

Chemical Access to D-Sarmentose Units Enables the Total Synthesis of Cardenolide Monoglycoside N-1 from *Nerium oleander*

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S Supporting Information

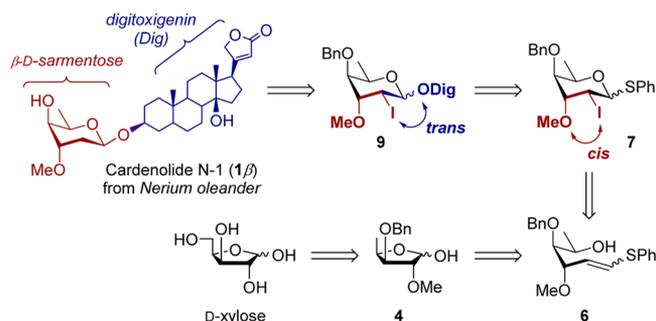
ABSTRACT: Herein we present a chemical approach for the ready preparation of D-sarmentosyl donors enabling the first total synthesis and structure validation of cardenolide N-1, a challenging 2,6-dideoxy-3-O-methyl-β-D-xylo-hexopyranoside extracted from *Nerium oleander* twigs that displays anti-inflammatory properties and cell growth inhibitory activity against tumor cells. The strategy highlights the synthetic value of the sequential methodology developed in our group for the synthesis of 2-deoxyglycosides. Key steps include Wittig–Horner olefination of a D-xylofuranose precursor, [I⁺]-induced 6-endo cyclization, and 1,2-*trans* stereoselective glycosylation.



Foxglove (*Digitalis purpurea*) and oleander (*Nerium oleander*) are medicinal plants^{1,2} used since ancient times as diuretics, abortifacients, and emetics as well as for the treatment of congestive cardiac insufficiency,^{1,3} and more recently as anticancer therapeutics.^{1,4} For example, Anvirzel and PBI-05204 are extracts of oleander known to possess cytotoxic and immunomodulatory effects.⁵ These herbal supplements contain cardenolides such as oleandrin as active ingredients. The general structure of such cardenolides is composed of an steroidal aglycone and a glycosidic component typically based on 2-deoxy and/or 2,6-dideoxy-saccharide scaffolds.⁶ Despite their prevalence, 2-deoxy and 2,6-dideoxyglycosides are typically obtained by tedious extractions since the lack of anchimeric assistance during glycosylation makes their stereoselective chemical synthesis problematic.⁷ Despite recent efforts in the preparation of 2-deoxy and 2,6-dideoxyglycosides,⁸ elaboration of “rare” deoxypranosyl configurations (e.g., D-sarmentose) still remains a laborious task.⁹ In this context, our group developed a general strategy for the synthesis of 2-deoxyglycosides of all configurations, being particularly effective for those with β-D-ribo and -xylo.^{10–14} Key steps of this methodology involve Wittig–Horner (WH) olefination of pyranoses to afford sulfanyl alkene derivatives, [I⁺]-induced 6-endo cyclization to give 2-iodo-1-thioglycosides, and subsequent 1,2-*trans* stereoselective glycosylation.

To prove the robustness of our methodology we envisaged the synthesis of cardenolide N-1 (**1β**),¹⁵ a glycosidic steroid extracted from *Nerium oleander* twigs (Scheme 1). The glycosyl moiety consists of a 2,6-dideoxy-3-O-methyl-β-D-xylo-hexopyranoside (β-D-sarmentose)^{15,16} with the C-1, C-3, and C-4 stereogenic centers in a relative *trans* configuration. We hypothesized that a 1,2-*trans* stereoselective β-glycosylation can be orchestrated by the presence of an ancillary equatorial I at C-2 in **7**. The position of this I group (*cis* to the C-3 substituent) is in turn controlled by the *inside-alkoxy effect*,¹⁷

Scheme 1. Retrosynthetic Analysis of Cardenolide N-1 (1β)



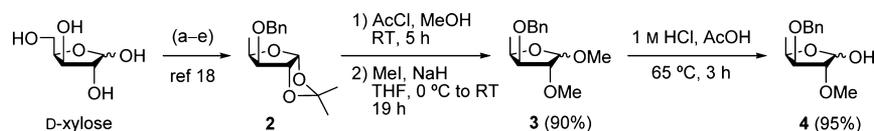
which dictates the more reactive conformation of the alkene during the [I⁺]-induced 6-endo cyclization of **6**.

The first step of the proposed synthesis involves the preparation of 5-deoxy-D-xylofuranose **2** (Scheme 2). First, 5-deoxy-D-xylofuranose **2** was prepared from D-xylose.¹⁸ Cleavage of isopropylidene acetal in **2** using AcCl/MeOH and subsequent methylation of the free hydroxyl at C-2 furnished **3** in 90% yield over two steps. Finally, acid-catalyzed hydrolysis proceeded smoothly to afford **4** in 95% yield.

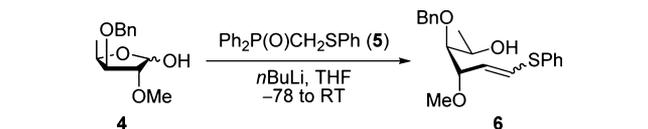
With precursor **4** in hand, WH olefination with phosphine oxide **5** was optimized (Table 1). Reaction employing excess *n*BuLi afforded a complex mixture of products (Table 1, entry 1) while equimolar amounts of **5** and *n*BuLi gave better results (Table 1, entries 2–6). WH reaction using 2.2 equiv of **5** afforded **6** in a low 22% yield as an inseparable 1:8 *Z/E* mixture (Table 1, entry 2). Extending the reaction time improved the yield to 41% while the *Z/E* ratio decreased (Table 1, entry 3). The use of up to 4 equiv of **5** was detrimental for the reaction (Table 1, entry 4). Reducing the

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Scheme 2. Preparation of 5-Deoxy-D-xylofuranose Precursor 4^a

^aReagents and conditions: (a) conc. H₂SO₄, acetone, rt, 1 h; (b) 0.4% aq. HCl, rt, 3 h; (c) TsCl, Et₃N, CH₂Cl₂, rt, 6 h; (d) LiAlH₄, Et₂O, 0 to 55 °C, 5 h; (e) BnBr, NaH, THF, 50 °C, 14 h.

Table 1. Optimization of Olefination of 4^a

entry	5 (equiv)	<i>n</i> BuLi (equiv)	time (h)	yield (%) ^b	Z/E ratio ^c
1	2	3.5	16	— ^d	ND
2	2.2	2.2	3.5	22	1:8
3	2.2	2.2	15	41	1:2.9
4	4	4	72	— ^e	1:1.2
5	2.5	2.5	48	83	1:1.5
6 ^f	3.2	3.2	24	52	1:5.3

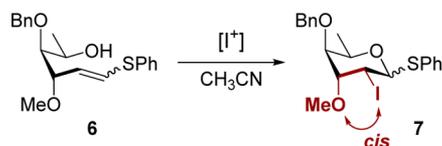
^aGeneral conditions: phosphine oxide 5, *n*BuLi, and D-xylofuranose 4 in dry THF unless otherwise indicated. ^bIsolated yield after purification by column chromatography. ^cDetermined by integration of the olefinic proton signals in the ¹H NMR spectrum of the crude reaction mixture. ^dDegradation. ^eIncomplete conversion. ^fThe fraction containing β-hydroxyphosphine oxide intermediate was treated with 60% NaH (1 mg mg⁻¹ crude) in dry THF to afford additional 6 in 29% yield and 20:1 Z/E ratio. ND = not determined.

amount of 5 to 2.5 equiv and extending the reaction time to 48 h improved the yield to 83% albeit with a reduction of stereoselectivity (1:1.5 Z/E) (Table 1, entry 5). When the reaction was quenched after 24 h, two fractions were obtained (Table 1, entry 6). The first consisted of 6 in 52% yield and 1:5.3 Z/E ratio, and the second contained a β-hydroxyphosphine oxide intermediate, which was subsequently treated with NaH to afford an additional fraction of 6 in 29% yield and 20:1 Z/E ratio. Since both Z- and E-isomers were completely consumed in the subsequent cyclization step (Table 2), optimal conditions were those affording the highest yield (Table 1, entry 5).

After optimizing the olefination of 4, [I⁺]-induced 6-*endo* cyclization of 6 was further examined (Table 2). Reaction with NIS resulted in mixtures due to the ready activation of 7 (Table 2, entry 1). Iodonium di-*sym*-collidine perchlorate (IDCP) successfully cyclized a 1:1.5 Z/E mixture of 6 to produce 7 in good yield (63%) and 1:2.7 α/β ratio (Table 2, entry 2). Addition of 4 Å molecular sieves (MS) was detrimental for the reaction (Table 2, entry 3). Notably, conducting the reaction at lower temperature improved the yield up to 84% (Table 2, entries 4–6) with moderate stereoselectivity (1:2.1 α/β). This result is in line with similar transformations using donors of D-*gulo* configuration.¹⁰

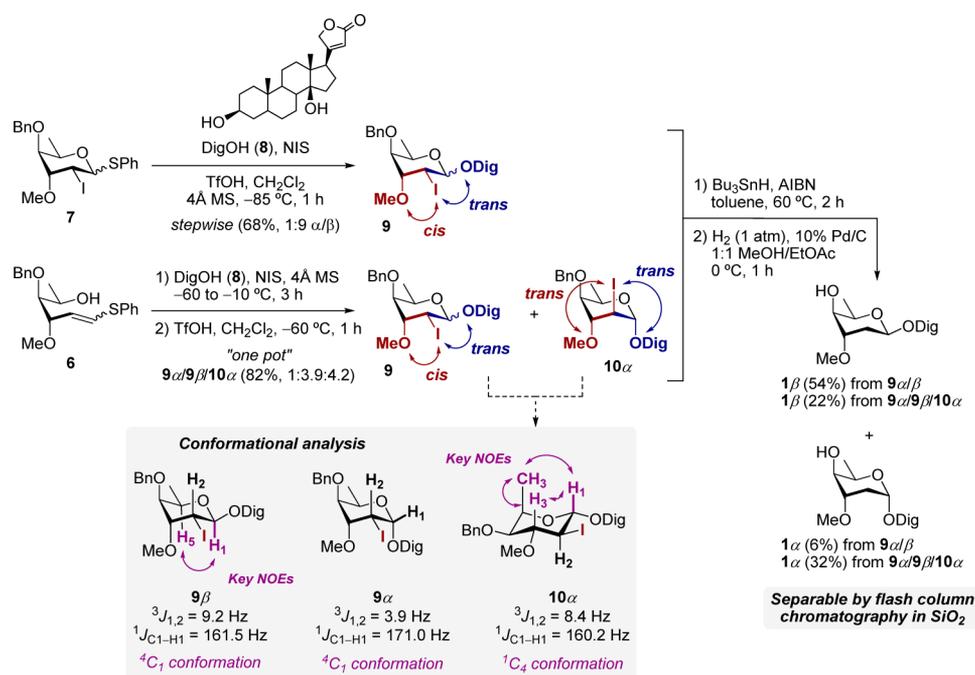
We next explored the stereoselective preparation of 2,6-dideoxy-2-iodohexopyranosyl glycosides and their subsequent elaboration to final cardenolide N-1 (1β) and its α-anomer (1α) (Scheme 3). Glycosylation of digitoxigenin 8 with 1-thioglycosyl donor 7 was first performed at -85 °C using NIS/TfOH as the promoter system. Under these mild conditions, 9 was obtained in 68% yield and 1:9 α/β ratio, which is in line with the results obtained with similar D-*gulo* donors and cholesterol as an acceptor (66%, 1:8 α/β).¹⁰

Alternatively, the straightforward “one-pot” version¹⁴ was achieved directly from 6. The reaction was started at -60 °C and then allowed to warm until cyclization was completed (ca. -10 °C); at that moment, the reaction mixture was recooled to -60 °C and TfOH was added to promote glycosylation. However, together with expected 9α/β, a substantial amount of 2-I-epimer 10α (D-*ido*) was also obtained. The lower product selectivity could be explained by the fact that higher temperatures are required in the “one-pot” protocol compared to those of the sequential method and the high reactivity of transient 7, which was consumed before addition of TfOH. The formation of 10α could be rationalized, as already described in our previous studies, by either the *in situ* formation of the corresponding glycal byproduct^{11,12} and its

Table 2. Optimization of Cyclization of 6^a

entry	[I ⁺] (equiv)	additive (equiv)	T (°C)	time (h)	yield (%) ^b	α/β ratio ^c
1	NIS (1.5)	NaHCO ₃ (1.5)	-40	1	— ^d	ND
2	IDCP (3)	—	-30 to -10	1	63	1:2.7
3	IDCP (3)	4 Å MS	-30 to -10	1	— ^d	ND
4	IDCP (3)	—	-40 to -30	3.5	63	ND
5	IDCP (3)	—	-45 to -42	3.5	70	ND
6	IDCP (3)	—	-45 to -42	1	84	1:2.1

^aGeneral conditions: Iodonium reagent and 6 (1:1.5 Z/E) in dry CH₃CN unless otherwise indicated. ^bIsolated yield after purification by column chromatography. ^cDetermined by integration of H₁ (7α) and H₂ (7β) in the ¹H NMR spectrum of the crude reaction mixture. ^dDegradation. ND = not determined, MS = molecular sieves.

Scheme 3. Synthesis and Conformational Analysis of 2-Deoxy-2-iodohexopyranosyl Glycosides **9** and **10 α** and Their Deprotection to Cardenolide N-1 (**1 β**) and Its α -Anomer (**1 α**)Table 3. Selected ¹H NMR^a Data of Natural and Synthetic Cardenolide N-1 (**1 β**) and Its α -Anomer (**1 α**)

ORTEP drawing of **1 α** with thermal ellipsoids drawn at the 50% probability level (H atoms omitted for clarity). ^aCoupling constants reported in Hz. ^bSee ref 15.

position	natural (1β) ^b	this work (1β)	this work (1α)
H-1	4.71 (dd, $J = 9.5, 2.6$)	4.71 (dd, $J = 9.5, 2.6$)	4.85 (dd, $J = 3.3$)
H-2	1.84–1.76 (m)	1.84–1.76 (m)	1.95–1.75 (m)
H-3	3.58 (q, $J = 2.9$)	3.58 (q, $J = 3.2$)	3.53 (q, $J = 4.0$)
H-4	3.39 (m)	3.41–3.35 (m)	3.47 (m)
H-5	3.91 (q, $J = 6.6$)	3.91 (qd, $J = 6.6, J = 1.1$)	4.33 (qd, $J = 6.8, J = 1.6$)
5-Me	1.23 (d, $J = 6.6$)	1.24 (d, $J = 6.6$)	1.17 (d, $J = 6.8$)
3-OMe	3.38 (s)	3.38 (s)	3.39 (s)

ORTEP drawing of **1 α** with thermal ellipsoids drawn at the 50% probability level (H atoms omitted for clarity). ^aCoupling constants reported in Hz. ^bSee ref 15.

subsequent [I⁺]-induced glycosylation or the alternative *outside-alkoxy* cyclization.¹⁴ Thus, stereoselective control in the stepwise approach seems more favorable for accessing cardenolide N-1 precursor **9 β** , whereas the improved selectivity toward **9 α** and **10 α** (both precursors of **1 α**) resulting from the “one-pot” method gives the opportunity to ultimately access the α -anomer (**1 α**) of Cardenolide N-1.

The configuration of 2,6-dideoxy-2-iodohexopyranosyl intermediates **9** and **10 α** and the conformation adopted were initially deduced after analysis of diagnostic coupling constants (Scheme 3). The large values of vicinal $^3J_{1,2} = 9.2$ in **9 β** and 8.4 Hz in **10 α** together with heteronuclear anomeric coupling constants $^1J_{C1-H1}$ ca. 160 Hz for both products suggest a relative *trans*-diaxial disposition between H₁ and H₂ that account for a 4C_1 conformation in **9 β** and the “inverted” 1C_4 in **10 α** . Moreover, key NOE contacts between H₁–H₅ in **9 β** and H₁–H₃–CH₃ in **10 α** are compatible with the previous assumption. Analogously, **9 α** showed characteristic features

indicative of a *cis* relative configuration between H₁ and H₂ typically found in α -glycosides adopting 4C_1 conformations, including the H₁ signal (4.74 ppm) shifted downfield compared to **9 β** (4.64 ppm) and values of coupling constants $^3J_{1,2} = 3.9$ Hz and $^1J_{C1-H1} = 171$ Hz.

Next, elaboration of intermediates **9** and **10 α** to final cardenolide N-1 (**1 β**) and its α -anomer (**1 α**) was carried out. Radical deiodination with Bu₃SnH/AIBN and hydrogenation¹⁹ of 4-OBn using 10% Pd/C at 0 °C resulted in final cardenolide N-1 (**1 β**) and its α -anomer (**1 α**) in 54% yield from **9 α/β** (stepwise) and 32% yield from **9 $\alpha/9\beta/10\alpha$** (“one pot”), respectively (Scheme 3).

The ¹H and ¹³C NMR data collected from **1 β** were identical to those reported for the natural product (Table 3), and the structure was further confirmed by ESI–MS, FTIR, and optical rotation [α]_D²⁰: –3.5 (*c* 0.23, CHCl₃) [lit. –1.3 (*c* 0.231, CHCl₃)].¹⁵ Key NOE peaks H₁–H₅ and $^1J_{C1-H1} = 162$ Hz indicate a 4C_1 conformation for **1 β** . The conformational

evaluation of **1 α** proved more challenging. The small values of vicinal coupling constants, the presence of only vicinal contacts in the NOESY experiment, and the ambiguous $^1J_{\text{C1-H1}}$ value of 165 Hz were not conclusive. Fortunately, X-ray diffraction (XRD) definitely confirmed the $^4\text{C}_1$ conformation in **1 α** .²⁰ Notably, the analysis of the stereoselectivity of final products also provides indirect evidence of the relative disposition of the I atom in precursors **9** and **10 α** .

In conclusion, the first total synthesis and structure validation of cardenolide N-1 (**1 β**) and its α -anomer (**1 α**) has been successfully accomplished. Key steps involved Wittig–Horner olefination, $[\text{I}^+]$ -induced 6-*endo* cyclization, and 1,2-*trans* stereoselective glycosylation. This synthesis illustrates the flexibility of our method for accessing 2-deoxyglycosides of “rare” configurations. Indeed, their ready preparation will afford sufficient material to perform robust evaluations of benefit for the medicinal and biological chemistry fields.

EXPERIMENTAL SECTION

General Remarks. Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a 400 MHz (for ^1H) and 100.6 MHz (for ^{13}C) spectrometer. Spectra were fully assigned using COSY, HSQC, HMBC, and NOESY. All chemical shifts are quoted on the δ scale in ppm using the residual solvent as an internal standard (^1H NMR: $\text{CDCl}_3 = 7.26$, $\text{CD}_3\text{OD} = 3.31$ and ^{13}C NMR: $\text{CDCl}_3 = 77.16$, $\text{CD}_3\text{OD} = 49.0$). Coupling constants (J) are reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, and app = apparent. Infrared (IR) spectra were recorded on an FTIR–ATR spectrophotometer. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Optical rotations were measured on a polarimeter with a path length of 1.0 dm and are reported with implied units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Concentrations (c) are given in g/100 mL. High-resolution mass spectra (HRMS) were recorded on an LC/MSD mass spectrometer with electrospray ionization (ESI). Nominal and exact m/z values are reported in daltons (D). Thin layer chromatography (TLC) was carried out using commercial aluminum backed sheets coated with silica gel. Visualization of the silica plates was achieved using a UV lamp ($\lambda_{\text{max}} = 254 \text{ nm}$) and/or staining with a 6% H_2SO_4 in EtOH solution dip followed by heating. Flash column chromatography was carried out using silica gel (230–400 mesh). Mobile phases are reported in relative composition (e.g., 1:1 EtOAc/hexane v/v). HPLC grade dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were dried using standard methods, and acetonitrile was dried using activated 3 Å molecular sieves. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. All reagents were used as received from commercial suppliers. All reactions using anhydrous conditions were performed using a flame-dried apparatus under an atmosphere of argon.

Methyl 3-O-Benzyl-5-deoxy-2-O-methyl- α/β -D-xylofuranoside (3). To a flask containing AcCl (4.5 mL, 63.30 mmol), dry MeOH (15 mL) was added slowly under argon at 0°C followed by a solution of **2**¹⁸ (3.9 g, 14.75 mmol) in MeOH (15 mL). After stirring at room temperature for 5 h, the reaction mixture was neutralized by addition of 30% aqueous NH_4OH (10 mL) and the mixture was extracted with EtOAc (4 \times 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude was then dissolved in THF (35 mL) and cooled to 0°C , and NaH (0.9 g, 22.50 mmol) was added portionwise under argon. After 15 min, MeI (1.8 mL, 28.90 mmol) was added and the reaction mixture stirred at room temperature. After 3 h, a second portion of MeI (0.72 mL, 11.56 mmol) was added and the mixture was stirred for 19 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (20 mL), and the solvent evaporated. The residue was redissolved

with EtOAc (100 mL) and washed with water and brine. The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (1:4 EtOAc/hexane) to afford **3** (3.35 g, 90% over two steps) as a 1.2:1 α/β mixture as a colorless syrup. Data were obtained from the mixture. FTIR–ATR (neat, ν_{max}) 3064, 3031, 2982, 2931, 2907, 2829, 2342, 2331, 1497, 1454, 1065, 1046, 1191, 1118, 738, 698; HRMS (TOF ES⁺) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{14}\text{H}_{20}\text{NaO}_4^+$ 275.1254; Found 275.1256. Data for **3 α** : ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.26 (m, 5H), 4.93 (d, $J = 4.4 \text{ Hz}$, 1H), 4.65 (d, $J = 11.8 \text{ Hz}$, 1H), 4.55 (d, $J = 11.8 \text{ Hz}$, 1H), 4.36 (p, $J = 6.6 \text{ Hz}$, 1H), 4.08 (dd, $J = 6.6 \text{ Hz}$, $J = 5.3 \text{ Hz}$, 1H), 3.84 (m, 1H), 3.44 (s, 3H), 3.43 (s, 3H), 1.27 (d, $J = 6.6 \text{ Hz}$, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 138.1, 128.4, 127.8, 127.6, 100.3, 86.7, 82.2, 73.8, 72.3, 58.5, 55.2, 15.7. Data for **3 β** : ^1H NMR (400 MHz, CDCl_3) δ 7.39–7.27 (m, 5H), 4.79 (d, $J = 1.7 \text{ Hz}$, 1H), 4.66 (d, $J = 12.2 \text{ Hz}$, 1H), 4.53 (d, $J = 12.2 \text{ Hz}$, 1H), 4.31 (p, $J = 6.6 \text{ Hz}$, 1H), 3.84 (m, 1H), 3.79 (m, 1H), 3.42 (s, 3H), 3.36 (s, 3H), 1.32 (d, $J = 6.6 \text{ Hz}$, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 138.3, 128.5, 127.9, 127.8, 107.9, 89.5, 82.2, 77.0, 72.1, 57.9, 55.7, 16.2.

3-O-Benzyl-5-deoxy-2-O-methyl- α/β -D-xylofuranose (4). To a solution of **3** (3.35 g, 13.27 mmol) in AcOH (15 mL), 1 M HCl (1 mL) was added at room temperature. The reaction mixture was warmed at 65°C and stirred for 3 h. The reaction mixture was then cooled to 0°C and neutralized with saturated aqueous NaHCO_3 (100 mL). The product was extracted with EtOAc (5 \times 30 mL), and the combined organic layers were washed with brine and dried over Na_2SO_4 . After filtration and solvent evaporation under reduced pressure, the residue was purified by column chromatography (1:1 EtOAc/hexane) to afford **4** (3.0 g, 95%) as a 1:1.3 α/β mixture as a colorless syrup. Data obtained from the mixture. R_f (1:1 EtOAc/hexane): 0.30; FTIR–ATR (neat, ν_{max}) 3421, 3031, 2979, 2932, 2830, 1454, 1117, 1062, 739, 698; HRMS (TOF ES⁺) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{13}\text{H}_{18}\text{NaO}_4^+$ 261.1097; Found 261.1100. Data for **4 α** : ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.28 (m, 5H), 5.46 (dd, $J = 8.6 \text{ Hz}$, $J = 4.4 \text{ Hz}$, 1H), 4.65 (d, $J = 12.1 \text{ Hz}$, 1H), 4.57 (d, $J = 12.1 \text{ Hz}$, 1H), 4.33–4.25 (m, 1H), 3.85–3.81 (m, 1H), 3.81 (dd, $J = 4.3 \text{ Hz}$, $J = 2.1 \text{ Hz}$, 1H), 3.74 (dd, $J = 4.4 \text{ Hz}$, $J = 2.1 \text{ Hz}$, 1H), 3.43 (s, 3H), 1.28 (d, $J = 6.5 \text{ Hz}$, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 137.8, 128.4, 128.1, 127.8, 95.2, 84.6, 81.7, 74.4, 72.0, 58.6, 14.6. Data for **4 β** : ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.28 (m, 5H), 5.17 (d, $J = 11.1 \text{ Hz}$, 1H), 4.69 (d, $J = 11.8 \text{ Hz}$, 1H), 4.57 (d, $J = 11.8 \text{ Hz}$, 1H), 4.33–4.25 (m, 1H), 3.79 (bs, 1H), 3.77 (m, 1H), 3.39 (s, 3H), 3.36–3.31 (m, 1H), 1.38 (d, $J = 6.6 \text{ Hz}$, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 137.3, 128.5, 127.8, 127.6, 100.6, 87.6, 81.1, 77.6, 72.3, 57.5, 15.4.

(Z/E)-4-O-Benzyl-3-O-methyl-1,2,6-trideoxy-1-phenylsulfanyl-D-xylo-hex-1-enitol (6). *n*BuLi (1.6 M in hexanes, 1.91 mL, 4.77 mmol) was added to a solution of diphenyl (phenylsulfanylmethyl)phosphine oxide **5**¹⁰ (1.58 g, 4.87 mmol) in dry THF (20 mL) at -78°C and the mixture was stirred at this temperature for 45 min. A solution of **4** (455 mg, 1.91 mmol) in dry THF (13 mL) was added to the orange solution at -78°C over a period of 30 min. The reaction mixture was gradually warmed up to room temperature and stirred for 48 h. After quenching the reaction mixture by addition of saturated aqueous NH_4Cl (50 mL), the product was extracted with Et_2O (4 \times 20 mL), the combined organic layers dried over Na_2SO_4 , filtered, and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (1:4 EtOAc/hexane) to afford **6** (546 mg, 83%) as an inseparable 1:1.5 Z/E mixture as a colorless syrup. Data obtained from the mixture. R_f (3:7 EtOAc/hexane): 0.38; FTIR–ATR (neat, ν_{max}) 3464, 3060, 3030, 2974, 2927, 2891, 2820, 1606, 1584, 1479, 1440, 1067, 736, 690; HRMS (TOF ES⁺) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{20}\text{H}_{24}\text{NaO}_3\text{S}^+$ 367.1338; Found 367.1353. Data for **6E**: ^1H NMR (400 MHz, CDCl_3) δ 7.43–7.23 (m, 10H), 6.50 (dd, $J = 15.2 \text{ Hz}$, $J = 0.8 \text{ Hz}$, 1H), 5.72 (dd, $J = 15.2 \text{ Hz}$, $J = 7.9 \text{ Hz}$, 1H), 4.83 (d, $J = 11.2 \text{ Hz}$, 1H), 4.59 (d, $J = 11.2 \text{ Hz}$, 1H), 3.91 (ddd, $J = 7.9 \text{ Hz}$, $J = 5.5 \text{ Hz}$, $J = 0.8 \text{ Hz}$, 1H), 3.98–3.84 (m, 1H), 3.34 (s, 3H), 3.21 (dd, $J = 5.5 \text{ Hz}$, $J = 4.1 \text{ Hz}$, 1H), 2.27 (d, $J = 6.2 \text{ Hz}$, 1H), 1.20 (d, $J = 6.4 \text{ Hz}$,

3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 138.3, 134.4, 130.5, 129.4, 128.6, 128.4, 128.3, 128.3, 128.0, 127.4, 85.3, 83.8, 75.5, 67.6, 57.1, 20.3. Data for **6Z**: ^1H NMR (400 MHz, CDCl_3) δ 7.43–7.23 (m, 10H), 6.55 (dd, $J = 9.6$ Hz, $J = 0.9$ Hz, 1H), 5.82 (dd, $J = 9.6$ Hz, $J = 9.0$ Hz, 1H), 4.91 (d, $J = 11.3$ Hz, 1H), 4.63 (d, $J = 11.3$ Hz, 1H), 4.45 (ddd, $J = 9.0$ Hz, $J = 4.9$ Hz, $J = 0.9$ Hz, 1H), 3.98–3.84 (m, 1H), 3.39 (s, 3H), 3.35–3.31 (m, 1H), 2.41 (d, $J = 5.5$ Hz, 1H), 1.23 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 138.3, 135.7, 129.6, 129.3, 129.3, 128.9, 128.6, 128.3, 128.0, 127.0, 84.8, 79.3, 75.4, 67.7, 57.1, 20.2.

Phenyl 4-O-Benzyl-2,6-dideoxy-2-iodo-3-O-methyl-1-thio- α / β -D-gulopyranoside (7). The isolated product decomposed in solution (light/temperature-sensitive) and was therefore quickly subjected to the next reaction. Sulfanyl alkene **6** (1:1.5 Z/E) (33 mg, 0.096 mmol) was dissolved in dry CH_3CN (1 mL), and the solution cooled to -45 °C. After addition of iodonium di-*sym*-collidine perchlorate (IDCP, 135 mg, 0.287 mmol), the reaction mixture was stirred at -40 °C and monitored by TLC. After 1 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and NaHCO_3 at -40 °C, and extracted. The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (1:9 EtOAc/hexane) to afford **7** (37.7 mg, 84%) as an inseparable 1:2.1 α/β mixture as a colorless syrup. Data obtained from the mixture. R_f (1:9 EtOAc/hexane): 0.27; FTIR–ATR (neat, ν_{max}) 3060, 3029, 2982, 2929, 2891, 2827, 2352, 2325, 1625, 1584, 1455, 1356, 1069, 1014, 740, 693; HRMS (TOF ES^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{20}\text{H}_{23}\text{INaO}_3\text{S}^+$ 493.0305; Found 493.0313. Selected data for **7 β** : ^1H NMR (400 MHz, CDCl_3) δ 7.64–7.25 (m, 10H), 5.00 (d, $J = 11.1$ Hz, 1H), 4.71–4.57 (m, 2H), 4.41 (dd, $J = 11.1$ Hz, $J = 3.3$ Hz, 1H), 4.05 (qd, $J = 6.5$ Hz, $J = 1.3$ Hz, 1H), 3.54 (t, $J = J = 3.3$ Hz, 1H), 3.40 (s, 3H), 3.22 (dd, $J = 3.3$ Hz, $J = 1.3$ Hz, 1H), 1.23 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 85.1, 80.4, 75.2, 72.7, 71.9, 59.2, 31.5, 16.4. Selected data for **7 α** : ^1H NMR (400 MHz, CDCl_3) δ 7.64–7.25 (m, 10H), 5.35 (bd, $J = 4.9$ Hz, 1H), 5.02 (dd, $J = 4.9$ Hz, $J = 3.0$ Hz, 1H), 4.71–4.57 (m, 3H), 3.48–3.43 (m, 4H), 3.37 (bs, 1H), 1.20 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 89.6.

Digitoxigenyl 4-O-Benzyl-2,6-dideoxy-2-iodo-3-O-methyl- α / β -D-gulopyranoside (9). To a Schlenk flask containing activated 4 Å MS and digitoxigenin **8** (21.7 mg, 0.058 mmol) azeotropically dried with toluene was transferred via cannula **7** (13 mg, 0.028 mmol) in dry CH_2Cl_2 (1 mL). After the mixture stirred for 30 min at -85 °C, NIS (18.6 mg, 0.083 mmol) azeotropically dried with toluene and TfOH (1 μL , 0.011 mmol) were subsequently added. After 1 h at -85 °C, the reaction was quenched by addition of saturated aqueous NaHCO_3 (5 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL). The product was extracted with CH_2Cl_2 (5 \times 5 mL), dried over Na_2SO_4 , and filtered, and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (1:1 EtOAc/hexane) to afford **9** (14 mg, 68%) as an inseparable 1:9 α/β mixture as a colorless syrup. Data were obtained from the mixture. R_f (1:1 EtOAc/hexane): 0.33; FTIR–ATR (neat, ν_{max}) 3482, 2931, 1742, 1621, 1453, 1130, 1068, 1026, 1002, 738; HRMS (TOF ES^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{37}\text{H}_{51}\text{INaO}_7^+$ 757.2572; Found 757.2577. Selected data for **9 β** : ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.27 (m, 5H), 5.86 (bt, $J = 1.7$ Hz, 1H), 4.99 (dd, $J = 18.1$ Hz, $J = 1.7$ Hz, 1H), 4.80 (dd, $J = 18.1$ Hz, $J = 1.7$ Hz, 1H), 4.64 (d, $J = 9.2$ Hz, 1H), 4.63 (d, $J = 12.1$ Hz, 1H), 4.58 (d, $J = 12.1$ Hz, 1H), 4.32 (dd, $J = 9.2$ Hz, $J = 3.3$ Hz, 1H), 4.01–3.91 (m, 2H), 3.50 (t, $J = 3.3$ Hz, 1H), 3.35 (s, 3H), 3.18 (dd, $J = 3.3$, $J = 1.3$ Hz, 1H), 2.77 (m, 1H), 2.20–1.18 (m, 21H), 1.18 (d, $J = 6.6$ Hz, 3H), 0.92 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 174.8, 174.7, 137.7, 128.6, 128.5, 128.3, 117.8, 97.6, 85.8, 81.2, 75.3, 73.6, 73.1, 73.0, 69.4, 59.4, 51.1, 49.7, 42.0, 40.2, 36.1, 36.0, 35.3, 33.5, 33.3, 30.1, 29.0, 27.0, 26.6, 26.6, 23.7, 21.5, 21.3, 16.7, 15.9. Selected data for **9 α** : ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.27 (m, 5H), 4.74 (d, $J = 3.9$ Hz, 1H), 4.68–4.52 (m, 2H), 4.26 (qd, $J = 6.7$ Hz, $J = 1.2$ Hz, 1H), 3.81–3.73 (m, 1H), 3.37–3.35 (m, 4H), 3.29 (m, 1H), 1.10 (d, $J = 6.7$

Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 97.1, 79.0, 76.1, 61.7, 59.4, 33.1, 16.5.

Consecutive “One-Pot” Cyclization and Glycosylation. To a Schlenk flask containing activated 4 Å MS and digitoxigenin **8** (110 mg, 0.29 mmol) azeotropically dried with toluene was transferred via cannula **7** (60 mg, 0.174 mmol) in CH_2Cl_2 (4.35 mL). After the mixture stirred for 30 min at -60 °C, NIS (117.3 mg, 0.52 mmol) was then added, and the reaction was gradually warmed up to -10 °C. After 3 h, the reaction mixture was cooled again to -60 °C and TfOH (7.5 μL , 0.035 mmol) was added. After 1 h at -60 °C, the reaction mixture was quenched by addition of a saturated solution of NaHCO_3 (5 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL). The product was extracted with CH_2Cl_2 (5 \times 5 mL), dried over Na_2SO_4 , and filtered, and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (1:1 EtOAc/hexane) to afford **9 α /9 β /10 α** (105 mg, 82%) as an inseparable 1:3.9:4.2 mixture as a yellowish syrup. Data were obtained from the mixture. R_f (1:1 EtOAc/hexane): 0.33; FTIR–ATR (neat, ν_{max}) 3480, 2931, 1741, 1620, 1453, 1131, 1066, 1026, 1002, 735; HRMS (TOF ES^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{37}\text{H}_{51}\text{INaO}_7^+$ 757.2572; Found 757.2575. Selected data for **10 α** : ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.27 (m, 5H), 4.85 (d, $J = 8.4$ Hz, 1H), 4.70 (d, $J = 11.7$ Hz, 1H), 4.57 (d, $J = 11.7$ Hz, 1H), 4.22–4.14 (m, 1H), 3.81–3.73 (m, 1H), 3.63 (s, 3H), 3.58–3.54 (m, 2H), 1.26 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ 97.0, 83.0, 80.7, 73.1, 68.7, 60.7, 33.2, 13.4. Spectroscopic data for **9 α / β** were identical to those reported above.

Digitoxigenyl 2,6-Dideoxy-3-O-methyl- β -D-xylo-pyranoside (1 β). To a solution of **9** (1:9 α/β) (11.7 mg, 0.016 mmol) in degassed toluene (0.7 mL) were successively added Bu_3SnH (12 μL , 0.045 mmol) and AIBN (1 mg, 0.006 mmol). The reaction mixture was heated at 60 °C for 2 h. After cooling down to room temperature, the reaction mixture was diluted with EtOAc (15 mL), the organic layer was washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated. The crude was filtered through a short path of SiO_2 (from 1:9 to 1:1 EtOAc/hexane and 5% Et_3N) to remove tin contaminants. Fractions containing the crude product were concentrated under reduced pressure and dissolved in 1:1 EtOAc/MeOH (1 mL), and 10% Pd/C (24 mg) was added. The mixture was stirred at 0 °C under a H_2 atmosphere (1 atm). After 1 h, the reaction mixture was diluted with EtOAc (15 mL) and filtered through a short path of Celite. The residue was purified by column chromatography (from 1:9 to 3:2 EtOAc/hexane and 5% Et_3N) to afford **1 β** (4.5 mg, 54% over two steps) and **1 α** (0.5 mg, 6% over two steps) as white solids. Data for **1 β** : R_f (3:2 EtOAc/hexane): 0.35; $[\alpha]_{\text{D}}^{20}$: -3.5 (c 0.23, CHCl_3); FTIR–ATR (neat, ν_{max}) 3450, 2855, 1781, 1742, 1666, 1619, 14228, 1362, 1260, 1171, 1096, 1026, 800; HRMS (TOF ES^+) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{30}\text{H}_{46}\text{NaO}_7^+$ 541.3136; Found 541.3129. ^1H NMR (400 MHz, CDCl_3) δ 5.87 (bt, $J = 1.5$ Hz, 1H), 4.99 (dd, $J = 18.2$ Hz, $J = 1.5$ Hz, 1H), 4.80 (dd, $J = 18.2$ Hz, $J = 1.5$ Hz, 1H), 4.71 (dd, $J = 9.5$ Hz, $J = 2.6$ Hz, 1H), 4.03 (bs, 1H), 3.91 (qd, $J = 6.6$ Hz, $J = 1.1$ Hz, 1H), 3.58 (q, $J = 3.2$ Hz, 1H), 3.41–3.35 (m, 4H), 2.78 (m, 1H), 2.23–2.05 (m, 3H), 1.95 (m, 21H), 1.24 (d, $J = 6.6$ Hz, 3H), 0.93 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) 174.7, 174.7, 117.8, 96.6, 85.8, 78.6, 73.6, 72.8, 69.2, 68.0, 57.3, 51.0, 49.7, 42.0, 40.2, 36.4, 35.9, 35.3, 33.3, 31.6, 30.3, 30.0, 27.0, 26.8, 26.8, 23.8, 21.5, 21.3, 16.7, 15.9. Characterization data were identical to those previously reported.¹⁵

Digitoxigenyl 2,6-Dideoxy-3-O-methyl- α -D-xylo-pyranoside (1 α). To a solution of **9 α /9 β /10 α** (1:3.9:4.2 ratio) (17 mg, 0.023 mmol) in degassed toluene (1 mL) were successively added Bu_3SnH (16 μL , 0.059 mmol) and AIBN (1.9 mg, 0.012 mmol). The reaction mixture was heated at 60 °C for 2 h. After cooling down to room temperature, the reaction mixture was diluted with EtOAc (15 mL), and the organic layer was washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated. The crude was filtered through a short path of SiO_2 (from 1:9 to 1:1 EtOAc/hexane and 5% Et_3N) to remove tin contaminants. Fractions containing the crude product were concentrated under reduced pressure and dissolved in 1:1 EtOAc/MeOH (1.3 mL), and 10% Pd/C (35 mg) was added. The mixture was stirred at 0 °C under a H_2 atmosphere (1 atm). After 1

h, the reaction mixture was diluted with EtOAc (15 mL) and filtered through a short path of Celite. The residue was purified by column chromatography (from 1:9 to 3:2 EtOAc/hexane and 5% Et₃N) to afford **1β** (2.6 mg, 22% over two steps) and **1α** (3.8 mg, 32% over two steps) as white solids. Data for **1α**: *R*_f (3:2 EtOAc/hexane): 0.24; [α]_D²⁰: +23.3 (c 0.33, CHCl₃); FTIR–ATR (neat, ν_{\max}) 3456, 2926, 1738, 1620, 1447, 1127, 1109, 1026, 984; HRMS (TOF ES⁺) *m/z*: [M + Na]⁺ Calcd for C₃₀H₄₆NaO₇⁺ 541.3136; Found 541.3140. ¹H NMR (400 MHz, CDCl₃) δ 5.87 (bt, *J* = 1.6 Hz, 1H), 4.99 (dd, *J* = 18.3 Hz, *J* = 1.6 Hz, 1H), 4.85 (bt, *J* = 3.3 Hz, 1H), 4.81 (dd, *J* = 18.3 Hz, *J* = 1.6 Hz, 1H), 4.33 (qd, *J* = 6.8 Hz, *J* = 1.6 Hz, 1H), 3.87 (bs, 1H), 3.53 (q, *J* = 4.0, 1H), 3.47 (m, 1H), 3.39 (s, 3H), 2.78 (m, 1H), 2.23–2.05 (m, 2H), 2.00–1.20 (m, 21H), 1.17 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 3H), 0.87 (s, 3H); ¹³C NMR (100.6 MHz, CDCl₃) 174.7, 174.7, 117.8, 95.5, 85.8, 76.3, 73.6, 72.7, 70.3, 63.2, 56.0, 51.1, 49.7, 42.1, 40.2, 36.9, 35.8, 35.4, 33.3, 32.4, 30.4, 22.7, 27.0, 26.9, 25.2, 24.0, 21.5, 21.4, 16.2, 15.9.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00210.

¹H and ¹³C NMR spectra for all new compounds (PDF)

X-ray crystallographic analysis of **1α** (CIF)

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Notes

The authors declare no competing financial interest.

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(20) (a) Crystallization was performed by slow diffusion of pentane to a solution of **1a** in THF at 4 °C. (b) CCDC 1525764 **1a** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.