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TOTAL SYNTHESIS OF (+)-PHYLLANTHOCINDIOL AND (+)-PHYLLANTHOSTATIN 3

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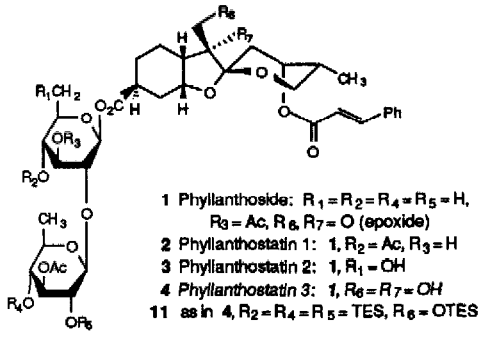
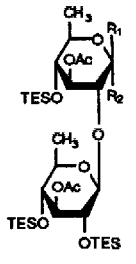
Summary: The antineoplastic glycoside (+)-phyllanthostatin 3 (**4**) has been synthesized for the first time, together with its aglycone (+)-phyllanthocindiol (**5**).

The quest for anticancer constituents of higher plants led to the characterization of phyllanthoside (**1**) and the phyllanthostatins (**2-4**), architecturally novel sesquiterpene glycosides extracted from the roots of the Central American tree *Phyllanthus acuminatus* Vahl.[1] All four compounds possess significant antineoplastic activity;[2] phyllanthoside currently awaits clinical trials at the U.S. National Cancer Institute.[3] Recently, we reported the first total syntheses of (+)-phyllanthoside, (-)-phyllanthostatin 1, and (+)-phyllanthostatin 2.[4] Herein we record the conclusion of this venture with the enantioselective construction of the remaining member of the family, (+)-phyllanthostatin 3 (**4**), and the corresponding aglycone (+)-phyllanthocindiol (**5**).

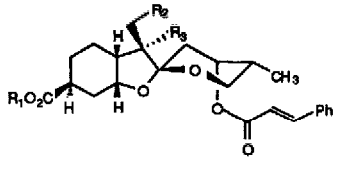
(+)-Phyllanthostatin 3 (**4**), a formal hydration product of phyllanthoside (**1**), differs from the latter only in the elaboration of the 7,14-epoxide to a vicinal diol moiety. The absolute stereochemistry was determined by total synthesis[4f] of the biologically inactive (+)-phyllanthocindiol methyl ester (**6**), a degradation product of **4**. Major obstacles to the synthesis of the phyllanthostatins include the stereoselective construction of the β-glycosyl ester linkage, as well as the propensity of these glycosides to undergo acetyl migration and solvolysis under mildly acidic or basic conditions.[1] *Our approach to* **4** *and* **5** *employs successful strategies and key* precursors developed through our earlier endeavors in this area.



1 Phyllanthoside: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = Ac$, $R_6, R_7 = O$ (epoxide)
2 Phyllanthostatin 1: **1**, $R_2 = Ac$, $R_3 = H$
3 Phyllanthostatin 2: **1**, $R_1 = OH$
4 *Phyllanthostatin 3:* **1**, $R_6 = R_7 = OH$
11 as in **4**, $R_2 = R_4 = R_5 = TES$, $R_6 = OTES$



7 $R_1, R_2 = H, OH$



5 Phyllanthocindiol: $R_1 = H$, $R_2 = R_3 = OH$
6 $R_1 = Me$, $R_2 = R_3 = OH$
8 $R_1 = H$, $R_2 = OTES$, $R_3 = OH$
9 $R_1 = CH_2CH_2TMS$, $R_2, R_3 = O$ (epoxide)
10 $R_1 = CH_2CH_2TMS$, $R_2 = R_3 = OH$

We anticipated that the protected disaccharide **7**, employed in the synthesis of phyllanthoside (**1**),[4a] could again be advantageously utilized. Accordingly, our initial objective was formation of the protected dihydroxy aglycone derivative **8** from epoxide (+)-**9**, an intermediate developed previously in our laboratory.[4b] Hydration of the epoxide moiety of **9** (*N*-methylpyrrolidinone, 15% H_2O, $NaHCO_3$, 130 °C, 76%)[5] furnished diol **10** {$[\alpha]_D^{20}$ +5.6° (*c* 0.32, $CHCl_3$)},[6] which upon dealkylation (*n*-Bu_4NF, DMSO, 50 °C, 87%)[7] gave

phyllanthocindiol (**5**) {$[\alpha]_D^{20}$ +29.2° (*c* 0.8, $CHCl_3$)}.[6] The identity of the 1,2-diol was established by esterification of **5** (CH_2N_2, Et_2O, 84%), affording (+)-phyllanthocindiol methyl ester (**6**) as a white solid {mp 126-127 °C; lit.[1] mp 127-128 °C; $[\alpha]_D^{20}$ +3.7° (*c* 0.88, $CHCl_3$); lit.[4f] $[\alpha]_D^{22.5}$ +3.4° (*c* 1.67, $CHCl_3$)}, identical [^{1}H NMR (500 MHz), ^{13}C NMR, IR, MS and TLC (2 solvent systems)] with an authentic sample provided by Professor David B. Collum (Cornell University).

Aglycone derivative **8** {$[\alpha]_D^{20}$ +45.8° (c 0.77, $CHCl_3$)}[6] was prepared by bissilylation of **5** (TESCl, Et_3N, cat. DMAP, DMF),[8] followed immediately by hydrolysis of the TES ester [aq K_2CO_3, MeOH/THF (3:1), 84% overall].[9] We turned next to coupling of precursors **7** and **8** via Mitsunobu glycosidation,[10] which was anticipated to proceed with inversion at the anomeric center.[10] Treatment of disaccharide **7** (3:1 α/β anomer ratio) and acid **8** (1.4 equiv) with DIAD (1.5 equiv) and Ph_3P (2.0 equiv, THF) afforded in 50% yield a 3:1 mixture of **11** {$[\alpha]_D^{20}$ +12.5° (*c* 0.28, $CHCl_3$)}[6] and the corresponding α-isomer. After separation of the anomers by preparative HPLC, desilylation of **11** ($HOAc/H_2O$/THF, 6:3:1, >98%) gave (+)-phyllanthostatin 3 (**4**) as a grey amorphous solid {$[\alpha]_D^{20}$ +16.8° (*c* 0.31, $CHCl_3$); lit.[1] $[\alpha]_D^{24}$ +15.7° (*c* 0.76, $CHCl_3$)}, identical {^{1}H NMR (500 MHz), ^{13}C NMR, IR, MS, and TLC (6 solvent systems)} with an authentic sample provided by Professor George R. Pettit (Arizona State University).

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