Glycosidations of 2-deoxy glycosyl dithiophosphates using a tagged iodine(III)-promoter for simple purification

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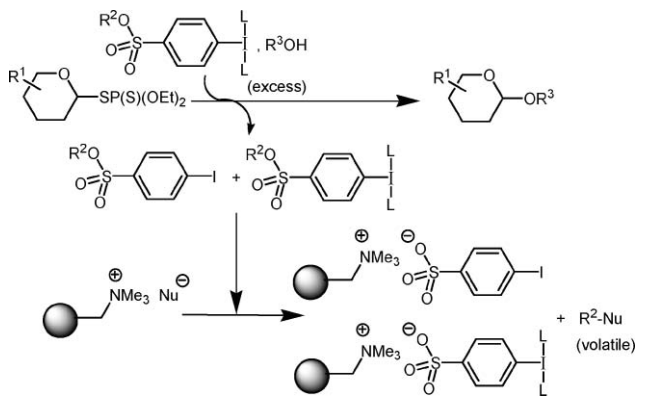
The preparation of the 4-i-butylsulfonate derivative of the Zefirov reagent (**5**) and its use in a novel purification strategy for iodine(III)-promoted glycosidations of 2-deoxy diethyldithiophosphate glycosides is described.

During the past decades, hypervalent iodine compounds have attracted increased interest as mild and selective oxidizing reagents.[1] Recently, iodine(III) chemistry has been extended to catalytic processes.[2] Iodobenzene is a common by-product and has to be removed chromatographically. As this can be a cumbersome task, concepts for facile purification have been developed that are commonly based on solid phase bound and perfluoro tagged iodine(III) reagents.[3,4]

All these concepts are based on the covalent attachment of the iodo moiety to the solid phase or a tag. Regeneration of the iodine(III) species requires reoxidation of the immobilized or tagged aryl iodide, which is not always a straightforward procedure. Alternatively, scavenger reagents can be used for easy removal of excess reagent as well as by-products.[3,5] Here, we report on a general scavenging concept that can be applied in iodine(III)-promoted glycosylations of complex glycosyl donors with aglycons (Scheme 1).

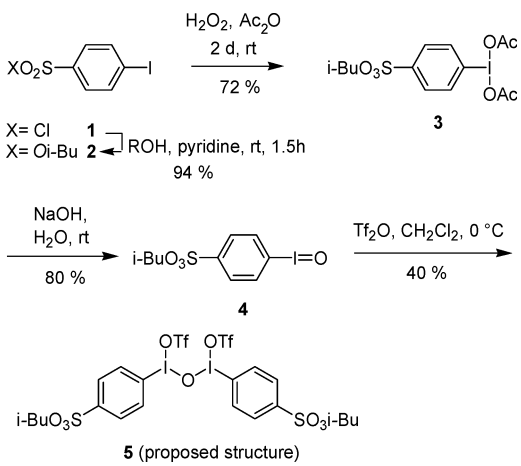


Scheme 1 The concept of a dormant ion exchange group for a new scavenging protocol in glycosidations.

The concept relies on a sulfonate ester tag, which acts as a dormant ion exchange group. Recently, we successfully applied this concept in several ionic and radical mediated iodine(III) reactions.[6]

Thus, the sulfonate anion is liberated by a S_N2-step, thereby being removed from solution by an anion exchange resin. Excess of the tagged iodine reagent is also removed by this method. As a polymer-bound nucleophile, we chose the azide anion, because the alkyl azide that is formed as by-product from the S_N2-displacement is a volatile compound.

The preparation of a set of tagged iodine(III) reagents started from commercially available *p*-iodo-benzenesulfonyl chloride **1** (pipsyl chloride), which was converted into the corresponding i-butyl sulfonate **2** (Scheme 2). Oxidation of **2**[7] yielded bis(acetoxy)iodoarene **3**, which was transformed into iodosylbenzene **4** and the Zefirov reagent **5**[8] both containing the dormant sulfonate anion. Like iodosylbenzene, derivative **4** is insoluble in organic solvents, very likely because of its oligomeric nature. In triflic anhydride, depolymerization proceeds within several minutes to afford a highly labile yellow solid (decomposition to *p*-iodophenylsulfonic acid occurs within a few hours in a glove-box), which is expected to be the tagged μ-oxo complex **5**.



Scheme 2 Preparation of iodanes **3–5**.[6]

In continuation of our research dedicated to the development of solid-phase assisted protocols for glycosidations using electrophilic polymer bound reagents[9] as well as scavengers,[10,11] we studied the concept of a dormant ion exchange group for the electrophilic activation of glycosyl donors and promotion of glycosidations.

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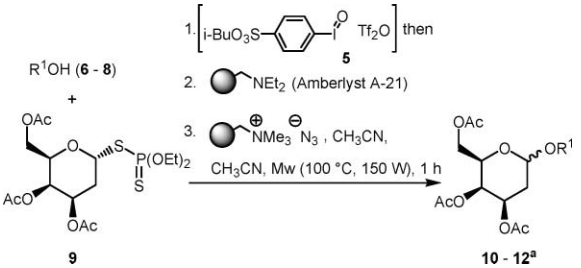
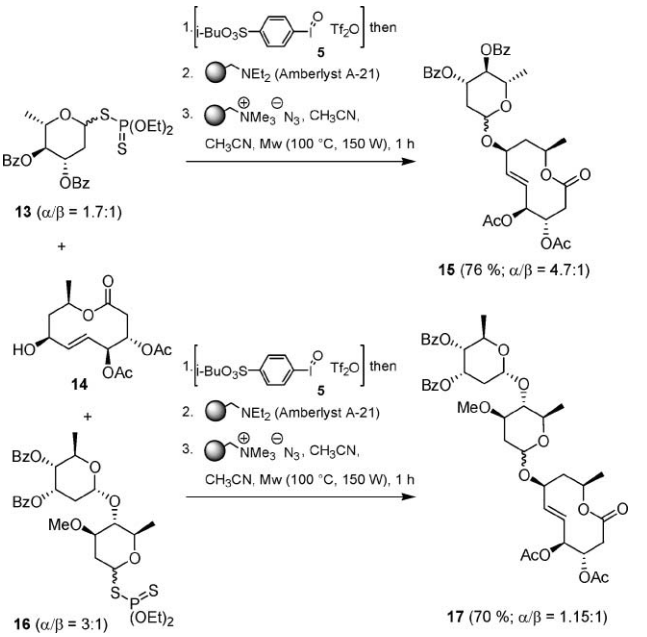
In this context, we already utilized this concept for phenylthioglycosides. However, we had experienced that only simple glycosyl acceptors like benzyl alcohol or 1:2,3:4-di-*O*-isopropylidene-galactose furnished the glycosidation products in good yields.[6] Therefore, we searched for other thio-based glycosyl donors that can be activated by iodine(III) reagents. We found that the rarely employed glycosyl diethyldithiophosphates (Schemes 1, 3 and 4 and Table 1) are very well suited as glycosyl donors. This glycosyl donor group was first introduced by Thiem *et al.*[12] and was recently applied for the synthesis of the trisaccharide unit of the chaperone down-regulator versipelostatin.[13] Complete activation occurs within minutes even at low temperature (−78 °C), and glycoconjugates **10–12** were formed in satisfactory yields. Here, we chose glycosyl acceptors of enhanced complexity such as the decanolides decarestrictines B and D.[14] In order to reduce work-up to a minimum, it is not only removal of the iodoarenes that has to be guaranteed, but also the scavenging of other by-products such as traces of TfOH, thiols, disulfides and oxygenated disulfides, which are formed during the glycosidation process. Except for glycoside **12**, the crude product was pure enough for complete NMR analysis of the anomeric mixture. Related



Scheme 3 Iodine(III)-promoted glycosidations of diethyldithiophosphate **9** and scavenging protocol. [a] See Table 1, footnote a.



Scheme 4 Iodine(III)-promoted preparation of decarestrictine-based glycoconjugates using diethyldithiophosphonates **13** and **16** as glycosyl donors.

Table 1

Glycosyl acceptor	Glycosidation product	α–β-ratio	Yield (%)
HO, OAc **6**	AcO, OAc, AcO, OAc **10**	3 : 1 3 : 1	92% for Tf_2O 73% for TMSOTf
O, O, OH, O **7**	OAc, AcO, OAc **11**	10 : 1	50%[b]
TBSO, TBSO, OH **8**	TBSO, TBSO, OAc, AcO, OAc **12**	1 : 0.9	72% Conversion 41% Isolated yield 28% **8**

[a] Isolated yield. [b] Scavenging of aryl iodide was not performed on **11**.

glycosidations in solution resulted in crude products that still contained thiophosphate-derived by-products after classical work-up.[13]

Thus, addition of Amberlyst A-21 removes traces of acidic by-products.[10] Finally, all sulfonate tagged iodine species are scavenged by the azido exchange resin under microwave irradiating conditions to yield the purified glycosidation products **10–12**.

Particularly important to note is the presence of the olefinic double bond in decarestrictine derivative **8** (leading to glycoside **12**), which is not affected by this electrophilic promoter system, despite the fact that hypervalent iodine reagents are known to react with olefins. In this example, we also detected glyconjugate by-products that originate from *O*-desilylations (<5%). Furthermore, formation of glycoside **12** is remarkable because 4,7-di-*O*-TBS protected decarestrictine D[9b] is a challenging glycosyl acceptor. The 3-OH group shows reduced reactivity for which the intramolecular hydrogen bond with the lactone carbonyl group has to be made responsible.[15] The high yielding formation of glycoside **10** using 4-acetoxybut-2-en-1-ol **6** as acceptor strongly supports this chemoselectivity toward olefinic double bonds. This example also demonstrates that activation of iodosyl arene **4** is favourably achieved with Tf_2O instead of TMSOTf.

In contrast, the partially protected decarestrictine D derivative **14**[9b] with a free hydroxyl group at C-7 shows enhanced reactivity as is demonstrated in the glycosidation with diethyldithiophosphate glycoside **13** (Scheme 4). Finally, we investigated the glycosidation of a disaccharide glycosyl donor **16**, composed of protected D-digitoxose and D-oleandrose with bis-*O*-acylated decarestrictine **14**. After two hours at −78 °C, full transformation was encountered and solid-phase assisted work-up yielded complex glycoconjugate **17** in good yield.

In conclusion, we developed a powerful glycosidation method for diethyldithiophosphates that utilizes a tagged version of Zefirov's reagent. In combination with the scavenging protocol, the method allows us to prepare glycoconjugates based on 2-deoxysugars. In principle, we believe that the i-butylsulfonyl tag and this scavenging concept are of general applicability for purification protocols of reagents as well as catalysts.

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Experimental

General remarks

^{1}H NMR, ^{13}C NMR and ^{1}H, ^{13}C-COSY as well as NOESY spectra were measured on an Avance 200/DPX (Bruker) with 200 MHz (50 MHz), Avance 400/DPX (Bruker) 400 MHz (100 MHz) and Avance 500/DRX (Bruker) respectively, using tetramethylsilane as the internal standard. If not otherwise noted, $CDCl_3$ was the solvent for all NMR experiments. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shift values of ^{13}C NMR spectra are reported as values in ppm relative to residual $CHCl_3$ (77 ppm) or CD_3OD (49 ppm) as internal standards. The multiplicities refer to the resonances in the off-resonance spectra and were elucidated using the distortionless enhancement by polarisation transfer (DEPT) spectral editing technique, with secondary pulses at 90 ° and 135°. Multiplicities are reported using the following abbreviations: s = singlet (due to quaternary carbon), d = doublet (methine), q = quartet (methyl), t = triplet (methylene). Mass spectra were recorded on a type LCT-spectrometer (Micromass) and on a type VG autospec (Micromass). Ion mass (m/z) signals are reported as values in atomic mass units followed, in parentheses, by the peak intensities relative to the base peak (100%). Optical rotations [α] were collected on a Polarimeter 341 (Perkin Elmer) at a wavelength of 589 nm and are given in 10^{-1} deg cm^2 g^{-1}. All solvents used were of reagent grade and were further dried. Reactions were monitored by thin layer chromatography (tlc) on silica gel 60 F^{254} (E. Merck, Darmstadt) and spots were detected either by UV-absorption or by charring with H_2SO_4–4-methoxybenzaldehyde in ethanol. Preparative column chromatography was performed on silica gel 60 (E. Merck, Darmstadt). For the synthesis of dithiophosphates, refer to ref. 12, 13 and 16.

Hazard warning

Aliphatic azides are regarded to be potentially explosive. For i-butyl azide, which is formed as a by-product and removed under reduced pressure here, no data are available in the literature. We never encountered any hazards during these studies. However, this observation does not exclude the possibility of explosions.

Preparation of tagged iodine(III) reagent 5

(2′-Methyl)-propyl-4-iodo-phenylsulfonate (2). To a solution of pipsyl chloride **1** (5.52 g, 18.2 mmol) in 20 mL absolute pyridine at rt was added i-butanol (1.68 mL, 1 eq.). After 90 min, the reaction was hydrolyzed by addition of 20 mL of a saturated $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 (3 times), and the combined organic layers were dried (Na_2SO_4). After concentration under reduced pressure, the crude product was co-distilled with toluene to remove traces of pyridine. The title product **2** was obtained as a colorless, amorphous solid (5.40 g, 15.9 mmol; 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 6H, J = 6.7), 1.95 (m, 1H), 3.82 (d, J = 6.5, 2H), 7.61 (d, J = 8.2, 2H), 7.92 (d, J = 8.2, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9 (q), 28.5 (d), 77.2 (t), 101.7 (s), 129.5 (d), 136.4 (d), 138.9 (s) ppm; HRMS (ESI): calculated for $C_{10}H_{13}IO_3S$ (M^+): 339.9630, observed 339.9633.

(2′-Methyl)-propyl-4-[bis(acetoxy)iodo]-phenylsulfonate (3). A mixture of 60 mL Ac_2O and 14 mL 30% H_2O_2 was kept for 4 h at 40 °C (keeping the exact temperature is essential) in the dark. It was then poured onto finely ground (2′-methyl)-propyl-4-iodo-phenylsulfonate **2** (6.06 g, 17.8 mmol) and cooled to room temperature. After 2 days, this reaction mixture was poured onto 150 mL of ice-water, and the crystals were allowed to grow for 5–10 minutes, before being recovered by filtration on a Büchner funnel. The crystalline material was then washed with another 150 mL of ice-water, dried under a high vacuum and the title compound **3** was collected as colorless crystals (5.89 g, 12.8 mmol; 72% yield). Mp 117–123 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J = 6.6, 6H), 2.04 (sept, J = 6.5, 1H), 3.92 (d, J = 6.5, 2H), 7.97 (d, J = 8.7, 2H), 8.26 (d, J = 8.0, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5 (q), 20.3 (q), 28.1 (d), 77.2 (t), 125.8 (s), 129.7 (d), 136.5 (d), 139.5 (s), 176.7 (s) ppm; HRMS (ESI): calculated for $C_{14}H_{19}IO_7S$ (M^+) 457.9896, observed 457.9903.

(2′-Methyl)-propyl-4-iodosyl-phenylsulfonate (4). Finely ground (2′-methyl)-propyl-4-[bis(acetoxy)iodo]-phenylsulfonate **3** (846 mg, 1.85 mmol) was placed in a 100 mL beaker and 30 mL of NaOH (3 N) was added over 5 minutes with vigorous stirring. The mixture was triturated with a spatula for 15 minutes in order to become homogeneous. After standing for 45 minutes, water was added (20 mL) with vigorous stirring, and the solid was collected on a Büchner funnel. It was returned to the beaker, triturated with water (40 mL) and collected again. Washing with water (3 times, 40 mL) and drying under a high vacuum yielded a yellowish solid **4** (523.4 mg; 1.47 mmol; 80% yield), which is insoluble in common solvents. Mp 151–153 °C (dec.); IR (film) 708, 729, 745, 768, 811, 843, 944, 976, 1091, 1176, 1182, 1357, 1469, 1568, 2962 cm^{-1}.

μ-Oxo-bis-[triflyloxy(4-isobutyl)benzenesulfonato]-iodane (5). In an oven dried round-bottom flask, under an argon atmosphere, freshly distilled CH_2Cl_2 (3 mL) was added to **4** (1 g, 2.80 mmol). After cooling to 0 °C, triflic anhydride (235 μL, 0.5 eq.) was added to the suspension, which immediately turned into a yellow solution. A yellow solid precipitated after 15–30 minutes, which was recovered by filtration under an argon atmosphere (using the Schlenk filtration technique) and dried under a high vacuum for 2 h. The title compound **5** was isolated (553 mg) and stored at 0 °C under an inert atmosphere (preferentially in a glove-box). This solid is very temperature sensitive and storage at room temperature (under an argon atmosphere) commonly affords 4-iodophenylsulfonic acid overnight. Although the title compound **5** was prepared freshly before each reaction, it can be stored as a suspension (in dichloromethane under argon at 0 °C) for several days, without a significant loss of activity. ^{1}H NMR (400 MHz, CD_3CN, CHD_2CN = 1.94 ppm) δ 0.74 (d, J = 6.6, 6H), 1.78–1.86 (m, 1H), 3.73 (d, J = 6.6, 2H), 7.90 (m, 2H), 8.21 (m, 2H) ppm; ^{13}C NMR (100 MHz, CD_3CN, CD_3CN = 1.32 ppm) δ 18.4 (q), 28.2 (d), 117.1 (t), 129.3 (d), 130.6 (d), 135.2 (s), 138.8 (s) ppm.

General procedure for the glycosidation of diethyldithiophosphates

To a solution of thioglycoside and glycosyl acceptor (azeotropically dried with toluene followed by 1 hour under a high vacuum) in a mixture of dry acetonitrile and nitromethane (4 : 1; 50 mL $mmol^{-1}$) was added freshly activated molecular sieves (4 Å, 1 g $mmol^{-1}$). This suspension was cooled to −80 °C.

The activating agent was freshly prepared by adding Tf_2O (0.5 eq.) or TMSOTf (1 eq.) to a suspension of compound **4** in absolute dichloromethane (5 mL $mmol^{-1}$) at 0 °C. Within a few minutes, a yellow precipitate was formed (formation of compound **5**) which, after dissolution in a minimum amount of dry acetonitrile, was transferred (1.3 eq.) to the reaction mixture described above. After completion of the reaction (monitored by tlc), dry Amberlyst A-21 (1 g $mmol^{-1}$) was added to terminate the reaction. Filtration through a pad of silica or celite afforded a crude oil, which was then submitted to the scavenging protocol.

The crude compound was dissolved in acetonitrile (20 mL $mmol^{-1}$) and azide resin was added (~2 g $mmol^{-1}$). The scavenging proceeds within 1 hour at 100 °C under microwave irradiating conditions (150 W) or within two days at 60 °C under thermal conditions. The compounds obtained were usually free of by-products. In order to collect analytically pure material, or for separation of anomers, a sample was chromatographically purified over silica gel.

1-*O*-[4′-*O*-Acetyl-(*Z*)-but-2′-enyl]-3,4,6-tri-*O*-acetyl-α/β-D-galactoside (10).

Tf_2O method. General procedure with thioglycoside **9** (43 mg, 0.1 mmol), glycosyl acceptor **6** (25 mg, 2 eq.) in CH_2Cl_2–CH_3NO_2 (4 + 1 mL) with MS 4 Å (100 mg) and oxidizing reagent (prepared from **4** (49 mg, 1.5 eq.) and Tf_2O (8.5 μL, 14 mg, 0.75 eq.) in 0.5 mL CH_2Cl_2), for 3 hours at 0 °C, followed by basic work-up (200 mg, A-21), and iodophenylsulfonate scavenging (200 mg azide resin, 2 mL CH_3CN, microwave irradiation) gave 22.4 mg α-**10** (59% yield), 5.8 mg β-**10** (15% yield) and 7.0 mg of an α–β-mixture (1 : 5; 18% yield) as a colorless oil after column chromatography (petroleum ether–AcOEt = 5 : 1). The overall yield is therefore 92% (α–β-ratio = 3 : 1).

TMSOTf method. General procedure with thioglycoside **9** (43 mg, 0.095 mmol), glycosyl acceptor **6** (25 mg, 2 eq.) in CH_2Cl_2–CH_3NO_2 (4 + 1 mL) with MS 4 Å (100 mg) and oxidizing reagent (prepared from **4** (49 mg, 1.5 eq.) and TMSOTf (25 μL, 1.5 eq.) in 0.5 mL CH_2Cl_2), for 3 hours at 0 °C followed by basic work-up (100 mg, A-21), and iodophenylsulfonate scavenging (200 mg azide resin, 2 mL CH_3CN, microwave irradiation) gave 30.3 mg **10** (73% yield) as an α–β-mixture (3 : 1). HRMS calcd for $C_{18}H_{26}O_{10}Na$ [M + Na] 425.1424, observed 425.1425, calcd for $C_{18}H_{25}O_{10}$ [M − H] 401.1448, observed 401.1455.

α-10. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (m, 1H, 2_{ax}-H), 1.97 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.08 (m, 1H, 2_{eq}-H), 2.13 (s, 3H, OAc), 4.06–4.22 (m, 5H, 5-H + 2 × 6-H + 2 × 1′-H), 4.64 (d, J = 5.1, 2H, 4′-H), 5.04 (bd, J = 3.1, 1H, 1-H), 5.28 (ddd, J = 12.6, 4.8, 3.1, 1H, 3-H), 5.32 (m, 1H, 4-H), 5.74 (m, 2H, 2′-H + 3′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 20.7, 20.8, 20.9, 30.0, 60.0, 62.5, 62.7, 66.1, 66.6, 66.8, 96.7, 127.3, 129.6, 170.0, 170.3, 170.5, 170.7 ppm. $[\alpha]_D^{20}$ = +75.3 (c 2.23, CH_2Cl_2).

β-10. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95–2.10 (m, 2H, 2_{ax}-H + 2_{eq}-H), 2.00 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.14 (s, 3H, OAc), 3.82 (ddd, J = 6.8, 6.5, 1.0, 1H, 5-H), 4.16 (bdd, J = 6.6, 1.4, 2H, 1′-H), 4.32 (dd, J = 12.4, 6.1, 1H, 6-H), 4.42 (dd, J = 12.4, 5.8, 1H, 6-H), 4.58–4.65 (m, 2H, 4′-H), 4.68 (dd, J = 12.9, 6.0, 1H, 1-H), 5.00 (ddd, J = 11.2, 6.4, 3.1, 1H, 3-H), 5.26 (dd, J = 3.1, 1.0, 1H, 4-H), 5.74 (m, 2H, 2′-H + 3′-H) ppm. $[\alpha]_D^{20}$ = +0.9 ° (c 0.58, CH_2Cl_2).

5-*O*-[3′,4′,6′-Tri-*O*-acetyl-α/β-D-galactosyl]-decarestrictine B (11). General procedure with thioglycoside **9** (25 mg, 0.05 mmol), decarestrictine B (12 mg, 1 eq.) in CH_2Cl_2–CH_3NO_2 (2 + 0.5 mL) with MS 4 Å (50 mg) and oxidizing reagent (prepared from **4** (30 mg, 1.5 eq.) and TMSOTf (15 μL, 1.5 eq.) in 0.5 mL CH_2Cl_2), for 5 hours at −80 °C, followed by basic work-up (100 mg, A-21), after column chromatography (petroleum ether–AcOEt = 2 : 1), gave 13.3 mg **11** (50% yield) of a colourless oil as an α–β-mixture (10 : 1). HRMS calcd for $C_{22}H_{31}O_{12}$ (M + H) 487.1816, observed 487.1802, calc for $C_{22}H_{29}O_{12}$ (M − H) 485.1659 observed 485.1661.

α-11. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 6.3, 3H, 10-H), 1.55 (ddd, J = 14.7, 11.4, 10.3, 1H, 8_{ax}-H), 1.86 (m, 1H, $2'_{ax}$-H), 1.98 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.13 (s, 3H, OAc), 2.15 (m, 1H, $2'_{eq}$-H), 2.34 (ddd, J = 14.7, 4.3, 0.9, 1H, 8_{eq}-H), 2.57 (dd, J = 14.3, 3.2, 1H, 4-H), 2.98 (ddd, J = 14.3, 4.4, 0.9, 1H,

4-H), 3.01 (dd, J = 9.3, 4.0, 1H, 6-H), 3.10 (ddd, J = 10.3, 4.3, 4.0, 1H, 7-H), 3.41 (d, J = 15.9, 1H, 2-H), 3.51 (d, J = 15.9, 1H, 2-H), 3.73 (ddd, J = 9.3, 4.4, 3.2, 1H, 5-H), 4.03 (dd, J = 11.2, 6.5, 1H, 6′-H), 4.07 (dd, J = 11.2, 6.5, 1H, 6′-H), 4.45 (ddd, J = 6.5, 6.5, 1.0, 1H, 5-H), 5.07 (ddq, J = 11.4, 6.3, 0.9, 1H, 9-H), 5.32 (ddd, J = 8.6, 4.8, 3.1, 1H, 3′-H), 5.34 (d, J = 3.5, 1H, 4′-H), 5.40 (bd, J = 3.0, 1H, 1′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 20.7, 20.8, 20.9, 30.3, 36.5, 47.4, 51.8, 54.2, 58.6, 62.4, 66.1, 66.5, 66.8, 69.1, 72.2, 95.0, 165.4, 170.0, 170.3, 170.4, 200.4 ppm.

The ^{1}H NMR data for the anomeric proton of β-**11**: δ 4.92 (dd, J = 9.5, 2.5, 1′-H).

3′,4′,6′-Tri-*O*-acetyl-α/β-D-galactosyl-(1′→3)-4,7-di-*O*-(*tert*-butyldimethylsilyl)-decarestrictine D (12). General procedure with thioglycoside **9** (23 mg, 0.05 mmol), 4,7-di-*O*-TBS-decarestrictine D (**8**) (23 mg, 1 eq.) in CH_2Cl_2–CH_3NO_2 (2 + 0.5 mL) with MS 4 Å (50 mg) and oxidizing reagent (prepared from **4** (30 mg, 1.6 eq.) and Tf_2O (5.5 μL, 0.8 eq.) in 0.5 mL CH_2Cl_2) for 13 hours at −78 °C, followed by basic work-up (200 mg, A-21), and iodophenylsulfonate scavenging (200 mg azide resin, 2 mL CH_3CN, microwave irradiation) gave 16.0 mg of **12** (α–β-mixture: 1 : 0.6; 41% yield) as a colourless oil after column chromatography (petroleum ether–AcOEt = 20 : 1). Unreacted decarestrictine D **8** was also recovered (28%) after purification. HRMS calcd for $C_{34}H_{59}O_{12}Si_2$ [M − H] 715.3545, observed 715.3539, calcd for $C_{34}H_{60}O_{12}NaSi_2$ [M + Na] 739.3521, observed 739.3518.

α-12. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00–0.12 (m, 12H, Si$Me_2{}^t$Bu), 0.85–0.97 (m, 18H, SiMe$_2{}^t$Bu), 1.21 (d, J = 5.5, 3H, 10-H), 1.65–1.87 (m, 2H, 8-H), 2.02 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.11–2.17 (m, 2H, 2′-H), 2.17 (s, 3H, OAc), 2.49 (dd, J = 14.0, 6.0, 1H, 2_{ax}-H), 2.58 (dd, J = 14.0, 1.3, 1H, 2_{eq}-H), 3.94 (ddd, J = 6.0, 4.1, 1.3, 1H, 3-H), 4.00–4.21 (m, 4H, 6′-H + 5′-H + 7-H), 4.32 (ddd, J = 4.1, 2.2, 1.9, 1H, 4-H), 4.92–4.99 (m, 1H, 9-H), 5.31–5.37 (m, 2H, 4′-H + 3′-H), 5.40 (bd, J = 2.8, 1H, 1′-H), 5.58 (dd, J = 15.7, 2.2, 1H, 5-H), 5.88 (ddd, J = 15.7, 9.5, 1.9, 1H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −5.0, −4.7, −4.2, 18.1, 18.2, 20.8, 20.8, 20.9, 21.4, 25.8, 25.8, 29.4, 29.6, 44.1, 62.7, 66.2, 66.6, 67.1, 68.0, 71.4, 73.3, 75.7, 93.7, 126.2, 136.5, 170.3, 170.4, 170.4, 170.5 ppm.

β-12. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00–0.12 (m, 12H, Si$Me_2{}^t$Bu), 0.85–0.97 (m, 18H, SiMe$_2{}^t$Bu), 1.22 (d, J = 6.14, 3H, 10-H), 1.65–1.87 (m, 2H, 8-H), 1.93–2.07 (m, 2H, 2′-H), 2.03 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.16 (s, 3H, OAc), 2.35 (dd, J = 14.3, 9.8, 1H, 2_{ax}-H), 2.83 (dd, J = 14.3, 3.6, 1H, 2_{eq}-H), 3.81 (dt, J = 6.7, 1.0, 1H, 5′-H), 3.87 (ddd, J = 9.8, 6.5, 3.6, 1H, 3-H), 4.00–4.21 (m, 4H, 4-H + 7-H + 6′-H), 4.80 (dd, J = 9.3, 3.4, 1H, 1′-H), 4.93–4.99 (m, 1H, 3′-H), 5.21 (ddq, J = 6.3, 6.3, 1.7, 1H, 9-H), 5.24 (bd, J = 3.0, 1H, 4′-H), 5.61 (dd, J = 16.0, 4.1, 1H, 5-H), 5.85 (ddd, J = 16.0, 9.2, 1.0, 1H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.8, −4.6, −4.4, 18.1, 18.1, 20.7, 20.8, 20.8, 21.6, 25.7, 25.8, 31.8, 38.2, 43.5, 61.8, 65.3, 67.9, 68.5, 70.9, 72.1, 73.5, 82.6, 101.1, 126.1, 138.6, 170.0, 170.4, 170.4, 170.5 ppm.

(3′,4′-Di-*O*-benzoyl-2-deoxy-α-L-arabino-hexopyranosyl)-(1′→7)-3,4-di-*O*-acetyl-decarestrictine D (15). General procedure with thioglycoside **13** (32 mg, 0.06 mmol), 3,4-di-OAc-decarestrictine D (18.4 mg, 1 eq.) in CH_2Cl_2–CH_3NO_2 (2 + 0.5 mL) with MS 4 Å (50 mg) and oxidizing reagent (prepared from **4** (33 mg, 1.5 eq.) and Tf_2O (7.7 μL, 13 mg, 0.75 eq.) in 0.5 mL CH_2Cl_2), for 15 hours at −78 °C, followed by basic work-up (120 mg, A-21), and iodophenylsulfonate scavenging (200 mg azide resin, 2 mL CH_3CN, microwave irradiation) gave 33.3 mg of **15** (76% yield; α–β-mixture = 4.7 : 1, determined by NMR on crude product). Purification by column chromatography led to substantial loss of material. However, pure samples of both anomers were obtained by semi-preparative HPLC purification: 7.3 mg of α′-**15**; 19% yield and 2.4 mg of β′-**15**; 6% yield. HRMS calcd for $C_{34}H_{38}O_{12}Na$ [M + Na] 661.2261, observed 661.2270.

α′-15. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 6.2, 3H), 1.28 (d, J = 6.4, 3H), 1.89–1.99 (m, 3H), 2.15 (s, 3H), 2.17 (s, 3H), 2.37 (ddd, J = 12.8, 5.1, 1.1, 1H), 2.56 (dd, J = 14.2, 2.3, 1H), 2.73 (dd, J = 14.2, 6.9, 1H), 4.03 (dq, J = 9.7, 6.2, 1H), 4.17 (ddd, J = 9.4, 8.4, 6.1, 1H), 4.95 (bd, J = 2.8, 1H), 5.03 (ddd, J = 6.9, 4.9, 2.3, 1H), 5.20 (dd, J = 9.7, 9.4, 1H), 5.21 (m, 1H), 5.37 (ddd, J = 4.9, 3.3, 1.4, 1H), 5.61 (ddd, J = 11.6, 9.5, 5.1, 1H), 5.65 (ddd, J = 16.0, 9.5, 1.4, 1H), 5.87 (dd, J = 16.0, 3.3, 1H), 7.33–7.41 (m, 4H), 7.46–7.54 (m, 2H), 7.90–8.00 (m, 4H) ppm.

β′-15. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, J = 6.4, 3H), 1.26 (d, J = 6.2, 3H), 1.89 (ddd, J = 12.3, 11.8, 9.9, 1H), 1.81–1.97 (m, 2H), 2.13 (s, 3H), 2.15 (s, 3H), 2.50 (ddd, J = 12.3, 5.1, 2.0, 1H), 2.59 (dd, J = 14.2, 2.8, 1H), 2.68 (dd, J = 14.2, 7.3, 1H), 3.62 (dq, J = 9.5, 6.2, 1H), 4.17 (ddd, J = 10.1, 9.6, 3.7, 1H), 4.69 (dd, J = 9.9, 2.0, 1H), 5.05 (ddd, J = 7.3, 5.2, 2.8, 1H), 5.15 (ddq, J = 10.7, 6.4, 2.2, 1H), 5.17 (dd, J = 9.5, 9.5, 1H), 5.28 (ddd, J = 11.8, 9.5, 5.1, 1H), 5.35 (ddd, J = 5.2, 3.5, 1.3, 1H), 5.77 (dd, J = 16.0, 3.5, 1H), 5.90 (ddd, J = 16.0, 9.5, 1.3, 1H), 7.33–7.40 (m, 4H), 7.47–7.54 (m, 2H), 7.90–7.95 (m, 4H) ppm.

(3″,4″-Di-*O*-benzoyl-α″-D-digitoxyl)-(1″→4′)-(α′/β′-D-oleandrosyl)-(1′→7)-3,4-di-*O*-acetyl decarestrictine D (17). General procedure with disaccharide **16** (40 mg, 0.06 mmol), 3,4-di-OAc-decarestrictine D (**14**) (18 mg, 1 eq.) in CH_2Cl_2–CH_3NO_2 (2 + 0.5 mL) with MS 4 Å (50 mg) and oxidizing reagent (prepared from **4** (30 mg, 1.4 eq.) and Tf_2O (7.1 μL, 0.7 eq.) in 0.5 mL CH_2Cl_2), for 15 hours at −78 °C, followed by basic work-up (120 mg, A-21), and iodophenylsulfonate scavenging (200 mg azide resin, 2 mL CH_3CN, microwave irradiation) gave, after purification, 15.7 mg of α′-**17** (33% yield), 12.9 mg of β′-**17** (28% yield) and 4.1 mg of a fraction of α–β-anomers (1 : 1; 9% yield). The overall yield of the reaction is 70% and the α–β-selectivity is 1.15 : 1. HRMS calcd $C_{41}H_{50}O_{15}Na$ [M + Na] 805.3047, observed 805.3053, calcd $C_{41}H_{49}O_{15}$ [M − H] 781.3071, observed 781.3076.

α′-17. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, J = 6.5, 3H), 1.26 (d, J = 6.5, 3H), 1.32 (d, J = 6.2, 3H), 1.50 (ddd, J = 12.9, 11.4, 3.5, 1H), 1.71 (ddd, J = 14.2, 11.1, 11.0, 1H), 1.89 (ddd, J = 14.2, 3.3, 1.5, 1H), 2.07 (s, 3H), 2.10–2.25 (m, 2H), 2.37 (s, 3H), 2.37 (ddd, J = 15.0, 3.7, 1.3, 1H), 2.60 (dd, J = 14.1, 3.3, 1H), 2.66 (dd, J = 14.1, 7.5, 1H), 3.24 (dd, J = 9.1, 8.9, 1H), 3.27 (s, 3H), 3.44 (ddd, J = 11.4, 8.9, 5.0, 1H), 3.63 (dq, J = 9.1, 6.2, 1H), 4.04 (ddd, J = 11.0, 9.2, 3.3, 1H), 4.59 (dq, J = 9.5, 6.5, 1H), 4.93 (bd, J = 3.5, 1H), 5.02 (dd, J = 9.5, 3.3, 1H), 5.12 (m, 2H), 5.35 (bdd, J = 4.5, 1.3, 1H), 5.38 (ddd, J = 6.0 3.6, 1.0, 1H), 5.65 (ddd, J = 3.7, 3.5, 3.3, 1H), 5.73 (dd, J = 16.0, 3.6, 1H), 5.87 (ddd, J = 16.0, 9.2, 1.0, 1H), 7.37 (m, 2H), 7.45 (m, 2H), 7.53 (m, 1H), 7.62 (m, 1H), 7.93 (m, 2H), 8.06 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 18.0, 20.9, 21.0, 21.5, 33.8, 34.1, 34.7,

39.8, 56.6, 62.9, 67.0, 67.3, 68.2, 70.6, 72.1, 73.0, 77.2, 78.9, 82.0, 95.6, 97.5, 122.9, 128.1–133.2 (12 C), 136.5, 165.6, 165.8, 169.0, 169.3, 169.9 ppm.

β′-17. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, $J = 6.3$, 3H), 1.26 (d, $J = 6.3$, 3H), 1.28–1.42 (m, 1H), 1.44 (d, $J = 6.0$, 3H), 1.81 (ddd, $J = 14.1$, 11.2, 11.2, 1H), 1.97 (ddd, $J = 14.1$, 3.2, 1.6, 1H), 2.15 (s, 3H), 2.17 (s, 3H), 2.10–2.23 (m, 2H), 2.38 (ddd, $J = 15.0$, 3.6, 1.1, 1H), 2.56 (dd, $J = 14.2$, 2.4, 1H), 2.70 (dd, $J = 14.2$, 7.1, 1H), 3.10–3.19 (m, 2H), 3.27 (s, 3H), 3.25 (dd, $J = 8.8$, 8.8, 1H), 4.27–4.35 (m, 2H), 4.60 (dq, $J = 9.7$, 6.3, 1H), 5.01 (dd, $J = 9.7$, 3.2, 1H), 5.05 (ddd, $J = 7.1$, 5.0, 2.4, 1H), 5.15–5.22 (m, 1H), 5.33–5.40 (m, 2H), 5.62 (ddd, $J = 3.6$, 3.4, 3.2, 1H), 5.63 (ddd, $J = 16.1$, 9.5, 1.2, 1H), 5.80 (dd, $J = 16.1$, 3.4, 1H), 7.30–8.10 (m, 10H) ppm.^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 18.5, 20.9, 21.0, 21.4, 33.5, 33.7, 35.7, 41.0, 56.3, 62.6, 67.4, 68.2, 70.8, 70.9, 72.0, 73.0, 76.4, 80.8, 81.4, 95.5, 97.1, 126.1, 127.5–133.5 (12 C), 134.2, 165.5, 165.9, 169.1, 169.5, 169.8 ppm.

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