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Tunable Approach for the Stereoselective Synthesis of 1-*C*-Diethylphosphono(difluoromethyl) Iminosugars as Glycosyl Phosphate Mimics

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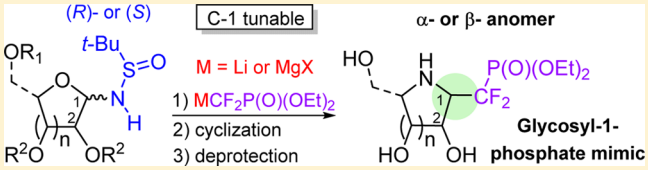
Supporting Information

ABSTRACT: An efficient methodology for the stereoselective and tunable addition of $LiCF_2P(O)(OEt)_2$ and $BrMgCF_2P(O)(OEt)_2$ reagents to *N*-*t*-butanesulfinyl glycosylamines is described with details on the stereochemical effects at play in this process. It provides a practical route to various 1-*C*-diethylphosphono(difluoromethyl) iminosugars as glycosyl phosphate and sugar nucleotide mimics.



N-protected-glycosylamines are valuable synthetic scaffolds in bioorganic and medicinal chemistry and precursors of a diversity of compounds of biological interest. In particular, such sugar derivatives behave as latent imine equivalents and are capable of reacting with a variety of carbon nucleophiles to provide 1,2-*syn* (e.g., *N*-carbonylated and *N*-benzyl-glycosylamines) or 1,2-*anti* (e.g., *N*-glycosylhydroxylamines) aminoalditols in good yields and moderate to good levels of stereoselectivity. After an activation-cyclization reaction sequence and further deprotections the related iminosugar-*C*-glycosyl compounds are obtained in good yields (Figure 1).[1]

As glycoside mimics, 1-C-substituted iminosugars are powerful inhibitors of glycosidases,[2] purine nucleoside phosphorylases, nucleoside hydrolases,[3] and also potential inhibitors of glycosyltransferases.[2a,4] They may also be employed as pharmacological chaperones to treat deficiencies resulting in improperly folded proteins.[5] *N*-*t*-Butanesulfinyl glycosylamines have recently emerged as more versatile synthetic intermediates en route to iminosugar-*C*-glycosides, although preliminary studies have shown that the Ellman's chiral auxiliary does not control the stereoselectivity at C-1 when simple organomagnesium reagents are used.[1] Pleasingly, we have recently observed that the stereoselectivity of the addition could be, in contrast, controlled by the chiral sulfinyl group when $LiCF_2P(O)(OEt)_2$ and $BrMgCF_2P(O)(OEt)_2$ reagents are used to give after the subsequent activation-cyclization steps 1-*C*-phosphono(difluoromethyl) iminosugars.

Such glycomimetics are attractive targets for the study of biochemical processes and in drug discovery. Indeed, since the pioneering studies of Blackburn[6] and Mc Kenna[7] in the early 1980s, C-difluorinated methylphosphonates have been shown to be relevant mimics of natural phosphates. The CF_2 motif is considered as an oxygen bioisoster and the difluoromethylphosphonates as isoelectronic phosphate analogs. Moreover, in contrast to the hydrolyzable P−O bond, the strength of the P−C bond provides these isosteric surrogates a remarkable metabolic resistance to phosphatase hydrolysis.[8] This outstanding feature has recently been applied to 1-phosphono-(difluoromethyl)-*C*-glycosides as mimics of sugar-1-phosphates,[9] and as potential inhibitors of glycosyltransferases,[10] and phosphoglucomutases.[11,12] So far, a single example of

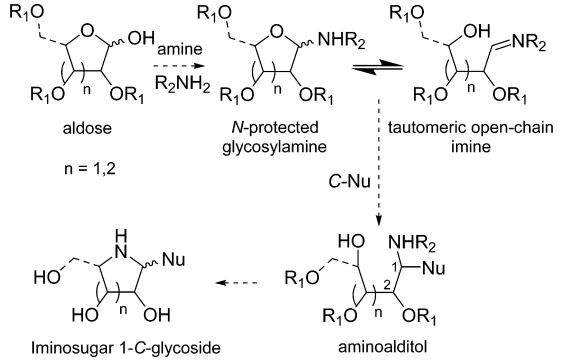


Figure 1. Protected glycosylamines: preparation and use in the synthesis of iminosugar *C*-glycosides.

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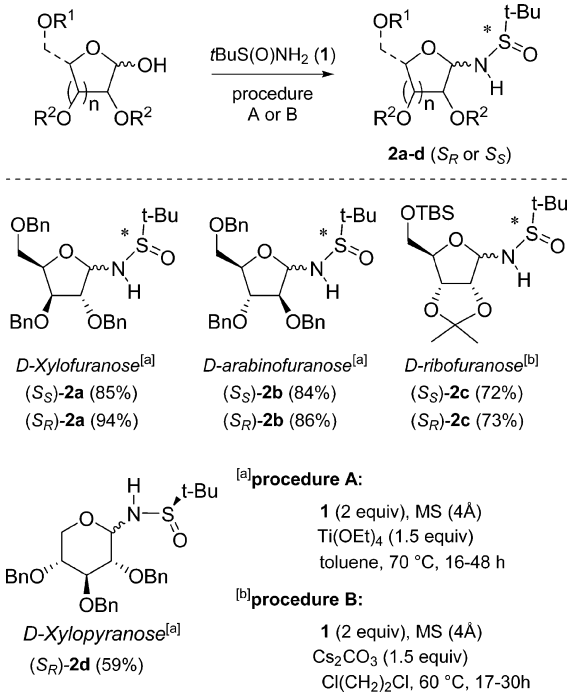
iminosugars (pyrrolidines) bearing a phosphono(difluoromethylene) group at the pseudoanomeric position has been reported by Behr and collaborators.[13] This area remained underexplored in part due to the rather disappointing activity of Behr's model compounds as chitin synthase inhibitors and in part to the lack of general synthetic strategies for the tailored preparation of α- and β-phosphono(difluoromethyl) iminosugars in pyrrolidine or piperidine series. A few examples of iminosugars carrying a C-phosphonomethyl substituent have also been reported.[4b,14]

We describe herein our results on the addition of M-$CF_2P(O)(OEt)_2$ reagents onto a range of *N*-*t*-butanesulfinyl glycosylamines with details on the stereochemical effects at play in this process. Transformation of the aminoalditols into related 1-C-phosphono(difluoromethyl) iminosugars is also reported. To our knowledge it is the first synthetic methodology to access (1*S*)- and (1*R*)-iminosugar-*C*-glycosides (i.e., mimics of α- and β-glycosides) in a C-1 tunable and predictable manner.

For the purpose of our study, a set of *N*-*t*-butanesulfinyl glycosylamines of interest was selected (**2a**–**d**, Scheme 1). The

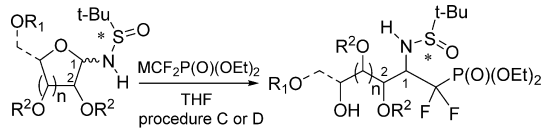
Scheme 1. Preparation of Sulfinylglycosylamines



model substrates were prepared in good yields (i.e., 72–94%) to afford D-*arabino*, D-*ribo*, or D-*xylo*-furanose derivatives **2b**, **2c**, **2a**, and D-*xylo*-pyranose **2d**.[15] Different protecting groups were incorporated (e.g., OBn, OTBS, etc.) to ensure a relatively high degree of diversity with a choice of furanose and pyranose chemical structures and (*R*)- or (*S*)- Ellman's chiral auxiliaries (e.g., (S_S)-**2** vs (S_R)-**2**).

Introduction of the $-CF_2P(O)(OEt)_2$ moiety was then performed using the corresponding organometallic species (M = Li, procedure C; M = MgX procedure D) to provide aminoalditols **3a**–**d** (Table 1). Optimization of the reaction conditions (solvents, additives, stoichiometry, etc.) was systematically accomplished for both metalated species (see SI for optimization tables). Overall, $LiCF_2P(O)(OEt)_2$ was generated from LDA (4.2 equiv) and $HCF_2P(O)(OEt)_2$ (4.3 equiv) in THF at −60 °C.[16]

Table 1. Addition of M-$CF_2P(O)(OEt)_2$ Metalated Species



2a-d (1 equiv) **3a-d**

entry	substrate	procedure[a]	product	**3** ratio (1*R*:1*S*)[b]	**3** yield (%)[c]
1	(S_S)-**2a**	C	(S_S)-**3a**	9:1	49
2	(S_S)-**2a**	D	(S_S)-**3a**	8:2	75
3	(S_R)-**2a**	C	(S_R)-**3a**	5:95	61
4	(S_R)-**2a**	D	(S_R)-**3a**	0:10	88
5	(S_S)-**2b**	C	(S_S)-**3b**	10:0	62
6	(S_S)-**2b**	D	(S_S)-**3b**	10:0	52
7	(S_R)-**2b**	C	(S_R)-**3b**	4:6	71
8	(S_R)-**2b**	D	(S_R)-**3b**	3:7	68
9	(S_S)-**2c**	C	(S_S)-**3c**	6:4	44
10	(S_S)-**2c**	D	(S_S)-**3c**		
11	(S_R)-**2c**	D	(S_R)-**3c**	0:10	85
12	(S_R)-**2d**	D	(S_R)-**3d**	0:10	72

[a]Procedure C: (1) *i*-Pr_2NLi, $F_2HCP(O)(OEt)_2$, THF, − 60 °C; (2) **2a**–**d**, − 60 to −30 °C, 1 h. Procedure D: (1) *i*-PrMgCl, LiBr, THF, − 20 °C, 5–10 min; (2) $BrF_2CP(O)(OEt)_2$, − 75 °C, 5–10 min; (3) **2a**–**d**, − 75 to −30 °C, 1.5 h. [b]d.r determined on crude mixture using ^1H NMR spectroscopy. [c]Isolated yields (column chromatography).

The much less stable Grignard analogue was in turn prepared by bromine–magnesium exchange, reacting diethyl bromodifluoro-methylphosphonate ($BrCF_2P(O)(OEt)_2$) with *i*-PrMgCl (1.2 M in Et_2O) and LiBr in THF at −75 °C.[17] Due to significant decomposition of the magnesium reagent during the course of the reaction, a large excess was mandatory (i.e., 8 equiv). In all cases, we noted by TLC analysis of the reaction mixtures that the anomers of the related *N*-sulfinyl-*N*-glycosides did not react at the same temperature (ca. − 60 °C vs −40 °C). We have observed similar results for the addition of commercial magnesium reagents to glycosylamines of type **2**.[1] The organolithium and organomagnesium derivatives were then added to compounds **2a**–**d** and the reaction mixtures were allowed to reach −30 °C over 1 and 1.5 h, respectively. The corresponding aminoalditols **3a**–**d** were obtained in moderate to good yields (44–88%) and modest to excellent diastereoselectivities (6:4 to 10:0). In general, addition of the lithium and magnesium species proceeded well, albeit with slightly lower efficiencies in the case of the lithiated phosphonate. Interestingly, the addition of $BrMgCF_2P(O)(OEt)_2$ was very efficient for (S_R)-**2c** (matched) but did not work on the (S_S)-**2c** epimer (mismatched situation). The addition of $LiCF_2P(O)(OEt)_2$ succeeded however on the latter substrate, though with partial deprotection of the TBS group (Table 1, entry 9–11).

The configuration at C-1 was then determined by nuclear Overhauser effect spectroscopy (NOESY) on cyclized products: in the general procedure E (Scheme 2), the major diastereomers of series **3a**–**d** were isolated, then mesylated and treated with a base to achieve cyclization (see Experimental Section, compounds **7a**–**d**); the sulfinyl protecting group was then removed with mild acid to generate the imino-*C*-glycosyl derivatives (1*S*)- and (1*R*)-**4a**–**d** (Scheme 2) on which NMR studies could be performed. Alternatively, the sulfinyl group was cleaved first and cyclization promoted from the free amine (procedure F), a procedure required for the formation of the less entropically favored iminohexitol (1*S*)-**4d** which did not cyclize under conditions E.

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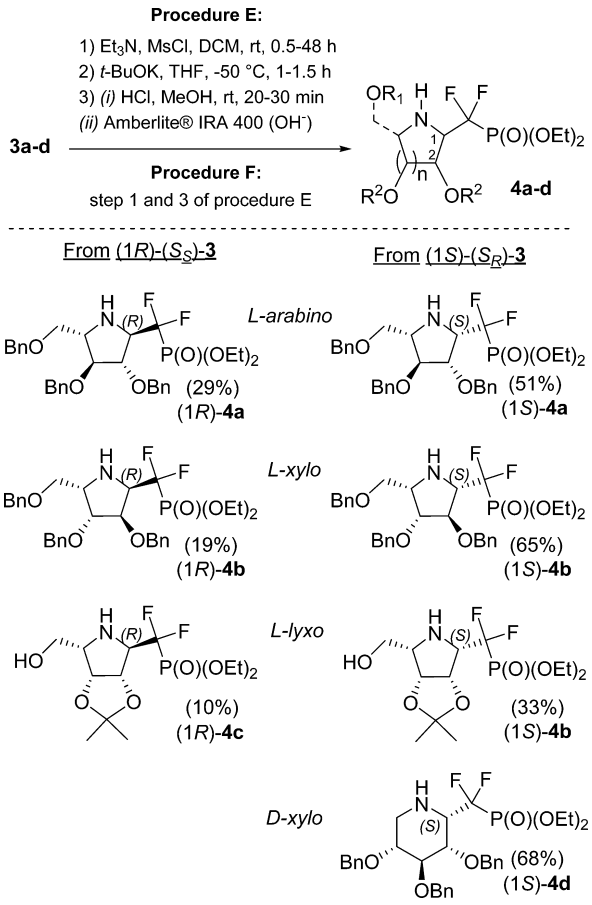
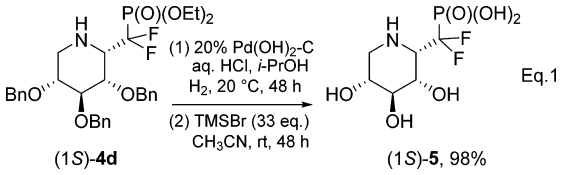
Scheme 2. Synthesis of Glycosyl Phosphate Mimics and Configuration Determination



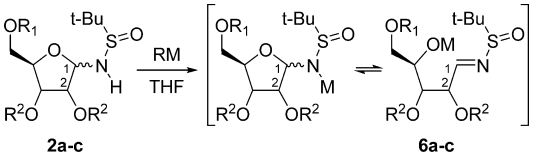
Remarkably, as shown in Scheme 2, the structures of the cyclized products reveal that the control of the stereochemistry at C-1 is dominated by the chiral auxiliary in all cases. As a rule, glycosylamines (S_S)-**2** give (1*R*)-(S_S)-**3a−d** (i.e., a pseudo α-anomer) and (S_R)-**2**, (1*S*)-(S_R)-**3a−d** (i.e., a pseudo β- anomer) respectively, as the major products. Nevertheless, match/mismatch effects are observed as one sulfinyl configuration leads to a much higher degree of stereoselectivity than the other (Table 1). It is important to note that, whatever the configuration of the sulfinyl group is, matching is observed for 1,2-*syn* iminoalditols **4a−d** and mismatching for 1,2-*anti* products.

Glycosyl-1-phosphates are central structural motifs that play pivotal role in numerous biological mediated processes.[15] The glucose-1-phosphate mimetic (1*S*)-**5** was thus prepared in good yield (98% over 2 steps, see eq 1) by hydrogenolysis and subsequent treatment of (1*S*)-**4d** with large excess of TMSBr (33 equiv) in CH_3CN.



Quantum chemical calculations were performed to rationalize the auxiliary effect and the match/mismatch behavior described in Table 1. The study is greatly complicated by the numerous possible aggregation states of the nucleophiles, and hence energetically accessible addition modes. For these reasons, the direct investigation of the activation barriers leading to the different addition products, to quantify the selectivities observed, was deemed intractable. Instead, we investigated the conformational preference of the *O*-metalated imine intermediates **6a−c**, obtained after the deprotonation of compounds **2a−c** (Scheme 3). We assumed that internal

Scheme 3. Formation of Intermediates 6a−c



complexation of the metal by either the imine and/or the various ether groups on the intermediate would be entropically favored versus solvent complexation, simplifying conformational investigation. We did not consider complexation of multiple organometallic species on the substrate, as we assumed the entropically favored internal complexation would dominate conformational control. We postulated that there could be a relation between the most stable conformations of **6a−c** and the selectivities observed, bringing qualitative insights on the addition process.

Thorough conformational sampling of the metalated (MgBr) intermediates was performed.[19] The benzyloxy groups on **6a** and **6b** were replaced by methoxy groups to simplify conformational sampling. After removal of duplicates and supplementary geometry optimizations, the resulting lowest energy conformations were fully optimized at the M06-2X[20]/6-31+G(d,p)[21] level, including SMD implicit solvation model for THF.[22] The DFT calculations were performed with Gaussian 09.[23] Only the lowest energy conformers are illustrated for the discussion (Figure 2), the complete analysis is included in the SI.

In all cases, the accessible imine face in the most stable conformations is representative of the major product observed. Furthermore, the intermediates leading to high selectivities ((S_R)-**6a**, (S_S)-**6b**, and (S_R)-**6c**), the most stable conformers are well-defined and present Cram-chelate orientation of the 2-stereogenic center. This would effectively lead to facile nucleophile chelation, imine activation, and unencumbered nucleophilic addition. In contrast, for the intermediates leading to low selectivities ((S_S)-**6a** and (S_R)-**6b**), either Cornforth-type or encumbered attack trajectories were found. Considering the large negative partial charge on the $MCF_2P(O)(OEt)_2$ nucleophilic moiety, due to the two fluorine atoms, the presence of an ether group in the nucleophile trajectory could result in strong electrostatic repulsion. In particular, for intermediate (S_R)-**6b**, leading to the lowest level of stereoselectivities, numerous low energy conformations with conflicting facial discrimination, were found.[19] The ribofuranose derivatives (**2c**) have a peculiar behavior. Due to the additional constraint from the acetonide protecting group, both intermediates (S_S)-**6c** and (S_R)-**6c** result in well-defined, low energy, Cram Chelate-like conformations. In these conformations, auxiliary *tert*-butyl group is constrained on either face of the imine. In (S_S)-**6c**, it is effectively blocking the *pro-S* face, leading to an unreactive intermediate.

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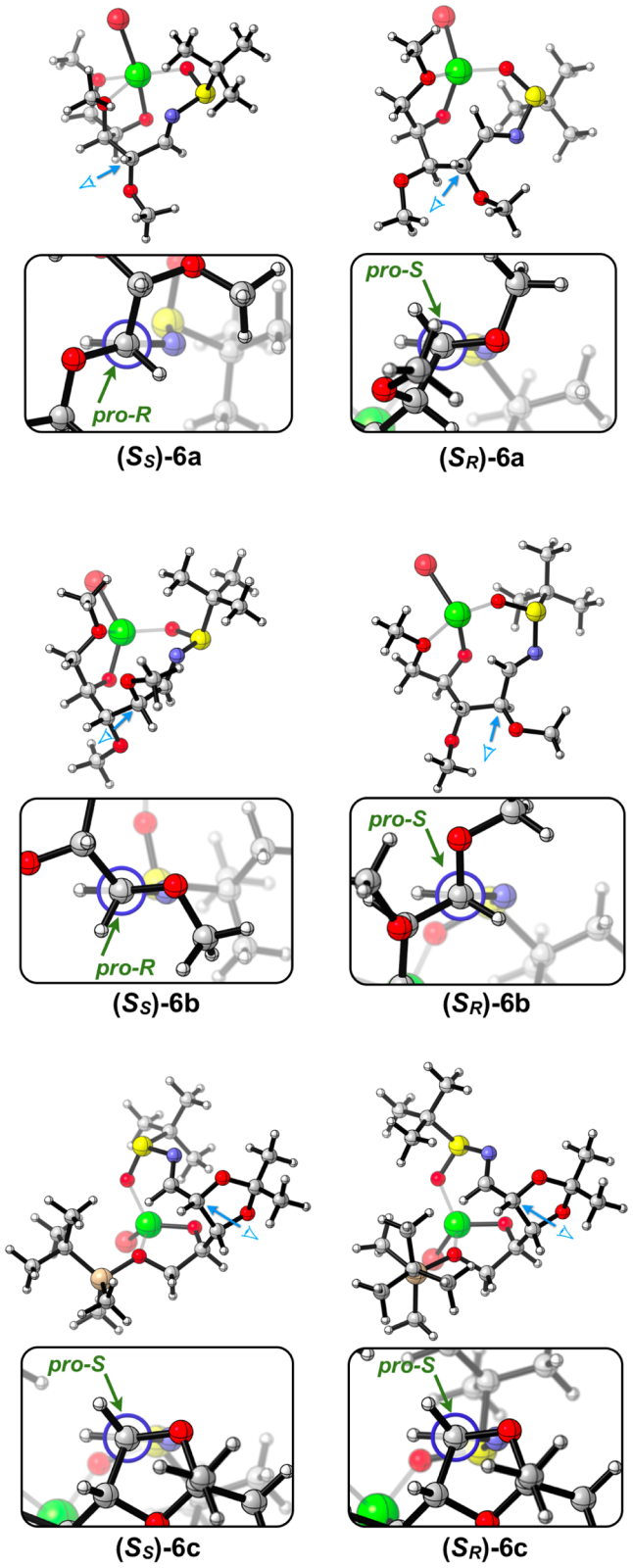

Figure 2. Structures and Newman projections of the lowest energy conformations found for intermediates **6a–c**.[18]

Interestingly, previously reported results using simple organomagnesium reagents did not show this peculiar match/mismatch behavior. The unique nature of the $MCF_2P(O)(OEt)_2$ reagents could greatly influence the aggregation state in solution and the effect of substituents in the nucleophilic attack trajectory. It seems clear, however, from the described structural analysis, that there is a correlation between the conformational preference of the opened metalated intermediates **6a–c** and the stereochemical outcome of the reaction.

In conclusion, we have developed an efficient methodology for the synthesis of glycosyl phosphate mimics based on an iminosugar scaffold and carrying a phosphonodifluoromethyl substituent. Such compounds are desirable probes or inhibitors for a large number of biological processes involving glycosyl phosphates and sugar nucleotides. The methodology has the great advantage of being tunable, i.e., the pseudoanomeric configuration of the glycosyl phosphate mimics can be chosen by selecting the configuration of the sulfinyl group in the starting *N*-*t*-butanesulfinyl glycosylamines. The methodology demonstrated a broad substrate scope and good protecting group tolerance. Insights into the reaction mechanism and factors controlling stereoselectivities were gained from quantum chemical calculations; these can be exploited to predict the selectivities in future novel substrates.

EXPERIMENTAL SECTION

General Remarks. Unless otherwise stated, all reagents were purchased from commercial sources and used as received. 2,3,5-Tri-*O*-benzyl-D-xylofuranose,[24] 2,3,4-tri-*O*-benzyl-D-xylopyranose,[25] (S_R)-**2c**,[26] (S_R)-**2a**, (S_S)-**2b**, (S_R)-**2b**, and (S_S)-**2c**,[1] were prepared following reported procedures. Diisopropylamine was distilled over KOH prior to use. *n*-BuLi and isopropylmagnesium chloride were titrated using salicylaldehyde phenylhydrazone as indicator.[27] Toluene (puriss. p.a., ACS reagent, ≥ 99.7% (GC)) and THF (99.9% GC) with 2,6-di-*tert*-butyl-4-methylphenol (250 mg/L) as stabilizer were purified by passage through a column containing activated alumina under nitrogen pressure (Dry Solvent Station GT S100, GlassTechnology, Geneva, CH). Dichloromethane (99.99% GC) was distilled from calcium hydride and used as solvent in reactions under anhydrous conditions. Four Å MS was activated by drying in an oven at 500 °C (48 h). It was then allowed to reach room temperature and kept over $CaCl_2$ in a desiccator prior to use. Amberlite IRA-400 was prepared in its OH^- form by passing 1 M KOH until the effluent is free from chloride ions, then washed with distilled H_2O until neutral and MeOH. NMR spectra were recorded at 298 K with a Bruker Avance III HD nanobay 400 MHz spectrometer equipped with a BBO probe. The nuclei-signal assignments were done with the aid of 1 D [^{1}H NMR, ^{13}C NMR, Distortionless Enhancement by Polarization Transfer (DEPT)] and 2 D Correlation Spectroscopy [(^{1}H–^{1}H COSY and ^{1}H–^{13}C Heteronuclear Single Quantum Coherence (HSQC)] experiments. When appropriate or in case of ambiguous proton and carbon, assignments were established using ^{19}F NMR, heteronuclear multiple-bond correlation (HMBC), and nuclear Overhauser effect spectroscopy (NOESY). ^{1}H NMR (400 MHz) chemical shift values are listed in parts per million (ppm) downfield from TMS as the internal standard or relative to the corresponding nondeuterated solvent. Data are reported as follows: chemical shift (ppm on the δ scale), multiplicity (s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, t = triplet, and m = multiplet), coupling constant *J* (Hz), and integration. ^{13}C NMR (101 MHz) chemical shifts are given in ppm relative to the corresponding nondeuterated solvent or TMS as the internal standard. ^{19}F NMR (376 MHz) chemical shifts are given in ppm relative to C_6F_6 as the internal standard. High-resolution mass spectra were recorded with a MaXis ESI qTOF ultrahigh-resolution mass spectrometer (FR2708, Orléans). 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 Perkin–Elmer 341 polarimeter in a thermostated (20 °C) 1 dm long cell with high-pressure sodium lamp and are reported as follow: $[\alpha]_D^T$ [solvent, *c* (g/100 mL)]. Analytical thin-layer chromatography (TLC) was performed with Merck Silica Gel 60 F254 precoated plates.

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Visualization of the developed chromatogram was performed under ultraviolet light (254 nm) and on staining by immersion in aqueous, acidic ceric ammonium molybdate (CAM; 470 mL H_2O, 28 mL H_2SO_4, 24 g ammonium molybdate, 0.5 g cerium ammonium nitrate) followed by heating on a hot plate. Normal phase flash chromatography was performed in air on silica gel 60 (230−400 mesh) with petroleum ether (PE, bp 40−65 °C) and ethyl acetate (EA) as eluents, unless otherwise stated. Reversed-phase chromatography was performed on an automated system (Reveleris flash chromatography system, Grace Materials Technologies, Epernon, FRA). C18 Reversed-phase Grace Reveleris (ultra pure 40 μm silica) flash cartridges were used with water (A) and acetonitrile (B) as eluents. Organic solutions were concentrated under reduced pressure with a Buchi rotary evaporator.

General Procedure for the Preparation of *N*-*tert*-Butanesulfinyl Glycosylamines 2a, 2b, and (S_R)-2d (GP A). The related aldose (1 equiv., 0.5 M) was dissolved in dry toluene in the presence of 4 Å activated molecular sieves under argon atmosphere and 2-methyl-2-propanesulfinamide **1** (2 equiv) was added. After 10 min of stirring at room temperature (ca. 20 °C), $Ti(OEt)_4$ (1.5 equiv) was inserted and the reaction mixture was stirred at 70 °C until no starting material was present (16−48 h). The slightly brown solution was then diluted (CH_2Cl_2) and molecular sieves were filtered through Celite. The mother liquor was recovered and stirred with brine during 5 min. The mixture was again filtered through Celite, the cake washed with CH_2Cl_2 and the phases were separated. The organic phase was dried ($MgSO_4$) filtered through a cotton plug and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, PE:EA) to provide the *N*-tert-butanesulfinyl glycosylamine in moderate to good yield.

*2,3,5-Tri-O-benzyl-(S_S)-N-tert-butanesulfinyl-α/β-D-xylofuranosylamine (S_S)-**2a**.* The titled compound (S_S)-**2a** was synthesized according to GP A and isolated as colorless oil (107 mg, 85%). Mixture of anomers which was not assigned (α/β 54:46). R_f 0.5 and 0.3 (SiO_2, PE:EA 5:5). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.38−7.19 (m, 15 H), 5.47 (dd, *J* = 4.3, 8.7 Hz, 0.46 H), 5.10 (br d, *J* = 11.2 Hz, 0.54 H), 4.83 (d, *J* = 8.8 Hz, 0.46 H), 4.64−4.47 (m, 6.1 H), 4.40 (d, *J* = 12.0 Hz, 0.48 H), 4.35−4.27 (m, 1 H), 4.16−4.11 (m, 0.54 H), 4.07−4.04 (m, 0.55 H), 4.04−4.01 (m, 0.46 H), 4.00−3.96 (m, 0.46 H), 3.81 (dd, *J* = 5.2, 9.9 Hz, 0.56 H), 3.72−3.61 (m, 1.52 H), 1.23 (s, 4.05 H), 1.02 (s, 4.96 H) ppm. IR (neat) 3281, 3031, 2867, 1454, 1364, 1207, 1067, 1028, 737 cm^{-1}. HRMS (ESI) *m*/*z*: calcd. for $C_{30}H_{38}NO_5S$ $[M+H]^+$ 524.246521, found 524.246368.

*2,3,4-Tri-O-benzyl-(S_R)-N-tert-butanesulfinyl-β-D-xylopyranosylamine (S_R)-**2d**.* The titled compound (S_R)-**2a** was synthesized according to GP A and isolated as colorless oil (220 mg, 59%). Mixture of anomers which was not assigned (α/β ∼ 6:4). R_f 0.5 (SiO_2, PE:EA 5:5). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.38−7.22 (m, 15 H), 5.07 (dd, *J* = 4.0, 8.1 Hz, 0.4 H), 4.93 (d, *J* = 11.0 Hz, 0.6 H), 4.84 (d, *J* = 7.9 Hz, 0.6 H), 4.82 (d, *J* = 7.6 Hz, 0.6 H), 4.75 (d, *J* = 11.3 Hz, 0.6 H), 4.72−4.53 (m, 4 H), 4.48 (dd, *J* = 5.1, 8.2 Hz, 0.6 H), 3.97−3.90 (m, 1.2 H), 3.85 (dd, *J* = 7.0, 12.1 Hz, 0.4 H), 3.76 (dd, *J* = 4.1, 12.1 Hz, 0.4 H), 3.73−3.57 (m, 1.6 H), 3.54 (dd, *J* = 4.0, 6.7 Hz, 0.4 H), 3.50−3.44 (m, 0.4 H), 3.33 (t, *J* = 8.2 Hz, 0.6 H), 3.27 (dd, 0.6 H, *J* = 10, 11.5 Hz), 1.18 (s, 3.6 H), 1.11 (s, 5.4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.4, 138.2, 138.2, 138.1, 137.8, 137.5, 128.8−127.9, 86.1, 84.5, 79.6, 79.4, 77.8, 77.4, 76.9, 75.5, 75.1, 74.5, 74.3, 73.2, 72.5, 72.4, 65.1, 62.1, 56.4, 55.9, 22.6, 22.4 ppm. IR (neat): 3223, 3030, 2869, 1454, 1363, 1313, 1207, 1071, 1028, 735· cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{30}H_{38}NO_5S$ $[M+H]^+$ 524.246521, found 524.246471.

General Procedure for the Diastereoselective Addition of (Diethylphosphinoyl)-difluoromethyllithium (GP C) and (Diethylphosphinoyl)-difluoromethylmagnesium Bromide (GP D) to *N*-*tert*-Butanesulfinyl Glycosylamines. *GP C.* A single-necked round-bottomed flask under argon atmosphere was charged with diisopropylamine (4.2 equiv) and dry THF. The solution was cooled to 0 °C (ice−water bath) and *n*-BuLi (1.6 M in THF, 4.2 equiv) was added dropwise. The yellow solution was then stirred for 30 min, after which, it was cooled to −60 °C (dry ice−acetone) and diethyl-(difluoromethyl)phosphonate (4.3 equiv) was added (dropwise addition) (flask A). Another single-necked round-bottomed flask under argon atmosphere was charged with *tert*-butanesulfinyl glycosylamine **2a−d** (1 equiv) and dry THF was added (solution B). Solution B was added to flask A (dropwise addition with a syringe) and the reaction mixture was allowed to reach −30 °C over 1 h. Aqueous NH_4Cl was added and the organic layer was diluted with EtOAc. The aqueous phase was discarded and the organic layer was dried over $MgSO_4$, filtered through a cotton plug, and concentrated *in vacuo*. The crude product was purified by SiO_2−column chromatography.

GP D. A single-necked round-bottomed flask under air atmosphere was charged with LiBr (8 equiv) and heated at 150 °C during 3 h under vacuum. The vessel was allowed reaching room temperature and argon atmosphere was installed. Dry THF was added and the suspension was cooled to −20 °C (dry ice−acetone). Isopropylmagnesium chloride (1.2 M in Et_2O, 8 equiv) was added dropwise and the mixture was cooled to −75 °C. Subsequent insertion of diethyl-(bromodifluoromethyl)phosphonate (8 equiv) was performed dropwise (flask A). A second single-necked round-bottomed flask was charged with *N*-*tert*-butanesulfinyl glycosylamine **2a−d** (1 equiv) and dissolved in dry THF under an atmosphere of argon (flask B). Solution B was added to flask A dropwise (syringe) and the reaction mixture was allowed to reach −30 °C over 1.5 h. Aqueous NH_4Cl was added and the two phases were separated. The organic layer was dried ($MgSO_4$), filtered through a cotton plug, and concentrated under vacuum. The crude mixture was purified by C18 reversed-phase chromatography.

*1-C-(1R)- and 1-C-(1S)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,5-tri-O-benzyl-1-(S_S)-N-tert-butanesulfinylamino-1-deoxy-D-xylitol (1R)-(S_S)-**3a** and (1S)-(S_S)-**3a**.* Following GP C, diisopropylamine (110 μL, 0.80 mmol) was dissolved in dry THF (1 mL) and *n*-BuLi (1.6 M in THF, 500 μL, 0.8 mmol) was added, followed by diethyl(difluoromethyl)phosphonate (130 μL, 0.86 mmol). (S_S)-**2a** (100 mg, 0.19 mmol) was dissolved in dry THF (1 mL). (S_S)-**3a** was obtained as a 9:1 mixture of diastereomers (66 mg, 49%). The two diastereomers were separated (SiO_2, PE:EA 55:45) to provide (1*R*)-(S_S)-**3a** (60 mg, 44.5%) and (1*S*)-(S_S)-**3a** (6 mg, 4.5%) as yellow oil.

Following GP D, LiBr (13 mg, 0.15 mmol) was added, followed by dry THF (1 mL), isopropylmagnesium chloride (1.2 M in Et_2O, 130 μL, 0.15 mmol) and diethyl(bromodifluoromethyl)phosphonate (28 μL, 0.15 mmol). (S_S)-**2a** (10 mg, 0.02 mmol) was dissolved in dry THF (1 mL). Compound (S_S)-**3a** was obtained as a mixture of diastereomers (8:2 (1*R*)-(S_S)-**3a**: (1*S*)-(S_S)-**3a**) in 75% yield.

(1*R*)-(S_S)-**3a**. R_f 0.3 (SiO_2, PE:EA 5:5). $[\alpha]_D^{20}$ + 32.5° (*c* 1.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.44−7.22 (m, 15 H), 5.08 (d, *J* = 6.7 Hz, 1 H), 4.90 (d, *J* = 11.3 Hz, 1 H), 4.73 (d, *J* = 10.7 Hz, 1 H), 4.57 (d, *J* = 10.7 Hz, 1 H), 4.50−4.39 (m, 3 H), 4.28−4.15 (m, 6 H), 4.11−4.04 (m, 2 H), 3.54−3.43 (m, 2 H), 1.36−1.29 (m, 6 H), 1.02 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.2, 137.9, 137.3, 128.9−127.7, 79.3, 76.4, 74.5, 73.3, 72.5, 71.5, 70.8, 65.0, 64.9, 59.6 (dd, *J* = 19.5, 39.3 Hz), 56.7, 22.6, 16.5, 16.5 (d, *J* = 5.1 Hz) ppm. ^{19}F NMR (235 MHz, $CDCl_3/C_6F_6$): δ − 114.1 (ddd, *J* = 12.9, 104.2, 303.3 Hz, F), − 118.7 (ddd, *J* = 18.5, 105.3, 303.3 Hz, F′) ppm. IR (neat): 3302, 2982, 2875, 1454, 1392, 1365, 1266, 1018, 733 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{35}H_{49}F_2NO_8PS$ $[M+H]^+$ 712.287908, found 712.287222.

(1*S*)-(S_S)-**3a**. R_f 0.2 (SiO_2, PE:EA 5:5). $[\alpha]_D^{20}$ + 7.2° (*c* 0.59, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.37−7.15 (m, 15 H), 4.86 (d, *J* = 10.7 Hz, 1 H), 4.81−4.73 (m, 2 H), 4.56−4.44 (m, 3 H), 4.40 (d, *J* = 11.8 Hz, 1 H), 4.36−4.32 (m, 4 H), 3.96−3.80 (m, 3 H), 3.59−3.54 (m, 1 H), 3.52−3.45 (m, 1 H), 3.08 (br s, 1 H), 1.42−1.33 (m, 6 H), 1.19 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.6, 138.1, 138.1, 128.5−127.6, 79.1 (d, *J* = 2.1 Hz), 76.4 (d, *J* = 5.0 Hz), 75.6, 74.7, 73.5, 70.8, 68.9, 65.6 (d, *J* = 7.7 Hz), 65.5 (d, *J* = 7.1 Hz), 59.0−58.6 (m), 57.6, 23.0, 16.5 (d, *J* = 5.5 Hz), 16.4 (d, *J* = 5.5 Hz) ppm. ^{19}F NMR (235 MHz, $CDCl_3/C_6F_6$): δ − 106.2 (ddd, *J* = 6.0, 103.3, 304.9 Hz, F), − 121.7 (ddd, *J* = 24.0, 100.8, 303.8 Hz, F′) ppm. IR (neat): 3356, 3031, 2927, 1454, 1393, 1258, 1088, 1021, 880,

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735 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{35}H_{49}F_2NO_8PS$ $[M+H]^+$ 712.287908, found 712.287781.

*1-C-(1S)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,5-tri-O-benzyl-1-(S_R)-N-tert-butanesulfinylamino-1-deoxy-D-xylitol (1S)-(S_R)-**3a**.* Following GP C, diisopropylamine (170 μL, 1.22 mmol), was dissolved in dry THF (1.5 mL) and *n*-BuLi (1.6 M in THF, 760 μL, 1.22 mmol) was added; followed by diethyl(difluoromethyl)-phosphonate (200 μL, 1.25 mmol). (S_R)-**2a** (153 mg, 0.29 mmol) was dissolved in dry THF (1.5 mL). (S_R)-**3a** was obtained as a mixture of diastereomers (dr >95:5). The two diastereomers were separated (SiO_2, PE:EA 55:45) to provide (1*S*)-(S_R)-**3a** (60 mg, 61%) as yellow oil.

Following GP D, LiBr (133 mg, 1.53 mmol) was added, followed by dry THF (6 mL), isopropylmagnesium chloride (1.2 M in Et_2O, 1.28 mL, 1.53 mmol), and diethyl(bromodifluoromethyl)phosphonate (270 μL, 1.53 mmol). (S_R)-**2a** (100 mg, 0.19 mmol) was dissolved in dry THF (4 mL). Compound (S_R)-**3a** was obtained as a single diastereomer. It was purified by Reveleris C18 reversed-phase flash chromatography (4 g cartridge, flow rate 5 mL·min^{-1}, H_2O/CH_3CN 6:4 to 2:8 (v/v) over 10 min then 2:8 until (S_R)-**3a** has eluted, t_R ~ 11.5 min) to provide (1*S*)-(S_R)-**3a** as yellow oil (120 mg, 88%).

(1*S*)-(S_R)-**3a**. R_f 0.3 (SiO_2, PE:EA 5:5). $[\alpha]_D^{20}$ − 12.2° (*c* 0.92, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.35−7.20 (m, 15 H), 4.81 (d, *J* = 10.7 Hz, 1 H), 4.76 (d, *J* = 11.5 Hz, 1 H), 4.72 (d, *J* = 8.0 Hz, 1 H), 4.71 (d, *J* = 10.8 Hz, 1 H), 4.53−4.39 (m, 4 H), 4.32−4.12 (m, 5 H), 4.06−4.00 (m, 1 H), 3.97 (d, *J* = 8.1 Hz, 1 H), 3.62 (d, *J* = 6.2 Hz, 1 H), 3.53 (dd, *J* = 6.9, 9.3 Hz, 1 H), 3.47 (dd, *J* = 5.6, 9.3 Hz, 1 H), 1.39−1.32 (m, 6 H), 1.27 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.4, 138.4, 138.3, 128.5−127.6, 78.1, 74.6, 74.3, 74.2, 73.4, 71.7, 68.3, 65.0 (d, *J* = 7.0 Hz), 64.8 (d, *J* = 6.9 Hz), 58.1−57.7 (m), 57.1, 22.9, 16.5 (d, *J* = 3.7 Hz), 16.5 (d, *J* = 3.9 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ − 114.4 (ddd, *J* = 12.3, 104.6, 303.4 Hz, F), − 119.4 (ddd, *J* = 18.6, 103.7, 303.7 Hz, F′) ppm. IR (neat): 3340, 3031, 2869, 1454, 1266, 1074, 1018, 734 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{35}H_{49}F_2NO_8PS$ $[M+H]^+$ 712.287908, found 712.287643.

*1-C-(1R)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,5-tri-O-benzyl-1-(S_S)-N-tert-butanesulfinylamino-1-deoxy-D-arabinitol (1R)-(S_S)-**3b**.* Following GP D, LiBr (66 mg, 0.76 mmol) was added, followed by dry THF (3 mL), isopropylmagnesium chloride (2 M in Et_2O, 0.38 mL, 0.76 mmol) and diethyl(bromodifluoromethyl)-phosphonate (130 μL, 0.76 mmol). (S_S)-**2b** (50 mg, 0.09 mmol) was dissolved in dry THF (2 mL). Compound (S_S)-**3b** was obtained as a single diastereomer. It was purified by Reveleris C18 reversed-phase flash chromatography (4 g cartridge, flow rate 10 mL·min^{-1}, H_2O/CH_3CN 6:4 to 0:10 (v/v), (1*R*)-(S_S)-**3b** t_R 11 min) to give (1*R*)-(S_S)-**3b** as a yellow oil (35 mg, 52%).

Following GP C, diisopropylamine (70 μL, 0.48 mmol) was dissolved in dry THF (0.5 mL) and *n*-BuLi (1.48 M in THF, 280 μL, 0.48 mmol) was added; followed by diethyl(difluoromethyl)-phosphonate (200 μL, 0.48 mmol). (S_S)-**2b** (50 mg, 0.095 mmol) was dissolved in dry THF (0.5 mL). (1*R*)-(S_S)-**3b** was obtained as a single diastereomer (62%), the yield of which was determined by ^1H NMR (400 MHz) analysis of the unpurified reaction mixture, using mesitylene as internal standard.

(1*R*)-(S_S)-**3b**. R_f 0.2 (SiO_2, PE:EA 6:4). $[\alpha]_D^{20}$ + 9.6° (*c* 1.01, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.37−7.12 (m, 15 H), 4.87 (d, *J* = 10.8 Hz, 1 H), 4.78−4.69 (m, 3 H), 4.63−4.50 (m, 4 H), 4.34 (d, *J* = 8.0 Hz, 1 H), 4.31−4.16 (m, 4 H), 4.02−3.95 (m, 1 H), 3.93−3.87 (m, 1 H), 3.75−3.65 (m, 2 H), 1.38−1.31 (m, 6 H), 1.27 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.6, 138.5, 138.2, 128.5−127.5, 79.5, 77.5, 75.0, 74.4, 73.6, 71.9, 71.7, 64.9, 64.8, 58.8−58.2 (m), 57.0, 22.9, 16.5 (d, *J* = 5.1 Hz), 16.5 (d, *J* = 5.0 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 116.0 (ddd, *J* = 13.0, 104.2, 303.2 Hz, F), − 120.5 (ddd, *J* = 18.5, 105.2, 303.2 Hz, F′) ppm. IR (neat): 3339, 2928, 2870, 1454, 1392, 1367, 1266, 1018, 736 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{35}H_{49}F_2NO_8PS$ $[M+H]^+$ 712.287908, found 712.287718.

*1-C-(1R)- and 1-C-(1S)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,5-tri-O-benzyl-1-(S_R)-N-tert-butanesulfinylamino-1-deoxy-D-arabinitol (1R)-(S_R)-**3b** and (1S)-(S_R)-**3b**.* Following GP D, LiBr (66 mg, 0.76 mmol) was added, followed by dry THF (3 mL), isopropylmagnesium chloride (2 M in Et_2O, 0.38 mL, 0.76 mmol), and diethyl(bromodifluoromethyl)phosphonate (130 μL, 0.76 mmol). (S_R)-**2b** (50 mg, 0.09 mmol) was dissolved in dry THF (2 mL). Compound (S_R)-**3b** was obtained as a 7:3 mixture of diastereomers which was purified by Reveleris C18 reversed-phase flash chromatography (4 g cartridge, flow rate 10 mL·min^{-1}, H_2O/CH_3CN 6:4 to 0:10 (v/v), mixture of two diastereomers t_R 8 min 20 s). The two diastereomers were then separated by column chromatography (SiO_2, PE:EA 6:4) to provide (1*R*)-(S_R)-**3b** (16 mg, 24%) and (1*S*)-(S_R)-**3b** (30 mg, 44%) as yellow oil.

Following GP C, diisopropylamine (70 μL, 0.48 mmol), was dissolved in dry THF (0.5 mL) and *n*-BuLi (1.48 M in THF, 280 μL, 0.48 mmol) was added. Diethyl(difluoromethyl)phosphonate (200 μL, 0.48 mmol) was then inserted. (S_R)-**2b** (50 mg, 0.095 mmol) was dissolved in dry THF (0.5 mL). The reaction mixture was allowed to reach 0 °C over 3 h. (S_R)-**3b** was obtained as a mixture of diastereomers (4:6 (1*R*)-(S_R)-**3b**:(1*S*)-(S_R)-**3b**) in 71% yield. Yield determined by ^1H NMR analysis (400 MHz) of the unpurified reaction mixture using mesitylene as internal standard.

(1*S*)-(S_R)-**3b**. R_f 0.3 (SiO_2, PE:EA 5:5). $[\alpha]_D^{20}$ − 27.5° (*c* = 1.45, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.44 (d, *J* = 7.1 Hz, 2 H), 7.36−7.23 (m, 13 H), 5.15 (d, *J* = 4.5 Hz, 1 H), 4.89 (d, *J* = 11.1 Hz, 1 H), 4.70 (d, *J* = 10.7 Hz, 1 H), 4.55−4.45 (m, 3 H), 4.39 (d, *J* = 11.2 Hz, 1 H), 4.33−4.17 (m, 6 H), 4.06 (s, 2 H), 3.71 (d, *J* = 9.9 Hz, 1 H), 3.56 (br dd, *J* = 3.2, 10.4 Hz, 1 H), 2.89 (br s, 1 H), 1.40−1.33 (m, 6 H), 0.97 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.2, 137.9, 137.2, 129.4−127.8, 80.4 (d, *J* = 2.5 Hz), 74.6−74.5 (m), 73.5, 73.2, 73.2, 71.4, 71.0, 65.1, 65.1, 59.6−59.0 (m), 56.6, 22.6, 16.6 (d, *J* = 5.7 Hz), 16.5 (d, *J* = 5.6 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 111.6 (ddd, *J* = 9.8, 102.6, 306.6 Hz, F), − 123.2 (dd, *J* = 105.6, 299.8 Hz, F′) ppm. IR (neat): 3303, 2919, 1455, 1393, 1366, 1268, 1027, 736 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{35}H_{49}F_2NO_8PS$ $[M+H]^+$ 712.287908, found 712.287690.

(1*R*)-(S_R)-**3b**. R_f 0.1 (SiO_2, PE:EA 5:5). $[\alpha]_D^{20}$ − 4.6° (*c* 1.58, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.36−7.22 (m, 13 H), 7.17−7.11 (m, 2 H), 4.84 (d, *J* = 10.7 Hz, 1 H), 4.73 (d, *J* = 10.7 Hz, 2 H), 4.62−4.46 (m, 4 H), 4.46−4.17 (m, 6 H), 3.94−3.86 (m, 1 H), 3.83−3.77 (m, 1 H), 3.73−3.65 (m, 2 H), 3.23 (d, *J* = 3.4 Hz, 1 H), 1.39−1.29 (m, 6 H), 1.23 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.4, 138.2, 138.2, 128.5−127.7, 78.9 (d, *J* = 2.1 Hz), 78.0 (d, *J* = 4.2 Hz), 75.2, 74.7, 73.6, 72.1, 71.3, 65.5 (d, *J* = 6.8 Hz), 65.4 (d, *J* = 7.0 Hz), 59.3−59.0 (m), 57.5, 23.0, 16.5 (d, *J* = 5.7 Hz), 16.4 (d, *J* = 5.9 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 108.6 (ddd, *J* = 6.5, 101.0, 305.4 Hz, F), − 122.0 (ddd, *J* = 23.6, 105.1, 305.5 Hz, F′) ppm. IR (neat): 3363, 3031, 2928, 1454, 1393, 1365, 1263, 1027, 736 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{35}H_{49}F_2NO_8PS$ $[M+H]^+$ 712.287908, found 712.287542.

*1-C-(1S)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-1-(S_R)-N-tert-butanesulfinylamino-1-deoxy-D-ribitol (1S)-(S_R)-**3c**.* Following GP D, LiBr (201 mg, 2.32 mmol) was added in dry THF (9.5 mL), followed by isopropylmagnesium chloride (1.76 M in Et_2O, 1.32 mL, 2.32 mmol) and diethyl(bromodifluoromethyl)phosphonate (410 μL, 2.32 mmol). (S_R)-*N*-*tert*-butanesulfinyl-5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-α,β-D-ribofuranosylamine (S_R)-**2c** (152 mg, 0.29 mmol) was dissolved in dry THF (6 mL). (S_R)-**3c** was obtained as a single diastereomer which was purified by Reveleris C18 reversed-phase flash chromatography (4 g cartridge, flow rate 10 mL.min^{-1}, H_2O/CH_3CN 6:4 to 0:10 (v/v), (1*S*)-(S_R)-**3c** t_R 12 min). (1*S*)-(S_R)-**3c** was obtained as yellow oil (147 mg, 85%).

(1*S*)-(S_R)-**3c**. R_f 0.4 (SiO_2, PE:EA 5:5). $[\alpha]_D^{20}$ − 51.8° (*c* 0.97, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 4.78 (d, *J* = 5.7 Hz, 1 H), 4.77−4.66 (m, 1 H), 4.49 (d, *J* = 7.2 Hz, 1 H), 4.34−4.17 (m, 6 H), 3.84−3.73 (m, 2 H), 1.51 (s, 3 H), 1.42−1.34 (m, 9 H), 1.13 (s, 9 H), 0.90 (s, 9 H), 0.07 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 109.1, 76.0, 72.5 (t, *J* = 3.2 Hz), 67.8, 64.9 (d, *J* = 6.7 Hz), 64.8 (d, *J* = 7.0 Hz), 64.7, 57.4, 56.4−55.8 (m), 27.2, 24.9, 26.1, 22.8, 18.6, 16.5 (d, *J* = 5.5 Hz), 16.5 (d, *J* = 5.7 Hz), − 5.2, − 5.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 112.8 (ddd, *J* = 8.2, 99.5, 304.3

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Hz, F), − 123.1 (ddd, J = 21.9, 108.6, 304.1 Hz, F′) ppm. IR (neat): 3367, 2985, 2931, 2857, 1473, 1383, 1264, 1044, 1020, 835 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{23}H_{49}F_2NO_8PSSi$ $[M+H]^+$ 596.264835, found 596.265100.

*1-C-(1R)- and 1-C-(1S)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-1-(S_S)-N-tert-butanesulfinylamino-1-deoxy-D-ribitol (1R)-(S_S)-**3c** and (1S)-(S_S)-**3c**.* Following GP C, diisopropylamine (290 μL, 2.0 mmol) was dissolved in dry THF (2.0 mL) and *n*-BuLi (1.36 M in hexanes, 1.47 mL, 2.0 mmol) was added; followed by diethyl(difluoromethyl)-phosphonate (320 μL, 2.0 mmol). 2,3,5-Tri-*O*-benzyl-(S_S)-*N*-*tert*-butanesulfinyl-α/β-D-xylofuranosylamine (S_S)-**2c** (163 mg, 0.40 mmol) was dissolved in dry THF (2.0 mL). The reaction mixture was allowed to reach −30 °C over 1.5 h. The titled compound was obtained as a mixture of diastereomers (6:4 (1*R*)-(S_S)-**3c**:(1*S*)-(S_S)-**3c**); both of which were separated on SiO_2−column chromatography (PE:EA 7:3 to 4:6) to provide (1*R*)-(S_S)-**3c** (70 mg, 29%) and (1*S*)-(S_S)-**3c** (34 mg, 14%).

(1*R*)-(S_S)-**3c**. R_f 0.2 (SiO_2, PE:EA 7:3). $[\alpha]_D^{20}$ + 37.8° (*c* 0.60, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 5.48 (d, J = 9.7 Hz, 1 H), 4.54 (br s, 1 H), 4.36−4.20 (m, 5 H), 4.11 (br s, 2 H), 3.85−3.75 (m, 2 H), 3.30 (br s, 1 H), 1.48 (s, 3 H), 1.41−1.33 (m, 9 H), 1.25 (s, 9 H), 0.90 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 108.2, 76.5, 75.4 (d, J = 3.3 Hz), 66.9, 65.1 (d, J = 8.0 Hz), 64.7 (d, J = 7.5 Hz), 64.0, 60.5−59.5 (m), 57.3, 26.2, 26.0, 22.8, 22.8, 18.5, 16.5 (d, J = 5.4 Hz), 16.5 (d, J = 5.8 Hz), − 5.2, − 5.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 111.2 (ddd, J = 15.7, 103.6, 304.8 Hz, F), − 118.8 (ddd, J = 14.4, 103.9, 304.7 Hz, F′) ppm. IR (neat): 3243, 2985, 2954, 2930, 2857, 1473, 1369, 1256, 1078, 1035, 836 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{23}H_{49}F_2NO_8PSSi$ $[M+H]^+$ 596.264835, found 596.264764.

(1*S*)-(S_S)-**3c**. R_f 0.2 (SiO_2, PE:EA 4:6). $[\alpha]_D^{20}$ + 21.9° (*c* 0.95, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 4.44−4.19 (m, 6 H), 4.06−3.93 (m, 2 H), 3.83−3.75 (m, 2 H), 3.66 (br s, 1 H), 1.47−1.40 (m, 6 H), 1.47−1.23 (m, 3 H), 1.33 (s, 3 H), 1.27 (s, 9 H), 0.91 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 109.3, 77.7, 77.0−76.8, 74.2, 66.1 (d, J = 6.0 Hz), 63.9, 63.8, 59.7−59.0 (m), 57.6, 27.5, 26.0, 24.6, 22.7, 18.5, 16.6 (d, J = 5.0 Hz), − 5.2, − 5.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 110.1 (dd, J = 100.6, 311.1 Hz, F), − 122.6 (ddd, J = 26.3, 105.2, 311.2 Hz, F′) ppm. IR (neat): 3246, 2954, 2930, 2858, 1473, 1383, 1287, 1258, 1061, 1047, 1020, 870 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{21}H_{43}F_2NO_7PSSi$ $[M+H]^+$ 550.222970, found 550.223129.

*1-C-(1S)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,4-tri-O-benzyl-1-(S_R)-N-tert-butanesulfinylamino-1-deoxy-D-xylitol (1S)-(S_R)-**3d**.* Following GP D, LiBr (305 mg, 3.51 mmol) was added, followed by dry THF (14 mL), isopropylmagnesium chloride (1.2 M in Et_2O, 2.93 mL, 3.51 mmol), and diethyl(bromodifluoromethyl)-phosphonate (620 μL, 3.51 mmol). (S_R)-**2d** (100 mg, 0.19 mmol) was dissolved in dry THF (9 mL). Compound (S_R)-**3d** was obtained as a single diastereomer which was purified by Reveleris C18 reversed-phase flash chromatography (80 g cartridge, flow rate 40 mL·min^{-1}, H_2O/CH_3CN 6:4 to 4:6 (v/v) over 15 min then 4:6 until (1*S*)-(S_R)-**3d** has eluted, t_R ∼ 21 min). (1*S*)-(S_R)-**3d**. 225 mg (72% yield). R_f 0.3 (SiO_2, PE:EA 4:6). $[\alpha]_D^{20}$ + 14.77° (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.40−7.22 (m, 15 H), 4.91 (d, J = 10.7 Hz, 1 H), 4.80 (d, J = 11.6 Hz, 1 H), 4.78 (d, J = 11.2 Hz, 1 H), 4.75−4.69 (m, 2 H), 4.67 (d, J = 11.2 Hz, 1 H), 4.66 (d, J = 11.6 Hz, 1 H), 4.46 (br d, J = 9.0 Hz, 1 H), 4.30 (dd, J = 3.1, 9.0 Hz, 1 H), 4.27−4.08 (m, 5 H), 3.88 (dd, J = 4.8, 1.2 Hz, 1 H), 3.83−3.71 (m, 2 H), 2.59 (s, 1 H), 1.33−1.23 (m, 15 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.6, 138.3, 138.3, 128.4−127.4, 119.2 (dd, J = 475.7, 266.0 Hz), 79.3, 78.9, 75.3, 74.9, 74.5, 72.7, 64.8 (d, J = 7.1 Hz), 64.0 (d, J = 7.1 Hz), 61.4, 59.1−58.5 (m), 57.1, 22.8, 16.4 (d, J = 5.1 Hz), 16.4 (d, J = 4.9 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 115.2 (ddd, J = 14.7, 103.4, 303.8 Hz, F), − 116.9 (ddd, J = 15.6, 106.5, 303.8 Hz, F′) ppm. IR (neat): 3439, 2929, 1727, 1455, 1267, 1073, 1026, 736 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{35}H_{49}F_2NO_8PS$ $[M+H]^+$ 712.287908, found 712.287517.

Determination of the Selectivity at C-1: Synthesis of 1-*C*-Diethylphosphono Iminosugars 4a−d Through General Procedure E (GP E) and General Procedure F (GP F). *Preparation of (1R)- and (1S)-**4a**, (1R)- and (1S)-**4b**, and (1S)-**4c** (GP E1−3). GP E1.* A single-necked round-bottomed flask under argon atmosphere was charged with enantiopure aminoalditol **3**, anhydrous CH_2Cl_2, and 4 Å MS. Et_3N was added, followed by MsCl and the reaction mixture was stirred at a given temperature for a given reaction time. Molecular sieves were then filtered through Celite, the cake rinsed with CH_2Cl_2, and the organic solution was washed with aq. NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 and combined organic phases were dried over $MgSO_4$. The organic layer was filtered over a cotton plug and the solvent was evaporated through rotary evaporation. The mesylated intermediate was used subsequently in the cyclization step without further purification.

GP E2. To a solution of mesylated compound in anhydrous THF under argon atmosphere was added *t*-BuOK and the reaction mixture was stirred at a given temperature for a given reaction time. Aqueous NH_4Cl was added and the mixture was extracted twice with EtOAc. Combined organic phases were washed with saturated aq. NaCl, dried over $MgSO_4$, filtered over a cotton plug, and concentrated under vacuum. The crude product was purified by column chromatography to give enantiopure iminoalditol **7**.

GP E3. A single-necked round-bottomed flask under argon atmosphere (flask A) was charged with AcCl and dry MeOH and the solution was stirred at room temperature (ca. 20 °C) for 30 min (solution A). Another flask (flask B) under argon atmosphere was charged with iminoalditol **7** and solution A was added through syringe to flask B. The reaction mixture was stirred at 20 °C for a given reaction time and resin Amberlite IRA-400 (OH^- form) was added until pH 8. The solution was filtered through a cotton plug and concentrated under vacuum to afford compound **4**.

*1-C-(1R)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,5-tri-O-benzyl-1-(S_S)-N-tert-butanesulfinyl-1,4-dideoxy-1,4-imino-L-arabinitol (1R)-(S_S)-**7a**.* The mesylated intermediate was generated according to the GP E1 using D-xylitol (1*R*)-(S_S)-**3a** (60 mg, 0.08 mmol), anhydrous CH_2Cl_2 (1 mL), Et_3N (24 μL, 0.18 mmol), and MsCl (13 μL, 0.17 mmol). The reaction mixture was stirred at 20 °C for 30 min. The mesylated intermediate was used subsequently in the cyclization step (GP E2) without further purification.

The titled compound was obtained according to the GP E2, using related crude mesylated intermediate, dry THF (1.5 mL), and *t*-BuOK (18 mg, 0.16 mmol). The reaction mixture was stirred at 20 °C for 20 min. The crude product was purified through column chromatography (SiO_2, PE:EA 7:3) to give imino-L-arabinitol (1*R*)-(S_S)-**7a** as colorless oil (16 mg, 29%).

(1*R*)-(S_S)-**7a**. R_f 0.2 (SiO_2, PE:EA 7:3). $[\alpha]_D^{20}$ + 71.6° (*c* 1.60, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.34−7.18 (m, 15 H), 4.60 (br s, 1 H), 4.58−4.37 (m, 8 H), 4.29 (br s, 1 H), 4.28−4.16 (m, 5 H), 3.71−3.61 (m, 1 H), 1.39−1.27 (m, 15 H) ppm.^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.6, 138.2, 137.8, 128.4−127.6, 83.8, 81.4 (d, J = 6.6 Hz), 73.2, 71.8, 70.9, 68.6, 68.3, 65.1 (d, J = 7.0 Hz), 64.9 (d, J = 7.0 Hz), 25.0, 16.5 (d, J = 5.0 Hz), 16.5 (d, J = 5.0 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 107.7 (dd, J = 99.5, 301.1 Hz, F), − 121.6 (ddd, J = 28.0, 106.8, 300.3 Hz, F′) ppm. IR (neat): 3031, 2930, 2868, 1455, 1270, 1100, 1072, 1028, 738 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{35}H_{47}F_2NO_7PS$ $[M+H]^+$ 694.277343, found 694.277720.

*1-C-(1R)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,5-tri-O-benzyl-1,4-dideoxy-1,4-imino-L-arabinitol (1R)-**4a**.* The titled compound was prepared according to the GP E3, using AcCl (7 μL, 0.10 mmol), dry MeOH (0.5 mL) and imino-L-arabinitol (1*R*)-(S_S)-**7a** (16 mg, 0.02 mmol). The reaction mixture was stirred overnight (ca. 16 h) to afford (1*R*)-**4a** in quantitative yield (13 mg, 100%). R_f 0.4 (SiO_2, PE:EA 6:4). $[\alpha]_D^{20}$ + 1.5° (*c* 1.26, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 7.38−7.23 (m, 15 H), 4.62 (d, J = 11.5 Hz, 1 H), 4.58 (d, J = 11.9 Hz, 1 H), 4.53−4.40 (m, 5 H), 4.33−4.22 (m, 4 H), 4.02−3.97 (m, 1 H), 3.82−3.70 (m, 1 H), 3.57 (dd, J = 3.2, 9.6 Hz, 1 H), 3.48 (dd, J = 4.7, 9.6 Hz, 1 H), 3.37−3.27 (m, 1 H), 2.62 (br s, 1 H), 1.37 (t, J = 7.1 Hz, 3 H), 1.31 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C

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NMR (101 MHz, $CDCl_3$/TMS): δ 138.3, 138.1, 138.0, 128.5−127.8, 85.7, 84.8 (dd, *J* = 3.2, 6.3 Hz), 73.3, 72.4, 72.3 (d, *J* = 1.8 Hz), 69.0, 64.8 (d, *J* = 6.5 Hz), 64.5 (d, *J* = 7.4 Hz), 64.3−64.2 (m), 61.6, 16.6−16.5 (m) ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 111.5 (ddd, *J* = 7.0, 103.0, 302.6 Hz, F), − 122.0 (ddd, *J* = 26.4, 104.1, 302.0 Hz, F′) ppm. IR (neat): 3030, 2917, 1862, 1454, 1264, 1091, 1074, 1017, 735 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{31}H_{39}F_2NO_6P$ $[M+H]^+$ 590.247757; found 590.247716.

*1-C-(1S)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,5-tri-O-benzyl-1-(S$_R$)-N-tert-butanesulfinyl-1,4-dideoxy-1,4-imino-L-arabinitol (1S)-(S$_R$)-**7a**.* The mesylated intermediate was generated according to the GP E1 using D-xylitol (1*S*)-(*S*$_R$)-**3a** (1.24 g, 1.74 mmol), anhydrous CH_2Cl_2 (17 mL), Et_3N (520 μL, 3.83 mmol), and MsCl (280 μL, 3.65 mmol). The reaction mixture was stirred at 20 °C for 50 min. The mesylated intermediate was used subsequently in the cyclization step (GP E2) without further purification.

The titled compound was obtained according to the GP E2, using related crude mesylated intermediate, dry THF (17 mL), and *t*-BuOK (390 mg, 3.48 mmol). *t*-BuOK was added at −50 °C and the reaction mixture was stirred at the same temperature during 40 min. The crude product was purified through column chromatography (SiO_2, PE:EA 7:3) to give imino-L-arabinitol (1*S*)-(*S*$_R$)-**7a** as yellow oil (0.63 g, 53%).

(1*S*)-(*S*$_R$)-**7a**. R_f 0.5 (SiO_2, PE:EA 5:5). $[\alpha]_D^{20}$ + 46.7° (*c* 1.70, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.42−7.14 (m, 15 H), 4.79 (d, *J* = 11.9 Hz, 1 H), 4.59 (d, *J* = 11.3 Hz, 1 H), 4.55−4.32 (m, 7 H), 4.29−4.01 (m, 5 H), 3.87 (t, *J* = 10.1 Hz, 1 H), 3.64 (dd, *J* = 4.5, 9.5 Hz, 1 H), 1.32 (t, *J* = 7.0 Hz, 3 H), 1.24 (s, 9 H), 1.18 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.3, 138.1, 137.9, 128.4−127.5, 83.8 (d, *J* = 6.7 Hz), 81.4, 73.0, 72.6, 70.6, 71.5−70.9 (m), 70.0, 64.7 (d, *J* = 7.2 Hz), 64.4 (d, *J* = 7.2 Hz), 58.7, 54.6, 23.6, 16.5 (d, *J* = 5.4 Hz), 16.3 (d, *J* = 5.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 100.1 (ddd, *J* = 9.5, 101.5, 297.2 Hz, F), − 116.0 (ddd, *J* = 22.0, 100.7, 297.9 Hz, F′). IR (neat): 2983, 2929, 2869, 1455, 1271, 1187, 1087, 1027, 738 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{35}H_{47}F_2NO_7PS$ $[M+H]^+$ 694.277343; found 694.277216.

*1-C-(1S)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,5-tri-O-benzyl-1,4-dideoxy-1,4-imino-L-arabinitol (1S)-**4a**.* The titled compound was prepared according to the GP E3, using AcCl (110 μL, 1.5 mmol), dry MeOH (3 mL) and imino-L-arabinitol (1*S*)-(*S*$_R$)-**7a** (210 mg, 0.3 mmol). The reaction mixture was stirred for 30 min to afford (1*S*)-**4a** in good yield (169 mg, 96%). R_f 0.4 (SiO_2, PE:EA 5:5). $[\alpha]_D^{20}$ − 0.8° (*c* 1.52, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.36−7.22 (m, 15 H), 4.61 (d, *J* = 11.8 Hz, 1 H), 4.57−4.44 (m, 5 H), 4.35−4.18 (m, 5 H), 3.91−3.78 (m, 2 H), 3.58 (dd, *J* = 6.3, 9.3 Hz, 1 H), 3.53 (dd, *J* = 6.1, 9.3 Hz, 1 H), 3.42−3.33 (m, 1 H), 2.41 (br s, 1 H), 1.37−1.30 (m, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.4, 138.2, 138.2, 128.5−127.7, 83.8, 83.3 (d, *J* = 5.8 Hz), 73.2, 72.2, 72.0, 71.9, 64.8 (d, *J* = 6.4 Hz), 64.7 (d, *J* = 7.1 Hz), 62.5, 61.0−60.6 (m), 16.6, 16.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 114.9 (dd, *J* = 7.2, 104.0, 306.1 Hz, F), − 119.4 (ddd, *J* = 22.7, 105.6, 306.3 Hz, F′) ppm. IR (neat): 3030, 2917, 1861, 1454, 1393, 1265, 1017, 735 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{31}H_{39}F_2NO_6P$ $[M+H]^+$ 590.247757, found 590.247549.

*1-C-(1R)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,5-tri-O-benzyl-1-(S$_S$)-N-tert-butanesulfinyl-1,4-dideoxy-1,4-imino-L-xylitol (1R)-(S$_S$)-**7b**.* The mesylated intermediate was generated according to the GP E1 using D-arabinitol (1*R*)-(*S*$_S$)-**3b** (86 mg, 0.12 mmol), anhydrous CH_2Cl_2 (2.5 mL), Et_3N (51 μL, 0.38 mmol), and MsCl (29 μL, 0.37 mmol). The reaction mixture was stirred at 20 °C for 1 h. The mesylated intermediate was used subsequently in the cyclization step (GP E2) without further purification.

The titled compound was obtained according to the GP E2, using related crude mesylated intermediate, dry THF (2.5 mL), and *t*-BuOK (27 mg, 0.24 mmol). *t*-BuOK was added at −50 °C and the reaction mixture was allowed to reach 20 °C over 1 h. The crude product was purified through column chromatography (SiO_2, PE:EA 6:4) to give imino-L-xylitol (1*R*)-(*S*$_S$)-**7b** as yellow oil (16 mg, 19%).

(1*R*)-(*S*$_S$)-**7b**. R_f 0.3 (SiO_2, PE:EA 6:4). $[\alpha]_D^{20}$ − 19.8° (*c* 1.57, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.39−7.18 (m, 15 H), 4.87 (d, *J* = 11.6 Hz, 1 H), 4.73−4.66 (m, 1 H), 4.75−4.51 (m, 5 H), 4.39 (d, *J* = 12.0 Hz, 1 H), 4.35−4.29 (m, 1 H), 4.24−3.95 (m, 6 H), 3.88 (d, *J* = 9.1 Hz, 1 H), 1.34 (s, 9 H), 1.30−1.24 (m, 3 H), 1.20−1.15 (m, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.9, 138.3, 138.2, 128.4−127.3, 82.1 (d, *J* = 2.1 Hz), 79.3 (d, *J* = 5.1 Hz), 74.1, 75.3, 73.2, 67.1, 64.5−64.4 (m), 64.2−63.9 (m), 60.3, 60.2, 25.4, 16.5 (d, *J* = 5.8 Hz), 16.3 (d, *J* = 5.8 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 104.2 (dd, *J* = 105.4, 301.3 Hz, F), − 118.2 (ddd, *J* = 25.2, 96.3, 298.5 Hz, F′) ppm. IR (neat): 3030, 2927, 2869, 1455, 1269, 1098, 1043, 1028, 738 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{35}H_{47}F_2NO_7PS$ $[M+H]^+$ 694.277343, found 694.278121.

*1-C-(1R)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,5-tri-O-benzyl-1,4-dideoxy-1,4-imino-L-xylitol (1R)-**4b**.* Xylitol (1*R*)-**4b** was prepared according to the GP E3, using AcCl (7 μL, 9.8 × 10^{-5} mol), dry MeOH (0.5 mL), and imino-L-arabinitol (1*R*)-(*S*$_S$)-**7b** (15 mg, 2.2 × 10^{-5} mol). The reaction mixture was stirred for 30 min to afford (1*R*)-**4b** as colorless oil in quantitative yield (12.7 mg). R_f 0.4 (SiO_2, PE:EA 5:5). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.39−7.19 (m, 15 H), 4.67 (d, *J* = 11.8 Hz, 1 H), 4.57−4.41 (m, 5 H), 4.33−4.18 (m, 5 H), 4.07 (br s, 1 H), 3.96 (dt, *J* = 6.3, 23.4 Hz, 1 H), 3.76−3.69 (m, 1 H), 3.68−3.59 (m, 1 H), 3.56−3.49 (m, 1 H), 1.33 (t, *J* = 6.8 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.4, 138.3, 138.2, 128.5−127.7, 83.0 (dd, *J* = 2.0, 6.6 Hz), 82.3, 73.4, 72.9, 72.6, 69.7, 64.8 (d, *J* = 6.4 Hz), 64.7 (d, *J* = 6.9 Hz), 59.7−59.5 (m), 58.5, 16.5, 16.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 114.5 (dd, *J* = 8.1, 104.3, 304.6 Hz, F), − 119.0 (ddd, *J* = 23.8, 105.6, 304.6 Hz, F′) ppm. IR (neat): 3030, 2925, 2857, 1455, 1394, 1367, 1267, 1097, 1027, 737 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{31}H_{39}F_2NO_6P$ $[M+H]^+$ 590.247757; found 590.247752.

*1-C-(1S)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,5-tri-O-benzyl-1-(S$_R$)-N-tert-butanesulfinyl-1,4-dideoxy-1,4-imino-L-xylitol (1S)-(S$_R$)-**7b**.* The mesylated intermediate was generated according to the GP E1 using D-arabinitol (1*S*)-(*S*$_R$)-**3b** (28 mg, 0.04 mmol), anhydrous CH_2Cl_2 (1.0 mL), Et_3N (18 μL, 0.13 mmol), and MsCl (9 μL, 0.12 mmol). The reaction mixture was stirred at 20 °C for 1 h. The mesylated intermediate was used subsequently in the cyclization step (GP E2) without further purification.

The titled compound (1*S*)-(*S*$_R$)-**7b** was obtained according to the GP E2, using related crude mesylated intermediate, dry THF (1.0 mL), and *t*-BuOK (13 mg, 0.12 mmol). *t*-BuOK was added at −50 °C and the reaction mixture was stirred for 1 h allowing the bath temperature to reach −40 °C. The crude product was purified through column chromatography (SiO_2, PE:EA 75:25) to give imino-L-xylitol (1*S*)-(*S*$_R$)-**7b** as yellow oil (18 mg, 65%).

(1*S*)-(*S*$_R$)-**7b**. R_f 0.8 (SiO_2, PE:EA 5:5). $[\alpha]_D^{20}$ − 33.5° (*c* 1.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.34−7.20 (m, 15 H), 4.87 (d, *J* = 10.6 Hz, 1 H), 4.71 (d, *J* = 11.1 Hz, 1 H), 4.65 (d, *J* = 10.8 Hz, 1 H), 4.53−4.41 (m, 3 H), 4.41−4.31 (m, 2 H), 4.31−4.19 (m, 2 H), 4.13−3.92 (m, 4 H), 3.85−3.78 (m, 1 H), 3.56 (br dd, *J* = 3.9, 9.7 Hz, 1 H), 1.35 (t, *J* = 6.9 Hz, 3 H), 1.23 (s, 9 H), 1.14 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.4, 138.0, 137.7, 128.4−127.4, 85.7 (d, *J* = 3.3 Hz), 80.5 (d, *J* = 6.8 Hz), 73.4, 73.0, 72.6, 69.8 (d, *J* = 4.9 Hz), 69.4−69.0 (m), 64.7 (d, *J* = 6.3 Hz), 64.5 (d, *J* = 6.8 Hz), 59.0, 52.4, 23.2, 16.4 (d, *J* = 5.6 Hz), 16.2 (d, *J* = 5.9 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 113.2 (ddd, *J* = 5.7, 94.4, 301.6 Hz, F), − 129.0 (ddd, *J* = 25.3, 110.3, 302.2 Hz, F′) ppm. IR (neat): 3032, 2914, 1455, 1364, 1272, 1096, 1036, 738 cm^{-1}. HRMS (ESI): *m*/*z* calcd. for $C_{35}H_{47}F_2NO_7PS$ $[M+H]^+$ 694.277343, found 694.277080.

*1-C-(1S)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,5-tri-O-benzyl-1,4-dideoxy-1,4-imino-L-xylitol (1S)-**4b**.* Xylitol (1*S*)-**4b** was prepared according to the GP E3, using AcCl (7 μL, 9.8 × 10^{-5} mol), dry MeOH (0.5 mL), and (1*S*)-(*S*$_R$)-**7b** (16 mg, 2.3 × 10^{-5} mol). The reaction mixture was stirred for 30 min to afford (1*S*)-**4b** as colorless oil in quantitative yield (13.6 mg). R_f 0.5 (SiO_2, PE:EA 5:5). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.39−7.25 (m, 15 H), 4.60−4.39 (m, 6 H), 4.33−4.22 (m, 5 H), 3.92 (br s, 1 H), 3.76−3.61 (m, 3 H), 3.57−3.51 (m, 1 H), 2.28 (br s, 1 H), 1.39−1.30 (m, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 138.3, 138.1, 137.8, 128.4−127.6, 82.3−82.2 (m), 82.1, 73.5, 72.0, 71.2, 69.4, 66.6−66.0 (m), 64.7 (d, *J* = 6.7

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Hz), 64.6 (d, J = 6.7 Hz), 60.7, 16.4 (d, J = 4.5 Hz), 16.3 (d, J = 4.5 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 115.9 (dd, J = 11.0, 103.8, 302.5 Hz, F), − 121.1 (ddd, J = 19.2, 104.2, 302.5 Hz, F′) ppm. IR (neat): 3030, 2918, 2856, 1454, 1394, 1263, 1026, 799, 737 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{31}H_{39}F_2NO_6P$ $[M+H]^+$ 590.247757, found 590.248297.

*1-C-(1S)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-1-(S_R)-N-tert-butanesulfinyl-1,4-dideoxy-1,4-imino-L-lyxitol (1S)-(S_R)-**7c**.* The mesylated intermediate was generated according to the GP E1 using D-ribitol (1S)-(S_R)-**3c** (46 mg, 0.08 mmol), anhydrous CH_2Cl_2 (1.5 mL), Et_3N (35 μL, 0.26 mmol), and MsCl (19 μL, 0.24 mmol). The reaction mixture was stirred at 20 °C for 2 h. The mesylated intermediate was used subsequently in the cyclization step (GP E2) without further purification.

The titled compound was obtained according to the GP E2, using related crude mesylated intermediate, dry THF (1.5 mL), and *t*-BuOK (18 mg, 0.16 mmol). *t*-BuOK was added at −50 °C and the reaction mixture was allowed to reach 0 °C over 1.5 h. The crude product was purified through column chromatography (SiO_2, PE:EA 6:4) to give imino-L-lyxitol (1S)-(S_R)-**7c** as colorless oil (22 mg, 50%).

(1S)-(S_R)-**7c**. $[\alpha]_D^{20}$ + 4.6° (*c* 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 5.04 (t, J = 7.4 Hz, 1 H), 4.73 (t, J = 7.3 Hz, 1 H), 4.42−4.19 (m, 5 H), 4.13−4.06 (m, 1 H), 4.03−3.96 (m, 1 H), 3.72 (dd, J = 8.1, 10.0 Hz, 1 H), 1.48 (s, 3 H), 1.41−1.35(m, 6 H), 1.32 (s, 3 H), 1.29 (s, 9 H), 0.89 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 114.9, 82.2, 79.5 (d, J = 5.0 Hz), 70.3−69.7 (m), 64.8−64.7 (m), 62.5 (d, J = 6.7 Hz), 59.2, 56.5, 26.1, 25.2, 24.7, 23.3, 18.6, 16.6 (d, J = 5.5 Hz), 16.5 (d, J = 5.6 Hz), − 5.2, − 5.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 104.1 (ddd, J = 9.4, 103.7, 300.3 Hz, F), − 118.9 (ddd, J = 25.6, 99.8, 300.3 Hz, F′) ppm. IR (neat): 3367, 2985, 2931, 2857, 1473, 1383, 1264, 1044, 1020, 835 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{23}H_{47}F_2NO_7PSSi$ $[M+H]^+$ 578.254270, found 578.254298.

*1-C-(1S)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-L-lyxitol (1S)-**4c**.* L-Lyxitol (1S)-**4c** was prepared according to the GP E3, using AcCl (14 μL, 0.19 mmol), dry MeOH (1 mL), and (1S)-(S_R)-**7c** (22 mg, 0.038 mmol). The reaction mixture was stirred for 3 h to afford (1S)-**4c** as colorless oil (9 mg, 66%). $[\alpha]_D^{20}$ − 8.6° (*c* 0.92, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 4.89 (dd, J = 4.0, 5.5 Hz, 1 H), 4.77−4.73 (m, 1 H), 4.38−4.26 (m, 4 H), 4.03 (dd, J = 3.4, 11.8 Hz, 1 H), 3.96−388 (m, 1 H), 3.42−3.32 (m, 1 H), 2.91−2.85 (m, 1 H), 1.51 (s, 3 H), 1.39 (br t, J = 7.0 Hz, 6 H), 1.26 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ 112.4, 82.9, 81.4 (d, J = 6.1 Hz), 65.3 (d, J = 6.8 Hz), 65.1 (d, J = 7.1 Hz), 63.2−62.8 (m), 62.3, 61.0, 25.6, 23.9, 16.5 (d, J = 2.0 Hz), 16.5 (d, J = 3.0 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 109.1 (ddd, J = 12.6, 106.9, 305.1 Hz, F), − 117.5 (ddd, J = 17.3, 98.7, 304.4 Hz, F′) ppm. IR (neat): 3447, 2983, 2932, 1556, 1374, 1269, 1209, 1040 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{13}H_{25}F_2NO_6P$ $[M+H]^+$ 360.138207, found 360.138160.

Preparation of (1*R*)-4c and (1*S*)-4d through General Procedure F (GP F). *1-C-(1R)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-L-lyxitol (1R)-**4c**.* A 25 mL flask under argon atmosphere was charged with D-ribitol (1R)-(S_S)-**3c** (96 mg, 0.16 mmol), anhydrous CH_2Cl_2 (3.5 mL), and 4 Å MS. Et_3N (89 μL, 0.66 mmol) was added, followed by MsCl (50 μL, 0.64 mmol) and the reaction mixture was stirred at 20 °C until no starting material was present (48 h). Molecular sieves were then filtered through Celite, the cake rinsed with CH_2Cl_2, and the organic phase was washed with aq. NH_4Cl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and combined organic extracts were dried over $MgSO_4$. The organic phase was filtered over a cotton plug and the solvent was evaporated through rotary evaporation to give the mesylated intermediate which was used subsequently in the cyclization step without further purification.

A 25 mL flask under argon atmosphere was charged with AcCl (60 μL, 0.8 mmol) and dry MeOH (3.5 mL) and the reaction mixture was stirred at 20 °C for 30 min (solution A). A second 25 mL flask under argon atmosphere (flask B) was charged with the mesylated intermediate and solution A was added via cannula to flask B. The reaction mixture was stirred for 1 h and resin Amberlite IRA-400 (OH^- form) was added until pH 8. The reaction mixture was stirred further during 2 h and the solution was filtered through a cotton plug and concentrated under reduced pressure. The titled compound was chromatographed (SiO_2, PE:EA 5:5) to afford (1R)-**4c** (5 mg, 10%).

(1R)-**4c**. R_f 0.2 (SiO_2, PE:EA 5:5). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 4.41−4.27 (m, 5 H), 4.24 (dd, J = 5.6, 9.1 Hz, 1 H), 3.87−3.78 (m, 2 H), 3.71 (dd, J = 4.9, 10.6 Hz, 1 H), 3.46−3.38 (m, 1 H), 1.45−1.36 (m, 9 H), 1.34 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ = 109.6, 100.1, 78.9, 76.0, 68.6, 65.6 (d, J = 8.1 Hz), 65.3 (d, J = 7.1 Hz), 64.8, 54.8−53.8 (m), 27.8, 25.7, 16.7 (d, J = 5.1 Hz), 16.5 (d, J = 6.1 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$): δ − 112.2 (ddd, J = 8.3, 106.4, 308.9 Hz, F), − 117.6 (ddd, J = 14.9, 100.3, 309.1 Hz, F′) ppm. HRMS (ESI): m/z calcd. for $C_{13}H_{25}F_2NO_6P$ $[M+H]^+$ 360.138207, found 360.138110.

*1-C-(1S)-1-[(1-Diethylphosphono)-1,1-difluoromethyl]-2,3,4-tri-O-benzyl-1,5-dideoxy-1,5-imino-D-xylitol (1S)-**4d**.* A single-necked round-bottomed flask under argon atmosphere was charged with D-xylitol (1S)-(S_R)-**3d** (27 mg, 0.04 mmol), anhydrous CH_2Cl_2 (1.5 mL), and 4 Å MS. Et_3N (12 μL, 0.09 mmol) was added, followed by MsCl (6 μL, 0.08 mmol) and the reaction mixture was stirred at 20 °C for 30 min. Molecular sieves were then filtered through Celite, the cake rinsed with CH_2Cl_2, and the organic solution was washed with aq. NH_4Cl (10 mL). The aqueous phase was extracted once with CH_2Cl_2 (10 mL) and combined organic phases were dried over $MgSO_4$. The organic layer was filtered over a cotton plug and the solvent was evaporated through rotary evaporation. The mesylated intermediate was used subsequently in the cyclization step without further purification.

A single-necked round-bottomed flask under argon atmosphere was charged with AcCl (60 μL, 0.8 mmol) and dry MeOH (1.5 mL) and the reaction mixture was stirred at 20 °C for 30 min (solution A). Another flask under argon atmosphere (flask B) was charged with crude mesylated D-xylitol and solution A was added through syringe to solution B. The reaction mixture was stirred for 30 min and resin Amberlite IRA-400 (OH^- form) was added until pH 8. The reaction mixture was stirred further for 15 min and the solution was filtered through a cotton plug. The solvents were evaporated under reduced pressure to afford (1S)-**4d** (16 mg, 68%) as colorless oil.

(1S)-**4d**. R_f 0.5 (SiO_2, PE:EA 5:5). $[\alpha]_D^{20}$ − 1.84° (*c* 1.35, $CHCl_3$). ^{1}H NMR (250 MHz, $(CD_3)_2CO$): δ 7.41−7.22 (m, 15 H), 4.70 (d, J = 11.5 Hz, 1 H), 4.69 (s, 2 H), 4.62 (d, J = 11.5 Hz, 1 H), 4.59 (s, 2 H), 4.32−4.15 (m, 4 H), 4.08 (br t, J = 4.1 Hz, 1 H), 3.89 (br t, J = 2.8 Hz, 1 H), 3.77−3.62 (m, 1 H), 3.49 (q, J = 3.4 Hz, 1 H), 3.10 (dd, J = 2.0, 12.0 Hz, 1 H), 3.01 (dd, J = 2.7, 14.5 Hz, 1 H), 2.80 (br s, 1 H), 1.36−1.25 (m, 6 H) ppm. ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ 140.0, 139.8, 139.5, 129.2−128.1, 75.2, 74.6−74.3 (br m), 73.5, 72.6, 71.8, 64.8 (d, J = 6.0 Hz), 64.4 (d, J = 6.6 Hz), 57.5−56.9 (m), 47.0, 16.8 (d, J = 4.9 Hz), 16.7 (d, J = 5.3 Hz) ppm. ^{19}F NMR (376 MHz, $(CDCl_3/C_6F_6)$: δ − 112.2 (br d, J = 302.3 Hz, F), − 119.8 (br d, J = 315.8 Hz, F′) ppm. IR (neat): 3030, 2980, 2928, 1455, 1392, 1268, 1092, 1027, 979, 736 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{31}H_{38}F_2NO_6P$ $[M+H]^+$ 590.247757, found 590.247725.

Hydrogenolysis of (1*S*)-4d to give Glucose-1-phosphate Mimic (1S)-5. *1-C-(1S)-1-[1,1-Difluoromethylphosphonic acid]-1,5-dideoxy-1,5-imino-D-xylitol (1S)-**5**.* A vigorously stirred suspension of (1S)-**4d** (16 mg, 0.03 mmol), 20% $Pd(OH)_2$−C (5 mg), and aq. HCl (1 N, 0.11 mmol, 110 μL) in *i*PrOH (0.5 mL) was degassed under vacuum and saturated with hydrogen (H_2-filled balloon) five times. The reaction mixture was stirred at 20 °C for 48 h under slightly positive pressure of hydrogen (balloon) and the mixture was filtered over Millipore membrane (0.2 μm). The solvents were evaporated under reduced pressure and the residual oil was dissolved in dry CH_3CN (1 mL). Me_3SiBr (130 μL, 0.98 mmol) was added and the reaction mixture was stirred at rt (ca. 20 °C) for 48 h. The solvents were evaporated and the residue was dissolved in H_2O (10 mL) and washed with CH_2Cl_2 (20 mL). After removal of H_2O the crude compound was purified by Sephadex LH20 (CH_2Cl_2/MeOH 1/1) to afford (1S)-**5** as colorless oil (16.5 mg, 98%). $[\alpha]_D^{20}$ − 8.60° (*c* 1.56,

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MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ 4.50 (br s, 1 H), 4.09−3.99 (m, 1 H), 3.98 (br s, 1 H), 3.92 (br s, 1 H), 3.54 (br d, J = 13.2 Hz, 1 H), 3.41−3.33 (m, 1 H) ppm. ^{13}C NMR (101 MHz, CD_3OD): δ 101.4, 68.2, 67.8, 58.7−58.0 (m), 48.6 ppm. ^{19}F NMR (376 MHz, CD_3OD/C_6F_6): δ − 113.3 (dd, J = 87.9, 303.0 Hz, F), − 120.8 (ddd, J = 15.9, 87.3, 304.4 Hz, F′) ppm. IR (neat): 3339, 2929, 1601, 1448, 1058 cm^{-1}. HRMS (ESI): m/z calcd. for $C_6H_{13}F_2NO_6P$ $[M+H]^+$ 264.044307, found 264.044025.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b03071.

Full Gaussian reference, general comments, conformational sampling protocol, structural analysis, and Cartesian coordinates of the lowest energy conformations (PDF)

Copies of the NMR spectra for all new compounds, optimization tables, full quantum chemical calculation details and results (PDF)

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Notes

The authors declare no competing financial interest.

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