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Total Synthesis of Candicanoside A, a Rearranged Cholestane Disaccharide, and Its 4′′-*O*-(*p*-Methoxybenzoate) Congener

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Candicanoside A (**1**) and its 4′′-*O*-(*p*-methoxybenzoate) derivative **2** are congeners of the novel 24(23→22)*abeo*-cholestane glycosides that occur in the genus *Ornithogalum* indigenous to Southern Africa and have remarkable cytostatic activities. These two saponins have been synthesized starting from dehydroisoandrosterone, D-glucose, and L-rhamnose in 37 and 44 steps, respectively. The reaction protocols feature a stereocontrolled stepwise glycosylation with glycosyl imidates as the donors. The synthesis of the rearranged steroid aglycon employs a 20-alkoxy radical-mediated functionalization of the angular 18-methyl group, a Johnson–Claisen rearrangement for the alkylation at C-20, an aldol condensation at C-22, and a photodeconjugation of an α,β-unsaturated lactone as the key steps.

Introduction

During the extensive research into the antitumor components of the genus *Ornithogalum* indigenous to Southern Africa,[1] Mimaki, Sashida, and co-workers disclosed a group of minor saponins that contain rearranged steroidal side-chains.[2,3] These novel 24(23→22)*abeo*-cholestane glycosides, such as **3**–**6** (Figure 1), exhibit considerable inhibitory activity against the growth of tumor cells depending on their saccharide structures. Thus, the α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosides (e.g., **3** and **5**) are inactive, whereas their 4′′-*O*-(*p*-methoxybenzoate) (MBz) derivatives (**4** and **6**) are highly cytostatic towards human leukemia HL-60 cells (IC_{50} = 0.019 and 0.052 μM, respectively).[2d,2e] Candicanoside A (**1**),[3] isolated from the fresh bulbs of *Galtonia candicans*, is unique in this family of saponins with a fused-ring scaffold resulting from acetal formation between the aldehyde group at C-23 and the hydroxy groups at C-16 and C-18. In addition, it is the only congener to show remarkable cytostatic activity (IC_{50} = 0.032 μM against the HL-60 cells) without benzoate substitution on the saccharide moiety.[2,3] Herein we report a full account of the total synthesis of Candicanoside A (**1**) and its 4′′-*O*-(*p*-methoxybenzoate) derivative **2**.[4]

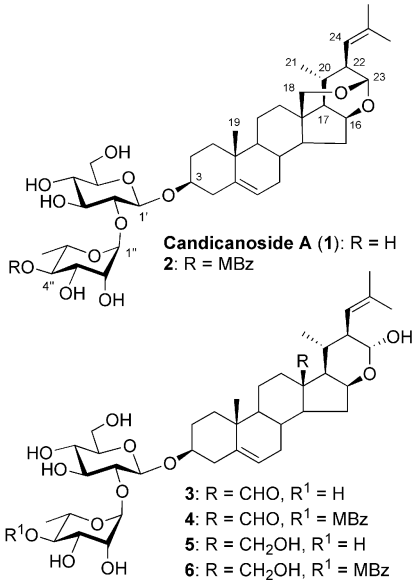

Figure 1. Candicanoside A (**1**) and its congeners **2**–**6**.

Results and Discussion

The assembly of the target disaccharide saponin **1** demands a mild and stereocontrolled approach to the glycosylation of the cholestane aglycon **7**, which contains two double bonds and an acetal function.[5] Thus, stepwise glycosylation with 3,4,6-tri-*O*-acetyl-2-*O*-[2-(azidomethyl)-benzoyl]-D-glucopyranosyl trichloroacetimidate (**8**) and 2,3,4-tri-*O*-benzoyl-L-rhamnopyranosyl trichloroacetimidate (**9**), which requires only a catalytic amount of the Lewis acid to promote the reaction,[6] was planned (Figure 2). The

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acetyl (Ac) and benzoyl (Bz) groups were permanent protecting groups; the 2-(azidomethyl)benzoyl (AZMB) group,[7] selectively removable in the presence of the acetyl groups, was chosen as a temporary protecting group that is able to serve as a neighboring participating group to control the construction of the 1,2-*trans*-glycosidic bond and meanwhile minimize the formation of the corresponding orthoester.[8]

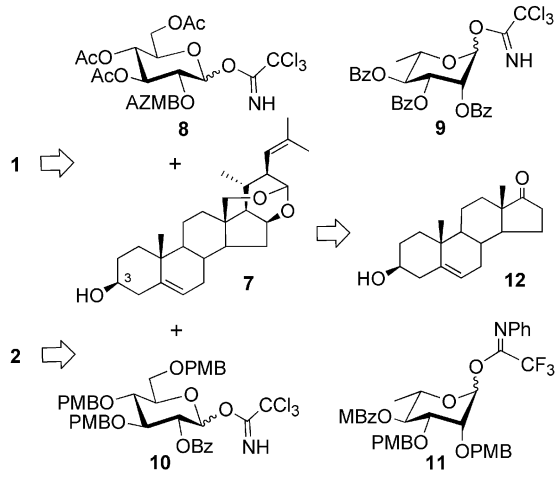


Figure 2. Retrosynthesis of the (1→2)-linked disaccharides **1** and **2**.

The assembly of the 4′′-*O*-benzoate congener **2**, however, requires a totally different arrangement of protecting groups. Thus, 3,4,6-tri-*O*-(*p*-methoxybenzyl)-2-*O*-benzoyl-D-glucopyranosyl trichloroacetimidate (**10**) and 2,3-di-*O*-(*p*-methoxybenzyl)-4-*O*-(*p*-methoxybenzoyl)-L-rhamnopyranosyl trifluoroacetimidate (**11**) were designed as the monosaccharide donors. The orthogonal *p*-methoxybenzyl (PMB) and Bz groups were chosen as the permanent and temporary protecting groups, respectively. Because of the poor stability of the armed rhamnosyl trichloroacetimidate, the trifluoroacetimidate counterpart **11** was used instead.[9]

Attempts at the Synthesis of the Steroid Aglycone 7

Starting from the cheap industrial material dehydroisoandrosterone **12**, we planned to commence the synthesis of the novel steroid **7** by installation of C-20 and C-21 at C-17 followed by elaboration of the 16,18,20-triol derivative **C** (Figure 3). Acetal formation with the 16,18-dihydroxy groups would provide compound **B**, which might undergo an intramolecular S_N2 substitution reaction to furnish the required fused-ring scaffold.

Thus, conversion of the steroidal 3-hydroxy-5,6-ene functionality in **12** into the 3,5-cyclo-6β-methoxy form (TsCl, pyridine, room temp., overnight; KOAc, HOMe, reflux, 5 h, 81%) followed by Wittig olefination at the C-17 ketone (Ph_3PEtBr, *t*BuOK, THF, reflux, 4 h, 84%) provided **13** (20-H: 5.11 ppm, qd, J = 7.2, 2.1 Hz; Scheme 1).[10] The allylic 16-CH_2 in **13** was oxidized with SeO_2 and *t*BuOOH (CH_2Cl_2, 0 °C, 92%).[10] The resulting 16-α-hydroxy group (16-H: 4.44 ppm, br. d, J = 4.0 Hz) was then reversed by Swern oxidation (DMSO, ClCOCOCl, CH_2Cl_2, –50 °C, 98%) and subsequent reduction ($NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF, 0 °C, 77%) to afford the 16-β-ol **14** (16-H: 4.35 ppm, t, J = 7.5 Hz) as the major product.[11] Protecting groups, including acetyl (Ac), triethylsilyl (TES), *tert*-butyldimethylsilyl (TBS), and benzyl (Bn), on the 16-β-OH of **14** were found susceptible to the hydroboration (BH_3 or 9-BBN)/oxidation (H_2O_2) process required to introduce a hydroxy group at C-20. Thus, 16β,20(*S*)-diol **15** was prepared from the corresponding 17(20)-ene-16-*O*-TES ether ($BH_3{\cdot}$THF, 45 °C; and then H_2O_2, Na_2CO_3, room temp.) stereoselectively in 92% yield (20-H: 4.11 ppm, m). Attempts to monoprotect the diol in **15** with TBS (TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C)[12] or the Bz group (Bu_2SnO, toluene, reflux; and then BzCl, THF, CH_2Cl_2, room temp.)[13] led to the 16β-*O*-TBS and -Bz derivative **16** (63%) or **17** (80%; 16-H: 5.64 ppm, m) as the major product, respectively. The structure of **16** was unambiguously confirmed by an X-ray diffraction analysis, which showed the β configuration of the 16-*O*-TBS ether and the *S* configuration at C-20 (Figure 4).[14]

The presence of 20-OH could facilitate the functionalization of the proximal 18-methyl group by 1,5-hydrogen transfer to the corresponding alkoxyl radical.[15] Thus, irradiation of **16** or **17** in the presence of iodine (1.0 equiv.) and (diacetoxyiodo)benzene (DIB) (1.1 equiv.) in cyclohexane with a 300-W tungsten lamp at room temp. provided the desired 18-iodide **18** (18-H: 3.91 and 3.46 ppm, 2 d, AB, J = 10.5 Hz) or **19** (18-H: 3.91 and 3.57 ppm, 2 d, AB, J = 10.5 Hz), respectively, albeit in moderate yields (22 and 44%, respectively).[16] Most of the starting materials were recovered, however, increasing the amounts of reagents or the reaction temperature led to more side-reactions. Addition of K_2CO_3 to the reaction mixture to neutralize the resulting acetic acid, which might affect the 3,5-cyclo-6-methoxy function in the substrate, raised the yield of **18** to 37%.[17] The use of other trivalent organoiodine reagents, that is, [bis(trifluoroacetoxy)iodo]benzene (TFIB) and iodosylbenzene (PhIO), led to similar results.[16] The 20-OH group should be blocked prior to hydrolysis of the 18-iodide

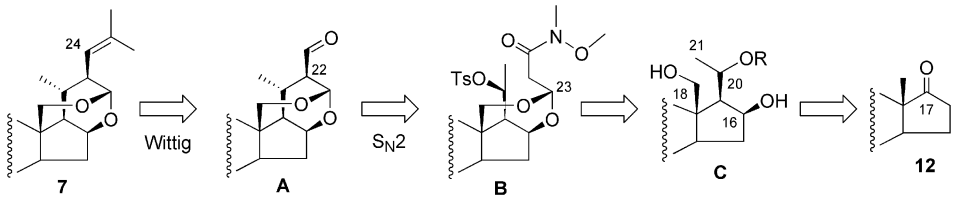
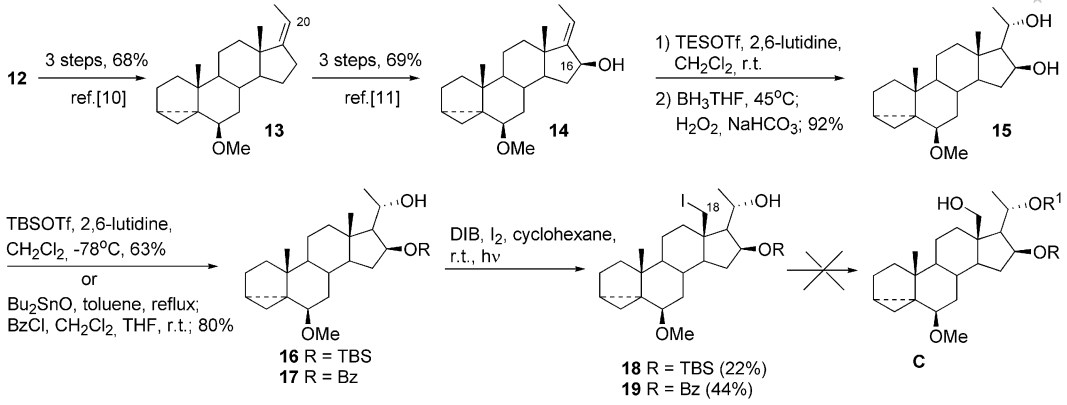


Figure 3. Retrosynthetic consideration of the steroid aglycon **7**.



Scheme 1. Attempts at the synthesis of the 16,18,20-triol derivative C.

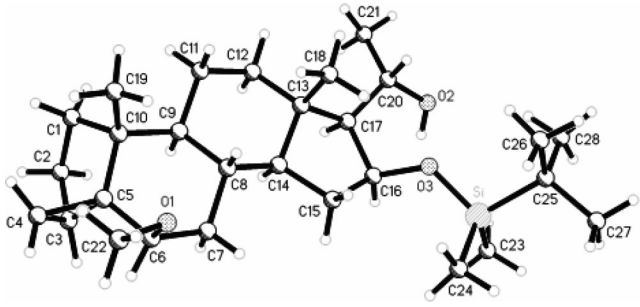


Figure 4. ORTEP drawing of compound **16**.

to avoid 18,20-anhydro formation. However, the 20-OH group in the 16β-*O*-TBS ether **18** was found to be inert towards protection with TBS or the methoxymethyl (MOM) group. Even acetylation under forced conditions (AcCl, pyridine, 50 °C, overnight) failed to provide the corresponding 20-*O*-acetate. In contrast, 20-OH in the 16β-*O*-Bz ester **19** was easily protected with a TBS or MOM group. Unfortunately, the resulting 16-*O*-Bz-20-*O*-TBS(or MOM)-18-iodide derivatives either stayed intact (Ag_2CO_3 or Ag_2O, dioxane, H_2O, 60 °C) or led to the 18,20-epoxy derivatives (mCPBA, CH_2Cl_2, H_2O, room temp.)[18] under hydrolytic conditions. These results might be explained by the stereohindrance of the 18-iodide in the presence of the proximal 16,17-β-substituents (Scheme 1).

Synthesis of the Steroid Aglycone 7

The previous attempts proved that the presence of the 16β-OR substituent affected the functionalization at the angular C-18 position. Thus, we planned to introduce 18-OH before elaboration of 16β-OH (Figure 5). C-22 and C-23 could then be installed at C-20 in diol **F** (possibly by allylic alkylation).[19] Introduction of the 16β-OH into **E** might facilitate lactone formation to give **D**, which could serve as the precursor to the target scaffold.

Thus, the (*Z*)-17(20)-olefin **13** was subjected to hydroboration (9-BBN, THF, room temp.) and oxidation (H_2O_2, NaOH, room temp.) to provide the 20-ol **20** stereoselectively (90%; 20-H: 3.71 ppm, m).[20] Irradiation of **20** in the presence of DIB and I_2 under a 300-W tungsten lamp for 30 min followed by oxidation of the 20-OH immediately with pyridinium chlorochromate (NaOAc, CH_2Cl_2, room temp.) provided the desired 18-iodo-20-ketone **21** (18-H: 3.36 and 3.21 ppm, 2 d, AB, J = 10.5 Hz) in a satisfactory 50% yield (cf. **16/17→18/19**).[17] Hydrolysis of the 18-iodide in **21** with AgOAc (dioxane, H_2O, 65 °C) proceeded smoothly, furnishing the 18,20-hemiketal **22** (18-H: 3.80 and 3.40 ppm, 2 d, AB, J = 9.0 Hz) in an excellent 92% yield (cf. **18/19→C**).[17] Reduction of **22** with $NaBH_4$ (CH_2Cl_2, MeOH, room temp.) yielded a mixture of the 18,20(*R*/*S*)-diols, which was subjected to selective acetylation (AcCl, pyridine, –20 °C) to provide the 18-acetoxy-20(*R*)-ol **23** (18-H: 4.40 and 3.90 ppm, 2 d, AB, J = 11.4 Hz; 20-H: 3.67 ppm, m) as an easily isolable major product (50% for two steps) (Scheme 2).[21]

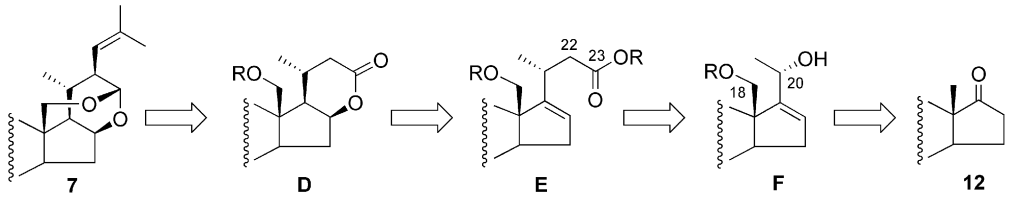
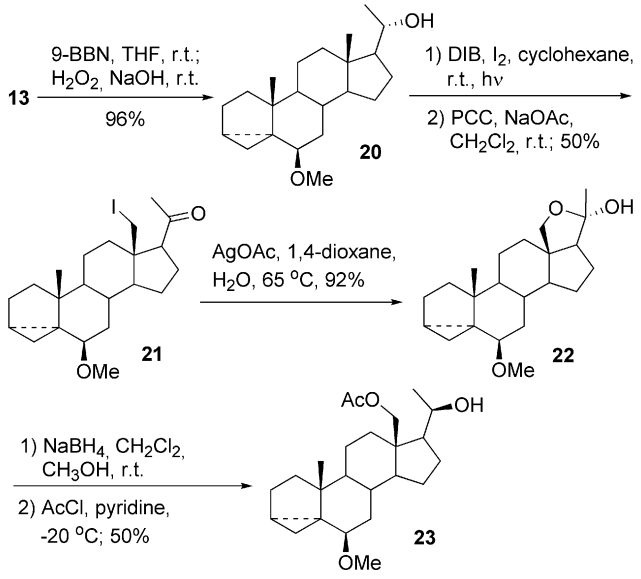


Figure 5. Reconsideration of the synthesis of the steroid aglycon **7**.



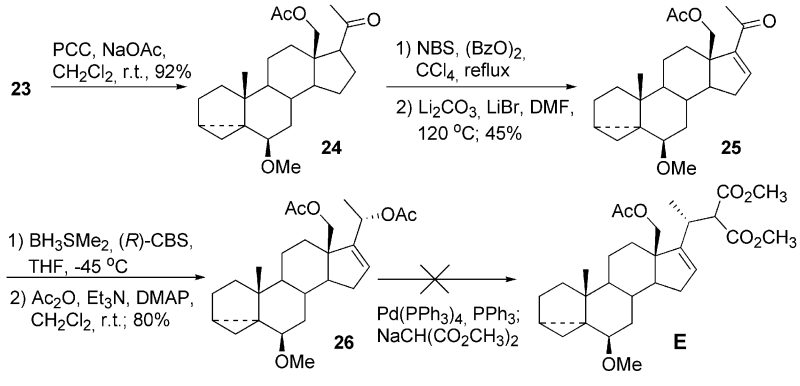
Scheme 2. Synthesis of the 18,20-diol derivative **23**.

The desired allylic 20-acetate **26** was then readily prepared from 20-ol **23** (Scheme 3); oxidation of **23** with PCC (NaOAc, CH_2Cl_2, room temp.) provided 20-ketone **24** (92%). Bromination [NBS, $(PhCO)_2$, CCl_4, reflux][22] of **24** followed by elimination (Li_2CO_3, LiBr, DMF, 120 °C)[23] yielded the enone **25** in 45% yield (16-H: 6.87 ppm, m). Reduction of the 20-ketone in **25** with $BH_3{\cdot}SMe_2$ in the presence of an equimolar amount of the chiral oxazaborolidine (*R*)-CBS {(*R*)-1-methyl-3,3-diphenyltetrahydro-3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole} (purchased from Aldrich) in THF at –45 °C afforded the 20(*S*)-alcohol,[24] which was directly subjected to acetylation to provide the acetate **26** (80% for two steps; 20-H: 5.61 ppm, m). Unfortunately, treatment of **26** with $[Pd(PPh_3)_4]$, Ph_3P, and $NaCH(CO_2CH_3)_2$ in THF did not lead to the alkylation product **E**. It might be that the additional 18-acetoxy group in **26**, compared with the steroid substrates used by Trost and Verhoeven for a similar alkylation,[25] led to the formation of a π-allylpalladium complex with the palladium at the α face and then prevented the approach of the dimethyl malonate from the β face.

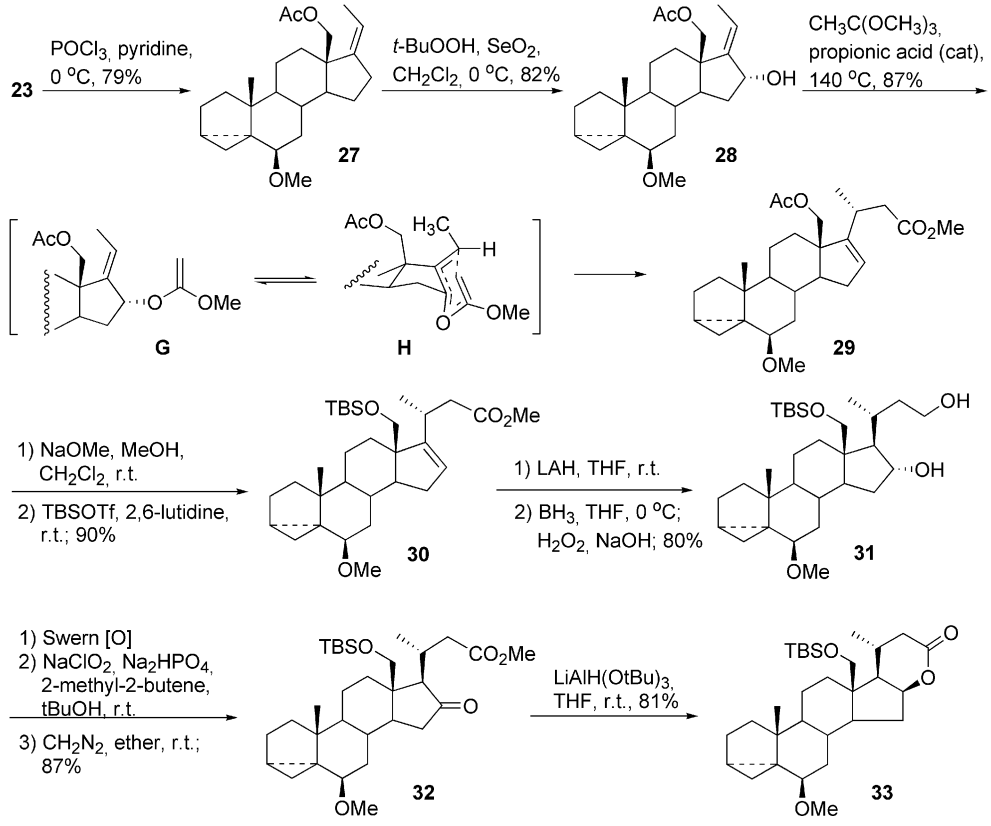
We then envisioned alkylation at C-20 from the α face of the steroid. Thus, Johnson–Claisen rearrangement of a 17(20)-en-16α-ol substrate (via the intermediates **G** and **H**, Scheme 4) turned out to be the choice. Treatment of 20-ol **23** with $POCl_3$ in pyridine at 0 °C yielded (*Z*)-17(20)-olefin **27** (79%; 20-H: 5.29 ppm, q, J = 7.2 Hz),[26] which was subjected to allylic oxidation with SeO_2 and *t*BuOOH (CH_2Cl_2, 0 °C) to afford the required 16α-ol **28** stereoselectively (82%; 16-H: 4.51 ppm, br. s).[27] Heating the allylic alcohol **28** at 140 °C with $CH_3C(OCH_3)_3$ in the presence of a catalytic amount of propionic acid gave the expected ester **29** (16-H: 5.53 ppm, br. s; H-21: 1.03 ppm, d, J = 7.2 Hz) in a stereoselective manner and in excellent yield (87%) with the 3,5-cyclo-6-methoxy protection intact.[28] The *R* configuration at C-20 is secured by the transition state **H** of the Johnson–Claisen rearrangement and confirmed by X-ray diffraction analysis of a derivative.[4]

Attempts to introduce a hydroxy group at C-16 in **29** by hydroboration/oxidation were found problematic under a variety of conditions; both the 18-*O*-Ac group and the C-23 ester could be reduced with boron hydrides. Thus, the 18-*O*-Ac group was removed (NaOMe, MeOH, CH_2Cl_2, room temp.) and the resulting hydroxy group was protected with TBS ether (TBSOTf, 2,6-lutidine, room temp.), leading to compound **30** (90%). Hydroboration/oxidation of **30** led to diol **31** (16-H: 4.22 ppm, m; 23-H: 3.86 and 3.73 ppm, m) as the major product in moderate yields (40–60%). Instead, the 23-ester in **30** was first reduced into the corresponding alcohol with $LiAlH_4$ (THF, room temp.) and subsequent treatment of the resulting 16(17)-en-23-ol with BH_3 (THF, 0 °C) followed by H_2O_2 and NaOH afforded the desired 16α,23-diol **31** stereoselectively in good yield (80%). We did try to protect the 18-OH with TBS ether instead of the acetate in **22**→**23**, however, the resulting 18-*O*-TBS-20-ol failed to provide the desired 17(20)-ene with $POCl_3$ (cf., **23**→**27**).

Swern oxidation of diol **31** (ClCOCOCl, DMSO, Et_3N, CH_2Cl_2) followed by further oxidation of the resulting 23-aldehyde ($NaClO_2$, Na_2HPO_4, 2-methyl-2-butene, *t*BuOH, room temp.) into the carboxylic acid[29] and subsequent methyl ester formation (CH_2N_2, ether, room temp.) provided the 16-keto 23-methyl ester **32** in 87% yield (for three



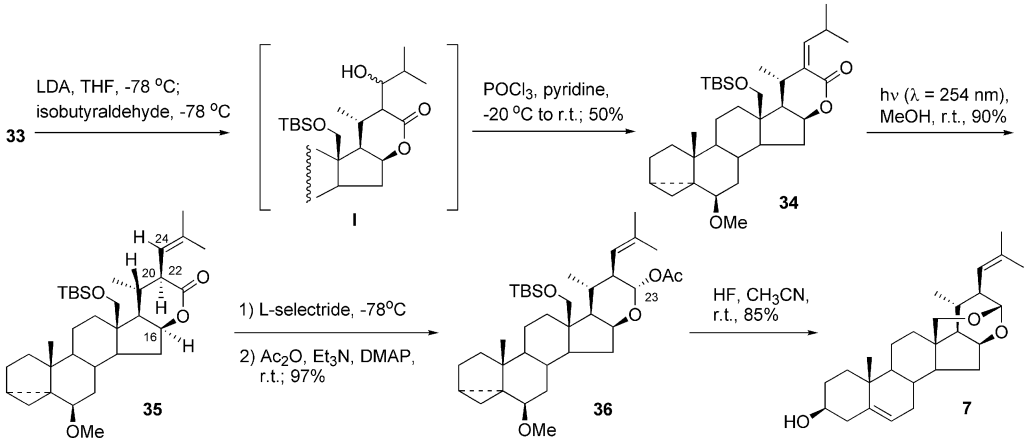
Scheme 3. Preparation of the allylic acetate **26** and attempts at allylic alkylation.



Scheme 4. Synthesis of lactone **33**.

steps). Selective reduction of the 16-ketone into the 16β-ol was achieved with $LiAlH(tBuO)_3$ in THF at room temp.[30] and simultaneous intramolecular lactone formation afforded **33** (81%; 16-H: 4.69 ppm, m). Other reducing agents, such as $NaBH_4/CeCl_3$[31] and L-selectride,[32] led to considerable amounts of the over-reduced acetal products.

The rest of the side-chain C-24–27 was then introduced onto C-22 (in lactone **33**) by aldol condensation (Scheme 5). Thus, treatment of **33** with LDA in THF at –78 °C followed by the addition of isobutyraldehyde provided a diastereoisomeric mixture of the aldol adduct **I**, which was dehydrated directly ($POCl_3$, pyridine, room temp.) to provide the α,β-unsaturated lactone **34** (24-H: 5.54 ppm, dd, J = 9.9, 2.7 Hz) in 50% yield. For the aldol reaction we also tried KHMDS as base,[33] the presence of HMPA in the solvent, and Bu_2BOTf/diisopropylethylamine,[34] but no improvements in the yields and stereoselectivities were found. Rearrangement of the conjugated 22,24-double bond (in lactone **34**) into the unconjugated 24,25-double bond was fortunately achieved by ultraviolet light (λ = 254 nm) irradiation,[35] providing **35** as a single stereoisomer (at C-22) in an excellent 90% yield. Other methods such as the use of DBU or LDA as base did not lead to the desired product.



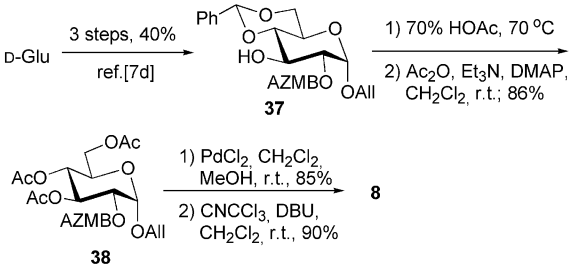
Scheme 5. Completion of the synthesis of the aglycon **7**.

NOE correlations between 22-H (δ = 2.89 ppm, dd, J = 12.3, 9.8 Hz) and 16-H (δ = 4.75 ppm, m), 24-H (δ = 5.06 ppm, d, J = 9.6 Hz) and 20-H (2.35–2.27 ppm, m), but not between 22-H and 20-H, were found, which proved the desired *R* configuration at C-22.

The lactone **35** was then reduced with L-selectride and the resulting lactol lithium was trapped in situ with acetic anhydride to give the acetate **36** in 97% yield (23-H: 5.73 ppm, d, J = 7.8 Hz).[36] Finally, HF (40% in water, CH_3CN, room temp.) was applied to remove the 18-*O*-TBS group in **36**. The desired 18,23-acetal was formed simultaneously. Meanwhile the 3-hydroxy-5,6-ene was recovered from the 3,5-cyclo-6-methoxy protection, which had stayed intact since the beginning of the synthesis, furnishing the desired aglycon **7** in 85% yield. The diagnostic ^{1}H NMR signals include those of 3-H (δ = 3.52 ppm, m), 6-H (δ = 5.37 ppm, m), 16-H (δ = 4.55 ppm, m), 18-H (3.98 and 3.46 ppm, 2 d, AB, J = 12.6 Hz), 23-H (δ = 4.99 ppm, d, J = 3.9 Hz), and 24-H (δ = 5.16 ppm, d, J = 9.6 Hz). Thus, the aglycon **7** was successfully elaborated in 23 steps and in 1.5% overall yield from the industrial material dehydroisoandrosterone **12**.

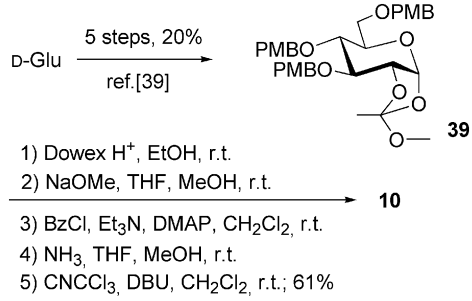
Preparation of the Monosaccharide Donors 8–11

The required perbenzoyl rhamnosyl trichloroacetimidate **9** was easily prepared from L-rhamnose in three steps (76% yield).[37] Three other imidate donors **8**, **10**, and **11** were synthesized as shown in Schemes 6, 7, and 8. The 2-OH of allyl 4,6-*O*-benzylidene-α-D-glucopyranoside could be selectively acylated with AZMBCl to give **37** (Scheme 6).[7d] Removal of the anomeric allyl group in the presence of a 4,6-*O*-benzylidene group might be problematic.[38] Thus, the 4,6-*O*-benzylidene group in **37** was removed (70% HOAc, 70 °C) and the resulting 3,4,6-triol was then acetylated (Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temp.) to provide **38** (86%). Cleavage of the α-allyl group in **38** proceeded well with $PdCl_2$ in a mixture of CH_2Cl_2 and MeOH at room temp. The resulting lactol was treated with $CNCCl_3$ in the presence of a catalytic amount of DBU (CH_2Cl_2, room temp.) to afford the desired α-trichloroacetimidate **8** in excellent yield (90%; 1-H: 6.71 ppm, d, J = 3.0 Hz).



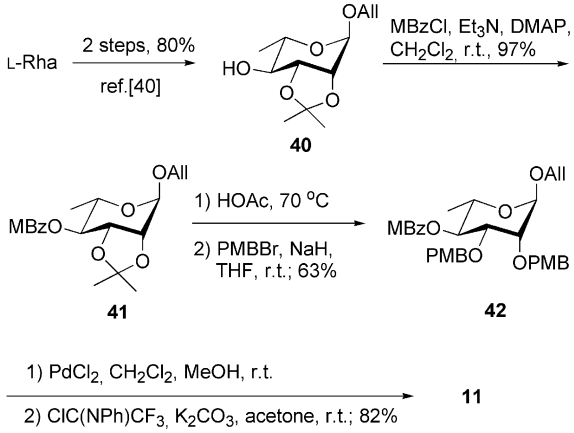
Scheme 6. Preparation of the glucopyranosyl trichloroacetimidate **8**.

In the synthesis of the glucopyranosyl trichloroacetimidate **10**, the 1,2-OH groups of glucopyranose were distinguished from the 3,4,6-OH groups by 1,2-orthoester formation (Scheme 7). Thus, compound **39** was prepared from D-glucose in five steps (20%) by a literature procedure.[39] Then 3,4,6-tri-*O*-PMB-1,2-orthoester **39** was converted into the desired α-trichloroacetimidate **10** (1-H: 6.61 ppm, d, J = 3.0 Hz) in five routine steps and in a good 61% overall yield. These steps include 1) cleavage of the orthoester (Dowex H^+, EtOH, room temp.) to afford the corresponding 2-*O*-acetyl derivative, 2) removal of the resulting Ac group (NaOMe, MeOH, THF, room temp.), 3) protection of the resulting 1,2-diol with Bz groups (BzCl, Et_3N, DMAP, CH_2Cl_2, room temp.), 4) selective removal of the anomeric Bz group (NH_3, THF, MeOH, room temp.), and 5) α-trichloroacetimidate formation ($CNCCl_3$, DBU, CH_2Cl_2, room temp.).



Scheme 7. Preparation of the glucopyranosyl trichloroacetimidate **10**.

Allyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**40**), prepared from L-rhamnose in two steps,[40] was treated with MBzCl in the presence of Et_3N and DMAP (CH_2Cl_2, room temp.) to provide the 4-*O*-MBz derivative **41** (97%; 4-H: 5.12 ppm, dd, J = 9.6, 8.1 Hz; Scheme 8). The isopropylidene group was then removed cleanly with 70% HOAc at 70 °C (90%) and the resulting 2,3-OH groups were protected with PMB groups (PMBBr, NaH, THF, room temp.) to give **42** (70%). Removal of the anomeric allyl group was achieved with $PdCl_2$ in a mixture of CH_2Cl_2 and MeOH at room temp. (89%) and the resulting lactol was converted readily into the desired trifluoroacetimidate **11** [ClC(NPh)CF_3, K_2CO_3, acetone, room temp., 92%], which could be purified by flash column chromatography on silica gel and



Scheme 8. Preparation of the rhamnopyranosyl trifluoroacetimidate **11**.

used directly in the subsequent glycosylation reaction.[9] The corresponding trichloroacetimidate counterpart decomposed completely upon silica gel chromatography.

Synthesis of Candicanoside A (1)

Glycosylation of steroid **7** with glucosyl trichloroacetimidate **8** bearing an AZMB group at 2-OH and promoted by TMSOTf (0.05 equiv.) in CH_2Cl_2 at 0 °C provided the desired β-glycoside **43** in only moderate yield (ca. 40%). The major byproduct was believed to be the corresponding orthoester. Therefore, TfOH was used instead as the promoter; the glycosylation reaction was completed in the presence of 0.2 equiv. of TfOH at room temp. within 1 h, furnishing **43** (1′-H: 4.75 ppm, d, J = 7.8 Hz) in an excellent 96% yield (Scheme 9). X-ray diffraction analysis of compound **43** not only proved the nascent β-glycosidic configuration, but also confirmed unambiguously the correctness of the synthesized aglycon (Figure 6). The 2′-*O*-AZMB group in **43** was removed cleanly in the presence of the Ac groups with PBu_3 in a wet THF solvent at room temp.[7] The resulting 2′-OH was successfully glycosylated with the perbenzoyl rhamnopyranosyl trichloroacetimidate **9** under similar conditions to those used in the previous glycosylation (0.2 equiv. TfOH, CH_2Cl_2, room temp.) to provide the disaccharide **45** in a good 81% yield (two steps; 1′′-H: 5.02 ppm, d, J = 3.9 Hz). Note that replacement of the perbenzoyl imidate **9** with its 2,3,4-tri-*O*-acetyl-rhamnopyranosyl trichloroacetimidate counterpart as the donor did not lead to the corresponding disaccharide under a variety of conditions (TfOH or TMSOTf, CH_2Cl_2, –78 °C to room temp.).[8] Finally, removal of the three Ac and three Bz groups on the saccharide residue in **45** was achieved with NaOMe in a mixed solvent of MeOH and THF at room temp., furnishing the target Candicanoside A (**1**) in 90% yield. The analytical data for **1** are in good agreement with those reported in the literature.[3] The diagnostic ^{1}H NMR signals include 1′-H (δ = 5.05 ppm, d, J = 6.3 Hz), 1′′-H (δ = 6.40 ppm, br. s), 3-H (δ = 3.96 ppm, m), 6-H (δ = 5.37 ppm, d, J = 9.0 Hz), 16-H (δ = 4.66 ppm, m), 18-H (4.04 and 3.55 ppm, 2 d, AB, J = 13.0 Hz), and 24-H (δ = 5.43 ppm, d, J = 9.0 Hz).

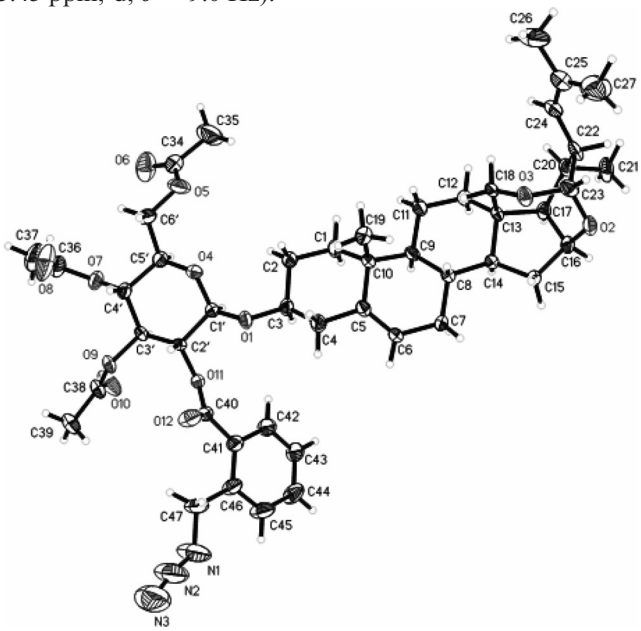
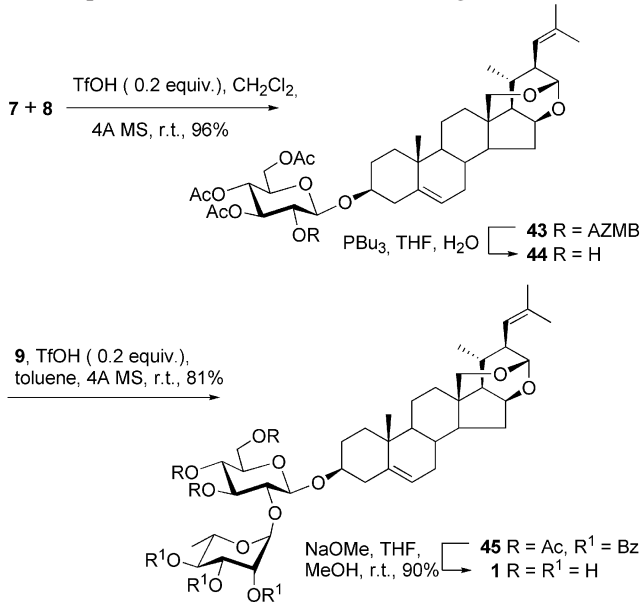


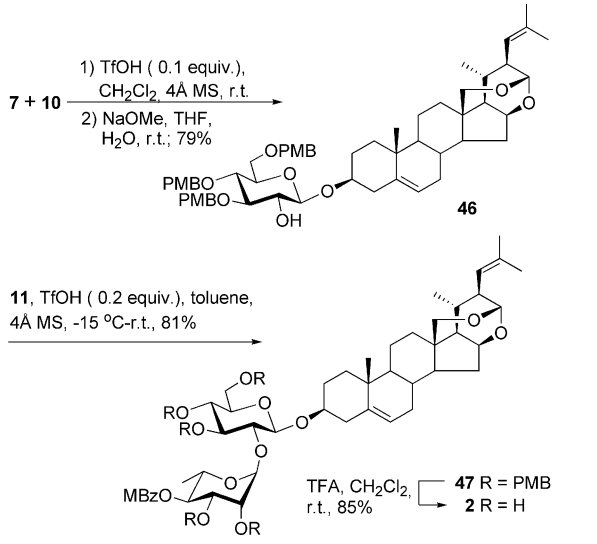
Figure 6. ORTEP drawing of compound **43**.

Synthesis of the 4′′-*O*-MBz Derivative 2

As with the previous coupling of steroid **7** with glucosyl imidate **8**, glycosylation of **7** with 3,4,6-tri-*O*-PMB-2-*O*-Bz-D-glucopyranosyl trichloroacetimidate (**10**) proceeded smoothly under the promotion of TfOH (0.1 equiv.) in CH_2Cl_2 at room temp. to provide the corresponding β-glycoside in 87% yield (Scheme 10). The 2-*O*-Bz group in the resulting glycoside was removed cleanly with NaOMe in a mixture of MeOH and THF at room temp. to afford **46**



Scheme 9. Completion of the synthesis of candicanoside A (**1**).



Scheme 10. Completion of the synthesis of compound **2**.

(91%). Glycosylation of the 2′-OH in **46** with the newly prepared 2,3-di-*O*-PMB-4-*O*-MBz-L-rhamnopyranosyl trifluoroacetimidate (**11**) under slightly modified conditions to those used for the previous glycosylation (0.2 equiv. TfOH, toluene, –15 °C to room temp.) led to the desired disaccharide **47** stereoselectively in good yield (81%; 1′′-H: 5.38 ppm, br. s). Attempts to remove the five PMB groups in **47** with DDQ led to complex mixtures. Gratifyingly, these PMB groups could be cleaved cleanly with 10% TFA in CH_2Cl_2 at room temp.[41] to furnish the target compound **2** in 85% yield. Comparison of the ^{1}H NMR spectra of **1** and **2** shows the presence of the MBz group at 4′′-OH in **2** leads to the downfield shift of 4′′-H from 4.36 ppm (in **1**) to 6.22 ppm (in **2**; dd, J = 9.9, 9.2 Hz).[2]

Conclusions

Candicanoside A (**1**) and its 4′′-*O*-(*p*-methoxybenzoate) derivative **2** are congeners of the novel 24(23→22)*abeo*-cholestane glycosides that occur in the genus *Ornithogalum* indigenous to Southern Africa and have remarkable cytostatic activity. These two (1→2)-linked disaccharides (**1** and **2**) have been synthesized by stepwise glycosylation with monosaccharide imidate donors **8**–**11** to form the glycosidic bonds in a stereocontrolled manner. The additional MBz group in **2** demanded a totally different protecting group arrangement (PMB as permanent and Bz as temporary protecting groups) compared with that employed in the synthesis of **1** (Ac and Bz as permanent and AZMB as temporary protecting groups). The rearranged steroid aglycon **7** was synthesized starting from dehydroisoandrosterone in 23 steps and 1.5% overall yield. Key steps include the 20-alkoxy radical-mediated functionalization of the angular 18-methyl group (**20**→**21**), Johnson–Claisen rearrangement for the alkylation at C-20 (**28**→**29**), aldol condensation at C-22 (**33**→**34**), ultraviolet-light-induced deconjugation of the α,β-conjugated lactone (**34**→**35**), and simultaneous acetal formation upon deprotection of the 18-*O*-TBS ether with HF (**36**→**7**). The stereochemistry of the transformations was well controlled by the substrates (except for the CBS reduction of **25**→**26**) and was unambiguously confirmed by X-ray diffraction analysis of the key compounds (**16**, **18**, and **43**). The natural saponin **1** and its congener **2** were successfully synthesized from dehydroisoandrosterone, D-glucose, and L-rhamnose in 37 (1.0% yield) and 44 steps (0.8% overall yield), respectively.

Experimental Section

General: All solvents were distilled prior to use except where noted. Commercially available reagents were used without further purification unless otherwise stated. All reactions sensitive to moisture or oxygen were conducted under an atmosphere of nitrogen or argon. Crushed 4 Å molecular sieves were activated by thorough flame-drying immediately prior to use. Flash column chromatography was performed on silica gel H (10–40 μ). Analytical thin layer chromatography (TLC) was performed on glass plates pre-coated with a 0.25 mm thickness of silica gel. The TLC plates were visualized with UV light and/or by staining with ethanolic phosphomolybdic acid (PMA) or acidic methanol. Optical rotations were measured at the sodium D-line at ambient temperature with a Perkin-Elmer 241MC polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance spectrometer at 300 and 75 MHz, respectively. Chemical shifts of ^{1}H NMR and ^{13}C NMR spectra are reported in ppm with a solvent resonance as an internal standard.

For the synthesis of compounds **1**, **7**, **8**, **20**–**23**, **27**–**38**, and **43**–**45**, see the Supporting Information in ref.[4]

16,20-Diol 15: 2,6-Lutidine (1.20 mL, 10.1 mmol) and TESOTf (0.92 mL, 4.04 mmol) were added to a solution of **14**[11] (666 mg, 2.02 mmol) in dry CH_2Cl_2 (5 mL). After stirring at room temp. for 1 h, the mixture was diluted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$, dried with Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel (petroleum ether/EtOAc, 20:1) to give the corresponding 16-*O*-TES ester as a colorless oil (896 mg, 100%). BH_3·THF (1.0 M in THF, 10 mL) was added to a solution of the resulting oil (896 mg, 2.02 mmol) in dry THF (10 mL). After being stirred at 45 °C overnight, the mixture was cooled in an ice bath and then saturated aqueous $NaHCO_3$ (30 mL) was added slowly, followed by the addition of 30% aqueous H_2O_2 (20 mL) over a period of 10–15 min. The resulting suspension was stirred at 0 °C for 2 h and then extracted twice with EtOAc. The combined organic layers were washed with 10% $NaHSO_4$, water, and brine, respectively, and then dried, and the solvents evaporated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 3:1) to afford **15** (645 mg, 92%) as a white foam. $[\alpha]_D^{23}$ = 59.3 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.50–4.45 (m, 1 H), 4.15–4.08 (m, 1 H), 3.31 (s, 3 H), 2.77 (t, J = 2.8 Hz, 1 H), 2.26–2.19 (m, 1 H), 1.27 (d, J = 6.4 Hz, 3 H), 1.04 (s, 3 H), 0.91 (s, 3 H), 0.65–0.63 (m, 1 H), 0.44–0.41 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.2, 73.2, 66.5, 63.0, 56.5, 54.0, 48.0, 43.4, 41.5, 39.7, 35.6, 35.2, 35.0, 33.3, 29.7, 24.9, 23.4, 22.2, 21.5, 19.3, 14.3, 13.1 ppm. HRMS (ESI): calcd. for $C_{22}H_{36}NaO_3$ $[M + Na]^+$ 371.2562; found 371.2565.

16-*O*-TBS-20-ol 16: A solution of **15** (78 mg, 0.22 mmol) in dry CH_2Cl_2 (1 mL) was cooled to –78 °C and then 2,6-lutidine (0.08 mL, 0.66 mmol) and TBSOTf (0.06 mL, 0.24 mmol) were added. The mixture was stirred at this temperature for 2 h and then MeOH was added and diluted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$, dried with Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give a residue, which was purified by silica gel column chromatography (petroleum ether/EtOAc, 20:1) to give **16** (63 mg, 63%) as a white foam. ^{1}H NMR (300 MHz, $CDC1_3$): δ = 4.56–4.50 (m, 1 H), 4.15–4.09 (m, 1 H), 3.38 (s, 3 H), 3.11 (m, 1 H), 2.82 (m, 1 H), 2.24–2.15 (m, 1 H), 1.26 (d, J = 6.3 Hz, 3 H), 1.08 (s, 3 H), 0.95 (s, 3 H), 0.87 (s, 9 H), 0.66 (d, J = 4.5 Hz, 1 H), 0.45 (dd, J = 7.8, 5.1 Hz, 1 H), 0.10 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.2, 74.2, 65.9, 63.4, 56.7, 54.3, 48.2, 43.5, 41.6, 39.6, 37.5, 35.6, 34.9, 33.3, 29.8, 25.8, 24.9, 22.4, 22.2, 21.1, 19.2, 17.7, 14.3, 13.3 ppm.

16-*O*-Bz-20-ol 17: Bu_2SnO (173 mL, 0.69 mmol) was added to a solution of **15** (100 mg, 0.29 mmol) in dry toluene (5 mL). The mixture was stirred at reflux for 3 h and was then cooled to room temp. and concentrated in vacuo. The residue was dissolved in THF and CH_2Cl_2 (v/v 4:1, 5 mL) and cooled to 0 °C. Then BzCl (0.07 mL, 0.60 mmol) was added. After stirring at room temp. for 12 h, the mixture was diluted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$, dried with Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give a residue, which was purified by silica gel column chromatography (petroleum ether/EtOAc, 8:1) to give **17** (114 mg, 80%) as a white foam. $[\alpha]_D^{20}$ = 21.6 (c =

1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03–8.00 (m, 2 H), 7.58–7.56 (m, 1 H), 7.48–7.43 (m, 2 H), 5.66–5.62 (m, 1 H), 4.10–4.05 (m, 1 H), 3.32 (s, 3 H), 2.78 (br. s, 1 H), 2.56–2.46 (m, 1 H), 1.30 (d, J = 6.5 Hz, 3 H), 1.09 (s, 3 H), 1.05 (s, 3 H), 0.68–0.65 (m, 1 H), 0.47–0.43 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 133.0, 130.2, 129.5, 128.4, 82.1, 76.4, 65.1, 63.3, 56.5, 54.4, 47.8, 43.3, 41.9, 39.2, 35.2, 34.8, 34.3, 33.2, 29.8, 24.9, 22.2, 22.1, 21.5, 19.2, 13.4, 13.0 ppm. HRMS (ESI): calcd. for $C_{29}H_{40}NaO_4$ $[M + Na]^+$ 475.2816; found 475.2819.

18-Iodide 18: A degassed mixture of **16** (64 mg, 0.14 mmol), DIB (89 mg, 0.27 mmol), iodine (35 mg, 0.14 mmol), and K_2CO_3 (38 mg, 0.27 mmol) in dry cyclohexane (2 mL) was irradiated with visible light (300-W tungsten filament lamp) for 2 h at reflux. The solution was washed with saturated aqueous $Na_2S_2O_3$ and the organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 30:1) to afford **18** (30 mg, 37%) as a white foam. ^1H NMR (300 MHz, $CDC1_3$): δ = 4.56–4.51 (m, 2 H), 3.92 and 3.45 (2 d, J = 10.5 Hz, 2 H, AB), 3.36 (s, 3 H), 2.81 (m, 1 H), 2.36–2.24 (m, 2 H), 1.36 (d, J = 6.0 Hz, 3 H), 1.03 (s, 3 H), 0.95 (s, 3 H), 0.91 (s, 9 H), 0.66 (d, J = 4.5 Hz, 1 H), 0.47 (dd, J = 7.8, 5.1 Hz, 1 H), 0.10 (s, 6 H) ppm.

18-Iodide 19: A degassed solution of **17** (90 mg, 0.20 mmol), DIB (78 mg, 0.22 mol), and iodine (56 mg, 0.22 mmol) in dry cyclohexane (7 mL) was irradiated with visible light (300 W) for 2 h. The solution was washed with saturated aqueous $Na_2S_2O_3$ and the organic phase was dried with Na_2SO_4 and then filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 6:1) to give **19** (51 mg, 44%) as a white foam. $[\alpha]_D^{24}$ = 72.6 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDC1_3$): δ = 8.06–8.05 (m, 2 H), 7.62–7.59 (m, 1 H), 7.53–7.48 (m, 2 H), 5.72–5.67 (m, 1 H), 4.66–4.61 (m, 1 H), 3.93 and 3.63 (2 d, J = 10.8 Hz, 2 H, AB), 3.32 (s, 3 H), 2.80 (br. s, 1 H), 2.60–2.52 (m, 1 H), 1.47 (d, J = 6.0 Hz, 3 H), 1.07 (s, 3 H), 0.70–0.68 (m, 1 H), 0.50–0.46 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 133.2, 130.0, 129.5, 128.6, 81.8, 76.0, 64.6, 64.1, 56.6, 55.4, 47.8, 44.1, 43.4, 38.6, 35.1, 34.7, 34.4, 33.2, 30.5, 24.8, 23.3, 21.5, 21.4, 19.2, 13.0, 9.5 ppm. HRMS (ESI): calcd. for $C_{29}H_{39}INaO_4$ $[M + Na]^+$ 601.1788; found 601.1785.

18-Acetoxy-20-one 24: PCC (342 mg, 1.60 mmol), NaOAc (324 mg, 3.90 mmol), and 4-Å MS were added to a solution of the 20-ol **23** (310 mg, 0.79 mmol) in CH_2Cl_2 (10 mL). After stirring at room temp. for 2 h, the mixture was filtered. The filtrates were concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 6:1) to give **24** (282 mg, 92%) as a white foam. $[\alpha]_D^{24}$ = 93.8 (c = 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.19 and 3.85 (2 d, J = 11.4 Hz, 2 H, AB), 3.30 (s, 3 H), 2.77 (m, 1 H), 2.58–2.48 (m, 2 H), 2.36 (m, 1 H), 2.21 (s, 3 H), 1.97 (s, 3 H), 1.01 (s, 3 H), 0.66 (t, J = 4.5 Hz, 1 H), 0.44 (dd, J = 7.8, 5.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.2, 170.6, 81.8, 62.1, 61.5, 56.5, 56.4, 48.1, 47.9, 43.4, 35.2, 35.0, 33.9, 33.3, 31.3, 30.6, 24.9, 24.0, 22.3, 21.5, 20.4, 19.3, 13.0 ppm. HRMS (ESI): calcd. for $C_{24}H_{36}NaO_4$ $[M + Na]^+$ 411.2510; found 411.2506.

16(17)-En-18-acetoxy-20-one 25: NBS (130 mg, 0.73 mmol) and $(BzO)_2$ (30 mg, 0.12 mmol) were added to a solution of **24** (200 mg, 0.52 mmol) in CCl_4 (5 mL). The mixture was stirred at reflux for 4 h and then filtered. The filtrates were concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 15:1) to give a colorless oil, which was dissolved in DMF (2 mL). Li_2CO_3 (85 mg, 1.15 mmol) and LiBr (60 mg, 0.69 mmol) were added to the DMF solution. The resulting mixture was stirred at 120 °C for 3 h and was then cooled to room temp. and diluted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$, dried with Na_2SO_4, and filtered. The filtrates were concentrated in vacuo to give a residue, which was purified by silica gel column chromatography (petroleum ether/EtOAc, 10:1) to afford **25** (90 mg, 45%) as a white foam. $[\alpha]_D^{23}$ = 94.8 (c = 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.86 (s, 1 H), 4.43 and 4.02 (2 d, J = 11.2 Hz, 2 H, AB), 3.34 (s, 3 H), 2.79 (br. s, 1 H), 2.62–2.57 (m, 1 H), 2.31–2.28 (m, 3 H), 2.26 (s, 3 H), 1.96 (s, 3 H), 1.05 (s, 3 H), 0.68 (t, J = 4.3 Hz, 1 H), 0.45 (dd, J = 7.6, 5.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.3, 171.2, 151.4, 146.1, 81.8, 65.0, 56.7, 56.6, 49.9, 48.4, 43.5, 35.4, 35.1, 33.0, 32.7, 31.8, 29.0, 27.2, 24.8, 22.2, 21.2, 21.0, 19.2, 13.2 ppm. HRMS (ESI): calcd. for $C_{24}H_{34}NaO_4$ $[M + Na]^+$ 409.2355; found 409.2356.

18,20-Diacetoxy-16(17)-ene 26: (*R*)-CBS (1.26 M in toluene, 0.30 mL, 0.37 mmol) and $BH_3{\cdot}SMe_2$ (5 M in THF, 0.15 mL, 0.75 mmol) were added to a stirred solution of **25** (50 mg, 0.13 mmol) in dry THF (2 mL) at –45 °C. After stirring for 1 h at –45 °C, the reaction was quenched with MeOH and the mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (2 mL) and then Et_3N (0.09 mL, 0.65 mmol), DMAP (5 mg, 0.04 mmol), and Ac_2O (0.05 mL, 0.53 mmol) were added. The mixture was stirred for 4 h at room temp. The reaction was quenched with MeOH and the mixture concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 10:1) to afford **26** (45 mg, 80%) as a white foam. $[\alpha]_D^{27}$ = 42.4 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.84 (s, 1 H), 5.62–5.61 (m, 1 H), 4.41 and 3.92 (2 d, J = 10.8 Hz, 2 H, AB), 3.34 (s, 3 H), 2.79 (br. s, 1 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 1.32 (d, J = 6.4 Hz, 3 H), 1.06 (s, 3 H), 0.68 (t, J = 4.4 Hz, 1 H), 0.46 (dd, J = 8.0, 5.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 170.0, 153.0, 126.7, 81.9, 68.7, 66.4, 57.1, 56.6, 49.1, 48.5, 43.5, 35.3, 35.1, 33.1, 31.3, 31.1, 29.6, 29.1, 24.8, 22.0, 21.8, 21.3, 20.9, 19.2, 13.1 ppm. HRMS (ESI): calcd. for $C_{26}H_{38}NaO_5$ $[M + Na]^+$ 453.2617; found 453.2614.

2-*O*-Benzoyl-3,4,6-tri-*O*-(*p*-methoxybenzyl)-α-D-glucopyranosyl Trichloroacetimidate (10): Dowex H^+ resin (260 mg) was added to a solution of the orthoester **39**[39] (2.6 g, 4.4 mmol) in 95% ethanol (30 mL). The mixture was stirred for 2 h at room temp. and then concentrated in vacuo. The residue was dissolved in THF and MeOH (v/v, 1:1, 20 mL) and NaOMe (23 mg, 0.44 mmol) was added. The mixture was stirred until TLC indicated the reaction was finished and was then neutralized with Dowex H^+ resin. The resulting mixture was filtered. The filtrates were concentrated to give a residue, which was purified by column chromatography on silica gel (petroleum ether/EtOAc, 3:1) to provide 3,4,6-tri-*O*-(*p*-methoxybenzyl)-D-glucopyranose (1.88 g, 80%) as a colorless syrup. Et_3N (1.2 mL, 8.4 mmol), DMAP (34 mg, 0.28 mmol), and BzCl (0.8 mL, 7 mmol) were added to a solution of the above product (1.5 g, 2.8 mmol) in dry CH_2Cl_2 (20 mL). The mixture was stirred at room temp. overnight and was then diluted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$, dried with Na_2SO_4, and filtered. The filtrates were concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel (petroleum ether/EtOAc, 5:1) to give 1,2-di-*O*-benzoyl-3,4,6-tri-*O*-(*p*-methoxybenzyl)-D-glucopyranoside (1.97 g, 95%) as a colorless syrup. This compound (748 mg, 1 mmol) was dissolved in THF and MeOH (v/v, 1:1, 20 mL) and the solution saturated with dry NH_3. The solution was kept at room temp. overnight and then concentrated. The residue was dissolved in a solution of CH_2Cl_2 (20 mL) and CCl_3CN (0.5 mL, 5.0 mmol) containing DBU (cat). The resulting mixture was stirred for 2 h at room temp. and then concentrated in vacuo. The residue was purified by silica gel column

chromatography (petroleum ether/EtOAc, 3:1) to afford **10** (639 mg, 80%) as a colorless syrup. $[\alpha]_D^{25}$ = 82.9 (*c* = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.47 (s, 1 H), 7.93 (d, *J* = 7.2 Hz, 2 H), 7.55–6.67 (m, 15 H), 6.61 (d, *J* = 3.3 Hz, 1 H), 5.53 (dd, *J* = 9.6, 3.3 Hz, 1 H), 4.78–4.72 (m, 2 H), 4.60 (d, *J* = 11.7 Hz, 1 H), 4.46 (dd, *J* = 11.4, 9.3 Hz, 2 H), 4.22 (t, *J* = 9.6 Hz, 1 H), 4.06–4.02 (m, 1 H), 3.89 (m, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.81–3.65 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 160.5, 159.3, 159.2, 159.1, 133.1, 130.1, 130.0, 129.8, 129.7, 129.5, 129.5, 129.3, 128.2, 113.7, 113.6, 94.1, 91.0, 78.9, 76.9, 74.9, 73.5, 73.0, 72.5, 67.4, 55.1, 55.1, 55.0 ppm.

Allyl 2,3-*O*-Isopropylidene-4-*O*-(*p*-methoxybenzoyl)-α-L-rhamnopyranoside (41): Et_3N (0.67 mL, 4.8 mmol), DMAP (24 mg, 0.2 mmol), and MBzCl (408 mg, 2.4 mmol) were added to a solution of **40**[40] (390 mg, 1.6 mmol) in dry CH_2Cl_2 (5 mL). The mixture was stirred at room temp. overnight and was then diluted with CH_2Cl_2. The organic phase was washed with $NaHCO_3$, dried with Na_2SO_4, and filtered. The filtrates were concentrated in vacuo to give a residue, which was purified by silica gel column chromatography (petroleum ether/EtOAc, 15:1) to afford **41** (25 mg, 97%) as a colorless syrup. $[\alpha]_D^{25}$ = –8.1 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03–7.99 (m, 2 H), 6.93–6.90 (m, 2 H), 6.00–5.91 (m, 1 H), 5.38–5.24 (m, 2 H), 5.14–5.08 (m, 2 H), 4.36 (dd, *J* = 7.8, 5.4 Hz, 1 H), 4.26–4.20 (m, 2 H), 4.09–4.03 (m, 1 H), 3.95–3.90 (m, 1 H), 3.87 (s, 3 H), 1.63 (s, 3 H), 1.37 (s, 3 H), 1.22 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 163.5, 133.5, 131.8, 122.1, 117.8, 113.5, 109.7, 96.1, 75.9, 75.8, 74.6, 68.1, 64.2, 55.4, 27.7, 26.3, 17.0 ppm. HRMS (ESI): calcd. for $C_{20}H_{26}NaO_7$ $[M + Na]^+$ 401.1575; found 401.1571.

Allyl 2,3-Di-*O*-(*p*-methoxybenzyl)-4-*O*-(*p*-methoxybenzoyl)-α-L-rhamnopyranoside (42): Compound **41** (600 mg, 1.59 mmol) was dissolved in 70% HOAc (6 mL). The mixture was stirred for 4 h at 70 °C and was then concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 2:1) to afford the corresponding 2,3-diol (485 mg, 90%) as a colorless syrup. NaH (140 mg, 3.5 mmol) was added to a solution of the diol (300 mg, 0.89 mmol) in dry THF (10 mL) at 0 °C. The mixture was stirred for 30 min at this temperature and then PMBBr (700 mg, 3.5 mmol) was added. After stirring at room temp. overnight, the mixture was diluted with EtOAc and then washed with saturated aq. NH_4Cl, dried with Na_2SO_4, and filtered. The filtrates were concentrated in vacuo to give a residue, which was purified by silica gel column chromatography (petroleum ether/EtOAc, 5:1) to afford **42** (360 mg, 70%) as a colorless syrup. $[\alpha]_D^{24}$ = 7.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.7 Hz, 2 H), 7.31–6.67 (m, 10 H), 5.88 (m, 1 H), 5.42 (t, *J* = 9.6 Hz, 1 H), 5.45–5.17 (m, 2 H), 4.80–4.61 (m, 3 H), 4.48 and 4.35 (2 d, *J* = 11.7 Hz, 2 H, AB), 4.18–4.13 (m, 1 H), 3.98–3.74 (m, 13 H), 1.22 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 163.5, 159.3, 159.2, 134.0, 131.8, 130.6, 130.5, 129.5, 129.1, 122.9, 116.9, 113.8, 113.9, 113.6, 97.9, 76.9, 74.6, 73.6, 72.7, 71.6, 67.9, 67.3, 55.4, 55.2, 55.1, 17.6 ppm. HRMS (ESI): calcd. for $C_{33}H_{38}NaO_9$ $[M + Na]^+$ 601.2414; found 601.2408.

2,3-Di-*O*-(*p*-methoxybenzyl)-4-*O*-(*p*-methoxybenzoyl)-α-L-rhamnopyranosyl Trifluoroacetimidate (11): A dark suspension of $PdCl_2$ (10 mg, 0.056 mmol) and compound **42** (70 mg, 0.12 mmol) in MeOH/CH_2Cl_2 (v/v, 1:1, 4 mL) was stirred at room temp. until TLC indicated that the reaction was complete. The mixture was filtered through a pad of Celite. The filtrates were concentrated in vacuo to give a dark syrup, which was purified by column chromatography on silica gel (petroleum ether/EtOAc/CH_2Cl_2, 5:1:1) to give a mixture of the α and β anomers (58 mg, 89%). K_2CO_3 (73 mg, 0.53 mmol) and ClC(NPh)CF_3 (70 mg, 0.34 mmol) were added to a stirred mixture of the above product (58 mg, 0.11 mmol) in acetone (2 mL). After stirring at room temp. overnight, the mixture was filtered and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 5:1) to afford **11** (70 mg, 92%) as a colorless syrup. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 9.0 Hz, 2 H), 7.35–6.73 (m, 15 H), 6.10 (m, 1 H), 5.49 (dd, *J* = 9.9, 9.6 Hz, 1 H), 4.73–4.58 (m, 2 H), 4.43 (m, 2 H), 3.98–3.75 (m, 12 H), 1.28 (d, *J* = 6.0 Hz, 3 H) ppm.

β-Glucopyranoside 46: A mixture of the steroid **7** (5 mg, 0.012 mmol), glucopyranosyl imidate **10** (20 mg, 0.024 mmol), and powered 4-Å molecular sieves in anhydrous CH_2Cl_2 (1 mL) was stirred for 1 h at room temp. under Ar and then a solution of TfOH in CH_2Cl_2 (0.1 equiv.) was added. After stirring for 1 h, Et_3N was added and then the resulting mixture was filtered. The filtrates were concentrated to give a residue, which was purified by column chromatography on silica gel (petroleum ether/EtOAc, 3:1) to provide the corresponding glycoside (11 mg, 87%) as a colorless syrup. NaOMe (cat.) was added to a stirred solution of the above glycoside (11 mg, 0.011 mmol) in THF and MeOH (v/v, 1:1, 2 mL). After stirring at room temp. overnight, the mixture was neutralized with Dowex 50-X8 (H^+) resin. The resin was filtered off and washed with CH_2Cl_2. The filtrate and washings were combined and concentrated. The residue was purified by silica gel column chromatography (petroleum ether–EtOAc, 5:1) to give **46** (9 mg, 91%) as a colorless syrup. $[\alpha]_D^{22}$ = –13.6 (*c* = 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.24 (m, 4 H), 7.08 (d, *J* = 8.4 Hz, 2 H), 6.88–6.81 (m, 6 H), 5.35 (br. s, 1 H), 5.15 (d, *J* = 9.0 Hz, 1 H), 5.00 (d, *J* = 3.9 Hz, 1 H), 4.87–4.73 (m, 3 H), 4.57–4.41 (m, 4 H), 4.33 (d, *J* = 7.2 Hz, 1 H), 3.98 and 3.64 (2 d, *J* = 12.6 Hz, 2 H, AB), 3.80–3.79 (m, 9 H), 3.70–3.45 (m, 7 H), 1.74 (s, 3 H), 1.66 (s, 3 H), 1.18 (d, *J* = 7.1 Hz, 3 H), 1.01 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 159.4, 140.7, 134.6, 131.3, 130.7, 129.5, 129.3, 124.9, 121.8, 114.0, 113.9, 101.5, 98.2, 84.6, 79.0, 77.7, 75.5, 74.9, 74.6, 74.5, 73.2, 73.1, 69.2, 66.6, 55.3, 55.3, 53.8, 53.0, 51.1, 47.5, 45.2, 39.1, 38.6, 37.5, 37.0, 35.6, 32.0, 31.8, 30.4, 29.8, 29.7, 26.1, 23.9, 21.1, 19.3, 18.3 ppm. HRMS (ESI): calcd. for $C_{57}H_{74}NaO_{11}$ $[M + Na]^+$ 957.5129; found 957.5123.

Disaccharide 47: A mixture of the **46** (8 mg, 0.009 mmol), the newly prepared rhamnosyl trifluoroacetimidate **11** (16 mg, 0.023 mmol), and powered 4-Å molecular sieves in anhydrous toluene (1 mL) was stirred for 1 h at room temp. under Ar. A solution of TfOH in toluene (0.1 equiv.) was added. After stirring for 1 h, Et_3N was added and the mixture was filtered. The filtrates were concentrated to give a residue, which was purified by silica gel column chromatography (petroleum ether/EtOAc, 3:1) to provide **47** (10 mg, 81%) as a white foam. $[\alpha]_D^{22}$ = 23.1 (*c* = 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 9.0 Hz, 2 H), 7.27–7.23 (m, 4 H), 7.10–6.99 (m, 6 H), 6.85–6.76 (m, 8 H), 6.66–6.62 (m, 4 H), 5.43–5.38 (m, 3 H), 5.16 (d, *J* = 9.0 Hz, 1 H), 5.00 (d, *J* = 4.2 Hz, 1 H), 4.82 and 4.32 (2 d, *J* = 12.0 Hz, 2 H, AB), 4.64–4.38 (m, 11 H), 3.98 (d, *J* = 12.9 Hz, 1 H), 3.90–3.85 (m, 4 H), 3.82–3.79 (m, 6 H), 3.75 (s, 3 H), 3.72–3.71 (m, 6 H), 3.71–3.45 (m, 8 H), 1.75 (s, 3 H), 1.67 (s, 3 H), 1.20 (d, *J* = 6.3 Hz, 3 H), 0.92 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 163.5, 159.5, 159.4, 159.2, 141.0, 134.6, 131.8, 130.9, 130.7, 130.4, 129.6, 129.3, 129.2, 129.1, 128.5, 124.8, 123.0, 121.7, 114.1, 113.9, 113.7, 113.6, 100.5, 98.6, 98.2, 86.0, 79.0, 78.4, 75.8, 75.3, 74.6, 74.4, 73.9, 73.2, 72.4, 71.6, 69.1, 67.2, 66.6, 55.5, 55.3, 55.3, 55.2, 53.8, 52.9, 51.1, 47.5, 45.2, 39.1, 38.8, 37.5, 37.1, 35.5, 32.1, 32.0, 30.4, 30.0, 29.7, 26.1, 23.9, 21.1, 19.3, 18.3, 17.4 ppm. HRMS (ESI): calcd. for $C_{87}H_{106}NaO_{19}$ $[M + Na]^+$ 1477.7225; found 1477.7221.

Compound 2: TFA (0.1 mL) was added to a solution of **47** (10 mg, 0.007 mmol) in CH_2Cl_2 (1 mL) at room temp. After stirring for 0.5 h at room temp., the reaction was quenched by the addition of $NaHCO_3$. The resulting mixture was extracted with EtOAc. The combined extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 5:1) to give **2** (5 mg, 85%) as a white solid. $[a]_D^{22} = -2.6$ ($c = 0.1$, MeOH). ^{1}H NMR (500 MHz, [D$_5$]pyridine): δ = 8.36–8.33 (m, 2 H), 7.12–7.07 (m, 2 H), 6.54 (s, 1 H), 6.22 (dd, J = 9.9, 9.2 Hz, 1 H), 5.60 (br. s, 1 H), 5.50 (d, J = 8.6 Hz, 1 H), 5.42 (d, J = 3.8 Hz, 1 H), 5.31–5.28 (m, 1 H), 5.15 (d, J = 7.5 Hz, 1 H), 4.92 (s, 1 H), 4.76–4.72 (m, 1 H), 4.61 (d, J = 11.8 Hz, 1 H), 4.47–4.35 (m, 3 H), 4.26 (dd, J = 9.4, 8.8 Hz, 1 H), 4.09 and 3.61 (2 d, J = 13.1 Hz, 2 H, AB), 4.08–4.00 (m, 2 H), 3.84 (s, 3 H), 3.02–2.96 (m, 1 H), 2.89–2.83 (m, 1 H), 2.65–2.60 (m, 1 H), 2.40–2.32 (m, 1 H), 2.25–2.15 (m, 1 H), 1.85 (s, 3 H), 1.70 (s, 3 H), 1.65 (d, J = 6.2 Hz, 3 H), 1.30 (d, J = 6.9 Hz, 3 H), 1.11 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_5$]pyridine): δ = 166.5, 164.1, 141.1, 134.5, 132.3, 125.8, 122.1, 114.3, 101.6, 101.2, 98.5, 79.7, 78.8, 78.2, 77.6, 76.9, 73.4, 72.7, 72.2, 70.7, 67.0, 66.8, 63.0, 55.7, 52.9, 51.3, 47.7, 45.9, 39.7, 39.2, 37.7, 37.4, 35.6, 32.5, 30.8, 30.6, 30.0, 26.2, 24.1, 21.4, 19.6, 18.3, 18.1 ppm. HRMS (ESI): calcd. for $C_{47}H_{66}NaO_{14}$ $[M + Na]^+$ 877.4347; found 877.4345.

CCDC-691105 (for **16**), -708846 (for **18**), and -691106 (for **43**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): Selected crystallographic data for compounds **16**, **18**, **43** and NMR spectra for all new compounds.

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