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Synthesis of α-Glucuronic Acid and Amide Derivatives in the Presence of a Participating 2-Acyl Protecting Group

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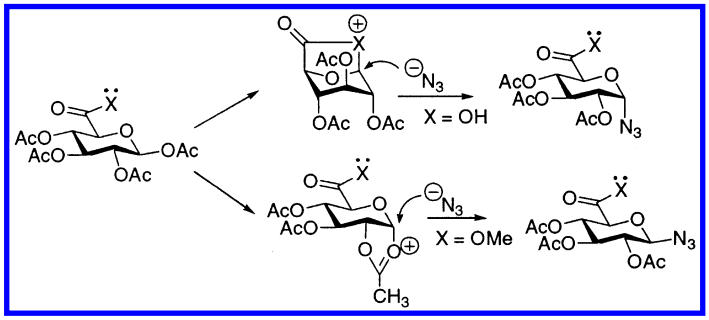
ABSTRACT



Participating acyl groups located at C-2 in glucosyl and related donors generally promote formation of 1,2-*trans*-glycosides. Reactions of some glucuronic acid donors with $TMSN_3/SnCl_4$ or $ROH/SnCl_4$ gave only the 1,2-*cis*-glycoside. The stereoselectivity is consistent with participation of the C-6 group. The methodology was used for the synthesis of a Kdn2en mimetic with the α-configuration.

The preparation of glycosides in a stereoselective manner is one of the most important goals for synthetic chemists. This is a result of the biological and medical importance of oligosaccharides, glycoproteins, and glycolipids,[1] due to interest in the synthesis of carbohydrate mimetics,[2] carbohydrate-based peptidomimetics,[3] and carbohydrate-based scaffolds for the synthesis of pharmacophore mapping libraries.[4] Such syntheses are challenging because of the complexity and diversity of saccharides found in nature. Much work has been carried out in development of strategies for synthesis of *O*-glycosides. Widely used methods include that of Koenigs and Knorr;[5] halide-assisted glycosylation;[6] the activation of thioglycosides,[7] glycosylfluorides,[8] trichoroacetimidates,[9] pentenyl glycosides,[10] glycosyl phosphites,[11] and sulfoxides;[12] the use of glycals[13] or enzymes;[14] and donors without protecting groups.[15] Recently research has

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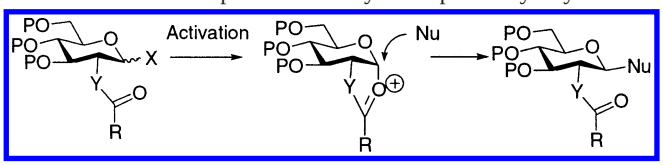
been concerned with automated solid-phase[16] and one-pot[17] oligosaccharide synthesis. N-Glycosylation is also important, particularly in relation to the synthesis of glycopeptides, glycoproteins, and peptidomimetics; the synthesis of molecules of this type are often carried out via glycosyl azides.[18] Protecting groups have been used to influence the stereoselectivity of reactions at the anomeric center. It is well-established that participating acyl groups located at C-2 in glucosyl and related donors generally promote formation of β-glycosides (Scheme 1), whereas the use of nonparticipating

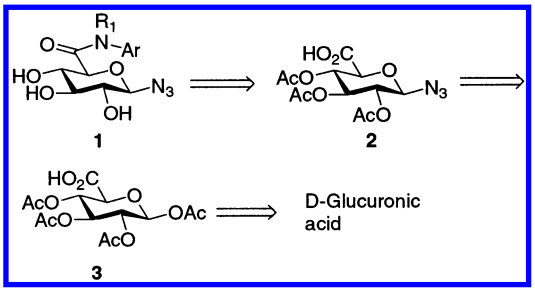
Scheme 1. Participation of 2-Acyl Groups in Glycosylation



groups (e.g., *O*-benzyl or azide) in solvents such as diethyl ether facilitate preferential formation of the α-glycoside.[19] We now describe highly stereoselective syntheses of α-glycosides of glucuronic acid derivatives even though the donors have participating *O*-acetate groups at C-2.

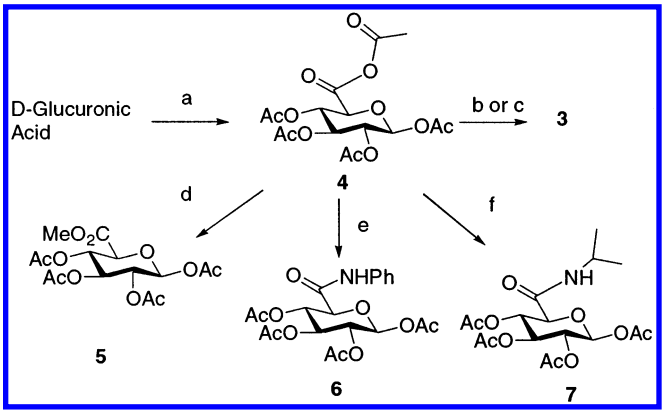
Our interest in the conformation of glycosylamides, in particular for the design of scaffolds for restricted presentation of divalent and multivalent ligands,[20] has prompted us to begin an investigation of the conformational preferences of amides such as **1**. The synthesis of glycosylamides of this type can in principle be achieved from carboxylic acids **2** and **3** (Scheme 2).

Scheme 2. Retrosynthetic Analysis of Glucuronyl Amides **1**



We could not reproduce the synthesis of **2** or **3** by the published procedures.[21] The acetylation of commercially available D-glucuronic acid in the presence of iodine followed by treatment with methanol in one pot gave the methyl ester **5**[22] rather than the carboxylic acid (Scheme 3) as reported.[21]

Scheme 3[a]



[a] Reagents and conditions: (a) Ac_2O, I_2, 70%; (b) H_2O, 91%; (c) PhNHMe (1.0 equiv), CH_2Cl_2, 15 h; (d) MeOH, 70%; (e) $PhNH_2$ (1.2 equiv), CH_2Cl_2, 15 h, 70%; (f) $^iPrNH_2$ (1.2 equiv) CH_2Cl_2, 15 h, 55%.

We found that isolation of the pure β-anhydride **4** was possible after crystallization of the residue obtained from the acetylation of glucuronic acid; this could be converted into the desired acid by reaction with water. The reaction of aniline and isopropylamine with **4** gave the amides **6** and **7**, respectively. Nucleophilic attack takes place at the carbonyl group nearest the pyranose in these cases; the reaction of the more hindered *N*-methylalanine gave **3** as a result of nucleophilic attack at the less congested carbonyl group.

After having completed the synthesis of **3** and related amides we next explored the introduction of a stable azide at the anomeric center using $SnCl_4$ and TMS-N_3. However, although the β-azide is, as expected, the major product from ester **5**,[22] the α-azide was obtained from **3** (entry 3, Table 1).[23] The reaction of other acid and amides derivatives (entries 4−6, Table 1) under similar conditions also gave the corresponding α-azide with no evidence of the β-azide detectable by NMR; the β-azides were prepared from **9** as outlined in Scheme 4 and used as standards in the analysis of the products.

When the reaction of the acetate **3** with $SnCl_4$ was repeated in the absence of trimethylsilyl azide, the 1,6-lactone **17**[24] was isolated (40-48%). Treatment of **17** with the Lewis acid in the presence of TMS-N_3 led only to formation of the

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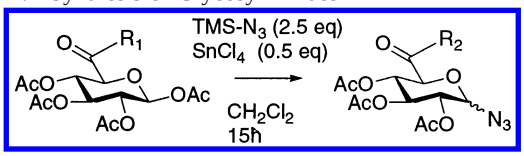
Table 1. Synthesis of Glycosyl Azides

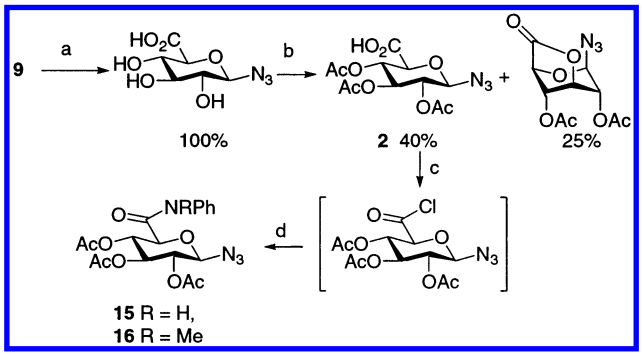


entry	R_1	R_2	product	% yield	α or β[c]
1	OMe	OMe	**9**	97[a]	β[22]
2	OAc	OH	**10**	97[a]	α/β[d]
3	OH	OH	**10**	84[b]	α
4	NH*i*Pr	NH*i*Pr	**12**	45[b]	α
5	NHPh	NHPh	**13**	62[b]	α
6	NMePh	NMePh	**14**	51[b]	α

[a] Yield of crude product. [b] Yields after purification. [c] Determined by ^{1}H NMR analysis of crude product. [d] Variable ratios of products were obtained.

α-azide **10** in 85% yield. A similar reaction of amide **6** in absence of TMS-N_3 led to isolation of the α-chloride **18**. When **18** was treated with the Lewis acid in the presence of

Scheme 4[a]



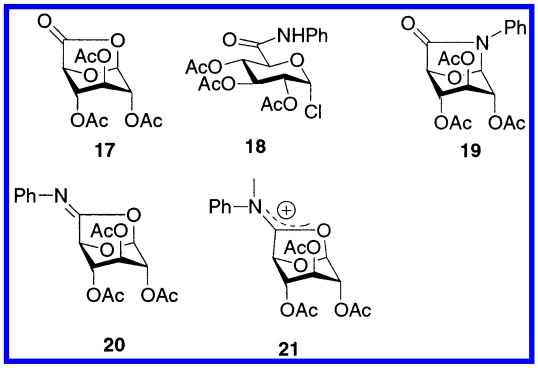
[a] Reagents and conditions: (a) LiOH, THF, H_2O, MeOH; (b) NaOAc, Ac_2O, then H_2O; (c) $(COCl)_2$ (1 equiv) CH_2Cl_2, DMF (cat.), 0 °C, 2.5 h; (d) PhNHR (1 equiv), pyridine (2 equiv), CH_2Cl_2, 30 min.

TMS-N_3 this again gave **13** as the sole product. The β-azides **2** and **16** were exposed to the Lewis acid, and no significant epimerization[25] to the α-azide occurred, indicating that this does not account for the observed stereoselectivity. These results are consistent with the formation of intermediates **17** and **19/20** during the course of the reactions, which upon further activation by the Lewis acid give the α-azide possibly by an S_N2 process. Intermediate **21** can similarly be used to explain the formation of **14**. Thus the stereoselectivity is consistent with remote participation of the acid or amide group; this is more important, under these conditions, than participation of the acetate group at C-2.

(25) ^{1}H NMR showed that <5% epimerization of the β-azide to the α-azide had occurred after 15 h in CH_2Cl_2.

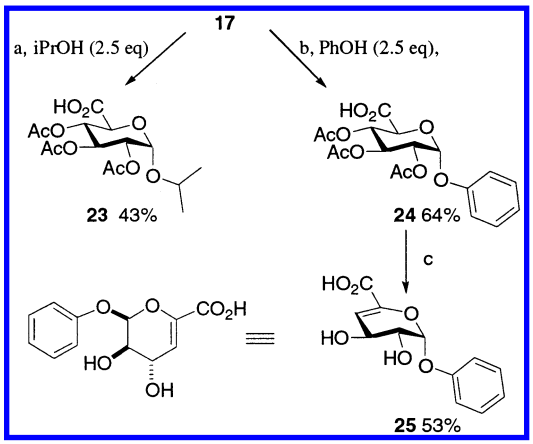
(26) Isolated yield after recrystallization.

(27) We found that 2,3,4-tri-*O*-acetyl-1-*O*-isopropyl-β-D-glucopyranuronic acid, methyl ester, prepared independently, gave significant amounts of the α-anomer (~50%) on treatment with $SnCl_4$ in CH_2Cl_2 after 15 h.



Preliminary investigations were carried out to assess the potential for using the 1,6-lactone **17** in the synthesis of *O*-glycosides (Scheme 5); its reaction with phenol proceeded

Scheme 5[a]



[a] Reagents and conditions: (a) $SnCl_4$ (0.5 equiv), TMSOTf (2.5 equiv), CH_2Cl_2 (dry), 15 h; (b) $SnCl_4$ (0.5 equiv), CH_2Cl_2 (dry), 15 h. Ac_2O, Py, DMAP (cat.) 72 h, then H_2O, then LiOH.

in 64% yield[26] to give only the α-glycoside **23**. Reaction of **17** with 2-propanol gave the α-glycoside in 43% isolated yield using a $SnCl_4$/TMSOTf mixture; the use of either $SnCl_4$ or TMSOTf on their own gave much lower yields. We find in general that workup of the reactions involving $SnCl_4$ is complicated by formation of emulsions; we find that dilution of the reaction mixture with dichloromethane followed by filtration through Celite before the various washes are carried out gives better yields and a more straightforward workup. Although yields have not yet been optimized there are some advantages: the lactone can be prepared in three steps in 35−40% overall yield from D-glucuronic acid without the need for chromatographic separations at any stage and the products from glycosylation could be extracted into aqueous bicarbonate, which simplified their purification. Epimerisation of the β-*O*-glucuronide to the α-anomer is possible under these conditions.[27] However, the β-glycoside could not be detected in the reaction mixtures in these two cases. We are currently investigating alternative conditions and strategies that may improve the recovery of product.

The synthesis of **25** from **24** was carried out to illustrate that this methodology could be useful in preparation of

molecules of biological interest; this molecule has structural features similar to those found in sialidase inhibitors including Kdn2en mimetics.[28] Thus elimination of acetic acid and concomitant introduction of an alkene between C-4 and C-5 was achieved by treatment of **24** with acetic anhydride and pyridine for 72 h;[29] this was followed by hydrolysis of the anhydride and acetate protecting groups to give **25**. Glucuronic acid based mimetics of Kdn2en have been prepared previously[30] by von Itzstein and co-workers and have the β-configuration; the chemistry described herein complements this approach and facilitates the synthesis of the Kdn2en mimetic **25**, which has the α-configuration as a structural probe for proteins that recognize sialic acid.

In summary, the synthesis of 1,2-*cis*-glucuronides[31] can be achieved even in the presence of 2-acyl participating groups, and the stereoselectivity can be explained by participation of remote acid or amide groups. The participation of remote groups might also account for the recent observations by Hunt and Seeberger; they found that formation of $\sim$1:1 mixtures of α- and β-glycosides during some solid-phase glycosylation reactions using a succinamyl linker even in the presence of a 2-OPiv group.[32] The results indicate that this and related approaches may be worth investigating more widely in synthesis of glycosides and for natural products and other biologically interesting molecules with similar structural features. We are currently exploring synthesis of oligosaccharides and other glycosides where participation of remote groups may influence stereoselectivity and reactivity. Uronic acid donors have low reactivity in carbohydrate chemistry, and their glycosylation reactions often do not proceed efficiently.[33] The possibility also exists for enhancing or tuning the reactivity of these and other donors using remote groups, and this is also being investigated. The results of these studies and the solution structures of amides **1** and related divalent compounds will be reported in due course.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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