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Chapter 3

The Cyanopivaloyl Ester: A New Protecting Group in the Assembly of Oligorhamnans

Introduction

The success of an oligosaccharide or glycoconjugate synthesis campaign hinges on the protecting group strategy followed. Protecting groups are key to discriminate the different hydroxyl and amino groups on the carbohydrate rings and have an important effect on the reactivity of the carbohydrate building block. As well, they can be decisive in the stereoselective outcome of a glycosylation. Neighboring group participation by a C-2-O-acyl group is an extremely powerful means to ensure the stereoselective formation of 1,2-trans-glycosidic linkages. Of all ester-type protecting groups, the pivaloyl (Piv) ester is least prone to provide orthoester side products, formed by attack of the nucleophile at the dioxolenium carbon instead of the anomeric center. The neopentyllic nature of the pivaloyl dioxolenium ion makes this intermediate significantly less susceptible to nucleophilic attack. Where this steric protection is beneficial during a glycosylation reaction, the bulk of the Piv group can pose a problem during the removal of this protecting group, necessitating harsh nucleophilic conditions for its removal. To enable cleavage of Piv-type esters under less strenuous conditions, various Piv-analogues have been introduced bearing a masked nucleophile four or five atoms away from the Piv-carbonyl group. Liberating this nucleophile sets the stage for intramolecular attack allowing the smooth deprotection of the Piv ester. Figure 1 depicts some members of the relay-cleavage pivaloyl family.

Figure 1. Pivaloyl analogues and the new PivCN.

2,2-Dimethylpentenoate can be cleaved by hydroboration of the double bond and ensuing base mediated cleavage. Piv-analogues and bear a distal, masked hydroxyl group that can be liberated by either fluoride or methanolate to release the internal nucleophile. Recently a para-methoxyphenyl based Piv-ester and azido-Piv group were introduced, that can be removed under oxidative and reductive conditions, respectively. The mutual orthogonality of these Piv-groups was exploited in the assembly a Streptococcus mutans oligosaccharide and also the applicability of the azido-Piv group in the solid phase assembly of a β-glucan oligomer was showed. In this chapter, a new relay-cleavage pivaloyl family member is introduced: the cyanopivaloyl (PivCN) group (Figure 1). This group was developed to streamline the global deprotection of oligosaccharides. It was reasoned that a pivaloyl group that is removable under hydrogenation conditions, commonly employed to remove benzyl esters in the final stage of an oligosaccharide synthesis, could abridge the endgame. As described in this chapter, the
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reagents to introduce the PivCN-group, cyanopivalic acid 8 and the corresponding acid chloride (9, PivCN-Cl) can be readily synthesized on large scale and the protective group can be easily introduced on carbohydrate building blocks. It is stable under commonly used reaction conditions and can be removed through reduction of the cyano-function. The PivCN group was applied in the assembly of two bacterial rhamnan structures: a tetrasaccharide, representing part of the backbone structure of the exopolysaccharide of Group A Streptococcus, and an Enterococcus faecium derived hexarhamnoside (figure 2, scheme 2).

**Figure 2.** Bacterial rhamnan structures.

Entrococcus faecium

Group A Streptococcus

**Results and Discussion**

The synthesis of required reagents, cyanopivalic acid and the corresponding chloride (PivCN-Cl) is depicted in Scheme 1. They can be generated through a three or four step reaction sequence in multigram quantities. Reaction of methyl isobutyrate with bromoacetonitrile under the influence of freshly prepared LDA, resulted in cyanide 7. Saponification of the methyl ester then provided acid 8, which can be reacted with oxalylchloride to yield acid chloride 9. Both reagents can be used without further purification.

**Scheme 1.** Synthesis of PivCN acid 8 and PivCN chloride 9.

\[ \text{Reagents and conditions: } a) \text{ diisopropylamine, n-BuLi, THF, } -78^\circ\text{C}, \text{ ii. } \text{Bromoacetonitrile, THF, } -78^\circ\text{C (44\% over 2 steps); b) KOH, H}_2\text{O/EtOH, } 95^\circ\text{C (86\%); c) (COCl)}_2, \text{ DCM, } 50^\circ\text{C (100\%).} \]

With acid 8 and chloride 9 in hand, the introduction of the PivCN ester and its use as a protecting group in oligosaccharide synthesis was explored. Two bacterial rhamnan structures, the backbone of the exopolysaccharide of Group A Streptococcus, and an Enterococcus faecium capsular polysaccharide derived hexarhamnoside, were chosen as synthetic targets to validate the performance of the PivCN group in oligosaccharide
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The Enterococcus faecium capsular polysaccharide is composed of trisaccharide repeating units featuring α-(1,3)- and α-(1,2)-rhamnosyl linkages, whereas the Group A Streptococcus repeating unit is a dirhamnoside with α-(1,3) and α-(1,2)-linkages (figure 2). The target structures for the current study are depicted in Scheme 2.

Scheme 2. Target compounds and retrosynthetic analysis.

Tetrasaccharide 10 and hexasaccharide 11 each contain two repeating units of the respective capsular polysaccharides. It was envisaged that these two target structures could be assembled from building blocks 12, 13 and 14, which are equipped with a levulinoyl group, that serves as a temporary protecting group, to be removed to allow elongation of the rhamnan chains, and/or a PivCN group, which serves as a permanent participating protecting group. Linker 15 is used to cap the reducing end of the target rhamnans and can serve as a handle for future conjugation chemistries.

The assembly of the building blocks is depicted in Scheme 3. Known diol 16 can be selectively alkylated on the C-3-OH through the intermediacy of the cyclic tin ketal with either benzylbromide or para-methoxybenzylchloride to give rhamnosides 17 and 18 in 86% and 73% yield respectively. Esterification of the C-2-hydroxyl group in 17 with levulinic acid yields donor 13 in excellent yield (96%). Thioglycoside 13 can be converted into the corresponding hemiacetal 19 by N-bromosuccinimide driven hydrolysis (78%). Installation of the N-phenyl trifluoroacetimidate group on the anomeric alcohol then delivers 20 in high yield (99%). para-Methoxybenzyl (PMB) protected rhamnoside 18 is treated with acid chloride 9 and pyridine at elevated temperature to provide fully protected compound 21 in 72% yield. Under standard esterification conditions, applying the PivCN acid in concert with N,N’-di-isopropylcarbodiimide (DIC) and 4-dimethylaminopyridine (DMAP), compound 21 was obtained in good yield (74%). To remove the PMB ether, deprotection conditions using trifluoroacetic acid and a thiol scavenger were explored.
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Besides the desired alcohol 22, these conditions also provided deoxy-L-glucoside 23, bearing the PivCN group at its C-3-OH and a C-2-thiophenol group, as a prominent side product. This product is likely the result of the mechanism depicted in Scheme 3. Under the acidic conditions used, the PivCN ester can be protonated and subsequently attacked by the neighboring C-3-alcohol. Migration of the PivCN ester to the C-3 position can be caused by the participating anomeric thiophenol moiety to provide an intermediate episulfonium ion. This is attacked at the anomeric center to provide deoxy-L-glucoside 23.31–33

Scheme 3. Building block synthesis.

Reagents and conditions: a) i. Bu₂SnO, toluene, 140°C, ii. BnBr, CsF, DMF (86%); b) LevOH, DIC, DMAP, DCM, 0°C (96%); c) NBS, acetone/H₂O (78%); d) CIC(=NPh)CF₃, Cs₂CO₃, acetone (99%); e) i. Bu₂SnO, toluene, 140°C, ii. PMBCl, CsF, DMF (73%); f) 8, DIC, DMAP, DCM (74%) or 9, 100°C, pyridine (72%); g) TFA, PhSH, DCM, 0°C (73%) or HCl/HFIP, TES, DCM/HFIP, 0°C (76%); h) LevOH, DIC, DMAP, DCM, 0°C (99%); i) TfOH, DCM, 0°C (93%).

As shown in Chapter 2, a catalytic amount of HCl in 2,2,2,3,3,3-hexafluoro-iso-propanol (HFIP) could be used to cleave electron rich benzyl ethers in a mild and fast manner.34 Application of these conditions proved effective here to remove the C-3-O-PMB from rhamnoside 21. The reaction time had to be carefully controlled as a prolonged reaction time led to activation of the anomeric thiophenol function. The liberated alcohol in compound 22 was masked with a levulinoyl group to provide building block 12. Rhamnoside 22 was also used to generate disaccharide building block 14. To this end, N-phenyltrifluoroacetimidate rhamnoside 20 and thiorhamnoside acceptor 22 were combined...
in a chemoselective glycosylation reaction to provide the dirhamnoside 14 in high yield (93%) and with complete stereoselectivity.

Having assembled the required building blocks, the two target oligosaccharides were assembled (Scheme 4). First, the linker-functionalized rhamnoside 24 was generated in a stereoselective, NIS/TMSOTf-mediated glycosylation\(^{35}\) of donor 12 with protected aminohexanol 15.

**Scheme 4.** Synthesis of the fully protected tetra- and hexasaccharide.

Reagents and conditions: a) 12, NIS, TMSOTf, DCM, 0°C (82%); b) H\(_2\)NNH\(_2\)•AcOH, pyridine/AcOH (73%); c) 20, NIS, TMSOTf, DCM, 0°C (93%); d) H\(_2\)NNH\(_2\)•AcOH, pyridine/AcOH (90%); e) 14, NIS, TMSOTf, DCM, 0°C (94%); f) H\(_2\)NNH\(_2\)•AcOH, pyridine/AcOH (90%); g) 14, NIS, TMSOTf, DCM, 0°C (52%); h) H\(_2\)NNH\(_2\)•AcOH, pyridine/AcOH (78%); i) 12, NIS, TMSOTf, DCM, -40°C (75%); j) H\(_2\)NNH\(_2\)•AcOH, pyridine/AcOH (67%); k) 14, NIS, TMSOTf, DCM, -40°C (88%); l) H\(_2\)NNH\(_2\)•AcOH, pyridine/AcOH (96%)

Next the levulinoyl ester was removed to provide the monosaccharide acceptor building block 25. Surprisingly, the deprotection of the levulinoyl group required optimization. Whereas the Lev group was readily removed from compound 12 in 78% yield, applying the same conditions on rhamnoside 24 resulted in a ~1:1 mixture of 25 and 25\(a\), in which the PivCN group migrated to the 3-O position. The modified Piv group does seem to have the
tendency to migrate, which could be elaborated to the remote effect of the CN group. When an excess of hydrazine acetate was used, the levulinoyl group was removed in 73% yield. This monosaccharide was elongated with monorhamnoside 13 to give dimer 26 in 93% yield. Liberation of the C-2”-OH by treatment of 26 with hydrazine set the stage for the next glycosylation. In this condensation, the dimers 14 and 27 were united to provide the fully protected target tetrasccharide 28 in high yield.

Next the assembly of the protected hexarhamnan 34 was undertaken. To this end linker bearing monorhamnose 25 and dirhamnoside 14 were coupled under the agency of NIS/TMSOTf to provide trisaccharide 30 in 52% yield. Delevulinuylation of 30 was followed by a glycosylation with monorhamnose donor 12 to provide the tetrasccharide 32 in 75% yield. Removal of the Lev-ester then paved the way for the final glycosylation in which tetramer 33 was elongated with dirhamnoside 14 giving the fully protected hexarhamnan in 88% yield.

With the two fragments in hands, global deprotection was commenced. First the levulinoyl groups were removed. Next all benzyl ethers and cyano groups were reduced by hydrogenolysis using Pd(OH)_{2}/C.

Scheme 5. Deprotection of the tetra- and hexasaccharide.

Reagents and conditions: a) i. Pd(OH)_{2}/C, AcOH, H_{2}, H_{2}O/THF/tBuOH, ii. Et_{3}N, H_{2}O (100%); b) i. Pd(OH)_{2}/C, AcOH, H_{2}, H_{2}O/THF/tBuOH, ii. Et_{3}N, H_{2}O (80%);

The reduction was achieved in two stages, the first of which was executed in THF/tBuOH/H_{2}O/AcOH solvent system. After filtration the partially deprotected hexasaccharide was taken up in water and subjected to a second hydrogen event. During the
hydrogenation AcOH was added to prevent deactivation of the catalyst. Reduction of the cyano-groups released the primary amines of the Piv-like esters, which under the reaction conditions used are protonated. To affect ring closure, release the 2,2-dimethyl-γ-butyrolactam and complete the removal of the PivCN esters the crude products were treated with triethylamine in water. The release of the 2,2-dimethyl-γ-butyrolactam could be easily followed by NMR analysis using the characteristic triplets of the liberated lactam. After completion of the reaction, the crude tetra- and hexasaccharide were purified by size exclusion chromatography to provide Group A Streptococcus tetrarhamnan 10 and Entrococcus faecium hexarhamnan 11 in 100% and 80% respectively.

Conclusion

The introduction of the cyanopivaloyl ester as a novel hydroxyl protecting group is described. It features a cyano moiety appended two atoms away from the ester carbonyl to allow for a relay-cleavage of the pivaloyl type ester. This cleavage mechanism alleviated one of the major drawbacks of the pivaloyl ester, that is, its difficult removal.

The applicability of the novel protecting group is shown in the assembly of two bacterial oligorhamnans. It represents a robust protecting group that tolerates many functional group manipulations and withstands both (Lewis) acidic as well as mild basic conditions. It is a new member of the family of pivaloyl-type protecting groups and may be used in combination with other pivaloyl type esters, such as the recently introduced azidopivaloyl group, as a (semi)-orthogonal pair for the streamlined synthesis of carbohydrates and other complex (bio)molecules.
Experimental Section

General experimental procedures. All chemicals were used as received unless stated otherwise. ¹H and ¹³C NMR spectra were recorded on a 400/100 MHz, 500/125 MHz, 600/150 MHz or a 850/214 MHz spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard. Coupling constants are given in Hz. All individual signals were assigned using 2D-NMR spectroscopy, HH-COSY, HSCQ and HMBC. IR spectra are reported in cm⁻¹. Flash chromatography was performed on silica gel 60 (0.04 – 0.063 mm). TLC-analysis was followed by detection with UV-absorption (254 nm) where applicable and by spraying with 20% sulfuric acid in ethanol followed by charring at ~150 °C or by spraying with a solution of (NH₄)₂MoO₄·xH₂O (25 g/l) and (NH₄)₂Ce(SO₄)₃·H₂O (10 g/l) in 10% sulfuric acid in water followed by charring at 50 °C. LC-MS standard eluents used were A: 100% H₂O, B: 100% acetonitrile, C: 1% TFA in H₂O. The column was used was a C18 column (4.6 mm × 50 mmL, 3µ particle size). All analyses were 13 min, with a flow-rate of 1 ml/min. High-resolution mass spectra were recorded on a LTQ-Orbitrap equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 275°C) with resolution R=60.000 at m/z=400 (mass range = 150-4000) and diocetylphthalate (m/z=391.28428) as “lock mass”. High resolution mass measurements were performed on a Synapt G2-Si MALDI-TOF mass spectrometer equipped with a 355-nm laser. 1 uL samples were spotted on the MALDI-plate, followed by applying 1 uL of the the matrix solution (2,5-dihydroxybenzoic acid 100 mg/mL dissolved in H₂O : ACN : dimethylaniline 1 : 1 : 0.02). A laser frequency of 1000 Hz (power set at 60%) was used.

Methyl 3-cyano-2,2-dimethylpropanoate (7) A solution of LDA was prepared by adding n-butyllithium in hexanes (1.6 M, 134.8 mL, 215.7 mmol, 1 eq.) drop wise to a solution of diisopropylamine (33.4 mL, 238 mmol, 1.1 eq.) in THF (310 mL) at -78°C under argon. After 45 min no more bubbles appeared and methyl isobutyrate (28.2 mL, 246 mmol, 1.13 eq.) was added. After 1h of stirring at -78°C, bromoacetoneitrile (19.5 mL, 280 mmol, 1.26 eq.) was added. The resulting dark mixture was allowed to warm up gradually to room temperature and stirred overnight. The reaction was neutralized by the addition of 1M HCl (90 mL) and 2M HCl (240 mL) at 0°C. The mixture was diluted with sat. aq. NaCl, followed by extraction with EtO (3x). The combined organic layers were washed with sat. aq. NaHCO₃ (6x), H₂O (6x) and sat. aq. NaCl (1x), dried over MgSO₄, and concentrated in vacuo. Purification by column chromatography (19:1 PE/EtOAc to 4:1 PE/EtOAc and coevaporation with CHCl₃ resulted in the title compound as a light yellow oil (13.45 g, 95.3 mmol). Analytical data are identical to literature precendence.³⁶

3-cyano-2,2-dimethylpropanoic acid (8) A suspension was formed by the addition of H₂O (205 mL) and EtOH (35 mL) to compound 7 (13.45 g, 95.3 mmol, 1 eq.). Lithium hydroxide (98%) (5.85 g, 244 mmol, 2.5 eq.) was added and the mixture was refluxed at 95°C for 5.5h. The mixture was cooled to 8°C, quenched with 1M HCl to pH = 1, diluted with H₂O and extracted with EtOAc (2x). The combined organic layers were washed with sat. aq. NaCl, dried over MgSO₄ and concentrated in vacuo. Coevaporation with DCM and CHCl₃ resulted in an oil that crystallized out as a light yellow solid (10.41 g, 81.89 mmol, 33% in two steps). IR (neat): 750, 974, 1231, 1412, 1585, 1699, 2264, 2544, 2884, 3192, 3368 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 11.12 (bs, 1H, OH), 2.63 (s, 2H, CH₂), 1.42 (s, 6H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ: 181.5 (C=O), 117.4 (CN), 41.0 (Cq), 27.8 (CH₂). HRMS: [M+H]+ calcd. for C₇H₁₀NO₂ 128.07061, found 128.07055.

3-cyano-2,2-dimethylpropanoyl chloride (9) After coevaporation with anhydrous toluene, acid 8 (5.53 g, 43.5 mmol, 1 eq.) was dissolved in DCM (110 mL). Oxalylchloride (8.4 mL, 97.8 mmol, 2.2 eq.) was added at room temperature and the solution was refluxed at 40°C for 40 min allowing the gases produced during the reaction to be stripped by a stream of argon, after which the water cooling was closed and the DCM was allowed to evaporate at 50°C for 2h. The reaction mixture was cooled and concentrated in vacuo. The obtained oil was used directly without further purification. ¹H NMR (400 MHz, CDCl₃) δ: 2.70 (s, 2H, CH₂), 1.49 (s, 6H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ: 177.6 (C=O), 116.3 (CN), 50.6 (Cq), 27.8 (CH₂), 24.5 (CH₃).
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Phenyl 4-O-benzyl-1-thio-α-L-rhamnopyranoside (16) A solution of 80% acetic acid (950 mL) was added to phenyl 4-O-benzyl-2,3-di-O-isopropylidene-1-thio-α-L-rhamnopyranoside28 (73.8 g, 191 mmol) and heated to 70°C and stirred overnight after which TLC analysis showed complete consumption of the starting material. The reaction was cooled down to 0°C, neutralized with Et3N, diluted with H2O and extracted with EtOAc (2x). The combined organic layers were washed with sat. aq. NaHCO3 (5x) and sat. aq. NaCl (1x), dried over MgSO4 and concentrated in vacuo. Crystallization (EtOH) at -20°C resulted in the title compound as a white solid (58.3 g, 168.3 mmol, 88%). TLC: Rf 0.51 (2:1 PE/EtOAc). Analytical data are identical to literature precedence.28

Phenyl 3,4-di-O-benzyl-1-thio-α-L-rhamnopyranoside (17) Diol 1629 (3.47 g, 10.0 mmol, 1 eq.) was coevaporated with anhydrous toluene two times under argon and dissolved in anhydrous toluene (100 mL). Dibutyltin oxide (3.00 g, 12.1 mmol, 1.2 eq.) was added and the white suspension was heated to 105°C. The reaction was stirred overnight after which the clear solution was cooled down and concentrated in vacuo. After three times coevaporation with anhydrous toluene under argon, the oil was dissolved in DMF (100 mL). BnBr (1.6 mL, 13.5 mmol, 1.3 eq.) and CsF (3.05 g, 20.1 mmol, 0.1 eq.) were added. After 6h, TLC-MS and TLC analysis showed complete reaction and the reaction mixture was diluted with EtOAc, washed with H2O (2x), sat. aq. NaCl (2x), dried over MgSO4 and concentrated in vacuo. Purification by column chromatography (PE to 2:1 PE/EtOAc) yielded the title compound as a colorless oil (3.76 g, 8.62 mmol, 86%). Rf = 0.77 (2:1 PE/EtOAc). Analytical data are identical to literature precedence.29

Phenyl 3,4-di-O-benzyl-2-O-levulinoyl-1-thio-α-L-rhamnopyranoside (13) After coevaporation with anhydrous toluene (2x) under argon, compound 17 (9.79 g, 22.5 mmol, 1 eq.) was dissolved in freshly distilled DCM and cooled to 0°C. Levulinic acid (6.38 mL, 62.9 mmol, 2.8 eq.), N,N-diisopropylcarbodiimide (4.92 mL, 31.4 mmol, 1.4 eq.) and 4-dimethylaminopyridine (0.31 g, 2.54 mmol, 0.1 eq.) were added at 0°C. After 1.5h the reaction was allowed to warm up to room temperature and stirred overnight. After TLC-MS showed complete consumption of the starting material, the mixture was filtered over Celite and the filtrate was washed with sat. aq. NaHCO3 (2x) and sat. aq. NaCl (1x). The organic layer was dried over MgSO4, concentrated in vacuo and coevaporated with anhydrous toluene. Purification by column chromatography (3:1 PE/EtOAc) and coevaporation with CHCl3 (2x) resulted in the title compound as a yellow oil (11.50 g, 21.51 mmol, 96%). TLC: Rf 0.38 (7:2 PE/EtOAc); IR (neat): 689, 733, 873, 835, 903, 1022, 1051, 1098, 1132, 1198, 1300, 1358, 1439, 1472, 1728, 2968 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ: 7.44-7.26 (m, 15H, CH-arom), 5.59 (m, 1H, H-2), 5.41 (d, 1H, J = 1.2 Hz, H-1), 4.93 (d, 1H, J = 10.8 Hz, CH2 Bn), 4.70 (d, 1H, J = 11.2 Hz, CH2 Bn), 4.63 (d, 1H, J = 10.8 Hz, CH2 Bn), 4.54 (d, 1H, J = 11.2 Hz, CH2 Bn), 4.22 (dd, 1H, J = 9.5, 4.2 Hz, H-5), 3.90 (dd, 1H, J = 9.3, 3.3 Hz, H-3), 3.48 (t, 1H, J = 9.4 Hz, H-4), 2.76-2.69 (m, 4H, 2x CH2 Lev), 2.16 (s, 3H, CH3 Lev), 1.33 (d, 3H, J = 2.6 Hz, CH3-O); 13C NMR (100 MHz, CDCl3) δ: 206.3 (C=O Lev ketone), 172.1 (C=O Lev), 138.5, 137.9, 134.0 (Cq), 131.9, 129.2, 128.5, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8 (CH-arom), 86.1 (C-1), 80.3 (C-4), 78.4 (C-3), 75.6 (CH3 Bn), 71.8 (CH3 Bn), 70.9 (C-2), 69.1 (C-5), 38.1 (CH3 Lev), 30.0 (CH3 Lev), 28.3 (CH2 Lev), 18.0 (CH2-6); HRMS: [M+NH4]+ calcld. for C35H35NO10 552.24144, found 552.24165.

3,4-di-O-benzyl-2-O-levulinoyl-α-B-L-rhamnopyranoside (19) Compound 13 (1.07 g, 2.00 mmol, 1 eq.) was dissolved in acetone/water 3:1 (10 mL) and cooled to 0°C. N-Bromosuccinimide (1.08 g, 6.07 mmol, 3 eq.) was added and the mixture was stirred at 0°C. The reaction was allowed to warm up to room temperature after 10 min and stirred overnight. The reaction was quenched by addition of sat. aq. Na2S2O5, diluted with EtOAc and the organic layer was washed with sat. aq. NaHCO3 (2x), H2O (1x) and sat. aq. NaCl (1x). The organic layer was dried over MgSO4 and concentrated in vacuo. Purification by column chromatography (3:1 to 1:1 PE/EtOAc) yielded hemiacetal 19 (0.692 g, 1.56 mmol, 78%). TLC: Rf 0.53 (1:1 PE/EtOAc); IR (neat): 696, 735, 837, 912, 988, 1028, 1042, 1063, 1155, 1207, 1362, 1717, 1738 cm⁻¹; NMR assignment for the major isomer: 1H NMR (400 MHz, CDCl3) δ: 7.33-7.2 (m, 10H, CH-arom), 5.25 (m, 1H, H-2), 5.03 (s, 1H, H-1), 4.91-4.87 (m, 1H, CH2 Bn), 4.72-4.58 (m, 2H, CH2 Bn), 4.51-4.45 (m, 1H, CH3 Bn), 4.00-3.93 (m, 2H, H-3, H-5), 3.40 (t, 1H, J = 9.2 Hz, H-4), 2.76-2.60 (m, 4H, 2x CH2 Lev), 2.11 (s, 3H, CH3 Lev), 1.27 (d, 3H, J = 6.2 Hz, CH3-6); 13C NMR (100 MHz, CDCl3) δ: 206.9 (C=O Lev
ketone), 172.1 (C=O Lev), 138.3, 137.9 (C\_\text{arom}), 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.6 (C\_\text{arom}), 91.9 (C-1), 80.0 (C-4), 77.4 (C-3), 75.2 (CH\_3\text{Bn}), 71.4 (CH\_2\text{Bn}), 69.6 (C-2), 67.3 (C-5), 37.9 (CH\_2\text{Lev}), 29.7 (CH\_3\text{Lev}), 28.0 (CH\_2\text{Lev}), 18.0 (CH\_3-6). HRMS: [M+ NH\_4]^+ calcd. for C\_25H\_13NO\_7: 460.23298, found 460.23299.

3,4-di-O-benzyl-2-O-levulinoyl-1-((N-[phenyl]-trifluoroacetimidoyl)-α/β-l-rhamnopyranoside (20) To a solution of compound 19 (0.65 g, 1.47 mmol, 1 eq.) in acetone (7.4 mL), were added CIC(=NPh)CF\_3 (0.27 mL, 1.78 mmol, 1.2 eq.) and Cs\_2CO\_3 (0.72 g, 2.21 mmol, 1.5 eq.) at 0°C. The reaction was allowed to warm up to room temperature after 40 min and stirred for an additional 20 min. TLC analysis showed complete consumption of starting material. The reaction was diluted with EtOAc and the organic layer was washed with H\_2O (2x) and sat. aq. NaCl (1x). The organic layer was dried over MgSO\_4 and concentrated in vacuo. Purification by column chromatography (7:1 PE/EtOAc to EtOAc) yielded the title compound in a 4:1 α/β-ratio (0.894 g, 1.456 mmol, 99%). TLC: R\_f 0.54 (4:1 PE/EtOAc); IR (neat): 696, 735, 839, 943, 985, 1028, 1072, 1119, 1153, 1207, 1312, 1364, 1454, 1717, 1740, 2922 cm\(^{-1}\); NMR assignment for the major isomer: \(^1\)H NMR (400 MHz, CDCl\_3) δ: 7.35-7.23 (m, 12H, CH\_\text{arom}), 7.09-7.06 (m, 1H, CH\_\text{arom}), 6.86-6.80 (m, 2H, CH\_\text{arom}), 6.17 (bs, 1H, H-1), 5.49 (s, 1H, H-2), 4.92 (d, 1H, J = 10.8 Hz, CH\_3\text{Bn}), 4.71 (d, 1H, J = 11.2 Hz, CH\_2\text{Bn}), 4.63 (d, 1H, J = 10.8, CH\_2\text{Bn}), 4.55 (d, 1H, J = 11.2 Hz, CH\_3\text{Bn}), 3.98 (dd, 1H, J = 9.2, 2.8 Hz, H-3), 3.90 (m, 1H, H-5), 3.50 (t, 1H, J = 9.2 Hz, H-4), 2.75-2.63 (m, 4H, 2x CH\_2\text{Lev}), 2.08 (s, 3H, CH\_3\text{Lev}), 1.36 (d, 1H, J = 6.0 Hz, CH\_3-Lev) 13^C NMR (100 MHz, CDCl\_3) δ: 205.8 (C=O Lev ketone), 171.6 (C=O Lev), 143.2, 138.0, 137.5 (C\_\text{arom}), 128.7, 128.3, 128.3, 128.2, 128.0, 127.8, 127.8, 124.4, 199.3 (CH\_\text{aom}), 94.2 (C-1), 79.1 (C-4), 77.2 (C-3), 75.5 (CH\_3\text{Bn}), 71.9 (CH\_2\text{Bn}), 70.4 (C-5), 67.6 (C-2), 37.7 (CH\_2\text{Lev}), 29.6 (CH\_3\text{Lev}), 27.9 (CH\_2\text{Lev}), 17.9 (CH\_3-6). TLC-MS: m/z = 636.35 (M+Na\(^+\)).

Phenyl 4-O-benzyl-3-O-p-methoxybenzyl-1-thio-α-l-rhamnopyranoside (18) Diol 16 (6.94 g, 20.0 mmol, 1 eq.) was coevaporated with anhydrous toluene two times under argon and dissolved in anhydrous toluene (200 mL). Dibutyltin oxide (5.99 g, 24.1 mmol, 1.2 eq.) was added to the mixture, which was stirred overnight at 105°C. The clear solution was cooled to 0°C, concentrated in vacuo and two times coevaporated with anhydrous toluene under argon. The oil was dissolved in DMF (200 mL), followed by the addition of p-methoxybenzyl chloride (3.1 mL, 22.9 mmol, 1.12 eq.) and Cs\_F (6.08 g, 40.0 mmol, 2 eq.). After heating the mixture to 80°C for 5h, TLC analysis showed complete reaction, and the reaction mixture was cooled to 0°C, diluted with H\_2O and extracted two times with EtOAc. The combined organic layers were washed with H\_2O (2x) and sat. aq. NaCl (2x). The organic layer was dried over MgSO\_4 and concentrated in vacuo. Purification by column chromatography (PE to 2:1 PE/EtOAc) and (5:1 PE/EtOAc to 2:1 PE/EtOAc) resulted in the title compound as a clear oil (6.83 g, 14.6 mmol, 73%). TLC: R\_f 0.75 (2:1 PE/EtOAc). Analytical data are identical to literature precendence.\(^29\)

Phenyl 4-O-benzyl-3-O-p-methoxybenzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-1-thio-α-l-rhamnopyranoside (21) Method A: Crude chloride 9 (5.53 g, 43.5 mmol, 2 eq.) was cooled to 0°C and dissolved in pyridine (20 mL). A solution of compound 18 (10.14 g, 21.7 mmol, 1 eq.) in pyridine (2x 20 mL) was added to the crude chloride. After an addition of another 50 mL pyridine, the resulting dark mixture was heated to 110°C. After 1h, TLC and TLC-MS analysis showed complete reaction and the mixture was cooled to 0°C. The reaction mixture was diluted with EtOAc and washed with H\_2O (1x), 1M HCl (2x) and sat. aq. NaCl (2x). The organic layer was dried over MgSO\_4, concentrated in vacuo and coevaporated with toluene. Purification by flash column chromatography (8:1 PE/EtOAc \(\rightarrow\) 3:1 PE/EtOAc) and (10:1 PE/EtOAc \(\rightarrow\) EtOAc) and coevaporation with CHCl\_3 resulted in the title compound as an oil (9.04 g, 15.7 mmol, 72%), which contained 5% byproduct.

Method B: Acid 8 (3.49 g, 27.5 mmol, 2 eq.) and compound 18 (6.41 g, 13.75 mmol, 1 eq.) were coevaporated twice with anhydrous toluene after which they were dissolved in dry DCM (35 mL). The solution was cooled to 0°C and DIC (2.37 mL, 15.13 mmol, 1.1 eq.) and DMAP (0.17 g, 1.37 mmol, 0.1 eq.) were added. The reaction was allowed to stir overnight, after which TLC analysis showed conversion of the starting material in a higher running spot. Filtration over Celite followed by washing with sat. aq. NaHCO\_3, the organic layer was dried over
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MgSO₄ and concentrated. Purification by flash column chromatography (PE/EtOAc 1:0 → 4:1) yielded the fully protected rhamnopyranoside as a yellow oil (5.86 g, 10.2 mmol, 74%). TLC: Rf 0.68 (3:1 PE/ EtOAc); IR (neat): 691, 739, 820, 1030, 1084, 1098, 1136, 1246, 1300, 1454, 1472, 1515, 1612, 1734, 2874, 2974 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.46-7.43 (m, 2H, CH₂arom), 7.32-7.22 (m, 10H, CH₃arom), 6.87-6.84 (m, 2H, CH₂arom), 5.62 (m, 1H, H-2), 5.37 (d, 1H, J = 1.2 Hz, H-1), 4.90 (d, 1H, J = 10.8 Hz, CH₂Bn), 4.64 (d, 1H, J = 10.8 Hz, CH₂Bn), 4.60 (d, 1H, J = 10.8 Hz, CH₂PMB), 4.47 (d, 1H, J = 10.4 Hz, CH₂PMB), 4.24 (dq, 1H, J = 9.4, 6.2 Hz, H-5), 3.90 (dd, 1H, J = 9.2, 3.2 Hz, H-3), 3.80 (s, 3H, OCH₃ PMB), 3.42 (t, 1H, J = 9.2 Hz, H-4), 2.56 (s, 2H, CH₂PivCN), 1.36 (s, 6H, 2x CH₃PivCN), 1.32 (3d, 3H, J = 6.0 Hz, H-6); ¹³C NMR (100 MHz, CDCl₃) δ: 174.1 (C=O PivCN), 159.5, 138.3, 133.7 (C₆C₅arom), 132.1, 132.1, 130.0, 129.8 (CH₃arom), 129.3 (C₆C₅arom), 128.3, 128.0, 127.9, 127.8 (CH₂arom), 117.6 (CN), 114.0, 113.9 (CH₂arom), 86.0 (C-1), 79.9 (C-4), 78.1 (C-3), 75.5 (CH₂Bn), 71.6 (CH₂PMB), 71.4 (C-2), 69.1 (C-5), 55.4 (CH₂PMB), 41.2 (C₆PivCN), 28.1 (CH₂PivCN), 24.9, 24.8 (CH₂PivCN), 18.0 (CH₃-6); HRMS: [M+N⁺]⁺ calc. for C₃₅H₃₅NO₅S 593.26798, found 593.26838.

Phenyl 4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-1-thio-α-L-rhamnopyranoside (22)

**Method A:** To a solution of compound 21 (8.47 g, 14.72 mmol, 1 eq.) in DCM (75 mL), thiophenol (1.65 mL, 16.12 mmol, 1.1 eq.) was added and the mixture was cooled down to 0 °C, after which trifluoroacetic acid (7.5 mL) was added. The reaction mixture was stirred for 3h, after which TLC-MS analysis showed complete consumption of the starting material. The mixture was diluted with Et₂O, washed with sat.aq. NaHCO₃ (4x), H₂O (1x) and sat. aq. NaCl (1x). The organic layer was dried over MgSO₄ and concentrated in vacuo. Purification by column chromatography (7:1 PE/EtOAc to 3:1 PE/EtOAc) and coevaporation with DCM and CHCl₃ resulted in the title compound as a clear oil (5.38 g, 10.88 mmol, 73%).

**Method B:** Compound 21 (3.085 g, 5.35 mmol) is dissolved in 27 mL DCM and 27 mL HFIP. The mixture was cooled to 0 °C and TES (2.56 mL, 16.05 mmol, 3 eq.) was added. 26.8 mL of a freshly prepared HCl/HFIP solution (0.2 M, 1 eq.) was added and the reaction was stirred for 7 minutes after which it was quenched with sat. aq. NaHCO₃. Purification by column chromatography (PE/ EtOAc 1:0 → 8:1) yielded 22 as a colorless oil (0.28 g, 0.175 mmol, 76%). TLC: Rf 0.38 (7:2 PE/EtOAc); IR (neat): 691, 739, 772, 847, 968, 1024, 1078, 1136, 1198, 1298, 1471, 1732, 2880, 2974, 3435 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.48-7.45 (m, 2H, CH₂arom), 7.36-7.27 (m, 8H, CH₃arom), 5.40 (m, 1H, H-2), 5.37 (d, 1H, J = 1.2 Hz, H-1), 4.79 (d, 2H, J = 4.4 Hz, CH₂Bn), 4.27 (dq, 1H, J = 9.4, 6.2 Hz, H-5), 4.09 (dd, 1H, J = 9.2, 2.8 Hz, H-3), 3.44 (t, 1H, J = 9.2 Hz, H-4), 2.59 (d, 2H, J = 4.8 Hz, CH₂PivCN), 2.05 (bs, 1H, OH), 1.39 (s, 6H, 2x CH₃PivCN), 1.38 (s, 3H, CH₃-6). ¹³C NMR (100 MHz, CDCl₃) δ: 174.3 (C=O PivCN), 138.0, 133.7 (C₆C₅arom), 132.1, 129.2, 128.7, 128.3, 128.2, 127.9 (CH₃arom), 118.0 (CN), 85.8 (C-1), 81.5 (C-4), 75.3 (CH₂Bn), 74.9 (C-2), 70.8 (C-3), 68.9 (C-5), 41.3 PivCN, 28.0 (CH₂PivCN), 25.0, 25.0 (CH₃PivCN), 18.1 (CH₃-6); HRMS: [M+N⁺]⁺ calc. for C₂₅H₂₅NO₅SNa 478.16586, found 478.16531.

Phenyl 4-O-benzyl-3-O-(3-cyano-2,2-dimethylpropanoyl)-1-thio-2-thiophenyl-α-L-rhamnopyranoside (23)

After coevaporation of compound 22 (2.47 g, 5.42 mmol, 1 eq.) with anhydrous toluene (2x) under argon, it was dissolved in distilled DCM (13.5 mL) and cooled to 0°C. Levulinic acid (1.54 mL, 15.2 mmol, 2.8 eq.), N,N′-diisopropylcarbodiimide (1.2 mL, 7.7 mmol, 1.4 eq.) and a catalytic amount of 4-dimethylaminopyridine (0.066 g, 0.54 mmol, 0.1 eq.) were added. After 30 min, TLC-MS analysis showed complete reaction and the mixture was filtered over Celite. The filtrate was washed with sat. aq. NaHCO₃ (2x), dried over MgSO₄ and concentrated in vacuo. Purification by
column chromatography (2:1 PE/EtOAc) and coevaporation with DCM and CHCl₃ resulted in the title compound as an oil (2.97 g, 5.36 mmol, 99%). TLC: Rᵣ 0.59 (2.1 PE/EtOAc); IR (neat): 692, 741, 912, 1084, 1099, 1132, 1150, 1204, 1300, 1362, 1474, 1717, 1740, 2976 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.46-7.43 (m, 2H, CH₃αα), 7.37-7.24 (m, 8H, CH₃αα), 5.54 (m, 1H, H-2), 5.36 (d, 1H, J = 1.2 Hz, H-1), 5.31 (dd, 1H, J = 9.6, 3.2 Hz, H-3), 4.78 (d, 1H, J = 11.2 Hz, CH₂Bn), 4.34 (dq, 1H, J = 9.4, 6.0 Hz, H-5), 3.64 (t, 1H, J = 9.6 Hz, H-4), 2.77-2.64 (m, 2H, CH₂Lev), 2.59 (d, 2H, J = 1.6 Hz, CH₂PivVN), 2.56-2.44 (m, 2H, CH₂Lev), 2.14 (s, 3H, CH₃Lev), 1.39 (s, 6H, 2x CH₂PivCN), 1.36 (s, 3H, CH₃αα). ¹³C NMR (100 MHz, CDCl₃) δ: 206.0 (C=O Lev ketone), 173.6, 171.1 (C=O PivVN, Lev), 137.7, 131.3 (C₂αα, C₆αα), 131.9, 129.0, 128.9, 128.3, 128.0, 127.8 (Cαα), 117.4 (CN), 85.2 (C-1), 78.1 (C-4), 74.8 (CH₂Bn), 72.2, 72.2 (C-2, C-3), 68.9 (C-5), 41.0 (C₁αα PivVN), 27.5 (CH₂Lev), 29.5 (CH₃Lev), 27.7, 27.6 (CH₂Lev, CH₂PivVN), 24.7, 24.6 (CH₂PivVN), 17.8 (CH₃-6); HRMS: [M+Na]+ calcd. for C₉₀H₅₁NO₃SNa 902.3545, found 902.35458.

N-benzyl-N-benzoxycarbonyl-5-aminopentan-4-yl-3-levulinoyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyranoside (24) Donor 12 (0.843 g, 1.52 mmol, 1 eq.) and acceptor 15 (1.552 g, 4.74 mmol, 3 eq.) were coevaporated three times with anhydrous toluene under an argon atmosphere before being dissolved in distilled DCM (17 mL) under an argon atmosphere. Activated molecular sieves (3Å) were added and the mixture was cooled to 0 °C and triflic acid (4.5 µL, 0.051 mmol, 0.1 eq.) were added. After 20 min the reaction was quenched by addition of 0.1 mL Et₃N. The reaction mixture was diluted with Et₂O and washed with H₂O (2x) and sat. aq. NaCl (2x). The organic layer was dried over MgSO₄ and concentrated in vacuo. Purification by size exclusion (1:1 DCM/MeOH) resulted in the title compound as a yellow oil (0.394 g, 0.448 mmol, 93%). TLC: Rᵣ 0.64 (7:2 PE/EtOAc); IR (neat): 700, 731, 845, 922, 989, 1028, 1082, 1117, 1156, 1204, 1364, 1452, 1717, 1740, 2930, 2974 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.45-7.20 (m, 20H, CH₃αα), 5.40 (m, 1H, H-2'), 5.31 (s, 2H, H-1, H-2), 5.07 (s, 1H, H-1'), 4.93 (d, 1H, J = 11.2 Hz, CH₂Bn), 4.79 (d, 1H, J = 10.8 Hz, CH₂Bn), 4.65-4.59 (m, 3H, CH₂Bn), 4.49 (d, 1H, J = 12 Hz, CH₂Bn), 4.22 (q, 1H, J = 6.0 Hz, H-5), 4.12 (dd, 1H, J = 9.6, 2.4 Hz, H-3), 3.80 (dd, 1H, J = 9.2, 3.2 Hz, H-3'), 3.60 (q, 1H, J = 6.0 Hz, H-5'), 3.53 (t, 1H, J = 9.6 Hz, H-4), 3.42 (t, 1H, J = 9.2 Hz, H-4'), 2.70-2.63 (m, 4H, 2x CH₂Lev), 2.45 (q, 2H, J = 14.0 Hz, CH₂PivVN), 2.13 (s, 3H, CH₃Lev), 1.29 (m, 12H, CH₂-6, CH₂-6', 2x CH₂PivCN); ¹³C NMR (100 MHz, CDCl₃) δ: 206.0 (C=O Lev ketone), 173.9, 171.7 (C=O PivVN, Lev), 138.5, 137.8, 137.6, 133.2 (C₂αα, C₆αα), 132.1, 131.9, 129.1, 128.8, 128.4, 128.3, 128.2, 128.1, 128.1, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5 (CH₃αα), 117.2 (CN), 99.7 (C-1'), 85.3 (C-1), 80.2 (C-4), 79.4 (C-4'), 77.05 (C-3), 76.8 (C-3'), 75.5 (CH₂Bn), 74.9 (CH₂Bn), 74.6 (C-2'), 71.1 (CH₂Bn), 69.2 (C-5), 68.9 (C-2'), 68.5 (C-5'), 40.9 (C₁αα PivVN), 37.9 (CH₂Lev), 29.7 (CH₃Lev), 28.0 (CH₂Lev), 27.6 (CH₂PivVN), 24.7, 24.6 (CH₂PivVN), 17.8, 17.8 (C-6, C-6'); HRMS: [M+Na]+ calcd. for C₉₀H₅₁NO₃SNa 902.35445, found 902.35458.
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(m, 4H, 2x CH₂), 1.40 (s, 6H, 2x CH₃ PivCN), 1.35 (d, 3H, J = 12.8 Hz, CH₃-6), 1.26 (m, 2H, CH₂); ¹³C NMR (100 MHz, CDCl₃) δ: 206.3 (C=O Lev ketone), 173.9, 171.8 (C=O PivCN, Lev), 137.9, 137.8 (C₆), 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.2 (CH₃am), 117.5 (CN), 97.0 (C-1), 78.3 (C-4), 75.0 (CH₂ Bn), 72.2 (C-3), 71.0 (C-2), 67.7 (CH₂), 67.5 (C-5), 67.1 (CH₂ Cbz), 50.5, 50.2 (CH₂ Bn), 47.1, 46.1 (CH₂), 41.2 (C₃ PivCN), 37.8 (CH₂ Lev), 29.8 (CH₂ Lev), 29.0 (CH₂), 27.9 (CH₂ PivCN, Lev), 27.5 (CH₂), 24.9, 24.9 (CH₃ PivCN), 23.3 (CH₂), 18.1 (CH₂-6). HRMS: [M+Na⁺] calc. for C₃₄H₃₂N₀₄OₙNa 793.36707, found 793.36653.

N-benzyl-N-benzoylcarbonyl-5-aminopentan-1-yl-4-benzyl-2-0-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyranoside (25) Compound 24 (0.212 g, 0.275 mmol, 1 eq.) was dissolved in pyridine (2.2 mL) and AcOH (0.55 mL). Hydrazine acetate (0.130 g, 1.41 mmol, 5 eq.) was added and the mixture was stirred for 30 min, after which TLC analysis showed complete reaction. The reaction mixture was quenched with acetone and diluted with EtOAc. The organic layer were washed with H₂O (3x) and sat. aq. NaCl (1x), dried over MgSO₄, concentrated in vacuo. Purification by column chromatography (2:1 PE/EtOAc) and coevaporation with CHCl₃ resulted in the title compound as an oil (0.135 g, 0.200 mmol, 73%). TLC: Rₜ 0.52 (2:1 PE/EtOAc); IR (neat): 696, 734, 976, 1028, 1061, 1128, 1227, 1300, 1368, 1422, 1454, 1472, 1694, 1734, 2934 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.35-7.24 (m, 14H, CH₃am), 7.17-7.16 (m, 1H, CH₃am), 5.16 (d, 2H, J = 12.4 Hz, CH₂Cbz), 5.09 (s, 1H, H-α), 4.82 (d, 1H, J = 11.2 Hz, CH₂ Bn), 4.69 (d, 1H, J = 11.2 Hz, CH₂ Bn), 4.64 (s, 1H, H-1), 4.48 (d, 2H, J = 6.8 Hz, CH₂ Bn), 4.07 (bs, 1H, H-3), 3.70 (m, 1H, H-5), 3.57 (m, 1H, CH₂), 3.32 (2H, J = 6.4 Hz, H-4), 3.31 (m, 1H, CH₂), 3.30-3.18 (m, 2H, CH₂), 2.58 (2H, J = 6.0 Hz, CH₂ PivCN), 1.54-1.48 (m, 4H, 2x CH₂), 1.39 (s, 6H, 2x CH₃ PivCN), 1.33 (d, 3H, J = 6.0 Hz, CH₃-6), 1.26 (m, 2H, CH₂). ¹³C NMR (100 MHz, CDCl₃) δ: 174.5 (C=O PivCN), 138.1, 137.9 (C₆ CH₃am), 128.6, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.3, 127.2 (CH₃am), 117.9 (CN), 97.1 (C-1), 81.3 (C-4), 75.2 (CH₂ Bn), 73.5 (C-2), 70.2 (C-3), 67.7 (CH₂), 67.5 (C-5), 67.2 (CH₂ Cbz), 50.5, 50.3 (CH₂ Cbz), 47.1, 46.1 (CH₂), 41.2 (C₃ PivCN), 29.7, 29.1 (CH₂), 28.0 (CH₂ PivCN), 27.5 (CH₂), 25.0, 24.9 (CH₃ PivCN), 23.4 (CH₂), 18.2 (CH₂-6); HRMS: [M+Na⁺] calc. for C₃₄H₃₂N₀₄O₉Na 695.33358, found 695.32958.

N-benzyl-N-benzoylcarbonyl-5-aminopentan-1-yl-4-benzyl-3-O-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyranoside (25a) TLC: Rₜ 0.22 (2:1 PE/EtOAc). ¹H NMR (400 MHz, CDCl₃) δ: 7.36-7.18 (m, 14H, CH₃am), 6.99 (m, 1H, CH₃am), 5.24 (dd, 1H, J = 14.8, 12.4 Hz, H-3), 5.17 (d, 2H, J = 12.4 Hz, CH₂ Cbz), 4.70-4.63 (m, 3H, H-1, CH₂ Bn), 4.50 (s, 2H, CH₂ Bn), 4.06 (s, 1H, H-2), 3.80 (bs, 1H, H-5), 3.64-3.59 (m, 2H, H-4, CH₂), 3.40-3.15 (m, 3H, 2x CH₂), 2.53 (d, 2H, J = 5.6 Hz, CH₂ PivCN), 1.60-1.43 (m, 4H, 2x CH₂), 1.34-1.28 (m, 11H, 2x CH₃ PivCN, CH₃-6, CH₂). ¹³C NMR (100 MHz, CDCl₃) δ: 174.0 (C=O PivCN), 138.0 (C₆), 128.7, 128.6, 128.0, 127.5, 127.4 (CH₃am), 118.4 (CN), 99.6 (C-1), 79.0 (C-4), 75.5 (C-3), 75.0 (CH₂ Bn), 69.5 (C-2), 67.7 (CH₂), 67.6 (C-3), 67.3 (CH₂ Cbz), 50.7, 50.4 (CH₂ Bn), 47.2, 46.3 (CH₂), 41.4 (C₃ PivCN), 29.8, 29.2 (CH₂), 28.3 (CH₂ PivCN), 25.1, 24.9 (CH₃ PivCN23.5 (CH₂), 18.2 (CH₂-6); HRMS: [M+H⁺] calc. for C₃₄H₃₄N₀₄O₉ 673.34834, found 673.34927.

N-benzyl-N-benzoylcarbonyl-5-aminopentan-1-yl-3-O-(3,4-di-O-benzyl-2,2-leucinoyl)-α-L-rhamnopyranosyl-(4-O-benzyl-2-0-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyranoside (26) Acceptor 25 (0.358 g, 0.533 mmol, 1 eq.) and donor 13 (0.352 g, 0.658 mmol, 1.2 eq.) were coevaporated three times with anhydrous toluene before being dissolved in distilled DCM (7.6 mL) under an argon atmosphere and stirred at room temperature for 20 min over activated molecular sieves (3Å). The reaction was cooled to 0°C, followed by the addition of NIS (0.178 g, 0.791 mmol, 1.44 eq.) and a solution of TMSOTf in distilled DCM (0.221 M, 0.24 mL, 0.053 mmol, 0.1 eq.) were added. After 40 min, TLC and TLC-MS showed complete consumption of the acceptor and the reaction was quenched with 0.1 mL Et₃N. The mixture was diluted with Et₂O and the organic layer was washed with H₂O (2x) and sat. aq. NaCl (2x), dried over MgSO₄ and concentrated in vacuo. Purification by size exclusion (1:1 DCM/MeOH) resulted in the title compound as a yellow oil (0.544 g, 0.496 mmol, 93%). TLC: Rₜ 0.64 (7:2 PE/EtOAc); ¹H NMR (400 MHz, CDCl₃) δ: 7.36-7.20 (m, 24H, CH₃am), 7.15 (m, 1H, CH₃am), 5.39 (m, 1H, H-2”), 5.15 (d, 2H, J = 13.2 Hz, CH₂ Cbz), 5.04 (s, 2H, H-1′, H-2),
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4.93 (d, 1H, J = 11.6 Hz, CH₂Bn), 4.77 (d, 1H, J = 10.8 Hz, CH₂Bn), 4.64-4.56 (m, 4H, H-1, 2xCH₂Bn), 4.49-4.46 (m, 3H, CH₂Bn), 4.11 (d, 1H, J = 8.8 Hz, H-3), 3.81 (dd, 1H, J = 9.2, 3.2 Hz, H-3'), 3.74 (m, 1H, H-5), 3.68-3.52 (m, 2H, H-5', CH₂), 3.44-3.38 (m, 2H, H-4, H-4'), 3.33-3.18 (m, 3H, CH₂), 2.71-2.63 (m, 4H, 2xCH₂Lev), 2.48 (q, 2H, J = 6.8 Hz, CH₂PivCN), 2.11 (s, 3H, CH₃Lev), 1.53-1.43 (m, 4H, CH₂), 1.31-1.27 (m, 14H, CH₂-6, CH-6', 2xCH₂PivCN, CH₂). ¹³C NMR (100 MHz, CDCl₃) δ: 205.9 (C=O Lev ketone), 174.0, 171.6 (C=O PivCN, Lev), 156.6 (C=O Cbz), 138.5, 137.8, 137.7, 137.6, 136.7 (Cq Crem), 128.9, 128.8, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 127.1 (CH₃onm), 117.2 (CN), 99.6 (C-1'), 96.4 (C-1), 80.1 (C-4), 79.4 (C-4'), 77.4 (C-3), 76.7 (C-3'), 75.5, 74.7 (CH₂Bn), 73.1 (C-2), 71.0 (CH₂Bn), 68.9 (C-2'), 68.2 (C-5'), 67.5 (C-5), 67.5 (CH₂), 66.9 (CH₂Bz), 50.4, 50.1 (CH₂Bn), 46.9, 46.0 (CH₂), 40.8 (Cq PivCN), 37.8 (CH₂ Lev), 29.6 (CH₂ Lev), 28.9 (CH₂), 28.0, 27.8, 27.5 (CH₂ PivCN, CH₂ Lev, CH₂), 24.7, 24.5 (CH₂ PivCN), 23.2 (CH₂), 17.9, 17.7 (CH₂-6, CH-6'). HRMS: [M+NH₄]⁺ calcd for C₅₀H₃₅N₃O₁₃ 1114.56348, found 1114.56494.

N-benzyl-N-benzyloxycarbonyl-5-aminopentanyl-3-O-(3,4-di-O-benzyl-1-R-hamnopyranosyl)-4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyanoside (27) Compound 26 (0.526 g, 0.479 mmol, 1 eq.) was dissolved in pyridine (3.8 mL), cooled to 0°C and AcOH (0.96 mL) was added, followed by the addition of hydrazine acetate (0.228 g, 2.48 mmol, 5 eq.). The mixture was allowed to warm up to room temperature and stirred for 1h. The reaction mixture was quenched with acetone and diluted with EtOAc. The organic layer was washed with H₂O (3x) and sat. aq. NaCl (1x), dried over MgSO₄, concentrated in vacuo.
Purification by column chromatography (2:1 PE/ EtOAc) and coevaporation with DCM and CHCl₃ resulted in the title compound as an oil (0.433 g, 0.433 mmol, 90%). TLC: Rf 0.64 (7:2 PE/EtOAc); IR (neat): 696, 733, 837, 914, 1028, 1072, 1126, 1209, 1248, 1300, 1366, 1422, 1452, 1472, 1695, 1734, 2872, 2932, 2972 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.36-7.20 (m, 24H, CH₂Ar), 7.15 (m, 1H, CH₂Ar), 5.16 (d, 2H, J = 12.8 Hz, CH₂Bz), 5.07 (s, 2H, H-1', H-2'), 4.88 (d, 1H, J = 11.6 Hz, CH₂Bn), 4.69-4.57 (m, 6H, H-1, 3xCH₂Bn), 4.48 (d, 2H, J = 8.4 Hz, CH₂Bn), 4.11 (m, 1H, H-3), 3.91 (s, 1H, H-2'), 3.71-3.68 (m, 2H, H-3', H-5), 3.60-3.54 (m, 2H, H-5, CH₂), 3.49-3.38 (m, 2H, H-4, H-4'), 3.37-3.33 (m, 3H, CH₃), 2.64 (bs, 1H, OH), 2.49 (q, 2H, J = 14.8 Hz, CH₂PivCN), 1.53 - 1.22 (m, 16H); ¹³C NMR (100 MHz, CDCl₃) δ: 174.0 (C=O PivCN), 138.6, 137.8, 136.8 (Cq Crem), 128.5, 128.4, 128.2, 128.0, 127.9, 127.9, 127.8, 127.7, 127.5, 127.5, 127.2 (CH₂Ar), 117.3 (CN), 101.6 (C-1'), 96.6 (C-1), 80.3 (C-4), 79.6 (C-4'), 79.0 (C-3'), 77.3 (C-3), 75.5 (CH₂Bn), 74.8 (CH₂Bn), 73.3 (C-2), 71.6 (CH₂Bn), 68.6 (C-2'), 68.0 (C-5'), 67.7 (CH₂), 67.6 (C-5), 67.1 (CH₂ Bz), 50.5, 50.2 (CH₂ Bn), 47.0, 46.0 (CH₂), 40.9 (Cq PivCN), 28.9 (CH₂), 27.7 (CH₂ PivCN), 27.4 (CH₂), 24.8, 24.7 (CH₂ PivCN), 23.2 (CH₂), 18.0, 17.7 (CH₂-6, CH-6'). HRMS: [M+NH₄]⁺ calcd for C₅₀H₃₅N₃O₁₃ 1016.52670, found 1016.52807.

N-benzyl-N-benzyloxycarbonyl-5-aminopentanyl-3-O-(2-O-(3-O-(3,4-di-O-benzyl-2-O-levulinoyl-α-L-rhamnopyranosyl)-4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyanosyl)-3,4-di-O-benzyl-α-L-rhamnopyanosyl)-4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyanoside (28) acceptor 27 (0.191 g, 0.193 mmol, 0.8 eq.) and donor 14 (0.220 g, 0.250 mmol, 1 eq.) were coevaporated three times with anhydrous toluene before being dissolved in distilled DCM (3.6 mL) under an argon atmosphere and stirred at room temperature for 20 min over activated molecular sieves (3Å). The reaction was cooled to 0°C, followed by the addition of NIS (0.0703 g, 0.312 mmol, 1.2 eq.) and a solution of TMSOTf in distilled DCM (0.221 M, 0.12 mL, 0.026 mmol, 0.1 eq.) were added. After 50 min, TLC and TLC-MS showed complete consumption of the acceptor and the reaction was quenched with 0.1 mL Et₃N. The mixture was diluted with Et₂O and the organic layer was washed with H₂O (1x) and sat. aq. NaCl (2x), dried over MgSO₄ and concentrated in vacuo. Purification by size exclusion (1:1 DCM/MeOH) resulted in the title compound as a yellow oil (0.320 g, 0.181 mmol, 94%). TLC: Rf 0.5 (2:1 PE/EtOAc); IR (neat): 696, 733, 893, 914, 980, 1072, 1128, 1206, 1362, 1452, 1697, 1736, 2932 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.34-7.15 (m, 40H, CH₂Ar), 5.41 (s, 1H, H-2''), 5.23 (s, 1H, H-2''), 5.16 (d, 2H, J = 9.6
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Hz, CH₃ Cbz), 5.07 (s, 1H, H-1’’’), 5.0 (s, 1H, H-2’’’), 4.97 (s, 1H, H-1’’’), 4.96-4.86 (m, 2H, CH₂ Bn), 4.84 (s, 1H, H-1’’’), 4.75 (d, 1H, J = 10.8 Hz, CH₂ Bn), 4.65-4.56 (m, 8H, H-1, 4x CH₂ Bn), 4.54-4.44 (m, 4H, 2x CH₂ Bn), 4.18 (dd, 1H, J = 9.6, 3.2 Hz, H-3’’’), 4.02 (d, 1H, J = 9.2 Hz, H-3), 3.83-3.77 (m, 3H, H-2’, H-3’’, H-5’’’), 3.72-3.68 (m, 3H, H-3’, H-5, H-5’), 3.60-3.36 (m, 1H, CH₃), 3.45-3.32 (m, 5H, H-4, H-4’, H-4’’, H-4’’’), 2.53-2.40 (m, 4H, 2x CH₂ PivCN), 2.14 (s, 3H, CH₃ Lev). 1.58 – 1.16 (m, 28H); ¹³C NMR (100 MHz, CDCl₃): δ 206.1 (C=O Lev ketone), 174.2, 173.8, 171.8 (C=O 2x PivCN, Lev), 138.7, 138.6, 138.2, 138.0, 137.9 (C₆ emojis), 128.8, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.1, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 127.5 (CH₂ emojis), 117.4 (CN), 101.4 (C-1’’’), 99.4 (C- arom), 98.5 (C-1’’’), 96.5 (C-1), 80.3, 80.0, 79.9, 79.6 (C-4, C-4’, C-4’’, C-4’’’), 78.6 (C-3’’’), 78.2 (C-3), 77.4, 77.1 (C-2’’, C-3’’’’), 75.8 (C-3’’’), 75.6, 75.5, 75.0, 75.0 (CH₂ Bn), 73.4 (C-2), 73.0 (C-2’’’), 72.0, 71.2 (CH₂ Bn), 69.0 (C-2’’’’), 68.7, 68.5, 68.4 (C-5), 67.8 (CH₂), 67.6 (C-5), 67.1 (CH₂ Cbz), 50.6, 50.3 (CH₂ Bn), 47.1, 46.1 (CH₂), 40.9 (C₆ PivCN), 38.0 (CH₂ Lev), 29.9 (CH₂ Lev), 29.0, 28.1, 27.9, 27.8, 27.7, 27.5 (2x CH₂ PivCN, CH₂ Lev, 2x CH₂), 24.8, 24.7, 24.7 (CH₂ PivCN), 23.3 (CH₃). 18.1, 18.0, 17.8, 17.8 (CH₂-6, CH₃-6’, CH₃-6’’, CH₃-6’’’’); HRMS: [M+NH₄]+ calcd. for C₈₀H₁₀₀N₄O₂₁ 1786.87623, found 1786.87609.

N-benzyl-N-benzoxycarbonyl-5-aminopentanyl-3-(2-O-(3-O-(3,4-di-O-benzyl-α-L-rhamnopyranosyl)-4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyranosyl)-3,4-di-O-benzyl-α-L-rhamnopyranosyl)-4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyranoside (29) Compound 28 (0.185 g, 0.104 mmol, 1 eq.) was dissolved in pyridine (0.82 mL) and AcOH (0.2 mL). Hydrazine acetate (0.050 g, 0.52 mmol, 5 eq.) was added and the mixture was stirred for 1h. TLC and TLC/MS analysis showed complete consumption of the starting material after which the reaction mixture was quenched with acetone and diluted with EtOAc. The organic layer were washed with H₂O and sat. aq. NaCl (1x), dried over MgSO₄, concentrated in vacuo. Purification by column chromatography (PE/EtOAc 4:1 → 2:1) resulted in the title compound as an oil (0.167 g, 0.099 mmol, 96%). TLC: Rf 0.59 (7.2 PE/EtOAc); IR (neat): 696, 733, 837, 912, 982, 1059, 1072, 1126, 1207, 1298, 1364, 1422, 1454, 1472, 1697, 1736, 1926, 2970 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.15 (m, 40H, CH₂ emojis), 5.26 (s, 1H, H-2’’’), 5.16 (d, 2H, J = 10.0 Hz, CH₂ Cbz), 5.11 (s, 1H, H-1’’’’), 4.99 (s, 1H, H-2’), 4.97 (s, 1H, H-1’’’), 4.91-4.87 (m, 3H, H-1’’, H₂ emojis), 4.69-4.54 (m, 10H, H-1, 5x CH₂ Bn), 4.52-4.47 (m, 3H, 2x CH₂ Bn), 4.17 (dd, 1H, J = 9.6, 3.2 Hz, H-3’’’), 4.02 (d, 1H, J = 7.2 Hz, H-3), 3.92 (s, 1H, H-2’’’’), 3.84 (s, 1H, H-2’’), 3.82-3.76 (m, 1H, H-5), 3.72-3.66 (m, 4H, H-3’, H-3’’’, H-5, H-5’), 3.58-3.49 (m, 1H, CH₂), 3.47-3.31 (m, 5H, H-4, H-4’, H-4’’’, H-4’’’’), 2.93-2.84 (m, 3H, CH₃), 2.56-2.44 (m, 4H, 2x CH₂ PivCN), 1.57 -1.16 (m, 28H); ¹³C NMR (100 MHz, CDCl₃): δ 174.2, 173.7 (C=O 2x PivCN), 138.7, 138.6, 138.3, 137.9, 137.9 (C₆ emojis), 128.6, 128.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 126.3 (CH₂ emojis), 117.5, 117.4 (CN), 101.4 (C-1’’’), 101.2 (C-1’’’’), 98.5 (C-1’’’’), 96.5 (C-1), 80.4, 80.0, 79.9, 79.7 (C-4, C-4’, C-4’’, C-4’’’), 79.2 (C-3’’’), 78.7 (C-3’’’’), 78.3 (C-3), 76.2 (C-3’’’’), 75.7’ (C-2’’’), 75.6, 75.5, 75.1, 75.0 (CH₂ Bn), 73.4 (C-2), 73.1 (C-2’’’), 72.0, 71.8 (CH₂ Bn), 68.7 (C-2’’’’), 68.5, 68.1 (C-5), 67.8 (CH₂), 67.6 (C-5), 67.2 (CH₂ Cbz), 50.6, 50.3 (CH₂ Bn), 47.1, 46.2 (CH₂), 41.0, 40.9 (C₆ PivCN), 29.8 (CH₂), 29.4, 29.1 (CH₂), 27.8, 27.8 (2x CH₂ PivCN), 24.9, 24.9, 24.8 (CH₂ PivCN), 23.3 (CH₃), 18.1, 18.0, 17.8 (CH₂-6, CH₃-6’, CH₃-6’’, CH₃-6’’’’); HRMS: [M+NH₄]+ calcd. for C₈₉H₁₀₉N₄O₂₁ 1688.83945, found 1688.84017.

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5-aminopentany-3-O-(2-O-(3-O-(α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (10) Tetrasaccharide 29 (0.0345 g, 0.0206 mmol) was dissolved in H₂O/THF/BuOH (3 mL:1.3 mL:1.3 mL) and several drops of acetic acid were added. The solution was purged with argon for 5 minutes after which Pd(OH)₂/C (60 mg, 20% wt loading) was added followed by another purge with argon for 5 minutes. The solution was purged with hydrogen for 5 minutes and kept under a hydrogen atmosphere overnight. The mixture was filtered over a Whatman filter, which was rinsed 3x with the H₂O/THF/BuOH mixture. The solution was concentrated and redissolved in 10 mL H₂O. Triethylamine (0.5 mL) was added and the reaction was stirred overnight. Purification using size exclusion chromatography (sephadex LH20 9:1 MeOH/H₂O) followed by two lyophilizations yielded fully deprotected tetrasaccharide 10 in quantitative yield (16.2 mg) as a white powder. †H NMR (D₂O, 500 MHz): δ 5.22 (s, 1H), 5.06 (s, 1H), 4.97 (s, 1H), 4.22 – 4.13 (m, 1H), 4.11 – 4.06 (m, 2H), 4.04 – 3.93 (m, 2H), 3.90 – 3.69 (m, 9H), 3.61 – 3.44 (m, 6H), 3.22 (q, 3H, J = 7.3, 7.3, 7.3 Hz), 3.06 – 2.99 (m, 2H), 2.64 (s, 2H), 1.77 – 1.63 (m, 5H), 1.54 – 1.42 (m, 2H), 1.37 – 1.23 (m, 25H); †C NMR (D₂O, 126 MHz): δ 102.4, 102.1, 100.8, 99.7 (4x C-1), 78.1, 77.5, 72.2, 72.0, 71.8, 71.4, 70.2, 70.2, 70.0, 69.9, 69.4, 69.3, 69.2, 68.7, 67.5, 46.8, 42.3, 39.4, 28.3, 28.1, 26.5, 25.8, 25.0, 22.5, 16.7, 16.7, 16.7, 16.6, 8.3. HRMS: [M+H]+ calcd. for C₉₀H₁₇₀NO₁₉ 688.33865, found 688.33825.

N-benzyl-N-benzyloxy carbonyl-5-aminopentany-3-O-(3-O-(3,4-di-O-benzyl-2-O-levulinoyl-α-L-rhamnopyranosyl)-4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyranosyl)-4-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyranoside (30) Acceptor 25 (0.204 g, 0.303 mmol, 1.1 eq.) and donor 14 (0.232 g, 0.264 mmol, 1 eq.) were coevaporated three times with anhydrous toluene before being dissolved in distilled DCM (3.8 mL) under an argon atmosphere and stirred at room temperature for 30 min over activated molecular sieves (3Å). The reaction was cooled to 0 °C, followed by the addition of NIS (0.073 g, 0.32 mmol, 1.2 eq.) and a solution of TMSOTf in distilled DCM (0.221 M, 0.12 mL, 0.027 mmol, 0.1 eq.) were added. After 100 min the reaction was quenched with 0.1 mL Et₃N, diluted with Et₂O and the organic layer was washed with H₂O (2x) and sat. aq. NaCl (2x). The organic layer was dried over MgSO₄ and concentrated in vacuo. Purification by size exclusion (1:1 DCM/MeOH) and coevaporation with CHCl₃ resulted in the title compound as a yellow oil (0.199 g, 0.138 mmol, 52%). TLC: Rf 0.31 (2:1 PE/EtOAc). †H NMR (400 MHz, CDCl₃): δ: 7.38-7.24 (m, 29H, CH₆(C₆H₅)), 7.16 (m, 1H, CH₆(C₆H₅)), 5.36 (m, 1H, H-2’’), 5.17-5.13 (m, 3H, H-2’, CH₂Cbz), 5.06 (s, 1H, H-2), 4.98 (s, 2H, H-1’’, H-1’’’), 4.89 (d, 1H, J = 11.2 Hz, CH₂Bn), 4.82 (d, 1H, J = 10.8 Hz, CH₂Bn), 4.76 (d, 1H, J = 10.8 Hz, CH₂Bn), 4.62-4.56 (m, 5H, H-1’, 2x CH₂Bn), 4.46-4.43 (m, 3H, 2x CH₂Bn), 4.11 (d, 1H, J = 7.2 Hz, H-3), 4.02 (dd, 1H, J = 9.6, 3.2 Hz, H-3’’), 3.73 (dd, 1H, J = 9.2, 3.2 Hz, H-3’’’), 3.66-3.54 (m, 4H, H-5, H-5’, H-5’’’, CH₂), 3.46-3.40 (m, 2H, H-4, H-4’’), 3.35 (t, 1H, J = 9.2 Hz, H-4’’’), 3.30-3.18 (m, 3H, CH₂), 2.71-2.62 (m, 4H, 2x CH₂Lev), 2.59 (q, 2H, J = 9.6 Hz, CH₂PivCN), 2.41 (q, 2H, J = 12.4 Hz, CH₂PivCN), 2.15 (s, 3H, CH₃Lev), 1.52 – 1.14 (m, 25H); †C NMR (100 MHz, CDCl₃): δ: 206.3 (C=O lev ketone), 174.4, 173.9, 171.8 (C=O PivCN, PivCN, Lev), 138.7, 138.0, 137.9, 137.9, 137.7 (C=O, Catom), 128.6, 128.5, 128.5, 128.4, 128.4, 128.2, 128.0, 128.0, 127.9, 127.9, 127.8, 127.6, 127.4 (CH₆(C₆H₅)), 117.5, 117.4 (CN), 99.9, 98.9 (C-1’, C-1’’’), 96.7 (C-1), 80.4 (C-4), 79.7 (C-4’’’), 79.5 (C-4’’), 77.4 (C-3’’’), 77.0 (C-3), 76.7 (C-3’’), 75.7, 75.2, 74.9 (CH₂Bn), 73.2 (C-2), 73.0 (C-2’’), 71.2 (CH₂Bn), 69.0 (C-2’’’), 68.7, 68.5, 67.8, (C-5, C-5’, C-5’’’), 67.7 (CH₂), 67.2 (CH₂Cbz), 50.6, 50.2 (CH₃Bn), 47.1, 46.2 (CH₂), 41.1, 40.9 (CpivCN), 38.1 (CH₂Lev), 29.9 (CH₂Lev), 29.8, 29.1 (CH₂), 28.1, 27.9, 27.7, 27.5 (2x CH₂ PivCN, CH₂Lev, CH₂), 25.0, 24.9, 24.8, 24.7 (CH₂ PivCN), 23.4 (CH₂), 18.1, 17.9 (CH₂-6, CH₂-6’, CH₂-6’’’). HRMS: [M+NH₄]+ calcd. for C₈₉H₁₀₃N₁₀O₁₉ 1459.72110, found 1459.72186.
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N-benzyl-N-benzyloxy carbonyl-5-aminopentanyl-3-O-(3-O-(3,4-di-O-benzyl-α-L-rhamnopyranosyl)-4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyranosyl)-4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyranoside (31) Compound 30 (0.195 g, 0.135 mmol, 1 eq.) was dissolved in pyridine (1.2 mL) and AcOH (0.3 mL). Hydrazine acetate (0.065 g, 0.69 mmol, 5 eq.) was added and the mixture was stirred for 45 min, after which TLC-MS analysis showed complete reaction. The reaction mixture was quenched with aceton and diluted with EtOAc. The organic layer were washed with H2O (3x) and sat. aq. NaCl (1x), dried over MgSO4, concentrated in vacuo. Purification by column chromatography (2:1 PE/EtOAc) and coevaporation with DCM and CHCl3 resulted in the title compound as an oil (0.141 g, 0.105 mmol, 78%). Rf = 0.59 (2:1 PE/EtOAc). IR (neat): 698, 733, 837, 917, 982, 1028, 1042, 1072, 1128, 1207, 1298, 1362, 1422, 1454, 1695, 1736, 2930, 2970 cm−1. 1H NMR (400 MHz, CDCl3) δ: 7.39-7.23 (m, 29H, CHarom), 7.15 (m, 1H, CHarom), 5.17-5.15 (m, 3H, H-2', CH2Cbz), 5.06 (m, 1H, H-2'), 5.03 (s, 1H, H-1''), 4.99 (s, 1H, H-1''), 4.86-4.81 (m, 2H, CH2Bn), 4.67 (d, 1H, J = 11.2 Hz, CH2Bn), 4.61-4.59 (m, 6H, H-1, 3x CH2Bn), 4.49-4.47 (m, 2H, CH2Bn), 4.13 (dd, 1H, J = 9.2, 2.4 Hz, H-3), 4.02 (dd, 1H, J = 9.6, 3.2 Hz, H-3'), 3.83 (m, 1H, H-2''), 3.69-3.53 (m, 5H, H-3'', H-5', H-5'''), CH3), 3.47-3.37 (m, 3H, H-4', H-4''), 3.27-3.18 (m, 3H, CH3), 2.58 (q, 2H, J = 8.4 Hz, CH2PivCN), 2.44 (q, 2H, J = 8.8 Hz, CH2PivCN), 1.52 - 1.14 (m, 25H). 13C NMR (100 MHz, CDCl3): δ 174.4, 173.8, (C=O PivCN), 138.6, 138.1, 138.0, 137.9, 137.7 (C4 Carom), 128.5, 128.5, 128.1, 128.0, 127.9, 127.9, 127.7, 127.6, 127.3 (CHarom), 117.4, 117.4 (CN), 101.8 (C-1''), 98.8 (C-1'), 96.7 (C-1), 80.4, 80.4, 79.5 (C-4', C-4'''), 79.0 (C-3''), 76.9 (C-3'), 76.6 (C-3), 75.5, 75.2, 74.9 (CH2Bn), 73.2 (C-2', C-2''), 71.8 (CH2 Bn), 68.7 (C-2'''), 68.7, 68.1, 67.8 (C-5', C-5''), 67.7 (CH3), 67.2 (CH2 Cbz), 50.6, 50.3 (CH2 Bn), 47.1, 46.1 (CH3), 41.2, 40.9 (Cq PivCN), 29.8, 29.4, 29.1 (CH3), 27.9, 27.7 (CH2 PivCN), 25.0, 24.9, 24.8, 24.7 (CH3 PivCN), 23.4 (CH3), 18.1, 17.9, 17.8 (CH2-6', CH2-6'''). HRMS: [M+NMe3]+ calcd. for C33H31N5O23 1361.68432, found 1361.68448.

N-benzyl-N-benzyloxycarbonyl-5-aminopentanyl-3-O-(3-O-(2-O-(4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-3-O-levulinoyl-α-L-rhamnopyranosyl)-4,3-di-O-benzyl-α-L-rhamnopyranosyl)-4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-α-L-rhamnopyranoside (32) Acceptor 31 (1.09 g, 0.81 mmol, 1.0 eq.) and donor 12 (0.68 g, 1.22 mmol, 1.5 eq.) were coevaporated three times with anhydrous toluene before being dissolved in dry DCM. The solution was stirred at room temperature on activated molecular sieves after which NIS (0.309 g, 1.377 mmol, 1.7 eq.) was added. The reaction mixture was cooled to ~40 °C and treated with 1.4 mL of a freshly prepared solution of TMSOTf in DCM (0.1 M, 1.4 mL, 0.17 eq.). After 65 minutes, TLC analysis showed complete consumption of the acceptor, and the reaction was quenched with 0.5 mL EtN. The mixture was dilute with EtOAc, washed with sat. aq. Na2S2O3, sat. aq. NaHCO3 and sat. aq. NaCl, dried over MgSO4 and concentrated. Column purification (hexanes/acetone 10:1 → 4:1) followed by size exclusion purification (DCM/MeOH 1:1) yielded tetrasaccharide 32 as a yellow oil (1.087 g, 0.608 mmol, 75%). TLC: Rf 0.62 (PE/EtOAc, 1/1, v/v); IR (neat): 698, 731, 979, 1074, 1128, 1454, 1697, 1737, 2245, 2877, 2935, 2976 cm−1. 1H NMR (CDCl3, 400 MHz): δ 7.37 - 7.13 (m, 35H), 5.44 - 5.36 (m, 1H), 5.33 (dd, 1H, J = 9.5, 3.3 Hz), 5.19 - 5.10 (m, 3H), 5.01 - 4.77 (m, 5H), 4.77 - 4.66 (m, 3H), 4.61 (dd, 5H, J = 11.0, 5.4 Hz), 4.52 (dd, 3H, J = 11.8, 3.7 Hz), 4.48 (s, 1H), 3.91 - 3.76 (m, 2H), 3.70 - 3.64 (m, 2H), 3.64 - 3.54 (m, 2H), 3.47 (m, 4H), 3.42 - 3.11 (m, 5H), 2.81 - 2.34 (m, 15H), 2.20 - 2.09 (m, 3H), 1.58 - 1.07 (m, 34H); 13C NMR (CDCl3, 101 MHz): δ 206.3, 174.3, 173.8, 173.7, 171.7, 138.8, 138.3, 138.0, 137.9, 137.8, 137.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.6, 127.5, 127.4, 127.3, 117.5, 117.3, 117.3, 107.3, 101.6, 98.7, 98.6, 96.6, 80.3, 79.7, 79.4, 79.0, 78.3, 77.7, 75.6, 75.3, 75.1, 74.9, 73.2, 73.1, 72.2, 72.0, 70.8, 68.8, 68.6, 68.1, 67.7, 67.6, 67.1, 41.1, 40.8, 37.8, 29.8, 29.1, 27.9, 27.9, 27.8, 27.6, 25.0, 24.9, 24.8, 24.8, 24.6, 23.3, 18.0, 17.9, 17.8, 17.7; HRMS (MALDI-TOF): [M+Na]+ calcd. for C106H122N10O24Na 1809.8341, found 1809.8353.
**The Cyanopivaloyl Ester: A New Protecting Group in the Assembly of Oligorhamnans**

\[ N\text{-benzyl-N-benzylxylocarbonyl-5-aminopentany1-3-O-(3-O(2-O(4-O-benzyl-2-O-(3-cyano-2,2-}
\text{dimethylpropanoyl)-a-L-rhamnopyranosyl)-3,4-di-O-benzyl-a-L-rhamnopyranosyl)-4-O-benzyl-2-O-(3-cyano-2,2-}
\text{dimethylpropanoyl)-a-L-rhamnopyranosyl)-4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-a-L-rhamnopyranoside (33) **

A solution of 32 (0.492 g, 0.275 mmol, 1.0 eq.) in pyridine/ACOH (2.9 mL:0.75 mL) was cooled to 0 °C and treated with \( \text{H}_2\text{NNH}_2/\text{AcOH} \) (0.124 g, 1.35 mmol, 5 eq.). After 90 minutes the reaction was quenched with acetone, diluted with EtOAc, washed with \( \text{H}_2\text{O} \) (2x) and sat. aq. \( \text{NaCl} \), dried over \( \text{MgSO}_4 \) and concentrated. Purification by column chromatography (hexanes/aceton 9:1 → 4:1) yielded the title compound 33 as a colorless oil (0.306 g, 0.18 mmol, 67%). TLC: \( R_f \) 0.74 (PE/\text{EtOAc}, 1/1, v/v); IR (neat): 696, 732, 979, 1028, 1055, 1128, 1454, 1697, 1735, 2245, 2933, 2974, 3030 cm\(^{-1}\); \(^1\) H NMR (500 MHz, \text{CDCl}_3) \( \delta \) 7.37 – 7.18 (m, 35H), 5.26 (dd, \( J = 3.1, 1.7 \) Hz, 1H), 5.19 – 5.13 (m, 3H), 5.13 – 5.02 (m, 3H), 5.00 – 4.93 (m, 3H), 4.90 – 4.79 (m, 4H), 4.78 – 4.62 (m, 5H), 4.62 – 4.59 (m, 2H), 4.59 – 4.42 (m, 8H), 4.11 (dt, \( J = 9.1, 4.6 \) Hz, 2H), 3.98 (dd, \( J = 9.5, 3.1 \) Hz, 1H), 3.85 – 3.72 (m, 3H), 3.67 (dd, \( J = 9.0, 2.8 \) Hz, 2H), 3.65 – 3.48 (m, 4H), 3.48 – 3.12 (m, 11H), 2.66 – 2.38 (m, 9H), 1.64 – 0.94 (m, 34H); \(^13\) C NMR (126 MHz, \text{CDCl}_3) \( \delta \) 174.4, 174.2, 174.0, 138.8, 138.7, 138.3, 138.1, 138.1, 138.0, 137.9, 137.7, 137.0, 132.3, 129.3, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 127.6, 127.3, 117.9, 117.4, 117.4, 101.7, 98.8, 96.7, 92.6, 91.9, 81.4, 81.3, 81.1, 80.4, 80.1, 79.8, 79.6, 79.5, 79.1, 78.9, 77.9, 77.6, 75.6, 75.3, 75.2, 75.2, 75.1, 74.9, 74.9, 73.8, 73.3, 73.3, 73.2, 73.0, 72.3, 71.8, 70.2, 69.8, 68.7, 68.2, 68.2, 67.8, 67.8, 67.6, 67.2, 50.7, 50.3, 47.2, 46.2, 41.2, 41.2, 40.9, 29.2, 28.1, 28.0, 27.9, 27.8, 27.6, 25.1, 25.0, 24.9, 24.9, 24.8, 24.7, 23.4, 18.3, 18.1, 17.9; HRMS (MALDI-TOF): [M+Na]\(^+\) calcd. for \( \text{C}_{97}\text{H}_{176}\text{NaO}_{22}\text{N}_{7} \) 1711.7973, found 1711.7979.

\[ N\text{-benzyl-N-benzylxylocarbonyl-5-aminopentany1-3-O-(3-O(2-O(4-O-benzyl-2-O-(3-cyano-2,2-}
\text{dimethylpropanoyl)-a-L-rhamnopyranosyl)-4-O-benzyl-2-O-(3-cyano-2,2-}
\text{dimethylpropanoyl)-a-L-rhamnopyranosyl)-4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-a-L-rhamnopyranosyl)-4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)-a-L-rhamnopyranoside (34) **

Donor 14 (0.15 g, 0.17 mmol, 1.5 eq.) and acceptor 33 (0.19 g, 0.11 mmol, 1.0 eq.) were coevaporated three times with anhydrous toluene and kept under argon, after which they were dissolved in anhydrous DCM. Activated molecular sieves were added and the mixture was stirred for 30 minutes at room temperature. After addition of NIS (0.042 g, 0.19 mmol, 1.7 eq.), the solution was cooled to -40°C, followed by addition of a freshly prepared DCM solution of TMSOTf (0.1 M, 0.18 mL, 0.018 mmol, 0.17 eq.). After TLC and TLC/MS analysis showed complete consumption of the acceptor, the reaction was quenched by addition of 0.3 mL \( \text{Et}_3\text{N} \) and allowed to warm up to room temperature. The mixture was diluted with \( \text{EtOAc} \), washed with sat \( \text{Na}_2\text{SO}_4 \) (aq), dried over \( \text{MgSO}_4 \) and concentrated. Column purification (hexanes/\text{EtOAc}) followed by size exclusion (1:1 DCM/MeOH) yielded fully protected hessecaxarhide 34 as yellow glass like solid (0.237 g, 0.096 mmol, 88%). TLC: \( R_f \) 0.74 (PE/\text{EtOAc}, 1/1, v/v); IR (neat): 698, 734, 981, 1028, 1043, 1201, 1454, 1697, 1737, 2247, 2875, 2933, 2972 cm\(^{-1}\); \(^1\) H NMR (400 MHz, \text{CDCl}_3): \( \delta \) 7.36 – 7.13 (m, 50H), 5.43 – 5.30 (m, 1H), 5.29 – 5.08 (m, 5H), 5.08 – 4.92 (m, 5H), 4.92 – 4.75 (m, 6H), 4.75 – 4.41 (m, 16H), 4.20 – 4.06 (m, 2H), 3.99 (ddd, 2H, \( J = 22.7, 9.5, 3.0 \) Hz), 3.85 – 3.11 (m, 20H), 2.74 – 2.48 (m, 8H), 2.48 – 2.35 (m, 5H), 2.15 (s, 3H), 1.60 – 1.03 (m, 46H); \(^13\) C NMR (\text{CDCl}_3, 101 MHz): \( \delta \) 206.2, 174.3, 174.0, 173.9, 171.8, 138.7, 138.7, 138.3, 138.0, 137.9, 137.9, 137.7, 137.6, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.3, 128.1, 127.9, 127.9, 127.8, 127.7, 127.7, 127.7, 127.7, 127.7, 127.7, 127.7, 127.7, 127.7.
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127.5, 127.3, 117.6, 117.4, 117.3, 100.0, 98.8, 98.5, 96.7, 80.6, 80.4, 79.6, 79.5, 77.0, 76.8, 75.6, 75.2, 74.9, 73.3, 73.2, 73.0, 72.8, 72.0, 71.2, 69.0, 68.8, 68.7, 68.5, 68.5, 67.2, 41.2, 41.1, 40.9, 40.9, 38.1, 29.9, 28.2, 27.9, 27.9, 27.7, 25.0, 24.8, 24.7, 24.7, 23.4, 18.1, 17.9, 17.9; HRMS (MALDI-TOF): [M+Na]^+ calculated for C_{116}H_{165}N_{30}O_{33}Na 2481.1436, found 2481.1436.

N-benzyl-N-benzyloxy carbonyl-5-aminopentanyl-3-O-(3-O-(3,4-di-O-benzyl-2-O-(3-O-(3,4-di-O-benzyl-α-L-rhamnopyranosyl)4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)α-L-rhamnopyranosyl)4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (35) Compound 34 (0.133 g, 0.054 mmol) was dissolved in 0.8 mL pyridine and 0.2 mL AcOH. The solution was cooled to 0 °C followed by addition of H$_2$NNH$_2$·AcOH (0.025 g, 0.27 mmol, 5 eq.) and stirred for 10 minutes at 0°C. After stirring at rt for 160 minutes, TLC and TLC/MS analysis showed complete conversion of the starting material and the reaction was quenched by addition of acetone. The mixture was diluted with EtOAc, washed with H$_2$O and sat. aq. NaCl, dried over MgSO$_4$ and concentrated. Column purification (hexanes/acetone) followed by size exclusion purification (DCM:MeOH 1/1) yielded the title hexasaccharide as a yellow glass-like solid (0.124 g, 0.052 mmol, 96%). TLC: R$_f$ 0.68 (PE/EtOAc, 1/1, v/v); IR (neat): 698, 734, 983, 1028, 1041, 1454, 1697, 1735, 2247, 2875, 2933, 2974 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.40 – 7.12 (m, 50H), 5.26 – 4.97 (m, 5H), 4.99 – 4.72 (m, 9H), 4.72 – 4.45 (m, 17H), 4.17 (dd, 1H, J = 9.5, 3.1 Hz), 4.13 – 4.05 (m, 1H), 3.99 (ddd, 2H, J = 21.0, 9.5, 3.1 Hz), 3.85 – 3.53 (m, 10H), 3.49 – 3.29 (m, 8H), 2.61 – 2.32 (m, 10H), 1.49 – 1.03 (m, 46H); $^1$C NMR (101 MHz, CDCl$_3$): δ 174.4, 174.0, 174.0, 173.9, 138.8, 138.7, 138.3, 138.3, 138.1, 138.0, 138.0, 137.9, 137.8, 137.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.4, 117.5, 117.4, 117.4, 117.4, 117.4, 110.1, 101.7, 98.8, 98.6, 98.5, 96.7, 80.6, 80.4, 80.1, 79.9, 79.6, 79.1, 78.8, 77.8, 76.9, 75.7, 75.5, 75.4, 75.3, 75.2, 75.0, 74.9, 74.7, 73.3, 73.2, 72.8, 72.0, 71.8, 68.9, 68.7, 68.6, 68.2, 67.8, 67.8, 67.3, 50.7, 46.2, 41.2, 40.9, 40.9, 29.2, 28.0, 27.9, 27.8, 27.8, 25.1, 25.0, 24.9, 24.9, 24.9, 24.8, 24.7, 23.4, 18.1, 17.9; HRMS (MALDI-TOF): [M+Na]$^+$ calculated for C$_{116}$H$_{165}$N$_{30}$O$_{33}$Na 2383.1068, found 2383.1064.

5-aminopentanyl-3-O-(3-O-(2-O-(3-O-(3,4-di-O-benzyl-2-O-(3-O-(3,4-di-O-benzyl-α-L-rhamnopyranosyl)4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)α-L-rhamnopyranosyl)4-O-benzyl-2-O-(3-cyano-2,2-dimethylpropanoyl)α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (11) Compound 35 (0.069 g, 0.029 mmol) was dissolved in a mixture H$_2$O/THF/tBuOH (3 mL:1.3 mL: 1.3 mL) followed by addition of several drops of acetic acid. The solution was purged for 5 minutes with argon. Pd(OH)$_2$/C (60 mg, 20% wt loading) was added and the solution was purged for another 5 minutes with argon. The solution was then purged with hydrogen for 5 minutes and kept under a hydrogen atmosphere overnight. The mixture was filtered over a Whatmann filter and concentrated. This procedure was repeated two times after which the residue was dissolved in 10 mL H$_2$O, followed by addition of 0.5 mL Et$_3$N. The mixture was stirred for 150 minutes and concentrated. Purification using size exclusion chromatography (sephadex LH20 9:1 MeOH/H$_2$O) followed by three lyophilizations yielded fully deprotected hexasaccharide as a white powder (23.8 mg, 24.4 mmol, 84%). $^1$H NMR (D$_2$O, 600
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$^{1}H$ NMR (D$_2$O, 400 MHz): $\delta$ 5.18 (s, 1H, H-1), 5.06 - 4.96 (m, 3H, 3x H-1), 4.92 (d, 1H, $J = 4.8$ Hz, H-1), 4.73 (s, 1H, H-1), 4.15 - 4.08 (m, 2H, 2 x H-2), 4.04 (s, 2H, 2 x H-2), 3.98 (s, 1H, H-2), 3.91 (m, 1H), 3.89 - 3.83 (m, 3H), 3.83 - 3.78 (m, 4H), 3.78 - 3.62 (m, 8H), 3.59 - 3.35 (m, 8H), 3.00 - 2.94 (m, 2H), 1.65 (m, 4H, CH$_2$), 1.45 (m, 2H, CH$_2$), 1.41 - 1.31 (m, 2H, CH$_2$), 1.25 (m, 18H, 6x CH$_3$-6); $^{13}$C NMR (D$_2$O, 151 MHz): $\delta$ 121.8, 103.4, 103.4, 103.2, 103.0, 101.8, 100.5 (6x C-1), 79.3, 79.2, 79.1, 79.0, 78.7 (6x C-2), 73.1, 73.0, 72.9, 72.6, 72.3, 72.2, 72.2, 71.1, 71.0, 71.0, 70.9, 70.8, 70.7, 70.3, 70.2, 70.2, 70.2, 70.1, 70.0, 69.7, 68.4 (6x C-3, 6x C-4, 6x C-5), 67.5, 47.6, 43.2, 40.4, 40.3 (CH$_3$), 29.2 (CH$_3$), 29.0, 27.5 (CH$_3$), 25.9, 23.4 (CH$_3$), 17.6, 17.6, 17.5 (6x CH$_3$), 9.2. HRMS (MALDI-TOF): [M+Na]$^+$ calculated for C$_{41}$H$_{73}$NO$_{25}$Na 1002.4364, found 1002.4359.
Chapter 3

References and notes

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