The Total Synthesis of (−)-Phyllanthostatin-1

Amos B. Smith III,* Karl J. Hale, and Henry A. Vaccaro

The Chemistry Department, The Laboratory for Research on the Structure of Matter and The Monell Chemical Senses Center, The University of Pennsylvania, Philadelphia PA 19104, U.S.A.

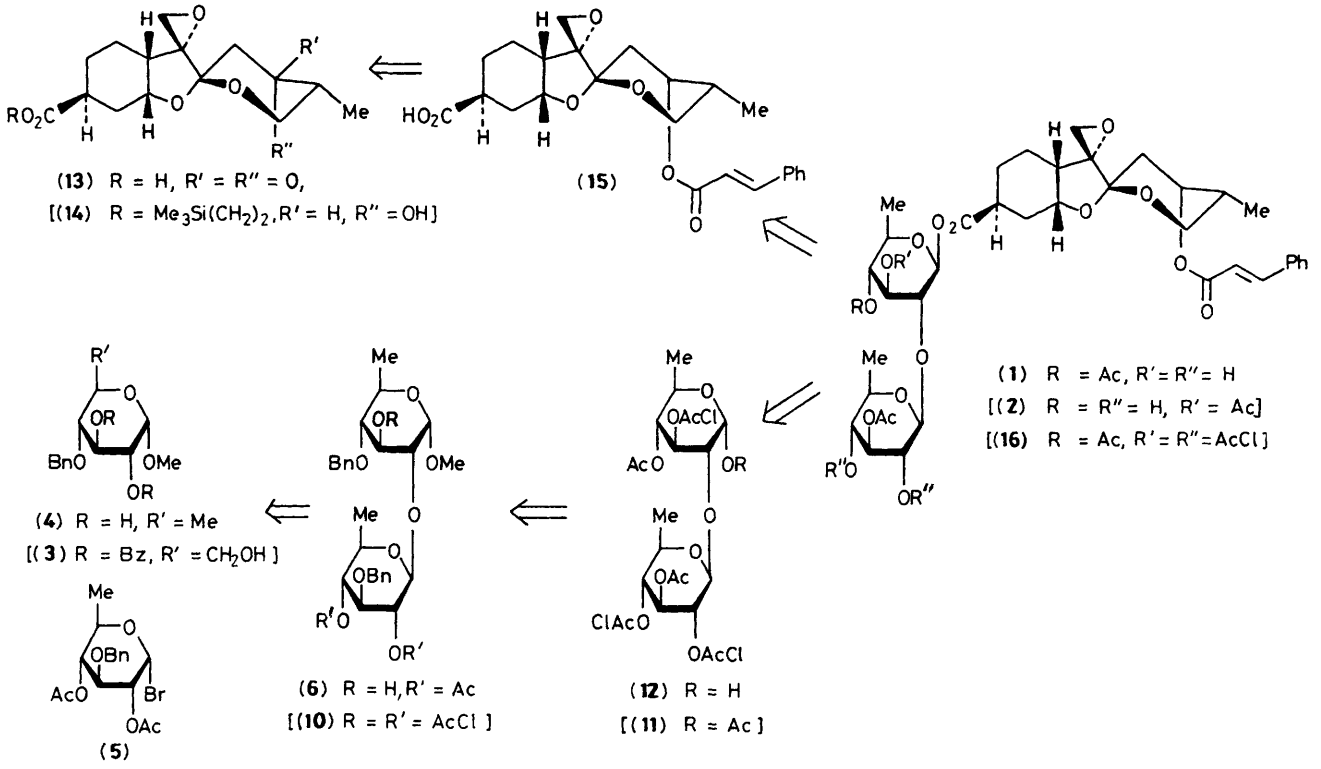
The first total synthesis of the important antitumour glycoside (−)-phyllanthostatin-1 (**1**) is described; the key steps include a regioselective Koenigs–Knorr reaction to establish the 1,2-*O*-linkage in disaccharide (**6**) and a stereoselective triphenylphosphine–di-isopropyl azodicarboxylate (TPP–DIAD) glycosidation of hemiacetal (**12**) with aglycone (**15**).

Several years ago, Pettit *et al.* isolated a series of structurally unique glycosyl esters known as the phyllanthostatins, from root extracts of the Costa Rican tree, *Phyllanthus accuminatus* Vahl.[1] Medical interest in these glycosides is now considerable, largely due to the discovery that (−)-phyllanthostatin-1 (**1**) and (+)-phyllanthoside (**2**) are extremely potent inhibitors of the NCI murine P388 and B16 carcinomas, and can retard the progression of a human melanoma cell line.†

† Initial human trials with (+)-phyllanthoside (**2**) are anticipated in early 1987; personal communication from Dr. Matthew Suffness, Chief, Natural Products Branch, Developmental Therapeutics Program, National Cancer Institute (NIH), Bethesda, Md. 20892.

Recently we described the first total synthesis of (+)-phyllanthoside;[2a] we now report a more expedient strategy for these important glycosides with a synthesis of (−)-phyllanthostatin-1 (**1**). Our approach involves a regioselective Koènigs–Knorr reaction[3] to create the 1,2-*O*-linked disaccharide moiety (**6**), a stereoselective triphenylphosphine–di-isopropyl azodicarboxylate (TPP–DIAD) glycosidation[4] to establish the β-ester linkage between the aglycone (**15**) and disaccharide (**12**), and use of the chloroacetate protecting group[5] to ensure positional integrity of the acetates.[6] These disconnections are depicted in retrosynthetic form in Scheme 1.

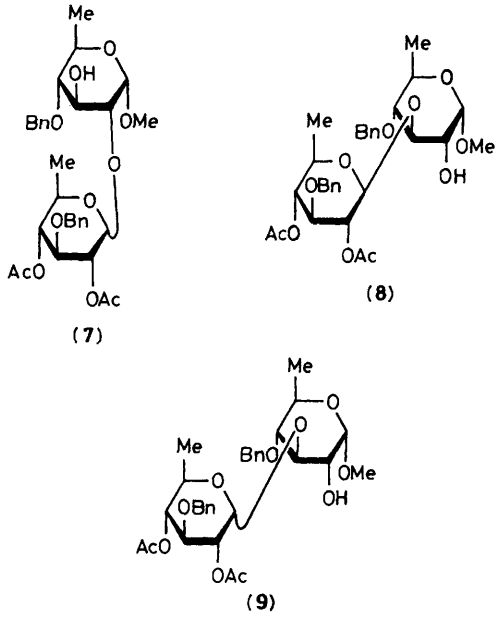
The first stage of the synthesis was assembly of disaccharide (**6**) from glycosyl bromide (**5**)[2a] and the crystalline diol (**4**)



Scheme 1. Bn = benzyl, Bz = benzoyl.

{m.p. 91—92 °C, $[\alpha]_D$ +139.2° (*c* 2, $CHCl_3$)}.‡ The latter was obtained in 57% overall yield from methyl 2,3-di-*O*-benzoyl-4-*O*-benzyl-α-D-glucopyranoside (**3**)[7] by bromination of the C(6)-hydroxy group [1.5 equiv., Ph_3P–CBr_4, tetrahydrofuran (THF), 15 min, room temp.],[8] radical-induced debromination [1.5 equiv., Bu_3SnH, cat. α,α′-azobis-isobutyronitrile (AIBN), C_6H_6 at reflux, 2 h],[9] and ester hydrolysis (NaOMe–MeOH, pH 9, 2 h, room temp.). Regioselective coupling between (**4**) and (**5**) was carried out at 55 °C using two equivalents of the diol in a mixture of nitromethane and benzene (3:2) containing mercury(II) cyanide as the promoter.[10] This led to a mixture of disaccharides (**6**)‡ {m.p. 168—168.5 °C, $[\alpha]_D$ +70.2° (*c* 1, $CHCl_3$)}, (**7**),‡ (**8**),‡ and (**9**),‡ which were isolated (flash chromatography) in yields of 48, 6, 12, and 1% respectively. Conversion of (**6**) into the tris-chloroacetate (**10**)‡ was accomplished in 68% yield by sequential treatment with methanolic sodium methoxide, and chloroacetic anhydride in pyridine for 2 hours at 0 °C. Acetolysis (2% H_2SO_4 in Ac_2O, 4 h, room temp.) of (**10**) caused rapid debenzylation and simultaneous removal of the anomeric methoxyl group to produce the crystalline tri-*O*-acetate (**11**)‡ {m.p. 212—214 °C, $[\alpha]_D$ +58.7° (*c* 1, $CHCl_3$)} in 76% yield. With the *O*-acetyl groups installed at the 3′ and 4 positions, all that remained to complete the synthesis of subtarget (**12**) was removal of the C(1)-acetate group. This was achieved by hydrolysis of the derived glycosyl bromide (30% HBr–AcOH, at reflux, 0.5 h), with moist silver carbonate in acetone[11] to deliver the crystalline α-hemiacetal (**12**)‡ {m.p. 164—165 °C, $[\alpha]_D$ +32.9° (*c* 1, $CHCl_3$)} in 66% yield.

Several synthetic sequences were attempted to prepare the aglycone (**15**). The most successful approach involved protection of acid (**13**)[2b] as its trimethylsilylethyl ester[12] and subsequent reduction of the C(10)-keto group with sodium borohydride in methanol–THF (10:1) at −20 °C;§ this gave a 5:1 mixture of isomers in favour of the axial alcohol (**14**)‡ {m.p. 65—67 °C, $[\alpha]_D$ +99.4° (*c* 0.51, $CHCl_3$)}. Cinnamoylation of (**14**) with *trans*-cinnamoyl chloride, followed by



Bn = benzyl

‡ All new compounds gave satisfactory spectroscopic and microanalytical data in accord with their assigned structures.

§ This level of selectivity was first observed by Collum and McGuirk, see ref. 2c.

deprotection of the resulting silyl ester with 3 equivalents of tetra-n-butyl ammonium fluoride in dimethyl sulphoxide (DMSO) at 50 °C, led to aglycone (**15**);‡ the overall yield for the four steps was 68%.

Having generated the required precursors [*i.e.*, (**12**) and (**15**)], the stage was now set for glycosidation with TPP–DIAD.[4] This occurred with total inversion at the anomeric centre to give exclusively the β-glycoside (**16**)‡ in 71% yield. *O*-Dechloroacetylation with hydrazine dithiocarbonate[5] in THF occurred without acetate migration[6] to afford (−)-phyllanthostatin-1 (**1**) in 41% yield, as a white, amorphous solid {m.p. 125—126 °C, $[\alpha]_D$ −4.0° (*c* 1, $CHCl_3$); lit.,[1] m.p. 125—126 °C, $[\alpha]_D$ −3.6° (*c* 0.83, $CHCl_3$)}, identical in all respects [i.r., ^1H n.m.r. (500 MHz), and t.l.c.] to an authentic sample kindly provided by Dr. Matthew Suffness (National Cancer Institute, N.I.H.).

In summary, the first total synthesis of (−)-phyllanthostatin-1 (**1**) has been achieved; the overall yield from (**3**) was 2.7%.¶

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¶ *Note added in proof:* Since submission of this manuscript, we have completed the first total synthesis of (+)-phyllanthostatin-2.

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