Stereoselective Glycoside Synthesis

Glycosidation Reactions of Silyl Ethers with Conformationally Inverted Donors Derived from Glucuronic Acid: Stereoselective Synthesis of Glycosides and 2-Deoxyglycosides**

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Stereoselective glycoside synthesis is of interest because of the biological and medical relevance of oligosaccharides, glycoproteins, glycolipids,[1] and other carbohydrate derivatives,[2] and a range of strategies have been developed to produce these compounds.[3] The 1,6-lactone derivative **2** (see Scheme 1) has potential for use in the synthesis of 1,2-*cis*-glycosides[4] but its application has been limited because of the low yields obtained from its reaction with alcohols.[5] We now report that the $SnCl_4$-catalyzed coupling of silyl ethers[6] with **2** provides α-*O*-glucuronides in significantly improved yields without loss of stereoselectivity. The methodology has been extended to the related 2-deoxylactones, which give α- or β-glycosides depending on the structure of the donor.

The preparation of **2** was carried out via the mixed anhydride **1** (Scheme 1) by an improved and shorter procedure than that previously described.[5] The donors **6** and **7** were also prepared, via glycal **4**, because of their potential for the synthesis of 2-deoxyglycosides, which are of biological interest.[7] Thus, the reaction of the allyl ester **3** with hydrogen bromide in acetic acid gave a glycosyl bromide intermediate

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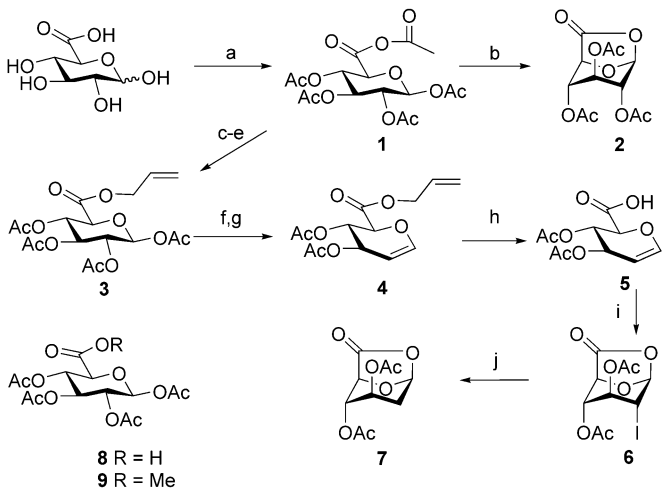
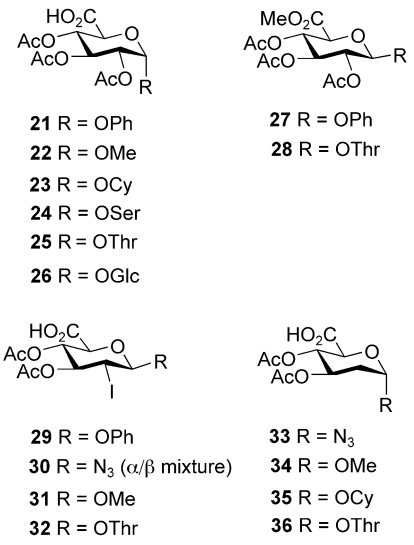


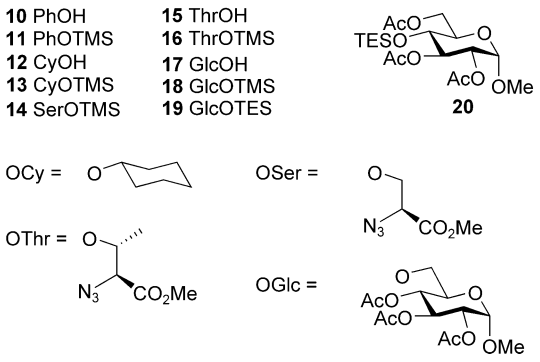
Scheme 1. Synthesis of glycosyl donors. Reagents and conditions: a) Ac_2O, I_2; b) $SnCl_4$, CH_2Cl_2; 65% over two steps; c) H_2O; d) $(COCl)_2$, DMF; e) allyl alcohol, C_5H_5N; 55% over three steps; f) HBr, AcOH; g) Zn dust, $CuSO_4$, AcONa, 50% aq AcOH; 50% over two steps; h) $[Pd(PPh_3)_4]$, pyrrolidine, MeCN, 0°C, 80%; i) NIS, MeCN, 50%; j) Bu_3SnH, AIBN, toluene, 110°C, 15 min, 90%. DMF = *N*,*N*-dimethylformamide, NIS = *N*-iodosuccinimide, AIBN = azobisisobutyronitrile.



Scheme 3. Glycosidation products from the $SnCl_4$-mediated reactions. The reactants and yields are listed in Table 1.

and this was subsequently converted into **4** by treatment with zinc dust, copper(II) sulfate, and sodium acetate in aqueous acetic acid as described previously for the corresponding methyl ester.[8] The allyl protecting group could be removed from **4**, to leave the glycal intact, by using $[Pd(PPh_3)_4]$ and pyrrolidine in acetonitrile to give **5**.[9] The reaction of **5** with NIS gave the lactone **6**, which was subsequently reduced to give **7** by using Bu_3SnH/AIBN.

The results of the glycosidation of these donors using a tin(IV) chloride catalyst[10] with the acceptors and products shown in Schemes 2 and 3, respectively, are listed in Table 1. Donor **2** gave α-glycosides in a highly stereoselective manner, despite the presence of the 2-*O*-acetyl group, in higher yields and conversions than the carboxylic acid **8**. This methodology was applied to the synthesis of glycosides derived from serine and threonine, with these amino acids being coupled as the azido derivatives (azido acids). An interesting observation was that the disaccharide **26** was obtained in higher yield with

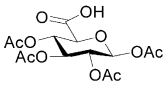
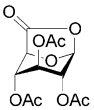
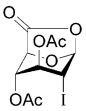
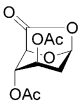
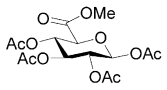


Scheme 2. Acceptors used in the glycosidation reactions. TMS = trimethylsilyl, TES = triethylsilyl, Cy = cyclohexyl.

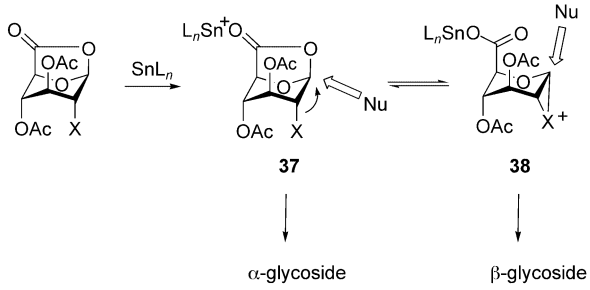
the TES acceptor **19** than with TMS acceptor **18**. The TES derivative **20** gave **26** as a result of acetate migration, presumably mediated by the catalyst, and subsequent glycosidation at the O6 position. The stereoselectivity observed for both **2** and **8** contrasted with that of the methyl ester **9**, which provided β-glucuronides in higher yields than were obtained with phenol or the alcohols. The 2-deoxyglycosyl donor **7** displayed the same behavior as **2** during the glycosidation, giving α anomers with high stereoselectivity, which is contrasts the situation with 2-deoxy-2-iodo derivative **6**, which gave β-glycosides.

Possible mechanistic pathways for the glycosidation reactions of the lactones are shown in Scheme 4. Donors **2** and **7** undergo reaction so that inversion of configuration at the C1 position by an S_N2 process occurs via an intermediate of type **37**. A pathway involving **38** would be expected to provide the β-glycoside for iodide **6**, a fact indicating that the iodine residue is a better participator than the 2-*O*-acetyl group. The lactone **2** is generated in situ from carboxylic acid **8** in a step that accounts for the stereoselectivity observed with **8**; the lower yields obtained result from its lower reactivity because all of its substituents are oriented equatorially and destabilize positive-charge formation during activation of the 1-OAc group.[11] The greater reactivity of the donor in the $^1C_4$ conformation is not unexpected and may be significant given the previously noted low reactivity of glucuronides.[12] Another conceivable pathway involves **2** or **7** first giving a β-glycoside that rapidly isomerizes to the α anomer. However, although anomerization of β-glucuronic acid derivatives is observed in the presence of $SnCl_4$, the rates appear too slow to account for this being the only pathway operating. The concept of using 1,6-anhydro-β-D-glucopyranosides and related compounds has been investigated previously for the synthesis of *O*-glycosides (MeOH as acceptor),[13] thioglycosides,[14] and *C*-glycosides;[15] these reactions gave mixtures or in some cases the pure α- or β-glycoside, for example, a β-glycoside was obtained from a 2-

Table 1: $SnCl_4$-mediated glycosidation reactions.[a]

Donor	Acceptor	Donor:acceptor:$SnCl_4$	Product[b] (yield [%])
	**11**	1:2.5:0.5	**21α** (35)
	13	1:2.5:0.5	**23α** (32)
	10	1:2.5:0.5	**21α** (64)
	11	1:2.5:0.5	**21α** (88)
	TMSOMe	1:0.66:0.33 (10 h)	**22α** (62)
	**12**	1:2.5:0.5	**23α** (11)
	13	1:2.5:0.5	**23α** (78)
	14	1:1.2:0.5	**24α** (51)
	16	1:4:1 (18 h)	**25α** (71)
	17	1:4:1 (6 h at RT, 12 h at 40°C)	**26α** (<10)
	18	1:4:1 (6 h at RT, 12 h at 40°C)	**26α** (44)
	19	1:4:1 (6 h at RT, 12 h at 40°C)	**26α** (58)
	20	1:4:1 (6 h at RT, 12 h at 40°C)	**26α** (56)
	**11**	1:2.5:0.5	**29β** (60)
	$TMSN_3$	1:2.5:0.5	**30α** (29); **30β** (47)
	TMSOMe	1:2.5:0.5 (5 h)	**31β** (39)
	16	1:4:1	**32β** (51)
	$TMSN_3$	1:2.5:0.5	**33α** (66)
	TMSOMe	1:0.66:0.33 (8 h)	**34α** (59)
	13	1:2.5:0.5	**35α** (57)
	16	1:4:1 (12 h)	**36α** (41)
	**10**	1:2.5:0.5	**27β** (66)
	11	1:2.5:0.5	**27β** (92)
	15	1:4:1	**28β** (<5)
	16	1:4:1	**28β** (75)

[a] All reactions were carried out in CH_2Cl_2 at RT for 15 h unless otherwise stated. [b] ^1H NMR spectroscopy analysis of the crude product was used to determine the ratio of α and β anomers; this was not subsequently altered by purification. When the second anomer is not reported it could not be detected.



Scheme 4. Possible mechanistic pathways to the α- and β-glycosidation products. L = ligand, Nu = nucleophile.

O-acetyl-1,6-anhydromaltose donor.[16] However, the participation of 2-*O*-acetyl groups, which normally dominates glycoside synthesis, is not important for **2** in its reaction with a wide range of acceptors. This contrasts with the general behavior of glucuronic acid donors, which have $^4C_1$ ground-state conformations.

There are practical and strategic advantages to using such lactones as described herein. The carboxylic acid is formally protected in the donor and acts as the leaving group in the glycosidation reaction; its release simplifies purification as the acid can be extracted into aqueous sodium hydrogen carbonate or can be separated from other by-products by solid-phase extraction. In addition, 2-deoxypyranuronic acids synthesized by this route should be more stable to acid than the corresponding 2-deoxypyranosides. There may be potential applications for the glycosyl azido acids as intermediates in glycoconjugate synthesis[17] and in Staudinger reactions.[18] It is now required that β-*O*-glucuronide drug conjugates, formed in animals and humans as part of detoxification, are tested before the parent drug can be approved and their synthesis is often not trivial;[19] investigation of coupling reactions of the appropriate silyl ethers with donor **9**, similar to the two cases shown herein, may also be worthwhile. These possibilities as well as the potential of these compounds as building blocks for the synthesis of glycosaminoglycan disaccharides[20] are currently being investigated.

Experimental Section

Glycosidation procedure: The glycosyl donor (0.4 mmol) was dissolved in dry CH_2Cl_2 (5 mL) in an N_2 atmosphere. $SnCl_4$ (Aldrich) and acceptor were then added, and the reaction mixture was left to stir (see Table 1 for reaction times). The mixture was then diluted with dichloromethane (10 mL), then saturated aqueous $NaHCO_3$ solution (15 mL) was added and the resulting mixture was stirred for 30 min. The mixture was filtered through celite, the layers were then separated, and the aqueous layer was acidified with acetic acid. The product was extracted with EtOAc (up to 10 × 10 mL), dried (Na_2SO_4), and filtered. The solvent was then removed to give the glycosidic product. If the glycosidic product was still detected in the aqueous layer then the water was removed by freeze drying and the residue was purified by column chromatography (EtOAc/MeOH gradient elution).

Further experimental details can be found in the Supporting Information.

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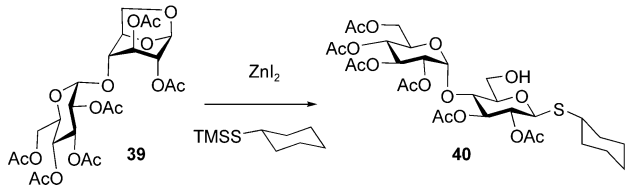

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