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# An Asymmetric Synthesis of (+)-Phyllanthocin

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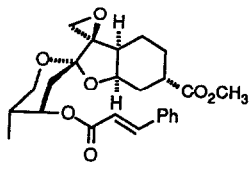
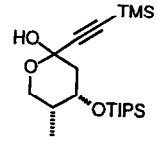
**Summary:** An enantiocontrolled synthesis of (+)-phyllanthocin from methyl R-3-hydroxyisobutyrate and the acrylic ester of D-pantolactone is accomplished in 20 steps in 5% overall yield.

Phyllanthocin,[1] the aglycone of the promising antitumor agent phyllanthoside,[2] represents an important synthetic target for understanding structure-activity relationships and for developing analogues of improved efficacy. The conciseness of our recently reported convergent strategy to racemic phyllanthocin based upon an enyne cycloreduction[3] induced us to develop an asymmetric synthesis. In this communication, we wish to record the realization of this goal.

The synthesis requires the obtention of the two halves 1 and 2 in enantiomerically pure form. Scheme 1 outlines our approach to the lactol half




Phyllanthocin

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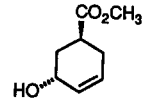
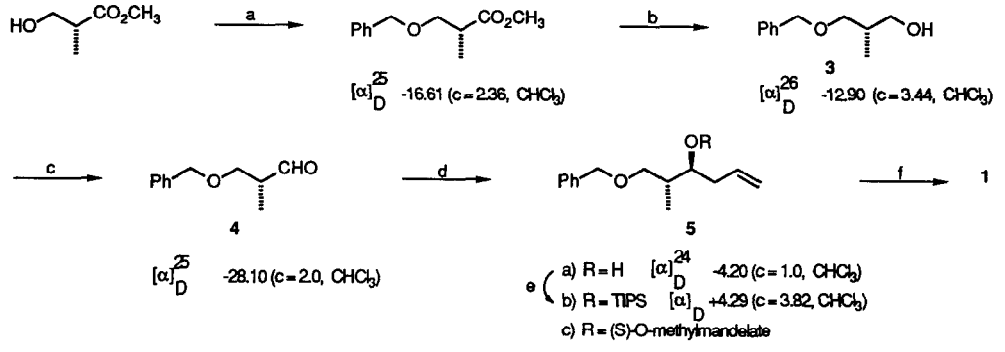



2

stemming from the commercial availability of methyl 3-hydroxyisobutyrate in either enantiomeric form. O-Benzylation uncomplicated by $\beta$-elimination was achieved in high yield by the protocol of Cramer using either triflic or trifluoracetic acid.[4] The remaining steps were unexceptional with the alcohol 3 and aldehyde 4 having optical rotations that were in excellent accord with literature values for these compounds obtained by different routes.[5] The enantiometic purity was assessed to be 87% at the stage of the alcohol 5a[6] by conversion to its O-methylmandelate ester 5c.[7] This sequence provided the lactol half in 35% overall yield.

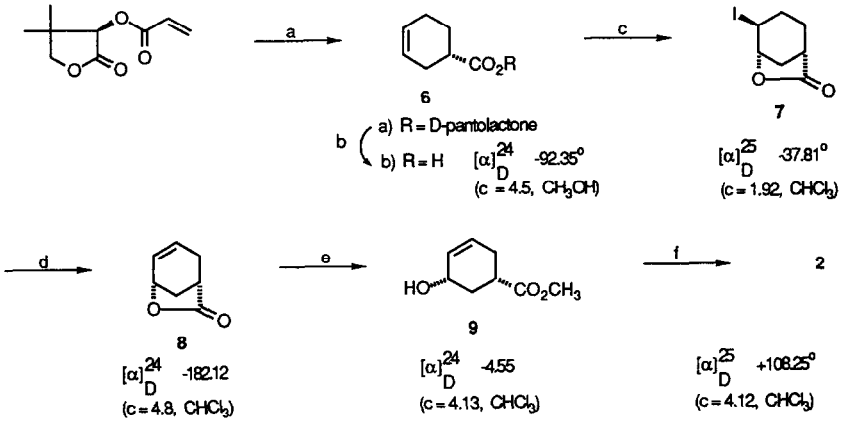
Scheme 1. Synthesis of 2-Hydroxy-2-trimethylsilylethynyl-4S-triisopropylsiloxy-5*R*-methyltetrahydropyran




a) $PhCH_2OC(=NH)CCl_3$, $CF_3SO_3H$, $CH_2Cl_2$, 0°, 91%; b) LAH, THF, -30°, 83%; c) DMSO, $(COCl)_2$, $(C_2H_5)_3N$, -60°, 97%; d) $CH_2=CHCH_2TMS$, $SnCl_4$, $CH_2Cl_2$, -78°, 93%; e) TIPS-$OSO_2CF_3$, 2,6-lutidine, $CH_2Cl_2$, 97%; f) for these steps see ref. 3, 53% overall.

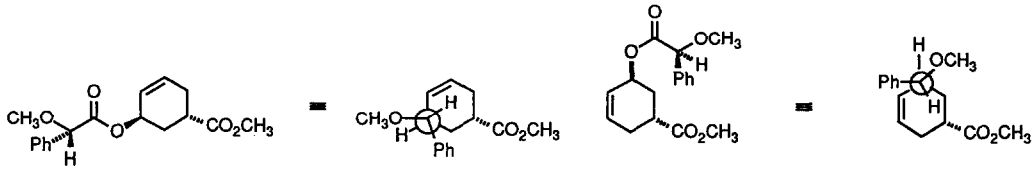
The hydroxyester half 2 made use of the asymmetric Diels-Alder protocol developed by Helmchen[8] as outlined in Scheme 2. Excellent agreement of optical rotations

Scheme 2. Synthesis of Methyl 3*R*-Hydroxycyclohex-4-en-1*S*-carboxylate



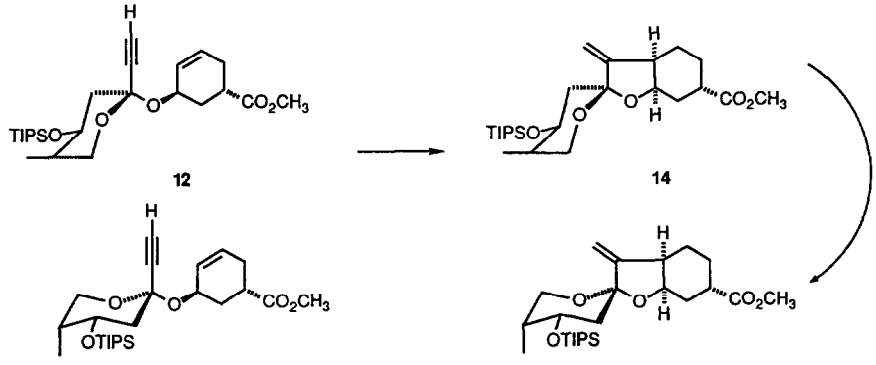

a) $CH_2=CHCH=CH_2$; $TiCl_4$, $CH_2Cl_2$-pet ether, 0°, 70%; b) LiOH, THF-$H_2O$, rt, 92%; c) KI, $I_2$, $NaHCO_3$, $H_2O$, rt, 91%; d) DBU, PhH, reflux, 91%; e) $Na_2CO_3$, $CH_3OH$, rt, 74%; f) see text 86%

literature was observed for 6b-8.[9] Assessment of the optical purity of cis-hydroxyester 9 via the O-methylmandelate[7] indicated a value of 97% ee. A key question relates to the $S_N2$ vs $S_N2'$ displacement during the alcohol inversion sequence. Subjecting the alcohol to Mitsunobu conditions [dppe, DEADCAT, $HCO_2H$, $(C_2H_5)_3N$, THF, 0°] followed directly by basic methanolysis gave an 86% yield of the *trans*-hydroxyester 2 (overall yield of Scheme 2 34%) whose ee was established as 62-70% by the O-methylmandelate technique. This analytical procedure also established that the reaction proceeded predominantly by direct $S_N2$ displacement. In particular, the absorptions for the olefin protons of the major enantiomer appear downfield ($\delta$ 5.83 and 6.04) relative to those of the minor enantiomer ($\delta$ 5.69 and 5.95) in accord with the model (cf 10 and 11).[7]



10 11

Coupling using K10 montmorillonite clay and desilylation (70% yield) produced a diastereomeric mixture of 12 and 13 which was directly reductively cyclized as before (82% yield) to 14 and 15.[3] The former was equilibrated [$Mg(OCOCF_3)_2$, $CF_3CO_2H$, $CH_2Cl_2$, rt][10] to the latter so that the single diastereomer 15 necessary for (+)-phyllanthocin was available. Remarkably, a kinetic discrimination occurred



12 14

13 15

during the coupling of 1 and 2 that led to production of 15 of high enantiomeric purity as evidenced by the enantiomeric purity of (+)-phyllanthocin obtained in 4 steps as previously recorded[3] $[\alpha]_D^{22}$ + 22.6°, mp 117-9°C which compares very favorably with the literature.[9-11] This asymmetric synthesis of (+)-phyllanthocin requires a total of 20 steps with a longest linear sequence being 15 in 5% overall yield from commercially available materials.

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