Synthesis of 1,6-Ansaglycosides

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Abstract: Two representatives of the 1,6-ansaglycoside class of compounds have been synthesized by different ring-closing strategies.

Key words: ansa compounds, ring closure, macrocycles, glycosides, carbohydrates, total synthesis, natural products

Liverworts are a rich source of structurally diverse and biologically active compounds.[2] Despite this fact bryophytes in general have been neglected by phytochemists for a long time because it was erroneously concluded that due to the absence of any toxic representatives among the bryophytes they are poor in secondary metabolites. It was only recently that this situation changed towards a more systematic investigation of natural products from this plant division. Apart from many known compounds, especially represented among terpenoid and phenolic structures, a considerable number of natural products with hitherto unknown carbon skeletons have been isolated and structurally characterized. The phenolic fraction of liverwort constituents is thereby dominated by bibenzyls. In recent years, however, the isolation of a number of new phenolic compounds, characterized by phenylpropane carbon frameworks, was described.[3] Among these constituents marchesin (**1**), named after *Marchesinia bongardiana*, from which it was isolated, displays one of the most striking constitutions[4] (Figure 1). Its intriguing structure is characterized by a macrolactone spanning the carbon atoms 1 and 6 of the glucose portion of a disaccharide known as neohesperidose (2-*O*-α-L-rhamnopyranosyl-D-glucopyranose). The aglycon part is composed of vanillic acid and an α-pyrone substituted naphthalene carboxylic acid, itself a natural product (scapaniapyrone A) isolated from the liverwort *Scapania undulata*.[5] Due to the presence of aromatic rings in the macrocyclic tether, marchesin **1** can be regarded as an ansa compound as well. We therefore chose the name of 1,6-ansaglycoside for this new class of compounds reflecting the most prominent features of its molecular architecture.

To the best of our knowledge only two additional natural products have been isolated which can be classified as 1,6-ansaglycosides: poriolide (**2**) and isoporiolide (**3**), isolated in the seventies from the Ericaceae *Leucothoe*

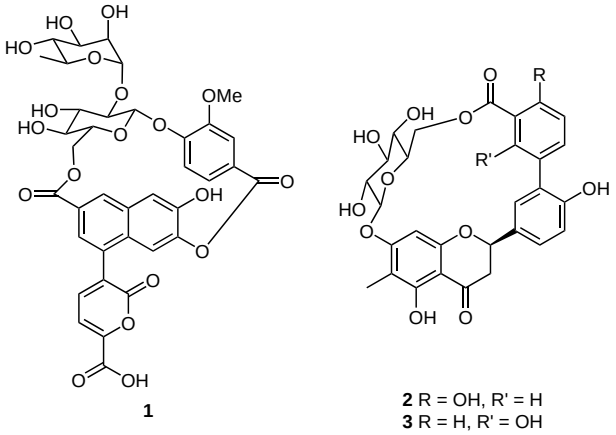

Figure 1 Structures of marchesin, poriolide and isoporiolide

keiskei.[6] These biphenyl substituted flavanone glycosides, like marchesin, are β-D-glucosides spanning the sugar backbone with the aglycon to form a macrocyclic lactone bridge between the primary hydroxyl group of the monosaccharide and a carboxylic acid moiety of the aglycon. Due to their pronounced antiviral properties, the isolation procedure of poriolide (**2**) and its isomer **3** has been patented.[7] Taking into account their scarcity as natural products it was not unexpected to find that no synthetic studies on 1,6-ansaglycosidic compounds have been published to date. Given the biological activity of poriolide (**2**) and the challenging structural complexity of 1,6-ansaglycosides in general we tackled a synthetic approach of this class of compounds. As a first approximation of the structural principle underlying the natural products **1**, **2** and **3**, we determined compounds **4** and **5** to be promising candidates for the first syntheses of 1,6-ansaglycosides.

Their relatively simple aglycon part is designed so as to form nineteen-membered rings with the sugar backbone mimicking the macrocycle of the natural products. Both

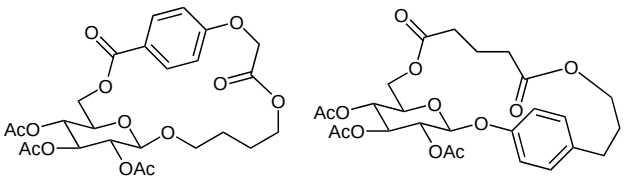

Figure 2 Structures of 1,6-ansaglycosides to be synthesized

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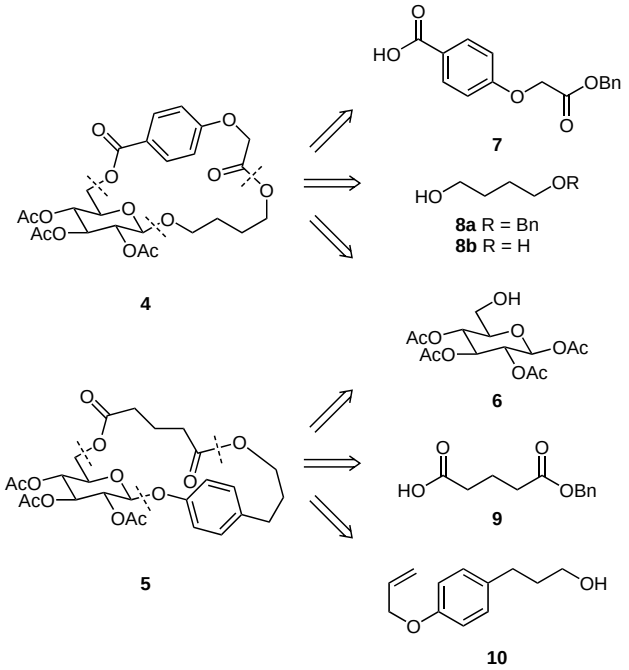
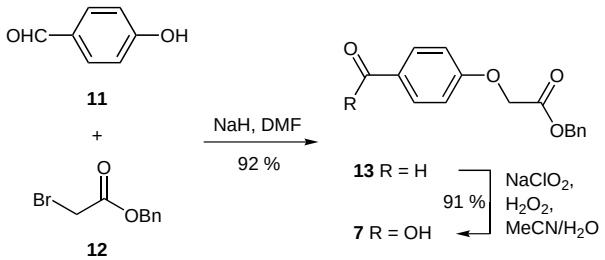
model compounds are β-glucosides containing a second lactone moiety in the tether in addition to the one bridging the sugar. As sites for potential ring closing reactions we identified the two lactone functionalities as well as the glycosidic bond. In the following paragraphs we describe our efforts towards a synthesis of compounds **4** and **5** (Figure 2).



Scheme 1 Retrosynthetic disconnection of compounds **4** and **5**

A short retrosynthetic analysis of compounds **4** and **5** (Scheme 1) reveals that strategic bond disconnections can be made at the sites indicated by dashed lines leading to three basic building blocks: 1,2,3,4-tetra-*O*-acetyl-β-D-glucose (**6**) is conveniently synthesized on a multigram scale according to a known procedure[8] and can be used to elaborate both ansaglycosides **4** and **5**. The monobenzylated and unprotected butane-1,4-diols **8a**,**b** are commercially available. The two step synthesis of carboxylic acid **7** is described in Scheme 2: etherification of 4-hydroxybenzaldehyde (**11**) with benzyl bromoacetate (**12**) under standard conditions leads to the alkylated aldehyde **13** which is subsequently oxidized by a modified Lindgren protocol[9] to yield building block **7** in excellent overall yield.

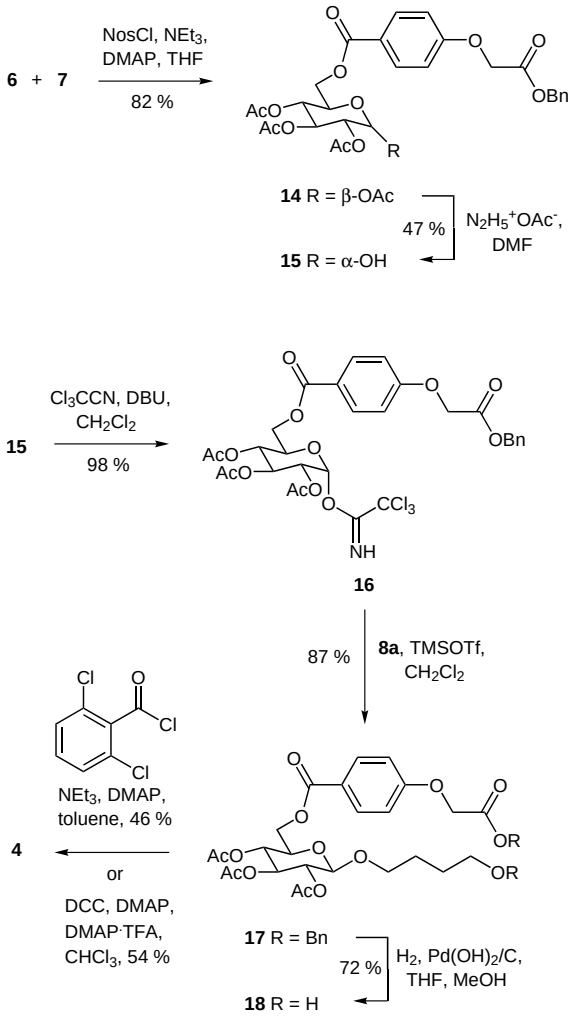


Scheme 2 Synthesis of building block **7**

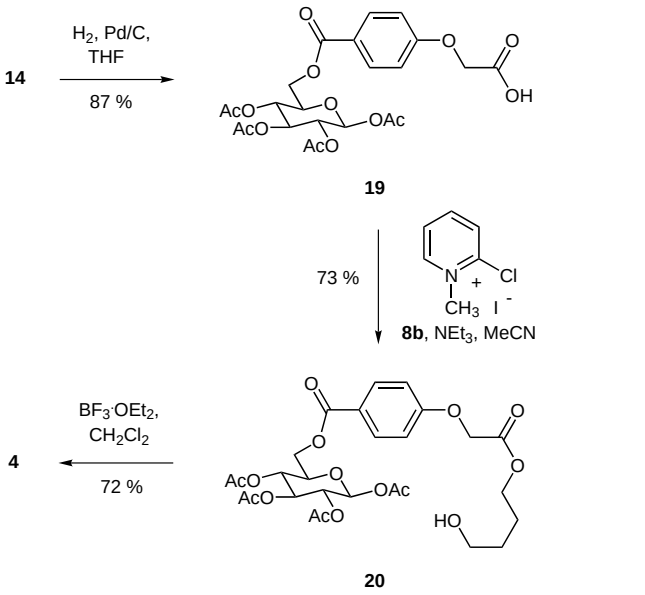
Considerable efforts were made to close the macrocyclic ring of ansaglycoside **4** at the lactone bridge on the primary hydroxyl group of the sugar. However, all macrolactonization protocols tested proved to be fruitless. We therefore proceeded to the second lactone moiety in compound **4** as a potential functionality for ring closing reactions. The synthesis of the corresponding cyclization precursor **18** is illustrated in Scheme 3.

We were surprised to be faced with severe difficulties to cleanly connect acid **7** to the hydroxyl group of carbohydrate building block **6**. This result might be attributed to a relatively facile acyl shift of the acetyl protecting group at O4 of the glucose derivative **6** to the primary hydroxyl group at C6 under the slightly basic reaction conditions for the esterification. This competitive process then led to a mixture of products as evidenced by TLC and the crude NMR spectra of these sluggish esterification reactions. After considerable experimentation a reliable method for attachment of the side chain **7** to glycoside **6** could be found: the in situ formation of the mixed anhydride of carboxylic acid **7** with 4-nitrobenzenesulfonic acid followed by addition of glucose derivative **6** gave the fully acylated glycoside **14** in 82% yield. In order for the glycosylation of alcohol **8a** to proceed, the anomeric acetate had to be transformed into the more reactive trichloroacetimidate. In the event regioselective deacylation of the anomeric ester group using hydrazinium acetate[10] gave lactol **15** in acceptable yields. Subsequent reaction with excess trichloroacetonitrile and catalytic amounts of DBU converted **15** to the anomeric trichloroacetimidate **16**. Glycosyl donor **16** was activated with trimethylsilyl trifluoromethanesulfonate in the presence of glycosyl acceptor **8a** leading to the protected cyclization precursor **17**. The coupling constant (7.1 Hz) for the anomeric proton in this compound indicates that the glycosylation reaction proceeded diastereoselectively to produce the β-glycoside as anticipated for acyl protecting groups on the adjacent O2 of the glucose moiety. Simultaneous deprotection of the benzyl ester and ether was accomplished by hydrogenolysis over Pearlman's catalyst.[11] Hydroxy acid **18** could be successfully lactonized by applying either the Yamaguchi[12] or the modified DCC[13] macrolactonization protocols, the latter giving slightly improved yields of ansaglycoside **4**. On the other hand we were unable to accomplish a ring closing reaction applying the Mukaiyama[14] or Mitsunobu[15] conditions for lactonization. The successful cyclization is evident from the ^{1}H NMR spectrum of product **4** which differs considerably from that of its precursor **18**. Whereas the latter does not show geminal couplings between the diastereotopic methylene protons the former does. This can be traced back to the rigid nature of the macrocycle resulting in a conformationally restricted behavior of compound **4** which is further supported by the occurrence of sharp signals in the NMR spectrum.

A considerably shorter and higher yielding pathway to ansaglycoside **4** could be achieved by the intramolecular glycosylation protocol shown in Scheme 4. Benzyl ester



Scheme 3 Synthesis of ansaglycoside **4** by macrolactonization

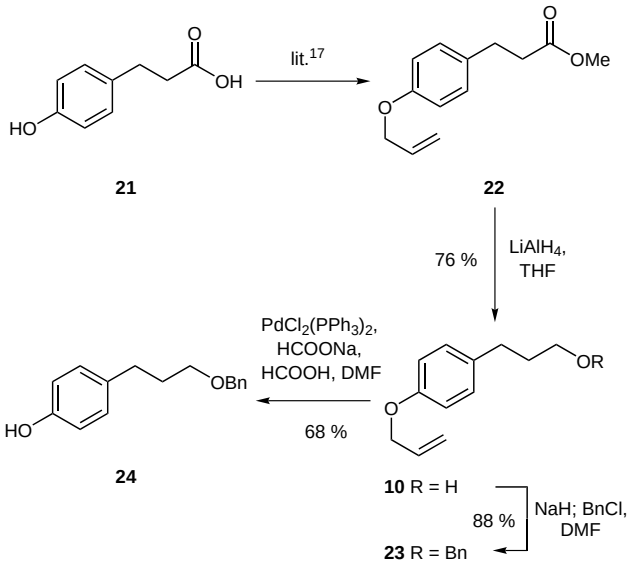


Scheme 4 Synthesis of ansaglycoside **4** by ring closing glycosylation

14 was deprotected under hydrogenolytic conditions to yield acid **19**. Esterification of that acid with excess butane-1,4-diol under Mukaiyama conditions[16] circumvented the need for hydroxyl protecting groups on the diol giving rise to compound **20**, which represents the desired cyclization precursor. In the ensuing glycosylation reaction it was interesting to find that under typical reaction conditions for glycosylation of phenols with glycosyl acetates (stoichiometric amounts of borontrifluoride etherate)[17] this intramolecular glycosylation of an aliphatic alcohol took place smoothly to deliver ansaglycoside **4** in a respectable yield of 73%. It is worth noting that an analogous intermolecular process is not viable and gives back recovered starting material only. The last scenario represents the most efficient entry to macrocycle **4** pointing towards a similarly successful strategy for the assembly of ansaglycoside **5**.

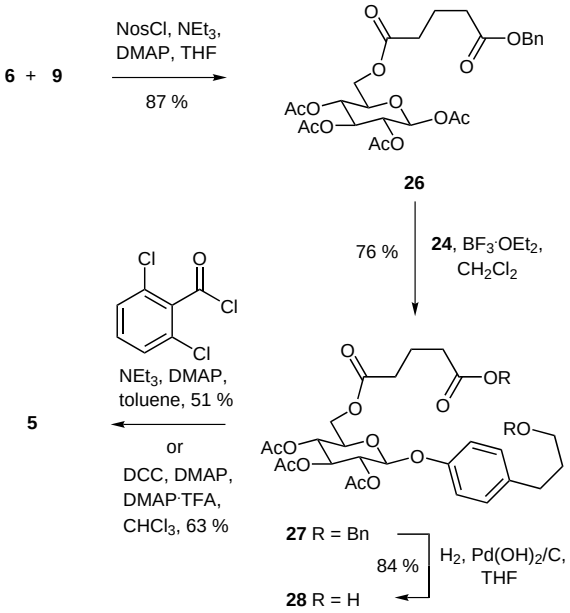
The synthetic route to that compound mimics the synthesis developed for compound **4** and is closely aligned to the retrosynthetic scheme for macrolactone **5** (Scheme 1).

In analogy to the related ansaglycoside **4** initial efforts were made to close the nineteen-membered ring via a macrolactonization protocol at the lactone moiety within the aglycon tether. One building block of the aglycon, alcohol **10**, could be synthesized in one step from the known allyl protected ester **22**[18] by $LiAlH_4$ reduction in 76% yield (Scheme 5).

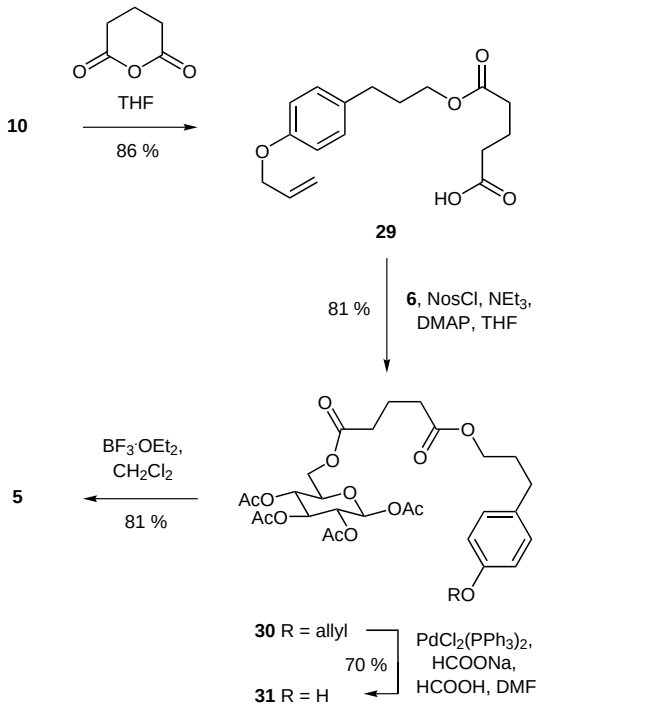


Scheme 5 Synthesis of phenol **24**

Ester **22** itself was accessible in two steps from commercially available 4-hydroxydihydrocinnamic acid (**21**). Benzyl protection of **10** and subsequent reductive cleavage of the phenolic allyl ether yielded phenol **24** in good overall yield. Glutaric acid monobenzyl ester (**9**) was made by a slightly modified literature preparation[19] simply by heating glutaric anhydride (**25**) with an equal amount of benzyl alcohol.



Scheme 6 Synthesis of ansaglycoside **5** by macrolactonization



Scheme 7 Synthesis of ansaglycoside **5** by ring closing glycosylation

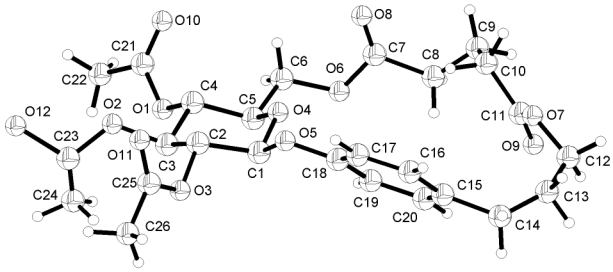


Figure 3 Crystal structure of ansaglycoside **5** (ORTEP)

Esterification of glucose building block **6** with acid **9** at the remaining unprotected primary hydroxyl group gave rise to compound **26**, which reacted with phenol **24** under standard glycosylation conditions[17] to give the fully protected cyclization precursor **27** (Scheme 6). Again, the coupling constant (7.5 Hz) for the anomeric proton at δ = 5.03 is indicative of a β-glycoside. Exhaustive debenzylation of this intermediate was achieved by applying Pearlman's catalyst.[11] Seco acid **28** thus obtained cyclized under Yamaguchi conditions[12] to give ansaglycoside **5** in 51% yield. As for macrocycle **4**, a slightly better yield could be obtained by carrying out the macrolactonization under the influence of DCC, DMAP and the trifluoroacetic acid salt thereof.[13] The crystal structure of this compound is shown in Figure 3. It should be noted that as in the case of **4** other macrolactonization methods could not be successfully applied to the synthesis of target structure **5**.

Since the intramolecular glycosylation of an ω-hydroxyglycosyl acetate proved so rewarding in the synthesis of macrolactone **4**, an analogous pathway was envisaged to access **5** as well. In the event, heating primary alcohol **10** with glutaric anhydride **25** gave monoester **29** in good yields (Scheme 7).

Connecting this intermediate to glucose building block **6** via the mixed anhydride with 4-nitrobenzenesulfonic acid produced compound **30**, which after reductive deprotection of the allyl ether cyclized smoothly to the ansaglycoside **5** under the influence of borontrifluoride etherate. The exceptionally high yield in the ring closing reaction enhanced the trend established during our synthetic efforts towards ansaglycoside **4** that the macrolactone is best closed by an intramolecular glycosylation strategy. Finally, it should be pointed out that as in the case of the related structure **4** all attempts to close the macrocycle at the lactone bridge incorporating the primary hydroxyl group of the sugar backbone did not lead to any cyclized product.

In conclusion we have shown for the first time that 1,6-ansaglycosidic structures found in the constitutionally complex and pharmacologically intriguing natural products **1**, **2** and **3** can be accessed synthetically.[20] During our studies it became unequivocally clear that the best method to close the macrocyclic ansa ring is a newly developed intramolecular glycosylation strategy. These preliminary studies on the synthesis of 1,6-ansaglycosides should pave the way for the elaboration of structurally more complex members of this interesting class of compounds.

NMR spectra were obtained with a Bruker AM 400. Chemical shifts (δ) are given in ppm relative to TMS. Mass spectra were recorded on a Finnigan MAT 90 (CI 120 eV, methane; EI 70 eV). Mps were measured on a Büchi mp apparatus (Dr. Tottoli). FTIR spectra were recorded on a Bio-Rad Excalibur FTS 3000 or on a Beckmann Acculab 8 (data not given in the text). Analytical TLC: Merck aluminum roll 0.2 mm (silica gel 60 HF_{254}); column chromatography: J.

T. Baker silica gel 60, 63–200 m; flash chromatography: Macherey–Nagel silica gel 60, 40–63 m. For catalytic hydrogenations the Parr hydrogenation apparatus was used. Solvents were dried and purified by conventional methods prior to use. Petroleum ether refers to the fraction with bp 40–60 ºC. All air or moisture sensitive reactions were carried out by inert gas techniques under nitrogen or argon.

Benzyl (4-Formylphenoxy)acetate (13)

To a suspension of sodium hydride (60% in mineral oil) (4.00 g, 100 mmol) in anhyd DMF (150 mL) was added portionwise 4-hydroxybenzaldehyde (12.2 g, 100 mmol) resulting in vigorous foaming of the reaction mixture. After complete addition the thick grayish white suspension was stirred for 30 min at r.t. Benzyl bromoacetate (23.0 g, 101 mmol) was added in one portion. The exothermic reaction caused the thick suspension to liquefy. After 30 min the reaction mixture was heated at 100 °C in an oil bath for 2 h. The suspension was subsequently stirred for 18 h at r.t. The mixture was poured onto a biphasic system consisting of H_2O (400 mL) and Et_2O (200 mL) and was stirred vigorously for 15 min. The aq phase was separated, extracted with Et_2O (2 × 150 mL) and the combined organic phases were washed with H_2O (3 × 200 mL), dried ($MgSO_4$) and evaporated. The crude product obtained as on orange oil (24.9 g, 92%) was pure enough to be used in the next step without further purification. An analytical sample was purified by filtration through a pad of silica gel using Et_2O as eluent.

^{1}H NMR ($CDCl_3$): δ = 9.86 (s, 1 H, CHO), 7.80 (d, 2 H, *J* = 8.8 Hz, ArH), 7.34–7.33 (m, 5 H, benzyl H), 6.97 (d, 2 H, *J* = 8.8 Hz, ArH), 5.23 (s, 2 H, $PhCH_2$), 4.73 (s, 2 H, $ArOCH_2CO_2Bn$).

^{13}C NMR ($CDCl_3$): δ = 190.6, 167.9, 162.6, 134.5, 131.9, 130.8, 128.6, 128.5, 114.9, 67.2, 65.2.

MS (CI): *m*/*z* (%) = 271 (100, M^+).

Benzyl (4-Carboxyphenoxy)acetate (7)

To a solution of benzyl (4-formylphenoxy)acetate (**13**) (27.0 g, 100 mmol) in MeCN (100 mL) was added successively aq hydrogen peroxide (30%; 11.8 mL, 104 mmol) and a solution of KH_2PO_4 (3.60 g, 23.2 mmol) in H_2O (40 mL) resulting in the formation of a biphasic mixture. A solution of sodium chlorite (tech. grade, 80% of $NaClO_2$) (15.8 g, 140 mmol) in H_2O (140 mL) was added dropwise within 2 h under cooling with an ice bath. After addition was complete, the ice bath was removed and the reaction mixture stirred for 18 h at r.t. During that time a one-phase reaction mixture had formed from which the desired product had crystallized. Two tips of a spatula (ca. 0.2 g) of solid sodium bisulfite were added and the product was collected by suction filtration. The crude product was washed with H_2O (3 ×) and dried in vacuo over P_4O_{10}.

Yield: 26.1 g (91%); colorless crystals; mp 126 °C (lit.[21] 132–134 °C).

^{1}H NMR ($CDCl_3$): δ = 8.05 (d, 2 H, *J* = 9.8 Hz, ArH), 7.35–7.34 (m, 5 H, benzyl H), 6.39 (d, 2 H, *J* = 9.8 Hz, ArH), 5.24 (s, 2 H, $PhCH_2$), 4.73 (s, 2 H, $ArOCH_2CO_2Bn$).

^{13}C NMR ($CDCl_3$): δ = 171.2, 168.1, 162.0, 135.0, 132.4, 128.7, 128.5, 122.8, 114.4, 67.2, 65.2.

MS (CI): *m*/*z* (%) = 286 (91, M^+).

Peracylated Glucose Derivative 14

To a solution of 4-nitrobenzenesulfonyl chloride (4.43 g, 20.0 mmol) and anhyd Et_3N (2.02 g, 20.0 mmol, 2.79 mL) in anhyd THF (100 mL) was added portionwise benzyl (4-carboxyphenoxy)acetate (5.81 g, 20.0 mmol) under cooling in an ice bath. Within a few minutes a precipitate of triethylamine hydrochloride appeared. The suspension was stirred for 2 h at r.t. A second portion of anhyd Et_3N (2.02 g, 20.0 mmol, 2.79 mL) was added followed by 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (6.97 g, 20.0 mmol) and DMAP (611 mg, 5.00 mmol). The heterogeneous mixture was stirred for 18 h at r.t. H_2O (100 mL) and Et_2O (100 mL) were added. The phases were separated and the aq phase was extracted with additional Et_2O (2 × 100 mL). The combined organic phases were washed with H_2O (100 mL) and aq NaOH (1 M; 2 × 50 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (SiO_2, Et_2O) to yield the pure product.

Yield: 10.0 g (82%); yellowish oil.

^{1}H NMR ($CDCl_3$): δ = 7.99 (d, 2 H, *J* = 8.8 Hz, ArH), 7.38–7.32 (m, 5 H, benzyl H), 6.92 (d, 2 H, *J* = 8.8 Hz, ArH), 5.76 (d, 1 H, *J* = 8.4 Hz, anomeric CH), 5.32–5.14 (m, 3 H, glucose H2, H3, H4), 5.22 (s, 2 H, $PhCH_2$), 4.72 (s, 2 H, $ArOCH_2CO_2Bn$), 4.47 (dd, 1 H, J_1 = 12.4, J_2 = 2.2 Hz, glucose H6), 4.36 (dd, 1 H, J_1 = 12.4, J_2 = 4.4 Hz, glucose H6), 3.99–3.95 (m, 1 H, glucose H5), 2.10 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 169.2, 169.2, 168.8, 168.1, 165.5, 161.7, 135.0, 131.9, 128.6, 128.6, 128.5, 124.4, 123.1, 114.4, 91.8, 72.9, 72.8, 70.4, 68.2, 67.2, 65.2, 62.0, 20.7, 20.5.

MS (CI): *m*/*z* (%) = 616 (3, M^+).

Anal. Calcd for $C_{30}H_{32}O_{14}$ (616.57): C, 58.44; H, 5.23. Found C, 58.51; H, 5.19.

Deacetylation of Glucose Derivative 14

To a solution of peracylated glucose derivative **14** (9.25 g, 15.0 mmol) in anhyd DMF (30 mL) was added hydrazinium acetate (1.52 g, 16.5 mmol). The reaction mixture was stirred for 90 min at 50 °C in an oil bath. After cooling to r.t., the homogeneous solution was poured onto H_2O (150 mL). Extraction with Et_2O (3 × 100 mL) and washing the combined organic phases with aq HCl (2 M; 2 × 100 mL) and aq NaOH (1 M; 100 mL) yielded after drying ($MgSO_4$) and evaporation of solvent the crude product which was purified by column chromatography (SiO_2, Et_2O) to give the product.

Yield: 4.04 g (47%); slightly orange oil.

^{1}H NMR ($CDCl_3$): δ = 7.99 (d, 2 H, *J* = 7.1 Hz, ArH), 7.38–7.32 (m, 5 H, benzyl H), 6.91 (d, 2 H, *J* = 7.1 Hz, ArH), 5.58 (t, 1 H, *J* = 9.8 Hz, glucose H), 5.46 (d, 1 H, *J* = 3.6 Hz, anomeric CH), 5.27–5.16 (m, 1 H, glucose H), 5.24 (s, 2 H, $PhCH_2$), 4.91 (dd, 1 H, J_1 = 10.4, J_2 = 3.6 Hz, glucose H), 4.71 (s, 2 H, $ArOCH_2CO_2Bn$), 4.48 (dd, 1 H, J_1 = 12.2, J_2 = 2.6 Hz, glucose H6), 4.40–4.34 (m, 1 H, glucose H5), 4.30 (dd, 1 H, J_1 = 12.2, J_2 = 4.0 Hz, glucose H6), 2.03 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 170.2, 169.6, 168.1, 165.8, 161.6, 135.0, 131.9, 128.6, 128.6, 128.5, 127.0, 123.2, 114.4, 90.1, 71.2, 70.1, 68.9, 67.2, 65.8, 62.4, 20.6, 20.6.

MS (CI): *m*/*z* (%) = 558 (11, $M^+ - H_2O$).

Trichloroacetimidate 16

To a solution of deacetylated glucose derivative **15** (2.87 g, 5.00 mmol) in anhyd CH_2Cl_2 (50 mL) was added trichloroacetonitrile (2.51 mL, 25.0 mmol) followed by a few drops of anhyd DBU. The solution was stirred for 18 h at r.t. The solvent and excess trichloroacetonitrile were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, Et_2O) to yield the pure product.

Yield: 3.52 g, (98%); brownish oil.

^{1}H NMR ($CDCl_3$): δ = 8.69 (s, 1 H, NH), 7.98 (d, 2 H, *J* = 7.0 Hz, ArH), 7.38–7.35 (m, 5 H, benzyl H), 6.91 (d, 2 H, *J* = 7.0 Hz, ArH), 6.58 (d, 1 H; *J* = 3.7 Hz, anomeric CH), 5.58 (t, 1 H, *J* = 9.8 Hz, glucose H), 5.29–5.22 (m, 1 H, glucose H), 5.23 (s, 2 H, $PhCH_2$), 5.16 (dd, 1 H, J_1 = 10.2, J_2 = 3.8 Hz, glucose H), 4.71 (s, 2 H, $ArOCH_2CO_2Bn$), 4.49–4.46 (m, 1 H, glucose H6), 4.39–4.33 (m, 2 H, glucose H5, H6), 2.05 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 169.9, 169.4, 168.0, 165.4, 161.6, 160.8, 135.0, 131.9, 128.6, 128.6, 128.5, 128.2, 123.1, 114.3, 92.9, 70.2, 70.6, 69.8, 68.2, 67.2, 65.8, 61.9, 20.6, 20.5, 20.4.

Glycosylation of Monobenzylated Butane-1,4-diol (8a) with Trichloroacetimidate 16

A solution of trichloroacetimidate **16** (3.52 g, 4.90 mmol) and 4-benzyloxy-1-butanol (**8a**) (973 mg, 5.40 mmol) in anhyd CH_2Cl_2 (20 mL) was cooled in a salt H_2O bath to approximately –20 °C. Within 15 min a solution of trimethylsilyl trifluoromethanesulfonate (0.1 M; 500 l, 0.50 mmol) in CH_2Cl_2 was added. After stirring for 1 h at –20 °C the reaction was quenched by the addition of a few drops of Et_3N. CH_2Cl_2 (100 mL) was added and the solution was washed with sat. aq K_2CO_3 (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give a crude product, which was purified by flash column chromatography (SiO_2, Et_2O–petroleum ether, 1:1) to give the pure product.

Yield: 3.24 g (87%); slightly yellow oil.

^{1}H NMR ($CDCl_3$): δ = 7.97 (d, 2 H, *J* = 8.1 Hz, ArH), 7.40–7.27 (m, 10 H, benzyl H), 6.93 (d, 2 H, *J* = 8.1 Hz, ArH), 5.47 (dd, 1 H, $J_1 = J_2$ = 8.4 Hz, glucose H), 5.22 (s, 2 H, $PhCH_2$), 5.10 (m 1 H, glucose H), 4.85 (dd, 1 H, J_1 = 8.4, J_2 = 5.9 Hz, glucose H), 4.76 (2 H, $ArOCH_2CO_2Bn$), 4.51–4.47 (m, 1 H, glucose H6), 4.48 (d, 1 H, *J* = 7.1 Hz, anomeric CH), 4.45 (s, 2 H, $PhCH_2$), 4.40–4.34 (m, 2 H, glucose H5, H6), 3.38 (t, 2 H, *J* = 6.5 Hz, OCH_2R), 3.15 (t, 2 H, *J* = 6.4 Hz, OCH_2R), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.14–0.98 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 170.0, 169.5, 169.2, 168.5, 165.8, 161.9, 134.2, 134.1, 132.0, 128.3, 128.3, 127.7, 127.6, 127.5, 127.4, 123.4, 114.9, 99.2, 72.9, 72.8, 72.4, 70.8, 69.3, 69.2, 69.0, 67.2, 65.9, 65.7, 26.4, 25.3, 20.7, 20.5, 20.4.

MS (CI): *m*/*z* (%) = 737 (7, M^+).

Anal. Calcd for $C_{39}H_{44}O_{14}$ (736.76): C, 63.58; H, 6.02. Found C, 63.62; H, 6.05.

Debenzylation of Glycoside 17

A solution of glycoside **17** (3.00 g, 4.07 mmol) and Pearlman's catalyst (0.60 g) in THF–MeOH (1:1; 200 mL) was hydrogenated in a Parr hydrogenation apparatus under a pressure of 35 psi for 18 h. The catalyst was filtered off and the resulting solution was concentrated. The crude product was purified by passing through a short plug of silica gel eluting with Et_2O to give the pure compound.

Yield: 1.63 g (72%); colorless oil.

^{1}H NMR ($CDCl_3$): δ = 8.06 (d, 2 H, *J* = 7.9 Hz, ArH), 7.02 (d, 2 H, *J* = 7.9 Hz, ArH), 5.52 (dd, 1 H, $J_1 = J_2$ = 8.6 Hz, glucose H), 5.19 (m 1 H, glucose H), 4.80 (dd, 1 H, J_1 = 8.2, J_2 = 5.3 Hz, glucose H), 4.73 (2 H, $ArOCH_2CO_2H$), 4.49–4.43 (m, 2 H, glucose H6 + anomeric CH), 4.39–4.31 (m, 2 H, glucose H5, H6), 3.35 (t, 2 H, *J* = 6.7 Hz, OCH_2R), 3.20 (t, 2 H, *J* = 6.3 Hz, OCH_2R), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.19–1.01 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 169.4, 169.3, 169.2, 168.9, 165.7, 162.0, 132.3, 124.1, 114.7, 99.5, 71.9, 71.0, 69.4, 69.3, 69.1, 68.6, 66.8, 65.7, 27.5, 25.9, 21.0, 20.8, 20.4.

MS (CI): *m*/*z* (%) = 558 (2, M^+ + 1).

Cyclization of Hydroxy Acid 18 According to the Yamaguchi Protocol

To a solution of hydroxy acid **18** (278 mg, 0.50 mmol) in anhyd THF (5 mL) was added anhyd Et_3N (56 mg, 0.55 mmol, 77 µl) followed by 2,6-dichlorobenzoyl chloride (105 mg, 0.50 mmol). After 2 h at r.t., the suspension was diluted with anhyd toluene (100 mL). DMAP (37 mg, 3.00 mmol) was added and the milky white suspension was stirred for 18 h at r.t. The solvent was evaporated and the residue purified by flash chromatography (SiO_2, Et_2O–petroleum ether, 1:1) to give the product.

Yield: 124 mg (46%); colorless oil.

^{1}H NMR ($CDCl_3$): δ = 8.07 (d, 2 H, *J* = 8.8 Hz, ArH), 6.96 (d, 2 H, *J* = 8.8 Hz, ArH), 5.45 (t, 1 H, *J* = 8.8 Hz, glucose H4), 5.11 (dd, 1 H, J_1 = 8.8, J_2 = 5.8 Hz, glucose H3), 4.86 (dd, 1 H, J_1 = 11.1, J_2 = 6.2 Hz, glucose H2), 4.82 (d, 2 H, *J* = 8.4 Hz, $ArOCH_2CO_2R$), 4.80 (dd, 1 H, J_1 = 11.7, J_2 = 3.1 Hz, glucose H6), 4.48 (d, 1 H, *J* = 5.3 Hz, anomeric CH), 4.21 (dd, 1 H, J_1 = 11.7, J_2 = 5.3 Hz, glucose H6), 4.10–4.03 (m, 2 H), 3.99–3.95 (m, 1 H, glucose H5), 3.19–3.13 (m, 1 H), 3.07–3.02 (m, 1 H), 2.08 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 1.17–0.95 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 170.0, 169.4, 169.2, 168.6, 165.9, 161.9, 132.0, 123.5, 114.9, 99.3, 73.6, 72.7, 70.8, 69.2, 69.0, 65.9, 64.9, 61.6, 26.3, 25.4, 20.7.

MS (CI): *m*/*z* (%) = 539 (22, M^+).

Anal. Calcd for $C_{25}H_{30}O_{13}$ (538.50): C, 55.76; H, 5.62. Found C, 55.69; H, 5.58.

Cyclization of Hydroxy Acid 18 According to the Modified DCC Protocol

To a refluxing solution of DCC (206 mg, 1.00 mmol), DMAP (183 mg, 1.50 mmol) and DMAP trifluoroacetate (236 mg, 1.00 mmol) in anhyd, EtOH-free $CHCl_3$ (50 mL) was added a solution of hydroxy acid **18** (278 mg, 0.50 mmol) in anhyd, EtOH-free $CHCl_3$ (50 mL) within 4 h. After complete addition, the resulting solution was refluxed for 16 h. After cooling to r.t., MeOH (2 mL) and HOAc (0.1 mL) were added and stirring was continued for 30 min at r.t. The precipitated *N*,*N*′-dicyclohexyl urea was filtered off and washed with portions of anhyd $CHCl_3$ (2 × 25 mL) . The filtrate was concentrated and the crude product obtained was purified by flash chromatography (silica gel; Et_2O–petroleum ether, 1:1) to give the product.

Yield: 145 mg (54%); colorless oil.

The spectral data obtained for the product matched those of the product from the previous experiment.

Hydrogenolysis of Benzyl Ester 15

Benzyl ester **15** (1.85 g, 3.00 mmol) was dissolved in THF (200 mL), 5% palladium on charcoal (0.40 g) was added and the resultant mixture was hydrogenated at 35 psi for 4 h. The catalyst was filtered off, the solvent evaporated and the residue purified by filtration through a short plug of silica gel eluting with Et_2O to give the product.

Yield: 1.38 g (87%); slightly yellow oil.

^{1}H NMR ($CDCl_3$): δ = 8.01 (d, 2 H, *J* = 8.8 Hz, ArH), 7.54 (br s, 1 H, OH), 6.95 (d, 2 H, *J* = 8.8 Hz, ArH), 5.76 (d, 1 H, *J* = 8.0 Hz, anomeric CH), 5.29 (t, 1 H, *J* = 9.3 Hz, glucose H), 5.22 (t, 1 H, *J* = 9.3 Hz, glucose H), 5.15 (t, 1 H, *J* = 8.4 Hz, glucose H), 4.72 (s, 2 H, $ArOCH_2CO_2H$), 4.48 (dd, 1 H, J_1 = 12.4, J_2 = 2.2 Hz, glucose H6), 4.35 (dd, 1 H, J_1 = 12.4, J_2 = 4.4 Hz, glucose H6), 3.99–3.95 (m, 1 H, glucose H5), 2.09 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 171.8, 170.2, 169.5, 169.4, 169.0, 165.6, 161.5, 132.0, 114.4, 112.0, 91.8, 73.0, 72.8, 70.5, 68.3, 64.7, 62.1, 24.9, 20.5.

MS (CI): *m*/*z* (%) = 467 (23, M^+ – HOAc).

Esterification of Carboxylic Acid 19 with Butane-1,4-diol (8b)

A solution of acid **19** (1.32 g, 2.50 mmol), butane-1,4-diol (1.13 g, 12.5 mmol), 2-chloro-1-methylpyridinium iodide (960 mg, 3.76 mmol) and anhyd Et_3N (760 mg, 7.52 mmol, 1.05 mL) in anhyd MeCN (50 mL) was refluxed for 3 h. The solvent was evaporated

and the solid residue partitioned between H_2O (50 mL) and EtOAc (150 mL). The phases were separated and the organic phase was washed with sat. aq $NaHCO_3$ (50 mL) and H_2O (2 × 50 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc).

Yield: 1.09 g (73%); orange oil.

^{1}H NMR ($CDCl_3$): δ = 8.01 (d, 2 H, *J* = 8.8 Hz, ArH), 6.94 (d, 2 H, *J* = 8.8 Hz, ArH), 5.76 (d, 1 H, *J* = 8.4 Hz, anomeric CH), 5.30 (t, 1 H, *J* = 9.3 Hz, glucose H), 5.23 (t, 1 H, *J* = 9.3 Hz, glucose H), 5.15 (t, 1 H, *J* = 9.3 Hz, glucose H), 4.70 (s, 2 H, $ArOCH_2CO_2R$), 4.47 (dd, 1 H, J_1 = 12.4, J_2 = 2.2 Hz, glucose H6), 4.35 (dd, 1 H, J_1 = 12.4, J_2 = 4.4 Hz, glucose H6), 4.25 (t, 2 H, *J* = 6.6 Hz), 4.00–3.96 (m, 1 H, glucose H5), 3.63 (t, 2 H), 2.28 (s, 1 H, OH), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 1.79–1.70 (m, 2 H), 1.62–1.54 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 170.0, 169.3, 169.2, 168.3, 165.5, 161.8, 131.9, 123.1, 114.4, 91.8, 72.9, 72.9, 70.5, 68.3, 65.4, 65.3, 62.1, 62.0, 28.9, 25.1, 20.9, 20.7, 20.5.

MS (CI): *m*/*z* (%) = 598 (5, M^+).

Intramolecular Glycosylation of ω-Hydroxyglycosyl Acetate 20

ω-Hydroxyglycosyl acetate **20** (300 mg, 0.50 mmol) was dissolved in anhyd CH_2Cl_2 (100 mL). $BF_3{\cdot}Et_2O$ complex (78 mg, 0.55 mmol, 69 μl) was added. The solution turned brightly yellow. After 48 h at r.t., DMAP (122 mg, 1.00 mmol) was added to quench the Lewis acid. The colorless solution was concentrated and purified by flash chromatography (SiO_2, Et_2O–petroleum ether, 1:1) to give the product.

Yield: 194 mg (72%); colorless oil.

The spectral data were in agreement with those for the same compound synthesized by the macrolactonization route.

3-(4-Allyloxyphenyl)-1-propanol (10)

To a suspension of $LiAlH_4$ (1.14 g, 30.0 mmol) in anhyd THF (100 mL) was added dropwise at ice bath temperature a solution of ethyl (4-allyloxyphenyl)dihydrocinnamate (**22**) (6.61 g, 30.0 mmol) in anhyd THF (50 mL). The mixture was stirred for 30 min at r.t., MeOH (10 mL) was added dropwise to quench residual hydride, followed by aq HCl (6 M; 100 mL) and Et_2O (100 mL). The phases were separated, the organic phase was washed with H_2O (50 mL) and sat. aq $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated. The oil obtained was pure according to TLC and NMR.

Yield: 4.36 g (76%); slightly yellow oil.

^{1}H NMR ($CDCl_3$): δ = 7.09 (d, 2 H, *J* = 8.4 Hz, ArH), 6.83 (d, 2 H, *J* = 8.4 Hz, ArH), 6.09–5.99 (m, 1 H, allyl H), 5.40 (d, 1 H, *J* = 17.2 Hz, allyl H), 5.27 (d, 1 H, *J* = 10.6 Hz, allyl H), 4.49 (d, 2 H, *J* = 5.3 Hz, allyl H), 3.63 (t, 2 H, *J* = 6.6 Hz), 2.68 (br s, 1 H, OH), 2.62 (t, 2 H, *J* = 7.1 Hz), 1.88–1.80 (m, 2 H)

^{13}C NMR ($CDCl_3$): δ = 156.8, 134.1, 133.5, 129.2, 117.5, 114.7, 68.9, 62.1, 34.3, 31.1.

MS (CI): *m*/*z* (%) = 192 (92, M^+).

Benzyl Protection of Alcohol 10

To a suspension of sodium hydride (60% in mineral oil) (800 mg, 20.0 mmol) in anhyd DMF (50 mL) was added dropwise a solution of alcohol **10** (3.85 g, 20.0 mmol) in anhyd DMF (10 mL). After 30 min at r.t., benzyl chloride (2.53 g, 20.0 mmol, 2.31 mL) was added. The mixture was stirred for 18 h at r.t., then poured onto H_2O (200 mL) and extracted with Et_2O (2 × 100 mL). The combined organic phases were washed with H_2O (3 × 50 mL), dried ($MgSO_4$) and concentrated. The crude product obtained was purified by column chromatography (SiO_2, Et_2O–petroleum ether, 1:2) yielding the pure product.

Yield: 4.95 g (88%); slightly yellow oil.

^{1}H NMR ($CDCl_3$): δ = 7.35–7.25 (m, 5 H, benzyl H), 7.05 (d, 2 H, *J* = 8.4 Hz, ArH), 6.81 (d, 2 H, *J* = 8.4 Hz, ArH), 6.06–5.97 (m, 1 H, allyl H), 5.38 (d, 1 H, *J* = 17.2 Hz, allyl H), 5.23 (d, 1 H, *J* = 10.6 Hz, allyl H), 4.47 (d, 2 H, *J* = 5.3 Hz, allyl H), 4.47 (s, 2 H, $PhCH_2$), 3.45 (t, 2 H, *J* = 6.2 Hz), 2.64 (t, 2 H, *J* = 7.5 Hz), 1.92–1.85 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 156.7, 138.6, 134.1, 133.5, 129.3, 128.3, 127.6, 127.4, 117.3, 114.6, 72.8, 69.4, 68.8, 31.5, 31.4.

MS (CI): *m*/*z* (%) = 282 (27, M^+).

Deallylation of 23

To a solution of allyl ether **23** (4.52 g, 16.0 mmol) in anhyd DMF (50 mL) was added sodium formate (2.72 g, 40.0 mmol), formic acid (1.53 mL, 40.0 mmol) and bis(triphenylphosphine)palladium dichloride (112 mg, 0.16 mmol). The mixture was stirred at 80 °C in an oil bath for 2 h. After cooling to r.t., H_2O (200 mL) was added and the mixture extracted with Et_2O (2 × 100 mL). The combined organic phases were successively washed with H_2O (100 mL), aq HCl (2 M; 2 × 100 mL) and sat. aq $NaHCO_3$ (100 mL). The product was extracted from the organic phase by washing with aq NaOH (1 M; 2 × 20 mL). The basic aq phase was back extracted with Et_2O (40 mL) and acidified under cooling with aq HCl (2 M). Extraction with Et_2O (2 × 50 mL) yielded after drying ($MgSO_4$) and evaporation of the solvent the crude product which was purified by column chromatography (SiO_2, Et_2O).

Yield: 2.64 g (68%); slightly yellow oil.

^{1}H NMR ($CDCl_3$): δ = 7.35–7.24 (m, 5 H, benzyl H), 6.93 (d, 2 H, *J* = 8.4 Hz, ArH), 6.67 (d, 2 H, *J* = 8.4 Hz, ArH), 4.50 (s, 2 H, $PhCH_2$), 3.47 (t, 2 H, *J* = 6.6 Hz), 2.59 (t, 2 H, *J* = 8.0 Hz), 1.88 (quint, 2 H, *J* = 7.1 Hz).

^{13}C NMR ($CDCl_3$): δ = 153.9, 138.1, 133.5, 129.4, 128.4, 127.8, 127.6, 115.2, 72.9, 69.5, 31.4, 31.3.

MS (CI): *m*/*z* (%) = 242 (20, M^+).

Anal. Calcd for $C_{16}H_{18}O_2$ (242.32): C, 79.31; H, 7.49. Found C, 79.34; H, 7.46.

Peracylated Glucose Derivative 26

To a solution of 4-nitrobenzenesulfonyl chloride (2.22 g, 10.0 mmol) and anhyd Et_3N (1.01 g, 10.0 mmol, 1.40 mL) in anhyd THF (50 mL) was added dropwise a solution of monobenzyl glutarate (2.22 g, 10.0 mmol) in anhyd THF (10 mL) under cooling in an ice bath. Within a few minutes a precipitate of triethylamine hydrochloride appeared. The suspension was stirred for 2 h at r.t. A second portion of anhyd Et_3N (1.01 g, 10.0 mmol, 1.40 mL) was added followed by 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (3.49 g, 10.0 mmol) and DMAP (250 mg, 2.00 mmol). The heterogeneous mixture was stirred for 18 h at r.t. H_2O (50 mL) and Et_2O (50 mL) were added. The phases were separated and the aq phase was extracted with additional Et_2O (2 × 50 mL). The combined organic phases were washed with H_2O (50 mL) and aq NaOH (1 M; 2 × 25 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by filtration through a plug of silica gel using Et_2O as eluent to yield the pure product.

Yield: 4.81 g (87%); yellowish oil.

^{1}H NMR ($CDCl_3$): δ = 7.32–7.30 (m, 5 H, benzyl H), 5.72 (d, 1 H, *J* = 8.0 Hz, anomeric CH), 5.25 (t, 1 H, *J* = 9.7 Hz, glucose H), 5.14–5.08 (m, 2 H, glucose H), 5.12 (s, 2 H, $PhCH_2$), 4.28 (dd, 1 H, J_1 = 12.4, J_2 = 4.9 Hz, glucose H6), 4.13 (dd, 1 H, J_1 = 12.4, J_2 = 2.2 Hz, glucose H6), 3.86–3.82 (m, 1 H, glucose H5), 2.42–2.39 (m, 4 H), 2.08 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 2.00–1.94 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 172.6, 172.3, 169.9, 169.2, 169.1, 168.6, 136.1, 128.5, 128.2, 91.7, 72.8, 72.8, 70.4, 66.2, 65.8, 61.5, 33.2, 32.9, 20.7, 20.5, 19.9, 15.2.

MS (CI): *m*/*z* (%) = 495 (8, M^+ – HOAc)

Glycosylation of Phenol 24 with Glycosyl Acetate 26

To a solution of phenol **24** (1.30 g, 5.36 mmol) and glycosyl acetate **26** (2.76 g, 5.00 mmol) in anhyd CH_2Cl_2 (20 mL) was added BF_3·Et_2O complex (760 mg, 5.36 mmol, 0.67 mL). The brightly yellow solution was stirred at r.t. for 18 h. The reaction mixture was diluted with CH_2Cl_2 (80 mL) and washed with aq NaOH (1 M; 2 × 50 mL). The organic phase was dried ($MgSO_4$) and concentrated to give the crude product, which was purified by column chromatography (SiO_2, Et_2O–petroleum ether, 1:1).

Yield: 2.79 g (76%); slightly yellow oil.

^{1}H NMR ($CDCl_3$): δ = 7.27–7.25 (m, 10 H, benzyl H), 7.08 (d, 2 H, *J* = 8.9 Hz, ArH), 6.89 (d, 2 H, *J* = 8.9 Hz, ArH), 5.31–5.21 (m, 2 H, glucose H), 5.16–5.10 (m, 1 H, glucose H), 5.10 (s, 2 H, $PhCH_2$), 5.03 (d, 1 H, *J* = 7.5 Hz, anomeric CH), 4.48 (s, 2 H, $PhCH_2$), 4.27 (dd, 1 H, J_1 = 12.4, J_2 = 5.3 Hz, glucose H6), 4.18 (dd, 1 H, J_1 = 12.4, J_2 = 2.2 Hz, glucose H6), 3.85–3.80 (m, 1 H, glucose H5), 3.46 (t, 2 H, *J* = 6.2 Hz), 2.66 (t, 2 H, *J* = 7.1 Hz), 2.42–2.38 (m, 4 H), 2.07–1.87 (m, 4 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 170.1, 170.1, 169.3, 169.2, 169.1, 155.1, 138.6, 137.0, 136.0, 129.4, 128.5, 128.3, 128.1, 127.6, 127.5, 117.0, 99.4, 72.9, 72.8, 72.0, 71.3, 69.4, 68.4, 66.2, 62.0, 33.2, 32.9, 31.5, 31.4, 20.5, 20.5, 19.9.

MS (CI): *m*/*z* (%) = 734 (2, M^+).

Anal. Calcd for $C_{40}H_{46}O_{13}$ (734.79): C, 65.30; H, 6.31. Found C, 65.38; H, 6.38.

Deprotection of Glycoside 27

A solution of dibenzyl protected glycoside **27** (1.37 g, 1.87 mmol) in MeOH (200 mL) was hydrogenated at 35 psi of hydrogen pressure over Pearlman's catalyst (270 mg) for 20 h at r.t. The catalyst was filtered off and the resulting solution was concentrated. The residue was taken up in Et_2O and filtered through a plug of silica gel eluting with additional Et_2O. Concentration gave the pure product.

Yield: 870 mg (84%); slightly orange oil.

^{1}H NMR ($CDCl_3$): δ = 7.12 (d, 2 H, *J* = 8.4 Hz, ArH), 6.91 (d, 2 H, *J* = 8.4 Hz, ArH), 5.31–5.22 (m, 2 H, glucose H), 5.17–5.09 (m, 1 H, glucose H), 5.05 (d, 1 H, *J* = 7.1 Hz, anomeric CH), 4.29–4.11 (m, 2 H, glucose H6), 3.90–3.82 (m, 1 H, glucose H5), 3.67 (t, 2 H, *J* = 6.2 Hz), 3.48 (s, 1 H, OH), 2.67 (t, 2 H, *J* = 8.0 Hz), 2.46–2.36 (m, 4 H), 2.11–1.84 (m, 4 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 173.0, 172.1, 170.3, 169.6, 169.5, 155.1, 137.0, 129.5, 117.1, 99.4, 72.8, 70.3, 67.9, 65.8, 62.8, 61.6, 33.2, 33.0, 31.3, 30.5, 20.5, 20.5, 19.9.

MS (CI): *m*/*z* (%) = 569 (7, $M^+ + CH_4$)

Cyclization of Hydroxy Acid 28 According to the Yamaguchi Protocol

To a solution of hydroxy acid **18** (277 mg, 0.50 mmol) in anhyd THF (5 mL) was added anhyd Et_3N (56 mg, 0.55 mmol, 77 μl) followed by 2,6-dichlorobenzoyl chloride (105 mg, 0.50 mmol). After 2 h at r.t., the suspension was diluted with anhyd toluene (100 mL). DMAP (37 mg, 3.00 mmol) was added and the milky white suspension was stirred for 18 h at r.t. The solvent was evaporated and the residue purified by flash chromatography (SiO_2, Et_2O–petroleum ether, 1:1) to give the product.

Yield: 137 mg (51%); colorless solid; mp 82 °C.

^{1}H NMR ($CDCl_3$): δ = 7.10 (d, 2 H, *J* = 8.4 Hz, ArH), 6.88 (d, 2 H, *J* = 8.4 Hz, ArH), 5.30 (t, 1 H, *J* = 6.2 Hz, glucose H3), 5.22 (t, 1 H, *J* = 7.1 Hz, glucose H2), 5.16 (d, 1 H, *J* = 7.0 Hz, anomeric CH), 5.05 (t, 1 H, *J* = 9.3 Hz, glucose H4), 4.31 (dd, 1 H, J_1 = 12.0, J_2 = 8.8 Hz, glucose H6), 4.28–4.22 (m, 1 H), 4.05–4.00 (m, 2 H), 3.94–3.89 (m, 1 H, glucose H5), 3.82–2.70 (m, 2 H), 2.30–2.22 (m, 2 H), 2.10–2.04 (m, 2 H), 2.07 (s, 3 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 1.98–1.88 (m, 2 H), 1.78–1.69 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 173.1, 172.2, 170.1, 169.5, 169.2, 154.2, 136.3, 129.5, 116.9, 97.8, 72.9, 72.0, 71.5, 69.3, 65.1, 62.8, 33.8, 33.3, 28.3, 20.6, 20.5, 19.8.

MS (CI): *m*/*z* (%) = 537 (100, M^+).

Anal. Calcd for $C_{26}H_{32}O_{12}$ (536.53): C, 58.21; H, 6.01. Found C, 58.18; H, 5.93.

Cyclization of Hydroxy Acid 28 According to the Modified DCC Protocol

To a refluxing solution of DCC (206 mg, 1.00 mmol), DMAP (183 mg, 1.50 mmol) and DMAP trifluoroacetate (236 mg, 1.00 mmol) in anhyd, EtOH-free $CHCl_3$ (50 mL) was added a solution of hydroxy acid **18** (277 mg, 0.50 mmol) in anhyd, EtOH-free $CHCl_3$ (50 mL) within 4 h. After complete addition the resulting solution was refluxed for 16 h. After cooling to r.t., MeOH (2 mL) and HOAc (0.1 mL) were added and stirring was continued for 30 min at r.t. The precipitated *N*,*N*′-dicyclohexyl urea was filtered off an washed with anhyd $CHCl_3$ (2 ×). The filtrate was concentrated and the crude product obtained was purified by flash chromatography (silica gel; Et_2O–petroleum ether, 1:1) to give the product as colorless solid.

Yield: 169 mg (63%); mp 82 °C.

The spectral data matched those for the product of the foregoing experiment

Glutaric Acid Monoester 29

A solution of 3-(4-allyloxyphenyl)propane-1-ol (**10**) (3.85 g, 20.0 mmol) and glutaric anhydride (2.28 g, 20.0 mmol) in anhyd THF (50 mL) was refluxed for 18 h. The reaction mixture was concentrated and the residue purified by column chromatography (SiO_2, Et_2O) to give the product.

Yield: 5.30 g (86%); slightly yellow oil.

^{1}H NMR ($CDCl_3$): δ = 7.07 (d, 2 H, *J* = 8.0 Hz, ArH), 6.84 (d, 2 H, *J* = 8.0 Hz, ArH), 6.09–5.99 (m, 1 H, allyl H), 5.40 (d, 1 H, *J* = 17.2 Hz, allyl H), 5.27 (d, 1 H, *J* = 10.2 Hz, allyl H), 4.50 (d, 2 H, *J* = 4.9 Hz, allyl H), 4.09 (t, 2 H, *J* = 6.6 Hz), 2.62 (t, 2 H, *J* = 7.5 Hz), 2.45–2.38 (m, 4 H), 1.99–1.84 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 178.7, 172.9, 156.9, 133.5, 133.4, 128.2, 117.4, 114.8, 68.9, 63.9, 33.2, 33.0, 31.2, 30.3, 19.8.

MS (CI): *m*/*z* (%) = 306 (5, M^+).

Peracylated Glucose Derivative 30

To a solution of 4-nitrobenzenesulfonyl chloride (1.11 g, 5.00 mmol) and anhyd Et_3N (0.50 g, 5.00 mmol, 0.70 mL) in anhyd THF (25 mL) was added dropwise a solution of 1.53 g (5.00 mmol) of glutaric monoester **29** in anhyd THF (10 mL) under cooling in an ice bath. Within a few minutes a precipitate of triethylamine hydrochloride appeared. The suspension was stirred for 2 h at r.t. A second portion of anhyd Et_3N (0.50 g, 5.00 mmol, 0.70 mL) was added followed by 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (1.75 g, 5.00 mmol) and DMAP (122 mg, 1.00 mmol). The heterogeneous mixture was stirred for 18 h at r.t. H_2O (50 mL) and Et_2O (50 mL) were added. The phases were separated and the aq phase was extracted with additional Et_2O (2 × 50 mL). The combined organic phases were washed with H_2O (50 mL) and aq NaOH (1 M; 2 × 25 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by

column chromatography (SiO_2, Et_2O–petroleum ether, 2:1) to yield the pure product.

Yield: 2.58 g (81%); yellowish oil.

^{1}H NMR ($CDCl_3$): δ = 7.08 (d, 2 H, *J* = 8.4 Hz, ArH), 6.84 (d, 2 H, *J* = 8.4 Hz, ArH), 6.10–6.00 (m, 1 H, allyl H), 5.71 (d, 1 H, *J* = 8.0 Hz, anomeric CH), 5.40 (d, 1 H, *J* = 17.2 Hz, allyl H), 5.26 (d, 1 H, *J* = 19.4 Hz, allyl H), 5.28–5.23 (m, 1 H, glucose H), 5.15–5.09 (m, 2 H, glucose H), 4.51 (d, 2 H, *J* = 5.3 Hz, allyl H), 4.30 (dd, 1 H, J_1 = 12.4 , J_2 = 4.4 Hz, glucose H6), 4.15–4.07 (m, 1 H, glucose H6), 4.09 (t, 2 H, *J* = 6.6 Hz), 3.86–3.82 (m, 1 H, glucose H5), 2.62 (t, 2 H, *J* = 7.1 Hz), 2.43 (t, 2 H, *J* = 7.1 Hz), 2.37 (t, 2 H, *J* = 7.5 Hz), 2.10 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.97 (s, 3 H), 2.08–1.88 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 173.0, 172.5, 170.0, 169.3, 169.1, 168.8, 157.0, 133.5, 133.4, 129.3, 117.4, 114.8, 91.7, 72.8, 70.3, 68.9, 67.9, 65.8, 63.8, 61.5, 33.2, 33.0, 31.2, 30.4, 20.7, 20.5, 19.9.

MS (CI): *m*/*z* (%) = 636 (16, M^+).

Deallylation of Glycoside 30

To a solution of glycoside **30** (1.91 g, 3.00 mmol) in anhyd DMF (20 mL) were added successively sodium formate (612 mg, 9.00 mmol), formic acid (0.23 mL, 9.00 mmol) as well as bis(triphenylphosphine)palladium dichloride (21 mg, 30 μmol). The heterogeneous mixture was heated at 80 °C in an oil bath for 2 h. After cooling to r.t., the reaction mixture was poured onto H_2O (100 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (50 mL), aq HCl (2 M; 2 × 25 mL) and sat. aq $NaHCO_3$. The combined organic phases were dried ($MgSO_4$) and concentrated. The residue obtained was purified by column chromatography (silica gel; Et_2O–petroleum ether, 2:1), eluting with a small amount of unreacted starting material. The product was finally eluted with Et_2O.

Yield: 1.25 g (70%); brownish yellow oil.

^{1}H NMR ($CDCl_3$): δ = 8.02 (s, 1 H, OH), 7.03 (d, 2 H, *J* = 8.4 Hz, ArH), 6.76 (d, 2 H, *J* = 8.4 Hz, ArH), 5.71 (d, 1 H, *J* = 8.4 Hz, anomeric CH), 5.26 (t, 1 H, *J* = 9.1 Hz, glucose H), 5.16–5.10 (m, 2 H, glucose H), 4.29 (dd, 1 H, J_1 = 12.4, J_2 = 4.4 Hz, glucose H6), 4.14 (dd, 1 H, J_1 = 12.4, J_2 = 2.2 Hz, glucose H6), 4.09 (t, 2 H, *J* = 6.2 Hz), 3.86–3.79 (m, 1 H, glucose H5), 2.62 (t, 2 H, *J* = 7.5 Hz), 2.41 (t, 2 H, *J* = 7.5 Hz), 2.35 (t, 2 H, *J* = 7.5 Hz), 2.10 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.01 (s, 3 H), 1.97–1.84 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 172.9, 172.6, 170.2, 169.4, 169.1, 162.9, 154.2, 133.0, 129.4, 115.3, 91.8, 72.9, 72.8, 70.4, 67.9, 63.9, 61.5, 33.2, 33.0, 31.3, 30.3, 20.7, 20.5, 19.9.

MS (CI): *m*/*z* (%) = 596 (2, M^+).

Intramolecular Glycosylation of ω-Hydroxyglycosyl Acetate 31

ω-Hydroxyglycosyl acetate **31** (298 mg, 0.50 mmol) was dissolved in anhyd CH_2Cl_2 (100 mL). $BF_3{\cdot}Et_2O$ complex (78 mg, 0.55 mmol, 69 μl) was added. The solution turned brightly yellow. After 48 h at r.t., DMAP (122 mg, 1.00 mmol) was added to quench the Lewis acid. The colorless solution was concentrated and purified by flash chromatography (SiO_2, Et_2O–petroleum ether, 2:1) to give the product.

Yield: 217 mg (81%); colorless solid; mp 82 °C.

The spectral data were in full agreement with those obtained from the product of the macrolactonization route.

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