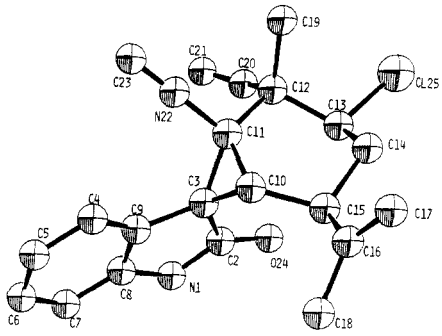

Figure 2. Computer-generated drawing of **1A** derived from the X-ray coordinates with hydrogens omitted for clarity.

as supplementary material. Figure 2 is a computer-generated perspective drawing of **1A** from the final X-ray coordinates showing the absolute stereochemistry of one molecule. The second independent molecule had a similar conformation but is not shown in Figure 2.

Indolinone **1A** has six contiguous asymmetric centers including three contiguous tetrasubstituted carbons. Its four fused rings are centered around a spiro-fused cyclopropane ring and pyrrolidone ring. The indolinone system is essentially planar and is virtually perpendicular to the cyclohexane ring which is in a half-chair conformation. This particular arrangement causes H13 to be 0.36 (0.41) Å[12] from the plane of the carbonyl and 2.33 (2.57) Å from the middle of the carbonyl bond C2–O24, which is consistent with the NMR observations (vide supra) that H13 in **1A** is 1.3 ppm downfield from its position in **2**.[13] Biogenetically, **1A** and **2** may both be thought as derived from tryptophan, two isoprene units and one carbon from the C-1 pool. The absolute stereochemistry of **2** has been assigned by analogy[5] and is opposite to that found for **1A**, except for C11.

The IR spectrum of compound **1B** indicated that it also contained an isonitrile (2135 cm^{-1}), an -NH (3430 cm^{-1}), and a carbonyl (1719 cm^{-1}). The absence of the Cl^- in **1B**, compared to **1A**, is apparent in the ^1H and ^{13}C NMR spectra (C13), as well as the HRMS (found 318.1732, calcd 318.1732 for $C_{21}H_{22}N_2O$).[6] These data indicate that **1B** is the deschloro derivatives of **1A**. We would like to suggest the name hapalindolinone for these indolinone-containing natural products and, in particular, hapalindolinone A and hapalindolinone B for compounds **1A** and **1B**, respectively.

With use of a modification of a procedure described by Bockaert et al.,[14] hapalindolinone A (**1A**) inhibits the binding of [^{3}H]arginine vasopressin to kidney tissue (v_2 receptor) with an IC_{50} of 37.5 ± 7.6 μM (n = 3). This compound also inhibits kidney (v_2) arginine vasopressin stimulated adenylate cyclase with an IC_{50} of 44.6 μM (n = 2).

Acknowledgment. We thank O. Hensens, J. Liesch, and C. Wichmann for valuable suggestions in confirming the reported structures.

Registry No. **1A**, 109151-56-6; **1B**, 109151-57-7.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **1A** (5 pages). Ordering information is given on any current masthead page.

(12) The numbers in parentheses are for the second independent molecule in the crystal structure.

(13) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon Press: Oxford, 1969; 2nd ed.; pp 88–92.

(14) Bockaert, J.; Roy, C.; Rajerison, R.; Jard, S. *J. Biol. Chem.* **1973**, *2480S*, 5922–5931.

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A Convergent Total Synthesis of (+)-Phyllanthocin

Summary: A highly convergent, enantioselective total synthesis of (+)-phyllanthocin (**1**), the aglycone of the antineoplastic agent phyllanthoside (**2**), has been achieved by employing a novel strategy that features a stereo- and regioselective dipolar cycloaddition of a nitrile oxide followed by the unmasking of the isoxazoline thus produced to give a key intermediate β-hydroxy ketone that was readily elaborated to the target natural product.

Sir: During the course of screening a variety of plants for potential anticancer agents, Kupchan isolated and characterized (+)-phyllanthocin (**1**), a novel bisabolane sesquiterpene that is the aglycone of the antineoplastic agent phyllanthoside (**2**).[2] In subsequent explorations, a closely related group of natural products known as the phyllanthostatins was discovered.[3] Owing to its promise as a therapeutically useful antitumor agent,[4] phyllanthoside (**2**) as well as the corresponding aglycone **1** have emerged as attractive targets for synthetic investigations.[5-10] It is indeed noteworthy that the absolute configuration of **1** was first ascertained by total synthesis,[5a] although the relative stereochemical relationships were originally established by single-crystal X-ray analysis.[2] Three subsequent accounts of the total synthesis of **1** in optically pure form have been recorded,[6-8] and the naturally occurring glycoside **2** itself has recently succumbed to total synthesis.[9] A highly convergent, enantioselective synthesis of **1** has been completed in our laboratories, and we now disclose the results of those efforts.[10]

The essential elements of our strategy for the asymmetric synthesis of **1** are adumbrated in a retrosynthetic format in Scheme I wherein assembly of the tricycle **3**, which also served as an intermediate in Williams' route

(1) Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award, 1980–1985.

(2) Kupchan, S. M.; La Voie, E. J.; Branfman, A. R.; Fei, B. Y.; Bright, W. M.; Bryan, R. F. *J. Am. Chem. Soc.* **1977**, *99*, 3199.

(3) (a) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P. *Can. J. Chem.* **1982**, *60*, 544. (b) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P.; Schmidt, J. M. *Ibid.* **1982**, *60*, 939. (c) Pettit, G. R.; Cragg, G. M.; Niven, M. L.; Nassimbeni, L. R. *Ibid.* **1983**, *61*, 2630. (d) Pettit, G. R.; Cragg, G. M.; Suffness, M. I.; Gust, D.; Boettner, F. E.; Williams, M.; Saenz-Renauld, J. A.; Brown, P.; Schmidt, J. M.; Ellis, P. D. *J. Org. Chem.* **1984**, *49*, 4258.

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(6) Williams, D. R.; Sih, S.-Y. *J. Am. Chem. Soc.* **1984**, *106*, 2949.

(7) (a) Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1985**, *50*, 3420. (b) Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27*, 4237.

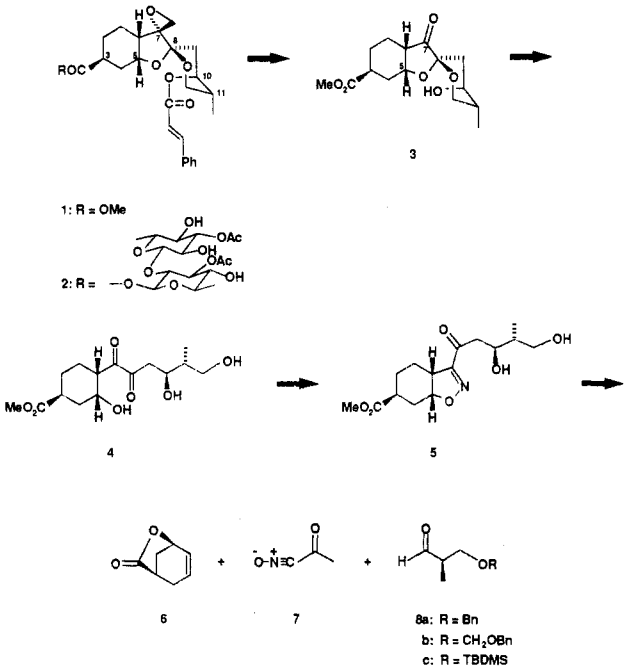
(8) Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269.

(9) Smith, A. B., III; Rivero, R. *J. Am. Chem. Soc.* **1987**, *109*, 1272.

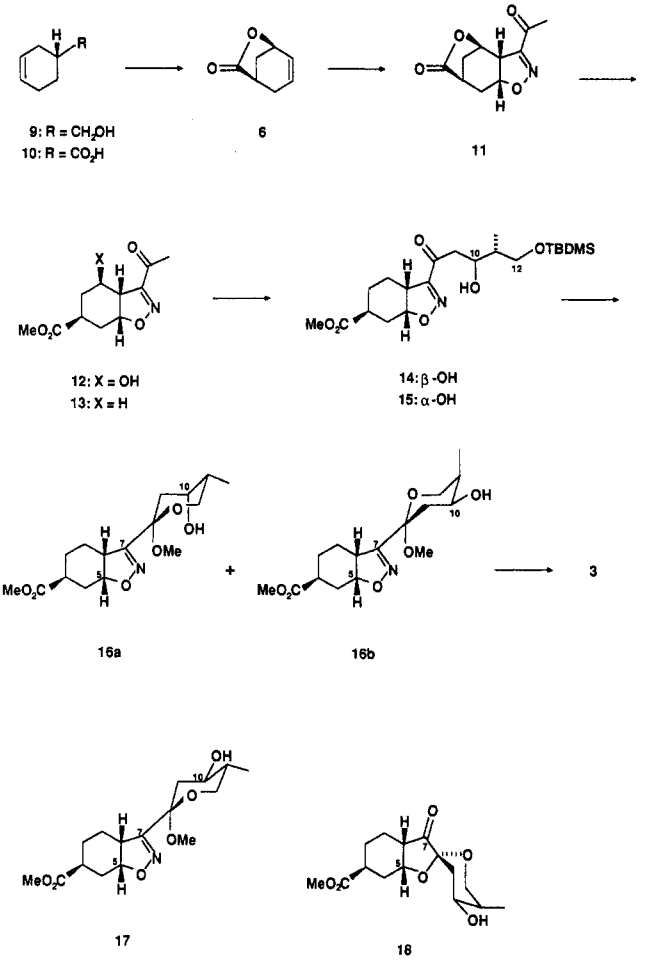
(10) These results were first presented at the 192nd National Meeting of the American Chemical Society, Anaheim, CA, September 1986; paper ORGN 291.

0022-3263/87/1952-3706$01.50/0

Scheme I



Scheme II



to **1**,[6] was perceived as the key subgoal. Complete dismantling of the spiro ketal array present in **3** then revealed the highly functionalized cyclohexane derivative **4** that may be further simplified to **5** upon recognition of the synthetic equivalency of a β-hydroxy ketone moiety with an isoxazoline ring.[11] Accordingly, **5** was envisaged to be accessible in a highly convergent fashion by the combination of the bicyclic, unsaturated lactone **6**, the nitrile oxide **7**, and a protected β-hydroxy aldehyde **8a–c**. Elimination of methyl cyclohex-3-enecarboxylate as a dipolarophile and a potential precursor to the hydrobenzofuran subunit of **1** stemmed from the reasonable hypothesis that its cycloaddition with **7** was not expected to proceed with a significant level of stereo- or regioselectivity.[12] In contrast, the sterically and electronically biased molecular framework present in **6** would ensure preferential attack by **7** from the less encumbered exo face with a predisposition for the attachment of the oxygen of the nitrile oxide to the terminus of the double bond distal to the allylic oxygen.[13]

In the event, the known, optically active carbinol **9**[14] was converted (PDC/DMF, room temperature, 24 h; 74%) to the corresponding carboxylic acid **10** ($[\alpha]_D$ 85.9°; 91% ee[15]) (Scheme II). Iodolactonization of **10** followed by base-induced dehydroiodination[16] afforded the optically active, unsaturated lactone **6** in 96% overall yield.[17] The optimal conditions for effecting the crucial dipolar cycloaddition involved the slow, thermal generation of the nitrile oxide **7** from acetohydroximoyl chloride in the presence of **6** (toluene, reflux, 18 h) to furnish the desired cycloadduct **11** in 45% yield together with two other diastereoisomeric adducts in lesser amounts (20% and 15% yields). Having thus served its intended purpose as a control element for the cycloaddition, the lactone moiety of **11** was then processed by methanolysis (K_2CO_3, MeOH, room temperature, 0.5 h; 85%) followed by excision of the hydroxyl group present in the intermediate hydroxy ester **12** by the action of tributyltin hydride upon the derived phenyl thionocarbonate[18] [(a) ClCSOPh (1.7 equiv), DMAP (2.0 equiv), CH_2Cl_2, room temperature, 26 h; 83%; (b) Bu_3SnH (1.1 equiv), catalyst AIBN, benzene, reflux, 2 h; 65% (74% based on recovered starting phenyl thionocarbonate)] to give **13**, the structure of which was secured by single-crystal X-ray analysis.[19]

(11) See, inter alia: (a) Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757. (b) Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123. (c) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826; **1982**, *104*, 4024. (d) Martin, S. F.; Dupre, B. *Tetrahedron Lett.* **1983**, *24*, 1337. (e) Kozikowski, A. P.; Ghosh, A. K. *Ibid.* **1983**, *24*, 2623. (f) Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366. (g) Kozikowski, A. P.; Stein, P. D. *Ibid.* **1984**, *49*, 2301. (h) Curran, D. P.; Scanga, S. A.; Fenk, C. J. *Ibid.* **1984**, *49*, 3474.

(12) This prediction was experimentally confirmed by the finding that the reaction of methyl cyclohex-3-enecarboxylate with **7** gave a mixture of four diastereomeric cycloadducts in approximately equal amounts.

(13) For example, see: (a) Caramella, P.; Cellerino, G. *Tetrahedron Lett.* **1974**, 229. (b) McAlduff, E. J.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1978**, *100*, 105. (c) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1984**, *49*, 2762. (d) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

(14) Boeckman, R. K., Jr.; Naegely, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 754. For a related synthesis of **10**, see: Masamune, S.; Reed, L. A., III; Davis, J. T.; Choy, W. *Ibid.* **1983**, *48*, 4441.

(15) A rotation of $[\alpha]_D$ 94.5° has been reported for the pure acid. Ceder, O.; Hansson, B. *Acta Chem. Scand.* **1970**, *24*, 2693.

(16) This procedure was identical with that reported in the literature for the preparation of racemic **6**. See: (a) Bartlett, P. A.; McQuaid, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7854. (b) Grewe, R.; Heinke, A.; Sommer, C. *Chem. Ber.* **1956**, *89*, 1978.

(17) The structure assigned to each compound was in accord with its ^1H and ^{13}C NMR, IR, and mass spectral characteristics. Analytical samples of all new compounds were obtained by preparative HPLC and gave satisfactory combustion analysis or identification of the molecular ion by high-resolution mass spectrometry. All yields are based upon isolation materials purified by chromatography or recrystallization.

(18) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059. (c) Ogilvie, K. K.; Hakimelahi, G. H.; Proba, Z. A.; Usman, N. *Tetrahedron Lett.* **1983**, *24*, 865.

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

The coupling of the two optically active subunits **13** and **8a-c**[20] required a chelation-controlled aldol reaction[21] to achieve high levels of stereochemical efficiency. Although the reactions between the trimethylsilyl enol ether derived from the methyl ketone **13** and the protected aldehydes **8a-c** in the presence of $SnCl_4$ (CH_2Cl_2, -78 → -20 °C) provided mixtures of the adducts **14** and **15** in which the desired diastereoisomer **14** dominated by as much as 9:1, the yields observed for these transformations were uniformly less than 20%. Alternatively, when the lithium enolate of **13** (LDA, THF, -78 °C, 0.75 h) was allowed to react with freshly prepared **8c**[7] (THF, -78 °C, 1 h), an easily separable mixture (1.2:1) of **14** and **15** was obtained in 78% combined yield.[22] Since the stereochemistry at C(10) in the undesired adduct **15** could be efficiently corrected after glycoside formation (vide infra), the modest level of stereoselectivity obtained in this directed aldol reaction represents a temporary nuisance rather than a serious flaw.

The fluoride-induced removal [5% aqueous HF (2-3 equiv), MeOH, room temperature, 20 h; 70-80%)] of the silyl ether protecting group from the C(12) hydroxyl of **14** proceeded with concomitant formation of the methyl glycosides **16a,b** (1:2.7), and **15** was converted into **17** by the same protocol. At this juncture the inversion of the hydroxyl group at C(10) of **17** was achieved in a straightforward fashion by sequential oxidation and highly stereoselective hydride reduction of the intermediate ketone to provide **16a** exclusively [(a) Py-SO_3, Me_2SO, Et_3N, room temperature 0.5 h; (b) L-Selectride, THF, -78 °C 0.5 h; 73% overall].[23] Liberation of the latent β-hydroxy ketone array at C(5)-C(7) of the isoxazolines **16a,b** [H_2 (55 psi), W-2 Raney Ni, $B(OH)_3$ (5 equiv), 15% aqueous MeOH, room temperature, 20 h; 82-89%] followed by a kinetically controlled, acid-catalyzed spiroketalization [CF_3SO_3H (5 mol %), CH_2Cl_2, room temperature, 2 h; 78%] delivered a separable mixture (18:1) of the spiro ketal **3** and a substance tentatively identified as **18**. The spiro ketal **3**, which was spectroscopically identical with Williams' intermediate,[6,24] was then subjected to sequential methylenation [$Me_2S(O)=CH_2$, THF, 0 °C, 0.5 h] of the C(7) carbonyl function and O-cinnamoylation (PhCH=CHCOCl, DMAP, CH_2Cl_2, reflux, 48 h)[6] to furnish synthetic (+)-phyllanthocin (**1**) that was spectroscopically identical with an authentic sample.[25]

Acknowledgment. We thank the National Institutes of Health (GM 31077) and the Robert A. Welch Foundation for generous support of this research. One of us (M.S.D.) is also grateful to the National Institutes of Health for a NRSA award. We are thankful to the National Science Foundation (CHE 8305785) and the National Institutes of Health (RR 01912) for providing NMR facilities. Finally, we thank Dr. Franz Scheidl of Hoffmann-LaRoche, Inc. for performing the combustion analyses.

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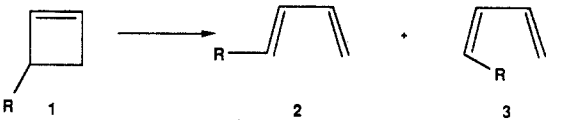
Prediction and Experimental Verification of the Stereoselective Electrocyclization of 3-Formylcyclobutene

Summary: 3-Formylcyclobutene has been synthesized from cyclobutene-1,1-dicarboxylic acid; it opens at 25-70 °C with an activation energy of 27 ± 1 kcal/mol to give exclusively (>98%) the *Z* product, in accord with predictions.

Sir: The thermally allowed conrotatory ring-opening of substituted cyclobutenes **1** may result in formation of either **2** or **3** (eq 1), the result of outward or inward rotation of the substituent. We previously developed a theory to



(1)

explain why the tendency for outward rotation increases as the substituent becomes a better donor.[1,2] In the case of a very strong acceptor, such as the BH_2 group, inward rotation was predicted to be favored.[1b] This theory has been used to rationalize other results which are clearly not sterically controlled.[2,3] We have now studied more conventional electron-withdrawing groups and report here the predictions stemming from these calculations, as well as an experimental test of the predictions.

The transition structures for inward and outward rotations of the CN group in 3-cyanocyclobutene and the CHO group in 3-formylcyclobutene were located with ab initio calculations involving full optimizations with the 3-21G basis set,[4] using Pople's GAUSSIAN 82 series of programs.[5] Harmonic frequency calculations verify that these are transition structures with only one imaginary frequency. Energies were evaluated with 6-31G* calculations[6] on the 3-21G geometries. We have found that substituent effects are correctly predicted with RHF theory, although correlation energy corrections are needed in order to obtain reasonable activation energies.[1a,b] Reactant and transition

(20) We thank Dr. Noal Cohen (Hoffmann-La Roche Inc.) for a generous sample of (*S*)-(+)-3-hydroxy-2-methylpropanoic acid used for the preparation of **8a-c**.

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(22) The corresponding directed aldol reactions of the lithium enolate of **13** with **8a,b** proceeded with comparable efficiency and diastereoselectivity (**14**/**15** = 1.1-1.8:1), but the removal of the benzyl and (benzyloxy)methyl protecting groups at later stages of the sequence proved difficult.

(23) Reduction of the intermediate ketone with sodium borohydride provided a mixture (9:1) of **16a** and **17**.

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

(25) We thank Professor S. D. Burke (University of South Carolina) for providing the ^1H NMR spectrum of **1** and Professor A. B. Smith, III, (University of Pennsylvania) for generous quantities of an authentic sample of **1**.

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