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A New Approach to Neuraminic Acid Analogues via 1,2-Oxazines

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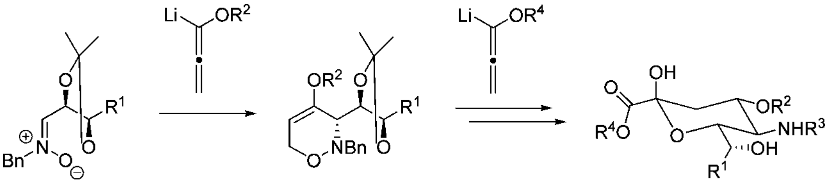
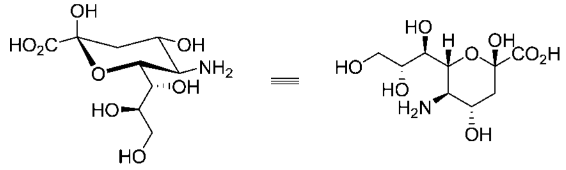
ABSTRACT



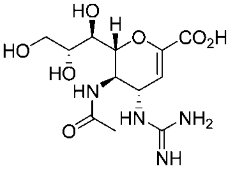
A new stereoselective and potentially very flexible ($C_5 + C_3 + C_1$) approach to neuraminic acid derivatives and analogues has been established using enantiopure nitrones and alkoxyallenes as C_3 and C_1 building blocks. Substituent OR^2 in position 4 of neuraminic acid analogues is defined by the alkoxyallene employed for the synthesis of the intermediate 1,2-oxazine. Side chain R^1 can be varied by using different precursor nitrones and introduction of different protection groups R^3 at the amino function is also possible.

Neuraminic acid (**1**) and its derivatives have important biological functions.[1] It has been demonstrated that several derivatives, in particular synthetic analogues, inhibit neuraminidases. This ability can be exploited for the treatment of influenza infections as it is actually achieved by drugs such as Relenza (zanamivir, **2**)[2] or Tamiflu (oseltamivir phosphate, **3**, Figure 1).[3] This ongoing interest and other applications make efficient and flexible syntheses of neuraminic acid analogues a matter of intense research.[4]

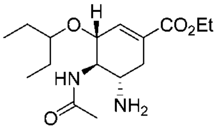
In this paper we present a new and potentially very flexible route to neuraminic acid analogues. As shown in the retrosynthetic analysis (Scheme 1), neuraminic acid analogue **A** can be obtained from protected α-ketoester **B**. The corresponding α-hydroxyester **C** should be available by chain elongation from aldehyde **D** by using lithiated alkoxyallene **E** as a C_1 building block.[5] A primary amino alcohol which can be oxidized to the crucial aldehyde **D** is accessible from 1,2-oxazine **F** by hydrogenolysis as shown previously by our group.[6] It is necessary to introduce an electron-withdrawing group R^3 at the amino function in order to avoid an intramolecular cyclization of aldehyde **D**. The required 1,2-



1 Neuraminic Acid



2 Zanamivir



3 Oseltamivir

Figure 1. Neuraminic acid **1** and its analogues **2** and **3**.

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(1) *Biology of the Sialic Acids*; Rosenberg, A., Ed.; Plenum Press: New York, 1995.

(2) von Itzstein, M.; et al. *Nature* **1993**, *363*, 418–423.

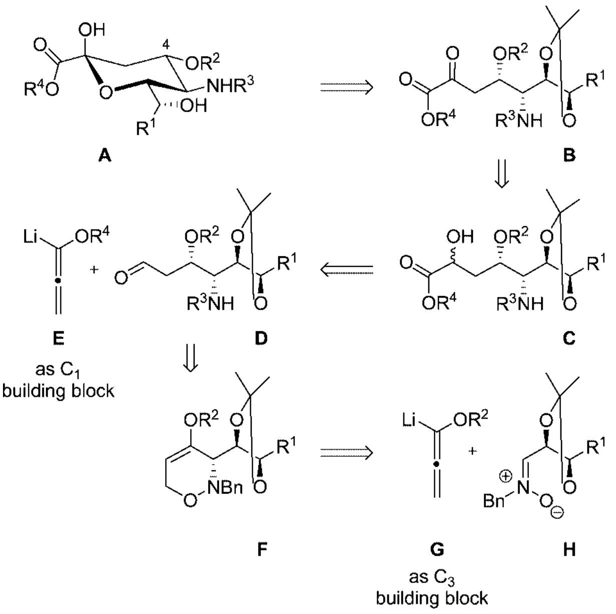
(3) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681–690.

(4) For recent reviews, see: (a) Hemeon, I.; Bennet, A. J. *Synthesis* **2007**, 1899–1926. (b) Kiefel, M. J.; von Itzstein, M. *Chem. Rev.* **2002**, *102*, 471–490.

(5) (a) Hormuth, S.; Reissig, H.-U.; Dorsch, D. *Liebigs Ann. Chem.* **1994**, 121–127. (b) Schade, W.; Reissig, H.-U. *J. Prakt. Chem.* **1999**, *341*, 685–686.

10.1021/ol802514m CCC: $40.75

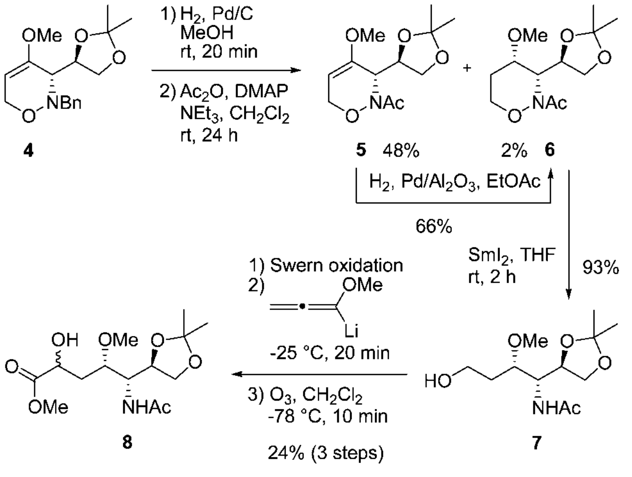
Scheme 1. Retrosynthetic Analysis



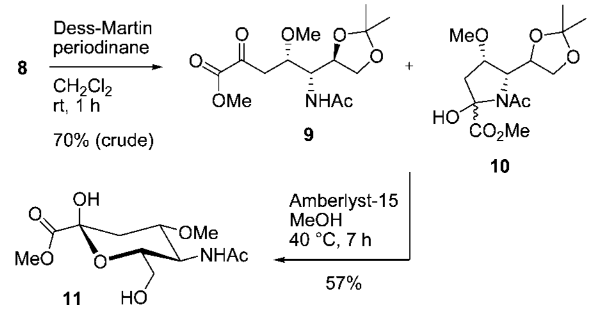
oxazines **F** can be synthesized diastereoselectively from enantiopure nitrones **H** using alkoxyallene **G**, now an essential C_3 building block.[7] The alkoxy substituent OR^2 will appear in position 4 of the corresponding neuraminic acid analogue. Different nitrones will allow the synthesis of side chains varying in length and configuration.

To examine the proposed strategy, we decided to employ 1,2-oxazine **4** as a model compound which is smoothly available from a L-glyceraldehyde-derived nitrone and lithiated methoxyallene.[8] Although most of our synthetic studies have been performed with the enantiomer of **4**, a sound basis of its reactivity was available.[6,8,9] Hydrogenolysis of **4** led to debenzylation followed by diastereoselective reduction of the double bond and finally N−O cleavage.[6] To avoid selectivity problems during the introduction of an *N*-protecting group to the resulting amino alcohol, the hydrogenolysis was interrupted before N−O cleavage and the debenzylated derivatives were acetylated to give 1,2-oxazine **5** and 1,2-oxazinane **6** (Scheme 2). In addition, 28% of starting material **4** could be reisolated. Longer reaction times resulted in lower yields of desired products because of N−O cleavage. The acetyl group was chosen for protection as it has the required electron-withdrawing properties and *N*-acetylneuraminic acids are the most important naturally occurring derivatives.[4,10] The enol ether double bond of 1,2-oxazine **5** was reduced with hydrogen in the presence of Pd/Al_2O_3 in ethyl acetate furnishing 1,2-oxazinane **6** as the major component of an 82:18 mixture of diastereomers (^1H NMR, crude), which were easily separated by column chromatography. Under these conditions, the *N*-acetylated N−O bond was stable. Its cleavage was smoothly achieved by samarium diiodide[11] leading to amino alcohol **7**. After Swern oxidation[12] to the aldehyde, addition of lithiated methoxyallene and ozonolysis, the carbon-chain elongated α-hydroxyester **8** was isolated as a mixture of diastereomers (ca. 1:1).

Scheme 2. Reduction and Chain Elongation of 1,2-Oxazine **4**



Scheme 3. Synthesis of Neuraminic Acid Analogue **11**



The α-hydroxyester **8** could easily be oxidized to α-ketoester **9** using Dess−Martin periodinane (Scheme 3).[13] In $CDCl_3$, a slow conversion of this product to the cyclic derivative **10** was observed, which is probably induced by traces of acid in the solvent. By mass spectrometry it was confirmed that no elimination had taken place, suggesting

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(6) Pulz, R.; Watanabe, T.; Schade, W.; Reissig, H.-U. *Synlett* **2000**, 983–986.

(7) 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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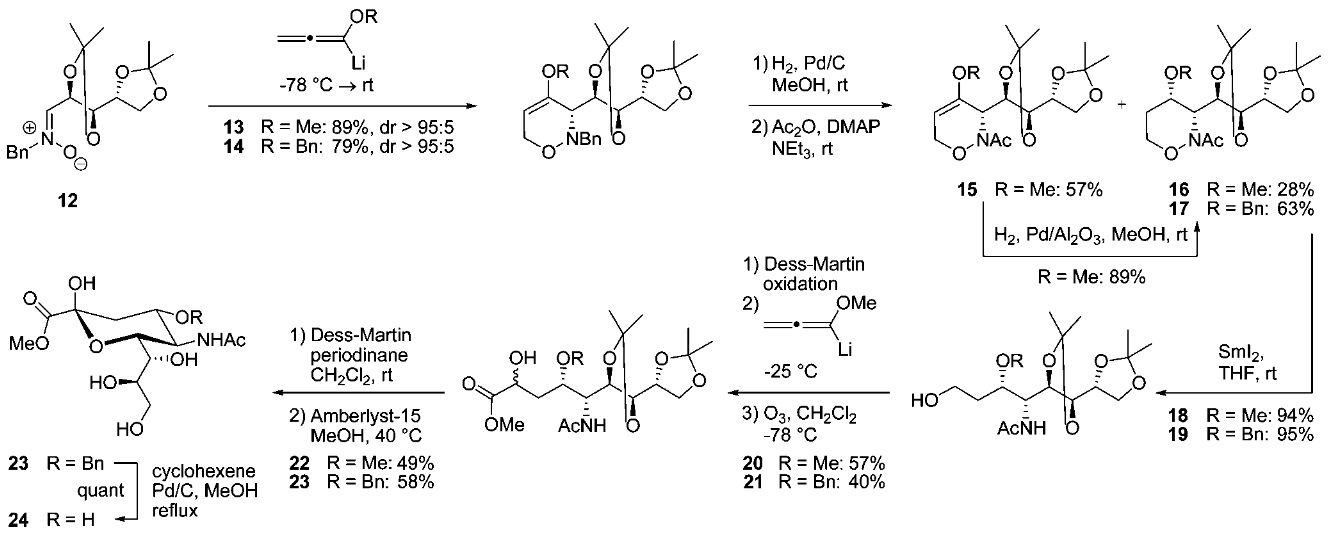
Scheme 4. Synthesis of Neuraminic Acid Derivatives **22**, **23**, and *N*-Acetylneuraminic Acid Methyl Ester **24**



that this cyclization should be reversible. The final acetal cleavage could be achieved under acidic conditions. For a similar derivative, Banwell et al. employed HCl in methanol.[14] We obtained good results using Amberlyst-15 in methanol at 40 °C. The mixture of the esters **9** and **10** was converted to the neuraminic acid analogue **11** with a methoxy group in position 4 and a short side chain in an overall yield of 3% starting from 1,2-oxazine **4**. No attempts to optimize this sequence have been made.

After this proof of principle, we applied the strategy to the synthesis of neuraminic acid derivatives with a complete 9-carbon backbone (Scheme 4) starting from the D-arabinose derived nitrone **12**,[15] which is easily accessible from D-mannitol. To introduce different substituents in position 4, methoxy- and benzyloxyallene were used for the synthesis. The methoxy-substituted 1,2-oxazine **13** has been prepared before,[7] but the yield could be improved to 89% by slight variations of the original procedure. Partial hydrogenolysis and acetylation led to 1,2-oxazine **15** and 1,2-oxazinane **16** in analogy to derivative **4**, but gratifyingly the yields were considerably higher. The hydrogenation of the enol ether double bond of **15** was smoothly achieved with a diastereoselectivity of 93:7 (^{1}H NMR, crude), giving pure 1,2-oxazinane **16** after column chromatography. Benzyloxy-substituted precursor **14** was also prepared from nitrone **12** in good yield and excellent diastereoselectivity. We were wondering which functional group of **14** (enol ether moiety, *O*-benzyl, or *N*-benzyl group) would be reduced first during hydrogenation, assuming that the N−O bond cleavage would still be the slowest step. When using 30 mol % of Pd/C in methanol, the hydrogenolysis of the *N*-benzyl group and the reduction of the double bond was faster than *O*-benzyl cleavage. This reactivity was ideal for the *N*-acetylation leading directly to 1,2-oxazinane **17** in good yield without any selectivity problems. Additionally, it was observed that by decreasing the amount of catalyst in order to slow down the speed of the reaction for easier monitoring by TLC, an increasing amount of an 1,2-oxazin-4-one was isolated, which apparently resulted from the enol formed by *O*-debenzylation before reduction of the enol ether double bond. The dependence of the product ratio on the amount of catalyst cannot be fully explained yet and will be discussed in more detail elsewhere.[16,17] The N−O bonds of *N*-acetylated 1,2-oxazinane derivatives **16** and **17** were cleaved with samarium diiodide in excellent yields. The conversion of the resulting aminoalcohols **18** and **19** to the required aldehydes was achieved by Dess−Martin oxidation which led to better results than Swern oxidation. After addition of lithiated methoxyallene and ozonolysis the α-hydroxyesters **20** and **21** were formed in moderate yields over three steps (dr ca. 1:1). Dess−Martin oxidation to the corresponding α-ketoesters followed by acetal cleavage provided *N*-acetylneuraminic acid derivatives **22** and **23** in moderate yields over two steps. Similar α-ketoesters have been deprotected using HCl/MeOH[18] or HF.[19] Here, the acetal cleavage was performed with Amberlyst-15 in methanol. Derivative **22**, bearing a methoxy group in position 4, was obtained in an overall yield of 19% over ten steps and derivative **23** with the benzyloxy group in 11% yield over nine steps. Under transfer hydrogenation conditions with cyclohexene, benzy-

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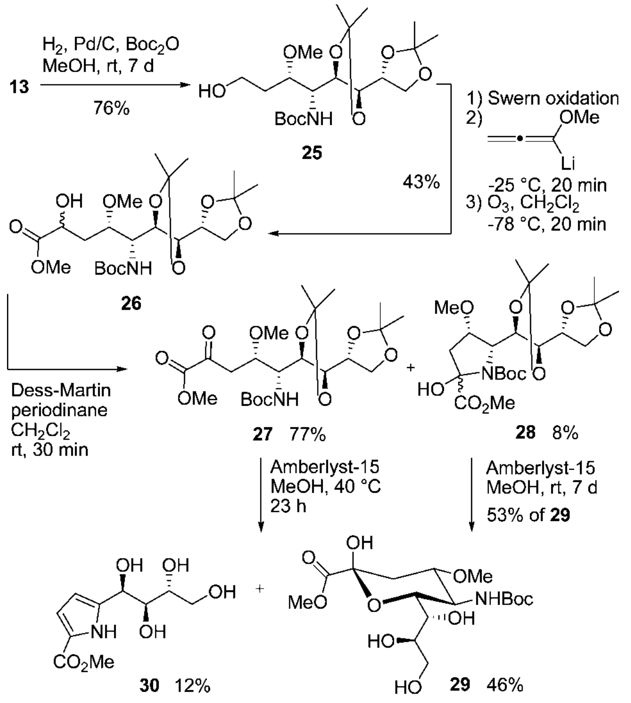
(17) As the rate of hydrogenation generally increases with the amount of starting material and high amounts of catalyst are necessary to achieve good yields of the desired product **17**, up-scaling of this partial hydrogenolysis is limited. If the reaction is too fast, it is not possible to stop it before *O*-debenzylation and N−O cleavage occur.

(18) Kang, S. H.; Choi, H.; Kim, J. S.; Youn, J.-H. *Chem. Commun.* **2000**, 227–228.

(19) (a) Liu, K.-G.; Yan, S.; Wu, Y.-L.; Yao, Z.-J. *J. Org. Chem.* **2002**, *67*, 6758–6763. (b) Liu, K.-G.; Yan, S.; Wu, Y.-L.; Yao, Z.-H. *Org. Lett.* **2004**, *6*, 2269–2272.

loxy derivative **23** was debenzylated quantitatively to afford the known[20] *N*-acetylneuraminic acid methyl ester **24**.

Scheme 5. Synthesis of Neuraminic Acid Derivative **29**



Applying an *N*-Boc protecting group instead of an *N*-acetyl group to the synthesis shortened the number of required steps because the *N*-Boc group was already introduced during the hydrogenolysis by adding Boc_2O to the reaction mixture (Scheme 5). Amino alcohol **25** was obtained in good yield (dr ca. 95:5). As the Boc-group has a weaker electron-withdrawing effect than the acetyl group, the Swern oxidation had to be carefully executed applying short reaction times and avoiding acidic workup. Otherwise an intramolecular cyclization occurs leading to a pyrrole derivative by elimination of water and methanol. As above, the aldehyde can be transformed into the α-hydroxyester **26** by addition of lithiated methoxyallene and ozonolysis in moderate yield over three steps (dr ca. 1:1). After Dess−Martin oxidation to α-ketoester **27**, the cyclic derivative **28** was isolated as a side product. By acetal cleavage with Amberlyst-15 in methanol both compounds could individually be converted into the neuraminic acid derivative **29** in yields of 46% and 53%, respectively. The overall yield for *N*-Boc-protected derivative **29** is 12% over eight steps.

During conversion of α-ketoester **27** to **29** the reaction has to be interrupted before completion because as a byproduct pyrrole **30** is slowly formed. Longer reaction times or higher temperatures led to a decrease of neuraminic acid derivative **29** and an increase of pyrrole derivative **30** in up to 30% yield. The biological activity of **30** may be interesting since its structure is closely related to a known immunosuppressive compound.[21]

In conclusion, a new $C_5 + C_3 + C_1$ strategy to neuraminic acid derivatives has successfully been devised using nitrones and alkoxyallenes as easily available starting materials. *N*-Acetyl derivatives **22**−**24** with different 4-substituents were stereoselectively prepared in reasonable quantities and with good overall yields. Similarly, the *N*-Boc-protected derivative **29** has been synthesized. The 4-substituent depends on the alkoxyallene used for the synthesis of the 1,2-oxazine. The structure of drugs such as zanamivir **2** and oseltamivir **3** reveals that variation of 4-substituents may be particularly important for new neuraminidase inhibitors. Starting from other nitrones the methodology developed also allows for the preparation of neuraminic acid analogues with differing chain lengths as demonstrated by the preparation of C_7-analogue **11**. These results show the flexibility of this new alkoxyallene-based[22] approach to neuraminic acid derivatives. Modifications of substituents and the configuration in different positions should be easily possible and will be investigated in due time.

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Supporting Information Available: Experimental procedures and complete characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] (a) Schwab, S. R.; Pereira, J. P.; Matloubian, M.; Xu, Y.; Huang, Y.; Cyster, J. G. *Science* **2005**, *309*, 1735–1739. For isolation and characterization of this compound, see: (b) Kröplien, U.; Rosdorfer, J. *J. Org. Chem.* **1985**, *50*, 1131–1133. For the synthesis, see: (c) Sweeny, J. G.; Ricks, E.; Estrada-Valdés, M. C.; Iacobucci, G. A. *J. Org. Chem.* **1985**, *50*, 1133–1134.

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