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Enantiopure Aminopyrans by a Lewis Acid Promoted Rearrangement of 1,2-Oxazines: Versatile Building Blocks for Oligosaccharide and Sugar Amino Acid Mimetics

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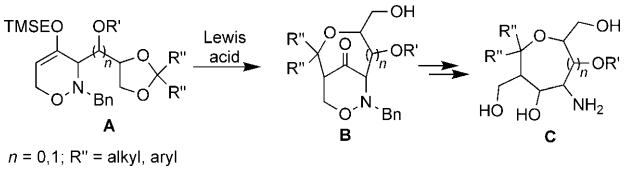
Abstract: 1,3-Dioxolanyl-substituted 1,2-oxazines, such as *syn*-**1** and *anti*-**1**, rearrange under Lewis acidic conditions to provide bicyclic products **2**–**5**. Subsequent reductive transformations afforded enantiopure 3-aminopyran derivatives such as **7** and **9** or their protected diastereomers **16** and **18**, which can be regarded as carbohydrate mimetics. An alternative sequence of transformations including selective oxidation of the primary hydroxyl groups in **21** and **24** led to two protected β-amino acid derivatives with carbohydrate-like backbone (sugar amino acids). Treatment of bicyclic ester **23** with samarium diiodide cleaved the N−O bond and furnished the unusual β-lactam **27** in excellent yield. Alternatively, γ-amino acid derivative **29** was efficiently prepared in a few steps. Fairly simple transformations gave azides **32** and **35** or alkyne **30** which are suitable substrates for the construction of oligosaccharide mimetics such as **34** by copper iodide catalyzed cycloadditions. With this report we demonstrate that enantiopure rearrangement products **2**–**5** are protected precursors of a variety of polyfunctionalized pyran derivatives with great potential for chemical biology.

Keywords: carbohydrates · heterocycles · Lewis acids · rearrangements · samarium · sugar amino acids

Introduction

The biological importance of carbohydrates in living cells continuously prompts chemists to develop new syntheses of small, soluble carbohydrate-based molecules, which may combat various diseases such as bacterial and viral infections, metastasis and inflammation. These mimetics of carbohydrates inhibit carbohydrate–protein interactions for example in glycosyl transferases, glycosidases or lectins. However, improved properties with regard to stability, specificity, affinity, or synthetic availability can make them advantageous compared to the natural ligands.[1] In this context we recently reported an approach to compounds such as 3-aminopyrans **C** ($n=0$) which can be regarded as mimetics of C-2 branched amino sugars without hydrolytically labile anomeric center. They are efficiently generated by Lewis acid promoted rearrangement of 1,2-oxazines **A** with bicyclic compounds **B** as key intermediates (Scheme 1).[2] Actually, not only six-membered heterocycles but also their seven-membered relatives **C** ($n=1$) have been prepared by this new approach.



Scheme 1. Approach to enantiopure 3-aminopyrans ($n=0$) and 4-aminooxepanes **C** ($n=1$) by Lewis acid promoted rearrangements of 1,2-oxazines **A**. Bn = benzyl, TMSE = 2-(trimethylsilyl)ethyl.

For all these compounds the required enantiopure 3,6-dihydro-2*H*-1,2-oxazines **A** are easily obtained in a stereocontrolled manner by [3+3]-cyclization of lithiated alkoxyallenes **D** and carbohydrate-derived aldonitrones **E** (Scheme 2).[3] Many highly functionalized compounds such as polyhydroxylated pyrrolidines or azetidines, aminopolyols

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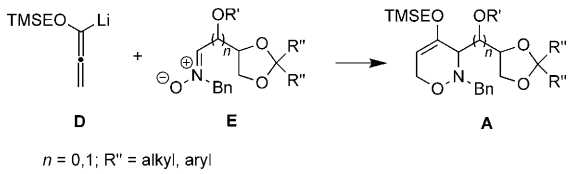


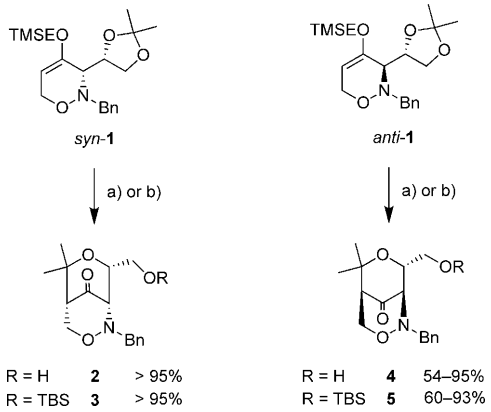
Scheme 2. Synthesis of 3,6-dihydro-2*H*-1,2-oxazines **A** starting from lithiated alkoxyallene **D** and carbohydrate-derived nitrones **E**.

and substituted tetrahydrofurans with known or potential biological activity have already been synthesized employing compounds **A** as key precursors.[4]

Here we present full details of our efforts towards the synthesis of a set of suitable building blocks for oligosaccharide or glycopeptide mimetics,[5,6] utilizing easily available intermediates **B** as relay compounds for subsequent chemoselective transformations.

Results and Discussion

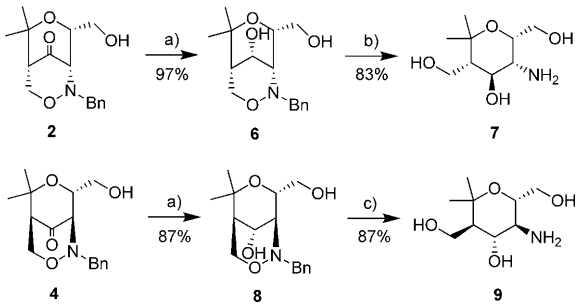
The crucial precursor 1,2-oxazines *syn*-**1** and *anti*-**1** smoothly underwent cyclization into bicyclic compounds **2**–**5** upon treatment with Lewis acids (Scheme 3). Under a variety examined Lewis acids tin tetrachloride and *tert*-butyldimethylsilyl triflate proved to be the best promoters giving the bicyclic products in good to excellent yields either as free alcohols **2** and **4** or directly as their TBS-protected derivatives **3** and **5**.[7,8] Whereas the reactions of *syn*-**1** reliably provided excellent yields, those of *anti*-**1** seem to be more dependent on the quality of the Lewis acid or other unknown factors which led to varying efficacy of this step in the *anti*-series. As a mechanism for these transformations we propose coordination of the Lewis acid (in equilibrium) to the external oxygen atom of the dioxolane moiety of *syn*/*anti*-**1** leading to ring opening. The subsequent intramolecular attack of the resulting stabilized carbenium ion onto the enol ether double bond forms the crucial new C–C bond. Finally, a fragmentation of the TMSE group generates the central carbonyl group of bicycles **2**–**5**. The TMSE group is important for this transformation; only the corresponding *p*-methoxybenzyl derivative gave similar results whereas other substituents examined led to a more complex outcome.[2,9]



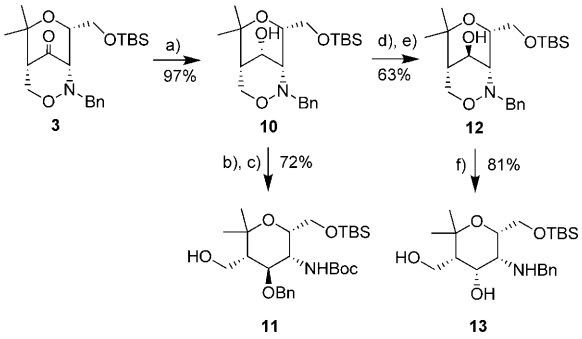
Scheme 3. Lewis acid promoted rearrangements of *syn*-**1** and *anti*-**1** into bicyclic products **2**–**5**. a) $SnCl_4$ (3 equiv), MeCN, −30 °C to RT, 6 h; b) TBSOTf, CH_2Cl_2, RT, 20 h. TBS = *tert*-butyldimethylsilyl; OTf = trifluoromethane sulfonate.

By a simple two-step sequence rearranged products **2** and **4** were converted into the two completely deprotected diastereomeric aminopyrans **7** and **9** (Scheme 4). Reduction with $NaBH_4$ afforded the corresponding alcohols **6** and **8**, both as single diastereomers in excellent yields and in enantiopure form. The geminal dimethyl group apparently blocks one side of the pyran motif thus effectively leading to exclusive attack of the hydride reagent from the opposite site. Subsequent hydrogenolyses in the presence of palladium on charcoal delivered the free aminopyrans **7** and **9** in good overall yields. This strategy allows for many synthetic modifications of these compounds at all three stages (bicyclic ketone, bicyclic alcohol or aminopyran). A convenient (and if required orthogonal) protection group strategy is therefore easily accomplished. An enantiopure sulfated derivative of aminopyran **7** has already been studied as carbohydrate mimicking ligand of gold nanoparticles, which bind to P- and L-selectins with extraordinary low IC_{50} values (picomolar range) and with good selectivity in favor of P-selectin.[10]

The synthetic route to aminopyran **11** demonstrates the possibility to introduce three orthogonal protecting groups in a straightforward manner (Scheme 5). The TBS group of **3** was directly introduced during the TBSOTf promoted rearrangement (Scheme 3). After reduction of the carbonyl group, the resulting alcohol **10** was benzylated followed by hydrogenolytic cleavage of the N–O bond in the presence of di-*tert*-butyl dicarbonate. The in situ protection of the resulting amine afforded product **11** in good overall yield. Alternatively, intermediate **10** was used for the preparation of an epimeric aminopyran by a Mitsunobu reaction.[11] The inversion of configuration was achieved by using *p*-nitrobenzoic acid, which is reported to be an effective reagent for hindered secondary alcohols.[12] A mild and selective method for the cleavage of the *p*-nitrobenzoic ester was employed to yield the configurationally inverted alcohol **12**.[13] Subsequent reaction with SmI_2 furnished the all-*cis*-configured aminopyran **13** by reductive cleavage of the N–O bond leaving the *N*-benzyl group untouched.[14]

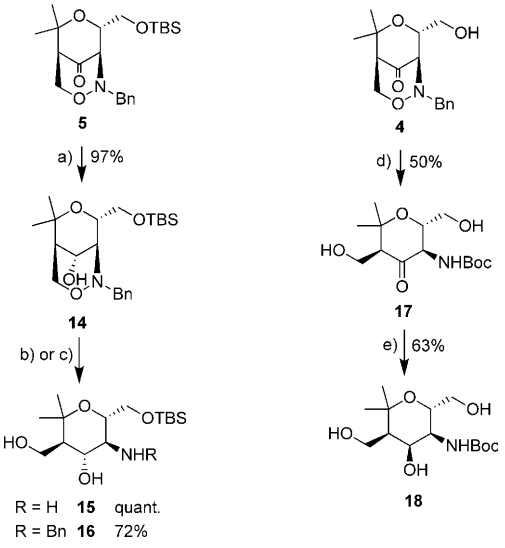


Scheme 4. Synthesis of deprotected aminopyran derivatives **7** and **9**. a) $NaBH_4$, EtOH, 0 °C, 3 h; b) H_2, Pd/C, MeOH, RT, 6 h; c) H_2, Pd/C, MeOH, RT, 1 d.



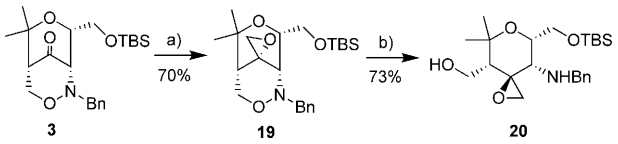
Scheme 5. Synthesis of protected pyran derivatives **11** and **13**. a) $NaBH_4$, EtOH, 0 °C, 4 h; b) NaH, BnBr, THF, 0 °C to RT, 2 h; c) H_2, Pd/C, Boc_2O, RT, 1 d; d) Diethyl azodicarboxylate (DEAD), PPh_3, *p*-nitrobenzoic acid, benzene, RT, 6 h; e) NaN_3, MeOH, 55 °C, 2 d; f) SmI_2, THF, RT, 3 h. Boc = *tert*-butoxycarbonyl.

By changing the order of reaction steps we were able to generate another configuration at the aminopyran core. This is exemplified by the synthesis of aminopyrans **15**/**16** and diastereomeric **18** starting from rearrangement products **4** or **5** (Scheme 6). Reduction of the carbonyl group of **5** followed by cleavage of the N–O bond of intermediate **14** either by hydrogenolysis or by reaction with SmI_2 afforded aminopyrans **15** or **16** with the same configuration as **9** (Scheme 4). On the other hand reductive cleavage of the N–O bond in **4** gave an access to aminopyranone **17**. Hydrogenolysis with in situ protection of the resulting amine with Boc_2O was crucial for a successful performance. Finally, reduction with $NaBH_4$ in ethanol stereoselectively provided aminopyran **18**[15] which completes the synthesis of a set of four diastereomers (**7**/**11**, **13**, **9**/**15** and **18**). The enantiomers of these aminopyran derivatives can easily be obtained when the L-glyceraldehyde derived 1,2-oxazines *ent-syn*-**1** and *ent-anti*-**1** are the precursor compounds.[16]



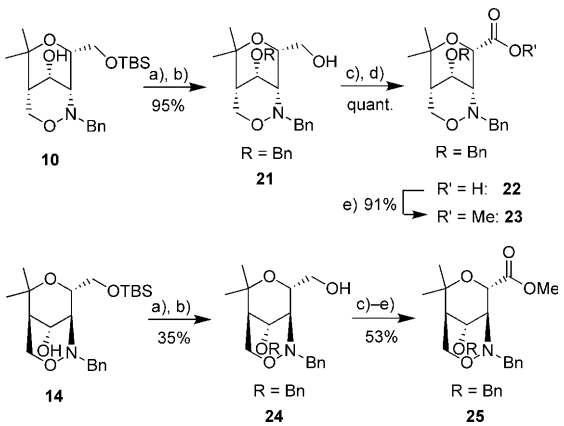
Scheme 6. Synthesis of aminopyran derivatives **15**–**18**. a) $NaBH_4$, EtOH, 0 °C, 4 h; b) H_2, Pd/C, MeOH, RT, 1 d; c) SmI_2, THF, RT, 3 d; d) H_2, Pd/C, Boc_2O, MeOH, RT, 18 h; e) $NaBH_4$, EtOH, RT, 7 h.

An example for an interesting synthetic modification of the carbonyl group of rearrangement product **3** is depicted in Scheme 7. When **3** was treated with the ylide derived from trimethylsulfoxonium iodide and *n*-butyllithium epoxide **19** was formed in good yield.[17] Finally, SmI_2 reduction furnished the aminopyran derivative **20** bearing a spirooxirane moiety which can certainly be used for further transformations, for instance carbohydrate mimetics with three side chains.[18]



Scheme 7. Synthesis of spirooxirane derivative **20**. a) $Me_3SO^+I^-$, *n*BuLi, −78 °C to RT, 12 h; b) SmI_2, THF, RT, 12 h.

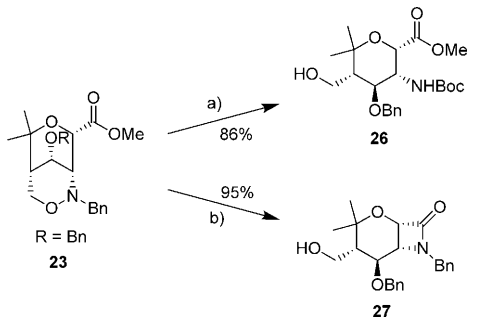
Sugar amino acids (SAA) are molecules that combine structural features of amino acids with those of carbohydrates.[19] They are found in nature largely as construction elements, but are also used as polyfunctionalized bridges between carbohydrates and amino acids.[20] Furthermore they can be incorporated into peptides allowing the engineering of carbohydrate binding sites. The bicyclic rearrangement products of this study represent excellent scaffolds for the synthesis of sugar amino acid mimetics. Benzyl protection of the secondary alcohol in **10** followed by tetrabutylammonium fluoride mediated cleavage of the TBS-group afforded compound **21** in excellent yield (Scheme 8). Subsequently, a two-step oxidation protocol delivered in one-pot carboxylic acid derivative **22**, which can be regarded as an internally protected β-amino acid and should therefore provide a suitable building block for the synthesis of glycopeptide mimetics.[21] Finally, esterification of the crude carboxylic acid **22** with trimethylsilyldiazomethane in a toluene/methanol mix-



Scheme 8. Synthesis of protected β-amino acids **23** and **25**. a) NaH, BnBr, THF, 0 °C to RT, 16 h; b) TBAF, THF, RT, 15 h; c) SO_3·pyridine, NEt_3, DMSO, RT, 16 h; d) $NaClO_2$, NaH_2PO_4, H_2O, RT, 3 h; e) $TMSCHN_2$, MeOH/toluene, RT, 2 h. TBAF = tetrabutylammonium fluoride; DMSO = dimethylsulfoxide.

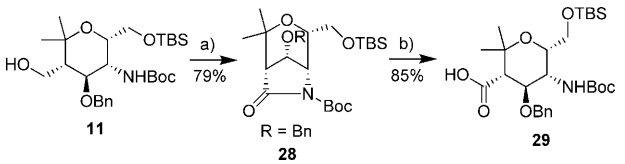
ture furnished methyl ester **23** in good yield.[22] Analogously to this sequence, the internally protected β-amino acid methyl ester **25** derived from the other diastereomeric series was synthesized starting from alcohol **14** via primary alcohol **24** in moderate overall yield.

Remarkably, reductive N–O bond cleavage of bicyclic ester **23** resulted in two different reaction pathways depending on the method used (Scheme 9). Hydrogenation with in situ Boc protection delivered the expected β-amino acid derivative **26** whereas after reaction with SmI_2 β-lactam **27** was isolated as the only product in excellent yield. We assume that homolytic cleavage of the N–O bond results in the formation of an aminyl radical, which is transformed into the corresponding anion by the second equivalent of SmI_2. The anion reacts with the methoxycarbonyl group under extrusion of a $MeOSmI_2$ species. The quite unusual bicycle **27** offers a variety of options for synthetic modifications leading to new interesting β-lactams.[23]



Scheme 9. Synthesis of β-amino acid derivative **26** and fused β-lactam **27**. a) H_2, Pd/C, Boc_2O, MeOH, RT, 3 d; b) SmI_2, THF, RT, 30 min.

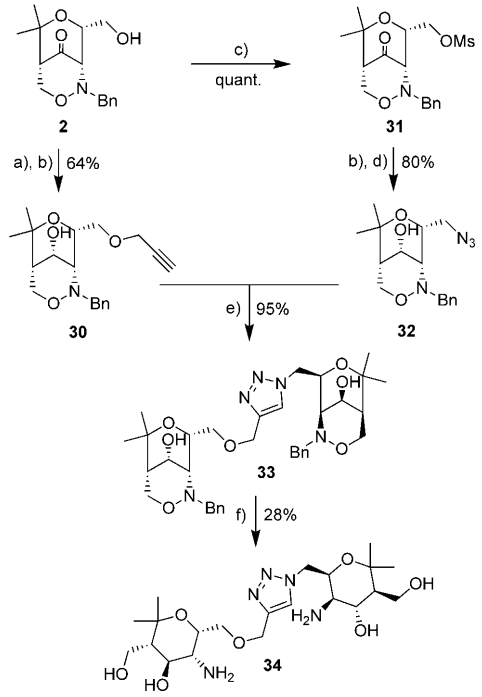
The synthesis of stereodefined γ-amino acids can be achieved by making use of the hydroxymethyl group of the appropriately protected aminopyran **11** (Scheme 10). All our efforts to directly convert **11** into carboxylic acid **29** so far led to γ-lactam **28**. This compound is smoothly formed by oxidation of **11** with PDC, subsequent in situ cyclization of the intermediate aldehyde with the Boc-protected amine moiety and a second oxidation to the lactam stage. Hydrolysis of **28** under basic conditions cleaved the amide bond and afforded the desired γ-amino acid derivative **29** in good yield. All described amino acid derivatives with carbohydrate-like backbone are suitable candidates for couplings



Scheme 10. Synthesis of protected γ-amino acid derivative **29**. a) PDC, Ac_2O, DMF, RT, 12 h; b) LiOH, THF/H_2O, RT, 12 h. PDC = pyridinium dichromate.

with proteinogenic amino acids[5] or other components to furnish peptide mimetics.[24]

Very recently, the Sharpless–Meldal variation of the 1,3-dipolar cycloaddition[25] of organic azides with alkynes ("click chemistry") has frequently been used for the synthesis of oligosaccharide mimetics.[26] Rearrangement product **2** provides an ideal starting point for the synthesis of substrates bearing either an alkyne or an azide moiety (Scheme 11). Treatment of **2** with sodium hydroxide and

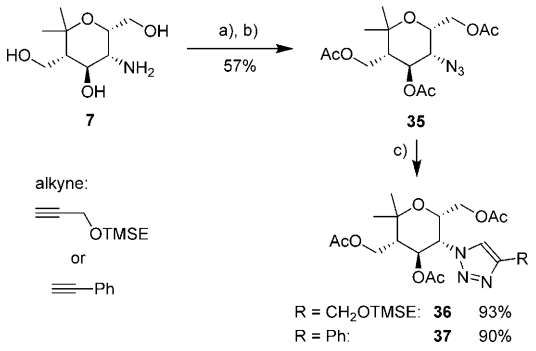


Scheme 11. Synthesis of building blocks **30** and **32** suitable for copper iodide catalyzed azide/alkyne cycloaddition leading to disaccharide mimetic **34**. a) NaOH, TBAI, propargyl bromide, H_2O, CH_2Cl_2, RT, 7 d; b) $NaBH_4$, EtOH, 0 °C, 4 h; c) MsCl, NEt_3, CH_2Cl_2, 0 °C, 4 h; d) NaN_3, DMF, 80 °C, 6 h; e) CuI, TBTA, Et_3N, MeCN, 40 °C, 48 h. f) H_2, Pd/C, MeOH, 2 d. TBAI = tetrabutylammonium iodide; Ms = mesyl; TBTA = tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine.

propargyl bromide followed by reduction of the carbonyl group with $NaBH_4$ provided alkyne **30**. Alternatively, compound **2** was treated with mesyl chloride quantitatively giving mesylate **31**. Subsequent reduction of the carbonyl group and treatment of the mesylate with sodium azide furnished primary azide **32** in good overall yield. The bicyclic constitution of azide derivative **32** and the configuration of the four stereogenic centers were proven by its X-ray crystal structure.[27] This analysis also confirms the configurations of the previously prepared bicyclic products. Intermediates **30** and **32** can be regarded as protected carbohydrate mimetics and their cycloadduct **33** was obtained in excellent yield by copper iodide catalysis in the presence of TBTA.[28] Hydrogenolytic cleavage of the N,O-bonds and debenzylation afforded the unprotected disaccharide mimetic **34**. The highly

polar compound required extensive purification to obtain it in spectroscopically pure form.

An alternative option to obtain building blocks for "click reactions" with alkynes involves the free amino group of aminopyrans such as **7** (Scheme 12). Secondary azide **35** was prepared upon treatment with nonafluorobutanesulfonyl azide[29] in the presence of copper sulfate,[26b] followed by acetylation of the free hydroxyl groups. Compounds like **35** can easily be prepared in gram quantities due to short syntheses and high yields. First model cycloadditions with simple alkynes afforded the triazole linked aminopyrans **36** and **37** in good yields. Further synthetic elaboration and deprotection of compounds such as **33**, **36** and **37** are currently under investigation.



Scheme 12. Synthesis of azido derivative **35** and first model cycloadditions. a) Nf-N_3, K_2CO_3, $CuSO_4{\cdot}5H_2O$, MeOH/H_2O 1:2, RT, 24 h; b) Ac_2O, pyridine, DMAP, 12 h, RT; c) alkyne, CuI, TBTA, Et_3N, MeCN, 40 °C, 24 h. Nf-N_3 = nonafluorobutanesulfonyl azide; Ac_2O = acetic anhydride; DMAP = 4-dimethylaminopyridine.

Conclusions

The Lewis acid promoted rearrangements of stereodefined 1,2-oxazines,[30] such as *syn*-**1** and *anti*-**1**, open new entries into the synthesis of uncommon amino sugar mimetics and sugar amino acids. All these compounds bear a hydrolytically stable geminal dimethyl group instead of an anomeric center. This particular structural feature can easily be modified by replacing the geminal dimethyl unit by other alkyl chains (including carbocycles) or by aryl groups.[2a] Starting from bicyclic rearrangement products **2**/**3** or **4**/**5**, four different diastereomers of enantiopure aminopyrans have been synthesized in few steps and with high yields. The enantiomers of these compounds are as easily available. Selective and orthogonal protection is possible due to the stepwise introduction of protective groups at different stages of the synthetic sequences. The introduction of these aminopyran derivatives into synthetic oligosaccharides should hence be an interesting option for the generation of new carbohydrate mimetics. For the same reason the rearrangement products **2**/**3** and **4**/**5** are excellent intermediates for the synthesis of sugar amino acid derivatives. This allows for the synthesis of peptide mimetics employing peptide coupling reactions. Alternatively, azides or alkynes derived from aminopyrans investigated in this report can be employed in 1,3-dipolar cycloadditions ("click chemistry") demonstrating the potential for other coupling processes leading to larger molecular arrangements such as **34** in an efficient fashion.

Experimental Section

General methods: See Supporting Information.

(1*S*,5*R*,8*S*)-2-Benzyl-8-hydroxymethyl-6,6-dimethyl-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-one (2): To a solution of 1,2-oxazine *syn*-**1** (500 mg, 1.28 mmol) in MeCN (10 mL) was added $SnCl_4$ (460 μL, 3.84 mmol) at −30 °C and the resulting solution was stirred until it slowly reached RT (6 h). Then the mixture was quenched by water. Addition of CH_2Cl_2 was followed by separation of the phases and the aqueous phase was extracted 3× with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and the solvent was removed in vacuo. Purification by column chromatography (silica gel, hexane/EtOAc 1:1) yielded **2** (372 mg, quant.) as colorless oil. $[\alpha]_D^{22} = +98.8$ ($c = 0.26$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.13$, 1.40 (2s, 3H each, Me), 2.15 (m, 1H, 5-H), 2.45 (br s, 1H, OH), 3.12 (m, 1H, 1-H), 3.73 (dd, $J = 7.2$, 13.5 Hz, 1H, 4-H), 3.89 (m, 1H, 4-H), 3.91 (m, 1H, 8-H), 3.92, 4.14 (2d, $J = 13.1$ Hz, 1H each, NCH_2), 4.50 (m, 2H, 8-CH_2), 7.21–7.29 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 23.9$, 26.8 (2q, Me), 58.0 (d, C-5), 59.3 (t, NCH_2), 63.2 (t, C-4), 69.0 (t, 8-CH_2), 70.4 (d, C-1), 75.0 (d, C-8), 88.1 (s, C-6), 127.6, 128.8, 129.0, 135.5 (3 d, s, Ph), 208.6 ppm (s, C-9); IR (film): $\tilde{\nu} = 3450$ (O-H), 3060–3030 (=C-H), 2975–2875 (C−H), 1730 (C=O), 1600 cm^{-1} (C=C); HRMS (EI, 80 eV, 120 °C): *m*/*z*: calcd for $C_{16}H_{21}NO_4$: 291.1471; found 291.1494 $[M]^+$.

(1*S*,5*R*,8*S*)-2-Benzyl-8-(*tert*-butyldimethylsiloxymethyl)-6,6-dimethyl-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-one (3): *syn*-**1** (1.00 g, 2.56 mmol) was dissolved in CH_2Cl_2 (20 mL), cooled to 0 °C and treated with TBSOTf (2.72 g, 10.2 mmol). After stirring at RT for 20 h, the mixture was cooled again to 0 °C and treated with NEt_3 (3.92 g, 3.84 mmol). The resulting solution was stirred for 30 min at 0 °C, and then sat. NH_4Cl solution was added. The layers were separated and the aqueous layer was extracted 3× with Et_2O. The combined organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo. Filtration over silica gel (pentane/EtOAc 7:1) yielded **3** (1.04 g, quant.) as colorless crystals. M.p. 65–66 °C; $[\alpha]_D^{22} = +64.5$ ($c = 0.36$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 0.08$, 0.09 (2s, 3H each, $SiMe_2$), 0.88 (s, 9H, *t*Bu), 1.24, 1.42 (2s, 3H each, Me), 2.38 (dd, $J = 3.0$, 5.8 Hz, 1H, 5-H), 3.39 (m, 1H, 1-H), 3.82 (dd, $J = 5.0$, 7.0 Hz, 1H, 8-CH_2), 3.96 (ddt, $J = 1.9$, 3.1, 7.0 Hz, 1H, 8-H), 4.00 (d, $J = 14.0$ Hz, 1H, NCH_2), 4.11 (t, $J = 7.0$ Hz, 1H, 8-CH_2), 4.19 (d, $J = 14.0$ Hz, 1H, NCH_2), 4.46 (dd, $J = 5.8$, 12.0 Hz, 1H, 4-H), 4.55 (dd, $J = 3.0$, 12.0 Hz, 1H, 4-H), 7.26–7.41 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = -5.3$ (q, $SiMe_2$), 18.1, 23.7 (s, q, *t*Bu), 26.7, 29.7 (2 q, Me), 58.1 (d, C-5), 60.2 (t, NCH_2), 61.6 (t, 8-CH_2), 68.8 (t, C-4), 70.5 (d, C-1), 76.2 (d, C-8), 78.3 (s, C-6), 127.4, 128.3, 128.7, 136.5 (3d, s, Ph), 208.2 ppm (s, C-9); IR (KBr): $\tilde{\nu} = 3060$–3030 (=C-H), 2975–2875 (C−H), 1730 (C=O), 1600 cm^{-1} (C=C); elemental analysis calcd (%) for $C_{22}H_{35}NO_4Si$ (405.6): C 65.15, H 8.70, N 3.45; found C 65.29, H 8.44, N 3.17.

(1*R*,5*S*,8*S*,9*S*)-2-Benzyl-8-hydroxymethyl-6,6-dimethyl-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (6): Compound **2** (239 mg, 0.820 mmol) was dissolved in ethanol (10 mL) and cooled to 0 °C. $NaBH_4$ (62 mg, 1.64 mmol) was added and the mixture was stirred for 3 h at RT. Then the solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 and H_2O. The layers were separated and the aqueous phase was extracted 2× with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and concentrated to dryness giving pure product **6** (234 mg, 97%) as colorless crystals. M.p. 143–145 °C; $[\alpha]_D^{22} = +71.5$ ($c = 0.75$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.33$, 1.49 (2s, 3H each, Me), 1.56 (m, 1H, 5-H), 2.72 (m, 1H, 1-H), 3.06 (d, $J = 3.3$ Hz, 1H, OH), 3.76 (ddd, $J = 3.6$, 9.0, 11.7 Hz, 1H, 8-CH_2), 3.91 (m, 1H, 8-CH_2), 4.05 (d, $J = 13.3$ Hz, 1H, NCH_2), 4.10–4.19 (m, 3H, 4-H, 8-H), 4.29 (d, $J = 13.3$ Hz, 1H, NCH_2), 4.63 (dd, $J = 3.3$, 6.3 Hz, 1H, 9-H), 7.21–7.32 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 25.9$, 26.5 (2q, Me), 42.7 (d, C-5), 57.0 (t, NCH_2),

59.5 (d, C-1), 62.6 (d, C-9), 65.6 (t, 8-CH_2), 66.2 (t, C-4), 67.0 (d, C-8), 73.3 (s, C-6), 127.6, 128.5, 128.6, 136.9 ppm (3d, s, Ph); IR (KBr): $\tilde{\nu}$= 3360 (O−H), 3090–3030 (=C-H), 2970–2870 cm^{-1} (C-H); elemental analysis calcd (%) for $C_{16}H_{23}NO_4$ (293.4): C 65.51, H 7.90, N 4.77; found C 65.45, H 7.68, N 4.47.

(2*S*,3*R*,4*S*,5*S*)-3-Amino-2,5-bis(hydroxymethyl)-6,6-dimethyltetrahydropyran-4-ol (7): A suspension of palladium on charcoal (10% Pd, 250 mg) in MeOH (6 mL) was saturated with hydrogen for 1 h. After addition of bicyclic alcohol **6** (173 mg, 0.590 mmol) in MeOH (4 mL), hydrogen was bubbled through the mixture for another 30 min and finally the reaction mixture was stirred under an atmosphere of hydrogen for 6 h. Filtration through a short pad of Celite and concentration of the solution to dryness yielded **7** (100 mg, 83%) as colorless crystals. M.p. 131–133 °C; $[\alpha]_D^{22}$= +26.7 (c=0.15, MeOH); ^{1}H NMR (CD_3OD, 500 MHz): δ=1.21, 1.35 (2s, 3H each, Me), 1.71 (ddd, J=5.1, 5.7, 7.5 Hz, 1H, 5-H), 2.86 (dd, J=3.8, 4.9 Hz, 1H, 3-H), 3.61 (dd, J=5.1, 11.2 Hz, 1H, 5-CH_2), 3.62–3.65 (m, 3H, 4-H, 2-CH_2), 3.81 (dd, J=5.7, 11.2 Hz, 1H, 5-CH_2), 3.97 ppm (dt, J= 3.8, 6.3 Hz, 1H, 2-H); ^{13}C NMR (CD_3OD, 125 MHz): δ=24.9, 26.9 (2q, Me), 49.0 (d, C-5), 55.7 (d, C-3), 62.2 (t, 2-CH_2), 62.4 (t, 5-CH_2), 70.4 (d, C-2), 75.3 (d, C-4), 75.4 ppm (s, C-6); IR (KBr): $\tilde{\nu}$=3370 (O-H), 2970–2900 cm^{-1} (C-H); HRMS (ESI-TOF): m/z: calcd for $C_9H_{20}NO_4$: 206.1392; found 206.1395 $[M+H]^+$.

(1*R*,5*S*,8*S*,9*R*)-2-Benzyl-8-(*tert*-butyldimethylsiloxymethyl)-6,6-dimethyl-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (12): Bicyclic alcohol **10** (725 mg, 1.78 mmol) was dissolved in benzene (40 mL). PPh_3 (2.34 g, 8.92 mmol) and *p*-nitrobenzoic acid (1.30 g, 7.78 mmol) were added to the stirred solution. To this solution, DEAD (1.59 mL, 8.77 mmol) was added dropwise at −10 °C. The mixture was stirred at this temperature for 1 h and then, at RT for 6 h. The volatile components were removed in vacuo and the resulting residue was subjected to column chromatography (silica gel, pentane/EtOAc 7:1) to yield (1*S*,5*R*,8*S*,9*R*)-4-nitrobenzoic acid 2-benzyl-8-(*tert*-butyldimethylsiloxymethyl)-6,6-dimethyl-3,7-dioxa-2-azabicyclo-[3.3.1]non-9-yl ester (797 mg, 81%) as colorless crystals. M.p. 108–110 °C; $[\alpha]_D^{22}$=−3.9 (c=0.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=−0.07, −0.04 (2s, 3H each, $SiMe_2$), 0.79 (s, 9H, *t*Bu), 1.26, 1.44 (2s, 3H each, Me), 2.94 (ddd, J=7.5, 8.1, 9.6 Hz, 1H, 5-H), 3.43 (dd, J=7.4, 7.8 Hz, 1H, 9-H), 3.59–3.65 (m, 3H, 8-H, 8-CH_2), 3.67 (d, J=12.4 Hz, 1H, NCH_2), 3.92 (dd, J=7.5, 9.5 Hz, 1H, 4-H), 4.13 (d, J=12.4 Hz, 1H, NCH_2), 4.25 (dd, J=8.1, 9.5 Hz, 1H, 4-H), 5.03 (t, J=9.6 Hz, 1H, 1-H), 7.03–7.26 (m, 5H, Ph), 7.94 (d, J=7.6 Hz, 2H, *p*$NO_2C_6H_4$), 8.21 ppm (d, J=7.6 Hz, 2H, *p*$NO_2C_6H_4$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=−5.3, −5.2 (2q, $SiMe_2$), 18.2, 25.8 (s, q, *t*Bu), 26.6, 28.2 (2q, Me), 48.8 (d, C-5), 60.2 (t, NCH_2), 63.3 (d, C-9), 64.3 (t, 8-CH_2), 68.0 (t, C-4), 69.7 (d, C-1), 71.6 (s, C-6), 71.8 (d, C-8), 127.5, 128.4, 128.9, 135.5 (3 d, s, Ph), 123.3, 130.9, 136.7, 150.4 (2 d, 2 s, *p*$NO_2C_6H_4$), 163.6 ppm (s, CO); IR (KBr): $\tilde{\nu}$=3120–3040 (=C-H), 2980–2860 (-C−H), 1760 (C=O), 1530 cm^{-1} (N=O); elemental analysis calcd (%) for $C_{29}H_{40}N_2O_7Si$ (556.7): C 62.57, H 7.24, N 5.03; found C 62.26, H 7.03, N 4.95.

The obtained product (100 mg, 0.180 mmol) was dissolved in MeOH (9 mL). To this solution, NaN_3 (160 mg, 1.46 mmol) was added and the solution was stirred at 55 °C for 2 d. Removal of MeOH in vacuo was followed by addition of water, then extraction with CH_2Cl_2 and concentration in vacuo to yield 88 mg of colorless oil. This crude product was subjected to column chromatography (silica gel, pentane/EtOAc 7:1) to give **12** (57 mg, 78%) as colorless oil. $[\alpha]_D^{22}$=+29.7 (c=0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=0.06 (s, 6H, $SiMe_2$), 0.88 (s, 9H, *t*Bu), 1.18, 1.36 (2s, 3H each, Me), 2.78 (dt, J=6.5, 10.3 Hz, 1H, 5-H), 3.05 (brs, 1H, OH), 3.22 (dd, J=6.5, 9.7 Hz, 1H, 9-H), 3.49 (dt, J=5.0, 9.7 Hz, 1H, 8-H), 3.55 (t, J=9.7 Hz, 1H, 1-H), 3.74 (t, J=10.3 Hz, 1H, 4-H), 3.75 (ddd, J=1.7, 9.7, 10.2 Hz, 1H, 8-CH_2), 3.78 (d, J=13.0 Hz, 1H, NCH_2), 3.79 (dd, J=5.0, 10.2 Hz, 1H, 8-CH_2), 4.10 (d, J=13.0 Hz, 1H, NCH_2), 4.13 (m, 1H, 4-H), 7.25–7.38 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=−5.4 (q, $SiMe_2$), 18.2, 25.8 (s, q, *t*Bu), 26.6, 28.3 (2q, Me), 48.7 (d, C-5), 61.3 (t, NCH_2), 65.4 (t, 8-CH_2), 67.1 (d, C-9), 67.6 (t, C-4), 67.9 (d, C-1), 71.4 (d, C-8), 71.7 (s, C-6), 127.5, 128.5, 129.0, 137.1 ppm (3d, s, Ph); IR (film): $\tilde{\nu}$=3430 (O−H), 3085–3030 (=C-H), 2950–2860 (C−H), 1550 cm^{-1} (C−O); HRMS (EI, 80 eV, 100 °C): m/z: calcd for $C_{21}H_{34}NO_4Si$: 407.2492; found 407.2484 $[M]^+$.

(3*S*,4*R*,5*R*,6*S*)-5-Benzylamino-6-(*tert*-butyldimethylsiloxymethyl)-3-hydroxymethyl-2,2-dimethyltetrahydropyran-4-ol (13): 1,2-Diiodoethane (230 mg, 0.810 mmol) and samarium (200 mg, 1.34 mmol) were transferred into a dried flask. THF (10 mL) was added. After the solution turned blue, the mixture was stirred for further 2 h. Compound **12** (100 mg, 0.245 mmol) was added and the reaction mixture was stirred for 3 h at RT. After addition of sat. $NaHCO_3$ solution the solution was decanted from the residue and the solvent was removed in vacuo. Product **13** (81 mg, 81%) was obtained as pale yellow oil. $[\alpha]_D^{22}$=−24.1 (c=0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=0.08, 0.09 (2s, 3H each, $SiMe_2$), 0.89 (s, 9H, *t*Bu), 1.15, 1.32 (2s, 3H each, Me), 2.12 (dd, J=9.1, 10.5 Hz, 1H, 3-H), 3.34 (dd, J=3.8, 10.2 Hz, 1H, 5-H), 3.53 (ddd, J=3.8, 4.5, 8.6 Hz, 1H, 6-H), 3.64 (d, J=12.5 Hz, 1H, NCH_2), 3.65 (dd, J=8.6, 9.6 Hz, 1H, 6-CH_2), 3.87 (dd, J=4.5, 9.6 Hz, 1H, 6-CH_2), 3.90 (dd, J= 9.1, 10.2 Hz, 1H, 4-H), 3.94 (m, 1H, 3-CH_2), 4.03 (d, J=12.5 Hz, 1H, NCH_2), 4.08 (m, 1H, 3-CH_2), 7.24–7.31 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=−5.7, −5.6 (2 q, $SiMe_2$), 18.1, 25.8 (s, q, *t*Bu), 24.5, 27.6 (2 q, Me), 41.3 (d, C-3), 51.6 (t, NCH_2), 60.9 (d, C-5), 62.3 (t, 3-CH_2), 67.0 (t, 6-CH_2), 70.4 (d, C-4), 72.0 (d, C-6), 74.4 (s, C-2), 127.3, 128.3, 128.4, 138.8 ppm (3d, s, Ph); IR (film): $\tilde{\nu}$=3310 (N−H, O−H), 3090–3030 (=C-H), 2950–2855 (C−H), 1250 cm^{-1} (C−O); HRMS (EI, 80 eV, 105 °C): m/z: calcd for $C_{22}H_{39}NO_4Si$: 409.2648; found 409.2662 $[M]^+$.

(3*R*,4*R*,5*S*,6*S*)-5-Benzylamino-6-(*tert*-butyldimethylsiloxymethyl)-3-hydroxymethyl-2,2-dimethyltetrahydropyran-4-ol (16): 1,2-Diiodoethane (114 mg, 0.410 mmol) and samarium (67 mg, 0.44 mmol) were transferred into a round-bottomed flask under argon. THF (5 mL) was added. After the solution turned blue, the mixture was stirred for further 2 h. Compound **14** (50 mg, 0.123 mmol) was added and the reaction mixture was stirred for 3 d at RT. After addition of sat. $NaHCO_3$ solution, the solution was decanted from the residue and the solvent was removed in vacuo. Product **16** (36 mg, 72%) was obtained as pale yellow oil. $[\alpha]_D^{22}$=+94.4 (c=0.47, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=0.06, 0.08 (2s, 3H each, $SiMe_2$), 0.10 (s, 9H, *t*Bu), 1.05, 1.26 (2s, 3H each, Me), 1.69 (ddd, J=3.2, 4.8, 8.0 Hz, 1H, 3-H), 2.66 (dt, J=1.1, 9.9 Hz, 1H, 5-H), 3.20 (brs, 1H, OH), 3.43 (m, 1H, 6-H), 3.65 (d, J=13.9 Hz, 1H, NCH_2), 3.67 (m, 1H, 4-H), 3.76 (d, J=13.9 Hz, 1H, NCH_2), 3.78 (dd, J=4.8, 11.3 Hz, 1H, 3-CH_2), 3.86 (dd, J=3.2, 11.3 Hz, 1H, 3-CH_2), 3.94 (dd, J=1.3, 13.0 Hz, 1H, 6-CH_2), 4.04 (dd, J=0.5, 13.0 Hz, 1H, 6-CH_2), 7.25–7.37 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=−5.3, −5.0 (2q, $SiMe_2$), 18.4, 25.9 (s, q, *t*Bu), 20.1, 29.3 (2q, Me), 52.1 (t, 6-CH_2), 53.0 (d, C-3), 62.8 (d, C-5), 64.3 (t, CH_2Ph), 65.1 (t, 3-CH_2), 72.1 (d, C-6), 73.8 (d, C-4), 74.3 (s, C-2), 127.6, 128.4, 128.7, 139.3 ppm (3d, s, Ph); IR (film): $\tilde{\nu}$=3360 (N−H), 3340 (O−H), 3090–3030 (=CH), 2950–2860 (C−H), 1250 cm^{-1} (C−O); HRMS (EI, 80 eV, 120 °C): m/z: calcd for $C_{22}H_{39}NO_4Si$: 409.2648; found 409.2656 $[M]^+$.

[(2*S*,3*R*,5*R*)-2,5-Bis(hydroxymethyl)-6,6-dimethyl-4-oxotetrahydropyran-3-yl]carbamic acid *tert*-butyl ester (17): A suspension of palladium on charcoal (10% Pd, 100 mg) in MeOH (2 mL) was saturated with hydrogen for 1 h. After addition of ketone **4** (130 mg, 0.446 mmol) and Boc_2O (149 mg, 0.675 mmol) in MeOH (1 mL), hydrogen was bubbled through the mixture for another 30 min and finally the reaction mixture was stirred under an atmosphere of hydrogen for 18 h. Filtration through a short pad of celite and concentration of the solution was followed by column chromatographic purification (silica gel, hexane/EtOAc 2:1) to yield **17** (68 mg, 50%) as colorless crystals. M.p. 135–138 °C; $[\alpha]_D^{22}$=−18.8 (c=0.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.00, 1.41 (2s, 3H each, Me), 1.41 (s, 9H, *t*Bu), 2.45 (brs, 1H, OH), 2.82 (dd, J=3.0, 8.4 Hz, 1H, 5-H), 3.38 (dd, J=2.1, 9.7 Hz, 1H, 2-H), 3.56 (dd, J=3.0, 11.6 Hz, 1H, 5′-H), 3.66–3.75 (m, 2H, 2′-H), 3.89 (dd, J=8.4, 11.6 Hz, 1H, 5′-H), 3.96 (brs, 1H, OH), 4.40 (dd, J=7.0, 9.7 Hz, 1H, 3-H), 5.61 ppm (d, J= 7.0 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=21.2, 28.9 (2q, Me), 28.1 (q, *t*Bu), 57.7 (d, C-3), 58.3 (t, C-5′), 61.7 (d, C-5), 62.3 (t, C-2′), 77.9 (d, C-2), 78.3, 81.0 (2s, *t*Bu, C-6), 156.7 (s, NCO), 207.0 ppm (s, C-4); IR (KBr): $\tilde{\nu}$=3600–3150 (O−H, N−H), 2990–2850 (C−H), 1680 cm^{-1} (C=O); HRMS (EI, 80 eV, 60 °C): m/z: calcd for $C_{14}H_{25}NO_6$: 303.1682; found 303.1680 $[M]^+$.

[(2*S*,3*S*,4*S*,3*R*)-4-Hydroxy-2,5-bis(hydroxymethyl)-6,6-dimethyltetrahydropyran-3-yl]carbamic acid *tert*-butyl ester (18): Compound **17** (40 mg, 0.13 mmol) was dissolved in ethanol (3 mL) and cooled to 0 °C. Sodium borohydride (12 mg, 0.32 mmol) was added and the mixture was stirred for 7 h at RT. Then CH_2Cl_2 and H_2O were added. The layers were separated and the aqueous phase was extracted 3× with CH_2Cl_2 and 1 time with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, hexane/EtOAc 1:2) gave **18** (25 mg, 63 %) as colorless crystals. M.p. 187–189 °C; $[\alpha]_D^{22}=+34.5$ ($c=0.24$, $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz): $\delta=1.24$, 1.25 (2 s, 3 H each, Me), 1.44 (s, 9 H, *t*Bu), 1.63 (ddd, $J=2.9$, 4.3, 9.2 Hz, 1 H, 5-H), 3.38 (dd, $J=2.9$, 10.5 Hz, 1 H, 3-H), 3.55 (dd, $J=5.6$, 12.0 Hz, 1 H, 2′-H), 3.58 (dd, $J=4.3$, 10.7 Hz, 1 H, 5′-H), 3.62 (dd, $J=2.1$, 12.0 Hz, 1 H, 2′-H), 3.69 (dd, $J=9.2$, 10.7 Hz, 1 H, 5′-H), 3.69 (m, 1 H, 2-H), 4.08 ppm (t, $J=2.9$ Hz, 1 H, 4-H); ^{13}C NMR (CD_3OD, 125 MHz): $\delta=23.0$, 31.9 (2 q, Me), 29.6 (q, *t*Bu), 53.4 (d, C-3), 53.6 (d, C-5), 61.7 (t, C-5′), 65.0 (t, C-2′), 68.4 (d, C-4), 71.6 (d, C-2), 75.6 (s, *t*Bu), 81.4 (s, C-6), 159.0 ppm (s, NCO); IR (KBr): $\tilde{\nu}=3550$–3250 (O–H, N–H), 3050–2850 (C–H), 1670 cm^{-1} (C=O); MS (FAB): *m*/*z* (%): 328 [M^++Na+H], 306 (16) [M^++H], 250 (30) [M^++H−C_4H_8], 206 (100) [M^++$C_5H_8O_2$], 57 (81) [tBu$^+$].

(1*R*,5*S*,8*S*,9*S*)-(2-Benzyl-9-benzyloxy-6,6-dimethyl-3,7-dioxa-2-azabicyclo-[3.3.1]non-8-yl)methanol (21): To a solution of (1*R*,5*S*,8*S*,9*S*)-2-benzyl-9-benzyloxy-8-*tert*-butyldimethylsiloxymethyl-6,6-dimethyl-3,7-dioxa-2-azabicyclo[3.3.1]nonane (200 mg, 0.402 mmol, for the synthesis see preparation of **11**) in THF (10 mL) was added TBAF (1 M solution in THF containing 5 % of H_2O, 2.00 mL, 2.00 mmol). The solution was stirred at RT for 15 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution and the aqueous layer was extracted 3× with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by column chromatography (silica gel, hexane/EtOAc 1:1) yielded **21** (150 mg, 97 %) as colorless oil. $[\alpha]_D^{22}=+63.5$ ($c=1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=1.39$, 1.52 (2 s, 3 H each, Me), 1.80 (ddd, $J=2.0$, 2.4, 3.2 Hz, 1 H, 5-H), 2.76 (dd, $J=1.6$, 3.2 Hz, 1 H, 1-H), 3.32 (br s, 1 H, OH), 3.73 (dd, $J=4.0$, 11.4 Hz, 1 H, 8-CH_2), 3.90 (dd, $J=5.1$, 11.4 Hz, 1 H, 8-CH_2), 4.08, 4.24 (AB system, $J_{AB}=12.9$ Hz, 2 H, NCH_2), 4.16 (m, 1 H, 8-H), 4.16 (dd, $J=2.0$, 12.0 Hz, 1 H, 4-H), 4.19 (dd, $J=2.4$, 12.0 Hz, 1 H, 4-H), 4.29 (t, $J=3.2$ Hz, 1 H, 9-H), 4.50, 4.66 (AB system, $J_{AB}=12.0$ Hz, 2 H, OCH_2Ph), 7.25–7.39 ppm (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=29.4$, 25.9 (2 q, Me), 39.6 (d, C-5), 56.7 (d, C-1), 57.2 (t, NCH_2), 65.2 (t, 8-CH_2), 66.6 (t, 4-CH_2), 68.0 (d, C-8), 70.2 (t, OCH_2Ph), 70.7 (d, C-9), 73.2 (s, C-6), 127.3, 128.5, 128.6, 128.9, 129.2, 129.9 (6 d, Ph), 136.7, 137.7 ppm (s, Ph); IR (film): $\tilde{\nu}=3440$ (O–H), 3110–3030 (=C-H), 2970–2880 cm^{-1} (C–H); HRMS (EI, 80 eV, 140 °C): *m*/*z*: calcd for $C_{23}H_{29}NO_4$: 383.2100; found 383.2122 $[M]^+$.

(1*R*,5*S*,8*S*,9*S*)-2-Benzyl-9-benzyloxy-6,6-dimethyl-3,7-dioxa-2-azabicyclo-[3.3.1]nonane-8-carboxylic acid (22): To a solution of alcohol **21** (303 mg, 0.790 mmol) in DMSO (10 mL) were added SO_3·pyridine (377 mg, 2.37 mmol) and Et_3N (600 μL, 3.96 mmol). The resulting mixture was stirred at RT for 16 h. A solution of $NaClO_2$ (80 %, 447 mg, 3.96 mmol) in H_2O (5 mL) and a solution of NaH_2PO_4 (546 mg, 3.96 mmol) in H_2O (5 mL) were added. After stirring the reaction mixture for 3 h at RT 0.1 M HCl was added to adjust pH ≈ 3. The resulting solution was extracted 3× with Et_2O/toluene 1:1. The combined organic layers were washed with water, dried with $MgSO_4$ and concentrated giving **22** (332 mg, quant.) as yellow oil. $[\alpha]_D^{22}=+16.3$ ($c=0.33$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=1.42$, 1.55 (2 s, 3 H each, Me), 1.79 (m, 1 H, 5-H), 3.53 (br s, 1 H, 1-H), 4.08, 4.19 (AB system, $J_{AB}=13.8$ Hz, 2 H, NCH_2), 4.09 (m, 1 H, 4-H), 4.20 (dd, $J=2.3$, 12.4 Hz, 1 H, 4-H), 4.40 (m, 1 H, 9-H), 4.64, 4.65 (AB system, $J_{AB}=11.3$ Hz, 2 H, OCH_2Ph), 4.80 (d, $J=2.2$ Hz, 1 H, 8-H), 7.23–7.57 ppm (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=26.1$, 29.1 (2 q, Me), 39.1 (d, C-5), 57.7 (d, C-1), 58.0 (t, NCH_2), 68.3 (t, C-4), 69.0 (d, C-8), 70.9 (t, OCH_2Ph), 73.4 (d, C-9), 76.0 (s, C-6), 127.4, 127.6, 128.0, 128.5, 128.8, 129.3, 137.1, 137.6 (6 d, 2 s, Ph), 172.0 ppm (s, CO_2); IR (film): $\tilde{\nu}=3370$ (O–H), 3090–3010 (=C-H), 2980–2870 (C–H), 1750 cm^{-1} (C=O); HRMS (EI, 80 eV, 120 °C): *m*/*z*: calcd for $C_{23}H_{27}NO_5$: 397.1889; found 397.1880 $[M]^+$.

(1*R*,5*S*,8*S*,9*S*)-2-Benzyl-9-benzyloxy-6,6-dimethyl-3,7-dioxa-2-azabicyclo-[3.3.1]nonane-8-carboxylic acid methyl ester (23): Crude acid **22** (119 mg, 0.300 mmol) was dissolved in MeOH/toluene 1:1 (10 mL) and treated with $TMSCHN_2$ (2 M in Et_2O, 300 μL, 0.600 mmol) at RT. The reaction mixture was stirred for 2 h and all volatile compounds were removed in vacuo. Purification by column chromatography (silica gel, hexane/EtOAc 3:1 → 1:1) yielded **25** (110 mg, 91 % from **21**) as yellowish oil. $[\alpha]_D^{22}=+12.8$ ($c=1.08$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=1.46$, 1.56 (2 s, 3 H each, Me), 1.76 (ddd, $J=1.8$, 2.5, 3.3 Hz, 1 H, 5-H), 3.36 (dd, $J=2.1$, 3.3 Hz, 1 H, 1-H), 3.74 (s, 3 H, OMe), 3.99 (dd, $J=1.8$, 12.2 Hz, 1 H, 4-H), 4.03, 4.08 (AB system, $J_{AB}=13.6$ Hz, 2 H, NCH_2), 4.23 (dd, $J=2.5$, 12.2 Hz, 1 H, 4-H), 4.27 (t, $J=3.3$ Hz, 1 H, 9-H), 4.60, 4.67 (AB system, $J_{AB}=11.9$ Hz, 2 H, OCH_2Ph), 4.87 (d, $J=2.1$ Hz, 1 H, 8-H), 7.23–7.40 ppm (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=25.5$, 29.0 (2 q, Me), 39.2 (d, C-5), 52.0 (q, OMe), 57.8 (t, NCH_2), 57.9 (d, C-1), 67.8 (t, C-4), 69.2 (d, C-8), 70.4 (t, OCH_2Ph), 74.0 (s, C-6), 74.4 (d, C-9), 127.2, 127.9, 128.0, 128.3, 128.5, 128.6, 137.4, 137.5 (6 d, 2 s, Ph), 172.1 ppm (s, CO_2); IR (film): $\tilde{\nu}=3160$–3030 (=C-H), 2990–2870 (C–H), 1760 cm^{-1} (C=O); HRMS (EI, 80 eV, 100 °C): *m*/*z*: calcd for $C_{24}H_{29}NO_5$: 411.2046; found 411.2053 $[M]^+$.

(2*S*,3*R*,4*S*,5*S*)-4-Benzyloxy-3-*tert*-butoxycarbonylamino-5-hydroxymethyl-6,6-dimethyltetrahydropyran-2-carboxylic acid methyl ester (26): A stirred suspension of Pd on charcoal (10 % Pd, 178 mg) in MeOH (5 mL) was saturated with hydrogen for 1 h. Then, a solution of methyl ester **23** (172 mg, 0.418 mmol) and Boc_2O (137 mg, 0.630 mmol) in MeOH (5 mL) was added and the mixture was stirred for 3 d under an atmosphere of hydrogen at RT. Filtration through a short pad of celite and concentration of the solution to dryness was followed by column chromatographic purification (silica gel, hexane/EtOAc 1:1) giving **26** (115 mg, 86 %) as colorless oil. $[\alpha]_D^{22}=+25.1$ ($c=3.42$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=1.46$, 1.51 (2 s, 3 H each, Me), 1.47 (s, 9 H, *t*Bu), 1.89 (m, 1 H, 5-H), 2.76 (m, 1 H, OH), 3.60–3.70 (m, 2 H, 5-CH_2), 3.70 (s, 3 H, OMe), 3.78 (m$_c$, 1 H, 4-H), 4.27 (m, 1 H, 3-H), 4.65, 4.85 (AB system, $J_{AB}=11.4$ Hz, 2 H, CH_2Ph), 4.71 (d, $J=3.0$ Hz, 1 H, 2-H), 5.74 (d, $J=9.5$ Hz, 1 H, NH), 7.32–7.42 ppm (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=25.5$, 26.7 (2 q, Me), 26.7 (q, *t*Bu), 47.3 (d, C-5), 51.1 (d, C-3), 51.9 (q, OMe), 62.7 (t, 5-CH_2), 69.9 (d, C-2), 71.9 (t, *C*H_2Ph), 75.4 (s, C-6), 79.5 (d, C-4), 79.6 (s, *t*Bu), 127.4, 127.7, 128.4, 137.6 ppm (3 d, s, Ph); IR (film): $\tilde{\nu}=3490$ (O–H), 3440 (N–H), 3110–3030 (=C-H), 2980–2870 (C–H), 1760, 1710 cm^{-1} (C=O); HRMS (EI, 80 eV, 100 °C): *m*/*z*: calcd for $C_{22}H_{33}NO_7$: 423.2257; found 423.2246 $[M]^+$.

(1*S*,4*S*,5*S*,6*R*)-7-Benzyl-5-benzyloxy-4-hydroxymethyl-3,3-dimethyl-2-oxa-7-azabicyclo[4.2.0]octan-8-one (27): 1,2-Diiodoethane (136 mg, 0.480 mmol) and samarium (79 mg, 0.53 mmol) were transferred into a dried flask. THF (7 mL) was added. After the solution turned blue, the mixture was stirred for further 2 h. Methyl ester **23** (90 mg, 0.22 mmol) in THF (3 mL) was added and the reaction mixture was stirred for 30 min. After addition of sat. $NaHCO_3$ solution the mixture was extracted 3× with EtOAc. The solution was dried with $MgSO_4$ and the solvent was removed in vacuo. Product **27** (79 mg, 95 %) was obtained in analytically pure form as colorless crystals. M.p. 112–113 °C; $[\alpha]_D^{22}=+25.0$ ($c=0.02$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=1.21$, 1.31 (2 s, 3 H each, Me), 1.66 (td, $J=5.2$, 10.5 Hz, 1 H, 4-H), 3.68 (m, 2 H, 4-CH_2), 3.70 (dd, $J=4.6$, 5.1 Hz, 1 H, 6-H), 3.89 (dd, $J=4.6$, 10.5 Hz, 1 H, 5-H), 4.23, 4.79 (AB system, $J_{AB}=15.7$ Hz, 2 H, NCH_2), 4.30, 4.42 (AB system, $J_{AB}=11.0$ Hz, 2 H, OCH_2Ph), 4.91 (d, $J=5.1$ Hz, 1 H, 1-H), 7.14–7.37 ppm (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=23.5$, 27.6 (2 q, Me), 44.7 (t, NCH_2), 49.8 (d, C-4), 58.9 (d, C-6), 61.9 (t, 4-CH_2), 72.1 (t, OCH_2Ph), 76.7 (d, C-5), 77.3 (d, C-1), 78.7 (s, C-3), 127.2, 127.5, 128.4, 128.7, 128.9, 129.3, 135.3, 136.9 (6 d, 2 s, Ph), 168.8 ppm (s, C-8); IR (KBr): $\tilde{\nu}=3430$ (O–H), 3110–3030 (=C-H), 2960–2860 (C–H), 1750 cm^{-1} (C=O); HRMS (EI, 80 eV, 200 °C): *m*/*z*: calcd for $C_{23}H_{27}NO_4$: 381.1940; found 381.1944 $[M]^+$.

(1*S*,4*S*,5*R*,8*S*)-8-Benzyloxy-4-(*tert*-butyldimethylsiloxymethyl)-2,2-dimethyl-7-oxo-3-oxa-6-azabicyclo[3.2.1]octane-6-carboxylic acid *tert*-butyl ester (28): Alcohol **11** (320 mg, 0.629 mmol) was dissolved in DMF (10 mL), then PDC (946 mg, 2.52 mmol) and Ac_2O (240 μL, 2.50 mmol) were added. The mixture was stirred for 12 h at RT. Then, Et_2O and H_2O

were added and the layers were separated. The organic layer was successively washed with H_2O, dried ($MgSO_4$), and the solvent was removed in vacuo. Purification by column chromatography (silica gel, hexane/EtOAc 4:1 → 1:1) yielded **28** (250 mg, 79%) as colorless crystals. M.p. 64–65 °C; $[\alpha]_D^{22} = +14.1$ ($c = 1.43$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 0.05$, 0.06 (2s, 3H each, $SiMe_2$), 0.88 (s, 9H, *t*Bu), 1.29, 1.47 (2s, 3H each, Me), 1.51 (s, 9H, *t*Bu), 2.43 (dd, $J = 1.6$, 4.9 Hz, 1H, 5-H), 3.57 (dd, $J = 6.5$, 10.6 Hz, 1H, 4-CH_2), 3.58 (dd, $J = 6.5$, 10.6 Hz, 1H, 4-CH_2), 4.15 (t, $J = 6.5$ Hz, 1H, 4-H), 4.15 (t, $J = 4.9$ Hz, 1H, 8-H), 4.30 (dd, $J = 1.6$, 4.9 Hz, 1H, 1-H), 4.60 (br s, 2H, CH_2Ph), 7.25–7.38 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 500 MHz): $\delta = -5.3$, −5.1 (2q, $SiMe_2$), 18.1 (s, *t*Bu), 24.5, 29.0 (2q, Me), 25.9 (q, *t*Bu), 28.0 (q, *t*Bu), 53.3 (d, C-5), 55.0 (d, C-1), 63.7 (t, 4-CH_2), 68.1 (d, C-4), 71.8 (t, *C*H_2Ph), 72.9 (d, C-2), 75.6 (d, C-8), 83.1 (s, *t*Bu), 127.5, 128.1, 128.6, 136.8 (3 d, s, Ph), 149.4 (s, NCO_2), 170.9 ppm (s, NCO); IR (KBr): $\tilde{\nu} = 3120$–3030 (=C-H), 2960–2860 (C−H), 1790 cm^{-1} (C=O); elemental analysis calcd (%) for $C_{27}H_{43}NO_6Si$ (505.3): C 64.12, H 8.57, N 2.77; found C 64.22, H 8.75, N 2.78.

(3*S*,4*S*,5*R*,6*S*)-4-Benzyloxy-5-*tert*-butoxycarbonylamino-6-*tert*-butyldimethylsiloxymethyl-2,2-dimethyltetrahydropyran-3-carboxylic acid (29): To a solution of γ-lactam **28** (434 mg, 0.858 mmol) in THF/H_2O 2:1 (9 mL) was added LiOH (103 mg, 4.29 mmol). The resulting mixture was stirred for 12 h. To the reaction mixture was added 0.1 M HCl to adjust pH ~3. The solution was extracted with EtOAc. The combined organic layers were washed with H_2O, dried with $MgSO_4$ and concentrated to dryness to yield **29** (392 mg, 85%) as colorless oil. $[\alpha]_D^{22} = -6.1$ ($c = 0.45$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 0.06$ (s, 6H, $SiMe_2$), 0.89 (s, 9H, *t*Bu), 1.26 (s, 9H, *t*Bu), 1.31, 1.52 (2s, 3H each, Me), 2.30 (d, $J = 4.8$ Hz, 1H, 3-H), 3.51 (dd, $J = 7.3$, 10.5 Hz, 1H, 6-CH_2), 3.63 (dd, $J = 4.4$, 10.5 Hz, 1H, 6-CH_2), 3.70 (dd, $J = 2.3$, 4.8 Hz, 1H, 5-H), 4.01 (dd, $J = 4.4$, 7.3 Hz, 1H, 6-H), 4.21 (t, $J = 4.8$ Hz, 1H, 4-H), 4.60, 4.69 (AB system, $J_{AB} = 11.7$ Hz, 2H, C*H*$_2$Ph), 5.78 (br s, 1H, NH), 7.23–7.37 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = -5.2$ (q, $SiMe_2$), 18.3 (s, *t*Bu), 21.4 (q, *t*Bu), 24.9 (q, *t*Bu), 29.3, 29.7 (2q, Me), 50.8 (d, C-5), 52.5 (d, C-3), 63.5 (t, 6-CH_2), 66.2 (d, C-6), 71.8 (s, C-2), 72.2 (t, *C*H_2Ph), 77.2 (s, *t*Bu), 77.8 (d, C-4), 127.6, 128.0, 128.6, 139.5 (3d, s, Ph), 157.7 (s, NCO_2), 175.0 ppm (s, CO_2H); IR (film): $\tilde{\nu} = 3490$–3340 (O−H, N−H), 3090–3000 (=C-H), 2980–2930 (C−H), 1740, 1730 cm^{-1} (C=O); HRMS (EI, 80 eV): *m*/*z*: calcd for $C_{27}H_{45}NO_7Si$: 523.2965; found 523.2956 $[M]^+$.

(1*R*,5*S*,8*S*,9*S*)-2-Benzyl-6,6-dimethyl-8-[(prop-2-ynyloxy)methyl]-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (30): To a solution of NaOH (2.77 g, 70.0 mmol) in H_2O (10 mL) was added CH_2Cl_2 (10 mL), compound **2** (415 mg, 1.40 mmol), TBAI (197 mg, 0.500 mmol) and propargyl bromide (80% wt in toluene, 1.4 mL, 7.0 mmol). The mixture was stirred for 7 d at RT. After extraction of the mixture 3× with CH_2Cl_2 the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by column chromatography (Al_2O_3, hexane/EtOAc 15:1) yielded (1*S*,5*S*,8*S*)-2-benzyl-8-((prop-2-ynyloxy)methyl)-6,6-dimethyl-3,7-dioxa-2-azabicyclo-[3.3.1]nonan-9-one (374 mg, 72%) as colorless oil. $[\alpha]_D^{22} = +77.0$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.21$, 1.41 (2s, 3H each, Me), 2.33 (m, 1H, 5-H), 2.37 (t, $J = 2.3$ Hz, 1H, C≡CH), 3.23 (m, 1H, 1-H), 3.78 (dd, $J = 5.6$, 9.1 Hz, 1H, 4-H), 3.90 (dd, $J = 7.0$, 9.1 Hz, 1H, 4-H), 3.97 (d, $J = 13.6$ Hz, NCH_2), 4.13 (m, 2H, NCH_2, 8-H), 4.08 (d, $J = 15.8$ Hz, 1H, C*H*$_2$C≡CH), 4.09 (d, $J = 15.8$ Hz, 1H, C*H*$_2$C≡CH), 4.47 (dt, $J = 5.5$, 12.1 Hz, 1H, 8-CH_2), 4.54 (dd, $J = 2.9$, 12.1 Hz, 1H, 8-CH_2), 7.25–7.37 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 23.8$, 26.7 (2 q, Me), 58.0 (t, NCH_2), 58.6 (t, *C*H_2C≡CH), 59.9 (d, C-5), 68.9 (d, C-1), 69.1 (t, 8-CH_2), 70.2 (t, C-4), 74.1 (d, C-8), 74.8 (s, C-6), 78.4 (s, *C*≡CH), 79.3 (d, C≡*C*H), 127.6, 128.3, 128.8, 136.2 (3 d, s, Ph), 207.9 ppm (s, CO); IR (film): $\tilde{\nu} = 3280$ (≡C-H), 3090–2870 (=C-H, C-H), 2120 (C≡C), 1730 cm^{-1} (C=O); HRMS (EI, 80 eV): *m*/*z*: calcd for $C_{19}H_{23}NO_4$: 329.1627; found 329.1620 $[M]^+$.

$NaBH_4$ (35 mg, 0.93 mmol) was added to a solution of the obtained product (90 mg, 0.27 mmol) in EtOH (5 mL) at 0 °C. The reaction was stirred for 1.5 h at that temperature. The solvent was removed in vacuo and CH_2Cl_2 and H_2O were added. The organic layer was separated and the aqueous layer was extracted 2× with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. Purification by column chromatography yielded **30** (80 mg, 89%) as colorless crystals. M.p. 101–103 °C; $[\alpha]_D^{22} = +92.5$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.31$, 1.48 (2s, 3H each, Me), 1.60 (m, 1H, 5-H), 2.00 (d, $J = 2.6$ Hz, 1H, OH), 2.39 (t, $J = 2.4$ Hz, 1H, C≡CH), 2.69 (t, $J = 1.8$ Hz, 1H, 1-H), 3.76 (dd, $J = 5.9$, 9.1 Hz, 1H, 4-H), 3.86 (dd, $J = 6.5$, 9.1 Hz, 1H, 4-H), 4.08 (dd, $J = 2.4$, 15.8 Hz, 1H, C*H*$_2$C≡CH), 4.13 (m, 3H, NCH_2, 8-CH_2), 4.17 (dd, $J = 2.4$, 15.8 Hz, 1H, C*H*$_2$C≡CH), 4.31 (d, $J = 13.6$ Hz, 1H, NCH_2), 4.40 (dt, $J = 2.0$, 6.4 Hz, 1H, 8-H), 4.67 (d, $J = 2.5$ Hz, 1H, 9-H), 7.25–7.37 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 26.5$, 29.5 (2q, Me), 42.6 (d, C-5), 57.5 (t, NCH_2), 57.7 (d, C-1), 58.4 (t, *C*H_2C≡CH), 65.1 (d, C-9), 66.5 (t, 8-CH_2), 67.3 (d, C-8), 70.8 (t, C-4), 73.2 (s, C-6), 74.4 (s, C≡CH), 79.8 (d, C≡*C*H), 127.3, 128.3, 128.5, 137.6 ppm (3d, s, Ph); IR (KBr): $\tilde{\nu} = 3440$ (O−H), 3280 (≡C-H), 3090–2870 (=C-H, C-H), 2120 cm^{-1} (C≡C); HRMS (ESI-TOF): *m*/*z*: calcd for 332.1862; found 332.1867 $[C_{19}H_{25}NO_4+H]^+$; elemental analysis calcd (%) for $C_{19}H_{25}NO_4$ (331.4): C 68.86, H 7.60, N 4.23; found C 68.36, H 7.62, N 4.21.

(1*S*,5*R*,8*S*)-Methanesulfonic acid (2-benzyl-6,6-dimethyl-9-oxo-3,7-dioxa-2-azabicyclo[3.3.1]non-8-yl)methyl ester (31): Methanesulfonyl chloride (63 μL, 0.78 mmol) and Et_3N (0.25 mL, 1.7 mmol) were added to a stirred solution of bicyclic ketone **2** (100 mg, 0.343 mmol) in dry CH_2Cl_2 (5 mL). After 4 h, the reaction mixture was diluted with dichloromethane and washed excessively with sat. $NaHCO_3$ solution. The crude product (176 mg) was purified by column chromatography (silica gel, hexane/EtOAc 1:1) to yield product **31** (129 mg, quant.) as colorless crystals. M.p. 124–126 °C; $[\alpha]_D^{22} = +58.3$ ($c = 0.60$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.20$, 1.41 (2s, 3H each, Me), 2.28 (td, $J = 2.0$, 4.0 Hz, 1H, 5-H), 2.94 (s, 3H, Ms), 3.05 (t, $J = 2.0$ Hz, 1H, 1-H), 3.93 (d, $J = 13.1$ Hz, 1H, NCH_2), 4.17 (d, $J = 13.1$ Hz, 1H, NCH_2), 4.18 (ddd, $J = 2.0$, 5.5, 6.4 Hz, 1H, 8-H), 4.35 (dd, $J = 5.5$, 10.4 Hz, 1H, 8-CH_2), 4.52 (dd, $J = 2.0$, 12.4 Hz, 1H, 4-H), 4.53 (dd, $J = 6.4$, 10.4 Hz, 1H, 8-CH_2), 4.60 (dd, $J = 4.0$, 12.4 Hz, 1H, 4-H), 7.25–7.34 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 23.6$, 26.6 (2q, Me), 37.3 (q, Ms), 57.7 (d, C-5), 58.4 (t, NCH_2), 68.2 (d, C-1), 68.8 (t, 8-CH_2), 69.2 (t, C-4), 72.9 (d, C-8), 78.6 (s, C-6), 127.9, 128.5, 129.1, 135.2 (3d, s, Ph), 207.5 ppm (s, CO); IR (KBr): $\tilde{\nu} = 3090$–3030 (=C-H), 2980–2880 (C-H), 1730 (C=O), 1340 cm^{-1} (SO_2); elemental analysis calcd (%) for $C_{17}H_{23}NO_6S$ (369.4): C 55.27, H 6.28, N 3.79; found C 54.90, H 6.01, N 3.43.

(1*R*,5*S*,8*R*,9*S*)-8-Azidomethyl-2-benzyl-6,6-dimethyl-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-ol (32): Compound **31** (713 mg, 1.93 mmol) was dissolved in ethanol (20 mL). The solution was cooled to 0 °C and $NaBH_4$ (130 mg, 3.44 mmol) was added. The resulting mixture was stirred for 3 h at RT. Then, the solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 and H_2O. The layers were separated and the aqueous phase was extracted 2× with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and concentrated to dryness giving (1*R*,5*S*,8*S*,9*S*)-methanesulfonic acid 2-benzyl-9-hydroxy-6,6-dimethyl-3,7-dioxa-2-azabicyclo[3.3.1]non-8-ylmethyl ester (672 mg, 98%) as colorless crystals. A solution of the obtained product (360 mg, 1.01 mmol) in DMF (3 mL) was treated with NaN_3 (196 mg, 3.03 mmol). The reaction mixture was heated to 80 °C and stirred for 6 h at this temperature. Then EtOAc (3 mL) was added and the mixture was washed with water, dried with Na_2SO_4 and concentrated. Recrystallization (hexane/EtOAc 2:1) yielded the pure product **32** (261 mg, 81%) as colorless crystals. M.p. 146–149 °C; $[\alpha]_D^{22} = +83.9$ ($c = 0.25$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.32$, 1.51 (2s, 3H each, Me), 1.58 (m, 1H, 5-H), 2.16 (br s, 1H, OH), 2.57 (t, $J = 1.7$ Hz, 1H, 1-H), 3.34 (dd, $J = 5.6$, 12.2 Hz, 1H, 4-H), 3.72 (dd, $J = 7.3$, 12.2 Hz, 1H, 4-H), 4.05 (d, $J = 13.3$ Hz, 1H, NCH_2), 4.08 (dd, $J = 2.4$, 12.3 Hz, 1H, 8-CH_2), 4.16 (dd, $J = 1.9$, 12.3 Hz, 1H, 8-CH_2), 4.31 (d, $J = 13.3$ Hz, 1H, NCH_2), 4.31 (m, 1H, 8-H), 4.68 (m, 1H, 9-H), 7.25–7.34 ppm (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 26.4$, 29.4 (2q, Me), 42.6 (d, C-5), 52.6 (t, C-4), 57.8 (t, NCH_2), 64.4 (d, C-1), 66.0 (d, C-9), 67.5 (t, 8-CH_2), 73.5 (d, C-8), 78.5 (s, C-6), 127.5, 128.4, 128.6, 137.4 ppm, (3d, s, Ph); IR (KBr): $\tilde{\nu} = 3450$ (O-H), 3090–3030 (=C-H), 2980–2850 (C-H), 2100 cm^{-1} (N_3); HRMS (EI, 80 eV, 120 °C): *m*/*z*: calcd for $C_{16}H_{22}N_4O_3$: 318.1692; found 318.1686 $[M]^+$.

Compound 33: To a solution of alkyne **30** (30 mg, 0.09 mmol) and azide **32** (30 mg, 0.090 mmol) in MeCN (2.5 mL) were added solutions of NEt_3 (1.9 mL, 0.02 mmol, 10 mM in MeCN), TBTA (1.9 mL, 0.02 mmol, 10 mM in MeCN), and CuI (1.9 mL, 0.02 mmol, 10 mM in MeCN). Argon was

bubbled through the mixture for 15 min and the reaction was stirred for 48 h at 40 °C. H_2O (5 mL) and EtOAc (5 mL) were added. The organic layer was separated and the aqueous layer was extracted 2× with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 3% MeOH in CH_2Cl_2) to give **33** (58 mg, 95%) as a colorless solid. M.p. 210–212 °C; $[\alpha]_D^{22} = +50.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$ with 2% CD_3OD, 500 MHz): $\delta = 1.31$, 1.37, 1.40, 1.57 (4s, 3H each, Me), 1.59 (m, 1H), 1.67 (m, 1H), 2.73 (brs, 1H), 3.15 (brs, 1H), 3.63 (dd, $J = 5.1$, 10.1 Hz, 1H), 3.74 (d, $J = 13.6$ Hz, 1H), 3.98–4.14 (m, 10H), 4.22–4.36 (m, 5H), 4.47–4.56 (m, 6H), 4.75 (t, $J = 3.3$ Hz, 1H), 5.41 (brs, 1H), 6.82 (m, 1H, Ph), 6.89 (t, $J = 7.3$ Hz, 2H, Ph), 7.19–7.24 (m, 3H, Ph), 7.29 (m, 2H, Ph), 7.64 ppm (s, 1H, triazole); ^{13}C NMR ($CDCl_3$, with 2% CD_3OD, 125 MHz): $\delta = 26.3$ (q), 29.3 (q), 41.8 (d), 42.0 (d), 52.6 (t), 57.0 (t), 57.1 (t), 57.2 (d), 57.6 (d), 63.0 (d), 63.8 (t), 64.1 (d), 66.1 (t), 66.3 (t), 66.9 (d), 67.6 (d), 70.7 (t), 73.4 (s), 73.8 (s), 77.2 (d), 124.0 (d, triazole), 127.1, 127.6, 128.1, 128.4, 128.5, 128.9, 137.1, 137.7 (6 d, 2 s, Ph), 144.0 (s, triazole); IR (KBr): $\tilde{\nu} = 3430$ (O–H), 3120–2970 cm^{-1} (C–H, =C-H); HRMS (ESI-TOF): m/z: calcd for $C_{35}H_{47}N_5O_7$: 650.3554; found 650.3575 $[M+H]^+$.

(3*S*,4*S*,5*R*,6*R*)-5-Amino-6-{[4-({[(2*S*,3*R*,4*S*,5*S*)-3-amino-4-hydroxy-5-(hydroxymethyl)-6,6-dimethyltetrahydro-2*H*-pyran-2-yl]methoxy}methyl)-1*H*-1,2,3-triazol-1-yl]methyl}-3-(hydroxymethyl)-2,2-dimethyltetrahydro-2*H*-pyran-4-ol (34): A suspension of Pd/C in MeOH (10 mL) containing substrate **33** (250 mg, 0.385 mmol) was saturated with H_2 for 1 h, then the mixture was stirred for 2 d, filtered through a pad of celite and MeOH was removed in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH (sat. with NH_3) 7:3) to yield product **34** (50 mg, 28%) as colorless oil. $[\alpha]_D^{22} = +31.6$ ($c = 0.50$, MeOH); ^{1}H NMR (CD_3OD, 700 MHz): $\delta = 1.12$, 1.19, 1.23, 1.36 (4s, 3H each, Me), 1.70–1.73 (m, 2H, 3a-H, 5b-H), 2.88 (dd, $J = 3.5$, 4.7 Hz, 1H, 5a-H), 2.94 (dd, $J = 3.7$, 4.9 Hz, 1H, 3b-H), 3.60–3.63 (m, 4H, 3a-CH_2, 5b-CH_2, 2b-CH_2), 3.68 (dd, $J = 4.7$, 7.7 Hz, 1H, 4a-H), 3.70 (dd, $J = 4.9$, 7.0 Hz, 1H, 4b-H), 3.81 (dd, $J = 5.7$, 11.5 Hz, 1H, 3a-CH_2 or 5b-CH_2), 3.84 (dd, $J = 5.4$, 11.4 Hz, 1H, 3a-CH_2 or 5b-CH_2), 4.16 (m, 1H, 2b-H), 4.23 (td, $J = 3.5$, 9.6 Hz, 1H, 6a-H), 4.45 (dd, $J = 9.6$, 14.1 Hz, 1H, 6a-CH_2), 4.62 (dd, $J = 3.5$, 14.1 Hz, 1H, 6a-CH_2), 4.66 (d, $J = 3.1$ Hz, 2H, OCH_2-triazole), 8.00 ppm (s, 1H, triazole); ^{13}C NMR (CD_3OD, 175 MHz): $\delta = 25.2$, 25.8, 27.2, 27.7 (4q, Me), 49.2, 49.4 (2 d, C-3a, C-5b), 52.6 (t, 6a-CH_2), 56.0 (d, C-5a), 56.7 (d, C-3b), 62.8, 62.9 (2t, 3a-CH_2, 5b-CH_2), 65.1 (t, OCH_2-triazole), 68.8 (d, C-2b), 70.3 (d, C-6a), 71.0 (t, 2b-CH_2), 74.9 (d, C-4b), 76.0 (d, C-4a), 76.3, 76.5 (2s, C-2a, C-6b), 126.0, 145.3 pm (d, s, triazole); IR (film): $\tilde{\nu} = 3430$ (N–H, O–H), 2930 (C–H), 1620 cm^{-1} (C=C); HRMS (ESI-TOF): m/z: calcd for $C_{21}H_{39}N_5O_7$: 474.2928; found 474.2957 $[M+H]^+$.

Acetic acid (3*S*,4*S*,5*R*,6*S*)-3.6-bis(acetoxymethyl)-5-azido-2,2-dimethyltetrahydropyran-4-yl ester (35): To a solution of amino alcohol **7** (150 mg, 0.730 mmol) in MeOH/H_2O 2:1 (3 mL) at RT were added $CuSO_4 \cdot 5H_2O$ (18 mg, 0.073 mol, 1 M solution in H_2O) and K_2CO_3 (101 mg, 0.73 mmol), followed by slow addition of Nf-N_3 (475 mg, 1.46 mmol). The mixture was stirred for 24 h, then glycine hydrochloride (554 mg, 5.00 mmol) was added in order to quench the reaction and the suspension was stirred for another 24 h. The mixture was filtered and the solvents were removed in vacuo. The crude solid was dissolved in pyridine (6 mL) and cooled to 0 °C. Then DMAP (3 mg, 0.02 mmol) and Ac_2O (690 μL, 7.30 mmol) were added and the mixture was stirred at RT for 12 h. The residue was taken up in Et_2O and washed with 1 M solution of HCl and brine followed by sat. $NaHCO_3$ solution. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc 9:1 → 3:2) to give **35** (150 mg, 57%) as colorless oil. $[\alpha]_D^{22} = +28.0$ ($c = 0.50$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.21$, 1.37 (2s, 3H each, Me), 2.01 (m, 1H, 3-H), 2.08 (s, 6H, Ac), 2.10 (s, 3H, Ac), 3.60 (dd, $J = 2.5$, 3.8 Hz, 1H, 5-H), 4.09–4.19 (m, 4H, 3-CH_2, 6-CH_2, 4-H), 4.40 (dd, $J = 6.5$, 11.4 Hz, 1H, 3-CH_2), 5.35 ppm (dd, $J = 4.2$, 5.2 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 20.8$, 20.9, 21.1 (3 q, Ac), 26.0, 26.3 (2 q, Me), 42.6 (d, C-3), 60.1 (d, C-5), 62.2 (t, 6-CH_2), 63.7 (t, 3-CH_2), 66.4 (d, C-4), 69.7 (d, C-6), 74.0 (s, C-2), 169.6, 170.6, 170.7 ppm (3s, Ac); IR (film): $\tilde{\nu} = 2980$–2720 (C-H), 2110 (N_3), 1750 cm^{-1} (C=O); HRMS (EI, 80 eV): m/z: calcd for $C_{13}H_{20}N_3O_6$: 314.1349; found 314.1352 $[M-CH_3CO]^+$.

Acetic acid (3*S*,4*S*,5*R*,6*S*)-4-acetoxy-6-acetoxymethyl-2,2-dimethyl-5-[4-(2-trimethylsilyl)ethoxymethyl-1*H*-1,2,3-triazol-1-yl]-tetrahydropyran-3-ylmethyl ester (36): To a solution of azide **35** (15 mg, 42 μmol) and trimethyl(2-(prop-2-ynyloxy)ethyl)silane (7.0 mg, 42 μmol) in MeCN (0.78 mL) were added solutions of NEt_3 (840 μL, 8.4 μmol, 10 mM in MeCN), TBTA (840 μL, 8.4 μmol, 10 mM in MeCN), and CuI (840 μL, 8.4 μmol, 10 mM in MeCN). Argon was bubbled through the mixture for 15 min and the reaction was stirred for 24 h at 40 °C. H_2O (3 mL) and EtOAc (3 mL) were added. The organic layer was separated and the aqueous layer was extracted 2× with EtOAc. The organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc 3:2 → EtOAc) to give **36** (20 mg, 93%) as a yellow oil. $[\alpha]_D^{22} = +9.0$ ($c = 0.50$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 0.97$ (m, 2H, CH_2TMS), 1.34, 1.39 (2s, 3H each, Me), 1.97, 1.99, 2.03 (3s, 3H each, OAc), 2.34 (m, 1H, 3-H), 3.59 (m, 2H, OCH_2), 3.63 (dd, $J = 7.3$, 11.9 Hz, 1H, 6-CH_2), 3.72 (dd, $J = 5.4$, 11.9 Hz, 1H, 6-CH_2), 4.01 (dd, $J = 5.4$, 11.9 Hz, 1H, 3-CH_2), 4.22 (dd, $J = 5.8$, 11.9 Hz, 1H, 3-CH_2), 4.42 (m, 1H, 6-H), 4.62 (s, 2H, triazole-CH_2), 5.05 (dd, $J = 5.0$, 6.9 Hz, 1H, 5-H), 5.44 (dd, $J = 6.9$, 12.3 Hz, 1H, 4-H), 7.76 ppm (s, 1H, triazole); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = -1.41$ (q, $SiMe_3$), 18.1, 20.6, 20.8 (3 q, Ac), 23.5, 25.9 (2 q, Me), 44.1 (d, C-3), 61.2 (t, 6-CH_2), 61.9 (t, 3-CH_2), 63.8 (t, triazole-CH_2), 65.1 (d, C-5), 67.8 (t, OCH_2), 67.7 (d, C-6), 72.0 (d, C-4), 76.6 (s, C-2), 121.1 (d, triazole), 146.5 (s, triazole), 169.6, 170.6, 170.7 ppm (3s, Ac); IR (film): $\tilde{\nu} = 3140$ (C=C), 2850–2980 (C-H), 1750 cm^{-1} (C=O); HRMS (ESI-TOF): m/z: calcd for $C_{23}H_{41}N_3O_8$: 514.2579; found 514.2585 $[M+H]^+$.

All other compounds: See the Supporting Information for syntheses and analytical data.

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[1] Reviews: a) *Carbohydrate Mimetics-Concepts and Methods* (Ed.: Y. Chapleur), Wiley-VCH, Weinheim, **1998**; b) P. Sears, C.-H. Wong, *Angew. Chem.* **1999**, *111*, 2446–2471; *Angew. Chem. Int. Ed.* **1999**, *38*, 2300–2324; c) P. Sears, C.-H. Wong, *Acc. Chem. Res.* **1999**, *32*, 376–385; d) T. Skrydstrup, B. Vauzeilles, J.-M. Beau in *Carbohydrates in Chemistry and Biology* (Eds.: B. Ernst, G. W. Hart, P. Sinaÿ), Wiley-VCH, Weinheim, **2000**, pp. 493–530; e) B. Werschkun, J. Thiem, *Top. Curr. Chem.* **2001**, *215*, 293–325; f) M. H. D. Postema, J. L. Piper, R. L. Betts, *Synlett* **2005**, 1345–1358. Selected contributions: g) E. R. Palmacci, P. H. Seeberger, *Org. Lett.* **2001**, *3*, 1547–1550; h) R. B. Hossany, M. A. Johnson, A. A. Eniade, B. M. Pinto, *Bioorg. Med. Chem.* **2004**, *12*, 3743–3754; i) P. Wipf, J. G. Pierce, N. Zhuang, *Org. Lett.* **2005**, *7*, 483–485.

[2] a) A. Al-Harrasi, H.-U. Reissig, *Angew. Chem.* **2005**, *117*, 6383–6387; *Angew. Chem. Int. Ed.* **2005**, *44*, 6227–6231. For a related rearrangement leading to compounds bearing an anomeric center, see: b) F. Pfrengle, D. Lentz, H.-U. Reissig, *Angew. Chem.* **2009**, *121*, 3211–3215; *Angew. Chem. Int. Ed.* **2009**, *48*, 3165–3169. For rearrangements of 1,2-oxazines leading to tricyclic structures, see: c) F. Pfrengle, A. Al-Harrasi, I. Brüdgam, H.-U. Reissig, *Eur. J. Org. Chem.* **2009**, 282–291.

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

[4] a) R. Pulz, T. Watanabe, W. Schade, H.-U. Reissig, *Synlett* **2000**, 983–986; b) V. Dekaris, H.-U. Reissig, unpublished results; c) R. Pulz, A. Al-Harrasi, H.-U. Reissig, *Synlett* **2002**, 817–819; d) R. Pulz, A. Al-Harrasi, H.-U. Reissig, *Org. Lett.* **2002**, *4*, 2353–2355; e) B. Bressel, B. Egart, A. Al-Harrasi, R. Pulz, H.-U. Reissig, I. Brüdgam, *Eur. J. Org. Chem.* **2008**, 467–474.

[5] For a preliminary communication of selected experiments, see: S. Yekta, V. Prisyazhnyuk, H.-U. Reissig, *Synlett* **2007**, 2069–2072.

[6] We want to concentrate in this contribution on the geminal dimethyl substituted derivatives for simplicity, for other alkyl substituents and aryl groups see ref. [2a]. The geminal dimethyl substituted pyran motif can be found as subunits of several biologically active natural products: a) X. M. Yu, G. Shen, B. S. J. Blagg, *J. Org. Chem.* **2004**, *69*, 7375–7378; b) Y.-S. Zhen, X.-Y. Ming, B. Yu, T. Otani, H. Sito, Y. Yanada, *J. Antibiot.* **1989**, *42*, 1294–1299; c) A. Arnone, G. Nasini, *J. Chem. Soc. Perkin Trans. 1* **1987**, 1353–1359.

[7] The reaction can also be run catalytically with trimethylsilyl triflate (0.05 equiv) giving the TMS-protected rearrangement product in 79% yield, see ref. [2a].

[8] In case of the rearrangement of 1,2-oxazine *anti*-**1** the yield strongly depends on the quality of the Lewis acid, the purity of the starting material, and on the dryness of the solvent used.

[9] For a Lewis acid catalyzed Mukaiyama-type aldol condensation of silyl enol ethers and acetals leading to tetrahydropyran-4-ones, see: G. S. Cockerill, P. Kocienski, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2093–2100. For the use of silyl triflates as Lewis acids in Mukaiyama-type aldol additions to acetals, see: a) S. Murata, M. Suzuki, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 3248–3249; b) S. Murata, M. Suzuki, R. Noyori, *Tetrahedron* **1988**, *44*, 4259–4275. For a Grignard-reagent induced aldol-cyclization of an acetal onto a ketone leading to tricyclic tetrahydropyran-4-ones, see: c) X. Gao, P. P. Seth, J. K. Bitok, N. I. Totah, *Synlett* **2005**, 819–823. For intramolecular aldol reactions toward pyran derivatives, see: d) S. Das, L.-S. Li, S. C. Sinha, *Org. Lett.* **2004**, *6*, 123–126; e) K. N. Cossey, R. L. Funk, *J. Am. Chem. Soc.* **2004**, *126*, 12216–12217. For a recent review on tetrahydropyran synthesis towards natural products, see: f) P. A. Clarke, S. Santos, *Eur. J. Org. Chem.* **2006**, 2045–2053. For selected recent examples on tetrahydropyran syntheses, see: g) H. Lee, K. W. Kim, J. Park, H. Kim, S. Kim, D. Kim, X. Hu, W. Yang, J. Hong, *Angew. Chem.* **2008**, *120*, 4268–4271; *Angew. Chem. Int. Ed.* **2008**, *47*, 4200–4203; h) R. Kartika, R. E. Taylor, *Angew. Chem.* **2007**, *119*, 6998–7001; *Angew. Chem. Int. Ed.* **2007**, *46*, 6874–6877; i) G.-Q. Tian, M. Shi, *Org. Lett.* **2007**, *9*, 2405–2408; j) F. Liu, T. P. Loh, *Org. Lett.* **2007**, *9*, 2063–2066.

[10] J. Dernedde, S. Enders, H.-U. Reissig, M. Roskamp, S. Schlecht, S. Yekta, *Chem. Commun.* **2009**, 932–934.

[11] Reviews: a) O. Mitsunobu, *Synthesis* **1981**, 1–28; b) D. L. Hughes, *Org. React.* **1992**, *42*, 335–656.

[12] B. R. Castro, *Org. React.* **1983**, *29*, 1–162.

[13] J. A. Gómez-Vidal, M. T. Forrester, R. B. Silverman, *Org. Lett.* **2001**, *3*, 2477–2479.

[14] For the cleavage of N,O-bonds by 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) J. Revuelta, S. Cicchi, A. Brandi, *Tetrahedron Lett.* **2004**, *45*, 8375–8377; d) I. S. Young, J. L. Williams, M. A. Kerr, *Org. Lett.* **2005**, *7*, 953–955. See also ref. [4d].

[15] The configuration was assigned by comparing the coupling constants of aminopyrans with different configurations: F. Pfrengle, Diploma thesis, Freie Universität Berlin (Germany), **2006**.

[16] For reaction sequences also employing the enantiomeric 1,2-oxazines, see ref. [2b], [4b] or [4e].

[17] Y. Kwon, Y. Lee, K. Lee, K. Kim, *Org. Lett.* **2004**, *6*, 3901–3904.

[18] Spirodioxaoctane derivatives of type **20** can also be found as substructures in natural products: H. Motoyoshi, M. Horigome, K. Ishigami, T. Yoshida, S. Horimouchi, M. Yoshida, H. Watanabe, T. Kitahara, *Biosci. Biotechnol. Biochem.* **2004**, *68*, 2178–2182.

[19] Reviews: a) S. A. W. Gruner, E. Locardi, E. Lohof, H. Kessler, *Chem. Rev.* **2002**, *102*, 491–514; b) F. Schweizer, *Angew. Chem.* **2002**, *114*, 240–264; *Angew. Chem. Int. Ed.* **2002**, *41*, 230–253; c) T. K. Chakraborty, P. Srinivasu, S. Tapadar, B. K. Mohan, *Glycoconjugate J.* **2005**, *22*, 83–93.

[20] a) M. Raunkjaer, F. El Oualid, G. A. van der Marel, H. S. Overkleeft, M. Overhand, *Org. Lett.* **2004**, *6*, 3167–3170; b) F. Sicherl, V. Wittmann, *Angew. Chem.* **2005**, *117*, 2133–2136; *Angew. Chem. Int. Ed.* **2005**, *44*, 2096–2099; c) S. Schröder, A. K. Schrey, A. Knoll, P. Reiss, B. Ziemer, U. Koert, *Eur. J. Org. Chem.* **2006**, 2766–2776; d) A. Dondoni, A. Massi, *Acc. Chem. Res.* **2006**, *39*, 451–463.

[21] Cleavage of the N,O-bond by hydrogenation can be regarded as a deprotection since it delivers a free amino and a free hydroxyl group derived from a chemically fairly inert precursor compound.

[22] F. Caturla, N. Carmen, V. Montserrat, *Tetrahedron Lett.* **1999**, *40*, 5957–5960.

[23] β-Lactams fused to different heterocycles are important structural motifs of β-lactam antibiotics: a) B. K. Hubbard, C. T. Walsh, *Angew. Chem.* **2003**, *115*, 752–789; *Angew. Chem. Int. Ed.* **2003**, *42*, 730–765; b) R. Nau, A. Eiffert, *Clin. Microbiol. Rev.* **2002**, *15*, 95–110; c) C. I. Samarendra, N. Maiti, R. Micetich, M. Daneshtalab, K. Atchison, O. A. Phillips, C. Kunugita, *J. Antibiot.* **1994**, *47*, 1030–1040. Pyran or sugar-fused β-lactams are intermediates in the synthesis of aminodeoxysugars: d) J. Gallucci, D.-C. Ha, D. J. Hart, *Tetrahedron* **1989**, *45*, 1283–1292, or of β-lactam antibiotics such as clavams or carbapenems: e) M. Chmielewski, J. Grodner, *J. Carbohydr. Chem.* **1992**, *11*, 691–698; f) A. Knierzinger, A. Vasella, *J. Chem. Soc. Chem. Commun.* **1984**, 9–11.

[24] Reviews: a) P. V. Murphy, *Eur. J. Org. Chem.* **2007**, 4177–4187; b) J. Vagner, H. Qu, V. J. Vruby, *Curr. Opin. Chem. Biol.* **2008**, *12*, 292–296; c) Special Issue on peptidomimetics: *Acc. Chem. Res.* **2008**, *41*, 1231–1438.

[25] a) R. Huisgen, *Angew. Chem.* **1963**, *75*, 604–637; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565–598; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708–2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; c) C. W. Tornoe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064; d) Recent review: M. Meldal, C. W. Tornoe, *Chem. Rev.* **2008**, *108*, 2952–3015.

[26] For examples of triazole-linked oligosaccharide mimetics, see: a) S. Hotha, S. Kashyap, *J. Org. Chem.* **2006**, *71*, 364–367; b) H. S. G. Beckmann, V. Wittmann, *Org. Lett.* **2007**, *9*, 1–4; c) H. Isobe, K. Cho, N. Solin, D. B. Werz, P. H. Seeberger, E. Nakamura, *Org. Lett.* **2007**, *9*, 4611–4614. Reviews: d) S. Dedola, S. A. Nepogodiev, R. A. Field, *Org. Biomol. Chem.* **2007**, *5*, 1006–1017; e) A. Dondoni, *Chem. Asian J.* **2007**, *2*, 700–708.

[27] A. Al-Harrasi, I. Brüdgam, H. Hartl, H.-U. Reissig, *Z. Kristallogr. New Cryst. Struct.* **2005**, *220*, 599–600.

[28] T. R. Chan, R. Hilgraf, K. B. Sharpless, V. V. Fokin, *Org. Lett.* **2004**, *6*, 2853–2855.

[29] P. B. Alper, S.-C. Hung, C.-H. Wong, *Tetrahedron Lett.* **1996**, *37*, 6029–6032.

[30] For 1,2-oxazine derivatives in synthesis, reviews: a) T. L. Gilchrist, *Chem. Soc. Rev.* **1983**, *12*, 53–73; b) P. G. Tsoungas, *Heterocycles* **2002**, *57*, 915–953; c) P. G. Tsoungas, *Heterocycles* **2002**, *57*, 1149–1178. Selected publications of our group: d) R. Pulz, S. Cicchi, A. Brandi, H.-U. Reissig, *Eur. J. Org. Chem.* **2003**, 1153–1156; e) E. Schmidt, H.-U. Reissig, R. Zimmer, *Synthesis* **2006**, 2074–2084. Review: f) M. Brasholz, H.-U. Reissig, R. Zimmer, *Acc. Chem. Res.* **2009**, *42*, 45–56. Selected recent publications of other groups: g) I. S. Young, M. A. Kerr, *Angew. Chem.* **2003**, *115*, 3131–3134; *Angew. Chem. Int. Ed.* **2003**, *42*, 3023–3026; h) F. Cardona, A. Goti, *Angew. Chem.* **2005**, *117*, 8042–8045; *Angew. Chem. Int. Ed.* **2005**, *44*, 7832–7835.

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