Total Synthesis of Caloporoside

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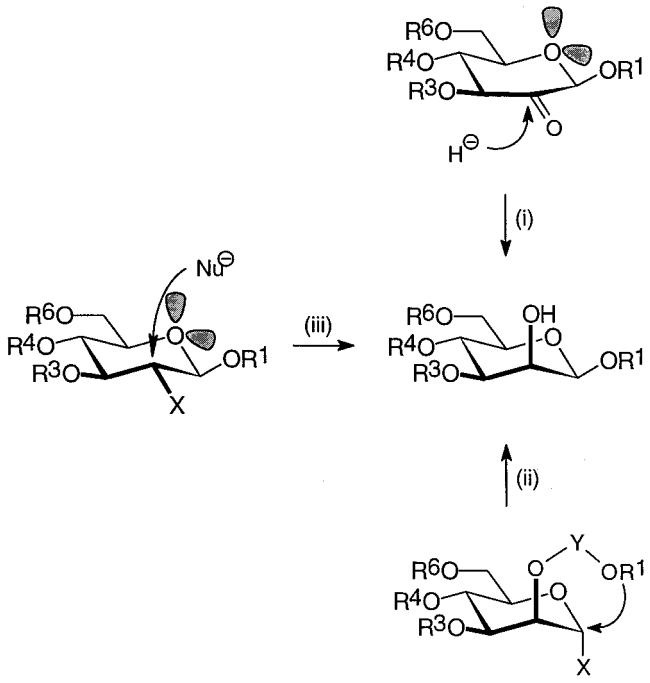
The first total synthesis of the fungal metabolite caloporoside **1**, a strong and selective inhibitor of phospholipase C, is described. Both sugar units of its complex disaccharidic segment were obtained from 3,4,6-tri-*O*-benzyl-D-glucopyranose **14** as a common building block, with D-gluco → D-manno inversions as the key strategic elements. This particular substitution reaction occurred readily on the acyclic segment (**27** → **28**), whereas ultrasonication was required to override adverse stereoelectronic effects upon formation of β-D-mannopyranoside unit **34**. The (16*R*)-hydroxyheptadecylsalicylic acid part of **1** was efficiently prepared by a palladium-catalyzed Suzuki cross coupling reaction of aryltriflate **7** with the 9-alkyl-9-BBN derivative formed from alkene **6** and 9-H-9-BBN.

Introduction

The efficient formation of β-D-mannopyranosidic linkages constitutes one of the ultimate challenges in oligosaccharide synthesis.[1] Conventional glycosidation strategies exploiting the anomeric effect of a pyranoside template and/or the anchimeric assistance of proper substituents on O-2 strongly disfavors this particular type of 1,2-cis arrangement. Despite some progress in direct β-D-mannoside syntheses[2] as well as in enzymatic mannosylation reactions,[3] the most efficient entries into this particular type of glycoside still rely on indirect methods (Scheme 1). Notable among them are (i) stereoselective reductions of β-D-*arabino*-hexopyranos-2-ulosides formed either directly via ulosyl bromide donors[4] or indirectly by oxidation of 2-O-unprotected β-glucosides,[5] (ii) well-designed molecular arrays using temporary linkers "Y" which transfer the aglycon in an entropically favored intramolecular process to the β-side of the glycosyl donor ("intramolecular aglycon delivery"),[6] and (iii) β-D-gluco → β-D-manno inversions via S_N2 processes.[7,8]

Scheme 1



While strategies (i) and (ii) usually require protecting group manipulations prior to the glycosylation event and are restricted to fairly reactive glycosyl acceptors R^1OH, method (iii) suffers from adverse stereoelectronic effects

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(2) For leading references, see: (a) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198. (b) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506. (c) Hodosi, G.; Kovác, P. *J. Am. Chem. Soc.* **1997**, *119*, 2335. (d) Kim, W.-S.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 7797. (d) Paulsen, H.; Lockhoff, O. *Chem. Ber.* **1981**, *114*, 3102. (e) Gorin, P. A. J.; Perlin, A. S. *Can. J. Chem.* **1961**, *39*, 2474. (f) Bebault, G. M.; Dutton, G. G. S. *Carbohydr. Res.* **1974**, *37*, 309. (g) Garegg, P. J.; Iversen, T. *Carbohydr. Res.* **1979**, *70*, C13. (h) Srivastava, V. K.; Schuerch, C. *J. Org. Chem.* **1981**, *46*, 1121.

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(6) (a) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087. (b) Stork, G.; La Clair, J. J. *J. Am. Chem. Soc.* **1996**, *118*, 247. (c) Dan, A.; Ito, Y.; Ogawa, T. *J. Org. Chem.* **1995**, *60*, 4680. (d) Ito, Y.; Ogawa, T. *Angew. Chem.* **1994**, *106*, 1843. (e) Dan, A.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1995**, *36*, 7487. (f) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376. (g) Barresi, F.; Hindsgaul, O. *Synlett* **1992**, 759.

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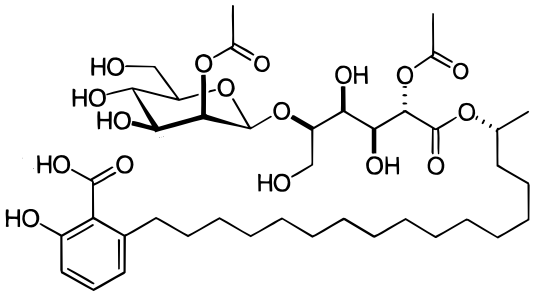
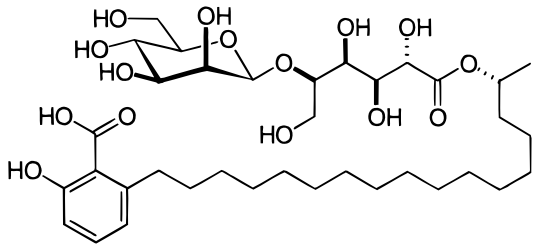
of the ring oxygen atom along the trajectory of the entering nucleophile, which generally impede nucleophilic substitutions at C-2.

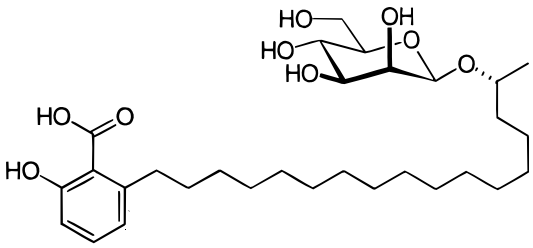
With this background in mind, the synthesis of caloporoside **1**,[9] a secondary metabolite isolated from *Caloporous dichrous*, represents a formidable task. The major problem is obviously posed by its β-D-mannopyranosyl-D-mannonic acid part, although further complications arise from the acylation pattern of this saccharidic segment: Only the axially oriented (and hence rather unreactive) O-2′ of the mannoside as well as the O-2 position of the acyclic mannonate unit are acetylated. Therefore the attentive choice of orthogonal protecting groups throughout the synthesis is of eminent importance for the regioselective introduction of the OAc residues as well as for avoiding any migration or cleavage of these esters during the final deprotection steps.



1



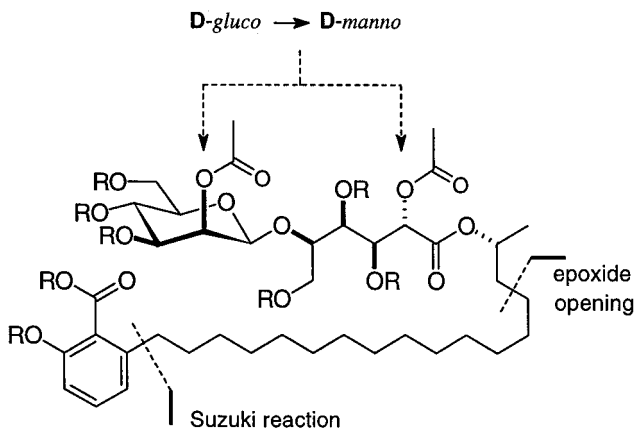
2



3

Caloporoside itself, as well as its deacylated analogue **2** and the monosaccharidic congener **3**, which were both isolated from a culture broth of the fungus HA 137-89,[10] are very attractive targets for total synthesis due to their pronounced physiological effects. Specifically, **1** has been shown to be a strong and selective inhibitor of phospholipase C, whereas **2** and **3** are inhibitors for the $GABA_A$/benzodiazepine chloride channel receptor complex and thus constitute neurotransmitter modulators of potential pharmacological relevance.

Scheme 2



Tatsuta et al. have recently reported syntheses of **2** and **3**.[11] In parallel work, we have outlined a modular entry into their common 6-alkylsalicylic acid "aglycon" as well as an efficient synthesis of compound **3** as the elementary member of this series of fungal metabolites based on the "ulosyl bromide strategy" (Scheme 1, method i) for the construction of the β-D-mannosidic linkage.[12] We now disclose the first total synthesis of caloporoside **1** itself with the proper acylation pattern, which relies on a highly efficient β-D-gluco → β-D-manno inversion promoted by ultrasound as the key step.

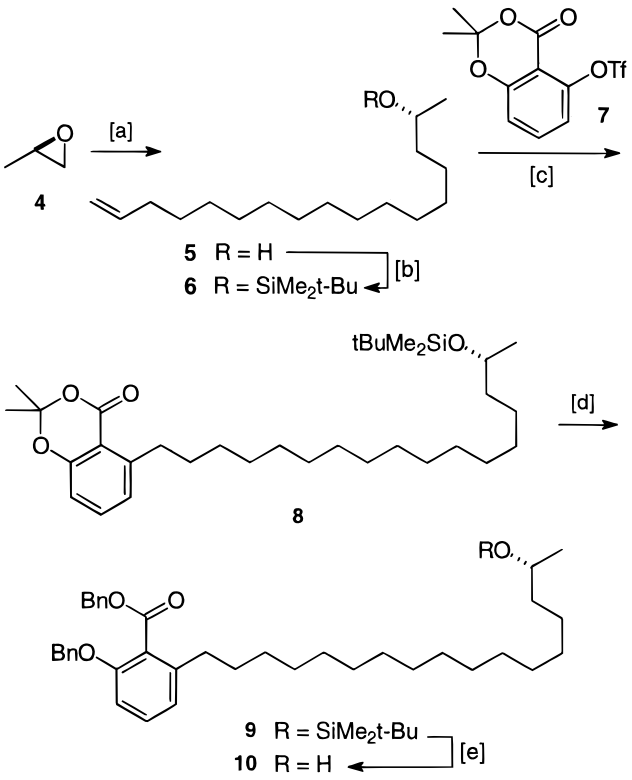
Results and Discussion

Retrosynthetic Analysis and Formation of the Building Blocks. Our retrosynthetic analysis is summarized in Scheme 2. The formation of the salicylic acid part essentially follows the route outlined previously: thus, (*R*)-propenoxide **4** delivers the chiral information and a Suzuki cross coupling is used to attach the alkyl chain to the salicylic acid nucleus.[12] Furthermore, we envisage two D-gluco → D-manno inversions to afford the proper stereochemistry in the sugar portion of **1**. This strategy has the inherent advantage that both units of the disaccharide can be traced back to the same glucose-derived precursor. By choosing benzyl protecting groups throughout this convergent synthesis, any scrambling of the acetyl residues of caloporoside in the final deprotection step should be precluded.

Reaction of 13-tetradecenylmagnesium bromide with (*R*)-propenoxide **4**[13] catalyzed by CuCl(COD) followed by silylation of the resulting enantiomerically pure alcohol **5** cleanly affords alkene **6** (Scheme 3). Its hydroboration with 9-H-9-BBN dimer and subsequent addition of NaOMe leads to a borate complex which undergoes an efficient cross-coupling reaction with aryl triflate **7** in the presence of $PdCl_2$(dppf) (2.5 mol %) and KBr as a stabilizing agent.[12,14] Treatment of **8** with the sodium salt of benzyl alcohol readily cleaves the isopropylidene group and affords the corresponding benzyl ester which is protected at the phenolic OH with $BnBr/K_2CO_3$ to provide compound **9**. Desilylation of the latter leads to alcohol **10** in excellent yield which is used as a first key building block for the assembly of **1**.

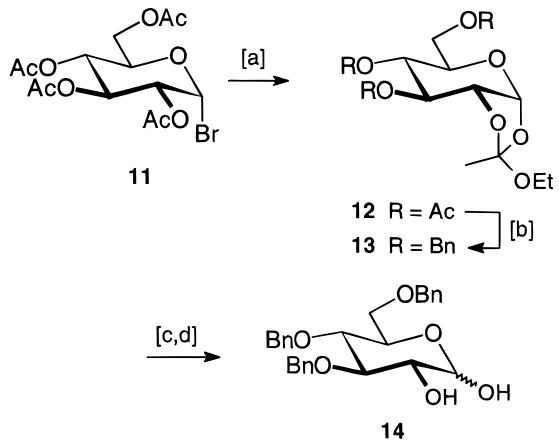
(9) Weber, W.; Schu, P.; Anke, T.; Velten, R.; Steglich, W. *J. Antibiot.* **1994**, *47*, 1188.
(10) Shan, R.; Anke, H.; Nielsen, M.; Sterner, O.; Witt, M. R. *Nat. Prod. Lett.* **1994**, *4*, 171.
(11) (a) Tatsuta, K.; Yasuda, S. *Tetrahedron Lett.* **1996**, 2453. (b) Tatsuta, K.; Yasuda, S. *J. Antibiot.* **1996**, *49*, 713.
(12) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071.
(13) Now readily available according to Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

Scheme 3[a]



[a] [a] 13-tetradecenylmagnesium bromide, CuCl(COD) (10 mol %), THF, −78 °C → rt, overnight, 86%; [b] TBDMSCl, imidazole, DMF, rt, 94%; [c] (i) $[9\text{-H-9-BBN}]_2$ (0.5 equiv), THF; (ii) NaOMe (1 equiv), KBr (1.1 equiv), $PdCl_2$(dppf) (2.5 mol %), THF, reflux, overnight, 86%; [d] (i) BnOH, NaH, DMF, 3 h, rt, 92%; (ii) BnBr, K_2CO_3, DMF, 4 h, reflux, 93%; [e] TBAF, THF, rt, 89%.

Scheme 4[a]

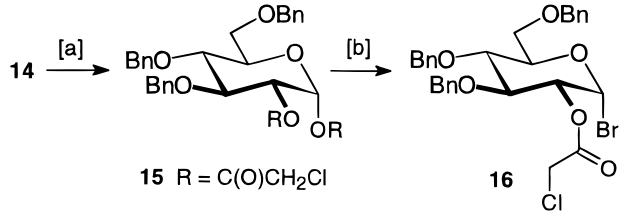


[a] [a] Bu_4NBr, *s*-collidine, EtOH, 85%; [b] BnBr, KOH, THF, 81%; [c] 2 N HCl, THF; [d] K_2CO_3, MeOH, 1 h, rt, 87% over two steps.

Acetobromoglucose **11** is converted into 3,4,6-tri-*O*-benzyl-D-glucopyranose **14** in four conventional steps on a multigram scale by closely following a literature protocol.[4a] This compound serves as a common intermediate for both sugar units of caloporoside (Scheme 4).

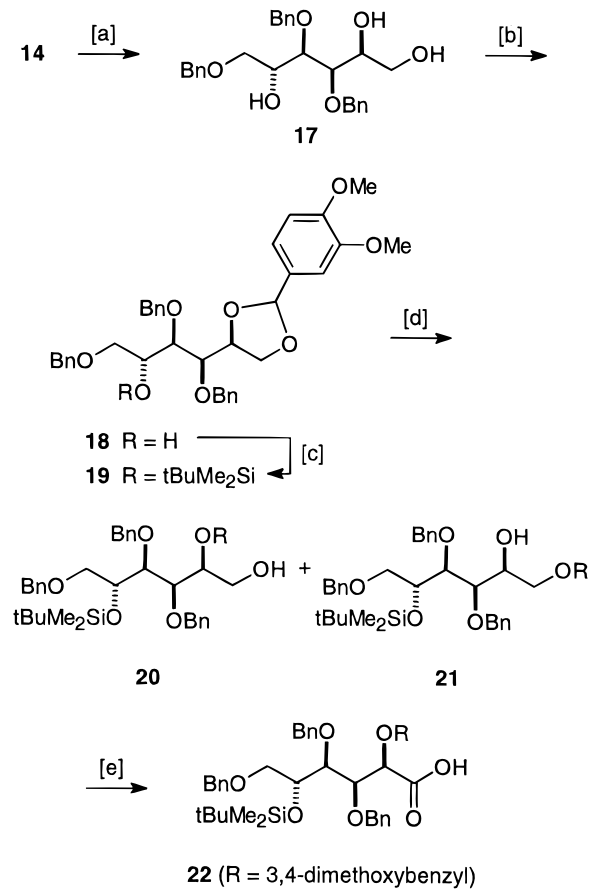
The second building block was obtained from **14** by simple acylation with chloroacetic acid anhydride and subsequent displacement of the anomeric ester group with HBr/HOAc. The crude glycosyl bromide **16** thus obtained was used without further purification (Scheme 5).

Scheme 5[a]



[a] [a] $(ClCH_2CO)_2O$, pyridine, −20 → −10 °C, 1.5 h, 85%; [b] HBr/HOAc, $CHCl_3$, 0 °C → rt, 3 h, 95%.

Scheme 6[a]



[a] [a] $NaBH_4$, THF/H_2O, 0 °C → rt, 2 h, 96%; [b] 3,4-dimethoxybenzaldehyde, H_2SO_4 cat., MS 3 Å, CH_2Cl_2, 3.5 h, 84%; [c] $tBuMe_2SiCl$, imidazole, DMF, 15 h, rt, 91%; [d] BH_3·THF, THF, reflux, 2 h, **20** (62%) + **21** (32%); [e] (i) Swern oxidation; (ii) $NaClO_2$, HSO_3NH_2, THF/H_2O, rt, 10 min, 93%.

Reduction of **14** with $NaBH_4$ provides triol **17** which is transformed into the dimethoxybenzylidene acetal **18** and then silylated as shown in Scheme 6. Subsequent reductive cleavage of the acetal in **19** is best achieved with BH_3·THF,[15] affording the desired primary alcohol **20** in 62% yield together with 32% of the regioisomeric product **21**; the latter can be readily separated by flash chromatography. Reducing agents other than borane for the cleavage of the acetal did not improve the isomeric

(14) Review: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. For applications of Suzuki reactions from our laboratory, see: (b) Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 11165. (c) Fürstner, A.; Seidel, G.; Gabor, B.; Kopiske, C.; Krüger, C.; Mynott, R. *Tetrahedron* **1995**, *51*, 8875. (d) Fürstner, A.; Nikolakis, K. *Liebigs Ann.* **1996**, 2107.

(15) (a) Fleming, B.; Bolker, H. I. *Can. J. Chem.* **1974**, *52*, 888. (b) See also: Tsuri, T.; Kamata, S. *Tetrahedron Lett.* **1985**, *26*, 5195.

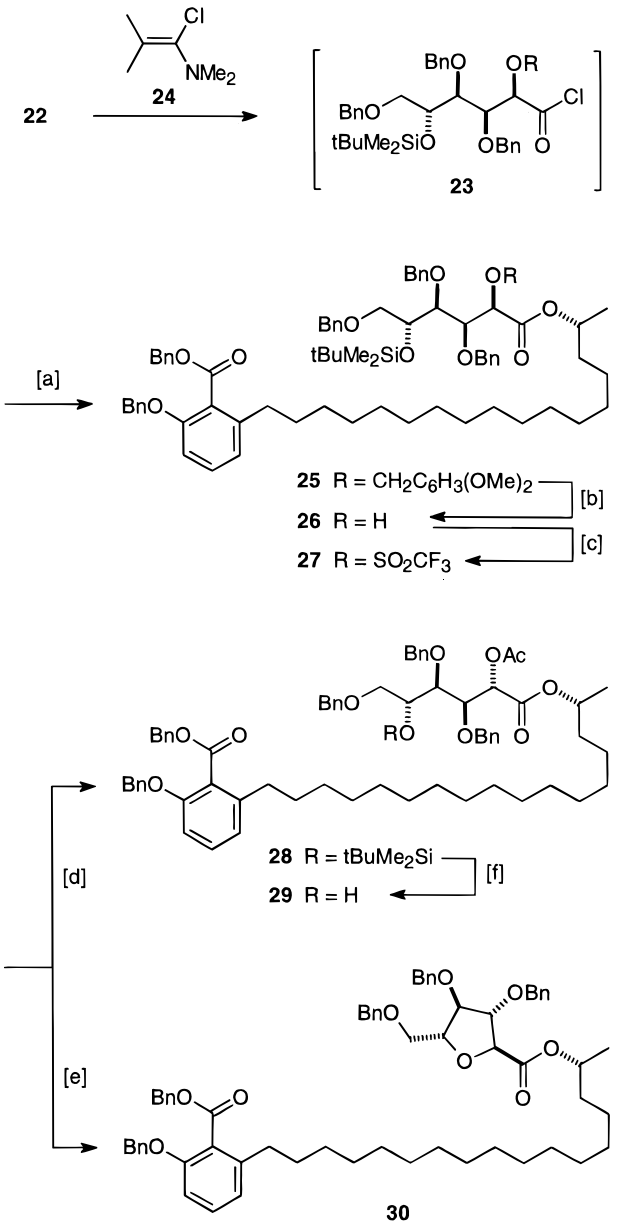
ratio but rather compromised the yields. Swern oxidation[16] of **20** followed by exposure of the resulting crude aldehyde to $NaClO_2/HSO_3NH_2$[17] in aqueous THF provides the properly protected gluconic acid **22** as the third building block for the synthesis of **1** (Scheme 6).

Assembly. With building blocks **10**, **16**, and **22** in hand, we tackled the assembly of the caloporoside skeleton. Thus, by using the chloroenamine reagent **24** developed by Ghosez et al.,[18] it was possible to convert the gluconic acid **22** under *strictly neutral* conditions into the corresponding acid chloride **23**, which was immediately trapped with alcohol **10**. As it proved difficult to separate the resulting ester **25** from traces of unreacted starting materials by flash chromatography, crude **25** was deprotected by oxidative cleavage of the dimethoxybenzyl group with DDQ in CH_2Cl_2.[19] The purification of the corresponding alcohol is readily achieved, leading to pure **26** in 74% yield over three steps without any racemization of the C-2 stereogenic center. Moreover, it should be mentioned that the use of the 3,4-*di*methoxybenzyl group was a key to success: while this group was readily split off by DDQ, the corresponding 4-*mono*methoxybenzyl ether could not be cleaved under these conditions (Scheme 7).

Treatment of alcohol **26** with trifluoromethanesulfonic acid anhydride in pyridine/CH_2Cl_2 affords the rather unstable triflate **27** which readily reacts to the desired D-mannonic acid ester **28** on addition of KOAc in DMF (Scheme 7). Surprisingly though, we noticed a pronounced effect of the temperature on this process: while the intermolecular substitution proceeds cleanly at ambient temperature, an intramolecular reaction prevails at 0 °C leading to the formation of the tetrahydrofuran derivative **30** via attack of the 5-OTBDMS ether rather than external KOAc onto the triflate.[20]

The desilylation of mannonate **28** turned out to be somewhat delicate: both the use of TBAF and of HF/MeCN lead to the concomitant cleavage of the mannonic acid ester, while pyridinium *p*-toluenesulfonate is totally ineffective. The use of $BF_3{\cdot}Et_2O$ in CH_2Cl_2, however, cleanly affords the desired alcohol **29** in 83% yield, which is glycosylated under modified Koenigs-Knorr conditions[21] with glucosyl bromide **16** using Ag^+ on silica/alumina as the promotor (Scheme 8).[22] Since the anchimeric assistance exerted by the chloroacetyl group directs the glycosylation to the β-side, disaccharide **31** is obtained in good yield and excellent selectivity; the chloroacetyl

Scheme 7[a]



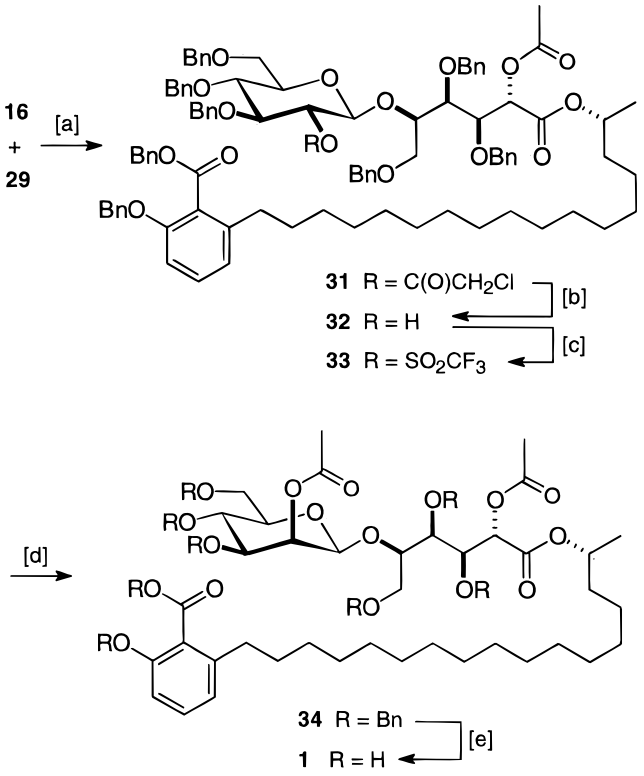
[a] [a] **10**, DMAP, CH_2Cl_2, 0 °C → rt, 16 h; [b] DDQ, CH_2Cl_2/H_2O, 0 °C → rt, 3.5 h, 74% (over last three steps steps); [c] triflic anhydride, CH_2Cl_2/pyridine, 0 °C, 15 min; [d] KOAc, DMF, rt, 1 h, 75%; [e] KOAc, DMF, 0 °C → rt, **30** (75%) + **28** (18%); [f] $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C → rt, 1.5 h, 83%.

residue can then be selectively cleaved off with thiourea[23] without affecting the resident 2-*O*-acetyl substituent on the mannonate entity (**31** → **32**).

This sets the stage for the crucial β-D-glucopyranoside → β-D-mannopyranoside inversion process: formation of triflate **33** under standard conditions followed by treatment with Bu_4NOAc in toluene cleanly provides the desired 2-*O*-acetyl-β-D-mannopyranosyl-D-mannonic acid ester **34** without any formation of the undesired gluco isomer interfering, provided that the reaction is carried out *with ultrasonication* (Scheme 8). In the NMR spectra, the observed coupling constants $J_{H1',H2'} \approx 1$ Hz and

(16) Review: Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(17) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. (b) Colombo, L.; Gennari, C.; Santandrea, M.; Narisano, E.; Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 136.
(18) (a) Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180. (b) Haveaux, B.; Dekoker, A.; Rens, M.; Sidani, A. R.; Toye, J.; Ghosez, L. *Org. Synth.* **1980**, *59*, 26.
(19) For a review, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991.
(20) For a review on carbohydrate-derived triflates, see: (a) Binkley, R. W.; Ambrose, M. G. *J. Carbohydr. Chem.* **1984**, *3*, 1. (b) See also: Stang, P. J.; Hanak, M.; Subramanian, R. L. *Synthesis* **1982**, 85. (c) Carbohydrate-derived triflates are prone to ring contraction via intramolecular substitution reactions, cf: Binkley, R. W. *J. Org. Chem.* **1992**, *57*, 2353. (d) Wheatley, J. R.; Bichard, C. J. F.; Mantell, S. J.; Son, J. C.; Hughes, D. J.; Fleet, G. W. J.; Brown, D. *J. Chem. Soc., Chem. Commun.* **1993**, 1065 and references cited.
(21) For reviews, see: (a) Paulsen, H. *Angew. Chem.* **1982**, *94*, 184; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155. (b) Schmidt, R. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 33.
(22) Van Boeckel, C. A. A.; Beetz, T.; Kock-van Dalen, A. C.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 596.
(23) For precedence, see i.a.: Naruto, M.; Ohno, K.; Naruse, N.; Takeuchi, H. *Tetrahedron Lett.* **1979**, 251.

Scheme 8[a]



[a] [a] Ag^+ on silica/alumina, MS 3 Å, CH_2Cl_2, −5 °C, 45 min, 74%; [b] thiourea, Na_2CO_3, EtOH/CH_2Cl_2, reflux, 4 h, 75%; [c] triflic anhydride, pyridine, rt, 45 min, 78%; [d] Bu_4NOAc, toluene, ultrasound, 16 h, 95%; [e] H_2 (1 atm), Pd/C (5%), MeOH + HOAc (1%), 22 h, 96%.

$J_{C1',H1'} = 156.8$ Hz confirm the β-D-*manno* arrangement.[24] Although similar ultrasound-assisted D-*gluco* → D-*manno* inversions using CsOAc have been recently described in the literature,[7b,c] we would like to stress the fact that Bu_4NOAc exhibits a far superior reactivity in this difficult substitution reaction and ensures a much more efficient product formation. Furthermore, it should be noted that attempts to effect the inversion under thermal conditions either failed to afford any **34** or led to rather complex mixtures if the reactions were run under more forcing conditions.

Hydrogenolysis of the eight benzyl protecting groups in the fully protected mannoside **34** over Pd on charcoal in MeOH/HOAc (1%) affords caloporoside **1** in near quantitative yield and completes the first total synthesis of this demanding target. Its spectroscopic and analytical data are in full agreement with those reported in the literature.[9]

While previous synthetic studies were able to devise elegant and efficient routes to the deacetylated analogue **2**[11] and the monosaccharidic congener **3**[11,12] of caloporoside, the synthesis outlined above is the first one to address the problems posed by the acylation pattern of this important target. The ultrasound-driven nucleophilic displacement of a 2-*O*-triflyl group by Bu_4NOAc installs the required β-D-mannosidic linkage and thereby solves the regiochemical issues. We are presently exploring the scope of this promising new approach to β-D-mannopyranosides in more detail.[25]

(24) For the assignment of the anomeric configuration via $J_{C,H}$, see: Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293.

Experimental Section

General. All reactions were carried out under Ar in predried glassware using Schlenk techniques. The solvents were dried by distillation over the drying agents indicated and were stored and transferred under Ar: CH_2Cl_2 (P_4O_{10}), toluene (Na/Ka), THF (magnesium/anthracene), DMF (Desmodur®, Bayer AG; dibutyltin dilaurate), pyridine (KOH), EtOH (Mg), MeOH (Mg). Flash chromatography: Merck silica gel (230−400 mesh) using hexane/ethyl acetate in various proportions as eluent. For the instrumentation used and the spectra formats see ref. 25f. Mp: Gallenkamp apparatus (uncorrected). Elemental analyses: Dornis & Kolbe, Mülheim. Commercially available reagents (Aldrich, Fluka) were used as received.

2-Benzyloxy-6-{[(16*R*)-*tert*-butyldimethylsilyloxy]-heptadecyl}benzoic Acid Benzyl Ester (9). Benzyl alcohol (10 mL) was added to a suspension of NaH (0.51 g, 22.18 mmol) in DMF (40 mL) at 0 °C, and the mixture was stirred for 30 min while being warmed to ambient temperature. Dioxinone **8** (4.00 g, 7.31 mmol)[12] was introduced and stirring was continued for 3 h. The suspension was neutralized with aqueous 1 N HCl, buffered with saturated aqueous $NaHCO_3$ (50 mL), and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water (50 mL) and dried over Na_2SO_4, and the solvents were removed in vacuo. Flash chromatography (hexane/ethyl acetate 15:1 → 10:1) of the residue yielded 2-hydroxy-6-{[(16*R*)-*tert*-butyldimethylsilyloxy]-heptadecyl}benzoic acid benzyl ester as a colorless oil (4.01 g, 92%): $[\alpha]^{20}_D$ −4.9° (*c* 8.1, $CHCl_3$); IR 3035, 2926, 2854, 1661, 1608, 1449, 1250, 1209, 835, 774; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.45 (m, 5H), 7.25 (m, 1H), 6.82 (dd, J = 8.3, 1.2, 1H), 6.67 (dd, J = 7.5, 1.2, 1H), 5.36 (s, 2H), 3.75 (m, 1H), 2.79 (m, 2H), 1.10 (d, J = 6.1, 3H), 1.02−1.42 (br, 28H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 164.3, 162.8, 134.9, 134.2, 129.0, 128.7, 128.7, 122.4, 115.6, 111.8, 68.6, 67.6, 39.8, 36.8, 32.4, 29.8, 29.7, 29.6, 29.6, 25.9, 25.8, 23.8, 18.6, −4.4, −4.7; MS *m*/*z* (rel intensity) 539 ([M − C_4H_9]$^+$, 7), 521 (32), 477 (5), 447 (5), 431 (46), 221 (9), 207 (9), 195 (7), 181 (3), 159 (9), 91 (100), 75 (12); $C_{37}H_{60}O_4Si$ (596.96) calcd C 74.45, H 10.13, found C 74.34, H 10.05. This compound (3.270 g, 5.48 mmol), K_2CO_3 (0.907 g, 6.56 mmol), and benzyl bromide (780 μL, 6.57 mmol) were refluxed in DMF (30 mL) for 4 h. Et_2O (150 mL) was added, and the mixture was successively washed with water (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). After drying of the organic layers over Na_2SO_4 and evaporation of the solvents, the residue was chromatographed (hexane/ethyl acetate 30:1 → 10:1), yielding compound **9** as a colorless oil (3.505 g, 93%): $[\alpha]^{20}_D$ −3.8° (*c* 2.3, $CHCl_3$); IR 3033, 2926, 2854, 1732, 1583, 1268, 835, 774, 696; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.24−7.42 (m, 10H), 7.21 (m, 1H), 6.79 (m, 2H), 5.33 (s, 2H), 5.07 (s, 2H), 3.75 (m, 1H), 2.52 (m, 2H), 1.27−1.54 (br, 28H), 1.11 (d, J = 6.0, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.2, 155.4, 141.6, 138.1, 136.8, 135.7, 130.2, 128.6, 128.4, 128.2, 127.8, 127.1, 124.0, 121.8, 109.9, 70.4, 68.7, 66.9, 39.8, 33.5, 31.3, 29.7, 29.6, 29.4, 25.9, 25.8, 23.8, 18.2, −4.4, −4.7; MS *m*/*z* (rel intensity) 629 ([M − C_4H_9]$^+$, 2), 611 (4), 585 (4), 567 (9), 521 (6), 493 (4), 431 (4), 417 (16), 181 (23), 91 (100); $C_{44}H_{66}O_4Si$ (687.09) calcd C 76.92, H 9.68, found 76.85, H 9.58.

2-Benzyloxy-6-[(16*R*)-hydroxyheptadecyl]benzoic Acid Benzyl Ester (10). Compound **9** (3.500 g, 5.09 mmol) was treated with TBAF (1.0 M in THF, 7.0 mL, 7.00 mmol) for 15 h at ambient temperature. Water (20 mL) was added and

(25) For recent syntheses of other bioactive targets from this laboratory, see: (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (b) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. (c) Fürstner, A.; Müller, T. *J. Org. Chem.* **1998**, *63*, 424. (d) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1997**, *119*, 2944. (e) Fürstner, A.; Seidel, G. *J. Org. Chem.* **1997**, *62*, 2332. (f) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792. (g) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005. (h) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746. (i) Fürstner, A.; Ernst, A.; Krause, H.; Ptock, A. *Tetrahedron* **1996**, *52*, 7329. (j) Fürstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637.

the mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. Flash chromatography (hexane/ethyl acetate) of the residue afforded alcohol **10** as a colorless solid (2.590 g, 89%): mp 50−51 °C; $[\alpha]^{25}_D$ −2.5° (*c* 3.4, $CHCl_3$); IR 3548, 3033, 2916, 2849, 1727, 1578, 1470, 1267; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.17−7.40 (m, 11H), 6.79 (m, 2H), 5.33 (s, 2H), 5.07 (s, 2H), 3.78 (m, 1H), 2.52 (m, 2H), 1.17 (d, J = 6.2, 3H), 1.20−1.60 (br, 28H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.2, 155.4, 141.6, 136.8, 135.7, 130.1, 128.6, 128.4, 128.1, 127.7, 127.1, 123.9, 121.8, 109.9, 70.3, 70.1, 66.9, 39.3, 33.4, 31.2, 29.6, 29.5, 29.4, 25.7, 23.4; MS *m*/*z* (rel intensity) 572 ([M]$^+$, 0.3), 481 (1), 463 (4), 448 (2), 375 (13), 357 (16), 181 (11), 151 (6), 91 (100); $C_{38}H_{52}O_4$ (572.83) calcd C 79.68, H 9.15, found 79.63, H 9.06.

3,4,6-Tri-*O*-benzyl-D-glucopyranose (14). A solution of ortho ester **13** (13.98 g, 26.9 mmol)[4a] in THF (70 mL) was treated with aqueous 2 N HCl (5 mL) for 45 min at ambient temperature. After neutralization with aqueous 2 N NaOH, Et_2O (200 mL) and saturated aqueous $NaHCO_3$ (50 mL) were added. The aqueous phase was extracted with Et_2O (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated. Flash chromatography (hexane/ethyl acetate 2:1 → 1:1) of the residue afforded a colorless syrup (12.55 g), which slowly crystallized upon standing. Subsequent deacetylation was achieved by stirring the product (12.55 g) and K_2CO_3 (1.30 g, 9.41 mmol) in MeOH (100 mL) for 1 h at room temperature. Neutralization with aqueous 1 N HCl, addition of water (100 mL) and Et_2O (200 mL), extraction of the aqueous layer with Et_2O (3 × 50 mL), drying of the organic layers over Na_2SO_4, evaporation of the solvents and a final flash chromatography (hexane/ethyl acetate 2:1 → 1:1) affords compound **14** as a colorless solid (10.49 g, 87% over both steps): mp 88−89 °C; $[\alpha]^{25}_D$ +46.6° (*c* 3.9, $CHCl_3$); IR 3355, 3031, 2869, 1453, 1150, 1069, 747, 697; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 96.6 (C-1, β-anomer), 92.2 (C-1, α-anomer); MS (ESI) 473 ([M + Na]$^+$), 489 ([M + K]$^+$); $C_{27}H_{30}O_6$ (450.53) calcd C 71.98, H 6.71, found C 71.78, H 6.72.

3,4,6-Tri-*O*-benzyl-1,2-di-*O*-chloroacetyl-α,β-D-glucopyranose (15). To a solution of diol **14** (6.14 g, 13.63 mmol) in pyridine (100 mL) was added chloroacetic anhydride (6.99 g; 40.89 mmol) at −20 °C, and the resulting mixture was stirred for 1.5 h at −10 to −20 °C. The excess of the anhydride was hydrolyzed by addition of saturated aqueous $NaHCO_3$ (50 mL), and the mixture was extracted with Et_2O (3 × 70 mL). The combined organic layers were successively washed with aqueous 1 N HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (50 mL), and water (50 mL). After drying of the organic layers (Na_2SO_4), the solvents were evaporated and the residue was co-distilled with toluene to remove excess pyridine. Flash chromatography (hexane/ethyl acetate 4:1) afforded compound **15** (7.01 g, 85%) as a colorless syrup which slowly crystallized upon standing: mp 73−74 °C; $[\alpha]^{20}_D$ +42.8° (*c* 3.7, $CHCl_3$); IR 3030, 2905, 2870, 1765, 1454, 1129, 1091, 1057, 751, 699; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.38 (d, J = 3.6, 1H, α-anomer), 5.67 (d, J = 8.2, 1H, β-anomer); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 93.1 (C-1, α-anomer), 91.4 (C-1, β-anomer); MS *m*/*z* (rel intensity) 511 ([M − 91]$^+$, 3), 417 (3), 311 (2), 221 (2), 181 (3), 127 (2), 91 (100); $C_{31}H_{32}Cl_2O_8$ (603.49) calcd C 61.70, H 5.34, Cl 11.75, found C 61.68, H 5.39, Cl 11.89.

3,4,6-Tri-*O*-benzyl-2-*O*-chloroacetyl-α-D-glucopyranosyl bromide (16). HBr (33% in AcOH, 1.1 mL, 4.49 mmol) was added to a solution of **15** (1.43 g, 2.36 mmol) in $CHCl_3$ (10 mL) at 0 °C. The reaction mixture was stirred for 3 h while slowly being warmed to ambient temperature. For workup, Et_2O (50 mL) was added and the organic layer was rapidly washed with water (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and water (20 mL). After drying of the organic phases over Na_2SO_4, the solvent was evaporated and the remaining residue was dried in vacuo (10^{-2} mbar). The resulting syrup (1.32 g, 95%) was processed without any further purification. As bromide **16** is quite unstable, it was stored at −18 °C under an inert atmosphere. For analytical purposes, bromide **16** was chromatographed (hexane/ethyl acetate 4:1) on a short column. Despite partial hydrolysis, an analytically pure sample could be obtained which exhibits the following properties: $[\alpha]^{20}_D$ +140.8° (*c* 4.2, $CHCl_3$); IR 3030, 2919, 2868, 1770, 1749, 1454, 1114, 1110, 737, 698; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15−7.36 (m, 15H), 6.64 (d, J = 3.9, 1H), 4.74−4.87 (m, 4H), 4.47−4.61 (m, 2H), 4.10 (m, J = 9.3, 1H), 4.06 (m, 1H), 3.96 and 3.84 (AB, J = 15.1, 2H), 3.79−3.91 (m, 2H), 3.67 (dd, J = 11.1, 1.9, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.4, 138.1, 137.7, 137.6, 128.5, 128.4, 127.9, 127.9, 127.7, 88.3, 80.2, 76.3, 75.7, 75.4, 75.4, 74.5, 73.5, 67.4, 40.4; $C_{29}H_{30}BrClO_6$ (589.91) calcd C 59.05, H 5.13, Br 13.55, Cl 6.01, found C 59.04, H 5.08, Br 13.38, Cl 5.91.

3,4,6-Tri-*O*-benzyl-D-glucitol (17). $NaBH_4$ (3.69 g, 97.50 mmol) was added to a solution of diol **14** (4.39 g, 9.75 mmol) in THF (50 mL) and H_2O (10 mL) at 0 °C, and the mixture was stirred at ambient temperature for 2 h. Then 10% citric acid (100 mL) was slowly introduced (gas evolution), the mixture was extracted with Et_2O (3 × 70 mL), the organic layers were washed with aqueous $NaHCO_3$ (50 mL) and dried over Na_2SO_4, and the solvent was removed. Flash chromatography (hexane/ethyl acetate 1/1 → ethyl acetate) of the residue yielded compound **17** (4.23 g, 96%) as a colorless syrup: $[\alpha]^{28}_D$ +19.3° (*c* 19.6, $CHCl_3$); IR 3424, 3030, 2870, 1497, 1454, 1090, 1072, 1028, 736, 698; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17−7.29 (m, 15H), 4.67 (A part of AB, J = 11.4, 1H), 4.47−4.57 (m, 5H), 4.03 (m, 1H), 3.91 (m, 1H), 3.73 (dd, J = 6.8, 4.9, 1H), 3.45−3.67 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8, 137.8, 137.6, 128.2, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 79.0, 78.0, 74.1, 73.5, 73.2, 71.1, 71.0, 70.9, 63.9; MS *m*/*z* (rel intensity) 361 ([M$^+$ − 91], 2), 313 (1), 255 (4), 193 (2), 181 (7), 163 (10), 91 (100); $C_{27}H_{32}O_6$ calcd C 71.66, H 7.13, found C 71.52, H 7.19.

3,4,6-Tri-*O*-benzyl-1,2-*O*-(3,4-dimethoxybenzylidene)-D-glucitol (18). Triol **17** (4.202 g, 9.29 mmol), 3,4-dimethoxybenzaldehyde (2.315 g, 13.93 mmol), concentrated H_2SO_4 (50 μL), and powdered molecular sieves (3 Å) were stirred in CH_2Cl_2 (50 mL) for 3.5 h at ambient temperature. The molecular sieves were filtered off and rinsed with ethyl acetate (100 mL), the combined filtrates were washed with aqueous $NaHCO_3$/NaCl (30 mL) and dried over Na_2SO_4, the solvents were evaporated, and the residue was purified by flash chromatography (hexane/ethyl acetate 4:1 → 2:1) yielding compound **18** (4.702 g, 84%) as a mixture of diastereoisomers: colorless syrup; IR 3502, 2870, 1518, 1454, 1266, 1089, 1028, 737, 699; MS *m*/*z* (rel intensity) 600 ([M]$^+$, 10), 509 (4), 343 (2), 255 (5), 209 (19), 181 (12), 166 (20), 151 (15), 101 (9), 91 (100); $C_{36}H_{40}O_8$ (600.70) calcd C 71.98, H 6.71, found C 71.76, H 6.85.

3,4,6-Tri-*O*-benzyl-1,2-*O*-(3,4-dimethoxybenzylidene)-5-*O*-*tert*-butyldimethylsilyl-D-glucitol (19). Compound **18** (4.534 g, 7.55 mmol) in DMF (30 mL) was reacted with $tBuMe_2SiCl$ (1.700 g, 11.32 mmol) and imidazole (0.771 g, 11.32 mmol) at ambient temperature for 15 h. Water (30 mL) was added, and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. Flash chromatography (hexane/ethyl acetate 10:1 → 4:1) afforded a mixture of both diastereomers of compound **19** as a colorless syrup (4.910 g, 91%): IR 2929, 2856, 1518, 1454, 1264, 1092, 1029, 836, 737, 698; MS *m*/*z* (rel intensity) 714 ([M]$^+$, 1), 657 (5), 293 (4), 241 (1), 231 (3), 209 (5), 181 (20), 165 (4), 151 (12), 117 (4), 91 (100); $C_{42}H_{54}O_8Si$ (714.97) calcd C 70.56, H 7.61, found C 70.42, H 7.54.

3,4,6-Tri-*O*-benzyl-2-*O*-(3,4-dimethoxybenzyl)-5-*O*-*tert*-butyldimethylsilyl-D-glucitol (20) and 3,4,6-Tri-*O*-benzyl-1-*O*-(3,4-dimethoxybenzyl)-5-*O*-*tert*-butyldimethylsilyl-D-glucitol (21). A solution of benzylidene acetal **19** (4.118 g, 5.76 mmol) and BH_3·THF complex (1.0 M in THF, 15.0 mL) in THF (45 mL) was refluxed for 2 h. Aqueous saturated $NaHCO_3$ (30 mL) was added dropwise at 0 °C in order to destroy excess borane. The mixture was extracted with ethyl acetate (1 × 100 mL, 2 × 50 mL), the combined organic layers were dried (Na_2SO_4) and evaporated, and the crude residue was chromatographed (hexane/ethyl acetate 4:1 → 2:1) affording compounds **20** (2.547 g, 62%) and **21** (1.305 g, 32%) as colorless syrups. Data for **20**: $[\alpha]^{25}_D$ +3.9° (*c* 7.1, $CHCl_3$); IR 3439, 2929, 2857, 1516, 1261, 1094, 1029, 836, 737, 698; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18−7.31 (m, 15H), 6.79−6.83 (m,

3H), 4.61 and 4.78 (AB, J = 11.3, 2H), 4.72 (A part of AB, J = 11.2, 1H), 4.38−4.47 (m, 4H), 4.34 (B part of AB, J = 11.4, 1H), 4.20 (m, 1H), 3.92 (m, 1H), 3.88 (dd, J = 7.1, 2.3, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.79 (dd, J = 9.7, 4.1, 1H), 3.74 (dd, J = 7.1, 1.7, 1H), 3.55 (dd, J = 9.7, 6.0, 1H), 3.50 (m, 1H), 3.36 (dd, J = 9.4, 6.1, 1H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.9, 148.6, 138.8, 138.3, 136.2, 130.6, 128.1, 128.1, 127.7, 127.5, 127.4, 127.3, 120.4, 111.2, 110.9, 82.2, 78.4, 74.6, 74.2, 73.2, 73.1, 72.9, 71.7, 71.2, 69.3, 55.8, 55.7, 25.8, 18.0, −4.8; MS m/z (rel intensity) 565 ([M − $C_9H_{11}O_2$]$^+$, 1), 459 (1), 277 (2), 241 (14), 210 (1), 181 (6), 151 (100), 91 (60); $C_{42}H_{56}O_8Si$ (716.98) calcd C 70.36, H 7.87, found C 70.43, H 7.92.

Data for **21**: $[\alpha]^{25}_D$ +0.3° (c 12.0, $CHCl_3$); IR 3525, 2929, 2856, 1516, 1454, 1262, 1095, 1029, 835, 737, 698; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26−7.31 (m, 15H), 6.78−6.85 (m, 3H), 4.65 and 4.82 (AB, J = 11.3, 2H), 4.67 and 4.74 (AB, J = 11.3, 2H), 4.53 and 4.58 (AB, J = 11.4, 2H), 4.45 (s, 2H), 4.14 (m, 1H), 3.69−3.89 (m, 5H), 3.84 (s, 3H), 3.77 (s, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.9, 148.6, 138.7, 138.2, 130.9, 128.3, 128.2, 128.1, 127.8, 127.6, 127.5, 127.4, 120.4, 111.3, 110.9, 81.7, 79.6, 79.0, 74.7, 74.3, 73.5, 73.2, 72.3, 72.1, 55.8, 55.7, 61.8, 25.8, 18.0, −4.5, −4.7; MS m/z (rel intensity) 716 ([M]$^+$, 0.2), 565 (0.4), 459 (2), 241 (23), 181 (8), 160 (2), 151 (100), 129 (2), 117 (2), 91 (73); $C_{42}H_{56}O_8Si$ (716.98) calcd C 70.36, H 7.87, found C 70.16, H 7.76.

3,4,6-Tri-*O*-benzyl-2-*O*-(3,4-dimethoxybenzyl)-5-*O*-*tert*-butyldimethylsilyl-D-gluconic Acid (22). DMSO (683 μL, 9.62 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of oxalyl chloride (413 μL, 4.81 mmol) in CH_2Cl_2 (20 mL) at −65 °C. After 5 min, alcohol **20** (1149 mg, 1.60 mmol) dissolved in CH_2Cl_2 (30 mL) was introduced and the reaction mixture was stirred for 1.5 h at that temperature. Et_3N (3.0 mL) was then added, and the mixture was allowed to warm to 0 °C. After the reaction was quenched with chilled water (50 mL), stirring was continued for 15 min at ambient temperature. The aqueous phase was extracted with ethyl acetate (2 × 50 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated. The residue was dried in vacuo (10^{-2} mbar) for 2 h to yield the crude aldehyde as a yellow syrup. This compound was dissolved in THF (60 mL) and poured into a solution of $NaClO_2$ (724 mg, 8.00 mmol) and sulfamic acid (680 mg, 7.00 mmol) in water (20 mL). After 10 min of stirring at rt, the reaction was quenched with aqueous $NaHCO_3$/NaCl, the aqueous phase was extracted with ethyl acetate (1 × 100 mL, 2 × 50 mL), the combined organic layers were dried over Na_2SO_4, the solvents were evaporated, and the residue was chromatographed (hexane/ethyl acetate 4:1, 2:1, 2:1 + 1% acetic acid) affording compound **22** as a colorless syrup (1095 mg, 93%). Traces of acetic acid were removed by repeated azeotropic distillation with toluene. **22**: $[\alpha]^{25}_D$ +4.9° (c 14, $CHCl_3$); IR 2930, 1754, 1725, 1517, 1262, 1139, 1094, 836, 735, 698; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19−7.31 (m, 15H), 6.85−6.89 (m, 2H), 6.75 (m, 1H), 4.69−4.79 (m, 4H), 4.57 (A part of AB, J = 11.0, 1H), 4.42−4.46 (m, 3H), 4.26 (d, J = 3.7, 1H), 4.14 (dd, J = 6.6, 3.7, 1H), 4.03 (m, 1H), 3.97 (dd, J = 6.6, 3.9, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.73 (dd, J = 9.7, 4.8, 1H), 3.50 (dd, J = 9.7, 5.1, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.5, 148.9, 148.9, 138.6, 138.0, 137.7, 129.4, 128.2, 128.1, 128.1, 127.8, 127.6, 127.6, 127.5, 127.3, 120.9, 111.7, 110.9, 81.0, 79.6, 77.9, 75.2, 74.8, 73.2, 73.1, 71.6, 55.8, 55.7, 25.8, 18.0, −4.6, −4.8; MS m/z (rel intensity) 579 ([M − $C_9H_{11}O_2$]$^+$, 1), 241 (14), 181 (10), 151 (100), 91 (90); $C_{42}H_{54}O_9Si$ (730.97) calcd C 69.01 H 7.45, found C 69.16, H 7.45.

2-Benzyloxy-6-{(16*R*)-[3,4,6-tri-*O*-benzyl-5-*O*-*tert*-butyldimethylsilyl-D-gluconoyloxy]heptadecyl}benzoic Acid Benzyl Ester (26). A solution of acid **22** (1044 mg, 1.43 mmol) and 1-dimethylamino-1-chloro-2-methyl-1-propene **24** (381 mg, 2.86 mmol)[18] in CH_2Cl_2 (15 mL) was stirred for 1.5 h at rt. The solvent was stripped off and the excess of Ghosez's reagent was removed in vacuo (2 h, 10^{-2} mbar). To a solution of the crude acid chloride **23** thus obtained in CH_2Cl_2 (20 mL) were added alcohol **10** (682 mg, 1.19 mmol) and DMAP (219 mg, 1.79 mmol) at 0 °C. The mixture was stirred overnight at rt and quenched with aqueous $NaHCO_3$/NaCl (20 mL), the aqueous phase was extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated. Flash chromatography (hexane/ethyl acetate 4:1) afforded ester **25** as a colorless syrup (1468 mg). Extensive chromatography was necessary to obtain an analytically pure sample of this product which exhibits the following properties: $[\alpha]^{25}_D$ −9.4 (c 3.3, $CHCl_3$); IR 3526, 2926, 2854, 1733, 1454, 1266, 1109, 1067, 837, 735, 697; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23−7.35 (m, 26H), 6.78 (m, 2H), 5.32 (s, 2H), 5.06 (s, 2H), 4.91 (m, 1H), 4.79−4.84 (m, 2H), 4.62 (B part of AB, J = 11.2, 1H), 4.39−4.56 (m, 4H), 4.19 (m, 1H), 4.08 (dA part of AB, J = 8.0, 1.6, 1H), 3.96 (dB part of AB, J = 8.0, 1.9, 1H), 3.79 (dd, J = 9.5, 6.8, 1H), 3.52 (dd, J = 9.5, 5.5, 1H), 3.21 (bs, 1H, OH), 2.52 (m, 2H), 1.15−1.55 (bs, 31H), 0.90 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 168.2, 155.4, 141.6, 138.9, 138.5, 138.3, 136.8, 135.7, 130.1, 128.6, 128.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 127.3, 127.1, 124.0, 121.8, 109.9, 83.3, 81.0, 74.9, 74.5, 73.3, 73.1, 73.0, 71.6, 71.4, 70.4, 66.9, 35.7, 33.4, 31.2, 29.7, 29.6, 29.6, 29.4, 29.4, 25.9, 25.3, 19.6, 18.1, −4.8, −4.8; MS (ESI) 1152 ([M + NH_4]$^+$); $C_{71}H_{94}O_{10}Si$ (1135.60) calcd C 75.10, H 8.34, found C 74.87, H 8.31.

For preparative purposes, crude **25** was used in the next step. DDQ (389 mg, 1.71 mmol) was added to a solution of **25** (1468 mg) as obtained above in CH_2Cl_2 (40 mL) and water (4 mL) at 0 °C, and the mixture was stirred for 3.5 h while reaching ambient temperature. The reaction was quenched with aqueous $NaHCO_3$/NaCl (50 mL), and the layers were separated. Standard extractive workup followed by flash chromatography (hexane/ethyl acetate 10:1 → 4:1) afforded compound **26** as a colorless syrup (1007 mg, 74% over the last three steps): $[\alpha]^{25}_D$ +5.5° (c 7.5, $CHCl_3$); IR 2926, 2854, 1731, 1583, 1454, 1266, 1107, 836, 736, 697; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19−7.36 (m, 26H), 6.94 (d, J = 1.8, 1H), 6.88 (dd, J = 8.1, 1.8, 1H), 6.74−6.81 (m, 3H), 5.33 (s, 2H), 5.06 (s, 2H), 4.91 (m, 1H), 4.61 and 4.82 (AB, J = 11.3, 2H), 4.73−4.77 (m, 2H), 4.68 (B part of AB, J = 11.2, 1H), 4.43−4.46 (m, 3H), 4.26 (d, J = 4.0, 1H), 4.12 (dd, J = 6.8, 4.0, 1H), 4.05 (m, 1H), 3.89 (dd, J = 6.8, 3.8, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.72 (dd, J = 9.8, 4.5, 1H), 3.47 (m, 1H), 2.52 (m, 2H), 1.15−1.55 (bs, 31H), 0.82 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 168.2, 155.4, 148.9, 148.7, 141.6, 139.0, 138.8, 138.3, 136.8, 135.7, 130.1, 130.1, 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 128.0, 127.9, 127.7, 127.5, 127.5, 127.4, 127.2, 127.1, 127.1, 124.0, 121.8, 120.9, 111.8, 110.8, 109.9, 81.6, 80.4, 79.1, 75.0, 74.7, 73.4, 73.2, 72.7, 72.1, 71.9, 70.4, 66.9, 55.8, 55.7, 35.8, 33.4, 31.2, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 25.9, 25.4, 19.8, 18.0, −4.5, −4.7; MS (ESI) 1302 ([M + NH_4]$^+$), 1307 ([M + Na]$^+$), 1323 ([M + K]$^+$); $C_{80}H_{104}O_{12}Si$ (1285.78) calcd C 74.73, H 8.15, found C 74.62, H 8.12.

2-Benzyloxy-6-{(16*R*)-[2-*O*-acetyl-3,4,6-tri-*O*-benzyl-5-*O*-*tert*-butyldimethylsilyl-D-mannonoyloxy]heptadecyl}-benzoic Acid Benzyl Ester (28). Trifluoromethanesulfonic acid anhydride (400 μL, 2.44 mmol) was added dropwise to a solution of gluconate **26** (1007 mg, 0.89 mmol) in CH_2Cl_2 (20 mL) and pyridine (5 mL) at 0 °C, and stirring was continued at that temperature for 15 min. The reaction mixture was quenched with aqueous $NaHCO_3$ (15 mL) and extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvents followed by flash chromatography (hexane/ethyl acetate 15:1 → 10:1) provided the corresponding triflate **27** as a colorless syrup (1009 mg, 90%).

A solution of triflate **27** (1009 mg, 0.80 mmol) in DMF (15 mL) was treated with KOAc (1000 mg, 10.19 mmol) for 1 h at rt. Water (30 mL) was added, the mixture was extracted with ethyl acetate (3 × 50 mL), the combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexane/ethyl acetate 10:1) affording acetate **28** as a colorless syrup (690 mg, 74%): $[\alpha]^{25}_D$ −11.9° (c 9.7, $CHCl_3$); IR 2927, 2854, 1732, 1454, 1265, 1107, 1065, 837, 736, 697; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20−7.35 (m, 26H), 6.78 (m, 2H), 5.33 (s, 2H), 5.26 (d, J = 2.5, 1H), 5.06

(s, 2H), 4.99 (m, 1H), 4.66−4.77 (m, 4H), 4.45 (s, 2H), 4.17 (m, 1H), 4.03 (dA, J = 7.6, 2.5, 1H), 3.93 (dB, J = 7.6, 3.0, 1H), 3.79 (dd, J = 9.6, 5.7, 1H), 3.53 (dd, J = 9.6, 5.4, 1H), 2.52 (m, 2H), 1.97 (s, 3H), 1.14−1.60 (bs, 28H), 1.15 (d, J = 6.3, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 168.2, 167.5, 155.5, 141.9, 141.6, 139.1, 138.5, 138.2, 136.8, 135.7, 130.1, 128.6, 128.4, 128.4, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.4, 127.3, 127.1, 124.0, 121.8, 109.9, 82.5, 79.9, 75.2, 74.4, 73.7, 73.3, 72.7, 72.6, 71.7, 70.4, 66.9, 35.9, 33.4, 31.2, 29.7, 29.6, 29.5, 29.5, 25.8, 25.2, 20.7, 19.7, 18.0, −4.6, −4.7; MS (ESI) 1194 ([M + NH_4]$^+$); $C_{73}H_{96}O_{11}Si$ (1177.64) calcd 74.45, H 8.22, found C 74.54, H 8.26.

Compound 30. KOAc (450 mg, 4.59 mmol) was added to a solution of the triflate **27** (702 mg, 0.55 mmol, prepared as described above) in DMF (10 mL) at 0 °C. The mixture was allowed to reach rt over a period of 2 h. A standard extractive workup followed by flash chromatography (hexane/ethyl acetate 4:1) afforded the tetrahydrofuran derivative **30** as a colorless syrup (414 mg, 75%) as well as compound **28** as a minor byproduct (117 mg, 18%). Data of compound **30**: $[\alpha]^{25}_D$ +8.9° (*c* 6.4, $CHCl_3$); IR 2926, 2854, 1728, 1583, 1454, 1269, 1108, 736, 697; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18−7.34 (m, 26H), 6.75−6.81 (m, 2H), 5.32 (s, 2H), 5.05 (s, 2H), 4.95 (m, 1H), 4.60−4.64 (m, 2H), 4.55 (s, 2H), 4.46−4.50 (m, 3H), 4.39 (m, 1H), 4.31 (m, 1H), 4.03 (dd, J = 4.2, 1.8, 1H), 3.64 (dA part of AB, J = 10.3, 5.4, 1H), 3.60 (dB part of AB, J = 10.3, 5.8, 1H), 2.52 (m, 2H), 1.13−1.67 (bs, 28H), 1.18 (d, J = 6.2, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 168.2, 155.4, 141.8, 141.5, 138.1, 137.6, 137.3, 136.8, 135.7, 130.1, 128.5, 128.4, 128.3, 128.1, 127.8, 127.8, 127.7, 127.6, 127.5, 127.0, 124.0, 121.7, 109.9, 86.6, 83.6, 82.9, 81.4, 73.3, 72.4, 71.7, 71.6, 70.3, 69.7, 66.9, 35.7, 33.4, 31.2, 29.6, 29.6, 29.5, 29.5, 29.4, 25.3, 19.8; MS (ESI) 1020 ([M + NH_4]$^+$), 1025 ([M + Na]$^+$), 1041 ([M + K]$^+$); $C_{65}H_{78}O_9$ (1003.32) calcd C 77.81, H 7.84, found C 77.72, H 7.84.

2-Benzyloxy-6-{(16*R*)-[2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-mannonoyloxy]heptadecyl}benzoic Acid Benzyl Ester (29). BF_3·OEt_2 (300 μL, 2.289 mmol) was added to a solution of compound **28** (576 mg, 0.489 mmol) in CH_2Cl_2 (20 mL) at 0 °C, and the mixture was stirred for 1.5 h while reaching ambient temperature. After addition of aqueous $NaHCO_3$/NaCl (20 mL), the aqueous phase was extracted with ethyl acetate (3 × 30 mL), the combined organic layers were dried over Na_2SO_4, the solvents were removed in vacuo, and the residue was chromatographed (hexane/ethyl acetate 4:1 → 2:1) yielding **29** as a colorless syrup (430 mg, 83%): $[\alpha]^{20}_D$ +2.6° (*c* 11.9, $CHCl_3$); IR 3544, 2926, 2854, 1734, 1454, 1267, 1107, 1065, 737, 698; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17−7.38 (m, 26H), 6.80 (d, J = 7.8, 1H), 6.76 (d, J = 8.3, 1H), 5.36 (d, J = 4.6, 1H), 5.32 (s, 2H), 5.06 (s, 2H), 4.93 (m, 1H), 4.72 (A part of AB, J = 11.5, 1H), 4.62−4.66 (m, 2H), 4.45−4.54 (m, 3H), 4.14 (m, 1H), 4.02 (m, 1H), 3.81 (dd, J = 7.4, 4.8, 1H), 3.58−3.68 (m, 2H), 2.58 (bs, 1H, OH), 2.52 (m, 2H), 2.03 (s, 3H), 1.14 (d, J = 6.3, 3H), 1.09−1.73 (bs, 28H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 168.2, 168.1, 155.4, 141.6, 138.0, 137.8, 137.7, 136.8, 135.7, 130.1, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 127.8, 127.7, 127.7, 127.0, 124.0, 121.8, 109.9, 78.9, 78.4, 74.3, 74.1, 73.4, 72.8, 72.6, 70.8, 70.4, 66.9, 35.7, 33.4, 31.2, 29.6, 29.6, 29.5, 29.5, 29.4, 25.1, 20.6, 19.5; MS (ESI) 1080 ([M + NH_4]$^+$), 1085 ([M + Na]$^+$), 1101 ([M + K]$^+$); $C_{67}H_{82}O_{11}$ (1063.37) calcd C 75.68, H 7.77, found C 75.71, H 7.78.

Disaccharide 31. A mixture of alcohol **29** (200 mg, 0.19 mmol), van Boeckel catalyst (420 mg),[22] and powdered molecular sieves (3 Å) in CH_2Cl_2 (5 mL) was stirred for 10 min at rt. After the solution was cooled to −5 °C, a solution of bromide **16** (300 mg, 0.51 mmol) in CH_2Cl_2 (3 mL) was slowly added and stirring was continued at that temperature for 45 min. The catalyst and the molecular sieves were filtered off and thoroughly rinsed with ethyl acetate. Evaporation of the combined filtrates followed by flash chromatography (hexane/ethyl acetate 4:1) of the remaining residue afforded glycoside **31** (218 mg, 74%) as a colorless syrup: $[\alpha]^{25}_D$ +10.8° (*c* 6.2, $CHCl_3$); IR 2926, 2854, 1743, 1454, 1369, 1269, 1266, 1063, 1028, 737, 698; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17−7.39 (m, 41H), 6.79 (d, J = 7.7, 1H), 6.75 (d, J = 8.3, 1H), 5.32 (s, 2H), 5.21 (d, J = 2.0, 1H), 5.00−5.05 (m, 3H), 4.92 (m, 1H), 4.77−4.83 (m, 2H), 4.72 (d, J = 8.0, 1H), 4.50−4.67 (m, 6H), 4.50 (A part of AB, J = 12.1, 1H), 4.38−4.42 (m, 3H), 4.20 (m, 1H), 4.03 (m, 2H), 3.84 (m, 1H), 3.55−3.79 (m, 7H), 3.43 (m, 1H), 2.52 (m, 2H), 1.94 (s, 3H), 1.13 (d, J = 6.3, 3H), 1.07−1.72 (bs, 28H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 168.1, 168.0, 165.8, 155.4, 141.5, 138.5, 138.1, 138.1, 138.0, 137.9, 137.8, 136.8, 135.7, 130.1, 128.5, 128.4, 128.3, 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.5, 127.4, 127.4, 127.0, 123.9, 121.7, 109.8, 100.2, 82.6, 79.8, 79.1, 78.7, 77.9, 75.0, 74.9, 74.5, 74.2, 73.4, 73.3, 72.8, 70.3, 68.5, 66.8, 40.5, 35.7, 33.4, 31.2, 29.6, 29.5, 29.5, 29.4, 29.4, 25.1, 20.4, 19.5; gated NMR ($CDCl_3$, 75 MHz) $J_{C1',H1'}$ = 160.2; MS (ESI) 1570 ([M + Na]$^+$); $C_{96}H_{111}ClO_{17}$ (1572.37) calcd C 73.33, H 7.12, found C 73.39, H 7.12.

Disaccharide 32. A solution of glycoside **31** (234 mg, 0.15 mmol), thiourea (170 mg, 2.23 mmol), and $NaHCO_3$ (94 mg, 1.12 mmol) in CH_2Cl_2 (2 mL) and EtOH (10 mL) was refluxed for 4 h. After addition of ethyl acetate (50 mL), the mixture was washed with water (2 × 30 mL) and the organic layers were dried over Na_2SO_4. Removal of the solvents followed by flash chromatography (hexane/ethyl acetate 4:1) provided compound **32** as a colorless syrup (167 mg, 75%): $[\alpha]^{25}_D$ −1.8° (*c* 6.6, $CHCl_3$); IR 3456, 2925, 2854, 1734, 1454, 1268, 1109, 1065, 736, 697; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14−7.41 (m, 41H), 6.79 (d, J = 6.8, 1H), 6.76 (d, J = 8.3, 1H), 5.32 (s, 2H), 5.30 (d, J = 4.2, 1H), 5.05 (s, 2H), 4.79 and 4.99 (AB, J = 11.2, 2H), 4.93 (m, 1H), 4.53 and 4.84 (AB, J = 10.9, 2H), 4.60−4.72 (m, 4H), 4.37−4.49 (m, 5H), 4.14−4.20 (m, 2H), 4.01 (m, 1H), 3.80 (dd, J = 10.5, 3.0, 1H), 3.68 (dd, J = 10.5, 6.2, 1H), 3.50−3.63 (m, 5H), 3.41 (m, 1H), 2.52 (m, 2H), 1.97 (s, 3H), 1.19−1.65 (m, 28H), 1.12 (d, J = 6.2, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 168.2, 168.1, 155.4, 141.6, 138.9, 138.3, 138.2, 138.2, 138.1, 137.5, 136.8, 135.7, 130.1, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 127.5, 127.0, 124.0, 121.8, 79.2, 78.9, 78.7, 77.1, 75.4, 75.2, 75.0, 74.8, 74.5, 74.0, 73.5, 73.4, 72.8, 70.4, 69.4, 69.0, 66.9, 35.8, 33.4, 31.2, 29.7, 29.5, 29.5, 29.4, 29.4, 25.2, 20.5, 19.6; MS (ESI) 1512 ([M + NH_4]$^+$), 1517 ([M + Na]$^+$), 1533 ([M + K]$^+$); $C_{94}H_{110}O_{16}$ (1495.89) calcd C 75.48, H 7.41, found C 75.42, H 7.40.

Disaccharide 34. Triflic anhydride (400 μL, 2.437 mmol) was added to a solution of compound **32** (273 mg, 0.183 mmol) in CH_2Cl_2 (8 mL) and pyridine (2 mL) at 0 °C. The mixture was warmed to ambient temperature and stirred for 45 min. The reaction mixture was quenched with aqueous $NaHCO_3$/NaCl (15 mL) and extracted with ethyl acetate (3 × 30 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated. Excess pyridine was removed by repeated azeotropic distillation with toluene. The residue was then purified by flash chromatography (hexane/ethyl acetate 10:1 → 4:1) affording triflate **33** as a pale yellow syrup (226 mg, 78%) which was processed without delay. A solution of this triflate (224 mg, 0.140 mmol) and Bu_4NOAc (450 mg, 1.396 mmol) in toluene (10 mL) was placed in an ultrasound cleaning bath (Brandelin Sonorex RK 514) for 16 h. Evaporation of the solvent followed by flash chromatography (hexane/ethyl acetate 4:1) gave compound **34** as a colorless syrup (205 mg, 95%): $[\alpha]^{20}_D$ −16.6° (*c* 6.6, $CHCl_3$); IR 2926, 2854, 1743, 1454, 1371, 1266, 1237, 1107, 1066, 737, 698; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15−7.38 (m, 41H), 6.79 (d, J = 7.7, 1H), 6.76 (d, J = 8.3, 1H), 5.64 (bd, J = 3.2, 1H), 5.32 (s, 2H), 5.20 (d, J = 5.0, 1H), 5.05 (s, 2H), 4.92 (m, 1H), 4.83 (A part of AB, J = 10.9, 1H), 4.60−4.76 (m, 6H), 4.38−4.54 (m, 6H), 4.25 (m, 1H), 4.08 (m, 1H), 3.99 (m, 1H), 3.88 (dd, J = 10.6, 2.9, 1H), 3.62−3.78 (m, 4H), 3.55 (dd, J = 9.3, 3.2, 1H), 3.38 (m, 1H), 2.52 (m, 2H), 2.12 (s, 3H), 1.96 (s, 3H), 1.11 (d, J = 6.3, 3H), 1.14−1.74 (m, 28H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 169.7, 168.3, 168.2, 155.4, 141.6, 138.4, 138.3, 138.2, 137.7, 136.8, 135.7, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.5, 127.4, 127.4, 127.0, 124.0, 121.8, 109.9, 98.3, 80.5, 79.2, 78.0, 75.5, 75.1, 74.5, 74.3, 73.3, 73.2, 73.0, 72.7, 71.4, 70.4, 70.2, 69.2, 68.3, 66.9, 35.8, 33.4,

31.2, 29.7, 29.5, 29.5, 29.4, 25.2, 21.0, 20.5, 19.5; gated NMR ($CDCl_3$, 75 MHz) $J_{C1',H1'} = 156.8$; $C_{96}H_{112}O_{17}$ (1537.92) calcd C 74.98, H 7.34, found C 75.08, H 7.23.

Caloporoside (1). A solution of compound **34** (141 mg, 0.092 mmol) in MeOH (20 mL) and acetic acid (200 μL) was stirred under H_2 (1 bar) in the presence of Pd on charcoal (50 mg, 5% w/w) for 22 h. The catalyst was filtered off and carefully rinsed with MeOH. The solvent was evaporated, and the remaining residue was dried in vacuo (10^{-2} mbar), thus affording caloporoside **1** as a colorless waxy solid (72 mg, 96%): $[\alpha]^{23}_D$ −33.0° (*c* 2.2, MeOH; lit.[9] $[\alpha]^{20}_D$ −32°, *c* 1.15, MeOH); IR 3424, 2924, 2853, 1741, 1658, 1455, 1378, 1245, 1070, 1030; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.28 (m, 1H), 6.77 (m, 2H), 5.42 (d, $J = 3.3$, 1H), 5.01 (m, 1H), 4.95 (bs, 1H), 4.84 (d, $J = 9.6$, 1H), 4.33 (d, $J = 9.6$, 1H), 3.92−3.99 (m, 3H), 3.59−3.71 (m, 4H), 3.51 (m, 1H), 3.36 (m, 1H), 2.93 (m, 2H), 2.19 (s, 3H), 2.12 (s, 3H), 1.51−1.76 (bs, 4H), 1.12−1.51 (bs, 24H), 1.27 (d, $J = 6.3$, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.2 (s), 172.1 (s), 171.9 (s), 162.5 (s), 147.1 (s), 134.3 (d), 123.2 (d), 116.0 (d), 99.5 (d), 78.4 (d), 78.4 (d), 78.3 (d), 73.9 (d), 73.8 (d), 73.7 (d), 70.4 (d), 69.9 (d), 69.7 (d), 63.6 (t), 63.4 (t), 37.3 (t), 37.0 (t), 33.5 (t), 31.1 (t), 31.1 (t), 31.0 (t), 30.9 (t), 30.8 (t), 26.6 (t), 21.5 (q), 20.7 (q), 20.5 (t); gated NMR (CD_3OD, 100 MHz) $J_{C1',H1'} = 161.1$; HRMS ($C_{17}H_{64}NaO_{17}$) calcd 839.404119, found 839.402645.

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