, 9-H), 4.49 (m_c, 1H, 8-CH_2), 4.62 (d, $J=9.1$ Hz, 1H, OH), 4.962, 4.964 (2 s, 1 H each, 6-H, 6′-H), 7.21–7.39 ppm (m, 10H, Ph); ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta=-5.4$, -5.3 (2 q, $SiMe_2$), 18.2, 25.9 (s, q, *t*Bu), 38.01, 38.02 (2 d, C-5, C-5′), 55.2 (q, OMe), 57.4, 58.0 (2 t, NCH_2), 57.8 (d, C-1), 58.5 (d, C-1′), 62.51, 62.52 (2 t, 8-CH_2, 8′-CH_2), 63.9 (d, C-9′), 66.4 (t, C-4), 66.6 (d, C-9), 66.7 (t, C′-4), 67.7 (d, C-8′), 68.3 (d, C-8), 101.2, 102.3 (2 d, C-6, C-6′), 127.1, 127.48, 127.50, 128.2, 128.4, 128.6, 137.0, 138.0 ppm (6 d, 2 s, Ph); IR (film): $\tilde{\nu}$ = 3470 (OH), 3090–2840 cm^{-1} (=C–H, C–H); ESI-TOF: m/z: calcd for $[M+H]^+$: 673.3515; found: 673.3475; elemental analysis calcd (%) for $C_{35}H_{52}N_2O_9Si$ (672.9): C 62.47, H 7.79, N 4.16; found: C 61.94, H 7.80, N 4.03.

α-D-Idopyranoside 44: A suspension of palladium on charcoal (10% Pd, 60 mg) in MeOH (4 mL) was saturated with hydrogen for 1 h. After addition of the above described product (67 mg, 0.10 mmol) in MeOH (3 mL), hydrogen was bubbled through the mixture for another 30 min and the reaction mixture was stirred under an atmosphere of hydrogen for 18 h. Filtration through a short pad of celite and concentration of the solution to dryness afforded **44** as colorless oil (35 mg, 73%). Purity according to NMR: >95%. $[\alpha]_D^{22}=+64.2$ ($c=0.55$, MeOH); ^{1}H NMR (CD_3OD, 500 MHz): $\delta=0.12$ (s, 6H, $SiMe_2$), 0.93 (s, 9H, *t*Bu), 1.65, 1.71 (dt, $J=11.6$, 4.3 Hz, 1H, dt, $J=11.9$, 4.7 Hz, 1H, 2-H, 2′-H), 2.88–2.92 (m, 2H, 4-H, 4′-H), 3.40 (s, 3H, OMe), 3.62–3.79 (m, 7H, 3-H, 3′-H, 6-H, 2-CH_2, 2′-CH_2), 3.83 (dd, $J=11.0$, 5.2 Hz, 1H, 6′-H), 3.88 (dd, $J=11.0$, 5.2 Hz, 1H, 6′-H), 4.02 (dd, $J=10.5$, 5.6 Hz, 1H, 6-H), 4.12 (dd, $J=10.1$, 5.2 Hz, 1H, 5′-H), 4.21 (m_c, 1H, 5-H), 4.76, 4.87–4.92 ppm (d, $J=4.7$ Hz, 1H, 1-H, m, 1H, hidden by solvent residue peak, 1-H, 1′-H); ^{13}C NMR (CD_3OD, 126 MHz): $\delta=-6.6$ (q, $SiMe_2$), 17.8, 25.1 (s, q, *t*Bu), 47.0–49.0 (2 d, C-2, C-2′), 54.0, 54.2 (2 d, C-4, C-4′), 54.7 (q, OMe), 59.5, 59.6 (2 t, 2-CH_2, 2′-CH_2), 62.5 (t, C-6), 67.1 (t, C-6′), 68.3 (d, C-5), 70.2 (d, C-5′), 70.7, 70.8 (2 d, C-3, C-3′), 99.1, 100.1 ppm (2 d, C-1, C-1′); IR (film): $\tilde{\nu}$ = 3375–3125 (OH, NH), 2970–2830 cm^{-1} (C–H); ESI-TOF: m/z: calcd for $[C_{21}H_{44}N_2O_9Si+H]^+$: 497.2889; found: 497.2890.

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