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A New Ring Closure Approach to Enantiopure 3,6-Dihydro-2*H*-pyrans: Stereodivergent Access to Carbohydrate Mimetics

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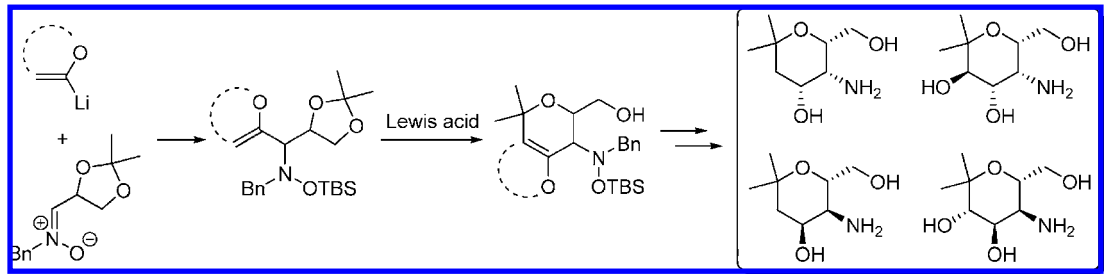
ABSTRACT



A set of enantiopure carbohydrate mimetics has been synthesized via Lewis acid promoted cyclization of 1,3-dioxolanyl-substituted enol ethers as a crucial new step providing highly functionalized 3,6-dihydro-2*H*-pyran derivatives. The flexible approach starting from glyceraldehyde-derived nitrone is comprised of only six simple steps smoothly allowing synthetic modifications at the different stages of the sequence. All reactions proceeded with good to excellent stereocontrol and can be performed with either of the two enantiomers.

Substituted pyran derivatives are structural subunits of a wide range of natural products and bioactive compounds. Their selective preparation in enantiopure form remains a continuous challenge for synthetic chemists.[1] Our group recently reported a new access to aminopyran derivatives such as **4**, which can be regarded as mimetics of C2-branched 4-amino sugars (Scheme 1).[2] A serendipitously discovered Lewis acid promoted rearrangement of 1,2-oxazines **2** furnished bicyclic compounds **3** as key intermediates. The required 3,6-dihydro-2*H*-1,2-oxazines **2** were obtained by stereoselective [3 + 3]-cyclizations of lithiated alkoxyallenes and D- or L-glyceraldehyde-derived nitrones **1**.[3] This sequence can be performed in a controlled stereodivergent manner allowing access to four possible stereoisomers of **3**.

With this achievement in mind, we envisioned the synthesis of aminopyrans such as **5**, employing a related strategy (Scheme 2). We considered 3,6-dihydropyran **6** as the key intermediate, which should be accessible by Lewis

† Responsible for X-ray analysis.

(1) For recent reviews on pyran synthesis, see: (a) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683–2723. (b) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–2053. For selected recent examples, see: (c) Hu, X.-H.; Liu, F.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 1741–1743. (d) McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 402–403. (e) O'Neil, G. W.; Fürstner, A. *Chem. Commun.* **2008**, 4294–4296. (f) Pospíšil, J.; Markó, I. E. *J. Am. Chem. Soc.* **2007**, *129*, 3516–3517. (g) Ichige, T.; Okano, Y.; Kanoh, N.; Nakata, M. *J. Am. Chem. Soc.* **2007**, *129*, 9862–9863. (h) Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 16480–16481. (i) Bolla, M. L.; Patterson, B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 16044–16045.

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(3) (a) Schade, W.; Reissig, H.-U. *Synlett* **1999**, 632–634. (b) Helms, M.; Schade, W.; Pulz, R.; Watanabe, T.; Al-Harrasi, A.; Fišera, L.; Hlobilová, I.; Zahn, G.; Reissig, H.-U. *Eur. J. Org. Chem.* **2005**, 1003–1019.

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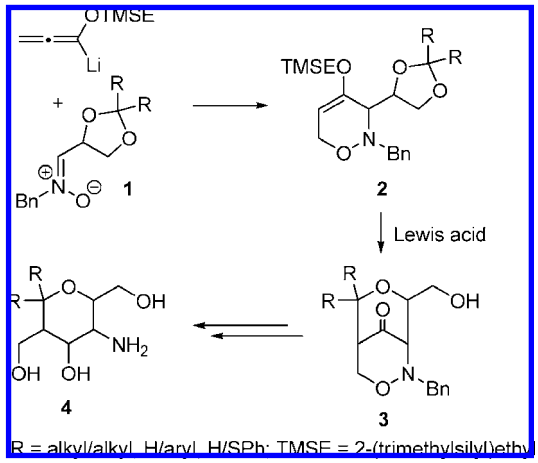
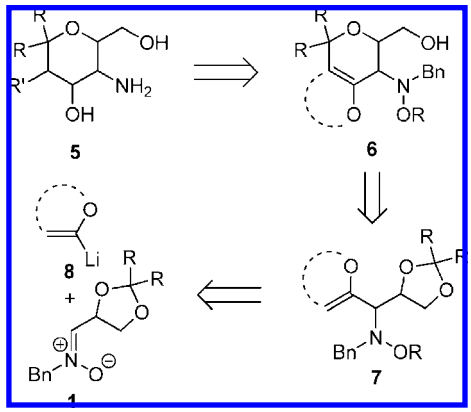
Scheme 1. Synthesis of Aminopyrans **4** via Lewis Acid Promoted Rearrangements of 1,2-Oxazines **2**



acid induced cyclization of protected hydroxylamine derivative **7**. Similarly to the approach to 1,2-oxazines **2**, the addition of lithiated enol ethers **8** to glyceraldehyde-derived nitrones **1** should afford the required hydroxylamine intermediates with a high level of stereocontrol.

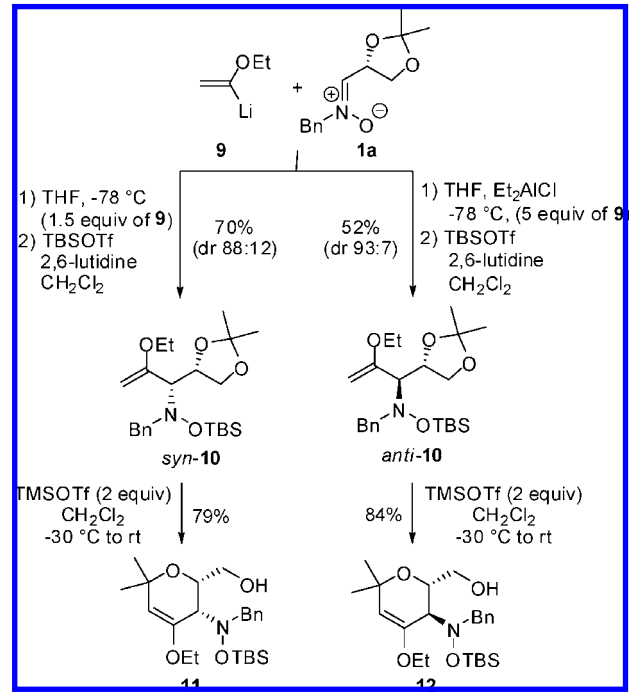
Scheme 2. Retrosynthetic Analysis of Aminopyrans **5**



To the best of our knowledge, the addition of lithiated enol ethers[4] to nitrones has not been described so far. The major concern we had about the feasibility of Scheme 2 was the cyclization step **7** → **6**, which has to occur without the geometrical constraint exhibited by the 1,2-oxazine moiety. We were also uncertain whether this step would proceed without the TMSE group undergoing a fast fragmentation in the transformation of **2** → **3** (Scheme 1).

Gratifyingly, when lithiated ethyl vinyl ether **9**[5] was reacted with D-glyceraldehyde-derived nitrone **1a**, hydroxylamine derivative *syn*-**10** was isolated after TBS protection in good yield and diastereoselectivity (Scheme 3).[6] As expected,[7] precomplexation of nitrone **1a** with Et_2AlCl before addition of **1a** switched the stereochemical outcome toward formation of *anti*-configured products, providing *anti*-**10** in slightly lower yield but with excellent diastereoselectivity. Protection of the primarily obtained hydroxylamine derivatives with the TBS group was essential for their stability during column chromatography, which smoothly allowed separation of the diastereomers.[8] The protected hydroxylamine derivatives *syn*- and *anti*-**10** were treated with

Scheme 3. Synthesis of Diastereomeric 3,6-Dihydro-2*H*-pyrans **11** and **12**



TMSOTf, smoothly affording the diastereomeric 3,6-dihydropyrans **11** or **12** in high yields. The new key cyclization step can be regarded as a Lewis acid promoted intramolecular aldol type reaction of an acetal with an enol ether or as a Prins type reaction.[9]

The enol ether moiety of **11** and **12** was subsequently exploited for functionalizations such as hydrolysis or dihy-

(4) Review: Friesen, R. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1969–2001.

(5) Lithiation of the enol ether was carried out under standard conditions: Friesen, R. W.; Sturino, C. F. *Sci. Synth.* **2005**, *8*, 841–862.

(6) For selected recent examples of the addition of organolithium compounds to nitrones, see: (a) Dondoni, A.; Nuzzi, A. *J. Org. Chem.* **2006**, *71*, 7574–7582. (b) Dullin, A.; Dufrasne, F.; Gelbcke, M.; Gust, R. *ChemMedChem* **2006**, *1*, 644–653. (c) Yu, C.-Y.; Huang, M.-H. *Org. Lett.* **2006**, *8*, 3021–3024. (d) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929–2947. Review: (e) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759–774.

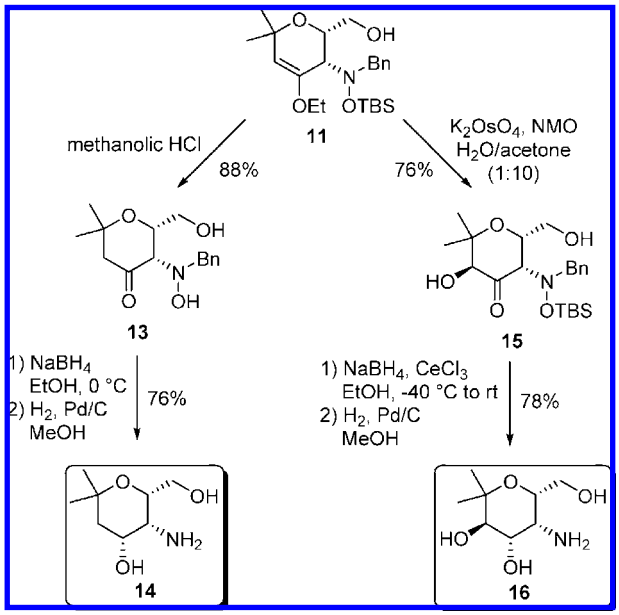
(7) For the stereodivergent addition of organometallic reagents to carbohydrate-derived nitrones, see: Dondoni, A.; Franco, S.; Junquera, F.; Merchán, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *Chem.—Eur. J.* **1995**, *1*, 505–520.

(8) Merino, P.; Tejero, T.; Mannucci, V.; Prestat, G.; Madec, D.; Poli, G. *Synlett* **2007**, 944–948.

(9) For related reactions, see: (a) Cockerill, G. S.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2093–2100. (b) Das, S.; Li, L.-S.; Sinha, S. C. *Org. Lett.* **2004**, *6*, 123–126.

droxylation. Treatment of **11** with HCl in methanol furnished ketone **13** by hydrolysis of the enol ether with concomitant loss of the TBS group (Scheme 4). Stereoselective reduction with $NaBH_4$ and final hydrogenolysis using Pd/C provided deprotected aminopyran **14** in good overall yield. To introduce an additional hydroxyl group, the enol ether double bond in **11** was dihydroxylated using a catalytic amount of K_2OsO_4. Formation of an intermediate hemiacetal was not observed, and α-hydroxy ketone **15** was directly isolated as a single diastereomer. Subsequent reduction with $NaBH_4$ and final hydrogenolysis furnished deprotected aminopyran **16** in good overall yield. The presence of $CeCl_3$ in the $NaBH_4$ reduction of ketone **15** turned out to be essential to achieve excellent diastereoselectivity.

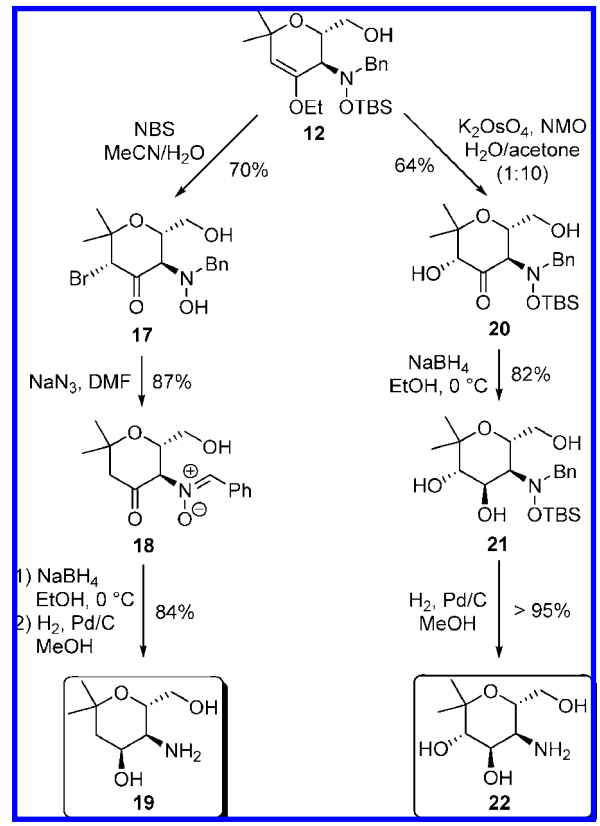
Scheme 4. Synthesis of Carbohydrate Mimetics **14** and **16**



When diastereomeric dihydropyran **12** was exposed to HCl, we could not achieve hydrolysis of the enol ether moiety but mainly observed decomposition. Fortunately, we were able to synthesize the desired aminopyran **19** by a "detour" employing α-bromo ketone **17** smoothly obtained by bromination of **12** with NBS (Scheme 5). During our attempts to substitute the bromo substituent in **17** by azide, we unexpectedly isolated nitrone **18** in high yield, apparently formed by an unusual internal redox reaction.[10] With this intermediate in hand, the stereoselective synthesis of aminopyran **19** could be performed in good overall yield. Unlike its hydrolysis, dihydroxylation of **12** was easily feasible, providing α-hydroxyketone **20** accompanied by considerable amounts (20−50%) of the hydroxylated hemiacetal. After reductive transformations of this mixture, aminopyran **22** was isolated as a single diastereomer in good overall yield. The

(10) For a mechanistic suggestion, see the Supporting Information.

Scheme 5. Synthesis of Carbohydrate Mimetics **19** and **22**



configuration of **22** was proven by X-ray crystallographic analysis of its protected precursor **21** (Figure 1).[11]

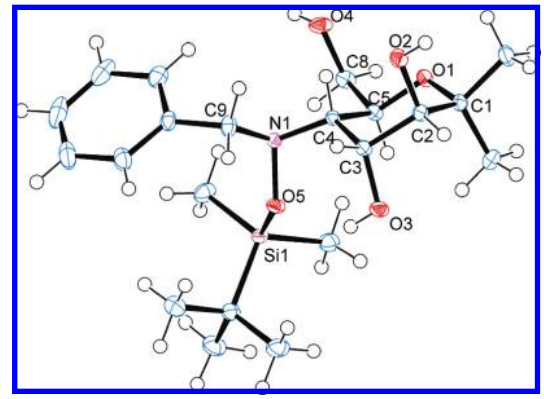
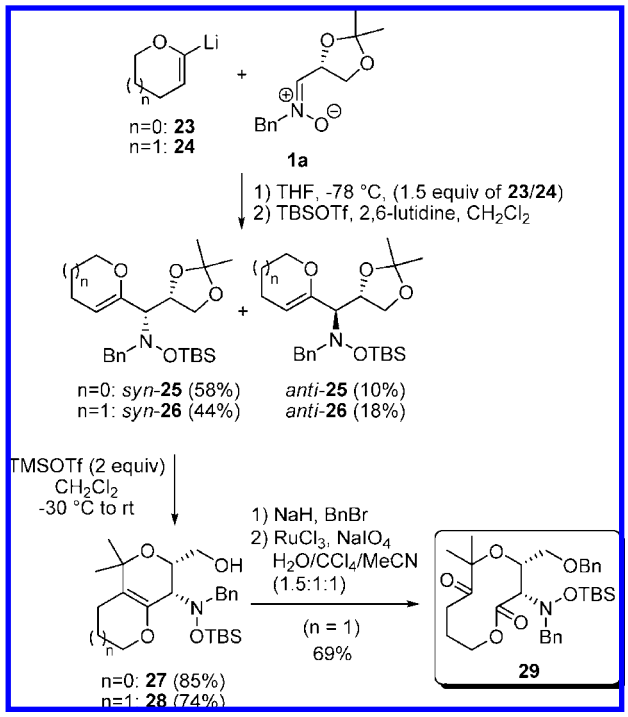


Figure 1. Molecule structure (ORTEP[13]) of aminopyran derivative **21**.

Compounds **14**, **16**, **19**, or **22** having a hydrolytically stable *gem*-dimethyl group at C1 can be regarded as mimetics of differently substituted and configured 4-amino carbohy-

(11) The configurations of aminopyrans **14**, **16**, and **19** were assigned by comparison of their NMR data (see Supporting Information).

Scheme 6. Synthesis of Bicyclic Dihydropyrans **27** and **28** and Macrolactone **29**



drates.[12] Their C2-branched analogues **4** already exhibited highly remarkable properties as ligands of gold nanoparticles in their multivalent binding to selectins. We currently evaluate the newly prepared aminopyrans toward their potential as components of new anti-inflammatory agents.[14]

Finally, not only ethyl vinyl ether but also cyclic enol ethers have been lithiated and reacted with nitrones. As a representative example, reaction of lithiated dihydrofuran **23** with nitrone **1a** followed by TBS protection smoothly furnished hydroxylamine derivatives *syn*- and *anti*-**25** (Scheme 6). Similarly, lithiated 2,3-dihydropyran **24** afforded *syn*- and *anti*-**26** in moderate yield and with reasonable diastereoselectivity.[15] When *syn*-**25** and *syn*-**26** were exposed to TMSOTf, bicyclic compounds **27** and **28** were obtained in high yield. To demonstrate the synthetic potential of compounds such as **28**, we performed an oxidative ring cleavage of its benzyl-protected derivative with $RuCl_3$ hence providing lactone **29** in good yield, which contains the L-γ-hydroxylthreonine moiety.[16]

In conclusion, we developed a rapid access to a set of novel carbohydrate mimetics via Lewis acid promoted cyclizations of 1,3-dioxolanyl-substituted hydroxylamine derivatives, which were obtained by stereodivergent addition of lithiated enol ethers to D-glyceraldehyde-derived nitrone **1a**. All of the reactions can be performed on a gram scale, and they proceeded with good stereocontrol. It should be emphasized that all compounds described in this communication are as easily accessible as their enantiomers with L-glyceraldehyde-derived nitrone as starting material. The prepared compounds are candidates to be incorporated into oligosaccharides or aminoglycosides, potentially leading to compounds with interesting antibacterial properties. Furthermore, starting from lithiated 3,4-dihydropyran and 2,3-dihydrofuran, bicyclic compounds **27** and **28** were prepared, which should provide access to unusual enantiopure heterocycles such as **29**.

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Supporting Information Available: Experimental procedures, characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Pre-complexation of **1a** switched the stereochemical outcome of the reactions toward *anti*-**25** and *anti*-**26** as the main diastereomers (d.r. 86:14 and d.r. 88:12).

(16) Silva, L. F., Jr.; Vasconcelos, R. S.; Nogueira, M. A. *Org. Lett.* **2008**, *10*, 1017–1020.