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Synthesis of novel carbohydrate mimetics via 1,2-oxazines*

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Abstract: The combination of lithiated alkoxyallenes with carbohydrate-derived nitrones constitutes a flexible entry to highly functionalized enantiopure 1,2-oxazine derivatives. They can be used as precursors for acyclic and cyclic carbohydrate-like products such as amino sugar alcohols, azetidine and pyrrolidine derivatives. The Lewis acid-promoted rearrangement of 1,3-dioxolanyl-substituted 1,2-oxazines to bicyclic compounds allows an efficient route to novel amino pyran and oxepane derivatives. After subsequent transformations, new carbohydrate mimetics or "real" carbohydrates were obtained in good yield and often in a stereodivergent fashion. These compounds have already been employed for the preparation of unusual di- and trisaccharide derivatives. Several of the products prepared showed interesting biological activities, e.g., as L- and P-selectin inhibitors with IC_{50} values in the subnanomolar range.

Keywords: allenes; carbohydrates; carbohydrate mimetics; nitrones; 1,2-oxazine derivatives; selectin inhibitors; stereocontrolled synthesis.

INTRODUCTION

Carbohydrates have immense importance in biological systems. They are the source of the metabolic energy supply, but also for the fine-tuning of cell–cell interactions and other crucial processes [1]. As a consequence, the chemistry and biochemistry of carbohydrate derivatives is an essential part of biochemical and medicinal research. Owing to the many functional groups and the configurational variety, the number of possible carbohydrate derivatives is huge. Therefore, the synthesis of carbohydrate derivatives is complicated, generally requiring many steps, and a range of selectivity problems has to be solved. The understanding of their biological activity is also difficult due to this complexity. Not surprisingly, the search for simplified compounds similar to carbohydrates, "carbohydrate mimetics", is a matter of current research efforts of many research groups in academia and the pharmaceutical industry [2]. Very often, fairly simple compounds influence biological processes in a similar fashion as natural carbohydrates and can hence lead to a better understanding of these processes. In the best case, the development of new selective drugs, which do not have the disadvantages of carbohydrates such as low oral availability or moderate metabolic stability owing to the glycosidic bonds, is possible.

In this report, we summarize our efforts using 1,2-oxazines for the preparation of a variety of compounds similar to carbohydrate structures. Combination of the C3 building-block alkoxyallene with nitrones not only allowed an entry to unusual carbohydrate derivatives, but also to carbohydrate mimet-

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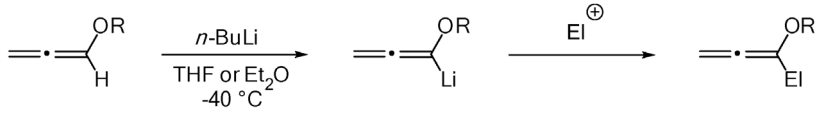
ics such as aza sugars, imino sugars, or carbohydrate-like amino pyran derivatives. Lithiated alkoxyallenes in general have been exploited by us and other groups for the (stereoselective) synthesis of a variety of heterocyclic compounds such as furans, pyrroles, pyridines, piperidine, and 1,2-oxazine derivatives. For the synthesis of rare carbohydrates, we also developed a flexible route via lithiated alkoxyallenes and furan intermediates [3]. These results in various areas of heterocyclic chemistry have been summarized in a number of reviews [4].

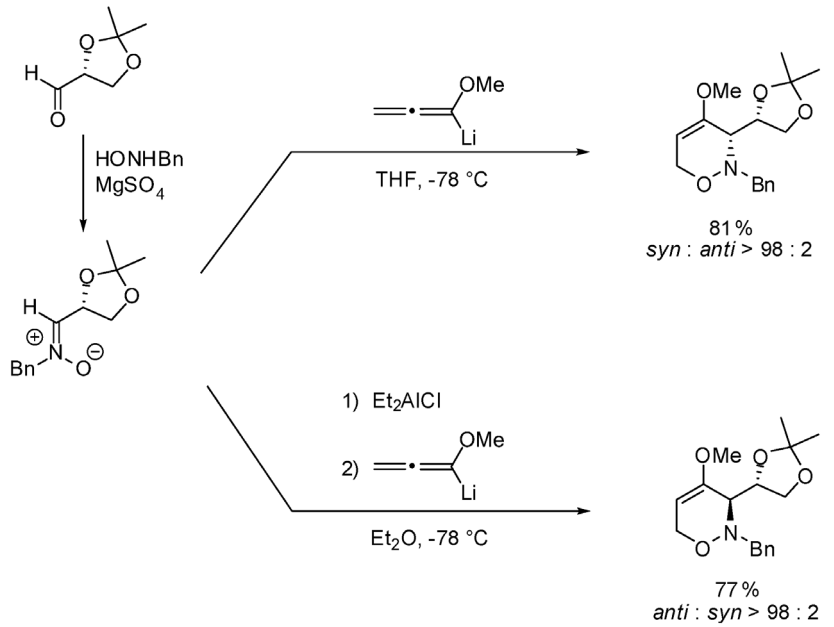
RESULTS AND DISCUSSION

Alkoxyallenes are, in general, prepared by base-catalyzed isomerization of the corresponding alkyl propargyl ethers, and their lithiation is smoothly achieved by treatment with *n*-butyllithium at low temperature in diethylether or tetrahydrofuran [5]. The resulting strong nucleophile is then combined with the required electrophile to generate the respective addition product (Scheme 1). As electrophiles we and others successfully employed carbonyl compounds [5,6], imines, nitriles, and nitrones [4]. Other electrophiles such as alkyl halides or hetero cumulenes are also suitable reaction partners.



Scheme 1 Generation of lithiated alkoxyallenes and addition to electrophiles.

When lithiated alkoxyallenes were combined with nitrones as electrophiles, we expected hydroxylamine derivatives as products. However, in most cases these compounds are not isolable but they directly cyclize to the corresponding 1,2-oxazine derivatives [7]. Scheme 2 illustrates one of the



Scheme 2 Novel stereodivergent entry to enantiopure 1,2-oxazines by reaction of a D-glyceraldehyde-derived nitrone with lithiated methoxyallene.

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most important examples of this overall [3 + 3] cyclization process studied by our group. The use of the D-glyceraldehyde-derived nitrone [8] as starting material not only provided us with highly substituted and functionalized enantiopure 1,2-oxazine derivatives, but this system also allows a stereodivergent approach to these target compounds. Whereas standard conditions furnished the corresponding *syn*-configured 1,2-oxazine derivative, a pre-complexation of the nitrone with a suitable Lewis acid such as diethyl aluminum chloride dramatically changed the reactive conformation of the electrophile, thus leading to the formation of the *anti*-configured 1,2-oxazine in good yield.

Starting from other carbohydrate-derived nitrones, stereoselective syntheses of a range of highly substituted enantiopure 1,2-oxazine derivatives were easily possible (Fig. 1). The framed compounds have been employed for a fairly short entry to neuraminic acid and its derivatives [9]. Amino acid-derived nitrones also provided highly functionalized 1,2-oxazines in a stereoselective fashion [7a].

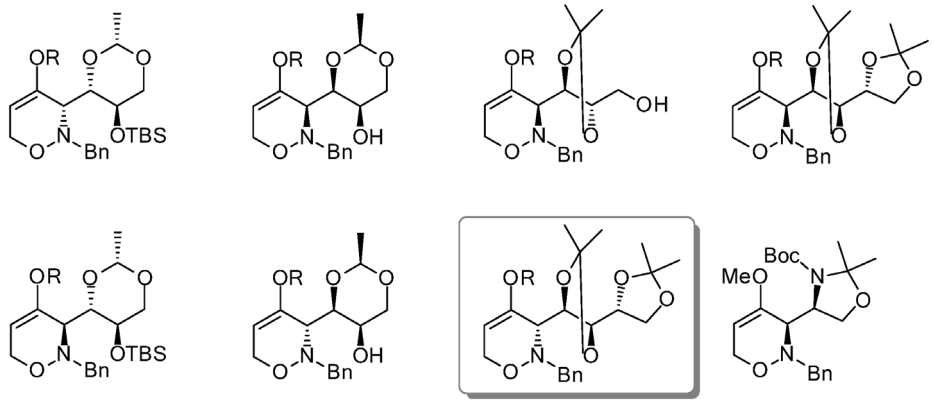

Fig. 1 New carbohydrate-derived *syn*- or *anti*-configured 1,2-oxazines with different side chains.

Since glyceraldehyde is easily available in both enantiomeric forms, the four stereoisomers of the corresponding 1,2-oxazines are smoothly available by the stereodivergent approach illustrated in Scheme 2. The six carbon atoms of these products are functionalized in a differentiated manner and hence allow a large number of chemical transformations. Therefore, they have been employed in our group as starting materials for the synthesis of a variety of highly functionalized compounds, most of them with high similarity to carbohydrates. The enol ether double bond of the 1,2-oxazines was used to introduce additional substituents X and Y (often in a stereoselective manner), the acetonide side chain could be cleaved under acidic conditions, whereas the weak N–O bond can be broken under reductive conditions. The most obvious target compounds are highlighted in Scheme 3. Amino sugars, imino sugars, and aza sugars (still containing the 1,2-oxazine skeleton) should be accessible within a few simple steps. Over the years other products have also been prepared from these model 1,2-oxazine derivatives. Figure 2 summarizes compounds prepared in simple procedures from the *syn*-configured 4-methoxy-substituted 1,2-oxazine derivative.

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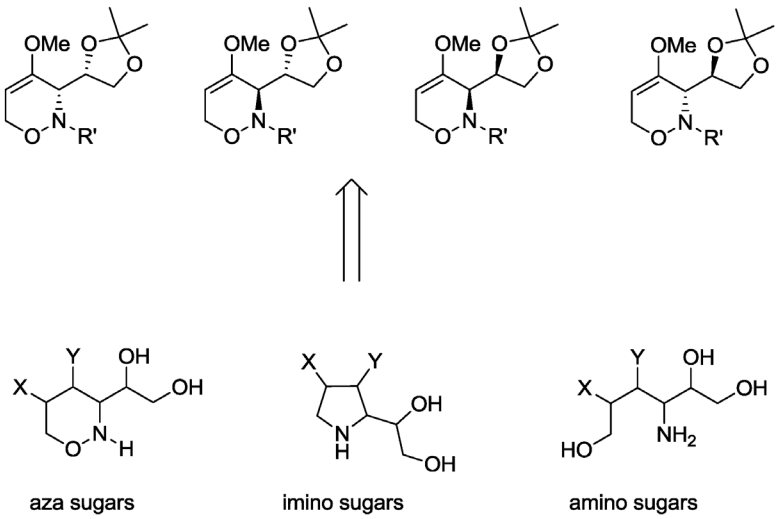


Scheme 3 D- and L-Glyceraldehyde-derived enantiopure *syn*- and *anti*-1,2-oxazine derivatives and possible target compounds.

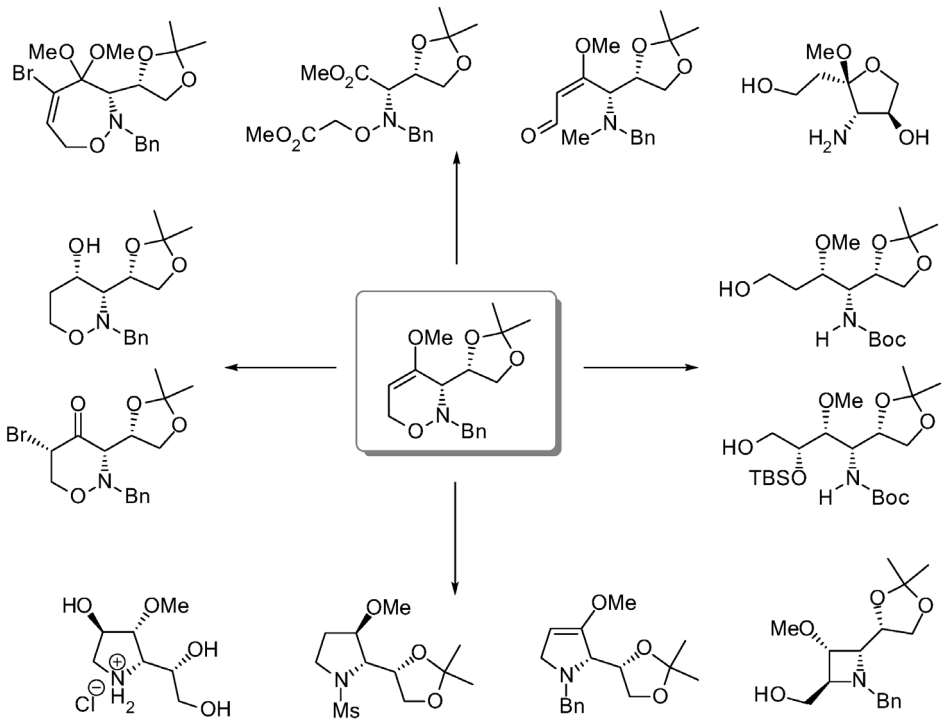
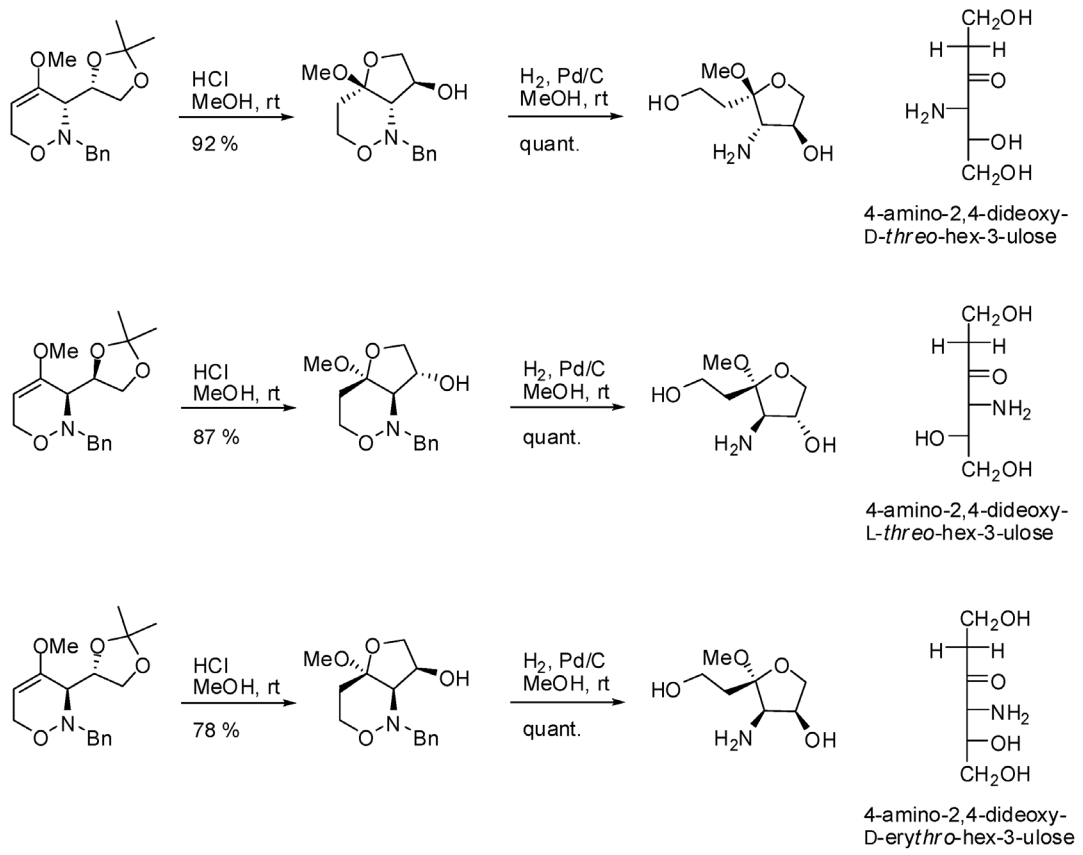


Fig. 2 Products obtained by simple transformations from the *syn*-configured 4-methoxy-1,2-oxazine.

As explicit examples, the syntheses of 4-amino-2,4-dideoxy-hex-3-ulose derivatives in three different configurations are depicted in Scheme 4. Acid treatment of the 1,2-oxazine derivatives led to a cleavage of the acetonide and a subsequent reaction with the enol ether unit to form bicyclic ketals. The exhaustive hydrogenolysis provided amino furan derivatives which are equivalent to the depicted ulose



Scheme 4 Acid-promoted cleavage and hydrogenolysis of 1,2-oxazines leading to stereoisomeric ulose derivatives.

derivatives. Three of the four possible stereoisomeric glyceraldehydes-derived 1,2-oxazines have been subjected to this two-step sequence employing protons and hydrogen as the most simple reagents [10].

The enol ether double bond of 1,2-oxazines is predestined to be employed for reactions with other electrophiles. One important option is the hydroboration, which proceeds regio- and stereoselectively and allows the introduction of an hydroxyl group at C-5 of the 1,2-oxazine ring. Applications leading to the target compounds proposed above (Scheme 3) are shown in Scheme 5. Here we used the 2-(trimethylsilyl)ethoxyallene as starting material since the (trimethylsilyl)ethyl (TMSE) group allows a deprotection under mild conditions in the final stages of a synthetic sequence. After stereoselective and almost quantitative hydroboration, the crucial 5-hydroxy-1,2-oxazine derivative can be used to prepare a fully deprotected 1,2-oxazine (aza sugar), an acyclic amino polyol (amino sugar), or cyclization products such as the shown azetidine or pyrrolidine derivatives (imino sugars) [11]. The polyhydroxylated pyrrolidine is known as a moderately strong α-L-fucosidase inhibitor [12].

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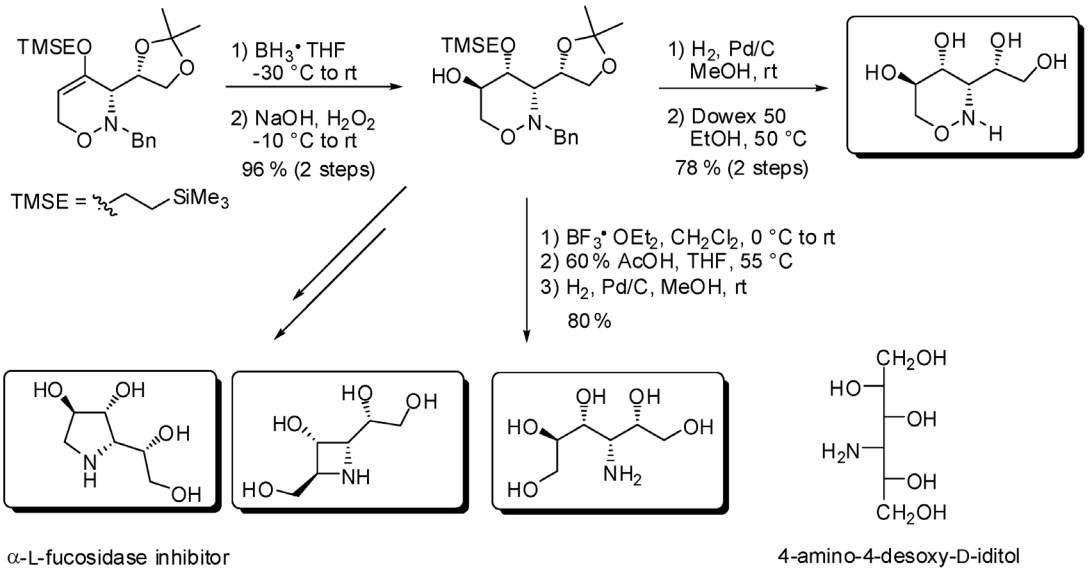
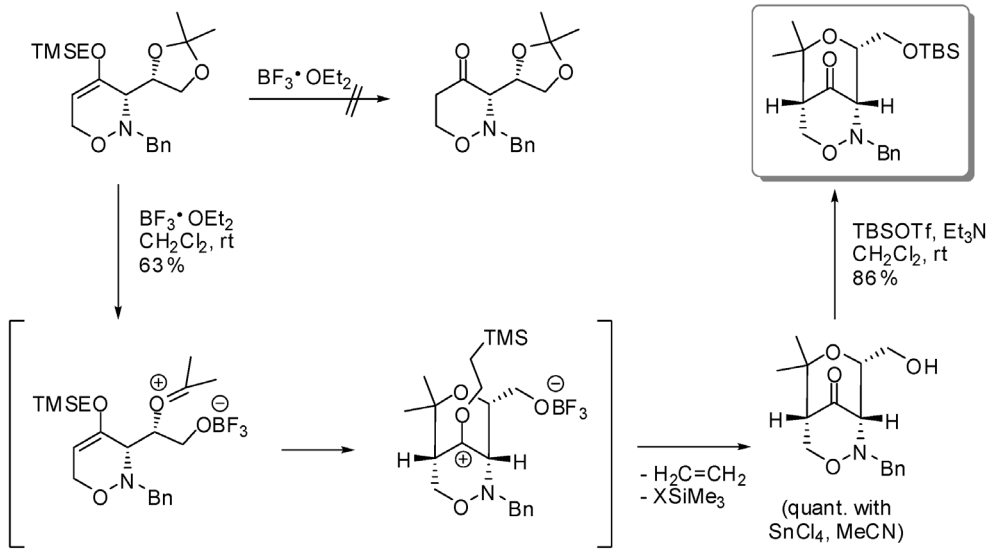


Scheme 5 Hydroboration of a *syn*-configured TMSE-substituted 1,2-oxazine and syntheses of acyclic or cyclic amino polyol derivatives.

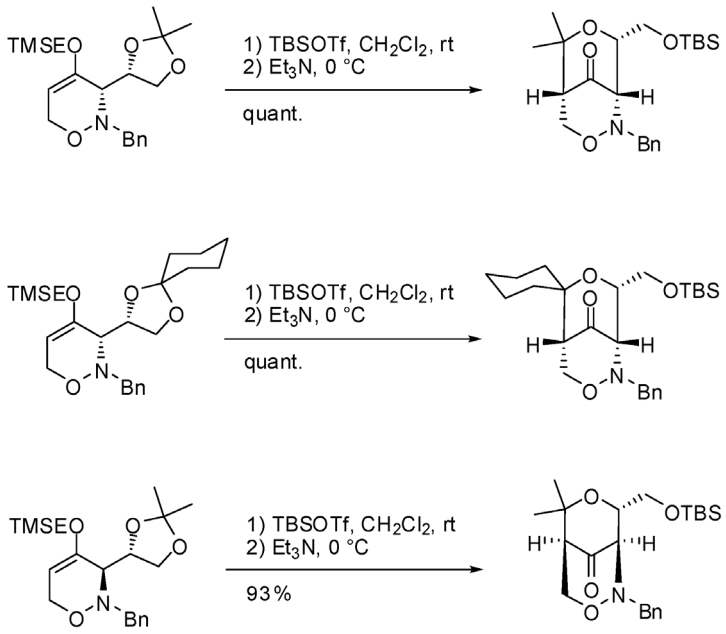
With the TMSE-protected 1,2-oxazine we initially tried to prepare the corresponding 1,2-oxazin-4-one, however, by treatment with fluoride or acid we could not obtain this compound. Surprisingly, the use of boron trifluoride etherate as Lewis acid induced a rearrangement providing us with an unexpected bicyclic 1,2-oxazine derivative (Scheme 6) [13]. Tin tetrachloride even improved the yield of this serendipitously discovered rearrangement involving Lewis acid-promoted cleavage of the acetonide, attack of the resulting carbenium ion to the enol ether moiety, and cleavage of the TMSE group.



Scheme 6 Novel synthesis of highly substituted amino pyran derivatives by Lewis acid-promoted rearrangement of 1,3-dioxolanyl-substituted 1,2-oxazines.

The ability of the involved alkoxy group to undergo a fast fragmentation is essential for the success of this reaction cascade [13b].

We immediately recognized the potential of this rearrangement for the preparation of unusually functionalized substituted pyran derivatives and therefore we studied the reaction in detail. *tert*-Butyldimethylsilyl triflate can not only serve as Lewis acid inducing the rearrangement, but in the presence of base directly protects the primary alcohol as silyl ether. The generality of this rearrangement was demonstrated with precursors bearing other substituents instead of the dimethyl unit or having *anti*-configuration (Scheme 7) [13a].



Scheme 7 Rearrangement of enantiopure 1,2-oxazines to bicyclic compounds with simultaneous *O*-protection.

Four stereoisomeric bicyclic compounds are accessible by this rearrangement from the glyceraldehydes-derived 1,2-oxazines. Their potential to serve as precursor for unusually substituted amino pyran derivatives is illustrated in Scheme 8. A stereoselective reduction of the carbonyl group introduces an additional stereogenic center, which (at least in certain examples) can be inverted by Mitsunobu reaction. Reductive cleavages either with hydrogen or by samarium diiodide provided the selectively protected amino pyran derivatives [13c]. Thus, a simple and stereodivergent entry to a variety of new enantiopure carbohydrate mimetics has been established.

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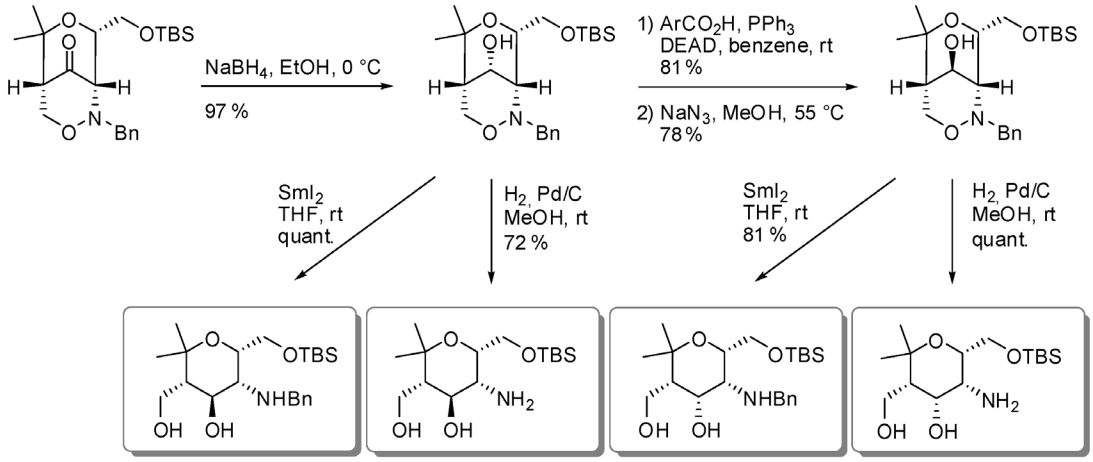
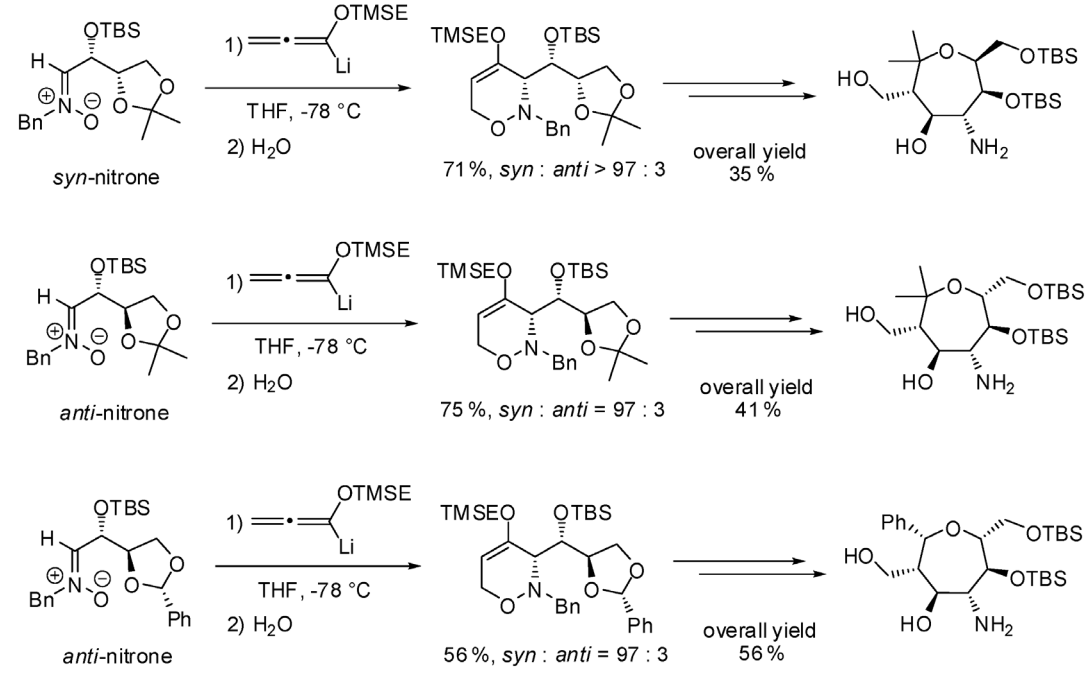


Scheme 8 Stereoselective syntheses of new amino pyran derivatives derived from bicyclic 1,2-oxazine derivatives.

Most gratifyingly, the rearrangement could successfully be extended to larger rings. The homologated nitrones shown in Scheme 9 were stereoselectively converted into the corresponding 1,2-oxazines and their Lewis acid-promoted rearrangements followed by reductive steps furnished a series of highly functionalized oxepane derivatives [13a].



Scheme 9 Stereoselective preparation of novel highly functionalized amino oxepane derivatives starting from the corresponding enantiopure nitrones.

The new amino pyran and oxepane derivatives are interesting carbohydrate-mimicking units which are ready to be tested for their biological activity. In close collaboration with the groups of Prof. Sabine Schlecht and Dr. Jens Dernedde, we found that amino pyrans connected via the amino group and a thiol linker to gold nanoparticles are excellent ligands for L- and P-selectins. Selectins are important proteins involved in the inflammation cascade, and the inhibition of their activity should interfere with these processes and possibly allow an anti-inflammatory therapy. Selectin inhibitors are, therefore, desired targets in medicinal chemistry [14]. Whereas unsulfated multivalent ligands bind fairly well to P-selectin (IC_{50} = 10 nM), but not to L-selectin, their stability is only low. Sulfation of the hydroxyl groups not only provided highly stable gold nanoparticles, but also led to exceptional IC_{50} values for L-selectin and P-selectin inhibition (Fig. 3). These negatively charged amino pyran conjugates cause inhibition in subnanomolar concentrations and show a moderate selectivity in favor of P-selectin. The simplified sulfated nanoparticles with serinol instead of the amino pyrans as amino polyol unit so far showed the best L- and P-selectin inhibition, but they are not selective [15]. Currently, the structure–activity relationships of these multivalent nanoparticle conjugates bearing 1,2-oxazine-derived amino oxepane, amino pyran, and amino furan substructures are under investigation.

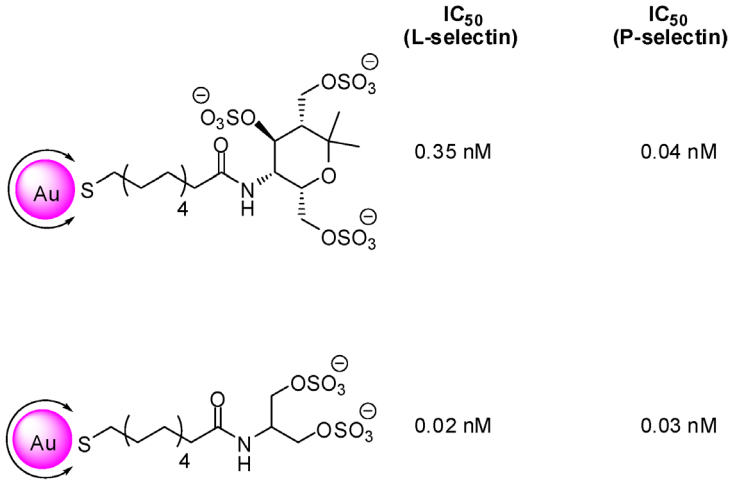


Fig. 3 IC_{50} values of 6 nm gold nanoparticles containing sulfated amino polyol end groups.

The rearrangement illustrated in Scheme 6 provided amino pyran derivatives, which we classify as carbohydrate mimetics. They contain one or two alkyl or aryl substituents R instead of a heteroatom X at C-1. We questioned ourselves whether it will be possible to replace R by an X group (Scheme 10), thus leading after a successful rearrangement to "real" carbohydrates containing an anomeric center. This would require the preparation of 1,2-oxazine derivatives containing this heteroatom X in the 1,3-dioxolane moiety.

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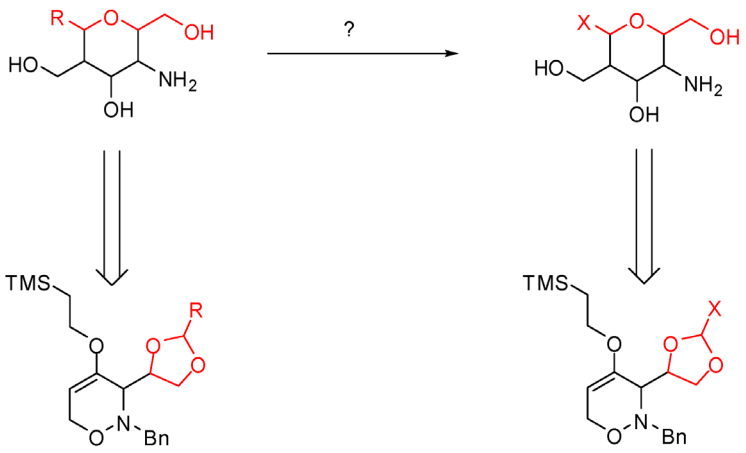
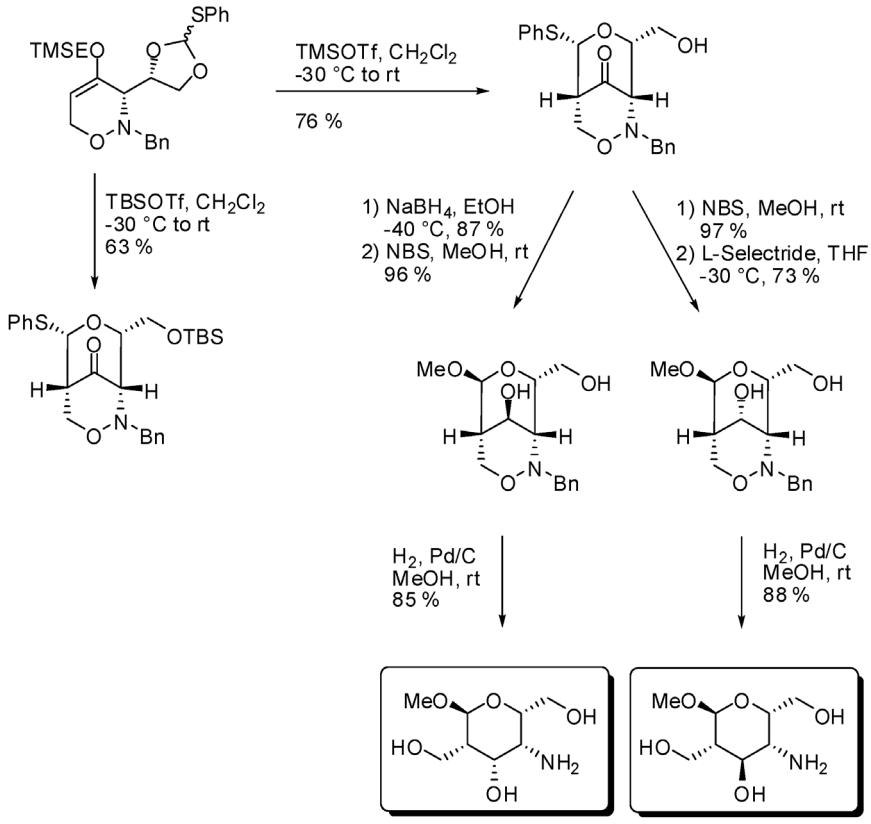


Scheme 10 Can we make "real" carbohydrates with substituents X similarily to the mimetics?

Only a few steps were required to modify the dimethyl-substituted 1,3-dioxolane substructure of the standard 1,2-oxazines by the phenylthio-substituted heterocycle [16], which underwent the desired Lewis acid-promoted rearrangement as anticipated (Scheme 11) [17]. The bicyclic 1,2-oxazine deriv-



Scheme 11 Stereodivergent approach to new branched amino sugars via Lewis acid-promoted rearrangement of 1,2-oxazines.

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ative, now with the crucial heteroatom in the correct position, was obtained in good yield. The thioacetal moiety not only allowed the connection to other carbohydrates or alcohols (see below), but could also be exploited for a stereodivergent approach to the branched monosaccharides depending on the sequence of steps employed. Reduction of the carbonyl group of the bicyclic 1,2-oxazine derivative by $NaBH_4$ stereoselectively occurred from the "back side". Subsequent methanolysis afforded the expected bicyclic compound, which after exhaustive reduction furnished the D-talose-configured branched amino pyran derivative. On the other hand, when the *N*-bromosuccinimide (NBS)-promoted methanolysis was performed first, the subsequent carbonyl reduction (here better with L-selectride) occurred with high preference from the "front side". In the end, the isomeric reduction product with D-idose configuration was obtained. The X-ray analysis of the D-idose-configured compound not only proved its relative configuration and hence the proposed stereoselectivity of the involved steps, but it also showed the twist-boat conformation of the pyran core with all substituents in a pseudo-equatorial position; only the methoxy group prefers the axial position owing to the anomeric effect (Fig. 4) [17a].

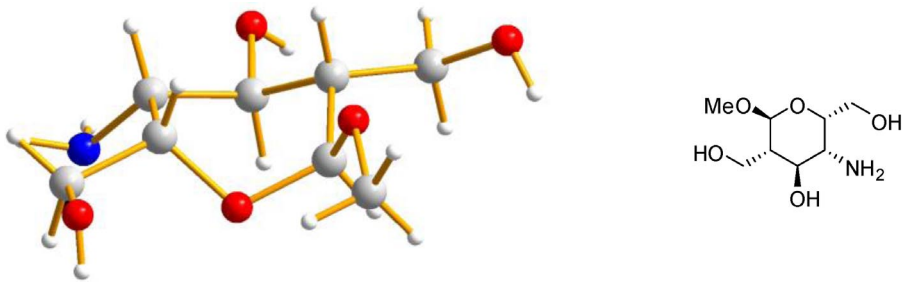


Fig. 4 Molecular structure of a 4-amino sugar derivative with D-idose configuration.

In Fig. 5 we summarize the four stereoisomeric branched amino sugars that are available by this route, either starting from the D-glyceraldehyde-derived 1,2-oxazine as in Scheme 11 or its L-glyceraldehyde-derived enantiomer, which provided L-talose- and L-idose-configured compounds.

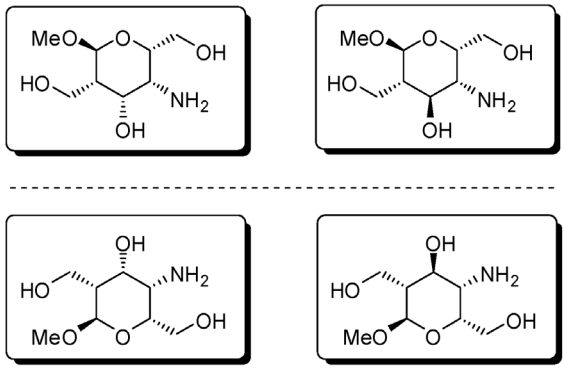
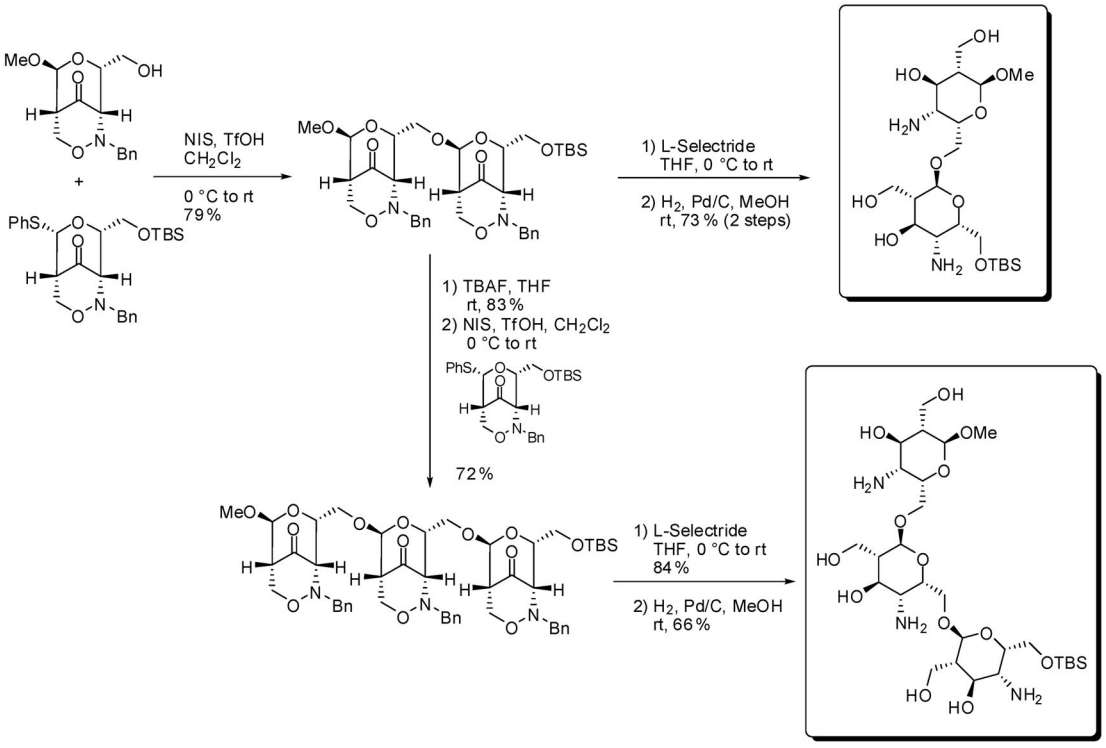


Fig. 5 Four stereoisomeric branched amino sugars available from phenylthio-substituted 1,2-oxazines.

We could demonstrate that the rearranged bicyclic 1,2-oxazines can directly be employed as specifically protected carbohydrate equivalents for di- and trisaccharide syntheses. The compound with a free primary alcohol function was directly coupled by NIS/TfOH-activation [18] to the phenylthio-substituted bicyclic 1,2-oxazine derivative to furnish a bis-1,2-oxazine derivative in a highly stereo-

selective fashion (Scheme 12). After removal of the silyl group, this protocol could be repeated and a tris-1,2-oxazine was obtained as product. Highly stereoselective reductions of the carbonyl groups followed by exhaustive hydrogenolyses afforded the expected di- and trisaccharides in good overall yields. These reactions show that the bicyclic 1,2-oxazine derivatives indeed serve as internally protected amino sugar equivalents allowing a simple entry to these unusual saccharides within a few steps. The feasibility of couplings of the phenylthio-substituted 1,2-oxazines with other carbohydrates or carbohydrate mimetics has also been demonstrated [17]. Overall, these processes show that a whole set of new carbohydrates or carbohydrate-like compounds with different configurations is easily available in a highly flexible and efficient manner.



Scheme 12 Synthesis of di- and trisaccharides with branched amino pyran units.

CONCLUSION

We could demonstrate that the stereodivergent [3 + 3] cyclization of carbohydrate-derived nitrones with lithiated alkoxyallenes furnishing specifically substituted enantiopure 1,2-oxazines is an efficient method to prepare chain-elongated carbohydrates derivatives. Subsequent simple chemo-, regio-, and stereoselective reactions allow an entry to a variety of interesting heterocyclic or acyclic compounds. Among them are enantiopure acyclic sugar alcohols or polyhydroxylated azetidine, pyrrolidine, amino pyran, and oxepane derivatives. The serendipitously discovered Lewis acid-induced rearrangement of 1,3-dioxolanyl-substituted 1,2-oxazine derivatives to bicyclic compounds established a route to novel carbohydrate mimetics and unusual carbohydrates. Several of the amino pyrans linked to gold nanoparticles have already shown exceptional biological activity, e.g., as multivalent inhibitors of L- and P-selectins with subnanomolar IC_{50} values.

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REFERENCES

1. Selected reports: (a) A. Varki. *Glycobiology* **3**, 97 (1993); (b) P. H. Seeberger, D. B. Werz. *Nature* **446**, 1046 (2007); and refs. therein.
2. Selected reviews: (a) P. Sears, C.-H. Wong. *Angew. Chem.* **111**, 2446 (1999); (b) P. Sears, C.-H. Wong. *Angew. Chem., Int. Ed.* **38**, 2300 (1999); (c) C.-H. Wong. *Acc. Chem. Res.* **32**, 376 (1999); (d) D. C. Koester, A. Holkenbrink, D. B. Werz. *Synthesis* 3217 (2010).
3. (a) M. Brasholz, H.-U. Reissig. *Angew. Chem.* **119**, 1659 (2007); (b) M. Brasholz, H.-U. Reissig. *Angew. Chem., Int. Ed.* **46**, 1634 (2007); (c) M. Brasholz, H.-U. Reissig. *Eur. J. Org. Chem*. 3595 (2009).
4. (a) R. Zimmer. *Synthesis* 165 (1993); (b) H.-U. Reissig, S. Hormuth, W. Schade, M. Okala Amombo, T. Watanabe, R. Pulz, A. Hausherr, R. Zimmer. *J. Heterocycl. Chem.* **37**, 597 (2000); (c) H.-U. Reissig, W. Schade, M. G. Okala Amombo, R. Pulz, A. Hausherr. *Pure Appl. Chem.* **74**, 175 (2002); (d) M. Brasholz, H.-U. Reissig, R. Zimmer. *Acc. Chem. Res.* **42**, 45 (2009); (e) T. Lechel, H.-U. Reissig. *Pure Appl. Chem*. **82**, 1835 (2010); (f) F. Pfrengle, H.-U. Reissig. *Chem. Sov. Rev.* **39**, 549 (2010).
5. (a) S. Hoff, L. Brandsma, J. F. Arens. *Recl. Trav. Chim. Pays-Bas* **87**, 916 (1968); (b) S. Hoff, L. Brandsma, J. F. Arens. *Recl. Trav. Chim. Pays-Bas* **88**, 609 (1969).
6. S. Hormuth, H.-U. Reissig. *J. Org. Chem.* **59**, 67 (1994).
7. (a) W. Schade, H.-U. Reissig. *Synlett* 632 (1999); (b) R. Pulz, S. Cicchi, A. Brandi, H.-U. Reissig. *Eur. J. Org. Chem.* 1153 (2003); (c) M. Helms, W. Schade, R. Pulz, T. Watanabe, A. Al-Harrasi, L. Fišera, I. Hlobilová, G. Zahn, H.-U. Reissig. *Eur. J. Org. Chem.* 1003 (2005).
8. (a) A. Dondoni, S. Franco, F. Junquera, F. L. Merchán, P. Merino, T. Tejero. *Synth. Commun*. **24**, 2537 (1994); for stereodivergent reactions of glyceraldehyde-derived nitrones, see: (b) A. Dondoni, S. Franco, F. Junquera, F. L. Merchán, P. Merino, T. Tejero, V. Bertolasi. *Chem.—Eur. J.* **1**, 505 (1995); review: (c) A. Dondoni. *Pure Appl. Chem.* **72**, 1577 (2000).
9. B. Bressel, H.-U. Reissig. *Org. Lett.* **11**, 527 (2009).
10. B. Bressel, B. Egart, A. Al-Harrasi, R. Pulz, H.-U. Reissig, I. Brüdgam. *Eur. J. Org. Chem*. 467 (2008).
11. (a) R. Pulz, A. Al-Harrasi, H.-U. Reissig. *Org. Lett*. **4**, 2353 (2002); (b) V. Dekaris, H.-U. Reissig. *Synlett* 42 (2010); (c) V. Dekaris, R. Pulz, A. Al-Harrasi, D. Lentz, H.-U. Reissig. *Eur. J. Org. Chem*. 3210 (2011).
12. (a) I. Lundt, R. Madsen, S. Al Daher, B. Winchester. *Tetrahedron* **50**, 7513 (1994); for recent reviews on glycosidase inhibitors, see: (b) B. G. Winchester. *Tetrahedron: Asymmetry* **20**, 645 (2009); (c) B. G. Davis. *Tetrahedron: Asymmetry* **20**, 652 (2009).
13. (a) A. Al-Harrasi, H.-U. Reissig. *Angew. Chem*. **117**, 6383 (2005); (b) A. Al-Harrasi, H.-U. Reissig. *Angew. Chem., Int. Ed*. **44**, 6227 (2005); (c) F. Pfrengle, A. Al-Harrasi, I. Brüdgam, H.-U. Reissig. *Eur. J. Org. Chem*. 282 (2009); (d) A. Al-Harrasi, F. Pfrengle, V. Prisyazhnyuk, S. Yekta, P. Koóš, H.-U. Reissig. *Chem.—Eur. J.* **15**, 11632 (2009).

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14. Review: R. Kranich, A. S. Busemann, D. Bock, S. Schroeter-Maas, D. Beyer, B. Heinemann, M. Meyer, K. Schierhorn, R. Zahlten, G. Wolff, E. M. Aydt. *J. Med. Chem.* **50**, 1101 (2007).
15. (a) J. Dernedde, S. Enders, H.-U. Reissig, M. Roskamp, S. Schlecht, S. Yekta. *Chem. Commun*. 932 (2009); (b) M. Roskamp, S. Enders, F. Pfrengle, S. Yekta, V. Dekaris, J. Dernedde, H.-U. Reissig, S. Schlecht. *Org. Biomol. Chem.* **9**, 7448 (2011).
16. F. Pfrengle, V. Dekaris, L. Schefzig, R. Zimmer, H.-U. Reissig. *Synlett* 2965 (2008).
17. (a) F. Pfrengle, D. Lentz, H.-U. Reissig. *Angew. Chem*. **121**, 3211 (2009); (b) F. Pfrengle, D. Lentz, H.-U. Reissig. *Angew. Chem., Int. Ed*. **48**, 3165 (2009); (c) F. Pfrengle, H.-U. Reissig. *Chem.—Eur. J.* **16**, 11915 (2010).
18. (a) G. H. Veeneman, S. H. van Leeuwen, J. H. van Boom. *Tetrahedron Lett.* **31**, 1331 (1990); (b) P. Konradsson, U. E. Udodong, B. Fraser-Reid. *Tetrahedron Lett.* **31**, 4313 (1990).

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