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A selective $Sc(OTf)_3$-catalyzed trialkylsilyl ether to acetyl ester exchange reaction with β-L-idopyranoside and 3,4-*O*-isopropylidene-β-D-galactopyranoside derivatives

Weijun Ke and Dennis M. Whitfield*

Institute for Biological Sciences, National Research Council, Ottawa, Canada ON K1A 0R6

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Abstract—The selective silylation of monosaccharide building blocks is useful for preparing complex oligosaccharides. We now report that the diol, methyl (dimethylthexylsilyl 3-*O*-pivaloyl-β-L-idopyranosyl)uronate, can be selectively silylated at the O-2 position by trialkylsilyl triflates. After protection of O-4, the O-2 silyl group can be selectively replaced by acetate by taking advantage of a trialkylsilyl–acetate exchange reaction catalyzed by $Sc(OTf)_3$ in the presence of acetic anhydride. The high O-2 selectivity is shown for triethylsilyl (TES), *tert*-butyldimethylsilyl (TBS), and triisopropylsilyl (TIPS). The selective cleavage reaction only worked well for TES and TBS derivatives. A selection of silyl triflates and silyl chlorides were used as silylating reagents with ethyl 3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside. In most cases, silylation afforded 2,6-di-*O*-silylated products in high yields. Studies on the cleavage reaction showed that only the primary silylated protecting groups were replaced by acetyl groups. This reaction worked with a variety of silyl protecting groups but not the *tert*-butyldiphenylsilyl (TBDPS) protecting group. Unfortunately, the 1-thioethyl group was also sensitive to the $Sc(OTf)_3$, leading in these conditions to α/β mixtures of the 1-acetates, which compromised the synthetic utility of this reaction for these compounds. The sequence presented here is a useful synthetic route to differentially protected L-iduronic acid building blocks.
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1. Introduction

Trialkylsilyl ethers are some of the most popular protecting groups of hydroxy functions in synthetic organic chemistry[1] and are routinely used in carbohydrate chemistry.[2] Silyl ethers are easy to introduce and to remove. They also have general stability for most nonacidic reagents and high solubility in nonpolar solvents. Typically, silyl ethers are obtained by the reaction of parent alcohols with the corresponding silyl halide in the presence of a stoichiometric amount of base.[1] Recently, some new silylation methods using different conditions have been reported, such as catalysis by $Sc(OTf)_3$,[3] $Cu(OTf)_2$,[4] palladium nanoparticles[5] and even a bonded fluorous phase.[6] Solvent-free O-silylation reactions[7] and silylation reactions[8] performed without a catalyst have also been reported. Selective silylation generally follows the pattern of primary > secondary > tertiary where the dominant determinant appears to be steric. A second strategy to achieve selective silylation is selective cleavage.[9] For example, acetyl chloride in methanol,[10] Pd(II) salts,[11] bismuth salts,[12] $SbCl_5$,[13] and $Sc(OTf)_3$ in acetonitrile–water[14] have been reported to effect silyl ether cleavage. Similarly, $Sc(OTf)_3$ in dichloromethane–acetic anhydride,[15] $Cu(OTf)_2$ in dichloromethane–acetic anhydride,[16] and $ZrCl_4$ in acetonitrile–acetic anhydride[17] have been reported to effect TBS ether to acetate exchange.

We have been interested in developing synthetic routes to a variety of monosaccharide building blocks that could be coupled to form oligosaccharides that

* Corresponding author. Tel.: +1 613 993 5265; fax: +1 613 952 9092; e-mail: dennis.whitfield@nrc-cnrc.gc.ca

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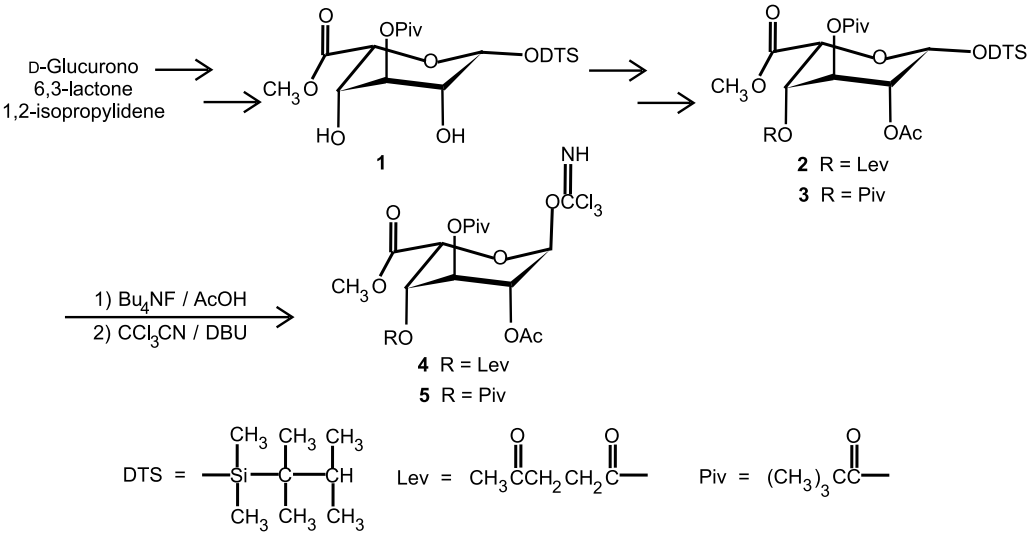
would serve to determine the key structural features necessary for binding to the cobra cardiotoxin proteins.[18] The modular synthesis of glycosaminoglycans requires straightforward methods for the production of large quantities of monosaccharide building blocks. In particular, the preparation of fully differentiated iduronic acids has proven particularly challenging.[19] Recently, we reported an efficient synthetic route to the diol, methyl (dimethylthexylsilyl 3-*O*-pivaloyl-β-L-idopyranosyl)uronate (**1**). Subsequent partially selective acylations led to the building blocks, methyl (dimethylthexylsilyl 2-*O*-acetyl-4-*O*-levulinoyl-3-*O*-pivaloyl-β-L-idopyranosyl)uronate (**2**) and methyl (dimethylthexylsilyl 2-*O*-acetyl-3,4-di-*O*-pivaloyl-β-L-idopyranosyl)uronate (**3**), in less than nine steps, by which two known heparin-like disaccharides were prepared via donors **4** and **5**.[20] Selective pivaloylation of **1** to **3** at O-4 using pivalic anhydride and $Sc(OTf)_3$ as catalyst gave a good yield, but acetylation on the route to **2** under similar conditions was less selective and prompted us to further investigate silylation reactions and acetylation reactions of diol **1**. This has led to an O-2 selective silylation reaction and a highly selective trialkylsilyl–acetate exchange reaction that are reported below.

2. Results and discussion

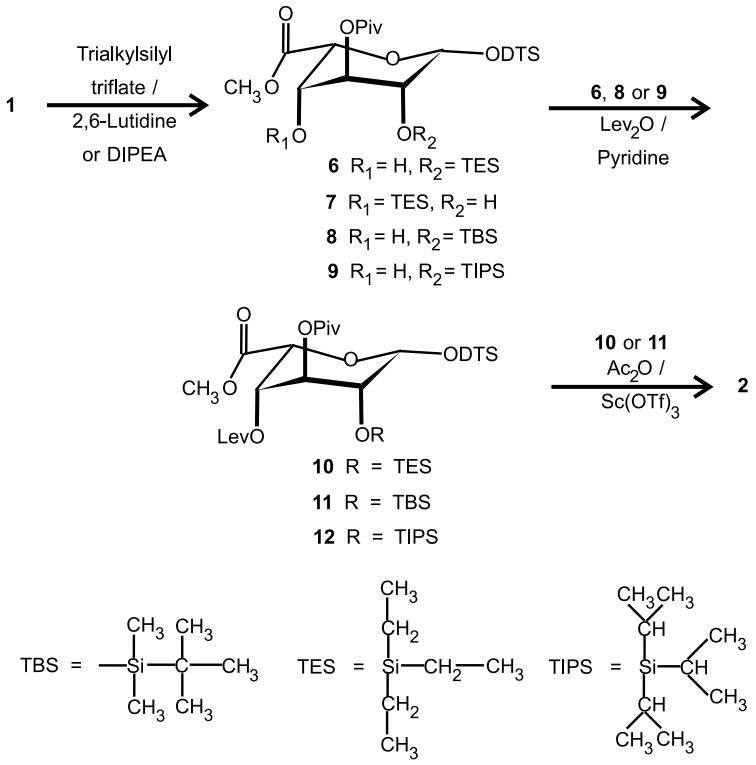
Our first attempt at selective silylation of diol **1** with 1.1 equiv of triethylsilyl triflate (TESOTf) in dichloromethane in the presence of 2.0 equiv of *N*,*N*′-diisopropylethylamine (DIPEA) gave monosilylated alcohol **6** (see Scheme 2). Detailed NMR studies led us to the surprising conclusion that the predominant product was the O-2 silylated ether. Small amounts of the 4-*O*-TES ether **7** could be isolated, too. This contrasts to the O-4-selective pivaloylation above and reports in the literature on the selective O-4 glycosylation of the 3-*O*-benzyl analogue of **1**.[21] As shown in Table 1, silylation with other commercially available triflates (TBSOTf and TIPSOTf) was also highly O-2 selective to yield **8** and **9**. The use of 2,6-lutidine as base led to the same selectivity but reduced yields (see Table 1).

Alcohols **6**, **8**, and **9** were converted into the O-4 levulinoylates **10**, **11**, and **12**, respectively, in acceptable yields by treatment with excess levulinic anhydride under different reaction conditions (see Table 2).

The trialkylsilyl groups were then exchanged for acetate by treating with 2.0 equiv of acetic anhydride and 0.1 equiv of $Sc(OTf)_3$ in dichloromethane at room temperature to give **2**. Less acetic anhydride or $Sc(OTf)_3$ only slowed the reaction, whereas more of either of these compounds increased the two side reactions. One, in reactions that did not go to completion, the isolated starting material was found to have undergone extensive anomerization. Anomerization proceeded with **2**, also, but to a much smaller extent, typically 3–5%. The mechanism of anomerization without cleavage or acetate exchange is unknown. Two, traces of more polar products tentatively identified as the products of cleavage of both silyl ethers increased. The reaction proceeded more slowly at −20 °C, and at much lower temperature proceeded very slowly, if at all. The selectivities at −20 °C did not change appreciably, and so operating at room temperature is the most convenient. Addition of water instead of acetic anhydride did not promote hydrolysis, as reported in Ref. 14 for different substrates. This result suggests a true exchange reaction, that is, not hydrolysis followed by acetylation, although the role of triflic acid and other variables would need to be carefully studied to definitively establish the mechanism.[22]



Scheme 1.



Scheme 2.

Table 1. Silylation of β-L-idopyranoside **1**[a]

Entry	Silane	Silane (equiv)	Base (2 equiv)	Yield (%)
1	TES	1.3	2,6-Lutidine	**6**(40), **7**(16)
2	TES	1.1	DIPEA	**6**(65), **7**(10)
3	TBS	1.3	2,6-Lutidine	**8**(44)
4	TBS	1.1	DIPEA	**8**(70)
5	TIPS	1.1	2,6-Lutidine	**9**(47)
6	TIPS	1.1	DIPEA	**9**(60)

[a] For structures of products, see Scheme 2.

Table 2. O-4 levulinoylates obtained from silylated products of β-L-idopyranoside **1**[a]

Entry	Silane	Solvent	Base	Time (h)	*T* (°C)	Yield (%)
1	TES **6**	CH_2Cl_2	DMAP	26	RT	**10**(64)
2	TBS **8**	Pyridine	Pyridine	25	50	**11**(17)
3	TBS **8**	$C_2H_4Cl_2$	DMAP	24	50	**11**(85)
4	TIPS **9**	$C_2H_4Cl_2$	DMAP	24	50	**12**(28)

[a] For structures of products, see Scheme 2.

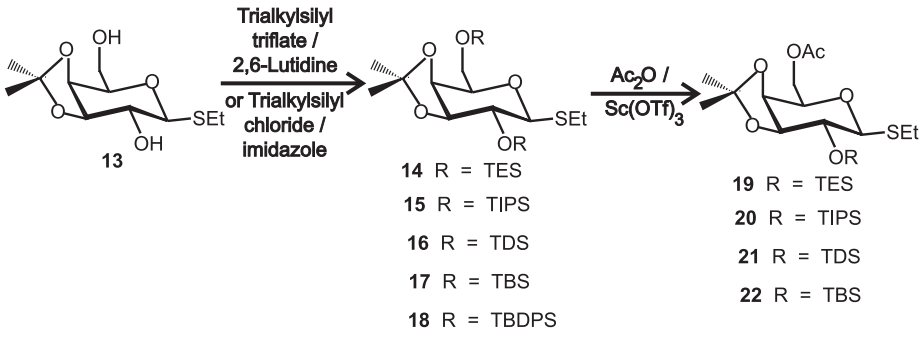
To finish the synthesis, a standard route consisting of fluoride-promoted hydrolysis of the anomeric dimethylthexyl (DTS) group of **2** followed by formation of the trichloroacetimidate **4**, was followed. Typically 65–70% yield for two steps was realized (see Scheme 1). The overall result is a highly efficient route to an L-iduronic acid donor **4** consisting of a six-step synthesis of **1** followed by silylation, levulinoylation and acetate exchange to **2** in an overall yield of 40% on multigram quantities.

To further assess the utility of this acetate–silyl ether exchange reaction, we studied the silylation and subsequent acetylation of the known compound, ethyl 3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (**13**), which was prepared according to the literature.[23,24] The results of silylation reactions of monosaccharide **13** are shown in Table 3.

Initially, we examined the silylation reactions of **13** with different trialkylsilyl triflates (Scheme 3). These reactions were performed in dichloromethane at 0 °C using 2,6-lutidine as base.[25] When TESOTf was used as silylating reagent, the 2,6-di-*O*-silylated product **14** was afforded in 69% yield. The reaction was very fast and was complete in less than 25 min. The 2,6-di-*O*-silylated compound **15** was obtained by silylating **13** with the more sterically demanding silylating reagent TIPSOTf in

Table 3. Silylation of β-D-galactopyranoside (**13**)

Entry	Silane	Solvent	Silane (equiv)	Time	*T* (°C)	Yield (%)
1	TESOTf	CH_2Cl_2	3	25 min	0	**14**(69)
2	TIPSOTf	CH_2Cl_2	3	3.5 h	0	**15**(92)
3	TDSCl	DMF	2.6	24 h	RT	**16**(68)
4	TBSCl	DMF	2.6	3.5 h	RT	**17**(88)
5	TBDPSCl	DMF	2.6	51 h	RT	**18**(79)



Scheme 3.

very high yield 92%; however, a longer time (3.5 h) was needed. As expected the larger silyl group requires a longer reaction time.

Next, we investigated the silylation reactions of monosaccharide **13** with various trialkylsilyl chlorides in DMF at room temperature in the presence of the organic base, imidazole (Scheme 3).[26] Although silyl chlorides are less active than silyl triflates, 2,6-di-*O*-silylated derivatives of compounds **16** (TDS), **17** (TBS), and **18** (TBDPS) were obtained in good yields of 68%, 88%, and 79%. As expected, the reaction times were much longer when silyl chlorides were used as silylating reagents. Thus reaction with TDSCl was finished in 24 h, whereas TBDPSCl took 51 h and TBSCl took 3.5 h to react completely, that is, TBSCl > TDSCl > TBDPSCl.

The silyl acetylation exchange reaction of all silylated products **14** to **18** were studied at 0 °C in CH_2Cl_2 catalyzed by 0.05 equiv of $Sc(OTf)_3$. Interestingly, only the 6-*O*-silyl protecting groups were substituted by acetyl groups and the 2-*O*-silyl protecting groups were kept unchanged, giving derivatives **19**–**22**. Thus, the primary silyl protecting groups could be selectively replaced by acetyl groups in the presence of secondary silyl protecting groups. However, no acetyl-exchange products were obtained with TBDPS **18**. In all cases the unanticipated cleavage of the anomeric 1-thioethyl groups competed, and in the case of the long reaction for **18**, the thioethyl group was completely cleaved. The products were α/β mixtures of the anomeric acetates. This side reaction is the main reason for the low yields (20–35%, see Table 4). Note that all reactions were run until complete disappearance of starting material was observed. Although more cases should be studied, a number of conclusions can be reached from the present examples. The approximate order of reactivity in this exchange reaction is TES ≈ TBS > TIPS ≈ TDS ≫ TBDPS. Coupled with the primary > secondary selectivity, these results suggest that synthetically useful reaction sequences based on this $Sc(OTf)_3$ acetyl–silyl exchange reaction can be developed. The combined result of the *O*-2 selective silylation reaction and this acetyl–silyl exchange reaction led to an efficient route to the building block **2**.

Table 4. Acetylation exchange reactions of silylated β-D-galactopyranosides **14** to **18**[a]

Entry	Disilyl ether	Time (h)	Yield (%)
1	TES **14**	1.5	**19**(33)
2	TIPS **15**	3.0	**20**(25)
3	TDS **16**	3.0	**21**(23)
4	TBS **17**	1.5	**22**(35)
5	TBDPS **18**	1.5	0

[a] Ac_2O (2.0 equiv) and $Sc(OTf)_3$ (0.05 equiv) in CH_2Cl_2 solvent at 0 °C.

3. Experimental

3.1. General methods

The ^1H NMR spectra were obtained on Varian VXR-500 (500 MHz) or Varian-400 (400 MHz) spectrometers with Me_4Si or the residue signal of the solvent as the internal standard. The ^{13}C NMR spectra were recorded on Varian-400 or Varian-200 spectrometers (100.55 or 50.32 MHz). Optical rotations were measured at 20 °C in a 1-dm cell on a Perkin–Elmer 341 polarimeter. Thin-layer chromatography (TLC) was performed on precoated plates of Silica Gel 60-F_{254} (E. Merck, Darmstadt) and visualized with H_2SO_4–H_2O (1:20 v/v), followed by heating. Unless otherwise stated, column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck). All solvents and reagents were purified and dried according to standard procedures.

3.2. Methyl (dimethylthexylsilyl 3-*O*-pivaloyl-2-*O*-triethylsilyl-β-L-idopyranosyl)uronate (6) and methyl (dimethylthexylsilyl 3-*O*-pivaloyl-4-*O*-triethylsilyl-β-L-idopyranosyl)uronate (7)

To compound **1** (0.35 g, 0.81 mmol) in CH_2Cl_2 (7 mL) at 0 °C under Ar, 2,6-lutidine (187.3 μL, 1.61 mmol, 2 equiv) and triethylsilyl triflate (0.24 mL, 1.3 equiv) were added. The solution was allowed to stir at 0 °C for 1 h, and then it was warmed to room temperature. The reaction was quenched with the addition of water (9.4 mL).

The organic layer was further washed with 5% $CuSO_4$ (3×9.4 mL) and water (3×9.4 mL), dried with Na_2SO_4, and filtered, and the CH_2Cl_2 was removed in vacuo. Chromatography (20:1 hexanes–EtOAc) gave 176 mg (40%) of product **6** and 71 mg (16%) of **7** as colorless oils (5:2 **6**:**7**); **6**: $[\alpha]_D$ +33.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.00 (br t, 1H, H-3), 4.84 (s, 1H, H-1), 4.33 (s, 1H, H-5), 3.98 (br, 1H, OH), 3.87 (br s, 1H, H-4), 3.79 (s, 3H, OCH_3), 3.65 (d, 1H, $J_{2,3}$ 2.9 Hz, H-2), 1.67 (m, 1H, CH), 1.21 (s, 9H, Piv), 0.98 (t, 9H, J_{CH_3,CH_2} 7.8 Hz, $3 \times CH_3$, TES), 0.87 (m, 12H, CH_3, DTS), 0.69 (q, 6H, J_{CH_2,CH_3} 7.8 Hz, CH_2, TES), 0.21, 0.19 ($2 \times$ s, 6H, $SiCH_3$); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 176.02 (C=O, Piv), 168.54 (C=O, ester), 94.45, 75.37, 70.94, 69.11, 67.69 (C-1, C-5, C-3, C-2, C-4), 52.15 (OCH_3), 38.81 (O=C–*C*, Piv), 33.83 (CH), 27.10 (CH_3, Piv), 25.26 (Si–*C*–C), 20.22, 20.09, 18.54, 18.42 ($4 \times CH_3$, DTS), 6.73 (CH_3, TES), 4.60 (CH_2, TES), −2.01, −3.13 ($2 \times CH_3$, $SiCH_3$); FABMS: *m*/*z* 549.4, $[M+H]^+$; HRMS Calcd for $C_{26}H_{53}O_8Si_2$ $[M+H]^+$: 549.3279. Found: 549.3184. Anal. Calcd for $C_{26}H_{52}O_8Si_2$: C, 56.90; H, 9.55. Found: C, 56.98; H, 9.88.

Compound **7**: $[\alpha]_D$ +23.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz $CDCl_3$): δ 5.03 (br t, 1H, H-3), 4.95 (s, 1H, H-1), 4.28 (s, 1H, H-5), 3.99 (s, 1H, H-4), 3.76 (s, 3H, OCH_3), 3.48 (br s, 1H, H-2), 3.13 (br, 1H, OH), 1.65 (m, 1H, CH), 1.21 (s, 9H, Piv), 0.95 (t, 9H, J_{CH_3,CH_2} 7.9 Hz, CH_3, TES), 0.87 (m, 12H, CH_3, DTS), 0.64 (m, 6H, CH_2, TES), 0.23, 0.19 ($2 \times$ s, 6H, $SiCH_3$); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 176.30 (C=O, Piv), 168.49 (C=O, ester), 94.84, 75.45, 71.15, 68.92, 67.66 (C-1, C-5, C-3, C-2, C-4), 52.12 (OCH_3), 38.81 (O=C–*C*, Piv), 34.01 (CH), 27.13 ($3CH_3$, Piv), 25.16 (Si–*C*–C), 20.37, 20.03, 18.63, 18.41 ($4 \times CH_3$, DTS), 6.61 (CH_3, TES), 4.49 (CH_2, TES), −1.93, −3.22 ($2 \times CH_3$, $SiCH_3$, DTS); HRMS Calcd for $C_{26}H_{53}O_8Si_2$ $[M+H]^+$: *m*/*z* 549.3279. Found: *m*/*z* 549.3157.

3.3. Methyl (dimethylthexylsilyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-pivaloyl-β-L-idopyranosyl)uronate (8)

To compound **1** (0.25 g, 0.58 mmol) in CH_2Cl_2 (5 mL) at 0 °C under Ar, 2,6-lutidine (133.8 μL, 1.15 mmol, 2 equiv) and *tert*-butyldimethylsilyl triflate (0.17 mL, 0.75 mmol, 1.3 equiv) were added. The solution was allowed to stir at 0 °C for 1 h, then it was warmed to room temperature. The reaction was quenched with the addition of water (6.0 mL). The organic layer was further washed with 5% aq $CuSO_4$ (3×6.0 mL) and water (3×6.0 mL), dried with Na_2SO_4, and filtered, and the CH_2Cl_2 was removed in vacuo. Purification by chromatography (25:1 hexanes–EtOAc) gave 0.14 g (44%) of product **8** as a colorless oil: $[\alpha]_D$ +36.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.01 (br s, 1H, H-3), 4.84 (d, 1H, $J_{1,2}$ 5.9 Hz, H-1), 4.33 (s, 1H, H-5), 3.93 (br, 1H, OH), 3.90 (s, 1H, H-4), 3.80 (s, 3H, OCH_3), 3.64 (br t, 1H, H-2), 1.66 (m, 1H, CH), 1.21 (s, 9H, Piv), 0.90 (s, 9H, CH_3, TBS), 0.87 (m, 12H, CH_3, DTS), 0.18 ($4 \times$ s, 12H, $SiCH_3$, DTS, TBS); ^{13} C NMR (50.32 MHz, $CDCl_3$): δ 176.24 (C=O, Piv), 168.50 (C=O, ester), 94.52, 75.25, 70.90, 69.22, 67.65 (C-1, C-5, C-3, C-2, C-4), 52.15 (OCH_3), 38.81 (O=C–*C*, Piv), 33.82 (CH), 27.10 ($3CH_3$, Piv), 25.74 ($3CH_3$, TBS), 25.23 (Si–*C*–C), 20.26, 20.20.10, 18.57, 18.44 ($4 \times CH_3$, DTS), 18.19 (Si–*C*, TBS), −1.96, −3.08, −4.63, −5.31 ($4 \times CH_3$, $SiCH_3$); FABMS: *m*/*z* 571.3, $[M+Na]^+$; HRMS Calcd for $C_{26}H_{51}O_8Si_2$ $[M-H]^+$: *m*/*z* 547.3123. Found: *m*/*z* 547.3182. Anal. Calcd for $C_{26}H_{52}O_8Si_2$: C, 56.90; H, 9.55. Found: C, 57.26; H, 9.26.

3.4. Methyl (dimethylthexylsilyl 3-*O*-pivaloyl-2-*O*-triisopropylsilyl-β-L-idopyranosyl)uronate (9)

To compound **1** (0.25 g, 0.58 mmol) in CH_2Cl_2 (5 mL) at 0 °C under Ar, 2,6-lutidine (133.8 μL, 1.15 mmol, 2 equiv) and triisopropylsilyl triflate (0.17 mL, 0.63 mmol, 1.1 equiv) were added. The solution was allowed to stir at 0 °C for 1 h, then warmed to room temperature. The reaction was quenched with the addition of water (6.0 mL). The organic layer was further washed with 5% aq $CuSO_4$ (3×6.0 mL) and water (3×6.0 mL), dried with Na_2SO_4, and filtered, and the CH_2Cl_2 was removed in vacuo. Purification by chromatography (20:1 hexanes–EtOAc) gave 0.16 g (47%) of product **9** as a colorless oil: $[\alpha]_D$ +27.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.12 (br t, 1H, H-3), 4.86 (s, 1H, H-1), 4.33 (s, 1H, H-5), 3.95 (br d, 1H, OH), 3.90 (br d, 1H, H-4), 3.82 (d, 1H, $J_{2,3}$ 3.1 Hz, H-2), 3.79 (s, 3H, OCH_3), 1.68 (m, 1H, CH), 1.21 (s, 9H, Piv), 1.19 (m, 3H, CH, isopropyl), 1.10 (m, 18H, CH_3, isopropyl), 0.86 (m, 12H, DTS), 0.20 (s, 6H, $SiCH_3$); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 176.20 (C=O, Piv), 168.44 (C=O, ester), 94.81, 75.39, 70.84, 69.56, 67.65 (C-1, C-5, C-3, C-2, C-4), 52.12 (OCH_3), 38.81 (O=C–*C*, Piv), 33.74 (CH), 27.10 ($3CH_3$, Piv), 25.26 (Si–*C*–C), 20.01, 18.37 ($2 \times 2CH_3$, DTS), 18.08 ($6CH_3$, CH_3, TIPS), 12.46 (3CH, CH, TIPS), −2.00, −3.13 ($2 \times CH_3$, $2 \times SiCH_3$); FABMS: Calcd for $C_{29}H_{59}O_8Si_2$ $[M+H]^+$: *m*/*z* 591.4. Found *m*/*z* 591.2.

3.5. Methyl dimethylthexylsilyl 4-*O*-levulinoyl-3-*O*-pivaloyl-2-*O*-triethylsilyl-β-L-idopyranosiduronate (10)

Alcohol **6** (1.88 g, 0.32 mmol) was dissolved in anhyd CH_2Cl_2 (30 mL), and DMAP (2.8 g, 6.7 equiv) was added. Then levulinic anhydride (3.27 g, 4.4 equiv) in CH_2Cl_2 (30 mL) was added dropwise. After for stirring 26 h, the solvents were removed in vacuo. The residue was purified on an MPLC column eluting with 10:1:1 hexanes–EtOAc–CH_2Cl_2 to yield **10** (1.43 g, 64%) as a colorless syrup; $[\alpha]_D$ +15.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR

($CDCl_3$): δ 4.98 (2 × s, 2H, H-3, H-4), 4.81 (d, 1H, $J_{1,2}$ 1.2 Hz, H-1), 4.41 (s, 1H, H-5), 3.78 (s, 3H, OCH_3), 3.52 (br d, 1H, $J_{2,1}$ 1.2 Hz, H-2), 2.66 (m, 4H, CH_2CH_2, Lev), 2.17 (s, 3H, CH_3, Lev), 1.67 (m, 1H, CH, DTS), 1.21 (s, 9H, Piv), 0.95 (m, 9H, CH_3, TES), 0.87 (m, 12H, CH_3, DTS), 0.69 (m, 6H, CH_2, TES), 0.21, 0.19 (2 × s, 6H, $SiCH_3$); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 206.17 (O=*C*–CH_3, Lev), 175.82 (C=O, Piv), 171.19 (O=C–O, Lev), 167.29 (O=*C*–OCH_3), 95.05, 73.22, 70.49, 67.81, 67.26 (C-1, C-5, C-3, C-2, C-4), 52.35 (OCH_3), 38.79 (O=C–*C*, Piv), 37.56 (CH_2, Lev), 33.82 (CH, DTS), 29.91 (CH_3, Lev), 28.08 (CH_2, Lev), 27.11 (CH_3, Piv), 25.26 (Si–*C*–C), 20.24, 20.08, 18.57, 18.44 (4 × CH_3, DTS), 6.91 (CH_3, TES), 4.79 (CH_2, TES), −1.96, −3.13 (2 × CH_3, $SiCH_3$); FABMS: Calcd for $C_{31}H_{59}O_{10}Si_2$ $[M+H]^+$: *m*/*z* 647.4. Found *m*/*z* 647.4.

3.6. Methyl dimethylthexylsilyl 2-*O*-*tert*-butyldimethylsilyl-4-*O*-levulinoyl-3-*O*-pivaloyl-β-L-idopyranosiduronate (11)

Alcohol **8** (0.18 g, 0.33 mmol) was dissolved in anhyd pyridine (3 mL), and levulinic anhydride (140 mg, 2.0 equiv) was added. The mixture was stirred at 50 °C for 25 h. Then the solvents were removed in vacuo. The residue was purified on flash column chromatography using 5:1:1 hexanes–EtOAc–CH_2Cl_2 as eluant. The final product **11** (35 mg, 17%) was obtained as a colorless syrup: $[\alpha]_D$ +17.3 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.01 (br t, 1H, H-4), 4.97 (br t, 1H, H-3), 4.81 (d, 1H, $J_{1,2}$ 1.2 Hz, H-1), 4.41 (d, 1H, $J_{5,4}$ 2.2 Hz, H-5), 3.78 (s, 3H, OCH_3), 3.51 (dd, 1H, $J_{1,2}$ 1.2 Hz, $J_{2,3}$ 1.8 Hz, H-2), 2.69, 2.55 (2 × m, 4H, CH_2CH_2, Lev), 2.17 (s, 3H, CH_3, Lev), 1.67 (m, 1H, CH, DTS), 1.21 (s, 9H, Piv), 0.90 (s, 9H, $3CH_3$, TBS), 0.87 (m, 12H, CH_3, DTS), 0.20, 0.11 (m, 12H, $SiCH_3$); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 206.22 (O=*C*–CH_3, Lev), 175.92 (C=O, Piv), 171.53 (O=C–O, Lev), 167.42 (O=*C*–OCH_3), 95.19, 73.34, 70.75, 67.96, 67.23 (C-1, C-5, C-3, C-2, C-4), 52.33 (OCH_3), 38.74 (O=C–*C*, Piv), 37.59 (CH_2, Lev), 33.75 (CH, DTS), 29.82 (CH_3, Lev), 27.93 (CH_2, Lev), 27.04 (CH_3, Piv), 25.79 (CH_3, TBS), 25.20 (Si–*C*–C), 20.22, 20.01, 18.52, 18.35 (4 × CH_3, DTS), 18.21 (C, TBS), −2.04, −3.18 (2 × CH_3, $SiCH_3$, DTS), −4.75, −5.09 (2 × CH_3, 2 × $SiCH_3$, TBS); HRMS Calcd for $C_{31}H_{59}O_{10}Si_2$ $[M+H]^+$: *m*/*z* 647.3647. Found: *m*/*z* 647.3756.

3.7. Methyl dimethylthexylsilyl 2-*O*-triisopropylsilyl-4-*O*-levulinoyl-3-*O*-pivaloyl-β-L-idopyranosiduronate (12)

Alcohol **9** (0.44 g, 0.80 mmol) was dissolved in anhyd 1,2-dichloroethane (5 mL), and DMAP (590 mg, 6.0 equiv), followed by levulinic anhydride (1.7 g, 10.0 equiv), were added. The mixture was stirred at 50 °C for 25 h. Then the solvents were removed in vacuo. The residue was purified on flash column chromatography using 8:1:1 hexanes–EtOAc–CH_2Cl_2. The final product **12** (156 mg, 28%) was obtained as a colorless syrup along with recovered **10** (142 mg, 32%): $[\alpha]_D$ +7.9 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.05 (m, 2H, H-4, H-3), 4.82 (d, 1H, $J_{1,2}$ 1.0 Hz, H-1), 4.40 (d, 1H, $J_{5,4}$ 1.6 Hz, H-5), 3.78 (s, 3H, OCH_3), 3.68 (m, 1H, H-2), 2.70 (m, 2H, CH_2CH_2, Lev), 2.56 (br t, 2H, J = 6.4 Hz, CH_2CH_2, Lev), 2.17 (s, 3H, CH_3, Lev), 1.69 (m, 1H, CH, DTS), 1.21 (s, 9H, Piv), 1.15 (m, 3H, 3CH, TIPS), 1.13, 1.11 (2 × s, 18H, CH_3, TIPS), 0.87 (m, 12H, CH_3, DTS), 0.20, 0.19 (2 × s, 6H, $SiCH_3$); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 206.11 (O=*C*–CH_3, Lev), 175.77 (C=O, Piv), 171.36 (O=C–O, Lev), 167.24 (O=*C*–OCH_3), 95.51, 73.52, 70.94, 68.20, 67.11 (C-1, C-5, C-3, C-2, C-4), 52.33 (OCH_3), 38.80 (O=C–*C*, Piv), 37.69 (CH_2, Lev), 33.75 (CH, DTS), 29.87 (CH_3, Lev), 28.04 (CH_2, Lev), 27.11 (CH_3, Piv), 25.30 (Si–*C*–C), 20.15, 19.99, 18.50, 18.36 (4 × CH_3, DTS), 18.25 (CH_3, TIPS), 12.64 (CH, TIPS), −1.96, −3.08 (2 × CH_3, $SiCH_3$, DTS); FABMS: Calcd for $C_{34}H_{65}O_{10}Si_2$ $[M+H]^+$: *m*/*z* 689.4. Found *m*/*z* 689.2.

3.8. Methyl dimethylthexylsilyl 2-*O*-acetyl-4-*O*-levulinoyl-3-*O*-pivaloyl-β-L-idopyranosiduronate (2)

3.8.1. Synthesis of 2 from sugar 10. The colorless syrup **10** (1.36 g, 2.1 mmol) was dissolved in dry CH_2Cl_2 (20 mL), followed by the addition of acetic anhydride (273 μL, 1.3 equiv) and $Sc(OTf)_3$ (53 mg, 0.05 equiv). The mixture was stirred at room temperature. After 1 h, the mixture was washed with water (3 × 13 mL) and then dried over anhyd Na_2SO_4. The organic phase was concentrated. The mixture was purified on an MPLC column eluting with 4:1:1 hexanes–EtOAc–CH_2Cl_2 to give product **2** (1.1 g, 91%) as a colorless oil.

3.8.2. Synthesis of 2 from sugar 11. The colorless syrup **11** (14.5 mg, 0.022 mmol) was dissolved in dry CH_2Cl_2 (1.0 mL), followed by the addition of acetic anhydride (4.6 μL, 2.0 equiv) and then $Sc(OTf)_3$ (1.1 mg, 0.1 equiv). The mixture was stirred at room temperature. After 2.5 h, the mixture was diluted with 10 mL of CH_2Cl_2 and washed with water (3 × 3 mL), then dried over anhyd Na_2SO_4. The organic phase was concentrated. The mixture was purified on flash column chromatography using 4:1:1 hexanes–EtOAc–CH_2Cl_2 and then 2:1:1 hexanes–EtOAc–CH_2Cl_2 to give product **2** (7.4 mg, 57%); $[\alpha]_D$ +29.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.18 (br t, 1H, 3-H), 5.05 (s, 1H, 1-H), 5.02 (br s, 1H, 4-H), 4.89 (br s, 1H, 2-H), 4.49 (d, 1H, $J_{5,4}$ 2.0 Hz, 5-H), 3.79 (s, 3H, OCH_3), 2.73, 2.57 (2 × m, 2 × 2H, CH_2CH_2, Lev), 2.18 (s, 3H, CH_3, Lev), 2.12 (s, 3H, CH_3, acetyl), 1.62 (m, 1H, CH, DTS), 1.23 (s, 9H, Piv), 0.86 (m, 12H, CH_3, DTS), 0.23, 0.16 (2 × s, 6H, $SiCH_3$); ^{13}C

NMR (50.32 MHz, $CDCl_3$): δ 205.96 (O=*C*–CH_3, Lev), 175.39 (C=O, Piv), 171.26 (O=C–O, Lev), 169.59 (O=C, Ac), 167.29 (O=*C*–OCH_3), 93.11, 72.61, 67.41, 66.91, 66.66 (C-1, C-5, C-3, C-2, C-4), 52.49 (OCH_3), 38.79 (O=C–*C*, Piv), 37.53 (CH_2, Lev), 33.92 (CH, DTS), 29.81 (CH_3, Lev), 27.74 (CH_2, Lev), 27.06 (CH_3, Piv), 24.96 (Si–*C*–C), 20.81 (CH_3, Ac), 20.09, 19.78, 18.54, 18.34 ($4\times CH_3$, DTS), 6.91 (CH_3, TES), 4.79 (CH_2, TES), −2.07, −3.65 (CH_3, $SiCH_3$); HRMS Calcd for $C_{27}H_{46}O_{11}Si$ M^+: *m/z* 574.2809. Found: *m/z* 574.2147.

3.9. Ethyl 3,4-*O*-isopropylidene-1-thio-2,6-di-*O*-triethylsilyl-β-D-galactopyranoside (14)

To compound **13** (0.25 g, 0.95 mmol) in CH_2Cl_2 at 0 °C under Ar, 2,6-lutidine (0.44 mL, 3.78 mmol) and triethylsilyl triflate (0.64 mL, 2.85 mmol) were added. The solution was allowed to stir at 0 °C for 25 min, then it was warmed to room temperature. The reaction was quenched with the addition of water (6.7 mL). The organic layer was further washed with 5% aq $CuSO_4$ (3×6.7 mL) and water (3×6.7 mL), dried with Na_2SO_4, and filtered, and the CH_2Cl_2 was removed in vacuo. Purification by chromatography (60:1 hexanes–EtOAc) gave 0.32 g (69%) of product **14** as a colorless oil: $[\alpha]_D$ −21.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.32 (d, 1H, $J_{1,2}$ 9.4 Hz, H-1), 4.21 (dd, 1H, $J_{4,5}$ 2.2 Hz, $J_{4,3}$ 5.7 Hz, H-4), 3.96 (br t, 1H, H-3), 3.86 (dd, 1H, $J_{Ha,5}$ 7.0 Hz, $J_{Ha,Hb}$ 9.9 Hz, Ha-6), 3.82 (dd, 1H, $J_{Hb,5}$ 5.9 Hz, $J_{Hb,Ha}$ 9.9 Hz, Hb-6b), 3.75 (ddd, 1H, $J_{4,5}$ 2.2 Hz, $J_{Hb,5}$ 5.9 Hz, $J_{Ha,5}$ 7.0 Hz, H-5), 3.58 (dd, 1H, $J_{2,1}$ 9.4 Hz, $J_{2,3}$ 6.3 Hz, H-2), 2.69 (m, 2H, CH_2, SEt), 1.49, 1.32 ($2\times$ s, 6H, $2\times CH_3$, isopropylidene), 1.27 (t, 3H, J_{CH_3,CH_2} 7.5 Hz, CH_3, SEt), 0.96 (m, 18H, CH_3, TES), 0.64 (m, 12H, CH_2, TES); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 109.43 (C, isopropylidene), 85.25, 80.41, 76.88, 74.06, 73.34, 61.98 (C-1, C-3, C-5, C-2, C-4, C-6), 28.16, 26.51 ($2\times CH_3$, isopropylidene), 24.68 (CH_2, SEt), 15.21 (CH_3, SEt), 7.09, 6.94 ($2\times CH_3$, TES), 5.21, 4.56 ($2\times CH_2$, TES); FABMS: *m/z* 491.2, $[M-H]^+$; HRMS Calcd for $C_{23}H_{47}O_5SSi_2$ $[M-H]^+$: *m/z* 491.2683. Found: *m/z* 491.3473. Anal. Calcd for $C_{23}H_{48}O_5SSi_2$: C, 56.05; H, 9.82. Found: C, 55.81; H, 9.93.

3.10. Ethyl 3,4-*O*-isopropylidene-1-thio-2,6-di-*O*-triisopropylsilyl-β-D-galactopyranoside (15)

To compound **13** (0.25 g, 0.95 mmol) in CH_2Cl_2 at 0 °C under Ar, 2,6-lutidine (0.44 mL, 3.78 mmol) and triisopropylsilyl triflate (0.77 mL, 2.85 mmol) were added. The solution was allowed to stir at 0 °C for 3.5 h, then it was warmed to room temperature. The reaction was quenched with the addition of water (6.7 mL). The organic layer was further washed with 5% aq $CuSO_4$ (3×6.7 mL) and water (3×6.7 mL), dried with Na_2SO_4, and filtered, and the CH_2Cl_2 was removed in vacuo. Purification by chromatography (60:1 hexanes–EtOAc) gave 0.50 g (92%) of product **15** as a colorless oil: $[\alpha]_D$ −34.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.45 (d, 1H, $J_{1,2}$ 7.6 Hz, H-1), 4.27 (br, 1H, H-4), 4.08 (br t, 1H, H-3), 3.90 (m, 2H, Ha-6, Hb-6), 3.82 (m, 2H, H-5, H-2), 2.70 (m, 2H, CH_2, SEt), 1.48, 1.31 ($2\times$ s, 6H, CH_3, isopropylidene), 1.27 (t, 3H, J_{CH_3,CH_2} 7.5 Hz, CH_3, SEt), 1.17 (m, 6H, CH, isopropyl), 1.08 (m, 36H, CH_3, isopropyl); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 109.48 (C, isopropylidene), 85.67, 79.58, 76.37, 73.88, 73.01, 62.57 (C-1, C-3, C-2, C-5, C-4, C-6), 27.71, 26.25 ($2\times CH_3$, isopropylidene), 25.11 (CH_2, SEt), 18.46, 18.41, 18.12 ($3\times CH_3$, TIPS), 15.18 (CH_3, SEt), 12.75, 12.15 ($2\times$ CH, TIPS); FABMS: *m/z* 575.3, $[M-H]^+$. Anal. Calcd for $C_{29}H_{60}O_5SSi_2$: C, 60.36; H, 10.48. Found: C, 60.58; H, 10.94.

3.11. Ethyl 2,6-di-*O*-dimethylthexylsilyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (16)

A mixture of compound **13** (0.50 g, 1.89 mmol), imidazole (0.64 g, 5 equiv), and dimethylthexylsilyl chloride (0.97 mL, 2.6 equiv) in DMF (7.6 mL) was stirred at room temperature. After 24 h, the reaction mixture was dissolved in CH_2Cl_2 (200 mL) and washed with water (3×50 mL). The CH_2Cl_2 solution was dried over Na_2SO_4, and filtered, and the solvent was evaporated under vacuum. MPLC on Silica Gel eluting with (80:1 hexanes–EtOAc) afforded 0.71 g (68%) of product **16** as a colorless oil: $[\alpha]_D$ −25.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (d, 1H, $J_{1,2}$ 9.4 Hz, H-1), 4.20 (dd, 1H, $J_{4,5}$ 2.0 Hz, $J_{4,3}$ 5.7 Hz, H-4), 3.97 (br t, 1H, $J_{3,4}$ 5.7 Hz, $J_{3,2}$ 6.3 Hz, H-3), 3.81 (m, 2H, Ha-6, Hb-6), 3.74 (m, 1H, H-5), 3.58 (dd, 1H, $J_{2,3}$ 6.3 Hz, $J_{2,1}$ 9.4 Hz, H-2), 2.68 (m, 2H, CH_2, SEt), 1.63 (m, 2H, CH, DTS), 1.49, 1.32 ($2\times$ s, 6H, CH_3, isopropylidene), 1.27 (t, 3H, J_{CH_3,CH_2} 7.5 Hz, CH_3, SEt), 0.86 (m, 24H, CH_3, DTS), 0.18, 0.17, 0.10 ($3\times$ s, 12H, $SiCH_3$); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 109.38 (C, isopropylidene), 85.11, 80.45, 76.82, 73.85, 73.41, 61.98 (C-1, C-3, C-5, C-2, C-4, C-6), 34.33, 34.20 ($2\times$ CH, DTS), 28.19, 26.59 ($2\times CH_3$, isopropylidene), 25.18 (SiC, DTS), 24.49 (CH_2, SEt), 20.44, 18.85, 18.74 ($3\times CH_3$, DTS), 15.22 (CH_3, SEt), −1.73, −2.30, −3.22, −3.35 ($4\times SiCH_3$); FABMS: *m/z* 547.4, $[M-H]^+$; HRMS Calcd for $C_{27}H_{55}O_5SSi_2$ $[M-H]^+$: *m/z* 547.3309. *m/z* Found: 547.3238. Anal. Calcd for $C_{27}H_{56}O_5SSi_2$: C, 59.07; H, 10.28. Found: C, 59.43; H, 10.60.

3.12. Ethyl 2,6-di-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (17)

A mixture of compound **13** (0.25 g, 0.95 mmol), imidazole (0.32 g, 5 equiv) and *tert*-butyldiphenylsilyl chloride

(0.37 g, 2.6 equiv) in DMF (4.0 mL) was stirred at room temperature. After 3.5 h, the reaction mixture was dissolved in CH_2Cl_2 (100 mL) and washed with water (3 × 25 mL). The CH_2Cl_2 solution was dried over Na_2SO_4, and filtered, and the solvent was evaporated under vacuum. MPLC on Silica Gel eluting with (70:1 hexanes–EtOAc) afforded 0.41 g (88%) of product **17** as a colorless oil; $[\alpha]_D$ −24.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.29 (d, 1H, $J_{1,2}$ 9.5 Hz, H-1), 4.20 (dd, 1H, $J_{4,5}$ 2.1 Hz, $J_{4,3}$ 5.6 Hz, H-4), 3.96 (br t, 1H, H-3), 3.83 (m, 2H, Ha-6, Hb-6), 3.75 (m, 1H, H-5), 3.57 (dd, 1H, $J_{2,3}$ 6.4 Hz, $J_{2,1}$ 9.5 Hz, H-2), 2.66 (m, 2H, CH_2, SEt), 1.49, 1.32 (2 × s, 6H, CH_3, isopropylidene), 1.27 (t, 3H, J_{CH_3,CH_2} 7.4 Hz, CH_3, SEt), 0.89 (m, 18H, CH_3, TBS), 0.14, 0.07 (m, 12H, $SiCH_3$); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 109.41 (C, isopropylidene), 85.09, 80.51, 76.86, 74.08, 73.40, 62.23 (C-1, C-3, C-5, C-2, C-4, C-6), 28.23, 26.58 (2 × CH_3, isopropylidene), 26.10, 25.96 (2 × CH_3, TBS), 24.47 (CH_2, SEt), 18.42 (C, TBS), 15.24 (CH_3, SEt), −3.89, −4.36, −5.09, −5.24 (4 × $SiCH_3$); FABMS: *m*/*z* 491.2, $[M - H]^+$; HRMS Calcd for $C_{23}H_{47}O_5SSi_2$ $[M - H]^+$: *m*/*z* 491.2683. Found: *m*/*z* 491.2627. Anal. Calcd for $C_{23}H_{48}O_5SSi_2$: C, 56.05; H: 9.82. Found: C, 56.45; H, 10.07.

3.13. Ethyl 2,6-di-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (18)

A mixture of compound **13** (0.25 g, 0.95 mmol), imidazole (0.32 g, 5 equiv) and dimethylthexylsilyl chloride (0.64 mL, 2.6 equiv) in DMF (4.0 mL) was stirred at 45 °C. After 51 h, the reaction mixture was dissolved in CH_2Cl_2 (100 mL) and washed with water (3 × 25 mL). The CH_2Cl_2 solution was dried over Na_2SO_4, and filtered, and the solvent was evaporated under vacuum. MPLC on Silica Gel eluting with (70:1 hexanes–EtOAc) afforded 0.55 g (79%) of product **18** as a colorless oil; $[\alpha]_D$ −9.3 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.70, 7.35 (2 × m, 10H, phenyl), 4.47 (d, 1H, $J_{1,2}$ 8.2 Hz, H-1), 4.27 (dd, 1H, $J_{4,5}$ 1.3 Hz, $J_{4,3}$ 6.1 Hz, H-4), 4.20 (br t, 1H, H-3), 3.86 (m, 3H, H-5, Ha-6, Hb-6), 3.72 (dd, 1H, $J_{2,3}$ 5.7 Hz, $J_{2,1}$ 8.2 Hz, H-2), 2.53, 2.39 (2 × m, 2H, CH_2, SEt), 1.21 (s, 3H, CH_3, isopropylidene), 1.14 (t, 3H, J_{CH_3,CH_2} 7.4 Hz, CH_3, SEt), 1.10 (s, 3H, CH_3, isopropylidene), 1.08, 1.04 (2 × s, 18H, CH_3, TBDPS); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 136.17, 136.13, 135.39, 135.34, 133.29, 133.21, 132.81, 129.39, 129.20, 127.43, 127.36, 127.17, 126.95 (phenyl), 109.53 (C, isopropylidene), 85.27, 79.26, 76.10, 73.98, 73.02, 62.92 (C-1, C-3, C-5, C-2, C-4, C-6), 27.30, 26.28 (2 × CH_3, TBDPS), 27.24, 26.28 (2 × CH_3, isopropylidene), 24.71 (CH_3, SEt), 19.86, 19.39 (2 × C, TBDPS), 15.05 (CH_3, SEt); FABMS: *m*/*z* 739.4, $[M - H]^+$; HRMS Calcd for $C_{43}H_{55}O_5SSi_2$ $[M - H]^+$: *m*/*z* 739.3309. Found: *m*/*z* 739.3487. Anal. Calcd for $C_{43}H_{56}O_5SSi_2$: C, 69.69; H: 7.62. Found: C, 70.09; H, 7.86.

3.14. Ethyl 6-*O*-acetyl-3,4-*O*-isopropylidene-1-thio-2-*O*-triethylsilyl-β-D-galactopyranoside (19)

To compound **14** (100 mg, 0.203 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under Ar, acetic anhydride (38.3 μL, 2 equiv) was added, followed by addition of $Sc(OTf)_3$ (5 mg, 0.05 equiv). After 1.5 h, the mixture was washed with water (3 × 13 mL) and then dried over anhyd Na_2SO_4. The organic phase was concentrated. The mixture was purified on an MPLC column eluting with 12:1:1 hexanes–EtOAc–CH_2Cl_2 to give 28 mg (33%) of product **19**; $[\alpha]_D$ +1.8 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.34 (d, 1H, $J_{1,2}$ 9.0 Hz, H-1), 4.32, 4.31 (d, 2H, $J_{Hb,5} = J_{Ha,5}$ 6.2 Hz, Ha-6, Hb-6), 4.16 (dd, 1H, $J_{4,5}$ 2.2 Hz, $J_{4,3}$ 5.9 Hz, H-4), 4.01 (br t, 1H, H-3), 3.92 (ddd, 1H, $J_{4,5}$ 2.2 Hz, $J_{5,Hb} = J_{5,Ha}$ 6.2 Hz, H-5), 3.62 (dd, 1H, $J_{2,1}$ 9.0 Hz, $J_{2,3}$ 6.2 Hz, H-2), 2.69 (m, 2H, CH_2, SEt), 2.07 (s, 3H, CH_3, Ac), 1.50, 1.33 (2 × s, 6H, CH_3, isopropylidene), 1.30 (t, 3H, J_{CH_3,CH_2} 7.6 Hz, CH_3, SEt), 0.98 (t, 9H, J_{CH_3,CH_2} 8.0 Hz, CH_3, TES), 0.67 (q, 6H, CH_2, TES); ^{13}C NMR (100.55 MHz, $CDCl_3$): δ 170.82 (C=O, Ac), 110.06 (C, isopropylidene), 85.50, 80.27, 73.99 (C-1, C-3, C-5), 73.60 (overlap, C-2, C-4), 63.82 (C-6), 27.77, 26.30 (2 × CH_3, isopropylidene), 24.89 (CH_2, SEt), 20.84 (CH_3, Ac), 15.08 (CH_3, SEt), 6.81 (CH_3, TES), 4.95 (CH_2, TES); FABMS: *m*/*z* 419.2, $[M - H]^+$; HRMS Calcd for $C_{19}H_{35}O_6SSi$ $[M - H]^+$: 419.1924. Found: 419.2395.

3.15. Ethyl 6-*O*-acetyl-3,4-*O*-isopropylidene-1-thio-2-*O*-triisopropylsilyl-β-D-galactopyranoside (20)

To compound **15** (117 mg, 0.203 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under Ar, acetic anhydride (38.3 μL, 2.0 equiv) was added, followed by addition of $Sc(OTf)_3$ (5 mg, 0.05 equiv). After 3 h, the mixture was washed with water (3 × 13 mL) and then dried over anhyd Na_2SO_4. The organic phase was concentrated. The mixture was purified on an MPLC column eluting with 18:1:1 hexanes–EtOAc–CH_2Cl_2 to give 23 mg (25%) of product **20**; $[\alpha]_D$ −16.3 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.51 (d, 1H, $J_{1,2}$ 6.6 Hz, H-1), 4.30 (s, 1H, Ha-6), 4.28 (s, 1H, H-4), 4.19 (m, 1H, Hb-6), 4.16 (br t, 1H, H-5), 3.96 (br t, 1H, H-3), 3.92 (br t, 1H, H-2), 2.71 (m, 1H, CH_2, SEt), 2.07 (s, 3H, CH_3, Ac), 1.50, 1.33 (2 × s, 6H, CH_3, isopropylidene), 1.28 (t, 3H, J_{CH_3,CH_2} 7.7 Hz, CH_3, SEt), 1.15 (m, 3H, CH, isopropyl), 1.09 (m, 18H, CH_3, isopropyl); ^{13}C NMR (100.55 MHz, $CDCl_3$): δ 171.15 (C=O, Ac), 110.54 (C, isopropylidene), 86.37, 79.23, 73.53, 73.47, 73.39, 64.16 (C-1, C-5, C-3, C-4, C-2, C-6), 27.48, 26.26 (2 × CH_3, isopropylidene), 25.82 (CH_2, SEt), 21.18 (CH_3, Ac),

18.50, 18.46 ($2\times CH_3$, isopropyl), 15.38 (CH_3, SEt), 12.76 (CH, isopropyl); FABMS: *m/z* 461.2, $[M-H]^+$; HRMS Calcd for $C_{22}H_{41}O_6SSi$ $[M-H]^+$: *m/z* 461.2393. Found: *m/z* 461.2706.

3.16. Ethyl 6-*O*-acetyl-2-*O*-dimethylthexylsilyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (21)

To compound **16** (111 mg, 0.203 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under Ar, acetic anhydride (38.3 μL, 2.0 equiv) was added, followed by the addition of $Sc(OTf)_3$ (5 mg, 0.05 equiv). After 3 h the mixture was washed with water (3×13 mL) and then dried over anhyd Na_2SO_4. The organic phase was concentrated. The mixture was purified on an MPLC column eluting with 16:1:1 hexanes–EtOAc–CH_2Cl_2 to give 20.8 mg (23%) of product **21**: $[\alpha]_D$ −5.9 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.32 (m, 3H, H-1, Ha-6, Hb-6), 4.15 (dd, 1H, $J_{4,5}$ 2.1 Hz, $J_{4,3}$ 5.7 Hz, H-4), 4.02 (br t, 1H, H-3), 3.92 (ddd, 1H, $J_{5,4}$ 2.1 Hz, $J_{5,Ha\text{-}6} = J_{5,Hb\text{-}6}$ 6.0 Hz, H-5), 3.63 (dd, 1H, $J_{2,3}$ 6.0 Hz, $J_{2,1}$ 8.7 Hz, H-2), 2.69 (m, 2H, CH_2, SEt), 2.07 (s, 3H, CH_3, Ac), 1.65 (m, 1H, CH, DTS), 1.50, 1.33 ($2\times$ s, 6H, CH_3, isopropylidene), 1.29 (t, 3H, J_{CH_3,CH_2} 7.6 Hz, CH_3, SEt), 0.87 (q, 12H, CH_3, DTS), 0.18, 0.17 ($2\times$ s, 6H, CH_3, $SiCH_3$); ^{13}C NMR (100.56 MHz, $CDCl_3$): δ 170.82 (C=O, Ac), 110.05 (C, isopropylidene), 85.48, 80.15, 73.90, 73.59, 73.36, 63.87 (C-1, C-3, C-5, C-4, C-2, C-6), 34.06 (CH, DTS), 27.75, 26.33 ($2\times CH_3$, isopropylidene), 24.99 (Si–*C*–C, DTS), 24.82 (CH_2, SEt), 20.84 (CH_3, Ac), 20.34, 20.30, 18.64 ($3\times CH_3$, DTS), 15.09 (CH_3, SEt), −2.12, −2.60 ($2\times SiCH_3$); FABMS: *m/z* 447.2, $[M-H]^+$; HRMS Calcd for $C_{21}H_{39}O_6SSi$ $[M-H]^+$: *m/z* 447.2236. Found: *m/z* 447.2126.

3.17. Ethyl 6-*O*-acetyl-2-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (22)

To compound **17** (100 mg, 0.203 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under Ar, acetic anhydride (38.3 μL, 2.0 equiv) was added, followed by the addition of $Sc(OTf)_3$ (5 mg, 0.05 equiv). After 1.5 h the mixture was washed with water (3×13 mL) and then dried over anhyd Na_2SO_4. The organic phase was concentrated. The mixture was purified on an MPLC column eluting with 25:1:1 hexanes–EtOAc–CH_2Cl_2 to give 30 mg (35%) of product **22**: $[\alpha]_D$ +0.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.31 (m, 3H, H-1, Ha-6, Hb-6), 4.15 (dd, 1H, $J_{4,5}$ 2.1 Hz, $J_{4,3}$ 5.7 Hz, H-4), 4.01 (br t, 1H, H-3), 3.92 (ddd, 1H, $J_{5,4}$ 2.1 Hz, $J_{5,Ha\text{-}6} = J_{5,Hb\text{-}6}$ 6.0 Hz, H-5), 3.60 (dd, 1H, $J_{2,3}$ 6.4 Hz, $J_{2,1}$ 9.0 Hz, H-2), 2.69 (m, 2H, CH_2, SEt), 2.07 (CH_3, Ac), 1.49, 1.33 ($2\times$ s, 6H, CH_3, isopropylidene), 1.29 (t, 3H, J_{CH_3,CH_2} 7.4 Hz, CH_3, SEt), 0.91 (s, 9H, CH_3, TBS), 0.14 (s, 6H, $SiCH_3$); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 170.84 (C=O, Ac), 110.04 (C, isopropylidene), 85.35, 80.33, 74.00, 73.65, 73.61, 63.84 (C-1, C-3, C-5, C-2, C-4, C-6), 27.85, 26.36 ($2\times CH_3$, isopropylidene), 25.89 (CH_3, TBS), 24.72 (CH_2, SEt), 20.86 (CH_3, Ac), 18.20 (C, TBS), 15.10 (CH_3, SEt), −4.26, −4.66 ($2\times SiCH_3$); FABMS: *m/z* 419.2, $[M-H]^+$; HRMS Calcd for $C_{19}H_{35}O_6SSi$ $[M-H]^+$: *m/z* 419.1924. Found: *m/z* 419.1949.

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References

1. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1999; (b) Kocienski, P. J. *Protective Groups*, 3rd ed.; George Thieme: New York, 1994.
2. Collins, P.; Ferrier, R. *Monosaccharides*; John Wiley and Sons: Toronto, 1995.
3. Suzuki, T.; Watahiki, T.; Oriyama, T. *Tetrahedron Lett.* **2000**, *41*, 8903–8906.
4. Firouzabadi, H.; Iranpoor, N.; Sobhani, S.; Ghassamipour, S.; Amoozgar, Z. *Tetrahedron Lett.* **2003**, *44*, 891–893.
5. Chung, M.-K.; Orlova, G.; Goddard, J. D.; Schlaf, M.; Harris, R.; Beveridge, T. J.; White, G.; Hallett, F. R. *J. Am. Chem. Soc.* **2002**, *124*, 10508–10518.
6. Biffis, A.; Zecca, M.; Basato, M. *Green Chem.* **2003**, *5*, 170–173.
7. Hatano, B.; Toyota, S.; Toda, F. *Green Chem.* **2001**, *3*, 140–142.
8. Watahiki, T.; Matsuzaki, M.; Oriyama, T. *Green Chem.* **2003**, *5*, 82–84.
9. (a) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031–1058; (b) Crouch, R. D. *Tetrahedron* **2004**, 5833–5871.
10. Khan, A. T.; Mondal, E. *Synlett* **2003**, 694–698.
11. (a) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705–708; (b) Rotulo-Sims, D.; Prunet, J. *Org. Lett.* **2002**, *4*, 4701–4704; (c) Sajiki, H.; Ikawa, T.; Hirota, K. *Tetrahedron Lett.* **2003**, *44*, 7407–7410.
12. Crouch, R. D.; Romany, C. A.; Kreshock, A. C.; Menconi, K. A.; Zile, J. L. *Tetrahedron Lett.* **2004**, *45*, 1279–1281.
13. Glória, P. M. C.; Prabhakar, S.; Lobo, A. M.; Gomes, M. J. S. *Tetrahedron Lett.* **2003**, *44*, 8819–8821.
14. Oriyama, T.; Kobayashi, Y.; Noda, K. *Synlett* **1998**, 1047–1048.
15. Eichler, E.; Yan, F.; Sealy, J.; Whitfield, D. M. *Tetrahedron* **2001**, 6679–6693.
16. Chandra, K. L.; Saravanan, C. P.; Singh, V. K. *Tetrahedron Lett.* **2001**, *42*, 5309–5311.
17. Reddy, C. S.; Smitha, G.; Chandrasekhar, S. *Tetrahedron Lett.* **2003**, *44*, 4693–4695.

18. (a) Sue, S.-C.; Brisson, J.-R.; Chang, S.-C.; Huang, W.-N.; Lee, S.-C.; Jarrell, H. C.; Wu, W. *Biochemistry* **2001**, *40*, 10436–10446; (b) Vyas, A. A.; Pan, J.-J.; Patel, H. V.; Vyas, K. A.; Chiang, C.-M.; Sheu, Y.-C.; Hwang, J.-K.; Wu, W. *J. Biol. Chem.* **1997**, *172*, 9661–9670; (c) Vyas, K. A.; Patel, H. V.; Vyas, A. A.; Wu, W. *Biochemistry* **1998**, *37*, 4527–4534.
19. Lohman, G. J. S.; Hunt, D. K.; Högermeier, J. A.; Seeberger, P. H. *J. Org. Chem.* **2003**, *68*, 7559–7561.
20. Ke, W.; Whitfield, D. M.; Gill, M.; Larocque, S.; Yu, S.-H. *Tetrahedron Lett.* **2003**, *44*, 7767–7770, The full properties of donor **4** will be described in a separate communication.
21. de Paz, J.-L.; Angulo, J.; Lassaletta, J.-M.; Nieto, P. M.; Redondo-Horcajo, M.; Lozano, R. M.; Giménez-Gallego, G.; Martín-Lomas, M. *ChemBioChem* **2001**, *2*, 673–685.
22. (a) Dumeunier, R.; Markó, I. E. *Tetrahedron Lett.* **2004**, *45*, 825–829; (b) Chandra, K. L.; Saravanan, P.; Singh, R. K.; Singh, V. K. *Tetrahedron* **2002**, *58*, 1369–1374.
23. Buskas, T.; Konradsson, P. *J. Carbohydr. Chem.* **2000**, *19*, 25–51.
24. (a) Åberg, P.-M.; Blomberg, L.; Lönn, H.; Norberg, T. *J. Carbohydr. Chem.* **1994**, *13*, 141–161; (b) Fried, J.; Walz, D. E. *J. Am. Chem. Soc.* **1949**, *71*, 140–143.
25. Murphy, P. V.; McDonnell, C.; Hämig, L.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron: Asymmetry* **2003**, *14*, 79–85.
26. (a) Singh, J.; DiMarco, J.; Kissick, T. P.; Deshpande, P.; Gougoutas, J. Z. *Carbohydr. Res.* **2002**, *337*, 565–568; (b) Arias-Pérez, M. S.; Jesús Santos, M. *Tetrahedron* **1996**, *52*, 10785–10798.