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Short and stereoselective synthesis of *C*-glycosylated glycine derivatives from glycals by radical addition and reduction†

Thomas Sommermann,[a] Boo Geun Kim,[a] Karl Peters,[b] Eva-Maria Peters[b] and Torsten Linker*[a]

[a] *Department of Chemistry, University of Potsdam, Karl-Liebknecht-Str. 24-25, Potsdam D-14476, Germany. E-mail: linker@chem.uni-potsdam.de; Fax: 49 331 9775056; Tel: 49 331 9775212*

[b] *Max-Planck-Institut für Festkörperforschung, Stuttgart D-70506, Germany. E-mail: karlpeters@gmx.net; Fax: 49 7152 332240; Tel: 49 7152 47511*

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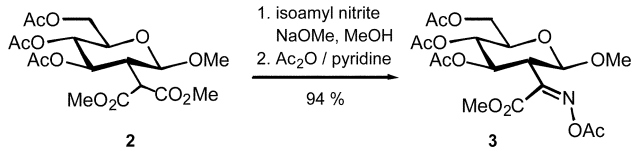
Only three steps are required for the convenient synthesis of 2-*C*-branched glyco-amino acids from glycals with good yields and stereoselectivities.

Glycopeptides and glycoproteins are an important family of compounds, which contain a carbohydrate and a peptide domain and are of current interest in bioorganic chemistry, due to their biological functions.[1,2] Recent research activities were especially focused on modified glycopeptides, where the common *O*- or *N*-glycosidic bond linkages were replaced by a carbon-based unit of greater stability and resistance towards enzymatic deglycosylation. Indeed, during the last decade several syntheses of such *C*-glycopeptides were reported in the literature.[2,3] Furthermore, glycine derivatives directly linked to carbohydrates are constituents of natural products and possess remarkable antibiotic activities.[4] However, many synthesis of *C*-glycosyl amino acids focused on the linkage at the anomeric position and required many reaction steps. Only very recently, Chandrasekaran and coworkers developed an elegant entry to 2-*C*-branched glyco-amino acids by the ring opening of 1,2-cyclopropanated sugars.[5] Herein we describe our approach for the synthesis of such *C*-glycosylated glycine derivatives in only three steps from commercially available glycals. The reaction sequence involves a radical addition and the reduction of C=N double bonds, which both proceed with good yields and stereoselectivities.

During the course of our investigations on transition-metal-mediated radical reactions, we developed a simple one-step entry to 2-*C*-branched carbohydrates by the addition of dimethyl malonate to various glycals in the presence of ceric(IV) ammonium nitrate (CAN).[6] Thus, the *gluco* isomer **2** was obtained in 62% yield from tri-*O*-acetyl-D-glucal (**1a**) and was chosen as the precursor for the synthesis of the desired *C*-glycosylated glycine derivatives.

The transformation of malonates into α-amino acids *via* the corresponding oximes is known since many years.[7] However, applications in carbohydrate chemistry were hitherto unknown, due to the drastic basic conditions. After careful optimization of the reaction, isoamyl nitrite was found as the reagent of choice for the introduction of the nitrogen functionality. Thus, the oxime ester **3** was isolated in excellent yield after acetylation (Scheme 1). NOE experiments indicated the exclusive formation of the *Z*-configured diastereomer, which can be rationalized in terms of steric repulsion between the *N*-*O*-acetyl group and the carbohydrate residue.



Scheme 1

† Electronic supplementary information (ESI) available: Experimental procedures and crystal data for gluco-(*S*)-**6**. See http://www.rsc.org/suppdata/cc/b4/b410120k/

Unfortunately, due to the drastic reaction conditions the transformation of other malonyl-substituted saccharides **2** into the corresponding oximes failed. To overcome this problem and to develop a general entry to 2-*C*-branched glyco-amino acids, we became interested in the introduction of the nitrogen functionality by the radical reaction in the first step. Due to its CH acidity, the nitroacetate **4** seemed to be an ideal precursor for such a transition-metal-mediated radical reaction. Indeed, the addition of nitroacetates to alkenes and arenes in the presence of $Mn(OAc)_3$ was reported in the literature,[8] but applications in carbohydrate chemistry were hitherto unknown. However, under the mild ceric(IV) ammonium nitrate (CAN) conditions, the addition of nitroacetate **4** to various glycals **1** proceeds smoothly, to afford the bicyclic isoxazoline *N*-oxides **5** in only one step in moderate yields and high diastereoselectivities (Scheme 2).

1a-d + **4** → **5a-d**

tri-*O*-acetyl-D-glucal (**1a**)	**5a** (45%)[a]
tri-*O*-acetyl-D-galactal (**1b**)	**5b** (47%)[a]
di-*O*-acetyl-D-xylal (**1c**)	**5c** (54%)[a]
hexa-*O*-acetyl-D-maltal (**1d**)	**5d** (59%)[a]

[a] Yields of isolated pure products. Minor C-2 diastereomers (13% for **1a**, 4% for **1b** 10% for **1d**) and other side products were separated by column chromatography.

Scheme 2

Furthermore, compared to the synthesis *via* the malonate **2**, the addition of nitro acetate **4** requires only one reaction step for the introduction of the nitrogen functionality from glycals. From the mechanistic point of view, CAN oxidizes the intermediary formed anomeric radical to a cation, which is intramolecularly trapped by the nitro group to afford the *cis*-bicyclic isoxazoline *N*-oxides **5**. The preferred formation of the depicted diastereomers can be rationalized by an *anti* attack of the radicals to the 3-*O*-acetyl group, in accordance with the addition of malonates.[6]

To obtain the desired glycine derivatives, the C=N double bonds had to be reduced in the next step, with especial interest on the diastereoselectivity. The hydrogenation of simple oximes is described in the literature with several palladium catalysts.[9] However, the additional ester groups in substrates **3** and **5** diminish the reactivity towards catalytic hydrogenation. Furthermore, the large steric demand of the carbohydrate moiety was problematic and resulted in slow heterogeneous reactions. Thus, some catalysts were unreactive and only palladium hydroxide at 40 bar hydrogen pressure led to 81% conversion of the oxime ester **3**. After acetylation the desired glycine derivatives **6** were isolated in good yield and diastereoselectivity. However, the isoxazoline *N*-oxides **5** did not react under such conditions (Table 1).

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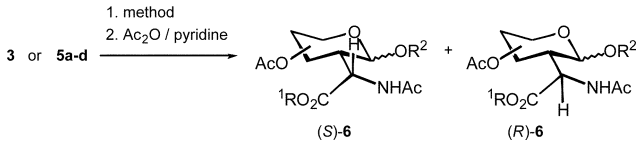

Table 1 Reduction of the carbohydrate *C*-analogs **3** and **5**

Substrate	Method	R^1	R^2	Conv. (%)	*S*:*R*	(*S*)-**6** (%)	(*R*)-**6** (%)
3	H_2, Pd/C	Me	Me	<5	—	—	—
3	H_2, PdO	Me	Me	<5	—	—	—
3	H_2, $Pd(OH)_2$	Me	Me	81	80:20	63	16
5a	H_2, $Pd(OH)_2$	Et	Ac	<5	—	—	—
5b	H_2, $Pd(OH)_2$	Et	Ac	<5	—	—	—
5c	H_2, $Pd(OH)_2$	Et	Ac	<5	—	—	—
5d	H_2, $Pd(OH)_2$	Et	Ac	<5	—	—	—
3	Hg/Al[a]	Me	Me	>98	80:20	67	17
5a	Hg/Al[a]	Et	Ac	95	77:23	68[b]	20[c]
5b	Hg/Al[a]	Et	Ac	92	70:30	58[d]	25[e]
5c	Hg/Al[a]	Et	Ac	92	85:15	70[f]	12[g]
5d	Hg/Al[a]	Et	Ac	90	94:6	82[h]	5[g]

[a] 5 equiv. of amalgam. [b] α:β = 28:72. [c] α:β = 25:75. [d] α:β = 31:69. [e] α:β = 26:74. [f] α:β = 11:89. [g] α:β not determined. [h] α:β = 23:77.

To overcome this problem and to develop a general entry to 2-*C*-branched glyco-amino acids, we investigated the reduction of the C=N double bonds by aluminium amalgam,[10] which mechanistically proceeds by an electron transfer. Indeed, now the electron poor oxime **3** and isoxazoline *N*-oxides **5a–d** did react smoothly with high conversions. After acetylation the diastereomeric *C*-glycosylated amino acids **6** were separated by column chromatography and isolated in good overall yields. Reduction of the bicyclic substrates **5** afforded α/β anomeric mixtures, due to the intermediary formed hemi-acetals, whereas oxime **3** gave exclusively the β-configured methyl glycoside (Table 1).

The catalytic hydrogenation and amalgam reductions proceed with moderate to high stereoselectivities, due to steric interactions with the carbohydrate residue. All main products have the same absolute configuration at the newly formed C-7 stereogenic center, which was established by comparison of the NMR spectra. Interestingly, the *gluco* (**3** and **5a**) and *xylo* (**5c**) isomers gave similar dr (77:23 to 85:15), whereas the *galacto* isomer **5b** reacts less selectively (70:30) and the *malto* isomer **5d** with higher selectivity (94:6). This can be rationalized by a predominant attack of the reductant from the *Re* side, which is hindered by the axial *O*-acetyl group in **5b** and even more preferred by the equatorial carbohydrate residue in **5d**. Thus, the main products of all reactions should have the *S* configuration at C-7.

However, due to the fast rotation of the C–C single bond, the determination of the configuration at the newly formed C-7 stereocenter was not possible by the coupling constants in the ^{1}H NMR spectra. Finally, the crystallization of the main isomer from the reduction of the *gluco*-oxime **3** was achieved, which was assigned unequivocally as the *S*-configured product by X-ray analysis (Fig. 1).‡ Interestingly, this is the opposite configuration of Chandrasekaran's *C*-glycosylated amino acids,[5] which is important for future applications in glycobiology.

In conclusion, the reaction sequence, radical addition to glycals and subsequent reduction, allows the simple synthesis of various glycosylated glycine derivatives in good overall yields. The addition of nitroacetates to glycals was realized for the first time. Both steps proceed with moderate to high stereoselectivities, affording the *S*-configured amino acids as the main products. The herein described new protocol is characterized by commercially available precursors and only three reaction steps. Studies of the scope and limitations of the reaction sequence and further applications for the synthesis of *C*-glycopeptides are in progress.

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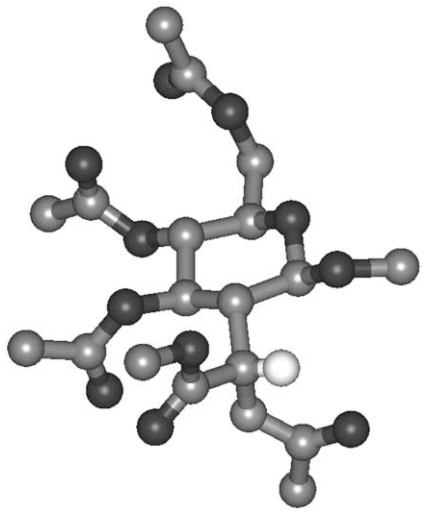

Fig. 1 X-Ray crystal structure of the *S*-configured amino acid **6**.‡

Notes and references

‡ *Crystal data* at 293 K for **6** with Mo-Kα radiation (λ = 71.073 pm): $C_{18}H_{27}NO_{11}$, M = 433.40, monoclinic, $P2_1$, a = 1028.7(2), b = 1073.4(2), c = 1061.4(2) pm, β = 107.24(2)°, V = 1119.4(3) × 10^6 pm^3, Z = 2, D_c = 1.286 g cm^{-3}, $2\theta_{max}$ = 55°, ω-scan, μ = 0.11 mm^{-1}, R = 0.069, wR = 0.138. Data collection: Bruker AXS P4. Refinement using SHELXTL-PLUS. CCDC 121989. See http://www.rsc.org/suppdata/cc/b4/b410120k/ for crystallographic data in .cif or other electronic format.

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