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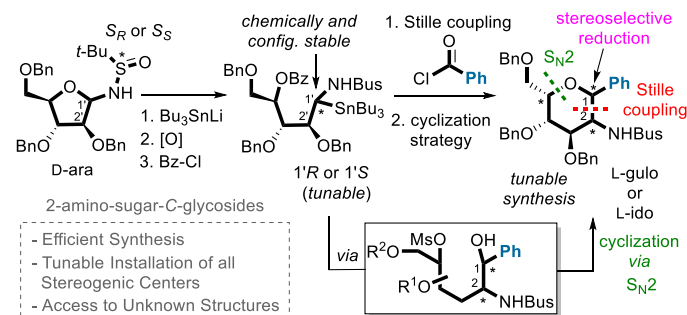
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A Tunable Approach to C-Linked Analogs of Glycosamines.

Tuniyazi Abuduaini,[†] Sizhe Li,[†] Vincent Roy,[†] Luigi A. Agrofoglio,[†] Olivier R. Martin,^{†,*} and Cyril Nicolas^{†,*}

[†]Institut de Chimie Organique et Analytique, UMR CNRS 7311, Université d'Orléans, Rue de Chartres, BP 6759, 45067 Orléans cedex 2, France.



ABSTRACT: The synthesis of (1*R*)-2-amino-2-deoxy-β-L-gulopyranosyl benzene, and the α and β form of 2-amino-2-deoxy-L-idopyranosyl benzene derivatives was accomplished through stereospecific addition of tributylstannyl lithium to readily available (*S_R*)- or (*S_S*)-*N*-*tert*-butanesulfinyl-arabinofuranosylamine building blocks, followed by stereoretentive Pd-catalyzed Migita–Kosugi–Stille cross-coupling, stereoselective reduction and an activation–cyclization strategy. Application of this methodology paves the way to new three-dimensional chemical space and preparation of unknown (non-natural) and complex 2-amino-2-deoxy sugars of biological interest.

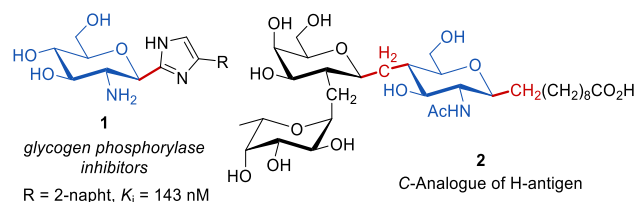


Figure 1. C-Glycoside Analogs of Natural Glycosamines.

2-Amino-2-deoxy-sugars and their *N*- and *O*-glycoconjugates are ubiquitous key biomolecules that are involved in numerous fundamental biological events.¹ Typical examples contain D-glucosamine,^{2–7} D-galactosamine,^{6,8} D-allosamine,⁹ and D-mannosamine.^{10,11}

Given the pivotal role of aminosugars in biological systems, several synthetic approaches have been devised to prepare their C-linked analogs. C-Glycosides are indeed insensitive to the action of hydrolytic enzymes *in vivo*, and, *per se* have become first choices to design mimics of the native *N*- and *O*-glycosides and as potential drug candidates.¹² Successful examples, in recent years, comprise compounds of type **1** and **2** as glycogen phosphorylase inhibitors and C-analogue of the H-antigen respectively (Figure 1).^{13,14}

As illustrated below, in Scheme 1 (see path a), the main routes developed so far for the preparation of 2-amino-2-deoxy-sugar-C-glycosides rely on the addition of the aglycone residue as C-nucleophiles to GlcNAc or GalNAc derivatives. Typically, the tactics focus on (1) Friedel–Crafts,¹⁵ or (2) metal-catalyzed alkylations of glycosyl halides,¹⁶ (3) radical-based reactions of xanthate precursors,¹⁷ or halo- and chalcogenoglycosides with olefins,¹⁸ or (4) Lewis acid mediated nucleophilic substitutions of anomeric halides, acetates, and glycosides.¹⁹

Other strategies involve formation of 1,2-oxiranes from glucals or galactals, regiospecific and stereospecific ring opening with aluminium, magnesium or lithium reagents at low temperature, but this requires further post-functionalization reactions, (Scheme 1, path b).²⁰

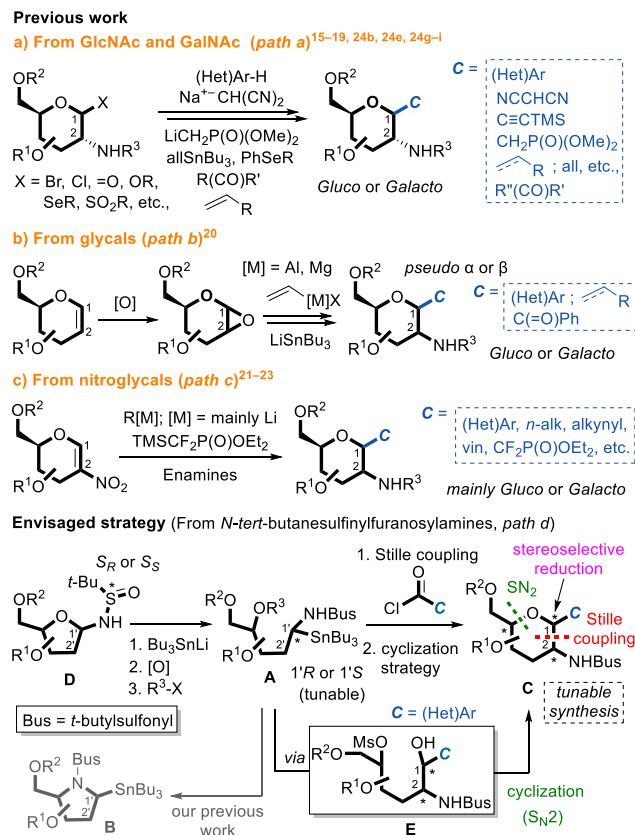
Lastly, 2-nitroglycals are also versatile intermediates *en route* to these important scaffolds. The nitroglycal compounds are mainly used in the course of Michael additions at C-1 with “soft” and “hard” nucleophiles such as malonates,²¹ allylzinc, vinyl and allyl magnesium species,²² or organolithium reagents,²³ to give the 2-amino-2-deoxyglycoside entities, upon reduction of the nitro group, in moderate to good diastereoselectivities (Scheme 1, path c).²⁴

By contrast with ‘common’ C-glycosides, there is only a limited number of methodologies to make C-glycosides from glycosamines: the high reactivity of the acetamido group and its strong ability as a participating group makes indeed the direct C-glycosylation of GlcNAc derivatives difficult. Synthesis of this family of glycomimetics thus remains a major challenge. There is great room for improvement.

In the course of our current studies on the chemistry of stannylated aminoalditols **A** ($R^3 = \text{H}$ or SO_2Me), mainly as precursors of chemically and configurationally stable 1-C-tributylstannyl iminosugars **B**, and iminosugar-C-glycosides, in particular,^{25,26} we have uncovered a new approach to aminosugar-C-glycosides **C**, in which the carbon skeleton of such compounds is generated through the formation of a C–C bond between C-1 and C-2 (Scheme 1, path d). This unprecedented method is based on the acylation of enantiopure α-aminostannanes **A** (*via* a stereoretentive Pd-catalyzed Migita–Kosugi–Stille reaction), readily available through the stereospecific addition of Bu_3SnLi to (*S_R*)- or (*S_S*)-*N*-*tert*-butanesulfinyl glycosylamines **D** (*dr* > 98:2).^{25,27} The acylating agent includes the C-1 of the carbon chain and

the aglycone that is to be carried by the aminosugar-C-glycoside. Stereoselective reduction of the resulting ketone leads to a diol which is then cyclized to a C-glycosyl compound *via* mesylation (e.g., **E**) and S_N2 reaction. Interestingly, the major advantage of this approach is the tunable generation of three contiguous chiral centers (at C-1, C-2, and C-5) and possibility to settle the two others (C-3, and C-4) using the chiral pool strategy. We report in this Note the first implementation of this methodology.

Scheme 1. Previous Methods and Envisaged Strategy for the Synthesis of C-Linked Analogs of Glycosamines.

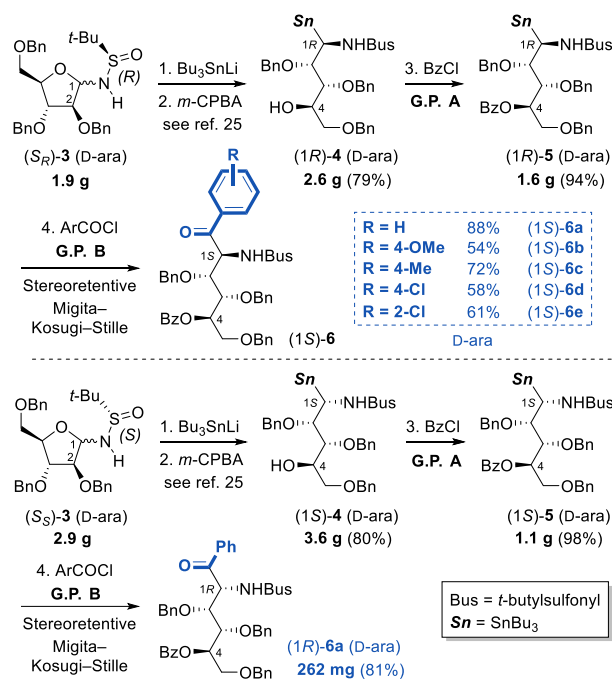


Previous work from our laboratory has indeed shown that the addition of Bu₃SnLi to *N*-tert-butanefulfinyl glycosylamines of type **3** is highly stereoselective (dr > 98:2) and stereospecific (i.e., the chiral sulfinyl auxiliary directs the stereoselectivity of the addition of the Bu₃Sn group). Through oxidation using *m*-CPBA, the *N*-protected α-sulfonamido-organostannanes of type **4** are then obtained in moderate to good overall yields (55–87%) as single diastereomers. Thus, as a rule, (*S*_R)-**3** gives (*1R*)-configured stannylated aminoalditol (*1R*)-**4** and (*S*_S)-**3** the (*1S*)-**4** epimer respectively (see Scheme 2, above).

To prove the feasibility of the envisaged strategy, tributylstannyl lithium (3.5 equiv.) was added to *D*-arabinofuranosylamine (*S*_R)-**3** at –78 °C in THF and the reaction mixture was allowed to reach –20 °C over 2 h. Subsequent oxidation (*m*-CPBA) provided the enantiopure chiral building block derivative (*1R*)-**4** in gram-scale (2.9 g, 79% over 2 steps, see Scheme 2 and ref. 25). In order to perform Pd-mediated coupling on this substrate, the secondary alcohol

function of compound (*1R*)-**4** was benzoylated under standard conditions at room temperature (r.t.) in the presence of TMEDA²⁸ (general procedure A (**G.P. A**)). Compound (*1R*)-**5** was afforded in 94% yield (1.6 g).

Scheme 2. Stereospecific Synthesis of Cross-Coupled Products (*1S*)-**6** and (*1R*)-**6**.



(1) (a) *i*-Pr₂NH (3.5 equiv.), *n*-BuLi (3.5 equiv.), THF, 0 °C, 30 min; (b) Bu₃SnH (3.5 equiv.), –78 °C, 15 min; (c) **3** (1 equiv.), THF, –78 °C to –20 °C over 2 h; (2) *m*-CPBA (1.1 equiv.), 0 °C, 30 min; (3) TMEDA (1.2 equiv.), BzCl (1.2 equiv.), MS (4Å), CH₂Cl₂, r.t., 2 h (**G.P. A**); (4) **5** (2 equiv.), Ar(CO)Cl (1 equiv.), Pd₂(dba)₃ (1.25 mol%), JackiePhos (5 mol%), CuCl (5 mol%), MS (4Å), 1,4-dioxane (0.03 M), 100 °C, 6 h (**G.P. B**).

Since the pioneering work of Eaborn,²⁹ Migita and Kosugi,³⁰ in the 1970's and the extensive mechanistic studies by Stille,³¹ and others, the Migita–Kosugi–Stille reaction has undeniably become one of the cornerstones in Pd-catalyzed C–C bond formation.^{32,33} The process is mild, operationally simple, and tolerates a wide variety of functional groups. Noteworthy, chiral glycosylstannanes have been shown to retain anomeric configuration when exposed to light or when heated at 110 °C for several days.^{20b} In our own research, we have also reported that anomeric tributyltin iminosugars can be stored at 5 °C under argon atmosphere for at least two years without erosion of the chirality at C-1.²⁵

The aminoalkylstannane (*1R*)-**5** was thus reacted with benzoyl chloride under conditions similar to the ones we developed for the asymmetric *C*sp³–*C*sp² Pd-catalyzed Migita–Kosugi–Stille coupling of chiral *C*sp³ tin-iminosugars.²⁵ It is worth mentioning that, in this investigation, as low as 1.25 mol% Pd₂(dba)₃ could be used with CuCl (5 mol%) as co-catalyst, and JackiePhos (5 mol%) as ligand without degradation of the reaction yield. As illustrated in Scheme 2, the efficacy of the coupling reaction was explored with a small range of variously substituted aryl chlorides (R = 4-OMe, 4-Me, 4-Cl, 2-Cl) under the conditions of **G.P. B**. Gratifyingly,

yields of the coupled derivatives (1*S*)-**6a–e** (absolute configurations were presumed from ¹H- and nOesy NMR analysis of the β-L-gulopyranosyl benzene derivative **10**, see Scheme 3 and ESI for details) were good for most products (54–88%).

Electronic effect studies from substituents in Pd-catalyzed coupling reactions have shown that electron withdrawing groups on the aryl(aryl) halide could facilitate oxidative addition and accordingly speed up the reaction rate.³⁴ This general trend was not examined, however, no significant influence of the electronic and steric nature of the substituents on the reaction yield could be observed (R = 4-OMe, 54%; R = 4-Cl, 58%; R = 2-Cl, 61%). Competitive β elimination of the benzyloxy moiety at C-2 to provide an unsaturated by-product was not detected, and no epimerization of the chiral center at C-1 was noted. It is difficult to give any mechanistic rationale at this point and in particular to determine whether copper participates with palladium in a bimetallic catalytic cycle or if it is only Pd-catalysis and Cu(I) acts as a ligand scavenger.^{29,32} We strongly believe that the stereoretentive cross-coupling reaction proceeds through a cyclic transition state for which a ligand dissociates prior to transmetalation.

Overall, the same synthetic sequence was also achieved in the (*S*)-*N*-*tert*-butanesulfinyl-D-arabinofuranosylamine series (e.g., (*S*)-**3**), and compounds (1*S*)-**4** (80%, 3.6 g), (1*S*)-**5** (98%, 1.1 g), and (1*R*)-**6a** (81%, 262 mg) were obtained in good yields on 5-, 4- and 1-mmol scales respectively (Scheme 2).

In the match case, D-arabinitol (1*S*)-**6a** was reduced through general procedure C (G.P. C, Scheme 3) using NaBH₄ in MeOH at r.t. to give (1*R*,2*R*)-amino hexitol **7** as the exclusive diastereomer (dr > 98:2 as determined by ¹H-NMR). Of note, this result corroborates the only literature precedent existing on the stereoselective reduction of a chiral α-*N*-*tert*-butanesulfinamido ketone.³⁵ In this work, Song and co-workers did not envisage any mechanism to justify the high selectivity in favor of the *trans* (anti) diastereomer. Although reducing agents such as NaBH₄ are commonly expected to produce Felkin–Anh products with moderate stereoselectivities,^{36,37} we think a simplified interpretation of this 1,2 asymmetric induction could be a nucleophilic attack via Cram Chelate-like conformation,³⁸ from which the hydride approaches along the Bürgi–Dunitz trajectory,³⁹ on the pro-*S* face containing the smaller group (H) (see T.S. in Scheme 3, and ESI for more details).

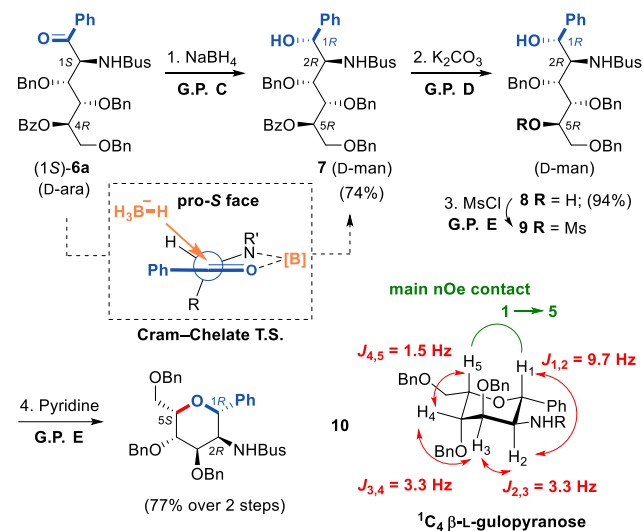
Next, removal of the benzoyl protecting group was achieved under G.P. D using K₂CO₃ (2.2 equiv.) in MeOH (**8**, 94%). Regioselective mesylation of the C-5–OH was performed (MsCl (2.1 equiv.), using catalytic amount of 4-dimethylaminopyridine (DMAP) in anhydrous pyridine and cyclization was accomplished in pyridine at 90 °C to provide 1-C-phenyl pyranoside **10** in 77% yield over two steps (G.P. E, Scheme 3).

NMR analysis of compound **10** by 1D and 2D techniques revealed a main nOe contact between H-1 and H-5, and coupling values of 9.7, 3.3, 3.3, and 1.5 Hz for ³J_{1,2}, ³J_{2,3}, ³J_{3,4} and ³J_{4,5} respectively.

Noteworthy, these data accounts for a ¹C₄ chair form of a β-L-configured gulopyranosyl derivative, thus confirming successive stereoretentive palladium-catalyzed C–C bond-formation, stereoselective reduction in favor of the 1,2-

trans adduct, and regioselective mesylation of the C-5–OH in compounds (1*R*)-**5**, (1*S*)-**6a**, and **8** respectively (see ESI for details on the conformational and retrosynthetic analysis of compound **10**). Interestingly, gulosamine is an unknown hexoamine monosaccharide present in compound **10** as a non-hydrolysable 1-C-phenyl derivative.

Scheme 3. Match Case: Synthesis of the ¹C₄ Chair Form of β-L-Gulopyranosyl benzene **10**.



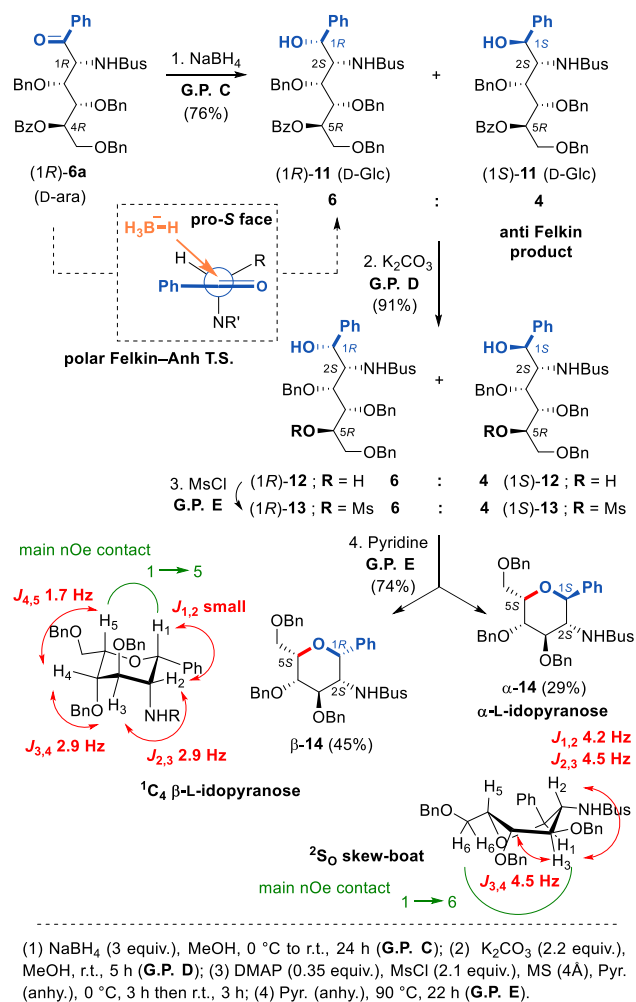
To increase the scope of the methodology, compound (1*R*)-**6a** was also reacted through G.P. C–E (Scheme 4). In the mismatch case, reduction with NaBH₄ gave the sulfonyl-amino-D-glucitol derivative **11** as a mixture of two diastereomers (6:4 ratio) at the C-1 position. As it could be expected, the major stereoisomer was the polar Felkin–Anh product (1*R*)-**11**, whereas the minor derivative was the anti-Felkin adduct (1*S*)-**11** (see SI for details).

Compounds (1*R*)-**11**, and (1*S*)-**11** could not be separated through regular SiO₂-chromatography. Thus, the mixture was subjected to general procedure D and the mixture of diols (1*R*)-**12** and (1*S*)-**12** (91%) cyclized through general procedure E (Scheme 4). The two diastereoisomers of compound **14** could then be separated and isolated in 45% and 29% yield.

¹H-NMR analysis of the major product showed a small coupling constant for H-1, and coupling constant values of 2.9, 2.9, and 1.7 Hz for ³J_{2,3}, ³J_{3,4} and ³J_{4,5} respectively. These three-bond couplings, altogether with the main nOe contact between H-1 and H-5 provide evidence for a ¹C₄ chair form of a β-L-idopyranosyl benzene derivative (e.g., β-**14**). A main nOe contact between H-1 and H-6 along with scalar coupling values of ³J_{1,2} = ca. 4.2 Hz; ³J_{2,3} = 4.5 Hz; ³J_{3,4} = 4.5 Hz were observed for the minor isomer. The data are not consistent with ¹C₄ and ⁴C₁ chair conformations, but with a ²S₀ skew form (twist-boat) (α-**14**), as has been observed for the α-L-idopyranose ring (see recent work).⁴⁰

Taken together, these informations thus establish for a second time a reaction sequence through stereoretentive Stille process, and regioselective mesylation of the less sterically hindered C5–OH of diols **8** and **12**.

Scheme 4. Mismatch Case: Synthesis of α - and β -L-Idopyranosyl benzene α -14 and β -14.



In conclusion, we have reported a new method for the simple preparation of glycosamine-*C*-glycosides of biological interest based on the unprecedented creation of the C-1–C-2 bond. This novel synthetic approach is characterized by the stereospecific addition of tributylstannyl lithium to readily available (*S_R*)- or (*S_S*)-*N*-*tert*-butanesulfinyl-furanosylamine building blocks, followed by stereoretentive Pd-catalyzed Migita–Kosugi–Stille cross-coupling with benzene derivatives promoted by catalytic amount of Cu(I). Next, stereoselective reduction of the generated chiral ketones, regioselective mesylation and cyclization readily afforded the valuable aminosugar derivatives in good overall yields. Importantly, the major advantage of this approach is the stepwise and tunable installation of three contiguous chiral centers (i.e., at C-1, C-2 and C-5) and the possibility of settling the two others using the chiral pool. This strategy might indeed provide an approach to unknown (non-natural) and complex 2-amino-2-deoxy sugars, which might be otherwise challenging to access.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all reagents were purchased from commercial suppliers and used as

received. All reactions to be performed under an inert atmosphere of argon were achieved using Schlenk techniques. Compounds (*S_R*)-3, (*S_S*)-3, (*1R*)-4 and (*1S*)-4 were prepared following reported procedures.²⁵ Molecular sieves (MS) 4 Å was activated by drying in an oven at 500 °C for 48 h. It was then allowed to reach room temperature (r.t., ca. 20 °C) and kept over CaCl_2 in a desiccator prior to use. NMR spectra were recorded at 298 K with a Bruker Avance III HD nanobay instrument (400 MHz for ^1H and 101 MHz for ^{13}C) equipped with a BBO probe. Chemical shift values are listed in parts per million (ppm). Tetramethylsilane (TMS) (δ 0), CHCl_3 (δ 7.26), or $\text{CHD}_2(\text{CO})\text{CD}_3$ (δ 2.05) served as an internal standard for ^1H NMR spectra. Data are reported as follows: chemical shift (ppm on the δ scale), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet and po = partially overlapped), coupling constant *J* (Hz), and integration. CDCl_3 (δ 77.16) or acetone- d_6 (δ 29.84, 206.26) was used as an internal standard for ^{13}C NMR spectra. Primary NMR data files were processed by MestReNova. High-resolution mass spectra (HRMS) were recorded with a Bruker MaXis ESI qTOF ultrahigh-resolution mass spectrometer (FR2708, Orléans) coupled to a Dionex Ultimate 3000 RSLC system. MS data were acquired in positive mode and were processed using Data Analysis 4.4 software (Bruker). For tin compounds, data values were reported from the major ^{120}Sn isotope. Infrared spectra were recorded with a Thermo Scientific Nicolet IS10 FTIR spectrometer using diamond ATR golden gate sampling and are reported in wave numbers (cm^{-1}). Specific optical rotations were measured with a JASCO P-2000 digital polarimeter, in a thermostated (20 °C) 1 dm long cell with high-pressure sodium lamp and are reported as follow: $[\alpha]_D^{25}$ [solvent, *c* (g/100 mL)]. Analytical thin-layer chromatography (TLC) was performed with Merck Silica Gel 60 F254 precoated plates. Visualization of the developed chromatogram was performed under ultraviolet light (254 nm) and on staining by immersion in aqueous, acidic ceric ammonium molybdate (CAM), followed by charring at 150 °C. Flash chromatography was performed in air on silica gel 60 (230–400 mesh) with petroleum ether (PE, bp 40–65 °C) and ethyl acetate as eluents, unless otherwise stated. Organic solutions were concentrated under reduced pressure with a Büchi rotary evaporator. The diastereomeric ratio (dr) was determined by ^1H NMR analysis of the unpurified product after aqueous workup and after isolation via column chromatography (SiO_2).

General Procedure for the O-Benzoylation of Compounds (1R)-4 and (1S)-4 (G.P. A). A single-necked round-bottomed flask under argon atmosphere was charged with the *D*-arabinitol substrate ((1R)-4 or (1S)-4), anhydrous CH_2Cl_2 , *N,N,N',N'*-Tetramethylethylenediamine (TMEDA, 1.2 equiv.), a magnetic stir bar, and 4 Å activated MS (ca. 0.85 g per mmol of substrate). The suspension mixture was pre-stirred at room temperature (r.t.) for 10 min, benzoyl chloride (1.2 equiv.) was subsequently added, and the reaction mixture was stirred further at the same temperature during 2 h. Next, a phosphate buffer solution (pH = 7) was added and the mixture was diluted with CH_2Cl_2 (ca. 25 mL). The phases were separated and the aqueous layer was extracted thrice with CH_2Cl_2 (ca. 3 × 25 mL). Combined organic extracts were washed with brine (ca. 25 mL), dried over MgSO_4 , filtered through a cotton plug and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to give the related O-protected *D*-arabinitol derivative in almost quantitative yield.

General Procedure for the Stille Cross-Coupling Reaction of Stannylated Aminoalditols (1R)-5 and (1S)-5 (G.P. B). An oven dried 2–5 mL microwave reaction vial was charged with stannylated aminoalditol derivative 5 (2.0

equiv.), Pd₂(dba)₃ (1.25 mol%), JackiePhos (5 mol%), CuCl (5 mol%), MS (4 Å) 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 acryloyl chloride (1.0 equiv.) were then added via syringe, the vial was sealed and the reaction mixture was heated (regular heating with an oil bath) during 6 h, at 100 °C under argon atmosphere. After cooling to rt, the cap was removed, the brown solution was diluted (CH₂Cl₂) and the mixture was filtered through celite®. Next, the cake was rinsed (CH₂Cl₂) and the filtrate solution was concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO₂) to give the cross-coupled product **6** in moderate to good yield (50–88%).

General Procedure for the Reduction of Compounds (1S)-6a and (1R)-6a (G.P. C). A single-necked round-bottomed flask under argon atmosphere was charged with the linear Stille cross-coupled product [(1S)-**6a** or (1R)-**6a**, 1 equiv.], dry MeOH (ca. 12 mL), NaBH₄ (3 equiv.) and a magnetic stir bar. The reaction mixture was stirred at 0 °C, and allowed to reach r.t. overnight (24 h). The solvent was then removed under reduced pressure and the crude residue was diluted with EtOAc (ca. 25 mL). The organic phase was washed with water (ca. 12 mL) and the aqueous phase was extracted thrice with EtOAc (ca. 3 × 25 mL). Next, combined organic extracts were dried (MgSO₄), filtered through a cotton plug and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel to provide the related alditol compound in good yield (74–76%).

General Procedure for the O-Debenzoylation of Compounds 7 and 11 (G.P. D). A single-necked round-bottomed flask under argon atmosphere was charged with compound **7** or **11** (1 equiv.), MeOH, K₂CO₃ (2.2 equiv.) and a magnetic stir bar, and the reaction mixture was stirred at 20 °C for 5 h. Once the reaction completed (TLC monitoring), the solvent was removed (rotary evaporation) and the residue was diluted with EtOAc (10–20 mL). The organic phase was filtered through a cotton plug and concentrated *in vacuo*. The crude product was purified by SiO₂-column chromatography to give the O-debenzoylated product in excellent yield (91–94%).

General Procedure for the Cyclization of Compounds 8 and 12 (G.P. E). A single-necked round-bottomed flask under argon atmosphere was charged with D-mannitol **8** or the mixture of D-glucitols (1R)- and (1S)-**12** (1 equiv.), anhydrous pyridine, 4-dimethylaminopyridine (DMAP, 0.35 equiv.), 4 Å activated molecular sieves (ca. 1.25 g per mmol of substrate), and a magnetic stir bar. The mixture was cooled down to 0 °C, and methanesulfonyl chloride (MsCl, 2.1 equiv.) was added (dropwise addition). The reaction mixture was stirred at 0 °C for 3 h and at 20 °C for 3 h. Next, the mixture was diluted with CH₂Cl₂ (20 mL) and the organic phase was washed with sat. aq. NH₄Cl (20 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL) and the combined organic phases were dried over MgSO₄, filtered through a cotton plug and concentrated *in vacuo*. The crude mesylated derivative was subsequently used in the cyclization step without further purification.

A mixture of the just generated mesylated intermediate in anhydrous pyridine was heated (oil bath) at 90 °C for 22 h. The solution mixture was allowed to reach r.t. and it was diluted with CH₂Cl₂ (ca. 10 mL). The organic phase was then washed with sat. aq. CuSO₄ (ca. 10 mL), and the aqueous phase was extracted thrice with CH₂Cl₂ (ca. 3 × 10 mL). Next, combined organic layers were dried over MgSO₄, filtered through a cotton plug and concentrated under reduced pressure. The expected

cyclized product was isolated after column chromatography over silica gel in good overall yield (74–77%).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/XX.XYZA/acs.joc.2c00XYZ>

Copies of ¹H NMR, and ¹³C {¹H} NMR spectra of compounds (1R)-**5**, (1S)-**5**, (1R)-**6a**, (1S)-**6a-e**, **7**, **8**, **9**, **10**, (1R)-**11** and (1S)-**11**, (1R)-**12** and (1S)-**12**, α-**14**, and β-**14**, including one- and two-dimensional NMR spectra, and retrosynthetic analysis of compounds **10**, α-**14** and β-**14** (PDF).

FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for all compounds mentioned hereabove.

AUTHOR INFORMATION

Corresponding Authors

Cyril Nicolas – Institut de Chimie Organique et Analytique, Equipe "Methodologies, Heterocyclic Chemistry, Green Chemistry" UMR CNRS 7311, Université d'Orléans, Rue de Chartres, BP 6759, 45067 Orléans cedex 2, France.

orcid.org/0000-0002-3748-2205

Email: cyril.nicolas@univ-orleans.fr

Olivier R. Martin – Institut de Chimie Organique et Analytique, UMR CNRS 7311, Université d'Orléans, Rue de Chartres, BP 6759, 45067 Orléans cedex 2, France.

Email: olivier.martin@univ-orleans.fr

Authors

Tuniyazi Abuduaini – Institut de Chimie Organique et Analytique, UMR CNRS 7311, Université d'Orléans, Rue de Chartres, BP 6759, 45067 Orléans cedex 2, France.

Sizhe Li – Institut de Chimie Organique et Analytique, UMR CNRS 7311, Université d'Orléans, Rue de Chartres, BP 6759, 45067 Orléans cedex 2, France.

Vincent Roy – Institut de Chimie Organique et Analytique, UMR CNRS 7311, Université d'Orléans, Rue de Chartres, BP 6759, 45067 Orléans cedex 2, France.

Luigi A. Agrofoglio – Institut de Chimie Organique et Analytique, UMR CNRS 7311, Université d'Orléans, Rue de Chartres, BP 6759, 45067 Orléans cedex 2, France.

Complete contact information is available at: <https://pubs.acs.org/XX.XYZA/acs.joc.2c00XYZ>

Author Contributions

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