Carbohydrates

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Stereodivergent De Novo Synthesis of Branched Amino Sugars by Lewis Acid Promoted Rearrangement of 1,2-Oxazines**

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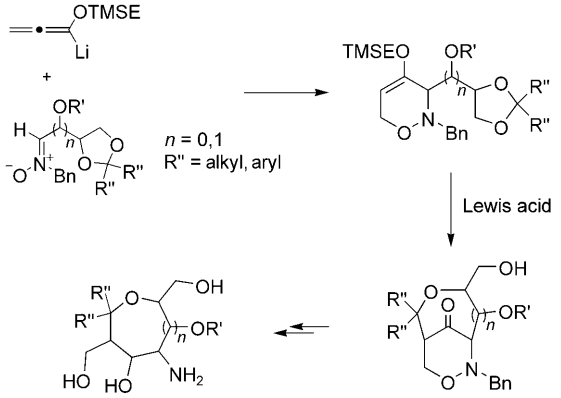
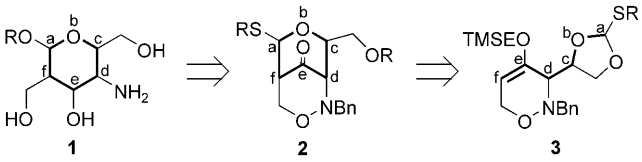
Amino sugars and C-branched sugars are components of a variety of antibiotics and other biologically active natural products.[1] Hence there is a considerable interest in natural product analogues having modified carbohydrate residues;[2] for example, analogues of vancomycin having different amino sugar derivatives, which show a high antibacterial activity against resistant strains.[3] Artificial C2-branched sugars were also used in metabolic oligosaccharide engineering[4] or as inhibitors in Lipid A biosynthesis.[5] Furthermore they are ideal building blocks for the synthesis of C-glycosides.[6] Carbon chains in the 2-position were mainly introduced by addition reactions to glycals[7] or rearrangements of C-glycosides.[8] Herein we describe an efficient and stereodivergent de novo synthesis of C2-branched amino sugars based on our investigations towards Lewis acid promoted rearrangements of 1,2-oxazines into bicyclic products (Scheme 1). These studies led to new carbohydrate mimetics having either tetrahydropyran or oxepane skeletons.[9]



Scheme 1. Enantiopure carbohydrate mimetics by using Lewis acid promoted rearrangements of 1,2-oxazines. TMSE = 2-(trimethylsilyl)-ethyl.

We discovered that appropriately modified 1,2-oxazine derivatives not only allow an entry into mimetics but also into "real" carbohydrates bearing an anomeric carbon center (Scheme 2). The amino sugar derivatives **1** are generated by

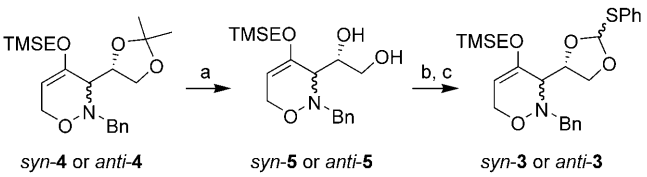


Scheme 2. Retrosynthesis of 4-amino sugar derivatives **1**.

reduction of the keto group and cleavage of the N–O bond in bicyclic compounds **2**, which are obtained by Lewis acid promoted rearrangement of 1,2-oxazines **3**. For the introduction of the desired anomeric center, an appropriate heteroatom has to be connected to C2 of the dioxolane ring of 1,2-oxazines **3** (a in Scheme 2). We chose the phenylthio group, which provided adequate electronic properties for the rearrangement and also served as a leaving group in subsequent glycosidation reactions. This strategy allows control of four stereogenic centers (c, d/f, e), which are constructed during this sequence.

The stereodivergent synthesis of the substrates **3** began with 1,2-oxazines *syn*-**4** and *anti*-**4**, which can be obtained in enantiopure form by the [3+3] cyclization of lithiated alkoxyallenes with aldonitrones on gram scale (Scheme 3).[10] To generate free diols *syn*-**5** and *anti*-**5** a new mild method ($InCl_3/H_2O$ in MeCN) was developed for the hydrolysis of acetonides, which avoided the formation of acid induced cyclization products.[11] The phenylthio-substituted 1,2-oxazines *syn*-**3** and *anti*-**3** were finally obtained via orthoesters[12] and subsequent substitution of the methoxy group by a phenylthio moiety.[13]

Treatment of *syn*-**3** and *anti*-**3** with trialkylsilyl triflates furnished the desired bicyclic ketones (Scheme 4). Compound



Scheme 3. Synthesis of 1,2-oxazines *syn*-**3** and *anti*-**3**. Reagents and conditions: a) $InCl_3$, H_2O, CH_2Cl_2 (*syn*-**5**: 84%; *anti*-**5**: 70%); b) $HC(OMe)_3$, CAN, CH_2Cl_2, RT, 1 h; c) $PhSSiMe_3$, TMSOTf, CH_2Cl_2, RT, 3 h (*syn*-**3**: 89%; *anti*-**3**: 66%, 2 steps). TMSOTf = trimethylsilyl trifluoromethanesulfonate; CAN = cerium ammonium nitrate.

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[+] X-ray crystallographic analysis

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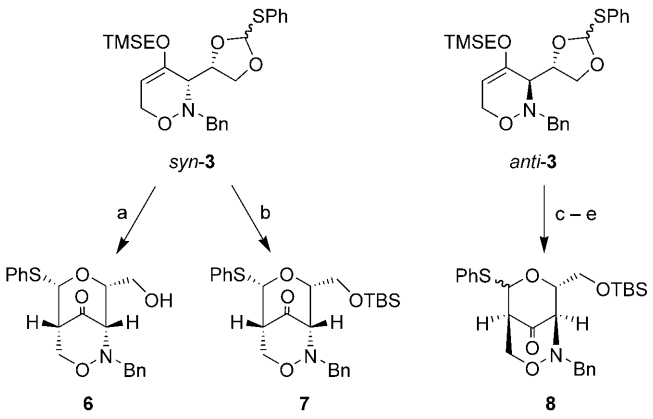
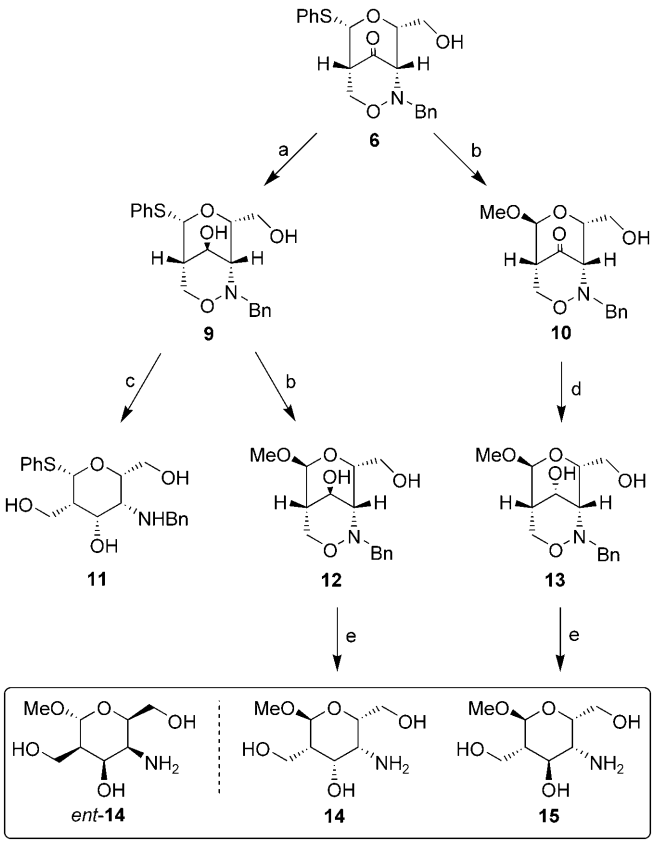


Scheme 4. Lewis acid promoted rearrangement of 1,2-oxazines *syn*-**3** and *anti*-**3** into bicyclic compounds **6**, **7**, and **8**. Reagents and conditions: a) 2 equiv TMSOTf, CH_2Cl_2, −30 °C→RT, 16 h (75%); b) 3 equiv TBSOTf, CH_2Cl_2, −30 °C→RT, 16 h (63%); c) 2.5 equiv TMSOTf, CH_2Cl_2, −30 °C→RT, 21 h; d) TBAF, THF, RT, 7 h; e) TBSOTf, NEt_3, CH_2Cl_2, RT, 3 h (50%, 3 steps, d.r. 3:1). TBS = *tert*-butyldimethylsilyl; TBAF = tetrabutylammonium fluoride.



Scheme 5. Synthesis of 4-amino sugar derivatives **11**, **14**, and **15**. Reagents and conditions: a) $NaBH_4$, EtOH, −40 °C, 3 h (90%); b) NBS, MeOH, RT, 30 min (**10**: 97%; **12**: 85%); c) SmI_2, THF, RT, 4 h (87%); d) $Li(sBu)_3BH$, THF, −30 °C, 3 h (73%); e) 1 bar H_2, 10% Pd/C, MeOH, RT, 17 h (**14**: 85%; **15**: 88%). NBS = *N*-bromosuccinimide.

6 or the TBS-protected derivative **7** were directly obtained as single diastereomers.[14,15] For *anti*-**3** a diastereomeric mixture of bicycles is initially generated; the mixture contained the TMS-protected substrate, the unprotected substrate, and internal hemiacetals. Subsequently, the mixture was treated with TBAF to remove the TMS groups and then reacted with TBSOTf to give compound **8**.[16]

The rearrangement products such as **6** turned out to be ideal starting materials for the stereodivergent synthesis of branched 4-amino sugars, which are easily accessed in three steps as free methyl glycosides **14** and **15** (Scheme 5). The reduction of the carbonyl group in **6** and then the substitution of the phenylthio moiety in the resulting product **9** using methanol furnished bicycle **12** as a single diastereomer. Both rings probably exist in a chairlike conformation, leading to the installation of the methoxy group exclusively in the axial position stabilized by the anomeric effect. Subsequent debenzylation and cleavage of the N–O bond by hydrogenation delivered the free methyl glycoside **14** having a D-talose configuration. Changing the order of the first two steps allows the synthesis of the diastereomer **13**, an epimer of **12** having a different configuration at C3. Reaction of **6** with NBS in methanol led to the formation of **10**, which has an axial methoxy group blocking the side of the pyran from which the subsequent reduction step should occur. The attack of the hydride reagent therefore occurred from the opposite side of the bicycle, selectively providing compound **13**, which upon hydrogenation afforded the free methyl glycoside **15** having a D-idose configuration. A 4-amino sugar derivative **11** having an all-*cis* configuration was obtained from **9** by reductive cleavage of the N–O bond using samarium diiodide.[17] The yields of all steps are good to excellent, permitting the synthesis of all compounds in gram quantities.

The known absolute configuration at C5 together with an X-ray crystallographic analysis of the 4-amino sugar derivative **15** unambiguously proves the configurations of products **9** through **15** (Figure 1).[18] The structure shows a twist-boat conformation with the *cis*-configured hydroxymethyl groups in the equatorial position.

All the compounds described can easily be obtained in either enantiomeric series, as exemplified by the synthesis of

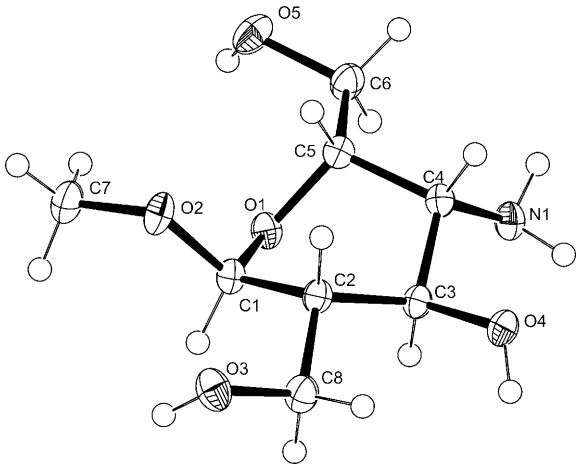
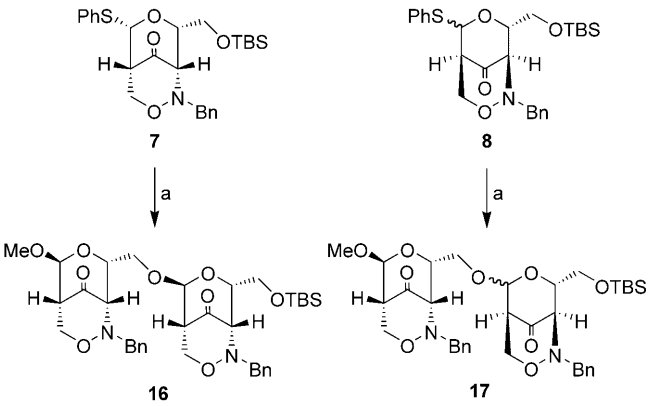


Figure 1. Molecule structure (ORTEP[19]) of 4-amino sugar derivative **15**. Thermal ellipsoids at 50% probability.

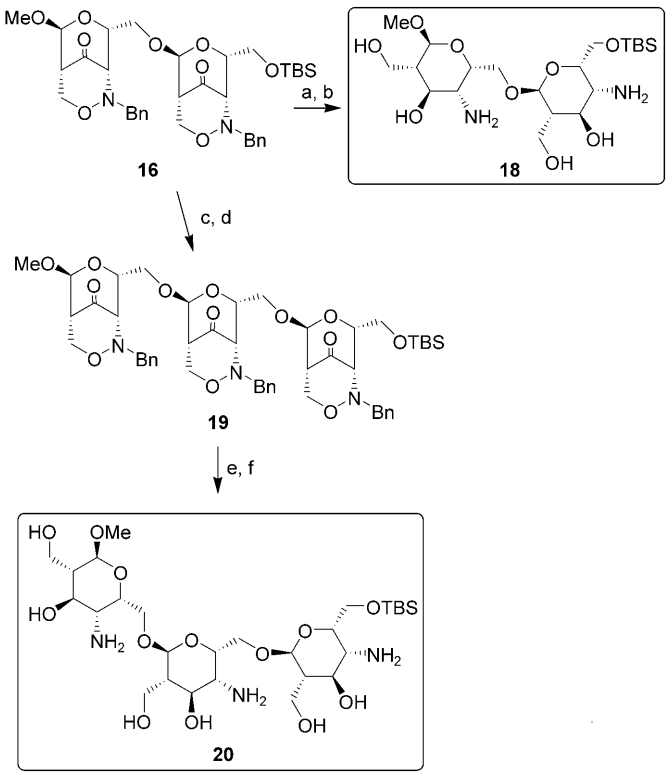
the amino sugars *ent*-**14** (having an L-talose configuration, Scheme 5) and *ent*-**15** (having an L-idose configuration) starting from L-glyceraldehyde-derived 1,2-oxazine *ent-syn*-**3**. Bicycle **8** (Scheme 4), derived from 1,2-oxazine *anti*-**3**, should lead to another set of two diastereomers and their enantiomers in a similar way. Altogether, this would give access to eight different stereoisomers.

The TBS-protected bicycles **7** and **8** can directly be used as glycosyl donor equivalents. To demonstrate this potential, **7** and **8** were connected to glycosyl acceptor **10** using NIS/TfOH.[20] The resulting disaccharide equivalent **16** was obtained in good yield as a single product, whereas **17** was identified as a mixture of two diastereomers (Scheme 6).

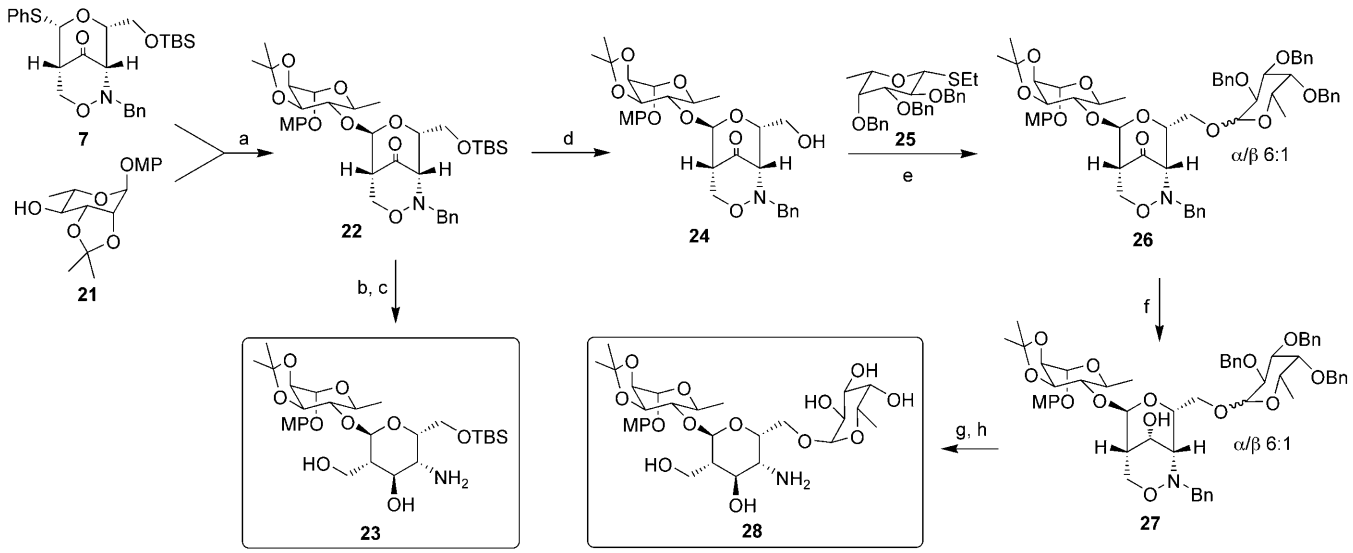


Scheme 6. Reactions of glycosyl donor equivalents **7** and **8**. Reagents and conditions: a) **10**, NIS, TfOH, 4 Å molecular sieves, CH_2Cl_2, RT, 4 h (**16**: 79%; **17**: 92%, d.r. 1:1.2). NIS = *N*-iodosuccinimide; TfOH = trifluoromethanesulfonic acid.

Disaccharide equivalent **16** could be transformed in two steps into the deprotected disaccharide **18** as a single diastereomer (Scheme 7). Alternatively, compound **16** can serve as a glycosyl acceptor after desilylation with TBAF. The reaction of desilylated **16** with **7** furnished the desired product **19**, from which trisaccharide **20** was obtained in a stereose-



Scheme 7. Synthesis of deprotected disaccharide **18** and trisaccharide **20**. Reagents and conditions: a) Li(*s*Bu)$_3$BH, THF, 0 °C, 3 h (73%); b) 1 bar H_2, 10% Pd/C, MeOH, RT, 19 h (73%); c) TBAF, THF, RT, 18 h (83%); d) **7**, NIS, TfOH, 4 Å molecular sieves, CH_2Cl_2, RT, 4 h (72%); e) Li(*s*Bu)$_3$BH, THF, 0 °C→RT, 3 h (84%); f) 1 bar H_2, 10% Pd/C, MeOH, RT, 45 h (66%).



Scheme 8. Synthesis of hybrid di- and trisaccharides **23** and **28**. Reagents and conditions: a) NIS, TfOH, 4 Å molecular sieves, CH_2Cl_2, RT, 4 h (89%); b) Li(*s*Bu)$_3$BH, THF, 0 °C, 3 h (86%); c) 1 bar H_2, 10% Pd/C, MeOH, RT, 21 h (52%); d) TBAF, THF, RT, 18 h (77%); e) NIS, 4 Å molecular sieves, CH_2Cl_2, RT, 1 h (80%); f) Li(*s*Bu)$_3$BH, THF, 0 °C, 3 h (84%); g) Crystallization of α-Fuc anomer from Et_2O (64%); h) 1 bar H_2, 10% Pd/C, MeOH/EtOAc (1:1), RT, 16 h (67%). MP = 4-methoxyphenyl.

lective manner. This repetitive method permits the synthesis of unusual oligosaccharides having different configurations or varying sizes, all of which should be interesting as potential aminoglycoside mimetics.[21]

The efficient syntheses of hybrid systems of the amino sugars, incorporating simple carbohydrates, are easily realized because of the late generation of the free amino sugar units from 1,2-oxazines, which serves to avoid difficult protection group manipulations. This synthesis of hybrid systems was exemplarily demonstrated using L-rhamnose and L-fucose (Scheme 8). Glycosidation of L-rhamnose derivative **21**[22] provided, in excellent yield, disaccharide equivalent **22**, which was stereoselectively transformed into hybrid disaccharide **23** by reduction with L-selectride and subsequent hydrogenolysis. Alternatively, removal of the TBS group in **22** gave alcohol **24**, affording a suitable glycosyl acceptor. Its reaction with commercially available fucosyl donor **25** delivered trisaccharide equivalent **26**, which was stereoselectively reduced to **27**. Hydrogenolysis using palladium on charcoal provided trisaccharide **28**. Building blocks such as **27** could also serve as interesting glycosyl acceptors in the synthesis of complex oligosaccharides.[23]

We have presented an efficient and stereodivergent synthesis of C2-branched 4-amino sugars by using a Lewis acid promoted rearrangement of 1,2-oxazines as the key step.[24] The resulting bicyclic products **7** and **8** can directly be used as (orthogonally) protected glycosyl donor equivalents in glycosidation reactions. Subsequent reductive transformations provide novel oligosaccharides having C2-branched 4-amino sugar units. Our strategy allows access to four different diastereomeric building blocks in both enantiomeric forms, and should therefore make it possible to synthesize a variety of novel saccharides and their analogues.

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