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Acid-Induced and Reductive Transformations of Enantiopure 3,6-Dihydro-2*H*-1,2-oxazines – Synthesis of Dideoxyamino Carbohydrate Derivatives

Bettina Bressel,[a] Boris Egart,[a] Ahmed Al-Harrasi,[a] Robert Pulz,[a] and Hans-Ulrich Reißig,*[a] Irene Brüdgam[a][‡]

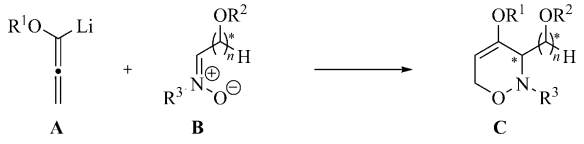
Dedicated to Professor Hans Paulsen on the occasion of his 85th birthday

Keywords: 1,2-Oxazines / Furans / Pyrans / Carbohydrates / Reductions / Samarium diiodide

Acid-catalyzed transformations of carbohydrate-derived 3,6-dihydro-2*H*-1,2-oxazines such as **1**, **5** and **13** provided a set of enantiopure furano-1,2-oxazines or pyrano-1,2-oxazines. The reaction conditions determined the degree of solvolysis of the compounds. An X-ray analysis of product **6** revealed an interesting network of hydrogen bonds. Reductive cleavage of the N–O bond of the 1,2-oxazines either by hydrogen/palladium or by samarium diiodide furnished enantiopure aminofuran and -pyran derivatives, e.g. **9** and **11** or compound **16**, which can be regarded as protected 4-amino-1,4-dideoxyhex-3-ulose or 4-amino-1,4-dideoxyoct-3-ulose derivatives. We thus have established a short and stereocontrolled route to amino carbohydrate derivatives with 1,2-oxazines as crucial relay compounds.

Introduction

In recent publications we reported that lithiated alkoxyallenes **A** smoothly add to chiral carbohydrate-derived nitrones **B** to provide 3,6-dihydro-2*H*-1,2-oxazine derivatives **C** by a [3+3] cyclization in a stereocontrolled manner (Scheme 1).[1]



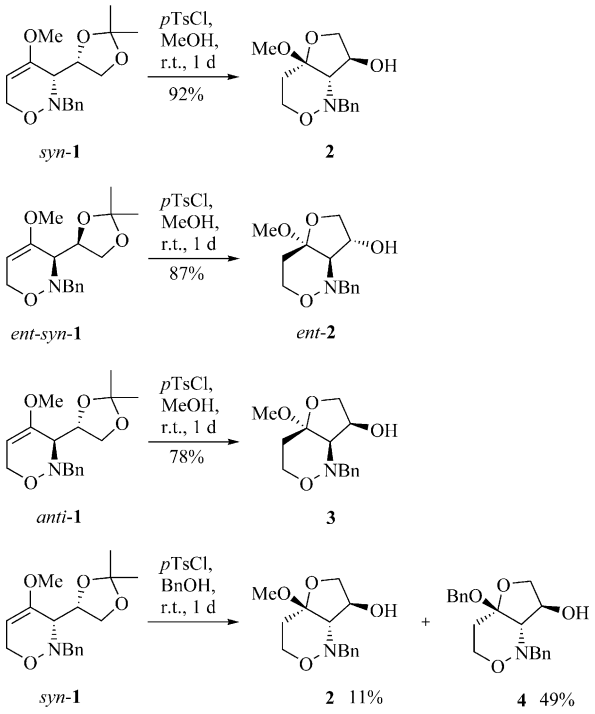
Scheme 1. Synthesis of 3,6-dihydro-2*H*-1,2-oxazines **C**.

The resulting heterocycles **C** are extremely versatile intermediates and serve as precursors for a variety of target compounds. Reductive,[2] acid-induced,[3] and Lewis-acid-promoted[4] transformations as well as cyclopropanations followed by palladium-catalyzed processes[5] have recently been reported by our group. These reaction sequences lead to enantiopure pyrrolidines, azetidines, and amino-substituted polyol derivatives or other interesting polyfunctionalized compounds. The synthetic potential of 2*H*-1,2-oxazines **C** thus nicely complements the chemistry of related 4*H*-1,2-oxazines[6] and 6*H*-1,2-oxazines[7] which were earlier investigated by our group. In this report we want to disclose the details of the acid-induced reactions of 3,6-dihydro-2*H*-1,2-oxazines **C**. The subsequent reductive steps provided new enantiopure dideoxyamino carbohydrate derivatives[8] in a simple fashion.

Results and Discussion

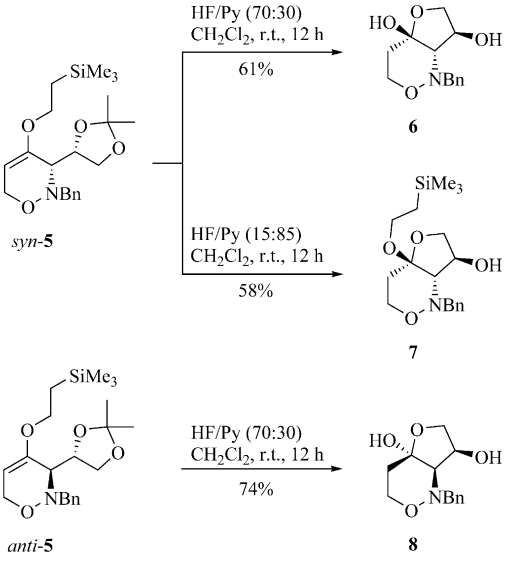
The 3,6-dihydro-2*H*-1,2-oxazines *syn*-**1**, its enantiomer *ent*-*syn*-**1**, and their diastereomer *anti*-**1** are smoothly available from lithiated methoxyallene and D- or L-glyceraldehyde-derived *N*-benzyl nitrone in a stereodivergent manner and fairly large scale.[1] They therefore served as first-choice substrates for the exploration of subsequent reactions of this class of enantiopure heterocycles. Treatment of these three isomers with *p*-toluenesulfonyl chloride in methanol furnished the three bicyclic furano-1,2-oxazine derivatives **2**, *ent*-**2**, and **3** in good yields (Scheme 2). When the rearrangement of *syn*-**1** was performed in benzyl alcohol, benzyloxy-substituted derivative **4** was obtained as main product, beside a small amount of the expected furano-1,2-oxazine **2**. These rearrangements are catalyzed by hydrochloric acid which is slowly generated by the reaction of the sulfonyl chloride with the solvent.[9] The detailed mechanism is presented below (Scheme 4). The configuration of bicycles **2**, **3**, and **4** with *cis* fusion of the two rings was proved by NOESY experiments and finally supported by the X-ray analysis of the related compound **6** (see below; Figures 1 and 2).

[a] Institut für Chemie und Biochemie, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany
Fax: +49-30-838-55367
E-mail: hans.reissig@chemie.fu-berlin.de
[‡] Responsible for X-ray analyses.



Scheme 2. Acid-induced rearrangements of 1,2-oxazines.

We also studied acid-promoted reactions of the two diastereomeric 2-(trimethylsilyl)ethoxy-substituted 3,6-dihydro-2*H*-1,2-oxazines *syn*-**5** and *anti*-**5**.[1b] Treatment of the *syn* isomer with pyridine/hydrogen fluoride (30% pyridine, 70% HF),[10] which is a milder acidic reagent than hydrochloric acid in methanol, afforded 61% of bicyclic semiketal **6** (Scheme 3). Addition of more pyridine (85% pyridine, 15% HF) reduced the acidity of this reagent even more and hence allowed isolation of 2-(trimethylsilyl)ethoxy-substituted ketal **7** in moderate yield. By employing the unbuffered pyridine/hydrogen fluoride the diastereomeric *anti*-**5** furnished 74% of the expected semiketal **8**.



Scheme 3. Acid-induced rearrangements of 2-(trimethylsilyl)-ethoxy-substituted 1,2-oxazines.

The relative configuration of semiketal **6** was unequivocally proven by an X-ray analysis clearly showing the *cis* fusion of the two rings and the *cis* arrangement of the two hydroxy groups (Figure 1).[11] The hydroxy group at the bridgehead occupies the thermodynamically more stable axial position (anomeric effect). This X-ray analysis also strongly supports the assignments for the closely related compounds **2** and **7**.

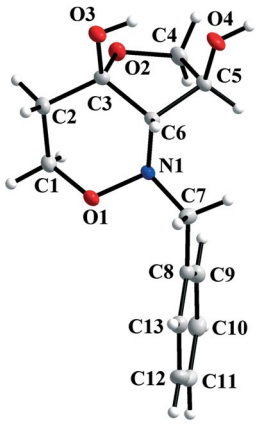


Figure 1. X-ray crystal structure of compound **6**.

The crystal structure of **6** reveals an intriguing network of intra- and intermolecular hydrogen bonds with a repetition unit of two bicyclic furano-1,2-oxazine molecules (Figure 2, the subsequent discussion starting at the left side of the Figure). The proton H3 is connected in a transannular fashion with O4, and H4 interacts with the furan oxygen atom O2A of the next molecule. The axial H3a forms an intramolecular hydrogen bond to the axial O4A like in the first molecule; however, H4a of this molecule interacts not with the furan oxygen atom of the next molecule but with O3. The distances between the different oxygen atoms involved in this network of hydrogen bonds are collected in Table 1.

The straightforward mechanism of these acid-induced rearrangements of 3,6-dihydro-2*H*-1,2-oxazines is depicted in Scheme 4. Acid-catalyzed cleavage of the dioxolane unit[10c] and protonation of the enol ether moiety provide a stabilized carbenium ion **D** which can undergo an intramolecular cyclization leading to bicyclic ketal **E** with the OR^1 group still being present. Further acid-induced dissociation to **F** can finally lead to products **G** bearing, depending on the solvent, either an alkoxy or a hydroxy group at the bridgehead. The equilibria of all steps allow thermodynamic control which leads to compounds **E** or **G** with axially exposed oxygen substituents at the anomeric bridgehead centre.

In general, the synthetic value of stereoselectively formed 1,2-oxazine derivatives is caused by the option that their N–O bond can be cleaved under fairly mild reaction conditions – usually by reductive methods.[12] When furano-1,2-oxazine **2** was reduced by employing standard conditions

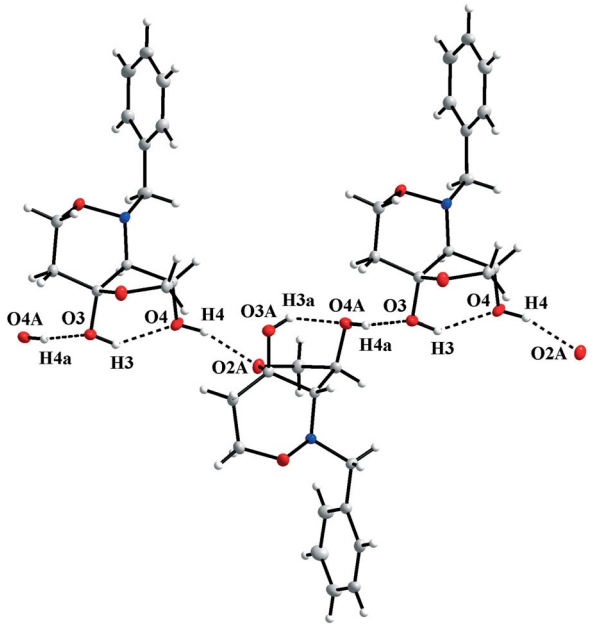
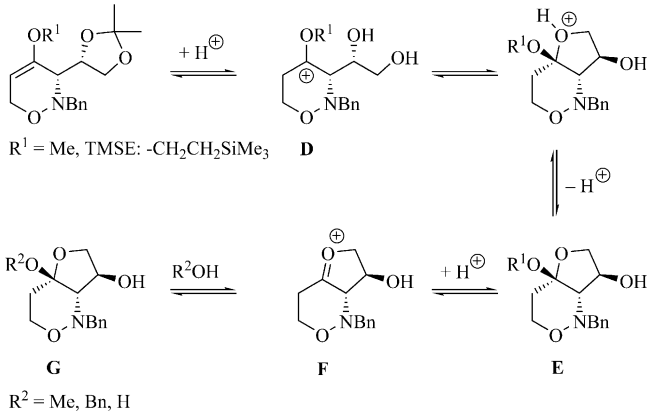


Figure 2. Hydrogen-bond networks within compound **6**.

Table 1. Hydrogen bonds of compound **6** with H···Acc distance < *r*(Acc) + 2.000 Å and Don–H···Acc angle > 110°.

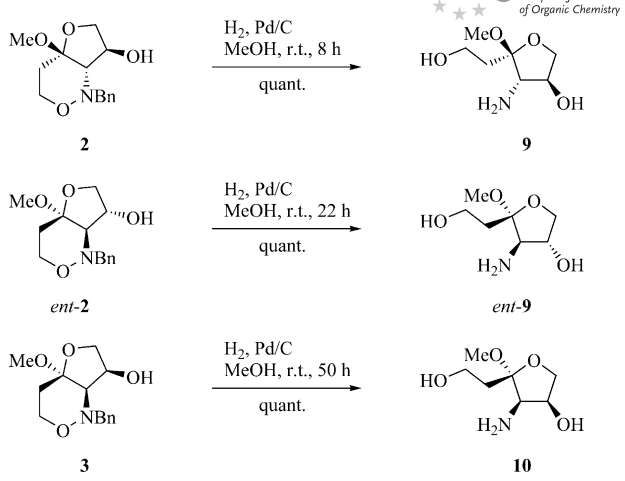
Don–H···Acc	Don–H	H···Acc	Do···Acc	Do–H···Acc
O(3)–H(3)···O(4)	0.87	2.02	2.75	141
O(3A)–H(3A)···O(4A)	0.79	2.09	2.77	144
O(4A)–H(4A)···O(3)[a]	0.81	1.96	2.76	171
O(4)–H(4)···O(2A)	0.87	1.97	2.81	163

[a] Symmetry transformations used to generate equivalent atoms: *x*, *y*, *z* – 1.



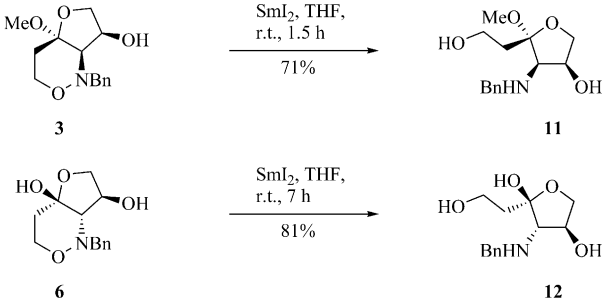
Scheme 4. Mechanism of acid-induced rearrangement.

(hydrogen/palladium in methanol) it was quantitatively transformed into trisubstituted 3-aminotetrahydrofuran derivative **9** (Scheme 5). This transformation requires removal of the *N*-benzyl group (very likely the first step) and N–O bond cleavage of the 1,2-oxazine ring. Similarly, enantiomer *ent*-**2** and diastereomer **3** provided *ent*-**9** and **10** in quantitative yield.



Scheme 5. Hydrogenation of furano-1,2-oxazine derivatives.

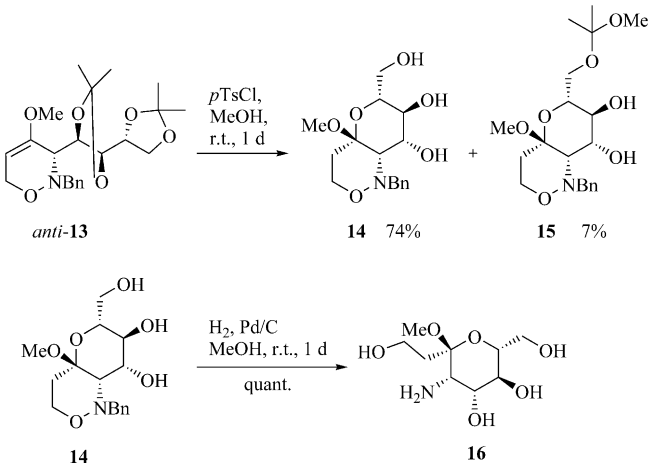
Whereas the removal of the *N*-benzyl group can hardly be avoided with hydrogen/palladium, samarium diiodide as reducing agent allows chemoselective cleavage of the N–O bond without touching the *N*-protecting group.[13] Furano-1,2-oxazines **3** and **6** were converted by SmI_2 into monocyclic 3-aminofuran derivatives **11** and **12** still containing the *N*-benzyl group (Scheme 6). Since compounds such as **2**, *ent*-**2**, **3**, and **7** will allow protection of their secondary hydroxy group, the corresponding ring-opened products are also available in selectively protected forms. It will therefore be easily possible to incorporate these amino carbohydrate derivatives into di- and oligosaccharides.



Scheme 6. Ring cleavage of furano-1,2-oxazines promoted by samarium diiodide.

D-Arabinose-based 3,6-dihydro-2*H*-1,2-oxazine *anti*-**13**[1b] was transformed by acid catalysis in methanol into the pyrano-1,2-oxazine derivative **14** in 74% yield. As a second product and result of an incomplete ketal cleavage, we isolated a compound in ca. 7% yield, for which we propose structure **15**. The longer side chain of *anti*-**13** allows the acid-catalyzed formation of the thermodynamically more favoured pyran ring instead of the furan ring observed for the dioxolanyl-substituted 1,2-oxazines shown in Scheme 2. In analogy to the furan derivatives the assumed *cis* fusion of the two rings of **14** was confirmed by NOESY experiments. When pyrano-1,2-oxazine **14** was exposed to hydrogen in the presence of palladium on charcoal the expected deprotected amino carbohydrate **16** was quantitatively ob-

tained. Selectively protected derivatives of this compound should be easily available if protections at the stage of **14** are performed (Scheme 7).



Scheme 7. Rearrangement of *anti*-**13** and hydrogenation of intermediate **14** leading to pyran derivative **16**.

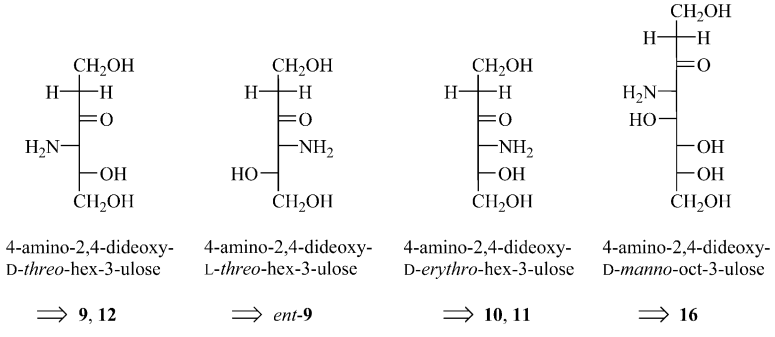
Conclusions

We demonstrated in this report that acidic treatment of easily available enantiopure carbohydrate-derived 3,6-dihydro-2*H*-1,2-oxazines smoothly provided furano- or pyrano-1,2-oxazines, which were further reduced to give enantiopure 3-aminofuran and 3-aminopyran derivatives such as **9**, *ent*-**9**, **10**, or **16**. The monocyclic compounds prepared are protected 4-amino-2,4-dideoxyhex-3-ulose[14] (with *erythro* or *threo* configurations) or *manno*-configured 4-amino-2,4-dideoxyoct-3-ulose derivatives[15] as illustrated in Scheme 8. We have hence developed a very short and entirely stereocontrolled route to these carbohydrate derivatives by using 1,2-oxazines of type **C** as crucial compounds.

In our synthetic concept we employ lithiated alkoxyallenes[16,17] for the efficient and stereocontrolled elongation of carbohydrate-derived nitrones by three functionalized carbon atoms. This leads to enantiopure 3,6-dihydro-2*H*-1,2-oxazines **C** as relay intermediates, which can be used for a manifold of subsequent reactions. Whereas in the present report the enol ether moiety of **C** just undergoes an acid-induced hydrolysis, it can also be used for the introduction of a variety of additional substituents at the 1,2-oxazine intermediate. An additional hydroxy group can be installed in a highly stereoselective manner by hydroboration,[18] and an intramolecular aldol-type reaction resulted in C–C bond formation[4a] and generation of novel bicyclic 1,2-oxazine derivatives. In all these functionalized 1,2-oxazines the N–O bond can be reductively cleaved which stereoselectively affords more complex amino-substituted polyols and related compounds.

Experimental Section

General Methods: Reactions were generally performed under argon in flame-dried flasks, and the components were added by syringe. Dichloromethane was distilled from calcium hydride and stored over molecular sieves (4 Å). Tetrahydrofuran was freshly distilled from sodium/benzophenone under argon. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck) or neutral alumina (Fluka). Unless otherwise stated, yields refer to analytically pure samples. ^{1}H NMR [$CHCl_3$ (δ = 7.26 ppm), TMS (δ = 0.00 ppm), MeOD (δ = 3.31 ppm), or DMSO (δ = 2.50 ppm) as internal standards] and ^{13}C NMR spectra [$CDCl_3$ (δ = 77.0 ppm), CD_3OD (δ = 49.0 ppm), or [D_6]DMSO (δ = 39.5 ppm) as internal standards] were recorded with Bruker AC 250, DRX 500, or AC 500 or Joel Eclipse 500 instruments in $CDCl_3$, CD_3OD, or [D_6]DMSO solutions. Integrals are in accordance with assignments; coupling constants are given in Hz. IR spectra were measured with an FTIR spectrometer Nicolet 5 SXC, Perkin–Elmer 205, or with a Nexus FT-IR instrument equipped with a Nicolet Smart DuraSamplIR ATR. MS and HRMS analyses were performed with Finnigan MAT 711 (EI, 80 eV, 8 kV), MAT 95 (EI, 70 eV), MAT CH7A (EI, 80 eV, 3 kV), CH5DF (FAB, 80 eV, 3 kV) and Varian Ionspec QFT-7 (ESI-FT ICRMS) instruments. The elemental analyses were recorded with "Elemental-Analyzers" (Perkin–Elmer or Carlo Erba). Melting points were measured with a Reichert apparatus or according to Boëtius with a Rapido apparatus and are uncorrected. Optical rotations ($[\alpha]_D$) were determined with Perkin–Elmer 141 or Perkin–Elmer 241 polarimeters at the temperatures given. Single-crystal X-ray data were collected with a Bruker SMART CCD diffractometer (Mo-K_α radiation, λ = 0.71073 Å, graphite monochromator), structure solution and refinement by SHELXS-97[19] and SHELXL-97[20] in the WINGX system.[21] CCDC-657955 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Starting materials *syn*-**1**, *anti*-**1**, *syn*-**5**, *anti*-**5**, and *anti*-**13** were prepared according to our published procedures.[1b] All other chemicals are commercially available and were used without further purification.



Scheme 8. Fischer projections of hypothetical products derived from **9**, **12**, *ent*-**9**, **10**, **11**, and **16**.

(3*R*,4′*R*)-2-Benzyl-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-4-methoxy-3,6-dihydro-2*H*-1,2-oxazine (*ent*-*syn*-1): In analogy to the preparation of *syn*-**1**,[1b] its enantiomer *ent*-*syn*-**1** was prepared from (*Z*)-*N*-(1-deoxy-2,3-*O*-isopropylidene-l-glycero-1-ylidene)benzylamine *N*-oxide[22,23] and lithiated methoxyallene. Yield: 71%. All spectroscopic data are identical with those of *syn*-**1**. $[\alpha]_D^{22}$ = –37.6 (*c* = 1.0, $CHCl_3$).[24] $C_{17}H_{23}NO_4$ (305.4): calcd. C 66.86, H 7.59, N 4.59; found C 66.81, H 7.69, N 4.67.

General Procedure 1 (GP 1): To a stirred solution of *p*-toluenesulfonyl chloride (*p*TsCl, 0.5 equiv.) in dry methanol (ca. 10 mL per mmol *p*TsCl) under dry argon, a solution of the 1,2-oxazine (1 equiv.) in dry methanol (ca. 10 mL per mmol *p*TsCl) was added. The mixture was stirred at room temperature for 24 h and then quenched with satd. aq. $NaHCO_3$ solution (ca. 20 mL per mmol *p*TsCl). The aqueous layer was extracted with dichloromethane, the combined organic phases were dried ($MgSO_4$), and the solvent was removed under vacuum.

(4a*S*,7*S*,7a*S*)-1-Benzyl-4a-methoxyhexahydro-1*H*-furano[3,2-*c*][1,2]-oxazin-7-ol (2): *p*TsCl (0.156 g, 0.819 mmol) and *syn*-**1** (0.500 g, 1.64 mmol) in dry methanol (10 mL each) were treated as described in **GP 1** (extraction with 3 × 20 mL dichloromethane). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 3:2) to give **2** as colourless crystals (0.400 g, 92%), m.p. 27–29 °C. $[\alpha]_D^{20}$ = +100.6 (*c* = 1.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.86 (ddd, *J* = 6.3, 11.9, 12.7 Hz, 1 H, 4-H), 2.12 (br. d, *J* ≈ 12.7 Hz, 1 H, 4-H), 3.13 (s, 1 H, 7a-H), 3.33 (s, 3 H, OMe), 3.44 (d, *J* = 11.7 Hz, 1 H, OH), 3.80 (dt, *J* = 2.7, 11.9 Hz, 1 H, 3-H), 3.80 (d, *J* = 15.2 Hz, 1 H, NCH_2), 3.88 (br. dd, *J* = 6.3, 11.9 Hz, 1 H, 3-H), 3.91 (dd, *J* = 1.5, 9.8 Hz, 1 H, 6-H), 4.05 (br. dd, *J* = 5.5, 11.7 Hz, 1 H, 7-H), 4.18 (d, *J* = 15.2 Hz, 1 H, NCH_2), 4.42 (dd, *J* = 5.5, 9.8 Hz, 1 H, 6-H), 7.25–7.41 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.4 (t, C-4), 47.8 (q, OMe), 59.7 (t, NCH_2), 65.8 (t, C-3), 74.6 (d, C-7), 76.2 (t, C-6), 76.3 (d, C-7a), 105.8 (s, C-4a), 127.1, 127.8, 128.3, 138.2 (3 d, s, Ph) ppm. IR (CCl_4): ṽ = 3480 (O–H), 3110–3030 (=C–H) 2940–2890 (C–H) cm^{-1}. $C_{14}H_{19}NO_4$ (265.3): calcd. C 63.38, H 7.22, N 5.28; found C 63.33, H 7.18, N 5.18.

(4a*R*,7*R*,7a*R*)-1-Benzyl-4a-methoxyhexahydro-1*H*-furano[3,2-*c*]-[1,2]oxazin-7-ol (*ent*-2): *p*TsCl (0.096 g, 0.50 mmol) and *ent*-*syn*-**1** (0.305 g, 1.00 mmol) in dry methanol (5 mL each) were treated as described in GP 1. After quenching with satd. aq. $NaHCO_3$ solution, water was added until the white precipitate was dissolved, and the aqueous phase was extracted with dichloromethane (6 × 15 mL). Flash chromatography (silica gel; hexane/ethyl acetate, 4:1) of the residue gave *ent*-**2** (0.230 g, 87%) as colourless oil. All spectroscopic data are identical with those of **2**. $[\alpha]_D^{20}$ = –106.8 (*c* = 1.0, $CHCl_3$). $C_{14}H_{19}NO_4$ (265.3): calcd. C 63.38, H 7.22, N 5.28; found C 63.36, H 7.34, N 5.34.

(4a*R*,7*S*,7a*R*)-1-Benzyl-4a-methoxyhexahydro-1*H*-furano[3,2-*c*]-[1,2]oxazin-7-ol (3): *p*TsCl (0.062 g, 0.325 mmol) and *anti*-**1** (0.200 g, 0.655 mmol) in dry methanol (4 mL each) were treated as described in GP 1 (extraction with 3 × 10 mL of dichloromethane). The residue was purified by column chromatography (silica gel; hexane/ethyl acetate, 3:2) to give **3** as colourless crystals (0.136 g, 78%), m.p. 66–68 °C. $[\alpha]_D^{24}$ = –75.9 (*c* = 0.54, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.07–2.13 (m, 2 H, 4-H), 3.10 (d, *J* = 6.8 Hz, 1 H, OH), 3.13 (d, *J* = 5.5 Hz, 1 H, 7a-H), 3.26 (s, 3 H, OMe), 3.82–3.87 (m, 2 H, 3-H), 3.84 (d, *J* = 14.3 Hz, 1 H, NCH_2), 3.93 (dd, *J* = 2.5, 9.5 Hz, 1 H, 6-H), 3.99 (dd, *J* = 4.6, 9.5 Hz, 1 H, 6-H), 4.28 (d, *J* = 14.3 Hz, 1 H, NCH_2), 4.53 (m_c, 1 H, 7-H), 7.19–7.38 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.0 (t, C-4), 48.4 (q, OMe), 61.3 (t, NCH_2), 64.7 (t, C-3), 71.3 (d, C-7a), 72.7 (d, C-7), 73.0 (t, C-6), 105.4 (s, C-4a), 127.3, 128.3, 128.5, 137.2 (3 d, s, Ph) ppm. IR (KBr): ṽ = 3460 (O–H), 3085–3030 (=C–H), 2960, 2890 (C–H) cm^{-1}. $C_{14}H_{19}NO_4$ (265.3): calcd. C 63.38, H 7.22, N 5.28; found C 63.72, H 7.28, N 5.24.

(4a*S*,7*S*,7a*S*)-1-Benzyl-4a-benzyloxyhexahydro-1*H*-furano[3,2-*c*]-[1,2]oxazin-7-ol (4): *p*TsCl (0.134 g, 0.701 mmol) and *syn*-**1** (0.430 g, 1.41 mmol) were treated as described in GP 1 by using benzyl alcohol (15 mL) instead of methanol (extraction with 3 × 15 mL of dichloromethane). The residue was purified by column chromatography (neutral alumina; hexane/ethyl acetate, 4:1) to give **4** as colourless oil (0.235 g, 49%) and **2** as colourless crystals (0.041 g, 11%). $[\alpha]_D^{20}$ = +73.6 (*c* = 0.42, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.03 (ddd, *J* = 6.2, 12.0, 12.8 Hz, 1 H, 4-H), 2.23 (br. d, *J* ≈ 12.8 Hz, 1 H, 4-H), 3.23 (s, 1 H, 7a-H), 3.33 (d, *J* = 12.0 Hz, 1 H, OH), 3.83 (d, *J* = 15.2 Hz, 1 H, NCH_2), 3.85 (dt, *J* = 2.6, 12.0 Hz, 1 H, 3-H), 3.91 (ddd, *J* = 1.0, 6.2, 12.0 Hz, 1 H, 3-H), 3.99 (dd, *J* = 1.4, 9.9 Hz, 1 H, 6-H), 4.09 (br. dd, *J* ≈ 5.5, 12.0 Hz, 1 H, 7-H), 4.21 (d, *J* = 15.2 Hz, 1 H, NCH_2), 4.49 (dd, *J* = 5.5, 9.9 Hz, 1 H, 6-H), 4.55 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.75 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 7.26–7.39 (m, 10 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.4 (t, C-4), 59.7 (t, NCH_2), 63.1 (t, OCH_2Ph), 65.8 (t, C-3), 74.6 (d, C-7), 76.4 (d, C-7a), 76.5 (t, C-6), 106.2 (s, C-4a), 127.1, 127.9, 128.0, 128.2, 128.3, 128.6, 137.4, 137.7 (6 d, 2 s, Ph) ppm. IR (film): ṽ = 3520 (O–H), 3030 (=C–H) 2960, 2890 (C–H) cm^{-1}. $C_{20}H_{23}NO_4$ (341.4): calcd. C 70.36, H 6.79, N 4.10; found C 70.59, H 6.86, N 4.50.

General Procedure 2 (GP 2): To a solution of **5** in dichloromethane (10 mL per 1 mmol of **5**) was added HF/Py (ratio and amount see individual experiments) at 0 °C, and the resulting solution was stirred at 0 °C for 5 min, then at room temperature for 12 h. The reaction mixture was then diluted with ethyl acetate (50 mL per 1 mmol of **5**) and washed twice with aq. $NaHCO_3$ solution (5%) and brine. The organic layer was dried ($MgSO_4$) and concentrated under vacuum.

(4a*S*,7*S*,7a*S*)-1-Benzylhexahydro-4a*H*-furano[3,2-*c*]-1,2-oxazine-4a,7-diol (6): *syn*-**5** (0.100 g, 0.255 mmol) was treated with HF/Py (0.12 mL of 70% HF in pyridine) in dichloromethane (3 mL) as described in GP 2. The resulting pale brown solid (0.046 g) was purified by flash chromatography (silica gel; hexane/ethyl acetate, 1:3) to give **6** (0.043 g, 66%) as pale yellow crystals. HPLC afforded **6** (0.039 g, 61%) as colourless crystals, m.p. 94–98 °C. $[\alpha]_D^{22}$ = +106.5 (*c* = 0.28, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.00–2.08 (m, 2 H, 4-H), 3.19 (br. s, 1 H, 7a-H), 3.30, 3.62 (2 br. s, 1 H each, OH), 3.79–3.86 (m, 2 H, 3-H), 3.83 (d, *J* = 15.1 Hz, 1 H, NCH_2), 4.09 (dd, *J* = 0.8, 9.8 Hz, 1 H, 6-H), 4.15 (d, *J* = 15.1 Hz, 1 H, NCH_2), 4.18 (br. d, *J* ≈ 4.8 Hz, 1 H, 7-H), 4.40 (dd, *J* = 4.8, 9.8 Hz, 1 H, 6-H), 7.24–7.29, 7.31–7.34 (2 m, 1 H, 4 H, Ph) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 34.5 (t, C-4), 60.0 (t, NCH_2), 66.0 (t, C-3), 74.9, 75.7, 75.9, (t, 2 d, C-6,7,7a), 103.2 (s, C-4a), 127.1, 128.2, 128.3, 137.4 (3 d, s, Ph) ppm. IR (KBr): ṽ = 3450–3300 (O–H), 3085–3025 (=C–H), 2985–2845 (C–H), 1675 (C=C) cm^{-1}. MS (EI, 80 eV, 50 °C): *m*/*z* (%) = 251 (29) $[M]^+$, 91 (100) $[CH_2Ph]^+$. HRMS (EI, 80 eV): calcd. for $C_{13}H_{17}NO_4$ $[M]^+$ 251.1158; found 251.1183. $C_{13}H_{17}NO_4$ (251.3): calcd. C 62.14, H 6.82, N 5.57; found C 62.22, H 6.81, N 5.18.

(4a*S*,7*S*,7a*S*)-1-Benzyl-4a-[2-(trimethylsilyl)ethoxy]hexahydro-1*H*-furano[3,2-*c*]1,2-oxazin-7-ol (7): *syn*-**5** (0.100 g, 0.255 mmol) was treated with HF/Py (0.12 mL of 15% HF in pyridine) in dichloromethane (3 mL) as described in GP 2. The resulting pale brown solid (0.057 g) was purified by column chromatography (silica gel; hexane/EtOAc, 4:1) to give **7** (0.053 g, 58%) as colourless crystals, m.p. 70–72 °C. $[\alpha]_D^{22}$ = +65.6 (*c* = 0.29, $CHCl_3$). ^{1}H NMR

(250 MHz, $CDCl_3$): δ = 0.03 (s, 9 H, $SiMe_3$), 0.87 (ddd, J = 5.3, 10.5, 13.8 Hz, 1 H, CH_2Si), 0.93 (ddd, J = 6.6, 11.1, 13.8 Hz, 1 H, CH_2Si), 1.91 (ddd, J = 6.3, 12.5, 13.0 Hz, 1 H, 4-H), 2.13 (br. d, $J \approx$ 13.0 Hz, 1 H, 4-H) 3.13 (s, 1 H, OH), 3.54 (ddd, J = 6.6, 9.1, 10.5 Hz, 1 H, OCH_2), 3.62 (d, J = 11.8 Hz, 1 H, 7a-H), 3.76–3.82 (m, 2 H, 3-H, OCH_2), 3.79 (d, J = 15.1 Hz, 1 H, NCH_2), 3.86 (br. dd, J = 6.3, 11.8 Hz, 1 H, 3-H), 3.94 (dd, J = 1.3, 9.8 Hz, 1 H, 6-H), 4.05 (br. dd, J = 5.4, 11.8 Hz, 1 H, 7-H), 4.17 (d, J = 15.1 Hz, 1 H, NCH_2), 4.42 (dd, J = 5.4, 9.8 Hz, 1 H, 6-H), 7.24–7.28, 7.30–7.35 (2 m, 1 H, 4 H, Ph) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = –1.4 (q, $SiMe_3$), 18.8 (t, CH_2Si), 31.2 (t, C-4), 57.7 (t, OCH_2), 59.8 (t, NCH_2), 65.8 (t, C-3), 74.7, 76.3, 76.5 (t, 2 d, C-6,7,7a), 105.6 (s, C-4a), 127.1, 128.20, 128.24, 137.5 (3 d, s, Ph) ppm. IR (KBr): $\tilde{\nu}$ = 3500 (O–H), 3060–3030 (=C–H), 2970–2855 (C–H) cm^{-1}. MS (EI, 80 eV, 50 °C): m/z (%) = 351 (16) $[M]^+$, 250 (4) $[M - C_2H_4SiMe_3]^+$, 234 (19) $[M - SiMe_3CH_2CH_2O]^+$, 91 (100) $[CH_2Ph]^+$, 73 (73) $[SiMe_3]^+$. HRMS (EI, 80 eV): calcd. for $C_{18}H_{29}NO_4Si$ $[M]^+$ 351.1857; found 351.1899.

(4a*R*,7*S*,7a*R*)-1-Benzylhexahydro-4a*H*-furano[3,2-*c*][1,2]oxazine-4a,7-diol (8): *anti*-**5** (0.200 g, 0.511 mmol) was treated with HF/Py (0.36 mL of 70% HF in pyridine) in dichloromethane (5 mL) as described in GP 2. The resulting pale yellow oil (0.150 g) was purified by flash chromatography (silica gel; hexane/EtOAc, 1:3) to give **8** (0.095 g, 74%) as colourless crystals, m.p. 82–84 °C. $[\alpha]_D^{22}$ = –9.1 (c = 0.52, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.05 (td, J = 6.3, 13.6 Hz, 1 H, 4-H), 2.15 (ddd, J = 6.3, 6.9, 13.6 Hz, 1 H, 4-H), 3.13 (d, J = 5.1 Hz, 1 H, 7a-H), 3.25 (br. s, 1 H, 7-OH), 3.48 (br. s, 1 H, 4a-OH), 3.83 (ddd, J = 6.3, 6.9, 10.7 Hz, 1 H, 3-H), 3.89 (d, J = 14.3 Hz, 1 H, NCH_2), 3.91 (td, J = 6.3, 10.7 Hz, 1 H, 3-H), 3.93 (dd, J = 2.8, 9.5 Hz, 1 H, 6-H), 4.10 (dd, J = 4.4, 9.5 Hz, 1 H, 6-H), 4.30 (d, J = 14.3 Hz, 1 H, NCH_2), 4.54 (m_c, 1 H, 7-H), 7.25–7.29, 7.31–7.38 (2 m, 1 H, 4 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.1 (t, C-4), 60.9 (t, NCH_2), 64.6 (t, C-3), 72.0 (d, C-7a), 72.4 (t, d, C-6,7), 102.5 (s, C-4a), 127.3, 128.3, 128.5, 137.0 (3 d, s, Ph) ppm. IR (KBr): $\tilde{\nu}$ = 3480–3360 (O–H), 3090–3030 (=C–H), 2950–2875 (C–H) cm^{-1}. MS (EI, 80 eV, 90 °C): m/z = 251 (16) $[M]^+$, 91 (100) $[CH_2Ph]^+$. HRMS (EI, 80 eV): calcd. for $C_{13}H_{17}NO_4$ $[M]^+$ 251.1158; found 251.1149. $C_{13}H_{17}NO_4$ (251.3): calcd. C 62.14, H 6.82, N 5.57; found C 62.02, H 6.62, N 5.42.

Methyl 4-Amino-2,4-dideoxy-α-D-*threo*-hex-3-ulofuranoside (9): Hydrogen was bubbled through a stirred suspension of Pd/C (10% Pd, 0.175 g) in dry methanol (8 mL) for 1 h. Then a solution of **2** (0.116 g, 0.437 mmol) in dry methanol (3 mL) was added, and the mixture was stirred under hydrogen (balloon) at normal pressure at room temperature for 8 h. Filtration through a pad of Celite® and removal of the solvent under vacuum provided **9** (0.077 g, quant.) as a colourless oil. $[\alpha]_D^{22}$ = +52.3 (c = 0.41, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD): δ = 1.91 (ddd, J = 6.2, 8.7, 15.4 Hz, 1 H, 2-H), 2.12 (td, J = 4.4, 15.4 Hz, 1 H, 2-H), 3.19 (s, 3 H, OMe), 3.22 (br. d, $J \approx$ 1.7 Hz, 1 H, 4-H), 3.58 (dd, J = 4.6, 9.5 Hz, 1 H, 6-H), 3.60–3.68 (m, 2 H, 1-H), 4.13 (ddd, J = 1.7, 4.6, 6.8 Hz, 1 H, 5-H), 4.30 (ddd, J = 0.5, 6.8, 9.5 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 32.3 (t, C-2), 48.0 (q, OMe), 58.0 (t, C-1), 66.1 (d, C-4), 73.6 (t, C-6), 78.7 (d, C-5), 111.0 (s, C-3) ppm. IR (film): $\tilde{\nu}$ = 3350 (N–H, O–H), 2950–2835 (C–H) cm^{-1}. MS (pos. FAB, 3 kV): m/z (%) = 178 (37) $[M + H]^+$, 160 (32) $[M - OH - NH_2]^+$, 146 (100) $[M - OMe]^+$, 128 (47) $[M - OH - OMe]^+$, 77 (50). HRMS (80 eV): calcd. for $C_7H_{14}NO_3$ $[M - OH]^+$ 160.0974; found 160.0967.

Methyl 4-Amino-2,4-dideoxy-α-L-*threo*-hex-3-ulofuranoside (*ent*-9): Hydrogen was bubbled through a stirred suspension of Pd/C (10% Pd, 0.122 g) in dry methanol (7 mL) for 1 h. Then a solution of *ent*-**2** (0.093 g, 0.35 mmol) in dry methanol (3 mL) was added, and the mixture was stirred under hydrogen (balloon) at normal pressure at room temperature for 22 h. Filtration through a pad of Celite® and removal of the solvent under vacuum provided *ent*-**9** [0.062 g, quant., purity > 95% (^{1}H NMR)] as colourless crystals, m.p. 74–77 °C. All spectroscopic data are identical with those of **9**. $[\alpha]_D^{22}$ = –68.5 (c = 1.0, $CHCl_3$).

Methyl 4-Amino-2,4-dideoxy-β-D-*erythro*-hex-3-ulofuranoside (10): Hydrogen was bubbled through a stirred suspension of Pd/C (10% Pd, 0.162 g) in dry methanol (11 mL) for 1 h. Then a solution of **3** (0.137 g, 0.52 mmol) in dry methanol (4 mL) was added and the mixture was stirred under hydrogen (balloon) at normal pressure at room temperature for 50 h. Filtration through a pad of Celite® and removal of the solvent under vacuum provided **10** [0.092 g, quant., purity > 95% (^{1}H NMR)] as colourless crystals, m.p. 57–59 °C. $[\alpha]_D^{23}$ = –90.6 (c = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD): δ = 1.98 (ddd, J = 6.1, 8.7, 15.0 Hz, 1 H, 2-H), 2.09 (td, J = 5.0, 15.0 Hz, 1 H, 2-H), 3.16 (s, 3 H, OMe), 3.22 (br. s, 1 H, 4-H), 3.60–3.69 (m, 3 H, 1-,6-H), 3.94 (dd, J = 6.7, 8.8 Hz, 1 H, 6-H), 4.54 (br. s, 1 H, 5-H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 33.5 (t, C-2), 48.3 (q, OMe), 58.4 (t, C-1), 60.2* (d, C-4), 72.2* (d, C-5), 72.3 (t, C-6), 111.7* (s, C-3) ppm; * signals appear as broad peaks. IR (ATR): $\tilde{\nu}$ = 3380, 3300, 3225 (N–H, O–H), 2960–2830 (C–H) cm^{-1}. MS (pos. ESI): m/z (%): 178 (70) $[M + H]^+$, 146 (100) $[M - MeO]^+$. HRMS (pos. ESI): calcd. for $C_7H_{16}NO_4$ $[M + H]^+$ 178.1074; found 178.1066.

4-(Benzylamino)-2,4-dideoxy-β-D-*erythro*-hex-3-ulofuranose (11): A blue solution of SmI_2 (0.1 m in THF, prepared under argon from 1,2-diiodoethane (1 equiv.) and samarium (1.2 equiv.), stored in the dark) was added under argon to a solution of **3** (0.027 g, 0.10 mmol) in dry THF (1 mL) over ca. 1.5 h until the blue colour persisted for 20 min (ca. 2 mL). Then the reaction was quenched with satd. aq. $NaHCO_3$ solution (0.3 mL) and filtered through Celite®. The solvent was removed under vacuum, and the residue was purified by column chromatography (neutral alumina; dichloromethane/methanol, 98:2, then 97:3) to give **11** (0.019 g, 71%) as a colourless oil. $[\alpha]_D^{23}$ = –76.5 (c = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.01 (ddd, J = 4.9, 6.3, 15.4 Hz, 1 H, 2-H), 2.11 (ddd, J = 4.7, 5.7, 15.4 Hz, 1 H, 2-H), 3.18 (s, 3 H, OMe), 3.25 (d, J = 5.4 Hz, 1 H, 4-H), 3.73–3.78 (m, 2 H, 1-H), 3.82 (d, J = 15.4 Hz, 1 H, NCH_2), 3.85 (d, J = 15.4 Hz, 1 H, NCH_2), 3.87 (br. d, $J \approx$ 10.1 Hz, 1 H, 6-H), 3.91 (dd, J = 3.3, 10.1 Hz, 1 H, 6-H), 4.28 (ddd, J = 0.9, 3.3, 5.4 Hz, 1 H, 5-H) ppm; OH and NH signals could not be detected. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.5 (t, C-2), 48.4 (q, OMe), 52.9 (t, NCH_2), 58.0 (t, C-1), 67.8 (d, C-4), 70.6 (d, C-5), 72.6 (t, C-6), 109.9 (s, C-3), 127.6, 128.4, 128.7, 138.3 (3 d, s, Ph) ppm. IR (ATR): $\tilde{\nu}$ = 3385 (N–H, O–H), 3090–3030 (=C–H), 2950–2835 (C–H) cm^{-1}. HRMS (pos. ESI): calcd. for $C_{14}H_{22}NO_4$ $[M + H]^+$ 268.1543; found 268.1557. $C_{14}H_{21}NO_4$ (267.3): calcd. C 62.90, H 7.92, N 5.24; found C 63.51, H 7.86, N 4.98.

4-(Benzylamino)-2,4-dideoxy-α-D-*threo*-hex-3-ulofuranose (12): Alternative procedure for the N–O cleavage with SmI_2: 1,2-Diiodoethane (0.437 g, 1.55 mmol) and samarium (0.253 g, 1.68 mmol) were transferred into a round-bottomed flask under argon. Dry THF (5 mL) was added, and the solution was stirred until a deep blue colour appeared (about 2 h). 1,2-Oxazine **6** (0.090 g, 0.358 mmol), dissolved in dry THF, was added, the reaction mixture was stirred at room temperature for 7 h and then quenched with satd. aq. $NaHCO_3$ solution (2 mL). The mixture was filtered through Celite®, the solvent was removed under vacuum, and the residue was filtered through silica gel (EtOAc) to give **12** (0.073 g, 81%) as

a colourless oil. $[\alpha]_D^{22}$ = +68.9 (*c* = 0.19, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.00–2.08 (m, 2 H, 2-H), 3.18 (br. s, 1 H, 6-H), 3.42 (br. s, 1 H, NH), 3.79–3.86 (m, 4 H, 1-H, 6-H, OH), 3.82 (d, *J* = 15.1 Hz, 1 H, NCH_2), 4.09 (dd, *J* = 1.0, 9.8 Hz, 1 H, 6-H), 4.15 (d, *J* = 15.1 Hz, 1 H, NCH_2), 4.18 (br. d, *J* ≈ 4.8 Hz, 1 H, 4-H), 4.40 (ddd, *J* = 0.4, 4.8, 9.8 Hz, 1 H, 5-H), 7.25–7.29, 7.31–7.35 (2 m, 1 H, 4 H, Ph) ppm; 2 OH signals could not be detected. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.4 (t, C-2), 59.9 (t, NCH_2), 65.9 (t, C-1), 74.9 (d, C-4), 75.7 (t, C-6), 75.8 (d, C-5), 103.2 (s, C-3), 127.1, 128.2, 128.3, 137.4 (3 d, s, Ph) ppm. IR (film): $\tilde{\nu}$ = 3430–3300 (O–H), 3090–3030 (=C–H), 2940–2875 (C–H) cm^{-1}. MS (EI, 80 eV, 100 °C): *m*/*z* (%) = 253 (1) $[M]^+$, 106 (76) $[C_7H_8N]^+$, 91 (100) $[CH_2Ph]^+$. HRMS (EI, 80 eV): calcd. for $C_{13}H_{19}NO_4$ $[M]^+$ 253.1321; found 253.1336.

Synthesis of 14 and 15: *p*TsCl (0.048 g, 0.25 mmol) and *anti*-**13** (0.203 g, 0.50 mmol) in dry methanol (3 mL each) were treated as described in GP 1. After quenching with satd. aq. $NaHCO_3$ solution, water was added until the white precipitate was dissolved, and the aqueous phase was extracted with dichloromethane (6× 10 mL). Flash chromatography of the residue (silica gel; hexane/ethyl acetate, 1:3, then 1:4) gave **14** (0.119 g, 73%) as colourless crystals, m.p. 128–132 °C, and unstable side product **15** (0.014 g, 7%) as colourless crystals.

(4a*S*,6*R*,7*S*,8*R*,8a*S*)-1-Benzyl-6-(hydroxymethyl)-4a-methoxyhexahydro-1*H*,3*H*-pyrano[3,2-*c*][1,2]oxazine-7,8-diol (14): $[\alpha]_D^{22}$ = +74.7 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 1.52 (dt, *J* = 5.8, 12.5 Hz, 1 H, 4-H), 1.92 (ddd, *J* = 1.0, 2.1, 12.5 Hz, 1 H, 4-H), 2.92 (d, *J* = 3.1 Hz, 1 H, 8a-H), 3.19 (s, 3 H, OMe), 3.32 (ddd, *J* = 1.9, 6.6, 9.4 Hz, 1 H, 6-H), 3.44 (d, *J* = 15.5 Hz, 1 H, NCH_2), 3.52 (ddd, *J* = 5.1, 9.4, 10.2 Hz, 1 H, 7-H), 3.53 (ddd, *J* = 5.9, 6.6, 11.5 Hz, 1 H, 6-CH_2), 3.66 (ddd, *J* = 1.0, 5.8, 11.3 Hz, 1 H, 3-H), 3.74 (ddd, *J* = 1.9, 5.9, 11.5 Hz, 1 H, 6-CH_2), 3.78 (ddd, *J* = 2.1, 11.3, 12.5 Hz, 1 H, 3-H), 4.18 (ddd, *J* = 3.1, 4.6, 10.2 Hz, 1 H, 8-H), 4.47 (t, *J* = 5.9 Hz, 1 H, 6-CH_2O*H*), 4.92 (d, *J* = 5.1 Hz, 1 H, 7-OH), 5.11 (d, *J* = 15.5 Hz, 1 H, NCH_2), 5.43 (d, *J* = 4.6 Hz, 1 H, 8-OH), 7.15–7.19, 7.25–7.31 (2 m, 1 H, 4 H, Ph) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 33.9 (t, C-4), 46.9 (q, OMe), 59.5 (t, NCH_2), 61.6 (t, 6-CH_2OH), 65.6 (t, C-3), 65.8 (d, C-7), 69.4 (d, C-8), 70.1 (d, C-8a), 76.6 (d, C-6), 97.1 (s, C-4a), 126.0, 127.5, 127.8, 140.1 (3 d, s, Ph) ppm. IR (KBr): $\tilde{\nu}$ = 3420 (OH), 3085–3030 (=C–H), 2960–2725 (C–H), 1605, 1495 (C=C) cm^{-1}. $C_{16}H_{23}NO_6$ (325.4): calcd. C 59.06, H 7.13, N 4.31; found C 59.06, H 6.96, N 4.25.

(4a*S*,6*R*,7*S*,8*R*,8a*S*)-1-Benzyl-4a-methoxy-6-[(1-methoxy-1-methylethoxy)methyl]hexahydro-1*H*,3*H*-pyrano[3,2-*c*][1,2]oxazine-7,8-diol (15): ^1H NMR (500 MHz, $CDCl_3$): δ = 1.41, 1.42 (2 s, 6 H, CMe_2), 1.70 (dt, *J* = 5.8, 12.6 Hz, 1 H, 4-H), 1.93 (ddd, *J* = 1.2, 2.4, 12.6 Hz, 1 H, 4-H), 2.73, 3.19 (2 br. s, 1 H each, OH), 3.20 (d, *J* = 3.1 Hz, 1 H, 8a-H), 3.268 (s, 3 H, CMe_2O*Me*), 3.270 (s, 3 H, 4a-OMe), 3.63 (ddd, *J* = 4.9, 6.4, 9.1 Hz, 1 H, 6-H), 3.65 (d, *J* = 15.3 Hz, 1 H, NCH_2), 3.70 (dd, *J* = 6.4, 9.5 Hz, 1 H, 6-CH_2), 3.76 (ddd, *J* = 1.2, 5.8, 11.5 Hz, 1 H, 3-H), 3.81 (dd, *J* = 4.9, 9.5 Hz, 1 H, 6-CH_2), 3.91 (ddd, *J* = 2.4, 11.5, 12.6 Hz, 1 H, 3-H), 4.01 (dd, *J* = 9.1, 10.2 Hz, 1 H, 7-H), 4.51 (dd, *J* = 3.1, 10.2 Hz, 1 H, 8-H), 5.08 (d, *J* = 15.3 Hz, 1 H, NCH_2), 7.20–7.23, 7.28–7.31, 7.37–7.39 (3 m, 1 H, 2 H, 2 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.31, 24.32 (2 q, C*Me*$_2$), 34.1 (t, C-4), 47.6 (q, 4a-OMe), 48.8 (q, CMe_2O*Me*), 60.1 (t, NCH_2), 62.9 (t, 6-CH_2), 66.3 (t, C-3), 68.9 (d, C-8a), 69.7 (d, C-7), 70.6 (d, C-8), 72.4 (d, C-6), 97.9 (s, C-4a), 100.6 (s, *C*Me_2), 126.3, 127.7, 128.0, 139.8 (3 d, s, Ph) ppm. Due to its instability the product could not be analysed by other methods.

Methyl 4-Amino-2,4-dideoxy-α-D-*manno*-oct-3-ulopyranoside (16): Hydrogen was bubbled through a stirred suspension of Pd/C (10% Pd, 0.192 g) in dry methanol (10 mL) for 1 h. Then a solution of **14** (0.194 g, 0.60 mmol) in dry methanol (2 mL) was added and the mixture was stirred under hydrogen (balloon) at normal pressure at room temperature for 26 h. Filtration through a pad of Celite® and removal of the solvent under vacuum provided **16** [0.142 g, quant., purity > 95% (^1H NMR)] as a colourless foam, m.p. 54–57 °C. $[\alpha]_D^{22}$ = +48.4 (*c* = 1.0, MeOH). ^1H NMR (500 MHz, CD_3OD): δ = 1.96 (ddd, *J* = 7.0, 7.9, 15.2 Hz, 1 H, 2-H), 2.05 (td, *J* = 5.4, 15.2 Hz, 1 H, 2-H), 3.06 (d, *J* = 4.0 Hz, 1 H, 4-H), 3.20 (s, 3 H, OMe), 3.35 (ddd, *J* = 2.2, 5.0, 9.6 Hz, 1 H, 7-H), 3.52 (t, *J* = 9.6 Hz, 1 H, 6-H), 3.58–3.64 (m, 2 H, 1-H), 3.73 (dd, *J* = 5.0, 11.8 Hz, 1 H, 7-CH_2), 3.80 (dd, *J* = 2.2, 11.8 Hz, 1 H, 7-CH_2), 3.89 (dd, *J* = 4.0, 9.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 34.5 (t, C-2), 48.0 (q, OMe), 56.7 (d, C-4), 57.7 (t, C-1), 62.7 (t, 7-CH_2), 67.6 (d, C-6), 72.0 (d, C-5), 75.3 (d, C-7), 103.3 (s, C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3435 (OH, NH), 2930–2830 (OH, NH, CH), 1645–1590 (NH) cm^{-1}. MS (pos. ESI): *m*/*z* (%): 238 (100) $[M + H]^+$, 206 (85) $[M - MeO]^+$. HRMS (pos. ESI): calcd. for $C_9H_{20}NO_6$ $[M + H]^+$ 238.1285; found 238.1284. $C_9H_{19}NO_6 \cdot 1/2H_2O$ (246.3): calcd. C 43.90, H 8.19, N 5.69; found C 44.01, H 7.98, N 5.47.

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[1] a) W. Schade, H.-U. Reißig, *Synlett* **1999**, 632–634; b) M. Helms, W. Schade, R. Pulz, T. Watanabe, A. Al-Harrasi, L. Fišera, I. Hlobilová, G. Zahn, H.-U. Reißig, *Eur. J. Org. Chem.* **2005**, 1003–1019; c) R. Pulz, S. Cicchi, A. Brandi, H.-U. Reißig, *Eur. J. Org. Chem.* **2003**, 1153–1156.
[2] R. Pulz, T. Watanabe, W. Schade, H.-U. Reißig, *Synlett* **2000**, 983–986.
[3] R. Pulz, A. Al-Harrasi, H.-U. Reißig, *Synlett* **2002**, 817–819.
[4] a) A. Al-Harrasi, H.-U. Reißig, *Angew. Chem.* **2005**, *117*, 6383–6387; *Angew. Chem. Int. Ed.* **2005**, *44*, 6227–6231; b) F. Pfrengle, A. Al-Harrasi, H.-U. Reißig, *Synlett* **2006**, 3498–3500.
[5] A. Al-Harrasi, H.-U. Reißig, *Synlett* **2005**, 2376–2378.
[6] H.-U. Reißig, C. Hippeli, T. Arnold, *Chem. Ber.* **1990**, *123*, 2403–2411.
[7] R. Zimmer, H.-U. Reißig, *Angew. Chem.* **1988**, *100*, 1576–1577; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1518–1519.
[8] For a review about deoxy sugar synthesis, see: A. Kirschning, M. Jesberger, K.-U. Schöning, *Synthesis* **2001**, 507–540.
[9] Employing directly hydrochloric acid in methanol furnished compounds **2** and **3** in inferior yields. Probably, low concentrations of HCl are advantageous for a clean transformation.
[10] a) G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojima, I. Kerekes, J. A. Olah, *J. Org. Chem.* **1979**, *44*, 3872–3881; b) G. A. Olah, J. G. Shih, G. K. S. Prakash, *Fluorine Containing Reagents in Organic Chemistry* in *Fluorine: The First Hundred Years* (Eds.: R. E. Banks, D. W. A. Sharp, J. C. Tatlow), Elsevier, New York, **1992**, p. 377–381; c) for cleavage of ketals, see: Y. Watanabe, Y. Kiyosawa, A. Tatsukawa, M. Hayashi, *Tetrahedron Lett.* **2001**, *42*, 4641–4643.
[11] In solution also only one epimer can be detected by NMR spectroscopy.
[12] For a non-reductive method, see: A. Al-Harrasi, H.-U. Reißig, *Synlett* **2005**, 1152–1154.
[13] For the cleavage of N–O bonds with SmI_2, see: a) G. E. Keck, S. F. McHardy, T. T. Wager, *Tetrahedron Lett.* **1995**, *36*, 7419–7422; b) J. L. Chiara, C. Destabel, P. Gallego, J. Marco-Contelles, *J. Org. Chem.* **1996**, *61*, 359–360; c) I. S. Young, J. L.

Williams, M. A. Kerr, *Org. Lett.* **2005**, *7*, 953–955; d) J. Revuelta, S. Cicchi, A. Brandi, *Tetrahedron Lett.* **2004**, *45*, 8375–8377 and references cited therein. See also refs.[4a,18]

[14] To the best of our knowledge, 4-amino-2,4-dideoxyhex-3-uloses have not been reported before. For a 2-deoxyhex-3-ulose, see: a) T. Bando, Y. Matsushima, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 593–596; for a 2-deoxyhex-3-ulose derivative, see: b) J. Mulzer, C. Pietschmann, J. Buschmann, P. Luger, *J. Org. Chem.* **1997**, *62*, 3938–3943; for 4-amino-4-deoxyhex-3-ulose derivatives, see: c) J. Yoshimura, M. Funabashi, *Carbohydr. Res.* **1969**, *11*, 278–281; for a 1,4-diamino-1,4-dideoxyhex-3-ulose derivative, see: d) M. Konishi, S. Kamata, T. Tsuno, K. Numata, H. Tsukiura, T. Naito, H. Kawaguchi, *J. Antibiot.* **1976**, *29*, 1152–1162.

[15] To the best of our knowledge, 4-amino-2,4-dideoxyoct-3-uloses have not been reported before. A 4-amino-2,4-dideoxyoct-3-ulosonic acid derivative is proposed as an intermediate in a thiazole synthesis: a) S. Knapp, B. Amorelli, G. A. Doss, *Tetrahedron Lett.* **2004**, *45*, 8507–8510; for a 1,2-dideoxyoct-3-ulose derivative, see: b) M. L. Wolfrom, D. I. Weisblat, E. F. Evans, J. B. Miller, *J. Am. Chem. Soc.* **1957**, *79*, 6454–6457; for synthesis and isolation of the first naturally occurring oct-3-ulose, see: c) R. Schaffer, A. Cohen, *J. Org. Chem.* **1963**, *28*, 1929–1930; d) K. Sakata, H. Hagiwara, A. Yagi, K. Ina, *Agric. Biol. Chem.* **1989**, *53*, 2539–2541.

[16] For a deoxy sugar synthesis using lithiated alkoxyallenes, see: M. Brasholz, H.-U. Reißig, *Angew. Chem.* **2007**, *119*, 1659–1662; *Angew. Chem. Int. Ed.* **2007**, *46*, 1634–1637.

[17] Reviews for the use of alkoxyallenes as building blocks in organic synthesis: a) R. Zimmer, H.-U. Reißig, *Donor-Substituted Allenes* in *Modern Allene Chemistry* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**, vol. 1, p. 425–492; b) R. Zimmer, *Synthesis* **1993**, 165–178; c) R. Zimmer, F. A. Khan, *J. Prakt. Chem./Chem.-Ztg.* **1996**, *338*, 92–94.

[18] R. Pulz, A. Al-Harrasi, H.-U. Reißig, *Org. Lett.* **2002**, *4*, 2353–2355.

[19] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467–473.

[20] G. M. Sheldrick, University of Göttingen, Germany, **1997**.

[21] L. J. Farrugia, *J. Appl. Crystallogr.* **1999**, *32*, 837–838.

[22] C. Hubschwerlen, J.-L. Specklin, J. Higelin, *Org. Synth.* **1995**, *72*, 1–5. The aldehyde was used in the next step[23] in dichloromethane without prior distillation.

[23] Y. Kita, O. Tamura, F. Itoh, H. Kishino, T. Miki, M. Kohno, Y. Tamura, *Chem. Pharm. Bull.* **1989**, *37*, 2002–2007.

[24] We want to correct the optical rotation of *syn*-**1**[1b] to $[a]_D^{22}$ = +35.0 (*c* = 1.0, $CHCl_3$).

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