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TETRAHEDRON: *ASYMMETRY*

Facile synthesis of fused furanosyl β-amino acids from protected sugar lactones: incorporation into a peptide chain

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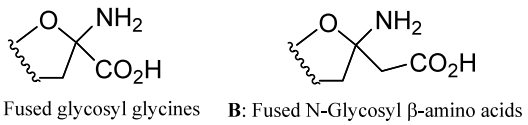
Abstract—The synthesis of fused furanosyl β-amino esters from protected sugar lactones is described, using the combination of a Wittig type reaction and 1,4-addition of benzylamine on the resulting glycosylidenes. This sequence of reactions afford either *N*-glycosyl-3-ulosonic acid esters, which are the β-analogues of anomeric sugar α-amino esters, or open-chain sugar β-enamino esters, when a retro-Michael reaction takes place after addition of benzylamine. Incorporation of the fused furanosyl β-amino ester **2a** into a peptide chain is also described.

Sugar amino acids (SAAs), which have been defined as chemical structures bearing both an amino and a carboxylate group on a regular carbohydrate framework are of current interest for organic chemists because they form part of a large number of natural products. They occur in nature as subunits of oligosaccharides (neuraminic acids) or in the cell wall of bacteria (muraminic acid).[1] Recently special efforts have been devoted to the elaboration of non natural sugar amino acids because of the extraordinary diversity offered by sugars as highly hydroxylated chiral templates.[2] These sugar amino acids can be incorporated into a regular peptide backbone, where they may function as dipeptide conformational surrogates.[3] For instance pyranoid[3f] and furanoid sugar amino acids have been incorporated into Leu-enkephalin in the Gly-Gly position as a dipeptide isostere.[4] SAAs can also be considered as monomer units in oligomerisation studies,[5] Such homooligomers, the so-called carbopeptoides[6] have shown great ability to fold in a specific manner in very short sequences.[7] Finally, SAAs can be regarded as a new class of scaffold for the construction of peptidomimetics.[8]

A special situation occurs when both the amino and carboxylate groups are carried by the anomeric centre of a sugar (Fig. 1, structure **A**). Our group and others have described the synthesis[9] and chemical manipulation of such fused glycosyl α-amino acids.[10,11]

β-Amino acids have been recognised as a very important class of compounds. They are found as fragments of many natural products[12] and are also valuable synthetic intermediates for the construction of more complex molecules, in the preparation of β-lactam antibiotics[13a] and in β-peptide synthesis.[13b] Recently, Hindsgaul et al. have published a paper dealing with the synthesis of α,α-disubstituted pyran diamides bearing a sugar β-amino acid core.[14] This has prompted us to publish our preliminary results concerning the synthesis and chemical manipulation of a series of glycosyl β-amino acids having the general structure **B** (Fig. 1), where the amino group is directly linked to the anomeric centre while the carboxylate is spaced from that carbon by a methylene group. Such structures can be regarded as β,β-disubstituted β-amino acids.

The synthesis of such structures requires a two carbon chain elongation of the sugar skeleton. This transformation was performed from protected aldonolactones using the Wittig type methodology developed in our group several years ago.[15] *exo*-Glycals like **1**, obtained this way, proved interesting intermediates in the synthesis of sugar derivatives.[16–18] They were found to be



A: Fused glycosyl glycines **B**: Fused N-Glycosyl β-amino acids

Figure 1.

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suitable precursors for the synthesis of *N*-glycosyl β-amino esters **2** by 1,4-addition of a nitrogen source[19] (Fig. 2).

For this purpose a series of diverse furano- and pyranoglycosylidenes (Fig. 3 and Fig. 4) were prepared. We first attempted to react the *gulo* compound **1a** with sodium azide in DMF but this reaction failed to give the expected β-azido ester.

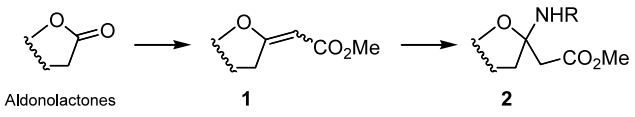


Figure 2.

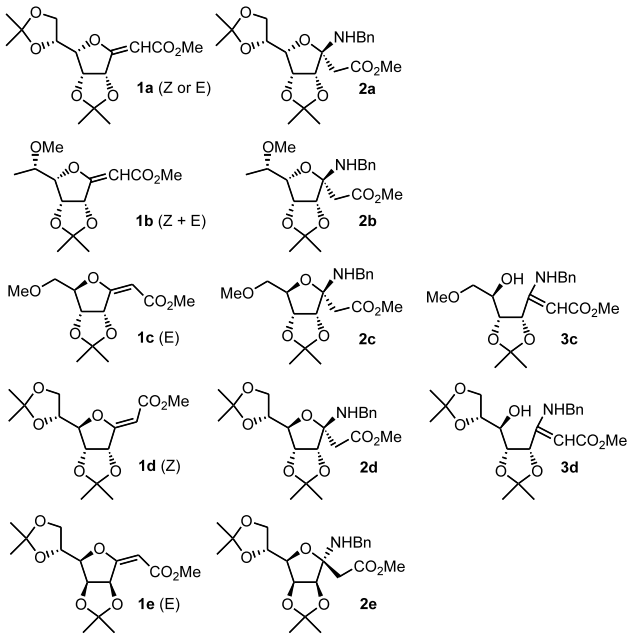


Figure 3. Structures of furanoglycosylidenes **1a**–**e** (left) and compounds obtained upon addition of benzylamines **2a**–**e** and **3c**,**d**.

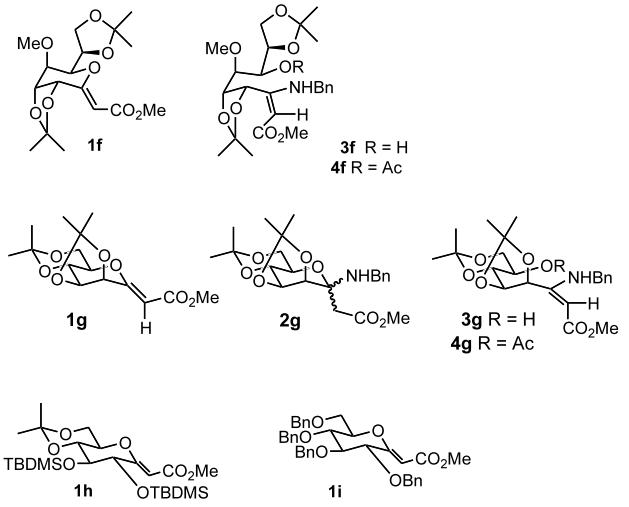
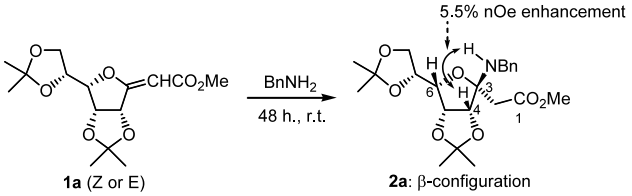


Figure 4. Structures of pyranoglycosylidenes **1f**–**i** and compounds obtained upon addition of benzylamine.

Thus, we turned to benzylamine[20] as a source of nitrogen and found that the reaction of **1a** in neat benzylamine at room temperature proceeds cleanly and with high conversion for the both *E* and *Z* isomers (Scheme 1 and Table 1: entries 1 and 2). It should be noted that despite the *N*,*O*-acetal character of the anomeric centre, only one isomer was isolated which formally results from the approach of benzylamine to the less crowded face of the sugar, i.e. *anti* to the fused acetonide. No equilibration of **2a** to the other anomer was observed at any stage of the reaction or during purification and this compound proved very stable even after storing for prolonged time. The configuration of the anomeric centre was first established by the observation of a strong NOE between N3*H* and C4*H* (ulosonic acids numbering, Scheme 1) and was confirmed by X-ray crystallographic analysis of compound **2a**.[21] We further investigated the reaction of benzylamine with other glycosylidenes, the results, which are shown in Table 1, deserve comment: Compounds **1e** (*Z*) and **1b** (*Z*- and *E*-mixture) gave good yields of the corresponding anomeric β-amino esters (82 and 73%, respectively). It is interesting to note that for the substrates **1a**, **1b** and **1e** all of the substituents are directed toward the same face of the sugar which allow an effective approach of the reagent. For all of these starting compounds only one configuration was obtained for the anomeric centre, the configuration in which the benzylamino group is *trans* to the 4,5-dioxolane moiety. The two last furanoglycosylidenes studied **1c** (D-*ribo*) and **1d** (D-*allo*) were converted to the Michael adducts **2c** and **2d** in 57 and 50% yields, respectively (78% based on recovered material). However, these two compounds were contaminated by trace amounts of the corresponding enamino esters **3c** and **3d**. The reactivity of pyranoglycosylidenes towards benzylamine addition was next examined.

On treatment with $BnNH_2$ for 14 days the D-*glycero*-D-*gulo* compound **1f** afforded exclusively the enamino ester **3f** arising from a retro-Michael process in 71% yield. The *manno* derivative **1g** was also reacted with $BnNH_2$ to give the enamino ester **3g** as the main product, the latter being accompanied by the Michael adduct **2g** in a 5/1 ratio as shown by ^1H NMR. Both compounds **3f** and **3g** were fully characterised as their acetate[22] (**4f** and **4g**, respectively). Compounds **1h** and **1i** having the *gluco* configuration remained unchanged even after prolonged reaction times. This lack of reactivity could arise from the bulky protecting groups present in these two molecules or maybe from the absence of a fused 2,3-isopropylidene acetal (sugar lac-



Scheme 1. Michael addition of benzylamine on compound **1a** and NOE measurements in **2a**.

Table 1. 1,4-Addition of benzylamine on glycosylidenes of type **1a–i**

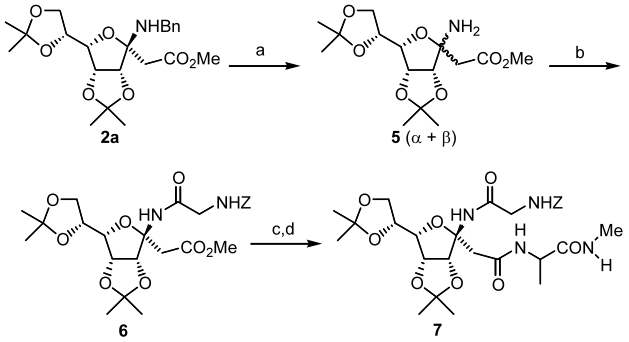
Entry	**1a–k**	Time (h)	Product(s) ratio	Yield (%)[a]	NH/4,5-dioxolane relationship[c]
1	**1a** (*Z*)	48	**2a**	89	*trans*
2	**1a** (*E*)	48	**2a**	91	*trans*
3	**1b** (*Z*+*E*)	48	**2b**	73	*trans*
4	**1c** (*Z*)	48	**2c**/**3c** (traces)	57	*trans*
5	**1d** (*Z*)	70	**2d**/**3d** (traces)	50, 78[b]	*trans*
6	**1e** (*Z*)	48	**2e**	82	*trans*
7	**1f** (*Z*)	14 days	**3f**	71, 98[b]	
8	**1g** (*Z*)	44	**2g**/**3g**: 1/5	73	Not determined
9	**1h** (*Z*)	96	Starting material	0	
10	**1i** (*Z*)	96	Starting material	0	

[a] Isolated yields after chromatography.
[b] Yields based on recovered material.
[c] The anomeric configuration was ascertained on the base of NOE measurements and by comparison of ^{1}H NMR data of compound **2a** of known configuration.

tone numbering). The fused acetonide ring, which is present in all the other substrates, make these starting materials quite rigid and could explain the enhanced reactivity of these substrates as Michael acceptors.

Another aim of this work was to demonstrate that fused anomeric β-amino esters previously synthesised could be incorporated into a peptide chain (Scheme 2). Compound **2a** was chosen as a model for this study. Catalytic hydrogenation of this compound afforded the free amine **5** which was isolated as an inseparable mixture of anomers. Coupling of this mixture with benzyloxycarbonylglycine (Z-GlyOH) using PyBOP as coupling reagent and TEA in DMF furnished the desired dipeptide **6** in 84% overall yield (two steps). Interestingly only one isomer was isolated. The anomeric configuration was unambiguously determined by the observation of a strong NOE between the anomeric NH and the two protons H-4 and H-6 (ulosonic acids numbering). This is only consistent with a trans relationship between the anomeric nitrogen and the 4,5-dioxolane ring.[11]

Extension from the C-terminus was next envisaged. Hydrolysis of the ester was performed with K_2CO_3 in MeOH and water. The coupling reaction of the resulting acid with Ala-NHMe using PyBop and TEA in DMF afforded the target tripeptide **7** as a glassy solid in 78% overall yield (two steps).



Scheme 2. *Reagents and conditions*: (a) H_2 1 atm, Pd/C 10%, EtOAc; (b) Z-GlyOH (1.1 equiv.), PyBOP (1.1 equiv.), Et_3N (1.1 equiv.), DMF, rt, 14 h.; 84% (two steps); (c) K_2CO_3 (1.1 equiv.), MeOH/H_2O: 10/1, rt, 48 h; (d) Ala-NHMe·HCl (1.1 equiv.), PyBOP (1.1 equiv.), Et_3N (2.2 equiv.), DMF, rt, 14 h; 78% (two steps).

In conclusion, the 1,4-addition of benzylamine has been performed on a series of glycosylidenes. It would appear that the expected Michael adducts **2** are either exclusively obtained or at least as the major compounds when the reaction is conducted with furanoglycosylidenes. In the case of pyrano compounds the open-chain enamino esters were the sole or the major compounds. The latter arises from 1,4-addition of benzylamine followed by a retro-Michael process, leading to the opening of the sugar. These β-enamino esters can be regarded as synthetic precursors of highly oxygenated β,β-disubstituted β-amino acids.[23] Compound **2a**[24] was used as a model to show that despite the *N*,*O*-acetal character of compounds of type **2** they can be manipulated as standard amino acids. With this aim in mind, the tripeptide **7**[25] was elaborated from **2a** in 65% overall yield (four steps). The scope and limitation of the incorporation of compounds **2** into peptide chains is currently under study in our laboratory.

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24. Analytical data for compound **2a**: mp 123°C; $[\alpha]_D^{26} = -9.6$ (*c* 0.9, $CHCl_3$); ν_{max} (KBr) 3357 (NH), 1730 (C=O); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.27 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.45 (br s, 6H, 2×CH_3), 2.10–2.23 (m, 1H, NH), 2.94 (d, 1H, J_{gem} 17.5 Hz, H-2), 3.14 (d, 1H, J_{gem} 17.5 Hz, H′-2), 3.65–3.88 (m, 6H, H-8, CO_2CH_3 and CH_2Ph), 4.06 (dd, 1H, $J_{5,6}$ 4.4, $J_{6,7}$ 8.0 Hz, H-6), 4.21 (dd, 1H, J_{gem} 8.0, $J_{7,8'}$ 6.5 Hz, H′-8), 4.40 (m, 1H, H-7), 4.45 (d, 1H, $J_{4,5}$ 5.8 Hz, H-4), 4.72 (dd, 1H, $J_{5,6}$ 4.4, $J_{4,5}$ 5.8 Hz, H-5), 7.20–7.38 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 171.5 (C=O), 140.3 (C_{ipso}), 128.4–126.8 (5C, Ar), 112.7 (acetal), 109.6 (acetal), 95.1 (C-3), 85.9, 81.0, 80.9, 75.5 (4C, C-4, C-5, C-6, C-7), 66.1 (C-8), 51.5 (CO_2CH_3), 45.1 (CH_2Ph), 34.8 (C-2), 26.8 (CH_3), 26.0 (CH_3), 25.3 (CH_3), 24.8 (CH_3). Anal. calcd for $C_{22}H_{31}NO_7$ (421.48): C, 62.69; H, 7.41; N, 3.32. Found: C, 62.73; H, 7.37; N, 3.36%.
25. Analytical data for compound **7**: mp 92–95°C (decomposition); $[\alpha]_D^{26} = +18.4$ (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (s, 1H, NH), 7.28–7.41 (m, 5H, Ar), 6.73 (d, 1H, *J* 7.5 Hz, NH_{Ala}), 6.57 (pseudo q, 1H, NHMe), 5.71 (pseudo t, 1H, NH_{Gly}), 5.20 (d, 1H, $J_{4,5}$ 5.7 Hz, H-4), 5.07–5.18 (m, 2H, CH_2Ph), 4.98 (pseudo t, 1H,

H-5), 4.42 (m, 1H, Hα_{Ala}), 4.16–4.31 (m, 3H, H-6, H-7 and H-8), 3.83–3.91 (m, 2H, 2×Hα_{Gly}), 3.70 (t, 1H, $J_{gem}=J_{7,8'}$ 7.5 Hz, H′-8), 2.77–2.90 (m, 5H, 2×H-2 and NHCH_3), 1.50 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.36 (d, 3H, J 7.2 Hz, $CH_{3\ Ala}$), 1.32 (s, 3H, CH_3), 1.27 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 172.6, 169.8, 169.6 (3×C=O), 156.4 (NH*C*OOCH$_2$), 136.1 (C_{ipso}), 128.0–128.4 (5C, Ar), 109.7 (acetal), 112.9 (acetal), 92.7 (C-3), 84.7 (C-4), 84.5 (C-6 or C-7), 81.7 (C-5), 76.1 (C-6 or C-7), 67.1 (*C*H$_2$Ph), 65.9 (C-8), 49.3 (Cα_{Ala}), 44.6 (Cα_{Gly}), 41.3 (C-2), 26.6, 26.3, 25.8, 25.4, 24.1 (5C, 4×CH_3 and NHCH$_3$), 17.9 ($CH_{3\ Ala}$).