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PHYLLANTHOSIDE-PHYLLANTHOSTATIN SYNTHETIC STUDIES. 6. AN AUGMENTED SPIROKETALIZATION TACTIC FOR THE TOTAL SYNTHESIS OF PHYLLANTHOCIN

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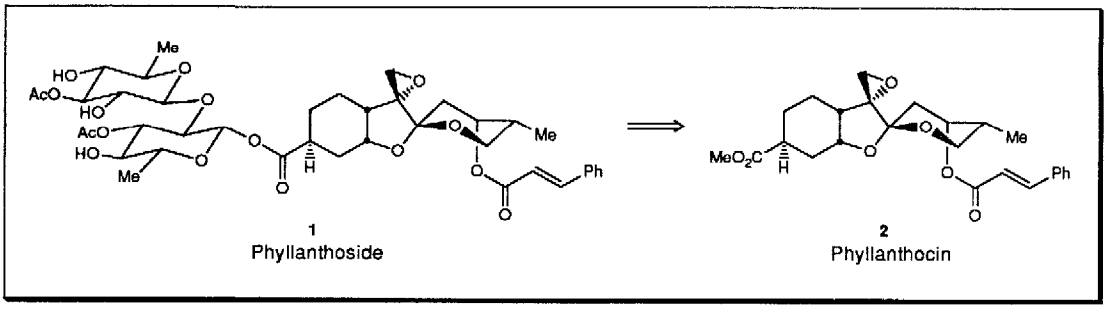
Summary: An enhanced spiroketalization maneuver permitting equilibration at both the C(8) and C(11) centers of spiroketals **17a,b** leads to a more concise and efficient synthesis of phyllanthocin (i.e., 21 steps, 5.6% overall yield).

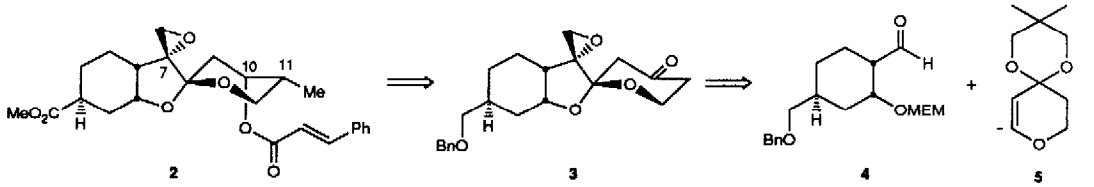
In 1987 we reported the first total synthesis[1] of the potent antitumor agent (+)-phyllanthoside (**1**),[2] now in phase 1 clinical trials in the U.K. Central to this achievement was the development of an effective approach to (+)-phyllanthocin (**2**),[3] the aglycone methyl ester of **1**.[1] Key elements of the latter venture included: (a) a highly stereoselective construction of



1 Phyllanthoside **2** Phyllanthocin

aldehyde **4** (Scheme 1); (b) addition of vinyl anion **5** to **4**, followed after oxidation by a novel, anomerically driven spiroketalization to furnish **3**; and (c) the regio-, chemo-, and stereoselective elaboration of the C(7) and C(10) carbonyl groups, with introduction of a methyl group at C(11). This stereochemically linear,[4] 23-step scheme could be executed in 4.5% overall yield to provide phyllanthocin (**2**) in very high enantiomeric purity.

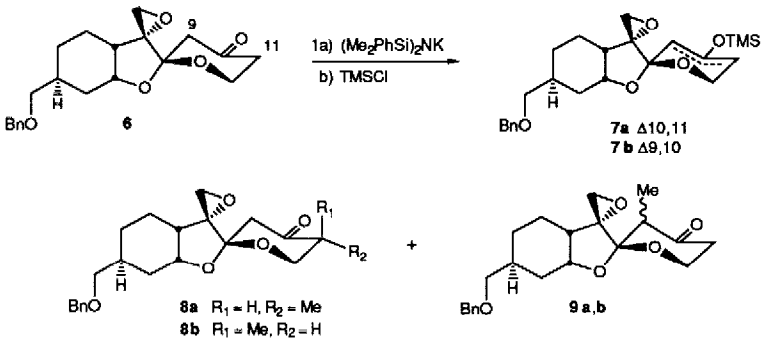
Scheme 1



2 **3** **4** **5**

A major problem in our first-generation synthesis involved incorporation of the C(11) methyl group. Direct alkylation of **3** under a variety of conditions proved fruitless; presumably the complexity of the product mixtures reflected, in part, the enhanced acidity of the C(9) methylene protons. This hurdle was overcome by trapping the enolate derived from **6** with TMSCl to give a favorable 83:17 ratio of enol silyl ethers **7a,b**; methylation via the method by Kuwajima[5] then furnished an

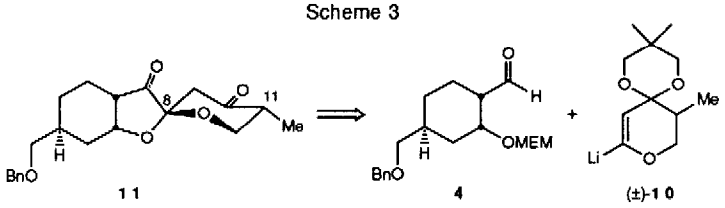
Scheme 2



83:17 mixture of **8a,b** and **9a,b** (Scheme 2). Equilibration of the methyl center with DBU provided the more stable equatorial isomer **8a** in 60% yield for the three steps.

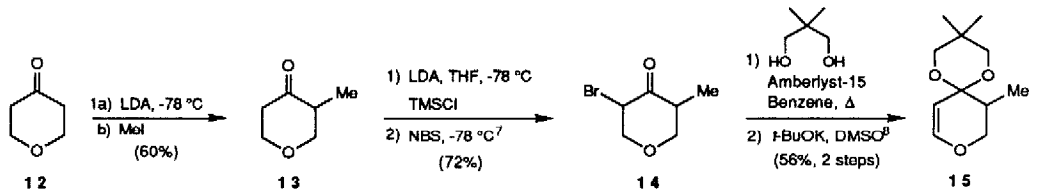
Although this sequence did effect regio- and stereoselective methylation at C(11), we nonetheless became intrigued by the possibility of incorporating the methyl group in **5**, prior to coupling with **4** and spiroketalization, to generate **8a** in a more concise and efficient manner. We were, however, committed to a stereochemically linear strategy. These considerations prompted us to explore the feasibility of controlling the C(11) stereocenter by equilibration in the spiroketalization process. Retrosynthetically, we envisioned an initial addition of lithiated methyl dihydropyran (±)-**10** to aldehyde **4** (Scheme 3). Importantly, this tactic would ensure completely the locus of the methyl group. Exposure to acid

Scheme 3



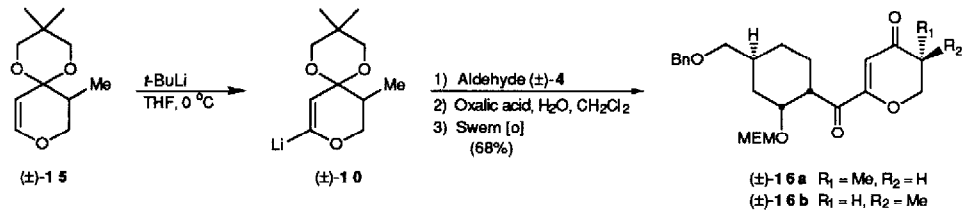
might then effect the desired stereoselective spiroketalization with concomitant C(11) equilibration to furnish **11.** It should be emphasized that this strategy contrasts markedly with the other stereochemically convergent syntheses of (+)-phyllanthocin,[6] wherein the correct absolute configuration at C(11) was secured prior to spiroketal construction.[4] The requisite methylated dihydropyran (±)-**15** was prepared in five steps from tetrahydropyran-4-one (**12**) as outlined in Scheme 4.[9]

Scheme 4



Diketones **16a**[9] and **16b**,[9] substrates for the augmented spiroketalization maneuver, were then readily assembled in racemic form via addition of the lithio derivative of **15** to **4**, followed by deketalization and Swern oxidation.[10] The overall

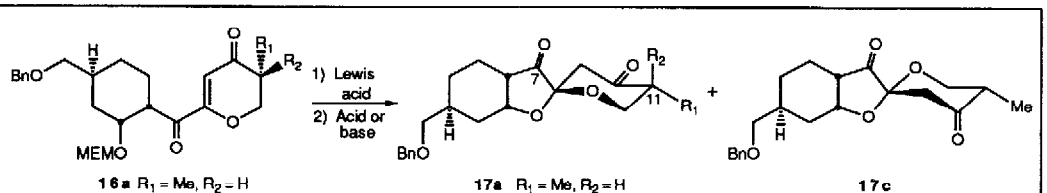
Scheme 5



(±)-**15** (±)-**10** (±)-**16a** R_1 = Me, R_2 = H; (±)-**16b** R_1 = H, R_2 = Me

yield for this three-step operation was 68%. After separation by preparative HPLC, the diketones were independently subjected to the cyclization protocol devised earlier.[1a] As outlined in Table I (entry 1), **16a** afforded a 115:2:1 mixture of spiroketals **17a-c**[9] (HPLC) in 61% yield. Similar treatment of **16b** (entry 2) again furnished **17a-c** in 57% yield; the ratio

Table 1. Spiroketalization-Equilibration of Diketones **16a,b**



16a R_1 = Me, R_2 = H; **16b** R_1 = H, R_2 = Me — **17a** R_1 = Me, R_2 = H; **17b** R_1 = H, R_2 = Me — **17c**

Entry	Starting material	Reaction conditions	Yield (%)	Ratio **17a:b:c**	Ratio **17(a+b):c**
1	**16a**	1) $ZnBr_2$, CH_2Cl_2 2) CSA, benzene, 4 days	61	115:2:1	117:1
2	**16b**	1) $ZnBr_2$, CH_2Cl_2 2) CSA, benzene, 4 days	57	1:14:2	8:1
3	**16a,b**	1) Me_2BBr, CH_2Cl_2, -78 °C 2) *p*-TsOH, benzene, 17 h	72	20:5:1	25:1
4	**16a,b**	1) Me_2BBr, CH_2Cl_2, -78 °C 2) *p*-TsOH, benzene, 6 days	63	21:3:1	24:1
5	**16a,b**	1) Me_2BBr, CH_2Cl_2, -78 °C 2) DBU, benzene, 24 h	49	27:5:1	32:1
6	**16a,b**	1) Me_2BBr, CH_2Cl_2, -78 °C 2) *p*-TsOH, benzene, 2 h 3) DBU, benzene, 24 h	64	44:7:1	51:1

however was 1:14:2. Camphorsulfonic acid thus proved ineffective for the requisite axial-equatorial equilibration of the C(11) methyl group. The stereochemistry of the major product in each case (**17a** and **17b**, respectively) suggested that the configurations of the diastereomeric reactants (**16a** and **16b**) were as indicated. The axial methyl epimer related to **17c** was not detected in any of the spiroketalizations.

In the next series of experiments (entries 3 and 4), the MEM group of **16a,b** was removed with Me_2BBr.[11] Exposure of the resultant mixture of alcohols to *p*-toluenesulfonic acid in place of CSA gave a 25:1 mixture of desired (**17a,b**) and undesired (**17c**) C(8) epimers in 63-72% yields, with **17a:b** ratios as high as 7:1 These results essentially mimicked our earlier spiroketal ratio, and also signaled the efficient C(11) equilibration envisioned *a priori*. We then explored treatment of the mixture of alcohols derived from **16a,b** with DBU in dry benzene (entry 5); DBU was previously employed for epimerization at C(11). This base-mediated spirocyclization afforded a 31.4:1 mixture of spiroketals **17a,b** and **17c**, but the yield was only 49%.

Best results (entry 6) vis-á-vis phyllanthocin were finally obtained by cyclization of the alcohol mixture with *p*-toluenesulfonic acid in benzene, followed by equilibration with DBU. Under these conditions, a 51:1 mixture of desired (**17a,b**) and undesired (**17c**) spiroketal epimers was obtained in 64% yield; the C(11) epimer ratio (**17a:b**) again approached 7:1. DBU treatment clearly enhanced the stereoselectivity at the C(8) spirocenter (cf., entries 3 and 4), presumably via a secondary elimination-recyclization pathway. Methylenation of **17a** then afforded (±)-**8a**, spectroscopically identical to (+)-**8a** employed in our synthesis of (+)-phyllanthocin.

In summary, we have devised an augmented spiroketalization tactic, permitting the highly stereocontrolled cyclization of **16a,b** with equilibration at both the C(8) and C(11) stereocenters. This maneuver leads to a more concise and efficient approach to phyllanthocin (21 steps, 5.6% overall yield), the aglycone methyl ester of the potentially important antitumor agent phyllanthoside.

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