Total Synthesis of Macroviracin D (BA-2836-4)

Jacek Mlynarski, Juliana Ruiz-Caro, and Alois Fürstner*[a]

Abstract: The first total synthesis of the complex glycolipid macroviracin D (BA-2836-4) (**1**) is described. This antivirally active metabolite isolated from the mycelium extracts of *Streptomyces* sp. BA-2836 incorporates a unique 46-membered macrodilactone motif decorated with glycosylated fatty acid appendices. Compound **1** consists of three identical subunits which are closely related to one of the segments found in cycloviracin B_1 (**2**), another antiviral glycoconjugate previously synthesized in our laboratory. Key steps of the synthesis route to **1** involve the stereoselective, ligand-controlled addition of the functionalized diorganozinc derivative **9** to aldehydes **8a**,**b**, a series of β-selective glycosidation reactions using appropriately protected trichloroacetimidate donors, and three esterifications via the Yamaguchi method; one of them is performed intramolecularly to forge the macrocyclic lactone ring of the target in 89% isolated yield. This total synthesis also firmly establishes the absolute configuration of the subunits of compound **1** as 3*R*,17*S*,23*R*.

Keywords: antiviral agents · carbohydrates · glycolipids · macrocycles · natural products

Introduction

The quest for novel antiviral agents has recently led to the discovery of a new family of structurally rather intriguing glycolipids isolated from the mycelium of *Streptomyces sp.* BA 2836, which exhibit surprisingly strong and selective activity against various human pathogens including herpes simplex-, human immunodeficiency- and varicella-zoster virus.[1,2] The homologous series of amphiphilic natural products was originally called "BA-2836 compound(s)" after the producing strain, but may be better termed "macroviracins"[3] in view of their remarkable macrocyclic dilactone core structure. Macroviracin D (BA-2836-4) **1** is a prototype member of this family, differing from its congeners only in the length of the fatty acid chains forming the central lactide ring and the appendices attached to it.

Our keen interest in bioactive glycoconjugates[4–8] let us to recognize a subtle relationship between **1** and cycloviracin B_1 (**2**),[9] yet another antivirally active dilactone derivative of bacterial origin which was subject to intense preparative and biological studies in this laboratory.[10,11] Specifically, the three subunits forming compound **1** closely resemble *one* of the inequivalent sectors of **2** (see Scheme 1). This then suggests that the macroviracins and the cycloviracins—while differing in their periphery—are constitutional isomers with respect to their core structures. While the ester linkages in **2** are attached to the proximal 2-O-methyl-glucoside residues, they extend to the distal sugar entities in the macroviracin series thus forming a 46-membered ring. This analysis was corroborated by a recent model study[3] which proved that the constitutive acid component **3** in **1** has in fact the same stereochemistry as the right wing of **2**. Since the latter had been unambiguously shown to be (3*R*,17*S*,23*R*)-configured by our total synthesis,[10,11] a viable plan for the conquest of **1** emerged. Outlined below is the successful reduction of this blueprint to practice.

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Results and Discussion

Only three closely related synthons representing the individual subunits of macroviracin D (**1**) are required for the assembly of this target. They merely differ in the chosen protecting groups which must be orthogonal to ensure selective formations of the different ester linkages. Therefore all building blocks can be derived from alcohol **4** which is easily prepared from pentadecanolide as the starting material on a multigram scale as previously outlined (Scheme 2).[10,11]

Glycosidation of **4** with the known trichloroacetimidates **5a**[12] and **5b**[10,11] promoted by TMSOTf in a mixed solvent system comprising CH_2Cl_2 and MeCN afforded the corresponding β-glycosides **6a** and **6b**, respectively, in excellent yields.[13] It is noteworthy, however, that the O-6 protecting group of the donor exerts a subtle influence on the stereochemical course of the reaction. While the perbenzylated

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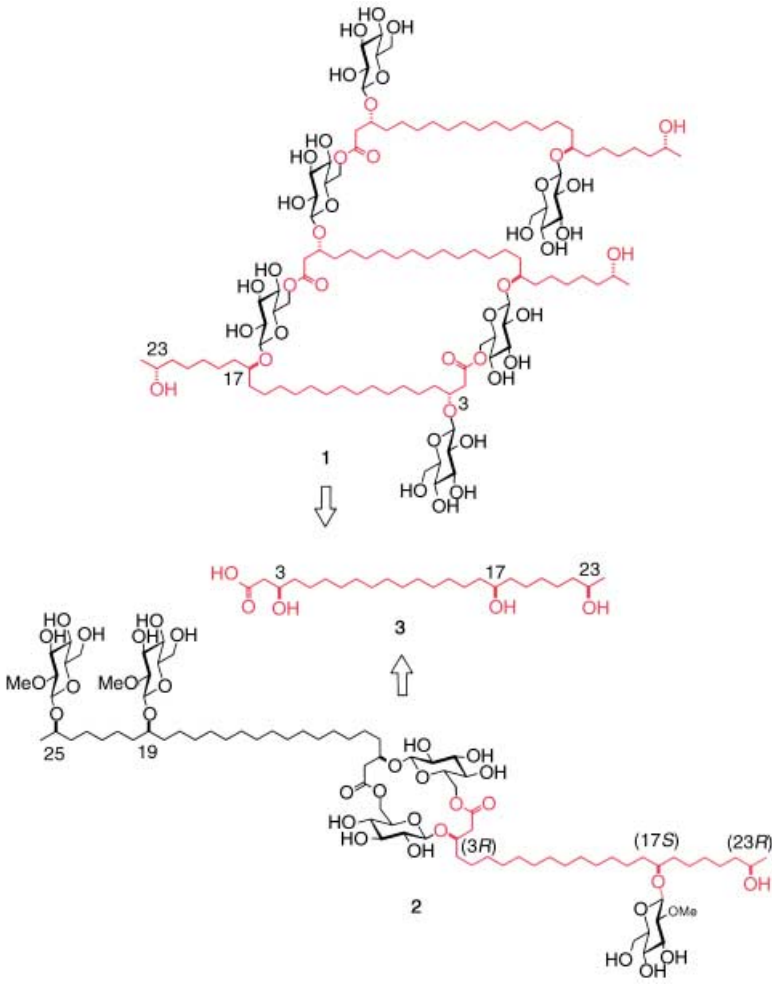


Scheme 1. Structure of macroviracin D (**1**) and comparison with cycloviracin B_1 (**2**).

derivative **5a** led to an exclusive formation of the desired product **6a**, its analogue **5b** bearing a 6-O-acetyl group reacts less selectively and afforded 15% of the α-anomer in addition to the required β-glycoside **6b**. The isomers, however, can be separated by conventional flash chromatography.

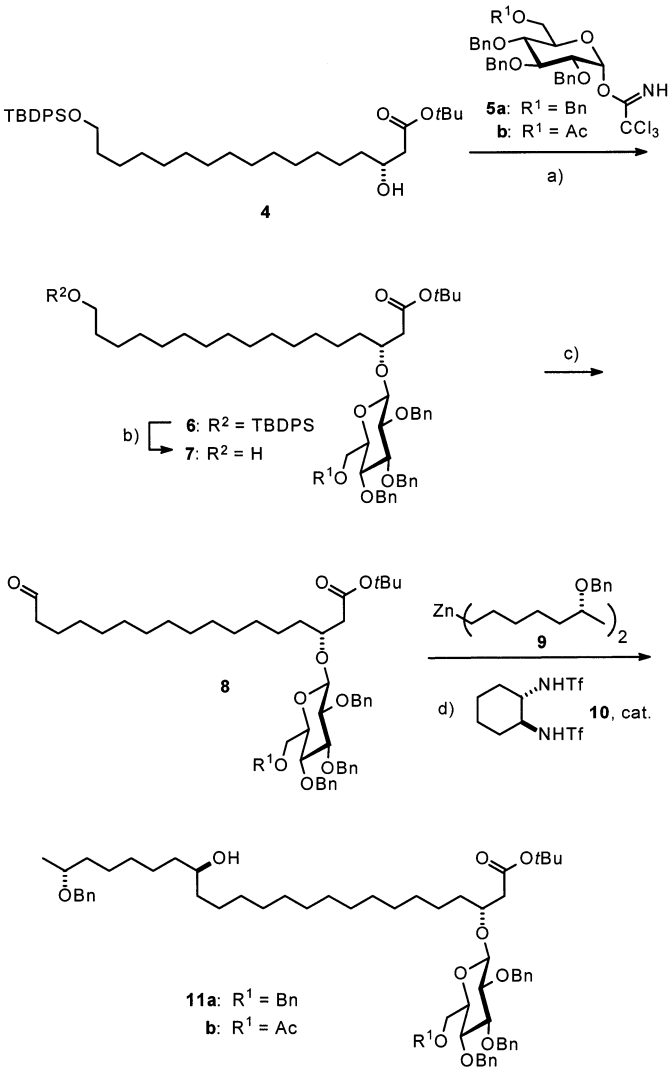
The terminal O-TBDPS-group was then cleaved by means of TBAF, thus liberating alcohols **7a**,**b** which were oxidized with PCC to the corresponding aldehydes **8a** and **8b**. Subsequent exposure of these compounds to the functionalized diorganozinc derivative **9** (prepared from iodide **15** by a Cu^I-catalyzed halogen/zinc exchange reaction[14] as shown in Scheme 3)[11] in the presence of a catalyst formed in situ from $Ti(OiPr)_4$ and (*S*,*S*)-bistriflate **10** as the stereochemical determinant[15,16] provided the secondary alcohols **11a**,**b** in excellent yields and thereby set the stage for the next glycosidation event.

To ensure the proper orthogonal protecting group regime required in the assembly stages, the perbenzylated derivative **11a** was independently glycosylated with **5a** and **5b** to give products **16** and **18** (Scheme 4). A comparison of the selectivities observed in these transformations reveals again the proclivity of the 6-O-acetylated donor **5b** for competing α-glycoside formation, while the perbenzylated donor **5a** does not show this bias. Treatment of compound **16** thus formed with F_3CCOOH furnished acid **17**, whereas its analogue **18** was deacetylated in 87% yield on treatment with NH_3 in MeOH/THF without affecting the *tert*-butyl ester moiety.

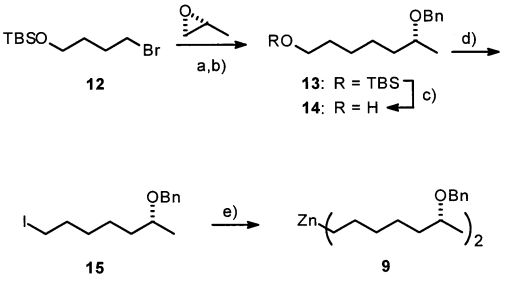
Along similar lines, the glycosidation of **11b** with donor **20**[17] bearing a 6-O-TBDPS group also leads to a mixture of both anomers of **21**, which could only be separated by preparative HPLC. Treatment of the major β-anomer with trifluoroacetic acid in CH_2Cl_2 resulted in a selective cleavage of the *tert*-butyl ester group while leaving the silylether moiety intact. Attempts to esterify the resulting acid **22** with alcohol **19** in the presence of DIC and DMAP were unrewarding; gratifyingly, however, application of the Yonemitsu variant[18] of the Yamaguchi esterification[19] procedure delivered ester **23** in 86% isolated yield (Scheme 5). Subsequent cleavage of the residual O-TBDPS ether with TBAF followed by deprotection of the *tert*-butyl ester group in the resulting product **24** was carried out in "one pot" in 67% overall yield.

Hydroxy acid **25** thus formed constitutes the key compound for the envisaged macrolactonization step. This transformation worked exquisitely well under standard Yamaguchi conditions,[19] providing the 46-membered dilactone derivative **26** in 89% isolated yield. We were pleased to find that its lactone linkages remained intact during the subsequent cleavage of the peripheral 6-O-acetyl group by solvolysis with NH_3 in MeOH, despite the very long reaction time necessary to drive this reaction to completion. The liberated primary hydroxyl function in **27** was then esterified with acid **17**, again by taking recourse to Yamaguchi's mixed anhydride methodology,[19] which furnished product **28** as the fully protected surrogate of macroviracin D in 74% yield (Scheme 6).

In contrast to our expectations, however, the ultimate deprotection step turned out to be particularly difficult. Benzyl ethers were chosen as protecting groups for all hydroxyl functions not involved in any of the esterification reactions to be carried out en route to **1**, not least because they can be cleaved under neutral conditions via standard hydrogenolysis. Moreover, benzyl ethers were successfully employed and removed without difficulty during our previous total synthesis of cycloviracin B_1 (**2**) and several related products.[10,11,20] Unfortunately, however, attempts to run the



Scheme 2. Preparation of the key glycolipidic fragment: a) donor **5a**, TMSOTf, CH_2Cl_2/MeCN, 91% (**6a**); or: donor **5b**, TMSOTf, CH_2Cl_2/MeCN, 74% (**6b**, +15% of the α-anomer); b) TBAF, THF, 90% (**7a**), 92% (**7b**); c) PCC, CH_2Cl_2; d) compound **9**, $Ti(OiPr)_4$, ligand **10**, toluene, 73% (**11a**, over both steps), 77% (**11b**, over both steps).



Scheme 3. Preparation of the functionalized diorganozinc reagent: a) i) Mg, THF; ii) cat. CuCl(COD), (*R*)-propene oxide, 70%; b) BnBr, NaH, 73%; c) TBAF, THF, 93%; d) I_2, imidazole, PPh_3, 89%; e) Et_2Zn (excess), cat. CuCN.

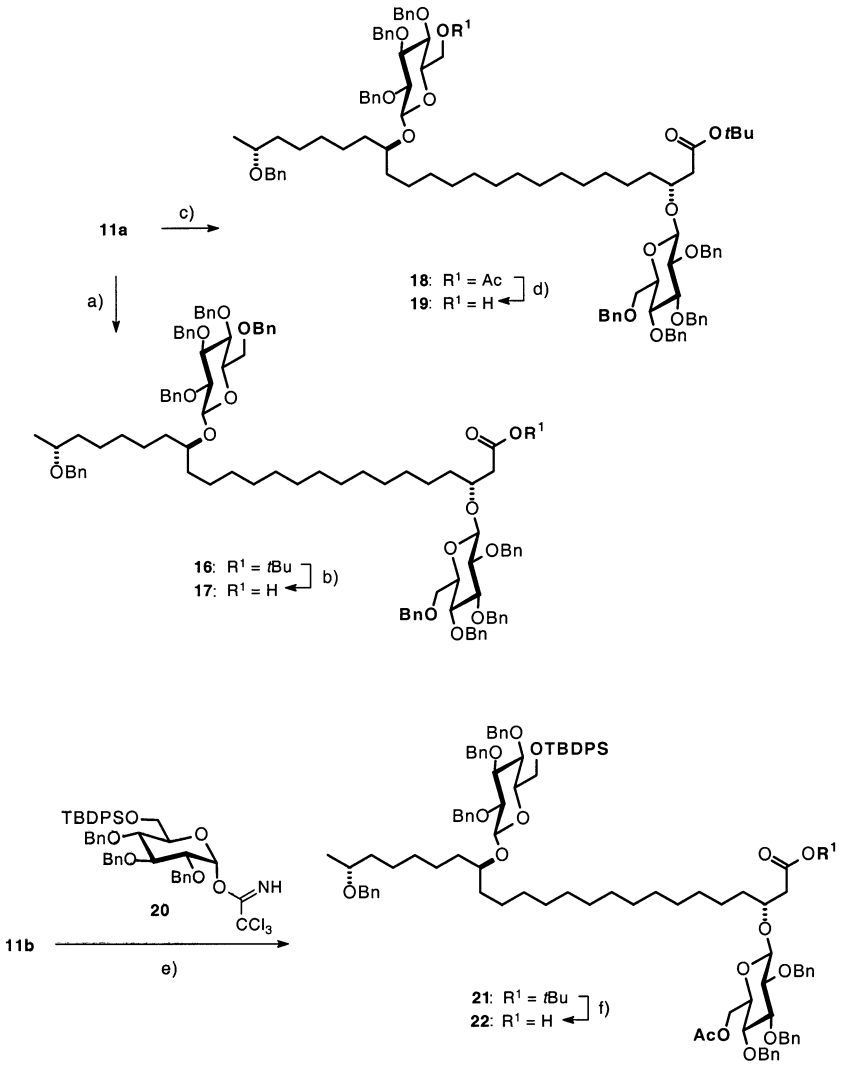
deprotection of **28** under the conditions successfully employed in the cycloviracin series using either MeOH or EtOH/EtOAc as the reaction medium resulted only in a collapse of the macrocyclic structure, giving rise to the methyl ester **29a** formed by exhaustive solvolysis of the trimeric construct. Similar degradations were observed using isopropanol, $CHCl_3$/MeOH/H_2O, or $CHCl_3$/acetone as solvents in the presence or absence of NH_4OAc as a buffer. After considerable experimentation it was found that the hydrogenolysis of **28** can be performed using $Pd(OH)_2$ as the precatalyst in *rigorously* dried EtOH which had to be directly distilled from Mg into a flame dried reaction flask prior to use. The reaction time is also critical and must not exceed 12 h. Under these conditions, macroviracin D (**1**) has been obtained in virtually quantitative yield. Its spectroscopic and analytical data are in agreement with those reported in the literature.[1] Particularly diagnostic is the direct comparison of the pattern signature in the ^1H and ^{13}C NMR spectra recorded at 600 and 150 MHz, respectively, with those depicted in reference [1]. Moreover, the high resolution ESI-MS of the sample is consistent with the intact trimeric structure.

In contrast to the difficulties encountered during the attempted deprotection reactions in various solvent systems we found that pure **1**, when kept in freshly distilled and carefully dried $[D_4]$MeOH, is stable for days and does not show any noticeable degradation. Trace impurities, however, may suffice to change this situation and can result in methanolysis with formation of the monomeric ester **29b** within less than 24 h. This sensitivity—which is in striking contrast to the resistance of the fully protected macrocycle **26** towards solvolysis in MeOH even in the presence of excess NH_3 (see above)—must be taken into account in any further evaluation of this lead compound in the search for novel antiviral agents.[21]

Experimental Section

General: All reactions were carried out under Ar in carefully dried glassware. The solvents used were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2 (P_4O_{10}), MeCN, Et_3N (CaH_2), MeOH (Mg), DMF, DMA (Desmodur, dibutyltin dilaurate), hexane, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh). IR: Nicolet FT-7199 spectrometer, wave numbers in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), HRMS: Finnigan MAT 95 or Bruker APEX III FT-ICR-MS (7 T magnet). Melting points: Gallenkamp melting point apparatus (uncorrected). Optical rotation: Perkin–Elmer 343 at $\lambda = 589$ nm (Na D-line). Elemental analyses: H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Lancaster, Aldrich) were used as received. NMR: Spectra were recorded on Bruker DPX 300, AV 400, or DMX 600 spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz.

(3*R*)-*tert*-Butyl [17-*tert*-butyldiphenylsilyloxy-3-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)oxy]heptadecanoate (6a): TMSOTf (20 μL) was added to a solution of alcohol **4** (1.0 g, 1.67 mmol) and trichloroacetimidate **5a** (1.37 g, 2.0 mmol) in CH_2Cl_2 and CH_3CN (1:1, 50 mL) at −50 °C and the resulting mixture was stirred for 30 min before it was allowed to reach ambient temperature. After neutralization with triethylamine and evaporation of the solvents, the residue was purified by chromatography (hexane/ethyl acetate 9:1) delivering the desired β-glycoside **6a** as a colorless syrup (1.7 g, 91%). $[\alpha] = +4.5$ ($c = 1.10$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.16$–7.41 and 7.64–7.69 (2m, 30H), 4.96–4.52 (4AB, 8H), 4.49 (d, 1H, $J = 7.8$ Hz), 4.09 (m, 1H), 3.73–3.58 (m, 6H), 3.44–3.38 (m, 2H), 2.80 (dd, 1H, $J = 5.3$, 15.1 Hz), 2.45 (dd, 1H, $J = 7.9$, 15.1 Hz), 1.42 (s, 9H), 1.15–1.62 (m, 26H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.7$, 138.7, 138.5, 138.3, 135.6, 129.4, 128.3–127.4, 103.1, 84.8, 82.4, 80.3, 77.9, 76.9, 75.7, 74.9, 74.8, 74.8, 73.4, 69.0,



Scheme 4. Preparation of the three required building blocks differing only in the lateral pattern of orthogonal protecting groups: a) donor **5a**, TMSOTf, CH_2Cl_2/MeCN, 88%; b) F_3CCOOH, CH_2Cl_2, 97%; c) donor **5b**, TMSOTf, CH_2Cl_2/MeCN, 58% (**18** + 22% of the α-anomer); d) NH_3, MeOH/THF, 87%; e) donor **20**, TMSOTf, CH_2Cl_2/MeCN, 79% (α:β 1:2.8); f) F_3CCOOH, CH_2Cl_2, 85%.

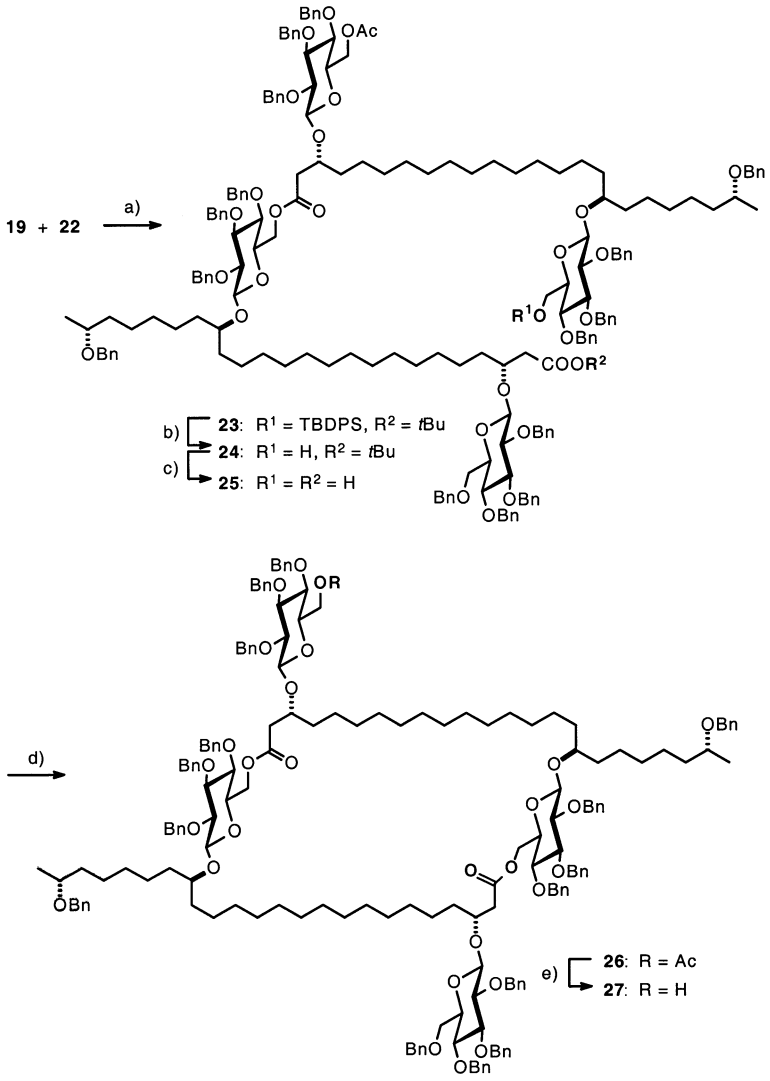
64.0, 42.3, 32.6, 28.8, 29.7–29.5, 29.4, 28.1, 26.9, 25.8, 25.0, 19.2; IR: $\tilde{\nu}$ = 3030, 2928, 2855, 1728, 1365, 1110, 1071 cm^{-1}; MS (ESI): *m*/*z*: 1141 $[M+Na]^+$; elemental analysis calcd (%) for $C_{71}H_{94}O_9Si$: C 76.17, H 8.46; found: C 76.04, H 8.37.

(3*R*)-*tert*-Butyl [17-*tert*-butyldiphenylsilyloxy-3-(2,3,4-tri-*O*-benzyl-6-*O*-acetyl-β-D-glucopyranosyl)oxy]heptadecanoate (6b): TMSOTf (15 μL) was added to a solution of alcohol **4** (500 mg, 0.83 mmol) and trichloroacetimidate **5b** (800 mg, 1.25 mmol) in CH_2Cl_2 and CH_3CN (1:1, 40 mL) at −50 °C and the resulting mixture was stirred for 30 min before it was allowed to reach ambient temperature. After neutralization with triethylamine and evaporation of the solvents, the residue was purified by flash chromatography (hexane/ethyl acetate 15:1). The first product to be eluted was the desired β-anomer **6b**. Colorless syrup (660 mg, 74%); $[\alpha]$ = +8.1 (*c* = 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.15 (m, 25H), 4.96–4.53 (3AB, 6H), 4.49 0(d, 1H, *J* = 7.8 Hz), 4.30 (d, 1H, *J* = 11.1 Hz), 4.20 (dd, 1H, *J* = 4.8, 11.7 Hz), 4.04 (m, 1H), 3.65 (t, 2H, *J* = 6.6 Hz), 3.62 (m, 1H), 3.49 (m, 2H), 3.39 (dd, 1H, *J* = 7.8, 9.1 Hz), 2.56 (dd, 1H, *J* = 5.3, 15.1 Hz), 2.41 (dd, 1H, *J* = 8.0, 15.1 Hz), 2.02 (s, 3H), 1.60–1.24 (m, 26H), 1.43 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 170.6, 138.4, 137.8, 135.6, 129.4, 128.4–127.5, 103.1, 84.8, 82.2, 80.3, 77.6, 77.4, 75.7, 74.9, 72.7, 64.0, 63.3, 42.2, 34.6, 32.6, 29.8–29.4, 28.1, 26.9, 25.8, 25.1, 20.8; IR: $\tilde{\nu}$ = 2928, 2855, 1744, 1731, 1454, 1235, 1071 cm^{-1}; elemental analysis calcd (%) for $C_{66}H_{90}O_{10}Si$: C 73.98, H 8.47; found: C 74.12, H 8.40.

The second fraction contained the corresponding α-anomer (160 mg, 15%) which showed the following properties: colorless syrup; $[\alpha]$ = +26.5 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.24 (m, 25H), 4.96 (d, 1H, *J* = 2.5 Hz), 4.99–4.54 (3AB, 6H), 4.29 (dd, 1H, *J* = 4.6, 11.9 Hz), 4.20 (dd, 1H, *J* = 2.1, 11.9 Hz), 4.04–3.93 (m, 3H), 3.65 (t, 2H, *J* = 6.6 Hz), 3.50 (dd, 1H, *J* = 3.7, 9.7 Hz), 3.46 (dd, 1H, *J* = 9.0 Hz), 2.53 (dd, 1H, *J* = 5.6, 15.5 Hz), 2.38 (dd, 1H, *J* = 6.9, 15.5 Hz), 2.01 (s, 3H), 1.65–1.24 (m, 26H), 1.43 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 170.6, 138.7, 138.12, 137.8, 135.5, 134.2, 129.4, 128.4–127.5, 95.7, 81.8, 80.5, 79.7, 77.5, 75.6, 75.1, 75.0, 72.9, 69.1, 64.0, 63.2, 40.7, 35.1, 32.6, 29.7–29.4, 28.1, 26.9, 25.8, 25.5, 20.8; elemental analysis calcd (%) for $C_{66}H_{90}O_{10}Si$: C 73.98, H 8.47; found: C 73.88, H 8.55.

(3*R*)-*tert*-Butyl [3-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-oxy]heptadecanoate (7a): A solution of compound **6a** (1.7 g, 1.52 mmol) and tetrabutylammonium fluoride trihydrate (505 mg, 1.6 mmol) in THF (10 mL) was stirred at ambient temperature until TLC analysis showed complete conversion (ca. 2 h). Evaporation of the solvent gave a viscous oil which was purified by flash chromatography (hexane/ethyl acetate 7:3) to yield alcohol **7a** as a colorless oil (1.2 g, 90%). $[\alpha]$ = +6.2 (*c* = 1.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.15 (m, 20H), 4.95–4.51 (4AB, 8H), 4.49 (d, 1H, *J* = 7.8 Hz), 4.09 (m, 1H), 3.72–3.57 (m, 6H), 3.43–2.38 (m, 2H), 2.80 (dd, 1H, *J* = 5.3, 15.1 Hz), 2.45 (dd, 1H, *J* = 8.0, 15.1 Hz), 1.60–1.19 (m, 26H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 138.7, 138.5, 138.3, 138.2, 128.3–127.4, 103.0, 84.8, 82.4, 80.3, 77.9, 76.9, 75.7, 74.9, 74.8, 74.8, 73.4, 68.9, 63.0, 42.3, 34.5, 32.8, 29.8, 29.6–29.4, 28.1, 25.7, 25.0; IR: $\tilde{\nu}$ = 3439, 2924, 2853, 1728, 1071 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{55}H_{76}O_9$+Na: 903.5387; found: 903.5394 $[M+Na]^+$.

(3*R*)-*tert*-Butyl [3-(6-*O*-acetyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl)-oxy]heptadecanoate (7b): A solution of compound **6b** (1.0 g, 1.30 mmol) and tetrabutylammonium fluoride trihydrate (440 mg, 1.40 mmol) in THF (10 mL) was stirred at ambient temperature until TLC analysis showed complete conversion (ca. 2 h). Evaporation of the solvent gave a viscous oil which was purified by flash chromatography (hexane/ethyl acetate 4:1) to yield alcohol **7b** as a colorless syrup (1.0 g, 92%). $[\alpha]$ = +12.2 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.20 (m, 15H), 4.96–4.53 (3AB, 6H), 4.49 (d, 1H, *J* = 7.8 Hz), 2.28 (d, 1H, *J* = 10.8 Hz), 4.20 (dd, 1H, *J* = 4.5, 11.6 Hz), 4.04 (m, 1H), 3.65 (m, 1H), 3.63 (t, 2H, *J* = 6.6 Hz), 3.48 (m, 2H), 3.40 (dd, 1H, *J* = 7.9, 9.1 Hz), 2.74 (dd, 1H, *J* = 5.4, 15.1 Hz), 2.42 (dd, 1H, *J* = 8.0, 15.2 Hz), 2.02 (s, 3H), 1.65–1.15 (m, 26H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 138.4, 138.3, 137.8, 128.4–127.6, 103.1, 84.8, 82.2, 80.3, 77.6, 77.4, 75.7, 74.9, 74.8, 72.7, 63.3, 63.1, 42.2, 34.6, 32.8, 29.7–29.4, 28.1, 25.7, 25.1, 20.8; IR: $\tilde{\nu}$ = 3438, 2926, 2854, 1744, 1728, 1367, 1070 cm^{-1}; MS (ESI): *m*/*z*: 855 $[M+Na]^+$; elemental analysis calcd (%) for $C_{50}H_{72}O_{10}$: C 72.08, H 8.71; found: C 72.14, H 8.63.



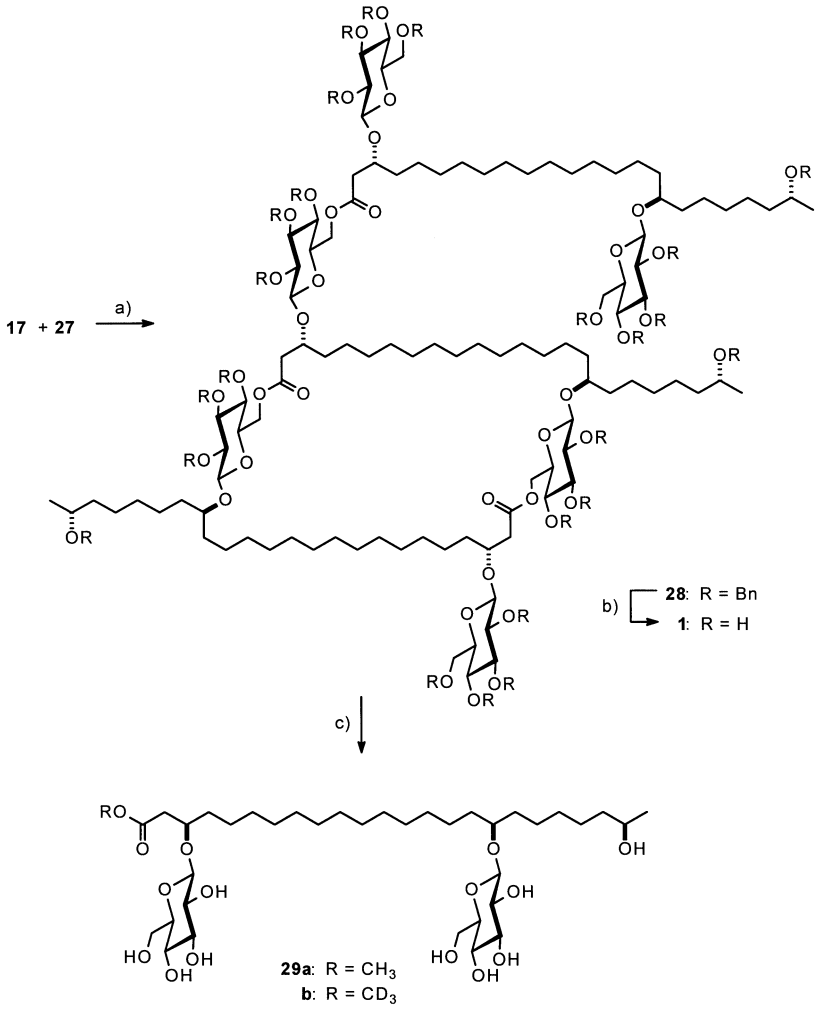
Scheme 5. Formation of the macrocyclic core: a) Et_3N, 2,4,6-trichlorobenzoyl chloride, toluene, DMAP, 86%; b) TBAF, THF; c) F_3CCOOH, CH_2Cl_2, 82% (over both steps); d) i) Et_3N, THF, 2,4,6-trichlorobenzoyl chloride; ii) slow addition to DMAP, toluene, 89%; e) NH_3 in MeOH, THF, 86%.

Compound 11a: A mixture of PCC (215 mg, 1.0 mmol) and alcohol **7a** (440 mg, 0.5 mmol) in dichloromethane (10 mL) was stirred at room temperature for 1.5 h before it was poured on top of a short silica gel column. Elution with hexane/ethyl acetate (4:1) gave crude aldehyde **8a** (920 mg, 96%) which was used directly in the next step. Characteristic data of **8a**: $[\alpha]_D^{20} = +6.3$ ($c = 1.15$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.75$ (t, 1H, $J = 1.9$ Hz), 7.10–7.35 (m, 20H), 4.96–4.52 (4AB, 8H), 4.49 (d, 1H, $J = 7.8$ Hz), 4.08 (m, 1H), 3.75–3.57 (m, 4H), 3.47–3.36 (m, 2H), 2.80 (dd, 1H, $J = 5.3$, 15.1 Hz), 2.45 (dd, 1H, $J = 8.0$, 15.1 Hz), 2.40 (td, 2H, $J = 1.9$, 7.4 Hz), 1.65–1.15 (m, 24H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 202.8$, 170.7, 138.6, 138.5, 138.3, 138.2, 128.3–127.5, 103.1, 84.8, 82.4, 80.3, 77.9, 76.9, 75.7, 74.9, 74.8, 74.8, 73.4, 68.9, 43.9, 42.3, 34.5, 29.8, 29.6–29.1, 28.1, 25.0, 22.1; IR: $\tilde{\nu} = 2926$, 2854, 2717, 1726, 1071 cm^{-1}; MS (ESI): m/z: 901 $[M+Na]^+$.

A solution of bis-triflate **10** (50 mg, 0.13 mmol) and $Ti(OiPr)_4$ (350 μL, 1.5 mmol) in toluene (2 mL) was stirred at 40°C for 30 min. After being cooled to −50°C, the zinc reagent **9** (1.5 mmol, 3 equiv)[11] was introduced prior to the addition of a solution of the crude aldehyde **8a** (ca. 0.5 mmol) in toluene (2 mL). The resulting mixture was slowly (1 h) warmed to −20°C, the reaction was quenched with sat. aq. NH_4Cl, diluted with *tert*-butyl methyl ether, and consecutively washed with 1M HCl, water and brine. The organic phase was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (hexane/ethyl acetate 4:1) to yield alcohol **11a** as a colorless syrup (350 mg, 73% over both steps). $[\alpha] = +1.1$ ($c = 1.10$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.25$–7.15 (m, 25H), 4.82–4.43 (5AB, 10H), 4.49 (d, 1H, $J = 7.8$ Hz), 4.08 (m, 1H), 3.75–3.35 (m, 8H), 2.80 (dd, 1H, $J = 5.4$, 15.1 Hz), 2.45 (dd, 1H, $J = 8.0$, 15.1 Hz), 1.62–1.15 (m, 36H), 1.42 (s, 9H), 1.18 (d, 3H, $J = 6.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 170.7, 139.1, 138.6, 138.5, 138.3, 138.2, 128.3–127.3, 103.1, 84.3, 82.4, 80.3, 77.9, 76.9, 75.7, 74.9, 74.9, 74.8, 73.4, 72.0, 70.2, 69.0, 42.3, 37.5, 37.4, 36.6, 34.5, 29.8–29.5, 28.1, 25.7, 25.6, 25.5, 25.0, 19.6; IR: $\tilde{\nu} =$ 3476, 2927, 2854, 1727, 1070 cm^{-1}; MS (ESI): m/z: 1107 $[M+Na]^+$; elemental analysis calcd (%) for $C_{69}H_{96}O_{10}$: C 76.35, H 8.91; found: C 76.33, H 8.79.

Compound 11b: A mixture of PCC (430 mg, 2.0 mmol) and alcohol **7b** (830 mg, 1.0 mmol) in dichloromethane (20 mL) was stirred at room temperature for 1.5 h before being poured onto a silica gel column. Elution with hexane/EtOAc (4:1) gave the crude aldehyde **8b** (770 mg, 98%) which was directly used in the next step. Characteristic data of **8b**: $[\alpha] = +13.0$ ($c = 0.60$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.75$ (t, 1H, $J = 1.9$ Hz), 7.30–7.20 (m, 15H), 4.96–4.53 (3AB, 6H), 4.49 (d, 1H, $J =$ 7.8 Hz), 4.30 (d, 1H, $J = 11.8$ Hz), 4.21 (dd, 1H, $J = 4.5$, 11.5 Hz), 4.04 (m, 1H), 3.65 (m, 1H), 3.49 (m, 2H), 3.40 (dd, 1H, $J = 7.9$, 9.1 Hz), 2.73 (dd, 1H, $J = 5.4$, 15.1 Hz), 2.44–2.34 (m, 3H), 2.02 (s, 3H), 1.65–1.15 (m, 24H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 202.9$, 170.7, 170.6, 138.4, 137.7, 128.4–127.6, 103.1, 84.8, 82.2, 80.4, 77.7, 77.4, 77.3, 75.7, 74.9, 74.8, 72.7, 63.3, 43.9, 42.2, 34.6, 28.8–29.2, 28.1, 25.1, 22.1, 20.8; IR: $\tilde{\nu} =$ 2926, 2854, 2717, 1743, 1727, 1070; MS (ESI): m/z: 853 $[M+Na]^+$.

A solution of bis-triflate **10** (113 mg, 0.3 mmol) and $Ti(OiPr)_4$ (700 μL, 3.0 mmol) in toluene (4 mL) was stirred at 40°C for 30 min. After the solution was cooled to −50°C, the zinc reagent **9** (3 mmol, 3 equiv) was added to this mixture prior to the addition of a solution of the crude aldehyde **8b** (1 mmol) in toluene (2 mL). The mixture was slowly (1 h) warmed to −20°C, the reaction was quenched with sat. aq. NH_4Cl and diluted with *tert*-butyl methyl ether, and the organic phase was successively washed with 1M HCl, water and brine. The organic phase was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (hexane/ethyl acetate 7:3) to yield alcohol **11b** as a colorless syrup (810 mg, 77% over both steps). $[\alpha] = +5.3$ ($c = 1.10$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.28$–7.15 (m, 20H), 4.96–4.43 (4AB, 8H), 4.48 (d, 1H, $J = 7.7$ Hz), 4.29 (d, 1H, $J = 10.7$ Hz), 4.20 (dd, 1H, $J =$ 4.5, 11.7 Hz), 4.01 (m, 1H), 3.69–3.44 (m, 5H), 3.40 (dd, 1H, $J = 7.8$, 9.1 Hz), 2.74 (dd, 1H, $J = 5.4$, 15.1 Hz), 2.40 (dd, 1H, $J = 8.0$, 15.1 Hz), 2.02 (s, 3H), 1.62–1.17 (m, 36H), 1.43 (s, 9H), 1.18 (d, 3H, $J = 6.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.6$, 138.4, 138.3, 137.8, 128.4–127.3, 103.1, 84.8, 82.3, 80.3, 77.7, 77.4, 75.7, 74.9, 74.9, 74.8, 72.7, 72.2, 70.3, 63.3, 42.2, 37.5, 37.4, 36.6, 34.6, 29.8–29.4, 28.1, 25.6, 25.6, 25.5, 25.1, 20.8,



Scheme 6. Completion of the total synthesis of macroviracin D: a) Et_3N, 2,4,6-trichlorobenzoyl chloride, toluene, DMAP, 74%; b) H_2 (1 atm), cat. $Pd(OH)_2$, anhydrous EtOH, quant.; c) H_2 (1 atm), Pd/C, MeOH, quant.

19.6; IR: $\tilde{\nu}$ = 3477, 2927, 2854, 1744, 1728, 1070 cm^{-1}; MS (ESI): *m/z*: 1059 $[M+Na]^+$; elemental analysis calcd (%) for $C_{64}H_{92}O_{11}$ (M_W = 1037.36): C 74.10, H 8.94; found: C 73.86, H 8.89.

Compound 16: TMSOTf (10 μL) was added to a solution of alcohol **11a** (350 mg, 0.32 mmol) and trichloroacetimidate **5a** (330 mg, 0.48 mmol) in CH_2Cl_2 and CH_3CN (1:1, 10 mL) at −50 °C and the resulting mixture was stirred for 30 min before it was warmed to −30 °C. After neutralization at that temperature with triethylamine and evaporation of the solvents, the residue was purified by flash chromatography (hexane/ethyl acetate 9:1) to give β-glycoside **16** as an oil (450 mg, 88%). $[\alpha]=+4.0$ ($c=0.90$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.40$–7.15 (m, 45H), 4.98–4.42 (9AB, 18H), 4.49 (d, 1H, $J=7.8$ Hz), 4.42 (d, 1H, $J=8.1$ Hz), 4.08 (m, 1H), 3.73–3.55 (m, 9H), 3.49–3.38 (m, 5H), 2.80 (dd, 1H, $J=5.4$, 15.1 Hz), 2.45 (dd, 1H, $J=7.9$, 15.1 Hz), 1.65–1.15 (m, 36H), 1.43 (s, 9H), 1.15 (d, 3H, $J=6.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.7$, 139.1, 138.7–138.2, 128.3–127.3, 103.1, 102.6, 84.9, 84.8, 82.4, 82.3, 80.3, 79.9, 78.0, 77.8, 76.9, 75.7, 75.6, 74.9–74.8, 73.6, 73.4, 70.2, 69.2, 68.9, 42.3, 36.6, 34.9, 34.5, 34.1, 30.1–29.5, 28.1, 25.5, 25.3, 25.2, 25.0, 19.6; IR: $\tilde{\nu}$ = 3080, 2926, 2854, 1727, 1070 cm^{-1}; MS (ESI): *m/z*: 1630 $[M+Na]^+$; elemental analysis calcd (%) for $C_{103}H_{130}O_{15}$: C 76.61, H 7.92; found: C 76.48, H 7.89.

Compound 17: A solution of ester **16** (300 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) and trifluoroacetic acid (0.5 mL) was stirred for 30 min. For work up, the solvent was evaporated and the residual trifluoroacetic acid was removed by repeated azeotropic distillation with toluene. Purification of the residue by flash chromatography (hexane/acetone 4:1) yielded acid **17** as an amorphous solid (880 mg, 97%). $[\alpha]=+11.0$ ($c=0.80$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.40$–7.15 (m, 45H), 4.97–4.42 (9AB, 18H), 4.46 (d, 1H, $J=7.9$ Hz), 4.42 (d, 1H, $J=7.8$ Hz), 4.04 (quint., 1H, $J=5.7$ Hz), 3.73–3.55 (m, 8H), 3.48–3.40 (m, 6H), 2.66 (dd, 1H, $J=6.5$, 15.4 Hz), 2.60 (dd, 1H, $J=4.7$, 15.3 Hz), 1.70–1.15 (m, 36H), 1.15 (d, 3H, $J=6.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=172.9$, 138.7, 138.6, 138.4, 128.5–127.4, 103.9, 102.6, 84.9, 84.7, 82.4, 82.0, 79.9, 78.8, 78.0, 77.7, 77.2, 75.7, 75.6, 74.9–74.8, 74.7, 74.4, 73.5, 73.4, 70.2, 96.2, 69.1, 41.2, 36.6, 35.3, 34.9, 34.0, 30.1, 29.9, 29.7–29.6, 29.5, 25.4, 25.3, 25.3, 25.1, 19.6; IR: $\tilde{\nu}$ = 3088, 3063, 3030, 2926, 2854, 1732, 1709, 1070 cm^{-1}; MS (ESI): *m/z*: 1574 $[M+Na]^+$; elemental analysis calcd (%) for $C_{99}H_{122}O_{15}$: C 76.61, H 7.92; found: C 76.54, H 8.07.

Compound 18: TMSOTf (10 μL) was added to a solution of alcohol **11a** (600 mg, 0.55 mmol) and trichloroacetimidate **5b** (530 mg, 0.83 mmol) in CH_2Cl_2 and CH_3CN (1:1, 20 mL) at −50 °C and the resulting mixture was stirred for 30 min before being warmed to ambient temperature. After neutralization with triethylamine and evaporation of the solvents, the residue was purified by flash chromatography (hexane/ethyl acetate 4:1). The first fraction to be eluted contained the desired β-anomer **18** as a colorless solid (500 mg, 58%). M.p. 46–47 °C; $[\alpha]=+7.8$ ($c=1.10$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.15$–7.25 (m, 40H), 4.97–4.41 (8AB, 16H), 4.49 (d, 1H, $J=7.8$ Hz), 4.42 (d, 1H, $J=8.1$ Hz), 4.31 (dd, 1H, $J=2.0$, 11.9 Hz), 4.17 (dd, 1H, $J=5.0$, 11.7 Hz), 4.08 (m, 1H), 3.70–3.58 (m, 6H), 3.52–3.38 (m, 6H), 2.80 (dd, 1H, $J=5.4$, 15.1 Hz), 2.45 (dd, 1H, $J=8.0$, 15.1 Hz), 2.01 (s, 3H), 1.68–1.18 (m, 36H), 1.42 (s, 9H), 1.15 (d, 3H, $J=6.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.7$, 170.6, 138.6–137.8, 128.4–127.3, 103.0, 102.6, 84.9, 84.8, 82.3, 82.3, 80.3, 80.2, 77.8, 77.7, 76.9, 75.7, 76.6, 74.9, 74.8, 74.8, 74.8, 74.7, 73.4, 72.6, 70.2, 68.9, 63.3, 42.2, 36.6, 34.8, 34.5, 34.1, 30.0, 29.8–29.7, 29.5, 28.1, 25.4, 25.2, 25.2, 25.0, 20.8, 19.6; IR: $\tilde{\nu}$ = 3030, 2928, 2855, 1743, 1728, 1070 cm^{-1}; MS (ESI): *m/z*: 1582 $[M+Na]^+$; elemental analysis calcd (%) for $C_{98}H_{126}O_{16}$: C 75.45, H 8.14; found: C 75.28, H 8.15.

The second fraction contained the corresponding α-anomer (190 mg, 22%) which showed the following analytical and spectroscopic properties: m.p. 57–58 °C; $[\alpha]=+26.4$ ($c=0.70$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.33$–7.15 (m, 40H), 4.93 (m, 1H), 5.02–4.43 (8AB, 16H), 4.49 (d, 1H, $J=7.8$ Hz), 4.30 (dd, 1H, $J=4.4$, 12.0 Hz), 4.20 (dd, 1H, $J=2.1$, 11.9 Hz), 4.09 (m, 1H), 3.73–3.38 (m, 12H), 2.80 (dd, 1H, $J=5.4$, 15.1 Hz), 2.45 (dd, 1H, $J=8.0$, 15.1 Hz), 2.00 (s, 3H), 1.65–1.15 (m, 36H), 1.43 (s, 9H), 1.17 (d, 3H, $J=6.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.7$, 170.7, 138.6–137.8, 128.4–127.4, 103.0, 95.5, 84.8, 82.3, 82.0, 80.3, 80.0, 78.3, 77.8, 77.5, 76.9, 75.7, 75.6, 75.0, 74.9, 74.9, 74.8, 74.7, 73.4, 73.2, 70.2, 68.9, 68.8, 63.2, 42.2, 36.6, 34.5, 34.4, 33.1, 30.0, 29.9–29.7, 29.5, 28.1, 25.8, 25.4, 25.0, 24.9, 20.8, 19.6; IR: $\tilde{\nu}$ = 3030, 2927, 2855, 1742, 1089, 1071 cm^{-1}; MS (ESI): *m/z*: 1582 $[M+Na]^+$; elemental analysis calcd (%) for $C_{98}H_{126}O_{16}$: C 75.45, H 8.14; found: C 75.54, H 7.99.

Compound 19: A saturated methanolic solution of ammonia (5 mL) was added to a solution of glycoside **18** (400 mg, 0.26 mmol) in THF (2 mL) and the resulting mixture was stirred for 4 d before it was concentrated

to dryness. The residue was purified by flash chromatography (hexane/ethyl acetate 4:1) to give alcohol **19** (340 mg, 87%). $[\alpha]=+3.5$ ($c=1.05$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.40$–7.15 (m, 40H), 4.96–4.41 (8AB, 16H), 4.48 (d, 1H, $J=7.8$ Hz), 4.45 (d, 1H, $J=7.9$ Hz), 4.09 (quint., 1H, $J=5.7$ Hz), 3.83 (dd, 1H, $J=2.5$, 11.8 Hz), 3.73–3.59 (m, 6H), 3.53 (t, 1H, $J=9.5$ Hz), 3.49–3.32 (m, 6H), 2.79 (dd, 1H, $J=5.4$, 15.1 Hz), 2.45 (dd, 1H, $J=8.0$, 15.1 Hz), 1.61–1.15 (m, 37H), 1.42 (s, 9H), 1.15 (d, 3H, $J=6.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.7$, 138.7–138.0, 128.4–127.3, 103.1, 102.5, 84.8, 84.7, 82.4, 82.3, 80.3, 80.1, 77.9, 77.8, 75.6, 75.6, 75.0, 74.9, 74.8, 73.4, 70.2, 69.0, 62.3, 42.3, 36.7, 34.9, 34.5, 34.2, 30.1, 29.8–29.5, 28.1, 25.4, 25.3, 25.2, 25.0, 19.6; IR: $\tilde{\nu}$ = 3479, 2926, 2855, 1728, 1497, 1070 cm^{-1}; MS (ESI): m/z: 1540 $[M+Na]^+$; elemental analysis calcd (%) for $C_{96}H_{124}O_{15}$: C 75.96, H 8.23; found: C 76.11, H 8.15.

Compound 21: TMSOTf (10 μL) was added to a solution of alcohol **11b** (500 mg, 0.48 mmol) and trichloroacetimidate **20** (520 mg, 0.62 mmol) in CH_2Cl_2 and CH_3CN (1:1, 10 mL) at −50 °C, and the resulting mixture was stirred for 30 min before being warmed to −10 °C. After neutralization at that temperature with triethylamine and evaporation of the solvents, the residue was purified by flash chromatography (hexane/ethyl acetate 9:1) to give a mixture of both anomers of product **21** (650 mg, 79%, α/β 1:2.8). These compounds were separated by preparative HPLC (Nucleosil-7-100-C18/A, acetonitrile/2-propanol 85:15). α-Anomer: syrup (112 mg, 14%). $[\alpha]=+19.2$ ($c=2.20$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.65$–7.14 (m, 45H), 4.99–4.45 (7AB, 14H), 4.75 (d, 1H, $J=3.7$ Hz), 4.50 (d, 1H, $J=7.9$ Hz), 4.29 (d, 1H, $J=10.7$ Hz), 4.20 (m, 1H), 4.08–4.00 (m, 1H), 3.95–3.78 (m, 3H), 3.59 (br quint., 1H, $J=5.7$ Hz), 3.69–3.35 (m, 8H), 2.75 (dd, 1H, $J=5.4$, 15.1 Hz), 2.41 (dd, 1H, $J=7.9$, 15.1 Hz), 2.02 (s, 3H), 1.62–1.16 (m, 36H), 1.42 (s, 9H), 1.10 (d, 3H, $J=6.1$ Hz), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.7$, 170.6, 138.5, 138.4, 138.3, 137.8, 135.8, 135.6, 133.7, 133.3, 129.5, 129.4, 128.4–127.2, 103.1, 95.0, 84.8, 82.3, 82.2, 80.6, 80.3, 78.1, 77.6, 77.4, 77.3, 75.7, 75.1, 74.9, 74.9, 73.2, 72.7, 71.8, 70.2, 63.3, 62.9, 42.2, 36.6, 34.6, 34.4, 32.9, 30.1, 29.8–29.7, 29.5, 28.1, 26.8, 25.7, 25.4, 25.1, 25.0, 20.8, 19.6, 19.3; IR: $\tilde{\nu}$ = 2928, 2855, 1742, 1240, 1071 cm^{-1}; MS (ESI): m/z: 1730 $[M+Na]^+$; elemental analysis calcd (%) for $C_{107}H_{138}O_{16}Si$: C 75.23, H 8.14; found: C 75.08, H 8.12.

The second fraction consists of the desired β-anomer **21**: syrup (270 mg, 32%). $[\alpha]=+4.4$ ($c=1.50$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.75$–7.10 (m, 45H), 5.05–4.42 (7AB, 14H), 4.50 (d, 1H, $J=7.8$ Hz), 4.48 (d, 1H, $J=7.7$ Hz), 4.29 (d, 1H, $J=10.8$ Hz), 4.21 (m, 1H), 4.03 (br quint., 1H, $J=5.4$ Hz), 3.95 (dd, 1H, $J=2.3$, 10.9 Hz), 3.87 (dd, 1H, $J=4.5$, 11.1 Hz), 3.73 (quint., 1H, $J=5.7$ Hz), 3.70–3.60 (m, 3H), 3.42–3.30 (m, 6H), 2.75 (dd, 1H, $J=5.4$, 15.1 Hz), 2.41 (dd, 1H, $J=7.9$, 15.1 Hz), 2.01 (s, 3H), 1.70–1.16 (m, 36H), 1.43 (s, 9H), 1.15 (d, 3H, $J=6.1$ Hz), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.7$, 170.6, 138.7, 138.7, 138.4, 138.3, 138.2, 138.8, 135.8, 135.5, 133.7, 133.2, 129.5, 128.4–127.3, 103.1, 102.1, 85.0, 84.8, 82.7. 82.3, 80.3, 78.9, 77.8, 77.6, 77.4, 77.2, 75.8, 75.7, 75.6, 74.9, 74.8, 74.8, 74.8, 72.7, 70.2, 63.3, 63.0, 42.2, 36.6, 34.9, 34.6, 33.5, 30.0, 30.0, 29.8–29.7, 29.5, 28.1, 26.8, 25.5, 25.4, 25.1, 25.0, 20.7, 19.6, 19.3; IR: $\tilde{\nu}$ = 3031, 2928, 2855, 1743, 1070 cm^{-1}; MS (ESI): m/z: 1730 $[M+Na]^+$; elemental analysis calcd (%) for $C_{107}H_{138}O_{16}Si$: C 75.23, H 8.14; found: C 75.48, H 8.04.

Compound 22: A solution of ester **21** (220 mg, 0.128 mmol) in CH_2Cl_2 (5 mL) and trifluoroacetic acid (0.5 mL) was stirred at ambient temperature for 30 min. The mixture was diluted with toluene, the solvent was distilled off, and residual trifluoroacetic acid was removed by repeated azeotropic distillation with toluene. Purification of the residue by flash chromatography (hexane/acetone 4:1) yielded acid **22** (180 mg, 85%) as an amorphous solid. $[\alpha]=+12.7$ ($c=0.60$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.70$–7.10 (m, 45H), 5.01–4.42 (7AB, 14H), 4.49 (d, 1H, $J=7.8$ Hz), 4.48 (d, 1H, $J=7.7$ Hz), 4.44–4.42 (m, 1H), 4.14 (dd, 1H, $J=4.4$, 11.9 Hz), 4.03 (quint., 1H, $J=5.2$ Hz), 3.92 (dd, 1H, $J=2.0$, 10.1 Hz), 3.85 (dd, 1H, $J=4.4$, 11.1 Hz), 3.73 (quint., 1H, $J=5.8$ Hz), 3.69–3.62 (m, 3H), 3.51 (t, 1H, $J=9.8$ Hz), 3.47–3.40 (m, 4H), 3.32 (m, 1H), 2.68 (dd, 1H, $J=6.7$, 15.3 Hz), 2.55 (dd, 1H, $J=4.9$, 15.3 Hz), 2.04 (s, 3H), 1.70–1.11 (m, 36H), 1.15 (d, 3H, $J=6.1$ Hz), 1.08 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta=173.5$, 171.5, 139.1, 138.7, 138.7, 138.4, 137.7, 135.8, 135.6, 129.5, 128.4–127.3, 103.7, 102.1, 85.0, 84.6, 82.7, 82.1, 79.0, 78.2, 77.8, 77.3, 75.75, 75.71, 74.99, 74.83, 72.8, 70.2, 62.9, 62.6, 41.0, 36.7, 35.5, 34.9, 33.4, 30.1, 30.0, 29.7, 29.7, 29.5, 26.8, 25.5, 25.4, 25.3, 25.0, 20.9, 19.6, 19.3; IR: $\tilde{\nu}$ =3065, 2927, 2855, 1735, 1704, 1068 cm^{-1}; MS (ESI-pos.): m/z: 1674 $[M+Na]^+$; elemental analysis calcd (%) for $C_{103}H_{130}O_{16}Si$: C 74.87, H 7.93; found: C 75.00, H 8.04.

Compound 23: Triethylamine (35 μL, 0.225 mmol) and 2,4,6-trichlorobenzoyl chloride (16 μL, 0.103 mmol) were added to a solution of acid **22** (140 mg, 0.085 mmol) in toluene (5 mL). The resulting mixture was stirred for 1.5 h before a solution of alcohol **19** (140 mg, 0.10 mmol) and DMAP (5 mg, 0.043 mmol) in toluene (3 mL) was introduced. After 1 h, the mixture was concentrated and the residue was purified by flash chromatography (hexane/acetone 9:1) to give ester **23** (230 mg, 86%) as a colorless syrup. $[\alpha]=+5.1$ ($c=1.70$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.75$–7.15 (m, 85H), 5.02–4.41 (m, 32H), 4.49 (d, 1H, $J=7.7$ Hz), 4.48 (d, 1H, $J=7.9$ Hz), 4.47 (d, 1H, $J=7.7$ Hz), 4.35–4.15 (m, 3H), 4.08 (m, 1H), 3.93 (d, 1H, $J=11.1$ Hz), 3.86 (dd, 1H, $J=4.4$, 11.1 Hz), 3.75 (quint., 1H, $J=5.6$ Hz), 3.74–3.57 (m, 10H), 3.50–3.30 (m, 12H), 2.90 (dd, 1H, $J=5.1$, 16.0 Hz), 2.80 (dd, 1H, $J=5.4$, 15.1 Hz), 2.51 (dd, 1H, $J=7.8$, 16.0 Hz), 2.47 (dd, 1H, $J=7.9$, 15.1 Hz), 1.99 (s, 3H), 1.70–1.10 (m, 72H), 1.42 (s, 9H), 1.15 (d, 6H, $J=6.1$ Hz), 1.06 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=171.0$, 170.7, 170.6, 138.6–138.2, 137.8, 135.8, 135.5, 133.6, 133.2, 129.5, 128.4–127.3, 103.7, 103.0, 102.4, 102.1, 85.0, 84.8, 84.7, 84.7, 82.6, 82.3, 82.3, 82.2, 80.3, 80.8, 78.9, 78.0, 77.8, 77.7, 77.6, 77.2, 75.7–75.6, 74.9–74.8, 74.7, 73.3, 72.6, 70.2, 68.9, 63.3, 63.1, 62.9, 42.2, 40.8, 36.6, 35.1, 34.9, 34.7, 34.5, 33.8, 33.4, 30.1–29.6, 28.1, 26.8, 25.5–25.4, 25.1–25.0, 20.8, 19.6, 19.2; IR: $\tilde{\nu}$ =3031, 2928, 2855, 1740, 1454, 1360, 1070 cm^{-1}; HRMS (ESI-pos.): m/z: calcd for $C_{199}H_{252}O_{30}Si$: 3149.22 found: 1613.86 $[M+2K]^{2+}$.

Compound 25: A solution of compound **23** (200 mg, 0.063 mmol) and tetrabutylammonium fluoride trihydrate (22 mg, 0.07 mmol) in THF (3 mL) was stirred at ambient temperature overnight. Evaporation of the solvent gave product **24** as a viscous oil which was dissolved in CH_2Cl_2 (5 mL) and treated with trifluoroacetic acid (0.5 mL) at ambient temperature for 30 min. For work up, the trifluoroacetic acid was removed by repeated azeotropic distillation with toluene. Purification of the residue by flash chromatography (hexane/acetone 4:1) yielded hydroxy acid **25** as a colorless oil (147 mg, 82%). $[\alpha]=+10.2$ ($c=1.74$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.35$–7.15 (m, 75H), 4.97–4.41 (m, 35H), 4.33 (d, 1H, $J=11.2$ Hz), 4.27 (br d, 1H, $J=11.3$ Hz), 4.20 (m, 1H), 4.05 (m, 2H), 3.84 (dd, 1H, $J=2.8$, 11.8 Hz), 3.70–3.56 (m, 8H), 3.54 (t, 1H, $J=9.5$ Hz), 3.42–3.32 (m, 14H), 2.88 (dd, 1H, $J=5.0$, 16.0 Hz), 2.68 (dd, 1H, $J=6.6$, 15.3 Hz), 2.59 (dd, 1H, $J=4.8$, 15.3 Hz), 2.52 (dd, 1H, $J=7.8$, 16.0 Hz), 1.99 (s, 3H), 1.64–1.10 (m, 72H), 1.15 (d, 6H, $J=6.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=173.1$, 170.9, 170.6, 139.0, 138.5–137.7, 137.5, 128.4, 127.2, 103.9, 103.7, 102.4, 84.7, 84.6, 82.3, 82.2, 82.1, 82.0, 80.1, 80.0, 78.7, 77.9, 77.7, 77.6, 77.5, 72.2, 75.7–75.6, 74.9–74.7, 74.6, 74.4, 73.4, 72.6, 70.1, 69.2, 63.2, 63.0, 62.2, 41.2, 40.8, 36.6, 35.3, 35.1, 34.8, 34.7, 34.1, 33.8, 30.0–29.7, 29.5, 25.4, 25.4, 25.3, 25.1, 20.8, 19.5; IR: $\tilde{\nu}$ = 3437, 3030, 2920, 2851, 1732, 1709, 1071 cm^{-1}; HRMS (ESI-pos.): m/z: calcd for $C_{179}H_{225}O_{30}$+K (potassium salt of the acid): 2893.50; found: 1485.74 $[M+2K]^{2+}$.

Compound 26: Triethylamine (26 μL, 0.19 mmol) was added to a solution of compound **25** (180 mg, 0.063 mmol) in THF (3 mL). After 10 min, the mixture was treated with 2,4,6-trichlorobenzoyl chloride (12 μL, 0.08 mmol) and stirring was continued for 2 h. The mixture was then diluted with anhydrous toluene (20 mL) and added over a period of 3 h via syringe pump to a refluxing solution of DMAP (118 mg, 0.9 mmol) in toluene (50 mL). After the addition was complete, reflux was continued for 1 h before the solvent was evaporated and the residue was purified by flash chromatography (hexane/ethyl acetate 4:1) to give macrolactone **26** as a colorless syrup (160 mg, 89%). $[\alpha]=+10.6$ ($c=0.65$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.35$–7.20 (m, 75H), 4.96–4.42 (m, 32H), 4.40 (d, 1H, $J=7.9$ Hz), 4.38 (d, 1H, $J=7.8$ Hz), 4.36–4.32 (m, 2H), 4.25 (d, 1H, $J=10.6$ Hz), 4.17 (dd, 1H, $J=4.5$, 11.7 Hz), 4.11 (m, 3H), 4.06 (quint., 1H, $J=6.3$ Hz), 3.68–3.55 (m, 9H), 3.52–3.34 (m, 13H), 2.92 (dd, 1H, $J=5.6$, 16.1 Hz), 2.85 (dd, 1H, $J=5.4$, 16.1 Hz), 2.52 (dd, 1H, $J=7.0$, 16.1 Hz), 2.48 (dd, 1H, $J=7.3$, 16.1 Hz), 1.93 (s, 3H), 1.65–1.10 (m, 72H), 1.15 (d, 3H, $J=6.1$ Hz), 1.14 (d, 3H, $J=6.1$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=171.1$, 171.0, 170.6, 139.1, 138.7, 138.5–138.3, 137.8, 137.7, 128.4, 128.4–127.5, 127.3, 103.8, 103.7, 102.9, 102.8, 84.9, 84.8, 84.7, 82.4, 82.3, 82.2, 80.7, 80.6, 78.2, 77.7, 77.6, 77.6, 75.7–75.6, 75.0–74.8, 74.7, 73.3, 72.7, 72.7, 70.2, 68.7, 63.6, 63.5, 63.1, 40.9, 40.8, 36.7, 35.3, 35.2, 35.1, 35.0, 34.5, 34.4, 30.1–29.7, 25.5, 25.4, 25.3, 25.3, 25.2, 20.8, 19.6; IR: $\tilde{\nu}$ = 2921,

2851, 1731, 1071 cm^{-1}; HRMS (ESI-pos.): m/z: calcd for $C_{179}H_{224}O_{29}$: 2837.54; found: 1457.77 $[M+2K]^{2+}$.

Compound 27: Lactone **26** (40 mg) was dissolved in THF (3 mL) and treated with a saturated methanolic solution of ammonia (3 mL). The resulting mixture was stirred for 8 d at ambient temperature and then evaporated to dryness. The residue was purified by flash chromatography (hexane/ethyl acetate 4:1) to give alcohol **27** as a colorless syrup (34 mg, 86%). $[\alpha]=+4.5$ ($c=1.70$, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) $\delta=$ 7.35–7.10 (m, 75H), 4.93–4.32 (m, 36H), 4.15–4.05 (m, 4H), 3.68–3.30 (m, 24H), 2.92 (dd, 1H, $J=5.6$, 16.2 Hz), 2.65 (dd, 1H, $J=8.3$, 15.5 Hz), 2.52 (dd, 1H, $J=7.0$, 16.1 Hz), 2.43 (dd, 1H, $J=3.6$, 15.4 Hz), 1.60–1.15 (m, 72H), 1.15 (d, 3H, $J=6.1$ Hz), 1.14 (d, 3H, $J=6.1$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=$172.1, 171.1, 139.2, 138.7, 138.6–137.7, 128.3–127.6, 103.8, 103.3, 103.2, 102.9, 84.9, 84.8, 84.8, 84.7, 82.5, 82.4, 82.3, 82.3, 81.4, 80.7, 78.4, 78.3, 78.2, 77.8, 77.7, 77.7, 75.6, 75.6, 75.1–73.3, 72.7, 70.2, 68.7, 64.2, 63.5, 62.5, 41.2, 40.9, 36.7, 35.9, 35.1, 35.0, 34.6, 30.1–29.7, 25.5–25.3, 19.6.

Compound 28: Triethylamine (4 μL, 0.03 mmol) and 2,4,6-trichlorobenzoyl chloride (2 μL, 0.012 mmol) were added to a solution of acid **17** (16 mg, 0.01 mmol) in toluene (2 mL). The resulting mixture was stirred for 1.5 h before a solution of alcohol **27** (15 mg, 0.005 mmol) and DMAP (0.6 mg, 0.005 mmol) in toluene (1 mL) was introduced. After stirring for 1 h, the mixture was concentrated and the residue was purified by flash chromatography (hexane/ethyl acetate 4:1) to give ester **28** as a colorless syrup (17 mg, 74%). $[\alpha]=+7.3$ ($c=1.70$, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): $\delta=$7.32–7.24 (m, 120H), 4.95–4.39 (24AB+m, 54H), 4.32 (m, 1H), 4.28 (m, 2H), 4.15–4.05 (m, 6H), 3.72–3.32 (m, 36H), 2.93 (dd, 2H, $J=5.5$, 16.3 Hz), 2.83 (dd, 1H, $J=5.3$, 15.9 Hz), 2.59 (dd, 1H, $J=7.5$, 15.8 Hz), 2.53 (dd, 1H, $J=6.9$, 16.1 Hz), 2.45 (dd, 1H, $J=7.2$, 16.1 Hz), 1.60–1.15 (m, 108H), 1.15 (d, 6H, $J=6.1$ Hz), 1.14 (d, 3H, $J=6.1$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=$171.1, 171.0, 170.9, 139.1, 138.7–138.2, 137.8, 137.7, 128.4–127.5, 127.4, 103.8, 103.7, 103.6, 102.8, 102.7, 102.6, 85.0, 84.9, 84.8, 84.7, 84.6, 82.4, 82.3, 82.3, 82.2, 82.2, 80.6, 80.4, 79.9, 78.2, 78.1, 78.0, 77.8, 77.7, 77.5, 75.6–75.5, 75.1–74.6, 73.6, 73.4, 73.3, 72.8, 72.7, 70.2, 69.2, 68.8, 68.7, 63.6, 63.5, 62.8, 40.9, 40.8, 36.7, 36.6, 36.0, 35.2, 35.0, 34.9, 34.4, 34.3, 34.1, 30.1–29.6, 25.5–25.1, 19.6; HRMS (ESI-pos.): m/z: calcd for $C_{276}H_{342}O_{42}$: 4328.4626; found: 1465.8091 $[M+3Na]^{3+}$.

Compound 1: $Pd(OH)_2$ (5 mg) was added to a solution of compound **28** (8.1 mg, 1.87 mmol) in carefully dried EtOH (6 mL) and the resulting suspension was stirred under H_2 (1 atm) for 12 h at ambient temperature. The catalyst was filtered off through a short pad of Celite, the Celite was rinsed with anhydrous EtOH, and the combined filtrates were evaporated giving compound **1** as an analytically pure white solid (4 mg, 100%). $[\alpha]_D^{25} = -21$ ($c=0.36$, CH_3OH) [lit.:[1] −27.2 ($c=1$)]; ^1H NMR (600 MHz, CD_3OD): $\delta=$4.55 (br s, 24H), 4.44 (dd, 1H, $J=1.9$, 11.6 Hz), 4.43 (dd, 1H, $J=1.9$, 11.6 Hz), 4.39 (dd, 1H, $J=1.9$, 11.7 Hz), 4.35 (d, 1H, $J=$ 7.9 Hz), 4.34 (d, 1H, $J=7.8$ Hz), 4.33 (d, 1H, $J=7.8$ Hz), 4.31 (d, 1H, $J=$ 7.7 Hz), 4.27 (d, 1H, $J=7.8$ Hz), 4.33–4.25 (m, 2H), 4.21 (dd, 1H, $J=5.8$, 11.7 Hz), 4.15 (dd, 1H, $J=7.6$, 11.8 Hz), 4.13 (dd, 1H, $J=7.5$, 11.8 Hz), 4.12–4.03 (m, 10H), 3.85–3.57 (m, 27H), 2.82 (dd, 1H, $J=6.2$, 15.8 Hz), 2.81 (m, 2H), 2.57 (dd, 1H, $J=5.9$, 15.3 Hz), 2.49 (dd, 1H, $J=5.6$, 15.6 Hz), 2.45 (dd, 1H, $J=6.5$, 15.7 Hz), 1.63–1.25 (m, 108H), 1.14 (d, 9H, $J=6.1$ Hz); ^{13}C NMR (150 MHz, CD_3OD): $\delta=$173.6, 173.4, 172.9, 104.7, 104.3, 104.3, 103.9, 103.9, 103.8, 103.4, 81.3, 81.2, 81.1, 80.5, 78.4, 78.2, 78.1, 78.0, 77.9, 77.7, 77.7, 75.3, 75.3, 75.2, 75.2, 75.1, 72.1, 71.8, 71.5, 71.4, 68.6, 65.4, 65.3, 64.8, 64.7, 63.0, 62.9, 62.8, 42.2, 40.2, 36.4, 36.2, 36.2, 36.0, 35.5, 34.9, 31.1–30.8, 26.9, 26.8, 26.6–26.1, 26.0, 23.6, 23.5; HMRS (ESI-pos.): calcd for $C_{108}H_{198}O_{42}$: 2167.33577; found: 1106.67026 $[M+2Na^{2+}]$.

Compound 29a: ^1H NMR (600 MHz, CD_3OD): $\delta=4.32$ (d, 1H, $J=$ 8.0 Hz), 4.30 (d, 1H, $J=8.0$ Hz), 4.08 (m, 1H), 3.84 (dd, 1H, $J=2.5$, 11.8 Hz), 3.81 (dd, 1H, $J=2.1$, 11.8 Hz), 3.72–3.68 (m, 2H), 3.67 (dd, 1H, $J=5.5$, 11.8 Hz), 3.63 (s, 3H), 3.63 (dd, 1H, $J=5.5$, 11.8 Hz), 3.34 (t, 1H, $J=8.9$ Hz), 3.33 (t, 1H, $J=8.8$ Hz), 3.32–3.20 (m, 4H), 3.15 (dd, 1H, $J=$ 7.8, 9.0 Hz), 3.12 (dd, 1H, $J=7.8$, 9.2 Hz), 2.71 (dd, 1H, $J=7.1$, 15.4 Hz), 2.51 (dd, 1H, $J=5.5$, 15.4 Hz), 1.66–1.26 (m, 36H), 1.13 (d, 3H, $J=$ 6.1 Hz); ^{13}C NMR (150 MHz, CD_3OD): $\delta=$174.4, 104.2, 103.4, 80.5, 78.2, 78.1, 78.0, 77.97, 77.7, 77.68, 75.3, 75.2, 71.8, 71.7, 68.6, 62.9, 49.3, 41.9, 40.1, 35.93, 35.90, 34.8, 31.0, 30.8, 30.75, 30.73, 30.72, 30.71, 30.6, 26.8, 26.3, 26.1, 26.0, 23.5.

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