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Stereoselective Synthesis of Iminosugar-C-Glycosides Through Addition of Organometallic Reagents to *N*-*tert*-Butanesulfinyl Glycosylamines: A Comprehensive Study

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Abstract: A comprehensive study of the preparation and reactivity of *N*-*tert*-butanesulfinyl glycosylamines with simple Grignard and organolithium reagents in batch vs. continuous flow chemistry is reported. As they readily react as latent imine equivalents with a variety of carbon nucleophiles, these carbohydrate derivatives constitute very useful precursors for the diastereoselective synthesis of bioactive compounds such as iminosugar-C-glycosides. A hybrid protocol, involving the addition of benzylmagnesium chloride to a (*S_R*)-arabinofuranosylamine substrate in flow, at room temperature, combined with a cyclization protocol in batch is also described for the first time. Of note, this semi-continuous flow process shortens the synthesis of imino-C-glycoside scaffolds to a single workday.

Introduction

Iminosugars are monosaccharide analogs in which the ring-oxygen has been replaced by nitrogen. They are found in many plants and microorganisms,^[1] and exhibit remarkable activities as glycosidase,^[2] and glycosyltransferase inhibitors,^[3] giving them high therapeutic value.^[1–4] Typical examples include Nojirimycin (**1a**), and its reduced form, 1-deoxynojirimycin (DNJ, **1b**) as well as the synthetic *N*-alkylated pharmaceuticals, Zavesca® (*N*-butyl-1-deoxynojirimycin, **1c**), and Miglitol® (*N*-[2-hydroxy-ethyl]-1-deoxynojirimycin, **1d**) to treat type I Gaucher and Niemann-Pick diseases,^[5,6] and to control glucose uptake in patients with type II diabetes respectively.^[7]

However, these surrogates lack the structural and stereochemical substitution patterns that are commonly present in the glycoside aglycone and, therefore, lack efficacy in their biological activities. Thus, iminosugar-C-glycosides, such as compounds **2–6**,^[8–13] which carry a chemically and configurationally stable C-linked substituent in the pseudo anomeric position are gaining renewed interest (Figure 1).^[4c,14]

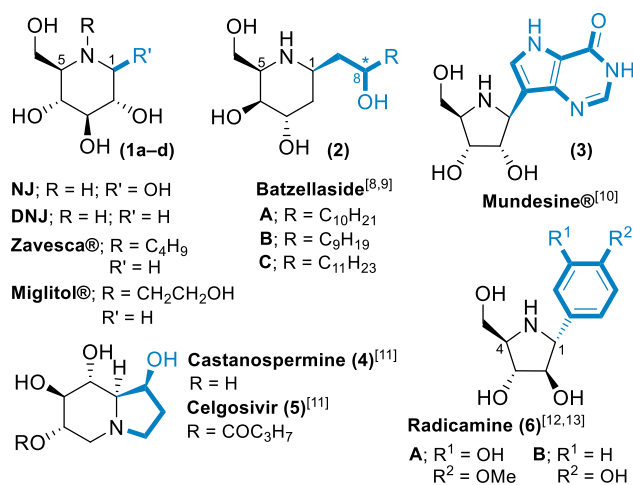
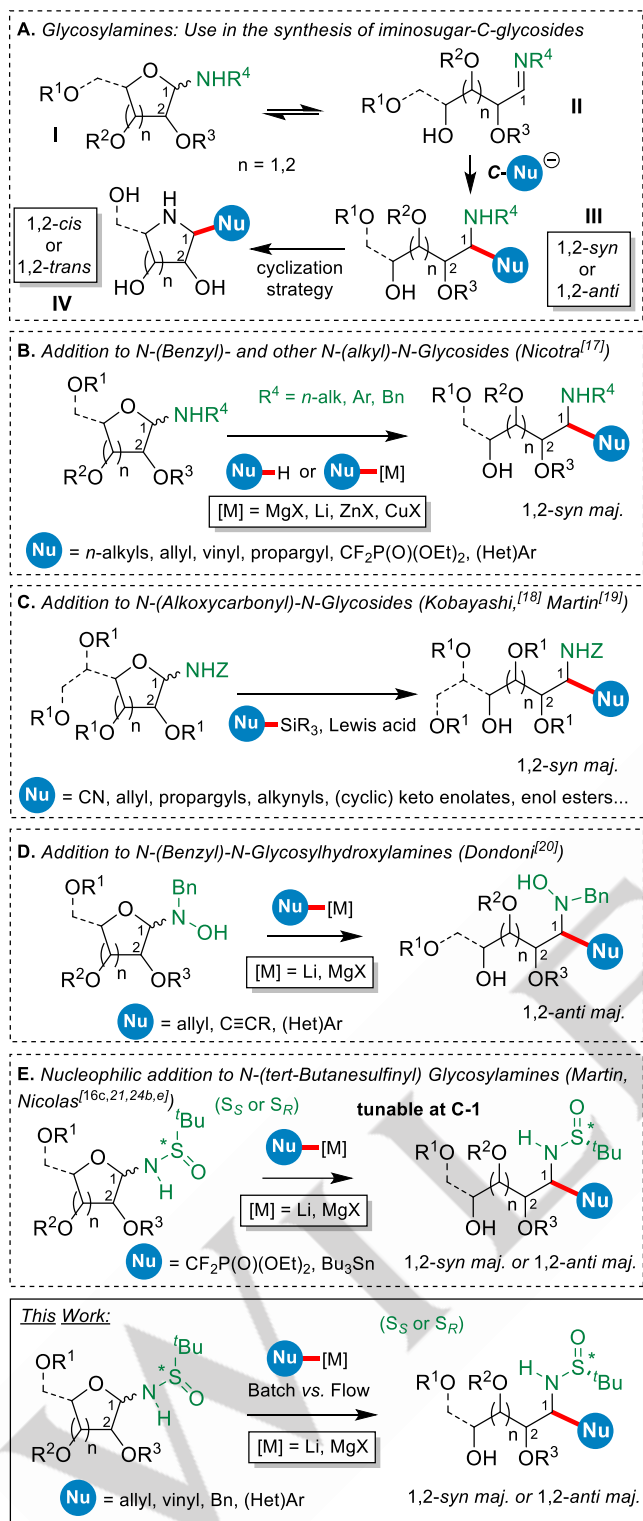


Figure 1. Selected examples of iminosugars and iminosugar-C-Glycosides with noticeable activities.



Scheme 1. State of the art and present work.

Their therapeutic properties generally exceed those of the parent 1-deoxyiminosugars.^[15] The synthesis of imino-*C*-glycosides represents a significant challenge,^[14f,16] due to their functional group density and inherent stereochemical complexity.

The main synthetic strategies developed so far have therefore often relied on using carbohydrates as chiral building blocks. A related approach developed by Nicotra (Scheme 1B),^[17] Kobayashi, and Martin (Scheme 1C),^[18,19] and Dondoni (Scheme 1D),^[20] takes advantage of the reactivity of *N*-glycosides (I).^[21] Indeed, in addition to their fundamental importance as precursors of *N*-linked glycoconjugates,^[22] glycosylamines (I) exhibit mutarotation.^[23] They are in equilibrium with a tautomeric open-chain imine (II) and are, therefore, able to react with *C*-nucleophiles, to provide 1,2-*syn* or 1,2-*anti* aminoalditols (III) with various levels of stereoselectivity and fair to good yields. After activation of the pendant alcohol (see intermediate III), iminosugar-*C*-glycosyl compounds (IV) are accessible in good overall yields (see Scheme 1A).

In the course of our studies towards glycomimetics of biological interest, we have also uncovered new *N*-glycoside substrates (Scheme 1E), and we have shown that these (*S_R*)- and (*S_S*)-*N*-*tert*-butanesulfinyl-*N*-glycosides **7** (see below) constituted superior starting materials for the stereoselective addition of organometallic reagents, and formation of imino-*C*-glycosyl compounds. In fact, addition of nucleophilic reagents to *N*-*tert*-butanesulfinyl glycosylamines **7** is highly stereoselective and tunable, hence offering major advantages over the previously used *N*-(benzyl)-*N*-(alkyl)-, *N*-(alkoxycarbonyl)- and *N*-hydroxybenzyl-*N*-glycosides.^[16c,21,24]

In this paper, we report a comprehensive study of the reactions of glycosylamines **7** with organolithium and organomagnesium reagents under batch or flow conditions, and the cyclization of the addition products to diverse type of imino-*C*-glycosyl compounds.

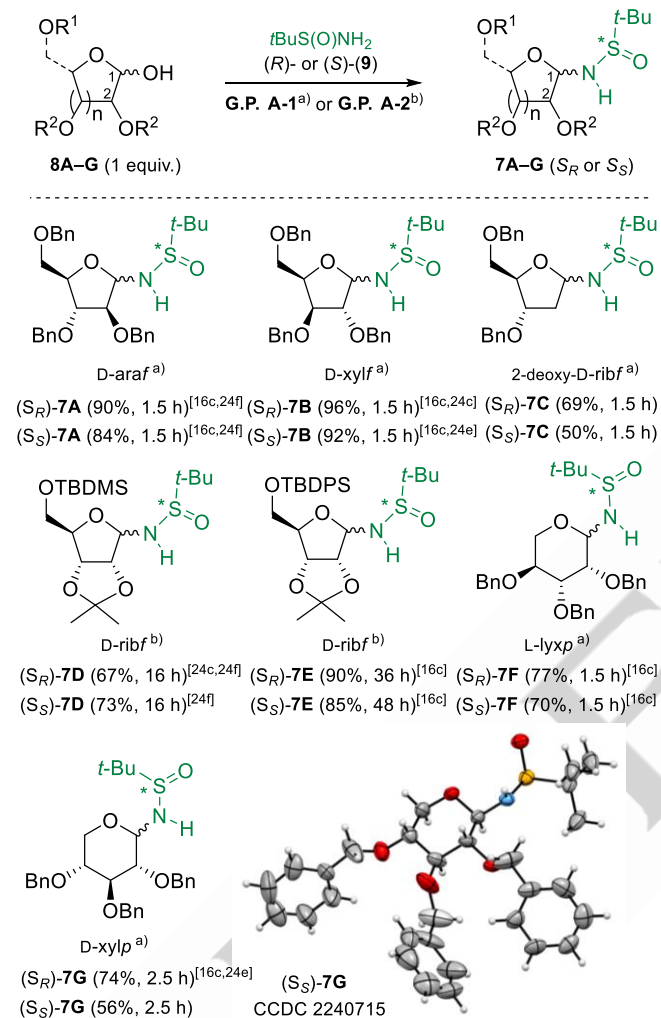
Results and Discussion

Synthesis of *N*-*tert*-Butanesulfinyl Glycosylamines **7A–G**

A large panel of *N*-*tert*-butanesulfinyl glycosylamines of interest can be prepared (**7A–G**, Scheme 2) with various protecting groups, furanose and pentopyranose structures and (*R*)- or (*S*)-Ellman's chiral auxiliaries (e. g., (*S_S*)-**7** or (*S_R*)-**7**). However, to date, we were not able to synthesize the hexopyranosylamines. Thus, for the synthesis of *O*-benzyl protected *N*-sulfinyl-*N*-pentosylamines, the typical conditions follow the addition of readily available *tri*-*O*-benzyl pentoses (**8A–C**, **8F** or **8G**) to a solution of Ti(OEt)₄ (1.5 equiv.) and commercial (*R*)-(+)- or (*S*)-(–)-2-methyl-2-propanesulfinamide ((*R*)- and (*S*)-**9**, 2 equiv.) in dry toluene. The reaction mixture is then heated for 1.5–2.5 h at 110°C under μW irradiation (general procedure A-1, G.P. A-1). Glycosylamines (*S_R*)- and (*S_S*)-**7A**, **7B**, **7C**, **7F** and **7G** were accordingly isolated in moderate to excellent yields (50–96%).

For the pentopyranosylamine counterparts (e. g., **7F** and **7G**), however, a noticeable reaction time increase is needed to promote imine formation and cyclization, probably due to entropic factors. The interplay between kinetics and thermodynamics was also emphasized by the generation of 2,3,4-*tri*-*O*-benzyl-*N*-*tert*-butanesulfinyl-*D*-xylopyranosylamine (*S_S*)-**7G** in reasonable yield (56%) as its crystalline beta form.^[25]

The acid sensitive sugar hemiaminals **7D** and **7E** were in turn obtained in good yields (67–90%) by refluxing a mixture of ribofuranose **8D** and **8E**, sulfonamide (*R*)- or (*S*)-**9** (2 equiv.) and Cs₂CO₃ (1.5 equiv.) in dichloroethane for 16–48 h (general procedure A-2, **G.P. A-2**). Of note, for the *O*-benzyl protected sugars no major differences were found between the thermal and μ W activation mode, whereas for the acid sensitive substrates, thermal heating was mandatory to avoid degradation.



Scheme 2. Synthesis of *N*-*tert*-Butanesulfinyl Glycosylamines **7A–G**. a) **G.P. A-1**: (*R*)- or (*S*)-**9** (2 equiv.), MS (4Å), Ti(OEt)₄ (1.5 equiv.), toluene, 110 °C, μ W, 1.5–2.5 h; b) **G.P. A-2**: (*R*)- or (*S*)-**9** (2 equiv.), MS (4Å), Cs₂CO₃ (1.5 equiv.), Cl(CH₂)₂Cl, Δ , 16–48 h.

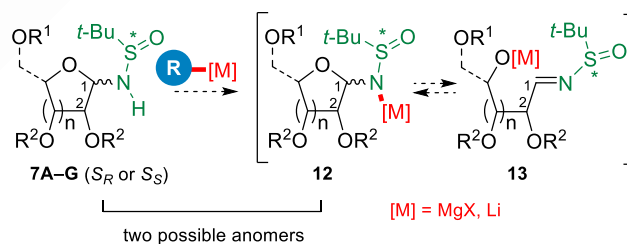
Interestingly, all of the *N*-sulfinylglycosylamines reported are reasonably hydrolytically stable (particularly, in the furanose form), allowing their isolation by normal silica gel chromatography. For instance, the two anomers (α/β) of compound (*S_R*)-**7A** can be separated (SiO₂ chromatography), although a slow epimerization was observed when the anomers were separately analyzed by NMR spectroscopy as solutions in CDCl₃. Furthermore, these glycosylamines can be handled in air at room temperature, but

prolonged storage at room temperature results in decomposition over a period of a few days. Decomposition can however be slowed down to months by storing the *N*-sulfinyl glycosylamines in closed containers at 5 °C under argon atmosphere.

Addition reactions

Conditions for the addition of Grignard reagents were investigated in our previous account.^[24f] Glycosylamines (*S_R*)- and (*S_S*)-**7A** were typically dissolved in dry THF and an excess (usually 3.5 equiv.) of commercial solutions of the reactive organomagnesium chemicals (e.g., benzyl- (**10a**), phenyl- (**10b**), vinyl- (**10c**), *n*-hexyl- (**10d**), and allyl- (**10i**) magnesium halides) was added dropwise at –60 °C. The reactions were then allowed to reach –20 °C over a period of 1.5 h to give the related 1,2-*syn* open-chain adducts **11Aa–d**, and **11Ai** in moderate to excellent yields (40–94%) and moderate to good degrees of diastereoselectivity (from 85:15 to 6:4, Table 1, entries 1, 3–5, 12, and 14–17, no LiCl added, see general procedure B-1 (**G.P. B-1**)). Gratifyingly, we noted that it was possible to improve the diastereoselectivity (*dr*) significantly through the addition of LiCl salts (general procedure B-2 (**G.P. B-2**), see compounds (*S_R*)- and (*S_S*)-**11Aa**, entries 2 and 13, and ref. 24f).

With the *N,O*-acetals (**7**) in hand, we then explored the addition of benzyl magnesium chloride, or vinylmagnesium bromide onto glycosylamines (*S_S*)-**7B**, (*S_R*)-**7D**, (*S_S*)-**7D**, and (*S_S*)-**7G** (entries 24–28). Interestingly, the 1,2-*syn* aminoalditol compounds were again obtained in good yields (50–84%) as major diastereomers (ca. 6:4 $\leq dr \leq$ 98:2), except for the glycosylamine derived from 2,3-*O*-isopropylidene ribofuranose scaffold **7D**, which afforded the 1,2-*anti* diastereomer predominantly (and hence to 1,2-*trans* configured iminosugar derivative after cyclization. *Vide infra*, section on cyclization and configuration determination).

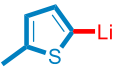
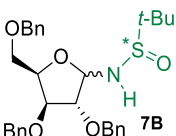
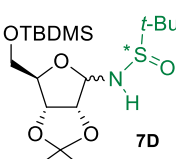
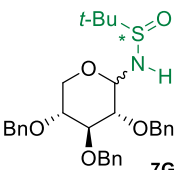
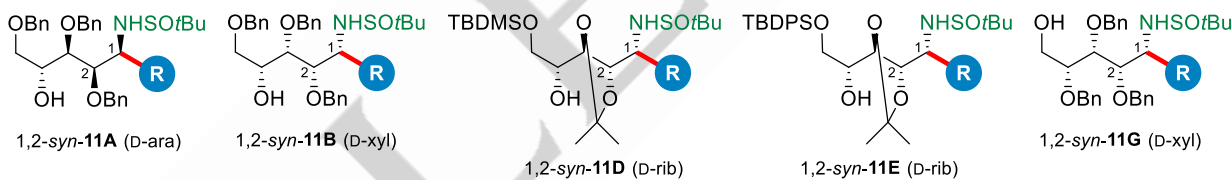


Scheme 3. Possible metalated intermediates.

Remarkably, in all the above cases, we noted by Thin Layer Chromatography (TLC) analysis of the reaction mixtures that the anomers of the related *N*-sulfinyl-*N*-glycosides did not react at the same temperature (e.g., –60 °C vs. –40 °C). As illustrated in our work,^[24f] and in Kuduk's studies,^[26] we postulated that one of the two possible metalated anomers of type **12** (see Scheme 3, [M] = MgX) could promote ring opening efficiently at low temperature (–60 °C) to form imine **13**, while the other would require higher temperature (–40 °C). This would most likely induce time-dependent diastereoselectivities, as we observed during our survey.

Table 1. Stereoselective addition of various organomagnesium and organolithium reagents onto *N-tert*-butanesulfinyl glycosylamines **7**

Entry	Glycosylamine	Auxilliary	R-[M]	R-[M] equiv.	Product	Yield (%) ^[a]	Syn : Anti (Config.) ^[b,c]	R _f ^[d]	Procedure										
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px;">G.P. B-1</td> <td style="padding: 2px;">-MgX (3.5 equiv.), -60 °C to -20 °C, 1.5 h</td> </tr> <tr> <td style="padding: 2px;">G.P. B-2</td> <td style="padding: 2px;">-MgX (3.5 equiv.), LiCl (3.5 equiv.), -60 °C to -20 °C, 1.5 h</td> </tr> <tr> <td style="padding: 2px;">G.P. B-3</td> <td style="padding: 2px;">-Li (4.5 equiv.), -78 °C, 1.5 h</td> </tr> <tr> <td style="padding: 2px;">G.P. B-4</td> <td style="padding: 2px;">-Li (5.0 equiv.), TMEDA (5.0 equiv.), -78 °C, 1.5 h</td> </tr> <tr> <td style="padding: 2px;">G.P. B-5</td> <td style="padding: 2px;">-Li (4.5 equiv.), LiCl (4.5 equiv.), -78 °C, 1.5 h</td> </tr> </table>										G.P. B-1	-MgX (3.5 equiv.), -60 °C to -20 °C, 1.5 h	G.P. B-2	-MgX (3.5 equiv.), LiCl (3.5 equiv.), -60 °C to -20 °C, 1.5 h	G.P. B-3	-Li (4.5 equiv.), -78 °C, 1.5 h	G.P. B-4	-Li (5.0 equiv.), TMEDA (5.0 equiv.), -78 °C, 1.5 h	G.P. B-5	-Li (4.5 equiv.), LiCl (4.5 equiv.), -78 °C, 1.5 h
G.P. B-1	-MgX (3.5 equiv.), -60 °C to -20 °C, 1.5 h																		
G.P. B-2	-MgX (3.5 equiv.), LiCl (3.5 equiv.), -60 °C to -20 °C, 1.5 h																		
G.P. B-3	-Li (4.5 equiv.), -78 °C, 1.5 h																		
G.P. B-4	-Li (5.0 equiv.), TMEDA (5.0 equiv.), -78 °C, 1.5 h																		
G.P. B-5	-Li (4.5 equiv.), LiCl (4.5 equiv.), -78 °C, 1.5 h																		
1		<i>S_R</i>		3.5	(<i>S_R</i>)- 11Aa	83	7:3 (<i>Syn maj.</i>)	0.6/0.55	G.P. B-1										
2	7A	<i>S_R</i>	10a	3.5	(<i>S_R</i>)- 11Aa	95	9:1 (<i>Syn maj.</i>)	–	G.P. B-2										
3	7A	<i>S_R</i>		3.5	(<i>S_R</i>)- 11Ab	69	7:3 (N.D.)	0.3	G.P. B-1										
4	7A	<i>S_R</i>		6	(<i>S_R</i>)- 11Ac	69	8:2 (N.D.)	0.5/0.3	G.P. B-1										
5	7A	<i>S_R</i>	10d <i>n</i> -Hex-MgBr	6	(<i>S_R</i>)- 11Ad	45	6:4 (N.D.)	0.5	G.P. B-1										
6	7A	<i>S_R</i>		5	(1 <i>R</i>)-(1 <i>S_R</i>)- 11Ae	53	> 98:2 (<i>Syn</i>)	0.4	G.P. B-4										
7	7A	<i>S_R</i>		4.5	(<i>S_R</i>)- 11Af	85	7:3 (<i>Syn maj.</i>)	0.5/0.3	G.P. B-3										
8	7A	<i>S_R</i>	10f	4.5	(<i>S_R</i>)- 11Af	100	85:15 (<i>Syn maj.</i>)	–	G.P. B-5										
9	7A	<i>S_R</i>		4.5	(<i>S_R</i>)- 11Ag	82	6:4 (<i>Syn maj.</i>)	0.2/0.1 ^[e]	G.P. B-3										
10	7A	<i>S_R</i>	10g	4.5	(<i>S_R</i>)- 11Ag	84	8:2 (<i>Syn maj.</i>)	–	G.P. B-5										
11	7A	<i>S_R</i>		4.5	(<i>S_R</i>)- 11Ah	40	5:1 (<i>Syn maj.</i>)	0.6/0.4	G.P. B-3										
12	7A	<i>S_S</i>	10a	3.5	(<i>S_S</i>)- 11Aa	94	85:15 (<i>Syn maj.</i>)	0.6/0.5	G.P. B-1										
13	7A	<i>S_S</i>	10a	3.5	(<i>S_S</i>)- 11Aa	83	97:3 (<i>Syn maj.</i>)	–	G.P. B-2										
14	7A	<i>S_S</i>	10b	3.5	(<i>S_S</i>)- 11Ab	57	7:3 (N.D.)	0.5/0.2	G.P. B-1										
15	7A	<i>S_S</i>	10c	6	(<i>S_S</i>)- 11Ac	62	8:2 (N.D.)	0.3/0.1	G.P. B-1										
16	7A	<i>S_S</i>		3.5	(<i>S_S</i>)- 11Ai	95	6:4 (<i>Syn maj.</i>)	0.5/0.3	G.P. B-1										
17	7A	<i>S_S</i>	10d	6	(<i>S_S</i>)- 11Ad	40	6:4 (N.D.)	0.5/0.4	G.P. B-1										
18	7A	<i>S_S</i>	10e	5	(<i>S_S</i>)- 11Ae	43	7:3 (<i>Syn maj.</i>)	0.5/0.2	G.P. B-4										

19	7A	S_S	10j 	5	(S_S)- 11Aj	75	85:15 (<i>Syn maj.</i>)	0.5/N.D.	G.P. B-4
20	7A	S_S	10f	4.5	(S_S)- 11Af	76	9:1 (<i>Syn maj.</i>)	N.D.	G.P. B-3
21	7A	S_S	10f	4.5	(S_S)- 11Af	82	96:4 (<i>Syn maj.</i>)	0.4	G.P. B-5
22	7A	S_S	10g	4.5	(1 <i>S</i>)-(1 <i>S</i>)- 11Ag	80	> 98:2 (<i>Syn</i>)	0.3	G.P. B-5
23	7A	S_S	10h	4.5	(1 <i>S</i>)-(1 <i>S</i>)- 11Ah	27	> 98:2 (<i>Syn</i>)	0.4	G.P. B-5
24		S_S	10a	3.5	(S_S)- 11Ba	68	7:3 (<i>Syn maj.</i>)	0.5	G.P. B-1
25		S_R	10a	3.5	(1 <i>R</i>)-(1 <i>R</i>)- 11Da	84	>98:2 (<i>Anti</i>)	0.6 ^[e]	G.P. B-1
26	7D	S_S	10c	3.5	(S_S)- 11Dc	50	55:45 (<i>Anti maj.</i>)	0.5/0.3	G.P. B-1
27	7D	S_S	10c	3.5	(S_S)- 11Dc	92	6:4 (<i>Anti maj.</i>)	–	G.P. B-2
28		S_S	10a	3.5	(S_S)- 11Ga	86	8:2 (<i>Syn maj.</i>)	0.3/0.2 ^[e]	G.P. B-1
									

[a] Isolated yield (column chromatography). [b] *dr* determined on crude mixture using ¹H-NMR (250 MHz) spectroscopy. [c] Configuration at C-1 determined by 2D NOESY analysis of the cyclized product **15** [d] (1st eluted fraction / 2nd eluted fraction). *R_f* determined on TLC (SiO₂) using petroleum ether : AcOEt 5:5 as eluent. [e] *R_f* determined on TLC (SiO₂) using petroleum ether : AcOEt 4:6 as eluent.

Having added a small range of Grignard reagents to our *N*-sulfinyl-*N*-glycosides of interest (**7**), the addition of lithium species was next considered. 4-(Trifluoromethyl)phenyl- (**10f**), 3,4-dimethoxyphenyl- (**10g**), and 2-naphthyl-lithium (**10h**) (4.5 equiv.) were hence generated through the addition of *n*-BuLi solution in hexanes to the corresponding bromides at –78°C, and they were subsequently added to glycosylamines (S_R)- and (S_S)-**7A** in anhydrous THF (Table 1, entries 7, 9, 11, and 20, general procedure B-3 (**G.P. B-3**)). Low to good yields (40–82%) and low to excellent diastereoselectivities (6:4 ≤ *dr* ≤ 9:1) were obtained in favor of the 1,2-*syn* products **11Af–Ah** (**G.P. B-3**). Meanwhile, deprotonation of furane (e.g., **10e**) and 2-methylthiophene (e.g., **10j**) was achieved through the addition of *n*-BuLi (5 equiv.) and tetramethylethylenediamine (TMEDA, 5 equiv.) as ligand (general procedure B-4, **G.P. B-4**) to give 1,2-*syn* alditols **11Ae**

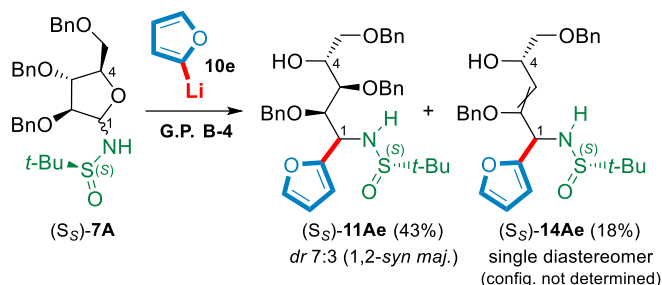
and **11Aj** in fair to good yields (43–75%) and 7:3 to > 98:2 diastereomeric ratio (Table 1, entries 6, 18 and 19).

Once again, LiCl additives (**G.P. B-5**) increased the *dr* significantly (see entry 7 vs. 8, 9 vs. 10 and 20 vs. 21 in Table 1). It is worth noting that in all reactions, due to the highly reactive and polar nature of the N–Li bond, the two lithiated stereoisomers **12** (Scheme 3, [M] = Li) reacted at –78°C and no raising of the reaction temperature was required. On the other hand, the strongly basic bias of the 2-furyllithium·TMEDA complex was showcased with (S_S)-**7A** through the formation of compound (S_S)-**14Ae** in moderate yield (18%) (Scheme 4).

This trend was also observed when 6 equiv. of the basic *n*-hexylmagnesium bromide reagent **10d** was added to glycosylamine (S_R)-**7A** (see table 1, entry 5, and SI, compound (S_R)-**14Ad**). It is worth mentioning that a *contrario* to *N*-

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glycosylhydroxylamines, *N*-(alkoxycarbonyl)-, *N*-(benzyl)- and *N*-(alkyl)-*N*-glycosides, the stereoisomers (**11Aa–Gj**) arising from **7** exhibited valuable ΔR_f on silica gel allowing a good separation by chromatography.



Scheme 4. Addition of furyllithium (**10e**) to compound (**(S_S)-7A**).

In the evaluation of alternative technologies to generate compounds **11A–D**, we considered an approach employing a continuous process. Flow chemistry is a well-recognized technique to handle transformations that are difficult to control in batches,^[27] such as reactions involving highly reactive species, especially organometallic reagents. Precise control of variables such as temperature, pressure, residence time and heat transfer explain the growing interest in this field. All these parameters significantly affect the reaction outcome improving yield and selectivity. As part of our ongoing interest in the transposition of techniques, we investigated the implementation of an efficient and general process to control the nucleophilic addition of organomagnesium reagents to **7** in continuous flow (SI, section 3.3 and 3.6). To perform the reaction, a solution A containing **7A** (0.19 mmol) in THF (2 mL) was introduced at 1.5 mL·min⁻¹ and mixed using a standard T-junction with a second solution B of the Grignard reagent (2.2 equiv) in THF or Et₂O (2 mL) pumped at the same flow rate. This combined solution was then passed through a tubular reactor (1 mm internal diameter, PTFE). The reaction was carried out repeatedly while varying the residence time and temperature. After optimization of each parameter, 100 seconds as residence time, and room temperature (vs. -60°C in Batch) were identified as optimal conditions which allowed to generate (**(S_R)-11Aa**) with the same efficiency and selectivity, with a drastic reduction in the number equivalents of benzyl magnesium chloride (**10a**) (2.2 equiv. vs. 3.5 equiv. in Batch). The same behavior was observed with a panel of Grignard reagents such as *vinMgBr* and *allMgBr* which furnished 1,2-*syn* (**(S_R)-11Ac**, (**(S_S)-11Ac**) and (**(S_S)-11Ai**) in very high yields and good diastereoselectivities. On the other hand, it is interesting to note that during the synthesis of (**(S_S)-11Ad**) by continuous flow chemistry, the reverse epimer was obtained in a 7:3 ratio (SI, Table S3, entries 16, 17). This trend was confirmed with (**(S_S)-11Aa**), from which the 1,2-*anti* isomer was isolated in good yield and good diastereoselectivity (SI, Table S3, entry 6, 8). This latter case evidences a control of the stereoselectivity during the addition of **10a** by the Ellman's chiral auxiliary. Hence, this opens the possibility to form either 1,2-*syn*-**11Aa** or 1,2-*anti*-**11Aa** (and

after cyclization the 1,2-*cis* or 1,2-*trans* 1-benzyl iminosugar derivative) by a flow process, from (**(S_R)-7A**) or (**(S_S)-7A**) respectively.

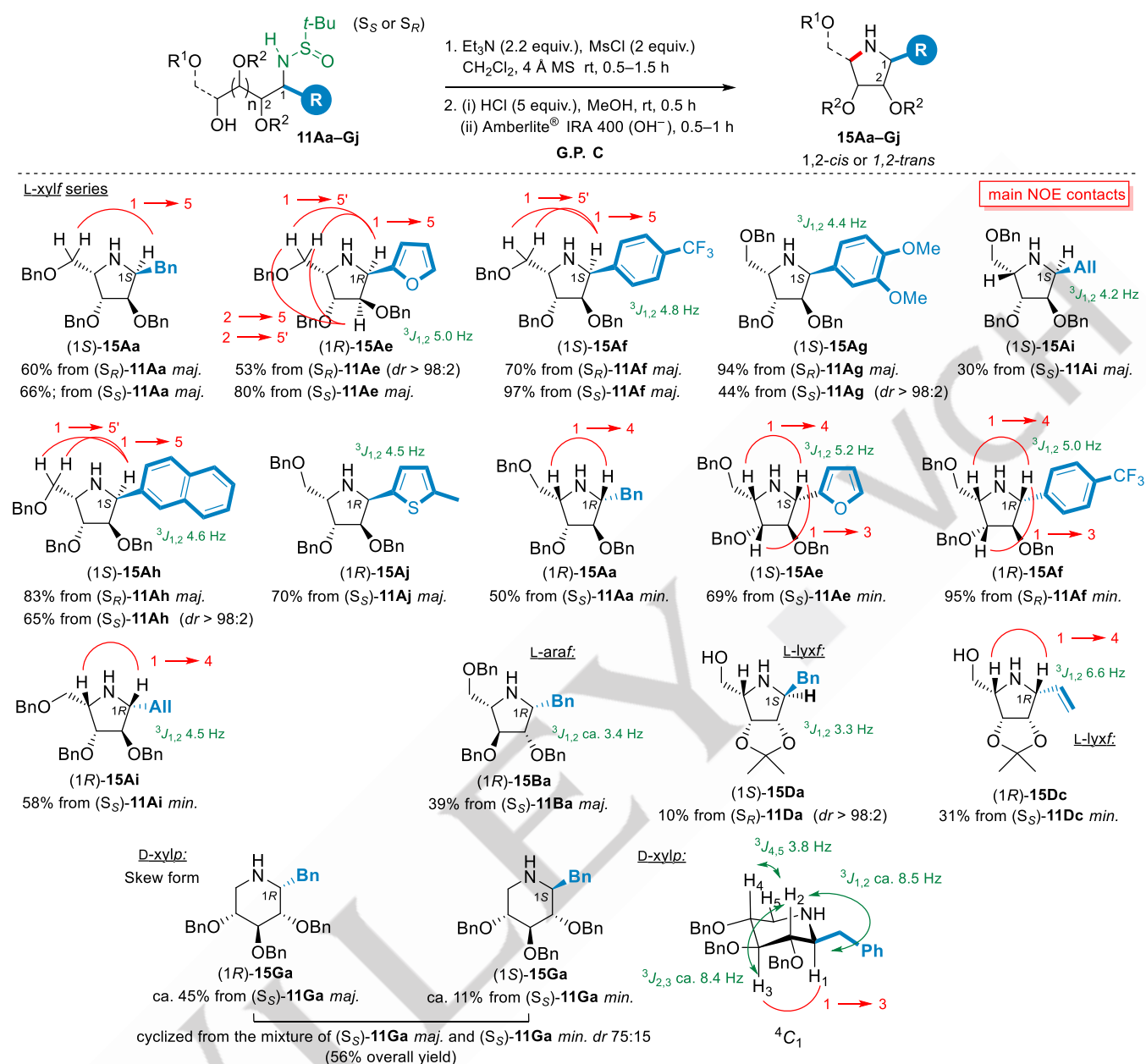
Cyclization reactions and Configuration Determination

The absolute configuration of the newly generated stereo centers was next confirmed through NOESY analysis of the cyclized products. As illustrated in Scheme 5, the minor and/or major diastereomers of alditols (**(S_R)-** and (**(S_S)-11Aa–Gj**) were independently cyclized (general procedure C, **G.P. C**) by means of a mesylation protocol (MsCl, Et₃N, CH₂Cl₂, 20 °C, 0.5–1.5h), subsequent cleavage of the sulfinyl group (HCl in MeOH), and neutralization through the addition of a basic ion-exchange resin (OH⁻ form), to afford, the ring closed iminosugar derivatives by a S_N2 reaction. In the *D-arabino* furanose series, from the major, (**(S_R)-** and (**(S_S)-1,2-*syn* iminoalditols **11A**, 1,2-*cis* iminosugar-C-glycosides, having the *L*-xylofuranose configuration and carrying 1-*C*-benzyl (**15Aa**), furyl (**15Ae**), 4-(trifluoromethyl)phenyl (**15Af**), 3,4-dimethoxyphenyl- (**15Ag**), allyl- (**15Ai**), 2-naphthyl (**15Ah**), and 2-methylthiophenyl (**15Aj**) substituents were obtained in moderate to excellent yields (30–97%). The 1,2-*trans* iminosugar derivatives **15Aa** (50%), **15Ae** (69%), **15Af** (95%), and **15Ai** (58%) were in turn isolated in good yields from the minor (**(S_S)-** or (**(S_R)-1,2-*anti* alditols **11A**. Thus, featuring a control of the stereochemistry by the sugar, with minor participation of the sulfinyl auxiliary in batch.****

Except for compounds (1*S*)-**15Ag**, (1*S*)-**15Ai**, and (1*R*)-**15Aj**, carrying respectively a 3,4-dimethoxyphenyl-, an allyl- and a 2-methylthiophenyl moiety, the 1,2-*cis* configuration was assigned thanks to the main NOE contacts between protons H-1 and H-5. In contrast, the 1,2-*trans* relationship was attributed thanks to NOE contacts between H-1 and H-3 (e.g., (1*S*)-**15Ae**, and (1*R*)-**15Af**) or H-1 and H-4 ((1*R*)-**15Aa**, (1*R*)-**15Ai**).

To further extend the scope of the reaction and demonstrate that the chiral sulfinyl group does not direct the stereoselectivity of the addition to **7** as a rule when simple Grignard and lithium reagents are used in batch, imino-*L*-arabinitol 1,2-*cis*-(1*R*)-**15Ba** (39%), and imino-*D*-xylitol 1,2-*cis*-(1*R*)-**15Ga** (ca. 45%), and 1,2-*trans*-(1*S*)-**15Ga** (ca. 11%) were also synthesized from (**(S_S)-11Ba**) *maj.* and the ca. 8:2 diastereomeric mixture of (**(S_S)-11Ga**) *maj.* and (**(S_S)-11Ga**) *min.* respectively. For compound (1*R*)-**15Ba**, the configuration was estimated, as H-1, H-4 and H-5 were overlapped in ¹H NMR. On the other hand, for compounds (1*R*)-**15Ga**, and (1*S*)-**15Ga**, ¹H NMR analysis of the major cyclized product showed scalar coupling values of presumably 3.8 Hz for ³J_{1,2}, and *J* = 6.3 Hz for ³J_{2,3}, and ³J_{3,4} respectively. The main NOE contacts between the pseudo-anomeric methylene group and H-3 and H-5', as well as H-5 with H-1, and H-5' with H-3 (see ESI) provided evidence for a skew form (twist boat) of a 1,2-*cis* 1-*C*-benzyl-imino-*D*-xylopyranosyl derivative. Main NOE contacts between protons H-1 and H-3, and scalar coupling values of ca. 8.5 Hz for ³J_{1,2}, and ³J_{2,3} were in turn observed for the minor 1-*C*-benzyl-iminoglycoside, thus featuring a ⁴C₁ chair form with a 1,2-*trans* configuration.

Sugars and glycosylamine substrates derived from 2,3-*O*-isopropylidene-*D*-ribofuranose are expected to give 1,2-*anti* adducts as major stereoisomers when reacted with simple Grignards and allyl zinc reagents.^[28,29]



Scheme 5. Synthesis of Iminosugar-C-glycosides **15** and Configuration Determination.

The imino-L-xylyl derivative **15Da** (10%) was thus synthesized next, from compound (*S_R*)-**11Da**. But, the CH₂ group and H-1 had almost same chemical shift in ¹H NMR whatever the conditions (use of various deuterated solvents, addition of an achiral europium (III) based chemical shift reagents, etc), which accordingly prevented any unambiguous NOE assignment. Also, as opposed to the study conducted by Behr and Defoin,^[30] we were not able to construct a clear model to assign the configuration at C-1 through determination of the respective coupling values ³J_{1,2} in compounds **15** (see above, Scheme 5).

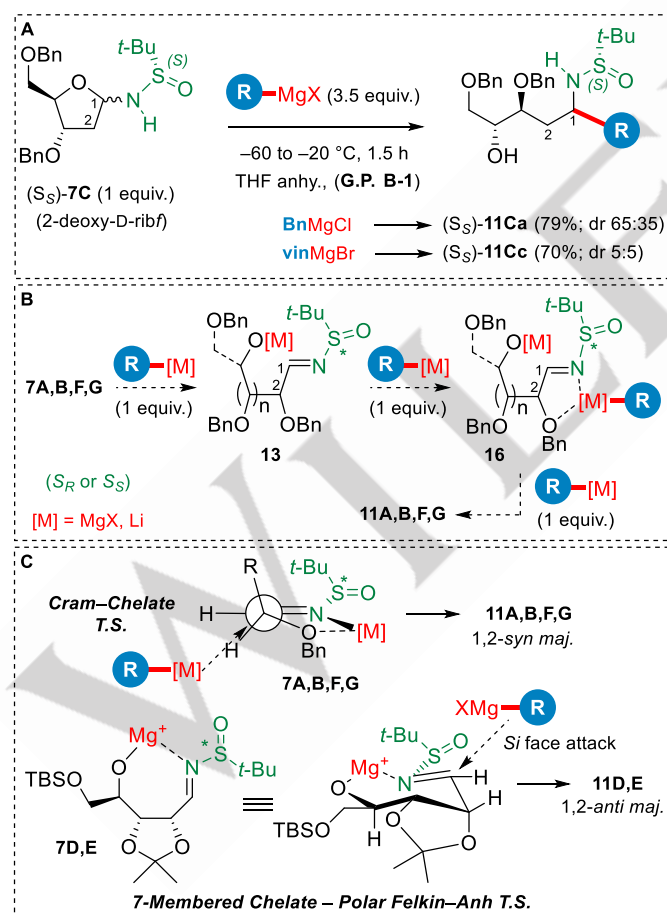
However, from the study of the literature,^[24e,28,29] we believed **15Da** was 1,2-*trans*. As a matter of fact, this was confirmed

through the isolation of compound (*1R*)-**15Dc** (31%) from (*S_S*)-**11Dc** min. Main NOE contacts between H-1 and H-4 unequivocally unraveling the 1,2-*syn* relationship of the minor diastereomer.

Mechanistic Investigations

We then focused our attention on elucidating the mechanism and the origin of the stereoselectivity during the ring-opening of *N*-sulfinyl-*N*-glycosides protected with *O*-benzyl groups (**7A,B,F,G**). As one may expect, treatment of 2-deoxy-D-ribofuranoside (*S_S*)-**7C** with vinMgBr (**10c**) under **G.P. B-1** resulted in the generation of a 1:1 mixture of iminoribitols (*1R*)- and (*1S*)-**11Cc** in good yield

(70%, Scheme 6A). Considering this outcome, and the results of the addition of **10c** to the *D-arabino* sulfinamides (S_R)- and (S_S)-**7A** (Table 1, entry 4, and 15) we then postulated that a simplified interpretation of the 1,2-*syn* asymmetric induction would be consistent with a Cram-chelate model,^[31] where the organometallic nucleophile approaches along the Bürgi–Dunitz trajectory,^[32] on the prochiral face containing the smaller group (H) (see Scheme 6C). However, when BnMgCl (**10a**) was added to (S_S)-**7C**, iminoalditol ($1S$)-**11Ca** was afforded in 79% yield with a *dr* of 65:35 (Scheme 6A). Regarding the multiple chelation sites of compounds **7** and **11**, the *match* and *mismatch* situations during the addition of **10a**, and **10f–10h** to glycosylamines (S_R)-**7A** and (S_S)-**7A** (e.g., Table 1, entry 8 vs. 21, and 10 vs. 22, or entry 1 vs. 12, and 7 vs. 20, with or without LiCl as additive), as well as the solution dynamics and reactivity profiles of organometallics (e.g., formation of mono- or multinuclear complexes, when in presence or in the absence of magnesium and lithium salts etc.),^[33,34] the mechanism must necessarily be more complex. Furthermore, it is important to mention that, at the bench, at least 3.5 equiv. of the metal anions are systematically mandatory to give compounds **11** in good yields. *De facto* 2.2 equiv. leave unconsumed starting materials (**7**), whereas more than 4.5 equiv. affords sulfinamide by-products of type **14**.



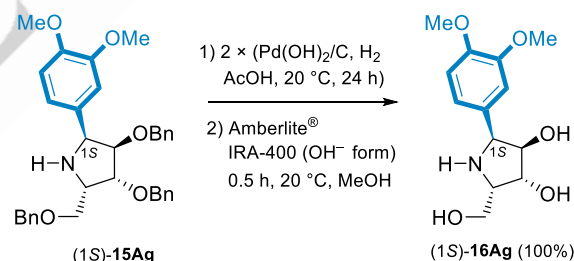
Scheme 6. Mechanistic investigations and simplified interpretation for the origin of the stereoselectivity during the ring-opening of *N*-sulfinyl-*N*-glycosides **7**.

A simple explanation could hence imply a process by which the first equivalent of the organometallic reagent deprotonates the NH moiety, promoting the formation of compounds **12** and **13**, from which the second equivalent might coordinate to the nitrogen and C-2-OBn substituents. The third equivalent could then add to the sulfinyl imine **16** (Scheme 6B) *via* Cram-chelate T.S. to give compounds **11A,B,F,G** in a 1,2-*syn* fashion.

On the other hand, for *D*-ribofuranose derivatives presenting 2,3-*O*-isopropylidene groups, it was proposed by Singh, Rao and others that the addition of organomagnesium nucleophiles can proceed *via* either a Conforth, Felkin–Ahn or 7-membered cyclic chelate transition state (T.S.).^[28,29] For the latter, the metalocycle can adopt either a chair-type conformation with the *O*-3 and *C*-5 substituents equatorial, and the trajectory of reagent approaching to be similar to that in polar Felkin–Ahn model. This model, as shown in Scheme 6C, was thus selected to describe formation of the 1,2-*anti* isomers.

Synthetic Application

To further diversify and extend the scope of our methodology, we also envisaged synthesizing an iminosugar endowed with pharmacological potential. Compound ($1S$)-**15Ag** was subjected to hydrogenolysis in the presence of H_2 , $\text{Pd}(\text{OH})_2/\text{C}$ (20%), in AcOH for 24 h at 20 °C. Partial deprotection of the molecule was noted and the reaction was repeated once to afford compound ($1S$)-**16Ag** as its HCl salt. Using anion exchange Amberlite IRA-400 (OH^-) resin, the final derivative was obtained in quantitative yield. Compound ($1S$)-**16Ag** is a Radicamine analogue in the *L*-xylo furanose series.



Scheme 7. Hydrogenolysis of compound ($1S$)-**15Ag**.

Single Working-day Synthesis of an Iminosugar-C-glycoside *via* Continuous Flow Process

In order to explore the benefit of continuous flow in the addition of Grignard reagents, we conducted an inspection to develop a semi-continuous process involving first, the synthesis of 1,2-*syn*-**17Aa** with a flow chemistry device, followed by the cyclization in a flask through activation with a MsCl solution. To achieve this purpose, the reactor outlet containing the magnesium alkoxide adduct was immediately poured into a well-stirred suspension of MsCl in THF at rt (Scheme 8) in a 50 mL round-bottom flask equipped with a BPR (Back Pressure Regulator) under argon. The reaction was stirred during 1.5 h, then the mesylated intermediate was treated with aq. NH_4Cl , and deprotected under

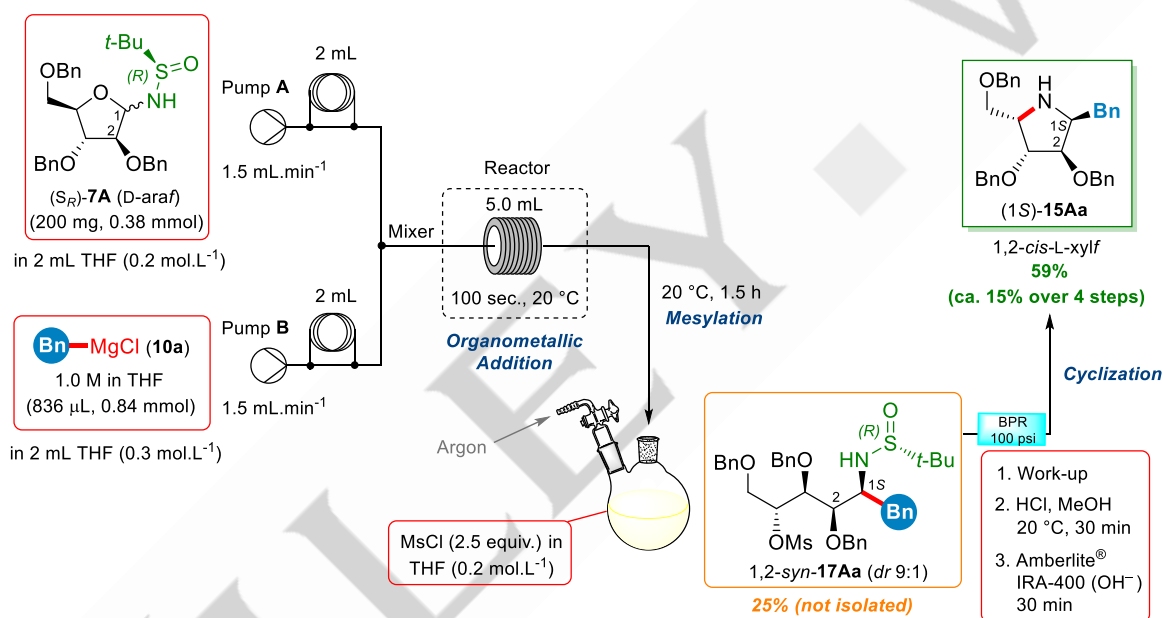
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acidic conditions (30 min), followed by adding a basic resin to the mixture to neutralize the mixture and cyclize the molecule *in situ*. This cascade procedure furnished (1*S*)-**15Aa** in 4 steps in ca. 15% overall yield. To our knowledge, this is the first process which enables an iminosugar-C-glycoside to be synthesized, in a single day from a readily available glycosylamine substrate.^[35]

Conclusion

In summary, we have revealed that ring-opening reactions of various types of *N*-sulfinyl-*N*-glycosides **7** with simple Grignard reagents and organolithium reagents such as benzyl- (**10a**), phenyl- (**10b**), vinyl- (**10c**), *n*-hexyl- (**10d**), and allyl- (**10i**) magnesium halides, or 4-(trifluoromethyl)phenyl- (**10f**), 3,4-dimethoxyphenyl- (**10g**), 2-naphthyl- (**10h**), furyl- (**10e**), and 2-methylthiophenyl- (**10j**) lithium afforded effectively the corresponding 1,2-*syn* acyclic 1,4- and 1,5-amino alcohols **11Aa–Gj** with moderate to high degrees of diastereoselectivity. The

stereoselectivity can be increased through the addition of lithium salts. The stereochemical outcome was mechanistically rationalized, and the synthetic utility of the methodology demonstrated by the stereoselective synthesis of 16 iminosugar-C-glycosides. An analogue of Radicamines A and B in the *L*-xylofuranose series was produced through hydrogenolysis of compound (1*S*)-**15Ag**. Of note, we also developed the ring-opening reactions under continuous-flow conditions. Pleasingly, we were able to perform the addition of Grignard reagents at room temperature and only 100 seconds residence time with same efficiency as batch chemistry. The products were isolated with good to excellent yields and good diastereoselectivities. The process was next extended to a semi-continuous process able to generate, in a single workday, imino-*L*-xylytol (1*S*)-**15Aa** from *N*-*tert*-butanesulfinyl glycosylamine (*S_R*)-**7A**. This new flow procedure will undoubtedly have a major impact on iminosugar synthesis in R&D studies.



Scheme 8. Straightforward Synthesis of Imino-*L*-xylytol (1*S*)-**15Aa** from Readily Available *N*-*tert*-butanesulfinyl glycosylamine (*S_R*)-**7A** via Combination of Continuous Flow and Batch Chemistry.

Experimental Section

General Procedures for the Synthesis of *O*-protected *N*-*tert*-Butanesulfinyl Glycosylamines (G. P. A).

G.P.A-1. A 10–20 mL Biotage® microwave reaction vial, under argon atmosphere, was charged with sugar hemiacetal protected by OBn groups (2.0 g, 1.0 equiv.), 4 Å activated molecular sieves (ca. 0.4 g per mmol of substrate), (*R*)-(+)- or (*S*)-(–)-2-methyl-2-propanesulfonamide (2.0 equiv.) and a microwave magnetic stir bar. Dry toluene (10 mL) 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 (20 mL, CH₂Cl₂/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 CH₂Cl₂. The phases were separated and the aqueous phase was extracted thrice with CH₂Cl₂ (3 × 25 mL). The combined organic layers were then dried over MgSO₄, filtered through a cotton plug and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography (SiO₂) to provide the related (*S_R*)- or (*S_S*)- *N*-*tert*-butanesulfinyl glycosylamine (**7A–C,F,G**) in moderate to excellent yield (50–96%).

G.P.A-2. A 25–50 mL oven dried single-necked round-bottomed flask equipped with a reflux condenser and an argon inlet was charged with 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene- α , β -D-ribofuranose **8D** (400 mg, 1.0 equiv.), or 5-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene- α , β -D-

ribofuranose **8E** (1.0 equiv.), (*R*)-(+)- or (*S*)-(-)-2-methyl-2-propanesulfonamide (2.0 equiv.), Cs₂CO₃ (1.5 equiv.), 4 Å activated MS (ca. 0.8 g per mmol of substrate), a magnetic stir bar, and anhydrous dichloroethane (5 mL) and the reaction mixture was stirred for 16–48 h at 70 °C. The brown suspension was then filtered through a cotton plug, the molecular sieves were rinsed (CH₂Cl₂) and the filtrate was washed with brine. The aqueous phase was next extracted thrice with CH₂Cl₂ (3 × 10 mL). Afterwards, the combined organic layers were dried over MgSO₄, filtered through a cotton plug and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO₂, petroleum ether/EtOAc, eluting with 1 vol % Et₃N) to provide (*S_R*)- or (*S_S*)-**7D,E** as a colorless oil in moderate to good yield (65–90%).

General Procedures for the Addition of Organomagnesium Species to *N*-*tert*-Butanesulfinyl Glycosylamines **7** in Batch (G.P. B-1–B-2).

G.P. B-1. An oven-dried 10-mL single-necked round-bottomed flask was charged with *N*-*tert*-butanesulfinyl glycosylamine **7** (100 mg, 1.0 equiv.) and flushed with argon for 15 min. Dry THF (1.5 mL) was inserted (syringe) and the solution was cooled to –60 °C (dry ice acetone bath). The Grignard reagent (3.5 equiv.) was then added dropwise (syringe) and the reaction mixture was stirred at –60 °C for 10 min. The solution was allowed to warm to –20 °C over 1.5 h. Next, the mixture was quenched by addition of aq. NH₄Cl (2 mL) and extracted thrice with EtOAc (3 × 20 mL). Combined organic phases were dried with Na₂SO₄, filtered through a cotton plug and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO₂) to afford the related alditol compound **11** in moderate to excellent yield (40–94%).

G.P. B-2. An oven-dried 10-mL single-necked round-bottomed flask was charged with LiCl (14 mg, 0.33 mmol) and heated for 3 h at 150 °C under vacuum atmosphere (120 mmHg). The flask was allowed to reach room temperature (ca. 20 °C) and argon was installed. Dry THF (1 mL) was added and the suspension was stirred at 50 °C until LiCl had dissolved (ca. 2 h). The reaction mixture was then cooled to –60 °C and benzylmagnesium chloride (1.16 mmol, 3.5 equiv.) was added *via* a syringe (dropwise addition). A solution of (*S_R*)- or (*S_S*)-**7A** (50 mg, ca. 96 μmol) in THF (1 mL) was subsequently added dropwise (syringe) and the yellow solution was stirred during 10 min at –60 °C. The reaction mixture was allowed to warm to –20 °C (1.5 h) and the mixture was quenched by aq. NH₄Cl addition (1 mL) and extracted thrice with EtOAc (3 × 10 mL). Combined organic phases were dried (Na₂SO₄), filtered through a cotton plug and the solvent was evaporated under reduced pressure. The crude product was purified by SiO₂-column chromatography to afford the related 1,2-*syn* alditol compound (*S_R*)- or (*S_S*)-**11A** in good yield (95% and 83% respectively) and good diastereoselectivity (9:1 and 97:3 respectively).

General Procedures for the Addition of Organolithium Reagents to *N*-*tert*-Butanesulfinyl Glycosylamines **7** in Batch (G.P. B-3–B-5).

G.P. B-3. An oven-dried single-necked round-bottomed flask under argon atmosphere was charged with dry THF and the flask was cooled down to –78 °C. The halogenated reagent (4.5 equiv.) was added, followed by *n*-BuLi (4.5 equiv.), dropwise and the white solution was stirred at –78 °C for 1 h. In parallel, another oven-dried single-necked round-bottomed flask under argon atmosphere was charged with the glycosylamine substrate **7** (1.0 equiv.), anhydrous THF and the solution mixture was cooled down to –78 °C (solution B). Solution A was added to solution B *via* cannula, and the reaction mixture was stirred at –78 °C for 1.5 h. Next, the mixture was quenched (aq. NH₄Cl), and the aqueous phase was extracted twice with EtOAc. Combined organic phases were dried (Na₂SO₄), filtered through a cotton plug and the solvents were evaporated under reduced pressure. The crude product was purified by SiO₂-column chromatography to afford the related alditol compound **11** in good yield (76–85%) and moderate to good *dr* (6:4 to 9:1).

G.P. B-4. An oven-dried single-necked round-bottomed flask under argon atmosphere was charged with anhydrous THF, furane or 2-

methylthiophene (5.0 equiv.) and *N,N,N,N*-tetramethylethylenediamine (TMEDA, 5.0 equiv.), and the solution mixture was cooled down to 0 °C (ice–water bath). *n*-BuLi (5.0 equiv.) was added, dropwise (syringe addition), and the mixture was stirred at 0 °C for 0.5 h or 2 h respectively (solution A). In parallel, another oven-dried single-necked round-bottomed flask under argon atmosphere was charged with (*S_R*)- or (*S_S*)-**7A** (1.0 equiv.), AlMe₃ (1.0 equiv.), in the case of the addition of 2-methylthiophene, and dry THF, and the solution mixture was cooled down to –78 °C (solution B). Next, solution A was cooled to –78 °C, and it was added to solution B *via* cannula. The reaction mixture was stirred for a given reaction time allowing the reaction contents to warm up to reach ambient temperature. The mixture was then quenched (aq. NH₄Cl), and it was extracted twice with EtOAc. Combined organic phases were dried with Na₂SO₄, filtered through a cotton plug and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO₂) to afford (*1R*)-(*S_R*)-**11Ae** (53%), (*S_S*)-**11Ae** (43%) or (*S_S*)-**11Aj** (75%) in moderate to good yield, and moderate to good *dr* (7:3 to >98:2).

G.P. B-5. An oven-dried single-necked round-bottomed flask, under air atmosphere, was charged with LiCl (4.5 equiv.) and heated for 3 h at 150 °C in vacuo (120 mmHg). Next, the flask was allowed to reach room temperature (ca. 20 °C) and argon was installed. Dry THF was added, and the suspension was stirred at 50 °C until LiCl had dissolved (ca. 2 h, solution A). In parallel, another oven-dried single-necked round-bottomed flask under argon atmosphere was charged with anhydrous toluene and/or dry THF, and cooled down to –78 °C. The halogenated reagent (4.5 equiv.) was added, followed by *n*-BuLi (4.5 equiv.), dropwise and the white solution (solution B) was stirred at –78 °C for 1 h. In a third flask under argon atmosphere, a solution of the glycosylamine substrate **7A** (1.0 equiv.) in anhydrous THF was cooled to –78 °C (Solution C). Solution A was cooled down to –78 °C and it was added to solution B *via* cannula. The solution mixture was subsequently added to solution C (cannula), and the reaction mixture was stirred at –78 °C for 1.5 h. Next, the reaction mixture was quenched (aq. NH₄Cl) and the aqueous phase was extracted twice with EtOAc. Combined organic phases were dried (Na₂SO₄), filtered through a cotton plug and the solvents were evaporated under reduced pressure. The crude product was purified by SiO₂-column chromatography to afford the related alditol compound **11A** in low to quantitative yield (27–100%) and good *dr* (5:1 to > 98:2).

General Procedure for the Addition of Grignard Reagents to *N*-*tert*-Butanesulfinyl Glycosylamine **7A** in Flow.

A solution A of **7A** (1.0 equiv.) in THF (2 mL) was flowed at 1.5 mL·min⁻¹ and mixed with a second solution B containing the Grignard reagent (2.2 equiv.) in THF (2 mL) also pumped at 1.5 mL·min⁻¹. The combined solution was then passed through a 5 mL linear reactor (1 mm internal diameter, PTFE). After a residence time of 100 seconds, the solution was poured into a solution of aq. NH₄Cl and extracted thrice with EtOAc. Combined organic phases were dried with Na₂SO₄, filtered through a cotton plug and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO₂) to afford the related 1,2-*syn* or 1,2-*anti* alditol compound **11A** in moderate to excellent yield (65–90%) and moderate to good *dr* (6:4 to 9:1).

General Procedure for the Cyclization of Sulfinylated Intermediates **11Aa–Gj** (G.P. C).

A single-necked round-bottomed flask under argon atmosphere was charged with enantiopure aminoalditol **11Aa–Gj** (1.0 equiv., 0.03–0.05 M), anhydrous CH₂Cl₂, and 4 Å MS (ca. 0.5 g per mmol of substrate). Et₃N (2.2 equiv.) was added, followed by MsCl (2.0 equiv.) and the reaction mixture was stirred at room temperature (ca. 20 °C) until no more starting material was present (30–90 min.). The mixture was then diluted (CH₂Cl₂), and molecular sieves were filtered through Celite®. The cake was rinsed (CH₂Cl₂), and the organic solution was washed with aq. NH₄Cl. Next, the aqueous phase was extracted twice (CH₂Cl₂), and combined organic

phases were dried over MgSO₄. The organic layer was filtered over a cotton plug and the solvent was evaporated through rotary evaporation. The mesylated intermediate was subsequently used in the cyclization step without further purification.

A single-necked round-bottomed flask under argon atmosphere was charged with AcCl (5 equiv., ca. 0.3 M) and dry MeOH and the mixture was stirred at 20 °C for 30 min (solution A). Another single-necked flask under argon atmosphere (flask B) was charged with dry MeOH and crude mesylated intermediate (0.3 M), and solution A was added using a syringe to flask B. The reaction mixture was stirred for 1 h. Amberlite IRA-400 (OH⁻ form) ion-exchange resin was then added until pH 8. The mixture was stirred further for 0.5–1 h at the same temperature and the suspension was filtered through a cotton plug. The solvents were evaporated under reduced pressure and the residue was purified by chromatography (SiO₂) to provide compound **15Aa–Gj** in low to good yield (10–97%).

Supporting Information

The data that support the findings of this study are available in the supplementary material of this article.

The authors have cited additional references within the Supporting Information.^[36–43]

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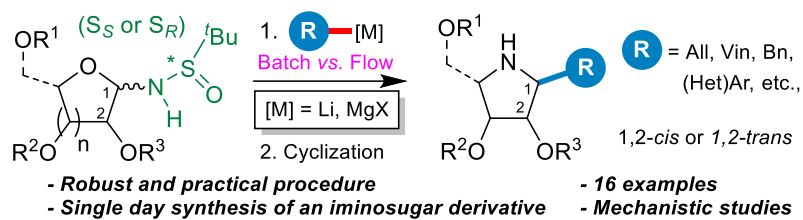
Keywords: *N*-*tert*-Butanesulfinyl glycosylamines • Grignard addition • Organolithium addition • Stereoselective Synthesis • Flow Chemistry • Iminosugar-C-glycosides

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A comprehensive study of the preparation and reactivity of *N*-*tert*-butanesulfinyl glycosylamines with simple Grignard and organo lithium reagents is reported. As they readily react as latent imine equivalents with a variety of carbon nucleophiles in batch and continuous flow chemistry, these carbohydrate derivatives constitute very useful precursors for the diastereoselective synthesis of bioactive compounds such as iminosugar-C-glycosides.