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Synthesis of rhamnosylated diosgenyl glucosides as mimetics of cytostatic steroidal saponins from *Ornithogalum saundersiae* and *Galtonia candicans*

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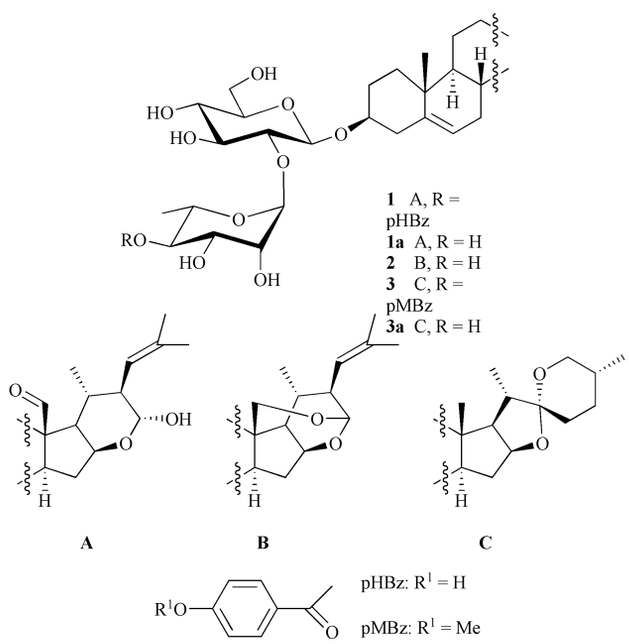
The synthesis of mimetic **3** of the steroid saponins **1** and **2** was investigated. As a substitute for the complex 22-homo-23-nor-steroid moieties **A** and **B** in **1** and **2** diosgenin **C** was introduced. The silyl protected thioorthoester **20** was successfully employed for glucosylation. After selective 2-*O*-deacetylation, the glucosylated diosgenyl acceptor **23** was rhamnosylated. The 4-*O*-*p*-methoxybenzoylated donor **12** gave only minor yields. By using the tri-*O*-benzoyl protected donor **15** the α-L-rhamnopyranosyl-(1⟶2)-β-D-glucopyranosyl-(1⟶3β)-diosgenin derivative **25** was obtained.

Introduction

Due to the coevolution of plants with different kinds of damaging organisms plant extracts and natural products obtained thereof show a broad spectrum of biological activities with a high potential for medicinal applications. A diverse class of compounds, concerning their effect and structure are the saponins, complex glycosides with a steroid, a steroid alkaloid or triterpene aglycon, which presumably support the plant in their defence against fungi. The main building blocks of these compounds consist of a relatively small number of common monosaccharides and the various sapogenins.

Several groups are involved in systematic research into the constitution and biological effects of this interesting class of compounds. Sashida and Mimaki *et al.* discovered the *p*-hydroxybenzoylated α-L-rhamnopyranosyl-(1⟶2)-β-D-glucopyranosyl-(1⟶3β)-22-homo-23-nor-cholestane derivative (**1**) from *Ornithogalum saundersiae*[1] and the non-acylated ketal **2** from *Galtonia candicans*.[2] They also showed these compounds to have high cytostatic potential concurrent with a low effect on non-transformed cells. As a part of our research on saponin chemistry,[3–5] our synthetic interest focussed on the sugar parts of these molecules. Therefore, the complex 22-homo-23-norcholestane steroid moiety was substituted by the easily accessible diosgenin **4** to give the structural mimetics **3** and **3a** as synthetic targets (Scheme 1).



Scheme 1 The rearranged Rha–Glc-cholestane glycoside (**1**, *Ornithogalum Saundersiae*, Liliaceae) shows potential cytostatic activity (IC_{50} = 21 nM for the Leukaemia HL-60 cell line and 18 nM for the Leukaemia MOLT-4 cell line), whereas only a small activity is found for the deacylated derivative **1a**. For the rearranged Rha–Glc-cholestane glycoside Candicanosid A (**2**, *Galtonia candicans*, Liliaceae), IC_{50} = 32 nM for the Leukaemia HL-60 cell line. Compounds **3** and **3a** are structural mimetics and are synthetic targets.

Results and Discussion

Synthesis of rhamnopyranosyl donors

L-Rhamnose is one of the few naturally occurring L-sugars. Because of the axially configured 2-position determination of the α- and β-glycosides by the $^3J_{1,2}$ coupling constants (0 to < *ca.* 3 Hz in ^{1}H NMR) is difficult. However, the anomeric configuration can be determined by ^{1}H coupled ^{13}C NMR with the $^1J_{CH}$ coupling constants in the range of 160 (α) to 170 Hz (β).[6–8] Scheme 2 shows the synthesis of the differentially protected methyl (**6/7**)[8] and ethyl thiorhamnopyranosides (**14**) from the 2,3,4-tri-*O*-acetylated compounds[8,9] by treatment of the L-rhamnopyranose tetraacetate (**5**)[10,11] with TMSSMe–TMSOTf and ethanethiol–BF_3·OEt_2, respectively. The isopropylidene group was introduced onto **6** and **7** resulting in an unprotected 4-position, which was protected with a *p*-methoxybenzoyl or TBDMS group, respectively. The former results in a donor with a suitable benzoate function, and the latter after glycosylation substitution with different benzoates leads to a library of saponins. Because of the anomeric effect, L-rhamnopyranose donors generally preferentially give α-glycosides. To enhance the tendency for α-glycoside formation, 2-*O*-acyl donors, in this case the benzoates **15/16**[9] were synthesized from **14**, which shows 1,2-*trans* selectivity in the glycosylations.

Synthesis of glucopyranosyl donors

In order to obtain selective protection of the 3, 4 and 6 positions of glucose, the orthoester methodology was chosen. To obtain a glucosyl donor which can be easily activated the thio derivative 3,4,6-tri-*O*-acetyl-1,2-*O*-(ethylthioethylidene)-

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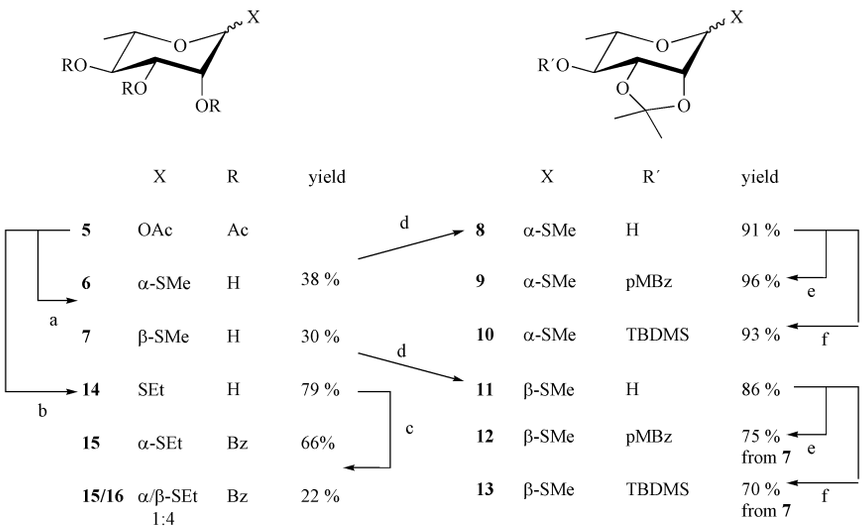
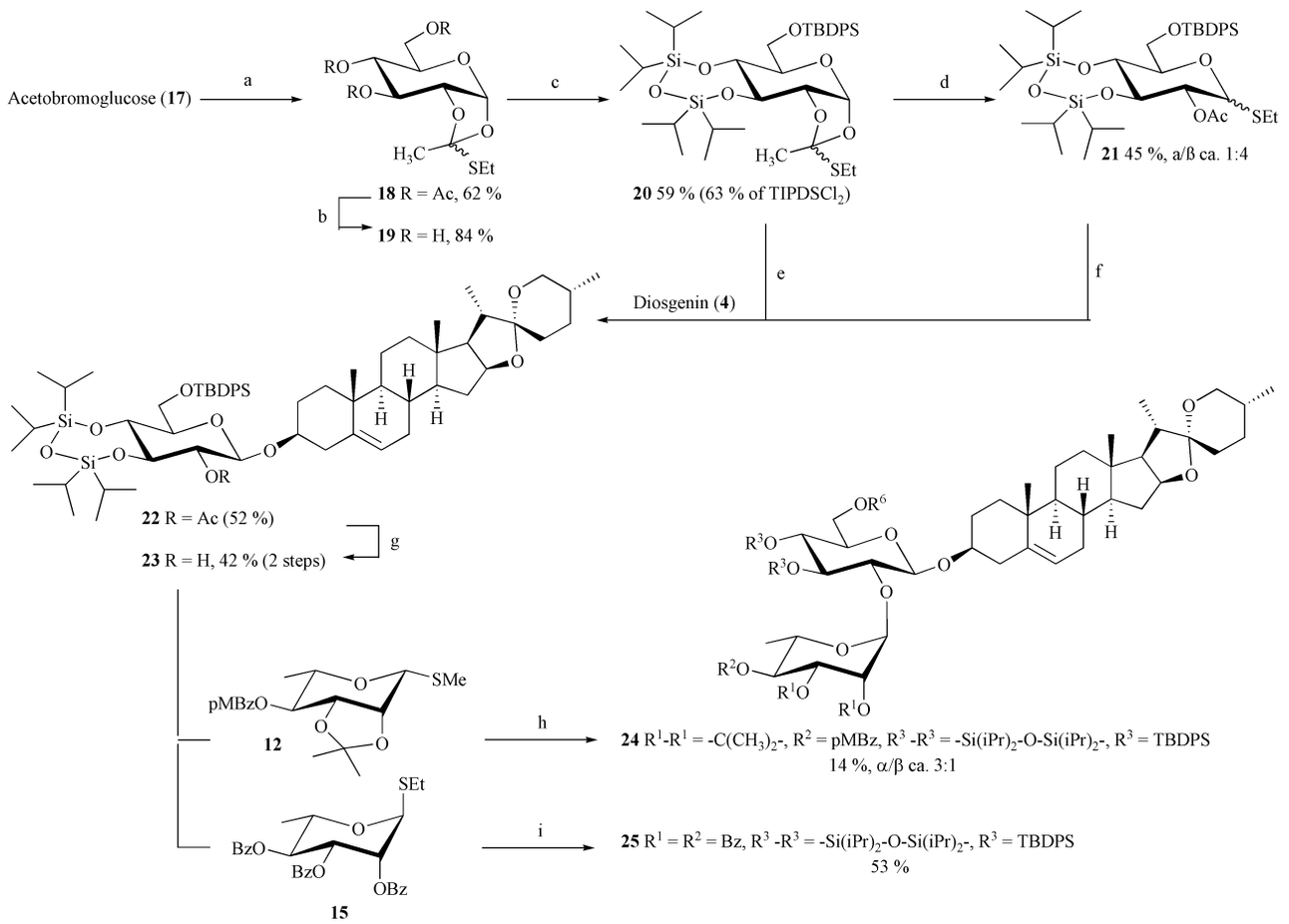


Scheme 2 *Reagents and conditions*: a: 1) TMSSMe, TMSOTf, CH_2Cl_2, Ar, 0 °C – > rt; 2) NaOMe–MeOH; b: 1) EtSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, Ar, 0 °C – > rt; 2) NaOMe–MeOH; c: benzoyl chloride, pyridine, DMAP (cat.) over night, 0 °C – > rt; d: dimethoxypropane, CH_2Cl_2, TosOH (cat.); e: pMBzCl, pyridine, CH_2Cl_2, 0 °C – > rt; f: TBDMSCl, DMF, imidazole.



Scheme 3 *Reagents and conditions*: a: EtSH, *sym*-collidine, NBu_4Br, anhydr. acetonitrile; b: NaOMe–MeOH; c: 1) TBDPSCl, 12 h; 2) $TIPDSCl_2$ (0.95 eq.), 6 h, 0 °C – > rt, argon, imidazole, DMF; d: EtSH, abs. CH_2Cl_2, Ar, TMSOTf (cat.), MS 4 Å, rt, 5 min; e: anhydr. Et_2O–CH_2Cl_2 1 : 1, argon, MS 4 Å; 1) NIS, 2 h; 2) TfOH (cat.), 2 h; f: DMTST, CH_2Cl_2, MS 4 Å, 24 h; g: K_2CO_3–MeOH; h: NIS, anhydr. Et_2O–CH_2Cl_2 1 : 1, argon, MS 4 Å; i: DMTST, Et_2O, MS 4 Å.

α-D-glucopyranose (**18**)[12] was synthesized in 62% yield (Scheme 3). After deacetylation, a two step silyl protection of the 6 position, with *tert*-butyldiphenylsilyl (TBDPS), and the 3,4-*trans*-diequatorial position, with the 1,2-*trans*-diol selective 1,1,3,3-tetraisopropyl-1,3-disiloxan-1,3-diyl (TIPDS) protecting group, was successful in yielding the thioorthoester donor **20**, which can be activated directly or rearranged to the thioglycoside **21**.

Glycosylations

The activation of thioglycosides by NIS–TfOH was first described by van Boom *et al.*[13] and was later modified by the same group for the activation of sugar thioorthoesters.[14] The donor **20** was activated by this procedure and **21** was activated by the DMTST (dimethyl(methylthio)sulfonium triflate) method for the glycosylation of diosgenin **4**. A mixture of

donor **20** and acceptor **4** was stirred in diethyl ether–dichloromethane 1 : 1, and *N*-iodosuccinimide (NIS) was added to activate the thio function to yield an intermediate diosgenin sugar orthoester within 2 h. This underwent rearrangement by addition of a catalytic amount of trifluoromethanesulfonic acid to give after another 2 h the 2-*O*-acetylated diosgenyl glucoside **22**.

The 2-*O*-acetate has to be cleaved in the next step without provoking a migration of the silyl group; to achieve this K_2CO_3–MeOH was used under mild conditions. Thus, the acceptor **23** was obtained in 42% yield in two steps.

A remarkably difficult step was the subsequent 2-*O*-rhamnosylation; donor **12** and acceptor **23** were reacted under NIS activation to give the target molecule **24** in poor yield. Some β-rhamnosylation occurred because of the missing acyl neighbouring group in position 2 and perhaps conformational influence caused by the isopropylidene group.

Acceptor **23** was rhamnosylated using the tri-*O*-benzoyl donor **15**[9] with activation by DMTST to yield the disaccharide saponin **25** in satisfactory yield. Further studies towards the target molecules are under investigation.

Experimental

General Procedures

Thin layer chromatography was performed on precoated plates of silica gel 60 (F_{254}, Merck) with detection by UV absorption or by spraying the plates with 20% ethanolic sulfuric acid and subsequent heating. Column chromatography was performed on silica gel 60 (230–400 mesh, 40–63 μm; Merck, Machery-Nagel or ICN) using the flash technique and the given solvents. NMR spectra were recorded with the Bruker spectrometers AMX-400 (400 MHz ^{1}H, 100.67 MHz ^{13}C) and DRX-500 (500 MHz ^{1}H, 125.77 MHz ^{13}C). Tetramethylsilane (0.00 ppm) was added as internal standard, or especially for silylated compounds, the solvent residual peak was used.[15] Signal multiplicity dd~t; ddd~dt: double doublet appearing as a pseudotriplet. Mass spectra were recorded with a Bruker Biflex™ III MALDI-TOF-Mass spectrometer (*positive reflector mode*, Matrix: DHB = dihydroxybenzoic acid).[16] Melting points were determined using an Olympus BH polarising microscope with a Mettler FP82 hot plate or an Apotec melting point apparatus and are not corrected. Optical rotations were determined with a Perkin-Elmer 241 PE polarimeter (Na_D = 589 nm); $[\alpha]$ values are measured in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed in the microanalytical laboratory of the Institute of Organic Chemistry of the University of Hamburg.

Solvents for the reactions were distilled or dried before use. Dichloromethane (CaH_2) and diethyl ether (sodium wire/benzophenone) for glycosylation reactions were dried freshly under argon before use or stored over MS 4 Å. Methanol was dried by refluxing over magnesium and subsequent distillation and then stored over MS 3 Å. Commercially available anhydr. acetonitrile, anhydr. pyridine and anhydr. DMF (Fluka) were used. Reagents were used with the available purity offered by the producer. DMTST was synthesized by a modified method according to the literature[17] and stored under argon with strict exclusion of moisture at *ca.* −15 °C. It was warmed to room temperature before use. Reactions in inert gas atmosphere were performed under a slight excess pressure of argon or nitrogen by the Schlenck or balloon technique in glassware which was heated under vacuum before use.[18] Molecular sieves were activated under high vacuum at *ca.* 130–250 °C for several hours (usually over night), cooled under a slight excess pressure of argon or nitrogen and used freshly activated.

Methyl 2,3-*O*-isopropylidene-4-*O*-*p*-methoxybenzoyl-1-thio-α-L-rhamnopyranoside (9)

In a 50 mL round flask compound **8**[8] (1.7 g, 5.5 mmol) was dissolved in pyridine (2 mL) and anhydr. dichloromethane (12 mL). After cooling in an ice bath *p*-methoxybenzoyl chloride (1 mL) was added slowly and the mixture was stirred for 6 d. Dichloromethane was added and the mixture was washed twice with saturated $NaHCO_3$ solution and once with water, dried over $MgSO_4$, filtered, evaporated and distilled with toluene. After flash chromatography compound **9** was obtained (1.955 g, 5.3 mmol, 96%). Colourless solid; $C_{18}H_{24}O_6S$ (MW 368.446 g mol^{-1}); mp: 89 °C; $[\alpha]_{546}$ = −24 (c = 0.57, $CHCl_3$); TLC (petroleum ether (PE)–ethyl acetate (EA) 1 : 1): R_f = 0.78 (UV, H_2SO_4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00, 7.05 (2 × d, 2 × 2H, $CH_3OC_6H_4COO$), 5.46 (s, 1H, H-1), 5.16 (dd, 1H, H-4, $^3J_{3,4}$ = 7.6, $^3J_{4,5}$ = 10.2 Hz), 4.31 (dd, 1H, H-3, $^3J_{2,3}$ = 5.6, $^3J_{3,4}$ = 7.6 Hz), 4.24 (d, 1H, H-2, $^3J_{2,3}$ = 5.6 Hz), 4.17 (dq, 1H, H-5, $^3J_{4,5}$ = 10.2, $^3J_{5,6}$ = 6.1 Hz), 3.85 (s, 3H, $CH_3OC_6H_4COO$), 2.16 (s, 3H, SCH_3), 1.62, 1.34 (2 × s, 2 × 3H, $C(CH_3)_2$), 1.22 (d, 3H, CH_3-6, $^3J_{5,6}$ = 6.1 Hz) ppm.

Methyl 4-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-1-thio-α-L-rhamnopyranoside (10)

In a 100 mL round flask compound **8**[8] (0.306 g, 1.00 mmol) was dissolved in anhydr. DMF (10 mL) and cooled in an ice bath. Imidazole (115 mg, 1.7 mmol) and *tert*-butyldimethylchlorosilane (257 mg, 1.7 mmol) were added and stirred for 5 d at rt. The reaction was monitored by TLC. After complete conversion of the starting material the reaction was stopped by addition of a ten-fold excess of toluene and the resulting mixture was washed three times with saturated $NaHCO_3$ solution and once with water, dried over sodium sulfate, filtered and evaporated. After flash chromatography (PE–EA 20 : 1) compound **10** (323 mg, 0.93 mmol, 93%) was obtained. Colourless syrup; $C_{16}H_{32}O_4SSi$ (MW 348.574 g mol^{-1}); $[\alpha]_{546}$ = −33 (c = 0.7, $CHCl_3$); TLC (PE–EA 20 : 1): R_f = 0.44 (H_2SO_4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.36 (s, 1H, H-1), 4.14 (d, 1H, H-2, $^3J_{2,3}$ = 5.6 Hz), 3.97 (dd, 1H, H-3, $^3J_{2,3}$ = 5.6, $^3J_{3,4}$ = 7.1 Hz), 3.87 (dq, 1H, H-5, $^3J_{4,5}$ = 9.7, $^3J_{5,6}$ = 6.1 Hz), 3.38 (dd, 1H, H-4, $^3J_{3,4}$ = 7.1, $^3J_{4,5}$ = 9.7 Hz), 2.11 (s, 3H, SCH_3), 1.52, 1.33 (2 × s, 2 × 3H, $C(CH_3)_2$), 1.24 (d, 3H, CH_3-6, $^3J_{5,6}$ = 6.1 Hz), 0.84 (s, 9H, $C(CH_3)_3$), 0.14, 0.09 (2 × s, 2 × 3H, $Si(CH_3)_2$) ppm. ^{13}C NMR (100.67 MHz, $CDCl_3$): δ = 109.0 ($C(CH_3)_2$), 81.3 (C-1), 78.9 (C-3), 76.8 (C-2), 76.4 (C-4), 66.6 (C-5), 28.2, 26.5 ($C(CH_3)_2$), 25.9 ($C(CH_3)_3$), 17.9 (C-6), 13.3 (SCH_3), −3.9, −4.9 ($Si(CH_3)_2$) ppm.

Methyl 2,3-*O*-isopropylidene-1-thio-β-L-rhamnopyranoside (11)

Compound **7**[8] (100 mg, 0.51 mmol), 2,2-dimethoxypropane (1 mL) and *p*-toluenesulfonic acid monohydrate (5 mg, 0.03 mmol) were stirred at rt. The reaction was monitored by TLC and stopped after 15 min by neutralisation with triethylamine (1.5 mL). The mixture was evaporated to dryness and after flash chromatography with (PE–EA 1 : 1) compound **11** (103 mg, 0.44 mmol, 86%) was obtained. Colourless solid; $C_{10}H_{18}O_4S$ (MW 234.314 g mol^{-1}); mp: 75 °C; $[\alpha]_{546}$ = +107 (c = 1.24, $CHCl_3$); TLC (PE–EA 1 : 3): R_f = 0.51 (H_2SO_4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.73 (d, 1H, H-1, $^3J_{1,2}$ = 2.0 Hz), 4.29 (dd, 1H, H-2, $^3J_{1,2}$ = 2.0, $^3J_{2,3}$ = 5.6 Hz), 3.98 (dd, 1H, H-3, $^3J_{2,3}$ = 5.6, $^3J_{3,4}$ = 7.1 Hz), 3.48 (ddd, 1H, H-4, $^3J_{4,OH}$ = 3.6, $^3J_{3,4}$ = 7.1, $^3J_{4,5}$ = 10.2 Hz), 3.27 (dq, 1H, H-5, $^3J_{4,5}$ = 9.7, $^3J_{5,6}$ = 6.1 Hz), 2.30 (s, 3H, SCH_3), 2.17 (d, 1H, OH, $^3J_{4,OH}$ = 4.1 Hz), 1.58, 1.55 (2 × s, 2 × 3H, $C(CH_3)_2$), 1.36 (d, 3H, CH_3-6, $^3J_{5,6}$ = 6.1 Hz) ppm. ^{13}C NMR (100.67 MHz, $CDCl_3$): δ = 110.5 (2 × $C(CH_3)_2$), 82.1 (C-1), 80.2 (C-3), 76.3 (C-2), 75.1 (C-4), 74.8 (C-5), 28.2, 26.4 (2 × $C(CH_3)_2$), 17.5 (C-6), 14.8 (SCH_3) ppm.

Methyl 2,3-*O*-isopropylidene-4-*O*-*p*-methoxybenzoyl-1-thio-β-L-rhamnopyranoside (12)

Compound **7**[8] (592 mg, 3.0 mmol), 2,2-dimethoxypropane (6 mL) and *p*-toluenesulfonic acid monohydrate (31 mg, 0.03 mmol) were stirred at rt. The reaction was monitored by

TLC and stopped after 30 min by neutralisation with triethylamine (8 mL). The mixture was evaporated to dryness and dissolved in anhydr. dichloromethane (1 mL) and pyridine (1.0 mL, 4 eq, 12 mmol). Then a solution of *p*-methoxybenzoyl chloride (614 mg, 3.6 mmol) in anhydr. dichloromethane (1 mL) was added dropwise at 0 °C. The reaction was stirred for 18 h while the temperature slowly increased to rt. Dichloromethane was added and the mixture was washed twice with saturated $NaHCO_3$ solution and once with water, dried over $MgSO_4$, filtered, evaporated and distilled with toluene. After flash chromatography (PE–EA 3 : 1) compound **12** (831 mg, 2.3 mmol, 75%) was obtained. Colourless solid; $C_{18}H_{24}O_6S$ (MW 368.446 g mol^{-1}); mp: 121 °C; $[\alpha]_{546}$ = +79 (c = 0.75, $CHCl_3$); TLC (PE–EA 1 : 1): R_f = 0.70 (UV, H_2SO_4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99, 6.92 (2 × d, 2 × 2H, $CH_3OC_6H_4COO$, ^3J = 9.2, 9.2 Hz), 5.16 (dd, 1H, H-4, $^3J_{3,4}$ = 7.1, $^3J_{4,5}$ = 9.1 Hz), 4.78 (d, 1H, H-1, $^3J_{1,2}$ = 2.0 Hz), 4.37 (dd, 1H, H-2, $^3J_{1,2}$ = 2.0, $^3J_{2,3}$ = 5.6 Hz), 3.87 (s, 3H, $CH_3OC_6H_4COO$), 4.30 (dd, 1H, H-3, $^3J_{2,3}$ = 5.6, $^3J_{3,4}$ = 7.1 Hz), 3.56 (dq, 1H, H-5, $^3J_{4,5}$ = 8.6, $^3J_{5,6}$ = 6.1 Hz), 2.32 (s, 3H, SCH_3), 1.65, 1.38 (2 × s, 2 × 3H, $C(CH_3)_2$), 1.30 (d, 3H, CH_3-6, $^3J_{5,6}$ = 6.1 Hz) ppm. ^{13}C NMR (100.67 MHz, $CDCl_3$): δ = 165.3 ($CH_3OC_6H_4COO$), 163.6, 122.1, 113.7 ($CH_3OC_6H_4COO$), 110.9 ($C(CH_3)_2$), 82.3 (C-1), 77.2 (C-3), 76.2 (C-2), 74.3 (C-4), 74.2 (C-5), 55.5 (OCH_3), 26.3, 27.6 ($C(CH_3)_2$), 17.9 (SCH_3), 14.8 (C-6) ppm.

Methyl 4-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-1-thio-β-L-rhamnopyranoside (13)

Compound **7**[8] (0.333 g, 1.71 mmol), 2,2-dimethoxypropane (4 mL) and *p*-toluenesulfonic acid monohydrate (16 mg, 0.03 mmol) were stirred at rt. The reaction was monitored by TLC and stopped after 20 min by neutralisation with triethylamine (5 mL). The mixture was evaporated to dryness, dissolved in anhydr. DMF (10 mL) and cooled in an ice bath. Imidazole (136 mg, 2 mmol) and *tert*-butyldimethylchlorosilane (301 mg, 2 mmol) were added and the mixture was stirred for 2 d at rt. The reaction was monitored by TLC. After complete conversion of the starting material the reaction was stopped by addition of a ten-fold excess of toluene and the resulting mixture was washed three times with saturated $NaHCO_3$ solution and once with water, dried over sodium sulfate, filtered and evaporated. After flash chromatography (PE–EA 20 : 1) compound **13** (417 mg, 1.20 mmol, 70%) was obtained. Colourless syrup; $C_{16}H_{32}O_4SSi$ (MW 348.574 g mol^{-1}); $[\alpha]_D$ = +54 (c = 1.4, $CHCl_3$); TLC (PE–EA 2 : 1): R_f = 0.76 (UV, H_2SO_4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.56 (d, 1H, H-1, $^3J_{1,2}$ = 1.0 Hz), 4.12 (dd, 1H, H-2, $^3J_{1,2}$ = 1.0, $^3J_{2,3}$ = 5.6 Hz), 3.80 (dd, 1H, H-3, $^3J_{2,3}$ = 6.6, $^3J_{3,4}$ = 6.6 Hz), 3.30 (dd, 1H, H-4, $^3J_{3,4}$ = 7.1, $^3J_{4,5}$ = 8.7 Hz), 3.09 (dq, 1H, H-5, $^3J_{4,5}$ = 8.7, $^3J_{5,6}$ = 6.6 Hz), 2.14 (s, 3H, SCH_3), 1.41, 1.22 (2 × s, 2 × 3H, $C(CH_3)_2$), 1.15 (d, 3H, CH_3-6, $^3J_{5,6}$ = 6.6 Hz), 0.75 (s, 9H, $C(CH_3)_3$), 0.14, 0.08 (2 × s, 2 × 3H, $Si(CH_3)_2$) ppm. ^{13}C NMR (100.67 MHz, $CDCl_3$): δ = 110.0 ($C(CH_3)_2$), 82.3 (C-1), 80.5 (C-3), 76.3 (C-2), 76.1 (C-5), 75.6 (C-4), 28.1, 26.4 ($C(CH_3)_2$), 25.9 ($C(CH_3)_3$), 18.2 (C-6), 14.8 (SCH_3), −4.0, −4.9 ($Si(CH_3)_2$) ppm.

Ethyl 2,3,4-tri-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (15) and ethyl 2,3,4-tri-*O*-benzoyl-1-thio-β-L-rhamnopyranoside (16)

In a 250 mL round flask L-rhamnopyranose tetraacetate[10,11] (**5**, 16.20 g, 48.75 mmol) was dissolved under an argon atmosphere in anhydr. dichloromethane (60 mL). The flask was sealed with a septum and an argon filled balloon was attached. Ethanethiol (5.78 mL, 78.00 mmol) was added by a syringe and the mixture was cooled in an ice bath. Then boron trifluoride–etherate (15.44 mL, 121.9 mmol) was added by a syringe. The reaction was monitored by TLC with PE–EA 2 : 1 (R_f (**5**) = 0.82, R_f (**14**) = 0.55) until conversion was complete after 90 min. The reaction was stopped by cooling in an ice bath, injecting triethylamine (20 mL) to the mixture and stirring for 10 min. The solvent was removed under reduced pressure. The resulting mixture was distilled with toluene four times and dissolved in methanol (150 mL); 1 M methanolic sodium methanolate was added until a pH of 9.5 was reached and the mixture was stirred over night. The solution was then neutralized with acetic acid, evaporated to dryness and dissolved in methanol. A suitable amount of silica gel was added and the methanol was removed under reduced pressure. The obtained powdery mixture was placed on a prepacked column (PE–EA 1 : 1) and chromatographed with PE–EA 1 : 1 ⟶ 1 : 2 ⟶ 0 : 1 ⟶ EA–MeOH 10 : 1. Compound **14** (8.05 g, 38.7 mmol 79%) was obtained and dissolved in pyridine (25 mL). The solution was cooled in an ice bath and benzoyl chloride (14.81 mL, 127.5 mmol) and DMAP (cat.) were added and the resulting solution was stirred over night at 0 °C ⟶ rt. The crude product was dissolved in dichloromethane and a suitable amount of silica gel was added. The dichloromethane was removed cautiously under reduced pressure and the obtained powdery mixture was placed on a prepacked column and chromatographed with PE–EA 9 : 1.

The pure α-anomer **15** (13.21 g, 25.4 mmol, 66%) and the anomeric mixture **15**–**16** (4.43 g, 8.51 mmol, 22%, α : β ≈ 1 : 4 by ^{1}H NMR) were obtained. **15**: colourless syrup; $C_{29}H_{28}O_7S$ (MW 520.594 g mol^{-1}); $[\alpha]_D$ = +91.9 (c = 0.9, $CHCl_3$); lit.:[9] no data given; TLC (PE–EA 2 : 1): R_f = 0.55 (PE–EA 9 : 1), R_f = 0.16 (UV, H_2SO_4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17, 8.00, 7.84 (3 × m, 3 × 2H, C_6H_5COO), 7.65–7.13 (m, 9H, C_6H_5COO), 5.82–5.69 (m, 3H, H-2, H-3, H-4), 5.50 (s, 1H, H-1), 5.57 (m, 1H, H-5), 2.83–2.67 (m, 2H, SCH_2CH_3), 1.39 (t, 3H, SCH_2CH_3, ^3J = 7.3 Hz) ppm. ^{13}C NMR (100.67 MHz, $CDCl_3$): δ = 165.72, 165.50, 165.36 (3 × C_6H_5COO), 133.47, 133.34, 133.13, 129.92–129.50, 129.30–128.30 (3 × C_6H_5COO), 82.35 (C-1, $^1J_{H,C}$ = 169.4 Hz), 72.82, 72.22 (C-2, C-3), 70.59 (C-4), 67.54 (C-5), 25.98 (SCH_2CH_3), 17.90 (C-6), 15.24 (SCH_2CH_3) ppm. **16**: syrup; $C_{29}H_{28}O_7S$ (MW 520.594 g mol^{-1}); TLC (PE–EA 2 : 1): R_f = 0.30, (PE–EA 9 : 1): R_f = 0.06 (UV, H_2SO_4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09, 7.96, 7.77 (3 × m, 3 × 2H, C_6H_5COO), 7.63–7.20 (m, 9H, C_6H_5COO), 5.98 (dd, 1H, H-2, $^3J_{1,2}$ = 1.0, $^3J_{2,3}$ = 3.1 Hz), 5.66–5.56 (m, 2H, H-3, H-4), 5.50 (d, 1H, H-1, $^3J_{1,2}$ = 0.8 Hz), 3.89 (m, 1H, H-5), 2.84–2.76 (m, 2H, SCH_2CH_3), 1.45 (d, 3H, CH_3-6, $^3J_{5,6}$ = 6.4 Hz), 1.32 (t, 3H, SCH_2CH_3, ^3J = 7.5 Hz) ppm. ^{13}C NMR (100.67 MHz, $CDCl_3$): δ = 165.71–165.63 (3 × C_6H_5COO), 133.36, 133.18, 130.19–129.69, 129.30–128.96, 128.55–128.25 (3 × C_6H_5COO), 82.53 (C-1), 75.30 (C-5), 72.70, 71.41 (C-3, C-4), 71.68 (C-2), 25.78 (SCH_2CH_3), 18.05 (C-6), 14.91 (SCH_2CH_3) ppm.

3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-ethylthioethylidene)-α-D-glucopyranose (18)

In a 250 mL round flask 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**17**, 20.75 g, 50.46 mmol)[19] was dissolved in anhydr. acetonitrile (55 mL) under an argon atmosphere and *sym*-collidine (8.63 mL, 65.1 mmol) and tetrabutylammonium bromide (1.65 g, 5 mmol) were added. The flask was sealed with a septum and an argon filled balloon was attached. Ethanethiol (5 mL, 67.7 mmol) was added by a syringe and the mixture was stirred overnight. The reaction was monitored by TLC until conversion was complete. The solvent was removed under reduced pressure. The resulting mixture was distilled with toluene four times, dissolved in peroxide-free diethyl ether and washed seven times with water to remove the collidinium hydrobromide; the residue was filtered and evaporated to dryness. The crude product was purified by flash chromatography (PE–EA–NEt_3 3 : 2 : 0.1) to obtain **18** (12.23 g, 31.17 mmol, 62%). Colourless syrup; $C_{16}H_{24}O_9S$ (MW 392.422 g mol^{-1}); $[\alpha]_D$ = +28.3 (c = 1, $CHCl_3$); lit.:[12] syrup, $[\alpha]_D$ = +32.1 (c = 1, $CHCl_3$); TLC (PE–EA–NEt_3 3 : 2 : 0.1): R_f = 0.46 (H_2SO_4). ^{1}H NMR (400 MHz, $CDCl_3$): δ_{exo} = 5.70 (d, 1H, H-1, $^3J_{1,2}$ = 5.1 Hz), 5.20 (dd~t, 1H, H-3, $^3J_{2,3}$ = 2.0, $^3J_{3,4}$ = 2.5 Hz), 4.90 (dd, 1H, H-4, $^3J_{3,4}$ = 2.5, $^3J_{4,5}$ = 9.7 Hz), 4.47 (dd, 1H, H-2,

$^3J_{1,2}$ = 5.1, $^3J_{2,3}$ = 2.0 Hz), 4.19 (d, 2H, H-6$_{a,b}$, $^3J_{5,6}$ = 4.1 Hz), 3.97 (ddd~dt, 1H, H-5, $^3J_{4,5}$ = 9.7, $^3J_{5,6a}$ = $^3J_{5,6b}$ = 4.1 Hz), 2.61 (q, 2H, SCH_2CH$_3$), 2.13 (s, 3H, CH_3COO), 2.09 (2 × s, 2 × 3H, 2 × CH_3COO), 1.96 (s, 3H, *endo*-CH_3C[OR]$_2$SEt,$_{exo}$), 1.25 (t, 3H, SCH$_2$CH_3, ^3J = 7.6 Hz) ppm. ^{13}C NMR (100.67 MHz, CDCl$_3$) δ_{exo} = 170.7, 169.7, 169.2 (CH$_3$*C*OO), 116.3 (CH$_3$*C*[OR]$_2$SEt), 97.3 (C-1), 73.1, 69.8, 68.4, 66.8 (C-2, C-3, C-4, C-5), 63.1 (C-6), 27.4 (*endo*-*C*H$_3$C[OR]$_2$SEt,$_{exo}$), 24.9 (S*C*H$_2$CH$_3$), 20.8 (*C*H$_3$COO), 15.1 (SCH$_2$*C*H$_3$) ppm.

1,2-*O*-(1-Ethylthioethylidene)-α-D-glucopyranose (19)

Compound **18**[12] (5.40 g, 13.76 mmol) was dissolved in anhydr. methanol (40 mL) under an argon atmosphere and a 1 M methanolic sodium methanolate solution (1.1 mL) was added. The reaction mixture was stirred for 1.5 h at rt and was monitored by TLC until conversion was complete (PE–EA–NEt$_3$ 3 : 2 : 0.1: R_f(**18**) = 0.46, R_f(**19**) = 0). The crude product was purified by flash chromatography (EA–EtOH–NEt$_3$ 10 : 1 : 0.1) to obtain **19** (3.06 g, 11.49 mmol, 84%), as well as 603 mg **19** together with some *sym*-collidine. Colourless oil; $C_{10}H_{18}O_6S$ (MW 266.312 g mol^{-1}); $[\alpha]_D$ = +6.5 (*c* = 1, CHCl$_3$); TLC (EA–EtOH–NEt$_3$ 10 : 1 : 0.1): R_f = 0.26 (H$_2$SO$_4$). ^{1}H NMR (400 MHz, CDCl$_3$): δ_{exo} = 5.79 (d, 1H, H-1, $^3J_{1,2}$ = 5.1 Hz), 4.42 (dd~t, 1H, H-2, $^3J_{1,2}$ = 5.1, $^3J_{2,3}$ = 4.6 Hz), 4.00 (dd~t, 1H, H-3, $^3J_{2,3}$ = 4.1, $^3J_{3,4}$ = 4.1 Hz), 3.90–3.82 (m, 2H, H-6a,b), 3.78 (dd, 1H, H-4, $^3J_{3,4}$ = 4.1, $^3J_{4,5}$ = 8.7), 3.66 (dd, 1H, H-5, $^3J_{4,5}$ = 9.2 Hz), 2.62 (q, 2H, SCH_2CH$_3$, ^3J = 7.6, 7.1 Hz), 1.93 (s, 3H, *endo*-CH_3C[OR]$_2$SEt,$_{exo}$), 1.25 (t, 3H, SCH$_2$CH_3, ^3J = 7.6, 7.1 Hz) ppm. ^{13}C NMR (100.67 MHz, CDCl$_3$): δ_{exo} = 116.0 (CH$_3$*C*[OR]$_2$SEt), 98.3 (C-1), 75.9, 73.2, 72.3, 69.1 (C-2, C-3, C-4, C-5), 62.2 (C-6), 28.0 (*endo*-*C*H$_3$C[OR]$_2$SEt,$_{exo}$), 24.9 (S*C*H$_2$CH$_3$), 14.2 (SCH$_2$*C*H$_3$) ppm.

6-*O*-*tert*-Butyldiphenylsilyl-3,4-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxane-1,3-diyl)-1,2-*O*-(1-ethylthioethylidene)-α-D-glucopyranose (20)

In a 10 mL round flask compound **19** (1.26 g, 4.74 mmol) was dissolved in anhydrous DMF (3 mL) under argon and imidazole (645 mg, 9.48 mmol) was added. The mixture was cooled in an ice bath while *tert*-butyldiphenylchlorosilane (1.21 mL, 4.74 mmol) was added, and stirred for 12 h at rt. The reaction was monitored by TLC (PE–EA–NEt$_3$ 10 : 1 : 0.1: R_f(**19**) = 0, R_f (intermediate) = 0.28). After complete conversion of the starting material to the intermediate the mixture was cooled again in an ice bath and another portion of imidazole (1.25 g, 18.4 mmol) and TIPDS-dichloride (1.42 mL, 4.45 mmol, 0.95 eq.) were added. The reaction was stirred in an ice bath for 6 h and observed by TLC (PE–EA–NEt$_3$ 10 : 1 : 0.1). After completion a 10-fold excess of toluene was added, the solution was washed three times with saturated NaHCO$_3$ solution and once with water, dried over sodium sulfate and evaporated. The product was purified by flash chromatography (PE–Et$_2$O–NEt$_3$ 30 : 1 : 0.015) to obtain compound **20** (2.095 g, 2.8 mmol, 63% based on TIPDS-dichloride, 59% based on **19**). Colourless solid; $C_{38}H_{62}O_7SSi_3$ (MW 747.217 g mol^{-1}); $[\alpha]_D$ = +64.5 (*c* = 1, CHCl$_3$); TLC (PE–EA–NEt$_3$ 10 : 1 : 0.1): R_f = 0.69; (PE–Et$_2$O–NEt$_3$ 30 : 1 : 0.1): R_f = 0.50 (UV, H$_2$SO$_4$). ^{1}H NMR (400 MHz, CDCl$_3$): δ_{exo} = 7.71–7.66 (m, 4H, *o*-Ph), 7.44–7.33 (m, 6H, Ph), 5.87 (d, 1H, H-1, $^3J_{1,2}$ = 5.1 Hz), 4.15 (dd~t, 1H, H-2, $^3J_{1,2}$ = 5.1, $^3J_{2,3}$ = 5.1 Hz), 3.98 (dd, 1H, H-6a, $^3J_{5,6a}$ = 2.1, $^2J_{6a,6b}$ = 11.2 Hz), 3.89 (dd, 1H, H-6b, $^3J_{5,6b}$ = 4.3, $^2J_{6a,6a}$ = 11.2 Hz), 3.79 (dd~t, 1H, H-3, $^3J_{2,3}$ = 5.1, $^3J_{3,4}$ = 4.6 Hz), 3.74 (m, 1H, H-4), 3.69 (m, 1H, H-5), 2.61 (q, 2H, SCH_2CH$_3$, ^3J = 7.6 Hz), 1.93 (s, 3H, *endo*-CH_3C[OR]$_2$SEt,$_{exo}$), 1.25 (t, 3H, SCH$_2$CH_3, ^3J = 7.6 Hz), 1.04 (s, 9H, *t*Bu), 1.10–0.91 (m, 28H, 4 × *i*Pr) ppm. ^{13}C NMR (100.67 MHz, CDCl$_3$): δ_{exo} = 133.8, 133.4, 135.9, 135.7, 129.6, 129.5, 127.5 (Ar), 114.7 (CH$_3$*C*[OR]$_2$SEt), 98.9 (C-1), 79.5 (C-3), 78.9 (C-2), 74.6 (C-5), 71.6 (C-4), 63.1 (C-6), 29.1 (*endo*-*C*H$_3$C[OR]$_2$SEt,$_{exo}$), 24.8 (S*C*H$_2$CH$_3$), 19.3 (*C*(CH$_3$)$_3$), 17.5–17.1 (*t*Bu-, CH(*C*H$_3$)$_2$), 15.2 (SCH$_2$*C*H$_3$), 13.0–12.2 (*C*H(CH$_3$)$_2$) ppm.

Ethyl 2-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-3,4-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxane-1,3-diyl)-1-thio-D-glucopyranoside (21)

In a 100 mL round flask compound **20** (935 mg, 1.25 mmol) was distilled with toluene three times. Then freshly activated MS 4 Å were added. The round flask was sealed with a septum, flushed with argon *via* a syringe, and an argon filled balloon was attached. Fresh anhydr. dichloromethane (20 mL) was added, and the mixture was stirred for 30 min at rt. Then ethanethiol (28 µL, 0.125 mmol) was added and stirring was continued for a further 30 min. In another round flask under strict anhydrous conditions and argon atmosphere a mixture of TMSOTf (0.23 mL) and anhydr. dichloromethane (0.77 mL) was freshly prepared. The orthoester rearrangement was started by the addition of a 0.1 mL of this mixture (≡ 23 µL, 0.125 mmol TMSOTf) to the reaction mixture and stopped after stirring for 5 min by addition of triethylamine (0.2 mL). The molecular sieves were filtered over Celite and washed with dichloromethane. The filtrate was evaporated and the resulting syrup was distilled twice with toluene. After flash chromatography with PE–Et$_2$O 30 : 1 compound **21** (419 mg, 0.56 mmol, 45%, α : β ≈ 1 : 4 by ^{1}H NMR) was obtained. Colourless solid; $C_{38}H_{62}O_7SSi_3$ (MW 747.217 g mol^{-1}); calc.: C 61.08, H 8.36; found: C 61.37, H 8.40%; TLC (PE–Et$_2$O–NEt$_3$ 30 : 1 : 0.1): R_f = 0.36 (UV, H$_2$SO$_4$). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.74–7.65 (m, 2 × 4H, 2 × *t*Bu*Ph*$_2$Si), 7.44–7.31 (m, 2 × 6H, 2 × *t*Bu*Ph*$_2$Si), 5.59 (d, 1H, H-1a, $^3J_{1,2}$ = 5.6 Hz), 4.99–4.92 (m, 2 × 1H, H-2a, H-2β), 4.44 (d, 1H, H-1β, $^3J_{1,2}$ = 10.2 Hz), 4.10 (ddd, 1H, H-5a, $^3J_{4,5}$ = 8.1, $^3J_{5,6a}$ = 2.0, $^3J_{5,6b}$ = 6.2 Hz), 3.97 (dd, 1H, H-6aβ, $^3J_{5,6a}$ = 2.0, $^2J_{6a,6b}$ = 11.2 Hz), 3.97–3.90 (m, 2H, H-3a, H-6aa), 3.83 (dd, 1H, H-6bβ, $^3J_{5,6b}$ = 5.6, $^2J_{6a,6b}$ = 11.2 Hz), 3.80 (dd, 1H, H-6ba, $^3J_{5,6b}$ = 6.1, $^2J_{6a,6b}$ = 11.2 Hz), 3.76–3.67 (m, 2H, H-3β, H-4β), 3.61 (dd, 1H, H-4a, $^3J_{3,4}$ = 9.7, $^3J_{4,5}$ = 8.1 Hz), 3.57 (ddd, 1H, H-5β, $^3J_{4,5}$ = 8.1, $^3J_{5,6}$ = 2.0, 6.1 Hz), 2.81–2.65 (m, 2H, S*C*H$_2$CH$_3$), 2.64–2.48 (m, 2H, SCH_2CH$_3$), 2.08 (2 ×s, 2 × 3H, 2 × CH_3COO), 1.28 (m, 3H, SCH$_2$CH_3), 1.24 (m, 3H, SCH$_2$-CH_3), 1.11–0.84 (m, 2 × *tBu*Ph$_2$Si, 2 × ROSi*iPr*$_2$OSi*iPr*$_2$OR) ppm. ^{13}C NMR (100.67 MHz, CDCl$_3$): δ = 169.40 (CH$_3$*C*OO), 135.81–135.32, 133.69, 133.42, 129.54–127.56 (2 × *t*Bu*Ph*$_2$Si), 82.83 (C-1β), 81.13 (C-5β), 80.70 (C-1a), 79.04, 73.00 (C-3β, C-4β), 83.17 (C-3a), 73.53 (C-4a), 72.89 (C-2a), 72.73 (C-5a), 72.06 (C-2β), 63.43 (C-6a, C-6β), 26.81 (2 × (*C*H$_3$)$_3$CPh$_2$Si), 23.69 (S*C*H$_2$CH$_3$β), 20.86 (*C*H$_3$COOβ), 19.25 ((CH$_3$)$_3$*C*Ph$_2$Si), 17.40–17.15 ((*C*H$_3$)$_2$CH), 14.86 (SCH$_2$*C*H$_3$β), 12.86, 12.74, 12.29, 12.14 (4 × (CH$_3$)$_2$*C*Hβ) ppm.

Diosgen-3β-yl 2-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxane-1,3-diyl)-β-D-glucopyranoside (22)

Method e (*cf.* Scheme 3). Diosgenin (**4**, 122 mg, 0.29 mmol), **20** (200 mg, 0.27 mmol), anhydr. diethyl ether (2.2 mL) and anhydr. dichloromethane (2.2 mL) were placed under an argon atmosphere in a dry two neck flask together with powdery and dry MS 4 Å (*ca.* 500 mg) and were stirred for 1 h. Then *N*-iodosuccinimide (61 mg, 0.27 mmol) was added. After another 2 h of stirring a solution (0.2 mL) of triflic acid (0.1 mL) in Et$_2$O–CH$_2$Cl$_2$ 1 : 1 (9.9 mL) was added *via* a syringe. The reaction was monitored by TLC (PE–EA 15 : 1). A five-fold excess of dichloromethane was added and molecular sieves were removed by filtration over Celite. The Celite was washed with dichloromethane. The red filtrate was decolorised with 10% aqueous sodium disulfite solution, washed once with saturated NaHCO$_3$, and dried over sodium sulfate. The solvent was removed and the crude product was purified twice by flash

chromatography (PE–EA 15 : 1) to give compound **22** (153 mg, 0.139 mmol, 52%).

Method *f* (*cf.* Scheme 3). Diosgenin (**4**, 232 mg, 0.56 mmol), **21** (380 mg, 0.51 mmol) and MS 4 Å (*ca.* 500 mg) were stirred under argon in dichloromethane (40 mL) for 1 h. Then DMTST (394 mg, 1.53 mmol) was added. The reaction mixture was stirred for 24 h at rt. After completion triethylamine (0.5 mL) was added and the mixture was stirred for another 10 min. The molecular sieves were removed by filtration over Celite, and the filtrate was evaporated in the presence of a suitable amount of silica gel. The obtained powdery mixture was placed on a prepacked column of silica gel and chromatographed with PE–EA 30 : 1 to give compound **22** (151 mg, 0.142 mmol, 28%).

Colourless solid; $C_{63}H_{98}O_{10}Si_3$ (MW 1099.703 g mol^{-1}); mp: 85.3 °C; $[\alpha]_D = -36.8$ ($c = 1$, $CHCl_3$); TLC (PE–EA 15 : 1): $R_f = 0.24$ (UV, H_2SO_4). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.68$ (d, 4H, Ar), 7.45–7.35 (m, 6H, Ar), 5.34 (br d, 1H, H-6, $^3J = 4.1$ Hz), 4.88 (dd~t, 1H, H-2′, $^3J_{1',2'}$, $^3J_{2',3'} = 8.7$ Hz), 4.51 (d, 1H, H-1′, $^3J_{1',2'} = 8.1$ Hz), 4.41 (q, 1H, H-16, $^3J = 7.1$, 7.6 Hz), 3.98 (dd, 1H, H-6′a, $^3J_{5',6'a} \approx 0$, $^2J_{6'a,6'b} = 10.7$ Hz), 3.80 (dd, 1H, H-6′b, $^3J_{5',6'b} = 6.6$, $^2J_{6'a,6'b} = 10.7$ Hz), 3.71 (dd~t, 1H, H-3′, $^3J_{2',3'} = 8.6$, $^3J_{3',4'} = 9.2$ Hz), 3.60 (dd~t, 1H, H-4′, $^3J_{3',4'} = 9.2$, $^3J_{4',5'} = 8.6$ Hz), 3.56–3.44 (m, 2H, H-3, H-26$_{eq}$), 3.41–3.34 (m, 2H, H-5′, H-26$_{ax}$), 2.33–2.18 (m, 2H), 2.05 (s, 3H, CH_3COO), 1.90–1.40, 1.29–0.76 (m, steroid H) ppm. ^{13}C NMR (100.67 MHz, $CDCl_3$): $\delta = 169.2$ (CH_3COO), 140.8 (C-5), 135.7, 135.5, 133.7, 133.6, 129.5, 127.5 (Ar), 121.4 (C-6), 109.3 (C-22), 99.7 (C-1′), 80.8 (C-16), 79.4 (C-3), 77.7 (C-3′), 76.9 (C-5′), 73.4 (C-2′), 66.7 (C-26), 63.8 (C-6′), 62.1, 56.5, 50.1, 41.6, 31.6, 30.3 (CH), 40.3, 36.9 (C-10, C-13), 39.7, 38.6, 37.4, 32.1, 32.0, 29.5, 28.8 (CH_2), 26.8 (C(CH_3)$_3$), 20.9 (CH_3COO), 17.3–17.1 (steroid C, CH(CH_3)$_2$), 19.4, 19.3, 16.4, 14.5 (C-18, −19, −21, −27), 12.7–12.1 (CH(CH$_3$)$_2$) ppm.

Diosgen-3β-yl 6-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxane-1,3-diyl)-β-D-glucopyranoside (23)

Diosgenin (**4**, 352 mg, 0.85 mmol), **20** (600 mg, 0.8 mmol), anhydr. diethyl ether (5 mL) and anhydr. dichloromethane (5 mL) were placed under argon atmosphere in a dry two neck flask together with powdery and dry MS 4 Å ((1 g) and were stirred for 1 h. Then *N*-iodosuccinimide (181 mg, 0.8 mmol) was added. After another 2 h of stirring a solution (0.2 mL) of triflic acid (0.1 mL) in Et_2O–CH_2Cl_2 1 : 1 (9.9 mL) was added *via* a syringe. The reaction was monitored by TLC (PE–EA 15 : 1, R_f(**22**) = 0.24). A five-fold excess of dichloromethane was added and molecular sieves were removed by filtration over Celite. The Celite was washed with dichloromethane. The red filtrate was decolorised with 10% aqueous sodium disulfite solution, washed once with saturated $NaHCO_3$, and dried over sodium sulfate. The solvent was removed and the crude product was purified twice by flash chromatography (PE–EA 15 : 1) to give compound **22**, which was converted as follows. Under argon the purified compound was placed in anhydr. methanol (10 mL) and small portions of dichloromethane were added until the solid was completely dissolved. A solution (5 mL) of potassium carbonate (5.6 g) in methanol (70 mL) was added and the reaction mixture was stirred for 3 d at rt. The reaction was monitored by TLC (PE–EA 15 : 1, R_f(**22**) = 0.24). The pH was lowered to 4 by stirring with Amberlite IR 120 (H^+). The resin was removed by filtration and the solvent was evaporated. The crude product was purified by flash chromatography (PE–EA 15 : 1) to give compound **23** (355 mg, 0.336 mmol, 42%). Colourless solid; $C_{61}H_{96}O_9Si_3$ (MW 1057.666 g mol^{-1}); mp: 92.8–93.3 °C; $[\alpha]_D = -46.5$ ($c = 1$, $CHCl_3$); TLC (PE–EA 15 : 1): $R_f = 0.15$ (UV, H_2SO_4). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.70$–7.65 (m, 4H, Ar), 7.43–7.30 (m, 6H, Ar), 5.35 (d, 1H, H-6, $^3J = 5.1$ Hz), 4.47 (d, 1H, H-1′, $^3J_{1',2'} = 8.1$ Hz), 4.41 (ddd~q, 1H, H-16, $^3J = 7.6$, 7.1 Hz), 3.98 (dd, 1H, H-6′a, $^3J_{5',6'a} = 1.5$, $^2J_{6'a,6'b} = 10.7$ Hz), 3.78 (dd, 1H, H-6′b, $^3J_{5',6'b} = 6.6$, $^2J_{6'a,6'b} = 10.7$ Hz), 3.70–3.59 (m, 2H, H-3, H-3′), 3.54 (dd~t, 1H, H-4′, $^3J = 9.2$, 8.6 Hz), 3.47 (dd, 1H, H-26$_{eq}$), 3.44–3.34 (m, 3H, H-2′, H-5′, H-26$_{ax}$), 2.43 (m, 1H), 2.32 (m, 2H), 2.09–0.76 (m, 68H, steroid H, *i*Pr, *t*Bu) ppm. ^{13}C NMR (100.67 MHz, $CDCl_3$): $\delta = 140.8$ (C-5), 135.7, 135.6, 133.6, 129.5, 127.6 (Ar), 121.2 (C-6), 109.3 (C-22), 100.7 (C-1′), 81.0 (C-16), 80.1, 79.0 (C-3, C-3′), 77.8, 74.2 (C-2′, C-5′), 73.2 (C-4′), 67.1 (C-26), 63.9 (C-6′), 62.1, 56.5, 41.6, 40.0, 38.9, 37.2, 32.2, 31.4, 30.7, 30.3, 30.0, 29.4, 28.3 (steroid C), 26.8 (C(CH_3)$_3$), 19.4, 19.3, 17.3–17.2, 16.3, 14.5 (C-18, −19, −21, −27, CH(CH_3)$_2$, C(CH_3)$_3$), 12.8–12.2 (CH(CH$_3$)$_2$) ppm.

Diosgen-3β-yl 6-*O*-*tert*-butyldiphenylsilyl-2-*O*-(2,3-*O*-isopropylidene-4-*O*-*p*-methoxybenzoyl-L-rhamnopyranosyl)-3,4-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxane-1,3-diyl)-β-D-glucopyranoside (24)

In a dried two neck flask the donor **12** (52 mg, 0.14 mmol) and acceptor **23** (112 mg, 0.106 mmol) were dissolved in anhydr. diethyl ether (1.1 mL) and anhydr. dichloromethane (1.1 mL) under an argon atmosphere. Powdery and activated molecular sieves 4 Å (*ca.* 1 g) were added and stirred for 1 h. Then NIS (32 mg, 0.14 mmol) was added and the reaction was monitored by TLC (PE–EA 10 : 1, R_f(**23**) = 0.20, R_f(**12**) = 0.04). A five-fold excess of dichloromethane was added and molecular sieves were removed by filtration over Celite. The Celite was washed with dichloromethane. The red filtrate was decolorised with 10% aqueous sodium disulfite solution, washed once with saturated $NaHCO_3$, and dried over sodium sulfate. The solvent was removed and the crude product was purified twice by flash chromatography (PE–EA 10 : 1) to give compound **24** (21 mg, 0.015 mmol, 14%, α : β = 2.9 : 1 by ^{1}H NMR). Colourless solid; $C_{78}H_{116}O_{15}Si_3$ (MW 1378.003 g mol^{-1}); TLC (PE–EA 10 : 1): $R_f = 0.13$ (UV, H_2SO_4). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.01$–7.95 (m, 2H, $CH_3OC_6H_4COO$), 7.70–7.65 (m, 4H, Ar), 7.43–7.31 (m, 6H, Ar), 6.87 (d, 2H, $CH_3OC_6H_4COO$, $^3J = 8.8$ Hz), 5.54 (s, 1H, H-1″), 5.40 (d, 1H, H-6, $^3J = 5.0$ Hz), 5.31 (d, 1H, H-6β, $^3J = 5.0$ Hz), 5.11 (d, 1H, H-1″β, $^3J_{1'',2''} = 1.3$ Hz), 5.08 (dd, 1H, H-4″, $^3J_{3'',4''} = 7.6$, $^3J_{4'',5''} = 10.6$ Hz), 5.02 (dd, 1H, H-4″β, $^3J_{3'',4''} = 6.0$, $^3J_{4'',5''} = 8.2$ Hz), 4.58 (d, 1H, H-1′β, $^3J_{1',2'} = 8.2$ Hz), 4.49 (d, 1H, H-1′, $^3J_{1',2'} = 7.9$ Hz), 4.47–4.38 (m, 2H, H-16, H-5″), 4.37–4.34 (m, 2H, H-2″β, H-3″β), 4.29 (dd, 1H, H-3″, $^3J_{2'',3''} = 5.4$, $^3J_{3'',4''} = 7.3$ Hz), 4.22 (d, 1H, H-2″, $^3J_{2'',3''} = 5.4$ Hz), 4.01–3.97 (m, 2H, H-6′a, H-6′aβ), 3.85 (s, 3H, OMe), 3.83–3.72 (m, 4H, H-3′, H-3′β, H-6′b, H-6′bβ), 3.71–3.62 (m, 2H, H-3, H-2′), 3.61–3.54 (m, 2H, H-3β, H-2′β), 3.54–3.44 (m, 4H, H-4′, H-4′β, H-26a, H-26aβ), 3.43–3.32 (m, 4H, H-5′, H-5′β, H-26b, H-26bβ), 2.47–0.75 (m, steroid H, ^{i}Pr, ^{t}Bu) ppm. ^{13}C NMR (100.67 MHz, $CDCl_3$): $\delta = 165.4$ ($CH_3OC_6H_4COO$), 135.6–127.6 (Ar), 121.6 (C-6), 113.5 (γ-$CH_3OC_6H_4COO$), 109.3 (C-22), 99.9 (C-1′), 97.4 (C-1″), 80.9 (C-3′), 80.8 (C-16), 79.0 (C-3), 77.5 (C-5′), 77.3 (C-2′), 75.9, 75.8 (C-2″, C-3″), 75.6 (C-4″), 73.0 (C-4′), 66.4 (C-26), 64.0 (C-6′, C-5″), 55.4 ($CH_3OC_6H_4COO$), 41.6–12.2 (steroid C, *i*Pr, *t*Bu) ppm.

Diosgen-3β-yl 2-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-glucopyranoside (25)

In a 100 mL round flask acceptor **23** (96 mg, 0.09 mmol) and donor **15**[9] (84 mg, 0.16 mmol, 1.8 eq) were dissolved under an argon atmosphere in fresh anhydr. diethyl ether (80 mL). MS 4 Å (*ca.* 2 g) was added, the flask was sealed with a septum, an argon filled balloon was attached and the mixture was stirred for 2 h at rt. The reaction was started by addition of DMTST (120 mg, 0.46 mmol, 5 eq.), and the mixture was stirred for 12 h at rt. To stop the reaction triethylamine (0.2 mL) was added and the mixture was stirred for 10 min. The molecular sieves were filtered over Celite. Silica gel (*ca.* 10 mL) was added to the

filtrate and the solvent was removed. The obtained powdery mixture was placed on a prepacked column of silica gel (PE–EA 30 : 1) and chromatographed with PE–EA 30 : 1 ⟶ PE–EA 10 : 1 to give compound **25** (74 mg, 0.05 mmol, 53%). Colourless plates; $C_{88}H_{118}O_{16}Si_3$ (MW 1516.125 g mol^{-1}); calc.: C 69.71, H 7.84; found: C 69.01, H 7.88%; mp: 117.6 °C; $[\alpha]_D$ = +27.7 (*c* = 1, $CHCl_3$); TLC (PE–EA 5 : 1): R_f = 0.36 (UV, H_2SO_4). MALDI TOF MS (DHB, positive mode): 1515.94 [M + H]$^+$ (calc.: 1515.78), 1537.98 [M + Na]$^+$ (calc.: 1537.76), 1553.94 [M + K]$^+$ (calc.: 1553.74). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04, 7.93, 7.80 (3 × dd, 3 × 2H, *o*-Bz, $J_{o,m}$ = 7.1, $J_{o,p}$ = 1.0, 1.5 Hz), 7.69 (dd, 4H, *o*-Si*Ph*$_2$*t*Bu, $J_{o,m}$ = 6.6, $J_{o,p}$ = 1.5 Hz), 7.60 (dt, 1H, *p*-Bz, $J_{m,p}$ = 7.6, $J_{o,p}$ = 1.0, 1.5 Hz), 7.52–7.45 (m, 2H, *m*/*p*-Bz), 7.45–7.21 (m, 11H, *m*/*p*-Bz, *m*/*p*-Si*Ph*$_2$*t*Bu), 5.83–5.77 (m, 2H, H-2″, H-3″), 5.63 (dd~t, 1H, H-4″, $^3J_{3'',4''}$ = 9.7, $^3J_{4'',5''}$ = 10.2 Hz), 5.53 (br s, 1H, H-1″, $J_{1'',2''} \approx$ 0 Hz), 5.45 (br d, 1H, H-6, *J* = 4.6 Hz), 4.94 (dq, 1H, H-5″, $^3J_{4'',5''}$ = 10.2, $^3J_{5'',6''}$ = 6.2 Hz), 4.64 (d, 1H, H-1′, $^3J_{1',2'}$ = 8.1 Hz), 4.44 (ddd~q, 1H, H-16, ^3J = 7.6, 14.8 Hz), 4.01 (dd, 1H, H-6′a, $^3J_{5',6'a}$ = 1.0, $^2J_{6'a,6'b}$ = 9.2 Hz), 3.91 (dd~t, 1H, H-3′, ^3J = 9.2, 8.2 Hz), 3.81–3.70 (m, 3H, H-3, H-2′, H-6′b), 3.54–3.42 (m, 3H, H-4′, H-5′, H-26a), 3.39 (dd~t, 1H, H-26b, *J* = 11.2, 10.7 Hz), 2.63 (m~dd, 1H, H-4eq, $^2J_{4eq,4ax}$ = 13.2, $^3J_{3,4eq}$ = 2.5 Hz), 2.46 (m~t, 1H, H-4ax, $^2J_{4eq,4ax}$ = 13.2, $^3J_{3,4ax}$ = 11.2 Hz), 2.16 (m~d, 1H, CH, *J* = 11.7 Hz), 2.07–1.97 (m, 2H, CH), 1.93–0.77 (m, steroid H, Si–*i*Pr), 1.37 (d, 3H, H-6″), 1.07 (bs, 9H, Si–*t*Bu). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 165.8, 165.7, 165.3 (3 × C_6H_5COO), 140.5 (C-5), 135.8–135.7 (Si*Ph*$_2$*t*Bu), 133.8–133.1 (*m*-Bz), 130.0–129.6 (*o*-Bz), 128.6–127.7 (Ar), 122.1 (C-6), 109.4 (C-22), 100.0 (C-1′), 98.2 (C-1″), 81.2 (C-3′), 81.0 (C-16), 79.5 (C-3), 76.8 (C-5′), 76.6 (C-2′), 73.6 (C-4′), 72.2 (C-4″), 70.5, 70.3 (C-2″, C-3″), 67.0 (C-26), 66.5 (C-5″), 64.2 (C-6′), 39.9 (C-4), 37.4, 37.0 (C-10, C-13), 62.3, 56.6, 50.2, 41.8, 31.7, 30.4 (C-8, C-9, C-14, C-17, C-20, C-25), 40.4, 39.2, 32.3, 32.1, 31.6, 30.2, 29.0, 20.9 (C-1, C-2, C-7, C-11, C-12, C-15, C-23, C-24), 26.9 (SiC(CH_3)$_3$), 19.4, 17.4, 16.4, 14.7 (C-18, C-19, C-21, C-27), 17.5–17.3 (SiCH(CH_3)$_2$, C-6″), 13.1, 12.7, 12.3, 12.1 (SiCH(CH_3)$_2$).

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