18 H), 0.72-1.03 (comp m, 30 H), 1.21 (d, J = 6.9 Hz, 3 H), 1.25 (d, J = 5.9 Hz, 3 H), 1.30-1.48 (m, 2 H), 1.61-1.73 (m, 2 H), 1.82-2.20 (comp m, 4 H), 2.06 (s, 3 H), 2.09 (s, 3 H), 2.39 (m, 1 H), 2.66 (m, 1 H), 2.95 (ABq, J_{AB} = 5.5 Hz, $\Delta\nu_{AB}$ = 3.6 Hz, 2 H), 3.00 (m, 1 H), 3.08 (dd, J = 9.9 and 8.1 Hz, 1 H), 3.23 (dd, $J_1 = J_2$ = 9.3 Hz, 1 H), 3.30-3.45 (m, 2 H), 3.49 (q, J = 8.0 Hz, 1 H), 3.67 (m, 1 H), 3.80 (dd, J = 10.0 and 3.9 Hz, 1 H), 3.98 (dd, $J_1 = J_2$ = 9.9 Hz, 1 H), 4.26 (d, J = 7.6 Hz, 1 H), 4.48 (m, 1 H), 4.83 (dd, $J_1 = J_2$ = 8.1 Hz, 1 H), 5.21 (m, 1 H), 5.27 (dd, J = 9.9 and 8.1 Hz, 1 H), 6.03 (d, J = 3.9 Hz, 1 H), 6.45 (d, J = 16.0 Hz, 1 H), 7.39 (m, 3 H), 7.55 (m, 2 H), 7.78 (d, J = 16.0 Hz, 1 H); high-resolution mass spectrum (CI, isobutane) m/z 1117.5417 [$(M - C_2H_5)^+$, calcd for $C_{56}H_{89}O_{17}Si_3$ 1117.5408].

(+)-α-Phyllanthoside (1α). Trisilyl ether **93** (5.0 mg, 0.0044 mmol) was dissolved in AcOH-H_2O-THF (6:3:1; 1.0 mL) at room temperature. After 23 h, the mixture was concentrated in vacuo by using a bulb-to-bulb distillation apparatus. Flash chromatography, with menthanol-chloroform (1:24) as eluant, gave 3.3 mg (94% yield) of α-phyllanthoside (**1α**): $[\alpha]^{22}_D$ +68.7° (c 0.6, $CHCl_3$); IR ($CHCl_3$) 3600-3300 (m), 3020 (m), 2950 (m), 1745 (s), 1710 (s), 1640 (m), 1450 (m), 1375 (m), 1310 (m), 1240 (s), 1170 (s), 1120 (s), 1075 (s), 1050 (s), 1010 (s), 945 (w), 795 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (d, J = 6.9 Hz, 3 H), 1.25 (dd, $J_1 = J_2$ = 5.9 Hz, 6 H), 1.30-1.48 (m, 2 H), 1.61-1.72 (m, 2 H), 1.77-2.10 (comp m, 8 H), 2.16 (s, 3 H), 2.18 (s, 3 H), 2.25 (m, 1 H), 2.64 (m, 1 H), 2.97 (s, 2 H), 3.16 (dd, $J_1 = J_2$ = 9.2 Hz, 1 H), 3.27-3.38 (m, 3 H), 3.43 (dd, J = 9.3 and 4.2 Hz, 1 H), 3.67 (m, 1 H), 3.79 (dd, J = 10.0 and 3.9 Hz, 1 H), 3.99 (dd, $J_1 = J_2$ = 11.5 Hz, 1 H), 4.31 (d, J = 7.7 Hz, 1 H), 4.46 (m, 1 H), 4.76 (dd, $J_1 = J_2$ = 9.4 Hz, 1 H), 5.15 (m, 1 H), 5.18 (dd, $J_1 = J_2$ = 9.7 Hz, 1 H), 6.14 (d, J = 3.8 Hz, 1 H), 6.52 (d, J = 16.0 Hz, 1 H), 7.39 (m, 3 H), 7.56 (m, 2 H), 7.78 (d, J = 16.0 Hz, 1 H). Anal. Calcd for $C_{40}H_{52}O_{17}$: C, 59.69; H, 6.51. Found: C, 59.73; H, 6.71.

Acknowledgment. We are pleased to acknowledge support of this investigation by the National Institutes of Health (National Cancer Institute) through Grant CA 19033. In addition, we thank Drs. George Furst, Patrick J. Carroll, and John Dykins of the University of Pennsylvania Spectroscopic Service Centers for assistance in securing and interpreting high-field NMR spectra, X-ray crystal structures, and mass spectra. Finally, we thank Dr. Christopher S. Shiner for helpful suggestions and critical comments.

Phyllanthoside-Phyllanthostatin Synthetic Studies. 9. Total Syntheses of (-)-Phyllanthostatin 1, (+)-Phyllanthostatin 2, and (+)-Phyllanthostatin 3

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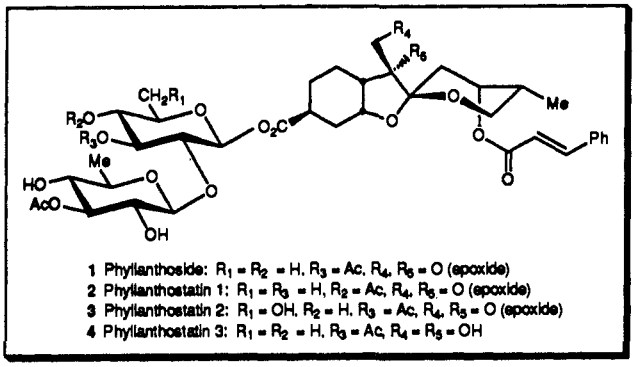
Contribution from the Department of Chemistry, the Laboratory for Research on the Structure of Matter, and the Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received June 8, 1990*

Abstract: Phyllanthostatins 1, 2, and 3 (**2-4**) have been synthesized for the first time. The unusual **1′→2β** glycosidic linkages of the disaccharide moieties were constructed via anchimerically-assisted Koenigs-Knorr reactions. The novel β-glycosyl esters were then generated through Mitsunobu coupling of suitably protected disaccharides with fully endowed aglycon carboxylic acids. For phyllanthostatins 1 and 2, the use of chloroacetate esters for disaccharide hydroxyl protection was explored. This tactic afforded a crystalline α-lactol precursor of **2**, which in turn furnished the requisite β-glycosyl ester exclusively. However, inefficient dechloroacetylation with hydrazine dithiocarbonate gave **2** and **3** in low yield. Triethylsilyl ether protection was uneventfully employed in the synthesis of phyllanthostatin 3 (**4**). Finally, a more convergent endgame for phyllanthoside (**1**) further exploited the aglycon precursor of **2** and **3**.

In the preceding paper in this issue we described the first (and, to date, the only) total synthesis of (+)-phyllanthoside (**1**), a novel bisabolane glycoside isolated by Kupchan in 1977 from the roots of the Central American tree *Phyllanthus acuminatus* Vahl.[1,2] Pettit reported the complete structures of **1** and of the closely related phyllanthostatins (**2-4**) in 1982.[3] The unusually selective cytotoxic properties and highly challenging architecture have established these glycosides as important targets for total synthesis.[4]

In this full account, we describe the completion of the first total syntheses of phyllanthostatins 1-3 (**2-4**) as well as a new endgame for phyllanthoside (**1**). These efforts comprise a second-generation approach to the phyllanthoside-phyllanthostatin antitumor glycosides, wherein we attempted to capitalize on the strengths of our initial strategy while addressing its shortcomings.[5]



1 Phyllanthoside: $R_1 = R_2$ = H, R_3 = Ac, R_4, R_5 = O (epoxide)
2 Phyllanthostatin 1: $R_1 = R_3$ = H, R_2 = Ac, R_4, R_5 = O (epoxide)
3 Phyllanthostatin 2: R_1 = OH, R_2 = H, R_3 = Ac, R_4, R_5 = O (epoxide)
4 Phyllanthostatin 3: $R_1 = R_2$ = H, R_3 = Ac, $R_4 = R_5$ = OH

(1) Smith, A. B., III; Rivero, R. A.; Hale, K. J.; Vaccaro, H. A. *J. Am. Chem. Soc.*, preceding paper in this issue.

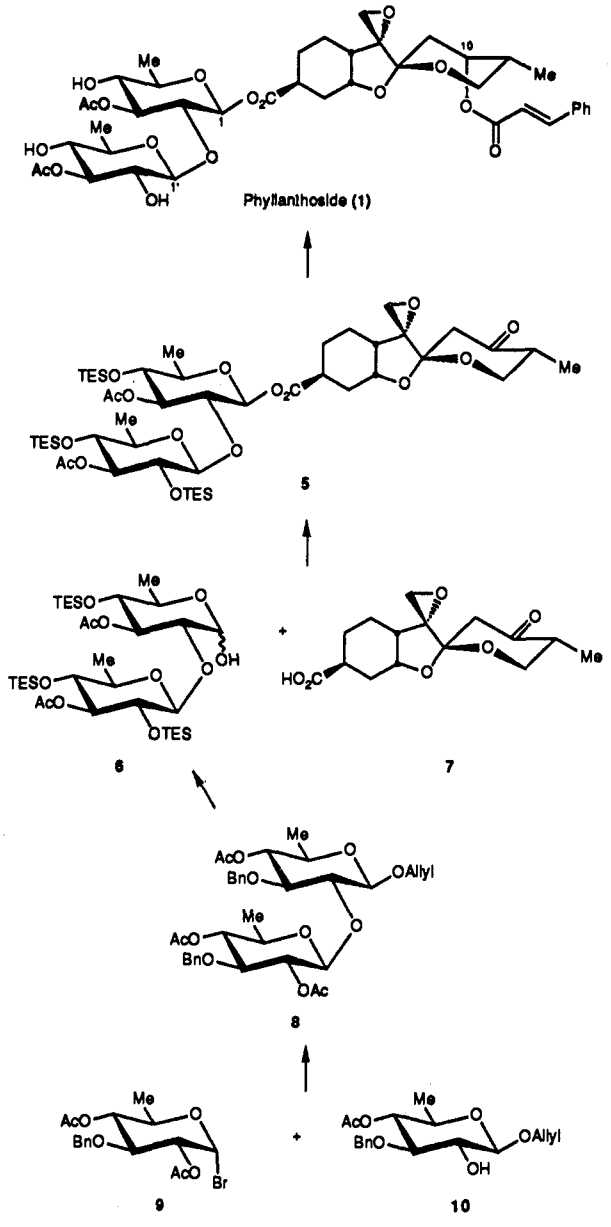
(2) Kupchan, S. M.; Lavoie, E. J.; Branfman, A. R.; Fri, B. Y.; Bright, W. M.; Bryan, R. F. *J. Am. Chem. Soc.* **1977**, *99*, 3199.

(3) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P.; Schmidt, J. M. *Can. J. Chem.* **1982**, *60*, 939. Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P. *Can. J. Chem.* **1982**, *60*, 544. Pettit, G. R.; Cragg, G. M.; Niven, M. L.; Nassimbeni, L. R. *Can. J. Chem.* **1983**, *61*, 2630. Pettit, G. R.; Cragg, G. M.; Suffness, M. I.; Gust, D.; Boettner, F. E.; Williams, M.; Saenz-Renauld, J. A.; Brown, P.; Schmidt, J. M.; Ellis, P. D. *J. Org. Chem.* **1984**, *49*, 4258. Also see: Pettit, G. R.; Schaufelberger, D. E.; Nieman, R. A.; Dufresne, C.; Saenz-Renauld, J. A. *J. Nat. Prod.* **1990**, *53*, 1406.

(4) Phyllanthoside (**1**) and phyllanthostatin 1 (**2**) are in phase 1 clinical trials under the auspices of the NCI-EORTC. Both compounds inhibit human breast cancer cell lines, with ED50s (μg/mL) against P388 of 0.27 and 0.19, respectively. Against P388 in vivo, the respective T/C values are 152% and 162-190% at doses of 6.68 and 4-16 mg/kg. Personal communication from Dr. Charles K. Grieshaber, Chief, Toxicology Branch, Developmental Therapeutics Program, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892. Also, see: Powis, G.; Moore, D. J. *J. Chromatogr.* **1985**, *342*, 129.

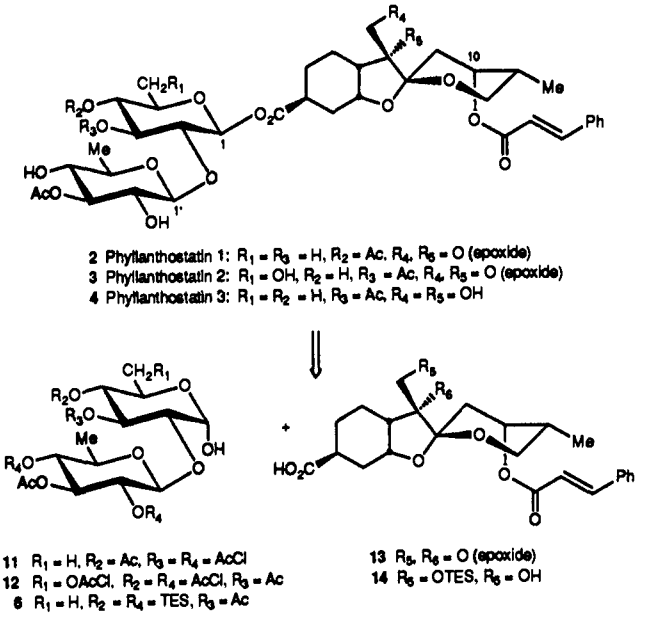
0002-7863/91/1513-2112$02.50/0

Scheme I. First-Generation Synthesis of Phyllanthoside



Retrosynthetic Analysis of the Phyllanthostatins: A Second-Generation Approach. A critical reappraisal of our earlier phyllanthoside synthesis (Scheme I) underscored the importance of three challenging problems: optimal selection of hydroxyl protecting groups, stereochemical control in glycosyl ester generation, and economic final elaboration of the target structure.[1] The previous route to **1** ultimately entailed a benzyl–acetyl interchange, necessitated by a requirement for anchimeric assistance in Koenigs–Knorr disaccharide formation, followed by reprotection with TES groups (i.e, **8** → **6**, Scheme I). Three-step removal of the *O*-allyl anomeric protecting group then gave a disappointing 2:1 (α/β) ratio of lactol anomers. As expected, the Mitsunobu glycosyl esterification developed in our laboratory[6] proceeded with inversion of the anomeric center, furnishing a corresponding 2:1 mixture of the desired β-glycosyl ester (**5**) and its α-anomer; however, the formation of a significant quantity of the undesired α-linked ester constituted a serious drawback. A further disadvantage of this route was the linearity of the final operations, wherein transformation of the C(10) carbonyl to the axial cinnamate ester was deferred until after the Mitsunobu coupling.

Scheme II. Retrosynthetic Analysis of Phyllanthostatins 1–3



These considerations led us to devise several new tactics for the phyllanthostatin synthetic venture. First, we envisioned a more convergent endgame, utilizing fully endowed aglycon units for glycosyl ester formation. In addition, we sought to employ more effective hydroxyl protecting groups. Whereas the stereoselective Koenigs–Knorr glycosidation was still deemed worthwhile despite the cumbersome protecting group interchange, replacement of the TES ethers by an alternative moiety was expected to afford greater efficiency in the construction of the individual disaccharides. The selection of such an alternative was, of course, complicated by severe constraints: (1) the lability of the phyllanthostatins toward acid and base as well as their susceptibility to reduction and acetate migration[7] necessitated deprotection under very mild, essentially neutral conditions, and (2) compatibility with Mitsunobu glycosyl ester formation and with the relatively vigorous conditions often required for removing anomeric hydroxyl protecting groups was essential. Foremost among several prospective choices, the chloroacetate moiety appeared to possess all of the requisite characteristics.[8] Importantly, these esters can be cleaved with nucleophiles such as hydrazine dithiocarbonate[9] and thiourea,[8] under conditions which avert acetyl migration. The use of chloroacetates would in turn permit masking of the anomeric hydroxyl as a methyl glycoside, simplifying the eventual deprotection of that position. Finally, we recognized that chloroacetylated carbohydrates are often crystalline. This attribute would generally facilitate the purification of intermediates and moreover might afford pure disaccharide α-lactols via fractional

(5) For the preceding papers in this series, see: (a) (+)-Phyllanthocin: Smith, A. B., III; Fukui, M. *Abstracts of Papers*, 187th National Meeting of the American Chemical Society, St. Louis, MO; American Chemical Society: Washington, DC, 1984; ORGN 6. Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269. Smith, A. B., III; Empfield, J. R.; Vaccaro, H. A. *Tetrahedron Lett.* **1989**, *30*, 7325. Smith, A. B., III; Fukui, M.; Vaccaro, H. A.; Empfield, J. R. *J. Am. Chem. Soc.*, a previous paper (contribution no. 7) in this issue. (b) (+)-Phyllanthoside (**1**): Smith, A. B., III; Fukui, M.; Rivero, R. A. *Abstracts of Papers*, 189th National Meeting of the American Chemical Society, Miami Beach, FL; American Chemical Society: Washington, DC, 1985; ORGN 82. Smith, A. B., III; Rivero, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 1272. (c) (−)-Phyllanthostatin 1 (**2**): Smith, A. B., III; Hale, K. J.; Vaccaro, H. A. *J. Chem. Soc., Chem. Commun.* **1987**, 1026. (d) (+)-Phyllanthostatin 2 (**3**): Smith, A. B., III; Hale, K. J.; Vaccaro, H. A. *Tetrahedron Lett.* **1987**, *28*, 5591. (e) (+)-Phyllanthostatin 3 (**4**) and (+)-phyllanthocindiol methyl ester: Vaccaro, H. A.; Rivero, R. A.; Smith, A. B., III *Tetrahedron Lett.* **1989**, *30*, 1465.

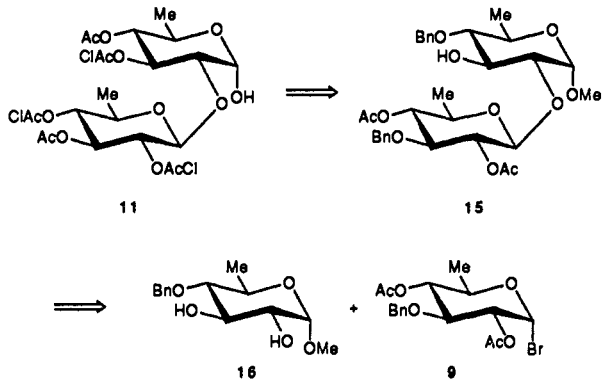
(6) Mitsunobu, O. *Synthesis* **1981**, 1. Smith, A. B., III; Hale, K. J.; Rivero, R. A. *Tetrahedron Lett.* **1986**, *27*, 5813.

(7) Pettit, G. R.; Cragg, G. M.; Suffness, M. I. *J. Org. Chem.* **1985**, *50*, 5060.

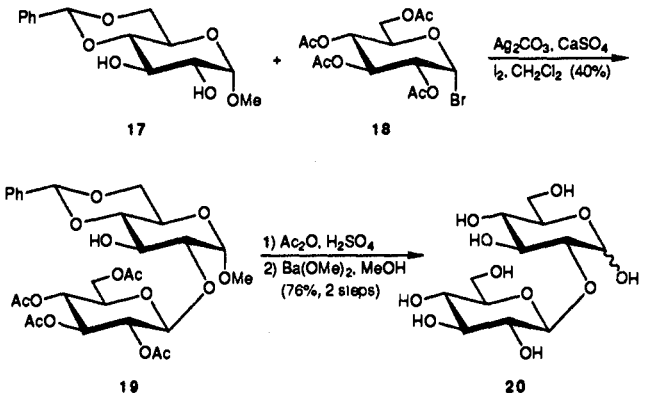
(8) Claudemans, C. P. J.; Bertolini, M. J. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., BeMiller, J. N., Eds.; Academic: New York, 1980; Vol. VIII, p 272, and references cited therein. See, also: Naruto, M.; Ohno, K.; Naruse, N.; Takeuchi, H. *Tetrahedron Lett.* **1979**, 251.

(9) van Boeckel, C. A. A.; Beetz, T. *Tetrahedron Lett.* **1983**, *24*, 3775.

Scheme III. Retrosynthetic Analysis of the Disaccharide Moiety in Phyllanthostatin 1



Scheme IV. Coxon–Fletcher Synthesis of Sophorose



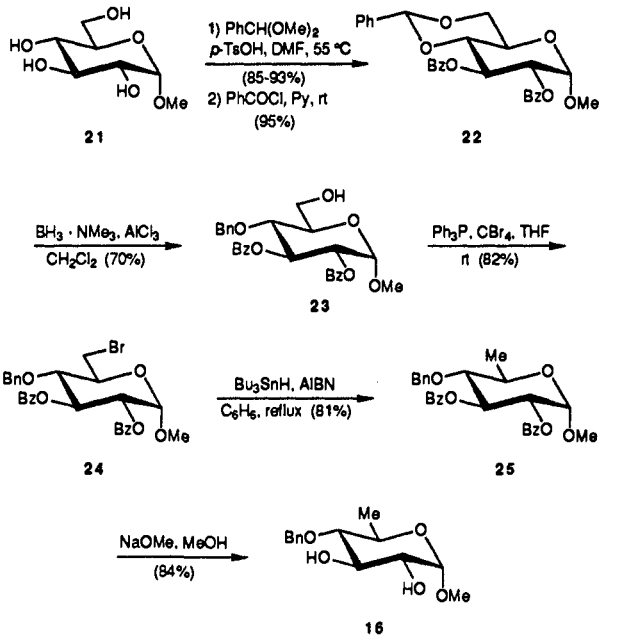
crystallization, thereby minimizing the formation of undesired α-glycosyl esters.

For implementation of this second-generation strategy, we selected glycosides **11** and **12** as disaccharide precursors of phyllanthostatins 1 and 2, respectively (Scheme II). Coupling of either substrate with the fully elaborated aglycon **13** via our Mitsunobu protocol[6] was judged to offer the most expedient approach to the β-glycosyl ester linkages. For phyllanthostatin 3 (**4**) we again envisioned a Mitsunobu glycosidation, in this case employing our previously prepared lactol **6**[1,5a] and the protected aglycon dihydroxy acid **14**.

Construction of Lactol 11, a Protected Phyllanthostatin 1 Disaccharide. Our approach to lactol **11** called for the intermediacy of disaccharide **15**. The most attractive route to **15** in turn involved a chemoselective Koenigs–Knorr reaction of the 2,3-diol **16** with glycosyl bromide **9**, prepared during our phyllanthoside synthesis[1,5a] (Scheme III). Such glycosidations have long been known in the carbohydrate literature; a particularly relevant example can be found in the 1961 Coxon and Fletcher synthesis of sophorose (**20**) (Scheme IV).[10] Accordingly, we undertook the preparation of diol **16** from commercially available methyl α-D-glucopyranoside (**21**).

The first two steps in our sequence involved benzylidenation and benzoylation of **21** to give **22** (Scheme V).[11] Following the earlier work of Garegg,[12] reduction of the benzylidene acetal with borane·trimethylamine and aluminum trichloride regioselectively installed a benzyl ether at O(4) and a hydroxyl group at O(6). The resulting alcohol (**23**) was then converted to bromide **24** (82%) upon treatment with triphenylphosphine and carbon tetrabromide in tetrahydrofuran.[13] The structure of **24** was deduced from its

Scheme V



^{13}C NMR spectrum; specifically, the C(6) resonance was shifted upfield by ca. 30 ppm to δ 33.3, presumably by enhanced shielding from the bromine substituent.[14] Radical-induced dehalogenation with tri-*n*-butylstannane[15] and azobisisobutyronitrile (AIBN) in benzene removed the bromine atom to furnish the requisite 6-deoxy sugar **25**. Although **25** could be isolated by flash chromatography, crystallization generally proved more convenient, affording the pure glycoside in 80–84% yield. The ^{1}H NMR spectrum of **25** was particularly diagnostic: the C(6) methyl resonated at high field (doublet, δ 1.35, $J_{5,6}$ = 6.3 Hz), whereas the signals for H(2) and H(3) appeared at low field (δ 5.12 and 5.99, respectively), indicative of *O*-benzoyl groups at positions 2 and 3. The coupling constants ($J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 10.2 Hz, $J_{4,5}$ = 9.5 Hz) confirmed the α-D-gluco configuration. To complete monosaccharide **16**, the benzoyl protecting groups were next removed with methanolic sodium methoxide[16] to afford 2,3-diol **16** after crystallization.

Chemo- and stereoselective coupling of **16** with **9** was performed at 55 °C, by using 1.5 equiv of the diol in a mixture of nitromethane and benzene (3:2) with mercury(II) cyanide as promoter[17] (Scheme VI). Analysis by TLC suggested the presence of four disaccharides, two major and two minor, in addition to unreacted diol **16**. Fractional crystallization furnished the predominate product in 41% yield; structure **15** was assigned on the basis of the 250-MHz ^{1}H NMR spectrum. Two acetate singlets (δ 1.99, 1.97), one methoxy (δ 3.34), and a C(3) hydroxyl (δ 2.56, $J_{3,OH}$ = 2.3 Hz) were particularly characteristic. The small $J_{1,2}$ splitting (3.5 Hz) together with large $J_{2,3}$ and $J_{3,4}$ couplings (9.8, 9.6 Hz) confirmed the α-D-gluco configuration of this pyranoside ring. The H(1′) resonance appeared at slightly higher field (δ 4.58), and, as expected for a β-glycosidic linkage, the coupling constant between H(1′) and H(2′) was substantial (9.2 Hz).

The additional disaccharides were purified by flash chromatography. The first fraction comprised a mixture of **26** and **15**, from which **26** crystallized in about 4% yield. The 500-MHz ^{1}H NMR spectrum revealed the α-configurations of both glycosidic linkages ($J_{1,2}$ = 3.9 Hz and $J_{1'2'}$ = 4.0 Hz), whereas the presence of a 1′,2-*O*-glycosidic linkage was ascertained from the coupling between H(3) and the hydroxyl proton at δ 2.62 ($J_{3,OH}$ = 2.7 Hz). The next component to elute was residual **15** (ca. 4% yield). The

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(11) Ansell, E. G.; Honeyman, J. *J. Chem. Soc.* **1952**, 2778.
(12) Ek, M.; Garegg, P. J.; Hultberg, H.; Oscarson, S. *J. Carbohydrate Chem.* **1983**, *2*, 305.
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(14) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: New York, 1972; p 133.
(15) Arita, H.; Ueda, N.; Matsushima, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 567.
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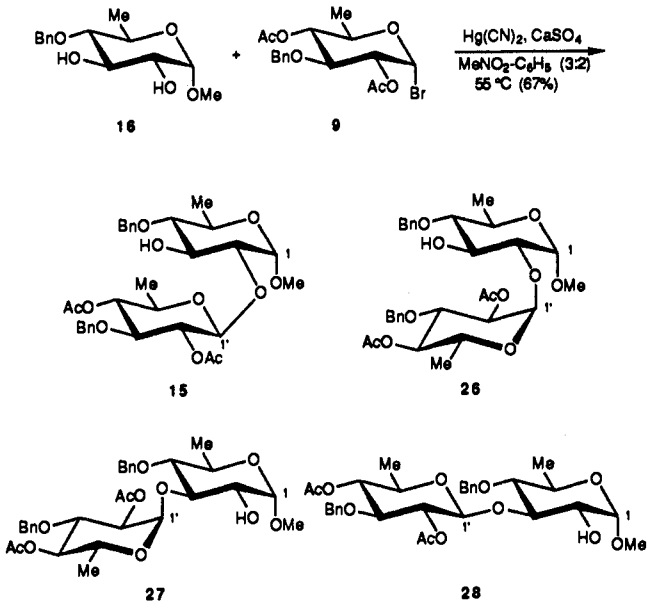
(17) Helferich, B.; Wedemeyer, K.-F. *Liebigs Ann. Chem.* **1949**, *563*, 139.

Scheme VI

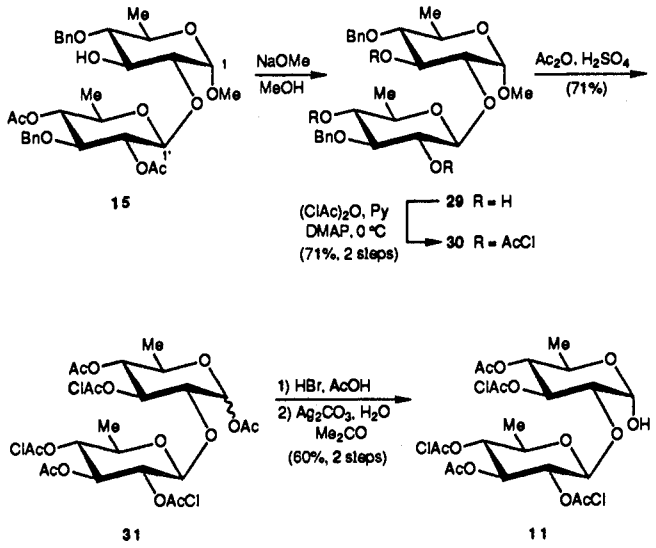


structure of the third product (1% yield)[18] has been tentatively assigned as **27** on the basis of ^{1}H NMR spectroscopy. The least mobile isomer **28** (12%)[18] gave rise to a largely first-order 250-MHz ^{1}H NMR spectrum, interpretable only in terms of the β,α-1′,3-*O*-linked disaccharide. The signals for H(2′) and H(4′) were easily identified as they both appeared at low field ($>\delta$ 4.8). Furthermore, the observed coupling constants ($J_{1'2'}$ = 8.0 Hz, $J_{2'3'}$ = 9.3 Hz, $J_{3'4'}$ = 9.5 Hz) were in full accord with the β-D-gluco configuration. The H(2) multiplet at δ 3.57 expressed large couplings to both the hydroxyl and H(3) protons ($J_{2,OH} = J_{2,3}$ = 9.8 Hz) as well as a small coupling to H(1). This pattern permitted assignment of the 1′,3-*O*-glycosidic linkage. The final component to elute was the starting diol **16**, usually recoverable in ca. 70–80% of the theoretical quantity.

Formation of such large amounts of α,α-1′,2- and α,α-1′,3-*O*-linked disaccharides from **9** is unusual when compared with glycosidations involving donors such as (α-bromo)tetraacetoxyglucose and may reflect the strong +I effect associated with C(6) deoxygenation.[19,20] The latter would decrease the electron deficiency of the glycosyl cation derived from **9**, thereby diminishing the participation of the O(2) acetate. Because the cyclic 1,2-acetoxonium ion is critical for directing the incoming nucleophile to the β-face, this effect would clearly lower the β/α-glycoside ratio.

Having successfully negotiated the chemoselective glycosidation, we next addressed the conversion of **15** into trischloroacetate **30** (Scheme VII). This operation entailed removal of the O(2′) and O(4′) acetates with methanolic sodium methoxide, followed by chloroacetylation of the resulting triol **29**. Attempted esterification with chloroacetyl chloride and pyridine at 0 °C[8] afforded no useful products. However, treatment of **29** with 6.5 equiv of chloroacetic anhydride and 3 equiv of (*N*,*N*-dimethylamino)pyridine[21] in pyridine for 2.5 h at 0 °C readily furnished **30** in 71% yield overall from **15**. Predictably, acetolysis of **30** at room temperature rapidly replaced the benzyl ethers (2–3 h), but, as expected for 6-

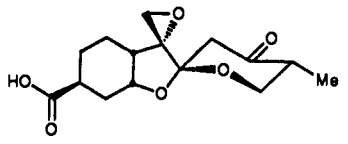
Scheme VII



deoxypyranosides,[20,22] complete reaction of the anomeric methoxyl group was much slower, requiring 48 h. Efforts to enhance the rate by increasing the concentration of acid catalyst resulted in significant fission of the 1′,2-*O*-glycosidic linkage. The ^{1}H NMR spectrum of **31** indicated a 20:1 mixture of α- and β-anomers; the α-glycosyl acetate was purified by fractional crystallization.

With the *O*-acetyl groups now successfully installed at C(3′) and C(4), all that remained to complete the synthesis of disaccharide **11** was deesterification of the C(1) acetate. This was most readily achieved by converting **31** to the corresponding glycosyl bromide and hydrolyzing the latter with silver carbonate in moist acetone;[23] the result was a 2:1 mixture (α/β) of anomers (Scheme VII). These lactols were readily equilibrated; moreover upon dissolution in an ethyl acetate–hexane mixture and standing in air for several hours, the requisite α-anomer **11** usually crystallized in ca. 60% yield overall from **31**. Careful comparison of the ^{1}H NMR spectra of **31** and **11** revealed that the OH proton in **11** resonated as a small doublet (δ 2.90, J = 2.4 Hz) and the H(1) resonance shifted to δ 5.27, confirming the regiochemical integrity of all remaining acetates.

Mitsunobu Glycosidation: Completion of (−)-Phyllanthostatin 1. Model Mitsunobu couplings of **11** with the aglycon analogue **7** established that no reaction occurred at low temperature (−50 °C to 0 °C).[6] We therefore performed the Mitsunobu glycosi-



7

dation of α-lactol **11** and the fully elaborated aglycon **13** at room temperature. To our delight, coupling proceeded with complete inversion at the anomeric center to afford β-glycosyl ester **33** in 61–71% yield (Scheme VIII). The structure of **33** was established via ^{1}H NMR spin-decoupling experiments. Specifically, H(1) and H(1′) appeared as doublets centered at δ 5.50 and 4.38, respectively. The large coupling constants ($J_{1,2}$ = 7.9 Hz, $J_{1',2'}$ = 8.2 Hz) provided strong evidence for the β-configurations of both glycosidic linkages. All remaining coupling constants were consistent with $^4C_1$ conformations of the sugar rings.[24]

A small amount (5–10%) of acyl hydrazide **32** (Scheme VIII) was also formed in this reaction, presumably via attack by di-

(18) Additional **27** and **28** were present in the reaction mixture. The isolated yields reflect difficulty encountered in separating these products from mercury(II) cyanide.

(19) A similar effect has been noted for L-rhamnosyl halides, which are considerably more reactive than the corresponding D-mannosyl halides, see: Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 165. Also, see: Eby, R.; Schuerch, C. *Carbohydr. Res.* **1974**, *34*, 79. Lucas, T. J.; Schuerch, C. *Carbohydr. Res.* **1975**, *39*, 39. Kronzer, F. J.; Schuerch, C. *Carbohydr. Res.* **1973**, *27*, 379. For a leading reference on the inductive effects of ring substituents in glycosidations, see: van Boeckel, C. A. A.; Beetz, T.; van Aelst, S. F. *Tetrahedron* **1984**, *40*, 4097.

(20) Bochkov, A. F.; Zaikov, G. E. *The Chemistry of the O-Glycosidic Bond: Formation & Cleavage*; Pergamon: Oxford, 1979.

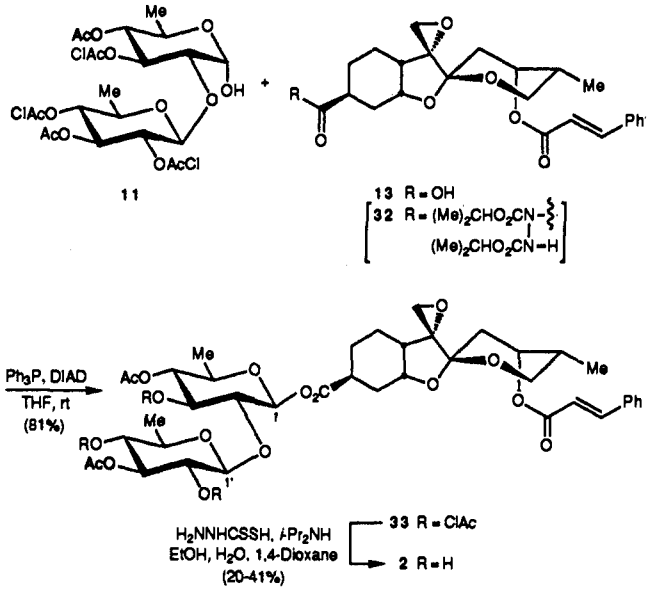
(21) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

(22) Aspinall, G. O.; Charlson, A. J.; Hirst, E. L.; Young, R. *J. Chem. Soc.* **1963**, 1696.

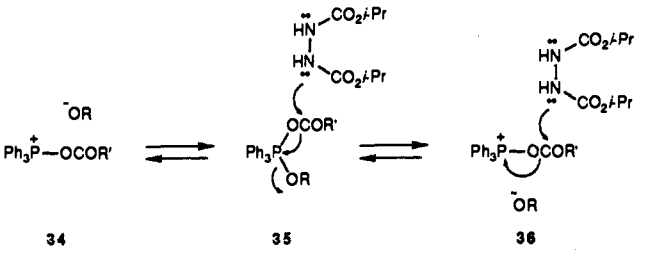
(23) Bonner, W. A. *J. Am. Chem. Soc.* **1958**, *80*, 3372.

(24) In the $^4C_1$ chair conformation, C(1) and C(4) lie below and above the plane containing the atoms C(2), C(3), C(5), and O(5), see: Reeves, R. E. *Adv. Carbohydr. Chem.* **1951**, *6*, 107.

Scheme VIII. Phyllanthostatin 1 Endgame



isopropyl hydrazinedicarboxylate upon acyloxyphosphonium ion **36** or mixed acyloxyphosphorane **35**. Indeed, Jenkins and Camp[25] have presented compelling evidence for equilibria involving **34-36** in Mitsunobu reactions of carbohydrate alcohols with carboxylic acids.

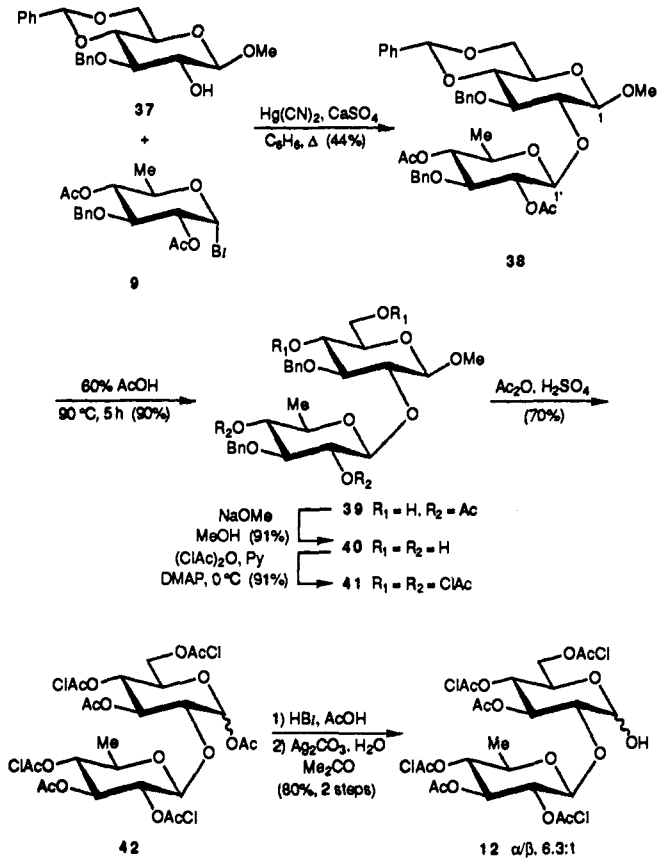


Disappointingly, attempted removal of the chloroacetate groups in **33** with thiourea[8] in ethanol or THF led only to decomposition under all conditions investigated. We therefore examined the hydrazine dithiocarbonate procedure introduced by van Boeckel and Beetz.[9] These workers recommended the use of reagent freshly prepared from carbon disulfide, hydrazine hydrate, acetic acid, and diisopropylethylamine in aqueous 1,4-dioxane. This protocol again led to significant product decomposition. Eventually, we discovered that elimination of the acetic acid and substitution of diisopropylamine for Hünig's base led to better results. These modifications afforded (−)-phyllanthostatin 1 (**2**) in yields ranging from 20 to 41%. Synthetic (−)-phyllanthostatin 1 was identical in all respects (500-MHz ^{1}H NMR, 125-MHz ^{13}C NMR, IR, HRMS, and TLC) with an authentic sample kindly provided by Dr. Matthew Suffness (National Institutes of Health, National Cancer Institute).

Significant problems associated with the use of hydrazine dithiocarbonate (HDTC) stem from the instability of the reagent. Indeed, in our hands freshly prepared stock solutions of HDTC generally lose their capability to dechloroacetylate within ca. 15–20 min. Presumably HDTC undergoes rapid breakdown to hydrogen sulfide and isothiocyanate, which in turn polymerizes. As a result, deprotections tend to stop prior to completion. Addition of excess reagent then leads to large amounts of polymeric byproducts, necessitating several preparative TLC or HPLC separations which correspondingly diminish the yields of pure products. Phyllanthostatin 1 (**2**) apparently undergoes side reactions with the excess reagent. Possible sites of attack include the cinnamoyl ester, the spiro epoxide, and/or the glycosyl ester.

(25) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045. Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3049.

Scheme IX



Total Synthesis of (+)-Phyllanthostatin 2: A Pyrrhic Victory. Our plan for constructing disaccharide lactol **12** rested upon the successful unification of glycosyl bromide **9** with the known alcohol **37**[26] to create **38**. Straightforward elaboration to **12** was then envisaged (Scheme IX).

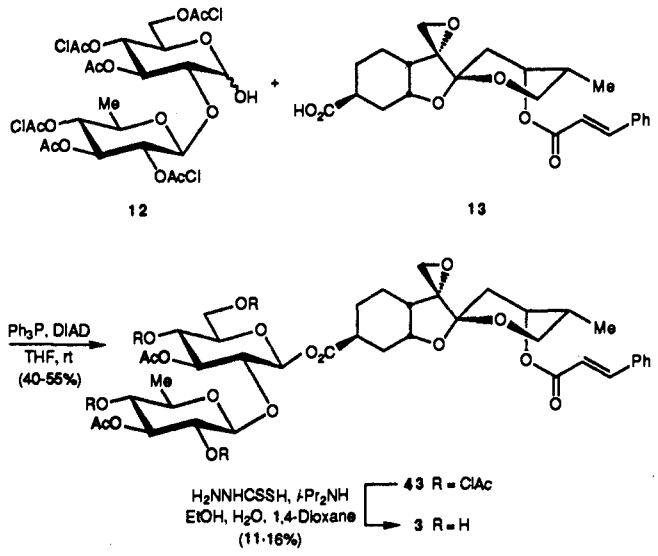
Toward this end, reaction of **37** with **9**[1,5a] and mercury(II) cyanide in benzene at reflux furnished a mixture of anomeric disaccharides in 67% yield (β/α = 8:1). Fractional crystallization afforded pure **38** in 44% yield. The identity of **38** was established through its 500-MHz ^{1}H NMR spectrum which revealed the presence of two acetates (δ 1.82 and 1.99), a methoxy group (δ 3.55), and a benzylidene methine (δ 5.56); the C(6′) methyl group resonated as a high-field doublet at δ 1.22 ($J_{5'6'}$ = 6.2 Hz). The β-configurations of the glycosidic bonds were deduced on the basis of large coupling constants for the anomeric protons ($J_{1,2}$ = 7.6 Hz, $J_{1'2'}$ = 7.9 Hz).

Debenzylidenation of **38** with 60% aqueous acetic acid then provided crystalline 4,6-diol **39** in 90% yield. The latter was subjected to Zemplen[16] deacetylation (91%), followed by facile chloroacetylation to deliver tetrachloroacetate **41** in 91% yield. As found with disaccharide **40**, the 500-MHz ^{1}H NMR spectrum of **41** displayed some second-order character, particularly the resonances associated with H(1), H(2), H(3), and H(4); H(1′), H(2′), and H(4′), however, were largely first-order. Acetolysis, effected by exposure of **41** to 2% sulfuric acid in acetic anhydride at room temperature for 2 days, afforded triacetate **42** in 70% yield. Finally, the derived deoxysophorosyl bromide was hydrolyzed with moist acetone containing silver carbonate as both promoter and acid scavenger to furnish **12** as an inseparable mixture of anomers in 80% overall yield. The α:β-ratio was 6.3:1, as judged by 500-MHz ^{1}H NMR spectroscopy.

Although TPP–DIAD glycosidation of **12** with **13** did generate **43** in 40–55% yield (Scheme X), the reaction proved surprisingly inefficient given our very satisfactory experience with this protocol.

(26) Lee, E. E.; Keaveney, G.; O'Colla, P. S. *Carbohydr. Res.* **1977**, *59*, 268.

Scheme X. Phyllanthostatin 2 Endgame



Among several byproducts, acyl hydrazide **32** (Scheme VIII) was most significant, accounting for ca. 30% of the acid consumed. As in our phyllanthostatin 1 synthesis, considerable difficulty was encountered during the attempted removal of the chloroacetate groups. Even our modified hydrazine dithiocarbonate reagent furnished phyllanthostatin 2 (**3**) in only 11–16% yields, while causing extensive decomposition. A possible acetate migration product also was isolated (2–3%). Other reagents, including *o*-phenylenediamine,[27] aqueous pyridine,[28] 2-aminoethanethiol,[27] thiosemicarbazide, and ammonia in toluene or methanol,[29] led in every case to total decomposition. Synthetic phyllanthostatin 2 was identical (500-MHz ^{1}H NMR, FAB MS, optical rotation, and TLC) with an authentic sample kindly provided by Dr. Suffness.

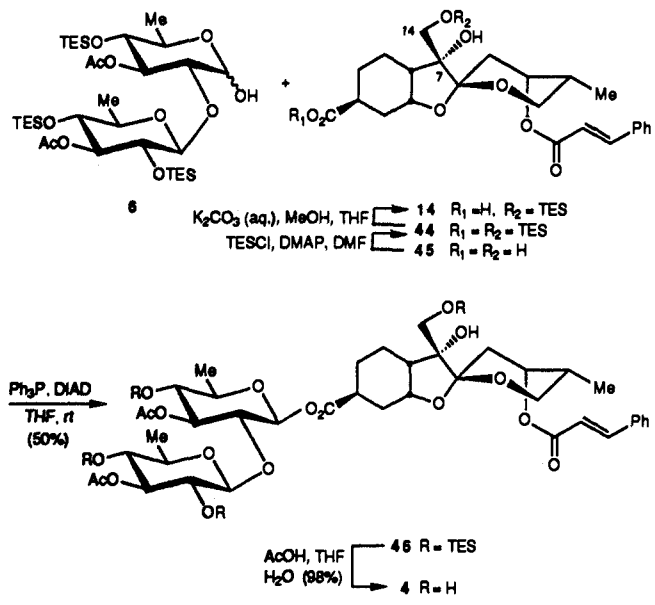
In an effort to improve upon this endgame, we explored the use of bromoacetate esters instead of chloroacetates as the hydroxyl protecting units. However, all attempts to effect bromoacetylation of tetraol **40** met with failure. Bromoacetylation of polyhydroxylated systems remains an unsolved problem in carbohydrate chemistry.

Total Synthesis of (+)-Phyllanthostatin 3: Completion of the Phyllanthoside-Phyllanthostatin Synthetic Venture. Phyllanthostatin 3 (**4**), a formal hydration product of phyllanthoside (**1**), contains a C(7,14) vicinal diol moiety in place of the 7,14-epoxide. Having secured a viable route to disaccharide **6** in our total synthesis of phyllanthoside, we anticipated that phyllanthostatin 3 could be constructed via preparation of the partially protected aglycon acid **14**, union of **14** with **6**, and deprotection (Scheme XI).[5e]

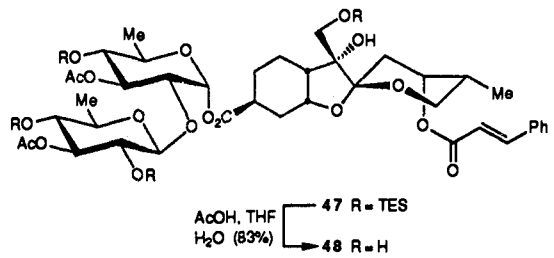
Thus, bissilylation of **45**,[30] followed by selective hydrolysis of the trimethylsilyl ester with aqueous potassium carbonate in methanol–THF (3:1),[31] furnished TES ether **14** in 84% overall yield. Mitsunobu coupling of **6** (3:1 α/β-anomer mixture) with **14** then afforded a 3:1 mixture of **46** and the corresponding α-anomer **47** in 50% yield. The yield based on recovered lactol was 95%. After separation of the anomers by preparative HPLC, hydrolysis of the triethylsilyl ethers provided (+)-phyllanthostatin 3 (**4**) as a grey amorphous solid (ca. 100% yield), identical in all respects [500-MHz ^{1}H NMR, 125-MHz ^{13}C NMR, IR, FAB-MS, and TLC (six solvent systems)] with an authentic sample provided by Professor George R. Pettit (Arizona State University).

(27) Cook, A. F.; Maichuk, D. T. *J. Org. Chem.* **1970**, *35*, 1940.
(28) Johnson, F.; Staikovsky, N. A.; Paton, A. C.; Carlson, A. A. *J. Am. Chem. Soc.* **1964**, *86*, 118. Also, see: Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981; p 55.
(29) Flandor, J.; Garciá-Lopéz, M. T.; de Las Heras, F. G.; Méndez-Castrillón, P. P. *Synthesis* **1985**, 1121.
(30) Hart, T. W.; Metcalf, D. A.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1979**, 156.
(31) Morton, D. R.; Thompson, J. L. *J. Org. Chem.* **1978**, *43*, 2102.

Scheme XI. Phyllanthostatin 3 Endgame



Synthesis of α-Phyllanthostatin 3: A Potentially Important Analogue. Although the mechanisms of action of the phyllanthostatins have not yet been studied in detail, it seems reasonable to postulate that their metabolism may involve cleavage of the labile β-glycosyl ester linkages. In order to explore this possibility, we have synthesized a number of phyllanthostatin analogues which differ both in the nature and the stereochemistry of the glycosidic linkage. One such analogue is α-phyllanthostatin 3 (**48**), prepared in 83% yield by acidic hydrolysis of the triethylsilyl ethers in **47**.



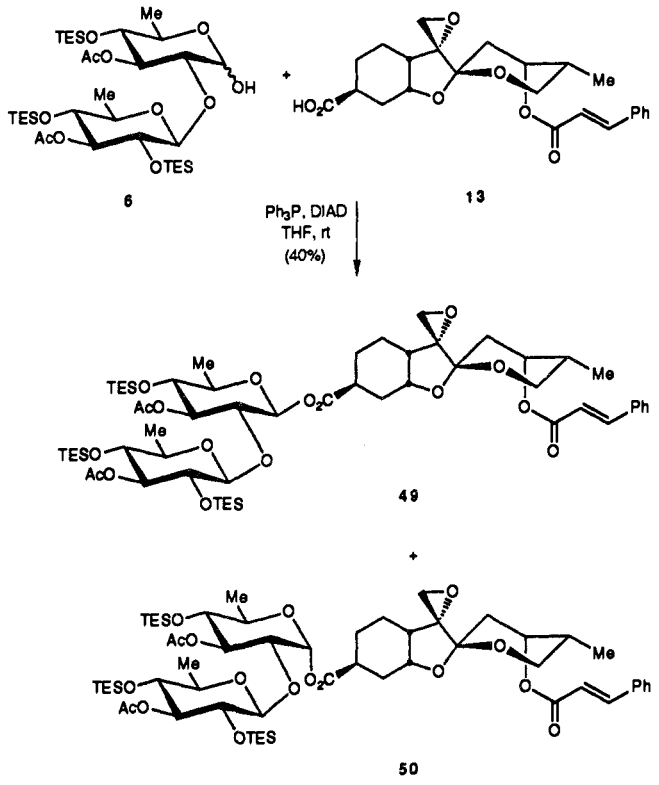
A New Endgame for (+)-Phyllanthoside. In 1987, we completed the first synthesis of (+)-phyllanthoside (**1**).[1,5a] We now describe a more concise endgame for **1**, utilizing the fully endowed aglycon **13**, which was employed in the construction of phyllanthostatins 1 and 2.[5c,d]

Mitsunobu coupling of **13** with lactol **6** (3:1 α/β-anomer ratio) affored a 3.7:1 mixture of **49** and the C(1) α-isomer (**50**) in 40% yield (66% based on recovered lactol) (Scheme XII). These anomers were readily separable by preparative HPLC. The glycosyl ester **49** thus obtained was identical (500-MHz ^{1}H and 125-MHz ^{13}C NMR, IR, FAB-MS and TLC) with synthetic **49** prepared earlier {mp 169.5–171.5 °C, $[\alpha]^{20}_D$ +9.0° (*c* 0.34, $CHCl_3$); lit.[1,5b] mp 169–170 °C, $[\alpha]^{24}_D$ +9.33° (*c* 0.75, $CHCl_3$)}. This tactic permits more convergent assembly of **1** by introducing the C(10) cinnamate moiety prior to glycosyl ester formation.

Comparison of the Hydroxyl Protection Strategies. In assessing the relative merits of the triethylsilyl and chloroacetate protecting groups, several criteria were evaluated: (1) the number of steps required to prepare the requisite disaccharides in a form suitable for glycosyl ester formation, (2) the overall efficiency of Mitsunobu coupling with the aglycon acids, and (3) the effectiveness of the protection and deprotection operations.

Although both approaches relied upon the Koenigs–Knorr reaction to establish the critical $1' \rightarrow 2\beta$ disaccharide linkages, the triethylsilyl moieties necessitated a somewhat lengthier preparation of the key lactol intermediate for phyllanthostatin 3. Moreover, removal of the C(1) allyl ether afforded a disap-

Scheme XII



pointing 2:1 ratio of lactol anomers. The Mitsunobu coupling, proceeding with complete inversion of the anomeric center, accordingly generated substantial amounts of the unwanted α-glycosyl ester. The major advantage conferred by triethylsilyl protection was the facile, highly efficient removal of this group under very mild conditions, without interference from acetate migration or destruction of the sensitive aglycon moiety.

In the chloroacetate approach, standard carbohydrate chemistry in conjunction with an *O*-methyl anomeric protecting group expeditiously furnished the lactol precursors of phyllanthostatins 1 and 2. In the former case, pure α-lactol **11** crystallized, whereupon the Mitsunobu reaction uneventfully generated the desired β-glycosyl ester exclusively. However, inefficient liberation of the target glycosides via dechloroacetylation proved to be the undoing of the chloroacetate strategy.

Summary. We have completed enantioselective syntheses of the entire phyllanthoside–phyllanthostatin family of antitumor glycosides, thereby confirming their assigned structures and absolute configurations. This venture occasioned the development of the Mitsunobu coupling protocol, an efficient new method which should prove useful in the synthesis of other complex natural products containing glycosyl esters.

Experimental Section[32]

Methyl 2,3-Di-*O*-benzoyl-4-*O*-benzyl-6-bromo-6-deoxy-α-D-glucopyranoside (24). Under argon, a solution of alcohol **23** (1.4 g, 2.85 mmol) in THF (15 mL) was cooled to 0 °C and treated with triphenylphosphine (1.1 g, 1.5 equiv) followed by carbon tetrabromide (1.4 g, 1.5 equiv). The mixture was stirred at room temperature for 30 min, and the resultant precipitate was filtered off. The solvent was concentrated in vacuo, and the product was purified by flash chromatography, with ethyl acetate–hexane (5:1) as eluant, to give 1.3 g (82% yield) of bromide **24** as a solid, mp 95.5–96.5 °C: $[\alpha]^{20}_D$ +191° (*c* 2.5, $CHCl_3$); IR ($CHCl_3$) 3050 (w), 1735 (s), 1608 (w), 1590 (w), 1460 (m), 1270 (s, br), 1100 (s, br), 710 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.42 (s, 3 H, MeO), 3.67 (m, 1 H, H-6b), 3.74 (m, 1 H, H-6a), 3.89 (dd, J = 9.1, 9.3 Hz, 1 H, H-4), 4.02 (m, 1 H, H-5), 4.63 (d, J = 10.8 Hz, 1 H, $PhCH_2$), 4.68 (d, J = 10.8 Hz, 1 H, $PhCH_2$), 5.17 (m, 2 H, H-1, H-2), 6.06 (m, 1 H, H-3), 7.99–7.15 (comp m, 15 H, Ph); ^{13}C NMR (52.3 Hz, $CDCl_3$) δ 165.9, 165.6, 133.2, 129.9, 129.7, 129.0, 128.4, 128.0, 97.1, 78.0, 75.0, 72.4, 72.1, 69.1, 55.6, 33.3. Anal. Calcd for $C_{28}H_{27}O_7Br$: C, 60.57; H, 4.91. Found: C, 60.42; H, 5.07.

Methyl 2,3-Di-*O*-benzoyl-4-*O*-benzyl-6-deoxy-α-D-glucopyranoside (25). To a solution of bromide **24** (36.2 g, 65.2 mmol) in benzene (200 mL) at room temperature under argon were added tri-*n*-butylstannane (27 mL, 1.5 equiv) and AIBN (100 mg, 0.01 equiv). The mixture was heated to reflux for 2 h, cooled to room temperature, and concentrated in vacuo. The residue was dissolved in hexane, and the resultant solution was cooled to −10 °C. The crystals that separated were collected, washed with hexane, and dried under vacuum. Recrystallization from ethyl acetate–hexane furnished 26.1 g (84% yield) of **25** as colorless needles, mp 99–100 °C: $[\alpha]^{20}_D$ +134° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3100 (w), 1730 (s), 1605 (w), 1585 (w), 1455 (m), 1280 (s), 1110 (s), 1070 (s), 710 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.35 (d, J = 6.3 Hz, 3 H, H-6), 3.37 (s, 3 H, MeO), 3.47 (dd, J = 9.5, 10.3 Hz, 1 H, H-4), 3.93 (m, J = 6.3, 9.5 Hz, 1 H, H-5), 4.57 (d, J = 11.0 Hz, 1 H, $PhCH_2$), 4.63 (d, J = 11.0 Hz, 1 H, $PhCH_2$), 5.03 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1), 5.12 (dd, J = 3.6, 10.2 Hz, 1 H, H-2), 5.99 (dd, J = 10.1, 10.2 Hz, 1 H, H-3), 7.98–7.11 (comp m, 15 H, Ph); ^{13}C NMR (52.3 MHz, $CDCl_3$) δ 166.1, 165.6, 133.2, 133.0, 129.9, 129.6, 128.3, 128.1, 127.9, 96.8, 81.9, 74.8, 72.6, 72.5, 66.5, 55.2, 17.8; high-resolution mass spectrum (CI, NH_3) m/z 477.1898 [$(M + H)^+$, calcd for $C_{28}H_{29}O_7$ 477.1913]. Anal. Calcd for $C_{28}H_{28}O_7$: C, 70.56; H, 5.93. Found: C, 70.64; H, 5.99.

Methyl 4-*O*-Benzyl-6-deoxy-α-D-glucopyranoside (16). A solution of **25** (14.4 g, 30.3 mmol) in methanol (150 mL) at room temperature was basified to pH 10 with 1 M methanolic sodium methoxide. After 2 h, the reaction mixture was neutralized with Amberlite IR-120 (H^+) resin, filtered, and concentrated in vacuo. Flash chromatography with $CHCl_3$–acetone (8:1) as eluant, or crystallization from cold benzene afforded 8.0 g (84% yield) of **16** as a solid. An analytically pure sample was obtained either by sublimation at 85 °C (0.1 mmHg) or by recrystallization from benzene to give white needles, mp 91–92 °C: $[\alpha]^{20}_D$ +139° (*c* 2, $CHCl_3$); IR ($CHCl_3$) 3530 (m, br), 3420 (m, br), 3010 (m), 2940 (m), 2915 (m), 2840 (w), 1500 (w), 1460 (m), 1140 (s), 1120 (s), 1060 (s, br), 895 (m), 700 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.27 (d, J = 6.3 Hz, 3 H, H-6), 2.10 (d, $J_{HO,2}$ = 9.5 Hz, 1 H), 2.53 (d, $J_{HO,3}$ = 2.1 Hz, 1 H, HO-3), 3.04 (dd, J = 9.1, 9.3 Hz, 1 H, H-4), 3.38 (s, 3 H, MeO), 3.49 (ddd, J = 3.9, 9.5, 9.5 Hz, 1 H, H-2), 3.70 (m, 1 H, H-5), 3.77 (ddd, J = 2.2, 9.2, 9.5 Hz, 1 H, H-3), 4.68 (d, J = 3.9 Hz, 1 H, H-1), 4.69 (d, J = 11.2 Hz, 1 H, $PhCH_2$), 4.83 (d, J = 11.2 Hz, 1 H, $PhCH_2$), 7.35–7.23 (comp m, 5 H, Ph); ^{13}C NMR (52.3 MHz, $CDCl_3$) δ 128.5, 127.9, 127.9, 98.8, 83.3, 75.1, 74.8, 72.9, 66.6, 55.2, 17.9. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.66; H, 7.52. Found: C, 62.72; H, 7.57.

Coupling of Nucleophilic Sugar 16 with Glucosyl Bromide 9. Under argon, a mixture of bromide **9** (2 g, 4.99 mmol), 2,3-diol **16** (2.0 g, 1.5 equiv), freshly crushed Drierite (4 g), mercuric cyanide (2.5 g, 2 equiv), nitromethane (20 mL), and benzene (13 mL) was heated to 55 °C for 1 h. The mixture was cooled to room temperature, filtered through a Celite pad, and concentrated in vacuo. The syrupy residue was then dissolved in chloroform, and the resultant precipitates were removed by filtration. The filtrate was washed with brine and water, dried over $MgSO_4$, and concentrated in vacuo. A solution of the residue in ethyl acetate–hexane was cooled to 0 °C overnight to afford 1.2 g (41% yield) of methyl 4-*O*-benzyl-6-deoxy-2-*O*-(2,4-di-*O*-acetyl-3-*O*-benzyl-6-deoxy-β-D-glucopyranosyl)-α-D-glucopyranoside (**15**) as a solid, mp 168–168.5 °C: $[\alpha]^{20}_D$ +70.2° (*c* 0.5, $CHCl_3$); IR 3550 (w, br), 3015 (m), 3005 (m),

(32) **Materials and Methods.** Reactions were carried out under an argon atmosphere with freshly distilled solvents in vacuum-flamed glassware, unless otherwise noted. All solvents were reagent grade. Ether and THF were distilled from sodium and benzophenone. Precoated silica gel plates (250 μm) with a fluorescent indicator (E. Merck) were used for analytical thin-layer chromatography. *n*-Butyllithium was standardized by titration with diphenylacetic acid. ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform solutions with a Bruker WP250, AM250 (250 MHz), or AM500 (500 MHz) spectrometer. Chemical shifts are reported in δ values relative to tetramethylsilane. All infrared spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Melting points were determined on either a Thomas-Hoover instrument or a Bristoline micro hot stage apparatus and are corrected. Microanalyses were performed by the Rockefeller University Microanalytical Laboratories under the direction of S. T. Bella or by Robertson Labs, Madison, NJ. High-resolution mass spectra were measured by the University of Pennsylvania Mass Spectrometry Service Center on a Hitachi-Perkin Elmer RMH-2 or a VG 70-70 Micromass spectrometer interfaced with a Kratos DS-50-s data system. Gas–liquid chromatography (GLC) analyses were performed on a Hewlett-Packard 5790A chromatograph equipped with a Hewlett Packard 25 m × 0.2 mm × 0.33 μm Ultra 1 (cross-linked methylsilicone) column. Chromatograms were recorded on a Hewlett-Packard 3390a integrator. High-pressure liquid chromatography (HPLC) was performed on a Waters analytical chromatograph equipped with a Model 6000A solvent delivery system, a U6K injector, and a R-400 refractive index detector or a Model 440 absorbance detector. A 4.6 mm × 25 cm column packed with 5 μm Ultrasphere-Si was employed.

2940 (m), 1755 (s), 1500 (w), 1455 (m), 1380 (s), 1235 (s), 1070 (s), 700 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.19 (d, J = 6.2 Hz, 3 H, H-6'), 1.24 (d, J = 6.3 Hz, 3 H, H-6), 1.97 (s, 3 H, OAc), 1.99 (s, 3 H, OAc), 2.56 (d, $J_{HO,3}$ = 2.3 Hz, 1 H, HO-3), 3.04 (dd, $J_1 = J_2$ = 9.1 Hz, 1 H, H-4), 3.34 (s, 3 H, OMe), 3.42 (dd, J = 3.6, 9.8 Hz, 1 H, H-2), 3.46 (m, 1 H, H-5'), 3.64 (dd, J = 9.4, 9.6 Hz, 1 H, H-3'), 3.71 (m, 1 H, H-5), 4.03 (ddd, J = 2.3, 9.6, 9.6 Hz, 1 H, H-3), 4.58 (d, J = 9.2 Hz, 1 H, H-1'), 4.59 (s, 2 H, $PhCH_2O$), 4.65 (d, J = 11.2 Hz, 1 H, $PhCH_2O$), 4.78 (d, J = 3.5 Hz, 1 H, H-1), 4.88 (dd, $J_1 = J_2$ = 9.4 Hz, 1 H, H-4'), 4.90 (d, J = 11.0 Hz, 1 H, $PhCH_2O$), 5.08 (dd, J = 8.0, 9.6 Hz, 1 H, H-2'), 7.35–7.2 (comp m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 169.4, 128.4, 127.9, 127.8, 127.7, 101.9, 98.9, 83.5, 82.0, 80.1, 74.7, 74.2, 73.5, 73.3, 72.4, 70.4, 66.2, 55.3, 20.9, 20.8, 18.0, 17.5; high-resolution mass spectrum (Cl, NH_3) m/z 606.3010 [$(M + NH_4)^+$, calcd for $C_{31}H_{44}NO_{11}$ 606.2914]. Anal. Calcd for $C_{31}H_{40}O_{11}$: C, 63.24; H, 6.85. Found: C, 62.96; H, 6.73.

The mother liquors were concentrated to a syrupy residue and purified by flash chromatography, with ethyl acetate–hexane (1:4, then 1:3) followed by chloroform–acetone (6:1) as eluants, to give 130 mg (4.4% yield) of **26**, 128 mg (4.4% yield) of **15**, 23 mg (1% yield) of **27**, 350 mg (12% yield) of **28**, and 550 mg (83% of theoretical recovery) of diol **16**.

26: solid, mp 163–164 °C; $[\alpha]^{20}_D$ +148° (c 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, J = 6.3 Hz, 3 H, H-6'), 1.26 (d, J = 6.3 Hz, 3 H, H-6), 1.94 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.62 (d, $J_{3,OH}$ = 2.7 Hz, 1 H), 3.06 (dd, J = 9.1, 9.2 Hz, 1 H, H-4), 3.33 (s, 3 H, OMe), 3.55 (dd, J = 3.6, 9.6 Hz, 1 H, H-2), 3.71 (m, 1 H, H-5), 3.99 (dd, J = 9.5, 9.7 Hz, 1 H, H-3'), 4.02 (ddd, J = 2.7, 9.2, 9.4 Hz, 1 H, H-3), 4.07 (m, 1 H, H-5'), 4.61 (d, J = 11.4 Hz, 1 H, $PhCH_2O$), 4.62 (d, J = 3.9 Hz, 1 H, H-1), 4.70 (dd, J_{AB} = 11.4 Hz, 2 H, $PhCH_2O$), 4.70 (dd, J = 3.8, 9.9 Hz, 1 H, H-2'), 4.82 (dd, J = 9.7, 9.8 Hz, 1 H, H-4'), 4.89 (d, J = 11.3 Hz, 1 H, $PhCH_2O$), 5.22 (d, J = 4.0 Hz, 1 H, H-1'), 7.34–7.24 (10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 128.4, 128.3, 127.9, 127.6, 127.4, 96.8, 94.3, 84.0, 78.2, 77.6, 77.2, 75.0, 74.8, 74.7, 74.2, 72.7, 66.2, 66.1, 55.0, 20.8, 20.7, 18.0, 17.3; high-resolution mass spectrum (Cl, NH_3) m/z 606.2949 [$(M + NH_4)^+$, calcd for $C_{31}H_{44}NO_{11}$ 606.2914].

28: oil; $[\alpha]^{20}_D$ +62.4° (c 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.12 (d, J = 6.1 Hz, 3 H), 1.23 (d, J = 6.2 Hz, 3 H), 1.99 (s, 3 H), 2.02 (s, 3 H), 2.26 (d, J = 9.7 Hz, 1 H), 3.06 (dd, J = 9.1, 9.3 Hz, 1 H), 3.08 (s, 3 H), 3.40 (comp m, 1 H), 3.57 (ddd, J = 3.8, 9.7, 9.7 Hz, 1 H), 3.66 (dd, $J_1 = J_2$ = 9.5 Hz, 1 H), 3.70 (m, 1 H), 3.92 (dd, $J_1 = J_2$ = 9.0 Hz, 1 H), 4.53 (d, J = 10.6 Hz, 1 H), 4.59 (s, 2 H), 4.65 (d, J = 3.8 Hz, 1 H), 4.88 (dd, $J_1 = J_2$ = 9.5 Hz, 1 H), 4.88 (d, J = 8.0 Hz, 1 H), 5.03 (d, J = 10.6 Hz, 1 H), 5.07 (dd, J = 9.3, 8.1 Hz, 1 H), 7.15–7.5 (comp m, 10 H); high-resolution mass spectrum (Cl, NH_3) m/z 606.2862 [$(M + NH_4)^+$, calcd for $C_{31}H_{44}NO_{11}$ 606.2914].

Methyl 4-*O*-Benzyl-6-deoxy-2-*O*-(3-*O*-benzyl-6-deoxy-β-D-glucopyranosyl)-α-D-glucopyranoside (29). A stirred suspension of **15** (6.4 g, 10.8 mmol) in methanol (150 mL) at room temperature under argon was basified to pH 9 with 1 M methanolic sodium methoxide. The mixture was stirred at room temperature overnight, neutralized with Amberlite IR-120(H^+) ion exchange resin, filtered, and concentrated in vacuo. Flash chromatography with ethyl acetate as eluant, gave 5.3 g (97% yield) of triol **29** as an amorphous solid: $[\alpha]^{20}_D$ +28.4° (c 1.0, $CHCl_3$); IR ($CHCl_3$) 3440 (w, br), 3020 (w), 2940 (w), 2920 (w), 1455 (w), 1070 (s), 700 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (d, J = 6.3 Hz, 3 H, H-6 or H-6'), 1.27 (d, J = 6.1 Hz, 3 H, H-6' or H-6), 2.14 (d, J = 2.6 Hz, 1 H, OH), 3.06 (dd, $J_1 = J_2$ = 9.3 Hz, 1 H, H-4), 3.08 (d, J = 3.0 Hz, 1 H, OH), 3.22 (ddd, J = 2.6, 9.0, 9.3 Hz, 1 H, H-4'), 3.22 (d, J = 2.3 Hz, 1 H, OH), 3.31 (dd, $J_1 = J_2$ = 9.1 Hz, 1 H, H-3'), 3.31 (m, 1 H, H-5'), 3.35 (s, 3 H, OMe), 3.54 (dd, J = 3.6, 9.8 Hz, 1 H, H-2), 3.61 (ddd, J = 2.3, 7.8, 10.2 Hz, 1 H, H-2'), 3.71 (m, 1 H, H-5), 4.08 (ddd, J = 2.0, 9.7, 9.9 Hz, 1 H, H-3), 4.46 (d, J = 7.9 Hz, 1 H, H-1'), 4.70 (d, J = 11.2 Hz, 1 H, $PhCH_2O$), 4.71 (d, J = 11.7 Hz, 1 H, $PhCH_2O$), 4.76 (d, $J_{1,2}$ = 3.6 Hz, 1 H, H-1), 4.82 (d, J = 11.2 Hz, 1 H, $PhCH_2O$), 4.95 (d, J = 11.7 Hz, 1 H), 7.25–7.34 (m, 10 H, Ph).

Methyl 3-*O*-(Chloroacetyl)-4-*O*-benzyl-6-deoxy-2-*O*-(2,4-bis-*O*-(chloroacetyl)-3-*O*-benzyl-6-deoxy-β-D-glucopyranosyl)-α-D-glucopyranoside (30). Under argon, a solution of triol **29** (3.4 g, 6.75 mmol) and 4-(dimethylamino)pyridine (2.5 g, 3 equiv) in pyridine (70 mL) was cooled to 0 °C, and chloroacetic anhydride (7.5 g, 6.5 equiv) was added. The mixture was stirred at 0 °C for 2.5 h, quenched with 10% aqueous HCl, and extracted with ethyl acetate. The organic extracts were washed with saturated $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated in vacuo, and the residual pyridine was then removed by coevaporation with toluene. Flash chromatography, with ethyl acetate–hexane (2:1) as eluant, furnished 3.6 g (73% yield) of **30** as a solid, mp 182–183 °C: $[\alpha]^{20}_D$ +15.9 (c 4.31, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (d, J = 6.1 Hz, 3 H, H-6' or H-6), 1.32 (d, J = 6.4 Hz, 3 H, H-6 or H-6'), 3.20 (dd, J = 9.3, 9.5 Hz, 1 H, H-4), 3.38 (s, 3 H, OMe), 3.48 (m, 1 H, H-5 or H-5'), 3.67–3.85 (complex m, 8 H), 3.97 (d, J_{AB} = 14.9 Hz, 1 H, $PhCH_2O$), 4.08 (d, J_{AB} = 14.9 Hz, 1 H, $PhCH_2O$), 4.45–4.85 (m, 4 H), 4.72 (d, J = 8.1 Hz, 1 H, H-1'), 4.90 (dd, $J_{4',5'}$ = 9.5 Hz, 1 H, H-4'), 5.03 (dd, J = 9.5 Hz, 1 H, H-2'), 5.47 (dd, J = 9.5, 9.7 Hz, 1 H, H-3), 7.16–7.50 (m, 10 H). Anal. Calcd for $C_{33}H_{39}O_{12}Cl_3$: C, 53.98; H, 5.36. Found: C, 54.15; H, 5.38.

1-*O*-Acetyl 3-*O*-(Chloroacetyl)-4-*O*-acetyl-6-deoxy-2-*O*-(2,4-bis-*O*-(chloroacetyl)-3-*O*-acetyl-6-deoxy-β-D-glucopyranosyl)-α-D-glucopyranoside (31). At room temperature under argon, a solution of **30** (1.2 g, 2.05 mmol) in acetic anhydride (9.8 mL) was treated dropwise with 2% sulfuric acid in acetic anhydride (13.5 mL). After 48 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl and extracted three times with ethyl acetate. The combined extracts were washed with saturated $NaHCO_3$ and H_2O, dried over $MgSO_4$, and concentrated in vacuo. Trituration with ether–hexane at 0 °C gave 930 mg (71% yield) of α-glycosyl acetate **31** as a solid, mp 212–214 °C: $[\alpha]^{20}_D$ +58.7° (c 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (d, J = 6.2 Hz, 3 H, H-6), 1.23 (d, J = 6.2 Hz, 3 H, H-6'), 1.97 (s, 3 H, OAc), 2.02 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 3.58 (m, 1 H, H-5'), 3.89 (dd, J = 3.9, 9.8 Hz, 1 H, H-2), 3.96–4.06 (m, 7 H, 3 OAcCl, H-5), 4.60 (d, J = 7.9 Hz, 1 H, H-1'), 4.80 (dd, J = 9.8, 9.8 Hz, 1 H, H-4), 4.82 (dd, $J_1 = J_2$ = 9.7 Hz, 1 H, H-4'), 4.89 (dd, J = 7.9, 9.7 Hz, 1 H, H-2'), 5.14 (dd, J = 9.5, 9.6 Hz, 1 H, H-3'), 5.38 (dd, $J_1 = J_2$ = 9.8 Hz, 1 H, H-3), 6.20 (d, $J_{1,2}$ = 3.9 Hz, 1 H, H-1). Anal. Calcd for $C_{23}H_{31}O_{14}Cl_3$: C, 43.28; H, 4.70. Found: C, 43.44; H, 4.75.

3-*O*-(Chloroacetyl)-4-*O*-acetyl-6-deoxy-2-*O*-(2,4-bis-*O*-(chloroacetyl)-3-*O*-acetyl-6-deoxy-β-D-glucopyranosyl)-α-D-glucopyranose (11). Under argon, an anhydrous 30% solution of HBr in acetic acid (10 mL) was added to glycosyl acetates **31α,β** (500 mg, 0.78 mmol) at room temperature, and the reaction mixture was then concentrated in vacuo at 80 °C. This procedure was repeated five times. Residual HBr and AcOH were removed by coevaporation with several portions of dry toluene. The residue was dissolved in acetone (9.0 mL) and water (1.0 mL), and the resultant solution was treated with silver carbonate (410 mg, 2 equiv) and allowed to stir in complete darkness. After 3 h, the mixture was filtered, and the filtrate was concentrated in vacuo. Flash chromatography, with $CHCl_3$–acetone (15:1) as eluant, gave an 11:1 mixture of α- and β-hemiacetals as an oil. Trituration with cold hexane–ethyl acetate (2:1) furnished pure α-anomer **11** (180 mg) as a solid. The mother liquor was then stored at room temperature overnight, whereupon additional **11** was crystallized (100 mg, 60% combined yield): mp 164–165 °C; $[\alpha]^{20}_D$ +32.9° (c 1, $CHCl_3$); IR ($CHCl_3$) 3530 (w, br), 3015 (w), 1760 (s), 1415 (w), 1375 (w), 1310 (m), 1285 (m), 1240 (s), 1160 (s), 1065 (s), 1005 (m), 930 (w), 800 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.16 (d, J = 6.3 Hz, 3 H, H-6), 1.24 (d, J = 6.2 Hz, 3 H, H-6'), 1.98 (s, 3 H, OAc), 2.01 (s, 3 H, OAc), 2.90 (d, J = 2.4 Hz, 1 H, OH), 3.61 (m, 1 H, H-5'), 3.80 (dd, J = 3.6, 9.7 Hz, 1 H, H-2), 3.97 (s, 2 H, OAcCl), 4.03 (s, 2 H, OAcCl), 4.00 (d, J = 15.0 Hz, 1 H, OAcCl), 4.08 (d, J = 15.0 Hz, 1 H, OAcCl), 4.13 (m, 1 H, H-5'), 4.65 (d, J = 8.0 Hz, 1 H, H-1'), 4.74 (dd, $J_1 = J_2$ = 9.7 Hz, 1 H, H-4), 4.83 (dd, $J_1 = J_2$ = 9.6 Hz, 1 H, H-4'), 4.95 (dd, $J_{1',2'}$ = 8.0, $J_{2',3'}$ = 9.8 Hz, 1 H, H-2'), 5.17 (dd, $J_1 = J_2$ = 9.6 Hz, 1 H, H-3'), 5.27 (br dd, J = 2.8, 3.1 Hz, 1 H, H-1), 5.41 (dd, $J_1 = J_2$ = 9.6 Hz, 1 H, H-3). Anal. Calcd for $C_{21}H_{29}O_{13}Cl_3$: C, 42.43; H, 4.69. Found: C, 42.25; H, 4.71.

1-*O*-Phyllanthocinoyl 3-*O*-(Chloroacetyl)-4-*O*-acetyl-6-deoxy-2-*O*-(2,4-bis-*O*-(chloroacetyl)-3-*O*-acetyl-6-deoxy-β-D-glucopyranosyl)-β-D-glucopyranoside (33). To a solution of lactol **11** (42 mg, 0.071 mmol), acid **13** (34.9 mg, 1.16 equiv), and triphenylphosphine (35.3 mg, 2 equiv) in dry THF (0.4 mL) at room temperature under argon was added diisopropyl azodicarboxylate (0.026 mL, 2 equiv). After 30 min, the mixture was concentrated in vacuo. Flash chromatography, with ether–hexane (3:2) as eluant, afforded **33** (42.5 mg, 61% yield) as a white powder, mp 103–104 °C: $[\alpha]^{20}_D$ +36.0° (c 0.57, $CHCl_3$); IR ($CHCl_3$) 3020 (w), 2960 (w), 2895 (w), 1765 (s), 1710 (m), 1645 (w), 1458 (w), 1420 (w), 1385 (w), 1320 (m), 1290 (m), 1240 (s), 1265 (s), 1230 (m), 1185 (s), 1155 (s), 1000 (m), 955 (w), 910 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.60–2.60 (comp m, 10 H), 0.85 (d, J = 6.9 Hz, 3 H, Me-15), 1.15 (d, J = 6.1 Hz, 3 H), 1.17 (d, J = 6.0 Hz, 3 H), 1.97 (s, 3 H, OAc), 2.02 (s, 3 H, OAc), 2.95 (s, 2 H, H-14), 3.33 (dd, J = 8.2, 9.0 Hz, 1 H), 3.45–3.70 (comp m, 4 H), 3.92–4.08 (comp m, 7 H), 4.38 (d, $J_{1',2'}$ = 8.2 Hz, 1 H, H-1'), 4.42 (m, 1 H), 4.66 (dd, J = 9.8, 9.8 Hz, 1 H), 4.73 (dd, J = 9.3, 9.8 Hz, 1 H), 4.81 (dd, J = 9.5, 9.9 Hz, 1 H), 5.09 (dd, J = 9.4, 9.6 Hz, 1 H), 5.13 (dd, $J_1 = J_2$ = 9.4 Hz, 1 H), 5.13 (br s, 1 H), 5.50 (d, $J_{1,2}$ = 7.9 Hz, 1 H, H-1), 6.51 (d, $J_{2',3'}$ = 16.1 Hz, 1 H), 7.26–7.59 (m, 5 H, Ph), 7.76 (d, J = 16.0 Hz, 1 H, H-3'); ^{13}C NMR (62.9 MHz, $CLCl_3$) δ 173.5, 170.2, 170.0, 166.8, 166.6, 166.3, 144.6, 134.5, 130.5, 129.1, 120.0, 118.8, 102.1, 100.1, 91.1, 77.2, 76.7, 74.8, 72.9, 72.7, 72.4, 72.0, 70.9, 70.3, 69.8, 69.5, 62.8, 50.0, 40.5, 40.3, 38.3, 37.2, 34.3, 33.1, 29.7, 29.6, 26.0, 21.9, 20.6, 20.5, 17.6, 17.2, 12.7. Anal. Calcd for $C_{45}H_{55}O_{20}Cl_3$: C, 53.40; H, 5.36. Found: C, 53.78; H, 5.50.

Hydrazine Dithiocarbonate (HDTC). A stock solution of hydrazine dithiocarbonate (HDTC) was prepared by dropwise addition of CS_2 (0.7

mL, 11.6 mmol) in dioxane (6 mL) to a cooled solution (0 °C) of hydrazine hydrate (0.73 mL, 12 mmol) in ethanol/water (30 mL, 2:1 v/v) containing diisopropylamine (2.61 mL, 23 mmol).

(−)-Phyllanthostatin 1 (2). A solution of **33** (8.6 mg, 0.008 mmol) in THF (1.0 mL) at room temperature was treated with a *freshly prepared* solution of hydrazine dithiocarbonate (HDTC, 0.08 mL, 3 equiv). The mixture was stirred for 10 min, whereupon additional *freshly prepared* HDTC (0.08 mL) was added. After an additional 15 min at room temperature, the mixture was concentrated in vacuo. Preparative TLC [0.5 mm × 20 cm × 20 cm, chloroform–methanol (12:1)] afforded slightly impure (−)-phyllanthostatin 1. Further purification by flash chromatography, with chloroform–methanol (12:1) as eluant, gave 1.8 mg (27% yield) of **2** as a white amorphous solid, mp 125–126 °C (lit.[3] mp 125–126 °C): $[\alpha]^{20}_D$ −4.0° (*c* 1.0, $CHCl_3$) [lit.[3] $[\alpha]^{20}_D$ −3.6° (*c* 0.83, $CHCl_3$)]; IR ($CHCl_3$) 3460 (w, br), 3040 (w), 3020 (w), 2940 (s), 1750 (s), 1720 (m), 1648 (w), 1470 (w), 1385 (m), 1318 (m), 1290 (m), 1250 (s), 1185 (w), 1170 (w), 1130 (w), 1085 (s), 1060 (s), 1030 (w), 1000 (w), 955 (w), 910 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, *J* = 6.9 Hz, 3 H, Me-15), 1.16 (d, *J* = 6.1 Hz, 3 H), 1.20–1.46 (comp m, 3 H), 1.25 (d, *J* = 5.5 Hz, 3 H, S-6′), 1.54 (m, 3 H), 1.66 (dd, superimposed on m, *J* = 3.2 and 15.4 Hz, 1 H), 1.76 (m, 1 H), 1.84–2.03 (m, 3 H), 2.00 (m, 1 H), 2.11 (s, 3 H, OAc), 2.18 (s, 3 H, OAc), 2.44 (m, 2 H), 2.55 (m, 1 H), 2.95 (ABq, J_{AB} = 5.3 Hz, $\Delta\nu_{AB}$ = 16.5 Hz, 2 H, H-14), 3.16 (dd, $J_1 = J_2$ = 9.4 Hz, 1 H, S-4′), 3.24 (m, 1 H, S-5′), 3.37 (dd, *J* = 7.9, 9.6 Hz, 1 H, S-2′), 3.46 (m, 2 H, S-5, H-12), 3.59 (dd, $J_1 = J_2$ = 9.4 Hz, 1 H, S-3), 3.94 (d, *J* = 7.8 Hz, 1 H, S-1′), 4.01 (dd, $J_1 = J_2$ = 11.4 Hz, 1 H, H-12), 4.44 (dd, $J_1 = J_2$ = 9.6 Hz, 1 H, S-4), 4.46 (m, 1 H, H-5), 4.87 (dd, $J_1 = J_2$ = 9.4 Hz, 1 H, S-3′), 5.09 (d, *J* = 2.5 Hz, 1 H, H-10), 5.37 (d, *J* = 8.2 Hz, 1 H, S-1), 6.68 (d, *J* = 16.0 Hz, 1 H, H-2′), 7.45–7.67 (m, 5 H, Ph), 7.81 (d, *J* = 16.0 Hz, 1 H); high-resolution mass spectrum (FAB, NBA matrix) *m/z* 827.3052 [(M + Na)$^+$, calcd for $C_{40}H_{52}O_{17}Na$ 827.3103].

Coupling of Nucleophilic Sugar 37 and Glycosyl Bromide (9). Under argon, mercuric cyanide (1.9 g, 7.52 mmol) was added to a mixture of **9** (2.76 g, 6.72 mmol), alcohol **37** (2.5 g, 1.0 equiv), freshly crushed $CaSO_4$ (5.0 g), and dry benzene (35 mL) at room temperature. The resultant mixture was heated to 70 °C for 45 min, cooled to room temperature, and filtered. Following concentration in vacuo, the residue was dissolved in chloroform, and the solution was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Upon trituration with hexane–ethyl acetate (3:1) at 0 °C, the product crystallized to give 2.1 g (44% yield) of **38** as a solid, mp 190.5–191 °C: $[\alpha]^{20}_D$ −54.3° (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3010 (w), 2880 (w), 1760 (s), 1460 (w), 1375 (m), 1235 (s), 1075 (s), 1030 (m), 1000 (m), 915 (w), 700 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, *J* = 6.2 Hz, 3 H, H-6′), 1.82 (s, 3 H, OAc), 1.99 (s, 3 H, OAc), 3.42 (m, 2 H, H-5 and H-5′), 3.55 (s, 3 H, OMe), 3.59 (dd, $J_1 = J_2$ = 9.3 Hz, 1 H), 3.62 (dd, $J_1 = J_2$ = 7.6 Hz, 1 H, H-2), 3.65–3.73 (comp m, 2 H), 3.76 (dd, $J_1 = J_2$ = 10.3 Hz, 1 H, $H\text{-}6_{ax}$), 4.35 (dd, *J* = 5.1, 10.5 Hz, 1 H, $H\text{-}6_{eq}$), 4.43 (d, *J* = 7.6 Hz, 1 H, H-1), 4.57 (s, 2 H, $PhCH_2O$), 4.72 (d, *J* = 11.1 Hz, 1 H, $PhCH_2O$), 4.84 (d, *J* = 11.1 Hz, 1 H, $PhCH_2O$), 4.83 (d, *J* = 7.9 Hz, 1 H, H-1′), 4.94 (dd, $J_1 = J_2$ = 9.5 Hz, 1 H, H-4′), 5.08 (dd, *J* = 8.0, 9.3 Hz, 1 H, H-2′), 5.56 (s, 1 H, PhCH), 7.22–7.45 (comp m, 15 H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 169.6, 138.3, 129.0, 128.4, 128.2, 127.9, 127.8, 127.7, 125.9, 103.7, 101.1, 100.6, 81.4, 80.7, 80.6, 80.2, 77.5, 76.5, 75.1, 74.2, 73.1, 73.0, 70.1, 68.7, 65.6, 57.3, 20.8, 17.5. Anal. Calcd for $C_{38}H_{44}O_{12}$: C, 65.88; H, 6.40. Found: C, 66.08; H, 6.23.

Methyl 3-*O*-Benzyl-2-*O*-(2,4-di-*O*-acetyl-3-*O*-benzyl-6-deoxy-β-D-glucopyranosyl)-β-D-glucopyranoside (39). A solution of **38** (1.4 g, 2.02 mmol) in THF (20 mL) at room temperature was treated with 60% aqueous acetic acid (50 mL), and the resultant mixture was heated to 90 °C. After 5 h, the mixture was concentrated in vacuo, and residual acetic acid was removed by coevaporation with several portions of toluene. Flash chromatography, with chloroform–acetone (7:1) and then chloroform–methanol (15:1) as eluant, gave 1.1 g (90% yield) of **39** as a solid, mp 175–175.5 °C: $[\alpha]^{20}_D$ −57.0° (*c*, 1, $CHCl_3$); IR ($CHCl_3$) 3700–3200 (br m), 3010 (m), 2940 (w), 2880 (w), 1760 (s), 1500 (w), 1460 (w), 1380 (m), 1230 (s), 1070 (s), 1040 (w), 915 (w), 705 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (d, *J* = 6.2 Hz, 3 H, H-6′), 1.90 (s, 3 H, OAc), 1.98 (d, *J* = 1.4 Hz, 1 H, OH), 2.00 (s, 3 H, OAc), 2.05 (d, *J* = 2.5 Hz, 1 H, OH), 3.28 (m, 1 H), 3.41–3.54 (comp m, 4 H), 3.54 (s, 3 H, OMe), 3.64 (dd, $J_1 = J_2$ = 9.4 Hz, 1 H, H-3′), 3.73 (m, 1 H, H-5, or H-5′), 3.83 (m, 1 H, H-5, or H-5), 4.36 (d, $J_{1,2}$ = 7.6 Hz, 1 H, H-1), 4.53 (d, *J* = 11.9 Hz, 1 H, $PhCH_2O$), 4.55 (s, 2 H, $PhCH_2O$), 4.83 (d, $J_{1',2'}$ = 8.1 Hz, 1 H, H-1′), 4.87 (d, *J* = 12.0 Hz, 1 H, $PhCH_2O$), 4.95 (dd, $J_1 = J_2$ = 9.5 Hz, 1 H, H-4′), 5.11 (dd, *J* = 9.4, 9.7 Hz, 1 H, H-2′), 7.17–7.35 (comp m, 10 H). Anal. Calcd for $C_{31}H_{40}O_{12}$: C, 61.58; H, 6.67. Found: C, 61.62; H, 6.56.

Methyl 3-*O*-Benzyl-2-*O*-(3-*O*-benzyl-6-deoxy-β-D-glucopyranosyl)-β-D-glucopyranoside (40). A solution of diacetate **39** (4.2 g, 6.9 mmol) in anhydrous methanol (50 mL) at room temperature under argon was basified to pH 9 and 1 M methanolic sodium methoxide. After stirring overnight, the mixture was neutralized with Amberlite IR-120 (H^+) ion exchange resin. The resin was then removed, and the filtrate was concentrated in vacuo. Flash chromatography, with chloroform–methanol (15:1) as eluant, afforded 3.3 g (91% yield) of **40** as a syrup which crystallized from ether to give a solid, mp 147–147.5 °C: $[\alpha]^{20}_D$ −55.9° (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3700–3200 (m, br), 3015 (m), 2960 (m), 2900 (m), 1505 (w), 1465 (m), 1390 (w), 1235 (m), 1120–1050 (s, br), 915 (w), 890 (w), 700 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (d, $J_{5',6'}$ = 6.1 Hz, 3 H, H-6′), 2.03 (dd, *J* = 5.7, 7.4 Hz, 1 H, OH-6), 2.22 (d, *J* = 2.3 Hz, 1 H, OH), 2.38 (d, *J* = 3.5 Hz, 1 H, OH), 3.19 (d, *J* = 2.2 Hz, 1 H, OH), 3.20 (m, superimposed on br d, 1 H), 3.28 (dd, $J_1 = J_2$ = 9.1 Hz, 1 H), 3.29 (m, superimposed on dd, 1 H), 3.35 (m, 1 H), 3.45 (ddd, *J* = 2.0, 8.7, 9.0 Hz, 1 H), 3.54 (s, 3 H, OMe), 3.55 (m, superimposed on s, 2 H), 3.64 (m, 1 H), 3.77 (m, 1 H, H-6a), 3.88 (m, 1 H, H-6b), 4.35 (d, *J* = 7.5 Hz, 1 H, H-1), 4.46 (d, *J* = 7.8 Hz, 1 H, H-1′), 4.73 (ABq, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 105 Hz, 2 H, $PhCH_2$), 4.93 (ABq, J_{AB} = 11.5 Hz, $\Delta\nu_{AB}$ = 5 Hz, 2 H, $PhCH_2$), 7.29–7.39 (comp m, 10 H, Ph). Anal. Calcd for $C_{27}H_{36}O_{10}$: C, 62.30; H, 6.97. Found: C, 62.19; H, 6.96.

Methyl 4,6-Bis-*O*-(chloroacetyl)-3-*O*-benzyl-2-*O*-(2,4-bis-*O*-(chloroacetyl)-3-*O*-benzyl-6-deoxy-β-D-glucopyranosyl)-β-D-glucopyranoside (41). A solution of tetraol **40** (700 mg, 1.34 mmol) and 4-(dimethylamino)pyridine (700 mg, 4.3 equiv) in dry pyridine (30 mL) was cooled to 0 °C under argon and chloroacetic anhydride (2.8 g, 12 equiv) was added. The mixture was stirred for 1.5 h at room temperature, quenched with 20% aqueous HCl, and extracted with chloroform. The extracts were then washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:2) as eluant, gave 930 mg (91% yield) of **41** as a crystalline solid, OAcCl), 158–159 °C: $[\alpha]^{20}_D$ −35.4° (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3020 (m), 2965 (w), 2895 (w), 1775 (s), 1505 (w), 1460 (m), 1420 (m), 1395 (m), 1368 (m), 1315 (s), 1290 (s), 1260 (s), 1210–1120 (s, br), 1080 (s), 1000 (s), 930 (w), 703 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.2 Hz, 3 H, H-6′), 3.49–3.55 (m, 2 H), 3.53 (s, 3 H, OMe), 3.60 (m, 1 H, H-5 or H-5′), 3.62–3.72 (comp m, 6 H), 3.79 (d, *J* = 14.6 Hz, 1 H, OAcCl), 3.86 (d, *J* = 14.5 Hz, 1 H, OAcCl), 4.09 (s, 2 H, OAcCl), 4.20 (dd, *J* = 2.6, 12.3 Hz, 1 H, H-6a), 4.29 (dd, *J* = 4.7, 12.2 Hz, 1 H, H-6b), 4.38 (m, 1 H, H-1), 4.46 (d, *J* = 12.2 Hz, 1 H, $PhCH_2$), 4.55 (d, *J* = 11.8 Hz, 1 H, $PhCH_2$), 4.60 (d, *J* = 11.8 Hz, 1 H, $PhCH_2$), 4.75 (d, *J* = 12.2 Hz, 1 H, $PhCH_2$), 4.84 (d, *J* = 8.1 Hz, 1 H, H-1′), 4.95 (dd, $J_1 = J_2$ = 9.5 Hz, 1 H, H-4′), 5.03 (m, 1 H, H-4), 5.12 (dd, $J_1 = J_2$ = 9.4 Hz, 1 H, H-2′), 7.20–7.35 (comp m, 10 H, Ph). Anal. Calcd for $C_{35}H_{40}Cl_4O_{14}$: C, 50.86; H, 4.88. Found: C, 50.79; H, 4.96.

1-*O*-Acetyl 4,6-Bis-*O*-(chloroacetyl)-3-*O*-acetyl-2-*O*-(2,4-bis-*O*-(chloroacetyl)-3-*O*-acetyl-6-deoxy-β-D-glucopyranosyl)-α-D-glucopyranoside (42). Under argon, a solution of 2% H_2SO_4 in acetic anhydride (5.0 mL) was added to a solution of **41** (0.9 g, 1.08 mmol) in acetic anhydride (5.0 mL) at room temperature. After 24 h, additional 2% H_2SO_4 in acetic anhydride (5.0 mL) was added. The reaction was stirred for 48 h and then cautiously poured into saturated $NaHCO_3$ solution. The mixture was extracted with chloroform, and the combined extracts were washed with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ether–hexane (3:2) as eluant, furnished 554 mg (70% yield) of **42** as an oil. The α-anomer (**42α**) was crystallized from ether–hexane, mp 185–185.5 °C: $[\alpha]^{20}_D$ +49.2° (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3020 (w), 3000 (w), 2980 (w), 2890 (w), 1770 (s), 1420 (w), 1385 (m), 1315 (m), 1290 (m), 1240 (s), 1164 (s), 1140 (s), 1090 (s), 1070 (s), 1045 (s), 1020 (s), 955 (w), 935 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.2 Hz, 3 H, H-6′), 1.97 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 2.17 (s, 3 H, OAc), 3.60 (m, 1 H, H-5′), 3.90 (dd, *J* = 3.8, 9.9 Hz, 1 H, H-2), 3.95–4.08 (comp m, 8 H, OAcCl), 4.10 (m, 1 H, H-5), 4.19 (dd, *J* = 2.2, 12.5 Hz, 1 H, H-6a), 4.36 (dd, *J* = 4.0, 12.5 Hz, 1 H, H-6b), 4.57 (d, *J* = 8.0 Hz, 1 H, H-1′), 4.83 (dd, $J_1 = J_2$ = 9.6 Hz, 1 H, H-4′), 4.91 (dd, *J* = 8.0, 9.8 Hz, 1 H, H-2′), 5.09 (dd, $J_1 = J_2$ = 10.0 Hz, 1 H, H-4), 5.16 (dd, *J* = 9.5, 9.7 Hz, 1 H, H-3′), 5.43 (dd, $J_1 = J_2$ = 9.8 Hz, 1 H, H-3), 6.26 (d, $J_{1,2}$ = 3.9 Hz, 1 H, H-1); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.3, 170.0, 168.7, 166.9, 166.4, 166.2, 165.9, 100.3, 90.1, 74.9, 74.6, 72.8, 71.8, 71.1, 70.1, 69.3, 68.7, 62.9, 40.5, 40.3, 40.2, 40.18, 20.8, 20.5, 17.2. Anal. Calcd for $C_{25}H_{32}O_{16}Cl_4$: C, 41.11; H, 4.42. Found: C, 41.44; H, 4.30.

4,6-Bis-*O*-(chloroacetyl)-3-*O*-acetyl-2-*O*-(2,4-bis-*O*-(chloroacetyl)-3-*O*-acetyl-6-deoxy-β-D-glucopyranosyl)-D-glucopyranose (12). A 30% solution of hydrogen bromide in acetic acid (15 mL) was added to a solution of tri-*O*-acetate **42** (300 mg, 0.4 mmol) in dichloromethane (2.0 mL) at room temperature under argon. After 3 h, the mixture was concentrated in vacuo and residual acid was removed by coevaporation with several portions of toluene. The crude product was then dissolved in acetone (5.0 mL) and water (1.0 mL) and silver carbonate (330 mg, 1.20 mmol) was added. The mixture was stirred in the dark for 8 h,

filtered, and concentrated in vacuo. Flash chromatography, with chloroform–acetone (8:1) as eluant, afforded 227 mg (80% yield) of **12** as an amorphous solid, mp 73–75 °C. The product was found by NMR to exist as a 6.25:1 mixture of α and β anomers in $CDCl_3$.

12α: $[\alpha]^{20}_D$ +33.8° (*c* 2.23, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, J = 6.2 Hz, 3 H, H-6′), 2.01 (s, 3 H, OAc), 2.09 (s, 3 H, OAc), 3.28 (br s, 1 H, OH-1), 3.64 (m, 1 H, H-5′), 3.76 (m, 1 H), 3.80 (dd, J = 3.6, 9.8 Hz, 1 H, H-2), 3.88–4.29 (comp m, 10 H), 4.64 (d, J = 8.0 Hz, 1 H, H-1′), 4.86 (dd, $J_1 = J_2$ = 9.6 Hz, 1 H, H-4′), 5.00 (dd, J = 8.0, 9.7 Hz, 1 H, H-2′), 5.06 (dd, J = 9.8, 9.8 Hz, 1 H, H-4), 5.21 (dd, $J_1 = J_2$ = 9.6 Hz, 1 H, H-3′), 5.35 (br d, J = 3.3 Hz, 1 H, H-1), 5.48 (dd, $J_1 = J_2$ = 9.6 Hz, 1 H, H-3). Anal. Calcd for $C_{24}H_{30}O_{16}Cl_4 \cdot {}^1/_2H_2O$: C, 39.74; H, 4.31. Found: C, 39.81; H, 4.15.

1-*O*-Phyllanthocinoyl 4,6-Bis-*O*-(chloroacetyl)-3-*O*-acetyl-2-*O*-(2,4-bis-*O*-(chloroacetyl)-3-*O*-acetyl-6-deoxy-β-D-glucopyranosyl)-β-D-glucopyranoside (43). A solution of **12** (70 mg, 0.0978 mmol), triphenylphosphine (52 mg, 2 equiv), and acid **13** (50 mg, 1.2 equiv) in THF (1.0 mL) under argon was treated with diisopropyl azodicarboxylate (0.04 mL, 2 equiv). After 30 min at room temperature, the mixture was concentrated in vacuo. Flash chromatography, with ether–hexane (2:1) as eluant, gave 59.9 mg (54% yield) of **43** as an amorphous solid, mp 102–104 °C: $[\alpha]^{20}_D$ +28.3° (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3015 (m), 2960 (w), 1770 (s), 1710 (m), 1655 (w), 1455 (w), 1420 (w), 1375 (w), 1320 (m), 1290 (m), 1235 (s), 1220 (s), 1165 (s), 1085 (s), 1060 (m), 1005 (m), 955 (w), 930 (w), 710 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.83 (d, J = 6.9 Hz, 3 H, H-15), 1.14–1.30 (comp m, 4 H), 1.18 (d, J = 6.1 Hz, 3 H, S-6′), 1.55–1.64 (comp m, 1 H), 1.75–2.13 (comp m, 5 H), 1.95 (s, 3 H, OAc), 2.08 (s, 3 H, OAc), 2.32 (m, 1 H, H-4), 2.51 (m, 1 H, H-3), 2.93 (s, 2 H, H-14), 3.30 (dd, J = 8.2, 9.1 Hz, 1 H, S-2), 3.40 (dd, J = 4.4, 11.5 Hz, 1 H, H-12$_{eq}$), 3.45 (m, 1 H, S-5′), 3.74 (m, 1 H, S-5), 3.90–4.12 (comp m, 8 H), 4.10 (dd, J = 2.1, 10.4 Hz, 1 H, S-6a), 4.29 (d, J = 8.2 Hz, 1 H, S-1′), 4.32 (dd, J = 4.4, 12.5 Hz, 1 H, S-6b), 4.40 (m, 1 H, H-5), 4.71 (dd, $J_1 = J_2$ = 9.5 Hz, 1 H, S-4′), 4.82 (dd, J = 8.1, 9.9 Hz, 1 H, S-2′), 4.97 (dd, J = 9.7, 9.8 Hz, 1 H, S-4), 5.07 (dd, $J_1 = J_2$ = 9.6 Hz, 1 H, S-3′), 5.11 (m, 1 H, H-10), 5.14 (dd, $J_1 = J_2$ = 9.4 Hz, 1 H, S-3), 5.48 (d, J = 8.0 Hz, 1 H, S-1), 6.49 (d, J = 15.9 Hz, 1 H, H-2′), 7.40–7.20 (m, 5 H, Ph), 7.74 (d, J = 15.9 Hz, 1 H, H-3′); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 173.4, 170.2, 170.2, 166.9, 166.5, 166.3, 166.1, 144.6, 134.6, 130.5, 129.1, 128.1, 118.9, 102.1, 100.3, 94.1, 74.8, 74.2, 72.5, 72.4, 72.0, 71.7, 70.9, 69.9, 69.5, 63.0, 62.8, 50.0, 40.5, 40.3, 40.2, 38.3, 37.2, 34.4, 33.1, 29.6, 26.0, 21.9, 20.9, 20.5, 17.6, 12.7. Anal. Calcd for $C_{47}H_{56}O_{22}Cl_4$: C, 51.17; H, 5.04. Found: C, 50.70; H, 5.04.

(+)-Phyllanthostatin 2 (3). A solution of *freshly prepared* hydrazine dithiocarbonate (HDTC, 0.3 mL, 7 equiv) was added to a solution of **43** (16 mg, 0.0144 mmol) in THF (0.2 mL) at room temperature. After 30 min, silica gel was added, and the mixture was concentrated in vacuo. The silicated product was purified initially by flash chromatography with chloroform–methanol (20:1) as eluant, and then by preparative HPLC to afford 1.8 mg (16% yield) of phyllanthostatin 2 (**3**) as an amorphous solid: $[\alpha]^{20}_D$ +9.4° (*c* 0.18, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, $J_{11,15}$ = 6.9 Hz, 3 H, H-15), 1.19–2.13 (comp m, 9 H), 1.22 (d, $J_{5',6'}$ = 6.0 Hz, 3 H, S-6′), 2.14 (s, 6 H, OAc), 2.25 (d, J = 2.7 Hz, 1 H, OH), 2.35 (br d, J = 13.2 Hz, 1 H), 2.48 (m, 1 H, H-3), 2.58 (d, J = 5.0 Hz, 1 H, OH), 2.61 (d, J = 6.5 Hz, 1 H, OH), 2.93 (ABq, J_{AB} = 5.2 Hz, $\Delta\nu_{AB}$ = 10.7 Hz, 2 H, H-14), 3.05 (dd, J = 8.1, 9.2 Hz, 1 H, S-2), 3.13 (m, 1 H), 3.18 (m, 1 H), 3.28 (m, 1 H), 3.37–3.44 (m, 2 H), 3.47 (br s, 1 H), 3.54 (td, J = 5.0, 9.5 Hz, 1 H), 3.73 (m, 1 H), 3.81 (m, 1 H), 3.97 (dd, $J_1 = J_2$ = 11.5 Hz, 1 H, H-12), 4.01 (d, J = 7.8 Hz, 1 H, S-1′), 4.43 (br q, J = 3.4 Hz, 1 H, H-5), 4.80 (dd, J = 9.6, 9.6 Hz, 1 H, S-3′), 4.94 (dd, J = 9.3, 9.5 Hz, 1 H, S-3), 5.10 (br d, J = 2.4 Hz, 1 H, H-10), 5.50 (d, J = 8.0 Hz, 1 H, S-1), 6.59 (d, J = 16.0 Hz, 1 H, H-2′), 7.40–7.60 (comp m, 5 H, Ph), 7.75 (d, J = 16.0 Hz, 1 H, H-3′).

14-*O*-TES Derivative of Phyllanthocindiol (14). A solution of phyllanthocindiol (**45**) (40.1 mg, 0.0898 mmol) and DMAP (catalytic amount) in DMF (2.0 mL) was treated with excess triethylsilyl chloride and triethylamine at room temperature under argon. After 2 days, the reaction was quenched with water. The mixture was extracted three times with ether, and the combined extracts were washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was dissolved in MeOH (7.5 mL) and THF (2.5 mL), aqueous K_2CO_3 (3.0 mL, 0.72 M) was added, and the resultant solution was stirred for 30 min. After neutralization with aqueous $KHSO_4$ (1.0 M) at 0 °C, the mixture was extracted twice with ether, and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography, with ethyl acetate–hexane (1:2) as eluant, gave 42.3 mg (84% yield) of acid **14** as an oil: $[\alpha]^{20}_D$ +45.8° (*c* 0.77, $CHCl_3$); IR ($CHCl_3$) 3760 (w), 3520 (m, br), 3280–3420 (m, br), 3000 (m), 2910–2980 (s, br), 2880 (s), 1660–1750 (s, br), 1640 (s), 1575 (w), 1493 (w), 1460 (s), 1450 (s), 1410 (m), 1387 (m), 1350 (m), 1160–1330 (s, br), 1120 (s), 970–1090 (s, br), 920 (m), 860 (m), 810 (s), 700 (m), 680 (m) cm^{-1}; ^1H NMR (500 MHz $CDCl_3$) δ 0.63 (q, J = 7.9 Hz, 6 H), 0.86 (d, J = 6.9 Hz, 3 H), 0.97 (dd, $J_1 = J_2$ = 7.9 Hz, 9 H), 1.43 (m, 1 H), 1.57 (m, 2 H), 1.88 (m, 1 H), 1.93–2.20 (comp m, 4 H), 2.01 (dd, superimposed on comp m, J = 15.1, 3.5 Hz, 1 H), 2.19 (dd, J = 15.1, 2.5 Hz, 1 H), 2.62 (br m, 1 H), 2.93 (br s, 1 H), 3.40 (dd, J = 11.2, 4.5 Hz, 1 H), 3.56 (d, J = 9.8 Hz, 1 H), 3.68 (d, J = 9.8 Hz, 1 H), 3.95 (dd, $J_1 = J_2$ = 11.2 Hz, 1 H), 4.19 (dd, J = 10.9, 6.3 Hz, 1 H), 5.17 (d, J = 2.3 Hz, 1 H), 6.47 (d, J = 15.9 Hz, 1 H), 7.33 (m, 3 H), 7.51 (m, 2 H), 7.75 (d, J = 15.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.7, 166.9, 144.6, 134.6, 130.0, 128.7, 128.1, 119.0, 105.2, 83.9, 72.7, 69.9, 64.5, 62.3, 42.3, 36.5, 33.9, 33.2, 29.5, 25.1, 20.2, 12.7, 6.72, 4.33; high-resolution mass spectrum (CI, NH_3) m/z 578.3145 [$(M + NH_4)^+$, calcd for $C_{30}H_{48}NO_8Si$ 578.3159].

Coupling of Disaccharide 6 with Aglycon Acid 14. A mixture of lactol **6** (14.1 mg, 0.0192 mmol), triphenylphosphine (10.1 mg, 2 equiv), and acid **14** (15.1 mg, 1.4 equiv) was dried over P_2O_5 at high vacuum (0.2 mmHg) overnight. The mixture was then dissolved in THF (0.15 mL) at room temperature under argon, and diisopropyl azodicarboxylate (5.6 μL, 1.5 equiv) was added. After 1 h, additional triphenylphosphine (5 mg, 1 equiv) and DIAD (2.8 μL, 0.75 equiv) were introduced, and the resultant solution was stirred for 1.5 h. Concentration in vacuo followed by flash chromatography, with ether–hexane (1:10, then 1:5) as eluant, furnished 6.7 mg (47% yield) of the less polar lactol **6** and 12.2 mg (50% yield) of a more polar mixture of glycosyl esters. The esters were separated by preparative HPLC [acetone–hexane (1:24)] to give 5.7 mg of β-anomer **46** and 1.6 mg of α-anomer **47** (3:1 ratio). The yield of **46** and **47** based on recovered lactol was 95%.

46: oil; $[\alpha]^{20}_D$ +12.5° (*c* 0.28, $CHCl_3$); IR ($CHCl_3$) 3520 (w), 2960 (s), 2955 (m), 2950 (m), 2880 (s), 1750 (s, br), 1700 (m), 1635 (w), 1455 (m), 1410 (w), 1360 (m), 1305 (m), 1200–1240 (s, br), 1170 (m), 1070–1130 (s, br), 1005 (s), 970 (m), 700–810 (m, br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.50–0.66 (comp m, 24 H), 0.85 (d, J = 8.9 Hz, 3 H), 0.87–0.99 (comp m, 36 H), 1.21 (d, J = 6.1 Hz, 3 H), 1.25 (d, J = 6.3 Hz, 3 H), 1.51–1.60 (comp m, 3 H), 1.91–1.95 (m, 2 H), 2.01–2.10 (comp m, 4 H), 2.09 (s, 3 H), 2.11 (s, 3 H), 2.14 (dd, J = 15.1, 6.9 Hz, 1 H), 2.70 (m, 1 H), 2.94 (s, 1 H), 3.20 (dd, $J_1 = J_2$ = 8.9 Hz, 1 H), 3.23 (dd, J = 9.2, 7.6 Hz, 1 H), 3.28 (dd, J = 9.0, 6.2 Hz, 1 H), 3.39 (dd, superimposed on dd, $J_1 = J_2$ = 8.9 Hz, 1 H), 3.39 (dd, $J_1 = J_2$ = 5.8 Hz, 1 H), 3.52–3.56 (m, 1 H), 3.53 (d, superimposed on m, J = 9.8 Hz, 1 H), 3.77 (dd, J = 9.1, 7.8 Hz, 1 H), 3.84 (d, J = 9.8 Hz, 1 H), 3.92 (dd, $J_1 = J_2$ = 11.4 Hz, 1 H), 4.23 (br dd, J = 9.9, 5.2 Hz, 1 H), 4.32 (d, J = 7.6 Hz, 1 H), 4.86 (dd, $J_1 = J_2$ = 9.1 Hz, 1 H), 5.09 (dd, $J_1 = J_2$ = 9.2 Hz, 1 H), 5.19 (d, J = 7.7 Hz, 1 H), 5.61 (d, J = 7.7 Hz, 1 H), 6.48 (d, J = 16.0 Hz, 1 H), 7.36–7.40 (m, 3 H), 7.54 (m, 2 H), 7.75 (d, J = 16.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 169.7, 169.3, 166.9, 144.6, 134.7, 130.0, 128.8, 128.1, 118.9, 106.6, 105.1, 101.9, 92.0, 83.5, 77.7, 75.4, 74.8, 74.6, 73.3, 73.2, 72.9, 72.5, 69.6, 64.4, 62.1, 41.7, 37.1, 33.8, 33.2, 29.3, 24.9, 21.7, 21.4, 20.1, 18.2, 17.9, 12.7, 6.82, 6.80, 6.71, 5.27, 5.20, 4.76, 4.34, 1.01.

47: oil; $[\alpha]^{20}_D$ +32.0° (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3520 (w), 2940 (s), 2920 (m), 2863 (m), 1740 (s, br), 1695 (m), 1630 (w), 1450 (m), 1407 (w), 1360 (m), 1300 (m), 1270 (m), 1180–1250 (s, br), 1160 (m), 1110 (s, br), 1080 (s, br), 1050 (s, br), 1005 (s), 950 (m), 700–840 (m, br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.44–0.66 (comp m, 24 H), 0.85 (d, J = 7.7 Hz, 3 H), 0.86–0.99 (comp m, 36 H), 1.22 (d, J = 6.2 Hz, 3 H), 1.26 (m, 3 H), 1.43–1.60 (m, 3 H), 1.84–1.94 (m, 2 H), 2.02–2.16 (comp m, 5 H), 2.07 (s, 3 H), 2.10 (s, 3 H), 2.76 (m, 1 H), 2.95 (s, 1 H), 3.22 (dd, J = 9.1, 7.7 Hz, 1 H), 3.28 (dd, $J_1 = J_2$ = 8.9 Hz, 1 H), 3.30–3.39 (m, 2 H), 3.36 (dd, superimposed on m, $J_1 = J_2$ = 9.3 Hz, 1 H), 3.55 (d, J = 9.6 Hz, 1 H), 3.71 (m, 1 H), 3.80–3.84 (m, 1 H), 3.83 (d, superimposed on m, J = 9.6 Hz, 1 H), 3.91 (dd, $J_1 = J_2$ = 11.4 Hz, 1 H), 4.28 (d, J = 7.5 Hz, 1 H), 4.32 (dd, J = 13.2, 7.9 Hz, 1 H), 4.85 (dd, $J_1 = J_2$ = 9.1 Hz, 1 H), 5.21 (br d, J = 2.9 Hz, 1 H), 5.28 (dd, $J_1 = J_2$ = 9.7 Hz, 1 H), 6.07 (d, J = 3.8 Hz, 1 H), 6.48 (d, J = 16.0 Hz, 1 H), 7.34–7.39 (m, 3 H), 7.55 (m, 2 H), 7.76 (d, J = 16.0 Hz, 1 H).

(+)-Phyllanthostatin 3 (4). A solution of TES ether **46** (5.7 mg, 0.0045 mmol) in THF (0.2 mL) at room temperature was treated with a mixture of AcOH, H_2O, and THF (6:3:1, 1.0 mL). After stirring for 21 h, the mixture was concentrated in vacuo via bulb-to-bulb distillation. Flash chromatography, with chloroform–methanol (22:3) as eluant, gave 4.0 mg (~100% yield) of (+)-phyllanthostatin 3 (**4**) as a gray-white amorphous solid: $[\alpha]^{20}_D$ +16.8 (*c* 0.31, $CHCl_3$); IR ($CHCl_3$) 3100–3580 (m, br), 3000 (w), 2920 (m), 2880 (w), 1740 (s, br), 1700 (s, br), 1630 (w), 1443 (w), 1365 (m), 1300 (m), 1270 (m), 1160–1240 (s, br), 1150 (m), 1070 (s), 1015 (m), 980 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, J = 6.9 Hz, 3 H), 1.25 (d, J = 5.9 Hz, 3 H), 1.28 (d, J = 6.1 Hz, 3 H), 1.38 (m, 2 H), 1.50–2.80 (br m, 5 H), 1.66 (m, 1 H), 1.71–1.80 (m, 3 H), 1.92–2.07 (m, 3 H), 2.15 (s, 3 H), 2.15 (s, 3 H), 2.18–2.24 (m, 2 H), 3.13 (dd, $J_1 = J_2$ = 9.2 Hz, 1 H), 3.14 (dd, J = 9.3, 8.4 Hz, 2 H), 3.21 (m, 1 H), 3.28 (dd, J = 9.5, 7.9 Hz, 1 H), 3.43 (m,

1 H), 3.44 (d, J = 11.4 Hz, 1 H), 3.52 (dd, J = 11.3, 4.4 Hz, 1 H), 4.03 (d, J = 11.4 Hz, 1 H), 4.04 (d, J = 7.7 Hz, 1 H), 4.04 (dd, $J_1 = J_2$ = 11.3 Hz, 1 H), 4.18 (dd, J = 7.5, 3.6 Hz, 1 H), 4.80 (dd, $J_1 = J_2$ = 9.3 Hz, 1 H), 4.90 (dd, $J_1 = J_2$ = 9.4 Hz, 1 H), 5.16 (br d, J = 2.4 Hz, 1 H), 5.49 (d, J = 8.0 Hz, 1 H), 6.58 (d, J = 16.0 Hz, 1 H), 7.41 (m, 3 H), 7.59 (m, 2 H), 7.75 (d, J = 16.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 172.6, 166.8, 144.6, 134.5, 130.3, 129.1, 128.3, 118.9, 106.5, 103.7, 92.1, 85.2, 78.3, 77.9, 77.8, 74.6, 74.3, 73.0, 72.8, 72.5, 72.1, 69.7, 66.7, 63.0, 43.5, 37.0, 36.0, 33.3, 29.9, 25.9, 21.1, 21.0, 20.3, 17.8, 17.4, 12.6; high-resolution mass spectrum (FAB, thioglycerol matrix) m/z 823.3375 [$(M + H)^+$, calcd for $C_{40}H_{55}O_{18}$ 823.3391].

(+)-α-Phyllanthostatin 3 (48). A solution of TES ether **47** (3.2 mg, 0.0025 mmol) in THF (0.2 mL) at room temperature was treated with a mixture of AcOH, H_2), and THF (6:3:1, 1.0 mL). After stirring for 48 h at room temperature, the mixture was concentrated in vacuo via bulb-to-bulb distillation. Flash chromatography, with chloroform–methanol (23:2) as eluant, afforded 1.7 mg (83% yield) of α-phyllanthostatin 3 (**48**) as a gray-white amorphous solid: $[\alpha]^{20}_D$ +62.9° (c 0.14, $CHCl_3$); IR ($CHCl_3$) 3060–3620 (m, br), 3000 (w), 2920 (m), 2840 (w), 1730 (s, br), 1700 (m, br), 1635 (w), 1450 (m), 1420 (w), 1368 (m), 1305 (m), 1180–1260 (s, br), 1170 (m), 1120 (m), 1070 (s, br), 1015 (m), 980 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, J = 6.9 Hz, 3 H), 1.19–1.30 (m, 2 H), 1.25 (d, J = 6.4 Hz, 3 H), 1.27 (d, J = 6.2 Hz, 3 H), 1.40 (m, 2 H), 1.68 (m, 1 H), 1.90 (ddd, J = 13.8, 8.9, 4.3 Hz, 1 H), 1.95–2.05 (comp m, 5 H), 2.13 (s, 3 H), 2.14 (s, 3 H), 2.24 (dd, J = 15.4, 2.9 Hz, 1 H), 2.36 (br m, 1 H), 2.49 (br s, 1 H), 2.64 (m, 2 H), 3.17 (dd, $J_1 = J_2$ = 9.1 Hz, 1 H), 3.28–3.36 (comp m, 3 H), 3.50 (m, 2 H), 3.66 (m, 1 H), 3.77 (dd, J = 9.9, 3.8 Hz, 1 H), 3.94 (br d, J = 11.4 Hz, 1 H), 4.03 (dd, $J_1 = J_2$ = 11.5 Hz, 1 H), 4.23 (q, J = 5.0 Hz, 1 H), 4.31 (d, J = 7.7 Hz, 1 H), 4.76 (dd, $J_1 = J_2$ = 9.3 Hz, 1 H), 5.15 (dd, $J_1 = J_2$ = 9.6 Hz, 1 H), 5.17 (d, J = 3.3 Hz, 1 H), 6.15 (d, J = 3.8 Hz, 1 H), 6.50 (d, J = 16.0 Hz, 1 H), 7.36 (m, 3 H), 7.54 (m, 2 H), 7.74 (d, J = 16.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 172.7, 172.5, 166.9, 144.9, 134.6, 130.1, 128.9, 128.2, 118.7, 106.5, 103.9, 90.9, 84.7, 78.0, 75.0, 74.4, 74.3, 72.9, 72.4, 71.9, 69.7, 69.6, 66.0, 62.7, 42.5, 37.2, 34.9, 33.4, 29.7, 29.2, 26.1, 21.0, 20.0, 17.5, 17.4, 12.6; high-resolution mass spectrum (FAB, thioglycerol matrix) m/z 823.3425 [$(M + H)^+$, calcd for $C_{40}H_{55}O_{18}$ 823.3391].

Coupling of Disaccharide 6 with Aglycon Acid 13. A mixture of lactol **6** (19.6 mg 0.0266 mmol), triphenylphosphine (14 mg, 2 equiv), and acid **13** (24.3 mg, 2.1 equiv) was dried over P_2O_5 at high vacuum (0.2 mmHg) overnight. Under argon, the mixture was dissolved in THF (0.25 mL) at room temperature, and diisopropyl azodicarboxylate (7.8 μL, 1.5 equiv) was added. After 1 h, additional triphenylphosphine (14 mg, 2 equiv) and DIAD (7.8 μL, 1.5 equiv) were introduced, and the resultant solution was stirred for an additional 30 min. Concentration in vacuo and flash chromatography, with ether–hexane (1:5) as eluant, gave 7.8 mg (40% yield) of the less polar lactol **6** and 12.2 mg (40% yield) of a more polar mixture of glycosyl esters. The esters were then separated by preparative HPLC [ether–hexane (2:1)] to give 7.5 mg of β-anomer **49** and 2.3 mg of α-anomer **50** (3:7:1 ratio). The yield of **49** and **50** based on recovered lactol was 66%.

49: colorless solid; mp 169.5–171.5 °C; $[\alpha]^{20}_D$ +9.0° (c 0.35, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2950 (s), 2930 (s, br), 2910 (s), 2870 (s), 1750 (s), 1705 (s), 1635 (m), 1450–1460 (m, br), 1410 (w), 1360–1380 (m, br), 1305 (m), 1288 (m), 1200–1240 (s, br), 1160–1175 (s, br), 1075–1120 (s, br), 1045 (s), 1005 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.44–0.64 (comp m, 18 H), 0.62 (d, J = 7.8 Hz, 3 H), 0.64–1.00 (comp m, 27 H), 1.21 (d, superimposed on m, J = 5.4 Hz, 6 H), 1.20–1.40 (m, 2 H), 1.56 (m, 1 H), 1.65 (dd, J = 15.4, 3.5 Hz, 1 H), 1.84–1.93 (m, 3 H), 1.94 (m, 1 H), 2.07 (s, 3 H), 2.11 (s, superimposed on m, 3 H), 2.12 (m, 1 H), 2.26 (br d, J = 14.8 Hz, 1 H), 2.57 (m, 1 H), 2.93 (ABq, J_{AB} = 5.3 Hz, $\Delta\nu_{AB}$ = 9.6 Hz, 2 H), 3.16–3.22 (m, 2 H), 3.28 (ddd, J = 12.2, 9.0, 6.0 Hz, 1 H), 3.35 (dd, $J_1 = J_2$ = 9.1 Hz, 1 H), 3.41 (dd, J = 11.3, 4.5 Hz, 1 H), 3.51 (ddd, J = 12.2, 9.0, 6.1 Hz, 1 H), 3.72 (dd, J = 9.1, 8.0 Hz, 1 H), 3.97 (dd, $J_1 = J_2$ = 11.3 Hz, 1 H), 4.31 (d, J = 7.5 Hz, 1 H), 4.43 (q, J = 3.5 Hz, 1 H), 4.85 (dd, $J_1 = J_2$ = 9.1 Hz, 1 H), 5.07 (dd, $J_1 = J_2$ = 9.2 Hz, 1 H), 5.16 (br d, J = 2.6 Hz, 1 H), 5.56 (d, J = 7.8 Hz, 1 H), 6.47 (d, J = 16.0 Hz, 1 H), 7.37 (m, 3 H), 7.53 (d, J = 6.6 Hz, 2 H), 7.75 (d, J = 16.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 169.6, 169.2, 166.7, 144.9, 134.6, 130.0, 128.9, 128.1, 118.7, 102.1, 102.0, 92.0, 77.6, 75.4, 74.8, 74.6, 73.3, 73.2, 72.6, 72.5, 70.8, 69.2, 62.7, 49.7, 38.3, 37.4, 34.3, 33.2, 29.0, 26.5, 22.0, 21.7, 21.4, 18.3, 17.9, 12.7, 6.80, 5.29, 5.20, 4.73; high-resolution mass spectrum (FAB, NBA matrix) m/z 1147.5751 [$(M + H)^+$, calcd for $C_{58}H_{95}O_{17}Si_3$ 1147.5877].

50: oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.41–0.62 (comp m, 16 H), 0.84 (dd, $J_1 = J_2$ = 7.9 Hz, 13 H), 0.95 (m, 19 H), 1.19 (d, J = 6.3 Hz, 3 H), 1.25 (d, superimposed on m, J = 6.0 Hz, 3 H), 1.24–1.42 (m, 2 H), 1.63 (m, 1 H), 1.66 (dd, superimposed on m, J = 15.3, 3.6 Hz, 1 H), 1.85–2.05 (m, 2 H), 1.89 (dd, superimposed on m, J = 15.3, 2.9 Hz, 1 H), 2.02–2.13 (m, 2 H), 2.06 (s, superimposed on m, 3 H), 2.08 (s, superimposed on m, 3 H), 2.36 (br d, J = 14.9 Hz, 1 H), 2.63 (m, 1 H), 2.94 (ABq, J_{AB} = 5.4 Hz, $\Delta\nu_{AB}$ = 3.6 Hz, 2 H), 3.08 (dd, J = 9.3, 7.6 Hz, 1 H), 3.23 (dd, $J_1 = J_2$ = 8.9 Hz, 1 H), 3.31 (m, 1 H), 3.35 (dd, $J_1 = J_2$ = 9.1 Hz, 1 H), 3.40 (dd, J = 11.3, 4.4 Hz, 1 H), 3.66 (ddd, J = 12.4, 8.9, 6.1 Hz, 1 H), 3.79 (dd, J = 10.4, 3.9 Hz, 1 H), 3.96 (dd, $J_1 = J_2$ = 11.3 Hz, 1 H), 4.25 (d, J = 7.6 Hz, 1 H), 4.46 (q, J = 3.6 Hz, 1 H), 4.83 (dd, $J_1 = J_2$ = 9.2 Hz, 1 H), 5.20 (br d, J = 2.6 Hz, 1 H), 5.26 (dd, $J_1 = J_2$ = 9.7 Hz, 1 H), 6.04 (d, J = 3.8 Hz, 1 H), 6.44 (d, J = 16.0 Hz, 1 H), 7.30–7.47 (m, 3 H), 7.52 (d, J = 7.2 Hz, 2 H), 7.77 (d, J = 16.0 Hz, 1 H); high-resolution mass spectrum (FAB, NBA matrix) m/z 1147.5735 [$(M + H)^+$, calcd for $C_{58}H_{95}O_{17}Si_3$ 1147.5877].

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Registry No. 1, 63166-73-4; **2**, 82209-93-6; **3**, 81558-18-1; **4**, 81558-17-0; **6** α-isomer, 109922-71-6; **6** β-isomer, 109922-70-5; **7**, 82167-83-7; **9**, 106711-52-8; **11**, 131589-90-7; **12** α-isomer, 116113-81-6; **12** β-isomer, 116113-82-7; **13**, 62948-37-2; **14**, 124516-73-0; **15**, 131589-91-8; **16**, 131589-92-9; **21**, 97-30-3; **23**, 89539-31-1; **24**, 131589-93-0; **25**, 131589-94-1; **26**, 114827-97-3; **27**, 114827-99-5; **28**, 114827-98-4; **29**, 131589-95-2; **30**, 114828-00-1; **31** α-isomer, 114828-01-2; **31** β-isomer, 131589-97-4; **32**, 116135-14-9; **33**, 114828-04-5; **37**, 129706-93-0; **38** β-isomer, 116113-76-9; **38** α-isomer, 131681-84-0; **39**, 116113-77-0; **40**, 131589-96-3; **41**, 116113-78-1; **42**, 116113-79-2; **43**, 116113-83-8; **44**, 131656-29-6; **45**, 124516-72-9; **46**, 124516-74-1; **47**, 124600-19-7; **48**, 131681-82-8; **49**, 106711-70-0; **50**, 131681-83-9.