Pergamon

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Tetrahedron Letters 44 (2003) 2489–2491

TETRAHEDRON LETTERS

A concise synthesis of glycosyl-α-amino acid derivatives via homologation of dialdoses into bromo uronic acids and esters

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Received 13 November 2002; revised 3 February 2003; accepted 3 February 2003

Abstract—The synthesis of the compounds of the title involves three steps from dialdoses. The reaction between potassium dibromoacetonitrile carbanion and protected dialdoses provides corresponding β-bromo-α-ketonitriles that are easily transformed into α-bromo esters by treatment with methanol or isopropanol or α-bromo acids by treatment with *t*-BuOH. Substitution of the bromine by sodium azide onto these last compounds and subsequent catalytic hydrogenation of the azide group afford the targeted glycosyl-α-amino acid derivatives. This methodology represents the most rapid access to the key α-amino acid moiety of polyoxins.

In continuation of our studies on the preparation of new and stable glycopeptides,[1] we report here a simple and short synthesis of 6-amino-6-deoxy pyranuronic and 5-amino-5-deoxy furanuronic acid derivatives, which are potentially interesting precursors of polyoxins and nikkomycins,[2] and represent also interesting building blocks for the construction of new glycopeptides.

We have previously reported on several applications of dihalogenoacetonitrile carbanions, and developed a synthesis of α-bromo esters, from carbonyl compounds using dibromoacetonitrile.[3] The application of this methodology to the easily available 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose **1a** and methyl-2,3-*O*-isopropylidene-α-D-*ribo*-pentodialdo-1,4-furanoside[4] **1b** chosen as model substrates cleanly afforded diastereomeric mixtures of α-bromo epoxynitrile intermediates **2**/**2′** which spontaneously isomerised into β-bromo-α-ketonitriles **3**/**3′** (Scheme 1).

The nitrile group of β-bromo-α-ketonitriles **3**/**3′** behave like a pseudohalogen that was displaced efficiently by a primary or a secondary alcohol to give the α-bromo esters **4**/**4′**. In the case of *t*-BuOH, the *t*-butyl ester was cleaved during the reaction into the acids **5**/**5′**. The esters **4**/**4′** and acids **5**/**5′** were easily purified on a silica gel chromatographic column with relatively good overall yields from dialdoses **1** (Table 1). As a result, the particular reactivity of such β-bromo-α-ketonitriles allowed the direct transformation of dialdoses **1** into α-bromouronic esters **4**/**4′** or acids **5**/**5′**. The epimeric ratios of **4**/**4′** and **5**/**5′** were determined by integration of the H-1 signals in the ^{1}H NMR spectra (250 MHz). The values obtained indicated a good overall diastereoselection, especially in the case of the α-D-*galacto* series. Treatment of α-bromo esters **4**/**4′** with NaN_3 led stereospecifically to the inverted α-azido esters **6**/**6′** but the stereospecificity was not perfect in the D-*galacto* series (entry 2) probably due the difficult substitution that needed a large excess of NaN_3 (10 equiv.) at 100°C for 9 h with **4aj**/**4′aj**. On the other hand the reaction between α-bromo ester **4bi**/**4′bi** (65/35) and NaN_3 afforded corresponding product **6bi**/**6′bi**[5] (38/62) with a total stereospecicity. In this case, a careful chromatographic separation of diastereomers[6] on silicagel was effected for the reason that the epimer with the (*S*)C5 configuration was a known key precursor of polyoxins (eluent: AcOEt/hexane: 1/6).[2h,k,u]

This stereospecific substitution allowed the assignment of the (*S*)C5 configuration to **6′bi** (and therefore (*R*)C5 to **6bi**) by comparison of the physical data of **6′bi** [^{1}H and ^{13}C NMR and $[\alpha]_D^{25} = -54.8$ (*c* 0.95, $CHCl_3$)] with those previously reported; lit.[2k] [^{1}H NMR and $[\alpha]_D^{24} = -53.3$ (*c* 1.41, $CHCl_3$); lit.[2h] ^{1}H and ^{13}C NMR and $[\alpha]_D^{23} = -52.2$ (*c* 1.62, $CHCl_3$); lit.[2u] $[\alpha]_D = -55.3$ (*c* 0.89, $CHCl_3$).

Keywords: glycopeptide; dialdoses; bromo uronic acids; bromo uronic esters; azido uronic acid derivatives; amino uronic acids; polyoxins.
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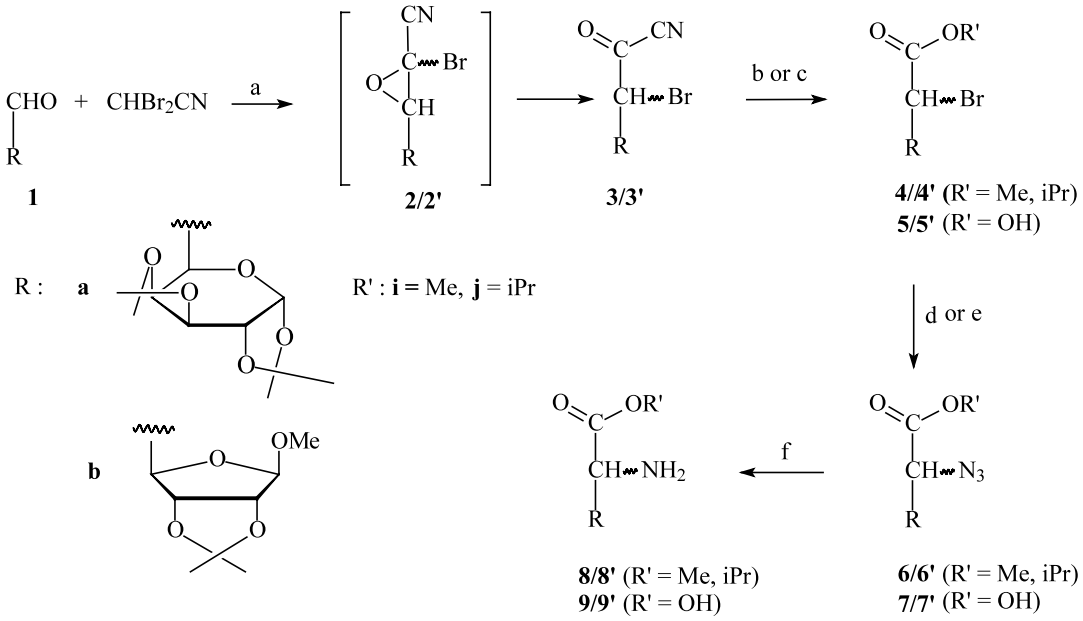
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00321-6



Scheme 1. Preparation of glycosyl α-amino acid derivatives. *Reagents and conditions*: (a) *i*-PrOK, *i*-PrOH, Et_2O, −5°C; (b) MeOH or *i*-PrOH, 40°C, 15 h; (c) *t*-BuOH, 30°C, 18 h; (d) NaN_3/DMF; (e) NaN_3/Et_3N/DMF; (f) H_2/Pd 10%/C, 20°C, 3 bar.

Table 1. Glycosyl α-amino acid derivatives and their precursors produced via Scheme 1

Entry	Starting substrate **1**	**4**–**5**/**4′**–**5′**	Yield[a] (%)[b]	**6**–**7**/**6′**–**7′**	Yield[a] (%)[b]	**8**–**9**/**8′**–**9′**	Yield[a] (%)[b]
1	**1a**	**4ai**/**4′ai**	47 (86/14)	–	–	–	–
2	**1a**	**4aj**/**4′aj**	68 (76/24)	**6aj**/**6′aj**	72 (39/61)	**8aj**/**8′aj**	100 (40/60)
3	**1b**	**4bi**/**4′bi**	55 (65/35)	**6bi**/**6′bi**	62 (38/62)	**8bi**/**8′bi**	100 (35/65)
4	**1b**	**4bj**/**4′bj**	48 (65/35)	**6bj**/**6′bj**	63 (35/65)	**8′bj**	100[c]
5	**1a**	**5a**/**5′a**	65 (79/21)	**7a**/**7′a**	66 (75/25)	**9a**/**9′a**	100 (76/24)
6	**1a**	**5b**/**5′b**	43 (58/42)	**7b**/**7′b**	57 (60/40)	**9b**/**9′b**	100 (66/33)

[a] Yield of purified products.
[b] Epimeric ratios were evaluated on the crude products.
[c] Evaluated relative to epimer **6′bj**.

The azidation of α-bromo acids **5**/**5′** involved the participation of the carboxylate anion to the bromide displacement by the azide anion and led, via a double inversion, to the mixture **7**/**7′** where the configuration of the major epimer was supposed to be (*R*)C5 in the case of **7b**. This assumption was based on a comparison of the NMR data of **7b** and **6bi**.

Finally, the two above routes provided a useful unambiguous method for the synthesis of azido uronic esters or acids with inverted epimeric ratios.

The α-azido esters **6**/**6′** and α-azido acids **7**/**7′** were then hydrogenated using Pd/C 10% as a catalyst in isopropanol, under a pressure of 3 bar, leading respectively to the expected glycosyl amino esters **8**/**8′** and glycosyl amino acids **9**/**9′** in quantitative yield with a complete retention of configuration. However, in the case of **6bj**/**6′bj**, we observed a difference in rates of hydrogenation of epimers leading after 4 h of reaction to the sole reduction of **6′bj** into **8′bj**, the unreacted epimer **6bj** being totally recovered. It was noteworthy that this total stereoselective hydrogenation of the sole epimer **6′bj** at the last step of the procedure allowed to avoid the tedious separation of the pure epimer precursors in the previous steps. This result is important, because **8′bj** is a key building block in great demand for the construction of polyoxins and numerous elaborated and less convenient syntheses are described for this type of ester.[2h,k,u]

In conclusion, the reaction of dialdoses with potassium dibromoacetonitrile anion in isopropanol allows the access to crude glycosyl β-bromo-α-ketonitriles that are immediately transformed into α-bromo uronic esters with methanol or isopropanol, or into α-bromo uronic acids with *t*-BuOH or water. Subsequent substitution of the bromine by sodium azide followed by a catalytic hydrogenation leads to glycosyl α-amino acid derivatives. This route constitutes an important synthetic potential for the conversion of dialdoses into glycosyl amino esters or glycosyl amino acids. It appears as the most rapid access to the key α-amino acid building block of polyoxins.

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4. The dialdose **1b** was distilled before use to limit the hydrated form of the aldehyde.
5. Methyl (methyl 5-azido-5-deoxy-2,3-*O*-isopropylidene-β-D-*allo*-furanosid)uronate **6′bi**: IR (KBr film/cm^{-1}) ν_{max}: 2110, 1740, 1375; ^1H NMR (250 MHz, $CDCl_3$): δ 5.05 (s, 1H), 4.79 (dd, 1H, $^3J_{H3-H2}=6$ Hz, $^3J_{H3-H4}=1$ Hz), 4.63 (d, 1H, $^3J_{H2-H3}=6$ Hz), 4.50–4.43 (m, 1H), 3.96 (d, 1H, $^3J_{H5-H4}=8.5$ Hz, 3.86 (s, 3H), 3.43 (s, 3H), 1.51–1.33 (s, s, 3H, 3H); ^{13}C NMR δ 168.5, 110.1, 106.9, 85.8, 85.1, 81.3, 64.2, 55.8, 52.9, 26.5, 25.0; MS FAB$^+$: m/z 288 (MH^+); $[\alpha]_D^{25}=-54.8$ (c 0.95, $CHCl_3$).
   Methyl (methyl 5-azido-5-deoxy-2,3-*O*-isopropylidene-β-L-*talo*-furanosid)uronate **6bi**: IR (KBr film/cm^{-1}) ν_{max}: 2110, 1740, 1375; ^1H NMR (250 MHz, $CDCl_3$): δ 5.00 (s, 1H), 4.87 (d, 1H, $^3J_{H3-H2}=6$ Hz), 4.61 (d, 1H, $^3J_{H2-H3}=6$ Hz), 4.50–4.43 (m, 1H), 3.86 (s, 3H), 3.83 (d, 1H, $^3J_{H5-H4}=10$ Hz), 3.55 (s, 3H), 1.51–1.34 (s, s, 3H, 3H); ^{13}C NMR δ 168.8, 110.3, 106.9, 86.3, 84.9, 81.7, 63.4, 55.8, 52.8, 26.5, 25.0; MS FAB: m/z 288 (MH^+).
6. Although the separation of diastereomers was possible in other cases, the chromatographic separation of pure epimers has not been actually effected. Physical data of pure epimers will be described in a full paper.