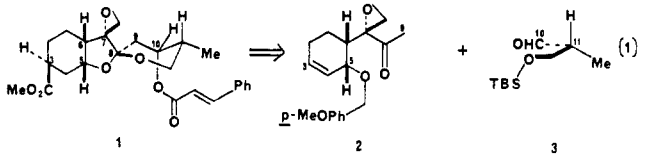
Total Synthesis of (+)-Phyllanthocin

Summary: A convergent, enantioselective total synthesis of (+)-phyllanthocin (1) has been accomplished, incorporating asymmetric epoxidation, directed-aldol condensation, and Rh(I)-catalyzed hydroformylation as key synthetic steps.

Sir: In 1977 Kupchan described the isolation and structural analysis (+)-phyllanthocin (1), a methanolysis product of the bisabolane glycoside phyllanthoside.[1] Pettit and co-workers have revised the original plant source identification from *Phyllanthus brasiliensis* to *P. acuminatus* and have characterized several related antineoplastic glycosides.[2] The significant levels of inhibition by phyllanthoside of the NCI murine B16 melanoma and the human myeloma cell line have led to extensive preclinical testing.[3] This chemotherapeutic potential in combination with a substantial structural challenge renders the aglycon an attractive target for total synthesis.[4] Our efforts resulting in an enantioselective synthesis of (+)-phyllanthocin (1) are reported here.

The brief antithetic sequence in eq 1 reveals the salient features of our convergent approach, relying upon a

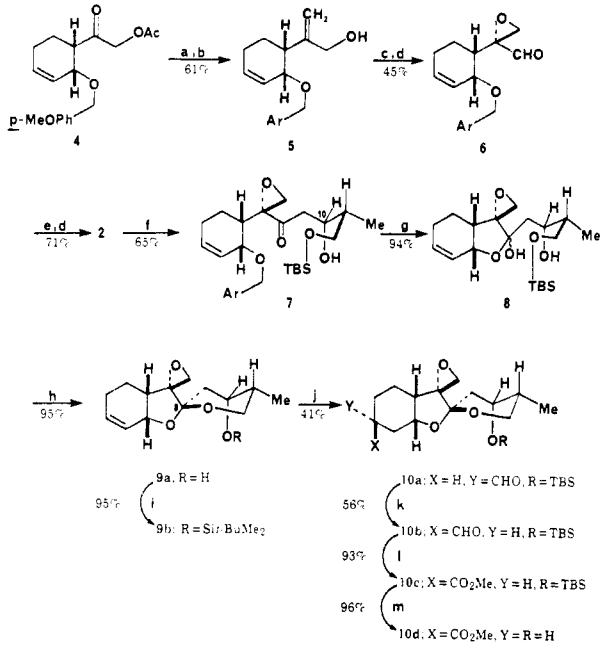


1 2 3 (1)

"Cram-cyclic" stereoselective aldol coupling of the enolate derived from epoxy ketone **2** and the aldehyde **3**.[5] In addition to the tactical requirement that the mixed-aldol partners **2** and **3** be optically pure, this approach carried the risk of postponing the introduction of the C3-methoxycarbonyl group to the last stage of the synthesis.

The synthetic sequence based upon this strategy is detailed in Scheme I.[6] A Diels–Alder cycloaddition between acetoxymethyl vinyl ketone[7] and 1-[(*p*-methoxybenzyl)oxy]butadiene[8] gave the 3,4-disubstituted cyclohexene **4** in 69% yield (cis/trans = 3.4). Wittig methylenation and acetate hydrolysis afforded the racemic alcohol **5** in 61% yield. Application of Sharpless' asymmetric epoxidation procedure[9] utilizing (+)-diethyl tartrate and titanium *tert*-butoxide[10] afforded in 95% yield an approximately

Scheme I[6] [a]



[a] (a) 1.3 equiv of $Ph_3P{=}CH_2$, THF, −100 °C; (b) K_2CO_3, MeOH, 25 °C; (c) *t*-BuOOH, (+)-diethyl tartrate, Ti(O-*t*-Bu)$_4$, CH_2Cl_2, −23 °C, 5.5 h; (d) Me_2SO, oxalyl chloride; Et_3N, CH_2Cl_2, −60 °C; (e) 5 equiv of MeLi, THF, −78 °C, 6 min; (f) LDA, THF, −78 °C, 1 h; **3**, −78 °C, 10 min; (g) DDQ, CH_2Cl_2/H_2O (19:1), 25 °C, 1 h; (h) 5% aqueous HF, CH_3CN, 25 °C, 10 min; (i) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min;[25] (j) 8 mol% $[(COD)RhOAc]_2$, PhH, 1:1 CO/H_2 (560 psi), 76 °C, 3.25 h; (k) 1 equiv of NaOMe, MeOH, 25 °C, 2 h; (l) $H_2Cr_2O_7$, aqueous acetone, 0 °C, 10 min; CH_2N_2, Et_2O, 0 → 25 °C; (m) 5% aqueous HF, CH_3CN, 0 °C, 2 h.

equal mixture of epoxy alcohol diastereomers, separable by chromatography on silica gel. The desired isomer [mp 73–73.5 °C, $[\alpha]^{25}_D$ −243° (*c* 1.54, CH_2Cl_2)][11] gave upon Swern oxidation[12] the aldehyde **6**. Addition of excess methyllithium (THF, −78 °C) followed by Swern oxidation provided the optically active epoxy ketone **2** [mp 86–86.5 °C, $[\alpha]^{25}_D$ −202° (*c* 1.84, CH_2Cl_2)] in 71% overall yield.

The desired aldehyde enantiomer **3** was readily obtained by standard procedures from commercially available (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate.[13] Condensation of the enolate derived from **2** (LDA, THF, −78 °C) with aldehyde **3** gave an easily separable 3.6:1 mixture of **7** (65%) and its C10 epimer. This "Cram-cyclic" diastereoselectivity is reminiscent of that reported by Masamune in a related reaction.[14] Sequential cleavage of the *p*-methoxybenzyl[15] and *tert*-butyldimethylsilyl (TBS)[16] protecting groups proceeded via the hemiacetal **8** to the spiroketal **9a** [oil, $[\alpha]^{26}_D$ +45° (*c* 1.79, CH_2Cl_2)]

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(10) The use of Ti(O-*i*-Pr)$_4$ led to significant amounts of epoxide-opened product incorporating the isopropoxide ligand. See: Lu, L. D.-L.; Johnson, R. A.; Finn, M. G.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 728.

(11) The desired epoxide diastereomer was identified by chemical and crystallographic correlation.

(12) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(13) (*R*)-(−)-Methyl 3-hydroxy-2-methylpropionate (Aldrich Chemical Co.) was converted to the *tert*-butyldimethylsilyl ether,[16] over-reduced with *i*-Bu_2AlH(CH_2Cl_2, −23 °C), and subjected to a Swern oxidation[12] to give the aldehyde **3** in 85% overall yield. The aldehyde was used without purification, as it suffered partial racemization during chromatography or distillation.

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in high yield. It is notable that the conditions employed for silyl ether cleavage (5% aqueous HF in CH_3CN) gave **9a** directly with complete stereoselectivity at C8. This contrasts with other spiroketalization conditions explored by us in which the C8-epimeric spiroketal is formed in predominance.[17] Thus the tetracyclic ring system of (+)-phyllanthocin was established in ten synthetic steps, with six asymmetric centers present in their correct absolute configurations.

It remained to introduce the C3-methoxycarbonyl substituent, thereby establishing the last of the seven stereocenters of phyllanthocin. After failing to effect a satisfactory result via hydrozirconation-[18] or hydroboration-based[19] methodologies, we turned to hydroformylation[20] for this purpose. In terms of functionality and architecture, the silyl ether **9b** was clearly an unusually complicated hydroformylation substrate. In a representative experiment, 1.0 mmol of the cyclohexene **9b** in 10 mL of benzene was placed in a Parr bomb (45 mL capacity) which was then charged with 0.08 mmol of $[(COD)RhOAc]_2$,[21] followed by CO and H_2 (1:1) to 560 psi. After heating at 76 °C (bath temperature) for 3.25 h, chromatographic purification on silica gel gave the C3-α- and C3-β-formyl products **10a** and **10b** in 21% and 20% yields, respectively. A single C4-formyl product was also isolated in 12% yield. Stereoisomer **10a** could be equilibrated (NaOMe, MeOH, 25 °C, 80%) to a 2.3:1 mixture of C3 epimers in which **10b** predominated.

With the carbon skeleton established, complete with stereochemical details, the total synthesis was finished by straightforward cosmetic adjustments. Oxidation of the formyl residue in **10b** to the carboxylic acid with Jones reagent at 0 °C and treatment of the crude product with ethereal diazomethane afforded the methyl ester **10c** [mp 89.5–91 °C, $[\alpha]^{25}_D$ +101° (*c* 1.95, CH_2Cl_2)] in 93% yield. Cleavage of the C10-silyl ether gave in 96% yield the known[4] axial alcohol **10d** [mp 130–130.5 °C (sealed capillary), $[\alpha]^{25}_D$ +126° (*c* 1.23, $CHCl_3$)].[22] Cinnamoylation by the procedure of Williams[4b] gave in 82% yield (+)-phyllanthocin (1) [mp 129–129.5 °C, $[\alpha]^{26}_D$ +27.2° (*c* 2.04, $CHCl_3$)][23] which was identical with an authentic sample by standard spectroscopic and chromatographic criteria.[24]

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Stereocontrol in the Intramolecular Diels–Alder Reaction. 7. Use of the Trimethylsilyl Group as a Removable Stereocontrol Element To Provide Greatly Enhanced Levels of Diastereoselection

Summary: Introduction of the trimethylsilyl group at defined locations in triene substrates which undergo closure by intramolecular Diels–Alder cycloaddition to both hydrindene and octalin systems results in greatly enhanced levels of diastereoselection.

Sir: A large volume of research during the past 10 years has been devoted to exploration of the intramolecular Diels–Alder reaction as a protocol for the stereocontrolled synthesis of complex molecules.[1,2] However, very high levels of diastereoselection (≥20:1) have not been attainable in most instances, since the nonbonded interactions responsible for the diastereoselection are of insufficient magnitude.[3,4] Only when steric and stereoelectronic factors are reinforcing or when the system is amenable to the use of Lewis acid catalysis do the observed levels of stereoselection reach those found for other types of C–C bond forming reactions.[5,6] Since we, as well as others,[7,8] have concluded that a few specific nonbonded interactions are the primary determinants of the stereochemical outcome, we set out to establish whether introduction of sterically demanding groups as control elements,[9] whose presence magnify the controlling nonbonded interaction in the transition states leading to the undesired stereoisomers, would permit the very high levels of diastereoselection

(17) For example, if, after cleavage of the *p*-methoxybenzyl ether, the silyl ether was cleaved with *n*-Bu_4NF in THF, no spiroketalization occurred. Induction of spiroketalization with CF_3CO_2H in CH_2Cl_2 led to a 1:3.8 mixture of **9a** and its C8 epimer. These isomers are readily distinguished by IR (intramolecular H-bond in **9a** to C8-axial oxygen) and ^1H NMR.

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(22) Although our mp and optical rotation data for **10d** differ from those reported [lit.[4b] mp 104 °C (sealed capillary), $[\alpha]^{26}_D$ +143.9° (*c* 0.79, $CHCl_3$)], the high field ^1H NMR and ^{13}C NMR data indicate that the two samples are identical.

(23) The literature values for the mp and $[\alpha]_D$ of (+)-phyllanthocin are as follows: mp 126–127 °C, $[\alpha]^{24}_D$ +25.2° (*c* 2.00, $CHCl_3$);[1] mp 120–121 °C, $[\alpha]^{33}_D$ +23.81° (*c* 1.26, $CHCl_3$);[2] mp 118–120 °C, $[\alpha]^{24}_D$ +24.9° (*c* 1.86, $CHCl_3$).[4b]

(24) We are indebted to Professor D. R. Williams of Indiana University for an authentic sample of (+)-phyllanthocin.

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