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Synthesis of Betavulgaroside III, a Representative Triterpene *seco*-Glycoside

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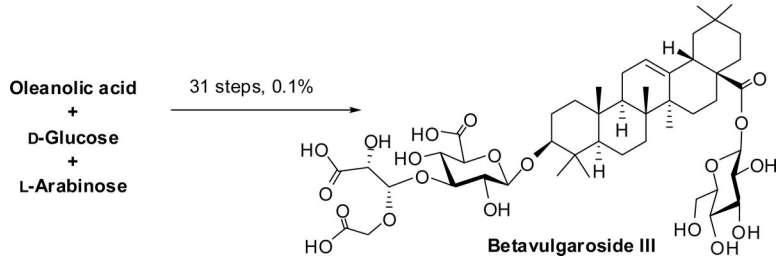

Triterpene *seco*-glycosides constitute a small family of the plant saponins which feature a terminal *seco*-saccharide appendage deriving supposedly from oxidative scission of a monosaccharide unit. Herein, we have developed synthetic approaches for the first time to the access to these molecules. Betavulgaroside III (**1**), a representative congener occurring in *Beta vulgaris* and *Achyranthes fauriei*, is successfully synthesized in a total of 31 steps with L-arabinose, D-glucose, and oleanolic acid as starting materials. The longest linear sequence requires 23 steps and in an overall 0.9% yield (from D-glucose). The synthesis features oxidative elaboration of the *seco*-saccharide unit prior to assembly of the triterpene 3,28-bisglycoside. This tactic has been proven superior, in the attempts to the synthesis of the more easily accessible 2″-*epi*-betavulgaroside III (**2**), to that employing oxidative cleavage of the terminal saccharide unit at an advanced triterpene 3,28-bisglycoside scaffold.

Introduction

Since 1994, Ida,[1] Yoshikawa,[2] Connolly,[3] Bourdy,[4] Lacaille-Dubois,[5] and their co-workers have disclosed over 20 triterpene *seco*-glycosides from six edible plants, i.e., *Achyranthes fauriei*, *Achyranthes bidentata*, *Beta vulgaris* (sugar beet), *Spinacia oleracea* (spinach), *Basella rubra* (Indian spinach), and *Pisonia umbellifera*. These novel saponins feature virtually an oxidative fragmentation of a terminal monosaccharide unit. The resulting acetal and carboxylic acid functions, together with the scarce occurrence of these compounds, make the isolation and structure elucidation extremely difficult. In fact, most of these compounds have been isolated after derivatization (e.g., methyl ester formation), and their stereochemistry in the terminal fragment remains unsolved. Another intriguing structural feature of the triterpene *seco*-glycosides is their mimicry of the sialyl Lewis X (sLe^x) structure,[6] a cell surface saccharide epitope with significance biological functions. In fact, a mixture of the triterpene *seco*-glycosides from *A. fauriei* showed inhibitory activities against the excess recruiting of neutrophiles to injured tissues 1000 times more potently than sLe^x.[1c] To explore synthetic approaches to the access to this type of interesting molecules, in conjugation with our long efforts on the synthesis of saponins,[7] we chose betavulgaroside III (**1**, Figure 1) as the first target of the triterpene *seco*-glycosides. This molecule, isolated from *B. vulgaris*[2a–c] and *A. fauriei* (as a trimethyl ester derivative),[1b] is a representative congener whose stereochemistry has been determined by correlation between common derivatives from known com-

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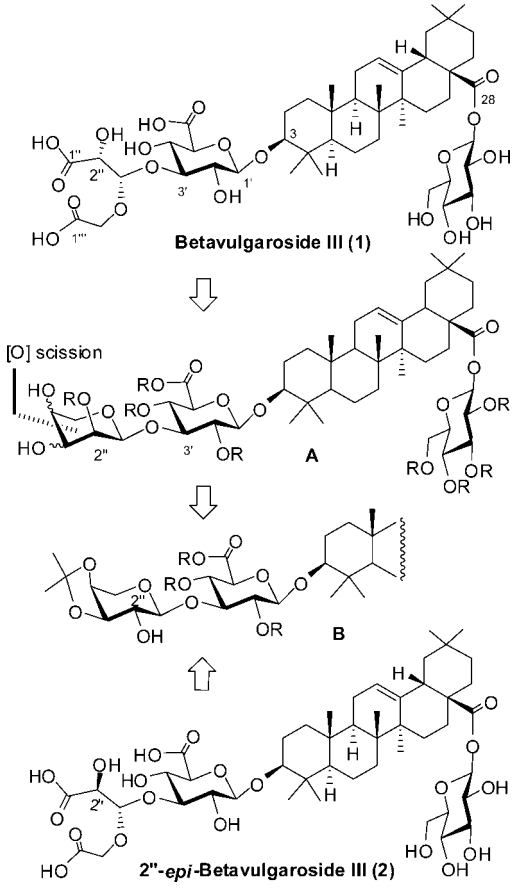


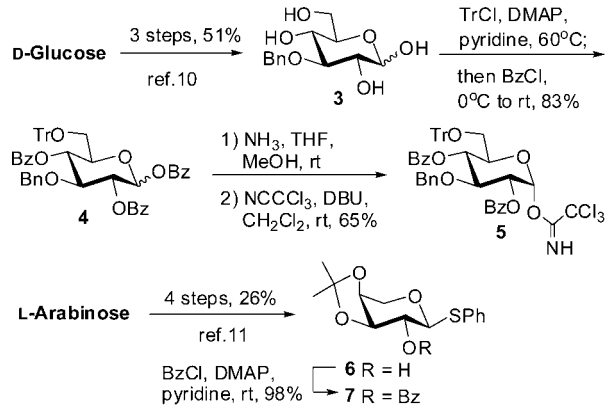
FIGURE 1. Betavulgaroside III (**1**), 2″-*epi*-betavulgaroside III (**2**), and the retrosynthetic perspective.

pounds.[2c] Herein, we report our synthetic studies toward betavulgaroside III (**1**).

Results and Discussion

Betavulgaroside III (**1**) would be derived from oleanane trisaccharide **A** via an oxidative scission of the vicinal 3,4-diol in the terminal pentose unit (Figure 1). The pentose unit should be in a form of 1,2-*cis*-α-L-pentopyranoside or 1,2-*cis*-β-D-pentopyranoside to meet the final stereochemistry requirement. However, direct construction of such a 1,2-*cis*-glycoside linkage is not a trivial task. A feasible alternative would be assembly of a 1,2-*trans*-glycoside followed by inversion of the 2-OH configuration.[8] Thus, α-L-arabinopyranoside (i.e., **B**) became a choice of the precursor, where the 1,2-*trans*-α-L-pyranosidic

SCHEME 1. Preparation of Monosaccharide Donors 5 and 7



linkage could be constructed stereoselectively by glycosylation with an arabinose donor equipped with a participating group at its 2-OH and the 3,4-*cis*-diol could be differentially protected with an acetal group. From this precursor, the 2″-*epi*-betavulgaroside III (**2**) turned out to be a straightforward target. Therefore, we explored the synthetic route toward **2** before elaboration of the target natural saponin **1**.

First-Generation Synthesis of 2″-*epi*-Betavulgaroside III (2). We have developed an efficient approach to the synthesis of oleanane-type triterpene 3,28-*O*-bisglycosides with β-D-glucuronide as the first monosaccharide unit attaching at the 3-OH.[9] Adopting modification of a similar synthetic sequence, the preparation of a trisaccharide precursor such as **15** met with no difficulty (Scheme 2). The required monosaccharide building blocks, i.e., 2,4-di-*O*-benzoyl-3-*O*-benzyl-6-*O*-trityl-D-glucopyranosyl trichloroacetimidate (**5**) and phenyl 3,4-*O*-isopropylidene-2-*O*-benzoyl-1-thio-α-L-arabinopyranoside (**7**), both equipped with a neighboring participating benzoyl group at the 2-OH, were readily prepared using routing transformations as shown in Scheme 1.

Coupling of oleanolic acid (**8**) with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**9**) under the optimized phase-transfer-catalyzed conditions (K_2CO_3, Bu_4NBr, $CH_2Cl_2-H_2O$, reflux) gave the 28-β-glucosyl ester **10** (89%; H-1′, 5.96 ppm, d, $J = 8.1$ Hz).[9,12] The remaining oleanane 3-OH was glycosylated with glucosyl imidate **5** in the presence of TBSOTf (0.1 equiv) to provide the 3-*O*-β-glucoside **11** in an excellent 92% yield (H-1′, 4.93 ppm, d, $J = 7.5$ Hz). Selective removal of the 3′-*O*-benzyl group in **11** via hydrogenolysis over Pd/C was unsuccessful, but leading to the complete cleavage of the 6′-*O*-trityl group as well (24 h) to afford 3′,6′-diol **12** (93%). The primary 6′-OH in **12** was then selectively protected with a TBS

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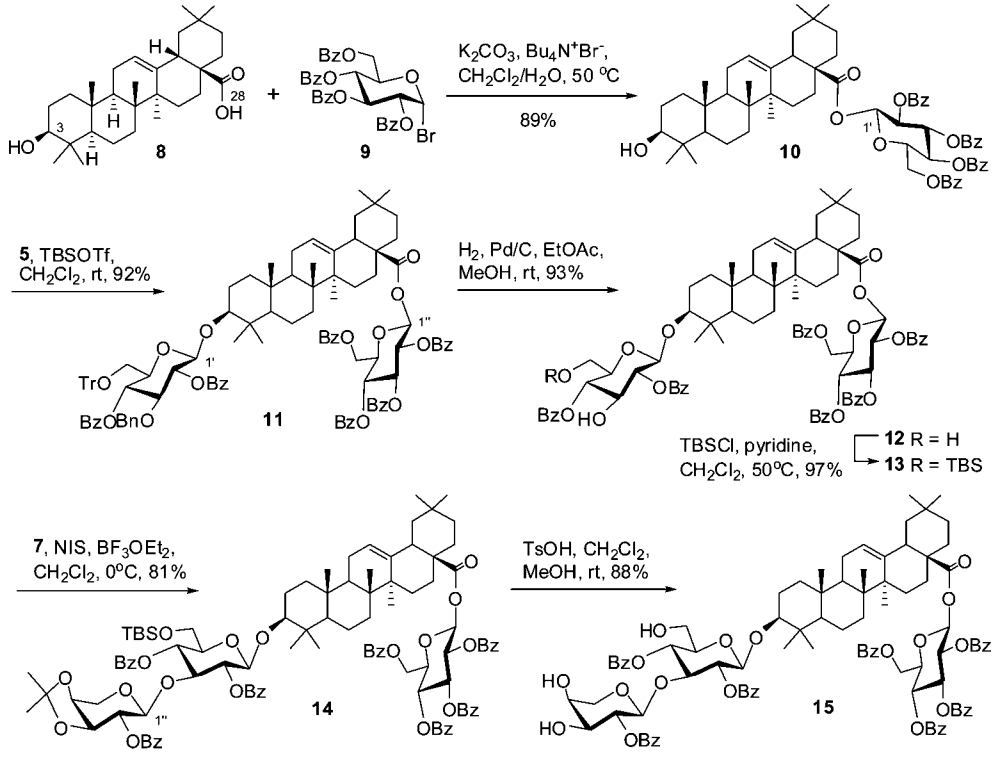
SCHEME 2. Linear Assembly of the Trisaccharide Precursor 15



ether to provide **13** (97%). Condensation of the 3′-OH (in **13**) with thioarabinoside **7** under the action of NIS and TMSOTf (and AgOTf as well)[13] led to the desired α-L-arabinopyranoside **14** in only moderate yields (<70%), due to the partial cleavage of the 6′-*O*-TBS ether. Nevertheless, the combination of NIS and BF_3OEt_2[14] as promoter was able to provide **14** in a satisfactory 81% yield. Treatment of the oleanane trisaccahride **14** with $TsOH \cdot H_2O$ in CH_2Cl_2/MeOH at rt effected removal of both the 2″,3″-*O*-isopropylidene and the 6′-*O*-TBS group, providing triol **15** in 88% yield.

The advanced trisaccahride precursor **15** was then subjected to oxidative cleavage of the 2″,3″-diol (Scheme 3). Treatment of **15** with $Pd(OAc)_4$ (in toluene or CH_3CN at rt) led to sluggish reaction.[2c,f,15] Using aq $NaIO_4$ as an oxidant,[16] the reaction (in $CHCl_3$ or THF at rt) proceeded faster; upon raising the temperature to 60 °C, the reaction completed within 2 h. The resulting hydrated bisaldehyde, and the 6′-OH as well, was further oxidized with the Jones reagent[17] to give supposedly the corresponding tris-carboxylic acid **C**. However, the product purified by careful chromatography on silica gel and ODS-silica gel was shown to be heterogeneous by an acquirement of a poorly diagnostic ^1H NMR spectrum. Thus, the product was subjected to methyl ester formation (CH_2N_2, EtOAc, rt); subsequent separation (on silica gel) led to two major compounds. The expected tris-methyl ester **16** was obtained in 43% yield (H-12, 5.24 ppm, s; C-12, 122.7 ppm), while the other product in 39% yield was determined to be the 11-one derivative **17** (H-12, 5.61 ppm, s; H-9, 2.9 ppm, d-like; C-11, 199.8 ppm; C-12, 128.1 ppm). The oxidation of the allylic 11-CH_2 of an oleanane derivative was not without precedent.[18] Alkaline removal of the benzoyl and methyl esters in **16** was found to be problematic. Treatment of **16** with NaOH (THF, MeOH, H_2O, rt) for 24 h led to the complete consumption of the starting **16**. Repeated chromatography of the resulting mixture on ODS-silica gel (MeOH−H_2O−TFA, 6:2:0.024) failed to give a homogeneous product. Thus, the collected mixture was treated with CH_2N_2 (MeOH–EtOAc, rt) to provide the methyl esters, which could be separated by silica gel (CH_2Cl_2−EtOAc, 1:1). The expected tris-methyl ester **18** was isolated as a major product in 46% yield. The other three minor products isolated were determined by ^1H NMR analysis to be the degraded compounds **D**, **E**,[19] and **F**,[20] indicating cleavage of the 28-glucosyl ester linkage (under alkaline conditions) and the terminal acetal moiety (likely under the acid treatment during chromatography on ODS-silica gel) could take place. Finally, removal of the methyl esters in **18** was effected with K_2CO_3 in

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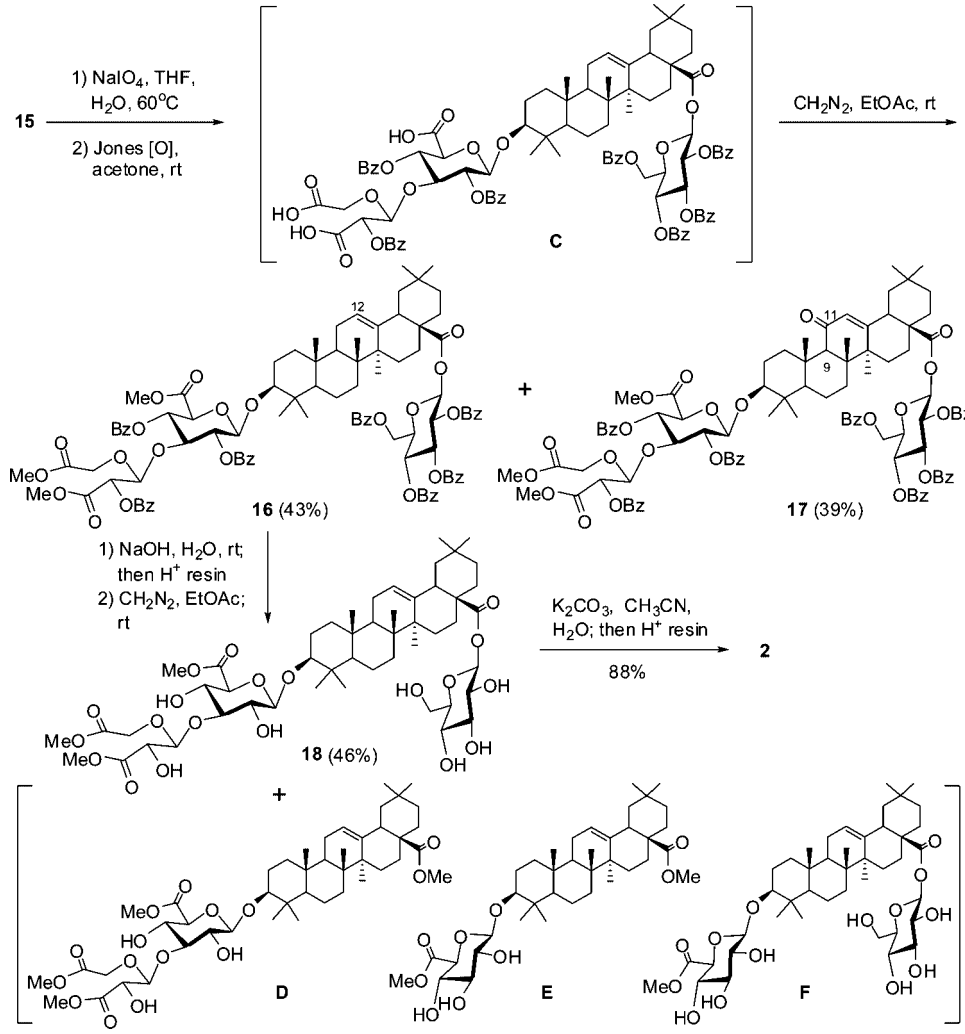
SCHEME 3. Completion of the First-Generation Synthesis of 2″-*epi*-Betavulgaroside III (2)



a mixed solvent of CH_3CN and H_2O,[2b] affording the desired 2″-*epi*-betavulgaroside III (**2**) in a good 88% yield.

Second-Generation Synthesis of 2″-*epi*-Betavulgaroside III (2). The above synthetic approach compromised with two low-yielding transformations: one was the oxidation of triol **15** (to give tris-carboxylic acid **C**); another was the final removal of the methyl and benzoyl protecting groups (**16** → **2**). Thus, we decided to elaborate the ester function in the 3-*O*-saccharide moiety before connecting to the oleanane aglycon to avoid the oxidation of the allylic 11-CH_2. In addition, benzyl group was chosen to protect the carboxylic acid function to facilitate the final removal (via hydrogenolysis).

The required *seco*-disaccharide donor **25** was prepared as shown in Scheme 4. Thus, treatment of the previous available glucosyl imidate **5** with HOAc and TMSOTf (0.1 equiv) provided 1-β-acetate **19** (95%; H-1, 5.94 ppm, d, $J = 8.1$ Hz). Removal of the 6-*O*-trityl group (in **19**) with $TsOH \cdot H_2O$ provided **20** (78%), compromised with the partial cleavage of the 1-*O*-acetyl group. Compound **20** was subjected to oxidation with Jones reagent to generate the 6-carboxylic acid function; subsequent removal of the 3-*O*-benzyl group with $NaBrO_3$ and $Na_2S_2O_4$ (EtOAc, H_2O, rt)[21] followed by benzyl ester formation (BnBr, $NaHCO_3$, DMF, 50 °C) furnished benzyl uronate **21** bearing a free 3-OH in good yield (77% for three steps). Glycosylation of **21** with thioarabinoside **7** under the action of NIS and AgOTf was able to afford the α-L-arabinosyl-(1→3)-glucuronide **22** in a high 87% yield (H-1′, 4.85 ppm, d, $J = 5.7$ Hz). The 3′,4′-*O*-isopropylidene group in **22** was removed with $TsOH \cdot H_2O$, giving diol **23** (78%). Treatment of **23** with $NaIO_4$ (THF, H_2O, 60 °C), followed by further oxidation of the resulting bis-aldehyde with $NaClO_2$ and NH_2SO_3H,[2f] and subsequent benzyl ester formation (BnBr, $NaHCO_3$, DMF) afforded the tris-benzyl ester **24** in an excellent 88% yield. Removal of the anomeric *O*-acetyl group was effected with $BnNH_2$ (THF, rt),[22] the resulting lactol was condensed with $NCCCl_3$ (DBU, CH_2Cl_2) to provide the desired *seco*-disaccharide trichloroacetimidate **25** in 98% yield.

Replacement of the previous benzoyl protecting groups in the 28-glucose unit with acetyl groups would further facilitate the final deprotection. Thus, peracetyl glucosyl α-bromide **26**,[12] in stead of the perbenzoyl counterpart **9**, was used to couple with oleanolic acid (**8**) under the similar phase-transfer-catalyzed conditions to provide the 28-β-glucosyl ester **27** (78%; H-1′, 5.57 ppm, d, $J = 7.8$ Hz) (Scheme 5). Condensation of **27** with

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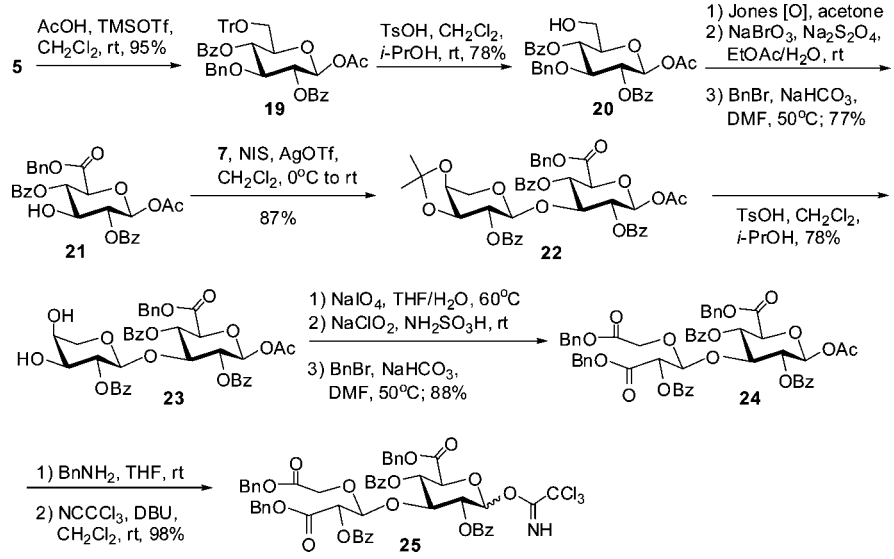
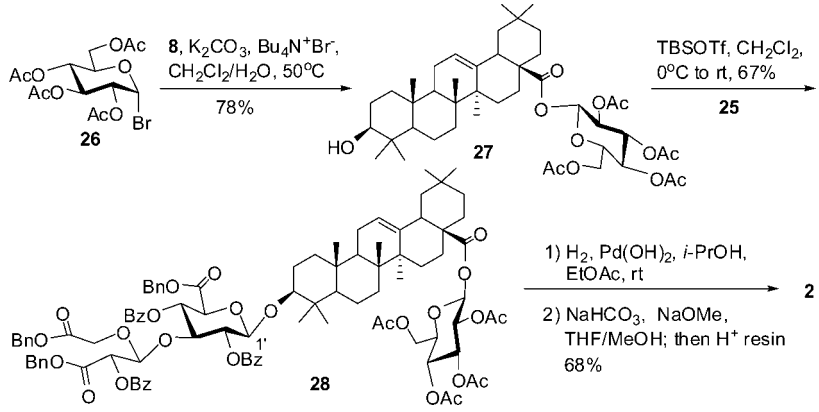
SCHEME 4. Preparation of the *seco*-Disaccharide Donor 25



SCHEME 5. Completion of the Second-Generation Synthesis of 2″-*epi*-Betavulgaroside III (2)



the *seco*-disaccharide imidate **25** under the normal conditions (0.1 equiv TBSOTf, CH_2Cl_2, 0 °C-rt) afforded the desired 3-*O*-β-glucuronide **28** in 67% yield (H-1′, 4.67 ppm, d, $J = 7.5$ Hz). Finally, the three benzyl groups were cleaved cleanly via hydrogenolysis over $Pd(OH)_2$ (*i*-PrOH, EtOAc, rt), and the four acetyl and three benzoyl groups were removed with NaOMe (THF, MeOH, rt). Acidification of the resulting mixture with H^+ resin and chromatography on ODS-silica gel (MeOH−H_2O−TFA, 6:2:0.024) afforded the 2″-*epi*-betavulgaroside III (**2**) in a good 68% yield.

Synthesis of Betavulgaroside III (1). Adopting the above approach to the synthesis of the natural betavulgaroside III (**1**) would require the preparation of *seco*-disaccharide donor **36** (Scheme 6), the 2′-epimer of the previous disaccharide donor **25**. The synthesis of **36**, shown in Scheme 6, involved reversion of the 2′-OH configuration on the α-L-arabinopyranosyl unit of the disaccharide **32**. To prepare **32**, a protecting group capable of neighboring participation and of being selectively removable in the presence of esters should be installed in the arabinose building block. The 2-(azidomethyl)benzoyl (AZMB) group turned out to be the choice.[9,23] Thus, phenyl 2-*O*-AZMB-3,4-*O*-isopropylidene-1-thioarabinopyranoside **29** was prepared (from **6**, 92%) and coupled with glucuronide **30**, which was prepared readily from **4** (four steps, 21% yield for the α-anomer; cf. **19**→**21**). Under the promotion of NIS and AgOTf, the coupled disaccharide **31** was obtained in a good 81% yield (H-1′, 4.95 ppm, d, $J = 5.4$ Hz). The 2′-*O*-AZMB group in **31** was then selectively taken off with Ph_3P (THF, H_2O, rt) to provide **32** (88%; H-1′, 4.43 ppm, d, $J = 6.9$ Hz). The resulting equatorial 2′-OH in **32** was successfully reversed via oxidation (Dess-Martin periodine, CH_2Cl_2, 50 °C) and subsequent reduction ($NaBH_4$, CH_2Cl_2−EtOAc−MeOH, 0 °C) to furnish the α-L-ribopyranoside **33** in a good 74% yield (H-1′, 4.99 ppm, d, $J =$ 4.8 Hz).[8] Worth noting is that we had prepared a 1-*O*-acetyl counterpart of the 1-*O*-benzoyl disaccharide **32** from arabinose **29** and the previously available glucuronide **21**, however, the 1-*O*-acetyl group could not survive during the reduction. The axial 2′-OH in **33** was protected with benzoyl group (BzCl, DMAP, pyridine, 50 °C) and the 3′,4′-*O*-isopropylidene group was removed ($TsOH \cdot H_2O$, CH_2Cl_2, MeOH, rt), providing **34** (81%). 3′,4′-Diol **34** was then subjected to the sequence of oxidative cleavage ($NaIO_4$, THF−H_2O, 60 °C), further oxidation of the resulting aldehyde to carboxylic acid ($NaClO_2$, NH_2SO_3H), and subsequent benzyl ester formation (cf. **23** → **24**) to furnish the tris-benzyl ester **35** in a satisfactory 75% yield. Selective removal of the anomeric benzoyl group in **35** was found to be difficult, comparing to the removal of the anomeric

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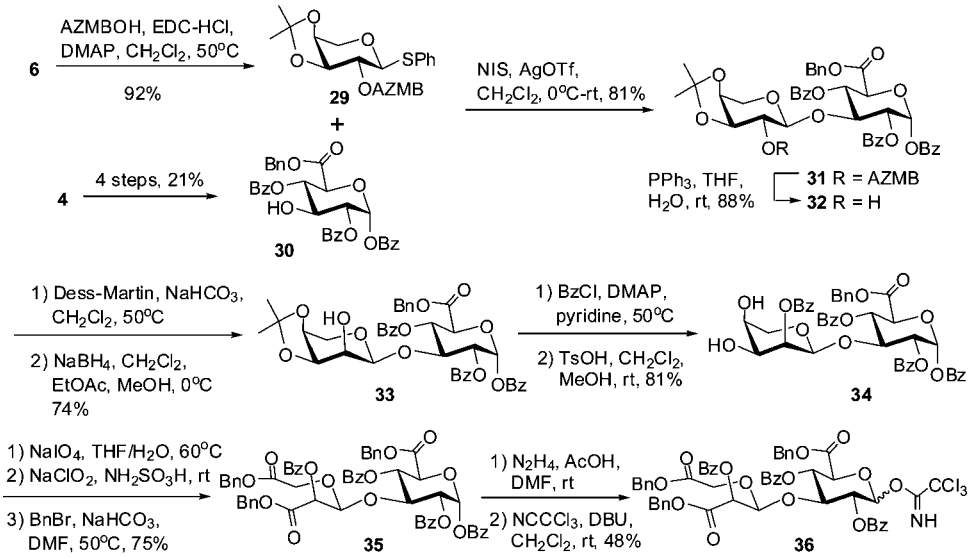
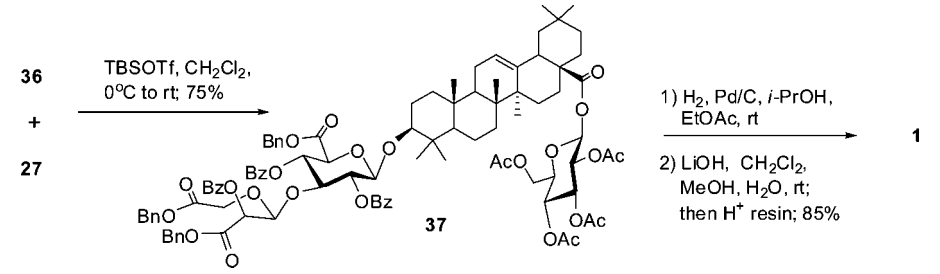
SCHEME 6. Preparation of the *seco*-Disaccharide Donor 36



SCHEME 7. Completion of the Total Synthesis of Betavulgaroside III (1)



acetyl group in **24**. Thus, treatment of **35** with $N_2H_4 \cdot$AcOH in DMF at rt afforded the lactol in moderate yield,[24] which was directly converted into the desired trichloroacetimidate **36** (48%).

Coupling of the *seco*-disaccharide imidate **36** with the 3-hydoxyl-oleanane-28-ester **27** under similar conditions for the coupling of **25** and **27** (Scheme 5, TBSOTf, CH_2Cl_2, 0 °C to rt) gave the coupled product **37** in a good 75% yield (Scheme 7). Finally, the three benzyl groups were cleaved cleanly via hydrogenolysis over Pd/C; the subsequent removal of the benzoyl and acetyl groups was found to be more effective with LiOH in a mixed solvent of CH_2Cl_2, MeOH, and H_2O (cf. with NaOMe for **28** → **2**, Scheme 5), furnishing the target molecule **1** in a good 85% yield. The analytical data of the synthetic **1** are in good accordance with those reported for the natural product.[25]

Conclusion

Triterpene *seco*-glycosides constitute a small family of the plant saponins, which feature a terminal *seco*-saccharide appendage deriving supposedly from oxidative fragmentation of a monosaccharide unit. These novel structures might present interesting bioactivities, such as the anti-inflammatory activities via mimicry of the sLe^x structure. The nascent acetal and carboxylic acid functions in the triterpene *seco*-glycosides make the isolation and structure elucidation extremely difficult. Herein, we have developed synthetic approaches for the first time to the access to these molecules. Betavulgaroside III (**1**), a representative congener with its stereochemistry having been determined, is successfully synthesized in a total of 31 steps with L-arabinose, D-glucose, and oleanolic acid as starting materials. The longest linear sequence requires 23 steps and in an overall yield of 0.9% (from D-glucose). The synthesis features elaboration of the *seco*-saccharide unit prior to assembly of the triterpene 3,28-bisglycoside. This strategy has been proven superior to a latter oxidative elaboration of the *seco*-saccharide unit at the triterpene 3,28-bis-glycoside scaffold in the attempts to the synthesis of the more easily accessible 2″-*epi*-betavulgaroside III (**2**).

Experimental Section

For the synthesis of compounds **4**, **5**, **7**, **11**−**25**, **29**, and **30**, see the Supporting Information.

2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl Oleanate (27). To a solution of oleanolic acid **8** (2.3 g, 5.0 mmol) and glucosyl bromide **26** (2.7 g, 1.3 equiv) in CH_2Cl_2 (100 mL) were added K_2CO_3 (8.7 g, 1.2 equiv), water (65 mL), and Bu_4NBr (170 mg, 0.1 equiv). The resulting mixture was refluxed for 6 h and was then diluted with CH_2Cl_2. The organic phase, after being washed with water and brine, respectively, was dried over Na_2SO_4 and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether−EtOAc, 4:1) to give **27** (3.07 g, 78%) as a white foam: $[\alpha]^{27}_D$ 37.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (d, J = 7.8 Hz, 1H), 5.31−5.09 (m, 4H), 4.27 (dd, J = 12.3, 4.5 Hz, 1H), 4.07−4.01 (m, 1H), 3.81−3.75 (m, 1H), 3.22−3.17 (m, 1H), 2.82−2.78 (m, 1H), 2.06 (s, 3H), 2.01 (s, 6H), 2.00 (s, 3H), 1.11 (s, 3H), 0.97 (s, 3H), 0.89 (s, 6H), 0.77 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

(24) Coutant, C.; Jacquinet, J.-C. *J. Chem. Soc. Perkin Trans. 1* **1995**, 1573.
(25) A comparison of the NMR spectra of the synthetic **1**, **2**, and the natural product is given in the Supporting Information.

175.5, 170.5, 170.0, 169.3, 168.8, 142.7, 122.7, 91.4, 78.7, 72.7, 69.7, 67.8, 61.3, 55.0, 47.4, 46.6, 45.6, 41.5, 40.8, 39.1, 38.6, 38.3, 36.8, 33.6, 32.9, 32.7, 31.6, 30.5, 27.9, 27.6, 27.0, 25.5, 23.3, 23.2, 22.7, 20.6, 20.5, 18.1, 16.8, 15.5, 15.2; HRMS (MALDI) calcd for $C_{44}H_{66}O_{12}Na$ $[M + Na]^+$ 809.4447, found 809.4449.

Tris-benzyl Ester 28. A mixture of the glycosyl imidate **25** (22 mg, 0.02 mmol), acceptor **27** (31 mg, 1.5 equiv), and powered 4 Å molecular sieves in anhyd CH_2Cl_2 (5 mL) was stirred at rt under Ar for 1 h. A solution of TBSOTf in CH_2Cl_2 (0.1 equiv) was at 0 °C added dropwise. After being stirred at rt for 1 h, the mixture was neutralized with Et_3N, filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether−EtOAc, 3:1) to give **28** (27 mg, 67%) as a white foam: $[\alpha]^{25}_D$ −0.6 (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.04−7.12 (m, 30H), 5.65−5.56 (m, 2H), 5.46 (t, J = 8.4 Hz, 1H), 5.38−5.34 (m, 3H), 5.25−5.09 (m, 5H), 5.04−4.90 (m, 4H), 4.76 (t, J = 9.0 Hz, 1H), 4.67 (d, J = 7.5 Hz, 1H), 4.31−4.18 (m, 2H), 4.10−3.77 (m, 4H), 3.09−3.04 (m, 1H), 2.85−2.78 (m, 1H), 2.06 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.08 (s, 3H), 0.90 (s, 6H), 0.86 (s, 3H), 0.69 (s, 3H), 0.63 (s, 3H), 0.59 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 170.6, 170.1, 169.5, 169.4, 168.9, 167.0, 166.0, 165.4, 164.8, 164.6, 142.7, 135.2, 134.9, 134.7, 133.2, 133.0, 132.8, 130.0, 129.7, 129.6, 129.3, 128.6, 128.5, 128.3, 128.2, 128.2, 128.0, 127.9, 122.8, 103.0, 100.0, 91.5, 90.1, 77.4, 77.2, 77.0, 76.6, 75.9, 73.5, 72.7, 72.3, 71.7, 70.4, 69.8, 67.8, 67.4, 67.0, 66.5, 62.7, 61.4, 55.3, 47.4, 46.7, 45.6, 41.5, 40.9, 39.1, 38.6, 36.5, 33.6, 32.9, 31.6, 30.5, 29.6, 27.6, 25.5, 23.4, 22.6, 20.6, 20.5, 16.8, 16.0, 15.2; HRMS (MALDI) calcd for $C_{97}H_{110}O_{27}Na$ $[M + Na]^+$ 1729.7127, found 1729.7161.

2″-*epi*-Betavulgaroside III (2). Compound **28** (40 mg, 0.023 mmol) was treated with $Pd(OH)_2$/C (cat.) under 1 atm of H_2 in *i*-PrOH−EtOAc (4 mL:2 mL) for 5 h. The mixture was then filtered. The filtrate was concentrated and dissolved in THF−MeOH (2 mL:2 mL). To this solution was added $NaHCO_3$ (6 mg, 3 equiv) at rt. After being stirred for 1 h, NaOMe (cat.) was added to the solution. The resulting mixture was stirred until TLC (CH_2Cl_2−MeOH−H_2O, 5:4:1) indicated that the reaction completed and was then acidified with Dowex 50-X8 (H^+) resin to pH = 3.0. The filtrates were concentrated and purified with reversed-phase ODS column chromatography (MeOH−H_2O−TFA, 6:2:0.024) to give **2** (15 mg, 68%) as a white solid: $[\alpha]^{27}_D$ 23.9 (*c* 0.5, MeOH); ^1H NMR (300 MHz, C_5D_5N) δ 6.33 (d, J = 7.8 Hz, 1H), 6.17 (brs, 1H), 5.40 (s, 1H), 5.30 (ABq, J = 17.3 Hz, 1H), 5.16 (ABq, J = 16.6 Hz, 1H), 5.13 (d, J = 4.6 Hz, 1H), 5.00 (d, J = 7.6 Hz, 1H), 4.65 (m, 2H), 4.49−4.16 (m, 7H), 4.04 (d, J = 9.0 Hz, 1H), 3.35−3.32 (m, 1H), 3.19−3.16 (m, 1H), 1.27 (s, 6H), 1.08 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, C_5D_5N) δ 176.4, 144.1, 122.8, 106.5, 106.2, 95.7, 89.2, 85.8, 79.3, 78.9, 77.5, 74.6, 74.1, 72.4, 71.2, 65.7, 62.3, 55.7, 48.0, 47.0, 46.2, 42.1, 41.7, 39.9, 39.5, 38.6, 36.9, 34.0, 33.1, 32.5, 30.7, 28.3, 28.1, 26.5, 26.2, 23.7, 23.6, 23.4, 18.5, 17.5, 16.9, 15.5; negative-mode ESIMS (*m*/*z*) 955.1 $[M - H]^+$, 937.1 $[M - H_3{}^+O]$; positive-mode ESIMS (*m*/*z*): 979.5 $[M + Na]^+$, 995.4 $[M + K]^+$; Positive-mode HRMS (MALDI) calcd for $C_{47}H_{72}O_{20}Na$ $[M + Na]^+$ 979.4509, found 979.4536.

3,4-*O*-Isopropylidene-2-*O*-(2-azidomethyl)benzoyl-α-L-arabinopyranosyl-(1→3)-[benzyl 1,2,4-tri-*O*-benzoyl-α-D-glucuronopyranoside] (31). To a mixture of **30** (850 mg, 1.43 mmol) and 4 Å molecular sieves in anhyd CH_2Cl_2 (30 mL) was added a solution of the thioglycoside **29** (1.26 g, 2.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C dropwise, followed by addition of NIS (660 mg, 3 equiv) and AgOTf (75 mg, 0.2 equiv). The mixture was stirred for 1 h at rt and filtrated. The filtrate was diluted with EtOAc, washed with aqueous 10% $Na_2S_2O_3$, and brine, respectively, and then dried over Na_2SO_4 and concentrated. Chromatography over silica gel (petroleum ether−EtOAc, 5:1) gave **31** (1.07 g, 81%) as a white foam: $[\alpha]^{26}_D$ 59.3 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.08−7.01 (m, 24H), 6.74 (d, J = 3.3 Hz, 1H), 5.62 (t, J = 9.9 Hz, 1H), 5.54 (dd, J = 9.6, 3.6 Hz, 1H), 5.22 (dd, J = 7.2, 6.3 Hz, 1H), 5.07 (ABq, J = 12.0 Hz, 2H), 4.95 (d, J = 5.4 Hz, 1H), 4.72 (t, J = 9.9 Hz, 1H), 5.05 (ABq, J = 15.0 Hz, 2H), 4.27 (dd, J = 13.5, 6.3 Hz, 1H), 4.11 (t, J = 7.2 Hz, 1H), 3.61 (dd, J = 12.0, 7.5 Hz, 1H), 3.41 (dd, J = 12.3, 6.3 Hz, 1H), 1.38 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 165.1, 164.5, 164.4, 163.9, 137.9, 134.2, 133.8, 133.5, 133.1, 132.6, 130.7, 129.9, 129.3, 129.1, 128.7, 128.6, 128.4, 128.3, 128.3, 128.1, 127.5, 111.0, 100.1, 89.5, 74.8, 74.8, 72.6, 71.5, 70.9, 70.2, 68.1, 61.4, 52.7, 27.3, 25.7; HRMS (MALDI) calcd for $C_{50}H_{45}N_3O_{15}Na$ $[M + Na]^+$ 950.2743, found 950.2765.

3,4-*O*-Isopropylidene-α-L-arabinopyranosyl-(1→3)-[benzyl 1,2,4-tri-*O*-benzoyl-α-D-glucuronopyranoside] (32). To a solution of **31** (173 mg, 0.19 mmol) in THF (3 mL) at rt was added water (36l 10 equiv), followed by Ph_3P (150 mg, 3 equiv). After being stirred overnight, the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether−CH_2Cl_2−EtOAc, 5:3:2) to yield **32** (126 mg, 88%) as a white solid: $[\alpha]^{23}_D$ 59.8 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.11−6.81 (m, 20H), 6.80 (d, J = 3.6 Hz, 1H), 5.68−5.57 (m, 2H), 5.16 (d, J = 12.3 Hz, 1H), 5.00 (d, J = 12.3 Hz, 1H), 4.73 (d, J = 9.9 Hz, 1H), 4.56 (t, J = 9.3 Hz, 1H), 4.43 (d, J = 6.9 Hz, 1H), 4.11−4.04 (m, 1H), 3.80 (t, J = 7.8 Hz, 1H), 3.52 (m, 1H), 3.40 (dd, J = 5.7, 12.3 Hz, 1H), 3.22 (dd, J = 5.1, 12.3 Hz, 1H), 1.38 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 165.6, 165.0, 164.0, 134.1, 133.9, 133.5, 133.3, 129.9, 129.8, 129.7, 129.2, 128.7, 128.6, 128.4, 128.4, 128.3, 128.3, 110.3, 103.4, 89.7, 76.9, 76.8, 73.1, 71.9, 71.0, 70.9, 70.2, 68.0, 62.3, 27.4, 25.3; HRMS (MALDI) calcd for $C_{42}H_{40}O_{14}Na$ $[M + Na]^+$ 791.2311, found 791.2329.

3,4-*O*-Isopropylidene-α-L-ribopyranosyl-(1→3)-[benzyl 1,2,4-tri-*O*-benzoyl-α-D-glucuronopyranoside] (33). To a solution of **32** (23 mg, 0.03 mml) in CH_2Cl_2 (3 mL) was added $NaHCO_3$ (10 mg, 4 equiv) and the Dess−Martin reagent (40 mg, 3 equiv). The resulting mixture was stirred at 50 °C for 2 h and then diluted with EtOAc. The organic phase, after being washed with aqueous 10% $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine, respectively, was dried over Na_2SO_4 and then concentrated in vacuo to give the crude ketone as a white solid. The crude ketone was dissolved in CH_2Cl_2−EtOAc−MeOH (1 mL:0.5 mL:0.5 mL), followed by addition of $NaBH_4$ (1.5 mg, 1.5 equiv) at 0 °C. After being stirred for 0.5 h at 0 °C, the mixture was neutralized with 1 N HCl and diluted with EtOAc. The organic phase, after being washed with saturated aqueous $NaHCO_3$ and brine, respectively, was dried over Na_2SO_4 and concentrated. Chromatography over silica gel (petroleum ether−CH_2Cl_2−EtOAc, 5:3:2) gave **33** (17 mg, 74%) as a white solid: $[\alpha]^{23}_D$ 20.9 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.10−6.79 (m, 20H), 6.78 (d, J = 3.6 Hz, 1H), 5.73−5.63 (m, 2H), 5.16 (d, J = 11.7 Hz, 1H), 4.99 (d, J = 4.8 Hz, 1H), 4.92 (d, J = 11.7 Hz, 1H), 4.68 (d, J = 7.5 Hz, 1H), 4.60 (t, J = 9.6 Hz, 1H), 4.19 (t, J = 4.5 Hz, 1H), 3.98−3.95 (m, 1H), 3.57−3.53 (m, 1H), 3.46−3.39 (m, 1H), 3.01−2.94 (dd, J = 6.9, 11.7 Hz, 1H), 2.38 (d, J = 11.7 Hz, 1H), 1.40 (s, 3H), 1.23 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 165.3, 165.2, 164.0, 134.0, 133.9, 133.5, 133.4, 129.9, 129.8, 129.6, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 127.5, 126.9, 110.2, 99.0, 89.6, 73.4, 71.2, 70.9, 70.4, 68.2, 66.0, 65.2, 58.0, 27.9, 26.0; HRMS (MALDI) calcd for $C_{42}H_{40}O_{14}Na$ $[M + Na]^+$ 791.2310, found 791.2307.

2-*O*-Benzoyl-α-L-ribopyranosyl-(1→3)-[benzyl 1,2,4-tri-*O*-benzoyl-α-D-glucuronopyranoside] (34). Compound **33** (23 mg, 0.03 mmol) was dissolved in dry pyridine (2 mL), and BzCl (0.01 mL, 3 equiv) was added under an Ar atmosphere at rt. The mixture was stirred at 50 °C for 1 h and was then concentrated and diluted with EtOAc. The organic phase, after being washed with aqueous 1 N HCl, saturated aqueous $NaHCO_3$, and brine, respectively, was dried over Na_2SO_4 and then concentrated in vacuo to give the crude product as a yellow oil. To the solution of the crude product in MeOH−CH_2Cl_2 (2 mL:4 mL) was added *p*-TsOH·H_2O (18 mg, 3 equiv). After being stirred at rt until TLC (petroleum ether−EtOAc, 1:1) indicated that the reaction completed, the mixture was

neutralized with Et_3N and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether−EtOAc−CH_2Cl_2, 1:1:1) to give **34** (23 mg, 81%) as a white solid: $[\alpha]^{26}_D$ 58.0 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06−7.09 (m, 25H), 6.77 (d, J = 3.6 Hz, 1H), 5.74 (t, J = 9.6 Hz, 1H), 5.56 (dd, J = 3.3, 9.6 Hz, 1H), 5.39 (d, J = 3.9 Hz, 1H), 5.16 (d, J = 11.7 Hz, 1H), 4.98 (d, J = 11.7 Hz, 1H), 4.88 (t, J = 3.3 Hz, 1H), 4.73−4.67 (m, 2H), 4.07 (br, 1H), 3.58 (br, 1H), 3.29 (dd, J = 5.7, 11.1 Hz, 1H), 3.01 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 165.5, 165.0, 164.7, 163.9, 134.0, 133.9, 133.8, 133.4, 133.4, 133.3, 130.1, 130.0, 129.8, 129.7, 129.6, 129.3, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 128.0, 97.4, 89.4, 74.9, 72.2, 71.0, 69.9, 69.3, 68.8, 68.2, 65.8, 58.5; HRMS (MALDI) calcd for $C_{46}H_{40}O_{15}Na$ $[M + Na]^+$ 855.2260, found 855.2266.

Tris-benzyl Ester 35. To a solution of compound **34** (23 mg, 0.028 mmol) in THF−H_2O (2 mL:1 mL) at rt was added $NaIO_4$ (60 mg, 10 equiv). The mixture was stirred at 50−60 °C for 2 h, followed by cooling to 0 °C and the subsequent addition of $NaClO_2$ (27 mg, 10 equiv) and NH_2SO_3H (27 mg, 10 equiv). The resulting mixture was stirred at rt for 0.5 h and then diluted with EtOAc. The organic phase, after being washed with aqueous 10% $Na_2S_2O_3$ and brine, respectively, was dried over Na_2SO_4 and concentrated to give the crude acid as foam. To a solution of the crude acid in dry DMF (1 mL) were added $NaHCO_3$ (35 mg, 15 equiv) and BnBr (0.05 mL, 15 equiv). The mixture was heated to 50 °C for 4 h and was then concentrated and diluted with EtOAc. The organic phase was washed with water and brine, respectively, and was then dried over Na_2SO_4 and concentrated. Chromatography over silica gel (petroleum ether−EtOAc, 3:1) gave **35** (22 mg, 75%) as a white foam: $[\alpha]^{25}_D$ 33.3 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06−7.06 (m, 35H), 6.80 (d, J = 3.0 Hz, 1H), 5.58 (t, J = 9.0 Hz, 1H), 5.51 (d, J = 4.2 Hz, 1H), 5.34−4.86 (m, 9H), 4.70 (d, J = 9.9 Hz, 1H), 4.16 (d, J = 4.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 166.9, 166.0, 165.1, 164.9, 164.8, 164.0, 134.9, 134.8, 134.1, 133.8, 133.3, 130.1, 129.9, 129.8, 129.7, 129.5, 128.9, 128.7, 128.6, 128.5,128.4, 128.4, 128.3, 128.2, 128.1, 126.9, 100.2, 89.4, 73.4, 72.7, 71.9, 69.7, 68.0, 67.1, 66.5, 62.4; HRMS (MALDI) calcd for $C_{60}H_{50}O_{17}Na$ $[M + Na]^+$ 1065.2940, found 1065.2926.

***seco*-Disaccharide Trichloroacetimidate 36.** To a solution of **35** (80 mg, 0.077 mmol) in DMF (3 mL) was added $N_2H_4\cdot$AcOH (10 mg, 1.5 equiv). The resulting mixture was stirred at rt overnight and was then diluted with EtOAc. The organic phase, after being washed with 1 N HCl, H_2O, and brine, respectively, was dried over Na_2SO_4 and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether−EtOAc, 3:1) to give the lactol as a yellow oil. To a solution of the lactol in dry CH_2Cl_2 (3 mL) were added excess $NCCCl_3$ and DBU (cat.). The mixture was stirred at rt for 1 h and was then concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether−EtOAc, 2.5:1) to give **36** (40 mg, 48%; the α-anomer predominates) as a colorless oil: ^{1}H NMR (300 MHz, CD_3COCD_3) δ 9.49 (s, 1H), 8.10−7.22 (m, 30H), 6.87 (d, J = 3.3 Hz, 1H), 5.70−5.63 (m, 2H), 5.46−5.30 (m, 3H), 5.22−5.00 (m, 6H), 4.83 (d, J = 9.9 Hz, 1H), 4.47 (ABq, J = 16.5 Hz, 2H); ESIMS *m*/*z*, 1104.2 $[M + Na]^+$; HRMS (MALDI) calcd for $C_{55}H_{46}NO_{16}Cl_3Na$ $[M + Na]^+$ 1104.1774, found 1104.1746.

Tris-benzyl Ester 37. A mixture of the glycosyl imidate **36** (40 mg, 0.037 mmol), acceptor **27** (58 mg, 1.5 equiv), and powered 4 Å molecular sieves in anhyd CH_2Cl_2 (5 mL) was stirred at rt under Ar for 1 h. A solution of TBSOTf in CH_2Cl_2 (0.1 equiv) was added dropwise at 0 °C. After being stirred at rt for 1 h, the mixture was neutralized with Et_3N and then filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether−EtOAc, 3:1) to give **37** (47 mg, 75%) as a white foam: $[\alpha]^{23}_D$ 7.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94−7.10 (m, 30H), 5.60−5.55 (m, 2H), 5.42 (t, J = 5.1 Hz, 1H), 5.35−5.31 (m, 2H), 5.24−5.09 (m, 5H), 5.05−5.94 (m, 4H), 4.78−4.74 (m, 1H), 4.70−4.64 (m, 2H), 4.27 (dd, J = 12.3, 3.6 Hz, 1H), 4.19−4.01 (m, 4H), 3.79−3.75 (m, 1H), 3.08−3.04 (m, 1H), 2.83−2.77 (m, 1H), 2.06 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.07 (s, 3H), 0.90 (s, 6H), 0.84 (s, 3H), 0.67 (s, 3H), 0.62 (s, 3H), 0.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 170.6, 170.1, 169.4, 169.2, 168.9, 166.9, 166.1, 165.2, 164.9, 164.5, 142.8, 135.2, 135.1, 134.7, 133.2, 133.1, 133.1, 129.9, 129.8, 129.7, 129.3, 129.3, 128.6, 128.6, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 122.9, 103.0, 100.0, 91.5, 90.2, 76.3, 73.6, 73.1, 72.8, 72.7, 72.4, 70.7, 69.9, 68.0, 67.6, 67.2, 66.4, 62.9, 61.5, 55.4, 47.5, 46.8, 45.7, 41.6, 41.0, 39.2, 38.7, 38.4, 36.6, 33.7, 33.0, 32.8, 31.7, 30.6, 27.7, 25.7, 25.6, 23.4, 22.8, 20.7, 20.5, 18.0, 16.9, 16.0, 15.2; HRMS (MALDI) calcd for $C_{97}H_{110}O_{27}Na$ $[M + Na]^+$ 1729.7127, found 1729.7128.

Betavulgaroside III (1). Compound **37** (18 mg, 0.01 mmol) was treated with 10% Pd/C (cat.) under 1 atm of H_2 in *i*-PrOH−EtOAc (1 mL: 2 mL) for 5 h. The mixture was filtered. The filtrate was concentrated and dissolved in CH_2Cl_2−MeOH−H_2O (1.5 mL:2 mL: 1.5 mL), followed by the addition of $LiOH\cdot H_2O$ (10 mg, 25 equiv). The resulting mixture was at rt stirred, until TLC (CH_2Cl_2−MeOH−H_2O, 5:4:1) indicated that the reaction completed. The mixture was acidified with Dowex 50-X8 (H^+) resin to pH = 3.0 and filtered. The filtrates were concentrated and purified by reversed-phase ODS column chromatography (MeOH−H_2O−TFA, 6:2:0.024) to afford **1** (8 mg, 85%) as a white solid: $[\alpha]^{23}_D$ 7.2 (*c* 0.1, MeOH), [lit.[2b] $[\alpha]^{28}_D$ 10.8 (*c* 0.1, MeOH)]; ^{1}H NMR (400 MHz, C_5D_5N) δ 6.33 (d, J = 8.0 Hz, 1H), 6.31 (brs, 1H), 5.40 (brs, 1H), 5.35 (brs, 1H), 5.31 (brs, 1H), 5.08 (ABq, J = 16.2 Hz, 1H), 4.99 (d, J = 7.8 Hz, 1H), 4.65−4.61 (m, 2H), 4.49−4.16 (m, 7H), 4.03 (m, 1H), 3.35 (dd, J = 11.4, 3.9 Hz, 1H), 3.19 (m, 1H), 1.27 (s, 6H), 1.08 (s, 3H), 0.96 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, C_5D_5N) δ 176.4, 174.8, 173.9, 172.4, 144.1, 122.8, 106.7, 105.4, 95.7, 89.1, 85.4, 79.3, 78.9, 77.6, 74.8, 74.1, 72.3, 71.1, 65.0, 62.2, 55.7, 47.9, 47.0, 46.2, 42.1, 41.7, 39.9, 39.5, 38.6, 36.9, 34.0, 33.1, 33.0, 32.5, 30.7, 28.2, 28.1, 26.6, 26.1, 23.7, 23.6, 23.4, 18.5, 17.5, 16.9, 15.5; negative-mode ESIMS (*m*/*z*) 955.1 $[M - H]^+$; positive-mode ESIMS (*m*/*z*) 979.5 $[M + Na]^+$, 995.4 $[M + K]^+$; positive-mode HRMS (MALDI) calcd for $C_{47}H_{72}O_{20}Na$ $[M + Na]^+$ 979.4509, found 979.4541.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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