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Stereospecific Synthesis of Glycoside Mimics Through Migita–Kosugi–Stille Cross-Coupling Reactions of Chemically and Configurationally Stable 1-*C*-Tributylstannyl Iminosugars

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Abstract. A process for the *de novo* synthesis of imino-*C*-glycosides is described. The methodology is based on the reaction of 1-C-stannylated iminosugars with various electrophiles under the conditions of Migita–Kosugi–Stille cross-couplings, which gives 1-C-substituted iminosugar derivatives in a stereoretentive process. The required iminoglycosyl stannanes are obtained by way of the highly stereoselective addition of tributylstannyllithium to (S_R)- or (S_S)-*N*-*tert*-butanesulfinyl glycosylamines, followed by an activation cyclization sequence. Most interestingly, the methodology is tunable: the configuration of the tin adduct is controlled exclusively by the *tert*-butanesulfinyl auxiliary, thus giving access after ring formation to 'α'-configured or 'β'-configured iminoglycosyl stannanes. With the subsequent stereoretentive C–C bond-forming process, the methodology allows the synthesis of pseudo anomers of imino-*C*-glycosyl compounds in a controlled fashion.

Keywords: 1-Metalated Iminosugars; Stannanes; C–C coupling; Stereospecific Reactions; Catalysis

Introduction

Glycomimetics are carbohydrate analogs designed to interfere with biochemical pathways wherein carbohydrates play key roles and are associated with pathological disorders.[1] As potential drug candidates, analogues of glycosides and glycoconjugates are gaining increased interest because of their ability to modulate the activity of carbohydrate-processing enzymes, or enhance their affinity for carbohydrate-recognizing proteins. One class of glycomimetics that is attracting currently a surge of interest is that of iminosugars (e.g., **1** and **2**, Fig. 1). These compounds exhibit remarkable activities as glycosidases and glycosyltransferases inhibitors, which bestow them high therapeutic value.[2] Thus, iminosugar derivatives have emerged as new drugs for example to control glucose uptake in non-insulin-dependent diabetes patients (Miglitol®, *N*-[2-hydroxy-ethyl]-1-deoxynojirimycin **1a**),[3] to salvage mutant enzymes in lysosomal diseases such as Fabry disease (Galafold®, 1-deoxygalactonojirimycin,[4] **1b**) or to treat type I Gaucher and Niemann-Pick diseases by inhibition of GlcCer synthase (Zavesca®, *N*-butyl-1-deoxynojirimycin **1c** (Fig. 1)).[5-6]

However, these saccharide surrogates lack the structural and stereochemical substitution patterns that are commonly embedded within the aglycone of glycosides and, as a result, lack selectivity in their biological activities.

In that respect, 1-C-substituted iminosugars (**2**), which carry a C-linked substituent at the pseudo anomeric position in a well-defined configuration, i.e. imino-*C*-glycosides, constitute highly relevant mimetics of glycosides or glycoconjugates, and enhance the biological and therapeutic potential of iminosugars.[2b],[2e],[7] For instance, certain imino-*C*-nucleosides have been identified as lead anticancer, antiviral and antibacterial compounds but also for the

treatment of metabolic and genetic diseases.[8] Mundesine® (Immucillin-H) **2a**, for example was approved in Japan for the treatment of relapsed/refractory peripheral T-cell lymphoma,[9] and BCX4430 (Immucillin-A) **2b** has been demonstrated to protect against both Ebola and Marburg viruses in rodents and monkeys, even when administered up to 48 h after infection (Fig. 1).[10]

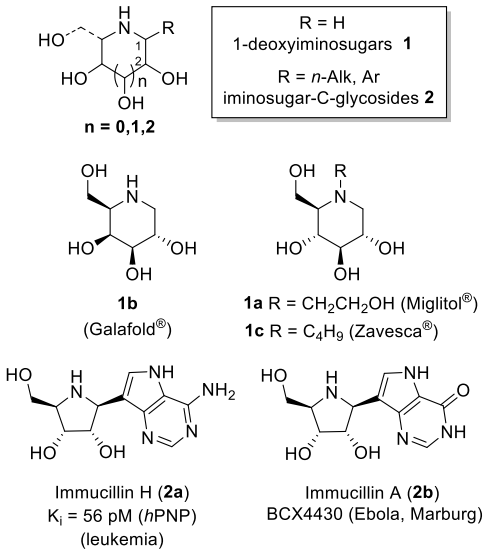


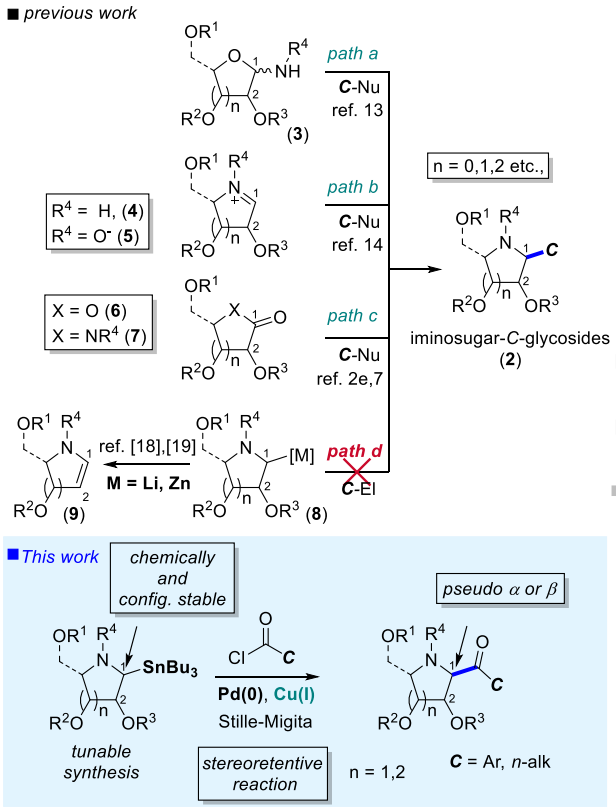
Figure 1. Chemical structures of iminosugar derivatives and imino-*C*-glycosides.

The synthesis of imino-*C*-glycosides represents a significant challenge and various elegant stereoselective methods have been developed for the *de novo* preparation of 1-C-substituted iminosugars,[11] or more frequently, from sugar substrates.[12] Most of the synthetic methods from sugars are based on the addition of carbon nucleophiles to glycosylamines (**3**) (*path a*),[13] cyclic imines (**4**), or cyclic nitrones (**5**) (*path b*),[14] lactones **6**, and lactames **7** (*path c*) (Scheme 1).[2b],[2e],[7],[15] These tactics often require long reaction sequences and give low overall yields. In addition, the stereochemistry is governed by the inherent chirality of the saccharide core, thus giving in most cases moderate diastereoselectivities.

As a result, there are only two methodologies reported so far whereby it is possible to generate either (1*S*)- or (1*R*)-imino-*C*-glycosides (i.e., mimics of α- and β-glycosides) with high specificity in a tunable, and predictable manner.[11b],[12g],[16] Furthermore, there is no report describing the more straightforward disconnection that would consist in functionalizing 1-deoxy iminosugars (**1**) at the C-1 position through a direct C(sp^3)–H bond activation or by a metal-catalyzed reaction using a stable 1-metallated iminosugar derivative and a carbon electrophile (*path d*).[17]

Indeed, prior studies on the direct functionalization of saturated cyclic amines and on the preparation of 1-metallated iminoalditol derivatives **8** (e.g., M = Li, Zn) have highlighted the critical problems associated with these routes (e.g. formation of iminoglycals of type **9** through elimination of the alkoxy group at C-2 (Scheme 1), poor functional group tolerance, and difficulties in controlling the α-stereoselectivity etc.).[18],[19]

To be successful, the envisioned strategy would largely depend on the choice of the metal to be installed at the C-1 position. This problem was recently addressed by Walczak and co-workers in the sugar series, by capitalizing on stereospecific cross-coupling reactions of anomeric stannanes with aromatic iodides, diaryliodonium triflates and acyl donors in the presence of palladium catalyst.[20] However, these methods are based on the use of activated glycosyl donors as precursors and are not applicable to the synthesis of iminoglycosyl stannanes.



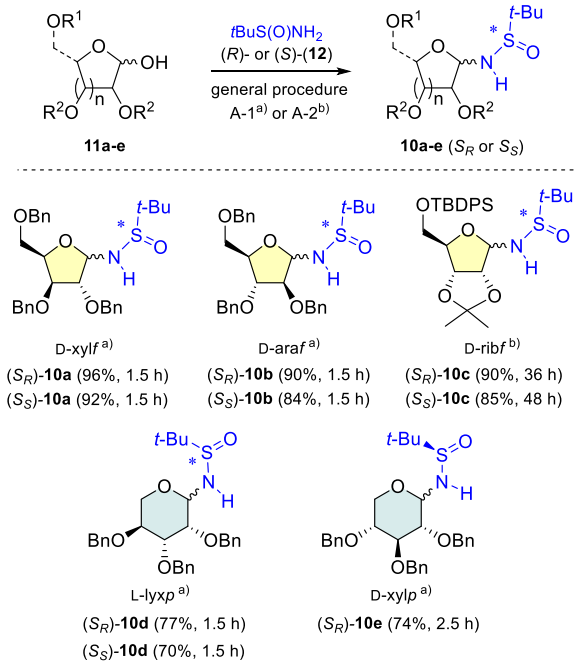
Scheme 1. Synthetic routes to iminosugar *C*-glycosides.

In our work, we have devised an efficient and stereoselective approach to iminoglycosyl stannanes whereby *path d* to imino-*C*-glycosides (Scheme 1) becomes feasible. In the course of our investigations on the reactivity of *N-tert*-butanesulfinyl glycosylamines (**10**), which are useful precursors of imino-*C*-glycosides by an addition-cyclisation strategy,[13] we wondered whether it would be possible to generate 1-stannylated iminoalditol derivatives by this methodology and use the resulting organometallic intermediates for the synthesis of diverse imino-*C*-glycosides. We describe herein that

it is indeed the case. We report in this article a new method of synthesis of imino-*C*-glycosyl compounds by way of the highly stereoselective and tunable addition of Bu_3SnLi onto (S_R)- and (S_S)-*N*-*t*-butanesulfinyl glycosylamines, followed by cyclisation to iminoglycosyl tributylstannanes and their stereospecific cross-coupling by Migita–Kosugi–Stille catalysis with a range of aroyl and alkanoyl chlorides, thus giving access in a fully stereocontrolled process to iminosugar-*C*-glycosides of either 'alpha' or 'beta' configuration.

Results and Discussion

Synthesis of Glycosylamines. At the outset of the study, a panel of *N*-*tert*-butanesulfinyl glycosylamines of interest was selected (**10a**–**e**, Scheme 2) with both furanose and pyranose structures and (*R*)- or (*S*)- Ellman's chiral auxiliaries (*e.g.*, (S_S)-**10** or (S_R)-**10**).[21] Starting from known tri-*O*-benzyl pentoses (**11a**–**e**), the formation of the *N*-sulfinyl glycosylamines of type **10** was executed under conditions improved from the ones we previously described.[12g],[22]



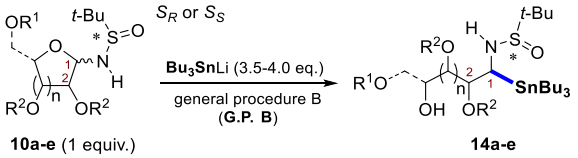
Scheme 2. Preparation of sulfinylglycosylamines **10a**–**e**. [a]**G.P. A-1**: **11** (2 equiv.), MS (4Å), $Ti(OEt)_4$ (1.5 equiv.), toluene, 110 °C, µW, 1.5–2.5 h; [b]**G.P. A-2**: **11** (2 equiv.), MS (4Å), Cs_2CO_3 (1.5 equiv.), $Cl(CH_2)_2Cl$, Δ, 36–48 h.

Using $Ti(OEt)_4$ (1.5 equiv.) as the promoter and commercial (*R*)-(+)- and (*S*)-(–)-2-methyl-2-propanesulfinamide ((*R*)- and (*S*)-**12**, 2 equiv.) in dry toluene, glycosylamines (S_R)- and (S_S)-**10a**, **10b**, **10d** and **10e** were isolated in excellent yields (70–96%) by heating for 1.5–2.5 h at 110 °C under µW irradiation (general procedure A-1, **G.P. A-1**). Interestingly, for the pyranosylamine motif ((S_R)-**10e**), a noticeable yield increase was observed (74% *vs.* 56%) and the reaction time was significantly shortened (2 h *vs.* 48 h) through the µW activation mode. The acid sensitive sugar hemiaminals (S_R)- and (S_S)-**10c** were in turn obtained in good yields (85% and 90% for (S_S)- and (S_R)-**10c**, resp.) by refluxing a mixture of ribofuranose **11c**, sulfinamide (*R*)- or (*S*)-**12** (2 equiv.) and Cs_2CO_3 (1.5 equiv.) in dichloroethane for 36–48 h (**G.P. A-2**).

Addition Reactions. Tributylstannyllithium (4.4 equiv.) was subsequently added to the glycosylamines **10a**–**e** at −78 °C.[12g],[22] We noted by TLC analysis that some of the lithiated *N*-sulfinylated intermediates (see below in Scheme 3, compounds of type **13**) may require increasing the temperature for a complete reaction. We have already observed similar results in the addition of simple organolithium and magnesium reagents to a variety of glycosylamines of type **10**.[12g],[22]

The reactions were thus followed by TLC analysis and allowed to reach a given temperature over 1.5–6 h (general procedure B, **G.P. B**). The corresponding stannylated aminoalditols **14a**−**e** were obtained in good yields (71−89%, Table 1, entries 1−7, 9), with a single notable exception: for the pyranoid derivative (S_S)-**10d** no conversion whatsoever was detected and the starting material was recovered unchanged (entry 8).

Table 1. Addition of Bu_3SnLi to glycosylamines **10a**–**e**.[a]



Entry	Substrate	Product	**14** ratio (1*R*:1*S*)[b]	**14** yield (%)[c]
1	(S_R)-**10a**	(1*R*)-(S_R)-**14a**	> 98:2	89
2	(S_S)-**10a**	(1*S*)-(S_S)-**14a**	> 2:98	81
3	(S_R)-**10b**	(1*R*)-(S_R)-**14b**	> 98:2	85
4	(S_S)-**10b**	(1*S*)-(S_S)-**14b**	> 2:98	87
5	(S_R)-**10c**	(1*R*)-(S_R)-**14c**	> 98:2	84
6	(S_S)-**10c**	(1*S*)-(S_S)-**14c**	> 2:98	81
7	(S_R)-**10d**	(1*R*)-(S_R)-**14d**	> 98:2	81
8	(S_S)-**10d**	–	–	nc[d]
9	(S_R)-**10e**	(1*R*)-(S_R)-**14e**	> 98:2	71

[a]**Typical conditions** (**G.P. B**): (1) *i*-Pr_2NH (3.5–4.0 equiv.), *n*-BuLi (3.5–4.0 equiv.), THF, 0 °C, 30 min; (2) Bu_3SnH (3.5–4.0 equiv.), – 78 °C, 15 min; (3) **10a**–**e**, THF, – 78 °C; (4) The reaction mixture is allowed to reach a given temperature over 1.5–6 h. [b]d.r determined on crude mixture using ^{1}H-NMR spectroscopy. [c]Isolated yields (column chromatography). [d]nc: no conversion.

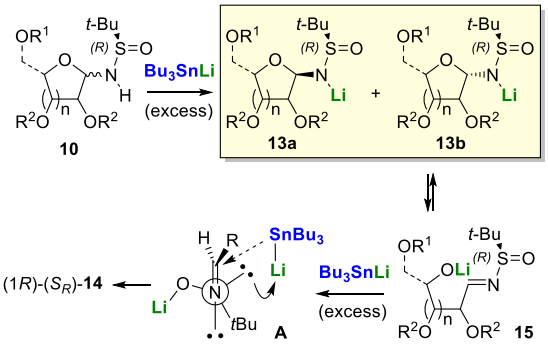
Remarkably, all the other *N*-sulfinylglycosylamines gave upon addition a single diastereomer (dr > 98:2) as indicated by NMR analysis of the crude mixtures. Furthermore, no

matched or mismatched situations could be observed, highlighting the fact that stereochemistry of the reaction appears to be solely controlled by the chiral sulfinyl auxiliary.

Most interestingly, the configuration of the newly formed stereogenic center is *R* when the S_R chiral group is used (*e.g.*, (S_R)-**10** gives (1*R*)-(S_R)-**14**), whereas diastereofacial selectivity is inverted when the S_S chiral group is employed (e.g., (1*S*)-(S_S)-**14** is formed from (S_S)-**10**).

These results are in opposition with those of Chong et al.,[23] who reported the addition of Bu_3SnLi to simple *tert*-butanesulfinylimines, the only literature precedent existing on this kind of reaction: the stereochemistry of their addition was consistent with a chelation-controlled transition state. Our results however appear to involve an open, non-chelation model such as that suggested by Plobeck et al., for the addition of conventional lithium reagents to *tert*-butanesulfinylimines in THF.[24]

In this model, it is likely that, in the lithiated species produced by excess tributylstannyllithium used to generate the reactive imine by ring opening, the lithium ion coordinates to the liberated alkoxide (**15**). The tin-lithium reagent then coordinates to the lone pair of the sulfoxide moiety and the addition proceeds through an acyclic transition state of type **A**, following the Felkin−Ahn rules (Scheme 3).[25]

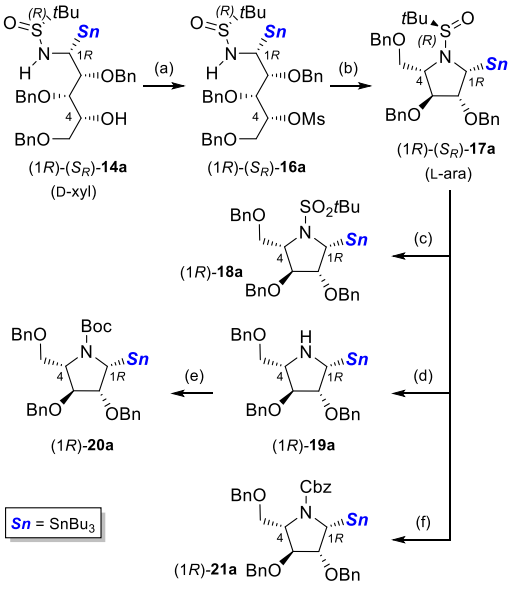


Scheme 3. Stereochemical model for the addition of Bu_3SnLi to compounds **10a**–**e**.

The high stereoselectivity of the addition is quite remarkable and it is important to note that the potential chelating effect of the sugar functions does not divert the stereochemical mechanism away from the sulfinyl group, thus providing high stereocontrol in a tunable mode.

The lack of reactivity of a single glycosylamine, namely pyranosylamine (S_S)-**10d** is surprising and may be rationalized. In our DFT calculations on the addition of $[M]CF_2P(O)(OEt)_2$ (M = Li, MgX) to compounds of type **10**, we assumed that internal complexation of the lithium ion by either the open-chain imine transient entity (**15**) and/or the various ether protecting groups would be entropically favored over solvent complexation.[12g] In the (S_S)-L-lyxopyranosylamine series, these interactions and possibly stereoelectronic factors might prevent opening of the metallated *N*-*tert*-butanesulfinyl-*N*-glycoside intermediate **13** (Scheme 3) to a reactive imine and therefore shut down the addition reaction.

Cyclization Reactions. As illustrated in Scheme 4, it was then possible to mesylate compound (1*R*)-(S_R)-**14a** (step a) through general procedure D-1 (**G.P. D-1**). As a bonus, the corresponding mesylated stannylsulfinamide (1*R*)-(S_R)-**16a** proved to be quite stable, surviving chromatography on silica gel and it was isolated in excellent yield (90%).



Scheme 4. Synthesis of anomeric iminosugar-1-tributylstannanes (1*R*)-(S_R)-**17a** and (1*R*)-**18**–**21a**. **Reagents and conditions**: (a) Et_3N (2.2 equiv.), MsCl (2.0 equiv.), CH_2Cl_2, MS (4Å), 20 °C, 1 h, 90% (**G.P. D-1**); (b) NaH (3.0 equiv.), THF, 20 °C, 30 min, 90% (**G.P. E-1**); (c) *m*-CPBA (ca. 1.5 equiv.), CH_2Cl_2, 0 °C, 1 h, 99% (**G.P. C-2**); (d) *(i)* AcCl (6.4 equiv.), MeOH, 20 °C, 30 min, *(ii)* Amberlite® IRA 400 (OH^-), 77%; (e) Et_3N (2.2 equiv.), Boc_2O (2.0 equiv.), DMAP (cat.), CH_3CN, 0 °C to rt, 30 min, 88% (55%, step d–e in a single pot); (f) step d, then Et_3N (2.2 equiv.), CbzCl (2.0 equiv.), CH_2Cl_2, 0 °C to rt, 1 h, 77%.

Our first attempts at cyclization using bulky bases such as *t*-BuOK or Et_3N in THF failed. Alternatively cleavage of the sulfinyl group (HCl in MeOH) and subsequent ring closure promoted by a basic resin was also unsuccessful.[12g],[13],[26] The problem could be solved using an excess of sodium hydride (NaH, 3 equiv.) in THF at room temperature. From D-*xylo* (1*R*)-(S_R)-**16a**, the L-*arabino* (1*R*)-(S_R)-**17a** was obtained in good yield (90%, step b, **G.P E-1**), resulting from an inversion of the configuration at C-4 upon ring closure. Oxidation of the labile sulfinyl group into a robust sulfonylamide was next carried

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out and compound (1*R*)-**18a** was obtained in almost quantitative yield (99%, step c) through general procedure C-2 (**G.P. C-2**).

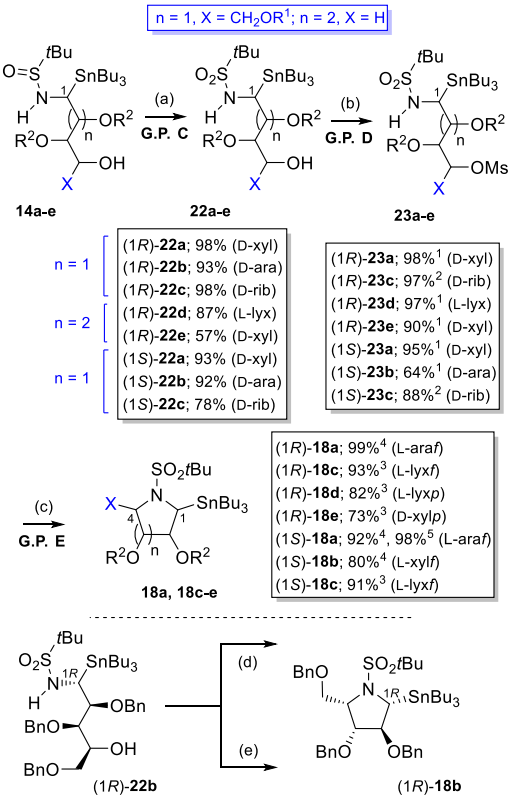
One of the advantages of the *tert*-butanesulfinyl auxiliary is that it can be easily removed by treatment with an acid to provide free amines.[27] Unlike Chong's investigations on α-sulfinylaminoorganostannanes,[23] we were able to remove the sulfinyl group in our sugar scaffold under acidic conditions (HCl, MeOH) without any noticeable degradation. Subsequent neutralization using a basic ion-exchange resin furnished (1*R*)-**19a** in good yield (77%, step d).

Compound (1*R*)-**19a** was thereafter reacted with Boc_2O in presence of DMAP in CH_3CN (step e) to provide the *N*-Boc derivative (1*R*)-**20a** (88%). Importantly, the formation of (1*R*)-**20a** could also be effectively promoted from (1*R*)-(S_R)-**17a**, carrying step d and e in a single pot, albeit with a slight decrease of the overall efficacy (55% *vs.* 68% overall). The *N*-Cbz protected iminosugar (1*R*)-**21a** was prepared similarly (see step f) and it was observed to exist as a 6:4 mixture of rotamers (77%).

the *tert*-butanesulfonyl (Bus) group was previously shown to be a useful protecting group, which could be used in Stille-type coupling reaction partners without notable degradation.[28] In addition, it can be removed under acidic conditions,[29] as shown in aminoacid chemistry,[30] and can be prepared from the *tert*-butanesulfinyl group via simple *m*-CPBA oxidation.[27],[29] It was thus selected as key protecting group for the rest of the study

As described in Scheme 5, oxidation of aminoalditol derivatives **14a**–**e** was thus performed with *m*-CPBA (**G.P. C**) to give sulfonamides **22a**–**c** (in D-*xylo*, D-*arabino* and D-*ribo* series and with (1*R*)- and (1*S*)- configurations) in good to excellent yields (78–98%). In the case of the (1*R*)-L-*lyxo* and D-*xylo* derivatives, both featuring a primary hydroxyl group, compound (1*R*)-**22d** was obtained in good yield (87%), and (1*R*)-**22e** was formed in a non-optimized 57% yield. As expected, no erosion of the stereochemistry at C-1 could be detected. In the D-*xylo*, D-*arabino* and L-*lyxo* series, the same mesylation procedure as the one reported in Scheme 4 was then utilized to form compounds **23a**–**b**, (1*R*)-**23d** and (1*R*)-**23e** (**G.P. D-1**)).

Surprisingly, for the D-*ribo* structure, the *tert*-butyldiphenylsilyl-protected pyrrole derivative **24** was isolated as a major by-product (see the Supporting Information (SI)). However, mesylation could be readily accomplished through **G.P. D-2** (DMAP (cat.), excess MsCl) in pyridine to afford (1*R*)-**23c** and (1*S*)-**23c** in 97% and 88% yield respectively. Cyclisation of mesylates **23a**–**23e** could then be efficiently performed under the conditions of **G.P.E**, using NaH at room temperature or at 70 °C, and in some cases under μW irradiation (Scheme 5). Alternatively, cyclisation could also be performed under Mitsunobu conditions (*e.g.* (1*R*)-**22b** gave (1*R*)-**18b** in moderate yield (66%), step e).



Scheme 5. Synthesis of stereochemically-defined pseudo anomeric iminosugar stannanes. **Reagents and conditions**: (a) *m*-CPBA (1.1 equiv.), CH_2Cl_2, 0 °C (to rt), 0.5–2 h (**G.P. C**); (b) Et_3N (2.2–4.2 equiv.), MsCl (2.0–4.0 equiv.), CH_2Cl_2, MS (4Å), rt, 0.5–1 h (**G.P. D-1**)[1] or DMAP (cat.), MsCl (4.0 equiv.), Pyr (solvent), 0 °C to rt, 6–12 h (**G.P. D-2**)[2]; (c) NaH (2.0–6.0 equiv.), THF, rt (**G.P. E-1**)[3], 70 °C (**G.P. E-2**)[4], 70 °C, μW (**G.P. E-3**)[5], 3–16 h; (d) **G.P D-1** and **G.P. E-2** in a single pot, 60%; (e) PPh_3 (1.1 equiv.), DEAD (1.1 equiv.), THF, –20 °C to rt, 1 h, 66%.

Gratifyingly, we found that cyclic, but also linear iminosugar stannanes **18a**–**e** and **22a**–**e** are chemically and configurationally stable. They can be purified by chromatography on silica gel, are stable against air and moisture, and retain anomeric configuration when exposed to light or when heated at 110 °C for several days. Furthermore, they can be stored at 0 °C under argon atmosphere for at least two years without erosion of the chirality at C-1.

Configuration Determination and *J*(C−Sn) as diagnostics. As summarized below in Fig. 2, the pseudo anomeric configuration of pyrrolidinyl iminosugar 1-stannanes was established based on the analysis of 2D nOesy spectra. The 1*R* configuration of L-arabinitols **17**–**21a** could be ascribed thanks to

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distinct nOe contacts between protons H-1 and H-4 in compounds (1*R*)-**18a** and (1*R*)-**19a**.

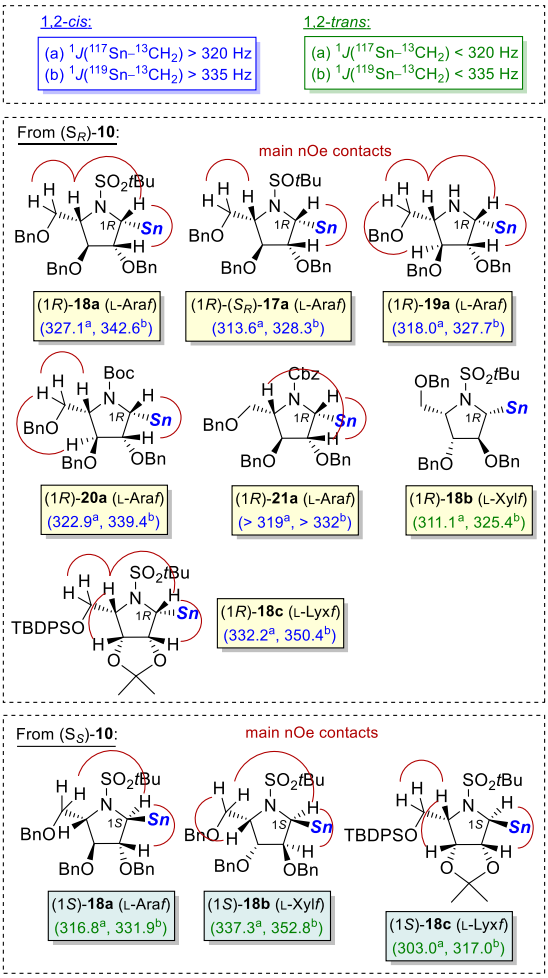

Figure 2. List of 1-stannyl pyrrolidinyl iminosugars, main nOe contacts and ^1J(Sn–C) values.

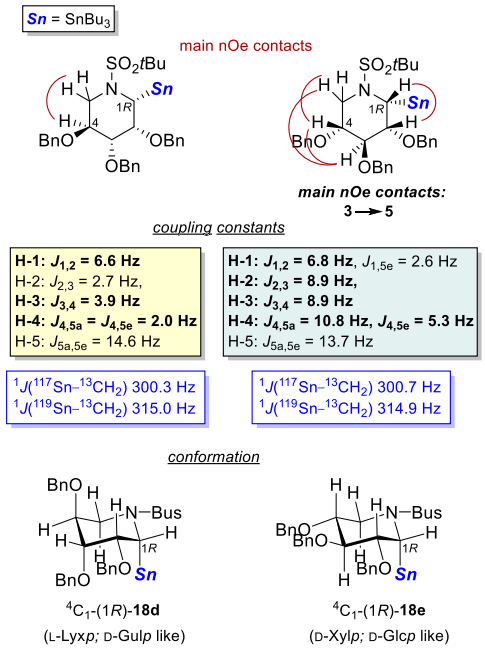

Figure 3. List of piperidinyl iminosugar 1-stannanes, main nOe contacts, coupling constants, conformations and ^1J(Sn–^{13}C-1) values.

The same relations were observed for L-arabinitol (1*R*)-**18c**. Regarding the L-xyl*f* series, the 1*S* configuration of **18b** could in turn, be attributed owing to the main nOe contacts between protons H-1 and H-5.

In the piperidine series, the 1*R* configuration and $^4C_1$ conformational arrangement of imino-L-lyxitol (1*R*)-**18d** and imino-D-xylitol (1*R*)-**18e** were unambiguously settled according to the value of the vicinal H,H-coupling constants between ring protons (Fig. 3). Noteworthy, both compounds exist in the conformation in which the stannyl group is axial, in spite of its bulkiness. This is consistent with the conformational properties of N-sulfonylated piperidines carrying a substituent on the alpha-carbon. For steric reasons ($A_{1,3}$ – type strain), the substituent adopts preferentially an axial position.[31]

The ^{13}C NMR data of the 1-stannylated iminosugars (see SI and Fig. 2 and Fig. 3), were then analyzed. Interestingly, they revealed a trend in the heteronuclear coupling constants between the ^{13}C-1 nucleus in the butyl chain and the anomeric ^{117}Sn/^{119}Sn nuclei.

As a rule, for the **N-sulfonylated and N-acylated** 1-C-stannylated iminoalditols with a pyrrolidine structure, in which the tin group is in a *cis* relationship with the group at C-2, the $^1J(^{117}Sn–^{13}C)$ coupling constants are above 320 Hz (335 Hz for $^1J(^{119}Sn–^{13}C)$). In contrast, in the C-1 stannanes in which the tin group is in a 1,2-*trans* orientation, these coupling constants are below these cutoffs. This trend however was not observed for pyrrolidines carrying a N-sulfinyl or N-H group ((1*R*)-(S_R)-**17a** and (1*R*)-**19a**).

For the six-membered piperidine series, we made observations similar to those reported for 1-tributystannyl hexopyranoses: the values of $^1J(^{117}Sn–^{13}C)$, when the tin group occupies the axial position in a $^4C_1$ pyranose conformer are smaller than 305 Hz (319 Hz for $^1J(^{119}Sn–^{13}C)$).[20e] Compounds (1*R*)-**18d** and (1*R*)-**18e** follow the rule, thus widening further this prediction tool.

At this point, we were also intrigued to see whether we could extend the tool and predict the C-1 configuration at an earlier stage of the synthesis. No such correlations emerged in compounds **14**, **22** and **23**, even when pushing the heteronuclear spin–spin coupling analysis through the whole *n*-butyl chain. Early investigations from Vasella on 1-stannylated glycosides have shown that ^1J(Sn–C) between the anomeric carbon and the tin substituent could be of interest in structural assignments.[32] Although no

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relationship between ^{1}J(Sn–^{13}C-1) values and the configuration at C-1 could be found in the N-sulfinylated 1-stannyl iminoalditols **14**, we were delighted to identify a correlation for the series of N-sulfonylated compounds **22**.

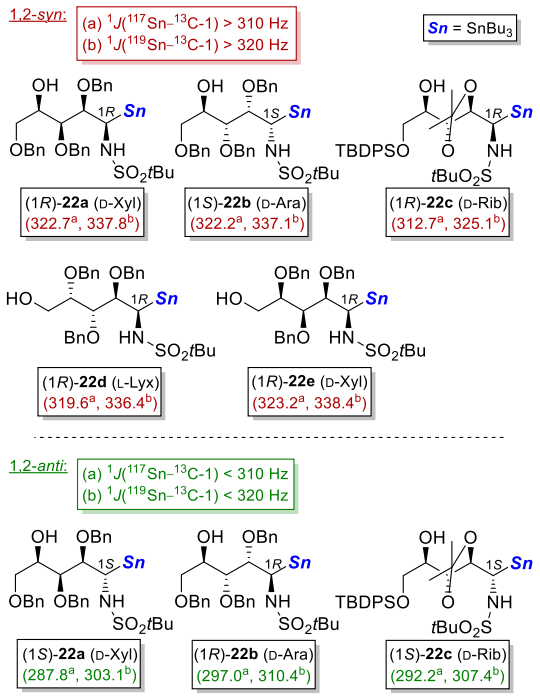


Figure 4. List of N-sulfonylated aminoalditol 1-stannanes **22**, and ^{1}J(Sn–^{13}C-1) trends.

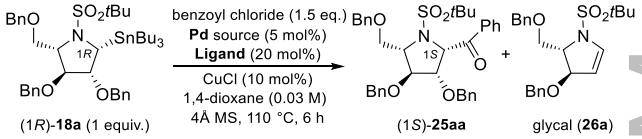
As a rule, for the iminoalditols of type **22**, in which the amino group is in a 1,2-*syn* relationship with the alkoxy group at C-2, the $^{1}J(^{117}Sn–^{13}C)$ coupling constants are above 310 Hz (320 Hz for $^{1}J(^{119}Sn–^{13}C)$), whereas the C-1 stannylated iminoalditols with a 1,2-*anti* orientation have ^{1}J(Sn–^{13}C) coupling constants below these cutoffs (see Fig. 4 and SI). Thus, it appears that the magnitude of this coupling constant is influenced by the configuration at the Sn-bearing carbon when steric effects are maximal and constitute a useful tool for configuration assignment.

Migita–Kosugi–Stille Reaction Development. We next decided to investigate the Pd-catalyzed Migita–Kosugi–Stille cross-coupling reactions of the anomeric iminosugar stannanes: this reaction might unlock the synthesis of a diversity of iminoglycoside analogs, as suggested by the stereospecific Pd-mediated coupling reactions of chiral C(sp^3) stannanes with aryl(aroyl) or alkyl(alkanoyl) halides.[20],[33]

Since the pioneering work of Eaborn,[34] Migita and Kosugi,[35] in the 1970's and the extensive mechanistic studies by Stille,[36] and others this reaction has progressively become one of the cornerstones in Pd-catalyzed C–C bond formation.[33],[37] It is a mild process that tolerates a wide variety of functional groups, and which is frequently used in the synthesis of molecules of high complexity. Furthermore, organostannanes are relatively insensitive to moisture and oxygen, allowing for harsher reaction conditions.

In the sugar series, anomeric glycosylstannanes have been described by Sinaÿ,[38] Kessler,[39] and Vasella,[32] and their first cross-coupling reactions with benzoyl chloride and a range of chloro(thio)carbonates were investigated by Falck.[40] The D-glucopyranosyl *C*-glycosides of interest were obtained in low to moderate yields, using excess electrophile, and with complete retention of configuration at the anomeric center. Walczak et al. recently demonstrated the scope and synthetic utility of the glycosylstannanes through coupling with aromatic iodides, diaryliodonium triflates and various thio- and selenoesters and generated an impressive array of mono- and oligo-saccharide-1-*C*-glycosides featuring free or diversely protected hydroxyl groups.[20] However, no example of such reaction has been reported so far from iminosugars.

Table 2. Stille–Migita reaction optimization.[a)]



Entry	Catalyst	Ligand	(1*S*)-**25aa** (%)[b)]	**26a** (%)[b)]
1	$Pd_2(dba)_3$	DPPE[c)]	7[i)]	N.D.[j)]
2	$Pd_2(dba)_3$	DPPF[d)]	16[i)]	N.D.[j)]
3	$Pd_2(dba)_3$	P(*o*-tol)$_3$	7[i)]	N.D.[j)]
4	$Pd_2(dba)_3$	P(Cy)$_3$[e)]	15[i)]	N.D.[j)]
5	$Pd_2(dba)_3$	P(Cy)$_3$[e)]	35	N.D.[j)]
6	$Pd_2(dba)_3$	PPh_3	33	N.D.[j)]
7	$Pd_2(dba)_3$	*R*-(+)-BINAP[f)]	0	N.D.[j)]
8	$Pd(PPh_3)_4$	–	31	N.D.[j)]
9	$Pd(PPh_3)_2Cl_2$	–	46	38
10	$Pd_2(dba)_3$	P(2-furyl)$_3$	36	N.D.[j)]
11	$Pd_2(dba)_3$	$AsPh_3$	18	N.D.[j)]
12	$Pd_2(dba)_3$	TTMPP[g)]	22	N.D.[j)]
13	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	40	N.D.[j)]
14	$Pd_2(dba)_3$	JackiePhos[h)]	51	3

[a)]**Typical reaction conditions**: Ar atmosphere, compound (1*R*)-**18a** (50 mg, 61.5 µmol, 1 equiv.), benzoyl chloride (1.5 equiv.), MS (4Å) (100 mg), $Pd_2(dba)_3$ (5 mol %), ligand (20 mol %), CuCl (10 mol %), heating at 110 °C for 6 h in 1,4-dioxane (0.03 M). [b)]Isolated yields (column chromatography). [c)]DPPE: bis(diphenylphosphino)ethane. [d)]DPPF: 1,1'-bis(diphenylphosphino)ferrocene. [e)]P(Cy)$_3$:

tricyclohexylphosphine. [f]BINAP: bis(diphenylphosphino)-1,1′-binaphthyl. [g]TTMPP: tris(2,4,6-trimethoxyphenyl)phosphine. [h]JackiePhos: 2-{Bis[3,5-bis(trifluoromethyl)phenyl]phosphino}-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl. [i]The reaction mixture was heated for 16 h. [j]N.D: not determined.

Based on the single literature precedent by Chong et al. on the Stille coupling of stereochemically defined α-sulfonamido-organostannanes,[28] and the aforementioned informations, optimization of the conditions for the Stille coupling of our iminoglycosyl stannanes with various electrophiles was thus started (Table 2). Robust L-*arabino* stannane (1*R*)-**18a** was selected as model substrate and the reaction was carried out with $Pd_2(dba)_3$ (5 mol%), 1,2-bis(diphenylphosphino)ethane (DPPE), copper(I)chloride (10 mol %) and benzoyl chloride (1.5 equiv.) in 1,4-dioxane for 16 h at 110 °C. A 7% yield of imino-*C*-glycoside **25aa** was obtained (entry 1).

Palladium sources, as well as ligand variation was next envisaged with a careful choice of the phosphine, presenting various steric and electronic properties (entries 1−14).[41]

JackiePhos is a biaryl diphenylphosphine ligand, initially reported by Buchwald for the Pd-catalyzed amidations of aryl halides.[42] It was recently shown by Walczak to be quite efficient for the cross-coupling reactions of anomeric stannanes.[20] Interestingly, with this ligand, the iminoarabinitol-*C*-glycoside **25aa** was obtained in a respectable yield of 51%, with trace amounts (3%) of the elimination product **26a** (entry 14).

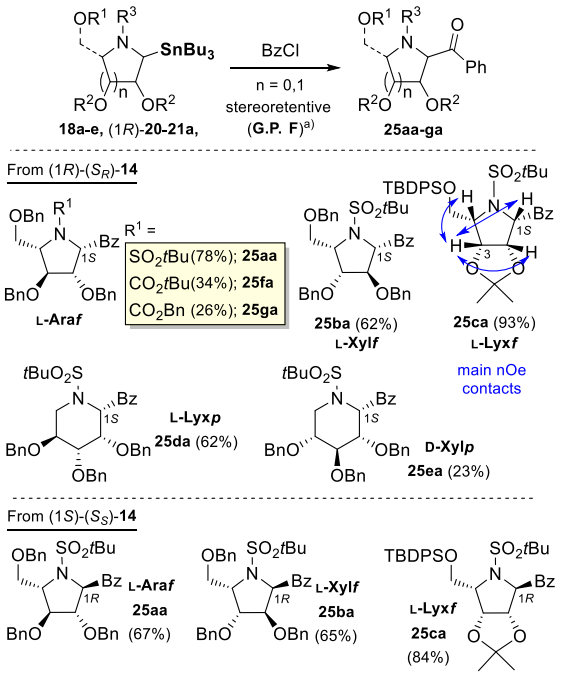
To fine-tune the reaction conditions solvent, additives, palladium and copper sources, stoichiometry of reagents, and reaction temperature were then screened (for details, see the SI). Noteworthy, based on the literature precedent that fluoride facilitates the Stille reaction,[43] KF was selected as an additive for the optimization studies, but no beneficial effect could be observed. Given the accelerating role of Cu salts, additives such as CuCl (0.05, 0.1, 1, 2, 3 equiv.), vs. CuI, CuBr or CuCN in combination with $Pd_2(dba)_3$ as precatalyst were also studied. Of note, while CuCN and CuBr generated a yield comparable to CuCl, almost no conversion could be detected with CuI. The yield of the Stille reaction may also be improved by the use of several equivalents of the Cu(I) salt, but in this transformation, as low as 5−10 mol % of CuCl could be used without degradation of the reaction yield. It is important to mention that increasing the amount of CuCl gave rise to increased quantity of elimination product **26a**.

Likewise, in polar solvents (CH_3CN, NMP, DMF, DMSO, DMA) the 1-substituted iminoarabinitol derivative **25aa** was not obtained, the reaction providing again mainly by-product **26a** (19% in DMA and 72% in DMSO). Aromatic solvents may suppress glycal formation,[20e] but in our case, the use of PhMe resulted in a lower yield of **25aa** (36%) and an increase of **26a** (18%). Other inorganic additives ($ZnCl_2$, $FeCl_3$, LiCl) were inefficient (typically 0% yield).

It is worth noting that all these results are consistent with a mechanism by a "closed" pathway (vs. the "open" pathway that leads to stereoinversion) involving a four-membered cyclic transition state and **complete retention of the configuration**. This also implies probable dissociation of one phosphine ligand prior to transmetalation. In addition, although no conversion was noted when the coupling reaction was performed without CuCl or $Pd_2(dba)_3$, at this point it is difficult to determine whether copper participates with palladium in a bimetallic catalytic cycle or if it is only Pd catalysis and Cu(I) acting as a ligand scavenger.[33],[44]

Overall the optimized conditions were the following: stannane (1*R*)-**18a** (1 or 2 equiv.), benzoyl chloride (1.5 or 1 equiv.), MS (4Å), $Pd_2(dba)_3$ (2.5 mol %), ligand (10 mol %), copper(I) chloride (10 mol %), heating at 110 °C for 6 h in 1,4-dioxane (see general procedure F, **G.P. F**), trace amounts (6%) of the elimination product being obtained.

Migita–Kosugi–Stille Reaction Scope. The optimized iminoglycosyl-benzoyl cross-coupling conditions were thereafter tested in reactions with various iminoalditol derivatives **18a**−**e**, (1*R*)-**20a** and (1*R*)-**21a**, (Scheme 6).

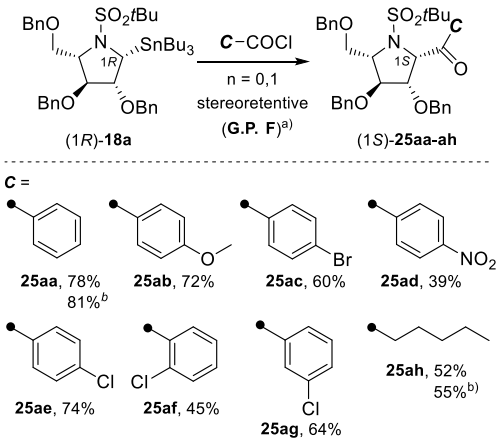


Scheme 6. Scope of C-glycosylation with anomeric iminoglycosyl tributylstannanes. [a]**Reaction Conditions**: Ar atmosphere, BzCl (1.0 equiv.), imino glycosyl stannane (2.0 equiv.), $Pd_2(dba)_3$ (2.5 mol %), JackiePhos (10 mol%), CuCl (10 mol %), 1,4-dioxane (0.03 M), MS (4Å), 110 °C, 6 h.

Pleasingly, we found that the general set of conditions is operational for the whole series of N-sulfonylated imino-L-*arabino*, L-*xylo* and L-*lyxo* alditols derivatives, giving rise to the corresponding C-glycosides in moderate to good yields (62−93%) and stereospecifically. The 1*S* configuration of **25ca** could be assigned thanks to distinct nOe contacts between protons H-1 and H-3. One notes that lower yields of the coupling products were obtained from D-*xylo* piperidine (1*R*)-**18e** (to give (1*S*)-**25ea**, 23% *e.g.*, 60% brsm) and from the two L-*arabino* pyrrolidines (1*R*)-**20** and **21a** ((1*S*)-**25fa** and (1*S*)-**25ga** formed in 34% and 26% yield respectively), which are not protected with a *tert*-butanesulfonyl group. For compounds **25fa** and **25ga**, the low yields can be explained by the formation of some deprotected products and some degradation.

Moreover, in case of the chemically stable imino-D-xylitol derivative (1*R*)-**25ea**, 24% of iminoglycal of type **26** (e.g., **26e**, see SI) was isolated along with 53% of unreacted 1-stannyl iminosugar (1*R*)-**18e**. For this particular substrate, the search for better ligands appear to be mandatory.

Importantly, N-sulfinylated compound (1*R*)-(S_R)-**17a** was also tested in the Pd-catalyzed cross-coupling, but total decomposition was observed. The scope of the reaction was next further explored using anomeric stannane (1*R*)-**18a** and a range of substituted aroyl chlorides and an *n*-alkanoyl reagent (Scheme 7).



Scheme 7. Scope of C-glycosylation with *n*-alkanoyl and aroyl chlorides. [a]**Reaction Conditions**: Ar atmosphere, chloride reagent (1.0 equiv.), imino glycosyl stannane (2.0 equiv.), $Pd_2(dba)_3$ (2.5 mol %), JackiePhos (10 mol%), CuCl (10 mol %), 1,4-dioxane (0.03 M), MS (4Å), 110 °C, 6 h. [b]Yields of coupling product through subsequent preparation of the chloride reagents.

Gratifyingly, the yield of the coupling was quite good for most products. The performance of the acylation reactions did not seem to be correlated with the electronic properties of the aroyl chloride reagents, except with a *p*-NO_2 group. However, sterics may be more important as it is observed that the yields of the reactions with *p*-Cl-, *m*-Cl- and *o*-Cl-benzoyl chloride decrease in this order (72%, 64% and 45% for **25ae**, **25ag** and **25af** resp.). Notably, with hexanoyl chloride, a significant 52% yield of **25ah** was achieved. Moreover, it is worth mentioning that the synthesis of the acyl chlorides from carboxylic acids (general procedure G, **G.P. G**), followed by cross-coupling with the anomeric iminosugar stannanes afforded **25aa** and **25ah** with an efficacy similar to commercial chlorides. These results thus open opportunities to incorporate acyl groups of greater complexity, such as for instance groups derived from amino acids or peptides for the synthesis of glycosyl aminoacids and glycopeptide mimics.[45] Overall, it was demonstrated that the stereospecificity of the cross-coupling reactions is linked exclusively to the C-1 configuration of both iminoglycosyl stannanes anomers, with retention of the 'anomeric' configuration; furthermore, the problem of competitive β elimination of the oxygen-based groups at C2 was addressed and the formation of unsaturated by-products **26** minimized. No epimerization of the chiral centers was noted.

Further data from literature, in particular from the work of Behr and Defoin on the configurational and conformational analysis of five–membered *N*-acyl-iminosugars, fully support our configurational assignments: it was shown that iminofuranosyl scaffolds tend to exhibit characteristic $J(2,3)$ and $J(4,5)$ coupling values for *cis*-relationships (J > 5.0 Hz) and J < 3 Hz for trans ones.[46] As regards the stannyl iminosugar derivatives, this general trend was observed for all our pyrrolidine related to pentofuranoses (see SI): $J(1,2)$ couplings when H-1 and H-2 are in *cis*-relationship were in the range of 4.3 to 6.0 Hz, whereas the coupling between H-1 and H-2 in 1,2-*trans* isomers is very small with H-1 appearing as a broad singlet. From the nOe analysis of L-lyxo derivative (1*S*)-**25ca** and ^{1}H NMR investigations on compounds of type **25**, it seems likely that the rule is conserved in the aroyl and hexanoyl imino-*C*-glycoside series (7.1 < J < 8.7 Hz for $J(1,2)$-*cis* and broad singlet for H-1 in 1,2-*trans* derivatives, see SI). As a result, based on literature precedents and on our investigations, anomeric stannanes undergo highly specific cross-coupling

reactions with *n*-alkanoyl and aroyl chlorides through a **stereoretentive** mechanism.

Conclusion

In conclusion, we have developed an efficient approach for the preparation of 1-C-stannylated iminosugar anomers and their utilization in Stille cross-coupling reactions. The methodology demonstrated a good substrate scope and protecting group tolerance and has the great advantage of being tunable, i.e., the pseudoanomeric configuration of the 1-C-stannyl iminosugars and of the resulting 1-C-acylated iminosugar-*C*-glycosides can be chosen by selecting the configuration of the sulfinyl group in the starting *N*-*tert*-butanesulfinyl glycosylamines.

The iminoglycosyl stannanes were prepared by way of the stereospecific addition of tributylstannyllithium to (S_R)- or (S_S)-*N*-*tert*-butanesulfinyl glycosylamines, followed by an oxidation and/or a mesylation-cyclization strategy. From *J*(C−Sn) data, a practical tool for the assessment of the chirality at C-1 was established. As a rule, (S_S)-glycosylamines [(S_S)-**10**] gave (1*S*)-configured stannylated iminosugar derivatives and (S_R)-glycosylamine [(S_R)-**10**], the (1*R*)-stereoisomer respectively. The iminosugar-derived organostannanes were then efficiently cross-coupled through Migita–Kosugi–Stille reactions with a range of variously substituted aroyl chlorides and an alkanoyl chloride, in a stereoretentive C–C bond forming process. Such compounds are desirable advanced intermediates for the synthesis of a diversity of glycoside mimics which could act as inhibitors of carbohydrate-processing enzymes. The generality of the Stille coupling was investigated on 12 1-C-stannyl anomers, exhibiting furanose-like and pyranose-like skeletons. Eighteen examples of coupling products from the various stannylated iminosaccharides were obtained in moderate to excellent yields. Under the optimized coupling conditions, the β-elimination pathway was suppressed using a bulky phosphine ligand (JackiePhos) and a high stereoselectivity of the process was attained. Experimental evidence support a mechanistic rationale according to which the anomeric stannanes undergo stereoretentive cross-coupling reaction by way of a four-membered cyclic transition state. Taken together, these methodologies represent original and powerful strategies providing iminosugar-*C*-glycosides through an effective and hitherto unprecedented transformation. This synthetic tool allows for late stage coupling of iminosugar moieties with various aglycones and thus provides a means of performing the synthesis of imino-C-glycosyl compounds in a diversity-oriented approach. Further extension of the coupling reaction to other electrophiles such as aryl halides or heterocyclic halides should significantly expand the scope of the process and is currently under investigations.

Experimental Section

General Procedures.

G.P. A-1. A 10–20 mL Biotage® microwave reaction vial, under argon atmosphere, was charged with sugar hemiacetal protected by OBn groups (1.0 equiv.), 4 Å activated molecular sieves (ca. 0.4 g per mmol of substrate), (*R*)-(+)- or (*S*)-(−)-2-methyl-2-propanesulfinamide (2.0 equiv.) and a microwave magnetic stir bar. Dry toluene was inserted and the mixture was stirred during 10 min at room temperature (rt, ca. 20 °C). Titanium(IV) ethoxide ($Ti(OEt)_4$, 1.5 equiv.) was then added, the vial was sealed and the reaction mixture was heated at 110 °C for 1.5−2.5 h under microwave irradiation. After cooling to room temperature, the cap was removed, the brown solution was diluted (CH_2Cl_2/brine 3:1, v/v) and the mixture was vigorously stirred for 10 min at 20 °C. Next, molecular sieves and the precipitate were filtered over celite® and the cake was rinsed with CH_2Cl_2. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. Combined organic layers were dried over $MgSO_4$, filtered through a cotton plug and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2) to provide the related (S_R)- or (S_S)- *N*-*tert*-butanesulfinyl glycosylamine (e.g., **10a**–**b** and **10d**–**e**) in good yield (70–96%).

G.P. A-2. An oven dried single-necked round-bottomed flask equipped with a reflux condenser and an argon inlet was charged with 5-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-α,β-D-ribofuranose **11c** (1.0 equiv.), (*R*)-(+)- or (*S*)-(−)-2-methyl-2-propanesulfinamide (2 equiv.), Cs_2CO_3 (1.5 equiv.), 4 Å activated MS (ca. 0.8 g per mmol of substrate), a magnetic stir bar, and anhydrous dichloroethane and the reaction mixture was stirred for 36−48 h at 70 °C. The brown suspension was then filtered through a cotton plug, the molecular sieves were rinsed (CH_2Cl_2) and the filtrate was washed with brine. The aqueous phase was next extracted, thrice with CH_2Cl_2. Afterwards, the combined organic layers were dried over $MgSO_4$, filtered through a cotton plug and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, petroleum ether/EtOAc, eluting with 1 vol % Et_3N) to provide (S_R)- and (S_S)-**10c** as colorless oils (90 and 85% respectively).

G.P. B. A single-necked round-bottomed flask under argon atmosphere was charged with diisopropylamine (3.5–4.0 equiv.) and dry THF. The solution was cooled to 0 °C (ice−water bath) and *n*-BuLi (2.5 M hexanes, 3.5–4.0 equiv.) was added dropwise. The resulting light yellow cloudy solution was stirred for 30 min, after which time it was cooled to −78 °C (dry ice−acetone) and tributyltin hydride (3.5−4.0 equiv.) was added (dropwise addition) (flask A). The mixture was stirred for 15 min at −78 °C. In parallel, another single-necked round-bottomed flask under argon atmosphere was charged with *tert*-butanesulfinyl glycosylamine ((S_R)- or (S_S)-**10a**−**e**, 1.0 equiv.) and dry THF was added (solution B). Solution B was added to flask A (dropwise addition with a syringe) at −78 °C and the reaction mixture was allowed to reach a given temperature over 1.5−6 h. Aqueous NH_4Cl was then added, the organic layer was diluted (EtOAc) and the aqueous phase was

extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through a cotton plug, and the solvents were removed *in vacuo*. The crude product (dr > 98:2) was purified by SiO_2−column chromatography to provide the tributylstannyl aminoalditol compound (e.g., (1*R*)-(S_R)- or (1*S*)-(S_R)-**14a**–**e**) as a single diastereomer (71–89%).

G.P. C-1. A single-necked round-bottomed flask under argon atmosphere was charged with open-chain stannane ((1*R*)-(S_R)- or (1*S*)-(S_R)-**14a**–**e**, 1.0 equiv.), a magnetic stir bar and anhydrous CH_2Cl_2. The reaction vessel was cooled-down to 0 °C (ice−water bath) and pure *meta*-chloroperoxybenzoic acid (1.1 equiv.) was added. The reaction mixture was stirred at 0 °C and it was allowed to reach room temperature over 1 h. Afterwards, when the reaction was complete, a sat. aq. solution of $NaHCO_3$ was added, followed by CH_2Cl_2 and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through a cotton plug and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to afford the oxidized product ((1*R*)- or (1*S*)-**22a**–**e**) in good yield.

G.P. C-2. Alternatively, *m*- CPBA (≤ 77 wt%) was used as received and the reaction mixture was stirred at 0 °C (ice−water bath). The progress of the reaction was monitored by TLC analysis of the crude mixture, and extra *m*- CPBA added if needed. When the reaction was complete (0.5−2 h), a sat. aq. solution of $Na_2S_2O_3$ was added, followed by CH_2Cl_2 and the aqueous phase was extracted thrice with CH_2Cl_2. The combined organic phases were washed sequentially with sat. aq. $Na_2S_2O_3$ solution, sat. aq. $NaHCO_3$ solution, brine and then dried over $MgSO_4$. After filtration of the organic phase through a cotton plug and solvent evaporation, the residue was purified by silica gel column chromatography.

G.P. D-1. A single-necked flask under argon atmosphere was charged with related aminoalditol compound (1.0 equiv.), anhydrous CH_2Cl_2 and a magnetic stir bar. Et_3N (2.2–4.2 equiv.) was added and the suspension mixture was stirred during 10 min at room temperature (ca. 20 °C). Then, MsCl (2.0–4.0 equiv.) was inserted and the reaction mixture was stirred at 20 °C until no more starting material was present (TLC analysis, 0.5–1 h). Next, the organic solution was washed with brine and the aqueous phase was extracted twice with CH_2Cl_2. Combined organic layers were dried over $MgSO_4$, filtered through a cotton plug and evaporated under reduced pressure. The mesylated intermediate of type **23** or (1*R*)-(S_R)-**16a** was obtained in good yield (64–98%) after purification through column chromatography (SiO_2).

G.P. D-2. A single-necked flask under argon atmosphere was charged with D-ribitol derivative (1*R*)-**22c** or (1*S*)-**22c** (1.0 equiv.), dry CH_2Cl_2 and a magnetic stir bar. The content was cooled down to 0 °C (ice–water bath) and a catalytic amount of 4-dimethylaminopyridine (DMAP, 1–2 mol%), followed by MsCl (4.0 equiv.), and anhydrous pyridine (15 mL/mmol of substrate) were added. The reaction mixture was then allowed to stir at 0 °C and reach room temperature over 6–12 h. The mixture was diluted (CH_2Cl_2) and the organic phase was washed with aq. HCl (1 M). Afterwards, the aqueous phase was extracted with CH_2Cl_2 (3 ×) and the combined organic layers were washed subsequently with an aq. sat. solution of $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered through a cotton plug and the solvents were evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the product ((1*R*)-**23c** or (1*S*)-**23c**) in excellent yield (88 and 97% respectively).

G.P. E-1. A single-necked flask under argon atmosphere was charged with related (1*R*)- or (1*S*)-mesylated 1-tributylstannyl aminoalditol of type **23** or (1*R*)-(S_R)-**16a** (1.0 equiv.), anhydrous THF, a magnetic stir bar and NaH (60% dispersion in mineral oil, 2.0–3.0 equiv.) and the reaction mixture was stirred at room temperature for a given reaction time (0.5–16 h). Next, the content was concentrated by rotary evaporation (≤ 20 °C) and the mixture was diluted with CH_2Cl_2 or EtOAc. The organic phase was successively washed with an aq. solution of HCl (1 M) at 0 °C, a sat. aq. solution of $NaHCO_3$ and brine (1 ×). The organic phase was then dried over $MgSO_4$, filtered through a cotton plug and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2) to give the corresponding enantiopure 1-stannyl-iminosugar derivative of type **18** or (1*R*)-(S_R)-**17a** in good yield (73–93%).

G.P. E-2. A single-necked flask under argon atmosphere was charged with related (1*R*)- or (1*S*)-mesylated 1-tributylstannyl aminoalditol of type **23** (1.0 equiv.), anhydrous THF, a magnetic stir bar and NaH (60% dispersion in mineral oil, 3.0–6.0 equiv.) and the reaction mixture was stirred at 70 °C for a given reaction time (10–16 h). Next, the content was concentrated by rotary evaporation (≤ 20 °C) and the mixture was diluted with CH_2Cl_2 or EtOAc. The organic phase was successively washed with an aq. solution of HCl (1 M) at 0 °C, a sat. aq. solution of $NaHCO_3$ and brine (1 ×). The organic phase was then dried over $MgSO_4$, filtered through a cotton plug and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2) to give the corresponding enantiopure 1-stannyl-iminosugar derivative (1*R*)- or (1*S*)-**18** in good yield (80–99%).

G.P. E-3. A microwave reaction vial under argon atmosphere was charged with (1*S*)-**23a** (83 mg, 90 µmol) and a microwave magnetic stir bar. Dry THF (2 mL) was inserted, followed by NaH (60% dispersion in mineral oil, 2.0–3.0 equiv.) and the mixture was heated at 70 °C, under microwave irradiation for 1 h. After cooling to room temperature, the mixture was processed as described in **G.P. E-1** and the crude product was purified by column chromatography (SiO_2). The enantiopure 1-stannyl-iminosugar derivative (1*S*)-**18a** was obtained in good yield (72 mg, 98%).

G.P. F. An oven dried 2−5 mL microwave reaction vial was charged with corresponding stannylated iminosugar derivative (2.0 equiv.), $Pd_2(dba)_3$ (2.5 mol%), JackiePhos (10 mol%), CuCl (10 mol%), 4 Å activated molecular sieves and a microwave magnetic stir bar. The reaction content was degassed under vacuum, and the flask was filled back with argon (Ar-filled balloon) three times. Dry 1,4-dioxane and the desired acyl chloride (1.0 equiv.) were then added via syringe, the vial was sealed and the reaction mixture was heated (regular heating) during 6 h, at 110 °C

under argon atmosphere. After cooling to room temperature, the cap was removed, the brown solution was diluted (CH_2Cl_2) and the mixture was filtered through celite®. Next, the cake was rinsed (CH_2Cl_2) and the filtrate solution was concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO_2) to give the cross-coupled product in moderate to good yield (26–93%).

G.P. G. To a stirred solution of a carboxylic acid derivative (1 equiv.) in anhydrous CH_2Cl_2 (5 mL per mmol of substrate) was successively added oxalyl chloride (4.1 equiv., dropwise addition) and a catalytic amount of DMF (one drop) at 0 °C under argon atmosphere. The mixture was allowed to reach room temperature (ca. 20 °C), and the reaction content was further stirred at the same temperature overnight (12 h). Next, the reaction mixture was diluted (CH_2Cl_2) and the organic phase was washed with a sat. aq. solution of Na_2CO_3 (3 ×). The organic phase was dried over $MgSO_4$, filtered through a cotton plug and evaporated under reduced pressure to afford the related alkanoyl or benzoyl chloride as a slightly yellow liquid. The product was subsequently used in the Stille cross-coupling reaction without further purification.

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FULL PAPER

Stereospecific Synthesis of Glycoside Mimics Through Migita–Kosugi–Stille Cross-Coupling Reactions of Chemically and Configurationally Stable 1-*C*-Tributylstannyl Iminosugars

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