Stereocontrolled synthesis of α-*C*-galactosamine derivatives promoted by samarium diiodide: an example of chelation controlled *C*-glycosylation

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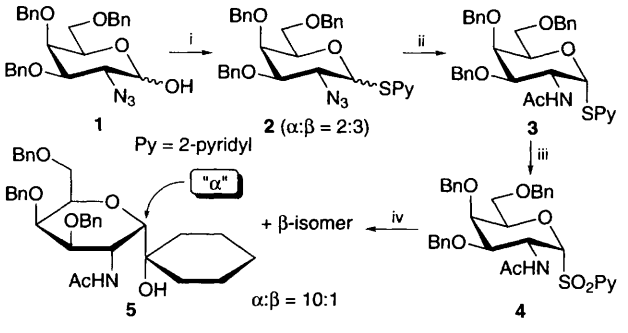
Direct coupling of the pyridylsulfone of *N*-acetylgalactosamine with aldehydes or ketones is promoted by samarium diiodide unexpectedly giving the corresponding α-*C*-glycosides.

In previous work we discovered that anomeric (glycosyl) organosamarium(III) species bearing a C(2)-alkoxy group display an exceptional stability towards β-elimination at room temperature.[1] Because of this, good to acceptable yields of 1,2-*trans*-*C*-glycosides were exclusively obtained under extremely mild conditions when reductive samariation of mannosyl and glucosyl pyridyl sulfones was performed in the presence of carbonyl compounds. As part of our overall interest in preparing *C*-glycoside analogues of biologically important sugars,[2] we recently required such a mimic of *N*-acetyl-D-galactosamine in either anomeric configuration.[3] We next examined the applicability of these samarium diiodide-promoted coupling reactions with galactosyl pyridylsulfones bearing a C(2)-acetamide functionality. The results of this work, which we present here, contrast the previous *trans*-selectivity observed for C(2)-substituted glycosyl pyridylsulfones[1] and explain the stereodirecting effect that an acetamido group may have in the β-position of a glycosyl organosamarium.

The synthesis of the required pyridylsulfone of *N*-acetylgalactosamine was easily obtained in four steps from the readily accessible hemiacetal **1**[4] as shown in Scheme 1. Reaction with PySSPy–PBu_3 combination[5] in CH_2Cl_2 afforded an α:β mixture (2:3) of isomeric pyridyl sulfides **2**. For the sake of simplicity in characterisation, the α-anomer **2** was carried through in the subsequent steps. Azide reduction was performed using the protocol published by Bartra *et al.*[6] employing stannous chloride and thiophenol, and gave the amine which was immediately converted to its acetamido derivative **3** (Ac_2O–pyridine) in a combined yield of 81% over the two steps. Further oxidation of the sulfide with MCPBA then afforded the desired sulfone **4** as colourless crystals (mp 151 °C, EtOAc–pentane).



Scheme 1 *Reagents and conditions*: i, 1.1 equiv. of PySSPy, 1.2 equiv. of PBu_3, CH_2Cl_2, 93% (α:β, 2:3); ii, 1.5 equiv. of $SnCl_2$, 6.0 equiv. of PhSH, 4.5 equiv. of Et_3N, MeCN, then Ac_2O, pyridine, 81%; iii, 3 equiv. of MCPBA, 7 equiv. of $NaHCO_3$, CH_2Cl_2, 0 °C, 89%; iv, 2.0 equiv. of cyclohexanone, 2.2 equiv. of SmI_2, THF, 20 °C, 75%

We originally anticipated a 1,2-*trans* selectivity in the *C*-glycosylation of **4** as previously noted for the glycosyl pyridylsulfones possessing a substituent at C(2),[1] but we were nevertheless somewhat sceptical as to the efficiency of these coupling reactions owing to the availability of an acidic proton on the acetamido group.† It therefore came as a surprise when treatment of a THF solution of pyridylsulfone **4** and 2 equiv. of cyclohexanone with samarium diiodide[7] (2 equiv.) at 20 °C afforded a 10:1 mixture of C_1-isomeric *C*-glycosides in 75% yield.‡ In addition, the major anomer was not the anticipated β-product, but rather the α-*C*-glycoside **5**, as seen from the small $J_{H\text{-}1,H\text{-}2}$ and $J_{H\text{-}2,H\text{-}3}$ coupling constants of 1.3 and 3.4 Hz respectively observed in the ^1H NMR spectrum. The results with other aliphatic ketones or aldehydes, as shown in Table 1, demonstrates that the reaction appears quite general furnishing the corresponding *C*-glycosides in comparable yields and with an α:β selectivity in the range 4:1 to 20:1. With the aldehydes, an approximately 5:1 stereoselectivity was observed at the newly-created exocyclic stereogenic centre. One exception was noted with a more functionalised aldehyde (entry 5), where a somewhat reduced stereoselectivity (2.3:1) was obtained. Interestingly, in the same case, condensation with the glycosyl organosamarium led to internal cyclisation of the formed samarium alkoxide with concomitant loss of the oxazolidinone moiety.

The above results were unambiguously confirmed by a single-crystal X-ray structure§ (see Fig. 1) of the major diastereoisomer (mp 137–138 °C, EtOAc–pentane) obtained from the condensation of pyridylsulfone **4** with cyclohexanecarbaldehyde (Table 1, entry 4). Although all the α-*C*-glycosides obtained display a solution conformation deviating from the normal $^4C_1$ conformation as determined from their ^1H NMR spectra, this is apparently the preferred conformation for the *C*-glycoside in solid state.¶ The configuration of the newly-created exocyclic stereocentre of this isomer was found to be *S*. We therefore tentatively assigned this stereochemistry to the

Table 1 SmI_2 promoted coupling of carbonyl compounds with glycosyl pyridylsulfones

Entry	Sulfone	Carbonyl compound	*C*-Glycoside (%)	Stereosel.	α:β
1	**4**	pentan-3-one	67	—	10:1
2	**4**	2-methylpropanal	72	5:1	12:1
3	**4**	octanal	69	6:1	9:1
4	**4**	cyclohexanecarbaldehyde	67	6:1	20:1
5	**4**	3-(4-oxobutanoyl)-1,3-oxazolin-2-one	80[a]	2.3:1	~4:1
6	**6**	pentan-3-one	31	—	0:1
7	**7**	cyclohexanone	86	—	1:1
8	**8**	cyclohexanone	—[b]	—	—

[a] Instead of the desired *C*-glycoside, compound **I** was obtained. [b] Only the product of elimination, tribenzylgalactal, was observed.

major diastereoisomer of the other examples displayed in Table 1 (entries 2, 3 and 5).

In an attempt to delineate the dominating factors involved in the preferred formation of the α-anomer from **4**, we examined the anomeric composition of the *C*-glycosides produced from the condensation of the galactosyl and 2-deoxygalactosyl pyridylsulfones **6** and **7** with a ketone substrate (Table 1, entries 6 and 7). Only the β-*C*-galactoside was obtained in a moderate yield with **6**, whereas in the case of the 2-deoxy derivative **7**, an approximately 1 : 1 mixture of *C*-glycoside anomers was observed. In addition, the attempted coupling of the C(2)-azido derivative **8** led only to the elimination product, tribenzyl-galactal. These observations, being in close agreement with those for the gluco-series,[1] suggest an important directing-effect played by the acetamido group of the intermediate glycosyl organosamarium.

The observed α-selectivity for pyridylsulfone **4** is explained in Scheme 2. Upon sulfone reduction, the kinetic α-oriented Sm^{III} species **9** is generated from the reductive samariation of the corresponding anomeric radical. Whereas with the previous glycosyl pyridyl sulfones possessing a C_2 equatorially oriented substituent, these anomeric organosamarium species undergo a configurational change to the thermodynamically favoured β-anomer,[1] in the case of **9**, a strong complexation between the samarium metal ion with the acetamido group may prevent this anomerisation. Instead an equatorially oriented C_1–Sm bond may be fulfilled if the species **9** undergoes a conformational change to an inverse chair or an intermediate half chair. Subsequent condensation then leads to the α-*C*-glycosides observed.

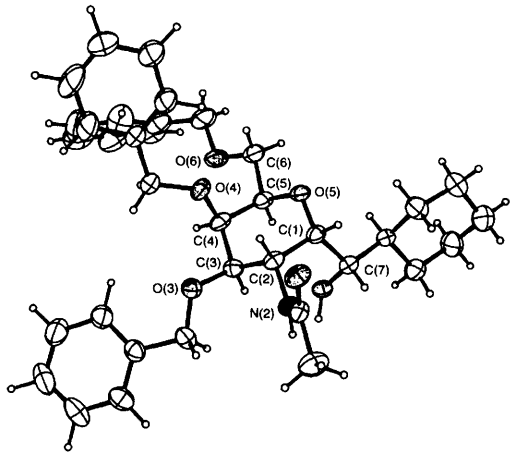
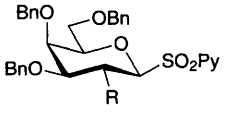
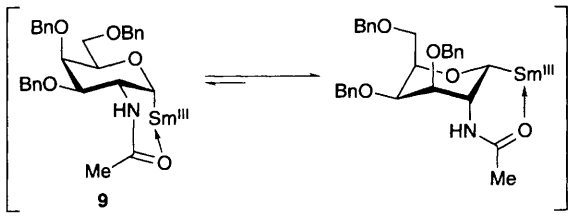


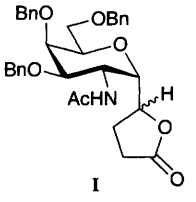
Fig. 1 Single-crystal X-ray structure of the major diastereoisomer obtained from sulfone **4** and cyclohexanecarbaldehyde



6 R = $OSiMe_3$
7 R = H
8 R = N_3



Scheme 2



Footnotes

† Hoffmann and Kessler have reported a somewhat related approach for the formation of a low temperature configurationally stable α-glycosyl anion from the reductive lithiation of a corrresponding 2-acetamidoglucosyl chloride at −95 °C [see ref. 3(*a*)]. It is necessary though that the acidic proton of the acetamido be deprotonated prior to the reduction.

‡ The corresponding β-isomer of **4** led to an identical result when treated with SmI_2 and cyclohexanone.

§ Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/155.

¶ *Selected data* for the major diastereoisomer obtained from sulfone **4** and cyclohexanecarbaldehyde. ^1H NMR (250 MHz, $CDCl_3$): δ 6.54 (d, 1 H, *J* 5.9 Hz, NH), 4.37 (ddd, 1 H, *J* 9.4, 6.2, 2.4 Hz, H-5), 4.23 (dd, 1 H, *J* 11.3, 9.4 Hz, H-6a), 4.13 (dd, 1 H, *J* 3.0, 2.9 Hz, H-3), 4.07 (dd, 1 H, *J* 3.4, 2.9 Hz, H-1), 4.05 (ddd, 1 H, *J* 5.9, 3.0, 2.9 Hz, H-2), 3.78 (dd, 1 H, *J* 6.2, 2.9 Hz, H-4), 3.73 (d, 1 H, *J* 11.3, 2.4 Hz, H-6b), 3.31 (ddd, 1 H, *J* 7.2, 5.0, 3.4 Hz, H-7).

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