Simple Modifications of Enantiopure 1,2-Oxazines Leading to Building Blocks for Carbohydrate and Peptide Mimetics

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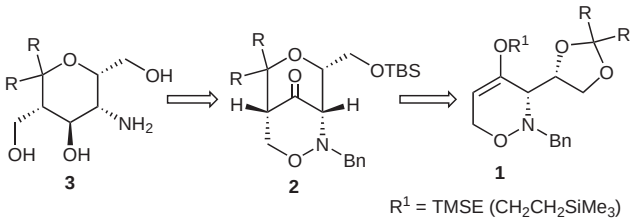
Abstract: Starting from easily available enantiopure pyran derivatives we prepared bicyclic γ-lactam **6**, azide **10**, and alkyne **18** using simple procedures. These compounds were crucial intermediates for the synthesis of γ-amino acid **8** and dipeptide **9** as well as triazoles **13**, **14**, and **19**, all containing a carbohydrate-mimicking aminopyran moiety. The generation of triazoles was particularly efficient by use of a recently reported modification of the click reaction.

Key words: pyrans, carbohydrates, peptides, sugar amino acids, oxidations, 1,3-dipolar cycloadditions

Due to their importance as building blocks, synthetic targets and biological tools, and their potential as drug targets, research toward facile and rapid access to carbohydrate and peptide derivatives has taken a crucial role in organic synthesis.[1] We previously reported the stereodivergent synthesis of enantiopure 1,2-oxazines such as **1** (Scheme 1) from the [3+3] cyclization of lithiated alkoxyallenes and glyceraldehyde-derived nitrones.[2] It was further demonstrated that 4-(2-trimethylsilyl)ethoxy-substituted 1,2-oxazines undergo Lewis acid mediated rearrangements, followed by fragmentation to generate bicyclic ketones **2** which can be available in gram quantities. The N–O bond cleavage of these compounds leads to diverse and highly functionalized enantiomerically pure aminopyrans which are regarded as carbohydrate mimetics **3**.[3] Several changes are possible at various positions on either compound **2** or **3**.

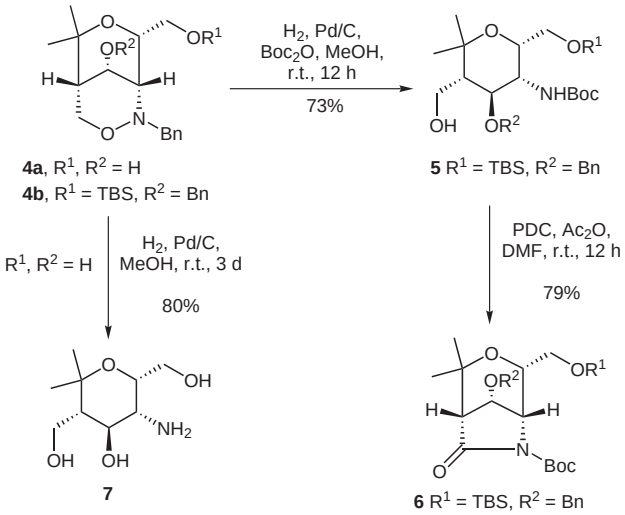


Scheme 1 Synthesis of enantiopure carbohydrate mimetics **3** from 3,6-dihydro-2*H*-1,2-oxazines **1**

Herein we report a series of simple modifications of our building blocks that allow rapid access to a variety of carbohydrate and peptide mimetics. This methodology is versatile and allows us to generate a wide range of highly functionalized and diverse compounds with potential biological activity.

Bicyclic pyran derivative **4a** – obtained via the reduction of the corresponding ketone **2** with sodium borohydride – upon hydrogenation in the presence of Pd on charcoal, led to enantiopure aminopolyol **7** in 80% yield (Scheme 2).[3,4] Similarly, hydrogenation of **4b**[5] with one equivalent of Boc_2O present for in situ protection of the amino group, afforded aminopyran derivative **5** with three different protecting groups. Using these simple methods various substituents or functionalities can be placed at differing positions of the compounds as desired. The substrates are therefore excellent precursors for the synthesis of novel enantiopure amino acids with a carbohydrate-like backbone.[1b]

We were interested in the oxidation of the remaining free primary hydroxyl group of **5** to the corresponding carboxylic acid as a precursor for peptide coupling with proteinogenic amino acids. All our efforts to perform this oxidation so far led to γ-lactam **6** which is apparently formed upon in situ cyclization of the Boc-protected amine with the carbonyl moiety formed during initial oxidation of the primary alcohol to an aldehyde (Scheme 2). After screening several reaction conditions, chromium-mediated oxidation resulted in 79% yield of γ-lactam derivative **6**.[6]



Scheme 2 Synthesis of γ-lactam **6** by oxidation of pyran derivative **5**

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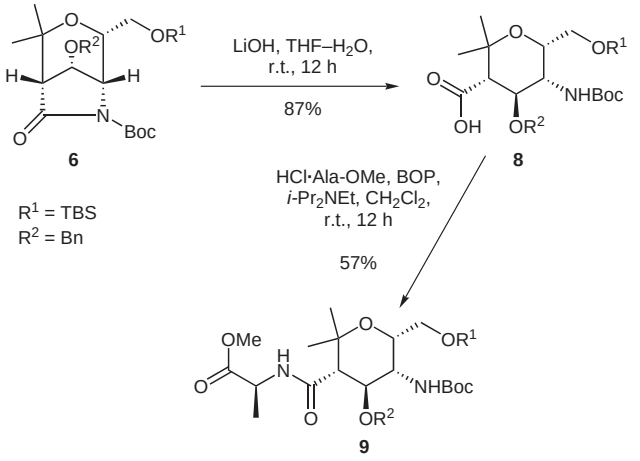
Hydrolysis of lactam **6** with LiOH in THF and water smoothly furnished γ-amino acid derivative **8** in 87% yield. Carboxylic acid **8** could then be coupled with L-alanine methyl ester hydrochloride in the presence of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate[7] (BOP) as an activating agent, using conditions previously optimized in our group,[8] yielding the desired pyrano-substituted amino acid **9** in 57% (Scheme 3). When *N*,*N*,*N*′,*N*′-tetramethylfluoroformamidinium hexafluorophosphate (TFFH) was used as the activating agent, under the same reaction conditions, **8** was cyclized to obtain bicyclic lactam **6** as the only observed product.

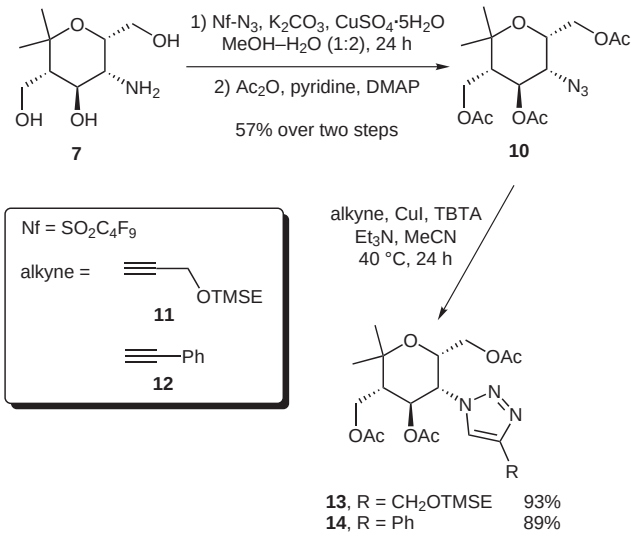


Scheme 3 Synthesis of pyrano-substituted amino ester **9** from *N*-Boc-protected amino acid derivative **8**

As a second new application of enantiopure carbohydrate mimetics we wanted to apply the Sharpless–Meldal variation of the 1,3-dipolar cycloaddition (Huisgen reaction) of an azide with an alkyne providing triazole-linked moieties.[9] Hence, secondary azide **10** was prepared upon treatment of aminopolyol **7** in the presence of copper sulfate and nonafluorobutanesulfonyl azide[10] (Nf-N_3) followed by in situ acetylation of the hydroxyl groups with acetic anhydride (Scheme 4).[11,12]

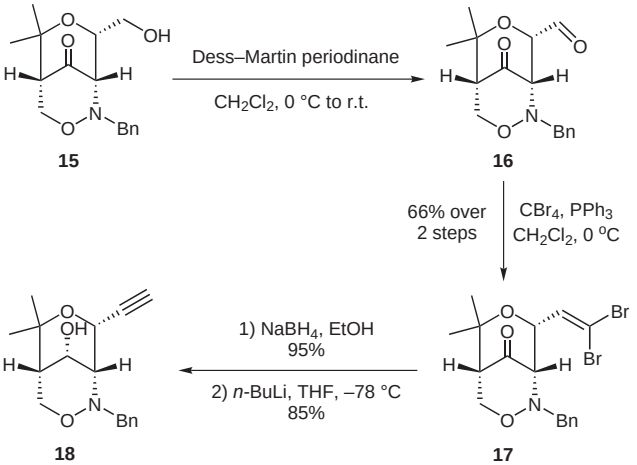
Azide **10** proved to be highly versatile in the Cu(I)-catalyzed [3+2] cycloaddition reactions with alkynes. After extensive screening, the best reaction conditions were found to be in the presence of CuI and tris(benzyltriazolylmethyl)amine (TBTA)[13] in acetonitrile at 40 °C.[14] Azide **10** was coupled with alkyne **11** to give the desired triazole **13** in 93% yield. Similarly, in the presence of phenyl acetylene **12**, cycloadduct **14** was obtained in excellent yield (Scheme 4).[15] The use of aqueous media afforded considerably lower conversion, presumably due to poor substrate solubility.

Scheme 5 outlines the preparation of alkyne derivative **18**. The known alcohol **15**[3] was oxidized with Dess–Martin periodinane (DMP) to afford aldehyde **16**.[16] After treatment of the reaction mixture with sodium thiosulfate to quench all DMP byproducts, the crude aldehyde was directly converted into the dibromo-alkene **17** upon reaction with carbon tetrabromide and triphenylphosphine (66% yield over two steps).[17]



Scheme 4 Copper-catalyzed cycloadditions of azido derivative **10** with terminal alkynes leading to triazoles **13** and **14**

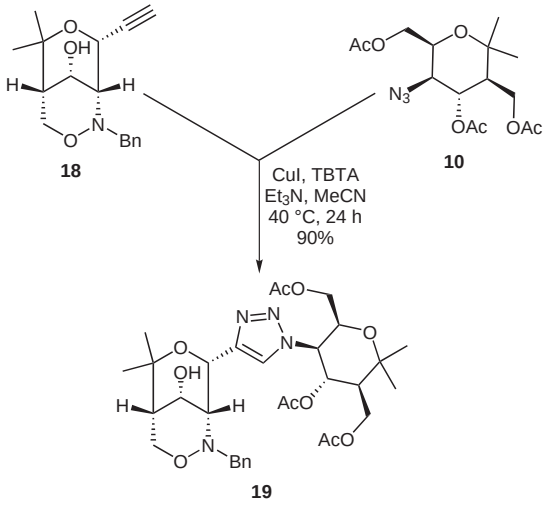
Direct lithiation of **17** with *n*-butyllithium gave the corresponding alkyne in only 45% yield along with a series of unidentifiable byproducts. In order to avoid possible nucleophilic attack of the reagent on the carbonyl group, the ketone was first reduced to the secondary alcohol with sodium borohydride (95% yield). Alkyne formation proceeded smoothly in the presence of *n*-butyllithium in THF at –78 °C to give the desired product in 85% yield (Scheme 5). Protection of the alcohol was therefore not necessary, however, 3.5 equivalents of the base instead of 2.5 equivalents were used.



Scheme 5 Conversion of enantiopure bicyclic 1,2-oxazinone derivative **15** into alkynyl-substituted product **18**

With alkyne **18** and azide **10** in hand, the optimized cycloaddition reaction in the presence of CuI and TBTA as shown in Scheme 4 proceeded smoothly to give the triazole-linked glycoconjugate **19** in excellent yield of 90% (Scheme 6).[18] This result is remarkable considering the high sterical congestion of both substrates.

Since selective deprotection and/or N–O bond cleavage will allow connection to other substrates by various methods, compounds such as **19** are versatile intermediates for the construction of oligosaccharide mimetics. The 1,2-oxazine-derived aminopyran building blocks presented in this communication will allow us to synthesize a wide range of conjugates with carbohydrates or carbohydrate mimetics as well as peptides with potential biological activity.[19]



Scheme 6 Synthesis of triazole-linked protected disaccharide mimetic **19**

Acknowledgment

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(5) Compound **4b** is obtained by the reduction of the corresponding TBS-protected ketone (see ref. 3) followed by protection of the secondary alcohol with BnBr.

(6) **Typical Procedure for the Conversion of 5 into 6**
Alcohol **5** (0.320 g, 0.629 mmol) was dissolved in anhyd DMF (10 mL), then PDC (0.946 g, 2.52 mmol) and Ac_2O (0.24 mL, 2.5 mmol) were added. The mixture was stirred for 12 h at r.t. 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 under reduced pressure. Purification by column chromatography (silica gel, hexane–EtOAc, 4:1 to 1:1) yielded 0.250 g (79%) of **6** as a colorless solid.
Analytical Data for *tert*-Butyl (1*S*,4*S*,5*R*,8*S*)-8-Benzyloxy-4-(*tert*-butyl-dimethylsiloxymethyl)-2,2-dimethyl-7-oxo-3-oxa-6-azabicyclo[3.2.1]octane-6-carboxylate (6)
$[\alpha]_D^{22}$ +14.1 (*c* 1.43, $CHCl_3$); mp 64–65 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.05, 0.06 (2 s, 3 H each, SiMe), 0.88 (s, 9 H, *t*-Bu), 1.29, 1.47 (2 s, 3 H each, Me), 1.51 (s, 9 H, *t*-Bu), 2.43 (dd, *J* = 1.6, 4.9 Hz, 1 H, 5-H), AB part of ABX system (δ_A = 3.57, δ_B = 3.58, $J_{A-X} = J_{B-X}$ = 6.5 Hz, J_{A-B} = 10.6 Hz, 2 H, 4-CH_2), 4.14 (t, *J* = 6.5 Hz, 1 H, 4-H), 4.15 (t, *J* = 4.9 Hz, 1 H, 8-H), 4.30 (dd, *J* = 1.6, 4.9 Hz, 1 H, 1-H), 4.60 (br s, 2 H, CH_2Ph) 7.25–7.38 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.3, –5.1 (2 q, SiMe), 18.1 (s, *t*-Bu), 25.9 (q, *t*-Bu), 24.5, 29.0 (2 q, Me), 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, CH_2Ph), 72.9 (s, 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 (s, NCO) ppm. IR (KBr): ν = 3115–3030 (=C–H), 2955–2855 (C–H), 1790 (C=O), 1720 (NCO_2) cm^{-1}. Anal. 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.

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(12) **Typical Procedure for the Conversion of 7 into 10**
To a solution of amino alcohol **7** (150 mg, 0.73 mmol) in MeOH–H_2O (2:1, 3 mL) at r.t. were added $CuSO_4 \cdot 5H_2O$ (18 mg, 0.073 mmol, 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) via syringe. The mixture was stirred for 24 h, then glycine hydrochloride (554 mg, 5 mmol) was added in order to quench the reaction mixture and the suspension was stirred for another 24 h. The mixture was filtered and the solvents were removed. The crude solid was dissolved in pyridine (6 mL) and cooled to 0 °C. Then DMAP (3 mg, 0.02 mmol) and Ac_2O (0.69 mL, 7.3 mmol) were added and the mixture was stirred at r.t. for 12 h. The residue was taken up in Et_2O and washed with a 1 M solution of HCl and brine followed by a sat. solution of $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, hexane–EtOAc, 9:1 to 6:4) to give **10** (150 mg, 57% over two steps) as a colorless oil.

Analytical Data for (3*S*,4*S*,5*R*,6*S*)-Acetic Acid 3,6-Bis-acetoxymethyl-5-azido-2,2-dimethyltetrahydropyran-4-yl ester (10)

$[\alpha]_D^{22}$ +28.0 (*c* 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21, 1.37 (2 s, 3 H each, Me), 2.01 (m_c, 1 H, 3-H), 2.08 (s, 6 H, COMe), 2.10 (s, 3 H, COMe) 3.60 (dd, *J* = 2.5, 3.8 Hz, 1 H, 5-H), 4.09–4.19 (m, 4 H, 3-CH_2, 6-CH_2, 4-H), 4.40 (dd, *J* = 6.5, 11.4 Hz, 1 H, 3-CH_2), 5.35 (dd, *J* = 4.2, 5.2 Hz, 1 H, 4-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 20.9, 21.1 (3 q, CO*Me*), 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 (3 s, CO) ppm. IR (film): ν = 2980–2715 (C–H), 2110 (N_3), 1745 (C=O) cm^{-1}. MS (pos. FAB): *m/z* = 380 $[M + Na]^+$, 358 $[M + H]^+$. HRMS (EI): *m/z* calcd for $C_{13}H_{20}N_3O_6$ $[M - CH_3CO]^+$: 314.1349; found: 314.1352.

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(15) **Typical Procedure for the Conversion of 10 into 14**

To a solution of azide **10** (15 mg, 42 μmol) and phenyl acetylene **12** (5.0 μL, 42 μmol) in MeCN (0.78 mL) were added solutions of Et_3N (840 μL, 8.4 μmol, 10 mM solution in MeCN), TBTA (8.4 μmol, 840 μL of a 10 mM solution in MeCN), and CuI (8.4 μmol, 840 μL of a 10 mM solution in MeCN). Argon was bubbled through the mixture for 15 min and the reaction was stirred for 24 h at 40 °C. Then H_2O (5 mL) and EtOAc (5 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, hexane–EtOAc, 6:4 to pure EtOAc) to give **14** (18 mg, 90% yield) as a colorless solid.

Analytical Data for (3*S*,4*S*,5*R*,6*S*)-Acetic Acid 4-Acetoxy-6-acetoxymethyl-2,2-dimethyl-5-{4-phenyl-[1,2,3]triazol-1-yl}tetrahydropyran-3-yl Methylester (14)

$[\alpha]_D^{22}$ +75.2 (*c* 0.25, $CHCl_3$); mp 136–138 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.39, 1.42 (2 s, 3 H each, Me), 1.98, 2.00, 2.05 (3 s, 3 H each, COMe), 2.37 (m_c, 1 H, 3-H), 3.72 (dd, *J* = 7.3, 11.8 Hz, 1 H, 6-CH_2), 3.81 (dd, *J* = 5.2, 11.8 Hz, 1 H, 6-CH_2), 4.05 (dd, *J* = 5.2, 11.8 Hz, 1 H, 3-CH_2), 4.25 (dd, *J* = 5.8, 11.8 Hz, 1 H, 3-CH_2), 4.47 (m_c, 1 H, 6-H), 5.07 (dd, *J* = 5.0, 7.0 Hz, 1 H, 5-H), 5.53 (dd, *J* = 7.0, 12.3 Hz, 1 H, 4-H), 7.34 (m_c, 1 H, Ph), 7.43 (m_c, 2 H, Ph), 7.85 (m_c, 2 H, Ph), 7.97 (s, 1 H, triazole) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6, 20.6, 20.9 (3 q, CO*Me*), 23.5, 25.9 (2 q, Me), 44.3 (d, C-3), 61.2 (t, 3-CH_2), 62.0 (t, 6-CH_2), 65.2 (d, C-5), 67.9 (d, C-6), 71.8 (d, C-4), 118.3 (d, triazole), 125.9, 128.3, 128.8, 130.2 (3 d, s, Ph), 148.5 (s, triazole), 169.7, 170.2, 170.4 (3 s, CO) ppm. IR (KBr): ν = 3030–3135 (=C), 2850–2975 (C–H), 1745 (C=O) cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{23}H_{30}N_3O_6$ $[M + H]^+$: 460.2078; found: 460.2091.

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