Application of Nitrile Oxide Cycloadditions to a Convergent, Asymmetric Synthesis of (+)-Phyllanthocin

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A highly convergent, enantioselective total synthesis of (+)-phyllanthocin (1), the aglycon of the novel antineoplastic agent phyllanthoside (2), has been accomplished. The key feature of the approach entailed the dipolar cycloaddition of the nitrile oxide **7** with the optically active, bicyclic lactone **6**, a substance that presented a sterically and electronically biased framework to ensure that this reaction proceeded with reasonable levels of regio- and stereoselectivity to afford **11** as the major product. The dispensible oxygen function at C(1) was removed from **11** in three straightforward operations to afford **18**, which underwent a directed aldol reaction with the protected aldehyde **8c** to give a mixture (1.2:1) of the two adducts **21c** and **22c**. Treatment of **21c** with hydrofluoric acid in methanol gave a mixture of methyl glycosides **23** and **24**. Similar treatment of **22c** afforded a single methyl glycoside **25**, which was transformed into **24** by oxidation and reduction. Unveiling of the latent β-hydroxy ketone array at C(5) and C(7) was achieved by hydrogenolysis and hydrolysis of the isoxazoline ring of **23** and **24** to give intermediates that underwent smooth acid-catalyzed, kinetic spiroketalization to furnish **3** as the major product. The spiroketal **3** was then converted into (+)-phyllanthocin (1) according to protocols previously developed by Williams.

Introduction

During the course of routine screening of a variety of plants for potential anticancer agents, in 1977 Kupchan isolated and characterized (+)-phyllanthocin (1) from the ethanol extract of the roots of *Phyllanthus acuminatus* Vahl.[2] Although **1** itself did not exhibit antineoplastic activity, the structure of the biologically active component was identified in 1982 by Pettit as being the bisabolane glycoside phyllanthoside (2),[3] which exhibited significant activity against murine P388 leukemia and B16 melanoma and is currently undergoing clinical trials.[3,4] In subsequent explorations, Pettit isolated a number of closely related antineoplastic glycosides known as phyllanthostatins.[3] Owing to its considerable promise as a therapeutically useful antitumor agent, phyllanthoside (2) as well as the corresponding aglycon **1** emerged as highly attractive targets for total synthesis.[5-10] These synthetic investigations have culminated in five accounts of the asymmetric total synthesis of **1**,[5-9] and the naturally occurring glycoside **2** itself has succumbed to total synthesis.[10] We recently completed a highly convergent, enantioselective synthesis of **1**,[9] and we now disclose the details of those endeavors.

The essential features of the strategy that eventuated in the asymmetric synthesis of **1** are outlined in Scheme I. Relatively straightforward modification of **1** in a retrosynthetic direction leads to the tricyclic spiroketal **3**, which also served as a key intermediate in Williams' approach to **1**.[6] Further dismantling of the spiroketal array present in **3** then unveils the highly functionalized cyclohexane **4**. The conversion of **4** into **3** by a synthetic path presumes that spiroketalization of **4** will proceed with a high degree of selectivity under either conditions of kinetic or thermodynamic control to provide the desired **3** as the major product. An examination of the literature provided sufficient precedent that such a transformation was likely to proceed in the requisite sense.[11] Closer inspection of the polyfunctionalized intermediate **4** reveals two different β-hydroxy keto arrays, one at C(5) and C(7) and the other at C(10) and C(8). The cis stereochemical relationship between the acyl and hydroxyl functions resident on the cyclohexane ring at C(5) and C(6) suggests that compound **4** might be derived from isoxazoline **5**. This analysis owes its genesis to the recognition of the synthetic equivalency of a β-hydroxy ketone moiety with an isoxazoline ring,[12]

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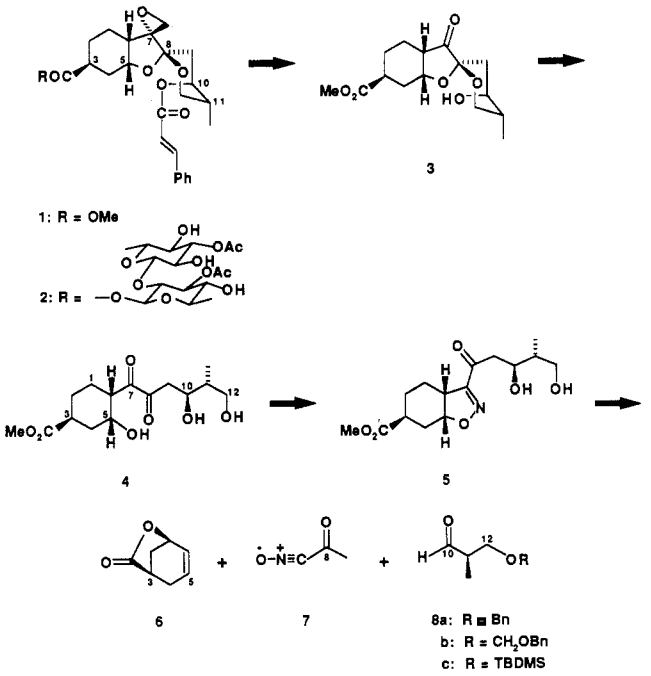
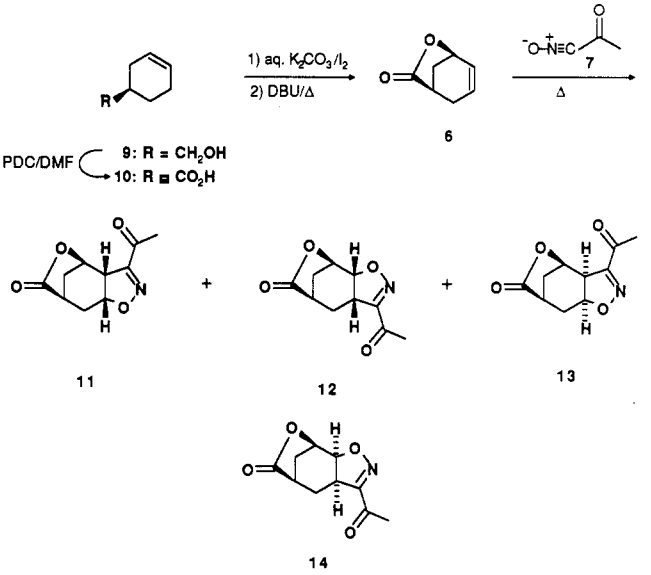
Scheme I



Scheme II



a ring system that is conveniently accessible from the [3 + 2] dipolar cycloaddition of a nitrile oxide with an alkene.[13]

Analysis of the challenges posed by the synthesis of the fused isoxazoline **5** suggested a convergent approach that would involve the combination of the enantiomerically pure bicyclic, unsaturated lactone **6**, the nitrile oxide **7**, and an enantiomerically pure, protected β-hydroxy aldehyde such as **8a–c**. The selection of **6** as the dipolarophile was predicated on several considerations. First, the candidacy of methyl cyclohex-3-enecarboxylate as a partner for the dipolar cycloaddition was rejected on the basis of the reasonable hypothesis that its cycloaddition with **7** would not be expected to proceed with a significant level of either stereo- or regioselectivity. This conjecture was convincingly verified in a preliminary experiment by the finding that reaction of methyl cyclohex-3-enecarboxylate with **7** gave a mixture of four diastereomeric cycloadducts in approximately equal amounts. In contrast, the bicyclic lactone **6** presents a sterically and electronically biased molecular framework to ensure that the nitrile oxide **7** will attack preferentially from the less encumbered exo face of the alkene with a predisposition for attachment of the oxygen of the nitrile oxide function to the terminus of the double bond distal to the allylic oxygen.[14] A second consideration that weighed in the selection of **6** as the dipolarophile was that known reactions could be easily marshalled to prepare **6** in optically pure form. Finally, we envisaged that the stereoselective construction of the bond between C(9) and C(10) could be achieved at an appropriate stage by chelation-controlled addition[15] of an enol derivative of the C(8) ketone moiety to a protected aldehyde of type **8a–c**.

Discussion

Having established the essential features of the synthetic approach, preparation of the requisite starting materials **6**, **7**, and **8a–c** was undertaken. Since the racemic lactone **6** had been previously reported,[16] it was a simple task to modify these original procedures to provide optically pure **6**. Thus, known[17] (*R*)-3-cyclohexene-1-methanol (**9**) was prepared in two steps via the asymmetric [4 + 2] cycloaddition between the acrylate ester of 8-phenylmenthol and 1,3-butadiene and reduction of the crude cycloadduct with lithium aluminum hydride.[18] Despite the observation that less than 2% of a diastereomeric substance could be detected by GC–MS after the asymmetric Diels–Alder reaction, the **9** thus obtained exhibited an optical purity of about 85% based upon its optical rotation {$[\alpha]^{24}_D$ = +81.8° (*c* 3.06, MeOH); lit.[17a] $[\alpha]^{22}_D$ = +96° (*c* 3.0, MeOH)}. Oxidation of **9** with pyridinium dichromate in dimethylformamide afforded the acid **10**, which was estimated to be only approximately 73% enantiomerically pure {$[\alpha]^{23}_D$ = +69.2° (*c* 7.36, MeOH); lit.[17a] $[\alpha]^{22}_D$ = +94.5° (*c* 7.0, MeOH)}, indicating that further racemization occurred during the oxidation. Consequently, a partial resolution

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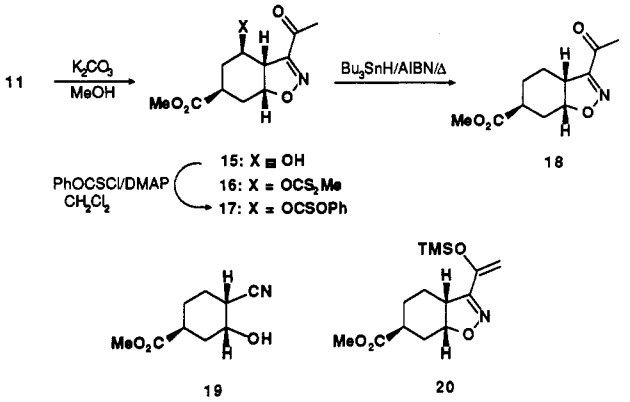
of **10** was performed by one recrystallization of its brucine salt to provide **10** whose optical purity was typically in the 90–95% range. With the optically active acid **10** thus secured, the dipolarophile **6** was prepared in 96% overall yield by treatment of **10** with iodine in aqueous sodium bicarbonate followed by dehydroiodination of the intermediate iodolactone upon reaction with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in refluxing benzene.[16]

The next stage of the synthesis required the development of a suitable protocol to achieve the crucial dipolar cycloaddition. After considerable experimentation, it was discovered that the optimal conditions for effecting this process involved the slow, thermal generation of the highly reactive nitrile oxide **7** from acetohydroximoyl chloride in refluxing toluene in the presence of **6**. When the reaction was executed in this fashion, the desired cycloadduct **11** was isolated in 45% yield together with two other diastereomeric adducts **12** (19%) and **13** (15%), (Scheme II). None of the isomeric cycloadduct **14** was isolated, but it could have been present in small amounts. It should be noted that use of other methods to generate the requisite nitrile oxide **7** from hydroximoyl chloride (e.g., $AgNO_3$[19] or Et_3N[20]) typically afforded more complicated reaction mixtures with the desired product **11** being isolated in lower yield. However, the ratio of **11**, **12**, and **13** remained essentially constant irrespective of the precise experimental conditions that were employed to effect the dipolar cycloaddition. Thus, the bicyclic lactone served its intended purpose as a regio- and stereochemical control element in the dipolar cycloaddition, although the induced selectivity was less than we had hoped.

The cycloadducts **11**, **12**, and **13** could be separated by preparative HPLC, and the structural assignments were based upon extensive ^1H NMR experiments. Clearly evident of the expected cis ring fusion were the coupling constants observed between the protons at the ring fusion; these values ranged from J = 9 to 10.3 Hz. Furthermore, the proton α to the oxygen on the isoxazoline ring of **11** appeared as a ddd (δ 5.04), and the coupling constants to the two adjacent methylene protons on the cyclohexane ring were J = 8.0 and 3.2 Hz. The other proton (δ 3.86) on the isoxazoline ring exhibited only a small (<1 Hz) coupling with the vicinal proton (δ 5.09) at the bridgehead of the bicyclic lactone ring and α to the lactone oxygen. This tentative assignment of the structure of **11** was confirmed at a subsequent stage by a single-crystal X-ray analysis of **18** (vide infra). The regioisomer **12** was similarly characterized by an observed vicinal coupling of J = 3.7 Hz between the proton (δ 4.78) α to the oxygen of the isoxazoline ring and the bridgehead proton (δ 5.01) adjacent to the ring oxygen of the bicyclic lactone; the remaining proton (δ 3.66) on the isoxazoline ring exhibited large coupling constants (J = 8.1, 10.0 Hz) with each of the two adjacent methylene protons. Each of the bridgehead protons on the isoxazoline ring of **13** were coupled to only one other vicinal proton. The proton (δ 4.82) α to the oxygen of the isoxazoline ring of **13** was coupled to only one of the adjacent methylene protons (J = 6.3 Hz), whereas the other proton (δ 3.51) on the isoxazoline ring was coupled (J = 2.5 Hz) with the downfield bridgehead proton (δ 4.86) on the lactone array.

Several preliminary attempts to construct the C(9)–C(10) bond via an aldol reaction using the cycloadduct **11** itself were unsuccessful, apparently owing to base-induced decomposition of the lactone array. However, the lactone moiety of **11** had already fulfilled its important role as a control element, and it was thus an appropriate time to modify the substitution pattern on the cyclohexane ring to correspond with that found in **1**. Straightforward processing of **11** by methanolysis in the presence of potassium carbonate afforded the hydroxy ester **15** in 85% yield (Scheme III). The optical purity of the **15** obtained was established to be approximately 95% based upon an analysis of the derived Mosher ester.[21]

Scheme III



The next task involved the replacement of the hydroxyl group at C(1) with a proton, and a variety of options were explored. Initial experiments to convert the hydroxyl group in **15** into the corresponding chloride by standard methods proceeded in only low yields. The mesylate derived from **15** could be prepared, but several attempts to effect its smooth reduction to give **18** were equally unavailing. Consequently, we examined techniques to remove the hydroxyl group via a process entailing radical deoxygenation.[22] Although the xanthate **16** could be prepared (Bu^t–OK; CS_2; MeI) and reduced with tri-*n*-butyltin hydride, the overall yields for the transformation to **18** were only modest, and the experimental conditions for the formation of **16** proved somewhat capricious. On the other hand, the related phenoxythionocarbonate **17** could be readily accessed from **15** by the action of chloro phenoxythionocarbonate in the presence of a slight excess of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in 83% yield. Interestingly, this reaction proceeded rather sluggishly in the absence of an excess of DMAP; alternative procedures using catalytic amounts of DMAP in the presence of different bases were completely ineffective. Subsequent treatment of **17** with tri-*n*-butyltin hydride completed the sequence to give **18** in 65% yield (74% based on consumed starting material, **17**) together with **17** (ca. 12%). It was necessary to carry this reaction to only partial completion in order to avoid attack by tin hydride upon the isoxazoline ring system itself, a process that led to the formation of variable quantities of the hydroxy nitrile **19**. However, under the optimized reaction conditions described, production of **19** was not observed. As mentioned previously, the relative stereochemistry of **18** was confirmed by a single-crystal X-ray analysis (Figure 1).[23]

The coupling of the two optically active subunits **18** and **8a–c**[24] would require a chelation-controlled aldol reaction

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(23) The single-crystal X-ray analysis was performed by Dr. Steven Larson at the University of Texas at Austin.

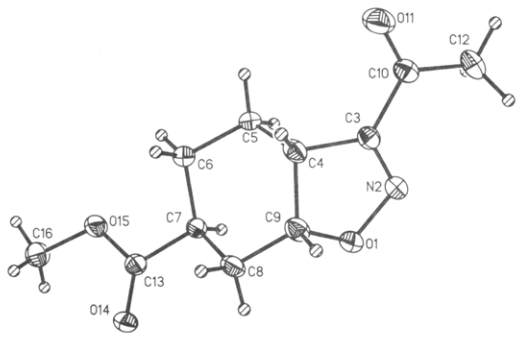
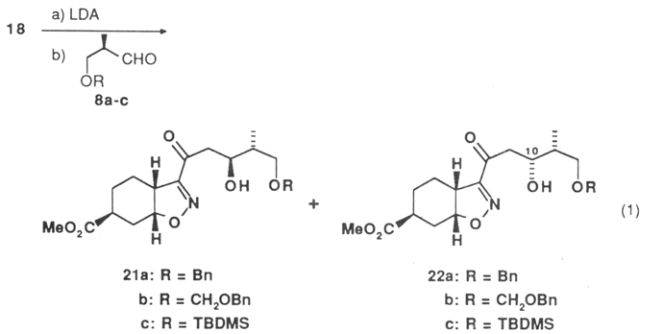


Figure 1. View (ORTEP plot) of **18** showing atom numbering scheme and non-hydrogen atoms as 50% thermal elipsoids.

or related process[15] to achieve high levels of stereochemical efficiency. To this end, the trimethylsilylenol ether **20** was prepared in 87% yield upon reaction of **18** with trimethylsilyl trifluoromethanesulfonate in 1,2-dichloroethane in the presence of triethylamine. The subsequent reactions of **20** with the protected β-hydroxy aldehydes **8a–c** in the presence of $SnCl_4$ (CH_2Cl_2, −78 → −20 °C) provided mixtures of the corresponding adducts **21a–c** and **22a–c** in which the desired anti adducts **21a–c** dominated by ratios of as much as 9–12:1; however, the yields of products obtained from these transformations were uniformly unacceptable, being generally less than 20%. Numerous variations of the experimental method and conditions were explored, including a survey of other Lewis acids, but no further improvement could be achieved. A major difficulty arose from the necessity of conducting the additions at −20 → −0 °C, whereupon various decomposition pathways intervened. Alternatively, when the lithium enolate generated from **18** was allowed to react with the aldehydes **8a–c**, readily separable mixtures, which ranged from approximately 1.2 to 1.8:1 depending upon the nature of the hydroxyl protecting group R, of the anti and syn adducts **21a–c** and **22a–c**, respectively, were consistently obtained in very good yield (75–85%) (eq 1).

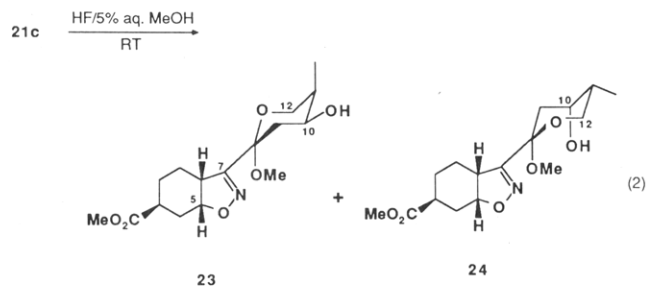


(1)

The anti/syn ratio obtained in these aldol reactions was slightly higher (1.4–1.8:1 vs 1.2:1) when **8a** and **8b** rather than **8c** were employed as the aldehydic partners.[15f-h] The presence of various Lewis acid additives including $ZnCl_2$,[15d,25] $SnCl_4$,[15c,25] Bu_3SnCl,[26] CuI,[27] $MgBr_2$,[25] and $TiCl(O\text{-}Pr^i)_3$[15c,28] afforded no discernible improvement in the diastereoselection in these processes.[29] Although the aldol reaction of the enolate derived from **18** with **8a** and **8b** afforded slightly better anti/syn ratios of adducts (1.4–1.8:1), the hydroxyl protecting groups proved difficult to remove selectively by standard procedures from **21a,b** and **22a,b** and substances derived therefrom. Consequently attention was focused upon the further transformations of **21c** and **22c** into **1**. Inasmuch as the configuration at C(10) of **22c** was epimeric to that required, it would be necessary to devise suitable tactics to effect the inversion at this center.

The stereochemical assignments for the anti adducts **21a–c** and the syn adducts **22a–c** were initially based upon previously observed trends in the ^{13}C NMR spectra for related anti and syn diastereomers.[30,31] Namely, in the ^{13}C NMR spectra for such substances, the relative position of the signal for the methyl group vicinal to the new hydroxyl function is a reliable diagnostic tool; it consistently appears at lower fields in the anti isomer compared to the syn isomer. Thus, the methyl group at C(11) of **21c** appears at δ = 13.0 ppm, whereas in **22c** it is found at δ = 10.8 ppm. Generally, the different chemical shifts of the relevant proton signals are of little use in assigning stereochemistry in systems related to **21a–c** and **22a–c**.[30,31] Further confirmation of these preliminary assignments is provided by the chemical conversion of **21c** and **22c** into **1** (vide infra).

During the course of preliminary experiments, we developed several methods for effecting the reduction and hydrolysis of isoxazolines to unveil β-hydroxy ketones.[12e] Somewhat surprisingly the isoxazoline ring of **21c** proved to be resistant not only to those conditions but also to a variety of others that had been previously reported to effect the crucial unmasking. We reasoned that conjugation of the isoxazoline ring with the ketone function at C(8) of **21c** lowered the reactivity of the isoxazoline array toward hydrogenolysis of the N–O bond, and we therefore turned to alternative tactics that involved the prior protection of the ketone function. This end was most expeditiously achieved by an internal ketalization process that was induced by reaction of the anti aldol **21c** with 5% aqueous hydrofluoric acid in methanol to provide a mixture (2.3–2.8:1) of the methyl glycosides **23** and **24** in 70–75% yield (eq 2).



(2)

In a similar fashion, when **22c** was treated with 5% aqueous hydrofluoric acid/methanol, a single methyl glycoside **25** was obtained (79%) in which both the methyl and the hydroxyl group reside in an equatorial orientation

(24) We thank Dr. Noal Cohen (Hoffmann-LaRoche, Inc.) for a generous sample of (*S*)-(+)-3-hydroxy-2-methylpropanoic acid that was used for the preparation of **8a,b**. The aldehydes **8a–c** were prepared by sequential protection of the hydroxyl group of either the corresponding methyl or ethyl ester, overreduction with DIBAL-H, and Swern oxidation (e.g., see in ref 7a).

(25) Uenishi, J.-I.; Tomozane, H.; Yamato, M. *Tetrahedron Lett.* **1985**, *26*, 3467.

(26) (a) Shenvi, S.; Stille, J. K. *Tetrahedron Lett.* **1982**, *23*, 627. (b) Labadie, S. S.; Stille, J. K. *Tetrahedron* **1984**, *40*, 2329. (c) Kobayashi, K.; Kawanisi, M.; Hitomi, T.; Kozima, S. *Chem. Lett.* **1983**, 851.

(27) For use of organocuprates in chelation-controlled additions to β-hydroxy aldehydes, see: Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035.

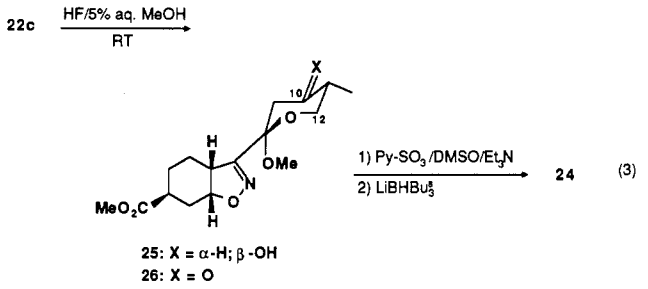
(28) (a) Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691. (b) Siegel, C.; Thorton, E. R. *Tetrahedron Lett.* **1986**, *27*, 457.

(29) Burke reported a 3.6:1 mixture of Cram/anti-Cram diastereomers in an aldol reaction using aldehyde **8c**.[7]

(30) Professor M. T. Reetz (Philipps-Universität Marburg), personal communication.

(31) (a) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294. (b) Heathcock, C. H.; Kiyooka, S.-I.; Blumenkopf, T. A. *Ibid.* **1984**, *49*, 4214.

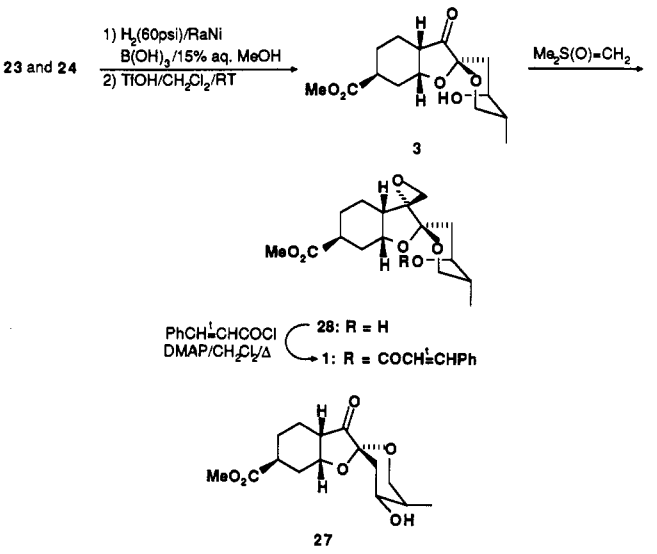
(eq 3). Inasmuch as the hydropyran ring in **25** offered a conformationally biased framework for stereoselective manipulations, it was an appropriate moment to effect the required inversion of configuration of the hydroxyl group at C(10). Oxidation of **25** with pyridine–sulfur trioxide in DMSO in the presence of triethylamine[32] yielded an intermediate ketone **26** that was reduced with a high level of stereoselectivity from the more accessible equatorial face using L-selectride to give **24** as the exclusive product (73% overall yield). Alternatively, reduction of **26** with sodium borohydride gave a mixture (9:1) of **24** and **25**.



The structural assignments of the methyl glycosides **23–25** were based upon ^{1}H NMR analyses, and several key observations may be made. For example, in **23** the gauche relationship of each of the protons at C(12) with the equatorial proton at C(11) is evidenced by the small coupling constant of J = 2.6 Hz. Moreover, the axial proton of the methylene group at C(9) exhibits two large couplings, one geminal (J = 13.1 Hz) and one vicinal to the axial proton at C(10) (J = 10.6 Hz). In compound **24**, the axial nature of the hydrogen at C(11) is clearly suggested by the vicinal coupling constants observed with the two protons at C(12) of J = 5.6 and 11.4 Hz. Furthermore the equatorial disposition of the proton at C(10) ($W_{1/2}$ = 10.6 Hz) is suggested by a coupling constant of approximately 3.0 Hz with each of the vicinal protons on C(9) and C(11). Interestingly, the proton on the axial hydroxyl group of **24**, which is presumably hydrogen bonded to the axial methoxy group, appears as a sharp doublet (δ 3.43, J = 9.6 Hz) coupled to the adjacent equatorial proton at C(10). Finally, the axial orientation of the proton at C(10) of **25** was evident from its observed trans-diaxial relationship with the axial proton at C(9) (J = 11.0 Hz). Furthermore, the axial proton on the C(12) methylene group is a triplet (J = 11.5 Hz), verifying its trans-diaxial relationship with the adjacent axial proton at C(11).

At this juncture, we were again confronted with the seemingly straightforward task of effecting the reductive and hydrolytic processing of **23** and **24** to provide intermediate β-hydroxy ketones that would undergo spiroketalization to deliver the desired spiroketal **3** (Scheme IV). Although some difficulties were initially encountered in achieving this conversion, we soon discovered that the latent β-hydroxy ketone array at C(5)–C(7) of the isoxazolines **23** and **24** were readily liberated upon treatment with W-2 Raney nickel in 15% aqueous methanol containing boric acid under an atmosphere of hydrogen (60 psi). The intermediate hydroxy keto glycosides were not characterized, but they were subjected directly to acid-catalyzed spiroketalization with trifluoromethanesulfonic acid in methylene chloride to give **3** in 68% overall yield together with another spiroketal, which has been tentatively identified as **27** (18:1). The spiroketal **3**, which was thus obtained was spectroscopically identical with Williams' intermediate.[33] The use of camphorsulfonic acid as the catalyst for inducing the spiroketalization afforded **3** in only moderate yield together with compounds that appeared to be various dehydration products. When either **3** or **27** was resubjected to the reaction conditions required for the initial spiroketalization, no equilibration could be detected, but prolonged exposure of **3** or **27** to these conditions led to eventual decomposition. These observations suggest that the spiroketalization of the intermediate hydroxy keto glycosides derived from both **23** and **24** is a kinetically controlled process.

Scheme IV



The synthesis of phyllanthocin (**1**) was then completed according to protocols previously developed by Williams.[6] Namely, reaction of **3** with dimethylsulfoxonium methylide afforded in 89% yield an intermediate epoxide **28** as a single stereoisomer. When **28** was acylated with cinnamoyl chloride in methylene chloride in the presence of DMAP, synthetic (+)-phyllanthocin (**1**), which was spectroscopically identical (^{1}H and ^{13}C NMR, IR, mass spectrum, and TLC) with an authentic sample,[34] was obtained in good yield.

Thus, a concise and highly convergent, enantioselective synthesis of (+)-phyllanthocin (**1**) has been completed. The overall strategy features the regio- and stereoselective [3 + 2] dipolar cycloaddition of a functionalized nitrile oxide to a bicyclic lactone to establish simultaneously the masked β-hydroxy keto array at C(5) and C(7) and the relative stereochemistry at centers at C(3), C(5), and C(6). The plan requires only 12 steps from the known acid **10** by a longest linear sequence that proceeded via the anti aldol adduct **21c**. Although the aldol reaction that forms the new carbon–carbon bond between C(9) and C(10) produced a mixture of the adducts **21c** and **22c**, the undesired syn isomer **22c** could be transformed to an intermediate along the main path in a simple three-step operation. The overall yield of **1** from **10** is thus 2.4%. The application of this general strategy to the asymmetric syntheses of related natural products is the subject of

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(33) We thank Professor D. R. Williams (Indiana University) for providing spectral data of **3** for comparison.

(34) We thank Professor S. D. Burke (University of Wisconsin, Madison) for providing the ^{1}H NMR spectrum of **1** and Professor A. B. Smith, III (University of Pennsylvania), for generous quantities of an authentic sample of **1** for comparison purposes.

current investigations in our laboratory, and these results will be described in due course.

Experimental Section

General Procedures. Unless otherwise noted, all starting materials were obtained from commercial suppliers and were used without further purification. Melting points are uncorrected. Ether, tetrahydrofuran (THF), benzene, and toluene were distilled from either sodium or potassium/benzophenone ketyl immediately prior to use. Triethylamine, dimethyl sulfoxide (DMSO), and dimethylformamide (DMF) were distilled from calcium hydride. All reactions involving organometallic reagents or other air-sensitive reagents were executed under an atmosphere of dry nitrogen, using oven-dried glassware. IR spectra were determined as solutions in $CHCl_3$. The ^1H and ^{13}C NMR spectra were determined as solutions in $CDCl_3$; splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; m, multiplet; comp, complex multiplet; br, broad. Preparative HPLC was performed on either a Waters Prep LC 500 instrument (sample size >500 mg), or on a semipreparative system using two Porasil A columns (0.6 m × 7.8 mm) (sample size <500 mg). Bulb-to-bulb distillations were executed on a Büchi GKR-50 Kugelrohr apparatus.

(*R*)-3-Cyclohexene-1-carboxylic Acid (10). (*R*)-3-Cyclohexene-1-methanol (**9**)[18c] (6.67 g, 59.5 mmol) in dry dimethylformamide (DMF) (19 mL) was added via syringe drive pump to a solution of pyridinium dichromate (PDC) (80.5 g, 214 mmol) in DMF (200 mL) over 8 h at room temperature. After completion of the addition, stirring was continued for an additional 16 h, whereupon the reaction mixture was poured into ice/water (1 L). This aqueous mixture was then extracted with ether (6 × 200 mL), and the combined organic extracts were washed with 1N HCl (400 mL) and then extracted with saturated aqueous $NaHCO_3$ solution (2 × 500 mL). (Evaporation of the ether layer afforded 0.7 g of the "dimeric ester", which was recycled by reduction with $LiAlH_4$ and oxidation). The combined $NaHCO_3$ extracts were carefully acidified with 6 N HCl until pH = 1 and then extracted with ether (2 × 500 mL). The ether extracts were dried ($MgSO_4$) and evaporated in vacuo to give a crude oil, which was distilled (bp 110 °C, 0.25 Torr, air bath) to yield 5.56 g (74%) of **10** that was determined to be 73% ee. {$[\alpha]^{23}_D$ = +69.2° (*c* 7.36, MeOH); lit.[17a] $[\alpha]^{22}_D$ = +94.5° (*c* 7.0, MeOH)}. In order to obtain acid of higher optical purity, brucine (46.8 g, 119 mmol) was added to a solution of acid **10** (14.9 g, 119 mmol) in dry acetone (300 mL). The mixture was heated at reflux for 35 min and then cooled to −25 °C for 16 h. The resulting white crystals were collected, washed with acetone, and dried to give 52.8 g (85%) of crude salt, which was recrystallized from acetone to yield 35.4 g (67%) of pure salt. These crystals were dissolved in 1 N aqueous hydrochloric acid (250 mL), and the solution was extracted with ether (3 × 200 mL). The ether extracts were dried ($MgSO_4$) and concentrated to give a crude oil, which was distilled (bp 90 °C, 0.2 Torr, air bath) to yield 8.41g (56%) of resolved acid **10** of 91% ee {$[\alpha]^{23}_D$ = +85.9° (*c* 5.37, MeOH)}. The mother liquor from the first recrystallization was evaporated to yield a crude solid (17.1 g, 32%), which was processed in a similar manner to yield 4.43 g (30%) of acid **10** of slightly lower (87%) optical purity {$[\alpha]^{23}_D$ = +82.1° (*c* 3.56, MeOH)}. In other experiments the optical purity of the **10** thus purified ranged from 90 to 95% based upon rotations.

(1*R*,2*R*,5*R*)-2-Iodo-7-oxabicyclo[3.2.1]octan-6-one. Acid **10** (4.40 g, 34.9 mmol) was added to a solution of $NaHCO_3$ (8.79 g 105 mmol) in water (85 mL), and the resulting mixture was stirred until it became homogeneous. The flask was then protected from light, and the mixture was treated in one portion with a solution of KI (34.75 g, 209 mmol) and iodine (9.29 g, 36.6 mmol) in water (85 mL). The reaction mixture was stirred at room temperature for 20 h and then extracted with $CHCl_3$ (5 × 75 mL). The organic extracts were combined, washed with 10% aqueous $Na_2S_2O_3$ (200 mL), 10% aqueous $NaHCO_3$ (200 mL), and water (100 mL), and then dried (Na_2SO_4). Removal of the solvent in vacuo yielded 8.58 g (98%) of iodo lactone as a yellow solid: mp 135–136 °C (from EtOH/ether, 1:3) (lit.[16a] mp 134 °C (racemic)). $[\alpha]^{24}_D$ = +37.6° (*c* 2.03, $CHCl_3$); ^1H NMR (90 MHz) δ 4.82 (br t, *J* = 5.2 Hz, 1 H), 4.51 (br t, *J* = 4.6 Hz, 1 H), 2.80 (d, *J* = 12.3 Hz, 1 H), 2.68–2.64 (m, 1 H), 2.50–2.33 (comp, 3 H), 2.12 (dd, *J* = 16.5, 4.9 Hz, 1 H), 1.95–1.78 (comp, 2 H); ^{13}C NMR (22.6 MHz) δ 177.5, 80.1, 38.5, 34.4, 29.6, 23.7, 23.0; IR 1780 cm^{-1}; mass spectrum *m/e* 251.9645 ($C_7H_9IO_2$ requires 251.9647), 125, 81 (base), 41.

(1*R*,5*R*)-7-Oxabicyclo[3.2.1]oct-2-en-6-one (6). Iodo lactone (23.69 g, 94.0 mmol) from the previous experiment was dissolved in dry toluene (250 mL) containing freshly distilled 1,3-diazabicyclo[5.4.0]undec-7-ene (DBU) (21.50 g, 140 mmol), and the mixture was heated at reflux for 6 h, cooled, and filtered, and the filtrate was concentrated under reduced pressure. The residue was distilled (63 °C, 0.1 Torr; lit.[16a] 110 °C, 15 Torr) to afford 11.40 g (98%) of **16** as a pale yellow oil: $[\alpha]^{23}_D$ = +179.2° (*c* 9.76, $CHCl_3$); ^1H NMR (200 MHz) δ 6.24 (m, 1 H), 5.85 (m, 1 H), 4.76 (t, *J* = 5.3 Hz, 1 H), 2.91 (m, 1 H), 2.50 (comp, 2 H), 2.49 (m, 1 H), 2.10 (d, *J* = 10.7 Hz, 1 H); ^{13}C NMR (22.6 MHz) δ 178.8, 129.8, 128.9, 72.8, 37.6, 33.9, 28.7; IR ($CHCl_3$) 1775, 1640 cm^{-1}; mass spectrum, *m/e* 124.0526 ($C_7H_8O_2$ requires 124.0524), 79 (base).

1,3-Dipolar Cycloaddition of 6 with Acetyl Nitrile Oxide. A mixture of unsaturated lactone **6** (9.84 g, 79.3 mmol) and acetyl hydroximoyl chloride (19.26 g, 158.5 mmol) was dissolved in dry toluene (550 mL) under nitrogen, and the mixture was heated at reflux for 16 h. After cooling to room temperature, the excess solvent was removed under reduced pressure, and the mixture was separated by preparative HPLC (Skelly B/EtOAc, 3:1) to give 7.52 g (45%) of **11**, 3.30 g (19%) of **12**, and 2.44 g (15%) of **13**.

(1*S*,3*R*,7*S*,8*R*)-6-Acetyl-4,9-dioxa-5-azatricyclo[6.2.1.0^{3,7}]undec-5-en-10-one (11): mp 96–97 °C (from ether/hexene, 1:1); $[\alpha]^{23}_D$ = −14.1° (*c* 7.04, $CHCl_3$); ^1H NMR (500 MHz) δ 5.09 (dd, *J* = 2.1, 6.0 Hz, 1 H), 5.04 (ddd, *J* = 3.2, 8.0, 10.3 Hz, 1 H), 3.86 (br d, *J* = 10.3 Hz, 1 H), 2.72–2.18 (comp, 5 H), 2.53 (s, 3 H), 1.80 (d, *J* = 12.5 Hz, 1 H); ^{13}C NMR (22.6 MHz) δ 192.9, 177.8, 156.9, 80.4, 75.1, 48.8, 34.7, 30.2, 29.6, 27.1; IR 1790, 1690, 1575 cm^{-1}; mass spectrum, *m/e* 209.0609 ($C_{10}H_{11}NO_4$ requires 209.0688), 166, 149, 121, 112, 101, 79, 43 (base). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30. Found: C, 57.51; H, 5.17.

(1*R*,2*R*,6*S*,8*R*)-5-Acetyl-3,10-dioxa-4-azatricyclo[6.2.1.0^{2,6}]undec-4-en-9-one (12): ^1H NMR (200 MHz) δ 5.01 (dd, *J* = 3.7, 5.8 Hz, 1 H), 4.78 (ddd, *J* = 1.2, 3.7, 10.0 Hz, 1 H), 3.66 (dt, *J* = 8.1, 10.0 Hz, 1 H), 2.67 (ddd, *J* = 1.0, 2.7, 4.3 Hz, 1 H), 2.52 (s, 3 H), 2.50 (ddt, *J* = 10.0, 14.1, 2.7 Hz, 1 H), 2.45 (dddd, *J* = 1.5, 2.2, 5.7, 12.5 Hz, 1 H), 1.99 (d, *J* = 12.5 Hz, 1 H), 1.55 (ddd, *J* = 4.3, 8.1, 14.1 Hz, 1 H); ^{13}C NMR (22.6 MHz) δ 191.4, 161.4, 80.3, 73.9, 38.2, 34.4, 29.2, 28.6, 26.0.

(1*S*,3*S*,7*R*,8*R*)-6-Acetyl-4,9-dioxa-5-azatricyclo[6.2.1.0^{3,7}]undec-5-en-10-one (13): ^1H NMR (200 MHz) δ 4.86 (dd, *J* = 2.5, 6.1 Hz, 1 H), 4.82 (dd, *J* = 6.3, 9.3 Hz, 1 H), 3.51 (dd, *J* = 2.5, 9.3 Hz, 1 H), 2.70 (m, 1 H), 2.61 (m, 1 H), 2.53 (s, 3 H), 2.50 (m, 1 H), 2.25 (ddd, *J* = 3.9, 6.3, 15.5 Hz, 1 H), 1.80 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR (22.6 MHz) δ 193.2, 176.9), 158.6, 79.9, 74.9, 47.3, 34.2, 32.8, 28.6, 26.6; IR 1770, 1690 cm^{-1}; mass spectrum, *m/e* 209.0609 ($C_{10}H_{11}NO_4$ requires 209.0688), 167, 149, 43 (base).

Methyl (1*S*,2*R*,4*S*,6*R*)-9-Acetyl-2-hydroxy-7-oxa-8-azabicyclo[4.3.0]non-8-ene-4-carboxylate (15). Lactone **11** (7.19 g, 34.4 mmol) was dissolved in MeOH (185 mL) containing K_2CO_3 (1.70 g, 12.3 mmol), and the solution was stirred at room temperature for 30 min. The mixture was neutralized with glacial acetic acid (1.3 mL), and then the solvent was removed by evaporation under reduced pressure to give the crude hydroxy ester **15**, which was purified by preparative silica gel chromatography (Skelly B/EtOAc, 1.5:1) to give 7.09 g (85%) of **15** as a clear oil. Preparation and analysis (capillary GLC and ^{19}F NMR) of the Mosher ester[21] derived from **15** indicated that it was approximately 95% optically pure, although it was difficult to effect complete conversion of **15** to the Mosher ester: $[\alpha]^{23}_D$ = +146° (*c* 4.20, $CHCl_3$); ^1H NMR (200 MHz) δ 4.78 (dq, *J* = 2.0, 4.0 Hz, 1 H), 4.00 (br s, 1 H), 3.73 (s, 3 H), 3.46 (m, 1 H), 3.00 (t, *J* = 8.0 Hz, 1 H), 2.59 (s, 3 H), 2.55 (m, 1 H), 2.49 (m, 1 H), 2.26 (m, 1 H), 2.49 (m, 1 H), 2.26 (m, 1 H), 1.95 (ddd, *J* = 2.0, 11.0, 16.0 Hz, 1 H), 1.40 (q, *J* = 11.0 Hz, 1 H); ^{13}C NMR (22.6 MHz) δ 196.0, 174.1, 162.7, 83.8, 69.6, 51.6, 50.9, 35.4, 32.0, 26.6, 26.3; IR 3480, 1730, 1680, 1560 cm^{-1}; mass spectrum, *m/e* 241.0944 ($C_{11}H_{15}NO_5$ requires 241.0950) 210, 180, 166, 138, 112 (base), 87, 70, 55, 43.

Methyl (1*S*,2*R*,4*S*,6*R*)-9-Acetyl-2-[(phenoxythionocarbonyl)oxy]-7-oxa-8-azabicyclo[4.3.0]non-8-ene-4-carboxylate (17). To a solution of 4-(*N*,*N*-dimethylamino)-

pyridine (DMAP) (2.83 g, 23.0 mmol) in dry CH_2Cl_2 (60 mL) was added slowly phenyl chlorothionocarbonate (3.38 g, 19.6 mmol) while the reaction temperature was kept at less than 5 °C. The resulting yellow suspension was stirred for 40 min, whereupon a solution of alcohol **15** (2.78 g, 11.5 mmol) in CH_2Cl_2 (25 mL) was added dropwise over 35 min. The mixture was allowed to warm to room temperature and stirred for 24 h, and the resulting mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with 1 N HCl (2 × 75 mL) and brine (2 × 50 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo and partial purification of the residue by silica gel chromatography (Skelly B/EtOAc, 2.5:1) yielded 3.62 g (83%) of thionocarbonate **17** as a thick red semisolid, which was recrystallized from hexane/ether (3:1) to yield pure **17** as a white solid: mp 87–88 °C; $[\alpha]^{23}_D$ = +81.7° (*c* 5.23, $CHCl_3$); ^{1}H NMR (200 MHz) δ 7.42 (m, 2 H), 7.30 (m, 1 H), 7.15 (m, 1 H), 5.60 (dq, *J* = 2.0, 4.0 Hz, 1 H), 4.90 (dt, *J* = 3.0, 7.0 Hz), 3.75 (s, 3 H), 3.59 (dd, *J* = 7.5, 8.5 Hz), 2.82 (m, 1 H), 2.51 (s, 3 H), 2.30–1.95 (comp, 2 H), 1.41–1.19 (comp, 2 H); ^{13}C NMR (22.6 MHz) δ 194.2, 192.5, 173.8, 161.0, 153.2, 129.4, 126.5, 121.8, 83.4, 79.4, 52.1, 46.7, 34.6, 28.6, 26.7, 26.4; IR 1740, 1700 cm^{-1}; mass spectrum, *m/e* 377.0947 ($C_{18}H_{19}NO_6S$ requires 377.0933), 376, 302, 244 (base), 180, 150, 120, 94, 77, 65, 43.

Methyl (1*R*,3*S*,6*R*)-7-Acetyl-9-oxa-8-azabicyclo[4.3.0]non-7-ene-3-carboxylate (18). Thionocarbonate **17** (1.18 g, 3.13 mmol) and anhydrous azobisisobutyronitrile (13 mg, 0.078 mmol) were dissolved in dry, degassed benzene (200 mL) under nitrogen, and freshly distilled tri-*n*-butyltin hydride (0.90 mL, 0.98 g, 3.35 mmol) was added. The flask was then plunged immediately into an oil bath preheated to 110 °C and brought quickly to reflux. After being heated for 2.5 h, the mixture was cooled, concentrated in vacuo, and the residue was purified by preparative HPLC (Skelly B/EtOAc, 5:1) to give 0.15 g (0.38 mmol) of recovered thionocarbonate **17** and 0.46 g (65%) of **18** as a white solid: mp 69 °C; $[\alpha]^{23}_D$ = +185° (*c* 2.86, $CHCl_3$); ^{1}H NMR (200 MHz) δ 4.65 (m, 1 H), 3.70 (s, 3 H), 3.20 (dt, *J* = 7.0, 10.0 Hz, 1 H), 2.62–2.45 (comp. 2 H), 2.50 (s, 3 H), 2.11–1.75 (comp, 3 H), 1.50–1.10 (comp, 2 H); ^{13}C NMR (22.6 MHz) δ 192.8, 175.0, 163.8, 82.5, 51.5, 41.1, 36.6, 26.6, 26.3, 24.4, 24.1. IR 1740, 1695, 1570 cm^{-1}; mass spectrum, *m/e* 225.1006 ($C_{11}H_{15}NO_4$ requires 225.1001), 194, 150, 122 (base), 106, 96, 80, 55. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.39; H, 6.69; N, 6.22.

Aldol Products 21c and 22c. Ketone **18** (364 mg, 1.62 mmol) and a small crystal of 1,10-phenanthroline were dissolved in dry THF (4.0 mL), and the mixture was treated at −78 °C with 3.39 mL (1.70 mmol) of freshly prepared 0.5 N lithium diisopropylamide (LDA) in THF (the red color of the indicator persisted). After stirring for 45 min, a solution of freshly prepared aldehyde **8c**[7a] (≈650 mg, 3.23 mmol) in THF (3.0 mL) was added via cannula, and the stirring was continued for 1 h at −78 °C and then 1 h at 0 °C. The reaction was quenched by the addition of saturated NH_4Cl (3 mL), and water (20 mL) and ether (20 mL) were added. The layers were separated, and the aqueous layer was extracted with ether (2 × 20 mL). The organic extracts were washed with brine (20 mL), combined, and dried (Na_2SO_4). Removal of the excess solvents in vacuo gave 887 mg of a crude mixture of the anti and syn aldol adducts **21c** and **22c**, respectively, which were separated by preparative HPLC (Skelly B/EtOAc, 4:1) to give **21c** (299 mg, 43%) and **22c** (238 mg, 34%).

For **21c**: ^{1}H NMR (360 MHz) δ 4.67–4.65 (p, *J* = 3.7 Hz, 1 H), 4.16–4.12 (m, 1 H), 3.77 (m, 1 H), 3.69 (s, 3 H), 3.61 (dd, *J* = 7.1, 10.1 Hz, 1 H), 3.25–3.18 (m, 1 H), 3.08 (dd, *J* = 8.9, 15.4 Hz, 1 H), 3.02 (dd, *J* = 3.8, 15.4 Hz, 1 H), 2.56 (m, 1 H), 2.48 (br d, 1 H), 2.08–2.01 (m, 1 H), 1.95 (dd, *J* = 4.0, 11.5 Hz, 1 H), 1.92–1.86 (comp, 2 H), 1.81–1.75 (m, 1 H), 1.42–1.34 (m, 1 H), 1.28–1.15 (m, 1 H), 0.99 (d, *J* = 8.1 Hz, 3 H), 0.88 (s, 9 H), 0.069 (s, 3 H), 0.064 (s, 3 H); ^{13}C NMR (90 MHz) δ 194.8, 174.9, 163.6, 82.2, 71.8, 66.4, 51.4, 44.3, 41.3, 40.0, 36.4, 27.1, 25.5, 24.1, 24,0, 17.8, 13.0, −5.9; IR 3350 (br), 1720, 1665, 845 cm^{-1}; mass spectrum, *m/e* 427.2381 ($C_{22}H_{37}NO_6Si$ requires 427.2390), 409, 369, 321, 281, 145 (base), 115, 101, 97, 75, 73, 59, 43.

For **22c**: ^{1}H NMR (360 MHz) δ 4.64 (m, 1 H), 4.37 (m, 1 H), 3.74 (dd, *J* = 4.2, 9.9 Hz, 1 H), 3.69 (s, 3 H), 3.65 (dd, *J* = 6.4, 10.0 Hz, 1 H), 3.27 (d, *J* = 4.2 Hz, 1 H), 3.25–3.18 (m, 1 H), 3.15 (dd, *J* = 9.8, 15.9 Hz, 1 H), 2.90 (dd, *J* = 3.2, 15.9 Hz, 1 H), 2.61–2.46 (comp, 2 H), 2.09–2.02 (m, 1 H), 1.98–1.96 (m, 1 H), 1.94–1.86 (m, 1 H), 1.84–1.77 (m, 1 H), 1.46–1.37 (m, 1 H), 1.25–1.15 (m, 1 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.069 (s, 3 H), 0.066 (s, 3 H); ^{13}C NMR (90 MHz) δ 194.9, 175.2, 163.8, 82.5, 70.2, 66.8, 51.6, 43.7, 41.5, 39.6, 36.7, 26.8, 25.7, 24.4, 24.2, 18.0, 10.8 −5.7; IR 3400 (br), 1720, 1680, 840 cm^{-1}; mass spectrum, *m/e* 427.2401 ($C_{22}H_{37}NO_4Si$ requires 427.2390), 352, 322, 282, 240, 145 (base), 122, 115, 97, 75, 43.

Methyl Glycosides 23 and 24 from Anti Aldol 21c. To a solution of **21c** (276 mg, 0.946 mmol) in MeOH (15.5 mL) under dry nitrogen was added slowly 5% aqueous hydrofluoric acid (0.78 mL, 1.94 mmol), and the solution was stirred for 20 h at room temperature. Solid sodium bicarbonate (217 mg, 2.59 mmol) was added, and the mixture was concentrated under reduced pressure to approximately 2 mL, whereupon it was poured into water (30 mL). The mixture was extracted with EtOAc (3 × 30 mL), and the extracts were washed with brine (20 mL), combined, and dried (Na_2SO_4). Evaporation of the excess solvent in vacuo provided a mixture of methyl glycosides, which could be separated by preparative HPLC (Skelly B/EtOAc, 2:3) to give the two methyl glycosides **23** (105 mg, 50%) and **24** (48 mg, 23%).

For **23**: ^{1}H NMR (360 MHz) δ 4.45–4.41 (m, 1 H), 4.23 (m, 1 H), 3.80 (dd, *J* = 2.6, 11.5 Hz, 1 H), 3.69 (s, 3 H), 3.59 (dd, *J* = 2.6, 11.5 Hz, 1 H), 3.33–3.04 (m, 1 H), 3.23 (s, 3 H), 2.84–2.77 (m, 1 H), 2.62–2.55 (m, 1 H), 2.49 (br dq, *J* = 1.9, 15.3 Hz, 1 H), 2.06–1.82 (comp, 4 H), 1.79 (dd, *J* = 10.5, 13.1 Hz, 1 H), 1.48–1.25 (comp, 2 H), 1.05 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (90 MHz) δ 175.6, 166.1, 99.4, 80.4, 65.5, 65.1, 51.7, 49.6, 43.7, 37.4, 37.3, 34.1, 27.2, 25.6, 25.4, 9.4; IR 3570, 3400 (br), 2920, 1722, 1440, 1040, 860 cm^{-1}; mass spectrum *m/e* 327.1678 ($C_{16}H_{25}NO_6$ requires 327.1682), 297, 296 (base), 268, 264, 242, 226, 210, 198, 182, 166, 150, 148, 123, 122, 113, 106, 97, 96, 95, 94, 81, 79, 71, 69, 67, 59, 55, 54, 43, 41.

For **24**: $[\alpha]_D$ = +106° (*c* 1.00, $CHCl_3$); ^{1}H NMR (360 MHz) δ 4.46 (m, 1 H), 3.82 (br dq, *J* = 9.6, 3.0 Hz, 1 H), 3.70 (s, 3 H), 3.60 (t, *J* = 11.4 Hz, 1 H), 3.56 (dd, *J* = 5.6, 11.4 Hz, 1 H), 3.43 (d, *J* = 9.6 Hz, 1 H), 3.28 (s, 3 H), 2.92 (dt, *J* = 6.8, 10.6 Hz, 1 H), 2.59 (tt, *J* = 3.1, 11.6 Hz, 1 H), 2.48 (comp d, 1 H), 2.42 (dd, *J* = 3.0, 14.5 Hz, 1 H), 2.04–1.81 (comp, 4 H), 1.35–1.20 (comp, 2 H), 0.93 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (90 MHz) δ 175.5, 165.4, 98.1, 79.8, 67.3, 61.6, 51.7, 49.7, 44.3, 40.5, 37.4, 33.9, 27.1, 25.4, 25.2, 12.8; IR ($CHCl_3$) 3460 (br), 2920, 1720, 1040, 860 cm^{-1}; mass spectrum, *m/e* 327.1674 ($C_{16}H_{25}NO_6$ requires 327.1682), 297, 296 (base), 295, 268, 264, 242, 240, 226, 210, 198, 182, 166, 150, 145, 122, 113, 106, 97, 96, 95, 85, 81, 79, 71, 67, 59, 55, 54, 43, 41.

Methyl Glycoside 25 from Syn Aldol 22c. To a solution of syn aldol **22c** (216 mg, 0.51 mmol) in MeOH (12.1 mL) under nitrogen was slowly added 5% aqueous hydrofluoric acid (0.61 mL, 1.52 mmol), and the mixture was stirred at room temperature for 21 h. Solid $NaHCO_3$ (128 mg, 1.52 mmol) was added, and the mixture was concentrated under reduced pressure to approximately 3 mL and then diluted with water (25 mL). The aqueous mixture was extracted with EtOAc (3 × 25 mL), and the extracts were washed with brine (2 × 20 mL) and dried (Na_2SO_4). Concentration of the organic extracts in vacuo provided a crude oil (162 mg), which was purified by preparative HPLC (Skelly B/EtOAc, 2:3) to give the methyl glycoside **25** (130 mg, 79%) as a colorless oil: ^{1}H NMR (360 MHz) δ 4.45 (m, 1 H), 3.72–3.66 (comp, 2 H), 3.69 (s, 3 H), 3.34 (t, *J* = 11.5 Hz, 1 H), 3.19 (s, 3 H), 2.88 (m, *J* = 3.5, 7.0, 13.7 Hz, 1 H), 2.60 (br dt, 1 H), 2.51–2.43 (m, 1 H), 2.46 (dd, *J* = 4.8, 12.8 Hz, 1 H), 2.03–1.83 (comp, 3 H), 1.70–1.60 (m, 1 H), 1.57 (dd, *J* = 11.0, 12.8 Hz, 1 H), 1.47–1.23 (comp, 2 H), 0.97 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (90 MHz) δ 175.5, 165.7, 99.0, 79.7, 69.4, 65.5, 51.7, 49.4, 44.3, 43.3, 38.2, 37.3, 27.1, 25.4, 25.2, 12.7; mass spectrum, *m/e* 327.1671 ($C_{16}H_{25}NO_6$ requires 327.1682), 296 (base), 277, 268, 264, 250, 242, 198, 182, 166, 148, 145, 122, 97, 84, 81, 79, 71, 67, 55, 43.

Conversion of Methyl Glycoside 25 to 24. To a solution of **25** (62 mg, 0.19 mmol) and dry triethylamine (0.40 mL, 0.29 g, 2.85 mmol) in dry DMSO (2 mL) at room temperature was rapidly added a solution of sulfur trioxide–pyridine complex[31] (182 mg, 1.14 mmol) in dry DMSO (2 mL), and stirring was continued for 30 min. Cold $CHCl_3$ (30 mL) was added, and the organic layer was washed sequentially with 5% aqueous tartaric acid (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL). Each of the washes was back-extracted with $CHCl_3$ (2 × 30 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give 82 mg of crude ketone **26**: mp 117–118.5 °C; ^{1}H NMR (360 MHz) δ 4.50 (m, 1 H), 4.07 (dd, *J* = 7.2, 11.0 Hz), 3.70

(s, 3 H), 3.64 (t, J = 11.2 Hz, 1 H), 3.23 (s, 3 H), 2.99–2.91 (m, 1 H), 2.94 (d, J = 14.3 Hz, 1 H), 2.70 (d, J = 14.2 Hz, 1 H), 2.72–2.68 (m, 1 H), 2.61–2.53 (m, 1 H), 2.52–2.48 (m, 1 H), 2.11–2.03 (m, 1 H), 2.02–1.95 (m, 1 H), 1.94–1.86 (m, 1 H), 1.42–1.22 (comp, 2 H), 1.01 (d, J = 6.5 Hz, 3 H); IR 2910, 1740, 1715 cm^{-1}; mass spectrum, m/e 293.1268 [M^+ – 32 (MeOH)] ($C_{15}H_{19}NO_5$ requires 293.1263), 266, 210, 182, 164, 151, 150, 122, 101, 97, 96, 94, 84, 81, 79, 69 (base), 59, 55, 42, 41.

To a solution of the crude ketone **26** (82 mg) obtained above in THF (2.5 mL) at –78 °C was added 1 N L-Selectride (0.21 mL) in THF. After the mixture was stirred for 30 min, MeOH (0.50 mL) was added, and the solution was allowed to warm to room temperature. After the solution was stirred for 20 additional min, 30% aqueous hydrogen peroxide (0.08 mL, 0.95 mmol) was added, and when the mild exotherm subsided (5 min), the mixture was poured into water (20 mL). The aqueous mixture was extracted with ether (3 × 20 mL), and the combined extracts were washed with brine (2 × 20 mL) and dried (Na_2SO_4). Removal of the excess solvent in vacuo gave 55 mg of crude **24**, which was purified by HPLC (Skelly B/EtOAc, 2:3) to provide 46 mg (73% overall for the two steps) of methyl glycoside **24** as a single diastereomer (capillary GLC and ^1H NMR analysis). This material was identical in all respects with **24** prepared previously.

Spiroketals 3 and 27. A mixture of methyl glycosides **23** and **24** (152 mg, 0.356 mmol) was dissolved in methanol/water (5:1, 3.6 mL) containing boric acid (116 mg, 1.87 mmol) and a small spatula of W-2 Raney nickel (ca. 100 mg), and the mixture was shaken in a Parr shaking apparatus under hydrogen gas (60 psi) for 24 h. The catalyst was removed by filtration through a small plug of Florisil, and the Raney nickel was washed throughly with hot ethyl acetate (5 × 5 mL). The combined filtrates were concentrated in vacuo, and the resulting mixture of crude hydroxy ketones (104 mg, 89%) was dissolved in dry CH_2Cl_2 (4.0 mL) under nitrogen at room temperature. A solution of 1 N trifluoromethanesulfonic acid in CH_2Cl_2 (0.08 mL) was added, and the reaction was stirred for about 30 min at room temperature. The mixture was then poured into saturated aqueous NH_4Cl (15 mL), and the aqueous mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give an oil (88 mg), which was determined (capillary GLC, 50 m BP 1, 250 °C) to be an 18:1 mixture of **3** and another substance tentatively identified as the spiroketal **27**, respectively. Separation of the components by preparative HPLC (Skelly B/EtOAc, 3:1) yielded spiroketals **3** (64 mg, 68%) and **27** (3 mg, 3%).

For spiroketal **3**: mp 90.7–91.5 °C; $[\alpha]^{23}_D$ = +57.1° (c 0.89, $CHCl_3$) (lit.[6] $[\alpha]_D$ = +60.4° (c 0.85, $CHCl_3$); ^1H NMR (360 MHz) δ 4.60 (m, 1 H), 3.87 (dq, J = 2.8, 9.8 Hz, 1 H), 3.72 (t, J = 11.7 Hz, 1 H), 3.69 (s, 3 H), 3.51 (dd, J = 5.0, 11.7 Hz, 1 H), 2.79 (d, J = 10.0 Hz, 1 H), 2.61 (tt, J = 3.6, 12.0 Hz), 2.42 (m, 1 H), 2.36 (m, 1 H), 2.17 (dd, J = 3.2, 14.2 Hz), 2.02–1.82 (comp. 4 H), 1.77 (dd, J = 3.2, 14.2 Hz, 1 H), 1.45–1.27 (comp, 2 H), 0.91 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (90 MHz) δ 209.3, 175.4, 99.4, 72.5, 67.3, 62.0, 51.8, 42.3, 36.6, 36.1, 34.3, 29.3, 26.0, 22.8, 12.9; IR 3450 (br), 2900, 1760, 1720, 1060, 890 cm^{-1} mass spectrum m/e 298, 280, 267, 249, 237, 140, 131 (base), 113, 108, 89, 80, 71, 43.

For spiroketal **27**: ^1H NMR (500 MHz) δ 4.65 (m, 1 H), 4.00 (m, 1 H), 3.77 (dd, J = 3.8, 11.9 Hz, 1 H), 3.67 (s, 3 H), 3.53 (dd, J = 7.5, 11.9 Hz, 1 H), 2.92 (br d, J = 8.9 Hz), 2.58 (tt, J = 3.7, 11.8 Hz, 1 H), 2.47 (m, 1 H), 2.29 (br d, 1 H), 1.94 (dd, J = 6.7, 14.0 Hz, 1 H), 1.98–1.90 (comp, 3 H), 1.87 (dd, J = 4.5, 14.0 Hz, 1 H), 1.81 (m, 1 H), 1.46–1.25 (comp, 2 H), 0.97 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (126 MHz) δ 211.8, 175.5 99.4, 71.9, 67.0, 65.2, 51.9, 42.6, 36.6, 35.4, 34.6, 29.1, 26.0, 23.2, 10.9; mass spectrum, m/e 298, 249, 211, 140, 131 (base), 113, 108, 89, 80, 71, 43.

Formation of Epoxide 28. To a stirred solution of spiroketal **3** (105 mg, 0.35 mmol) in dry THF (23 mL) at room temperature under nitrogen was added a stock solution of dimethylsulfoxonium methylide (4.0 mL, 0.53 M) in DMSO. After 1 h, the reaction was quenched by the sequential addition of water (1 mL) and saturated aqueous NH_4Cl (1 mL), and then it was poured into brine (10 mL). The aqueous mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts were dried (Na_2SO_4). Evaporation of the solvent in vacuo furnished a crude **28**, which was purified by silica gel chromatography (Skelly B/EtOAc, 3:1) to give 98 mg (89%) of pure epoxide **28** as a white solid. An analytical sample was prepared by recrystallization from ether/hexane: mp 129.0–129.8 °C (lit. mp 104 °C,[6] 130–130.5 °C[7]); $[\alpha]^{23}_D$ = +145° (c 0.81, $CHCl_3$) {lit. $[\alpha]^{26}_D$ = +143.9° (c 0.79, $CHCl_3$),[6] $[\alpha]^{25}_D$ = +126° (c 1.23, $CHCl_3$)[7]}; ^1H NMR (360 MHz) δ 4.44 (q, J = 3.6 Hz, 1 H), 3.80 (dq, J = 3.6, 10.1 Hz, 1 H), 3.72 (t, J = 11.8 Hz, 1 H), 3.69 (s, 3 H), 3.40 (dd, J = 4.9, 11.5 Hz, 1 H), 3.15 (d, J = 10.3 Hz, 1 H), 2.92 (s, 2 H), 2.62 (tt, J = 3.6, 11.9 Hz, 1 H), 2.28 (br d, J = 14.8 Hz, 1 H), 2.03–1.96 (comp, 2 H), 1.87–1.62 (comp, 4 H), 1.59 (dd, J = 3.2, 14.6 Hz, 1 H), 1.48–1.25 (comp, 2 H), 0.88 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (90 MHz) δ 176.0, 103.6, 73.9, 70.4, 68.0, 62.4, 51.6, 49.8, 38.2, 37.2, 36.8, 34.6 29.7, 26.3, 22.0, 13.0; IR 3480, 2910, 1720, 1435, 1165, 1130, 1080, 1055, 990 cm^{-1}; mass spectrum, m/e (no M^+) 282, 264, 263, 277, 224, 191, 182, 164, 149, 139, 131, 123, 113, 108, 105, 95, 81, 71 (base), 43.

Synthetic (+)-Phyllanthocin (1). A solution of epoxide **28** (81 mg, 0.26 mmol) in dry CH_2Cl_2 (14 mL) containing 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (132 mg, 1.08 mmol) and freshly distilled cinnamoyl chloride (137 mg, 0.85 mmol) was stirred for 20 min at room temperature, and then the mixture was heated at reflux for 24 h. The reaction was quenched by pouring into saturated aqueous NH_4Cl (20 mL), and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The extracts were combined, washed with brine (20 mL), and dried (Na_2SO_4). Removal of the excess solvents in vacuo provided 81 mg of crude product, which was purified by preparative HPLC (Skelly B/EtOAc, 3:1) and then by recrystallization from ether/hexene to furnish synthetic phyllanthocin (1) as a crystalline white solid (44 mg, 40%): mp 115–116 °C (lit. 126–127 °C,[2] 120–121 °C,[3d] 118–120 °C,[6] 129–129.5 °C,[7]); $[\alpha]_D$ = +26.7° (c 1.36, $CHCl_3$) {lit. $[\alpha]_D$ = +25.2° (c 2.00, $CHCl_3$),[2] +23.81° (c 1.26, $CHCl_3$),[3d] +24.9° (c 1.86, $CHCl_3$),[6] +27.2° (c 2.04, $CHCl_3$)[7]}. The synthetic **1** thus obtained was spectroscopically identical (^1H and ^{13}C NMR, IR, mass spectrum, and TLC) with an authentic sample.[34]

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Registry No. **1**, 62948-37-2; **3**, 89690-43-7; **6**, 109667-78-9; **7**, 51983-63-2; **8c**, 97826-89-6; **9**, 5709-99-9; **10**, 5709-98-8; **11**, 109586-30-3; **12**, 119680-63-6; **13**, 119719-63-0; **15**, 109586-31-4; **17**, 119680-64-7; **18**, 109586-32-5; **21c**, 109586-33-6; **22c**, 109784-18-1; **23**, 119719-64-1; **23** (hydroxy ketone deriv), 109667-83-6; **24**, 119719-65-2; **24** (hydroxy ketone deriv), 109586-37-0; **25**, 119719-66-3; **26**, 119680-65-8; **27**, 119719-67-4; **28**, 82167-85-9; (1*R*,2*R*,5*R*)-2-iodo-7-oxabicyclo[3.2.1]octan-6-one, 119719-61-8; acetylhydroximoyl chloride, 5471-68-1; phenyl chlorothionocarbonate, 1005-56-7; cinnamoyl chloride, 102-92-1; (*R*)-methyl 3-hydroxy-2-methylpropionate, 72657-23-9; (*R*)-methyl 3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropionate, 105859-44-7; (*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropan-1-ol, 105859-45-8.

Supplementary Material Available: Data from single-crystal X-ray analysis of **18** (10 pages). Ordering information is given on any current masthead page.