# Acid-Mediated Transformations of Enantiopure 3,6-Dihydro-2*H*-1,2-oxazines into Functionalised Aminotetrahydrofuran Derivatives

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*Received 24 September 2009*

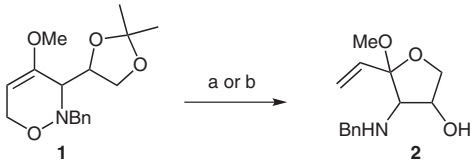
**Abstract:** Two new routes to substituted aminotetrahydrofuran derivatives have been investigated. Treatment of 3,6-dihydro-2*H*-1,2-oxazines with hydrochloric acid in the presence of zinc provided 4-benzylamino-5-hydroxy furanose derivatives which contain a quaternary anomeric centre with a vinyl unit. Upon mesylation and subsequent heating in aqueous media 5-hydroxy-3,4,5,6-tetrahydro-1,2-oxazines were converted into novel bicyclic 1,2-oxazines with complete regio- and stereoselectivity. Cleavage of the N–O bond and subsequent debenzylation furnished enantiopure polyhydroxylated aminotetrahydrofuran derivatives which are promising ligands for selectin inhibition studies.

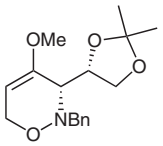
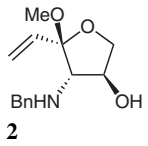
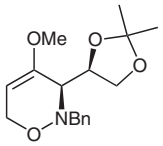
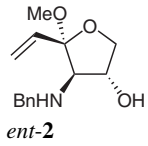
**Key words:** 1,2-oxazine, furan, amine, reduction, zinc, amino sugar

Over the past years we could demonstrate the surprisingly diverse synthetic versatility of lithiated alkoxyallenes. The stereoselective addition of these C3-intermediates to various electrophiles[1] allowed valuable transformations and it enabled the construction of numerous heterocyclic frameworks.[2] Among the target compounds, furan derivatives played an important role in our research. Two major pathways led to the desired compounds, either by metal-catalysed cyclisation of allenyl alcohols to dihydrofurans[3] or by acid-induced transformations of 3,6-dihydro-2*H*-1,2-oxazines **1** to furans and furanosides.[4] In this letter we are presenting two new methods for the stereoselective preparation of substituted aminofuran derivatives including useful subsequent modifications of the initially formed cyclisation products, which nicely supplement earlier results. Precursors for both newly introduced acid-catalysed transformations are 3,6-dihydro-2*H*-1,2-oxazines **1** which are easily accessible by addition of lithiated alkoxyallenes to nitrones in stereocontrolled fashion.[5]

The first conversion is directly performed with **1** using hydrochloric acid and zinc (Table 1).[6,7] Treatment of *syn*-**1** for one day under these conditions afforded vinyl-substituted aminofuranoside **2** with 55% yield, whereas *ent*-**2** was isolated in 43% yield after six hours reaction time starting from *ent-syn*-**1**. We applied these conditions also to *anti*-**1** (the C-3 epimer of *syn*-**1**), but the respective aminofuran derivative was not observed. The only product isolated in little amounts was a methyl furanoside with an intact 1,2-oxazine ring whose formation was already described by our group.[4]

**Table 1** Acid-Mediated Transformation of 3,5-Dihydro-2*H*-1,2-oxazines **1** into Aminofuran Derivatives **2**[a]



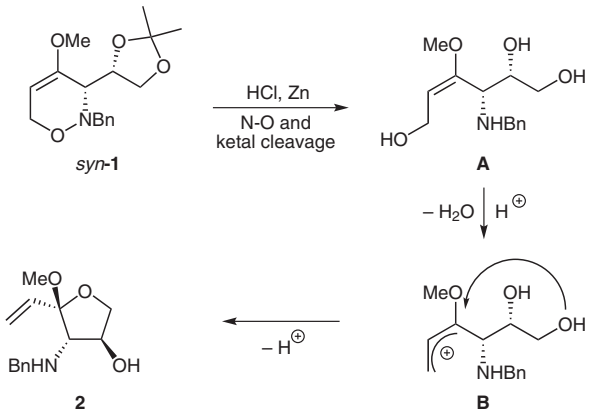

| 1,2-Oxazine | Conditions | Product | Yield (%) |
|---|---|---|---|
|  *syn*-**1** | a |  **2** | 55 |
|  *ent-syn*-**1** | b |  *ent*-**2** | 43 |

[a] *Reagents and conditions*: (a) 3 N HCl (5 equiv), Zn (20 equiv), MeOH, r.t., 1 d; (b) 3 N HCl (5 equiv), Zn (20 equiv), MeOH, r.t., 6 h.

With respect to the possible reaction mechanism we suggest an initial reductive N–O bond and an acid-promoted ketal cleavage to form acyclic allylic alcohol **A** (Scheme 1). Under the acidic conditions a fairly stabilised allylic cation **B** is readily generated, which is then trapped intramolecularly by the primary hydroxy group forming the kinetically and thermodynamically preferred five-membered ring in a stereoselective fashion. Loss of a proton completes the reaction leading to **2**. The relative configuration at the anomeric centre could not be proved rigorously so far. We tried an iodocyclization with *ent*-**2**, but unfortunately neither a cyclisation involving the amino group nor the hydroxy group took place. The NOESY spectrum of *ent*-**2** shows correlation peaks between both benzylic protons and one of the terminal vinylic protons, which indicates that the given assignment is more likely and in agreement with that of previously reported aminofuran derivatives.[4]

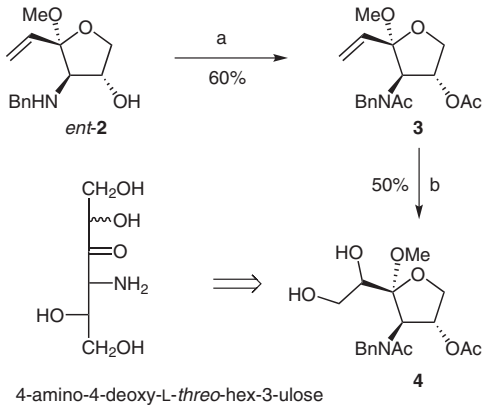
Since the vinyl group of *ent*-**2** is an attractive feature for subsequent transformations we performed a few preliminary experiments. First choices were olefin metathesis and dihydroxylation. In order to prevent side reactions *ent*-**2** was first diacetylated with acetic anhydride in the

*SYNLETT* 2010, No. 1, pp 0047–0050
Advanced online publication: 02.12.2009
DOI: 10.1055/s-0029-1218532; Art ID: G33109ST



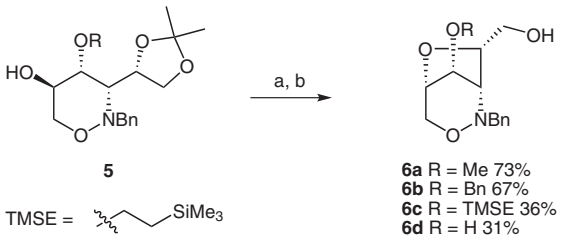

**Scheme 1** Proposed mechanism for transformation of *syn*-**1** to generate aminofuran derivative **2**

presence of triethylamine and DMAP to yield compound **3** in 60% (Scheme 2). With respect to olefin metathesis we tried homodimerisation as well as cross metathesis but did not succeed in any case. Fortunately, dihydroxylation was possible although a rather long reaction time was required. In the presence of potassium osmate, NMO, and methanesulfonamide compound **3** was stereoselectively converted into the respective dihydroxylated product **4** within 19 days at room temperature in 50% yield (Scheme 2).[8] The configuration at the newly formed stereogenic centre is unknown and currently under investigation. The low reactivity of the vinyl group might be due to the steric hindrance exhibited by the highly substituted furan ring. Amino ketose derivatives such as **4** are thus available (in both enantiomeric forms) after three simple steps.



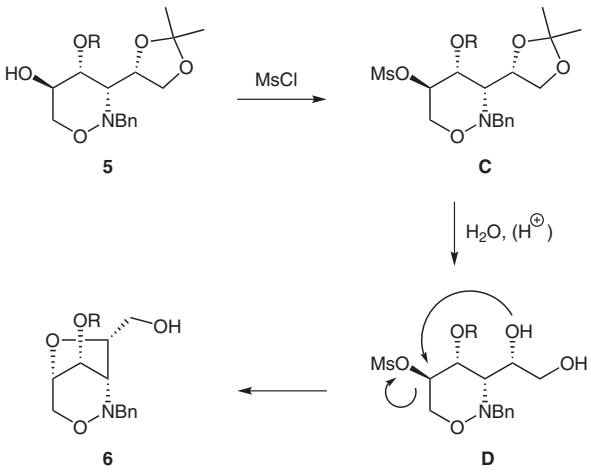

**Scheme 2** Acetylation of *ent*-**2** and subsequent dihydroxylation of **3** leading to aminofuran derivative **4**. *Reagents and conditions*: (a) $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$, r.t., 1 d; (b) $K_2OsO_4{\cdot}H_2O$, NMO, methanesulfonamide, *t*-BuOH–$H_2O$ (1:1), r.t., 19 d.

The second acid-mediated transformation starts from 5-hydroxy-1,2-oxazine derivatives which can routinely be synthesised by hydroboration of 3,6-dihydro-2*H*-1,2-oxazines **1** and subsequent oxidative workup.[9] Three differently protected 1,2-oxazines **5a–c** were first mesylated within one day at room temperature, and the resulting products were heated either as crude or as purified compounds in an acetonitrile–water mixture at 90–100 °C for one day. This protocol resulted in regio- and stereoselective formation of the novel bicyclic 1,2-oxazine derivatives **6a–c** in good yields (Scheme 3).[10] In the case of the TMSE-protected precursor cleavage of this group could not be avoided and in addition to 36% of **6c** 31% of **6d** were isolated.




**Scheme 3** Acid-mediated transformation of 5-hydroxy-3,4,5,6-tetrahydro-1,2-oxazines **5a–c** into bicyclic compounds **6**. *Reagents and conditions*: (a) MsCl, pyridine, r.t., 1 d; (b) MeCN–$H_2O$ (1:1 or 3:1), 90–100 °C, 1 d.

A plausible mechanism for the furan ring formation is presented in Scheme 4. Mesylate **C** suffers ketal cleavage when exposed to acetonitrile–water at higher temperature furnishing diol **D**. A subsequent intramolecular nucleophilic displacement of the mesylate generates bicyclic 1,2-oxazine derivative **6**. At least traces of acid are required for the initial ketal cleavage. If the crude mesylation products were used remaining pyridinium salts may act as proton source. In case of purified mesylate **C** as starting material, protons are probably generated by partial hydrolysis of the mesylate in the aqueous environment.

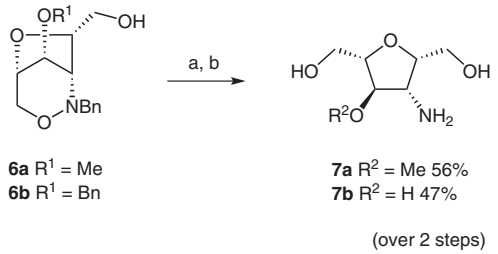



**Scheme 4** Mechanism for transformation of 1,2-oxazine derivatives **5** into bicyclic compounds **6**

The observed stereoselectivity is a result of an $S_N2$-type process for the ring closure. To prove this assumption, we conducted the reaction sequence also with the C-5 epimer of **5b**. In this case no cyclisation product was observed, but a triol resulting from simple hydrolysis of the mesylate and ketal moieties. Thus involvement of an $S_N1$-type reaction via a carbenium ion is fairly unlikely. Regiose-

lective formation of a furan ring instead of the respective pyran system is apparently strongly favoured. The constitution of compounds **6** was proven by its $^1$H NMR spectra in $CD_3CN$, which showed a triplet for the hydroxy group proton.

An attractive feature in 1,2-oxazine derivatives is generally the relatively weak N–O bond which can be cleaved under mild conditions furnishing amino alcohols. We tried this transformation also with the new bicyclic compounds **6a**–**b**. Since the standard protocol employing samarium diiodide for reductive ring opening[9] did not lead to full conversion, we again switched to the combination of hydrochloric acid and zinc in methanol which proved to be more reliable for this compound class (Scheme 5). Finally, removal of the benzyl groups was achieved by catalytic hydrogenolysis giving polyhydroxylated amino tetrahydrofurans **7a** and **7b** in moderate overall yields. The NMR data of these products clearly indicate that they contain a furan core rather than a pyran ring, which further proves the regioselective formation of a five-membered heterocycle during the cyclisation described in Schemes 3 and 4. Compounds **7a** and **7b** are promising components for the preparation of gold-nanoparticle-based multivalent selectin inhibitors.[11,12]




**6a** $R^1$ = Me
**6b** $R^1$ = Bn

**7a** $R^2$ = Me 56%
**7b** $R^2$ = H 47%

(over 2 steps)

**Scheme 5** N–O bond cleavage and deprotection of **6a**,**b** leading to amino furan derivatives **7**. *Reagents and conditions*: (a) 3 N HCl, Zn, MeOH, r.t., 1.5 h; (b) $H_2$, Pd/C, MeOH, r.t., 1 d.

In conclusion, we found two new methods for acid-promoted transformations of 1,2-oxazine derivatives into new highly functionalised aminotetrahydrofuran derivatives. The first reaction provided vinyl-substituted compounds which can be used for further functionalisations whereas the second protocol involved 5-mesyloxy-substituted 3,4,5,6-tetrahydro-1,2-oxazines which were regio- and stereoselectively transformed into novel bicyclic 1,2-oxazine derivatives. Reductive cleavage of the N–O bond and debenzylation furnished hydroxylated amino furans. All resulting products should be of interest as new unusual amino sugar derivatives.

## Acknowledgment

The authors thank the Deutsche Forschungsgemeinschaft (RE 514/11 and SFB 765), the Fonds der Chemischen Industrie, and the Bayer Schering Pharma AG for financial support. We gratefully acknowledge the experimental assistance of Sebastian Fischer and the help of Dr. R. Zimmer during preparation of this manuscript.

## References and Notes

(1) For reviews, see: (a) Zimmer, R. *Synthesis* **1993**, 165. (b) Zimmer, R.; Reissig, H.-U. In *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, **2004**, 425.

(2) For reviews, see: (a) Reissig, H.-U.; Hormuth, S.; Schade, W.; Okala Amombo, M.; Watanabe, T.; Pulz, R.; Hausherr, A.; Zimmer, R. *J. Heterocycl. Chem.* **2000**, *37*, 597. (b) Reissig, H.-U.; Schade, W.; Okala Amombo, M. G.; Pulz, R.; Hausherr, A. *Pure Appl. Chem.* **2002**, *74*, 175. (c) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45.

(3) (a) Flögel, O.; Reissig, H.-U. *Eur. J. Org. Chem.* **2004**, 2797. (b) Chowdhury, M. A.; Reissig, H.-U. *Synlett* **2006**, 2383. (c) Brasholz, M.; Reissig, H.-U. *Synlett* **2007**, 1294. (d) Brasholz, M.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **2007**, *46*, 1634; *Angew. Chem.* **2007**, *119*, 1659. (e) Brasholz, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2009**, 3595.

(4) (a) Pfrengle, F.; Al-Harrasi, A.; Reissig, H.-U. *Synlett* **2006**, 3498. (b) Bressel, B.; Egart, B.; Al-Harrasi, A.; Pulz, R.; Reissig, H.-U.; Brüdgam, I. *Eur. J. Org. Chem.* **2008**, 467. (c) Pfrengle, F.; Al-Harrasi, A.; Brüdgam, I.; Reissig, H.-U. *Eur. J. Org. Chem.* **2009**, 282.

(5) (a) Schade, W.; Reissig, H.-U. *Synlett* **1999**, 632. (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.

(6) Kumaran, S.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2006**, 3211.

(7) **Typical Procedure for Furan Synthesis**, **Conversion of *ent-syn*-1 into *ent*-2**
1,2-Oxazine *ent-syn*-**1** (200 mg, 0.655 mmol) was dissolved in MeOH (13 mL). Then Zn dust (214 mg, 3.27 mmol) and 3 N HCl (4.36 mL, 13.1 mmol) were added. The mixture was stirred for 6 h at r.t. Upon completion of the reaction the mixture was neutralised with solid $NaHCO_3$, $H_2O$ was added and extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$ and filtrated, and solvents were removed in vacuo. Purification via silica gel column chromatography (hexane–EtOAc) afforded *ent*-**2** (70 mg, 43%) as a colourless oil.
**Analytical Data of Methyl-4-benzylamino-1,2,4-trideoxy-α-L-*threo*-hex-1-en-3-ulofuranoside (*ent*-2)**
$[\alpha]_D^{20}$ +64.3 (*c* 0.80, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): δ = 2.84 ($s_{br}$, 2 H, NH, OH), 2.93 (d, *J* = 6.7 Hz, 1 H, 4-H), 3.20 (s, 3 H, OMe), 3.68 (dd, *J* = 5.3, 9.3 Hz, 1 H, 6-H), 3.74, 3.97 (2 d, *J* = 12.9 Hz, 2 H, $NCH_2$), 4.01 (dd, *J* = 7.1, 9.3 Hz, 1 H, 6-H), 4.17 (ddd, *J* = 5.3, 6.7, 7.1 Hz, 1 H, 5-H), 5.32 (dd, *J* = 1.6, 10.8 Hz, 1 H, 1-H), 5.55 (dd, *J* = 1.6, 17.4 Hz, 1 H, 1-H), 5.87 (dd, *J* = 10.8, 17.4 Hz, 1 H, 2-H), 7.23–7.26, 7.30–7.34 (2 m, 5 H, Ph) ppm. $^{13}$C NMR (126 MHz, $CDCl_3$): δ = 49.3 (q, OMe), 52.2 (t, $NCH_2$), 70.8 (t, C-6), 73.9 (d, C-4), 76.5 (d, C-5), 105.0 (s, C-3), 118.2 (t, C-1), 127.1, 128.2, 128.4, 139.9 (3 d, s, Ph) 136.2 (d, C-2) ppm. IR (film): 3410, 3330 (OH, NH), 3090–3030 (=CH), 2990–2830 (CH), 1605, 1585, 1495 (C=C) $cm^{-1}$. HRMS (ESI-TOF-MS): *m/z* calcd for $C_{14}H_{19}NO_3$ $[M + H]^+$: 250.1438; found: 250.1443. Anal. Calcd for $C_{14}H_{19}NO_3$ (249.3): C, 67.45; H, 7.68; N, 5.62. Found: C, 67.01; H, 7.66; N, 5.53.

(8) Product **4** contained small amounts (ca. 5%) of one byproduct, possibly the second epimer with respect to the newly formed stereogenic centre.

(9) (a) Pulz, R.; Al-Harrasi, A.; Reissig, H.-U. *Org. Lett.* **2002**, *4*, 2353. (b) Dekaris, V.; Reissig, H.-U. *Synlett* **2010**, 42.

(10) **Typical Procedure for the Synthesis of Bicyclic 1,2-Oxazines**, **Conversion of 5a into 6a**
To a solution of **5a** (734 mg, 2.27 mmol) in pyridine (10 mL) under argon at r.t. MsCl (0.296 mL, 3.82 mmol) was added. The mixture was stirred 1 d at r.t., quenched with 5% $CuSO_4$ solution (4 mL), and extracted three times with $Et_2O$. The combined organic layers were washed twice with $H_2O$ and dried with $MgSO_4$. After filtration and removal of the solvents the crude product was dissolved in MeCN (2.5 mL), $H_2O$ (2.5 mL) was added, the mixture was placed in a sealed tube and heated 1 d at 100 °C. After completion of the reaction the mixture was extracted with $Et_2O$ (3 × 5 mL), the combined organic layers were dried with $MgSO_4$, filtrated, and the solvents removed in vacuo. Purification via silica gel column chromatography (hexane–EtOAc) afforded bicyclic compound **6a** (440 mg, 73% over both steps) as a colourless oil.
**Analytical Data of (1*S*,5*S*,7*S*,8*R*)-(2-Benzyl-8-methoxy-3,6-dioxa-2-azabicyclo[3.2.1]oct-7-yl)methanol (6a)**
$[\alpha]_D^{20}$ +23.4 (*c* 0.71, $CHCl_3$). $^1$H NMR (500 MHz, $CD_3CN$): δ = 2.84 (t, *J* = 5.8 Hz, 1 H, OH), 3.33 (s, 3 H, OMe), 3.51 ($m_c$, 1 H, 1-H), 3.55 (ddd, *J* = 0.8, 4.1, 11.4 Hz, 1 H, 4-$H_A$), 3.56 (d, *J* = 11.4 Hz, 1 H, 4-$H_B$), 3.98–4.02 (m, 3 H, 8-H, 1′-H), AB system ($\delta_A$ = 4.03, $\delta_B$ = 4.10, *J* = 13.9 Hz, 2 H, $NCH_2$), 4.10–4.14 (m, 1 H, 7-H), 4.26 (dd, *J* = 0.8, 4.1 Hz, 1 H, 5-H), 7.24–7.28, 7.31–7.36 (2 m, 5 H, Ph) ppm. $^{13}$C NMR (126 MHz, $CD_3CN$): δ = 55.8 (q, OMe), 58.5 (t, $NCH_2$), 61.7 (t, C-1′), 65.6 (d, C-1), 69.6 (t, C-4), 76.3 (d, C-5), 81.0 (d, C-8), 81.6 (d, C-7), 128.1, 129.2, 129.6, 139.3 (3d, s, Ph) ppm. IR (film): 3420 (OH), 3085–3030 (=CH), 2930–2830 (CH) $cm^{-1}$. MS (EI, 80 eV, 150 °C): *m/z* (%) = 265 (21) [$M^+$], 91 (100) $[C_7H_7]^+$, 71 (29), 43 (28). Anal. Calcd for $C_{14}H_{19}NO_4$ (265.3): C, 63.38; H, 7.22; N, 5.28. Found: C, 62.90; H, 7.51; N, 5.27.

(11) For the examination of another carbohydrate mimetic as component of gold-nanoparticle-based multivalent selectin inhibitors, see: Dernedde, J.; Enders, S.; Reissig, H.-U.; Roskamp, M.; Schlecht, S.; Yekta, S. *Chem. Commun.* **2009**, 932.

(12) Gold nanoparticles with sulfated aminotetrahydrofuran derivative **7a** were tested in a similar way as described in ref. 11. Excellent activity and selectivity were observed with $IC_{50}$ values of 390 pm for L-selectin and 50 pm for P-selectin. Dekaris, V.; Dernedde, J.; Enders, S.; Reissig, H.-U.; Roskamp, M.; Schlecht, *unpublished results*.