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A STEREOSELECTIVE SYNTHESIS OF 2-ACETAMIDO-2-DEOXY-C-GLUCOSIDES: GLYCOSYL DIANIONS AS KEY INTERMEDIATES

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Abstract: α- Or β-*C*-2-acetamido-2-deoxy-*C*-glucosides can be obtained from the configurationally stable anomeric glycosyl dianions which are prepared by reductive lithiation (α) or transmetallation of the tin compound (β). Different electrophiles react selectively at the anomeric center.

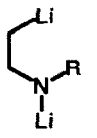
C-Glycosides[1] are stable analogs to *O*- and *N*-glycosides, and thus can serve as potential antimetabolites in biological probes. Although, 2-amino sugars are commonly found in glycoconjugates,[2] aminoglycoside antibiotics[3] and antigenic determinants on cell surfaces,[4] only a few synthesis of *C*-glycosides derived from D-glucosamine have been reported. This is mainly due to the required conditions of the conventional approach to *C*-glycosides using Lewis acid catalyzed addition of carbon nucleophiles to activated carbohydrate derivatives. The incompatibility of amino and amido substituents with these conditions was reported by Nicotra and coworkers.[5] Therefore, different strategies were investigated to solve this problem, using either 2-azido sugars,[6] or *C*-elongation of furanoses and pyranoses with subsequent cyclization of the obtained olefins,[5] respectively, or hetero [4+2] cycloadditions of C_1-alkylglycals and azo compounds.[7] In addition, the direct coupling of 2-acetamido-2-deoxy-D-glucopyranosyl chloride with potassium diethylmalonate has recently been reported.[8]

Although the described routes provide *C*-β and - more widely - α-glycosyl compounds, they mainly lack general application, proceed in multistep synthesis, or afford the desired *C*-glycosides in poor to moderate yields.

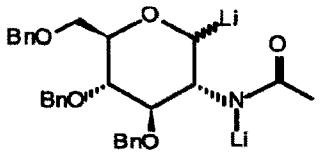
Recently, we reported the direct coupling of electrophiles with a glycosyl dianion which yielded α-*C*-glycosides in good yields.[9,10] Therefore, we were interested to investigate, if this new method could be used for the synthesis of *C*-glycosides of D-glucosamine. Dianions of type **1** (**Figure 1**) have been extensively applied by Barluenga

and coworkers.[11] The lithiated benzamide **1a** in this organolithium compound encouraged us to try the analogous acetamide corresponding to the natural occurring *N*-acetyl-D-glucosamine. We report herein our preliminary results on the direct coupling reaction between glycosyl dianions of type **2** and different electrophiles.

1a: R = PhCO
1b: R = Ph



1



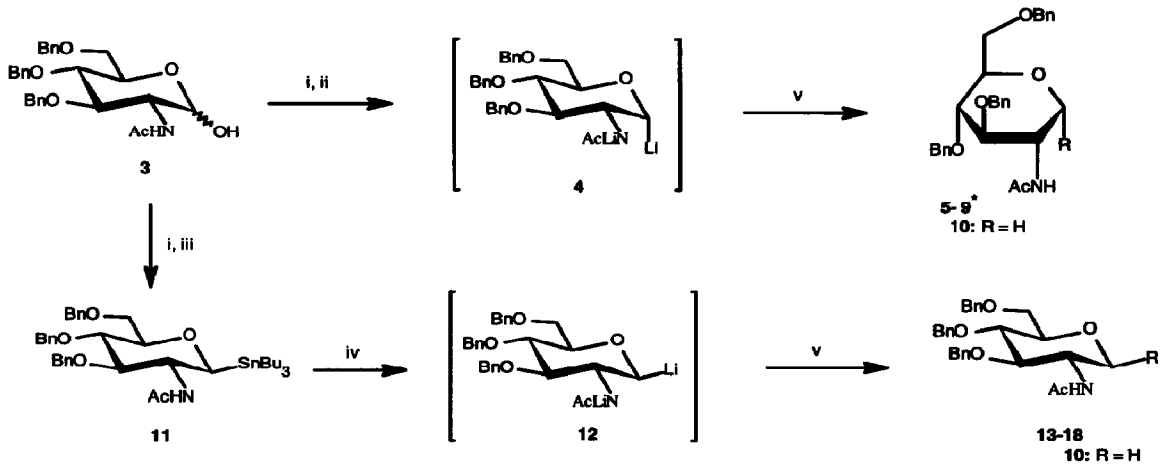
2

Figure 1

As outlined in **Scheme 1** the α- or β-C-glycosides were synthesized from 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-glucopyranose **3**, which was prepared from N-acetyl-D-glucosamine in 3 steps.[12]

The α-*C*-glycosides were obtained by treating **3** with thionylchloride (23°C, 15 min), followed by deprotonation with butyllithium (1.1 eq., THF, -95°C, 1 min) and addition of lithium naphthalenide (2.1 eq., -95°C, 5 min) providing the postulated dianion intermediate **4**, which subsequently was reacted with deuterated methanol (entry 1), different aldehydes (entry 2-4), or dimethylsulfate (entry 5). The deuteration yielded 74% of reduction products, i.e. 58% α-compound **5**, about 3% β-compound **13** and 13% protonated product **10** (R=H). Similar treatment of **4** with benzaldehyde, isobutyraldehyde and acroleine (1.3 eq., -78°C, 15 min, respectively) gave diastereomeric mixtures of **6a/b-8a/b** (ratio ~1:2) in 72 to 54% overall yield. The less reactive dimethyl sulfate (1.3 eq., -78°C → -55°C, 1h) provided product **9** in 26% yield,[13] together with large amounts of **10**.

The corresponding β-*C*-glycosides were prepared by transmetallation of the β–glucopyranosylstannane **11** and treating the generated dianion **12** with electrophiles. **11** was synthesized from **3** by thionylchloride, followed by amide deprotonation with butyllithium (1.0 eq., -78°C, 1 min) and addition of tributylstannyllithium (1.3 eq., -78°C, 30 min) in 68 to 86% yield. The generation of the dianion **12** was achieved by deprotonation (1.0 eq. BuLi, 5 min) of the amide proton at -78°C followed by the metal exchange (1.0 to 1.5 eq. BuLi, 3 min) at -65°C.[14] We have observed, that the exchange was only complete, when the colour of the solution turned red at the end of the addition, otherwise variable amounts of the stannane **11** were recovered.[15] Treating the generated glycosyl dianion **12** with deuterated methanol provided compound **13** in 80% yield together with 18% of **10**. No α–product could be observed by ^{2}H NMR (see also **Table 1**, entry 6). The analogous reactions, using aldehydes (entry 7-10) as electrophiles (1.3 to 1.5 eq, 15 min) gave the diastereomeric mixtures **14a/b-17a/b** (ratio ~1:1.5) in 76 to 80% yield together with **10** in 10 to 18% yield. Dimethyl sulfate provided the methylated product **18** in moderate yield,[16]



Scheme 1. Synthesis of α- or β-*C*-glycosides. Reagents and conditions: (i) $SOCl_2$, $CHCl_3/PhCH_3$ 1:1, 23°C, 15 min (ii) 1.) 1.0 eq. BuLi, THF, -95°C, 1 min 2.) 2.1 eq. lithium naphthalenide, -95°C, 5 min (iii) 1.) 1.0 eq. BuLi, THF, -78°C, 1 min 2.) 1.3 eq. Bu_3SnLi, THF, -78°C, 30 min. 3.) NH_4Cl_{aq}. (iv) 1.) 1.0 eq. BuLi, THF, -78°C, 5 min. 2.) 1.0 to 1.5 eq. BuLi, THF, -65°C, 3 min. (v) 1.) 1.3 to 1.5 eq. electrophile. 2.) NH_4Cl_{aq}.

Table 1. Results of *C*-glycosylation

entry	electrophile	product[a]	R		yield %[b]	a : b[c]	α : β[d]
1	MeOD	**5**	D	α	58(74)[e]		17 : 1[f]
2	PhCHO	**6a/b**	CH(OH)Ph	α	72	1 : 1.9	15 : 1
3	iPrCHO	**7a/b**	CH(OH)iPr	α	64	1 : 2.2	17 : 1
4	vinylCHO	**8a/b**	CH(OH)vinyl	α	54	1 : 2.0	n.d.
5	Me_2SO_4	**9**	Me	α	26		16 : 1
6	MeOD	**13**	D	β	80 (98)[e]		≤1 : 100[f]
7	PhCHO	**14a/b**	CH(OH)Ph	β	80	1.4 : 1	
8	iPrCHO	**15a/b**	CH(OH)iPr	β	76	1 : 1.6	
9	vinylCHO	**16a/b**	CH(OH)vinyl	β	80	1.3 : 1	
10	MeCHO	**17a/b**	CH(OH)Me	β	80	1.5 : 1	
11	Me_2SO_4	**18**	Me	β	44		

[a] All products gave satisfactory ^1H- and ^{13}C NMR. [b] Overall isolated yields of the α-products starting from **3**. Isolated yields of β-anomers. [c] Deduced from ^1H NMR and isolated yields. a: Less polar diastereoisomer. [d] Ratio determined by HPLC; The authentity of the minor (β-products) compound was proven by mixing the appropriate β-*C*-glycosides to the crude reaction mixtures of the α-products. [e] The yield was calculated by ^1H- and ^2H NMR data. Isolated yields of isotopomers are given in parenthesis. [f] Determined by ^2H NMR.

* The conformation of products **6-9** deviate from the usual $^4C_1$ chair.

again with a large amount of **10** (see entry 5).

In summary, we have described an efficient method for the direct and stereoselective preparation of either α-or β-*C*-glycosides of *N*-acetyl-D-glucosamine. The glycosyl dianions **4** and **12** are configurationally stable under the conditions described and no β–elimination of the anomeric carbanion was observed. Furthermore, the lithiated amide did not react with the used nucleophiles nor electrophiles.

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13. ^{1}H NMR (500 MHz, $CDCl_3$) for **9**: δ 7.37-7.18 (m, 15 H, arom. H), 6.55 (br, 1 H, NH), 4.60-4.44 (m, 6 H, CH_2Ph), 4.20 (dd, 1 H, H-5), 4.13 (br, 1 H, H-2), 4.08 (d, 1 H, H-1), 3.84 (dd, 1 H, H-6a), 3.72 (dd, 1 H, H-6b), 3.56 (br, 2 H, H-3, H-4), 1.84 (s, $COCH_3$), 1.09 (d, 3 H, CH_3).
14. Attempts to perform the transmetallation at -78°C were unsuccessful.
15. We performed most reactions with a total amount of 2.0 to 2.3 eq. of butyllithium, sufficient to assure deprotonation and complete transmetallation.
16. ^{1}H NMR (500 MHz, $CDCl_3$) for **18**: δ 7.37-7.13 (m, 15 H, arom. H), 5.09 (d, J = 9.2 Hz, 1 H, NH), 4.84-4.57 (m, 6 H, CH_2Ph), 3.69 (m, 3 H, H-6a, H-6b, H-2), 3.61 (dd, J = 9.5, 9.5 Hz, 1 H, H-4), 3.55 (dd, 1 H, H-3), 3.43 (ddd, 1 H, H-5), 3.38 (dd, J = 6.1, 9.6 Hz, 1 H, H-1), 1.80 (s, 3 H, $COCH_3$), 1.21 (d, J = 6.1 Hz, 3 H, CH_3).

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