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Total Synthesis of the Triglycosyl Phenolic Glycolipid PGL-tb1 from *Mycobacterium tuberculosis***

Santiago Barroso, Riccardo Castelli, Marc P. Baggelaar, Danny Geerdink, Bjorn ter Horst, Eva Casas-Arce, Herman S. Overkleeft, Gijsbert A. van der Marel, Jeroen D. C. Codée, and Adriaan J. Minnaard**

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Contents

I. General remarks	S2
II. Experimental procedures	S3
III. NMR spectra	S31

I. General remarks

All reactions were performed using oven or flame-dried glassware and dry solvents. Solvents were distilled prior to use: MTBE, Et₂O and THF (Na/benzophenone), DCM (CaH₂). 2,4,6-tri-*tert*-Butyl Pyrimidine (TTBP) was prepared according to Martinez, A. G. *et al. J. Org. Chem.* **1992**, *57*, 1627. All other reagents were purchased from Sigma Aldrich, Acros, TCI Europe, Alfa Aesar, Merck, Apollo Scientific, Chempur or Fluorochem, and used without further purification unless noted otherwise. Grignard and organolithium reagents were titrated using *s*-BuOH and catalytic amounts of 1,10-phenanthroline. All moisture sensitive reactions were performed under an argon or nitrogen atmosphere. Traces of water were removed from starting compounds by co-evaporation with toluene.

¹H- and ¹³C-NMR spectra were recorded on a Varian AMX400 or a Varian 400-MR (400, 100.59 MHz, respectively) or a Bruker AV 400 MHz spectrometer at 400.2 (1H) and 100.6 (13C) MHz using CDCl₃ or CD₃OD as solvent, unless stated otherwise. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl₃: δ 7.26 for ¹H, δ 77.0 for ¹³C, CD₃OD: δ 3.31 for ¹H). Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, dd = double doublet, td = triple doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants *J* (Hz), and integration. Due to the (multiple) long alkyl chains in some of the compounds we were not able to resolve all the individual ¹³C signals in the spectra. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific LTQ Orbitrap XL or on an AEI-MS-902 spectrometer. IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm⁻¹. Optical rotations were measured on a Propol automatic polarimeter (Sodium D-line, λ = 589 nm). HPLC analysis was performed on a Chiralcel AD, 250 x 4.6 mm column with an ELS detector (ELSD).

Flash chromatography was performed using SiliCycle silica gel type SiliaFlash P60 (230 – 400 mesh) as obtained from Screening Devices or with automated column chromatography using a Reveleris flash system purchased from Grace Davison Discovery Sciences. Size exclusion chromatography was performed on Sephadex LH20 (eluent MeOH/CH₂Cl₂, 1:1). TLC analysis was performed on Merck silica gel 60/Kieselguhr F254, 0.25 mm. Compounds were visualized using either Seebach's reagent (a mixture of phosphomolybdic acid (25 g), cerium (IV) sulfate (7.5 g), H₂O (500 mL) and H₂SO₄ (25 mL)) or a KMnO₄ stain (K₂CO₃ (40 g), KMnO₄ (6 g), H₂O (600 mL) and 10% NaOH (5 mL)).

II. Experimental procedures

Scheme 1. Reagents and conditions: a) $\text{Cu}(\text{OTf})_2$ (0.5 mol%), (*S,R,R*)-Leggy phosphoramidite (1 mol%), Me_2Zn , toluene, -25°C , overnight. Then, EtI , HMPA, 0°C , 83%, >20:1 trans/cis, 95% *ee* (for *trans*); b) *m*-CPBA, CH_2Cl_2 , reflux, 60%; c) K_2CO_3 , MeOH, RT; d) NaH, MeI, DMF, RT, 92%; e) DIBAL-H, Et_2O , -84°C , 86%; f) Ethyl diazoacetate, NbCl_5 (5 mol%), CH_2Cl_2 , 86%; g) (*R*)- $[(\text{RuCl}(\text{tol-BINAP}))_2(\mu\text{-Cl})_3[\text{NH}_2\text{Me}_2]]$ (1 mol%), 20 bar H_2 , EtOH, RT, 76%, *de* >99.5%; h) AlMe_3 , $\text{MeNH}(\text{OMe})\cdot\text{HCl}$, THF, 73%. HMPA=hexamethyl phosphoramidite, *m*-CPBA=*m*-chloroperbenzoic acid, DIBAL-H=diisobutylaluminum hydride.

(6*S*,7*R*)-7-methoxy-6-methylnonanal (**15**)

Diisobutylaluminum hydride (1 M in DCM, 4.33 mL, 4.33 mmol) was added dropwise to a stirred solution of (7*R*)-methoxy-(6*S*)-methylnonanoic acid methyl ester (**13**)¹ (780 mg, 3.61 mmol) in Et_2O (10 mL) at -84°C under nitrogen. After completion of the reaction (20 min), as indicated by TLC (pentane- Et_2O 85:115), few drops of MeOH was added to quench the reaction and the solution warmed up to RT. A saturated solution of Rochelle's salt (3 mL) was added and the mixture stirred for 30 min. Then, the reaction was diluted with Et_2O (40 mL), layers were separated and the organic layer was washed with brine (5 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the product was purified by column chromatography to give aldehyde **15** (560 mg, 3.01 mmol, 89% yield) as a colorless oil and with a small amount of the related alcohol (18 mg, 3% yield). Spectroscopic data was in agreement with the previous report.¹

¹ E. Casas-Arce, B. ter Horst, B. L. Feringa, A. J. Minnaard, *Chem. Eur. J.* **2008**, *14*, 4157–4159

(8S,9R)-ethyl 9-methoxy-8-methyl-3-oxoundecanoate (16)

NbCl₅ (38.9 mg, 0.144 mmol) was added to a stirred solution of aldehyde **15** (536 mg, 2.88 mmol) in DCM (30 mL) under nitrogen. After 5 minutes, ethyl diazoacetate (0.527 mL, 4.32 mmol) was added dropwise to this solution, taking care of the gas evolution. After completion of the reaction (2 h), as indicated by TLC (pentane-Et₂O 85:115), the reaction mixture was mixed with water (30 mL). The organic layer was separated and the aqueous was extracted with dichloromethane (2x10 mL). The combined organic extracts were washed with brine (10 mL) and then dried (Na₂SO₄). The DCM was removed under reduced pressure and the product was purified by column chromatography to give **16** (677 mg, 2.49 mmol, 86% yield) as a colorless oil.

$$[\alpha]_D^{22} = -4.0^\circ (c = 1.0, \text{CHCl}_3)$$

¹H NMR (400 MHz, CDCl₃) δ 4.16 (q, *J* = 7.1 Hz, 2H), 3.40 (s, 3H), 3.30 (s, 1H), 2.82 (ddd, *J* = 7.4, 5.3, 4.1 Hz, 2H), 2.51 (t, *J* = 7.3 Hz, 1H), 1.70 – 1.51 (m, 5H), 1.48 – 1.29 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.28 – 1.14 (m, 2H), 1.06 (m, 1H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 202.8 (s), 167.2 (s), 86.5 (d), 61.3 (t), 57.3 (q), 49.2 (t), 42.9 (t), 34.6 (d), 32.3 (t), 26.9 (t), 23.7 (t), 22.3 (t), 14.7 (q), 14.0 (q), 9.9 (q).

HRMS (ESI+) *m/z*: Calcd for C₁₅H₂₈O₄Na (*M*+Na⁺) 295.1885, found 295.1866.

(3R,8S,9R)-ethyl 3-hydroxy-9-methoxy-8-methylundecanoate (17)

(*R*)-[(RuCl(tol-BINAP))₂(μ-Cl)₃][NH₂Me₂] (34.4 mg, 0.019 mmol) was added to a solution of ketoester **16** (525 mg, 1.93 mmol) in degassed EtOH (10 mL) under nitrogen. This solution was placed in an autoclave and purged with N₂ and H₂. Hydrogen was introduced (20 bar) and the reaction mixture was stirred at room temperature overnight. After the hydrogen pressure was released, toluene (20 mL) was added and the solution was concentrated under reduced pressure to remove most of the ethanol. This mixture was directly purified by flash chromatography to give **18** (400 mg, 1.46 mmol, 76% yield) as a colorless oil.

A reference mixture of epimers was obtained by reduction of **17** with NaBH₄ to determine the diastereoselectivity of the reaction by chiral HPLC using the following conditions: Chiralcel AD, 250 x 4.6 mm; eluent: heptane/IPA, 95:5; 6.56 min (major), 6.92 min (minor); *de* >99.5%.

$$[\alpha]_D^{22} = -15.8^\circ (c = 1.0, \text{CHCl}_3)$$

¹H NMR (400 MHz, CDCl₃) δ 4.13 (q, *J* = 7.1 Hz, 2H), 3.96 (m, 1H), 3.29 (s, 3H), 3.01 (d, *J* = 3.8 Hz, 1H), 2.82 (ddd, *J* = 7.7, 5.1, 4.0 Hz, 1H), 2.46 (dd, *J* = 16.3, 3.3 Hz, 1H), 2.35 (dd, *J* = 16.4, 8.9 Hz, 1H), 1.75 –

1.57 (m, 1H), 1.55 – 1.27 (m, 7H), 1.23 (t, $J = 7.1$ Hz, 3H), 1.30 – 1.10 (m, 2H), 1.11 – 0.97 (m, 1H), 0.87 (t, $J = 7.4$ Hz, 3H), 0.79 (d, $J = 6.9$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 173.0 (s), 88.1 (d), 67.9 (d), 60.5 (t), 57.3 (q), 41.3 (t), 36.5 (t), 34.7 (d), 32.5 (t), 27.4 (t), 25.7 (t), 22.3 (t), 14.7 (q), 14.1 (q), 10.0 (q).

HRMS (ESI+) m/z : Calcd for $\text{C}_{15}\text{H}_{31}\text{O}_4$ ($\text{M}+\text{H}^+$) 275.2217, found 275.2205.

(3R,8S,9R)-3-hydroxy-N,9-dimethoxy-N,8-dimethylundecanamide (**18**)

A solution of AlMe_3 in toluene (2 M, 2.71 mL, 5.41 mmol) was added to a stirred mixture of *N,O*-dimethylhydroxylamine hydrochloride (528 mg, 5.41 mmol) in THF (15 mL) at 0 °C. The reaction was stirred for 2 h while warming up slowly to RT. Afterwards, the reaction was cooled down to 0 °C and a solution of the hydroxyester **17** (495 mg, 1.80 mmol) was slowly added. After completion of the reaction as indicated by TLC (pentane-Et₂O 3:7, 4 h), the reaction was quenched with a 20% Rochelle's salt solution (5 mL) and stirred for 30 min. Then, EtOAc (100 mL) and 2 M aq. NaOH (5 mL) were added. The organic layer was separated and the aqueous layer extracted with EtOAc (2x20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL) and then dried (Na_2SO_4). The solvent was removed under reduced pressure and the product was purified by column chromatography to give **18** (382 mg, 1.32 mmol, 73% yield) as colorless oil.

$[\alpha]_{\text{D}}^{22} = -48.6^\circ$ ($c = 1.0$, CHCl_3)

^1H NMR (400 MHz, CDCl_3) δ 4.01 (m, 1H), 3.77 (s, 1H), 3.68 (s, 3H), 3.33 (s, 3H), 3.19 (s, 3H), 2.86 (ddd, $J = 7.6, 5.0, 4.0$ Hz, 1H), 2.66 (d, $J = 16.6$ Hz, 1H), 2.43 (dd, $J = 17.0, 9.7$ Hz, 1H), 1.69 (d, $J = 6.6$ Hz, 1H), 1.61 – 1.17 (m, 12H), 1.17 – 1.04 (m, 1H), 0.90 (t, $J = 7.4$ Hz, 3H), 0.82 (d, $J = 6.8$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 173.6 (s), 86.4 (d), 67.6 (d), 61.0 (q), 57.1 (q), 38.0 (t), 36.4 (t), 34.5 (d), 32.4 (t), 31.5 (q), 27.3 (t), 25.6 (t), 22.1 (t), 14.5 (q), 9.8 (q).

HRMS (ESI+) m/z : Calcd for $C_{15}H_{32}NO_4$ ($M+H^+$) 290.2331, found 290.2314.

Scheme 2. Preparation of building blocks **22** and **4**. Reagents and conditions: a) NaH, 1,3-diaminopropane, 70 °C, 61%; b) *n*BuLi, TMSCl, THF, -40 °C to RT; c) *p*-TsCl, pyridine, CHCl₃, RT, 87%; d) NaI, acetone, RT, 86%; e) **22**, *t*BuLi, Et₂O, -84 °C, 2h, then amide **18**, 81%; f) NH₄BH(OAc)₃, MeCN, AcOH, THF, -25 °C, 76%; g) MeOH, K₂CO₃, RT, quant.; TMS=trimethylsilyl, *p*-TsCl=*p*-toluenesulfonyl chloride.

15-Hexadecyn-1-ol (**19**)

NaH (60% in mineral oil, 6.41 g, 147 mmol) was washed with pentane and carefully added to a flask containing 1,3-diaminopropane (70 mL, highly hygroscopic!). The reaction was heated at 50 °C until it became clear (approx. 1 h). Then, the mixture was cooled down to RT and the alkyne **5** (5.0 g, 21 mmol) was added. The reaction was heated to 69 °C and stirred for 24 h. Subsequently, the mixture was poured into a beaker containing an ice-water mixture and extracted with Et₂O (3x75 mL). The combined organic extracts were washed with 0.1 M aq. HCl (30 mL), brine, and dried (Na₂SO₄). The solvent was removed under reduced pressure and the product was purified by column chromatography to give **19** (3.05 g, 12.8 mmol, 61% yield) as a white solid. Spectroscopic data were in agreement with the literature.²

² F. M. Menger, X. Y. Chen, S. Brocchini, H. P. Hopkins, D. Hamilton, *J. Am. Chem. Soc.* **1993**, *115*, 6600–6608

^1H NMR (400 MHz, CDCl_3) δ 3.60 (t, J = 6.7 Hz, 2H), 2.15 (dt, J = 2.6 Hz, J = 7.1 Hz, 2H), 1.91 (t, J = 2.6 Hz, 1H), 1.67 (s, 1H), 1.52 (m, 4H), 1.38-1.24 (m, 20H).

^{13}C NMR (101 MHz, CDCl_3) δ 84.6 (s), 67.9 (d), 62.8 (t), 32.6 (t), 29.56 (t), 29.54 (t), 29.52 (t), 29.43 (t), 29.37 (t), 29.03 (t), 28.6 (t), 28.4 (t), 25.6 (t), 18.3 (t).

16-(trimethylsilyl)hexadec-15-yn-1-ol (**20**)

$n\text{BuLi}$ (1.6 M, 15.7 mL, 25.1 mmol) was added to a solution of alkynol **19** (2.72 g, 11.4 mmol) in THF (150 mL) at -45°C . The reaction was stirred for 3 h, allowing the reaction to slowly reach RT during this time. After that, TMSCl (3.2 mL, 25.1 mmol) was added and the cloudy mixture became clear in few min. The reaction was followed by quenching some drops of the reaction in Et_2O -aq. NH_4Cl and analyzing the organic layer by TLC (pentane- EtOAc 9:1). When full conversion was observed (TLC, ca 1.5 h), aq. HCl (2 M, 5 mL) was added to the reaction and the mixture was stirred for 30 min. Then, most of the THF was removed under reduced pressure, water was added (60 mL) and the mixture was extracted with EtOAc (3x20 mL). The solvent was removed under reduced pressure and the product was purified by column chromatography to give **20** (3.25 g, 10.5 mmol, 92% yield) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 3.62 (t, J = 6.7 Hz, 2H), 2.19 (t, J = 7.2 Hz, 2H), 1.58-1.44 (m, 5H), 1.29 (m, 20H), 0.13 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ 107.8 (s), 84.2 (s), 63.0 (t), 32.8 (t), 29.6 (t), 29.58 (t), 29.56 (t), 29.45 (t), 29.41 (t), 29.04 (t), 28.76 (t), 28.60 (t), 25.7 (t), 19.8 (t), 0.2 (q).

HRMS (ESI+) m/z : Calcd for $\text{C}_{19}\text{H}_{38}\text{OSiNa}$ ($\text{M}+\text{Na}^+$) 333.2584, found 333.2581.

16-(trimethylsilyl)hexadec-15-yn-1-yl 4-toluenesulfonate (**21**)

Alkyne **20** (2.3 g, 7.4 mmol) and pyridine (1.8 mL, 22 mmol) were dissolved in CHCl_3 (10 mL) and stirred at 0°C . Then, p -toluenesulfonyl chloride (2.82 g, 14.8 mmol) was added to this solution and the reaction was stirred until full conversion was observed by TLC (5 h). Subsequently, the reaction was diluted with Et_2O (75 mL), washed with water (10 mL), aq. HCl (2 M, 10 mL), aq. sat. NaHCO_3 (10 mL), and brine (10 mL). The organic extract was dried (MgSO_4), the solvent removed under reduced pressure, and the product was purified by column chromatography to give **21** (3.0 g, 6.5 mmol, 87% yield) as a colorless solid.

¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.01 (t, *J* = 6.5 Hz, 2H), 2.44 (s, 3H), 2.20 (t, *J* = 7.2 Hz, 2H), 1.62 (dt, *J* = 6.6 Hz, *J* = 13.5 Hz, 2H), 1.50 (dt, *J* = 6.6 Hz, *J* = 13.5 Hz, 2H), 1.40-1.21 (m, 20H), 0.14 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 144.5 (s), 133.2 (s), 129.7 (d), 127.8 (d), 107.7 (s), 84.2 (s), 70.7 (d), 29.58 (d), 29.56 (d), 29.54 (d), 29.45 (d), 29.35 (d), 29.04 (d), 28.89 (d), 28.78 (d), 28.75 (d), 28.59 (d), 25.29 (d), 21.59 (d), 19.8 (d), 0.2 (q).

HRMS (ESI+) *m/z*: Calcd for C₂₆H₄₄O₃SSiNa (M+Na⁺) 487.2678, found 487.2686.

(16-iodohexadec-1-yn-1-yl)trimethylsilane (**22**)

Tosylate **21** (1.71 g, 3.68 mmol) and sodium iodide (1.82 g, 12.1 mmol) were dissolved in acetone (40 mL) under nitrogen. The reaction was stirred until full conversion was observed by TLC (48 h). Then, the reaction was diluted in EtOAc (50 mL), most of the acetone was removed under reduced pressure and more EtOAc (50 mL) was added. The reaction was washed with aq. Na₂S₂O₃ (10%, 10 mL), water (10 mL) and brine (10 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure and the product purified to get **22** (1.33 g, 3.16 mmol, 86% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 3.18 (t, *J* = 7.1 Hz, 2H), 2.21 (t, *J* = 7.1 Hz, 2H), 1.82 (q, *J* = 7.1 Hz, 2H), 1.51 (q, *J* = 7.1 Hz, 2H), 1.41-1.33 (m, 2H), 1.31-1.24 (m, 18H), 0.14 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 107.7 (q), 84.2 (q), 33.6 (t), 30.5 (t), 29.59 (t), 29.55 (t), 29.52 (t), 29.46 (t), 29.40 (t), 29.05 (t), 28.76 (t), 28.61 (t), 28.52 (t), 19.8 (t), 7.2 (t), 0.18 (q).

HRMS (ESI+) *m/z*: Calcd for C₁₉H₃₇ISiNa (M+Na⁺) 443.1607, found 443.1609

(3R,4S,9R)-9-hydroxy-3-methoxy-4-methyl-27-(trimethylsilyl)heptacos-26-yn-11-one (**23**)

Tert-BuLi (1.7 M, 3.58 mL, 6.08 mmol) was added to a stirred solution of iodoalkyne **22** (1.59 g, 3.79 mmol) in Et₂O (40 mL) at -84°C (EtOAc / liq. N₂ bath). After 1 h at this temperature, a solution of Weinreb amide **18** (332 mg, 1.15 mmol) in Et₂O (20 mL) was added to the reaction. The reaction was stirred until full conversion was observed by TLC (1 h). Then a saturated aqueous solution of NH₄Cl (10 mL) was added to quench the reaction. The mixture was diluted with additional Et₂O (20 mL), the aqueous layer was removed and the organic layer washed with water (10 mL) and brine (10 mL). Et₂O was removed under reduced pressure and the product was purified by column chromatography to give compound **23** (484 mg, 0.926 mmol, 81% yield) as a colorless oil.

$[\alpha]_D^{22} = -13.6^\circ$ ($c = 1.0$, CHCl_3)

^1H NMR (400 MHz, CDCl_3) δ 4.00 (m, 1H), 3.31 (s, $J = 0.6$ Hz, 3H), 3.07 (s, 1H), 2.85 (ddd, $J = 7.7, 5.2, 4.2$ Hz, 1H), 2.57 (dd, $J = 17.4, 2.6$ Hz, 1H), 2.47 (dd, $J = 17.4, 8.9$ Hz, 1H), 2.40 (t, $J = 7.4$ Hz, 2H), 2.19 (t, $J = 7.1$ Hz, 2H), 1.72 – 1.62 (m, 1H), 1.60 – 1.32 (m, 13H), 1.31 – 1.15 (m, 20H), 1.13 – 1.01 (m, 1H), 0.89 (t, $J = 7.4$ Hz, 3H), 0.81 (d, $J = 6.7$ Hz, 3H), 0.12 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ 212.6 (s), 107.7 (s), 86.6 (d), 84.2 (s), 67.6 (d), 57.3 (q), 48.9 (t), 43.7 (t), 36.4 (t), 34.8 (d), 32.6 (t), 29.59 (t), 29.55 (t), 29.54 (t), 29.44 (t), 29.41 (t), 29.34 (t), 29.13 (t), 29.0 (t), 28.8 (t), 28.6 (t), 27.4 (t), 25.8 (t), 23.6 (t), 22.3 (t), 19.8 (t), 14.8 (q), 10.0 (q), 0.1 (q).

HRMS (ESI+) m/z : Calcd for $\text{C}_{32}\text{H}_{62}\text{O}_3\text{SiNa}$ ($\text{M}+\text{Na}^+$) 545.4366, found 545.4355.

(3R,4S,9R,11R)-3-methoxy-4-methyl-27-(trimethylsilyl)heptacos-26-yne-9,11-diol (**24**)

Tetramethylammonium triacetoxyborohydride (1.69 g, 6.43 mmol) was added in portions over 30 min to a solution of **23** (480 mg, 0.918 mmol) in a 1:1 mixture of AcOH and MeCN (80 mL) and THF (3 mL) at -25°C . The reaction was stirred at this temperature during 5.5 h when TLC analysis showed full conversion (solvents were removed from the TLC spot with a heat gun before eluting with a pentane-Et₂O 75:25 mixture). Subsequently, the reaction was quenched with an aqueous solution of Rochelle's salt (20%, 20 mL) and stirred at RT for 30 min. Subsequently, water (300 mL) was added to the reaction and the mixture was extracted with DCM (4x75 mL) and Et₂O (75 mL). The organic extracts were combined and neutralized by adding water (30 mL) and solid NaHCO_3 until pH >7. Then the aqueous layer was separated and the organic layer was washed with water (20 mL), brine (20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the product purified by column chromatography to give compound **24** (360 mg, 0.686 mmol, 75% yield) as a white waxy solid.

Notes: the hydroxy ketone had a low solubility in the AcOH-MeCN solvent mixture at -25°C , therefore a high dilution was required. The reaction was not heterogeneous but cloudy, although it was not determined whether that was because of the low solubility or because AcOH was freezing.

$[\alpha]_D^{22} = -4.0^\circ$ ($c = 1.0$, CHCl_3)

^1H NMR (400 MHz, CDCl_3) δ 3.89 (m, 2H), 3.31 (s, 3H), 2.85 (ddd, $J = 7.6, 5.3, 3.9$ Hz, 1H), 2.79 (br s, 2H), 2.18 (t, $J = 7.2$ Hz, 2H), 1.73 – 1.60 (m, 1H), 1.56 (t, $J = 5.6$ Hz, 2H), 1.53 – 1.30 (m, 15H), 1.33 – 1.16 (m, 20H), 1.13 – 1.01 (m, 1H), 0.89 (t, $J = 7.3$ Hz, 3H), 0.81 (d, $J = 6.8$ Hz, 3H), 0.12 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ 107.7 (s), 86.7 (d), 84.2 (s), 69.30 (d), 69.25 (d), 57.3 (q), 42.2 (t), 37.45 (t), 37.43 (t), 34.8 (d), 32.6 (t), 29.63 (t), 29.62 (t), 29.60 (t), 29.55 (t), 29.45 (t), 29.03 (t), 28.74 (t), 28.58 (t), 27.5 (t), 26.1 (t), 25.8 (t), 22.3 (t), 19.8 (t), 14.8 (q), 10.0 (q), 0.1 (q).

HRMS (ESI+) m/z : Calcd for $\text{C}_{32}\text{H}_{64}\text{O}_3\text{SiNa}$ ($\text{M}+\text{Na}^+$) 547.4517, found 547.4514.

(3R,4S,9R,11R)-3-methoxy-4-methylheptacos-26-yne-9,11-diol (4)

K₂CO₃ (142 mg, 10.3 mmol) was added to a solution of diol **24** in MeOH (15 mL) and the reaction stirred overnight at RT. Then, the reaction was diluted with EtOAc (50 mL), washed with water (2x10 mL) and brine (10 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure and the product purified by short column chromatography to give compound **4** (312 mg, 0.689 mmol, quantitative) as a white waxy solid.

$$[\alpha]_D^{22} = -5.8^\circ (c = 1.0, \text{CHCl}_3)$$

¹H NMR (400 MHz, CDCl₃) δ 3.92 (m, 2H), 3.32 (s, 3H), 2.86 (ddd, *J* = 7.7, 5.2, 4.3 Hz, 1H), 2.40 (s, 2H), 2.17 (td, *J* = 7.1, 2.7 Hz, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.73 – 1.63 (m, 1H), 1.59 (t, *J* = 5.6 Hz, 2H), 1.45 (dddd, *J* = 23.6, 21.3, 10.8, 5.0 Hz, 14H), 1.34 – 1.16 (m, 21H), 1.16 – 1.01 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 86.7 (d), 84.8 (s), 69.42 (d), 69.37 (d), 68.0 (d), 57.5 (q), 42.3 (t), 37.48 (t), 37.47 (t), 34.8 (d), 32.6 (t), 29.63 (t), 29.58 (t), 29.48 (t), 29.08 (t), 28.7 (t), 28.5 (t), 27.5 (t), 26.1 (t), 25.8 (t), 22.3 (t), 18.4 (t), 14.8 (q), 10.0 (q).

HRMS (ESI⁺) *m/z*: Calcd for C₂₉H₅₆O₃Na (M+Na⁺) 475.4122, found 475.4123.

Scheme 3. Reagents and conditions: a) (i) Ac₂O 8 eq., Pyridine 8 eq., DMAP 0.05 eq. 0 °C to RT; (ii) p-Iodophenol 2 eq; BF₃·Et₂O 2 eq, DCM, RT, 80% (two steps); b) (i) MeONa 0.05 eq MeOH, RT; (ii) 2,2-

dimethoxy-propane 3.7 eq, CSA 0.1 eq, acetone, RT, 94% two steps; c) NaH 1.1 eq, BnBr 1.1 eq, DMF, 0 °C to RT, 90%; d) THF/H₂O/TFA = 4/1/1 (v/v/v), RT, 87%; e) Bu₂SnO 1eq, toluene, Dean-Stark reflux; then allyl bromide 1.5 eq, TBAI 0.3 eq, toluene 90 °C, 67%; f) MeI 2 eq, NaH 1.5 eq, DMF, 0 °C to RT, 86%; g) PdCl₂, 0.05 eq, MeOH, RT 91%.

***p*-iodophenyl 2,3,4-tri-*O*-acetyl- α -L-rhamnopyranoside (**S1**)**

Peracetylated rhamnose³ (3.5 g, 10.5 mmol) and *p*-iodophenol (4.6 g, 21.0 mmol) were dissolved in CH₂Cl₂ (150 mL) at room temperature. BF₃·Et₂O (2.26 mL, 17.9 mmol) was added and the mixture was stirred at RT for 6 h. When the reaction was judged to be complete by TLC analysis, it was quenched by the addition of an equal volume of saturated aqueous solution of NaHCO₃. The organic layer was further washed with NaHCO₃, a solution of NaOH (3.0 g in 100 mL H₂O) and brine. After drying with Na₂SO₄, the solvent was removed under reduced pressure. Flash chromatography of the residue over silica gel using 4:1 petroleum ether - EtOAc yielded 4.1 g, 8.4 mmol, of **S1** (80%) as white solid.

$[\alpha]_D^{22} = -81.8^\circ$ ($c = 0.37$, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 5.48 (dd, $J = 10.1, 3.3$ Hz, 1H), 5.41 (m, 2H), 5.15 (t, $J = 10.0$ Hz, 1H), 3.93 (dq, $J = 10.0, 6.2$ Hz, 1H), 2.19 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.20 (d, $J = 6.3$ Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.15, 170.06, 155.71, 138.57, 118.69, 95.62, 85.52, 70.87, 69.59, 68.86, 67.37, 21.02, 20.92, 20.87, 17.53.

IR: 2982, 1748, 1485, 1369, 1219, 1130, 1034, 984, 822 cm⁻¹

HRMS (ESI⁺): m/z [M + NH₄]⁺ calcd for C₁₈H₂₅INO₈ 510.0619 found 510.0616

***p*-iodophenyl 2,3-*O*-isopropylidene- α -L-rhamnopyranoside (**S2**)**

³ G. M. Beaubault, G. G. S. Dutton, C. K. Warfield, *Carb. Res.* **1974**, *34*, 174

Compound **S1** (4.0 g, 8.13 mmol) was dissolved in MeOH (150 mL) and a freshly cut piece of Na (10.1 mg, 0.44 mmol) was added at RT. The mixture was stirred for 16 h before being neutralized by the addition of amberlite IR-120 (H⁺) resin until neutral pH (as indicated by pH-paper). The mixture was filtered and concentrated under reduced pressure to obtain the intermediate triol that was dissolved in acetone (120 mL) and charged with 2,2-dimethoxypropane (3.7 mL, 30 mmol) and D-(+)-10-camphorsulfonic acid (174 mg, 0.75 mmol). The mixture was stirred at RT for 15 h and then neutralized with Et₃N. The volatiles were partially removed under reduced pressure, and the crude material was redissolved in AcOEt, and washed with water and brine. After drying with Na₂SO₄, the solvent was removed under reduced pressure. Flash chromatography of the residue over silica gel using 4:1 petroleum ether - EtOAc yielded 2.87 g, 7.06 mmol of **S2** (94%) as white solid.

$[\alpha]_D^{22} = -74.8^\circ$ ($c = 0.41$, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.55 (m, 2H), 6.87 – 6.81 (m, 2H), 5.68 (s, 1H), 4.34 (d, $J = 5.7$ Hz, 1H), 4.25 – 4.19 (m, 1H), 3.72 (dq, $J = 9.8, 6.2$ Hz, 1H), 3.45 (ddd, $J = 9.7, 7.4, 4.1$ Hz, 1H), 2.57 (d, $J = 4.1$ Hz, 1H), 1.57 (s, 3H), 1.40 (s, 3H), 1.23 (d, $J = 6.2$ Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 156.06, 138.53, 118.76, 110.01, 95.52, 85.02, 78.54, 75.83, 74.68, 66.77, 28.18, 26.42, 17.43.

IR: 3433, 2982, 2931, 1586, 1485, 1384, 1219, 1141, 1080, 1030, 991, 930, 818 cm⁻¹

HRMS (ESI⁺): m/z [M + NH₄]⁺ calcd for C₁₅H₂₃INO₅ 424.0615; found: 424.0614

***p*-iodophenyl 2,3-*O*-isopropylidene-4-*O*-benzyl- α -L-rhamnopyranoside (**S3**)**

Compound **S2** (2.84 g, 7.0 mmol) was dissolved in DMF (100 mL). The solution was briefly degassed at 40 °C under reduced pressure before it was cooled to 0 °C. Benzyl bromide (1.1 mL, 9.0 mmol) and NaH (215 mg, 9.0 mmol) were sequentially added and the obtained mixture was allowed to warm to RT while being stirred at room temperature for 16 h. The reaction was quenched by carefully adding MeOH at 0 °C and an equal amount of water was added. The mixture was extracted with four portions of diethylether; the combined organic layers were washed with saturated aqueous NaHCO₃, pure water and finally brine. The solvent was dried with Na₂SO₄ and removed under reduced pressure. Flash chromatography of the residue over silica gel using 15:1 petroleum ether - EtOAc yielded 2.87 g, 6.3 mmol of **S3** (90%) as white solid.

$[\alpha]_D^{22} = -94.0^\circ$ ($c = 0.40$, CHCl_3)

^1H NMR (400 MHz, CDCl_3) δ 7.59 – 7.53 (m, 2H), 7.39 – 7.23 (m, 5H), 6.85 – 6.79 (m, 2H), 5.66 (s, 1H), 4.91 (d, $J = 11.6$ Hz, 1H), 4.64 (d, $J = 11.6$ Hz, 1H), 4.45 – 4.38 (m, 1H), 4.34 (d, $J = 5.8$ Hz, 1H), 3.80 – 3.70 (m, 1H), 3.27 (dd, $J = 9.8, 7.0$ Hz, 1H), 1.54 (s, 3H), 1.41 (s, 3H), 1.21 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 156.05, 138.48, 138.25, 128.43, 128.12, 127.82, 118.75, 109.70, 95.41, 84.92, 80.93, 78.63, 75.90, 73.12, 65.81, 28.10, 26.53, 17.98.

IR: 2982, 2931, 2913, 1586, 1485, 1454, 1381, 1219, 1165, 1123, 1080, 1030, 991, 864, 822, 737, 698 cm^{-1}

HRMS (ESI⁺): m/z $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{22}\text{H}_{29}\text{INO}_5$: 514.1085; found: 514.1082

***p*-iodophenyl 4-*O*-benzyl- α -L-rhamnopyranoside (**S4**)**

Compound **S3** (2.8 g, 5.64 mmol) was dissolved in a mixture of THF (70 mL) and H_2O (18 mL). After being cooled to 0°C , trifluoroacetic acid (18 mL) was added. The mixture was then warmed to RT and stirred at the same temperature for 16 h. All the volatile materials were then removed under reduced pressure, and the residue coevaporated two times with a small amount of toluene. The crude material was directly subjected to flash chromatography over silica gel using 8:3 petroleum ether – EtOAc, to yield 2.2 g, 2.24 mmol of **S4** (87%) as white solid.

$[\alpha]_D^{22} = -112.0^\circ$ ($c = 0.43$, CHCl_3)

^1H NMR (400 MHz, CDCl_3) δ 7.52 (d, $J = 8.8$ Hz, 2H), 7.37 – 7.21 (m, 5H), 6.77 (d, $J = 8.9$ Hz, 2H), 5.42 (s, 1H), 4.79 – 4.64 (m, 2H), 4.08 (m, 2H), 3.75 (dq, $J = 12.4, 6.2$ Hz, 1H), 3.43 (t, $J = 9.2$ Hz, 1H), 3.27 (s, 2H), 1.27 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 155.90, 138.42, 138.03, 128.68, 128.12, 127.93, 118.59, 97.36, 84.95, 81.33, 75.16, 71.26, 70.85, 68.30, 18.10.

IR: 3426, 2928, 1485, 1230, 1103, 1072, 1022, 983, 736, 698 cm^{-1}

HRMS (ESI⁺): m/z $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{19}\text{H}_{25}\text{INO}_5$: 474.0772 found: 474.0771

***p*-iodophenyl 3-*O*-allyl-4-*O*-benzyl- α -L-rhamnopyranoside (**S5**)**

Compound **S4** (1.23 g, 2.7 mmol) was suspended in toluene. Dibutyltin oxide (DBTO) (0.67 g, 2.7 mmol) was added and the resulting suspension was heated to reflux. The generated water was removed employing a Dean-Stark cooling device, and the clear solution obtained was refluxed for 1 h. The reaction mixture was then cooled to RT and allyl-bromide (0.35 mL, 4.05 mmol) and TBAI (300 mg, 0.81 mmol) were added. The mixture was then heated to 90 °C and stirred for 10 h. After cooling to room temperature, the mixture was washed with H₂O, NaHCO₃ (aq.) and brine. The organic layer was dried (Na₂SO₄) and the filtered over a pad of celite; the solvent was removed under reduced pressure. Flash chromatography of the residue over silica gel using 4:1 petroleum ether - EtOAc yielded 896 mg, 1.8 mmol of **S5** (67%) as pale yellow oil.

$[\alpha]_D^{22} = -87.7^\circ$ ($c = 0.44$, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.60 – 7.53 (m, 2H), 7.42 – 7.27 (m, 5H), 6.86 – 6.80 (m, 2H), 6.00 (ddt, $J = 17.0, 10.5, 5.6$ Hz, 1H), 5.52 (d, $J = 1.5$ Hz, 1H), 5.38 (dq, $J = 17.2, 1.5$ Hz, 1H), 5.26 (dd, $J = 10.4, 1.4$ Hz, 1H), 4.89 (d, $J = 10.8$ Hz, 1H), 4.65 (d, $J = 10.8$ Hz, 1H), 4.32 – 4.16 (m, 3H), 3.91 (dd, $J = 9.1, 3.4$ Hz, 1H), 3.76 (dq, $J = 9.8, 6.2$ Hz, 1H), 3.50 (t, $J = 9.4$ Hz, 1H), 2.76 (s, 1H), 1.27 (d, $J = 6.2$ Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 156.00, 138.43, 138.27, 134.49, 128.53, 128.13, 127.93, 118.65, 117.68, 97.02, 84.84, 79.72, 79.35, 75.58, 71.23, 68.53, 68.29, 17.99.

IR: 3426, 2924, 1728, 1581, 1485, 1234, 1099, 1076, 987, 925, 822, 748, 698 cm⁻¹

HRMS (ESI⁺): m/z [M + NH₄]⁺ calcd for C₂₂H₂₉INO₅: 514.1085 found: 514.10841

***p*-iodophenyl 2-*O*-methyl-3-*O*-allyl-4-*O*-benzyl- α -L-rhamnopyranoside (**S6**)**

Compound **S5** (415 mg, 0.83 mmol) was dissolved in DMF, and the mixture was rapidly degassed under reduced pressure at 40 °C before being cooled to 0 °C. MeI (0.1 mL, 1.7 mmol) and NaH (30 mg, 1.25 mmol) were added and the reaction mixture was allowed to warm to RT over the course of 15 h. The reaction was quenched by the careful addition of MeOH. The reaction mixture was diluted with water and extracted with four portions of diethyl ether. The combined organic layers were washed successively with saturated aqueous NaHCO₃, H₂O and brine. The solvent was dried with Na₂SO₄ and removed under reduced pressure. Flash chromatography of the residue over silica gel using 4:1 petroleum ether - EtOAc yielded 365 mg, 0.72 mmol of **S6** (86%) as colorless oil.

$[\alpha]_D^{22} = -73.3^\circ$ ($c = 0.30$, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.60 – 7.53 (m, 2H), 7.39 – 7.25 (m, 5H), 6.86 – 6.79 (m, 2H), 6.08 – 5.96 (m, 1H), 5.51 (d, $J = 1.8$ Hz, 1H), 5.38 (dq, $J = 17.2, 1.6$ Hz, 1H), 5.24 (dd, $J = 10.4, 1.5$ Hz, 1H), 4.95 (d, $J = 10.7$ Hz, 1H), 4.63 (d, $J = 10.8$ Hz, 1H), 4.31 – 4.22 (m, 2H), 3.93 (dd, $J = 9.4, 3.2$ Hz, 1H), 3.76 – 3.66 (m, 2H), 3.60 (s, 3H), 3.55 (t, $J = 9.5$ Hz, 1H), 1.27 (d, $J = 6.2$ Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 156.16, 138.49, 138.44, 134.95, 128.50, 128.13, 127.83, 118.64, 117.26, 95.48, 84.82, 80.25, 79.25, 78.02, 75.64, 71.57, 68.86, 59.71, 18.04.

IR: 2924, 1485, 1454, 1277, 1234, 1138, 1099, 1045, 991, 922, 822, 745, 698

HRMS (ESI⁺): m/z [M + NH₄]⁺ calcd for C₂₃H₃₁INO₅: 528.1241; found: 528.1242

***p*-iodophenyl 2-*O*-methyl-4-*O*-benzyl- α -L-rhamnopyranoside (**8**)**

Compound **S6** (330 mg, 0.64 mmol) was dissolved in MeOH (10 mL) and PdCl₂ (5.7 mg, 0.03 mmol) was added. The mixture was stirred at room temperature for 15 h, the black precipitate formed during the course of the reaction was discarded by filtration over a pad of celite. The residue was added to saturated aqueous NaHCO₃ and diluted with AcOEt. The layers were separated and the water layer was further extracted with one portion of EtOAc. The combined organic layers were washed with brine and dried with Na₂SO₄. The solvent was removed under reduced pressure. Flash chromatography of the residue over silica gel using 3:1 petroleum ether - EtOAc yielded 273 mg, 0.58 mmol of **8** (91%) as colorless oil.

$[\alpha]_D^{22} = -93.1^\circ$ ($c = 0.35$, CHCl₃)

^1H NMR (400 MHz, CDCl_3) δ 7.60 – 7.54 (m, 2H), 7.40 – 7.26 (m, 5H), 6.86 – 6.81 (m, 2H), 5.53 (d, J = 1.4 Hz, 1H), 4.92 (d, J = 11.1 Hz, 1H), 4.69 (d, J = 11.1 Hz, 1H), 4.12 (td, J = 7.9, 7.3, 4.5 Hz, 1H), 3.76 – 3.69 (m, 1H), 3.67 (dd, J = 3.7, 1.7 Hz, 1H), 3.56 (s, 3H), 3.34 (t, J = 9.3 Hz, 1H), 2.50 (d, J = 8.1 Hz, 1H), 1.28 (d, J = 6.2 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 156.18, 138.46, 138.35, 128.55, 128.06, 127.92, 118.64, 94.47, 84.89, 81.93, 80.42, 75.30, 71.47, 68.21, 59.29, 18.11.

IR: 3450, 2928, 1588, 1485, 1385, 1277, 1231, 1096, 995, 822, 745 cm^{-1}

HRMS (ESI⁺): m/z $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{INO}_5$: 488.0928 found: 488.0929

Scheme 4. Reagents and conditions: a) Bu_2SnO 1eq, toluene, Dean-Stark reflux; then allylBr 1.5 eq, TBAI 0.3 eq, toluene 110 $^\circ\text{C}$, 75%; b) BzCl 1.4 eq, NaH 1.4 eq, DMF, 0 $^\circ\text{C}$ to RT, 85%.

Phenyl 3-*O*-allyl-4-*O*-benzyl-1-thio- α -L-rhamnopyranoside (S8)

Compound **S7**⁴ (1.0 g, 2.9 mmol) was suspended in toluene (120 mL). Bu_2SnO (0.72 g, 2.9 mmol) was added and the suspension was heated to reflux and the water formed was removed with the aid of a Dean-Stark reflux condenser. The reaction mixture was further refluxed for 1 h, when it was allowed to cool to RT. TBAI (321 mg, 0.87 mmol), TBAB (280 mg, 0.87 mmol) and allyl bromide (0.38 mL, 4.35 mmol) were added. The mixture was heated to reflux with stirring for 6 h. After cooling to room

⁴ Zegelaar-Jaarsveld, K.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron*, **1992**, 48, 10133

temperature, the mixture was washed with water, saturated aqueous NaHCO₃ and brine. The organic layer was dried (Na₂SO₄), filtered over celite and the volatiles were removed under reduced pressure. Flash chromatography of the residue over silica gel using 4:1 petroleum ether - EtOAc yielded 813 mg, 2.2 mmol of **S8** (75%) as colorless oil.

$$[\alpha]_D^{22} = -189.4^\circ (c = 0.42, \text{CHCl}_3)$$

¹H NMR (400 MHz, CDCl₃) δ 7.47-7.42 (m, 2H), 7.38 – 7.17 (m, 8H), 6.06 – 5.82 (m, 1H), 5.54 (d, J = 1.2 Hz, 1H), 5.33 (dd, J = 17.2, 1.5 Hz, 1H), 5.22 (dd, J = 10.4, 1.3 Hz, 1H), 4.86 (d, J = 10.9 Hz, 1H), 4.63 (d, J = 10.9 Hz, 1H), 4.25 (dd, J = 3.2, 1.5 Hz, 1H), 4.23 – 4.11 (m, 3H), 3.74 (dd, J = 9.1, 3.2 Hz, 1H), 3.50 (t, J = 9.3 Hz, 1H), 2.86 (s, 1H), 1.30 (d, J = 6.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 138.33, 134.36, 134.25, 131.32, 129.05, 128.45, 128.07, 127.83, 127.31, 117.79, 87.11, 80.10, 79.74, 75.46, 71.05, 70.25, 68.79, 17.84.

IR: 3421, 2916, 2870, 1581, 3181, 1211, 1099, 1084, 984, 926, 741, 694

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₂₂H₂₆NaO₄S: 404.1444; found: 404.1437

Phenyl 2-*O*-benzoyl-3-*O*-allyl-4-*O*-benzyl-1-thio- α -L-rhamnopyranoside (**9**)

Compound **S8** (0.89 g, 2.33 mmol) was dissolved in DMF (80 mL). The solution was partially degassed at 40 °C under reduced pressure before it was cooled to 0 °C. Benzoyl chloride (0.38 mL, 3.3 mmol) and NaH (78 mg, 3.3 mmol) were added and the resulting mixture was directly warmed to RT by replacing the ice-water bath with a water bath and stirring for 1 h. Upon disappearance of the starting material as judged by TLC analysis, the reaction was quenched by the addition of saturated aqueous NaHCO₃. After the addition of more water, the mixture was extracted with five portions of diethyl ether. The combined organic layers were washed again with water and finally brine, before being dried with Na₂SO₄. The solvents were removed under reduced pressure and the crude submitted to flash chromatography over silica gel using 15:1 petroleum ether – EtOAc to yield 0.97 g, 1.98 mmol of **9** (85%) as colorless oil.

$$[\alpha]_D^{22} = -92.1^\circ (c = 0.38, \text{CHCl}_3)$$

¹H NMR (400 MHz, CDCl₃) δ 8.12 – 8.05 (m, 2H), 7.63 – 7.56 (m, 1H), 7.52 – 7.44 (m, 4H), 7.43 – 7.23 (m, 8H), 5.98 – 5.86 (m, 1H), 5.79 (dd, J = 3.1, 1.7 Hz, 1H), 5.56 (d, J = 1.4 Hz, 1H), 5.33 (dq, J = 17.2, 1.5

Hz, 1H), 5.20 (dq, $J = 10.4, 1.5$ Hz, 1H), 4.98 (d, $J = 10.8$ Hz, 1H), 4.70 (d, $J = 10.8$ Hz, 1H), 4.38 – 4.21 (m, 2H), 4.20 – 4.07 (m, 1H), 3.96 (dd, $J = 9.3, 3.2$ Hz, 1H), 3.62 (t, $J = 9.4$ Hz, 1H), 1.41 (d, $J = 6.4$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 165.74, 138.40, 134.48, 134.06, 133.35, 131.81, 129.98, 129.96, 129.19, 128.53, 128.51, 128.30, 127.91, 127.72, 117.72, 86.31, 80.24, 78.13, 75.61, 71.45, 70.83, 69.18, 18.14.

IR: 2905, 1724, 1450, 1381, 1265, 1177, 1096, 1026, 988, 918, 849, 745, 710 cm^{-1}

HRMS (ESI⁺): m/z $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{29}\text{H}_{34}\text{NO}_5\text{S}$: 508.2152 found: 508.2162

Scheme 5. Reagents and conditions: (a) Ac_2O 4.3 eq, pyridine 4.3 eq,, DMAP 0.16 eq, AcOEt , 0 to 50 $^\circ\text{C}$, 83%.

Phenyl 2-*O*-methyl-3,4-di-*O*-acetyl-1-thio- β -L-fucopyranoside (**10**)

Compound **S9**⁵ (1.45 g, 5.36 mmol) was suspended in EtOAc (50 mL) and pyridine (1.8 mL, 23 mmol) was added. The suspension was cooled to 0 $^\circ\text{C}$ before acetic anhydride (2.2 mL, 23 mmol) and DMAP (100 mg, 0.88 mmol) were added. The reaction mixture was then warmed to 50 $^\circ\text{C}$ and stirred 3 h, cooled again to 0 $^\circ\text{C}$ in order to destroy the excess of acetic anhydride by the addition of MeOH . The mixture was dissolved in EtOAc and washed with water, diluted HCl , saturated aqueous NaHCO_3 and brine. The organic layer was dried Na_2SO_4 and concentrated under reduced pressure. Flash chromatography of the residue over silica gel using 4:1 petroleum ether - EtOAc yielded 1.6 g, 4.5 mmol of **10** (83%) as white solid.

$[\alpha]_{\text{D}} +6.3^\circ$ ($c = 1.18$, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 7.71 – 7.47 (m, 2H), 7.36 – 7.28 (m, 3H), 5.24 (dd, $J = 3.4, 1.0$ Hz, 1H), 4.95 (dd, $J = 9.7, 3.3$ Hz, 1H), 4.61 (d, $J = 9.7$ Hz, 1H), 3.78 (qd, $J = 6.4, 1.1$ Hz, 1H), 3.52 (s, 3H), 3.42 (t, $J = 9.7$ Hz, 1H), 2.16 (s, 3H), 2.03 (s, 3H), 1.21 (d, $J = 6.4$ Hz, 3H).

⁵ Paquette, L. A.; Barriault, L.; Pissarnitski, D.; Johnston, J. N. *J. Am. Chem. Soc.*, **2000**, *122*, 619

^{13}C NMR (101 MHz, CDCl_3) δ 170.67, 170.17, 133.58, 132.17, 128.96, 127.72, 87.53, 76.59, 74.87, 72.92, 70.94, 61.10, 20.99, 20.87, 16.67.

IR: 2936, 1744, 1439, 1369, 1242, 1223, 1126, 1080, 1022, 914, 744 cm^{-1}

HRMS (ESI $^{+}$): m/z $[\text{M} + \text{NH}_4]^{+}$ calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_6\text{S}$: 372.1475 found: 372.1475

Scheme 6. Assembly of trisaccharide 7.

(2-*O*-benzoyl-3-*O*-allyl-4-*O*-benzyl- α -L-rhamnopyranosyl)-(1 $\rightarrow$ 3)-*p*-iodophenyl 2-*O*-methyl-4-*O*-benzyl- α -L-rhamnopyranoside (25)

Compound donor **9** (515 mg, 1.05 mmol), acceptor **8** (380 mg, 0.81 mmol) and *N*-(thiophenyl)- ϵ -caprolactam **S10** (232 mg, 1.05 mmol) were co-evaporated with toluene. 2,4,6-tri-*tert*-Butyl pyrimidine (TTBP) (260 mg, 1.05 mmol) was added. The mixture was dissolved in freshly distilled CH_2Cl_2 (5 mL), and stirred for 20 min at ambient temperature before it was cooled to -25°C . TiF_4 (268 mg, 160 μL , 0.95 mmol) was added. The mixture was stirred until it reached RT and was finally quenched by the addition of saturated aqueous NaHCO_3 and extracted with Et_2O . The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated under reduced pressure. Flash

chromatography of the residue over silica gel using 8:1 petroleum ether - EtOAc yielded 489 mg, 0.58 mmol of disaccharide **25** (71%) as colorless oil.

$$[\alpha]_D^{22} = -65.1^\circ (c = 0.44, \text{CHCl}_3)$$

^1H NMR (400 MHz, CDCl_3) δ 8.11 – 8.05 (m, 2H), 7.65 – 7.53 (m, 3H), 7.49 (t, $J = 7.7$ Hz, 2H), 7.42 – 7.20 (m, 10H), 6.86 – 6.79 (m, 2H), 5.87 (ddd, $J = 22.7, 10.7, 5.6$ Hz, 1H), 5.70 (dd, $J = 3.1, 1.9$ Hz, 1H), 5.50 (d, $J = 1.7$ Hz, 1H), 5.28 – 5.19 (m, 2H), 5.09 (dd, $J = 10.4, 1.4$ Hz, 1H), 4.94 (dd, $J = 21.4, 10.8$ Hz, 2H), 4.67 (dd, $J = 19.7, 10.9$ Hz, 2H), 4.29 – 4.16 (m, 2H), 4.11 – 4.01 (m, 3H), 3.78 – 3.67 (m, 2H), 3.63 – 3.51 (m, 5H), 1.42 (d, $J = 6.2$ Hz, 3H), 1.26 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 165.61, 156.22, 138.51, 138.47, 137.96, 134.77, 133.26, 130.06, 129.98, 128.57, 128.51, 128.49, 128.35, 128.10, 127.92, 127.89, 118.65, 117.15, 99.93, 94.78, 84.90, 80.13, 80.03, 79.98, 78.87, 77.75, 75.68, 75.55, 70.69, 69.88, 69.06, 68.58, 59.06, 18.50, 18.10.

IR: 2974, 2927, 2855, 1724, 1485, 1454, 1385, 1358, 1269, 1234, 1099, 1045, 999, 922, 748, 698

HRMS (ESI⁺): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{43}\text{H}_{47}\text{IO}_{10}\text{Na}$: 873.2106 found: 873.2111

(3-*O*-allyl-4-*O*-benzyl- α -L-rhamnopyranosyl)-(1→3)-*p*-iodophenyl 2-*O*-methyl-4-*O*-benzyl- α -L-rhamnopyranoside (26**)**

Compound **25** (505 mg, 0.59 mmol) was dissolved in MeOH. A small piece of freshly cut sodium was added and the solution was stirred for 16 h. The catalyst was depleted by the addition of amberlite IR-120 (H^+) resin. The mixture was filtered and concentrated under reduced pressure; the crude product was judged to be pure enough to be used for the subsequent step without further purification.

$$[\alpha]_D^{22} = -104.8^\circ (c = 1.76, \text{CHCl}_3)$$

^1H NMR (400 MHz, CDCl_3) δ 7.61 – 7.54 (m, 2H), 7.41 – 7.27 (m, 10H), 6.88 – 6.80 (m, 2H), 5.93 (ddt, $J = 16.0, 10.9, 5.6$ Hz, 1H), 5.49 (d, $J = 1.6$ Hz, 1H), 5.29 (dd, $J = 17.2, 1.5$ Hz, 1H), 5.20 – 5.15 (m, 2H), 4.89 (d, $J = 10.9$ Hz, 1H), 4.80 (d, $J = 10.9$ Hz, 1H), 4.64 (dd, $J = 14.0, 11.0$ Hz, 2H), 4.20 (dd, $J = 9.5, 3.2$ Hz, 1H), 4.16 – 4.04 (m, 3H), 4.01 – 3.91 (m, 1H), 3.80 (dd, $J = 9.1, 3.3$ Hz, 1H), 3.76 – 3.67 (m, 2H), 3.50 (d, $J = 22.0$ Hz, 5H), 2.47 (s, 1H), 1.35 (d, $J = 6.3$ Hz, 2H), 1.25 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 156.22, 138.48, 138.44, 138.10, 134.64, 128.63, 128.51, 128.17, 127.97, 127.89, 127.84, 118.70, 117.41, 101.50, 94.80, 84.91, 80.30, 80.02, 79.91, 79.55, 78.85, 75.56, 75.49, 71.07, 69.19, 68.98, 68.14, 59.05, 18.21, 18.05.

IR: 3450, 2974, 2931, 2874, 1485, 1385, 1231, 1099, 1080, 1026, 999, 925, 822, 748

HRMS (ESI⁺): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{36}\text{H}_{43}\text{IO}_9\text{Na}$: 769.1844 found: 769.1845

(2-*O*-benzyl-3-*O*-allyl-4-*O*-benzyl- α -L-rhamnopyranosyl)-(1 $\rightarrow$ 3)-*p*-iodophenyl-2-*O*-methyl-4-*O*-benzyl- α -L-rhamnopyranoside **27**

Crude **26** (440 mg, 0.59 mmol) was dissolved in DMF (60 mL). The solution was briefly degassed at 40 °C under reduced pressure before it was cooled to 0 °C. Benzyl bromide (105 μL , 89 mmol) and NaH (21.2 mg, 0.89 mmol) were added. The mixture was stirred at RT for 2 h before being quenched with a few drops of MeOH. The solution was diluted with water and extracted with three portions of diethyl ether and washed with NaHCO_3 and water. The combined organic layers were washed with brine and dried with Na_2SO_4 . The volatiles were removed under reduced pressure and subsequent flash chromatography of the residue over silica gel using 7:1 petroleum ether - EtOAc yielded 430 mg, 0.51 mmol of benzylate disaccharide **27** (87%) as colorless glassy solid.

$[\alpha]_{\text{D}}^{22} = -66.6^\circ$ ($c = 0.53$, CHCl_3)

^1H NMR (400 MHz, CDCl_3) δ 7.62 – 7.56 (m, 2H), 7.41 – 7.25 (m, 15H), 6.89 – 6.83 (m, 2H), 5.93 (ddt, $J = 17.1, 10.6, 5.3$ Hz, 1H), 5.49 (d, $J = 1.6$ Hz, 1H), 5.30 (dq, $J = 17.2, 1.6$ Hz, 1H), 5.20 – 5.13 (m, 2H), 4.97 (d, $J = 10.9$ Hz, 1H), 4.75 (d, $J = 11.4$ Hz, 1H), 4.67 (d, $J = 10.9$ Hz, 1H), 4.64 – 4.53 (m, 3H), 4.20 (dd, $J = 9.6, 3.2$ Hz, 1H), 4.10 – 4.05 (m, 2H), 3.94 (dq, $J = 9.6, 6.2$ Hz, 1H), 3.87 – 3.81 (m, 2H), 3.79 – 3.68 (m, 2H), 3.68 – 3.59 (m, 1H), 3.56 – 3.48 (m, 4H), 1.39 (d, $J = 6.2$ Hz, 3H), 1.24 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 156.27, 138.77, 138.45, 138.40, 138.32, 135.12, 128.57, 128.46, 128.35, 128.18, 127.81, 127.76, 127.71, 127.61, 127.24, 118.70, 116.59, 100.50, 94.88, 84.90, 80.41, 80.15, 80.06, 79.68, 78.75, 75.68, 75.49, 75.10, 72.72, 71.11, 69.03, 68.85, 59.04, 18.34, 18.03.

IR: 2974, 2928, 2866, 1585, 1485, 1454, 1354, 1285, 1231, 1178, 1099, 1042, 995, 922, 887, 822, 737, 698, 640

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₄₃H₄₉IO₉Na: 859.2313 found: 859.2316

(2,4-di-*O*-benzyl- α -L-rhamnopyranosyl)-(1 $\rightarrow$ 3)-*p*-iodophenyl-2-*O*-methyl-4-*O*-benzyl- α -L-rhamnopyranoside (28**)**

Compound **27** (280 mg, 0.33 mmol) was dissolved in MeOH (6 mL). PdCl₂ (3 mg, 0.02 mmol) was added and the mixture stirred at RT for 16 h. The precipitated material was separated by filtering the mixture over a pad of celite and the filtrate was concentrated under reduced pressure. The crude material was directly subjected to flash chromatography over silica gel using 3:1 petroleum ether - EtOAc to obtain 218 mg, 0.273 mmol of disaccharide **28** (82%) as colorless oil.

$[\alpha]_D^{22} = -78.9^\circ$ ($c = 0.95$, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.55 (m, 2H), 7.41 – 7.15 (m, 15H), 6.88 – 6.82 (m, 2H), 5.48 (d, $J = 1.6$ Hz, 1H), 5.21 (s, 1H), 4.91 (d, $J = 11.2$ Hz, 1H), 4.79 (d, $J = 11.5$ Hz, 1H), 4.69 (dd, $J = 11.3, 9.0$ Hz, 2H), 4.41 (d, $J = 11.7$ Hz, 1H), 4.26 – 4.15 (m, 2H), 4.02 (td, $J = 9.3, 3.7$ Hz, 1H), 3.96 – 3.85 (m, 1H), 3.79 – 3.68 (m, 3H), 3.54 (m, 4H), 3.36 (t, $J = 9.3$ Hz, 1H), 2.28 (d, $J = 9.4$ Hz, 1H), 1.38 (d, $J = 6.3$ Hz, 3H), 1.26 (d, $J = 6.2$ Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 156.26, 138.61, 138.49, 138.39, 137.77, 128.59, 128.54, 128.13, 128.01, 127.89, 127.83, 127.74, 127.12, 118.71, 99.36, 95.10, 84.92, 82.21, 80.40, 80.22, 79.28, 78.50, 75.26, 75.11, 72.74, 71.68, 69.20, 68.06, 59.31, 18.31, 18.09.

IR: 3549, 2974, 2932, 2827, 1586, 1485, 1385, 1366, 1281, 1177, 1138, 1099, 1030, 999, 918, 822, 737, 698 cm⁻¹

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₄₀H₄₅IO₉Na 819.2000 found 819.2003

(2-*O*-methyl-3,4-di-*O*-acetyl-α-L-fucopyranosyl)-(1→3)-(2,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-*p*-iodophenyl-2-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (29**)**

Disaccharide acceptor **28** (51 mg, 0.14 mmol), fucose donor **10** (76 mg, 0.10 mmol) and *N*-(thiophenyl)-ε-caprolactam **S10** (32 mg, 0.14 mmol) were co-evaporated with toluene. 2,4,6-tri-*tert*-Butyl pyrimidine (TTBP) (36 mg, 0.14 mmol) was added and the mixture was dissolved in freshly distilled CH₂Cl₂ (5 mL). The solution was stirred for 20 min at ambient temperature before being cooled to -25 °C. Tf₂O (39 mg, 23 μL, 0.14 mmol) was added. The mixture was stirred and allowed to reach RT. It was then quenched by the addition of Et₃N. The mixture was concentrated under reduced pressure and directly purified by flash chromatography over silica gel using 4:1 petroleum ether - EtOAc and subsequent size exclusion chromatography (Sephadex LH-20) using 1:1 MeOH-CH₂Cl₂, yielding 51 mg, 0.05 mmol of trisaccharide **29** (52%) as colorless oil.

$[\alpha]_D^{22} = -116.5^\circ$ ($c = 0.50$, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, $J = 9.0$ Hz, 2H), 7.40 – 7.22 (m, 15 H), 6.85 (d, $J = 9.0$ Hz, 2H), 5.49 (d, $J = 1.4$ Hz, 1H), 5.34 – 5.23 (m, 3H), 5.15 (d, $J = 11.5$ Hz, 1H), 5.05 (d, $J = 2.6$ Hz, 1H), 4.83 (d, $J = 11.5$ Hz, 1H), 4.67 – 4.59 (m, 3H), 4.29 – 4.19 (m, 2H), 4.11 (dd, $J = 9.5, 3.1$ Hz, 1H), 4.00 – 3.92 (m, 1H), 3.84 – 3.63 (m, 5H), 3.58 – 3.47 (m, 5H), 3.26 (s, 3H), 2.13 (s, 3H), 2.03 (s, 3H), 1.35 (d, $J = 6.2$ Hz, 3H), 1.23 (d, $J = 6.2$ Hz, 3H), 0.76 (d, $J = 6.5$ Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 170.63, 170.15, 156.29, 139.24, 138.50, 138.28, 137.89, 128.67, 128.60, 128.31, 127.89, 127.82, 127.42, 127.35, 127.24, 118.71, 99.65, 99.36, 94.80, 84.93, 80.20, 79.95, 79.89, 79.74, 78.15, 75.78, 75.19, 74.86, 71.57, 71.35, 70.29, 69.06, 68.99, 64.58, 59.34, 58.97, 21.11, 20.84, 18.32, 18.07, 16.07.

IR: 2982, 2932, 2900, 1747, 1582, 1485, 1454, 1369, 1315, 1238, 1130, 1099, 1076, 1042, 999, 976, 918, 822, 737, 698 cm⁻¹

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₅₁H₆₁IO₁₅Na 1063.2947; found 1040.2954

(2-*O*-methyl-α-L-fucopyranosyl)-(1→3)-(2,4-di-*O*-benzyl-α-L-rhamnopyranosyl)-(1→3)-*p*-iodophenyl-2-*O*-methyl-4-*O*-benzyl-α-L-rhamnopyranoside (30)

Trisaccharide **29** (45 mg, 0.04 mmol) was dissolved in MeOH. A freshly cut piece of sodium was added and the solution was stirred for 16 h. The reaction was quenched adding Amberlite IR-120 (H⁺ form) resin, stirring the obtained heterogeneous mixture until judged neutral by pH-paper. The mixture was filtered and concentrated under reduced pressure and the crude material obtained was used for the subsequent step without further purification.

$[\alpha]_D^{22} = -108.2^\circ$ ($c = 0.39$, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.62 – 7.53 (m, 2H), 7.40 – 7.18 (m, 15H), 6.90 – 6.81 (m, 2H), 5.50 (d, $J = 1.5$ Hz, 1H), 5.24 (s, 2H), 5.11 (d, $J = 11.6$ Hz, 1H), 4.87 (d, $J = 11.5$ Hz, 1H), 4.66 (dd, $J = 19.5, 11.6$ Hz, 2H), 4.54 (d, $J = 12.2$ Hz, 1H), 4.28 – 4.12 (m, 2H), 4.08 (dd, $J = 9.4, 3.0$ Hz, 1H), 4.02 – 3.91 (m, 2H), 3.91 – 3.68 (m, 4H), 3.68 – 3.49 (m, 6H), 3.42 (dd, $J = 10.0, 3.5$ Hz, 1H), 3.26 (s, 3H), 2.60 (s, 1H), 2.32 (s, 1H), 1.33 (d, $J = 6.2$ Hz, 3H), 1.25 (d, $J = 6.2$ Hz, 3H), 1.02 (d, $J = 6.6$ Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 156.27, 139.10, 138.49, 138.36, 138.28, 128.59, 128.37, 128.35, 127.84, 127.60, 127.46, 127.38, 127.19, 127.07, 118.69, 99.32, 98.78, 94.81, 84.92, 80.25, 79.99, 79.58, 79.04, 78.34, 75.19, 71.41, 71.38, 69.39, 69.09, 68.91, 65.80, 59.05, 58.32, 18.39, 18.09, 16.37.

IR: 3479, 3444, 2974, 2932, 2855, 1485, 1454, 1385, 1354, 1281, 1126, 1099, 1042, 999, 972, 822, 737, 698 cm⁻¹

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₄₇H₅₇IO₁₃Na: 979.2736; found: 979.2740

(2,3,4-tri-*O*-methyl- α -L-fucopyranosyl)-(1 $\rightarrow$ 3)-(2,4-di-*O*-benzyl- α -L-rhamnopyranosyl)-(1 $\rightarrow$ 3)-*p*-iodophenyl-2-*O*-methyl-4-*O*-benzyl- α -L-rhamnopyranoside (7)

Crude **30** (36 mg, 0.04 mmol) was dissolved in DMF and cooled to 0 °C. MeI (43 mg, 19 μ L, 0.30 mmol) and NaH (7.1 mg, 0.30 mmol) were added. The mixture was stirred at RT for 16 h before being quenched by the careful addition MeOH at 0 °C. The crude mixture was diluted with water, and extracted with three portions of diethyl ether. The combined organic layers were washed with brine and dried over Na₂SO₄. The solvents were removed under reduced pressure and the crude subjected to flash chromatography over silica gel using 4:1 petroleum ether - EtOAc to obtain 31 mg, 0.03 mmol of trisaccharide **7** (85%) as a transparent glassy solid.

$[\alpha]_D^{22} = -115.3^\circ$ ($c = 0.52$, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, $J = 8.8$ Hz, 2H), 7.40 – 7.23 (m, 15H), 6.85 (d, $J = 8.8$ Hz, 2H), 5.49 (s, 1H), 5.27 – 5.14 (m, 3H), 4.85 (d, $J = 11.5$ Hz, 1H), 4.71 – 4.52 (m, 3H), 4.28 – 4.18 (m, 2H), 4.09 (dd, $J = 9.4, 2.9$ Hz, 1H), 3.95 (dq, $J = 12.3, 6.0$ Hz, 1H), 3.86 – 3.47 (m, 17H), 3.32 (s, 3H), 3.21 (s, 1H), 1.34 (d, $J = 6.2$ Hz, 3H), 1.23 (d, $J = 6.1$ Hz, 3H), 0.97 (d, $J = 6.5$ Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 156.29, 139.21, 138.52, 138.48, 138.41, 128.55, 128.36, 128.32, 127.77, 127.61, 127.54, 127.43, 127.29, 127.24, 118.71, 99.66, 99.51, 94.92, 84.89, 80.47, 80.23, 79.94, 79.88, 79.57, 79.23, 79.01, 77.93, 75.10, 74.85, 71.52, 69.10, 68.89, 66.43, 61.85, 59.24, 59.11, 58.08, 18.36, 18.05, 16.67.

IR: 2974, 2928, 2828, 1485, 1454, 1358, 1323, 1231, 1096, 1042, 955, 918, 822, 737, 698

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₄₉H₆₁IO₁₃Na: 1007.3049; found: 1007.3055

Scheme 7. Completion of the total synthesis of **1**. a) PdCl₂(PPh₃)₂ (5 mol%), PPh₃ (5 mol%), CuI (10 mol%), Et₃N, 40 °C, 51% (36% of **4** recovered); b) EDC·HCl, DMAP, CDCl₃, 72%; c) Pd/C, 1 bar H₂, EtOAc, EtOH, RT, 86%. EDC·HCl=*N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride, DMAP=4-(dimethylamino)pyridine, TMS=trimethylsilyl.

2-O-methyl-2,3-di-O-methyl- α -L-fucopyranose)-(1 $\rightarrow$ 3)-(2-O-benzyl-4-O-benzyl- α -L-rhamnopyranoside)-(1 $\rightarrow$ 3)-(((3R,4S,9R,11R)-27-(4-hydroxyphenyl)-3-methoxy-4-methylheptacos-26-yne-9,11-diol)-yl 2-O-methyl-4-O-benzyl- α -L-rhamnopyranoside) (31**)**

A stock solution of catalyst was prepared by mixing PPh₃ (3.3 mg, 13 μ mol), CuI (4.8 mg, 25 μ mol) and PdCl₂(PPh₃)₂ (8.8 mg, 13 μ mol) in freshly distilled Et₃N (6 mL) and stirring this solution at 40 °C for 15 min. Then, 0.6 mL of this stock solution (equivalent loadings of 5 mol% Pd, 5 mol% PPh₃ and 10 mol% Cu) was added to a solution of compound **4** (22.6 mg, 50 μ mol) and trisaccharide **7** (24.6 mg, 25 μ mol) in freshly distilled Et₃N (0.3 mL). The reaction was then stirred at 40 °C for 1.5 h. The reaction was

diluted with Et₂O (50 mL), washed with aq. HCl (2 M, 2x7 mL) and brine (7 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure and the product was purified by column chromatography (from pentane-Et₂O 1:1 to pure Et₂O), giving compound **31** (16.7 mg, 13 μmol, 51% yield) and unreacted trisaccharide **7** (8.8 mg, 8.9 μmol, 36% recovery). Unreacted compound **31** was not quantified.

$$[\alpha]_D^{22} = -79.8^\circ (c = 1.0, \text{CHCl}_3)$$

¹H NMR (400 MHz, CDCl₃, contaminated with BHT) δ 7.36 – 7.14 (m, 17H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.49 (d, *J* = 1.5 Hz, 1H), 5.20 (d, *J* = 1.2 Hz, 1H), 5.19 (s, 1H), 5.16 (d, *J* = 11.5 Hz, 1H), 4.83 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.54 (d, *J* = 12.3 Hz, 1H), 4.24 – 4.17 (m, 2H), 4.06 (dd, *J* = 9.5, 2.9 Hz, 1H), 3.98 – 3.87 (m, 3H), 3.79 (dd, *J* = 2.8, 1.9 Hz, 1H), 3.76 – 3.70 (m, 2H), 3.69 – 3.54 (m, 5H), 3.52 (s, 3H), 3.50 (s, 3H), 3.48 (s, 3H), 3.31 (s, 3H), 3.30 (s, *J* = 6.2 Hz, 3H), 3.18 (s, 1H), 2.85 (ddd, *J* = 7.5, 5.1, 4.1 Hz, 1H), 2.49 (br s, 2H), 2.35 (t, *J* = 7.1 Hz, 2H), 1.72 – 1.02 (m, 39H), 1.31 (d, *J* = 6.2 Hz, 3H), 1.20 (d, *J* = 6.2 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 155.6 (s), 139.1 (s), 138.4 (s), 138.3 (s), 132.8 (d), 128.4 (d), 128.20 (d), 128.17 (d), 127.59 (d), 127.47 (d), 127.37 (d), 127.26 (d), 127.15 (d), 127.10 (d), 117.9 (s), 116.1 (d), 99.5 (d), 99.4 (d), 94.7 (d), 89.4 (s), 86.7 (d), 80.4 (d), 80.2 (d), 79.99 (s), 79.9 (d), 79.8 (d), 79.5 (d), 79.2 (d), 78.9 (d), 77.8 (d), 74.9 (t), 74.7 (t), 71.4 (t), 69.47 (d), 69.42 (d), 68.89 (d), 68.8 (q), 66.3 (q), 61.7 (q), 59.1 (q), 58.9 (q), 57.9 (q), 57.4 (q), 42.3 (t), 37.5 (t), 34.8 (d), 32.6 (t), 29.68 (t), 29.64 (t), 29.62 (t), 29.61 (t), 29.60 (t), 29.53 (t), 29.2 (t), 28.9 (t), 28.8 (t), 27.5 (t), 26.1 (t), 25.8 (t), 22.4 (t), 19.4 (t), 18.2 (q), 17.9 (q), 16.5 (q), 14.8 (q), 10.1 (q).

HRMS (ESI+) *m/z*: Calcd for C₇₈H₁₁₆O₁₆Na (M+Na⁺) 1331.816, found 1331.824.

2-O-methyl-2,3-di-O-methyl- α -L-fucopyranose)-(1 $\rightarrow$ 3)-(2-O-benzyl-4-O-benzyl- α -L-rhamnopyranoside)-(1 $\rightarrow$ 3)-(((3*R*,4*S*,9*R*,11*R*)-27-(4-hydroxyphenyl)-3-methoxy-4-

A mixture of diol **31** (16.6 mg, 13 μ mol), mycocerosic acid **2** (18.3 mg, 38 μ mol), EDC hydrochloride (14.6 mg, 76 μ mol) and DMAP (18.6 mg, 152 μ mol) were dissolved in CDCl_3 (0.5 mL) and stirred overnight. After inspection by ^1H NMR of the crude mixture whether the reaction was complete, the reaction was quenched adding HCl (1 M in Et_2O solution, 0.2 mL), diluted with toluene and the solvents were partially removed under a nitrogen flow. The crude was purified by column chromatography (pentane- Et_2O from 2:1 to 1:1) to give product **32** (20.3 mg, 9.1 μ mol, 72%).

Note: conversion was monitored by ^1H NMR following the integration of signals at δ 3.95 ppm (3H in the diol, 1H in the diester) and δ 4.81 ppm (1H in the diol, 3H in the diester).

$$[\alpha]_D^{22} = -55.4^\circ (c = 1.0, \text{CHCl}_3)$$

^1H NMR (400 MHz, CDCl_3 , contaminated with BHT) 7.42 – 7.20 (m, 17H), 6.97 (d, $J = 7.9$ Hz, 2H), 5.51 (s, 1H), 5.22 (s, 1H), 5.21 (s, 1H), 5.18 (d, $J = 12.2$ Hz, 1H), 4.93 – 4.78 (m, 3H), 4.66 (d, $J = 11.7$ Hz, 1H), 4.61 (d, $J = 11.5$ Hz, 1H), 4.56 (d, $J = 12.3$ Hz, 1H), 4.27 – 4.17 (m, 2H), 4.09 (dd, $J = 9.3, 2.3$ Hz, 1H), 3.95 (dq, $J = 12.7, 6.1$ Hz, 1H), 3.81 (br s, 1H), 3.79 – 3.53 (m, 7H), 3.54 (s, 3H), 3.53 (s, 3H), 3.50 (s, 3H), 3.33 (s, 3H), 3.32 (s, 3H), 3.20 (s, 1H), 2.85 (ddd, $J = 7.5, 5.1, 4.1$ Hz, 1H), 2.59 – 2.43 (m, 2H), 2.37 (t, $J = 7.0$ Hz, 2H), 1.81 – 0.83 (m, 178H).

^{13}C NMR (101 MHz, CDCl_3) δ 175.97 (s), 175.94 (s), 155.6 (s), 139.1 (s), 138.4 (s), 138.3 (s), 132.8 (s), 128.4 (d), 128.02 (d), 128.16 (d), 127.59 (d), 127.46 (d), 127.37 (d), 127.26 (d), 127.15 (d), 127.09 (d), 117.9 (s), 116.1 (d), 99.5 (d), 99.4 (d), 94.7 (d), 89.34 (s), 86.63 (d), 80.37 (d), 80.18 (d), 79.96 (s), 79.91 (d), 79.78 (d), 79.47 (d), 79.17 (d), 78.91 (d), 77.84 (d), 74.94 (t), 74.69 (t), 71.39 (t), 70.26 (d), 70.10 (d), 68.88 (d), 68.75 (d), 66.31 (d), 61.68 (q), 59.08 (q), 58.92 (q), 57.95 (q), 57.36 (q), 45.50 (t), 45.28 (t), 40.98 (t), 40.96 (t), 38.43 (t), 37.76 (t), 37.72 (t), 36.61 (t), 34.79 (d), 34.69 (t), 34.66 (t), 32.61 (t), 31.91 (t), 30.08 (t), 29.92 (d), 29.78 (t), 29.70 (t), 29.65 (t), 29.62 (t), 29.60 (t), 29.54 (t), 29.35 (t), 29.22 (t), 29.00 (t), 28.88 (t), 28.03 (d), 27.47 (t), 27.19 (d), 26.95 (t), 25.54 (t), 25.15 (t), 22.68 (t), 22.33 (q), 20.75 (q), 20.45 (q), 20.40 (q), 20.37 (q), 19.40 (t), 18.42 (q), 18.41 (q), 18.20 (q), 17.90 (q), 16.51 (q), 14.70 (q), 14.11 (q), 10.09 (q).

HRMS (ESI+) m/z : Calcd for $\text{C}_{142}\text{H}_{240}\text{O}_{18}\text{Na}$ ($\text{M}+\text{Na}^+$) 2257.779, found 2257.796.

PGL-tb1 (**1**)

Palladium on carbon (10%-dry basis Degussa type E101 NE/W, 19.2 mg of wet compound) was added to a solution of diester **32** (20.2 mg, 9.0 μmol) in EtOAc (0.8 mL) and EtOH (0.2 mL) under nitrogen. A balloon of H_2 was added to the set-up and the reaction was stirred for 20 h. Then, the catalyst was removed by filtration through a plug of cotton and celite, eluting with additional EtOAc (20 mL). The solvent was removed under reduced pressure and the crude was purified by column chromatography to give PGL-tb1 (**1**) (15.2 mg, 7.7 μmol , 86%) as a solid. Spectroscopic data coincide with that reported for the natural product.⁶

$$[\alpha]_{\text{D}}^{22} = -44.4^\circ (c = 1.0, \text{CHCl}_3)$$

^1H NMR (400 MHz, CDCl_3) δ 7.09 (d, $J = 8.3$ Hz, 2H), 6.98 (d, $J = 8.3$ Hz, 2H), 5.50 (s, 1H), 5.14 (s, 2H), 4.89-4.81 (m, 2H), 4.10 (s, 1H), 4.08-4.03 (m, 2H), 3.93 (qd, $J = 6.2$ Hz, $J = 12.6$ Hz, 1H), 3.81-3.75 (m, 3H), 3.70-3.62 (m, 4H), 3.60 (s, 3H), 3.57 (s, 3H), 3.51 (s, 3H), 3.48 (s, 3H), 3.47 (s, 1H), 3.32 (m, 3H), 2.85 (ddd, $J = 4.4$ Hz, $J = 5.4$ Hz, $J = 7.2$ Hz, 1H), 2.56-2.50 (m, 4H), 1.81–0.83 (m, 184H).

^{13}C NMR (101 MHz, CDCl_3) δ 175.98 (s), 175.95 (s), 154.5 (s), 136.9 (s), 129.3 (d), 116.1 (d), 102.1 (d), 100.8 (d), 94.9 (d), 86.6 (d), 83.1 (d), 81.0 (d), 80.02 (d), 79.89 (d), 78.94 (d), 78.78 (d), 71.72 (d), 71.59 (d), 71.17 (d), 70.28 (d), 70.11 (d), 69.02 (d), 68.60 (d), 67.50 (d), 61.88 (q), 60.25 (q), 58.55 (q), 57.72 (q), 57.36 (q), 45.50 (t), 45.28 (t), 40.98 (t), 40.96 (t), 38.43 (t), 37.76 (d), 37.73 (d), 36.61 (t), 35.13 (t), 34.79 (t), 34.71 (t), 34.68 (t), 34.65 (t), 32.61 (t), 31.92 (t), 31.70 (t), 30.08 (t), 29.93 (t),

⁶ (a) M. Daffé, C. Lacave, M.-A. Lanéelle, G. Lanéelle, *Eur. J. Biochem.* **1987**, 167, 155–160. (b) M. Daffé, P. Servin, *Eur. J. Biochem.* **1989**, 185, 157–162.

29.78 (t), 29.70 (t), 29.65 (t), 29.58 (t), 29.55 (t), 29.35 (t), 28.03 (d), 27.47 (t), 27.19 (d), 26.96 (t), 25.54 (t), 25.15 (t), 22.68 (t), 22.33 (t), 20.75 (q), 20.45 (q), 20.40 (q), 20.37 (q), 18.42 (q), 18.41 (q), 17.83 (q), 17.77 (q), 16.64 (q), 14.70 (q), 14.11 (q), 10.09 (q).

HRMS (ESI+) m/z: Calcd for $C_{121}H_{226}O_{18}Na$ (M+Na⁺) 1991.670, found 1991.681.

III. NMR spectra

16

4

19

20

21

22

23

24

4

S5

S6

S8

9

10

25

26

27

30

7

31 (contaminated with BHT)

32 (contaminated with BHT)

PGL-tb1 (1)